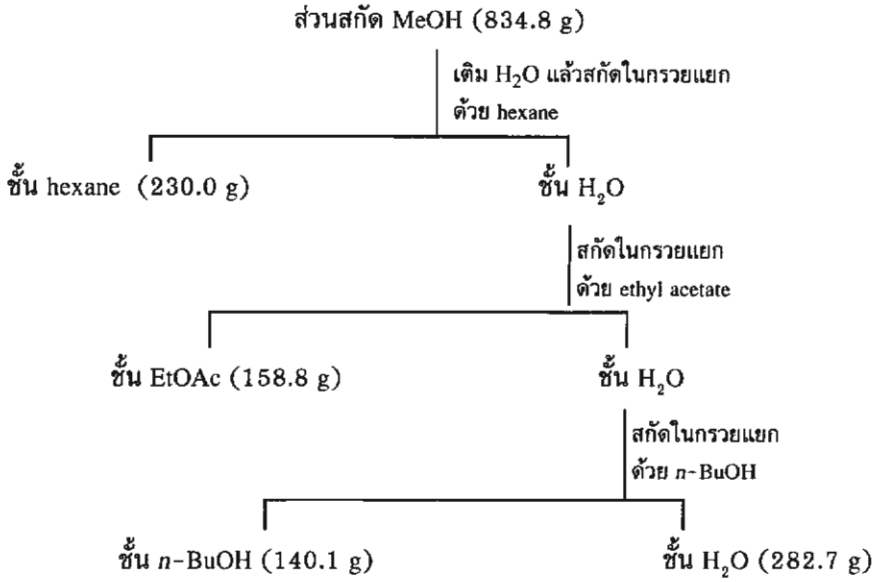
เนื่องจากสาร 6 มีปริมาณน้อย ไม่เพียงพอต่อการเก็บข้อมูลทางสเปคโทรสโคปีได้เต็มที่ จึงได้เก็บข้อมูลทางสเปคโทรสโคปีบางอย่างไปบ้าง ซึ่งยังไม่สามารถที่จะหาโครงสร้างได้ แต่ได้ทำการทดสอบ cytotoxic activity ไปแล้ว โดยที่คาดหวังว่าจะแยกสารตัวนี้ได้จากส่วนสกัดของพืชที่เก็บครั้งที่ 2

7.2 การแยกสารจากส่วนเหนือดิน (aerial part, PX) ของตัวอย่างที่ 2 ของ *Phyllanthus taxodiifolius*

เนื่องจากสารบางตัวที่แยกจากตัวอย่างพืชที่ 1 ของ *Phyllanthus taxodiifolius* มีปริมาณน้อยไม่เพียงพอต่อการศึกษาหาโครงสร้างอย่างสมบูรณ์ และไม่เพียงพอต่อการทดสอบฤทธิ์ทางชีวภาพในระดับลึกลงไปอีก จึงได้ทำการสกัด *Phyllanthus taxodiifolius* ที่เก็บมาครั้งที่ 2 ด้วย MeOH ตามรายละเอียดที่แสดงในตารางที่ 2 ได้ส่วนสกัด MeOH 834.9 g ได้แบ่งไปทดสอบฤทธิ์ทางชีวภาพเบื้องต้นเล็กน้อย ที่เหลือนำไปทำ partition ต่อด้วยตัวทำละลายที่มีขั้วต่ำกว่า ได้ผลการสกัดตามที่แสดงไว้ในแผนผังที่ 5

แผนผังที่ 5

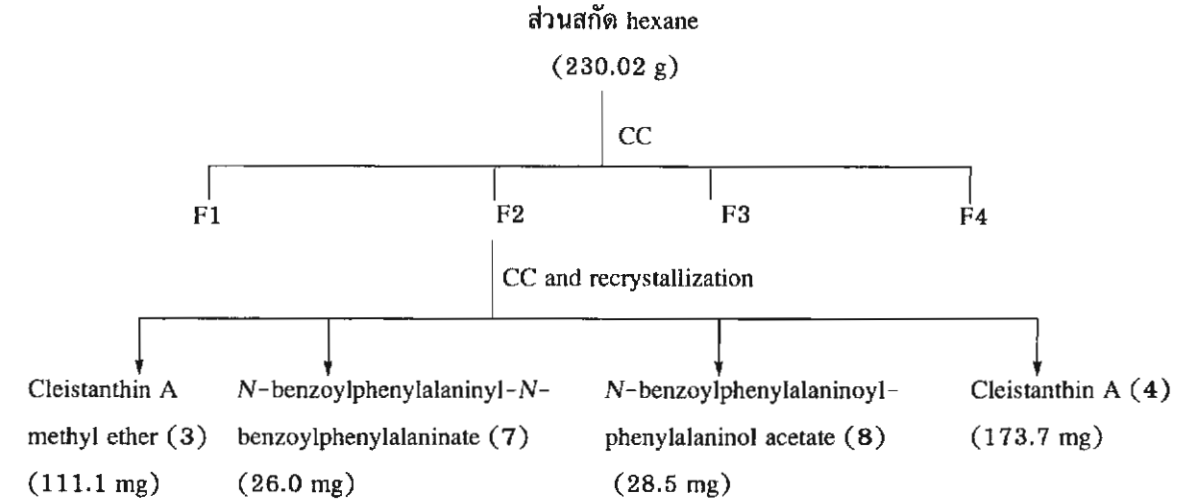


ผลการทดสอบ cytotoxic activity ของส่วนสกัดย่อยอยู่ในเกณฑ์ดีมาก ตามที่แสดงไว้ก่อนแล้วในตารางที่ 6

- **การแยกสารองค์ประกอบจากส่วนสกัด hexane ของ *Phyllanthus taxodiifolius* (ตัวอย่างที่ 2)**

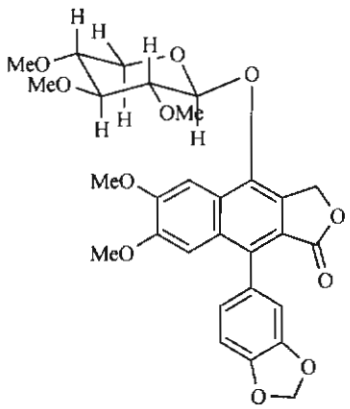
ได้นำส่วนสกัด hexane (230.02 g) มาแยกด้วย column chromatography โดยใช้ silica gel เป็น stationary phase โดยเริ่ม elute ด้วย pure hexane เพิ่ม % ของ dichloromethane ไปเรื่อย ๆ จนถึง pure dichloromethane แล้วค่อย ๆ เพิ่ม % ของ methanol ใน dichloromethane ไปจนถึง pure methanol ได้ทำการเก็บสารละลายที่ออกจาก column ทีละ 500 mL นำแต่ละส่วนที่เก็บไประเหยแห้งด้วย rotary evaporator แล้วรวมส่วนสกัดที่แสดง TLC คล้าย ๆ กันเข้าเป็น fractions ต่าง ๆ ปรากฏว่ารวมได้ 4 fractions ตามที่ได้แสดงไว้ในแผนผังที่ 6

แผนผังที่ 6

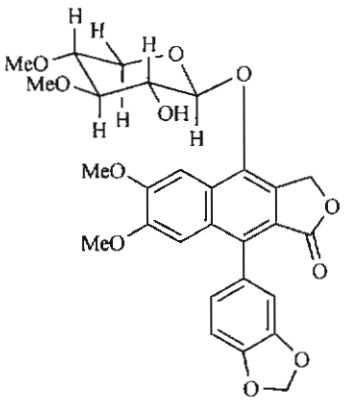


CC = column chromatography

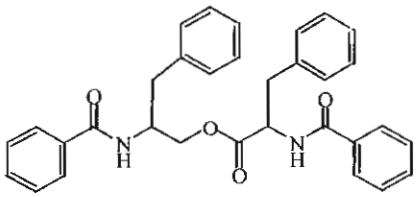
จาก fraction F2 สามารถแยกสารได้ 4 ตัว ได้แก่ Cleistanthin methyl ether (**3**), Cleistanthin A (**4**), *N*-benzoylphenylalaninyl-*N*-benzoylphenylalaninate (**7**) และ *N*-benzoylphenylalaninoylphenyl-alaninol acetate (**8**) ซึ่งมีโครงสร้างดังแสดงข้างล่าง



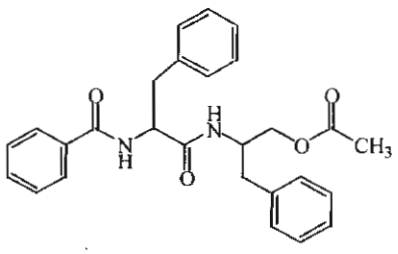
Cleistanthin A methyl ether (**3**)



Cleistanthin A (**4**)



N-benzoylphenylalaninyl-*N*-benzoylphenylalaninate (**7**)



N-benzoylphenylalaninoylphenylalaninol acetate (**8**)

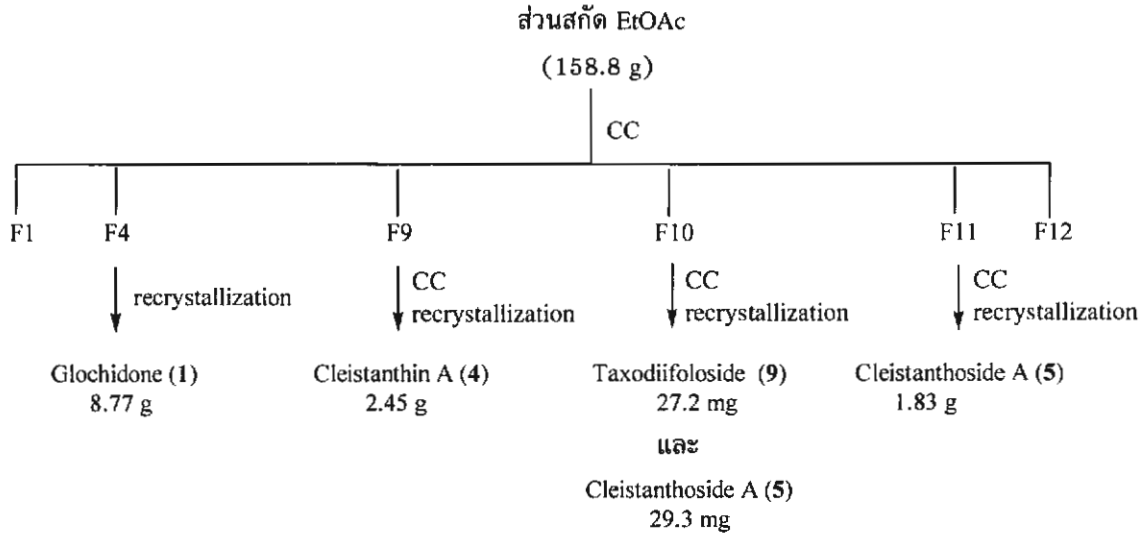
สาร 3 และ 4 แยกได้มาก่อนใน batch ที่เก็บครั้งที่ 1 แต่สาร 7 และ 8 ยังไม่เคยได้มาก่อนเลย แต่ก็เป็นสารที่ known สำหรับการแยก F1, F3 และ F4 ยังอยู่ระหว่างดำเนินการต่อไป

- **การแยกสารองค์ประกอบจากส่วนสกัด EtOAc ของ *Phyllanthus taxodiifolius* (ตัวอย่างที่ 2)**

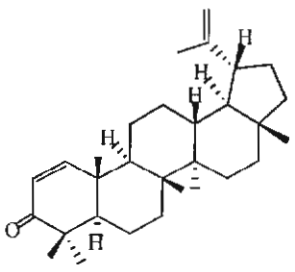
ได้นำส่วนสกัด EtOAc (158.8 g) มาแยกด้วย column chromatography โดยใช้ silica gel เป็น stationary phase โดยเริ่ม elute ด้วย pure hexane แล้วค่อย ๆ เพิ่ม % ของ dichloromethane ไปเรื่อย ๆ จนถึง pure dichloromethane แล้วค่อย ๆ เพิ่ม % ของ methanol ใน dichloromethane ไปจนถึง pure methanol ได้ทำการเก็บสารละลายที่ออกจาก column ทีละ 500 mL นำแต่ละส่วนที่เก็บไประเหยแห้งด้วย rotary evaporator แล้วรวมส่วนสกัดที่แสดง TLC คล้าย ๆ กันเข้าเป็น fractions ต่าง ๆ ปรากฏว่ารวมได้ 12 fractions หลังจากที่ทำการแยกต่อด้วยวิธี recrystallization หรือ column chromatography ตามด้วย recrystallization แล้ว สามารถแยกสารได้ 4 ตัว ได้แก่ Glochidone (**1**) จาก F4, Cleistanthin A (**4**) จาก F9, Taxodiifoloside (**9**) กับ Cleistanthoside A (**5**) จาก F10 และ Cleistanthoside A (**5**) จาก F11 ตามที่ได้แสดงไว้ในแผนผังที่ 7 และมีโครงสร้างดังแสดงข้างล่าง

Taxodiifoloside (**9**) เป็นสารใหม่ที่ยังไม่มีใครรายงานมาก่อน มีโครงสร้างเป็น monoacetate ของ Cleistanthoside A (**5**)

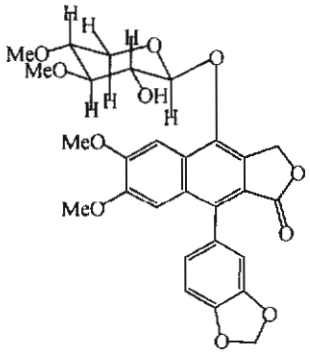
แผนผังที่ 7



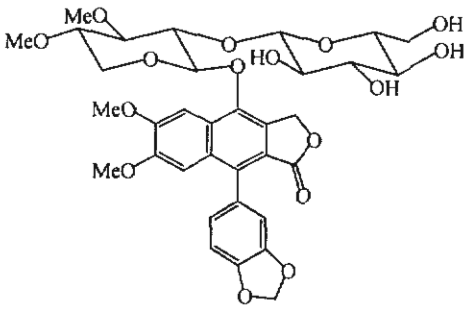
CC = column chromatography



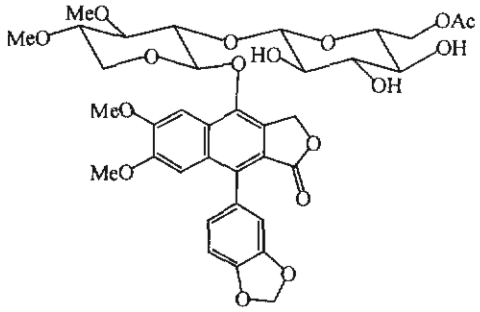
Glochidone (**1**)



Cleistanthin A (**4**)



Cleistanthoside A (5)

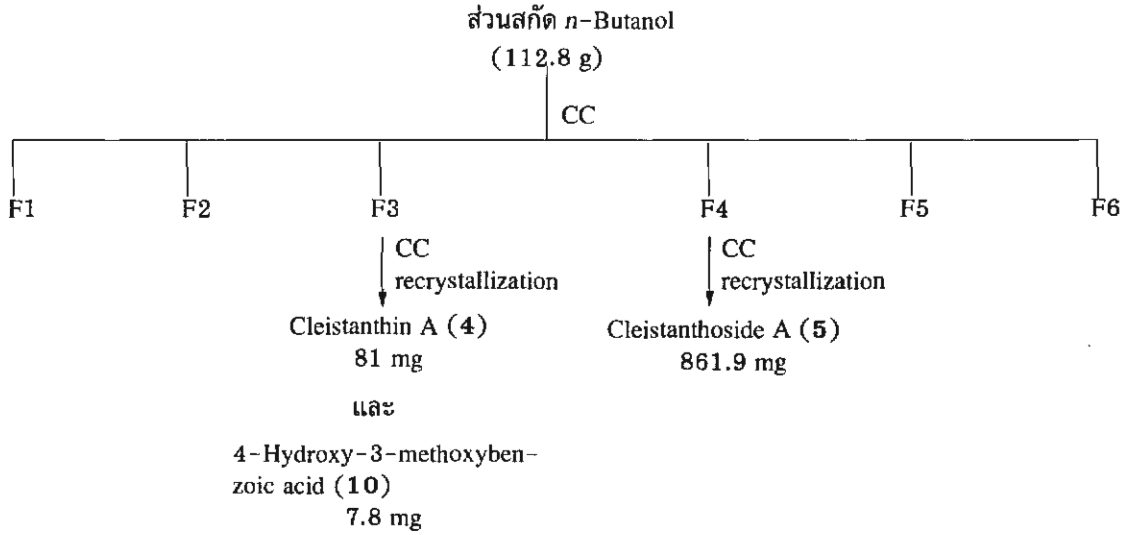


Taxodiifoloside (9)

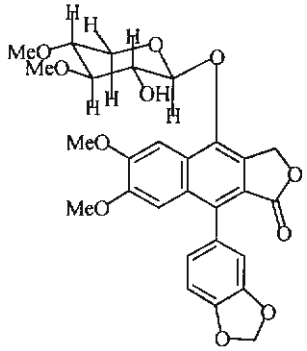
- การแยกสารองค์ประกอบจากส่วนสกัด *n*-butanol ของ *Phyllanthus taxodiifolius* (ตัวอย่างที่ 2)

ได้นำส่วนสกัด *n*-butanol (112.8 g) มาแยกด้วย column chromatography โดยใช้ silica gel เป็น stationary phase โดยเริ่ม elute ด้วย pure CH_2Cl_2 แล้วค่อย ๆ เพิ่ม % ของ MeOH ไปเรื่อย ๆ จนถึง 30% MeOH-CH_2Cl_2 แล้วสุดท้ายใช้ pure MeOH ได้ทำการเก็บสารละลายที่ออกจาก column ทีละ 500 mL นำแต่ละส่วนที่เก็บไประเหยแห้งด้วย rotary evaporator แล้วรวมส่วนสกัดที่แสดง TLC คล้าย ๆ กันเข้าเป็น fractions ต่าง ๆ ปรากฏว่ารวมได้ 6 fractions หลังจากที่ทำการแยกต่อด้วยวิธี column chromatography ตามด้วย recrystallization แล้ว สามารถแยกสารได้ 3 ตัว ได้แก่ cleistanthin A (**4**) กับ 4-hydroxy-3-methoxybenzoic acid (**10**) จาก F3 และ cleistanthoside A (**5**) จาก F4 ดังแสดงในแผนผังที่ 8

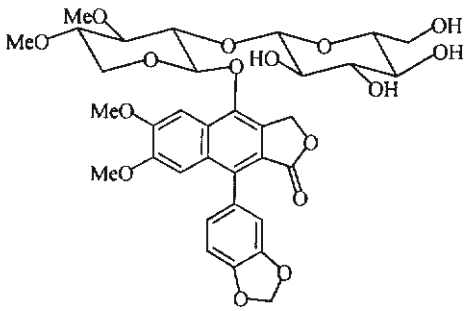
แผนผังที่ 8



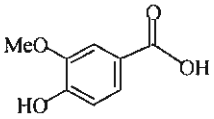
CC = column chromatography



Cleistanthin A (**4**)



Cleistanthoside A (**5**)



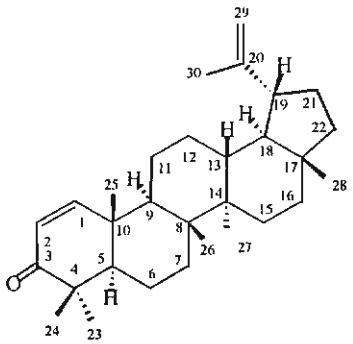
4-Hydroxy-3-methoxybenzoic acid (**10**)

8. การพิสูจน์โครงสร้างของสารองค์ประกอบที่บริสุทธิ์จาก *Phyllanthus taxodiifolius*

ได้ทำการพิสูจน์โครงสร้างของสารบริสุทธิ์ที่แยกได้จาก *Phyllanthus taxodiifolius* โดยใช้ข้อมูลทางสเปค โทรสโคปีประกอบการพิจารณา

Physical data ของสารที่บริสุทธิ์จาก *Phyllanthus taxodiifolius*

Compound 1 (Glochidone)



Glochidone (**1**)

$C_{30}H_{48}O$

colourless needles from CH_2Cl_2-MeOH, m.p. 166.0-166.6 °C [Lit.[1] 164-165 °C, $CHCl_3$-MeOH, Lit.[2] 163-164 °C, $CHCl_3$-MeOH]

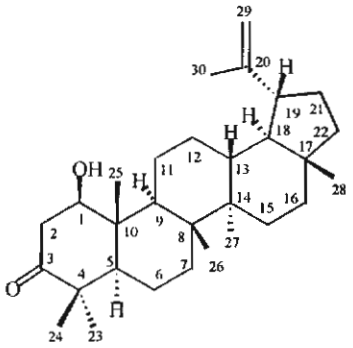
$[\alpha]_{589}^{30}$ +72.38° (*c* 0.1 $CHCl_3$) [Lit. $[\alpha]_D^{24}$ +73.41° (*c* 2.0, $CHCl_3$)]

FT-IR ($CHCl_3$): ν_{max} 1662 (C=O), 1457, 1382, 1284, 1161, 1103, 947, 888, 826 cm^{-1}

EIMS *m/z* (rel. int.): 422 $[M]^+$(20), 229 (69), 203 (34), 191 (53), 175 (23), 161 (35), 150 (100), 137 (73), 121 (45), 109 (58), 95 (75), 83 (97), 69 (30), 55 (17)

^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): ดูตารางที่ 9

Compound 2 (Glochidonol)



Glochidonol (**2**)

$C_{30}H_{48}O_2$

colourless needles from CH_2Cl_2-MeOH , m.p. 223.2-224.1°C [Lit.[3] 228- 230 °C, benzene]

$[\alpha]_{589}^{30}$: +45.1° (*c* 0.1, $CHCl_3$) [Lit. $[\alpha]_D$+46.0° (*c* 1.0, $CHCl_3$)]

FT-IR (KBr) ν_{max} = 3422 (OH), 1713 (C=O), 1641, 1459, 1381, 1346, 1287, 1253, 1238, 1208, 1144, 1110, 1089, 1074, 1025, 1009, 985, 949, 918, 882, 859 cm^{-1}

EIMS *m/z* (rel. int.): 440 $[M]^+$(0.7), 422 (5), 327 (3), 229 (9), 203 (6), 189 (6), 175 (4), 161 (5), 147 (7), 135 (10), 121 (18), 114 (100), 107 (18), 95 (17), 82 (12), 70 (10), 56 (7)

^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): ดูตารางที่ 9

Glochidone (**1**) และ Glochidonol (**2**) เป็นสารที่ known และพบในพืชทั้งในสกุล *Glochidion*[1-3] และ *Phyllanthus*[4] มาก่อน นอกจากนี้ยังพบเป็น metabolites ของ bird's nest fungi อีกด้วย[5]

ตารางที่ 9 300 MHz ^{1}H- และ 75 MHz ^{13}C-NMR data ของสาร **1** และ **2** ใน $CDCl_3$

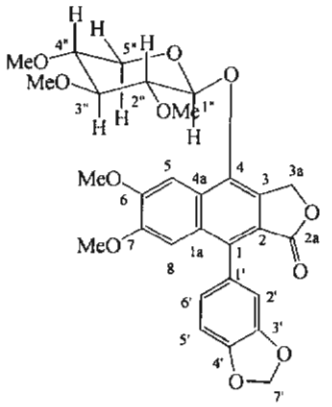
Position	δ_H		δ_C	
	1	**2**	**1**	**2**
1	7.10 (d, 10.2)	3.90 (m)	159.87	79.58
2	5.79 (d, 10.2)	a) 2.22 (dd, 14.4, 8.1)	125.14	45.08
		b) 3.01 (dd, 14.4, 3.5)		
3	-	-	205.55	215.97
4	-	-	43.63	47.11
5	1.56 (obsc.)	1.34 (obsc.)	53.42	51.30
6	1.52 (obsc.)	1.57 (obsc.)	19.01	19.59
7	a) 1.48 (obsc.)	1.44 (obsc.)	33.75	32.88
	b) 1.54 (obsc.)			
8	-	-	41.74	41.10
9	1.53 (obsc.)	1.52 (obsc.)	44.42	50.65
10	-	-	39.54	42.88
11	a) 1.38 (obsc.)	a) 1.35 (obsc.)	21.23	22.98
	b) 1.63 (obsc.)	b) 1.84 (obsc.)		
12	a) 1.12 (obsc.)	a) 1.12 (obsc.)	25.08	25.11
	b) 1.76 (obsc.)	b) 1.71 (obsc.)		
13	1.73 (obsc.)	1.71 (obsc.)	38.21	37.93
14	-	-	43.00	42.92
15	a) 1.01 (obsc.)	a) 1.05 (obsc.)	27.36	27.46
	b) 1.69 (obsc.)	b) 1.69 (obsc.)		
16	a) 1.39 (obsc.)	a) 1.36 (obsc.)	35.48	35.48
	b) 1.53 (obsc.)	b) 1.50 (obsc.)		
17	-	-	43.09	42.93
18	1.39 (obsc.)	1.38 (obsc.)	48.14	48.21
19	2.40 (ddd, 11.1, 11.1, 5.7)	2.38 (ddd, 11.0, 11.0, 5.7)	47.88	47.90
20	-	-	150.74	150.72
21	a) 1.30 (obsc.)	a) 1.33 (obsc.)	29.79	29.74
	b) 1.92 (obsc.)	b) 1.92 (obsc.)		
22	a) 1.19 (obsc.)	a) 1.20 (obsc.)	39.96	39.94
	b) 1.39 (obsc.)	b) 1.41 (obsc.)		
23	1.13 (s)	1.06 (s)	27.79	27.94
24	1.08 (s)	1.04 (s)	21.41	19.81
25	1.07 (s)	0.83 (s)	19.19	11.81
26	1.11 (s)	1.06 (s)	16.45	15.92
27	0.96 (s)	0.98 (s)	14.42	14.42
28	0.81 (s)	0.80 (s)	18.03	18.01
29	a) 4.58 (d, 1.5)	a) 4.57 (d, 1.4)	109.49	109.46
	b) 4.70 (d, 2.3)	b) 4.68 (d, 2.2)		
30	1.69 (s)	1.68 (s)	19.32	19.25

หมายเหตุ Chemical shifts given in ppm using TMS as internal reference; multiplicities and coupling constants (Hz) are given in parentheses; obsc. = obscured signals.

ข้อมูลทาง Nuclear magnetic resonance spectroscopy ตามที่แสดงไว้ในตารางที่ 9 ซึ่ง ^{13}C-NMR spectral data นั้นมีค่าใกล้เคียงกับค่าที่ระบุใน literature[5]

การ assign ค่า chemical shifts ของ protons และ carbons ที่ตำแหน่งต่าง ๆ นั้น ทำได้โดยอาศัยข้อมูลจาก 2D-NMR spectra (COSY, HMQC และ HMBC) นอกจากนี้ stereochemistry ของสารนั้น assign ได้โดยอาศัยข้อมูลจาก NOE enhancement experiments

Compound 3 (Cleistanthin A methyl ether)



Cleistanthin A methyl ether (**3**)

$C_{29}H_{30}O_{11}$

white powder from EtOH, m.p. 211-215 °C [Lit.[6] 214-215 °C, ether petroleum ether]

$[\alpha]_{589}^{27}$:-50° (*c* 1.0, $CHCl_3$)

FT-IR (KBr): ν_{max} = 1760 (C=O ของ γ-lactone), 1624 and 1508 , 1479, 1456, 1434, 1391, 1336, 1265, 1231, 1215, 1169, 1097, 1061, 1039, 1007, 982, 932 (methylenedioxy), 865 cm^{-1}

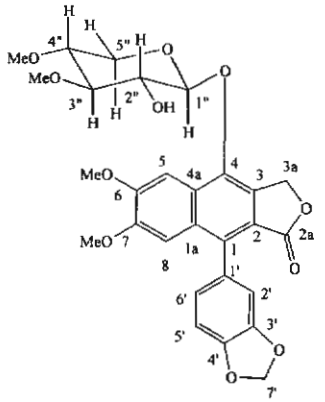
UV (EtOH): λ_{max} (log ε) = 221 (4.56), 258 (4.93), 292 (4.22), 314 (4.22), 349 (3.91) nm

EIMS *m/z* (rel. int.): 380 (M^+-sugar)(100), 351(3), 321 (7), 293 (13), 143 (18), 111 (13), 102 (7), 75 (17).

HRMS *m/z* (rel. int.): รอผลการวัด

^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): ดูตารางที่ 10

Compound 4 (Cleistanthin A)



Cleistanthin A (4)

$C_{28}H_{30}O_{11}$

white powder from EtOH, m.p. 140-141.3 °C [Lit.[6] 135-136 °C MeOH]

$[\alpha]_{589}^{27}$:-69.6° (*c* 1.02, $CHCl_3$) [Lit. [$\alpha]_D$-67.2° ($CHCl_3$)]

FT-IR (KBr): ν_{max} = 3481, 1742 (C=O ของ lactone), 1623, 1593, 1509, 1479, 1453, 1433, 1390, 1370, 1354, 1337, 1327, 1265, 1235, 1215, 1195, 1173, 1157, 1108, 1087, 1036, 1009, 991, 952, 935, 917, 885, 867, 841, 816, 786, 772 cm^{-1}

UV (EtOH): λ_{max} (log ε) = 221 (4.50), 258 (4.89), 292 (4.17), 313 (4.19), 348 (3.86) nm

EIMS *m/z* (rel. int.): 380 (M^+-sugar)(100), 362 (2), 351 (4), 335 (4), 321 (7), 293 (13), 229 (4), 69 (2)

HRMS *m/z* (rel. int.): รอผลการวัด

^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): ดูตารางที่ 10

สาร 3 และ 4 เป็นสารที่มีผู้รายงานมาก่อนจาก *Cleistanthus collinus*[6-8] และ *Cleistanthus petulus*[9-10]

แม้ว่า ^{1}H- และ^{13}C-NMR data ใน literature จะใกล้เคียงกับ data ของเราก็ตาม แต่ว่าการ assign chemical shift แตกต่างกันออกไปบ้าง ซึ่งกลุ่มวิจัยได้พยายาม assign โดยใช้ 2D-NMR data เข้าช่วย จึงสามารถทำการ assign chemical shifts ต่าง ๆ ได้ ซึ่งกลุ่มวิจัยคิดว่าน่าจะถูกต้องมากกว่าใน literature ซึ่งการ assign chemical shifts ทำโดยไม่มีข้อมูลเกี่ยวกับการ correlations จาก 2D-NMR spectra

ข้อมูลจาก IR, ^{1}H NMR และ ^{13}C NMR สนับสนุนว่าสาร 3 และ 4 เป็นสารจำพวก 1-arylnaphthalide lignans[11] ตารางที่ 10 แสดง ^{1}H- และ ^{13}C-NMR data ของสาร 3 และ 4 ใน $CDCl_3$ ข้อสังเกตจาก ^{13}C-NMR data จะเห็นว่าทั้งสาร 3 และ 4 นั้น แสดง chemical shifts ที่บาง carbons เป็น 2 ค่า[12] ทั้งนี้เคยมีผู้รายงานว่า เกิดขึ้นเนื่องจาก hindered rotation รอบ C1-C1' ซึ่งแต่ละ signal นั้นพิสูจน์ได้จาก 2D-NMR data คือใช้ HMQC ซึ่งแสดง direct correlations ของ carbon และ proton ที่จับกันโดยตรง

การ assign ค่า chemical shifts ของ protons และ carbons ที่ตำแหน่งต่าง ๆ นั้น ทำได้โดยอาศัยข้อมูลจาก 2D-NMR spectra (COSY, HMQC และ HMBC) และจากค่า coupling constant ของ protons บนวงของ น้ำตาลทำให้สามารถยืนยัน stereochemistry ของ หมู่ OH และ OMe บนวงของ sugar ตารางที่ 11 แสดง HMBC correlations ของสาร 3 และ 4

ตารางที่ 10 แสดง 500 MHz ^{1}H- และ 125 MHz ^{13}C-NMR data ของสาร **3** และ **4** ใน $CDCl_3$

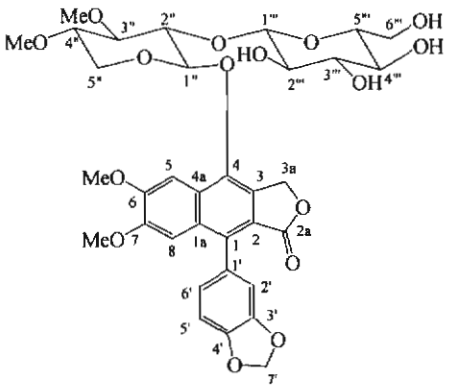
Position	δ_H		δ_C	
	3	**4**	**3**	**4**
1	-	-	136.37	135.86, 135.85
1a	-	-	130.79	130.63
2	-	-	119.21	119.13
2a	-	-	169.74	169.79
3	-	-	130.95, 130.93	128.90, 128.85
3a	5.510, 5.505 (d each , 1H, 15.0 Hz)	5.514, 5.510 (d each, 1H, 14.8 Hz)	67.28	67.29
	5.424, 5.420 (d each , 1H, 15.0 Hz)	5.444, 5.540 (d each, 1H, 14.8 Hz)		
4	-	-	144.29	144.07
4a	-	-	127.02	126.79
5	7.85 (s, 1H)	7.93 (s, 1H)	100.64	100.99
6	-	-	151.92	151.774, 151.767
7	-	-	150.15	150.14
8	7.10 (s, 1H)	7.08 (s, 1H)	106.27	106.03
1′	-	-	128.32	128.35
2′	6.83 (obsc., 1H)	6.84 (d, 1H, 1.6 Hz)	110.67	110.68
3′ and 4′	-	-	147.47	147.42, 147.41
5′	6.97 (d, 1H, 8.1 Hz)	6.96 (d, 1H, 7.8 Hz)	108.13	108.13
6′	6.80 (obsc., 1H)	6.81 (dd, 1H, 7.8, 1.6 Hz)	123.57, 123.53	123.55
7′	6.098, 6.096 (d each, 1H, 1.5 Hz)	6.10 (d, 1H, 1.3 Hz)	101.18	101.18
	6.052, 6.049 (d each, 1H, 1.5 Hz)	6.05 (d, 1H, 1.3 Hz)		
1″	4.76 (d, 1H, 7.6 Hz)	5.049, 5.043 (d each, 1H, 5.6 Hz)	105.10	103.42, 103.39
2″	3.41 (dd, 1H, 8.6, 7.6 Hz)	3.93 (m, 1H)	83.45	71.08, 71.04
3″	3.23 (t, 1H, 8.6 Hz)	3.39, 3.38 (t each , 7.0 Hz)	85.47	82.07, 82.02
4″	3.39 (ddd, 9.8, 8.6, 5.2 Hz)	3.46 (ddd, 1H, 7.0, 7.0, 3.7 Hz)	79.34	78.18, 78.16
5″(1)	4.027, 4.025 (dd each , 11.8, 5.2 Hz)	4.12 (dd, 12.0, 3.7 Hz)	63.43	61.61, 61.59
5″(2)	3.06 (dd, 11.4, 10.2 Hz)	3.359, 3.356 (dd each, 1H, 12.0, 7.0 Hz)		
6-OMe	4.06 (s, 3H)	4.06 (s, 3H)	56.07	56.17
7-OMe	3.81 (s, 3H)	3.81 (s, 3H)	55.79	55.77
2″-OH	-	3.258, 3.247 (br d each, 1H)	-	-
2″-OMe	3.84 (s, 3H)	-	61.21	-
3″-OMe	3.69 (s, 3H)	3.69 (s, 3H)	60.67	60.04, 60.02
4″-OMe	3.50 (s, 3H)	3.50 (s, 3H)	58.70	57.93

หมายเหตุ Chemical shifts given in ppm using TMS as internal reference; multiplicities and coupling constants (Hz) are given in parentheses; 1", 2", 3", 4" and 5" are positions on the sugar ring.

ตารางที่ 11 HMBC correlations observed ของสาร **3** และ **4** ใน $CDCl_3$

C	**3** correlated H	**4** correlated H
1	5, 8, 2', 6'	5 , 8, 2', 6'
1a	5, 8	5, 8
2	3a	3a
2a	3a	3a
3	3a	3a
3a	-	-
4	3a, 5, 8, 1"	5, 8, 3a, 1"
4a	3a, 5, 8	5, 8, 3a
5	8, 6-OMe	8, 6-OMe
6	5, 8, 6-OMe	5, 8, 6-OMe
7	5, 8, 7-OMe	5, 8, 7-OMe
8	5, 7-OMe	5, 7-OMe
1'	5'	5'
2'	6'	5', 6'
3' and 4'	2', 5', 6', 7'	2', 5', 6', 7'
5'	-	2'
6'	2'	2'
7'	-	-
1"	2", 5"(a), 5"(b)	2", 3", 5"(a), 5"(b)
2"	1", 3", 2"-OMe	1", 3"
3"	1", 2", 4", 5"(a), 5"(b), 3"-OMe	1", 2", 4", 5"(a), 5"(b), 3"-OMe
4"	2", 3", 5"(a), 5"(b), 4"-OMe	2", 3", 5"(a), 5"(b), 4"-OMe
5"	1", 3", 4"	1", 3", 4"
6-OMe	-	-
7-OMe	-	-
2"-OMe	2"	-
3"-OMe	3"	3"
4"-OMe	4"	4"

Compound 5 (Cleistanthoside A)



Cleistanthoside A (5)

$C_{34}H_{38}O_{18}$

white powder from EtOH, m.p. 237-240 °C [Lit.[10] 238-241 °C from MeOH]

$[\alpha]_{589}^{26}$ -5.7° (*c* 1.0, MeOH) [Lit.[10] $[\alpha]_D$-7.3°, (*c* 1.04, dioxane)

FT-IR (KBr): ν_{max} = 3449 (O-H), 1759 (C=O lactone), 1624, 1508, 1481, 1457, 1436, 1390, 1340, 1265, 1230, 1215, 1193, 1169, 1121, 1073, 1038, 1004, 932, 865, 812, 793, 770, 730 cm^{-1}

UV (MeOH): λ_{max} (log ε) = 220 (3.20), 258 (4.58), 292 (3.85), 313 (3.88), 348 (3.55)

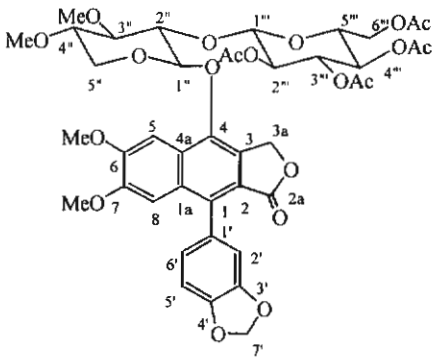
EIMS *m/z* (rel. int.): 380 (M^+-sugar)(100), 351 (9), 335 (8), 306 (6), 321 (17), 293 (36), 263 (6), 160 (9), 130 (5), 102 (8), 59 (10)

HRMS *m/z* (rel. int.): รอผลการวัด

สาร 5 เป็นสาร known มีชื่อว่า cleistantoside A แยกได้จาก heartwood ของ *Cleistanthus patulus* Muell.[10]

เนื่องจาก resolution ของ ^{1}H NMR spectrum ไม่ว่าจะ record ใน solvent ใด ๆ ไม่ดีนัก จึงได้เตรียมเป็นอนุพันธ์ tetraacetate (**5a**) แล้ววิเคราะห์โครงสร้างของ **5** ผ่าน **5a** แทน การหาโครงสร้างของสาร **5** นั้น ทำได้จากวิเคราะห์ข้อมูลจาก ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HMQC HMBC และ NOESY spectra ของอนุพันธ์ tetraacetate **5a** ซึ่งการ assign ^{1}H และ ^{13}C signals ต่าง ๆ เป็นดังแสดงในตารางที่ 12

Compound 5a (Cleistanthoside A tetraacetate)



Cleistanthoside A tetraacetate (**5a**)

$C_{42}H_{46}O_{20}$

white powder from MeOH, m.p. 136.5-138.1 °C [Lit.[10] 136-139 °C]

$[\alpha]_{589}^{27}$ -35.0° (*c* 1.0, $CHCl_3$) [Lit.[10] $[\alpha]_D$ -25.1° (*c* 1.0, $CHCl_3$)]

FT-IR (KBr): ν_{max} = 1759 (broad C=O of lactone and C=O of acetate), 1623, 1509, 1481, 1457, 1436, 1369, 1344, 1264, 1229, 1169, 1120, 1062, 1038, 932, 908, 868, 841, 812, 793, 770 cm^{-1}

FT-IR ($CHCl_3$): ν_{max} = 1756 (broad C=O of lactone and C=O of acetate), 1623,, 1599, 1507, 1482, 1456, 1435, 1369, 1337, 1263, 1168, 1120, 1097, 1063, 1041, 1014, 936, 909, 868, 841 cm^{-1}

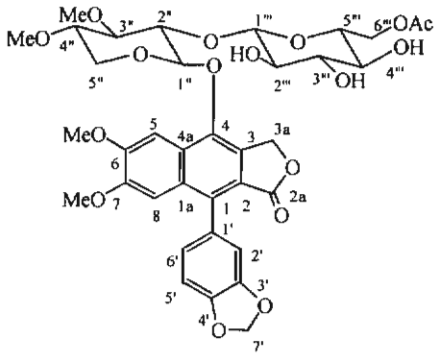
UV (EtOH): λ_{max} (log ε) = 222 (4.25), 258 (4.64), 291 (3.92), 311 (3.93), 348 (3.61) nm

HR-MS: รอผลการวัด

^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): ดูตารางที่ 12

Cleistanthoside A tetraacetate (**5a**) เป็น known ซึ่งมีผู้รายงานว่าเตรียมขึ้นได้จาก Cleistanthoside A (**5**)[10]

Compound 9 (Taxodiifoloside, New compound)



Taxodiifoloside (9)

$C_{36}H_{40}O_{17}$,

white powder from EtOAc-hexane, m.p. 142.3-143.1°C

$[\alpha]_{589}^{27}$ -34° (*c* 0.5, $CHCl_3$)

FT-IR (KBr): ν_{max} = 3419, 1756 (C=O of lactone), 1742 (C=O of acetate), 1623, 1507, 1482, 1456, 1437, 1386, 1345, 1264, 1230, 1216, 1169, 1076, 1037, 1008, 930, 871, 841, 812, 793, 770 cm^{-1}

UV (EtOH): λ_{max} (log ε) = 223 (3.92), 2.58 (4.31), 294 (3.67), 314 (3.70), 349 (3.46)

HR-MS *m/z* (rel. int.): รอผลการวัด

^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): ดูตารางที่ 12

ตารางที่ 12 500 MHz ^{1}H- และ 125 MHz ^{13}C-NMR data ของสาร **5**-tetraacetae และ **9** ใน $CDCl_3$

Position	δ_H		δ_C	
	5a	**9**	**5a**	**9**
1	-	-	136.20	136.42
1a	-	-	130.75	130.76, 130.70
2	-	-	119.19	119.13
2a	-	-	169.66	169.74
3	-	-	130.62, 130.58	130.81
3a	5.53 (d, 1H, 15.0 Hz)	5.557, 5.556 (d each, 1H, 15.0 Hz)	67.30	67.28
	5.439, 5.432 (d each, 1H, 15.0 Hz)	5.424, 5.418 (d each, 1H, 15.0 Hz)		
4	-	-	143.96, 143.94	143.72
4a	-	-	126.86, 126.84	126.86
5	7.83 (s, 1H)	7.932, 7.927 (s, 1H)	101.30, 101.28	101.52
6	-	-	151.78	151.95
7	-	-	150.20	150.29
8	7.08 (s, 1H)	7.08 (s, 1H)	106.21	106.21
1′	-	-	128.35	128.32
2′	6.84 (obsc., 1H)	6.82 (obsc., 1H)	110.69, 110.62	110.71, 110.61
3′ and 4′	-	-	147.45	147.53
5′	6.96 (d, 1H, 8.1 Hz)	6.96 (d, 1H, 7.8 Hz)	108.11	108.19
6′	6.80 (obsc., 1H)	6.79 (obsc., 1H)	123.58,123.49	123.61,123.50
7′	6.10 (d , 1H, 1.1 Hz)	6.099, 6.097 (d each, 1H, 1.4 Hz)	101.15	101.22
	6.05 (d , 1H, 1.1 Hz)	6.055, 6.053 (d each, 1H, 1.4 Hz)		
1"	4.92 (d, 1H, 7.2 Hz)	4.996, 4.993 (d each, 1H, 7.0 Hz)	103.06	103.27
2"	3.89 (obsc., 1H)	3.937, 3.934 (dd each, 1H, 8.3, 7.0 Hz)	80.28, 80.23	80.99, 80.92
3"	3.28 (t, 1H, 8.5 Hz)	3.43 (t, 1H, 8.3 Hz)	84.51	83.08
4"	3.42 (m, 1H)	3.46 (obsc., 1H)	79.91	79.56
5"	4.02 (dd, 1H, 11.8, 5.0 Hz)	4.037, 4.034 (dd each, 1H, 12.1, 4.6 Hz)	62.99	62.54
	3.11 (dd, 1H, 11.8, 9.5 Hz)	3.132, 3.131 (dd each, 1H, 12.1, 8.8 Hz)		
1"'	5.08 (obsc. 1H)	4.68 (d, 1H, 7.6 Hz)	101.80,101.78	105.91, 105.87
2"'	5.07 (obsc., 1H)	3.48 (dd, 1H, 9.1, 7.6 Hz)	71.86	75.32
3"'	5.26 (t, 1H, 8.9 Hz)	3.64 (t, 1H, 9.1 Hz)	73.06	75.74
4"'	5.10 (obsc., 1H)	3.41 (t, 1H, 9.1 Hz)	68.14	69.61
5"'	3.72 (m, 1H)	3.51 (ddd, 1H, 9.1, 4.7, 2.0 Hz)	72.04	74.76
6"'(a)	4.173, 4.166 (dd each, 1H, 12.2, 3.3 Hz)	4.38 (dd, 1H, 12.3, 4.7 Hz)	61.37	63.06
6"'(b)	3.93 (obsc. 1H)	4.09 (obsc., 1H)		
6-OMe	4.14 (s, 3H)	4.11 (s, 3H)	56.47	56.53
7-OMe	3.81 (s, 3H)	3.81 (s, 3H)	55.76	55.81
3"-OMe	3.62 (s, 3H)	3.74 (s, 3H)	60.64	60.78
4"-OMe	3.47 (s, 3H)	3.47 (s, 3H)	58.28	58.23
2"'-COMe	2.12 (S, 3H)	-	20.76	-
3"'-COMe	2.04 (s, 3H)	-	20.52	-
4"'-COMe	2.01 (s, 3H)	-	20.45	-
6"'-COMe	1.81 (s, 3H)	1.79 (s, 3H)	20.17	20.20
2"'-COMe	-	-	169.25	-
3"'-COMe	-	-	170.20	-
4"'-COMe	-	-	169.27	-
6"'-COMe	-	-	170.25	171.54
OH	-	4.69 (1H), 3.34 (1H), 3.29 (1H)	-	-

หมายเหตุ Chemical shifts given in ppm using TMS as internal reference; multiplicities and coupling constants (Hz) are given in parentheses; 1", 2", 3", 4" and 5" are positions on the sugar ring.

obsc. = obscured signal

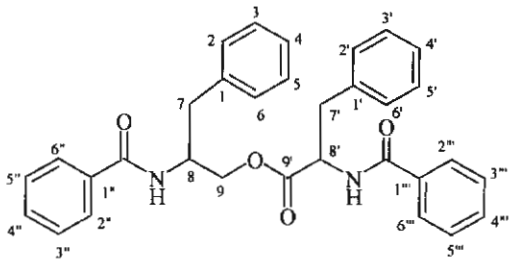
ตารางที่ 13 HMBC correlations observed ของสาร **5a** และ **9** ใน $CDCl_3$

C	**5a** correlated H	**9** correlated H
1	5, 8, 2', 6'	5, 8, 2', 6'
1a	5, 8	5, 8
2	3a	3a
2a	3a	3a
3	3a	3a
3a	-	-
4	5, 8, 3a, 1"	5, 8, 3a, 1"
4a	5, 8, 3a	5, 8, 3a
5	8, 6-OMe	8, 6-OMe
6	5, 8, 6-OMe	5, 8, 6-OMe
7	5, 8, 7-OMe	5, 8, 7-OMe
8	5, 7-OMe	5, 7-OMe
1'	5'	5'
2'	6'	6'
3' and 4'	2', 5', 6', 7'	2', 5', 6', 7'
5'	6'	6'
6'	2', 5'	2'
7'	-	-
1"	2", 3", 5"(a), 5"(b)	2", 3", 5"(a), 5"(b)
2"	1", 3", 1"'	3", 1"'
3"	1", 2", 4", 5"(a), 5"(b), 3"-OMe	1", 2", 4", 5"(a), 5"(b), 3"-OMe,
4"	2", 3", 5"(a), 5"(b), 4"-OMe	3", 5"(a), 5"(b), 4"-OMe
5"	1", 3", 4"	1"
1"'	2", 3"', 5"'	2", 2"'
2"'	1"', 3"', 4"', 2"'-O(CO)*Me*	1"', 3"'
3"'	1"', 2"', 4"', 3"'-O(CO)*Me*	1"', 2"', 4"'
4"'	2"', 3"', 5"', 6"'(a), 6"'(b), 4"'-O(CO)*Me*	3"', 5"', 6"'(b)
5"'	1"', 4"', 6"'(a), 6"'(b)	1"', 4"', 6"'(b)
6"'	4"', 6"'-O(CO)*Me*	4"', 6"'-O(CO)*Me*
6-OMe	-	-
7-OMe	-	-
3"-OMe	3"	3"
4"-OMe	4"	4"

การ assign chemical shifts ในสาร **5a** และ **9** ก็ประสบกับปัญหาอย่างมาก ทั้งนี้เพราะว่าเมื่อ concentration เปลี่ยน chemical shifts ก็เปลี่ยนด้วย และ chemical shifts ทั้งใน ^{1}H และ ^{13}C NMR spectra จะมีบางตำแหน่งที่แสดง chemical shifts 2 ค่า[12] ซึ่งเกิดจาก hindered rotation รอบ C1-C1' bond เช่นเดียวกับใน cleistanthin A methyl ether (**3**) และ cleistanthin A (**4**) แต่กลุ่มวิจัยของเราได้ใช้ข้อมูลจาก 2D-NMR data (COSY, HMQC, HMBC) ช่วยในการ assign ค่า chemical shifts ต่าง ๆ จึงเชื่อว่าการ assign ของเราน่าจะถูก

ต้องมากกว่าใน literature ซึ่ง assign ^{1}H และ ^{13}C chemical shifts โดยไม่มี correlation data จาก 2D-NMR experiments มาสนับสนุน ตารางที่ 13 แสดง HMBC correlations ของสาร **5a** และ **9**

Compound 7 (*N*-Benzoylphenylalaninyl-*N*-benzoylphenylalaninate)



N-Benzoylphenylalaninyl-*N*-benzoylphenylalaninate (7)

$C_{32}H_{30}O_4N_2$

white powder from EtOAc-hexane, m.p. 207.1-208.1 °C [Lit.[13] 212.5-213 °C]

$[\alpha]_{589}^{27}$ -25.2° (c 0.5, $CHCl_3$)[Lit.[14] $[\alpha]_D$ -98.6° (*c* 0.76, C_5H_5N), Lit.[14] $[\alpha]_D$ -78.7° (*c* 0.14, EtOH)

IR ν_{max} ($CHCl_3$): 3440 (N-H), 1744 (C=O of ester), 1659 (C=O of amide), 1604, 1581, 1517, 1486, 1456, 1388, 1354, 1295, 1180, 1101, 1029, 917 cm^{-1}

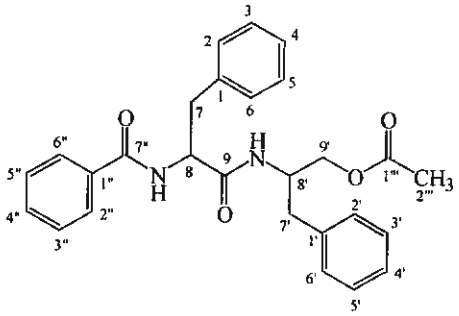
UV (EtOH): λ_{max} (log ε) = 223 (4.28)

ESI-MS *m/z* (rel. int.): 529 $[M+Na]^+$(100), 507 (65), 256 (42), 238 (16), 149 (7)

^{1}H NMR ($CDCl_3$, 500 MHz): 7.63 (dd, 2H, H-2", H-6"), 7.59 (dd, 2H, 8 and 1.2 Hz, H-2"', H-6"'), 7.42 (t, 1H, 7.6 Hz, H-4"'), 7.36 (t, 1H, 7.4 Hz, H-4"), 7.31 (t, 1H, 8 Hz, H-3"', H-5"'), 7.26-7.20 (m, 6H, H-3, H-3', H-3", H-5, H-5', H-5"), 7.20-7.12 (obscured signal, 4H, H-2, H-2', H-4, H4', H-6, H-6'), 6.66 (d, 1H, 10-NH), 6.57 (d, 1H, 10'-NH), 4.84 (ddd, 1H, 6.6, 6.6, 6.6 Hz, H-8'), 4.55 (m, 1H, H-8), 4.47 (dd, 1H, 11.4, 3.3 Hz, H-9a), 3.95 (dd, 1H, 11.4, 4.3 Hz, H-9b), 3.22 (dd, 1H, 13.9 and 6.5, H-7'a), 3.14 (dd, 1H, 13.9, 7.1 Hz, H-7'b), 2.92 (dd, 1H, 13.7 and 6.5 Hz, H-7a), 2.81 (dd, 1H, 13.7 and 8.4 Hz, H-7b)

^{13}C NMR ($CDCl_3$, 125 MHz): 171.88 (C-9'), 167.41 (C-7"'), 167.21 (C-7"), 137.16 (C-1), 135.80 (C-1'), 134.24 (C-1"), 133.38 (C-1"'), 131.96 (C-4"'), 131.35 (C-4"), 129.28 (C-2, C-6), 129.16 (C-2', C-6'), 128.84, 128.67, 128.63 , 128.40 (aromatic carbon *meta*- to CH_2R), 127.35 (C-4'), 127.10 (C-2", C-6"), 127.04 (C-2"', C-6"'), 126.78 (C-4), 65.44 (C-9), 54.46 (C-8'), 50.28 (C-8), 37.55 (C-7'), 37.27 (C-7).

Compound 8 (*N*-Benzoylphenylalaninoylphenylalaninol acetate)



N-Benzoylphenylalaninoylphenylalaninol acetate (**8**)

$C_{27}H_{28}O_4N_2$

White powder from EtOAc-hexane

m.p. 175.6-176.2 °C [Lit.[15] 175 °C, 184 °C, Lit.[13] 182-183.5 °C]

$[\alpha]_{589}^{27}$ -26° (*c* 0.1, $CHCl_3$)

Lit.[15] L,L m.p. 184 °C $[\alpha]_{589}^{26}$ -40° (*c*1.0, $CHCl_3$)

D,D m.p. 185 °C $[\alpha]_{589}^{26}$ +40.6° (*c*1.0, $CHCl_3$)

D,L m.p. 175 °C $[\alpha]_{589}^{26}$ -5° (*c*1.0, $CHCl_3$)

L,D m.p. 175 °C $[\alpha]_{589}^{26}$ +4.8 (*c*1.0, $CHCl_3$)

IR ν_{max} (KBr): 3429 (NH), 1726 (C=O ester), 1662 (C=O amide), 1632 (C=O amide), 1603, 1580, 1535, 1493, 1468, 1453, 1392, 1373, 1323, 1263, 1198, 1151, 1126, 1053, 1126, 1052, 1034, 936, 914 cm^{-1}

UV (EtOH): λ_{max} (log ε) = 224 (4.02)

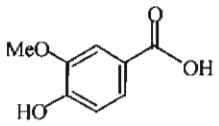
ESI-MS *m/z* (rel. int.): 467 $[M+Na]^+$(100), 194 (5)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (m, 2H, H-2", H-6"), 7.53 (m, 1H, H-4"), 7.44 (m, 2H, H-3", H-5"), 7.20-7.30 (m, 5H, H-2, H-3, H-4, H-5, H-6), 7.05-7.19 (m, 3H, H-3', H-4', H-5'), 7.07 (m, 2H, H-2', H-6') 6.82 (d, 1H, 7.6 Hz, 10-NH), 6.09 (d, 1H, 8.6 Hz, 10'-NH), 4.79 (ddd, 1H, 8.6, 8.5, 5.9 Hz, H-8), 4.35 (m, 1H, H-8'), 3.93 (dd, 1H, 11.3, 4.9 H-9'a), 3.82 (dd, 1H, dd, 1H, 11.3, 4.2 Hz, H-9'b), 3.22 (dd, 1H, 13.6, 5.9 Hz, H-7a), 3.08 (dd, 1H, 13.6, 8.5 Hz, H-7b), 2.77 (dd, 1H. 13.8, 6.8 Hz, H-7'a), 2.73 (dd, 1H, 13.8, 7.5 Hz, H-7'b), 2.02 (s, 3H, H-2"')

^{13}C NMR ($CDCl_3$, 125 MHz): 170.72 (C-1"'), 170.28 (C-9), 167.11 (C-7"), 136.70 (C-1'), 136.61 (C-1), 133.68 (C-1"), 131.87 (C-4"), 129.28 (C-2, C-6), 129.11 (C-2', C-6'), 128.72 (C-3, C-5), 128.60 (C-3", C-5"), 128.55 (C-3', C-5'), 127.10 (C-4), 127.04 (C-2", C-6"), 126.71 (C-4'), 64.58 (C-9'), 54.96 (C-8), 49.46 (C-8'), 38.40 (C-7), 37.43 (C-7'), 20.74 (C-2"')

จะเห็นว่า ขณะนี้ค่า optical ที่วัดได้ยังแตกต่างจากใน literature อยู่มาก จึงยังไม่สามารถสรุป configurations ที่ chiral centers ในสารทั้งสองได้ คิดว่าจะต้องทำการ recrystallize สารอีก แล้ววัดทั้งค่า $[\alpha]_D$ และ melting points ใหม่

Compound 10 (4-Hydroxy-3-methoxybenzoic acid)[16]



10

ได้พิสูจน์โครงสร้างโดยเทียบ physical properties และ ^{1}H NMR data กับ data ที่รายงานใน literature[16]

9. การทดสอบฤทธิ์ cytotoxic activity ของสารบริสุทธิ์ที่แยกได้จาก *Phyllanthus taxodiifolius*

ได้จัดให้มีการทดสอบ cytotoxic activity ของสารบริสุทธิ์ที่แยกได้ แต่ขณะนี้ได้ผลการทดสอบมา 6 ตัว ดังแสดงในตารางที่ 14

ตารางที่ 14 ผล cytotoxic activity ของสาร 1-9

Compound	EC_{50} (μg/mL)					
	Cell line					
	P-388	KB	Col-2	BCA-1	Lu-1	ASK
1	16.257	>20	>20	16.080	>20	>20
2	>20	>20	>20	3.87	>20	>20
3	0.112	0.016	0.076	0.028	0.021	0.275
4	0.053	0.003	0.029	0.014	0.008	0.128
5	>20	>20	>20	>20	>20	>20
6	>20	2.805	7.84	12.17	7.06	>20
7	-	-	-	-	-	-
8	-	-	-	-	-	-
9	-	-	-	-	-	-

หมายเหตุ $ED_{50} \leq 5$ μg/mL = active; - รอผลการทดสอบ

P-388: murine lymphocytic leukemia, KB: human nasopharyngeal carcinoma, COL-2: human colon cancer, BCA-1: human breast cancer, Lu-1: human lung cancer, ASK: rat glioma

จะเห็นว่า สาร 3 และ 4 มีผลการทดสอบดีมากดังแสดงในตารางที่ 14 สาร 1 และ สาร 5 นั้น inactive ในทุก cell lines ที่ทดสอบ สาร 2 นั้น active เฉพาะใน BCA-1 cell line แต่ไม่เด่นนัก สาร 6 นั้น active เฉพาะใน KB cell line แต่ไม่เด่นนัก ส่วนสาร 7-9 นั้นยังรอผลการทดสอบอยู่

10. การแยกสารองค์ประกอบจาก *Phyllanthus acutissima* และการทดสอบ cytotoxic activity ของส่วนแยกย่อยต่าง ๆ

เนื่องจากผลการทดสอบ cytotoxic activity ของส่วนสกัด MeOH ของ *Phyllanthus acutissima* อยู่ในเกณฑ์ดีมากมีค่า ED_{50} <4 mg/ml ในหลาย cell lines (ดูผลการทดสอบได้ในตารางที่ 3) และเมื่อนำมาทำ partition ได้เป็นส่วนสกัด hexanes, EtOAc, *n*-BuOH และน้ำแล้ว ได้จัดให้มีการทดสอบ cytotoxic activity ของส่วนสกัดย่อยด้วย พบว่า ส่วนสกัด ethyl acetate ให้ผลการทดสอบดีที่สุด (ดูผลการทดอสอบได้ในตารางที่ 6) จึงเห็นสมควรที่จะทำการศึกษาทางเคมีต่อไป

ได้ทำการแยกส่วนสกัด ethyl acetate (25.36 g) ของ *Phyllanthus acutissima* โดยใช้ column chromatography และใช้ acetone-hexane เป็น eluent สามารถแยก ได้ทั้งหมด 10 fractions ได้ส่ง fractions ต่าง ๆ ที่แยกได้ไปทดสอบ cytotoxic activity ที่ภาคสรีรวิทยาผลการทดสอบมีบาง fractions ที่แสดง activity อยู่ในเกณฑ์ดีดังแสดงในตารางที่ 15

ตารางที่ 15 ผลการทดสอบ cytotoxic activity ของ fractions ย่อยที่แยกได้จาก *Phyllanthus acutissima*

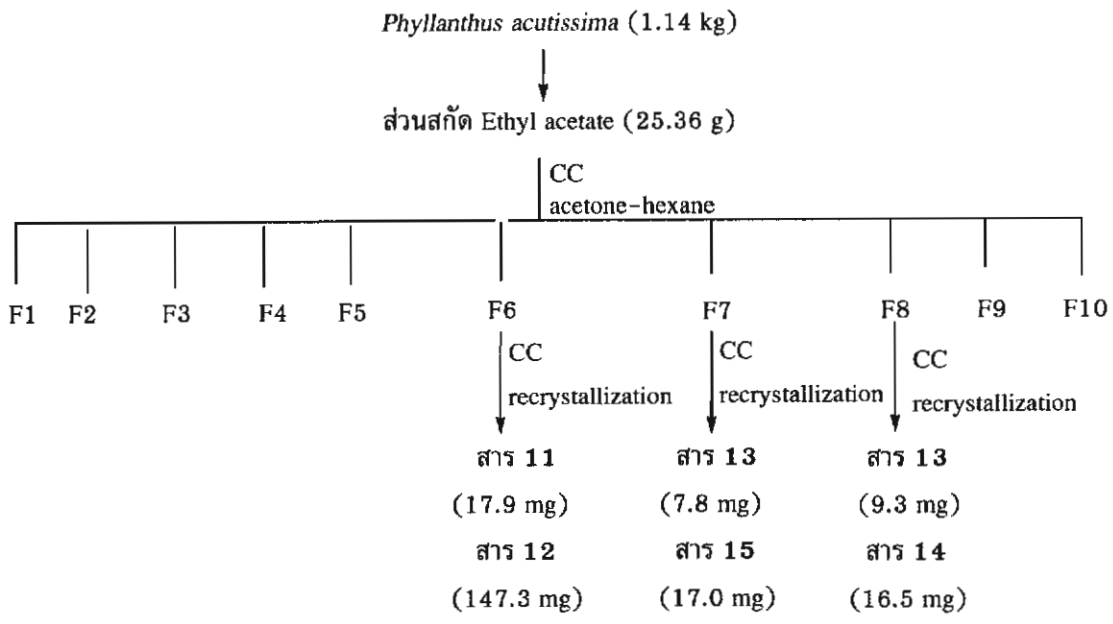
Fraction	Cell line					
	P-388	KB	Col-2	BCA-1	Lu-1	ASK
1	>20	>20	>20	>20	>20	>20
2	11.63	>20	>20	>20	>20	>20
3	11.9	>20	>20	>20	>20	>20
4	9.09	>20	>20	>20	>20	>20
5	9.1	18.03	19.56	13.41	>20	>20
6	7.09	15.42	15.30	9.6	17.89	16.43
7	1.3	17.48	>20	>20	>20	>17.9
8	<4	<4	<4	<4	4.81	<4
9	3.06	9.78	14.29	13.32	>20	>20
10	>20	>20	>20	>20	>20	>20

หมายเหตุ ค่าEC_{50} < 20 µg/ml จึงถือว่าแสดง activity

P-388: murine lymphocytic leukemia, KB: human nasopharyngeal carcinoma, COL-2: human colon cancer, BCA-1: human breast cancer, Lu-1: human lung cancer, ASK: rat glioma

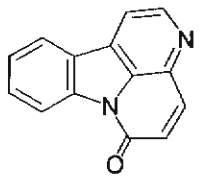
ได้ทำการแยกส่วนสกัด F6, F7 และ F8 ต่อ โดย column chromatography สามารถแยกสารได้ 5 ตัว คือ **11-15** ดังแสดงในแผนผังที่ 9

แผนผังที่ 9

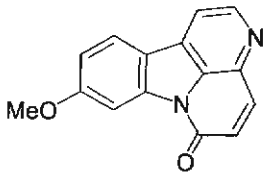


11. การพิสูจน์โครงสร้างของสาร 11-15

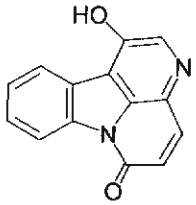
ได้ทำการพิสูจน์โครงสร้างของสาร **11-15** พบว่าเป็นจำพวก canthin-6-one alkaloids ทั้ง 4 ตัว ส่วนสาร **15** เป็นสารจำพวก coumarin มีชื่อเรียกว่า scopolatin ซึ่งมีสูตรโครงสร้างดังแสดง



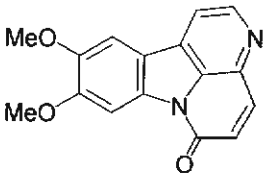
11



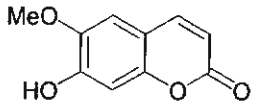
12



13



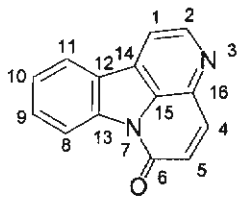
14



15

Physical properties และ spectroscopic data ของสาร 11-15

Compound 11 (Canthin-6-one)[17]



11

$C_{14}H_8ON_2$

Yellow needles

m.p. 154.0-155.5 °C (Lit.[17] 155-156 °C)

IR ν_{max} ($CHCl_3$): 3014, 1682, 1637, 1604, 1562, 1488, 1449, 1395, 1436, 1394, 1337, 1315, 1305, 1244, 1192, 1108, 1143, 1109, 1057, 846 cm^{-1}

UV λ_{max} (EtOH) nm (log ε): 226 (4.68), 251 (4.45), 259 (4.43), 268 (4.41), 297 (4.26), 361 (4.41), 379 (4.38)

EIMS (70 ev) *m/z*: 220 $[M]^+$ (100), 192 (78), 193 (29), 221 (20), 166 (6), 138 (7), 140 (4), 113 (3), 88 (3)

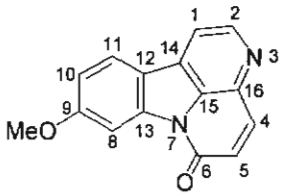
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.81 (d, J = 5.0 Hz, H-2), 8.65 (dd, J = 8.2 Hz, 0.7 Hz, H-8), 8.09 (ddd, J = 7.8, 1.1, 0.7 Hz, H-11), 8.02 (dd, J = 9.9, 0.6 Hz, H-4), 7.95 (d, J = 5.0 Hz, H-1), 7.70 (m, H-9), 7.52 (m, H-10), 6.98 (d, J = 9.9 Hz, H-5)

^{13}C NMR ($CDCl_3$): δ 116.35 (C-1), 117.29 (C-8), 122.64 (C-11), 124.39 (C-12), 125.63 (C-10), 128.92 (C-5), 130.27 (C-14), 130.86 (C-9), 132.04 (C-15), 136.24 (C-16), 139.45 (C-13), 139.62 (C-4), 145.84 (C-2), 159.51 (C-6)

หมายเหตุ การ assign ^{1}H และ ^{13}C signals นั้น อาศัยข้อมูลจาก 2D-correlation spectra (COSY, HMQC, HMBC และ NOESY)

สาร **11** เป็นสาร known แยกได้จาก *Ailanthus altissima*[17] และ *Eurycoma longifolia*[18]

Compound 12 (9-Methoxycanthin-6-one)[19]



12

$C_{15}H_{10}O_2N_2$

Yellow needles CH_2Cl_2-MeOH

m.p. 178.5-179.5 °C (Lit.[19] 177-179 °C)

IR ν_{max} ($CHCl_3$): 3013, 2970, 1683, 1635, 1611, 1496, 1454, 1439, 1425, 1393, 1351, 1333, 1314, 1280, 1247, 1152, 1111, 1096, 1031, 847 cm^{-1}

UV λ_{max} (EtOH) nm (log ε): 262 (4.73), 269 (4.89), 305 (4.40), 347 (4.57)

EIMS (70 ev) *m/z* 250 [M^+] (100), 235 (5), 221 (50), 207 (30), 192 (16), 179 (29), 164 (3), 153 (10)

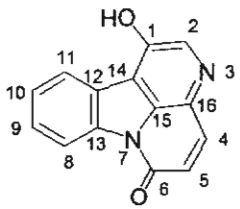
^{1}H NMR ($CDCl_3$): δ 8.65 (d, J = 5.0 Hz, H-2), 8.03 (d, J = 2.4 Hz, H-8), 7.89 (d, J = 9.8 Hz, H-4), 7.78 (d, J = 8.6 Hz, H-11), 7.69 (d, J = 5.0 Hz, H-1), 6.93 (dd, J = 8.6, 2.4Hz, H-10), 6.83 (d, J = 9.8 Hz, H-5), 3.90 (s, 9-OMe)

^{13}C NMR ($CDCl_3$): δ 55.91 (9-OMe), 101.18 (C-8), 114.07 (C-10), 115.40 (C-1), 117.08 (C-12), 123.20 (C-11), 128.39 (C-5), 130.29 (C-14), 132.18 (C-15), 135.57 (C-16), 139.77 (C-4), 141.10 (C-13), 145.90 (C-2), 159.58 (C-6), 162.40 (C-9)

หมายเหตุ การ assign ^{1}H และ ^{13}C signals นั้น อาศัยข้อมูลจาก 2D-correlation spectra (COSY, HMQC, HMBC และ NOESY)

สาร **12** เป็นสาร known แยกได้จาก *Simaba multiflora*[19] และ Eurycoma longifolia[20]

Compound 13 (1-Hydroxycanthin-6-one)[21]



13

$C_{14}H_8O_2N_2$

Yellow Solid CH_2Cl_2-MeOH

m.p. 224-225 °C (Lit.[21] 220 °C)

IR ν_{max} (KBr): 3422, 1671, 1636, 1602, 1579, 1443, 1352, 1328, 1259, 1243, 1216, 833, 790, 742 cm^{-1}

UV λ_{max} (MeOH) nm (log ε): 269 (3.74, 278 (3.79), 285 (3.65), 301 (3.64), 340 (3.62), 364 (3.71), 372 (3.96)

EIMS (70 ev) m/z 236 $[M]^+$ (100), 208 (66), 206 (29), 153 (41), 118 (23), 209 (18), 129 (18)

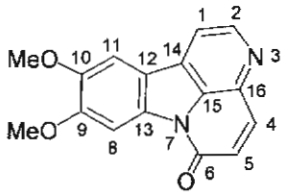
^1H NMR ($CDCl_3$: MeOH, 1:1): δ 8.66 (d, J = 8.2 Hz, H-8), 8.34 (s, H-2), 8.29 (d, J = 7.7 Hz, H-11), 7.96 (d, J = 9.7 Hz, H-4), 7.68 (dd, J = 7.6, 7.7 Hz, H-9), 7.56 (dd, J = 7.6, 7.7 Hz, H-10), 6.82 (d, J = 9.7 Hz, H-5)

^{13}C NMR ($CDCl_3$): δ 116.09 (C-14), 116.70 (C-8), 123.85 (C-5 and C-12), 124.35 (C-11), 125.73 (C-10), 128.12 (C-16), 129.21 (C-9), 133.62 (C-15), 135.04 (C-2), 138.26 (C-13), 138.26 (C-13), 138.45 (C-4), 151.48 (C-1), 160.61 (C-6)

หมายเหตุ การ assign ^1H และ ^{13}C signals นั้น อาศัยข้อมูลจาก 2D-correlation spectra (COSY, HMQC, HMBC และ NOESY)

สาร 13 เป็นสาร known แยกได้จาก *Ailanthus firaldii*[21]

Compound 14 (9,10-Dimethoxycanthin-6-one)[18]



14

$C_{18}H_{12}O_3N_2$

Yellow needles

m.p. 212-214 °C dec. (Lit.[18] 213-215 °C)

IR νmax ($CHCl_3$): 3025, 2968, 1672, 1633, 1587, 1486, 1464, 1439, 1414, 1393, 1362, 1338, 1303, 1283, 1235, 1191, 1184, 1157, 1118, 1057, 1020, 928, 841 cm^{-1}

UV λ_{max} (EtOH) nm (log ε): 229 (4.32), 272 (4.30), 280 (4.38), 299 (3.97), 309 (3.93), 360 (4.03), 374 (4.00)

EIMS (70 ev) m/z: 280 [M]+(100), 265 (14), 237 (88), 209 (43), 194 (28), 181 (10), 167 (26), 139 (10), 127 (5)

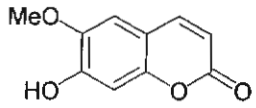
^1H NMR ($CDCl_3$): δ 8.77 (d, J = 5.0 Hz, H-2), 8.17 (s, H-8), 7.99 (d, J = 9.8 Hz, H-4), 7.82 (d, J = 5.0 Hz, H-1), 7.44 (s, H-11), 6.94 (d, J = 9.8 Hz, H-5), 4.08 (s, 9-OMe), 4.03 (s, 10-OMe)

^{13}C NMR ($CDCl_3$): δ 56.39 (10-OMe), 56.57 (9-OMe), 100.23 (C-8), 104.00 (C-11), 115.47 (C-1), 116.33 (C-12), 128.57 (C-5), 130.58 (C-14), 131.89 (C-15), 134.55 (C-13), 135.69 (C-16), 139.59 (C-4), 145.73 (C-2), 147.99 (C-10), 152.26 (C-6)

หมายเหตุ การ assign ^{1}H และ ^{13}C signals นั้น อาศัยข้อมูลจาก 2D-correlation spectra (COSY, HMQC, HMBC และ NOESY)

สาร **14** เป็นสาร known แยกได้จาก *Eurycoma longifolia*[18]

Compound 15 (Scopoletin)[22]



15

$C_{10}H_8O_4$

Yellow needles

m.p. 201.8 -202.4 °C (Lit.[22] 203-205 °C)

IR ν_{max} (KBr): 3294, 1703, 1608, 1561, 1509, 1455, 1434, 1291, 1263, 1141, 1016, 923, 857, 529 cm^{-1}

UV λ_{max} (EtOH) nm (log ε): 226 (4.24), 250 (3.79), 257 (3.75), 295 (3.80), 343 (4.18)

EIMS (70 ev) *m/z*: 192 $[M]^{+}$(75), 193 (100), 164 (35), 149 (27), 121 (27), 70 (12)

^{1}H NMR (CD_3COCD_3): δ 8.80 (br, 7-OH), 7.83 (d, J = 9.5 Hz, H-4), 7.18 (s, H-5), 6.78 (s, H-8), 6.16 (d, J = 9.5 Hz, H-3)

^{13}C NMR (CD_3COCD_3): δ 56.66 (6-OMe), 103.67 (C-8), 109.91 (C-5), 112.04 (C-4a), 113.25 (C-3), 144.61 (C-4), 145.93 (C-1a), 151.09 (C-6), 151.81 (C-7), 161.26 (C-2)

หมายเหตุ การ assign ^{1}H และ ^{13}C signals นั้น อาศัยข้อมูลจาก 2D-correlation spectra (COSY, HMQC, HMBC และ NOESY)

สาร **15** เป็นสาร known แยกได้จาก *Simaba multiflora*[22]

ในการแยกสารจาก EtOAc extract ของ *Phyllanthus acutissima* (ตัวอย่างที่ 2) ซึ่งมีปริมาณมากกว่าปรากฏว่า สามารถแยกสาร triterpenes ได้อีก 2 ตัว คือสาร **16** และ **17** ซึ่งเป็น analogues กัน การวิเคราะห์ทาง nuclear magnetic resonance ในเบื้องต้น พบว่า มี cyclopropane ring อยู่ที่ตำแหน่ง 13, 14 เพราะ H-13 และ H-14 มี HMBC correlations กับ C-17 สารทั้งสองต่างมี olefinic protons 2 ตัว นอกจากนี้ยังพบ aromatic protons อยู่ในโครงสร้างทั้ง 2 อีกด้วย คาดว่าเป็นสารใหม่ทั้ง 2 ตัว แต่เนื่องจากเพิ่งแยกสาร 2 ตัวนี้ได้ และสารทั้งสองเป็นสารที่โมเลกุลใหญ่มาก จึงยังคงต้องศึกษาโครงสร้างด้วยเทคนิคทางสเปคโทรสโคปีเพิ่มเติมอีก ขณะนี้ไม่สามารถนำข้อมูลมาสรุปในรายงานครั้งนี้ได้

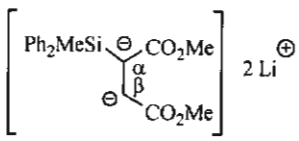
ได้จัดให้มีการทดสอบ cytotoxic activity ของสารบริสุทธิ์ทุกตัวที่แยกได้ แต่ยังรอผลการทดสอบอยู่ กลุ่มวิจัยจะได้รวบรวมเพื่อการตีพิมพ์ต่อไป

บทวิจารณ์

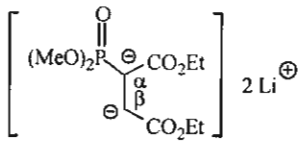
สรุปผลงานวิจัยในรอบ 3 ปี

- **ด้านการสังเคราะห์**

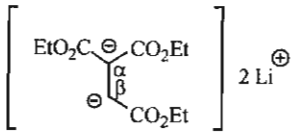
ได้ศึกษาปฏิกิริยาของ vicinal dianions **3**, **4**, **18**, **42** และ **70** โดยพบว่า vicinal dianion ทุกตัวทำปฏิกิริยากับ electrophiles เช่น carbonyl compounds เป็นแบบ regioselective ที่ β-carbon



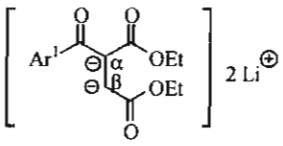
3



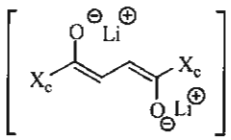
4



18

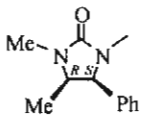


42

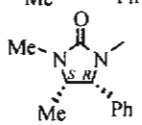


70a,70b

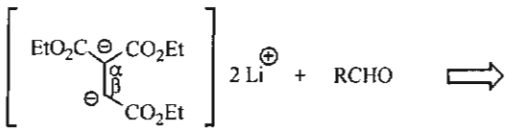
70a X_c =



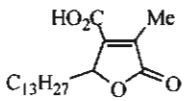
70b X_c =



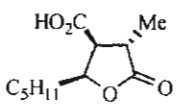
ได้แสดงให้เห็นประโยชน์ของ vicinal dianion **18** ว่าเป็น reagent ที่สามารถใช้เตรียม α,β,γ-trisubstituted γ-butyrolactone natural products ได้เช่น (±)-lichesterinic acid (**27**), (±)-phaseolinic acid (**28**), (±)-nephromopsinic acid (**29**), (±)-rocellaric acid (**30**) และ (±)-dihydroprotolichesterinic acid (**31**) ได้



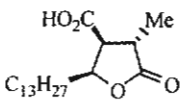
18



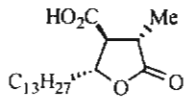
27



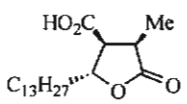
28



29

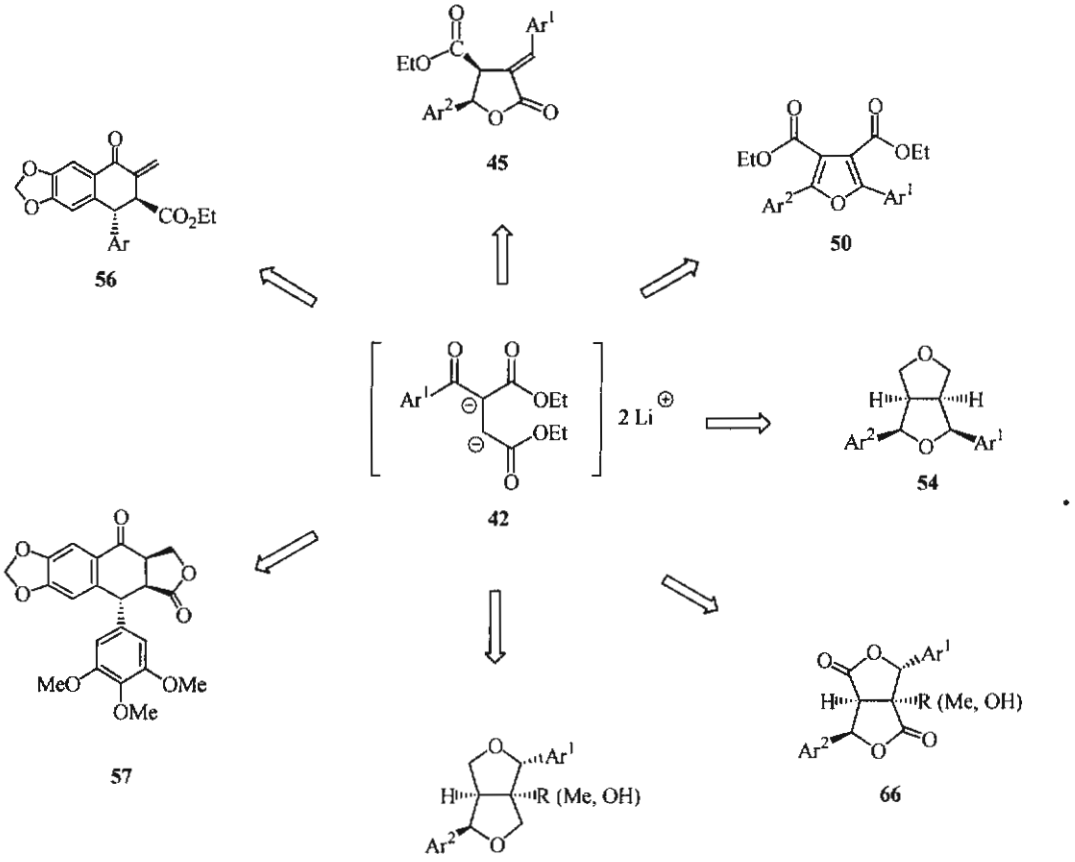


30



31

นอกจากนี้ยังพบว่าสามารถใช้ vicinal dianion **42** สำหรับเตรียมสารประกอบ α-arylidene paraconic ester **45**, tetrasubstituted furans **50**, furofurans **54**, thuriferic acid ethyl esters **57**, picropodophyllone **(57)**, bislactones **66**, และ furofurans **68** รวมทั้ง gmelinol **(68f)**ซึ่งมี anti-malarial activity



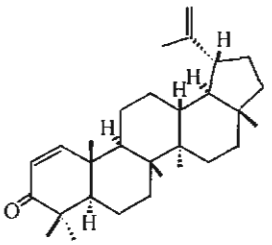
ส่วน vicinal dianion **70b** ใช้เป็น reagent สำหรับการเตรียม (*R*)-arylmethyl-γ-butyrolactones **75b** ได้ ซึ่งเป็นสารเริ่มต้นที่สำคัญสำหรับการเตรียม lignan natural products ต่าง ๆ ได้ตามที่มีผู้รายงานไว้ใน literature

- **ด้านผลิตภัณฑ์ธรรมชาติ**

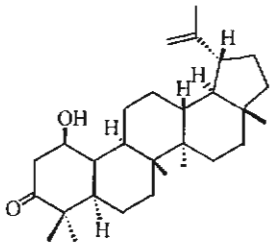
สำหรับงานวิจัยด้านผลิตภัณฑ์ธรรมชาตินั้น กลุ่มวิจัยได้ที่ตั้งเป้าหมายว่าจะค้นหาพืชสมุนไพรไทยที่มีสารองค์ประกอบจำพวก lignans ใหม่ ๆ ที่อาจมี cytotoxic activity และมีแนวโน้มว่าจะพัฒนาเป็นยารักษามะเร็งได้ ได้เก็บและทำการทดสอบ cytotoxic activity ของพืชในสกุล *Phyllanthus* (วงศ์ Euphorbiaceae) รวมทั้งหมด 18

สปีชีส์ ในจำนวนนี้พบว่า *Phyllanthus taxodiifolius* และ *Phyllanthus acutissima* นั้นแสดง potent cytotoxic acitivity และได้ทำการศึกษาทางเคมีของพืชทั้ง 2 สปีชีส์นี้อย่างละเอียด

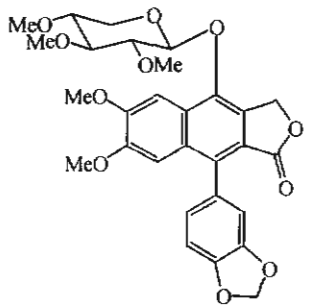
จาก *Phyllanthus taxodiifolius* พบสาร triterpenes 2 ตัว ได้แก่ glochidone (1) และ glochidonol (2) พบสารจำพวก lignan glycosides 4 ตัว ได้แก่ cleistanthin A methyl ether (3), cleistanthin A (4), cleistanthoside A (5) และสาร lignan glycoside ใหม่ คือ taxodiifoloside (9) ซึ่งมีโครงสร้างเป็น monoacetate ของ cleistanthoside A พบสารจำพวก amide 2 ตัว ได้แก่ *N*-benzoylphenylalaninyl-*N*-benzoylphenylalaninate (7) และ *N*-benzoylphenylalaninoylphenylalaninol acetate (8) นอกจากนี้ยังพบสารอนุพันธ์ของกรดเบนโซอิก คือ 4-hydroxy--3-methoxybenzoic acid (10)



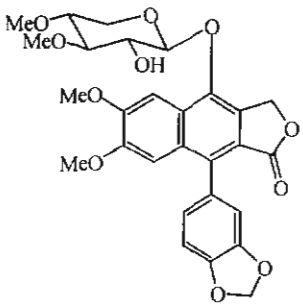
1



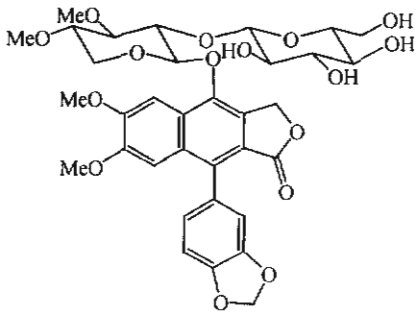
2



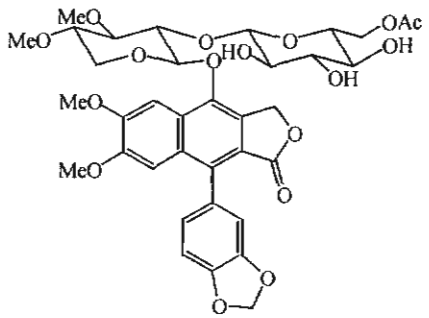
3



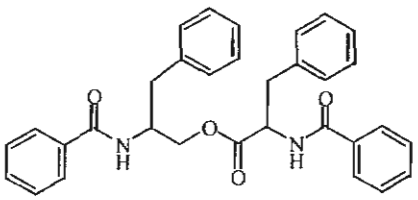
4



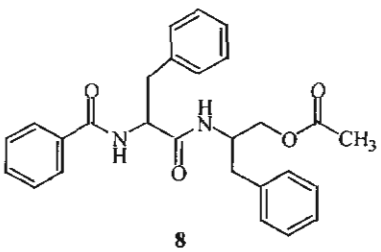
5



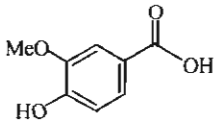
9 (New)



7



8



10

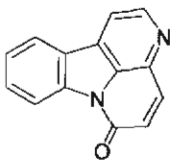
ได้ทำการวิเคราะห์หาโครงสร้างโดยวิธีทาง spectroscopy และการเปรียบเทียบกับใน literature แต่เนื่องจากเป็นข้อมูลที่ได้จาก literature ไม่ค่อยสมบูรณ์นัก ซึ่งข้อมูลสำหรับสารบางตัว ได้มีรายงานแต่เฉพาะ ^{1}H NMR และ บางตัวก็มี ^{13}C NMR ด้วย แต่ไม่มีการทำ 2D-NMR experiments เพื่อการ assign ตำแหน่ง chemical shifts ต่าง ๆ ดังนั้นกลุ่มวิจัยของเราจึงน่าจะมีการ assign chemical shifts ได้ถูกต้องมากกว่า เนื่องจากได้ทำ 2D-NMR experiments ของสาร lignans ที่แยกได้ สำหรับสาร 5 นั้นการละลายไม่ดีนักจึงได้เตรียมเป็นอนุพันธ์ tetraacetate คือ cleistanthoside A tetraacetate (**5a**) โดยปฏิกิริยากับ acetic anhydride และ *N*,*N*-dimethylaminopyridine (DMAP) ที่อุณหภูมิห้อง แล้วได้ทำการวิเคราะห์โครงสร้างของ cleistanthoside A tetraacetate (**5a**) แทน cleistanthoside A (**5**) แม้ว่าได้ทำ 2D-NMR experiment ของ **5** แล้วก็ตาม แต่การวิเคราะห์ทำไม่ได้ดีเนื่องจากสัญญาณขึ้นซ้อนกันและ broad มาก

ได้ทำ methylation ของ cleistanthin A (**4**) โดยปฏิกิริยากับ methyl iodide/NaH/DMSO ปรากฏว่าได้ product ที่มี ^{1}H NMR เหมือน cleistanthin A methyl ether (**3**) ทุกประการ จึงสรุปได้ว่า สาร **3** เป็น analogue ของสาร **4** ขณะนี้ได้พยายามทำ monoacetylation ของสาร **5** ด้วย เพื่อพิสูจน์ว่า สาร **9** เป็น analogue ของสาร **5** แต่ยังไม่ได้นำสาร **9** ไปทำ fully acetylation ทั้งนี้เพราะมีอยู่ปริมาณน้อยต้องทำการวัด physical properties ต่าง ๆ ก่อน และยังต้องทดสอบ cytotoxic activity อีกด้วย ส่วนสาร **6** มีปริมาณน้อยมากไม่สามารถหาโครงสร้างได้ และยังไม่พบในตัวอย่างพืชที่เก็บครั้งที่ 2 ด้วย

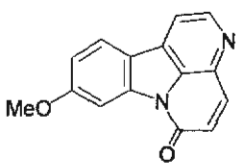
ในแต่ละขั้นตอนของงานวิจัยด้านนี้ได้ทำการทดสอบ cytotoxic activity โดยตลอด ทั้งในส่วนสกัด ใน fractions และในสารบริสุทธิ์ ได้ผลการทดสอบ cytotoxic activity ของสารที่แยกได้ ซึ่งพบว่าสาร **3** และ **4** มีผลการทดสอบอยู่ในเกณฑ์ดีมาก (สาร **3**: ED_{50} ใน P-388 cell line 0.112 μg/mL ใน KB cell line 0.016 μg/mL ใน Col-2 cell line 0.076 μg/mL ใน BCA-1 cell line 0.028 μg/mL ใน Lu-1 cell line 0.021 μg/mL และใน ASK cell line 0.275 μg/mL; สาร **4** ED_{50} ใน P-388 cell line 0.053 μg/mL ใน KB cell line 0.003 μg/mL ใน Col-2 cell line 0.029 μg/mL ใน BCA-1 0.014 μg/mL ใน Lu-1 cell line 0.008 μg/mL และใน ASK cell line 0.128 μg/mL) สำหรับ สาร **5** และ สาร **6** นั้นไม่ active ขณะนี้ยังรอผลการทดสอบสาร **7**-**9** อยู่

ขณะนี้กำลังรอผลการวัดทาง high resolution mass spectrometry และรอผลการทดสอบ cytotoxic activity จึงได้เริ่มเตรียม manuscript เพื่อการตีพิมพ์งานที่เกี่ยวกับ *Phyllanthus taxodiifolius* นี้ไปบ้างแล้ว

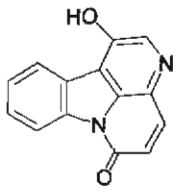
การศึกษาสารองค์ประกอบจาก *Phyllanthus acutissima* ตัวอย่างที่ 1 นั้น พบสารจำพวก alkaloids 4 ตัว และ coumarin อีก 1 ตัว alkaloids ทั้ง 4 ตัวเป็นชนิด canthin-6-one alkaloid ได้แก่ canthin-6-one (**11**), 9-methoxy-canthin-6-one (**12**), 1-hydroxycanthin-6-one (**13**), 9,10-dimethoxycanthin-6-one (**14**) ส่วน coumarin ที่แยกได้คือ scopoletin (**15**)



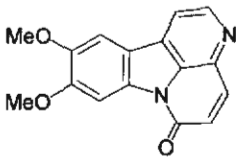
11



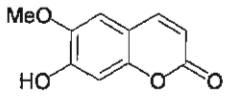
12



13



14



15

เนื่องจาก *Phyllanthus acutissima* ตัวอย่างที่ 1 มีปริมาณน้อย จึงแยกสารไม่ได้มากนัก จึงได้ทำการแยกสารจาก *Phyllanthus acutissima* ตัวอย่างที่ 2 ซึ่งมีปริมาณมากกว่า ปรากฏว่าแยกสาร triterpenes ได้ 2 ตัว คือ สาร **16** และ **17** สารทั้ง 2 ต่างมี cyclopropane ring อยู่ที่ตำแหน่ง 13, 14 มี olefinic protons 2 protons และมี aromatic protons อยู่ในโครงสร้างด้วย คาดว่าเป็นสารใหม่ทั้ง 2 ตัว แต่เนื่องจากเพิ่งแยกสาร 2 ตัวนี้ได้ และสารทั้งสองเป็นสารที่โมเลกุลใหญ่มาก (M^+ = 614 และ 658) จึงยังคงต้องศึกษาโครงสร้างด้วยเทคนิคทางสเปคโทรสโคปีเพิ่มเติมต่อไปอีก ขณะนี้ไม่สามารถนำข้อมูลมาสรุปในรายงานครั้งนี้ได้ และยังรอผลการทดสอบ cytotoxic activity อยู่ด้วย กลุ่มวิจัยจะได้รวบรวมเพื่อการตีพิมพ์ต่อไป

เอกสารอ้างอิง

เอกสารอ้างอิง

ด้านการสังเคราะห์

1. Methylenolactocin

   Isolation: Park, B.K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751.

   Synthesis: Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829 and references cited therein: Lertvorachon, J.; Meepowpan, P.; Thebtaranonth, Y. *Tetrahedron* **1998**, *54*.

2. Protolichesterinic acid

   Isolation: Murta, M.M.; de Azevedo, M.B.M.; Greene, A. *J. Org. Chem.* **1993**, *58*, 7537 and references cited therein.

   Synthesis: Ghatak, A.; Sarkar, S.; Ghosh, S. *Tetrahedron* **1997**, *53*, 17335 and references cited therein.

3. Crump, R.A.N.C.; Fleming, I.; Hill, J.H.M.; Parker, D.; Reddy, N.L.; Watersom, D. *J. Chem. Soc. Perkin Trans. I* **1992**, 3277.

4. Linke, S.; Kurz, J.; Lipinsik, D.; Gau, W. *Liebigs Ann. Chem.* **1980**, 542.

5. Aftab, T.; Carter, C.; Chrislieb, M.; Hart, J.; Nelson, A. *J. Chem. Soc. Perkin Trans. I*, **2000**, 711.

6. Lichesterinic acid

   Isolation: Cavallito, C.J.; Fruehauf, D.M. *J. Am. Chem. Soc.* **1948**, *70*, 3724.

   Synthesis: D' Onofrio, F.; Margarita, R.; Parlanti, L.: Piancatelli, G.; Sbraga, M. *Chem. Commun.* **1998**, 185 and references cited therein.

7. Phaseolinic acid

   Isolation: Mahato, S.B.; Siddiqui, K.A.I.; Bhattacharya, G.; Ghosal, T.; Miyahara, K.; Sholichin, M.; Kawasaki, T. *J. Nat. Prod.* **1987**, *50*, 245.

   Synthesis: Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385.

8. Nephromopsinic acid

   Isolation: Asano, M.; Azumi, T. *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 995; van Tamelen, E.E.; Rosenberg Bach, S. *J. Amer. Chem. Soc.* **1958**, *80*, 3079; Huneck, S.; Follmann, G. *Z. Naturforsch. B* **1967**, *22*, 666.

   Synthesis: Forster, A.; Fitremann, J.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 7097 and references cited therein; Mulzer, J.; Kattner, L.; Strecker, A.R.; Schroder, C.; Buschmann, J.; Lehmann, C.; Luger, P. Highly Felkin-Ahn selective Hiyama addition of chiral allylic bromides to aldehydes. Application to the first synthesis of nephromopsinic acid and its enantiomer. *J. Amer. Chem. Soc.* **1991**, *113*, 4218.

9. Roccellaric acid

   Isolation: Bruckner, C.H.; Reissig, H.U. *J. Org. Chem.* **1998**, *53*, 2440.

   Synthesis: Sibi, M.P.; Ji, J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 274; Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron Asym.* **1993**, *4*, 457.

10. Dihydroprotolichesterinic acid
Isolation: Huneck, S.; Follmann, G. *Z. Naturforsch. B* **1967**, *22*, 666.
Synthesis: Mandal, P.K.; Roy, S,C. *Tetrahedron* **1999**, *44*, 11395: Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron Asym.* **1993**, *4*, 457.
11. Hwang, E.I.; Yun, B.S.; Kim, Y.K.; Kwon, B.M.; Kim, H.G.; Lee, H.B.; Jeong, W.J.; Kim, S.K. *J. Antibiot.* **2000**, *53*, 903.
12. (a) Stetter, H.; Kuhlman, H. *Org. React.* **1991**, *40*, 407.
(b) Albright, J.D. *Tetrahedron* **1983**, *39*, 3207.
(c) Reutrakul, V.; Nimgirawath, S.; Panichanun, S.; Ratananukul, P. *Chem. Lett.* **1979**, 399.
13. San Feliciano, A.; Lopez, J.L.; Medarde, M.; Mignel del Corral J.M.; de Pascual-Teresa, B.; Puebla, P. *Tetrahedron* **1988**, *44*, 7255.
14. (a) Murphy, W.S.; Wattanasin, S. *J. Chem. Soc. Perkin Trans. 1* **1982**, 271.
(b) Andrews, R.C.; Teague, S.J.; Meyers, A.I. J. Am. Chem. Soc. **1988**, 110, 7854.
(c) Yoshida, S.; Yamanaka, T.; Miyake, T.; Moritani, Y.; Ohmizu, H.; Iwasaki; T. *Tetrahedron* **1997** *53*, 9585.
15. (a) Wards, R.S. *Synthesis* **1992**, 719.
(b) Peterson, J.R.; Do, H.D.; Rogers, R.D. *Synthesis* **1991**, 275 and references cited .
(c) Canel, C.; Moraes, R.M.; Dayan F.E.; Ferreira, D. *Phytochemistry* **2000**, *54*, 115.
16. (a) Anjaneyulu, A.S.R.; Rao, V.K.; Row, L.R.; Subrahmanyam, C.; Pelter, A.; Ward, R.S. *Tetrahedron* **1975**, *31*, 1277.
(b) Griggith, R.; Chanphen, R.; Leach, S.P.; Keller, P.A. *Biorg. & Med. Chem. Lett.* **2002**, *12*, 539.

ด้านผลิตภัณฑ์ธรรมชาติ

1. Ganguly, A.K.; Govindachari, T.R., Mohamed, P.A., Rahimtulla, A.D.; Viswanathan, N. *Tetrahedron* **1966**, *22*, 1513.
2. Srivastava R.; Kulshreshtha, D.K. *Phytochemistry* **1988**, *27*, 3575.
3. Wai-Haan, H.; Man-Moon, L. *Phytochemistry* **1978**, *17*, 156.
4. Matsunaga, S.; Tanaka, R.; Takaoka, Y.; In, Y.; Ishida, T.; Rahmani, M.; Ismail, H.B.M. *Phytochemistry* **1993**, *32*, 165.
5. Ayer, W.A.; Flanagan, R.J.; Reffstrup, T. *Tetrahedron* **1984**, *40*, 2069.
6. Anjaneyulu, A.S.R.; Atchuta Rahmaiah, P. Ramachandra Row, L. Venkateswarlu, R.; Pelter, A.; Wards, R.S. *Tetrahedron* **1981**, *37*, 3641.
7. Govindachari, T.R.; Sathe, S.S.; Viswanathan, N.; Pai, B.R.; Srinivasan, M. *Tetrahedron* **1969**, *25*, 2815.
8. Govindachari, T.R.; Sathe, S.S.; Viswanathan, N.; Pai, B.R.; Srinivasan, M. *Tetrahedron Lett.* **1967**, 3517.
9. Sastry, K.V.; Venkata Rao, E. Buchanan, J.G.; Sturgeon, R.J. *Phytochemistry* **1987**, *26*, 1153.
10. Sastry, K.V.; Venkata Rao, E. *Planta Med.* **1983**, *47*, 227.
11. Ghosal, S.; Chauhan, R.P.S.; Srivastava, R.S. *Phytochemistry* **1974**, *13*, 1933.

12. Bachmann, T.L.; Ghia F.; Torssell, K.B.G. *Phytochemistry* **1993**, *33*, 189.

13. Catalán, C.A.N.; de Heluani, C.S.; Kotowicz, C.; Gedris, T.E.; Herz, W. *Phytochemistry* **2003**, *64*, 625.

14. McCorkindale, N.J.; Baxter, R.L.; Roy, T.P.; Shields, H.S.; Stewart R.M.; Hutchinson, S.A. *Tetrahedron* **1978**, *34*, 2791.

15. Ishiguro K.; Nagata, S.; Fugumoto, H.; Yamaki, M.; Takago, S.; Isoi, K. *Phytochemistry* **1991**, *30*, 3639..

16. Lee, C.-K.; Lee, P.-H.; Kuo Y.-H. *J. Chin. Chem. Soc.*, **2001**, *48*, 1053.

17. Ohmoto, T.; Tanaka, R.; Nakaido, T. *Chem. Pharm. Bull.* **1976**, *24*, 1532.

18. Mitsunaga, K.; Koike, K.; Tanaka, T.; Ohkowa, Y.; Kobayashi, Y.; Ohmoto, T. *Phytochemistry* **1994**, *35*, 799.

19. Polonsky, J.; Gallas, J.; Varenne, J.; Prange, T.; Pascard, C. *Tetrahedron Lett.* **1982**, *23*, 869.

20. Kardono, L.B.S.; Angerhofer, C.K.; Tsausi, S.; Padmawinata, K.; Pezzuto, J.M.; Kinghorn, A.D. *J. Nat. Prod.* **1991**, *54*, 1360.

21. Khan, S.A.; Shamsuddin K.M. *Phytochemistry* **1981**, *20*, 2062.

22. Arisawa, M.; Kinghorn A.D.; Cordell, G.A.; Farnsworth, N.R. *J. Nat. Prod.* **1983**, *46*, 222.

Output ที่ได้จากโครงการ

Output ที่ได้จากโครงการ

ผลงานวิจัยที่ได้ตีพิมพ์แล้ว

1. "Vicinal Dianion of Triethyl Ethanetricarboxylate: Syntheses of (±)-Lichesterinic Acid, (±)-Phaseolinic Acid, (±)-Nephromopsinic Acid, (±)-Rocellaric Acid and (±)-Dihydroprotolichesterinic Acid" M. Pohmakotr, W. Harnying, P. Tuchinda, and V. Reutrakul, *Helv. Chem. Acta* **2002**, *85*, 3792.
2. "Vicinal dianions of diethyl α-aroylsuccinates: a general synthetic route to α-aroyl- and α-arylidene-γ-butyrolactones" M. Pohmakotr, L. Sampaongoen, Arisara Issaree, P. Tuchinda and V. Reutrakul, *Tetrahedron Lett.* **2003**, *44*, 6717.
3. "Vicinal dianions of diethyl α-aroylsuccinates: preparation of functionalized-2,3-dihydrofurans and furans, and diaxial 2,4-diaryl-3,7-bicyclo[3.3.0]octanes" M. Pohmakotr, A. Issaree, L. Sampaongoen, P. Tuchinda and V. Reutrakul, *Tetrahedron Lett.* **2003**, *44*, 7937.
4. "Highly diastereoselective alkylation of vicinal dianions of chiral succinic acid derivatives: a new general strategy to (*R*)-β-arylmethyl-γ-butyrolactones" M. Pohmakotr, D. Soorukram, P. Tuchinda, S. Prabpai, P. Kongsaeree, V. Reutrakul, *Tetrahedron Lett.* **2004**, *45*, 4315.

ผลงานวิจัยที่กำลังจะตีพิมพ์

กำลังเตรียม manuscripts และทำเพิ่มเติม

1. Synthesis of Thuriferic Acid Ethyl Ester and Analogues and Picropodophyllone คาดว่าจะ submit ไปตีพิมพ์ใน Tetrahedron
2. A General Synthetic Route to 1-Substituted-2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes: Synthesis of Gmelinol คาดว่าจะ submit ไปตีพิมพ์ใน Organic Letters
3. Lignan glycosides from *Phyllanthus taxodiifolius* คาดว่าจะ submit ไปตีพิมพ์ใน Planta Medica
4. Triterpenes and alkaloids from *Phyllanthus accutissima* คาดว่าจะ submit ไปตีพิมพ์ใน Tetrahedron

Abstract ในการประชุมวิชาการนอกประเทศ

1. เสนอผลงานแบบ oral Communication เรื่อง "Synthetic Utilities of Vicinal Dianions of Succinic Acid Derivatives" ในการประชุม " The 7th International Symposium on Carbanion Chemistry (ISCC-7)" ที่ University of Alicante (Spain) ระหว่างวันที่ 7-11 July 2004 บทคัดย่อหมายเลข C-27

Abstract ในการประชุมวิชาการในประเทศของนักศึกษา
แบบปากเปล่า

1. เสนอผลงานของนักศึกษาแบบ oral เรื่อง "Synthetic approach to tetrasubstituted dihydrofurans and tetrahydrofurans" ในการประชุม Perch conference II ที่โรงแรมจอมเทียน ปาล์มบีช รีสอร์ท เมืองพัทยา ชลบุรี ระหว่างวันที่ 11-14 พฤษภาคม 2546 บทคัดย่อหมายเลข OC-O14
2. เสนอผลงานของนักศึกษาแบบ oral เรื่อง "Dianions of a-aroylsuccinic esters: Synthesis of Thuriferic acid and analogues" ในการประชุม Perch conference II ที่โรงแรมจอมเทียน ปาล์มบีช รีสอร์ท เมืองพัทยา ชลบุรี ระหว่างวันที่ 11-14 พฤษภาคม 2546 บทคัดย่อหมายเลข OC-O15

แบบโปสเตอร์

1. เสนอผลงานของนักศึกษาแบบโปสเตอร์ เรื่อง "Dianions of α-aroylsuccinic esters: Synthesis of a Podophyllotoxin Precursor" ในการประชุม Perch conference I ที่โรงแรมการ์เด้นซีวิวรีสอร์ท เมืองพัทยา ชลบุรี ระหว่างวันที่ 12-15 พฤษภาคม 2545 บทคัดย่อหมายเลข OC-P21
2. เสนอผลงานของนักศึกษาแบบโปสเตอร์ เรื่อง "Reaction of vicinal dianion derived from triethyl ethanetricarboxylate" ในการประชุม Perch conference I ที่โรงแรมการ์เด้นซีวิวรีสอร์ท เมืองพัทยา ชลบุรี ระหว่างวันที่ 12-15 พฤษภาคม 2545 บทคัดย่อหมายเลข OC-P24
3. เสนอผลงานของนักศึกษาแบบโปสเตอร์เรื่อง "Reaction of vicinal dianions derived from α-aroylsuccinic esters: Synthesis of some 2,6-diaryl-3,7-dioxabicyclo(3.3.0)octane-4,8-diones" ในการประชุม Perch conference II ที่โรงแรมจอมเทียน ปาล์มบีช รีสอร์ท เมืองพัทยา ชลบุรี ระหว่างวันที่ 11-14 พฤษภาคม 2546 บทคัดย่อหมายเลข OC-P19
4. เสนอผลงานของนักศึกษาแบบโปสเตอร์เรื่อง "Synthetic approach to furofuran lignans" ในการประชุม Perch conference III ที่โรงแรมจอมเทียน ปาล์มบีช รีสอร์ท เมืองพัทยา ชลบุรี ระหว่างวันที่ 9-12 พฤษภาคม 2547 บทคัดย่อหมายเลข OC-P24
5. เสนอผลงานของนักศึกษาแบบโปสเตอร์เรื่อง "Isolation and structure identification of bioactive compounds form *Phyllanthus taxodiifolius*" ในการประชุม Perch conference III ที่โรงแรมจอมเทียน ปาล์มบีช รีสอร์ท เมืองพัทยา ชลบุรี ระหว่างวันที่ 9-12 พฤษภาคม 2547 บทคัดย่อหมายเลข OC-P7

ภาคผนวก

Vicinal Dianion of Triethyl Ethanetricarboxylate: Syntheses of (±)-Lichesterinic Acid, (±)-Phaseolinic Acid, (±)-Nephromopsinic Acid, (±)-Rocellaric Acid, and (±)-Dihydroprotolichesterinic Acid

by **Manat Pohmakotr***, **Wacharee Harnying**, **Patoomratana Tuchinda**, and **Vichai Reutrakul**

Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand (tel.: 066-02-2015158; fax: 066-02-2477050; e-mail: scmpk@mahidol.ac.th)

Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

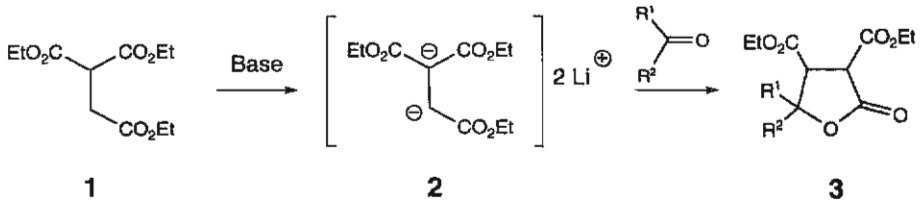
The vicinal dianion **2** derived from triethyl ethanetricarboxylate reacted regioselectively with aldehydes and ketones at C(β) to provide paraconic acid derivatives **5a**–**f** in moderate to high yields as mixtures of diastereoisomers. The paraconic acid derivatives **5e** and **5f** were utilized as the starting materials for the syntheses of (±)-lichesterinic acid (**12**), (±)-phaseolinic acid (**13**), (±)-nephromopsinic acid (**14**), (±)-rocellaric acid (**15**), and (±)-dihydroprotolichesterinic acid (**16**).

1. Introduction. – Dianions of numerous classes of organic compounds have been reported and played important roles in organic synthesis due to their high reactivity and regioselectivity towards electrophiles [1]. The reactions of these dianions have led to the development of new synthetic methods of many classes of organic compounds. Amongst these dianions, the dianions derived from succinic acid derivatives and succinic esters were found to be versatile reagents for the preparation of various types of compounds [2–14].

The vicinal dianions of dialkyl succinates underwent mono- or dialkylation [2] [3] and condensation reactions [4] with appropriate alkylating agents to give good yields of products. We have reported that the vicinal dianion of diethyl succinate could undergo hydroxyalkylation reactions with aliphatic aldehydes and ketones to afford paraconic esters, which could be readily converted into 4-carboxy-2,3-dialkyl-substituted 2-cyclopentenones [3]. Futhermore, paraconic esters have attracted considerable interest because their basic skeletons, trisubstituted γ-butyrolactones, are found in many natural products possessing interesting biological properties.

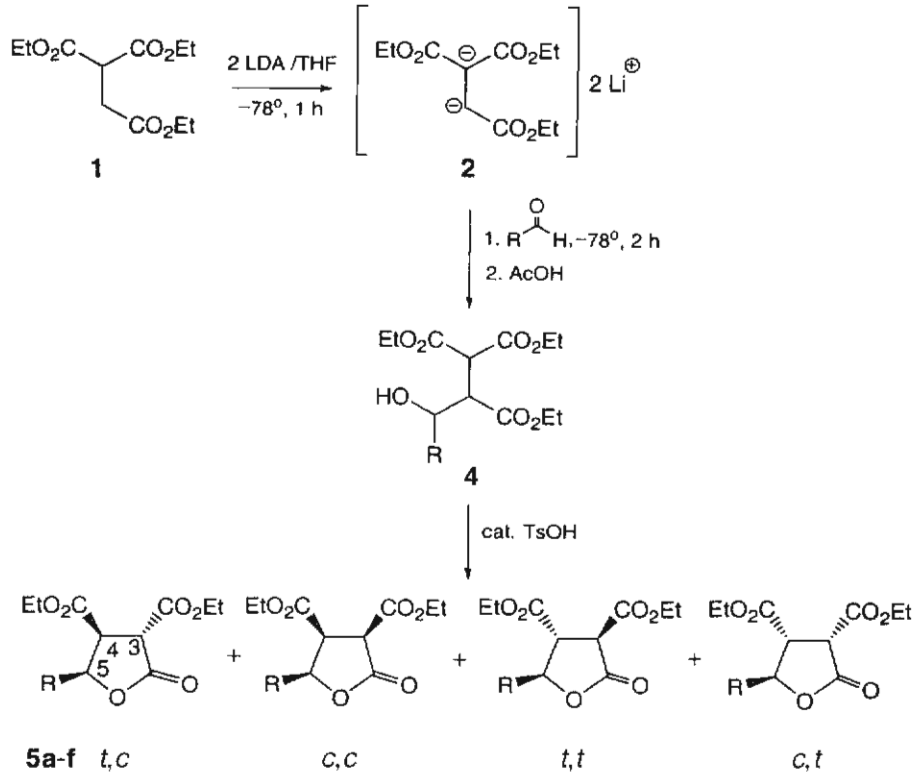
Our previous results, concerning the reactions of diethyl succinate dianion with electrophiles [3], prompted us to study the generation of the vicinal dianion **2** and the regioselectivity towards electrophiles. This dianion has not been previously reported and is expected to be generated by double deprotonation of triethyl ethanetricarboxylate (**1**) upon treatment with appropriate bases as shown in *Scheme 1*. The reaction of the vicinal dianion **2** with carbonyl compounds would provide a new synthetic pathway to functionalized 3,4,5-trisubstituted γ-lactones of type **3**. The lactones of type **3** appear to be useful as synthetic intermediates for the synthesis of several natural α-alkyl-substituted γ-lactones, such as methylenolactocin (**10**) [15], protolichesterinic acid (**11**) [16], lichesterinic acid (**12**) [17], phaseolinic acid (**13**) [18], nephromopsinic acid (**14**) [19], rocellaric acid (**15**) [20], and dihydroprotolichesterinic acid (**16**) [21].

Scheme 1. *Proposed Synthetic Route to γ-Lactone* **3** *by the Reaction of Dianion* **2** *with Carbonyl Compounds*



2. Results and Discussion. – *2.1 Reaction of Dianion* **2** *with Carbonyl Compounds.* Dianion **2** could be easily generated by reacting triester **1** with 2 equiv. of lithium diisopropylamide (LDA) in THF at −78° for 1 h. When dianion **2** was allowed to react with 1.5 equiv. of piperonal (= 1,3-benzodioxole-5-carboxaldehyde) at −78° for 2 h, the resulting product mainly consisted of an adduct **4a** (R = 1,3-benzodioxol-5-yl; *Scheme 2*) accompanied by a small amount of the expected γ-lactone **5a** after acidic (1.5M HCl) workup. However, the adduct **4a** could be easily converted into γ-lactone **5a** by treatment of the crude product **4a** with a catalytic amount of *p*-toluenesulfonic acid

Scheme 2. *Generation and Reactions of Dianion* **2** *with Aldehydes*

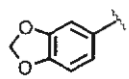
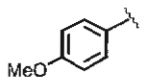


(TsOH) in CH_2Cl_2 at room temperature. More conveniently, complete lactonization could be achieved when the reaction mixture was first quenched with AcOH at −78° and warmed to room temperature, followed by addtion of a catalytic amount of TsOH and stirring at the same temperature overnight. This procedure was used as the standard condition for the reactions of the dianion **2** with other carbonyl compounds (*Scheme 2*).

The γ-lactone **5a** was obtained as a mixture of four diastereoisomers (*t,c*, *c,c*, *t,t*, and *c,t* isomers, *c* = *cis*, *t* = *trans*) in a ratio of 71:11:16:2 in 78% yield. The relative configurations of these compounds were assigned by their ^{1}H-NMR spectra. Attempted separation of the diastereoisomers of **5a** was performed by prep. TLC to give two bands, a less polar (14% yield) consisting of a 11:89 mixture *c,t*/*t,t*-**5a** and a more polar (64% yield) consisting of a 86:14 mixture of *t,c*/*c,c*-**5a**. The pure diastereoisomer *t,c*-**5a** could be obtained by fractional crystallization from AcOEt/hexane.

Having succeeded in preparing compound **5a**, we next investigated the reaction of dianion **2** with other aldehydes as summarized in *Table 1*. Moderate to high yields of γ-lactones **5a**–**f** could be achieved. The *cis*- and *trans*-configuration at the 4,5-positions of compounds **5a**–**c** and **5e,f** could be assigned by their ^{1}H-NMR data (see *Table 2*).

Table 1. *Preparation of γ-Lactones* **5a**–**f**

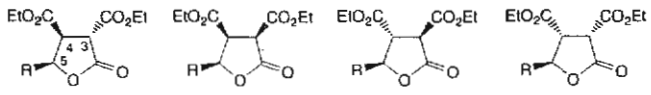
Product	R	Yield[a]) [%]	*t,c*/*c,c*/*t,t*/*c,t*
5a		78	71:11:16:2[b])[c])
5b		81	79:4:14:3[c])
5c	Ph	78	71:6:19:4[d])
5d	^{t}Bu	53	(80:20)[e])
5e	$Me(CH_2)_4$	55	79:6:15:trace[f])
5f	$Me(CH_2)_{12}$	62	86:3:11:trace[f])

[a]) Isolated yield. [b]) Calculated from *Fractions 1* and *2*. [c]) Determined by ^{1}H-NMR (H–C(5)) of the isolated product. [d]) Determined by ^{1}H-NMR (H–C(5)) of the crude product. [e]) The configuration could not be assigned, and the ratio was determined by ^{1}H-NMR (H–C(3)) of the crude product. [f]) Determined by ^{1}H-NMR (H–C(3) and H–C(5)) of the crude product.

The coupling constants J_{cis} and J_{trans} of H–C(5) (OC*H*Ar) of **5a**–**c**,**e**,**f**, which appeared as *d* in the range of δ 4.46–5.97, were 5.2–8.0 and 8.9–9.3 Hz, resp. (see *Table 2*). The configurational assignment of the 3,4-positions of the *t,t* and *c,c* isomers could be accomplished by determining of the coupling constants of H–C(3), which appeared as *d* varying in the range δ 3.67–4.09 ($J_{trans} \approx 7.3–10.8$ and $J_{cis} \approx 7.2–9.5$ Hz). However, the assignments of the *t,c* and *c,t* isomers were ambiguous.

To get more insight into the reaction of dianion **2**, we investigated the reaction of dianion **2** with ketones. As expected, the desired γ-lactones **5g**–**k** were obtained in moderate yields. The results are summarized in *Table 3*. The structures of compounds **5g**–**k** were established by their spectral data.

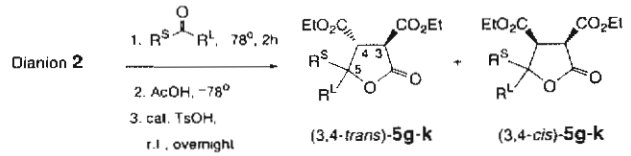
Table 2. *Significant ^{1}H-NMR Data of γ-Lactones* **5a–c** *and* **5e,f**



t,c *c,c* *t,t* *c,t*

		H–C(3) (*d*)		H–C(4) (*dd*)		H–C(5) (*d*)	
		δ [ppm]	*J*(3,4) [Hz]	δ [ppm]	*J*(3,4), *J*(4,5) [Hz]	δ [ppm]	*J*(4,5) [Hz]
5a	*t,c*	4.11	7.3	4.07	7.5 (app. *t*)	5.73	7.5
	c,c	–	–	–	–	5.47	5.7
	t,t	3.98	10.7	3.76	10.7, 8.9	5.37	8.9
	c,t	3.92	9.4	3.45	9.4 (app. *t*)	5.79	9.3
5b	*t,c*	4.20	7.6	4.15	7.7 (app. *t*)	5.84	8.0
	c,c	–	–	–	–	5.58	5.7
	t,t	4.06	10.8	–	–	5.47	9.1
	c,t	3.99	9.3	3.53	9.3 (app. *t*)	5.90	9.3
5c	*t,c*	–	–	–	–	5.91	7.0
	c,c	3.95	7.2	–	–	5.65	5.7
	t,t	4.09	10.6	–	–	5.56	8.9
	c,t	4.02	9.3	3.57	9.1 (app. *t*)	5.97	8.9
5e	*t,c*	3.88	8.0	3.81	8.0 (app. *t*)	–	–
	c,c	3.67	7.3	–	–	–	–
	t,t	3.89	10.3	–	10.2, 8.6	–	–
	c,t	–	9.4	–	9.2 (app. *t*)	–	–
5f	*t,c*	3.99	8.0	3.92	7.9 (app. *t*)	–	–
	c,c	3.76	7.3	–	–	4.46	5.2
	t,t	3.98	10.2	3.54	10.2, 8.7	–	–
	c,t	3.84	9.5	3.22	9.4 (app. *t*)	–	–

Table 3. *Preparation of γ-Lactones* **5g–k**



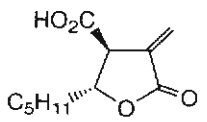
	R^S	R^L	Yield[a]) [%]	3,4-Position *cis*/*trans*[b])
5g	Me	Me	45	0:100
5h	$-(CH_2)_5-$		58	0:100
5i	Ph	Ph	41	14:86
5j	Me	Ph	39	almost *trans*[c])
5k	Me	Et	37	37:63[d])

[a]) Isolated yield. [b]) Determined by ^{1}H-NMR (H–C(3)). The *cis*/*trans* ratio of **5g–k** could be calculated from (*c,t* + *c,c*)/(*t,c* + *t,t*). [c]) **5j** was obtained as a mixture of four diastereoisomers, which contained predominantly only one diastereoisomer. [d]) **5k** was obtained as a mixture of four diastereoisomers whose ratio was determined by ^{1}H-NMR (*Me*CH_2C).

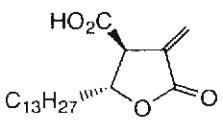
The *cis*- and *trans*-configuration at the 3,4-positions of **5g–k** could be assigned by the coupling constants $J(3,4)$ in the ^{1}H-NMR spectra: $J_{cis} = 6.6$ Hz and $J_{trans} = 9.3–11.7$ Hz, resp.

As summarized in *Table 1*, the major isomer obtained from the reaction of dianion **2** with aldehydes was the *t,c* isomer in all cases. The observed high stereoselectivity can be explained by assuming the involvement of the (*E*)-configuration of the dienolate form of dianion **2**, *i.e.*, (*E*)-**2**, as shown in *Scheme 3*. Our assumption was based on the well established fact that esters appear to give (*E*)-enolates [22] upon deprotonation with LDA. The relative stereochemical outcome at C(4) and C(5) of γ-lactone **5** was determined by using the models of the 6-membered transition states **6A** and **6B** of the aldol condensation of dianion (*E*)-**2** with aldehydes at –78°. Due to the less important 2,3-steric interaction between the aryl or alkyl and alkoxy groups, the transition state **6A** is more favored than the transition state **6B**. Consequently, the addition preferentially proceeds *via* the alkoxide intermediate *anti*-**7** rather than the *syn*-**7**. These alkoxides are then protonated upon hydrolysis with acid to afford the hydroxy esters **8** and **9**, respectively. Compound **8** is lactonized under thermodynamic-control conditions to give the more stable lactone *t,c*-**5** as the major isomer and the less stable lactone *c,c*-**5** as the minor isomer. Similarly, lactonization of hydroxy ester **9** leads to the formation of *t,t*-**5** and *c,t*-**5** (*Scheme 3*).

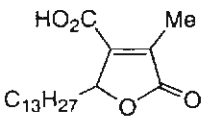
2.2. *Syntheses of (±)-Lichesterinic Acid* (**12**), *(±)-Phaseolinic Acid* (**13**), *(±)-Nephromopsinic Acid* (**14**), *(±)-Rocellaric Acid* (**15**), *and (±)-Dihydroprotolichesterinic Acid* (**16**). The synthesis of trisubstituted γ-butyrolactones, in particular the β-carboxy derivatives (paraconic acids), has attracted considerable attention in recent years, because of the wide range of their biological activities. Some of these compounds are methylenolactocin (**10**) [15], protolichesterinic acid (**11**) [16], lichesterinic acid (**12**) [17], phaseolinic acid (**13**) [18], nephromopsinic acid (**14**) [19], rocellaric acid (**15**) [20], and dihydroprotolichesterinic acid (**16**) [21]. Several synthetic approaches towards



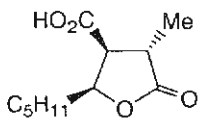
10
Methylenolactocin



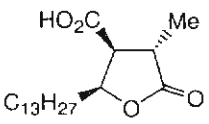
11
Protolichesterinic acid



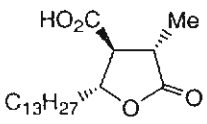
12
Lichesterinic acid



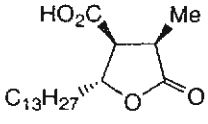
13
Phaseolinic acid



14
Nephromopsinic acid

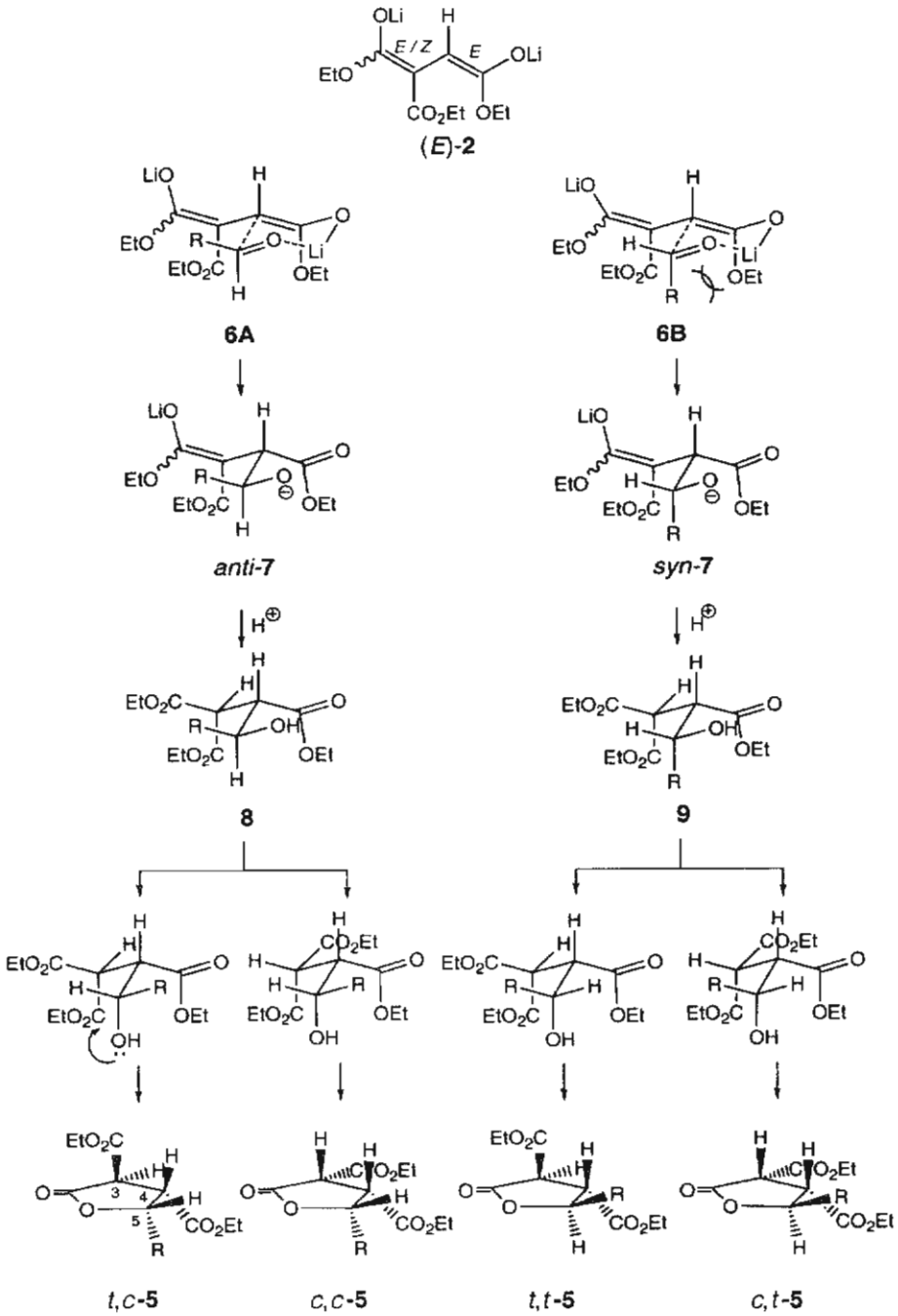


15
Rocellaric acid



16
Dihydroprotolichesterinic acid

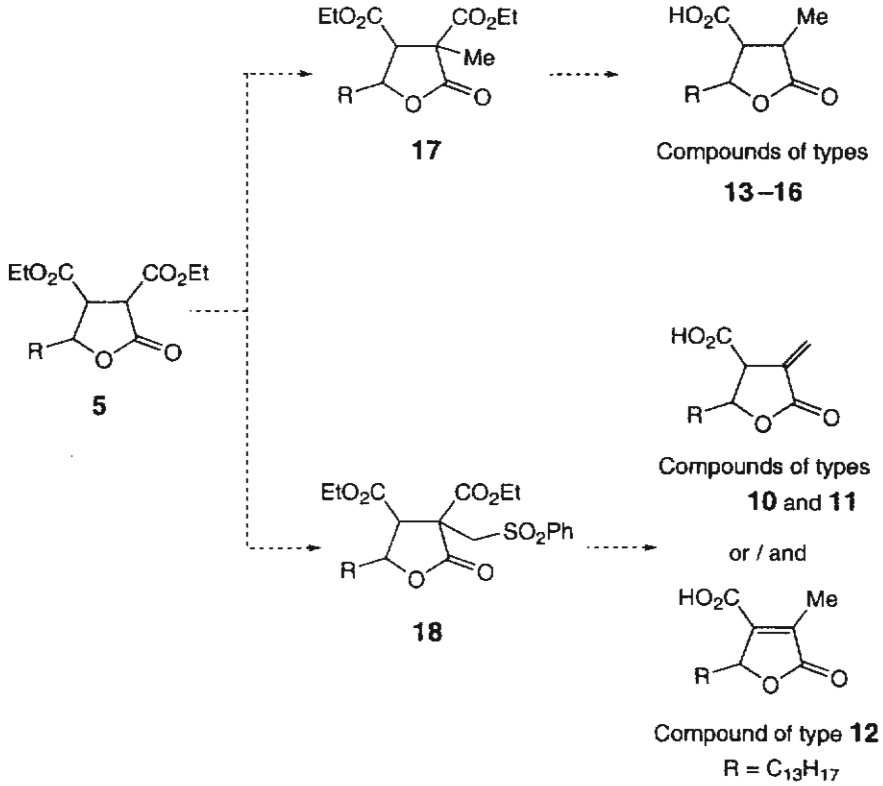
Scheme 3. *Proposed Transitions for the Stereochemical Course of the Addition Reactions of the Dianion* **2** *to Aldehydes*



these molecules either in racemic or pure enantiomeric form have been developed by a number of research groups over the past decade.

Since γ-lactones of type **5** could be readily obtained by the reaction of dianion **2** with aldehydes, we herein demonstrate the synthetic utility of this type of lactones for the syntheses of some naturally occurring α,β,γ-trisubstituted γ-lactones. As proposed in *Scheme 4*, we consider compounds **17** and **18** as important intermediates in the synthetic transformation of **5** into the corresponding natural products of types **13**–**16** and types **11** and **12**, respectively. Both γ-lactones **17** and **18** should be easily prepared from **5** by simple base-catalyzed methylation and (phenylthio)methylation followed by oxidation, respectively. Hydrolysis followed by decarboxylation of compound **17** would afford the desired compounds of types **13**–**16**. Similarly, compound **18** would be transformed into the corresponding compounds of types **10**–**12** by a tandem hydrolytic decarboxylative desulfonylation.

Scheme 4. *Proposed Synthetic Strategy to Natural Products* **10**–**16**

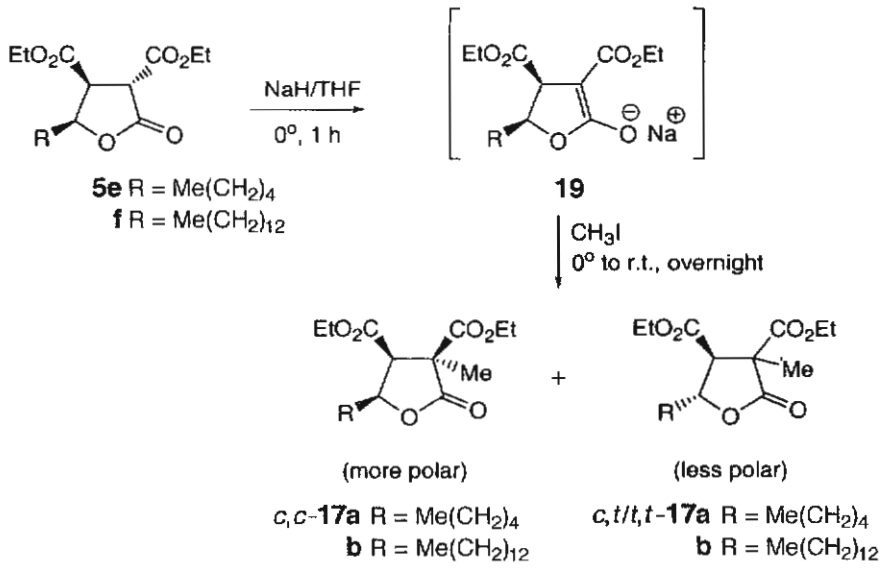


2.3. *α-Alkylation of α,β-Bis(ethoxycarbonyl)-Substituted γ-Lactones* **5e** *and* **5f**. Methylation of the diastereoisomer mixtures of **5e** or **5f** could be achieved by employing MeI/NaH in THF at 0°. Good yields of the α-methylated γ-lactones **17a** and **17b** were obtained. The diastereoisomer mixture of **5e** (*t,c*/(*t,t* + *c,c*)/*c,t* 70:27:3) provided compound *c,c*-**17a** (67% yield) and an inseparable mixture *c,t*/*t,t*-**17a** (60:40)

in 23% yield, while the diastereoisomer mixture of **5f** (*t,c*/(*t,t* + *c,c*) 63:34) gave compound *c,c*-**17b** (67% yield) and an iseparable mixture *c,t*/*t,t*-**17b** (51:49) in 25% yield.

The *c,c*-**17** was obtained as the major isomer. This can be rationalized by the assumption that methylation of the enolate anion **19** occurs from the less-hindered side avoiding the steric interaction with the ethoxycarbonyl group at C(4) (*Scheme 5*). The isomers *c,c*-**17a** and -**17b** could be easily separated from the isomer mixtures of *c,t*/*t,t*-**17a** and -**17b** respectively, by radial chromatography on silica-gel.

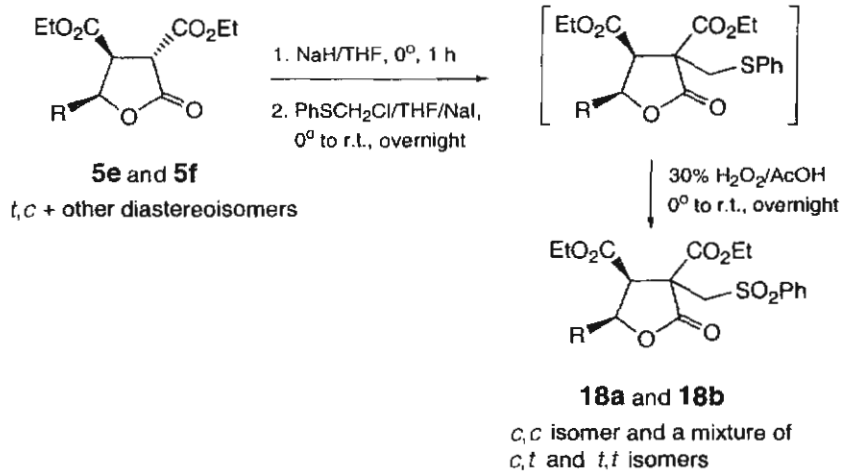
Scheme 5. *Base-Catalyzed Methylation of γ-Lactone* **5**



The relative configuration at the 4,5-positions of **17a** and **17b** could be assigned by the coupling constants observed for H–C(4), which appeared in the ^{1}H-NMR spectra as *d* at δ 3.30 (J_{cis} = 6.6–6.8 Hz) and 2.84–3.67 (J_{trans} = 9.7–9.9 Hz).

Having succeeded in preparing compounds **17**, we then prepared next α-(phenylsulfonyl)methyl-α,β-bis(ethoxycarbonyl)-substituted γ-lactones **18a** and **18b** by treatment of the γ-lactones **5e** and **5f** with $PhSCH_2Cl$/NaH in THF at 0° in the presence of NaI, followed by oxidation with H_2O_2/AcOH (*Scheme 6*). Thus, γ-lactone **5e** (*t,c*/*c,c*/*t,t*/*c,t* 82:6:11:trace) provided **18a** (98% yield) which contained mainly the *c,c* isomer and a small amount of other isomers. Similarly, γ-lactone **5f** containing mostly the *t,c* isomer and a small amount of other isomers afforded *c,c*-**18b** (88% yield) and an inseparable mixture *c,t*/*t,t*-**18b** (73:27:5% yield) (*Scheme 6*). We assumed that the *c,c* isomer of **18** was obtained as the major isomer. This can be explained as discussed above for the formation of the *c,c* isomer of compound **17**.

Scheme 6. *Preparation of α-(Phenylsulfonyl)methylated γ-Lactone* **18**

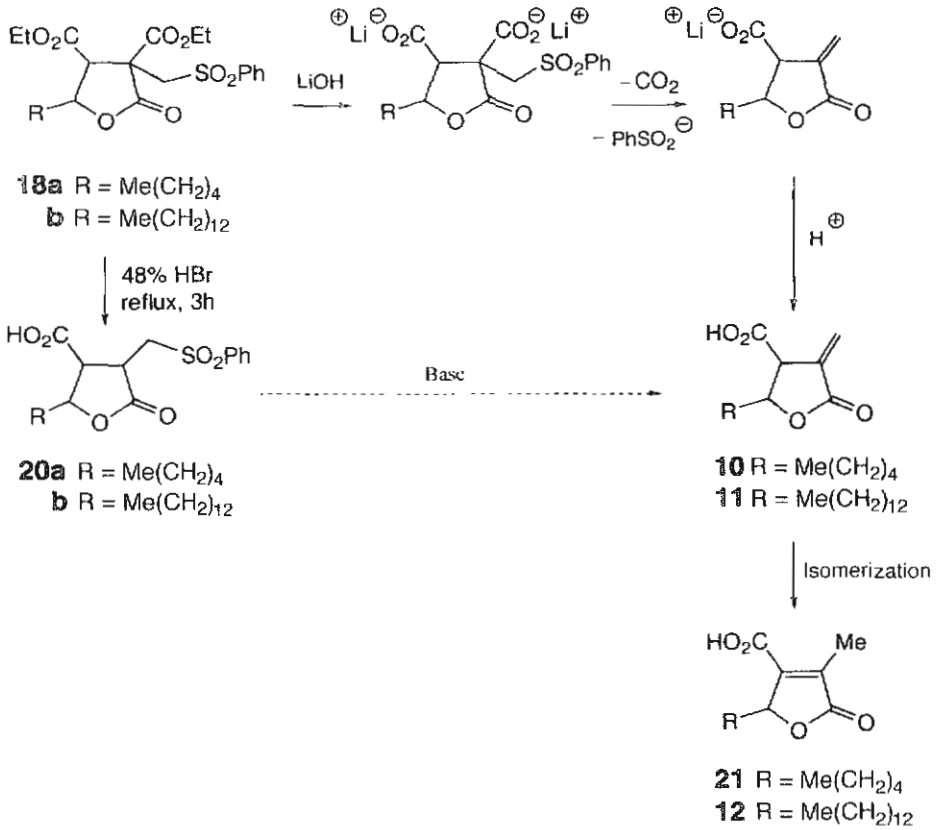


2.4. *Attempted Preparation of (±)-Methylenolactocin* (**10**) *and Preparation of (±)-Lichesterinic Acid* (**12**). As proposed in *Scheme 7*, hydrolysis of **18a** followed by base-catalyzed elimination of the expected product **20** should afford the desired methylenolactocin (**10**). Thus, treatment of **18a** containing mainly the *c,c* isomer with 48% HBr solution under reflux for 3 h provided the desired compound **20** in 48% yield, consisting of a *t,c*/*c,c*/*t,t* isomer mixture 32:64:4. Similarly, hydrolysis of a 41:59 mixture of *t,t*/*c,t*-**18a** gave **20** as a 85:15 mixture of *c,t*/*t,t* isomers in 65% yield. Attempts to convert compound **20** to the expected methylenolactocin (**10**) under various conditions, *e.g.*, LDA or DBU as a base in THF or CH_2Cl_2 as a solvent, were investigated. All experiments led to a complex mixture of unidentified products besides a small amount of **10** and compound **21** ($R = C_5H_{11}$) as revealed by the ^{1}H-NMR spectra.

During our investigation for the hydrolysis of **18a** to compound **20**, we found that the reaction of a diastereoisomer mixture of **18a** with LiOH (4 equiv.) in THF/H_2O under reflux for 3 h followed by stirring overnight provided butenolactone **21** ($R = Me(CH_2)_4$) in 69% yield. The formation of butenolactone **21** ($R = Me(CH_2)_4$) resulted from a tandem ester hydrolysisdecarboxylative elimination of the phenylsulfonyl group followed by isomerization of the initially formed exocyclic methylene group. By employing this advantage, (±)-lichesterinic acid (**12**) could be synthesized in 26% yield from γ-lactone **18b** (*Scheme 7*).

2.5. *Syntheses of (±)-Phaseolinic Acid* (**13**), *(±)-Nephromopsinic Acid* (**14**), *(±)-Rocellaric Acid* (**15**), *and (±)-Dihydroprotolichesterinic Acid* (**16**). The facile accessibility of γ-lactones *c,c*-**17a** and *c,c*-**17b** prompted us to try to convert them into the desired paraconic acids **13**–**16** by sequential hydrolysis and decarboxylation, expecting to be able to control the configurations at the 3-, 4-, and 5-positions. Thus, hydrolysis of γ-lactone *c,c*-**17a** by refluxing with 48% HBr solution for 5 h afforded an inseparable 62:38 mixture of paraconic acid **22** and (±)-phaseolinic acid (**13**) in 89% yield (*Scheme 8*). The same results were obtained when *c,c*-**17b** was treated with 48%

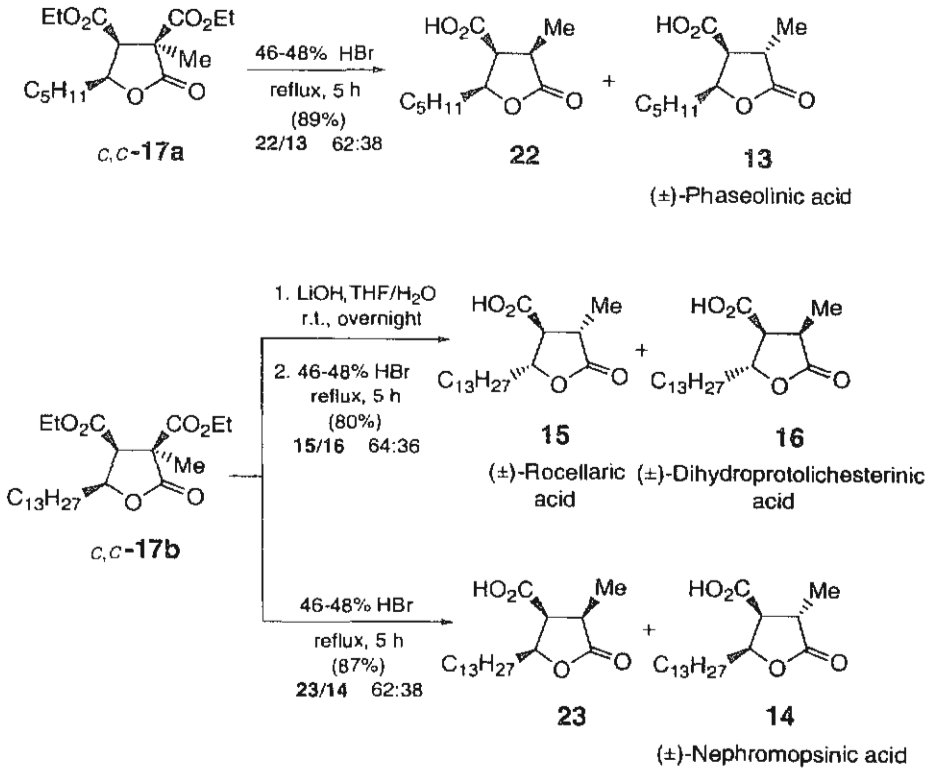
Scheme 7. *Preparation of (±)-Lichesterinic Acid* (**12**)



HBr solution under the same conditions; an inseparable 62:38 mixture of paraconic acid **23** and (±)-nephromopsinic acid (**14**) was obtained in 87% yield. It should be noted that under the hydrolytic conditions with 48% HBr solution, there was no isomerization at C(4) and C(5). Both (±)-phaseolinic acid (**13**) and (±)-nephromopsinic acid (**14**) could be separated from paraconic acids **22** and **23**, respectively, as their methyl ester derivatives formed by dicyclohexylcarbodiimide/MeOH treatment.

Hydrolysis of *c,c*-**17b** under basic conditions was also studied using LiOH/THF/H_2O at room temperature. The reaction led to incomplete hydrolysis as revealed by the ^{1}H-NMR spectrum of the crude product obtained. It was found that one ethoxycarbonyl group still remained. However, when the crude product was further treated with 48% HBr solution under reflux for 5 h, a 64:36 mixture of (±)-rocellaric acid (**15**) and (±)-dihydroprotolichesterinic acid (**16**) was obtained in 80% yield (*Scheme 8*). The results indicated that *c,c*-**17b** was isomerized to the thermodynamically more stable 4,5-*trans* isomer by LiOH during the hydrolysis in the first step, before the ethoxycarbonyl group was hydrolyzed. Good yield (72%) of a mixture **15**/**16** with the same ratio was obtained when a 73:27 mixture *c,t*/*t,t*-**17b** was hydrolyzed under the same conditions (LiOH and then 48% HBr solution under reflux).

Scheme 8. *Preparation of Natural Products* **13**–**16**



The separation of paraconic acids **15** and **16** from each other by chromatography was unsuccessful. Isomerization of (±)-dihydroprotolichesterinic acid (**16**) to (±)-rocellaric acid (**15**) was investigated. It was anticipated that this isomerization was successful by treatment of a 66 : 34 mixture **15**/**16** with 2 equiv. of LDA in THF at 0 for 1 h, followed by quenching with AcOH. The resulting product was a 89 : 11 mixture **15**/**16**. The major isomer, (±)-rocellaric acid (**15**), was separated by fractional crystallization (AcOEt) in 72% yield, whereas the minor (±)-dihydroprotolichesterinic acid (**16**) could not be separated in pure form. However, **16** could be isolated as its methyl ester.

3. Conclusions. – We demonstrated that the reaction of dianion **2** with carbonyl compounds afforded the expected paraconic acids **5a**–**k** as mixtures of diastereoisomers containing the *t,c*-isomer as the major isomer. Moreover, paraconic acids **5e** and **5f** could be used as starting materials for the syntheses of the natural products (±)-lichesterinic acid (**12**), (±)-phaseolinic acid (**13**), (±)-nephromopsinic acid (**14**), (±)-rocellaric acid (**15**), and (±)-dihydroprotolichesterinic acid (**16**). The desired natural compounds **13**–**16** could be prepared with retention of configuration at C(4) and C(5) by hydrolysis of the corresponding paraconic acid **17** (*c,c* isomer) and **17** (*c,t*/*t,t* isomers) (obtained by methylation of **5e** and **5f**) in refluxing 48% HBr solution. The products

13–**16** were separated as their methyl esters. (±)-Lichesterinic acid (**12**) was prepared by treatment of α-[(phenylsulfonyl)methyl]-γ-lactone **18b** with LiOH in THF/H_2O. However, attempted synthesis of (±)-methylenolactocin (**10**) by elimination of the phenylsulfonyl group from compound **18a** was unsuccessful.

We thank the *Thailand Research Fund* for financial support (BRG/22/2544) to *M. P.* and the award of a *Senior Research Scholar* to *V. R. W. H.* is grateful to the *Development and Promotion of Science and Technology Talent Project* (*DSPT*) for a scholarship. Thanks are also made to the *Higher Education Development Project*, Postgraduate Education and Research Program in Chemistry, for partial support.

Experimental Part

1. *General.* THF was distilled from sodium-benzophenone ketyl (sodium oxidodiphenylmethyl). The molarity of BuLi (in hexane) was determined by titration with diphenylacetic acid in THF at 0°. $^iPr_2NH$ was distilled over CaH_2; CH_2Cl_2 and acetone were distilled over P_2O_5. All glasswares and syringes were oven-dried and kept in a dessicator before use. Radial chromatography: plates prepared with *Merck* silica-gel PF_{254} containing $CaSO_4 \cdot 1/2\,H_2O$ type *60* (TLC Art. 7749), prep. plates with *Merck* silica-gel *60* (PF_{254}, Art. 7747). FC = flash column chromatography. M.p.: *Büchi 501* melting-point apparatus, uncorrected. IR Spectra: *Jasco A-302* or *Perkin-Elmer 683* spectrometer; in cm^{-1}. NMR Spectra: *Bruker DPX-300* (^1H at 300 MHz, ^{13}C at 75 MHz) or *Bruker DPX-400* (^1H at 400 MHz) spectrometer; in $CDCl_3$ with $SiMe_4$ as internal standard; chemical shifts δ in ppm downfield from $SiMe_4$, *J* in Hz. MS: *Finnigan MAT* mass spectrometer; in m/z (rel. %). Elemental analyses: *Perkin-Elmer* elemental analyzer *2400 CHN*.

2. *Generation and Reactions of Dianion* **2** *with Carbonyl Compounds. Diethyl 2-(1,3-Benzodioxol-5-yl)tetrahydro-5-oxofuran-3,4-dicarboxylate* (**5a**): *General Procedure* (*G.P.*). A soln. of triethyl 1,1,2-ethanetricarboxylate (493 mg, 2.0 mmol) in THF (2 ml) was added dropwise at −78° to a THF soln. of lithium diisopropylamide (LDA) under Ar (prepared by reacting $^iPr_2NH$ (0.7 ml, 5 mmol) in THF (8 ml) with 1.25M BuLi in hexane (3.5 ml, 4.4 mmol) at −78° for 30 min). After stirring at −78° for 1 h, a THF (2 ml) soln. of piperonal (1.3813 g, 2.5 mmol) was added dropwise to the pale yellow soln. of the dianion **2**. Stirring was continued at −78° for 2 h, then the reaction was quenched with AcOH (4 ml). The resulting mixture was warmed to r.t., and TsOH (monohydrate) was added as a catalyst. After stirring overnight, the mixture was diluted with H_2O (50 ml) and extracted with AcOEt (3 × 30 ml). The combined org. layer was washed with 10% $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated, and the crude product purified by prep. TLC (SiO_2, 20% AcOEt/hexane; double runs) to give two bands of **5a** (*Fr. 1* and *2*).

Fr. 1 (less polar) yielded a yellow viscous liquid: *c,t/t,t*-**5a** 11:89 (96 mg, 14%). IR (neat): 2984*m*, 2939*m*, 2907*m*, 1789*s*, 1738*s*, 1633*w*, 1612*m*, 1506*s*, 1493*s*, 1449*s*, 1398*m*, 1374*m*, 1303*s*, 1253*s*, 1197*s*, 1160*s*, 1038*s*, 929*m*, 859*m*, 815*m*, 705*m*. ^1H-NMR (300 MHz, $CDCl_3$): 6.88–6.70 (*m*, 3 arom. H); 5.92 (*t,t*) and 5.91 (*c,t*) (each *s*, OCH_2O); 5.79 (*c,t*), 5.37 (*t,t*) (each *d*, *J* = 9.25 and 8.9, resp., OC*H*Ar); 4.24 (*q*, *J* = 7.2, OCH_2Me of *t,t*); 4.20–4.05 (*m*, 2 OCH_2Me of *c,t* and OCH_2Me of *t,t*); 3.98 (*t,t*) and 3.92 (*c,t*) (each *d*, *J* = 10.7 and 9.4, resp., O_2CCHCO_2); 3.76 (*dd*, *J* = 10.7, 8.9, C*H*CO_2Et of *t,t*); 3.45 (app. *t*, *J* = 9.4, C*H*CO_2Et of *c,t*); 1.27 (app. *t*, *J* = 7.2, OCH_2*Me*); 1.16 (app. *t*, *J* = 7.2, OCH_2*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.1 (C=O); 168.9 (C=O); 166.2 (C–O); 148.3 (C); 148.1 (C); 130.6 (C, *c,t*) and 130.4 (C, *t,t*); 120.5 (CH, *c,t*), 120.4 (CH, *t,t*); 108.2 (CH, *t,t*) and 108.1 (CH, *c,t*); 106.6 (CH, *c,t*), 106.5 (CH, *t,t*); 101.4 (OCH_2O, *t,t*) and 101.3 (OCH_2O, *c,t*); 63.6 (OCH_2, *c,t*), 62.6 (OCH_2, *t,t*); 62.0 (OCH_2, *t,t*), 61.6 (OCH_2, *c,t*); 51.9 (CH, *t,t*), 51.5 (CH, *c,t*); 50.6 (CH, *t,t*), 50.5 (CH, *c,t*); 13.9 (Me, *t,t*) and 13.8 (Me, *c,t*); 13.88 (Me).

Fr. 2 (more polar) yielded a pale yellow solid: *t,c/c,c*-**5a** 86:14 (448 mg, 64%). ^1H-NMR (300 MHz, $CDCl_3$): 6.82–6.63 (*m*, 3 arom. H); 5.91 (*t,c*) and 5.90 (*c,c*) (each *s*, OCH_2O); 5.73 (*t,c*), 5.37 (*c,c*) (each *d*, *J* = 7.5 and 5.7, resp., OC*H*Ar); 4.24 (app. *q*, *J* = 7.2, OCH_2Me of *t,c* and *c,c*); 4.11 (*d*, *J* = 7.3, O_2CCHCO_2 of *t,c*); 4.07 (app. *t*, *J* = 7.5, C*H*CO_2Et of *t,c*); 3.91–3.71 (*m*, OCH_2Me of *t,c* and OCH_2Me, COCHCO, and C*H*CO_2Et of *c,c*); 1.28 (*t,c*) and 1.27 (*c,c*) (each *t*, *J* = 7.2 and 7.4, resp., OCH_2*Me*); 0.95 (*t,c*) and 0.94 (*c,c*) (each *t*, *J* = 7.2 and 7.7, resp., OCH_2*Me*).

The pale yellow solid obtained from the *Fr. 2* (diastereoisomer mixture) was recrystallized from AcOEt/hexane to give pure *t,c*-**5a**. White solid. M.p. 84–85°. IR (nujol): 3071*w*, 3046*w*, 2989*s*, 1797*s*, 1728*s*, 1610*w*, 1505*s*, 1486*m*, 1448*s*, 1413*m*, 1369*s*, 1324*s*, 1261*s*, 1238*s*, 1213*s*, 1199*s*, 1141*s*, 1043*s*, 1018*s*, 939*m*, 908*m*, 871*m*, 805*m*. ^1H-NMR (400 MHz, $CDCl_3$): 6.80 (*d*, *J* = 8.0, 1 arom. H); 6.74 (*d*, *J* = 8.0, 1 arom. H); 6.72 (*s*, 1 arom. H); 5.99 (*s*, OCH_2O); 5.82 (*d*, *J* = 8.0, OC*H*Ar); 4.32 (*q*, *J* = 7.2, 1 OCH_2Me); 4.19 (*d*, *J* = 7.2, O_2CCHCO_2); 4.15 (app. *t*,

$J = 7.6$, $CHCO_2Et$); 3.98–3.81 (*m*, 1 OCH_2Me); 1.37 (*t*, $J = 7.2$, OCH_2Me); 1.04 (*t*, $J = 7.2$, 1 OCH_2Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.8 (C=O); 168.1 (C=O); 166.1 (C=O); 148.1 (C); 147.8 (C); 128.3 (C); 119.7 (CH); 108.1 (CH); 106.2(CH); 101.3 (OCH_2O); 79.9 ($OCHAr$); 62.7 (CH_2O); 61.6 (CH_2O); 49.8 (CH); 48.4 (CH); 13.9 (Me); 13.6 (Me). EI-MS: 350 (100, M^+), 321 (0.83), 304 (13), 287 (2), 275 (9), 259 (10), 247 (4), 230 (19), 215 (4), 203 (27), 190 (12), 173 (17), 149 (85), 127 (79), 99 (69), 93 (6), 71 (4), 65 (10), 53 (8), 45 (4). Anal. calc. for $C_{17}H_{18}O_8$ (350.33): C 58.29, H 5.18; found: C 58.20, H 5.13.

Diethyl Tetrahydro-2-(4-methoxyphenyl)-5-oxofuran-3,4-dicarboxylate (**5b**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and the THF (5 ml) soln. of anisaldehyde (384 mg, 2.8 mmol). The crude product was purified by prep. TLC (SiO_2, 20% AcOEt/hexane; double runs): 79 : 4 : 14 : 3 mixture *t,c*/*c,c*/*t,t*/*c,t*-**5b** (545 mg, 81%). Pale yellow solid. ^1H-NMR (300 MHz, $CDCl_3$): 7.37–7.24 (*m*, 2 arom. H of *c,t*, *c,c*, and *t,t*); 7.16 (*d*, $J = 8.7$, 2 arom. H of *t,c*); 6.93, 6.87 (each app. *d*, $J = 8.7$, 2 arom. H); 5.90 (*c,t*), 5.84 (*t,c*), 5.58 (*c,c*), 5.47 (*t,t*) (each *d*, $J = 9.3$, 7.8, 5.7, and 9.1, resp., $OCHAr$); 4.30 (*q*, $J = 7.2$, OCH_2Me of *t,c*); 4.35–4.10 (*m*, 2 OCH_2Me of *c,t* and *t,t*, OCH_2Me of *c,c*); 4.20 (*t,c*), 4.06 (*t,t*), 3.99 (*c,t*) (each *d*, $J = 7.6$, 10.8, and 9.3, resp., COCHCO); 4.15 (*t,c*), 3.53 (*c,t*) (each app. *t*, $J = 7.7$ and 9.3, resp., $CHCO_2Et$); 3.95–3.69 (*m*, OCH_2Me of *t,c*, OCH_2Me, COCHCO and $CHCO_2Et$ of *c,c*, $CHCO_2Et$ of *t,t*, OMe of *c,t*, *c,c*, and *t,t*); 3.79 (*s*, OMe of *t,c*); 1.35 (*t,c*), 1.34 (*c,t* and *t,t*), 1.29 (*c,c*) (each *t*, $J = 7.2$, OCH_2Me); 1.24 (*c,t*), 1.22 (*t,t*), 0.95 (*t,c*), 0.92 (*c,c*) (each *t*, $J = 7.2$, 7.2, 7.2, and 7.6, resp., OCH_2Me).

The pale yellow solid of diastereoisomer mixture **5b** was recrystallized from AcOEt/hexane: pure *t,c*-**5b**. White solid. M.p. 82–83°. IR (nujol): 1801*s*, 1740*s*, 1693*w*, 1614*m*, 1581*w*, 1516*m*, 1454*m*, 1326*s*, 1304*m*, 1257*m*, 1241*m*, 1215*m*, 1181*m*, 1137*m*, 1015*m*, 968*m*, 847*m*, 806*m*. ^1H-NMR (400 MHz, $CDCl_3$): 7.18 (*d*, $J = 8.8$, 1 arom. H); 6.90 (*d*, $J = 8.8$, 1 arom. H); 5.87 (*d*, $J = 8.0$, $OCHAr$); 4.33 (*q*, $J = 7.2$, OCH_2Me); 4.22 (*d*, $J = 7.2$, O_2CCHCO_2); 4.18 (app. *t*, $J = 7.8$, $CHCO_2Et$); 3.94–3.72 (*m*, OCH_2Me); 3.82 (*s*, ArOMe); 1.37 (*t*, $J = 7.2$, OCH_2Me); 0.98 (*t*, $J = 7.2$, OCH_2Me). ^{13}C NMR (75 MHz, $CDCl_3$): 170.0 (C=O); 168.3 (C=O); 166.3 (C=O); 160.1 (C); 127.3 (CH, 2 peaks merged); 126.6 (C); 113.9 (CH, 2 peaks merged); 80.0 ($OCHAr$); 62.7 (OCH_2); 61.5 (OCH_2), 55.2 (OMe); 49.8 (CH); 48.5 (CH); 13.6 (Me). EI-MS: 336 (29, M^+), 318 (2), 307 (1), 289 (8), 273 (1), 263 (9), 245 (5), 233 (2), 216 (10), 200 (40), 189 (17), 173 (22), 154 (32), 145 (18), 135 (81), 127 (100), 99 (93), 92 (7), 77 (22), 63 (6), 55 (13), 43 (6). Anal. calc. for $C_{17}H_{20}O_7$ (336.35): C 60.71, H 5.99; found: C 60.38, H 5.78.

Diethyl Tetrahydro-2-oxo-5-phenylfuran-3,4-dicarboxylate (**5c**). According to the *G.P.* with dianion **2** (2.0 mmol) in THF (10 ml) and a THF (2 ml) soln. of benzaldehyde (0.3 ml, 2.97 mmol). The crude product, a 71 : 6 : 19 : 4 mixture *t,c*/*c,c*/*t,t*/*c,t*-**5c**, was purified by radial chromatography (SiO_2, 8% AcOEt/hexane): 68 : 11 : 18 : 3 mixture *t,c*/*c,c*/*t,t*/*c,t*-**5c** (478 mg, 78%). Pale yellow liquid. ^1H-NMR (400 MHz, $CDCl_3$): 7.48–7.24 (*m*, 5 arom. H); 5.97 (*c,t*), 5.91 (*t,c*), 5.65 (*c,c*) and 5.56 (*t,t*) (each *d*, $J = 8.9$, 7.0, 5.7, and 8.9, resp., $OCHAr$); 4.33 (*q*, $J = 7.1$, OCH_2Me of *t,c*); 4.31–4.12 (*m*, COCHCO and $CHCO_2Et$ of *t,c*, 2 OCH_2Me of *c,t* and *t,t*, and OCH_2Me of *c,c*); 4.09 (*t,t*), 4.02 (*c,t*), 3.95 (*c,c*) (each *d*, $J = 10.6$, 9.3, and 7.2, resp., COCHCO); 3.92–3.67 (*m*, OCH_2Me of *t,c*, OCH_2Me and $CHCO_2Et$ of *c,c*, $CHCO_2Et$ of *t,t*); 3.57 (*t*, $CHCO_2Et$ of *c,t*); 1.37 (*t,c*), 1.35 (*c,t* and *t,t*), 1.32 (*c,c*) (each *t*, $J = 7.2$, 7.2, and 7.2, resp., OCH_2Me); 1.28 (*c,t*), 1.25 (*t,t*), 0.92 (*t,c*), and 0.87 (*c,c*) (each *t*, $J = 7.0$, 7.1, 7.2, and 7.2, resp., OCH_2Me).

Attempted separation of the diastereoisomers was made by prep. TLC (SiO_2, 20% AcOEt/hexane; double runs) to give two bands of **5c** (*Fr. 1* and *2*).

Fr. 1 (less polar) yielded *c,t*/*t,t*-**5c** (9 : 91) contaminated with a small amount of *t,c*-**5c**. IR (neat): 3067*m*, 3038*m*, 2985*m*, 2940*m*, 2909*m*, 1789*s*, 1738*s*, 1498*m*, 1458*m*, 1372*m*, 1354*m*, 1305*s*, 1256*s*, 1213*s*, 1199*s*, 1157*s*, 1020*s*, 976*m*, 918*m*, 857*m*, 760*m*, 701*s*. ^1H-NMR (300 MHz, $CDCl_3$): 7.46–7.35 (*m*, 5 arom. H); 5.96 (*c,t*), 5.54 (*t,t*) (each *d*, $J = 9.0$ and 8.8, resp., $OCHAr$); 4.34–4.15 (*m*, 2 OCH_2Me); 4.07 (*t,t*), 4.00 (*c,t*) (each *d*, $J = 10.8$ and 9.4, resp., COCHCO); 3.87 (*dd*, $J = 10.4$, 8.9, $CHCO_2Et$ of *t,t*); 3.55 (app. *t*, $J = 9.1$, $CHCO_2Et$ of *c,t*); 1.33 (app. *t*, $J = 7.2$, OCH_2Me); 1.24 (app. *t*, $J = 7.2$, OCH_2Me). ^{13}C-NMR (75 MHz, $CDCl_3$; major isomer *t,t*-**5c**): 169.2 (C=O); 169.1 (C=O); 166.2 (C=O); 136.8 (C); 129.2 (CH); 128.7 (CH); 126.1 (CH); 80.8 (OCH); 62.6 (OCH_2); 62.0 (OCH_2); 51.9 (CH); 50.6 (CH); 13.92 (Me); 13.89 (Me).

Fr. 2 (more polar) yielded a 95 : 5 mixture of the major *t,c*-**5c** contaminated with a small amount of *c,c*- and *t,t*-**5c**. Pale yellow liquid. IR (neat): 3066*w*, 3036*w*, 2985*m*, 2940*m*, 2907*m*, 1791*s*, 1733*s*, 1607*w*, 1498*m*, 1457*m*, 1400*m*, 1382*m*, 1372*m*, 1314*s*, 1214*s*, 1159*s*, 1097*m*, 1020*s*, 964*m*, 855*m*, 752*m*, 700*s*. ^1H-NMR (300 MHz, $CDCl_3$): 7.41–7.20 (*m*, 5 arom. H); 5.89 (*d*, $J = 7.6$, $OCHAr$); 4.31 (*q*, $J = 7.1$, OCH_2Me); 4.20–4.13 (*m*, COCHCO, $CHCO_2Et$); 3.89–3.64 (*m*, OCH_2Me); 1.35 (*t*, $J = 7.2$, OCH_2Me); 0.90 (*t*, $J = 7.2$, OCH_2Me). ^{13}C-NMR (75 MHz, $CDCl_3$; major isomer *t,c*-**5c**): 169.9 (C=O); 168.1 (C=O); 166.1 (C=O); 134.6 (C); 129.0 (CH); 128.3 (CH, 2 peaks merged); 125.7 (CH, 2 peaks merged); 80.0 ($OCHAr$); 62.6 (OCH_2); 61.4 (OCH_2); 49.7 (CH); 48.9 (CH); 13.8 (Me); 13.2 (Me). EI-MS: 306 (15, M^+), 278 (0.33), 260 (22), 243 (1), 232 (29), 215 (5), 203 (4),

186 (32), 173 (47), 159 (33), 145 (13), 127 (70), 115 (65), 105 (100), 99 (97), 91 (12), 82 (16), 77 (52), 63 (8), 51 (19), 45 (7). Anal. calc. for $C_{16}H_{18}O_6$ (306.32): C 62.74, H 5.92; found: C 62.56, H 5.90.

*Diethyl 2-(*tert*-Butyl)tetrahydro-5-oxofuran-3,4-dicarboxylate* (**5d**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and a THF (2 ml) soln. of pivaldehyde (231 mg, 2.7 mmol). The crude product, a 80:20 mixture of two diastereoisomers, was purified by prep. TLC (SiO_2, 20% AcOEt/hexane; multiple runs): **5d** (305 mg, 53%) as a 79:21 mixture of two diastereoisomers. Colorless liquid. IR (neat): 2981*s*, 2910*m*, 2879*m*, 1792*s*, 1737*s*, 1482*m*, 1448*m*, 1407*m*, 1385*m*, 1371*s*, 1330*s*, 1275*s*, 1249*s*, 1196*s*, 1180*s*, 1159*s*, 1095*m*, 1029*s*, 1001*s*, 931*m*, 861*m*, 682*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.51 (app. *d*, $J = 7.2$, CHO of the major diastereoisomer); 4.34–4.06 (*m*, 2 OCH_2Me and C*H*O of the minor diastereoisomer); 3.97 (major), 3.76 (minor) (each *d*, $J = 6.0$ and 6.5, resp., COCHCO); 3.80 (app. *t*, $J = 6.6$, C*H*CO_2Et of the major diastereoisomer); 3.54 (*dd*, $J = 6.5$, 4.6, C*H*CO_2Et of the minor diastereoisomer); 1.35–1.23 (*m*, 2 OCH$_2$*Me*); 1.05 (minor), 1.02 (major) (each *s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.8 (C=O); 169.7 (C=O); 166.1 (C=O); 87.3 (OCH, major), 86.1 (OCH, minor); 62.5 (OCH_2, major), 61.8 (OCH_2, minor); 61.7 (OCH_2, major), 61.3 (OCH_2, minor); 50.7 (CH, major), 50.3 (CH, minor); 46.7 (CH, major), 46.4 (CH, minor); 34.7 (C, major), 33.3 (C, minor); 25.5 (Me); 13.9 (Me); 13.6 (Me, major), 13.5 (Me, minor). EI-MS: 287 (1.3, $[M+1]^+$), 271 (1), 253 (0.37), 241 (15), 230 (85), 213 (11), 201 (17), 195 (7), 183 (49), 173 (32), 157 (65), 137 (6), 127 (47), 111 (17), 99 (44), 84 (18), 71 (17), 57 (100), 41 (66). Anal. calc. for $C_{14}H_{22}O_6$ (286.33): C 58.73, H 7.75; found: C 58.68, H 8.05.

Diethyl Tetrahydro-2-oxo-5-pentylfuran-3,4-dicarboxylate (**5e**). According to the *G.P.*, with dianion **2** (5.0 mmol) in THF (25 ml) and a THF (5 ml) soln. of hexanal (0.76 ml, 6.2 mmol). The crude product, a 79:6:15:trace mixture *t,c/c,c/t,t/c,t*-**5e**, was purified by FC (SiO_2, 10% AcOEt/hexane): 82:6:11:trace mixture *t,c/c,c/t,t/c,t*-**5e** (826 mg, 55%). Colorless liquid. IR (neat): 2958*s*, 2936*s*, 2873*m*, 1790*s*, 1738*s*, 1468*m*, 1371*m*, 1305*s*, 1256*s*, 1177*s*, 1021*s*, 858*m*, 730*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.74–4.67 (*m*, CHO of *t,c*); 4.41 (*dt*, $J =$ 4.1, 8.4, CHO of *t,t*); 4.40–4.35 (*m*, CHO of *c,c*); 4.24–4.08 (*m*, 2 OCH_2Me); 3.89 (*t,t*); 3.88 (*t,c*), 3.67 (*c,c*) (each *d*, $J = 10.1$, 8.0, and 7.3, resp., COCHCO); 3.81 (app. *t*, $J = 8.0$, C*H*CO_2Et of *t,c*); 3.48–3.41 (*m*, C*H*CO_2Et of *c,c* and *t,t*); 1.84–1.14 (*m*, $(CH_2)_3$, 2 OCH$_2$*Me*); 0.82–0.77 (*m*, $(CH_2)_4$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$, major isomer *t,c*-**5e**): 169.8 (C=O); 168.9 (C=O); 166.4 (C=O); 79.1 (OCH); 62.5 (OCH_2); 61.8 (OCH_2); 48.7 (CH); 47.7 (CH); 31.3 (CH_2); 31.2 (CH_2); 25.1 (CH_2); 22.3 (CH_2); 14.0 (Me); 13.9 (Me); 13.8 (Me). EI-MS: 301 (1.4, $[M+1]^+$), 300 (0.89, M^+), 285 (0.55), 273 (0.32), 254 (28), 237 (9), 227 (57), 218 (1.4), 209 (12), 201 (27), 183 (100), 173 (72), 169 (69), 155 (48), 145 (17), 137 (20), 127 (98), 109 (31), 99 (92), 81 (28), 71 (19), 67 (20), 55 (48), 43 (36), 32 (14). Anal. calc. for $C_{15}H_{24}O_6$ (300.36): C 59.99, H 8.05; found: C 59.96, H 7.99.

Attempted separation of the diastereoisomers was made by FC (SiO_2, 8% AcOEt/hexane) to provide *Fr. 1* and *2* of **5e**.

Fr. 1 (less polar) yielded a 5:29:3:63 mixture *c,t/t,c/c,c/t,t*-**5e** contaminated with a small amount of the starting material. Pale yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.94 (*c,t*), 4.52 (*t,t*) (each *dt*, $J = 3.2$, 9.0, and 4.1, 8.4, resp., CHO); 4.81 (*t,c*), 4.47 (*c,c*) (each *m*, CHO); 4.35–4.14 (*m*, 2 OCH_2Me); 4.00 (*t,c*), 3.99 (*t,t*), 3.86 (*c,t*), 3.75 (*c,c*) (each *d*, $J = 8.4$, 10.1, 8.0, and 7.3, resp., COCHCO); 3.93 (*t,c*), 3.23 (*c,t*) (each *t*, $J = 7.9$ and 9.2, C*H*CO_2Et); 3.56 (app. *dd*, $J = 10.2$, 8.6, C*H*CO_2Et of *c,c* and *t,t*); 2.00–1.20 (series of *m*, $(CH_2)_4$, 2 OCH$_2$*Me*); 0.90 (*m*, $(CH_2)_3$*Me*).

Fr. 2 (more polar) yielded the major diastereoisomer *t,c*-**5e** contaminated with a small amount of *c,c*- and *t,t*-**5e**. Colorless liquid. ^{1}H-NMR (400 Hz, $CDCl_3$): 4.81 (*m*, CHO); 4.29 (*q*, $J = 7.2$, OCH_2Me); 4.24 (*dq*, $J = 1.4$, 7.1, OCH_2Me); 3.99 (*d*, $J = 8.3$, COCHCO); 3.92 (*t*, $J = 7.9$, C*H*CO_2Et); 1.96–1.24 (series of *m*, $(CH_2)_4$, 2 OCH$_2$*Me*); 0.90 (*m*, $(CH_2)_4$*Me*).

Diethyl Tetrahydro-2-oxo-5-tridecylfuran-3,4-dicarboxylate (**5f**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and a THF (2 ml) soln. of tetradecanal (571 mg, 2.7 mmol). The crude product, a 86:3:11:trace mixture *t,c/c,c/t,t/c,t*-**5f**, was purified by FC (SiO_2, 10% AcOEt/hexane): 87:3:10:trace mixture *t,c/c,c/t,t/c,t*-**5f** (513 mg, 62%). Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.83–4.77 (*m*, CHO of *t,c*); 4.51 (*t,t*), 4.46 (*c,c*) (each *dt*, $J = 4.0$, 8.4, and 5.2, 8.7, resp., CHO); 4.34–4.18 (*m*, 2 OCH_2Me); 3.99 (app. *d*, $J = 8.0$, COCHCO of *t,c* and *t,t*); 3.92 (app. *t*, $J = 7.9$, C*H*CO_2Et of *t,c*); 3.76 (*d*, $J = 7.3$, COCHCO of *c,c*); 3.59–3.52 (*m*, C*H*CO_2Et of *c,c* and *t,t*), 1.95–1.18 (*m*, $(CH_2)_{12}$, 2 OCH$_2$*Me*); 0.89 (app. *t*, $J = 6.8$, $(CH_2)_{12}$*Me*).

Attempted separation of the diastereoisomers was performed by FC (SiO_2, 5% AcOEt/hexane) to provide *Fr. 1* and *2* of **5f**.

Fr. 1 (less polar) yielded a 92:8 mixture of *t,t/c,t*-**5f**. Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.92 (*m*, CHO of *c,t*); 4.50 (*dt*, $J = 4.0$, 8.2, CHO of *t,t*); 4.30 (*q*, $J = 7.2$, OCH_2Me); 4.23 (*q*, $J = 7.2$, OCH_2Me); 3.98 (*t,t*).

3.84 (*c,t*) (each *d*, J = 10.2 and 9.5, resp., COCHCO); 3.54 (*dd*, J = 10.2, 8.7, *CH*CO_2Et of *t,t*); 3.22 (*t*, J = 9.4, *CH*CO_2Et of *c,t*); 1.94–1.20 (series of *m*, $(CH_2)_{12}$, 2 OCH_2*Me*); 0.88 (app. *t*, J = 6.6, $(CH_2)_{12}$*Me*).

Fr. 2 (more polar) yielded a colorless liquid of a mixture of the starting material and the desired *t,c*/(*c,c* + *t,t*)-**5f** as a 81 : 19 diastereoisomer mixture, which could not be separated by FC. However, the product could be separated from the starting material by distillation at 126°/0.5 Torr. The same diastereoisomer ratio *t,c*/(*c,c* + *t,t*)-**5f** was obtained as prior to the distillation. IR (neat): 2925*s*, 2854*s*, 1790*s*, 1738*s*, 1467*m*, 1371*m*, 1303*m*, 1258*m*, 1177*s*, 1097*m*. ^{1}H-NMR (400 MHz, $CDCl_3$; major isomer *t,c*-**5f**): 4.81 (*m*, CHO); 4.33–4.18 (*m*, 2 OCH_2Me); 3.98 (*d*, J = 8.0, COCHCO); 3.91 (*t*, J = 7.8, *CH*CO_2Et); 1.62–1.22 (*m*, $(CH_2)_{12}$, 2 OCH_2*Me*); 0.88 (*m*, $(CH_2)_{12}$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$; the major isomer *t,c*-**5f**): 169.8 (C=O); 168.9 (C=O); 166.4 (C=O); 79.1 (OCH); 62.6 (OCH_2); 61.8 (OCH_2); 48.7 (CH); 47.8 (CH); 31.9 (CH_2); 31.4 (CH_2); 29.7 (CH_2); 29.6 (CH_2, 2 peaks merged); 29.5 (CH_2); 29.4 (CH_2); 29.3 (CH_2, 2 peaks merged); 29.1 (CH_2); 25.5 (CH_2); 22.7 (CH_2); 14.1 (Me, 2 peaks merged); 14.0 (Me). EI-MS: 412 (2, M^+), 367 (7), 339 (100), 311 (1), 293 (6), 281 (39), 247 (2), 229 (7), 218 (4), 201 (6), 183 (16), 173 (17), 155 (8), 145 (9), 127 (22), 109 (7), 99 (20), 95 (11), 81 (13), 69 (13), 55 (27), 43 (31), 32 (40). Anal. calc. for $C_{25}H_{36}O_6$ (412.58): C 66.96, H 9.77; found: C 66.93, H 10.04.

Diethyl Tetrahydro-2,2-dimethyl-5-oxofuran-3,4-dicarboxylate (**5g**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and a soln. of 1.0M acetone in THF (3.0 ml, 3.0 mmol). The crude product was purified by prep. TLC (SiO_2, 30% AcOEt/hexane): **5g** (230 mg, 45%). Colorless liquid. IR (neat): 2985*s*, 2941*m*, 1784*s*, 1738*s*, 1467*m*, 1448*m*, 1378*s*, 1323*s*, 1292*s*, 1220*s*, 1183*s*, 1162*s*, 1115*s*, 1030*s*, 953*m*, 907*m*, 858*m*, 693*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.19–4.03 (*m*, 2 OCH_2Me); 4.03 (*d*, J_{trans} = 11.6, COCHCO); 3.58 (*d*, J_{trans} = 11.6, *CH*CO_2Et); 1.56 (*s*, MeC), 1.21 (*t*, J = 7.4, OCH_2*Me*), 1.19 (*s*, MeC), 1.18 (*t*, J = 7.4, OCH_2*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.5 (C=O); 168.2 (C=O); 166.3 (C=O); 82.9 (OC); 62.2 (OCH_2); 61.7 (OCH_2); 53.5 (CH); 49.0 (CH); 27.9 (CH); 23.2 (Me); 13.8 (Me); 13.78 (Me). EI-MS: 259 (11, $[M+1]^+$), 243 (17), 230 (0.6), 213 (17), 197 (54), 185 (9), 169 (18), 151 (8), 141 (100), 127 (30), 113 (34), 99 (23), 82 (4), 67 (8), 55 (5), 43 (13), 30 (1). Anal. calc. for $C_{12}H_{18}O_6$ (258.28): C 55.81, H 7.03; found: C 55.82, H 7.35.

Diethyl 2-Oxo-1-oxaspiro[4.5]decane-3,4-dicarboxylate (**5h**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and a THF (2 ml) soln. of cyclohexanone (263 mg, 2.7 mmol). The crude product was purified by FC (SiO_2, 8% AcOEt/hexane): **5h** (344 mg, 58%). M.p. 47–48° (from Et_2O/hexane). White solid. IR (neat): 2983*m*, 2940*s*, 1784*s*, 1738*s*, 1465*m*, 1450*m*, 1376*s*, 1322*s*, 1299*s*, 1265*s*, 1219*s*, 1186*s*, 1125*s*, 1029*s*, 960*s*, 921*m*, 863*m*, 720*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.30–4.19 (*m*, 2 OCH_2Me); 4.18 (*d*, J_{trans} = 11.5, COCHCO); 3.59 (*d*, J_{trans} = 11.5, *CH*CO_2Et); 2.03–1.90, 1.80–1.58 (2 sets of *m*, $(CH_2)_5$); 1.34 (*t*, J = 7.0, OCH_2*Me*) 1.32 (*t*, J = 7.2, OCH_2*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.6 (C=O); 168.2 (C=O); 166.4 (C=O), 84.4 (O–C); 62.1 (OCH_2); 61.6 (OCH_2); 53.9 (CH); 48.7 (CH); 36.7 (CH_2); 32.1 (CH_2), 24.5 (CH_2); 22.2 (CH_2); 21.1 (CH_2); 13.9 (Me); 13.8 (Me). EI-MS: 298 (7, M^+), 252 (100), 234 (28), 224 (29), 206 (60), 181 (84), 167 (23), 161 (13), 151 (24), 135 (40), 127 (70), 107 (20), 99 (66), 91 (13), 79 (21), 69 (16), 55 (23), 41 (10). Anal. calc. for $C_{14}H_{22}O_6$ (298.34): C 60.39, H 7.43; found: C 60.18, H 7.72.

Diethyl Tetrahydro-5-oxo-2,2-diphenylfuran-3,4-dicarboxylate (**5i**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and a THF (2 ml) soln. of benzophenone (457 mg, 2.5 mmol). The crude product was purified by prep. TLC (SiO_2, 8% AcOEt/hexane; double runs) to give a pale yellow viscous liquid of **5i** (307 mg, 41%) as a 86 : 14 *trans*/*cis* mixture, which was crystallized from AcOEt/hexane to afford a white solid (115 mg) as a 66 : 34 *trans*/*cis* mixture. M.p. 95–96°. IR (neat): 3060*m*, 3025*m*, 2955*s*, 1806*s*, 1747*s*, 1727*s*, 1599*w*, 1494*m*, 1448*s*, 1377*s*, 1349*m*, 1310*s*, 1250*s*, 1235*s*, 1219*s*, 1183*s*, 1165*s*, 1110*m*, 1083*m*, 1045*s*, 1026*s*, 988*s*, 966*m*, 928*w*, 917*w*, 905*w*, 892*m*, 848*w*, 823*w*, 755*s*, 726*m*, 697*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.68–7.64 (*trans*), 7.52–7.48 (*cis*) (each *m*, 2 arom. H); 7.39–7.05 (*m*, 8 arom. H); 4.65 (*trans*), 4.33 (*cis*) (each *d*, J = 9.3 and 6.6, resp., COCHCO); 4.26 (*trans*), 3.62 (*cis*) (each *d*, J = 9.3 and 6.6, resp., *CH*CO_2Et); 4.24–4.02 (*m*, OCH_2Me of *cis* isomer); 4.11 (*q*, J = 7.3, OCH_2Me of *trans* isomer); 3.90–3.63 (*m*, OCH_2Me); 1.21 (*cis*), 1.17 (*trans*) (each *t*, J = 7.0 and 7.3, resp., OCH_2*Me*); 0.94 (*trans*), 0.80 (*cis*) (each *t*, J = 7.0 and 7.3, resp., OCH_2*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.9 (C=O, *trans*), 168.8 (C=O, *cis*); 168.0 (C=O, *trans*), 167.8 (C=O, *cis*); 165.8 (C=O, *trans*), 164.7 (C=O, *cis*); 141.0 (C, *trans*), 140.7 (C, *cis*); 139.4 (C, *trans*), 139.0 (C, *cis*); 129.0 (CH); 128.6 (CH); 128.4 (CH); 128.3 (CH); 128.1 (CH); 128.0 (CH); 127.9 (CH); 127.1 (CH); 125.9 (CH); 125.3 (CH); 125.1 (CH); 89.4 (OC, *trans*), 87.5 (OC, *cis*); 62.5 (OCH_2, *trans*), 62.0 (OCH_2, *cis*); 61.9 (OCH_2, *trans*), 61.2 (OCH_2, *cis*); 53.5 (CH, *trans*), 53.1 (CH, *cis*); 49.3 (CH, *trans*), 49.0 (CH, *cis*); 13.9 (Me, *cis*), 13.8 (Me, *trans*); 13.5 (Me, *trans*), 13.3 (Me, *cis*). EI-MS: 382 (2, M^+), 337 (3), 309 (0.8), 291 (2), 273 (0.7), 259 (3), 247 (2), 231 (2), 219 (2), 200 (100), 191 (16), 183 (40), 165 (6), 154 (36), 127 (65), 115 (3), 105 (37), 99 (37), 77 (17), 51 (4). Anal. calc. for $C_{22}H_{22}O_6$ (382.43): C 69.10, H 5.80; found: C 69.46, H 5.53.

Diethyl Tetrahydro-2-methyl-5-oxo-2-phenylfuran-3,4-dicarboxylate (**5j**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and a THF (2 ml) soln. of acetophenone (0.3 ml, 2.56 mmol). The crude product was purified by prep. TLC (SiO_2, 10% AcOEt/hexane; multiple runs): **5j** (252 mg, 39%). Yellow liquid containing mainly one diastereoisomer (by ^{1}H- and ^{13}C-NMR (strong peaks due to *CH* and 2 other small signals, presumably arising from *CH* of the other 2 diastereoisomers)). IR (neat): 3063*w*, 2985*m*, 2940*m*, 2907*m*, 1789*s*, 1738*s*, 1604*w*, 1498*m*, 1466*m*, 1448*m*, 1380*m*, 1322*s*, 1284*s*, 1212*s*, 1176*s*, 1125*m*, 1028*s*, 907*m*, 859*m*, 793*m*, 754*m*, 700*s*. ^{1}H-NMR (300 MHz, $CDCl_3$; major isomer): 7.40–7.23 (*m*, 5 arom. H); 4.34–4.23 (*m*, OCH_2Me); 4.14 (*d*, J = 11.0, COCHCO); 3.94 (*d*, J = 11.0, *CH*CO_2Et); 4.01–3.82 (*m*, OCH_2Me); 2.07 (*s*, MeC); 1.33 (*t*, J = 7.2, 2 OCH_2*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$; major isomer): 169.4 (C=O); 167.4 (C=O); 166.2 (C=O); 138.8 (C); 128.4 (CH); 128.3 (CH); 124.7 (CH); 85.5 (O–C); 62.4 (OCH_2); 61.6 (OCH_2); 55.8 (CH); 48.8 (CH); 27.9 (Me); 13.8 (Me); 13.6 (Me). EI-MS: 320 (5, M^+), 305 (5), 275 (3), 259 (33), 247 (1), 231 (12), 213 (7), 200 (100), 189 (3), 173 (2), 154 (26), 145 (3), 127 (84), 115 (8), 105 (37), 99 (41), 77 (15), 43 (5). Anal. calc. for $C_{17}H_{20}O_6$ (320.35): C 63.74, H 6.29; found: C 63.84, H 6.63.

Diethyl 2-Ethyltetrahydro-2-methyl-5-oxofuran-3,4-dicarboxylate (**5k**). According to the *G.P.*, with dianion **2** (2.0 mmol) in THF (10 ml) and a THF (2 ml) soln. of butan-2-one (0.23 ml, 2.7 mmol). The crude product, a 53:10:16:21 mixture of 4 diastereoisomers, was purified by FC (SiO_2, 8% AcOEt/hexane): colorless liquid of **5k** (202 mg, 37% yield) as a mixture of 4 diastereoisomers. The ratio of diastereoisomers was determined by integration of the *Me*CH_2C signals, *i.e.*, 4 sets of *t* at δ 0.91 (J = 7.4), 0.99 (J = 7.4), 1.069 (J = 7.3), and 1.073 (J = 7.3). However, only the ^{1}H-NMR data of two isomers (*trans* at the 3,4-positions) could be assigned, whereas the remaining two isomers (*cis* at the 3,4-positions) could not clearly be identified. IR (neat; diastereoisomer mixture): 2983*s*, 2943*m*, 1784*s*, 1737*s*, 1466*m*, 1384*s*, 1311*s*, 1271*s*, 1223*s*, 1180*s*, 1118*s*, 1029*s*, 951*m*, 904*m*, 861*m*, 708*m*. ^{1}H-NMR (300 MHz, $CDCl_3$; 2 3,4-*trans* isomers): 4.34–4.17 (*m*, 2 OCH_2Me, and COCHCO of the minor isomer); 4.16 (*d*, J = 11.7, COCHCO of the major isomer); 3.78 (minor), 3.76 (major) (each *d*, J = 11.1 and 11.7, resp., *CH*CO_2Et); 2.02 (minor), 1.60 (major) (each *m*, CCH_2Me); 1.65 (*s*, MeC of the major isomer); 1.37–1.29 (*m*, 2 OCH_2*Me* and MeC of the minor isomer); 1.07 (minor), 0.99 (major) (each *t*, J = 7.3 and 7.4, resp., CCH_2*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$; major isomer: 168.6 (C=O); 168.1 (C=O); 166.4 (C=O); 85.1(O–C); 62.1 (OCH_2); 61.5 (OCH_2); 53.9 (CH); 49.1 (CH); 29.0 (CH_2); 24.8 (Me); 13.7 (Me, two peaks merged); 7.3 (Me). EI-MS: 273 (0.92, $[M+1]^+$), 257 (3), 243 (50), 227 (8), 209 (8), 197 (100), 181 (9), 169 (29), 155 (33), 141 (16), 127 (30), 109 (12), 99 (18), 81 (7), 69 (3), 55 (4), 43 (9). Anal. calc. for $C_{13}H_{20}O_6$ (272.31): C 57.34, H 7.40; found: C 57.30, H 7.73.

When the colorless liquid of **5k** was left standing at r.t., it crystallized. Upon addition of hexane, a white solid of the major isomer was obtained as a single diastereoisomer. M.p. 49.5–51°. IR (nujol): 1781*s*, 1730*s*, 1384*s*, 1374*s*, 1312*s*, 1272*s*, 1221*s*, 1198*s*, 1180*s*, 1160*s*, 1118*s*, 1028*s*, 952*m*, 906*m*, 862*m*, 802*m*, 710*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.31 (*q*, J = 7.1, OCH_2Me); 4.24 (*m*, *ABX*$_3$, OCH_2Me); 4.17 (*d*, J = 11.7, COCHCO); 3.76 (*d*, J = 11.7, *CH*CO_2Et); 1.68, 1.55 (2 sets of *sext.*, *ABX*$_3$, CCH_2Me); 1.66 (*s*, MeC); 1.35 (*t*, J = 7.1, OCH_2*Me*); 1.32 (*t*, J = 7.1, OCH_2*Me*); 1.00 (*t*, J = 7.4, CCH_2*Me*).

3. *Preparation of* **17a**,**b**. *Diethyl Tetrahydro-3-methyl-2-oxo-5-pentylfuran-3,4-dicarboxylate* (**17a**). A THF (5 ml) soln. of a 70:27:3 mixture *t,c*/(*t,t* + *c,c*)/*c,t*-**5e** (1.50 g, 5.0 mmol) was added dropwise at 0° to a suspension of NaH (153 mg, 5.10 mmol; 80% dispersion in oil) in THF (10 ml). After stirring at 0° for 1 h, MeI (0.5 ml, 0.80 mmol) was added. The mixture was slowly warmed from 0° to r.t. overnight (15 h), then quenched with 0.5M HCl (0.5 ml), diluted with H_2O (50 ml), and extracted with AcOEt (3 × 30 ml). The combined extracts were washed with 5% $Na_2S_2O_5$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated. The crude product was purified by radial chromatography (SiO_2, 5% AcOEt/hexane) to give *Fr. 1* and *2* of **17a**.

Fr. 1 (less polar) yielded an inseparable 60:40 mixture *c,t*/*t,t*-**17a** (368 mg, 23%). Colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.85 (*dt*, J = 9.1, 3.2, CHO of *c,t*); 4.69 (*ddd*, J = 9.7, 8.5, 4.1, CHO of *t,t*); 4.30 (*q*, J = 7.1, OCH_2Me of *t,t*); 4.27–4.10 (*m*, 2 OCH_2Me of *c,t*, and OCH_2Me of *t,t*); 3.67 (*t,t*), 2.84 (*c,t*) (each *d*, J = 9.7 and 9.8, resp., *CH*CO_2Et); 1.96–1.24 (*m*, $(CH_2)_4$, 2 OCH_2*Me*); 1.65 (*c,t*), 1.44 (*t,t*) (each *s*, Me); 0.93–0.87 (*m*, $(CH_2)_4$*Me*).

Fr. 2 (more polar) yielded pure *c,c*-**17a** (1.0453 g, 67%). Colorless liquid. IR (neat): 2982*s*, 2957*s*, 2937*s*, 2873*m*, 1799*s*, 1743*s*, 1732*s*, 1464*m*, 1375*m*, 1348*m*, 1327*m*, 1296*s*, 1234*s*, 1203*s*, 1125*s*, 1097*s*, 1063*m*, 1018*s*, 949*m*, 858*m*, 773*m*, 731*m*, 693*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.63–4.55 (*m*, CHO); 4.27–4.13 (*m*, 2 OCH_2Me); 3.30 (*d*, J = 6.8, *CH*CO_2Et); 1.80–1.22 (*m*, $(CH_2)_4$, $(CH_2)_4$*Me*); 1.65 (*s*, MeC); 0.91–0.87 (*m*, $(CH_2)_4$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.3 (C=O); 169.1 (C=O); 168.8 (C=O); 77.0 (CH); 61.8 (OCH_2); 61.2 (OCH_2); 54.5 (CH); 53.0 (C); 31.3 (CH_2); 30.8 (CH_2); 25.5 (CH_2); 22.3 (CH_2); 21.5 (Me); 13.9 (Me); 13.8 (Me). EI-MS: 315 (20, $[M+1]^+$), 269 (27), 251 (1), 241 (10), 223 (9), 215 (4), 197 (45), 169 (100), 151 (19), 141 (36), 123 (29), 113

(45), 95 (19), 81 (11), 69 (8), 55 (8), 41 (10). Anal. calc. for $C_{16}H_{26}O_6$ (314.39): C 61.13, H 8.34; found: C 61.04, H 8.39.

Diethyl Tetrahydro-3-methyl-2-oxo-5-tridecylfuran-3,4-dicarboxylate (**17b**). As described for **17a**, with a THF (3 ml) soln. of a 66:34:trace mixture *t,cl(t,t* + *c,c)/c,t*-**5f** (1.24 g, 3.0 mmol), a THF (6 ml) suspension of NaH (80% dispersion in oil, 93 mg, 3.10 mmol), and MeI (0.32 ml, 5.10 mmol). The crude product, a 75:13:12 mixture of three diastereoisomers, was purified by radial chromatography (SiO_2, 5% AcOEt/hexane) to give *Fr. 1* and *2* of **17b**.

Fr. 1 (less polar) yielded an inseparable 51:49 mixture *c,t/t,t*-**17b** (353 mg, 25%). Colorless liquid. IR (neat): 2925*s*, 2854*s*, 1785*s*, 1741*s*, 1465*m*, 1380*m*, 1353*m*, 1300*m*, 1208*s*, 1106*m*, 1021*m*, 980*m*, 860*m*, 722*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.84 (*dt*, *J* = 3.3, 9.1, CHO of *c,t*); 4.69 (*ddd*, *J* = 9.5, 8.2, 4.2, CHO of *t,t*); 4.34–4.40 (*m*, 2 OCH_2Me); 3.67 (*t,t*), 2.86 (*c,t*) (each *d*, *J* = 9.9, $CHCO_2$Et); 1.95–1.20 (*m*, $(CH_2)_{12}$, 2 OCH_2Me); 1.64 (*c,t*), 1.44 (*t,t*) (each *s*. Me); 0.88 (app. *t*, *J* = 6.6, $(CH_2)_{12}Me$).

Fr. 2 (more polar) yielded pure *c,c*-**17b** (851 mg, 67%). White solid. M.p. 48–49° (from hexane). IR (nujol): 1788*s*, 1738*m*, 1721*s*, 1472*s*, 1326*m*, 1237*m*, 1210*s*, 1132*m*, 1121*m*, 1094*m*, 1030*m*, 1008*m*, 995*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.58 (*ddd*, *J* = 9.2, 6.6, 4.2, CHO); 4.25 (*q*, *J* = 7.1, OCH_2Me); 4.20 (*q*, *J* = 7.1, OCH_2Me); 3.30 (*d*, *J* = 6.6, $CHCO_2$Et); 1.80–1.24 (*m*, $(CH_2)_{12}$, 2 OCH_2Me); 1.66 (*s*, Me); 0.90 (app. *t*, *J* = 6.9, $(CH_2)_{12}Me$). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.4 (C=O); 169.2 (C=O); 169.0 (C=O); 77.1 (CH); 62.0 (OCH_2); 61.3 (OCH_2); 54.7 (CH); 53.1 (C); 31.9 (CH_2); 31.0 (CH_2); 29.7 (CH_2); 29.6 (CH_2); 29.6 (CH_2); 29.5 (CH_2); 29.4 (CH_2); 29.3 (CH_2); 29.2 (CH_2); 26.0 (CH_2); 22.7 (CH_2); 21.7 (Me); 14.1 (Me); 14.0 (Me); 13.9 (Me). EI-MS: 427 (2, $[M+1]^+$), 381 (13), 353 (9), 336 (7), 309 (19), 281(100), 253 (2), 235 (8), 197 (4), 187 (17), 169 (7), 141 (24), 123 (6), 113 (31), 95 (12), 81 (10), 69 (10), 57 (14), 43 (23). Anal. calc. for $C_{24}H_{42}O_6$ (426.61): C 67.57, H 9.92; found: C 67.73, H 9.82.

4. *Preparation of* **18a**,**b**. *Diethyl Tetrahydro-2-oxo-5-pentyl-3-[(phenylsulfonyl)methyl]furan-3,4-dicarboxylate* (**18a**). A THF (8 ml) soln. of a 82:6:11:trace mixutre *t,c/c,c/t,t/c,t*-**5e** (2.61 g, 8.6 mmol), was added dropwise at 0° to a suspension of NaH (80% dispersion in oil; 264 mg, 8.78 mmol) in THF (18 ml). After stirring at 0° for 1 h, a THF (10 ml) soln. of chloromethyl phenyl sulfide (2.064 g, 13.0 mmol) was added, followed by the addition of a THF (10 ml) soln. of NaI (2.004 g, 13.0 mmol). The mixture was stirred and slowly warmed from 0° to r.t. overnight (15 h), then quenched with 0.5M HCl (5 ml), diluted with H_2O (50 ml), and extracted with AcOEt (3 × 50 ml). The combined extract was washed with 5% $Na_2S_2O_5$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated. The crude product was purified by FC (SiO_2, 5% AcOEt/hexane) to give *Fr. 1* and *2* of the corresponding sulfide.

Fr. 1 (less polar) yielded an inseparable 70:30 mixture of *c,t* and *t,t* sulfide (149 mg, 4%). Colorless liquid. IR (neat): 3060*w*, 2958*m*, 2934*m*, 2862*m*, 1783*s*, 1743*s*, 1583*m*, 1467*m*, 1440*m*, 1390*m*, 1370*m*, 1353*m*, 1300*m*, 1271*m*, 1231*s*, 1197*s*, 1115*m*, 1097*m*, 1025*s*, 944*m*, 859*m*, 745*m*, 692*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.47–7.39 (*m*, 2 arom. H); 7.34–7.21 (*m*, 3 arom. H); 4.98 (*t,t*), 4.88 (*c,t*) (each *dt*, *J* = 3.7, 8.6 and 3.2, 8.7, resp., CHO); 4.31–4.00 (*m*, 2 OCH_2Me); 3.88, 3.64 (each *d*, *AB*, *J* = 14.4, CH_2SPh of *c,t*); 3.84 (*t,t*), 3.61 (*c,t*) (each *d*, *J* = 9.0 and 9.3, resp., $CHCO_2$Et); 3.73, 3.69 (each *d*, *AB*, *J* = 13.6, CH_2SPh of *t,t*); 1.92, 1.71 (2 sets of *m*, CH_2); 1.62–1.18 (*m*, 2 OCH_2Me, $(CH_2)_3$); 0.93 (m. Me).

Fr. 2 (more polar) yielded pure *c,c* sulfide (3.36 g, 92 %). Pale yellow liwuid. IR (nujol): 3059*w*, 2957*m*, 2933*m*, 2872*m*, 1781*s*, 1739*s*, 1583*m*, 1469*m*, 1440*m*, 1370*m*, 1306*m*, 1191*s*, 1125*m*, 1096*m*, 1066*m*, 1017*s*, 946*m*, 860*m*, 746*m*, 692*m*. ^{1}H-NMR (400 Hz, $CDCl_3$): 7.43–7.39 (*m*, 2 arom. H); 7.32–7.20 (*m*, 3 arom. H); 4.59 (*ddd*, *J* = 9.8, 7.5, 4.1, CHO); 4.14 (*q*, *J* = 7.1, OCH_2Me); 4.07 (*m*, *ABX*$_3$, OCH_2Me); 3.86 (*d*, *J* = 7.5, $CHCO_2$Et); 3.68 (*d*, *J* = 14.1, 1 H, CH_2SPh); 3.50 (*d*, *J* = 14.1, 1 H, CH_2SPh); 1.79, 1.66 (2 sets of *m*, CH_2); 1.51, 1.37 (2 sets of *m*, CH_2); 1.29 (*m*, CH_3); 1.22 (*t*, *J* = 7.1, OCH_2Me); 1.21 (*t*, *J* = 7.1, OCH_2Me); 0.88 (app. *t*, *J* = 6.7, $(CH_2)_4Me$). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.7 (C=O); 168.5 (C=O); 166.9 (C=O); 134.4 (S–C); 130.8 (CH); 129.1 (CH); 127.4 (CH); 78.0 (CH); 62.3 (OCH_2); 61.2 (OCH_2); 58.5 (C); 49.9 (CH); 38.4 (CH_2); 31.2 (CH_2); 30.8 (CH_2); 25.5 (CH_2); 22.3 (CH_2); 13.9 (Me); 13.8 (Me); 13.6 (Me). EI-MS: 422 (37, M^+), 399 (1), 393 (0.25), 377 (3), 365 (0.27), 348 (4), 331 (5), 313 (0.53), 299 (66), 287 (1), 275 (9), 253 (24), 225 (8), 207 (5), 175(4), 158 (11), 147 (9), 135 (5), 123 (100), 109 (33), 99 (20), 77 (12), 65 (15), 55 (16), 43 (22). Anal. calc. for $C_{22}H_{30}O_6S$ (422.55): C 62.54, H 7.16; found: C 62.78, H 7.18.

The crude sulfide, obtained from the reaction of a 82:6:11:trace mixture *t,c/c,c/t,t/c,t*-**5e** (1.21 g, 4.0 mmol) with chloromethyl phenyl sulfide (1.01 g, 6.3 mmol) and NaI (900 mg, 6.0 mmol) under the conditions described above, was dissolved in AcOH (25 ml) and cooled to 0°. Aq. H_2O_2 (30% soln., 6.0 ml, 60 mmol) was added dropwise, then the mixture was stirred and slowly warmed from 0° to r.t. overnight (15 h). After usual workup, the crude product, mainly one diastereoisomer (by ^{1}H-NMR), was purified by radial chromatography (SiO_2,

8% AcOEt/hexane): **18a** (1.76 g, 97%) as a mixture of diastereoisomers containing mainly the *c,c* isomer and trace amounts of the other isomers. Colorless viscous liquid. IR (neat): 3066*m*, 2957*s*, 2934*s*, 2872*m*, 1784*s*, 1745*s*, 1585*m*, 1467*m*, 1448*m*, 1394*m*, 1371*m*, 1327*s*, 1311*s*, 1246*s*, 1196*s*, 1155*s*, 1085*s*, 1070*s*, 1017*s*, 949*m*, 861*m*, 804*m*, 750*m*, 723*m*, 690*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.92 (app. *d*, $J = 7.3$, 2 arom. H); 7.70 (app. *t*, $J = 7.4$, 1 arom. H); 7.60 (app. *t*, $J = 7.6$, 2 arom. H); 4.95 (*m*, CHO); 4.67 (*d*, $J = 8.9$, $CHCO_2Et$); 4.20 (m, 2 OCH_2CH_3); 3.93, 3.88 (each *d*, *AB*, $J = 14.8$, CH_2SO_2Ph); 1.93, 1.84 (2 sets of *m*, CH_2); 1.35 (*m*, $(CH_3)_2$); 1.30 (*t*, $J = 7.1$, OCH_2Me); 1.26 (*t*, $J = 7.2$, OCH_2Me); 0.91 (*m*, $(CH_2)_4Me$). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.2 (C=O); 168.5 (C=O); 166.7 (C=O); 140.6 (SO_2C), 135.0 (CH); 130.1 (CH); 130.0 (CH); 79.7 (OCH); 63.8 (OCH_2), 62.4 (OCH_2); 58.3 (CH_2SO_2Ph); 55.4 (C); 49.4 (CH); 32.0 (CH_2); 31.7 (CH_2); 26.5 (CH_2); 23.1 (CH_2); 14.64 (Me); 14.59 (Me); 14.31 (CH_2). EI-MS 455 (2, M^-), 437 (0.63), 409 (14), 381 (21), 363 (2), 337 (11), 317 (3), 281 (2), 269 (8), 253 (7), 239 (5), 223 (45), 195 (25), 169 (33), 141 (44), 125 (41), 111 (11), 95 (16), 77 (100), 67 (27), 51 (37), 43 (53).

Diethyl Tetrahydro-2-oxo-3-[(phenylsulfonyl)methyl]-5-tridecylfuran-3,4-dicarbocylate (**18b**). A THF (3 ml) soln. of a diastereoisomer mixture containing mainly *t,c*-**5f** and a small amount of the others isomers (825 mg, 2.0 mmol) was added dropwise at 0° to a suspension of NaH (80% dispersion in oil; 64 mg, 2.1 mmol) in THF (4 ml). After stirring at 0° for 1 h, a THF (6 ml) soln. of chloromethyl phenyl sulfide (478 mg, 3.0 mmol) was added, followed by the addition of NaI (450 mg, 3.0 mmol). The mixture was stirred and slowly warmed from 0° to r.t. overnight (15 h).

The crude product obtained from this reaction was dissolved in AcOH (12 ml) and cooled to 0°. Aq. H_2O_2 (30% soln.; 3.0 ml, 30 mmol) was added dropwise, then the mixture was stirred and slowly warmed from 0° to r.t. overnight (15 h). After usual workup, the crude product was purified by radial chromatography (SiO_2, 8% AcOEt/hexane) to give *Fr. 1* and *2* of **18b**.

Fr. 1 (less polar) yielded an inseparable 73 : 27 mixture *c,t*/*t,t*-**18b** (55 mg, 5%). Pale yellow liquid. IR (neat): 3066*w*, 2925*s*, 2854*s*, 1785*s*, 1746*s*, 1585*w*, 1466*m*, 1448*m*, 1393*m*, 1371*m*, 1356*m*, 1323*s*, 1311*s*, 1203*s*, 1161*s*, 1086*m*, 1023*m*, 947*m*, 838*m*, 857*m*, 783*m*, 746*m*, 723*m*, 689*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.96 (*c,t*), 7.89 (*t,t*) (each app. *dd*, $J = 8.3$, 1.3 and 8.2, 1.4, resp., 2 arom. H); 7.74–7.55 (*m*, 3 arom. H); 5.02 (*t,t*), 4.97 (*c,t*) (each *dt*, $J = 3.7$, 8.0 and 3.2, 8.9, resp., CHO); 4.35–3.97 (*m*, 2 OCH_2Me and $CHCO_2Et$ of *c,t* and *t,t*; and CH_2SO_2Ph of *t,t*); 4.10, 3.91 (each *d*, *AB*, $J = 14.7$, CH_2SO_2Ph of *c,t*); 2.10–1.20 (*m*, $(CH_2)_{12}$, 2 OCH_2Me), 0.88 (app. *t*, $J = 6.6$, $(CH_2)_{12}Me$).

Fr. 2 (more polar) yielded pure *c,c*-**18b** (1.0013 g, 88%). White solid. M.p. 73–74° (AcOEt/hexane). IR (neat): 3064*w*, 3002*m*, 1779*s*, 1721*s*, 1587*w*, 1471*m*, 1447*m*, 1404*m*, 1376*m*, 1345*m*, 1324*s*, 1298*m*, 1259*s*, 1244*s*, 1230*s*, 1159*s*, 1120*m*, 1088*m*, 1071*m*, 1023*m*, 1008*m*, 963*m*, 867*m*, 855*m*, 803*m*, 748*m*, 725*m*, 687*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.95 (app. *dd*, $J = 7.9$, 1.2, 2 arom. H); 7.70 (*t*, $J = 7.4$, 1 arom. H); 7.60 (*t*, $J = 7.7$, 2 arom. H); 4.95 (*m*, CHO); 4.68 (*d*, $J = 8.9$, $CHCO_2Et$); 4.29–4.12 (*m*, 2 OCH_2Me); 3.94, 3.88 (each *d*, *AB*, $J = 14.8$, CH_2SO_2Ph); 1.95, 1.85 (2 sets of *m*, CH_2); 1.63, 1.46 (2 sets of *m*, CH_2); 1.28 (*m*, $(CH_2)_{10}$, 2 OCH_2Me); 0.89 (m, $(CH_2)_4Me$). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.5 (C=O); 167.9 (C=O); 166.1 (C=O); 139.9 (SO_2C(arom.)); 134.3 (CH); 129.4 (CH, 2 peaks merged); 127.8 (CH, 2 peaks merged); 79.1 (OCH); 63.1 (OCH_2); 61.7 (OCH_2); 57.7 (CH_2SO_2Ar); 54.7 (C); 48.8 (CH_2); 31.9 (CH_2); 31.1 (CH_2); 29.62 (CH_2); 29.59 (CH_2, 2 peaks merged); 29.47 (CH_2); 29.40 (CH_2); 29.29 (CH_2); 29.20 (CH_2); 26.1 (CH_2); 22.6 (CH_2); 14.1 (Me); 14.0 (Me); 13.6 (Me). EI-MS: 567 (4, $[M+1]^+$), 551 (0.61), 520 (23), 493 (82), 477 (6), 447 (7), 419 (6), 397 (2), 381 (31), 365 (2), 351 (7), 335 (56), 307 (19), 281 (100), 261 (10), 233 (11), 206 (19), 193 (5), 165 (98), 141 (35), 125 (49), 109 (16), 95 (26), 77 (84), 67 (35), 57 (50), 43 (91). Anal. calc. for $C_{30}H_{46}O_8S$ (566.77): C 63.58, H 8.18; found: C 63.59, H 8.39.

5. *Preparation of* **20a** *and* **12**. *Tetrahydro-5-oxo-2-pentyl-4-[(phenylsulfonyl)methyl]furan-3-carboxylic Acid* (**20a**). γ-Lactone *c,c*-**18a** (1.5001 g, 3.30 mmol) containing a small amount of the other isomers was refluxed in 48% HBr soln. (20 ml) for 3 h. The resulting mixture was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layers was washed with sat. aq. $NaHCO_3$ soln. (3 × 30 ml). The basic soln. was acidified to pH 2 with 6M HCl and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. phase was washed with H_2O and brine, dried (Na_2SO_4), and evaporated and the residue recrystallized from AcOEt/hexane: 32 : 64 : 4 mixture *t,c*/*c,c*/*t,t*-**20a** (562 mg, 48%). White solid. M.p. 155–157°. IR (nujol): 3282*m*, 3069*w*, 1771*s*, 1717*s*, 1589*w*, 1308*m*, 1283*m*, 1220*m*, 1188*m*, 1163*m*, 1151*m*, 1087*m*, 994*m*, 984*m*, 931*m*, 836*m*, 790*m*, 742*m*, 720*m*, 685*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.99–7.92 (*m*, 2 arom. H); 7.75–7.68 (*m*, 1 arom. H); 7.65–7.58 (*m*, 1 arom. H); 6.00 (br. *s*, CO_2H); 4.85 (*m*, CHO of *t,c*); 4.59 (app. *q*, $J = 6.4$, CHO of *c,c*); 4.50 (*dt*, $J = 3.7$, 8.8, CHO of *t,t*); 3.89 (*t*, $J = 9.1$, $CHCO_2H$ of *t,c*); 3.79 (*dd*, $J = 6.7$, 5.4, $CHCO_2H$ of *c,c*); 3.77–3.55 (*m*, 2 H, $CHCH_2SO_2Ph$ and CH_2SO_2Ph of *t,c* and *t,t*; and CH_2SO_2Ph of *c,c*); 3.46 (*ddd*, $J = 10.8$, 6.8, 3.7, $CHCH_2SO_2Ph$ of

c,c); 3.35–3.25 (*m*, 2 H, C*H*CO_2H and CH_2SO_2Ph of *t,t*); 3.30 (*dd*, *J* = 14.4, 10.1, 1 H, CH_2SO_2Ph of *t,c*); 1.77 (*q*, *J* = 7.5, CH_2 of *c,c*); 2.00–1.25 (*m*, $(CH_2)_4$ of *t,c* and *t,t*, and 3 CH_2 of *c,c*); 0.93–0.85 (*m*, $(CH_2)_4$*Me*). EI-MS: 355 (3, $[M+1]^+$), 337 (2), 290 (2), 265 (9), 245 (1), 237 (6), 213 (46), 195 (8), 177 (7), 162 (21), 148 (58), 125 (42), 113 (15), 94 (22), 85 (77), 77 (100), 67 (34), 55 (30), 41 (42). Anal. calc. for $C_{17}H_{22}O_4S$ (354.43): C 57.61, H 6.26; found: C 57.52, H 6.43.

(±)-Lichesterinic Acid (**12**). To an aq. soln. of LiOH·H_2O (263 mg, 6.0 mmol, 1.5 ml) was added a THF (15 ml) soln. of *c,c/t,t*-**18b** (779 mg, 1.40 mmol). The mixture was refluxed for 3 h and then stirred at r.t. overnight. The resulting mixture was diluted with H_2O (50 ml) and extracted with AcOEt (3 × 30 ml) to remove the unhydrolyzed ester. The aq. phase was then acidified to pH 2 with 6M HCl and extracted with AcOEt (3 × 30 ml). The combined org. layer was washed with H_2O and brine, dried (Na_2SO_4) and evaporated. The white solid, a mixture of **12** and an unidentified compound (310 mg), was recrystallized from AcOEt: (114 mg, 26%). White solid. M.p. 117.5–118.5° ([23] m.p. 114–115° (AcOH)). IR (nujol): 2740*m*, 2632*m*, 2533*m*, 1732*s*, 1704*s*, 1527*w*, 1422*m*, 1341*m*, 1325*m*, 1206*s*, 1153*m*, 1134*m*, 1044*m*, 963*m*, 936*m*, 890*m*, 760*m*, 714*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.14 (*m*, CHO); 2.90 (br. *s*, CO_2H); 2.26 (*d*, *J* = 2.1, MeC=C); 2.14, 1.61 (2 sets of *m*, CH_2); 1.48–1.22 (*m*, 11 CH_2); 0.90 (app. *t*, $(CH_2)_{12}$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.7 (C=O); 166.3 (C=O); 146.8 (C); 139.8 (C); 81.4 (OCH); 32.7 (CH_2); 31.9 (CH_2); 29.65 (CH_2); 29.62 (CH_2, 2 peaks merged); 29.58 (CH_2); 29.50 (CH_2); 29.37 (CH_2); 29.33 (CH_2); 29.22 (CH_2); 24.8 (CH_2); 22.7 (CH_2); 14.1 (Me); 11.0 (Me). Anal. calc. for $C_{19}H_{32}O_3$ (324.47): C 70.34, H 9.94; found: C 70.29, H 9.61.

6. *(±)-Rocellaric Acid* (**15**) *and (±)-Dihydroprotolichesterinic Acid* (**16**). To a soln. of LiOH·H_2O (188 mg, 4.50 mmol) in H_2O (0.5 ml) was added a THF (4.5 ml) soln. of the pure *c,c*-**17b** (473 mg, 1.10 mmol). The mixture was stirred at r.t. overnight. After usual workup as described before, the crude product obtained (464 mg) was treated with 48% HBr soln. (6 ml) and refluxed for 5 h. The resulting mixture was diluted with H_2O (20 ml) and extracted with AcOEt (3 × 30 ml). The combined org. layers were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The solid was crystallized from AcOEt/hexane: 64:36 mixture **15/16** (289 mg, 80%). White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.70 (*q*, *J* = 6.4, CHO of the minor isomer); 4.48 (*dt*, *J* = 8.7, 3.8, CHO of the major isomer); 3.16 (minor), 2.70 (major) (each *dd*, *J* = 9.2, 6.4 and 11.1, 9.4, resp., C*H*CO_2H); 3.08–2.92 (*m*, C*H*Me); 1.88–1.63 (*m*, CH_2); 1.60–1.20 (*m*, 11 CH_2); 1.37 (major), 1.30 (minor) (each *d*, *J* = 7.0 and 7.4, CH*Me*); 0.88 (app. *t*, *J* = 6.6, $(CH_2)_{12}$*Me*).

Base-Catalyzed Isomerization of **16** *to* **15**. A soln. of 1.56M BuLi in hexane (1.5 ml, 2.34 mmol) was added dropwise to a soln. of ^{i}Pr$_2$NH (0.36 ml, 2.5 mmol) in THF (4 ml) at 0° under Ar. After stirring at 0° for 30 min, a THF (1.5 ml) soln. of a 64:36 mixture **15/16** (305 mg, 0.94 mmol) was added dropwise. The mixture was stirred at 0° for 1 h and then quenched with AcOH. The mixture was allowed to reach r.t. and acidified to pH 2 with 1M HCl. Usual workup gave a brownish crystalline 89:11 mixture **15/16**. Fractional crystallization from AcOEt afforded pure **15** (219 mg, 72%). Colorless crystals. M.p. 98–99° [24]. IR (nujol): 1747*s*, 1715*s*, 1471*s*, 1455*s*, 1434*m*, 1398*m*, 1361*m*, 1314*m*, 1256*m*, 1222*m*, 1206*m*, 1172*m*, 1146*m*, 1126*m*, 1103*m*, 1015*m*, 973*m*, 944*m*, 894*m*, 718*m*, 698*m*, 671*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.85 (br., CO_2H); 4.49 (*ddd*, *J* = 9.1, 8.6, 4.0, CHO), 2.99 (*dq*, *J* = 11.4, 7.1, C*H*Me); 2.71 (*dd*, *J* = 11.1, 9.5, C*H*CO_2H); 1.77 (*m*, CH_2); 1.60–1.21 (*m*, 11 CH_2); 1.37 (*d*, *J* = 7.2, CH*Me*); 0.88 (app. *t*, *J* = 6.6, $(CH_2)_{12}$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.7 (C=O); 176.1 (C=O); 79.4 (OCH); 53.9 (CH); 39.8 (CH); 34.9 (CH_2); 31.9 (CH_2); 29.7 (CH_2); 29.6 (CH_2); 29.57 (CH_2); 29.47 (CH_2); 29.36 (CH_2); 29.32 (CH_2); 29.20 (CH_2); 25.3 (CH_2); 22.7 (CH_2); 14.5 (Me); 14.1 (Me). EI-MS: 326 (5, M^+), 308 (3), 290 (1), 281 (20), 263 (3), 253 (23), 235 (11), 207 (3), 194 (2), 168 (3), 154 (10), 143 (10), 132 (17), 123 (8), 114 (18), 97 (28), 87 (23), 81 (20), 69 (44), 55 (51), 41 (100), 32 (5). Anal. calc. for $C_{19}H_{34}O_4$ (336.57): C 69.90, H 10.50; found: C 70.09, H 10.42.

Compound **16** could not be separated from the residue in pure form.

Methyl Esters of (±)-Rocellaric Acid (**15**) *and (±)-Dihydroprotolichesterinic Acid* (**16**). To a soln. of a 64:36 mixture **15/16** (258 mg, 0.79 mmol) in dry MeOH (3 ml) was added a soln. of dicyclohexylcarbodiimide (DCC; 260 mg, 1.26 mmol) in dry MeOH (1 ml). The mixture was stirred at r.t. overnight. The precipitates were then filtered off. After evaporation, the crude product, a 80:20 mixture of methyl esters of **15** and **16**, was purified by radial chromatography (SiO_2, 2% AcOEt/hexane) to give *Fr. 1* and *2* of methyl esters of **15** and **16**.

Fr. 1 (less polar) yielded the methyl ester of **15** (180 mg, 67%). White solid. M.p. 40–41° (hexane) [23]. IR (nujol): 1783*s*, 1743*s*, 1435*m*, 1320*m*, 1281*m*, 1265*m*, 1252*m*, 1203*m*, 1171*m*, 1105*m*, 1122*m*, 1065*m*, 998*m*, 980*m*, 968*m*, 937*m*, 724*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.45 (app. *dt*, *J* = 4.1, 8.5, CHO); 3.78 (*s*, CO_2Me); 2.96 (*dq*, *J* = 11.5, 7.2, C*H*Me); 2.66 (*dd*, *J* = 11.1, 9.5, C*H*CO_2Me); 1.73 (*m*, CH_2); 1.58–1.20 (*m*, 11 CH_2); 1.32 (*d*, *J* = 7.2, C*H*Me); 0.88 (app. *t*, *J* = 6.6, $(CH_2)_{12}$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.7(C=O); 171.1 (C=O); 79.5 (OCH); 54.1 (CH); 52.5 (OMe); 39.8 (CH); 34.8 (CH_2); 31.8 (CH_2); 29.60 (CH_2); 29.57 (CH_2, 2 peaks merged);

29.53 (CH_2); 29.42 (CH_2); 29.38 (CH_2); 29.36 (CH_2); 29.32 (CH_2); 29.28 (CH_2); 29.21 (CH_2); 29.15 (CH_2); 25.2 (CH_2); 22.6 (CH_2); 14.4 (Me); 14.0 (Me). EI-MS: 340 (6, M^+), 322 (4), 308 (8), 294 (14), 281 (60), 267 (80), 253 (4), 235 (15), 207 (9), 182 (6), 168 (15), 154 (44), 146 (40), 129 (82), 109 (28), 101 (77), 81 (30), 69 (100), 55 (53), 41 (89).

Fr. 2 (more polar) yielded the methyl ester of **16** (22 mg, 8%) [24]. White solid. M.p. 50.0–50.5° (hexane). IR (nujol): 1770*s*, 1724*s*, 1464*s*, 1345*m*, 1220*m*, 1205*m*, 1181*s*, 1126*m*, 1092*m*, 1071*m*, 1016*m*, 986*m*, 964*m*, 917*m*, 802*m*, 720*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.70 (*q*, *J* = 6.4, CHO); 3.75 (*s*, CO_2Me); 3.11 (*dd*, *J* = 9.4, 7.4, *CH*CO_2Me); 2.97 (*dq*, *J* = 9.4, 7.4, *CH*Me); 1.70–1.62 (*m*, CH_2); 1.57–1.20 (*m*, 11 CH_2); 1.22 (*d*, *J* = 7.6, CH*Me*); 0.88 (app. *t*, *J* = 6.7, $(CH_2)_{12}$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.3 (C=O); 170.5 (C=O); 79.4 (OCH); 52.1 (CH); 50.0 (Me); 37.1(CH_2); 34.7 (CH_2); 31.9 (CH_2); 29.62 (CH_2); 29.59 (CH_2, 2 peaks merged); 29.55 (CH_2); 29.44 (CH_2); 29.35 (CH_2); 29.30 (CH_2); 29.17 (CH_2); 25.3 (CH_2); 22.6 (CH_2); 14.1 (Me); 11.9 (Me).

7. *(±)-Nephromopsinic Acid* (**14**). Pure *c,c*-**17b** (400 mg, 0.94 mmol) was refluxed in 48% HBr soln. (10 ml) for 5 h. The resulting mixture was diluted with H_2O (50 ml) and extracted with AcOEt (3 × 30 ml). The combined org. layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was crystallized from AcOEt/hexane: 62:38 mixture **23/14** (265 mg, 87%). White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.72 (*m*, CHO of the minor isomer); 4.46 (*dt*, *J* = 5.1, 8.7, CHO of the major isomer); 3.35 (major), 3.24 (minor) (each *dd*, *J* = 7.4, 5.2 and 9.8, 8.3, resp., *CH*CO_2H); 3.06 (*dq*, *J* = 9.8, 7.1, *CH*Me of the minor isomer); 2.96 (*m*, *CH*Me of the major isomer); 1.92–1.24 (series of *m*, 12 CH_2 of both isomers, and CH*Me* of the minor isomer); 1.34 (*d*, *J* = 7.1, CH*Me* of the major isomer); 0.90 (app. *t*, *J* = 6.8, 3 H, $(CH_2)_{12}$*Me*).

Methyl Ester of (±)-Nephromopsinic Acid (**14**). To a soln. of the 38:62 mixture **14/23** (258 mg, 0.79 mmol) in dry MeOH (4 ml) and dry CH_2Cl_2 (0.5 ml) was added a soln. of DCC (280 mg, 1.35 mmol) in dry MeOH (1 ml). After stirring at r.t. overnight, the precipitates were filtered off and washed with AcOEt. The filtrate was evaporated, and the crude product purified by FC (SiO_2, 5% AcOEt/hexane): methyl ester of (±)-rocellaric acid (**15**; 46 mg, 15%; the formation of (±)-rocellaric acid methyl ester may be due to the equilibration at C(α) and C(β) of the initiallly formed methyl ester of **23**) and methyl ester of **14** (85 mg, 28%). White solid. M.p. 62–62.5 (AcOEt/hexane) [19e]. IR (nujol): 1781*s*, 1734*s*, 1429*m*, 1385*m*, 1338*m*, 1249*m*, 1205*s*, 1168*m*, 1133*m*, 1094*m*, 1076*m*, 1005*s*, 982*m*, 930*m*, 739*m*, 723*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.65 (*m*, CHO); 3.77 (*s*, CO_2Me); 3.18 (*dd*, *J* = 9.8, 8.3, *CH*CO_2Me); 3.05 (*dq*, *J* = 10.0, 7.0, *CH*Me); 1.60–1.22 (*m*, $(CH_2)_{12}$*Me*); 1.29 (*d*, *J* = 7.1, CH*Me*); 0.88 (app. *t*, *J* = 6.6, $(CH_2)_{12}$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.5 (C=O); 170.1 (C=O); 77.5 (OCH); 52.3 (CH); 51.7 (Me); 36.3 (CH); 31.9 (CH_2); 31.2 (CH_2); 29.63 (CH_2); 29.60 (CH_2, 2 peaks merged); 29.57 (CH_2); 29.55 (CH_2); 29.45 (CH_2); 29.37 (CH_2); 29.31 (CH_2); 29.16 (CH_2); 25.6 (CH_2); 22.6 (CH_2); 14.4 (Me); 14.1 (Me).

8. *(±)-Phaseolinic Acid* (**13**). Pure *c,c*-**17a** (746 mg, 2.37 mmol) was refluxed in 48% HBr soln. (12 ml) for 5 h. The resulting mixture was diluted with H_2O (30 ml) and extracted with AcOEt (3 × 30 ml). The combined org. layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The solid was recrystallized from AcOEt/hexane: 38:62 mixture **13/22** (450 mg, 89%). ^{1}H-NMR (300 MHz, $CDCl_3$): 4.70 (*m*, CHO of the minor isomer); 4.44 (*dt*, *J* = 8.4, 5.1, CHO of the major isomer); 3.50 (br., COOH); 3.33 (major), 3.22 (minor) (each *dd*, *J* = 7.3, 5.2 and 9.6, 8.3, resp., *CH*CO_2H); 3.03 (*dq*, *J* = 9.9, 7.1, *CH*Me of the minor isomer); 2.94 (*quint.*, *J* = 7.2, *CH*Me of the major isomer); 1.92–1.25 (*m*, $(CH_2)_4$, and CH*Me*); 0.89 (*m*, $(CH_2)_4$*Me*).

Methyl Ester of (±)-Phaseolinic Acid (**13**). To a soln. of a 38:62 mixture **13/22** (405 mg, 1.90 mmol) in dry MeOH (4 ml) was added a soln. of DCC (613 mg, 3.0 mmol) in dry MeOH (2 ml). After stirring at r.t. overnight, the precipitate was filtered off and washed with AcOEt. The filtrate was evaporated to give the crude product, which was purified by radial chromatography (SiO_2, 2% AcOEt/hexane): methyl ester of **13** (178 mg, 41%) as a colorless liquid and methyl ester of **22** (110 mg, 26% yield) as a colorless liquid. Methyl ester of **13** (less polar) [25]: IR (neat): 2956*s*, 2936*s*, 2861*m*, 1781*s*, 1740*s*, 1457*m*, 1438*m*, 1381*m*, 1340*m*, 1248*m*, 1205*s*, 1182*s*, 1133*m*, 1114*m*, 1075*m*, 1051*m*, 1004*s*, 929*m*, 738*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.66 (*ddd*, *J* = 9.9, 8.2, 3.3, CHO); 3.78 (*s*, CO_2*Me*); 3.19 (*dd*, *J* = 10.0, 8.2, *CH*CO_2Me); 3.06 (*dq*, *J* = 10.0, 7.1, *CH*Me); 1.60–1.48 (*m*, CH_2); 1.46–1.24 (*m*, 3 CH_2); 1.30 (*d*, *J* = 7.1, CH*Me*); 0.90 (app. *t*, *J* = 6.8, $(CH_2)_4$*Me*). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.5 (C=O); 170.1 (C=O); 77.5 (OCH); 52.2 (OMe); 51.6 (CH); 36.3 (CH); 31.3 (CH_2); 31.1 (CH_3); 25.2 (CH_2); 22.3 (CH_2); 14.3 (Me); 13.8 (Me). EI-MS: 229 (0.92, $[M+1]^+$), 308 (3), 210 (0.86), 197 (4), 182 (5), 169 (12), 157 (34), 141 (4), 129 (77), 113 (13), 97 (39), 88 (10), 81 (10), 69 (100), 59 (35), 55 (31), 41 (52), 32 (5). Anal. calc. for $C_{12}H_{20}O_4$ (228.30): C 63.14, H 8.83; found: C 63.01, H 8.92.

Methyl ester of **22** (more polar): IR (neat): 2955*s*, 2862*m*, 1781*s*, 1738*s*, 1463*m*, 1439*m*, 1397*m*, 1380*m*, 1343*m*, 1271*m*, 1199*s*, 1177*s*, 1128*m*, 1099*m*, 1038*m*, 1016*m*, 995*m*, 931*m*, 879*m*, 797*m*, 772*m*, 729*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.40 (*m*, CHO); 3.70 (*s*, CO_2Me); 3.31 (*dd*, $J = 7.5, 5.3$, $CHCO_2Me$); 2.90 (*m*, *CH*Me); 1.75–1.22 (series of *m*, $(CH_2)_4Me$); 1.19 (*d*, $J = 7.2$, CH*Me*); 0.85 (*m*, $(CH_2)_4Me$). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.0 (C=O); 170.0 (C=O); 78.8 (OCH); 51.4 (OMe); 50.3 (CH); 38.8 (CH); 31.2 (CH_2); 30.6 (CH_2); 25.3 (CH_2); 22.2 (CH_2); 13.7 (Me); 10.1 (Me). EI-MS: 229 (9, $[M+1]^+$), 211 (2), 197 (8), 184 (5), 169 (51), 157 (14), 141 (12), 129 (29), 113 (29), 101 (46), 97 (22), 85 (16), 81 (28), 69 (100), 59 (47), 55 (40), 41 (63).

REFERENCES

[1] C. M. Thompson, in 'Dianion Chemistry in Organic Synthesis', CRC Press, 1994.
[2] N. R. Long, M. W. Rathke, *Synth. Commun.* **1981**, *11*, 687.
[3] M. Pohmakotr, V. Reutrakul , T. Phongpradit, A. Chansri, *Chem. Lett.* **1982**, 687.
[4] K. Furata, A. Misumi, A. Mori, N. Ikeda, H. Yamamoto, *Tetrahedron Lett.* **1984**, *25*, 669.
[5] K. Furata, N. Ikeda, H. Yamamoto, *Tetrahedron Lett.* **1984**, *25*, 675.
[6] K. K. Mahalanabis, M. Mumtaz, V. Snieckus, *Tetrahedron Lett.* **1982**, *23*, 3971.
[7] K. K. Mahalanabis, M. Mumtaz, V. Snieckus, *Tetrahedron Lett.* **1982**, *23*, 3975.
[8] M. P. Cooke Jr., *Tetrahedron Lett.* **1981**, *22*, 381.
[9] P. J. Garratt, R. Zahler, *Tetrahedron Lett.* **1979**, 73; K. G. Bilyard, P. J. Garratt, A. J. Underwood, R. Zahler, *Tetrahedron Lett.* **1979**, 1815.
[10] P. J. Garratt, J. R. Porter, *Tetrahedron Lett.* **1987**, *28*, 351; P. J. Garratt, M. Pielke, J. R. Porter, *Tetrahedron Lett.* **1987**, *28*, 589.
[11] C. W. Doecke, P. J. Garratt, *J. Chem. Soc., Chem. Commun.* **1981**, 873; K. G. Bilyard, P. J. Garratt, *Tetrahedron Lett.* **1981**, *22*, 1755; J.-G. Jun, B. P. Mundy, *Bull. Korean Chem. Soc.* **1987**, *8*, 310; E. J. Corey, W.-G. Su, *Tetrahedron Lett.* **1987**, *28*, 5241.
[12] C. Girard, R. Bloch, *Tetrahedron Lett.* **1982**, *23*, 3683.
[13] T. J. Donohoe, R. R. Harji, R. P. C. Cousins, *Chem. Commun.* **1999**, 141.
[14] E. Lee, S. J. Choi, H. Kim, H. O. Han, Y. K. Kim, S. J. Min, S. H. Son, S. M. Lim, W. S. Jang, *Angew. Chem., Int. Ed.* **2002**, *41*, 176; A. S. Kende, Y. Fujii, J. S. Mendoza, *J. Am. Chem. Soc.* **1990**, *112*, 9645; A. S. Kende, J. S. Mendoza, Y. Fujii, *Tetrahedron* **1993**, *49*, 8015; A. Misumi, K. Iwanaga, K. Furata, H. Yamamoto, *J. Am. Chem. Soc.* **1985**, *107*, 3343.
[15] B. K. Park, M. Nakagawa, A. Hirota, M. Nakayama, *J. Antibiot.* **1988**, *41*, 751; Y. Masaki, H. Arasaki, A. Itoh, *Tetrahedron Lett.* **1999**, *40*, 4829 and ref. cit. therein; J. Lertvorachon, P. Meepowpan, Y. Thebtaranonth, *Tetrahedron* **1998**, *54*, 14341.
[16] M. M. Murta, M. B. M. de Azevedo, A. Greene, *J. Org. Chem.* **1993**, *58*, 7537 and ref. cit. therein; A. Ghatak, S. Sarkar, S. Ghosh, *Tetrahedron* **1997**, *53*, 17335 and ref. cit. therein.
[17] C. J. Cavallito, D. M. Fruehauf, *J. Am. Chem. Soc.* 1948, 70, 3724; F. D' Onofrio, R. Margarita, L. Parlanti, G. Piancatelli, M. Sbraga, *Chem. Commun.* **1998**, 185 and ref. cit. therein.
[18] S. B. Mahato, K. A. I. Siddiqui, G. Bhattacharya, T. Ghosal, K. Miyahara, M. Sholichin, T. Kawasaki, *J. Nat. Prod.* **1987**, *50*, 245; S. Drioli, F. Felluga, C. Forzato, P. Nitti, G. Pitacco, E. Valentin, *J. Org. Chem.* **1998**, *63*, 2385; T. P. Loh, P. L. Lye, *Tetrahedron Lett.* **2001**, *42*, 3511; P. A. Jacobi, P. Herradura, *Tetrahedron Lett.* **1996**, *37*, 8297.
[19] M. Asano, T. Azumi, *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 995; E. E. van Tamelen, R. S. Bach, *J. Am. Chem. Soc.* **1958**, *80*, 3079; S. Huneck, G. Follmann, *Z. Naturforsch. B* **1967**, *22*, 666; A. Forster, J. Fitremann, P. Renaud, *Tetrahedron Lett.* **1998**, *39*, 7097 and ref. cit. therein; J. Mulzer, L. Kattner, A. R. Strecker, C. Schroder, J. Buschmann, C. Lehmann, P. Luger, *J. Am. Chem. Soc.* **1991**, *113*, 4218.
[20] C. H. Bruckner, H. U. Reissig, *J. Org. Chem.* **1998**, *53*, 2440; M. P. Sibi, J. Ji, *Angew. Chem., Int. Ed.* **1997**, *36*, 274; J. Mulzer, N. Salimi, H. Hartl, *Tetrahedron: Asymmetry* **1993**, *4*, 457; M. Bella, R. Margarita, C. Orlando, M. Orsini, L. Parlanti, G. Piancatelli, *Tetrahedron Lett.* **2000**, *41*, 561; C. Boehm, O. Reiser, *Org. Lett.* **2001**, *3*, 1315.
[21] S. Huneck, G. Follmann, *Z. Naturforsch. B* **1967**, *22*, 666; P. K. Mandal, S. C. Roy, *Tetrahedron* **1999**, *44*, 11395.
[22] R. E. Ireland, R. H. Muller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868; D. A. Evans, C. H. Heathcock, in 'Asymmetric Synthesis', Vol. 3, Part B, Ed. J. D. Morrison, Academic Press, New York, 1984.

[23] T. Martin, C. M. Rodriguez, V. S. Martin, *J. Org. Chem.* **1996**, *61*, 6450; M. P. Sibi, P. K. Deshpande, A. J. Loggia, *Synlett* **1996**, 343.
[24] P. K. Mandal, S. C. Roy, *Tetrahedron* **1999**, *55*, 11395.
[25] S. Drioli, F. Felluga,C. Forzato, P. Nihi, G. Pitacco, E. Valentin *J. Org. Chem.* **1998**, *63*, 2385.

Received June 27, 2002

Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6717–6720

TETRAHEDRON LETTERS

Vicinal dianions of diethyl α-aroylsuccinates: a general synthetic route to α-aroyl- and α-arylidene-γ-butyrolactones

Manat Pohmakotr,* Laddawan Sampaongoen, Arisara Issaree, Patoomratana Tuchinda and Vichai Reutrakul

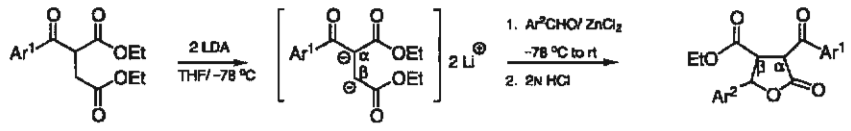
Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

Received 29 May 2003; revised 14 June 2003; accepted 27 June 2003

Abstract—Vicinal dianions derived from diethyl α-aroylsuccinates were found to react with carbonyl compounds β-regioselectively to afford α-aroyl-γ-butyrolactones, which were converted into α-arylidene-γ-butyrolactones by reduction with H_2/Pd–C followed by elimination employing methanesulfonyl chloride in pyridine. The method provides a general and convenient route to α-aroyl- and α-arylidene-γ-butyrolactones.

Carbon–carbon bond forming reactions based on the reactions of dianions are of interest, because high regio- and stereoselectivities towards electrophiles have been achieved.[1] Among these dianions, the vicinal dianions of succinic acid derivatives were extensively demonstrated to be useful reagents for the preparation of various classes of compounds.[2] In the course of our study on using succinic acid derivatives as versatile building blocks for synthesis of some natural products containing the γ-butyrolactone nucleus including lignans, we have recently reported the syntheses of (±)-lichesterinic acid, (±)-phaseolinic acid, (±)-nephromopsinic acid and (±)-dihydroprotolichesterinic acid by making use of the vicinal dianion derived from triethyl ethanetricarboxylate.[3] In continuation of our above results, we wish to report herein the reactions of vicinal dianions of α-aroylsuccinic esters with carbonyl compounds. It could be envisaged that these vicinal dianions would react with carbonyl compounds β-regioselectively to provide α-aroyl-γ-butyrolactones, which would be useful as the precursors for many synthetic manipulations. In this communication, the preparation of α-arylidene-γ-butyrolactones[4] from α-aroyl-γ-butyrolactones is also reported.

The vicinal dianion **2a** was readily generated by treatment of α-benzoylsuccinic ester **1a**[5] with lithium diisopropylamide (LDA, 2.1 equiv.) in tetrahydrofuran (THF) at −78°C for 1 h. The reaction of the vicinal dianion **2a** with benzaldehyde (1.1 equiv.) in the presence of $ZnCl_2$ (1.1 equiv.) at −78°C for 2 h, followed by slowly warming up to rt overnight afforded the expected α-aroyl-γ-butyrolactone **3a** in 74% yield as a mixture of diastereomers after quenching with 2N HCl. The formation of γ-butyrolactone **3a** revealed that the vicinal dianion **2** combined with benzaldehyde regioselectively at the β-carbon to furnish the β-hydroxy adduct which underwent lactonisation upon acidic



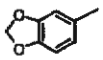
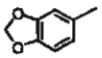
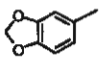
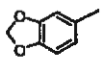
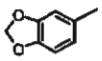
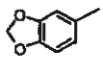
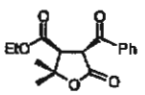
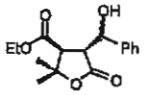
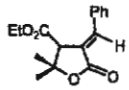
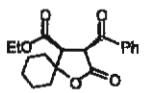
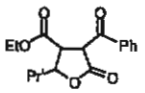
Scheme 1.

Keywords: dianions; diethyl α-aroylsuccinates; α-arylidene-γ-butyrolactones; α-aroyl-γ-butyrolactones.
* Corresponding author. Tel.: 066-02-2015158; fax: 066-02-6445126; e-mail: scmpk@mahidol.ac.th

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01622-8

work-up. Exclusive β-regioselectivities of the vicinal dianion **2a** with other aromatic aldehydes and isobutyraldehyde, as well as acetone and cyclohexanone (Table 1, entries 1–3 and 10–12) were observed (Scheme 1). Moderate to good yields of the corresponding γ-butyrolactones **3** as diastereomeric mixtures were obtained. The reactions of vicinal dianions **2b** and **2c** with aromatic aldehydes under the same conditions gave moderate yields of γ-butyrolactones **3** as mixtures of diastereomers (Table 1, entries 4–9). The 3,4-*trans*-4,5-*cis*-isomer (TC-isomer) of γ-butyrolactones **3a–i** could be obtained in pure form by preparative thin-layer chromatography (silica gel). The relative stereochemistries of the TC-isomer of **3a** was concluded from NOE experiments.[6]

Table 1. Preparation of α-aroyl-γ-butyrolacones **3** and α-arylidene-γ-lactones **5**

Entry	1	Electrophile	Ar^1	Ar^2	% Yields		
					3[a, b, c]	4[a] (diastereomeric ratio)	5[a]
1	1a	Benzaldehyde	Ph	Ph	3a, 74 (61)	4a, quant. (90 :10)	5a, 60[f]
2	1a	Piperonal	Ph		3b, 71 (63)	4b, 61 (84 : 16)	5b, 92
3	1a	4-Methoxybenzaldehyde	Ph	4-MeOPh	3c, 65 (52)	4c, 65 (88 : 12)	5c, 91
4	1b	Benzaldehyde		Ph	3d, 50 (43)	4d, quant.[d]	5d, 75[f]
5	1b	Piperonal			3e, 47 (37)	4e, 93[e]	5e, 90
6	1b	4-Methoxybenzaldehyde		4-MeOPh	3f, 51 (43)	4f, quant. (90 :10)	5f, 75[f]
7	1c	Benzaldehyde	4-MeOPh	Ph	3g, 64 (55)	4g, 80 (88 : 12)	5g, 95
8	1c	Piperonal	4-MeOPh		3h, 65 (56)	4h, 87[d]	5h, 91
9	1c	4-Methoxybenzaldehyde	4-MeOPh	4-MeOPh	3i, 57 (50)	–[g]	–[g]
10	1a	Acetone			3j (50)	 4i, 83 (65 : 35)	 5i, 83
11	1a	Cyclohexanone			3k (70)	–[g]	–[g]
12	1a	Isobutyraldehyde			3l, 63	–[g]	–[g]

[a] Isolated yields.

[b] Yields of the isolated 3,4-*trans*-4,5-*cis*-isomers of **3a-i** and the *trans*-isomers of **3j** and **3k** are given in parentheses.

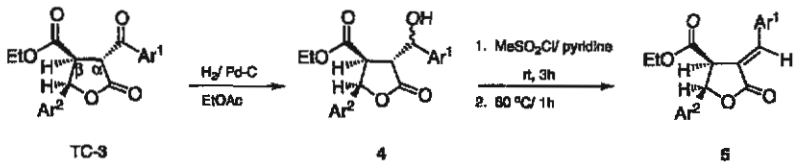
[c] Obtained as mixtures of diastereomers.

[d] The ratio of diastereomers was not determined.

[e] Obtained as a single diastereomer.

[f] Overall yields based on compounds **3a**, **3d** and **3f**.

[g] The reactions were not carried out.



Scheme 2.

Having obtained functionalized γ-butyrolactones **3** in an efficient way, we next demonstrated the synthetic utility of these γ-butyrolactones as precursors for syntheses of α-arylidene-γ-butyrolactones **5**. These synthetic transformations could be simply accomplished by successive reduction and elimination reactions. Thus, TC-**3a** was subjected to a catalytic hydrogenation (H_2/Pd–C/EtOAc) to furnish alcohol **4a** as a 90:10 mixture of diastereomers, which was further treated with methanesulfonyl chloride in pyridine at rt for 3 h followed by heating at 60°C for 1 h to give *E*-benzylidene-γ-butyrolactone **5a** in 60% overall yield (Scheme 2). As shown in Table 1, compounds **5b–i** were prepared in good overall yields as *E*-isomers.[7] The explanation for the formation of the *E*-isomer as the sole product could be due to the fact that elimination of the initially formed mesylate group of compound **4** proceeded via an E_2-elimination followed by a conjugate addition–elimination of pyridine to the initially formed α-arylidene-γ-butyrolactones to lead to the thermodynamically more stable *E*-isomer. An E_{1cb} mechanism may also be responsible for these results. The *cis*-stereochemistry at C-4 and C-5 was confirmed by the NOE experiments of compound **3h**.[8]

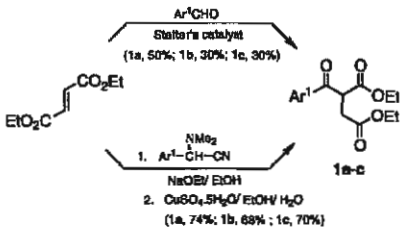
In summary, we have shown that the vicinal dianions derived from α-aroylsuccinic esters react with carbonyl compounds regioselectively at the β-carbon in the presence of $ZnCl_2$ to furnish α-aroyl-γ-butyrolactones in moderate yields. These compounds could be used as useful precursors for the preparation of α-arylidene-γ-butyrolactones. Thus, our method described herein provides a general synthetic route to α-arylidene-γ-butyrolactones.

Acknowledgements

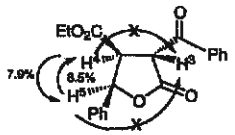
We thank the Thailand Research Fund for financial support (BRG/22/2544) to M.P. and the award of a Senior Research Scholar to V.R. Thanks are also made to the Higher Education Development Project: Postgraduate Education and Research Program in Chemistry for support. We are grateful to Professor Paul Knochel, LMU, Munich, Germany, for the HRMS and CHN determination of some compounds.

References

1. Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRP Press: Boca Raton, 1994.
2. (a) Lim, S.-M.; Lang, W.-S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 176–178; (b) Kende, A. S.; Mendoza, J. S.; Fujii, Y. *Tetrahedron* **1993**, *49*, 8015–8038; (c) Izawa, T.; Ogino, Y.; Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron* **1992**, *48*, 1573–1580; (d) Kende, A. S.; Fujii, Y.; Mendoza, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 9645–9646; (e) Mitsumi, A.; Iwanaga, K.; Furata, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343–3345.
3. Pohmakotr, M.; Harnying, W.; Tuchinda, P.; Reutrakul, V. *Helv. Chim. Acta* **2002**, *85*, 3793–3813.
4. For some recent syntheses, see: (a) Reddy, G. S.; Neelakantan, P.; Iyengar, D. S.; *Synth. Commun.* **2002**, *32*, 2601–2604; (b) Mali, R. S.; Babu, K. N. *Helv. Chim. Acta* **2002**, *85*, 3525–2530; (c) Consorti, C.; Ebeling, G.; Dupont, J. *Tetrahedron Lett.* **2002**, *43*, 753–755; (d) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 2381–2382; (e) Jiaang, W.-T.; Wang, C.-L.; Tseng, A.; Chen, S.-T. *Heterocycles* **2000**, *53*, 1569–1572; (f) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L. *Synthesis* **1997**, 1061–1066; (g) Ishibashi, H.; Ito, K.; Tabuchi, M.; Ikeda, M. *Heterocycles* **1991**, *32*, 1279–1282; (f) Lee, E.; Hur, C.-U.; Jeong, Y.-C.; Rhee, Y.-H.; Chang, M.-H. *J. Chem. Soc., Chem. Commun.* **1991**, 1314–1315; (g) Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Aust. J. Chem.* **1988**, *41*, 251–261; (h) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1986**, *27*, 641–644; (i) Tanaka, K.; Unema, H.; Yamgishi, N.; Ono, N.; Kaji, A. *Chem. Lett.* **1978**, 653–656; (j) Janecki, T.; Blaszezyk, E. *Synthesis* **2001**, 403–408; (k) Castulik, J.; Mazal, C. *Tetrahedron Lett.* **2001**, *41*, 2741–2744.
5. α-Aroylsuccinic esters **1** were prepared by reacting α-*N*,*N*-dimethylaminonitriles derived from aromatic aldehydes with diethyl fumarate in ethanol employing NaOEt as a base followed by hydrolysis of the resulting adducts with $CuSO_4$.[9] Alternatively, these compounds could also be achieved by conjugate addition of aromatic aldehydes to diethyl fumarate catalysed by Stetter's catalyst [3-benzyl-5-(2-dihydroxy-ethyl)-4-methylthiazolium chloride] in ethanol at 80°C for 15 h.[10]



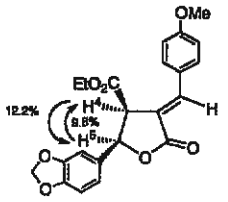
6. Irradiation of H-4 resulted in 7.9% enhancement of H-5, but there was no effect on H-3. The enhancement of 8.5% of H-4 was observed, when H-5 was irradiated, but there was no enhancement of H-3.



TC-3a

7. The chemical shifts of the benzylidene protons of compounds **5** appeared as doublets (J=1.5–1.8 Hz) at δ 7.6–7.75 ppm, comparable to the chemical shifts of the E-isomers of some related compounds reported in the literature, see for examples: (a) Hwang, E.-I.; Yun, B.-S.; Kim, Y.-K.; Kwon, B.-M.; Kim, H.-G.; Lee, H.-B.; Jeong, W.-J.; Kim, S.-U. *J. Antibiot.* **2000**, *53*, 903–911; (b) Banerji, J.; Das, B.; Chatterjee, A.; Shoolery, J. N. *Phytochemistry* **1984**, *23*, 2323–2327; (c) Stevens, D. R.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 633–637.

8. Enhancements of 9.8 and 12.2% of **H-4** and H-5 of **5h** were observed upon irradiation of H-5 and H-4, respectively.



5h

9. (a) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207–3233 and references cited therein; (b) Reutrakul, V.; Nimgirawath, S.; Panichanun, S.; Ratananukul, P. *Chem. Lett.* **1979**, 399–400.

10. (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–712; (b) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407–438.

Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7937–7940

TETRAHEDRON LETTERS

Vicinal dianions of diethyl α-aroylsuccinates: preparation of functionalized-2,3-dihydrofurans and -furans, and diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes

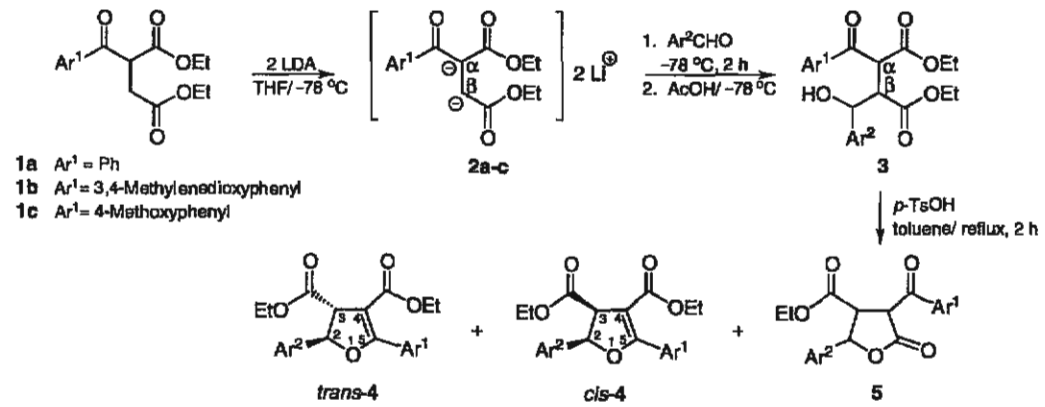
Manat Pohmakotr,* Arisara Issaree, Laddawan Sampaongoen, Patoomratana Tuchinda and Vichai Reutrakul

Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

Received 17 July 2003; revised 19 August 2003; accepted 1 September 2003

Abstract—Vicinal dianions of diethyl α-aroylsuccinates react with aromatic aldehydes to provide functionalized 2,3-dihydrofurans as the major products together with γ-butyrolactones after treatment of the adducts obtained with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene. *cis*-2,3-Dihydrofurans are used as precursors for the preparation of tetrasubstituted furans and diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes.

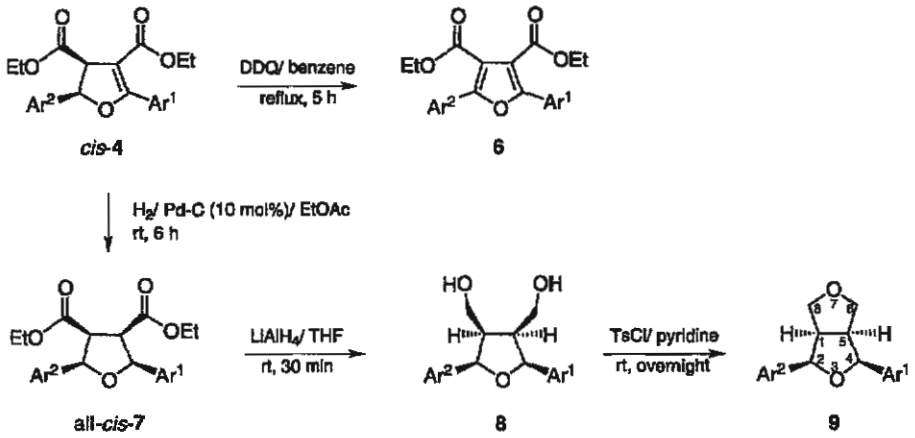
Substituted 2,3-dihydrofurans and furans are important classes of compounds due to their presence in a wide range of biologically active synthetic and natural products.[1] Moreover, some of them have been shown to be useful synthetic intermediates.[2] Therefore, efficient and general synthetic routes to these heterocycles[3,4] are of interest. As part of our program devoted to the development of synthetic routes to these classes of compounds, a general method for the synthesis of substituted 2,3-dihydrofurans and furans based on the chemistry of vicinal dianions derived from α-aroylsuccinic esters was investigated. We have recently described that these vicinal dianions react with carbonyl compounds in the presence of $ZnCl_2$ exclusively at the β-carbon to provide α-aroyl-γ-butyrolactones, which were demonstrated as useful intermediates for the preparation of naturally occurring α-arylidene-γ-butyrolactones.[5] In connection with these results, we wish to report the preparation of functionalized-2,3-dihydrofurans and -furans as well as diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes utilizing the vicinal dianions of diethyl α-aroylsuccinates as shown in Schemes 1 and 2.



Scheme 1.

* Corresponding author. Tel.: +66-022015158; fax: +66-026445126; e-mail: scmpk@mahidol.ac.th

0040-4039/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.09.005



Scheme 2.

The reaction of the vicinal dianion **2a** derived from **1a** by employing LDA (2 equiv.) in THF at −78°C for 1 h with benzaldehyde (1 equiv.) at −78°C for 2 h followed by quenching the reaction mixture with glacial acetic acid at the same temperature provided the crude adduct **3a**. Without purification, this was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene for 2 h to afford the expected dihydrofuran **4a**[6] in 71% yield as a mixture of *cis*- and *trans*-isomers together with γ-butyrolactone **5a** (13% yield). *cis*-**4a** was obtained in 59% yield as the major isomer after chromatography on silica gel. Under the standard conditions, the vicinal dianions **2a–c** reacted with aromatic aldehydes to give moderate yields of the desired dihydrofurans **4a–k** as mixtures of *cis*- and *trans*-isomers together with 5–15% yields of the corresponding γ-butyrolactones **5**. In all cases, the *cis*-isomers were obtained as the major isomers, and in most cases could be isolated pure by chromatography as summarized in Table 1. The relative *cis* and *trans* stereochemistries of compounds **4** were established by the coupling constants between H-2 and H-3 (J_{cis}= 10.9–11.0 Hz and J_{trans}= 6.8–7.1 Hz) and the results of NOE experiments.[7]

Having succeeded in preparing in one-step the dihydrofurans **4** possessing aryl substituents, we further illustrated the synthetic utility of our method by the preparation of 2,5-diaryl-3,4-dicarboethoxyfurans, which are important precursors for syntheses of lignans[2g,h,8] and 2,4-diaryl substituted 3,7-dioxabicyclo[3.3.0]octanes **9**. Thus, conversion of *cis*-**4** into furan **6** could be achieved smoothly by dehydrogenation employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene for 5 h.[9] Furans **6a–f** were obtained in good yields (Table 2). Dehydrogenation of *trans*-**4** was found to proceed slower than *cis*-**4** under the standard conditions. Thus, when a mixture of *cis*- and *trans*-**4b** was treated with DDQ in benzene under reflux for 5 h, the *cis*-isomer **4b** was completely converted into furan **6b**, while the *trans*-isomer **4b** was still present in the mixture as shown by thin-layer chromatography. The reaction was complete after refluxing for 20 h and **6b** was obtained in 92%

Table 1. Preparation of 2,3-dihydrofurans **4**

Entry	1	Electrophile	Ar^1	Ar^2	% Yields[a]				
					4	*cis*-4	*trans*-4	*cis*-4+*trans*-4 (*cis*:*trans*)	5[b]
1	**1a**	Benzaldehyde	Ph	Ph	**4a**	59	12	–	13
2	**1a**	Piperonal	Ph	Piperonyl	**4b**	41	10	–	5
3	**1a**	4-Methoxybenzaldehyde	Ph	4-MeOPh	**4c**	50	13	–	11
4	**1a**	Isobutyraldehyde	Ph	*i*-Pr	**4d**	–	–	63 (66:34)	–[c]
5	**1b**	Benzaldehyde	Piperonyl	Ph	**4e**	41	7	–	7
6	**1b**	Piperonal	Piperonyl	Piperonyl	**4f**	26	–	13 (80:20)	8
7	**1b**	4-Methoxybenzaldehyde	Piperonyl	4-MeOPh	**4g**	30	–	11 (74:26)	10
8	**1b**	Isobutyraldehyde	Piperonyl	*i*-Pr	**4h**	–	–	55 (67:33)	–[c]
9	**1c**	Benzaldehyde	4-MeOPh	Ph	**4i**	53	–[c]	–	15
10	**1c**	Piperonal	4-MeOPh	Piperonyl	**4j**	39	11	-	11
11	**1c**	4-Methoxybenzaldehyde	4-MeOPh	4-MeOPh	**4k**	37	–[c]	-	13

[a] Isolated yields. All compounds were fully characterized by IR, MS, 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra as well as by elemental analyses or HRMS.

[b] Contained mainly the 3,4-*trans*-4,5-*cis*-isomer.

[c] Could not be isolated.

Table 2. Preparation of compounds 6–9

cis-4	Ar^1	Ar^2	% Yields[a]			
			6	7	8	9
cis-**4a**	Ph	Ph	**6a**, 85	**7a**, 85	**8a**, 83	**9a**, 70
cis-**4b**	Ph	Piperonyl	**6b**, 95	**7b**, 86	**8b**, 89	**9b**, 82
cis-**4c**	Ph	4-MeOPh	**6c**, 90	**7c**, 88	**8c**, 82	**9c**, 75
cis-**4e**	Piperonyl	Ph	**6b**, 93	–[b]	–[b]	–[b]
cis-**4f**	Piperonyl	Piperonyl	**6d**, 94	**7d**, 86	**8d**, 80	**9d**, 74
cis-**4i**	4-MeOPh	Ph	**6c**, 96	–[b]	–[b]	–[b]
cis-**4j**	4-MeOPh	Piperonyl	**6e**, 95	**7e**, 89	**8e**, 84	**9e**, 75
cis-**4k**	4-MeOPh	4-MeOPh	**6f**, 93	**7f**, 83	**8f**, 82	**9f**, 76

[a] Isolated yields. All compounds were fully characterized by IR, MS, 300 MHz ^1H and 75 MHz ^{13}C NMR spectra as well as by elemental analyses or HRMS.

[b] The reactions were not performed.

yield. On the other hand, tetrahydrofurotetrahydrofurans **9** were prepared in good overall yields by a simple three-step synthesis starting from *cis*-dihydrofurans **4**. Catalytic hydrogenation (10% Pd on C) of *cis*-**4a** in ethyl acetate at rt afforded a good yield (85%) of the all-*cis*-**7a** as the sole isomer. Reduction of **7a** with $LiAlH_4$ in THF at rt for 30 min gave **8a** in 83% yield after chromatography on silica gel. Treatment of **8a** with *p*-toluenesulfonyl chloride in pyridine[10] at rt overnight furnished the expected tetrahydrofurotetrahydrofuran **9a** in 70% yield. The ^1H and ^{13}C NMR data of **9a** were consistent with reported values.[11] Thus, the formation of **9a** as the sole product and in good yield confirmed the all-*cis*-stereochemistry in **7a**. Under the same reaction sequence and conditions, tetrahydrofurotetrahydrofurans **7b–f** were prepared in good yields from *cis*-2,3-dihydrofurans **4b**, **4c**, **4f**, **4j** and **4k**, respectively.

In summary, our results demonstrate that the vicinal dianions derived from diethyl α-aroylsuccinates react with aldehydes regioselectively at the β-carbon to provide a mixture of *cis*- and *trans*-2,3-dihydrofurans as the major products along with γ-butyrolactones. This method provides an easy entry to 2,5-diaryl substituted dihydrofurans, of which both aryl groups can be varied by using appropriate α-aroylsuccinic esters and aromatic aldehydes. Furthermore, *cis*-2,3-dihydrofurans have been proved to be very useful for the preparation of 2,5-diaryl-3,4-dicarboethoxyfurans and diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes.

Acknowledgements

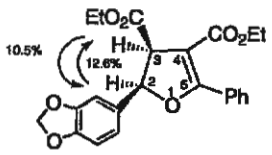
We thank the Thailand Research Fund for financial support (BRG/22/2544) to M.P. and the award of a Senior Research Scholar to V.R. A.I. thanks the Ministry of University Affairs for a scholarship. Thanks are also made to the Higher Education Development Project: Postgraduate Education and Research Program in Chemistry (PERCH) for support. We are grateful to Professor Paul Knochel, LMU, Munich, Germany, for the HRMS and CHN determination of some compounds.

References

1. (a) Dean, F. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1982; Vol. 30, pp. 167–238; (b) Dean, F. M.; Sargent, M. V. *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Cheeseman, G. W. H., Eds.; Pergamon: New York, 1984; Vol. 4, Part 3, pp. 531–598; (c) Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217–242; Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243–287; (d) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 3838–3848; (e) Mortensen, D. S.; Rodriguez, A. L.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2521–2524; (f) Dikshit, D. K.; Singh, S.; Singh, M. M.; Kamboj, V. P. *Indian J. Chem. B* **1990**, *29B*, 954–960; (g) Peterson, J. R.; Horsley, D. B.; Brozik, J. A.; Rogers, R. D. *Acta Cryst., Sect. C C45* 1164–1167.
2. (a) Garzino, F.; Méou, A.; Brun, P. *Eur. J. Org. Chem.* **2003**, 1410–1414; (b) Garzino, F.; Méou, A.; Brun, P. *Synthesis* **2003**, 598–602; (c) Garzino, F.; Méou, A.; Brun, P. *Tetrahedron Lett.* **2002**, *43*, 5049–5051; (d) Aldous, D. J.; Dalencon, A. J.; Steel, P. G. *Org. Lett.* **2002**, *4*, 1159–1162; (e) Garzino, F.; Méou, A.; Brun, P. *Tetrahedron Lett.* **2002**, *41*, 9803–9807; (f) Yang, F. Z.; Trost, M. K.; Fristad, W. E. *Tetrahedron Lett.* **1987**, *28*, 1493–1496; (g) Wu, A.; Wang, M.; Pan, X. *Synth. Commun.* **1997**, *27*, 2087–2091; (h) Schneiders, G. E.; Stevenson, R. *J. Org. Chem.* **1981**, *46*, 2969–2971.
3. For some recent syntheses of dihydrofurans, see: (a) Trost, B. M.; Rhee, Y.-H. *J. Am. Chem. Soc.* **2003**, *125*, 7482–7483; (b) Calo, V.; Scordari, F.; Nacci, A.; Schingaro, E.; D'Accolti, L.; Monopoli, A. *J. Org. Chem.* **2003**, *68*, 4406–4409 and references cited therein; (c) Zhang, Y.; Raines, A. J.; Flowers, II, R. A. *Org. Lett.* **2003**, *5*, 2363–2365; (d) Antonioletti, R.; Malancona, S.; Cattruzza, F.; Bovicelli, P. *Tetrahedron* **2003**, *59*, 1673–1678; (e) Antonioletti, R.; Malancona, S.; Bovicelli, P. *Tetrahedron* **2002**, *58*, 8825–8831; (f) Feldman, K. S.; Wrobleski, M. L. *J. Org. Chem.* **2000**, *65*, 8659–8668; (g) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641–2645; (h) Garrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, *63*, 9406–9413; (i) Doyle, M. P.;

Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210–7215; (j) Alonso, I.; Carretero, J. C.; Garrido, J. L.; Magro, V.; Pedregal, C. *J. Org. Chem.* **1997**, *62*, 5682–5683; (k) Hagiwara, H.; Sato, K.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* **1997**, *38*, 2103–2106; (l) Roy, S. C.; Mandel, P. K. *Tetrahedron* **1996**, *52*, 2193–2198.

4. (a) For a review on recent syntheses of furans, see: Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020; (b) Rao, H. S. P.; Jothilingam, S. *J. Org. Chem.* **2003**, *68*, 5392–5394; (c) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681–2684; (d) Kim, J. T.; Kelin, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98–101; (e) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 184–186; (f) Aurrecoechea, J. M.; Pe'rez, E. *Tetrahedron Lett.* **2003**, *44*, 3263–3266; (g) Yavari, I.; Anary-Abbasinejad, M.; Alizadeh, A. *Tetrahedron Lett.* **2003**, *43*, 4503–4505; (h) Aurrecoechea, J. M.; Pe'rez, E. *Tetrahedron Lett.* **2001**, *42*, 3839–3841; (i) Nair, V.; Vinod, A. U. *Chem. Commun.* **2000**, 1019–1020; (j) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117–118; (k) Pei, W.; Pei, J.; Li, S.; Ye, X. *Synthesis* **2000**, 2069–2077.
5. Pohmakotr, M.; Sampaongoen, L.; Issaree, A.; Tuchinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2003**, *44*, 6717–6720.
6. Acid- or Lewis acid-catalyzed formation of dihydrofurans from γ-hydroxy carbonyl compounds, see: (a) Box, V. G. S.; Brown, D. P. *Heterocycles* **1991**, *32*, 1273–1277; (b) Reissig, H. U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3139–3150; (c) Mukaiyama, T.; Hayashi, M.; Ichikawa, J. *Chem. Lett.* **1986**, 1157–1160; (d) Reissig, H. U.; Reichelt, I.; Lorey, H. *Liebigs Ann. Chem.* **1986**, 1924–1939.
7. NOE experiments for *cis*-**4b** and *trans*-**4b** were carried out. The results are as shown below. Upon irradiation of H-2 and H-3, *cis*-**4b** showed the NOE effects of H-3 (12.6%) and H-2 (10.5%), but displayed no enhancements in case of *trans*-**4b**.



cis-**4b**

The coupling constants J_{cis} of compounds **4** are larger than J_{trans}.[4f]

8. For a recent review, see: Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96.
9. Dehydrogenation of dihydrofurans to furans using DDQ, see: (a) Garzino, F.; Méou, A.; Brun, P. *Helv. Chim. Acta* **2002**, *85*, 1989–1998; (b) Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Parker, M. A.; Nichols, D. E. *J. Med. Chem.* **2001**, *44*, 1003–1010; (c) Axelle, A.; Frédérique, T.; Gérald, G.; Jean-Yves, M. *Synthesis* **1999**, 1241–1245; (d) Hirota, T.; Matsushita, T.; Sasaki, K.; Kashino, S. *Heterocycles* **1995**, *41*, 2565–2574; (e) Clawson, P.; Lunn, P. M.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 153–161.
10. Preparation of tetrahydrofurans from 1,4-diols employing *p*-toluenesulfonyl chloride or methanesulfonyl chloride in pyridine, see: (a) Brown, R. C. D.; Bataille, C. J. R.; Hinks, J. D. *Tetrahedron Lett.* **2001**, *41*, 473–475; (b) Brown, R. C. D.; Bataille, C. J. R.; Bruton, G.; Hinks, J. D.; Swain, N. A. *J. Org. Chem.* **2001**, *66*, 6719–6728; (c) Dantzig, A.; LaLonde, R. T.; Ramdayal, F.; Shepard, R. L.; Yanai, K.; Zhang, M. *J. Med. Chem.* **2001**, *44*, 180–185; (d) Yamaguchi, S.; Tanaka, T.; Kinoshita, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2158–2160; (e) Ohmizu, H.; Ogiku, T.; Iwasaki, T. *Heterocycles* **2000**, *52*, 1399–1409; (f) Ogiku, T.; Yoshida, S.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 1148–1153; (g) Tomioka, K.; Koga, K. *Heterocycles* **1979**, *12*, 1523–1528.
11. Pelter, A.; Ward, R. S.; Collins, P.; Venkateswarlu, R.; Kamashi, C. *Tetrahedron Lett.* **1992**, *33*, 4361–4364.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
ELSEVIER
Tetrahedron Letters 45 (2004) 4315–4318

Highly diastereoselective alkylation of vicinal dianions of chiral succinic acid derivatives: a new general strategy to (*R*)-β-arylmethyl-γ-butyrolactones

Manat Pohmakotr,* Darunee Soorukram, Patoomratana Tuchinda, Samran Prabpai, Palangpon Kongsaeree and Vichai Reutrakul

Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

Received 12 December 2003; revised 8 March 2004; accepted 2 April 2004

Abstract—The vicinal dianions derived from chiral succinic acid derivatives, 1,4-bis[(4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl]butane-1,4-dione and 1,4-bis[(4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl]butane-1,4-dione react with arylmethyl bromides with high diastereo- and regio-selectivity to provide the corresponding chiral α-arylmethylated succinic acid derivatives; the (*R*)-products are converted into (*R*)-β-arylmethyl-γ-butyrolactones and (*R*)-α-arylmethyl-γ-butyrolactones.

Succinic acid derivatives are of importance because they can serve as four-carbon building blocks in organic synthesis. Having considered the basic skeleton of many classes of compounds such as lignans[1] possessing a γ-butyrolactone or tetrahydrofuran nucleus, it was found that such compounds consisting of a four-carbon unit could be considered as a carbon backbone derived from succinic acid derivatives. Therefore, considerable attention has been focused on the synthetic utilities of succinic acid derivatives.[2] In connection with our recent reports on the synthetic utilities of vicinal dianions derived from α-aroylsuccinic esters as useful reagents for the synthesis of α-arylideneparaconic esters and furofurans,[3] it is of interest to extend our investigation on new synthetic strategies to chiral γ-butyrolactone frameworks, especially some bioactive naturally occurring γ-butyrolactone lignans. We therefore studied the generation and diastereoselective alkylation of vicinal dianions derived from chiral succinic acid derivatives.[4] This study is focused on a new general diastereoselective synthesis of chiral β-arylmethylated γ-butyrolactones, which are versatile intermediates for the asymmetric syntheses of lignans. Several synthetic approaches for the optically active β-arylmethyl-γ-butyrolactones have been published.[5] The vicinal dianion **2a** was generated by reacting chiral succinic acid derivative **1a** with 2 equiv of LDA in THF at −78 °C for 1 h. Treatment of **2a** with 1 equiv of benzyl bromide at −78 °C for 5 h afforded the benzylated product **3a** in 50% yield as a single diastereomer, together with the recovered starting material **1a** in 41% yield. A better yield of **3a** (75%) was obtained, when 2.2 equiv of benzyl bromide were employed under the same conditions. It is noteworthy that the reaction using 1 or 2 equiv of benzyl bromide gave only the monobenzylated product **3a**.[6,7] The (*S*)-configuration at the new stereocenter of compound **3a** was confirmed by converting into the corresponding known (*S*)-α-benzylsuccinic acid.[8] When the reaction was carried out in the presence of DMPU and slowly warmed up from −78 °C to room temperature overnight, a complex mixture of products was obtained as revealed by TLC and ^{1}H NMR data. Having the standard conditions, we next investigated the reactions of the vicinal dianion **2a** with methyl iodide and allyl bromide. The products **3b** and **3c** were also obtained as a single diastereomer in moderate yields as indicated in Table 1 (entries 2 and 3, Scheme 1).

Similarly, the vicinal dianion **2b** could be generated from **1b** and reacted with arylmethyl bromides (2.2 equiv) at −78 °C for 5 h to give arylmethylated products **4a–c** in moderate yields (Table 1, entries 4–6). The reaction proceeded with high diastereo- and regio-selectivities; all compounds **4a–c** were obtained as a single diastereomer. The configuration of the new chiral center of **4b** was proved to be (*R*) by single crystal X-ray diffraction

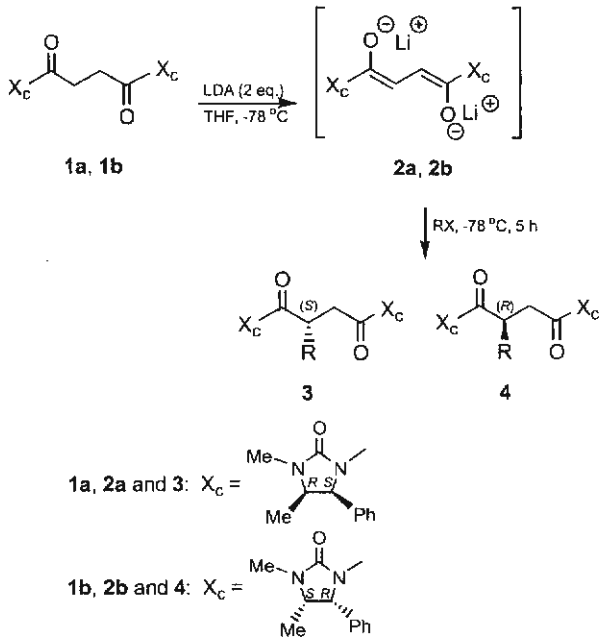
Keywords: Vicinal dianion; Chiral succinic acid; γ-butyrolactone.
* Corresponding author. Tel.: +66-02-2015158; fax: +66-02-6445126; e-mail: scmpk@mahidol.ac.th

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.008

Table 1. Alkylation of vicinal dianions **2a** and **2b**

Entry	1	RX	3[b] or 4[b], R =	Yield (%)[a]
1	**1a**	$PhCH_2Br$	**3a**, $PhCH_2$	75
2	**1a**	MeI	**3b**, Me	48
3	**1a**	$CH_2{=}CHCH_2Br$	**3c**, $CH_2{=}CHCH_2$	49
4	**1b**	3,4-$MeOPhCH_2Br$	**4a**, 3,4-$MeOPhCH_2$	53
5	**1b**	3-$MeOPhCH_2Br$	**4b**, 3-$MeOPhCH_2$	67
6	**1b**	3,4-$CH_2(O)_2PhCH_2Br$	**4c**, 3,4-$CH_2(O)_2PhCH_2$	67

[a] Isolated yields. All compounds were fully characterized by ^1H NMR, ^{13}C NMR, MS, and CHN analyses or HRMS.
[b] The specific rotation values, $[\alpha]_D^{28}$ of **3a–c** and **4a–c** are as follows: **3a**; +127.84 (*c* 0.51, MeOH); **3b**, +117.45 (*c* 0.55, $CHCl_3$); **3c**, +107.50 (*c* 0.64, $CHCl_3$); **4a**, −45.02 (*c* 0.31, $CHCl_3$); **4b**, −64.57 (*c* 0.70, $CHCl_3$); **4c**, +46.85 (*c* 0.29, $CHCl_3$).



Scheme 1.

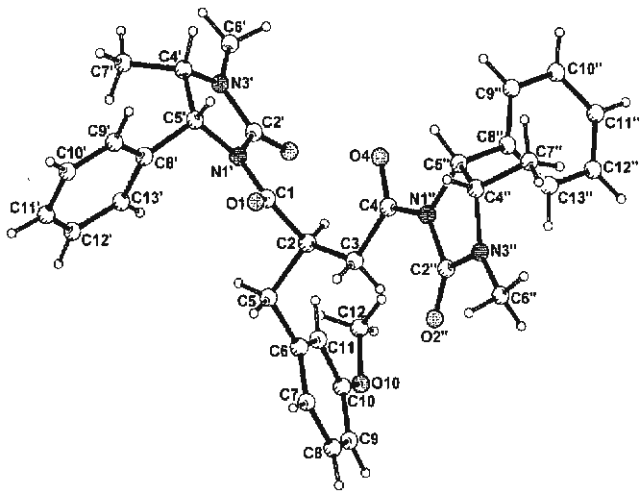


Figure 1. Crystal structure of compound **4b**.

analysis[9] (Fig. 1). which suggested the simple model for the stereochemical course of the benzylation of the vicinal dianion **2b** shown in Figure 2.

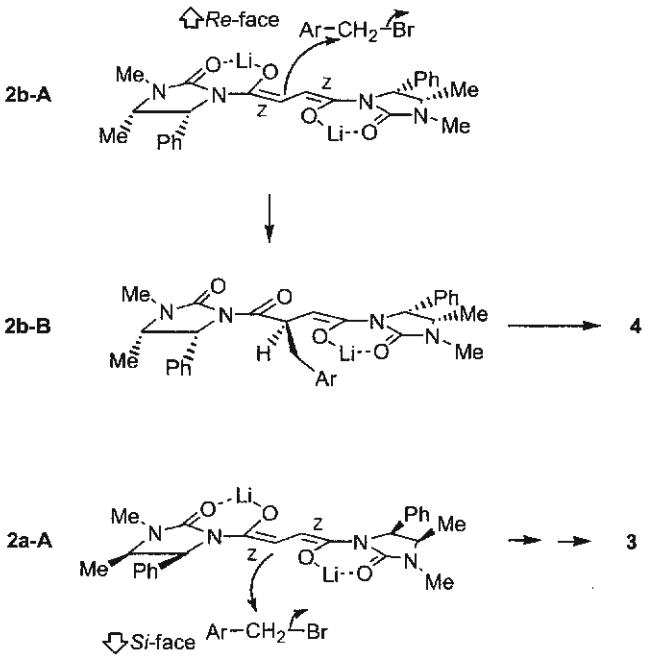
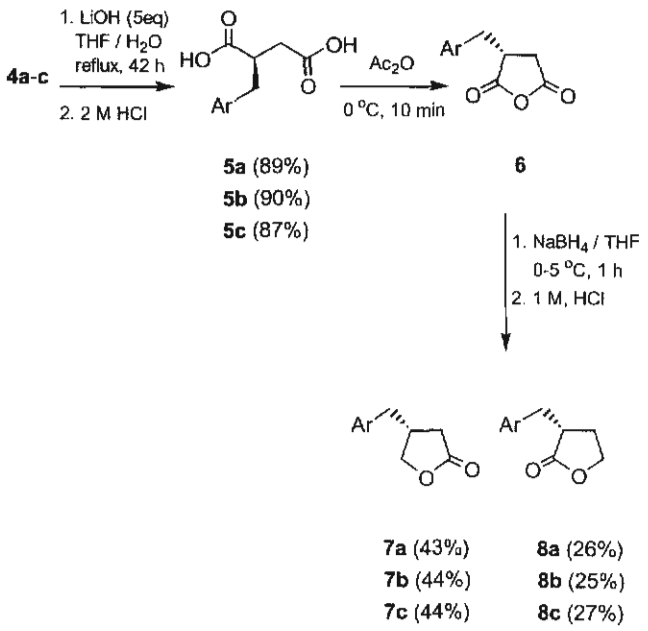


Figure 2. Proposed models for the stereochemical course of the alkylation of the vicinal dianions **2a** and **2b**.

Based on the evidence that Li-chelated (*Z*)-enolates were formed upon treatment of 1-acyl-2-imidazolidinones with LDA,[10] the vicinal dianion intermediate **2b** is proposed to exist in the (*Z*,*Z*)-configuration possessing the defined six-membered ring chelate structure **2b–A**. In the formation of **4a–c**, the arylmethyl bromides would approach from the *Re*-face of the vicinal dianion **2b–A** to avoid the steric repulsion with phenyl and methyl groups leading to an intermediate **2b–B**. The second arylmethylation of **2b–B** does not occur due to the steric hindrance between the α-arylmethyl and the chiral auxiliary phenyl groups. As similar model **2a–A** may also be applied to the alkylation of the vicinal dianion **2a**, in which the alkylating agent approaches from the *Si*-face (Fig. 2).

Having established that highly diastereoselective alkylation of the vicinal dianion **2b** furnishes the single diastereomer of compounds **4a–c** possessing the (*R*)-configuration at the α-carbon, we turn our attention to the preparation of (+)-β-arylmethyl-γ-butyrolactones. This could be accomplished by a hydrolysis–anhydride



Scheme 2.

formation–reduction sequence, starting from chiral succinic acid derivatives **4** (Scheme 2).

Thus, hydrolyses of **4a–c** employing LiOH (5 equiv) in aqueous THF under reflux for 40–42 h provided the corresponding succinic acid derivatives **5a–c** in good yields after acidic work-up.[11] Treatment of these acids with excess Ac_2O at 0 °C afforded the corresponding acid anhydrides **6** in quantitative yields. Reduction of **6** with $NaBH_4$ in THF at 0–5 °C for 1 h afforded the mixtures of the expected (*R*)-β-arylmethyl-γ-butyrolactones **7**[12] and (*R*)-α-arylmethyl-γ-butyrolactones **8**,[12] which could be separated by chromatography on silica gel.

In conclusion, we have described a general entry to an enantioselective synthesis of (*R*)-β-arylmethyl-γ-butyrolactones. The method involves highly regio- and diastereoselective arylmethylations of the vicinal dianions derived from chiral succinic acid derivatives, 1,4-bis[(4*R*,5*S*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl]butane-1,4-dione and 1,4-bis[(4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimi-dazolidin-1-yl]butane-1,4-dione. It is anticipated that the methodology described herein will find a number of useful applications in asymmetric synthesis of lignans.

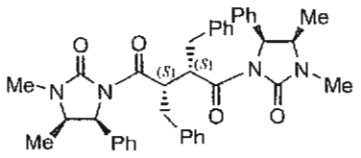
Acknowledgements

We thank the Thailand Research Fund for financial support (BRG/22/2544) to M.P. and the award of a Senior Research Scholar to V.R. D.S. thanks the Development and Promotion of Science and Technology Talent Project (DPST) for a scholarship. Thanks are also made to the Higher Education Development Project: Postgraduate Education and Research Program in Chemistry (PERCH) for support. We are grateful to Professor Paul Knochel, LMU, Munich, Germany, for the HRMS and CHN determination of some compounds.

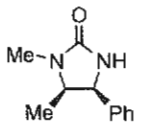
References and notes

1. Ayres, D. C.; Loike, J. D. *Lignans: Chemical, Biologic and Clinical Properties*; Cambridge University Pres Cambridge, 1990; Ward, R. S. *Nat. Prod. Rep.* **1999**, *1* 75–96.
2. For examples, see: (a) Csa'ky, A. G.; Plumet, J. *Chen Soc. Rev.* **2001**, *30*, 313–320; (b) Sibi, M. P.; Liu, P.; Ji, J Hajra, S.; Chen, J. *J. Org. Chem.* **2002**, *67*, 1738–1745; (c Sibi, M. P.; Hasegawa, H. *Org. Lett.* **2002**, *4*, 3347–334 (d) Langer, T.; Illich, M.; Helmchen, G. *Synlett* **199** 1137–1139; (e) Beckett, R. P.; Crimmin, M. J.; Davis, M H.; Spavold, Z. *Synlett* **1993**, 137–138.
3. (a) Pohmakotr, M.; Sampaongoen, L.; Issaree, A.; Tuc hinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2003**, *44*, 6717 6720;; (b) Pohmakotr, M.; Issaree, A.; Sampaongoen, L. Tuchinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2003**, *44* 7937–7940.
4. Syntheses based on vicinal anion of (−)-dimenthyl succi nate, see: (a) Lee, E.; Choi, S.-J.; Kim, H.; Han, H.-O. Kim, Y.-K.; Min, S.-I.; Son, S.-H.; Lim, S.-M.; Jang W.-S. *Angew. Chem., Int. Ed.* **2002**, *41*, 176–179; (b Kende, A. S.; Fujii, Y.; Mendoza, J. S. *J. Am. Chem. Soc* **1990**, *112*, 9645–9646; (c) Misumi, A.; Iwanaga, K. Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985** *107*, 3343–3345.
5. (a) Bolm, C.; Palazzi, C.; Francio, G.; Leitner, W. *Chem Commun.* **2002**, 1588–1589; (b) Doyle, M. P.; Hu, W. Valenzuela, M. V. *J. Org. Chem.* **2002**, *67*, 2954–2959, an references cited therein; (c) Caro, Y.; Masaguer, C. F. Ravina, E. *Tetrahedron: Asymmetry* **2001**, *12*, 1723–1726 (d) Takekawa, Y.; Shishido, K. *J. Org. Chem.* **2001**, *66* 8490–8503; (e) Kamlage, S.; Sefkow, M.; Zimmermann, N. Peter, M. G. *Synlett* **2002**, 77–80; (f) Kamlage, S.; Sefkow M.; Pool-Zobel, B. L.; Peter, M. G. *Chem. Commun.* **2001** 331–332; (g) Sibi, M. P.; Liu, P.; Johnson, M. D. *Can. J Chem.* **2000**, *78*, 133–138; (h) Chenevert, R.; Mohammadi Ziarani, G.; Caron, D.; Dasser, M. *Can. J. Chem.* **1999**, *77* 223–226; (i) Brinksma, J.; Deen, H. V. D.; Oeveren, A. V. Feringa, B. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4159- 4163; (j) Charlton, J. L.; Chee, G. *Can. J. Chem.* **1997**, *75* 1076–1083; (k) Gagnon, R.; Gagnon, G.; Groussain, E. Pedragosa-Moreau, S.; Richardson, P. F.; Roberts, S. M. Willetts, A. J.; Alphand, V.; Letreton, J.; Furstoss, R. *J Chem. Soc., Perkin Trans. 1* **1995**, 2527–2528; (l) Lemoult, S C.; Richardson, P. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 89–91; (m) Itoh, T.; Chika, J.; Takagi, Y. Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717–5723; (n Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron* **1993**, *49* 1793–1806; (o) Koch, S. S. C.; Chamberlin, A. R. *J. Org Chem.* **1993**, *58*, 2725–2737; (p) Filho, H. C. A.; Filho, U. F L.; Pinheiro, S.; Vasconcellos, M. L. A. A.; Costa, P. R. R *Tetrahedron: Asymmetry* **1994**, *5*, 1219–1220; (q) Takano S.; Ohashi, K.; Sugihara, T.; Ogasawara, K. *Chem. Lett.* **1991**, 203–206; (r) Morimoto, T.; Chiba, M.; Achiwa, K *Tetrahedron Lett.* **1990**, *31*, 261–264; (s) Morimoto, T. Chiba, M.; Achiwa, K. *Heterocycles* **1990**, *30*, 363–366; (t Shao, L.; Miyata, S.; Muramatsu, H.; Kawano, H.; Ishii, Y. Saburi, M.; Uchida, Y. *J. Chem. Soc., Perkin Trans. 1* **1990** 1441–1445; (u) Yoda, H.; Kitayama, H.; Katagiri, T. Takabe, K. *Tetrahedron* **1990**, *48*, 3313–3322.
6. Treatment of **1a** with 1 equiv of LDA, followed by reacting with 1 or 2 equiv of benzyl bromide under the standard conditions provided a low yield of the expected product **3a**.
7. Attempts to prove the presence of the vicinal dianion **2a** by quenching with D_2O were unsuccessful. No deuterium incorporation was observed as revealed by ^1H NMR and MS. In spite of these results, it was still assumed that the

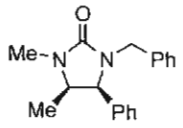
vicinal dianion **2a** was generated under the conditions described. This may be due to a strong H-bonded complex between diisopropylamine and the dilithiated derivative. Such interaction effecting incomplete deuteration of the generated lithium derivative was reported by Seebach (Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta*, **1985**, *68*, 1373–1393). The reaction of the vicinal dianion **2a** with 2.2 equiv of benzyl bromide at −78 °C to room temperature overnight (12–16 h) afforded dibenzylated product **9** in 20–30% yields together with 30–40% yields of the chiral auxiliary, (4*S*,5*R*)-(+)-1,5-dimethyl-4-phenyl-2-imidazolidinone and compound **11**. The formation of **9** supported the presence of the vicinal dianion **2a**. Compound **9** was obtained as a single diastereomer and its structure is proposed as shown below. The results also indicated that the vicinal dianion **2a** slowly decomposed during warming from −78 °C to rt to provide **10** and **11**.



9, $[\alpha]_D^{25}$ = +146.3 (*c* 1.226, $CHCl_3$)



10



11

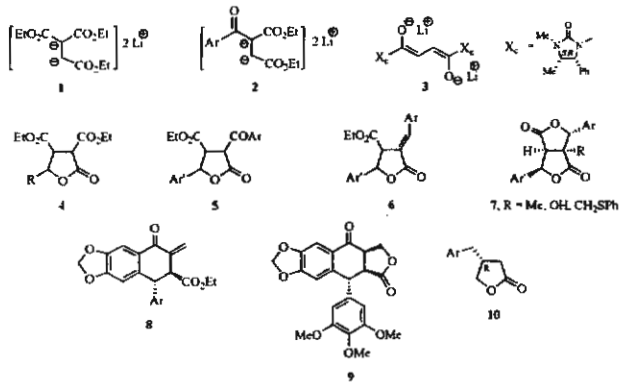
8. $[\alpha]_D^{31}$ (observed) −20.19 (*c* 2.08, EtOAc). Lit. $[\alpha]_D^{25}$ −27 (*c* 2, EtOAc); Cohen, S. G.; Milovanovic, A. *J. Am. Chem. Soc.* **1968**, *90*, 3495–3502.
9. Crystal data for **4b**: $C_{34}H_{38}N_4O_5$, MW = 582.70, orthorhombic, space group $P2_12_12_1$, $a = 8.1187(5)$, $b = 10.1120(5)$, $c = 38.5830(5)$ Å, $V = 3167.5(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.222$ Mg/m^3. A total of 2,115 unique reflections (1,724 observed, $|F_o| > 4\sigma|F_o|$) were measured at room temperature from a $0.30 \times 0.15 \times 0.15$ mm^3 colorless crystal using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) on a Bruker–Nonius kappaCCD diffractometer. The crystal structure was solved by direct methods using SIR-97, and then all atoms except hydrogen atoms were refined anisotropically on F^2 using SHELXL-97 to give a final *R*-factor of 0.0493 and $wR = 0.1130$ (all data). Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, ENGLAND (CCDC 216625).
10. Kise, N.; Ueda, T.; Kumuda, K.; Terao, Y.; Ueda, N. *J. Org. Chem.* **2000**, *65*, 464–468, and references cited therein.
11. The chiral auxillary was recovered in 85–95% yields and could be reused without loss of diastereoselectivity.
12. Specific rotation values for **7a–c** and **8a–c**. **7a**: $[\alpha]_D^{28}$ +8.75 (*c* 0.32, $CHCl_3$); Lit.[5i]: $[\alpha]_D^{24}$ +8.3 (*c* 1.33, $CHCl_3$). **7b**: $[\alpha]_D^{31}$ +7.31 (*c* 0.74, $CHCl_3$); Lit.[5k]: $[\alpha]_D^{20}$ +6.41 (*c* 2.08, $CHCl_3$). **7c**: $[\alpha]_D^{30}$ +5.12 (*c* 1.13, $CHCl_3$); Lit.[5j] $[\alpha]_D^{20}$ +5.2 (1.14, $CHCl_3$). **8a**: $[\alpha]_D^{28}$ −58.00 (*c* 0.20, $CHCl_3$). **8b**: $[\alpha]_D^{31}$ −53.78 (*c* 0.48, $CHCl_3$). **8c**: $[\alpha]_D^{28}$ −51.34 (*c* 0.26, $CHCl_3$).

SYNTHETIC UTILITIES OF VICINAL DIANIONS OF SUCCINIC ACID DERIVATIVES

MANAT POHMAKOTR

Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand. E-mail: scmpk@ mahidol.ac.th

Carbon-carbon bond formations based on the reactions of dianions are of interest, because high regio- and stereoselectivities towards electrophiles have been achieved. Among these dianions, the vicinal dianions of succinic acid derivatives have been extensively demonstrated to be useful reagents for the preparation of various classes of compounds. In the course of our study on using succinic acid derivatives as versatile 4-carbon building blocks for synthesis of some natural products containing the γ-butyrolactone nucleus, including lignans; we investigated the reactions of the vicinal dianions **1**, **2** and **3**, which could be obtained by treatment of triethyl ethanetricarboxylate, diethyl α-aroylsuccinates and (4*S*,5*R*)-3,4-(dimethyl-2-oxo-5-phenylimidazolidin-1-yl)butane-1,4-dione with 2 equivalents of lithium diisopropylamide in tetrahydrofuran at –78 °C for 1h. The vicinal dianions **1** and **2** reacted with carbonyl compounds regioselectively at β-carbon to furnish the corresponding β-hydroxy adducts which underwent lactonisation to provide γ-butyrolactones **4** and **5**, respectively, upon acidic work-up. These γ-butyrolactones were found to be versatile inter-mediates for preparation of various types of compounds. Thus, γ-butyrolactones of type **4** were converted into (±)-lichesterinic acid, (±)-phaseolinic acid, (±)-nephromopsinic acid and (±)-dihydroprotolichesterinic acid. Furthermore, α-aroyl-γ-butyrolactones **5** were used as starting materials for syntheses of α-arylidene-γ-butyrolactones **6**, 2,6-diaryl-3,7-dioxabicyclo [3.3.0]octane-4,8-diones **7**, thuriferic acid ethyl ester and analogues **8**, and picrodophyllone **9**. Highly diastereoselective alkylation of chiral vicinal dianion **3** was also investigated. The method provided a new general strategy to (*R*)-β-arylmethyl-γ-butyrolactones **10**, which are important precusors for syntheses of some lignan natural products.



OC-O14

Synthetic Approach to Tetrasubstituted Dihydrofurans and Tetrahydrofurans

Arisara Issaree, Manat Pohmakotr, Patoomratana Tuchinda and Vichai Reutrakul

Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand.

Objective

To search for a new general synthetic route to tetrasubstituted dihydrofurans and tetrahydrofurans, which are important classes of compounds for preparation of some lignan natural products.

Methods

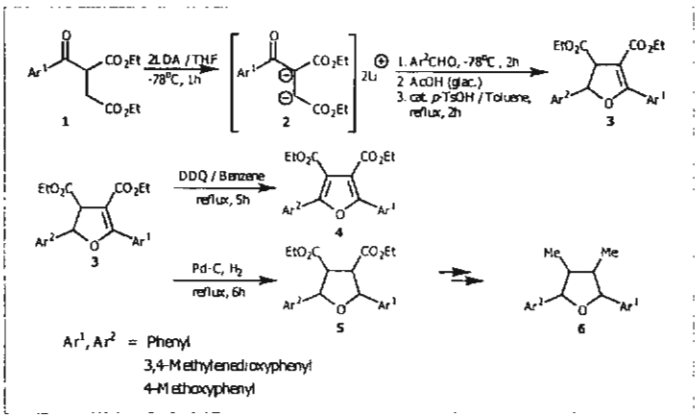
α-Aroyl succinic ester **1** in THF was added to a solution of lithium diisopropylamide at -78 °C for 1h. The dianion **2** obtained was reacted with aromatic aldehyde at -78 °C for 2h to give dihydrofuran **3** after quenching with glacial acetic acid and refluxing with *p*-TsOH in toluene for 2h. Dihydrofuran **3** could be smoothly converted to furan **4** by treatment with DDQ in refluxing benzene. Moreover, tetrahydrofuran **5** could be synthesized by carrying out a catalytic hydrogenation.

Results

The reaction of the dianion **2** with aromatic aldehydes afforded the expected dihydrofuran **3** in moderate to good yield as a mixture of two diastereomers which consisted of *cis*-dihydrofuran as the major isomer. Compound **3** underwent dehydrogenation reaction to furan **4** in high yield by employing DDQ. Catalytic hydrogenation of compound **3** gave tetrahydrofuran **5** in good yield. Synthetic study for preparing 2,5-diaryl-3,4-dimethyltetrahydrofuran **6** from tetrahydrofuran **5** will be investigated.

Conclusion

This method can be used as a general method to prepare tetrasubstituted dihydrofurans of the type **3** and tetrahydrofurans of the type **5**.



Keywords: vicinal dianion, α-aroyl succinic ester, furan, dihydrofuran, tetrahydrofuran

Selected References:

1. Sampaongoen, L. (2002). Vicinal dianion of diethyl α-aroyl succinate: preparation of α-arylidene-β-carboethoxy-γ-lactones. M.Sc. Thesis in Organic Chemistry, Faculty of Graduate Studies, Mahidol University.
2. Ward, R.S. (1999). Lignans, neolignans and related compounds. *Nat. Prod. Rep. 16*, 75-96.

OC-O15

Dianions of α-Aroylsuccinic Esters: Synthesis of Thuriferic acid and Analogues

Taweechote Komutkul, Manat Pohmakotr, Patoomratana Tuchinda and Vichai Reutrakul

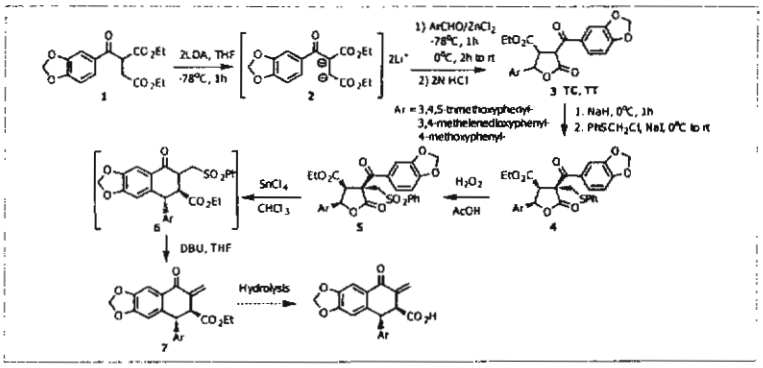
Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand.

Objective

To demonstrate the synthetic utilities of dianions derived from a-aroylsuccinic esters for preparing thuriferic acid and analogues.

Methods

α-Aroylsuccinic ester 1 could be doubly deprotonated by using 2 equivalents of LDA in THF at -78 °C for 1 h to give dianion 2, which reacted with aromatic aldehydes in the presence of zinc chloride to give γ-lactones 3 as a mixture of two diastereomers. Treatment of γ-lactones 3 with NaH in THF and a solution of $PhSCH_2Cl$ in the presence of NaI at 0 °C to room temperature overnight gave γ-lactones 4, which were readily oxidized with H_2O_2 in glacial acetic acid to give γ-lactones 5. Treatment of γ-lactones 5 with $SnCl_4$ in $CHCl_3$ gave the crude products 6, which were subjected to elimination of the phenylsulfonyl group by using DBU to provide thuriferic acid ethyl esters 7.



Results

The reaction of the vicinal dianion 2 with aromatic aldehydes led to γ-lactones 3 as a mixture of *trans,cis* (TC) and *trans,trans* (TT) diastereomers which consisted of the TC-isomer as the major isomer. Alkylation of γ-lactones 3 with $PhSCH_2Cl$ followed by oxidation gave γ-lactones 5 in high yield. Lewis acid-catalyzed rearrangement of γ-lactones 5 gave the crude products 6, which were reacted with DBU to lead to the desired thuriferic acid ethyl esters 7.

Conclusion

The reactions of the vicinal dianion 2 derived from a-aroylsuccinic ester with aromatic aldehydes provided γ-lactones 3, which could be used as the starting materials for preparation of thuriferic acid ethyl esters 7.

Keywords: vicinal dianion, γ-lactone, thuriferic acid ethyl ester

Selected References:

1. Thompson, C.M. (1994). Dianion Chemistry in Organic Synthesis, CRC Press.
2. Peterson, J.R., Do, H.D. & Roger, R.D. (1991). Anticancer agent development; 6. Application of the heterocycles annulation-rearrangement strategy in the synthesis of a podophyllotoxin. *Synthesis* 275-277.
3. San feliciaiano, A., Lopez, J.L., Medarde, M., Miguel Del Corral, J.M., Pascual-Teresa de, B. & Puebla, P. (1988). Thuriferic acid. A novel lignan type from *Juniperus thurifera*. *Tetrahedron* 44(23), 7255-7260.

OC-P21

Dianions of α-Aroylsuccinic Esters:
Synthesis of a Podophyllotoxin Precursor

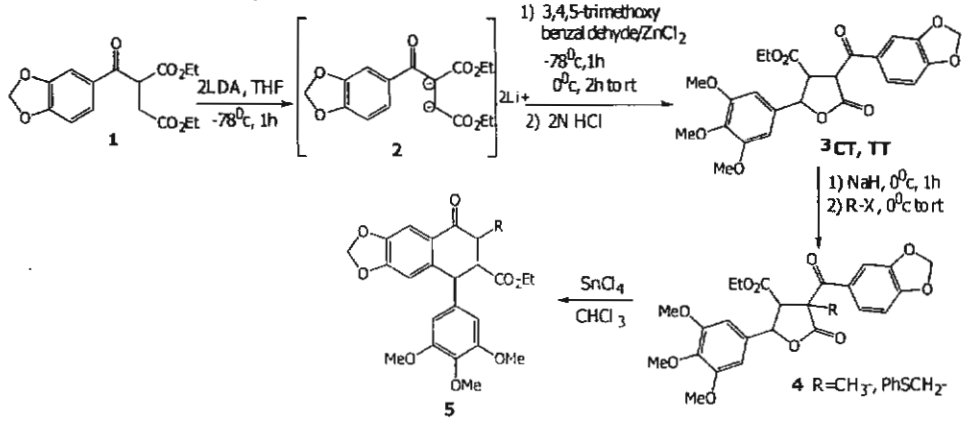
Taweechote komutkul, Manat Pohmakotr, Patoomratana Tuchinda and Vichai Reutrakul
Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand.

Objectives

To study the generation and application of dianions derived from α-aroylsuccinic esters

Methods

α-Aroylsuccinic ester **1** could be doubly deprotonated by using 2.1 equivalents of LDA in THF at -78°C for 1 h to give the dianion **2** which reacted with 3,4,5,-trimethoxybenzaldehyde which was activated by using zinc chloride. The γ-lactone **3** was obtained as a mixture of *cis,trans* (**CT**) and *trans,trans* (**TT**) diastereomers. Alkylation and lewis acid rearrangement of the γ-lactone **3** led to the γ-oxo ester **5**.



Results

The reaction of the vicinal dianion **2** with 3,4,5-trimethoxybenzaldehyde led to the γ-lactone **3** as a mixture of two diastereomers which consisted of the **CT**-isomer as the major isomer. Alkylation followed by Lewis acid-catalyzed rearrangement of γ-lactone **3** gave the expected γ-oxo ester **5**, which is a podophyllotoxin precursor.

Conclusion

The γ-oxo ester **5** could be synthesized from the γ-lactone **3**, which was derived from the reaction of the vicinal dianion **2** with 3,4,5-trimethoxybenzaldehyde. The γ-oxo ester **5** (R = H) could be used as the starting material for synthesis of podophyllotoxin and derivatives as appeared in the literature.

Keywords: vicinal dianion, γ-lactone, γ-oxo ester

Selected references:

1. Thomson, C.M. (1994). Dianion Chemistry in Organic Synthesis. CRC Press.
2. Peterson, J.R., Do, H.D., & Rogers, R.D. (1991). Anticancer Agent Development; 6. Application of the Heterocycle Annulation-Rearrangement Strategy in the Synthesis of a Podophyllotoxin. *Synthesis*, 275-277.
3. Ward, R.S. (1992). Synthesis of Podophyllotoxin and Related Compounds. *Synthesis*, 719-730.

OC-P24

Reaction of Vicinal Dianion Derived from Triethyl Ethanetricarboxylate

Tipwan Mophuang, Wacharee Harnying, Manat Pohmakotr, Patoomratana Tuchinda and Vichai Reutrakul
Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand.

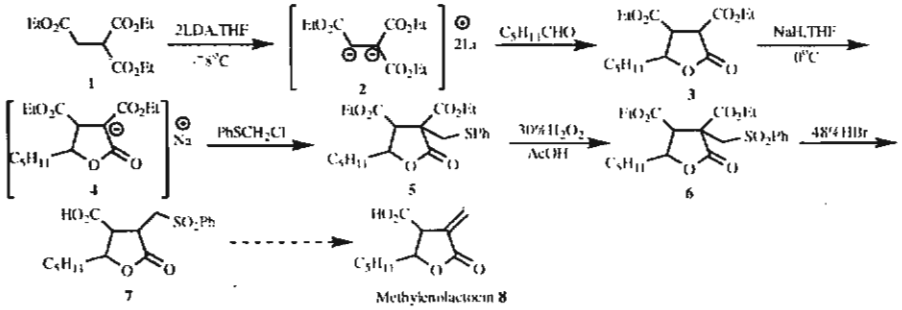
Objective

To study the reactions of vicinal dianion derived from triethyl ethanetricarboxylate: synthetic study towards synthesis of methylenolactocin.

Methods

The dianion **2** could be generated by reacting triester **1** with 2 equivalents of LDA in THF at -78° C for 1 h under argon atmosphere. The dianion **2** was treated with a solution of carpronal- dehyde and stirred at -78°C for 2 h, quenched with glacial acetic acid and the crude product obtained was then treated with a catalytic amount of *p*-TsOH to provide the γ-lactone **3**. Treatment of γ- lactone **3** with NaH in THF (0°C for 1 h) and a solution of chloromethyl phenyl sulfide in the presence of NaI at 0°C to room temperature overnight gave a crude product, which was oxidized with 30% H_2O_2 in a glacial acetic acid to give γ-lactone **6**. Hydrolysis of γ-lactone **6** with 48% HBr gave compound **7**. Elimination of the phenylsulfonyl group of compound **7** to the expected methyle- nolactocin **8** under various conditions (LDA, sat. $NaHCO_3$) were studied. All attempts led to unsatisfactory results.

Results



The reaction of dianion **2** with carpronaldehyde gave γ-lactone **3** as a mixture of *trans,cis* (**TC**) *trans,trans* (**TT**) *cis,cis* (**CC**) and *cis,trans* (**CT**) diastereomers which consisted of the **TC**-isomer as the major isomer in 60% combined yield. Alkylation of γ-lactone **3** with chloromethyl phenyl sulfide followed by oxidation gave γ-lactone **6** in 52% yield. Hydrolysis of γ-lactone **6** with 48% HBr gave compound **7** in 70% yield. Elimination of phenylsulfonyl group of compound **7** were to methylenolactocin **8** was studied.

Conclusion

The reaction of vicinal dianion **2** derived from triethyl ethanetricarboxylate **1** with carpronaldehyde afforded the expected γ-lactone **3** as a mixture of diastereomers, which could be used as the starting material for the study of synthesis of natural product methylenolactocin **8**.

Keywords: vicinal dianion, γ-lactones, methylenolactocin.

Selected references:

Thomson, C.M. (1994). Dianion Chemistry in Organic Synthesis, CRC Press.

OC-P19

Reactions of Vicinal Dianions Derived from α-Aroylsuccinic Esters: Synthesis of Some 2,6-Diaryl-3,7-dioxabicyclo(3.3.0)octane-4,8-diones

Tipwan Mophuang, Manat Pohmakotr, Patoomratana Tuchinda and Vichai Reutrakul

Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand.

Objective

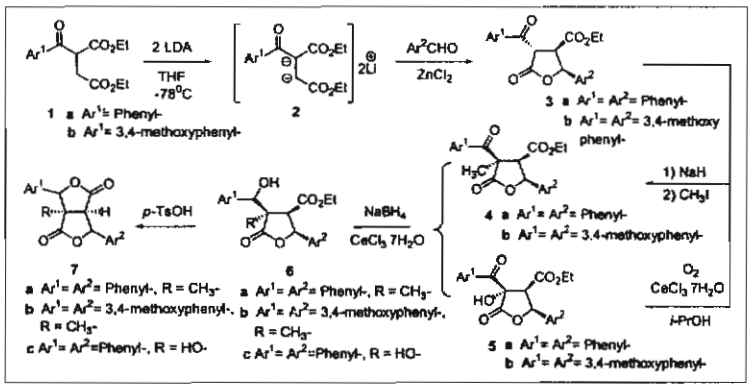
2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones were synthesized from trisubstitued paraconic esters obtained from the reactions of dianions derived from a-aroyl succinic esters with aromatic aldehydes.

Methods

α-Aroylsuccinic esters 1 were deprotonated with 2 equivalents of LDA in THF at -78 °C for 1h followed by addition of aromatic aldehydes in the presence of zinc chloride to give products 3. *Trans,cis*-3 was treated with NaH and methyl iodide to give compounds 4. Compounds 5 were obtained from 3 by treatment with $CeCl_3 7H_2O$ in *i*-PrOH under an oxygen atmosphere at 80 °C. Treatment of 4 or 5 with $NaBH_4$ gave compounds 6, which were cyclized to bislactones 7 by treatment with *p*-TsOH in refluxing toluene.

Results

The dianions 2 could be generated by treatment of α-aroylsuccinic esters 1 with 2 equivalents of LDA in THF at –78°C for 1 h and reacted with aromatic aldehydes in the presence of zinc chloride to give γ-lactones 3 as a mixture of four diastereomers, which consisted of *trans,cis*-(TC) as a major isomer. Methylation of TC-3 gave products CC-4. Hydroxylation of TC-3a with molecular oxygen catalyzed by $CeCl_3 \cdot 7H_2O$ gave compound 5a. No trace of compound 5b was observed under the same conditions. This may be due to the insolubility of the starting material 3b in *i*-PrOH. Reduction of compounds 4 or 5 with $NaBH_4$ gave 6, which underwent lactonization to afford bislactones 7 upon treatment 6 with *p*-TsOH.



Conclusion

Compounds of type 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones could be synthesized by employing synthetic utilities of dianions of α-aroylsuccinic esters.

Keywords: α-aroylsuccinic ester, vicinal dianion, γ-lactone, bislactone

Selected References:

1. Thompson, C.M. (1994). Dianion Chemistry in Organic Synthesis, CRC Press.
2. Christoffers, J. & Werner, T. (2002). Cerium-catalyzed a-oxidation of β-dicarbonyl compounds with molecular oxygen. *Synlett*, 119-121.

OC-P24

Synthetic Approach to Furofuran Lignans

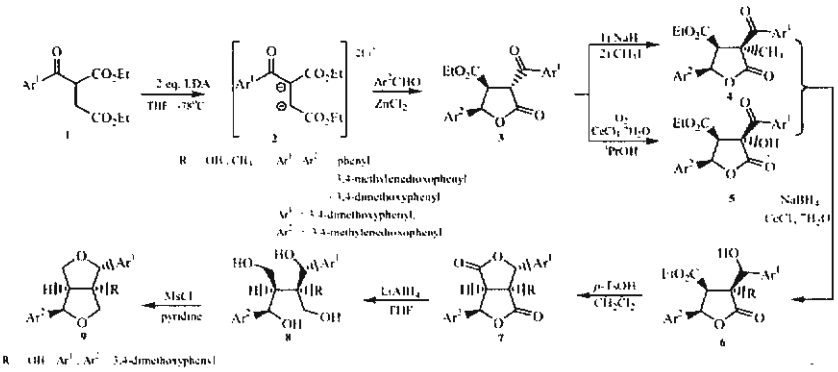
Attapol Pinsa, Manat Pohmakotr, Patoomratana Tuchinda and Vichai Reutrakul
Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand.

Objective

To develop a new general synthetic route to furofuran lignans including gmelinol, an antimalarial agent, which was isolated from the heartwood of *Gmelina arborea*.

Methods

The synthetic route of furofuran lignans was summarized as shown in Scheme 1.



Gmelinol

Scheme 1

Results

α-Aroylsuccinic esters **1** were deprotonated by using 2 equivalents of LDA to give vicinal dianions **2**. The reaction of vicinal dianions **2** with aromatic aldehydes in the presence of $ZnCl_2$ led to γ-lactones **3** as a mixture of four diastereomers, which consisted of *trans,cis* (*TC*) as the major isomer. Methylation of ***TC*-3** with NaH and MeI gave ***CC*-4**. ***TC*-3** was hydroxylated by using $CeCl_3.7H_2O$ in *i*-PrOH under flush of oxygen at 50°C, producing **CC-5**. Compounds **4** and **5** was then selectively reduced with $NaBH_4/CeCl_3.7H_2O$ to give compounds **6**, which were cyclized to bislactones **7** by treatment with *p*-TsOH. Reduction of compounds **7** by using $LiAlH_4$ and followed by cyclization with MsCl in pyridine provided furofuran lignans **9**.

Conclusion

The reactions of the vicinal dianions **2** derived from α-aroylsuccinic esters with aromatic aldehydes provided γ-lactones **3**, which could be used as the starting materials for the preparation of furofuran lignans **9**.

Keywords: vicinal dianion, α-aroylsuccinic ester, γ-lactone, bislactone, furofuran lignan

Selected References

1. Mophuang, T., (2003). Reaction of vicinal dianion derived from α-aroylsuccinic ester: synthesis of *some 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones. M.Sc. Thesis in Organic Chemistry. Faculty of Graduate Studies, Mahidol University.*
2. Christoffers, J., Werner, T., Unger, S., Frey, W. (2003). Preperation of acyloins by cerium-catalyzed, direct hydroxylation of β-dicarbonyl compounds with molecular oxygen. *Eur. J. Org. Chem.*, 425- 431.

OC-P7

Isolation and Structure Identification of Bioactive Compounds from *Phyllanthus taxodiifolius*

Anawat Kumkao,[a] Patoomratana Tuchinda,[a] Manat Pohmakotr,[a] Vichai Reutakul,[a] Chalobon Yoosook,[b] Samaisukh Sophasan[c] and Thawatchai Santisuk[d]

[a]Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand
[b]Department of Microbiology, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand
[c]Department of Physiology, Faculty of Science, Mahidol University, Rama VI Rd, Bangkok 10400, Thailand
[d]The Forest Herbarium, Royal Forest Department Bangkok 10900 Thailand

Objective

To isolate and identify the chemical constituents from the arial part of *Phyllanthus taxodifolius*

Methods

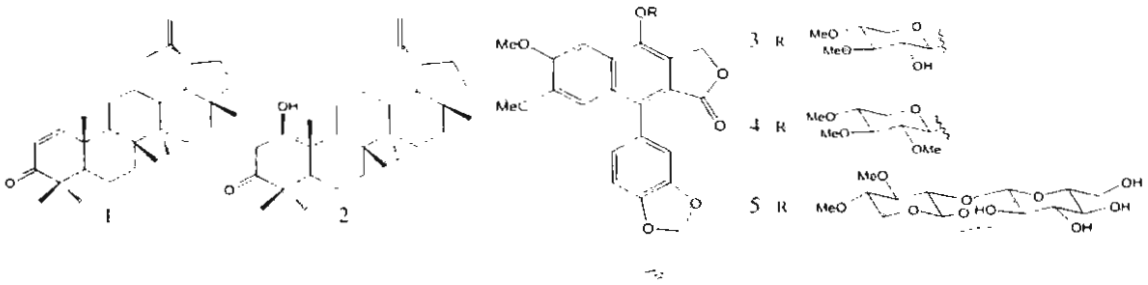
Air-dried, finely powdered arial part of *Phyllanthus taxodiifolius* were successively extracted with methanol. After evaporation of methanol, the partitions between various organic layers and water were carried out. Removal of solvents afforded the hexane, ethyl acetate, *n*-butanol and water extracts, respectively. The isolation of the chemical constituents was performed mainly by column chromatography and recystallization.

Results

The investigation of the arial part of *Phyllanthus taxodiifolius* has led to the isolation of glochidone (**1**), glochidonol (**2**), cleistanthin A (**3**), cleistanthin methyl ether (**4**) and cleistanthoside A (**5**). The structures were assigned by spectroscopic techniques.

Conclusion

Compounds **1-5** are known compounds. Compounds **3** and **4** showed cytotoxic and anti-HIV activities.



Keywords: *Phyllanthus taxodiifolius*, Cytotoxic and anti-HIV activities

Selected References

1. Sastry, K. V. & Venkata Rao, E (1983). Isolation and structure of cleistanthoside A. *J.Med. Chem.*, *47*, 227-229
2. Govindachari, T.R. Sathe, S. S. & Viswanathan N.(1969). Chemical constituents of *cleistanthus collinus* . *Tetrahedron*, *25*, 2815-2821.
3. Wilium A. Ayer, J. Richard, Flanagan and Torsten Reffstrup. (1984). Metabolites of bird's nest fungi "New triterpenoid carboxylic acids from *Cyahus* and *Cyathus pygmaeus*". *Tetrahedron*, *40*(11), 2069-2082.