รายงานวิจัยฉบับสมบูรณ์

โครงการ

The New Syntheses of Central Binaphthalene Building Block, Core of the Anti-HIV Michellamine Alkaloids, Using Organolithiation Reactions

TRG4680008

โดย

นายนพพร ทัศนา

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

มิถุนายน 2548

สัญญาเลขที่ TRG4680008

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สังกัด
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Nopporn Thasana

บทคัดย่อ

รหัสโครงการ : TRG4680008

ชื่อโครงการ : การสังเคราะห์สารประกอบไบแนพทาลีน หน่วยโครงสร้างหลัก ของสารมิเซลรามีนอัลคาลอยด์ โดยการใช้ปฏิกิริยาออร์กาโนลิธิเอชั่น

ชื่อนักวิจัย : นายนพพร ทัศนา

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งานวิจัยได้นำเสนอกระบวนการการสังเคราะห์สารไดออสไพรอล ที่แยกได้จากต้นมะเกลือ ซึ่งผลลดของมะเกลือถูกใช้เป็นสมุนไพรพื้นบ้านในการขับพยาธิปากขอ ไดออสไพรอลเป็นสารประกอบไบแนพทาลีนหรือไดเมอริกของแนพทอลซึ่งเชื่อมติดกันที่ตำแหน่งคาร์บอน 2 และ 2' นอกจากนี้พบว่าเป็นแกนกลางของมิเซลรามีน ซึ่งเป็นสารประกอบไดเมอริกแนพทิลไอโซควิโนลีนอัลคาลอยด์ ที่มีฤทธิ์ต่อต้านเชื้อไวรัสเอดส์

งานวิจัยนี้ ได้เสนอกระบวนการการสังเคราะห์สารไดออสไพรอล 3 วิธี โดยการใช้ปฏิกิริยาออร์กาโนลิธิเอชั่น เป็นขั้นตอนสำคัญในการสังเคราะห์สารมัธยันต์สำคัญของทุกวิธี รวมถึงปฏิกิริยาการปิดวงเพื่อให้ได้สารไดออสไพรอล โดยทุกวิธีสามารถเตรียมได้จากปฏิกิริยาที่ไม่ยุ่งยากซับซ้อนและสารตั้งต้นที่หาง่ายและราคาไม่แพง

วิธีแรก เป็นการใช้ปฏิกิริยาออร์กาโนลิธิเอชันและทรานส์เมทัลเลชัน ในการสังเคราะห์สารมัธยันต์ที่มีแกนกลางเป็นสายเฮกซาไดอีน จากสารตั้งต้น ไดโบรโมเฮกซาไดอีน 1 โมเลกุล กับอนุพันธ์ของ 2-อัลคอกซี-4-เมทิลเบนซาไมด์ 2 โมเลกุล ก่อนที่จะทำปฏิกิริยาการปิดวงจากด้านใน เพื่อให้ได้สารไดออสไพรอล

วิธีที่สอง เป็นการใช้ปฏิกิริยาออร์กาโนลิธิเอชันและทรานส์เมทัลเลชัน จากสารประกอบไบเอริลคาร์บอกซาไมด์ 1 โมเลกุล และ เบต้าเมทาลิลคลอไรด์ 2 โมเลกุล ที่ตำแหน่งที่ 4 และ 4' เพื่อให้ได้สารมัธยันต์ ที่พร้อมจะทำปฏิกิริยาการปิดวงจากด้านนอก เพื่อให้ได้สารไดออสไพรอล

วิธีสุดท้าย เป็นการใช้ปฏิกิริยาออร์กาโนลิธิเอชันในการสังเคราะห์อนุพันธ์ของแนพทาลีน ที่ถูกนำไปใช้ในปฏิกิริยาการสังเคราะห์สารไดออสไพรอล โดยปฏิกิริยซูซูกิแบบปกติและแบบประยุกต์ จากเฮโลแนพทาลีน 1 โมเลกุล และแนพทาลีนโบโรนิก 1 โมเลกุล

คำหลัก : ไดออสไพรอล ไบแนพทาลีน ปฏิกิริยาออร์กาโนลิธิเอชัน

Abstract

Project Code : TRG4680008

Project Title : New Syntheses of Central Binaphthalene Building Block, Core of the Anti-HIV Michellamine Alkaloids, Using Organolithiation Reactions

Investigator : Mr. Nopporn Thasana

Institute : Chulabhorn Research Institute

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Project Period : 1 July 2003 – 30 June 2005

- The syntheses of diospyrol were reported. Diospyrol isolated from *Diospyros mollis* Griff., a shrub growing in South-East Asian countries, was used as an anthelmintic. It has a dimeric naphthalene skeleton with a C-2/C-2' linkage as the core of michellamine, the dimeric naphthylisoquinoline alkaloid. Michellamines B has shown in vitro activity against human immunodeficiency virus (HIV) strains in lymphocytes in culture. In this chemistry, the chemistry of organolithiation reaction was applied to the 3 synthetic routes of diospyrol. It was not only used as crucial steps for the synthesis of all of the key intermediates but also in the last steps for the ring closure of diospyrol synthesis. All the steps were efficient routes and prepared from available materials.

The first, using organolithiation and transmetallation the key intermediate, 1,6-dibenzamidehexa-2,4-diene, was achieved from 2 molecules of 2-alkoxy-4-methylbenzamide and a molecule of dibromo-2,4-hexadiene. The ring closure to form diospyrol was also studied using organolithiation cyclization and various bases.

The second, the key intermediate of this route was successfully prepared using organolithiation and transmetallation at C-4 and C-4' positions of biarylcarboxamide. The Li/M species was then trapped with β-methalylchloride. The formation of diospyrol by ring closure was successfully studied using various lithium bases.

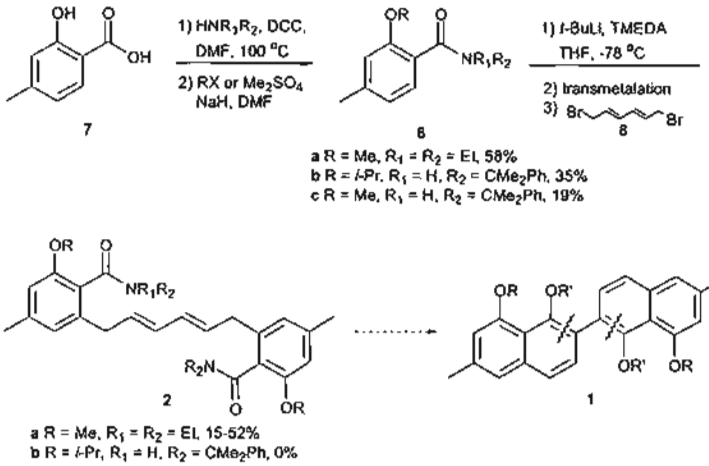
In the last step, organolithiation was applied to the synthesis of naphthol which was further used to prepared both halonaphthalene and naphthalene boronic acid as key intermediates. Diospyrol was achieved through the key intermediates by both the convenient classical Suzuki cross-coupling reaction and the modified Suzuki cross-coupling reaction.

Keywords : Diospyrol, Binaphthalene, Organolithiation Reaction

Executive Summary

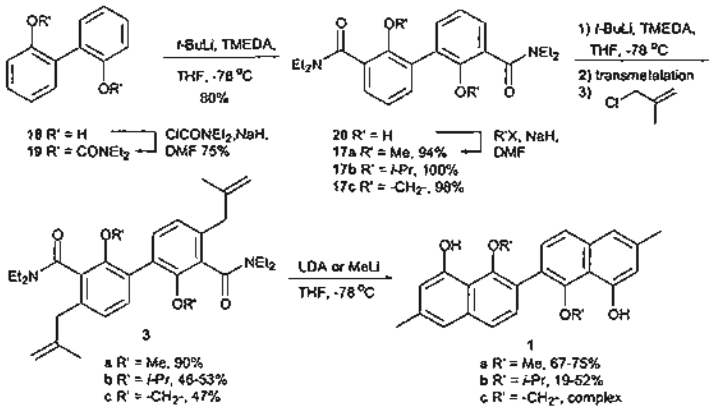
Route A (8+6+8): Synthesis of diospyrol via bisallylation and doublecyclization

In the first route, we accomplished the preparation of key intermediate **2** using directed *ortho* metalation (DoM) and transmetalation followed by double allylation. Various base and methodologies for cyclization to binaphthalene have been used but the cyclization product was not observed. Now compound **2** is still under investigation for the cyclization.



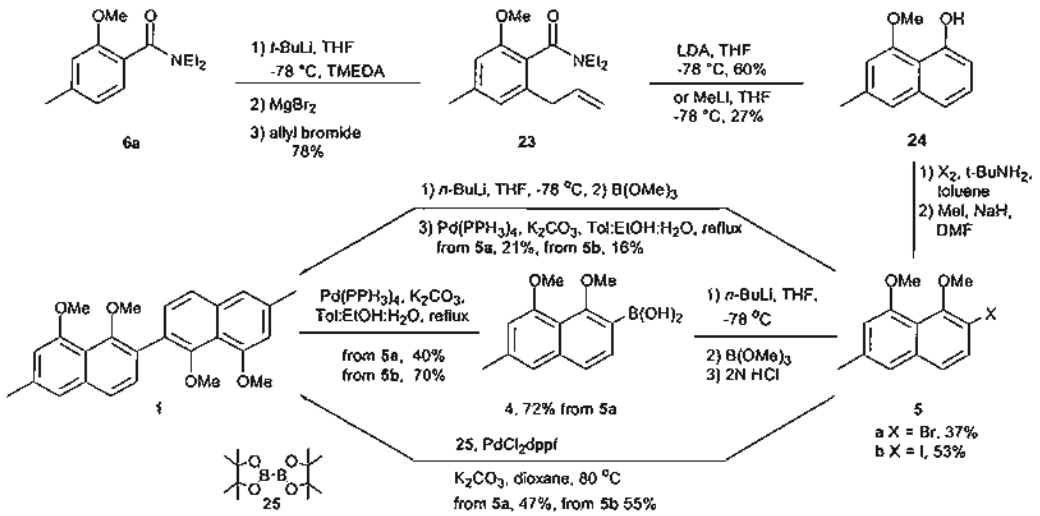
Route B (4+7+7+4): Synthesis of diospyrol via DoM/Fries rearrangement, transmetalation, biallylation and doublecyclization

In this route, we have successfully developed a direct approach for the conversion of biphenol to binaphthol and applied to the synthesis of diospyrol. The application of directed *ortho* metalation (DoM), Fries rearrangement and transmetalation followed by allylation and cyclization is reported for the conversion of biphenol to binaphthol as a means for the synthesis of diospyrol. The methodology should be applicable to the synthesis of related oxygen heterocycles.



Route C (11+11): Synthesis of diospyrol via modified Suzuki cross-coupling reaction

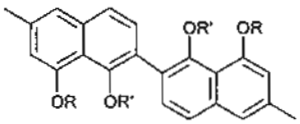
In the last route, we have successfully synthesized tetramethoxydiospyrol using classical and modified Suzuki-Miyaura cross-coupling reaction of naphthalene derivatives. Tetramethoxydiospyrol was synthesized from the two key intermediates, halonaphthalene and naphthaleneboronic acid derivatives. The naphthol was synthesized via the cyclization of *ortho*-allylbenzamide intermediate. Moreover, tetramethoxydiospyrol could be conveniently obtained by a one-pot modified *in situ* Suzuki coupling. The iodonaphthalene was found to react more efficiently than bromonaphthalene in the cross-coupling reaction.



New Syntheses of Central Binaphthalene Building Block, Core of the Anti-HIV Michellamine Alkaloids, Using Organolithiation Reactions

Introduction

Diospyrol (R = R' = H) was isolated from *Diospyros mollis* Griff., a shrub growing in South-East Asian countries. It has a dimeric naphthalene skeleton with a C-2/C-2' linkage between both the 1-naphthol ring system.[1]



DiospyroltetraGlu R = R' = Glu
Diospyrol R = R' = H

Figure 1 Diospyrol derivatives

In Thailand, extracts of the fresh berries of this plant, 2-2.5 cm in diameter in summer, have long been used as an anthelmintic and the black berries are used as a black dye.[2] Diospyrol was obtained by extraction with ether,[1a] acetone or ethanol followed by precipitation with aqueous acetic acid. The phenol, especially diospyrol, was assumed to be the main constituent for anthelmintic action and dying.

Figure 2 *Diospyrol mollis*

Michellamines are a growing class of novel naphthylisoquinoline alkaloids.[3] They were isolated from the tropical Cameroonian liana *Ancistrocladus korupensis* (Ancistrocladaceae) which is a rich source of structurally, biosynthetically, and pharmacologically intriguing mono and dimeric naphthylisoquinoline alkaloids.[3] Michellamines are unprecedented dimeric naphthylisoquinoline alkaloids with a C-5/C-8' linkage between the naphthalene and the isoquinoline ring system. Michellamines B, along with its isomers, michellamine A and C, has shown in vitro activity against human immunodeficiency virus (HIV) strains in lymphocytes in culture.[3a] It has been reported to

protect human lymphoblastoid CEM-SS cells against 11 strains of HIV-1 with EC_{50} values of 1 to 13 μM and low toxicity to the cells. Michellamine B, the most studied compound of this group, also showed interesting activity to protect MT-2 cells from both AZT-resistant and pyridone-resistant strains of HIV-1.[3b] Their structures are composed of two important units, 1,3-dimethyltetrahydroisoquinoline and the core binaphthol whose structure resembled diospyrol.

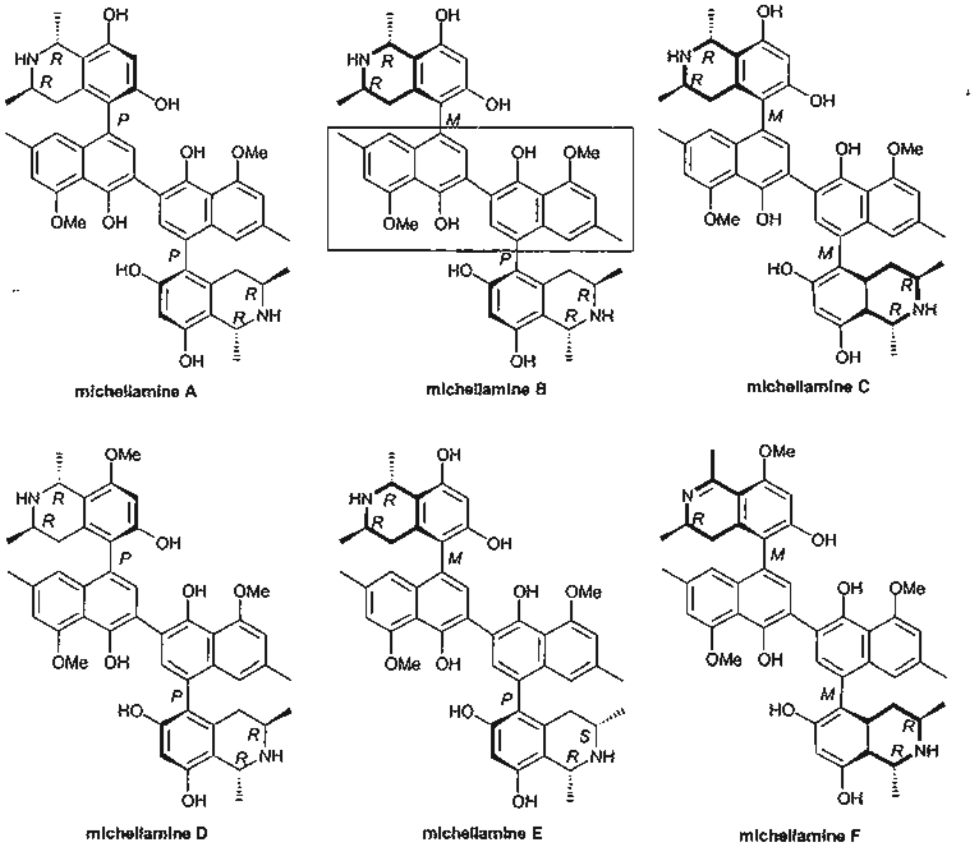


Figure 3 Michellamine alkaloids

Moreover, monomeric naphthylisoquinoline alkaloids, korupensamine A-D, with a C-5/C-8' linkage between the naphthalene and the isoquinoline ring system, isolated from the same plant, *A. korupensis,* was essentially inactive against HIV.[4] In contrast, they have shown significant antimalarial activity against *Plasmodium falciparum* and *P. berghei* whereas the michellamines exhibited very weak antimalarial activity.[4]

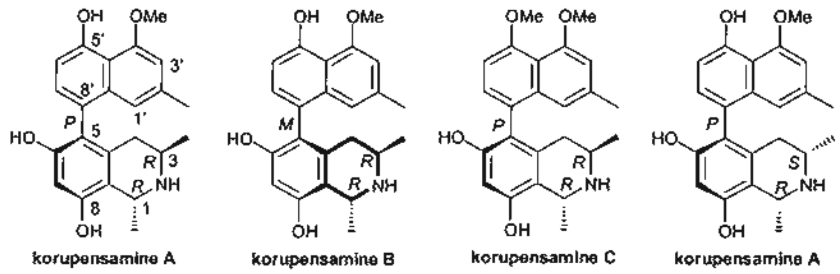


Figure 4 Korupensamine alkaloids

As well as the ancistrobertsonine alkaloids, isolated from *Ancistrocladus robertsoniorum*, a tropical liana indigenous to Kenya, belonging to the small monogeneric family of Ancistrocladaceae, showed moderate antimalaria activities.[5] Dioncophyllines alkaloids, the chemical constituents of the small tropical plant families Dioncophyllaceae and Ancistrocladaceae, showed a broad spectrum of biological activities. As an example, dioncophylline B, isolated from the West African liana, endemic to the Ivory Coast, Sierra Leone, and Liberia, *Triphyophyllum peltatum* (Hutch. et Dalz.),[6] showed high antimalarial and fungicidal activities.[7]

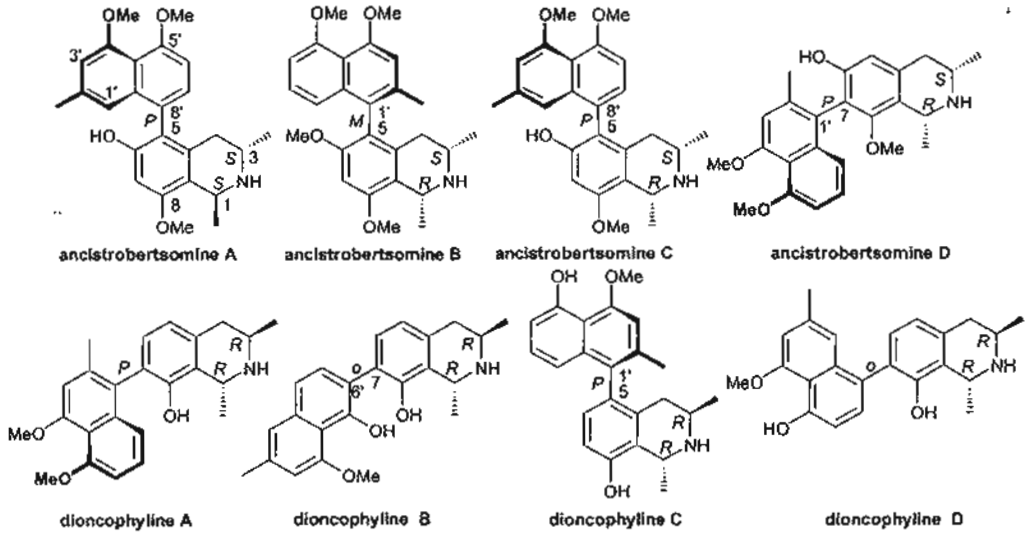


Figure 5 Ancistrobertsonine and dioncophylline alkaloids

Not only have monomeric naphthylisoquinoline alkaloids been shown to have significant antimalarial activity but some unusual dimeric naphthylisoquinoline alkaloid, jozimine A,[8] was found to exhibit weak antimalarial activity as well as the unnatural 'dimer' of the ancistrocladine alkaloid, jozimine B, a constitutionally unsymmetric bis-naphthlisoquinoline.[8] Whereas jozimine C, prepared by oxidative dimerization of dioncophylline C, showed a good portion of anti-HIV activity, its antimalarial activity was lower than that its natural monomeric half.[8]

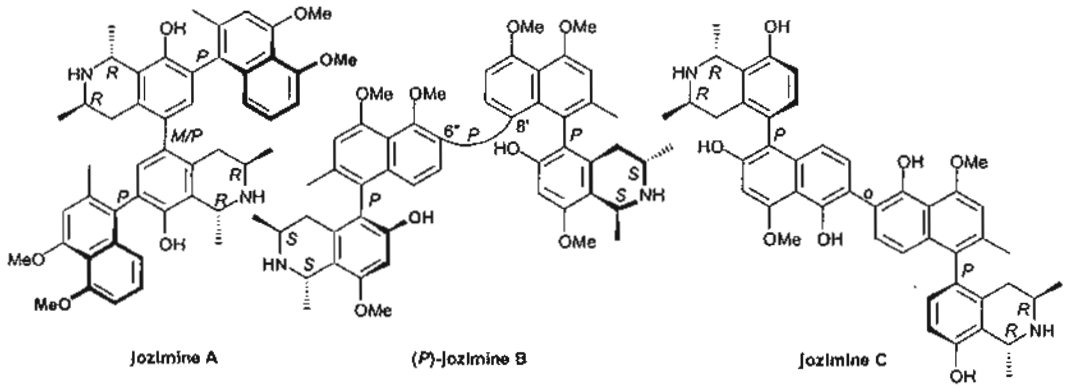
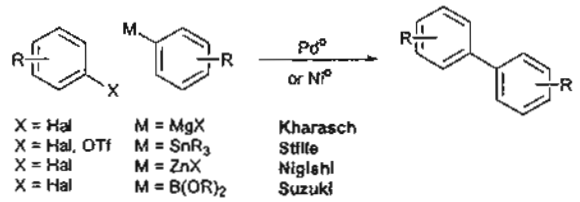


Figure 6 Jozimine alkaloids

Since the detection of michellamines, a broad series of natural and unnatural dimeric naphthylisoquinolines have been synthesized, aiming at the discovery of hopefully more active and simultaneously less toxic structural analogs.[9-13] The synthesis of this interesting structural feature challenged many synthetic groups to establish the pharmacophoric elements necessary for anti-HIV activity and to provide a source of antimalarial drug more accessible than natural sources.

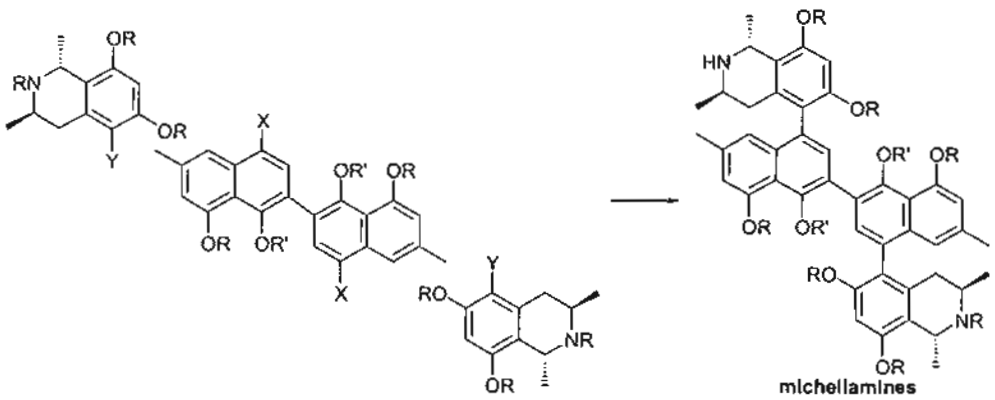
Most biaryl compounds were synthesized by organometallic chemistry using catalytic cross coupling reaction.[14] A general aim of transition metal-catalysed organic synthesis is carbon-carbon (C-C) bond formation. In this respect, the Palladium-catalysis cross coupling is one of the most efficient methods for the construction of C-C bond.



Scheme 1 C-C Bond formation by organometallic chemistry using Pd or Ni catalysis cross-coupling

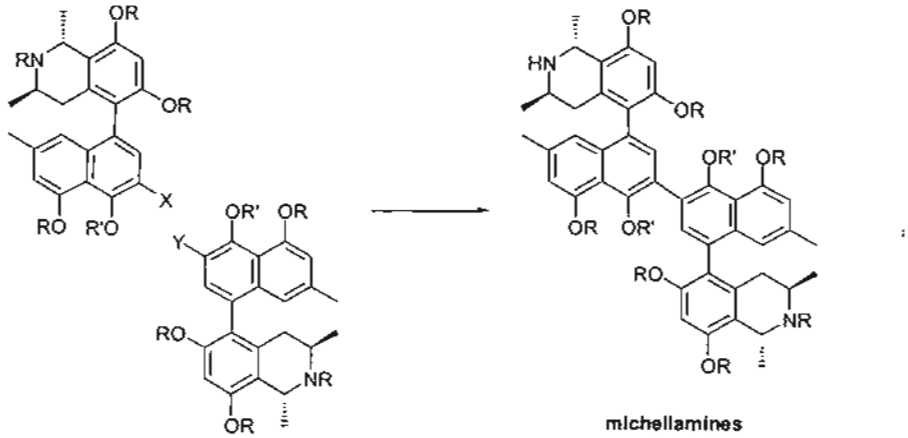
The most commonly used catalytic methods in naphthylisoquinoline alkaloid synthesis are Suzuki-Miyaura coupling (organoboranes),[10] Negishi coupling (organozines),[10f] and Stille coupling (organostannanes).[10f,11] The Suzuki-Miyaura cross coupling reaction is the most popular in recent times to produce biaryl compounds.[15] In some cases, moreover, the organocopper,[10g,16] organosilver,[10d,e,12] and organolead[12] reactions have been used in the oxidative coupling reaction. These reactions enable the preparation of both symmetrical and unsymmetrical biaryls in a cross-coupling reaction and invariably proceed using either palladium or nickel catalysts. Bringmann *et. al.* developed the lactone methodology to synthesize the regio and stereoselective of axially chiral naphthylisoquinoline alkaloids and other michellamine-'half' derivatives.[13]

The dimeric naphthylisoquinolines were typically synthesized in two fashions. The first is the synthesis of binaphthalene core (building block) and consequently coupling with two equivalents of isoquinoline species using organometallic cross-coupling reaction (Scheme 2).[10a,g]



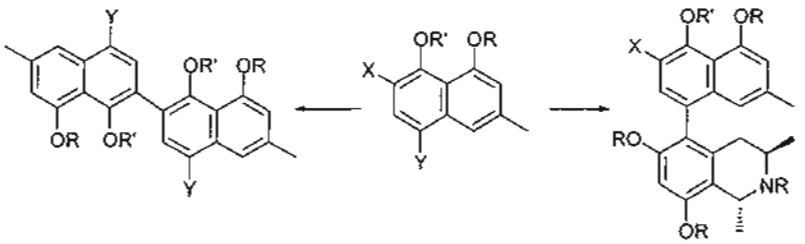
Scheme 2 Synthesis of michellamines by organometallic cross-coupling of binaphthalene core with isoquinoline

The second is the synthesis of monomeric half, naphthylisoquinoline alkaloids, and using organometallic reaction to form oxidative dimerization (Scheme 3).[10d,e,12]



Scheme 3 Synthesis of michellamines by oxidative dimerization of naphthylisoquinolines

From both methodologies, the binaphalene derivatives and monomeric naphthylisoquinoline alkaloids are also biaryl compounds which synthesized by the organometallic coupling reaction either two molecules of naphthalene units or a naphthalene unit and an isoquinoline.



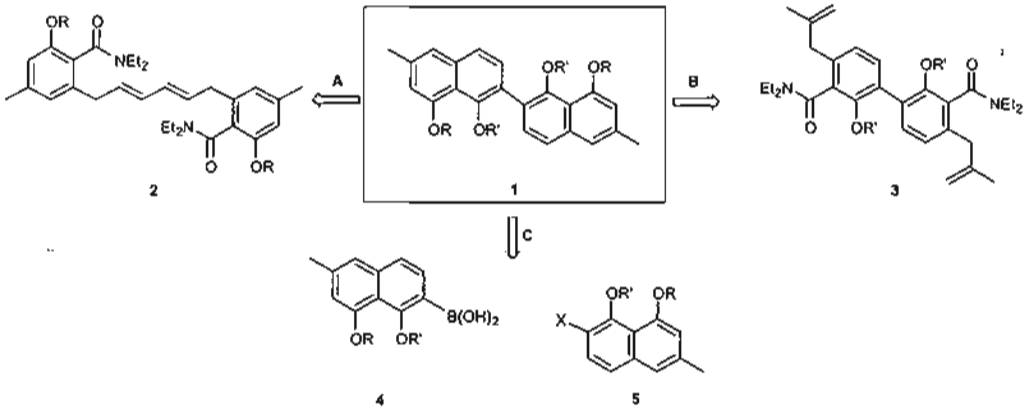
Scheme 4 Two synthetic pathways of binaphthalene and naphthylisoquinoline from naphthalene

Over the years, the synthesis of diospyrol derivatives has challenged many synthetic groups.[17] The interest in this molecule has been intensified by the isolation of the binaphthylisoquinoline alkaloids reported to exhibit many activities. We also are interested to synthesize dimeric core of diospyrol derivative using organolithiation adduct as key intermediates.

Results and Discussion

Retrosynthetic analysis

At first we undertook the syntheses of central core of michellamine alkaloids from double allylation/cyclization of both intermediates **2** (route A) and **3** (route B). In route A, bisallyl core could be generated via dianion formation and ring closure to form binaphthol. On the other hand biallyl intermediate **3** could also be formed via dianion and cyclized to binaphthalene derivatives **1**.

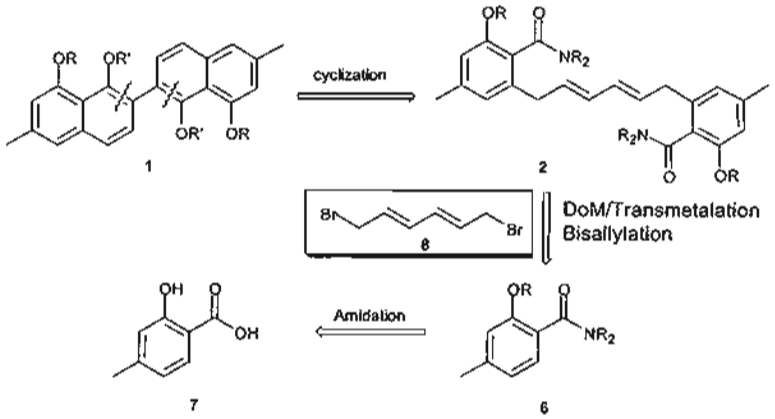


2 1 3 4 5

Scheme 5 Retrosynthetic plans of binaphthalene derivatives **1**

During this work we extend to route C, breaking the C_2 symmetric bond gave rise to two naphthalene units. Using the organolithiation reaction, we planned to synthesize both naphthaleneboronic acid **4** and halonaphthalene **5** and then Suzuki cross-coupling reaction to form binaphthalene derivatives **1**.

Route A (8+6+8): Synthesis of diospyrol via bisallylation and doublecyclization

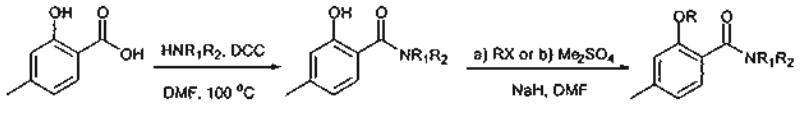


1 2 8 7 6

Scheme 6 Retrosynthetic plan of diospyrol derivative **1** via bisallylation and doublecyclization

The first stage of the synthesis of diospyrol **1** on this route required the preparation of 2-alkoxyl-4-methylbenzamide **6** which was used as precursor of key intermediate **2**. Compound **6** could be synthesized from 4-methylsalicylic acid **7** by amidation and methylation (R = Me) or isopropoxylation (R = *i*-Pr). Biallylation of compound **6** with 1,6-dibromohexa-2,4-diene **8** using DoM/transmetalation could yield to key intermediate **2** as shown in Scheme 6.

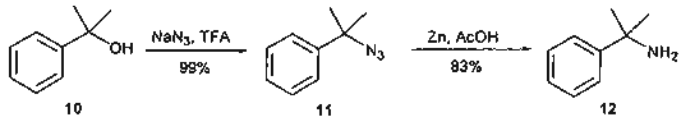
Synthesis of N,N-dialkyl-2-alkoxyl-4-methylbenzamide 6



Scheme 7 Synthesis of *N,N*-dialkyl-2-alkoxyl-4-methylbenzamide **6**

N,N-dialkyl-2-alkoxyl-4-methylbenzamide derivatives **6** were prepared from 4-methylsalicylic acid **7** by amidation with amine (HNR_1R_2) in the presence of dicyclohexyl carbodiimide (DCC) in DMF to give *N,N*-dialkyl-2-hydroxy-4-methylbenzamide **9** (57-66%) which was protected with alkyl halide or dimethyl sulfate in the presence of NaH in DMF to afford *N,N*-dialkyl-2-alkoxyl-4-methylbenzamide derivatives **6a-c** in good to moderate yield (80-52%) as shown in Scheme 7.

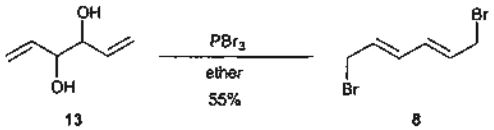
Synthesis of α,α-dimethylbenzylamine 12[18]



Scheme 8 Synthesis of α,α-dimethylbenzylamine **12**

Tertiary alcohol **10** was converted to azide **11** using NaN_3 and TFA in high yield (99%). The azide **11** was simply reduced with active zinc metal in acetic acid to afford a satisfactory yield (83%) of the α,α-dimethylbenzylamine **12** (Scheme 8).[18]

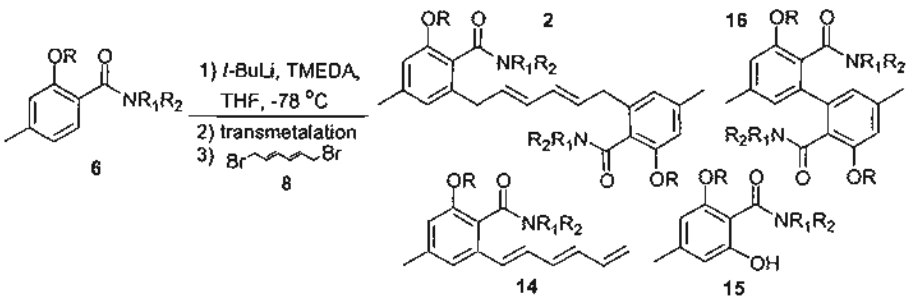
Synthesis of (E,E)-1,6-dibromohexa-2,4-diene 8[19]



Scheme 9 Synthesis of (E,E)-1,6-dibromohexa-2,4-diene **8**

A solution of hexa-1,6-diene-3,4-diol **13** in anhydrous ether was added dropwise to phosphorous tribromide to give (*E,E*)-1,6-dibromohexa-2,4-diene **8** in moderate yield (55%) as shown in Scheme 9.[19]

Synthesis of key intermediate 2



Scheme 10 Synthesis of key intermediate **2**

The synthesis of key intermediate **2** was studied by using directed *ortho* metalation (DoM) of benzamide **6** to deprotonation/transmetalation and coupling with 1,6-dibromohexa-2,4-diene **8** (ratio amide **6**:dibromo **8** 2:1) as shown in Scheme 10 and Table 1. Compound **6a** was *ortho* lithiated using *t*-BuLi/TMEDA in THF at -78 °C, transmetalated with CuCN/LiCl[20] and trapped with dibromohexadiene **8** to give the desired intermediate **2** in moderated yield (42%) (entry 1). Increasing of dibromohexadione **8** (ratio amide **6**:dibromo **8** 1.3:1) gave lower yield of key intermediate **2** and monoalllylation adduct **14** was also obtained (entry 2).

In contrast, the *ortho* lithiation, transmetalation and bisallaylation of secondary bulkyamide **6b** failed to receive target compound with identical procedure (entry 3). An attempt to use the complex metalating reagent, $CuBr.Me_2S$,[21] failed; the *ortho* oxidation adduct **15** and dimeric coupling compound **16** were obtained together with recover starting amide **6b** (entry 4). The Nigishi cross-coupling[10f] was also examined. The compound **6a** was *ortho* lithiated using *t*-BuLi/TMEDA in THF at -78 °C, transmetalated with $ZnCl_2$[22] and coupled with dibromohexadione **8** using $Pd(PPh_3)_4$ as catalytic cross-coupling reaction.

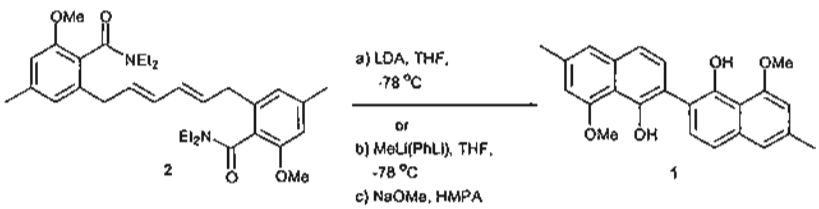
Table 1 The synthesis of intermediate **2** using DoM/bisallylation

Entry	starting	Amide : dibromo	metal	additive	Bisallyl adduct **2** (%)	Monoallyl adduct **14** (%)	Oxidation adduct **15** (%)	Dimeric coupling **16** (%)
1[a]	**6a**	2:1	CuCN	LiCl	42	-	trace	-
2[b]	**6a**	1.3:1	CuCN	LiCl	15	19	trace	-
3[c]	**6b**	2:1	CuCN	LiCl	-	-	12	-
4[d]	**6b**	2:1	CuBr. Me_2S	-	-	-	10	10
5[e]	**6a**	2:1	$ZnCl_2$	-	52	-	-	-

Starting recover: [a] 0%, [b] 17%, [c] 22%, [d] 43%, [e] using $Pd(PPh_3)_4$ as catalyse

Synthesis of diospyrol derivative 1

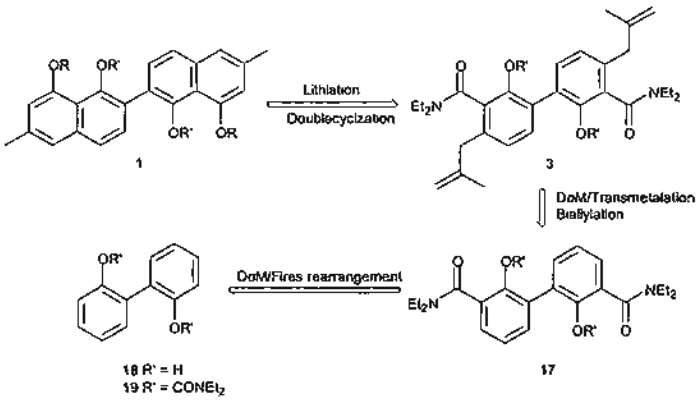
We have investigated various bases and conditions for the base-induced double cyclization of compounds **2**.[23] When compounds **2** were treated with 2 equiv of LDA in THF,[23a-d] a complex mixture of products was obtained. Increasing LDA to 2.5 and 3 equiv also failed to obtain diospyrol **1**.



Scheme 11 Synthesis of diospyrol derivative **1**

The cyclization of key intermediate **2** gave complex mixture on treatment with MeLi[23a-d] or PhLi. Other attempt to cyclise with NaOMe in the presence of HMPA at 60 °C[23e] to give diospyrol **1** also failed.

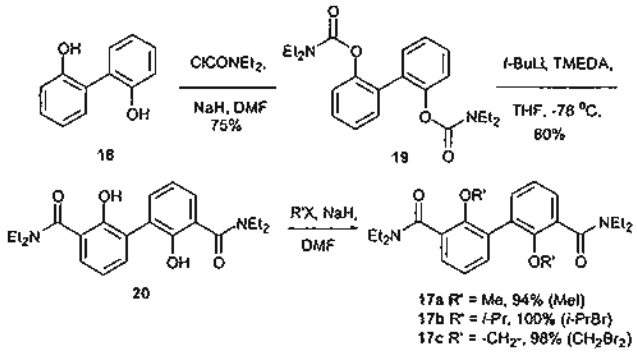
Route B (4+7+7+4): Synthesis of diospyrol via DoM/Fries rearrangement, transmetalation, biallylation and doublecyclization



Scheme 12 Retrosynthetic plan of diospyrol derivative **1** via DoM/Fries rearrangement, transmetalation, biallylation and doublecyclization

In this route we planned to use the application of directed *ortho* metalation (DoM),[24] Fries rearrangement,[25] transmetalation-biallylation,[26] and doublecyclization[23,27] as the Snieckus's chemistry[28] for the synthesis of diospyrol derivative **1**. Compound **17** could be prepared by starting from commercially available 2,2'-dihydroxybiphenyl **18** which protected with *N,N*-diethylchloroformate to yield biphenyldicarbamate **19**. Compound **19** could be lithiated to form double anionic *ortho*-Fries rearrangement and protected with various alkylating reagents to give *N,N*-diethyl-2,2'-dialkoxyl-1,1'-biphenyl-3,3'-dicarboxamides **17**. They could also be *ortho* lithiated, transmetalated and trapped with β-methalyl chloride as one-pot reaction to give the required intermediates **3** as shown in Scheme 12. In the last step, the cyclization of key intermediate **3** will be studied using organolithiation reaction.

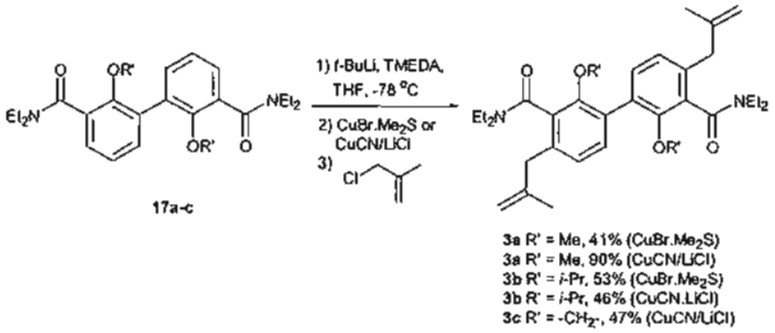
Synthesis of N,N-diethyl-2,2'-dialkoxy-1,1'-biphenyl-3,3'-dicarboxamide 17



Scheme 13 Synthesis of *N,N*-diethyl-2,2'-dialkoxy-1,1'-biphenyl-3,3'-dicarboxamide **17**

N,N-Diethyl-2,2'-dialkoxyl-1,1'-biphenyl-3,3'-dicarboxamide derivatives **17a-c** were prepared in excellent yield (94-100%) by directed *ortho* metalation (DoM) and Fries rearrangement of 2,2'-dicarbamate-1,1'-biphenyl **19** using *t*-BuLi and TMEDA in THF at -78 °C to give *N,N*-diethyl-2,2'-dihydroxy-1,1'-biphenyl-3,3'-dicarboxamide **20** in good yield (80%) which was protected with various alkylating reagents, MeI for **17a** (R' = Me), *i*-PrBr for **17b** (R' = *i*-Pr), CH_2Br_2 for **17c** (R' = -CH_2-), in presence of NaH in DMF as shown in Scheme 13. 2,2'-Dihydroxy-1,1'-biphenyl **18** was protected to 2,2'-dicarbamate-1,1'-biphenyl **19** in good yield (75%) with *N,N*-diethylchloroformate in the presence of NaH in DMF.

Synthesis of key intermediate, N,N-diethyl-2,2'-dialkoxy-4,4'-dimethalyl-1,1'-biphenyl-3,3'-dicarboxamide 3[20,21]



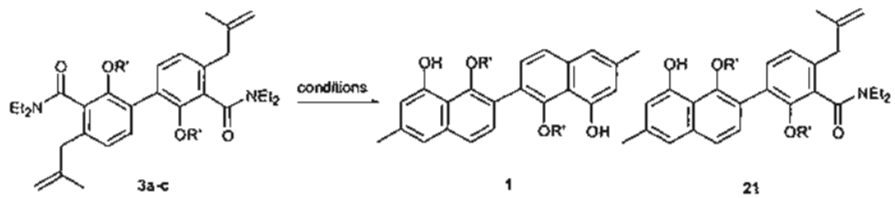
Scheme 14

N,N-Diethyl-2,2'-dimethoxy-1,1'-biphenyl-3,3'-dicarboxamide **17a** was deprotonated using *t*-BuLi, TMEDA in THF at -78 °C, transmetalated with CuBr.Me_2S and trapped with β-methalyl chloride to give *N,N*-diethyl-2,2'-dialkoxy-4,4'-dimethalyl-1,1'-biphenyl-3,3'-dicarboxamide **3a** in moderate yield (41%). By using CuCN/LiCl[20] replaced CuBr.Me_2S,[21] a higher yield was obtained in 90%. Compounds **3b** and **3c** were obtained in moderate yield by using either CuCN/LiCl[20] or CuBr.Me_2S.[21] The ^1H and ^{13}C NMR spectra of key intermediates **3a-c** are shown in Table 2.

Next is the organolithiation cyclization of *N,N*-diethyl-2,2'-dialkoxyl-4,4'-diallyl-1,1'-biphenyl-3,3'-dicarboxamides **3a-c** to afford our target, diospyrol derivatives **1**.

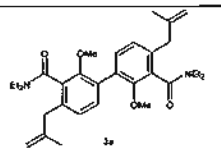
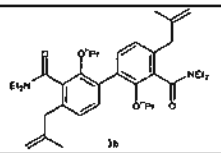
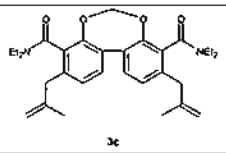
Synthesis of diospyrol derivatives 1

In the last step, the cyclization of key intermediate **3a-c** was studied using LDA and MeLi as shown in Scheme 15 and Table 3.



Scheme 15 Synthesis of diospyrol derivatives **1**

Table 2 The ^{1}H and ^{13}C NMR spectra of key intermediates **3a-c**

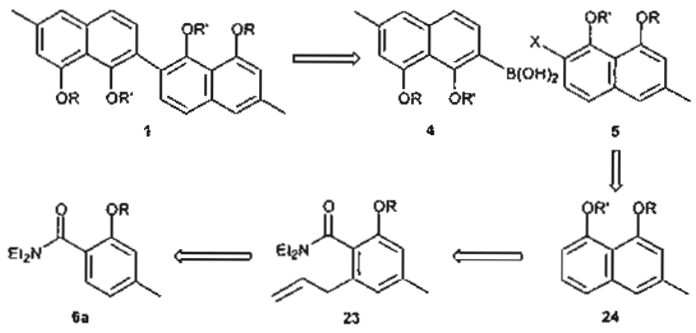
position	 3a		 3b		 3c	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	129.6	-	NO	-	124.2	-
2	153.7	-	152.2	-	150.2	-
3	132.1	-	NO	-	130.7	-
4	137.0	-	137.1	-	136.9	-
5	125.0	6.98 d 7.9	124.8	7.02 bd 7.6	125.6	7.12 d 8.1
6	131.0	7.24 d 7.9	130.8	7.49 bs	127.9	7.52 d 8.1
7	167.9	-	168.2	-	167.1	-
1'	129.0	-	NO	-	123.2	-
2'	153.7	-	151.1	-	152.1	-
3'	131.7	-	NO	-	129.7	-
4'	137.2	-	137.5	-	136.9	-
5'	124.7	6.97 d 7.9	123.8	7.02 bd 7.6	125.0	7.06 d 8.3
6'	131.3	7.12 d 7.9	131.8	7.15 d 7.8	128.3	7.67 d 8.4
7'	168.0	-	168.2	-	167.1	-
1"	40.7	3.27 bs	40.9	3.32 bs	40.6	3.29, 3.34 ABq 15.5
2"	143.5	-	144.0	-	143.4	-
3"	112.9	4.65 d 0.8 4.80 bs	112.5	4.68 bs 4.83 bs	113.2	4.74 s 4.88 s
4"	22.4	1.65 s	22.4	1.70 s	22.4	1.72 s
1"'	40.7	3.25 bs	40.9	3.28 bs	40.5	3.31 s
2"'	143.5	-	144.0	-	143.4	-
3"'	113.0	4.68 d 0.8 4.80 bs	112.7	4.71 bs 4.83 bs	113.1	4.72 s 4.88 s
4"'	22.4	1.67 s	22.4	1.70 s	22.4	1.71 s
4xNCH_2	38.5, 38.6 42.9, 43.1	3.45-3.51 m 3.04-3.10 m	38.5, 38.7 42.9, 43.1	3.43-3.56 m 3.13-3.29 m	38.3, 42.8	3.45-3.73 m 3.05-3.20 m
4xCH_3	12.6, 12.7 13.4, 13.7	1.17 t 7.1 1.04 t 7.1	12.7, 12.8 13.6, 13.7	1.26 t 7.0 1.13 t 7.0	12.6, 12.7 13.6	1.22, 1.25 t 7.1 1.00, 1.07 t 7.1
2xOCH_3	61.1, 61.5	3.30 s, 3.50 s	-	-	-	-
2xO^{i}-Pr	-		74. 6, 75.5 22.5	3.98 p 5.8 1.01 d 5.2	-	-
OCH_2O	-	-	-	-	100.4 96.8	5.58 s 5.37, 5.65 d 6.2

We have investigated various bases and conditions for the base-induced double cyclization of compounds **3**.[23,29] When compounds **3a** was treated with 5 equiv and 10 equiv of LDA in THF, complex mixture of products were obtained (entries 1 and 2). Treatment of compound **3b** with 5 equiv of LDA gave the required product **1b** in 21% yield together with the half-cyclised product **21b** in 33% yield (entry 4). Increasing LDA to 10 equiv gave lower yields of both compounds **1b** and **21b** (entry 5). It was gratifying to find that compound **3a** could be induced to cyclise to the corresponding binaphthol by using MeLi.[23a-d] The required binaphthol **1a** (R' = Me) was isolated in good yield (75%) when 6 equiv MeLi (entry 10) was used and lower yield (67%) was obtained when 4 equiv MeLi was employed (entry 9). The MeLi induced cyclization was also applied successfully to compoundd **3b**, the required product **1b** was obtained in 52% when 6 equiv of MeLi was used (entry 11).

Compound **3c** gave a complex mixture on treatment with LDA and MeLi (entries 6, 7 and 12). An attempt to activate the carboxamide group of compound **3a** with Tf_2O in the presence of pyridine[29] to induce cyclization also failed (entry 3). The two-step double cyclization and methylation of the intermediate **3a** to tetramethoxydiospyrol **1** was also examined in a one-pot process and provided a good yield (75%) of the product. The reaction was carried out using 6 equiv MeLi for double cyclization and the crude product was used in the next step without purification by methylation with MeI in presence of NaH in DMF. The NMR spectra of the tetramethoxydiospyrol **1** so obtained was identical with the compound obtained by another route.[17] The tetramethoxydiospyrol **1** could be demethylated to diospyrol by previously published procedure.[17a,c]

Route C (11+11): Synthesis of diospyrol via modified Suzuki cross-coupling reaction

Retrosynthetic analysis suggested that breaking the C_2 symmetric bond gave rise to two naphthalene units as shown in Scheme 5. In our approach, we planned to utilize the Suzuki-Miyaura cross-coupling[13] of naphthalene derivatives i.e. halonaphthalene **5** and naphthaleneboronic acid **4**, for the synthesis of compound **1** (Scheme 16).



Scheme 16 Retrosynthetic plan of diospyrol derivative **1** via modified Suzuki cross-coupling reaction

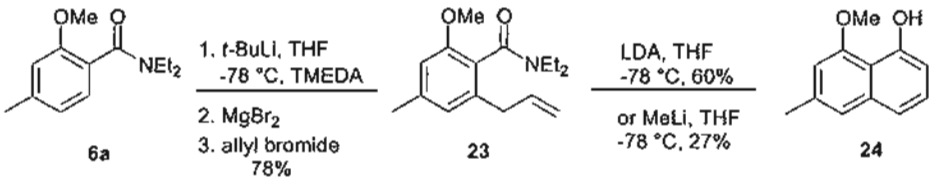
Table 3 Double ring-closure of key intermediates **3a-c**

Entry	R	conditions	yield of **1** (%)	yield of **21** (%)
1	Me	5 equiv LDA	complex	
2	Me	10 equiv LDA	complex	
3	Me	Tf_2O, py, 0 °C then 6 equiv LDA	NA[a]	
4	*i*-Pr	5 equiv LDA	21	33
5	*i*-Pr	10 equiv LDA	19	29
6	$-CH_2-$	5 equiv LDA	complex	
7	$-CH_2-$	10 equiv LDA	complex	
8	Me	2 equiv MeLi	NA[b]	
9	Me	4 equiv MeLi	67	-
10	Me	6 equiv MeLi	75	-
11	*i*-Pr	6 equiv MeLi	52	-
12	$-CH_2-$	6 equiv MeLi	complex	

[a]starting recover 50% [b]starting recover 77%

The naphthol precursor **24** was required for the synthesis of the first key intermediate, halonaphthalene **5**. Many synthetic methodologies have been devised for synthesis of the naphthol derivatives.[23] We adopted the procedure developed by Snieckus[28] et al. using organolithiation for the synthesis of naphthol **24**. The naphthol **24** could be synthesised from the cyclization of allylbenzamide **23** which could prepared from 2-methoxy-4-methylbenzyl amide **6a**. The compound **6a** was previously prepared from 4-methylsalicylic acid **7** as shown in Scheme 7.

Synthesis of 1-hydroxy-8-methoxy-6-methylnaphthalene 24

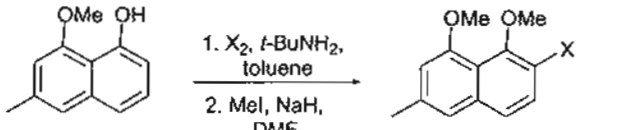


Scheme 17 Synthesis of 1-hydroxy-8-methoxy-6-methylnaphthalene **24**

The naphthol **24** was synthesized in 60% yield by cyclization of the *ortho* allylbenzamide **23** in the presence of excess LDA.[23] The use of methyllithium (MeLi)[23] as a base led also to the cyclised adduct **24** but in lower yield (27%). The precursor allylbenzamide **23** was synthesized in one-pot by selective *ortho* metalation of benzamide **6a**[30] with *t*-BuLi followed by transmetalation with $MgBr_2$ and

the resulting organomagnesium intermediate was trapped with allylbromide to give the product in 78% yield (Scheme 17).[31]

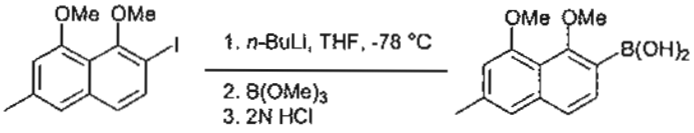
Synthesis of 1,8-dimethoxy-2-halo-6-methylnaphthalene 5



Scheme 18 Synthesis of 1,8-dimethoxy-2-halo-6-methylnaphthalene **5**

The first key intermediate, halonaphthalene **5**, was synthesized using selective *ortho* halogenation[32] of naphthol precursor **24** followed by methylation. The selective *ortho* halogenation of naphthol **24** with bromine or iodine in the presence of *t*-butylamine and further methylation gave bromonaphthalene **5a** (37%, 2 steps) and iodonaphthalene **5b** (53%, 2 steps), respectively.

Synthesis of 1,8-dimethoxy-6-methylnaphthalene-2-boronic acid 4

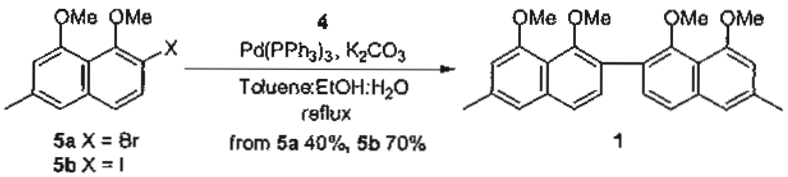


Scheme 19 Synthesis of 1,8-dimethoxy-6-methylnaphthalene-2-boronic acid **4**

The other key intermediate, naphthaleneboronic acid **4**, was prepared in 72% yield from iodonaphthalene **5b** under metal-halogen exchange condition[33] followed by quenching with $B(OMe)_3$ and hydrolysis with 2*N* HCl.

Synthesis of tetramethoxydiospyrol 1

Using the Classical Suzuki-Miyaura cross-coupling



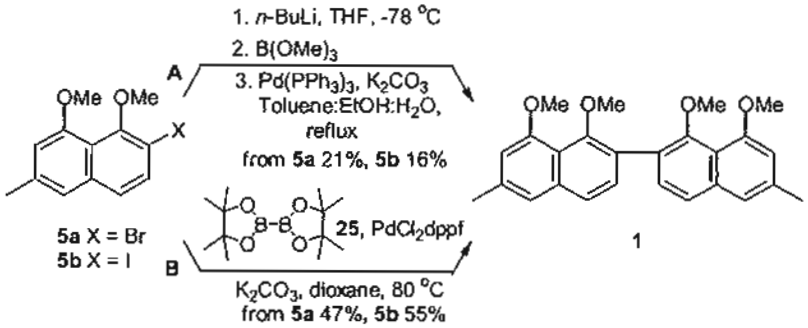
Scheme 20 Synthesis of tetramethoxydiospyrol **1** using the Classical Suzuki-Miyaura cross-coupling

With both key intermediates in hand, the Suzuki-Miyaura cross-coupling was studied.[15,34] The classical Suzuki-Miyaura cross-coupling was carried out by refluxing naphthaleneboronic acid **4** with both bromonaphthalene **5a** and iodonaphthalene **5b** with 3 mol% $Pd(PPh_3)_4$ and K_2CO_3 in a mixed solvent system (Toluene:EtOH:H_2O = 3:3:2, 8 mL) at 115-120 °C for 19 h to obtain tetramethoxydiospyrol **1** (R = R' = Me) in 40 and 70% yield, respectively. The tetramethoxydiospyrol **1** could be converted to the natural diospyrol **1** (R = R' = H) by known method.[17a,c]

Using the modified in-situ Suzuki cross-coupling

The modified one-pot, *in situ* Suzuki cross-coupling were developed by Keay[34] and Bräse[35]'s groups. Both protocols prepared 0.5 equiv of arylboronic compound *in situ* from 1.0 equiv of

haloarene followed by Suzuki-Miyaura cross-coupling in the same flask. The first protocol (Method A)[34] prepared arylboronic ester by metal-halogen exchange with *n*-BuLi followed by quenching with $B(OMe)_3$ whereas in the second protocol (Method B)[35] the arylboronic ester was prepared by reacting haloarene directly with bis(pinacolato)diborane **25** under palladium catalyst. We have utilized both protocols for the *in situ* cross-coupling of both bromonaphthalene **5a** and iodonaphthalene **5b** as shown in scheme 21.



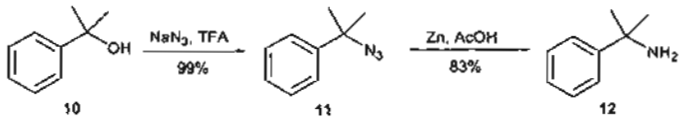
Scheme 21 Synthesis of tetramethoxydiospyrol **1** using the modified in-situ Suzuki cross-coupling

By using method A, the product 1 was obtained in 21 and 16% yield when bromo compound and iodo compound were used respectively and the product **1** was obtained in 47 and 55% yield when method B was employed.

Experimental

Route A (8+6+8): Synthesis of diospyrol via bisallylation and doublecyclization

Synthesis of α,α-dimethylbenzylamine 12[18]



(TRG-DiosRA-2&3)

A mixture of 2-methyl-2-phenylpropanol **10** (6.98 g, 50 mmol) and sodium azide (6.63 g, mmol) in $CHCl_3$ (100 mL) was cooled to -5 °C. A solution of TFA (20 mL) in $CHCl_3$ (100 mL) was added at such a rate that the temperature does not exceed 0 °C. After addition, the cooling bath was removed. The mixture was stirred for 6 h, and left overnight at ambient temperature. An excess of concentrated ammonia was added to the mixture. The organic layer was separated, washed with water, (anhyd Na_2SO_4), and concentrated to give colorless oil (8.0 g, 99%) as azide adduct **11** which was reduced to amine in next step.

A mixture of 2-azide-2-phenylpropane 11 (4.02 g, 25 mmol) and activated zinc metal (2 g) in THF (50 mL) was added dropwise AcOH (10 mL) and stirred until no more foaming occurred. After 24 h, the zinc metal was filtered and the residue was removed in a rotary evaporator to give syrup (2.79 g, 83%) as α,α-dimethylbenzylamine **12**.

α,α-dimethylbenzylamine 12[18]

$C_9H_{13}N$ (135)

Viscous oil

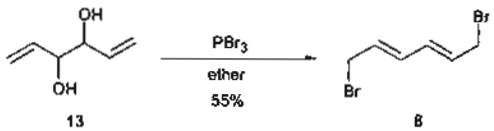
IR (Neat): 3354, 2965, 1602, 1495, 1445 cm^{-1}

MS (EI): 136 (M^++1, 32), 121 (10), 120 (100), 119 (42), 91 (68)

^1H NMR ($CDCl_3$; 200 MHz): ppm 1.49 (s, 6H, 2xCH_3), 2.14 (bs, 2H, NH_2), 7.21 (t, *J* = 8.0 Hz, 1H, ArH-4), 7.33 (dt, *J* = 7.4, 1.6 Hz, 2H, ArH-3,5), 7.49 (d, *J* = 8.0 Hz, 2H, ArH-2,6)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 32.5 (q, 2xCH_3), 52.4 (s, C-α), 124.5 (d, CH-2,6), 126.1 (d, CH-4), 128.1 (d, CH-3,5), 149.9 (s, C-1)

Synthesis of (E,E)-1,6-dibromohexa-2,4-diene 8[19]



(TRG-Dios-28)

A solution of hexa-1,5-diene-3,4-diol **13** (9.964 g, 8.7 mmol) in anhydrous ether (50 mL) was added dropwise to phosphoroustribromide (20.26 g, excess) in an ice bath cooled round-bottom flask equipped with a dropping funnel and magnetic stirrer. After the addition was complete, the mixture was allowed to warm to room temperature and was then set aside to overnight. It was then poured slowly with stirring into ice-water and the resulting mixture neutralized by careful addition of saturated

aqueous sodium carbonate. The product was extracted with ether (3x) and the combine extract was washed with saturated brine, dried (anhyd Na_2SO_4), and evaporated under reduce pressure to yield the crude crystalline, 1,6-dibromohexa-2,4-diene **8** (11.5148 g, 55%).

1,6-dibromo-2,4-hexadiene 8

$C_6H_6Br_2$ (240)

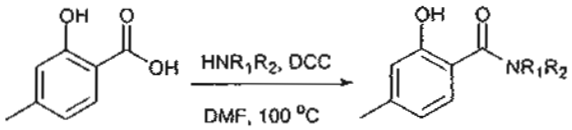
White solid (EtOAc:hexane); mp 87-88 °C (lit[19] 85-86 °C)

IR (KBr): 1435, 1188, 1044, 990, 879, 802, 581 cm^{-1}

^1H NMR ($CDCl_3$; 200 MHz): ppm 4.02 (d, J = 8.2 Hz, 4H, 2xCH_2-1,6), 5.94 (m, 2H, =CH-2,5), 6.28 (m, 2H, =CH-3,4)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 32.4 (t, 2xCH_2-1,6), 130.6 (d, 2=CH), 133.0 (d, 2=CH)

Synthesis of 2-hydroxy-4-methylbenzamide 9



7

9a $R_1 = R_2$ = Et, 66%
9b R_1 = H, R_2 = CMe_2Ph, 57%

(TRG-Dios-23)

A mixture of 4-methylsalicylic acid **7** (15.23 g, 100 mmol), *N,N*-diethylamine (15 mL, 150 mmol) and dicyclohexylcarbodiimide (22.6 g, 110 mmol) in DMF (100 mL) was heated at 100 °C for 48 h. The mixture was allowed to room temperature and DCC was precipitated. After filtration to remove DCC, the crude residue was distillated to remove excess DMF. The brown solid oil was purified by column chromatography using EtOAc and hexane as eluent gave colorless solid **9a** (13.671 g, 66%).

***N,N*-diethyl-2-hydroxy-4-methylbenzamide 9a**

$C_{12}H_{17}NO_2$ (207)

White solid (EtOAc:hexane); mp 107-109 °C

IR (KBr): 3166, 2987, 1609, 1435, 1417, 1297, 1233, 807 cm^{-1}

MS (EI): 208 (M^++1, 100), 207 ($M^\bullet$, 23), 206 (71), 135 (73)

^1H NMR ($CDCl_3$; 200 MHz): ppm 1.28 (t, J = 7.4 Hz, 6H, 2xCH_3), 2.32 (s, 3H, CH_3), 3.52 (q, J = 7.4 Hz, 4H, 2xNCH_2), 6.65 (d, J = 7.2 Hz, 1H, ArH-5), 6.82 (s, 1H, ArH-3), 7.16 (d, J = 7.2 Hz, 1H, H-6)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 13.0 (q, 2xCH_3), 21.0 (q, CH_3), 41.5 (t, 2xCH_2), 116.9 (s, C-1), 117.4 (d, CH-3), 119.2 (d, CH-5), 126.8 (d, CH-6), 141.7 (s, C-4), 156.6 (s, C-2), 170.9 (s, CON)

HRFABMS (pos) Calcd for $C_{12}H_{17}NO_2$ 208.1338; Found 208.1340

(TRG-Dios-12)

A mixture of 4-methylsalicylic acid **7** (0.306 g, 2 mmol), α,α-dimethylbenzylamine (0.270 g, 2 mmol) and dicyclohexylcarbodiimide (0.412 g, 2 mmol) in DMF (2 mL) was heated at 100 °C for 48 h. The mixture was quenched with water and extracted with CH_2Cl_2 (4x). The combine organic layer

was washed with water, aqueous Na_2CO_3, dried (anhyd Na_2SO_4) and evaporated to give brown solid (0.4346 g). Purification on column chromatography on silica gel using EtOAc and hexane as eluent gave colorless solid **9b** (0.304 g, 57%).

***N*-α,α-dimethylbenzyl-2-hydroxy-4-methylbenzamide 9b**

$C_{17}H_{19}NO_2$ (269)

Colorless crystals (EtOAc:hexane); mp 158-160 °C

IR (KBr): 3257, 3058, 1625, 1525, 1312, 1257 cm^{-1}

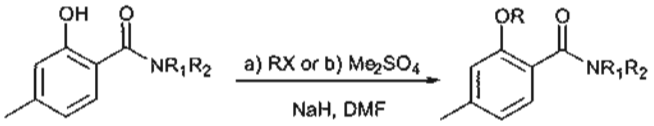
MS (EI) 269 (M^+, 7), 204 (15), 176 (11), 152 (28), 151 (100), 135 (27), 134 (92), 119 (21), 106 (23), 105 (27), 91 (71)

^1H NMR ($CDCl_3$; 200 MHz): ppm 1.82 (s, 6H, 2xCH_3), 2.33 (s, 3H, CH_3), 6.53 (bs, 1H, NH), 6.67 (d, *J* = 8.0 Hz, 1H, ArH-5), 6.78 (s, 1H, ArH-3), 7.27-7.46 (m, 6H, ArH), 12.2 (s, 1H, OH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.4 (q, CH_3), 29.2 (q, 2xCH_3), 56.3 (s, C-α), 112.3 (s, C-1), 118.7 (d, CH-3), 119.7 (d, CH-5), 124.5 (d, CH-2',6'), 125.3 (d, CH-6), 126.8 (d, CH-4'), 128.5 (d, CH-3',5'), 145.0 (s, C-4), 146.4 (s, C-1'), 161.3 (s, C-2), 169.3 (s, CON)

HRFABMS (pos) Calcd for $C_{17}H_{19}NO_2$ 270.1498; Found 270.1499

Synthesis of 2-alkoxy-4-methylbenzamide 6



9a,b

6a R = Me, R_1 = R_2 = Et 80%[a]
6b R = *i*-Pr, R_1 = H, R_2 = CMe_2Ph, 61%[a]
6c R =Me, R_1 = H, R_2 = CMe_2Ph, 52%[b], 33%[a]
6d R =Me, R_1 = Me, R_2 = CMe_2Ph, 5%[a]

(TRG-Dios-25)

Iodomethane (4.0 mL, excess) was added to a suspension of *N,N*-diethyl-2-hydroxy-4-methylbenzamide **9a** (4.14 g, 20 mmol) and NaH (0.8 g) in DMF (30 mL) under Ar atmosphere. The resulting mixture was heated to reflux and stirred overnight. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4) and evaporated to give brown oil. Purification on preparative chromatography using EtOAc and hexane as eluent gave *N,N*-diethyl-2-methoxy-4-methylbenzamide **6a** (3.5408 g, 80%).

***N,N*-diethyl-2-methoxy-4-methylbenzamide 6a**

$C_{13}H_{19}NO_2$ (221)

White solid (EtOAc:hexane); mp 49-51 °C

IR (KBr): 2962, 2935, 1626, 1461, 1432, 1280, 1087, 1037 cm^{-1}

MS (EI): 222 (M^++1, 43), 221 (M+, 26), 220 (100), 190 (10), 149 (89), 91 (40)

^1H NMR ($CDCl_3$; 200 MHz): ppm 0.97 (t, *J* = 6.6 Hz, 3H, CH_3), 1.12 (t, *J* = 6.6 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.10 (q, *J* = 7.4 Hz, 2H, NCH_2), 3.50 (q, *J* = 6.6 Hz, 2H, NCH_2), 6.66 (s, 1H, ArH-3), 6.71 (d, *J* = 7.4 Hz, 1H, ArH-5), 7.01 (d, *J* = 8.0 Hz, 1H, H-6)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 12.7 (q, CH_3), 13.8 (q, CH_3), 21.5 (q, CH_3), 38.6 (t, CH_2), 42.6 (t, CH_2), 55.2 (q, OCH_3), 111.6 (d, CH-3), 121.1 (d, CH-5), 123.8 (s, C-1), 127.0 (d, CH-6), 139.9 (s, C-4), 154.9 (s, C-2), 168.9 (s, CON)

HRFABMS (pos) Calcd for $C_{13}H_{19}NO_2$ 222.1494; Found 222.1491

(TRG-Dios-15)

2-Bromopropane (0.3 mL) was added dropwise to a suspension of *N*-α,α-dimethylbenzyl-2-hydroxy-4-methylbenzamide **9b** (0.271 g, 1 mmol) and NaH (0.04 g) in DMF (1 mL) under Ar atmosphere at 0 °C. The mixture was allowed to room temperature and stirred for overnight. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combine organic layer was washed water, brine, dried (anhyd Na_2SO_4) and evaporated to give a pale yellow oil. Purification on preparative chromatography using EtOAc and hexane as eluent gave colorless oil **6b** (0.1896 g, 61%).

***N*-α,α-dimethylbenzyl-2-isopropoxy-4-methylbenzamide 6b**

$C_{20}H_{20}NO_2$ (311)

Yellow oil

IR (Neat): 3382, 2974, 1661, 1610, 1532, 1493, 1448, 1385, 1295, 1253, 1108 cm^{-1}

MS (EI): 312 (M^++1, 47), 311 (M^+, 69), 296 (71), 268 (26), 219 (27), 178 (55), 177 (100), 161 (51), 135 (88), 134 (95)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.39 (d, *J* = 5.8 Hz, 6H, 2xCH_3), 1.82 (s, 6H, 2xCH_3), 2.37 (s, 3H, CH_3), 4.76 (h, *J* = 5.8 Hz, 1H, OCH), 6.79 (s, 1H, ArH-3), 6.84 (d, *J* = 8.0 Hz, 1H, ArH-5), 7.22 (dt, *J* = 7.2, 1.4 Hz, 1H, ArH-4'), 7.34 (t, *J* = 7.2 Hz, 2H, ArH-3',5'), 7.47 (d, *J* = 8.2 Hz, 2H, ArH-2',6'), 8.05 (d, *J* = 8.0 Hz, 1H, ArH-6), 8.66 (bs, 1H, NH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.6 (q, CH_3), 22.1 (q, 2xCH_3), 29.3 (q, 2xCH_3), 55.6 (s, C-α), 71.6 (d, OCH), 114.3 (d, CH-3), 120.4 (s, C-1), 121.9 (d, CH-5), 124.8 (d, CH-2',6'), 126.3 (d, CH-4'), 128.2 (d, CH-3',5'), 132.1 (d, CH-6), 143.0 (s, C-4), 147.3 (s, C-1'), 155.5 (s, C-2), 164.3 (s, CON)

HRFABMS (pos) Calcd for $C_{20}H_{20}NO_2$ 312.1964; Found 312.1965

(TRG-Dios-20)

Iodomethane (2.0 mL, excess) was added to a suspension of *N*-α,α-dimethylbenzyl-2-hydroxy-4-methylbenzamide **9b** (1.006 g, 4 mmol) and NaH (0.48 g) in DMF (5 mL) under Ar atmosphere. The resulting mixture was heated to reflux and stirred for overnight. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4) and evaporated to give a brown oil. Purification on preparative chromatography using EtOAc and hexane as eluent gave monomethylation **6c** (0.3781 g, 33%) together with dimethylation adduct **6d** (0.0574 g, 5%).

(TRG-Dios-22)

Dimethylsulfate (1.0 mL, excess) was added to a suspension of *N*-α,α-dimethylbenzyl-2-hydroxy-4-methylbenzamide **9b** (0.270 g, 1 mmol) and NaH (0.096 g) in DMF (2 mL) under Ar atmosphere. The resulting mixture was heated to reflux and stirred for 36 h. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4) and evaporated to give a brown oil. Purification on preparative chromatography using EtOAc and hexane as eluent gave only monomethylation adduct **6c** (0.1482 g, 52%).

***N*-α,α-dimethylbenzyl-2-methoxy-4-methylbenzamide 6c**

$C_{18}H_{21}NO_2$ (283)

Viscous oil

IR (Neat): 3391, 2973, 1660, 1611, 1536, 1495, 1463, 1297, 1254, 1171, 1032 cm^{-1}

MS (EI): 284 (M^++1, 21), 283 (M^+, 26), 268 (8), 192 (10), (191 (10), 150 (17), 149 (100)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.83 (s, 6H, 2xCH_3), 2.39 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.79 (s, 1H, ArH-3), 6.87 (d, *J* = 8.0 Hz, 1H, ArH-5), 7.23 (dt, *J* = 7.2, 1.4 Hz, 1H, ArH-4'), 7.34 (t, *J* = 7.4 Hz, 2H, ArH-3',5'), 7.48 (dd, *J* = 7.2, 1.2 Hz, 2H, ArH-2',6'), 8.06 (d, *J* = 8.0 Hz, 1H, ArH-6), 8.40 (bs, 1H, NH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.4 (q, CH_3), 29.2 (q, 2xCH_3), 55.5 (s, C-α), 55.6 (q, OCH_3), 111.8 (d, CH-3), 119.3 (s, C-1), 121.9 (d, CH-5), 124.5 (d, CH-2',6'), 126.2 (d, CH-4'), 128.1 (d, CH-3',5'), 131.8 (d, CH-6), 143.1 (s, C-1'), 147.3 (s, C-4), 157.0 (s, C-2), 163.8 (s, CON)

HRFABMS (pos) Calcd for $C_{18}H_{21}NO_2$ 284.1650; Found 284.1651

4,*N*-dimethyl-N-α,α-dimethylbenzyl-2-methoxybenzamide 6d

$C_{19}H_{23}NO_2$ (297)

Viscous oil

IR (Neat): 3410, 2977, 1639, 1578, 1465, 1373, 1258, 1127, 1050 cm^{-1}

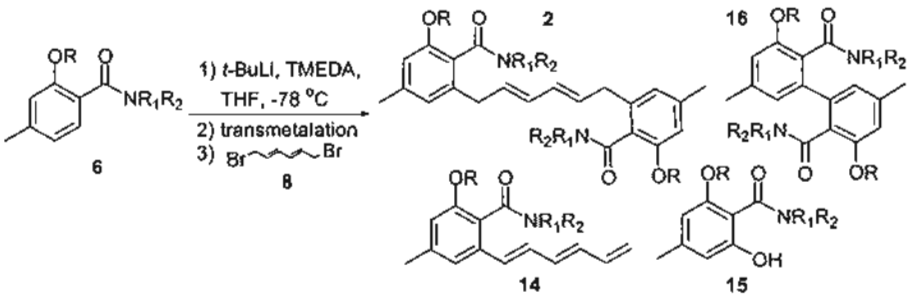
MS (EI): 298 (M^++1, 6), 297 (M^+, 1), 284 (26), 283 (13), 180 (100), 162 (16), 149 (90), 136 (16), 91 (37)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.79 (s, 6H, 2xCH_3), 2.34 (s, 3H, CH_3), 2.86 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 6.68 (s, 1H, ArH-3), 6.76 (d, *J* = 7.2 Hz, 1H, ArH-5), 7.11 (d, *J* = 7.4 Hz, 1H, ArH-6), 7.13 (dt, *J* = 7.2, 1.4 Hz, 1H, ArH-4'), 7.32 (t, *J* = 7.4 Hz, 2H, ArH-3',5'), 7.43 (d, *J* = 7.4 Hz, 2H, ArH-2',6')

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.6 (q, CH_3), 28.2 (q, 2xCH_3), 34.4 (q, NCH_3), 55.6 (q, OCH_3), 61.6 (s, C-α), 111.7 (s, C-1), 111.8 (d, CH-3), 121.4 (d, CH-5), 124.6 (d, CH-2',6'), 125.9 (d, CH-4'), 127.8 (d, CH-6), 128.1 (d, CH-3',5'), 140.1 (s, C-1'), 148.5 (s, C-4), 155.2 (s, C-2), 169.8 (s, CON)

HRFABMS (pos) Calcd for $C_{19}H_{23}NO_2$ 298.1807; Found 298.1809

Synthesis of key intermediate 2



Using CuCN.LiCl[20]

(TRG-Dios-30) R = Me, R_1 = R_2 = Et

To a solution of 1.7 M *t*-BuLi (5.9 mL, 10.0 mmol) and TMEDA (1.5 mL, 10.0 mmol) in dry THF (40 mL) was slowly added, at -78 °C, a solution of *N,N*-diethyl-2-methoxy-4-methylbenzamide **6a** (1.8695 g, 8.86 mmol) in THF (40 mL). The mixture was stirred for 45 min to generate *ortho*-lithiated anion. The reaction was transmetalated (Li/Cu) with the solution of CuCN (0.8956 g, 10.0 mmol) and LiCl (0.4239 g, 10.0 mmol) in THF (20 mL). After 45 min of stirring, a solution of 1,6-dibromo-2,4-hexadiene (1.660 g, 6.9 mmol) in THF (10 mL) was slowly added at -78 °C. The reaction was allowed to warm to room temperature slowly and stirred for 3 h. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed water, brine, dried (anhyd Na_2SO_4) and evaporated to give an oily residue which was purified by PLC using EtOAc and hexane as eluent to yield the doubleallylation adduct **2a** (0.3016 g, 15%), monoallylation adduct **14a** (0.4986 g, 19%) together with the recovered starting compound **6a** (0.3366 g, 17%) and trace of oxidation adduct **15a**.

Using $ZnCl_2$[22]

(TRG-Dios-117) R = Me, R_1 = R_2 = Et

A solution of 1.7 M *t*-BuLi (3.8 mL, 6.25 mmol) in pentane was added to the solution of TMEDA (1.5 mL, 10.0 mmol) in dry THF (10 mL) in a dried 50 mL flask which was charged with N_2 balloon at -78 °C. After 45 min, the solution of *N,N*-diethyl-2-methoxy-4-methylbenzamide **6a** (1.1045 g, 5 mmol) in THF (5 mL) was added dropwise to generate *ortho*-lithiated species. The yellow-brown solution was stirred at-78 °C for 45 min and further transmetalated (Li/Zn) with the solution of $ZnCl_2$ (0.8549 g, 6.25 mmol) in THF (10 mL). After 30 min of stirring, the Li/Zn species was allowed to warm to r.t. and stirred for 30 min. A mixture of 1,6-dibromo-2,4-hexadiene **8** (0.4803 g, 2 mmol), $Pd(PPh_3)_4$ (0.0577 g, 0.05 mmol) and K_2CO_3 (0.8638 g, 6.25 mmol) was added. The mixture was heated to reflux under N_2 atmosphere overnight. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed water, brine, dried (anhyd Na_2SO_4) and evaporated to give an oily residue which was purified by PLC using EtOAc and hexane as eluent to yield the doubleallylation adduct **2a** (0.5932 g, 57%) as viscous oil.

1,6-di-(*N,N*-diethyl-2-dimethoxy-4-dimethylbenxamide)hexa-2,4-diene 2a

$C_{32}H_{42}N_2O_4$ (520)

Viscous oil

IR ($CHCl_3$): 2973, 2935, 1610, 1460, 1429, 1286, 1089, 754 cm^{-1}

MS (EI): 521 (M^++1, 13), 520 (M+, 6), 489 (14), 443 (25), 260 (100), 222 (55), 220 (54)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 0.93 (t, *J* = 6.6 Hz, 6H, 2xCH_3), 1.15 (t, *J* = 6.6 Hz, 6H, 2xCH_3), 2.24 (s, 6H, 2xCH_3), 3.00 (m, 4H, 2xNCH_2), 3.19 (d, *J* = 6.6 Hz, 4H, 2x$ArCH_2$), 3.28 (m, 2H, NCH_2), 3.63 (s, 6H, 2xOCH_3), 3.63 (m, 2H, NCH_2), 5.60 (m, 2H, 2=CH), 5.97 (bd, *J* = 13.2 Hz, 2H, 2=CH), 6.48 (s, 2H, ArH-4,4'), 6.65 (s, 2H, ArH-6,6')

^{13}C NMR ($CDCl_3$; 100 MHz): ppm 12.6 (q, 2xCH_3), 13.5 (q, 2xCH_3), 21.5 (q, 2xCH_3), 35.7 (t, 2xCH_2), 38.3 (t, 2xNCH_2), 42.6 (t, 2xNCH_2), 55.3 (q, 2xOCH_3), 109.3 (d, 2xCH-4,4'), 122.2 (d, 2xCH-6,6'), 123.3 (s, 2xC-2,2'), 130.5 (d, 2x=CH), 131.4 (d, 2x=CH), 137.8 (s, 2xC), 139.2 (s, 2xC), 155.2 (s, 2xC), 168.1 (s, 2xCON)

HRFABMS *micro*TOF (pos) Calcd for $C_{32}H_{42}N_2O_4$ 521.3376; Found 521.3374

***N,N*-diethyl-2-(hexa-1,3,5-trienyl)-6-methoxy-4-methylbenzamide 14a**

$C_{19}H_{25}NO_2$ (299)

Semi-solid

IR (KBr): 2969, 2935, 1704, 1609, 1461, 1310, 1287, 1090 cm^{-1}

MS (EI): 301 (M^++2, 8), 276 (14), 261 (8), 246 (22), 221 (15), 220 (85), 205 (21), 204 (24), 190 (20), 177 (21), 175 (22), 158 (16), 149 (100)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 0.99 (t, *J* = 7.0 Hz, 3H, CH_3), 1.24 (t, *J* = 7.0 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.09 (q, *J* = 7.0 Hz, 2H, NCH_2), 3.50 (m, 1H, NCH), 3.75 (m, 1H, NCH), 3.77 (s, 3H, OCH_3), 5.14 (bs, 1H, =CH), 5.24 (bs, 1H, =CH), 6.30-6.50 (m, 4H, 4x=CH), 6.60 (s, 1H, ArH-3), 6.80 (m, 1H, =CH), 7.03 (s, 1H, ArH-5)

^{13}C NMR ($CDCl_3$; 100 MHz): ppm 12.8 (q, CH_3), 13.7 (q, CH_3), 21.8 (q, CH_3), 38.7 (t, CH_2), 42.6 (t, CH_2), 55.5 (q, OCH_3), 110.7 (d, CH-3), 117.7 (t, $=CH_2$), 117.8 (d, CH-5), 129.4 (d, =CH), 130.8 (d, =CH), 133.4 (d, =CH), 134.2 (d, =CH), 134.8* (s, C-4), 136.9 (d, =CH), 139.1* (s, C-6), 155.5 (s, C-2), 168.0 (s, CON) * signal maybe interchangeble

***N,N*-diethyl-2-hydroxy -6-methoxy-4-methylbenzamide 15a**

$C_{13}H_{19}NO_3$ (237)

White solid (EtOAc : hexane); mp 171-173 °C

IR (KBr): 3104, 2976, 1592, 1519, 1443, 1414, 1360, 1284, 1229, 1099, 817, 777 cm^{-1}

MS (EI): 238 (M^++1, 11), 237 (M^+, 31), 220 (48), 206 (31), 165 (100), 164 (29), 121 (19)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.36 (bt, *J* = 7.0 Hz, 6H, 2xCH_3), 2.20 (s, 3H, CH_3), 3.38 (bq, *J* = 7.0 Hz, 4H, 2xNCH_2), 3.75 (s, 3H, OCH_3), 6.18 (s, 1H, ArH-3), 6.28 (s, 1H, ArH-5), 8.27 (bs, 1H, OH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 13.3 (q, 2xCH_3), 21.7 (q, CH_3), 41.1 (t, NCH_2), 55.5 (q, OCH_3), 103.2 (s, CH-5), 109.7 (s, C-1), 110.6 (d, CH-3), 141.1 (s, C-4), 156.0* (s, C-2), 156.1* (s, C-6), 168.1 (s, CON) * signal maybe interchangeble

HRFABMS (pos) Calcd for $C_{13}H_{19}NO_3$ 238.14430; Found 238.14416

Using CuBr.Me_2S[21]

(TRG-Dios-16) R = ^{i}Pr, R_1 = H, R_2 = CMe_2Ph

A solution of *N*-α,α-dimethylbenzyl-2-isopropoxy-4-methylbenzamide **6b** (0.120 g, 0.38 mmol) in THF (1 mL) was added to a solution of 1.7 M *t*-BuLi (0.47 mL, 0.8 mmol) and TMEDA (0.12 mL, 0.8 mmol) in THF (7 mL) under Ar atmosphere at -78 °C. The mixture was stirred for 30 min at -78 °C to generate *ortho*-lithiated anion. The suspension of CuBr.Me_2S (0.16 g, 0.8 mmol) in THF (1 mL) was added to transmetalate (Li/Cu). The reaction was stirred for 30 min and allowed to 0 °C for 10 min and then cooled down to -78 °C again. The solution of 1,6-dibromo-2,4-hexadiene **8** (0.048 g, 0.19 mmol) in THF (1 mL) was added. The reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction was quenched with sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed water, brine, dried (anhyd Na_2SO_4) and evaporated to give an oily residue which was purified by PLC using EtOAc and hexane as eluent to yield the oxidation adduct **15b** (0.0121 g, 10%), dimeric compound **16b** (0.0113 g, 10%) together with recovered starting compound **6b** (0.0516 g, 43%).

Using CuCN.LiCl[20]

(TRG-Dios-18) R = ^{i}Pr, R_1 = H, R_2 = CMe_2Ph

To a solution of 1.7 M *t*-BuLi (0.3 mL, 0.5 mmol) and TMEDA (0.08 mL, 0.5 mmol) in dry THF (5 mL) was slowly added, at -78 °C, a solution of *N*-α,α-dimethylbenzyl-2-isopropoxy-4-methylbenzamide **6b** (0.1406 g, 0.45 mmol) in THF (2 mL). The mixture was stirred for 30 min to generate *ortho*-lithiated anion. The reaction was transmetalated (Li/Cu) with the solution of CuCN (0.045 g, 0.5 mmol) and LiCl (0.022 g, 0.5 mmol) in THF (2 mL). After 45 min of stirring, a solution of 1,6-dibromo-2,4-hexadiene **8** (0.052 g, 0.22 mmol) in THF (1 mL) was slowly added at -78 °C. The reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction was quenched with sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed water, brine, dried (anhyd Na_2SO_4) and evaporated to give an oily residue which was purified by PLC using EtOAc and hexane as eluent to yield the oxidation adduct **15b** (0.0183 g, 12%) together with the recovered starting compound **6b** (0.0312 g, 22%).

***N*-α,α-dimethylbenzyl-2-hydroxy-6-isopropoxy-4-methylbenzamide 15b**

$C_{20}H_{20}NO_3$ (327)

Yellow oil

IR (Neat): 3366, 2928, 2853, 1639, 1542, 1449, 1372, 1311, 1223, 1108, 699 cm^{-1}

MS (EI): 328 (M^++1, 73), 327 (M^+, 95), 233 (22), 209 (90), 192 (32), 191 (33), 190 (38), 168 (29), 167 (44), 151 (20), 150 (100)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.30 (d, J = 5.8 Hz, 6H, 2xCH_3), 1.75 (s, 6H, 2xCH_3), 2.25 (s, 3H, CH_3), 4.75 (h, J = 5.8 Hz, 1H, OCH), 6.17 (s, 1H, ArH-3), 6.37 (s, 1H, ArH-5), 7.20-7.40 (m, 5H, PhH), 9.00 (bs, 1H, OH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.0 (q, CH_3), 21.5 (q, 2xCH_3), 29.5 (q, 2xCH_3), 56.0 (s, C-α), 72.2 (d, OCH), 104.4 (d, CH-3), 112.0 (d, CH-5), 120.0 (s, C-1), 125.0 (d, CH-2',6'), 126.8 (d, CH-4'), 128.2 (d, CH-3',5'), 143.0 (s, C-4), 146.8 (s, C-1'), 156.5 (s, C-6), 164.5 (s, C-2), 169.7 (s, CON)

HRFABMS (pos) Calcd for $C_{20}H_{20}NO_3$ 328.1913; Found 328.1914

bis-*N*-α,α-dimethylbenzyl-3,3'-diisopropoxy-5,5'-dimethylbiphenyl-2,2'-dicarboxamide 16b

$C_{40}H_{38}N_2O_4$ (620)

White solid (EtOAc:hexane); mp >230 °C (dec)

IR (KBr): 3261, 2974, 2933, 1646, 1603, 1542, 1448, 1383, 1272, 1113, 698 cm^{-1}

MS (EI): 621 (M^++1, 4), 459 (34), 458 (100), 422 (22), 340 (77), 298 (25)

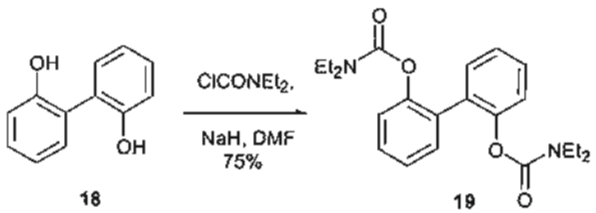
^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.25 (m, 24H, 8xCH_3), 2.28 (s, 6H, 2xCH_3), 4.58 (h, J = 5.8 Hz, 2H, 2xOCH), 6.60 (s, 2H, ArH-4,4'), 6.69 (s, 2H, ArH-4,4'), 7.05-7.20 (m, 10H, 2xArH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.6 (q, CH_3), 22.2 (q, 2xCH_3), 22.3 (q, 2xCH_3), 28.5 (q, 2xCH_3), 29.7 (q, 2xCH_3), 56.2 (s, 2xC-α), 71.1 (d, 2xOCH), 114.0 (d, CH-4,4'), 122.6 (d, CH-6,6'), 123.0 (d, CH-2,2'), 125.0 (d, CH-2",2'",6",6'"), 126.0 (d, CH-4",4'"), 127.9 (d, CH-3",3'",5",5'"), 139.1 (s, C-1,1'), 140.1 (s, C-5,5'), 146.9 (s, C-1",1'"), 154.5 (s, C-3,3'), 164.3 (s, 2xCON)

HRFABMS (pos) Calcd for $C_{40}H_{38}N_2O_4$ 621.3697; Found 621.3694

Route B (4+7+7+4): Synthesis of diospyrol via DoM/Fries rearrangement, transmetalation, biallylation and doublecyclization

Synthesis of 2,2'-N,N-diethylcarbamoyl-1,1'-biphenyl 19



18 **19**

(nt-5e1)

A mixture of 2,2'-dihydroxybiphenyl **18** (18.6942 g, 0.10 mol) and 60% in oil sodium hydride (10.0587 g) in DMF (80 mL) was added diethylcarbamoyl chloride (28.9146 g, 0.20 mol) at 0 °C. The reaction was stirred at room temperature and then heated to 100 °C for 21 h until the starting material was completely consumed. The reaction was quenched with NH_4Cl and extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, dried (anhyd Na_2SO_4), and evaporated to give a viscous oil. The residue was distillated to remove excess DMF and then purified by flash column chromatography using EtOAc:hexane as eluent to give a pale yellow oil **19** (28.6794 g, 75%).

2,2'-*N,N*-diethylcarbamoyl-1,1'-biphenyl 19

$C_{22}H_{28}N_2O_4$ (384)

Pale-yellow oil

IR (Neat): 2976, 1719, 1475, 1418, 1274, 1202, 1155 cm^{-1}

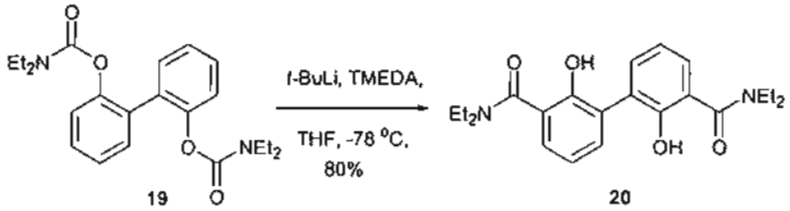
MS (EI): 384 (M^+, 23), 312 (20), 311 (95), 209 (21), 208 (100), 196 (19), 195 (61), 182 (18), 181 (17), 100 (34)

^1H NMR ($CDCl_3$; 200 MHz): ppm 0.87 (bt, J = 7.0 Hz, 6H, $2xCH_3$), 0.99 (bt, J = 7.0 Hz, 6H, $2xCH_3$), 3.15 (m, 8H, $4xCH_2$), 7.28 (m, 8H, ArH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 13.0 (q, $2xCH_3$), 13.5 (q, $2xCH_3$), 41.4 (t, $2xCH_2$), 41.8 (t, $2xCH_2$), 122.5 (d, CH-3,3'), 124.8 (d, CH-5,5'), 128.4 (d, CH-6,6'), 130.9 (d, CH-4,4'), 149.0 (s, C-2,2'), 156.6 (s, $2xOCONR_2$), C-1,1' not observed

HRFABMS (pos) Calcd for $C_{22}H_{28}N_2O_4$ 385.2127; Found 385.2124

Synthesis of 2,2'-dihydroxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide 20



(nt-5e2)[24,25]

To a solution of 1.7 M *t*-BuLi (30 mL, 50 mmol) and TMEDA (7.5 mL, 50 mmol) in dry THF (100 mL) was slowly added a solution of 2,2'-*N,N*-diethylcarbamoyl-1,1'-biphenyl **19** (7.68 g, 20 mmol) in THF (50 mL) at -78 °C under N_2 atmosphere. The stirred reaction mixture was allowed to attain room temperature overnight and treated with a saturated NH_4Cl solution. The organic solvent was removed in vacuum and the remaining solution was extracted with CH_2Cl_2. The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4), and evaporated to give a viscous oil. After purification by flash column chromatography using EtOAc:hexane as eluent, the white solid **20** was obtained (6.1396 g, 80%).

2,2'-dihydroxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide 20

$C_{22}H_{28}N_2O_4$ (384)

White solid (EtOAc:hexane); mp 140-141 °C

IR (KBr): 3428, 2981, 1600, 1572, 1488, 1450, 1408, 1353, 1311, 1259, 1141 cm^{-1}

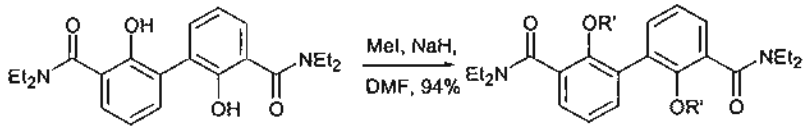
MS (EI): 385 (M^++1, 20), 384 (M^+, 72), 383 (51), 313 (78), 312 (46), 311 (82), 310 (45), 295 (21), 285 (72), 283 (38), 240 (27), 239 (100)

^1H NMR ($CDCl_3$; 200 MHz): ppm 1.27 (t, J = 7.0 Hz, 12H, $4xCH_3$), 3.53 (q, J = 7.0 Hz, 8H, $4xCH_2$), 6.99 (t, J = 7.2, 7.8 Hz, 2H, H-5,5'), 7.31 (dd, J = 1.8, 7.8 Hz, 2H, H-4,4'), 7.38 (dd, J = 2.0, 7.7 Hz, 2H, H-6,6')

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 13.4 (q, 4xCH_3), 41.2 (t, 4xCH_2), 119.3 (d, CH-5,5'), 120.8 (s, C-1,1'), 127.1 (d, CH-4,4'), 127.2 (s, C-3,3'), 133.7 (d,CH-6,6'), 149.0 (s, C-2,2'), 171.0 (s, 2x$CONR_2$)

HRFABMS (pos) Calcd for $C_{22}H_{28}N_2O_4$ 385.2127; Found 385.2128

Synthesis of 2,2'-dimethoxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide 17a



20 **17a**

(nt-5e3)

To a stirred suspension of 60% in oil sodium hydride (0.305 g) in DMF (4 mL) was added a solution of 2,2'-dihydroxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **20** (0.70 g, 1.8 mmol) in DMF (2 mL) at room temperature. The reaction mixture was stirred for 1 h and methyl iodide (0.5 mL, 8 mmol) was then added and stirred for overnight. Water was slowly added and extracted with CH_2Cl_2. The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4), and evaporated to give a viscous oil. After purification by flash column chromatography using EtOAc:hexane as eluent, the white solid, 2,2'-dimethoxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **17a** (0.6973 g, 94%) was obtained.

2,2'-dimethoxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide 17a

$C_{24}H_{32}N_2O_4$ (412)

White solid (EtOAc:hexane); mp 90-92 °C

IR (KBr): 3447,2970, 1630, 1481, 1457, 1431, 1383, 1291, 1245 cm^{-1}

MS (EI): 412 (M^+, 36), 411 (26), 381 (39), 340 (100), 338 (19), 308 (34)

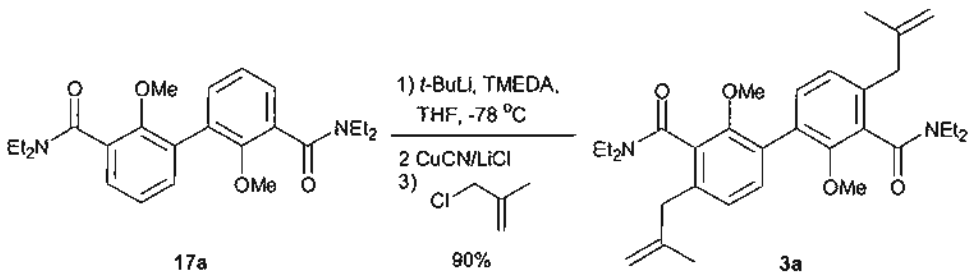
FABMS (pos): 413 (M^++1, 87), 340 (100)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.09 (m, 6H, 2xCH_3), 1.27 (t, *J* = 7.0 Hz, 6H, 2xCH_3), 3.26-3.76 (m, 8H, 4xCH_2), 3.46 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 7.19-7.33 (m, 6H, ArH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 12.7 (q, 2xCH_3), 13.8 (q, 2xCH_3), 39.0 (t, 2xCH_2), 43.0 (t, 2xCH_2), 61.4 (q, 2xOCH_3), 123.8 (d, CH-5,5'), 127.1* (d, CH-4), 127.2* (d, CH-4'), 153.4 (s, C-2,2'), 168.7 (s, 2x$CONR_2$), C-1,1' and C-3,3' not observed

HRFABMS (pos) Calcd for $C_{24}H_{32}N_2O_4$ 413.2440; Found 413.2445

***Sythesis of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide* 3a**



17a 90% **3a**

(TRG-Dios-96)

A 1.7 M solution of *t*-BuLi in pentane (1.7 mL, 2.75 mmol) was added dropwise to solution of TMEDA (0.4 mL, 2.75 mmol) in THF (10 mL) at -78 °C under N_2 atmosphere. The resulting pale yellow solution was stirred for 1 h at this temperature. The solution of 2,2'-dimethoxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **17a** (0.4772 g, 1.1 mmol) in THF (5 mL) was added dropwise over 1-2 min to generate *ortho*-lithiation. Anion formation was allowed to proceed for 1 h at this temperature before transmetalate (Li/Cu) by solution of CuCN (0.246 g, 2.75 mmol) and LiCl (0.1166 g, 2.75 mmol) in THF (5 mL).

After 1.5 h, β-methallychloride (0.4 mL, 4.4 mmol) was added. The reaction was stirred at -78 °C for 2-3 h and then allowed to warm to room temperature for overnight. The reaction was quenched with NH_4Cl and extracted with CH_2Cl_2. The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4), and evaporated to give viscous oil. The residue was purified by flash column chromatography using EtOAc:hexane as eluent to give pale yellow oil **3a** (0.4780 g, 90%).

2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide 3a

$C_{32}H_{44}N_2O_4$ (520)

Pale-yellow solid (EtOAc:hexane); mp 155-157 °C

IR ($CHCl_3$): 2982, 1619, 1460, 1382, 1289, 1217 cm^{-1}

MS (EI): 520 (M^+, 52), 489 (7), 449 (25), 448 (87), 447 939), 420 (18), 375 (100), 374 (28)

FABMS (pos): 521 (M^++1, 6), 448 (25), 147 (53), 73 (100)

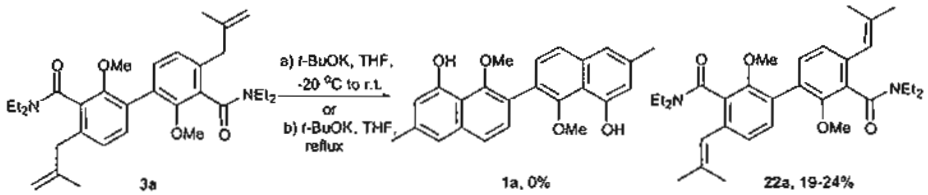
^{1}H NMR ($CDCl_3$; 400 MHz): ppm 0.90 (t, *J* = 7.1 Hz, 3H, CH_3),1.04 (t, *J* = 7.1 Hz, 3H, CH_3), 1.17 (t, *J* = 7.1 Hz, 6H, 2xCH_3), 1.65 (s, 3H, CH_3-4"), 1.67 (s, 3H, CH_3-4'"), 3.04-3.10 (m, 4H, 2xNCH_2), 3.25 (bs, 2H, $ArCH_2$-1"), 3.27 (bs, 2H, $ArCH_2$-1'"), 3.30 (s, 3H, OCH_3), 3.45-3.51 (m, 4H, 2xNCH_2), 3.50 (s, 3H, OCH_3), 4.65 (bs, 1H, =CH-3"), 4.68 (bs, 1H, =CH-3'"), 4.87 (bs, 2H, =CH-3",3'"), 6.98 (d, *J* = 7.9 Hz, 1H, ArH-5), 6.97 (d, *J* = 7.9 Hz, 1H, ArH-5'), 7.12 (d, *J* = 7.9 Hz, 1H, ArH-6'), 7.24 (d, *J* = 7.9 Hz, 1H, ArH-6)

^{13}C NMR ($CDCl_3$; 100 MHz): ppm 12.7 (q, 2xCH_3), 13.4 (q, CH_3), 13.7 (q, CH_3), 22.4 (q, 2xCH_3, C-4",4'"), 38.5 (t, CH_2), 38.6 (t, CH_2), 40.7 (t, 2xCH_2-1",1'"), 42.9 (t, CH_2), 43.1 (t, CH_2), 61.1 (q, OCH_3), 61.5 (q, OCH_3), 112.9 (t, =CH_2-3"), 113.0 (t, =CH_2-3'"), 124.7 (d, =CH-5'), 125.0 (d, =CH-5), 129.0 (s, C-1'), 129.6 (s, C-1), 131.0 (d, =CH-6), 131.3 (d, =CH-6'), 131.7 (s, C-3'), 132.1 (s, C-3), 137.0 (s, C-4), 137.2 (s, C-4'), 143.5 (s, 2x =C-2",2'"), 153.7 (s, 2xC-2,2'), 167.9 (s, $CONR_2$-7), 168.0 (s, $CONR_2$-7')

HRFABMS (pos) Calcd for $C_{32}H_{44}N_2O_4$ 521.3378; Found 521.3374

Synthesis of 1,1'-dimethoxy-6,6'-dimethyl-2,2'-binaphthalenyl-8,8'-diol 1a

A) Using *t*-BuOK as base



(nt-5e10)

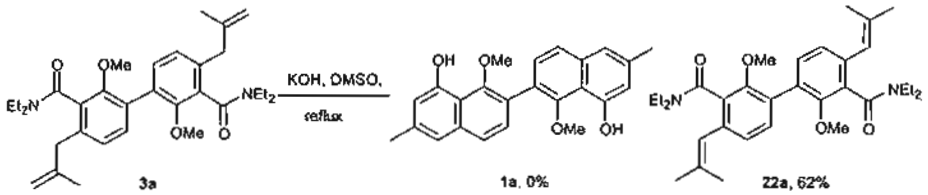
In a round bottom flask, *t*-BuOK (0.4494 mmol) was dried at 90-100 °C for 3h and charged with Ar after vaccum. Fresh dried THF (5 mL) was introduced to *t*-BuOK in one portion at 0 °C. The mixture was vigorously stirred for 30 min. The resulting milky suspension was cooled down to -20 °C with an ice-MeOH bath. 3,3'-*N,N*-Diethylcarboxamide-2,2'-dihydroxy-1,1'-biphenyl **3a** (0.2035 g, 0.4 mmol) in dry THF (2 mL) was added dropwise to the suspension. The resulting yellow suspension was stirred at this temperature for 30 min and then allowed to warm to RT for overnight to give orange suspension.

The reaction was quenched with 2N HCl and extracted with CH_2Cl_2. The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4), and evaporated to give a viscous oil. After purification by flash column chromatography using EtOAc:hexane as eluent, the isomerisation compound, 2,2'-dimethoxy-4,4'-bis(2-methylpropenyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **22a** (0.0369 g, 19%) was obtained.

(nt-5e12)

On the other hand, if the resulting yellow suspension was heated to reflux for overnight, the isomerisation compound, 2,2'-dimethoxy-4,4'-bis(2-methylpropenyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **22a** (0.0286 g, 24%) was obtained (using starting compound **3a** 0.1206 g, 0.2 mmol).

B) Using KOH as base



(nt-5e57)

A mixture of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3a** (0.1209 g, 0.2 mmol) and KOH (0.1406 g) in DMSO (4 mL) was heated to reflux for 14 h. The reaction was quenched with 2N HCl and extracted with CH_2Cl_2. The combine organic layer was washed with water, brine, dried (anhyd Na_2SO_4), and evaporated to give a viscous oil. After purification by flash column chromatography using EtOAc:hexane as eluent, the isomerisation compound, 2,2'-dimethoxy-4,4'-bis(2-methylpropenyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **22a** (0.0738 g, 62%) was obtained.