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Two new efficient preparations of enantiopure 2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl

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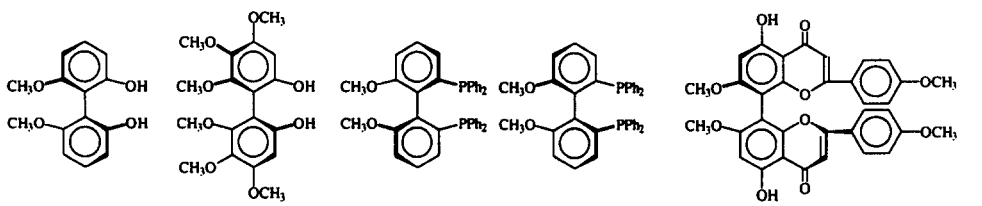
Abstract: Two new useful methods for the preparation of diol **1** starting from available compounds are described. Separation of the two enantiomers entails resolution of racemic diol **1** via the corresponding diastereomeric *N*-methylated phosphorothioamidates. Their separation by recrystallization followed by reduction afforded diol (a*S*)-**1** and (a*R*)-**1** in 100% and 72% ee, respectively. © 1997 Elsevier Science Ltd. All rights reserved.

Substituted biphenyls which have hindered rotation about the 1,1′-bond are chiral. By introducing proper substituents at the ortho positions, biphenyl derivatives become configuratively stable[1]. C_2 symmetric *ortho* hydroxylated biphenyls (e.g. **2**–**5**) have become increasingly important not only for their wide application in asymmetric synthesis[2] and catalysis[3] but also for their presence in many structures of pharmacologically active natural products[4] and agrochemicals[5]. Furthermore they can be readily recognized as configurationally stable analogues of the widely used 1,1′-binaphthalene-2,2′-diol.

Since we are interested in developing methods to prepare C_2 symmetric biphenols with hindered rotation about the 1,1′ bond, herein we describe two new preparations and a method of resolution of 2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl **1**. Although papers support the configurational stability of diol **1**[6], to the best of our knowledge, only two methods[7,8] have been appeared in the literature on its synthesis and both of them prepare diol **1** only in (a*S*) enantiomeric pure form.



(a*S*)-**1** (a*S*)-**2**[2] (a*R*)-**3**[3] (a*S*)-**4**[3] (a*S*)-**5**[4]

As shown in Scheme 1, one method starts from tetrol **6**, readily available by known procedure[9], whereas the other one uses as starting material the commercially available 3-methoxy-phenol **9**.

The overall yield of method *1* was limited by step *1a*. Beside *mono*dioxepine **7** (55% yield) and starting material, we have also obtained the corresponding *bis* dioxepine, in 3% yield. Lower temperature and longer reaction time did not change the result. Method *2*, gives a lower overall yield than method *1* providing diol **1** in only four steps. The coupling reaction of diiodo derivative **11** gave a mixture of products from which we were able to identify acetals **8** and **12**. We presume the presence of other homologs in the reaction mixture. In fact the yield of **1** improved when step *2d* was carried out without purification and isolation of the starting mixture of coupling. All compounds obtained are air stable, easly separated and purified by crystallization or flash chromatography. Compounds **7**, **8**, **11** and **12** are crystalline solid.

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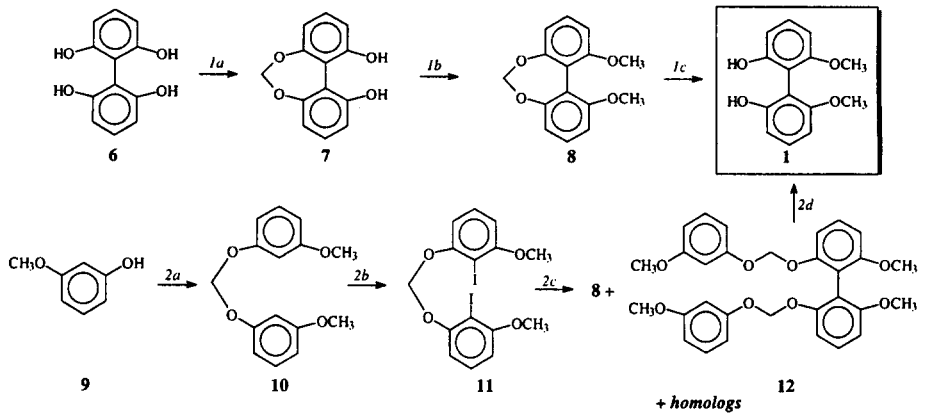
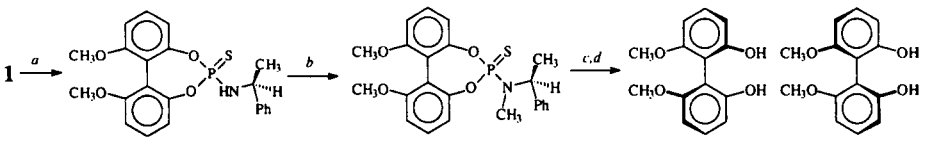


Scheme 1. Method *1*: *a*. CH_2I_2, K_2CO_3, DMF. *b*. CH_3I, CH_2Cl_2, TBAOH. *c*. 2.2 M CH_3COCl, CH_3OH. Overall yield 55%. Method *2*: *a*. CH_2I_2, K_2CO_3, DMF. *b*. *n*-BuLi, I_2, ether. *c*. Cu, 200°C. *d*. 2.2 M CH_3COCl, CH_3OH. Overall yield 40%.

With the aim of obtaining diol **1** in enantiomerically pure forms, we carried out the resolution of racemic **1** *via* preparation of the corresponding phosphorothioamidates derived from (*S*)-(−)-α-methylbenzylamine, following a method optimized in our laboratory[10].

Reaction of diol **1** with equimolar quantities of (*S*)-(−)-α-methylbenzyldichlorophosphorothioamidate **13**[10] in the presence of pyridine gave, in 90% yield, phosphorothioamidates (a*R*, *S*)-**14** and (a*S*, *S*)-**14** in a 1:1 ratio (Scheme 2).



a. (S)-(-)-$Cl_2P(S)NHCH(CH_3)Ph$ (**13**), pyridine; *b*. CH_3I, TBAOH, CH_2Cl_2; *c*. selective recrystallization; *d*. $LiAlH_4$, THF.

Scheme 2.

While several attempts to separate diastereomers (a*R*, *S*)-**14** and (a*S*, *S*)-**14** were not successful, a sharp difference in solubility of the two diastereomers **14** was observed after *N*-methylation. When phosphorothioamidates (a*R*, *S*)-**14** and (a*S*, *S*)-**14** were treated with CH_3I in phase-transfer catalysis, *N*-methyl phosphorothioamidates (a*R*, *S*)-**15** and (a*S*, *S*)-**15** were produced in 1:1 ratio and in 90% yield. Diastereopure (a*S*, *S*)-**15** was readily separated by only one recrystallization ($CHCl_3$–EtOH) and in 86% yield. Diastereomer (a*R*, *S*)-**15** was obtained in 72% de and in high yield although a little crop of diastereopure (a*R*, *S*)-**15** has been crystallized from the mixture of the diastereomers **15**. Each phosphorothioamidate **15**, in the presence of $LiAlH_4$ in THF, afforded diol (a*S*)-**1** and (a*R*)-**1** in 100% and 72% ee, respectively and in 90% yield. The enantiomeric purity of diol **1** was related to the diastereomeric purity of phosphorothioamidates **15** which was verified by ^1H NMR and ^{31}P NMR. The assignment of the absolute configuration of (a*S*)-(−)-2,2′-dihydroxy-6,6′-dimethoxy-1,1′-biphenyl **1** was made by comparation to the sign of the specific rotation of that found in the literature[7]. (*S*)-(−)-α-methylbenzylamine and (*S*)-(−)-*N*, α-dimethylbenzylamine were recovered without lose of enantiomeric purity.

In conclusion we have described two effective methods for the preparation of diol **1** and an easy resolution procedure that allows diol (a*S*)-**1** to be obtained in high yield and in enantiopure form by only one recrystallization and diol (a*R*)-**1** in 72% ee. Furthermore the resolution method allows enantiopure (*S*)-(−)-*N*, α-dimethylbenzylamine to be obtained in a secondary expensive chiral amine.

This resolution methodology should prove to be very useful for the availability of a variety of axially chiral *ortho* biphenols in enantiomeric form.

Experimental section

Method 1

7: A solution of 2,2′,6,6′-tetrol-1,1′-biphenylene **6** (2 g, 9.16 mmol), K_2CO_3 (2.53 g, 18.33 mmol) in dry DMF (20 mL) was stirred at 20°C for 1 h under N_2. A solution of CH_2I_2 (2.45 g, 9.16 mmol) in dry DMF (10 mL) was added dropwise and the heterogeneus mixture was stirred for 72 h. The reaction mixture was then quenched with 100 mL of H_2O. A solution of 10% HCl was added until neutral pH. The organic phase was extracted with ether (5×20 mL), dried over Na_2SO_4 and rotoevaporated to give **7** as colourless solid. The product was purified by flash chromatography (CH_2Cl_2–petroleum, 1:1) to give **7** (55% yield). **7**: mp 161–3°C; ^{1}H NMR δ 5.55 (s, 2H), 6.82 (bs, 2H), 6.89 (d, J=8.4 Hz, Ar, 2H), 6.90 (d, J=8.4 Hz, Ar, 2H), 7.27 (t, J=8.4 Hz, Ar, 2H); Anal. Calcd for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38; Found: C, 67.71; H, 4.40.

8: To a diphasic solution of **7** (0.25 g, 1.1 mmol) and tetrabutylammoniumhydroxide (TBAOH) (3.26 mmol, 40% aqueous solution) in CH_2Cl_2(10 mL) a solution of CH_3I (0.75 g, 4.84 mmol) in CH_2Cl_2 (5 mL) was slowly added. After stirring at rt for 12 h, the reaction mixture was poured into 100 mL of H_2O. A solution of 10% HCl was added until neutral pH. The organic phase was extracted with CH_2Cl_2 (5×20 mL), dried over Na_2SO_4 and rotoevaporated. Purification by flash chromatography (CH_2Cl_2) afforded **8** (80% yield) as a colorless solid. **8**: mp 125–7°C;^{1}H NMR δ 3.86 (s, 6H), 5.53 (s, 2H), 6.85 (dd, J=0.9, 8.4 Hz, Ar, 2H), 6.90 (dd, J=0.9, 8.4 Hz, Ar, 2H), 7.33 (t, J= 8.4 Hz, Ar, 2H); Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46; Found: C, 69.64; H, 5.25.

1: To an ice cooled solution of **8** (0.21 g, 0.8 mmol) in CH_3OH (43 mL), CH_3COCl (7.6 g, 96 mmol) was slowly added. After stirring at rt for 96 h, the reaction mixture was poured in 100 mL of H_2O and extracted with ether (5×20 mL). The organic extracts were collected, dried over Na_2SO_4 and rotoevaporated. Purification by flash chromatography (CH_2Cl_2) afforded **1** (90% yield) as a colorless solid. **1**: mp 127–9°C; ^{1}H NMR δ 3.79 (s, 6H), 5.00 (s, 2H), 6.64 (d, J=8.4 Hz, Ar, 2H), 6.75 (d, J=8.4 Hz, Ar, 2H), 7.34 (t, J=8.4 Hz, Ar, 2H).

Method 2

10: Following the same procedure described for **7**, acetal **10** (95% yield) was obtained as colorless oil: ^{1}H NMR δ 3.81 (s, 6H), 5.73 (s, 2H), 6.64 (dd, J=1.4 and 8.4 Hz, Ar, 2H), 6.72 (m, Ar, 2H), 6.76 (dd, J=1.4 and 8.4 Hz, Ar, 2H), 7.24 (t, J=8.4 Hz, 2H, Ar).

11: To a solution of **10** (0.14 g, 1 mmol) in dry ether (10 mL), *n*-BuLi (1.6 M in hexanes, 1.28 mL, 2.2 mmol) was added dropwise under stirring at rt under N_2. After 24 h the solution was cooled at −50°C and I_2 (0.55 g, 2.2 mmol) was added in one portion. The mixture of reaction was allowed to reach at rt for 12 h. The excess of I_2 was reduced with a saturated aqueous solution of Na_2SO_3 and organic layer was extracted with ether (2×100 mL), dried over Na_2SO_4 and evaporated to obtain **11** (95% yield) as pale yiellow solid: m.p. 110–2°C; ^{1}H NMR δ 3.87 (s, 6H), 5.82 (s, 2H), 6.55 (dd, J=1.2 and 8.4 Hz, Ar, 2H), 6.95 (dd, J=1.2 and 8.4, Ar, 2H), 7.28 (t, J=8.4, 2H, Ar); Anal. Calcd for $C_{15}H_{14}O_4I_2$: C, 35.18; H, 2.76; I, 49.56; Found: C, 35.56; H, 2.72.

Coupling of ***11***

A mixture of **11** (2 g, 5.2 mmol) and Cu powder (8 g, 125.9 mmol) was heated in a porcelain crucible at 250°C for 1 h. The mixture was treated with ether in order to separate the inorganic insoluble products. Ether was evaporated to give a solid residue which was purified by flash chromatography (petroleum). The following products have been eluted: **8** (15% yield), **12** (20% yield) and an undefinite mixture of homologs (60% yield). **12**: ^{1}H NMR δ 3.56 (s, 6H), 3.70 (s, 6H), 5.44 (AB, J=7.5 Hz, 4H), 6.48–6.54 (series of m, Ar, 6H), 6.64 (d, J=8.4 Hz, Ar, 2H), 6.90 (d, J=8.4 Hz, Ar, 2H), 7.05 (t,

J=8.4 Hz, Ar, 2H), 7.28 (t, J=8.4 Hz, Ar, 2H). Anal. Calcd for $C_{30}H_{28}O_8$: C, 69.76; H, 5.46; Found: C, 69.40; H, 5.65.

1: The coupling mixture derived from the above preparation was treated following the same procedure described for **1** in method *1c*. Purification by flash chromatography (CH_2Cl_2) afforded **1** (50% yield) as a colorless solid.

*(a*R, S*)-14 and (a*S, S*)-14*

Following the procedure described in ref. [10], a ca. 1:1 diasteromeric mixture of (a*R*, *S*)-**14** and (a*S*, *S*)-**14** (90% yield) was obtained as a colorless solid. **14** (one diast.): ^{1}H NMR δ 1.56 (d, J=6.9 Hz, Ar, 3H), 3.52 (m, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 4.55 (m, 1H), 6.69 (d, J=8.4 Hz, Ar, 1H), 6.80–7.40 (series of m, Ar, 10H); ^{31}P NMR δ 79.1. **14** (one diast.): ^{1}H NMR δ 1.52 (d, J=6.9 Hz, Ar, 3H), 3.52 (m, 1H), 3.80 (s, 3H), 3.85 (s, 3H), 4.55 (m, 1H), 6.16 (d, J=8.4 Hz, Ar, 1H), 7.80–7.40 (series of m, Ar, 10H); ^{31}P NMR δ 78.3; Anal. Calcd for $C_{22}H_{22}O_4NPS$: C, 72.70; H, 6.10; Found: C, 72.65; H, 6.00.

*(a*R, S*)-15 and (a*S, S*)-15*

An equimolar solution of (a*R*, *S*)-**14** and (a*S*, *S*)-**14** (1.0 g, 2.4 mmol) was treated following the same procedure used for **8** in method *1b*. Purification by flash chromatography (CH_2Cl_2) afforded (a*R*, *S*)-**15** and (a*S*, *S*)-**15** as a colorless solid (0.96 g, 90% yield). One crystallization from $CHCl_3$-C_2H_5OH gave diastereopure (a*S*, *S*)-**15** as colorless crystals (0.41 g, 86% yield). A little crop of diasteropure (a*R*, *S*)-**15** crystallized (0.023 g, 5% yield) from the solution of diastereomers. The solution was then rotoevaporated to dryness to obtain a diastereomeric mixture (0.53 g) of (a*R*, *S*)-**15** and (a*S*, *S*)-**15** in 86: 14 ratio, respectively. (a*S*, *S*)-**15**: mp 143–5°C; ^{1}H NMR δ 1.69 (d, J=6.9 Hz, Ar, 3H), 2.16 (d, J=9.9 Hz, Ar, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 5.70 (m, 1H), 6.80–7.50 (series of m, Ar, 11H); ^{31}P NMR δ 83.13; $[\alpha]^{20}_D$ +69.9 (c 1, $CHCl_3$). (a*R*, *S*)-**15**: mp 165–6°C; ^{1}H NMR 1.51 (d, J=6.9 Hz, Ar, 3H), 2.26 (d, J=9.9 Hz, Ar, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 5.60 (m, 1H), 6.40–7.60 (series of m, Ar, 11H); ^{31}P NMR δ 82.42; $[\alpha]^{20}_D$ −100.1 (c 0.5, $CHCl_3$); Anal. Calcd for $C_{23}H_{24}O_4NPS$: C, 62.57; H, 5.48; Found: C, 62.11; H, 5.69.

*Reduction of (a*S, S*)-15*

Diastereomerically pure (a*S*, *S*)-**15** (0.44 g, 1 mmol) in dry THF (15 mL) was cooled at 0°C under N_2. $LiAlH_4$ (0.38 g, 10 mmol) was added in one portion under vigorous magnetic stirring. After 48 h at 60°C. The reaction mixture was cooled and very dilute solution of HCl (50 mL) was cautiously added until the solution tested slightly acidic. The organic solution was then evaporated to give enantiopure (*S*)-(−)-**1** as colourless solid which was purified by flash chromatography using CH_2Cl_2 as eluent. (*S*)-(−)-**1**: (90% yield); $[\alpha]^{20}_D$ −167.0 (c 1, $CHCl_3$) [lit.[7] $[\alpha]^{20}_D$ −144.0 (c 0.77, $CHCl_3$)].

*Reduction of (a*R, S*)-15*

Following the above procedure, diastereomer (a*R*, *S*)-**15** in 72% de was undergone to reduction with $LiAlH_4$ to give (a*R*)-**1**: (90% yield); $[\alpha]^{20}_D$ +103.68 (c 1, $CHCl_3$).

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References

1. Meyers, A. I. and Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682. Bringmann, G. and Vitt, D. *J. Org. Chem.* **1995**, *60*, 7674. Wolf, C.; König, W. A.; Roussel, C. *Liebigs Ann.* **1995**, 781. Kamikawa, K. and Uemura, M. *Tetrahedron Lett.* **1996**, *37*, 6359. Wolf, C.; Hochmuth, D. H.; König, W. A.; Roussel, C. *Liebigs Ann.* **1996**, 367.

2. Rossiter, B. E. and Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. Rawson, D. and Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1992**, 494.
3. Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51. Consiglio, G. and Indolese, A. *Organometallics* **1991**, *10*, 3425. Schimid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370. Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479.
4. Okuda, T.; Yoshida, T.; Ashida, M.; Yazaki, K. *J. Chem. Soc., Perkin Trans. I* **1983**, 1765. Buckleton, J. S.; Cambie, R. C.; Clark, G. R.; Craw, P. A.; Rickard, C. E. F.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1988**, *41*, 305. Rizzacasa, M. K. and Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1991**, 278. Saá, J. M. and Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963. Costero, A. M. and Pitarch, M. *J. Org. Chem.* **1994**, *59*, 2939. Zhang, F -J.; Lin, G -Q.; Huang, Q -C. *J. Org. Chem.* **1995**, *60*, 6427. Chau, P.; Czuba, I. R.; Rizzacasa, M. A. *J. Org. Chem.* **1996**, *61*, 7101.
5. Bhatia, M. S. and Pawan, J. *Experientia* **1976**, *32*, 1111. Naidu, M. S. R. and Naga Raju, C. *Magn. Res. Chem.* **1988**, *26*, 438.
6. Insole, J. M. *J. Chem. Soc. Perkin Trans 2* **1972**, 1168. Kawano, N.; Okigawa, M.; Hasaka, N.; Kouno, I.; Kawahara, Y.; Fujita, Y. *J. Org. Chem.* **1981**, *46*, 389. Nelson, T. D. and Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061.
7. Moorlag, H. and Meyers, A. *Tetrahedron Lett.* **1993**, *34*, 6993.
8. Harada, T.; Yoshida, T.; Inoue, A.; Takeuchi, M.; Oku, A. *Synlett* **1995**, 283.
9. Frantsi, M.; Lindsten, G.; Wennerstrom, O. *Acta Chem. Scand.* **1982**, 135.
10. Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1993**, *58*, 1748.

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