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Synthesis and Resolution of a New Chiral C_2-Symmetric Bisphenol: *trans*-1,2-Bis(2-hydroxyphenyl)cyclopentane

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Abstract: The title compound was prepared in six steps from dicumarol. Subsequent resolution with *O*-methylmandelic acid gave either enantiomer in ≥98% ee. © 1997 Elsevier Science Ltd.

The endowment of chemical systems with the property of chirality is an increasingly important problem. Typical approaches involve either the incorporation of commercially available (or known) chiral units into existing achiral systems or the design of new chemical systems around the structure of such chiral units. Some of the most widely-applicable and useful chiral units for this purpose are 1,1'-binaphthalene-2,2'-diol (BINOL, **1**) and its derivatives.[1] Despite this remarkable, but limited utility, very little effort has been reported to develop BINOL-like phenols with markedly different core structures.[2,3] Motivated by our continued interest in chiral C_2-symmetric reagents and ligands,[4] we considered the possibility of developing a new class of bis(hydroxyaryls) (BOAs) with two basic characteristics: (1) an orientation of aromatic groups capable of producing cyclic structures bearing an enveloping C_2-symmetric chiral wall[5,6] (Figure 1); and (2) a hydrocarbon scaffolding for maximal stability. Cyclopentane **2** was targeted as a prototype of such a class of compounds.[7] Recently, the synthesis and resolution of a structurally-related dioxolane, **3**, was described.[2] We report here the first synthesis and resolution of cyclopentane **2**, for which we propose the trivial name "BOPCOP."

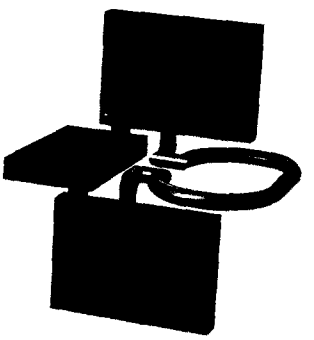
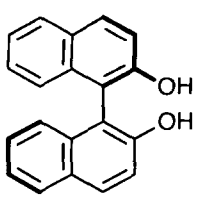
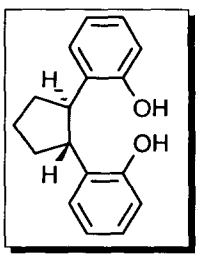


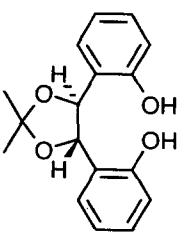
Figure 1. Cyclic structure with a C_2-symmetric chiral wall.



1

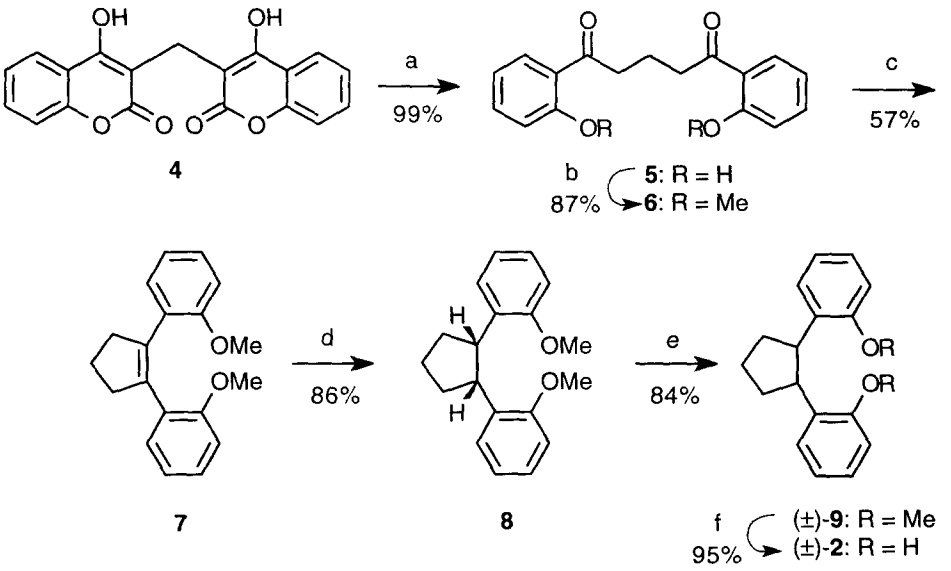


2



3

Scheme 1.[a]

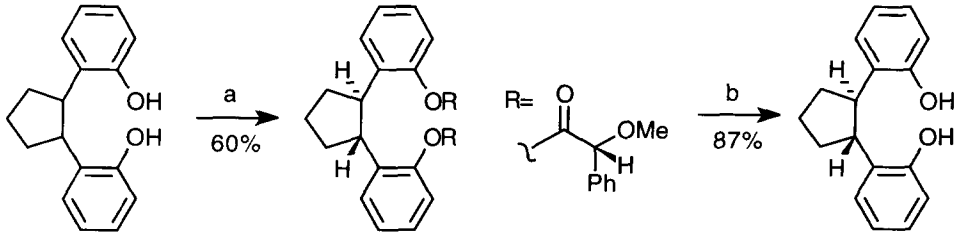


[a] (a) (1) 10% KOH (aq.), reflux, 12 h (2) Conc. HCl; (b) Me_2SO_4 / KOH, EtOH; (c) $TiCl_4$ / Zn, THF, rt, 22 h; (d) Et_3SiH / CF_3CO_2H, CH_2Cl_2, rt, 24 h; (e) KO^tBu, DMSO, 100 °C, 6 h; (f) BBr_3, CH_2Cl_2, 0 °C - rt, 5.5 h.

Racemic BOPCOP was prepared in six steps from commercially-available dicumarol (**4**) (Scheme 1). Decarboxylative hydrolysis of **4** (99%)[8] followed by dimethylation of the resulting bisphenol **5** with Me_2SO_4 / KOH in EtOH[9] yielded diketone **6** (87%). Reductive cyclization of **6** with $TiCl_4$ / Zn in THF[10] afforded cyclopentene **7** (57%), which was reduced with Et_3SiH / CF_3CO_2H in CH_2Cl_2[11] to the *cis*-cyclopentane **8** (86%).[12] Isomerization of **8** with KO^tBu in DMSO[13] gave the desired *trans* isomer **9**[14] (84%) which was demethylated with BBr_3,[15] yielding (±)-**2** (95%). It is noteworthy that no distillation or chromatography steps were required in this reaction sequence .

BOPCOP was resolved via its *O*-methylmandelic acid diester (Scheme 2). Esterification of (±)-**2** with (*R*)-(-)-*O*-methylmandelic acid (DCC, DMAP)[16] followed by flash chromatography (1:1 *n*-hexane-ether) gave disester **10** and the corresponding diastereomer as a 1:1 mixture. Crystallization of this mixture from 2:1 Skelly B-ether yielded **10** (60%) in ≥98% de (^1H NMR). Single-crystal X-ray diffraction revealed the assigned (*R*, *R*) ring stereochemistry.[17] Hydrolysis of diester **10** with K_2CO_3 / MeOH / H_2O[18] afforded (*R*, *R*)-(-)-**2** in ≥98% ee {$[\alpha]_D^{24}$ = -93.7 (*c* 0.95, $CHCl_3$)}, determined by re-esterification with (*R*)-(-)-*O*-methylmandelic acid and integration of the ^1H NMR methoxy signals of the resulting diester. A similar resolution using (*S*)-(+)-*O*-methylmandelic acid gave (*S*, *S*)-(+)-**2**, also in ≥98% ee {$[\alpha]_D^{24}$ = +93.7 (*c* 0.95, $CHCl_3$)}.

Scheme 2.[a]



(±)-**2** **10** (*R*, *R*)-(-)-**2**

[a] (a) (*R*)-(-)-*O*-methylmandelic acid, DCC, DMAP, CH_2Cl_2, rt, 5 h. (b) K_2CO_2, MeOH, H_2O, rt, 12 h.

In conclusion, we have developed a straightforward synthetic route to BOA **2** in enantiopure form. The use of this and similar C_2-symmetric BOAs in systems originally employing BINOL, and the development of unique applications for such BOAs should provide numerous intriguing arenas of investigation.

ACKNOWLEDGMENT

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SELECTED SPECTROSCOPIC DATA

2: ^{13}C NMR ($CDCl_3$ 75 MHz): δ (ppm) 152.9 (s), 130.9 (s), 127.4 (d), 127.0 (d), 121.0 (d), 115.5 (d), 45.6 (d), 27.8 (t), 23.9 (t); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.09 (br s, 2 H), 7.18 (d, J = 7.1 Hz, 2 H), 7.10 (td, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 2 H), 6.93-6.83 (m, 4 H), 3.41 (br s, 2 H), 2.18-1.89 (m, 6 H).

7: ^{13}C NMR ($CDCl_3$ 75 MHz): δ (ppm) 156.9 (s), 137.2 (s), 129.8 (d), 128.5 (s), 127.5 (d), 120.1 (d), 110.7 (d), 55.1 (q), 37.7 (t), 23.0 (t); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.09 (td, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 2 H), 6.91 (dd, J_1 = 7.6 Hz, J_2 = 1.7 Hz, 2 H), 6.78-6.68 (m, 4 H), 3.61 (s, 6 H), 2.89 (t, J = 7.5 Hz, 4 H), 2.07 (quintet, J = 7.5 Hz, 2 H).

8: ^{13}C NMR ($CDCl_3$ 75 MHz): δ (ppm) 157.3 (s), 131.7 (s), 127.8 (d) 126.2 (d), 119.2 (d), 109.1 (d), 54.8 (q), 41.9 (d), 30.3 (t), 24.3 (t); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 6.96 (t, J = 7.8 Hz, 2 H), 6.75 (d, J = 7.4 Hz, 2 H), 6.65 (t, J = 7.5 Hz, 2 H), 6.53 (d, J = 8.1 Hz, 2 H), 3.89 (br s, 2 H), 3.47 (s, 6 H), 2.08-1.95 (m, 5 H), 1.88-1.72 (m, 1 H).

9: ^{13}C NMR ($CDCl_3$ 75 MHz): δ (ppm) 157.7 (s), 132.9 (s), 127.1 (d), 126.4 (d), 120.5 (d), 110.4 (d), 55.4 (q), 44.0 (d), 34.0 (t), 24.0 (t); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.21 (d, J = 7.6 Hz, 2 H), 7.04 (t, J = 7.9 Hz, 2 H), 6.82-6.74 (m, 4 H), 3.72 (s, 6 H), 3.70-3.63 (m, 2 H), 2.35-2.23 (m, 2 H), 1.92-1.82 (m, 2 H), 1.71-1.46 (m, 2 H).

10: ^{13}C NMR ($CDCl_3$ 75 MHz): δ (ppm) 169.1 (s), 148.2 (s), 136.2 (s), 135.0 (s), 129.4, 128.9, 127.6, 126.9, 126.6, 126.4, 121.6 (d), 82.4 (d), 57.3 (q), 43.2 (d), 34.1 (t), 22.6 (t); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.61-7.34 (m, 10 H), 7.05-6.83 (m, 4 H), 6.82 (dd, J_1 = 1.4 Hz, J_2 = 7.7 Hz, 2 H), 6.48 (dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 2 H), 5.00 (s, 2 H), 3.46 (s, 6 H), 2.47-2.37 (m, 2 H), 1.66-1.56 (m, 2 H), 1.40-1.28 (m, 2 H), 1.00-0.90 (m, 2 H). ***Diastereomer***: ^{13}C NMR ($CDCl_3$ 75 MHz): δ (ppm) 169.1 (s), 148.6 (s), 136.0 (s), 134.8 (s), 129.1, 128.8, 127.3, 126.81, 126.76, 126.7, 121.7 (d), 82.5 (d), 57.4 (q), 42.6 (d), 33.5 (t), 22.3 (t); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.61-7.31 (m, 10 H), 7.09-6.96 (m, 4 H), 6.87 (dd, J_1 = 1.7 Hz, J_2 = 7.6 Hz, 2 H), 6.72 (dd, J_1 = 1.7 Hz, J_2 = 7.5 Hz, 2 H), 5.01 (s, 2 H), 3.49 (s, 6 H), 2.56-2.52 (m, 2 H), 1.62-1.52 (m, 2 H), 1.25-1.15 (m, 2 H), 1.00-0.86 (m, 2 H).

REFERENCES AND NOTES

1. For a review, see: Rosoni, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. For a superb bibliography on numerous recent uses of binaphthols, see reference 5.
2. Yamamoto, H.; Kobayashi, S.; Kanemasa, S. *Tetrahedron: Asymmetry* **1996**, *7*, 149.
3. For a chiral C_2-symmetric catechol, see: Kelly, T.R.; Chandrakumar, N.S.; Saha, J.K. *J. Org. Chem.* **1989**, *54*, 980.
4. Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581.
5. For a biaryl-based approach, see: Bao, J.; Wulff, W.D. Dominy, J.B.; Fumo, M.J.; Grant, E.B.; Rob, A.C.; Whitcomb, M.C.; Yeung, S.-M.; Ostrander, R.L.; Rheingold, A.L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.
6. Properly positioned aryl groups are thought to play key roles in a variety of chiral recognition phenomena. For a review, see: Jones, G.B.; Chapman, B.J. *Synthesis* **1995**, 475.
7. To our knowledge, the only other bis(hydroxyphenyl)cyclopentane ever reported is the 4-hydroxyphenyl analog of **2**: (a) Meuller, G.P.; Fleckenstein, J.G.; Tallent, W.H. *J. Am. Chem. Soc.* **1951**, *73*, 2651. For a related coumarin dimer-derived cyclobutane, see: (b) Saigo, K.; Sekimoto, K.; Yonezawa, N.; Ishi, F.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1006. The diphenylphosphino analog of **2** has been prepared in enantiopure form: (c) Fukada, N.; Mashima, K.; Matsumura, Y.; Takaya, H. *Tetrahedron Lett.* **1990**, *31*, 7185.
8. Stahmann, M.A.; Huebner, F.; Link, K.P. *J. Biol. Chem.* **1941**, *138*, 513.
9. Johnson, W.S.; Keller, R.T. *Org. Synth. Coll. Vol.* **1963**, *4*, 836.
10. We made several modifications to a published titanium-based coupling procedure: Tirado-Reeves, J.; Oliver, M.A.; Fronczek, F.R.; Gandour, D. *J. Org. Chem.* **1984**, *49*, 1627. **Experimental:** To an ice bath-cooled solution of **6** (5.00 g, 16.0 mmol, 1.0 eq) in THF (150 mL) under nitrogen with vigorous stirring was added dropwise neat $TiCl_4$ (7.0 mL, 64 mmol, 4.0 eq). After 5 min, the resulting orange-yellow suspension was treated with commercial zinc dust (8.37 g, 128 mmol, 8.0 eq) in a single portion, producing a copious precipitate and a dark brown color. The ice bath was removed and the thick mixture was stirred at room temperature for 24 h (after 15 min, the reaction had thinned considerably). Water (140 mL) and ether (280 mL) were added, and the mixture was stirred for 5 min. (Note: the following filtration and aqueous workup should be performed within 60 min to avoid the precipitation of intractable titanium salts.) The biphasic mixture was filtered through a pad of celite and the purple aqueous phase was extracted with ether (2x50 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL) and then dried over $MgSO_4$. Solvent was removed *in vacuo* and the oily residue was pumped under vacuum (0.05 mm Hg, rt) overnight, yielding an orange solid / oil mixture which was triturated with hot Skelly B (2x50 mL). Evaporation of the solution followed by crystallization of the resulting residue from Skelly B yielded cyclopentene **7** as yellow prisms (2.58 g, 57%): mp 76-77 °C.
11. Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Synthesis* **1974**, 633.
12. Relative stereochemical assignments for **8** and **9** are based on NMR data (^1H and ^{13}C) and reactivity behavior. The difference in ^1H NMR chemical shift of the benzylic protons of **8** and **9** (0.2 ppm) is consistent in magnitude (0.3-0.6 ppm) and direction (upfield for *trans* isomer) with previous ^1H NMR data for 1,2-diarylcyclopentanes. Note: (a) Curtin, D.Y.; Dayagi, S. *Can. J. Chem.* **1964**, *42*, 867. The downfield benzylic ^{13}C NMR signal for **9** relative to **8** (2.1 ppm) agrees with an empirical rule that predicts a *ca.* 2.5 ppm downfield shift for every *anti* vicinal hydrogen-hydrogen interaction: (b) Whitesell, J.K.; Minton, M.A. *J. Am. Chem. Soc.* **1987**, *109*, 225.
13. Curtin, D.Y.; Bender, P.E.; Hetzer, D.S. *J. Org. Chem.* **1971**, *36*, 565.
14. A *trans / cis* ratio of 97:3 was obtained based on ^1H NMR spectra of the crude reaction product. An additional product was also present (*ca.* 10%). This impurity may result from monodemethylation during the basic isomerization conditions.
15. McOmie, J.F.W.; Watts, M.L.; West, D.E. *Tetrahedron* **1968**, *24*, 2289.
16. See reference 2 and: Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J. Org. Chem.* **1986**, *51*, 2370.
17. We thank Dr. Vincent Lynch for this analysis. Details will be published elsewhere.
18. Whitesell, J.K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.

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