Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4417–4427

TETRAHEDRON: *ASYMMETRY*

Chiral nonracemic C_2-symmetric biphenyls by desymmetrization of 6,6′,2,2′-tetramethoxy-1,1′-biphenyl

Giovanna Delogu,[a,*] Davide Fabbri,[a] Maria Antonietta Dettori,[a] Alessandra Forni[b,†] and Gianluigi Casalone[b]

[a]*Istituto CNR Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici, Via Vienna 2, I-07100 Sassari, Italy*

[b]*Centro del CNR per lo Studio delle Relazioni tra Struttura e Reattività Chimica, Via Golgi 19, I-20133 Milan, Italy*

Received 5 October 2000; accepted 11 October 2000

Abstract

Regioselective bromination of the title biphenyl **1** at the 3 and 3′ positions and simultaneous desymmetrization of the biphenyl has been achieved. Metal–halide exchange at the 3,3′ positions facilitated the introduction of functional groups in good yield. Regioselective reduction was obtained by using $(CH_3)_3SiI$, L-Selectride and HI according to the functional groups on the biphenyls. Resolution of 6,6′,2,2′-tetramethoxy-3,3′-dimethyl-1,1′-biphenyl **3** was achieved by its conversion to the corresponding phosphorothioamidate diastereomers of the (*S*)-(−)-α-methylbenzylamine. The absolute configuration of (*M*)-(+)-**3** was confirmed by X-ray analysis of the corresponding diastereomer.

1. Introduction

The ability of the biphenyl system in transmitting conformational information[1] has attracted considerable interest around this structure which is used in ligands in catalysis[2] and, recently, in the chemistry of biologically active compounds, as synthetic ionophores,[3] as artificial ion channels which specifically recognize biomembranes[4] and in the molecular recognition of disaccharides.[5] This has stimulated many research groups to investigate new synthetic approaches to prepare enantiopure biphenyls with interesting features.[6]

Because of the interesting proprieties of C_2-symmetric hydroxylated biphenyls in the chemistry of bioactive compounds[7] as well as in asymmetric catalysis,[8] we considered the possibility of developing a new class of C_2-symmetric heterosubstituted biphenols starting from 6,6′,2,2′-tetra-

* Corresponding author. E-mail: g.delogu@iatcapa.ss.cnr.it

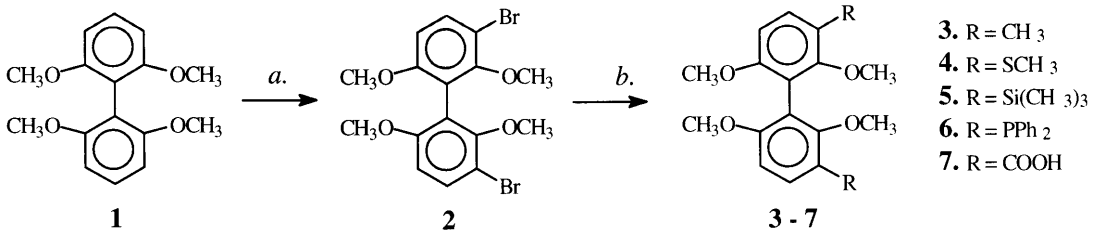
† Author to whom inquires concerning the X-ray structure analysis should be directed. E-mail: aforni@csrsrc.mi.cnr.it

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00410-9

methoxy-1,1′-biphenyl **1**. Substituents at the 3 and 3′ positions provide desymmetrization of the prochiral biphenyl **1** and supply little but significant stereochemical modifications to the structure. In fact, the diversified size and shape of functional groups at the 3 and 3′ positions should influence the asymmetry of the biphenyl and therefore its ability to form stable Lewis acid complexes. Our starting point was to construct 3,3′-heterodisubstituted biphenols with a stereogenic axis by using easy and inexpensive reaction steps.

2. Results and discussion

6,6′,2,2′-Tetramethoxybiphenyl **1** was prepared in two steps in 80% overall yield, starting from commercially available 1,3-dimethoxybenzene by a known literature procedure.[9] Bromination of biphenyl **1** in the presence of [BTEA·Br_3] in CH_2Cl_2 at rt, gave biphenyl **2** in 80% yield[10] (Scheme 1). Desymmetrization of the prochiral biphenyl **1** as well as complete regioselectivity were achieved in only one reaction step. Compound **2**, solid, air stable, easily purified, showed a clear separation after injection on chiral HPLC ($\alpha = 1.4$) on account of restricted rotation about the stereogenic axis.

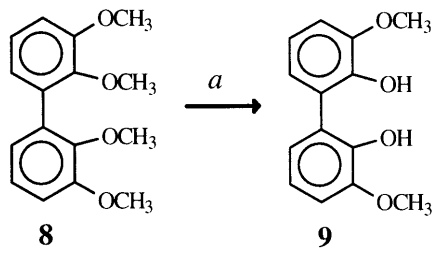


Scheme 1. (a) [BTEA·Br_3], CH_3OH, CH_2Cl_2, rt, 80% yield; (b) *n*-BuLi, benzene–ether, rt, then electrophile, at −50°C (**3**, 60% yield; **4**, 58% yield; **5**, 57% yield; **6**, 41% yield; **7**, 83% yield)

When **2** was treated with 2.2 equiv. of *n*-BuLi at rt in a mixture of dry benzene–ether, metal–halide exchange proceeded rapidly giving, after quenching at −50°C with the appropriate electrophile, derivatives **3**–**7** in satisfactory yields. We chose this synthetic strategy to prepare 3,3′-disubstituted chiral biphenols because it provided an efficient means of functionalizing the aromatic ring. Considerable work was done in optimizing experimental conditions of metal–halide exchange in such a way that rigorous reaction conditions are not required.

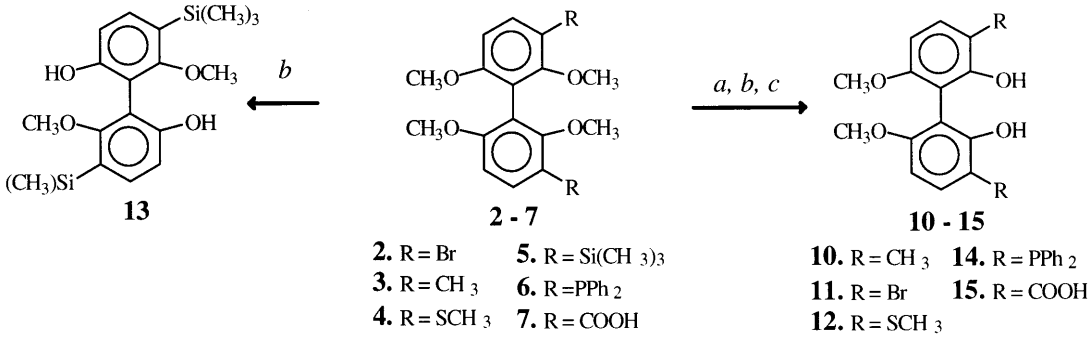
All compounds prepared are solid, air stable and were easily separated and purified by flash chromatography using appropriate solvent mixtures. Our strategy was to transform biphenyls **3**–**7** into the corresponding 2,2′-diols in order to achieve their resolution and therefore, their application in catalysis as well as in asymmetric synthesis.

Although demethylations of methyl phenyl ether in the presence of BBr_3 or $(CH_3)_3SiI$ have been widely used as a method for preparing phenols,[11] the factors which govern both reactivity and regioselectivity of methyl biphenyl ether toward *O*-demethylation reaction are poorly investigated.[12] In fact the presence of other functional groups as well as the position in the biphenyl rings should change the reactivity of the methoxy groups and the expected reaction pathway.[13] For example, when we treated 3,3′,2,2′-tetramethoxybiphenyl **8**[14] with 2/3 equiv. of BBr_3 at −50°C or with 2 equiv. of $(CH_3)_3SiI$ at rt, *O*-demethylation took place selectively and 3,3′-dimethoxy-2,2′-dihydroxybiphenyl **9** was obtained in up to 90% yield (Scheme 2).



Scheme 2. (a) BBr_3 (2/3 equiv.) at −50°C in $CHCl_3$, 90% yield, or $(CH_3)_3SiI$ (2 equiv.) at rt in CH_2Cl_2, 88% yield

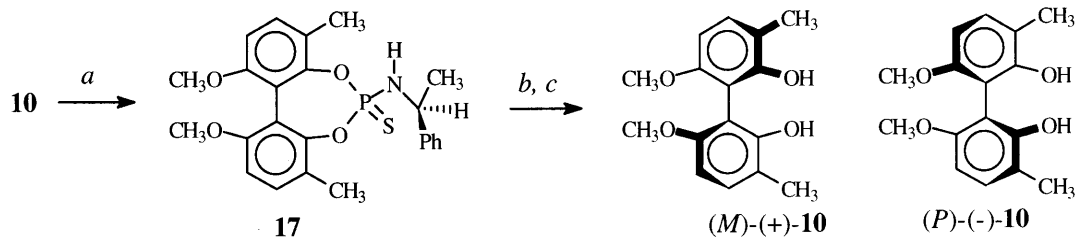
On the contrary, when we treated 6,6′,2,2′-tetramethoxy-3,3′-dibromobiphenyl **2** in the presence of BBr_3 at −50°C or $(CH_3)_3SiI$ at rt, a mixture of products was recovered. An identical result was obtained employing biphenyls **5**–**7** under the same *O*-demethylating conditions. It should be noted that complete desulfurization was achieved by treatment of biphenyl **4** with 2 equiv. of $(CH_3)_3SiI$ at rt in CH_2Cl_2 giving tetramethoxybiphenyl **1** in 80% yield. On exchanging substituents at the 3 and 3′ positions with a methyl group, e.g. compound **3**, selective *O*-demethylation took place in the presence of 2 equiv. of $(CH_3)_3SiI$ at rt and biphenol **10** was obtained in 90% yield (Scheme 3a). NMR spectroscopic data of **10** show evidence of the preservation of the C_2-symmetry axis.



Scheme 3. (a) When R = CH_3: $(CH_3)_3SiI$ at rt in CH_2Cl_2, 88% yield; (b) when R = Br, R = SCH_3, R = $Si(CH_3)_3$, R = PPh_2: L-Selectride (2.2 equiv.), refluxing THF (**11**, 81% yield; **12**, 78% yield; **13**, 61% yield; **14**, 65% yield, isolated as *P*-oxide); (c) when R = COOH: refluxing 57% HI solution, **15**, 65% yield

We were able to identify the methoxyl groups involved in the reduction of **3** by transformation of the biphenol **10** in the phosphorothioamidate **17** with (*S*)-(−)-$Cl_2P(S)NHCH(CH_3)Ph$ **16**, in the presence of pyridine (Scheme 4). We chose a cheap chiral source, (*S*)-(−)-α-methylbenzylamine that was used in an equimolar ratio and recovered, under the reduction condition, without loss of enantiomeric purity.[14] Phosphorothioamidates (*M*,*S*)-**17** and (*P*,*S*)-**17** were produced in 1:1 ratio and were separated by one recrystallization from CH_2Cl_2–EtOH in 99 and 66% de, respectively. Attempted recrystallizations of the diastereomeric mixture did not increase the de of (*P*,*S*)-**17** that appears as oil. Both structure and absolute configuration of diastereopure (*M*,*S*)-(−)-**17** were defined unequivocally by X-ray analysis. A perspective view of the molecule with the atom numbering is reported in Fig. 1.

The dihedral angle τ between the least-squares planes of the two phenyl rings in (*M*,*S*)-(−)-**17** measures 49.93(9)°. This value can be usefully compared with the corresponding ones found in related compounds, in order to illustrate the role of the seven-membered ring comprising the



Scheme 4. (a) (*S*)-(−)-$Cl_2P(S)NHCHCH_3Ph$ (**16**), pyridine, reflux, 80% yield; (b) separation by recrystallization from CH_2Cl_2–EtOH; (c) $LiAlH_4$, THF, rt, 90–88% yield

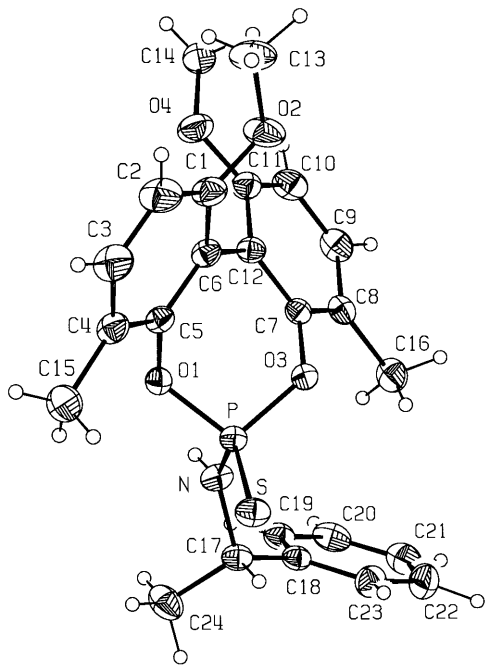


Figure 1. ORTEP plot of diastereomer (*M*,*S*)-(−)-**17** with atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability

two *ortho*-positions in determining the biphenyl distortion. For the analogous doubly bridged biphenyl derivative (compound **3** of Ref. 15), only somewhat lower values were found ($\tau = 45.89°$ and $\tau = 44.58°$ for the two independent molecules of the asymmetric unit, respectively). For the related derivative where the *ortho*-positions are not bridged (compound **5a** of Ref. 15), the dihedral angle is instead definitively greater, τ measuring 75.49°. The constraint imposed by the O–P–O bridge on the biphenyl skeleton causes the oxygen atoms of the methoxy groups, O2 and O4, to be separated by 2.787(3) Å, a value significantly lower than the sum of their van der Waals radii (1.5 Å for each O[16]). On the other hand, for the derivative without a bridge,[15] the shortest O···O distances, equal to 3.217 and 3.445 Å, exceed by far such a limit. The intramolecular repulsive interaction between O2 and O4 is partially stabilized by an hydrogen bond of O2 with the N–H group of a symmetry related molecule [$d(N^{(i)}\cdots O)$ is equal to 3.632(3) Å, and the angle $N^{(i)}$–$H^{(i)}\cdots O$ measures 165(2)°, where (i) = $x-1,y,z$]. This intermolecular interaction is responsible of a significant deviation of 0.216(2) Å of O2 from the l.s. plane of the

ring C1–C6, to be compared with the corresponding value for O4, 0.091(2) Å. As a consequence of the nonbonded interaction between O2 and O4, the bond angles insisting on the C1 and C11 carbon atoms in the *ortho*-positions are not symmetric. The angles C6–C1–O2 and C12–C11–O4 measure 116.6(3) and 116.1(2)°, while the angles C2–C1–O2 and C10–C11–O4 measure 123.5(3) and 124.1(2)°, respectively. These values can be compared with those of the corresponding four angles at the other *ortho*-positions, ranging from 117.6(2) to 118.3(2)°.

Each phosphorothioamidate **17**, in the presence of $LiAlH_4$ in THF, afforded diols (*M*)-(+)-**10** and (*P*)-(−)-**10** in 99 and 66% ee, respectively. The enantiomeric purity of each diol **10** was related to the diastereomeric excess of the corresponding phosphorothioamidate **17**, which was verified by ^{1}H NMR and ^{31}P NMR. Phosphorothioamidates **17** are configurationally stable in solution at rt in most solvents and show interconversion of the stereogenic axis with a half-time of 48 h by warming at 140°C in dimethyl-d_6-sulfoxide. High optical stability was observed also for diol (*M*)-(+)-**10**, which racemize with an half-time of 80 h by warming at 120°C in xylene.

With the aim of transforming biphenyls **2** and **4**–**7** in the corresponding diols, we investigated a reagent active in the reduction of aryl methyl ethers with halide functions.[17] Regioselective deprotection of biphenyl **2** in the biphenol **11** occurred rapidly in 81% yield using 2.2 equiv. of L-Selectride in refluxing THF (Scheme 3b). The success of the reduction prompted us to use L-Selectride for the *O*-demethylation of the heterosubstituted biphenyls **4**–**7**. Complete regioselectivity was achieved in one reaction step in biphenols **12**–**14** (Scheme 3b), whereas a mixture of products was recovered after treatment of biphenyl **7** with L-Selectride. Finally, biphenol **15** was obtained, in satisfactory yield, by treatment of **7** with a refluxing 57% solution of HI as described for analogous compounds (Scheme 3c).[18] NMR spectroscopic data of **11**–**15** show evidence of the preservation of the C_2-symmetry axis for all of the biphenyls reduced.

We were able to assign structure of regioisomer **12** by comparison of the ^{1}H and ^{13}C NMR spectra with those of an identical sample obtained by us under a different synthetic strategy.[19] NOE enhancement was used to determine the position of methoxyl groups and therefore the assignment of the regioisomers **11**, **13**, **14** and **15**. Irradiation of the methoxyl signal of **11**, **14** and **15** at the proper resonance gave large NOE only at the aromatic doublet which lies at high field (Table 1, entries 1, 3 and 4). Thus, the methoxyl groups were considered to be located at

Table 1
NOE enhancement experiments

Entry	Biphenyl	Aromatics (δ)		Hydroxyl groups (δ)	Methoxyl groups (δ)	NOE (protons involved)
		H-4,4′	H-5,5′			
1	**11**	7.48	6.53	5.43	3.74	15.1% (H-5,5′ with methoxyl groups)
2	**13**	7.40	6.90	6.39	3.51	14.8% (hydroxyl with methoxyl groups)
3	**14**[a]	7.03	6.53	10.09	3.75	14.3% (H-5,5′ with methoxyl groups)
4	**15**[b]	7.94	6.70	–	3.78	19.3% (H-5,5′ with methoxyl groups)

[a] Detected as *P*-oxide.
[b] ^{1}H NMR spectrum in acetone-d_6.

6,6′ positions, and the aromatics which lie at high field were then assigned to H-5,5′. If the methoxyl groups were located at 2 and 2′ positions, no NOE would be detected between methoxyl groups and aromatic protons of the biphenyl. This situation appeared, on the contrary, in biphenyl **13**. When the methoxyl signal of **13** was irradiated, no NOE effect was detected at any aromatic protons, whereas an increase in the intensity of the hydroxyl signal at 6.39 δ was observed and a significant NOE of 14.8% was detected (Table 1, entry 2). Therefore, it is reasonable to assume biphenol **13** adopts the less hindered *anti* conformation. In turn, irradiation of the H-5,5′ signal of **13** at 6.90 δ affected both signals of the hydroxyl groups (NOE 4.3%) and H-4,4′ (NOE 7.9%).

The reaction pathway observed in the reduction of **5** with L-Selectride is in disagreement with the regioselectivity observed in the deprotection of sterically congested ethers using the reducing agent.[17] Probably, the bulkiness of the trimethylsilyl groups in biphenyl **13** does not allow the attack of L-Selectride on the methoxyl groups in 2,2′ positions.

The efficiency of our synthetic procedure can be attributed to the regioselective bromination of tetramethoxy **1** at the 3 and 3′ positions with simultaneous desymmetrization of biphenyl **1** as well as the regioselective reduction of tetramethoxybiphenyls to the corresponding C_2-symmetric biphenols **10**–**15**. It is reasonable consider that methyl groups at the 3,3′ positions make biphenol (*M*)-(+)-**10** thermally and chemically very stable. Although a variety of approaches have been developed in order to prepare chiral hydroxylated 3,3′-disubstituted[20] biphenyls, we believe that the simplicity of this synthetic strategy and the resolution procedure make it a useful and inexpensive alternative.

3. Experimental section

3.1. General procedures

Melting points were determined on a Büchi 530 apparatus and are uncorrected. Infrared spectra was taken on a Perkin–Elmer 1720-X FTIR spectrometer. 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 (double 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. HPLC analysis was performed at rt with a Perkin–Elmer Series 4 Liquid Chromatograph using Chiralcel OD column (10 μm, 25 cm×0.46 I.D.) at a flow rate of 0.6 mL/min, 254 UV detection, using a mixture of 98:2 w/w *n*-hexane:2-propanol as mobile phase. Tetrahydrofuran (THF) and benzene were freshly distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was dried over CaH_2 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. 2,2′,6,6′-Tetramethoxy-3,3′-dibromo-1,1′-biphenyl **2**

To a solution of **1** (0.5 g, 1.82 mmol) in CH_2Cl_2 (40 mL) and CH_3OH (20 mL), BTEA·Br_3 (1.73 g, 4.00 mmol) was added in one pot. The reaction mixture was stirred at rt for 12 h until the initial orange color faded. Aqueous $Na_2S_2O_5$ was added to the mixture and the organic phase was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 to obtain **2** as an orange solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum as eluent (0.63 g, 80%): mp 115–116°C; ^{1}H NMR δ 3.54 (s, 6H), 3.68 (s, 6H), 6.65 (d, $J=8.7$ Hz, Ar, 2H), 7.50 (d, $J=8.7$ Hz, Ar, 2H); ^{13}C NMR δ 56.01, 60.54, 108.06, 108.21, 119.19, 132.73, 155.64, 157.69; anal. calcd for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73; found: C, 44.56; H, 3.60.

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

To a solution of **2** (1 equiv.) in a 1:1 mixture of dry benzene and ether (20 mL), *n*-BuLi (1.6 M in hexanes, 3 equiv.) was added dropwise at rt under N_2. After 12 h, the solution was cooled at −50°C and the appropriate electrophile (3 equiv.) was added dropwise. The mixture was allowed to reach rt within 12 h. Water and 10% HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4 and evaporated to afford a solid. After purification by flash chromatography by using a 1:1 mixture of CH_2Cl_2:petroleum as eluent, the derivatives **3**–**7** were obtained.

3.4. 2,2′,6,6′-Tetramethoxy-3,3′-dimethyl-1,1′-biphenyl **3**

Using CH_3I as electrophile, biphenyl **3** was obtained: yield 60%; mp 95–96°C [lit.[21] 101°C]; ^{1}H NMR δ 2.32 (s, 6H), 3.45 (s, 6H), 3.75 (s, 6H), 6.73 (d, $J=8.1$ Hz, Ar, 2H), 7.20 (d, $J=8.1$ Hz, Ar, 2H); ^{13}C NMR δ 15.79, 55.98, 59.73, 106.46, 123.17, 130.25, 130.87, 156.63, 157.16; anal. calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33; found: C, 71.60; H, 7.40.

3.5. 2,2′,6,6′-Tetramethoxy-3,3′-dimethylmercapto-1,1′-biphenyl **4**

Using $(CH_3S)_2$ as electrophile, biphenyl **4** was obtained: yield 58%; mp 126–128°C; ^{1}H NMR δ 2.43 (s, 6H), 3.57 (s, 6H), 3.71 (s, 6H), 6.67 (d, $J=8.7$ Hz, Ar, 2H), 7.23 (d, $J=8.7$ Hz, Ar, 2H); ^{13}C NMR δ 16.15, 55.98, 60.05, 107.23, 118.11, 123.06, 128.20, 155.50, 156.86; anal. calcd for $C_{18}H_{22}O_4S_2$: C, 58.99; H, 6.05; found: C, 58.70; H, 5.98.

3.6. 2,2′,6,6′-Tetramethoxy-3,3′-bis(trimethylsilyl)-1,1′-biphenyl **5**

Using $(CH_3)_3SiCl$ as electrophile, biphenyl **5** was obtained: yield 57%; mp 95–97°C; ^{1}H NMR δ 0.29 (s, 18H), 3.51 (s, 6H), 3.76 (s, 6H), 6.74 (d, $J=8.1$ Hz, Ar, 2H), 7.41 (d, $J=8.1$ Hz, Ar, 2H); ^{13}C NMR δ −0.34, 55.82, 59.90, 105.61, 116.06, 123.65, 135.13, 160.34, 164.71; anal. calcd for $C_{22}H_{34}O_4Si_2$: C, 63.11; H, 8.19; found: C, 62.79; H, 8.22.

3.7. 2,2′,6,6′-Tetramethoxy-3,3′-bis(diphenylphosphyl)-1,1′-biphenyl **6**

Using Ph_2PCl as electrophile, biphenyl **6** was obtained: yield 41%; mp 216–217°C; ^{1}H NMR δ 3.50 (s, 6H), 3.73 (s, 6H), 6.60–6.80 (series of m, Ar, 4H), 7.20–7.40 (series of m, Ar, 20H);

^{13}C NMR (aliphatic) δ 55.85, 60.90 (d, $^{4}J_{CP}=8.13$ Hz); ^{31}P NMR δ −16.30; anal. calcd for $C_{40}H_{36}O_4P_2$: C, 74.76; H, 5.65; found: C, 74.54; H, 5.32.

3.8. 2,2′,6,6′-Tetramethoxy-3,3′-dicarboxy-1,1′-biphenyl **7**

Using dry CO_2 as electrophile, biphenyl **7** was obtained: 83%; mp 237–239°C [lit.[22] 239–240°C]; ^{1}H NMR δ 3.53 (s, 6H), 3.83 (s, 6H), 6.92 (d, $J=9.0$ Hz, Ar, 2H), 8.24 (d, $J=9.0$ Hz, Ar, 2H); ^{13}C NMR δ 56.25, 62.15, 107.59, 114.77, 115.77, 134.93, 158.75, 162.65, 165.60; anal. calcd for $C_{18}H_{18}O_8$: C, 59.67; H, 5.01; found: C, 59.40; H, 4.80.

3.9. 6,6′-Dimethoxy-3,3′-dimethyl-2,2′-dihydroxy-1,1′-biphenyl **10**

To a stirred solution of **3** (0.70 g, 2.3 mmol) in dry CH_2Cl_2 (30 mL) at rt and under N_2, $(CH_3)_3SiI$ (0.94 g, 4.7 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 30 min, saturated with salt and the organic phase extracted with ether. The extract was dried (Na_2SO_4) and concentrated to afford a brown solid. The crude material was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum, as eluent to give **10** (0.59 g, 88%): mp 110°C; ^{1}H NMR δ 2.24 (s, 6H), 3.73 (s, 6H), 5.06 (bs, 2H), 6.53 (d, $J=8.4$ Hz, Ar, 2H), 7.15 (d, $J=8.4$ Hz, Ar, 2H); ^{13}C NMR δ 15.65. 56.01, 103.06, 117.71, 131.41, 153.07, 156.02, 176.15; anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61; found: C, 69.75; H, 6.80.

3.10. Dibenzo-(d,f)(1,3,2)-dioxaphosphepin-6-amine-1,11-dimethoxy-4,8-dimethyl-N-(1-phenylethyl)-6-sulfide **17**

N-((*S*)-α-Methylbenzyl)dichlorothiophosphoroamidate **16** (0.45 g, 1.7 mmol) was added dropwise to a solution of **10** (0.3 g, 1.1 mmol) in pyridine (20 mL) at rt under N_2. After 12 h under reflux, 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 a 1:1 mixture of CH_2Cl_2:petroleum, as eluent, to give **17** as a 1:1 mixture of the two diastereomers (*M*,S)-**17** and (*P*,*S*)-**17** as an orange solid (0.40 g, 80%). The two isomers were separated by crystallization (CH_2Cl_2–EtOH) (*M*,*S*)-**17** (crystals), 99% de: mp 172°C. ^{1}H NMR δ 1.42 (d, $J=6.9$ Hz, 3H), 2.07 (s, 3H), 2.34 (s, 3H), 3.55 (t, $^{2}J_{HP}$ 9.9 Hz and $^{2}J_{HH}$ 9.9 Hz, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 4.88 (m, 1H), 6.70–6.80 (series of m, Ar, 2H), 7.10–7.35 (series of m, Ar, 7H); ^{13}C NMR (aliphatic) δ 15.98, 16.68, 25.08 (d, $^{2}J_{CP}=6.1$ Hz), 53.94, 56.27, 56.35); ^{31}P NMR δ 76.70; anal. calcd for $C_{24}H_{26}NO_4PS$: C, 63.28; H, 5.75; N, 3.07; found: C, 63.46; H, 5.51; N, 2.90; $[\alpha]_D^{20}$ −228.5 (*c* 1, $CHCl_3$). (*P*,*S*)-**17** (oil), 66% de: ^{1}H NMR δ 1.50 (d, $J=6.6$ Hz, 3H), 2.08 (s, 3H), 2.43 (s, 3H), 3.62 (t, $^{2}J_{HP}$ 9.9 Hz and $^{2}J_{HH}$ 9.9 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 4.8 (m, 1H), 6.70–6.80 (series of m, Ar, 2H), 7.10–7.35 (series of m, Ar, 7H); ^{31}P NMR δ 76.35.

3.11. (M)-(+)-6,6′-Dimethoxy-3,3′-dimethyl-2,2′-dihydroxy-1,1′-biphenyl **10**

A solution of (*M*,*S*)-**17** (99% de) (1 g, 2.55 mmol) in dry THF (30 mL) was cooled at 0°C under N_2. $LiAlH_4$ (0.46 g, 12 mmol) was added in portions with vigorous magnetic stirring. After 12 h, water and 10% 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 by using CH_2Cl_2 as eluent, enantiomerically pure (*M*)-(+)-**10** (0.24 g, 90%) was obtained. (*M*)-(+)-**10**: mp 110°C; $[\alpha]_D^{20}$ 156.1 (*c* 1, $CHCl_3$).

3.12. (P)-(–)-6,6′-Dimethoxy-3,3′-dimethyl-2,2′-dihydroxy-1,1′-biphenyl **10**

Using the above procedure, diastereomer (*P*,*S*)-**17** (66% de) gave (*P*)-(–)-**10**: (88%); $[\alpha]_D^{20}$ –109.0 (*c* 0.5, $CHCl_3$).

3.13. General procedure of reduction in the presence of L-Selectride

L-Selectride (1 M in THF) (2.2 equiv.) was added dropwise at rt under N_2 to the tetramethoxybiphenyl (1 equiv.). After 7–10 h at 65°C the reaction mixture was cooled at rt 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 the corresponding biphenol.

3.14. 6,6′-Dimethoxy-3,3′-dibromo-2,2′-dihydroxy-1,1′-biphenyl **11**

Using the above procedure, biphenol **11** was obtained: yield 81%; mp 132–133°C. ^{1}H NMR δ 3.74 (s, 6H), 5.43 (s, 2H), 6.53 (d, $J=9.0$ Hz, Ar, 2H), 7.48 (d, $J=9.0$ Hz, Ar, 2H); ^{13}C NMR δ 56.24, 101.90, 104.92, 132.27, 145.07, 150.83, 157.86; anal. calcd for $C_{14}H_{12}Br_2O_4$: C, 41.62; H, 2.99; found: C, 41.99; H, 3.12.

3.15. 6,6′-Dimethoxy-3,3′-dimercapto-2,2′-dihydroxy-1,1′-biphenyl **12**

Using the above procedure, biphenol **12** was obtained: yield 78%; mp 132–133°C. ^{1}H NMR δ 2.32 (s, 6H), 3.75 (s, 6H), 6.58 (d, $J=8.4$ Hz, Ar, 2H), 6.07 (s, 2H), 7.49 (d, $J=8.4$ Hz, Ar, 2H); ^{13}C NMR δ 20.10, 56.06, 103.97, 113.06, 134.97, 145.07, 154.82, 159.36; anal. calcd for $C_{16}H_{18}O_4S_2$: C, 56.78; H, 5.36; found: C, 56.89; H, 5.49.

3.16. 6,6′-Dimethoxy-3,3′-bis(trimethylsilyl)-2,2′-dihydroxy-1,1′-biphenyl **13**

Using the above procedure, biphenol **13** was obtained: yield 61%; mp 123–125°C. ^{1}H NMR δ 0.29 (s, 18H), 3.51 (s, 6H), 6.39 (s, 2H), 6.90 (d, $J=7.8$ Hz, Ar, 2H), 7.40 (d, $J=7.8$ Hz, Ar, 2H); ^{13}C NMR δ –0.34, 60.69, 113.67, 114.08, 124.32, 136.58, 156.66, 162.45; anal. calcd for $C_{20}H_{30}O_4\ Si_2$: C, 71.87; H, 5.65; found: C, 71.99; H, 6.00.

3.17. 6,6′-Dimethoxy-3,3′-bis(diphenylphosphinyl)-2,2′-dihydroxy-1,1′-biphenyl **14**

Using the above procedure, biphenol **14** was obtained and was isolated as bis *P*-oxide: yield 65%; mp 157–159°C; ^{1}H NMR δ 3.75 (s, 6H), 6.53 (dd, $J=8.7$, $^4J_{HP}=2.3$ Hz, Ar, 2H), 7.03 (dd, $J=8.7$, $^3J_{HP}=13.2$ Hz, Ar, 2H), 7.44–7.75 (series of m, Ar, 20H), 10.85 (s, 2H); ^{13}C NMR (aliphatic) δ 55.97; ^{31}P NMR δ 40.18; anal. calcd for $C_{38}H_{32}O_6P_2$: C, 70.59; H, 4.99; found: C, 70.30; H, 5.18.

3.18. 6,6′-Dimethoxy-3,3′-dicarboxy-2,2′-dihydroxy-1,1′-biphenyl **15**

To a stirred solution of **7** (0.14 g, 0.38 mmol) in water (10 mL) at rt and under N_2, a solution of HI (57% in water, 0.43 g, 0.35 mL, 1.93 mmol) was added. The mixture was stirred under reflux for 2 h. Water (50 mL) was added and the organic phase was extracted with CH_2Cl_2 (2×50 mL). Then, ether was added to the aqueous phase and the organic phase was extracted with ether (3×50 mL). The ether layer was dried (Na_2SO_4) and concentrated to afford **15** as a yellow solid (0.08 g, 65%): mp 186–188°C; IR (Nujol) 1646; ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 6H), 5.72 (s, 2H), 6.65 (d, J=9.0 Hz, Ar, 2H), 7.78 (d, J=9.0 Hz, Ar, 2H); ^{1}H NMR (acetone-d_6) δ 3.78 (s, 6H), 6.70 (d, J=9.0 Hz, Ar, 2H), 7.94 (d, J=9.0 Hz, Ar, 2H); ^{13}C NMR (DMSO-d_6) δ 56.77, 103.44, 106.89, 110.14, 131.74, 161.23, 163.32, 172.92; anal. calcd for $C_{16}H_{14}O_8$: C, 57.49; H, 4.22; found: C, 57.27; H, 4.13.

3.19. X-Ray structure determination of (M,S)-(−)-**17**

Diffracted intensities were collected with a Brucker P4 diffractometer, using graphite monochromated Mo Kα radiation = 0.71073 Å. Crystal description: colorless prism 0.35×0.30×0.28 mm. M_r = 455.49, orthorhombic, space group $P2_12_12_1$, a = 7.774(1), b = 11.283(2), c = 26.294(3) Å, V = 2306.4(6) Å^3, Z = 4, T = 293(2) K, μ = 0.240 mm^{-1}. ω Scans, 5787 measured reflections, 4638 independent reflections, 3904 reflections with $I>2\sigma(I)$, R_{int} = 0.023, 3.9°<2θ< 52.5°. The structure was solved by SIR92 and refined on F^2 by full matrix least-squares using SHELX97. 4638 reflections used in refinement, 384 parameters. Heavy atoms were anisotropic, H atoms isotropic. Flack parameter[23] for determination of the absolute configuration = 0.03(8). Final R = 0.0375 and wR = 0.0880 for data with $I>2\sigma(I)$, $(\Delta/\sigma)_{max}$ = 0.003, $\Delta\rho_{max}$ = 0.142 e Å^{-3}, $\Delta\rho_{min}$ = −0.231 e Å^{-3}.

Acknowledgements

This work was supported by the CNR, Rome, and partially by Sardinia Autonomous Region.

References

1. Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426. Costero, A. M.; Pitarch, M.; Andreu, C.; Ochando, L. E.; Amigó, J. M.; Debaerdemaeker, T. *Tetrahedron* **1996**, *52*, 669. Fabris, F.; De Lucchi, O.; Lucchini, V. *J. Org. Chem.* **1997** *62*, 7156. Feldman, K. S.; Sahasrabudhe, K. *J. Org. Chem.* **1999**, *64*, 209.
2. Jendralla, H.; Li, C. H.; Paulus, E. *Tetrahedron: Asymmetry* **1994**, *5*, 1297. Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S. Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479.
3. Kaneda, T.; Umeda, S.; Tanigawa, H.; Misumi, S. *J. Am. Chem. Soc.* **1985**, *107*, 4802. Costero, A.; Pitarch, M.; *J. Org. Chem.* **1994**, *59*, 2939. Baret, P.; Beaujolais, V.; Béguin, C.; Gaude, D.; Pierre, J.-L.; Serratrice, G. *Eur. J. Inorg. Chem.* **1998**, 613.
4. Baumeister, B.; Sakai, N.; Matile, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1955.
5. Dusemund, C.; Mikami, M.; Shinkai, S. *Chem. Lett.* **1995**, 157.
6. Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed.* **1994**, *33*, 1842. Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, *4*, 525. Degnan, A. P.; Meyer, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762. Tuyet, T. M. T.; Harada, T.; Hashimoto, K.; Hatsuda, M.; Oku, A. *J. Org. Chem.* **2000**, *65*, 1335.

7. Lin, G.-Q.; Zhong, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1369. Delogu, G.; Fabbri, D. *Tetrahedron: Asymmetry* **1997**, *8*, 759. Delogu, G.; Fabbri, D.; Dettori, M. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2819. Kyasnoor, R. V.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1998**, 2713.
8. Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315. Fehz, M. J.; Consiglio, G.; Scalone, M.; Schimd, R. *J. Org. Chem.* **1999**, *64*, 5768. Reetz, M.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179.
9. VanArendonk, A. M.; Cupery, M. E.; Adams, R. *J. Am. Chem. Soc.* **1933**, *55*, 4225. Frantsi, M.; Lindsten, G.; Wennerström, O. *Acta Chem. Scand. B* **1982**, *36*, 135.
10. Benzyltriethylammonium tribromide [BTEA·Br_3] was used instead of benzyltrimethylammonium tribromide [BTMA·Br_3]. Kajigaeshi, S.; Moriwarki, M.; Tanaka, T.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *J. Chem. Soc., Perkin Trans 1* **1990**, 897.
11. Felix, A. *J. Org. Chem.* **1974**, *39*, 1427. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. Minamikawa, J.; Brossi, A. *Tetrahedron Lett.* **1978**, 3085. Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444.
12. Costero, A. M.; Pitarch, M. *J. Chem. Res. (S)* **1994**, 120.
13. Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans* 1 **1988**, 2425.
14. Previously prepared by us. Delogu, G.; Fabbri, D.; Dettori, M. A.; Casalone, G.; Forni, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1827.
15. Delogu, G.; Fabbri, D.; Valle, G. *Phosphorus, Sulphur Silicon* **1997**, *128*, 31.
16. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
17. Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, *35*, 8727.
18. Gilman, H.; Swiss, J.; Cheney, L. *J. Am. Chem. Soc.* **1940**, *62*, 1963.
19. Capozzi, G.; Delogu, G.; Dettori, M. A.; Fabbri, D.; Menichetti, S.; Nativi, C.; Nuti, R. *Tetrahedron Lett.* **1999**, *40*, 4421.
20. Kawano, N.; Okigawa, M.; Hasaka, N.; Kouno, I.; Kawahara, Y.; Fujita, Y. *J. Org. Chem.* **1981**, *46*, 389. Lin, G.-Q.; Zhong, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1369. Harada, T.; Ueda, S.; Tuyet, T. M. T.; Inoue, A.; Fujita, K.; Takeuchi, M.; Ogawa, N.; Oku, A.; Shiro, M. *Tetrahedron* **1997**, *53*, 16663.
21. Kanakalakshmi, B.; Mathai, K. P.; Sethna, S. *J. Ind. Chem. Soc.* **1966**, *43*, 469.
22. Kawano, N.; Okigawa, M.; Hasaka, N.; Kouno, I.; Kawahara, Y.; Fujita, Y. *J. Org. Chem.* **1981**, *46*, 389.
23. Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.