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TETRAHEDRON: *ASYMMETRY*

6,6′-Dibromo-3,3′-dimethoxy-2,2′-dihydroxy-1,1′-biphenyl: preparation and resolution

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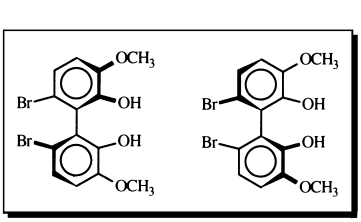
Abstract

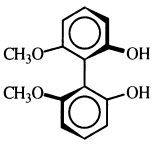
A pratical route to prepare the title biphenyl **1** starting from 3,3′,2,2′-tetramethoxy-1,1′-biphenyl **2** is described. Resolution of **1** was achieved by its conversion into the corresponding diastereomeric menthyl-dicarbonate. The absolute configuration of (*P*)-(+)-**1** was confirmed by X-ray analysis of the related diastereomer.

1. Introduction

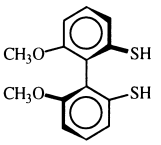
The geometrical possibilities offered by the chemical transformation of the biphenyl skeleton make it a versatile building block in drug synthesis[1] and in catalysis.[2] The growing number of hydroxylated biphenyls isolated from natural sources[3] establishes the biphenol unit as the backbone for the preparation of biologically active compounds. We have recently developed[4] inexpensive synthetic and resolution procedures for the preparation of enantiopure hydroxylated biphenyls with a C_2 symmetry axis, e.g. **3** and **4**.



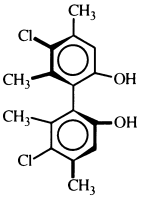
(*M*)-**1** (*P*)-**1**



(*M*)-**3**



(*M*)-**4**



(*P*)-**5**

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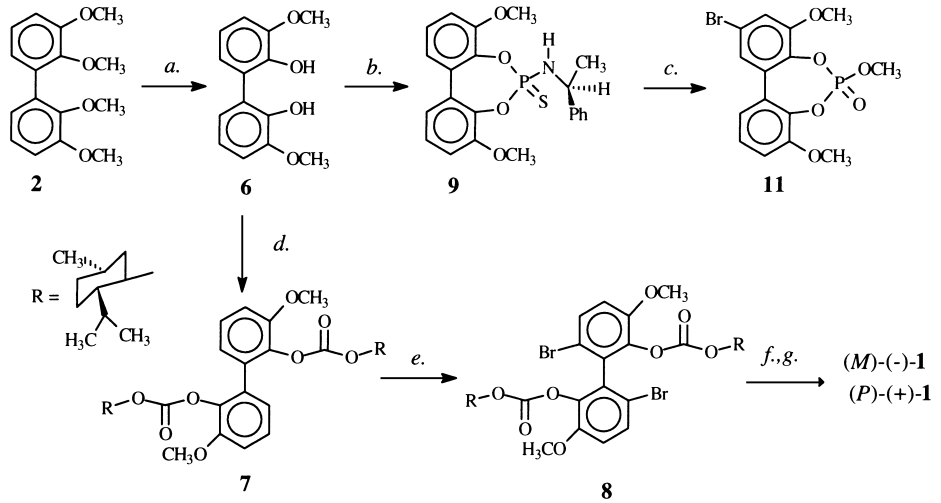
Hydroxylated biphenyls containing bromo substituents assume an important role in therapy as antibacterials as well as anti-HIV-1 agents.[5] The presence of bromo or chloro functionality in hydroxylated biaryls makes them effective chiral ligands or chiral activators (e.g. **5**) in asymmetric catalytic processes.[6] In fact, the halide improves the Lewis acidity and provides small but significant changes in the biphenol conformation. Slight variations in structural and electronic properties of the chiral ligand often induce important changes in the efficiency of asymmetric catalysis,[6,7] as well as in therapy, the relative position of bromine in hydroxylated biphenyls being of primary importance on the biological activity.[8] Our starting point was to design a new dibromobiphenol in enantiopure form. Bromo substitution at the 6,6′-positions may have a more decisive influence on the torsional angle and therefore on the reactivity and stereoselectivity of **1**. Furthermore, dimethoxy functionality at the 3,3′-positions should improve chemical and biological activity of dibromobiphenol **1**.

2. Results and discussion

In order to develop a synthetically useful method we have used 2,2′,3,3′-tetramethoxy-1,1′-biphenyl **2** as the starting biphenyl. Compound **2** was prepared in two steps in 80% overall yield, by known procedures,[9] starting from commercially available 1,2-dimethoxybenzene. Regioselective reduction of biphenyl **2** to diol **6** and successive treatment with 2.2 equiv. of (–)-menthylchloroformate gave dicarbonates **7** in high yield. Bromination of **7** under the usual conditions failed, whereas in the presence of [BTEA·Br_3] using $ZnCl_2$, we were able to obtain the two diastereomers **8** in 79% yield[10] (Scheme 1). Complete regioselectivity as well as conformational stability of dibromo derivative **8** were achieved in only one reaction step. All compounds prepared were solids, air stable, and easily separated and purified by flash chromatography using appropriate solvent mixtures.



Scheme 1. (a) BBr_3, CH_2Cl_2, –70°C, 90% yield; (b) (*S*)-(–)-$Cl_2P(S)NHCH(CH_3)Ph$ **10**, py, 80% yield; (c) [BTEA·Br_3], CH_2Cl_2, CH_3OH, 50°C, 80% yield; (d) (1*R*,2*S*,5*R*)-(–)-menthyl chloroformate, Et_3N, benzene or toluene, rt, 88% yield; (e) [BTEA·Br_3], $ZnCl_2$, CH_3COOH, 60°C, 79% yield; (f) separation of diastereomers; (g) $LiAlH_4$, THF, rt, 90% yield

Each diastereomer **8** was readily separated by flash chromatography with 99 and 95% *de*, respectively.[11] Reduction of the carbonate group was performed with $LiAlH_4$, in 90% yield at rt, to give diol (*P*)-**1** and (*M*)-**1** in 99 and 95% *ee*, respectively. In order to apply an alternative and cheaper resolution procedure of **1**, we prepared the phosphorothioamidate **9**, treating **6** with (*S*)-(–)-$Cl_2P(S)NHCH(CH_3)Ph$ **10** in the presence of pyridine.[12] In this case we chose a cheaper chiral source, (*S*)-(–)-α-methylbenzylamine, which was used in equimolar ratio and which we expected to recover, under reduction condition, without loss of enantiomeric purity. Unfortunately, under the usual bromination conditions[10] and using a mixture of MeOH and CH_2Cl_2 as solvent, phosphorothioamidate **9** gave phosphorothioate **11** as the main product. All attempts to carry out bromination of **9** at the 6,6′-positions, failed.

One diastereomer **8** was further purified by two recrystallizations from CH_2Cl_2–EtOH and its structure was defined unequivocally by X-ray analysis. The asymmetric unit of the crystal structure of diastereomer **8** comprises two molecules identical in conformation at the biphenyl structure. The plot of one molecule, as reported in Fig. 1, shows the *P* configuration for this diastereomer. The conformational stability of **8** is confirmed by the large value of the dihedral angle between the least-squares planes of the two aromatic rings. For the two molecules of the asymmetric unit the dihedral angles measure 86.1(2)° and 87.6(3)°, which compare well to the values measured for conformationally stable biphenyls.[13] Further indication of the stability of this diastereomer comes from an analysis of the intramolecular distances between the *ortho* substituents. The shortest Br···Br and Br···O separations are 4.024(1) Å and 3.936(4) Å, respectively,

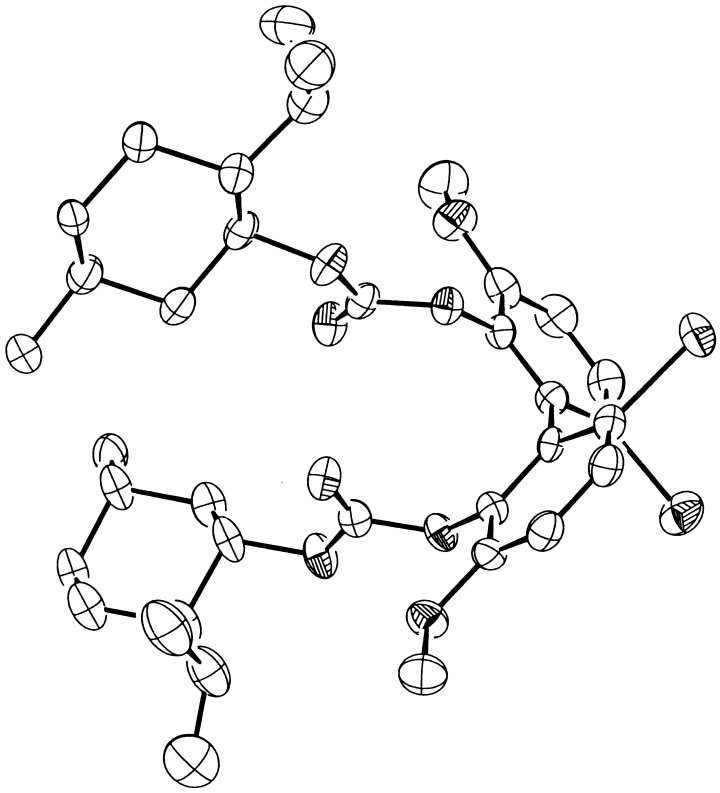


Figure 1. ORTEP plot of diastereomer **8**. Displacement ellipsoids are drawn at the 20% probability level

which are significantly greater than the corresponding sums of the van der Waals radii of 3.7 Å and 3.4 Å, as given by Bondi.[14]

Crystals of diastereomer **8**, under mild reduction conditions, gave (*P*)-(+)-6,6′-dibromo-3,3′-dimethoxy-2,2′-dihydroxy-1,1′-biphenyl **1** which have quite a high atropisomerization barrier in solution in most solvents. Interconversion of the biphenyl structure was monitored by NMR spectroscopy. Enantiopure biphenyl **1** does not racemize in organic solution even when heated to 150°C for 20 h. Bromobiphenol **1** is thermally and chemically very stable.

In conclusion, both enantiomers of **1** were readily prepared from commercially available starting materials by using a straightforward method. Our strategy takes advantage of two key steps: (1) the regioselective reduction of **2**; and (2) regioselective bromination of **7** and formation of conformationally stable biphenyl **8**. The stereochemical features of biphenol **1**, governed both by the size and shape of the substituents at the 3,3′- and 6,6′-positions and by the high value of torsional angle, are a promising approach to the development of an efficient chiral Lewis acid catalyst.

We are currently exploring the scope of the 6,6′-dibromo-3,3′-dimethoxy-2,2′-dihydroxy-1,1′-biphenyl **1** in asymmetric catalysis as well as in the agro- and biological field.

3. Experimental

3.1. General procedures

Melting points were determined on a Büchi 530 apparatus and are uncorrected. All ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded in $CDCl_3$ solution with a Varian VXR 5000 spectrometer at 299.94, 75.42 and 121.42 MHz, respectively. ^{31}P NMR chemical shifts are relative to H_3PO_4 (external standard) in $CDCl_3$. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet). Elemental analyses were performed using an elemental analyzer Perkin–Elmer model 240 C. Optical rotations were measured with a Perkin–Elmer 343 spectropolarimeter. Tetrahydrofuran (THF), benzene and toluene were freshly distilled from sodium benzophenone ketyl. Pyridine (py) and triethylamine (Et_3N) were dried over KOH and distilled before use. All reagents were of commercial quality and used as purchased. Flash chromatography was carried out with silica gel 60 (230–400 mesh, Kiesgel, EM Reagents) eluting with appropriate solution in the stated v:v proportions. Analytical thin-layer chromatography (TLC) was performed with 0.25 mm thick silica gel plates (Polygram® Sil G/UV_{254}, Macherey–Nagel). The purity of all new compounds was judged to be >98% by ^{1}H NMR and ^{13}C NMR spectral determination.

3.2. 3,3′-Dimethoxy-2,2′-dihydroxy-1,1′-biphenyl **6**

To a stirred solution of **2** (2 g, 7.3 mmol) in CH_2Cl_2 (30 mL) at –70°C under N_2, BBr_3 (0.45 mL, 4.8 mmol) was added. The cooling bath was removed and the mixture was stirred at rt for 24 h. The crude reaction was poured into ice-water, stirred for 30 min, saturated with salt and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentred to afford a brown solid. The crude material was purified by flash chromatography using a 1:5 mixture of CH_2Cl_2:petroleum as eluent to give **6** (1.62 g, 90%): mp 139.0°C [lit.[15] mp 142.5–143°C]. ^{1}H NMR δ 3.92 (s, 6H), 6.15 (bs, 2H), 6.89–7.00 (series of m, Ar, 6H); ^{13}C NMR δ 56.00, 110.12, 121.14, 125.31, 127.82, 142.34, 149.98.

3.3. [1,1′-Biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methylethyl)cyclohexyl]carbonic ester 7

A solution of **6** (2.10 g, 8.50 mmol) and Et_3N (2 mL) in benzene (15 mL) was added, dropwise, to a solution of (–)-(1*R*,2*S*,5*R*)-menthyl chloroformate (4.10 g, 18.76 mmol) in benzene (15 mL) at rt under N_2. The solution was stirred at rt for 1 h, washed with 10% HCl and water and the organic phase extracted with CH_2Cl_2. The crude, dried over Na_2SO_4, gave a colourless solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent to give **7** (4.57 g, 88%): mp 202–204°C. ^{1}H NMR δ 0.66 (d, J = 6.9 Hz, 6H), 0.78 (d, J = 6.9 Hz, 6H), 0.84 (d, J = 6.9 Hz, 6H), 0.80–1.95 (series of m, 18H), 3.79 (s, 6H), 4.44 (m, 2H), 6.84 (d, J = 7.8 Hz, Ar, 2H), 6.90 (d, J = 7.8 Hz, Ar, 2H), 7.20 (t, J = 7.8 Hz, Ar, 2H); ^{13}C NMR δ 16.15, 20.70, 21.95, 23.20, 25.76, 31.31, 34.00, 40.37, 46.87, 55.93, 70.04, 111.76, 122.32, 125.94, 137.83, 151.62, 152.64. Anal. calcd for $C_{36}H_{50}O_8$: C, 70.79; H, 8.25; found: C, 70.83; H, 8.10.

3.4. 6,6′-Bis(bromo)[1,1′-biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methylethyl)cyclohexyl]-carbonic ester 8

To a solution of **7** (5 g, 8.2 mmol) in acetic acid (40 mL) BTEA·Br_3 (7.78 g, 18.0 mmol) and $ZnCl_2$ (2.78 g, 20.5 mmol) were added in one pot. The reaction mixture was stirred at 60°C for 5 h until the initial orange colour faded. Aqueous $Na_2S_2O_5$ was added to the mixture and the organic phase was then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 to obtain a 1:1 mixture of the two diastereomers (*P*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8** and (*M*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8** as an orange solid that was separated by flash chromatography using a 1:1 mixture of CH_2Cl_2: petroleum as eluent (4.98 g, 79%). (*P*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8**: first diastereomer eluted with R_f = 0.4 (2.0 g, 40%), 99% *de*, mp 175°C. ^{1}H NMR δ 0.70 (d, J = 6.6 Hz, 6H), 0.77 (d, J = 6.6 Hz, 6H), 0.86 (d, J = 6.6 Hz, 6H), 0.85–2.10 (series of m, 18H), 3.81 (s, 6H), 4.45 (m, 2H), 6.87 (d, J = 8.7 Hz, Ar, 2H), 7.40 (d, J = 8.7 Hz, Ar, 2H); ^{13}C NMR δ 16.37, 20.66, 21.99, 23.37, 25.85, 31.49, 34.06, 40.28, 46.99, 56.08, 79.34, 113.49, 114.59, 129.95, 131.28, 139.15, 151.04, 151.67. Anal. calcd for $C_{36}H_{48}Br_2O_8$: C, 56.26; H, 6.29; found: C, 56.82; H, 6.20; $[\alpha]_D^{20}$ –95.3 (*c* 1, $CHCl_3$). (*M*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8**: second diastereomer eluted with R_f = 0.3 (2.2 g, 44%), 95% *de*, mp 113–115°C. ^{1}H NMR δ 0.72 (d, J = 6.6 Hz, 6H), 0.81 (d, J = 6.6 Hz, 6H), 0.85 (d, J = 6.6 Hz, 6H), 0.85–2.10 (series of m, 18H), 3.81 (s, 6H), 4.45 (m, 2H), 6.87 (d, J = 8.7 Hz, Ar, 2H), 7.42 (d, J = 8.7 Hz, Ar, 2H); ^{13}C NMR δ 16.14, 20.64, 21.95, 23.21, 25.82, 31.25, 34.00, 40.14, 46.77, 56.96, 79.30, 113.37, 114.39, 129.88, 131.14, 150.89, 151.29, 151.97. Anal. calcd for $C_{36}H_{48}Br_2O_8$: C, 56.26; H, 6.29; found: C, 56.87; H, 6.19; $[\alpha]_D^{20}$ +27.1 (*c* 1, $CHCl_3$).

3.5. (P)-(+)-6,6′-Dibromo-3,3′-dimethoxy-2,2′-dihydroxy-1,1′-biphenyl 1

A solution of (*P*)-**8** (99% *de*) (0.5 g, 0.65 mmol) in dry THF (30 mL) was cooled at 0°C under N_2. $LiAlH_4$ (0.23 g, 6 mmol) was added in portions with vigorous magnetic stirring. After 12 h at rt, water and 10% HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4 and evaporated to afford a colourless solid. After purification by flash chromatography using CH_2Cl_2 as eluent, enantiomerically pure (*P*)-**1** (0.24 g, 90%) and enantiomerically pure (–)-menthol (0.80 g, 85%) were obtained. (*P*)-**1**: mp 143–145°C. ^{1}H NMR δ 3.90 (s, 6H), 5.75 (bs, 2H), 6.81 (d, J = 8.4 Hz, Ar, 2H), 7.19 (d, J = 8.4 Hz, Ar, 2H); ^{13}C NMR δ 56.05, 111.51, 115.66, 123.03, 144.23, 144.99, 145.87. Anal. calcd for $C_{14}H_{12}Br_2O_4$: C, 41.62; H, 2.99; found: C, 41.58; H, 3.03. $[\alpha]_D^{20}$ +6.44 (*c* 0.7, $CHCl_3$), $[\alpha]_D^{20}$ +26.3 (*c* 0.5, THF).

3.6. (M)-6,6′-Dibromo-3,3′-dimethoxy-2,2′-dihydroxy-1,1′-biphenyl **1**

Using the above procedure, diastereomer (*M*)-**8** (95% *de*) gave (*M*)-**1** (0.24 g, 90%); $[\alpha]_D^{20}$ –6.24 (*c* 0.8, $CHCl_3$), $[\alpha]_D^{20}$ –25.5 (*c* 0.8, THF). Enantiomerically pure (–)-menthol (0.85 g, 87%) was recovered.

3.7. 4,4′-Dimethoxy-6-N-(α-methylbenzyl)aminedibenzo-(d,f)(1,3,2)dioxaphosphepin-6-oxide **9**

N-((*S*)-α-Methylbenzyl)dichlorothiophosphoroamidate **10** (0.52 g, 2.0 mmol) was added dropwise to a solution of **6** (0.42 g, 1.70 mmol) in py (50 mL) at rt under N_2. After 12 h under reflux, the reaction mixture was cooled and acidified with 10% H_2SO_4. Water was added and the organic phase was extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated to dryness to obtain a colourless solid. The crude was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent to give **9** (0.58 g, 80%): mp 165°C. ^{1}H NMR δ 1.41 (d, $J=6.6$ Hz, 3H), 3.63 (s, 3H), 3.65 (s, 3H), 4.20 (bs, 1H), 4.60 (m, 1H), 6.60–7.70 (series of m, Ar, 11H); ^{31}P NMR δ 80.27. Anal. calcd for $C_{21}H_{22}O_4NPS$: C, 60.71; H, 5.34; found: C, 60.65; H, 5.40.

3.8. 4,4′-Dimethoxy-2-bromo-6-methoxydibenzo-(d,f)(1,3,2)dioxaphosphepin-6-oxide **11**

To a solution of **9** (0.36 g, 0.85 mmol) in CH_2Cl_2 (20 mL) and CH_3OH (5 mL) BTEA·Br_3 (1.1 g, 2.52 mmol) was added. The reaction mixture was stirred at 50°C under N_2 for 5 h until the initial orange colour faded. Aqueous $Na_2S_2O_5$ was added to the mixture, then the organic phase was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 to obtain an orange solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent to give **11** (0.25 g, 80%): mp 180–182°C. ^{1}H NMR δ 3.90 (s, 3H), 3.92 (s, 3H), 3.40 (d, $J=11.7$ Hz, 3H), 7.00 (d, $J=7.8$ Hz, Ar, 1H), 7.08 (d, $J=7.8$ Hz, Ar, 1H), 7.12 (d, $J=2.1$ Hz, Ar, 1H), 7.20 (d, $J=2.1$ Hz, Ar, 1H), 7.25 (t, $J=7.8$ Hz, Ar, 1H); ^{31}P NMR δ 3.71. Anal. calcd for $C_{15}H_{14}BrO_6P$: C, 44.91; H, 3.52; found: C, 44.93; H, 3.40.

3.9. X-Ray structure determination of **8**

Diffracted intensities were collected with a Bruker P4 diffractometer, using graphite monochromated Mo-Kα radiation = 0.71073 Å. Crystal description: colourless prism 0.46×0.43×0.35 mm. $M_r = 1537.13$, monoclinic, space group $P2_1$, $a = 13.813(1)$ Å, $b = 18.078(2)$ Å, $c = 15.846(2)$ Å, $\beta = 102.386(8)^\circ$, $V = 3864.8(7)$ Å, $Z = 2$, $T = 293(2)$ K, $\mu = 2.143$ mm, $\omega/2\theta$ scans, $3.6^\circ < 2\theta < 50^\circ$, empirical absorption correction via ψ-scans. The structure was solved by SIR92 and refined on F^2 by full matrix least-squares using SHELX97. Heavy atoms were anisotropic, H atoms isotropic. Flack parameter[16] for determination of the absolute configuration = –0.010(8). Final $R = 0.058$ and $wR = 0.13$ for data with $I > 2\sigma(I)$; 13422 reflections, 1055 parameters, 688 restraints. Restraints were applied for the refinement of the menthyl groups of one molecule and of the isopropyl groups of the other molecule of the asymmetric unit, which are affected by a high disorder.

Acknowledgements

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