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Diastereoselective Synthesis of 3-(2-((*N*,*N*-Dimethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexan-3-ols, in Racemic and Optically Active Series: X-ray Determination of Their Relative Configuration

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We describe herein the diastereoselective synthesis of 3-(2-((*N*,*N*-dimethylamino)methyl)-ferrocenyl)-4-(4-methoxyphenyl)-hexan-3-ols. The relative configurations of these amino alcohols (pR^*,3R^*,4S^*), **5(a+b)**, and (pR^*,3S^*,4R^*), **6(a+b)**, were unambiguously determined by X-ray diffraction analysis. In the optically active series, the absolute configuration is related to that of the starting 1-((*N*,*N*-dimethylamino)methyl)-2-lithioferrocene, **7**. The orientation of nucleophilic addition of this lithiated reactant on the chiral ketone 4-(4-methoxyphenyl)hexan-3-one, **2** is under ketonic chiral center control, and independent of the planar chirality of the lithiated ferrocene entity. This reaction opens a route to the synthesis of ferrocene analogs of hexestrol and diethylstilbestrol. Compounds **5(a+b)** and **6(a+b)** crystallize in the monoclinic space group $P2_1/n$ with $Z = 4$ and $P2_1/a$ with $Z = 8$, respectively. The main structural feature of **5(a+b)** is a strong intramolecular hydrogen bond between the hydroxyl and the amino groups ($d_{N-O} = 2.74$ Å). Compound **6(a+b)** exists in two conformations, one which is similar to compound **5(a+b)** with a hydrogen bond ($d_{N-O} = 2.73$ Å), and the other which does not have such a hydrogen bond.

Introduction

π-Transition metal complexes have been shown to be widely useful in the field of organic chemistry especially in enantioselective synthesis.[1] In the last few years these kinds of complexes have been employed as auxiliary substances in biochemistry.[2] Two strategies have been developed for obtaining biologically active organometallic molecules: (i) modification of natural products by grafting an organometallic moiety, taking care to maintain a good affinity for the receptors (this method has been used by Jaouen et al., in the case of steroid hormones[3]); (ii) generating natural product analogs by organometallic synthetic methods (thus Sokolov and co-workers prepared ferrocene compounds equivalent to prostaglandins[4])

In this work, we focus on the synthesis of ferrocene amino alcohols presenting the same relative and/or absolute configuration as the steroid skeleton.[5] The choice of ferrocene as an organometallic core has been made for the following reasons: (i) Ferrocene has a well established and widely developed chemistry including chiral stereochemistry which is very important for resolution in the course of our syntheses. (ii) More than 30 years of studies have shown that ferrocenes may be generally considered as nontoxic. A drug used against iron deficiency anemia, which has been used for many years in Russia under the trade name "Ferrocenon", is the sodium salt of *o*-ferrocenylbenzoic acid. Metabolism of ferrocenes as xenobiotics proceeds by demetalation. (iii) Ferricinium salts exhibit antitumor activity and appear to be a step in the metabolism of ferrocene compounds.[6]

Thus, it is possible to conceive specific drugs with potential antitumor properties and rather limited secondary effects. In a previous publication, it was reported that a ferrocene derivative similar to estradiol was recognized by specific receptors.[7] We describe here the diastereoselective synthesis, identification, physico-chem-

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(2) Ryabov, A. D. *Angew. Chem., Int. Ed. Engl.*

(3) Jaouen, G.; Vessieres A. *Pure Appl. Chem.* **1989**, *61*, 56.

(4) Sokolov, V. I.; Troiskaya, L. L.; Krushchova, N. S. *J. Organomet. Chem.* **1988**, *250*, 439.

(5) The approach used for the calculation was based first by considering previous crystallographic data for ferrocene derivatives (Vichard, D. Thesis, University P. et M. Curie, France, 1992) and by minimizing the energy according to the PC model program. We thank Professor M. McGlinchey for this calculation.

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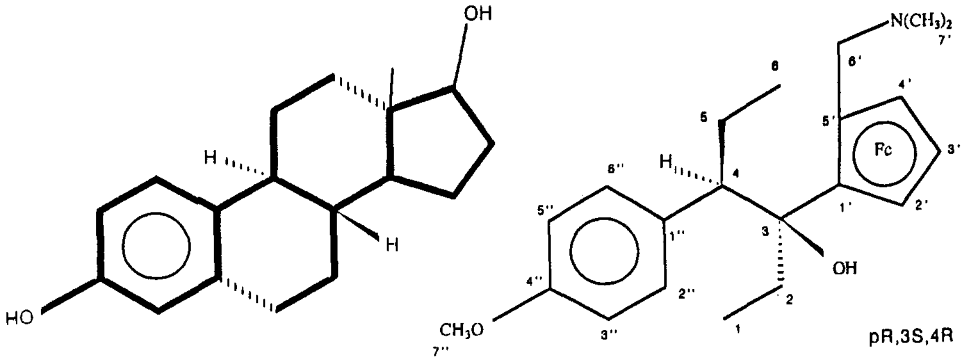
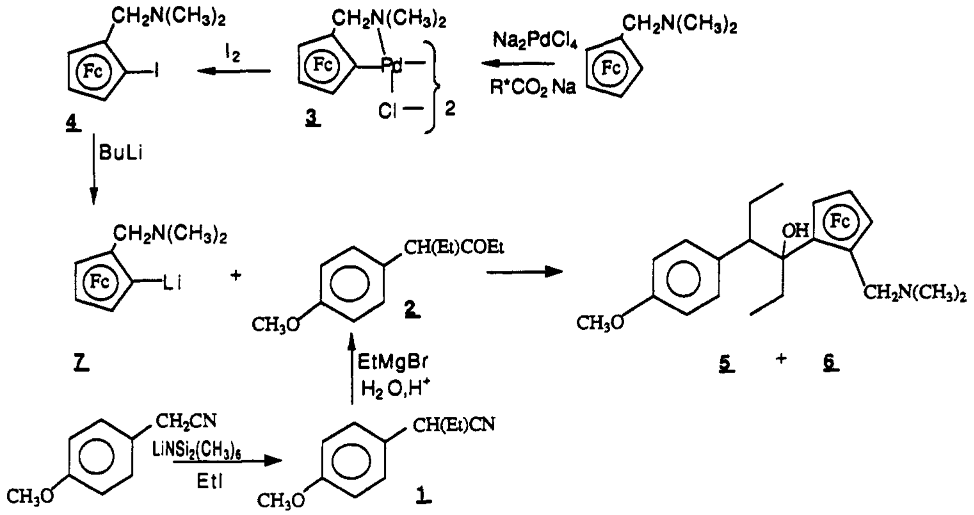


Figure 1. Comparison between estradiol and the structure of our target molecule.

Scheme 1



ical properties, and X-ray structures of amino alcohols possessing the same relative and/or absolute configurations as the steroid skeleton (Figure 1).

Discussion

The pathway for the synthesis of the amino alcohols is represented in Scheme 1. The key step in the synthesis is based on the nucleophilic addition of the lithiated ((*N*,*N*-dimethylamino)methyl)ferrocene, 7, to ketone 2. In all cases the reaction was carried out with racemic ketone, whereas the lithiated compound may be racemic or optically active.

The lithiated ferrocenyl compound 7 possesses a plane of chirality while the ketone 2 presents a chiral center. During the reaction, a new asymmetric carbon, C(3), is formed so that, in the racemic or optically active series, it is theoretically expected that four isomers distinguishable by NMR would be formed if the reaction is not stereoselective. In fact, two diastereomers, 5 and 6, were obtained in almost equal quantities and isolated by chromatography on silica gel. This result can be ascribed to a complete stereoselectivity for this reaction, under the control of one element of chirality in the transition state.

The stereoselectivity of the reaction of carbonyl groups with lithiated ferrocenes has been previously described. Tirouflet and co-workers[8] studied the action of chiral lithiated ferrocenes on prochiral aromatic aldehydes. In this approach they found that the lithiated compound does not discriminate between the two enantiotropic faces of the carbonyl group. In the optically active series, Ugi and co-workers[9] confirmed these results. Whereas they observed the predominant formation of one diastereomer, the authors explain this result as a consequence of the thermodynamic instability of the minor diastereomer. The configuration of the new center in the major diastereomer isolated was established by X-ray diffraction[9] and provides evidence on the correlation between the planar chirality (p*S*) of the ferrocene moiety and the (*S*) configuration of the new chiral center.

Watanabe and co-workers,[10] in the reaction of chiral lithiated ferrocenes with aromatic or aliphatic aldehydes, found that the stereoselectivity of the reaction depends on the nature of the substituent in the α position of the carbonyl group. In the case of aromatic aldehydes the stereoselectivity was lower, but for the pivalic aldehyde, one of the two diastereomers formed is predominant, the major product having an (*S*) configuration of the carbinol center starting from a (p*S*) lithiated ferrocene entity.

In our case we are also dealing with an aliphatic ketone and, considering the previous results, we assumed that the configuration of the amino alcohols 5 and 6 formed in the reaction between ketone 2 and lithiated ((*N*,*N*-dimethylamino)methyl)ferrocene, 7 might be pR^*,3R^*,4R^* and pR^*,3R^*,4S^*.[11] X-ray structures of **5(a+b)** and **6(a+b)** were determined for the racemic series and provided

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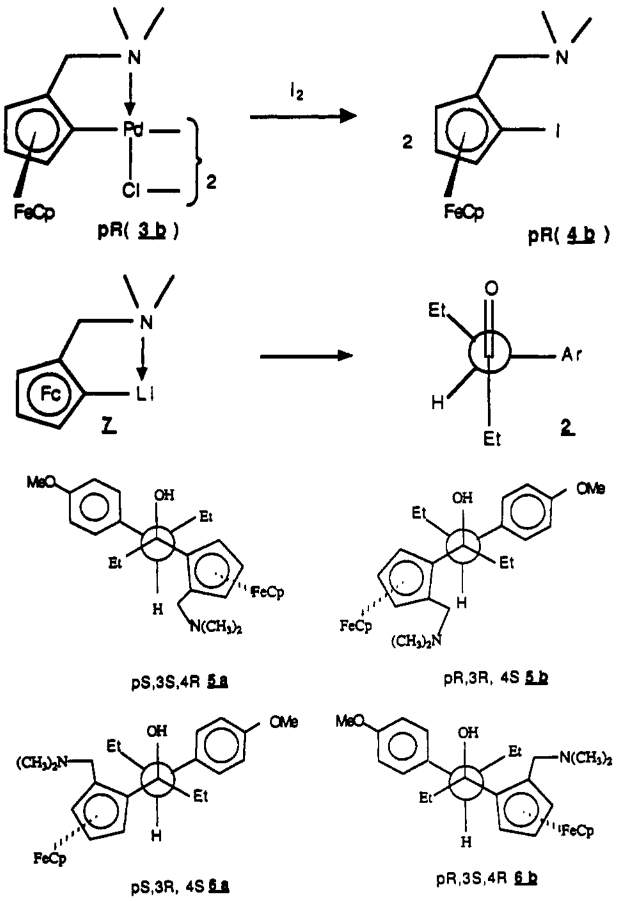

Figure 2. Obtainment of the optically pure iodate ferrocenic compound (p*R*)-**4b** and orientation of the nucleophilic attack (top two equations) and two pairs of enantiomers obtained by action of the racemic (((*N*,*N*-dimethylamino)methyl)ferrocenyl)lithium on the ketone **2** (bottom four structures).

evidence that the relative configurations are respectively p*R**,3*R**,4*S** for the more polar isomer **5(a+b)** and p*R**,3*S**,4*R** for **6(a+b)**.

The starred symbols are the relative configurations. The symbol (p*R*) or (p*S*) represents the configurations of the plane of chirality according to Ugi's notation in the case of disubstituted ferrocene compounds.[12]

In this example, the stereoselectivity is controlled by steric and torsional factors. According to Felkin's rules,[13] when the reaction proceeds via "reactant-like" transition states, the chiral center at the α position adjacent to the ketonic function (C(3)) appears to be a much more efficient inductor to influence the configuration of the new chiral center (C(4)) than the plane of chirality of lithiated ((*N*,*N*-dimethylamino)methyl)ferrocene, 7.

The chirality of the disubstituted ferrocene moiety 4 is generated in a controlled fashion by asymmetric cyclopalladation following the procedure elaborated previously.[14] The lithiated reagent 7 prepared through the iodide intermediate 4 from the ferrocene palladated compound 3 retains its initial configuration. From the known configuration of the starting ferrocene moiety, the absolute configurations of the pair of enantiomers created (**5** and **6**; Figure 2) can be determined unambiguously.

Table 1. Crystallographic Data for 5(a+b)

chemical formula	$C_{26}H_{35}O_2NFe$
fw	449.4
cryst syst	monoclinic
space group	$P2_1/n$
Z	4
a, Å	9.866(2)
b, Å	7.618(2)
c, Å	31.138(17)
β, deg	90.31(3)
V, Å^3	2340(2)
F(000)	960
ρ(calcd), g·cm^{-3}	1.27
μ(Mo Kα), cm^{-1}	6.6
cryst size, mm	0.22 × 0.40 × 0.60
diffractometer	CAD4
monochromator	graphite
radiation (λ, Å)	Mo Kα (0.710 70)
temp, °C	20
scan type	$\omega/2\theta$
scan range θ, deg	0.8 + 0.34 tan θ
2θ range, deg	2–46
no. of reflctn collected	3245
no. of reflctn used (criteria)	1871 ($I > 3\sigma(I)$)
R	0.071
R_w[a]	0.072
ab corr[b]	min 0.79, max 1.33
secondary ext	no
weighting scheme	unit weights
rms (shift/esd) (last ref)	0.49
no. of ls param	268

[a] $R_w = [\sum_i w_i(F_o - F_c)^2/\sum_i w_i F_o^2]^{1/2}$. [b] Difabs: Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 159.

Table 2. Fractional Parameters for 5(a+b), $C_{26}H_{35}O_2NFe$

atom	x/a	y/b	z/c	U(eq), Å^2	U(iso), Å^2
Fe(1)	0.0270(1)	0.1518(2)	0.20537(4)	0.0517	
O(1)	–0.1412(5)	0.1798(9)	0.0834(2)	0.0457	
O(2)	–0.747(1)	0.460(2)	0.0194(4)	0.1475	
N(1)	0.0544(7)	–0.077(1)	0.0754(3)	0.0548	
C(1)	–0.283(1)	0.432(1)	0.1778(3)	0.0656	
C(2)	–0.2149(9)	0.381(1)	0.1354(3)	0.0512	
C(3)	–0.2013(8)	0.185(1)	0.1257(3)	0.0442	
C(4)	–0.3437(8)	0.095(1)	0.1230(3)	0.0383	
C(5)	–0.3324(9)	–0.102(1)	0.1125(3)	0.0566	
C(6)	–0.469(1)	–0.197(1)	0.1144(4)	0.0741	
C(1′)	–0.1153(8)	0.084(1)	0.1583(3)	0.0406	
C(2′)	0.0144(8)	0.006(1)	0.1504(3)	0.0408	
C(3′)	0.048(1)	–0.101(1)	0.1868(3)	0.0560	
C(4′)	–0.059(1)	–0.086(1)	0.2166(3)	0.0663	
C(5′)	–0.1577(9)	0.028(1)	0.1998(3)	0.0489	
C(6′)	0.1066(8)	0.022(1)	0.1123(3)	0.0502	
C(7′)	0.048(1)	–0.265(2)	0.0845(4)	0.0774	
C(8′)	0.141(1)	–0.042(2)	0.0374(3)	0.0798	
C(9′)	0.171(1)	0.340(2)	0.1971(3)	0.0716	
C(10′)	0.213(1)	0.215(2)	0.2291(4)	0.0790	
C(11′)	0.120(1)	0.219(2)	0.2618(4)	0.0883	
C(12′)	0.020(1)	0.337(2)	0.2527(4)	0.0766	
C(13′)	0.047(1)	0.416(1)	0.2130(4)	0.0678	
C(1″)	–0.4409(8)	0.184(1)	0.0927(3)	0.0497	
C(2″)	–0.5493(9)	0.279(1)	0.1089(4)	0.0645	
C(3″)	–0.640(1)	0.359(2)	0.0837(5)	0.0932	
C(4″)	–0.632(1)	0.347(2)	0.0406(6)	0.0755	
C(5″)	–0.529(1)	0.258(2)	0.0224(4)	0.0845	
C(6″)	–0.432(1)	0.173(2)	0.0490(3)	0.0747	
C(7″)	–0.730(2)	0.418(2)	–0.0199(5)		0.134(6)

Structure and Physico-Chemical Properties of the Amino Alcohols 5 and 6. Structural analyses have been carried out by X-ray diffraction on the racemic compounds **5(a+b)** and **6(a+b)**. The ORTEP plots of **5** and **6** are shown in Figures 3 and 4a,b, respectively, while the crystallographic data and fractional parameters are given in Tables 1–4, respectively. Selected bond distances and angles are given in Tables 5–7.

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(14) Sokolov, V. I.; Troiskaya, L. L.; Reutov, O. A. *J. Organomet. Chem.* **1979**, *182*, 537.

Table 3. Crystallographic Data for 6(a+b)

chemical formula	$C_{26}H_{35}O_2NFe$
fw	449.4
cryst syst	monoclinic
space group	$P2_1/a$
Z	8
a, Å	7.998(2)
b, Å	56.436(1)
c, Å	10.378(2)
β, deg	96.10(2)
V, Å^3	4658(8)
$F(000)$	1920
ρ(calcd), g·cm^{-3}	1.28
μ(Mo Kα), cm^{-1}	6.66
cryst size, mm	0.40 × 0.42 × 0.50
diffractometer	CAD4
monochromator	graphite
radiation (λ, Å)	Mo Kα (0.710 70)
temp, °C	20
scan type	$\omega/2\theta$
scan range θ, deg	0.8 + 0.34 tan θ
2θ range, deg	2–50
no. of reflctn collected	7906
no. of reflctn used (criteria)	4819 ($I > 3\sigma(I)$)
R	0.061
R_w[a]	0.067
abs corr[b]	min 0.71, max 1.15
secondary ext	31 × 10^{-6}
weighting scheme	unit weights
rms (shift/esd) (last ref)	0.84
no. of ls params	754

[a] $R_w = [\sum_i w_i(F_o - F_c)^2/\sum_i w_i F_o^2]^{1/2}$. [b] Difabs: Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 159.

Table 4. Fractional Parameters for 6(a+b), $C_{26}H_{35}O_2NFe$

atom	x/a	y/b	z/c	U(eq), Å^2
Fe(1)	0.1844(1)	0.10692(2)	1.0754(1)	0.0411
O(1)	0.0312(6)	0.03858(9)	1.1572(4)	0.0448
O(2)	−0.4209(7)	0.0165(1)	1.6547(6)	0.0708
N(1)	0.1441(8)	0.0343(1)	0.9146(6)	0.0457
C(1)	−0.280(1)	0.0506(2)	0.9695(8)	0.0615
C(2)	−0.2473(9)	0.0562(1)	1.1142(8)	0.0505
C(3)	−0.0580(8)	0.0601(1)	1.1652(7)	0.0378
C(4)	−0.0461(9)	0.0674(1)	1.3100(7)	0.0459
C(5)	0.138(1)	0.0672(2)	1.3712(8)	0.0632
C(6)	0.160(1)	0.0792(2)	1.5013(9)	0.0772
C(1′)	0.0051(9)	0.0794(1)	1.0779(7)	0.0395
C(2′)	0.1140(9)	0.0764(1)	0.9758(7)	0.0376
C(3′)	0.094(1)	0.0967(1)	0.8946(7)	0.0496
C(4′)	−0.020(1)	0.1124(2)	0.9428(8)	0.0552
C(5′)	−0.0714(9)	0.1020(1)	1.0569(8)	0.0472
C(6′)	0.2321(9)	0.0566(2)	0.9565(7)	0.0488
C(7′)	0.061(1)	0.0362(2)	0.7834(8)	0.0658
C(8′)	0.265(1)	0.0143(2)	0.9221(9)	0.0682
C(9′)	0.3943(9)	0.1048(2)	0.2084(8)	0.0479
C(10′)	0.277(1)	0.1208(1)	1.2505(8)	0.0527
C(11′)	0.249(1)	0.1391(2)	1.1562(9)	0.0526
C(12′)	0.352(1)	0.1336(2)	1.0572(9)	0.0616
C(13′)	0.4396(9)	0.1125(2)	1.0887(8)	0.0569
C(1″)	−0.1532(9)	0.0530(1)	1.3925(7)	0.0461
C(2″)	−0.132(1)	0.0289(2)	1.4088(7)	0.0478
C(3″)	−0.217(1)	0.0158(1)	1.4950(7)	0.0492
C(4″)	−0.328(1)	0.0279(2)	1.5668(8)	0.0546
C(5″)	−0.356(1)	0.0512(2)	1.5502(9)	0.0663
C(6″)	−0.270(1)	0.0640(2)	1.4632(8)	0.0612
C(7″)	−0.382(1)	−0.0069(2)	1.6881(9)	0.0654
Fe(21)	0.7645(1)	0.17441(2)	0.41228(9)	0.0395
O(21)	0.9687(6)	0.16312(8)	0.7328(4)	0.0426
O(22)	1.2936(7)	0.2305(1)	1.2333(4)	0.0489
N(21)	0.5299(8)	0.1331(1)	0.7092(6)	0.0515
C(21)	0.619(1)	0.1986(2)	0.8551(9)	0.0614
C(22)	0.7546(9)	0.1800(1)	0.8431(6)	0.0443
C(23)	0.8575(8)	0.1835(1)	0.7273(6)	0.0317
C(24)	0.9600(8)	0.2067(1)	0.7392(6)	0.0334
C(25)	1.093(1)	0.2074(2)	0.6422(7)	0.0456
C(26)	1.170(1)	0.2319(2)	0.6309(9)	0.0677
C(21′)	0.7373(8)	0.1828(1)	0.6027(6)	0.0320
C(22′)	0.6329(9)	0.1625(1)	0.5573(6)	0.0378
C(23′)	0.5230(9)	0.1708(2)	0.4495(7)	0.0462
C(24′)	0.5555 (9)	0.1950(1)	0.4268(7)	0.0439
C(25′)	0.6873(8)	0.2021(1)	0.5209(6)	0.0382
C(26′)	0.6364(9)	0.1375(1)	0.6033(7)	0.0484
C(27′)	0.355(1)	0.1399(2)	0.6715(9)	0.0681
C(28′)	0.546(1)	0.1085(2)	0.7455(9)	0.0649
C(29′)	1.003(1)	0.1635(2)	0.3895(7)	0.0559
C(30′)	0.883(1)	0.1458(2)	0.349(1)	0.0621
C(31′)	0.776(1)	0.1553(2)	0.2468(9)	0.0645
C(32′)	0.824(1)	0.1788(2)	0.2269(8)	0.0708
C(33′)	0.964(1)	0.1837(2)	0.3128(8)	0.0609
C(21″)	1.0420(8)	0.2124(1)	0.8748(6)	0.0352
C(22″)	1.1581(9)	0.1976(1)	0.9415(7)	0.0406
C(23″)	1.2405(8)	0.2043(1)	1.0608(6)	0.0406
C(24″)	1.2054(8)	0.2255(1)	1.1158(6)	0.0358
C(25″)	1.0875(9)	0.2405(1)	1.0518(6)	0.0412
C(26″)	1.0087(9)	0.2337(1)	0.9325(7)	0.0441
C(27″)	1.274(1)	0.2533(2)	1.2862(8)	0.0605

The main characteristic features of these structures are the following: (1) The two ethyl groups are in a trans orientation toward the C(3)–C(4) bond, as are the aromatic and ferrocene rings. For the more polar isomer **5** there are four symmetry-related molecules in each unit cell (two of each optical isomer **5a** and **5b**). The relative positions of the nitrogen and oxygen atoms are characterized by a short N–O distance (2.74 Å). This value, consistent with the formation of a strong intramolecular H bond, can be correlated with those obtained by Ugi and co-workers[9] and by Brocard and Maciejewski[15] on similar structures in which a corresponding bond distance of 2.84 Å was found. (2) For the less polar isomer **6** the situation is somewhat different. The asymmetric unit consists of molecules with two different geometries as shown in Figure 4a,b. In one of them (molecule 1; Figure 4a) the distance between the nitrogen and oxygen atoms (2.73 Å) is very close to that found in **5**. In the other conformation (molecule 2; Figure 4b) this distance is much longer (3.96 Å); clearly there is no hydrogen bond of the OH–N type so it is reasonable to consider the existence of a hydrogen bond between the hydroxyl group and the iron atom (d_{O-Fe} = 3.60 Å).

These results are confirmed by IR spectra which were measured in KBr and in CCl_4 in the ν(OH) region. The spectrum of the less polar diastereomer, **6**, shows two bands at 3560 and 3280 cm^{-1}. There is no difference between the spectra in the solid state and in dilute solution ($C = 5 \times 10^{-2}$–10^{-3} mol/L). It follows that all the hydroxyl groups of **6** are involved in intramolecular hydrogen bond formation. The assignment of ν(OH) bands is straightforward in view of previous work on similar compounds.[16] The high frequency band (3560 cm^{-1}) is assigned to the OH group bonded with the iron atom. The position of the second band (3280 cm^{-1}) corresponds to stable intramolecular hydrogen bond of the OH–N type (d_{OH-N} = 2.73 Å). We calculated the ratio of these two conformations in CCl_4 and found them to be 27% for OH–Fe and 73% for OH–N.

The more polar compound **5** shows only one conformation with a hydrogen bond of the OH–N type (ν = 3280 cm^{-1} in CCl_4). The IR spectrum in the solid state also supports the existence of an intramolecular hydrogen bond. Thus, in contrast with diastereomer **6** which involves two conformations with the OH–Fe or OH–N intramolecular hydrogen bond, isomer **5** exhibits only one conformation

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[17] Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 159.

Table 5. Selected Interatomic Distances (Å) and Bond Angles (deg) for $C_{26}H_{35}O_2NFe$ (5)

Fe(1)–C(1′)	2.090(8)	Fe(1)–C(2′)	2.045(6)
Fe(1)–C(3′)	3.020(9)	Fe(1)–C(4′)	2.03(1)
Fe(1)–C(5′)	2.059(9)	Fe(1)–C(9′)	2.04(1)
Fe(1)–C(10′)	2.03(1)	Fe(1)–C(11′)	2.04(1)
Fe(1)–C(12′)	2.04(1)	Fe(1)–C(13′)	2.04(1)
O(1)–C(3)	1.446(9)	O(2)–C(4″)	1.56(1)
O(2)–C(7″)	1.27(2)	N(1)–C(6′)	1.46(1)
N(1)–C(7′)	1.46(1)	N(1)–C(8′)	1.49(1)
C(1)–C(2)	1.54(1)	C(2)–C(3)	1.53(1)
C(3)–C(4)	1.56(1)	C(3)–C(1′)	1.53(1)
C(4)–C(5)	1.51(1)	C(4)–C(1″)	1.51(1)
C(5)–C(6)	1.53(1)	C(1′)–C(2′)	1.43(1)
C(1′)–C(5′)	1.43(1)	C(2′)–C(3′)	1.43(1)
C(2′)–C(6′)	1.50(1)	C(3′)–C(4′)	1.41(1)
C(1′)–C(5′)	1.40(1)	C(9′)–C(10′)	1.44(2)
C(9′)–C(13′)	1.45(1)	C(10′)–C(11′)	1.37(2)
C(11′)–C(12′)	1.36(1)	C(12′)–C(13′)	1.40(1)
C(1″)–C(2″)	1.39(1)	C(1″)–C(6″)	1.37(1)
C(2″)–C(3″)	1.33(1)	C(3″)–C(4″)	1.35(2)
C(4″)–C(5″)	1.35(2)	C(5″)–C(6″)	1.42(2)
C(7″)–O(2)–C(4″)	99.8(13)	C(7′)–N(1)–C(6′)	111.5(9)
C(8′)–N(1)–C(6′)	109.2(8)	C(8′)–N(1)–O(7′)	110.7(9)
C(3)–C(2)–C(1)	117.1(8)	C(2)–C(3)–O(1)	104.0(7)
C(4)–C(3)–O(1)	108.2(6)	C(4)–C(3)–C(2)	111.0(7)
C(1′)–C(3)–O(1)	111.3(6)	C(1′)–C(3)–C(2)	114.1(7)
C(1′)–C(3)–C(4)	108.1(7)	C(5)–C(4)–C(3)	111.8(7)
C(1″)–C(4)–C(3)	113.8(7)	C(1″)–C(4)–C(5)	110.8(8)
C(6)–C(5)–C(4)	112.8(8)	C(2′)–C(1′)–C(3)	126.1(8)
C(5′)–C(1′)–C(3)	126.1(7)	C(5′)–C(1′)–C(2′)	107.2(7)
C(3′)–C(2′)–C(1′)	107.6(7)	C(6′)–C(2′)–C(1′)	130.2(8)
C(6′)–C(2′)–C(3′)	122.2(8)	C(4′)–C(3′)–C(2′)	107.7(8)
C(5′)–C(4′)–C(3′)	109.1(9)	C(4′)–C(5′)–C(1′)	108.4(8)
C(2′)–C(6′)–N(1)	111.4(7)	C(13′)–C(9′)–C(10′)	105.6(10)
C(11′)–C(10′)–C(9′)	108.1(11)	C(12′)–C(11′)–C(10′)	110.0(12)
C(13′)–C(12′)–C(11′)	109.4(11)	C(12′)–C(13′)–C(9′)	106.9(10)
C(2″)–C(1″)–C(4)	119.8(9)	C(6″)–C(1″)–C(1)	123.5(9)
C(6″)–C(1″)–C(2″)	116.6(9)	C(3″)–C(2″)–C(1″)	122.6(12)
C(4″)–C(3″)–C(2″)	121.2(14)	C(3″)–C(1″)–O(2)	110.0(15)
C(5″)–C(4″)–O(2)	130.1(16)	C(5″)–C(4″)–C(3″)	119.7(11)
C(6″)–C(5″)–C(4″)	119.5(12)	C(5″)–C(6″)–C(1″)	120.4(11)

with an intramolecular bond of the OH–N type. However, molecules of 5 are partly self-associated in the solid state.

Conclusion

This paper describes the diastereoselective synthesis of ferrocene amino alcohols, involving the addition of a planar chiral lithiated amino ferrocene derivative to a racemic and prochiral ketone. We have identified the main role of the asymmetric carbon in the α position, in the stereoselectivity of this reaction.

This reaction leads to the formation of two diastereomers which have been isolated and identified. The X-ray diffraction analyses of the racemic products allow one to assign unambiguously the relative configurations. Two conformations stabilized by intramolecular hydrogen bonds between the hydroxyl group and either the nitrogen or the iron atom were found for the less polar diastereomer 6 in solution (IR) as well as in the solid state (IR, X-ray data).

Experimental Section

The crystals were obtained from a racemic mixture of 5 or 6, after three separations on silica gel plates (60 F254 Merck) eluting with pentane/triethylamine (10:1). The solutions of 5 or 6 were allowed to crystallize at −20 °C in a mixture of ether and heptane. The orange crystals obtained were not suitable for X-ray analysis and were dissolved in ether/pentane, from which slow evaporation gave good material for X-ray studies.

X-ray Study of 5(a+b). Intensity data were collected at room temperature on a Nonius CAD4 diffractometer using Mo Kα radiation. Accurate cell dimensions and an orientation matrix were obtained from least squares refinement of the settling angles of 25 well defined reflections. No decay in the intensities of two standard reflections was observed during the course of data collection. This compound crystallizes in the monoclinic space group $P2_1/n$ with $Z = 4$ and cell dimensions $a = 9.866(2)$ Å, $b = 7.618(2)$ Å, $c = 31.138(17)$ Å, $\beta = 90.31(3)°$, $v = 2340(2)$ Å^3. Complete crystal data and crystal data parameters are listed in Tables 1 and 2. The usual corrections for Lorentz and polarization effects were applied.

Table 6. Selected Interatomic Distances (Å) for $C_{26}H_{35}O_2NFe$ (6)

Molecule 1			
Fe(1)–C(1′)	2.116(7)	Fe(1)–C(2′)	2.057(7)
Fe(1)–C(3′)	2.022(8)	Fe(1)–C(4′)	2.048(7)
Fe(1)–C(5′)	2.054(8)	Fe(1)–C(9′)	2.061(7)
Fe(1)–C(10′)	2.043(8)	Fe(1)–C(11′)	2.044(8)
Fe(1)–C(12′)	2.036(8)	Fe(1)–C(13′)	2.056(8)
O(1)–C(3)	1.415(8)	O(2)–C(4″)	1.395(9)
O(2)–C(7″)	1.39(1)	N(1)–C(6′)	1.482(9)
N(1)–C(7′)	1.45(1)	N(1)–C(8′)	1.48(1)
C(1)–C(2)	1.53(1)	C(2)–C(3)	1.566(9)
C(3)–C(4)	1.55(1)	C(3)–C(1′)	1.54(1)
C(4)–C(5)	1.54(1)	C(4)–C(1″)	1.51(1)
C(5)–C(6)	1.51(1)	C(1′)–C(2′)	1.45(1)
C(1′)–C(5′)	1.42(1)	C(2′)–C(3′)	1.42(1)
C(2′)–C(6′)	1.49(1)	C(3′)–C(4′)	1.41(1)
C(4′)–C(5′)	1.42(1)	C(9′)–C(10′)	1.41(1)
C(9′)–C(13′)	1.40(1)	C(10′)–C(11′)	1.42(1)
C(11′)–C(12′)	1.42(1)	C(12′)–C(13′)	1.40(1)
C(1″)–C(2″)	1.38(1)	C(1″)–C(6″)	1.39(1)
C(2″)–C(3″)	1.39(1)	C(3″)–C(4″)	1.40(1)
C(4″)–C(5″)	1.34(1)	C(5″)–C(6″)	1.40(1)
Molecule 2			
Fe(21)–C(21′)	2.066(6)	Fe(21)–C(22′)	2.040(7)
Fe(21)–C(23′)	2.020(7)	Fe(21)–C(24′)	2.054(7)
Fe(21)–C(25′)	2.061(7)	Fe(21)–C(29′)	2.041(9)
Fe(21)–C(30′)	2.018(9)	Fe(21)–C(31′)	2.040(8)
Fe(21)–C(32′)	2.045(9)	Fe(21)–C(33′)	2.061(8)
O(21)–C(23)	1.449(8)	O(22)–C(24″)	1.373(7)
O(22)–C(27″)	1.41(1)	N(21)–C(26′)	1.180(9)
N(21)–C(27′)	1.46(1)	N(21)–C(28′)	1.44(1)
C(21)–C(22)	1.53(1)	C(22)–C(23)	1.540(9)
C(23)–C(24)	1.543(9)	C(23)–C(21′)	1.528(8)
C(24)–C(25)	1.510(9)	C(24)–C(21″)	1.523(9)
C(25)–C(26)	1.53(1)	C(21′)–C(22′)	1.465(9)
C(21′)–C(25′)	1.414(9)	C(22′)–C(23′)	1.43(1)
C(22′)–C(26′)	1.49(1)	C(23′)–C(24′)	1.42(1)
C(24′)–C(25′)	1.418(9)	C(29′)–C(30′)	1.42(1)
C(29′)–C(33′)	1.40(1)	C(30′)–C(31′)	1.39(1)
C(31′)–C(32′)	1.40(1)	C(32′)–C(33′)	1.39(1)
C(21″)–C(22″)	1.380(9)	C(21″)–C(26″)	1.38(1)
C(22″)–C(23″)	1.391(9)	C(23″)–C(24″)	1.37(1)
C(24″)–C(25″)	1.38(1)	C(25″)–C(26″)	1.384(9)

Computations were performed by using CRYSTALS[18] adapted to a Microvax-II computer. Scattering factors and corrections for anomalous dispersion were from ref 19. The structure was resolved by direct methods (SHELX86[20]) and refined by least squares with anisotropic thermal parameters for all non-hydrogen atoms except the methoxy carbon C(7). The relatively large thermal parameters values for the methoxy atoms (O(2) and C(7)) are probably due to some disorder; however attempts to solve this disorder were unsuccessful. Hydrogen atoms were introduced as fixed contributors in theoretical positions (with $U(\mathrm{iso}) = 1.2U(\mathrm{eq})$ of the related carbon atom) and their coordinates recalculated after each refinement cycle. The structure was refined to $R = 0.071$ and $R_w = 0.072$ with the use of 1871 reflections for 268 least squares parameters.

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(18) Watkin, D. J.; Carruthers, J. R.; Betteridge, P. W. CRYSTALS User Guide, Chemical Crystallography Laboratory, University of Oxford, Oxford, England, 1986.

(19) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.

(20) Sheldrick, G. M. SHELXS86, Program for Crystal Structure Solution. University of Göttinge, 1986.

Table 7. Selected Bond Angles (deg) for $C_{26}H_{35}O_2NFe$ (6)

Molecule 1			
C(7″)–O(2)–C(4″)	118.5(7)	C(7′)–N(1)–C(6′)	111.5(6)
C(8′)–N(1)–C(6′)	110.2(6)	C(8′)–N(1)–C(7′)	109.7(6)
C(3)–C(2)–C(1)	114.6(6)	C(2)–C(3)–O(1)	109.5(6)
C(4)–C(3)–O(1)	107.8(6)	C(4)–C(3)–C(2)	108.8(6)
C(1′)–C(3)–O(1)	112.0(6)	C(1′)–C(3)–C(2)	105.5(6)
C(1′)–C(3)–C(4)	113.1(6)	C(5)–C(4)–C(3)	110.8(6)
C(1″)–C(4)–C(3)	115.2(6)	C(1″)–C(4)–C(5)	109.7(6)
C(6)–C(5)–C(4)	112.4(8)	C(2′)–C(1′)–C(3)	127.4(6)
C(5′)–C(1′)–C(3)	124.3(7)	C(5′)–C(1′)–C(2′)	106.0(6)
C(3′)–C(2′)–C(1′)	107.4(6)	C(6′)–C(2′)–C(1′)	128.7(7)
C(6′)–C(2′)–C(3′)	123.9(7)	C(4′)–C(3′)–C(2′)	109.6(7)
C(5′)–C(4′)–C(3′)	106.8(7)	C(4′)–C(5′)–C(1′)	110.0(7)
C(2′)–C(6′)–N(1)	112.8(6)	C(13′)–C(9′)–C(10′)	108.7(8)
C(11′)–C(10′)–C(9′)	108.2(7)	C(12′)–C(11′)–C(10′)	106.2(8)
C(13′)–C(12′)–C(11′)	109.4(8)	C(12′)–C(13′)–C(9′)	107.5(7)
C(2″)–C(1″)–C(4)	122.1(7)	C(6″)–C(1″)–C(4)	120.7(7)
C(6″)–C(1″)–C(2″)	117.0(7)	C(3″)–C(2″)–C(1″)	123.0(7)
C(4″)–C(3″)–C(2″)	117.6(8)	C(3″)–C(4″)–O(2)	122.6(8)
C(5″)–C(4″)–O(2)	116.1(8)	C(5″)–C(4″)–C(3″)	121.2(8)
C(6″)–C(5″)–C(4″)	120.0(8)	C(5″)–C(6″)–C(1″)	121.1(8)
Molecule 2			
C(27″)–O(22)–C(24″)	117.8(6)	C(27′)–N(21)–C(26′)	111.5(6)
C(28′)–N(21)–C(26′)	108.1(7)	C(28′)–N(21)–C(27′)	112.2(7)
C(23)–C(22)–C(21)	114.8(7)	C(22)–C(23)–O(21)	104.2(5)
C(24)–C(23)–O(21)	110.5(5)	C(24)–C(23)–O(22)	111.7(5)
C(21′)–C(23)–O(21)	110.1(5)	C(21′)–C(23)–C(22)	108.5(5)
C(21′)–C(23)–O(24)	111.7(5)	C(25)–C(24)–C(23)	111.5(6)
C(21″)–C(24)–C(23)	115.3(5)	C(21″)–C(24)–C(25)	109.8(5)
C(26)–C(25)–C(24)	112.8(7)	C(22′)–C(21′)–C(23)	125.2(6)
C(25′)–C(21′)–C(23)	127.0(6)	C(25′)–C(21′)–C(22′)	107.2(6)
C(23′)–C(22′)–C(21′)	106.2(6)	C(26′)–C(22′)–C(21′)	130.3(6)
C(26′)–C(22′)–C(23′)	123.4(6)	C(24′)–C(23′)–C(22′)	109.7(6)
C(25′)–C(24′)–C(23′)	107.3(6)	C(24′)–C(25′)–C(21′)	109.6(6)
C(22′)–C(26′)–N(21)	113.7(7)	C(33′)–C(29′)–C(30′)	107.6(8)
C(31′)–C(30′)–C(29′)	107.2(9)	C(32′)–C(31′)–C(30′)	108.7(9)
C(33′)–C(32′)–C(31′)	108.1(9)	C(32′)–C(33′)–C(29′)	108.4(9)
C(22″)–C(21″)–C(24)	122.4(6)	C(26″)–C(21″)–C(24)	120.1(6)
C(26″)–C(21″)–C(22″)	117.1(6)	C(23″)–C(22″)–C(21″)	120.8(7)
C(24″)–C(23″)–C(22″)	120.6(6)	C(23″)–C(24″)–O(22)	116.2(6)
C(25″)–C(24″)–O(22)	124.1(6)	C(25″)–C(24″)–C(23″)	119.7(6)
C(26″)–C(25″)–C(24″)	118.7(7)	C(25″)–C(26″)–C(21″)	122.7(7)

X-ray Study of 6(a+b). The same procedure as for **5(a+b)** was applied. This compound crystallizes in the monoclinic space group $P2_1/a$ with $Z = 8$ and cell dimensions $a = 7.998(2)$ Å, $b = 56.436(11)$ Å, $c = 10.369(2)$ Å, $\beta = 96.10(2)°$, $V = 4658(8)$ Å^3. Complete crystal data and crystal data parameters are listed in Tables 3 and 4. Here, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from a difference Fourier map. Their coordinates were refined with an overall variable isotropic thermal parameter. The structure was refined to $R = 0.061$ and $R_w = 0.067$ with the use of 4819 reflections for 754 least squares parameters.

General Synthetic Considerations. All IR samples were neat film or KBr pellets, and the NMR solvent was $CDCl_3$. ^1H NMR data are presented as follows: chemical shift on the δ scale, relative to TMS (multiplicity, number of protons, coupling constants in hertz). ^{13}C NMR data are presented as follows: chemical shift on the δ scale, relative to solvent as 77.0 ppm. NMR spectra were acquired on a Bruker AM 250 spectrometer, and IR spectra were recorded on a Specord M-82 spectrometer. Mass spectra were obtained on a Nermag R 10-G spectrometer. The adsorbent used for column chromatography was silica gel 60 GF_{254}. Tetrahydrofuran and ether were dried over sodium–benzophenone before use.

2-(4-Methoxyphenyl)butyronitrile, 1. (4-Methoxyphenyl)-acetonitrile (Janssen, 2.95 g, 0.02 mol) was stirred under argon at –50 °C in 20 mL of anhydrous THF. Next, 8 mL of butyllithium (2.5 M, Janssen, 0.02 mol in hexane solution) was added dropwise, followed by 3.22 g (0.02 mol) of 1,1,1,3,3,3-hexamethyldisilazane (Aldrich) diluted in 10 mL of ether. The solution turned yellow and then green, and after 1.5 h it became deep dark red. Iodoethane (4.0 g, 0.025 mol) was then added, and the mixture was allowed to warm to room temperature. After hydrolysis with water (100 mL), the solution was extracted with ether (3 × 30 mL), washed with water (40 mL), dried ($MgSO_4$), and evaporated to give 5.2 g of a crude oil. The substituted nitrile was separated from the unreacted nitrile by flash chromatography on silica gel (1:4 ether/pentane). The head fraction containing **1** was crystallized from pentane to give 2.33 g of white crystals (66.4% yield). ^1H NMR: δ 1.03 (t, 3, J = 7.5), 1.86 (m, 2), 3.65 (t, 1, J = 7.5), 3.74 (s, 3), 6.85 (d, 2, J = 9.2), 7.20 (d, 2, J = 9.2).

4-(4-Methoxyphenyl)hexan-3-one, 2. **1** (4.0 g, 0.023 mol) in 15 mL of anhydrous ether was added under argon to a stirred solution of ethylmagnesium bromide (0.55 mol). The mixture was then refluxed for 18 h. After addition of a solution of NH_4Cl, the mixture was hydrolyzed by a 15% solution of HCl, refluxed a further 18 h, then extracted with ether, and purified by flash chromatography (first with pentane and then pentane mixed with 10% of ether). The overall yield was 3.08 g of **2** (0.015 mol,

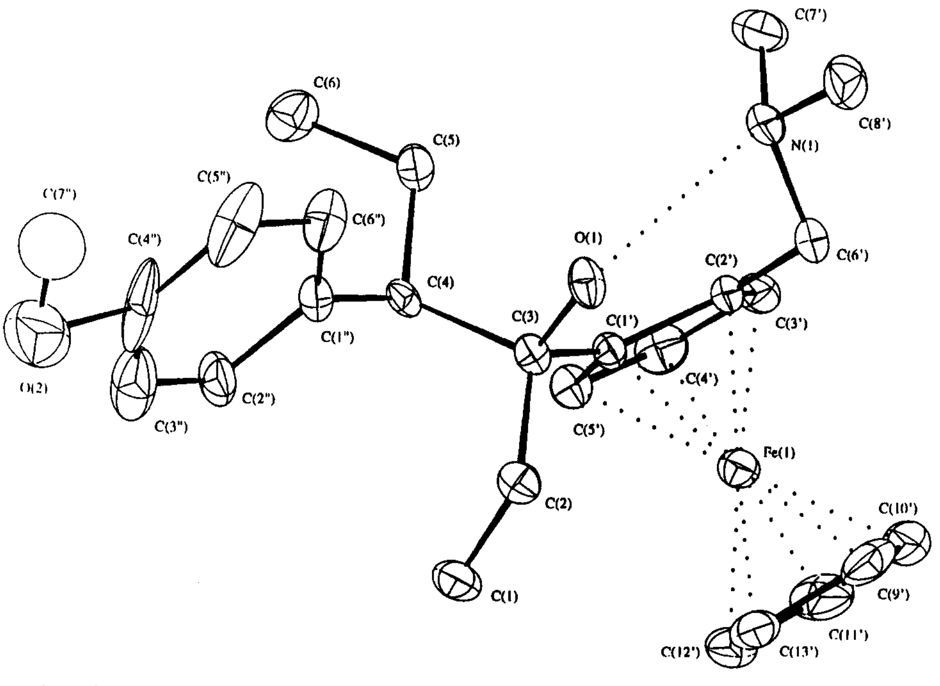

Figure 3. ORTEP plot of **5a**.

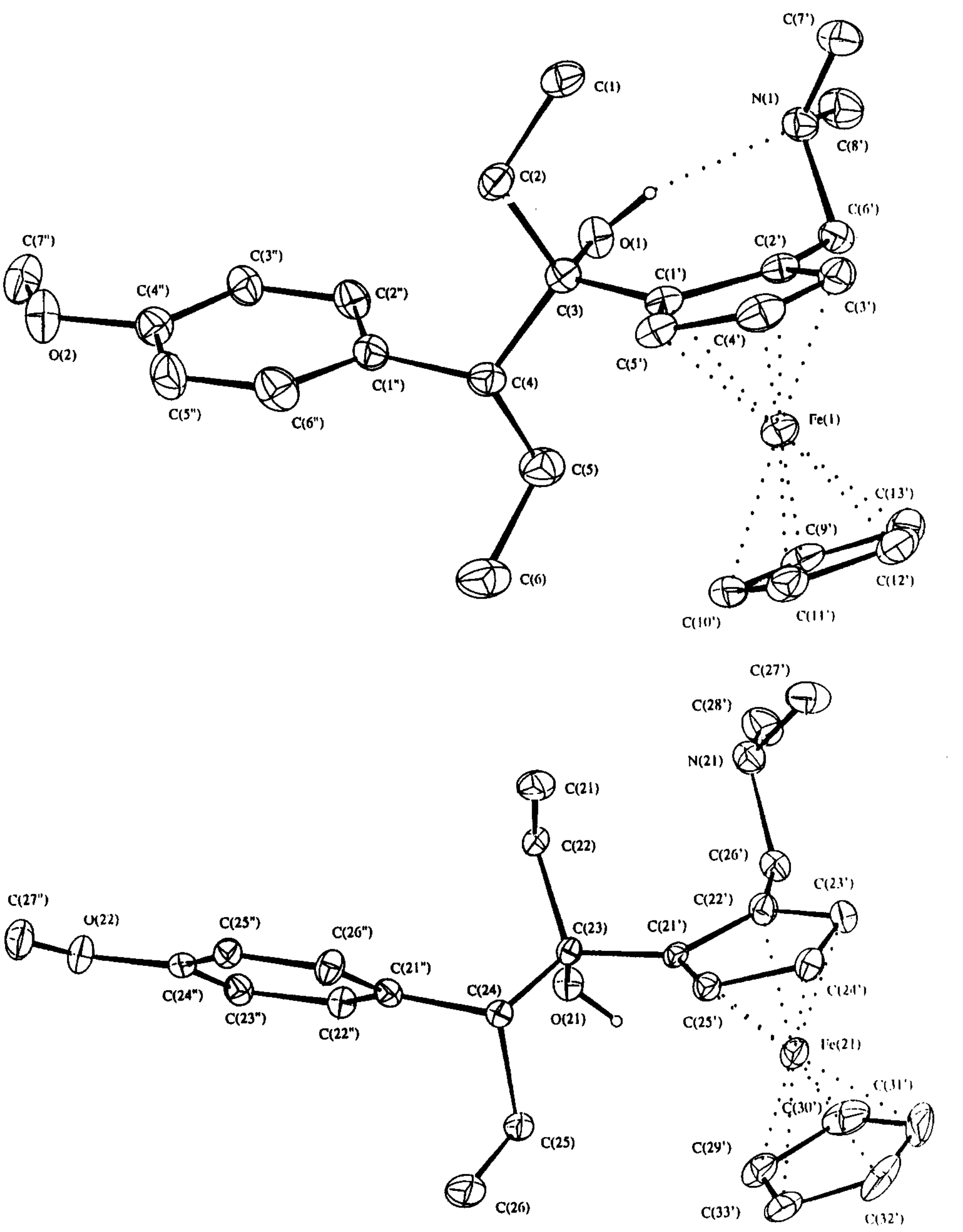

Figure 4. (a, top) ORTEP plot of **6b** showing molecule 1. (b, bottom) ORTEP plot of **6b** showing molecule 2.

65%). ^{1}H NMR: δ 0.81 (t, 3, *J* = 7.4), 0.95 (t, 3, *J* = 7.3), 1.59–1.76 (m, 2), 1.94–2.09 (m, 1), 2.24–2.48 (m, 2), 3.48 (t, 3, *J* = 7.4), 3.77 (s, 1), 6.85 (d, 2, *J* = 8.7), 7.12 (d, 2, *J* = 8.7).

***rac*-3-(2-((*N*,*N*-Dimethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexan-3-ol, 5(a+b) and 6(a+b).** To 1.2 g (5.0 mmol) of ((*N*,*N*-dimethylamino)methyl)ferrocene (Strem) in anhydrous ether under argon at room temperature was added 7 mL (7 mmol) of butyllithium (1 M solution in ether). After 40 min, 1.4 g (6.8 mmol) of **2** in 15 mL of ether was added at −50 °C and the mixture allowed to reach room temperature and stirred overnight. The solution was hydrolyzed and neutralized (Na$_2$CO$_3$), and the ethereal layer, after being dried (MgSO$_4$), was then evaporated. The crude oil was then purified by TLC on silica (the plates had to be eluted first with 1:8 Et$_3$N/hexane and dried to prevent the formation of tails). The two diastereoisomers (0.70 g; 31%) isolated were obtained as oils, yielding 0.30 g for the more polar isomer **5** and 0.40 g of the less polar isomer **6**. After some days the products **5** and **6** crystallize spontaneously.

(p*R,3*R**,4*S**)-5(a+b).** ^{1}H NMR: δ 0.48 (t, 3, *J* = 7.3), 1.12 (m, 1), 1.15 (t, 3, *J* = 7.3), 1.4 (m, 1), 1.75 (m, 1), 2.13 (m, 1), 2.20 (s, 6), 2.45 (dd, 1), 2.50 (d, 1, *J* = 12.1), 3.77 (s, 3), 3.93 (dd, 1, *J* = 2.4, *J* = 1.4), 3.96 (d, 1, *J* = 12.0), 3.99 (dd, 1, *J* = 2.4, *J* = 1.4), 4.09 (t, 1, *J* = 2.4), 4.12 (s, 5), 6.76 (d, 2, *J* = 8.7), 7.15 (d, 2, *J* = 8.7). ^{13}C NMR: δ 8.7, 12.8, 23.8, 36, 44.2, 55.7, 57.5, 60, 66, 68, 69, 69.4, 70, 82, 99, 112.8, 131, 134, 158. Mp: 98 °C. MS (DCI, NH$_3$): *m*/*e* 450 (MH$^+$). Anal. Calcd for C$_{26}$H$_{35}$O$_2$NFe: C, 69.48; H, 7.85; N, 3.11. Found: C, 69.56; H, 7.89; N, 3.19.

(p*R,3*S**,4*R**)-6(a+b).** ^{1}H NMR: δ 0.36 (t, 3, *J* = 7.3), 0.78 (t, 3, *J* = 7.3), 1.32 (m, 2), 1.95 (m, 1), 2.17 (s, 6), 2.71 (d, 1, *J* = 12.4), 2.77 (dd, 1), 3.67 (d, 1, *J* = 12.3), 3.80 (s, 3), 3.90 (t, 1, *J* = 2.4), 4.10 (dd, 1, *J* = 2.4, *J* = 1.4), 4.15 (dd, 1, *J* = 2.4, *J* = 1.4), 4.17 (s, 5), 6.63 (d, 2, *J* = 8.3), 7.26 (d, 2, *J* = 8.4). ^{13}C NMR: δ 8.3, 12.8, 24, 37, 44.6, 55, 57, 59.2, 60.3, 65, 68.4, 69.4, 70.5, 82, 99, 113, 130, 135, 158. Mp: 87 °C. MS (DCI, NH$_3$): *m*/*e* 450 (MH$^+$). Anal. Calcd for C$_{26}$H$_{35}$O$_2$NFe: C, 69.48; H, 7.85; N, 3.11. Found: C, 69.53; H, 7.98; N, 2.97.

Preparation of Optically Active 3-(2-((*N*,*N*-Dimethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexan-3-ols, 5 and 6. (1) (p*S*)-bis(μ-Chloro)bis(2-((*N*,*N*-Dimethylamino)methyl)ferrocenyl-*N*)dipalladium, 3. Optically pure *N*-acetyl-D-leucine (3.46 g, 0.02 mol) was dissolved in a solution of sodium hydroxide (0.8 g in 100 mL of water; 0.02 mol), and the solution was mixed with a solution of 5.88 g (0.02 mol) of sodium tetrachloropalladate in 300 mL of methanol. The mixture was stirred and pH adjusted to 7.8–8.0 by the dropwise addition of aqueous sodium hydroxide (50%). Then 4.86 g (0.02 mol) of

((*N*,*N*-dimethylamino)methyl)ferrocene in 100 mL of methanol was added and the mixture was allowed to stand overnight. Methanol was partly removed and water added to obtain crude **3** as a precipitate, which was filtered and dried in vacuo. This solid was dissolved in benzene and heptane added. The solution was concentrated in vacuo, and 3.7 g (48%) of (p*S*)-**3** as a red orange solid was recovered after filtration. $[\alpha]_D$ = −447° (*c* = 0.53; CH_2Cl_2, ee 68%). The other enantiomer, (p*R*)-**3**, was prepared in the same way using *N*-acetyl-L-leucine as the chiral inductor. $[\alpha]_D$ = +400° (*c* = 0.52; CH_2Cl_2, ee 60%).

(2) (p*S*)- and (p*R*)-1-((*N*,*N*-Dimethylamino)methyl)-2-iodoferrocene, 4. (p*S*)-**3** or (p*R*)-**3** (3.7 g, 4.8 mmol) dissolved in CH_2Cl_2 was added to a solution of 500 mL of CH_2Cl_2 containing 10 g (79 mmol) of iodine. The mixture was stirred for 2 h at room temperature. Afterward the solution was filtered and washed with aqueous $Na_2S_2O_3$. Removal of the solvent yielded an oil which was purified by chromatography: first eluted by hexane, then by a mixture of triethylamine/hexane (1:5) (*m* = 1.74 g; 4.7 mmol; 55% yield).

(3) Reaction of the Optically Active Lithiated Ferrocene Compound with Ketone 2. (a) To 1.4 g (3.8 mmol) of (p*S*)-**4a** in anhydrous ether under argon was added 8 mL (0.55 mmol) of butyllithium in hexane at −70 °C. After 0.5 h, 0.52 g (2.53 mmol) of **2** diluted in ether was added and the mixture was stirred overnight at room temperature. The solution was hydrolyzed and neutralized (Na_2CO_3), and the ethereal layer, after being dried ($MgSO_4$), was evaporated. The crude oil was then purified on a silica column. The two diastereoisomers (0.47 g, 46%) are isolated in a 1:1 ratio as an oil. (p*S*,3*S*,4*R*)-**5a**: $[\alpha]_D$ = −36.4° (*c* = 2.64 in ethanol). (p*S*,3*R*,4*S*)-**6a**: $[\alpha]_D$ = −35.4° (*c* = 2.60 in ethanol).

(b) From 1.84 g (5.0 mmol) of (p*R*)-**4b** and 1.4 g (6.8 mmol) of ketone **2** was obtained 0.48 g (20%) of a mixture of the diastereoisomers, leading after chromatographic separation to 0.37 g of the more polar isomer **5b** and 0.10 g of the less polar isomer **6b**. (p*R*,3*R*,4*S*)-**5b**: $[\alpha]_D$ = +39.7° (*c* = 2.9 in ethanol). (p*R*,3*S*,4*R*)-**6b**: $[\alpha]_D$ = +36.4° (*c* = 3.18 in ethanol).

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Supplementary Material Available: Tables of bond angles, interatomic distances, and anisotropic thermal parameters (7 pages). Ordering information is given on any current masthead page.

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