2,2'-dimethoxy-4,4'-bis(2-methylpropenyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide 22a

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

Pale-yellow solid (EtOAc:hexane); mp 92-94 °C

IR (KBr): 2971, 2927, 1636, 1461, 1360, 1282, 1226, 1029 cm^{-1}

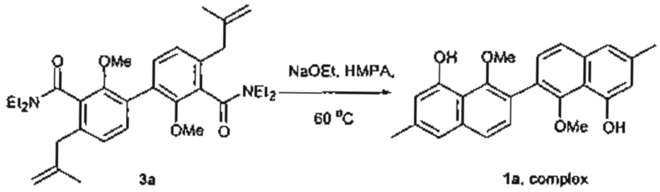
FABMS (pos): 521 (M^++1, 80), 448 (100)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.05 (t, J = 7.2 Hz, 6H, 2xCH_3), 1.24 (t, J = 7.0 Hz, 6H, 2xCH_3), 1.85 (s, 6H, 2xCH_3), 1.88 (s, 6H, 2xCH_3), 3.11 (m, 4H, 2xNCH_2), 3.43 (s, 6H, 2xOCH_3), 3.58 (m, 4H, 2xNCH_2), 6.20 (s, 2H, 2x =CH), 7.07 (d, J = 8.2 Hz, 1H, ArH-5), 7.08 (d, J = 8.2 Hz, 1H, ArH-5'), 7.27 (d, J = 7.8 Hz, 1H, ArH-6), 7.36 (d, J = 8.2 Hz, 1H, ArH-6')

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 12.7 (q, 2xCH_3), 13.5 (q, CH_3), 13.6 (q, CH_3), 19.6 (q, 2xCH_3), 26.5 (q, 2xCH_3), 38.6 (t, CH_2), 38.7 (t, CH_2), 42.7 (t, CH_2), 42.9 (t, CH_2), 61.4 (q, OCH_3), 61.8 (q, OCH_3), 121.9 (t, 2x =CH), 124.8 (d, =CH-5), 125.0 (d, =CH-5'), 126.7 (s, C-1), 129.1 (s, C-3'), 129.5 (s, C-1'), 130.8 (d, =CH-6'), 131.0 (d, =CH-6), 131.6 (s, C-3), 136.2 (s, C-4'), 136.3 (s, C-4), 137.2 (s, 2x =C), 153.4 (s, C-2), 153.7 (s, C-2'), 168.1 (s, 2x$CONR_2$)

HRFABMS (pos) Calcd for $C_{32}H_{44}N_2O_4$ 521.3378; Found 521.3377

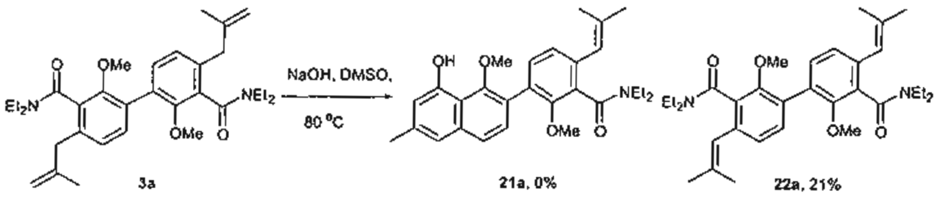
C) Using NaOEt as base



(nt-5e13)

NaOEt was fleshly prepared from Na and absolute EtOH. In a dried round bottom flask, NaOEt (0.2144 g) was suspended in dried HMPA (2 mL). To the suspension 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3a** (0.1227 g, 0.2 mmol) in HMPA (1 mL) was added at RT. The yellow suspension was stirred for 2 h and was allowed to warm to 60 °C overnight. 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. The residue was distillated to remove excess HMPA and then purified by PLC using EtOAc:hexane as eluent to give complex mixture.

D) Using NaH as base



(nt-5e56)

To a stirred suspension of 60% in oil sodium hydride (0.1264 g) in DMSO (2 mL) was added a solution of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3a** (0.1796 g, 0.3 mmol) in DMSO (2 mL) at room temperature. The reaction mixture was stirred at r.t. for 1 h and then was allowed to heat to 80 °C 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 purifiation by flash column chromatography using EtOAc:hexane as eluent, the monocyclisation adduct *N,N*-diethyl-3-(8-hydroxy-1-methoxy-6-methylnaphthalene-2-yl)-2-methoxy-6-(2-methylpropenyl)benzamide **21a** (0.0184 g, 14%) was obtained together with isomerisation compound, 2,2'-dimethoxy-4,4'-bis(2-methylpropenyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **22a** (0.0373 g, 21%).

***N,N*-diethyl-3-(8-hydroxy-1-methoxy-6-methylnaphthalene-2-yl)-2-methoxy-6-(2-methylpropenyl)benzamide 21a**

$C_{27}H_{31}NO_4$ (433)

Pale-yellow semi-solid

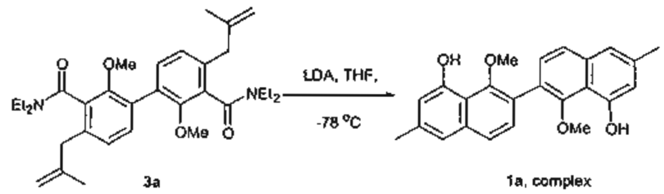
IR (KBr): 2934, 1627, 1460, 1356, 1272, 1223, 1019 cm^{-1}

MS (EI): 434 (M^++1, 4), 433 (M^+, 4), 403 (6), 402 (20), 401 (15), 360 (4), 331 (7), 330 (26), 326 (100), 328 (70), 314 (15), 301 (17)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 1.20 (m, 6H, 2xCH_3), 1.93 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.28 (m, 4H, 2xNCH_2), 3.69 (s, 3H, OCH_3), 6.22 (s, 1H, =CH), 6.51 (bs, 1H, OH), 6.83 (s, 1H, NaphtH-7), 6.95 (d, J = 8.2 Hz, 1H, ArH-5), 7.18 (s, 1H, NaphtH-5), 7.32 (d, J = 8.0 Hz, 1H, NaphtH-4), 7.38 (d, J = 8.0 Hz, 1H, NaphtH-3), 7.60 (d, J = 8.2 Hz, 1H, ArH-4)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 13.3 (q, 2xCH_3), 19.7 (q, CH_3), 21.7 (q, CH_3), 26.5 (q, CH_3), 29.7 (t, 2xCH_2), 62.7 (q, OCH_3), 113.3 (d, C_{Napht}-7), 118.6* (d, C_{Napht}-5), 122.1 (d, =CH), 122.3* (d, C_{Ph}-5), 123.3 (s, C-), 123.6 (s, C-), 125.2 (d, C_{Napht}-4), 129.5* (d, C_{Napht}-3), 130.6 (d, C_{Ph}-4), 136.7 (s, C-), 136.8 (s, C-), 137.5 (s, C-), 138.4 (s, C-), 149.6 (s, C-), 153.7 (s, C-), 168.3 (s, $CONR_2$)

E) Using LDA as base



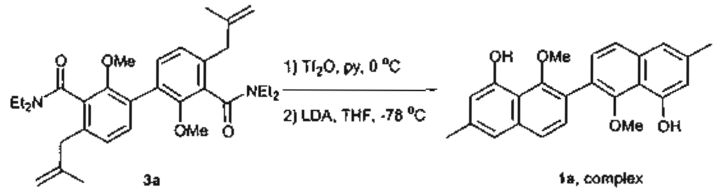
3a

1a, complex

(nt-5e15)

A solution of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3a** (0.2397 g, 0.5 mmol) in THF (5 mL) was added dropwise to a solution of 1.0 M *n*-BuLi (10 mL, 10 mmol) and diisopropylamide (1.4 mL, 10 mmol) in THF (15 mL) at -78 °C under Ar atmosphere. The deep violet solution was maintained for 2 h at this temperature and then quenched with 2N HCl. The reaction was quenched with 2N HCl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine, and dried (anhyd Na_2SO_4). After evaporation a complex mixture (0.0962 g) formed which did not showed any signal of our target.

F) Using LDA as base and activated with triflic anhydride

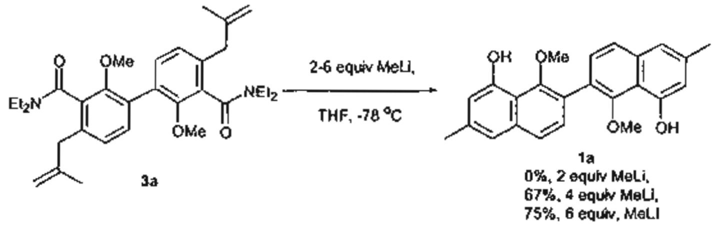


(nt-5e16)

To a solution of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3a** (0.0813 g, 0.15 mmol) in THF (3 mL) was atctivated with triflic anhydride (0.1464 g, 0.5 mmol) and pyridine (0.2 mL) at 0 °C to iminium trifate.

The iminium trifate portion was added dropwise to solution of 1.1 M *n*-BuLi (0.9 mL, 1.0 mmol) and diisopropylamide (0.14 mL, 1.0 mmol) in THF (2 mL) at -78 °C under Ar atmosphere. The mixture was stirred at this temperature and allowed to warm to RT. The reaction was quenched with sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine, dried (anhyd Na_2SO_4) and evaporated to give black crude residue. The resulting crude adduct was purified by PLC to give starting recover **3a** (0.0415 g, 50%).

G) Using MeLi as base (nt-5e8, 2eq) (TRG-Dios-97, 103, 6-4eq)



(TRG-Dios-97)

To a stirred THF (5 mL) solution of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide (0.1316 g, 0.25 mmol) at -78 °C under Ar was added 1.1 mL of a 1.4 M solution of MeLi (1.5 mmol) in Et_2O. The solution turned deep violet and was allowed to warm to *r.t.* and stirred at this temperature for overnight. The reaction was quenched by the addition of 20 mL of sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine and dried (anhyd Na_2SO_4). After evaporation gave crude adduct 0.1196 g which was purified by PLC using CH_2Cl_2:hexane (2:1) as eluent to give white solid as 1,1'-dimethoxy-6,6'-dimethyl-2,2'-binaphthalenyl-8,8-diol **1a** (0.0699 g, 75%).

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

$C_{24}H_{22}O_4$ (374)

Colorless solid (EtOAc:hexane); mp 234-236 °C

IR (KBr): 3321, 2926, 1637, 1573, 1460, 1376, 1354, 1058 cm^{-1}

MS (EI): 374 (M^+, 61), 356 (15), 343 (23), 342 (81), 329 (36), 328 (100)

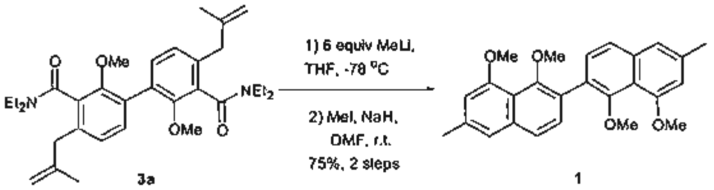
FABMS (neg): inactive

^{1}H NMR ($CDCl_3$; 400 MHz) ppm 2.47 (s, 6H, 2xCH_3), 3.58 (s, 6H, 2xCH_3), 6.82 (d, J = 1.4 Hz, 2H, ArH-7,7'), 7.17 (bs, 2H, ArH-5,5'), 7.50 (d, J = 8.5 Hz, 2H, ArH-4,4'), 7.58 (d, J = 8.5 Hz, 2H, ArH-3,3')

^{13}C NMR ($CDCl_3$; 100 MHz) ppm 21.7 (q, 2xCH_3), 61.8 (q, 2xOCH_3), 112.9 (d, C_{Napht}-7,7'), 115.5 (s, C-8a,8a'), 118.4 (d, C_{Napht}-5,5'), 123.7 (s, C-2,2'), 124.3 (d, C_{Napht}-4,4'), 129.1 (d, C_{Napht}-3,3'), 136.5 (s, C-4a,4a'), 138.7 (s, C-6,6'), 153.4 (s, C-1,1'), 154.1 (s, C-8,8')

HRMS microTOF (ESI+) Calcd for $C_{24}H_{22}O_4$ 375.1591; Found 375.1584

Synthesis of 1,1',8,8'-tetramethoxy-6,6'-dimethyl-2,2'-binaphthalene (tetramethoxydiospyrol)



(TRG-Dios-98)

To a stirred THF (4 mL) solution of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3a** (0.0804 g, 0.15 mmol) at -78 °C under Ar was added 0.64 mL of a 1.4 M solution of MeLi (0.9 mmol) in Et_2O. The solution turned deep violet and was allowed to warm to RT and stirred at this temperature for overnight. The reaction was quenched by the addition of 20 mL of sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine and dried (Na_2SO_4). After evaporation a crude adduct formed as a solid which was used for methylation in next step without purification.

The mixture of crude solid and NaH (0.028 g, 1 mmol) was dissolved with DMF (1 ML). To a suspension MeI (0.3 mL) was added dropwise at 0 °C. The reaction was stirred at RT for 1 h, quenched with water and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine and dried (anhyd Na_2SO_4). Purification by PLC using CH_2Cl_2:hexane (2:1) as eluent to give white solid as tetramethoxydiospyrol 1 (0.045 g, 75% for 2 steps).

1,1',8,8'-tetramethoxy-6,6'-dimethyl-2,2'-binaphthalene (tetramethoxydiospyrol) 1

$C_{26}H_{26}O_4$ (402)

White solid (benzene); mp 239-239.5 °C (lit[17a] 232 °C, lit[17c] 243 °C)

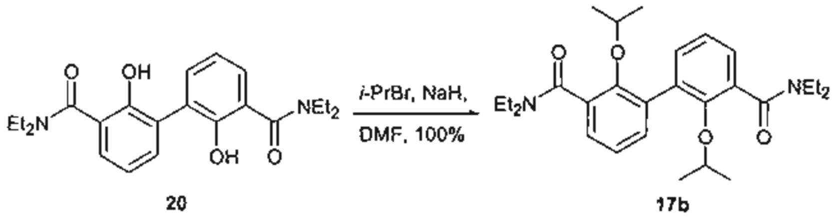
IR (KBr): 1625, 1563, 1451, 1338, 1262 cm^{-1}

MS (EI): 403 ($M+1^+$, 29), 402 (M^+, 100), 357 (21), 341 (25), 298 (8)

^{1}H NMR ($CDCl_3$; 200 MHz): ppm 2.50 (s, 6H, 2xCH_3), 3.55 (s, 6H, 2xOCH_3), 4.01 (s, 6H, 2xOCH_3), 6.73 (s, 2H, ArH-7,7'), 7.26 (s, 2H, ArH-5,5'), 7.52 (d, J = 16.4 Hz, 2H, ArH-4,4'), 7.83 (d, J = 16.8 Hz, 2H, ArH-3,3')

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.8 (q, 2xCH_3), 56.1 (q, 2xOCH_3), 61.4 (q, 2xOCH_3), 108.0, 118.6, 120.0, 122.7, 128.5, 130.8, 135.0, 137.2, 153.6, 156.2

Synthesis of 2,2'-diisoproxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide17b



(NFT-BINAPOPrBr-20)

To a stirred suspension of 60% in oil sodium hydride (0.20 g) in DMF (5 mL) was added a solution of 2,2'-dihydroxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **20** (0.8716 g, 2.2 mmol) in DMF (5 mL) at room temperature. The reaction mixture was stirred for 1 h and 2-brompropane (1.0 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 viscous oil. After purification by flash column chromatography using EtOAc:hexane as eluent, the white solid, 2,2'-diisoproxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **17b** (1.0984 g, 100%) was obtained.

2,2'-diisoproxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide 17b

$C_{28}H_{40}N_2O_4$ (468)

White solid (EtOAc:hexane); mp 114-116 °C

IR (KBr): 2967, 1627, 1428, 1287, 1224, 1112, 1089, 933, 792 cm^{-1}

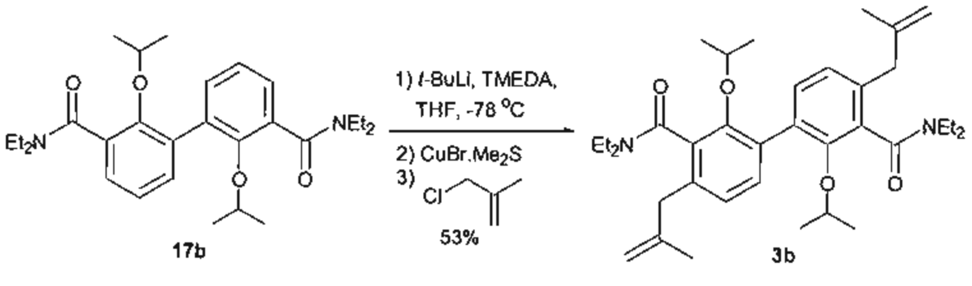
MS (EI): 468 (M^+, 58), 467 (100), 425 (45), 409 (48), 383 (36), 239 (63), 212 (60), 72 (49)

^1H NMR ($CDCl_3$; 400 MHz): ppm 0.96 (bd, J = 5.7 Hz, 6H, $2xCH_3$), 1.00 (d, J = 6.1 Hz, 6H, $2xCH_3$), 1.07 (t, J = 7.1 Hz, 6H, $2xCH_3$), 1.26 (t, J = 7.1 Hz, 6H, $2xCH_3$), 3.22 (h, J = 7.2 Hz, 1H, OCH), 3.30 (m, 4H, $2xNCH_2$), 3.48 (m, 2H, NCH_2), 3.83 (m, 2H, NCH_2), 3.98 (h, J = 7.2 Hz, 1H, OCH), 7.16 (t, J = 7.5 Hz, 2H, ArH-5,5'), 7.29 (m, 4H, ArH-4,4',6,6')

^{13}C NMR ($CDCl_3$; 100 MHz): ppm 12.8 (q, $2xCH_3$), 13.9 (q, $2xCH_3$), 22.3 (q,$4xCH_3$), 39.1 (t, $2xCH_2$), 42.8 (t, $2xCH_2$), 74.8 (d, OCH), 75.7 (d, OCH), 123.5 (d, CH-5,5'), 127.4* (d, CH-4), 128.1* (d, CH-4'), 131.7* (d, CH-6), 132.5* (d, CH-6'), 152.0 (s, C-2,2'), 169.2 (s, $2xCONR_2$), C-1,1' and C-3,3' not observed

HRFABMS (pos) Calcd for $C_{28}H_{40}N_2O_4$ 469.3066; Found 469.3067

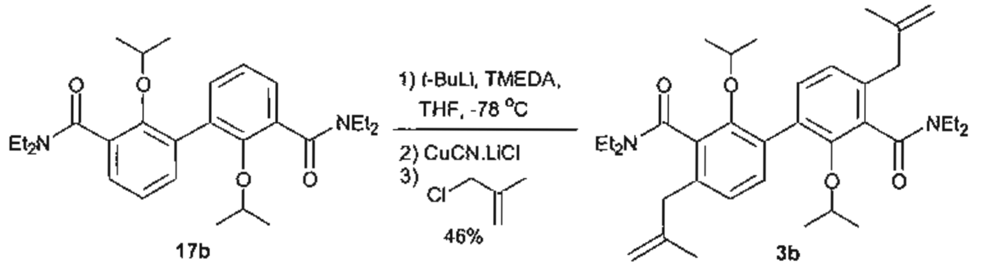
Synthesis of 2,2'-diisoproxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide 3b



Using $CuBr.Me_2S$ (NFT-BINAPOPC4Cl-12)

A 1.7 M solution of *t*-BuLi in pentane (1.8 mL, 3.0 mmol) was added dropwise to solution of TMEDA (0.43 mL, 3.0 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'-diisoproxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **17b** (0.2344 g, 0.5 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 transmetalation (Li/Cu) by solution of $CuBr.Me_2S$ (0.4246 g, 2.0 mmol) in THF (5 mL).

After 1.5 h, β-methallychloride (0.6 mL, 6.0 mmol) was added. The reaction was stirred at -78 °C for 2 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 white solid **3b** (0.1521 g, 53%).



Using CuCN/LiCl (TRG-Dios-100)

Alternatively, using CuCN/LiCl for transmetalation, 1.7 M solution of *t*-BuLi in pentane (0.75 mL, 1.25 mmol) was added dropwise to solution of TMEDA (0.19 mL, 1.25 mmol) in THF (5 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'-diisoproxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **17b** (0.2319 g, 0.5 mmol) in THF (2 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 (0.112 g, 1.25 mmol) and LiCl (0.053 g, 1.25 mmol) in THF (3 mL).

After 1.5 h, β-methallychloride (0.2 mL, 2.0 mmol) was added. The reaction was stirred at -78 °C for 2 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 a viscous oil. The residue was purified by flash column chromatography using EtOAc:hexane as eluent to give white solid **3b** (0.1315 g, 46%).

2,2'-diisoproxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide 3b

$C_{36}H_{52}N_2O_4$ (576)

Yellow oil

IR ($CHCl_3$): 2999, 1719, 1635, 1562, 1435, 1381, 1320, 1278, 1225, 1108 cm^{-1}

MS (EI): 576 (M^+, 26), 534 (24), 517 (38), 503 (29), 491 (23), 475 (24), 462 (79), 461 (67), 446 (24), 420 (47), 419 (39), 404 (36), 389 (39), 364 (31), 348 (45), 347 (100), 346 (84), 331 (71)

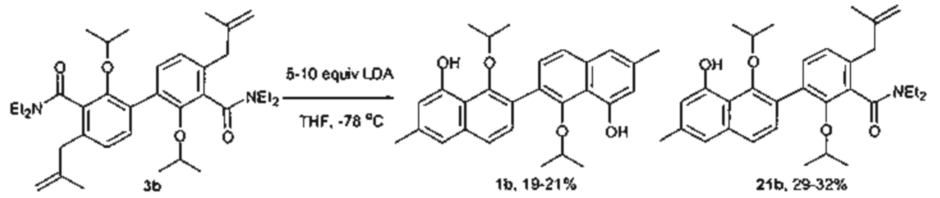
^{1}H NMR ($CDCl_3$; 400 MHz): ppm 0.67 (b, 6H, 2xCH_3), 1.00 (bd, *J* = 5.2 Hz, 6H, 2xCH_3), 1.13 (t, *J* = 7.0 Hz, 6H, 2xCH_3), 1.26 (t, *J* = 7.0 Hz, 6H, 2xCH_3), 1.70 (s, 6H, 2xCH_3-4",4"'), 3.13-3.29 (m, 4H, 2xNCH_2), 3.28 (bs, 2H, ArCH_2-1"'), 3.32 (bs, 2H, ArCH_2-2"), 3.43-3.56 (m, 4H, 2xNCH_2), 4.68 (bs, 1H, =CH-3"), 4.71 (bs, 1H, =CH-3"'), 4.83 (bs, 2H, =CH-3",3"'), 7.02 (d, *J* = 7.6 Hz, 2H, ArH-5,5'), 7.15 (d, *J* = 7.8 Hz, 1H, ArH-6'), 7.49 (bs, 1H, ArH-6)

^{13}C NMR ($CDCl_3$; 100 MHz): ppm 12.7 (q, CH_3), 12.8 (q, CH_3), 13.6 (q, CH_3), 13.7 (q, CH_3), 22.4 (q, 2xCH_3, C-4",4"'), 22.5 (q, 4xCH_3), 38.5 (t, NCH_2), 38.7 (t, NCH_2), 40.9 (t, 2xCH_2, C-1",1"'), 42.9 (t, NCH_2), 43.1 (t, NCH_2), 74.6 (d, OCH), 75.5 (d, OCH), 112.5 (t, =CH_2, C-3"), 112.7 (t, =CH_2, C-3"'), 123.8 (d, CH-5'), 124.8 (d, CH-5), 130.8 (d, C-6), 131.8 (d, C-6'), 144.0 (s, 2x =C-2",2"'), 151.1 (s, C-2'), 152.2 (s, C-2), 168.2 (s, 2x$CONR_2$), C-1, 1', 3, and 3' not observed

HRFABMS (pos) Calcd for $C_{36}H_{52}N_2O_4$ 577.4005; Found 577.4005

Synthesis of 1,1'-diisopropoxy-6,6'-dimethyl-2,2'-binaphthalenyl-8,8'-diol 1b

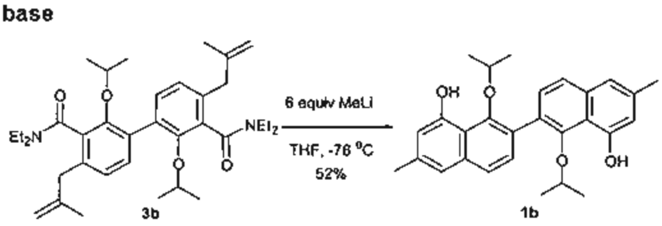
A) Using LDA as base



(NFT-BINAPOPLDA-23)

A solution of 2,2'-diisoproxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3b** (0.1164 g, 0.2 mmol) in THF (5 mL) was added dropwise to solution of 2.5 M *n*-BuLi (1.0 mL, 1.0 mmol) and diisopropylamide (0.14 mL, 1.0 mmol) in THF (5 mL) at -78 °C under Ar atmosphere. The deep violet solution was maintained for 2 h at this temperature and then was kept at r.t. overnight. The reaction was quenched with 2N HCl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine, dried (anhyd Na_2SO_4) and evaporated to give pale yellow viscous oil. After purifiation by flash column chromatography using EtOAc:hexane as eluent, the doublecyclisation adduct, 1,1'-diisopropoxy-6,6'-dimethyl-2,2'-binaphthalenyl-8,8'-diol **1b** (0.018 g, 21%) was obtained together with monocyclisation adduct, *N,N*-diethyl-3-hydroxy-(8-hydroxy-1-isopropoxy-6-methylnaphthalen-2-yl)-2-isopropoxy-6-(2-methylpropenyl)benzamide **21b** (0.032 g, 32%).

B) Using MeLi as base



(NFT-BINAPOPLDA-13)

To a stirred THF (4 mL) solution of 2,2'-diisoproxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bis-diethylamide **3b** (0.1315 g, 0.20 mmol) at -78 °C under Ar was added 0.85 mL of a 1.4 M solution of MeLi in Et_2O. The solution turned deep violet and was allowed to warm to RT and stirred at this temperature for overnight. The reaction was quenched by the addition of 20 mL of sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine and dried (anhyd Na_2SO_4). After evaporation gave crude adduct 0.1196 g which was purified by PLC using CH_2Cl_2:hexane (1:1) as eluent to give white solid as 1,1'-diisopropoxy-6,6'-dimethyl-2,2'-binaphthalenyl-8,8'-diol **1b** (0.0441 g, 52%).

1,1'-diisopropoxy-6,6'-dimethyl-2,2'-binaphthalenyl-8,8'-diol 1b

$C_{28}H_{30}O_4$ (430)

Pale-yellow solid (EtOAc:hexane); mp >240 °C

IR (Neat): 3336, 2922, 1638, 1570, 1462, 1377 cm^{-1}

MS (EI): 430 (M^+, 22), 388 (24), 328 (21), 274 (24), 186 (17), 174 (37), 173 (100)

^1H NMR ($CDCl_3$; 200 MHz): ppm 1.00 (d, J = 6.0 Hz, 12H, 4xCH_3), 2.39 (s, 6H, 2xCH_3), 3.94 (h, J = 6.0, 2H, 2xOCH), 6.70 (d, J = 1.0 Hz, 2H, ArH-7,7'), 7.07 (bs, 2H, ArH-5,5'), 7.46 (d, J = 8.0 Hz, 2H, ArH-4,4'), 7.51 (d, J = 8.0 Hz, 2H, ArH-3,3'), 10.03 (s, 2H, 2xOH)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 22.7 (q, 2xCH_3), 24.5 (q, 2xCH_3), 77.0 (d, 2xOCH), 112.0-112.7 (d, 2xCH-7,7'), 117.5-118.1 (d, 2xCH-5,5'), 123.9-124.1 (d, 2xCH-4,4'), 124.5 (s, C-), 128.8-129.1 (d, 2xCH-3,3'), 136.2 (s, C-), 138.0 (s, C-), 143.2 (s, C-), 150.4 (s, 2xC-), 154.7 (s, 2xC-)

HRMS microTOF (APCI+) Calcd for $C_{28}H_{30}O_4$ 431.2217; Found 431.2200

***N,N*-diethyl-3-(8-hydroxy-1-isopropoxy-6-methylnaphthalen-2-yl)-2-isopropoxy-6-(2-methylpropenyl)benzamide 21b**

$C_{32}H_{41}NO_4$ (503)

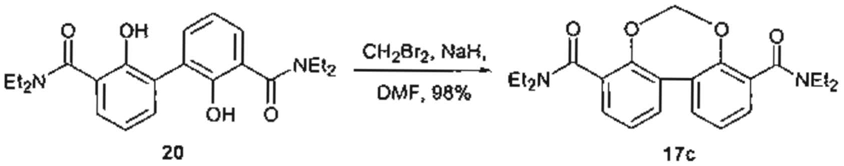
Pale-yellow semi-solid

IR (Neat): 3327, 2977, 2930, 1636, 1436, 1381, 1287, 1224, 1105, 1055 cm^{-1}

^1H NMR ($CDCl_3$; 200 MHz): ppm 1.20 (m, 6H, 2xCH_3), 1.93 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.28 (m, 4H, 2xNCH_2), 3.69 (s, 3H, OCH_3), 6.22 (s, 1H, =CH), 6.51 (bs, 1H, OH), 6.83 (s, 1H, NaphtH-7), 6.95 (d, J = 8.2 Hz, 1H, ArH-5), 7.18 (s, 1H, NaphtH-5), 7.32 (d, J = 8.0 Hz, 1H, NaphtH-4), 7.38 (d, J = 8.0 Hz, 1H, NaphtH-3), 7.60 (d, J = 8.2 Hz, 1H, ArH-4)

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 13.3 (q, 2xCH_3), 19.7 (q, CH_3), 21.7 (q, CH_3), 26.5 (q, CH_3), 29.7 (t, 2xCH_2), 62.7 (q, OCH_3), 113.3 (d, C_{Napht}-7), 118.6* (d, C_{Napht}-5), 122.1 (d, =CH), 122.3* (d, C_{Ph}-5), 123.3 (s, C-), 123.6 (s, C-), 125.2 (d, C_{Napht}-4), 129.5* (d, C_{Napht}-3), 130.6 (d, C_{Ph}-4), 136.7 (s, C-), 136.8 (s, C-), 137.5 (s, C-), 138.4 (s, C-), 149.6 (s, C-), 153.7 (s, C-), 168.3 (s, $CONR_2$)

Synthesis of 5,7-dioxadibenzo[a,c]cycloheptane-4,8-dicarboxylic acid bis-diethylamide 17c



(TRG-Dios-24)

To a stirred suspension of 60% in oil sodium hydride (0.08 g) in DMF (1 mL) was added a solution of 2,2'-dihydroxybiphenyl-3,3'-dicarboxylic acid bis-diethylamide **20** (0.3986 g, 1 mmol) in DMF (1 mL) at room temperature. The reaction mixture was stirred for 1 h and dibromomethane (0.5 mL) 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 viscous oil. After purification by flash column chromatography using EtOAc:hexane as eluent, the white solid, 5,7-dioxadibenzo[*a*,*c*]cycloheptane-4,8-dicarboxylic acid bis-diethylamide **17c** (0.3878 g, 98%) was obtained.

5,7-dioxadibenzo[*a*,*c*]cycloheptane-4,8-dicarboxylic acid bis-diethylamide 17c

$C_{23}H_{28}N_2O_4$ (396)

White solid (EtOAc:hexane); mp 159-161 °C

IR (KBr): 2976, 1627, 1489, 1434, 1292, 1078, 1013 cm^{-1}

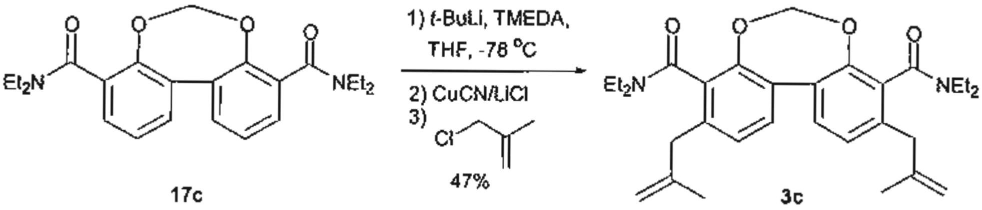
MS (EI): 396 (M$^+$, 17), 395 (23), 297 (84), 294 (19), 157 (24), 139 (93), 86 (100)

^{1}H NMR ($CDCl_3$; 400 MHz, run at 60 °C): ppm 1.05 (t, *J* = 7.0 Hz, 6H, 2xCH_3), 1.25 (t, *J* = 7.0 Hz, 6H, 2xCH_3), 3.20 (q, *J* = 7.0 Hz, 4H, 2xNCH_2), 3.58 (m, 4H, 2xNCH_2), 5.66 (s, 2H, OCH_2O), 7.28 (m, 4H, ArH-5,5',6,6'), 7.59 (d, *J* = 6.3 Hz, 2H, ArH-4,4')

^{13}C NMR ($CDCl_3$; 100 MHz): ppm 12.8 (q, 2xCH_3), 14.0 (q, 2xCH_3), 38.9 (t, 2xCH_2), 43.0 (t, 2xCH_2), 102.5 (t, OCH_2O), 124.9 (d, CH-6,6'), 126.6 (d, CH-5,5'), 128.9 (d, CH-4,4'), 132.0 (s, C-3,3'), 150.0 (s, C-2,2'), 167.8 (s, 2x$CONR_2$), C-1,1' not observed

HRFABMS (pos) Calcd for $C_{23}H_{28}N_2O_4$ 397.2127; Found 397.2129

***Synthesis of 3,9-bis-(2-methylallyl)-5,7-dioxadibenzo[a,c]cycloheptane-4,8-dicarboxylic acid bis-diethylamide* 3c**



(TRG-Dios-76)

A solution of 1.7 M solution of *t*-BuLi in pentane (0.75 mL, 1.25 mmol) was added dropwise to a solution of TMEDA (0.19 mL, 1.25 mmol) in THF (5 mL) at -78 °C under N_2 atmosphere. The resulting pale yellow solution was stirred for 1 h at this temperature. The solution of 5,7-dioxadibenzo[*a*,*c*]cycloheptane-4,8-dicarboxylic acid bis-diethylamide **17c** (0.1891 g, 0.5 mmol) in

THF (2 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 transmetalation (Li/Cu) by solution of CuCN (0.112 g, 1.25 mmol) and LiCl (0.053 g, 1.25 mmol) in THF (3 mL).

After 1.5 h, β-methallychloride (0.2 mL, 2.0 mmol) was added. The reaction was stirred at -78 °C for 2 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 white solid **3c** (0.1195 g, 47%).

3,9-bis-(2-methylallyl)-5,7-dioxadibenzo[*a,c*]cycloheptane-4,8-dicarboxylic acid bis-diethylamide 3c

$C_{31}H_{40}N_2O_4$ (504)

White solid (EtOAc:hexane); mp 120-122 °C

IR (KBr): 3451, 2976, 2932, 1630, 1455, 1381, 1287, 1223, 1077, 1025, 754 cm^{-1}

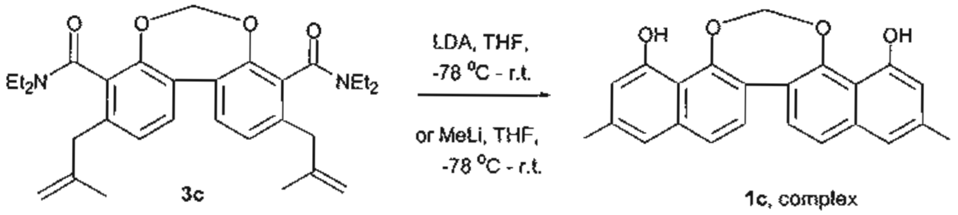
MS (EI): 505 (M^++1, 9), 504 (M^+, 6), 452 (26), 451 (97), 450 (52), 432 (10), 379 (49), 378 (100), 377 (85), 348 (41), 347 (50), 305 (24)

^{1}H NMR ($CDCl_3$; 400 MHz): ppm 1.00 (t, *J* = 7.1 Hz, 3H, CH_3),1.07 (t, *J* = 7.1 Hz, 3H, CH_3), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 1.71 (s, 3H, CH_3-4‴), 1.72 (s, 3H, CH_3-4″), 3.05-3.20 (m, 4H, 2xNCH_2), 3.29, 3.24 (ABq, *J* = 15.5 Hz, 2H, ArCH_2-1″), 3.31 (bs, 2H, ArCH_2-1‴), 3.45-3.73 (m, 4H, 2xNCH_2), 4.72 (bs, 1H, =CH-3‴), 4.74 (bs, 1H, =CH-3″), 4.88 (bs, 2H, =CH-3″,3‴), 5.37, 5.65 (d, *J* = 6.2 Hz, 2H, OCH_2O), 5.58 (s, 2H, OCH_2O), 7.06 (d, *J* = 8.3 Hz, 1H, ArH-5′), 7.12 (d, *J* = 8.1 Hz, 1H, ArH-5), 7.52 (d, *J* = 8.1 Hz, 1H, ArH-6), 7.67 (d, *J* = 8.3 Hz, 1H, ArH-6′)

^{13}C NMR ($CDCl_3$; 100 MHz): ppm 12.6 (q, CH_3), 12.7 (q, CH_3), 13.7 (q, 2xCH_3), 22.4 (q, 2xCH_3, C-4″,4‴), 38.3 (t, 2xCH_2), 40.5 (t, CH_2-1‴), 40.6 (t, CH_2-1″), 42.8 (t, 2xCH_2), 96.8 (t, OCH_2O), 100.4 (t, OCH_2O), 113.1 (t, =CH_2-3‴), 113.2 (t, =CH_2-3″), 123.2 (s, C-1′), 124.2 (s, C-1), 125.0 (d, =CH-5′), 125.6 (d, =CH-5), 127.9 (d, =CH-6), 128.3 (d, =CH-6′), 129.7 (s, C-3′), 130.7 (s, C-3), 136.9 (s, 2xC-4,4′), 143.4 (s, 2x =C-2″,2‴), 150.2 (s, C-2), 152.1 (s, C-2′), 167.1 (s, 2x$CONR_2$-7,7′)

HRFABMS (pos) Calcd for $C_{31}H_{40}N_2O_4$ 505.3066; Found 505.3070

Cyclization of 3,9-bis-(2-methylallyl)-5,7-dioxadibenzo[a,c]cycloheptane-4,8-dicarboxylic acid bis-diethylamide 1c



3c

1c, complex

A) Using LDA as base (TRG-Dios-80, 84)

A solution of 3,9-bis-(2-methylallyl)-5,7-dioxadibenzo[*a,c*]cycloheptane-4,8-dicarboxylic acid bis-diethylamide **3c** (0.1294 g, 0.25 mmol) in THF (5 mL) was added dropwise to solution of 2.5 M *n*-

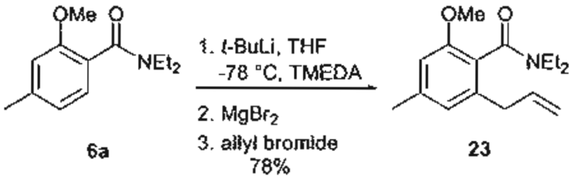
BuLi (0.4 mL, 1.0 mmol) and diisopropylamide (0.15 mL, 1.0 mmol) in THF (5 mL) at -78 °C under Ar atmosphere. The deep violet solution was maintained for 2 h at this temperature and then was allowed to r.t. overnight. The reaction was quenched with 2N HCl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine, dried (anhyd Na_2SO_4), and evaporated to give pale yellow viscous oil as complex mixture. After purifiation by flash column chromatography using EtOAc:hexane as eluent, no any fraction show signal of our target molecule.

B) Using MeLi as base (TRG-Dios-99)

To a stirred THF (3 mL) solution of 3,9-bis-(2-methylallyl)-5,7-dioxadibenzo[**a,c**]cycloheptane-4,8-dicarboxylic acid bis-diethylamide **3c** (0.05 g, 0.1 mmol) at -78 °C under Ar was added 0.43 mL of a 1.4 M solution of MeLi (0.6 mmol) in Et_2O. The solution turned deep violet and was allowed to warm to RT and stirred at this temperature for overnight. The reaction was quenched by the addition of 10 mL of sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine, and dried (anhyd Na_2SO_4). After evaporation gave complex adduct which did not show any signal of our target molecule.

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

Synthesis of N,N-Diethyl-2-allyl-6-methoxy-4-methylbenzamide 23



To a stirred solution of *N,N*-diethyl-6-methoxy-4-methylbenzamide **6a** (2.0 g, 9.05 mmol) and TMEDA (1.5 mL, 10.0 mmol) in anhyd THF (50 mL) at -78 °C was slowly added *t*-BuLi (1.0 M, 10.85 mL, 10.85 mmol) and further stirred for 1 h. $MgBr_2$ etherate (4 mL) was added and the soln was warmed to r.t. The mixture was recooled to -78 °C and continued to stir for 40 min. Allyl bromide (1.5 mL, 17.96 mmol) was then added and the reaction mixture was warmed to r.t. and stirred overnight. Sat. NH_4Cl was added and extracted with CH_2Cl_2 (2x40 mL), washed with H_2O, brine, and dried (anhyd Na_2SO_4). CH_2Cl_2 was evaporated to dryness to give a viscous oil (2.5 g). Further purification by column chromatography (SiO_2, 25% EtOAc/hexane) gave the required allylamide **23** as viscous oil (1.85 g, 78%) together with starting compound (230 mg).

***N,N*-Diethyl-2-allyl-6-methoxy-4-methylbenzamide 23**

$C_{14}H_{18}NO_2$ (261)

Viscous oil

IR (KBr): 1631, 1578 cm^{-1}

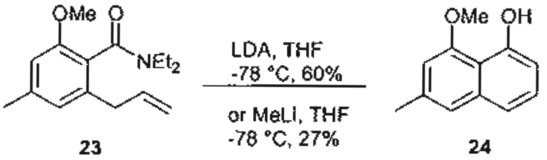
MS (EI): 262 (M^{+}+1, 42), 261 (M^{+}, 32), 190 (24), 189 (100), 188 (76), 161 (88), 161 (88), 143 (27), 105 (23)

^{1}H NMR (CDCl$_3$, 200 MHz): ppm 1.02 (t, J = 7 Hz, 3H, CH$_3$), 1.24 (t, J = 7 Hz, 3H, CH$_3$), 2.32 (s, 3H, CH$_3$), 3.05 (m, 2H, NCH$_2$), 3.30 (d, J = 7 Hz, 2H, CH$_2$), 3.40 (m, 1H, NCH), 3.77 (m, 1H, NCH), 3.77 (s, 3H, OCH$_3$), 5.07 (m, 2H, =CH$_2$), 5.93 (m, 1H, =CH), 6.56 (s, 1H, H-5), 6.66 (s, 1H, H-3)

^{13}C NMR (CDCl$_3$, 50 MHz): ppm 12.7, 13.7, 21.6, 36.9, 38.3, 42.6, 55.4, 109.4, 116.0, 122.3, 123.5, 136.7, 137.6, 139.23, 155.4, 168.2

HRMS-FAB: *m/z* [M+H$^+$] Calcd for $C_{18}H_{23}NO_2$: 262.1807; Found: 262.1806

Synthesis of 6-Methyl-8-methoxy-1-naphthol 24



A) Using LDA as base

Diisopropylamine (2.4 mL, 16.86 mmol) was added by syringe to 50 mL of anhyd THF. *n*-BuLi (1.2 M, 13.4 mL) was added at -78 °C and the solution was warmed to 0 °C and further stirred for 20 min. The solution was then cooled to -78 °C and a solution of allylamide **23** (2.0 g, 7.66 mmol) in anhyd THF (20 mL) was slowly added and stirring was continued at -78 °C for 3 h and then warmed to r.t. overnight. Sat. NH$_4$Cl was added and extracted with CH$_2$Cl$_2$ (2x40 mL), washed with H$_2$O, brine, and dried (anhyd Na$_2$SO$_4$). Further purification by column chromatography (SiO$_2$, CH$_2$Cl$_2$) gave the required naphthol **24** as pale brown viscous oil (860.0 mg, 60%).

B) Using MeLi as base

To a stirred THF (2 mL) solution of allylamide **23** (0.524 g, 0.2 mmol) at -78 °C under Ar was added 0.43 mL of a 1.4 M solution of MeLi (0.6 mmol) in Et$_2$O. The solution turned deep violet and was allowed to warm to r.t. and stirred at this temperature for overnight. The reaction was quenched by the addition of 10 mL of sat NH$_4$Cl and extracted with CH$_2$Cl$_2$. The organic layer was combined, washed with water, brine and dried (anhyd Na$_2$SO$_4$). Further purification by column chromatography (SiO$_2$, CH$_2$Cl$_2$) gave the required naphthol **24** as pale brown viscous oil (0.086 mg, 27%).

6-Methyl-8-methoxy-1-naphthol 24[31]

$C_{12}H_{12}O_2$ (188)

Pale brown viscous oil

IR (KBr): 3404 cm^{-1}

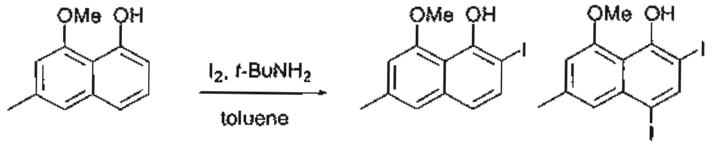
MS (EI): 189 (M$^+$+1, 16), 188 (M$^+$, 100), 145 (9), 115 (7)

^{1}H NMR (CDCl$_3$, 200 MHz) ppm 2.42 (s, 3H, CH$_3$), 3.99 (s, 3H, OCH$_3$), 6.56 (d, J = 1.2 Hz, 1H, H-7), 6.79 (dd, J = 7.6, 1.2 Hz, 1H, H-2), 7.16 (s, 1H, H-5), 7.18 (dd, J = 7.6, 1.2 Hz, 1H, H-4), 7.30 (t, J = 8 Hz, 1H, H-3), 9.25 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 50 MHz) ppm 21.8, 56.0, 106.1, 109.5, 113.3, 118.2, 120.8, 127.7, 135.5, 136.9, 154.4, 155.9

HRMS-FAB: *m/z* $[M-H^-]$ Calcd for $C_{12}H_{12}O_2$: 187.0759; Found: 187.0753

Representative procedure for the halogenation of 6-methyl-8-methoxy-1-naphthol 24



24 **26**, **58%** **27**, **14%**

To a stirred soln of *t*-butylamine (2.14 mL, 20.27 mmol) in dry toluene (20 mL) was added a soln of I_2 (2.58 g, 10.16 mmol) in dry toluene (35 mL) at r.t. and further stirred for 1 h. The resulting soln was then transferred to a stirred soln of naphthol **24** (1.91 g, 10.16 mmol) in dry toluene (25 mL) at 0 °C via canular. After the addition was complete, the reaction was further stirred for 10 min. Sat. $Na_2S_2O_3$ (30 mL) was added and extracted with EtOAc (30 mL). The combined extracts were washed with water, dried (anhyd Na_2SO_4) and evaporated to dryness. Further purification was carried out by column chromatography (SiO_2, 5% EtOAc/Hexane) to obtain *o*-iodonaphthol **26** (1.87 g, 58%) and *o,p*-diiodonaphthol **27** (603.6 mg, 14%).

2-Iodo-6-methyl-8-methoxy-1-naphthol 26

$C_{12}H_{11}IO_2$ (314)

White solid (CH_2Cl_2:hexane); mp 116-116.5 °C

IR (KBr): 3320, 1626, 1603, 1579, 1495, 1403, 1370 cm^{-1}

MS (EI): *m/z* (%) 315 (M^++1, 12), 314 (M^+, 100), 299 (34), 188 (26), 172 (34)

^{1}H NMR ($CDCl_3$, 200 MHz): ppm 2.42 (s, 3H, CH_3), 4.01 (s, 3H, OCH_3), 6.62 (s, 1H, H-7), 6.95 (d, *J* = 8.8 Hz, 1H, H-4), 7.14 (s, 1H, H-5), 7.64 (d, *J* = 8.8 Hz, 1H, H-3), 10.16 (s, 1H, OH)

^{13}C NMR (50 MHz, $CDCl_3$): ppm 21.9, 56.3, 107.0, 113.1, 119.7, 120.8, 136.4, 136.5, 153.2, 154.8

HRMS-FAB: *m/z* $[M-H^-]$ calcd for $C_{12}H_{11}IO_2$: 312.9724; found: 312.9726

2,4-Diiodo-6-methyl-8-methoxy-1-naphthol 27

$C_{12}H_{10}I_2O_2$ (440)

White solid (CH_2Cl_2:hexane); decomposed

IR (KBr): 3266, 1623, 1604, 1557, 1449, 1407, 1355 cm^{-1}

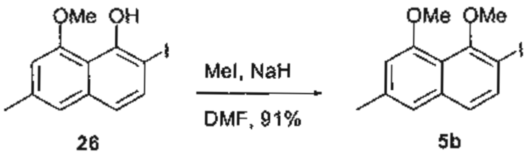
MS (EI): *m/z* (%) 441 (M^++1, 14), 440 (M^+, 100), 425 (27), 298 (25)

^{1}H NMR ($CDCl_3$, 200 MHz): ppm 2.49 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 6.71 (s, 1H, H-7), 7.43 (s, 1H, H-5), 8.25 (s, 1H, H-3), 10.38 (s, 1H, OH)

^{13}C NMR ($CDCl_3$, 50 MHz): ppm 22.2, 56.7, 85.8, 107.8, 113.4, 125.7, 136.3, 138.2, 146.2, 154.4, 154.8

Anal. Calcd for $C_{12}H_{10}I_2O_2$: C, 32.76; H, 2.29. Found: C, 33.01; H, 2.12

Representative procedure for methylation of 2-iodo-1-hydroxy-8-methoxy-6-methylnaphthalene 26



To a stirred suspension of NaH (60% in oil) (179 mg, 5.97 mmol) in DMF (5 mL) was added a soln of iodonaphthol **26** (1.25 g, 3.98 mmol) in DMF (10 mL) at r.t. The reaction mixture was stirred for 1 h and MeI (0.5 mL, 8 mmol) was then added and stirred overnight. H_2O was slowly added and extracted with EtOAc (2x25 mL). The combined EtOAc extracts were washed with water, brine and dried (anhyd Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, 2-5% EtOAc/Hexane) to obtain 1,8-dimethoxy-2-iodo-6-methylnaphthalene **5b** as viscous oil (1.19 g, 91%).

1,8-Dimethoxy-2-iodo-6-methylnaphthalene 5b

$C_{13}H_{13}IO_2$ (328)

Viscous oil

IR (Neat): 2929, 1625, 1568, 1454, 1330 cm^{-1}

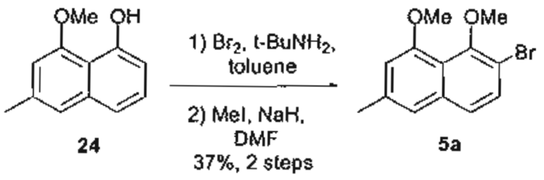
MS (EI): *m/z* (%) 329 (M^++1, 19), 328 (M^+, 100)

^1H NMR ($CDCl_3$, 200 MHz): ppm 2.45 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.72 (s, 1H, H-7), 7.17 (s, 1H, H-5), 7.20 (d, J = 8.8 Hz. 1H, H-4), 7.72 (d, J = 8.8 Hz, 1H, H-3)

^{13}C NMR ($CDCl_3$, 50 MHz): ppm 21.8, 56.3, 61.7, 88.5, 108.9, 119.0, 120.1, 125.2, 135.9, 136.8, 137.6, 155.0, 155.9

HRMS-FAB: *m/z* [$M+H^+$] Calcd for $C_{13}H_{13}IO_2$: 329.0037; Found: 329.0030

Synthesis of 2-bromo-1,8-dimethoxy-6-methylnaphthalene 5a



To a stirred solution of *t*-butylamine (0.2 mL, 2.0 mmol) in dry toluene (2 mL) was added a solution of Br_2 (0.167 g, 1.0 mmol) in dry toluene (2 mL) at -78 °C and further stirred for 1 h. The resulting solution was then transferred to a stirred solution of naphthol **24** (0.1812 g, 1.0 mmol) in dry toluene (1 mL) at 0 °C via canular. After the addition was complete, the reaction was further stirred for 2 h. The reaction was quenched with water and extracted with EtOAc (30 mL). The combined extracts was washed with water, dried (anhyd Na_2SO_4) and evaporated to dryness. Further purification was carried out by column chromatography (SiO_2, 10% EtOAc/Hexane) to obtain crude residue which was used for methylation in the next step without purification.

To a stirred suspension of NaH (60% in oil) (0.08 g) in DMF (1 mL) was added a solution of bromonaphthol residue in DMF (1 mL) at r.t. The reaction mixture was stirred for 10 min and MeI (0.5 mL) was then added and stirred 2-3 h. The reaction was quenched with water and extracted with CH_2Cl_2. The combined extracts were washed with water, dried (anhyd Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, 10% EtOAc/Hexane) to obtain 1,8-dimethoxy-2-bromo-6-methylnaphthalene **5a** as viscous oil (0.118 g, 37% 2 steps).

2-bromo-1,8-dimethoxy-6-methylnaphthalene 5a

$C_{13}H_{13}BrO_2$ (280)

Viscous oil

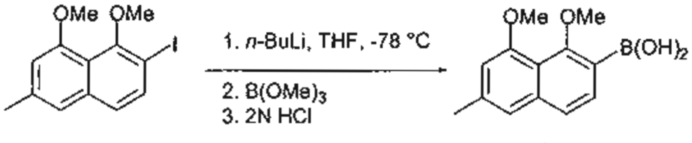
IR (Neat): 2940, 2840, 1597, 1462, 1355, 1264, 1079, 747 cm^{-1}

MS (GC): *m/z* (%) 282 (M^++2, 100), 280 (M^+, 97), 209 (28), 207 (33), 186 (83), 158 (91), 139 (30), 128 (81), 115 (56)

^{1}H NMR ($CDCl_3$, 200 MHz): ppm 2.39 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.67 (s, 1H, H-7), 7.10 (s, 1H, H-5), 7.23 (d, *J* = 8.8 Hz, 1H, H-4), 7.47 (d, *J* = 8.8 Hz, 1H, H-3)

^{13}C NMR ($CDCl_3$, 50 MHz): ppm 21.8, 56.3, 61.6, 109.1, 113.9, 119.6, 120.1, 124.6, 130.6, 136.6, 136.7, 153.1, 155.3

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



5b 72% **4**

To a stirred solution of iodonaphthalene **5b** (301.7 mg, 0.92 mmol) in THF (7 mL) at -78 °C under argon atm was added *n*-BuLi (1.12 mL, 1.84 mmol) followed immediately by $B(OMe)_3$ (200 μL, 1.78 mmol). After stirring at -78 °C for 30 min, the reaction mixture was warmed to r.t. and stirred for 1 h. The resulting mixture was quenched with 2*N* HCl and extracted with CH_2Cl_2 (2x20 mL). The combined extracts were washed with water, brine, and dried (anhyd Na_2SO_4). The solvent was removed to obtain a crude boronic acid which was purified by PLC (SiO_2, 1% $MeOH/CH_2Cl_2$) to give boronic acid **4** as white solid (163 mg, 72%).

1,8-Dimethoxy-6-methylnaphthalene-2-boronic acid 4

$C_{13}H_{15}BO_4$ (246)

White solid (CH_2Cl_2:hexane); mp 157.5-158 °C

IR (KBr): 2937(broad), 1610, 1605, 1572, 1467, 1376 cm^{-1}

MS (EI): *m/z* (%) = 245 (27), 231 (14), 204 (75), 202 (15), 201 (22), 191 (22)

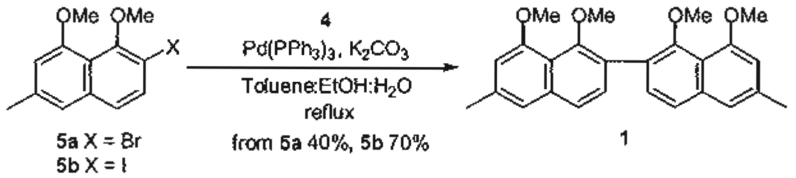
^{1}H NMR ($CDCl_3$, 200 MHz): ppm 2.49 (s, 3 H, CH_3), 3.9 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 6.71 (s, 2 H, 2 OH), 6.74 (s, 1 H, H-7), 7.24 (s, 1 H, H-5), 7.52 (d, *J* = 16.4 Hz, 1 H, H-4), 7.83 (d, *J* = 16.8 Hz, 1 H, H-3)

^{13}C NMR ($CDCl_3$, 50 MHz): ppm 21.9, 56.1, 63.8, 108.4, 117.3, 120.4, 123.9, 132.0, 137.7, 139.9, 155.7, 163.8

Anal. Calcd for $C_{13}H_{15}BO_4$: C, 63.45; H, 6.14. Found: C, 63.32; H, 5.77

Preparation of tetramethoxydiospyrol 1

Using classical Suzuki-Miyaura cross-coupling reaction

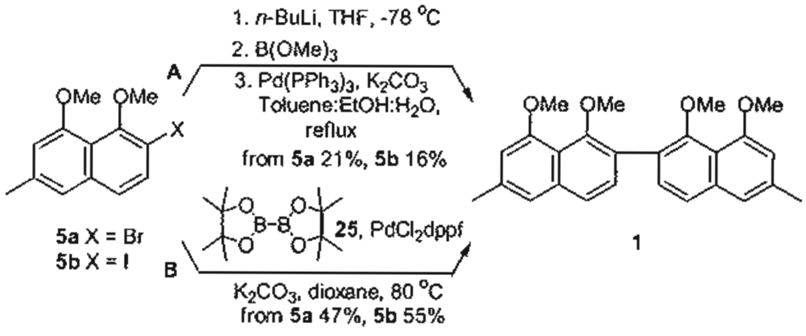


5a X = Br
5b X = I

1

A mixture of iodonaphthalene **5b** (158.5 mg, 0.48 mmol), naphthaleneboronic acid **4** (118.9 mg, 0.48 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol%) and K_2CO_3 (133 mg, 0.96 mmol) in a mixture of toluene:EtOH:H_2O (3:3:2, 8 mL) was refluxed at 115-120 °C for 19 h. After cooling of the reaction mixture, water was added and extracted with EtOAc (2x20 mL). The combined EtOAc extracts were washed with water, brine and dried (anhyd Na_2SO_4). Further purification was carried out by PLC (SiO_2, 0.5% MeOH/CH_2Cl_2) to give tetramethoxydiospyrol which was recrystallized from benzene to afford compound 1 as white crystal (136.2 mg, 70%).

Using modified *in situ* Suzuki cross-coupling



5a X = Br
5b X = I

1

Method A

To a solution of bromonaphthalene **5a** (150 mg, 0.5 mmol) in THF (10 mL) at -78 °C was added 0.5 equiv of 0.77 M of *n*-BuLi (0.4 mL) followed by 6 equiv of $B(OMe)_3$ (0.8 mL). The resulting solution was warmed to r.t. for 4 h and subsequently stirred overnight under argon atm. To the solution were then added toluene (6 mL), EtOH (6 mL), water (4 mL), K_2CO_3 (130 mg, 1.0 mmol), and $Pd(PPh_3)_4$ (2 mg, 10 mol%). The resulting mixture was refluxed under argon atm for 10 h. The reaction was allowed to warm to r.t. and extracted with CH_2Cl_2 (3x30mL). The organic phases were combined, washed with H_2O, dried (anhyd Na_2SO_4), and concentrated under reduced pressure to afford the crude binaphthalene which was purified on PLC to yield recovered bromonaphthalene **5a** (60 mg, 37%), tetramethoxydiospyrol **1** (40 mg, 21%) and debromonaphthalene (30 mg, 26%).

Method B

A mixture of iodonaphthalene **5b** (165.4 mg, 0.5 mmol), bis(pinacolato)diboron (63.5 mg, 0.25 mmol), $PdCl_2dppf$ (14.6 mg, 4 mol%), and K_2CO_3 (207 mg, 1.5 mmol) in dioxane (5 mL) was heated at 80 °C for 16 h. After cooling of the reaction mixture, water was added and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water, 20% aq NaOH, and dried (anhyd Na_2SO_4). Further purification was carried out by PLC (SiO_2, 0.5% $MeOH/CH_2Cl_2$) to give a white solid of tetramethoxydiospyrol **1** (54.9 mg, 55%)

Tetramethoxydiospyrol 1

$C_{26}H_{26}O_4$ (402)

White solid (Benzene); mp 239-239.5 °C (lit[17a] 232 °C, lit[17c] 243 °C)

IR (KBr): 1625, 1563, 1451, 1338, 1262 cm^{-1}

MS (EI): *m/z* (%) 403 ($M+1^+$, 29), 402 (M+, 100), 357 (21), 341 (25), 298 (8).

^1H NMR ($CDCl_3$; 200 MHz): ppm 2.50 (s, 6 H, $2xCH_3$), 3.55 (s, 6 H, $2xOCH_3$), 4.01 (s, 6 H, $2xOCH_3$), 6.73 (s, 2 H, H-7,7'), 7.26 (s, 2 H, H-5,5'), 7.52 (d, *J* = 16.4 Hz, 2 H, H-4,4'), 7.83 (d, *J* = 16.8 Hz, 2 H, H-3,3')

^{13}C NMR ($CDCl_3$; 50 MHz): ppm 21.8, 56.1, 61.4, 108.0, 118.6, 120.0, 122.7, 128.5, 130.8, 135.0, 137.2, 153.6, 156.2

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Output

Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.

ผลงานตีพิมพ์ในระหว่างที่ได้รับทุนจาก สกว. มีจำนวน 3 บทความ โดยเป็นผลงานที่ได้เสนออยู่ในโครงการวิจัย 2 บทความ และเป็นบทความที่ได้ศึกษาในระหว่างที่ได้รับทุนจาก สกว. อีกจำนวน 1 บทความ

นอกจากนี้ ได้นำเสนอผลงานวิจัยในรูปแบบโปสเตอร์ทั้งในและต่างประเทศ มีจำนวน 7 บทความ

ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ (Publications)

1. **Nopporn Thasana**, Somchai Pisuthjaroenpong, Somsak Ruchirawat. "Two Protocols for the conversion of Biphenol to Binaphthol: Synthesis of Diospyrol" Synlett, accepted.
2. Poolsak Sahakitpichan, **Nopporn Thasana**, Somsak Ruchirawat. "Efficient Synthesis of Diospyrol via Suuzuki-Miyaura and Modified in situ Cross-Coupling" *Synthesis* **2005**, inpress.
3. Rattana Worayuthakarn, **Nopporn Thasana**, Somsak Ruchirawat. "An Effective Route to Imidazoloisoquinolines and Benzo[a]quinolizidines", manuscript submitted.

การนำเสนอผลงานวิจัยในต่างประเทศ (International Presentations)

1. **Thasana, N.**; Mahidol, C.; Ruchirawat, S. Total synthesis of wrightiadione. *ICOB-4 & ISCNP-24*, New Delhi, India, **2004**, P-390
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Title: Two Protocols for the Conversion of Biphenol to Binaphthol: Synthesis of Diospyrol

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Two Protocols for the Conversion of Biphenol to Binaphthol: Synthesis of Diospyrol

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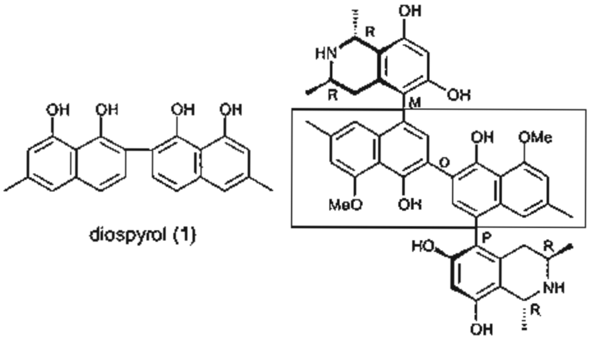
Abstract: The application of directed *ortho* metalation (DoM), Fries rearrangement and transmetalation followed by allylation and cyclization is reported for the conversion of biphenol to binaphthol as a means for the synthesis of diospyrol. Furthermore, the same transformation can be accomplished by the reaction of the dienolate anion of an α,β-unsaturated amide with an aryne intermediate.

Key words: Arynes, Biaryls, Ring Closure, Directed *ortho* Metalation, Fries rearrangement,

The regiospecific preparation and modification of polysubstituted aromatic molecules has remained a fundamental problem in organic synthesis in both industrial and academic laboratories.[1,2] The directed *ortho* metalation (DoM) reaction, discovered 70 years ago by Gilman[3] and Wittig,[4] has been extensively studied and exploited for the regioselective construction of polysubstituted aromatics and heteroaromatics.

Diospyrol (**1**) has been isolated from *Diospyros mollis*, a tree distributed throughout Thailand. It has a dimeric naphthalene skeleton with a C-2/C-2' linkage between the 1-naphthol ring systems.[5] The fresh berries of this plant have long been used especially as anthelmintics.[6] Recently michellamine alkaloids have been isolated and reported to exhibit potent anti-HIV activity.[7] Their structures are composed of two important units, a 1,3-dimethyltetrahydroisqunoline and the core binaphthol. The structure of the core binaphthol is also similar to diospyrol. Michellamine B, the most studied compound of this group, showed interesting activity to protect MT-2 cells from both AZT-resistant and pyridone-resistant strains of HIV-1.[8] Several strategies have been evolved for the construction of this unit.[9,10]

We envisaged two pathways for the synthesis of the binaphthol, both starting from biphenol as shown in Scheme 1. In route A, the binaphthol could be derived from the double cyclization of the allyl carbanion onto the adjacent carboxamide group in compound **3**. Compound **3** could be synthesized from the *o*-allylation of carboxamide **4** which could be obtained from the biphenol **5**. In the second pathway as shown in route B it was planned that binaphthol could be directly generated via aryne annulation. It was anticipated that the trapping of bisaryne **8**, derived from tetrabromobiphenylether **6**, with diene **9**, generated from unsaturated amide **7**, could lead directly to the binaphthol **2**. An alternative mechanism for the formation of the same binaphthol **2** could involve the sequential reactions of the monoaryne derived from compound **6** with diene **9** followed by the reaction of another monoaryne and diene **9**. The tetrabromobiphenylether **6** could be easily obtained from the same biphenol **5** as used in the first pathway.



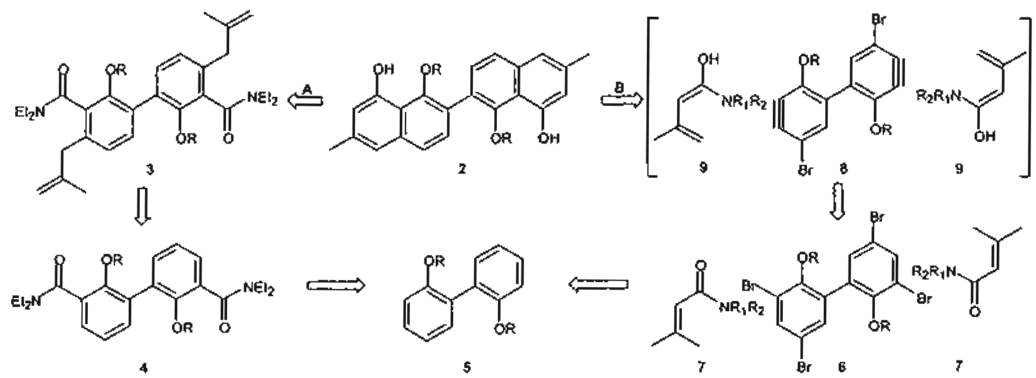
diospyrol (1)

Michellamine B

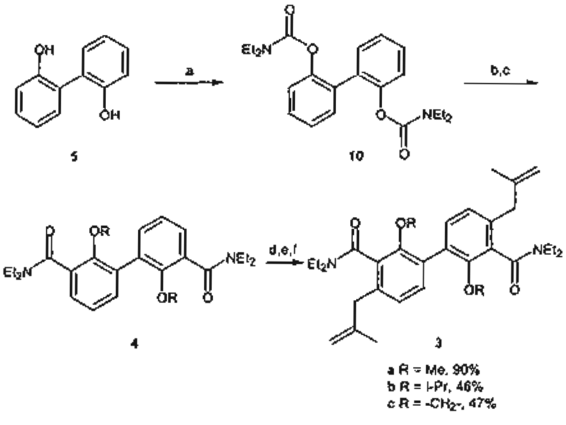
Figure Structure of diospyrol (**1**) and michellamine B

Herein, harnessing Snieckus chemistry, we report the application of directed *ortho* metalation (DoM),[11] Fries rearrangement,[12] transmetalation-bis-allylation,[13] and double cyclization to the synthesis of binaphthol **2**. We also report the aryne cycloaddition reaction[10] of dienolate anion **9** of α,β-unsaturated amide **7** with tetrabromobiphenylether **6** in the presence of strong base affording diospyrol derivative **2**.

Commercially available biphenol **5** was first reacted with *N,N*-diethylcarbamoyl chloride and NaH in DMF to yield dicarbamate **10** (75%) as shown in scheme 1.[11] *N,N*-Diethyl-2,2'-dihydroxy-1,1'-biphenyl-3,3'-dicarboxamide **4** (R = H) was obtained in good yield (80%) by double anionic *ortho*-Fries rearrangement[12] of 2,2'-dicarbamate-1,1'-biphenyl **10** using *t*-BuLi and TMEDA.[14] Compound **4** (R = H) was then protected as its methyl ether, isopropyl ether and methylenedioxy ether by reaction with MeI, 2-bromopropane or dibromomethane to give *N,N*-diethyl-2,2'-dialkoxyl-1,1'-biphenyl-3,3'-dicarboxamides **4a-c** in excellent yield (94-100%). These were *ortho* lithiated using *t*-BuLi/TMEDA in THF at -78 °C, transmetalated with CuCN/LiCl[13] and trapped with β-methallyl chloride in a one-pot reaction.



Scheme 1 Synthetic plans for the conversion of biphenol to binaphthol



Scheme 2 Reagents and conditions: a) $ClCONEt_2$, NaH, DMF (75%); b) *t*-BuLi, TMEDA, THF, -78 °C (80%);[14] c) RX, NaH, DMF (**4a**: R = Me, 94%, **4b**: R = *i*-Pr, 100%, **4c**: R = $-CH_2-$, 98%); d) *t*-BuLi, TMEDA, THF, -78 °C; e) CuCN, LiCl, THF; f) β-Methallyl chloride (**3a**: 90% over 3 steps, **3b**: 46% over 3 steps,[15] **3c**: 47% over 3 steps).

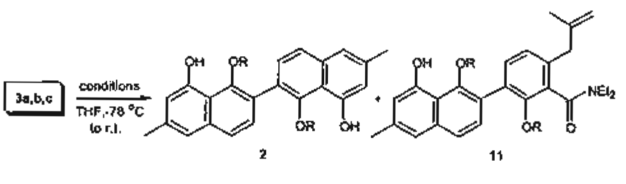
The reaction was allowed to warm to room temperature and stirred overnight to give the required compounds **3a-c** in moderate to good yields as shown in Scheme 2.

We have investigated various bases and conditions for the base-induced double cyclization of compounds **3**. When compound **3a** was treated with 5 equiv or 10 equiv of LDA in THF, complex mixtures of products were obtained. Treatment of compound **3b** with 5 equiv of LDA gave the desired product **2b** in 21% yield together with the half-cyclised product **11b** in 33% yield (entry 3). Increasing the amount of LDA to 10 equiv gave lower yields of both compounds **2b** and **11b** (entry 4). It was gratifying to find that compound **3a** could be induced to cyclize to the corresponding binaphthol by using MeLi.[16] The desired binaphthol **2a** (R = Me) was isolated in good yield (75%) when 6 equiv of MeLi (entry 6)[17] were used but in lower yield (67%) when only 4 equiv of MeLi were employed (entry 5). When the MeLi induced cyclization (6 equiv of MeLi) was also applied to compound **3b**, the required product **2b** was obtained in 52% (entry 7).

Compound **3c** gave a complex mixture on treatment with LDA and MeLi.[16] Attempts to activate the carboxamide group of compound **3a** with Tf_2O in the presence of pyridine[18] to induce cyclization also failed.

The two-step double cyclization and methylation of the intermediate **3a** to tetramethoxydiospyrol 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 spectroscopic data of the compound obtained were identical with those derived from tetramethoxydiospyrol synthesized by another route.[9] The tetramethoxydiospyrol could be demethylated to diospyrol by the previously published procedure.[9b,c]

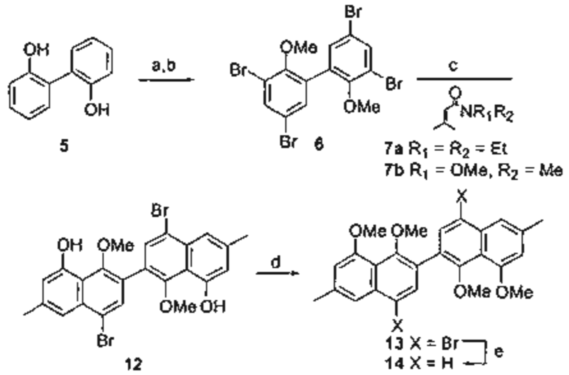
Table 1 Double ring-closure of key intermediates 3a-c



Entry	R	conditions	yield of 2 (%)	yield of 11 (%)
1	Me	5 equiv LDA	complex mixture	
2	Me	10 equiv LDA	complex mixture	
3	*i*-Pr	5 equiv LDA	21	33
4	*i*-Pr	10 equiv LDA	19	29
5	Me	4 equiv MeLi	67	-
6	Me	6 equiv MeLi[17]	75	-
7	*i*-Pr	6 equiv MeLi	52	-

The remarkably regiospecific of the aryne annulation reaction[10] has been extensively used for the synthesis of naphthols. As an extension of this type of synthetically useful cycloaddition reaction, we were interested in the application of this approach for the synthesis of binaphthols in general and the synthesis of diospyrol in particular. With this idea in mind, biphenol **5** was converted to tetrabromo-2,2'-dihydroxybiphenyl by bromination with bromine in

HOAc in quantitative yield. The tetrabromophenol was methylated using dimethylsulfate and K_2CO_3 in refluxing acetone to give tetrabromo-2,2'-dimethoxybiphenyl **6** in 67% yield.



Scheme 3 Reagents and conditions: a) Br_2, AcOH; b) Me_2SO_4, K_2CO_3, acetone, reflux (67%, 2 steps); c) LTMP, THF, -78 °C (20% from **7a**,[19] 14% from **7b**); d) Me_2SO_4, K_2CO_3, acetone, reflux (96%); e) *n*-Bu_3SnH, AIBN, reflux (81%).

Having the tetrabromobiphenyl ether **6** in hand, the aryne annulation was then investigated. *N,N*-Diethylsenecioamide **7a** was treated with an excess of LDA at -78 °C in THF in order to generate the lithiated amide. The tetrabromobiphenylether **6** was added to the solution to generate the aryne and the mixture was allowed to warm to room temperature. After purification, the undesired LDA addition products were obtained.

To overcome this problem, the more hindered base, LTMP, was used. Treatment of tetrabromobiphenoldimethylether **6** with an excess of LTMP and *N,N*-diethylsenecioamide **7a** gave dibromodiospyrol adduct **12** directly in 20% yield together with other unidentified products.[19] Using the Weinreb amide **7b**, a lower yield (14%) of binaphthol **12** was obtained.

Methylation of 4,4'-dibromodiospyrol **12** with dimethylsulfate in the presence of K_2CO_3 in refluxing acetone gave 4,4'-dibromodiospyrol tetramethylether **13** in high yield (96%) which was converted to diospyrol tetramethylether **14** by debromination with tributyltin hydride in good yield (81%).[20] The dibromodiospyrol derivative was recently synthesized by a different approach.[21] Significantly, the remaining bromine group can be used as a handle for further coupling.

In summary, we have successfully developed two direct approaches for the conversion of biphenol to binaphthol and applied to the synthesis of diospyrol. The methodology should be applicable to the synthesis of related oxygen heterocycles.

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(14) **Directed *ortho* metalation (DoM) and Fries rearrangement:** To a solution *t*-BuLi (1.7 M, 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 (**10**) (7.68 g, 20 mmol) in THF (50 mL) at -78 °C under N_2 atmosphere. The stirred reaction mixture was allowed to attain r. t. overnight and treated with a sat. NH_4Cl solution. The organic solvent was

removed in vacuo and the remaining solution was 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. After purification by flash column chromatography using EtOAc-hexane as eluent, 2,2'-dihydroxybiphenyl-3,3'-dicarboxylic acid bisdiethylamide (**4**) was obtained (6.14 g, 80%) as a white solid: mp 140-141 °C (EtOAc-hexane). IR (KBr): 3428, 2981, 1600, 1572, 1488, 1450, 1408, 1353, 1311, 1259, 1141 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.0 Hz, 12 H), 3.53 (q, J = 7.0 Hz, 8 H), 6.99 (t, J = 7.2, 7.8 Hz, 2 H), 7.31 (dd, J = 1.8, 7.8 Hz, 2 H), 7.38 (dd, J = 2.0, 7.7 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.4, 41.2, 119.3, 120.8, 127.1, 127.2, 133.7, 149.0, 171.0. MS (EI): *m/z* (%) = 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). HRMS (FAB): *m/z* calcd for $C_{22}H_{28}N_2O_4$ [M + H^{+}]: 385.2127; found: 385.2128.

(15) Yield of 3b was improved to 53% using $CuBr.Me_2S$.

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(17) **Representative procedure for the double ring-closure:** To a stirred THF (5 mL) solution of 2,2'-dimethoxy-4,4'-bis(2-methylallyl)biphenyl-3,3'-dicarboxylic acid bisdiethylamide (**3a**) (0.1316 g, 0.25 mmol) at -78 °C under Ar was added a solution of MeLi (1.4 M, 1.1 mL, 1.5 mmol) in Et_2O. The solution turned deep violet and was allowed to warm to r.t. and stirred at this temperature overnight. The reaction was quenched by the addition of 20 mL of sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was combined, washed with water, brine and dried (anhyd Na_2SO_4). The crude product obtained after evaporation of CH_2Cl_2 was purified by PLC using CH_2Cl_2-hexane (2:1) as eluent to give white solid as 1,1'-dimethoxy-6,6'-dimethyl-2,2'-binaphthalenyl-8,8-diol (**1a**) (0.0699 g, 75%): mp 234-236 °C (EtOAc-hexane). IR (KBr): 3321, 2926, 1637, 1573, 1460, 1378, 1354, 1058 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 6 H), 3.58 (s, 6 H), 6.82 (d, J = 1.4 Hz, 2 H), 7.17 (bs, 2 H), 7.50 (d, J = 8.5 Hz, 2 H), 7.58 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 61.8, 112.9, 115.5, 118.4, 123.7, 124.3, 129.1, 136.5, 138.7, 153.4, 154.1. MS (EI): *m/z* (%) = 374 (M^{+}, 61), 356 (15), 343 (23), 342 (81), 329 (36), 328 (100). HRMS microTOF (ESI): *m/z* calcd for $C_{24}H_{22}O_4$ [M + H^{+}]: 375.1591; found: 375.1584.

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(19) **Representative procedure for the aryne annulation:** A solution of lithium 2,2,6,6-tetramethylpiperidine (LTMP) (6.4 mmol) was prepared at 0 °C from 2,2,6,6-tetramethylpiperidine (1.1 mL) and *n*-BuLi (4.95 mL) in dry THF (20 mL). After 30 min, the solution was cooled to -78 °C and a solution of *N,N*-diethyl seneciomide (**7a**) (0.66 g, 4.3 mmol) in dry THF (5 mL) was added and stirred at this temperature for 1 h. A solution of tetrabromo-2,2'-dimethoxybiphenyl **6** (0.57 g, 1.1 mmol) in dry THF (15 mL) was added dropwise, the reaction turned to dark red. After the addition was complete, the reaction was slowly warmed to r.t. and stirred overnight. Sat. NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, brine and dried (Na_2SO_4) and evaporated to dryness. Further purification was carried out by PLC (SiO_2, 4% EtOAc-hexane) to obtain binaphthol **12** (0.117 g, 20%). Compound **12**: mp 249-250 °C (EtOAc-hexane). IR ($CHCl_3$): 3344 (OH), 3010, 1636, 1369, 803 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 6 H), 3.61 (s, 6 H), 6.91 (d, J = 1.3 Hz, 2 H), 7.56 (d, J = 0.9 Hz, 2 H), 7.84 (s, 2 H), 9.76 (s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0, 62.3, 114.3, 116.3, 118.2, 118.3, 123.1, 132.1, 134.4, 140.4, 153.4, 154.4. MS (EI): *m/z* = 534 (M^{+}+2, 50), 532 (M^{+}, 100), 530 (48), 488 (41), 486 (84), 484 (42). Anal. calcd for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79; found: C, 54.27; H, 3.76.

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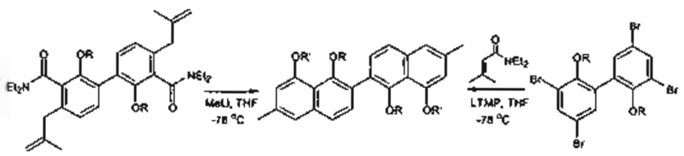
Two Protocols for the Conversion of Biphenol to Binaphthol: Synthesis of Diospyrol



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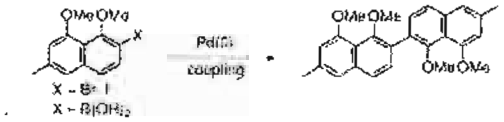

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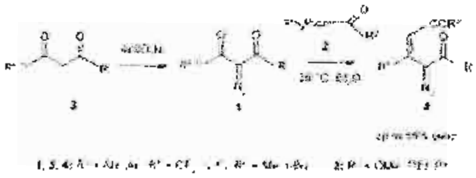

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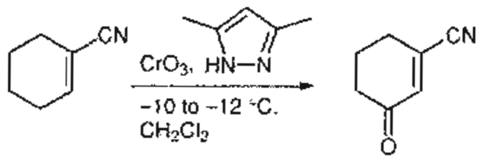

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Efficient Synthesis of Diospyrol via Suzuki–Miyaura and Modified in Situ Cross-Coupling

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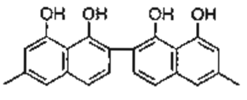
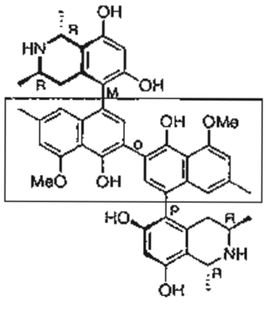
Abstract: Tetramethoxydiospyrol was synthesized via Suzuki–Miyaura cross-coupling of the two key intermediates, halonaphthalene and naphthaleneboronic acid derivatives, which were derived from the same naphthol. Moreover, the product could be conveniently obtained by a one-pot modified in situ Suzuki coupling. The naphthol was synthesized via the cyclization of *ortho*-allylbenzamide intermediate.

Key words: biaryls, Suzuki–Miyaura cross-coupling, metalation, diospyrol

Diospyrol[1] (**1a**), a symmetrical dimeric naphthol, was isolated from *Diospyros mollis* berries widely used in Thailand as an anthelmintic.[2] Over the years, the synthesis of this interesting structural motif has challenged many synthetic groups.[3,4] The interest in this molecule was intensified by the recent isolation of the michellamine alkaloids reported to exhibit potent anti-HIV activity.[5] The structure of michellamine, typified by michellamine B, composed of two important structural units, i.e. 1,3-dimethyltetrahydroisoquinoline and the core binaphthol, which is structurally similar to diospyrol (Figure 1).



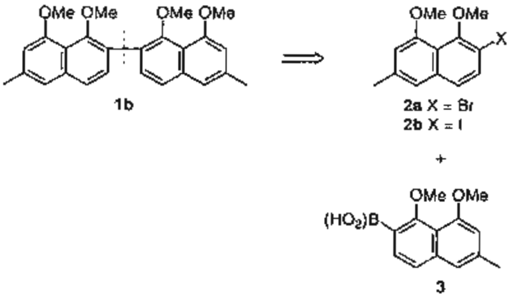
Diospyrol **1a**



Michellamine B

Figure 1 Diospyrol (**1a**) and michellamine B

Retrosynthetic analysis suggested that breaking the C_2 symmetric bond can form two naphthalene units as shown in Scheme 1. In our approach, we planned to utilize the Suzuki–Miyaura cross-coupling[6] of naphthalene derivatives, i.e. halonaphthalene **2** and naphthaleneboronic acid **3**, for the synthesis of this compound. Herein we report both the classical and modified in situ Suzuki cross-coupling for the synthesis of diospyrol.



Scheme 1 Retrosynthetic analysis of tetramethoxydiospyrol (**1b**)

The naphthol precursor **6** was required for the synthesis of the first key intermediate, halonaphthalene **2**. Many synthetic methodologies have been devised for synthesis of the naphthol derivatives.[7] We adopted the procedure developed by Snieckus et al.[7d] for the synthesis of our naphthol derivative. The naphthol **6** was synthesized in 60% yield by cyclization of the *o*-allylbenzamide **5** in the presence of excess LDA. The use of methyllithium as a base led also to the cyclized adduct **6** but in lower yield (27%).[7g] The precursor allylbenzamide **5** was synthesized in one pot by selective *ortho* metalation[8] of benzamide **4**[9] with *t*-BuLi followed by transmetalation with $MgBr_2$ and the resulting organomagnesium intermediate was trapped with allyl bromide to give the product in 78% yield (Scheme 2).

The first key intermediate, halonaphthalene **2**, could be synthesized using selective *ortho* halogenation[10] of naphthol precursor **6** followed by methylation. The selective *ortho* halogenation of naphthol **6** with bromine or iodine in the presence of *tert*-butylamine and further methylation gave bromonaphthalene **2a** (37%, two steps) and io-

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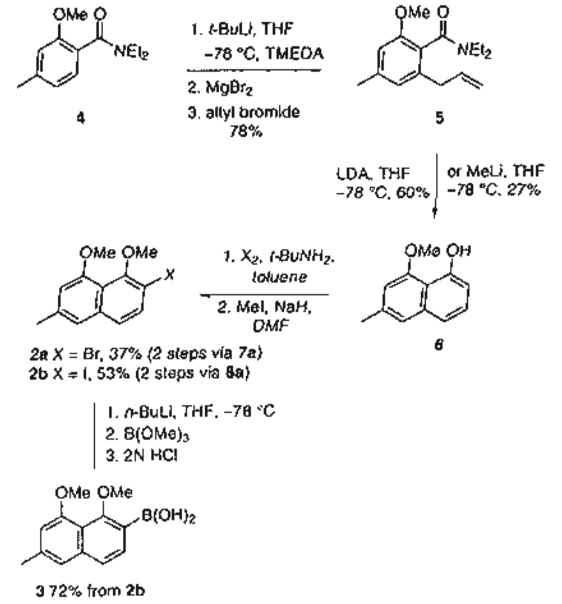
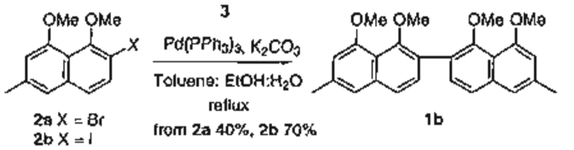


Scheme 2 Synthesis of key intermediate halonaphthalene **2** and naphthaleneboronic acid **3**

donaphthalene **2b** (53%, two steps), respectively.[11] The other key intermediate, naphthaleneboronic acid **3**, could be prepared in 72% yield from iodonaphthalene **2b** under metal–halogen exchange condition[12] followed by quenching with B(OMe)$_3$ and hydrolysis with 2 N HCl.

With both key intermediates in hand, the Suzuki–Miyaura cross-coupling was studied.[6,13] The classical Suzuki–Miyaura cross-coupling was carried out by refluxing naphthaleneboronic acid **3** with both bromonaphthalene **2a** and iodonaphthalene **2b** in the presence of 3 mol% Pd(PPh$_3$)$_4$ and K$_2$CO$_3$ in a mixed solvent system (toluene–EtOH–H$_2$O = 3:3:2) at 115–120 °C for 19 hours to obtain tetramethoxydiospyrol (**1b**) in 40 and 70% yield, respectively (Scheme 3). The tetramethoxydiospyrol (**1b**) could be converted to the natural diospyrol **1a** by a known method.[3a,c]

The modified one-pot, in situ Suzuki cross-coupling was developed by Keay[13] and Bräse's[14] groups. Both protocols involved the preparation of 0.5 equivalent of arylboronic *compound in situ from 1.0 equivalent of haloarene followed by Suzuki–Miyaura cross-coupling in the same flask. In the first protocol (Method A)[13] arylboronic ester* was prepared by metal–halogen exchange with *n*-BuLi followed by quenching with B(OMe)$_3$ whereas in the second protocol (Method B)[14] the arylboronic ester was prepared by reacting haloarene directly with bis(pinacolato)diboron (**9**) under palladium catalyst. We have utilized both protocols for the in situ cross-coupling of both bromonaphthalene **2a** and iodonaphthalene **2b** as shown in Scheme 4. By using method A, the product **1b** was obtained in 21 and 16% yield when bromo compound and iodo compound were used respectively and the product was obtained in 47 and 55% yield when method B was employed.



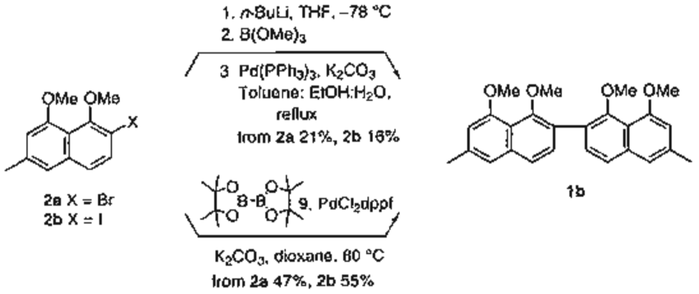
Scheme 3 Classical Suzuki–Miyaura cross-coupling of the synthesis of tetramethoxydiospyrol (**1b**)

In summary, we have successfully synthesized tetramethoxydiospyrol using classical and modified Suzuki–Miyaura cross-coupling reaction of naphthalene derivatives which were prepared from the same common naphthol intermediate. The iodonaphthalene was found to react more efficiently than bromonaphthalene in the cross-coupling reaction.

All commercial solvents and reagents were used without purification prior to use. THF was distilled from benzophenone ketyl under argon. Column chromatography purifications were carried out using silica gel (70–30 mesh).

2-Allyl-*N*,*N*-diethyl-6-methoxy-4-methylbenzamide (5)

To a stirred solution of *N*,*N*-diethyl-6-methoxy-4-methylbenzamide (**4**; 2.0 g, 9.05 mmol) and TMEDA (1.5 mL, 10.0 mmol) in anhyd THF (50 mL) at −78 °C was slowly added *t*-BuLi (1.0 M, 10.85 mL, 10.85 mmol) and the mixture was further stirred for 1 h. MgBr$_2$ etherate (4 mL) was added and the solution was warmed to r.t. The mixture was recooled to −78 °C and the stirring was continued for 40 min. Allyl bromide (1.5 mL, 17.96 mmol) was then added and the mixture was warmed to r.t. and stirred overnight. Aq sat. NH$_4$Cl



Scheme 4 The modified in-situ Suzuki cross-coupling for the synthesis of tetramethoxydiospyrol (**1b**)

was added and the mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with H_2O, brine and dried (Na_2SO_4). CH_2Cl_2 was evaporated to dryness to give a crude viscous oil (2.5 g). Further purification by column chromatography (SiO_2, 25% EtOAc–hexane) gave the required allylamide **5** as viscous oil (1.85 g, 78%) together with the starting compound (230 mg).

IR (KBr): 1631, 1578 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7 Hz, 3 H, CH_3), 1.24 (t, *J* = 7 Hz, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 3.05 (m, 2 H, NCH_2), 3.30 (d, *J* = 7 Hz, 2 H, CH_2), 3.40 (m, 1 H, NCH), 3.77 (m, 1 H, NCH), 3.77 (s, 3 H, OCH_3), 5.07 (m, 2 H, =CH_2), 5.93 (m, 1 H, =CH), 6.56 (s, 1 H, H-5), 6.66 (s, 1 H, H-3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.7, 13.7, 21.6, 36.9, 38.3, 42.6, 55.4, 109.4, 116.0, 122.3, 123.5, 136.7, 137.6, 139.23, 155.4, 168.2.

MS (EI, 70 eV): *m/z* (%) = 105 (23), 143 (27), 161 (88), 188 (76), 189 (100), 190 (24), 261 (32, [M$^+$]), 262 (42, [M + H$^+$]).

HRMS-FAB: *m/z* [M + H$^+$] calcd for $C_{16}H_{23}NO_2$: 262.1807; found: 262.1806.

8-Methoxy-6-methyl-1-naphthol (6)

Diisopropylamine (2.4 mL, 16.86 mmol) was added by syringe to anhyd THF (50 mL). *n*-BuLi (1.2 M, 13.4 mL) was added at –78 °C and the mixture was warmed to 0 °C and further stirred for 20 min. The mixture was then cooled to –78 °C and a solution of allylamide **5** (2.0 g, 7.66 mmol) in anhyd THF (20 mL) was slowly added. The mixture was stirred at –78 °C for 3 h and then warmed to r.t. overnight. Aq sat. NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with H_2O, brine and dried (Na_2SO_4). Further purification by column chromatography (SiO_2, CH_2Cl_2) gave the required naphthol **6** as pale brown viscous oil (860.0 mg, 60%).[15]

IR (KBr): 3404 (s) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 6.56 (d, *J* = 1.2 Hz, 1 H, H-7), 6.79 (dd, *J* = 7.6, 1.2 Hz, 1 H, H-2), 7.16 (s, 1 H, H-5), 7.18 (dd, *J* = 7.6, 1.2 Hz, 1 H, H-4), 7.30 (t, *J* = 8 Hz, 1 H, H-3), 9.25 (s, 1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 56.0, 106.1, 109.5, 113.3, 118.2, 120.8, 127.7, 135.5, 136.9, 154.4, 155.9.

MS (EI, 70 eV): *m/z* (%) = 115 (7), 145 (9), 188 (100, [M$^+$]), 189 (16, [M + H$^+$]).

HRMS-FAB: *m/z* [M – H$^-$] calcd for $C_{12}H_{12}O_2$: 187.0759; found: 187.0753.

2-Iodo-8-methoxy-6-methyl-1-naphthol (8a) and 2,4-Diiodo-8-methoxy-6-methyl-1-naphthol (8b)

To a stirred solution of *tert*-butylamine (2.14 mL, 20.27 mmol) in anhyd toluene (20 mL) was added a solution of I_2 (2.58 g, 10.16 mmol) in anhyd toluene (35 mL) at r.t. and the mixture was further stirred for 1 h. The resulting mixture was then transferred to a stirred solution of naphthol **6** (1.91 g, 10.16 mmol) in anhyd toluene (25 mL) at 0 °C via canula. After the addition was complete, the reaction was further stirred for 10 min. Aq sat. $Na_2S_2O_3$ (30 mL) was added and the mixture was extracted with EtOAc (30 mL), and the Et_2O layer was washed with H_2O and brine. The combined extracts were dried (Na_2SO_4) and evaporated to dryness. Further purification was carried out by column chromatography (SiO_2, 5% EtOAc–hexane) to obtain *o*-iodonaphthol **8a** (1.87 g, 58%) and *o,p*-diiodonaphthol **8b** (603.6 mg, 14%).[11]

8a

Mp 116–116.5 °C (CH_2Cl_2–hexane).

IR (KBr): 3320, 1626, 1603, 1579, 1495, 1403, 1370 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 4.01 (s, 3 H, OCH_3), 6.62 (s, 1 H, H-7), 6.95 (d, *J* = 8.8 Hz, 1 H, H-4), 7.14 (s, 1 H, H-5), 7.64 (d, *J* = 8.8 Hz, 1 H, H-3), 10.16 (s, 1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9, 56.3, 107.0, 113.1, 119.7, 120.8, 136.4, 136.5, 153.2, 154.8.

MS (EI, 70 eV): *m/z* (%) = 172 (34), 188 (26), 299 (34), 314 (100, [M$^+$]), 315 (12, [M + H$^+$]).

HRMS-FAB: *m/z* [M – H$^-$] calcd for $C_{12}H_{11}IO_2$: 312.9724; found: 312.9726.

8b

Mp ? (dec.) (CH_2Cl_2–hexane).

IR (KBr): 3266, 1623, 1604, 1557, 1449, 1407, 1355 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 4.05 (s, 3 H, OCH_3), 6.71 (s, 1 H, H-7), 7.43 (s, 1 H, H-5), 8.25 (s, 1 H, H-3), 10.38 (s, 1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.2, 56.7, 85.8, 107.8, 113.4, 125.7, 136.3, 138.2, 146.2, 154.4, 154.8.

MS (EI, 70 eV): *m/z* (%) = 298 (25), 425 (27), 440 (100, [M$^+$]), 441 (14, [M + H$^+$]).

Anal. Calcd for $C_{12}H_{10}I_2O_2$: C, 32.76; H, 2.29. Found: C, 33.01; H, 2.12.

Methylation of 1-Hydroxy-2-iodo-8-methoxy-6-methylnaphthalene (8a): 2-Iodo-1,8-dimethoxy-6-methylnaphthalene (2b); Typical Procedure

To a stirred suspension of NaH (80% in oil, 179 mg, 5.97 mmol) in DMF (5 mL) was added a solution of iodonaphthol **8a** (1.25 g, 3.98 mmol) in DMF (10 mL) at r.t. The mixture was stirred for 1 h and MeI (0.5 mL, 8 mmol) was then added and the mixture was stirred overnight. H_2O was slowly added and the mixture was extracted with EtOAc (2 × 25 mL). The combined EtOAc extracts were washed with H_2O, brine and dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2, 2–5% EtOAc–Hexane) to obtain **2b** as viscous oil (1.19 g, 91%).

IR (neat): 2929, 1625, 1568, 1454, 1330 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 6.72 (s, 1 H, H-7), 7.17 (s, 1 H, H-5), 7.20 (d, *J* = 8.8 Hz, 1 H, H-4), 7.72 (d, *J* = 8.8 Hz, 1 H, H-3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 56.3, 61.7, 88.5, 108.9, 119.0, 120.1, 125.2, 135.9, 136.8, 137.6, 155.0, 155.9.

MS (EI, 70 eV): *m/z* (%) = 328 (100, [M$^+$]), 329 (19, [M + H$^+$]).

HRMS-FAB: *m/z* [M + H$^+$] calcd for $C_{13}H_{13}IO_2$: 329.0037; found: 329.0030.

2-Bromo-1,8-dimethoxy-6-methylnaphthalene (2a)

Viscous oil.

IR (neat): 2940, 2840, 1597, 1462, 1355, 1264, 1079, 747 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.67 (s, 1 H, H-7), 7.10 (s, 1 H, H-5), 7.23 (d, *J* = 8.8 Hz, 1 H, H-4), 7.47 (d, *J* = 8.8 Hz, 1 H, H-3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 56.3, 61.6, 109.1, 113.9, 119.6, 120.1, 124.6, 130.6, 136.6, 136.7, 153.1, 155.3.

MS (GC, 70 eV): *m/z* (%) = 115 (56), 128 (81), 139 (30), 158 (91), 186 (83), 207 (33), 209 (28), 280 (97, [M$^+$]), 282 (100, [M$^+$ + 2]).

1,8-Dimethoxy-6-methylnaphthalene-2-boronic Acid (3)

To a stirred solution of iodonaphthalene **2b** (301.7 mg, 0.92 mmol) in THF (7 mL) at –78 °C under argon was added *n*-BuLi (1.12 mL, 1.84 mmol) followed immediately by $B(OMe)_3$ (200 μL, 1.78

mmol). After stirring at –78 °C for 30 min, the mixture was warmed to r.t. and stirred for 1 h. The resulting mixture was quenched with 2 N HCl and extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were washed with H_2O and brine and dried (Na_2SO_4). The solvent was removed to obtain the crude boronic acid which was purified by column chromatography (SiO_2, 1% MeOH–CH_2Cl_2) to give boronic acid **3** as white solid (163 mg, 72%); mp 157.5–158 °C (CH_2Cl_2–hexane).

IR (KBr): 2937(br), 1610, 1605, 1572, 1467, 1376 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 3.9 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 6.71 (s, 2 H, 2 OH), 6.74 (s, 1 H, H-7), 7.24 (s, 1 H, H-5), 7.52 (d, J = 16.4 Hz, 1 H, H-4), 7.83 (d, J = 16.8 Hz, 1 H, H-3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9, 56.1, 63.8, 108.4, 117.3, 120.4, 123.9, 132.0, 137.7, 139.9, 155.7, 163.8.

MS (EI, 70 eV): m/z (%) = 191 (22), 201 (22), 202 (15), 204 (75), 231 (14), 245 (27), 246 (100, [M$^+$]), 247 (14, [M + H$^+$]).

Anal. Calcd for $C_{13}H_{15}BO_4$: C, 63.45; H, 6.14. Found: C, 63.32; H, 5.77.

Tetramethoxydiospyrol (1b) by Classical Suzuki–Miyaura Cross-Coupling Reaction

A mixture of iodonaphthalene **2b** (158.5 mg, 0.48 mmol), naphthaleneboronic acid **3** (118.9 mg, 0.48 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol%) and K_2CO_3 (133 mg, 0.96 mmol) in a mixture of toluene–EtOH–H_2O (3:3:2, 8 mL) was refluxed at 115–120 °C for 19 h. After cooling the mixture, H_2O was added and extracted with EtOAc (2 × 20 mL). The combined EtOAc extracts were washed with H_2O, brine and dried (Na_2SO_4). Further purification was carried out by column chromatography (SiO_2, 0.5% MeOH–CH_2Cl_2) to give tetramethoxydiospyrol (**1b**) which was recrystallized from benzene to afford **1b** as white crystals (136.2 mg, 70%).

Tetramethoxydiospyrol (1b) Modified in situ Suzuki Cross-Coupling

Method A:[13] To a solution of bromonaphthalene (150 mg, 0.5 mmol) in THF (10 mL) at –78 °C was added 0.5 equiv of 0.77 M of n-BuLi (0.4 mL) followed by 6 equiv of $B(OMe)_3$ (0.8 mL). The resulting solution was warmed to r.t. for 4 h and subsequently stirred overnight under argon. To the solution were then added toluene (6 mL), EtOH (6 mL), H_2O (4 mL), K_2CO_3 (130 mg, 1.0 mmol), and $Pd(PPh_3)_4$ (2 mg, 10 mol%). The resulting mixture was refluxed under argon for 10 h. The reaction was allowed to warm to r.t. and extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were combined, washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude binaphthalene which was purified on PLC to yield recovered bromonaphthalene **2a** (60 mg, 37%), tetramethoxydiospyrol (**1b**) (40 mg, 21%) and debromonaphthalene (30 mg, 26%).[16]

Method B:[14] A mixture of iodonaphthalene **2b** (165.4 mg, 0.5 mmol), bis(pinacolato)diboron (**9**; 63.5 mg, 0.25 mmol), $PdCl_2dppf$ (14.6 mg, 4 mol%), and K_2CO_3 (207 mg, 1.5 mmol) in dioxane (5 mL) was heated at 80 °C for 16 h. After cooling the mixture, H_2O was added and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with H_2O, 20% aq NaOH, and dried (Na_2SO_4). Further purification was carried out by column chromatography (SiO_2, 0.5% MeOH–CH_2Cl_2) to give tetramethoxydiospyrol (**1b**) (54.9 mg, 55%) as a white solid; mp (benzene) 239–239.5 °C (Lit.[1a] mp 232 °C, Lit.[1d] mp 243 °C).

IR (KBr): 1625, 1563, 1451, 1338, 1262 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 6 H, 2 CH_3), 3.55 (s, 6 H, 2 OCH_3), 4.01 (s, 6 H, 2 OCH_3), 6.73 (s, 2 H, H-7,7′), 7.26 (s, 2 H, H-5,5′), 7.52 (d, J = 16.4 Hz, 2 H, H-4,4′), 7.83 (d, J = 16.8 Hz, 2 H, H-3,3′).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 56.1, 61.4, 108.0, 118.6, 120.0, 122.7, 128.5, 130.8, 135.0, 137.2, 153.6, 156.2.

MS (EI, 70 eV): m/z (%) = 298 (8), 341 (25), 357 (21), 402 (100, [M$^+$]), 403 (29, [M + H$^+$]).

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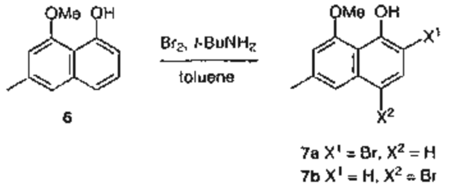
(11) The bromination of naphthol **6** also gave *para* halogenated product. Compounds **7a** and **7b** were further methylated without purification.



6

7a X^1 = Br, X^2 = H
7b X^1 = H, X^2 = Br

Scheme 5

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(16) 1,8-Dimethoxy-3-methylnaphthalene[17] obtained as dehalogenation adduct from half-Suzuki cross-coupling was a white solid; mp 89–90 °C (MeOH). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.47 (s, 3 H, CH$_3$), 3.98 (s, 6 H, 2 OCH$_3$), 6.69 (d, J = 1.0 Hz, 1 H), 6.78 (dd, J = 6.2, 8.4 Hz, 1 H), 7.19 (br s, 1 H), 7.35 (m, 2 H). ^{13}C NMR (50 MHz, CDCl$_3$): δ = 21.7, 56.2, 56.3, 105.2, 108.2, 115.6, 120.0, 120.2, 126.4, 136.1, 137.5, 156.8, 157.0. MS (EI, 70 eV): m/z (%) = 128 (71), 129 (99), 159 (58), 201 (100) 202 (50, [M$^+$]).

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