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TETRAHEDRON: *ASYMMETRY*

1,1′-Spirobiindane-7,7′-diol: a novel, C_2-symmetric chiral ligand

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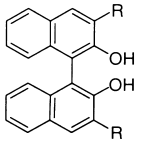
Abstract

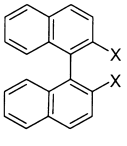
A novel, C_2-symmetric chiral diol (**16**) was prepared in six steps from *m*-anisaldehyde and resolved via its bis-L-menthoxycarboxylate.

1. Introduction

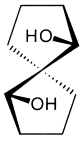
Biaryls, most notably 1,1′-binaphthalene derivatives (e.g. **1**[1] and **2**[2]), occupy a prominent position among C_2-symmetric chiral auxiliaries and ligands for asymmetric synthesis.[3] By contrast, spiranes, another class of molecules with axial chirality,[4] have received relatively little attention from the point of view of ligand design. In fact, only derivatives of *cis,cis*-spiro[4,4]nonane-1,6-diol **3** appear to have been employed in asymmetric synthesis.[5] Crown ethers incorporating the spirobifluorene moiety (e.g. **4**) were utilized, but only in asymmetric binding studies.[6] Despite their limited use, spiranes possess a number of useful characteristics which make their further exploration worthwhile.



1: BINOL (R =H) and derivatives (R = Ph, $SiAr_3$)[1]



2: BINAP (X = PPh_2)[2a] BINAPO (X = O-PPh_2)[2b]



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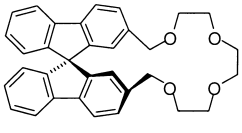

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The configurational stability (and therefore, practical utility) of biaryls depends on the restricted rotation about the central bond and thus, ultimately, on the bulk of the *ortho*-substituents. By contrast, spiranes contain a quaternary center, which makes their racemization virtually impossible, regardless of the substitution pattern. In addition, the spirocyclic framework is considerably more rigid[5] than that of biaryls, since conformational changes involve distortion of the entire molecule, not merely rotation about

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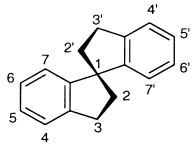
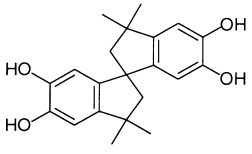
a single bond. This property may prove useful in designing chiral catalysts, since it can be expected to minimize the number of possible conformations of the catalytic species.

The structure of 1,1′-spirobiindane (**5**)[7a] offers a promising combination of chemical robustness and conformational rigidity. Although a large number of 1,1′-spirobiindane derivatives have been prepared[7] (e.g. **6**,[7b] **7**,[7c] **8**[7d]) and some of them resolved,[7c,e,8] their potential in chiral ligand design remains unexplored. In order to form an efficient chelating agent, 1,1′-spirobiindane needs to be substituted with coordinating groups in positions 7 and 7′, i.e. in the 'bay region' (cf. **9**).



5: 1,1-spirobiindane
(S-(-)-isomer shown)



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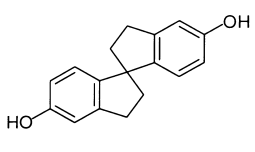

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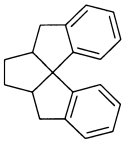

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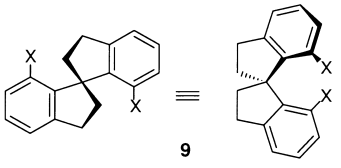

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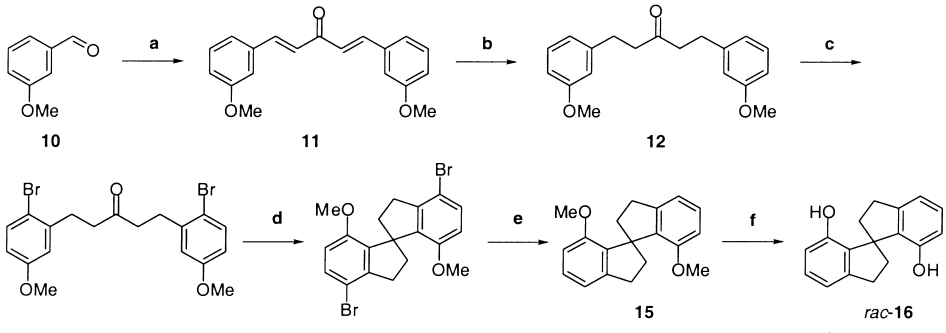
2. Results and discussion

1,1′-Spirobiindanes are generally prepared by double cyclization of 1,5-diphenyl-3-pentanone derivatives.[7b–d] However, since the condensation tends to occur *para*, rather than *ortho*, to the substituents already present in the aromatic ring, a known literature procedure[7c,d] was modified in order to prepare the simplest 'spiroanalog' of BINOL, 1,1′-spirobiindane-7,7′-diol, **16** (Scheme 1).



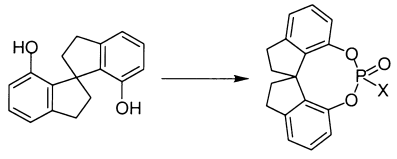
Reaction Conditions: (a) 0.5 eq Me_2CO, NaOH, 50% EtOH-H_2O, rt, 2h, 62%;[9] (b) Raney Ni, Me_2CO, rt, 1 atm. H_2, 1 day; (c) 2.5 eq Br_2, 3.5 eq pyridine, CH_2Cl_2; -10 °C to rt, 4h; (d) polyphosphoric acid, 105 °C, 5.5h, 57% for 3 steps;[7d] (e) *n*-BuLi (4 eq), THF, -78 °C, 1h; EtOH, 93%; (f) 2.3 eq BBr_3, CH_2Cl_2, -78 °C to rt overnight, 85%.

Scheme 1.

m-Anisaldehyde was condensed with acetone to produce 1,5-bis-*m*-anisyl-1,4-pentadien-3-one[7c] **11**, following a general procedure.[9,10] The dienone was hydrogenated (Raney Ni, rt, atmospheric pressure) to produce virtually pure 1,5-bis-*m*-anisyl-3-pentanone[7c,10] **12**, which was used directly in the next step

without purification. In order to direct the bis-cyclization *ortho*- to the methoxy groups, it was necessary to block the *para*-positions with removable substituents. This was accomplished by treating crude **12** with bromine in CH_2Cl_2 in the presence of pyridine. The bis-brominated product **13** was sufficiently pure for the cyclization step. Cyclization in polyphosphoric acid[7d] gave crystalline spirobiindane derivative **14**.[11] Debromination of **14** followed by demethylation afforded racemic **16** in 28% overall yield from *m*-anisaldehyde.

Initially, resolution of (±)-**16** was attempted using methods commonly used for BINOL derivatives. Thus, cyclic phosphoryl chloride (±)-**17** was prepared in quantitative yield by treatment of (±)-**16** with $POCl_3$ and NEt_3 (Scheme 2). Addition of lithium (*S*)-α-phenethylamide produced a mixture of diastereomeric cyclic α-phenethylphosphamides[12] **18a** and **b**, inseparable by recrystallization and poorly separable by chromatography (MPLC). Likewise, attempts to resolve (±)-**16** via the brucine salt of acid (±)-**19** or via the bis-camphorsulfonate of **16** proved unsuccessful.



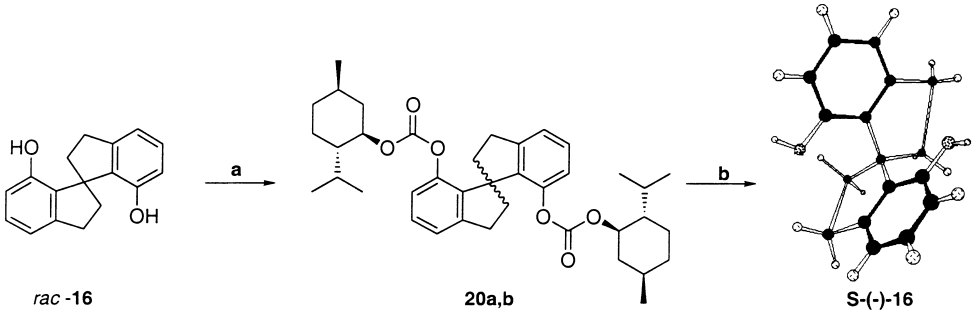
(±)-**16**

(±)-**17** **X = Cl**
18a and **b** **X = *S*-α-PhCH(Me)NH**
(±)-**19** **X = OH**

Reaction conditions: $POCl_3$, NEt_3, CH_2Cl_2.

Scheme 2.

Gratifyingly, efficient resolution was finally achieved by treating (±)-**16** with L-menthyl chloroformate and NEt_3 (Scheme 3).



rac -**16** **20a,b** **S-(-)-16**

Reaction conditions: (a) 2.4 eq *L*-menthyl chloroformate, 3.7 eq NEt_3, 0.1 eq DMAP, CH_2Cl_2, rt, 9h, flash chromatography (3% Et_2O in hexanes, silica gel), 95% **17a**, 85% **17b**; (b) $N_2H_4 \cdot H_2O$, THF, reflux, 1.5h; from **17a:** 86% of R-(+)-**16**, $[\alpha]_D^{25}$ = +32.5 (c 1.0, $CHCl_3$); from **17b:** 91% of S-(-)-**16:** $[\alpha]_D^{25}$ = -32.7 (c 1.0, $CHCl_3$).

Scheme 3.

The resulting diastereomers of **20** were easily separable by flash chromatography: diastereomer **20a** was an oil; **20b** was a crystalline compound. The absolute stereochemistry was determined by X-ray analysis of **20b** (*S*-configuration of the spirobiindane moiety).[13,14] Pure enantiomers, (*R*)-(+)-**16** and (*S*)-(−)-**16**, were best obtained by hydrazinolysis of **20a** and **20b**, respectively. Enantiomerically pure (+)-

and (−)-**16** were efficiently recrystallized from boiling hexanes in which they were less soluble than the racemate.

Future work concerning the use of 1,1′-spirobiindane-7,7′-diol (tentatively named SPINOL) will be reported in due course.

3. Experimental

3.1. General

Tetrahydrofuran was purified by distillation from potassium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. All other reagents were reagent grade and purified where necessary. Reactions were monitored by thin layer chromatography (TLC) using 250 mm Whatman precoated silica gel plates. Flash column chromatography was performed over EM Science Laboratories silica gel (230–400 mesh). Melting points were measured on a Mel-Temp capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer in $CDCl_3$. The chemical shifts are reported as δ values (ppm) relative to TMS. Infrared spectra were recorded on a Nicolet 20SXB FT-IR spectrophotometer (NaCl plates). Optical rotations were measured on a Perkin–Elmer 141 polarimeter (Na lamp).

3.2. 1,5-Bis-m-anisyl-1,4-pentadien-3-one[7c,9] (11)

A solution of distilled *m*-anisaldehyde (10.0 g, 73.4 mmol) and acetone (2.70 ml, 36.8 mmol) in 10 ml of ethanol was added dropwise to a solution of 7.5 g of NaOH in 132 ml of 50% aqueous ethanol, stirring in a water bath at rt. The mixture was stirred for 2 h, then diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and separated by chromatography (hexanes:EtOAc, 5:1) to produce 6.66 g (62% yield) of slightly contaminated **11** as a yellow oil which solidified on standing.

^{1}H NMR: 3.83 (s, 6H), 6.97 (dd, J=2 Hz, J=8 Hz, 2H), 7.07 (d, J=16 Hz, 2H), 7.14 (m, J=2 Hz, 2H), 7.22 (br d, 8 Hz, 2H), 7.34 (t, 8 Hz, 2H), 7.71 (d, J=16 Hz, 2H); ^{13}C NMR: 55.3, 113.2, 116.3, 121.1, 125.6, 129.9, 136.1, 143.3, 159.9, 188.9; IR (film, cm^{-1}): 1256, 1620, 1652 (dienone).

3.3. 1,5-Bis-m-anisyl-3-pentanone[7c,10] (12)

A solution of **11** (1.00 g, 3.4 mmol) in 20 ml of acetone was stirred with Raney Ni (3–4 g) under an atmosphere of hydrogen at rt, monitoring the reaction progress by TLC and adding more catalyst as necessary. When the starting material had disappeared (ca. 1 day), the catalyst was filtered off, washed with acetone, and the filtrate rotary evaporated. The product (0.99 g) was obtained as a colorless oil containing ca. 2% of the saturated alcohol.

^{1}H NMR: 2.71 (t, J=8 Hz, 4H), 2.86 (t, J=8 Hz, 4H), 3.78 (s, 6H), 6.73 (m, 4H), 7.19 (t, J=8 Hz, 2H); ^{13}C NMR: 29.7, 44.4, 55.1, 111.4, 114.0, 120.6, 129.5, 142.6, 159.7, 209.0; IR (film, cm^{-1}): 1259, 1601, 1713 (C=O).

3.4. 1,5-Bis-(2-bromo-5-methoxyphenyl)-3-pentanone (13)

The crude **12** was dissolved in CH_2Cl_2, pyridine (1 ml, 12 mmol, 3.5 equiv.) was added, and the mixture was cooled to −10°C. A solution of bromine in CH_2Cl_2 (10% v/v, 4.4 ml, 8.6 mmol, 2.5 equiv.)

was added dropwise. After the addition was complete, the reaction mixture was allowed to warm to rt and stirred until the starting material had disappeared (by NMR, ca. 4 h). The mixture was shaken with aqueous $NaHSO_3$ to remove excess bromine, washed with dilute HCl and water and dried (Na_2SO_4). Evaporation gave 1.48 g of **13** as a light-yellow oil containing ca. 5% impurities by NMR. The product solidified into a wax on standing.

^{1}H NMR: 2.74 (t, J=8 Hz, 4H), 2.96 (t, J=8 Hz, 4H), 3.81 (s, 6H), 6.63 (dd, J=3 Hz, 9 Hz, 2H), 6.78 (d, J=3 Hz, 2H), 7.39 (d, J=9 Hz, 2H); ^{13}C NMR: 30.6, 42.5, 55.4, 113.6, 114.6, 116.1, 133.3, 141.2, 159.0, 208.4; IR (film, cm^{-1}): 1241; 1472; 1715 (C=O).

*3.5. 4,4′-Dibromo-7,7′-dimethoxy-1,1′-spirobiindane (**14**)*

The crude **13** was stirred with 13 g of polyphosphoric acid at 105°C for 5.5 h. The mixture was poured into water, extracted with Et_2O, then with CH_2Cl_2. The extract was rotary evaporated with silica gel, and eluted through a pad of silica gel with hexanes:EtOAc, 9:1. The eluate was evaporated, and the crystalline residue was recrystallized from hexanes:EtOAc to give 846 mg of **14** (57% for 3 steps). A 65% yield of **14** was obtained from chromatographically purified **13**. Mp 157–158°C; ^{1}H NMR: 2.16 (m, 2H), 2.31 (m, 2H), 2.96 (m, 2H), 3.05 (m, 2H), 3.52 (s, 6H), 6.52 (d, J=9 Hz, 2H), 7.26 (d, J=9 Hz, 2H); ^{13}C NMR: 33.1, 37.8, 55.3, 61.8, 110.4, 110.7, 130.3, 138.0, 144.8, 155.5; IR (film, cm^{-1}): 1263, 1471.

*3.6. 7,7′-Dimethoxy-1,1′-spirobiindane (**15**)*

A solution of **14** (1.215 g, 2.773 mmol) in 24 ml of THF in a flame-dried flask, under nitrogen, was cooled to −78°C and treated with *n*-BuLi (4.4 ml, 2.5 M solution in hexanes, 4 equiv.). After 1 h, the reaction mixture was quenched by addition of 1 ml of EtOH, worked up with CH_2Cl_2 and water, and dried (Na_2SO_4). The solution was evaporated, and the residue was recrystallized from hexanes to give 726 mg of the product (93% yield).

Mp 139–140°C; ^{1}H NMR: 2.16 (m, 2H), 2.32 (m, 2H), 2.99 (m, 2H), 3.03 (m, 2H), 3.52 (s, 6H), 6.62 (d, J=8 Hz, 2H), 6.85 (d, J=8 Hz, 2H), 7.12 (t, J=8 Hz, 2H); ^{13}C NMR: 31.6, 38.8, 55.2, 59.2, 108.6, 116.8, 127.5, 136.9, 145.3, 156.5; IR (film, cm^{-1}): 772.

3.7. rac-*1,1′-Spirobiindane-7,7′-diol (**16**)*

A solution of **15** (759 mg, 2.71 mmol) in 12 ml of CH_2Cl_2 in a flame-dried flask, under nitrogen, was cooled to −78°C, treated with 1 M BBr_3 in CH_2Cl_2 (6.2 ml, 2.3 equiv.) and allowed to warm to rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with water until washings had neutral reaction. The solution was dried (Na_2SO_4), evaporated, and the residue was recrystallized from hexanes to give 582 mg of the product (85% yield).

Mp 115–116°C; ^{1}H NMR: 2.19 (m, 2H), 2.30 (m, 2H), 3.03 (m, 4H), 4.61 (s, 2H), 6.68 (d, J=8 Hz, 2H), 6.89 (d, J=8 Hz, 2H), 7.17 (t, J=8 Hz, 2H); ^{13}C NMR: 31.2, 37.4, 57.4, 114.3, 117.7, 129.9, 130.4, 145.8, 152.9; IR (film, cm^{-1}): 778, 1463, 1586, 3524 (O–H).

*3.8. 7,7′-Bis-(L-menthyloxy-carbonyloxy)-1,1′-spirobiindane (**20a** and **20b**)*

L-Menthyl chloroformate (1.7 ml, 7.93 mmol, 2.43 equiv.) was added to a stirring solution of *rac*-**16** (822 mg, 3.26 mmol), NEt_3 (1.7 ml, 12.2 mmol, 3.74 equiv.), and DMAP (40 mg, 0.33 mmol, 0.1 equiv.) in 33 ml of CH_2Cl_2 under nitrogen. After stirring for 9 h at rt, the mixture was washed with water, dilute

HCl, and brine. The solution was dried (Na_2SO_4), evaporated, and the residue was chromatographed (3% Et_2O in hexanes, 7 inch silica gel column) to give 956 mg of pure **20a** as a colorless oil (95% yield), 852 mg of pure crystalline **20b** (85% yield), and 168 mg of mixed fractions from which additional **20b** could be obtained by recrystallization from hexanes.

20a: ^{1}H NMR: 0.68 (d, 6H), 0.81 (m, 4H), 0.83 (d, 6H), 0.90 (d, 6H), 0.94 (m, 2H), 1.24 (m, 2H), 1.40 (m, 2H), 1.59 (m, 4H), 1.75 (m, 2H), 1.84 (m, 2H), 2.24 (m, 2H), 2.36 (m, 2H), 3.05 (m, 4H), 4.30 (ddd, 2H), 6.95 (d, J=8 Hz, 2H), 7.07 (d, J=8 Hz), 7.18 (t, J=8 Hz, 2H); ^{13}C NMR: 16.1, 20.8, 22.0, 23.0, 25.5, 31.19, 31.24, 34.0, 38.8, 40.2, 46.5, 59.1, 78.6, 120.0, 122.1, 128.0, 139.0, 145.8, 147.7, 152.7; IR (film, cm^{-1}): 1231, 1755 (C=O).

20b: mp 185.5–186°C; ^{1}H NMR: 0.67 (d, 6H), 0.81 (m, 4H), 0.82 (d, 6H), 0.88 (d, 6H), 0.90 (m, 2H), 1.21 (m, 2H), 1.37 (m, 2H), 1.51 (m, 2H), 1.58 (m, 4H), 1.87 (m, 2H), 2.96 (m, 2H), 3.01 (m, 2H), 4.35 (ddd, 2H), 6.92 (d, J=8 Hz, 2H), 7.10 (d, J=8 Hz, 2H), 7.19 (t, J=8 Hz, 2H); ^{13}C NMR: 16.0, 20.7, 21.9, 23.0, 25.5, 31.1, 31.3, 34.0, 38.3, 40.4, 46.7, 58.9, 78.6, 120.4, 122.2, 128.0, 139.2, 145.6, 147.5, 153.2; IR (film, cm^{-1}): 1237, 1268, 1755 (C=O).

*3.9. (S)-(−)- and (R)-(+)-1,1′-Spirobiindane-7,7′-diol ((S)-(−)-**16** and (R)-(+)-**16**)*

A solution of **20b** (712 mg, 1.15 mmol) and 0.4 ml of hydrazine hydrate in 7.5 ml of THF was refluxed under nitrogen for 2 h. The mixture was diluted with CH_2Cl_2, washed with dilute HCl, water, and dried (Na_2SO_4). Chromatography (hexanes:EtOAc, 6:1) followed by recrystallization from boiling hexanes afforded 266 mg of (*S*)-(−)-**16** as fine needles (91% yield). The opposite enantiomer, (*R*)-(+)-**16**, was obtained analogously from **20a** in 86% yield. The enantiomers were less soluble in hexanes than the racemate. Repeated recrystallization did not raise the melting point.

(*S*)-(−)-**16**: mp 155–156°C; $[\alpha]_D^{25}$=−32.7 (c 1.0, $CHCl_3$); (*R*)-(+)-**16**: mp 155.5–156°C; $[\alpha]_D^{25}$=+32.5 (c 1.0, $CHCl_3$).

Acknowledgements

VBB is grateful to his Graduate Advisor, Professor V. H. Rawal, for his support and useful discussions on this project. This work was sponsored in part by a GAANN Fellowship (Department of Education).

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10. Although preparation of 1,5-bis-*m*-anisyl-3-pentanone via this route has been described,[7c] difficulties were encountered in repeating the condensation step according to the published procedure. In addition, reduction with Raney nickel as a catalyst proved to be more convenient than with Pd/C, causing very little over-reduction to the alcohol and thus obviating the need for purification.
11. An alternative cyclization method ($POCl_3$, $SnCl_4$, PhH, reflux)[7e] afforded, at best, 39% yield.
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13. Although spiranes possess axial symmetry, for purposes of nomenclature they are treated as having a chiral center.[4] Configurationally, (*S*)-(−)-SPINOL corresponds to (*R*)-(+)-BINOL.
14. Correspondence regarding the X-ray data should be addressed to Professor Arnold L. Rheingold, University of Delaware.