รายงานวิจัยฉบับสมบูรณ์

โครงการ

ภาษาไทย **ปฏิกิริยาการปิดวงของอัลฟา-ซัลฟินีลคาร์แบนอิออนสำหรับการเตรียมสารผลิตภัณฑ์ธรรมชาติจำพวก 1-เอซาไบไซคลิก, อัลลีนีลิดีน-2-ไซโคลเพนทีโนนและเพนทีโนไมซิน**

ภาษาอังกฤษ **Cyclisation Reaction of α-Sulfinyl Carbanions as a General Route for the Preparation of Some 1-Azabicyclic Natural Products, 5-Allenylidene-2-cyclopentenones and Pentenomycins**

โดย ศาสตราจารย์ ดร. มนัส พรหมโคตร และคณะ
ภาควิชาเคมี คณะวิทยาศาสตร์
มหาวิทยาลัยมหิดล

(31 กรกฎาคม 2549 – 31 กรกฎาคม 2552)

สัญญาเลขที่ BRG49800005

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คณะผู้วิจัย	**สังกัด**
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สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

สารบัญ

หน้า

6. ภาคผนวก

ผลงานวิจัยที่ตีพิมพ์ในวารสารวิชาการระดับนานาชาติ

ภาคผนวก (4.1.1) "Intramolecular Acylation of α-Sulfinyl Carbanions with Masked α,β-Unsaturated Esters: A General Strategy to 5-Alkylidene-2-cyclopentenones"

ภาคผนวก (4.1.2) "The Morita-Baylis-Hillman Reaction of Masked 5-Alkylidene-2-cyclopentenones : A General Entry to 5-Alkylidene-2-(hydroxyalkyl)-2-cyclopentenones"

ภาคผนวก (4.1.3) "Concise syntheses of substituted indolizidine alkaloids via cyclization based on α-sulfinyl carbanions: preparation of (±)-indolizidines 167B and 209D, their epimers, and (±)-tashiromine"

ภาคผนวก (4.1.4) "Asymmetric synthesis of pentenomycin I, epipentenomycin I, and their analogs"

ภาคผนวก (4.1.5) "A new strategy for the synthesis of (±)-lupinine and (±)-epilupinine *via* cyclization of α-sulfinyl carbanions"

ภาคผนวก (4.1.6) "A synthetic strategy to pyrrolidines and piperidines based on cyclization of α-sulfinyl carbanions"

ภาคผนวก (4.1.7) "Asymmetric total synthesis of (+)-swainsonine"

ผลงานที่ได้ตีพิมพ์และอ้างอิง (เป็นผลงานต่อเนื่องของทุน BRG/22/2544 และ CHE-RES-RG)

ภาคผนวก (4.2.1) "Stereoselective synthesis of β-carboethoxy-γ-lactams via imino Mukaiyama-aldol type reaction of 1,4-bis(trimethylsilyloxy)-1,4-butadiene"

ภาคผนวก (4.2.2) "Highly diastereoselective synthesis of β-carboxy-γ-lactams and their ethyl esters via $Sc(OTf)_3$-catalyzed imino Mukaiyama-aldol type reaction of 2,5-bis(trimethylsilyloxy)furan with imines"

ภาคผนวก (4.2.3) "*gem*-Difluoromethylation of α- and γ-ketoesters: preparation of *gem*-difluorinated α-hydroxyesters and γ-butyrolactones"

ภาคผนวก (4.2.4) "Fluoride-catalyzed addition of $PhSCF_2SiMe_3$ to *N*-substituted cyclic imides followed by radical cyclization: general synthetic strategy of *gem*-difluoromethylenated 1-azabicyclic compounds"

สัญญาเลขที่ BRG49800005

โครงการ

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ภาษาอังกฤษ **Cyclisation Reaction of α-Sulfinyl Carbanions as a General Route for the Preparation of Some 1-Azabicyclic Natural Products, 5-Allenylidene-2-cyclopentenones and Pentenomycins**

รายงานในช่วงตั้งแต่วันที่	31 กรกฎาคม 2549 ถึงวันที่ 31 กรกฎาคม 2552
ชื่อหัวหน้าโครงการ:	ศาสตราจารย์ ดร. มนัส พรหมโคตร
ผู้ร่วมโครงการ:	รองศาสตราจารย์ ดร. ปทุมรัตน์ ตู้จินดา
หน่วยงาน:	ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล

Abstract

The synthetic utilities of the cyclization reactions based on α-sulfinyl carbanions have been successfully demonstrated for the preparation of 5-alkylidene-2-cyclopentenones, 5-alkylidene-2-hydroxyalkyl-2-cyclopentenones, enantiomers of pentenomycin I, epipentenomycin I, desoxypentenomycin and analogs. Moreover, the synthetic strategy was employed for the syntheses of 1-azabicyclic alkaloids; (±)-tashiromine, indolizidine 167B, indolizidine 209D, (±)-lupinine , (±)-epilupinine, (+)-swainsonine as well as substituted pyrrolidines and piperidines, starting from appropriate lactams or amides.

Keywords: intramolecular cyclization, α-sulfinyl carbanions, 5-alkylidene-2-cyclopentenones, 5-alkylidene-2-hydroxyalkyl-2-cyclopentenones, pentenomycin I, epipentenomycin I, desoxypentenomycin, (±)-tashiromine, indolizidine 167B, indolizidine 209D, (±)-lupinine , (±)-epilupinine, (+)-swainsonine, pyrrolidines, piperidines.

บทคัดย่อ

(ได้ประยุกต์ใช้ปฏิกิริยา cyclization based on α-sulfinyl carbanions ในการเตรียม 5-alkylidene-2-cyclopentenones, 5-alkylidene-2-hydroxyalkyl-2-cyclopentenones, enantiomers ของ pentenomycin I, epipentenomycin I, desoxypentenomycin และ analogs, (±)-tashiromine, indolizidine 167B, indolizidine 209D, (±)-lupinine , (±)-epilupinine, (+)-swainsonine, substituted pyrrolidines, และ substituted piperidines)

Keywords: intramolecular cyclization, α-sulfinyl carbanions, 5-alkylidene-2-cyclopentenones, 5-alkylidene-2-hydroxyalkyl-2-cyclopentenones, pentenomycin I, epipentenomycin I, desoxypentenomycin, (±)-tashiromine, indolizidine 167B, indolizidine 209D, (±)-lupinine , (±)-epilupinine, (+)-swainsonine, pyrrolidines, piperidines.

Executive Summary

ผลงานวิจัยของการนำปฏิกิริยา intramolecular acylation ของ α-sulfinyl carbanion ไปใช้ในการเตรียมสารประกอบ cyclopentenones และ 1- azabicyclic natural product บางตัว พอสรุปได้ดังนี้

1. การศึกษาวิธีการเตรียมสารประกอบ 5-allenylidene-2-cyclopentenones
2. การเตรียม 5-allenylidene-2-cyclopentenones และ 5-alkylidene-2-hydroxyalhyl-2-cyclopentenones
3. การเตรียม pentenomycin I, epipentenomycin I, และ analogs แบบอสมมาตร
4. การเตรียม (±)-tashiromine, (±)-indolizidine 167B, (±)-indolizidine 209D , (±)-lupinine และ (±)-epilupinine
5. การเตรียม piperidines และ pyrrolidines
6. การเตรียม (+)-swainsonine

1. การดำเนินงาน ได้ดำเนินงานตามแผนที่วางไว้ทุกประการ

2. สรุปผลการดำเนินงาน

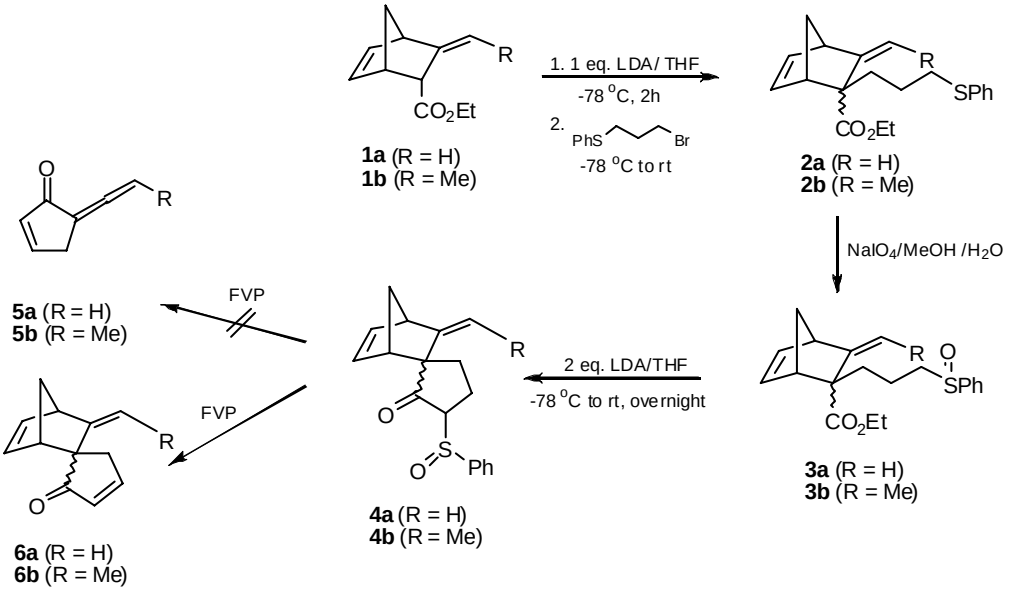
ผลงานวิจัยของการนำปฏิกิริยา intramolecular acylation ของ α-sulfinyl carbanion ไปใช้ในการเตรียมสารประกอบ cyclopentenones และ 1- azabicyclic natural product บางตัว พอสรุปได้ดังนี้

7. การศึกษาวิธีการเตรียมสารประกอบ 5-allenylidene-2-cyclopentenones
8. การเตรียม 5-allenylidene-2-cyclopentenones และ 5-alkylidene-2-hydroxyalhyl-2-cyclopentenones
9. การเตรียม pentenomycin I, epipentenomycin I, และ analogs แบบอสมมาตร
10. การเตรียม (±)-tashiromine, (±)-indolizidine 167B, (±)-indolizidine 209D , (±)-lupinine และ (±)-epilupinine
11. การเตรียม piperidines และ pyrrolidines
12. การเตรียม (+)-swainsonine

2.1 การศึกษาการเตรียมสารประกอบ 5-Allenylidene-2-cyclopentenones 5

ในระยะแรกของงานวิจัย ได้มุ่งเน้นหาวิธีการเตรียมสารประกอบ 5-allenylidene-2-cyclopentenones **5** โดยเริ่มต้นจากสาร **1** โดยใช้ปฏิกิริยา intramolecular acylation ของ α-sulfinyl carbanion และปฏิกิริยา Retro-Diels-Alder ดังแสดงไว้ใน แผนผังที่ **1**

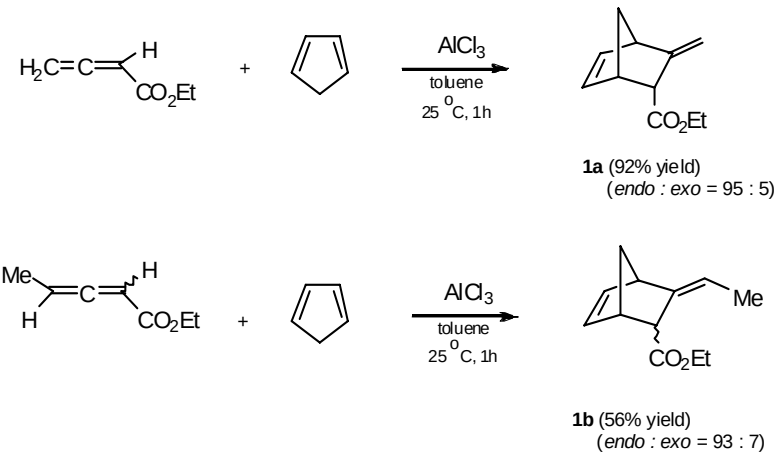
แผนผังที่ 1



2.1.1 การเตรียมสารเริ่มต้น 1a และ 1b

สามารถเตรียมสารได้โดยทำปฏิกิริยา Diels-Alder ระหว่าง allenic esters กับ cyclopentadiene โดยใช้ $AlCl_3$ เป็น catalyst ดังแสดงไว้ใน แผนผังที่ 2

แผนผังที่ 2



2.1.2 การเตรียมสาร 2 และ สาร 3

สามารถเตรียมสาร **2a** และ **3b** โดยให้ lithium enolate anion ที่เตรียมได้จากสาร **1a** หรือ **1b** ทำปฏิกิริยากับ LDA (1.1 equiv) ใน THF ที่ -78 °C (2 ชม.) ทำปฏิกิริยากับ 3-bromo-1-phenylsylfanylpropane ที่ -78 °C ถึงอุณหภูมิห้องจะได้สาร **2a** 92% yield และสาร **2b** 72% yield โดยมีอัตราส่วนของ *endo: exo* = 97:3 เมื่อได้สาร sulfide **2a** และ **2b** แล้วก็นำไปทำ oxidation โดยใช้ $NaIO_4$/MeOH/H_2O ที่อุณหภูมิ 0-5 °C จะทำให้ได้สารเริ่มต้น sulfoxide **3a** (95%) และ **3b** (81%) (แผนผัง ที่ 1)

2.1.3 การเตรียมสาร 4 โดยปฏิกิริยา Cyclization ของ α-Sulfinyl Carbanion

เมื่อให้สาร sulfoxide **3a** หรือ **3b** ทำปฏิกิริยากับ LDA (2.2 equiv) ใน THF ที่ -78 °C จะได้ α-sulfinyl carbanion ของ sulfoxide **3a** หรือ **3b** ซึ่งจะเกิดปฏิกิริยา intramolecular acylation of α-sulfinyl carbanion หลังจากที่ค่อยๆปล่อยให้อุณหภูมิสูงขึ้นช้าๆ จาก -78 °C มายังอุณหภูมิห้อง (16 ชม.) หลังจาก work-up และ chromatography จะได้สาร spirocyclopentanones **4a** (80% yield) และ **4b** (67% yield) โดยทั้งสองกรณีจะได้สารเป็นส่วนผสมของ diastereomers ซึ่งไม่มีความจำเป็นที่จะต้องแยกสำหรับการศึกษาในขั้นต่อไป

2.1.4 การศึกษาการเตรียมสาร 5-Allenylidene-2-cyclopentenones จากสาร 4 โดยทำ ปฏิกิริยา Retro-Diels-Alder โดยทำ Flash Vacuum Pyrolysis (FVP)

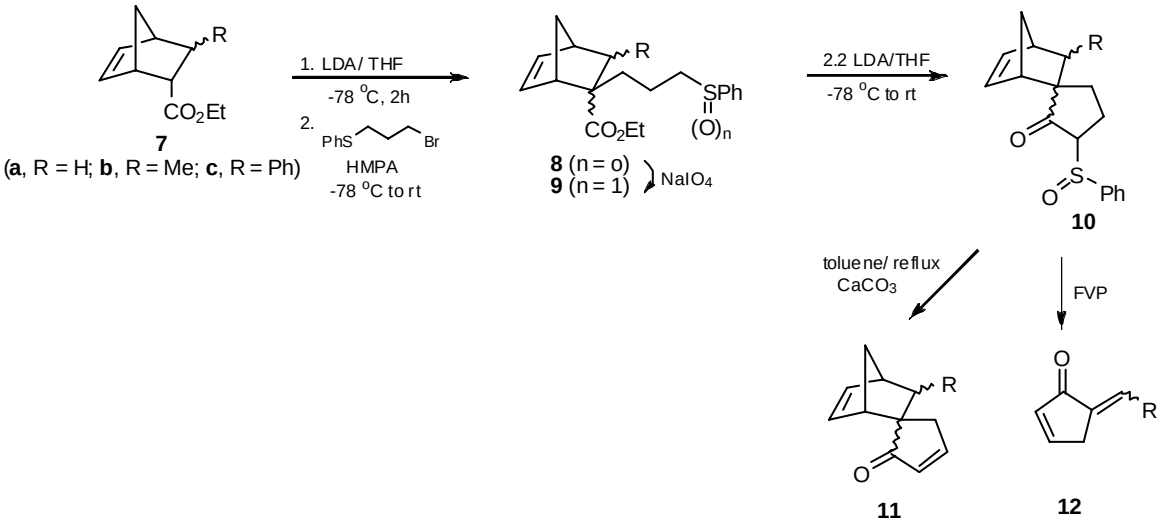
เมื่อนำสาร **4a** มาทำ FVP ที่ 375 °C (0.05 torr) จะได้สาร **6a** ถึง 86% yield โดยไม่พบสาร **5a** ที่ต้องการเลย แสดงว่า Retro-Diels-Alder reaction ไม่เกิด แต่จะเกิด sulfoxide elimination ดังนั้นจึงได้เพิ่มอุณหภูมิในการทำ FVP สูงขึ้นถึง 400 °C พบว่าจะไม่ได้สาร **6a** และ **5a** จากการวิเคราะห์ ^{1}H NMR ของ product ที่ได้จะ complex มาก รวมทั้งจากการวิเคราะห์ทาง TLC (thin-layer chromatography) จะเห็นว่าประกอบด้วยสารหลายตัวซึ่งไม่คุ้มค่าที่จะพยายามแยก

ในทำนองเดียวกันเมื่อนำสาร **4b** มาทำ FVP ที่ 385 °C (0.05 torr) ก็จะได้สาร **6b** 50% yield แต่จะไม่พบสาร **5b** ที่ต้องการ

2.2 วิธีการเตรียมสารประกอบ 5-Alkylidene-2-cyclopentenones 12 โดยใช้ปฏิกิริยา Intramolecular Acylation of α-Sulfinyl carbanions

เนื่องจากว่ามีปัญหาในการศึกษาหาวิธีทั่วไปในการเตรียมสาร 5-allenylidene-2-cyclopentenones **5** ได้ศึกษาหาวิธีการทั่วไปสำหรับการเตรียมสาร 5-alkylidene-2-cyclopentenones **12** โดยใช้ปฏิกิริยา intramolecular acylation ของ α-sulfinyl carbanions เช่นเดียวกัน ดังแสดงไว้ในแผนผังที่ 3 โดยเริ่มต้นจาก cyclopentadiene-α,β-unsaturated ester Diels-Alder adducts **7**

แผนผังที่ 3

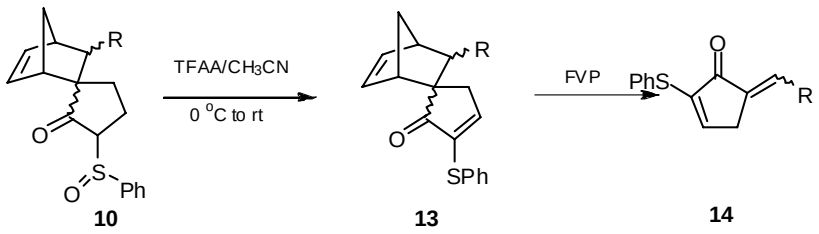


เมื่อให้ bicyclic ester **7** ทำปฏิกิริยากับ LDA ใน THF ที่อุณหภูมิ -78 °C (2 ชม.) จะได้ enolate anion ซึ่งทำปฏิกิริยากับ $PhS(CH)_3Br$ โดยมี HMPA เป็น co-solvent ที่ -78 °C ถึงอุณหภูมิห้องจะได้ sulfide **8** ซึ่งจะนำไปทำ oxidation โดยใช้ $NaIO_4/MeOH/H_2O$ ที่ 0 °C ถึง 5 °C จะได้ sulfoxide **9** ซึ่งเป็นสารที่สำคัญที่จะนำไปใช้เตรียม spirocyclopcntanene **12** โดยทำปฏิกิริยากับ 2.2 equiv LDA ใน THF ที่ -78 °C ถึงอุณหภูมิห้องเพื่อ generate α-sulfinyl carbanion ซึ่งจะเกิด cyclisation โดยเกิด intramolecular acylation ของ α-sulfinyl carbanion สาร **10** นี้จะเป็น precursor สำหรับการเตรียม 5-alkylidene-2-cyclopentenones **12** โดยทำ FVP พบว่าเตรียมสาร **12** ได้ใน % yield ที่ดี

นอกจากนี้ยังพบว่าเมื่อนำสาร **10** มาทำ sulfoxide elimination โดย reflux ใน toluene โดยมี $CaCO_3$ อยู่ด้วยจะได้สาร spirocyclopcntenone **11** ซึ่งสารนี้จะนำไปเตรียม highly functionalized cycolpentenones ซึ่งจะได้กล่าวต่อไป

เพื่อที่จะแสดงให้เห็นถึงประโยชน์ของสาร **10** ซึ่งได้จาก intramolecular acylation of α-sulfinyl carbanion จึงได้ศึกษาปฏิกิริยา Pummerer rearrangement เพื่อที่จะใช้เป็นวิธีการเตรียมสาร phenyl sulfanylsubstituted spirocyclopentenone **16** ซึ่งอาจจะมีประโยชน์ในการใช้เป็นสารเริ่มต้นสำหรับการเตรียมสารที่เป็นผลิตภัณฑ์ธรรมชาติบางตัวต่อไปได้ ดังนั้นเมื่อทำปฏิกิริยาสาร **10** กับ trifluoroacetic anhydride (TFAA) ใน CH_3CN ที่ 0 °C ถึงอุณหภูมิห้องจะได้สาร **13** ใน % yield ที่ดี เมื่อนำสาร **13** ไปทำ FVP จะได้สาร **14** (ดูแผนผังที่ 4)

แผนผังที่ 4

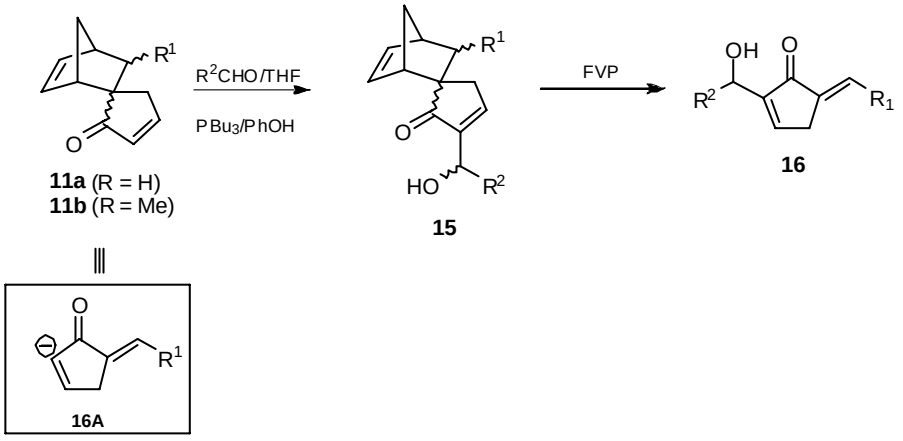


10 **13** **14**

2.3 การศึกษาประโยชน์ของสาร 11 สำหรับเป็นสารเริ่มต้นในการเตรียม 5-Alkylidene-2-(hydroxyalkyl)-2-cyclopentenones 16

เมื่อพิจารณาดูโครงสร้างของสาร **16** แล้วจะเห็นว่าควรจะเตรียมยากเท่าที่ทราบยังไม่มีวิธีการเตรียมสารประเภทนี้ จึงคิดว่าน่าจะใช้สาร **11** เป็น synthetic equivalent ของ **16A** ดังนั้นจึงได้ศึกษาปฏิกิริยา Morita-Baylis-Hillman โดยใช้ Bu_3P เป็น catalyst และมี phenol เป็น proton source เมื่อให้สาร **11** ทำปฏิกิริยากับ aldehydes โดยใช้ Bu_3P เป็น catalyst และมี PhOH อยู่ด้วยเป็น Bronsted acid ใน THF ที่อุณหภูมิห้องเป็นเวลา 1 ชม. จะได้สาร **15** ใน % yield ที่ดี และเมื่อนำสาร **15** ไปทำ FVP จะได้สารประกอบ **16** ตามที่ต้องการ ผลการทดลองแสดงให้เห็นว่าสาร **11** สามารถใช้เป็น synthetic equivalent **16A** ได้

แผนผังที่ 5



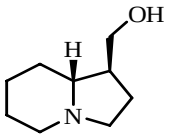
11a (R = H)
11b (R = Me)

15 **16**

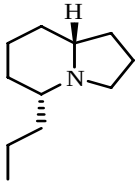
16A

2.4 การเตรียม Substituted Indolizidine Alkaloids: (±)-Tashiromine (17) Indolizidine 167B (18) และ Indolizidine 209D (19)

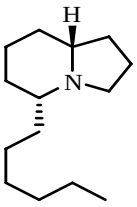
ได้ศึกษาวิธีการเตรียมสารประกอบ substituted indolizidines (±)-tashiromine **(20)** (±)-indolizidine 167B **(21)** และ indolizidine 209D (**19**)



(±)-Tashiromine **(17)**



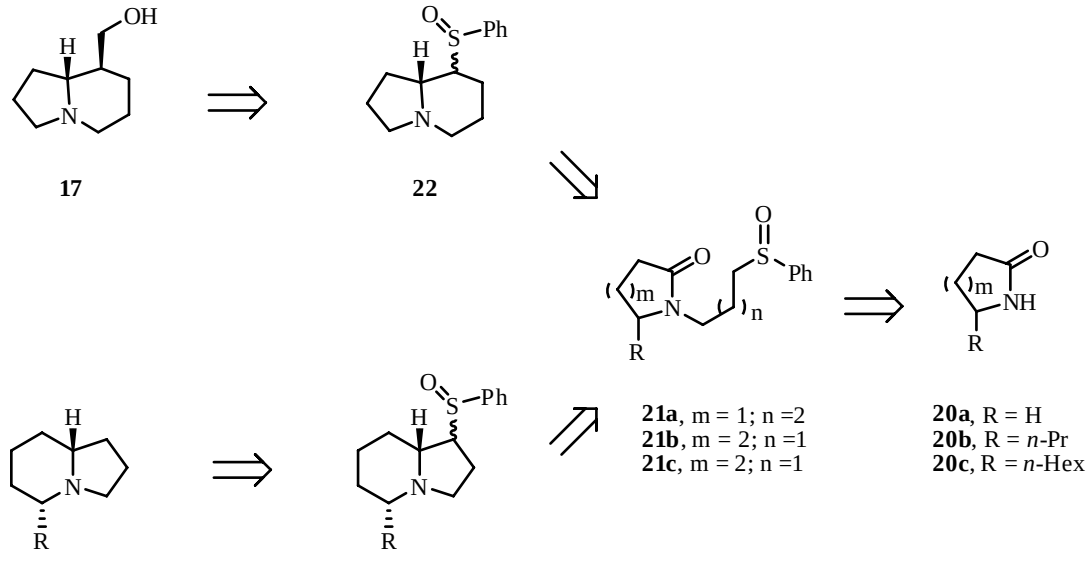
(±)-Indolizidine 167B **(18)**



(±)-Indolizidine 209D **(19)**

Tashiromine **(17)** แยกได้จากพืช *Maackai tashiroi* พบในเขต subtropical Asia[1] ส่วน indolizidines 167B **(18)** indolizidine 209D **(19)** แยกได้จากผิวหนังของ neotropical frogs family Dendrobatidae ของภูมิภาคอเมริกากลางและอเมริกาใต้[2] แผนการเตรียมโดยใช้ประโยชน์จากปฏิกิริยา cyclisation ของ α-sulfinyl carbanions ที่ได้พัฒนาขึ้นมาตามที่ได้ตีพิมพ์ผลงานไปแล้ว โดยเริ่มต้นจาก lactam **20** ตามที่ได้แสดง retrosynthetic analysis ไว้ในแผนผัง 6 สารที่สำคัญในการที่จะสร้าง indolizidine ring ของสาร **22** และ **23**ที่ต้องการ โดยทำปฏิกิริยา cyclisation ของ α-sulfinyl carbanions ที่เตรียมมาจากสาร **21** ควรจะเตรียมสาร **21** ได้โดยง่ายจาก lactam **20** สาร **22** และ **23** จะเป็น precursors สำหรับการเตรียม (±)-tashiromine **(17)** indolizidines 167B **(18)** และ 209D **(19)** ต่อไป

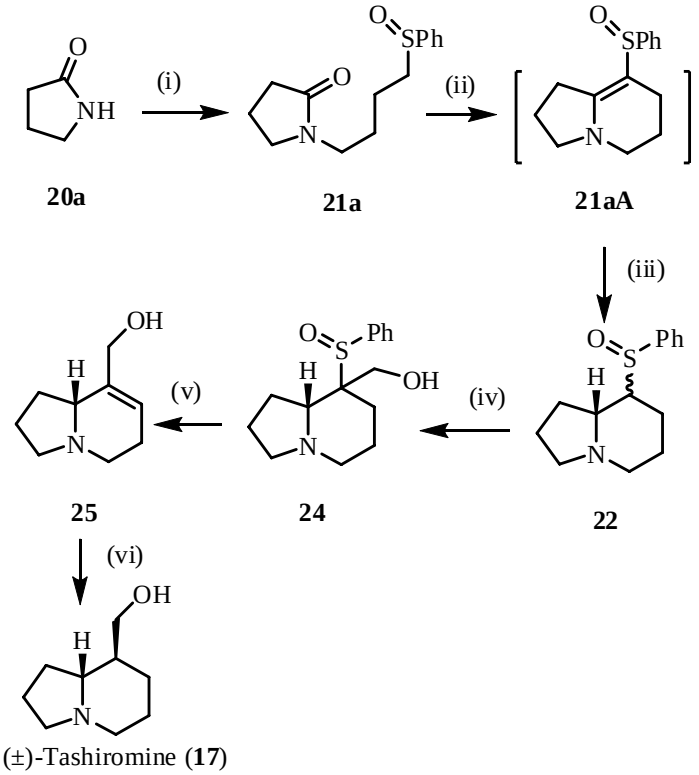
แผนผังที่ 6



2.4.1 การสังเคราะห์ (±)-Tashiromine (17)

การเตรียมเป็นไปดังแสดงในแผนผัง 7 โดยเริ่มจาก γ-lactams **23** (m = 1, R = H) โดยทำปฏิกิริยา *N*-alkylation ด้วย $PhS(CH_2)_4Br$, NaH/DMF ที่ 0 °C ถึงอุณหภูมิห้องแล้วนำ product ที่ได้ไปทำ oxidation โดยใช้ $NaIO_4$, $MeOH/H_2O$ ที่ 0 °C ถึงอุณหภูมิห้องจะได้สาร **24a** ใน % yield ที่ดี เมื่อให้ **24a** ทำปฏิกิริยากับ LiHMDS/THF ที่ -78 °C ถึงอุณหภูมิห้อง จะเกิดปฏิกิริยา cyclisation ของ α-sulfinyl carbanions ที่ถูก generate ขึ้นมาจากสาร **24a** ทำให้ได้สาร **24aA** ซึ่งไม่เสถียร จึงทำปฏิกิริยา reduction ด้วย $NaBH_4$/MeOH ที่ 0 °C ถึงอุณหภูมิห้องจะได้สาร indolizidine **25** (69% yield) เป็นส่วนผสมของ diastereomer นำสาร **25** ไปทำ α-hydroxymethylation โดย generate α-sulfinyl carbanion ของสาร **25** ก่อน โดยให้ทำปฏิกิริยากับ LDA/THF และ paraformaldehyde จะทำให้ได้สาร **27** (55% yield) ทำปฏิกิริยา pyrolysis สาร **27** โดย reflux ใน tolucne จะได้สาร **8** (47%) ซึ่งเมื่อนำไปทำปฏิกิริยา catalytic hydrogenation (H_2, Pd/C) จะได้ (±)-tashiromine **(20)** ที่ต้องการ 86% yield

แผนผังที่ 7



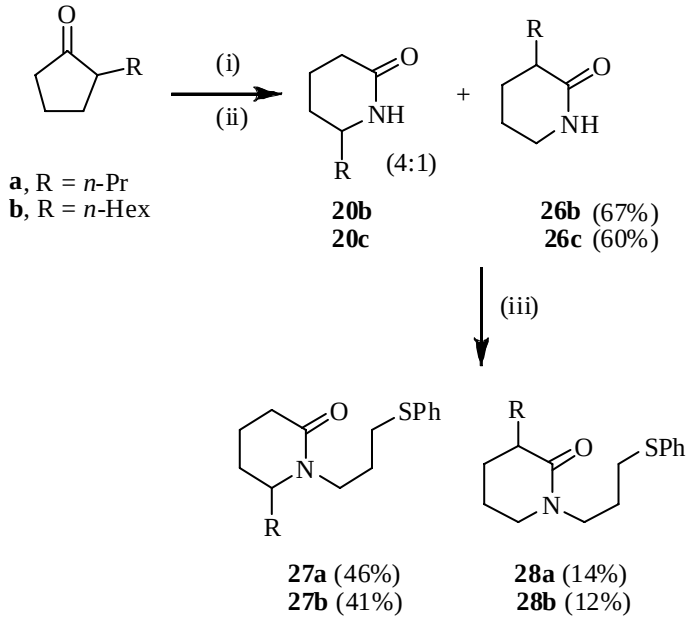
Reagents and conditions: (i) NaH, DMF, $PhS(CH_2)_4Br$, 0 °C to rt (75%); then $NaIO_4$, MeOH, H_2O, 0 °C to rt overnight (70%); (ii) LiHMDS, THF, -78 °C to rt overnight; (iii) $NaBH_4$, MeOH,

0 °C to rt (69 % yield from **24a**); (iv) LDA, THF, $(CH_2O)_n$, -78 °C to rt overnight (55%); (v) toluene, reflux, 8 h (47%); (vi) H_2, Pd/C, (86%).

2.4.2 การสังเคราะห์ (±)-Indolizidines 167B (18) และ 209D (19)

ตามที่แสดงไว้ในแผนผังที่ 6 lactam **20c** (R = *n*-Pr; m = 2) และ **20c** (R = *n*-Hex; m = 2) เป็นสารเริ่มต้นที่จำเป็นสำหรับการเตรียม (±)-indolizidines 167B **(18)** และ 209D **(19)** ดังนั้นในขั้นแรกจึงมีความจำเป็นที่จะต้องเตรียม lactams **20b** และ **20c** ตามที่แสดงไว้ในแผนผังที่ 8 โดยเริ่มต้นจาก 2-propyl- และ 2-hexylcyclopentanone ซึ่งเตรียมให้จากการทำปฏิกิริยา alkylation ของสารประกอบ 2-carboethoxycyclopentanone ด้วย *n*-propyl bromide หรือ *n*-hexyl bromide โดยใช้ anh. K_2CO_3/acetone แล้วนำ product ที่ได้มาทำ decarboxylation โดยใช้ NaCl/DMSO หรือ NaCN/DMSO

แผนผังที่ 8

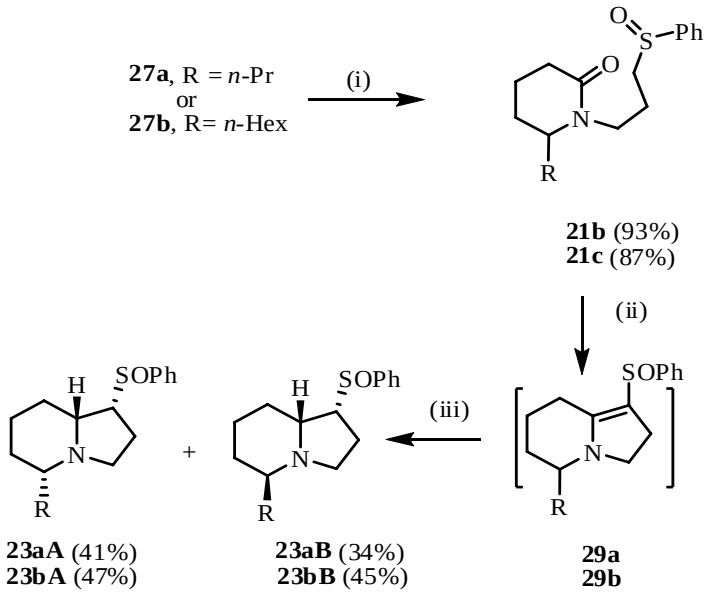


Reagents and conditions: (i) $NH_2OH.HCl$, ethanol; (ii) TsCl, NaOH, acetone, rt, overnight; (iii) NaH, DMF, $PhS(CH_2)_3Br$, 0 ^oC to rt, overnight.

ดังแสดงในแผนผังที่ 8 ปฏิกิริยา Beckmann Rearrangement ของ oxime derivatives ของสาร 2-propylcyclopentanone และ 2-hexylcyclopentanone โดยใช้ NaOH/*p*-TsCl/acetone ที่อุณหภูมิห้องจะได้ส่วนผสมของ lactams **20b**/**26b** และ **20c**/**26c** ตามลำดับ (สาร lactam **26** เป็น regiosomer ที่เกิดขึ้นมาพร้อมกับสาร lactam **20** ส่วนผสมระหว่าง lactams **20** และ **26** มีสัดส่วนประมาณ 4:1 เนื่องจากไม่สามารถแยก lactam **20** ที่ต้องการออกจาก lactam **26** ที่ไม่ต้องการได้โดยวิธี chromatography จึงนำส่วนผสมของ **20** และ **26** ไปทำปฏิกิริยาต่อกับ $PhS(CH_2)_3Br$/NaH/DMF จะได้ส่วนผสมของสาร **27** และ **28** ซึ่งสามารถแยกออกจากกันได้โดยง่าย โดยทำ chromatography สาร lactam **27b** และ **27c** เป็น precursors ที่ต้องการสำหรับการสังเคราะห์ (±)-indolizidine 167B **(18)** และ (±)-indolizidine 209D **(19)**

ดังนั้นจึงนำสาร **27b** และ **27c** มาทำ oxidation ให้ได้ sulfoxides **21b** และ **21c** ตามที่ต้องการโดยใช้ $NaIO_4$/MeOH/H_2O ปฏิกิริยา cyclisation ของ α-sulfinyl carbanions ที่ derived มาจาก **21b** และ **21c** โดยใช้ LiHMDS/THF/-78 ^oC ถึงอุณหภูมิห้องจะได้สารประกอบ indolizidine **29** (R = *n*-Pr และ R = *n*-Hex) ซึ่งไม่เสถียร ยังได้ทำปฏิกิริยา reduction ต่อโดยใช้ $NaBH_4$/MeOH จะทำให้ได้สาร **23a** และ 2**3b** โดยเป็นส่วนผสมของ 2 diastereomers ตามแสดงในแผนผังที่ 9

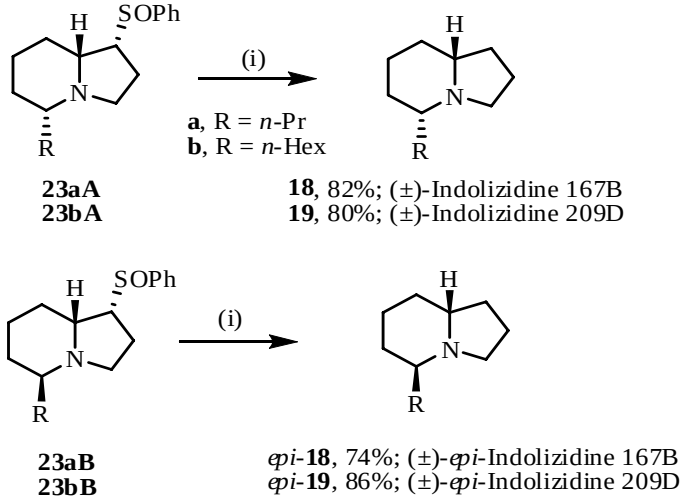
แผนผังที่ 9



Reagents and conditions: (i) $NaIO_4$, MeOH, H_2O, O ^oC to rt, overnight; (ii) LiHMDS, THF, -78 ^oC to rt overnight; (iii) $NaBH_4$, MeOH, O ^oC to rt, overnight.

ขั้นตอนสุดท้ายสำหรับการเตรียม (±)-indolizidine 167B **(18)** และ (±)-indolizidine 209D **(19)** คือการนำ diastereomer A และ B ของสาร indolizidines **23a** และ **23b** ไปทำปฏิกิริยา reductive cleavage โดยใช้ Nickel Boride (Ni_2B) ซึ่งเตรียมขึ้นมาแล้วใช้เลยจาก $NiCl_2.6H_2O/NaBH_4$ ใน MeOH:THF (3:1) ดังนั้นเมื่อนำสาร **23aA** มาทำปฏิกิริยากับ Ni_2B จะได้สาร (±)-indolizidines 167B **(18)** 82% yield ในทำนองเดียวกันสาร **23bA** จะทำปฏิกิริยากับ Ni_2B ได้สาร (±)-indolizidines 209D **(19)** 80% yield ส่วนสาร **23aB** และ **23bB** เมื่อนำ reductive cleavage โดยใช้ Ni_2B จะได้ (±)-*epi*-indolizidine 167B (*epi*-**18**) และ (±)-*epi*-indolizidline 209D (*epi*-**19**) ตามลำดับดังได้สรุปไว้ในแผนผังที่ 10

แผนผังที่ 10



Reagents and conditions: (i) $NiCl_2.6\ H_2O$-$NaBH_4$, MeOH-THF (3:1), 0 ^oC to rt, 2 h.

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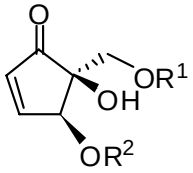
2. (a) Daly, J. W.; Spande, T. F. *Amphibian Alkaloids: Chemistry, Pharmacology and Biology.* In *Alkaloid: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York 1986; 4: 1-274. (b) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M. *Toxicon* **1978**, *16*, 163. (c) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987,** *25*, 1023.

3. (a) Michael, J. P. In Alkaloids; Cordell, G. A.. Ed.; Academic Press: London, 2001; Vol. 55, pp. 92-258. (b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T, K.; Albequerque, E. X. *Neurochemical Res*. **1986**, *11*, 1227.

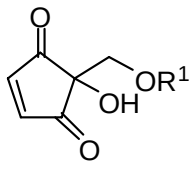
2.5 การเตรียม Pentenomycin I และ Epipentenomycin I

จากการที่ได้พัฒนาวิธีการสังเคราะห์สารประกอบ cyclopentenones โดยใช้ปฏิกิริยาintramolecular acylation of α-sulfinyl carbanions จึงทำให้เราสนใจประยุกต์ใช้วิธีการที่ได้พัฒนาขึ้นในการเตรียมสารผลิตภัณฑ์ธรรมชาติ pentenomycin I และ epipentenomycin I ตลอดจน analogs ของมัน

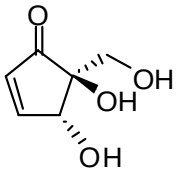
สาร pentenomycin I-III (**30**-**32**) และ dehydropentenomycin (**33**) เป็นสาร antibiotics ที่มี oxygenated cyclopentenones เป็น core structure สาร pentenomycin I (**30**) และ pentenomycin II (**31**) แยกได้จาก *Streptomyces eurythermus*[1] ส่วนสาร **32** และ **33** แยกจาก *Streptoverticilium eurocidicum*[2] และ *Streptomyces cattaleya*[2b] ตามลำดับ ส่วน epipentenomycin (**34**) แยกได้จาก *Perziza sp.*[3]



Pentenomycin I (**30**) $R^1 = R^2 = H$
Pentenomycin II (**31**) $R^1 = H$, $R^2 = Ac$
Pentenomycin III (**32**) $R^1 = Ac$, $R^2 = H$



Dehydropentenomycin (**33**)

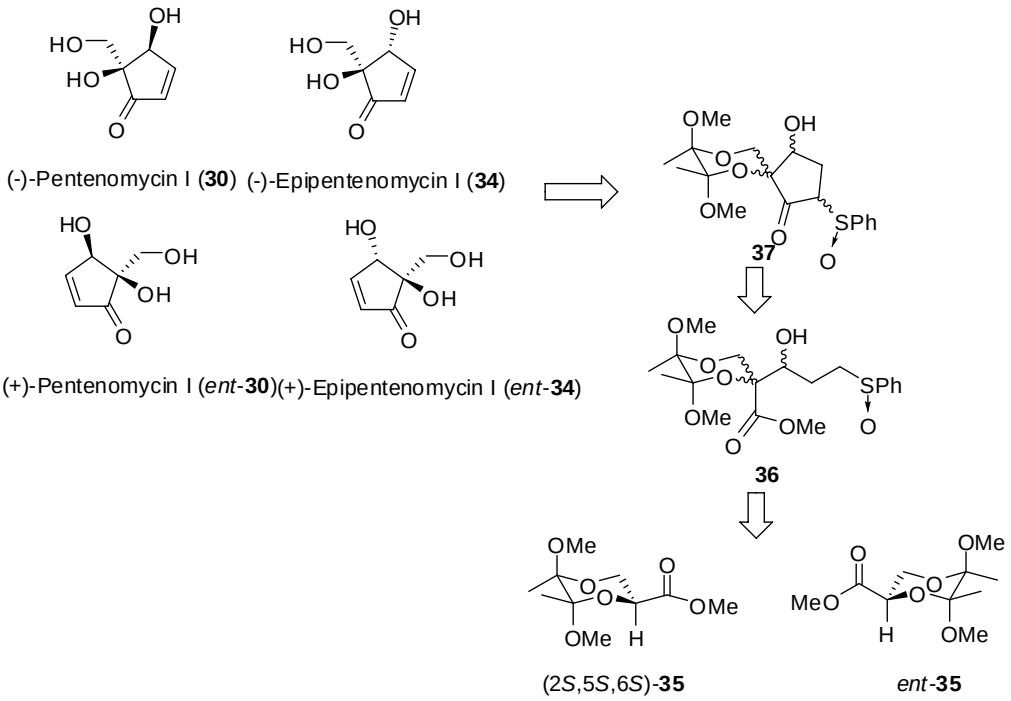


Epipentenomycin I (**34**)

ในการศึกษานี้จะทำ asymmetric synthesis ของสาร (–)-pentenomycin I (**30**) และ (–)-epipentenomycin I (**34**) และ enantiomers ของสารทั้งสอง (*ent*-**30**) และ *ent*-**35**) [4,5] โดยดำเนินการตามแผนที่แสดงใน retro-synthetic plan ที่แสดงใน แผนผังที่ 11 โดยจะเริ่มต้นจากสาร chiral ester (*2S,5S,6S*)-**35** หรือ *ent*-**35** สาร chiral ester ทั้งสองตัวสามารถเตรียมได้ง่ายจาก L-ascorbic acid และ D-mannitol ตามลำดับตามวิธีของ Ley[6] โดยคิดว่าสาร **36** ควรจะเตรียมโดยให้ enolate anion ของ chiral ester **35** ทำปฏิกิริยากับ 3-phenylsulfanylpropanal ตามด้วย oxidation ของ adduct ที่เกิดขึ้น สาร **36** ที่ได้ควรจะมี hydroxyalkyl group อยู่

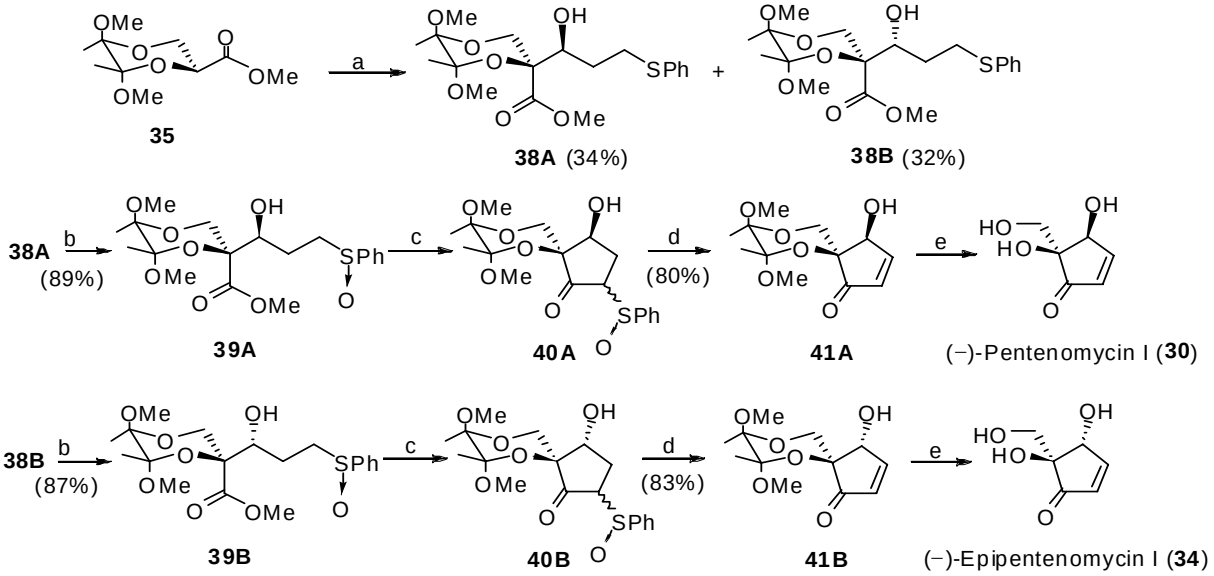
equatorial position เมื่อนำ **36** มาทำปฏิกิริยากับ LDA ก็ควรจะเกิด intramolecular acylation of α-sulfinyl carbanion นำไปสู่สาร **37** ซึ่งเป็น key intermediate ในการเตรียม pentenomycins โดยจะทำ pyrolysis และ hydrolysis ของ product ที่ได้จากการทำ pysolysis (แผนผังที่ 11)

แผนผังที่ 11



ดังนั้นจึงได้เริ่มศึกษาวิธีการเตรียมสาร (–)-pentenomycin I (**30**) และ (–)-epipentenomycin I (**34**) จาก chiral ester (*2S,5S,6S*)-**35** โดยเริ่มจากการเตรียม enolate anion ของ (*2S,5S,6S*)-**35** โดยให้ทำปฏิกิริยากับ lithium diisopropylamide (LDA) หลังจากนั้นให้ทำปฏิกิริยากับ 3-phenylsulfanylpropanal จะได้ส่วนผสมของ diastereomeric mixture **38A** และ **38B** (ประมาณ 1:1) ซึ่งสามารถแยกออกจากกันได้ โดยพบว่า hydroxyalkylation เกิดแบบ stereoselective เข้าทางด้าน equatorial ของ enolate anion ของ chiral ester (*2S,5S,6S*)-**35** [7] เท่านั้นซึ่งตรงตามรายงานของ S. Ley [8] เมื่อได้สาร **38A** และ **38B** แล้วก็นำไปทำปฏิกิริยา oxidation ด้วย $NaIO_4$ จะได้สาร sulfoxide **39A** และ **39B** ตามลำดับ เมื่อนำสาร **39A** มาทำปฏิกิริยา cyclization โดยใช้ LDA เป็น base จะได้สาร **40A** ซึ่งจะเกิดปฏิกิริยา sulfoxide elimination เมื่อทำ pyrolysis โดย reflux ใน toluene จะได้ hydroxycyclopentenone **41A** เมื่อทำ hydrolysis สาร **41A** ด้วย TFA/H_2O จะได้ (–)-pentenomycin I (**30**) ในทำนองเดียวกันสาร **38B** จะให้ (–)-epipentenomycin I (**5**) (ดูแผนผังที่ 12)

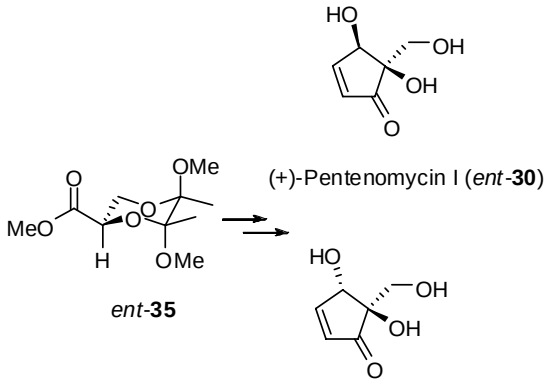
แผนผังที่ 12



Reagents and Conditions: (a) LDA, THF, −78 °C, then $PhS(CH_2)_2CHO$; (b) $NaIO_4$, MeOH, H_2O; (c) LDA (3.5 equiv), THF,−78 °C, 2 h then 0 °C, 2 h; (d) toluene, $CaCO_3$, reflux, 15 h; (e) 90% TFA, 0 °C, 5 h.

เราสามารถเตรียม (+)-pentenomycin I (*ent*-**30**) และ (+)-epipentenomycin I (*ent*-**34**) ได้เช่นเดียวกันโดยทำปฏิกิริยาเหมือนที่แสดงในแผนผังที่ 12 เพียงแต่เริ่มค้นจาก (2S,5R,6R)-ester **35** (*ent*-**35**) (ดูแผนผังที่ 13)

แผนผังที่ 13



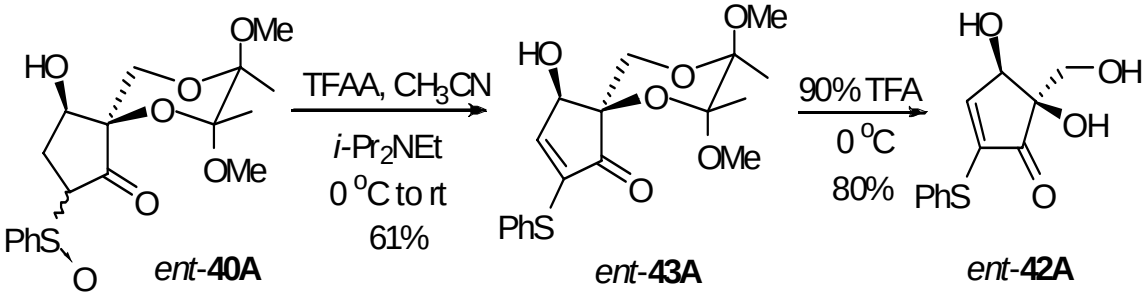
2.6 การเตรียม Analogs ของ *ent*-Pentenomycin I

เพื่อแสดงถึงประโยชน์ของวิธีการสังเคราะห์ที่ได้พัฒนาขึ้น จึงใช้วิธีที่ได้พัฒนาขึ้นสังเคราะห์ analogs ของ pentenomycin I โดยคิดว่า analogs เหล่านี้จะแสดงผล antibiotic activities ที่น่าสนใจหรืออาจใช้เป็น precursor ในการเตรียมสาร highly oxygenated cyclopentanoids ตัวอื่นๆ

2.6.1 การเตรียมสาร *ent*-α-Phenylsulfanylpentenomycin I (*ent*-42A)

สามารถเตรียมสาร *ent*-**42A** ได้โดยทำปฏิกิริยา Pummerrer rearrangement ของสาร *ent*-**40A** ซึ่งจะได้สาร *ent*-**43A** ก่อน แล้วค่อยทำปฏิกิริยา hydrolysis จะได้สาร *ent*-**42A** ตามต้องการดังแสดงในแผนผังที่ 14

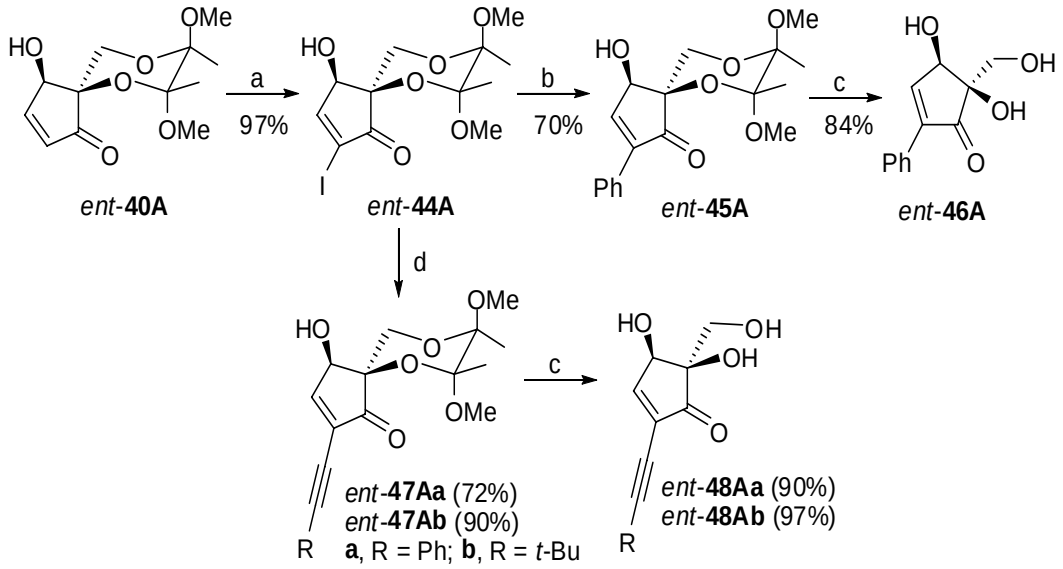
แผนผังที่ 14



2.6.2 การเตรียม Pentenomycin Analogs *ent*-44A และ *ent*-46A

เพื่อแสดงให้เห็นว่าสาร *ent*-**40A** สามารถใช้เป็นสารเริ่มต้นในการเตรียม α-aryl และ α-alkynylsubstituted pentenomycin derivatives ได้จึงเตรียมสาร *ent*-**44A** ขึ้นมาโดยให้ *ent*-**40A** ทำปฏิกิริยากับ I_2/pyridine/CCl_4[9] สาร *ent*-**44A** เป็นสารเริ่มต้นในการทำ Suzuki-Miyaura[10] และ Sonogashira[11] couplings พบว่าเมื่อทำ Suzuki-Miyaura coupling โดยให้ *ent*-**44A** ทำปฏิกิริยากับ phenylboronic acid โดยใช้ $PdCl_2(PPh_3)_2$ เป็น catalyst จะได้สาร *ent*-**45A** ซึ่งเมื่อทำ hydrolysis จะได้ pentenomycin analog *ent*-**46A** ในทำนองเดียวกันปฏิกิริยา Sonogashira coupling ของสาร *ent*-**44A** กับ phenyl- และ *t*-butylacetylene โดยใช้ conditions ดังแสดงในแผนผังที่ 15 จะได้ coupling products *ent*-**47A**a และ *ent*-**47Ab** ซึ่งเมื่อนำไปทำ hydrolysis จะได้ pentenomycin analogs *ent*-**48Aa** และ *ent*-**48Ab** ตามลำดับ (ดูแผนผังที่ 15)

แผนผังที่ 15



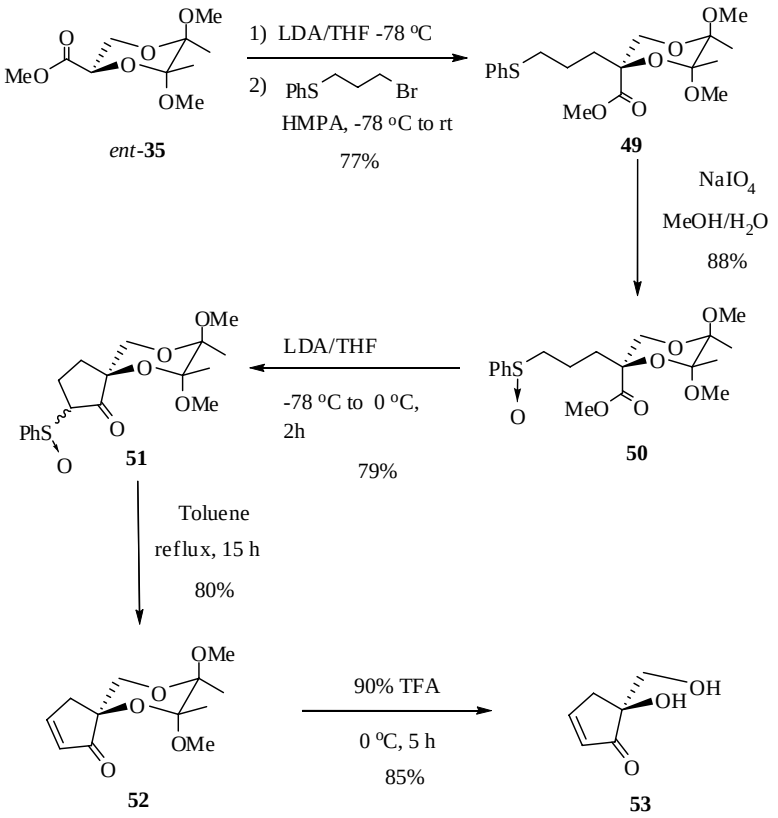
Reagents and Conditions: (a) I_2, pyridine, CCl_4; (b) $PhB(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3, THF, 60 ^oC; (c) 90% TFA, 0 ^oC, 5 h; (d) Phenylacetylene or *t*-Butylacetylene, $PdCl_2(PPh_3)$, CuI, *i*-Pr_2NH, THF, 0 ^oC, 45 min.

2.7 การเตรียม (+)-Desoxypentenomycin 53 และ Analogs 56, 59 และ 60

หลังจากประสบความสำเร็จในการเตรียม pentenomycin I และ epipentenomycin I แบบ อสมมาตร พร้อมทั้งได้เตรียม analogs ของมันด้วย ได้สนใจในการเตรียมสารประกอบ(+)-desoxypentenomycin (**53**) ซึ่งอาจจะมีคุณสมบัติทางชีววิทยาที่น่าสนใจ โดยใช้ปฏิกิริยา intramolecular acylation of α-sulfinyl carbanion

การสังเคราะห์เริ่มต้นจาก chiral ester (2S,5R,6R)-ester **35** (*ent*-**35**) ซึ่งเตรียมได้ง่ายจาก D-mannitol ดังได้กล่าวไว้ในรายงานครั้งที่แล้ว สารเริ่มต้นที่สำคัญสำหรับการทำ intermolecular acylation ของ α-sulfinyl carbanion เพื่อสร้าง cyclopentenone ring ได้ สามารถเตรียมได้โดยให้ enolate anion ของ ester *ent*-**35** ทำปฏิกิริยากับ 1-bromo-3-phenylsulfanylpropane ใน THF/HMPA ที่ -78 °C ถึง อุณหภูมิห้องจะได้สาร **49** ซึ่งพบว่า alkylation จะเกิดทางด้าน equatorial เท่านั้น เมื่อนำสาร **49** มาทำปฏิกิริยา oxidation โดยใช้ $NaIO_4$ ใน methanol จะได้สาร **50** เมื่อทำปฏิกิริยา cyclization โดยใช้ LDA ใน THF ที่ -78 °C 2 ชั่วโมง และ 0 °C 2 ชั่วโมง จะได้สาร **51** ซึ่งนำไปทำปฏิกิริยา sulfoxide elimination จะได้ cyclopentenone **52** ซึ่งเป็น precursor สำหรับการเตรียม สาร (+)-desoxypententenonuycin (**19**) โดยการทำ hydrolysis ใช้ 90% TFA ดังได้สรุปไว้ในแผนผังที่ 16

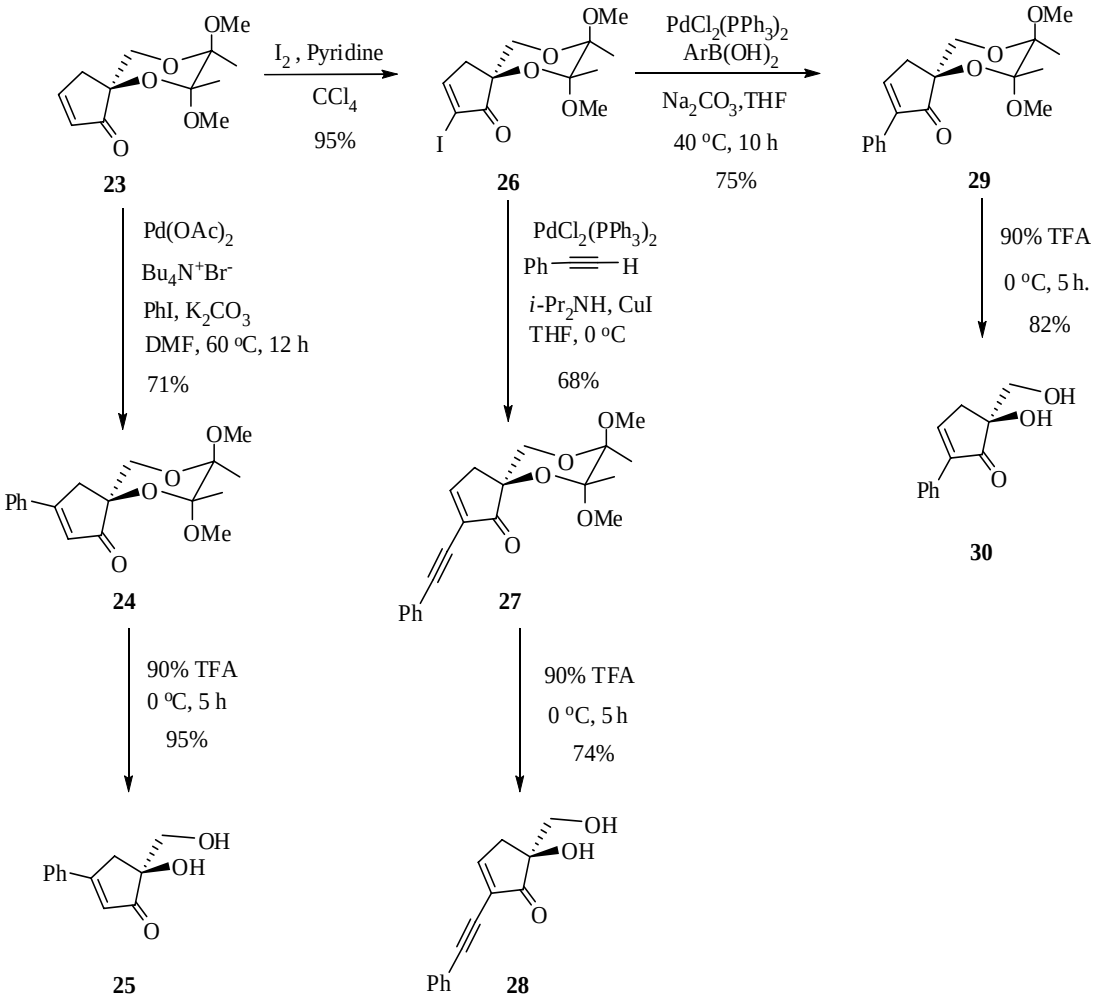
แผนผังที่ 16



เนื่องจากคิดว่าสารประกอบ highly oxygenated cyclopentenones ประเภทสาร **52**, **53** และ analogs ตัวอื่นๆควรจะมีประโยชน์มากในการใช้เป็นสารเริ่มต้น สำหรับการเตรียมสารตัวอื่นๆ ที่มีโครงสร้างยุ่งยากมากขึ้น ซึ่งจะเป็นประโยชน์มากในแง่ของ organic synthesis ดังนั้นจึงใช้สาร **52** เป็นสารเริ่มต้นในการเตรียม analogues ของ (+)-desoxypentenomycin (**53**)โดยจะทำปฏิกิริยา Heck, Sonogashira และ Miyaura-Suzuki coupling

เมื่อให้สาร **52** ทำปฏิกิริยา Heck coupling กับ iodobenzene โดยมี $Pd(OAc)_2$ เป็น catalyst จะได้ coupling product **57** ซึ่งเมื่อนำไปทำ hydrolysis โดยใช้ TFA จะได้สาร **59** (แผนผังที่ 17) ได้ศึกษาการเตรียม 2-subsituted analogs ของสาร **53**โดยเริ่มจากสาร **52**โดยต้องเตรียมสาร α-iodocyclopentenone **54** ขึ้นมาก่อน โดยให้ สาร **52** ทำปฏิกิริยากับ I_2/pyridine เมื่อนำสาร **54** มาทำปฏิกิริยา Miyara-Suzuki และ Sonogashira ดังแสดงในแผนผังที่ 17 จะสามารถเตรียมสาร **55** และ **58** ได้ซึ่งนำไปทำ hydrolysis จะได้ 2-subsituted desoxypentenomycin analogs **56** และ **60**

แผนผังที่ 17



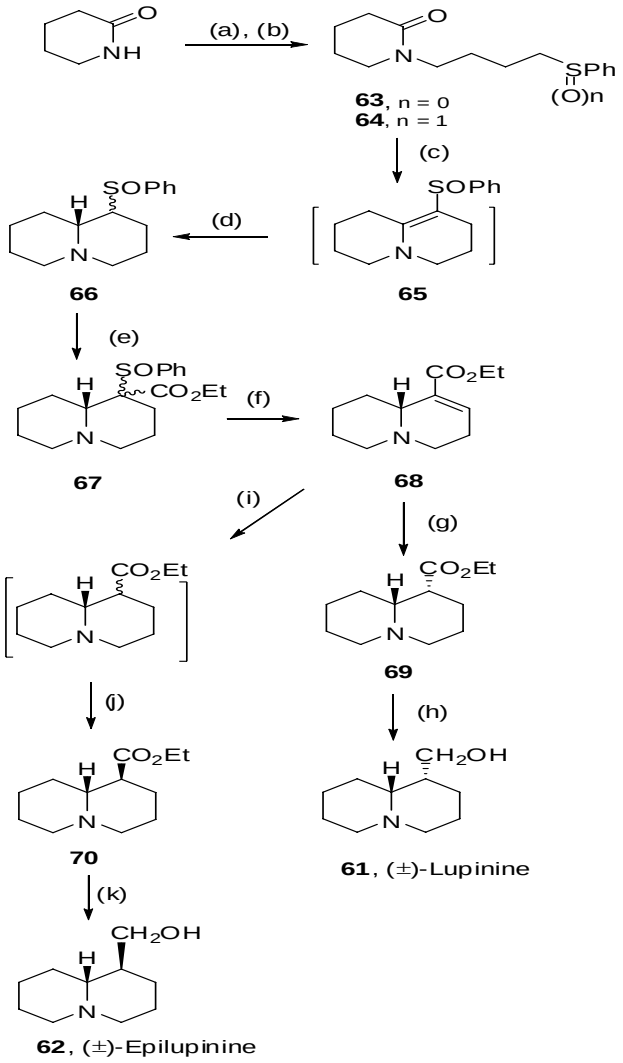
2.8 การเตรียม (±)-Lupinine (61) และ (±)-Epilupinine (62)

สาร lupinine และ epilupinine เป็น quinolizidine alkaloid แยกได้จากพืชสกุล lupinus ตัวมันเองและอนุพันธ์มีคุณสมบัติทางชีววิทยาที่น่าสนใจ จึงทำให้สนใจที่จะใช้วิธีการที่ได้พัฒนาขึ้นในการสังเคราะห์สารทั้งสองตัวดังแสดงในแผนผังที่ 18 การสังเคราะห์เริ่มจากสาร δ-valerolactam โดยทำปฏิกิริยา *N*-alkylation โดยใช้NaH/DMF/PhS$(CH_2)_4$Br จะได้สาร **63** ซึ่งนำไปทำปฏิกิริยา oxidation โดยใช้ $NaIO_4$ จะได้สารเริ่มต้น **64** ซึ่งจะใช้เป็นสาร intermediate ที่สำคัญสำหรับการสังเคราะห์ ทำปฏิกิริยา cyclization **64** เพื่อให้ได้สาร quinolizidine **65**โดยใช้ lithium hexamethyldisilazide (LiHMDS) ใน THF ที่ -78 °C ถึงอุณหภูมิห้อง จะได้สาร **65** ก่อน ซึ่งไม่ stable จึงทำ reduction ด้วย $NaBH_4$ ให้ได้ quinolizidine **66** ซึ่งเป็นสารที่สำคัญการเตรียม (±)-lupinine (**61**) และ (±)-epilupinine (**62**) โดยต้องเตรียมสาร **67** จากสาร **66** โดยทำ α-carboethoxylation ของสาร **66** ใช้ LDA/THF เพื่อเตรียม α-sulfinyl carbanion แล้ว trap ด้วย ethyl chloroformate จะทำให้ได้สาร **67** ซึ่งนำไปทำ sulfoxide elimination โดย reflux ใน

toluene จะได้สาร **68** เมื่อนำสาร **68** ทำปฏิกิริยา catalytic hydrogenation โดยใช้ PtO_2 เป็น catalyst จะได้ quinolizidine ester **69** เพียง isomer เดียว หลังจากนั้นนำสาร **69** ไปทำ reduction ด้วย $LiAlH_4$ ใน ether จะได้ (±)-lupinine (**61**)

ในทำนองเดียวกันสามารถเตรียมสาร (±)-epilupinine (**62**) ที่ต้องการได้โดยเริ่มจากสาร **68** โดยทำปฏิกิริยา reduction ของ α,β-unsaturated ester moiety ด้วย Mg/MeOH แล้วตามด้วยทำ transesterification และ epimerization ด้วย NaOEt/EtOH จะได้ quinolizidine ester **70** เพียง isomer เดียว เมื่อทำ reduction สาร ester **70** ด้วย $LiAlH_4$/ether จะได้สาร (±)-epilupinine (**62**) ที่ต้องการ (รายละเอียดดังแสดงในแผนผังที่ 18)

แผนผังที่ 18



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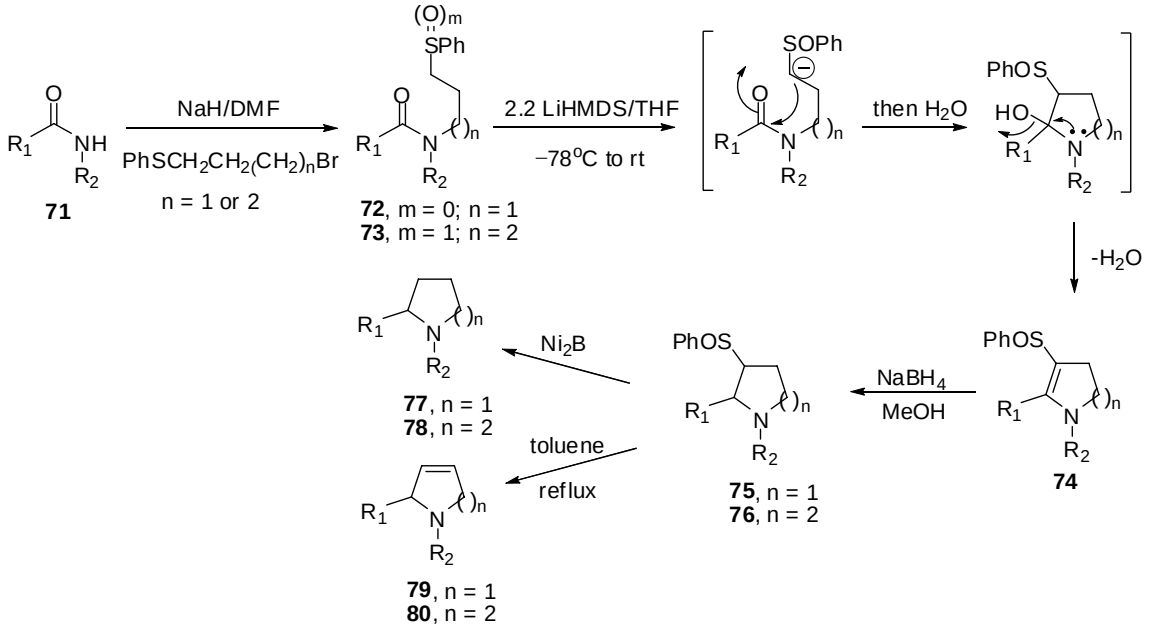
2.9 การสังเคราะห์สารประเภท Pyrrolidines และ Piperidines โดยการประยุกต์ใช้ปฏิกิริยา Cyclization ของ α-Sulfinyl Carbanions

กลุ่มวิจัยของเราได้แสดงให้เห็นประโยชน์ทางปฏิกิริยา cyclization ของ α-sulfinyl carbanions ทั้งแบบ intramolecular acylation และ intramolecular nucleophilic addition ที่ carbonyl group ของ lactams ว่าสามารถใช้เป็นวิธีการง่ายๆ ในการเตรียมสารประกอบ highly functionalized cyclopentenones[1,2] รวมถึงการเตรียมสารผลิตภัณฑ์ธรรมชาติ pentenomycin I และ epipentenomycin I แบบอสมมาตร[3] และสารผลิตภัณฑ์ธรรมชาติ indolizidines 167B และ 209D[4,5] lipinine และ epilnpinine[6] ตามที่ได้รายงานไปแล้ว กลุ่มวิจัยของเรามีความสนใจต่อเนื่องจากงานดังกล่าวในการที่จะใช้เป็นวิธีการทั่วไปในการสังเคราะห์สารประกอบ pyrrolidines และ piperidines ซึ่งเป็นสารประกอบที่พบมากในสารผลิตภัณฑ์ธรรมชาติที่มีฤทธิ์ทางชีววิทยา[7,8] โดยการสังเคราะห์จะเริ่มต้นจากสารเริ่มต้น amides ดังแสดงในแผนผังที่ 19 จะเห็นว่าขั้นตอนที่สำคัญคือปฏิกิริยา cyclization ของ α-sulfinyl carbanions ที่เตรียมมาจาก sulfoxide **73** เนื่องจากเป็นขั้นตอนของการสร้าง piperidine และ pyrrolidine ring

แผนผังที่ 19



ตามที่ได้แสดงไว้ในแผนผังที่ 19 สามารถเตรียมสาร sulfoxide **3** (n = 1 or 2**)** ได้จากสารประกอบ amides **71** โดยใช้ 1-bromo-3-phenylsulfanylpropane หรือ 1-bromo-3-phenylsulfanylbutane โดยใช้ sodium hydride เป็น base และ *N,N*-dimethylformamide (DMF) เป็น solvent ซึ่งจะได้สาร sulfide **72** เมื่อทำปฏิกิริยา oxidation สาร **72** ด้วย $NaIO_4$ ใน H_2O/MeOH

ที่ 0 °C จะได้สาร sulfoxide **73** ตามที่ต้องการ เมื่อนำสาร sulfoxide **73** มาทำปฏิกิริยากับ lithium hexamethyldisilazide ใน tetrahydrofuran ที่ -78 °C ถึงอุณหภูมิห้อง จะได้สาร **74** ซึ่งพบว่าสารประเภทนี้จะไม่ค่อย stable ถ้าหากเก็บไว้หรือพยายามแยกให้บริสุทธิ์โดยวิธี chromatography ดังนั้นจึงนำ crude product ของสาร **74** ที่เตรียมได้ไปทำปฏิกิริยา reduction ต่อโดยใช้ $NaBH_4$/MeOH จะได้ pyrrolidine sulfoxides **75** (68-90% yield) หรือ piperidine sulfoxides **76** (67-72% yield) โดยสาร **75** และ **76** ที่ได้จะได้เป็น diastereomeric mixture ซึ่งในบางกรณีสามารถแยก pure diastereomer ได้ ทั้งสาร **75** และ **76** (diastereomeric mixture) เป็น precursor สำหรับการเตรียมสาร pyrrolidines **77** และ piperidines **78** โดยทำปฏิกิริยา reductive desulfurization โดยใช้ Ni_2B ใน MeOH เป็น reducing agent และนอกจากนี้ยังใช้เป็นสารเริ่มต้นสำหรับการเตรียม 1,5-dihydropyrrolidines **79** และ unsaturated piperidines **80** เมื่อนำไปทำปฏิกิริยา sulfoxide elimination โดย reflux ใน toluene (ดูรายละเอียดในภาคผนวก)

Table. Preparation of compounds **71**-**73** and **75**-**78**.

entry							% yields[a]		
	71	n	R_1	R_2	**72**	**73**	**75** or **76**[b]	**77** or **78**	**79** or **80**
1	**71a**	1	Ph	Ph	**72a**, 84	**73a**, 90	**75a**, 70	**77a**, 68	**79a**, 65
2	**71b**	1	CH_3	Ph	**72b**, 88	**73b**, 92	**75b**, 68	**77b**, 60	-[c]
3	**71c**	1	*n*-Pr	Ph	**72c**, 80	**73c**, 90	**75c**, 71	**77c**, 62	-[c]
4	**71d**	1	Ph	$PhCH_2$	**72d**, 75	**73d**, 91,	**75d**, 90	-[c]	**79d**, 65
5	**71a**	2	Ph	Ph	**72e**, 82	**73e**, 90	**76a**, 72	**78a**, 61	**80a**, 76
6	**71b**	2	CH3	Ph	**72f**, 85	**73f**, 90	**76b**, 67	**78b**, 70	**80b**, 72

[a]Isolated yields.

[b]Obtained as mixtures of diastereomers.

[c]Not performed.

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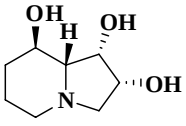
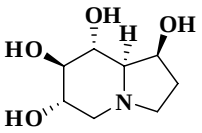
2.10 การสังเคราะห์ (+)-Swainsonine (81)

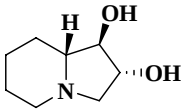
Swainsonine เป็น polyhydroxylated indolizidine แยกได้จาก fungus *Rhizoctonia ligumicola*[1] และพืชหลายชนิด[2] (–)-swainsonine มีคุณสมบัติทางชีวภาพที่น่าสนใจ เช่น glycosidase inhibitor นอกจากนี้ยังพบว่ามีคุณสมบัติอื่นๆ ด้วย คือ antibacterial, antiviral, antimetastatic หรือ antidiabetes activity ส่วน (+)-swainsonine เป็น potent inhibitor of naringinase นอกจากนี้ unnatural analogs ของ swainsonine ยังมีคุณสมบัติทางชีวภาพที่น่าสนใจ ดังนั้นจึงมีผู้สนใจที่ศึกษาวิธีการสังเคราะห์สารดังกล่าว[3]



(–)-Swainsonine



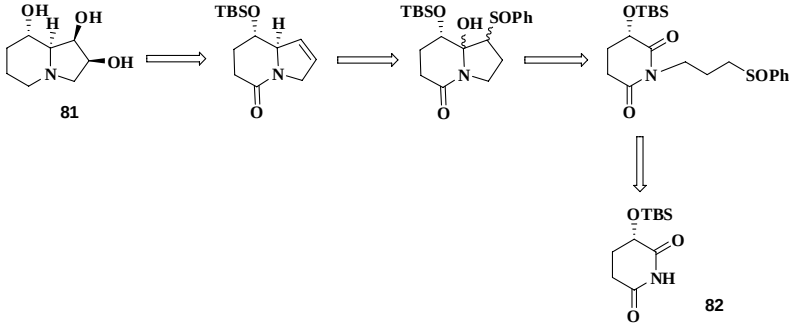
(+)-Castanospermine



(–)-Lentiginosine

การสังเคราะห์ (+)-swainsonine (**81**) สามารถทำได้โดยใช้ปฏิกิริยา α-sulfinyl carbanion cyclization เป็นปฏิกิริยาหลัก โดยเริ่มต้นจาก chiral α-hydroxyimide **82** ดังแสดง retro-synthetic plan ดังแสดงในแผนผัง 20

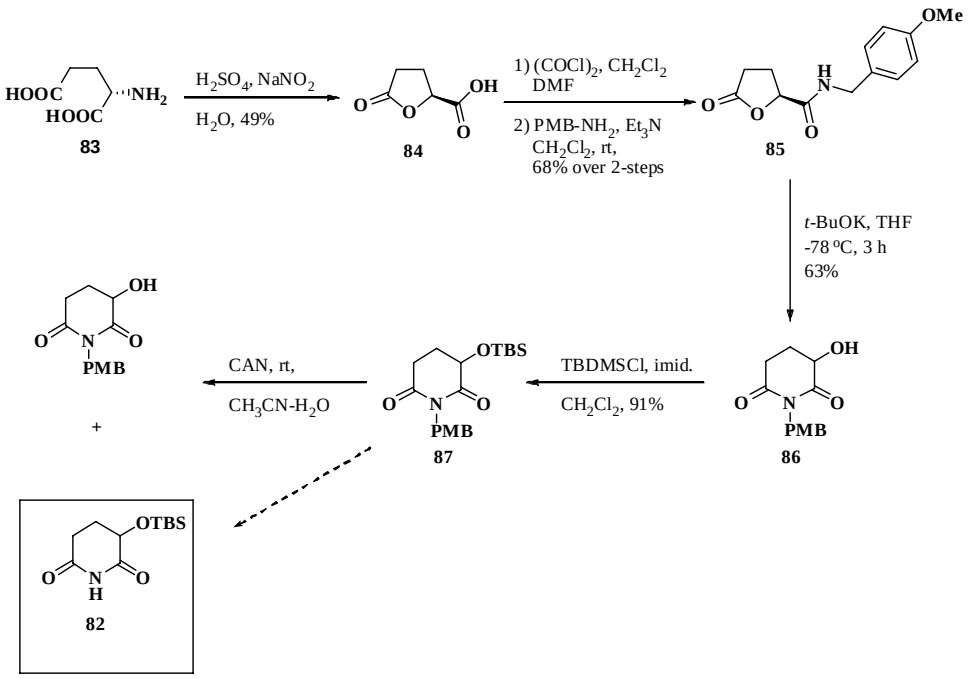
แผนผังที่ 20



2.10.1 การเตรียม chiral imide 82

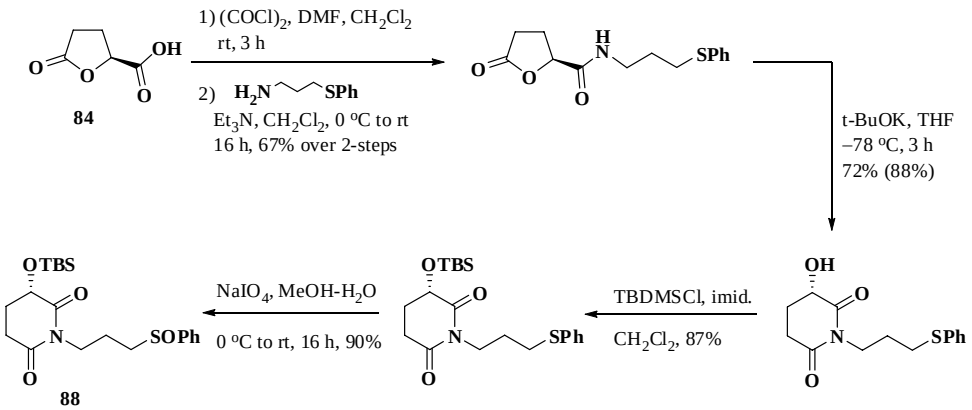
ได้พยายามเตรียม chiral imide **82** โดยทำตามวิธีที่มีผู้รายงานไว้ (ดังแสดงในแผนผังที่ 21) โดยเริ่มจาก L-glutamic acid (**83**)[4] เราสามารถเตรียมสาร **84**, **85**, **86** และ **87** ได้ทุกตัว แต่ขั้นตอนสุดท้ายที่มีปัญหาคือ การทำ Oxidative hydrolysis ของหมู่ p-methoxyphenyl ของสาร **87** เพื่อให้ได้สาร **82** ที่ต้องการ แต่พบว่าไม่สามารถแยกสาร **82** ที่ต้องการให้บริสุทธิ์ได้และได้ **82** ใน %yield ที่ต่ำมาก ดังนั้นจึงได้

แผนผังที่ 21



การสังเคราะห์สาร chiral α-hydroxy imide **88** ซึ่งเป็นสารเริ่มต้นสำหรับการศึกษาปฏิกิริยา cyclization ที่จะนำไปสู่การเตรียม (+)-swainsonine โดยเริ่มต้นจาก chiral α-lactone carboxylic acid **84** ดังแสดงในแผนผังที่ 22 สามารถเตรียมสาร chiral sulfinyl imide **88** ใน %yield ที่ดี

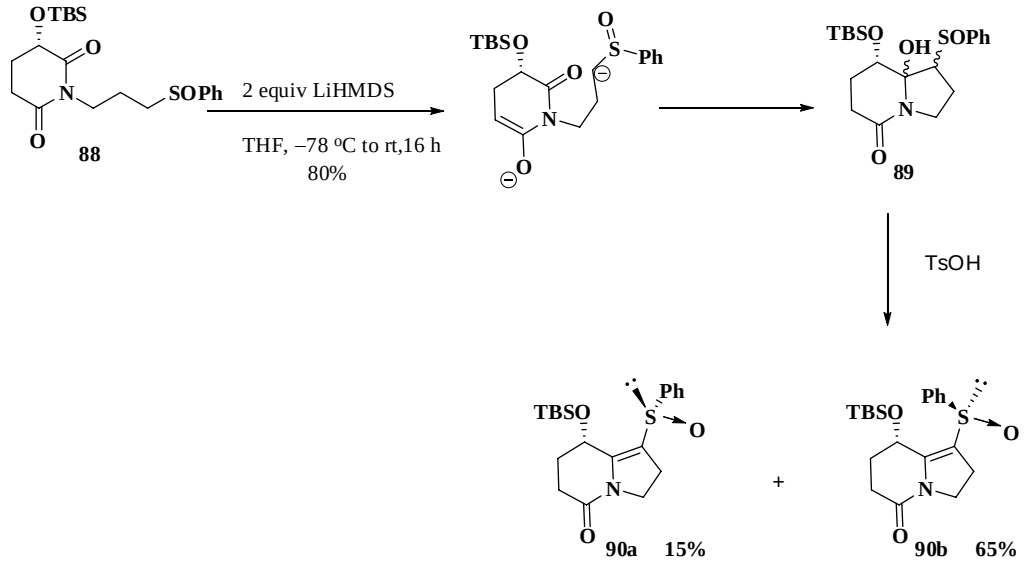
แผนผังที่ 22



2.10.2 ปฏิกิริยา cyclization ของ chiral sulfinyl imide 88

ทราบว่าเมื่อให้ 88 ทำปฏิกิริยากับ LiHMDS (2 equivalents) ใน THF ที่ –78 °C ถึงอุณหภูมิห้อง (16 ชม.) จะได้ cyclizedproduct **89** (80%yield) เป็นของผสมของ diastereomers ซึ่งไม่ได้พยายามแยกแต่นำสาร **89** ไปทำปฏิกิริยากับ *p*-toluenesulfonic acid/CH_2Cl_2/reflux (16 ชม.) จะได้สาร **90** (80%yield) โดยเป็นส่วนผสมของ 2 diastereomers **90a** (15%) และ **96b** (65%) ซึ่งสามารถแยกออกจากกันได้ ดังแสดงในแผนผังที่ 23

แผนผังที่ 23



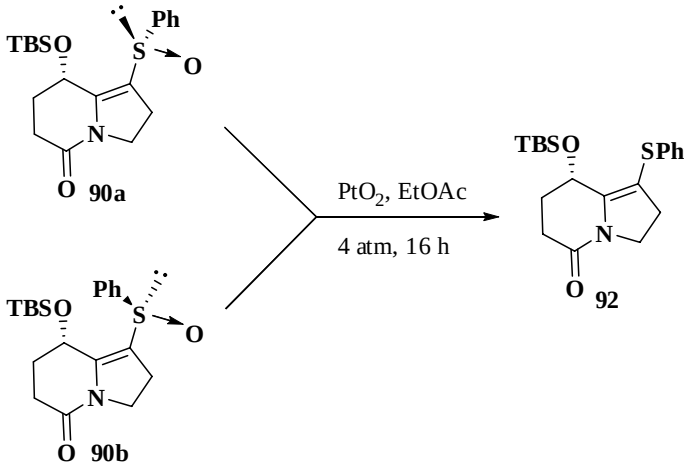
การที่ใช้ LiHMDS 2 equivalents เนื่องจากต้องการ protect หมู่ carbonyl ของ cyclic imide ให้อยู่ใน form ของ enolate ดังนั้นการ cyclize ของ α-sulfinyl carbanion จะเกิดได้เฉพาะกับ carbonyl group ที่อยู่ติดกับ OTBS group เท่านั้น ปฏิกิริยา cyclization ของสาร **88** โดยใช้ 1 equivalent ของ LiHMDS ให้ %yield ของสาร **89** ใน %yield ที่ต่ำ

2.10.3 การเตรียมสาร 91 จากสาร 90

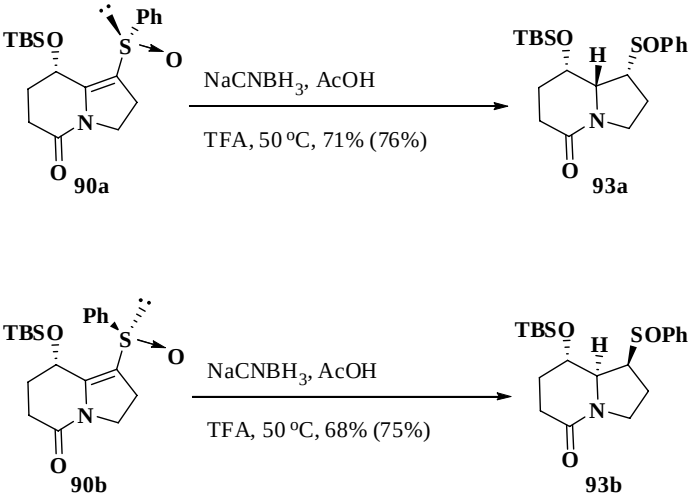
สาร **91** ถือว่าเป็น key intermediate สำหรับการเตรียม (+)-swainsonine (**81**) เนื่องจากว่าถ้าทำ sulfoxide elimination ของสาร **91** ตามด้วย cis-dihydroxylation แล้วควรจะได้ (+)-swainsonine (**81**) ตามต้องการ ดังนั้นจึงมีความจำเป็นที่ต้องทำ reduction usiterated sulfoxide **90** ให้ได้สาร **91**

ในเบื้องต้นได้ศึกษาปฏิกิริยา catalytic hydrogenation ของสาร **90**a **90**b โดยใช้ PtO_2 เป็น catalyst ใน ethyl acetate ที่ 4 atm. เวลา 16 ชม. พบว่าทั้งสองตัวจะให้สาร sulfide **92** ประมาณ 58%yield (แผนผังที่ 24) หลังจากนั้นได้พยายามทดลองใช้ปฏิกิริยา reduction อื่นๆ เช่น $Et_3SiH/TFA/CH_2Cl_2$, $NaCNBH_3$/AcOH, $NaCNBH_3$/MeOH, $NaBH_4$/MeOH ซึ่งต่างก็ให้ผลไม่เป็นที่พอใจ โดยส่วนมากแล้วจะได้สารเริ่มต้นกลับคืนมาเกือบหมด แต่พบว่าเมื่อใช้ $NaCNBH_4$ ใน AcOH และ 10 mol% CF_3CO_2H ที่ 50 °C (5 ชม.) ปฏิกิริยา reduction ของ **90a** จะได้ 76%yield ของ reduction product **93a** ส่วน **90b** จะให้ **93b** 75% เมื่อทำปฏิกิริยาภายใต้ conditions เดียวกัน (ดูแผนผังที่ 25)

แผนผังที่ 24



แผนผังที่ 25

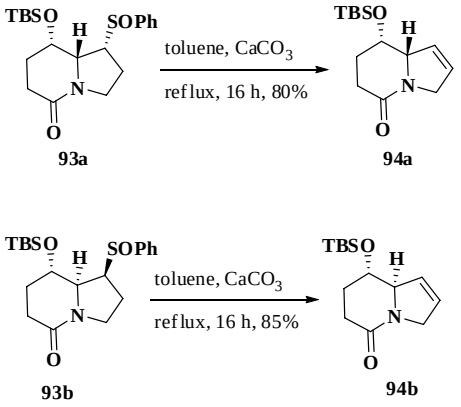


Relative stereochemistry ของ **93a** และ **93b** สามารถ confirm โดยใช้ NOE experiment ส่วนโครงสร้างของมัน confirm โดย ‘H-NMR, ^{13}C-NMR, HMQC และ COSY-45

2.10.4 การเตรียมสาร 94a และ 94b โดยทำปฏิกิริยา sulfoxide elimination

เมื่อนำ **93a** และ **93b** มาทำ sulfoxide elimination โดย reflux ใน toluene และมี $CaCO_3$ อยู่ด้วยจะได้ **94a** และ **94b** 84-85% yield แผนผังที่ 26

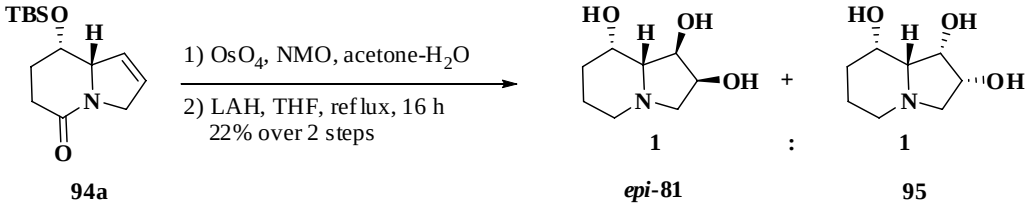
แผนผังที่ 26



2.10.5 การเตรียมสาร (+)-*epi*-Swainsonine (*epi*-81)

ได้พยายามเตรียม (+)-*epi*-swainsonine (epi-**81**) โดยเริ่มต้นจาก **94a** พบว่าเมื่อให้ **94a** ทำปฏิกิริยากับ OsO_4/NMO (*N*-methylmorpholine oxide) ใน acetone-H_2O ตามด้วยปฏิกิริยา reduction โดยใช้ $LiAlH_4$/THF/reflux จะได้ 22% yield ของส่วนผสมระหว่าง *epi*-swainsonine และ **95** ในอัตราส่วน 1:1 แต่ไม่สามารถแยกออกจากกันได้อัตราส่วนหาได้โดย ‘H-NMR (ดูแผนผังที่ 27)

แผนผังที่ 27

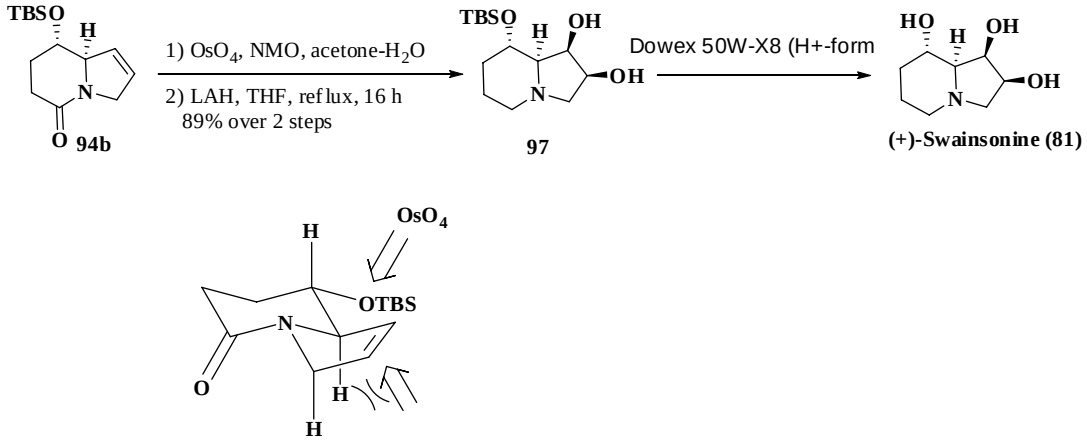


2.10.6 การเตรียมสาร (+)-Swainsonine (81)

ทำปฏิกิริยา sulfoxide elimination ของสาร **94b** จะได้ **96** 85%yield ซึ่งนำไปทำปฏิกิริยา *cis*-dihydroxylation กับ OsO_4/NMO/acetone- H_2O และตามด้วย reduction ด้วย $LiAEH_4$ จะได้ **97** ที่ต้องการเพียงตัวเดียว 88%yield แสดงว่า *cis*-dihydroxylation เกิดแบบ stereoselectivity สูงมาก

โครงสร้างและ relative stereochemistry ของ **97** สามารถ confirm ด้วย ^{1}H-, ^{13}C-NMR, และ NOE-experiments เมื่อทำการ cleavage ของ TBS group ด้วย Dowex 5OW-X8(H^+form) ใน MeOH (24 ชม.) จะได้ (+)-episwainsonine (**81**) ที่ต้องการถึง 94 %yield ค่า spectroscopic data ต่างๆ รวมถึงค่า optical rotation $[\alpha]_D$+78.97(c.0.63, MeOH) จะตรงและใกล้เคียงกับค่าที่รายงานใน literature[5] (ดูแผนผังที่ 28)

แผนผังที่ 28



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   (b) Keck, G. E.; Romer, D. R. An acylnitroso cycloaddition approach to the synthesis of highly oxygenated indolizidine aldaloids. *J. Org. Chem.* **1993**, *58*, 6083-6089.

3. สรุปผลงานวิจัยในรอบ 3 ปี ที่ได้ดำเนินการ

ได้ประยุกต์ใช้ปฏิกิริยา cyclization based on α-sulfinyl carbanions ในการเตรียม 5-alkylidene-2-cyclopentenones, 5-alkylidene-2-hydroxyalkyl-2-cyclopentenones, enantiomers ของ pentenomycin I, epipentenomycin I, desoxypentenomycin และ analogs, (±)-tashiromine, indolizidine 167B, indolizidine 209D, (±)-lupinine , (±)-epilupinine, (+)-swainsonine, substituted pyrrolidines, และ substituted piperidines

4. ผลงานที่ได้ตีพิมพ์ซึ่งเป็นส่วนหนึ่งของโครงการวิจัยนี้

4.1 ผลงานวิจัยที่ตีพิมพ์ในวารสารวิชาการระดับนานาชาติ

4.1.1 Pohmakotr, M.; Thamapipol, S.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2007**, *63***,** 4328-4337. “Intramolecular Acylation of α-Sulfinyl Carbanions with Masked α,β-Unsaturated Esters: A General Strategy to 5-Alkylidene-2-cyclopentenones”.

4.1.2 Pohmakotr, M.; Thamapipol, S,; Tuchinda, P.; Prabpai, S.; Kongsaeree, P.; Reutrakul, V. *J. Org.Chem.* **2007**, *72***,** 5418-5420. “The Morita-Baylis-Hillman Reaction of Masked 5-Alkylidene-2-cyclopentenones : A General Entry to 5-Alkylidene-2-(hydroxyalkyl)-2-cyclopentenones”.

4.1.3 Pohmakotr, M.; Prateeptongkum, S.; Chooprayoon, S.; Tuchinda, P.; Reutrakul, V. Tetrahedron, **2008**, *64*, 2339-2347. “Concise syntheses of substituted indolizidine alkaloids via cyclization based on α-sulfinyl carbanions: preparation of (±)-indolizidines 167B and 209D, their epimers, and (±)-tashiromine”.

4.1.4 Pohmakotr, M.; Kambutong, S.; Tuchinda, P.; Kuhakarn, C. *Tetrahedron* **2008**, *64*, 6315-6323. “Asymmetric synthesis of pentenomycin I, epipentenomycin I, and their analogs”.

4.1.5 Pohmakotr, M.; Seubsai, A.; Numeechai, P.; Tuchinda, P. *Synthesis* **2008**, 1733-1736. “A new strategy for the synthesis of (±)-lupinine and (±)-epilupinine *via* cyclization of α-sulfinyl carbanions”.

4.1.6 Sakulsaknimitr, W.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. “A synthetic strategy to piperidines and pyrrolidines, *ARKIVOC* **2009**, submitted”.

4.1.7 Chooprayoon, S.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V. manuscript in preparation; to be submitted to *J. Org. Chem***. 2009**. “Asymmetric synthesis of (–)-swainsonine *via* cyclization of α-sulfinyl carbanions”.

4.2 ผลงานที่ได้ตีพิมพ์และอ้างอิง (เป็นผลงานต่อเนื่องของทุน BRG/22/2544 และ CHE-RES-RG)

4.2.1 Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *Tetrahedron* **2007**, *63*, 4328-4337. “Stereoselective synthesis of β-carboethoxy-γ-lactams via imino Mukaiyama-aldol type reaction of 1,4-bis(trimethylsilyloxy)-1,4-butadiene”.

4.2.2 Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Reutrakul, V. *J. Org. Chem.* **2007**, *72*, 5016-5019. "Highly diastereoselective synthesis of β-carboxy-γ-lactams and their ethyl esters via $Sc(OTf)_3$-catalyzed imino Mukaiyama-aldol type reaction of 2,5-bis(trimethylsilyloxy)furan with imines".

4.2.3 Pohmakotr, M.; Panichakul, D.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2007**, *63*, 9429-9436. "*gem*-Difluoromethylation of α- and γ-ketoesters: preparation of *gem*-difluorinated α-hydroxyesters and γ-butyrolactones".

4.2.4 Bootwicha, T.; Panichakul, D.; Kuhakarn, C.; Prabpai, S.; Konsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2009**, *74*, 3798-3805. "Fluoride-catalyzed addition of $PhSCF_2SiMe_3$ to *N*-substituted cyclic imides followed by radical cyclization: general synthetic strategy of *gem*-difluoromethylenated 1-azabicyclic compounds".

5. กิจกรรมอื่นๆ ที่เกี่ยวข้อง

การนำเสนอผลงานวิจัยในการประชุมวิชาการระดับนานาชาติ

ได้รับเชิญไปร่วมประชุมและบรรยาย 1st International Conference on Cutting-Edge Organic Chemistry in Asia, October 16-20, 2006 Tiruru, Naha, Okinawa, Japan.

ได้นำผลงานวิจัยไปบรรยายตามคำเชิญของ Asian Core Program ที่ประเทศสิงคโปร์ (2007) ประเทศไต้หวัน (2007) ประเทศเกาหลี (2007) และประเทศญี่ปุ่น (2008)

1. ประเทศสิงคโปร์ ระหว่างวันที่ 1 สิงหาคม 2007 – 4 สิงหาคม 2007 ที่ Nanyang Technological University (NTU) และที่สถาบัน Institute of Chemical and Engineering Science (ICES)
2. ประเทศไต้หวัน ระหว่างวันที่ 8 สิงหาคม 2007 – 14 สิงหาคม 2007 ที่ National Tsing Hua University, National Taiwan University และ National Taiwan Normal University
3. ประเทศเกาหลี ระหว่างวันที่ 26 กันยายน 2007 – 31 กันยายน 2007 ที่ Yonsei University, KAIST และ POSTEC
4. ประเทศญี่ปุ่น ระหว่างวันที่ 27 เมษายน 2008 – 4 พฤษภาคม 2008 ที่ Kyoto University, Nagoya University, Chiba University และ Tokyo Institute of Technology

ลงนาม .....

(ศาสตราจารย์ ดร. มนัส พรหมโคตร)

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Intramolecular acylation of α-sulfinyl carbanions with masked α,β-unsaturated esters: a general strategy to 5-alkylidene-2-cyclopentenones

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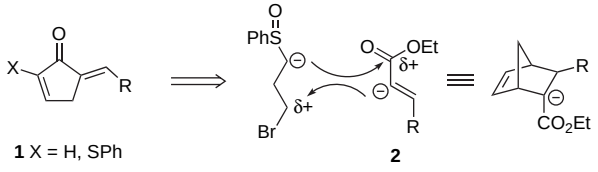
Abstract—A general method for the preparation of 5-alkylidene-2-cyclopentenones and their 2-phenylsulfanyl substituted derivatives, involving the intramolecular acylation of α-sulfinyl carbanions with cyclopentadiene-α,β-unsaturated esters as the key reaction followed by flash vacuum pyrolysis, is described. The reactions start from readily available Diels–Alder adducts, synthons of α-carbanions of α,β-unsaturated esters.

1. Introduction

Functionalized cyclopentenones are a commonly encountered structural unit in a number of prostaglandins and various bioactive natural products.[1] Furthermore, they are found to be versatile building block for the synthesis of some bioactive compounds possessing cyclopentane units. The development of strategies for the construction of these units and related structures has been of considerable interest in synthetic organic chemistry. These methods include the intramolecular aldol reaction,[2] the Pauson–Khand reaction,[3] the Nazarov cyclization,[4,5] and metal–carbene strategies.[6] As part of our study on the intramolecular acylation of α-sulfinyl carbanions for the preparation of cyclopentenone derivatives,[7] we have reported a general synthesis of 5-alkylidene-4-hydroxy-2-cyclopentenones.[8] In the present work, a general route to 5-alkylidene-2-cyclopentenones[9] and 5-alkylidene-2-phenylsulfanyl-2-cyclopentenones **1** is reported.

Our annulation strategy is based on the reaction of an α-carbanion synthon **2** of α,β-unsaturated esters with 3-bromo-1-phenylsulfinylpropane followed by a tandem intramolecular acylation and sulfoxide elimination as outlined in Scheme 1. Cyclopentadiene-α,β-unsaturated ester Diels–Alder adducts were used as masked α-carbanions of α,β-unsaturated esters **2**.[10]

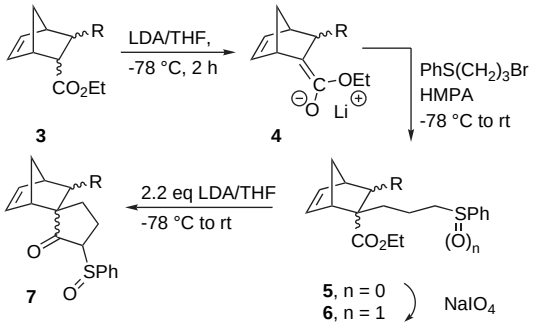


1 X = H, SPh **2**

Scheme 1.

2. Results and discussion

The synthetic route for the preparation of 5-alkylidene-2-cyclopentenones started from readily available bicyclic esters **3**. The key reaction involves intramolecular acylation of the α-sulfinyl carbanions derived from sulfoxides **6** leading to spirocyclopentanones **7** (Scheme 2), which are precursors for the preparation of cyclopentenones **8**, **9**, and **11** (Scheme 3).



3 **4** **7**

Scheme 2.

The results of preparations are summarized in Table 1. The requisite starting sulfoxides **5** were obtained in two steps,

Keywords: α-Sulfinyl carbanion; Intramolecular acylation; 5-Alkylidene-2-cyclopentenones.
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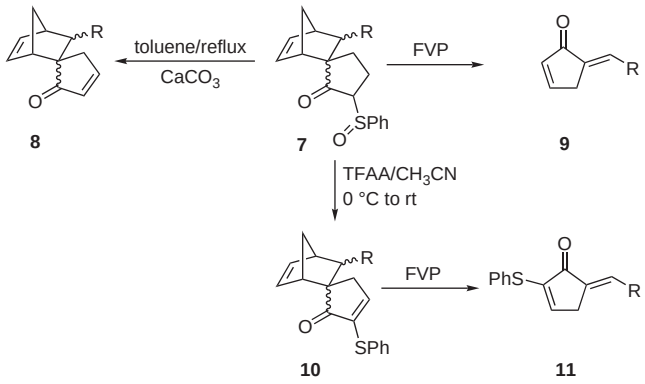
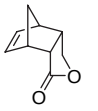
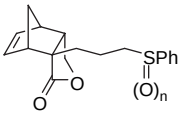
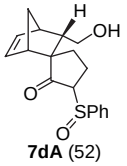
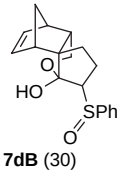
doi:10.1016/j.tet.2006.12.036



Scheme 3.

Table 1. Preparation of compounds **5**, **6**, and **7**

Entry	**3** (*endo*:*exo*)	Yields of **5** (%)[a,b]	Yields of **6** (%)[a,b]	Yields of **7** (%)[a,b]
1	**3a**, R=H (>99:1)	**5a** (90)	**6a** (98)	**7a** (90)
2	**3b**, R=CH_3 (50:50)	**5b** (67)	**6b** (84)	**7b** (80)
3	**3c**, R=Ph (65:35)	**5c** (60)	**6c** (85)	**7c** (70)
4	 **3d**, (>99:1)	 **5d**, n = 0 (47) **6d**, n = 1 (80)	 **7dA** (52)  **7dB** (30)	

[a] Yields of isolated products.
[b] Obtained as a mixture of diastereomers (see Section 4).

beginning with bicyclic esters **3**. Thus, treatment of a mixture (*endo*:*exo* >99:1 with respect to the ester group) of bicyclic ester **3a** with lithium diisopropylamide (LDA, 1.1 equiv) in THF at −78 °C (2 h), followed by trapping of the resulting enolate anion **4a** with 3-bromo-1-phenylsulfanylpropane in the presence of hexamethylphosphoramide (HMPA) at −78 °C to room temperature overnight afforded the corresponding alkylated product **5a** in 90% yield after chromatography, as a 86:14 mixture of *endo*:*exo* esters. The *endo* stereoselectivity for the formation of **5a** was presumably due to the fact that alkylation of the preformed enolate anion **4a** occurred preferentially from the less hindered *exo*-face leading to an *endo*-ester **5a** as the major isomer. Attempted separation of both isomers by preparative thin-layer chromatography was unsuccessful. Only a small amount of the *endo*-ester **5a** was obtained. Similarly, **5b** and **5c** were prepared as mixtures of diastereomers, employing the standard conditions as for **5a** starting from the mixtures of *endo*- and *exo*-isomers of bicyclic esters **3b** and **3c**. The 2-*endo*,3-*exo*- and 2-*endo*,3-*endo*-isomers of **5c** could be separated by preparative thin-layer chromatography in 44 and 16% yields, respectively. On the other hand, a 7:29:11:53 mixture of four diastereomers of **5b** was achieved under the standard conditions and the major 2-*endo*,3-*exo*-isomer of **5b** was obtained in a small amount after careful preparative thin-layer chromatography. The major 2-*endo*,3-*exo*-isomers of **5b** and **5c** could be explained from the fact that alkylation of the enolate anions **4b** and **4c** occurred from the less hindered *exo*-face. Alkylation of compound **3d** gave the alkylated product **5d** in 47% yield as the sole product. A comparable yield (45%) of **5d** was achieved when the alkylation was performed in the presence of 1 equiv of NaI instead of HMPA. The relative stereochemistry at 2- and 3-positions of 2-*endo*,3-*exo*-**5b** and the minor 2-*endo*,3-*endo*-isomer of **5c** was confirmed by NOE experiments as indicated in Figures 1 and 2.

Oxidation of the diastereomeric mixtures of **5a–c** and **5d** was accomplished by using $NaIO_4$ in aqueous methanol at 0 °C to room temperature to furnish the corresponding sulfoxides **6a–d** in good yields as diastereomeric mixtures. The 2-*endo*,3-*exo*-isomer of **6c** was isolated in pure form by preparative thin-layer chromatography, and its relative stereochemistry was established by the NOE experiment as illustrated in Figure 3.

Cyclization of the diastereomeric mixtures of the sulfoxides **6** to the required spiro-ketosulfoxides **7** was successfully effected by using LDA (2.2 equiv) in THF at −78 °C for 2 h, and at 0 °C for 2 h, followed by slowly warming up to room temperature overnight. The reaction proceeded via the intramolecular acylation of the initially formed α-sulfinyl carbanions of the sulfoxides **6**. As expected, spiro-ketosulfoxides **7a–c** were obtained in good yields as mixtures of diastereomers. Attempts to separate these diastereomers were not made, since it was expected that all of them could be converted into the required 5-alkylidene-2-cyclopentenones **9** and **11**. On the other hand, under the standard

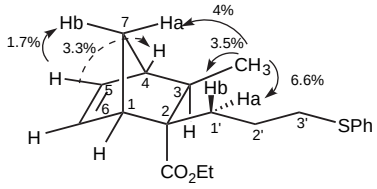


Figure 1. Observed NOE for 2-*endo*,3-*exo*-**5b**.

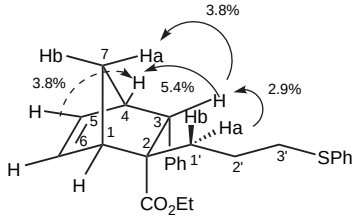


Figure 2. Observed NOE for the minor 2-*endo*,3-*endo*-isomer of **5c**.

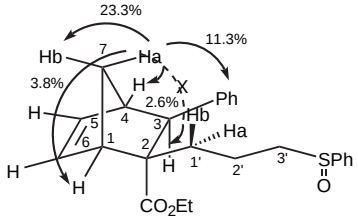


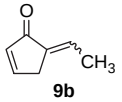
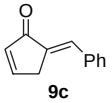
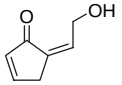
Figure 3. Observed NOE for the 2-*endo*,3-*exo*-isomer of **6c**.

conditions for the cyclization, the sulfoxide **6d** provided a mixture of compounds **7dA** and **7dB** in 52 and 30% yields, respectively. The formation of **7dB** resulted from lactol formation of the initially cyclized product **7dA**. The results are summarized in Table 1.

Having the spiro-ketosulfoxides **7** in hand, the sulfoxide elimination of **7a** and **7b** was investigated. Under reflux in toluene in the presence of $CaCO_3$ for 15 h, **7a** and **7b** provided the corresponding spirocyclopentenones **8a** and **8b** in 70 and 75% yields, respectively, as mixtures of diastereomers. No traces of α-alkylidene cyclopentenones **9a**,**b** arisen from the retro-Diels–Alder reactions of compounds **7a** and **7b** could be detected. However, flash vacuum pyrolysis of the diastereomeric mixtures of spiro-ketosulfoxides **7a–c** and **7dB** at 375–450 °C (0.03–0.05 mmHg) gave quantitative yields of the corresponding α-alkylidene cyclopentenones **9a–c**. Compounds **9b** and **9c** were obtained in good yields after preparative thin-layer chromatography, while compound **9a** is unstable due to rapid polymerization: purification was unsuccessful by preparative thin-layer chromatography. A low yield of compound **9d** (30% yield) was obtained presumably due to its decomposition under the pyrolytic conditions. The formation of **9** resulted from the tandem reaction involving the sulfoxide elimination followed by the retro-Diels–Alder reaction. The results are shown in Table 2.

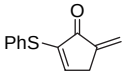
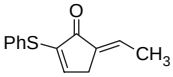
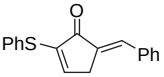
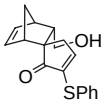
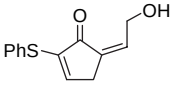
It was anticipated that the spiro-ketosulfoxides **7** could be used as precursors to functionalized cyclopentenones of types **10** and **11**, which might be useful for further synthetic applications. Thus, the spiro-ketosulfoxides **7a–c** were transformed into the corresponding phenylsulfanyl-substituted spirocyclopentenones **10a–c** in good yields by performing the second generation Pummerer rearrangement using trifluoroacetic anhydride in acetonitrile at 0 °C to room temperature overnight (Scheme 3). Flash vacuum pyrolyses of **10a–c** afforded good yields of the expected cyclopentenones **11a–c**. However, under the same conditions, **10d** provided **11d** in only 20% yield (Scheme 3 and Table 3).

Table 2. Preparation of 5-alkylidene-2-cyclopentenones **9**

Entry	Spiro-sulfoxide **7**	Product **9**	% Yield[a] (*E*:*Z* ratio)
1	**7a**	 **9a**	Quantitative
2	**7b**	 **9b**	82 (83:17)[b]
3	**7c**	 **9c**	85 (*E*-isomer)
4	**7d**	 **9d**	30 (*Z*-isomer)

[a] Isolated yields.
[b] The ratio was determined by integration of the ethylenic proton of the crude product.

Table 3. Preparation of spirocyclopentenones **10** by the Pummerer rearrangement of **7** and their pyrolyses to 2-phenylsulfanyl-5-alkylidene-2-cyclopentenones **11**

Entry	**7**	**10**[a] (% Yield)	**11**[a] (% Yield)
1	**7a**, R=H (87:13)	**10a** (80)	 **11a** (93)
2	**7b**, R=CH_3	**10b** (74)	 **11b** (96)
3	**7c**, R=Ph (78:22)	**10c** (78)	 **11c** (76)
4	**7dA** and **7dB**	 **10d** (78)	 **11d** (20)

[a] Yields of isolated products.

This result may be due to its rapid decomposition under the FVP conditions.

3. Conclusion

In summary, the synthetic utility of the intramolecular acylation of α-sulfinyl carbanion as a general method for the syntheses of 5-alkylidene-2-cyclopentenones and their 2-phenylsulfanyl substituted derivatives, starting from Diels–Alder adducts of cyclopentadiene-α,β-unsaturated esters, is demonstrated. The method could be applied to the preparation of a wide range of cyclopentanoid natural products.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz), Bruker DPX-400 (400 MHz), and Bruker DPX-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The chemical shifts (δ) reported are given in parts per million (ppm) and the coupling constants (J) are in hertz (Hz). Melting points were recorded on a Buchi 501 Melting Point Apparatus and are uncorrected. The IR spectra were recorded on a GX FTIR system Perkin–Elmer infrared spectrometer. The mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded on HR-TOF-MS Micromass model, Chiangmai University. The elemental analyses were performed by a Perkin–Elmer Elemental Analyzer 2400 CHN. All glasswares and syringes were oven-dried and kept in a desiccator before use. The molarity of *n*-BuLi (in hexane) was determined by titration with diphenylacetic acid in THF at 0 °C. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Acetonitrile, dichloromethane, diisopropylamine, hexamethylphosphoramide (HMPA), triethylamine, and toluene were dried by

distilling over calcium hydride. Merck silica gel 60H and 60 PF_{245} were used for column chromatography and preparative thin-layer chromatography, respectively.

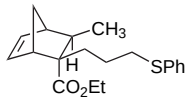
4.2. Preparation of sulfides 5

4.2.1. Ethyl 2-(3′-phenylsulfanylpropyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (5a). *General procedure*: A THF solution (4 mL) of *endo*-**3a** (1.66 g, 10 mmol) was added slowly to a solution of LDA (12 mmol) at −78 °C under an argon atmosphere [prepared by reacting diisopropylamine (1.7 mL, 12 mmol) in THF (30 mL) with *n*-BuLi (1.41 M in hexane, 8.5 mL, 12 mmol) at −78 °C]. After stirring at −78 °C for 2 h, HMPA (2.0 mL) was added, followed by the addition of a THF (10 mL) solution of 3-bromo-1-phenylsulfanylpropane (2.52 g, 12 mmol). The resulting solution was stirred at −78 °C to room temperature overnight, quenched with a saturated aqueous NH_4Cl solution (40 mL), and extracted with hexanes (5×100 mL). The combined organic layers were washed with water and brine, and dried (anhyd Na_2SO_4). The organic phase was concentrated to give a 86:14 mixture of *endo*- and *exo*-isomers of the crude product as a viscous liquid. The ratio of the isomers was determined by ^{1}H NMR of the olefinic protons. The crude product was purified by column chromatography (silica gel, 0.5–2% ethyl acetate in hexanes) to give a pure colorless viscous liquid of a 86:14 ratio of *endo*:*exo*-**5a** (2.86 g, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.12 (m, 10H, Ar*H* of *endo*- and *exo*-isomers), 6.23 (m, 1H, C*H*═CH of *exo*-isomer), 6.15 (dd, *J*=5.6, 3.0 Hz, 1H, C*H*═CH of *endo*-isomer), 6.04 (m, 1H, CH═C*H* of *exo*-isomer), 5.96 (dd, *J*=5.6, 2.8 Hz, 1H, CH═C*H* of *endo*-isomer), 4.10–3.95 (m, 4H, $CO_2CH_2CH_3$ of *endo*- and *exo*-isomers), 2.98–2.77 [m, 8H, (CH_2SPh and CHCH═CHC*H*) of *endo*- and *exo*-isomers], 2.20–1.37 (m, 16H, $CH_2(CH_2)_2$SPh, CH_2CCO_2Et, CH_2CH_2SPh, and CH_2 of *endo*- and *exo*-isomers), 1.27–1.15 (m, 6H, $CO_2CH_2CH_3$ of *endo*- and *exo*-isomers).

A pure *endo*-**5a** was obtained in 68% yield after preparative thin-layer chromatography (PLC) (2% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.16 (m, 5H, Ar*H*), 6.16 (dd, *J*=5.6, 2.9 Hz, 1H, C*H*═CH), 5.99 (dd, *J*=5.6, 2.8 Hz, 1H, CH═C*H*), 4.04 (m, 2H, $CO_2CH_2CH_3$), 2.90 (t, *J*=6.9 Hz, 2H, CH_2SPh), 2.84 (br s, 2H, C*H*CH═CHC*H*), 2.05 (dt, *J*=12.5, 4.8 Hz, 1H, C*H*$(CH_2)_2$SPh), 1.88 (dd, *J*=12.0, 2.5 Hz, 1H, C*H*$HCCO_2Et$), 1.80–1.40 (m, 6H, $CHCH_2CH_2$SPh, $CHCCO_2Et$, and CH_2), 1.19 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0 (C═O), 138.2 (CH), 136.3 (C), 134.6 (CH), 129.1 (2×CH), 128.8 (2×CH), 125.8 (CH), 60.1 (CH_2), 54.3 (C), 50.7 (CH), 47.1 (CH_2), 42.6 (CH), 39.0 (CH_2), 35.7 (CH_2), 33.9 (SCH_2), 25.5 (CH_2), 14.2 (CH_3). IR (neat): ν_{max} 3060w, 2976s, 1728s, 1584w, 1481m, 1439m, 1334m, 1243s, 1184s, 1159s, 1114m, 1096m, 1060m, 1026m, 739s, 712s, 691m cm^{-1}. MS: *m*/*z* (%) relative intensity 318 (M^++2, 6), 317 (M^++1, 25), 316 (M^+, 50), 273 (7), 272 (19), 271 (100), 250 (13), 242 (15), 205 (8), 176 (12), 165 (15), 160 (21), 149 (77), 141 (49), 134 (13), 114 (19), 95 (12), 67 (24), 66 (8). Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.11; H, 7.64. Found: C, 72.19; H, 7.80.

4.2.2. Ethyl 2-(3′-phenylsulfanylpropyl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carboxylate (5b). According to the general procedure described for compound **5a**, a solution of a 50:50 mixture of *endo*- and *exo*-**3b** (0.45 g, 2.5 mmol) in THF (1 mL) was added dropwise to a THF (8 mL) solution of LDA (3 mmol) at −78 °C under an argon atmosphere. After stirring at −78 °C for 2 h, HMPA (1.2 mL) was added followed by the addition of a THF (3 mL) solution of 3-bromo-1-phenylsulfanylpropane (0.578 g, 2.5 mmol). After usual work-up, the crude product was purified by column chromatography (silica gel, 0.5–2% ethyl acetate in hexanes) to give a pure colorless viscous liquid of **5b** (0.554 g, 67% yield) as a 7:29:11:53 mixture of *exo*,*endo*: *endo*,*endo*:*exo*,*exo*:*endo*,*exo*-isomers. The mixture was used for further oxidation.

Compound **5b** (a mixture of four isomers): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.14 (m, Ar*H*), 6.37 (dd, *J*=5.4, 3.0 Hz, C*H*═CH), 6.20 (dd, *J*=5.6, 3.0 Hz, C*H*═CH), 6.14–6.04 (m, CH═C*H*), 4.16–3.90 (m, $CO_2CH_2CH_3$), 3.03 (br s, C*H*CH═CHCH), 3.00–2.77 (m, CH_2SPh and C*H*CH═CHCH), 2.66 and 2.61 (each br s, CHCH═CHC*H*), 2.38 (br s, CHCH═CHC*H*), 2.19–1.98 (m, C*H*CH_3 and C*H*HCH_2CH_2SPh), 1.93–1.45 (m, $CH_2CH_2CH_2$SPh and CH_2), 1.43 (d, *J*=8.7 Hz, CH*H*), 1.35 (dd, *J*=9.0, 1.6 Hz, CH*H*), 1.28–1.14 (m, $CO_2CH_2CH_3$ and $CHCH_3$), 1.10 (d, *J*=7.2 Hz, $CHCH_3$), 0.92 (d, *J*=7.2 Hz, $CHCH_3$), 0.86 (d, *J*=7.2 Hz, $CHCH_3$).

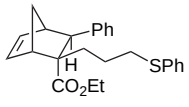


endo,*exo*-**5b**

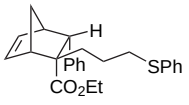
A pure colorless viscous liquid of *endo*,*exo*-isomer of **5b** was obtained in a small quantity by careful preparative thin-layer chromatography. *endo*,*exo*-**5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.03 (m, 5H, Ar*H*), 6.10 (dd, *J*=5.4, 3.0 Hz, 1H, C*H*═CH), 5.99 (dd, *J*=5.4, 2.7 Hz, 1H, CH═C*H*), 3.91 (m, 2H, $CO_2CH_2CH_3$), 2.83 (t, *J*=6.6 Hz, 2H, CH_2SPh), 2.72 (br s, 1H, C*H*CH═CHCH), 2.27 (br s, 1H, CHCH═CHC*H*), 1.95 (dq, *J*=7.0, 1.4 Hz, 1H, C*H*CH_3), 1.82–1.40 (m, 5H, $CH_2CH_2CH_2$SPh and C*H*H), 1.26 (dd, *J*=9.0, 1.5 Hz, 1H, CH*H*), 1.08 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.00 (d, *J*=7.0 Hz, 3H, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7 (C═O), 138.2 (CH), 136.2 (C), 136.2 (CH), 129.2 (2×CH), 128.8 (2×CH), 125.9 (CH), 59.9 (CH_2), 55.4 (C), 49.7 (CH), 49.4 (CH), 43.7 (CH_2), 40.6 (CH), 34.2 (CH_2), 34.1 (SCH_2), 25.8 (CH_2), 16.8 (CH_3), 14.2 (CH_3). IR (neat): ν_{max} 3059w, 2963s, 1725s, 1585w, 1481m, 1439m, 1240s, 1175m, 1148m, 1026m, 738s, 718m, 691m cm^{-1}. MS: *m*/*z* (%) relative intensity 331 (M^++1, 13), 330 (M^+, 26), 286 (19), 285 (100), 265 (14), 264 (54), 219 (18), 191 (12), 190 (27), 156 (17), 155 (98), 149 (38), 127 (33), 109 (20), 82 (48), 79 (20), 77 (9), 65 (7). Anal. Calcd for $C_{20}H_{26}O_2S$: C, 72.69; H, 7.93. Found: C, 72.83; H, 8.18.

4.2.3. Ethyl 2-(3′-phenylsulfanylpropyl)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxylate (5c). According to the general procedure described for compound **5a**, a solution of a 65:35 mixture of *endo*- and *exo*-**3c** (0.60 g, 2.5 mmol)

in THF (1 mL) was added dropwise to a solution of LDA (3 mmol) in THF (8 mL) at −78 °C under an argon atmosphere. After stirring at −78 °C for 2 h, HMPA (1.2 mL) was added, followed by the addition of a THF (4 mL) solution of 3-bromo-1-phenylsulfanylpropane (0.695 g, 3 mmol). After usual work-up, the crude product was purified by column chromatography (silica gel, 0.2–2% ethyl acetate in hexanes) to give **5c** (0.631 g, 64% yield) as a 70:30 mixture of *endo*,*exo*- and *endo*,*endo*-isomers.



endo,exo-**5c**



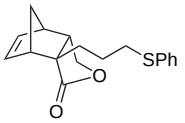
endo,endo-**5c**

A mixture of *endo*,*exo*- and *endo*,*endo*-**5c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.01 (m, 20H, Ar*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 6.67 (m, 1H, C*H*=CH of *endo*,*endo*-isomer), 6.36 (dd, J=5.4, 3.2 Hz, 1H, C*H*=CH of *endo*,*exo*-isomer), 6.22 (m, 2H, CH=C*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 4.09 (m, 2H, $CO_2CH_2CH_3$ of *endo*,*exo*-isomer), 3.65 (m, 1H, CO_2CHHCH_3 of *endo*,*endo*-isomer), 3.37 (m, 1H, CO_2CHHCH_3 of *endo*,*endo*-isomer), 3.25 (s, 1H, C*H*Ph of *endo*,*exo*-isomer), 3.11 (d, J=3.0 Hz, 1H, C*H*Ph of *endo*,*endo*-isomer), 3.02–2.83 [m, 6H, C*H*CH=CHC*H* of *endo*,*exo*-isomers and (C*H*CH=CHC*H* and CH_2SPh) of *endo*,*endo*-isomer], 2.54 (m, 2H, CH_2SPh of *endo*,*exo*-isomer), 2.35 (dt, J=12.8, 4.1 Hz, 1H, C*H*H$(CH_2)_2$SPh of *endo*,*endo*-isomer), 2.02 (d, J=9.0 Hz, 1H, C*H*H of *endo*,*exo*-isomer), 1.94–1.67 (m, 3H, CH*H*C*H*HCH$_2$SPh and C*H*H of *endo*,*endo*-isomer), 1.65–1.47 [m, 4H, (CH*H* and CH*H*CH$_2$SPh) of *endo*,*endo*-isomer and (CH*H* and C*H*H$(CH_2)_2$SPh) of *endo*,*exo*-isomer], 1.45–1.17 (m, 6H, C*H*HCH$_2$SPh, $CO_2CH_2CH_3$ and CH*H*$(CH_2)_2$SPh of *endo*,*exo*-isomer), 0.12 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$ of *endo*,*endo*-isomer).

The *endo*,*exo*- and *endo*,*endo*-isomers were separated by PLC to give *endo*,*exo*-**5c** (0.433 g, 44% yield) and *endo*,*endo*-**5c** (0.158 g, 16% yield) as pale yellow viscous liquids. *endo*,*exo*-**5c** (less polar): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.00 (m, 10H, Ar*H*), 6.29 (dd, J=5.5, 3.2 Hz, 1H, C*H*=CH), 6.12 (dd, J=5.5, 2.8 Hz, 1H, CH=C*H*), 4.00 (m, 2H, $CO_2CH_2CH_3$), 3.17 (br s, 1H, C*H*Ph), 2.90 (br s, 1H, C*H*CH=CHCH), 2.85 (br s, 1H, CHCH=CHC*H*), 2.45 (m, 2H, CH_2SPh), 1.92 (d, J=8.7 Hz, 1H, C*H*H), 1.54 (dd, J=8.7, 1.3 Hz, 1H, CH*H*), 1.39 (m, 1H, C*H*H$(CH_2)_2$SPh), 1.30–1.10 (m, 6H, CH*H*C*H*$_2$CH$_2$SPh and $CO_2CH_2CH_3$). IR (neat): ν_{max} 3060m, 2974s, 1721s, 1601m, 1584m, 1495m, 1481s, 1454s, 1320m, 1237s, 1169s, 1148s, 1092s, 1025s, 740s, 703s, 692s cm^{-1}. MS: *m*/*z* (%) relative intensity 393 (M^++1, 5), 392 (M^+, 3), 348 (11), 347 (46), 327 (21), 326 (85), 319 (8), 281 (9), 252 (16), 235 (11), 224 (7), 218 (15), 217 (78), 189 (25), 177 (34), 171 (47), 150 (30), 149 (43), 143 (100), 142 (37), 128 (19), 115 (18), 91 (14), 66 (7), 65 (8).

endo,*endo*-**5c** (more polar): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–6.90 (m, 10H, Ar*H*), 6.58 (dd, J=5.2, 3.2 Hz, 1H, C*H*=CH), 6.13 (dd, J=5.2, 3.0 Hz, 1H, CH=C*H*), 3.56 (dq, J=10.7, 7.1, 7.1 Hz, 1H, CO_2CHHCH_3), 3.29 (dq, J=10.7, 7.2, 7.1 Hz, 1H, CO_2CHHCH_3), 3.05 (d, J=2.9 Hz, 1H, C*H*Ph), 2.91 (br s, 1H, C*H*CH=CHCH), 2.87–2.76 (m, 3H, CHCH=CHC*H* and CH_2SPh), 2.27 (dt, J=12.7, 4.1 Hz, 1H, C*H*H$(CH_2)_2$SPh), 1.87–1.61 (m, 3H, CH*H*C*H*HCH$_2$SPh and C*H*H), 1.49–1.27 (m, 2H, CH*H* and CH*H*CH$_2$SPh), 0.55 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (C=O), 142.5 (C), 139.9 (CH), 136.2 (C), 133.9 (CH), 129.2 (2×CH), 128.8 (2×CH), 128.6 (2×CH), 127.5 (2×CH), 126.1 (CH), 125.9 (CH), 63.1 (C), 60.0 (CH), 59.8 (CH_2), 49.4 (CH), 48.2 (CH), 47.8 (CH_2), 40.6 (CH_2), 33.9 (SCH_2), 25.4 (CH_2), 13.3 (CH_3). IR (neat): ν_{max} 3060w, 2975s, 1721s, 1602w, 1584m, 1495m, 1480m, 1454m, 1439m, 1319w, 1237s, 1169m, 1148m, 1093m, 1026m, 740s, 703m, 691m cm^{-1}. MS: *m*/*z* (%) relative intensity 392 (M^+, 1), 348 (5), 327 (4), 326 (21), 320 (22), 319 (84), 281 (7), 252 (13), 241 (22), 236 (12), 235 (13), 218 (15), 217 (56), 209 (59), 189 (31), 182 (22), 177 (30), 171 (47), 167 (17), 165 (14), 149 (45), 143 (100), 142 (38), 141 (24), 128 (39), 123 (16), 115 (38), 91 (29), 77 (16), 65 (12). HRMS (ESI-TOF) calcd for $C_{25}H_{28}O_2SNa$: 415.1708; found: 415.1708.

4.2.4. 2-(3′-Phenylsulfanylpropyl)-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactone (5d). According to the general procedure described for compound **5a**, a solution of *endo*-**3d** (0.376 g, 2.5 mmol) in THF (1 mL) was added dropwise to a solution of LDA (3.75 mmol) in THF (8 mL) at −78 °C under an argon atmosphere. After stirring at −78 °C for 2 h, HMPA (1.2 mL) was added followed by the addition of a THF (5 mL) solution of 3-bromo-1-phenylsulfanylpropane (2.31 g, 10 mmol). After usual work-up, the crude product was purified by column chromatography (silica gel, 10–20% ethyl acetate in hexanes) to give a colorless solid of *endo*-**5d** (0.354 g, 47% yield, mp 70–72 °C) and the starting material **3d** (0.131 g, 35% yield). The reaction proceeded to give a comparable yield of **5d** (45% yield), when NaI (0.09 g, 0.6 mmol) was used instead of HMPA.



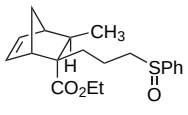
endo-**5d**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.05 (m, 5H, Ar*H*), 6.23 (dd, J=5.2, 2.8 Hz, 1H, C*H*=CH), 6.17 (dd, J=5.2, 2.8 Hz, 1H, CH=C*H*), 4.00 (app. t, J=9.6 Hz, 1H, CO_2CHH), 3.65 (dd, J=9.6, 2.8 Hz, 1H, CO_2CHH), 3.00–2.85 (m, 2H, C*H*HSPh and C*H*CH=CHCH), 2.85–2.71 (m, 2H, CH*H*SPh and CHCH=CHC*H*), 2.55 (td, J=8.7, 3.6 Hz, 1H, C*H*CH$_2$OCO), 2.05 (m, 1H, C*H*HCH$_2$CH$_2$SPh), 1.77–1.53 (m, 5H, CH_2 and CH*H*C*H*$_2$CH$_2$SPh). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0 (C=O), 137.9 (CH), 136.0 (C), 134.5 (CH), 129.3 (2×CH), 128.9 (2×CH), 126.1 (CH), 69.3 (CH_2), 58.7 (C), 51.4 (CH), 49.8 (CH_2), 46.6 (CH), 45.2 (CH), 35.9 (CH_2), 33.8 (CH_2), 26.00 (CH_2). IR (neat): ν_{max} 3060w, 2972s, 2909m, 1757s, 1583m, 1481m, 1439m, 1381m, 1229m, 1181s, 1148m, 1057m, 1000m, 742s, 692m cm^{-1}. MS: *m*/*z* (%) relative intensity 301 (M^++1, 23), 300 (M^+, 30), 234 (12), 191 (16), 135 (3), 125 (100), 110 (9), 97 (5), 81 (10), 79 (22), 77 (13), 66 (8), 65 (7). Anal. Calcd for $C_{18}H_{20}O_2S$: C, 71.96; H, 6.71. Found: C, 71.69; H, 6.71.

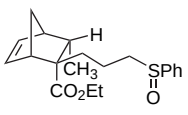
4.3. Preparation of sulfoxides 6

4.3.1. Ethyl 2-(3′-phenylsulfinylpropyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (6a). *General procedure*: A solution of *endo*-**5a** (3.91 g, 12.37 mmol) in methanol (50 mL) was added dropwise to a suspension of powdered $NaIO_4$ (2.65 g, 12.37 mmol) in water (17 mL) at 0 °C. The mixture was stirred at 0 °C to room temperature overnight. The precipitates of $NaIO_3$ were filtered and washed several times with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over anhyd Na_2SO_4. Filtration followed by evaporation gave a yellow liquid, which was purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to furnish a pure colorless viscous liquid of *endo*-**6a** (4.03 g, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.37 (m, 5H, Ar*H*), 6.07 (dd, *J*=5.5, 2.9 Hz, 1H, C*H*=CH), 5.89 (dd, *J*=5.5, 2.7 Hz, 1H, CH=C*H*), 3.95 (m, 2H, $CO_2CH_2CH_3$), 2.70, (m, 4H, CH_2SOPh and C*H*CH=CHC*H*), 2.02–1.28 (m, 8H, $CH_2CH_2CH_2$SOPh, CH_2, and CH_2CCO_2Et), 1.10 (dt, *J*=7.1, 2.3 Hz, 3H, $CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7 (2×C=O), 143.8 and 143.7 (C), 138.3 and 138.2 (CH), 134.5 and 134.5 (CH), 130.9 (2×CH), 129.1 (4×CH), 123.9 (4×CH), 60.2 (2×CH_2), 57.4 and 57.3 (CH_2), 54.4 (2×C), 50.7 and 50.6 (CH), 47.1 (2×CH_2), 42.6 (2×CH), 39.1 and 39.0 (CH_2), 35.8 and 35.6 (CH_2), 19.3 and 19.2 (CH_2), 14.2 (2×CH_3). IR (neat): ν_{max} 3060m, 2976s, 1728s, 1583w, 1478m, 1445s, 1336m, 1240s, 1185s, 1160s, 1087s, 1044s, 751s, 713s, 693m cm^{-1}. MS: *m*/*z* (%) relative intensity 334 (M^++1, 8), 333 (M^+, 36), 315 (26), 287 (13), 267 (16), 221 (39), 161 (16), 143 (52), 141 (100), 114 (54), 96 (29), 91 (16), 67 (26), 66 (10). Anal. Calcd for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28. Found: C, 69.09; H, 7.52.

4.3.2. Ethyl 2-(3′-phenylsulfinylpropyl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carboxylate (6b). According to the general procedure described for compound **6a**, a mixture of powdered $NaIO_4$ (1.35 g, 6.32 mmol) in water (8 mL) and a solution of a 7:29:11:53 mixture of diastereomers of **5b** (2.00 g, 6.32 mmol) in methanol (23 mL) was stirred at 0 °C to room temperature overnight. The organic layer was separated and the aqueous layer was extracted with ethyl acetate and concentrated to give a 4:20:6:70 diastereomeric mixture of isomers of a crude product **6b** as a viscous liquid. The crude product was purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to give a pure colorless viscous liquid of **6b** (1.84 g, 84% yield) as a 93:7 mixture of *endo*,*exo*- and *endo*,*endo*-isomers.



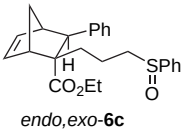
endo,exo-**6b**



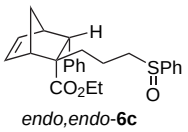
endo,endo-**6b**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.34 (m, 10H, Ar*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 6.22 (m, 1H, C*H*=CH of *endo*,*endo*-isomer), 6.07 (dd, *J*=5.5, 3.0 Hz, 1H, C*H*=CH of *endo*,*exo*-isomer), 5.95 (dd, *J*=5.5, 2.7 Hz, 2H, CH=C*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 4.07–3.77 (m, 4H, $CO_2CH_2CH_3$ of *endo*,*exo*- and *endo*,*endo*-isomers), 2.79–2.57 (m, 6H, CH_2SOPh and C*H*CH=CHCH of *endo*,*exo*- and *endo*,*endo*-isomers), 2.49 (br s, 1H, CHCH=CHC*H* of *endo*,*endo*-isomer), 2.25 (br s, 1H, CHCH=CHC*H* of *endo*,*exo*-isomer), 2.00–1.80 [m, 3H, (C*H*CH_3 and C*H*HCH_2CH_2SOPh) of *endo*,*endo*-isomer and C*H*CH_3 of *endo*,*exo*-isomer], 1.80–1.34 [m, 10H, (CH_2 and CH*H*CH_2CH_2SOPh) of *endo*,*endo*-isomer and (C*H*H and $CH_2CH_2CH_2$SOPh) of *endo*,*exo*-isomer], 1.26 (dd, *J*=9.1, 1.4 Hz, 1H, CH*H* of *endo*,*exo*-isomer), 1.15 (dt, *J*=7.6, 1.7 Hz, 3H, $CO_2CH_2CH_3$ of *endo*,*endo*-isomer), 1.10 (m, 3H, $CO_2CH_2CH_3$ of *endo*,*exo*-isomer), 0.95 (d, *J*=7.3 Hz, 3H, CHCH_3 of *endo*,*exo*-isomer), 0.78 (m, 3H, CHCH_3 of *endo*,*endo*-isomer). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4 (2×C=O), 143.9 and 143.7 (C), 138.2 (2×CH), 136.2 and 136.1 (CH), 131.0 and 130.9 (CH), 129.2 and 129.1 (2×CH), 124.0 (4×CH), 60.0 and 60.0 (CH_2), 57.7 and 57.3 (CH_2), 55.4 (2×C), 49.5 and 49.1 (CH), 48.9 and 48.3 (CH), 45.9 and 43.7 (CH_2), 40.7 and 40.6 (CH), 34.1 and 34.0 (CH_2), 19.5 and 18.9 (CH_2), 16.8 (2×CH_3), 14.2 (2×CH_3). IR (neat): ν_{max} 3059w, 2963s, 1722s, 1583w, 1463m, 1444m, 1369m, 1384m, 1340w, 1237s, 1176m, 1145m, 1088s, 1050s, 1023m, 749m, 693m cm^{-1}. MS: *m*/*z* (%) relative intensity 348 (M^++1, 12), 347 (M^+, 52), 329 (28), 301 (23), 283 (18), 281 (18), 236 (13), 235 (81), 175 (14), 156 (17), 155 (100), 147 (14), 128 (16), 127 (45), 110 (44), 105 (12), 91 (17), 82 (94), 79 (62), 77 (21), 66 (8). HRMS (ESI-TOF) calcd for $C_{20}H_{27}O_3S$: 347.1681; found: 347.1681.

4.3.3. Ethyl 2-(3′-phenylsulfinylpropyl)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxylate (6c). According to the general procedure described for compound **6a**, a mixture of powdered $NaIO_4$ (0.565 g, 2.64 mmol) in water (4 mL) and a solution of a 70:30 diastereomeric mixture of *endo*,*exo*- and *endo*,*endo*-**5c** (0.864 g, 2.20 mmol) in methanol (8 mL) was stirred at 0 °C to room temperature overnight. The crude product was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to give a pure pale yellow viscous liquid of **6c** (0.77 g, 85% yield) as a 67:33 diastereomeric mixture of *endo*,*exo*- and *endo*,*endo*-isomers.



endo,exo-**6c**



endo,endo-**6c**

A mixture of *endo*,*exo*- and *endo*,*endo*-**6c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.45 (m, 10H, SOAr*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 7.38–6.95 (m, 10H, Ar*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 6.65 (br s, 1H, C*H*=CH of *endo*,*endo*-isomer), 6.35 (m, 1H, C*H*=CH of *endo*,*exo*-isomer), 6.23 (br s, 2H, CH=C*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 4.20–3.98 (m, 2H, CO_2CH_2 of *endo*,*exo*-isomer), 3.64 (m, 1H, CO_2CHH of *endo*,*endo*-isomer), 3.37 (m, 1H, CO_2CH*H* of *endo*,*endo*-isomer), 3.24 (s, 1H, C*H*Ph of *endo*,*exo*-isomer), 3.09 (d, *J*=3.0 Hz, 1H, C*H*Ph of *endo*,*endo*-isomer), 3.00 (br s, 2H, C*H*CH=CHCH of *endo*,*exo*- and *endo*,*endo*-isomers), 2.94 (br s, 1H, CHCH=CHC*H* of *endo*,*exo*-isomer), 2.89 (br s, 1H, CHCH=CHC*H* of *endo*,*endo*-isomer), 2.78 (m, 2H,

CH_2SOPh of *endo*,*endo*-isomer), 2.53–2.20 (m, 3H, CH_2SOPh of *endo*,*exo*-isomer and $CH(CH_2)_2$SOPh of *endo*,*endo*-isomer), 2.00–1.05 [m, 14H, (CH_2 and $CHHCH_2CH_2$SOPh) of *endo*,*endo*-isomer and (CH_2, $CH_2CH_2CH_2$SOPh and $CO_2CH_2CH_3$) of *endo*,*exo*-isomer], 0.64 (td, J=13.1, 6.8 Hz, 3H, $CO_2CH_2CH_3$ of *endo*,*endo*-isomer).

A pure *endo*,*exo*-**6c** was partially obtained by PLC as a pale yellow viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.34 (m, 5H, SOAr*H*), 7.30–7.05 (m, 5H, Ar*H*), 6.29 (m, 1H, C*H*=CH), 6.14 (m, 1H, CH=C*H*), 4.01 (m, 2H, $CO_2CH_2CH_3$), 3.17 (d, J=2.2 Hz, 1H, C*H*Ph), 2.95 (d, J=6.7 Hz, 1H, C*H*CH=CHCH), 2.85 (br s, 1H, CHCH=CHC*H*), 2.46–2.14 (m, 2H, CH_2SOPh), 1.95–1.00 (m, 9H, $CH_2CH_2CH_2$SOPh, $CO_2CH_2CH_3$, and CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2 (2×C=O), 143.8 and 143.4 (C), 141.5 and 141.5 (C), 139.7 (2×CH), 137.4 (2×CH), 130.9 and 130.7 (CH), 129.1 and 129.0 (2×CH), 127.9 (8×CH), 126.1 (2×CH), 123.9 and 123.8 (2×CH), 60.44 and 60.36 (CH_2), 57.65 and 56.63 (OSCH), 57.1 (2×C), 51.68 and 51.65 (CH), 48.1 and 48.0 (CH), 47.2 (2×CH), 45.31 and 45.27 (CH_2), 36.0 and 35.8 (CH_2), 19.2 and 17.9 (CH_2), 14.3 and 14.2 (CH_3). IR (neat): ν_{max} 3060m, 3028m, 2977s, 1728s, 1716s, 1602m, 1583w, 1495m, 1478m, 1454s, 1445s, 1368m, 1323m, 1234s, 1165s, 1145s, 1089s, 1046s, 911m, 750s, 701s cm^{-1}. MS: *m*/*z* (%) relative intensity 409 (M^+, 10), 391 (3), 344 (11), 343 (41), 297 (31), 283 (7), 279 (6), 247 (13), 217 (39), 209 (9), 189 (27), 172 (18), 171 (100), 144 (21), 143 (67), 129 (19), 128 (20), 117 (15), 115 (19), 91 (15), 77 (6), 66 (5), 65 (6). HRMS (ESI-TOF) calcd for $C_{25}H_{28}O_3SNa$: 431.1657; found: 431.1656.

4.3.4. 2-(3′-Phenylsulfinylpropyl)-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactone (6d). According to the general procedure described for compound **6a**, a mixture of powdered $NaIO_4$ (0.757 g, 3.54 mmol) in water (5 mL) and a solution of *endo*-**5d** (0.887 g, 2.95 mmol) in methanol (10 mL) was stirred at 0 °C to room temperature overnight. The crude product was purified by column chromatography (silica gel, 40–50% ethyl acetate in hexanes) to give a pure colorless solid of *endo*-**6d** (0.75 g, 80% yield, mp 86–88 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.40 (m, 5H, Ar*H*), 6.24 (br s, 2H, C*H*=C*H*), 4.10 (td, J=23.4, 9.3 Hz, 1H, CO_2CHHCH_3), 3.70 (m, 1H, CO_2CHHCH_3), 3.00 (br s, 1H, C*H*CH=CHCH), 2.85–2.61 (m, 4H, CH_2SOPh, C*H*CH_2OCO, and CHCH=CHC*H*), 2.61–1.41 (m, 6H, $CH_2CH_2CH_2$SOPh and CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.7 (2×C=O), 143.6 and 143.1 (C), 137.5 (2×CH), 134.5 (2×CH), 130.9 (2×CH), 129.1 (4×CH), 123.7 and 123.6 (2×CH), 69.2 (2×CH_2O), 58.6 (2×C), 57.0 and 56.4 (CH_2), 51.3 and 51.2 (CH), 49.7 and 49.6 (CH_2), 46.50 and 46.48 (CH), 44.72 and 44.67 (CH), 35.9 and 35.3 (CH_2), 20.0 and 18.7 (CH_2). IR (neat): ν_{max} 3061w, 2973s, 1755s, 1643w, 1479m, 1444m, 1382m, 1342w, 1219m, 1183s, 1147m, 1088m, 1038s, 999s, 751s, 694m cm^{-1}. MS: *m*/*z* (%) relative intensity 317 (M^+, 10), 299 (2), 251 (3), 199 (11), 191 (6), 126 (9), 125 (100), 115 (4), 107 (3), 97 (16), 91 (9), 81 (17), 79 (50), 78 (10), 77 (28), 66 (7), 65 (8). HRMS (ESI-TOF) calcd for $C_{18}H_{20}O_3SNa$: 339.1031; found: 339.1031.

4.4. Preparation of spiro-sulfoxides 7 by cyclization of sulfoxides 6

4.4.1. 2′-Oxo-3′-phenylsulfinylcyclopentane-1′-spiro-2-bicyclo[2.2.1]hept-5-ene (7a). *General procedure*: A solution of a 86:14 mixture of *endo*- and *exo*-**6a** (0.50 g, 1.5 mmol) in THF (4.50 mL) was added dropwise at −78 °C to a solution of lithium diisopropylamide (LDA) under an argon atmosphere [prepared by reacting diisopropylamine (0.47 mL, 3.30 mmol) in THF (5 mL) with *n*-BuLi (1.41 M in hexane, 2.55 mL, 3.30 mmol) at −78 °C for 1 h]. The mixture was stirred at −78 °C for 2 h, 0 °C for 2 h and then quenched with a saturated NH_4Cl solution (6 mL). The mixture was extracted with EtOAc (3×25 mL). The combined organic layers were washed with water, brine and dried over anhyd Na_2SO_4. After removal of solvent under reduced pressure, a crude product **7a** was purified by preparative thin-layer chromatography (silica gel, 20% ethyl acetate in hexanes) to give three bands (PLC_1, PLC_2, and PLC_3) of **7a** (0.387 g, 90% combined yield) as a diastereomeric mixture.

PLC_1 (less polar): a pure isomer as a white solid (43 mg, 10% yield, mp 116–118 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.36 (m, 5H, Ar*H*), 6.23 (dd, J=5.5, 3.0 Hz, 1H, C*H*=CH), 6.05 (dd, J=5.5, 3.1 Hz, 1H, CH=C*H*), 3.26 (dd, J=9.8, 8.6 Hz, 1H, C*H*SOPh), 3.15 (br s, 1H, C*H*CH=CHCH), 2.86 (br s, 1H, CHCH=CHC*H*), 2.37 (m, 1H, C*H*HCH_2CHSOPh), 2.10 (dd, J=11.5, 3.6 Hz, 1H, C*H*HCCO), 1.85–1.31 (m, 4H, C*H*H and CH*H*CH_2CHSOPh), 1.21 (d, J=8.9 Hz, 1H, CH*H*), 0.74 (dd, J=11.5, 2.9 Hz, 1H, CH*H*CCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.0 (C=O), 142.3 (C), 140.6 (CH), 133.4 (CH), 130.9 (CH), 129.2 (2×CH), 123.9 (2×CH), 71.4 (CH), 57.5 (C), 45.58 (CH), 45.56 (CH_2), 43.1 (CH), 37.6 (CH_2), 33.0 (CH_2), 14.8 (CH_2). IR (Nujol): ν_{max} 2955s, 1724m, 1334w, 1235w, 1163w, 1086w, 1046m, 1029w, 754w, 740w, 725m, 691w cm^{-1}. MS: *m*/*z* (%) relative intensity 287 (M^++1, 14), 269 (6), 162 (12), 161 (100), 143 (20), 133 (10), 128 (12), 126 (8), 117 (6), 105 (13), 97 (12), 95 (35), 91 (21), 79 (11), 78 (14), 77 (11), 67 (17), 66 (11), 65 (12).

PLC_2 (more polar): a pure isomer as a white solid (0.168 g, 39% yield, mp 119–121 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61–7.36 (m, 5H, Ar*H*), 6.22 (dd, J=5.6, 3.0 Hz, 1H, C*H*=CH), 5.80 (dd, J=5.6, 2.9 Hz, 1H, CH=C*H*), 3.24 (app. t, J=9.6 Hz, 1H, C*H*SOPh), 3.07 (br s, 1H, C*H*CH=CHCH), 2.83 (br s, 1H, CHCH=CHC*H*), 2.50 (m, 1H, C*H*HCH_2CHSOPh), 2.07 (dd, J=12.4, 7.2 Hz, 1H, C*H*HCHSOPh), 1.95 (dd, J=12.4, 6.8 Hz, 1H, CH*H*CHSOPh), 1.60–1.33 (m, 5H, CH_2, CH_2CCO and CH*H*CH_2CHSOPh). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.1 (C=O), 142.4 (C), 137.8 (CH), 132.6 (CH), 130.9 (CH), 129.2 (2×CH), 123.9 (2×CH), 71.1 (CH), 56.9 (C), 49.0 (CH), 48.6 (CH_2), 42.9 (CH), 38.4 (CH_2), 35.0 (CH_2), 15.0 (CH_2). IR (Nujol): ν_{max} 2955s, 1727m, 1334w, 1238w, 1085w, 1048m, 1020w, 760w, 743w, 728m, 692w cm^{-1}. MS: *m*/*z* (%) relative intensity 286 (M^+, 3), 267 (11), 243 (23), 231 (23), 205 (14), 203 (12), 201 (20), 193 (19), 181 (69), 178 (24), 149 (31), 143 (23), 131 (100), 125 (34), 121 (22), 109 (21), 99 (24), 97 (21), 95 (26), 93 (25), 83 (24), 81 (41), 79 (27), 77 (22), 69 (80), 67 (38), 65 (12), 51 (8).

PLC_3 (most polar): a 69:31 mixture of two isomers (A- and B-isomers) (0.176 g, 41% yield, mp 122–125 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.45 (m, 10H, Ar*H* of A- and B-isomers), 6.31 (dd, *J*=5.5, 3.0 Hz, 1H, C*H*=CH of B-isomer), 6.20 (dd, *J*=5.5, 3.1 Hz, 1H, C*H*=CH of A-isomer), 5.94 (dd, *J*=5.5, 2.8 Hz, 1H, CH=C*H* of B-isomer), 5.68 (dd, *J*=5.5, 2.9 Hz, 1H, CH=C*H* of A-isomer), 3.82 (app. t, *J*=9.3 Hz, 1H, C*H*SOPh of A-isomer), 3.41 (dd, *J*=9.4, 5.2 Hz, 1H, C*H*SOPh of B-isomer), 2.94 (br s, 1H, C*H*CH=CHCH of B-isomer), 2.84 (br s, 1H, C*H*CH=CHCH of A-isomer), 2.75 (br s, 1H, CHCH=CHC*H* of B-isomer), 2.51 (m, 1H, C*H*HCH$_2$CHSOPh of B-isomer), 2.43–2.30 (m, 2H, C*H*HCH$_2$CHSOPh and CHCH=CHC*H* of A-isomer), 2.28–2.12 (m, 2H, CH*H*CH$_2$CHSOPh of A- and B-isomers), 2.10–1.84 (m, 4H, CH_2CHSOPh of A- and B-isomers), 1.66 (d, *J*=11.8 Hz, 1H, C*H*HCCO of B-isomer), 1.60–1.22 [m, 7H, (CH_2, CH*H*CCO, and CH_2CCO) of A-isomer and (CH_2 and CH*H*CCO) of B-isomer]. ^{13}C NMR (75 MHz, $CDCl_3$) of A-isomer: δ 212.1 (C=O), 140.6 (C), 137.6 (CH), 132.7 (CH), 131.5 (CH), 128.9 (2×CH), 125.3 (2×CH), 69.0 (CH), 56.7 (C), 49.5 (CH), 48.8 (CH_2), 42.7 (CH), 39.8 (CH_2), 35.7 (CH_2), 19.7 (CH_2); B-isomer: δ 213.0 (C=O), 142.7 (C), 138.3 (CH), 132.3 (CH), 131.0 (CH), 129.2 (2×CH), 124.2 (2×CH), 71.0 (CH), 56.9 (C), 51.2 (CH), 49.3 (CH_2), 43.0 (CH), 39.1 (CH_2), 36.5 (CH_2), 17.0 (CH_2). IR (Nujol): ν_{max} 2956s, 1735m, 1476m, 1444m, 1334m, 1238w, 1083m, 1042m, 1024m, 755m, 746m, 721m, 689m cm^{-1}. MS: *m*/*z* (%) relative intensity 286 (M^+, 8), 281 (18), 243 (16), 231 (22), 203 (27), 201 (46), 193 (26), 181 (60), 159 (25), 149 (57), 143 (27), 131 (94), 125 (100), 121 (32), 117 (34), 109 (31), 99 (82), 97 (35), 95 (54), 93 (46), 91 (40), 81 (80), 79 (41), 77 (35), 69 (86), 67 (53). Anal. Calcd for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.64. Found: C, 71.15; H, 6.50.

4.4.2. 2′-Oxo-3′-phenylsulfinylcyclopentane-1′-spiro-2-(3-methylbicyclo[2.2.1]hept-5-ene) (7b). According to the general procedure described for compound **7a**, a diastereomeric mixture of **6b** (0.79 g, 2.28 mmol) was reacted with LDA (5.02 mmol) in THF (7 mL) to give a crude product, which was purified by preparative thin-layer chromatography (silica gel, 20% ethyl acetate in hexanes) to give three bands (PLC_1, PLC_2, and PLC_3) of **7b** (0.548 g, 80% combined yield) as a diastereomeric mixture.

PLC_1 (less polar): a pale yellow solid of a mixture of diastereomers (0.137 g, 20% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.38 (m, Ar*H*), 6.30–6.20 (m, olefinic protons), 6.18–5.98 (m, olefinic protons), 4.10 (m, C*H*SOPh of the minor isomer), 3.30–3.17 [m, (C*H*SOPh and C*H*CH=CHCH) of the major isomer and C*H*SOPh of the minor isomer], 2.86 (br s, C*H*CH=CHCH of the minor isomer), 2.75–2.55 (m, C*H*CH=CHC*H* of the major and minor isomers), 2.54–1.75 [m, CH_2CH$_2$CHSOPh of the major isomer and (CH_2CH$_2$CHSOPh, C*H*H, and CHCH=CHC*H*) of the minor isomer], 1.70 (d, *J*=8.7 Hz, C*H*H of the major isomer), 1.67–0.50 [m, CH_2, (CH_2CHSOPh and C*H*CH_3) of the major and minor isomers], 0.13 (d, *J*=7.3 Hz, CHCH_3 of the minor isomer). IR ($CHCl_3$): ν_{max} 3064w, 3010s, 2969s, 1726s, 1584w, 1478m, 1445m, 1345w, 1317m, 1158m, 1085s, 1048m, 691m, 665m cm^{-1}. MS: *m*/*z* (%) relative intensity 300 (M^+, 2), 251 (5), 235 (9), 217 (8), 175 (33), 157 (15), 149 (10), 147 (10), 133 (9), 129 (13), 125 (12), 110 (13), 109 (100), 105 (18), 97 (16), 93 (25), 91 (46), 81 (27), 79 (54), 77 (59), 66 (13), 65 (23).

PLC_2 (more polar): a pale yellow solid of a mixture of diastereomers (0.158 g, 23% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.35 (m, Ar*H*), 6.30–6.20 (m, olefinic protons), 6.29–6.00 (m, olefinic protons), 5.77 (dd, *J*=5.2, 2.8 Hz, olefinic proton of the major isomer), 5.60 (dd, *J*=5.6, 2.8 Hz, olefinic proton of the minor isomer), 4.01 (d, *J*=9.3 Hz, C*H*SOPh of the minor isomer), 3.90–3.69 (m, C*H*SOPh of the minor isomer), 3.20 (m, C*H*SOPh of the major isomer), 3.02 (br s, C*H*CH=CHCH of the major isomer), 2.90 (br s, C*H*CH=CHCH of the minor isomer), 2.85 (br s, C*H*CH=CHCH of minor isomer), 2.73–1.13 (m, CHCH=CHC*H*, CH_2CH_2CHSOPh, C*H*CH_3 and CH_2 of the major and minor isomers), 1.10–0.63 (m, CHCH_3 of the major and minor isomers), 0.55 (d, *J*=7.2 Hz, CHCH_3 of the minor isomer), 0.35 (d, *J*=7.3 Hz, CHCH_3 of the minor isomer). IR ($CHCl_3$): ν_{max} 3067w, 3010s, 2968s, 1728s, 1584w, 1478m, 1458m, 1445m, 1341w, 1315m, 1150m, 1086s, 1042m, 1023m, 690m cm^{-1}. MS: *m*/*z* (%) relative intensity 300 (M^+, 2), 251 (2), 235 (11), 176 (17), 175 (100), 157 (53), 147 (28), 142 (17), 133 (17), 129 (27), 125 (22), 119 (20), 115 (17), 110 (19), 109 (99), 105 (34), 97 (38), 93 (19), 91 (60), 81 (30), 79 (66), 77 (55), 66 (22), 65 (31).

PLC_3 (most polar): a pale yellow viscous liquid of a 66:34 mixture of two diastereomers (A- and B-isomers) (0.253 g, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.45 (m, 10H, Ar*H* of A- and B-isomers), 6.39 (dd, *J*=5.7, 3.1 Hz, 1H, C*H*=CH of A-isomer), 6.26 (dd, *J*=5.6, 3.1 Hz, 1H, C*H*=CH of B-isomer), 5.76 (dd, *J*=5.7, 2.9 Hz, 1H, CH=C*H* of A-isomer), 5.56 (dd, *J*=5.6, 2.9 Hz, 1H, CH=C*H* of B-isomer), 3.76 (dd, *J*=10.4, 8.9 Hz, 1H, C*H*SOPh of B-isomer), 3.39 (dd, *J*=9.8, 3.3 Hz, 1H, C*H*SOPh of A-isomer), 2.71 (br s, 1H, C*H*CH=CHCH of A-isomer), 2.55–2.47 (m, 3H, C*H*CH=CHCH of A-isomer and CH_2CH$_2$CHSOPh of B-isomer), 2.43–2.23 (m, 4H, CH_2CH$_2$CHSOPh of A-isomer and C*H*CH=CHC*H* of B-isomer), 2.08–1.68 [m, 6H, (CH_2CHSOPh and C*H*CH_3) of A-isomer and (CH_2CHSOPh and C*H*CH_3) of B-isomer], 1.66 (d, *J*=8.9 Hz, 1H, C*H*H of A-isomer), 1.52 (d, *J*=8.8 Hz, 1H, C*H*H of B-isomer), 1.45 (ddd, *J*=8.9, 3.5, 1.7 Hz, 1H, CH*H* of A-isomer), 1.33 (ddd, *J*=8.8, 3.3, 1.7 Hz, 1H, CH*H* of B-isomer), 1.01 (d, *J*=7.2 Hz, 3H, CHCH_3 of A-isomer), 0.93 (d, *J*=7.2 Hz, 3H, CHCH_3 of B-isomer). ^{13}C NMR (100 MHz, $CDCl_3$) of A-isomer: δ 213.6 (CO), 143.7 (C), 139.9 (CH), 131.8 (CH), 131.6 (CH), 129.8 (2×CH), 125.0 (2×CH), 71.3 (CH), 60.0 (C), 52.9 (CH), 51.3 (CH), 47.1 (CH_2), 41.2 (CH), 32.4 (CH_2), 18.8 (CH_2), 18.3 (CH_3); B-isomer: δ 212.4 (CO), 153.2 (C), 138.8 (CH), 132.8 (CH), 132.1 (CH), 129.5 (2×CH), 126.0 (2×CH), 69.7 (CH), 60.0 (C), 51.2 (CH), 51.2 (CH), 46.7 (CH_2), 41.8 (CH), 31.1 (CH_2), 20.9 (CH_2), 18.3 (CH_3). IR ($CHCl_3$): ν_{max} 3066w, 3010s, 2969s, 1726s, 1584w, 1478m, 1464m, 1445m, 1332w, 1154w, 1086m, 1048m, 1024m, 691m cm^{-1}. MS: *m*/*z* (%) relative intensity 300 (M^+, 10), 254 (6), 217 (10), 175 (74), 157 (43), 147 (21), 142 (18), 129 (25), 110 (31), 109 (100), 105 (28), 97 (17), 91 (56), 81 (33), 79 (62), 77 (44), 66 (18), 65 (22). Anal. Calcd for $C_{18}H_{20}O_2S$: C, 71.97; H, 6.71. Found: C, 71.83; H, 6.87.

4.4.3. 2′-Oxo-3′-phenylsulfinylcyclopentane-1′-spiro-2-(3-phenyl-bicyclo[2.2.1]hept-5-ene) (7c). According to the general procedure described for compound **7a**, a 70:30 mixture of *endo*,*exo*- and *endo*,*endo*-**6c** (1.27 g, 3.22 mmol) was reacted with LDA (7.09 mmol) in THF (10 mL) to give a crude product, which was purified by preparative thin-layer chromatography (silica gel, 20% ethyl acetate in hexanes) to give two bands (PLC_1 and PLC_2) of **7c** (0.817 g, 70% combined yield) as a diastereomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$) of a mixture of four diastereomers of **7c** (A-, B-, C-, and D-isomers): δ 7.59–7.36 (m, 20H, SOAr*H*), 7.29–6.88 (m, 20H, Ar*H*), 6.46 (m, 3H, C*H*=CH of A-, B-, and D-isomers), 6.35 (m, 2H, CH=C*H* of A-isomer and C*H*=CH of C-isomer), 5.94 (dd, *J*=5.5, 2.9 Hz, CH=C*H* of D-isomer), 5.88 (dd, *J*=5.6, 2.9 Hz, 1H, CH=C*H* of B-isomer), 5.73 (dd, *J*=5.5, 2.9 Hz, 1H, CH=C*H* of C-isomer), 3.58 (app. t, *J*=9.4 Hz, 1H, C*H*SOPh of C-isomer), 3.39 (dd, *J*=9.3, 4.6 Hz, 1H, C*H*SOPh of B-isomer), 3.33 (d, *J*=2.9 Hz, 1H, C*H*Ph of A-isomer), 3.24–2.82 [m, 10H, C*H*CH=CHC*H* of A-isomer, (C*H*CH=CHCH and C*H*Ph) of B- and C-isomers and (C*H*SOPh, C*H*CH=CHC*H*, and C*H*Ph) of D-isomer], 2.77 (br s, 1H, CHCH=CHC*H* of B-isomer), 2.60 (dd, *J*=9.5, 6.6 Hz, 1H, C*H*SOPh of A-isomer), 2.50 (br s, 1H, CHCH=CHC*H* of C-isomer), 2.43–2.02 (m, 7H, CH_2CO of A-, B-, and C-isomers and C*H*HCO of D-isomer), 1.95 (d, *J*=8.9 Hz, 2H, C*H*H of A- and D-isomers), 1.90–1.12 [m, 16H, (CH*H* and CH_2CHSOPh) of A-isomer, (CH_2 and CH_2CHSOPh) of B- and C-isomers and (CH_2 and CH*H*CH_2CHSOPh) of D-isomer].

PLC_1 (less polar): 0.630 g, 54% yield as a yellow solid of three isomers (A-, B-, and C-isomers). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.32 (m, 15H, SOAr*H*), 7.30–6.88 (m, 15H, Ar*H*), 6.45 (m, 2H, C*H*=CH of A- and B-isomers), 6.35 (m, 2H, CH=C*H* of A-isomer and C*H*=CH of C-isomer), 5.87 (dd, *J*=5.6, 2.8 Hz, CH=C*H* of B-isomer), 5.72 (dd, *J*=5.6, 2.9 Hz, 1H, CH=C*H* of C-isomer), 3.59 (app. t, *J*=9.4 Hz, 1H, C*H*SOPh of C-isomer), 3.38 (dd, *J*=9.3, 4.6 Hz, 1H, C*H*SOPh of B-isomer), 3.33 (d, *J*=2.9 Hz, 1H, C*H*Ph of A-isomer), 3.13–2.86 [m, 6H, C*H*CH=CHC*H* of A-isomer and (C*H*CH=CHCH and C*H*Ph) of B- and C-isomers], 2.76 (br s, 1H, CHCH=CHC*H* of B-isomer), 2.60 (dd, *J*=9.6, 6.6 Hz, 1H, C*H*SOPh of A-isomer), 2.50 (br s, 1H, CHCH=CHC*H* of C-isomer), 2.44–2.02 (m, 6H, CH_2CO of A-, B-, and C-isomers), 1.95 (d, *J*=8.2 Hz, 1H, C*H*H of A-isomer), 1.90–1.10 [m, 11H, (CH*H* and CH_2CHSOPh) of A-isomer and (CH_2 and CH_2CHSOPh) of B- and C-isomers]. IR ($CHCl_3$): ν_{max} 3436w, 3066w, 3012s, 1729s, 1602w, 1498w, 1478w, 1445m, 1332w, 1241m, 1175w, 1153w, 1086m, 1050m, 706m cm^{-1}. MS: *m*/*z* (%) relative intensity 363 (M^+, 1), 298 (3), 297 (14), 237 (16), 236 (4), 219 (3), 173 (5), 172 (31), 171 (100), 170 (10), 169 (30), 153 (20), 141 (11), 129 (11), 128 (14), 115 (13), 91 (7), 78 (7), 66 (4), 65 (6).

PLC_2 (more polar): a pale yellow solid of a pure D-isomer (0.187 g, 16% yield, mp 142–144 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.32 (m, 5H, SOAr*H*), 7.30–6.84 (m, 5H, Ar*H*), 6.44 (dd, *J*=5.4, 3.2 Hz, 1H, C*H*=CH), 5.94 (dd, *J*=5.4, 2.9 Hz, 1H, CH=C*H*), 3.26–3.12 (m, 2H, C*H*CH=CHCH and C*H*SOPh), 3.08 (br s, 1H, CHCH=CHC*H*), 3.00 (br s, 1H, C*H*Ph), 2.39 (m, 1H, C*H*HCH$_2$CHSOPh), 1.95 (d, *J*=8.8 Hz, 1H, C*H*H), 1.67 (d, *J*=8.8 Hz, 1H, CH*H*), 1.45 (m, 1H, CH*H*CH$_2$CHSOPh), 1.40–1.10 (m, 2H, CH_2CHSOPh). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6 (C=O), 142.1 (C), 141.9 (C), 139.3 (CH), 133.7 (CH), 130.8 (CH), 129.1 (2×CH), 128.4 (2×CH), 128.1 (2×CH), 126.2 (CH), 123.8 (2×CH), 70.8 (CH), 61.2 (C), 52.3 (CH), 49.1 (CH), 48.4 (CH), 47.9 (CH_2), 31.5 (CH_2), 14.9 (CH_2). IR ($CHCl_3$): ν_{max} 3066w, 3010m, 1729s, 1602w, 1584w, 1498m, 1478w, 1446m, 1332w, 1242m, 1153m, 1086m, 1051m, 705m cm^{-1}. MS: *m*/*z* (%) relative intensity 363 (M^+, 2), 297 (13), 237 (42), 236 (12), 219 (10), 172 (31), 171 (100), 170 (14), 169 (38), 154 (9), 153 (21), 129 (16), 128 (20), 115 (18), 92 (15), 78 (7), 66 (5), 65 (6). Anal. Calcd for $C_{23}H_{22}O_2S$: C, 76.21; H, 6.12. Found: C, 76.06; H, 6.32.

4.4.4. 2′-Oxo-3′-phenylsulfinylcyclopentane-1′-spiro-2-(3-hydroxymethylbicyclo[2.2.1]hept-5-ene) (7dA) and compound 7dB. According to the general procedure described for compound **7a**, a 90:10 diastereomeric mixture of **6d** (0.442 g, 1.40 mmol) was reacted with LDA (3.08 mmol) in THF (4.5 mL) to give a crude product, which was purified by preparative thin-layer chromatography (silica gel, 70% ethyl acetate in hexanes) to afford two bands (PLC_1 and PLC_2) of products (0.365 g, 82% combined yield).

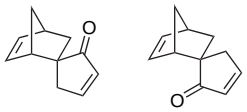
PLC_1 (less polar) was obtained as a colorless solid of a single diastereomer of **7dB** (0.135 g, 30% yield, mp 134–136 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75–7.47 (m, 5H, Ar*H*), 6.57 (dd, *J*=5.6, 3.0 Hz, 1H, C*H*=CH), 6.15 (dd, *J*=5.6, 2.9 Hz, 1H, CH=C*H*), 4.10 (app. t, *J*=8.5 Hz, 1H, C*H*HO), 3.49 (app. t, *J*=8.5 Hz, 1H, CH*H*O), 3.05 (dd, *J*=12.0, 6.1 Hz, 1H, C*H*SOPh), 2.87–2.74 (m, 2H, C*H*CH=CHCH and C*H*CH$_2$O), 2.65 (br s, 1H, O*H*), 2.58 (br s, 1H, CHCH=CHC*H*), 2.00–1.70 (m, 5H, CH_2C*H*HCHSOPh and CH_2), 1.27 (m, 1H, CH*H*CHSOPh). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4 (C), 138.8 (CH), 132.5 (CH), 131.5 (CH), 129.2 (2×CH), 124.5 (2×CH), 112.2 (C–O), 74.6 (CH), 70.7 (CH_2), 68.2 (C), 60.3 (CH), 53.7 (CH_2), 51.6 (CH), 44.3 (CH), 39.4 (CH_2), 23.2 (CH_2). IR (Nujol): ν_{max} 3385m, 3053w, 2956s, 1441m, 1253w, 1242w, 1173w, 1027m, 1013m, 995m, 748m, 700w cm^{-1}. MS: *m*/*z* (%) relative intensity 316 (M^+, 1), 299 (12), 233 (48), 191 (75), 173 (50), 160 (36), 153 (38), 145 (64), 135 (28), 129 (30), 125 (100), 117 (49), 97 (32), 91 (68), 79 (61), 77 (60), 66 (39), 65 (37), 51 (26). HRMS (ESI-TOF) calcd for $C_{18}H_{20}O_3SNa$: 339.1031; found: 339.1031.

PLC_2 (more polar) was obtained as a pale yellow solid of **7dA** (0.231 g, 52% yield) as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.35 (m, Ar*H*), 6.52 (m, an olefinic proton of the minor isomer), 6.40 (dd, *J*=5.6, 3.0 Hz, olefinic proton of the major isomer), 6.27 (m, an olefinic proton of the major isomer), 6.20 (m, an olefinic proton of the minor isomer), 6.15–5.95 (m, olefinic protons of the minor isomer), 4.04 (app. t, *J*=8.6 Hz, C*H*HOH of the major isomer), 3.70 (app. t, *J*=8.8 Hz, C*H*HOH of the minor isomer), 3.50–3.28 (m, CH*H*OH of the major and minor isomers), 3.22 (app. t, *J*=10.7 Hz, C*H*SOPh of the minor isomer), 3.14–2.95 (m, C*H*SOPh of the major and minor isomers), 2.88–2.50 [m, (C*H*CH=CHC*H* and C*H*CH$_2$OH) of the major isomer and C*H*CH=CHC*H* of

the minor isomer], 2.50–2.08 (m, C*H*$_2$CH$_2$CHSOPh, O*H*, and C*H*CH$_2$OH) of the minor isomer and (C*H*HCH$_2$CHSOPh and O*H*) of the major isomer), 2.08–1.45 [m, (CH*H*CH$_2$CHSOPh and C*H*$_2$) of the major and minor isomers], 1.35 (d, *J*=9.4 Hz, CH*H* of the minor isomer). IR (neat): ν_{max} 3419s, 3060m, 2964s, 2874s, 1728s, 1651w, 1583w, 1479s, 1445s, 1341m, 1256s, 1085s, 1046s, 997s, 752s, 695s cm^{-1}. MS: *m*/*z* (%) relative intensity 317 (M$^+$, 4), 299 (13), 233 (38), 191 (86), 173 (53), 160 (32), 153 (33), 145 (59), 135 (23), 131 (23), 126 (29), 125 (100), 117 (44), 107 (28), 97 (26), 92 (68), 79 (62), 77 (39), 66 (28), 65 (28), 51 (19). HRMS (ESI-TOF) calcd for $C_{18}H_{20}O_3SNa$: 339.1031; found: 339.1029.

4.5. Preparation of spirocyclopentenones 8

4.5.1. 2′-Oxocyclopent-3′-ene-1′-spiro-2-bicyclo[2.2.1]-hept-5-ene (8a). A diastereomeric mixture of **7a** (1 g, 3.5 mmol) was dissolved in dry toluene (10 mL) and dry $CaCO_3$ (0.35 g, 3.5 mmol) was added. The mixture was refluxed under an argon atmosphere overnight. The precipitate of $CaCO_3$ was filtered and washed with ethyl acetate. The organic layer was concentrated to give an 88:12 mixture of *endo*- and *exo*-**8a**, which was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to give two fractions of **8a** (0.395 g, 70% combined yield).

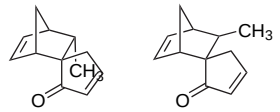


exo-**8a** *endo*-**8a**

The first fraction (less polar) of a 91:9 mixture of *endo*- and *exo*-**8a** was obtained as a pale yellow liquid (45 mg, 8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (td, *J*=5.8, 2.8 Hz, 2H, C*H*=CHCO of *endo*- and *exo*-isomers), 6.38 (dd, *J*=5.6, 3.1 Hz, 1H, C*H*=CH of *exo*-isomer), 6.34 (m, 1H, C*H*=CH of *endo*-isomer), 6.17 [dd, *J*=5.4, 2.9 Hz, 2H, (CH=C*H* and CH=C*H*CO) of *exo*-isomer and CH=C*H*CO of *endo*-isomer], 5.97 (dd, *J*=5.7, 3.1 Hz, 1H, CH=C*H* of *endo*-isomer), 2.94 (br s, 1H, C*H*CH=CHCH of *endo*- and *exo*-isomers), 2.82 (dd, *J*=18.7, 2.8 Hz, 1H, C*H*HCCO of *endo*-isomer), 2.71–2.57 [m, 4H, (C*H*HCH=CHCO and CHCH=CHC*H*) of *exo*- and *endo*-isomers], 2.38 (dd, *J*=19.5, 2.3 Hz, 1H, CH*H*CH=CHCO of *exo*-isomer), 2.28 (d, *J*=8.5 Hz, 1H, C*H*H of *exo*-isomer), 2.12 (dd, *J*=11.4, 3.6 Hz, 1H, C*H*HCCO of *exo*-isomer), 1.69 (dd, *J*=11.5, 3.7 Hz, 1H, C*H*HCCO of *endo*-isomer), 1.59–1.44 (m, 3H, C*H*$_2$ and CH*H*CCO of *endo*-isomer), 1.32 (d, *J*=8.5 Hz, 1H, CH*H* of *exo*-isomer), 1.08 (dd, *J*=11.4, 2.9 Hz, 1H, CH*H*CCO of *exo*-isomer). IR (neat): ν_{max} 3063m, 2964s, 1695s, 1592m, 1475m, 1442m, 1344s, 1307m, 1147s, 1086m, 1016m, 798m, 755m, 723m, 690w, 596w cm^{-1}. MS: *m*/*z* (%) relative intensity 160 (M$^+$, 78), 149 (89), 131 (76), 130 (35), 129 (36), 125 (54), 115 (36), 105 (56), 99 (40), 91 (80), 81 (59), 78 (45), 77 (100), 67 (67), 55 (79).

The second fraction (more polar) of *endo*-**8a** was obtained as a pale yellow liquid (0.35 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (td, *J*=5.9, 2.7 Hz, 1H, C*H*=CHCO), 6.35 (dd, *J*=5.5, 3.0 Hz, 1H, C*H*=CH), 6.16 (td, *J*=5.9, 2.2 Hz, 1H, CH=C*H*CO), 5.99 (dd, *J*=5.5, 2.9 Hz, 1H, CH=C*H*), 2.98 (d, *J*=0.7 Hz, 1H, C*H*CH=CHCH), 2.90 (dd, *J*=19.0, 2.2 Hz, 1H, C*H*HCH=CHCO), 2.73 (dd, *J*=19.0, 2.4 Hz, 1H, CH*H*CH=CHCO), 2.51 (br s, 1H, CHCH=CHC*H*), 1.69 (dd, *J*=11.9, 3.6 Hz, 1H, C*H*HCCO), 1.50 (m, 3H, C*H*$_2$ and CH*H*CCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8 (C=O), 161.0 (CH), 133.6 (CH), 132.6 (CH), 54.6 (CH), 52.4 (C), 50.1 (CH$_2$), 47.2 (CH$_2$), 43.5 (CH), 39.3 (CH$_2$). IR (neat): ν_{max} 3063m, 2964s, 1699s, 1593m, 1475m, 1443m, 1328s, 1309m, 1146s, 1078m, 797m, 753s, 717m, 687s, 595s cm^{-1}. MS: *m*/*z* (%) relative intensity 160 (M$^+$, 4), 159 (15), 141 (28), 131 (11), 125 (100), 115 (8), 109 (21), 97 (23), 95 (28), 91 (10), 77 (56), 65 (21), 51 (18). HRMS (ESI-TOF) calcd for $C_{11}H_{12}ONa$: 183.0786; found: 183.0786.

4.5.2. 2′-Oxocyclopent-3′-ene-1′-spiro-2-(3-methyl-bicyclo[2.2.1]hept-5-ene) (8b). A diastereomeric mixture of **7b** (0.40 g, 1.33 mmol) was dissolved in dry toluene (5 mL) and dry $CaCO_3$ (0.13 g, 1.33 mmol) was added. The mixture was refluxed under an argon atmosphere overnight. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to give two fractions of **8b** (0.174 g, 75% combined yield).



endo,endo-**8b** *endo,exo*-**8b**

The first fraction (less polar) was obtained as a pale yellow liquid of pure *endo*,*endo*-**8b** (21 mg, 19% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (td, *J*=5.9, 2.8 Hz, 1H, C*H*=CHCO), 6.31 (2dd, *J*=5.7, 2.9 Hz, 2H, C*H*=C*H*), 6.06 (td, *J*=5.9, 2.1 Hz, 1H, CH=C*H*CO), 2.90 (td, ABX system, *J*=19.2, 2.4 Hz, 1H, C*H*HCH=CHCO), 2.79 (td, ABX system, *J*=19.2, 2.5 Hz, 1H, CH*H*CH=CHCO), 2.74 (m, 1H, CHCH=CHC*H*), 2.57 (br s, 1H, C*H*CH=CHCH), 2.37 (dq, *J*=7.2, 3.3 Hz, 1H, C*H*CH$_3$), 1.57 (d, *J*=8.4 Hz, 1H, C*H*H), 1.51 (td, *J*=8.4, 1.7 Hz, 1H, CH*H*), 0.84 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.5 (C=O), 161.7 (CH), 136.7 (CH), 135.6 (CH), 135.1 (CH), 55.6 (CH), 50.4 (CH), 50.0 (CH$_2$), 49.7 (CH$_2$), 49.6 (CH), 30.3 (C), 17.0 (CH$_3$). IR ($CHCl_3$): ν_{max} 3064w, 3020m, 2965m, 2876w, 1694s, 1596w, 1448m, 1346m, 1325m, 1261w, 1147s, 1085m, 1014m, 688m, 597s cm^{-1}. MS: *m*/*z* (%) relative intensity 175 (M$^+$+1, 7), 167 (11), 149 (34), 141 (12), 125 (100), 109 (28), 99 (36), 97 (31), 95 (11), 91 (13), 81 (27), 79 (13), 77 (59), 69 (18), 67 (12), 65 (18). HRMS (ESI-TOF) calcd for $C_{12}H_{14}ONa$: 197.0942; found: 197.0943.

The second fraction (more polar) was obtained as a 73:37 mixture of *endo*,*exo*- and *endo*,*endo*-isomers (0.13 g, 56% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.50 (m, 2H, C*H*=CHCO of *endo*,*exo*- and *endo*,*endo*-isomers), 6.34 (dd, *J*=5.6, 3.2 Hz, 1H, C*H*=CH of *endo*,*exo*-isomer), 6.20 (m, 2H, C*H*=C*H* of *endo*,*endo*-isomer), 6.02 (td, *J*=3.6, 2.2 Hz, 1H, CH=C*H*CO of *endo*,*exo*-isomer), 5.96 (td, *J*=3.6, 2.2 Hz, 1H, CH=C*H*CO of *endo*,*endo*-isomer), 5.83 (dd, *J*=5.6,

2.9 Hz, 1H, CH=C*H* of *endo*,*exo*-isomer), 2.90 (dd, *J*=19.0, 2.1 Hz, 1H, C*H*HCH=CHCO of *endo*,*exo*-isomer), 2.80 (dd, *J*=19.2, 2.3 Hz, 1H, C*H*HCH=CHCO of *endo*,*endo*-isomer), 2.74–2.60 (m, 2H, CH*H*CH=CHCO and C*H*CH=CHCH of *endo*,*endo*-isomer), 2.47 (br s, 1H, CHCH=CHC*H* of *endo*,*endo*-isomer), 2.42 (br s, 1H, C*H*CH=CHCH of *endo*,*exo*-isomer), 2.37 (br s, 1H, CHCH=CHC*H* of *endo*,*exo*-isomer), 2.32–2.22 (m, 2H, CH*H*CH=CHCO of *endo*,*exo*-isomer and C*H*CH_3 of *endo*,*endo*-isomer), 1.74 (q, *J*=7.0 Hz, 1H, C*H*CH_3 of *endo*,*exo*-isomer), 1.55–1.33 (m, 4H, CH_2 of *endo*,*exo*- and *endo*,*endo*-isomers), 0.94 (d, *J*=7.0 Hz, 3H, CHCH_3 of *endo*,*exo*-isomer), 0.74 (d, *J*=7.2 Hz, 3H, CHCH_3 of *endo*,*endo*-isomer). IR (neat): ν_{max} 3063m, 2960s, 2873m, 1698s, 1594m, 1449m, 1376w, 1343m, 1200m, 1147s, 1078m, 1016w, 753m, 730m, 688m, 596s cm^{-1}. MS: *m*/*z* (%) relative intensity 175 (M^++1, 28), 174 (M^+, 41), 173 (26), 161 (17), 149 (20), 147 (30), 145 (30), 133 (35), 131 (34), 125 (23), 115 (20), 110 (25), 109 (100), 107 (26), 95 (22), 91 (62), 81 (30), 79 (48), 77 (46), 67 (14), 66 (20), 65 (23), 51 (13).

4.6. Flash vacuum pyrolysis of compounds 6 leading to 5-alkylidene-2-cyclopentenones

4.6.1. 5-Methylene-2-cyclopentenone (9a).[9b] Flash vacuum pyrolysis of a diastereomeric mixture of **7a** (100 mg, 0.35 mmol) (conditions: oven temperature 240 °C; column temperature 375 °C; pressure 0.03 mmHg) gave a crude colorless pyrolysate of **9a** in quantitative yield. Purification of **9a** was unsuccessful due to its rapid decomposition. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (app. t, *J*=3.1 Hz, 1H, C*H*=CHCO), 6.30 (td, *J*=5.7, 3.0 Hz, 1H, CH=C*H*CO), 6.03 (s, 1H, C*H*H=CCO), 5.37 (s, 1H, CH*H*=CCO), 3.17 (s, 2H, CH_2). IR ($CHCl_3$): ν_{max} 3015s, 2970m, 1701s, 1650s, 1582m, 1430m, 1416m, 1344m, 1253m, 1138m, 933m, 909s, 836m, 747m, 697m cm^{-1}. MS: *m*/*z* (%) relative intensity 95 (M^++1, 100).

4.6.2. 5-Ethylidene-2-cyclopentenone (9b).[9c] Flash vacuum pyrolysis of a diastereomeric mixture of **7b** (100 mg, 0.33 mmol) gave a 85:15 mixture of *E*:*Z*-isomers of a crude pyrolysate of **9b**, which was purified by preparative thin-layer chromatography (silica gel, 15% ethyl acetate in hexanes) to give a yellow liquid of the *E*-isomer of **9b** (28 mg, 82% yield). The *Z*-isomer of **9b** was not obtained in pure form. ^{1}H NMR (300 MHz, $CDCl_3$) of the crude product of **9b** containing a mixture of *E*- and *Z*-isomers: δ 7.60–7.00 (m, 7H, C*H*=CHCO of *E*- and *Z*-isomers), 6.63 (q, *J*=6.9 Hz, 1H, C=C*H*CH_3 of *E*-isomer), 6.30 (app. d, *J*=6.0 Hz, 2H, CH=C*H*CO of *E*- and *Z*-isomers), 6.13 (m, 1H, C=C*H*CH_3 of *Z*-isomer), 3.13 (br s, 2H, CH_2 of *E*-isomer), 2.54 (s, 2H, CH_2 of *Z*-isomer), 2.18 (d, *J*=7.3 Hz, 3H, C=CHCH_3 of *Z*-isomer), 1.82 (d, *J*=6.9 Hz, 3H, C=CHCH_3 of *E*-isomer).

(*E*)-**9b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (m, 1H, C*H*=CHCO), 6.59 (q, *J*=7.0 Hz, 1H, C=C*H*CH_3), 6.28 (td, *J*=5.9, 2.1 Hz, 1H, CH=C*H*CO), 3.13 (br s, 2H, CH_2), 1.81 (d, *J*=7.0 Hz, 3H, C=CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2 (C=O), 156.8 (CH), 135.9 (CH), 135.1 (C), 130.7 (CH), 31.8 (CH_2), 15.0 (CH_3). IR (neat): ν_{max} 3058m, 2961m, 2915m, 1699s, 1656s, 1582m, 1440m, 1415m, 1351m, 1272m, 1222s, 1092w, 977w, 940m, 782s, 765s, 737s cm^{-1}. MS: *m*/*z* (%) relative intensity 219 ($2M^+$+2, 9), 218 ($2M^+$+1, 46), 168 (M^++60, 11), 149 (M^++41, 15), 110 (M^++2, 100), 109 (M^++1, 90), 108 (M^+, 23), 95 (15), 91 (17), 81 (40), 79 (67), 77 (42), 66 (21), 65 (23), 51 (13).

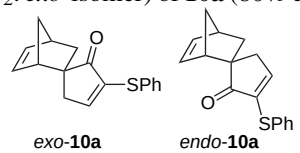
4.6.3. 5-Phenylidene-2-cyclopentenone (9c).[9c] Flash vacuum pyrolysis of PLC_2 of **7c** (100 mg, 0.28 mmol) gave a crude pyrolysate of the (*E*)-isomer of **9c**, which was purified by preparative thin-layer chromatography (silica gel, 15% ethyl acetate in hexanes) to give a pale yellow solid of (*E*)-**9c** (40.5 mg, 85% yield, mp 66–69 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 1H, C*H*Ph), 7.63–7.32 (m, 6H, Ar*H* and C*H*=CHCO), 6.48 (td, *J*=6.0, 2.1 Hz, 1H, CH=C*H*CO), 3.59 (d, *J*=1.7 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5 (C=O), 157.1 (CH), 135.5 (CH), 135.1 (C), 132.3 (C), 132.1 (CH), 130.4 (2×CH), 129.5 (CH), 128.9 (2×CH), 34.3 (CH_2). IR (Nujol): ν_{max} 1688s, 1633s, 1590m, 1572m, 1493m, 1374w, 1292w, 1273m, 1228m, 1186s, 1099m, 950m, 789s, 690m cm^{-1}. MS: *m*/*z* (%) relative intensity 171 (M^++1, 8), 170 (34), 169 (100), 143 (16), 141 (36), 116 (8), 115 (29), 89 (6), 63 (6).

4.6.4. 5-(Hydroxymethyl)methylidene-2-cyclopentenone (9d). Flash vacuum pyrolysis of a mixture of diastereomeric mixture of **7dA** (70 mg, 0.22 mmol) (conditions: oven temperature 250 °C, column temperature 450 °C, pressure 0.05 mmHg) gave a crude pyrolysate of **9d**, which was purified by preparative thin-layer chromatography (silica gel, 40% ethyl acetate in hexanes) to give a pale yellow liquid of a labile (*Z*)-**9d** (8.3 mg, 30% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (m, 1H, C*H*=CHCO), 6.60 (app. t, *J*=5.4 Hz, 1H, C*H*CH_2OH), 6.34 (td, *J*=6.0, 2.2 Hz, 1H, CH=C*H*CO), 4.43 (d, *J*=5.4 Hz, 2H, CH_2OH), 3.23 (s, 2H, CH_2), 1.60 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6 (C=O), 157.6 (CH), 135.8 (CH), 132.6 (C), 129.3 and 129.1 (CH), 60.9 (CH_2OH), 32.2 (CH_2). IR (neat): ν_{max} 3420s, 2964s, 2926s, 1699s, 1447w, 1413w, 1261s, 1091s, 1022s, 800s, 736w cm^{-1}. MS: *m*/*z* (%) relative intensity 125 (M^++1, 21), 124 (M^+, 8), 123 (18), 121 (23), 120 (16), 115 (13), 111 (24), 105 (23), 97 (28), 95 (100), 92 (38), 91 (28), 83 (29), 81 (39), 78 (58), 77 (66), 71 (22), 69 (28), 67 (73), 65 (42), 63 (23), 57 (32), 55 (42), 51 (20). HRMS (ESI-TOF) calcd for $C_7H_8O_2SNa$: 147.0422; found: 147.0424.

4.7. The Pummerer rearrangement of spiro-sulfoxides 6: preparation of spirocyclopentenones 10

4.7.1. 2′-Oxo-3′-phenylsulfanylcyclopent-3′-ene-1′-spiro-2-bicyclo[2.2.1]hept-5-ene (10a). *General procedure*: Trifluoroacetic anhydride (0.08 mL, 0.60 mmol) was added slowly to an acetonitrile solution (3 mL) of an 88:12 diastereomeric mixture of **7a** (0.172 g, 0.6 mmol) under an argon atmosphere at 0 °C. The resulting solution was stirred at 0 °C to room temperature overnight. The mixture was quenched with water (3 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were washed with water, brine and dried over anhyd Na_2SO_4. The organic phase was concentrated and purified by column chromatography to give an 88:12 mixture of *endo*- and *exo*-isomers of **10a**. The mixture of *endo*- and *exo*-**10a** were separated

by preparative thin-layer chromatography (silica gel, 5–10% ethyl acetate in hexanes) to give two fractions (PLC_1: *endo*-isomer and PLC_2: *exo*-isomer) of **10a** (80% combined yield).



exo-**10a** *endo*-**10a**

PLC_1 (less polar) was obtained as a pale yellow solid of *exo*-**10a** (16.7 mg, 10% yield, mp 118–119 °C): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.21 (m, 5H, Ar*H*), 6.83 (t, *J*=2.9 Hz, 1H, C*H*=CSAr), 6.30 (dd, *J*=5.5, 3.0 Hz, 1H, C*H*=CH), 6.06 (dd, *J*=5.5, 2.9 Hz, 1H, CH=C*H*), 2.89 (br s, 1H, C*H*CH=CHCH), 2.68 (br s, 1H, CHCH=CHC*H*), 2.47 (dd, *J*=19.4, 3.1 Hz, 1H, C*H*HCH=CSAr), 2.30–2.15 (m, 2H, CH*H*CH=CSAr and C*H*H), 2.10 (dd, *J*=11.4, 3.6 Hz, 1H, C*H*HCCO), 1.26 (d, *J*=8.5 Hz, 1H, CH*H*), 1.03 (dd, *J*=11.4, 2.9 Hz, 1H, CH*H*CCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5 (C=O), 153.1 (CH), 141.2 (C), 140.8 (CH), 135.2 (CH), 133.3 (2×CH), 131.3 (C), 129.4 (2×CH), 128.4 (CH), 53.7 (C), 51.3 (CH), 46.8 (CH_2), 43.2 (CH), 42.9 (CH_2), 41.6 (CH_2). IR ($CHCl_3$): ν_{max} 3064w, 3012m, 2967m, 1698s, 1630m, 1582m, 1477m, 1441m, 1373m, 1301m, 1276m, 1025m, 991w, 692m cm^{-1}. MS: *m*/*z* (%) relative intensity 268 (M^+, 42), 235 (5), 219 (13), 218 (15), 204 (20), 203 (100), 202 (16), 174 (11), 173 (13), 167 (14), 149 (20), 141 (11), 129 (13), 97 (24), 91 (9), 77 (9), 65 (18).

PLC_2 (more polar) was obtained as a pale yellow solid of *endo*-**10a** (0.112 g, 70% yield, mp 128–130 °C): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.27 (m, 5H, Ar*H*), 6.92 (t, *J*=2.9 Hz, 1H, C*H*=CSAr), 6.34 (dd, *J*=5.4, 3.1 Hz, 1H, C*H*=CH), 5.97 (dd, *J*=5.4, 2.9 Hz, 1H, CH=C*H*), 2.98 (br s, 1H, C*H*CH=CHCH), 2.82 (dd, *J*=18.7, 2.7 Hz, 1H, C*H*HCH=CSAr), 2.64 (dd, *J*=18.7, 3.2 Hz, 1H, CH*H*CH=CSAr), 2.58 (br s, 1H, CHCH=CHC*H*), 1.71 (dd, *J*=11.5, 3.7 Hz, 1H, C*H*HCCO), 1.60–1.40 (m, 3H, CH_2 and CH*H*CCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2 (C=O), 151.8 (CH), 141.8 (C), 138.2 (CH), 133.3 (CH), 132.5 (2×CH), 131.3 (C), 129.4 (2×CH), 128.3 (CH), 54.9 (CH), 53.6 (C), 49.9 (CH_2), 45.7 (CH_2), 43.6 (CH), 39.8 (CH_2). IR (Nujol): ν_{max} 3059w, 1699s, 1577m, 1468m, 1283m, 1273m, 1021m, 992m, 758m, 693m, 634w cm^{-1}. MS: *m*/*z* (%) relative intensity 270 (M^++2, 19), 269 (M^++1, 79), 268 (M^+, 100), 235 (7), 203 (53), 202 (15), 174 (21), 173 (24), 159 (14), 158 (17), 141 (10), 129 (11), 115 (5), 97 (15), 91 (9), 65 (7). Anal. Calcd for $C_{17}H_{16}OS$: C, 76.08; H, 6.01. Found: C, 75.75; H, 6.02.

4.7.2. 2′-Oxo-3′-phenylsulfanylcyclopent-3′-ene-1′-spiro-2-(3-methylbicyclo[2.2.1]hept-5-ene) (10b). According to the general procedure described for compound **10a**, the reaction of a diastereomeric mixture of **7b** (0.20 g, 0.66 mmol) with an acetonitrile solution (3 mL) of trifluoroacetic anhydride (0.08 mL, 0.60 mmol) gave a crude product of a 34:44:13:9 mixture of isomers of **10b**. It was purified by preparative thin-layer chromatography (silica gel, 5–10% ethyl acetate in hexanes) to give three fractions (PLC_1, PLC_2, and PLC_3) of **10b** (0.138 g, 74% combined yield). A mixture of *endo*,*endo*- and *endo*,*exo*-isomers (A- and B-isomers) and *exo*,*exo*- and *exo*,*endo*-isomers (C- and D-isomers) of **10b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.20 (m, 20H, Ar*H*), 6.95 (t, *J*=3.0 Hz, 1H, C*H*=CSAr of B-isomer), 6.92–6.85 (m, 3H, C*H*=CSAr of A-, C-, and D-isomers), 6.42 (dd, *J*=5.6, 3.0 Hz, 2H, C*H*=CH of B- and D-isomers), 6.37–6.19 (m, 4H, C*H*=C*H* of A- and C-isomers), 6.12 (m, 1H, CH=C*H* of D-isomer), 5.90 (dd, *J*=5.6, 2.8 Hz, 1H, CH=C*H* of B-isomer), 2.81 (dd, *J*=18.8, 2.8 Hz, 1H, C*H*HCH=CSAr of B-isomer), 2.86–1.92 [m, 19H, (CH_2CH=CSAr, C*H*CH=CHC*H*, and C*H*CH_3) of A-isomer, (CH*H*CH=CSAr and C*H*CH=CHC*H*) of B-isomer, (CH_2CH=CSAr, C*H*CH=CHC*H*, C*H*CH_3, and C*H*H) of C-isomer and (CH_2CH=CSAr, C*H*CH=CHC*H*, and C*H*CH_3) of D-isomer], 1.87 (q, *J*=7.5 Hz, 1H, C*H*CH_3 of B-isomer), 1.70–1.20 (m, 7H, CH_2 of A-, B-, and D-isomers and CH*H* of C-isomer), 1.04 (d, *J*=7.5 Hz, 3H, CHC*H*$_3$ of B-isomer), 0.94 (d, *J*=7.8 Hz, 3H, CHC*H*$_3$ of D-isomer), 0.85 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$ of A-isomer), 0.76 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$ of C-isomer).

exo,*exo*-**10b**(C) *exo*,*endo*-**10b**(D)

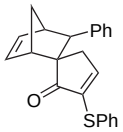
PLC_1 (less polar) was obtained as a yellow liquid of a 1.5:1 mixture of *exo*,*exo*- and *exo*,*endo*-diastereomers (C- and D-isomers) (37 mg, 20% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10H, Ar*H* of C- and D-isomers), 6.84 (t, *J*=3.0 Hz, 1H, C*H*=CSAr of C-isomer), 6.80 (t, *J*=3.0 Hz, 1H, C*H*=CSAr of D-isomer), 6.34 (dd, *J*=5.6, 3.1 Hz, 1H, C*H*=CH of D-isomer), 6.26 (dd, *J*=5.4, 3.0 Hz, 1H, C*H*=CH of C-isomer), 6.14 (dd, *J*=5.4, 3.1 Hz, 1H, CH=C*H* of C-isomer), 6.04 (dd, *J*=5.6, 2.9 Hz, 1H, CH=C*H* of D-isomer), 2.72–2.61 (m, 4H, C*H*CH=CHC*H* of C- and D-isomers), 2.49–2.28 (m, 4H, C*H*HCH=CSAr and C*H*CH_3 of C- and D-isomers), 2.28–2.17 (m, 2H, C*H*H of C-isomer and CH*H*CH=CSAr of D-isomer), 2.08 (dd, *J*=19.5, 3.1 Hz, 1H, CH*H*CH=CSAr of C-isomer), 1.56 (d, *J*=7.3 Hz, 1H, C*H*H of D-isomer), 1.31 (d, *J*=7.3 Hz, 1H, CH*H* of D-isomer), 1.24 (d, *J*=8.6 Hz, 1H, CH*H* of C-isomer), 0.96 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$ of D-isomer), 0.66 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$ of C-isomer). IR ($CHCl_3$): ν_{max} 3064w, 2966m, 1695s, 1630w, 1583w, 1477m, 1441m, 1374m, 1302w, 1261m, 1087w, 1024w, 691m cm^{-1}. MS: *m*/*z* (%) relative intensity 282 (M^+, 44), 218 (16), 217 (100), 216 (22), 188 (12), 173 (15), 111 (10), 110 (18), 91 (6), 79 (8), 77 (7), 66 (6), 65 (6).

PLC_2 (more polar) was obtained as a yellow solid of *endo*,*endo*-**10b** (A-isomer) (53 mg, 28% yield, mp 65–66 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.20 (m, 5H, Ar*H*), 6.82 (t, *J*=2.9 Hz, 1H, C*H*=CSAr), 6.27–6.15 (m, 2H, C*H*=C*H*), 2.75 (dd, *J*=19.0, 2.9 Hz, 1H, C*H*HCH=CSAr), 2.68–2.56 (m, 2H, C*H*CH=CHCH and CH*H*CH=CSAr), 2.54 (br s, 1H, CHCH=CHC*H*), 2.30 (dq, *J*=7.1, 3.2 Hz, 1H, C*H*CH_3), 1.45 (m, 2H, CH_2), 0.77 (d, *J*=7.1 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.8 (C=O), 152.0 (CH), 142.3 (C), 135.7 (CH), 135.2 (CH), 133.5 (2×CH), 131.3 (C), 129.3 (2×CH), 128.3 (CH), 57.2 (C), 55.2 (CH), 50.0 (CH), 49.1 (CH_2), 49.0 (CH), 47.3 (CH_2), 16.3 (CH_3). IR (neat): ν_{max} 3061m, 2961s, 1699s, 1622s, 1583m, 1477m, 1440m, 1373m,

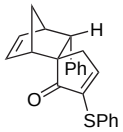
1299m, 1146m, 1024m, 990m, 743m, 692m cm^{-1}. MS: *m*/*z* (%) relative intensity 282 (M^+, 100), 249 (13), 232 (15), 218 (15), 217 (75), 216 (59), 188 (32), 183 (23), 173 (40), 111 (26), 110 (63), 91 (22), 79 (16), 77 (25), 66 (18), 65 (14).

PLC_3 (most polar) was obtained as a yellow solid of *endo*,*exo*-**10b** (B-isomer) (49 mg, 26% yield, mp 86–87 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.28 (m, 5H, Ar*H*), 6.96 (t, *J*=3.0 Hz, 1H, C*H*=CSAr), 6.41 (dd, *J*=5.5, 3.0 Hz, 1H, C*H*=CH), 5.89 (dd, *J*=5.5, 2.8 Hz, 1H, CH=C*H*), 2.90 (dd, *J*=18.9, 2.7 Hz, 1H, C*H*HCH=CSAr), 2.52 (br s, 2H, C*H*CH=CHC*H*), 2.28 (dd, *J*=18.9, 3.2 Hz, 1H, C*H*HCH=CSAr), 1.87 (dq, *J*=7.3, 1.6 Hz, 1H, C*H*CH_3), 1.58 (d, *J*=8.7 Hz, 1H, C*H*H), 1.46 (dd, *J*=8.7, 1.6 Hz, 1H, CH*H*), 1.03 (d, *J*=7.3 Hz, 3H, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5 (C=O), 152.5 (CH), 141.2 (C), 139.1 (CH), 133.1 (2×CH), 131.8 (CH), 131.4 (C), 129.3 (2×CH), 128.3 (CH), 56.8 (C), 56.6 (CH), 51.0 (CH), 47.3 (CH_2), 41.6 (CH), 39.5 (CH_2), 18.7 (CH_3). IR (Nujol): ν_{max} 3056w, 1695s, 1577m, 1456s, 1279m, 1020w, 1000w, 833m, 758m, 733m, 697m cm^{-1}. MS: *m*/*z* (%) relative intensity 282 (M^+, 100), 249 (9), 218 (17), 217 (94), 216 (48), 188 (21), 173 (30), 112 (21), 110 (28), 91 (11), 80 (11), 77 (11), 66 (9), 65 (7). HRMS (ESI-TOF) calcd for $C_{18}H_{18}OSNa$: 305.0976; found: 305.0976.

4.7.3. 2′-Oxo-3′-phenylsulfanylcyclopent-3′-ene-1′-spiro-2-(3-phenylbicyclo[2.2.1]hept-5-ene) (10c). According to the general procedure described for compound **10a**, the reaction of a diastereomeric mixture of **7c** (0.281 g, 0.78 mmol) with an acetonitrile solution (4 mL) of trifluoroacetic anhydride (0.10 mL, 0.78 mmol) gave a 78:22 mixture of *endo*,*exo*- and *endo*,*endo*-isomers of **10c**. The mixture of isomers was separated by preparative thin-layer chromatography (silica gel, 5–10% ethyl acetate in hexanes) to give two fractions (PLC_1 and PLC_2) of **10c** (0.208 g, 78% combined yield). A mixture of *endo*,*exo*- and *endo*,*endo*-**10c**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–6.90 [m, 21H, (Ar*H* and SAr*H*) of *endo*,*exo*-isomer and (Ar*H*, C*H*=CSAr, and SAr*H*) of *endo*,*endo*-isomer], 6.72 (t, *J*=3.0 Hz, 1H, C*H*=CSAr of *endo*,*exo*-isomer), 6.54–6.45 (m, 2H, C*H*=CH of *endo*,*exo*- and *endo*,*endo*-isomers), 6.21 (dd, *J*=5.6, 3.1 Hz, 1H, CH=C*H* of *endo*,*endo*-isomer), 6.04 (dd, *J*=5.5, 2.8 Hz, 1H, CH=C*H* of *endo*,*exo*-isomer), 3.68 (d, *J*=3.0 Hz, 1H, C*H*Ar of *endo*,*endo*-isomer), 3.18 (br s, 1H, C*H*CH=CHCH of *endo*,*endo*-isomer), 3.15–2.99 [m, 3H, (C*H*Ar and C*H*CH=CHCH) of *endo*,*exo*-isomer and C*H*HCH=CSAr of *endo*,*endo*-isomer), 2.85 (dd, *J*=19.1, 3.2 Hz, 1H, CH*H*CH=CSAr of *endo*,*endo*-isomer), 2.63 (br s, 2H, CHCH=CHC*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 2.15–1.94 (2dd, *J*=20.3, 2.8 Hz, 2H, CH_2CH=CSAr of *endo*,*exo*-isomer), 1.85 (d, AB system, *J*=8.6 Hz, 1H, C*H*H of *endo*,*exo*-isomer), 1.68 (d, *J*=8.7 Hz, 2H, CH*H* of *endo*,*exo*- and *endo*,*endo*-isomers), 1.59 (d, *J*=8.6 Hz, 1H, CH*H* of *endo*,*endo*-isomer).



endo,*exo*-**10c**

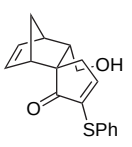


endo,*endo*-**10c**

PLC_1 (less polar) was obtained as a yellow solid of *endo*,*exo*-**10c** (0.154 g, 57% yield, mp 95–98 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–6.90 (m, 10H, Ar*H* and SAr*H*), 6.73 (t, *J*=3.0 Hz, 1H, C*H*=CSAr), 6.49 (dd, *J*=5.5, 3.3 Hz, 1H, C*H*=CH), 6.05 (dd, *J*=5.5, 2.8 Hz, 1H, CH=C*H*), 3.08 (br s, 1H, C*H*CH=CHCH), 3.02 (s, 1H, C*H*Ar), 2.64 (br s, 1H, CHCH=CHC*H*), 2.15–1.98 (2dd, *J*=20.7, 2.7 Hz, 2H, CH_2CH=CSAr), 1.85 (d, *J*=8.6 Hz, 1H, C*H*H), 1.66 (dd, *J*=8.6, 1.6 Hz, 1H, CH*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2 (C=O), 153.7 (CH), 142.3 (C), 141.0 (C), 139.7 (CH), 133.6 (CH), 133.1 (2×CH), 131.4 (C), 129.3 (2×CH), 128.6 (2×CH), 128.3 (CH), 127.7 (2×CH), 126.3 (CH), 58.2 (C), 55.4 (CH), 54.1 (CH), 49.4 (CH_2), 48.4 (CHAr), 40.9 (CH_2). IR (Nujol): ν_{max} 3055w, 1695s, 1580m, 1456s, 1274m, 1023m, 1005w, 839m, 751m, 734m, 702m cm^{-1}. MS: *m*/*z* (%) relative intensity 344 (M^+, 31), 279 (15), 278 (52), 277 (27), 173 (15), 170 (19), 169 (100), 142 (14), 141 (47), 129 (9), 116 (14), 115 (25), 91 (10), 65 (4).

PLC_2 (more polar) was obtained as a pale yellow solid of *endo*,*endo*-**10c** (54 mg, 20% yield, mp 118–120 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–6.95 (m, 11H, Ar*H*, SAr*H* and C*H*=CSAr), 6.57 (dd, *J*=5.3, 2.9 Hz, 1H, C*H*=CH), 6.28 (dd, *J*=5.3, 3.2 Hz, 1H, CH=C*H*), 3.74 (d, *J*=2.5 Hz, 1H, C*H*Ar), 3.26 (br s, 1H, C*H*CH=CHCH), 3.16 (dd, *J*=19.1, 2.8 Hz, 1H, C*H*HCH=CSAr), 2.91 (dd, *J*=19.1, 3.1 Hz, 1H, CH*H*CH=CSAr), 2.64 (br s, 1H, CHCH=CHC*H*), 1.74 (d, *J*=8.5 Hz, 1H, C*H*H), 1.65 (d, *J*=8.5 Hz, 1H, CH*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0 (C=O), 151.8 (CH), 142.5 (C), 140.4 (C), 135.8 (CH), 135.3 (CH), 132.7 (2×CH), 131.5 (C), 129.2 (2×CH), 128.6 (2×CH), 127.9 (CH), 127.8 (2×CH), 126.1 (CH), 61.3 (CH), 59.6 (C), 55.5 (CH), 49.9 (CH_2), 48.1 (CHAr), 47.7 (CH_2). IR (neat): ν_{max} 3060s, 3025s, 2959s, 2247w, 2053w, 1952w, 1885w, 1714s, 1695s, 1682s, 1582s, 1496s, 1479s, 1441s, 1339s, 1277s, 1190m, 1147m, 1024m, 911m, 741s, 701s cm^{-1}. MS: *m*/*z* (%) relative intensity 344 (M^+, 2), 280 (6), 279 (21), 278 (75), 173 (14), 170 (19), 169 (100), 142 (14), 141 (40), 129 (9), 116 (11), 115 (25), 91 (10), 65 (5). Anal. Calcd for $C_{23}H_{20}OS$: C, 80.20; H, 5.85. Found: C, 79.97; H, 5.71.

4.7.4. 2′-Oxo-3′-phenylsulfanylcyclopent-3′-ene-1′-spiro-2-(3-hydroxymethyl)bicyclo[2.2.1]hept-5-ene (10d). According to the general procedure described for compound **10a**, the reaction of a mixture of **7dA** and **7dB** (0.316 g, 1 mmol) with an acetonitrile solution (5 mL) of trifluoroacetic anhydride (0.13 mL, 1 mmol) gave a crude product, which was purified by preparative thin-layer chromatography (silica gel, 5–10% ethyl acetate in hexanes) to give a pure white solid of **10d** (0.232 g, 78% yield, mp 150–152 °C).



^1H NMR (400 MHz, $CDCl_3$): δ 7.58–7.33 (m, 5H, Ar*H*), 7.00 (t, *J*=3.0 Hz, 1H, C*H*=CSAr), 6.33 (dd, *J*=5.6, 3.2 Hz, 1H, C*H*=CH), 6.18 (dd, *J*=5.6, 2.8 Hz, 1H, CH=C*H*), 3.60 (m, 2H, CHCH_2OH), 2.96–2.92 (m, 2H,

C*H*CH=CHCH, and C*H*HCH=CSAr), 2.75 (dd, *J*=18.8, 3.2 Hz, 1H, CH*H*CH=CSAr), 2.64 (br s, 1H, CHCH=CHC*H*), 2.56 (ddd, *J*=9.2, 5.5, 3.1 Hz, 1H, C*H*CH_2OH), 2.05 (br s, 1H, O*H*), 1.63–1.56 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6 (C=O), 153.5 (CH), 142.3 (C), 136.5 (CH), 135.2 (CH), 133.8 (2×CH), 132.0 (C), 130.0 (2×CH), 129.0 (CH), 63.4 (CH_2), 58.7 (CH), 56.9 (C), 56.0 (CH), 50.1 (CH_2), 47.9 (CH_2), 46.4 (CH). IR ($CHCl_3$): ν_{max} 3456m, 3026s, 3013s, 2971s, 1695s, 1583m, 1476m, 1441m, 1339m, 1305m, 1281m, 1025s, 833s, 692m cm^{-1}. MS: *m*/*z* (%) relative intensity 298 (M^+, 8), 268 (32), 267 (25), 203 (17), 190 (30), 186 (18), 171 (23), 158 (100), 157 (58), 147 (10), 144 (14), 130 (18), 129 (54), 128 (33), 115 (19), 110 (16), 105 (9), 91 (16), 77 (15), 66 (17), 65 (18). HRMS (ESI-TOF) calcd for $C_{18}H_{18}O_2SNa$: 321.0925; found: 321.0927.

4.8. Flash vacuum pyrolysis of compounds 10 leading to cyclopentenones 11

4.8.1. 5-Methylidene-2-phenylsulfanyl-2-cyclopentenone (11a). Flash vacuum pyrolysis of a 87:13 mixture of *endo*- and *exo*-**10a** (51 mg, 0.19 mmol) gave a crude pyrolysate, which was purified by preparative thin-layer chromatography (silica gel, 5–7% ethyl acetate in hexanes) to give a pale yellow solid of **11a** (39 mg, 93% yield, mp 76–78 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.30 (m, 5H, Ar*H*), 6.85 (dt, *J*=2.9, 0.9 Hz, 1H, C*H*=CSAr), 6.18 (m, *J*=0.9 Hz, 1H, C*H*H=CCO), 5.49 (app. d, *J*=0.9 Hz, 1H, CH*H*=CCO), 3.20 (td, *J*=2.8, 1.5 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5 (C=O), 148.2 (CH), 145.0 (C), 140.6 (C), 133.9 (2×CH), 130.5 (C), 129.5 (2×CH), 128.7 (CH), 118.6 (CH_2), 32.9 (CH_2). IR (Nujol): ν_{max} 2727w, 1699s, 1646m, 1581m, 1307m, 1282m, 1024m, 838w, 742s, 691s cm^{-1}. MS: *m*/*z* (%) relative intensity 204 (M^++2, 8), 203 (M^++1, 28), 202 (M^+, 100), 201 (18), 174 (25), 173 (48), 141 (11), 129 (11), 97 (42), 65 (12). HRMS (ESI-TOF) calcd for $C_{12}H_{11}OS$: 203.0531; found: 203.0531.

4.8.2. 5-Ethylidene-2-phenylsulfanyl-2-cyclopentenone (11b). Flash vacuum pyrolysis of a pure diastereomer of **10b** obtained from PLC_3 (47.4 mg, 0.168 mmol) gave a crude pyrolysate, which was purified by preparative thin-layer chromatography (silica gel, 5–7% ethyl acetate in hexanes) to give a pale yellow solid of (*E*)-isomer of **11b** (45.4 mg, 96% yield, mp 66–68 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.30 (m, 5H, Ar*H*), 6.80–6.65 (m, 2H, C*H*=CSAr and C=C*H*CH_3), 3.13 (br s, 2H, CH_2), 1.90 (d, *J*=7.1 Hz, 3H, C=CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3 (C=O), 146.8 (CH), 144.9 (C), 134.9 (C), 133.7 and 133.7 (2×CH), 132.4 and 132.3 (CH), 131.0 and 130.9 (C), 129.5 and 129.4 (2×CH), 128.53 and 128.49 (CH), 30.9 (CH_2), 15.1 and 15.0 (CH_3). IR (neat): ν_{max} 2925m, 1696s, 1658s, 1651s, 1475w, 1440m, 1378m, 1263m, 1087w, 1024m, 865m, 740m, 690m cm^{-1}. MS: *m*/*z* (%) relative intensity 218 (M^++2, 18), 217 (M^++1, 36), 216 (M^+, 100), 188 (34), 183 (23), 173 (47), 155 (16), 149 (15), 111 (31), 110 (74), 79 (18), 78 (17), 77 (43), 66 (14), 65 (15). HRMS (ESI-TOF) calcd for $C_{13}H_{13}OS$: 217.0687; found: 217.0687.

4.8.3. 5-Phenylidene-2-phenylsulfanyl-2-cyclopentenone (11c). Flash vacuum pyrolysis of a 78:22 mixture of *endo*,*exo*- and *endo*,*endo*-**10c** (100 mg, 0.29 mmol) gave a 86:14 mixture of (*E*)- and (*Z*)-**11c**. The crude product was purified by preparative thin-layer chromatography (silica gel, 5–7% ethyl acetate in hexanes) to give a pale yellow solid of (*E*)-**11c** (60 mg, 76% yield, mp 104–105 °C). A mixture of (*E*)- and (*Z*)-**11c** of the crude product: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.00 (m, 22H, Ar*H*, SAr*H* and C=C*H*Ar of *E*- and *Z*-isomers), 6.78 (app. t, *J*=2.6 Hz, 1H, ArSC=C*H* of *E*-isomer), 6.69 (app. s, 1H, ArSC=C*H* of *Z*-isomer), 3.44 (m, 2H, CH_2 of *E*- and *Z*-isomers).

(*E*)-**11c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.17 (m, 11H, Ar*H*, SAr*H* and C=C*H*Ar), 6.75 (m, 1H, C*H*=CSAr), 3.39 (app. t, *J*=2.2 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5 (C=O), 146.9 (CH), 144.6 (C), 134.9 (C), 133.8 (2×CH), 133.1 (CH), 131.9 (CH), 130.6 (C), 130.5 (2×CH), 129.7 (CH), 129.5 (2×CH), 128.9 (2×CH), 128.6 (CH), 33.4 (CH_2). IR (Nujol): ν_{max} 1687m, 1637m, 1568w, 1449m, 1285m, 1181m, 916m, 771m, 758m, 747m, 690m cm^{-1}. MS: *m*/*z* (%) relative intensity 280 (M^++2, 35), 279 (M^++1, 23), 278 (M^+, 100), 277 (17), 250 (9), 234 (13), 218 (15), 178 (27), 173 (33), 171 (38), 169 (78), 167 (17), 149 (15), 110 (15). HRMS (ESI-TOF) calcd for $C_{18}H_{14}OSNa$: 301.0663; found: 301.0663.

4.8.4. 5-(Hydroxymethyl)methylidene-2-phenylsulfanyl-2-cyclopentenone (11d). Flash vacuum pyrolysis of **10d** (100 mg, 0.29 mmol) (conditions: oven temperature 240 °C, column temperature 425 °C, pressure 0.05 mmHg) gave a crude pyrolysate, which was purified by preparative thin-layer chromatography (silica gel, 15% ethyl acetate in hexanes) to give a pale yellow liquid of (*Z*)-**11d** (13.5 mg, 20% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.25 (m, 5H, Ar*H*), 6.72 (s, 1H, C*H*=CSAr), 6.58 (t, *J*=6.1 Hz, 1H, C=C*H*CH_2OH), 4.71 (d, *J*=6.1 Hz, 2H, C=CHC*H*$_2$OH), 3.15 (s, 2H, CH_2), 1.60 (br s, 1H, O*H*). HRMS (ESI-TOF) calcd for $C_{13}H_{12}O_2SNa$: 255.0456; found: 255.0461.

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JOC*Note*

Morita−Baylis−Hillman Reaction of Masked 5-Alkylidene-2-cyclopentenones: General Entry to 5-Alkylidene-2-(hydroxyalkyl)-2-cyclopentenones

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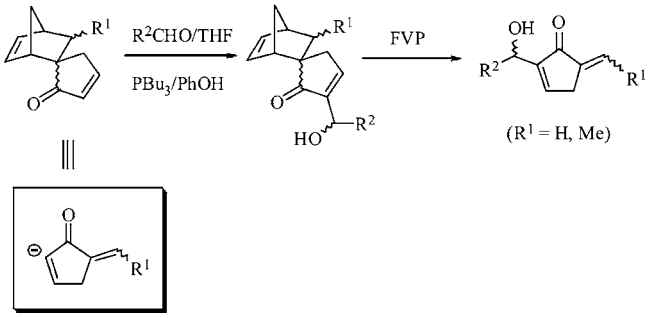
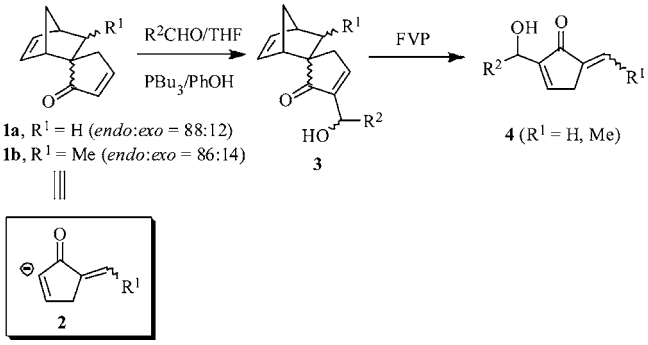


The reaction of masked 5-alkylidene-2-cyclopentenones with aldehydes catalyzed by tributylphosphine in the presence of phenol provided the corresponding Morita−Baylis−Hillman adducts, which were subjected to flash vacuum pyrolysis to afford 5-alkylidene-2-(hydroxyalkyl)-2-cyclopentenones.

The Morita−Baylis−Hillman (MBH) reaction is one of the most versatile carbon−carbon bond forming reactions at the α-carbon of activated alkenes with various types of electrophiles, providing a convenient method for the synthesis of α-functionalized activated alkenes.[1] A considerable amount of effort has been devoted to the improvement of reaction conditions, employing a wide range of organocatalysts such as DABCO, DBU, phosphines, and Lewis acids, which allow the MBH reaction to be applied with a broad range of activated alkenes and electrophiles.[2] Moreover, the MBH reaction has been applied to catalytic asymmetric synthesis using a chiral catalyst.[3] The MBH adducts have also proven to be versatile precursors for further synthetic transformation.[4]

It is anticipated that a general entry to 5-alkylidene-2-(hydroxyalkyl)-2-cyclopentenones of the type **4** could be achieved by utilizing the spiro-cyclopentenone **1**[5] as a carbanion synthon **2**. The reaction of **1** with aldehydes, using MBH-type reaction conditions followed by pyrolysis, would give the highly functionalized cyclopentenones **4** (Scheme 1), which may be used as useful precursors for further synthetic manipulation leading to highly substituted cyclopentanoid natural products.

SCHEME 1. Preparation of 5-Alkylidene-2-(hydroxyalkyl)-2-cyclopentenones 4 by the MBH Reactions of 1a and 1b with Aldehydes Followed by FVP



To the best of our knowledge, there have been no reports on utilizing such a synthon for the preparation of this type of compound previously. The use of tertiary phosphines as Lewis bases has been described previously.[2a,b,e,m,6] In general, the reactions proceed completely in a short period of time. Initially,

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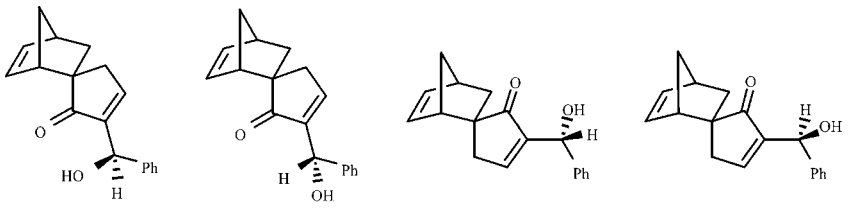
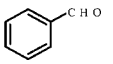
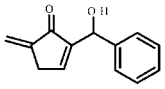
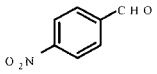
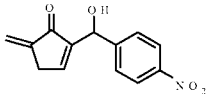
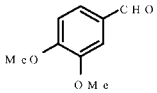
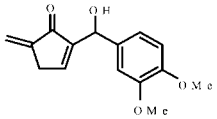
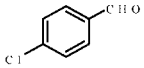
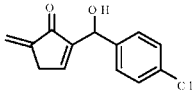
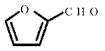
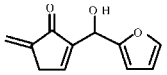
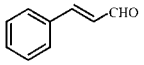
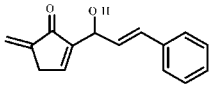
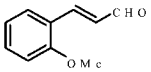
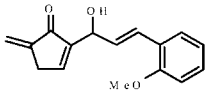
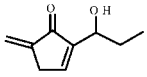
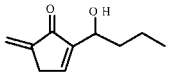
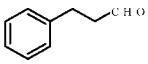
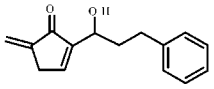


FIGURE 1. Diastereomers of *endo*-**3a** (A and B) and *exo*-**3a** (C and D) obtained from the MBH reaction of **1a** (*endo*:*exo* = 88:12) with benzaldehyde.

TABLE 1. Preparation of Compounds 3 by the MBH Reaction of 1a with Aldehydes Catalyzed by PBu_3 in the Presence of Phenol in THF and Their FVP to Highly Functionalized Cyclopentenones 4

Entry	RCHO	**3** (% yield)[a,b]		**4** (% yield)[a]
1		**3a** (82)		**4a** (86)[c]
2		**3b** (60)		**4b** (68)[c]
3		**3c** (80)		**4c** (70)
4		**3d** (78)		**4d** (75)[c]
5		**3e** (75)		**4e** (80)[c]
6		**3f** (74)		**4f** (49)
7		**3g** (73)		**4g** (45)
8		**3h** (74)		**4h** (76)[c]
9		**3i** (80)		**4i** (85)[c]
10		**3j** (74)		**4j** (82)[c]

[a] Yields refer to the purified products. [b] Obtained as mixtures of diastereomers of endo- and exo-isomers. [c] Quantitative yield of the crude product was obtained.

the reaction of **1a** (endo/exo isomers = 88:12) with benzaldehyde (1.5 equiv) in the presence of 20 mol % PBu_3[6] as an organocatalyst and 20 mol % phenol[7] at room temperature for 1 h gave mainly the starting materials and a small amount of the expected MBH adduct. Fortunately, the reaction performed at the same temperature overnight (15 h) afforded the expected MBH adduct **3a** (R^2 = Ph) in 82% yield after chromatography as a 46:42:12:trace mixture of diastereomers, presumably *endo*-**3a** (Figure 1A), *endo*-**3a** (Figure 1B), *exo*-**3a** (Figure 1C), and *exo*-**3a** (Figure 1D), respectively (Figure 1). To further probe the scope of the reaction, **1** was reacted with various aliphatic and aromatic aldehydes including unsaturated aldehydes. Thus, the MBH adducts **3b**−**j** were prepared in good yield by employing standard conditions. The results are summarized in Table 1. In all cases, the reactions provided mixtures of four diastereomers as indicated in Figure 1. Separation of these diastereomers was not attempted because they were expected to lead to the same 2-(hydroxyalkyl)-5-methylene-2-cyclopentenones **4** after flash vacuum pyrolysis. However, *endo*-**3b** (Figure 2A) and *endo*-**3b** (Figure 2B) (Figure 2) obtained from

(7) Phenol acts as an intramolecular H-bonding donor (a Brønsted acid) to accelerate the reaction; see ref 2m.

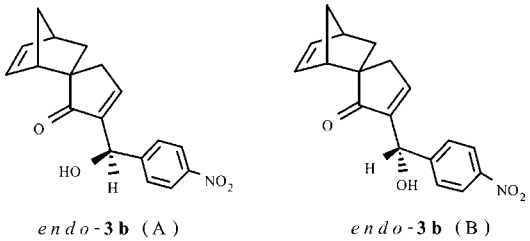
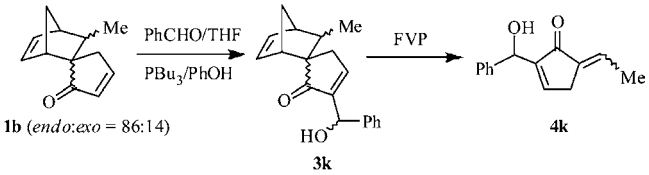


FIGURE 2. Diastereomers *endo*-**3b** (A) and *endo*-**3b** (B) obtained from the reaction of **1a** (*endo:exo* = 88:12) with *p*-nitrobenzaldehyde of which the stereochemistries were confirmed by X-ray crystallography.

SCHEME 2. Preparation of 5-Alkylidenecyclopentenone 4k



the reaction of **1a** with 4-nitrobenzaldehyde were successfully separated by chromatography. Their structures and relative stereochemistry were established by X-ray crystallography (see Supporting Information). It should be noted that the reaction of **1a** with cyclopentanone or cyclohexanone, instead of an aldehyde, gave no MBH adducts, presumably due to the steric effect and the low electrophilicity of the carbonyl carbons.

Having succeeded in preparing the MBH adducts **3a**−**j,** we then turned our attention to the generation of the required 2-(hydroxyalkyl)-5-methylene-2-cyclopentenones **4**. Thus, flash vacuum pyrolysis of **3a**−**j** at 375 °C/0.05 mmHg afforded the corresponding cyclopentenones **4a**−**j** in moderate to good yields after chromatography. Low yields of cyclopentenones **4f**,**g** (Table 1, entries 6 and 7) were obtained due to their decomposition during purification as monitored by ^{1}H NMR analyses.

To demonstrate the generality of this method, the MBH reaction of **1b** (endo/exo isomers = 86:14) was investigated. A crude MBH adduct **3k** was obtained in good yield as a 43:37:20:trace mixture of diastereomers, when **1b** was treated with benzaldehyde under standard conditions. Further flash vacuum pyrolysis of **3k** afforded the required cyclopentenone **4k** as a mixture of *E* and *Z* isomers (88:12). Purification of the crude pyrolysate provided a colorless liquid of a 98:2 mixture of *E* and *Z* isomers of **4k** in 68% yield (Scheme 2).

In summary, we have successfully developed a general and convenient method for the synthesis of 2-(hydroxyalkyl)-5-methylenecyclopentenones via the MBH reaction of a masked 5-alkylidene-2-cyclopentenone **1**, followed by the FVP of the resulting adducts. These highly functionalized cyclopentenones appear to be versatile precursors for further synthetic manipulations, and efforts in this area are in progress.

Experimental Section

General Procedure for the Preparation of MBH Adducts 3. 2′-Oxo-3′-hydroxy(phenyl)methylcyclopent-3′-ene-1′-spiro-2-bicyclo[2.2.1]hept-5-ene (3a). To a solution of **1a** (1.30 g, 1.875 mmol), benzaldehyde (0.298 g, 2.81 mmol), and phenol (0.035 g, 0.375 mmol) was added PBu_3 (0.093 mL, 0.375 mmol) at 15 °C under an argon atmosphere. After stirring at room temperature overnight (15 h), the organic solution was concentrated to give a crude liquid, which was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give a 46:42:12:trace mixture of diastereomers. The ratio was determined by ^{1}H NMR of the olefinic protons. Attempted separation of diastereomers was made by chromatotron (silica gel, 10% EtOAc in hexanes) to give two fractions of **3a** (0.412 g, 82% combined yield).

The first fraction (less polar) was obtained as a pale yellow solid containing a 77:18:5 mixture of three isomers (0.2197 g, 44% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−7.16 (m, 15H), 7.06 (m, 3H), 6.32−6.18 (m, 3H), 6.06 (dd, J = 5.5, 2.9 Hz, 1H), 5.90 (dd, J = 5.5, 2.9 Hz, 1H), 5.58 (dd, J = 5.6, 3.0 Hz, 1H), 5.49 (s, 1H), 5.44 (s, 2H), 3.60 (br s, OH), 2.95−2.78 (m, 3H), 2.71 (dt, J = 17.5, 2.0 Hz, 1H), 2.55 (app. d, J = 17.5 Hz, 1H), 2.50−2.10 (m, 9H), 2.09−1.98 (m, 2H), 1.60 (dd, J = 11.9, 3.7 Hz, 1H), 1.47−1.06 (m, 5H), 1.02 (m, 2H); MS: *m*/*z* (%) relative intensity 266 (M^+, 2), 248 (9), 183 (100).

The second fraction (more polar) was obtained as a pale yellow viscous liquid of pure *endo*-**3a** (0.1915 g, 38% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.15 (m, 5H), 7.05 (s, 1H), 6.25 (dd, J = 5.4, 3.1 Hz, 1H), 5.84 (dd, J = 5.4, 2.9 Hz, 1H), 5.46 (s, 1H), 3.65 (br s, OH), 2.90 (br s, 1H), 2.71 (dt, J = 18.9, 2.0 Hz, 1H), 2.54 (dt, J = 18.9, 2.2 Hz, 1H), 2.42 (br s, 1H), 1.62 (dd, J = 11.7, 3.7 Hz, 1H), 1.48−1.33 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3, 155.4, 146.5, 141.3, 138.1, 132.5, 128.4, 127.7, 126.3, 70.2, 54.8, 54.0, 50.0, 45.0, 43.6, 39.6; IR ($CHCl_3$): ν_{max} 3474 m, 1687s, 1635 m, 1494 m, 1456 m cm^{-1}; MS: *m*/*z* (%) relative intensity 266 (M^+, 2), 248 (11), 183 (100). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.15; H, 6.75.

Preparation of Cyclopentenones 4 from MBH Adducts 3 by Flash Vacuum Pyrolysis 2-(Hydroxy(phenyl)methyl)-5-methylene-2-cyclopentenone (4a). General Procedure. Flash vacuum pyrolysis of **3a** (50 mg, 0.19 mmol) (conditions: oven temperature 240 °C, column temperature 375 °C, pressure 0.07 mmHg) gave a crude pyrolysate, which was purified by chromatotron (silica gel, 15% ethyl acetate in hexanes) to give a pale yellow solid of **4a** (33 mg, 86% yield, mp 116−118 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.25 (m, 5H), 7.20 (app. sept., J = 1.3 Hz, 1H), 6.14 (m, 1H), 5.62 (d, J = 1.3 Hz, 1H), 5.49 (s, 1H), 3.18 (app. quint., J = 1.9 Hz, 2H), 3.10 (br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 152.6, 149.3, 141.7, 141.1, 128.5, 127.9, 126.4, 118.3, 70.2, 32.1; IR ($CHCl_3$): ν_{max} 3487 m, 1696 s, 1649 m, 1622 w, 1493 w cm^{-1}; MS: *m*/*z* (%) relative intensity 201 (M^+ + 1, 10), 200 (M^+, 58), 199 (100). HRMS (ESI-TOF) for $C_{13}H_{12}O_2Na$: calcd, 223.0735; found, 223.0735.

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Supporting Information Available: Complete experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS, X-ray, and/or elemental analysis) for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Concise syntheses of substituted indolizidine alkaloids via cyclization based on α-sulfinyl carbanions: preparation of (±)-indolizidines 167B and 209D, their epimers, and (±)-tashiromine

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Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

Abstract

(±)-Indolizidines 167B and 209D, their epimers and (±)-tashiromine have been successfully synthesized, starting from simple γ- or α-lactams. The strategy involves the cyclization of α-sulfinyl carbanion onto the carbonyl group of the lactam ring as the key step, leading to the indolizidines containing the phenylsulfinyl group, which are used as precursors for the preparation of the title compounds.

Keywords: Cyclization; α-Sulfinyl carbanion; (±)-Tashiromine; (±)-Indolizidine 167B; (±)-Indolizidine 209D

1. Introduction

Indolizidine alkaloids[1] constitute a class of natural products, which include a large number of pharmaceutically important substances. Tashiromine (**1**) and indolizidines 167B (**2a**) and 209D (**2b**) (Fig. 1) are simple representatives of the series of this class of alkaloids. Tashiromine (**1**) was isolated from the stems of a leguminous plant *Maackia tashiroi*, a deciduous shrub of subtropical Asia.[2,3] Indolizidines 167B (**2a**) and 209D (**2b**) have been isolated from the skin secretions of neotropical frogs of the family Dendrobatidae,[4,5] from Central and South America. These compounds have been shown to function as noncompetitive blockers for muscle type and ganglionic nicotinic receptor channels.[6] Because of the interesting structural features and potent biological activities of these alkaloids and often minute natural abundance, a number of synthetic methodologies of indolizidines have been developed.[3,6,7]

As part of our ongoing research on the cyclization based on the α-sulfinyl carbanions, we have recently reported a general synthetic method for the preparation of 1-azabicyclo[*m.n.*0] alkanes, starting from lactams.[8] In continuation of our successful results, we herein report a concise synthesis of (±)-tashiromine (**1**), (±)-indolizidines 167B (**2a**) and 209D (**2b**), and their epimers. Our retrosynthetic analysis is outlined in Scheme 1. It is anticipated that the syntheses of (±)-tashiromine (**1**) and (±)-indolizidines 167B (**2a**) and 209D (**2b**) would be accomplished by cyclization of α-sulfinyl carbanions onto the carbonyl group of the lactam moiety providing the key intermediates **5** and **6**. The presence of the phenylsulfinyl group in indolizidines **5** and **6** would permit further synthetic transformation at the α-carbon. The intermediate of type **5** (R=H) would be used as the precursor for the preparation of (±)-tashiromine (**1**) by α-hydroxymethylation followed by reductive cleavage of the phenylsulfinyl group. Reductive desulfurization of the resulting indolizidine **6** would provide the

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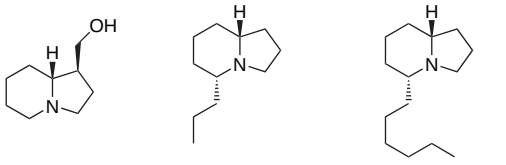


1 Tashiromine **2a** Indolizidine 167B **2b** Indolizidine 209D

Figure 1.

required indolizidines **2a** and **2b**. We anticipated that the key starting sulfinyl lactam **4** could be easily prepared from lactam **3** by N-alkylation, using 3-bromo-1-phenylsulfanylpropane or 4-bromo-1-phenylsulfanylbutane, followed by oxidation.

2. Results and discussion

*2.1. Synthesis of (±)-tashiromine (**1**)*

Our investigation began with the preparation of (±)-tashiromine (**1**), starting from commercially available γ-lactam **3a** (R=H; *n*=1). N-Alkylation of γ-lactam **3a** with 4-bromo-1-phenylsulfanylbutane, employing NaH as a base in DMF at 0 °C to room temperature overnight, afforded the corresponding sulfide in 75% yield after column chromatography on silica gel, which was oxidized with $NaIO_4$ in aqueous methanol at 0 °C to give the required starting sulfoxide **4a** (*m*=1; *n*=2) in 70% yield. Cyclization of the sulfoxide **4a** to indolizidine **5** was achieved by treatment with 2.2 equiv of lithium hexamethyldisilazide (LiHDMS) in THF at −78 °C to room temperature overnight, followed by reduction of the resulting crude cyclized product **4aA** with $NaBH_4$ in methanol at 0 °C for 4 h to provide indolizidine **5** in 69% yield as a mixture of inseparable diastereomers. It was found that the cyclized product **4aA** was slowly decomposed during attempted isolation by chromatography on silica gel. It was therefore converted to the corresponding indolizidine **5** by reduction with $NaBH_4$. Compound **4aA** was formed by the intramolecular nucleophilic addition of the initially formed α-sulfinyl carbanion derived from **4a** onto the carbonyl group of the lactam moiety followed by elimination of the hydroxy group during work-up.[8]

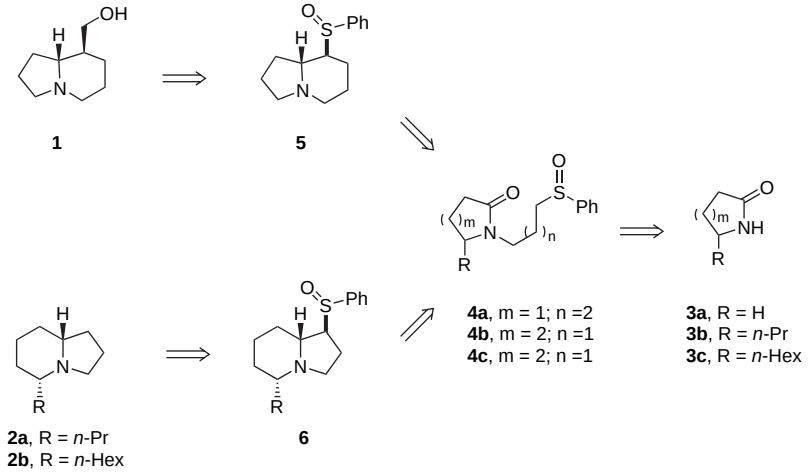
Having the key intermediate indolizidine **5** in hand, the next step was to carry out the α-hydroxymethylation at the α-carbon of the phenylsulfinyl group, following by reductive cleavage. Thus, the α-sulfinyl carbanion of indolizidine **5** generated using lithium diisopropylamide (1.4 equiv) in THF at −78 °C for 1 h was treated with paraformaldehyde (1.2 equiv) to furnish the corresponding diastereomeric mixture of hydroxymethylated indolizidine **7** in 55% yield after chromatography. Pyrolysis of **7** by refluxing in dry toluene in the presence of $CaCO_3$ provided unsaturated indolizidine **8** in 47% yield, which underwent highly stereoselective hydrogenation in ethyl acetate using Pd/C as catalyst to give (±)-tashiromine (**1**) in 86% yield (Scheme 2).

*2.2. Synthesis of indolizidines 167B (**2a**) and 209D (**2b**)*

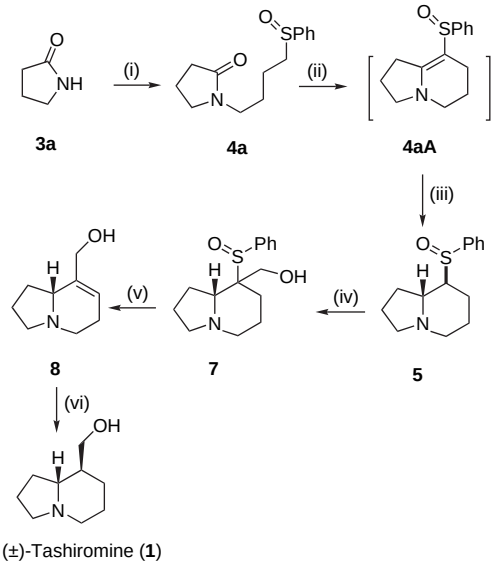
Synthesis of the requisite δ-lactams **3b** and **3c** was achieved by Beckmann rearrangement of oxime derivatives of 2-propylcyclopentanone and 2-hexylcyclopentanone employing NaOH/*p*-TsCl in acetone at room temperature overnight. It was found that inseparable mixtures (4:1) of required δ-lactams **3b/9b** and **3c/9c** were obtained in 67% and 60% yields, respectively. The mixture of **3** and **9** was used directly in the next step (Scheme 3).

Treatment of the mixture of **3b** and **9b** with 1-bromo-3-phenylsulfanylpropane using NaH in DMF at 0 °C overnight afforded **10a** and **11a** in 46% and 14% yields, respectively. Under the same conditions, the mixture of **3c** and **9c** gave **10b** and **11b** in 41% and 12% yields, respectively. Subsequent oxidation of sulfides **10a** and **10b** with $NaIO_4$ in aqueous methanol at 0 °C afforded the corresponding sulfoxides **4b** and **4c** in good yields as diastereomeric mixtures (Scheme 4).

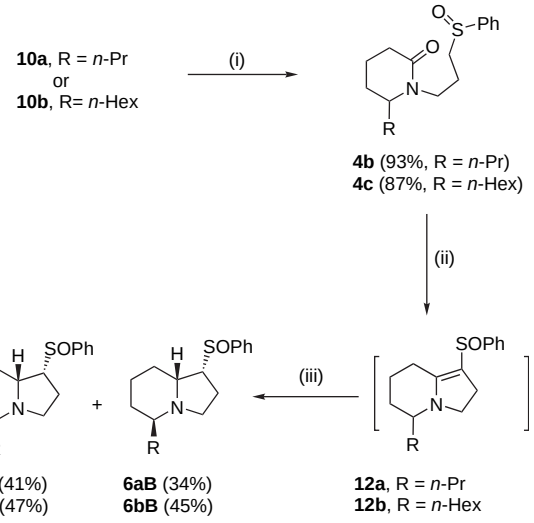
Cyclization of the sulfoxides **4b** and **4c** to the corresponding 1-azabicyclic compounds **12a** and **12b** was accomplished by employing LiHMDS in THF at −78 °C to room temperature overnight. Due to the rapid decomposition of **12a** and



Scheme 1. Retrosynthetic analysis.



Scheme 2. *Reaction conditions*: (i) NaH, DMF, $PhS(CH_2)_4Br$, 0 °C to rt (75%); then $NaIO_4$, MeOH, H_2O, 0 °C to rt overnight (70%); (ii) LiHMDS, THF, −78 °C to rt overnight; (iii) $NaBH_4$, MeOH, 0 °C to rt (69% yield from **4a**); (iv) LDA, THF, $(CH_2O)_n$, −78 °C to rt overnight (55%); (v) toluene, reflux for 8 h (47%); (vi) H_2, Pd/C (86%).



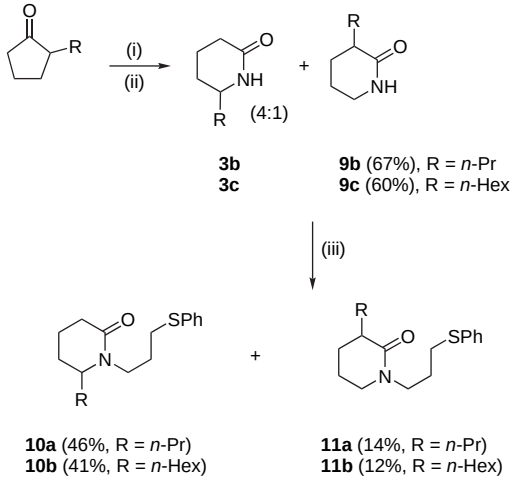
Scheme 4. *Reaction conditions*: (i) $NaIO_4$, MeOH, H_2O, 0 °C to rt overnight; (ii) LiHMDS, THF, −78 °C to rt overnight; (iii) $NaBH_4$, MeOH, 0 °C to rt overnight.

12b during chromatography on silica gel, they were used without purification for the reduction with $NaBH_4$ in MeOH to provide a mixture of two diastereomers of **6aA/6aB** and **6bA/6bB**, respectively, in good overall yields (Scheme 4).

The complete assignment of ^{1}H NMR chemical shifts of **6aA**, **6aB** and **6bA**, **6bB** was made by comparing their ^{1}H NMR spectral data with those of **13** (Fig. 2) (for preparation and complete characterization of **13**, see Supplementary data).

The relative stereochemistry of **6aA/6bA** and **6aB/6bB** was also made by comparison of the chemical shifts of C-5 protons with those of **13**. The chemical shifts of C_5-H_a of **6aA** and **6bA** appear at higher field than C_5-H_e of **6aB** and **6bB**. C_5-H_e of the latter diastereomers resonate at lower field due to strong deshielding effect caused by the proximate nitrogen lone pair electrons.[9] Moreover, compounds **6aA** and **6bA** exhibit strong infrared Bohlmann bands at 2778 and 2783 cm^{-1}, respectively, indicating that the hydrogen on carbon atoms adjacent to the nitrogen oriented trans to lone pair electrons.[10] These characteristic absorption bands in the infrared spectra were not found in compounds **6aB** and **6bB**.

To complete the synthesis of **2a** and **2b** from **6aA** and **6bA** by reductive desulfurization, we began our study with 6% Na(Hg)/MeOH/NaH_2PO_4 or Raney-nickel. All attempts led to unsatisfactory results, providing mainly the recovered starting materials. Fortunately, reductive desulfurization of **6aA** and **6bA** was successfully made by employing nickel boride (Ni_2B).[11] Thus, treatment of **6aA** and **6bA** with Ni_2B, generated in situ from $NiCl_2\cdot 6H_2O$ and $NaBH_4$ in a mixture of MeOH and THF (3:1), at 0 °C to room temperature gave the required (±)-indolizidines 167B (**2a**) and 209 D (**2b**) in 82% and 80% yields, respectively. Their spectroscopic data were



Scheme 3. *Reaction conditions*: (i) $NH_2OH\cdot HCl$, ethanol; (ii) TsCl, NaOH, acetone, rt, overnight; (iii) NaH, DMF, $PhS(CH_2)_3Br$, 0 °C to rt, overnight.

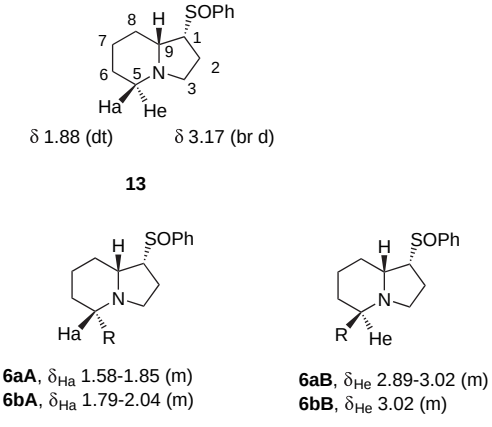
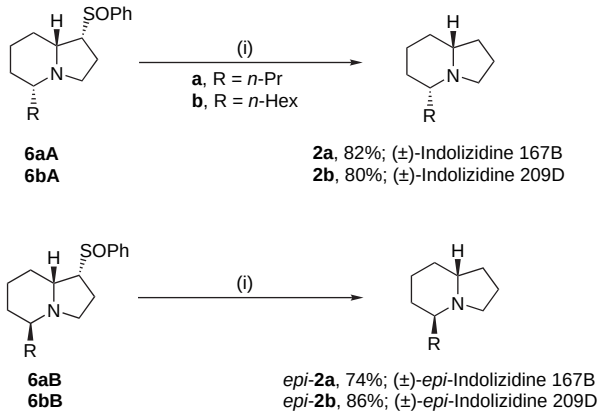


Figure 2. Comparing of ^{1}H NMR data of C-5 protons of compounds **6aA/6aB** and **6bA/6bB** with compound **13**.

consistent with those of the reported values in the literature.[7e] Similarly, under the same reduction conditions, the diastereomers **6aB** and **6bB** furnished the corresponding (±)-*epi*-indolizidine 167B (**2a**) and (±)-*epi*-indolizidine 209D (**2b**)[7e] in 74% and 86% yields (Scheme 5).



Scheme 5. *Reaction conditions*: (i) $NiCl_2 \cdot 6H_2O/NaBH_4$, MeOH/THF (3:1), 0 °C to rt, 2 h.

3. Conclusion

In conclusion, we have developed a concise method for the synthesis of (±)-tashiromine (**1**), (±)-indolizidine 167B (**2a**) and 209D (**2b**), and their epimers, starting from 2-propyl or 2-hexyl substituted δ-lactams, respectively. The synthesis demonstrates the utilities of the cyclization of α-sulfinyl carbanions onto the carbonyl group of the lactam rings as a convenient entry to the indolizidines containing the sulfoxide functional group that can be employed as the key indolizidines for the preparation of the title compounds.

4. Experimental

4.1. General methods

The ^{1}H NMR spectra were recorded on either Bruker DPX-300 (300 MHz) or Bruker Avance-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin–Elmer 683 infrared spectrometer. The mass spectra were recorded using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on MS Micromass model VQ-TOF2. Elemental analyses were performed by a Perkin–Elmer Elemental Analyzer 2400 CHN. Melting points were recorded on a Büchi 501 Melting Point Apparatus and uncorrected. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dry *N*,*N*-dimethylformamide (DMF) was obtained by distilling over calcium hydride. Other common solvents (hexanes, ethyl acetate, methanol, and acetone) were distilled before use. All glasswares and syringes were oven-dried and kept in a dessicator before use. Preparative thin layer chromatography and column chromatography were performed using Merck silica gel $60F_{254}$ (Merck, Art. 7749) and silica gel 60H (Merck, Art. 7736), respectively.

4.2. Preparation of (±)-tashiromine (*1*)

4.2.1. 1-(4-Phenylsulfinylbutyl)pyrrolidin-2-one (*4a*)

General procedure. To a suspension of NaH (1.55 g, 38.7 mmol, 80% suspension in mineral oil) in DMF (58 mL), a DMF (12 mL) solution of γ-lactam (3.0 g, 35 mmol) was slowly added at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h until the generation of hydrogen ceased and 1-bromo-4-phenylsulfanylbutane (9.5 g, 38.7 mmol) was then added. After the reaction mixture was stirred at 0 °C to room temperature overnight, it was poured into ice-water and extracted with EtOAc (4×100 mL). The combined organic layers were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a residue, which was purified by column chromatography on silica gel (20% EtOAc in hexanes) to give a pale yellow liquid of 1-(4-phenylsulfanylbutyl)pyrrolidin-2-one (6.6 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.22 (m, 4H), 7.19–7.13 (m, 1H), 3.38–3.19 (m, 4H), 2.94 (t, *J*=6.5 Hz, 2H), 2.36 (t, *J*=8.0 Hz, 2H), 1.95 (quint, *J*=7.5 Hz, 2H), 1.74–1.56 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 136.3, 129.1 (2C), 128.8 (2C), 125.8, 46.9, 41.7, 33.1, 30.9, 26.0 (2C), 17.8. IR (neat): ν_{max} 1681 (s), 1583 (m), 1480 (s), 1463 (s), 1290 (s), 1267 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 250 (M^++1, 9), 140 (71), 123 (11), 98 (100), 70 (32), 68 (9). HRMS (ESI): calcd for $C_{14}H_{20}NOS$, 250.1267; found, 250.1232.

A solution of 1-(4-phenylsulfanylbutyl)pyrrolidin-2-one (5.0 g, 20 mmol) in MeOH (11 mL) was slowly added to a suspension of $NaIO_4$ (4.7 g, 22 mmol) in MeOH (48 mL) and H_2O (12 mL) at 0 °C. The mixture was stirred vigorously and slowly warmed up to room temperature overnight (12 h). The precipitates of $NaIO_3$ were filtered and washed several times with EtOAc (3×60 mL). The combined extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a pale yellow liquid of a crude product, which was purified by column chromatography (100% EtOAc) to afford a colorless viscous liquid of **4a** (3.75 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31 (m, 2H), 7.31–7.19 (m, 3H), 3.34–3.10 (m, 4H), 2.71–2.52 (m, 2H), 2.08 (t, *J*=7.8 Hz, 2H), 1.78–1.66 (m, 2H), 1.23–1.59 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 142.8, 130.2, 128.5 (2C), 123.2 (2C), 55.3, 46.2, 40.7, 30.2, 25.0, 18.4, 17.1. IR (neat): ν_{max} 1679 (s), 1494 (m), 1464 (s), 1443 (s), 1290 (s), 1087 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 266 (M^++1, 51), 248 (39), 165 (23), 163 (22), 140 (87), 138 (30), 98 (100), 70 (47). HRMS (ESI): calcd for $C_{14}H_{20}NO_2S$, 266.1216; found, 266.1182.

4.2.2. 8-Phenylsulfinyl-1,2,3,5,6,7,8,9-octahydroindolizine (**5**)

General procedure. A THF (18 mL) solution of **4a** (2.29 g, 8.64 mmol) was added dropwise to a cooled (−78 °C) THF (100 mL) solution of LiHMDS [prepared by reacting *n*-BuLi (1.36 M in hexane; 14 mL, 19 mmol) with THF (93 mL) solution of hexamethyldisilazane (HMDS) (4.3 mL, 20.7 mmol) at −78 °C for 30 min] under an argon atmosphere. The resulting mixture was stirred and slowly warmed up from −78 °C to room temperature overnight (15 h). The resulting yellow solution was quenched with H_2O and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo afforded a viscous liquid of a crude product **4aA**, which was directly subjected to reduction using $NaBH_4$ as described below.

To a solution of the crude product **4aA** in MeOH (21 mL) at 0 °C under argon atmosphere, $NaBH_4$ (3.9 g, 103.6 mmol) was gradually added over 15 min. The mixture was stirred at room temperature overnight, diluted with 1 N NaOH (63 mL) and H_2O (38 mL), and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2, 10% MeOH in EtOAc containing 0.15% NH_4OH solution) to afford a mixture of three diastereomers of **5** (1.49 g, 69% yield).

F_1 (less polar) was obtained as a yellow viscous liquid of a mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64−7.58 (m, 2H, Ar*H*), 7.57−7.42 (m, 8H, Ar*H*), 3.13 (dt, *J*=8.6, 1.9 Hz, 1H), 3.09−3.01 (m, 3H), 2.81−2.79 (m, 1H), 2.52−2.35 (m, 4H), 2.32−2.18 (m, 2H), 2.18−1.98 (m, 2H), 1.98−1.43 (m, 13H), 1.26−1.22 (m, 1H), 1.07 (dq, *J*=12.6, 4.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 141.2, 131.2, 130.5, 128.9 (2C), 128.9 (2C), 125.4 (2C), 124.2 (2C), 66.1, 65.7, 63.8, 63.4, 53.9, 53.2, 51.7, 29.4, 29.2, 24.8, 24.2, 23.4, 20.9, 20.6, 18.1. IR (neat): ν_{max} 2939 (s), 2788 (s), 1582 (w), 1478 (m), 1461 (m), 1443 (s), 1362 (s), 1086 (s), 1045 (s), 749 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 250 (M^++1, 13), 124 (53), 123 (85), 122 (100), 96 (47). HRMS (EI): calcd for $C_{14}H_{20}NOS$, 250.1260; found, 250.1259.

F_2 (more polar) was obtained as a colorless viscous liquid of a single diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64−7.52 (m, 2H, Ar*H*), 7.49−7.36 (m, 3H, Ar*H*), 3.16−2.92 (m, 3H), 2.57−2.39 (m, 1H), 2.41−1.59 (m, 8H), 1.58−1.34 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 130.7, 129.2 (2C), 124.6 (2C), 63.9, 63.3, 54.4, 51.9, 25.8, 22.8, 21.3, 20.9. IR (neat): ν_{max} 2938 (s), 2786 (s), 1582 (w), 1442 (s), 1041 (s), 753 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 250 (M^++1, 1), 232 (100), 122 (63), 96 (35), 94 (14). HRMS (ESI): calcd for $C_{14}H_{20}NOS$, 250.1260; found, 250.1262.

4.2.3. [1,2,3,5,6,7,8,9-Octahydro-8-(phenylsulfinyl)indolizin-8-yl]methanol (**7**)

n-BuLi (1.36 M in hexane; 4.0 mL, 5.4 mmol) was added to a cooled (−78 °C) THF (5 mL) solution of diisopropylamine (0.86 mL, 6 mmol) under an argon atmosphere. After stirring at −78 °C for 30 min, a THF (12 mL) solution of **5** (1.0 g, 4 mmol) was added dropwise and allowed to stir for 30 min. Paraformaldehyde (145 mg, 4.8 mmol) was added as a solid to the resulting solution at −78 °C and the resulting mixture was allowed to stir and slowly warmed up to room temperature overnight (15 h). The resulting yellow solution was quenched with H_2O and extracted with EtOAc (3×70 mL). The combined organic extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 10% MeOH in EtOAc) to afford a pale yellow viscous liquid of **7** (0.62 g, 55% yield) as a mixture of three diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79−7.70 (m, 3H), 7.56−7.39 (m, 12H), 4.42 (d, *J*=11.7 Hz, 1H), 4.17−4.06 (m, 2H), 3.81 (d, *J*=11.4 Hz), 3.51 (d, *J*=12.7 Hz, 1H), 3.31 (d, *J*=10.6 Hz, 1H), 3.23−3.13 (m, 3H), 3.13−2.94 (m, 3H), 2.76−2.59 (m, 1H), 2.49−1.52 (m, 31H), 1.43−1.39 (m, 1H), 1.21−1.03 (m, 2H), 0.82 (dt, *J*=4.79, 13.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 138.6, 137.8, 131.8 (2C), 131.6 (2C), 128.9 (2C), 128.7 (2C), 126.7 (2C), 126.2 (3C), 125.9 (2C), 69.9, 67.7, 67.6, 66.2, 64.6, 62.5, 62.4, 61.2, 60.4, 54.1, 53.9, 53.6, 52.8, 52.3, 52.2, 29.7, 28.1, 27.2, 25.3, 24.4, 23.9, 22.7, 22.6, 21.8, 20.9, 20.9, 20.6. IR (neat): ν_{max} 3367 (br), 2709 (s), 1582 (w), 1475 (w), 1443 (s), 1032 (s), 749 (s), 699 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 280 (M^++1, 1), 153 (32), 136 (100), 122 (15). HRMS (ESI): calcd for $C_{15}H_{22}NO_2S$, 280.1366; found, 280.1353.

4.2.4. (1,2,3,5,6,8a-Hexahydroindolizin-8-yl)methanol (**8**)

A toluene (15 mL) solution of **7** (0.32 g, 1.17 mmol) in the presence of $CaCO_3$ was stirred at reflux under an argon atmosphere for 8 h. $CaCO_3$ was filtered off and the filtrate was evaporated to dryness to give a crude product, which was purified by preparative thin layer chromatography (SiO_2, 30% MeOH in EtOAc) to give a pale brown liquid of **8** (89 mg, 47% yield). ^{1}H NMR (300 Hz, $CDCl_3$): δ 5.61 (br s, 1H), 4.25 (br s, 1H), 3.98 (br s, 2H), 3.20 (t, 1H, *J*=7.8 Hz), 2.88−2.79 (m, 1H), 2.65−2.79 (m, 2H), 2.59−2.46 (m, 1H), 2.15 (br s, 2H), 2.19−2.06 (m, 1H), 1.91−1.63 (m, 2H), 1.56−1.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 120.1, 64.5, 60.1, 52.9, 46.3, 27.9, 24.7, 22.1. IR (neat): ν_{max} 3351 (br), 2876 (s), 2729 (s), 1663 (m), 1576 (w), 1457 (s), 1434 (s), 1062 (s), 1018 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 154 (M^++1, 36), 152 (36), 136 (16), 122 (100), 120 (23), 94 (14), 79 (12). HRMS (ESI): calcd for $C_9H_{16}NO$, 154.1226; found, 154.1230.

4.2.5. (±)-Tashiromine (**1**)

To a suspension of 10% Pd/C (40 mg, 0.038 mmol) in EtOAc (2 mL), an EtOAc (3 mL) solution of **8** (58 mg, 0.38 mmol) was slowly added at room temperature under hydrogen atmosphere. The reaction mixture was allowed to stir overnight (15 h) followed by filtration over Celite. The filtrate was evaporated in vacuo to give a crude product, which was purified by preparative thin layer chromatography (Al_2O_3,

100% EtOAc) to give a pale yellow viscous liquid of (±)-tashiromine (**1**) (51 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64–3.52 (m, 1H), 3.49–3.38 (m, 1H), 3.14–3.01 (m, 2H), 2.17–1.36 (m, 11H), 1.11–0.99 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.5, 65.6, 54.0, 52.6, 44.2, 28.9, 27.4, 24.9, 20.6. IR (neat): ν_{max} 3392 (br), 2799 (s), 1648 (m), 1445 (m) cm^{-1}. MS: *m/z* (%) relative intensity 156 (M^++1, 100), 154 (74), 136 (39), 110 (26), 84 (64). HRMS (ESI): calcd for $C_9H_{18}NO$, 156.1383; found, 156.1393. The spectroscopic data are consistent with the literature.[2,3f,3g]

4.3. Preparation of (±)-indolizidine 167B (*2a*) and 209D (*2b*)

4.3.1. 6-Propyl-2-piperidone (*3b*)[12]

General procedure. To a solution of hydroxylamine hydrochloride (0.28 g, 4.0 mmol) and NaOH (0.22 g) in EtOH (5 mL) was added a solution of 2-propylcyclopentanone (0.39 g, 3.1 mmol) in EtOH (1 mL). The mixture was stirred at reflux for 2 h, poured into ice-water after cooling to room temperature, and extracted with EtOAc (3×15 mL). The combined organic layers were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by evaporation gave a crude product of a *syn*- and *anti*-mixture of 2-propylcyclopentanone oxime. A solution of the crude product of 2-propylcyclopentanone oxime (0.41 g, 2.9 mmol) in acetone (3.8 mL) was treated with 1 N NaOH (5 mL) at 0 °C and *p*-TsCl (0.72 g, 3.8 mmol) in acetone (2.2 mL) was added dropwise. Aftre stirring the resulting mixture for 18 h at 25 °C, it was diluted with H_2O (8 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. The crude product was purified by column chromatography (SiO_2, 30% EtOAc in hexanes) to afford a white solid of a 4:1 mixture of 6-propylvalerolactam (**3b**) and 3-propylvalerolactam (**9b**) (0.293 g, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (br s, 1H), 6.42 (br s, 1H), 3.39–3.31 (m, 1H), 3.31–3.19 (m, 2H), 2.44–2.16 (m, 3H), 1.99–1.20 (m, 16H), 0.92 and 0.91 (each t, *J*=7.1 Hz, 2×3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 172.4, 52.7, 42.2, 40.6, 38.9, 33.5, 31.2, 28.2, 25.9, 21.1, 20.0, 19.6, 18.4, 13.9, 13.8. IR (Nujol): ν_{max} 1667 (s), 1462 (s), 1403 (m), 1377 (s), 1333 (m) cm^{-1}. MS: *m/z* (%) relative intensity 143 (M^++2, 9), 142 (M^++1, 100), 98 (50), 70 (29).

4.3.2. 6-Hexyl-2-piperidone (*3c*)

According to the general procedure described for **3b**, hydroxylamine hydrochloride (2.02 g, 29.01 mmol) in an ethanol (50 mL) solution of NaOH (30 mmol) was reacted with a solution of 2-hexylcyclopentanone (3.88 g, 23.10 mmol). The crude product obtained from the above reaction was treated with 1 N NaOH (30 mL) and a solution of *p*-TsCl (5.68 g, 29.82 mmol) in acetone (17 mL). After the usual work-up, the crude product was purified by column chromatography (SiO_2, 30% EtOAc in hexanes) to afford a yellow liquid of a 4:1 mixture of 6-hexylvalerolactam (**3c**) and 3-hexylvalerolactam (**9c**) (2.54 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55 (br s, 1H), 6.34 (br s, 1H), 3.37–3.17 (m, 3H), 2.43–2.13 (m, 3H), 1.96–1.12 (m, 28H), 0.91–0.79 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 172.4, 53.0, 42.2, 40.8, 36.8, 31.6, 31.5, 31.4, 31.2, 29.2, 29.0, 28.2, 26.8, 25.9, 25.1, 22.5, 22.4, 21.2, 19.6, 13.9, 13.9. IR (Nujol): ν_{max} 1668 (s), 1485 (s), 1469 (s), 1403 (s), 1377 (m), 1346 (m) cm^{-1}. MS: *m/z* (%) relative intensity 184 (M^++1, 8), 183 (M^+, 9), 112 (22), 99 (21), 98 (100), 70 (58), 55 (70). HRMS (ESI): calcd for $C_{11}H_{21}NONa$, 206.1521; found, 206.1522.

4.3.3. Preparation of a mixture of 6-alkyl-1-(3-phenylsulfanylpropyl)piperidin-2-one *10* and 3-alkyl-1-(3-phenylsulfanylpropyl)piperidin-2-one *11*

*4.3.3.1. A mixture of 6-propyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**10a**) and 3-propyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**11a**). General procedure*. To a suspension of NaH (1.01 g, 33.75 mmol, 80% suspension in mineral oil) in DMF (80 mL), a DMF (7 mL) solution of a 4:1 mixture of **3b** and **9b** (3.16 g, 22.41 mmol) was slowly added at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h until the generation of hydrogen ceased and 1-bromo-3-phenylsulfanylpropane (6.20 g, 26.84 mmol) was then added. After the reaction mixture was stirred at 0 °C to room temperature overnight (15 h), it was quenched with water and extracted with EtOAc (4×80 mL). The combined organic layers were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a residue, which was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give a pale yellow liquid of **10a** (2.99 g, 46% yield) and **11a** (0.94 g, 14% yield).

Compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.21 and 7.19–7.11 (each m, 5H), 3.86 (ddd, *J*=14.1, 8.0, 5.6 Hz, 1H), 3.31–3.21 (m, 1H), 2.99 (ddd, *J*=13.7, 8.3, 5.6 Hz, 1H), 2.91 (t, *J*=7.2 Hz, 2H), 2.38–2.26 (m, 2H), 1.99–1.09 (m, 10H), 0.91 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 136.9, 129.8 (2C), 129.5 (2C), 126.5, 57.2, 45.1, 35.4, 32.5, 31.9, 27.7, 26.7, 19.9, 17.7, 14.6. IR (neat): ν_{max} 1637 (s), 1585 (m), 1473 (s), 1418 (m), 1360 (m) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 8), 183 (12), 182 (100), 113 (22). HRMS (ESI): calcd for $C_{17}H_{25}NONaS$, 314.1555; found, 314.1553.

Compound **11a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.09 (m, 5H), 3.47–3.28 (m, 2H), 3.23–3.08 (m, 2H), 2.83 (t, *J*=7.4 Hz, 2H), 2.25–2.13 (m, 1H), 1.92–1.13 (m, 10H), 0.85 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 136.2, 129.1 (2C), 128.8 (2C), 125.9, 48.1, 46.3, 41.2, 34.0, 31.1, 26.8, 26.2, 21.6, 20.1, 14.0. IR (neat): ν_{max} 1636 (s), 1584 (m), 1490 (s), 1464 (s), 1439 (s), 740 (s) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 1), 291 (M^+, 2), 183 (13), 182 (100), 154 (15).

*4.3.3.2. A mixture of 6-hexyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**10b**) and 3-hexyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**11b**)*. According to the general procedure described for **10a**, a 4:1 mixture of **3c** and **9c** (4:1) (1.40 g,

7.65 mmol) in DMF (3 mL) was treated with NaH (0.29 g, 9.58 mmol, 80% suspension in mineral oil) and 1-bromo-3-phenylsulfanylpropane (2.11 g, 9.13 mmol) in DMF (16 mL) to afford a crude product, which was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give a pale yellow liquid of **10b** (1.0412 g, 41% yield) and **11b** (0.3094 g, 12% yield).

Compound **10b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.13 (m, 5H), 3.88 (ddd, J=13.8, 8.2, 6.0 Hz, 1H), 3.32–3.21 (m, 1H), 3.00 (ddd, J=13.7, 8.2, 5.7 Hz, 1H), 2.93 (t, J=7.2 Hz, 2H), 2.39–2.28 (m, 2H), 2.02–1.09 (m, 16H), 0.90 (t, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 136.2, 129.1 (2C), 128.8 (2C), 125.9, 56.8, 44.4, 32.5, 31.8, 31.6, 31.2, 29.1, 27.0, 26.0, 26.0, 22.5, 17.0, 14.0. IR (neat): ν_{max} 1640 (s), 1585 (w), 1470 (s), 1439 (s), 1275 (m), 738 (s) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 4), 225 (15), 224 (100). HRMS (ESI): calcd for $C_{20}H_{31}NONaS$, 356.2024; found, 356.2024.

Compound **11b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.10 (m, 5H), 3.54–3.34 (m, 2H), 3.29–3.13 (m, 2H), 2.90 (t, J=7.3 Hz, 2H), 2.30–2.17 (m, 1H), 1.98–1.17 (m, 16H), 0.96–0.79 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 136.1, 128.9 (2C), 128.6 (2C), 125.7, 47.9, 46.1, 41.2, 31.7, 31.5, 30.9, 29.1, 26.8, 26.6, 26.1, 22.4, 21.5, 13.8. IR (neat): ν_{max} 1637 (s), 1584 (m), 1490 (m), 1465 (m), 1439 (m), 1352 (m) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 3), 225 (15), 224 (100), 196 (14), 168 (15).

*4.3.3.3. 6-Propyl-1-(3-phenylsulfinylpropyl)piperidin-2-one (**4b**).* According to the general procedure as described for **4a**, a solution of **10a** (0.21 g, 0.72 mmol) in MeOH (0.5 mL) was reacted with $NaIO_4$ (0.16 g, 0.75 mmol) in MeOH (1.6 mL) and H_2O (0.4 mL). The crude product obtained was purified by column chromatography (SiO_2, 100% EtOAc) to afford a colorless viscous liquid of **4b** (0.204 g, 93% yield) as a 1:1 mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.58 and 7.57–7.45 (each m, 2×5H), 4.02–3.87 (m, 2H), 3.40–3.22 (m, 2H), 3.05–2.68 (m, 6H), 2.42–2.22 (m, 4H), 2.21–1.11 (m, 20H), 0.94 (t, J=7.2 Hz, 3H), 0.93 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 143.6, 143.5, 130.8 (4C), 129.1 (4C), 123.9, 123.8, 56.2, 56.2, 54.7, 54.5, 43.8, 43.6, 34.6, 34.6, 31.8, 31.7, 26.0, 25.9, 20.5, 20.5, 19.2 (2C), 16.9 (2C), 13.9 (2C); IR (neat): ν_{max} 3055 (w), 2955 (m), 2872 (m), 1634 (s), 1473 (m), 1446 (m), 1086 (m), 1045 (m), 751 (m) cm^{-1}. MS: *m/z* (%) relative intensity 308 (M^++1, 7), 290 (29), 182 (100), 180 (27), 112 (67). HRMS (ESI): calcd for $C_{17}H_{25}NO_2NaS$, 330.1504; found, 330.1511.

*4.3.3.4. 6-Hexyl-1-(3-phenylsulfinylpropyl)piperidin-2-one (**4c**).* According to the general procedure described for **4a**, a solution of **10b** (2.38 g, 7.15 mmol) in MeOH (5 mL) was treated with a suspension of $NaIO_4$ (1.68 g, 7.85 mmol) in MeOH (16 mL) and H_2O (4 mL). The crude product was purified by column chromatography (SiO_2, 100% EtOAc) to afford a colorless viscous liquid of **4c** (2.18 g, 87% yield) as a mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.57 and 7.57–7.44 (each m, 2×5H), 4.03–3.88 (m, 2H), 3.40–3.19 (m, 2H), 3.05–2.67 (m, 6H), 2.42–2.20 (m, 4H), 2.19–1.08 (m, 32H), 0.89 (t, J=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 143.6, 143.5, 130.8 (4C), 129.1 (4C), 123.9, 123.8, 56.5, 56.4, 54.7, 54.5, 43.8, 43.6, 32.5, 32.4, 31.8, 31.7, 31.6 (2C), 29.1 (2C), 25.9 (4C), 22.4 (2C), 20.5, 20.5, 16.9 (2C), 13.9 (2C). IR (neat): ν_{max} 1634 (s), 1471 (s), 1444 (m), 1087 (m), 1046 (s), 749 (m) cm^{-1}. MS: *m/z* (%) relative intensity 350 (M^++1, 3), 224 (100), 222 (29), 138 (20), 112 (69). HRMS (ESI): calcd for $C_{20}H_{31}NO_2NaS$, 372.1973; found, 372.1974.

*4.3.3.5. 1-Phenylsulfinyl-5-propyl-1,2,3,5,6,7,8,9-octahydroindolizine (**6a**).* According to the general procedure for the preparation of **5**, a THF (12 mL) solution of **4b** (1.86 g, 6.06 mmol) was treated with LiHMDS (14.4 mmol) to afford a crude product (1.73 g, 5.99 mmol), which was dissolved in methanol (30 mL) followed by treatment with $NaBH_4$ (1.49 g, 39.4 mmol) in a small portion over 15 min. The crude product obtained was purified by column chromatography (SiO_2, 2% MeOH in EtOAc containing 0.15% NH_4OH solution) to afford two separated diastereomers of **6aA** and **6aB**.

F_1 (less polar) was obtained as a yellow solid of **6aA** [0.72 g, 41% yield; mp 66–68 °C (EtOAc)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.21 (m, 5H), 3.09 (dt, J=8.4, 1.1 Hz, 1H), 2.91–2.78 (m, 1H), 2.23–2.04 (m, 2H), 1.85–1.58 (m, 5H), 1.50–1.30 (m, 2H), 1.28–0.90 (m, 6H), 0.68 (t, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 130.2, 128.9 (2C), 124.2 (2C), 66.8, 66.4, 63.9, 50.5, 36.3, 29.7, 27.6, 24.9, 18.6, 17.6, 14.4. IR (Nujol): ν_{max} 2778 (s), 1441 (s), 1047 (s), 751 (s) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 5), 274 (83), 164 (34), 124 (60), 122 (100).

F_2 (more polar) was obtained as a yellow solid of **6aB** [0.60 g, 34% yield; mp 81–83 °C (EtOAc)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.33 (m, 5H), 3.02–2.89 (m, 3H), 2.85 (dt, J=8.6, 2.5 Hz, 1H), 2.55 (q, J=8.0 Hz, 1H), 2.38–2.23 (m, 1H), 1.96–1.55 (m, 4H), 1.53–1.00 (m, 7H), 0.83 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 130.3, 128.8 (2C), 124.1 (2C), 65.9, 56.9, 55.1, 48.1, 26.9, 26.2, 25.7, 20.6, 19.1, 17.5, 14.2. IR (Nujol): ν_{max} 2780 (m), 1582 (w), 1457 (m), 1441 (m), 1041 (s), 748 (m) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 21), 274 (75), 122 (100), 96 (21). HRMS (ESI): calcd for $C_{17}H_{25}NONaS$, 314.1555; found, 314.1549.

*4.3.3.6. 1-Phenylsulfinyl-5-hexyl-1,2,3,5,6,7,8,9-octahydroindolizine (**6b**).* According to the general procedure described for **5**, the reaction of LiHMDS (15.4 mmol) in THF (77 mL) with a THF (14 mL) solution of **4c** (2.42 g, 6.93 mmol) gave a viscous liquid of a crude product (2.20 g, 6.65 mmol). The crude product obtained was dissolved in MeOH (34 mL) and treated with $NaBH_4$ (1.62 g, 42.63 mmol). After the usual work-up, the crude product was purified by column chromatography (SiO_2, 2% MeOH in EtOAc containing 0.15%

NH_4OH solution) to afford two separated diastereomers **6bA** and **6bB**.

F_1 (less polar) was obtained as a yellow solid of **6bA** [1.08 g, 47% yield; mp 54–56 °C (EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.59–7.37 (m, 5H), 3.09 (t, J=8.2 Hz, 1H), 3.05 (ddd, J=9.3, 7.7, 6.0 Hz, 1H), 2.42–2.26 (m, 2H), 2.04–1.79 (m, 5H), 1.72–1.52 (m, 2H), 1.47–1.10 (m, 12H), 0.88 (t, J=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 130.3, 128.9 (2C), 124.2 (2C), 66.8, 66.4, 64.2, 50.6, 34.0, 31.7, 29.8, 29.6, 27.7, 25.5, 24.9, 22.5, 17.6, 14.0. IR (Nujol): ν_{max} 2783 (s), 1441 (s), 1376 (s), 1084 (s), 1045 (s), 751 (s), 704 (s) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 1), 316 (30), 122 (100), 94 (16).

F_2 (more polar) was obtained as a yellow solid of **6bB** [1.04 g, 45% yield; mp 58–60 °C (EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88–7.59 (m, 5H), 3.10–2.91 (m, 3H), 2.91 (dt, J=8.6, 2.3 Hz, 1H), 2.62 (q, J=8.0 Hz, 1H), 2.47–2.24 (m, 1H), 2.03–1.63 (m, 4H), 1.60–1.06 (m, 13H), 0.88 (t, J=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 130.3, 128.8 (2C), 124.1 (2C), 65.9, 56.9, 55.4, 48.1, 31.8, 29.5, 27.4, 27.1, 25.8, 23.5, 22.5, 19.2, 17.5, 14.0; IR (Nujol): ν_{max} 2783 (m), 1461 (m), 1039 (s), 750 (m) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 1), 316 (29), 248 (10), 123 (25), 122 (100). HRMS (ESI): calcd for $C_{20}H_{32}NOS$, 334.2205; found, 334.2209.

*4.3.3.7. (±)-Indolizidine 167B (**2a**). General procedure*. A stirred solution of **6aA** (0.21 g, 0.72 mmol) and $NiCl_2\cdot 6H_2O$ (1.56 g, 6.56 mmol) in a 1:3 mixture of THF and MeOH (6 mL) was cooled to 0 °C. $NaBH_4$ (0.79 g, 20.79 mmol) was added in small portions within 20 min at such a rate that the temperature was kept below 10 °C. The mixture was stirred at room temperature for 2 h. The black precipitate was filtered off over Celite and washed with hexanes (3×20 mL). The combined extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a colorless liquid of a crude product, which was purified by column chromatography (Al_2O_3, hexanes) to afford a colorless liquid of (±)-indolizidine 167B (**2a**) (0.098 g, 82% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.29 (dt, J=8.7, 2.2 Hz, 1H, C_3-H_e), 1.97 (q, J=9.0 Hz, 1H, C_3-H_a), 1.93–1.09 (m, 16H), 0.91 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.6, 64.3, 52.0, 37.4, 31.5, 31.3, 31.1, 25.2, 20.9, 19.6, 15.0. IR (neat): ν_{max} 2781 (s), 1458 (m), 1129 (m), 1056 (w) cm^{-1}. MS: *m/z* (%) relative intensity 168 (M^++1, 6), 124 (100), 96 (73), 81 (21). The spectroscopic data were consistent with the literature.[7e]

*4.3.3.8. (±)-epi-Indolizidine 167B (epi-**2a**)*. According to the general procedure described for (±)-indolizidine 167B (**2a**), a reaction of **6aB** (0.28 g, 0.96 mmol), $NiCl_2\cdot 6H_2O$ (2.08 g, 8.75 mmol), and $NaBH_4$ (1.14 g, 30 mmol) in a mixture of THF (2.5 mL) and MeOH (7.5 mL) gave a pale yellow liquid of a crude product, which was purified by column chromatography (Al_2O_3, 100% hexanes) to afford a colorless liquid of *epi*-**2a** (0.118 g, 74% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.01–2.93 (m, 1H), 2.88 (dt, J=8.9, 3.4 Hz, 1H, C_3-H_e), 2.71 (q, J=8.2 Hz, 1H, C_3-H_a), 2.63–2.52 (m, 1H), 1.91–1.31 (m, 14H), 0.94 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 55.8, 49.3, 31.5, 31.0, 28.0, 26.5, 21.4, 21.3, 19.8, 14.9; IR (neat): ν_{max} 2930 (s), 2872 (s), 2804 (m), 1457 (m) cm^{-1}. MS: *m/z* (%) relative intensity 168 (M^++1, 9), 167 (M^+, 67), 150 (26), 149 (100), 124 (40), 122 (38), 96 (31), 55 (25). The spectroscopic data were consistent with the literature.[7e]

*4.3.3.9. (±)-Indolizidine 209D (**2b**)*. According to the general procedure described for (±)-indolizidine 167B (**2a**), the reaction of **6bA** (0.23 g, 0.69 mmol), $NiCl_2\cdot 6H_2O$ (1.63 g, 6.86 mmol), and $NaBH_4$ (0.79 g, 20.79 mmol) in a mixture of THF (2 mL) and MeOH (6 mL) gave a pale yellow liquid of a crude product, which was purified by column chromatography (Al_2O_3, hexanes) to afford a colorless liquid of (±)-indolizidine 209D (**2b**) (0.116 g, 80% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.26 (dt, J=8.7, 2.0 Hz, 1H, C_3-H_e), 1.97 (q, J=8.8 Hz, 1H, C_3-H_a), 1.92–1.07 (m, 22H), 0.89 (app t, J=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.6, 64.5, 52.1, 35.2, 32.4, 31.5, 31.4, 31.1, 30.3, 26.4, 25.3, 23.2, 21.0, 14.6; IR (neat): ν_{max} 2781 (s), 1457 (m), 1381 (m), 1129 (m) cm^{-1}. MS: *m/z* (%) relative intensity 210 (M^++1, 6), 149 (35), 124 (100), 96 (43). The spectroscopic data were consistent with the literature.[7e]

*4.3.3.10. (±)-epi-Indolizidine 209D (epi-**2b**)*. According to the general procedure described for (±)-indolizidine 167B (**2a**), a reaction of **6bB** (0.236 g, 0.71 mmol), $NiCl_2\cdot 6H_2O$ (1.64 g, 6.90 mmol), and $NaBH_4$ (0.79 g, 20.79 mmol) in a mixture of THF (2 mL) and MeOH (6 mL) gave a pale yellow liquid of a crude product, which was purified by column chromatography (Al_2O_3, 100% hexanes) to afford a colorless liquid of *epi*-**2b** (0.127 g, 86% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 2.97–2.87 (m, 1H, C_5-H), 2.82 (dt, J=8.8, 3.2 Hz, 1H, C_3-H_e), 2.64 (q, J=8.4 Hz, 1H, C_3-H_a), 2.53–2.40 (m, 1H), 1.94–1.01 (m, 20H), 0.92–0.79 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 55.1, 48.7, 31.9, 31.2, 30.6, 29.6, 27.6, 27.5, 23.4, 22.6, 20.8, 19.3, 14.0. IR (neat): ν_{max} 2929 (s), 2859 (s), 2804 (m), 1459 (m) cm^{-1}. MS: *m/z* (%) relative intensity 209 (M^+, 2), 149 (28), 124 (100), 96 (53). The spectroscopic data were consistent with the literature.[7e]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2008.01.008.

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Asymmetric synthesis of pentenomycin I, epipentenomycin I, and their analogs

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ABSTRACT

The synthetic utility of the intramolecular acylation of α-sulfinyl carbanions as an efficient and general synthetic approach for the preparation of (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**) and their enantiomers (*ent*-**1** and *ent*-**5**), starting from chiral (2*S*,5*S*,6*S*)-ester **6** and *ent*-**6**, respectively, has been demonstrated. Easy accesses to pentenomycin analogs have also been demonstrated through the Pummerer, Suzuki–Miyaura, and Sonogashira reactions.

1. Introduction

Natural products containing highly oxygenated cyclopentenoid skeleton, for example, cryptosporiopsin,[1] kjellmanianone,[2] reductiomycin,[3] and didemnenones,[4] have attracted considerable attention due to their interesting biological activities. Among these classes of compounds, pentenomycins I–III (**1**–**3**) and dehydropentenomycin (**4**) are representatives of small highly oxygenated cyclopentenone antibiotics (Fig. 1). Pentenomycin I (**1**) and pentenomycin II (**2**) were first isolated from aerobic culture broths of a mutant strain of *Streptomyces eurythermus*.[5] Pentenomycin III (**3**)[6a] and dehydropentenomycin (**4**)[6b] (antibiotic G-2201-C) were isolated from *Streptoverticillium eurocidicum* SF-1768 and *Streptomyces cattleya*, respectively. (+)-Epipentenomycin I (*ent*-**5**) was found in carpophores of *Perziza* sp. collected from horse manure.[7] Pentenomycins I and II (**1** and **2**) exhibit moderate to strong activity in vitro against a variety of both Gram-positive and Gram-negative bacteria.[5] Because of their important biological activities as well as their highly oxygenated structures, there have been several studies directed toward the synthesis of pentenomycins and analogs in both enantiomeric and racemic forms.[8,9]

2. Results and discussion

Previously, we reported intramolecular acylation of α-sulfinyl carbanions as general strategies for the preparation of highly functionalized cyclopentenones,[10] cyclohexenones,[11] and α,β-unsaturated-γ- and δ-butyrolactones.[12] The method was successfully applied to the racemic synthesis of (±)-pentenomycin I (**1**) and (±)-epipentenomycin I (**5**) as well as dehydropentenomycin I (**4**), starting from (±)-methyl glycerate acetonide.[13] We report herein asymmetric synthesis of pentenomycin I and epipentenomycin I and their analogs starting from an appropriate chiral ester **6** or *ent*-**6**.[14] A retrosynthetic analysis of (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**) and their enantiomers is presented in Figure 2. Of interest to our laboratory is the convergent synthesis of highly functionalized cyclopentenones via intramolecular acylation of α-sulfinyl carbanions.[10,13] Accordingly, we anticipated that the key feature of our retrosynthetic analysis is a diastereoselective hydroxyalkylation of the enolate anion derived from chiral ester **6** with 3-phenylsulfanylpropanal, which, after oxidation, leads to the expected equatorial-sulfoxide **8**. The sulfinylcyclopentanone **9** would be constructed via the intramolecular acylation of α-sulfinyl carbanion generated from sulfinylester **8**. Finally, pyrolysis followed by hydrolysis should provide the required pentenomycin I (**1**) and epipentenomycin I (**5**) with high enantioselectivity. In the forward synthetic sense, (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**) are derived from chiral ester **6** while *ent*-**6** provides (+)-pentenomycin I (*ent*-**1**) and (+)-epipentenomycin I (*ent*-**5**).

Efforts toward the synthesis of (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**) began with the chiral ester **6** (Scheme 1).

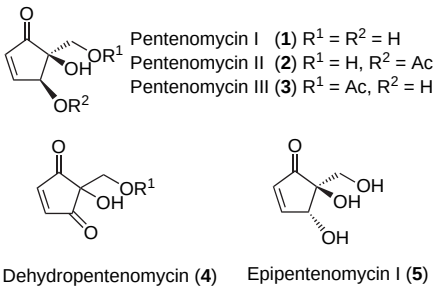

Figure 1. Pentenomycins, dehydropentenomycin, and epipentenomycin I.

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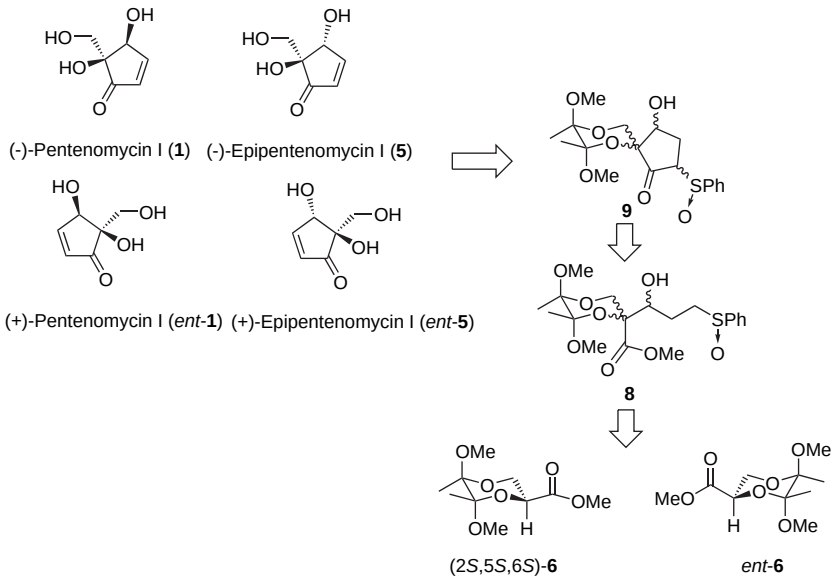
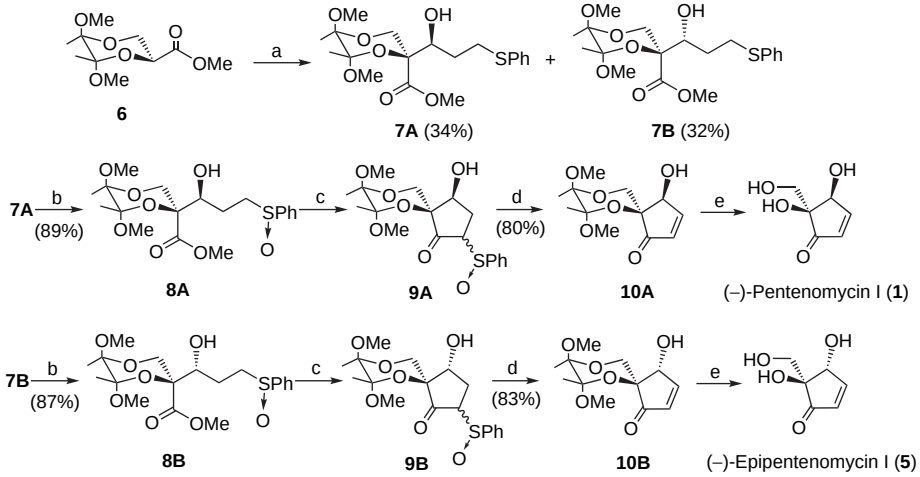


Figure 2. Retrosynthetic analysis.

Ley and co-workers previously reported that the enolate anions of (2*S*,5*S*,6*S*)-ester **6** and *ent*-**6** reacted with electrophiles at the equatorial position with high stereoselectivity.[14,15] Thus, treatment of (2*S*,5*S*,6*S*)-ester **6** with lithium diisopropylamide (LDA) (1.25 equiv) followed by reaction with 3-phenylsulfanylpropanal afforded the expected sulfide **7** in 66% yield as a mixture of diastereomers. Separation of the diastereomers was made by column chromatography to give **7A** and **7B** in 34 and 32% yields, respectively. It is worth mentioning that axial adducts were not observed as revealed by ^{1}H NMR, ^{13}C NMR as well as TLC analysis. Oxidation of sulfides **7A** and **7B** with sodium metaperiodate ($NaIO_4$, 1.2 equiv) in aqueous methanol at 0 °C to room temperature overnight gave the corresponding sulfoxides **8A** and **8B** in 89 and 87% yields, respectively, each as a mixture of diastereomers. Treatment of **8A** or **8B** with LDA (3.5 equiv) in THF at −78 °C for 2 h and 0 °C for 2 h followed by quenching with saturated ammonium chloride solution afforded spiroketosulfoxide **9A** or **9B**, each as a mixture of diastereomers in quantitative yield. Subsequent sulfoxide elimination of the crude products **9A** and **9B** in refluxing toluene in the presence of $CaCO_3$ for 15 h yielded the corresponding hydroxylspirocyclopentenones **10A** and **10B** in 80 and 83% yields, respectively. Eventually, hydrolysis of the butanediacetal (BDA) protecting group of **10A** and **10B** using 90% TFA at 0 °C for 5 h readily afforded (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**) in quantitative yield. Chemical structures and optical properties of the synthesized (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**) were established and confirmed by comparing the ^{1}H NMR and ^{13}C NMR as well as the sign of the optical rotations with those reported in the literature. The data are in good agreement with the reported values.[5,9]

Having accomplished the synthesis of (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**), the syntheses of their corresponding enantiomers, i.e., (+)-pentenomycin I (*ent*-**1**) and (+)-epipentenomycin I (*ent*-**5**), respectively, were straightforward starting from *ent*-**6** using the reaction conditions described in Scheme 1. Yields in each step were comparable to those obtained in the prior synthetic route starting from (2*S*,5*S*,6*S*)-ester **6**. The spectroscopic data and optical properties of (+)-pentenomycin I (*ent*-**1**) and (+)-epipentenomycin I (*ent*-**5**) were in agreement with those reported in the literature (Fig. 3).[7]

At this stage, we would like to demonstrate the synthetic versatility of our synthesis by preparing some pentenomycin analogs from common intermediates isolated from our synthetic approach to the pentenomycins. Accordingly, spiroketosulfoxide *ent*-**9A** was



Scheme 1. Synthesis of (−)-pentenomycin I (**1**) and (−)-epipentenomycin I (**5**). Reagents and conditions: (a) LDA, THF, −78 °C, then $PhS(CH_2)_2CHO$; (b) $NaIO_4$, MeOH, H_2O; (c) LDA (3.5 equiv), THF, −78 °C, 2 h then 0 °C, 2 h; (d) toluene, $CaCO_3$, reflux, 15 h; (e) 90% TFA, 0 °C, 5 h.

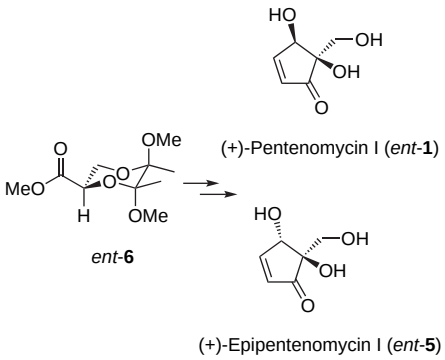
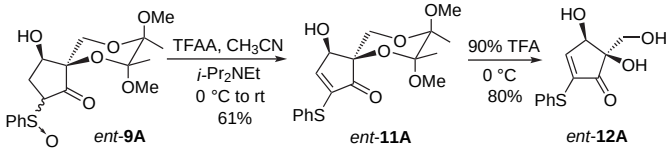


Figure 3. Synthetic approach to *ent*-**1** and *ent*-**5**.

subjected to the Pummerer rearrangement.[16] Reaction employing acetic anhydride led to the recovery of the starting material. Gratifyingly, treatment of *ent*-**9A** with trifluoroacetic anhydride (1.1 equiv) and ethyldiisopropylamine in acetonitrile at 0 °C to room temperature overnight, after chromatography, provided *ent*-**11A** in 61% yield (Scheme 2). Subsequent standard hydrolysis of the BDA-protecting group (90% aqueous TFA, 0 °C, 5 h) provided α-phenylsulfanylpentenomycin (*ent*-**12A**) in 80% yield as colorless crystals. Highly oxygenated cyclopentenones of type *ent*-**11A** and *ent*-**12A** may be useful as starting materials for further synthetic manipulation.



Scheme 2. Preparation of *ent*-α-phenylsulfanylpentenomycin I (*ent*-**12A**).

Compound *ent*-**10A** has proven to be a crucial intermediate for the synthesis of α-aryl- and α-alkynyl-substituted pentenomycin derivatives by employing the Suzuki–Miyaura and Sonogashira reactions, respectively (Scheme 3). Initially, α-iodo derivative *ent*-**13A** was prepared by treatment of *ent*-**10A** with I_2 in the presence of an amine base such as DMAP and pyridine. Under optimal conditions, I_2/pyridine in CCl_4,[17] *ent*-**13A** was obtained in 97% yield from *ent*-**10A**.

The Suzuki–Miyaura coupling reaction[18] of *ent*-**13A** with phenylboronic acid was carried out by treatment of *ent*-**13A** with phenylboronic acid in THF in the presence of 10 mol % $PdCl_2(PPh_3)_2$ and Na_2CO_3 at 40 °C for 15 h under an argon atmosphere to afford the expected α-phenyl-substituted derivative *ent*-**14A** in 70% yield together with 25% yield of the recovered starting material. The reaction employing K_2CO_3 in THF and DMF provided low yield of *ent*-**14A**. α-Phenylspirocyclopentenone *ent*-**14A** was hydrolyzed under standard conditions to give the corresponding α-phenylpentenomycin *ent*-**15A** as a white solid in 84% yield after chromatography.

Our success of the Suzuki–Miyaura coupling reaction of *ent*-**14A** led us to further investigate the Sonogashira coupling reaction.[19] The optimum conditions were found to employ $PdCl_2(PPh_3)_2$, CuI, and diisopropylamine in THF. The reactions of *ent*-**13A** with both phenylacetylene and *tert*-butylacetylene were completed within 45 min and gave good yields of the corresponding coupling products *ent*-**16Aa**,**b** (Scheme 3).

3. Conclusion

The work described in this article demonstrated the synthetic utility of the intramolecular acylation of α-sulfinyl carbanions as an efficient and general synthetic approach for the preparation of both enantiomers of pentenomycin I and epipentenomycin I, starting from readily available chiral ester (2*S*,5*S*,6*S*)-**6** and *ent*-**6**. Syntheses of pentenomycin analogs have been carried out via the Pummerer, Suzuki–Miyaura, and Sonogashira reactions. Compound *ent*-**10A**, a precursor for *ent*-pentenomycin I (*ent*-**1**), was employed as a versatile starting material for the preparation of α-alkynyl- and α-phenyl-substituted pentenomycins.

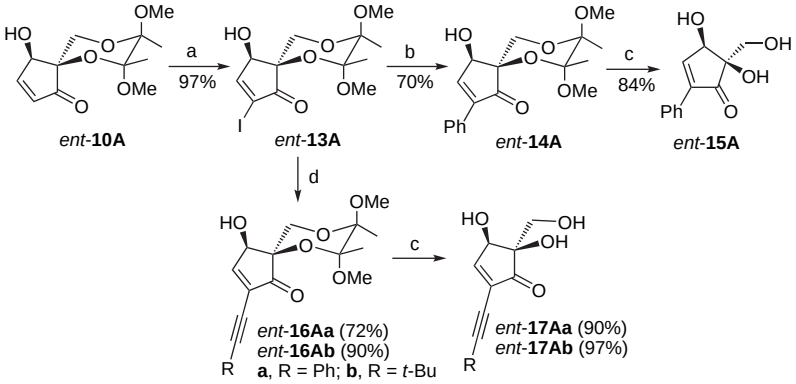
4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR were recorded on a Bruker DPX-300 or a Bruker DPX-500 spectrometer. IR spectra were recorded either with a Jasco A-302 or a Perkin–Elmer 683 infrared spectrometer. Mass spectra were performed on a Thermo Finnigan Polaris Q mass spectrometer. Microanalyses were performed with a Perkin–Elmer Elemental analyzer 2400 CHN. High resolution MS were obtained from either HR-TOF-MS Micromass model VQ-TOF2 or Finnigan MAT 95 mass spectrometer. All chemicals used are of commercial grade.

4.2. (2*S*,5*S*,6*S*)-2-(1′-Hydroxy-3′-(phenylsulfanyl)propyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylic acid methyl ester (7)

General procedure A: a THF (15 mL) solution of (2*S*,5*S*,6*S*)-ester **6** (5.39 g, 23.00 mmol) was added slowly to a THF (25 mL) solution



Scheme 3. Preparation of *ent*-**15A** and *ent*-**17A**. Reagents and conditions: (a) I_2, pyridine, CCl_4; (b) $PhB(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3, THF, 60 °C; (c) 90% TFA, 0 °C, 5 h; (d) phenylacetylene or *tert*-butylacetylene, $PdCl_2(PPh_3)$, CuI, *i*-Pr_2NH, THF, 0 °C, 45 min.

of LDA [(28.75 mmol), prepared by reacting *N*,*N*-diisopropylamine (4.53 mL, 32.2 mmol) with *n*-BuLi (1.35 M in hexane, 22.0 mL, 28.75 mmol)] at −78 °C. The mixture was stirred at −78 °C for 2 h. To this solution was added a THF (5.75 mL) solution of 3-phenylsulfanylpropanal [freshly prepared by reacting of Et_3N (4.0 mL, 28.75 mmol), thiophenol (4.57 mL, 36.0 mmol) with acrolein (1.90 mL, 28.75 mmol)]. The resulting mixture was stirred at −78 °C for 2 h and quenched with saturated aqueous NH_4Cl solution (30 mL). Layers were separated and the aqueous phase was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4. The organic phase was concentrated (aspirator then in vacuo) to give a crude pale yellow liquid, which was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes). The less polar fraction was **7A** (3.129 g, 34% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.00 (m, 5H, Ar*H*), 3.98 (d, *J*=11.6 Hz, 1H, C–CH*H*), 3.96–3.89 (m, 1H, C–C*H*), 3.86 (d, *J*=11.6 Hz, 1H, C–C*H*H), 3.53 (s, 3H, CO_2CH_3), 3.15 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.10–3.05 (m, 2H, CH*H*–CH_2 and br O*H*), 2.90–2.78 (m, 1H, C*H*H–CH_2), 1.50–1.35 (m, 1H, CH–CH*H*), 1.35–1.20 (m, 4H, CH_3, CH–C*H*H), 1.20 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7 (C=O), 135.6 (C), 129.2 (2×CH), 128.7 (2×CH), 125.8 (CH), 99.7 (C), 97.6 (C), 76.1 (CH), 72.6 (CH), 56.4 (CH_2), 52.1 (CH), 50.2 (CH), 48.0 (CH_3), 30.0 (CH_3), 28.4 (CH_3), 17.5 (CH_3), 17.4 (CH_3). IR (neat): ν_{max} 3480 m, 1739 s, 1584 m, 1482 s, 1375 s, 1148 s, 1037 s, 740 m, 692 m cm^{-1}. MS: *m*/*z* (% relative intensity): 400 (M^+, 0.6), 337 (46), 143 (100), 136 (81), 123 (62), 110 (58), 93 (45). HRMS (ESI-TOF) calcd for $C_{19}H_{28}O_7SNa$: 423.1453; found: 423.1454. $[\alpha]_D^{29}$ +139.7 (*c* 0.9, $CHCl_3$). The more polar fraction was **7B** (2.945 g, 32% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.06 (m, 5H, Ar*H*), 4.05 (d, *J*=11.7 Hz, 1H, CH*H*), 3.76 (dd, *J*=8.8, 3.9 Hz, 1H, C*H*O), 3.69 (s, 3H, CO_2CH_3), 3.65 (d, *J*=11.7 Hz, 1H, C*H*H), 3.19 (s, 2×3H, OCH_3), 3.11–3.03 (m, 1H, C*H*H–CH_2), 2.96–2.85 (m, 1H, C*H*H–CH_2), 2.10–1.85 (br s, 1H, O*H*), 1.61–1.49 (m, 2H, CH–CH_2), 1.24 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8 (C=O), 135.9 (C), 129.4 (2×CH), 128.8 (2×CH), 126.0 (CH), 99.4 (C), 97.9 (C), 75.3 (C), 73.3 (CH), 59.5 (CH_2), 52.1 (CH_3), 50.5 (CH_3), 48.2 (CH_3), 30.4 (CH_2), 30.3 (CH_2), 17.7 (CH_3), 17.6 (CH_3). IR (neat): ν_{max} 3480 m, 1739 s, 1634 w, 1585 m, 1482 m, 1440 s, 1252 s, 1147 s, 1101 s, 1050 s, 1037 m cm^{-1}. MS: *m*/*z* (% relative intensity): 400 (M^+, 0.2), 251 (47), 220 (45), 192 (49), 143 (100), 136 (92), 123 (76), 110 (82). HRMS (ESI-TOF) calcd for $C_{19}H_{28}O_7SNa$: 423.1453; found: 423.1450. $[\alpha]_D^{29}$ +60.6 (*c* 1.75, $CHCl_3$).

4.3. (2*R*,5*R*,6*R*)-2-(1′-Hydroxy-3′-(phenylsulfanyl)propyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylic acid methyl ester (*ent*-7)

According to the general procedure A, a THF (15 mL) solution of (2*R*,5*R*,6*R*)-ester *ent*-**6** (4.683 g, 20.0 mmol) was treated with a THF (20 mL) solution of LDA (25 mmol) at −78 °C. The resulting solution was reacted with a THF (5 mL) solution of 3-phenylsulfanylpropanal [freshly prepared from Et_3N (3.48 mL, 25.0 mmol), thiophenol (3.98 mL, 31.25 mmol) and acrolein (1.65 mL, 25.0 mmol)]. The crude product was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to give two separable diastereomers of *ent*-**7**. A less polar fraction was *ent*-**7A** (2.637 g, 33% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.00 (m, 5H, Ar*H*), 3.98 (d, *J*=11.6 Hz, 1H, C–CH*H*), 3.96–3.89 (m, 1H, C–C*H*), 3.86 (d, *J*=11.6 Hz, 1H, C–C*H*H), 3.53 (s, 3H, CO_2CH_3), 3.15 (s, 3H, –OCH_3), 3.12 (s, 3H, OCH_3), 3.10–3.05 (m, 1H, CH*H*–CH_2), 2.90–2.78 (m, 2H, C*H*H–CH_2 and br O*H*), 1.50–1.35 (m, 1H, CH–CH*H*), 1.35–1.20 (m, 4H, CH_3, CH–C*H*H), 1.20 (s, 3H, CH_3). $[\alpha]_D^{29}$ −110.6 (*c* 0.98, $CHCl_3$). A more polar fraction was *ent*-**7B** (liquid, 2.482 g, 31% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.06 (m, 5H, Ar*H*), 4.05 (d, *J*=11.7 Hz, 1H, CH*H*), 3.76 (dd, *J*=8.8, 3.9 Hz, 1H, C–C*H*), 3.66 (s, 3H, CO_2CH_3), 3.65 (d, *J*=11.7 Hz, 1H, C*H*H), 3.19 (s, 2×3H, OCH_3), 3.11–3.03 (m, 1H, C*H*H–CH_2), 2.96–2.85 (m, 1H, C*H*H–CH_2), 1.56–1.49 (m, 3H, CH–CH_2 and br O*H*), 1.24 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). $[\alpha]_D^{29}$ −67.0 (*c* 1.76, $CHCl_3$).

4.4. (2*S*,5*S*,6*S*,1′*S*)-2-(1′-Hydroxy-3′-(phenylsulfinyl)propyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylic acid methyl ester (8A)

General procedure B: a solution of (2*S*,5*S*,6*S*,1′*S*)-**7A** (3.00 g, 7.48 mmol) in methanol (36 mL) was added dropwise to a suspension of $NaIO_4$ (0.942 g, 8.976 mmol) in water (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C to room temperature overnight. The precipitate of $NaIO_3$ was filtered and washed several times with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. Filtration followed by evaporation (aspirator then in vacuo) gave a yellow liquid of the crude product, which was purified by column chromatography (silica gel, 80% ethyl acetate in hexanes) to furnish a pale yellow liquid of (2*S*,5*S*,6*S*,1′*S*)-**8A** (2.776 g, 89% yield) as a 1:1 mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.60–7.42 (m, 2×5H, Ar*H*), 4.12 (d, *J*=11.5 Hz, 1H, OC*H*H), 4.04 (d, *J*=11.5 Hz, 1H, OCH*H*), 3.81 (d, *J*=11.5 Hz, 1H, OCH*H*), 3.77 (d, *J*=11.5 Hz, 1H, OC*H*H), 3.69–3.61 (br s, 4H, OCH_3 and C*H*OH), 3.62 (s, 3H, OCH_3), 3.30 (br, 1H, O*H*), 3.16 (s, 3H, OCH_3), 3.14 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 3.20–3.02 (m, 3×1H, C*H*H–CH_2 and C*H*OH), 2.85 (br, 1H, O*H*), 2.83–2.65 (m, 2×1H, CH*H*–CH_2), 1.80–1.40 (m, 2×2H, CH_2–CH), 1.21 (s, 2×3H, CH_3), 1.17 (s, 2×3H, –CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (C=O), 171.3 (C=O), 143.1 (C), 142.7 (C), 130.8 (2×CH), 129.06 (2×CH), 129.02 (2×CH), 123.9 (2×CH), 123.8 (2×CH), 99.64 (C), 99.61 (C), 97.69 (C), 97.67 (C), 75.6 (C), 75.4 (C), 73.7 (CH), 73.3 (CH), 58.0 (CH_2), 57.5 (CH_2), 54.0 (CH_2), 53.9 (CH_2), 53.3 (2×C), 52.3 (CH_3), 52.1 (CH_3), 50.2 (2×CH_3), 48.0 (CH_3), 47.9 (CH_3), 23.2 (CH_2), 22.8 (CH_2), 17.5 (CH_3), 17.4 (CH_3). IR (neat): ν_{max} 3364 m, 1738 s, 1732 s, 1445 s, 1374 s, 1251 s, 1146 s, 1046 m, 883 s, 751 m, 692 m cm^{-1}. MS: *m*/*z* (% relative intensity): 416 (M^+, 0.3), 143 (87), 125 (65), 109 (64), 93 (48), 83 (59), 73 (100). HRMS (ESI-TOF) calcd for $C_{19}H_{28}O_8SNa$: 439.1403; found: 439.1390.

4.5. (2*S*,5*S*,6*S*,1′*R*)-2-(1′-Hydroxy-3′-(phenylsulfinyl)propyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylic acid methyl ester (8B)

According to the general procedure B, a solution of (2*S*,5*S*,6*S*,1′*R*)-**7B** (2.019 g, 5.00 mmol) in methanol (24.00 mL) was treated with $NaIO_4$ (0.634 g, 6.0 mmol) in water (24 mL) at 0 °C to room temperature overnight to give a crude product, which was purified by column chromatography (silica gel, 80% ethyl acetate in hexanes) to furnish a yellow syrup of (2*S*,5*S*,6*S*,1′*R*)-**8B** (1.828 g, 87% yield) as 1:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.58–7.31 (m, 2×5H, Ar*H*), 4.15 (d, *J*=11.5 Hz, 1H, O–C*H*H), 4.12 (d, 1H, *J*=11.5 Hz, O–CH*H*), 3.71 (s, 3H, OCH_3), 3.69 (m, 2×1H, C*H*–OH), 3.68 (s, 3H, CO_2CH_3), 3.56 (d, *J*=11.5 Hz, 2×1H, OCH*H*), 3.18 (s, 3H, OCH_3), 3.14 (s, 2×3H, OCH_3), 3.10 (s, 3H, OCH_3), 3.10–3.01 (m, 2×1H, CH*H*–CH_2), 2.90–2.62 (m, 2×2H, CH*H*–CH and br O*H*), 2.20–1.91 (m, 2×1H, C*H*H–CH), 1.69–1.61 (m, 2×1H, CH–CH*H*), 1.21 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4 (C=O), 172.1 (C=O), 143.1 (C), 142.0 (C), 131.0 (CH), 130.9 (CH), 129.2 (2×CH), 129.1 (2×CH), 124.2 (2×CH), 124.0 (2×CH), 99.37 (C), 99.32 (C), 97.9 (2×C), 75.0 (C), 74.9 (C), 74.1 (CH), 73.8 (CH), 58.6 (CH_2), 58.2 (CH_2), 54.7 (CH_2), 53.7 (CH_2), 52.3 (CH_3), 52.2 (CH_3), 50.35 (2×CH_3), 48.1 (CH_3), 48.0 (CH_3), 25.2 (CH_2), 24.7 (CH_2), 17.64 (2×CH_3), 17.58 (2×CH_3). IR (neat): ν_{max} 3554 s, 2923 s, 2583 s, 1726 s, 1455 s, 1377 s, 1303 m, 1253 m, 1145 s cm^{-1}. MS: *m*/*z* (% relative intensity): 416 (M^+, 0.1), 143 (78), 141.2 (78), 125 (55), 115 (100), 109

(48), 83 (74). HRMS (ESI) calcd for $C_{19}H_{28}O_8SNa$: 439.1403; found: 439.1400.

4.6. (2*R*,5*R*,6*R*,1′*R*)-2-(1′-Hydroxy-3′-(phenylsulfinyl)propyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylic acid methyl ester (*ent*-8A)

According to the general procedure B, a solution of (2*R*,5*R*,6*R*,1′*R*)-*ent*-**7A** (2.082 g, 5.20 mmol) in methanol (25 mL) was treated with $NaIO_4$ (0.654 g, 1.39 mmol) in water (10 mL) at 0 °C to room temperature overnight to give a crude product, which was purified by column chromatography (silica gel, 80% ethyl acetate in hexanes) to furnish a pale yellow syrup of (2*R*,5*R*,6*R*,1′*R*)-*ent*-**8A** (1.832 g, 87% yield) as a mixture of diastereomers. The ^{1}H NMR spectrum was identical to that of **8A**: ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.60–7.42 (m, 2×5H, Ar*H*), 4.12 (d, *J*=11.5 Hz, 1H, OC*H*H), 4.04 (d, *J*=11.5 Hz, 1H, OCH*H*), 3.81 (d, *J*=11.5 Hz, 1H, OCH*H*), 3.77 (d, *J*=11.5 Hz, 1H, OC*H*H), 3.69 (s, 3H, OCH_3), 3.62 (s, 4H, OCH_3 and C*H*OH), 3.16 (s, 4H, OCH_3 and C*H*OH), 3.14 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 3.02 (m, 2×1H, C*H*H–CH_2), 2.83–2.75 (m, 2×1H, –CH*H*–CH_2), 2.70 (br s, 2×1H, O*H*), 1.80–1.40 (m, 2×2H, CH_2–CH), 1.21 (s, 2×3H, CH_3), 1.17 (s, 2×3H, CH_3).

4.7. (2*R*,5*R*,6*R*,1′*S*)-2-(1′-Hydroxy-3′-(phenylsulfinyl)propyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylic acid methyl ester (*ent*-8B)

According to the general procedure B, a solution of (2*R*,5*R*,6*R*,1′*S*)-*ent*-**7B** (2.403 g, 6.00 mmol) in methanol (38 mL) was treated with $NaIO_4$ (0.755 g, 1.60 mmol) and water (10 mL) at 0 °C to room temperature overnight to give a pale yellow syrup of a crude product, which was purified by column chromatography (silica gel, 80% ethyl acetate in hexanes) to furnish a pale yellow syrup of (2*R*,5*R*,6*R*,1′*S*)-*ent*-**8B** (2.125 g, 85% yield) as a mixture of diastereomers. The ^{1}H NMR spectrum was identical to that of **8B**: ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.51–7.40 (m, 2×5H, Ar*H*), 4.22 (d, *J*=11.5 Hz, 1H, OC*H*H), 4.19 (d, *J*=11.5 Hz, 1H, OCH*H*), 3.78 (s, 3H, CO_2CH_3), 3.76 (m, 2×1H, C*H*OH), 3.75 (s, 3H, CO_2CH_3), 3.63 (d, 2×1H, *J*=11.5 Hz, OCH*H*), 3.25 (s, 3H, OCH_3), 3.21 (s, 2×3H, OCH_3), 3.17 (s, 3H, OCH_3), 3.05–2.75 (m, 2×2H, CH_2–CH_2 and br O*H*), 2.88 (m, 2×1H, CH*H*–CH), 2.04–1.98 (m, 2×1H, C*H*H–CH), 1.76–1.68 (m, 2×1H, CH–CH*H*), 1.28 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.24 (s, 3H, CH_3).

4.8. (2*S*,5*S*,6*S*,5′*S*)-5′-Hydroxy-2′-oxo-3′-phenylsulfinyl spirocyclopentane-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane (9A)

General procedure C: a THF (11 mL) solution of (2*S*,5*S*,6*S*,5′*S*)-**8A** (1.806 g, 5.00 mmol) was slowly added to a cooled (−78 °C) THF (12 mL) solution of LDA [(17.50 mmol), prepared by reacting *N*,*N*-diisopropylamine (2.76 mL, 19.6 mmol) with *n*-BuLi (1.35 M in hexane, 13.35 mL, 17.5 mmol)]. The reaction mixture was stirred at −78 °C for 2 h and at 0 °C for 2 h. The resulting dark-orange solution was quenched with saturated aqueous NH_4Cl solution (40 mL) and extracted with ethyl acetate (3×30 mL). The organic phase was washed with water (30 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The crude product obtained was purified by column chromatography (silica gel, 30–65% ethyl acetate in hexanes) to give two fractions of **9A**. Fraction I (less polar) was obtained as a white solid (0.317 g, 19% yield, mp 172–175 °C; a single diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.54 (m, 5H, Ar*H*), 4.25 (d, *J*=8.8 Hz, 1H, C–C*H*H), 4.00–3.95 (m, 2H, C–CH*H* and C*H*H–CHOH), 3.74 (d, *J*=11.6 Hz, 1H, SOC*H*), 3.28 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 2.72 (ddd, *J*=15.7, 11.6, 4.3 Hz, 1H, CH*H*–CHOH), 2.01 (d, *J*=15.7 Hz, 1H, C*H*OH), 1.65 (br s, 1H, O*H*), 1.32 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.9 (C=O), 140.2 (C), 131.5 (CH), 129.5 (2×CH), 124.1 (2×CH), 99.5 (C), 97.9 (C), 77.0 (C), 71.9 (CH), 69.5 (CH), 57.1 (CH_2), 49.1 (CH_3), 48.2 (CH_3), 26.5 (CH_2), 18.1 (CH_3), 17.7 (CH_3). IR ($CHCl_3$): ν_{max} 3290 w, 1755 s, 1445 m, 1146 s, 1114 s, 1032 m, 969 m cm^{-1}. MS: *m*/*z* (% relative intensity): 384 (M^+, 0.7), 227 (66), 195 (61), 126 (53), 115 (99), 101 (55), 73 (100). HRMS (ESI-TOF) calcd for $C_{18}H_{24}O_7SNa$: 407.1140; found: 407.1140. $[\alpha]_D^{29}$ +375.0 (*c* 0.60, $CHCl_3$). Fraction II (more polar) was obtained as a pale yellow viscous liquid (0.716 g, 43% yield; a mixture of two diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.61–7.42 (m, 10H, Ar*H*), 4.19 (br, 1H), 3.95 (br, 1H), 3.95 (d, *J*=12.3 Hz, 1H), 3.78–3.73 (m, 3H), 3.44 (dd, *J*=12.2, 10.4 Hz, 2H), 3.19 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 2.89 (s, 3H, OCH_3), 2.81 (d, *J*=15.5 Hz, 1H), 2.42 (br d, *J*=15.5 Hz, 1H), 1.51 (dd, *J*=13.7, 10.0 Hz, 2H), 1.40–1.10 (br, 2H, O*H*), 1.25 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.14 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205 (C=O), 203.8 (C=O), 142.5 (C), 138 (C), 131.4 (CH), 131.0 (2×CH), 129.2 (2×CH), 128.9 (2×CH), 124.7 (CH), 123.8 (2×CH), 99.4 (C), 99.1 (C), 98.2 (C), 97.9 (C), 76.6 (C), 75.4 (C), 74.4 (CH), 72.7 (CH), 69.1 (CH), 63.3 (CH), 57.3 (CH_2), 56.5 (CH_2), 49.5 (CH_3), 48.7 (CH_3), 48.3 (CH_3), 48.1 (CH_3), 31.4 (CH_2), 23.2 (CH_2), 18.2 (2×CH_3), 17.7 (CH_3), 17.6 (CH_3). IR ($CHCl_3$): ν_{max} 3368 w, 3028 m, 1755 s, 1445 m, 1147 s, 1112 s, 1036 m cm^{-1}. MS: *m*/*z* (% relative intensity): 384 (M^+, 0.4), 227 (43), 195 (56), 125 (77), 115 (74), 111 (88), 109 (48), 99 (61), 97 (43), 73 (100). HRMS (ESI-TOF) calcd for $C_{18}H_{24}O_7SNa$: 407.1132; found: 407.1108.

4.9. (2*S*,5*S*,6*S*,5′*R*)-5′-Hydroxy-2′-oxo-3′-phenylsulfinyl spirocyclopentane-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane (9B)

According to the general procedure C, a THF (10 mL) solution of (2*S*,5*S*,6*S*,5′*R*)-**8B** (1.611 g, 4.45 mmol) was added slowly to a cooled (−78 °C) THF (10 mL) solution of LDA (15.60 mmol). After stirring at −78 °C for 2 h, the mixture was stirred at 0 °C for 2 h and quenched with saturated aqueous NH_4Cl solution (40 mL) and extracted with ethyl acetate (3×30 mL). The organic phase was washed with water (30 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. The crude product obtained was purified by column chromatography (silica gel, 30–65% ethyl acetate in hexanes) to give two fractions of **9B**. Fraction I (less polar) was obtained as a white solid of (0.267 g, 18% yield, 165–168 °C; a single diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.34 (m, 5H, Ar*H*), 4.19 (dd, *J*=5.0, 3.0 Hz, 1H, C*H*OH), 4.03 (d, *J*=11.9 Hz, 1H, OC*H*H), 3.74 (d, *J*=11.9 Hz, 1H, OCH*H*), 3.56 (t, *J*=9.1 Hz, 1H, CH_2–C*H*), 3.28 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.56 (ddd, *J*=14.5, 9.1, 5.0 Hz, 1H, C*H*H), 1.80 (ddd, *J*=15.6, 11.9, 3.0 Hz, 1H, CH*H*), 1.6 (br s, 1H, O*H*), 1.36 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3 (C=O), 141.3 (C), 131.2 (CH), 129.3 (2×CH), 123.8 (2×CH), 100.6 (C), 99.3 (C), 81.1 (C), 70.9 (CH), 67.7 (CH), 58.3 (CH_2), 48.9 (CH_3), 48.1 (CH_3), 21.5 (CH_2), 18.6 (CH_3), 18.3 (CH_3). IR ($CHCl_3$): ν_{max} 3288 m, 1749 s, 1460 m, 1377 m, 1145 m, 1032 m cm^{-1}. MS: *m*/*z* (% relative intensity): 384 (M^+, 0.5), 153 (57), 149 (54), 126 (71), 111 (90), 109 (55), 73 (100). HRMS (ESI-TOF) calcd for $C_{18}H_{24}O_7Na$: 407.1140; found: 407.1140. $[\alpha]_D^{29}$ +305.9 (*c* 0.35, $CHCl_3$). Fraction II (more polar) was obtained as a pale yellow liquid (0.654 g, 44% yield; mixture of two diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.63–7.45 (m, 10H, Ar*H*), 4.20 (dd, *J*=10.1, 6.0 Hz, 1H), 3.74–3.65 (m, 3H), 3.42–3.30 (m, 1H), 3.30 (s, 3H, OCH_3), 3.27–3.05 (m, 5H), 3.23 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 2.71–2.65 (m, 1H), 2.56–2.40 (m, 1H), 2.39–2.29 (m, 1H), 1.90–1.74 (m, 1H), 1.31 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.21 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3 (C=O), 204.8 (C=O), 142.6 (C), 139.6 (C), 131.9 (CH), 131.2 (CH), 129.3 (2×CH), 129.1 (2×CH), 125.2 (2×CH), 123.9 (2×CH),

100.2 (C), 99.7 (C), 98.6 (C), 98.4 (C), 78.3 (C), 75.6 (C), 71.0 (CH), 70.2 (CH), 69.1 (CH), 66.8 (CH), 58.1 (CH_2), 57.5 (CH_2), 49.6 (CH_3), 48.9 (CH_3), 48.3 (CH_3), 48.0 (CH_3), 25.8 (CH_2), 22.9 (CH_2), 18.3 (CH_3), 18.1 (CH_3), 17.9 (CH_3), 17.8 (CH_3). IR ($CHCl_3$): ν_{max} 3386 m, 1754 s, 1445 m, 1376 m, 1147 s, 1112 s, 1055 m, 1036 m cm^{-1}. MS: *m*/*z* (% relative intensity): 385 (M^++1, 0.6), 227 (61), 195 (47), 126 (75), 115 (79), 109 (51), 69 (100). HRMS (ESI-TOF) calcd for $C_{18}H_{24}O_7Na$: 407.1140; found: 407.1136.

4.10. (2*R*,5*R*,6*R*,5′*R*)-5′-Hydroxy-2′-oxo-3′-phenylsulfinyl spirocyclopentane-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-9A)

According to the general procedure C, a THF (10 mL) solution of (2*R*,5*R*,6*R*,5′*R*)-*ent*-**8A** (1.695 g, 4.69 mmol) was treated with a THF (12 mL) solution of LDA (16.42 mmol) to provide a crude product, which was purified by column chromatography (silica gel, 30–65% ethyl acetate in hexanes) to give two fractions of *ent*-**9A**. Fraction I (less polar) was obtained as a white solid (0.3129 g, 20% yield, mp 174–175 °C; a single diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.54 (m, 5H, Ar*H*), 4.25 (d, *J*=8.8 Hz, 1H, C–C*H*H), 4.00–3.95 (m, 1H, C–CH*H*), 3.74 (d, *J*=11.6 Hz, 1H, S(O)C*H*), 4.00–3.90 (m, 1H, C*H*H–CHOH), 3.28 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 2.72 (ddd, *J*=15.7, 11.6, 4.3 Hz, 1H, CH*H*–CHOH), 2.01 (d, *J*=15.7 Hz, 1H, C*H*OH), 1.75 (br s, 1H, O*H*), 1.32 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). $[\alpha]_D^{29}$ −380.9 (*c* 0.31, $CHCl_3$). Fraction II (more polar) was obtained as a yellow liquid (0.655 g, 42% yield; mixture of two diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.61–7.42 (m, 2×5H, Ar*H*), 4.15 (br, 1H), 3.95 (br, 1H), 3.81 (d, *J*=12.3 Hz, 1H), 3.80–3.61 (m, 3H), 3.44 (dd, *J*=12.2, 10.4 Hz, 2H), 3.19 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 2.89 (s, 3H, OCH_3), 2.81 (d, *J*=14.5 Hz, 1H), 2.42 (d, *J*=15.5 Hz, 1H), 1.51 (dd, *J*=13.7, 10.0 Hz, 2H), 1.30–1.11 (br, 2×1H, O*H*), 1.25 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.14 (s, 3H, CH_3).

4.11. (2*R*,5*R*,6*R*,5′*S*)-5′-Hydroxy-2′-oxo-3′-phenylsulfinyl spirocyclopentane-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-9B)

According to the general procedure C, a THF (10 mL) solution of (2*R*,5*R*,6*R*,5′*S*)-*ent*-**8B** (2.080 g, 5.00 mmol) was treated with a THF (12 mL) solution of LDA (17.47 mmol) to provide a crude product, which was purified by column chromatography (silica gel, 30–65% ethyl acetate in hexanes) to give two fractions of *ent*-**9B**. Fraction I (less polar) was obtained as a white solid (0.439 g, 17% yield, mp 167–169 °C; a single diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.34 (m, 5H, Ar*H*), 4.19 (dd, *J*=5.0, 3.0 Hz, 1H, C*H*OH), 4.03 (d, *J*=11.9 Hz, 1H, OC*H*H), 3.74 (d, *J*=11.9 Hz, 1H, OCH*H*), 3.56 (t, *J*=9.1 Hz, 1H, CH_2–C*H*), 3.28 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.56 (ddd, *J*=14.5, 9.1, 5.0 Hz, 1H, C*H*H), 1.80 (ddd, *J*=15.6, 11.9, 3.0 Hz, 1H, CH*H*), 1.68 (br, 1H, O*H*), 1.36 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). $[\alpha]_D^{29}$ −306.86 (*c* 0.35, $CHCl_3$). Fraction II (more polar) was obtained as a pale yellow liquid (0.712 g, 43% yield; a mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$, data are reported for both diastereomers): δ 7.63–7.45 (m, 2×5H, Ar*H*), 4.20 (dd, *J*=10.1, 6.0 Hz, 1H), 3.75–3.68 (m, 2H), 3.37 (d, *J*=11.9 Hz, 1H), 3.30 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.25–3.18 (m, 2H), 3.21 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 3.10 (d, *J*=11.9 Hz, 1H), 3.09 (d, *J*=16.2 Hz, 1H), 2.71–2.65 (m, 1H), 2.56–2.40 (m, 1H), 2.39–2.29 (m, 1H), 2.81–1.94 (m, 1H), 1.80–1.78 (br, 2×1H, O*H*), 1.31 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.21 (s, 3H, CH_3).

4.12. (2*S*,5*S*,6*S*,5′*S*)-5′-Hydroxy-2′-oxospirocyclopent-3′-ene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (10A)

A mixture of diastereomers of (2*S*,5*S*,6*S*,5′*S*)-**9A** (0.385 g, 1.00 mmol) and anhydrous $CaCO_3$ (3.0 g) in dry toluene (15 mL) was refluxed at 110 °C for 10 h under an argon atmosphere. After removal of toluene (aspirator then in vacuo), the residue was purified by column chromatography (silica gel, 23% ethyl acetate in hexanes) to give a single diastereomer of (2*S*,5*S*,6*S*,5′*S*)-**10A** as a white solid (0.205 g, 80% yield, mp 96–99 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, *J*=6.1 Hz, 1H, =CH_β), 6.28 (dd, *J*=6.1 Hz, 1H, =CH_α), 4.59 (s, 1H, CC*H*), 4.22 (d, *J*=10.9 Hz, 1H, CH*H*), 3.46 (s, 3H, OCH_3), 3.34 (d, *J*=10.9 Hz, 1H, C*H*H), 3.31 (s, 3H, OCH_3), 1.34 (s, 3H, CH_3), 1.33 (br s, 1H, O*H*), 1.31 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1 (C=O), 161.1 (CH), 133.6 (CH), 133.9 (CH), 100.9 (C), 99.98 (C), 77.1 (C), 63.6 (CH_2), 48.6 (CH_3), 48.0 (CH_3), 18.78 (CH_3), 18.73 (CH_3). IR (Nujol): ν_{max} 3501 m, 1728 s, 1596 w, 1463 m, 1150 s, 1114 s, 1075 s cm^{-1}. MS: *m*/*z* (% relative intensity): 258 (M^+, 0.8), 195 (76), 110 (71), 109 (20), 101 (37), 89 (36), 82 (52), 73 (100), 55 (23), 53 (23). HRMS (ESI-TOF) calcd for $C_{12}H_{18}O_6Na$: 281.1001; found: 281.1002. $[\alpha]_D^{29}$ +58.6 (*c* 1.33, $CHCl_3$).

4.13. (2*S*,5*S*,6*S*,5′*R*)-5′-Hydroxy-2′-oxospirocyclopent-3′-ene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (10B)

A mixture of diastereomers of (2*S*,5*S*,6*S*,5′*R*)-**9B** (0.365 g, 0.95 mmol) and anhydrous $CaCO_3$ (3.0 g) in dry toluene (15 mL) was refluxed at 110 °C for 10 h under an argon atmosphere. After removal of toluene (aspirator then in vacuo), the residue was purified by column chromatography (silica gel, 27% ethyl acetate in hexanes) to give a single diastereomer of (2*S*,5*S*,6*S*,5′*R*)-**10B** as a colorless liquid (0.201 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (dd, *J*=5.9 Hz, 1H, =CH_β), 6.14 (dd, *J*=5.9 Hz, 1H, =CH_α), 4.87 (s, 1H, CC*H*), 4.11 (d, *J*=10.9 Hz, 1H, CH*H*), 3.77 (d, *J*=10.9 Hz, 1H, C*H*H), 3.41 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.32 (br s, 1H, O*H*), 1.45 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4 (C=O), 160.5 (CH), 132.9 (CH), 100.58 (C), 100.52 (C), 81.1 (C), 79.9 (CH), 60.3 (CH_2), 49.2 (CH_3), 48.4 (CH_3), 18.8 (CH_3), 18.6 (CH_3). IR ($CHCl_3$): ν_{max} 3565 w, 1725 s, 1597 w, 1456 w, 1376 m, 1153 s, 1141 s cm^{-1}. MS: *m*/*z* (% relative intensity): 258 (M^+, 0.8), 110 (71), 89 (36), 82 (52), 74 (100). HRMS (ESI-TOF) calcd for $C_{12}H_{18}O_6Na$: 281.1001; found: 281.1001. $[\alpha]_D^{29}$ +76.2 (*c* 0.18, $CHCl_3$).

4.14. (2*R*,5*R*,6*R*,5′*R*)-5′-Hydroxy-2′-oxospirocyclopent-3′-ene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-10A)

A mixture of (2*R*,5*R*,6*R*,5′*R*)-*ent*-**9A** (0.351 g, 0.91 mmol) and anhydrous $CaCO_3$ (3.0 g) was refluxed in dry toluene (15 mL) for 10 h under an argon atmosphere. The crude product was purified by column chromatography (silica gel, 23% ethyl acetate in hexanes) to give a single diastereomer of (2*R*,5*R*,6*R*,5′*R*)-*ent*-**10A** as a white solid (0.189 g, 80% yield, mp 97–101 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, *J*=6.1 Hz, 1H, =CH_β), 6.28 (dd, *J*=6.1 Hz, 1H, =CH_α), 4.59 (s, 1H, CC*H*), 4.30 (d, *J*=10.9 Hz, 1H, CH*H*), 3.52 (s, 3H, OCH_3), 3.40 (d, *J*=10.9 Hz, 1H, C*H*H), 3.39 (s, 3H, OCH_3), 1.80 (br s, 1H, O*H*), 1.42 (s, 3H, CH_3), 1.41 (s, 3H, CH_3). $[\alpha]_D^{29}$ −52.8 (*c* 0.175, $CHCl_3$).

4.15. (2*R*,5*R*,6*R*,5′*S*)-5′-Hydroxy-2′-oxospirocyclopent-3′-ene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-10B)

A mixture of (2*R*,5*R*,6*R*,5′*S*)-*ent*-**9B** (0.2176 g, 0.57 mmol) and anhydrous $CaCO_3$ (3.0 g) in dry toluene (10 mL) was refluxed at 110 °C for 10 h under an argon atmosphere. The crude product was purified by column chromatography (silica gel, 27% ethyl acetate in hexanes) to give a single diastereomer of (2*R*,5*R*,6*R*,5′*S*)-*ent*-**10B** as a colorless liquid (0.1227 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (dd, *J*=5.9 Hz, 1H, =CH_β), 6.23 (dd, *J*=5.9 Hz, 1H, =CH_α), 4.95 (s, 1H, CC*H*), 4.18 (d, *J*=10.9 Hz, 1H, CH*H*), 3.85 (d, *J*=10.9 Hz, 1H, C*H*H), 3.49 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 1.80 (br s, 1H, O*H*), 1.45 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). $[\alpha]_D^{29}$ −74.1 (*c* 0.2053, $CHCl_3$).

4.16. (−)-Pentenomycin I (1)

(2*S*,5*S*,6*S*,5′*S*)-**10A** (0.118 g, 0.45 mmol) was treated with 90% trifluoroacetic acid (7 mL) at 0 °C. The mixture was slowly warmed up to room temperature for 5 h. The solvents were freeze-dried overnight to give a crude product, which was purified by preparative thin layer chromatography (PLC, silica gel, 1% MeOH in EtOAc) to give (−)-pentenomycin I (**1**) (54 mg, 83% yield) as an amorphous powder (viscous liquid or syrup on standing). ^{1}H NMR (300 MHz, D_2O): δ 7.73 (dd, J=4.4, 2.7 Hz, 1H, =CH_β), 6.32 (d, J=4.4 Hz, 1H, =CH_α), 4.73 (s, 1H, CHOH), 3.72 (ABq, J=11.8 Hz, 1H, CH_AH$_B$–OH), 3.69 (ABq, J=11.8 Hz, 1H, CH$_A$$H_B$–OH). ^{13}C NMR (75 MHz, D_2O): δ 210.1 (C=O), 164.9 (CH), 133.7 (CH), 76.6 (C), 71.9 (CH), 63.3 (CH_2). IR (neat): ν_{max} 3416 s, 1712 s, 1636 m, 1385 m, 1262 m, 1162 m, 1047 m cm^{-1}. MS: m/z (% relative intensity): 145 (M^++1, 12), 125 (100), 99 (70), 95 (56), 81 (77), 67 (71). $[\alpha]_D^{29}$ −31.2 (*c* 1.50, EtOH) (lit.[5] $[\alpha]_D$ −32.0 (*c* 0.3, EtOH)).

4.17. (+)-Pentenomycin I (*ent*-1)

(2*R*,5*R*,6*R*,5′*R*)-*ent*-**10A** (0.135 g, 0.52 mmol) was treated with 90% trifluoroacetic acid (8 mL) at 0 °C to room temperature for 5 h. The solvents were freeze-dried overnight to give a crude product, which was purified by PLC (silica gel, 2% MeOH in EtOAc) to give [(+)-pentenomycin I (*ent*-**1**) (61 mg, 82% yield) as an amorphous powder (viscous liquid or syrup on standing). ^{1}H NMR (300 MHz, D_2O): δ 7.73 (dd, J=4.4, 2.7 Hz, 1H, =CH_β), 6.32 (d, J=4.4 Hz, 1H, =CH_α), 4.73 (s, 1H, CHOH), 3.72 (ABq, J=11.8 Hz, 1H, CH_AH$_B$–OH), 3.69 (ABq, J=11.8 Hz, 1H, CH$_A$$H_B$–OH). $[\alpha]_D^{29}$ +37.1 (*c* 0.28, EtOH) (lit.[9e] $[\alpha]_D$ +30.0 (*c* 0.1, EtOH)).

4.18. (+)-Epipentenomycin I (*ent*-5)

(2*R*,5*R*,6*R*,5′*S*)-*ent*-**10B** (0.153 g, 0.59 mmol) was treated with 90% trifluoroacetic acid (9 mL) at 0 °C to room temperature for 5 h. The solvents were freeze-dried overnight to give a crude product, which was purified by PLC (silica gel, 4% MeOH in EtOAc) to give (+)-epipentenomycin I (*ent*-**5**) (69 mg, 81% yield) as a colorless viscous liquid. ^{1}H NMR (300 MHz, D_2O): δ 7.79 (dd, J=6.1, 2.3 Hz, 1H, =CH_β), 6.47 (d, J=6.1 Hz, 1H, =CH_α), 4.85–4.60 (m, 1H, CHOH), 3.84 (d, J=12.0 Hz, 1H, CHH), 3.63 (d, J=12.0 Hz, 1H, CHH). $[\alpha]_D^{29}$ +68.9 (*c* 0.25, EtOH) (lit.[7] $[\alpha]_D$ +130.0 (*c* 0.51, H_2O)).

4.19. (−)-Epipentenomycin I (5)

(2*S*,5*S*,6*S*,5′*R*)-**10B** (0.086 g, 0.33 mmol) was treated with 90% trifluoroacetic acid (5 mL) at 0 °C. The mixture was slowly warmed up to room temperature for 5 h. The solvents were freeze-dried overnight to give a crude product, which was purified by PLC (silica gel, 1% MeOH in EtOAc) to give (−)-epipentenomycin I (**5**) (40 mg, 80% yield) as a colorless viscous liquid. ^{1}H NMR (300 MHz, D_2O): δ 7.79 (dd, J=6.1, 2.3 Hz, 1H, =CH_β), 6.47 (d, J=6.1 Hz, 1H, =CH_α), 4.85–4.60 (m, 1H, CHOH), 3.84 (d, J=12.0 Hz, 1H, CHH), 3.63 (d, J=12.0 Hz, 1H, CHH). ^{13}C NMR (75 MHz, D_2O): δ 215.9 (C=O), 161.7 (CH), 135.6 (CH), 102.3 (C), 79.3 (CH), 65.0 (CH_2). IR (neat): ν_{max} 3449 s, 1722 m, 1638 s, 1259 m, 1106 s, 1044 m, 925 s cm^{-1}. MS: m/z (% relative intensity): 145 (M^++1, 12), 135 (23), 121 (32), 113 (100), 97 (46), 95 (53), 81 (57). $[\alpha]_D^{29}$ −74.1 (*c* 0.20, EtOH) (lit.[9f] $[\alpha]_D$ −75.3 (*c* 1.15, MeOH)).

4.20. (2*R*,5*R*,6*R*,5′*R*)-5′-Hydroxy-2′-oxo-3′-phenylsulfanyl spirocyclopentene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-11A)

Trifluoroacetic anhydride (0.14 mL, 1.10 mmol) was added to a cooled (0 °C) solution of (2*R*,5*R*,6*R*,5′*R*)-*ent*-**9A** (0.258 g, 1.00 mmol) in acetonitrile (5 mL) followed by the addition of diisopropylethylamine (0.11 mL, 0.8 mmol). After stirring at room temperature overnight (12 h), a dark-brown solution was quenched with 1 M HCl and extracted with ethyl acetate. The organic phase was washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. The crude product obtained was purified by PLC (silica gel, 22% ethyl acetate in hexanes) to give (2*R*,5*R*,6*R*,5′*R*)-*ent*-**11A** as a pale yellow viscous liquid (0.285 g, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.40 (m, 2H, ArH), 7.40–7.33 (m, 3H, ArH), 6.65 (d, J=3.1 Hz, 1H, CH=C), 4.42 (d, J=3.1 Hz, 1H, CHOH), 4.27 (d, J=5.5 Hz, 1H, CHH), 3.44 (s, 3H, OCH_3), 3.35 (d, J=5.5 Hz, 1H, CHH), 3.26 (s, 3H, OCH_3), 1.50 (br s, 1H, OH), 1.35 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9 (C=O), 148.3 (CH), 143.6 (C), 134.6 (2×CH), 129.7 (2×CH), 129.4 (CH), 128.8 (C), 99.6 (C), 98.1 (C), 82.2 (CH), 77.1 (C), 61.1 (CH_2), 50.0 (CH_3), 48.2 (CH_3), 17.74 (CH_3), 17.71 (CH_3). IR (neat): ν_{max} 3427 m, 1731 s, 1558 w, 1384 m, 1124 s, 1043 s, 754 s cm^{-1}. MS: m/z (% relative intensity): 367 (M^++1, 0.5), 139 (56), 123 (56), 123 (100), 111 (68). HRMS (ESI-TOF) calcd for $C_{18}H_{22}O_6SNa$: 389.1027; found: 389.1015. $[\alpha]_D^{29}$ −85.35 (*c* 1.14, $CHCl_3$).

4.21. (+)-4,5-Dihydroxy-2-phenylsulfanyl-5-hydroxymethyl-2-cyclopentenone (*ent*-12A)

(2*R*,5*R*,6*R*,5′*R*)-*ent*-**11A** (0.122 g, 0.34 mmol) was stirred with 90% trifluoroacetic acid (4 mL) at 0 °C. The mixture was slowly warmed up to room temperature for 3.5 h. The solvent was freeze-dried overnight to give a crude product, which was purified by PLC (silica gel, 77% EtOAc in hexanes) to give *ent*-**12A** as colorless crystals (67.2 g, 80% yield, mp 134–136 °C). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.61–7.44 (m, 5H, ArH), 6.71 (d, J=2.8 Hz, 1H, =CH), 4.57 (d, J=2.8 Hz, 1H, CHOH), 3.83 (d, J=11.6 Hz, 1H, CHH), 3.65 (d, J=11.6 Hz, 1H, CHH), 2.9 (br s, 3H OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7 (C=O), 147.9 (CH), 146.8 (C), 134.9 (2×CH), 130.8 (2×CH), 130.3 (CH), 102.0 (C), 78.6 (CH), 76.5 (C), 65.6 (CH_2). IR (Nujol): ν_{max} 3528 m, 1723 s, 1456 m, 1115 s, 1040 m, 769 s cm^{-1}. MS: m/z (% relative intensity): 252 (M^++1, 45), 250 (34), 234 (100), 91 (31), 69 (34). HRMS (ESI-TOF) calcd for $C_{12}H_{12}O_4SNa$: 275.0333; found: 275.0346. $[\alpha]_D^{29}$ +81.8 (*c* 0.17, $CHCl_3$).

4.22. (2*R*,5*R*,6*R*,5′*R*)-5′-Hydroxy-2′-oxo-3′-iodospiro-cyclopent-3′-ene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-13A)

A solution of (2*R*,5*R*,6*R*,5′*R*)-*ent*-**10A** (0.625 g, 2.41 mmol), pyridine (5 mL), and carbon tetrachloride (5 mL) was added to a solution of iodine (2.43 g, 9.64 mmol) in pyridine (5 mL) and carbon tetrachloride (5 mL). After stirring for 1 h at room temperature in the dark, the mixture was diluted with Et_2O (3×15 mL) and washed successively with water (20 mL), 1 M HCl (5 mL), saturated $Na_2S_2O_3$ (20 mL), and brine (15 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (silica gel, 20% EtOAc in hexanes) to give *ent*-**13A** as a white solid (0.901 g, 97% yield, mp 98–100 °C), which was unstable on standing at room temperature. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J=2.7 Hz, 1H, =CH), 4.49 (d, J=2.7 Hz, 1H, CHOH), 4.24 (d, J=11.2 Hz, 1H, CHH), 3.99–3.89 (br, 1H, OH), 3.43 (s, 3H, OCH_3), 3.37 (d, J=11.2 Hz, 1H, CHH), 3.30 (s, 3H, OCH_3), 1.34 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0 (C=O), 166.4 (CH), 104.4 (C), 101.1 (C), 99.9 (C), 75.2 (CH), 74.7 (C), 63.1 (CH_2), 48.7 (CH_3), 48.1 (CH_3), 18.68 (CH_3), 18.60 (CH_3). IR (Nujol): ν_{max} 3388 s, 1715 s, 1631 m, 1452 m, 1115 m, 1049 m cm^{-1}. MS: m/z (% relative intensity): 384 (M^+, 0.27), 250 (45), 141 (41), 110 (100). HRMS (ESI-TOF) calcd for $C_{12}H_{17}O_6NaI$: 406.9968; found: 406.9969. $[\alpha]_D^{29}$ −27.29 (*c* 0.98, $CHCl_3$).

4.23. (2*R*,5*R*,6*R*,5′*R*)-2′-Oxo-3′-phenylspirocyclopent-3′-ene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-14A)

A round-bottomed flask was charged with phenylboronic acid (46 mg, 0.38 mmol), (2*R*,5*R*,6*R*,5′*R*)-*ent*-**13A** (96 mg, 0.249 mmol), and $PdCl_2(PPh_3)_2$ (10 mg, 0.012 mmol, 5 mol %). THF (1.5 mL) was added followed by 2 M Na_2CO_3 (0.7 mL, 1.8 mmol). The resulting reaction mixture was heated at 40 °C under an argon atmosphere overnight. The mixture was cooled to room temperature and ethyl acetate (10 mL) was added followed by saturated $NaHCO_3$ (20 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with 0.5 N NaOH (2×10 mL), brine (2×10 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave the a crude product, which was purified by column chromatography (silica gel, 25% EtOAc in hexanes) to give (2*R*,5*R*,6*R*,5′*R*)-*ent*-**14A** as a white solid (58.5 g, 70% yield, mp 171–172 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80–7.75 (m, 2H, Ar*H*), 7.71 (d, *J*=2.1 Hz, 1H, =C*H*), 7.38–7.30 (m, 3H, Ar*H*), 4.87 (d, *J*=2.1 Hz, 1H, C*H*OH), 3.89 (d, *J*=11.1 Hz, 1H, CH*H*), 3.74 (d, *J*=11.1 Hz, 1H, CH*H*), 3.43 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 1.47 (s, 3H, CH_3), 1.35 (br s, 1H, O*H*), 1.34 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6 (C=O), 153.4 (CH), 141.1 (C), 130.0 (C), 129.3 (CH), 128.5 (2×CH), 127.1 (2×CH), 99.5 (C), 98.0 (C), 83.2 (C), 76.3 (CH), 61.2 (CH_2), 50.1 (CH_3), 48.2 (CH_3), 17.7 (2×CH_3). IR (neat): ν_{max} 3522 s, 1722 s, 1449 s, 1104 s, 1032 s, 997 s cm^{-1}. MS: *m*/*z* (% relative intensity): 334 (M^++1, 1), 234 (54), 142 (24), 140 (100), 114 (73). HRMS (ESI-TOF) calcd for $C_{18}H_{22}O_6Na$: 357.1313; found: 387.1304. $[\alpha]_D^{29}$ −290.7 (*c* 0.15, $CHCl_3$).

4.24. (+)-4,5-Dihydroxy-5-hydroxymethyl-2-phenyl-2-cyclopentenone (*ent*-15A)

(2*R*,5*R*,6*R*,5′*R*)-*ent*-**14A** (50 mg, 0.176 mmol) was treated with 90% trifluoroacetic acid (1 mL) at 0 °C. The mixture was slowly warmed up to room temperature for 3.5 h. The solvent was freeze-dried overnight to give a crude product, which was purified by PLC (silica gel, 67% EtOAc in hexanes) to give *ent*-**15A** as a white solid (27 mg, 90% yield, mp 127–130 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.71 (m, 3H, Ar*H* and =C*H*), 7.43–7.39 (m, 3H, Ar*H*), 4.83 (d, *J*=2.6 Hz, 1H, C*H*OH), 3.91 (d, *J*=11.7 Hz, 1H, C*H*H), 3.77 (d, *J*=11.7 Hz, 1H, CH*H*), 2.40 (s, 3H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7 (C=O), 151.8 (CH), 143.7 (C), 129.5 (C), 128.7 (CH), 128.0 (2×CH), 127.3 (2×CH), 101.4 (C), 76.5 (CH), 65.7 (CH_2). IR (Nujol): ν_{max} 3417 m, 1704 s, 1597 m, 1571 m, 1449 m, 1038 m, 759 s, 701 m cm^{-1}. MS: *m*/*z* (% relative intensity): 221 (M^+, 0.54), 189 (100), 115 (34), 91 (57), 77 (13). HRMS (ESI-TOF) calcd for $C_{12}H_{12}O_4Na$: 463.1360; found: 463.1347. $[\alpha]_D^{29}$ +23.8 (*c* 0.31, EtOH).

4.25. (2*R*,5*R*,6*R*,5′*R*)-5′-Hydroxy-2′-oxo-3′-phenylacetylenyl spirocyclopent-3′-ene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-16Aa)

General procedure D: a mixture of (2*R*,5*R*,6*R*,5′*R*)-*ent*-**13A** (132 mg, 0.342 mmol), phenylacetylene (0.174 mL, 1.71 mmol), $PdCl_2(PPh_3)_2$ (12.3 mg, 0.015 mmol, 5 mol %), and CuI (8.6 mg, 0.034 mmol) was treated with *N*,*N*-diisopropylamine (0.14 mL, 1.026 mmol) at 0 °C. The resulting yellow to dark-brown solution was stirred at 0 °C for 1 h. The mixture was partitioned with Et_2O and 1 M HCl. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Filtration and concentration gave the crude reaction mixture, which was purified by column chromatography (silica gel, 21% EtOAc in hexanes) to give *ent*-**16Aa** as a pale yellow viscous liquid (88.8 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J*=2.07 Hz, 1H, =C*H*), 7.61–7.50 (m, 2H, Ar*H*), 7.34–7.30 (m, 3H, Ar*H*), 5.00 (d, *J*=2.07 Hz, 1H, C*H*OH), 4.25 (d, *J*=10.71 Hz, 1H, C*H*H), 3.90 (d, *J*=10.71 Hz, 1H, CH*H*), 3.51 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 1.44 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.33 (br s, 1H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9 (C=O), 159.5 (CH), 132.0 (2×CH), 129.2 (CH), 128.9 (C), 128.3 (2×CH), 121.9 (C), 109.79 (C), 100.74 (C), 97.5 (C), 81.6 (C), 78.6 (CH), 60.4 (CH_2), 49.4 (CH_3), 48.6 (CH_3), 29.6 (CH), 18.9 (CH_3), 18.7 (CH_3). IR (neat) ν_{max} 3497 s, 2221 m, 1732 s, 1615 m, 1457 m, 1039 m, 755 m cm^{-1}. MS: *m*/*z* (% relative intensity): 358 (M^+, 0.3), 336 (26), 220 (100), 149 (29), 93 (34), 73 (51). HRMS (ESI-TOF) calcd for $C_{20}H_{22}O_6Na$: 381.1409; found: 381.1442. $[\alpha]_D^{29}$ −29.87 (*c* 0.23, $CHCl_3$).

4.26. (2*R*,5*R*,6*R*,5′*R*)-3′-*tert*-Butylacetylenyl-5′-hydroxy-2′-oxospirocyclopentene-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxane (*ent*-16Ab)

According to the general procedure D as described for *ent*-**16Aa**, the reaction of (2*R*,5*R*,6*R*,5′*R*)-*ent*-**13A** (173 mg, 0.450 mmol), *tert*-butylacetylene (0.164 mL, 2.25 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol, 5 mol %), CuI (9 mg, 0.045 mmol), and *N*,*N*-diisopropylamine (0.19 mL, 1.35 mmol) provided a crude product, which was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to give *ent*-**16Ab** as a white solid (152.8 mg, 90% yield, 139–141 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, *J*=2.5 Hz, 1H, =C*H*), 4.85 (d, *J*=2.5 Hz, 1H, C*H*OH), 4.28 (d, *J*=10.8 Hz, 1H, –CH*H*), 3.77 (d, *J*=10.8 Hz, 1H, C*H*H), 3.42 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 1.60 (br s, 1H, O*H*), 1.35 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.23 (s, 3×3H, CCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4 (C=O), 158.8 (CH), 129.3 (C), 107.5 (C), 100.7 (C), 81.6 (C), 78.5 (CH), 77.2 (C), 68.9 (C), 60.5 (CH_2), 49.4 (CH_3), 48.6 (CH_2), 30.6 (3×CH_3), 28.1 (C), 18.9 (CH_3), 18.8 (CH_3). IR (film): ν_{max} 3479 m, 2222 w, 1731 s, 1455 m, 1265 s, 1114 s, 1036 s cm^{-1}. MS: *m*/*z* (% relative intensity): 338 (M^+, 0.6), 175 (100), 147 (33), 119 (24), 115 (47), 91 (60). HRMS (ESI-TOF) calcd for $C_{18}H_{26}O_6Na$: 361.1619; found: 361.1629. $[\alpha]_D^{29}$ −29.73 (*c* 0.4, $CHCl_3$).

4.27. (+)-4,5-Dihydroxy-5-(hydroxymethyl)-2-phenylacetylenyl-2-cyclopentenone (*ent*-17Aa)

(2*R*,5*R*,6*R*,5′*R*)-*ent*-**16Aa** (86 mg, 0.238 mmol) was treated with 90% trifluoroacetic acid (1 mL) at 0 °C. The mixture was slowly warmed up to room temperature for 3.5 h. The solvent was freeze-dried overnight to give a crude product, which was purified by PLC (silica gel, 70% EtOAc in hexanes) to give *ent*-**17Aa** as a colorless viscous liquid (45.5 mg, 90% yield). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.65 (br s, 1H, =C*H*), 7.61–7.50 (m, 2H, Ar*H*), 7.40–7.28 (m, 3H, Ar*H*), 4.78 (br s, 1H, C*H*OH), 3.90–3.0 (m, 5H, CH_2 and 3×O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2 (C=O), 161.9 (CH), 131.7 (C), 131.5 (2×CH), 129.4 (C), 129.1 (CH), 128.5 (2×CH), 102.6 (C), 90.9 (C), 77.0 (CH), 74.7 (C), 64.5 (CH_2). IR (film): ν_{max} 3424 s, 3019 m, 2241 m, 1730 m, 1620 m cm^{-1}. MS: *m*/*z* (% relative intensity): 243 (M^+−1, 0.9), 125 (67), 78 (100). HRMS (ESI-TOF) calcd for $C_{14}H_{12}O_4Na$: 267.0632; found: 267.0646. $[\alpha]_D^{29}$ +16.0 (*c* 0.50, EtOH).

4.28. (+)-*tert*-2-Butylacetylenyl-4,5-dihydroxy-5-(hydroxymethyl)-2-cyclopentenone (*ent*-17Ab)

(2*R*,5*R*,6*R*,5′*R*)-*ent*-**16Ab** (69 mg, 0.292 mmol) was treated with 90% trifluoroacetic acid (1 mL) at 0 °C. The crude product was purified by PLC (silica gel, 60% EtOAc in hexanes) to give (+)-*ent*-**17Ab** as a white solid (23.3 mg, 97% yield, mp 98–101 °C). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.38 (d, *J*=2.2 Hz, 1H, =C*H*), 4.89 (br, 1H, O*H*), 4.64 (br, 1H, C*H*OH), 4.50 (br, 1H, O*H*), 3.62 (br, 2H, CH_2), 3.58 (br, 1H, O*H*), 3.05 (s, 3×3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6 (C=O), 161.6 (CH), 129.9 (C), 106.6 (C), 81.6 (C), 77.8 (CH), 70.6 (C), 76.6 (C), 65.4 (CH_2), 30.5 (3×CH_3). IR (Nujol): ν_{max} 3418 s, 1714 s, 1633 s, 1465 m, 1050 s, 757 s cm^{-1}. MS: *m*/*z* (% relative intensity): 223 (M^+, 2), 167 (31), 149 (100), 125 (26), 91 (51), 81 (29). HRMS

(ESI-TOF) calcd for $C_{12}H_{16}O_4Na$: 247.0938; found: 247.0928. $[\alpha]_D^{29}$ +21.84 (*c* 0.2, $CHCl_3$).

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A New Strategy for the Synthesis of (±)-Lupinine and (±)-Epilupinine via Cyclization of α-Sulfinyl Carbanions

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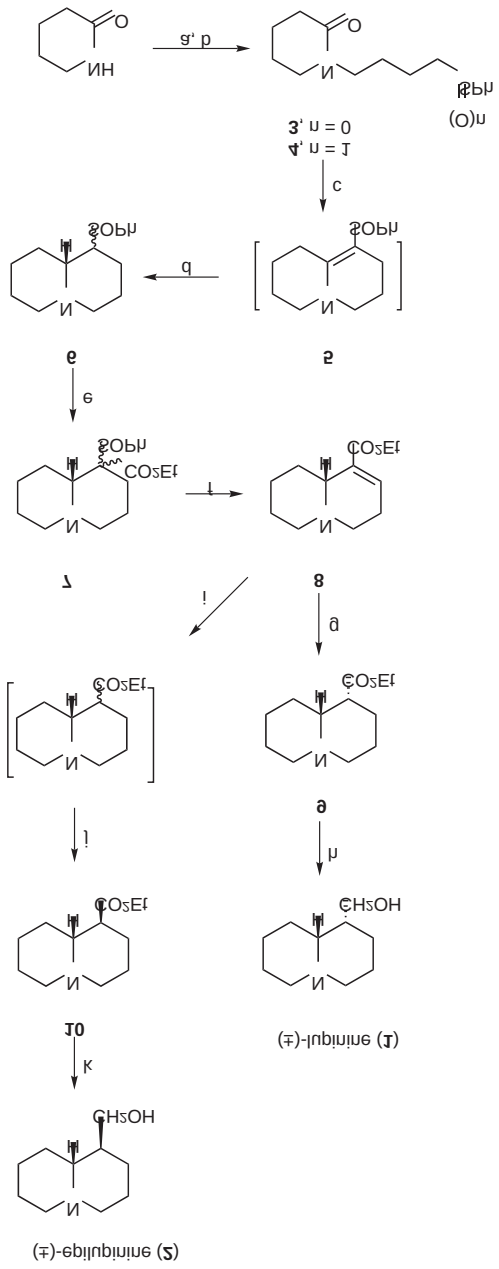
Abstract: (±)-Lupinine and (±)-epilupinine have been prepared starting from commercially available δ-valerolactam. The synthetic route involves the advantages of the cyclization based on α-sulfinyl carbanions.

Key words: (±)-lupinine, (±)-epilupinine, α-sulfinyl carbanion, cyclization

Quinolizidine alkaloids are important class of compounds as they are frequently encountered in a large number of natural products. Among these compounds, the lupin alkaloids are of particular interest due to their wide range of biological activities. Lupinine and epilupinine belonging to this class of alkaloid have been isolated from the aerial parts of plants in genus *Lupinus*, such as *Lupinus leteus*, *Lupinus albu.*[1] growing wild in North Africa, South Europe, North America, and Australia. Their relatively simple bicyclic quinolizidine structures and the interesting biological activities have challenged organic chemists to find an efficient approach to the synthesis of lupinine and epilupinine.[2]

We have recently developed a general route to 1-azabicyclo[m.n.0]alkanes including the quinolizidine skeleton via cyclization based on α-sulfinyl carbanions.[3] It is anticipated that the use of this method would permit a simple preparation of (±)-lupinine (**1**) and (±)-epilupinine (**2**). As summarized in Scheme 1, our strategy involves an intramolecular nucleophilic addition of α-sulfinyl carbanion onto the carbonyl group of the amide moiety leading to the key intermediate quinolizidine containing a phenylsulfinyl group. The synthesis started with N-alkylation of the readily available δ-valerolactam with 4-bromo-1-phenylsulfanylbutane employing NaH in DMF at 0 °C to room temperature to give sulfide **3** in 91% yield. This was followed by oxidation with $NaIO_4$ in aqueous methanol at 0 °C to room temperature to provide the corresponding sulfoxide **4** in 91% yield. The key cyclization step for the construction of the quinolizidine derivative **5** was carried out by treatment of the sulfoxide **4** with 2.2 equivalents of



Scheme 1 *Reagents and conditions:* (a) NaH, DMF, $PhS(CH_2)_4Br$, 0 °C to r.t.; (b) $NaIO_4$, MeOH, H_2O, 0 °C; (c) LiHMDS, THF, –78 °C to r.t.; (d) $NaBH_4$, MeOH, 0 °C; (e) LDA (1.5 equiv), THF, –78 °C (1 h); ethyl chloroformate (2.2 equiv), –78 °C, 2 h and r.t., 1 h; (f) toluene, reflux; (g) H_2, PtO_2, MeOH; (h) $LiAlH_4$, Et_2O; (i) Mg, MeOH, 2 h; (j) NaOEt, EtOH, reflux, overnight; (k) $LiAlH_4$, Et_2O.

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lithium hexamethyldisilazide (LiHMDS) in THF overnight at –78 °C to room temperature, followed by reduction of the labile unsaturated quinolizidine **5** with $NaBH_4$ in methanol at 0 °C. The expected quinolizidine **6** was obtained in 94% overall yield as a mixture of two diastereomers, the ratio of which ratio could not be determined by ^1H NMR spectroscopy. However, the major 1,8*a*-*cis*-isomer could be obtained by fractional crystallization from ethyl acetate.

The formation of compound **5** resulted from the intramolecular nucleophilic addition of the α-sulfinyl carbanion derived from the sulfoxide lactam **4** onto the amide group followed by dehydration during workup.

The key starting intermediate **8** was prepared in two steps by carboethoxylation of the sulfinylquinolizidine **6** and sulfoxide elimination. Thus, lithiation of the diastereomeric mixture of **6** with lithium diisopropylamide (LDA)[4] in THF followed by treatment with ethyl chloroformate gave compound **7**, which was subjected to sulfoxide elimination by refluxing in anhydrous toluene to give the required compound **8** in 48% yield after chromatographic purification.

Having compound **8** in hand, the preparation of (±)-lupinine (**1**) and (±)-epilupinine (**2**) was performed as summarized in Scheme 1. Catalytic hydrogenation of unsaturated ester **8** using PtO_2 as a catalyst in methanol afforded *cis*-quinolizidine ester **9** in 80% yield as the sole isomer. Reduction of the ester group of **9** with $LiAlH_4$ in anhydrous diethyl ether furnished (±)-lupinine (**1**) in 80% yield.[5a,b] On the other hand, the reaction of **8** with Mg in methanol under reflux provided a mixture of *cis*- and *trans*-isomers of the corresponding mixture of methyl and ethyl ester derivatives of **10**. Treatment of **10** with sodium ethoxide in refluxing ethanol was done in order to equilibrate the less stable *cis*-isomer to the thermodynamically more stable *trans*-isomer of the quinolizidine ester **10** and to perform transesterification of the methyl ester into the ethyl ester (78% yield).[6] Finally, (±)-epilupinine (**2**) was prepared in 71% yield by reduction of *trans*-quinoline ester **10** with $LiAlH_4$ in diethyl ether.[5a]

In summary, we have demonstrated a short entry to (±)-lupinine (**1**) and (±)-epilupinine (**2**) starting from commercially available δ-valerolactam by using the synthetic utilities of cyclization based on α-sulfinyl carbanions.

The ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Melting points were recorded on a Büchi 501 Melting Point Apparatus and were uncorrected. The IR spectra were recorded on a GX FT-IR system Perkin-Elmer IR spectrometer. The mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded on HR-TOF-MS Micromass spectrometer. The elemental analyses were performed by a Perkin-Elmer Elemental Analyzer 2400 CHN. All glassware and syringes were oven-dried and kept in a desiccator before use. The molarity of *n*-BuLi (in hexane) was determined by titration with diphenylacetic acid in THF at 0 °C. THF was distilled from sodium benzophenone ketyl. *i*-Pr_2NH, hexamethyldisilazane, and toluene were dried by distilling over CaH_2. Merck silica gel 60H and 60 PF_{245} were used for column chromatography and preparative TLC, respectively.

1-(4-Phenylsulfanylbutyl)piperidin-2-one (3)

To a suspension of NaH (2.42 g, 55 mmol, 55% suspension in mineral oil) in DMF (100 mL) was slowly added a DMF (8 mL) solution of δ-valerolactam (5.0 g, 50 mmol) at 0 °C under argon. The mixture was stirred for 1 h until the generation of H_2 ceased, and 1-bromo-4-phenylsulfanylbutane (1.594 g, 55 mmol) was then added. After stirring the mixture overnight (15 h) at 0 °C to r.t., it was quenched with H_2O (2 × 50 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). Filtration followed by evaporation in vacuo afforded a residue, which was purified by column chromatography (SiO_2, 80% in hexanes) to give **3** as a pale yellow liquid; yield: 12.09 g (91%).

IR (neat): 1638, 1584, 1494, 1481, 1466, 1353, 1300, 741, 692 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.17 and 7.10–7.06 (2 m, 5 H), 3.28 (t, *J* = 6.8 Hz, 2 H), 3.15 (br s, 2 H), 2.87 (t, *J* = 6.5 Hz, 2 H,), 2.27 (br s, 2 H, CH_2CON), 1.67–1.58 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6 (C=O), 136.3 (C), 129.0 (2 CH), 128.7 (2 CH), 125.7 (CH), 47.6 (CH_2), 46.2 (CH_2), 33.2 (CH_2), 32.2 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 23.1 (CH_2), 21.2 (CH_2).

MS: *m*/*z* (%) = 264 (M^+ + 1), 154 (100), 112 (77), 84 (71), 56 (18).

Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.63; H, 8.04; N, 5.32. Found: C, 68.33; H, 8.22; N, 5.02.

1-(4-Phenylsulfinylbutyl)piperidin-2-one (4)

A solution of **3** (6.32 g, 24 mmol) in MeOH (15 mL) was slowly added to a cooled (0 °C) suspension of $NaIO_4$ (5.6487 g, 26 mmol) in MeOH (58 mL) and H_2O (14 mL). The mixture was stirred vigorously and slowly warmed up overnight (16 h) from 0 °C to r.t. The precipitate of $NaIO_3$ was filtered and washed with EtOAc (4 × 70 mL). The combined extracts were washed with H_2O (2 × 25 mL) and brine (25 mL), and dried (Na_2SO_4). Filtration followed by evaporation in vacuo gave a residue, which was purified by column chromatography (SiO_2, 100% EtOAc to 2% MeOH in EtOAc) to provide **4** as a colorless viscous liquid; yield: 6.073 g (91%).

IR (neat): 1634, 1496, 1467, 1444, 1044, 753, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.48 and 7.42–7.38 (2 m, 5 H), 3.2 (app t, *J* = 5.9 Hz, 2 H), 3.12 (br s, 2 H), 2.74 (q, *J* = 8.8 Hz, 2 H), 2.20 (br s, 2 H), 1.67–1.58 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4 (C=O), 143.2 (C), 130.6 (CH), 128.8 (2 CH), 123.6 (2 CH), 55.9 (CH_2), 44.4 (CH_2), 45.4 (CH_2), 31.8 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 20.9 (CH_2), 18.9 (CH_2).

MS: *m*/*z* (%) = 279 (M^+, 2), 262 (78), 165 (47), 154 (86), 112 (69), 84 (100), 56 (44).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{21}NO_2S$: 279.1298; found: 279.1291.

1-Benzenesulfinyloctahydroquinolizidine (6)

n-BuLi (1.35 M in hexane; 52.93 mL, 71.45 mmol) was added to a cooled (–78 °C) THF (292 mL) solution of hexamethyldisilazane (HMDS) (1 mL, 4.8 mmol) under argon. After stirring at –78 °C for 40 min, a THF (64 mL) solution of **4** (9.061 g, 32 mmol) was added dropwise. The resulting mixture was allowed to stir and slowly warmed up overnight (15 h) from –78 °C to r.t. The resulting yellow solution was quenched with H_2O (100 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL) and dried (Na_2SO_4). Filtration followed by evaporation in vacuo to dryness afforded a viscous yellow liquid of crude 9-benzenesulfinyl-1,3,4,6,7,8-hexahydro-2*H*-quinolizine (**5**; yield: 8.22 g, 31 mmol), which was

directly subjected to reduction by using $NaBH_4$ as follows. To a solution of the crude product **5** in MeOH (160 mL) at 3–5 °C under argon, was added $NaBH_4$ (7.614 g, 201 mmol) in a small portion over 4 h. The mixture was stirred for 1 h at the same temperature, diluted with aq 1 N NaOH (100 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). Filtration followed by evaporation in vacuo gave a residue, which was purified by column chromatography (SiO_2, 2% MeOH in EtOAc containing 0.15% NH_4OH) to afford a white semi-solid of **6** as a mixture of two diastereomers; yield: 8.034 g (94%). The major diastereomer could be obtained by fractional crystallization from EtOAc to give 1,9-*cis*-**6** as a white solid; mp 112–113 °C). The minor diastereomer could not be separated.

IR (Nujol): 2749, 1463, 1446, 1302, 1084, 1034, 752, 690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.63 and 7.53–7.43 (2 m, 5 H), 3.01 (m, 2 H), 2.73 (t, *J* = 4.0 Hz, 1 H), 2.41 (app d, *J* = 11.9 Hz, 1 H), 2.30–2.18 (m, 2 H), 2.20–2.10 (m, 1 H), 2.14–2.06 (m, 1 H), 2.06–1.93 (m, 1 H), 1.89–1.80 (m, 1 H), 1.79–1.63 (m, 1 H), 1.55–1.46 (m, 3 H), 1.49–1.40 (m, 1 H), 1.38–1.27 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9 (C), 130.5 (CH), 129.0 (2 CH), 124.7 (2 CH), 66.3 (CH), 62.9 (CH), 56.8 (CH_2), 54.4 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 23.9 (CH_2), 22.9 (CH_2), 21.9 (CH_2).

MS: *m*/*z* (%) = 264 (M^+ + 1, 8), 246 (100), 136 (93), 110 (30).

Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.04; H, 8.04; N, 5.32. Found: C, 68.26; H, 8.15; N, 5.67.

3,6,7,8,9,9a-Hexahydro-4*H*-quinolizine-1-carboxylic Acid Ethyl Ester (8)

A solution of **6** (3.95 g, 15 mmol) in THF (30 mL) was added dropwise at –78 °C to a THF solution of LDA [prepared by reacting *i*-Pr_2NH (3.50 mL, 24.75 mmol) in THF (90 mL) with *n*-BuLi (1.35 M in hexane, 16.7 mL. 22.5 mmol) at –78 °C for 30 min] under argon. After stirring for 30 min, ethyl chloroformate (3.15 mL, 33 mmol) was added dropwise. The resulting mixture was stirred at –78 °C for 2 h and at r.t. for 1 h. It was quenched with H_2O (50 mL) and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried (Na_2SO_4). The organic phase was concentrated to give a yellow viscous liquid of the crude product 1-benzenesulfinyloctahydroquinolizine-1-carboxylic acid ethyl ester (**7**), which was directly subjected to sulfoxide elimination by refluxing in toluene as follows. A solution of the crude product **7** (3.954 g, 12 mmol) in anhyd toluene (140 mL) in the presence of $CaCO_3$ (0.5 g) was stirred at reflux under argon for 16 h. The mixture was filtered and the filtrate was evaporated to dryness to give a crude product, which was purified by column chromatography (SiO_2, 80% EtOAc in hexanes) to provide **8**[5a] as a yellow liquid; yield: 1.52 g (48%).

IR (neat): 1714, 1466, 1255, 1173, 1097, 1051 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.78–6.76 (m, 1 H), 4.19–1.03 (m, 2 H), 2.98–2.94 (m, 1 H), 2.89–2.84 (m, 1 H), 2.78–2.73 (m, 1 H), 2.48–2.33 (m, 1 H), 2.46–2.33 (m, 1 H), 2.17–2.11 (m, 1 H), 2.11–2.05 (m, 1 H), 2.02–2.01 (m, 1 H), 1.76–1.71 (m, 1 H), 1.64–1.45 (m, 2 H), 1.45–1.31 (m, 1 H,), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.20–1.06 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C=O), 136.7 (CH), 133.8 (C), 60.2 (CH), 59.9 (CH_2), 55.9 (CH_2), 48.8 (CH_2), 28.5 (CH_2), 26.3 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 14.1 (CH_3).

MS: *m*/*z* (%) = 210 (M^+ + 1, 100), 209 (M^+, 39), 180 (94), 137 (53), 136 (40), 124 (47).

These spectroscopic data are in agreement with those reported in the literature.[5a]

Ethyl (1*R**,9a*R**)-Octahydro-2*H*-quinolizine-1-carboxylate (9)

To a solution of **8** (70 mg, 0.364 mmol) in anhyd MeOH (2 mL) was added PtO_2 (8.25 mg, 0.0364 mmol). The reaction flask was connected via a two-way tap connected to a balloon of H_2 at atmospheric pressure and a vacuum pump. It was evacuated and flushed with H_2 several times to remove the air. Then it was stirred for 16 h while maintaining an atmosphere of H_2 at a slight positive pressure. At the end of this time, the H_2 was disconnected and the reaction flask was flushed with N_2. The catalyst was removed by filtration, followed by evaporation in vacuo to provide a residue, which was purified by TLC (SiO_2, 0.15% NH_4OH in EtOAc) to give **9** as a pale yellow liquid; yield: 61 mg (80%).

IR (neat): 1733, 1444, 1373, 1318, 1146, 1035 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.11 (m, 2 H, OCH_2), 2.87–2.84 (m, 2 H), 2.05 (t, *J* = 4.1 Hz, 1 H), 2.15–1.93 (m, 4 H), 1.90–1.80 (m, 1 H), 1.75–1.65 (m, 1 H), 1.65–1.40 (m, 6 H), 1.30–1.15 (m, 1 H), 1.18 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4 (C=O), 62.6 (CH), 59.8 (CH_2), 56.9 (CH_2), 54.6 (CH_2), 44.4 (CH), 28.5 (CH_2), 26.1 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 22.1 (CH_2), 14.2 (CH_3).

MS: *m*/*z* (%) = 211 (M^+, 14), 182 (60), 137 (100), 110 (57), 98 (40), 82 (39).

These spectroscopic data are in agreement with those reported in the literature.[5a,b]

1*R**,9a*R**)-Octahydro-2*H*-quinolizine-1-ylmethanol [(±)-Lupinine (1)]

A solution of **9a** (83 mg, 0.393 mmol) in anhyd Et_2O (3 mL) was added to a stirred suspension of $LiAlH_4$ (33 mg, 0.865 mmol) in anhyd Et_2O (2 mL) at 0 °C under argon. The resulting mixture was refluxed for 4 h, cooled to 0 °C, and quenched by sequential addition of EtOAc (5 mL) and H_2O (0.5 mL). The mixture was filtered through Celite. The filtrate was evaporated to give a crude product, which was purified by TLC on silica gel (SiO_2, 0.15% NH_4OH in EtOAc) to give (±)-lupinine (**1**) as a pale yellow solid; yield: 49 mg (74% yield); mp 55–56 °C (EtOAc) (Lit.[5a] mp 55–57 °C).

IR (neat): 3391, 1468, 1445, 1351, 1296, 1067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.12 (br s, 1 H, OH), 4.07 (d, *J* = 7.0 Hz, 1 H), 3.63 (d, *J* = 10.8 Hz, 1 H), 2.81–2.74 (m, 2 H), 2.12–1.64 (m, 7 H), 1.60–1.45 (m, 6 H), 1.30–1.25 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.6 (CH_2), 64.9 (CH), 56.9 (2 CH_2), 38.2 (CH), 30.9 (CH), 29.4 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 22.8 (CH_2).

MS: *m*/*z* (%) = 169 (M^+, 42), 168 (89), 152 (94), 138 (82), 110 (61), 98 (100), 83 (50).

These spectroscopic data are in agreement with those reported in the literature.[7]

Ethyl (1*R**,9a*S**)-Octahydro-2*H*-quinolizine-1-carboxylate (10)[6a,b]

A solution of **8** (1.033 g, 0.48 mmol) in MeOH (5 mL) and Mg turnings (0.12 g, 4.80 mmol) were stirred and refluxed under argon for 3 h, then cooled to r.t. and diluted with H_2O (50 mL). The white precipitate was filtered and washed with EtOAc (4 × 50 mL). The combined organic layers were washed with H_2O (2 × 25 mL) and brine (25 mL), and dried (Na_2SO_4). The organic phase was concentrated to give a pale yellow viscous liquid of a crude product containing a mixture of ethyl and methyl octahydro-2*H*-quinolizine-1-ylmethanol (90.1 mg), which was directly subjected to epimerization and transesterification by using in NaOEt in EtOH as follows. A solution of the crude product in EtOH (2 mL) at r.t. under argon was added to a NaOEt solution in EtOH [2 mL, prepared by reacting Na (40 mg, 1.74 mmol) with EtOH (2 mL)]. The mixture was stirred

under reflux overnight (16 h). After cooling the mixture to r.t., it was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL) and dried (Na_2SO_4). The organic phase was concentrated to give a pale yellow viscous liquid of the crude product, which was purified by TLC on silica gel (SiO_2, 0.15% NH_4OH in EtOAc) to give **10** as a pale yellow liquid of; yield: 79 mg (78%).

IR (neat): 1733, 1445, 1259, 1172, 1131, 1035 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.07 (q, *J* = 7.1 Hz, 2 H), 2.75 (t, *J* = 11.3 Hz, 2 H), 2.24–2.16 (m, 1 H), 2.07–1.92 (m, 3 H), 1.88–1.83 (m, 1 H), 1.64–1.37 (m, 7 H), 1.28–1.13 (m, 2 H), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8 (C=O), 63.5 (CH), 60.2 (CH_2), 56.6 (CH_2), 55.9 (CH_2), 49.3 (CH), 30.7 (CH_2), 28.6 (CH_2), 25.6 (CH_2), 24.4 (CH_2), 24.2 (CH_2), 14.2 (CH_3).

MS: *m*/*z* (%) = 211 (M^+, 20), 182 (100), 178 (31), 138 (69), 110 (62), 96 (60), 83 (43).

These spectroscopic data are in agreement with those reported in the literature.[6a,b]

(1*R,9a*S**)-Octahydro-2*H*-quinolizine-1-ylmethanol [(±)-Epilupinine (2)]**

As described for (±)-lupinine (**1**), a solution of **10** (80 mg, 0.38 mmol) in anhyd Et_2O (3 mL) was added to a stirred suspension of $LiAlH_4$ (32 mg, 0.83 mmol) in anhyd Et_2O (2mL) at 0 °C under argon to give (±)-epilupinine (**2**) as a colorless solid; yield. 45 mg (71%); mp 80–81 °C (Lit.[7a] mp 79–80 °C.

IR (neat): 3347, 1466, 1358, 1296, 1113, 1067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (dq, *J* = 15.7, 3.2 Hz, 2 H), 2.77 (t, *J* = 11.9 Hz, 2 H), 2.03–1.44 (m, 3 H), 1.86–1.55 (m, 8 H), 1.45–1.35 (m, 1 H), 1.30–1.10 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.3 (CH), 64.1 (CH_2), 56.5 (CH_2), 56.1 (CH_2), 43.1 (CH), 28.9 (CH_2), 27.7 (CH_2), 24.8 (CH_2), 24.2 (CH_2), 24.1 (CH_2).

MS: *m*/*z* (%) = 169 (M^+, 44), 168 (93), 152 (91), 138 (84), 124 (68), 110 (64), 96 (100), 82 (83).

These spectroscopic data are in agreement with those reported in the literature.[7]

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A synthetic strategy to pyrrolidines and piperidines based on cyclization of α-sulfinyl carbanions

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Abstract
A general synthetic strategy for the preparation of pyrrolidines, piperidines and their unsaturated analogs is described, which involves intramolecular cyclization of α-sulfinyl carbanions onto the carbonyl group of the readily prepared *N*-phenylsulfinylpropyl- or *N*-phenylsulfinylbutylamides, followed by reductive desulfurization or sulfoxide elimination of the resulting cyclized products.

Keywords: α-Sulfinyl carbanion, pyrrolidines, piperidines, intramolecular cyclization

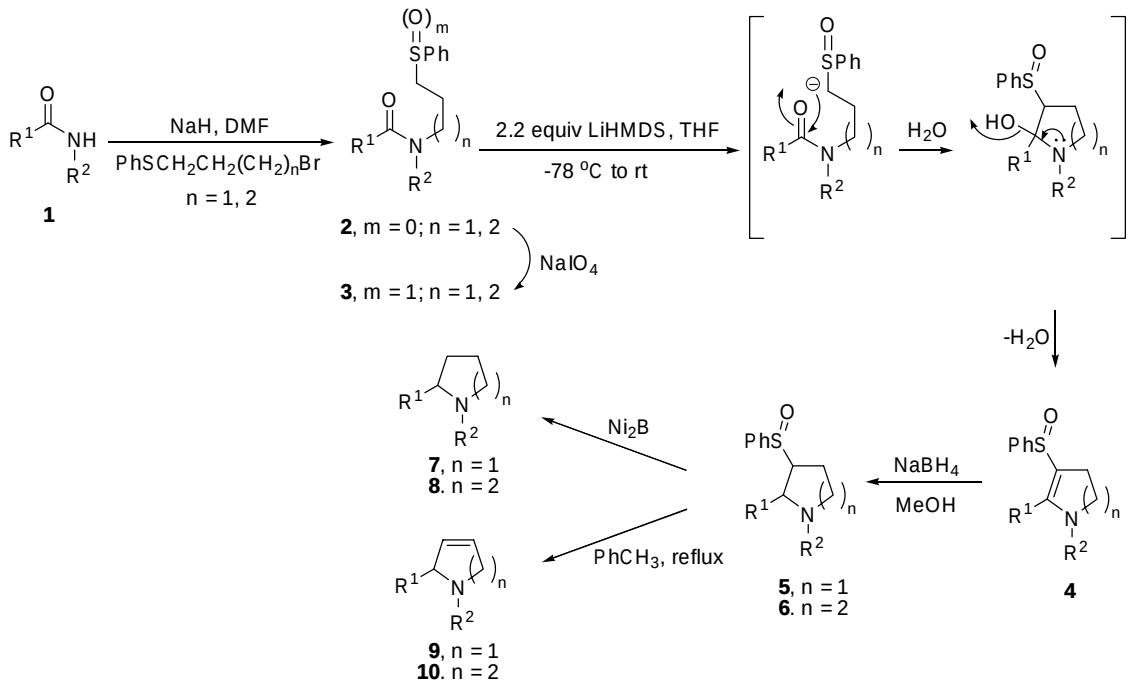
Introduction

N-Heterocycles occur in many interesting classes of compounds, for example, naturally occurring substances, pharmaceuticals, polymers, electronic materials, and sensors. In particular, pyrrolidine and piperidine derivatives are present in a large number of physiologically interesting natural products.[1] As a result, a considerable number of synthetic approaches to pyrrolidines and piperidines have been reviewed[2] and the search for alternative, general, and convenient procedures for their synthesis is still desirable. As part of our research program on the synthetic utility of cyclization based on α-sulfinyl carbanions for the preparation of 1-azabicyclic compounds,[3-5] we report a general route for the preparation of pyrrolidines and piperidines starting from simple amides.

Results and Discussion

The pyrrolidine and piperidine derivatives **5**–**6** were prepared according to the synthetic analysis outlined in Scheme 1, which involves N-alkylation of secondary amides with 1-bromo-3-phenylsulfanylpropane or 1-bromo-4-phenylsulfanylbutane, and oxidation of the resulting adducts to the corresponding sulfoxides followed by α-sulfinyl carbanions- mediated cyclization,

and reduction. The synthetic utility of our syntheses was further demonstrated by preparing substituted pyrrolidines or piperidines **7**, **8** as well as their unsaturated analogs **9**, **10**.



Scheme 1. Synthetic pathway.

The required starting sulfoxides **3** (*n* = 1 or 2) were prepared in good yields by treatment of the secondary amides **1** with 1-bromo-3-phenylsulfanylpropane or 1-bromo-4-phenylsulfanylbutane, using NaH as a base in *N*,*N*-dimethylformamide (DMF) at 0 ºC followed by oxidation of the resulting sulfides **2** with $NaIO_4$ in aqueous methanol at 0 ºC to room temperature overnight. The results are summarized in Table 1.

Having the starting sulfoxides in hand, we explored the intramolecular cyclization, exploiting compound **3a** as a model substrate. In preliminary experiments, treatment of the sulfoxide **3a** with 1.0 or 1.2 equivalents of lithium hexamethyldisilazide (LiHMDS) in THF at –78 ^{o}C followed by slowly warming to room temperature overnight (12-16 h) led to a low yield of the expected cyclized product **4a**. The starting sulfoxide **3a** still remained, as revealed by thin-layer chromatography and ^{1}H NMR analyses of the crude product. It is worth mentioning that the obtained cyclized product **4a** decomposed slowly upon standing, or purification on silica gel. To circumvent the decomposition problem, the crude material after the cyclization step was immediately subjected to reduction, employing $NaBH_4$ in methanol. A good yield (66%) of phenylsulfinylpyrrolidine **5a** was obtained when 2.0–2.2 equivalents of LiHMDS were employed for the cyclization step, followed by reduction of the initial cyclized product **4a** with $NaBH_4$ in methanol at room temperature. By performing the sequential cyclization and reduction reaction under the same reaction conditions as for **5a**, the phenylsulfinylpyrrolidines **5b**–**d** and

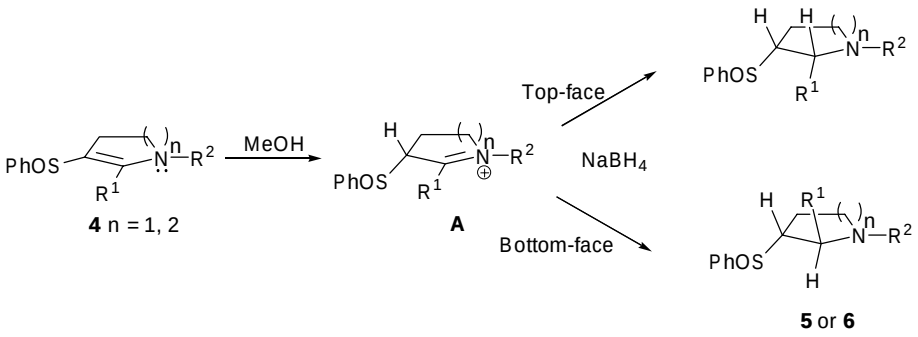
piperidines **6a** and **b** were prepared in moderate to good yields from the corresponding starting sulfoxides **3b**–**d** and **3e**–**f**, respectively, as summarized in Table 1.

Table 1. Pyrrolidine and piperidine derivatives prepared by this methodology

Entry	Amide	R^1	R^2	Product yields (%)[a]					
	1			**2**	n	**3**	**5**[b] or **6**[b]	**7** or **8**	**9** or **10**
1	**1a**	Ph	Ph	**2a**, 84	1	**3a**, 90	**5a**, 66	**7a**, 68	**9a**, 65
2	**1b**	Me	Ph	**2b**, 88	1	**3b**, 92	**5b**, 50	**7b**, 60	[c]
3	**1c**	*n*-Pr	Ph	**2c**, 80	1	**3c**, 90	**5c**, 57	**7c**, 62	[c]
4	**1d**	Ph	Bn	**2d**, 57	1	**3d**, 91	**5d**, 58	[c]	**9d**, 65
5	**1a**	Ph	Ph	**2e**, 82	2	**3e**, 90	**6a**, 72	**8a**, 61	**10a**, 76
6	**1b**	Me	Ph	**2f**, 85	2	**3f**, 90	**6b**, 56	**8b**, 70	**10b**, 72

[a] Isolated yields. [b] Obtained as mixtures of diastereomers. [c] Not performed.

It is worth noting that the phenylsulfinylpyrrolidines **5a**–**d** and phenylsulfinylpiperidines **6a**–**b**, in all cases, were obtained as a mixture of diastereomers. A maximum of four diastereoisomer was expected from those possess three chiral centers and their stereochemical outcomes can be explained as shown in Scheme 2. It was believed that the iminium ions **A** readily formed under protic conditions. Subsequent reduction by sodium borohydride gave **5a**–**d** and **6a**–**b**. Since the hydride anion can access the iminium ion from both the top- and the bottom-face of the iminium ions, this resulted in the formation of diastereomeric products of **5** and **6**.

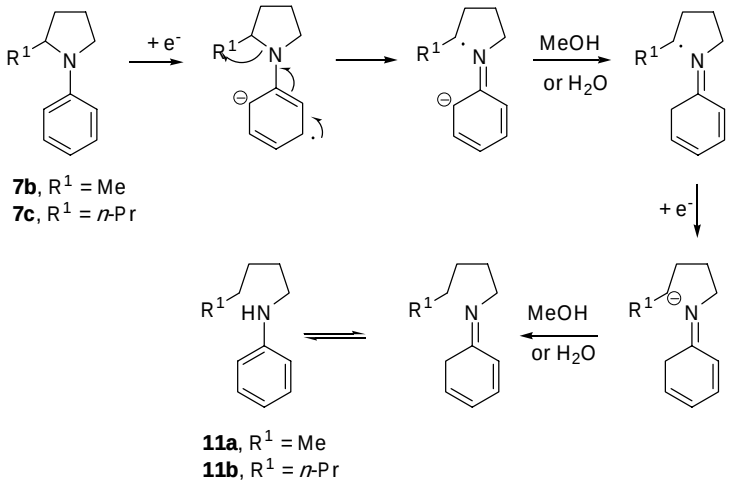


Scheme 2. Formation of compounds **5a–d** and **6a–b**.

Having established the efficient access to pyrrolidine and piperidine core units, we envisioned that the presence of the phenylsulfinyl group in compounds **5** and **6** makes them useful for further synthetic manipulation. The preparation of pyrrolidines **7** and piperidines **8** as well as their unsaturated analogs **9** and **10** from compounds **5** and **6** were demonstrated. Thus, reductive cleavage of the phenylsulfinyl group of **5a** was carried out by treatment with an excess of nickel boride (Ni_2B)[6] in methanol at 3–5 ºC, affording pyrrolidine **7a** in 68% yield (Table 1,

entry 1). Similarly, reductive desulfurization of **5b**–**c** and **6a**–**b** gave the corresponding pyrrolidines **7b**–**c** and piperidines **8a**–**b** in 60–70% yields as summarized in Table 1 (entries 2–3 and 5–6).

It was observed that further reductive cleavage of the carbon–nitrogen bond of pyrrolidines **7b** and **7c** occurred to give the corresponding ring–opening products *N*-pentylaniline **11a** and *N*-heptylaniline **11b** in 14 and 15% yields, respectively. The formation of both compounds arose presumably by the hydrogenolysis of the initially formed **7b** and **7c** via a mechanism as proposed in Scheme 3.



Scheme 3. Plausible mechanism for the formation of **11a** or **11b** from the corresponding compounds **7b** or **7c**.

Finally, the pyrrolidines **5a**, **5d** and piperidines **6a**–**b** were subjected to sulfoxide elimination conditions (toluene, reflux), leading to the corresponding unsaturated derivatives **9a**, **9b** and **10a**–**b** in 65–76% yields as shown in Table 1 (entries 1, 4, 5 and 6).

Conclusions

Cyclization based on α-sulfinyl carbanions is shown to be a useful, general strategy for the preparation of substituted pyrrolidines and piperidines, and their unsaturated analogs, starting from simple amides.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker DPX-300 or a Bruker DPX-500 spectrometer. IR spectra were recorded either with a Jasco A-302 or a Perkin Elmer 683 Infrared

spectrometer. Mass spectra were performed on a Thermo Finnigan Polaris Q mass spectrometer. High resolution MS were obtained from either HR–TOF–MS Micromass model VQ-TOF2 or Finnigan MAT 95 mass spectrometer. Microanalyses were performed with a Perkin–Elmer Elemental Analyzer 2400 CHN. Melting points were determined on a Buchi 501 Melting Point Apparatus and were uncorrected. Tetrahydrofuran (THF) was freshly distilled from sodium–benzophenone ketyl. The molarity of *n*-BuLi (in hexane) was determined by titration with diphenylacetic acid in THF at 0 ºC. The reactions dealing with anions were carried out under an argon atmosphere. Preparative plates were performed using Merck silica gel 60 PF_{254}. Column chromatography was performed on Merck silica gel 60 H. Radial chromatography on a Chromatotron was performed with Merck silica gel 60 PF_{254}.

Sulfide 2. General procedure

To a suspension of NaH (1.1 equiv.) in DMF (~0.37 M) at 0 ºC, was added a solution of amide (1 equiv.) in DMF (~1 M) under an argon atmosphere. The reaction mixture was stirred for 1 h until the generation of hydrogen ceased. To this mixture, was added a solution of 1-bromo-3-phenylsulfanylpropane (1.1 equiv.) in DMF (~2.75 M). After the reaction mixture was stirred at 0 ºC to room temperature overnight (15 h), it was quenched with water and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O, brine, dried (anhydrous Na_2SO_4), and filtered. Removal of solvent gave a residue, which was further purified by column chromatography (silica gel) to furnish the analytically pure product.

***N*-Phenyl-*N*-(3-phenylsulfanylpropyl)benzamide (2a).** Prepared from *N*-phenylbenzamide (1.97 g, 10 mmol) and 1-bromo-3-phenylsulfanylpropane (2.7052 g, 11 mmol). Column chromatography (10% EtOAc–hexanes) gave **2a** (2.9079 g, 84%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.14 (m, 13H, Ar*H*), 7.02 (app. d, *J* = 7.6 Hz, 2H, Ar*H*), 4.12 (t, *J* = 7.4 Hz, 2H, NCH_2), 3.02 (t, *J* = 7.4 Hz, 2H, CH_2S), 2.04 (quintet, *J* = 7.4 Hz, 2H, NCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.14 (C=O), 143.91 (C), 136.74 (C), 136.68 (C), 130.3 (2 x CH), 130.2 (CH), 129.8 (2 x CH), 129.5 (2 x CH), 129.3 (2 x CH), 128.3 (4 x CH), 127.3 (CH), 126.8 (CH), 49.9 (CH_2), 32.2 (CH_2), 28.0 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1642, 1595, 1579, 1493, 739, 699. MS: *m/z* (% relative intensity): 347 (M^+, 6), 238 (100), 210 (8), 106 (15), 105 (73), 77 (34). HRMS (ESI–TOF): *m/z* [M^+] Calcd for $C_{22}H_{21}NOS$: 347.1344. Found: 347.1335.

***N*-Phenyl-*N*-(3-phenylsulfanylpropyl)acetamide (2b).** Prepared employing *N*-phenylacetamide (4.0551 g, 30 mmol and 1-bromo-3-phenylsulfanylpropane (7.6283 g, 33 mmol). Column chromatography (10% EtOAc–hexanes) gave **2b** (7.5079 g, 88%; pale yellow liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.01(m, 10H, Ar*H*), 3.82 (t, *J* = 7.3 Hz, 2H, NCH_2), 2.90 (t, *J* = 7.4 Hz, 2H, CH_2S), 1.90–1.71 (m, 2H, NCH_2CH_2), 1.81 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (C=O), 142.4 (C), 135.9 (C), 129.8 (2 x CH), 129.8 (2 x CH), 128.8 (2 x CH), 128.1 (CH), 127.8 (2 x CH), 126.1 (CH), 48.3 (CH_2), 31.4 (CH_2), 27.3 (CH_2), 22.5 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1656, 1595, 1496, 1397, 741, 701. MS: *m/z* (% relative intensity): 286 ($M+H^+$, 7), 285 (M^+, 2), 176 (100), 134 (33), 106 (46), 79 (6), 77 (10). Anal. Calcd for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.34; H, 6.66; N, 4.66.

***N*-Phenyl-*N*-(3-phenylsulfanylpropyl)butyramide (2c).** Prepared from *N*-phenylbutyramide (3.5401 g, 20 mmol) and 1-bromo-3-phenylsulfanylpropane (5.082 g, 22 mmol). Column chromatography (10% EtOAc–hexanes) gave **2c** (4.9587g, 80%; pale yellow liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.05 (m, 10H, Ar*H*), 3.83 (t, *J* = 7.3 Hz, 2H, NCH_2), 2.93 (t, *J* = 7.3 Hz, 2H, CH_2S), 2.11–1.91 (m, 2H, $CH_2CH_2CH_2$), 1.91–1.75 (m, 2H, CH_2CO), 1.70–1.50 (m, 2H, CH_3CH_2), 0.83 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (C=O), 142.5 (C), 136.1 (C), 129.7 (3 x CH), 129.5 (CH), 128.8 (2 x CH), 128.2 (2 x CH), 127.8 (CH), 126.1 (CH), 48.2 (CH_2), 36.2 (CH_2), 31.4 (CH_2), 27.5 (CH_2), 18.8 (CH_2), 13.8 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1655, 1595, 1495, 740, 701. MS: *m/z* (% relative intensity): 314 (M^++1, 19), 313 (M^+, 3), 205 (16), 204 (100), 134 (28), 106 (48), 77 (10). HRMS (ESI–TOF): *m/z* [M+Na$^+$]. Calcd for $C_{19}H_{23}NOSNa$: 336.1398. Found: 336.1395.

***N*-Benzyl-*N*-(3-phenylsulfanylpropyl)benzamide (2d).** Prepared from *N*-benzylbenzamide (4.55 g, 20 mmol) and 1-bromo-3-phenylsulfanylpropane (5.082 g, 22 mmol. Column chromatography (40% EtOAc–hexanes) gave **2d** (4.1154 g, 57%; colorless liquid) as a mixture of two rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.00 (m, 15H, Ar*H*), 4.75 and 4.49 (each br. peak, 2H, NCH_2Ph), 3.55 and 3.26 (each br. peak, 2H, NCH_2CH_2), 2.94 and 2.63 (each br. peak, 2H, CH_2CH_2S), 2.13 and 1.78 (each br. peak, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): 172.8 (C=O), 137.02 (3 x C), 130.2 (2 x CH), 129.6 (2 x CH), 129.4 (CH), 129.2 (2 x CH), 128.8 (CH), 128.3 (2 x CH), 127.6 (CH), 127.2 (2 x CH), 126.8 (CH). All CH_2 peaks split into two peaks due to rotamers: 53.6 (CH_2), 48.2 (CH_2), 47.8 (CH_2), 44.5 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 28.2 (CH_2), 27.3 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1634, 1578, 1496, 738, 700. MS: *m/z* (% relative intensity): 361 (M^+, 3), 256 (74), 252 (98), 224 (9), 151 (8), 105 (100), 77 (35). HRMS (ESI–TOF): *m/z* [M+H$^+$] Calcd for $C_{23}H_{24}NOS$: 362.1579. Found: 362.1574.

***N*-Phenyl-*N*-(4-phenylsulfanylbutyl)benzamide (2e).** Prepared from *N*-phenylbenzamide (5.872 g, 30 mmol) and 1-bromo-4-phenylsulfanylbutane (8.085 g, 33 mmol). Column chromatography (40% EtOAc–hexanes) gave **2e** (8.6640 g, 82%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.08 (m, 13H, Ar*H*), 7.01–6.93 (m, 2H, Ar*H*), 3.92 (t, *J* = 7.0 Hz, 2H, NCH_2CH_2), 2.92 (t, *J* = 6.8 Hz, 2H, CH_2CH_2S), 1.83–1.64 (m, 4H, CH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (C=O), 143.9 (C), 137.1 (C), 136.8 (C), 130.1 (CH), 129.9 (2 x CH), 129.8 (2 x CH), 129.5 (2 x CH), 129.3 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 126.5 (CH), 50.3 (CH_2), 33.9 (CH_2), 27.5 (CH_2), 27.2 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1643, 1595, 1493, 739, 699. MS: *m/z* (% relative intensity): 361 (M^+, 2), 197 (14), 146 (8), 105 (100), 77 (33). HRMS (ESI–TOF): *m/z* [M+Na$^+$] Calcd for $C_{23}H_{23}NOSNa$: 384.1399; Found: 384.1398.

***N*-Phenyl-*N*-(4-phenylsulfanylbutyl)acetamide (2f).** Prepared employing *N*-phenylacetamide (4.0551 g, 30 mmol) and 1-bromo-4-phenylsulfanylbutane (8.0850 g, 33 mmol). Column chromatography (40% EtOAc–hexanes) gave **2f** (7.5264 g, 85%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.21 (m, 7H, Ar*H*), 7.20–7.07 (m, 3H, Ar*H*), 3.70 (br. t, *J* = 6.7 Hz, 2H, NCH_2CH_2), 2.91 (br. t, *J* = 6.7 Hz, 2H, CH_2CH_2S), 1.80 (s, 3H, CH_3), 1.70–1.55 (m, 4H, CH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (C=O), 142.8 (C), 136.4 (C), 129.7 (2 x CH), 129.1 (2 x CH), 128.8 (2 x CH), 128.01 (2 x CH), 127.8 (CH), 125.8 (CH), 48.2 (CH_2), 33.2

(CH_2), 26.8 (CH_2), 26.3 (CH_2), 22.7 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1658, 1595, 1496, 1481, 1439, 1301, 740, 701. MS: *m/z* (% relative intensity): 299 (M^+, 2), 191 (13), 190 (92), 148 (21), 135 (9), 123 (7), 106 (100), 93 (16), 79 (6), 77 (10). Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N,4.68. Found: C, 72.28; H, 7.02; N, 4.46.

Sulfoxide 3. General procedure

To a suspension of $NaIO_4$ (1.1 equiv) in 2:1 of MeOH : H_2O (~0.5 M) at 0 ºC, was slowly added a solution of **2** (1 equiv) in MeOH (~0.67 M). The resulting mixture was stirred vigorously and slowly warmed up from 0 ºC to room temperature overnight. The precipitates of $NaIO_3$ were filtered and washed with EtOAc (3 x 50 mL). The combined organic mixtures were washed with H_2O, brine and dried (anhydrous Na_2SO_4). Filtration followed by evaporation gave a crude product, which was purified by column chromatography (silica gel) to provide an analytically pure product.

***N*-Phenyl-*N*-(3-phenylsulfinylpropyl)benzamide (3a).** Compound **2a** (2.4186 g, 6.96 mmol) was employed. Column chromatography (50% EtOAc–hexanes to 100% EtOAc) provided **3a** (2.3374 g, 90%, pale yellow viscous oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.53 (m, 2H, Ar*H*), 7.49–7.41 (m, 3H, Ar*H*), 7.25–7.05 (m, 8H, Ar*H*), 6.96–6.90 (m, 2H, Ar*H*), 4.03 (t, *J* = 7.0 Hz, 2H, NCH_2CH$_2$), 3.00–2.74 (m, 2H, CH_2), 2.18–1.85 (m, 2H, CH_2SO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3 (C=O), 144.2 (C), 143.5 (C), 136.4 (C), 131.6 (CH), 130.3 (CH), 129.9 (2 x CH), 129.9(2 x CH), 129.2 (2 x CH), 128.4 (4 x CH), 127.6 (CH), 124.6 (2 x CH), 55.3 (CH_2), 49.5 (CH_2), 21.5 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1639, 1594, 1578, 1494, 1087, 1044, 749, 730. MS: *m/z* (% relative intensity): 363 (M^+, 1), 238 (40), 198 (25), 132 (23), 105 (100), 77 (40). HRMS (ESI–TOF): *m/z* [M+Na^+] Calcd for $C_{22}H_{21}NO_2SNa$: 386.1191. Found: 386.1191.

***N*-Phenyl-*N*-(3-phenylsulfinylpropyl)acetamide (3b).** Compound **2b** (5.7082 g, 20 mmol) was employed. Column chromatography (100% EtOAc to 5% MeOH in EtOAc) provided **3b** (1.2431 g, 92%; viscous liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.47 (m, 5H, Ar*H*), 7.47–7.32 (m, 3H, Ar*H*), 7.12 (app. d, *J* = 7.3, 2H, Ar*H*), 3.82 (t, *J* = 6.9 Hz, 2H, NCH_2CH$_2$), 3.02–2.70 (m, 2H, CH$_2$CH_2SO), 2.11–1.72 (m, 2H, CH$_2$CH_2CH$_2$), 1.83 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8 (C=O), 143.5 (C), 142.4 (C), 130.9 (CH), 129.9 (2 x CH), 129.2 (2 x CH), 128.2 (CH), 128.0 (2 x CH), 123.9 (2 x CH), 54.4 (CH_2), 47.6 (CH_2), 22.7 (CH_3), 20.6 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1655, 1595, 1496, 1044, 750, 701. MS: *m/z* (% relative intensity): 302 (M+H^+, 1), 176 (98), 134 (26), 132 (37), 106 (100), 77 (15). HRMS (ESI–TOF): *m/z* [M+Na^+] Calcd for $C_{17}H_{19}NO_2SNa$: 324.1034. Found: 324.1035.

***N*-Phenyl-*N*-(3-phenylsulfinylpropyl)butyramide (3c).** Compound **2c** (1.5650 g, 5 mmol) was employed. Column chromatography (80% EtOAc–hexanes to 5% MeOH in EtOAc) provided **3c** (1.4775 g, 90%; pale yellow viscous liquid). ^{1}H NMR (300 MHz, $CDCl_3$): 7.69–7.30 (m, 8H, Ar*H*), 7.10 (d, *J* = 6.93 Hz, 2H, Ar*H*), 3.91–3.71 (m, 2H, NCH_2), 3.04–2.88 (m, 1H, C*H*HSO), 2.85–2.72 (m, 1H, CH*H*SO), 2.15–1.91 (m, 3H, C*H*HCH$_2$C=O and CH_2C=O), 1.90–1.72 (m, 1H, CH*H*CH$_2$C=O) 1.56 (sextet, *J* = 7.4 Hz, 2H, CH$_3$CH_2), 0.80 (t, *J* = 7.4 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.98 (C=O), 144.2 (C), 142.8 (C), 131.6 (CH), 130.5 (2 x CH),

129.9 (2 x CH), 128.9 (2 x CH), 128.8 (CH), 124.7 (2 x CH), 55.3 (CH_2), 48.4 (CH_2), 36.8 (CH_2), 21.4 (CH_2), 19.5 (CH_2), 14.4 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1650, 1594, 1495, 1043, 750, 702. MS: *m/z* (% relative intensity: 329 (M^+, 1), 242 (16), 204 (100), 132 (34), 106 (95), 77 (15). HRMS (ESI–TOF): *m/z* [M+Na^+] Calcd for $C_{19}H_{23}NO_2SNa$: 352.1449. Found: 352.1347.

***N*-Benzyl-*N*-(3-phenylsulfinylpropyl)benzamide (3d).** Compound **2d** (3.1602 g, 8.75 mmol) was employed. Column chromatography (100% EtOAc to 5% MeOH in EtOAc) provided **3d** (3.0127 g, 91%; colorless viscous liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.01 (m, 15H, Ar*H*), 4.75 and 4.50 (each br. peak, 2H, NC*H*$_2$Ph), 3.51 and 3.26 (each br. peak, 2H, NC*H*$_2$CH$_2$CH$_2$), 2.94 and 2.82 (each br. peak, 2H, CH$_2$CH$_2$C*H*$_2$S), 2.15–1.96 (br. , 2H, CH$_2$C*H*$_2$CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.32 (C=O), 143.56 (C), 136.45 (C), 136.12 (C), 131.02 (CH), 129.65 (CH), 129.29 (CH), 129.27 (2 x CH), 129.85 (2 x CH), 128.57 (2 x CH), 127.71 (CH), 126.54 (2 x CH), 123.94 (3 x CH), 54.65 (CH_2), 52.40 (CH_2), 43.17 (CH_2), 20.02 (CH_2), 14.18 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1631, 1496, 1047, 749, 700. MS: *m/z* (% relative intensity): 378 (M+H^+, 15), 272 (42), 252 (79), 146 (43), 105 (100), 91 (84), 77 (44). HRMS (ESI–TOF): *m/z* [M+Na^+] Calcd for $C_{23}H_{23}NO_2SNa$: 400.1347. Found: 400.1343.

***N*-Phenyl-*N*-(4-phenylsulfinylbutyl)benzamide (3e).** Compound **2e** (6.2503 g, 17.30 mmol) was employed. Column chromatography (100% EtOAc to 5% MeOH in EtOAc) provided **3e** (5.8645 g, 90%; pale yellow viscous liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.43 (m, 5H, Ar*H*), 7.26–7.06 (m, 8H, Ar*H*), 6.99–6.92 (m, 2H, Ar*H*), 3.92 (t, *J* = 6.98 Hz, 2H, NC*H*$_2$CH$_2$), 2.96–2.75 (m, 2H, CH$_2$C*H*$_2$S), 1.90–1.55 (m, 4H, 2 x C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (C=O), 143.5 (C), 142.9 (C), 135.8 (C) 130.9 (CH), 129.5 (CH), 129.1 (4 x CH), 128.5 (2 x CH), 127.6 (4 x CH), 126.7 (CH), 123.9 (2 x CH), 56.3 (CH_2), 49.3 (CH_2), 26.4 (CH_2), 19.2 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1643, 1595, 1494, 1044, 752, 699. MS: *m/z* (% relative intensity): 359 (M^+-H_2O, 36), 252 (13), 146 (42), 105 (100), 77 (45). HRMS (ESI–TOF): *m/z* [M+H^+] Calcd for $C_{23}H_{24}NO_2S$: 378.1528. Found: 378.1526.

***N*-Phenyl-*N*-(4-phenylsulfinylbutyl)acetamide (3f).** Compound **2f** (0.8405 g, 2.80 mmol) was employed. Column chromatography (100% EtOAc to 5% MeOH in EtOAc) provided **3f** (3.0127 g, 90%; colorless viscous liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.47 (m, 5H, Ar*H*), 7.46–7.32 (m, 3H, Ar*H*), 7.15–7.08 (m, 2H, Ar*H*), 3.70 (t, *J* = 7.0 Hz, 2H, NC*H*$_2$CH$_2$), 2.94–2.72 (m, 2H, CH$_2$C*H*$_2$S), 1.82 (s, 3H, C*H*$_3$), 1.85–1.53 (m, 4H, 2 x C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (C=O), 143.5 (C), 142.6 (C), 130.8 (CH), 129.7 (2 x CH), 129.1 (2 x CH), 127.9 (CH), 127.8 (2 x CH), 123.9 (2 x CH), 56.3 (CH_2), 47.9 (CH_2), 26.5 (CH_2), 22.6 (CH_3), 19.03 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1652, 1595, 1496, 1036, 752, 701. MS: *m/z* (% relative intensity): 298 (M+H^+-H_2O, 62), 256 (38), 146 (94), 106 (100), 77 (21). HRMS (ESI–TOF): *m/z* [M+H^+] Calcd for $C_{18}H_{22}NO_2S$: 316.1371. Found: 316.1372.

Pyrrolidine sulfoxides 5 and piperidine sulfoxides 6. General procedure

To a cooled (–78 ºC) solution of hexamethyldisilazane (2.4 equiv.) in THF (~0.3 M) under an argon atmosphere, was added *n*-BuLi (2.2 equiv.). After stirring at –78 ºC for 30 min, a solution of compound **3** (1 equiv.) in THF (~0.5 *M*) was added dropwise. The resulting mixture was slowly warmed up from –78 ºC to room temperature overnight (15 h). The resulting red solution

was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with H_2O, brine, dried (anhydrous Na_2SO_4) and filtered. The filtrate was evaporated to yield a viscous oil of a crude product which was directly subjected to reduction by using $NaBH_4$.

To a solution of the crude product in MeOH (~0.25 *M*) at 3–5 ºC under an argon atmosphere, $NaBH_4$ (5.73 equiv) was gradually added over 15 min. The mixture was stirred for 2 h at the same temperature before it was diluted with 1 N NaOH (20 mL) and H_2O (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine and dried (anhydrous Na_2SO_4). Filtration followed by evaporation afforded a crude product as a mixture of diastereomers which was further purified by column chromatography (silica gel).

1,2-Diphenyl-3-(phenylsulfinyl)pyrrolidine (5a). Compound **3a** (1.2841 g, 3.54 mmol) was employed to produce the title compound. Column chromatography (40% EtOAc–hexanes) gave three fractions (F_1, F_2 and F_3) of **5a**.

F_1 (Isomer A, less polar): (0.2083 g, 17%; a white solid of a single isomer of **5a**; mp 136–137 ºC after crystallization from EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): 7.72–7.58 (m, 5H, Ar*H*), 7.35 (m, 3H, Ar*H*), 7.18–7.05 (m, 4H, Ar*H*), 6.75 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.47 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.32 (s, 1H, NC*H*Ph), 3.30–3.10 (m, 2H, CH_2CH_2N), 2.79 (ddd, *J* = 8.8, 3.6, 1.2 Hz, 1H, CH_2CHSO), 2.47–2.35 (m, 1H, C*H*HCH$_2$N), 2.19–2.08 (m, 1H, CH*H*CH$_2$N). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141. (C), 141.3 (2 x C), 132.1 (CH), 130.2 (2 x CH), 129.9 (2 x CH), 129.3 (CH), 129.1 (CH), 128.1 (CH), 125.9 (2 x CH), 125.3 (2 x CH), 119.3 (CH), 114.4 (2 x CH), 71.03 (CH), 66.4 (CH), 42.8 (CH_2), 23.4 (CH_2). IR ($CHCl_3$) ν_{max}/cm^{-1}: 1603, 1506, 1477, 750, 702. MS: *m/z* (% relative intensity): 348 (M+H$^+$, 22), 330 (56), 220 (33), 132 (52), 106 (100), 77 (48). HRMS (ESI–TOF): *m/z* [M$^+$] Calcd for $C_{22}H_{21}NOS$: 347.1344; Found: 347.1347.

F_2 (mixture of isomers B and C, more polar): (0.3091 g, 28%; pale yellow syrup of a 3:2 mixture of isomer B : isomer C of **5a**). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers): 7.71–7.64 (m, 2H, Ar*H*), 7.55–7.40 (m, 8H, Ar*H*), 7.36–7.23 (m, 10H, Ar*H*), 6.97–6.91 (m, 4H, Ar*H*), 6.56–6.51 (m, 2H, Ar*H*), 6.07–6.02 (m, 4H, Ar*H*), 5.32 (d, *J* = 2.1 Hz, 1H, NC*H*Ph of isomer B), 4.79 (d, *J* = 9.3 Hz, 1H, NC*H*Ph of isomer C), 3.31–3.20 (m, 1H, C*H*SOPh of isomer C), 2.89–2.82 (m, 1H, C*H*SOPh of isomer B), 2.52–2.35 (m, 2H, C*H*$_2$N of isomer B), 2.32–2.18 (m, 2H, C*H*$_2$CH$_2$N of isomer B), 2.07–1.84 (m, 2H, C*H*$_2$N of isomer C), 1.58–1.51 (m , 1H, C*H*HCH$_2$N of isomer C), 1.35–1.19 (m, 1H, CH*H*CH$_2$N of isomer C). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of two diastereomers): δ 147.4 (C), 147.2 (C), 141.3 (C), 141.2 (C), 141. (C), 140.2 (C), 131.9 (CH), 131.2 (CH), 129.3 (2 x CH), 129.3 (2 x CH), 129.1 (2 x CH), 129.0 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.01 (CH), 127.4 (CH), 125.9 (2 x CH), 124.5 (2 x CH), 117.4 (CH), 117.3 (CH), 112.7 (2 x CH), 112.5 (2 x CH), 75.9 (CH), 73.5 (CH), 68.02 (CH), 67.1 (CH), 42.2 (CH_2), 41.3 (CH_2), 24.03 (CH_2), 20.1 (CH_2). IR ($CHCl_3$) ν_{max}/cm^{-1}: 1603, 1507, 1477, 1452, 1028. MS: *m/z* (% relative intensity): 348 (M$^+$+1, 8), 330 (34), 220 (38), 147 (92), 132 (72), 117 (32), 106 (100), 93 (32), 77 (65).

F_3 (Isomer D, most polar): (0.2821 g, 21%; a white solid of a single isomer of **5a**; mp 132–133 ºC after crystallization from EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): 7.64–7.52 (m, 5H, Ar*H*), 7.47–7.30 (m, 5H, Ar*H*), 7.06 (t, *J* = 7.6 Hz, 2H, Ar*H*), 6.72 (d, *J* = 7.60 Hz, 1H, Ar*H*), 6.15 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.06 (d, *J* = 8.4 Hz, 1H, NC*H*Ph), 3.12–3.02 (m, 1H, CH_2C*H*SO), 2.52 (t, *J* = 6.8 Hz, 2H, $CH_2C\mathit{H}_2N$), 1.97–1.85 (m, 1H, C*H*HCH_2N), 1.65–1.55 (m, 1H, CH*H*CH_2N). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.1 (C), 141.6 (C), 141.5 (C), 131.7 (CH), 129.9 (2 x CH), 129.8 (2 x CH), 129.5 (2 x CH), 129.3 (CH), 127.6 (2 x CH), 125.4 (2 x CH), 119.1 (CH), 114.1 (2 x CH), 74.9 (CH), 68.3 (CH), 42.9 (CH_2), 23.0 (CH_2). IR ($CHCl_3$) ν_{max}/cm^{-1}: 1603, 1506, 1487, 1036. MS: *m/z* (% relative intensity): 348 ($M+H^+$, 4), 147 (100), 132 (92), 106 (90), 93 (42), 77 (66).

2-Methyl-1-phenyl-3-(phenylsulfinyl)pyrrolidine (5b). Compound **3b** (1.6032 g, 5.32 mmol) was employed to produce the title compound. ^{1}H NMR of the crude product exhibited a 9:1 ratio of two diasteroisomers. Column chromatography (20% to 50% EtOAc–hexanes) gave a major isomer of **5b** (0.7556 g, 50%; a white solid; mp 151–153 ºC after crystallization from EtOAc–hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): 7.71–7.63 (m, 2H, Ar*H*), 7.57–7.45 (m, 3H, Ar*H*), 7.26–7.15 (m, 2H, Ar*H*), 6.68 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.53 (d, *J* = 8.1 Hz, 2H, Ar*H*), 4.12 (quint., *J* = 6.6 Hz, 1H, NC*H*CH_3), 3.49 (dt, *J* = 9.1, 1.8 Hz, 1H, CH_2C*H*HN), 3.36–3.24 (m, 1H, CH_2C*H*SO), 3.22 (q, *J* = 8.9 Hz, 1H, CH_2CH*H*N), 2.80–2.61 (m, 1H, C*H*HCH_2N, 2.09–1.91 (m, 1H, CH*H*CH_2N), 1.39 (d, *J* = 6.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.56 (C), 143.20 (C), 131.10 (2 x CH), 129.23 (3 x CH), 124.22 (2 x CH), 116.34 (2 x CH), 111.83 (CH), 66.36 (CH), 54.54 (CH), 45.37 (CH_2), 19.79 (CH_2), 14.78 (CH_3). IR (Nujol) ν_{max}/cm^{-1}: 1598, 1502, 1489, 1032, 749. MS: *m/z* (% relative intensity): 386 (M^++1, 6), 268 (100), 160 (46), 158 (89), 118 (25), 77 (28). Anal Calcd for $C_{17}H_{19}NOS$; C, 71.54; H, 6.71; N, 4.91 Found: C, 71.45; H, 6.63; N, 4.87.

1-Phenyl-3-phenylsulfinyl-2-propylpyrrolidine (5c). Compound **3c** (1.2801 g, 3.80 mmol) was employed to produce the title compound. Column chromatography (30% EtOAc–hexanes) gave three fractions (F_1, F_2 and F_3) of **5c**.

F_1 (less polar): (0.5292 g, 44%; a white solid of a pure isomer of **5c**; mp 107–109 ºC after crystallization from EtOAc–hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): 7.72–7.61 (m, 2H, Ar*H*), 7.59–7.50 (m, 3H, Ar*H*), 7.24 (t, *J* = 7.8 Hz, 2H, Ar*H*), 6.72 (t, *J* = 7.2 Hz, 1H, Ar*H*), 6.56 (d, *J* = 8.1 Hz, 2H, Ar*H*), 4.10 (dt, *J* = 11.4, 6.7 Hz, 1H, NC*H*$CH_2CH_2CH_3$), 3.56 (td, *J* = 9.0, 1.7 Hz, 1H, CH_2CH*H*N), 3.26 (t, *J* = 7.1 Hz, 1H, CH_2C*H*HN), 3.20–3.15 (m, 1H, CH_2C*H*SO), 2.73–2.61 (m, 1H, C*H*HCH_2N), 2.10–1.90 (m, 1H, C*H*HCH_2CH_3), 2.00–1.82 (m, 1H, CH*H*CH_2N), 1.80–1.52 (m, 3H, CH*H*CH_2CH_3), 1.01 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6 (C), 143.5 (C), 130.9 (CH), 129.2 (2 x CH), 129.1 (2 x CH), 124.2 (2 x CH), 116.3 (CH), 111.9 (2 x CH), 66.3 (CH), 59.01 (CH), 46.3 (CH_2), 32.9 (CH_2), 20.3 (CH_2), 20.04 (CH_2), 14.5 (CH_3). IR (Nujol) ν_{max}/cm^{-1}: 1594, 1505*s*, 1043, 1033, 745, 690. MS: *m/z* (% relative intensity): 313 (M^+, 27), 296 (69), 188 (59), 145 (46), 144 (32). Anal Calcd for $C_{19}H_{23}NOS$; C, 72.80; H, 7.40; N, 4.47 Found: C, 73.15; H, 7.18; N, 4.31.

F_2 (more polar): (0.0819 g, 7%; pale yellow syrup of a pure isomer of **5c**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.81–7.69 (m, 2H, Ar*H*), 7.60–7.50 (m, 3H, Ar*H*), 7.28–7.16 (m, 2H, Ar*H*), 6.70 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.58 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.44 (q, *J* = 6.1 Hz, 1H, NC*H*$CH_2CH_2CH_3$), 3.52–3.36 (m, 2H, CH_2C*H*HN and CH_2C*H*SO), 3.18 (q, *J* = 8.9 Hz, 1H, CH_2CH*H*N), 2.17–2.02 (m, 2H, C*H*$_2CH_2$N), 1.90–1.30 (m, 4H, NCHC*H*$_2$C*H*$_2CH_3$) 0.98 (t, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7 (C), 142.9 (C), 131.8 (CH), 129.4 (2 x CH), 129.2 (2 x CH), 124.9 (2 x CH), 116.2 (CH), 111.8 (2 x CH), 68.9 (CH), 58.3 (CH), 46.7 (CH_2), 32.1 (CH_2), 24.7 (CH_2), 20.1 (CH_2), 14.6 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1599, 1505, 1043, 1033, 748, 692. MS: *m/z* (% relative intensity): 313 (M^+, 21), 296 (42), 188 (100), 158 (30), 145 (76), 104 (28), 77 (21).

F_3 (most polar): (0.0706 g, 6%; yellow syrup of a pure isomer of **5c**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.71–7.64 (m, 2H, Ar*H*), 7.57–7.45 (m, 3H, Ar*H*), 7.25–7.15 (m, 2H, Ar*H*), 6.80–6.65 (m, 1H, Ar*H*), 6.55–6.40 (m, 2H, Ar*H*), 3.67 (app. d, *J* = 8.4 Hz, 1H, NC*H*$CH_2CH_2CH_3$), 3.48 (td, *J* = 9.2, 1.9 Hz, 1H, CH_2C*H*HN), 3.32 (t, *J* = 9.2 Hz, 1H, CH_2CH*H*N), 3.30–3.25 (m, 1H, CH_2C*H*SO), 2.82–2.68 (m, 1H, C*H*HCH_2N), 2.48–2.31 (m, 1H, CH*H*CH_2N), 1.69–1.52 (m, 1H, NCHC*H*HCH_2), 1.41–1.19 (m, 1H, NCHCH*H*CH_2), 1.06–0.79 (m, 2H, CH_2C*H*$_2CH_3$), 0.71 (t, *J* = 7.1 Hz, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.04 (C), 142.6 (C), 131.8 (2 x CH), 129.3(2 x CH), 129.3 (2 x CH), 125.4 (2 x CH), 116.3 (CH), 112.0 (CH), 70.3 (CH), 58.1 (CH), 46.3 (CH_2), 34.4 (CH_2), 23.5 (CH_2), 18.7 (CH_2), 13.6 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1594, 1505, 1043, 1033, 745, 690. MS: *m/z* (% relative intensity): 313 (M^+, 2), 187 (82), 159 (100), 144 (48), 104 (20), 77 (19).

1-Benzyl-2-phenyl-3-(phenylsulfinyl)pyrrolidine (5d). Compound **3d** (2.6514 g, 7.03 mmol) was employed to produce the title compound. Column chromatography (50% EtOAc–hexanes) gave two fractions (F_1 and F_2) of **5d**.

F_1 (less polar): (1.2828 g, 50%; colorless needles of a pure isomer of **5d**; mp 146–148 ºC after crystallization from EtOAc–hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): 7.61 (app. d, *J* = 7.3 Hz, 2H, Ar*H*), 7.49–7.20 (m, 13H, Ar*H*), 3.96 (d, *J* = 13.4 Hz, 1H, NC*H*HPh), 3.86 (d, *J* = 8.1 Hz, 1H, NC*H*Ph), 3.39–3.30 (m, 1H, C*H*SO), 3.22 (t, *J* = 8.4 Hz, 1H, CH_2C*H*HN), 3.06 (d, *J* = 13.4 Hz, 1H, NCH*H*Ph), 2.70–2.53 (m, 1H, C*H*HCH_2N), 2.20 (q, *J* = 8.6 Hz, 1H, CH_2CH*H*N), 1.70–1.55 (m, 1H, CH*H*CH_2N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9 (C), 138.2 (C), 137.3 (C), 130.2 (CH), 129.1 (CH), 128.8 (2 x CH), 128.6 (2 x CH), 128.6 (2 x CH), 128.2 (CH), 128.1 (2 x CH), 126.9 (CH), 124.2 (3 x CH), 71.4 (CH), 68.9 (CH), 57.3 (CH_2), 51.7 (CH_2), 19.02 (CH_2). IR (nujol) ν_{max}/cm^{-1}: 1495, 1455, 1040, 746, 710. MS: *m/z* (% relative intensity): 362 (M+H^+, 16), 344 (76), 326 (15), 236 (44), 91 (100). Anal. Calcd for $C_{23}H_{23}NOS$: C, 76.42; H, 6.59; N, 3.52. Found: C, 76.52; H, 6.59; N, 3.52.

F_2 (more polar): (0.2015 g, 8%; yellow viscous oil of a pure isomer of **5d**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.60 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.57–7.51 (m, 2H, Ar*H*), 7.43–7.08 (m, 11H, Ar*H*), 3.99 (d, *J* = 8.5 Hz, 1H, NC*H*Ph), 3.80 (d, *J* = 13.3 Hz, 1H, NC*H*HPh), 3.44 (q, *J* = 8.9 Hz, 1H, C*H*SO), 3.25 (d, *J* = 13.2 Hz, 1H, NCH*H*Ph), 3.04 (t, *J* = 8.1 Hz, 1H, CH_2C*H*HN), 2.19–2.04 (m, 1H, CH_2CH*H*N), 1.60–1.43 (m, 1H, C*H*HCH_2N), 1.25–1.10 (m, 1H, CH*H*CH_2N). ^{13}C NMR (75

MHz, $CDCl_3$): δ 143.2 (C), 138.3 (C), 137.2 (C), 131.3 (CH), 129.6 (2 x CH), 128.9 (3 x CH), 128.6 (CH), 128.3 (2 x CH), 128.1 (CH), 128.1 (2 x CH), 126.9 (CH), 125.6 (2 x CH), 70.3 (CH), 69.4 (CH), 57.1 (CH_2), 51.3 (CH_2), 26.3 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1494, 1453, 1046, 699. MS: *m/z* (% relative intensity): 362 ($M+H^+$, 4), 344 (40), 236 (16), 144 (11), 92 (8), 91 (100).

1,2-Diphenyl-3-phenylsulfinylpiperidine (6a). Compound **3e** (2.8425 g, 8.12 mmol) was employed to produce the title compound. Column chromatography (40% EtOAc–hexanes) afforded three fractions (F_1, F_2 and F_3) of **6a**.

F_1 (less polar): (0.6605 g, 22%; pale yellow syrup of a pure isomer of **6a**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.60–7.45 (m, 5H, Ar*H*), 7.27–6.95 (m, 7H, Ar*H*), 6.62 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.40 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.20 (s, 1H, NC*H*CH), 2.98–2.80 (m, 2H, $CH_2C\mathit{H}_2N$), 2.51–2.40 (m, 1H, CHC*H*SO), 2.17–2.00 (m, 1H, C*H*HCH_2N), 1.87–1.60 (m, 2H, CH*H*CH_2N and C*H*HCHSO), 1.53–1.32 (m, 1H, CH*H*CHSO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4 (C), 141.2(C), 140.8 (C), 131.3 (CH), 129.5 (2 x CH), 129.2 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 125.2 (2 x CH), 124.5 (2 x CH), 117.6 (CH), 112.9 (2 x CH), 70.4 (CH), 68.6 (CH), 43.4 (CH_2), 26.7 (CH_2), 20.02 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1600, 1504, 1476, 1454, 1260, 1088, 1019, 799. MS: *m/z* (% relative intensity): 362 ($M+H^+$, 6), 344 (43), 254 (26), 132 (46), 106 (100), 91 (32), 77 (37).

F_2 (mixture of two isomers, more polar): (0.6822 g, 23%; pale yellow syrup of a 1:1 mixture of isomers of **6a**. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of two diastereomers): 7.64–7.61 (m, 2H, Ar*H*), 7.52–7.33 (m, 8H, Ar*H*), 7.32–7.18 (m, 10H, Ar*H*), 7.09–6.98 (m, 4H, Ar*H*), 6.63–6.58 (m, 2H, Ar*H*), 6.33–6.30 (m, 4H, Ar*H*), 5.27 (d, *J* = 3.6 Hz, 1H, NC*H*Ph of an isomer), 4.87 (d, *J* = 9.2 Hz, 1H, NC*H*Ph of an isomer), 3.12–3.00 (m, 1H, C*H*SOPh of an isomer), 2.52 (q, *J* = 4.7 Hz, 1H C*H*SOPh of an isomer), 2.68–2.50 (m, 4H, $CH_2C\mathit{H}_2$NPh of both isomers), 1.86–1.60 (m, 2H, CH_2), 1.44–1.24 (m, 1H of CH_2), 1.12–0.75 (m, 6H, CH_2 of both isomers). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of two diastereomers): δ 147.3 (C), 147.1 (C), 141.8 (C), 141.3 (C), 141.2 (C), 140.3 (C), 131.8 (CH), 131.1 (CH), 129.3 (2 x CH), 129.2 (2 x CH), 129.1 (2 x CH), 129.1 (2 X CH), 128.6 (2 x CH), 128.5 (2 x CH), 127.9 (2 x CH), 127.3 (2 x CH), 125.8 (2 X CH), 125.6 (2 x CH), 124.3 (2 x CH), 117.7 (CH), 117.6 (CH), 113.2 (2 x CH), 112.9 (2 x CH), 75.8 (CH), 73.1 (CH), 69.9 (CH), 69.4 (CH), 43.5 (CH_2), 43.1 (CH_2), 27.7(CH_2), 26.3 (CH_2), 22.2 (CH_2), 17.8 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1603, 1506, 1086, 1027, 997. MS: *m/z* (% relative intensity): 362 ($M+H^+$, 2), 254 (17), 236 (13), 130 (24), 126 (22), 106 (100), 77 (33).

F_3 (most polar): (0.7906 g, 27%; pale yellow syrup of a pure isomer of **6a**). ^{1}H NMR (500 MHz, $CDCl_3$): 7.67–7.51 (m, 5H, Ar*H*), 7.48–7.30 (m, 5H, Ar*H*), 7.20–7.15 (m, 1H, Ar*H*), 6.78 (t, *J* = 7.2 Hz, 1H, Ar*H*), 6.52 (d, *J* = 7.2 Hz, 2H, Ar*H*), 5.04 (d, *J* = 8.0 Hz, 1H, NC*H*CH), 3.15–2.95 (m, 1H, C*H*SOPh), 2.87–2.72 (m, 2H, CH_2NPh), 1.65–1.53 (m, 1H, C*H*HCH_2), 1.48–1.34 (m, 1H, CH*H*CH_2), 1.29–1.80 (m, 2H, CH*H*CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3 (C), 141.8 (C), 141.0 (C), 131.7 (CH), 130.2 (2 x CH), 129.9 (2 x CH), 129.9 (2 x CH), 129.35 (2 X CH), 129.08 (CH), 127.49 (2 x CH), 125.48 (2 X CH), 119.12 (CH), 114.3 (2 x CH), 74.9 (CH), 69.3

(CH), 44.6 (CH_2), 27.5 (CH_2), 21.3 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1601, 1505, 1477, 1455. MS: *m/z* (% relative intensity): 362 ($M+H^+$, 2), 254 (17), 130 (26), 106 (100), 77 (32). HRMS (ESI–TOF): *m/z* [M^+] Calcd for $C_{23}H_{23}NOS$: 361.1500. Found: 361.1511.

2-Methyl-1-phenyl-3-phenylsulfinylpiperidine (6b). Compound **3f** (1.6013 g, 5.08 mmol) was employed to produce the title compound. Column chromatography (20% EtOAc–hexanes) gave three fractions (F_1, F_2 and F_3) of **6b**.

F_1 (lees polar): (0.3139 g, 21%; a white solid of a pure isomer of **6b**; mp 121–122 ºC after crystallization from EtOAc–hexanes). ^1H NMR (300 MHz, $CDCl_3$): 7.68–7.48 (m, 5H, Ar*H*), 7.24 (t, *J* = 7.9 Hz, 2H, Ar*H*), 6.80 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.52 (d, *J* = 7.7 Hz, 2H, Ar*H*), 4.40–4.25 (m, 1H, NC*H*CH), 3.37–3.18 (m, 2H, $CH_2C\mathit{H}_2N$), 2.40–2.29 (m, 1H, CHC*H*SO), 2.26–1.94 (m, 3H, $C\mathit{H}_2CH_2N$ and C*H*HCHSO), 2.00–1.80 (m, 1H, CH*H*CHSO), 1.14 (d, *J* = 6.6 Hz, 3H, $C\mathit{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.9 (C), 141.1 (C), 131.2 (2 x CH), 129.4 (3 x CH), 124.6 (2 x CH), 118.5 (CH), 113.6 (2 x CH), 67.5 (CH), 65.6 (CH), 44.3 (CH_2), 27.3 (CH_2), 20.9 (CH_2), 20.7 (CH_3). IR ($CHCl_3$) ν_{max}/cm^{-1}: 1603, 1506, 1478, 1085, 997, 692. MS: *m/z* (% relative intensity): 300 ($M+H^+$, 37), 282 (52), 207 (19), 192 (45), 174 (42), 172 (48).

F_2 (more polar): (0.3101 g, 20%; yellow syrup of a pure isomer of **6b**). ^1H NMR (300 MHz, $CDCl_3$): 7.66–7.54 (m, 2H, Ar*H*), 7.48–7.31 (m, 3H, Ar*H*), 7.09 (t, *J* = 7.9 Hz, 2H, Ar*H*), 6.65 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.47 (d, *J* = 8.3 Hz, 2H, Ar*H*), 4.19 (quintet, *J* = 6.4 Hz, 1H, NC*H*CH), 3.01–2.83 (m, 2H, $CH_2C\mathit{H}_2N$), 2.80–2.70 (m, 1H, CHC*H*SO), 1.73–1.30 (m, 4H, $C\mathit{H}_2C\mathit{H}_2CHSO$), 1.23 (d, *J* = 6.3 Hz, 3H, $C\mathit{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5 (C), 142.2 (C), 131.6 (CH), 129.2 (2 x CH), 129.2 (2 x CH), 125.4 (2 x CH), 117.6 (CH), 112.9 (2 x CH), 67.9 (CH), 68.2 (CH), 43.4 (CH_2), 26.5 (CH_2), 22.5 (CH_2), 20.8 (CH_3). IR ($CHCl_3$) ν_{max}/cm^{-1}: 1603, 1506, 1444, 1085, 996. MS: *m/z* (% relative intensity): 300 ($M+H^+$, 19), 282 (18), 207 (28), 192 (28), 172 (28), 146 (14), 132 (9), 118 (19), 106 (100), 77 (25).

F_3 (most polar): (0.2182 g, 15%; a white solid of a pure isomer of **6b**; mp 109–111 ºC after crystallization from EtOAc–hexanes). ^1H NMR (300 MHz, $CDCl_3$): 7.68–7.45 (m, 5H, Ar*H*), 7.17 (t, *J* = 7.8 Hz, 2H, Ar*H*), 6.72 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.52 (d, *J* = 8.3 Hz, 2H, Ar*H*), 4.52–4.40 (m, 1H, NC*H*CH), 2.92 (t, *J* = 6.8 Hz, 2H, $CH_2C\mathit{H}_2N$), 2.58–2.54 (m Hz, 1H, CHC*H*SO), 1.97–1.67 (m, 2H, $C\mathit{H}_2CH_2N$), 1.51–1.45 (m, 1H, C*H*HCHSO), 1.42 (d, *J* = 6.5 Hz, 3H, CH_3), 1.21–1.10 (m, 1H, CH*H*CHSO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6 (C), 142.8 (C), 130.9 (CH), 129.2 (4 x CH), 124.2 (2 x CH), 117.6 (CH), 112.9 (2 x CH), 69.7 (CH), 68.03 (CH), 43.7 (CH_2), 28.4 (CH_2), 21.02 (CH_2), 18.1 (CH_3). IR ($CHCl_3$) ν_{max}/cm^{-1}: 1603, 1506, 1444, 1086, 1020. MS: *m/z* (% relative intensity): 300 ($M+H^+$, 25), 282 (43), 192 (41), 172 (49), 118 (26), 106 (100), 77 (42).

Pyrrolidine 7 and Piperidine 8. General procedure

To a stirred 0 ºC solution of compound **5** or **6** (1 equiv) and $NiCl_2{\cdot}6H_2O$ (10 equiv) in solvent (see details for each reaction), was added portionwise $NaBH_4$ (30 equiv) at such a rate that the temperature was kept below 10 ºC (about 20 min). The resulting mixture was stirred at room temperature for 2 h. The black precipitate was filtered off over Celite and washed several times

with EtOAc. The organic phase was washed with H_2O, brine, dried (anhydrous Na_2SO_4) and filtered. Removal of solvent gave a crude product which was further purified by radial chromatography (silica gel).

1,2-Diphenylpyrrolidine (7a).[7,8] Compound **5a** as a mixture of isomers (0.1735 g, 0.50 mmol) and MeOH (6 mL) was employed to yield, after radial chromatography (100% hexanes), compound **7a** (0.0758 g, 68%; pale yellow liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.05 (m, 5H, Ar*H*), 6.71–6.59 (m, 3H, Ar*H*), 6.62 (d, *J* = 7.7 Hz, 2H, Ar*H*), 4.65–4.56 (dd, *J* = 7.4, 5.0 Hz, 1H, NC*H*Ph), 3.06 (t, *J* = 6.6 Hz, 2H, C*H*$_2$N), 1.90–1.50 (m, 4H, C*H*$_2$C*H*$_2$CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.9 (C), 144.46 (C), 129.26 (2 x CH), 128.46 (2 x CH), 127.56 (CH), 125.79 (2 x CH), 118.59 (CH), 113.9 (2 x CH), 74.2 (CH), 44.9 (CH_2), 36.5 (CH_2), 25.5 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1603, 1505, 1477, 750, 700. MS: *m/z* (% relative intensity): 224 (M+H$^+$, 11), 23 (M$^+$, 21), 147 (11), 146 (52), 106 (100), 93 (16), 77 (36).

2-Methyl-1-phenylpyrrolidine (7b).[9] Compound **5b** as a single isomer (0.4671 g, 1.64 mmol), THF (8 mL) and MeOH (24 mL) were employed to yield, after radial chromatography (100% hexanes), compound **7b** and *N*-pentylaniline (**11a**).

F$_1$ (less polar): **7b** (0.1577 g, 60%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16–7.08 (m, 2H, Ar*H*), 6.59–6.49 (m, 3H, Ar*H*), 3.80–3.76 (m, 1H, NC*H*CH$_3$), 3.35–3.29 (m,1H, C*H*HN), 3.13–3.01 (m, 1H, CH*H*N), 2.08–1.82 (m, 3H, C*H*$_2$C*H*H), 1.65–1.58 (m, 1H, CH$_2$CH*H*), 1.11 (d, *J* = 6.9 Hz, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1 (C), 129.1 (2 x CH), 115.1 (CH), 111.7 (2 x CH), 53.5 (CH), 48.1 (CH_2), 32.9 (CH_2), 23.2 (CH_2), 19.3 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1599, 1505, 1459, 1362, 1162, 1036, 994, 745, 691. MS: *m/z* (% relative intensity): 161 (M$^+$, 29), 157 (5), 146 (100), 145 (6), 130 (6), 125 (12), 117 (9), 111 (6), 104 (25), 99 (9), 91 (10), 81 (9), 77 (29), 71 (8), 57 (9).

F$_2$ (more polar): *N*-pentylaniline (**11a**)[8] (0.0374 g, 14%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12–7.07 (m, 2H, Ar*H*), 6.76–6.64 (m, 3H, Ar*H*), 3.16 (t, *J* = 7.1 Hz, 2H, NC*H*$_2$CH$_2$), 1.79–1.57 (m, 2H, C*H*$_2$CH$_2$N), 1.52–1.30 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 1.05–0.91 (m, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4 (C), 129.2 (2 x CH), 117.1 (CH), 112.7 (2 x CH), 44.0 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.5 (CH_2), 14.01 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1604, 1506, 1321, 747, 692. MS: *m/z* (% relative intensity): 163 (M$^+$, 23), 149 (34), 106 (68), 93 (100), 77 (36), 71 (40).

1-Phenyl-2-propylpyrrolidine (7c).[6] Compound **5c** as a mixture of isomers (0.1768 g, 0.56 mmol), THF (3 mL) and MeOH (9 mL) were employed to yield, after radial chromatography (100% hexanes), compound **7c** and *N*-heptylaniline (**11b**).

F$_1$ (less polar): **7c** (0.0662 g, 62%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.24 (m, 2H, Ar*H*), 6.71–6.59 (m, 3H, Ar*H*), 3.78–3.61 (m, 1H, NC*H*CH$_2$), 3.47 (app. t, *J* = 7.4 Hz, 1H, CH$_2$C*H*HN), 3.25–3.10 (m, 1H, CH$_2$CH*H*N), 2.18–1.25 (m, 8H of CH$_2$), 1.02 (t, *J* = 7.2 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.30 (C), 129.12 (2 x CH), 115.08 (CH), 111.74 (2 x CH), 58.36 (CH), 48.18 (CH_2), 35.28 (CH_2), 30.24 (CH_2), 23.43 (CH_2), 19.85 (CH_2), 14.20 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1598, 1505, 1479, 745, 691. MS: *m/z* (% relative intensity): 189 (M$^+$, 20), 188 (60), 146 (100), 117 (28), 104 (24), 77 (28).

F_2 (more polar): *N*-heptylaniline (**11b**)[10] (0.0160 g, 15%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–7.07 (m, 2H, ArH), 6.64–6.52 (m, 3H, ArH), 3.02 (t, *J* = 7.1 Hz, 2H, PhNC*H*$_2$), 1.55 (app. quint., *J* = 7.4 Hz, 2H, C*H*$_2$), 1.40–1.05 (m, 8H, 4 x C*H*$_2$), 0.81 (t, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.40 (C), 129.20 (2 x CH), 117.18 (CH), 112.78 (2 x CH), 44.09 (CH_2), 31.80 (CH_2), 29.54 (CH_2), 29.10 (CH_2), 27.13 (CH_2), 22.60 (CH_2), 14.07 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1603, 1505, 1365, 747, 691. MS: *m/z* (% relative intensity): 191 (M^+, 25), 149 (37), 106 (100), 97 (22), 81 (31), 77 (26).

1,2-Diphenylpiperidine (8a).[11] Compound **6a** as a mixture of isomers (0.3705 g, 1.03 mmol), and MeOH (20 mL) were employed to yield, after radial chromatography (100% hexanes), compound **8a** (0.1470 g, 61%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.13 (m, 5H, Ar*H*), 7.07 (br. t, *J* = 7.8 Hz, 2H, Ar*H*), 6.61 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.49 (d, *J* = 7.8 Hz, 2H, Ar*H*), 4.68 (app. t, *J* = 6.6 Hz, 1H, NC*H*Ph), 3.12 (t, *J* = 7.0 Hz, 2H, CH_2C*H*$_2$N), 1.97–1.28 (m, 6H, 3 x C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 (C), 144.6 (C), 129.2 (2 x CH), 128.4 (2 x CH), 127.5 (CH), 125.8 (2 x CH), 117.4 (CH), 112.9 (2 x CH), 74.3 (CH), 43.9 (CH_2), 38.6 (CH_2), 29.1 (CH_2), 23.3 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1603, 1506, 1028, 750, 700. MS: *m/z* (%) relative intensity 237 (M^+, 6), 160 (15), 106 (100), 93 (12), 77 (25).

2-Methyl-1-phenylpiperidine (8b).[9] Compound **6b** as a mixture of isomers (0.1615 g, 0.54 mmol) and MeOH (11 mL) were employed to yield, after radial chromatography (100% hexanes), compound **8b** (0.0658 g, 70%; colorless liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.17 (m, 2H, Ar*H*), 6.74–6.70 (m, 1H, Ar*H*), 6.65–6.62 (m, 2H, Ar*H*), 3.85–3.80 (m, 1H, NC*H*CH_3), 3.14 (t, *J* = 7.0 Hz, 2H, CH_2C*H*$_2$N), 1.63–1.60 (m, 1H of CH_2), 1.60–1.40 (m, 5H of CH_2), 1.21 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.7 (C), 129.9 (2 x CH), 118.2 (CH), 113.7 (2 x CH), 68.6 (CH), 44.8 (CH_2), 39.6 (CH_2), 30.1 (CH_2), 24.2 (CH_3), 23.9 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1603, 1508, 1477, 1322, 750, 693. MS: *m/z* (% relative intensity): 175 (M^+, 1), 106 (100), 93 (4), 79 (14), 77 (16).

Unsaturated derivatives 9 and 10. General procedure

A solution of compound **5** or **6** in dry toluene (~0.05 M) was refluxed under an argon atmosphere overnight. After cooling to room temperature, the resulting solution was concentrated to give a crude product, which was further purified by radial chromatography (silica gel).

1,2-Diphenyl-2,5-dihydro-1*H*-pyrrole (9a). Compound **5a** as a mixture of isomers (0.1730 g, 0.49 mmol) was employed to produce, after radial chromatography (100% hexanes), compound **9a** (0.0704 g, 65%; pale yellow liquid). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.09 (m, 8H, Ar*H*), 6.83–6.78 (m, 2H, Ar*H*), 5.96–5.87 (m, 2H, CH_2*H*C=C*H*CH), 5.16–5.10 (m, 1H, NC*H*Ph), 3.80–3.70 (m, 2H, NC*H*$_2$CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5 (C), 142.3 (C), 136.3 (CH), 129.4 (2 x CH), 128.6 (CH), 128.5 (2 x CH), 127.7 (CH), 126.2 (2 x CH), 126.03 (CH), 120.7 (CH), 115.7 (CH), 74.2 (CH), 47.7 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1602, 1505, 1452, 750, 695. MS: *m/z* (% relative intensity): 221 (M^+, 47), 220 (15), 146 (100), 132 (41), 117 (42), 93 (68), 77 (51). HRMS (ESI–TOF): *m/z* [M^+] Calcd for $C_{16}H_{15}N$: 221.1204. Found: 221.1211.

1-Benzyl-2-phenyl-2,5-dihydro-1*H*-pyrrole (9d). Compound **5d** as a mixture of isomers (0.4826 g, 1.34 mmol) was employed to produce, after radial chromatography (100% hexanes), compound **9d** (0.2046 g, 65%; yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.32–7.08 (m, 8H, Ar*H*), 5.81–5.74 (m, 1H, HC=C*H*CH), 5.68–5.59 (m, 1H, CH_2C*H*=CH), 4.54–4.50 (m, 1H, NC*H*Ph), 3.89 (d, *J* = 13.3 Hz, 1H, NC*H*HPh), 3.76–3.61 (m, 1H, CHCHHN), 3.48 (d, J = 13.4 Hz, 1H, NCHHPh), 3.30–3.18 (m, 1H, CHCHHN). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8 (C), 140.5 (C), 133.4 (CH), 129.9 (2 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.5 (2 x CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 74.9 (CH), 59.8 (CH_2), 58.1 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1490, 1452, 1372, 1029, 759, 738, 700 cm^{-1}. MS: m/z (% relative intensity): 236 (M^++1, 100), 235 (M^+, 45), 234 (29), 158 (45), 144 (42), 91 (80). HRMS (ESI–TOF): m/z [M+H$^+$] Calcd for $C_{17}H_{18}N$: 236.1439. Found: 236.1449.

1,2-Diphenyl-1,2,3,6-tetrahydropyridine (10a).[12] Compound **6a** as a mixture of isomers (0.2013 g, 0.55 mmol) was employed to produce, after radial chromatography (100% hexanes), compound **10a** (0.0983 g, 76%; pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.27 (m, 5H, Ar*H*), 7.25–7.18 (m, 2H, Ar*H*), 6.75 (br. t, *J* = 7.6 Hz, 1H, Ar*H*), 6.63 (br. d, *J* = 7.6 Hz, 2H, Ar*H*) 5.83–5.78 (m, 2H, *H*C=C*H*), 5.24–5.18 (m, 1H, NC*H*Ph), 3.22 (t, *J* = 7.0 Hz, 2H, CH_2N), 2.47–2.37 (m, 2H, CHCH_2CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 (C), 143.1 (C), 134.9 (CH), 129.2 (2 x CH), 128.7 (CH), 128.5 (2 x CH), 127.6 (CH), 126.1 (2 x CH), 117.6 (CH), 113.1 (2 x CH), 74.9 (CH), 43.1 (CH_2), 32.0 (CH_2). IR (neat) ν_{max}/cm^{-1}: 1602, 1505, 1475, 749, 694. MS: *m/z* (%) relative intensity 235 (M^+, 8), 146 (6), 130 (33), 106 (100), 77 (36).

2-Methyl-1-phenyl-1,2,5,6-tetrahydropyridine (10b). Compound **6b** as a mixture of isomers (0.1015 g, 0.33 mmol) was employed to produce, after radial chromatography (100% hexanes), compound **10b** (0.0411 g, 72%; pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (br. t, *J* = 7.9 Hz, 2H, Ar*H*), 6.64 (br. t, *J* = 7.3 Hz, 1H, Ar*H*), 6.53 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.60–5.52 (m, 2H, *H*C=C*H*), 4.28–4.12 (m, 1H, NC*H*CH$_3$), 3.10 (t, *J* = 6.8 Hz, 2H, CH_2N), 2.34–2.19 (m, 2H, CHCH_2CH$_2$), 1.19 (d, *J* = 6.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 (C), 136.7 (CH), 129.2 (2 x CH), 127.3 (CH), 117.6 (CH), 113.1 (2 x CH), 68.6 (CH), 43.3 (CH_2), 31.9 (CH_2), 23.8 (CH_3). IR (neat) ν_{max}/cm^{-1}: 1603, 1506, 1320, 750, 693. MS: *m/z* (% relative intensity): 173 (M^+, 1), 106 (100), 79 (28), 77 (43). HRMS (ESI–TOF): *m/z* [M^+] Calcd for $C_{12}H_{15}N$: 173.1204. Found: 173.1211.

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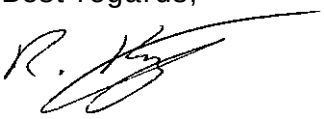

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Asymmetric total synthesis of (+)-swainsonine

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A concise asymmetric synthesis of (+)-swainsonine (*ent*-**1**) is described starting from **2**, which was readily prepared from commercially available L-glutamic acid. The method features installation of the indolizidine ring via an intramolecular cyclisation of α-sulfinyl carbanion as a key step. (+)-Swainsonine was obtained in 9.4% overall yield in 10 steps.

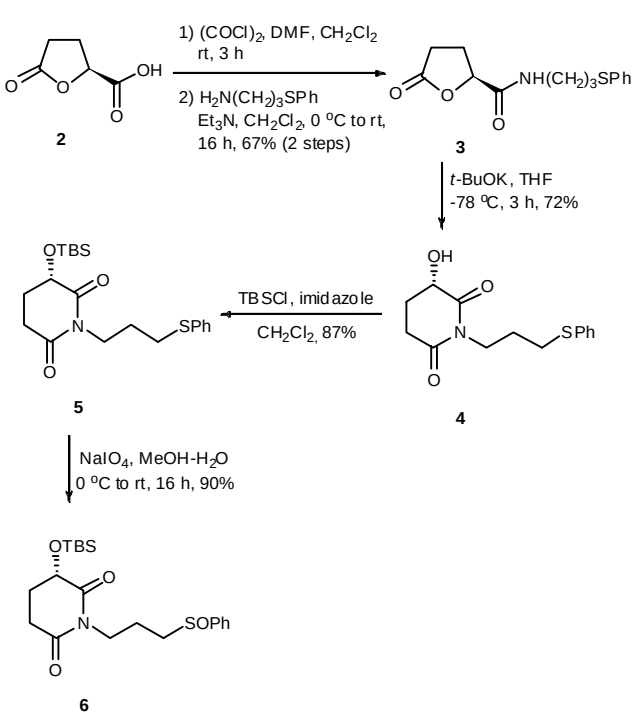
Introduction

Polyhydroxylated indolizidine alkaloids have attracted significant attention to synthetic community due to their interesting structures and potent biological activities.[1,2] Among those, (–)-swainsonine (**1**), which was first isolated from the fungus *Rhizoctonia leguminicola*[3] and later found in several plants and fungi,[4] exhibits potent and selective glycosidase inhibitory properties.[5] It has also been tested as a treatment for cancer, HIV and immunological disorders.[6] Its biological importance and interesting structure has triggered a number of synthetic approaches towards the total syntheses of natural occurring (–)-swainsonine (**1**) and its analogues[7,8] as well as (+)-swainsonine (*ent*-**1**).[9] These classes of molecules are still attractive targets for organic chemists to develop new synthetic strategies and methodologies.

Our analysis of efficient route to (+)-swainsonine (*ent*-**1**) evolved from our previously reported work on intramolecular cyclisation of α-sulfinyl carbanions as convenient strategies to the preparation of 1-azabicyclic compounds.[10] In the early studies, we had demonstrated the synthetic utility of this strategy for syntheses of (±)-tashiromine, (±)-lupinine, (±)-epilupinine, and (±)-indolizidines 167B and 209D.[11,12] To further advance our synthetic methodology, we describe herein a concise asymmetric synthesis of (+)-swainsonine (*ent*-**1**) via intramolecular cyclisation of α-sulfinyl carbanions.

Results and discussion

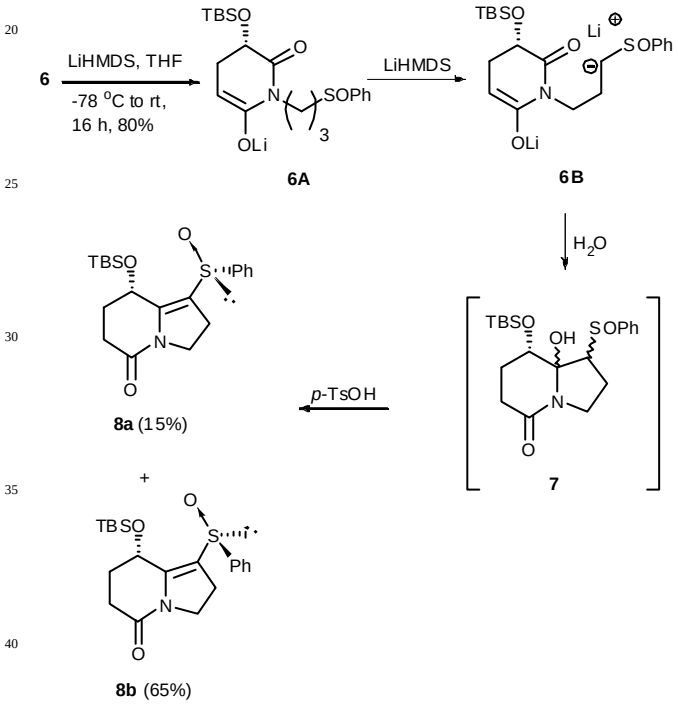
As shown in Scheme 1, the synthesis of (+)-swainsonine (*ent*-**1**) commenced with chiral carboxylic acid **2**, which was readily prepared from L-glutamic acid by following the previously reported procedure.[13] The carboxylic acid **2** was treated with oxalyl chloride in CH_2Cl_2 in the presence of a catalytic amount of DMF followed by gentle addition of 3-phenylsulfanyl-1-aminopropane and triethylamine at room temperature for 16 h to afford amide **3** in 67% yield. The requisite chiral hydroxyimide **4** was obtained in 72% yield by treatment of the amide **3** with *t*-BuOK in THF at –78 °C for 3 h. The hydroxyl group of **4** was protected with TBS group under standard conditions (TBSCl, imidazole, DMF, 0 °C to room temperature) which afforded **5** in 87% yield. Subsequent sulfide oxidation with sodium metaperiodate ($NaIO_4$) in aqueous methanol furnished the prerequisite chiral sulfinylimide **6** in 90% yield as an inseparable mixture of two diastereomers (Scheme 1).



Scheme 1 Preparation of the starting chiral sulfinylimide **6** from L-glutamic acid.

Through extensive investigation of various experimental parameters particularly the mole equivalents of lithium hexamethyldisilazide (LiHMDS) employed, we established that cyclisation of **6** to give **7** required treatment of **6** with 2.2 equiv of LiHMDS in THF at –78 °C followed by slowly warming up to room temperature for 16 h. Recovery of **6** was observed when LiHMDS was utilised in lesser amount. These results implied competitive proton abstraction that occurred preferentially at the α-imide proton rather than the α-proton adjacent to the phenylsulfinyl moiety of sulfinylimide **6**. Therefore, proton abstraction of the initially formed enolate **6A** by a second equivalent of LiHMDS gave α-sulfinyl

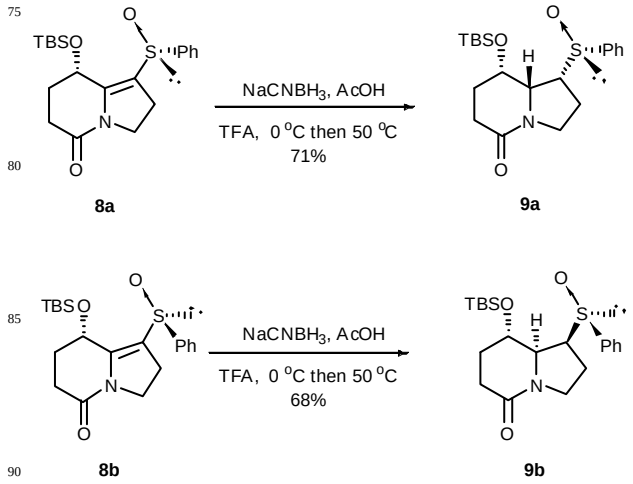
carbanion **6B** which readily underwent cyclisation to yield hydroxyindolizidine **7**. Formation of the enolate **6A** was found crucial to protection of the carbonyl group at the 6-position from the intramolecular nucleophilic attack by the α-sulfinyl carbanion. On this basis, cyclisation took place chemoselectively at the carbonyl carbon at the 2-position. Without prior purification, the crude residue of hydroxyindolizidine **7** was exposed to *p*-TsOH in refluxing CH_2Cl_2 to afford, after column chromatography, **8a** and **8b** in 15% and 65% yields, respectively. Poorer yields were obtained if the reactions were carried out at room temperature for 16-36 h, leading to **8** in 25-30% yield. The structures of compounds **8a** and **8b** were established by ^{1}H NMR (500 MHz), COSY-45 and HMQC spectra (see Supporting Information). Since the absolute configurations at the sulfinyl groups of **8a** and **8b** were not determined, it was tentatively assumed that **8a** and **8b** possess *R*- and *S*-configurations, respectively, as shown in Scheme 2.



Scheme 2 Intramolecular cyclisation of α-sulfinyl carbanion derived from **6** to **8a** and **8b**.

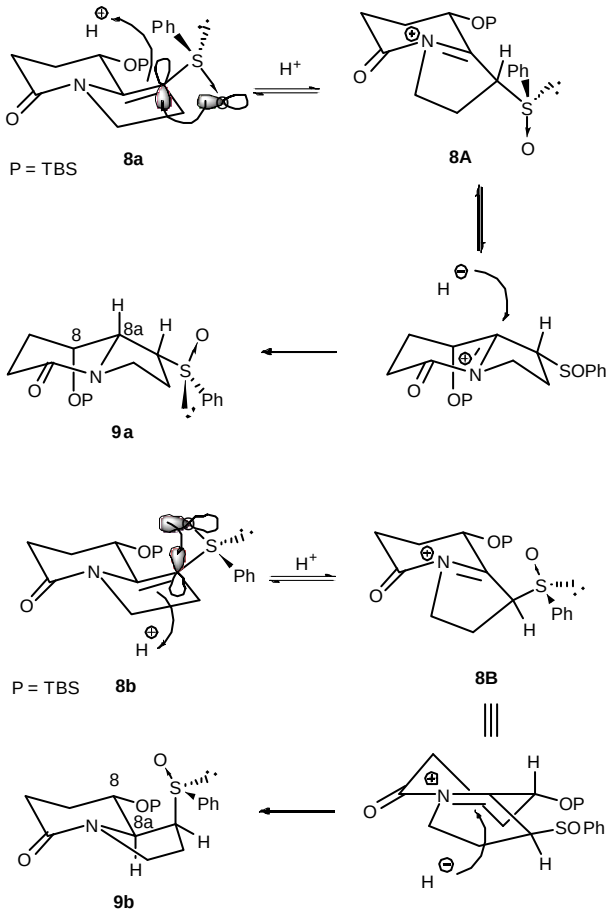
With the success on the construction of the core indolizidine structure, conversion of the unsaturated phenylsulfinyl derivatives **8** into the corresponding saturated phenylsulfoxide **9** was attempted. Initially, catalytic hydrogenation of a diastereomeric mixture of **8a** and **8b** using atmospheric pressure of hydrogen gas in the presence of PtO_2 as a catalyst in ethyl acetate at room temperature for 16 h gave complete recovery of the starting material. By performing the reaction under 4 atm of H_2, each diastereomer **8a** or **8b** underwent reductive deoxygenation of the sulfoxide to furnish the corresponding phenylsulfanyl derivative in 58% yield. Comparable yield (50%) was also obtained, when the reaction was performed under 1 atm of H_2 and in the presence of 10 mol% of trifluoroacetic acid.

Efforts to carry out the reduction using Et_3SiH as a hydride source under acidic conditions were briefly investigated. Treatment of **8** as a diastereomeric mixture with 3 equivalents of Et_3SiH in the presence of trifluoroacetic acid (2 equiv) at 0 °C to room temperature for 16 h yielded the required reduction product **9** in only 20% yield along with a complex mixture of unidentified products. The reactions employing $NaBH_4$/MeOH, $NaCNBH_3$/MeOH, $NaCNBH_3$/AcOH or $NaCNBH_3$/AcOH/TFA (10 mol%) at 0 °C to room temperature for 16 h did not give the reduction product **9** but led to recovery of the starting material. Gratefully, treatment of **8a** or **8b** using $NaCNBH_3$/AcOH/TFA (10 mol%) at 0 °C followed by heating at 50 °C for 5 h furnished the respective product **9a** or **9b** in good yields, each as a single isomer (Scheme 3).



Scheme 3 Reduction of **8a** and **8b** to the corresponding sulfoxides **9a** and **9b**.

The stereoselectivity of the reduction was realised and the stereochemical outcomes can be rationalized by Cieplak effect as shown in Scheme 4.[14] Facial selection of protonation was governed by homoconjugative assistance of the lone-pair electrons of the oxygen atom of the sulfinyl group (Cieplak effect) and minimized steric interaction between the phenyl group and the silyloxy group. As a result, **8a** underwent protonation leading to an iminium intermediate **8A**. Subsequent trapping by a hydride from the less sterically hindered face furnished the reduction product **9a** whose bridgehead hydrogen is relatively *trans* to the silyloxy group. According to the same reasons, protonation of **8b** occurred from the opposite face to that of **8a** leading to an iminium intermediate **8B**. A hydride approaches from the bottom face leading to the reduction product **9b** whose bridgehead hydrogen is relatively *cis* to the silyloxy group. The relative stereochemistries at 8- and 8*a*-position of **9a** and **9b** were assigned by means of NOE experiments as shown in Figure 1. It is worth mentioning that the relative stereochemistries obtained in **9a** and **9b** also supported and were in good agreement with the absolute stereochemistries assigned for the sulfinyl groups of **8a** and **8b**.



Scheme 4 Proposed transition states for the reduction of **8a** and **8b** to the corresponding **9a** and **9b**.

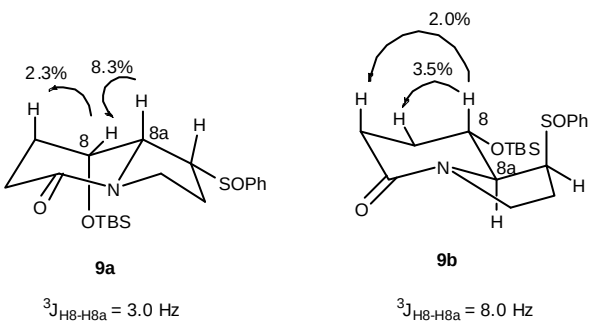
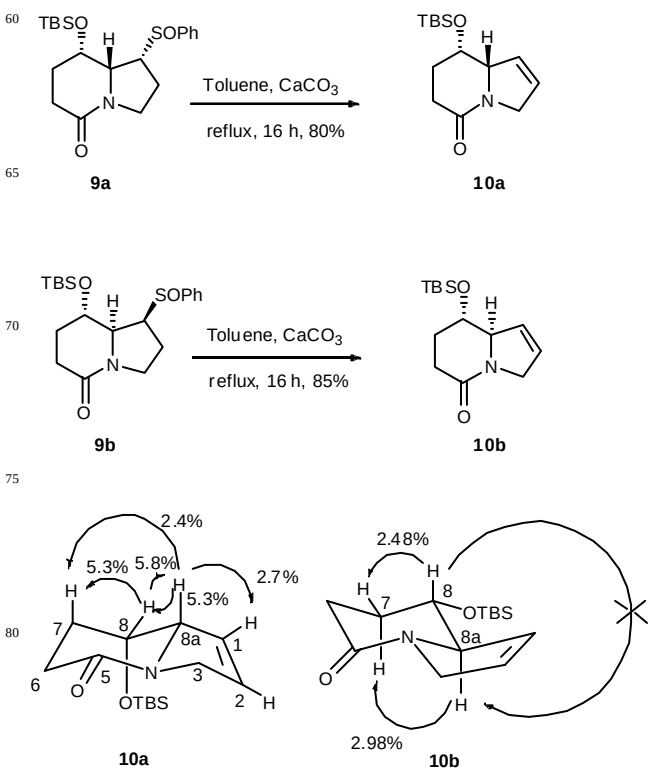
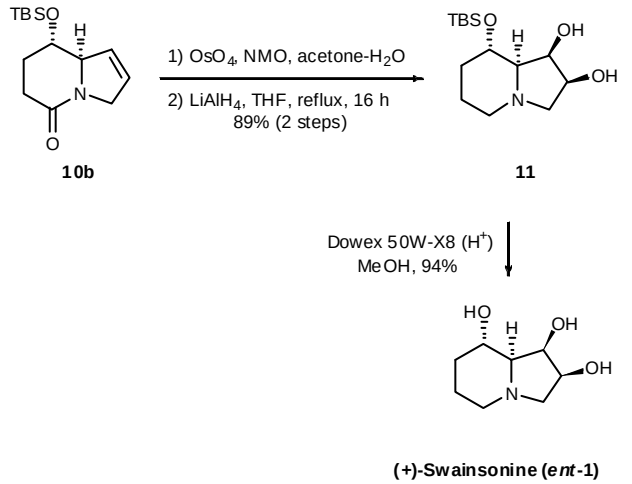


Figure 1 NOE experiments of **9a** and **9b**.

Removal of the phenylsulfinyl group in compounds **9a** and **9b** was achieved by pyrolysis under refluxing toluene in the presence of anhydrous $CaCO_3$ to afford the corresponding compounds **10a** and **10b** in 80% and 85% yields, respectively, as shown in Scheme 5. The relative stereochemistries assigned to the 8- and 8*a*-positions of **10a** and **10b** are based upon the NOE experiments (Scheme 5).



Scheme 5 Sulfoxide elimination of **9a** and **9b** to **10a** and **10b** and their NOE experiments.



Scheme 6 Conversion of **10b** to (+)-swainsonine (*ent*-**1**).

To complete the synthesis of (+)-swainsonine (*ent*-**1**), *cis*-dihydroxylation of **10b** with NMO and a catalytic amount of OsO_4 in aqueous acetone provided the crude dihydroxylated product. Without chromatographic purification, the crude mixture was subjected to reduction using LAH in refluxing THF to give **11** in 89% yield as a single isomer without contamination of the isomer (Scheme 6). The facial selectivity

in the osmylation of **10b** can be rationalised according to Hirama's explanation.[9] The oxidizing agent approaches to the double bond of **10b** from the face opposite to the two axially oriented allylic hydrogens (H_3 and H_{8a}) to avoid the two 1,2-torsional strain since the 1,3-steric interaction is less important when the reagent is small.

Finally, removal of the silyl-protected swainsonine **11** was primarily carried out under standard conditions (TBAF, THF, room temperature, 16 h). The ^{1}H-NMR spectrum of crude product indicated the characteristic signals of the expected (+)-swainsonine (*ent*-**1**) but it was unable to be isolated in pure form by using conventional chromatography. Attempted deprotection using KF in aqueous methanol at room temperature for 16 h led to recovery of the starting compound **11**. Fortunately, treatment of **11** with Dowex 50W-X8 (H^+ form) in methanol at room temperature for 24 h afforded 94% yield of (+)-swainsonine (*ent*-**1**). The ^{1}H-NMR data (see, Supporting Information) as well as the optical rotation ($[\alpha]_D^{25}$ +78.97 (*c* 0.63, MeOH)) of our synthesized product were consistent with the values reported in the literature.[9,15] The relative stereochemistries at 1-, 2-, 8- and 8*a*-positions of (+)-swainsonine (*ent*-**1**) were assigned by the NOE experiments.

Conclusions

The synthesis of (+)-swainsonine (*ent*-**1**) reported here is concise and highly efficient. The synthetic strategy illustrates the utility of α-sulfinyl carbanion cyclization. We believe that this strategy can be tailored to the preparation of a range of biologically active polyhydroxylated indolizidine and quinolizidine alkaolids by starting from appropriate chiral imides or lactams.

Experimental

General

The ^{1}H NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance-500 (125 MHz) using residual non-deuterated solvent peak as an internal standard. Assignments of individual signals were carried out using COSY, HMQC, HMBC, DEPT experiments. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. The mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on an MS Micromass model VQ-TOF2. Melting points were recorded on a Buchi 501 Melting Point Apparatus and were uncorrected. The optical rotations were recorded on a Jasco DIP-370 Digital Polarimeter.

(*S*)-5-Oxotetrahydrofuran-2-carboxylic acid (2)

To a solution of L-glutamic acid (18.0 g, 122.4 mmol) and $NaNO_2$ (9.29 g, 134.6 mmol) in H_2O (120 mL), was slowly added 2 N H_2SO_4 (60 mL) at 0 °C. After the mixture was allowed to stir at 0 °C for 3 h, it was slowly warmed up to room temperature and stirring was continued for an additional 16 h. The resulting colorless solution was concentrated until a white and sticky mixture was obtained. The mixture was diluted using hot acetone followed by filtration. The filtrate was concentrated to give a colorless viscous liquid which was diluted with EtOAc. The EtOAc solution was stirred in anhydrous Na_2SO_4 at room temperature for 16 h. Filtration and removal of solvent furnished a white solid of compound **2** [7.8 g, 49% yield, m.p. 71.2-72.4 °C, $[\alpha]_D^{25}$ +9.17 (*c* 1.1, MeOH)] [Lit.[13b] $[\alpha]_D^{20}$ +10.6 (*c* 5.0, MeOH)]. The spectroscopic data are consistent with the literature.[13b] ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.84 (br s, 1H), 5.04-5.00 (m, 1H), 2.56-2.17 (m, 3H), 2.47-2.39 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.9, 173.5, 75.1, 26.6, 25.8. IR (neat): *v* 3451 (O-H), 1760 (C=O) cm^{-1}. MS (EI) [m/z (% relative intensity)]: 131 (M^+ + H, 13), 86 (5), 85 (100), 59 (4), 58 (54), 55 (4).

(*S*)-5-Oxo-*N*-(3-(phenylsulfanyl)propyl)tetrahydrofuran-2-carboxamide (3)

A solution of carboxylic acid **2** (5.7 g, 44.0 mmol) and oxalyl chloride (4.5 mL, 52.8 mmol) in CH_2Cl_2 (100 mL) in the presence of a catalytic amount of *N*,*N*-dimethylformamide (DMF) was stirred at room temperature for 3 h. An excess of oxalyl chloride was removed *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (90 mL). The resulting solution was brought to 0 °C followed by addition of triethylamine (7.3 mL, 52.8 mmol) and a solution of 3-(phenylsulfanyl)propan-1-amine (8.8 mL, 52.8 mmol) in CH_2Cl_2 (30 mL) under an argon atmosphere. After being stirred at room temperature overnight (16 h), water (20 mL) was added. Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a white solid of **3** [8.2 g, 67% yield, m.p. 77.3-77.9 °C, $[\alpha]_D^{24}$ –7.68 (*c* 0.86, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35-7.28 (m, 4H), 7.22-7.18 (m, 1H), 6.59 (br s, 1H), 4.83 (t, *J* = 7.1 Hz, 1H), 3.49-3.37 (m, 2H), 2.94 (t, *J* = 7.1 Hz, 2H), 2.67-2.61 (m, 1H), 2.58-2.52 (m, 2H), 2.36-2.26 (m, 1H), 1.90-1.84 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.6, 169.3, 135.7, 129.6, 129.0, 126.3, 77.4, 38.3, 31.3, 28.7, 27.5, 25.8. IR (neat): *v* 3367 (N-H), 1780 (C=O, lactone), 1652 (C=O, amide) cm^{-1}. MS (EI) [m/z (% relative intensity)]: 280 (M^+ + H, 46), 279 (M^+, 25), 171 (10), 170 (100), 142 (7), 109 (5). HRMS (ESI-TOF) Calc. for $C_{14}H_{18}NO_3S$ $(M + H)^+$, 280.1007; found, 280.1016.

(*S*)-3-Hydroxy-1-(3-(phenylsulfanyl)propyl)piperidine-2,6-dione (4)

To a suspension of potassium *tert*-butoxide (1.86 g, 16.6 mmol) in THF (10 mL), was added a solution of **3** (8.0 g, 28.7 mmol) in THF (80 mL) at –78 °C under an argon atmosphere. After being stirred for 3 h at –78 °C, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 40% EtOAc in hexanes) to give a white solid of **4** [5.8 g, 72% yield, m.p. 76.7-78.3 °C, $[\alpha]_D^{24}$ –26.75 (*c* 0.88, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35-

7.26 (m, 4H, Ar*H*), 7.21-7.17 (m, 1H, Ar*H*), 4.21 (ddd, *J* = 12.5, 5.5, 1.3 Hz, 1H, CH_2CHOH), 3.95 (dt, *J* = 13.3, 6.8 Hz, 1H, $NCHHCH_2$), 3.86 (dt, *J* = 13.3, 6.8 Hz, 1H, $NCHHCH_2$), 3.53 (d, *J* = 1.3 Hz, 1H, O*H*), 2.90 (t, *J* = 7.3 Hz, 2H, CH_2SPh), 2.89 (ddd, *J* = 18.0, 4.7, 2.6 Hz, 1H, $COCHHCH_2$) 2.63 (ddd, *J* = 18.0, 13.8, 5.4 Hz, 1H, $COCHHCH_2$), 2.36-2.31 (m, 1H, $CH_2CHHCHOH$), 1.94-1.84 (m, 3H, $CH_2CHHCHOH$ and $NCH_2CH_2CH_2$). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.2 (C=O), 171.1 (C=O), 136.0 (C), 129.8 (2 × CH), 128.9 (2 × CH), 126.3 (CH), 68.3 (CH), 39.6 (CH_2), 31.6 (CH_2), 30.8 (CH_2), 27.4 (CH_2), 25.3 (CH_2). IR (film): *v* 3460 (O-H), 1731, 1674 cm^{-1}. MS (EI) [m/z (% relative intensity)]: 280 (M^+ + H, 35), 279 (M^+, 42), 170 (100), 151 (10), 142 (28), 58 (7). HRMS (ESI-TOF) Calc. for $C_{14}H_{18}NO_3S$ $[M + H]^+$, 280.1007; found, 280.0997.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(3-(phenylsulfanyl)propyl)piperidine-2,6-dione (5)

To a mixture of **4** (5.5 g, 19.7 mmol), imidazole (2.7 g, 39.0 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 (40 mL) at 0 °C under an argon atmosphere, was slowly added a solution of *tert*-butyldimethylchlorosilane (3.54 g, 23.6 mmol) in CH_2Cl_2 (20 mL). After being stirred at room temperature overnight, water (10 mL) was added. The aqueous phase was separated and the organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to give a colourless viscous liquid of **5** [6.74 g, 87% yield, $[\alpha]_D^{24}$ –10.83 (*c* 0.75, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35-7.33 (m, 2H, Ar*H*), 7.29-7.26 (m, 2H, Ar*H*), 7.19-7.16 (m, 1H, Ar*H*), 4.29 (dd, *J* = 8.0, 4.1 Hz, 1H, CH_2CHOSi), 3.86 (t, *J* = 7.2 Hz, 2H, NCH_2CH_2), 2.93-2.87 (m, 1H, $COCHHCH_2$), 2.88 (t, *J* = 7.5 Hz, 2H, CH_2SPh), 2.59 (ddd, *J* = 17.8, 8.1, 5.3 Hz, 1H, $COCHHCH_2$), 2.06-1.97 (m, 2H, CH_2CH_2CHOSi), 1.85 (quint, *J* = 7.3 Hz, 2H, $NCH_2CH_2CH_2$), 0.96 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.3 (C=O), 171.8 (C=O), 135.2 (C), 129.7 (2 × CH), 128.9 (2 × CH), 126.1 (CH), 69.3 (CH), 39.0 (CH_2), 31.5 (CH_2), 29.1 (CH_2), 27.5 (CH_2), 26.5 (CH_2), 25.6 (3 × CH_3), 18.2 (C), –4.7(CH_3), –5.4(CH_3). IR (neat): *v* 1735, 1685 cm^{-1}; MS (EI) [m/z (% relative intensity)]: 394 (M^+ + H, 5), 336 (47), 151 (100), 123 (20), 75 (4). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_3SSi$ $[M + H]^+$, 394.1872; found, 394.1795.

(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(3-(phenylsulfinyl)propyl)piperidine-2,6-dione (6)

A solution of **5** (6.7 g, 17.0 mmol) in MeOH (10 mL) was slowly added to a suspension of $NaIO_4$ (4.0 g, 18.7 mmol) in MeOH (48 mL) and H_2O (12 mL) at 0 °C. The mixture was vigorously stirred and slowly warmed up to room temperature overnight (12 h). The precipitates of $NaIO_3$ were filtered and washed with EtOAc (3 × 60 mL). The combined extracts were washed with H_2O (3 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 70% EtOAc in hexanes) to afford a colourless viscous liquid of **6** as a mixture of two diastereomers (6.3 g, 90% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.63-7.61 (m, 4H), 7.53-7.49 (m, 6H), 4.31-4.29 (m, 2H), 3.92-3.82 (m, 4H), 2.9-2.74 (m, 6H), 2.63-2.60 (m, 2H), 2.09-1.94 (m, 6H), 1.88-1.79 (m, 2H), 0.90 and 0.86 (s each, 18H), 0.14 and 0.13 (s each, 12H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.46, 172.44, 171.85, 171.77, 143.6, 130.95, 130.93, 129.2, 124.02, 124.01, 69.22, 69.20, 54.74, 54.67, 38.58, 38.52, 29.14, 29.08, 26.4, 25.6, 21.1, 18.2, –4.7, –5.4. IR (neat): *v* 1732, 1682 cm^{-1}. MS (EI) [m/z (% relative intensity)]: 410 (M^+ + H, 6), 352 (42), 284 (21), 226 (53), 167 (100), 143 (11), 109 (9). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_4SSi$ $[M + H]^+$, 410.1821; found, 410.1833.

(8*S*)-8-(*tert*-Butyldimethylsilyloxy)-1-(phenylsulfinyl)-2,3,7,8-tetrahydroindolizin-5(6*H*)-ones (8a) and (8b)

A solution of sulfoxide **6** (6.2 g, 15 mmol) in THF (18 mL) was added dropwise to a cooled (–78 °C) THF (100 mL) solution of LiHMDS [prepared by reacting *n*-BuLi (1.35 M in hexane; 25 mL, 33.75 mmol) with a solution of hexamethyldisilazane (HMDS) (7.6 mL, 36.4 mmol) in THF (40 mL) at –78 °C for 45 min] under an argon atmosphere. The resulting mixture was stirred and slowly warmed up from –78 °C to room temperature overnight (15 h). The resulting yellow solution was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by removal of solvents furnished a crude residue of hydroxyindolizidine **7** (4.9 g) which was used in the next step without prior purification. A crude residue of **7** (4.9 g) was diluted with CH_2Cl_2 (50 mL). The resulting solution was added a catalytic amount of *p*-TsOH and the mixture was brought to refluxing temperature under an argon atmosphere for 16 h. The resulting solution was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic extracts were washed with H_2O (3 × 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 100% EtOAc) to afford colourless viscous liquid of **8a** (0.71 g, 15% yield) and **8b** (3.07 g, 65% yield).

F_1 (less polar) was obtained as a colourless viscous liquid of **8a**; $[\alpha]_D^{25}$ +40.04 (*c* 1.17, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.55-7.48 (m, 5H), 5.20 (dd, *J* = 4.0, 2.2 Hz, 1H), 3.91 (ddd, *J* = 12.0, 12.0, 5.6 Hz, 1H), 3.76 (ddd, *J* = 12.0, 12.0, 8.2 Hz, 1H), 2.94-2.85 (m, 2H), 2.47 (ddd, *J* = 17.3, 4.8, 2.8 Hz, 1H), 2.17-2.12 (m, 1H), 2.07 (ddd, *J* = 15.7, 11.5, 8.2 Hz, 1H), 1.88-1.84 (m, 1H), 0.94 (s, 9H), 0.29 (s, 3H), 0.28 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.9, 148.8, 142.2, 130.6, 129.2, 124.2, 120.8, 60.0, 44.3, 28.8, 27.1, 25.7, 22.2, 18.0, –4.4, –4.8. IR ($CHCl_3$): *v* 1667, 1627 cm^{-1}. MS (EI) [m/z (% relative intensity)]: 391 (M^+, 0.3), 334 (100), 229 (86), 225 (88), 210 (45), 188 (43), 150 (40), 75 (34); HRMS (ESI-TOF) Calc. for $C_{20}H_{30}NO_3SSi$ $[M + H]^+$, 392.1716; found, 392.1722.

F_2 (more polar) was obtained as a colourless viscous liquid of **8b**; $[\alpha]_D^{25}$ –32.82 (*c* 1.01, $CHCl_3$). ^{1}H-NMR (500 MHz,

$CDCl_3$): δ 7.58-7.50 (m, 2H), 7.49-7.29 (m, 3H), 5.18-5.17 (m, 1H), 3.87 (ddd, *J* = 12.0, 12.0, 6.7 Hz, 1H), 3.78 (ddd, *J* = 12.0, 12.0, 7.1 Hz, 1H), 2.83 (ddd, *J* = 16.1, 11.8, 7.1 Hz, 1H), 2.74 (ddd, *J* = 17.0, 12.5, 4.9 Hz, 1H), 2.44 (dt, *J* = 17.2, 3.8 Hz, 1H), 2.08-2.00 (m, 2H), 1.97-1.90 (m, 1H), 0.90 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.7, 149.6, 141.6, 130.2, 129.0, 124.4, 120.4, 60.7, 44.3, 28.5, 27.0, 25.6, 22.2, 17.8, –4.40, –4.36. IR ($CHCl_3$): *v* 1671, 1628 cm^{-1}. MS (EI) [m/z (% relative intensity)]: 391 (M^+, 0.8), 334 (87), 225 (100), 170 (12), 125 (10); HRMS (ESI-TOF) Calc. for $C_{20}H_{30}NO_3SSi$ $[M + H]^+$, 392.1716; found, 392.1704.

(1*R*,8*S*,8*aR*)-8-(*tert*-Butyldimethylsilyloxy)-1-(*R*)-phenylsulfinyl)hexahydroindolizin-5(1*H*)-one (9a)

To a solution of **8a** (0.7 g, 1.8 mmol) in AcOH (5 mL) in the presence of a catalytic amount of TFA (0.02 mL) at 0 °C under an argon atmosphere, $NaCNBH_3$ (0.4 g, 5.3 mmol) was gradually added over 15 min. The mixture was stirred at 50 °C for 5 h. The resulting mixture was diluted with 1 N NaOH (5 mL) and H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave a crude product, which was purified by column chromatography (SiO_2, 100% EtOAc) to afford a colourless viscous liquid of **9a** [0.5 g, 71% yield; 76% yield calculated based on the recovered **8a**, $[\alpha]_D^{25}$ –90.07 (*c* 0.95, $CHCl_3$)] and **8a** (34 mg). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.58-7.52 (m, 3H), 4.55 (dt, *J* = 5.6, 3.0 Hz, 1H), 4.14 (ddd, *J* = 11.5, 8.6, 5.6 Hz, 1H), 3.77 (dd, *J* = 7.0, 3.1 Hz, 1H), 3.33 (app. q, *J* = 7.1 Hz, 1H), 3.26 (ddd, *J* = 11.5, 8.2, 6.7 Hz, 1H), 2.58 (dt, *J* = 17.7, 7.8 Hz, 1H), 2.43-2.33 (m, 2H), 2.22-2.15 (m, 1H), 1.95-1.87 (m, 2H), 0.99 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.6, 144.6, 131.1, 129.4, 124.5, 66.4, 66.1, 62.7, 44.9, 29.3, 27.7, 26.1, 22.2, 18.2, –3.8, –4.2. IR ($CHCl_3$): *v* 1635 (C=O) cm^{-1}. MS (EI) [m/z (% relative intensity)]: 394 (M^+ + H, 6), 336 (68), 268 (57), 210 (50), 136 (100), 73 (43). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_3SSi$ $[M + H]^+$, 394.1872; found, 394.1865.

(1*S*,8*S*,8*aS*)-8-(*tert*-Butyldimethylsilyloxy)-1-(*S*)-phenylsulfinyl)hexahydroindolizin-5(1*H*)-one (9b)

By following the procedure described for **9a**, a solution of **8b** (2.9 g, 7.4 mmol) in AcOH (20 mL) in the presence of a catalytic amount of TFA (0.01 mL) at 0 °C was treated with $NaCNBH_3$ (4.9 g, 22.2 mmol) to give a crude product, which was purified by column chromatography (SiO_2, 100% EtOAc) to afford **8b** (0.2 g) and a colourless viscous liquid of **9b** [1.97 g, 68% yield; 75% yield based on recovered **8b**, $[\alpha]_D^{25}$ +132.14 (*c* 1,05, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.56-7.29 (m, 3H), 4.80 (ddd, *J* = 10.4, 8.1, 3.8 Hz, 1H), 3.82 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.54 (dd, *J* = 6.1, 4.3 Hz, 1H), 3.29 (t, *J* = 10.6 Hz, 1H), 3.16 (dd, *J* = 18.5, 9.3 Hz, 1H), 2.55 (ddd, *J* = 17.8, 5.6, 3.4 Hz, 1H), 2.44 (ddd, *J* = 17.8, 11.9, 5.8 Hz, 1H), 2.16-2.10 (m, 1H), 1.94-1.73 (m, 3H), 0.94 (s, 9H), 0.29 (s, 3H), 0.19 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.3, 142.0, 132.1, 129.3, 125.6, 67.7, 66.6, 66.0, 43.0, 31.1, 29.6, 25.8, 23.7, 17.9, –4.4. IR ($CHCl_3$): *v* 1635 (C=O) cm^{-1}. MS (EI) [m/z (% relative intensity)]: 394 (M^+ + H, 5), 336 (60), 268 (64), 210 (78), 136 (100), 108 (30), 73 (41). HRMS (ESI-TOF) Calc. for $C_{20}H_{32}NO_3SSi$ $[M + H]^+$, 394.1872; found, 394.1909.

(8*S*,8*aS*)-8-(*tert*-Butyldimethylsilyloxy)-6,7,8,8*a*-tetrahydroindolizin-5(3*H*)-one (10a)

A toluene (5 mL) solution of **9a** (0.38 g, 0.97 mmol) in the presence of $CaCO_3$ (30 mg) was stirred at reflux under an argon atmosphere for 16 h. $CaCO_3$ was filtered off and the filtrate was evaporated to dryness to give a crude product, which was purified by preparative thin-layer chromatography (SiO_2, 100% EtOAc) to give a colourless viscous liquid of **10a** [0.21 g, 80% yield, $[\alpha]_D^{25}$ –53.73 (*c* 1.10, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.93-5.90 (m 1H), 5.69-5.66 (m, 1H), 4.53-4.48 (m, 1H), 4.37-4.35 (m, 1H), 4.24-4.22 (m, 1H), 4.05-4.01 (m, 1H), 2.49 (dt, *J* = 17.8, 9.1 Hz, 1H), 2.40 (ddd, *J* = 17.8, 6.7, 4.3 Hz), 1.94-1.90 (m, 2H), 0.82 (s, 9H), 0.05 (s, 3H), 0.08 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.3, 127.3, 127.0, 68.9, 65.1, 53.3, 28.7, 26.7, 25.5, 17.9, –4.6, –4.9. IR ($CHCl_3$): *v* 1639 (C=O) cm^{-1}. MS (EI) [m/z (% relative intensity)]: 267 (M^+, 9), 242 (46), 224 (57), 210 (92), 196 (45), 150 (81), 122 (36), 81 (39), 75 (100). HRMS (ESI-TOF) Calc. for $C_{14}H_{26}NO_2Si$ $[M + H]^+$, 268.1733; found, 268.1730.

(8*S*,8*aR*)-8-(*tert*-Butyldimethylsilyloxy)-6,7,8,8*a*-tetrahydroindolizin-5(3*H*)-one (10b)[9]

According to the procedure described for **10a**, a toluene (15 mL) solution of **9b** (1.97g, 5.0 mmol) in the presence of $CaCO_3$ (100 mg) was stirred at reflux under an argon atmosphere for 16 h. Purification by preparative thin-layer chromatography (SiO_2, 100% EtOAc) yielded a colourless viscous liquid of **10b** [1.07 g, 80% yield, $[\alpha]_D^{25}$ –53.73 (*c* 1.10, $CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.96-5.90 (m, 2H), 4.50-4.46 (m, 1H), 4.17-4.14 (m, 1H), 4.06-4.03 (m, 1H), 3.57 (td, *J* = 9.5, 5.2 Hz, 1H), 2.63 (ddd, *J* = 17.8, 8.5, 3.6 Hz, 1H), 2.42 (dt, *J* = 17.9, 8.5 Hz, 1H), 2.05-1.99 (m, 1H), 1.84-1.75 (m, 1H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.4, 128.5, 126.7, 71.1, 69.1, 53.2, 30.2, 29.7, 25.6, 17.9, –4.3, –4.8. IR ($CHCl_3$): *v* 1638 (C=O), 1613 cm^{-1}. MS (EI) [m/z (% relative intensity)]: 267 (M^+, 9), 210 (100) 196 (29), 150 (44), 122 (29), 81 (31), 75 (71). HRMS (ESI-TOF) Calc. for $C_{14}H_{26}NO_2Si$ $[M + H]^+$, 268.1733; found, 268.1741.

(1*R*,2*S*,8*S*,8*aR*)-8-(*tert*-butyldimethylsilyloxy)octahydroindolizine-1,2-diol (11)

To a solution of **10b** (0.47 g, 1.75 mmol) in a 3:1 mixture of acetone-H_2O (6 mL) was added *N*-methylmorpholine *N*-oxide (0.48 g, 3.5 mmol) and 4% aqueous OsO_4, (1.0 mL). The reaction mixture was stirred at room temperature for 3 h. After addition of aqueous $NaHSO_3$ solution (3 mL), the mixture was stirred for an additional 1 h at room temperature and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent gave the corresponding dihydroxlated product, which was used for in the next step

without purification.

To a suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in THF (30 mL), the crude dihydroxylated product was added. The mixture was heated at reflux for 16 h. Under ice cooling, the mixture was quenched by careful addition of water (4.0 mL) and 1 N NaOH (4.0 mL). The resulting mixture was filtered over a celite pad and the filtrate was concentrated to afford a viscous liquid of **11** [0.45 g, 89% yield, $[\alpha]_D^{25}$ +29.34 (c 1.06, $CHCl_3$)]. ^{1}H-NMR (500 MHz, CD_3OD): δ 4.19 (ddd, J = 7.9, 5.8, 2.3 Hz, 1H), 4.07 (dd, J = 5.9, 3.5 Hz, 1H), 3.89 (ddd, J = 10.3, 9.0, 4.8 Hz, 1H), 2.89 (br d, J = 2.3 Hz, 1H), 2.87 (br d, J = 2.3 Hz, 1H), 2.42 (dd, J = 10.5, 7.8 Hz, 1H), 1.98-194 (m, 1H), 1.85 (td, J = 11.4, 3.1 Hz, 1H), 1.74 (dd, J = 8.9, 3.5 Hz, 1H), 1.66-1.51 (m, 2H), 1.23-1.14 (m, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). ^{13}C-NMR (125 MHz, CD_3OD): δ 75.5, 70.9, 70.0, 68.4, 63.0, 53.2, 35.2, 26.4, 24.5, 18.8, –4.1, –4.5. IR (KBr): 3399 (O-H), 1472, 1247, 1112 cm^{-1}. MS (EI) [m/z (% relative intensity)]: 288 (M^+ + H, 3), 230 (100), 212 (32), 138 (20), 120 (52), 116 (30), 75 (16). HRMS (ESI-TOF) Calc. for $C_{14}H_{30}NO_3Si$ $[M + H]^+$, 288.1995; found, 288.1961.

(+)-Swainsonine (*ent*-1)

A mixture of **11** (90 mg, 0.31 mmol) and a cation exchange resin, Dowex 50W-X8 (H^+ form), in MeOH was stirred at room temperature for 24 h. The resin was filtered off and washed with 10% NH_4OH (30 mL). The filtrate was evaporated to dryness followed by lyophilization to give a white solid of (+)-swainsonine (*ent*-**1**) [51 mg, 94% yield, m.p. 140-143 ^{o}C, $[\alpha]_D^{25}$ +78.97 (*c* 0.63, MeOH): Lit.[9] m.p. 143-145 ^{o}C, $[\alpha]_D$ +83.3 (*c* 0.5, MeOH); Lit.[15b] m.p. 142-143 ^{o}C, $[\alpha]_D$ +84.3 (*c* 1.02, H_2O)].

^{1}H-NMR (500 MHz, CD_3OD): δ 4.25-4.19 (m, 2H), 3.79 (ddd, J = 11.2, 10.1, 4.6 Hz, 1H), 2.96-2.93 (m, 2H), 2.48 (dd, J = 10.4, 7.5 Hz, 1H), 2.04-2.01 (m, 1H), 1.96 (td, J = 11.9, 2.5 Hz, 1H), 1.82 (dd, J = 9.1, 3.0 Hz, 1H), 1.70-1.68 (m, 1H) 1.64-1.55 (m, 1H), 1.22 (qd, J = 12.9, 4.6 Hz, 1H). ^{13}C-NMR (125 MHz, CD_3OD): δ 75.1, 70.6, 69.8, 66.8, 62.8, 53.0, 33.9, 24.3. IR (neat): ν 3367 (O-H), 1643, 1448, 1384, 1145, 1084 cm^{-1}. MS (EI) [m/z (% relative intensity)]: 173 (M^+, 5), 155 (36), 120 (17), 110 (27), 96 (100), 84 (26), 68 (12). HRMS (ESI-TOF): Calc. for $C_8H_{16}NO_3$ $[M + H]^+$, 174.1125; found, 174.1150.

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Notes and references

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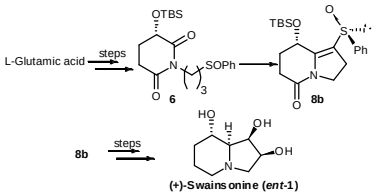
GRAPHICAL ABSTRACT



A CONCISE ASYMMETRIC SYNTHESIS OF (+)-SWAINSONINE (*ent*-**1**) IS DESCRIBED. THE METHOD FEATURES INSTALLATION OF THE INDOLIZIDINE RING VIA AN INTRAMOLECULAR CYCLISATION OF α SULFINYL CARBANION AS A KEY STEP.

Asymmetric Total Synthesis of (+)-Swainsonine

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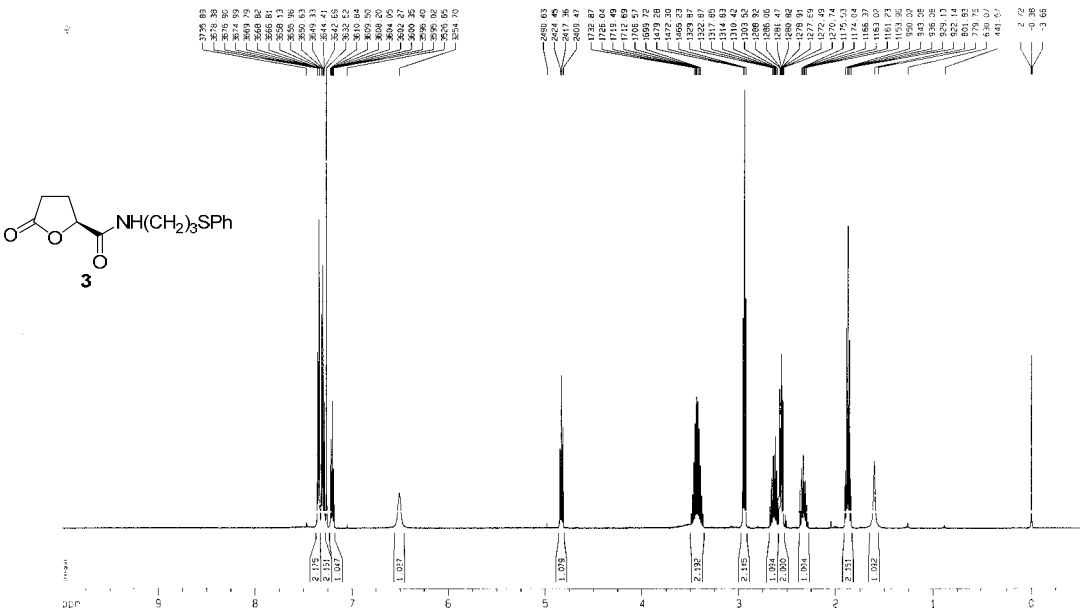
1. ^{1}H and ^{13}C spectra

^{1}H-NMR spectrum of **3** (500 MHz, $CDCl_3$)



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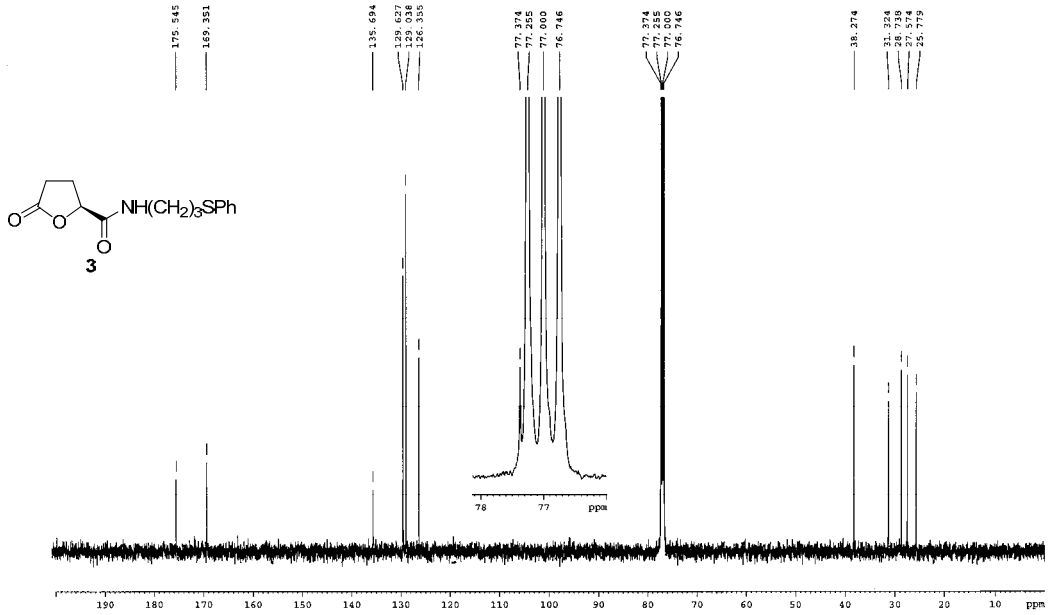

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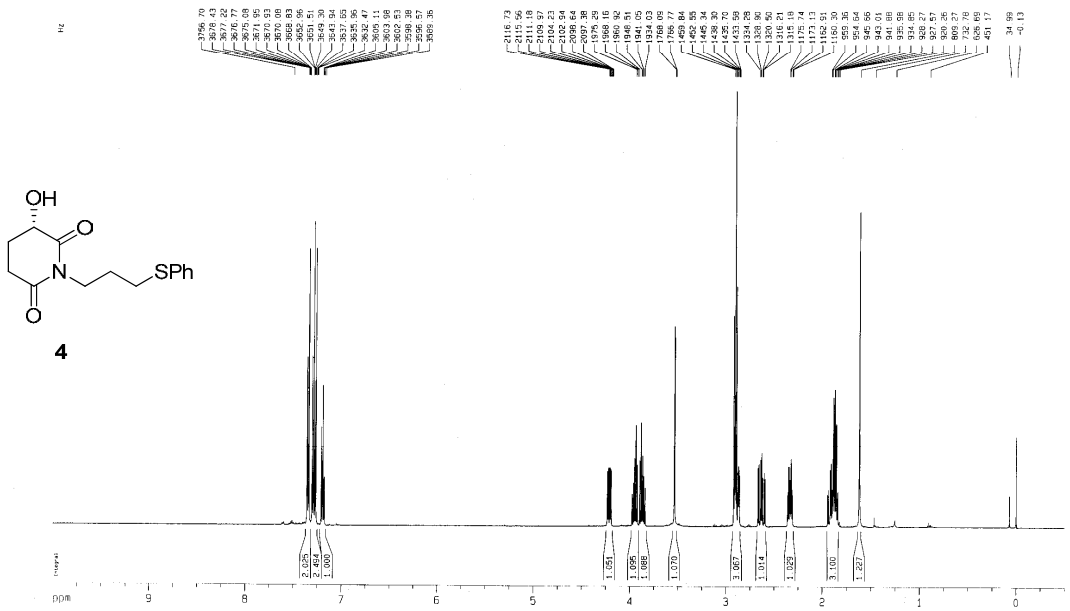
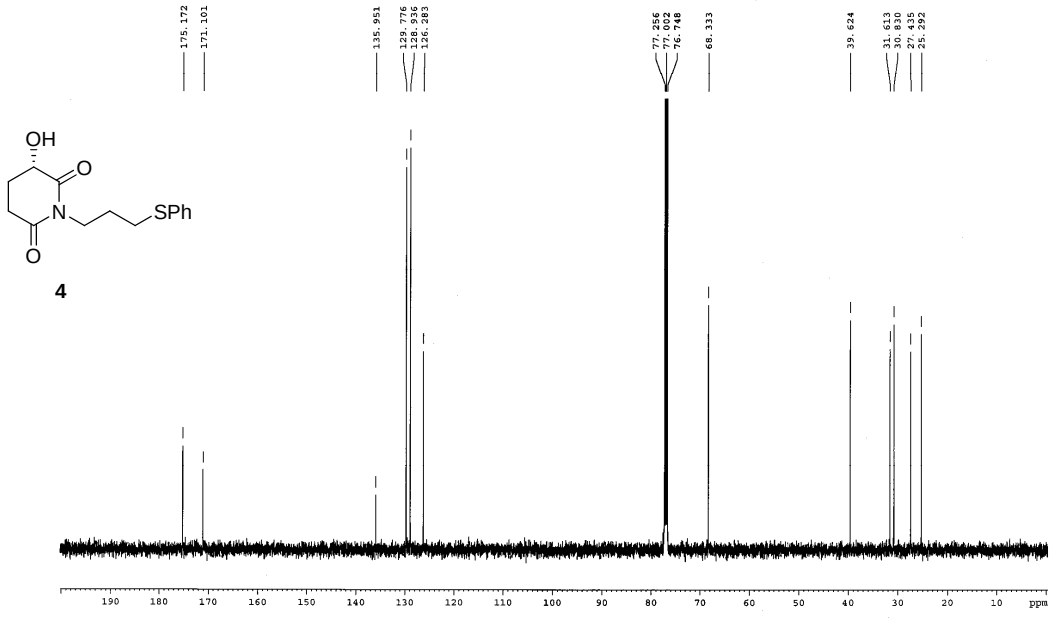


^{13}C-NMR spectrum of **4** (125 MHz, $CDCl_3$)



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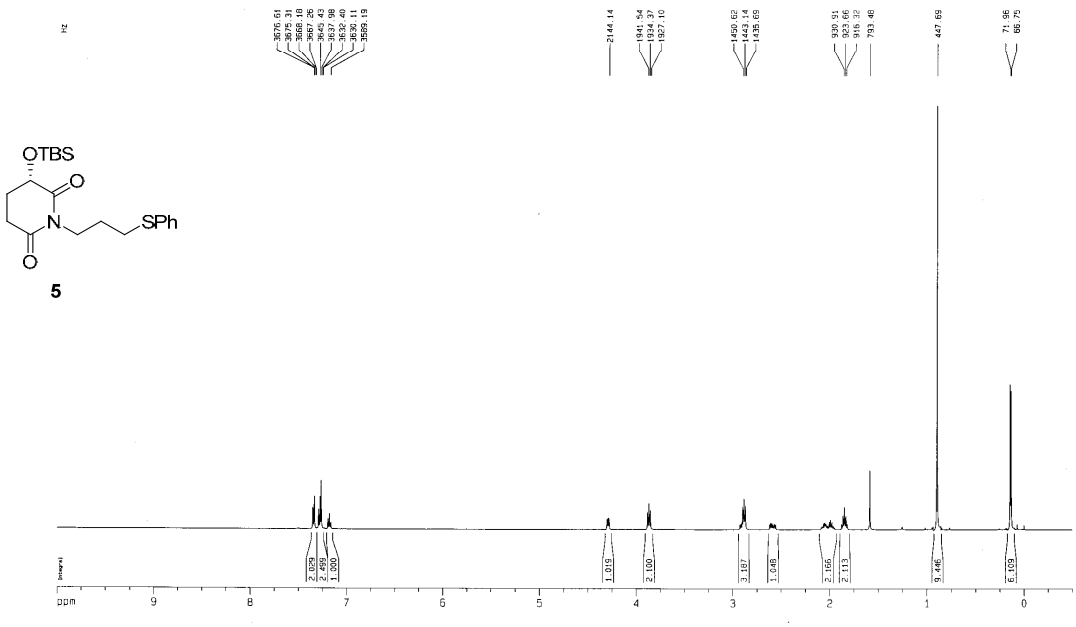

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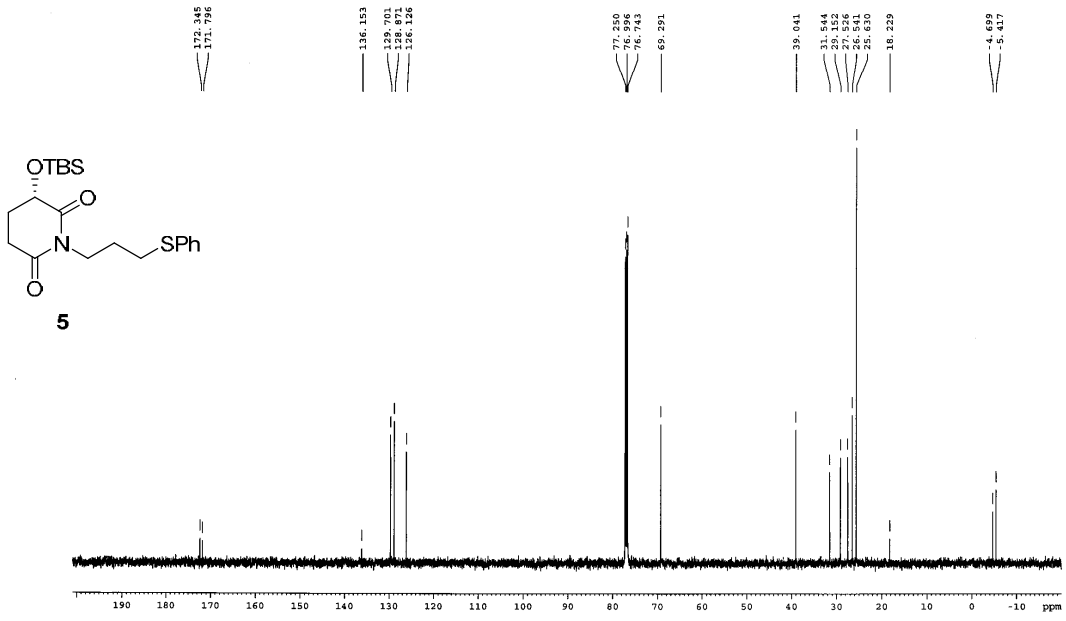

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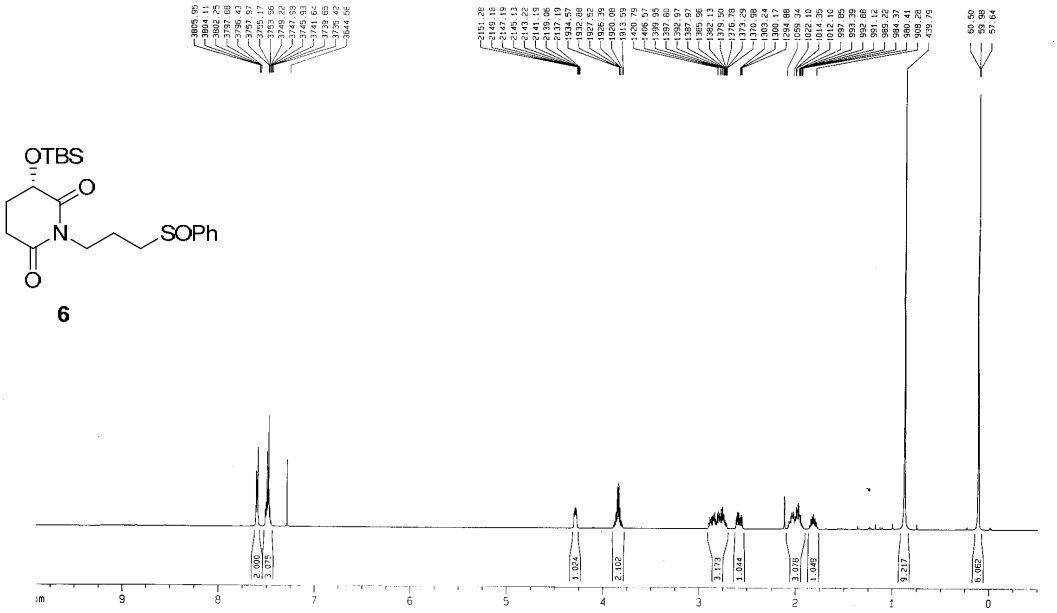
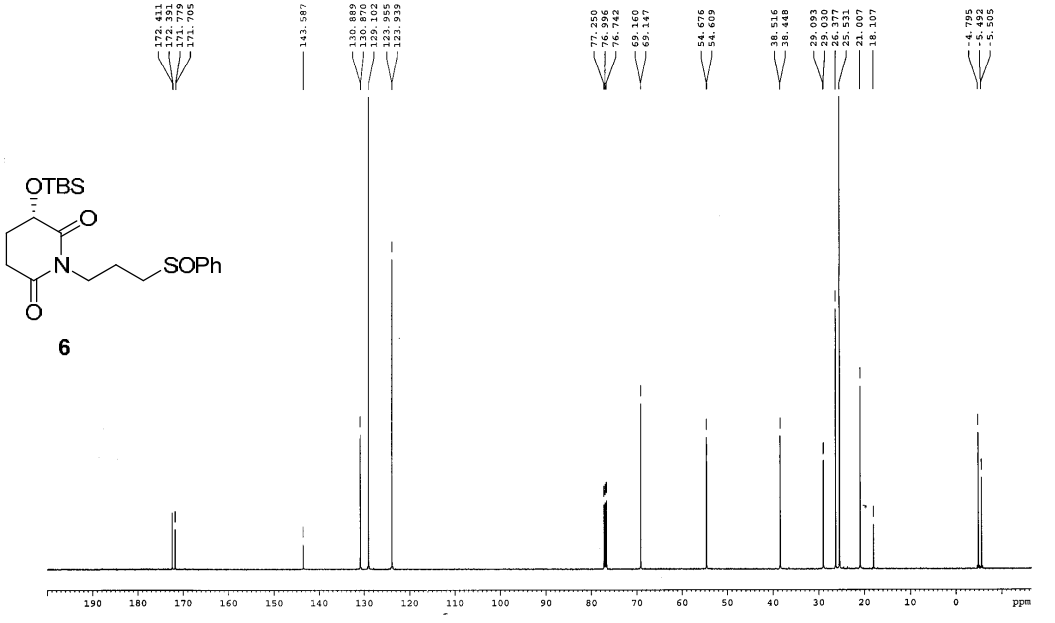


^{13}C-NMR spectrum of **6** (125 MHz, $CDCl_3$)



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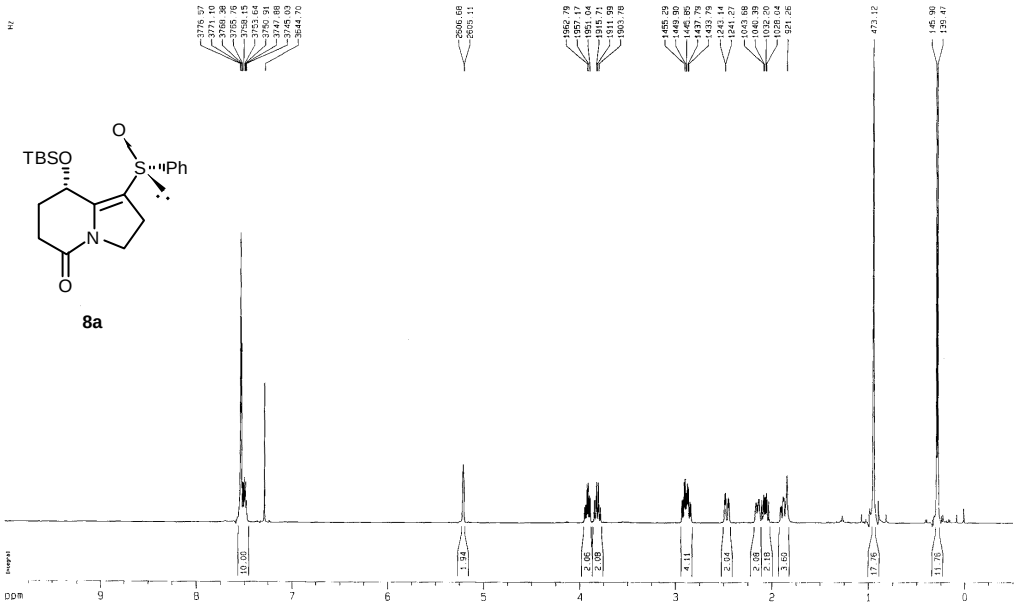


^{13}C-NMR spectrum of **8a** (500 MHz, $CDCl_3$)

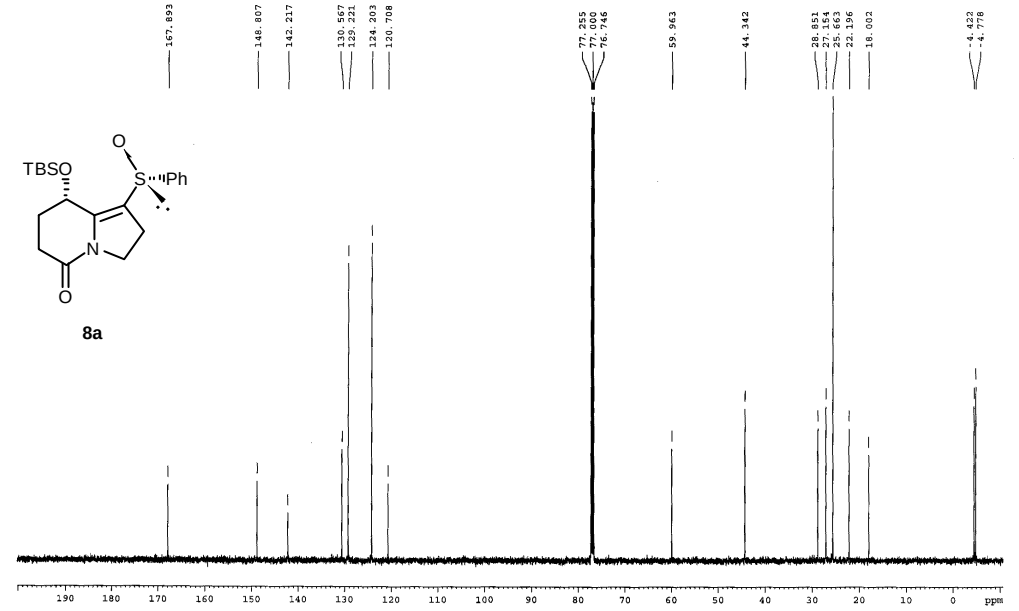
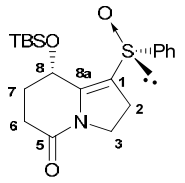


Table 1. 500 MHz COSY-45 correlations of some protons of compound **8a**.



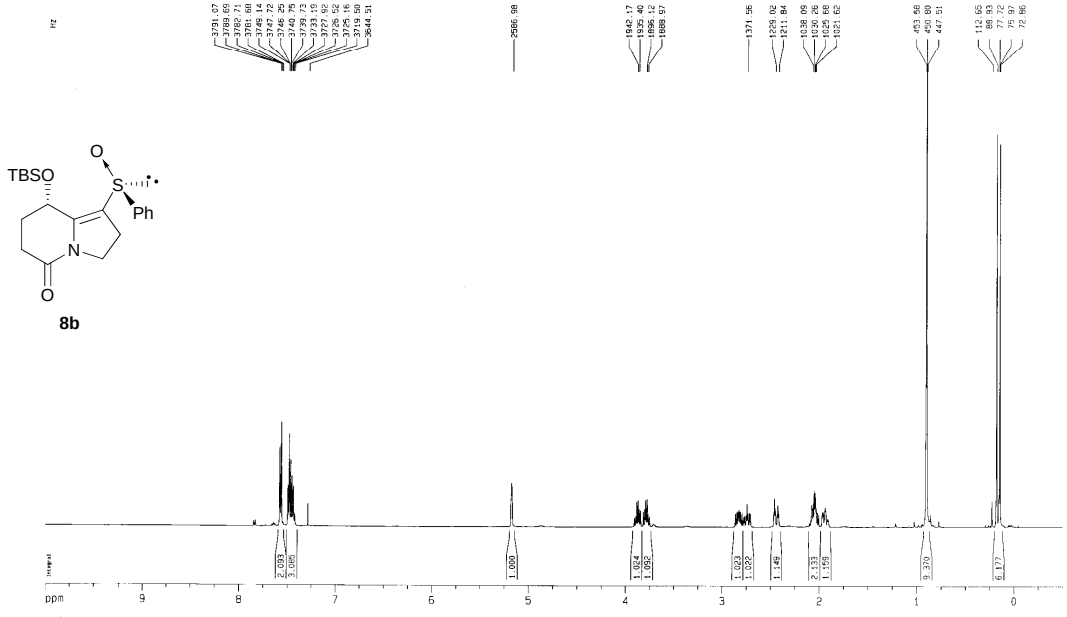
8a

δ_H (ppm)	δ_H (ppm) of correlated protons
5.20 (C_8-*H*)	2.17-2.12 (C_6-*H*), 1.88 (C_7-*H*)
2.94-2.85 (C_6-*H*)	1.88 (C_7-*H*), 2.47 (C_7-*H*)
2.47 (C_7-*H*)	1.88 (C_7-*H*)
2.17-2.12 (C_6-*H*)	1.88 (C_7-*H*)
3.91 (C_3-*H*)	2.94-2.85 (C_2-*H*), 2.07 (C_2-*H*)
3.76 (C_3-*H*)	2.94-2.85 (C_2-*H*), 2.07 (C_2-*H*)

Table 2. Observed C-H correlations from HMQC spectrum of **8a**.

δ_C (ppm)	δ_H (ppm)	Assignment
167.9	-	C_5
148.8	-	C_{8a}
120.8	-	C_2
60.0	5.20 (dd, *J* = 4.0, 2.2 Hz, 1H)	C_8
44.3	3.91 (ddd, *J* = 12.0, 12.0, 5.6 Hz, 1H) and 3.76 (ddd, *J* = 12.0, 12.0, 8.2 Hz, 1H)	C_3
28.8	2.47 (ddd, *J* = 17.3, 4.8, 2.8 Hz, 1H) and 1.88 (m 1H)	C_7
27.1	2.94-2.85 (m, 1H) and 2.17-2.12 (m, 1H)	C_6
22.2	2.94-2.85 (m, 1H) and 2.07 (ddd, *J* = 15.7, 11.5, 8.2 Hz, 1H)	C_2

^{1}H-NMR spectrum of **8b** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **8b** (125 MHz, $CDCl_3$)

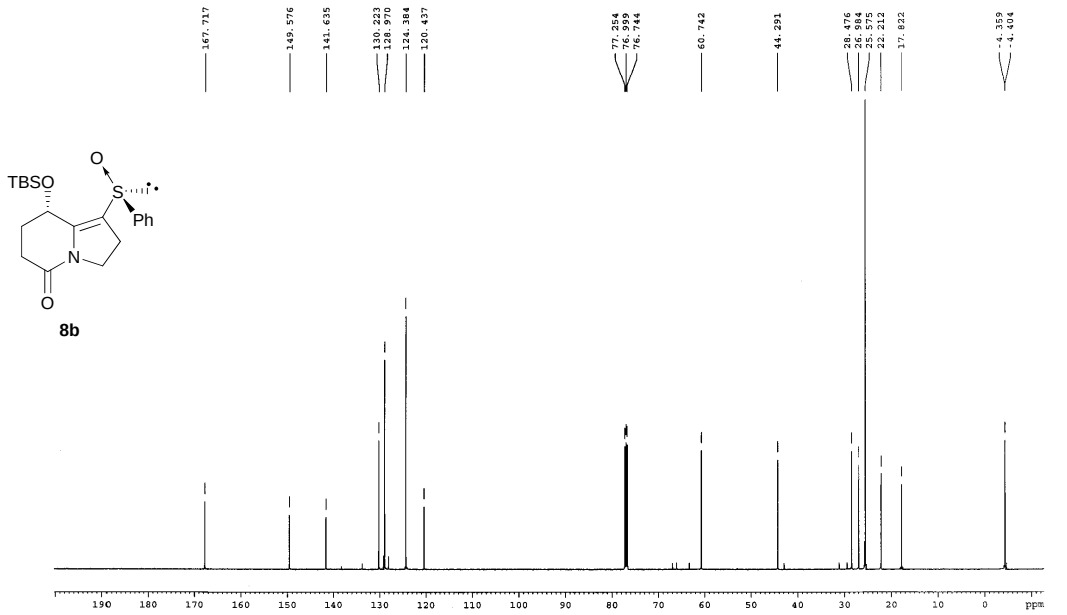
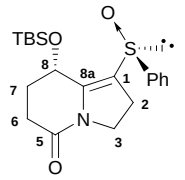


Table 3. 500 MHz COSY-45 correlations of some protons of compound **8b**.



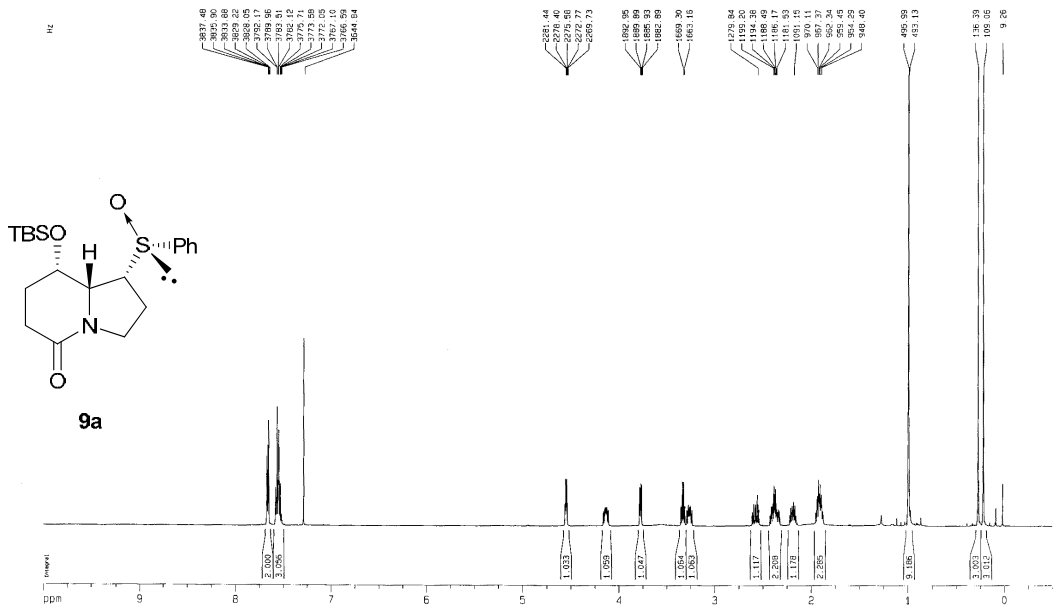
8b

δ_H (ppm)	δ_H (ppm) of correlated protons
5.18-5.17 (C_8-*H*)	1.97-1.90 (C_7-*H*)
3.87 (C_3-*H*)	2.08-2.00 (C_2-*H*), 2.83 (C_2-*H*)
3.78 (C_3-*H*)	2.08-2.00 (C_2-*H*), 2.83 (C_2-*H*)
2.83 (C_2-*H*)	2.08-2.00 (C_2-*H*)
2.74 (C_6-*H*)	1.97-1.90 (C_7-*H*)
2.44 (C_6-*H*)	1.97-1.90 (C_7-*H*)

Table 4. Observed C-H correlations from HMQC spectrum of **8b**.

δ_C (ppm)	δ_H (ppm)	Assignment
167.7	-	C_5
149.5	-	C_{8a}
141.6	-	C_1
60.7	5.18-5.17 (m, 1H)	C_8
44.3	3.87 (ddd, *J* = 12.0, 12.0, 6.7 Hz, 1H) and 3.78 (ddd, *J* = 12.0, 12.0, 7.1 Hz, 1H)	C_3
28.5	2.08-2.00 (m, 2H) and 1.97-1.90 (m, 1H)	C_7
27.0	2.74 (ddd, *J* = 17.0, 12.5, 4.9 Hz, 1H) and 2.44 (dt, *J* = 17.2, 3.8 Hz, 1H)	C_6
22.2	2.83 (ddd, *J* = 16.1, 11.8, 7.1 Hz, 1H) and 2.08-2.00 (m, 2H)	C_2

^{1}H-NMR spectrum of **9a** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **9a** (125 MHz, $CDCl_3$)

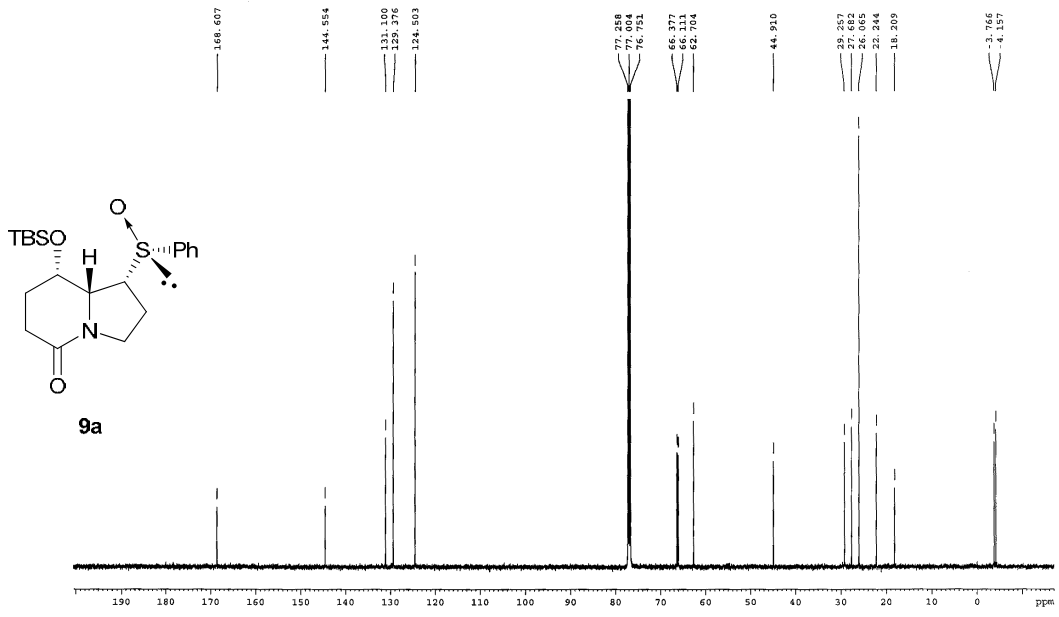
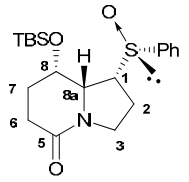


Table 5. 500 MHz COSY-45 correlations ofsome protons of compound **9a**.



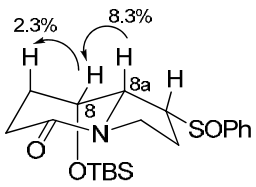
9a

δ_H (ppm)	δ_H (ppm) of correlated protons
4.55 (C_8-*H*)	1.95-1.87 (C_7-*H*), 2.22-2.15 (C_7-*H*), 3.77 (C_{8a}-*H*)
4.14 (C_3-*H*)	1.95-1.87 (C_2-*H*), 2.43-2.33 (C_2-*H*), 3.26 (C_3-*H*)
3.77 (C_{8a}-*H*)	3.33 (C_1-*H*)
3.33 (C_1-*H*)	1.95-1.87 (C_2-*H*), 2.43-2.33 (C_2-*H*)
3.26 (C_3-*H*)	1.95-1.87 (C_2-*H*), 2.43-2.33 (C_2-*H*)
2.58 (C_6-*H*)	1.95-1.87 (C_7-*H*), 2.22-2.15 (C_7-*H*), 2.43-2.33 (C_6-*H*)
2.22-2.15 (C_7-*H*)	1.95-1.87 (C_7-*H*)

Table 6. Observed C-H correlations from HMQC spectrum of **9a**.

δ_C (ppm)	δ_H (ppm)	Assignment
168.6	-	C_5
66.4	4.55 (dt, *J* = 5.6, 3.0 Hz, 1H)	C_8
66.1	3.33 (app. q, *J* = 7.1 Hz, 1H)	C_1
62.7	3.77 (dd, *J* = 7.0, 3.1 Hz, 1H)	C_{8a}
44.9	4.14 (ddd, *J* = 11.5, 8.6, 5.6 Hz, 1H) and 3.26 (ddd, *J* = 11.5, 8.2, 6.7 Hz, 1H)	C_3
29.3	2.22-2.15 (m, 1H) and 1.95-1.87 (m, 2H)	C_7
27.7	2.58 (dt, *J* = 17.7, 7.8 Hz, 1H) and 2.43-2.33 (m, 2H)	C_6
22.2	2.43-2.33 (m, 2H) and 1.95-1.87 (m, 2H)	C_2

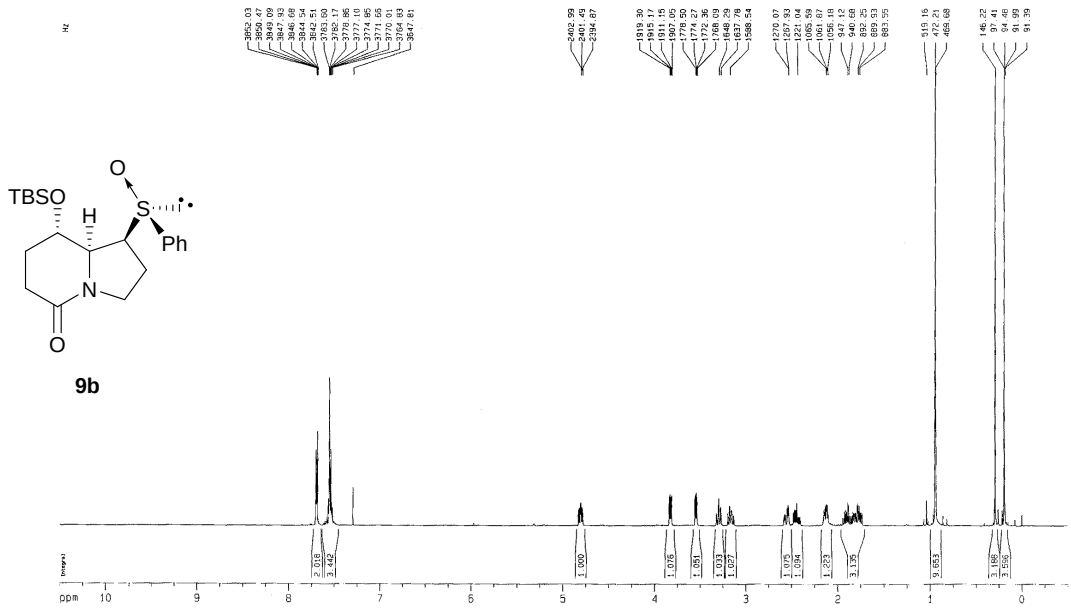
Table 7. NOE enhancements observed in compound **9a**.



9a

Irradiation	Results
C_1-*H*	2.7% enhancement of C_3-H_a 8.9% enhancement of C_{8a}-*H* 3.7% enhancement of C_2-H_a
C_{8a}-*H*	8.3% enhancement of C_8-*H* 8.7% enhancement of C_1-*H* 3.9% enhancement of C_2-H_a
C_8-*H*	8.1% enhancement of C_8-*H* 2.3% enhancement of C_7-H_a 3.0% enhancement of C_2-H_a

^{1}H-NMR spectrum of **9b** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **9b** (125 MHz, $CDCl_3$)

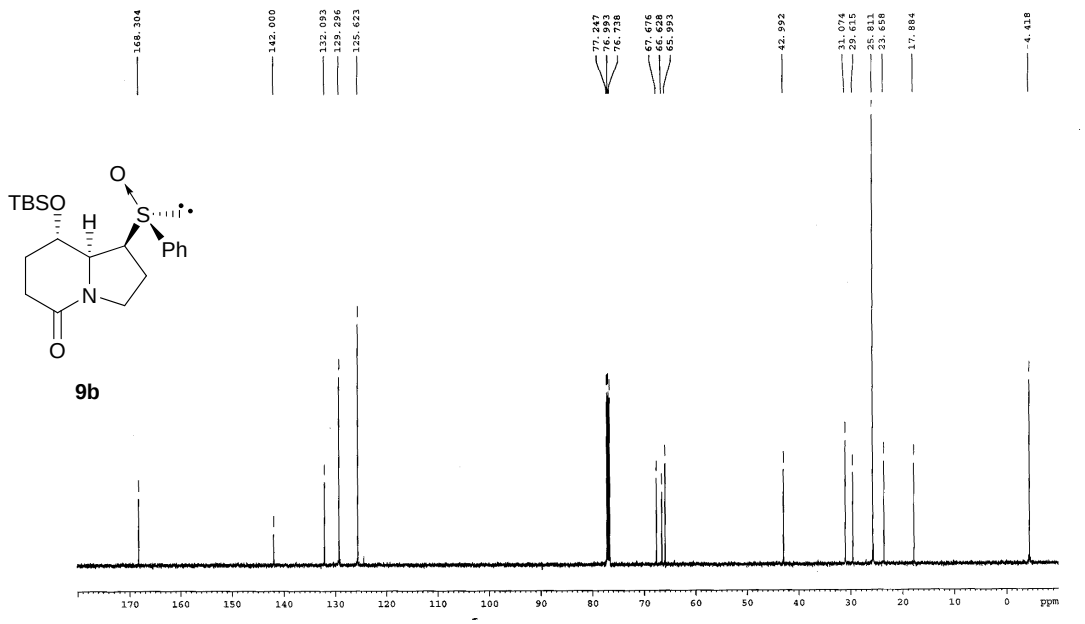
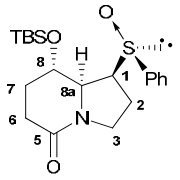


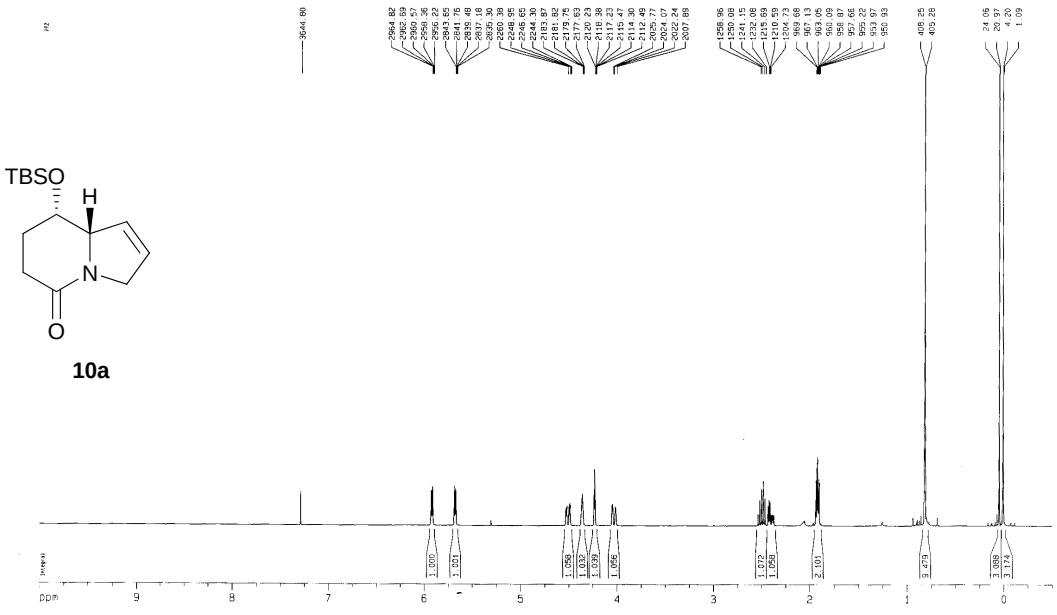
Table 8. 500 MHz COSY-45 correlations of some protons of compound **9b**.



9b

δ_H (ppm)	δ_H (ppm) of correlated protons
4.80 (C_8-*H*)	1.94-1.73 (C_7-*H*), 3.82 (C_{8a}-*H*)
3.82 (C_{8a}-*H*)	3.54 (C_1-*H*)
3.54 (C_1-*H*)	1.94-1.73 (C_2-*H*)
3.29 (C_3-*H*)	1.78-1.73 (C_2-*H*), 1.94-1.87 (C_2-*H*), 3.16 (C_3-*H*)
3.16 (C_3-*H*)	1.94-1.73 (C_2-*H*), 1.94-1.73 (C_2-*H*)
2.55 (C_6-*H*)	1.94-1.73 (C_7-*H*), 2.16-2.10 (C_7-*H*), 2.44 (C_6-*H*)
2.44(C_6-*H*)	1.94-1.73 (C_7-*H*), 2.16-2.10 (C_7-*H*)
2.16-2.10 (C_7-*H*)	1.94-1.73 (C_7-*H*)

^{1}H-NMR spectrum of **10a** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of **10a** (125 MHz, $CDCl_3$)

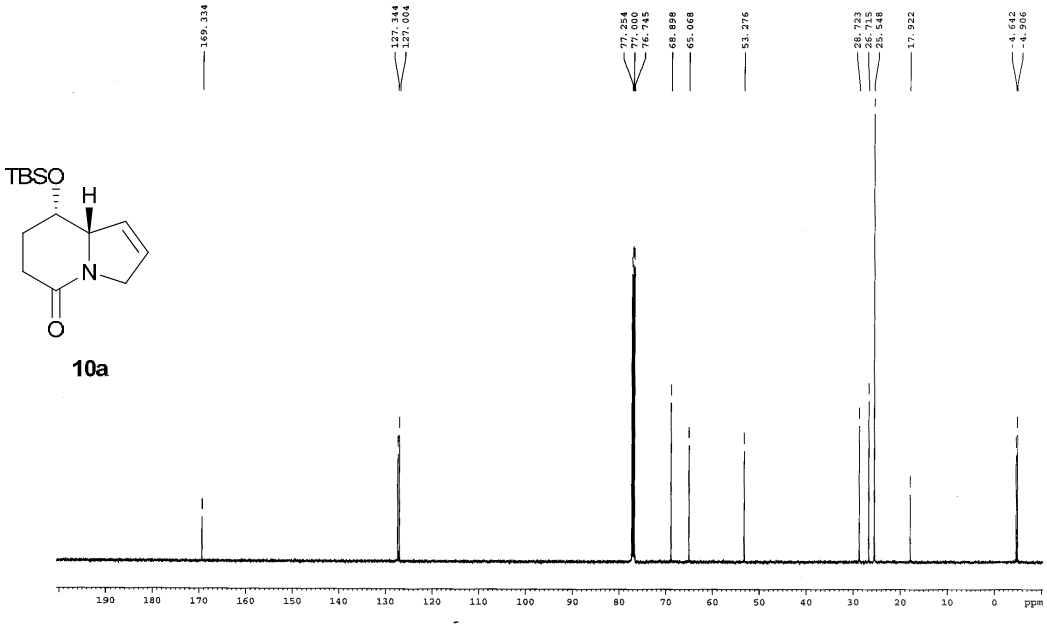
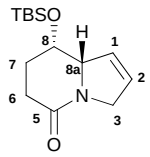


Table 9. 500 MHz COSY-45 correlations of some protons of compound **10a**.



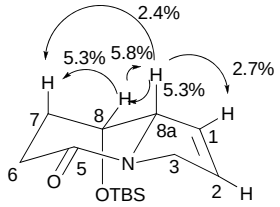
10a

δ_H (ppm)	δ_H (ppm) of correlated protons
5.93-5.90 (C_2-*H*)	4.05-4.01 (C_3-*H*), 4.37-4.35 (C_{8a}-*H*), 4.53-4.48 (C_3-*H*), 5.69-5.66 (C_1-*H*)
5.69-5.66 (C_1-*H*)	4.05-4.01 (C_3-*H*), 4.37-4.35 (C_{8a}-*H*), 4.53-4.48 (C_3-*H*)
4.53-4.48 (C_3-*H*)	4.05-4.01 (C_3-*H*)
4.24-4.22 (C_8-*H*)	1.94-1.90 (C_7-*H*)
2.49 (C_6-*H*)	1.94-1.90 (C_7-*H*)
2.40 (C_6-*H*)	1.94-1.90 (C_7-*H*)

Table 10. Observed C-H correlations from HMQC spectrum of **10a**.

δ_C (ppm)	δ_H (ppm)	Assignment
169.3	-	C_5
127.3	5.69-5.66 (m, 1H)	C_1
127.0	5.93-5.90 (m, 1H)	C_2
68.9	4.37-4.35 (m, 1H)	C_{8a}
65.1	4.24-4.22 (m, 1H)	C_8
53.3	4.53-4.48 (m, 1H) and 4.05-4.01 (m, 1H)	C_3
28.7	1.94-1.90 (m, 2H)	C_7
26.7	2.49 (dt, *J* = 17.8, 9.1 Hz, 1H) and 2.40 (ddd, *J* = 17.8, 6.7, 4.3 Hz, 1H)	C_6

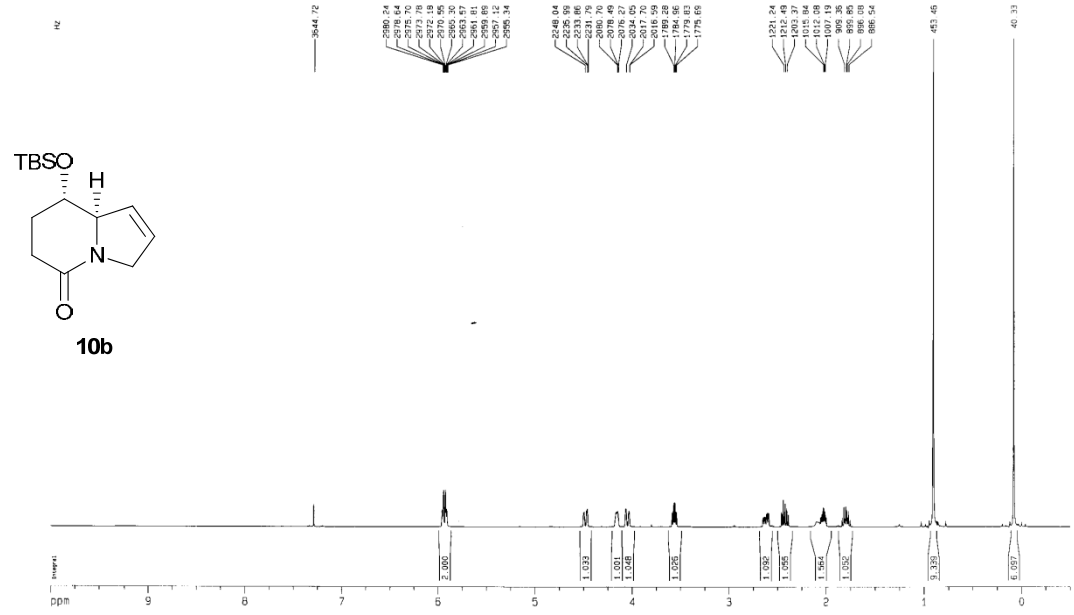
Table 11. NOE enhancements observed in compound **10a**.



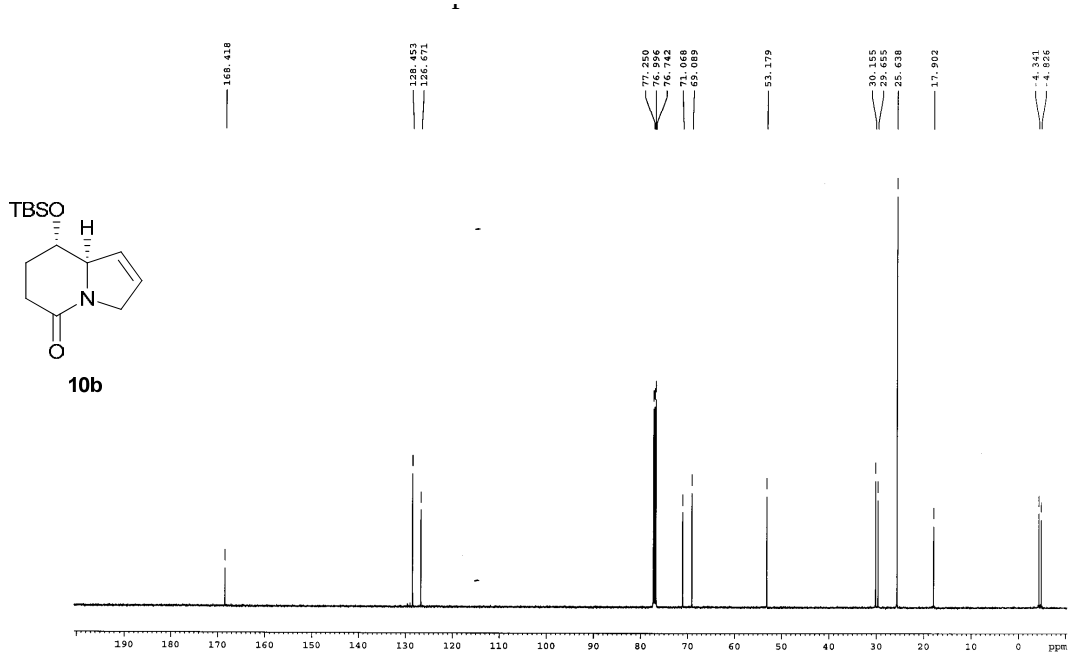
10a

Irradiation	Results
C_8-*H*	5.81% enhancement of C_{8a}-*H* 5.3% enhancement of C_7-H_a
C_{8a}-*H*	5.3% enhancement of C_8-*H* 2.70% enhancement of C_1-*H* 2.4% enhancement of C_7-H_a

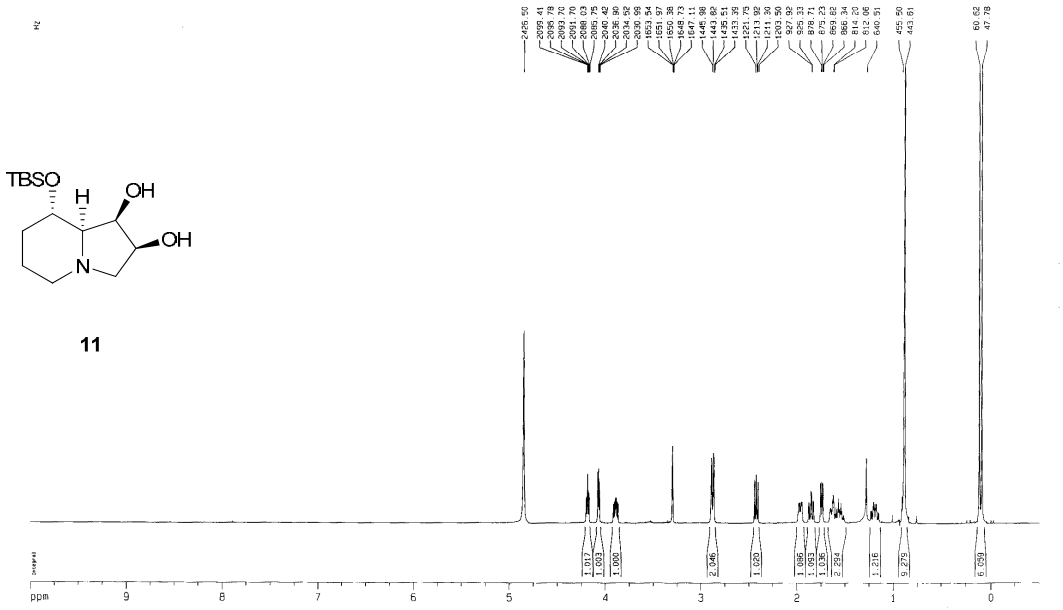
^{1}H-NMR spectrum of **10b** (500 MHz, $CDCl_3$)



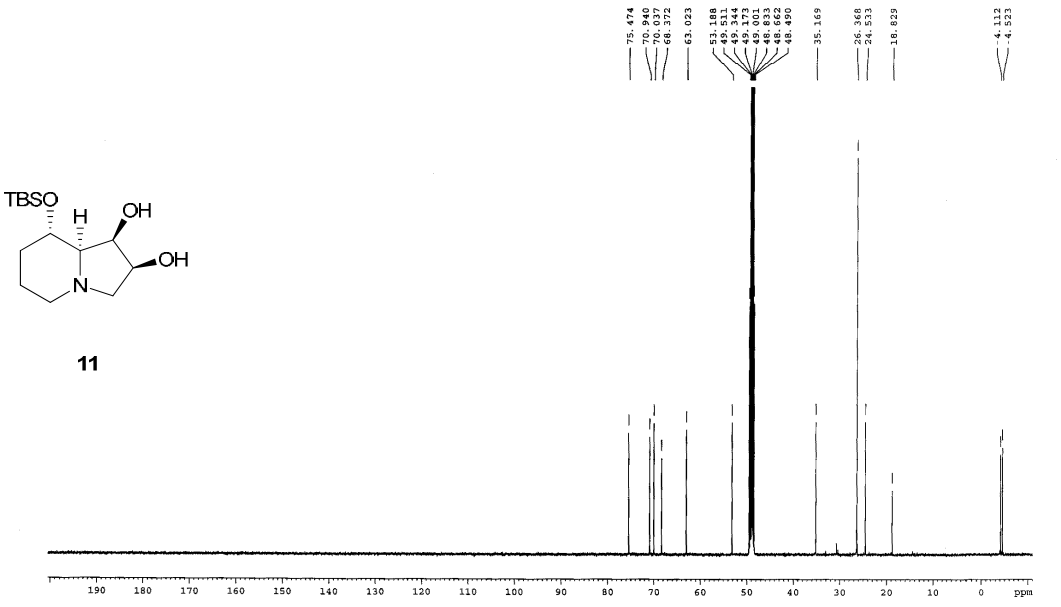
^{13}C-NMR spectrum of **10b** (125 MHz, $CDCl_3$)



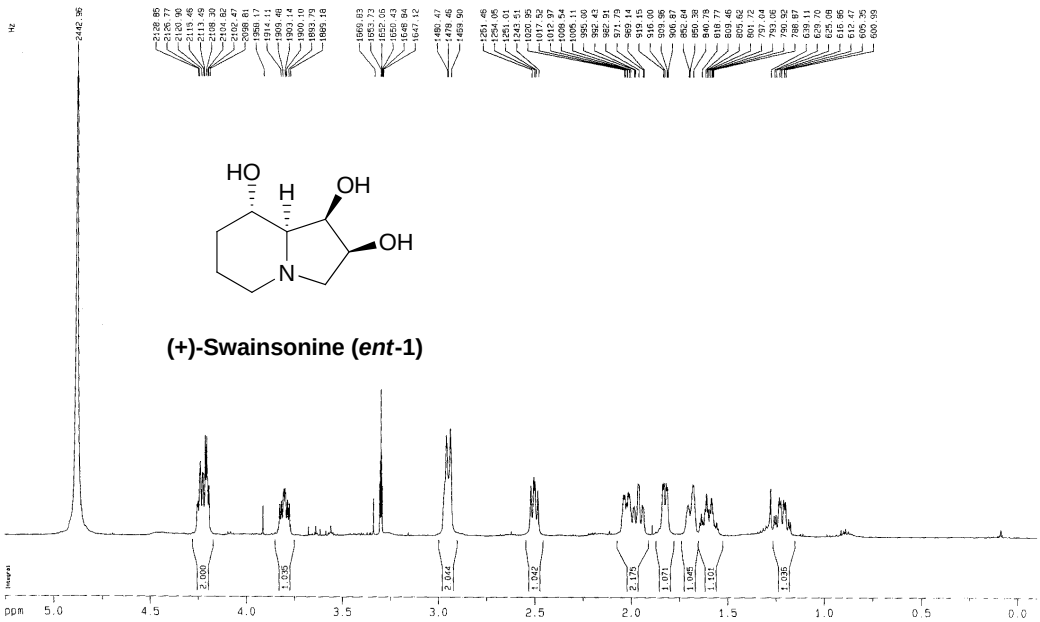
^{1}H-NMR spectrum of **11** (500 MHz, CD_3OD)



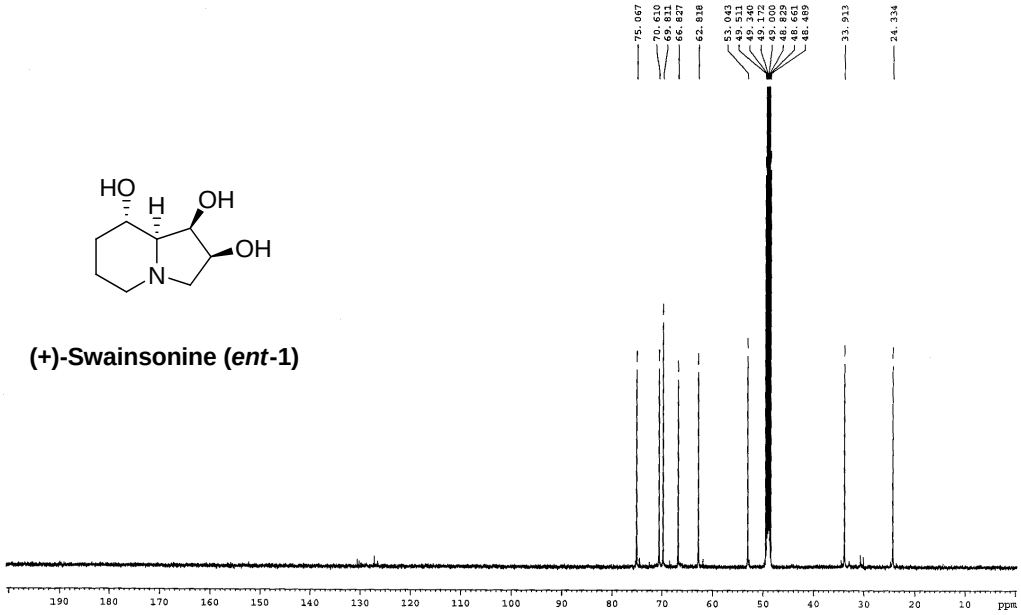
^{13}C-NMR spectrum of **11** (125 MHz, CD_3OD)



^{1}H-NMR spectrum of (+)-swainsonine (***ent*-1**) (500 MHz, CD_3OD)



^{13}C-NMR spectrum of (+)-swainsonine (***ent*-1**) (125 MHz, CD_3OD)



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Stereoselective synthesis of β-carboethoxy-γ-lactams via imino Mukaiyama aldol-type reaction of 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene

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Abstract—The reaction of the (bis)trimethylsilyloxy derivative of diethyl succinate with imines in the presence of $ZnCl_2$ provides a general stereoselective entry to β-carboethoxy-γ-lactams.

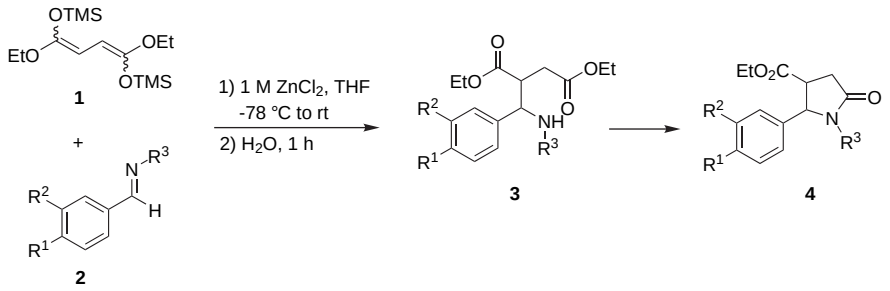
1. Introduction

The γ-lactam structure is an important subunit widely found in many classes of nitrogen heterocycles.[1] Moreover, this class of compound can be utilised as a versatile starting material for many synthetic manipulations.[2] Numerous synthetic methods for the construction of γ-lactams have been, therefore, extensively investigated. The general methods are based on Rh-catalysed intramolecular C–H insertion of diazo derivatives,[3] Pd-catalysed cyclisation,[4] *N*-heterocyclic carbene-catalysed addition of enals to imines,[5] addition of homoenolates to imines,[6] ring-expansion of β-lactams[7] and cycloaddition strategies.[8]

In continuation of our work in developing new synthetic methods using succinic ester derivatives as four-carbon building blocks,[9] it was anticipated that the reaction of (bis)trimethylsilyloxy derivative **1** derived from diethyl succinate[10] with imine **2** in the presence of a Lewis acid[11] would lead to adduct **3**, which should undergo subsequent cyclisation to afford β-carboethoxy-γ-lactam **4** (Scheme 1).

2. Results and discussion

1,4-Bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene **1** was readily prepared according to Rathke's procedure.[10] The ^1H and ^{13}C NMR spectra of **1** revealed that it was a mixture of at least two geometrical isomers in the ratio of 2:3. In the preliminary study, a search for a Lewis acid suitable for promoting the reaction was carried out. A collection of Lewis acids ($BF_3{\cdot}OEt_2$, $SnCl_4$, $Yb(OTf)_3$, $ZnBr_2$ and $ZnCl_2$) was employed to mediate the reaction of (bis)trimethylsilyloxy derivative **1** derived from diethyl succinate[10] with imine **2g** (Table 1). The best yield of lactam **4g** (48%) was obtained when the reaction was carried out in



Scheme 1.

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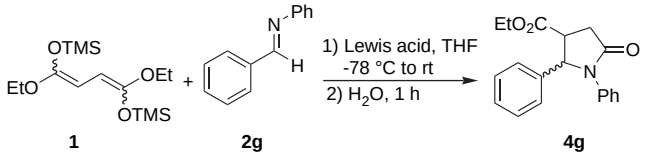
Table 1. Lewis acid optimization



1 **2g** **4g**

Entry	Lewis acid	% Lactam **4a**[a] (cis/trans)[b]
1	$BF_3 \cdot OEt_2$	36 (30:70)
2	$SnCl_4$	27 (27:73)
3	$Yb(OTf)_3$	36 (24:76)
4	$ZnBr_2$	41 (30:70)
5	$ZnCl_2$	48 (20:80)

[a] Isolated yields.
[b] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude product.

the presence of $ZnCl_2$ (Table 1, entry 5). Therefore, $ZnCl_2$ was chosen for further study in order to test the generality of the reaction.

The scope of the Mukaiyama aldol-type reaction of 1,4-bis-(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene **1** with a range of imine derivatives was examined under the optimised conditions using $ZnCl_2$ as a Lewis acid (Table 2). Treatment of **1** (1 equiv), as a 2:3 mixture of stereoisomers, with imine **2a** (R^3=benzyl) (1 equiv) in THF in the presence of $ZnCl_2$ (1 equiv, 1 M solution in THF) at –78 °C to room temperature overnight provided γ-lactam **4a** in 70% yield, as a 90:10 mixture of cis- and trans-isomer (J_{cis}=9.2 Hz and J_{trans}=5.4 Hz) (Table 2, entry 1).[12] No trace of the corresponding β-lactam was observed. Similar results were obtained when **1** was reacted with imines **2b–e** to afford good yields of the expected *cis*- and *trans*-γ-lactam **4b–e** (Table 2, entries 2–5).

However, the reaction of **1** with imine **2f** under the same conditions gave a mixture of γ-lactam **4f** (57% yield, cis/trans=75:25) and an uncyclised adduct **3f** (33% yield, *diastereomeric ratio*=42:58). Fortunately, treatment of the crude mixture of **3f** (*diastereomeric ratio*=42:58) and **4f** (cis/trans=75:25) with 1 equiv of K_2CO_3 under refluxing ethanol (4 h) led to complete cyclisation of the initial adduct **3f** to the desired γ-lactam **4f** (90% yield, cis/trans=20:80) (J_{cis}=9.3 Hz and J_{trans}=5.8 Hz). The equivalent of base (K_2CO_3) employed is critical to the stereochemistry of the γ-lactam. When an excess of K_2CO_3 (3 equiv) was employed, a 10:90 ratio of cis- and trans-isomer **4f** resulted. This observation indicated that the *cis*-**4f** having a larger coupling constant (J_{cis}=9.3 Hz) was isomerised to a thermodynamically more stable *trans*-**4f** whose coupling constant was smaller (J_{trans}=5.8 Hz). This experiment confirmed the assigned stereochemistry of both *cis*- and *trans*-γ-lactam **4**.

Table 2. Reaction of compound **1** with imines **2** catalysed by $ZnCl_2$

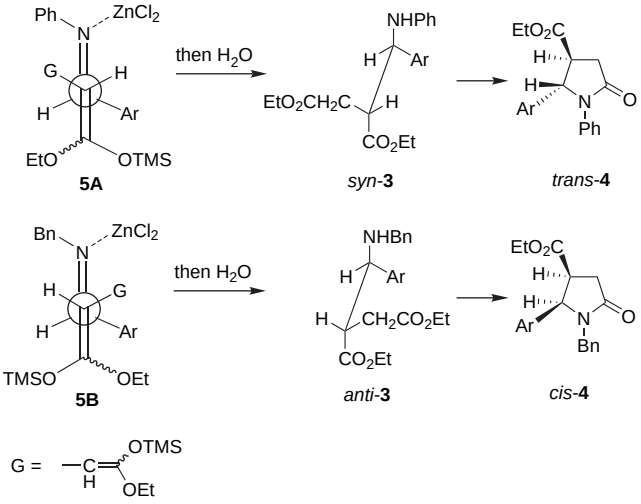
Entry	Imine **2**				% Lactam **4**[a] (cis/trans)[b]	% Adduct **3**[a] (*diastereomeric ratio*)[b]
	2	R^1	R^2	R^3		
1	**2a**	H	H	Bn	**4a**, 70 (90:10)	**3a** (—)
2	**2b**	OMe	H	Bn	**4b**, 72 (90:10)	**3b** (—)
3	**2c**	Cl	H	Bn	**4c**, 76 (92:8)	**3c** (—)
4	**2d**	NO_2	H	Bn	**4d**, 70 (92:8)	**3d** (—)
5	**2e**	H	OMe	Bn	**4e**, 75 (85:15)	**3e** (—)
6	**2f**	OMe	OMe	Bn	**4f**, 57 (75:25)	**3f**, 33 (42:58)
7	**2g**	H	H	Ph	**4g**, 48 (20:80)	**3g**, 32 (83:17)
8	**2h**	Cl	H	Ph	**4h**, 48 (9:91)	**3h**, 36 (60:40)
9	**2i**	NO_2	H	Ph	**4i**, 16 (0:100)	**3i**, 62 (50:50)
10	**2j**	H	OMe	Ph	**4j**, 81 (25:75)	**3j**, 13 (42:58)
11	**2k**	OMe	OMe	Ph	**4k**, 33 (16:84)	**3k**, 53 (60:40)
12	**2l**	OMe	H	Ph	**4l**, 83 (20:80)	**3l** (—)

[a] Isolated yields.
[b] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude products.

With the optimum conditions established, we sought to examine the reaction with other *N*-phenylimines. Therefore, **1** and **2g** were subjected to the standard conditions, resulting in a mixture of γ-lactam **4g** (48% yield, cis/trans=20:80) and uncyclised adduct **3g** (32% yield, *diastereomeric ratio*=83:17) (Table 2, entry 7). To our surprise, the reaction of **1** with *N*-phenylimine **2g** gave the *trans*-γ-lactam **4g** as the major isomer. It should be noted that, the stereochemical outcomes are in sharp contrast to those observed when *N*-benzyl imines were employed as imine partners. Treatment of the crude mixture of **3g** and **4g** with anhydrous K_2CO_3 (1 equiv) in refluxing ethanol furnished γ-lactam **4g** in 82% yield as a 10:90 mixture of cis- and trans-isomer. As summarised in Table 2 (entries 8–12), the mixtures of adducts **3h–k** and γ-lactams **4h–k** were afforded from the condensation of **1** with imines **2h–k**, except for the reaction with **2l**, where only γ-lactam **4l** was obtained as the sole product (Table 2, entry 12). The reactions of the mixtures of **3g/4g**, **3j/4j** and **3k/4k** (Table 2, entries 7, 10 and 11) with anhydrous K_2CO_3 in absolute ethanol under reflux for 4 h led to complete cyclisation and furnished the corresponding γ-lactams **4g** (82% yield, cis/trans=10:90), **4j** (90% yield, cis/trans=0:100) and **4k** (75% yield, cis/trans=5:95), respectively.

At this point, on the basis of the stereochemistry seen in the reactions summarised in Table 2, we shall advance a model for the mechanism of Lewis acid mediated reactions of (bis)-trimethylsilyloxy derivative **1** with *N*-phenyl imines and *N*-benzyl imines. The transition state model employed to explain the stereochemical outcomes observed in our study has been proposed based on previous report by Mukaiyama.[13] The work described Lewis base catalysed Mannich-type reactions between trimethylsilyl enol ethers and *N*-tosyl imines, irrespective of geometries of the silyl enol ethers, to give the corresponding adducts with stereoconvergent (*anti*) selectivity.

The reaction was assumed to undergo via the staggered acyclic transition states. Selectivity was achieved by the steric effect in the way that repulsion of the group attached to nitrogen atom and substituent of the enol ether being greater than that of an aryl group of imine and the group on nitrogen atom. In our current study, we employed Lewis acid ($ZnCl_2$) to catalyse the reaction. It is assumed that $ZnCl_2$ occupies a coordination site on the nitrogen atom such that it is cis to the substituent at the imine carbon (Scheme 2). In the case of *N*-benzyl imines, the selectivity was achieved by the steric effect caused by the repulsive interaction of the benzyl group and the substituent G of **1**, leading preferably to *anti*-adduct **3** via transition state **5B** (Scheme 2). This observation is analogous to the results previously reported by Mukaiyama.[13] Except for **3f**, most often, the firstly formed *anti*-adduct **3**



Scheme 2.

was not isolated but underwent cyclisation under the reaction conditions to yield *cis*-γ-lactam **4**. Opposite stereoselectivity was observed when *N*-phenyl imines were employed as the reaction partners. This could be attributed to a greater steric demanding of $ZnCl_2$ causing 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene **1** to approach the *N*-phenyl imines such that the substituent G being *anti* to the $ZnCl_2$ (transition state **5A**, Scheme 2), leading to *syn*-adduct **3**. However, due to a poor nucleophilicity of the nitrogen atom of the *N*-phenyl amine, cyclisation did not readily occur and a mixture of adduct **3** as a mixture of two diastereoisomers in varying ratio[14] and γ-lactam **4** (favouring trans-isomer) was obtained. We believed that cyclisation of the *syn*-adduct **3** to *trans*-γ-lactam **4** proceeded more rapidly than that of the *anti*-adduct **3** to *cis*-γ-lactam **4**. Therefore, the observed diastereoselectivity of adducts **3g–k** in the *N*-phenyl series does not reflect the cis/trans ratios of the γ-lactams **4g–k**. Attempted separation of both isomers of **4a–f** by preparative thin-layer chromatography (silica gel) was unsuccessful, except for *cis*-**4a** wherein a white solid was obtained upon standing at room temperature.

Ultimately, the isomerisation of *cis*-γ-lactam to the thermodynamically more stable *trans*-γ-lactam was investigated. Thus, treatment of a mixture of *cis*- and *trans*-γ-lactam **4a–d** and **4f** with catalytic DBU in THF at room temperature overnight furnished the *trans*-γ-lactams **4a–d** and **4f** as the major isomer. The results are listed in Table 3.

Table 3. Equilibration of cis/trans mixture of γ-lactam **4** employing DBU (0.25 equiv) in THF at rt

γ-Lactam **4** (cis/trans)[a]	% Yield[b] of γ-lactam **4** (trans/cis)[c]
4a (90:10)	80 (80:20)
4b (90:10)	85 (85:15)
4c (92:8)	80 (90:10)
4d (92:8)	60 (80:20)
4f (80:20)	70 (90:10)

[a] Isolated products were used.
[b] Isolated yields.
[c] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the isolated products.

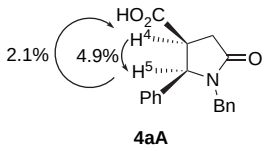


Figure 1.

The cis or trans stereochemistry of γ-lactam **4a** was conclusively established by the NOE experiment of the corresponding carboxylic acid derivative **4aA** of *cis*-γ-lactam **4a**, which was obtained by hydrolysis of the 90:10 mixture of **4a** employing 6 M HCl in dioxane under reflux for 1 h (Fig. 1).

3. Conclusion

In conclusion, we have established an efficient stereoselective synthesis of γ-lactams possessing β-carboethoxy group by treatment of bis(trimethylsilyloxy) derivative of diethyl succinate with imines catalysed by $ZnCl_2$. This type of compound might be useful as starting materials in organic synthesis. Simplicity of the procedure, readily available starting materials and a possible stereocontrol of the reaction are noteworthy. Work aimed at enantioselective synthesis of this type of γ-lactam is currently underway.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz), Bruker DPX-400 (400 MHz) and Bruker DPX-500 (500 MHz) spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard. The chemical shifts (δ) reported are given in parts per million (ppm) and the coupling constants (J) are in hertz (Hz). Melting points were recorded on a Buchi 501 Melting Point Apparatus and were uncorrected. The IR spectra were recorded on a GX FTIR system Perkin–Elmer infrared spectrometer. The EI mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded on HR-TOF-MS Micromass model at Chiangmai University. The elemental analyses were performed by a Perkin–Elmer Elemental Analyzer 2400 CHN. Merck silica gel 60 PF_{254} was used for preparative thin-layer chromatography.

4.2. Reaction of the 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene (1) with imines using $ZnCl_2$ as a catalyst

4.2.1. Ethyl 1-benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylate (4a).

4.2.1.1. General procedure. A mixture of imine **2a** (0.195 g, 1 mmol) and zinc chloride solution (1 M in THF, 1 mL) was added dropwise at –78 °C to a solution of 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene (**1**) (0.318 g, 1 mmol) in THF (2 mL) under an argon atmosphere. The resulting mixture was slowly warmed up to room temperature overnight (16 h). The resulting mixture was quenched with H_2O, stirred to reach room temperature

for 1 h, and then extracted with EtOAc (3×30 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product **4a**, which consisted of a 90:10 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a 90:10 mixture of cis/trans isomer of **4a** (0.226 g, 70% yield). The pale yellow solid obtained from PLC was recrystallised from *i*-PrOH–/hexanes to give a white solid of a pure *cis*-**4a** isomer (0.203 g, 62%, mp 80–81 °C) and a pale yellow oil of *trans*-**4a** (0.023 g, 8% yield) contaminated with a small amount of *cis*-**4a**.

4.2.1.2. *cis*-4a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 6H), 7.18–7.01 (m, 4H), 5.15 (d, J=14.7 Hz, 1H), 4.63 (d, J_{cis}=9.2 Hz, 1H), 3.80–3.48 (m, 3H), 3.43 (d, J=14.7 Hz, 1H), 3.21 (dd, J=17.3, 10.2 Hz, 1H), 2.62 (dd, J=17.3, 9.2 Hz, 1H), 0.87 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 169.9, 135.9, 135.7, 128.8, 128.7, 128.6, 128.4, 127.7, 127.6, 62.2, 60.9, 44.5, 43.0, 31.9, 13.9. IR ($CHCl_3$): ν_{max} 1734 (C=O of ester), 1683 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 324 ([M+1]$^+$, 23), 323 ([M]$^+$, 6), 232 (100), 119 (18), 118 (32), 117 (13), 105 (6), 91 (27), 77 (4), 65 (6). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.57; H, 6.80; N, 4.44.

4.2.1.3. *trans*-4a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 3H), 7.25–7.15 (m, 3H), 7.15–7.01 (m, 2H), 7.01–6.91 (m, 2H), 5.03 (d, J=14.7 Hz, 1H), 4.53 (d, J_{trans}=5.4 Hz, 1H), 4.04 (q, J=7.1 Hz, 2H), 3.41 (d, J=14.7 Hz, 1H), 3.20–2.60 (m, 3H), 1.09 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 172.1, 138.9, 135.5, 129.1, 128.6, 128.4, 127.6, 126.9, 63.6, 61.3, 46.0, 44.4, 33.5, 14.0. IR (neat): ν_{max} 1732 (C=O of ester), 1695 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 324 ([M+1]$^+$, 23), 323 ([M]$^+$, 6), 232 (100), 119 (18), 118 (32), 117 (13), 105 (6), 91 (27), 77 (4), 65 (6). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_3$ [M+Na]$^+$: 346.1419; found: 346.1415.

4.2.2. Ethyl 1-benzyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (4b). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2b** (0.225 g, 1 mmol) under an argon atmosphere. A crude product **4b**, which consisted of a 90:10 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow solid of product **4b** (0.254 g, 72% yield, cis/trans=90:10, mp=55–56 °C). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.29–7.10 (m, 4H, Ar*H* of cis- and trans-isomer), 7.10–6.89 (m, 10H, Ar*H* of cis- and trans-isomer), 6.89–6.71 (m, 4H Ar*H* of cis- and trans-isomer), 5.07* (d, J=14.7 Hz, 1H), 5.00 (d, J=14.7 Hz, 1H), 4.57* (d, J_{cis}=9.3 Hz, 1H), 4.49 (d, J_{trans}=5.8 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.48–3.80* (m, 3H), 3.76 (s, 3H), 3.73* (s, 3H), 3.35 (d, J=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 3.00–2.90 (m, 1H), 2.85–2.65 (m, 2H), 3.18* (dd, J=17.3, 10.3 Hz, 1H), 2.53* (dd, J=17.3, 9.3 Hz, 1H), 1.09 (t, J=7.1 Hz, 3H), 0.85* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.6, 172.1, 169.9*, 159.8*, 159.6, 135.9*, 135.6, 128.7 (cis- and trans-isomer), 128.6*, 128.4, 128.35*, 128.3, 128.1, 127.6*, 127.5, 127.4*, 114.3, 113.9*, 63.1, 61.7*, 61.2, 60.9*, 55.2, 55.16*, 46.1, 44.3*, 44.2, 42,9*, 33.6, 31.9*, 13.9, 13.6*. IR (KBr): ν_{max} 1726 (C=O of ester), 1675 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 354 ([M+1]$^+$, 9), 353 ([M]$^+$, 18), 262 (100), 119 (23), 118 (25), 91 (84), 77 (10), 65 (13). HRMS (ESI-TOF) calcd for $C_{21}H_{23}NO_4Na$ [M+Na]$^+$: 376.1525; found: 376.1525.

4.2.3. Ethyl 1-benzyl-2-(4-chlorophenyl)-5-oxopyrrolidine-3-carboxylate (4c). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2c** (0.229 g, 1 mmol) under an argon atmosphere. A crude product **4c**, which consisted of a 92:8 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow oil of product **4c** (0.271 g, 76% yield, cis/trans=92:8). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.80 (m, 18H, Ar*H* of cis- and trans-isomer), 5.08* (d, J=14.7 Hz, 1H), 5.03 (d, J=14.7 Hz, 1H), 4.58* (d, J_{cis}=9.3 Hz, 1H), 4.49 (d, J_{trans}=5.4 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.90–3.30* (m, 3H), 3.33 (d, J=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 2.55* (dd, J=17.3, 9.4 Hz, 1H), 3.09* (dd, J=17.3, 10.2 Hz, 1H), 3.10–2.85 (m, 1H), 2.85–2.60 (m, 2H), 1.09 (t, J=7.1 Hz, 3H), 0.85* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.6, 172.8, 169.7*, 137.5, 135.6*, 135.3, 134.6*, 134.3 (cis- and trans-isomer), 129.3, 128.9, 128.8*, 128.7 (cis- and trans-isomer), 128.3*, 127.8*, 127.6, 62.9, 61.5*, 61.4, 60.9*, 46.0, 44.5*, 44.4, 42.8*, 33.4, 31.7*, 13.9, 13.6*. IR (neat): ν_{max} 1724 (C=O of ester), 1678 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 358 ([M+1]$^+$, 15), 357([M]$^+$, 7), 266 (100), 119 (28), 118 (33), 91 (50), 77 (4), 65 (14). HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3ClNa$ [M+Na]$^+$: 380.1029; found: 380.1028.

4.2.4. Ethyl 1-benzyl-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (4d). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2d** (0.241 g, 1 mmol) under an argon atmosphere. A crude product **4d**, which consisted of a 92:8 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a brown oil of product **4d** (0.257 g, 70% yield, cis/trans=92:8). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 8.20 (d, J=8.5 Hz, 4H, Ar*H* of cis- and trans-isomer), 7.40–7.20 (m, 10H, Ar*H* of cis- and trans-isomer), 7.15–7.00 (m, 4H Ar*H* of cis- and trans-isomer), 5.16* (d, J=14.7 Hz, 1H), 5.00 (d, J=14.7 Hz, 1H), 4.69* (d, J_{cis}=9.4 Hz, 1H), 4.62 (d, J_{trans}=6.0 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.85–3.40* (m, 3H), 3.37 (d, J=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 3.08* (dd, J=17.4, 10.2 Hz, 1H), 2.57* (dd, J=17.4, 9.4 Hz, 1H), 3.10–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.10 (t, J=7.1 Hz, 3H), 0.93* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.7, 171.4, 169.4*, 148.1*, 146.4, 143.4 (cis- and trans-isomer), 135.2*, 134.9, 128.9*, 128.7, 128.6 (cis- and trans-isomer), 128.4*, 128.3, 128.0*, 127.9, 124.3, 123.8*, 62.8, 61.7, 61.5*, 61.2*, 45.8, 44.9*, 44.8, 42.8*, 33.3, 31.7*, 14.0, 13.7*. IR (neat): ν_{max} 1732 (C=O of ester),

1695 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 369 ($[M+1]^+$, 9), 368 ($[M]^+$, 13), 274 (100), 147 (30), 146 (56), 119 (27), 118 (47), 116 (20), 115 (13), 106 (23), 104 (52), 91 (80), 77 (8), 65 (20). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 64.21; H, 5.47; N, 7.60. Found: C, 64.24; H, 5.13; N, 7.75.

4.2.5. Ethyl 1-benzyl-2-(3-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (4e). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2e** (0.225 g, 1 mmol) under an argon atmosphere. A crude product **4e**, which consisted of an 85:15 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow solid of product **4e** (0.264 g, 75% yield, cis/trans=85:15, mp=160–164 °C). ^1H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.53 (m, 18H, Ar*H* of cis- and trans-isomer), 5.10* (d, *J*=14.7 Hz, 1H), 5.02 (d, *J*=14.7 Hz, 1H), 4.58 (d, *J*=9.2 Hz, 1H), 4.51* (d, *J*=5.5 Hz, 1H), 4.05 (q, *J*=7.1 Hz, 2H), 3.80–3.25* (m, 3H), 3.81* (s, 3H), 3.83 (s, 3H), 3.37 (d, *J*=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 3.21* (dd, *J*=17.3, 10.2 Hz, 1H), 2.55* (dd, *J*=17.3, 9.3 Hz, 1H), 3.10–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.16 (t, *J*=7.1 Hz, 3H), 0.87* (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 173.1*, 172.8, 172.1, 169.9*, 160.2, 159.7*, 140.6, 137.3*, 135.9*, 135.6, 130.2*, 129.7, 128.6*, 128.5, 128.43*, 128.40, 127.7*, 127.6, 119.8*, 119.0, 113.9*, 113.86, 113.3*, 112.3, 63.5, 62.1*, 61.3, 60.8*, 55.24, 55.2*, 45.8, 44.5*, 44.4, 42.9*, 33.5, 31.9*, 14.0, 13.6. IR (neat): ν_{max} 1732 (C═O of ester), 1695 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 354 ($[M+1]^+$, 23), 353 ($[M]^+$, 6), 225 (50), 147 (39), 146 (28), 119 (28), 118 (51), 104 (34), 91 (100), 77 (18), 65 (25). HRMS (ESI-TOF) calcd for $C_{21}H_{24}NO_4$ $[M+1]^+$: 354.1705; found: 354.1705.

4.2.6. Ethyl 1-benzyl-2-(3,4-dimethoxyphenyl)-5-oxopyrrolidine-3-carboxylate (4f) and diethyl 2-[(benzylamino)-(3,4-dimethoxyphenyl)methyl]succinate (3f). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2f** (0.255 g, 1 mmol) under an argon atmosphere. A crude product **4f** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow oil of a 75:25 mixture of cis/trans isomer of product **4f** (0.218 g, 57% yield cis/trans=75:25) and an adduct **3f** (0.141 g, 33% yield) as a 42:58 mixture of isomers.

4.2.6.1. Carboxylate 4f. ^1H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.53 (m, 16H, ArH of cis- and trans-isomer), 5.05* (d, *J*=14.6 Hz, 1H), 4.96 (d, *J*=14.6 Hz, 1H), 4.56* (d, *J*=9.3 Hz, 1H), 4.47 (d, *J*=6.0 Hz, 1H), 4.02 (q, *J*=7.1 Hz, 2H), 3.30–3.90* (m, 3H), 3.82 (s, 3H), 3.80* (s, 3H), 3.74 (s, 6H, OC*H*$_3$ of cis- and trans-isomer), 3.37 (d, *J*=14.6 Hz, 2H, NC*H*HAr of cis- and trans-isomer), 3.21* (dd, *J*=17.3, 10.1 Hz, 1H), 2.55* (dd, *J*=17.3, 9.4 Hz, 1H), 3.05–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.10 (t, *J*=7.1 Hz, 3H), 0.84* (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.6, 172.1, 170.0*, 149.4, 149.2*, 149.1, 149.0*, 135.9*, 135.7, 131.0, 128.6*, 128.4, 128.37 (cis- and trans-isomer), 127.9*, 127.6*, 127.5, 120.1*, 119.5, 111.2, 110.9*, 110.4*, 109.4, 63.6, 62.1*, 61.2, 60.8*, 55.84*, 55.8, 46.1, 44.45, 44.4*, 42.9*, 33.7, 31.9*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1720 (C═O of ester), 1673 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 384 ($[M+1]^+$, 23), 383 ($[M]^+$, 6), 292 (58), 149 (66), 146 (28), 119 (22), 118 (23), 104 (12), 91 (100), 77 (32), 65 (26), 55 (44). HRMS (ESI-TOF) calcd for $C_{22}H_{25}NO_5Na$ $[M+Na]^+$: 408.1630; found: 408.1630.

4.2.6.2. Succinate 3f. ^1H NMR (300 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.00 (t, *J*=8.1 Hz, 4H, Ar*H* of major- and minor-isomer), 6.80–6.68 (m, 6H, Ar*H* of major- and minor-isomer), 6.60–6.50 (m, 2H, Ar*H* of major- and minor-isomer), 6.50–6.39 (m, 4H Ar*H* of major- and minor-isomer), 4.63* (d, J_{minor}=5.4 Hz, 1H), 4.45 (d, J_{major}=6.8 Hz, 1H), 4.09–3.95 (m, 8H, OCH_2CH$_3$ of major- and minor-isomer), 3.77 (s, 16H, OCH_3 and NCH_2Ar of major- and minor-isomer), 3.26–3.20 (m, 1H), 3.20–3.10* (m, 1H), 2.74 (dd, *J*=17.1, 10.1 Hz, 2H, CHCH*H*CO of major- and minor-isomer), 2.45–2.32 (m, 2H, CHC*H*HCO of major- and minor-isomer), 1.22–1.02 (m, 12H, OCH$_2$CH_3 of major- and minor-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, minor-isomer marked as *): δ 173.3, 172.7*, 172.0*, 171.6, 149.2, 149.1*, 148.4, 146.8*, 146.7 (major- and minor-isomer), 133.0, 132.3*, 129.04, 129.0*, 119.1, 119.0*, 117.8*, 117.6, 113.7*, 113.4, 111.14*, 111.1, 109.7*, 109.5, 61.1*, 61.0, 60.8, 60.3*, 58.7, 58.6*, 55.85, 55.8*, 48.1, 48.0*, 44.45, 44.4*, 34.8, 32.1*, 14.03, 14.0*. IR (neat): ν_{max} 3395 (N–H), 1732 (C═O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 429 ($[M]^+$, 0.05), 242 (100), 104 (32), 91 (1), 77 (10). HRMS (ESI-TOF) calcd for $C_{24}H_{31}NO_6$ $[M]^+$: 429.2151; found: 429.2150.

4.2.7. Ethyl 5-oxo-1,2-diphenylpyrrolidine-3-carboxylate (4g) and diethyl 2-(phenyl(phenylamino)methyl)succinate (3g). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2g** (0.181 g, 1 mmol) under an argon atmosphere. A crude product **4g** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.110 g, 36% yield as a pale yellow solid, mp=115–116 °C) and cis-isomer (38 mg, 12% yield as a yellow oil) of **4g**, and an adduct **3g** (0.113 g, 32% yield) as an 83:17 mixture of isomers.

4.2.7.1. *trans*-4g. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J*=7.6 Hz, 2H), 7.35–7.19 (m, 7H), 7.06 (t, *J*=7.5 Hz, 1H), 5.53 (d, J_{trans}=4.6 Hz, 1H), 4.22 (q, *J*=7.1 Hz, 2H), 3.20–2.80 (m, 3H), 1.27 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.15, 172.1, 139.7, 137.5, 129.0, 128.7, 128.2, 126.1, 125.3, 122.7, 65.8, 61.6, 46.4, 34.3, 14.1. IR ($CHCl_3$): ν_{max} 1731 (C═O of ester), 1698 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 310 ($[M+1]^+$, 24), 309 ($[M]^+$, 97), 236 (100), 208 (99), 180 (71), 91 (24), 77 (38), 50 (11). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.79; H, 6.25; N, 4.41.

4.2.7.2. *cis*-4g. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J*=7.9 Hz, 2H) 7.35–7.10 (m, 7H), 7.06 (t, *J*=7.3 Hz, 1H), 5.48 (d, J_{cis}=8.8 Hz, 1H), 3.88–3.65 (m, 3H), 3.32 (dd, *J*=17.3, 10.2 Hz, 1H), 2.72 (dd, *J*=17.3, 8.8 Hz, 1H), 0.99

(t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 169.5, 137.8, 136.2, 128.7, 128.62, 128.6, 127.0, 125.3, 122.1, 65.1, 61.0, 43.7, 32.9, 13.7. IR (neat): ν_{max} 1732 (C=O of ester), 1707 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 310 ([M+1]$^+$, 29), 309 ([M]$^+$, 75), 281 (51), 236 (100), 208 (78), 91 (21), 77 (33), 65 (3). HRMS (ESI-TOF) calcd for $C_{19}H_{19}NO_3Na$ [M+Na]$^+$: 332.1263; found: 332.1263.

4.2.7.3. Succinate 3g. ^{1}H NMR (300 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.40–6.40 (m, 20H, Ar*H* of major- and minor-isomer), 4.67* (d, J_{minor}=5.5 Hz, 1H), 4.52 (d, J_{major}=6.5 Hz, 1H), 4.10–3.90 (m, 8H, OC*H*$_2$CH$_3$ of major- and minor-isomer), 3.35–3.20* (m, 1H), 3.20–3.10 (m, 1H), 2.85–2.70 (m, 2H, CHCH*H*CO of major- and minor-isomer), 2.45–2.30 (m, 2H, CHC*H*HCO of major- and minor-isomer), 1.12 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer), 1.03 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, minor-isomer marked as *): δ 173.2, 172.6*, 172.0*, 171.5, 146.6*, 146.5, 140.4, 139.8*, 129.1, 129.0*, 128.6 (major- and minor-isomer), 127.5 (major- and minor-isomer), 126.8*, 126.7, 117.8, 117.5*, 113.6*, 113.3, 61.1*, 61.0, 60.8 (major- and minor-isomer), 58.7 (major- and minor-isomer), 48.0, 47.9*, 34.5, 32.0*, 14.04 (major- and minor-isomer), 13.96 (major- and minor-isomer). IR (neat): ν_{max} 3386 (N–H), 1734 (C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 356 ([M+1]$^+$, 8), 355 ([M]$^+$, 1), 182 (100), 180 (4), 104 (16), 91 (1), 77 (12). HRMS (ESI-TOF) calcd for $C_{22}H_{25}O_5Na$ [M+Na]$^+$: 356.1862; found: 356.1862.

4.2.8. Ethyl 2-(4-chlorophenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4h) and diethyl 2-[(4-chlorophenyl)-(phenylamino)methyl]succinate (3h). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2h** (0215 g, 1 mmol) under an argon atmosphere. A crude product **4h** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.141 g, 41% yield, as a pale yellow solid, mp=117–119 °C) and cis-isomer (27 mg, 7% yield, as a yellow oil) product of **4h**, and an adduct **3h** (0.140 g, 36% yield as a 60:40 mixture of isomers).

4.2.8.1. *trans*-4h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 2H), 7.20–7.05 (m, 6H), 7.01 (m, 1H), 5.44 (d, J_{trans}=4.8 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.00–2.70 (m, 3H), 1.20 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 138.2, 137.1, 134.0, 129.2, 128.8, 127.7, 125.6, 122.7, 65.0, 61.7, 46.4, 34.3, 14.1. IR (neat): ν_{max} 1731 (C=O of ester), 1714 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 344 ([M+1]$^+$, 16), 343 ([M]$^+$, 68), 270 (83), 242 (100), 240 (23), 216 (59), 91 (9), 77 (81), 55 (12). Anal. Calcd for $C_{19}H_{18}NO_3Cl$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.17; H, 4.92; N, 4.00.

4.2.8.2. *cis*-4h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.21–7.16 (m, 4H), 7.16–6.95 (m, 3H), 5.41 (d, J_{cis}=8.8 Hz, 1H), 3.90–3.60 (m, 3H), 3.22 (dd, J=17.3, 10.5 Hz, 1H), 2.67 (dd, J=17.3, 9.3 Hz, 1H), 0.96 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 169.4, 137.4, 134.8, 134.5, 128.6, 128.4, 125.5, 122.1, 64.4, 61.2, 43.4, 32.8, 13.7. IR ($CHCl_3$): ν_{max} 1732 (C=O of ester), 1698 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 344 ([M+1]$^+$, 21), 343 ([M]$^+$, 93), 270 (90), 242 (100), 216 (71), 91 (9), 77 (53), 50 (12). HRMS (ESI-TOF) calcd for $C_{19}H_{19}NO_3Cl$ [M+1]$^+$: 344.1503; found: 344.1502.

4.2.8.3. Succinate 3h. ^{1}H NMR (400 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.40–7.20 (m, 8H, Ar*H* of major- and minor-isomer), 7.09 (t, J=8.0 Hz, 4H, Ar*H* of major- and minor-isomer), 6.67 (t, J=6.8 Hz, 4H, Ar*H* of major- and minor-isomer), 6.65 (t, J=7.3 Hz, 2H, Ar*H* of major- and minor-isomer), 4.78 (d, J_{major}=5.6 Hz, 1H), 4.63* (d, J_{minor}=5.6 Hz, 1H), 4.20–4.05 (m, 8H, OC*H*$_2$CH$_3$ of major- and minor-isomer), 3.45–3.35* (m, 1H), 3.35–3.25 (m, 1H), 2.91–2.80 (m, 2H, CHCH*H*CO of major- and minor-isomer), 2.60–2.40 (m, 2H, CHC*H*HCO of major- and minor-isomer), 1.22 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer), 1.13 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer). ^{13}C NMR (125 MHz, $CDCl_3$, minor-isomer marked as *): δ 173.9*, 173.3, 172.7, 172.2*, 147.3*, 147.15, 141.1 (major- and minor-isomer), 140.6 (major- and minor-isomer), 129.8*, 129.7, 129.3 (major- and minor-isomer), 128.3 (major- and minor-isomer), 127.5, 127.4*, 118.5*, 118.3, 114.4, 114.1*, 61.8, 61.7*, 61.5 (major- and minor-isomer), 59.5, 59.4*, 48.6 (major- and minor-isomer) 35.2*, 32.8, 14.7 (major- and minor-isomer), 14.66 (major- and minor-isomer). IR (neat): ν_{max} 3396 (N–H), 1731(C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 401 ([M+1]$^+$, 6), 400 ([M]$^+$, 4), 227 (100), 212 (50), 104 (15), 91 (2), 77 (11). HRMS (ESI-TOF) calcd for $C_{21}H_{25}NO_4Cl$ [M+1]$^+$: 390.1472; found: 390.1471.

4.2.9. Ethyl 2-(4-nitrophenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4i) and diethyl 2-((4-nitrophenyl)-(phenylamino)methyl)succinate (3i). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2i** (0.226 g, 1 mmol) under an argon atmosphere. A crude product **4i** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer **4i** (58 mg, 16% yield, as a pale yellow solid, mp=132–133 °C) and an adduct **3i** (0.248 g, 62% yield, as a 50:50 mixture of isomers).

4.2.9.1. *trans*-4i. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, J=8.6 Hz, 2H), 7.38 (d, J=8.6 Hz, 2H), 7.35–7.10 (m, 4H), 7.02 (m, 1H), 5.60 (d, J_{trans}=5.1 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.10–2.81 (m, 3H), 1.22 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 171.4, 147.7, 147.0, 137.0, 129.0, 127.3, 125.9, 124.3, 122.6, 64.7, 62.0, 46.1, 34.3, 14.1. IR (neat): ν_{max} 1731 (C=O of ester), 1714 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 354 ([M]$^+$, 1), 242 (100), 216 (59), 91 (15), 77 (92), 55 (10). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.21; H, 5.47; N, 7.60. Found: C, 64.24; H, 5.13; N, 7.75.

4.2.9.2. Succinate 3i. ^{1}H NMR (400 MHz, $CDCl_3$, one isomer marked as *): δ 8.19 (d, J=8.8 Hz, 4H, Ar*H* of both isomers), 7.53 (m, 4H, Ar*H* of both isomers), 7.10 (m, 4H, Ar*H* of both isomers), 6.70 (q, J=7.2 Hz, 2H, Ar*H* of both isomers), 6.47 (m, 4H, Ar*H* of both isomers), 5.10* (br, 1H), 4.75 (br, 1H), 4.86 (d, J_{major}=5.3 Hz, 1H), 4.79* (d, J_{minor}=5.1 Hz, 1H), 4.05–4.20 (m, 8H, OC*H*$_2$CH$_3$ of both isomers), 3.30–3.43 (m, 2H, CH$_2$C*H*CO$_2$Et of both

isomers), 2.90 (dd, J=17.0, 8.2 Hz, 1H), 2.84* (dd, J=17.0, 9.5 Hz, 1H), 2.66* (dd, J=17.0, 5.6 Hz, 1H), 2.43 (dd, J=17.0, 4.8 Hz, 1H), 1.23* (t, J=7.1 Hz, 3H), 1.22 (t, J=7.1 Hz, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.10* (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, one isomer marked as *): δ 173.2*, 172.6, 172.3, 171.9*, 149.3*, 148.5, 148.2, 148.1*, 146.6*, 146.5, 130.0*, 129.9, 128.6, 128.4*, 124.6, 124.5*, 119.2, 118.9*, 114.3, 113.9*, 62.2, 62.0*, 61.7 (both isomers), 59.1, 58.5*, 48.13, 48.07*, 35.0*, 32.8, 14.7 (both isomers), 14.6 (both isomers). IR (neat): ν_{max} 3400 (N–H), 1731 (C=O of ester) cm^{-1}. MS: m/z (%) relative intensity 401 ([M+1]$^+$, 6), 400 ([M]$^+$, 4), 227 (100), 212 (50), 104 (15), 91 (2), 77 (11). HRMS (ESI-TOF) calcd for $C_{21}H_{24}N_2O_5ClNa$ [M+Na]$^+$: 423.1532; found: 423.1531.

4.2.10. Ethyl 2-(3-methoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4j) and diethyl 2-[(3-methoxyphenyl)(phenylamino)methyl]succinate (3j). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2j** (0.211 g, 1 mmol) under an argon atmosphere. A crude product **4j** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.205 g, 61% yield, as a pale yellow solid, mp=117–119 °C) and cis-isomer (69 mg, 20% yield, as a yellow oil) of product **4j** (0.274 g, 81% yield), and an adduct **3j** (50 mg, 13% yield as a 42:58 mixture of isomers).

4.2.10.1. *trans*-4j. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J=7.7 Hz, 2H), 7.30–7.10 (m, 3H), 7.00 (t, J=7.3 Hz, 1H), 6.80–6.50 (m, 3H), 5.42 (d, J_{trans}=4.5 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.66 (s, 3H), 2.80–3.10 (m, 3H), 1.21 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 172.1, 160.0, 141.4, 137.5, 130.2, 128.8, 125.4, 122.7, 118.3, 113.4, 111.9, 65.8, 61.7, 55.2, 46.7, 34.4, 14.2. IR (neat): ν_{max} 1732 (C=O of ester), 1706 (C=O of amide) cm^{-1}. MS: m/z (%) relative intensity 340 ([M+1]$^+$, 7), 339 ([M]$^+$, 76), 210 (100), 91 (31), 77 (78), 55 (12). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_4$ [M+1]$^+$: 340.1549; found: 340.1545.

4.2.10.2. *cis*-4j. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J=8.3 Hz, 2H), 7.25–7.05 (m, 3H), 7.01 (t, J=7.3 Hz, 1H), 6.80–6.60 (m, 3H), 5.37 (d, J_{cis}=8.8 Hz, 1H), 3.90–3.60 (m, 3H), 3.67 (s, 3H), 3.24 (dd, J=17.3, 10.8 Hz, 1H), 2.64 (dd, J=17.3, 8.8 Hz, 1H), 0.96 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 169.5, 159.8, 137.8, 129.7, 128.8, 125.3, 122.1, 119.2, 113.6, 113.0, 65.0, 61.1, 55.2, 43.7, 33.0, 13.8. IR ($CHCl_3$): ν_{max} 1736 (C=O of ester), 1697 (C=O of amide) cm^{-1}. MS: m/z (%) relative intensity 340 ([M+1]$^+$, 21), 339 ([M]$^+$, 100), 266 (92), 91 (11), 77 (29), 55 (6). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_4$ [M+1]$^+$: 340.1549; found: 340.1550.

4.2.10.3. Succinate 3j. ^{1}H NMR (300 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.09 (t, J=8.3 Hz, 4H, Ar*H* of major- and minor-isomer), 6.94 (t, J=7.6 Hz, 4H, Ar*H* of major- and minor-isomer), 6.90–6.45 (m, 8H, Ar*H* of major- and minor-isomer), 6.39 (t, J=7.3 Hz, 2H, Ar*H* of major- and minor-isomer), 4.62* (d, J_{minor}=5.3 Hz, 1H), 4.44 (d, J_{major}=6.8 Hz, 1H), 4.10–3.90 (m, 8H, OC*H*$_2$CH$_3$ of major- and minor-isomer), 3.37 (s, 6H, OC*H*$_3$ of major- and minor-isomer), 3.30–3.20* (m, 1H), 3.20–3.10 (m, 1H), 2.80–2.60 (m, 2H, CHCH*H*CO of major- and minor-isomer), 2.40–2.25 (m 2H, CHC*H*HCO of major- and minor-isomer), 1.15–0.90 (m, 12H, OCH$_2$C*H*$_3$ of major- and minor-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, both isomers): δ 173.9, 172.2, 160.5, 147.2, 143.0, 130.3, 129.7, 119.8, 118.2, 114.0, 113.5, 113.2, 61.7, 61.5, 59.5, 55.8, 48.6, 35.2, 14.7, 14.6. IR (neat): ν_{max} 3385 (N–H), 1721 (C=O of ester) cm^{-1}. MS: m/z (%) relative intensity 386 ([M+1]$^+$, 32), 385 ([M]$^+$, 4), 215 (100), 104 (26), 91 (3), 77 (16). HRMS (ESI-TOF) calcd for $C_{22}H_{28}NO_5$ [M+1]$^+$: 386.1969; found: 386.1967.

4.2.11. Preparation of ethyl 2-(3,4-dimethoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4k) and diethyl 2-[(3,4-dimethoxyphenyl)(phenylamino)methyl]succinate (3k). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2k** (0.242 g, 1 mmol) under an argon atmosphere. A crude product **4k** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.099 g, 26% yield, as a pale yellow solid, mp=136–137 °C) and cis-isomer (28 mg, 7% yield, as a yellow oil) of product **4k**, and an adduct **3k** (0.220 g, 53% yield as a 60:40 mixture of isomers).

4.2.11.1. *trans*-4k. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J=8.4 Hz, 2H), 7.20–6.90 (m, 4H), 6.80–6.50 (m, 2H), 5.39 (d, J_{trans}=5.0 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.78–3.08 (m, 3H), 1.21 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 172.0, 149.4, 148.8, 137.5, 132.0, 128.7, 125.5, 122.9, 118.7, 111.3, 108.9, 66.0, 61.6, 55.9, 55.8, 46.7, 34.5, 14.1. IR ($CHCl_3$): ν_{max} 1731 (C=O of ester), 1695 (C=O of amide) cm^{-1}. MS: m/z (%) relative intensity 371 ([M+2]$^+$, 6), 370 ([M+1]$^+$, 24), 369 ([M]$^+$, 100), 240 (57), 91 (12), 77 (22). HRMS (ESI-TOF) calcd for $C_{21}H_{23}NO_5Na$ [M+Na]$^+$: 392.1474; found: 392.1477.

4.2.11.2. *cis*-4k. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, J=8.1 Hz, 2H), 7.26 (t, J=6.7 Hz, 2H), 7.09 (t, J=7.4 Hz, 1H), 6.70 (s, 2H), 6.67 (s, 1H), 5.43 (d, J_{cis}=8.8 Hz, 1H), 3.75–3.95 (m, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.31 (dd, J=17.3, 10.0 Hz, 1H), 2.72 (dd, J=17.3, 8.9 Hz, 1H), 1.03 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 169.7, 149.2, 149.1, 137.9, 128.8, 128.6, 125.4, 122.3, 119.6, 111.1, 110.1, 65.0, 55.9, 55.8, 43.8, 33.1, 29.7, 13.8. IR ($CHCl_3$): ν_{max} 1731 (C=O of ester), 1696 (C=O of amide) cm^{-1}. MS: m/z (%) relative intensity 371 ([M+2]$^+$, 7), 370 ([M+1]$^+$, 37), 369 ([M]$^+$, 100), 91 (12), 77 (30). HRMS (ESI-TOF) calcd for $C_{21}H_{23}NO_5Na$ [M+Na]$^+$: 392.1474; found: 392.1477.

4.2.11.3. Succinate 3k. ^{1}H NMR (400 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.00 (t, J=8.1 Hz, 4H, Ar*H* of major- and minor-isomer), 6.80–6.68 (m, 6H, Ar*H* of major- and minor-isomer), 6.60–6.50 (m, 2H, Ar*H* of major- and minor-isomer), 6.50–6.39 (m, 4H, Ar*H* of major- and minor-isomer), 4.63 (d, J=5.4 Hz, 1H), 4.45* (d, J=6.9 Hz, 1H), 4.85 (br, 1H, N*H* of major- and minor-isomer), 4.09 (q, J=7.1 Hz, 4H), 4.08* (q, J=7.1 Hz, 4H), 3.84 (s, 12H, OC*H*$_3$ of major- and minor-isomer), 3.40–3.30* (m, 1H), 3.30–3.20 (m, 1H), 2.74 (dd, J=17.1, 10.1 Hz, 1H,

CHCH*H*CO of major- and minor-isomer), 2.45–2.32 (m, CHC*H*HCO of major- and minor-isomer), 1.21* (t, J=7.1 Hz, 3H), 1.20 (t, J=7.1 Hz, 3H), 1.16 (t, J=7.1 Hz, 3H), 1.15* (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, minor-isomer marked as *): δ 174.0*, 173.4, 172.7, 171.3*, 149.85*, 149.8, 149.05*, 149.0, 147.4, 147.3*, 133.7*, 133.0, 129.73*, 129.7, 119.8*, 119.7, 118.5, 118.3*, 114.4, 114.1*, 111.8, 111.76*, 110.4, 110.2*, 61.8, 61.7*, 61.5 (major- and minor-isomer), 59.4*, 59.2, 56.53*, 56.5, 48.8*, 48.7, 35.2*, 32.8, 14.74, 14.7*. IR (neat): ν_{max} 3395 (N–H), 1732 (C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 416 ([M+1]$^+$, 7), 415 ([M]$^+$, 2), 242 (100), 104 (32), 91 (1), 77 (10). HRMS (ESI-TOF) calcd for $C_{25}H_{30}NO_6$ [M+1]$^+$: 416.2073; found: 416.2070.

4.2.12. Preparation of ethyl 2-(4-methoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4l). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2l** (0.211 g, 1 mmol) under an argon atmosphere. A crude product **4l** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.210 g, 62% yield as a pale yellow oil) and cis-isomer (71 mg, 21% yield as a pale yellow oil) of product **4l**.

4.2.12.1. *trans*-4l. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J=7.8 Hz, 2H), 7.16 (t, J=7.3 Hz, 2H), 7.08 (d, J=8.6 Hz, 2H), 6.99 (t, J=7.3 Hz, 1H), 6.78 (d, J=8.6 Hz, 2H), 5.39 (d, J_{trans}=4.9 Hz, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.66 (s, 3H), 2.75–3.10 (m, 3H), 1.19 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 172.0, 159.3, 137.4, 131.5, 128.6, 127.4, 125.3, 122.9, 114.3, 65.4, 61.5, 55.1, 46.7, 34.4, 14.1. IR (neat): ν_{max} 1732 (C=O of ester), 1704 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 340 ([M+1]$^+$, 24), 339 ([M]$^+$, 55), 210 (100), 91 (43), 77 (65). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_4$ [M+1]$^+$: 340.1549; found: 340.1549.

4.2.12.2. *cis*-4l. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J=8.0 Hz, 2H), 7.15 (m, 2H), 7.05 (t, J=8.7 Hz, 3H), 6.74 (d, J=8.7 Hz, 2H), 5.38 (d, J_{cis}=8.8 Hz, 1H), 3.90–3.60 (m, 3H), 3.68 (s, 3H), 3.28 (dd, J=17.5, 10.9 Hz, 1H), 2.67 (dd, J=17.5, 8.9 Hz, 1H), 0.97 (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 169.6, 159.6, 137.8, 128.7, 128.2, 128.0, 125.2, 122.2, 113.9, 64.7, 61.0, 55.1, 43.7, 32.9, 13.8. IR ($CHCl_3$): ν_{max} 1732 (C=O of ester), 1697 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 340 ([M+1]$^+$, 20), 339 ([M]$^+$, 100), 266 (61), 210 (90), 91 (16), 77 (22). HRMS (ESI-TOF) calcd for $C_{20}H_{21}NO_4Na$ [M+Na]$^+$: 362.1368; found: 362.1368.

4.2.13. Cyclisation of a mixture of 3g and 4g to γ-lactam 4g. According to the general procedure as described for compound **4a**, a solution of **1** (0.320 g, 1 mmol) in THF (2 mL) and imine **2g** (0.181 g, 1 mmol) were employed, after aqueous work-up, to yield the crude material. Without chromatographic purification, the crude product was treated with K_2CO_3 (0.138 g, 1 mmol) in dry EtOH (20 mL) and the mixture was refluxed for 4 h under an argon atmosphere. After the mixture was cooled to room temperature, the reaction mixture was quenched with 1 M HCl, and EtOH was removed (aspirator). The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a mixture of cis/trans isomer of **4g** (82% yield, cis/trans=10:90).

4.2.14. Cyclisation of a mixture of 3j and 4j to γ-lactam 4j. According to the general procedure as described for compound **4a**, a solution of **1** (0.316 g, 1 mmol) in THF (2 mL) and imine **2j** (0.211 g, 1 mmol) were employed, after aqueous work-up, to yield the crude material. Without chromatographic purification, the crude product was treated with K_2CO_3 (0.138 g, 1 mmol) in dry EtOH (20 mL) and the mixture was refluxed for 4 h under an argon atmosphere. After the mixture was cooled to room temperature, the reaction mixture was quenched with 1 M HCl, and EtOH was removed (aspirator). The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a mixture of cis/trans isomer of **4j** (82% yield, cis/trans=0:100).

4.2.15. Cyclisation of a mixture of 3k and 4k to γ-lactam 4k. According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) and imine **2k** (0.241 g, 1 mmol) were employed, after aqueous work-up, to yield the crude material. Without chromatographic purification, the crude product was treated with K_2CO_3 (0.138 g, 1 mmol) in dry EtOH (20 mL) and the mixture was refluxed for 4 h under an argon atmosphere. After the mixture was cooled to room temperature, the reaction mixture was quenched with 1 M HCl, and EtOH was removed (aspirator). The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a mixture of cis/trans isomer of **4k** (82% yield, cis/trans=5:95).

4.3. Isomerisation of *cis*-γ-lactam 4 to *trans*-γ-lactam 4

4.3.1. General procedure. To a solution of the mixture of diastereomers of **4a** (87.5 mg, 0.25 mmol) in THF (1 mL) was added dropwise a THF solution of DBU (10 mg, 0.063 mmol) at 0 °C under an argon atmosphere. The reaction mixture was slowly warmed up to room temperature and stirred for 2 days. It was quenched with 0.5 N HCl (0.5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The crude product, which consisted of an 80:20 mixture of trans/cis diastereomer was purified by preparative thin-layer chromatography SiO_2, 20% EtOAc in hexanes) to give a yellow oil (70 mg, 80% yield, trans/cis=80:20). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.45–7.00 (m, 20H, Ar*H* of trans- and cis-isomer), 5.10* (d, J=14.7 Hz, 1H), 5.09 (d, J=14.7 Hz, 1H), 4.68* (d, J_{cis}=9.3 Hz, 1H), 4.60 (d, J_{trans}=5.5 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.55–3.80* (m, 3H), 3.48 (d, J=14.7 Hz, 1H), 3.42* (d, J=14.7 Hz, 1H), 3.17*

(dd, J=17.3, 10.2 Hz, 1H) 2.60* (dd, J=17.3, 9.3 Hz, 1H), 3.10–2.90 (m, 1H), 2.90–2.70 (m, 2H), 1.16 (t, J=7.1 Hz, 3H), 0.87* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 173.1*, 172.7, 172.0, 169.9*, 138.8, 135.7*, 135.6*, 135.5, 129.1*, 129.0, 128.5*, 128.4, 128.3*, 128.2, 127.5*, 127.4, 126.8*, 126.7, 63.5, 62.1*, 61.2, 60.7*, 45.8, 44.4*, 44.3, 42.8*, 33.3, 31.7*, 13.9, 13.5*. IR ($CHCl_3$): ν_{max} 1731 (C=O of ester), 1682 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 324 ([M+1]$^+$, 3), 323 ([M]$^+$, 9), 232 (100), 146 (10), 145 (8), 119 (9), 118 (18), 91 (31), 77 (5), 65 (7). HRMS (ESI-TOF) calcd for $C_{20}H_{21}NO_3Na$ [M+Na]$^+$: 346.1411; found: 346.1419.

4.3.2. Isomerisation of γ-lactam 4b. According to the general procedure, a solution of **4b** (0.1765 g, 0.5 mmol) in THF (1 mL) was reacted with a THF solution of DBU (20 mg, 0.12 mmol) to give an 85:15 mixture of trans/cis isomer of **4b**. It was purified by thin-layer chromatography (SiO_2, 20% EtOAc in hexanes) to afford a pale yellow oil of **4b** (0.1498 g, 85% yield, trans/cis=85:15). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.29–7.10 (m, 6H, Ar*H* of trans- and cis-isomer), 7.10–6.89 (m, 8H, Ar*H* of trans- and cis-isomer), 6.89–6.71 (m, 4H, Ar*H* of trans- and cis-isomer), 5.06* (d, J=14.7 Hz, 1H), 4.99 (d, J=14.7 Hz, 1H), 4.57* (d, J_{cis}=9.3 Hz, 1H), 4.48 (d, J_{trans}=5.8 Hz, 1H), 4.00 (q, J=7.1 Hz, 2H), 3.80–3.48* (m, 3H), 3.75 (s, 3H), 3.73* (s, 3H), 3.40 (d, J=14.7 Hz, 2H, NCH*H*Ar of trans- and cis-isomer), 3.05–2.85 (m, 1H), 2.85–2.65 (m, 2H), 3.12* (dd, J=17.3, 10.3 Hz, 1H), 2.54* (dd, J=17.3, 9.3 Hz, 1H), 1.09 (t, J=7.1 Hz, 3H), 0.85* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 174.8*, 172.9 (trans- and cis-isomer), 172.2, 159.7 (trans- and cis-isomer), 135.5 (trans- and cis-isomer), 130.6 (trans- and cis-isomer), 128.7*, 128.5, 128.44*, 128.4, 128.3*, 128.2, 127.7, 127.3*, 114.4, 114.0*, 63.3, 63.2*, 61.8*, 61.3, 55.3, 55.26*, 46.2, 45.9*, 44.4*, 44.3, 33.7, 31.9*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1735 (C=O of ester), 1683 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 354 ([M+1]$^+$, 9), 353 ([M]$^+$, 18), 262 (100), 119 (23), 118 (25), 91 (84), 77 (10), 65 (13). HRMS (ESI-TOF) calcd for $C_{21}H_{24}NO_4Na$ [M+Na]$^+$: 376.1525; found: 376.1524.

4.3.3. Isomerisation of γ-lactam 4c. According to the general procedure, a solution of **4c** (0.168 g, 0.46 mmol) in THF (1 mL) was reacted with a THF solution of DBU (18 mg, 0.12 mmol) to give a crude product, which consisted of a 90:10 mixture of trans/cis isomer of **4c**. It was purified by preparative thin-layer chromatography SiO_2, 20% EtOAc in hexanes) to give a pale yellow oil of **4c** (0.135 g, 80% yield, trans/cis=90:10). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked *): δ 7.30–6.80 (m, 18H, Ar*H* of trans- and cis-isomer), 5.08* (d, J=14.7 Hz, 1H), 5.02 (d, J=14.7 Hz, 1H), 4.58* (d, J_{cis}=9.3 Hz, 1H), 4.50 (d, J_{trans}=5.7 Hz, 1H), 4.03 (q, J=7.1 Hz, 2H), 3.90–3.40* (m, 3H), 3.45 (d, J=14.7 Hz, 2H, NCH*H*Ar of trans- and cis-isomer), 2.56* (dd, J=17.3, 9.40 Hz, 1H), 3.10* (dd, J=17.3, 10.2 Hz, 1H), 3.05–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.09 (t, J=7.1 Hz, 3H), 0.83* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 174.1*, 173.0*, 172.9, 171.8, 137.5*, 137.4, 135.2 (trans- and cis-isomer), 134.4 (trans- and cis-isomer), 129.3, 129.0*, 128.9*, 128.6, 128.44*, 128.45, 127.9*, 127.7, 63.0 (trans- and cis-isomer), 61.5, 60.4*, 46.0, 45.7*, 44.5, 42.8*, 33.5, 31.8*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1735 (C=O of ester), 1686 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 358 ([M+1]$^+$, 15), 357([M]$^+$, 10), 266 (100), 119 (15), 118 (25), 91 (43), 77 (5), 65 (11). HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3ClNa$ [M+Na]$^+$: 380.1022; found: 380.1029.

4.3.4. Isomerisation of γ-lactam 4d. According to the general procedure, a solution of **4d** (0.190 g, 0.5 mmol) in THF (1 mL) was reacted with a THF solution of DBU (20 mg, 0.13 mmol) to give a crude product, which consisted of an 80:20 mixture of trans/cis isomer of **4d**. Purification by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes) afforded a pale yellow oil of **4d** (0.114 g, 60% yield, trans/cis=80:20). γ-Lactam **4d**: ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 8.17 (d, J=8.7 Hz, 4H, Ar*H* of trans- and cis-isomer), 7.27 (d, J=8.7 Hz, 4H, Ar*H* of trans- and cis-isomer), 7.15–7.35 (m, 6H, Ar*H* of trans- and cis-isomer), 6.95–6.85 (m, 4H, Ar*H* of trans- and cis-isomer), 5.16* (d, J=14.7 Hz, 1H), 5.05 (d, J=14.7 Hz, 1H), 4.71* (d, J_{cis}=9.4 Hz, 1H), 4.64 (d, J_{trans}=5.8 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.40–3.85* (m, 3H), 3.45 (d, J=14.7 Hz, 2H, NCH*H*Ar of trans- and cis-isomer), 3.10* (dd, J=17.4, 10.2 Hz, 1H), 2.61* (dd, J=17.4, 9.4 Hz, 1H), 3.00–2.85 (m, 1H), 2.85–2.60 (m, 2H), 1.11 (d, J=7.1 Hz, 3H), 0.86* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) of the major trans-isomer: δ 172.7, 171.3, 148.0, 146.4, 134.9, 128.7, 128.3, 127.9, 127.86, 124.3, 62.8, 61.7, 45.8, 44.8, 33.2, 14.0. IR (neat): ν_{max} 1733 (C=O of ester), 1691 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 369 ([M+1]$^+$, 3), 368 ([M]$^+$, 11), 274 (100), 119 (8), 118 (19), 91 (41), 77 (5), 65 (9). HRMS (ESI-TOF) calcd for $C_{20}H_{20}N_2O_5Na$ [M+Na]$^+$: 391.1270; found: 391.1269.

4.3.5. Isomerisation of γ-lactam 4f. According to the general procedure, a solution of **4f** (0.191 g, 0.5 mmol) in THF (1 mL) was reacted with a THF solution of DBU (20 mg, 0.13 mmol) to give a crude product, which consisted of a 90:10 mixture of trans/cis isomer of **4f**. Purification by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes) afforded a pale yellow oil of **4f** (0.133 g, 70% yield, trans/cis=90:10). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.53 (m, 16H, Ar*H* of trans- and cis-isomer), 5.13* (d, J=14.6 Hz, 1H), 5.04 (d, J=14.6 Hz, 1H), 4.64* (d, J_{cis}=9.3 Hz, 1H), 4.55 (d, J_{trans}=6.0 Hz, 1H), 4.10 (q, J=7.1 Hz, 2H), 3.90–3.30* (m, 3H), 3.90 (s, 3H), 3.88* (s, 3H), 3.82 (s, 6H, OCH_3 of trans- and cis-isomer), 3.56 (d, J=14.6 Hz, 1H), 3.48* (d, J=14.6 Hz, 1H), 3.21* (d, J=17.3, 10.1 Hz, 1H), 2.55*(dd, J=17.3, 9.4 Hz, 1H), 3.10–3.00 (m, 1H), 2.90–2.65 (m, 2H), 1.10 (d, J=7.1 Hz, 3H), 0.84* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 173.0*, 172.7, 172.2, 170.0*, 149.5, 149.2*, 149.1, 149.0*, 136.0*, 135.7, 131.1 (trans- and cis-isomer), 128.6*, 128.5, 128.4 (trans- and cis-isomer), 128.0*, 127.7*, 120.2, 119.5*, 111.2, 110.9*, 110.4*, 109.5, 63.6, 62.1*, 61.3, 60.8*, 55.9, 55.8*, 46.2, 44.5, 44.47*, 42.9*, 33.8, 32.0*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1730 (C=O of ester), 1682 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 384 ([M+1]$^+$, 8), 383 ([M]$^+$, 34), 292 (100), 119 (11), 118 (17), 91 (56), 77 (6), 65 (12). HRMS (ESI-TOF) calcd for $C_{22}H_{25}NO_5Na$ [M+Na]$^+$: 406.1630; found: 406.1631.

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14. Assignment of isomer was not carried out since the coupling constants of each isomer are in the same degree.

JOC*Note*

Highly Diastereoselective Synthesis of β-Carboxy-γ-lactams and Their Ethyl Esters via $Sc(OTf)_3$-Catalyzed Imino Mukaiyama-Aldol Type Reaction of 2,5-Bis(trimethylsilyloxy)furan with Imines

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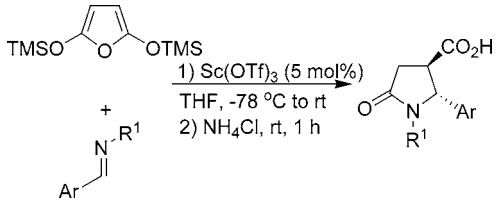
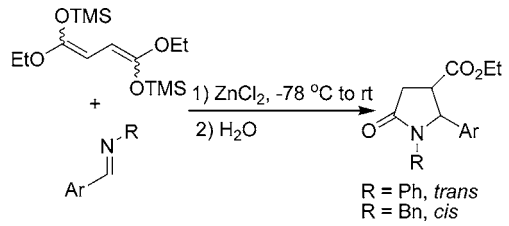


Functionalized γ-lactams are found to be crucial intermediates in the synthesis of biologically important natural products. We herein described a highly diastereoselective synthesis of β-carboxy-γ-lactams and their ethyl ester derivatives, in high yields with high diastereomeric ratio, via the Mukaiyama-aldol type reaction of 2,5-bis(trimethysilyloxy)furan with imines, employing $Sc(OTf)_3$ as a catalyst.

The construction of γ-lactam functionality has been a topic of great interest for many years since the γ-lactam unit is a prominent structural feature found in a number of biologically active natural products.[1] In addition, functionalized γ-lactams have also proven to be attractive synthetic targets, and crucial intermediates in the synthesis of numerous natural products.[1] Therefore, considerable efforts were directed to a great number of synthetic approaches to γ-lactam synthons. As they are considered the general methods for assembling γ-lactam unit, they are based on Rh-catalyzed intramolecular C−H insertion of diazo derivatives,[2] Pd-catalyzed cyclization,[3] *N*-heterocyclic carbene catalyzed addition of enals to imines,[4] addition of homoenolates to imines,[5] ring expansion of β-lactams,[6] and cycloaddition strategies.[7]

Recently, we have developed an alternative approach to β-carboethoxy-γ-lactam synthesis. The methodology is based on the reaction of bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene with imines via imino Mukaiyama-aldol type reaction mediated by $ZnCl_2$. Regarding the stereochemical outcome, the relative stereochemistry of the carboethoxy group at C-β and the aryl group at C-γ depends on the type of substituent on the nitrogen atom of the imines (eq 1).[8]



(1)

We now report our findings on a highly diastereoselective synthesis of the trans isomers of β-carboxy-γ-aryl-γ-lactams and their ethyl esters from the reaction of 2,5-bis(trimethylsilyloxy)furan (**1**) and imines catalyzed by $Sc(OTf)_3$. The 2,5-bis(trimethylsilyloxy)furan (**1**) was prepared according to the previously reported procedure.[9a] It has been used for the synthesis of γ-hydroxybutenolides[9] and as diene for the Diels−Alder reactions.[10] With 2,5-bis(trimethylsilyloxy)furan (**1**) in hand, we next examined the Lewis acid suitable for promoting the reaction. A collection of Lewis acids, i.e., $Ti(O^iPr)_4$ and $M(OTf)_x$, were tested and *N*-benzylimine derived from benzaldehyde was selected as a model substrate (Table 1). Compound **1** was treated with a THF solution of imine **2a** and Lewis acid at −78 °C and the reaction was allowed to proceed at room temperature (16 h). After being exposed to acidic aqueous stirring (NH_4Cl) at room temperature for 1 h followed by conventional workup, it provided γ-lactamcarboxylic acid **3a** with excellent diastereoselectivity (99:1 of trans:cis), which was

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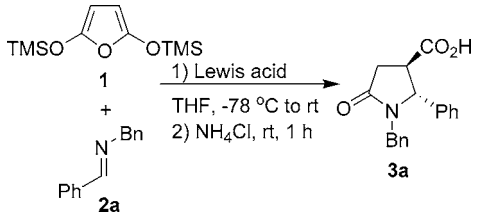
TABLE 1. Screening of Lewis Acids



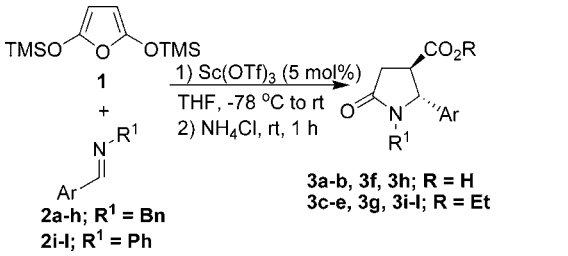
entry	Lewis acid[a]	yield (%);[b] trans:cis[c]
1	$Ti(O^iPr)_4$	60; 99:1
2	$Sc(OTf)_3$	86; 99:1
3	$Yb(OTf)_3$	67; 99:1
4	$Zn(OTf)_2$	74; 99:1
5	$In(OTf)_3$	80; 99:1

[a] 100 mol % for $Ti(O^iPr)_4$ and 5 mol % for $M(OTf)_x$. [b] Isolated yields after crystallization from ^{i}PrOH. [c] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude products before crystallization.

determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude product. Pure *trans*-**3a**, with yields ranging from 60% to 86% depending on the types of Lewis acid employed, was obtained after single crystallization from ^{i}PrOH. A stoichiometric amount of $Ti(O^iPr)_4$ showed moderate reactivity, affording lactam **3a** in moderate yield (60%, Table 1, entry 1). Metal triflates, $Yb(OTf)_3$, $Zn(OTf)_2$, $In(OTf)_3$, and $Sc(OTf)_3$, as catalysts gave better results (67−86%, Table 1, entries 2−5). Among these, $Sc(OTf)_3$ was found to be the best catalyst. In addition, $Sc(OTf)_3$-catalyzed Mukaiyama-aldol reactions and imine activation are extensively documented.[11]

The $Sc(OTf)_3$-catalyzed imino Mukaiyama-aldol type reaction of 2,5-bis(trimethylsilyloxy)furan (**1**) was further studied with other imine substrates and the results were summarized in Table 2. The diastereomeric ratios in all cases as shown in Table 2 were established from the ^{1}H NMR integration of the crude materials of the γ-lactamcarboxylic acids. The γ-lactam products were isolated either as the carboxylic acid derivative in the case when the crystallization was allowed or as ethyl ester by exposure of the crude mixture to $SOCl_2$ (3 equiv) in ethanol, −78 °C to room temperature for 5 h, followed by chromatographic purification and crystallization. Measurement of the diastereomeric ratios of the ethyl ester derivatives by ^{1}H NMR integration of the crude materials confirmed that no epimerization took placed under the esterification reaction conditions employed. Finally, relative stereochemistry of the γ-lactam products was established and assigned by analogy with our previous work.[8] Generally, *N*-benzylimine substrates (Table 2, entries 1−8) produced γ-lactam products with good to moderate yields (63−89%) with high diastereoselectivity (trans:cis = 99:1) except for *N*-benzylimine derived from 3,4-dimethoxybenzaldehyde (Table 2, entry 4, inseparable mixture of trans:cis = 90:10). From the experimental results, there is no obvious relationship between the electron density of the Ar group of the arylimine substrates and the yields of the corresponding γ-lactam products. The reaction of *N*-phenylimime also proceeded under the same reaction conditions, however,

TABLE 2. $Sc(OTf)_3$-Catalyzed Reaction of Compound 1 with Imines 2a−*l*



entry	imine 2	imine Ar	lactam 3	yield (%);[a] trans:cis[b]
1	**2a**	C_6H_5	**3a**	86; 99:1
2	**2b**	4-$MeOC_6H_4$	**3b**	72; 99:1
3	**2c**	3-$MeOC_6H_4$	**3c**	74; 99:1
4	**2d**	3,4-$(MeO)_2C_6H_3$	**3d**	65; 90:10
5	**2e**	4-MeC_6H_4	**3e**	70; 99:1
6	**2f**	4-ClC_6H_4	**3f**	89; 99:1
7	**2g**	4-$NO_2C_6H_4$	**3g**	63; 99:1
8	**2h**	2-furyl	**3h**	75; 99:1
9	**2i**	C_6H_5	**3i**	60; 80:20
10	**2j**	4-$MeOC_6H_4$	**3j**	70; 80:20
11	**2k**	3,4-$MeOC_6H_3$	**3k**	60; 80:20
12	**2*l***	4-ClC_6H_4	**3l**	65; 90:10

[a] Isolated yields of the acid or ethyl ester derivatives. [b] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude lactamcarboxylic acids before crystallization or exposure to esterification.

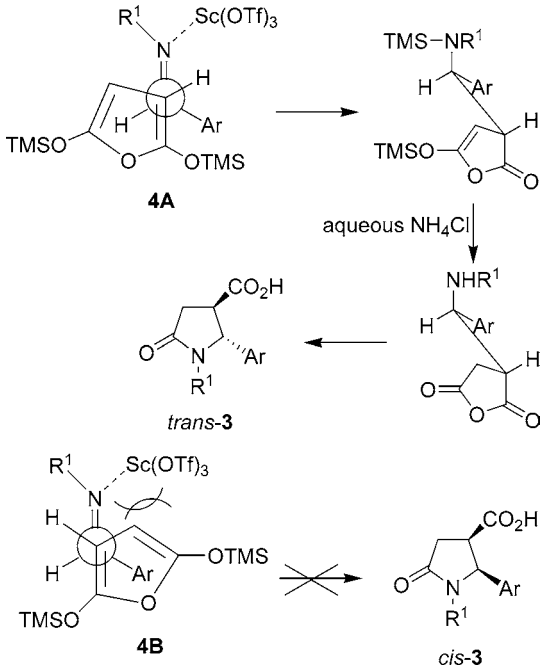
with lower yields and diminished diastereoselectivity (60−70% yields with trans:cis = 80:20 to 90:10; Table 2, entries 9−12). These results are in sharp contrast to our earlier work on the $ZnCl_2$-catalyzed reaction of bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene with *N*-benzyl- and *N*-phenylimimes (eq 1).[8] It is worth emphasizing that in the present work the trans isomer is preferentially formed regardless of the type of substituent (phenyl or benzyl) on the imine nitrogen. Even though the diastereoselectivities are moderate in case of *N*-phenylamine, pure diastereomer can be obtained by simple chromatographic purification.

On the basis of our previous report and our current studies, the possible mechanistic pathway of the imino Mukaiyama-aldol reaction of 2,5-bis(trimethylsilyloxy)furan (**1**) and imines catalyzed by $Sc(OTf)_3$ is illustrated in Scheme 1. The reaction was proposed to proceed via the staggered acyclic transition state.[12] It is assumed that the $Sc(OTf)_3$ occupied a coordination site on the nitrogen atom of the imine such that it is cis to the Ar group of the imine carbon. Now 2,5-bis(trimethylsilyloxy)furan (**1**) can approach the imine by transition state **4A** or **4B**. It is envisioned that the diastereoselectivity was governed by the steric effect caused by repulsion interaction of the $Sc(OTf)_3$ and the carbon atom (C_β) of the furan ring. Therefore, transition state **4A** is more favorable by positioning the least steric hydrogen atom at C_β of the furan ring being cis to the $Sc(OTf)_3$, leading preferably to trans γ-lactam after aqueous workup. The reaction of *N*-phenylimines with compound **1** leading to lower diastereoselection may result from slow cyclization due to the low nucleophilicity of the nitrogen atom. Thus, the equilibration at the stereogenic α-carbon adjacent to the anhydride group occurred.

(11) (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15−27. (b) Maity, B. C.; Puranik, V. G.; Sarkar, A. *Synlett* **2002**, 504−506. (c) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206−1215. (d) Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549−555.

(12) Fujisawa, H.; Takahashi, E.; Mukaiyama, T. *Chem. Eur. J.* **2006**, *12*, 5082−5093.

SCHEME 1



In summary, we have developed an efficient and highly diastereoselective synthesis of β-carboxy-γ-aryl-γ-lactams and their ethyl esters from the reaction of 2,5-bis(trimethylsilyloxy)-furan and imines catalyzed by $Sc(OTf)_3$. The methodology offers an alternative and efficient method for the synthesis of functionalized γ-lactams in terms of simplicity of the procedure, readily available starting materials, mild reaction conditions, and high diastereoselectivity. A study of the enantioselective synthesis of this type of γ-lactam is currently underway.

Experimental Section

General Procedure for the Reaction of 2,5-Bis(trimethylsilyloxy)furan (1) with Imines, Using $Sc(OTf)_3$ as a Catalyst. To a 50 mL round-bottomed flask charged with $Sc(OTf)_3$ (49 mg, 0.05 mmol) was added a solution of imine (1 mmol) in THF (1 mL) at room temperature. The mixture was further stirred at room temperature under an argon atmosphere for 30 min. The mixture was brought to −78 °C (dry ice−acetone) and a solution of 2,5-bis(trimethylsilyloxy)furan (**1**) (0.244 g, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. After 16 h, saturated aqueous NH_4Cl (2 mL) was added and the mixture was stirred at room temperature for 1 h before it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. Removal of solvents (aspirator then vacuo) yielded a crude γ-lactamcarboxylic acid whose diastereomeric ratio was determined by ^{1}H NMR integration. The crude material was purified by crystallization to yield the acid derivative or conversion to ethyl ester derivative ($SOCl_2$, EtOH, −78 °C to rt) before chromatographic purification when the crystallization of the first formed acid was found difficult.

Preparation of 1-Benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylic Acid (3a). To a 50 mL round-bottomed flask charged with $Sc(OTf)_3$ (49 mg, 0.05 mmol) was added a solution of imine **2a** (0.195 g, 1 mmol) in THF (1 mL) at room temperature. The mixture was further stirred at room temperature under an argon atmosphere for 30 min. The mixture was brought to −78 °C (dry ice−acetone) and a solution of 2,5-bis(trimethylsilyloxy)furan (**1**) (0.244 g, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. After 16 h, saturated aqueous NH_4Cl (2 mL) was added and the mixture was stirred at room temperature for 1 h before it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the diastereomeric ratio of the crude γ-lactamcarboxylic acid **3a** was determined by ^{1}H NMR integration to consist of a 99:1 mixture of trans:cis isomer. A pure trans isomer of **3a** was obtained after single crystallization from ^{i}PrOH (0.253 g, 86%, mp 171−172 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−6.95 (m, 10H), 5.09 (d, J = 14.7 Hz, 1H), 4.63 (d, J = 5.6 Hz, 1H), 3.47 (d, J = 14.7 Hz, 1H), 3.15−3.05 (m, 1H), 3.00−2.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 173.0, 138.6, 135.4, 129.2, 128.7, 128.6, 128.4, 127.7, 127.0, 63.5, 45.6, 44.5, 33.5. IR (KBr) ν_{max} 3448, 3033, 1731, 1655 cm^{-1}. MS m/z (%) relative intensity 296 ([M + 1]$^+$, 5), 295 ([M]$^+$, 30), 204 (100), 147 (22), 146 (51), 132 (29), 119 (19), 118 (60), 117 (13), 115 (22), 104 (45), 91 (42), 77 (11), 65 (14). HRMS (ESI-TOF) calcd for $C_{18}H_{17}NO_3Na$ [M + Na]$^+$ 318.1106, found 318.1110.

Preparation of Ethyl 5-Oxo-1,2-diphenylpyrrolidine-3-carboxylate (3i). To a 50 mL round-bottomed flask charged with $Sc(OTf)_3$ (49 mg, 0.05 mmol) was added a solution of imine **2i** (0.185 g, 1 mmol) in THF (1 mL) at room temperature. The mixture was further stirred at room temperature under an argon atmosphere for 30 min. The mixture was brought to −78 °C (dry ice−acetone) and a solution of 2,5-bis(trimethylsilyloxy)furan (**1**) (0.244 g, 1 mmol) in THF (2 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. After 16 h, saturated aqueous NH_4Cl (2 mL) was added and the mixture was stirred at room temperature for 1 h before it was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the diastereomeric ratio of the crude γ-lactamcarboxylic acid was determined by ^{1}H NMR integration to consist of an 80:20 mixture of trans:cis isomers. The ethyl ester derivative was then prepared according to General Procedure A: Thionyl chloride (0.2 mL, 3 mmol) was added dropwise to a stirred −78 °C dry EtOH (20 mL) solution. To this mixture was added a solution of a crude γ-lactamcarboxylic acid in dry EtOH (5 mL). The reaction mixture was allowed to warm to room temperature under an argon atmosphere. After 5 h, EtOH was removed (aspirator). The residue was quenched by slow addition of saturated aqueous Na_2CO_3 at 0 °C. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated. A crude ethyl ester residue was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs). The higher R_f was *trans*-**3i** (0.161 g, 52%, a pale yellow solid, mp 115−116 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.35−7.19 (m, 7H), 7.06 (t, J = 7.5 Hz, 1H), 5.53 (d, J_{trans} = 4.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.20−2.80 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.15, 172.09, 139.7, 137.5, 129.0, 128.7, 128.2, 126.1, 125.3, 122.7, 65.8, 61.6, 46.4, 34.3, 14.1. IR ($CHCl_3$) ν_{max} 1731 (C═O of ester), 1698 (C═O of amide) cm^{-1}. MS m/z (%) relative intensity 310 ([M + 1]$^+$, 24), 309 ([M]$^+$ 97), 236 (100), 208 (99), 180 (71), 91 (24), 77 (38), 50 (11). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.79; H, 6.25; N, 4.41. The lower R_f was *cis*-**3i** (25 mg, 8%, a pale yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 7.9 Hz, 2H) 7.35−7.10 (m, 7H), 7.06 (t, J = 7.3 Hz, 1H), 5.48 (d, J_{cis} = 8.8 Hz, 1H), 3.88−3.65 (m, 3H), 3.32 (dd, J = 17.3, 10.2 Hz, 1H), 2.72 (dd, J = 17.3, 8.8 Hz, 1H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 169.5, 137.8, 136.2, 128.7, 128.62, 128.60, 127.0, 125.3, 122.1, 65.1, 61.0, 43.7, 32.9, 13.7. IR (neat) ν_{max} 1732 (C═O of ester), 1707 (C═O of amide) cm^{-1}. MS m/z (%) relative

intensity 310 ([M + 1]$^+$, 29), 309 ([M]$^+$, 75), 281 (51), 236 (100), 208 (78), 91 (21), 77 (33), 65 (3). HRMS (ESI-TOF) calcd for $C_{19}H_{19}NO_3Na$ [M + Na]$^+$ 332.1263, found 332.1263.

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Supporting Information Available: Experimental details and characterization data of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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gem-Difluoromethylation of α- and γ-ketoesters: preparation of *gem*-difluorinated α-hydroxyesters and γ-butyrolactones

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Abstract—$PhSCF_2SiMe_3$ has been demonstrated as difluoromethyl carbanion synthon ($^-CF_2H$). It reacts chemoselectively with α- and γ-ketoesters at the keto group in the presence of a catalytic amount of TBAF in THF to give the corresponding α-hydroxy ester adducts as well as γ-*gem*-difluorophenylsulfanylmethylated-γ-butyrolactones in good yields. Reductive cleavage of the phenylsulfanyl group of these products employing Bu_3SnH/AIBN gives the corresponding *gem*-difluoromethylated α-hydroxyesters and γ-butyrolactones in good yields.

1. Introduction

Organofluorine compounds have received remarkable interest due to their utilities in several fields, such as medicinal, biological, and agricultural chemistry.[1] These compounds have been found to display interesting biological effects, which are attributed to the unique properties of the fluorine atom. Because of the potential applications in many fields, the fluorine-containing analogues of natural products as well as development of new synthetic methods for the incorporation of fluorine atom(s) into organic molecules have been extensively investigated.[2] Of particular interest is the introduction of a *gem*-difluoromethyl moiety into organic molecules. It has been reported that the difluoromethyl group (CF_2H) is isosteric and isopolar to a CH_2OH group.[1b,3] Direct methods for the preparation of *gem*-difluorinated compounds by reacting appropriate substrates with fluorinating agents such as DAST,[4] SF_4,[5] TBAF,[6] BrF_3,[7] Selectfluor[8] or NFSI[9] have been reported. Several nucleophilic *gem*-difluoromethylation building blocks employing difluoromethylphenylsulfone ($PhSO_2CF_2H$),[10] bromodifluoromethylphenylsulfone ($PhSO_2CF_2Br$),[11] (trifluoromethyl)trimethylsilane (CF_3SiMe_3),[12] [(difluoromethyl)(phenylsulfonyl)]trimethylsilane ($PhSO_2CF_2SiMe_3$),[13] [(difluoromethyl)(phenylsulfanyl)]trimethylsilane ($PhSCF_2SiMe_3$) (**1**),[14] and [difluoro(phenylseleno)methyl]trimethylsilane ($PhSeCF_2SiMe_3$)[15] have been extensively studied.

The report by Prakash et al.,[13,14b] Hu,[14c] and our recent complementary studies[14a] on the use of **1** as the *gem*-difluoromethylated building block with carbonyl compounds demonstrated the versatility of this strategy. We envisaged that with α-, β-, and γ-ketoesters as the carbonyl components, this technology would lead to high functionalized *gem*-difluoromethylated derivatives. We are pleased to report that such studies have been successful. Additionally, the chemoselectivity of **1** with γ-ketoesters led to γ-butyrolactones possessing *gem*-difluoromethyl group at γ-position.

2. Results and discussion

Initially, the reaction of **1** with methyl benzoate catalyzed by TBAF was studied. It was found that no expected benzoylated product, α,α-difluoro-α-phenylsulfanylacetophenone, could be detected. Methyl benzoate was completely recovered. Prakash[4b,16] reported that the same reaction using tetrabutylammonium triphenyldifluorosilicate (TBAT) provided a moderate yield of the expected benzoylated product. The reaction employing TBAF implied that the reaction of **1** toward ketoesters might be chemoselective providing the adducts arisen from the addition to only the keto functional group. Indeed, the treatment of α-ketoester **2a** with 1 equiv of **1** in the presence of 10 mol % of TBAF in THF at −78 °C to room temperature afforded the expected adduct **3a** in 68% yield after chromatography (Scheme 1 and Table 1, Entry 1). The best result was observed when 2 equiv of **1** was employed under the same conditions; **3a** was isolated in 87% yield (Table 1, Entry 1). Following the standard conditions, a variety of adducts of type **3** were prepared in good yields from a wide range of α-ketoesters (Scheme 1). The results are summarized in Table 1. Having the adducts **3** in hands, reductive cleavage of the phenylsulfanyl group to

Keywords: *gem*-Difluoromethylation; *gem*-Difluorinated γ-butyrolactones; *gem*-Difluorinated α-hydroxyesters; [(Difluoromethyl)(phenylsulfanyl)]trimethylsilane.
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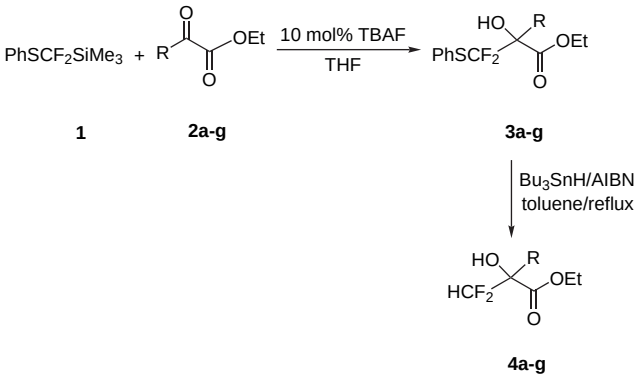
the corresponding *gem*-difluorinated compounds **4** was achieved by treatment with Bu_3SnH/AIBN in refluxing toluene for 15 h (Table 1).

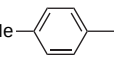
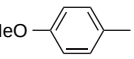
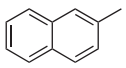
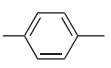
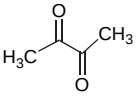
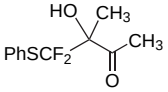


Scheme 1.

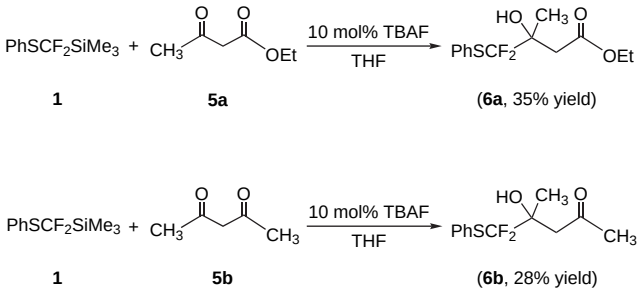
To investigate the generality of the reaction, we studied the reaction of **1** with β-ketoesters and β-diketones, which contain highly acidic methylene protons. The reaction of **1** with highly enolizable ethyl acetoacetate (**5a**) and 2,4-pentanedione (**5b**) under the standard conditions provided low yields of the corresponding adducts **5a** and **5b** (Scheme 2). The results may be due to competitive proton abstraction of the methylene protons of ethyl acetoacetate (**5a**) and 2,4-pentadione (**5b**) during the reaction.

Encouraged by the above results, we expected that when a γ-ketoester **7** was reacted under the same reaction conditions,

Table 1. Preparation of adducts **3** by fluoride-catalyzed addition of $PhSCF_2SiMe_3$ (**1**) to α-ketoesters **2** and their reduction to *gem*-difluorinated adducts **4**

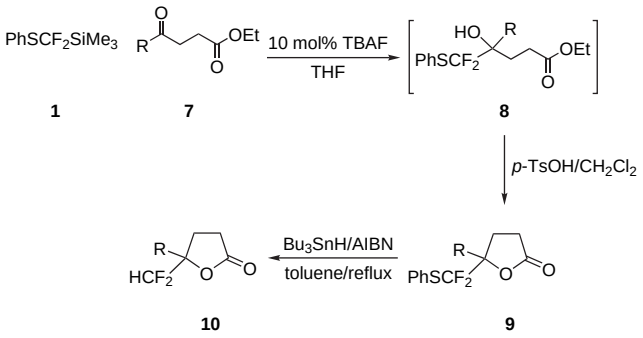
Entry	α-Ketoesters **2**	Adducts **3**[a,b] (%)	Products **4**[a] (%)
1	**2a**, R=CH_3	**3a**, 87 (68)[c]	**4a**, —[d]
2	**2b**, R=Ph	**3b**, 77 (60)[c]	**4b**, 74
3	**2c**, R = 	**3c**, 91 (65)[c]	**4c**, 80
4	**2d**, R = 	**3d**, 98	**4d**, 88
5	**2e**, R = 	**3e**, 98	**4e**, 91
6	**2f**, R = 	**3f**, 77	**4f**, 89
7	**2g**, R = 	**3g**, 96	**4g**, 90
8	**2h** 	 **3h**, 80 (77)[c]	—[d]

[a] Isolated yields by preparative thin-layer chromatography on silica gel.
[b] Two equivalents of **1** was employed.
[c] Yields given in parentheses are of the products obtained from the reaction using 1 equiv of **1**.
[d] The reductive product could not be isolated due to its volatility.



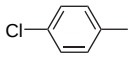
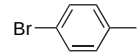
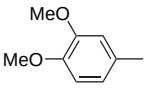
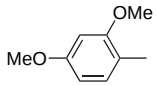
Scheme 2.

high chemoselectivity of the reaction leading to an adduct of type **8** would be obtained. Lactonization of the adduct **8** would furnish the corresponding γ-butyrolactone **9** containing *gem*-difluoro moieties (Scheme 3). As expected, fluoride-catalyzed addition reaction of **1** (2 equiv) with γ-ketoester **7a** proceeded with high chemoselectivity to give a mixture of adduct **8a** and γ-butyrolactone **9a**, which was treated with a catalytic amount of *p*-TsOH in CH_2Cl_2 to furnish γ-butyrolactone **9a** in 90% yield. The results for the preparation of γ-butyrolactones **9** are summarized in Table 2. Treatment of **9a** with Bu_3SnH and a catalytic amount of AIBN in refluxing toluene for 15 h afforded *gem*-difluorinated adduct **10a** in 76% yield. Under the same conditions, *gem*-difluorinated adducts **10** were prepared in good yields as summarized in Table 2.



Scheme 3.

Table 2. Preparation of *gem*-difluorinated γ-butyrolactones **9** and **10**

Entry	γ-Ketoesters **7**	**9**[a] (%)	**10**[a] (%)
1	**7a**, R=Ph	**9a**, 90	**10a**, 76
2	**7b**, R = 	**9b**, 72	**10b**, 74
3	**7c**, R = 	**9c**, 75	**10c**, 80[b] (R=Ph)
4	**7d**, R = 	**9d**, 93	**10d**, 85
5	**7e**, R = 	**9e**, 72	**10e**, 82

[a] Isolated yields by preparative thin-layer chromatography on silica gel.
[b] Both C–S and C–Br bonds were cleaved.

3. Conclusion

In conclusion, we have demonstrated a general and efficient *gem*-difluoromethylation of α-, β-, and γ-ketoesters by a two-step fluoride-catalyzed (phenylsulfanyl)difluoromethylation employing $PhSCF_2SiMe_3$ and reductive cleavage of the phenylsulfanyl group strategy. $PhSCF_2SiMe_3$ can be considered as a versatile difluoromethyl carbanion equivalent ($^-CF_2H$).

4. Experimental

4.1. General methods

The ^1H NMR spectra were recorded on either Bruker DPX-300 (300 MHz) or Bruker Avance-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. The ^{19}F NMR spectra were recorded on a Bruker Avance-500 (470 MHz) spectrometer and chemical shifts (δ) were measured with fluorotrichloromethane (δ=0) as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. The mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on an MS Micromass model VQ-TOF2. Elemental analyses were performed by a Perkin Elmer Elemental Analyzer 2400 CHN. Melting points were recorded on a Buechi 501 Melting Point Apparatus and uncorrected. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dry dichloromethane (CH_2Cl_2) and dry *N*,*N*-dimethylformamide (DMF) were obtained by distilling over phosphorous pentoxide and calcium hydride, respectively, and stored over molecular sieves (4 Å). Other common solvents (hexanes, ethyl acetate, methanol, and acetone) were distilled before use. All glasswares and syringes were oven dried and kept in a dessicator before use. Radial chromatography (chromatotron) and column chromatography were performed by using Merck silica gel 60 F_{254} (Art. 7749) and silica gel 60H (Art. 7736), respectively.

The starting compound $PhSCF_2SiMe_3$ (**1**) was prepared according to the literature procedure.[10e]

4.2. Preparation of compounds 3 by fluoride-catalyzed condensation of compound 1 with α-ketoesters

4.2.1. Preparation of ethyl 3,3-difluoro-2-hydroxy-2-methyl-3-(phenylsulfanyl)propanoate (3a). *General procedure*. To a mixture of compound **1** (0.928 g, 4.0 mmol) and ethyl pyruvate (**2a**) (0.232 g, 2.0 mmol) in THF (5 mL) was added 10 mol % TBAF (0.4 mL, 0.4 mmol, 1 M solution in THF). The reaction mixture was stirred at −78 °C to room temperature overnight, quenched with 1 M HCl (3 mL), and extracted with EtOAc (3×25 mL). The combined organic phases were washed successively with water and brine, and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by radial chromatography (SiO_2, 10% EtOAc in hexanes) to give a white solid of **3a** (0.240 g, 87% yield, mp=55–57 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=7.0 Hz, 2H, Ar*H*), 7.45–7.31 (m, 3H, Ar*H*), 4.40–4.30 (m, 2H, CH_2), 4.00 (br s, 1H, O*H*), 1.65 (s, 3H, CH_3), 1.35 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (C=O), 136.7 (CH), 129.9 (CH), 129.0 (2×CH), 128.9 (t, *J*=289.0 Hz, CF_2), 128.8 (CH), 125.5 (C), 78.0 (t, *J*=25.5 Hz, C), 63.2 (CH_2), 20.0 (CH_3), 13.8 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.74 (d, *J*=205.7 Hz, 1F), −83.48 (d, *J*=205.7 Hz, 1F). IR ($CHCl_3$): ν_{max} 3510 (OH), 1733 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 276 (M^+, 11), 231 (7), 203 (4), 185 (20), 183 (22), 159 (100), 109 (19), 77 (20). Anal. Calcd for $C_{12}H_{14}F_2O_3S$: C, 52.16; H, 5.11. Found: C, 52.34; H, 4.99.

4.2.2. Ethyl 3,3-difluoro-2-hydroxy-2-phenyl-3-(phenylsulfanyl)propanoate (3b). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl 2-oxo-2-phenylacetate (**2b**) (0.356 g, 2.0 mmol) in THF (5 mL) afforded a white solid of **3b** (0.260 g, 77% yield, mp=62–64 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 2H, Ar*H*), 7.54–7.50 (m, 2H, Ar*H*), 7.35–7.33 (m, 4H, Ar*H*), 7.30–7.28 (m, 2H, Ar*H*), 4.60 (br s, 1H, O*H*), 4.47–4.37 (m, 1H, CH*H*), 4.35–4.28 (m, 1H, C*H*H), 1.35 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (C=O), 136.8 (CH), 134.8 (C), 134.1 (CH), 130.0 (C), 129.8 (CH), 129.1 (CH), 128.9 (2×CH), 128.3 (t, *J*=290.9 Hz, CF_2), 128.0 (2×CH), 127.3 (CH), 125.9 (CH), 80.5 (t, *J*=25.7 Hz, C), 64.0 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −79.08 (d, *J*=205.6 Hz, 1F), −80.24 (d, *J*=205.6 Hz, 1F). IR (Nujol): ν_{max} 3475 (OH), 1719 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 339 (M^+, 6), 319 (24), 301 (17), 300 (13), 299 (59), 257 (43), 217 (26), 209 (25), 197 (18), 185 (15), 179 (23), 105 (100), 77 (25). Anal. Calcd for $C_{17}H_{16}F_2O_3S$: C, 60.34; H, 4.77. Found: C, 60.73; H, 4.81.

4.2.3. Ethyl 3,3-difluoro-2-hydroxy-3-(phenylsulfanyl)-2-*p*-tolylpropanoate (3c). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl α-oxo-*p*-tolylacetate (**2c**) (0.380 g, 2.0 mmol) in THF (5 mL) afforded a pale yellow liquid of **3c** (0.320 g, 91% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.2 Hz, 2H, Ar*H*), 7.50 (d, *J*=7.3 Hz, 2H, Ar*H*), 7.38–7.22 (m, 3H, Ar*H*), 7.15 (d, *J*=8.2 Hz, 2H, Ar*H*), 4.60 (br s, 1H, O*H*), 4.45–4.30 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.35 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (C=O), 136.6 (2×CH), 131.1 (C), 129.6 (CH), 128.7 (2×CH), 128.6 (2×CH), 128.4 (t, *J*=290.9 Hz, CF_2), 128.3 (C), 127.1 (2×CH), 125.7 (C), 80.3 (t, *J*=25.6 Hz, C), 63.7 (CH_2), 20.8 (CH_3), 13.6 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.89 (d, *J*=205.5 Hz, 1F), −79.99 (d, *J*=205.5 Hz, 1F). IR (neat): ν_{max} 3475 (OH), 1728 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 352 (M^+, 6), 316 (22), 315 (100), 313 (34), 287 (10), 271 (25), 231 (11), 119 (23). HRMS (ESI-TOF) calcd for $C_{18}H_{18}F_2O_3SNa$ $[M+Na]^+$: 375.0842; found: 375.0832.

4.2.4. Ethyl 3,3-difluoro-2-hydroxy-2-(4-methoxyphenyl)-3-(phenylsulfanyl)propanoate (3d). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl α-oxo-*p*-methoxyphenylacetate (**2d**) (0.382 g, 2.0 mmol) in THF (5 mL) afforded a yellow liquid of **3d** (0.360 g, 98% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J*=8.8 Hz, 2H, Ar*H*), 7.70 (d, *J*=7.2 Hz, 2H,

Ar*H*), 7.50–7.45 (m, 1H, Ar*H*), 7.40–7.35 (m, 2H, Ar*H*), 7.04–7.00 (m, 2H, Ar*H*), 4.75 (br s, 1H, O*H*), 4.50–4.40 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.35 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (C=O), 160.0 (C), 136.9 (C), 136.6 (CH), 130.6 (CH), 129.6 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (t, J=290.7 Hz, CF_2), 125.9 (C), 113.3 (CH), 80.2 (t, J=25.7 Hz, C), 63.7 (CH_2), 54.9 (CH_3), 13.7 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −79.08 (d, J=205.4 Hz, 1F), −80.20 (d, J=205.4 Hz, 1F). IR (neat): ν_{max} 3479 (OH), 1732 (C=O) cm^{-1}. MS: m/z (%) relative intensity 368 (M^+, 0.1), 275 (2), 247 (9), 209 (29), 159 (3), 136 (9), 135 (100), 109 (2), 108 (3), 107 (4), 77 (10). HRMS (ESI-TOF) calcd for $C_{18}H_{18}F_2O_4SNa$ $[M+Na]^+$: 391.0792; found: 391.0782.

4.2.5. Ethyl 3,3-difluoro-2-hydroxy-2-(2-methoxyphenyl)-3-(phenylsulfanyl)propanoate (3e). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl α-oxo-*o*-methoxyphenylacetate (**2e**) (0.382 g, 2.0 mmol) in THF (5 mL) afforded a white solid of **3e** (0.361 g, 98% yield, mp=89–91 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, J=7.9, 1.3 Hz, 1H, Ar*H*), 7.70–7.65 (m, 2H, Ar*H*), 7.45–7.30 (m, 4H, Ar*H*), 7.02 (ddd, J=7.9, 7.9, 1.3 Hz, 1H, Ar*H*), 6.85 (dd, J=8.3, 0.9 Hz, 1H, Ar*H*), 4.80 (br s, 1H, O*H*), 4.38–4.25 (m, 2H, CH_2), 3.75 (s, 3H, CH_3), 1.25 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2 (C=O), 157.5 (C), 136.9 (2×CH), 130.3 (2×CH), 129.2 (2×CH), 129.0 (2×CH), 128.6 (t, J=290.6 Hz, CF_2), 124.7 (C), 120.5 (CH), 111.7 (CH), 80.5 (t, J=25.0 Hz, C), 62.9 (CH_2), 55.6 (OCH_3), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −76.31 (d, J=208.2 Hz, 1F), −78.85 (d, J=208.2 Hz, 1F). IR (neat): ν_{max} 3451 (OH), 1747 (C=O) cm^{-1}. MS: m/z (%) relative intensity 368 (M^+, 0.2), 209 (13), 136 (9), 135 (100), 123 (7), 109 (5), 107 (4), 77 (28). Anal. Calcd for $C_{18}H_{18}F_2O_4S$: C, 58.69; H, 4.92. Found: C, 58.44; H, 4.92.

4.2.6. Ethyl 3,3-difluoro-2-hydroxy-2-(naphthalene-2-yl)-3-(phenylsulfanyl)propanoate (3f). According to the general procedure, the reaction of **1** (1.392 g, 6.0 mmol) with ethyl α-oxo-β-naphthylacetate (**2f**) (0.678 g, 3.0 mmol) in THF (5 mL) afforded a pale yellow liquid of **3f** (0.895 g, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (s, 1H, Ar*H*), 8.00 (d, J=8.8 Hz, 1H, Ar*H*), 7.79–7.78 (m, 1H, Ar*H*), 7.77–7.76 (m, 2H, Ar*H*), 7.55–7.53 (m, 4H, Ar*H*), 7.45–7.40 (m, 1H, Ar*H*), 7.35–7.30 (m, 2H, Ar*H*), 4.70 (br s, 1H, O*H*), 4.50–4.43 (m, 1H, C*H*H), 4.41–4.35 (m, 1H, CH*H*), 1.35–1.30 (m, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0 (C=O), 136.8 (2×CH), 133.4 (C), 132.8 (C), 131.6 (C), 130.9 (C), 129.8 (CH), 128.9 (2×CH), 128.8 (CH), 128.6 (t, J=246.5 Hz, CF_2), 127.6 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.2 (CH), 124.6 (CH), 80.7 (t, J=26.0 Hz, C), 64.1 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.78 (d, J=205.9 Hz, 1F), −79.72 (d, J=205.9 Hz, 1F). IR (neat): ν_{max} 3472 (OH), 1732 (C=O) cm^{-1}. MS: m/z (%) relative intensity 388 (M^+, 2), 351 (6), 307 (3), 278 (3), 267 (5), 259 (4), 247 (6), 229 (13), 156 (13), 155 (100), 128 (13), 127 (41), 126 (4), 77 (3). Anal. Calcd for $C_{21}H_{18}F_2O_3S$: C, 64.93; H, 4.67. Found: C, 65.03; H, 4.63.

4.2.7. Ethyl 2-(4-bromophenyl)-3,3-difluoro-2-hydroxy-3-(phenylsulfanyl)propanoate (3g). According to the general procedure, the reaction of **1** (1.392 g, 6.0 mmol) with ethyl α-oxo-*p*-bromophenylacetate (**2g**) (0.768 g, 3.0 mmol) in THF (5 mL) afforded a pale yellow liquid of **3g** (1.190 g, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75–7.55 (d, J=8.8 Hz, 2H, Ar*H*), 7.50–7.42 (m, 4H, Ar*H*), 7.35–7.33 (m, 1H, Ar*H*), 7.25–7.23 (m, 2H, Ar*H*), 4.48 (br s, 1H, O*H*), 4.37–4.30 (m, 1H, C*H*H), 4.27–4.23 (m, 1H, CH*H*), 1.25 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5 (C=O), 136.8 (2×CH), 133.0 (C), 131.2 (2×CH), 129.9 (CH), 129.2 (2×CH), 128.9 (2×CH), 128.1 (t, J=290.9 Hz, CF_2), 125.6 (C), 123.7 (C), 80.2 (t, J=26.2 Hz, C), 64.3 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −79.21 (d, J=206.6 Hz, 1F), −80.37 (d, J=206.6 Hz, 1F). IR (neat): ν_{max} 3470 (OH), 1732 (C=O) cm^{-1}. MS: m/z (%) relative intensity 415 (M^+, 5), 397 (5), 381 (13), 379 (25), 376 (15), 337 (17), 335 (15), 309 (14), 307 (13), 259 (12), 257 (25), 256 (74), 224 (22), 185 (100), 183 (99), 159 (10), 155 (12). Anal. Calcd for $C_{17}H_{15}BrF_2O_3S$: C, 48.93; H, 3.62. Found: C, 49.02; H, 3.53.

4.2.8. 4,4-Difluoro-3-hydroxy-3-methyl-4-(phenylsulfanyl)butan-2-one (3h). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with 2,3-butanedione (**2h**) (0.17 g, 2.0 mmol) in THF (5 mL) afforded a white solid of **3h** (0.394 g, 80% yield, mp=55–58 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J=7.1 Hz, 2H, Ar*H*), 7.45–7.32 (m, 3H, Ar*H*), 4.55 (br s, 1H, O*H*), 2.35 (s, 3H, CH_3), 1.60 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.1 (C=O), 136.8 (CH), 133.1 (CH), 130.0 (CH), 129.3 (CH), 129.2 (C), 129.0 (CH), 125.5 (t, J=285.3 Hz, CF_2), 81.7 (t, J=25.7 Hz, C), 25.1 (CH_3), 20.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ −79.80 (d, J=208.0 Hz, 1F), −81.50 (d, J=208.0 Hz, 1F). IR ($CHCl_3$): ν_{max} 3442 (OH), 1717 (C=O) cm^{-1}. MS: m/z (%) relative intensity 246 (M^+, 40), 203 (57), 159 (31), 121 (50), 110 (100), 109 (34), 77 (26). Anal. Calcd for $C_{11}H_{12}F_2O_2S$: C, 53.65; H, 4.91. Found: C, 53.64; H, 4.81.

4.2.9. Ethyl 4,4-difluoro-3-hydroxy-3-methyl-4-(phenylsulfanyl)butanoate (6a). According to the general procedure, the reaction of **1** (0.928 g, 4.0 mmol) with ethyl acetoacetate (**5a**) (0.26 g, 2.0 mmol) in THF (5 mL) afforded a colorless liquid of **6a** (0.163 g, 28% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J=7.0 Hz, 2H, Ar*H*), 7.35–7.30 (m, 1H, Ar*H*), 7.29–7.26 (m, 2H, Ar*H*), 4.75 (br s, 1H, O*H*), 4.25–4.15 (m, 2H, CH_2), 2.80 (d, J=15.9 Hz, 1H, C*H*H), 2.50 (d, J=15.9 Hz, 1H, CH*H*), 1.50 (s, 1H, CH_3), 1.20 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1 (C=O), 136.8 (2×CH), 131.5 (t, J=285.8 Hz, CF_2), 129.8 (CH), 128.9 (2×CH), 125.9 (C), 77.0 (t, J=24.1 Hz, C), 61.3 (CH_2), 39.3 (CH_2), 23.3 (CH_3), 14.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −83.80 (d, J=204.9 Hz, 1F), −84.28 (d, J=204.9 Hz, 1F). IR (neat): ν_{max} 3441 (OH), 1714 (C=O) cm^{-1}. MS: m/z (%) relative intensity 290 (M^+, 1), 197 (11), 177 (16), 149 (18), 135 (12), 131 (100), 110 (10), 109 (12), 103 (26), 85 (58). HRMS (ESI-TOF) calcd for $C_{13}H_{16}F_2O_3SNa$ $[M+Na]^+$: 313.0686; found: 313.0688.

4.2.10. 5,5-Difluoro-4-hydroxy-4-methyl-5-(phenylsulfanyl)pentan-2-one (6b). According to the general procedure,

the reaction of **1** (0.928 g, 4.0 mmol) with 2,4-pentanedione (**5b**) (0.2 g, 2.0 mmol) in THF (5 mL) afforded a colorless liquid of **6b** (0.184 g, 35% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64–7.62 (m, 2H, Ar*H*), 7.45–7.25 (m, 1H, Ar*H*), 7.40–7.37 (m, 2H, Ar*H*), 3.12 (d, J=16.9 Hz, 1H, C*H*H), 2.60 (d, J=16.9 Hz, 1H, CH*H*), 2.44 (s, 3H, CH_3), 1.60 (br s, 1H, O*H*), 1.50 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.4 (C=O), 137.5 (CH), 133.0 (t, J=286.0 Hz, CF_2), 130.7 (2×CH), 129.9 (2×CH), 127.2 (C), 76.9 (t, J=23.9 Hz, C), 47.9 (CH_2), 32.3 (CH_3), 22.7 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.86 (d, J=204.2 Hz, 1F), −83.82 (d, J=204.2 Hz, 1F). IR ($CHCl_3$): ν_{max} 3020 (OH), 1705 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 260 (M^+, 2), 202 (6), 160 (23), 159 (18), 110 (16), 109 (18), 101 (100), 77 (16), 65 (14), 59 (63). HRMS (ESI-TOF) calcd for $C_{12}H_{14}F_2O_2SNa$ $[M+Na]^+$: 283.0580; found: 283.0571.

4.3. Preparation of compounds 9 by fluoride-catalyzed condensation of compound 1 with γ-ketoesters

4.3.1. 5-(Difluoro(phenylsulfanyl)methyl)-5-phenyldihydrofuran-2(3*H*)-one (9a). *General procedure*. To a mixture of compound **1** (0.696 g, 3.0 mmol) and ethyl 4-oxo-4-phenylbutanoate (**7a**) (0.412 g, 2.0 mmol) in THF (5 mL) was added 10 mol % TBAF (0.3 mL, 0.3 mmol, 1 M solution in THF). The reaction mixture was stirred at −78 °C to room temperature overnight (15 h), quenched with 1 M HCl (3 mL), and extracted with EtOAc (3×25 mL). The organic phase was washed successively with water and brine, and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was treated with *p*-TsOH in CH_2Cl_2 at 0 °C. The resulting mixture was stirred at room temperature overnight (15 h) and extracted with EtOAc (3×20 mL). The combined organic phase was washed successively with water and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by radial chromatography (SiO_2, 30% EtOAc in hexanes) to give a pale yellow solid of **9a** (0.578 g, 90% yield, mp=75–78 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59–7.55 (m, 2H, Ar*H*), 7.51–7.48 (m, 2H, Ar*H*), 7.43–7.37 (m, 4H, Ar*H*), 7.33–7.29 (m, 2H, Ar*H*), 3.18–3.09 (m, 1H, C*H*H), 2.80–2.72 (m, 1H, CH*H*), 2.58–2.50 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.7 (C=O), 136.7 (2×CH), 130.0 (CH), 129.9 (C), 129.2 (CH), 129.1 (t, J=286.9 Hz, CF_2), 129.0 (2×CH), 128.4 (2×CH), 126.4 (2×CH), 122.7 (C), 88.3 (t, J=24.2 Hz, C), 30.2 (CH_2), 28.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.30 (d, J=209.4 Hz, 1F), −85.29 (d, J=209.4 Hz, 1F). IR (KBr): ν_{max} 1802 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 321 (M^+, 1), 162 (12), 161 (100), 133 (19), 117 (4), 115 (10), 106 (3), 105 (19), 77 (8). HRMS (ESI-TOF) calcd for $C_{17}H_{14}F_2O_2SNa$ $[M+Na]^+$: 343.0580; found: 343.0579.

4.3.2. 5-(4-Chlorophenyl)-5-(difluoro(phenylsulfanyl)methyl)dihydrofuran-2(3*H*)-one (9b). According to the general procedure, the reaction of **1** (0.464 g, 2.0 mmol) with ethyl 4-(chlorophenyl)-4-oxobutanoate (**7b**) (0.238 g, 1.0 mmol) in THF (3 mL) afforded a white crystal of **9b** (0.263 g, 72% yield, mp=102–104 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J=7.8 Hz, 4H, Ar*H*), 7.35–7.31 (m, 3H, Ar*H*), 7.28–7.22 (m, 2H, Ar*H*), 3.09–3.01 (m, 1H, C*H*H), 2.76–2.68 (m, 1H, CH*H*), 2.53–2.38 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4 (C=O), 136.7 (2×CH), 135.5 (C), 131.3 (C), 130.1 (CH), 129.0 (2×CH), 128.7 (2×CH), 127.9 (2×CH), 126.7 (t, J=223.1 Hz, CF_2), 124.9 (C), 88.0 (t, J=26.6 Hz, C), 30.2 (CH_2), 28.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.41 (d, J=210.1 Hz, 1F), −85.43 (d, J=210.1 Hz, 1F). IR (Nujol): ν_{max} 1799 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 355 (M^+, 2), 197 (33), 196 (11), 195 (100), 169 (10), 167 (11), 161 (5), 151 (8), 149 (16), 141 (20), 139 (64), 115 (10), 111 (23), 75 (9). Anal. Calcd for $C_{17}H_{13}ClF_2O_2S$: C, 57.55; H, 3.69. Found: C, 57.31; H, 3.41.

4.3.3. 5-(4-Bromophenyl)-5-(difluoro(phenylsulfanyl)methyl)dihydrofuran-2(3*H*)-one (9c). According to the general procedure, the reaction of **1** (0.930 g, 4.0 mmol) with ethyl 4-(bromophenyl)-4-oxobutanoate (**7c**) (0.568 g, 2.0 mmol) in THF (5 mL) afforded a white crystal of **9c** (0.544 g, 70% yield, mp=103–104 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58–7.55 (m, 2H, Ar*H*), 7.50–7.48 (m, 2H, Ar*H*), 7.45–7.40 (m, 3H, Ar*H*), 7.36–7.31 (m, 2H, Ar*H*), 3.15–3.10 (m, 1H, C*H*H), 2.82–2.76 (m, 1H, CH*H*), 2.60–2.46 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4 (C=O), 136.7 (2×CH), 136.0 (C), 131.7 (2×CH), 130.1 (CH), 129.0 (2×CH), 128.9 (t, J=286.9 Hz, CF_2), 128.2 (2×CH), 124.9 (C), 123.7 (C), 88.0 (t, J=26.6 Hz, C), 30.1 (CH_2), 28.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.46 (d, J=210.3 Hz, 1F), −85.49 (d, J=210.3 Hz, 1F). IR (Nujol): ν_{max} 1799 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 399 (M^+, 2), 242 (11), 241 (100), 240 (13), 239 (97), 213 (16), 211 (16), 185 (18), 183 (19), 116 (10), 77 (44). Anal. Calcd for $C_{17}H_{13}BrF_2O_2S$: C, 51.14; H, 3.19. Found: C, 51.40; H, 3.19.

4.3.4. 5-(Difluoro(phenylsulfanyl)methyl)-5-(2,5-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (9d). According to the general procedure, the reaction of compound **1** (1.92 g, 8.0 mmol) with ethyl 4-(2,5-dimethoxyphenyl)-4-oxobutanoate (**7d**) (1.30 g, 4.0 mmol) in THF (6 mL) afforded a white crystal of **9d** (1.427 g, 93% yield, mp=104–105 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J=8.0 Hz, 2H, Ar*H*), 7.40 (dd, J=7.0, 1.0 Hz, 1H, Ar*H*), 7.35–7.30 (m, 3H, Ar*H*), 6.95–6.88 (m, 2H, Ar*H*), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.25–3.19 (m, 1H, C*H*H), 2.82–2.69 (m, 2H, CH_2), 2.60–2.50 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2 (C=O), 153.4 (C), 151.1 (C), 136.8 (2×CH), 130.0 (t, J=289.0 Hz, CF_2), 129.8 (CH), 128.9 (2×CH), 125.8 (C), 125.6 (C), 116.1 (CH), 114.5 (CH), 113.4 (CH), 88.5 (d, J=26.8 Hz, C), 56.1 (CH_3), 55.9 (CH_3), 29.5 (CH_2), 28.4 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −80.96 (d, J=205.1 Hz, 1F), −84.15 (d, J=205.1 Hz, 1F). IR (KBr): ν_{max} 1788 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 380 (M^+, 14), 222 (14), 221 (100), 194 (12), 193 (97), 165 (15), 161 (16), 137 (9), 109 (4), 77 (8). Anal. Calcd for $C_{19}H_{18}F_2O_4S$: C, 59.99; H, 4.77. Found: C, 59.69; H, 4.66.

4.3.5. 5-(Difluoro(phenylsulfanyl)methyl)-5-(3,4-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (9e). According to the general procedure, the reaction of **1** (0.464 g, 2.0 mmol) with ethyl 4-(2,5-dimethoxyphenyl)-4-oxobutanoate (**7e**) (0.262 g, 1.0 mmol) in THF (3 mL) afforded a white crystal of **9e** (0.273 g, 72% yield, mp=102–105 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H, Ar*H*), 7.45–7.40 (m, 1H, Ar*H*), 7.35–7.30 (m, 2H,

Ar*H*), 7.15–7.10 (m, 2H, Ar*H*), 6.90 (d, *J*=8.4 Hz, 1H, Ar*H*), 3.15–3.08 (m, 1H, C*H*H), 2.85 (s, 6H, 2×OCH_3), 2.81–2.73 (m, 1H, CH*H*), 2.62–2.51 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8 (C=O), 149.8 (C), 148.8 (C), 136.6 (2×CH), 131.6 (CH), 129.3 (t, *J*=286.9 Hz, CF_2), 129.0 (C), 128.9 (2×CH), 125.3 (C), 119.0 (CH), 110.8 (CH), 109.8 (CH), 88.2 (t, *J*=24.3 Hz, C), 56.1 (CH_3), 55.9 (CH_3), 30.1 (CH_2), 28.1 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.31 (d, *J*=208.7 Hz, 1F), −85.18 (d, *J*=208.7 Hz, 1F). IR (Nujol): ν_{max} 1793 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 380 (M$^+$, 4), 266 (15), 222 (13), 221 (100), 193 (7), 192 (5), 166 (6), 165 (42), 125 (5), 91 (9). Anal. Calcd for $C_{19}H_{18}F_2O_4S$: C, 59.99; H, 4.77. Found: C, 60.25; H, 4.75.

4.4. Preparation of *gem*-difluorinated compounds 4 and 10

4.4.1. Ethyl 3,3-difluoro-2-hydroxy-2-phenylpropanoate (4b). *General procedure*. Argon was bubbled through a solution of **3b** (0.338 g, 1.0 mmol) in dry toluene (5 mL) for 30 min and Bu_3SnH (0.47 mL, 1.75 mmol) was added. Deoxygenation was continued for 5 min. AIBN (25 mg, 0.15 mmol) was added and the solution was refluxed for 15 h. Volatiles were evaporated and the residue was dissolved in EtOAc (5 mL). The solution was stirred overnight with KF/H_2O (30 mg /0.3 mL) and extracted with EtOAc (3×20 mL). The organic phase was washed successively with water and brine, and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by radial chromatography (SiO_2, hexanes then 20% EtOAc in hexanes) to give a colorless liquid of **4b** (0.170 g, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J*=7.6 Hz, 2H, Ar*H*), 7.45–7.31 (m, 3H, Ar*H*), 6.25 (t, *J*=54.4 Hz, 1H, CF_2H), 4.40–4.20 (m, 2H, CH_2), 3.90 (br s, 1H, O*H*), 1.35 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (C=O), 134.6 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 125.9 (CH), 125.7 (CH), 114.7 (t, *J*=247.9 Hz, CF_2H), 77.9 (t, *J*=21.1 Hz, C), 63.5 (CH_2), 13.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.15 (dd, *J*=278.0, 54.5 Hz, 1F), −133.86 (dd, *J*=278.0, 54.5 Hz, 1F). IR (neat): ν_{max} 3494 (OH), 1739 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 231 (M$^+$, 88), 214 (16), 213 (100), 194 (14), 193 (50), 179 (11), 109 (10), 105 (16). HRMS (ESI-TOF) calcd for $C_{11}H_{12}F_2O_3Na$ [M+Na]$^+$: 253.0652; found: 253.0649.

4.4.2. Ethyl 3,3-difluoro-2-hydroxy-2-*p*-tolylpropanoate (4c). According to the general procedure, the reaction of **3c** (0.352 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **4c** (0.236 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.3 Hz, 2H, Ar*H*), 7.10 (d, *J*=7.8 Hz, 2H, Ar*H*), 6.12 (t, *J*=54.4 Hz, 1H, CF_2H), 4.23–4.20 (m, 2H, CH_2), 3.95 (br s, 1H, O*H*), 2.10 (s, 3H, CH_3), 1.08 (t, *J*=6.9 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (C=O), 138.9 (C), 136.7 (C), 129.6 (CH), 129.4 (CH), 125.8 (CH), 125.5 (CH), 114.8 (t, *J*=247.6 Hz, CF_2H), 77.8 (t, *J*=20.9 Hz, C), 63.4 (CH_2), 20.9 (CH_3), 13.8 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.20 (dd, *J*=276.8, 54.3 Hz, 1F), −134.00 (dd, *J*=276.8, 54.3 Hz, 1F). IR (neat): ν_{max} 3501 (OH), 1739 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 245 (M$^+$, 4), 228 (13), 227 (100), 209 (7), 207 (22), 193 (10). HRMS (ESI-TOF) calcd for $C_{12}H_{14}F_2O_3Na$ [M+Na]$^+$: 267.0809; found: 267.0810.

4.4.3. Ethyl 3,3-difluoro-2-hydroxy-2-(4-methoxyphenyl)propanoate (4d). According to the general procedure, the reaction of **3d** (0.574 g, 1.5 mmol) with Bu_3SnH (2.6 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **4d** (0.338 g, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60–7.50 (m, 2H, Ar*H*), 7.00–6.80 (m, 2H, Ar*H*), 6.20 (t, *J*=54.5 Hz, 1H, CF_2H), 4.35–4.20 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 1.30 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (C=O), 160.1 (C), 127.3 (2×CH), 126.5 (C), 114.7 (t, *J*=248.0 Hz, CF_2H), 114.0 (2×CH), 77.6 (t, *J*=21.1 Hz, C), 63.5 (CH_2), 55.3 (CH_3), 14.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.96 (dd, *J*=276.8, 54.5 Hz, 1F), −133.93 (dd, *J*=276.8, 54.5 Hz, 1F). IR (neat): ν_{max} 3492 (OH), 1739 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 260 (M$^+$, 4), 259 (25), 244 (14), 143 (100), 209 (15), 187 (28), 140 (6), 139 (63), 135 (33), 109 (5), 91 (4), 77 (5). Anal. Calcd for $C_{12}H_{14}F_2O_4$: C, 55.38; H, 5.42. Found: C, 55.06; H, 5.54.

4.4.4. Ethyl 3,3-difluoro-2-hydroxy-2-(2-methoxyphenyl)propanoate (4e). According to the general procedure, the reaction of **3e** (0.259 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a white solid of **4e** (0.170 g, 91% yield, mp=73–75 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J*=7.8 Hz, 1H, Ar*H*), 7.35–7.30 (m, 1H, Ar*H*), 7.05 (ddd, *J*=7.8, 7.8, 1.1 Hz, 1H, Ar*H*), 6.90 (dd, *J*=8.3, 0.7 Hz, 1H, Ar*H*), 6.52 (t, *J*=54.5 Hz, 1H, CF_2H), 4.28–4.25 (m, 2H, CH_2), 4.20 (br s, 1H, O*H*), 3.85 (s, 3H, CH_3), 1.25 (t, *J*=7.8 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, acetone-d_6): δ 170.6 (C=O), 157.5 (C), 130.8 (CH), 128.7 (CH), 126.2 (C), 121.3 (CH), 115.0 (t, *J*=243.5 Hz, CF_2H), 112.2 (CH), 77.6 (t, *J*=21.2 Hz, C), 62.4 (CH_2), 55.9 (OCH_3), 14.2 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.69 (dd, *J*=280.1, 54.5 Hz, 1F), −132.14 (dd, *J*=280.1, 54.5 Hz, 1F). IR (Nujol): ν_{max} 3452 (OH), 1716 (C=O) cm^{-1}. MS: *m*/*z* (%) relative intensity 260 (M$^+$, 10), 243 (54), 188 (6), 187 (62), 167 (17), 157 (13), 139 (29), 135 (28), 121 (9), 109 (73), 107 (7), 92 (10), 91 (100), 77 (21), 65 (22). Anal. Calcd for $C_{12}H_{14}F_2O_4$: C, 55.38; H, 5.42. Found: C, 55.25; H, 5.34.

4.4.5. Ethyl 3,3-difluoro-2-hydroxy-2-(naphthalene-2-yl)propanoate (4f). According to the general procedure, the reaction of **3f** (0.679 g, 1.8 mmol) with Bu_3SnH (3.15 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **4f** (0.437 g, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12–8.10 (d, *J*=1.2 Hz, 1H, Ar*H*), 7.80–7.76 (m, 3H, Ar*H*), 7.68–7.65 (dd, *J*=8.8, 1.8 Hz, 1H, Ar*H*), 7.45–7.40 (m, 2H, Ar*H*), 6.27 (t, *J*=54.3 Hz, 1H, CF_2H), 4.35–4.22 (m, 2H, CH_2), 4.00 (br s, 1H, O*H*), 1.25 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6 (C=O), 133.3 (C), 132.9 (C), 131.9 (C), 128.5 (CH), 128.4 (CH), 127.5 (CH), 126.9 (CH), 126.5 (CH), 125.8 (CH), 123.1 (CH), 114.8 (t, *J*=248.1 Hz, CF_2H), 78.1 (t, *J*=21.1 Hz, C), 63.6 (CH_2), 14.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.97 (dd, *J*=277.3, 54.5 Hz, 1F), −133.45 (dd, *J*=277.3, 54.5 Hz,

1F). IR (neat): ν_{max} 3493 (OH), 1739 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 280 (M^+, 17), 263 (30), 215 (10), 207 (17), 159 (47), 156 (14), 155 (100), 133 (10), 128 (23), 127 (49), 126 (11). Anal. Calcd for $C_{15}H_{14}F_2O_3$: C, 64.28; H, 5.03. Found: C, 64.43; H, 5.05.

4.4.6. 5-(Difluoromethyl)-5-phenyldihydrofuran-2(3*H*)-one (10a). According to the general procedure, the reaction of **9a** (0.354 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **10a** (0.160 g, 76% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.30 (m, 5H, Ar*H*), 5.80 (t, *J*=55.5 Hz, 1H, CF_2H), 2.98–2.93 (m, 1H, C*H*H), 2.82–2.74 (m, 1H, CH*H*), 2.61–2.54 (m, 1H, CH*H*), 2.51–2.45 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9 (C=O), 136.6 (C), 129.1 (2×CH), 128.7 (CH), 125.8 (2×CH), 115.1 (t, *J*=248.8 Hz, CF_2H), 85.4 (t, *J*=23.7 Hz, C), 27.9 (CH_2), 27.7 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.88 (dd, *J*=279.7, 55.7 Hz, 1F), −130.52 (dd, *J*=279.7, 55.7 Hz, 1F). IR (neat): ν_{max} 1794 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 213 (M^+, 5), 162 (12), 161 (100), 133 (28), 117 (5), 105 (37), 91 (3), 77 (14). Anal. Calcd for $C_{11}H_{10}F_2O_2$: C, 62.26; H, 4.75. Found: C, 62.65; H, 4.62.

4.4.7. 5-(4-Chlorophenyl)-5-(difluoromethyl)dihydrofuran-2(3*H*)-one (10b). According to the general procedure, the reaction of **9b** (0.354 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a colorless liquid of **10b** (0.182 g, 74% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.55–7.40 (m, 4H, Ar*H*), 5.75 (t, *J*=55.7 Hz, CF_2H), 3.00–2.90 (m, 1H, C*H*H), 2.85–2.70 (m, 1H, CH*H*), 2.65–2.55 (m, 1H, C*H*H), 2.50–2.38 (m, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.6 (C=O), 135.4 (C), 135.0 (C), 129.0 (2×CH), 127.3 (2×CH), 114.8 (t, *J*=249.0 Hz, CF_2H), 85.0 (t, *J*=23.9 Hz, C), 27.9 (CH_2), 27.8 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −130.13 (d, *J*=55.4 Hz, 2F). IR (neat): ν_{max} 1799 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 247 (M^+, 6), 197 (34), 196 (12), 195 (100), 167 (24), 149 (7), 141 (13), 139 (33), 115 (5). Anal. Calcd for $C_{11}H_9F_2O_2$: C, 53.57; H, 3.68. Found: C, 53.66; H, 3.58.

4.4.8. 5-(Difluoromethyl)-5-(2,5-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (10d). According to the general procedure, the reaction of **9d** (0.39 g, 1.0 mmol) with Bu_3SnH (1.75 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a white crystal of **10d** (0.232 g, 85% yield, mp=85–87 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, *J*=2.2, 0.9 Hz, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 6.85–6.80 (m, 2H, Ar*H*), 6.25 (t, *J*=54.2 Hz, CF_2H), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.95 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5 (C=O), 154.0 (C), 149.2 (C), 126.3 (C), 114.2 (t, *J*=245.8 Hz, CF_2H), 112.5 (CH), 122.4 (CH), 112.2 (CH), 85.4 (dd, *J*=21.3, 18.3 Hz, C), 55.9 (2×OCH_3), 29.2 (CH_2), 27.8 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −128.53 (dd, *J*=279.7, 54.8 Hz, 1F), −134.03 (dd, *J*=279.7, 54.8 Hz, 1F). IR (Nujol): ν_{max} 1790 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 272 (M^+, 50), 221 (57), 194 (12), 193 (100), 165 (21), 150 (10), 137 (12), 107 (4), 77 (6), 55 (14). Anal. Calcd for $C_{13}H_{14}F_2O_4$: C, 57.35; H, 5.18. Found: C, 57.48; H, 5.26.

4.4.9. 5-(Difluoromethyl)-5-(3,4-dimethoxyphenyl)dihydrofuran-2(3*H*)-one (10e). According to the general procedure, the reaction of **9e** (0.19 g, 0.5 mmol) with Bu_3SnH (0.88 mmol) and a catalytic amount of AIBN in toluene (5 mL) afforded a white crystal of **10e** (0.112 g, 82% yield, mp=92–94 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 7.00–6.95 (m, 2H, Ar*H*), 6.90–6.80 (m, 1H, Ar*H*), 5.85 (t, *J*=55.8 Hz, CF_2H), 3.95 (s, 6H, 2×OCH_3), 2.96–2.85 (m, 1H, C*H*H), 2.83–2.75 (m, 1H, CH*H*), 2.64–2.57 (m, 1H, C*H*H), 2.53–2.45 (m, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.0 (C=O), 149.7 (C), 149.1 (C), 128.8 (C), 118.3 (CH), 115.1 (t, *J*=248.7 Hz, CF_2H), 111.1 (CH), 109.1 (CH), 85.3 (t, *J*=23.6 Hz, C), 56.0 (OCH_3), 55.9 (OCH_3), 28.0 (CH_2), 27.6 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.65 (dd, *J*=281.1, 56.5 Hz, 1F), −130.30 (dd, *J*=281.1, 56.5 Hz, 1F). IR (Nujol): ν_{max} 1779 (C=O) cm^{-1}. MS: *m/z* (%) relative intensity 272 (M^+, 20), 222 (11), 221 (100), 193 (12), 166 (10), 165 (47), 137 (5), 122 (4), 91 (3), 79 (4), 77 (6). Anal. Calcd for $C_{13}H_{14}F_2O_4$: C, 57.35; H, 5.18. Found: C, 57.59; H, 4.88.

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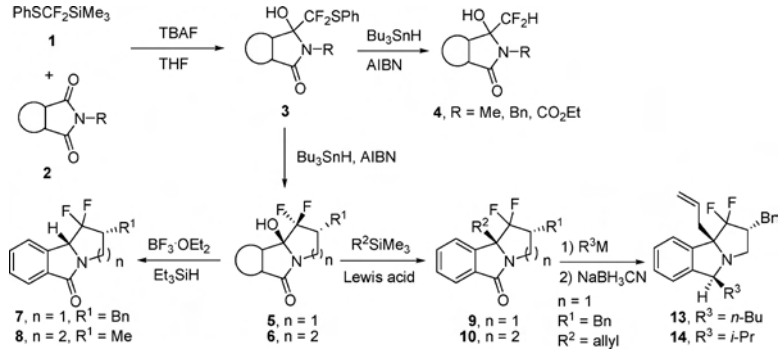

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Fluoride-Catalyzed Addition of $PhSCF_2SiMe_3$ to *N*-Substituted Cyclic Imides Followed by Radical Cyclization: General Synthetic Strategy of *gem*-Difluoromethylenated 1-Azabicyclic Compounds

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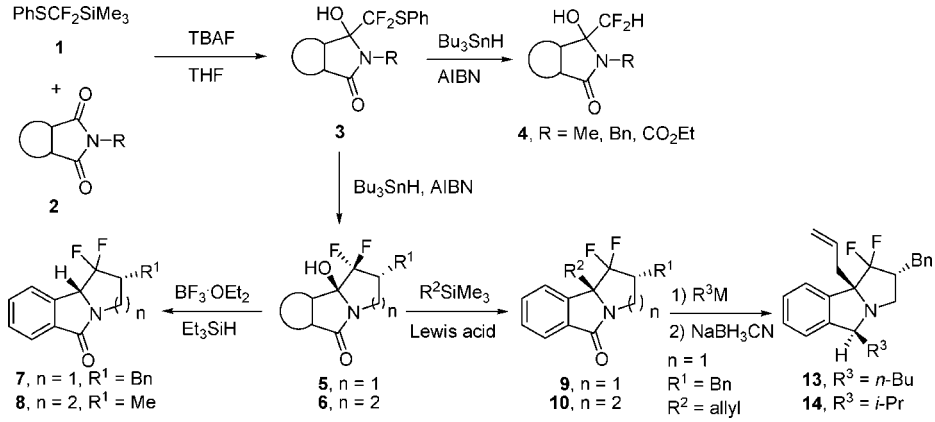

$PhSCF_2SiMe_3$ (**1**) was found, for the first time, to undergo fluoride-catalyzed nucleophilic difluoro(phenylsulfanyl)methylation reaction to cyclic imides **2**, affording the corresponding adducts **3** in moderate to good yields. Reductive cleavage of the phenylsulfanyl group of *N*-alkylated adducts **3** with Bu_3SnH/AIBN yielded *gem*-difluoromethylated products **4**. Under the same reduction conditions, *N*-alkenylated and *N*-alkynylated adducts **3** afforded the corresponding *gem*-difluoromethylenated 1-azabicyclic compounds **5** and **6** with *trans* stereoselectivity. These compounds were employed as precursors for preparing substituted *gem*-difluoromethylenated pyrrolizidinones and indolizidinones **7** and **8** by treatment with $Et_3SiH/BF_3 \cdot OEt_2$, and compounds **9** and **10** by nucleophilic displacement of the hydroxyl group, using organosilanes in the presence of $BF_3 \cdot OEt_2$. The synthesis of highly substituted *gem*-difluoromethylenated pyrrolizidines **13** and **14** was also demonstrated.

Introduction

gem-Difluoromethylene moiety has been incorporated into bioactive compounds due to its properties as an isopolar and isosteric substituent for an oxygen.[1] The presence of the *gem*-difluoromethylene group can enhance the biological properties of drug molecules.[2] Therefore, syntheses of *gem*-difluoromethylenated analogs of natural products have been extensively investigated.[3] Few general synthetic methods for constructing

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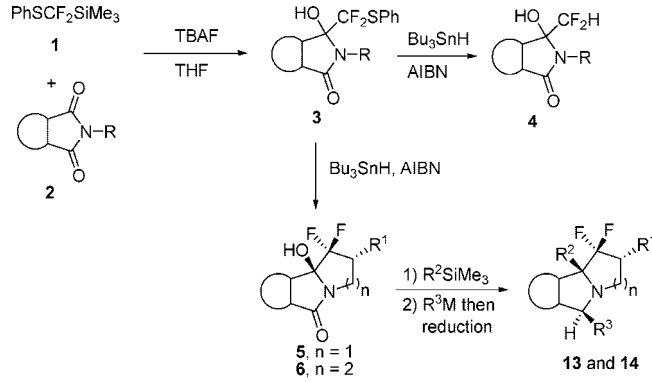
gem-difluoromethylenated compounds were previously reported.[4] It is still desirable to develop new flexible and facile strategies for the preparation of these compounds. Recently, $PhSCF_2SiMe_3$ (**1**) has been demonstrated as a useful *gem*-difluoromethylene building block.[5] Compound **1** reacts extensively with carbonyl derivatives,[6] γ-ketoesters,[7] imines,[8] and alkyl bromides,[9] providing convenient routes for the preparation of the corresponding *gem*-difluoromethylated alcohols, γ-lactones, amines, and alkanes, respectively. Furthermore, the stereoselective difluoromethylenation of chiral imines using $PhSCF_2SiMe_3$ (**1**) and the synthesis of chiral disubstituted *gem*-difluoromethylenated pyrrolidines have been recently reported.[10a] In addition, alternative new entries to assemble various fluorinated *S*-, *O*-, and *N*-heterocycles have also been developed.[10b−d]

As a part of our ongoing research interest in developing methodologies for the preparation of 1-azabicyclic derivatives,[11] we sought for a general method to synthesize *gem*-difluoromethylenated 1-azabicyclic analogs, employing **1** as a *gem*-difluoromethylene building block. It has been demonstrated that cyclic imides can undergo fluoride-catalyzed trifluoromethylation, using (trifluoromethyl)trimethylsilane (CF_3SiMe_3).[12] Hence, it is anticipated that fluoride-catalyzed nucleophilic difluoro-

SCHEME 1. Fluoride-Catalyzed Nucleophilic Difluoro(phenylsulfanyl)methylation of 1 with Imides 2 and Synthetic Conversion of the Resulting Adducts 3 into Compounds 4, 5, and 6 and Subsequently to Compounds 13 and 14



(phenylsulfanyl)methylation of **1** to cyclic imides **2** would generate the corresponding adducts **3**. When R groups of adducts **3** are allylic and homoallylic, reductive cleavage of the corresponding phenylsulfanyl moiety could afford radical intermediate that should then undergo intramolecular radical cyclization, providing *gem*-difluoromethylenated 1-azabicyclic compounds **5** and **6**, respectively (Scheme 1). Furthermore, nucleophilic displacement of the hydroxyl group and subsequent organometallic addition to carbonyl group followed by reduction would lead to highly substituted difluoromethylenated 1-azabicyclic compounds **13** and **14**. The proposed synthetic operations are summarized in Scheme 1.

Results and Discussion

The initial investigation involved fluoride-catalyzed nucleophilic difluoro(phenylsulfanyl)methylation of imide **2a** with $PhSCF_2SiMe_3$ (**1**). The expected adduct **3a** was obtained in 95% yield when the reaction was carried out using 10 mol % of anhydrous tetrabutylammonium fluoride (TBAF) in dry THF at −78 °C to room temperature overnight followed by acidic workup (2 M HCl; Table 1, entry 1). To demonstrate the generality of the reaction, the reactions of **1** with *N*-substituted phthalimide and succinimide derivatives, which were prepared by base-catalyzed *N*-alkylation of imides[13] with alkylating agents (Table 1, entries 1−6, 8, 10−13, 15 and 17), Mitsunobu reaction of imides with alcohols[14] (Table 1, entries 7, 14 and 16), and cross-olefin metathesis[15] of *N*-alkenylated imides with alkenes (Table 1, entries 9 and 18), were investigated. The results are summarized in Table 1. Except for some cases, the reactions of **1** with imide derivatives conducted under the standard conditions as for **3a** readily gave the corresponding adducts; yields range from moderate to good (Table 1). In case of imide **2i**, under the standard conditions, adduct with double bond transposition was obtained as a major product (33% yield). Gratifyingly, the reaction employing tetrabutylammonium triphenyldifluorosilicate (TBAT) in place of TBAF gave adduct **3i** in moderate yield

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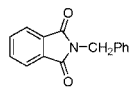
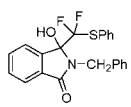
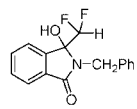
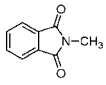
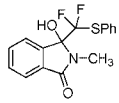
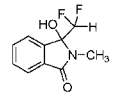
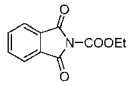
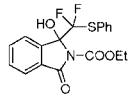
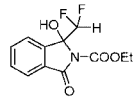
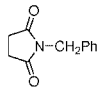
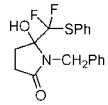
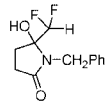
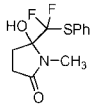
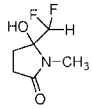
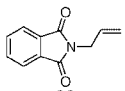
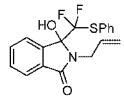
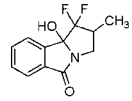
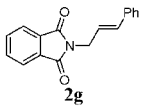
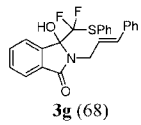
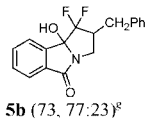
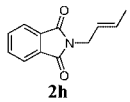
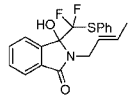
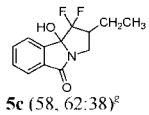
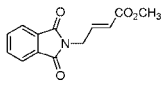
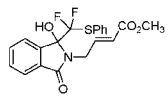
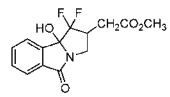
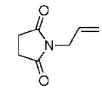
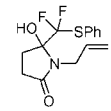
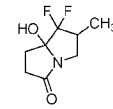
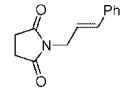
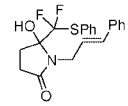
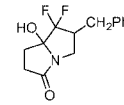
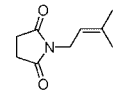
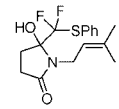
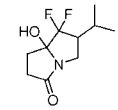
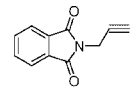
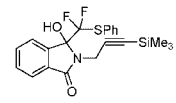
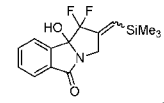
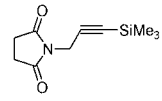
TABLE 1. Preparation of Adducts 3, *gem*-Difluoromethylated Lactams 4, and *gem*-Difluoromethylenated 1-Azabicyclic Compounds 5 or 6

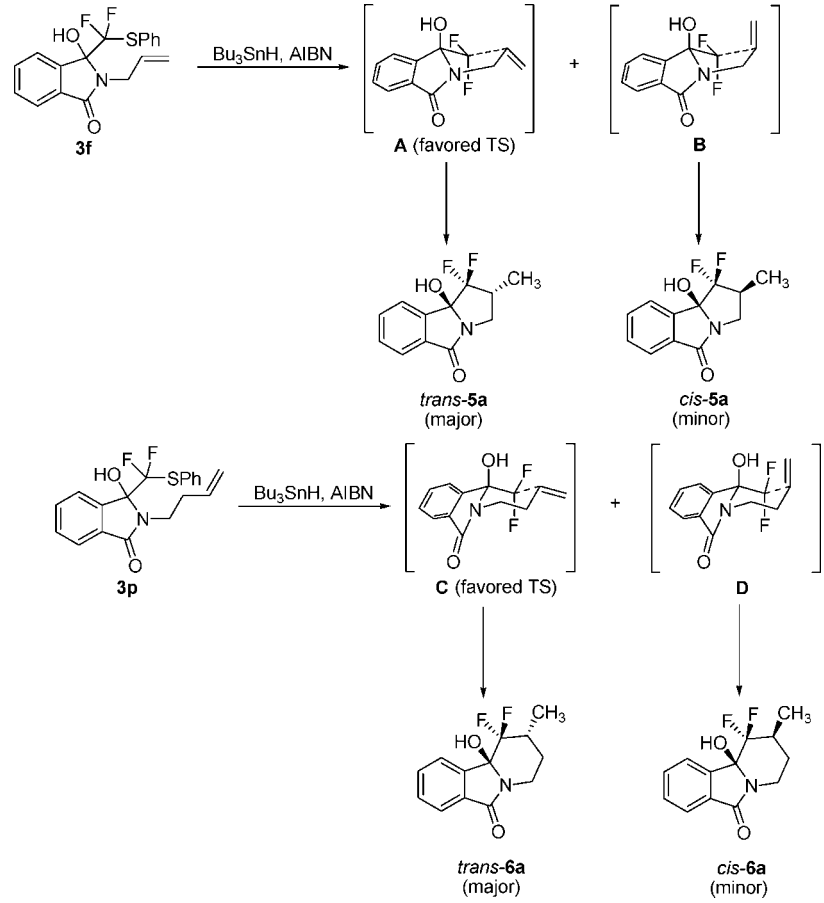
entry	imides **2**	**3** (% yield)[a, b]	**4**, **5** or **6** (% yield[a], *trans* : *cis*)
1	 **2a**	 **3a** (95)	 **4a** (80)
2	 **2b**	 **3b** (70)	 **4b** (70)
3	 **2c**	 **3c** (64)	 **4c** (78)
4	 **2d**	 **3d** (73)	 **4d** (66)
5	 **2e**	 **3e** (68)	 **4e** (86)
6	 **2f**	 **3f** (69)	 **5a** (73, 94:6)[g]
7	 **2g**	 **3g** (68)	 **5b** (73, 77:23)[g]
8	 **2h**	 **3h** (90, *E*:*Z*=79:21)[f]	 **5c** (58, 62:38)[g]
9	 **2i**	 **3i** (55)[d]	 **5d** (51, 52:48)[g]
10	 **2j**	 **3j** (62)	 **5e** (81, 90:10)[g]
11	 **2k**	 **3k** (68)	 **5f** (87, 66:34)[g]
12	 **2l**	 **3l** (83)	 **5g** (85, 64:36)[g]
13	 **2m**	 **3m** (68)[c]	 **5h** (73, *E*:*Z*=80:20)[f]
14	 **2n**	**3n** (45)[c]	**5i** (60, *E*:*Z*=85:15)[f]
15	**2o**	**3o** (50)[e]	**5j** (45, 50:50)[g]
16	**2p**	**3p** (76)	**6a** (63, 77:23)[g]
17	**2q**	**3q** (62)	**6b** (63, 72:28)[g]
18	**2r**	**3r** (77)	**6c** (61, 70:30)[g]

[a] Isolated yields. [b] Unless otherwise noted, all reactions were carried out employing 10 mol % TBAF/THF, −78 °C to rt. [c] By using 10 mol % TBAT/DMF, −78 °C to rt. [d] By using 10 mol % TBAT/THF, −78 to 15 °C, 5 h. [e] By using 10 mol % TBAT/THF, −78 °C to rt. [f] Ratio of *E*- and *Z*-isomers was determined by ^{1}H NMR integration of the crude product. [g] Ratios of isomers (*trans*/*cis*) were determined by ^{1}H NMR integration of the crude products.

(55%) and the double bond transposition adduct was not observed (Table 1, entry 9). It is also worth mentioning that the reaction of **1** with *N*-trimethylsilylpropargyl succinimide **2n** under the standard conditions furnished the expected product **3n** in only 2% yield, but the desilylated adduct **3o** was obtained as a major product (30% yield). However, the reaction employing 10 mol % of TBAT in dry DMF at −78 °C to room temperature gave the desired product **3n** in 45% yield together with **3o** (10% yield; Table 1, entry 14). Similar results, that is, **3n** (40% yield) and **3o** (8% yield) were obtained when the reaction was carried out using THF as the solvent. Interestingly, treatment of **1** with *N*-propargylphthalimide **2m** employing 10 mol % TBAT in DMF at −78 °C to room temperature unexpectedly provided trimethylsilylated derivative **3m** in 68% yield (Table 1, entry 13).

The reductive desulfenylation of adducts **3a**−**e** was achieved by treating with Bu_3SnH and a catalytic amount of AIBN in refluxing toluene. The *gem*-difluoromethylated products **4a**−**e** were obtained in moderate to good yields (66−86%; Table 1,

SCHEME 2. Proposed Transition States for the Radical Cyclization



entries 1−5).[6b,16] The *gem*-difluoromethyl radical intermediate, generated by CF_2−SPh bond cleavage of the adducts **3** containing the *N*-unsaturated substituents, could be trapped intramolecularly by an unsaturated functional moiety,[17] affording *gem*-difluoromethylenated 1-azabicyclic compounds **5**. Thus, under similar radical conditions, intramolecular radical cyclization of **3f** readily proceeded to provide **5a** in 73% yield as a 94:6 mixture of *trans*- to *cis*-isomers together with a small amount of the corresponding reduced product. A single *trans*-**5a** was obtained in pure form after purification by either preparative thin-layer chromatography on silica gel or crystallization. Its relative stereochemistry was established by X-ray crystallography (see Supporting Information).

To demonstrate the efficiency and viability of our methodology, series of *gem*-difluoromethylenated pyrrolizidine derivatives **5b**−**g**, as mixtures of isomers, were synthesized, in moderate to good yields, by treatment of adducts **3g**−**l** under standard radical conditions (Table 1, entries 7−12). Based on the X-ray crystallographic data of the major *trans*-isomer of **5a**, we assumed that the *trans*-isomers of **5b**−**g** were the major isomers. Notably, similar radical cyclization of *N*-propargyl substituted adducts proceeded smoothly, providing the cyclized products in moderate yields (Table 1, entries 13−15). Cyclization of silylated alkynyl derivatives **3m** and **3n** afforded compounds **5h** and **5i** as a mixture of *E*- and *Z*-isomers. The *E*-isomer was obtained as a major isomer, of which the stereochemistry was established by NOE experiments (see Supporting Information). Irradiation of the olefinic proton of **5h** or **5i** led to no enhancement of the allylic protons. The formation of tributylstannylated product **5j** (Table 1, entry 15) presumably resulted from consecutive addition of the tributylstannyl group to the triple bond followed by *gem*-difluoromethyl radical addition to the resulting vinylstannane derivative.[18] The presence of the exocyclic methylene moiety in compounds of types **5h** and **5i** should be valuable for further synthetic modification.

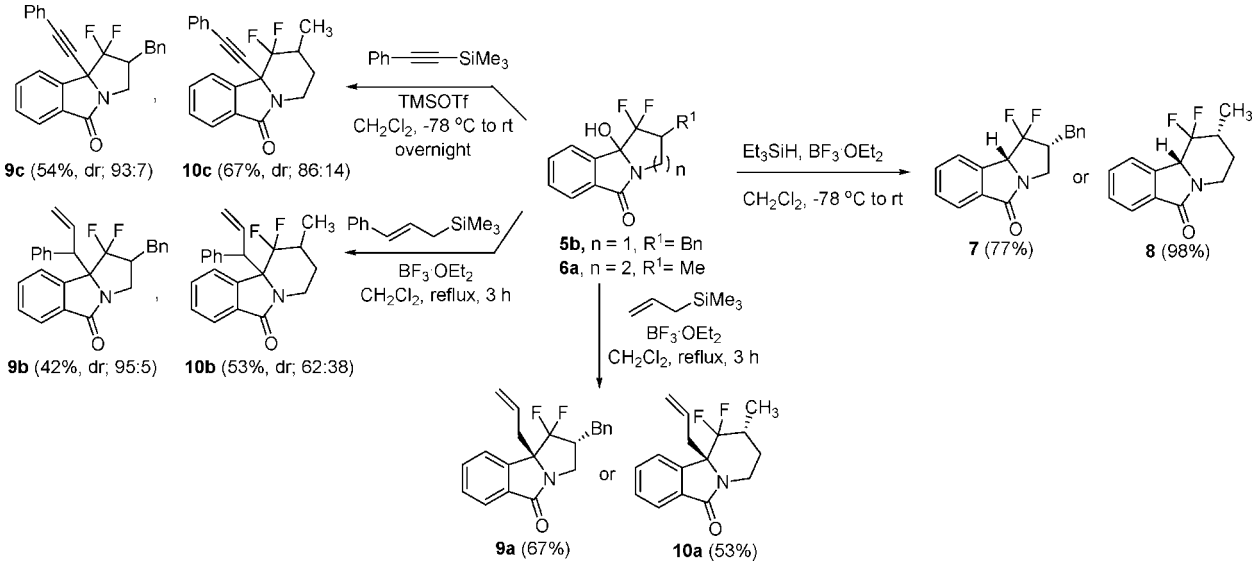
Having established an efficient access to *gem*-difluoromethylenated pyrrolizidine derivatives **5**, we further demonstrated that our method could be used as a general route for the synthesis of *gem*-difluoromethylenated indolizidine derivatives **6**. Thus, *N*-homoallylated adducts **3p**−**r** were treated with Bu_3SnH/AIBN in refluxing toluene, yielding the corresponding *gem*-difluoromethylenated indolizidines **6a**−**c** as a mixture of *trans*- and *cis*-isomers (Table 1, entries 16−18). The relative stereochemistry of the major *trans*-**6a** was confirmed by X-ray crystallography (see Supporting Information).

(16) Buttle, L. A.; Motherwell, W. B. *Tetrahedron Lett.* **1994**, *35*, 3995–3998.

(17) Radical mediated the construction of 1-azabicyclic compounds, see for examples: (a) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: New York, 2003. (b) Chen, M.-J.; Tsai, Y.-M. *Tetrahedron Lett.* **2007**, *48*, 6271–6274. (c) Bryans, J. S.; Large, J. M.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2905–2910. (d) Keusenkothen, P. F.; Smith, M. B. *Tetrahedron* **1992**, *48*, 2977–2992. (e) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802–4809. (f) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397–5400. (g) Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201–8209. (h) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209–8217. (i) Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *Tetrahedron Lett.* **1982**, *23*, 4765–4768.

(18) (a) Huang, J.-M.; Hong, S.-C.; Wu, K.-L.; Tsai, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 3047–3050. (b) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831–4834. (c) Capella, L.; Montevecchi, P. C.; Nanni, D. J. *J. Org. Chem.* **1994**, *59*, 3368–3374.

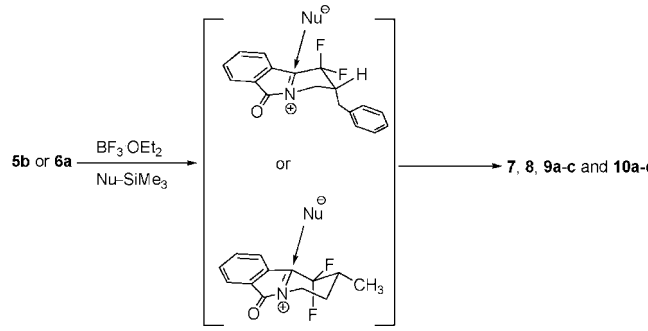
SCHEME 3. Lewis Acid-Catalyzed Nucleophilic Substitution of the Hydroxyl Group of Compounds 5b and 6a



The stereochemical outcomes of compounds **5** and **6** can be rationalized as shown in Scheme 2. The radical mediated cyclization was proposed to proceed via 5-*exo* or 6-*exo* cyclization mode.[19] Transition states **A** and **C** are energetically more favorable due to minimized steric interaction between the pseudoaxial hydroxyl group and the vinylic double bond, resulting in the formation of thermodynamically more stable *trans*-isomer of pyrrolidine or piperidine heterocycles.

Having a general route to synthesize derivatives **5** and **6**, we subsequently focused on the synthetic utilities of these adducts as precursors for the preparation of substituted *gem*-difluoromethylenated pyrrolizidines and indolizidines. It is anticipated that the presence of hydroxyl group in adducts **5** and **6** should provide a convenient access to an iminium intermediate,[20,21] which, in principle, can be trapped by an appropriate nucleophile. The results are summarized in Scheme 3. The adducts **5b** (*trans*/*cis*; 77:23) and **6a** (*trans*/*cis*; 88:12) were reduced with $BF_3 \cdot OEt_2$ and Et_3SiH[22] in CH_2Cl_2 at −78 °C to room temperature, generating the corresponding lactams **7** (77% yield) and **8** (98% yield) as a single isomer, as confirmed by the NOE experiments (see Supporting Information). Alkylation of **5b** with Grignard reagents (MeMgBr or *i*-PrMgCl in THF in the presence of $BF_3 \cdot OEt_2$ at 0 °C to rt, overnight) or organocoppers (*n*-Bu_2CuLi or *n*-$Bu_2Cu(CN)Li_2$ in THF in the presence of $BF_3 \cdot OEt_2$ at −30 °C to rt overnight) was unsuccessful, and only starting material was recovered. However, allylation reaction of **5b**, employing allyltrimethylsilane with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at −78 °C to rt overnight, led to **9a** in low yield (10% yield) together with recovery of **5b**. Gratifyingly, when the reaction was performed under refluxing conditions for 3 h, **9a** was obtained in moderate yield (67% yield). Similarly, under the same conditions, **10a** was synthesized in 53% yield from the corresponding compound **6a**. Both compounds **9a** and **10a** were obtained as a single isomer (see Supporting Information). Similarly, treatment of **5b** and **6a** with cinnamyltrimethylsilane afforded adducts **9b** and **10b**, respectively, as a mixture of diastereomers, as shown in Scheme 3. The reactions of **5b** and **6a** with phenyltrimethylsilylacetylene employing trimethylsilyl triflate (TMSOTf) as the Lewis acid at −78 °C to rt overnight provided the respective adducts **9c** (54% yield as a 93:7 mixture of isomers) and **10c** (67% yield as a 86:14 mixture of isomers). The use of $BF_3 \cdot OEt_2$, $SnCl_4$, and $TiCl_4$ did not furnish to the desired products but led to the recovery of the starting material **5b** and phenylacetylene. This result may be due to extensive decomposition of phenyltrimethylsilylacetylene to phenylacetylene prior to its addition to iminium ion intermediate. The relative *trans* stereochemistries of adducts **7** and **9** could be rationalized based on the fact that the nucleophiles (hydride or organosilanes) attack the initially formed iminium ion intermediate from the face opposite to the benzyl group to avoid steric interaction (Scheme 4). In addition, attack of nucleophiles to the iminium ion derived from **6a** from the pseudoaxial direction

SCHEME 4. Proposed Transition States for the Formation of *trans*-Isomers of Products 7−10



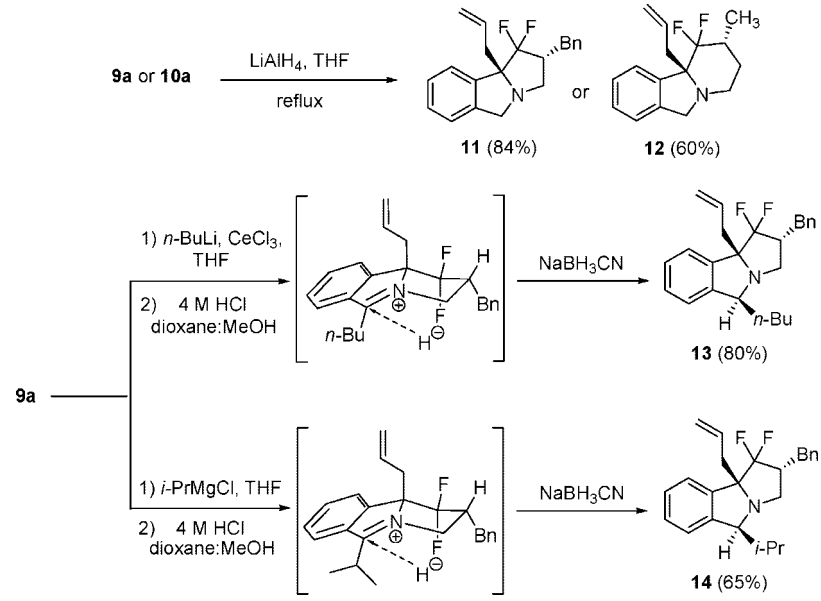
(19) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.

(20) For reviews on *N*-acyliminium ion chemistry, see: (a) de Koning, H.; Speckamp, W. N. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme Medical Publishers: New York, 1995; Vol. E21, p 1953. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.

(21) For some recent examples on the reactions of *N*-acyliminium ions with carbon nucleophiles, see: (a) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577–1580. (b) Vieira, A. S.; Ferreira, F.; Fiorante, P. F.; Guadagnin, R. C.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 3306–3314. (c) Morgan, I. R.; Yazici, A.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 1409–1419. (d) Yu, D.-S.; Xu, W.-X.; Liu, L.-X.; Haung, P.-Q. *Synlett* **2008**, 1189–1192. (e) Zhang, F.; Simpkins, N. S.; Wilson, C. *Tetrahedron Lett.* **2007**, *48*, 5942–5947. (f) Tranchant, M.-J.; Moine, C.; Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V. *Tetrahedron Lett.* **2006**, *47*, 4477–4480. (g) Osante, I.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2004**, *45*, 1253–1256. (h) Ollero, L.; Mentink, G.; Rutjes, F. P. J. T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 1331–1334.

(22) For an example, see Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651–1657.

SCHEME 5. Preparation of Alkyl-Substituted *gem*-Difluoromethylenated Pyrrolizidines 11, 13, and 14 and Indolizidine 12



could be further explained by stereoelectronic principle, leading preferably to the *trans*-isomers of adducts **8** and **10**.

The conversions of compounds **9a** and **10a** to alkyl-substituted *gem*-difluoromethylenated pyrrolizidines and indolizidines proceeded smoothly (Scheme 5). Reduction of compounds **9a** and **10a** using $LiAlH_4$ in refluxing THF provided the corresponding *gem*-difluoromethylenated pyrrolizidine **11** (84% yield) and indolizidine **12** (60% yield), respectively (Scheme 5). The reaction of **9a** with *n*-BuLi/$CeCl_3$ in THF[23] followed by acidification generating in situ iminium ion intermediate, which was subsequently reduced by sodium cyanoborohydride ($NaBH_3CN$) to afford butyl-substituted *gem*-difluoromethylenated pyrrolizidine **13** in 80% yield as a single diastereomer. Similarly, a single diastereomer of isopropyl-substituted *gem*-difluoromethylenated pyrrolizidine **14** was produced in 65% yield. The relative stereochemistries of compounds **11**−**14** were established by NOE experiments (see Supporting Information). The observed stereochemical outcomes of the reactions can be explained that the addition of organometallic reagents followed by acidification afforded iminium ions which were preferably reduced from the less sterically hindered face opposite to the allyl substituent (Scheme 5). It is worth mentioning that compound **10a** did not react with either *n*-BuLi/$CeCl_3$ or *i*-PrMgCl in THF under the same conditions as for **9a**.

Conclusion

In conclusion, we have successfully developed for the novel fluoride-catalyzed nucleophilic difluoro(phenylsulfanyl)methylation reactions of $PhSCF_2SiMe_3$ to succinic and phthalimide derivatives. The resulting adducts were employed as useful precursors for the preparation of *gem*-difluoromethylenated pyrrolizidines and indolizidines. The synthetic operation involves sequential intramolecular radical cyclization, nucleophilic displacement of the hydroxyl functionality using Lewis acid/allyltrimethylsilanes or trimethylsilylacetylenes, organometallic addition employing *n*-BuLi/$CeCl_3$ and *i*-PrMgCl onto the carbonyl group of the γ-lactam moiety, followed by reduction of the resulting adducts with $NaBH_3CN$. The synthetic application of our method for preparation of *gem*-difluoromethylenated analogs of some polyhydroxylated natural products is currently being investigated.

(23) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398–404.

Experimental Section

General Procedure for the Preparation of Compounds 3. 2-Benzyl-3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-isoindolin-1-one (3a). To a mixture of compound **1** (0.928 g, 4 mmol) and 2-benzylisoindoline-1,3-dione (**2a**; 0.470 g, 2 mmol) in THF (5 mL), was added 10 mol % TBAF (0.4 mL, 0.4 mmol, 1 M solution in THF). The reaction mixture was stirred at −78 °C followed by slowly warming up to room temperature overnight. The solution was quenched with 1 M HCl (3 mL) and extracted with EtOAc (3 × 25 mL). The organic phase was washed successively with water and brine and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by radial chromatography (SiO_2, 10−20% EtOAc in hexanes) to give a white crystal of **3a** (0.753 g, 95% yield, mp = 142−144 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86−7.83 (m, 1H, Ar*H*), 7.72−7.68 (m, 1H, Ar*H*), 7.60−7.58 (m, 2H, Ar*H*), 7.35−7.25 (m, 3H, Ar*H*), 7.20−7.10 (m, 7H, Ar*H*), 4.95 (d, J = 15.6 Hz, 1H, C*H*H), 4.45 (d, J = 15.6 Hz, 1H, CH*H*), 3.85 (br s, 1H, O*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.3 (C=O), 141.9 (C), 137.5 (2 × C), 136.7 (2 × CH), 132.8 (CH), 131.5 (C), 131.0 (2 × CH), 130.1 (CH), 129.24 (t, J = 187.5 Hz, CF_2), 129.0 (2 × CH), 128.5 (3 × CH), 127.4 (CH), 124.2 (CH), 123.8 (CH), 91.2 (t, J = 25.0 Hz, C), 43.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −80.48 (d, J = 211.0 Hz, 1F), −81.57 (d, J = 211.0 Hz, 1F). IR (nujol): ν_{max} 3207br, 1682s, 1612s, 1612m, 1497m, 1471s, 1456s, 1455s, 1427m, 1397s, 1361s, 1163s, 1137m, 1108m, 1073m, 1061s, 1027m, 1012m, 974m, 945m, 907m, 897m, 886m, 845m, 823m, 770s, 752s, 709s, 700s, 690s cm^{-1}. MS: *m*/*z* (%) relative intensity 398 (M^+, 10), 380 (7), 250 (6), 238 (47), 161 (11), 160 (100), 91 (20), 65 (7). HRMS (ESI-TOF) Calcd for $C_{22}H_{17}F_2NO_2SNa$ [M + Na]$^+$, 420.0846; found, 420.0851.

General Procedure for the Reductive Cyclization of Compounds 3 to Compounds 5. Preparation of 1,1-Difluoro-9b-hydroxy-2-methyl-2,3-dihydro-1*H*-pyrrolo[2,1-a]isoindol-5(9b*H*)-one (5a). Argon was bubbled through a solution of **3f** (0.374 g, 1 mmol) in toluene (2 mL) for 30 min, and a mixture of Bu_3SnH (0.47 mL, 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in toluene

(8 mL) was added dropwise at reflux over a 1 h period followed by refluxing for an additional 4 h. Volatiles were evaporated and the tin byproduct were removed by column chromatography (SiO_2, CH_2Cl_2 then EtOAc) to give a crude product, which was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to afford white crystals of **5a** (0.191 g, 73% yield, mp = 122−125 °C) as a 94:6 mixture of *trans*- and *cis*-isomers. ^{1}H NMR (500 MHz, $CDCl_3$, *cis*-isomer marked*): δ 7.68−7.64 (m, 6H, ArH of *trans*- and *cis*-isomers), 7.57−7.55 (m, 2H, ArH of *trans*- and *cis*-isomers), 4.12* (dd, J = 12.0, 9.3 Hz, 1H, CHH), 3.72 (br s, 2H, OH of *trans*- and *cis*-isomers), 3.68−3.63 (m, 1H, CHH), 3.39−3.27 (m, 3H, CHH of the *trans*-isomer and CH of *trans*- and *cis*-isomers), 3.13* (dd, J = 12.0, 4.9 Hz, 1H, CHH), 1.50* (d, J = 7.5 Hz, 3H, CH_3), 1.19 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7 (C═O), 141.4 (C), 133.2 (CH), 132.9 (C), 130.9 (CH), 123.9 (CH), 123.2 (CH), 122.9 (t, J = 258.2 Hz, CF_2), 93.1 (t, J = 25.1 Hz, C), 46.4 (d, J = 7.4 Hz, CH_2), 39.3 (t, J = 22.7 Hz, CH), 9.5 (d, J = 7.1 Hz, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$, *cis*-isomer marked*): δ −101.16* (dd, J = 232.2, 23.5 Hz, 1F), −126.86* (d, J = 232.2 Hz, 1F), −127.82 (dd, J = 220.9, 24.9 Hz, 1F), −129.60 (dd, J = 220.9, 6.8 Hz, 1F). IR (nujol): ν_{max} 3237br, 1681s, 1616s, 1469s, 1378m, 1239m, 1147m, 1123m, 1958m, 1003m, 759s, 709m, 701m, 604m cm^{-1}. MS: *m*/*z* (%) relative intensity 239 (M^+, 33), 203 (22), 201 (62), 200 (100), 188 (66), 172 (23), 161 (34), 160 (42), 145 (27), 133 (48), 132 (22), 125 (25), 117 (59), 91 (28), 77 (41). HRMS (ESI-TOF) Calcd for $C_{12}H_{11}F_2NO_2Na$ $[M + Na]^+$, 262.0656; found, 262.0634.

General Procedure for the Preparation of Compounds 9 and 10. Preparation of (2*R,9b*R**)-9b-Allyl-2-benzyl-1,1-difluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*a*]isoindol-5(9b*H*)-one (9a).** $BF_3 \cdot OEt_2$ (0.6 mL, 4.93 mmol) and allyltrimethylsilane (2.6 mL, 16.5 mmol) were added to a stirred solution of **5b** (1.04 g, 3.3 mmol) in CH_2Cl_2 (12 mL) at room temperature and the mixture was heated at reflux for 3 h. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by preparative thin-layer chromatography (SiO_2, 10% EtOAc in hexanes) to give a white solid of **9a** as a *trans*-isomer (0.75 g, 67% yield, mp = 91−93 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, J = 7.6 Hz, 1H, ArH), 7.63 (td, J = 7.5, 1.2 Hz, 1H, ArH), 7.54 (td, J = 7.5, 1.0 Hz, 1H, ArH), 7.50 (d, J = 7.6 Hz, 1H, ArH), 7.35 (t, J = 7.6 Hz, 2H, ArH), 7.30−7.25 (m, 3H, ArH), 5.31 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H, CH), 5.03 (dd, J = 17.1, 1.4 Hz, 1H, CHH), 4.97 (d, J = 10.0 Hz, 1H, CHH), 3.73 (dd, J = 12.1, 8.7 Hz, 1H, CHH), 3.56 (dd, J = 12.1, 9.5 Hz, 1H, CHH), 3.39−3.29 (m, 1H, CH), 3.11 (dd, J = 13.9, 5.3 Hz, 1H, CHH), 2.91 (dd, J = 14.1, 7.0 Hz, 1H, CHH), 2.75 (dd, J = 13.9, 9.4 Hz, 2H, CHH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1 (C═O), 142.8 (d, J = 4.3 Hz, C), 137.9 (C), 133.8 (C), 132.4 (CH), 129.7 (CH), 129.4 (CH), 128.74 (2 × CH), 128.67 (2 × CH), 126.8 (CH), 124.9 (dd, J = 263.4, 255.4 Hz, CF_2), 124.2 (CH), 122.5 (CH), 120.2 (CH_2), 74.5 (t, J = 25.3 Hz, C), 48.3 (t, J = 22.6 Hz, CH), 45.1 (d, J = 7.4 Hz, CH_2), 37.0 (d, J = 2.4 Hz, CH_2), 32.9 (d, J = 7.8 Hz, CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −118.14 (dd, J = 226.5, 23.0 Hz, 1F), −121.05 (dd, J = 226.5, 7.1 Hz, 1F). IR (KBr): ν_{max} 1703s, 1643w, 1612w, 1491w, 1467m, 1363s, 1220s, 1049s, 751m, 704s cm^{-1}. MS: *m*/*z* (%) relative intensity 340 (M^+ + 1, 11), 339 (M^+, 2), 298 (100), 249 (20), 91 (64), 65 (11). HRMS (ESI-TOF) Calcd for $C_{21}H_{19}F_2NONa$ $[M + Na]^+$, 362.1332; found, 362.1319.

Preparation of (2*R,9b*R**)-9b-Allyl-2-benzyl-1,1-difluoro-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole (11).** To a suspension of $LiAlH_4$ (4.3 mg, 1.13 mmol) in THF (3 mL) was added a solution of **9a** (0.153 g, 0.45 mmol) in THF (4 mL). The mixture was heated at reflux overnight and quenched at 0 °C by careful addition of water (0.5 mL) followed by 1 M NaOH (0.5 mL). The resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. Purification of the crude product by column chromatography (SiO_2, 5% EtOAc in hexanes) gave a pale yellow oil of 11 (0.123 g, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30−7.25 (m, 5H, ArH), 7.21−7.15 (m, 4H, ArH), 5.50 (ddt, J = 17.2, 10.1, 7.0 Hz, 1H, CH), 4.95 (dd, J = 17.2, 1.8 Hz, 1H, CHH), 4.91 (d, J = 10.2 Hz, 1H, CHH), 4.23 (d, J = 15.1 Hz, 1H, CHH), 3.76 (d, J = 15.1 Hz, 1H, CHH), 3.29 (t, J = 7.4 Hz, 1H, CHH), 3.02 (dd, J = 13.9, 5.1 Hz, 1H, CHH), 2.90−2.86 (m, 1H, CH), 2.63−2.58 (m, 2H, CHH, CHH), 2.46 (dd, J = 13.9, 7.4 Hz, 1H, CHH), 2.42 (ddd, J = 11.2, 9.1, 1.7 Hz, 1H, CHH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.7 (C), 139.1 (C), 138.8 (d, J = 7.5 Hz, C), 132.8 (d, J = 1.4 Hz, CH), 128.6 (2 × CH), 128.5 (2 × CH), 127.9 (CH), 127.0 (CH), 126.9 (t, J = 261.0 Hz, CF_2), 126.3 (CH), 123.9 (CH), 122.5 (CH), 118.4 (CH_2), 81.5 (t, J = 22.8 Hz, C), 60.2 (CH_2), 57.3 (d, J = 9.1 Hz, CH_2), 46.6 (t, J = 21.6 Hz, CH), 43.1 (t, J = 3.0 Hz, CH_2), 31.0 (d, J = 6.0 Hz, CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −109.23 (dd, J = 224.2, 23.0 Hz, 1F), −115.08 (dd, J = 223.7, 6.1 Hz, 1F). IR (neat): ν_{max} 1641m, 1456s, 1218s, 724s cm^{-1}. MS: *m*/*z* (%) relative intensity 278 (9), 236 (100), 216 (7), 194 (18), 176 (7), 130 (6). HRMS (ESI-TOF) Calcd for $C_{21}H_{22}F_2N$ $[M + H]^+$, 326.1722; found, 326.1767.

Preparation of (2*R,5*S**,9b*R**)-9b-Allyl-2-benzyl-5-butyl-1,1-difluoro-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole (13).** To a solution of $CeCl_3$ (0.65 g, 1.75 mmol) in THF (5 mL) was added *n*-BuLi (1.2 mL, 1.74 mmol, 1.46 M solution in hexane) at −78 °C. After stirring at −78 °C for 1 h, a solution of **9a** (0.12 g, 0.35 mmol) in THF (5 mL) was added. The mixture was stirred at −78 °C for 10 h and then gradually warmed to −20 °C, and quenched by the addition of 4 M HCl-dioxane in MeOH (4 M HCl-dioxane/MeOH, 1:29, 5 mL) followed by excess $NaBH_3CN$. The resulting reaction mixture was stirred at 0 °C for 1 h and 10% aqueous NaOH solution (5 mL) was then added. The mixture was diluted with CH_2Cl_2 and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by radial chromatography (SiO_2, 5% EtOAc in hexanes) to afford a colorless oil of **13** (0.094 g, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.18 (m, 8H, ArH), 7.13−7.11 (m, 1H, ArH), 5.59 (ddt, J = 17.3, 10.4, 7.1 Hz, 1H, CH), 4.96−4.92 (m, 2H, CH_2), 3.83 (dd, J = 9.1, 3.4 Hz, 1H, CH), 3.40 (t, J = 7.9 Hz, 1H, CHH), 3.04 (dd, J = 13.7, 4.9 Hz, 1H, CHH), 2.97−2.90 (m, 1H, CH), 2.63 (dd, J = 13.7, 9.7 Hz, 1H, CHH), 2.57−2.53 (m, 2H, CHH, CHH), 2.47 (dd, J = 13.9, 7.3 Hz, 1H, CHH), 1.72−1.68 (m, 1H, CHH), 1.52−1.26 (m, 5H, CHH, 2 × CH_2), 0.89 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9 (C), 139.2 (C), 138.2 (d, J = 6.8 Hz, C), 133.9 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 127.9 (CH), 127.0 (dd, J = 263.5, 251.9 Hz, CF_2), 127.0 (CH), 126.3 (CH), 123.0 (CH), 122.3 (CH), 118.0 (CH_2), 80.5 (t, J = 22.0 Hz, C), 73.5 (CH), 58.4 (d, J = 9.6 Hz, CH_2), 46.3 (t, J = 22.0 Hz, CH), 43.0 (d, J = 3.8 Hz, CH_2), 38.1 (CH_2), 31.7 (d, J = 5.5 Hz, CH_2), 29.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −113.12 (dd, J = 222.3, 24.4 Hz, 1F), −120.03 (d, J = 222.3 Hz, 1F). IR (neat): ν_{max} 1642w, 1496m, 1455m, 1220s, 760m, 700s cm^{-1}. MS: *m*/*z* (%) relative intensity 382 (M^+ + 1, 14), 340 (100), 324 (9), 284 (7), 117 (12), 91 (16). HRMS (ESI-TOF) Calcd for $C_{25}H_{30}F_2N$ $[M + H]^+$, 382.2348; found, 382.2322.

Preparation of (2*R,5*S**,9b*R**)-9b-Allyl-2-benzyl-1,1-difluoro-5-isopropyl-2,3,5,9b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoindole (14).** *i*-Propylmagnesium chloride (0.3 mL, 0.6 mmol, 2 M solution in THF) was slowly added to a solution of 9a (0.04 g, 0.12 mmol) in THF (1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was cooled to 0 °C and 4 M HCl-dioxane in MeOH (4 M HCl-dioxane/MeOH, 1:29, 5 mL) was added, followed by the addition of excess $NaBH_3CN$. After removal of the ice-bath, the reaction mixture was stirred for an additional 1 h and 10% aqueous NaOH solution (5 mL) was then added. The mixture was diluted with CH_2Cl_2 and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were

washed with brine and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by radial chromatography (SiO_2, hexanes then 5% EtOAc in hexanes) to afford a pale yellow solid of **14** (0.029 g, 65% yield, mp = 87−89 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.14 (m, 9H, ArH), 5.88−5.80 (m, 1H, CH), 5.06 (d, J = 17.2 Hz, 1H, CHH), 5.02 (d, J = 10.1 Hz, 1H, CHH), 3.79 (d, J = 4.7 Hz, 1H, CH), 3.41 (dd, J = 9.3, 7.7 Hz, 1H, CHH), 3.03 (dd, J = 13.8, 4.7 Hz, 1H, CHH), 3.03−2.93 (m, 1H, CH), 2.65−2.59 (m, 2H, CHH, CHH), 2.55 (t, J = 9.9 Hz, 1H, CHH), 2.49−2.45 (m, 1H, CHH), 1.97−1.90 (m, 1H, $CH(CH_3)_2$), 1.04 (d, J = 6.8 Hz, 3H, CH_3), 0.76 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3 (C), 139.4 (d, J = 6.8 Hz, C), 139.3 (C), 134.3 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 127.8 (CH), 127.0 (dd, J = 264.0, 251.8 Hz, CF_2), 126.9 (CH), 126.3 (CH), 122.8 (CH), 122.7 (CH), 118.0 (CH_2), 80.0 (t, J = 22.0 Hz, C), 79.8 (CH), 59.2 (d, J = 9.8 Hz, CH_2), 46.5 (t, J = 21.1 Hz, CH), 43.0 (d, J = 4.3 Hz, CH_2), 34.0 (CH), 31.9 (d, J = 5.9 Hz, CH_2), 20.6 (CH_3), 18.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −112.35 (dd, J = 222.8, 24.9 Hz, 1F), −120.23 (d, J = 222.3 Hz, 1F). IR (KBr): ν_{max} 3074br, 1458m, 1210s, 1017s, 761s, 699s cm^{-1}. MS: *m*/*z* (%) relative intensity 368 ($M^+ + 1$, 7), 326 (100), 284 (26), 117 (14), 91 (14). HRMS (ESI-TOF) Calcd for $C_{24}H_{28}F_2N$ $[M + H]^+$, 368.2192; found, 368.2243.

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Supporting Information Available: Experimental details and characterization data for all compounds and CIF data for single-crystal X-ray analyses of *trans*-**5a** and *trans*-**6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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