Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1451–1458

TETRAHEDRON: *ASYMMETRY*

C_2-Symmetric sulfur derivatives of 2,2′,3,3′-tetramethoxybiphenyl

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Received 27 April 2001; accepted 24 May 2001

Abstract—A practical route to prepare dithioether, thiophene and thiophene *S*-dioxide derivatives of 2,2′,3,3′-tetramethoxy-1,1′-biphenyl **1** is described. Resolution of 6,6′-bis(methylthio)-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diol **15** was achieved and its absolute configuration was assigned by X-ray analysis of the corresponding phosphorothioamidate diastereomer **18**.

1. Introduction

The rapid development of biphenol chemistry in materials science[1] as well as in catalysis,[2,3] and in particular the increasing interest in sulfur-containing biphenyls,[4] has encouraged us to investigate the preparation of these compounds. Substituted dibenzothiophenes[5] attract the attention of research groups involved in desulfurization reactions since dibenzothiophenes are present in diesel fuel and represent a stringent environmental problem. Synthesis of new substituted dibenzothiophenes and their respective *S*-dioxides should lead to a greater knowledge of hydrodesulfurization mechanisms and provide new ideas for the design of more effective and selective catalysts.[6]

Biphenyl thioethers are used as ligands in Cu(II) and Cu(I) complex models.[7] In these compounds the steric constraints of the biphenyl moiety allow control of the geometry at the metal ion site and the presence of bulky substituents in the biphenyl moiety forces the metal complexes into specific geometries. In fact, the structural features of these synthetic models have been shown to recreate many of the properties of the naturally occurring systems.[8] Biphenyl thioethers are also attracting attention as linkers[9] by virtue of the flexible geometry of biphenyl as well as the propensity of the thioether linkage to be inert to a broad spectrum of reaction conditions.

Furthermore, transannular interactions between sulfur atoms are of interest in determining the geometry, reactivity and biological proprieties of *S*-disubstituted molecules.[10] Although the design and preparation of chiral hydroxylated biphenyls is of central interest in the chemistry of biologically active substances[11] very little has been developed around homochiral sulfur-containing hydroxylated biphenyls.[12]

We have recently reported the use of 2,2′,3,3′-tetramethoxybiphenyl **1**[13] as a key intermediate for the preparation of enantiopure dibromobiphenol **2**[14] (Fig. 1). In our continuous studies on the chemistry of this class of compounds, we have investigated the synthesis of their sulfur derivatives.

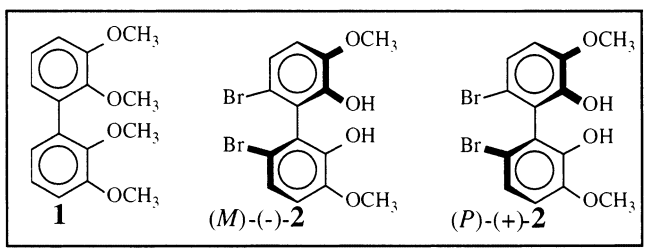

Figure 1.

2. Results and discussion

We applied a synthetic strategy that would allow us to substitute both bromine atoms of **2** with two dithiomethyl groups by metal–halide exchange reaction. We protected the hydroxyl groups of **2** and treated

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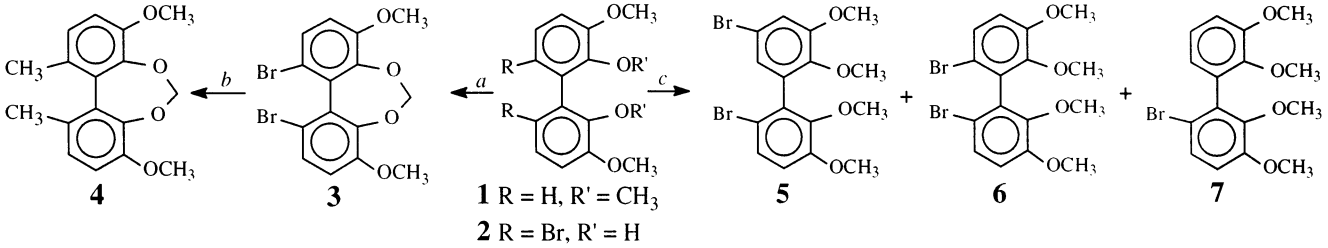


Scheme 1. When R = Br, R′ = H: (a) K_2CO_3, CH_2I_2 DMF, 70°C, 70% yield; (b) *n*-BuLi in dry THF at −50°C, then CH_3I, 25% yield. When R = Br, R′ = CH_3: (c) [BTEA·Br_3], CH_2Cl_2, MeOH, rt, **5** (45% yield), **6** (50% yield), **7** (5% yield).

acetal **3** with *n*-BuLi at −50°C in dry THF (Scheme 1a). We chose this synthetic strategy because it provided an efficient means of functionalizing the biphenyl at the 6- and 6′-positions. Since the two acetal enantiomers (+)-**3** and (−)-**3** are available starting from biphenyl **2**, the method would have allowed us to form enantiopure 6,6′-disubstituted biphenyls. Initially we quenched the reaction mixture with iodomethane, a reactive electrophile, in order to optimize the experimental conditions (Scheme 1b).

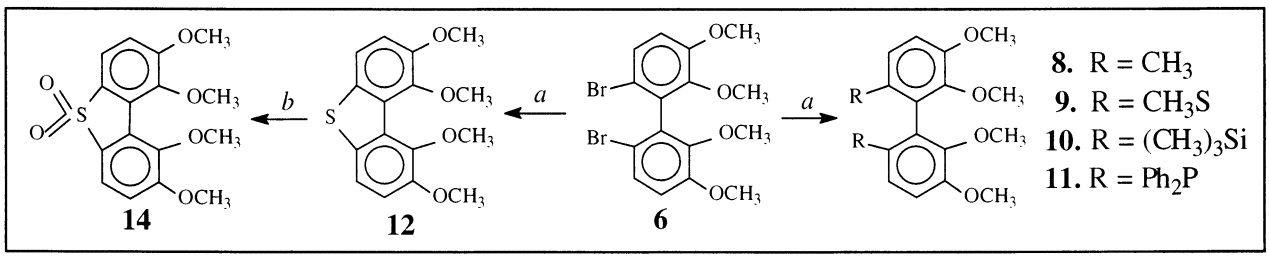
Although repeated attempts at changing the reaction conditions (temperature, reaction time, different alkyllithium reagents) were made in order to increase the yield, biphenyl **4** was obtained in at best only 25% yield. Difficulties encountered in the preparation of **4** prompted us to increase the reactivity of the starting material towards the metal–halide exchange reaction. 3,3′,2,2′-Tetramethoxybiphenyl **1** was brominated at rt by treatment with BTEA·Br_3 using a dichloromethane–methanol mixture as the solvent (Scheme 1c).[15] Altering the reaction conditions allowed us to reduce bromination at the aromatic ring, which is strongly activated to electrophilic substitution. These reactions were not regioselective and biphenyls **5**, **6** and **7** were recovered in 45, 50 and 5% yield, respectively (Scheme 1c).

Biphenyl **6**, which possesses a C_2 symmetry axis, was treated with 2.2 equiv. of *n*-BuLi at −50°C in dry THF. Metal–halide exchange proceeded rapidly giving, after quenching at −50°C with the appropriate electrophile, derivatives **8**–**12** (Scheme 2a).

We used several electrophiles so as to introduce different functionalities at the 6,6′ positions. It was anticipated that the size and nature of the electrophile would influence the yield of the product since sterically congested positions at the biphenyl are involved in the reaction. In all experiments, debromination of biphenyl **6** was observed as a side reaction. When iodomethane and methyldisulfide were used as electrophiles, biphenyls **8** and **9** were obtained in 65 and 63% yield, respectively. Low yields were seen when bulky electrophiles such as chlorotrimethylsilane and chlorodiphenylphosphine were used. Biphenyls **10** and **11**[3] were obtained in 25 and 31% yield, respectively.

Use of sulfur monochloride as the electrophile gave dibenzothiophene **12** in 80% yield, whereas from reaction with elemental sulfur, biphenyl **12** was recovered in lower yield from a mixture of products. 1,2,8,9-Tetramethoxy-dibenzo[*c*,*e*][1,2]-dithiin **13** was not detected.[16] No resolution of thiophene **12** or of thiophene *S*-dioxide **14** (the latter obtained by oxidation of **12** in the presence of 2 equiv. of *m*CPBA) was observed after injection on chiral HPLC.[17a] This is in accord with the literature reports for similar compounds,[18] although we expected that the presence of methoxy groups at the 1, 2, 8 and 9 positions of the dibenzothiophene backbone would lead to a considerable deviation from planarity and aid separation of the two enantiomers of dibenzothiophenes **12** and **14**. In contrast, biphenyl **6** showed a clear separation ($\alpha = 1.4$) in the two enantiomers after analysis by chiral HPLC.[17b]

All of the compounds prepared which possess a C_2 symmetry axis were easily purified by flash chromatography. Our strategy was to transform biphenyl **9** in the corresponding 2,2′-diol **15** in order to achieve its resolution and wide application as a ligand both in catalysis and bioinorganic chemistry. Previously[19] we have observed that complete desulfurization was achieved when biphenyl 2,2′,6,6′-tetramethoxy-3,3′-dithiomethyl-1,1′-biphenyl **16** was treated with 2 equiv. of $(CH_3)_3SiI$ at rt in CH_2Cl_2 giving 2,2′,6,6′-tetramethoxy-1,1′-biphenyl **17** in 80% yield. Surprisingly, on switching the positions of the thiomethyl and methoxyl groups, e.g.



Scheme 2. (a) *n*-BuLi, dry THF, −50°C, then electrophile, −50°C→rt (**8**, CH_3I, 65% yield; **9**, CH_3SSCH_3, 63% yield; **10**, $(CH_3)_3SiI$, 25% yield; **11**, PPh_2Cl, 31% yield; **12**, S_2Cl_2, 80% yield); (b) *m*CPBA in CH_2Cl_2 at rt, 80% yield.

compound **9**, regioselective *O*-demethylation occurred at the *ortho–ortho′* positions in 90% yield in the presence of 2.2 equiv. of $(CH_3)_3SiI$ at rt (Scheme 3a).

In order to apply a rapid resolution procedure of **15**, we prepared the phosphorothioamidate **18**, treating **15** with (*S*)-(−)-$Cl_2P(S)NHCH(CH_3)Ph$ **19**, in the presence of pyridine (Scheme 3b).[20] In this case we chose a cheap chiral source, (*S*)-(−)-α-methylbenzylamine, that was used in equimolar ratio and that we expected to recover, under reduction conditions, without loss of enantiomeric purity. Diastereomers **18** were obtained in 75% yield but, unfortunately, all attempts to separate the two diastereomers failed. Among the several chiral resolving agents applied to the resolution of biaryl diols[21] we preferred to use, according to our experience in this field,[22] (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate as a result of its efficiency and the generally practical separation of the corresponding diastereomers. Treatment of (±)-**15** with 2.2 equiv. of this resolving agent in benzene or toluene and in the presence of Et_3N at rt gave diastereomers (*M*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**20** and (*P*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**20** in 88% yield (Scheme 3c).

Diastereomers **20** were readily separated by flash chromatography and were isolated with ≥99% d.e. Reduction of each dicarbonate diastereomer **20** with $LiAlH_4$ provided enantiopure diols (*M*)-**15** and (*P*)-**15** in virtually quantitative yield (Scheme 3d, e). X-ray diffraction analysis of (−)-**20**, aimed at correlating the absolute configuration with the specific rotation, in order to achieve information on distortion of the biphenyl unit, was first attempted. Unfortunately all attempts failed because the crystals were unstable and broke down within a few minutes. They contain co-crystallized solvent which is lost too quickly to allow X-ray analysis. Then we decided to transform diol (+)-**15** into the phosphorothioamidate (+)-**18** and to submit crystals of the latter compound to diffraction analysis. Both the structure and absolute configuration of (*P*,*S*)-(+)-**18** were determined unequivocally by X-ray analysis. A perspective view of the molecule, showing the atom numbering scheme, is reported in Fig. 2.

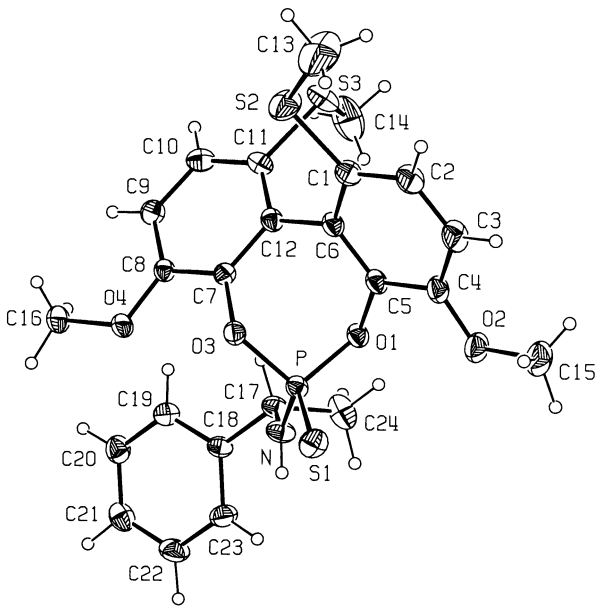
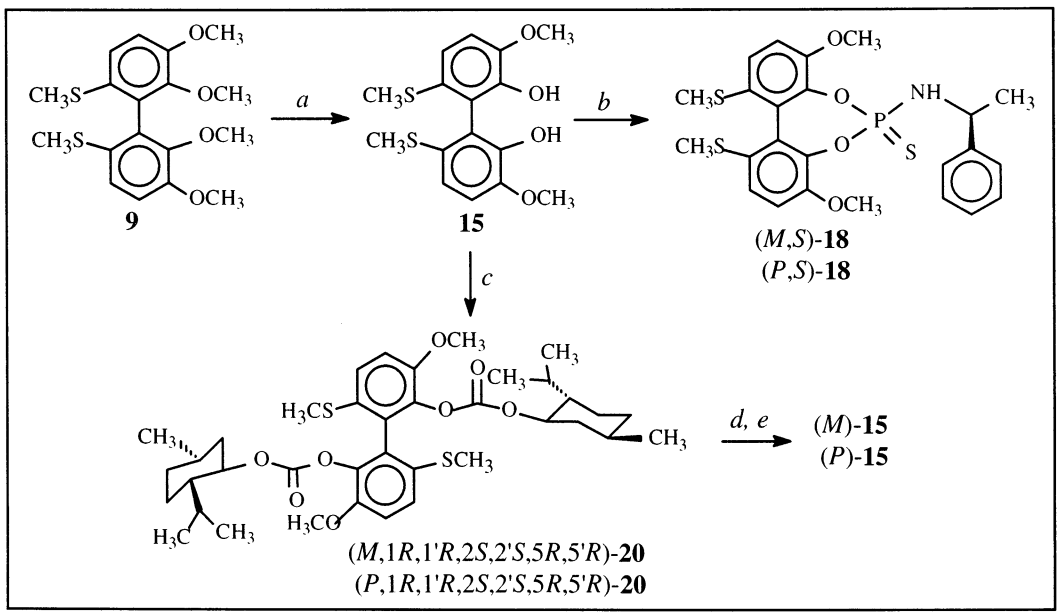


Figure 2. ORTEP plot of diastereomer (*P*,*S*)-(+)-**18** with atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability.



Scheme 3. (a) $(CH_3)_3SiI$ (2.2 equiv.) at rt in CH_2Cl_2, 80% yield; (b) (*S*)-(−)-$Cl_2P(S)NHCHCH_3Ph$ **19**, pyridine, 85°C, 75% yield; (c) (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate, Et_3N, benzene or toluene, rt, 88% yield; (d) separation by flash chromatography; (e) $LiAlH_4$, THF, rt, 90% yield.

The presence of the two bulky thiomethyl groups at the *ortho*- and *ortho′*-positions in (*P*,*S*)-(+)-**18** causes significant distortion of the biphenyl skeleton. The dihedral angle (τ) between the least-squares planes of the two phenyl rings measures 54.49(9)° and the resulting separation between S(2) and S(3) is 3.310(1) Å, which indicates a strong repulsive interatomic interaction (cf. the sum of the sulfur van der Waals radii, 3.6 Å[23]). The repulsive interaction between the sulfur atoms is further reduced through other geometrical factors. Both sulfur atoms are significantly driven away from the phenyl ring to which they are bonded. The distance of S(2) from the plane of the ring, C(1)–C(6), is equal to 0.226(1) Å and the corresponding distance of S(3) from C(7)–C(12) is 0.243(1) Å. Moreover, the bond angles indicate that the C(1) and C(11) carbon atoms are not symmetric. The angles S(2)–C(1)–C(2) and S(2)–C(1)–C(6) measure 123.0(2) and 118.2(2)°, respectively, indicating that the S(2)–C(1) bond is driven towards the biphenyl bond. The corresponding angles S(3)–C(11)–C(10) and S(3)–C(11)–C(12) measure 118.5(2) and 121.7(2)°, respectively, showing that S(3)–C(11) is driven away from the biphenyl bond. This asymmetry of the thiomethyl groups can also be seen in the slightly different interatomic distances where S(2)···C(12) is 3.070(2) Å and S(3)···C(6) is 3.174(3) Å.

It is interesting to compare this structure with that of the related phosphorothioamidate derivative with methoxyl groups at the *ortho*-*ortho′* positions (compound **17** of Ref. 19). In that structure $\tau = 49.93(9)°$, showing clearly the intramolecular effect of the reduced overcrowding of the oxygen atoms with respect to the sulfur atoms. It is also worth noting the completely different orientation which the $C(CH_3)Ph$ group assumes in the two structures (compare Fig. 2 with figure 1 of Ref. 19). For example, the S(1)–P–N–C(17) torsions measure −171.7(2) and −18.6(2)°, in the dithiomethyl and the dimethoxy[19] derivatives, respectively. In this case the different, still near isoenergetic, geometries are exclusively imputable to the different intermolecular packing forces.

The enantiomeric purity of each diol **15** was related to the diastereomeric excess of the corresponding phosphorothioamidate **18**, which was verified by ^{1}H NMR. Interconversion of the biphenyl structure was monitored by NMR spectroscopy. Diastereomer (*M*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**20** does not racemize at the stereogenic axis in organic solvents even when heated to 160°C for 12 h in DMSO-d_6.

In summary, the article gives a contribution to the chemistry of sulfur-containing hydroxylated biphenyls and 2,2′,3,3′-tetramethoxy-1,1′-biphenyl **1** has proved to be a versatile starting material for the efficient preparation of such compounds. Both enantiomers of the new biphenyl thioether **15** were obtained by a practical route. Crystallographic data for diastereomer (*P*,*S*)-(+)-**18** gave important information on the torsional angle, which has been influenced by the bulky dithiomethyl groups at the *ortho*-*ortho′* positions.

Dibenzothiophene **12** and its *S*-dioxide **14** represent the first example of dibenzothiophene with four substitutions at 1,2,8,9 positions. Studies in order to achieve more information on the conformation distortion of structures **12** and **13** are under investigation.

3. Experimental

3.1. General procedures

Melting points were determined on a Büchi 530 apparatus and are uncorrected. All ^{1}H NMR and ^{13}C 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) or dd (doublet of doublets). 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. Triethylamine (Et_3N) was dried over KOH, *N*,*N*-dimethylformamide (DMF) was dried over 4 Å molecular sieves and both solvents were distilled before use. All reagents were of commercial quality and used as purchased. 3-Chloroperoxybenzoic acid (*m*CPBA) was used with 50–55% purity. 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).

3.2. 1,1-Dibromo-4,8-bis(methoxy)dibenzo[2,1-*d*:1′,2′-*f*]-[1,3]dioxepine 3

To a solution of **2** (0.94 g, 2.32 mmol) and K_2CO_3 (0.96 g, 6.97 mmol) in dry DMF (30 mL), CH_2I_2 (0.94 g, 3.49 mmol) was added, under N_2. The reaction mixture was stirred at 70°C under N_2 for 12 h. Water (200 mL) was added to the mixture and the organic phase was extracted with ether (2×50 mL). The organic layer was dried over Na_2SO_4 to obtain **3** as an orange solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent (0.67 g, 70%): mp 230–232°C; ^{1}H NMR δ 3.90 (s, 6H), 5.43 (s, 2H), 6.91 (d, J=9.1 Hz, Ar, 2H), 7.48 (d, J=9.1 Hz, Ar, 2H); ^{13}C NMR δ 56.42, 101.38, 113.73, 113.78, 130.09, 134.07, 142.14, 151.28. Anal. calcd for $C_{15}H_{12}Br_2O_4$: C, 43.30; H, 2.91; found: C, 43.39; H, 3.33%.

The same procedure was employed starting from enantiopure diols (*M*)-(−)-**2** (95% e.e.) and (*P*)-(+)-**2** (99% e.e.), to obtain (*M*)-(+)-**3**, $[\alpha]_D^{20} = 377.3$ (*c* 1, $CHCl_3$), and (*P*)-(−)-**3**, $[\alpha]_D^{20} = -393.2$ (*c* 1, $CHCl_3$), respectively.

3.3. 1,11-Bis(methyl)-4,8-bis(methoxy)dibenzo-[2,1-*d*:1′,2′-*f*][1,3]dioxepine 4

To a stirred solution of **3** (1 g, 2.4 mmol) in dry THF

(20 mL), *n*-BuLi (1.6 M in hexanes, 3.3 mL, 5.28 mmol) was added dropwise at −50°C under N_2. After 4 h, CH_3I (1.42 g, 10 mmol) was added dropwise. The mixture was allowed to warm to rt over 12 h. Water and 10% aqueous HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4 and the solvent evaporated to afford a solid. After purification by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent, **4** was obtained as a white solid (0.17 g, 25%): mp 128–129°C; ^{1}H NMR δ 2.14 (s, 6H), 3.87 (s, 6H), 5.42 (s, 2H), 6.93 (d, J=8.7 Hz, Ar, 2H), 7.07 (d, J=8.7 Hz, Ar, 2H); ^{13}C NMR δ 19.22, 56.30, 101.00, 112.04, 120.60, 125.23, 127.20, 129.27, 145.22. Anal. calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34; found: C, 71.10; H, 6.20%.

3.4. Bromination of 3,3′,2,2′-tetramethoxy-1,1′-biphenyl 1

To a solution of **1** (1 g, 3.64 mmol) in CH_2Cl_2 (20 mL) and CH_3OH (5 mL), BTEA·Br_3 (6.93 g, 16.05 mmol) was added. The reaction mixture was stirred at rt under N_2 for 5 h until the initial orange color 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 and the solvent evaporated to obtain an orange solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent. Compounds **5** (0.70 g, 45%), **6** (0.78 g, 50%) and **7** (0.06 g, 5%) were obtained and properly separated.

3.5. 5,6′-Dibromo-2,2′,3,3′-tetramethoxy-1,1′-biphenyl 5

Mp 212–213°C; ^{1}H NMR δ 3.64 (s, 6H), 3.86 (s, 3H), 3.88 (s, 3H), 6.82 (d, J=9 Hz, Ar, 1H), 6.84 (d, J=2.4 Hz, Ar, 1H), 7.05 (d, J=2.4 Hz, Ar, 1H), 7.32 (d, J=9 Hz, Ar, 1H); ^{13}C NMR δ 56.97, 55.98, 60.50, 60.84, 113.24, 114.42, 115.53, 116.63, 125.28, 127.35, 132.89, 133.46, 145.90, 147.87, 152.20, 153.33. Anal. calcd for $C_{16}H_{16}Br_2O_4$: C, 44.66; H, 3.75; found: C, 44.70; H, 3.87%.

3.6. 6,6′-Dibromo-2,2′,3,3′-tetramethoxy-1,1′-biphenyl 6

Mp 110–122°C; ^{1}H NMR δ 3.70 (s, 6H), 3.89 (s, 6H), 6.88 (d, J=8.7 Hz, Ar, 2H), 7.37 (d, J=8.7 Hz, Ar, 2H); ^{13}C NMR δ 56.84, 60.53, 113.23, 114.62, 127.27, 133.48, 147.53, 152.15. Anal. calcd for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73; found: C, 44.53; H, 3.80%.

3.7. 6-Bromo-2,2′,3,3′-tetramethoxy-1,1′-biphenyl 7

Mp 104–105°C; ^{1}H NMR δ 3.63 (s, 3H), 3.68 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 6.68 (dd, J=1.8, 7.8 Hz, Ar, 1H), 6.82 (d, J=8.1 Hz, Ar, 1H), 6.96 (dd, J=1.8, 7.8 Hz, Ar, 1H), 7.10 (t, J=8.1 Hz, Ar, 1H), 7.33 (d, J=8.1 Hz, Ar); ^{13}C NMR δ 55.71, 55.95, 60.45, 60.75, 112.11, 112.87, 114.88, 122.74, 123.49, 127.26, 132.14, 134.28, 146.56, 147.97, 152.22, 152.68. Anal. calcd for $C_{16}H_{17}BrO_4$: C, 54.41; H, 4.85; found: C, 53.91; H, 5.01%.

3.8. General procedure of metal–halide exchange and quenching with electrophiles

To a stirred solution of **6** (1 equiv.) in dry THF (20 mL), *n*-BuLi (1.6 M in hexanes, 2.2 equiv.) was added dropwise at −50°C under N_2. After 4 h the appropriate electrophile (2.6 equiv.) was added dropwise. The mixture was allowed to warm to rt over 12 h. Water (100 mL) and 10% aqueous HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4 and the solvent evaporated to afford a solid. After purification by flash chromatography using a mixture ($\sim$1:1) of CH_2Cl_2:petroleum as the eluent, biphenyls **8**–**12** were obtained in pure form.

3.9. 6,6′-Dimethyl-2,2,3,3′-tetramethoxy-1,1′-biphenyl 8

65%; mp 145–146°C; ^{1}H NMR δ 1.88 (s, 6H), 3.61 (s, 6H), 3.85 (s, 6H), 6.83 (d, J=9 Hz, Ar, 2H), 6.95 (d, J=9 Hz, Ar, 2H); ^{13}C NMR δ 16.80, 55.51, 60.02, 111.12, 124.48, 129.08, 131.57, 150.40, 159.09. Anal. calcd for $C_{18}H_{22}O_4$: C, 71.49; H, 7.34; found: C, 71.59; H, 7.21%.

3.10. 6,6′-Dithiomethyl-2,2,3,3′-tetramethoxy-1,1′-biphenyl 9

63%; mp 201–202°C; ^{1}H NMR δ 2.34 (s, 6H), 3.70 (s, 6H), 3.88 (s, 6H), 6.98 (d, J=8.7 Hz, Ar, 2H), 7.06 (d, J=8.7 Hz, Ar, 2H); ^{13}C NMR δ 16.69, 55.60, 60.29, 111.52, 121.78, 129.84, 130.40, 146.74, 150.56. Anal. calcd for $C_{18}H_{22}O_4S_2$: C, 58.99; H, 6.05; found: C, 59.37; H, 6.12%.

3.11. 6,6′-Bis(trimethylsilyl)-2,2,3,3′-tetramethoxy-1,1′-biphenyl 10

25%; oil; ^{1}H NMR δ −0.91 (s, 18H), 3.69 (s, 6H), 3.89 (s, 6H), 6.94 (d, J=8.1 Hz, Ar, 2H), 7.25 (d, J=8.1 Hz, Ar, 2H); ^{13}C NMR δ 0.13, 55.39, 60.00, 110.95, 129.70, 132.56, 138.44, 152.49, 175.95. Anal. calcd for $C_{22}H_{34}O_4Si_2$: C, 63.11; H, 8.19; found: C, 63.50; H, 8.12%.

3.12. 6,6′-Bis(diphenylphosphyl)-2,2,3,3′-tetramethoxy-1,1′-biphenyl 11

31%; mp 170–172°C [lit.[3] mp 171–172°C]; ^{1}H NMR δ 3.32 (s, 6H), 3.89 (s, 6H), 6.85–7.35 (series of m, Ar, 24H); ^{13}C NMR (aliphatic only) δ 55.40, 60.18; ^{31}P NMR δ −16.30.

3.13. 1,2,8,9-Tetra(methoxy)dibenzo[2,1-*b*:1′,2′*d*]-thiophene 12

80%; oil; ^{1}H NMR δ 3.90 (s, 6H), 3.94 (s, 6H), 7.13 (d, J=8.4 Hz, Ar, 2H), 7.45 (d, J=8.4 Hz, Ar, 2H); ^{13}C NMR δ 56.63, 62.27, 112.73, 117.84, 129.34, 133.26, 146.48, 151.08. Anal. calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; found: C, 63.00; H, 5.22%.

3.14. 1,2,8,9-Tetra(methoxy)dibenzo[2,1-*b*:1′,2′-*d*]thiophene-*S*-dioxide 14

To a solution of **12** (1 g, 4.16 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of *m*-chloroperbenzoic acid (55% purity, 5.18 g, 15 mmol) in CH_2Cl_2 with stirring at 0°C under N_2. The mixture was allowed to warm to rt over 12 h. Water (100 mL) was added, and the organic layer was separated and washed with a saturated solution of $Na_2S_2O_5$ and $NaHCO_3$. The organic solution was dried over Na_2SO_4 and the solvent evaporated to afford a solid, which was purified by flash chromatography using CH_2Cl_2 as eluent. Biphenyl **14** was obtained as a colorless solid (1.12 g, 80%); mp 185–187°C; ^{1}H NMR δ 3.82 (s, 6H), 3.93 (s, 6H), 7.03 (d, $J=8.7$ Hz, Ar, 2H), 7.55 (d, $J=8.7$ Hz, Ar, 2H); ^{13}C NMR δ 56.35, 62.39, 112.67, 118.55, 122.99, 123.16, 124.00, 130.88. Anal. calcd for $C_{16}H_{16}O_6S$: C, 57.13; H, 4.79; found: C, 57.19; H, 4.62%.

3.15. 6,6′-Bis(methylthio)-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diol 15

To a solution of **9** (1.4 g, 3.8 mmol) in CH_2Cl_2 (30 mL) at rt and under N_2, $(CH_3)_3SiI$ (1.7 g, 8.4 mmol) was added. The mixture was stirred at rt for 12 h. MeOH (10 mL) was added and the mixture was poured into ice water, stirred for 0.5 h, saturated with salt and extracted with ether. The organic extract was dried (Na_2SO_4) and evaporated to afford a brown solid. The crude material was purified by flash chromatography using CH_2Cl_2 as eluent, to give **15** as an oil (1.15 g, 90%); ^{1}H NMR δ 2.35 (s, 6H), 3.90 (s, 6H), 5.67 (bs, 2H), 6.91 (d, AB, $J=8.7$ Hz, Ar, 4H); ^{13}C NMR δ 16.73. 55.97, 111.15, 118.00, 130.40, 130.71, 143.49, 144.87. Anal. calcd for $C_{16}H_{18}O_4S_2$: C, 56.78; H, 5.36; found: C, 56.29; H, 5.40%.

3.16. Dibenzo-[*d*,*f*][1,3,2]-dioxaphosphepin-6-amine-1,11-bis(methylthio)-4,8-dimethoxy-*N*-(1-phenylethyl)-6-sulfide 18

N-((*S*)-α-Methylbenzyl)-dichlorothiophosphoroamidate **19** (0.17 g, 0.7 mmol) was added dropwise to a solution of **15** (0.18 g, 0.53 mmol) in pyridine (20 mL) at rt under N_2. After stirring the mixture under reflux for 12 h, the reaction mixture was cooled and made acidic 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 colorless solid. The crude was purified by flash chromatography using CH_2Cl_2 as eluent, to give **18** as a 1:1 mixture of the two diastereomers (*P*,*S*)-**18** and (*M*,*S*)-**18** (0.21 g, 75%). (*P*,*S*)-**18**: ^{1}H NMR δ 1.52 (d, $J=5.1$ Hz, 3H), 2.21 (s, 3H), 2.28 (s, 3H), 3.51 (m, 1H), 3.67 (s, 3H), 3.93 (s, 3H), 4.80 (m, 1H), 6.80–7.40 (series of m, Ar, 9H); ^{13}C NMR (aliphatic only) δ 19.35, 19.60, 25.38, 53.00, 55.21, 56.60; ^{31}P NMR δ 77.71. (*M*,*S*)-**18**: ^{1}H NMR δ 1.48 (d, $J=5.1$ Hz, 3H), 2.06 (s, 3H), 2.33 (s, 3H), 3.42 (s, 3H), 3.51 (m, 1H), 3.80 (s, 3H), 4.80 (m, 1H), 6.80–7.40 (series of m, Ar, 9H); ^{13}C NMR (aliphatic only) δ 19.28, 19.55, 25.23, 53.04, 55.43, 56.70; ^{31}P NMR δ 76.80.

The same procedure was employed starting from enantiopure diol (*P*)-(+)-**15** to obtain (+)-(*P*,*S*)-**18**, which was recrystallized from CH_2Cl_2:*n*-hexane to obtain crystals suitable for X-ray analysis. (+)-(*P*,*S*)-**18**: mp 180°C; $[\alpha]_D^{20}=+75.5$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{24}H_{26}NO_4PS_3$: C, 55.48; H, 5.05; N, 2.70; found: C, 55.54; H, 5.10; N, 2.44%.

3.17. 6,6′-Bis(methylthio)-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl-*O*,*O*′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbonic ester 20

A solution of (±)-**15** (0.32 g, 0.95 mmol) and Et_3N (2 mL) in benzene or toluene (15 mL) was added, dropwise, to a solution of (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate (0.45 g, 2.05 mmol) in benzene or toluene (15 mL) at rt under N_2. The solution was stirred at rt for 1 h, washed with 10% aqueous HCl and water and the organic phase extracted with CH_2Cl_2. The crude, dried over Na_2SO_4, gave **20** (0.56 g, 88%) as a 1:1 mixture of two diastereomers that were completely separated by flash chromatography using CH_2Cl_2 as eluent.

(*M*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**20**: mp 170–171°C; ^{1}H NMR δ 0.71 (d, $J=6.9$ Hz, 6H), 0.82 (d, $J=6.9$ Hz, 6H), 0.89 (d, $J=6.9$ Hz, 6H), 0.80–1.95 (series of m, 18H), 2.32 (s, 6H), 3.82 (s, 6H), 4.45 (m, 2H), 6.98 (d, $J=8.7$ Hz, Ar, 2H), 7.24 (d, $J=8.7$ Hz, Ar, 2H); ^{13}C NMR δ 16.38, 17.45, 20.68, 22.04, 23.42, 25.81, 31.56, 34.11, 40.30, 46.99, 55.92, 78.98, 112.85, 125.50, 128.87, 130.58, 138.70, 149.6, 152.11; $[\alpha]_D^{20}=-98.8$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{38}H_{54}O_8S_2$: C, 64.93; H, 7.74; found: C, 64.32; H, 7.71%.

(*P*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**20**: mp 69–70°C; ^{1}H NMR δ 0.73 (d, $J=6.9$ Hz, 6H), 0.84 (d, $J=6.9$ Hz, 6H), 0.86 (d, $J=6.9$ Hz, 6H), 0.80–1.95 (series of m, 18H), 2.34 (s, 6H), 3.83 (s, 6H), 4.45 (m, 2H), 6.99 (d, $J=8.4$ Hz, Ar, 2H), 7.25 (d, $J=8.4$ Hz, Ar, 2H); ^{13}C NMR δ 16.17, 17.96, 20.63, 21.96, 23.27, 25.82, 31.24, 34.06, 40.19, 46.78, 55.86, 78.95, 112.70, 126.18, 130.56, 138.56, 149.80, 151.56, 153.57; $[\alpha]_D^{20}=54.9$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{38}H_{54}O_8S_2$: C, 64.93; H, 7.74; found: C, 64.88; H, 7.34%.

3.18. (*M*)-(−)-6,6′-Bis(methylthio)-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diol 15

A solution of (*M*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(−)-**20** (1.8 g, 2.55 mmol) in dry THF (30 mL) was cooled at 0°C under N_2. To this solution, $LiAlH_4$ (0.46 g, 12 mmol) was added in portions with vigorous magnetic stirring. After stirring the mixture for 12 h at rt, water and then 10% aqueous HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4 and evaporated to afford a colorless solid. After purification by flash chromatography using a 1:4 mixture of ethyl acetate:petroleum, as eluent, enantiomerically pure (*M*)-(−)-**15** (0.77 g, 90%) and enantiomerically pure (−)-menthol (0.72 g, 90%) were obtained. (*M*)-(−)-**15**: $[\alpha]_D^{20}=-16.0$ (*c* 1, $CHCl_3$).

3.19. (*P*)-(+)-6,6′-Bis(methylthio)-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diol 15

Using the above procedure, diastereomer (*P*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-**20** (99% d.e.) gave (*P*)-(+)-**15** (90%); $[\alpha]_D^{20}=+16.3$ (*c* 0.5, $CHCl_3$).

3.20. X-Ray structure determination of (*P*,*S*)-(+)-18

Diffracted intensities were collected with a Bruker P4 diffractometer, using graphite-monochromated Mo-Kα radiation = 0.71073 Å. Crystal description: colorless prism 0.40×0.39×0.32 mm. $M_r=519.61$, monoclinic, space group $P2_1$, $a=9.880(1)$, $b=8.308(1)$, $c=15.667(2)$ Å, $\beta=104.40(1)°$, $V=1245.6(3)$ Å^3, $Z=2$, $T=293(2)$ K, $\mu=0.393$ mm^{-1}. $\omega/2\theta$ scans, 7527 measured reflections, 6949 independent reflections, 5670 reflections with $I>2\sigma(I)$, $R_{int}=0.020$, $4.3°<2\theta<60.0°$. The structure was solved by SIR-92 and refined on F^2 by full-matrix least-squares using SHELXL-97. 6949 reflections used in refinement, 367 parameters. Heavy atoms were anisotropic, H atoms isotropic. Flack parameter[24] for determination of the absolute configuration = 0.00(7). Final $R=0.0453$ and $wR=0.1010$ for data with $I>2\sigma(I)$, $(\Delta/\sigma)_{max}=0.004$, $\Delta\rho_{max}=0.422$ e Å^{-3}, $\Delta\rho_{min}=-0.167$ e Å^{-3}.

Acknowledgements

This work was supported by the C.N.R., Rome, and partially by Sardinia Autonomous Region.

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