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Stereoselective oxazaborolidine–borane reduction of biphenyl alkyl diketones–lignin models: enantiopure dehydrodiapocynol derivatives

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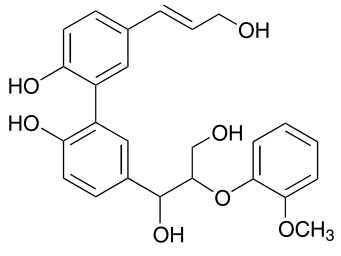
Abstract—Asymmetric reduction of two conformationally flexible biphenyl alkyl diketones **9** and **10** with (*R*)-oxazaborolidine **3**-borane system was successfully carried out and the corresponding biphenyl alcohols **11** and **12** were obtained in high yield and e.e. with predominance of the homochiral (*S*,*S*) dicarbinols. The absolute configuration of diastereopure dehydrodiapocynol derivative (*S*,*S*)-**14** was assigned by crystallographic analysis which confirms the known stereochemical course of CBS-catalysed reduction of ketones and gives useful information on spatial arrangement.

1. Introduction

Lignin is a complex heteropolymer of hydroxycinnamyl alcohols and, second to cellulose, is the most abundant biopolymer on Earth.[1] An important feature of the chemical structure of wood lignins is the presence of *ortho*,*ortho*′-dihydroxybiphenyl structures that are especially prominent in the Gymnosperm wood, namely softwood lignins.[2] Recently there has been a great effort to investigate *ortho*,*ortho*′-dihydroxybiphenyl-5,5′-dicarbinols (e.g. **1** and **2**) as lignin models in order to understand factors which govern the coupling and the cross-coupling of the phenol units.[3]

Although it was generally assumed that the synthesis of lignin is not enzymatically controlled, different research groups have recently demonstrated that some proteins can produce defined stereoisomers of lignin models.[4] This observation proposes new biosynthetic pathways on the degradation of lignin-derived aromatic compounds and it might give the connection between lignin and homochiral naturally occurring lignans. Therefore, the synthesis of enantiopure lignin models should be undertaken and among them, the preparation of homochiral *ortho*,*ortho*′-dihydroxybiphenyl-5,5′-dicarbinols should be considered. *ortho*,*ortho*′-Dihydroxybiphenyl-5,5′-dicarbinols are the building block of



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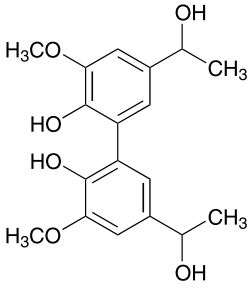

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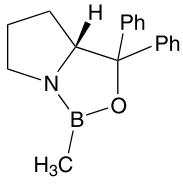
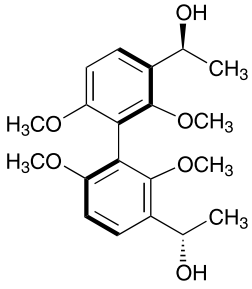


(*R*)-**3**



(*aR*,*S*,*S*)- (–)-**4**

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bioactive molecules[5] and useful models for understanding the biosynthesis and stereochemistry of natural occurring compounds which possess the biphenyl structure.[6]

Recently, we have successfully applied the stereoselective ketone reduction with oxazaborolidine–borane systems[7] to configurationally stable biphenyl alkyl mono- and diketones for the preparation of the corresponding biphenyl alcohols (up to >98% e.e.). The effectiveness of the reduction process was dictated by the geometry of the biphenyl methyl ketone whose axial chirality drives the attack of the reducing agent on the opposite faces of the carbonyl group in different extents. A chiral cooperative effect between the stereogenic axis and the first stereogenic centre on the biphenyl structure formed in the reduction reaction was demonstrated in the preparation of biphenyl methyl alcohol **4**.[8]

We thought that the asymmetry associated with the chiral axis in conformationally flexible biphenyls could also be improved by asymmetric induction of stereogenic centers. Indeed, axial chirality induction has been observed in flexible biphenyls by steric and electronic interactions in complex formation as well as in dynamic processes.[9]

A lot of effort has been devoted to the design of new chiral flexible biphenyls, more available than configurationally stable *ortho*-tetrasubstituted biphenyls.[10] *ortho*,*ortho*′-Disubstituted biphenyls with particular geometries can give an important contribution to the understanding the origins of enantioselectivity in catalytic as well as in stoichiometric processes.[11] As a part of an ongoing program on the preparation of chiral biphenyls, we have now applied the stereoselective oxazaborolidine–borane reduction to biphenyldiketones **9** and **10**, on the assumption that the latent asymmetry due to the chiral axis in the two conformationally flexible biphenyls **9** and **10** could be involved in the formation of the diol and could play an important role in determining the stereochemistry of each prostereogenic centre.

2. Results and discussion

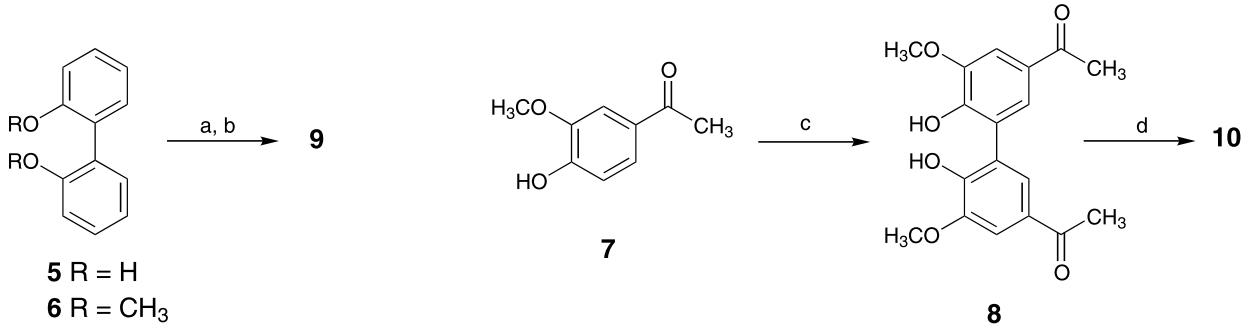
Our interest in the natural occurring biphenyls[8,12] prompted us to prepare homochiral derivatives of dehydroapocynol **2**, a C_2-biphenyl carbinol–lignin model,[3d–e,13] by means of the stereoselective reduction of ketones **9** and **10** with (*R*)-oxazaborolidine **3**–$BH_3{\cdot}Me_2S$ system under the same conditions previously employed for configurationally stable biphenyl methyl ketones.[8]

Biphenol **5** was protected at the hydroxyl groups in the presence of K_2CO_3 and methyl iodide in acetone or DMF and then acylated at the 5,5′ positions by treatment with acetic anhydride and iodine to give biphenyl **9** in 28% yield.[14] Oxidative coupling of the natural acetovanillone **7** was performed in the presence of potassium persulfate and iron(II) sulfate heptahydrate by improving a known procedure[15] to afford biphenyl **8** in 81% yield, which was subsequently *O*-methylated to give diketone **10** (Scheme 1).

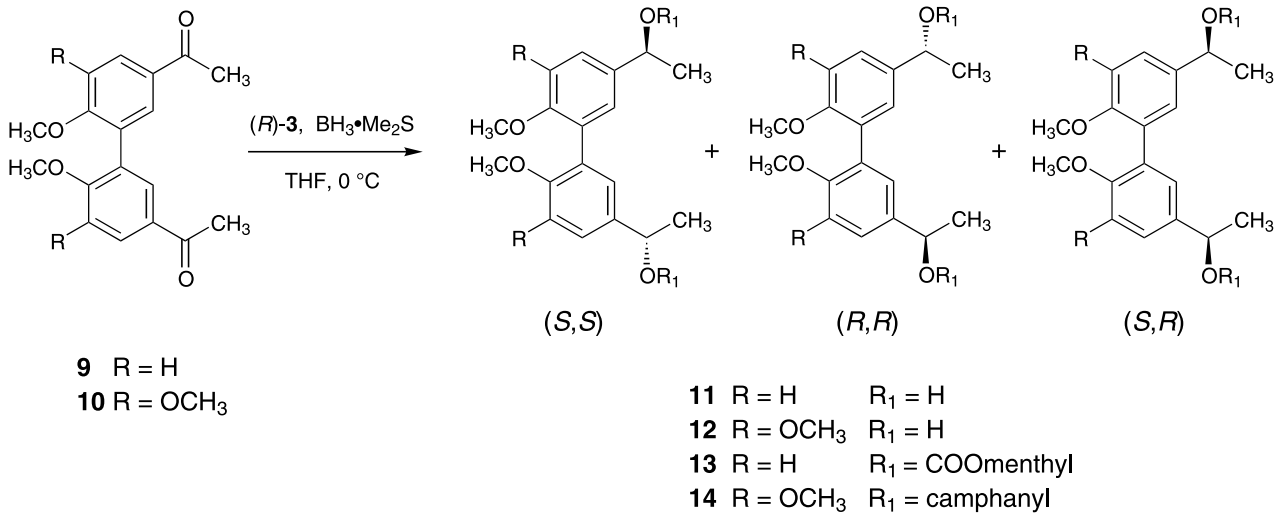
When biphenyls **9** and **10**, respectively, were treated with $BH_3{\cdot}Me_2S$ (1:2 diketone:borane ratio) in the presence of 60% mol of (*R*)-oxazaborolidine **3** in THF at 0°C to rt, complete reduction was observed whitin 1 h and predominance of the homochiral (*S*,*S*)-dicarbinols was achieved in both cases (Scheme 2) according to the known stereochemical course of CBS-catalysed reduction of ketones.[7e]

Attempts to determine the stereoisomeric composition of **11** by chiral HPLC analysis of the free carbinol or the corresponding diacetate, as well by chiral ^1H NMR in the presence of $Eu(hfc)_3$ failed, whereas suitable HPLC separation was achieved after derivatization of the two hydroxyl groups of **11** with (1*R*,2*S*,5*R*)-menthyl chloroformate in the presence of DMAP to give **13** in virtually quantitative yield. Chiral HPLC analysis of the menthylcarbonate **13** gave a >99% e.e. for (*S*,*S*)-**11**, which was obtained from asymmetric reduction beside 6% of the *meso*-diol (*S*,*R*)-**11**.

Diol (*S*,*S*)-**12** was obtained in enantiomerically pure form (>99% e.e.) along with 4% of the *meso* diastereoisomer (*S*,*R*)-**12** as measured from chiral



Scheme 1. *Reagents and conditions*: (a) K_2CO_3, MeI, acetone, 4 h at 50°C then rt; (b) Ac_2O, I_2, reflux 48 h; (c) $K_2S_2O_8$, $FeSO_4{\cdot}7H_2O$, 2 days at rt; (d) KOH, MeI, 96% EtOH, 13 h at 50°C.



Scheme 2.

HPLC analysis of the unprotected dicarbinol **12** mixture.

The observed high diastereoselectivity in the reduction of **9** and **10** (88 and 92% d.e., respectively) is noteworthy, since the reported oxazaborolidine–borane reduction of C_2-symmetrical aryl diketones generally proceeded with lower *dl*/*meso* ratio.[16] The use of stoichiometric oxazaborolidine, excess of borane or addition of specific additives in some instances improved the diastereoselectivity of the reaction[16a,d,f] whereas better results have been reported for the asymmetric reduction of diketones with B-chlorodiisopino-campheylborane.[17]

With respect to the CBS-catalyzed reduction of 4-methoxy- or 3,4-dimethoxyacetophenone, which can be considered the monomeric ketones related to **9** and **10**, or 4-hydroxy-3-methoxyacetophenone to give apocynol,[18] the stereoselective reaction course observed with **9** and **10** as substrates could be additionally influenced by the presence of the stereogenic axis, in some way conformationally fixed during the coordination of ketone with (*R*)-**3** and the subsequent hydride transfer step. Although the configurational stability of biphenyls is mainly related to the bulkiness at the four *ortho* positions, the presence of *meta* substituents should be considered.[19] The influence of *meta* substituents is rather related to steric than electronic effects and could account for the slight difference in the diastereomeric excess of **11** and **12**.

In order to assign unequivocally the absolute configuration at the two stereocentres of the dicarbinol (*S*,*S*)-**12**, as envisaged by the preferred approach postulated by Corey and Itsumo, we looked for the best protecting groups for carbinol (*S*,*S*)-**12** which would allow us to afford suitable crystals for X-ray diffraction analysis. Treatment of **12** with (1*R*,2*S*,5*R*)-menthyl chloroformate allowed the separation of homochiral and *meso*-isomer of **12** as menthyl carbonates by flash chromatography, but it was not possible to obtain suitable crystals for the X-ray analysis. When (*S*,*S*)-**12** was reacted with 3 equiv. of (−)-(1*S*,4*R*)-camphanic acid chloride and DMAP at room temperature using CH_2Cl_2 as solvent, the diastereopure camphanic derivative (*S*,*S*)-**14** was recovered in 60% yield after column chromatography and crystallization from EtOH.[20]

Crystallographic analysis of the diastereopure camphanic derivative (*S*,*S*)-**14** confirmed the absolute configuration and stereoselectivity of the CBS-mechanism[7e] and provided important information about the conformation of the biphenyl unit, in particular on the dihedral angle between the benzene rings. Since biphenyl **14** is a dehydroapocynol derivative, crystallographic data of enantiopure (*S*,*S*)-**14** increases our knowledge on the spatial arrangement of the residual lignin,[21] on the correlation with absolute configuration[4] and on the luminescence properties.[22]

A perspective view of (*S*,*S*)-**14**, showing the atom numbering scheme, is shown in Figure 1. The absolute configuration *M* at the biphenyl bond was established on the basis of the known stereogenic centres of the camphanyl unit.

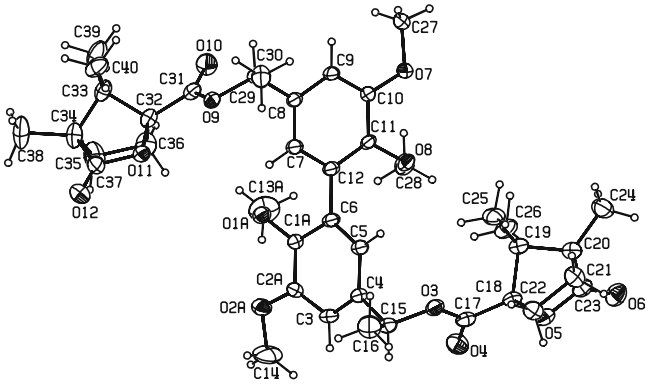


Figure 1. ORTEP[23] plot of diastereomer (*S*,*S*)-**14** with atom numbering scheme. Displacement ellipsoids are drawn at the 20% probability.

In compound (*S*,*S*)-**14**, the biphenyl skeleton assumes the *transoid* conformation, with C5–C6–C12–C7 torsion angle χ equal to −106.8(3)°. The dihedral angle τ between the least-squares planes through the biphenyl rings is equal to 71.4(1)°.[24] In Table 1 some structural properties of (*S*,*S*)-**14** are compared with those of other lignin model compounds having the same structural elements of (*S*,*S*)-**14**, as depicted in Figure 2. That is, two alkoxy groups at *ortho*,*ortho′* positions of the biphenyl, two methoxy groups at the *meta* positions adjacent to the *ortho*-substituted positions, and alkyl or acetate groups at the other two *meta* positions. Their crystallographic data were retrieved from the Cambridge Structural Database (CSD version 5.24, no refcode restrictions applied).[25]

From the values of the torsion angle χ, no preference for the *transoid* or *cisoid* conformation of the biphenyl stands out, both forms occurring approximately with the same probability. The dihedral angle τ is found to cover a large range of values in these structures, where the minimum, 50.9°, and the maximum dihedral, 71.6°, are both observed in *ortho*,*ortho′*-methoxy substituted biphenyls. This indicates that the conformation assumed by the biphenyl in the crystal cannot be explained by just the steric requirements of the *ortho*-substituents, but the effects of *meta*-substituents and of packing forces should be also taken into account. These effects seem not relevant in determining the inter-ring bond length C6–C12, the observed differences between the compounds reported in Table 1 being of the order of the experimental error.

Table 1. Structural properties of lignin model compounds[a]

Compound	χ	τ	Inter-ring bond
(*S*,*S*)-**14**[b]	−106.8	71.4	1.496
1 of Ref. 3c	64.4	65.1	1.493
1 of Ref. 21c	−56.4	60.0	1.490
2 of Ref. 21c	−57.1, −115.3[c]	60.1, 65.1[c]	1.490, 1.500[c]
6 of Ref. 21b	−48.0	50.9	1.499
2 of Ref. 21a	119.5	59.8	1.492
3 of Ref. 21a	125.2, −120.4[c]	53.1, 59.1[c]	1.491, 1.495[c]

[a] χ is the torsion angle C5–C6–C12–C7, where the same atom numbering scheme of the present work (see Fig. 1) is used for all compounds, and τ is the dihedral angle between the least-squares planes through the two phenyl rings. Distances in Å, angles in degrees.

[b] This work.

[c] Values for the two molecules of the asymmetric unit.

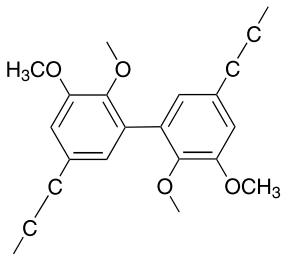


Figure 2.

3. Conclusions

We have successfully applied the effectiveness of the (*R*)-oxazaborolidine **3** in the stereoselective reduction of two prochiral biphenyl ketones **9** and **10** to give the corresponding homochiral diols, which are valuable intermediates in the preparation of new ligands[11a,26] and bioactive molecules[5,6] and useful models for understanding the stereochemistry of dehydrodiapocynol, a biphenyl–lignin model.

The CBS-oxazaborolidine protocol has been shown to be a direct method to achieve biphenyl methyl dicarbinols in enantiopure form and high yield. Although conformationally flexible biphenyl methyl ketones were used as substrates, an influence of the stereogenic axis should be taken into account in the stereoselectivity of the reduction reaction. However, selected experiments are necessary to investigate the influence of the biphenyl substitution pattern, and its relation with the molecular stereogenic axis, on the stereochemical course of the (*R*)-**3**/$BH_3{\cdot}Me_2S$ reduction of this class of diketones. This study is currently in progress.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance™ 400 spectrometer. Chemical shift (δ) are given as ppm relative to the residual solvent peak. Coupling constants (J) are in Hz. Melting points are uncorrected. Optical rotations were measured on a DIP 135 JASCO instrument. THF was distilled under argon from sodium benzophenone ketyl. DMF and CH_2Cl_2 were dried over 4 Å molecular sieves. (*R*)-Methyl-CBS-oxazaborolidine, (*R*)-CBS, was purchased from Aldrich as 1 M solution in toluene. All the CBS-catalyzed reactions were carried out under argon using standard Schlenk techniques. Column chromatography was performed on silica gel 60 (70–230 mesh) using the specified eluants. Chiral HPLC analyses were carried out on Chiracel® OD column (Daicel Chemical Industries) using *n*-hexane/*iso*-propanol mixtures as a mobile phase and detection by UV–vis detector at 225 nm.

4.2. 2,2′-Dimethoxy-1,1′-biphenyl, 6

To a solution of commercially available 2,2′-dihydroxy-1,1′-biphenyl **5** (10.2 g, 54.7 mmol) in dry DMF (120 mL), K_2CO_3 (16.53 g, 119.6 mmol) was added in one portion under nitrogen. The reaction mixture was stirred at 50°C for 1 h, then 1 h at rt. A solution of CH_3I (8 mL, 128.5 mmol) in dry DMF (15 mL) was slowly added at rt; the mixture was then mantained at 50°C for 3 h and 4 h at rt. The reaction was quenched with water (2000 mL). The organic phase was extracted with CH_2Cl_2, stirred for 2 h with a solution of 10% NaOH (400 mL), washed with water (200 ml) and dried with Na_2SO_4 to give pure biphenyl **6** (10.1 g, 87% yield). Mp 152–153°C (Lit.[27] 154–5°C); ^1H NMR: δ 3.78 (6H, s), 6.99 (2H, d, $J=8.1$), 7.02 (2H, dd, $J=8.1$

and 1.8), 7.26 (2H, dd, $J=8.1$ and 1.8), 7.34 (2H, dd, $J=8.1$ and 1.8); ^{13}C NMR: δ 55.68, 111.31, 126.09, 127.80, 128.58, 131.45, 157.02.

4.3. 1,1′-(6,6′-Dimethoxy-1,1′-biphenyl-3,3′-diyl)-diethanone, 9

A mixture of 2,2′-dimethoxy-1,1′-biphenyl **6** (1.0 g, 4.7 mmol), acetic anhydride (1.05 g, 10.3 mmol) and iodine (0.19 g, 0.75 mmol) was refluxed for 48 h. The dark brown solution was poured into 50 mL of water and then extracted with CH_2Cl_2. The organic phase was successively washed with dilute K_2CO_3, sodium bisulfite and water and then dried over Na_2SO_4. After removal of the solvent the crude product was purified by flash-chromatography (petroleum ether:AcOEt 7:3) to give 400 mg of compound **9** (28% yield). Mp 140–141°C (Lit.[28] 162–164°C); ^{1}H NMR: δ 2.58 (6H, s), 3.85 (6H, s), 7.01 (2H, d, $J=8.8$), 7.85 (2H, d, $J=2.4$), 8.02 (2H, dd, $J=8.8$ and 2.4); ^{13}C NMR: δ 26.37, 55.86, 110.31, 126.78, 129.92, 130.27, 131.91, 160.94, 196.77.

4.4. 1,1′-(6,6′-Dihydroxy-5,5′-dimethoxy-1,1′-biphenyl-3,3′-diyl)diethanone, 8

To a well stirred solution of 4-acetyl-2-methoxyphenol (acetovanillone) **7** (6.0 g, 36.1 mmol) in water (1000 mL) and acetone (30 mL), $K_2S_2O_8$ (6.0 g, 22.2 mmol) and $FeSO_4$ (4.0 g, 1.4 mmol) were added in one portion at rt. The reaction mixture was stirred for 2 days at rt, then the precipitate product was separated by filtration and repeatedly washed with water and then pentanes to give biphenyl **8** (4.8 g, 81% yield). Mp 306–308°C (Lit.[15] 308–10°C); ^{1}H NMR: (DMSO-d_6) δ 2.60 (6H, s), 4.02 (6H, s), 6.35 (2H, s), 7.58 (2H, d, $J=2.4$), 7.62 (2H, d, $J=2.4$); ^{13}C NMR: δ 27.13, 56.77, 110.30, 125.08, 125.90, 128.48, 147.00, 149.64, 196.62.

4.5. 1,1′-(5,5′,6,6′-Tetramethoxy-1,1′-biphenyl-3,3′-diyl)-diethanone, 10

To a suspension of diketone **8** (0.5 g, 1.5 mmol) in 96% EtOH (3 mL), a 10% aqueous solution of KOH was added (5 mL) under nitrogen. The mixture was heated at 50°C for 1 h, then CH_3I (0.3 mL, 5 mmol) was added and the mixture heated at 50°C for 12 h. After cooling at 10°C, the reaction mixture was treated with 10% HCl until pH 3 and extracted with CH_2Cl_2. The organic phases were collected, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash chromatography (petroleum ether:AcOEt 2:1) to obtain diketone **10** (0.2 g, 40% yield) as white solid. Mp 138–139°C, ^{1}H NMR: δ 2.56 (6H, s), 3.74 (6H, s), 3.97 (6H, s), 7.48 (2H, d, $J=2.0$), 7.60 (2H, d, $J=2.0$); ^{13}C NMR: δ 26.45, 55.99, 60.85, 110.89, 124.68, 131.36, 132.60, 151.08, 152.80, 197.01.

4.6. General procedure for the asymmetric reduction

In a typical procedure, (*R*)-CBS (0.36 mmol, 0.36 mL of 1 M solution in toluene) was dissolved in THF (8 mL) under argon and cooled to 0°C. From a syringe charged with $BH_3{\cdot}Me_2S$ (2 M in THF, 0.6 mL, 1.2 mmol), 20% of the final amount was added to the catalyst solution. After 10 min of stirring, the remaining $BH_3{\cdot}Me_2S$ and a solution of ketone (0.6 mmol) were simultaneously added by syringe pump over 20 min. The reaction mixture was then stirred at rt and stopped when quantitative conversion of the substrate was observed by TLC analysis. At completion, the reaction was quenched by careful dropwise addition of MeOH (2 mL), diluted with sat. NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and taken to dryness under vacuum to give a residue that was purified by column chromatography.

4.7. (1*S*,1′*S*)-1,1′-(6,6′-Dimethoxy-1,1′-biphenyl-3,3′-diyl)-diethanol, (−)-11

Reduction of ketone **9** according to the procedure described above afforded a residue that was purified on a silica gel column (CH_2Cl_2:AcOEt 3:2) to afford pure (−)-**11** as a white solid (85% yield, >99% e.e., 94:6 diastereoisomeric ratio), mp 124–125°C, $[\alpha]_D^{22}=-35.2$ (*c* 0.25, $CHCl_3$); ^{1}H NMR: δ 1.53 (6H, d, $J=6.4$, 2×*Me*-CH), 3.79 (6H, s, 2×-OMe), 4.90 (2H, q, $J=6.4$, 2×-C*H*OH), 6.98 (2H, d, $J=8.4$, H-5 and 5′), 7.27 (2H, d, $J=2.3$, H-2 and 2′), 7.37 (2H, dd, $J=8.4$ and 2.3, H-4 and 4′); ^{13}C NMR: δ 24.85, 55.84, 70.03, 111.05, 125.77, 127.68, 128.83, 137.60, 156.46. Anal. calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.68; H, 7.42%.

The diastereoisomeric and enantiomeric composition of (−)-**11** was determined by conversion into the corresponding dimenthylcarbonate **13** and HPLC analysis on chiral column.

4.8. (1*S*,1′*S*)-1,1′-(6,6′-Dimethoxy-1,1′-biphenyl-3,3′-diyl)-diethanol-bis-(1*R*,2*S*,5*R*)-menthylcarbonate, (−)-13

As general procedure, (±)-**11** (45 mg, 0.15 mmol) was dissolved in CH_2Cl_2 and treated with (−)-(1*R*,2*S*,5*R*)-menthylchloroformate (0.082 mL, 0.38 mmol) and DMAP (46 mg, 0.38 mmol). The mixture was stirred at 45°C until TLC analysis showed complete conversion of the substrate. The reaction was quenched by addition of water and extracted with sat. NH_4Cl and then with brine. The organic phases were pooled and the solvent removed under vacuum to give a residue that was purified on a silica gel column (petroleum ether:CH_2Cl_2 1:1) to give the dimenthyl derivative **13** as an inseparable mixture of the expected three diastereoisomers. HPLC analysis of this mixture on chiral column (*n*-hexane:2-PrOH 98:2, flow rate 0.5 mL/min) gave three different peaks in 1:2:1 ratio at t_R/min = 8.9 (1*S*,1′*S*-**13**), 10.1 (1*R*,1′*S*-**13**) and 13.4 (1*R*,1′*R*-**13**).

When a sample of (−)-**11** obtained by asymmetric reduction was analysed following this procedure, its enantiomeric purity was assessed as >99%, whereas the diastereoisomeric ratio was 94:6.

(1*S*,1′*S*)-**13**: $[\alpha]_D^{22}=-68.5$ (*c* 0.87, $CHCl_3$); ^1H NMR: δ 0.70 (6H, d, $J=6.9$, 2×Me), 0.84 (6H, d, $J=7.0$, 2×Me), 0.93 (10H, d, $J=6.3$, 2×Me overlapped to a multiplet for 2×CH_2), 1.04 (4H, m, 2×CH_2), 1.38 (2H, bt, 2×CH),1.61 (6H, d, $J=6.5$, 2×*Me*-CHOH), 1.68 (4H, m, 2×CH_2), 1.90 (2H, dq, $J=6.9$ and 2.4, 2×CH), 2.10 (2H, m, 2×CH), 3.77 (6H, s, 2×-OMe), 4.5 (2H, dt, $J=10.9$ and 4.3, 2×-C*H*OCO), 5.73 (2H, q, $J=6.5$, 2×-C*H*OH), 6.95 (2H, d, $J=8.4$, H-5 and 5′), 7.25 (2H, d, $J=2.1$, H-2 and 2′), 7.35 (2H, dd, $J=8.4$ and 2.1, H-4 and 4′); ^{13}C NMR: δ 16.18, 20.66, 21.99, 22.27, 23.35, 25.99, 31.42, 34.15, 40.79, 47.02, 55.77, 75.77, 78.20, 110.92, 126.59, 127.56, 129.37, 132.96, 154.35, 156.83. Anal. calcd for $C_{40}H_{58}O_8$: C, 72.04; H, 8.77. Found: C, 72.26; H, 8.83%.

4.9. (1*S*,1′*S*)-1,1′-(5,5′,6,6′-Tetramethoxy-1,1′-biphenyl-3,3′-diyl)diethanol, (−)-12

Asymmetric reduction of diketone **10** according the general procedure described above afforded diol (−)-**12** in 87% isolated yield, >99% e.e. and 96:4 diastereoisomeric ratio; $[\alpha]_D^{22}=-29.6$ (*c* 0.66, $CHCl_3$); ^1H NMR: δ 1.53 (6H, d, $J=6.4$, 2×*Me*-CH), 3.67 (6H, s, 2×-OMe), 3.94 (6H, s, 2×-OMe), 4.89 (2H, q, $J=6.4$, 2×-C*H*OH), 6.85 (2H, d, $J=1.9$, 2×Ar-H), 7.02 (2H, d, $J=1.9$, 2×Ar-H); ^{13}C NMR: δ 25.08, 55.87, 60.65, 70.27, 109.00, 120.10, 132.46, 140.97, 146.00, 156.78. HPLC: *n*-hexane:2-PrOH 85:15, flow rate 0.7 mL/min, t_R/min = 17.6 (1*S*,1′*S*), 21.3 (1*R*,1′*S*), 33.5 (1*R*,1′*R*); Anal. calcd for $C_{20}H_{26}O_6$: C, 66.28; H 7.23. Found: C, 66.43; H, 7.31%.

4.10. (1*S*,1′*S*)-1,1′-(5,5′,6,6′-Tetramethoxy-1,1′-biphenyl-3,3′-diyl)diethanol-bis-(1*S*,4*R*)-camphanate ester, (−)-14

To a solution of (−)-**12** (100 mg, 0.28 mmol) in dry CH_2Cl_2 (20 mL), DMAP (234 mg, 1.9 mmol) was added at rt under nitrogen. A solution of (−)-(1*S*,4*R*)-camphanic chloride (182 mg, 0.84 mmol) in dry CH_2Cl_2 (15 mL) was slowly added. After stirring 12 at rt, the reaction mixture was cooled at 0°C and treated with 10% HCl until pH 3. The aqueous layer was extracted with CH_2Cl_2, the organic phases recollected, dried over Na_2SO_4 and evaporated to dryness. The crude residue was purified by flash chromatography (petroleum ether:AcOEt 1:1) to obtain ester (−)-**14** (120 mg, 60% yield) as white solid. Mp 64–65°C, $[\alpha]_D^{22}=-52.5$ (*c* 0.86, $CHCl_3$); ^1H NMR: δ 0.27 (6H, s, $J=6.4$, 2×Me), 1.02 (6H, s, $J=6.4$, 2×Me), 1.10 (6H, s, $J=6.4$, 2×Me); 1.60 (6H, d, $J=6.6$, 2×Me), 1.67 (2H, ddd, $J=13.2$, 9.4 and 4.2, -CH); 1.90 (2H, ddd, $J=13.2$, 11.2 and 4.4, -CH); 2.00 (2H, ddd, $J=13.6$, 9.4 and 4.4, -CH); 2.04 (2H, ddd, $J=13.6$, 11.2 and 4.2, -CH); 3.62 (6H, s, 2×-OMe), 3.91 (6H, s, 2×-OMe), 6.00 (2H, q, $J=6.4$, 2×-C*H*OH), 6.87 (2H, d, $J=2.4$, 2×Ar-H), 6.95 (2H, d, $J=2.4$, 2×Ar-H); ^{13}C NMR: δ 9.69, 16.68, 16.81, 22.06, 28.94, 30.55, 54.23, 54.81, 55.93, 60.66, 73.67, 91.00, 109.99, 120.97, 132.41, 135.73, 146.64, 152.71, 166.81, 178.27. Suitable crystals for X-diffractrometric analysis were achieved after crystallization from 96% EtOH.

4.11. X-Ray structure determination of (*S*,*S*)-14

Crystal description: colourless prism 0.34×0.22×0.16 mm. $M_r=722.80$, orthorhombic, space group $P2_12_12_1$, $a=6.339(1)$, $b=23.816(5)$, $c=25.641(5)$ Å, $V=3871.0(14)$ Å^3, $Z=4$, $T=293(2)$ K, $\mu=0.091$ mm^{-1}. X-Ray data were collected on a Bruker Smart Apex CCD area detector using graphite-monochromated Mo Kα radiation ($\lambda=0.71073$ Å). Data reduction was made using SAINT programs; absorption corrections based on multiscan were obtained by SADABS.[29] 39920 measured reflections, 6011 independent reflections, 3907 reflections with $I>2\sigma(I)$, $3.18<2\theta<59.84°$, $R_{int}=0.042$. The structure was solved by SIR-92[30] and refined on F^2 by full-matrix least-squares using SHELXL-97.[31] Refinement on 6011 reflections, 518 parameters, 17 restraints. Owing to the lack of heavy atoms in the structure, equivalent reflections, including Friedel opposites, were merged and $\delta f''$ values were set to zero. Final $R=0.0494$, $wR=0.1183$ for data with $F^2>2\sigma(F^2)$, $(\Delta/\sigma)_{max}=0.000$, $\Delta\rho_{max}=0.14$, $\Delta\rho_{min}=-0.15$ e Å^{-3}. In the course of the structure refinement, it became evident that one of the aromatic rings (that labelled from C1 to C6) is partially disordered, the O-substituted ring carbon atoms C1 and C2 statistically assuming two positions, above and below the plane of the other carbon atoms of the ring. The methoxy groups bonded to them required themselves to be refined in two positions. In Figure 1 only the conformation having statistical weight equal to 0.68, labelled as A, is reported.

Tables of atomic coordinates, anisotropic thermal parameters, bond lengths and angles of (*S*,*S*)-**14** may be obtained free of charge from The Director CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK, on quoting the deposition number CCDC 210955, the names of the authors and the journal citation (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk; web site: http://www.ccdc.cam.ac.uk).

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