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Stereoselective synthesis of chiral atropisomerically stable ferrocenyldiols containing a biphenyl unit

Angela Patti,[a,*] Sonia Pedotti,[a] Alessandra Forni[b] and Gianluigi Casalone[b]

[a]*Istituto di Chimica Biomolecolare del CNR—Sez. di Catania, Via del Santuario 110, I-95028 Valverde CT, Italy*
[b]*Istituto di Scienze e Tecnologie Molecolari del CNR, Via Golgi 19, I-20133 Milano, Italy*

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Abstract—Two different ferrocenyldiketones **1** and **2** containing a biphenyl unit were prepared by Ni(0) promoted homocoupling of suitable ferrocenyl-aryl halides. The atropisomeric stability of the corresponding diols and other related derivatives was investigated. Chiral 2,2′-bis-(ferrocenylhydroxymethyl)-1,1′-biphenyl, (−)-**5c**, and 1(1,1′)-ferrocena-2,5-dihydroxy-3,4(1,2)dibenzenacyclopentaphane, (+)-**6a** and (−)-**6b**, were prepared as single diastereoisomers with defined central and axial chiralities by CBS-catalyzed asymmetric reduction of **1** and **2**, respectively. During the reaction, that proceeded with high stereoselectivity affording the above mentioned diols in satisfactory enantiomeric excess, we noticed the occurrence of an unusual reductive deoxygenation process. Absolute configurations of the chiral diols were assigned by means of X-ray crystallographic and circular dichroism analyses.

1. Introduction

Biaryl atropisomeric compounds have attracted considerable interest due to their frequent occurrence in nature,[1] biological activity[2] and wide application in asymmetric catalysis,[3] where the specific chiral environment created by a stereogenic axis plays a relevant role in obtaining efficient asymmetric induction. Their conformational properties and the synthetic methodologies for their preparation in optically active form[4] have been extensively studied.

Although for the most part stable atropisomers are *ortho–ortho′* tetrasubstituted biaryls, a sufficiently high rotational barrier about the biaryl linkage has been shown in some sterically congested tri- or disubstituted biphenyls;[5] the twisting of the biphenyl skeleton can also be induced by metal complexation of conformationally flexible 2,2′-disubstituted biphenyls giving rise to stable axially chiral metal complexes.[6] Due to a restriction in the rotation around a single bond, other classes of compounds such as 1-naphthylcarbinols and 1-naphthylamines,[7] naphthylaryl and pyrimidine derivatives,[8] 2,2′-bridged-1,1-biaryls[9] and hindered tertiary aromatic amides[10] can exist as atropisomers.

As a part of our research program on chiral ferrocenes, we were interested in ferrocenyl compounds with axial chirality, which have been investigated less than the plethora of known ferrocenyl derivatives possessing central and/or planar chirality.[11] Axially chiral ferrocenes usually contain a binaphthyl moiety[12] and more recently, pseudobiarylic ligands with a functionalized aryl group directly connected to a planar chiral ferrocene have been developed and found to be very active as catalysts in different asymmetric reactions.[13]

With the aim of evaluating the influence, in terms of sterical hindrance to the biaryl rotation, of a ferrocenyl substituent on the biphenyl backbone we originally prepared the 2,2′-disubstituted biphenyl **1**, which was found conformationally flexible whereas the corresponding diols **5a–c** showed sufficient atropisomeric stability to be detected and isolated.[14] Herein, we also considered the ferrocenyl-aryl macrocyclic diketone **2** and report the asymmetric reduction of both **1** and **2** to give the corresponding chiral and atropisomerically stable diols as valuable starting materials for the preparation of a novel class of ferrocenyl derivatives potentially useful in catalysis and host–guest recognition fields.

* Corresponding author. Tel.: +39 0957212136; fax: +39 0957212141; e-mail: angela.patti@icb.cnr.it

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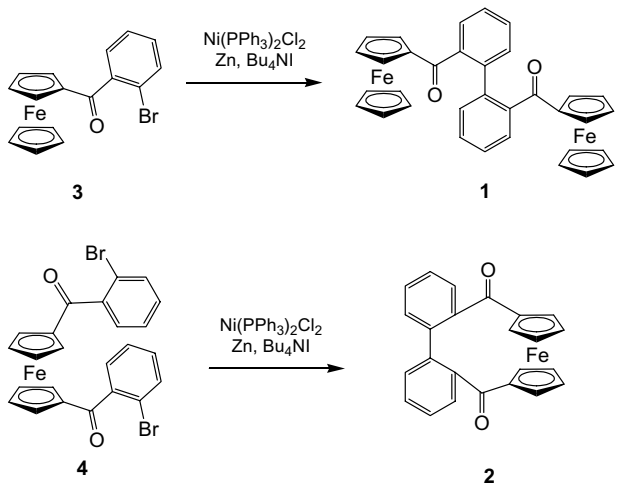
2. Results and discussion

2.1. Homocoupling reactions

Diketones **1** and **2** were obtained by Ni(0) promoted homocoupling of (2-bromobenzoyl)ferrocene, **3** and 1,1′-bis(2-bromobenzoyl)ferrocene, **4**, respectively, both easily accessible in high yield by conventional Friedel–Crafts acylation of ferrocene.[15] The active Ni(0) complex was generated in situ from $Ni(PPh_3)_2Cl_2$ and zinc in the presence of Bu_4NI at 60 °C in THF[16] and after the addition of the substrate, the reaction proceeded smoothly within a few hours. Different conditions for the homocoupling of **3** were examined and the presence of an excess of zinc was found to be essential to achieve high conversion of the substrate, either with stoichiometric or sub-stoichiometric amounts of the nickel complex. Intramolecular homocoupling of **4** gave diketone **2** in about 45% yield, together with non-identified polymeric compounds (Table 1).



In order to have more direct access to target diols **5** and **6**, the homocoupling of the alcohols deriving from **3** or **4**, as well as their methoxy- and acetoxy derivatives, was also tried, but the reactions almost exclusively gave the hydrodehalogenation product of the starting ferrocene.

Table 1. Nickel-promoted homocoupling of ferrocenyl-aryl halides

Ketone	Ketone–$Ni(PPh_3)_2Cl_2$–Zn molar ratio[a]	Time (h)	Product (%)[b]
3	1:1:5	2	**1** (85)
3	1:1:2.5	3	**1** (85)
3	1:1:1	24	—
3	1:0.5:5	20	**1** (55)
3	1:0.5:2.5	20	**1** (40)
4	1:1:5	4	**2** (45)

[a] Bu_4NI in 1:1 ratio with Zn was always used.
[b] Isolated yield.

Chiral HPLC analysis of **1** in different chromatographic systems always showed a single peak, whereas **2** in our standard conditions (Chiralcel OD, *n*-hexane–EtOH 9:1, flow 0.5 mL/min) gave a very broad peak, which evolved into two peaks separated by a large plateau-like region when the eluent flow rate was increased up to 1.5 mL/min, indicative of column enantiomer-interconversion occurring at a rate similar to that of the separation process.[17]

^1H and ^{13}C NMR spectra of **1** and **2** showed a reduced number of resonances, as expected for C_2-symmetric molecules; the two α- and the two β-positions on the substituted cyclopentadienyl ring were found equivalent in diketone **1**, due to the freedom of the rotation about the two carbonyl groups, but not in **2**. As a consequence of some degree of rigidity in the molecule, four distinct ferrocenylic resonances were observed in the ^1H NMR spectrum of **2**, one of them being largely differentiated and at high chemical shift (δ 5.18 ppm), may be because it pointed into the deshielding region of the carbonyl group. As reported for other carbonyl-containing ferrocenophanes, in the most reasonable conformation the two carbonyl groups of **2** should be in a *trans*-disposition and coplanar to the cyclopentadienyl rings (Fig. 1).[18]

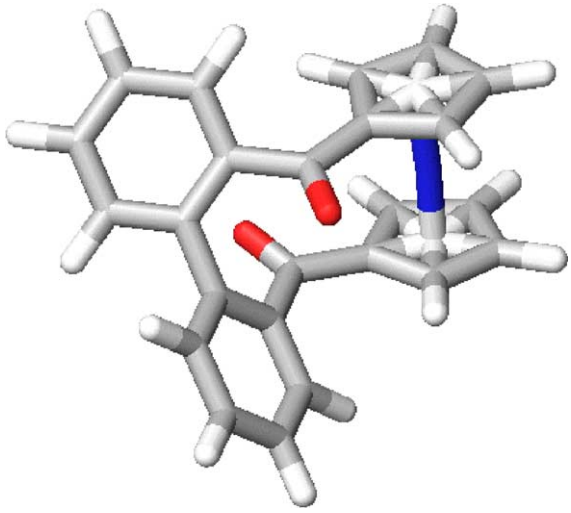
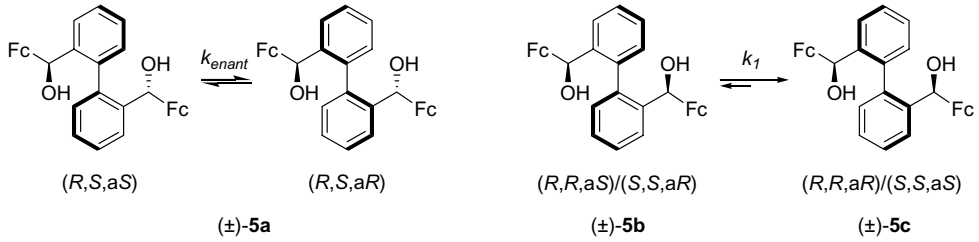


Figure 1. MM2-minimized model of **2**.

2.2. Conformational stability of diols deriving from 1 and 2

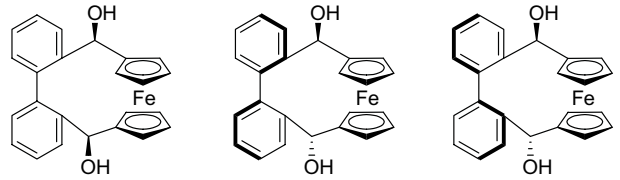
We have recently shown that chemical reduction (LAH) of **1** gives diol **5**, which exists in three diastereomeric forms **5a**–**c** with different combinations of central and axial chirality and sufficient atropisomeric stability to allow their detection and separation. However, diol **5a** suffers racemization and diol **5b**, whose formation is kinetically favoured, atropisomerizes to **5c**, which is thermodynamically more stable (Scheme 1).[14] Since the reverse process from **5c** to **5b** does not occur, it seems evident that only **5c** can be obtained in enantiomerically and diastereoisomerically pure form.

In the same way, from the chemical reduction of diketone **2**, the three diastereoisomeric diols **6a**–**c** can be



Scheme 1. Atropisomeric equilibria for diols **5a**–**c**. In hexane at 23 °C, $k_{enant} = 0.74 \times 10^{-5}$ and $k_1 = 1.68 \times 10^{-5}$ were determined.[14]

obtained, namely the (*R*,*S*,a*R*)/(*S*,*R*,a*S*)-isomer (±)-**6a** and the two C_2-symmetrical (*R*,*R*,a*R*)/(*S*,*S*,a*S*)-(±)-**6b** and (*R*,*R*,a*S*)/(*S*,*S*,a*R*)-(±)-**6c** diols (Scheme 2).



Scheme 2. Possible diastereoisomeric diols deriving from **2**.

The reduction of **2** with $NaBH_4$ proceeded stereoselectively, as previously observed for **1**, giving only diol (±)-**6a**, easily identified from its NMR spectra showing distinct resonances for each proton (and carbon) in the molecule in agreement with the lack of symmetry. Eight separate resonances were observed for the ferrocenylic protons, two of which appearing at unusual high field (δ 3.55 and 3.87) and assignable to one of the α-protons in each cyclopentadienyl ring, which lies over a distal phenyl ring.[19] The hydroxylic protons gave two doublets at 1.43 and 1.94 ppm with quite different coupling constant, 11.7 and 3.1 Hz, respectively, the chemical shifts of which were not influenced by the dilution. The absence of inter- or intramolecular hydrogen bonding was evident from the IR spectrum, which showed two sharp bands at 3611 and 3565 cm^{-1}. Chiral HPLC analysis of (±)-**6a** showed two baseline well-resolved peaks in a 1:1 ratio; single enantiomers of **6a** were collected and allowed to stand in hexane–EtOH solution at room temperature or 45 °C for various lengths of time giving no evidence of racemization.

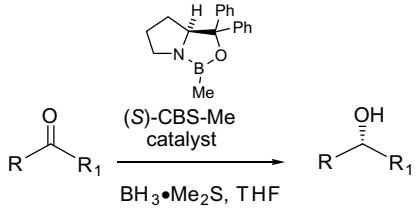
LAH reduction of **2** afforded two diols, (±)-**6a** and a single symmetrical one, (±)-**6b**, the other possible symmetrical diol (±)-**6c** never being observed. The ratio of **6a**:**6b** was found dependent upon the experimental conditions; when the reaction was carried out in the presence of a large excess of LAH, so that a complete reduction was achieved nearly instantaneously, a ratio of 20:80 for **6a**:**6b** was observed. This ratio was reversed when a controlled reduction of **2** was performed by the portionwise addition of LAH.

The conformational stability of (±)-**6b** was assessed by heating the diol in different solvents at temperatures up to 100 °C for 24 h; the formation of the atropisomeric diol (±)-**6c** was not observed in any case.

In the hypothesis that the presence of an hydroxyl group is sufficient to lower the conformational flexibility of the intermediate ketoalcohol with respect to the parent **2**, two possible ketoalcohols were expected, namely the (a*R*,*R*/a*S*,*S*) and (a*S*,*R*/a*R*,*S*) diastereomers, each one giving rise to (±)-**6a** in addition to a symmetric diol by further reduction. The absence of (±)-**6c** could be due to a marked difference in the energy formation or conformational stability of these ketoalcohols; the occurrence of an irreversible fast atropisomerization from **6c** to **6b** seemed less probable taking into account the higher rigidity of the involved molecules compared to **5b** and **5c**, where the analogous isomerization process was detected.

2.3. Asymmetric reduction of diketone 1

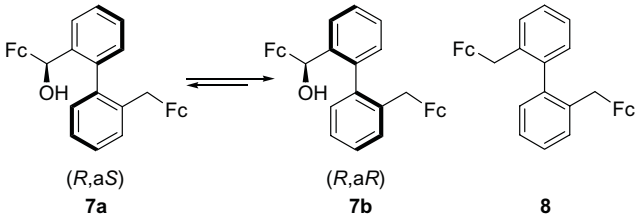
Among the available methodologies for the asymmetric reduction of the carbonyl group, we resorted to the CBS-catalyzed reaction[20] (Scheme 3) that we have successfully applied in the synthesis of other biphenyl carbinols.[21]



Scheme 3. General CBS-catalyzed asymmetric reduction of ketones.

However, using our standard conditions (30% equiv of catalyst, THF, rt), after 6 h the conversion of diketone was negligible. As a result the reaction was carried out at 45 °C. At this temperature, **1** was reduced to the corresponding alcohol but a careful choice of the reaction time was necessary, since other products, namely **7a** and **7b**, could also form (Scheme 4).

In the NMR spectra of **7a** and **7b**, single resonances were observed for each proton and carbon in the molecules indicating the lack of symmetry; diagnostical AB systems centred at 3.58 and 3.13 ppm related with methylenic carbons indicated the structure of 2-ferrocenylhydroxymethyl-2′-ferrocenylmethyl-1,1′-biphenyl



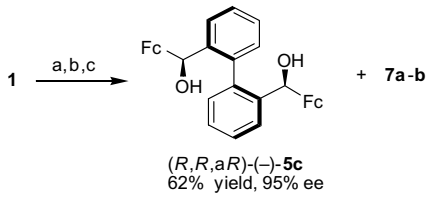
Scheme 4. Deoxygenation products obtained in the CBS-catalyzed reduction of **1**.

for both compounds. This assignment, confirmed by ESI-MS analysis, implies that **7a** and **7b** are diastereomers differing in their relative central and axial chirality. Their (*R*)-configuration on the stereogenic carbons was assigned from the stereochemical course of the reaction (see infra), whereas the axial configuration was assigned here arbitrarily.

During the chromatographic purification of **7a** and **7b**, we noticed their mutual interconversion by rotation around the biphenyl bond; in fact, starting from enriched fractions of **7a** or **7b** the same final equilibrium ratio 68:32 was reached in a hexane solution in 24 h. This finding indicated a lower atropisomeric stability with respect to the parent diols **5a**–**c**,[22] probably because an intramolecular hydrogen bond, which has been invoked as the origin of atropisomerism in some sterically congested 2,2′-substituted biphenyl carbinols,[5d] is not possible in **7a**,**b**. When the CBS-catalyzed reduction of **1** was prolonged for 8 h, both diols **5a**–**c** and monoalcohols **7a**,**b** further reacted giving **8** as the final product. Compound **8**, possessing no more stereogenic carbons, showed two peaks separated by a plateau-like region in the chiral HPLC analysis as was expected for two fast interconverting atropisomers.[23]

Although reductive deoxygenation of α-ferrocenyl carbonyls and alcohols to alkylferrocenes promoted by borane-dimethyl sulfide in CH_2Cl_2 has been described,[24] this reaction appeared to be minimized in the presence of oxazaborolidine catalyst so that the reduction of ferrocenylketones was reported to afford the expected alcohols in high yield.[15] In the case in hand, since **7a** and **7b** were obtained in optically active form, it seems reasonable that their formation occurred after the stereoselective reduction of the carbonyl group(s) of **1**. Blank runs carried out in THF at 45 °C in the presence of borane-dimethyl sulfide, but not the catalyst, showed that neither **1** nor **5** reacted during 24 h. However, in the reported conditions (CH_2Cl_2, room temperature, 24 h) diketone **1** gave 2-ferrocenylcarbonyl-2′-ferrocenylethyl-1,1′biphenyl as the main product; in the same conditions, diol **5** reacted faster than **1** affording **8**.

In a preparative run, two solutions in THF of borane and **1** were simultaneously added at 0 °C to a solution of (*S*)-CBS-Me over 20 min. The mixture was warmed to 45 °C and left to react for 3 h, monitoring the reaction course by HPLC for the disappearance of the starting diketone. After quenching with MeOH and the usual work-up, the mixture contained about 68% of **5a**–**c**, 27% of **7a**,**b** and 5% of **8**. After removal of the catalyst by filtration over a short column of silica eluting with AcOEt, the mixture was left in hexane at 45 °C overnight to allow the complete atropisomerization of **5b** into **5c**. The final diastereoisomeric ratio **5c**:**5a**, measured as 97:3, confirmed the high diastereoselectivity previously observed in the CBS-catalyzed reduction of other biphenyl diketones. After chromatographic purification, (−)-**5c** was obtained in 62% yield and 95% ee (Scheme 5).



Scheme 5. CBS-catalyzed reduction of **1**. Reagents and conditions: (a) (*S*)-CBS-Me (30% equiv), $BH_3{\cdot}Me_2S$ (1 equiv), THF, 45 °C; (b) quenching and removal of the catalyst; (c) *n*-hexane, 45 °C, 20 h.

In order to minimize the formation of monoalcohols **7a**,**b**, a CBS-catalyzed reduction using 0.5 equiv of borane was also tried, but the starting compound **1** was recovered unchanged after 24 h. Carrying out the reaction in toluene (1.1 equiv $BH_3{\cdot}Me_2S$, 45 °C) did not give substantial differences in the amount of formed **7a**,**b** and **8**, whereas (−)-**5c** was obtained in slightly lower enantiomeric purity (91% ee). As an alternative procedure, the asymmetric transfer hydrogenation of **1** using the Noyori's catalyst[25] was also performed, without any evidence of reaction.

Attempts to obtain suitable crystals of (−)-**5c** for X-ray crystallographic analysis were unsuccessful, but when the diol was left to stand in CH_2Cl_2/*n*-hexane solution at room temperature for several days, slow spontaneous intramolecular dehydratation occurred with crystals of the cyclic ether (+)-**9** separated from the solution.

X-ray crystallographic analysis allowed us to assign the absolute configuration (*R*,*R*,a*R*) to (+)-**9** (Fig. 2); since the formation of (+)-**9** from (−)-**5c** occurs with retention of the configuration on the stereogenic carbons,[14] the same configuration (*R*,*R*,a*R*) was assigned to (−)-**5c**. This configuration is in agreement with the known stereochemical course of the CBS-catalyzed reduction[20] and with the axial chirality, which we previously suggested from Molecular Mechanics calculations.[14]

2.4. Asymmetric reduction of diketone 2

The asymmetric reduction of **2**, which was carried out by applying the same procedure as for **1**, after 1 h at 45 °C afforded the expected diols **6a** and **6b** in a 3.2:1 ratio together with monoalcohol **10** as a side product (22%) deriving from the above mentioned over-reduction process (Scheme 6). Both (+)-**6a** and (−)-**6b** were obtained in high enantiomeric purity (92% and 95% ee, respectively), whereas (+)-**10** was obtained with

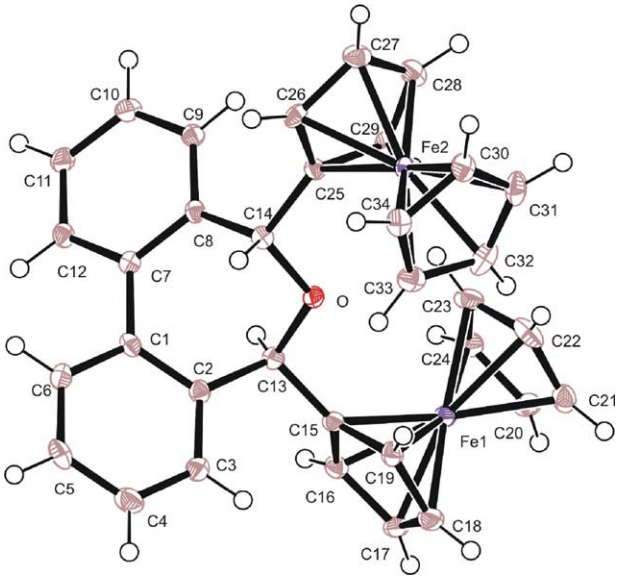


Figure 2. ORTEP plot of (+)-**9** with atom numbering scheme. Displacement ellipsoids at 50% probability level.

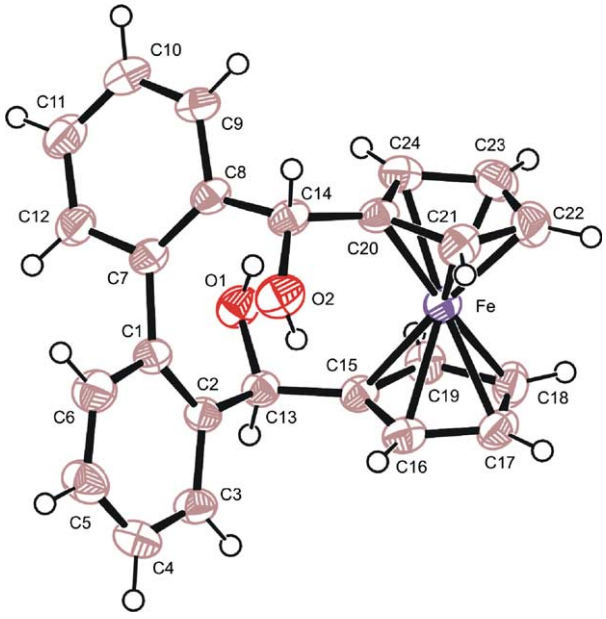


Figure 3. ORTEP plot of (−)-**6b** with atom numbering scheme. Displacement ellipsoids at 50% probability level.

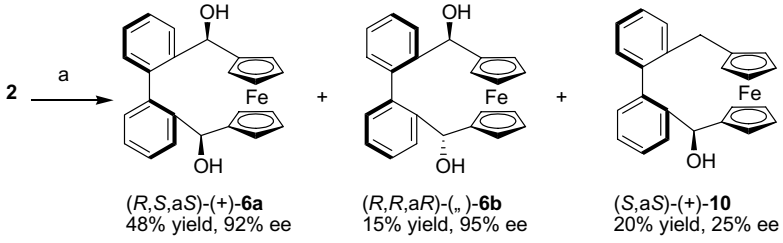
25% ee; prolonging the reaction time, (+)-**10** was isolated as the main product (60%) with 52% ee and the ratio **6a**:**6b** dropped to 1.5:1 so that a preferential conversion of **6a** into **10** could be deduced. Neither the other possible diastereoisomeric monoalcohol nor the product deriving from the deoxygenation of both stereogenic carbons were detected.

The predominance of the (+)-**6a** diol having an opposite configuration on the stereogenic carbons should imply the occurrence to some degree of an unselective hydride transfer from borane (either as free-borane or $-OBH_2$ in the first formed ketoalcohol) to the carbonyl group, such as has been invoked to explain the formation of *meso* diastereoisomer in the CBS-catalyzed reduction of some symmetrical diketones.[26] However, in this case, both (+)-**6a** and (−)-**6b** were obtained in high enantiomeric purity and stereoselectivity. The reaction course seemed to be driven towards the achievement of the atropisomers with the matched configuration, since only some of the possible products were formed. The absolute configuration of (−)-**6b** was established by single crystal X-ray analysis as (a*R*,*R*,*R*) as shown in Figure 3.

Since attempts to obtain suitable crystals of (+)-**6a** were unsuccessful, we compared its CD spectrum with those obtained for (−)-**6b** and (+)-**10**. All CD spectra (Fig. 4) displayed two Cotton effects (CE's) in the region 300–600 nm, centred at about 330 and 450 nm and usually ascribed to ferrocenylic d–d ligand field forbidden transitions.[27] At lower wavelengths, the CE's related to the absorption bands of the biphenylic chromophore were observed. The CD spectra of (−)-**6b** and (+)-**10** are in a mirror like relationship so that an (a*S*,*S*)-configuration could be assigned to the major enantiomer of the monoalcohol **10**.[28] Diol (+)-**6a** showed a CD spectrum similar to that of (+)-**10**, with the exception of the band centred at 218 nm, which appeared as a bisignate exciton couplet with positive CE at 226 nm and negative CE at 210 nm. Although the coupling of the two ^1B_b transitions located on the distinct phenyl rings is in principle possible for all the three compounds in hand, the suitable geometry in terms of the dihedral angle between the aromatic molecular planes is probably present only in (+)-**6a**; the observed couplet is indicative of a positive chirality[29] and the (a*S*,*R*,*S*)-configuration was then assigned to (+)-**6a**.

2.5. Crystal structures of (+)-9 and (−)-6b

The biphenyl skeleton in (+)-**9** (see Fig. 2) assumes a quite reduced distortion, owing to the presence of the ether bridge connecting its *ortho–ortho′* positions, similar to that observed in previously reported structures



Scheme 6. CBS-catalyzed reduction of **2**. Reagents and conditions: (a) (*S*)-CBS-Me (30% equiv), $BH_3{\cdot}Me_2S$ (1 equiv), THF, 45 °C, 1 h.

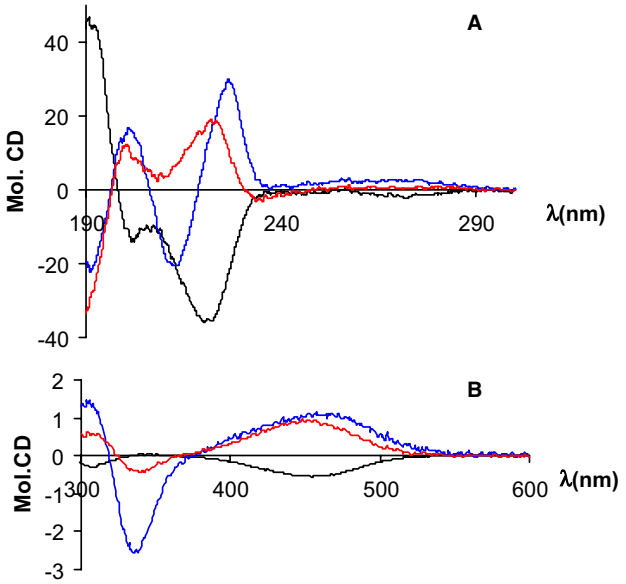


Figure 4. CD spectra in the 190–300 nm (A) and 300–600 nm (B) regions of 92% ee (+)-**6a** (blue), 95% ee (−)-**6b** (black) and 52% ee (+)-**10** (red). For better clarity, the 300–600 nm region of the spectrum of (+)-**10** is amplified fivefold.

of phosphorothioamidate biphenyls.[30] The dihedral angle τ between the least-squares (l.s.) planes through the biphenyl rings measures 41.4(1)°. On the other hand, in (−)-**6b** (see Fig. 3) the biphenyl appears to be strongly distorted, as indicated by both the dihedral τ, 79.3(1)°, and the deviation of the biphenyl rings from coaxiality. In fact, atoms C4 and C10 are pushed outwards by 0.330(4) and 0.289(4) Å, respectively, with respect to the line through C1 and C7. For comparison, atoms C4 and C10 in (+)-**9** are located at only 0.062(5) and 0.089(5) Å, respectively, from the same line.

The distortion of the biphenyl in (−)-**6b** is clearly due to the large dimensions of the ferrocenyl unit bridging its *ortho–ortho′* positions. Steric hindrance associated to the latter group is also responsible for other observed geometrical deviations. Bond angles of the bridge are larger than the standard sp^2 and sp^3 values [C1–C2–C13 and C7–C8–C14 measure 126.0(2)° and 126.1(2)°, respectively; C2–C13–C15 and C8–C14–C20 measure 113.7(2)° and 114.0(2)°, respectively]. Moreover, the ferrocenyl unit of (−)-**6b** is slightly distorted with respect to the usual geometry, which is observed in (+)-**9**. The mean distance between iron and the l.s. planes through the cyclopentane rings (Cp) is 1.6586(3) Å in (−)-**6b**, slightly longer than the corresponding value 1.6378(5) Å observed in (+)-**9**. In both molecules, the l.s. planes through the Cp rings are roughly parallel. However, the corresponding dihedral angle in (−)-**6b**, 4.9(1)°, is significantly larger than both the dihedral angles measured for (+)-**9**, 1.0(1)° and 0.6(1)° for the ferrocenyls with Fe1 and Fe2, respectively. The angle between the geometrical centres (gc1 and gc2) of the Cp rings and the iron atom in (−)-**6b** is 175.8°, while in (+)-**9** the two iron atoms are almost collinear to their respective gc1 and gc2 centres (179.0° for Fe1 and 179.7° for Fe2).

A further difference between the ferrocenyl units in the two compounds concerns the conformation of their Cp rings. An almost staggered conformation is found in the ferrocenyl of (−)-**6b**, the pseudo-torsion angles Cx–gc1–gc2–Cx′ (Cx and Cx′ are in turn, respectively, the carbon atoms of the two Cp rings) measuring 30.2(2)° on average. On the other hand, both ferrocenyls of (+)-**9** adopt a nearly eclipsed conformation, the pseudo-torsion angles being 1.9(3)° and −4.6(3)° on average.

It is interesting to note that a survey of the Cambridge Structural Database (November 2003, version 5.25)[31] reveals that these are the first deposited structures containing both biphenyl and ferrocenyl units. In the only related structure, a binaphthyl-bridged *ortho*,*ortho′*-disubstituted ferrocene,[19] the biaryl unit undergoes a similar distortion as found in (−)-**6b**, the dihedral angle between the halves of the binaphthyl moiety being 74.2(2)°. On the other hand, a larger distortion was observed in the ferrocenyl moiety, whose Cp rings form a dihedral angle equal to 12.3(3)°. This can be clearly assigned to the reduced dimensions of the ferrocene bridge, compared with those of (−)-**6b**.

3. Conclusions

In conclusion, three new chiral ferrocenyl diols possessing a biphenyl unit, which exist as stable atropisomers, were firstly prepared by asymmetric CBS-catalyzed reduction of the corresponding biphenyldiketones. The reduction proceeded with high stereoselectivity, with a concomitant side-reaction leading to deoxygenated compounds. Although the starting diketones were conformationally flexible, high diastereomeric control of the axial chirality was achieved in the corresponding diols. The presence of the additional axial chirality in these ferrocenyl diols could be useful in molecular recognition, while their applications as catalysts or stereoselective hosts are under investigation. Alternative procedures to obtain the diols and the related derivatives, in higher yields, are also currently in progress.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400.13 and 100.62 MHz, respectively. Chemical shifts (δ) are given as parts per million relative to the residual solvent peak and coupling constants (J) are in Hertz. Melting points are uncorrected. Optical rotations were measured on a DIP 135 JASCO instrument. THF was distilled under argon from sodium/benzophenone. $BH_3{\cdot}Me_2S$ (2 M solution in THF) and (*S*)-CBS-Me (1 M solution in toluene) were purchased from Aldrich. Column chromatography was performed on silica gel 60 (70–230 mesh) using the specified eluants. Chiral HPLC analyses were carried out on a Chiracel® OD column (Daicel Chemical Industries) using *n*-hexane–EtOH mixtures as a mobile phase and detection by UV–vis detector at 225 nm. CD spectra were registered at room

temperature (0.1 cell length) on a JASCO spectropolarimeter.

4.2. General procedure for the homocoupling

In a flame dried flask, under an argon atmosphere, $NiCl_2(PPh_3)_2$ (916 mg, 1.4 mmol), freshly activated Zn dust (458 mg, 7 mmol) and Bu_4NI (517 mg, 7 mmol) were suspended with THF (30 mL). The resulting greenish suspension turned up to dark red upon warming at 60 °C. After 15 min of stirring, a THF solution (25 mL) of **3** (516 mg, 1.4 mmol) was added and the suspension left to react for 2 h at 60 °C. The solution was then filtered on Celite and the filtrate taken to dryness. The residue was chromatographed on Si gel column to give **1**[14] in 85% yield.

4.3. 1(1,1′)-Ferrocena-2,5-dione-3,4(1,2)dibenzenacyclohexaphane 2

Compound **4** was reacted according to the above procedure and the reaction mixture purified on Si gel column (R_f 0.41, *n*-hexane–AcOEt 7:3) to afford **2** in 45% yield as a deep red solid, mp 196–197 °C. HPLC: *n*-hexane–EtOH 9:1 flow 1.5 mL/min, t_R/min = 6.7 and 12.7. IR (CCl_4) ν 1654, 1264 cm^{-1}; ^1H NMR: δ 4.49 (br s, 2H), 4.51 (br s, 2H), 4.64 (br s, 2H), 5.18 (br s, 2H), 7.35–7.41 (m, 4H), 7.58 (m, 4H); ^{13}C NMR: δ 72.2, 72.9, 73.9, 75.5, 80.4, 126.5, 127.1, 130.6, 131.4, 139.5, 139.9, 197.5. ESI-MS *m*/*z* 393 [MH^+]. Anal. Calcd for $C_{24}H_{16}FeO_2$: C, 73.49; H, 4.11. Found: C, 73.35; H, 4.18.

4.4. Asymmetric reduction of 1

(*S*)-CBS-Me (0.22 mmol, 0.22 mL of 1 M solution in toluene) was dissolved in THF (10 mL) under argon and cooled to 0 °C. From a syringe charged with $BH_3{\cdot}Me_2S$ (2 M in THF, 0.36 mL, 0.72 mmol) dissolved in 10 mL of THF, 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 **1** (200 mg, 0.36 mmol, in 10 mL of THF) were simultaneously added by syringe pump within 20 min at 0 °C. The reaction mixture was then warmed at 45 °C and the reaction course monitored by HPLC and TLC. As soon as the quantitative conversion of the substrate was observed, the reaction was quenched by careful dropwise addition of MeOH (2 mL), diluted with satd NH_4Cl (50 mL) and extracted with AcOEt (3 × 30 mL). The organic layer was washed with brine, dried over Na_2SO_4 and taken to dryness under vacuum to give a residue that was charged on a short silica gel column, which was eluted with removal of the solvent; the residue was dissolved in hexane and the solution maintained at 45 °C overnight. The solution was then taken to dryness and the residue purified by column chromatography.

Elution with *n*-hexane–AcOEt 14:1 first gave compound **8** (8 mg, 4 % yield) and then compounds **7a**,**b** (48 mg, 24% yield), whereas diol **5c** was obtained by subsequent elution with *n*-hexane–AcOEt 85:15.

4.4.1. (a*R*,*R*,*R*)-2,2′-Bis-(hydroxymethylferrocenyl)-1,1′-biphenyl (−)-5c. (125 mg, 62% yield, 95% ee), R_f 0.24 (*n*-hexane–AcOEt 85:15); HPLC: *n*-hexane–EtOH 98:2, flow 0.5 mL/min, t_R/min = 42.4 and 46.8. $[\alpha]_D = -22.5$ (*c* 1.10, $CHCl_3$); CD (*n*-hexane) λ_{ext} 454 ($\Delta\varepsilon$ +0.2), 236 ($\Delta\varepsilon$ −1.9), 220 ($\Delta\varepsilon$ +20.4). ^1H and ^{13}C NMR as previously reported.[14]

4.4.2. (a*S*,*R*/a*R*,*R*)-2-Ferrocenylhydroxymethyl-2′- ferrocenylmethyl-1,1′-biphenyl 7a/7b. Major diastereoisomer R_f 0.25 (*n*-hexane–AcOEt 14:1); HPLC: *n*-hexane–EtOH 98:2, flow 0.5 mL/min, t_R/min = 22.9 and 23.7. Minor diastereoisomer R_f 0.16 (*n*-hexane–AcOEt 14:1); HPLC: *n*-hexane–EtOH 98:2, flow 0.5 mL/min, t_R/min = 26.5 and 31.4. $[\alpha]_D = -25.7$ (*c* 0.3, *n*-hexane, equilibrium mixture of the two diastereoisomers in 68:32 ratio, 87% ee). IR (CCl_4) ν 3552, 3097, 2924, 1106 cm^{-1}. From the NMR spectra of the diastereoisomeric mixture, the resonances for the major and the minor diastereoisomer could be extracted. Major diastereoisomer, ^1H NMR: δ 2.16 (d, $J = 2.5$, 1H), 3.56 and 3.59 (AX system, d, $J = 15.2$, 1H each), 3.80 (br s, 1H), 3.87 (br s, 1H), 3.92 (m, 2H), 4.00–4.18 (overlapped signals with the singlets for unsubstituted Cp at δ 4.04 and 4.14), 5.02 (d, $J = 2.5$, 1H), 6.95 (d, $J = 7.6$, 1H), 7.06 (m, 1H), 7.15–7.23 (m, 1H), 7.24–7.32 (m, 3H), 7.40 (t, $J = 7.4$, 1H), 7.71 (d, $J = 7.7$, 1H). ^{13}C NMR: δ 33.7, 65.8, 67.0–69.3 (overlapped signals), 87.6, 95.1, 125.4, 126.3, 126.9, 127.6, 127.7, 129.2, 129.7, 130.6, 139.1, 139.4, 139.7, 142.0. Minor diastereoisomer, ^1H NMR: δ 2.43 (d, $J = 2.3$, 1H), 3.03 and 3.15 (AB system, d, $J = 15.9$, 1H each), 3.67 (br s, 1H), 3.90 (br s, 1H), 3.96 (s, 5H), 4.00–4.18 (overlapped signals), 4.20 (s, 5H), 4.32 (br s, 1H), 5.25 (d, $J = 2.3$, 1H), 7.06 (m, 1H), 7.15–7.23 (m, 1H), 7.24–7.32 (m, 4H), 7.40 (t, $J = 7.4$, 1H), 7.77 (d, $J = 7.8$, 1H). ^{13}C NMR: δ 33.5, 65.6, 67.0–69.3 (overlapped signals), 87.1, 94.9, 125.6, 126.1, 126.8, 127.5, 127.7, 128.7, 129.5, 130.1, 139.4, 139.5, 140.3, 141.1.

ESI-MS (+): *m*/*z* 566.2 [M^+]. Anal. Calcd for $C_{34}H_{30}Fe_2O$: C, 72.11; H, 5.34. Found: C, 71.99; H, 5.22.

4.4.3. 2,2′-Ferrocenylethyl-1,1′-biphenyl 8. R_f 0.29 (*n*-hexane–CH_2Cl_2 4:1); yellow solid, mp 144 °C; HPLC: *n*-hexane–EtOH 99:1 flow 0.3 mL/min, t_R/min = 21.3 and 23.2. IR (CCl_4) ν 3097, 2962, 1261 cm^{-1}. ^1H NMR: δ 3.36 (s, 4H), 3.90 (br s, 2H), 3.94 (br s, 2H), 4.02 (br s, 14H), 7.08 (d, $J = 7.2$, 2H), 7.22–7.29 (6H, m). ^{13}C NMR: δ 33.5, 67.3, 67.4, 68.8, 69.2, 87.7, 125.6, 127.4, 129.0, 128.3, 129.9, 139.9, 140.2. Anal. Calcd for $C_{34}H_{30}Fe_2$: C, 74.21; H, 5.49. Found: C, 74.08; H, 5.36.

4.5. (a*R*,*R*,*R*,)-3-Oxa-2,4-diferrocenyl-1,5(1,2)-dibenzenacyclopentaphane (+)-9

$[\alpha]_D = +44.9$ (*c* 0.15, $CHCl_3$); ^1H and ^{13}C NMR as previously reported.[14] CD (*n*-hexane) λ_{ext} 464 ($\Delta\varepsilon$ +0.3), 304 ($\Delta\varepsilon$ −0.4), 241 ($\Delta\varepsilon$ +20.1), 218 ($\Delta\varepsilon$ +63.8).

4.6. Asymmetric reduction of 2

According to the procedure described above, ketone **2** (200 mg, 0.51 mmol) was reduced with $BH_3{\cdot}Me_2S$ (2 M in THF, 0.51 mL, 0.10 mmol) in the presence of (*S*)-CBS-Me (0.31 mmol, 0.31 mL of 1 M solution in toluene). Quantitative conversion of the substrate was observed by TLC analysis after 1 h at 45 °C and the reaction immediately quenched by the addition of MeOH (5 mL). After the usual work-up, the residue was purified on Silica gel column (*n*-hexane–AcOEt 8:2).

4.6.1. (a*S*,*R*,*S*)-1(1,1′)-Ferrocena-2,5-dihydroxy-3,4(1,2) dibenzenacyclopentaphane (+)-6a. R_f 0.19 (*n*-hexane–AcOEt 8:2). Yellow solid (97 mg, 48% yield, 92% ee), mp 180–182 °C; $[\alpha]_D = +88.9$ (*c* 0.68, CH_3CN); HPLC: *n*-hexane–EtOH 9:1, flow 0.5 mL/min, t_R/min = 19.7 (a*S*,*R*,*S*) and 38.6 (a*R*,*R*,*S*); CD (CH_3CN) λ_{ext} 454 ($\Delta\varepsilon$ +1.0), 335 ($\Delta\varepsilon$ −2.5), 275 ($\Delta\varepsilon$ +2.8), 226 ($\Delta\varepsilon$ +29.8), 213 ($\Delta\varepsilon$ −20.4), 201 ($\Delta\varepsilon$ +16.7). IR (CCl_4) *v* 3611, 3565, 1186 cm^{-1}; ^1H NMR: δ 1.43 (d, $J = 11.7$, 1H, –OH), 1.94 (d, $J = 3.1$, 1H, –OH), 3.55 (br s, 1H), 3.87 (br s, 1H), 4.05 (br s, 1H), 4.07 (br s, 1H), 4.17 (br s, 1H), 4.20 (br s, 1H), 4.24 (br s, 1H), 4.32 (br s, 1H), 5.49 (m, 2H), 7.10 (m, 1H), 7.23 (m, 1H), 7.34–7.37 (m, 4H), 7.47 (m, 1H), 7.62 (d, $J = 7.7$); ^{13}C NMR: δ 65.3, 67.0, 68.0, 68.6, 69.0, 69.1, 69.2, 69.4, 70.7, 73.1, 91.0, 95.9, 126.6, 126.7, 126.9, 127.4, 127.6, 128.7, 130.6, 131.4, 138.0, 139.0, 139.3, 140.5. ESI-MS *m*/*z* 396 [M^+], 418 [(M−H)·Na^+]. Anal. Calcd for $C_{24}H_{20}FeO_2$: C, 72.74; H, 5.09. Found: C, 72.65; H, 4.99.

4.6.2. (a*R*,*R*,*R*)-1(1,1′)-Ferrocena-2,5-dihydroxy-3,4(1,2)-dibenzenacyclopentaphane (−)-6b. R_f 0.37 (*n*-hexane–AcOEt 8:2). Yellow solid (30 mg, 15% yield, 95% ee) mp 205–207 °C; $[\alpha]_D = -56.8$ (*c* 0.44, EtOH); HPLC: *n*-hexane–EtOH 9:1, flow 0.5 mL/min, t_R/min = 16.3 (a*R*,*R*,*R*) and 17.8 (a*S*,*S*,*S*). CD (CH_3CN) λ_{ext} 455 ($\Delta\varepsilon$ −0.5), 272 ($\Delta\varepsilon$ −2.1), 220 ($\Delta\varepsilon$ −35.6), 202 ($\Delta\varepsilon$ −14.0); IR (CCl_4) *v* 3562, 1185 cm^{-1}; ^1H NMR: δ 1.56 (d, $J = 11.6$, 2H, –OH), 3.69 (br s, 2H), 4.11 (br s, 2H), 4.13 (br s, 2H), 4.32 (br s, 2H), 5.47 (d, $J = 11.6$, 1H), 7.06 (br t, 2H), 7.32–7.34 (m, 6H); ^{13}C NMR: δ 66.2, 68.1, 68.4, 70.2, 72.9, 97.0, 126.1, 126.6, 128.8, 133.5, 138.1, 139.3. ESI-MS *m*/*z* 396 [M^+], 418 [(M−H)·Na^+]. Anal. Calcd for $C_{24}H_{20}FeO_2$: C, 72.74; H, 5.09. Found: C, 72.61; H, 4.97.

4.6.3. (a*S*,*S*)-1(1,1′)-Ferrocena-2,5-dihydroxy-3,4(1,2)-dibenzenacyclopentaphane (+)-10. R_f 0.56 (*n*-hexane–AcOEt 80:20). Yellow solid (38 mg, 20% yield, 52% ee), mp 185–186 °C; $[\alpha]_D = +57.3$ (*c* 0.19, CH_3CN); HPLC: *n*-hexane–EtOH 98:2, flow 0.5 mL/min, t_R/min = 16.6 (a*S*,*S*) and 17.8 (a*R*,*R*). CD (CH_3CN) λ_{ext} 453 ($\Delta\varepsilon$ +0.2), 338 ($\Delta\varepsilon$ −0.08), 234 ($\Delta\varepsilon$ −3.0), 222 ($\Delta\varepsilon$ +19.0), 200 ($\Delta\varepsilon$ +11.9). IR (CCl_4) *v* 3563, 1480, 1437, 1185 cm^{-1}; ^1H NMR: δ 1.65 (d, $J = 11.8$, 1H, –OH), 3.46 (s, 2H), 3.52 (br s, 1H), 3.81 (br s, 1H), 3.93 (br s, 1H), 3.97 (br s, 1H), 3.98 (br s, 1H), 4.13 (br s, 1H), 4.15 (br s, 1H), 4.20 (br s, 1H), 5.53 (d, $J = 11.8$, 1H), 7.11 (m, 2H), 7.31–7.38 (m, 6H); ^{13}C NMR: δ 32.0, 64.8, 66.7, 67.8, 68.0, 68.9, 69.1, 69.5, 73.3, 89.6, 95.4, 125.6, 126.3, 126.4, 127.2, 128.9, 130.9, 131.3, 131.9, 135.9, 138.9, 139.2, 142.1. ESI-MS *m*/*z* 363 [M−OH^+], 380 [M^+], 403 [M·Na^+] Anal. Calcd for $C_{24}H_{20}FeO$: C, 75.81; H, 4.21. Found: C, 75.68; H, 4.19.

4.7. X-ray structural determination

The intensity data for (+)-**9** and (−)-**6b** were collected on a Bruker Smart Apex CCD area detector using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Data reduction was made using SAINT programs; absorption corrections based on multiscan were obtained by SADABS.[32] The structures were solved by SIR-92[33] and refined on F^2 by full-matrix least-squares using SHELXL-97.[34] All the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included as 'riding' and not refined. The ORTEP-III program was used for molecular diagrams.[35]

Crystal data and results of the refinement for (+)-**9**: yellow rhombic prism $0.22 \times 0.16 \times 0.08$ mm, $M_r = 564.26$, monoclinic, space group $P2_1$, $a = 11.654(2)$ Å, $b = 9.1218(18)$ Å, $c = 12.899(3)$ Å, $\beta = 110.10(3)°$, $V = 1287.7(4)$ Å^3, $Z = 2$, $T = 90(2)$ K, $\mu = 1.153$ mm^{-1}. 12,528 measured reflections, 5228 independent reflections, 5026 reflections with $I > 2\sigma(I)$, $3.36 < 2\theta < 60.00°$, $R_{int} = 0.0186$. Refinement on 5228 reflections, 334 parameters, 1 restraint (floating origin). Flack parameter[36] for determination of the absolute configuration = 0.010(15). Final $R = 0.0298$, $wR = 0.0814$ for data with $F^2 > 2\sigma(F^2)$, $(\Delta/\sigma)_{max} < 0.001$, $\Delta\rho_{max} = 0.57$, $\Delta\rho_{min} = -0.51$ e Å^{-3}.

Crystal data and results of the refinement for (−)-**6b**: orange prism $0.22 \times 0.17 \times 0.12$ mm, $M_r = 396.25$, monoclinic, space group $P2_1$, $a = 10.538(2)$ Å, $b = 7.8106(16)$ Å, $c = 10.780(2)$ Å, $\beta = 101.56(3)°$, $V = 869.3(3)$ Å^3, $Z = 2$, $T = 293(2)$ K, $\mu = 0.884$ mm^{-1}. 18,799 measured reflections, 6270 independent reflections, 5784 reflections with $I > 2\sigma(I)$, $3.86 < 2\theta < 65.00°$, $R_{int} = 0.0274$. Refinement on 6270 reflections, 244 parameters, 1 restraint (floating origin). Flack parameter[36] = 0.033(12). Final $R = 0.0457$, $wR = 0.1028$ for data with $F^2 > 2\sigma(F^2)$, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.59$, $\Delta\rho_{min} = -0.33$ e Å^{-3}.

Tables of atomic coordinates, anisotropic thermal parameters, bond lengths and angles of (+)-**9** and (−)-**6b** may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK, on quoting the deposition numbers CCDC 276985 and 276986, respectively, 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).

References

1. Selected examples in: (a) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475–503; (b) Charlton, J. L. *J. Nat. Prod.* **1998**, *61*, 1447–1551; (c) Jossang, A.; Fodor, P.; Bodo, B. *J. Org. Chem.* **1998**, *63*, 7162–7167; (d) Seo,

E.-K.; Huang, L.; Wall, M. E.; Wani, M.; Navarro, H.; Mukherjiee, R.; Farnsworth, N. R.; Kinghorn, A. D. *J. Nat. Prod.* **1999**, *62*, 1484–1487; (e) Day, S. H.; Wang, J.-P.Won, S.-J.; Lin, C.-N. *J. Nat. Prod.* **2001**, *64*, 608–611.

2. (a) Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 1335–1336; (b) Bovy, P. R.; Collins, J. T.; Olins, G. M.; McMahon, E. G.; Hutton, W. C. *J. Med. Chem.* **1991**, *34*, 2410–2414; (c) Deck, L. M.; Vander Jagt, D. L.; Royer, R. E. *J. Med. Chem.* **1991**, *34*, 3301–3305; (d) Fukuyama, Y.; Akasawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737–2741; (e) Berry, D. E.; MacKenzie, L.; Shultis, E. A.; Chan, J. A. *J. Org. Chem.* **1992**, *57*, 420–422; (f) Nicolau, K. C.; Boddy, C. N.; Bräse, S.; Wissinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152; (g) Puckhaber, L. S.; Dowd, M. K.; Stipanovic, R. D.; Howell, C. R. *J. Agric. Food Chem.* **2002**, *50*, 7017–7021, and references cited therein.
3. (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350; (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494; (c) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809–3844; (d) Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450–3458; (e) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211; (f) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667.
4. (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153–8156; (b) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375–1384; (c) Kamikawa, T.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455–3466; (d) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052; (e) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615–624; (f) Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 331–343; (g) Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517–9520; (h) Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron* **2004**, *60*, 4459–4473.
5. (a) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682–685; (b) Weber, E.; Skobridis, K.; Wierig, A.; Stathi, S.; Nassimbeni, L. R.; Niven, M. L. *Angew. Chem., Int. Ed.* **1993**, *32*, 606–608; (c) Goldfuss, B.; Rominger, F. *Tetrahedron* **2000**, *56*, 881–884; (d) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **2005**, *46*, 319–322.
6. (a) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuij, Y.; Ikeda, I. *J. Org. Chem.* **2000**, *65*, 3326–3333; (b) Mikami, K.; Aikawa, K.; Korenaga, T. *Org. Lett.* **2001**, *3*, 243–245; (c) Delogu, G.; Vallée, Y. *Recent Res. Devel. Org. Chem.* **2002**, *6*, 1–39; (d) Mikami, K.; Aikawa, K.; Yusa, Y. *Org. Lett.* **2002**, *4*, 95–97.
7. (a) Casarini, D.; Foresti, E.; Lunazzi, L.; Macciantelli, D. *J. Am. Chem. Soc.* **1988**, *110*, 4527–4532; (b) Davalli, S.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1739–1747; (c) Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1997**, *62*, 3315–3323; (d) Wolf, C.; Pranatharthiharan, L.; Ramagosa, R. B. *Tetrahedron Lett.* **2002**, *43*, 8563–8567.
8. (a) Casarini, D.; Mazzanti, A.; Alvarez, A. M. *J. Org. Chem.* **2000**, *65*, 3200–3206; (b) Garcia, M. B.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Orelli, L. R. *J. Org. Chem.* **2001**, *66*, 6679–6684; (c) Spivey, A. C.; Charbonneau, P.; Fekner, T.; Hochmuth, D. H.; Maddaford, A.; Malardier-Jugroot, C.; Redgrave, A. J.; Whitehead, M. A. *J. Org. Chem.* **2001**, *66*, 7394–7401; (d) Sakamoto, M.; Utsumi, N.; Ando, M.; Saeki, M.; Mino, T.; Fujita, T.; Katoh, A.; Nishio, T.; Kashima, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4360–4363; (e) Yoshikawa, S.; Odaira, J.; Kitamura, Y.; Bedekar, A. V.; Furuta, T.; Tanaka, K. *Tetrahedron* **2004**, *60*, 2225–2234; (f) Grilli, S.; Lunazzi, L.; Mazzanti, A.; Pinamonti, M. *Tetrahedron* **2004**, *60*, 4451–4458.
9. (a) Mislow, K.; Hyden, S.; Schaefer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1449–1455; (b) Isaksson, R.; Rashidi-Ranjbar, P.; Sandstrom, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, *5*, 1147–1152; (c) Mazaleyrat, J.-P.; Gaucher, A.; Savrda, J.; Wakselman, M. *Tetrahedron: Asymmetry* **1997**, *8*, 619–631; (d) Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656–5657; (e) Herrbach, A.; Marinetti, A.; Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2003**, *68*, 4897–4905; (f) Lenev, D. A.; Lyssenko, K. A.; Golovanov, D. G.; Weingart, O.; Buß, V.; Kostyanovsky, R. G. *Tetrahedron: Asymmetry* **2004**, *15*, 537–543.
10. (a) Clayden, J.; Lund, A.; Youssef, L. H. *Org. Lett.* **2001**, *3*, 4133–4136; (b) Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem. Eur. J.* **2002**, *8*, 1279–1289.
11. For recent reviews see: (a) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407; (b) Lotz, M.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4708–4711; (c) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101–3118; (d) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659–667; (e) Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313–328.
12. (a) Widhalm, M.; Nettekoven, U.; Mereiter, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4369–4391; (b) Kasak, P.; Miklas, R.; Putala, M. *J. Organomet. Chem.* **2001**, *637–639*, 318–326; (c) Hua, D. H.; McGill, J. W.; Ueda, M.; Stephany, H. A. *J. Organomet. Chem.* **2001**, *637–639*, 832–836; (d) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471–7472.
13. (a) Bringmann, G.; Hinrichs, J.; Peters, K.; Peters, E.-M. *J. Org. Chem.* **2001**, *66*, 629–632; (b) Lotz, M.; Kramer, G.; Knochel, P. *Chem. Commun.* **2002**, 2546–2547; (c) Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982–7994; (d) Jensenm, J. F.; Søtofte, I.; Sørensen, H. O.; Johannsen, M. *J. Org. Chem.* **2003**, *68*, 1258–1265.
14. Patti, A.; Pedotti, S. *Tetrahedron: Asymmetry* **2005**, *16*, 965–970.
15. (a) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950–968; (b) Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem. Eur. J.* **2002**, *8*, 843–852.
16. Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80–87.
17. (a) Gasparrini, F.; Lunazzi, L.; Misiti, D.; Villani, C. *Acc. Chem. Res.* **1995**, *28*, 163–170; (b) Ceccacci, F.; Mancini, G.; Mencarelli, P.; Villani, C. *Tetrahedron: Asymmetry* **2003**, *14*, 3117–3122.
18. (a) Hammond, P. J.; Bell, A. P.; Hall, C. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 707–715; (b) Hall, C. D.; Truong, T.-K.-U.; Nyburg, S. C. *J. Organomet. Chem.* **1997**, *547*, 281–286.
19. Foxman, B. M.; Rosenblum, M.; Sokolov, V.; Krushchova, N. *Organometallics* **1993**, *12*, 4805–4809.
20. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. J.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926; (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
21. (a) Delogu, G.; Fabbri, D.; de Candia, C.; Patti, A.; Pedotti, S. *Tetrahedron: Asymmetry* **2002**, *13*, 891–898; (b) Delogu, G.; Dettori, M. A.; Patti, A.; Pedotti, S.; Forni, A.; Casalone, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2467–2474.
22. Kinetic constants $k = 6 \times 10^{-3}$ for the conversion of the minor diastereoisomer into the major one and $k = 3 \times 10^{-3}$ for the reverse process were determined in *n*-hexane at 25 °C.

23. On the basis of the data here and previously[14] discussed, a rough order for the atropisomeric stability could be deduced as **1** < **8** < **7b** ≅ **7a** < **5a** < **5b** ≪ **5c**. The increase in the conformational fixation, which seems to be related with the presence of an hybridized sp^3 α-carbon bearing an hydroxyl group, becomes more pronounced when an intramolecular hydrogen bond is possible.
24. Kim, D.-H.; Ryu, E.-S.; Cho, C. S.; Shim, S. C.; Kim, H.-S.; Kim, T.-J. *Organometallics* **2000**, *19*, 5784–5786.
25. (a) Hashiguchi, S.; Kujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563; (b) Haack, K.-J.; Hashiguchi, S.; Kujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285–288; (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
26. (a) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888–3889; (b) Bach, J.; Berenguer, R.; Garcia, J.; Lopez, M.; Manzanal, J.; Vilarrasa, J. *Tetrahedron* **1998**, *54*, 14947–14962; (c) Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3883–3886.
27. Janowska, I.; Zakrezewski, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3271–3273.
28. This assignment was also supported by the chemical correlation between (−)-**6b** and (−)-**10**, since the reaction of (−)-**6b** with $BH_3{\cdot}Me_2$ and (*S*)-CBS-Me as in the asymmetric reduction of **2** afforded (−)-**10** with the same enantiomeric purity of the starting diol.
29. (a) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983; (b) Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671–1682; (c) Di Bari, L.; Pescitelli, G.; Salvadori, P. *J. Am. Chem. Soc.* **1999**, *121*, 7998–8004.
30. Delogu, G.; Fabbri, D.; Dettori, M. A.; Forni, A.; Casalone, G. *Tetrahedron: Asymmetry* **2004**, *15*, 275–282.
31. Allen, F. H. *Acta Cryst. Sect. B* **2002**, *58*, 380–388.
32. Bruker *SMART, SAINT and SADABS*; Bruker AXS: Madison, WI, 1997.
33. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
34. Sheldrick, G. M. *SHELX-97. Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
35. Burnett, M. N., Johnson, C. K. *ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations*, Oak Ridge National Laboratory Report ORNL-6895, 1996.
36. Flack, H. D. *Acta Crystallogr. Sect. A* **1983**, *39*, 876–881.