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Chemoenzymatic access to all four enantiopure stereoisomers of 1-ferrocenyl-1,3-butanediol

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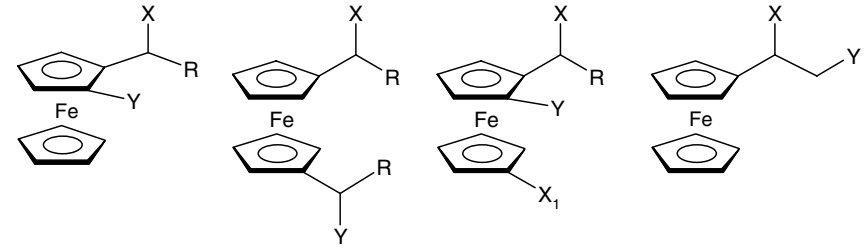
Abstract—The kinetic resolution of ferrocenyl aldol **2** was achieved by a lipase-catalyzed esterification in organic solvent. Lipase from *Candida antarctica* was also found effective in promoting the enantioselective alcoholysis of acetate (±)-**3** with *n*-BuOH. Both enantiomers of **2** were obtained in enantiopure form and subjected to chemical reduction to afford the corresponding *syn*- and *anti*-diols. These diols serve as starting materials for the preparation of new ferrocenyl amino alcohols bearing two stereocenters in the side chain.

1. Introduction

Most enantioselective catalysts are transition metal ion complexes with a difunctionalized chiral ligand.[1] Chiral ferrocenes are widely employed as ligands,[2] due to their peculiar chemistry, which allows the relatively easy introduction of different functional groups, and the stereochemistry[3] that is related with the specific pattern of substitution.

Derivatives of type **I** possessing either planar or both central and planar chiralities are accessible by the diastereoselective metalation/electrophilic quenching sequence of suitable chiral ferrocenes.[4] C_2-Symmetric ligands of type **II** are usually prepared by asymmetric reduction of the corresponding diketones and subsequent nucleophilic substitution of the diacetoxy derivatives.[5] Unsymmetrical 1,1′-disubstituted ferrocenes as well as derivatives **III** have been also prepared.[2d,6] In all these cases, the synthetic approach is highly modular and it is possible to easily vary the nature of the substituent(s) tuning their steric and electronic properties to optimize the catalyst performances. JOSIPHOS-,[7] FERRIPHOS-,[8] Taniaphos-,[9] and MOPF-families[10] of ligands, developed using this approach, are efficient catalysts for several asymmetric reactions. Derivatives **IV**, bearing



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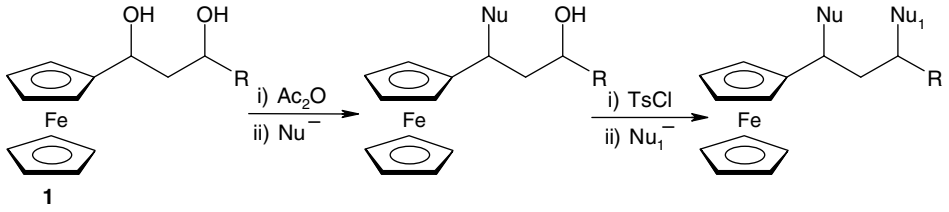
one or more stereogenic carbons on the side chain, have been prepared with different methodologies, including asymmetric dihydroxylation, nucleophilic opening of intermediate epoxides, and addition of ferrocencarboxaldehyde to chiral aminoalcohols, all leading to α,β-disubstituted ferrocenes.[11]

Although the 1,3-disposition of two coordinating groups, as in derivatives **I**, appears to be suitable for complexation with a metal via formation of a six-membered cyclic chelate, chiral ferrocenes with this type of structural motif on the side chain have not yet been reported.[12] We envisaged that diols of general structure **1** could be useful starting materials for the preparation of a new class of ferrocenyl ligands exploiting the selective substitution of an acetoxygroup at the α-position with respect the cyclopentadienyl ring[13] and the conventional displacement of a hydroxyl group by a nucleophile.



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As a first example of this approach, we herein report the preparation of all, enantiopure, stereoisomers of 1-ferrocenyl-1,3-dihydroxybutane, and their conversion into new ferrocenyl-1,3-amino alcohols.

2. Results and discussion

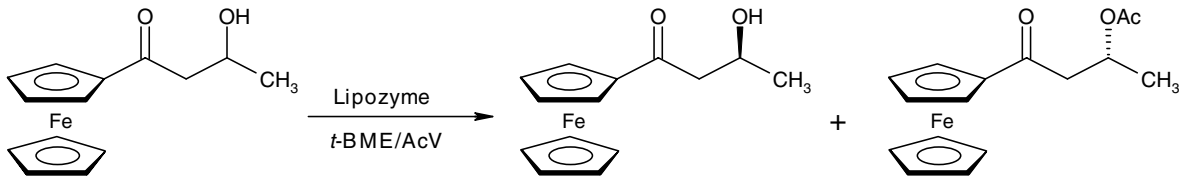
Since acyclic 1,3-diols, in a *syn* or *anti* relationship, are recurring units in a large variety of biologically active natural compounds,[14] several methods have been developed for their diastereoselective synthesis starting from different substrates such as 1,3-diketones,[15] β-hydroxyketones,[16] 1,3-dienes, or enones.[17] To gain access to enantiopure 1,3-chiral diols, significant efforts have been focused on the asymmetric hydrogenation or reduction of diketones and β-hydroxyketones[18] as well as asymmetric aldol reactions.[19]

Optically active aldols are important precursors of 1,3-diols or related derivatives, since the chirality at the hydroxyl center of a β-hydroxyketone can be used to control the stereochemistry at the other site,[16] hence we recognized aldol **2** as a valuable starting material for the preparation of new ferrocenyl derivatives bearing two stereogenic centers on the side chain in a 1,3-disposition.

Among the chemical and biochemical[19a,20] methods available for the preparation of enantiopure aldols, we resorted to the kinetic resolution of aldol (±)-**2** by lipase catalyzed esterification in organic solvent, which we found to be effective in the resolution of other ferrocenyl alcohols.[21]

Ferrocenyl aldol (±)-**2** was obtained in high yield by condensation of acetylferrocene with acetaldehyde and subjected to lipase-catalyzed esterification with vinyl acetate (AcV) in *tert*-butyl methyl ether (*t*-BME) at 45 °C. Lipases from *Pseudomonas cepacia* (PSL-D), *Candida antarctica* (Novozym 435), and *Mucor miehei* (Lypozyme) all displayed high enantioselectivity (E >200)[22] and the same stereopreference, whereas the lipase from *Candida rugosa* gave acetate **3** in nearly racemic form. In a preparative run, carried out in the presence of Lypozyme, after 24 h the reaction mixture contained the unreacted alcohol (*S*)-**2** and the acetate (*R*)-**3** in a 1:1 ratio. After purification by column chromatography, (*S*)-**2** and (*R*)-**3** were obtained in theoretical yield with >99% enantiomeric purity, as assessed by chiral HPLC analyses (Scheme 1).

The (*S*)-absolute configuration of the unreacted alcohol, which is in agreement with the known stereopreference of the lipase employed,[23] was assigned by comparison of the NMR spectra of its (*R*)- and (*S*)-MTPA esters (Mosher's method), since a $\Delta\delta^{SR} = -0.080$ was evidenced for the methyl group and $\Delta\delta^{SR} = +0.038$ and $\Delta\delta^{SR} = +0.007$ for the methylenic protons, which are observed as an AB system.[24]



(±)-**2**

(−)-(*S*)-**2**
>99% *ee*

(+)-(*R*)-**3**
>99% *ee*

Scheme 1. Kinetic resolution of (±)-**2** by lipase-catalyzed esterification.

Reduction of (*S*)-**2** with $NaBH_4$ gave two diastereoisomeric diols (+)-**4** and (−)-**5** in about a 60:40 ratio, easily separable by chromatography, the major one being the *syn*-isomer (see later); since acetate **3** suffered extensive degradation (mainly to the corresponding enone) during the hydrolytic treatment, diols (−)-**4** and (+)-**5** were obtained in a 60:40 ratio via direct reduction of (*R*)-**3** with $LiAlH_4$ (Scheme 2).

Aldol (*R*)-**2**, in principle, could be obtained from (*R*)-**3** by subjecting it to alcoholysis with *n*-BuOH in the presence of a lipase with an (*R*)-stereopreference; however, among the four lipases tested, only Novozym 435 was found able to promote the reaction giving (*R*)-**2**. In the presence of the other lipases, the reaction did not occur at all and the substrate was recovered unaltered.

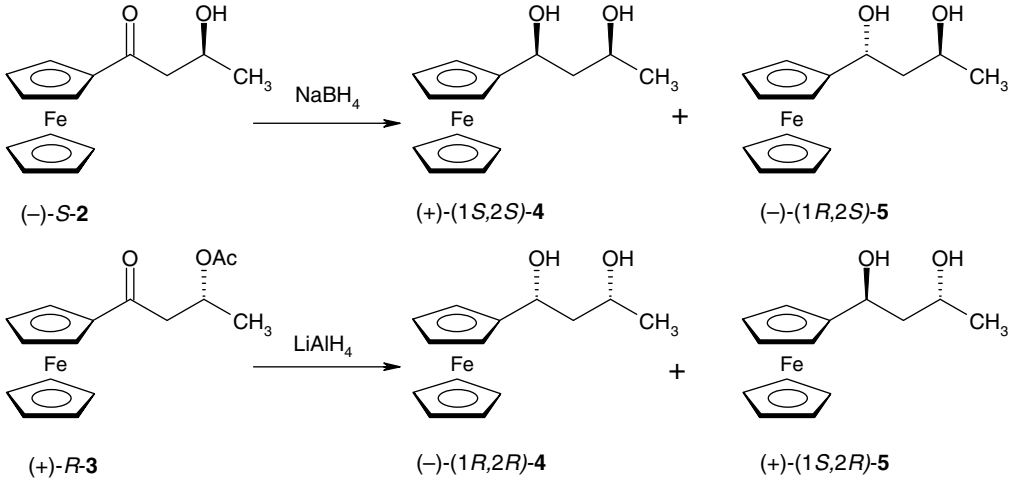
The recognition ability of Novozym in the alcoholysis reaction was also exploited for the kinetic resolution of (±)-**3**, which proceeded with high enantioselectivity affording nearly enantiopure (*R*)-**2** and (*S*)-**3** (Scheme 3).

Diol (+)-**4** was converted into the corresponding diacetate (+)-**6**, which was then treated with NaN_3 in acetonitrile/water medium to afford (+)-**7** as a single product, since the nucleophilic attack occurred regioselectively at the α-position with respect to the cyclopentadienylic ring. Subsequent reduction of the azido group afforded the *syn*-amino alcohol (+)-**8**, whose stereochemistry (see infra) confirmed that the nucleophilic displacement of the α-ferrocenyl acetoxygroup proceeded with complete retention of configuration. In the same way, acetylation of (−)-**5** gave diacetate (−)-**9**, which in turn afforded the *anti*-aminoalcohol (−)-**11** (Scheme 4).

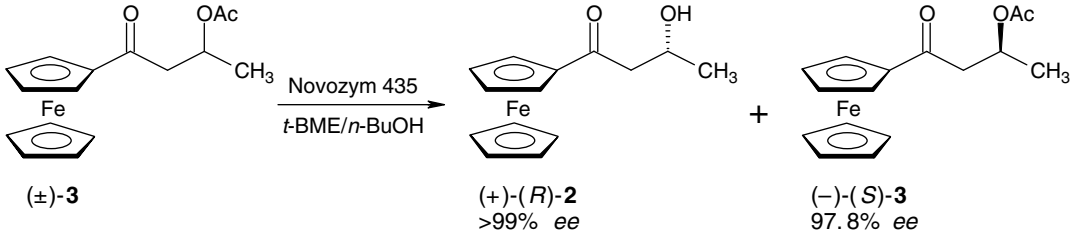
2.1. Stereochemical assignments

The relative configuration of diols deriving from **2** could be assigned on the basis of their ^{13}C NMR chemical shifts since, according Hoffmann's criteria,[25] $[(\delta_C C\text{-}1) + (\delta_C C\text{-}3)]syn > [(\delta_C C\text{-}1) + (\delta_C C\text{-}3)]anti$ was observed. The assignment was further confirmed by applying the recently developed 'isotopic perturbation method', which relies on the variation of the OH chemical shifts in the OH/OH and OH/OD isotopomers;[26] in our hands $\Delta\delta = -23.4$ and -11.6 ppb were measured for the hydroxyl groups of diol **4**, whereas the OH-resonances of diol **5** were almost unaffected.

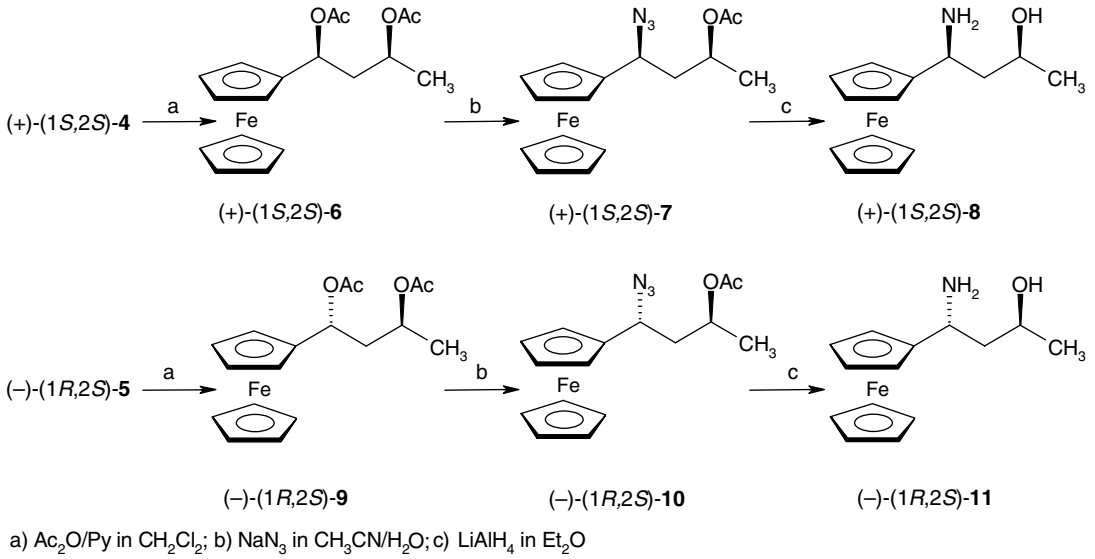
A detailed analysis of the coupling constants (*J*, expressed in Hertz) also allowed us to differentiate the two isomeric diols **4** and **5**; considering that the hydrogen-bonded conformation of a *syn*-diol should approximate a chair cyclohexane with two equatorial substituents (Fig. 1A) one of the methylenic protons (H-2a) is in a diaxial relationship with both H-1 and H-3 while the other one (H-2b) is in a equatorial–axial disposition. Indeed, when the ^1H NMR spectrum of **4** was registered in a dilute solution of CD_2Cl_2,[26] the H-2a protons appeared as a double double doublet with $J_{gem} = 14.2$ and comparable $J_{H2a\text{–}H1} = 9.6$ and $J_{H2a\text{–}H3} =$



Scheme 2. Preparation of all stereoisomers of 1-ferrocenyl-1,3-dihydroxybutane in enantiopure form.



Scheme 3. Kinetic resolution of (±)-**3** by lipase-catalyzed alcoholysis.



Scheme 4. Synthesis of ferrocenyl-1,3-amino alcohols.

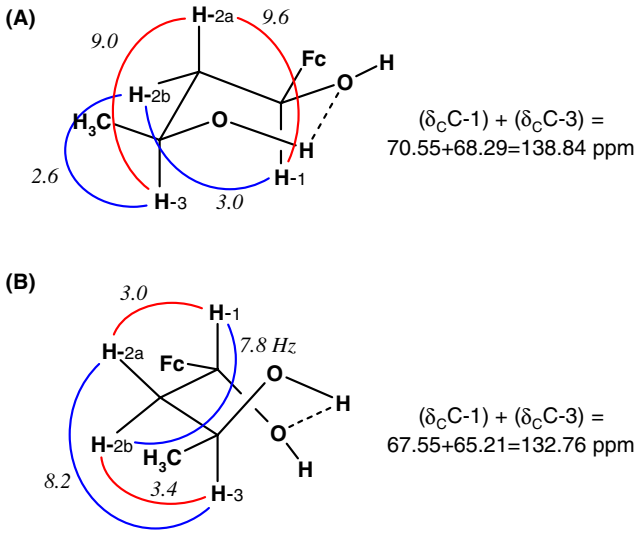


Figure 1. Proposed conformations and observed *J* values (in Hertz) for diols **4** (A) and **5** (B) in CD_2Cl_2.

9.0; conversely, in the H-2b double double doublet $J = 3.0$ and $J = 2.6$ with H-1 and H-3, respectively, were measured.

In the ^1H NMR spectrum of **5**, the methylenic proton H-2a showed $J_{H2a–H1} = 3.0$ and $J_{H2a–H3} = 8.2$ whereas H-2b had $J_{H2b–H1} = 7.8$ and $J_{H2b–H3} = 3.4$; these *J* values are in agreement with a twist-boat conformation (Fig. 1B), which would avoid the 1,3-diaxial interaction (CH_3–H-1) present in a chair-like conformation. The preference for a twist-boat conformation has been also postulated for the acetonides of *anti*-diols[27] and allowed differentiation from the *syn*-diol isomers.

On the basis of the same arguments, the relative configuration could be assigned to amino alcohol (+)-**8** and (−)-**11**, which showed the same coupling constant pattern of the parent diols (Fig. 2).

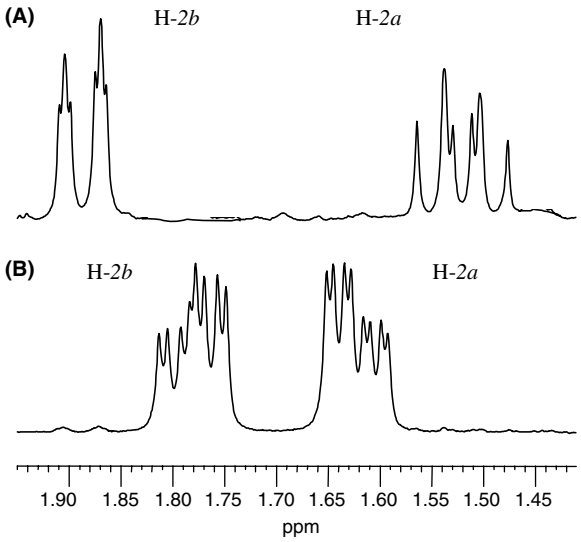


Figure 2. Methylenic region in the proton NMR spectra ($CDCl_3$) of aminoalcohols *syn* (+)-**8** (A) and *anti* (−)-**11** (B).

3. Conclusions

By using lipase-catalyzed transesterification reactions, we have gained access to both enantiomers of ferrocenyl aldol **2**, which were in turn reduced to afford all the four isomers of 1-ferrocenyl-1,3-dihydroxybutane. The chemical yield of each isomeric diol could be easily increased by reducing the carbonyl group of enantiopure **2** with one of the reported diastereoselective procedures.[16] Due to the occurrence of nucleophilic displacement at the α-position, with respect the ferrocene moiety, with complete regioselectivity and retention of the configuration,

enantiopure diols **4** and **5** could serve as useful starting materials for the preparation of related amino alcohols. As an example, the preparation and characterization of ferrocenyl aminoalcohols (+)-**8** and (−)-**9** are described herein.

The extension of this methodology to other ferrocenyl derivatives bearing two substituents in the 1,3-position of the side chain as well as the evaluation of the catalytic properties of this class of ferrocene-based ligands is currently under investigation.

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. In the ^{1}H NMR assignment Cp and Cp′ refers to protons on the substituted and unsubstituted cyclopentadienyl ring, respectively. Melting points are uncorrected. Optical rotations were measured on a DIP 135 JASCO instrument. Novozym 435 (immobilized lipase from *C. antarctica*) and PS-D I (immobilized lipase from *P. cepacia*) were purchased from Aldrich. Lypozyme™ (immobilized lipase from *M. miehei*) was from Fluka. Column chromatography was performed on silica gel 60 (230–400 mesh) using the specified eluants. Chiral HPLC analyses were carried out on Chiracel® OD column (Daicel Chemical Industries) using *n*-hexane/2-PrOH mixtures as a mobile phase and detection by UV–vis detector at 225 nm.

4.2. Synthesis of (±)-1-ferrocenyl-3-hydroxybutan-1-one, (±)-2

A solution of *n*-butyl lithium (6.4 mL of a 1.6 M solution in hexanes, 10.24 mmol) was added at −15 °C to a solution of di-isopropylamine (1.6 mL, 11.42 mmol) in sodium-dried THF (10 mL). After stirring for 30 min, a solution of acetylferrocene (1 g, 4.38 mmol) in 15 mL of THF was added portionwise over 30 min. The mixture was stirred for 1 h at −15 °C, after which was added the acetaldehyde (0.740 mL, 13.19 mmol) dropwise over 30 min. After 10 min, the reaction mixture was diluted with NH_4Cl and extracted with AcOEt (50 mL × 3). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a residue that was purified on silica gel column eluting with *n*-hexane/AcOEt 70:30 to give (±)-**2** as a dark orange solid (850 mg, 3.12 mmol, 72% yield), mp 98–99 °C, $R_f = 0.25$ (*n*-hexane/AcOEt 70:30). ^{1}H NMR: δ 1.29 (d, $J = 6.3$, 3H, –CH_3), 2.79 (dd, $J = 8.9$ and 17.2, 1H, H-2a), 2.89 (dd, $J = 2.6$ and 17.2, 1H, H-2b), 3.60 (br s, 1H, –OH), 4.23 (s, 5H, Cp′), 4.37 (m, 1H, H-3), 4.55 (s, 2H, Cp), 4.77 (br s, 1H, Cp), 4.81 (br s, 1H, Cp); ^{13}C NMR: δ 22.54, 47.32, 64.21, 69.29, 69.33, 69.94, 78.69, 205.31. Anal. Calcd for $C_{14}H_{16}FeO_2$: C, 61.79; H, 5.93. Found: C, 61.96; H, 5.98.

4.3. Lipase-catalyzed esterification of (±)-2

Ferrocenyl aldol (±)-**2** (500 mg, 1.84 mmol) was dissolved in 50 mL of *t*-BME and to this solution Lypozyme™ (500 mg) and vinyl acetate (0.530 mL, 3 equiv) were added. The suspension was shaken at 300 rpm at 45 °C; aliquots were drawn at regular time intervals and analyzed by chiral HPLC analysis. When the conversion of the substrate reached 50% (24 h), the enzyme was filtered off and the solution evaporated to dryness. The residue was purified by column chromatography (*n*-hexane/AcOEt 70:30) to give (+)-**3** (270 mg, 0.86 mmol, 47% yield, ee >99%) and (−)-**2** (245 mg, 0.90 mmol, 49% yield, ee >99%).

4.3.1. (*R*)-1-Ferrocenyl-3-acetoxybutan-1-one, (+)-3. $[\alpha]_D = +91.7$ (*c* 0.63, $CHCl_3$); HPLC: *n*-hexane/2-PrOH 9:1, flow 0.7 mL/min, t_R/min = 14.28 (*S*) and 15.5 (*R*). ^{1}H NMR: δ 1.37 (d, $J = 6.3$, 3H, –CH_3), 2.04 (s, 3H, –OAc), 2.77 (dd, $J = 6.4$ and 16.0, 1H, H-2a), 3.18 (dd, $J = 6.6$ and 16.0, 1H, H-2b), 4.23 (s, 5H, Cp′), 4.53 (br s, 2H, Cp), 4.77 (br s, 1H, Cp), 4.84 (br s, 1H, Cp), 5.44 (m, 1H, H-3); ^{13}C NMR: δ 20.12, 21.34, 45.59, 67.60, 69.30, 69.34, 69.83, 72.46, 78.93, 170.26, 200.67. Anal. Calcd for $C_{16}H_{18}FeO_3$: C, 61.17; H, 5.78. Found: C, 61.45; H, 5.83.

4.3.2. (*S*)-1-Ferrocenyl-3-hydroxybutan-1-one, (−)-2. $[\alpha]_D = -25.0$ (*c* 0.24, $CHCl_3$); HPLC: *n*-hexane/2-PrOH 9:1, flow 0.7 mL/min, t_R/min = 18.6 (*S*) and 33.2 (*R*).

4.4. Reduction of (−)-2 with $NaBH_4$

Aldol (−)-**2** (245 mg, 0.90 mmol, >99% ee) was dissolved in THF/MeOH (10 mL, 9:1) and $NaBH_4$ (60 mg, 1.72 mmol) was added. The reaction mixture was stirred at rt for 3 h; the excess $NaBH_4$ was quenched with MeOH and the reaction mixture extracted twice with AcOEt. The combined organic extracts were dried over Na_2SO_4 and evaporated under a reduced pressure to give a residue that was purified on silica gel column, (*n*-hexane/AcOEt 70:30) to give (+)-**4** (140 mg, 0.51 mmol, 57% yield) and (−)-**5** (97 mg, 0.35 mmol, 38% yield).

4.4.1. (1*S*,3*S*)-1-Ferrocenyl-1,3-dihydroxybutane, (+)-4. Yellow solid, mp 105–106 °C, $R_f = 0.21$ (*n*-hexane/AcOEt 70:30), $[\alpha]_D = +27.0$ (*c* 0.75, $CHCl_3$); HPLC: *n*-hexane/2-PrOH 9:1, flow 0.7 mL/min, t_R/min = 27.9 (1*R*,3*R*) and 32.4 (1*S*,3*S*). ^{1}H NMR: δ 1.23 (d, $J = 6.2$, 3H, –CH_3), 1.78 (m, 2H, H-2), 2.53 (d, $J = 3.1$, 1H, –(C1)–OH), 3.46 (s, 1H, –(C3)–OH), 4.12 (m, 1H, H-3), 4.14 (br s, 3H, Cp), 4.22 (s, 5H, Cp′), 4.25 (br s, 1H, Cp), 4.60 (m, 1H, H-1); ^{13}C NMR: δ 23.76, 46.21, 65.58, 66.54, 68.03, 68.09, 68.29, 68.35, 70.55, 93.64. Anal. Calcd for $C_{14}H_{18}FeO_2$: C, 61.34; H, 6.62. Found: C, 61.54; H, 6.69.

4.4.2. (1*R*,3*S*)-1-Ferrocenyl-1,3-dihydroxybutane, (−)-5. Yellow solid, mp 91–92 °C, $R_f = 0.16$ (*n*-hexane/AcOEt 70:30), $[\alpha]_D = -11.8$ (*c* 0.68, $CHCl_3$); HPLC: *n*-hexane/2-PrOH 9:1, flow 0.7 mL/min, t_R/min = 27.6 (1*R*,3*S*) and 31.8 (1*S*,3*R*). ^{1}H NMR: δ 1.24 (d, $J = 6.2$,

3H, –CH_3), 1.77 (ddd, 1H, $J = 3.0$, 8.0, and 14.3, H-2a), 1.85 (ddd, 1H, $J = 3.6$, 8.3, and 14.3, H-2b), 2.45 (s, 1H, –(C1)–OH), 2.70 (s, 1H, –(C3)–OH), 4.11 (m, 1H, H-3), 4.19 (br s, 3H, Cp), 4.21 (s, 5H, Cp′), 4.30 (br s, 1H, Cp), 4.73 (m, 1H, H-1); ^{13}C NMR: δ 23.48, 45.52, 65.21, 65.60, 66.66, 67.55, 67.96, 68.34, 93.32. Anal. Calcd for $C_{14}H_{18}FeO_2$: C, 61.34; H, 6.62. Found: C, 61.66; H, 6.58.

4.5. Reduction of (+)-3 with $LiAlH_4$

To a solution of (+)-**3** (270 mg, 0.99 mmol, >99% ee) in dry ether (10 mL) was added $LiAlH_4$ (56 mg, 1.48 mmol) and the mixture stirred at room temperature for 1 h. At completion, the reaction was quenched by dropwise addition of water (2 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 purified on silica gel column as above to afford (−)-**4** (140 mg, 0.51 mmol, 57% yield), $[\alpha]_D = -26.9$ (*c* 0.95, $CHCl_3$), and (+)-**5** (97 mg, 0.35 mmol, 38% yield), $[\alpha]_D = +11.5$ (*c* 0.4, $CHCl_3$).

4.6. Lipase-catalyzed alcoholysis of (±)-3

Novozym 435 (300 mg) was added to a solution of (±)-**3** (300 mg, 1.1 mmol) in *t*-BME (30 mL) containing *n*-BuOH (0.35 mL, 3.83 mmol). The suspension was shaken at 45 °C (300 rpm) and the reaction course monitored by chiral HPLC analysis. After 30 h, the enzyme was filtered off and the solution taken to dryness. The residue was purified by column chromatography (*n*-hexane/AcOEt 70:30) to afford (−)-**3** (178 mg, 0.54 mmol, 49% yield, 97.9% ee), $[\alpha]_D = -91.0$ (*c* 0.56, $CHCl_3$) and (+)-**2** (143 mg, 0.53 mmol, 48% yield, ee >99%), $[\alpha]_D = +24.8$ (*c* 1.1, $CHCl_3$).

4.7. (1*S*,3*S*)-1-Ferrocenyl-1,3-diacetoxybutane, (+)-6

To a solution of (+)-**4** (120 mg, 0.43 mmol) in CH_2Cl_2, pyridine and excess acetic anhydride were added and the reaction was stirred at room temperature for 24 h. The reaction mixture was evaporated to dryness under reduced pressure to give (+)-**6** (131 mg, 0.40 mmol, 95% yield), $R_f = 0.22$ (*n*-hexane/AcOEt 90:10), $[\alpha]_D = +77.9$ (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 1.29 (d, $J = 6.3$, 3H, –CH_3), 2.05 (s, 3H, –OAc), 2.07 (m, 1H, H-2a), 2.09 (s, 3H, –OAc), 2.24 (m, 1H, H-2b), 4.15 (s, 5H, Cp′), 4.17 (br s, 3H, Cp), 4.27 (br s, 1H, Cp), 4.93 (m, 1H, H-3), 5.85 (dd, $J = 4.0$ and 9.0, 1H, H-1); ^{13}C NMR: δ 19.80, 21.24, 21.35, 40.99, 66.46, 67.55, 67.94, 68.27, 68.32, 68.72, 69.16, 87.43, 170.36. Anal. Calcd for $C_{18}H_{22}FeO_4$: C, 60.35; H, 6.19. Found: C, 60.54; H, 6.25.

4.8. (1*R*,3*S*)-1-Ferrocenyl-1,3-diacetoxybutane, (−)-9

Diol (−)-**5** (100 mg, 0.37 mmol) was acetylated as above to give (−)-**9** (113 mg, 0.35 mmol, 95% yield), $R_f = 0.22$ (*n*-hexane/AcOEt 90:10), $[\alpha]_D = -49.5$ (*c* 0.9, $CHCl_3$); ^{1}H NMR: δ 1.30 (d, $J = 6.4$, 3H, –CH_3), 2.04 (br s, 4H, –OAc and H-2a), 2.09 (s, 3H, –OAc), 2.23 (m, 1H, H-2b), 4.18 (s, 8H, Cp′ and Cp), 4.32 (s, 1H, Cp), 4.99 (m, 1H, H-3), 5.85 (dd, $J = 2.2$ and 11.0, 1H, H-1); ^{13}C NMR: δ 20.53, 21.10, 21.26, 40.72, 66.12, 67.19, 68.01, 68.17, 68.40, 68.80, 87.14, 170.40, 170.63. Anal. Calcd for $C_{18}H_{22}FeO_4$: C, 60.35; H, 6.19. Found: C, 60.48; H, 6.22.

4.9. (1*S*,3*S*)-1-Azido-1-ferrocenyl-3-acetoxybutane, (+)-7

To a solution of (+)-**6** (125 mg, 0.35 mmol) in CH_3CN (5 mL) was added NaN_3 (23 mg, 0.35 mmol) dissolved in H_2O (1 mL) and the mixture was maintained under stirring at room temperature for 2 h. The reaction mixture was then extracted twice with AcOEt. The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a yellow oil (+)-**7** (100 mg, 0.29 mmol, 82% yield). $R_f = 0.32$ (*n*-hexane/AcOEt 90:10), $[\alpha]_D = +26.6$ (*c* 0.90, $CHCl_3$); ^{1}H NMR: δ 1.31 (d, $J = 6.5$, 3H, –CH_3), 2.00 (ddd, $J = 4.7$, 6.4, and 14.5, 1H, H-2a), 2.08 (s, 3H, –OAc), 2.14 (ddd, $J = 6.9$, 9.5, and 14.5, 1H, H-2b), 4.15 (br s, 1H, Cp), 4.21 (m, 9H, Cp, Cp′ and H-1), 5.05 (m, 1H, H-3); ^{13}C NMR: δ 19.83, 21.36, 41.16, 59.04, 66.37, 66.71, 68.13, 68.34, 68.60, 68.89, 88.15, 170.42. Anal. Calcd for $C_{16}H_{19}FeN_3O_2$: C, 56.32; H, 5.61; N, 12.32. Found: C, 56.48; H, 5.64; N, 12.45.

4.10. (1*R*,3*S*)-1-Azido-1-ferrocenyl-3-acetoxybutane, (−)-10

The treatment of (−)-**9** (100 mg, 0.30 mmol) with NaN_3 as above, afforded (−)-**10** as a yellow oil (85 mg, 0.25 mmol, 83% yield), $R_f = 0.32$ (*n*-hexane/AcOEt 90:10), $[\alpha]_D = -70.7$ (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 1.32 (d, $J = 6.3$, 3H, –CH_3), 1.85 (ddd, $J = 2.8$, 11.1, and 14.5, 1H, H-2a), 2.12 (s, 3H, –OAc), 2.20 (ddd, $J = 2.5$, 9.9, and 14.5, 1H, H-2b), 4.16 (br s, 1H, Cp), 4.20–4.31 (m, 9H, Cp, Cp′ and H-1), 5.14 (m, 1H, H-3); ^{13}C NMR: δ 20.57, 21.35, 41.40, 58.76, 65.95, 67.35, 68.29, 68.38, 68.43, 68.88, 87.69, 170.54. Anal. Calcd for $C_{16}H_{19}Fe\,N_3O_2$: C, 56.32; H, 5.61; N, 12.32. Found: C, 56.58; H, 5.67; N, 12.38.

4.11. (1*S*,3*S*)-1-Amino-1-ferrocenyl-3-hydroxybutane, (+)-8

To a solution of (+)-**7** (100 mg, 0.29 mmol) in dry ethyl ether (5 mL) was added $LiAlH_4$ (23 mg, 0.60 mmol) and the mixture was stirred at 0 °C for 3 h. After completion, the reaction was quenched by the careful dropwise addition of H_2O and extracted with ethyl ether. 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 (AcOEt/MeOH/triethylamine 90:5:5) to give (+)-**8** as a yellow solid (57 mg, 0.21 mmol, 72% yield), mp 81–82 °C, $R_f = 0.30$ (AcOEt/MeOH/triethylamine 90:5:5), $[\alpha]_D = +20.5$ (*c* 0.53, EtOH); ^{1}H NMR: δ 1.22 (d, $J = 6.2$, 3H, –CH_3), 1.53 (ddd, $J = 9.8$, 11.2, and 14.1, 1H, H-2a), 1.90 (ddd, $J = 2.1$, 2.5, and 14.1, 1H, H-2b), 3.77 (dd, $J = 2.5$ and 11.2, 1H, H-1) 4.09 (m, 3H, Cp and H-3), 4.15 (m, 2H, Cp), 4.17 (s, 5H, Cp′); ^{13}C NMR: δ 23.91, 44.84, 51.62, 65.32, 65.52, 67.63, 67.72, 68.36,

68.91, 95.87. Anal. Calcd for $C_{14}H_{19}FeNO$: C, 61.56; H, 7.01; N, 5.13. Found: C, 61.69; H, 7.08; N, 5.18.

4.12. (1*R*,3*S*)-1-Amino-1-ferrocenyl-3-hydroxybutane, (−)-11

The reduction of (−)-**10** (85 mg, 0.25 mmol) with $LiAlH_4$ as above gave (−)-**11** (52 mg, 0.19 mmol, 75% yield), mp 79 °C, $R_f = 0.25$ (AcOEt/MeOH/TEA 90:5:5), $[\alpha]_D = -6.9$ (*c* 0.42, EtOH); ^{1}H NMR: δ 1.17 (d, $J = 6.3$, 3H, $-CH_3$), 1.62 (ddd, $J = 2.6$, 6.8, and 14.2, 1H, H-2a), 1.78 (ddd, $J = 3.3$, 8.4, and 14.2, 1H, H-2b), 3.97 (m, 1H, H-1) 4.11–4.17 (m, 9H, Cp, Cp′ and H-3), 4.30 (br s, 1H, Cp); ^{13}C NMR: δ 23.32, 44.48, 48.78, 65.44, 65.50, 66.33, 67.47, 67.70, 68.35, 95.58. Anal. Calcd for $C_{14}H_{19}FeNO$: C, 61.56; H, 7.01; N, 5.13. Found: C, 61.72; H, 7.07; N, 5.16.

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