Ionic Hydrogenation of Chiral (α-Hydroxyalkyl)ferrocenes: Different Stereochemistry for Their Diastereomeric 2-((*N*,*N*-Dimethylamino)methyl) Derivatives. X-ray Determination of the Relative Configurations of Reduced Products

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Received December 7, 1993[⊗]

This paper describes the ionic hydrogenation of (p*R**,3*R**,4*S**)- and (p*R**,3*S**,4*R**)-3-(2-((*N*,*N*-dimethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexan-3-ols (**1** and **2**, respectively, in racemic and optically active series). These compounds are the keys in the synthesis of ferrocene derivatives possessing potentially hormonal properties. In this reaction, trifluoroacetic acid was used as the protonating reagent and sodium borohydride as the reducing agent. In each case, the reduction leads exclusively to the formation of only one compound. We observe for **1** a selective attack of the hydride on the same side as the leaving group and on the opposite side for **2**, leading to reduced products **3** and **4** as (p*S**,3*S**,4*R**)- and (p*S**,3*S**,4*S**)-3-(2-((*N*,*N*-dimethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexane, respectively. The relative configurations of **3** and **4** were unambiguously determined by X-ray diffraction analysis of the methylammonium iodides **7** and **8** derived from **3** and **4** (through the corresponding phenols **5** and **6**). **7** crystallizes in the monoclinic $P2_1$ space group with half of a molecule of methanol and one-fourth of a molecule of acetone (a = 7.350(1) Å, b = 27.721(7) Å, c = 14.161(2) Å, β = 97.42(1)°, and V = 2861(5) Å^3) with Z = 4. **8** crystallizes in the monoclinic $P2_1/a$ space group with one hydrogen-bonded molecule of water (a = 10.180(2) Å, b = 15.429(2) Å, c = 17.517(3) Å, β = 104.53(1)°, and V = 2663(9) Å^3) with Z = 4.

Introduction

Our target molecules designed to structurally mimic hexestrol possess three elements of chirality (Figure 1).

In order to obtain the correct relative configuration as that of *meso*-hexestrol, it is necessary to control the relative configurations of C(3) and C(4). We have prepared the starting tertiary alcohols **1** and **2** using a chiral lithiated ferrocene reagent.[1] The relative configurations of **1** and **2** were determined by X-ray analysis of the racemic materials.[1] It can be seen that formally replacing the hydroxyl function by a hydrogen atom gives the expected relative configuration for C(3) and C(4) compared to hexestrol (Figure 2). With **1** and **2** as the starting materials in racemic and optically active series, the target is to maintain the stereochemistry of C(3) through the reduction. Ionic hydrogenation is a useful means to reach this end.

Ionic hydrogenation of tertiary alcohols using silanes, under acidic conditions, has been previously described for both ferrocene and cymantrene derivatives.[2] In all cases, reduction occurs with high yields, without elimination. Similar procedures, derived from the Kur-

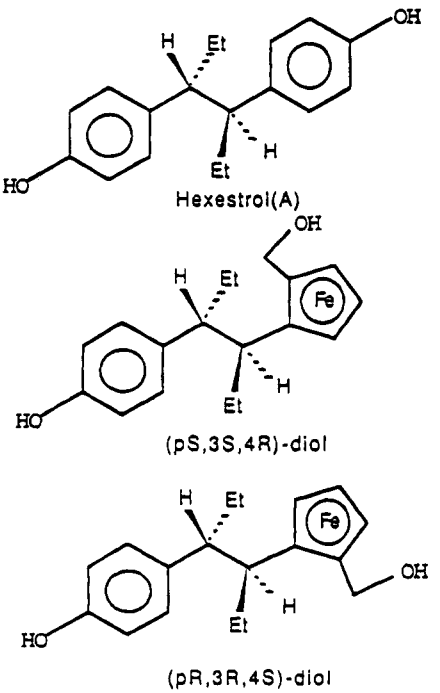

Figure 1.

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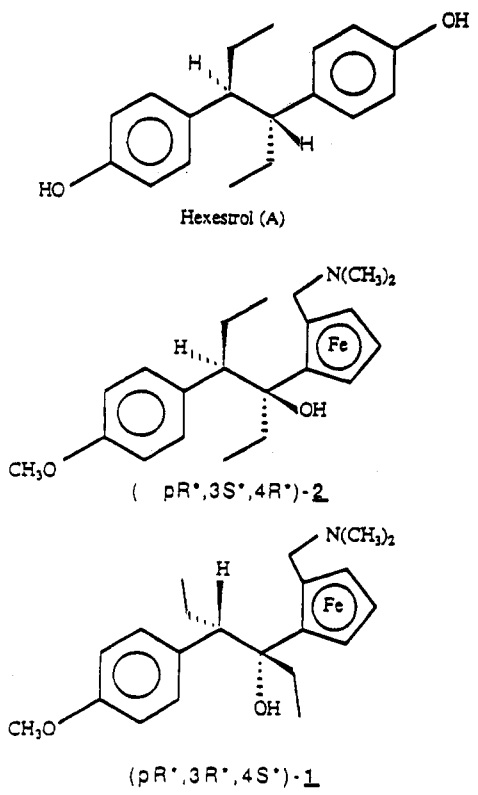

Figure 2.

sanov–Parnes reaction, employed $NaBH_4$ as hydride donor[3] and $AlCl_3$ as Lewis acid.[4] Recently Nicholas and Siegel described an application of ionic hydrogenation using the heterogenous system $NaBH_4$/TFA in the case of propargylic alcohols complexed by $[Co_2(CO)_6]$.[5]

Davies and Donohoe[6] have reviewed the stereochemical problems in ionic hydrogenation or nucleophilic substitution of chiral chromium tricarbonyl benzylic alcohols. These authors noticed that, due to the stabilization of a chiral carbenium center by the metallic atom, the stereochemical course of the reaction generally evolves through a double-inversion mechanism, resulting in an apparent retention of configuration (Figure 3). In the ferrocenyl series, the stereochemistry of nucleophilic substitutions via a carbenium ion has been widely studied by Ugi[7] and othor authors.[8] They found that all these reactions occur with total retention of configuration.

Nevertheless, some examples indicate that this rule is not a general feature. These exceptions primarily concern fused rigid systems (wherein the geometric constraints are serious), such as $Cr(CO)_3$ tetralol or indanol complexes in which hydroxyl groups are fixed as exo or endo with regard to the chromium tricarbonyl moiety. It was reported that for nucleophilic substitution including ionic hydrogenation there is retention of configuration for the exo diastereomer and inversion for the endo diastereomer[9] (Figure 4). In this series of complexes, the difference in stereoselectivity obtained results from the opposite ionization mechanisms (exo or endo), whereas the nucleophilic attack on the carbenium ion proceeds exclusively from the exo side. For ortho-substituted aromatic complexes, the stereochemistry of nucleophilic substitution can be related to the ratio of the two diastereomeric cations resulting in a diastereoselectivity during the nucleophilic attack step, if one of them is predominant.[9]

Diastereoselectivity can also be observed in the carbocationic systems which are known to be fluxional[10] and consequently may lose their initial chiral character. For example, Nicholas and Siegel[5] found that reduction followed by demetalation of either 17α- or 17β-ethynylestradiol–$[Co_2(CO)_6]$ leads to the same β-ethynyl product with high selectivity (>90% one epimer). This result can be ascribed to steric and torsional factors occuring in an "earlier transition state."[11] We have observed the same stereochemistry in the reduction of the carbenium ion derived from 17β-ethynylestradiol–$[Mo_2Cp_2(CO)_4]$, in which the metallic complex entity is isolobal with those studied by Nicholas and Siegel.[12]

The behavior of 17α-ferrocenylestradiol is surprising; it is reduced by $NaBH_4$/TFA with predominant inversion of configuration, leading to the corresponding 17β-ferrocenyl derivative.[13] This is very different from the stereochemical course for simple ferrocenyl alcohols or their esters (acetate, mesylate, ...), for which total retention of configuration was reported.[7,8] These results demonstrate that the stereochemical course of the reaction is not only dependent on the stabilizing properties of the metal but also on the nature of the substituents around the carbenium ion center. The amino alcohols presented, **1** and **2**, fall in the class of ortho-substituted aromatic ring systems. The stereochemical course of the ionic hydrogenation of **1** and **2** was defined by X-ray structures of the reduced products, as the ammonium iodide salts **7** and **8** (after deprotection of the methoxy group), as described below.

Results and Discussion

Our attempts to reduce the amino alcohols **1** and **2**, synthesized previously[1] by the Kursanov–Parnes reaction, were unsuccessful and invariably led to the formation of a mixture of tertiary and quaternary olefins. The formation of olefins revealed that a carbenium ion was formed first, followed by an elimination reaction instead of nucleophilic substitution by the hydride carried by triethylsilane. It is reasonable to explain this behavior by the hydride donor character of the reducing reagent; we then chose to employ a stronger one. Conversely, using $NaBH_4$ as hydride donor produces **3** and **4** with rather limited elimination (Scheme 1). The asterisks

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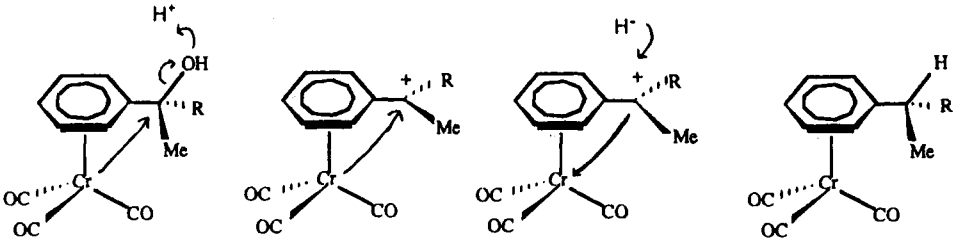


Figure 3.

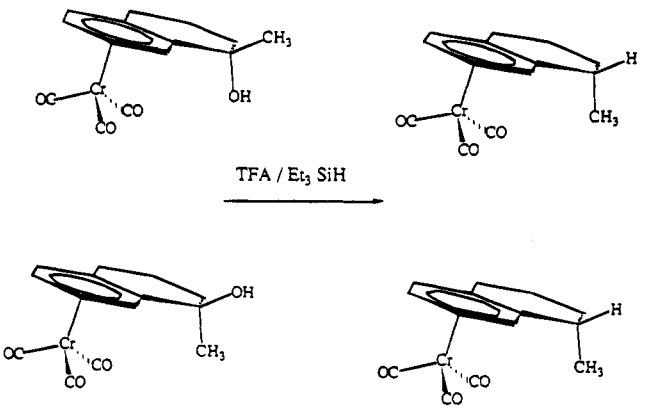
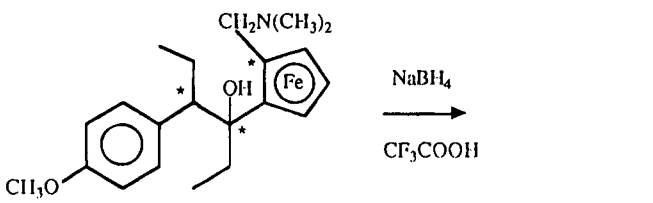
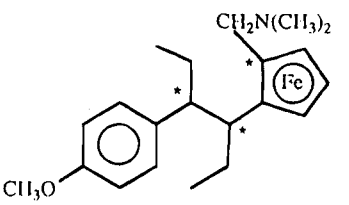


Figure 4.

Scheme 1



(pR*, 3R*,4S*) - 1
(pR*, 3S*,4R*) - 2



(pS*, 3S*,4R*) - 3
(pS*, 3S*,4S*) - 4

denote the relative configurations. The symbols p*R* and p*S* represent the configurations of the plane of chirality according to Ugi's notation in the case of disubstituted ferrocene compounds.[7]

Relative configurations of (p*S**,3*S**,4*R**)- and (p*S**,3*S**,4*S**)-3-(2-((*N*,*N*-diethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexane (**3** and **4**, respectively) were determined by X-ray diffraction analysis on the methylammonium iodide derivatives **7** and **8**, respectively, obtained from **5** and **6** by the action of an excess of iodomethane in acetone (compounds **5** and **6** are the corresponding phenols of **3** and **4**). The stereochemical course of the reaction is different for each diastereomer: **1** gives **3** retaining the configuration of C(3), while **2** leads to **4** with inversion of this configuration.

This dramatic change in stereoselectivity is accompanied by a great difference in the reactivity. After 15 min of reaction, we obtain **4** in 72% yield and **3** in 20% yield. In each case, unreacted starting material can be recovered. It is possible to increase the yield of **3** to 70% using consecutive repeated cycles of additions of sodium borohydride and trifluoroacetic acid. To explain the reactivity of each diastereomer **1** and **2**, we must examine their conformations in solution. We have recently demonstrated by IR studies (in solution and the solid state) and confirmed by X-ray diffraction that **1** exists as a single conformer, whereas **2** exists as an equilibrium mixture of two different conformers.[1] **1** exhibits a strong hydrogen bond between the hydroxyl and amino groups, while **2** presents two different types of H-bonds involving hydroxyl and amino groups as in **1** (conformer **2a**) or the hydroxyl group and iron atom (conformer **2b**). The existence of this "metallic" type of hydrogen bond was described in detail by Epstein.[14]

The formation of the H-bond between hydroxyl and amino groups (conformer **2a**) introduces a steric constraint involving the ferrocenyl entity and the ethyl and phenyl substituents of C(3). Thus, even if this H-bond is geometrically and energetically favored, another conformation exists which involves a weaker H-bond between the iron atom and the hydroxyl group (conformer **2b**). In this second case, the steric relief caused by the trans orientation of the aromatic rings counterbalances the loss of energy associated with the change in the type of intramolecular bonds.

The ability of compound **2** to exist in two well-defined conformations could explain the difference of reactivity from **1** toward ionic hydrogenation. The protonation step is certainly disfavored for both conformers **1a** and **2a** because of the strength of their intramolecular hydrogen bond ($R(CH_3)_2N\cdots HOR'$). However, diastereomer **2** can be protonated more readily because of conformer **2b**, which exhibits a weaker H-bond involving the iron atom. For **1a**, the ionization step following the elimination of H_2O can be assisted by the iron atom, leading directly to the less sterically hindered carbenium ion C_1^+. In the case of compound **2**, the less hindered cation C_2^+ can be obtained in two different ways. The first one (A), in which the assistance of iron is possible, leads to the most hindered cation evolving to C_2^+ by a rotation around the C1−C3 bond. In the second (B), the leaving group departs from the same face as that occupied by the metallic entity, giving C_2^+ directly (Figure 5). Further attack of the hydride taking place on the exo face (with respect to the iron atom) leads to the reduced products (p*S**,3*S**,4*R**)-**3** and (p*S**,3*S**,4*S*)-**4**, respectively.

Structure and Physicochemical Properties of the Corresponding Quaternary Ammonium Iodide Derivatives 7 and 8. It was not possible to obtain crystals directly of **3** and **4**, but it was easier to prepare the quaternary ammonium iodide derivatives **7** and **8** from the corresponding phenol compounds **5** and **6** by

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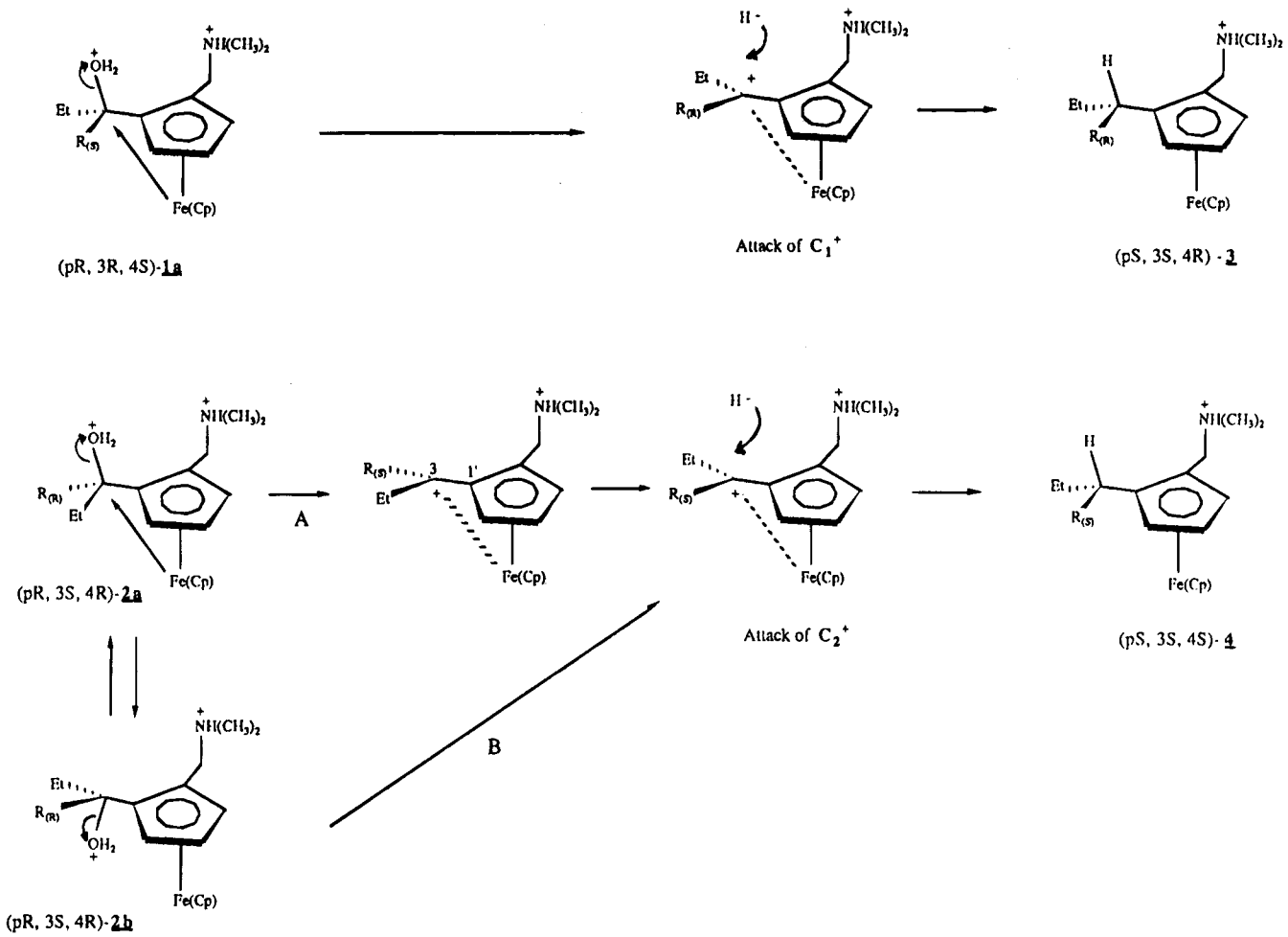

Figure 5.

addition of an excess of iodomethane to solutions of **5** or **6** in acetone. The solid pale yellow microcrystals obtained were recrystallized in acetone to which small amounts of 95% methanol were added. Structural analyses have been carried out by X-ray diffraction studies on the racemic compounds.

For (p*S**,3*S**,4*R**)-**7**, the asymmetric unit consists of two molecular units (1 and 2, see Table 2) accompanied by one molecule of methanol and approximately half a molecule of acetone. Crystallographic data, fractional parameters, and the main interatomic distances and bond angles are given in Tables 1–4. An ORTEP view of one of the molecules contained in the crystal unit is presented in Figure 6. The main features of this structure are the opposite position of the ammonium group and iron atom compared to that of the cyclopentadienyl ligand and the trans disposition of ethyl groups on C(3) and C(4).

(p*S**,3*S**,4*S**)-**8** crystallizes with one molecule of water. A hydrogen bond exists between the molecule of water and the phenolic group ($d_{O(1)-O(2)}$ = 2.71 Å). Crystallographic data, fractional parameters, and selected bonds and angles are given in Tables 5–7. An ORTEP view of the molecule is presented in Figure 7; the main feature of this structure is the relative trans disposition of the hydrogen atoms in C(3) and C(4) as observed in compound **7**. This situation leads to the cis disposition of the aromatic entity and the η^5-Cp moiety. Thisgeometry constrains the plane of the arene to be perpendicular to that of the π-bonded Cp unit.

Table 1. Crystallographic Data for 7

chem formula	$C_{26}H_{36}ONFeI{\cdot}0.5CH_3OH{\cdot}0.25OC_3H_6$
fw	591.8
cryst syst	monoclinic
space group	$P2_1$
Z	4
a, Å	7.350(1)
b, Å	27.721(7)
c, Å	14.161(2)
β, deg	97.42(1)
V, Å^3	2861(5)
F(000)	1212
ϱ(calcd), g cm^{-3}	1.37
μ(Mo Kα), cm^{-1}	16.1
diffractometer	CAD4
monochromator	graphite
radiation	Mo Kα (λ = 0.710 70 Å)
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 rflns collected	5127
no. of rflns used (criteria)	3954 ($I > 3\sigma(I)$)
R	0.044
R_w[a]	0.052
abs cor[b]	min 0.81, max 1.34
secondary extinctn cor	11×10^{-6}
weighting scheme	unit weights
rms (shift/esd) (last ref)	0.68
least-squares params	567

[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.

Conclusion

This work is the first example, in a ferrocenyl acyclic series, of inversion of configuration in ionic hydrogena-

Table 2. Fractional Parameters for $C_{26}H_{36}FeI{\cdot}0.5SCH_3OH{\cdot}0.25OC_3H_6$ (7)

atom	x/a	y/b	z/c	U(eq) (U(iso)),[a] Å²
		Molecule 1		
I(1)	0.7181(1)	0.17478(5)	0.41416(7)	0.0658
Fe(1)	0.0324(2)	0.02028(7)	0.7327(1)	0.0428
O(1)	−0.298(2)	0.3584(4)	0.7065(9)	0.0942
N(1)	0.208(2)	0.0738(5)	0.462(1)	0.0703
C(1)	−0.250(2)	0.1283(6)	0.801(1)	0.0629
C(2)	−0.215(2)	0.1335(5)	0.700(1)	0.0517
C(3)	−0.010(2)	0.1379(4)	0.6839(9)	0.0396
C(4)	0.088(1)	0.1815(5)	0.7400(8)	0.0428
C(5)	0.278(2)	0.1885(5)	0.710(1)	0.0586
C(6)	0.390(2)	0.2264(6)	0.768(1)	0.0731
C(1′)	0.100(1)	0.0915(4)	0.7019(9)	0.0393
C(2′)	0.152(2)	0.0586(5)	0.6342(9)	0.0444
C(3′)	0.274(2)	0.0236(4)	0.682(1)	0.0454
C(4′)	0.296(2)	0.0364(5)	0.780(1)	0.0489
C(5′)	0.188(2)	0.0754(4)	0.7904(9)	0.0448
C(6′)	0.078(2)	0.0547(5)	0.530(1)	0.0595
C(7′)	0.106(3)	0.0703(9)	0.362(1)	0.1065
C(8′)	0.383(3)	0.0466(7)	0.473(1)	0.0847
C(9′)	0.250(2)	0.1249(6)	0.483(1)	0.0697
C(10′)	−0.240(2)	0.0101(5)	0.745(1)	0.0619
C(11′)	−0.134(2)	−0.0046(5)	0.827(1)	0.0605
C(12′)	−0.010(2)	−0.0409(5)	0.803(1)	0.0573
C(13′)	−0.042(2)	−0.0489(5)	0.707(1)	0.0602
C(14′)	−0.190(2)	−0.0163(6)	0.668(1)	0.0670
C(1″)	−0.020(2)	0.2267(4)	0.7278(9)	0.0449
C(2″)	−0.079(2)	0.2474(5)	0.6419(9)	0.0475
C(3″)	−0.172(2)	0.2903(5)	0.632(1)	0.0586
C(4″)	−0.205(2)	0.3150(5)	0.711(1)	0.0671
C(5″)	−0.148(2)	0.2967(5)	0.800(1)	0.0668
C(6″)	−0.054(2)	0.2541(5)	0.808(1)	0.0562
		Molecule 2		
I(21)	0.3523(2)	−0.09576(5)	0.52491(9)	0.0876
Fe(21)	0.4306(2)	0.34385(7)	0.1192(1)	0.0439
O(21)	0.740(2)	0.0049(5)	0.093(1)	0.1004
N(21)	0.245(1)	0.2838(4)	0.3800(8)	0.0557
C(21)	0.695(2)	0.2376(6)	0.026(1)	0.0611
C(22)	0.666(2)	0.2286(5)	0.1306(9)	0.0518
C(23)	0.465(2)	0.2251(4)	0.1478(8)	0.0405
C(24)	0.361(2)	0.1839(5)	0.0889(8)	0.0475
C(25)	0.172(2)	0.1746(5)	0.122(1)	0.0577
C(26)	0.052(2)	0.1393(6)	0.059(1)	0.0746
C(21′)	0.360(2)	0.2731(4)	0.1353(9)	0.0422
C(22′)	0.307(2)	0.3026(4)	0.2099(9)	0.0417
C(23′)	0.185(2)	0.3391(5)	0.1672(9)	0.0500
C(24′)	0.166(2)	0.3317(5)	0.067(1)	0.0529
C(25′)	0.268(2)	0.2914(5)	0.048(1)	0.0485
C(26′)	0.380(2)	0.2997(4)	0.311(1)	0.0463
C(27′)	0.102(2)	0.3195(7)	0.384(1)	0.0797
C(28′)	0.346(2)	0.2792(6)	0.475(1)	0.0765
C(29′)	0.168(2)	0.2369(7)	0.346(1)	0.0755
C(30′)	0.700(2)	0.3543(6)	0.109(1)	0.0663
C(31′)	0.660(2)	0.3750(6)	0.192(1)	0.0629
C(32′)	0.526(2)	0.4084(6)	0.171(1)	0.0661
C(33′)	0.484(2)	0.4104(6)	0.071(1)	0.0678
C(34′)	0.592(2)	0.3770(7)	0.032(1)	0.0745
C(21″)	0.465(2)	0.1375(5)	0.0914(9)	0.0451
C(22″)	0.526(2)	0.1140(5)	0.178(1)	0.0561
C(23″)	0.620(2)	0.0706(6)	0.178(1)	0.0707
C(24″)	0.650(2)	0.0481(5)	0.094(1)	0.0572
C(25″)	0.591(2)	0.0700(5)	0.011(1)	0.0625
C(26″)	0.499(2)	0.1156(5)	0.009(1)	0.0576
		Solvent Molecules		
O(3)	0.241(1)	0.9540(3)	0.1769(6)	0.056(2)*
C(10)	0.179(3)	0.9830(7)	0.103(1)	0.191(6)*
O(4)	0.818(3)	0.9655(8)	0.276(2)	0.089(7)*
C(7)	0.787(4)	0.925(1)	0.290(2)	0.071(9)*
C(8)	0.823(5)	0.901(1)	0.381(2)	0.09(1)*
C(9)	0.754(6)	0.892(1)	0.222(3)	0.11(2)*

[a] The asterisk indicates a U(iso) value.

tion. It is noteworthy that dramatic changes in the stereoselectivity and in the reactivity are observed as a function of the diastereomer considered.

Table 3. Main Interatomic Distances (Å) for $C_{26}H_{36}OFeI{\cdot}0.5CH_3OH{\cdot}0.25OC_3H_6$ (7)

	Molecule 1		
Fe(1)—C(1′)	2.10(1)	Fe(1)—C(2′)	2.04(1)
Fe(1)—C(3′)	2.00(1)	Fe(1)—C(4′)	2.02(1)
Fe(1)—C(5′)	2.02(1)	Fe(1)—C(10′)	2.05(1)
Fe(1)—C(11′)	2.05(1)	Fe(1)—C(12′)	2.01(1)
Fe(1)—C(13′)	2.02(1)	Fe(1)—C(14′)	2.03(1)
O(1)—C(4″)	1.38(2)	N(1)—C(6′)	1.54(2)
N(1)—C(7′)	1.52(2)	N(1)—C(8′)	1.48(2)
N(1)—C(9′)	1.47(2)	C(1)—C(2)	1.49(2)
C(2)—C(3)	1.56(2)	C(3)—C(4)	1.57(2)
C(3)—C(1′)	1.52(2)	C(4)—C(5)	1.53(2)
C(4)—C(1″)	1.48(2)	C(5)—C(6)	1.51(2)
	Molecule 2		
Fe(21)—C(21′)	2.05(1)	Fe(21)—C(22′)	2.02(1)
Fe(21)—C(23′)	2.01(1)	Fe(21)—C(24′)	2.02(1)
Fe(21)—C(25′)	2.06(1)	Fe(21)—C(210′)	2.03(1)
Fe(21)—C(211′)	2.05(1)	Fe(21)—C(212′)	2.02(2)
Fe(21)—C(213′)	2.02(1)	Fe(21)—C(214′)	2.04(1)
O(21)—C(24″)	1.37(2)	N(21)—C(26′)	1.54(2)
N(21)—C(27′)	1.45(2)	N(21)—C(28′)	1.45(2)
N(21)—C(29′)	1.48(2)	C(21)—C(22)	1.54(2)
C(22)—C(23)	1.53(2)	C(23)—C(24)	1.56(2)
C(23)—C(21′)	1.54(2)	C(24)—C(25)	1.55(2)
C(24)—C(21″)	1.49(2)	C(25)—C(26)	1.52(2)

Table 4. Main Bond Angles (deg) for $C_{26}H_{36}OFeI{\cdot}0.5CH_3OH{\cdot}0.25OC_3H_6$ (7)

	Molecule 1		
C(7′)—N(1)—C(6′)	106.9(13)	C(9′)—N(1)—C(6′)	109.8(12)
C(8′)—N(1)—C(7′)	112.4(15)	C(9′)—N(1)—C(8′)	108.2(14)
C(9′)—N(1)—C(7′)	108.3(15)	C(4)—C(3)—C(2)	111.9(10)
C(3)—C(2)—C(1)	116.0(11)	C(1′)—C(3)—C(4)	111.8(9)
C(1′)—C(3)—C(2)	114.1(10)	C(1″)—C(4)—C(3)	113.0(9)
C(5)—C(4)—C(3)	109.3(10)	C(6)—C(5)—C(4)	113.0(12)
C(1″)—C(4)—C(5)	110.7(10)	C(5′)—C(1′)—C(3)	126.3(11)
C(2′)—C(1′)—C(3)	128.1(11)	C(6′)—C(2′)—C(3′)	122.5(12)
C(6′)—C(2′)—C(1′)	128.0(12)	C(2′)—C(6′)—N(1)	114.5(12)
C(6″)—C(1″)—C(4)	120.6(11)	C(2″)—C(1″)—C(4)	124.3(11)
C(3″)—C(4′)—O(1)	122.4(15)	C(5″)—C(4″)—O(1)	117.5(14)
C(8′)—N(1)—C(6′)	111.2(12)		
	Molecule 2		
C(27′)—N(21)—C(26′)	111.1(11)	C(29′)—N(21)—C(26′)	107.3(10)
C(28′)—N(21)—C(27′)	107.9(13)	C(29′)—N(21)—C(28′)	110.7(13)
C(29′)—N(21)—C(27′)	111.1(13)	C(24)—C(23)—C(22)	112.1(10)
C(23)—C(22)—C(21)	114.8(11)	C(21′)—C(23)—C(24)	111.7(9)
C(21′)—C(23)—C(22)	114.1(10)	C(21″)—C(24)—C(23)	114.0(10)
C(25)—C(24)—C(23)	111.1(10)	C(26)—C(25)—C(24)	113.9(12)
C(21″)—C(24)—C(25)	109.1(11)	C(25′)—C(21′)—C(23)	125.8(11)
C(22′)—C(21′)—C(23)	126.3(11)	C(26′)—C(22′)—C(23′)	125.6(11)
C(26′)—C(22′)—C(21′)	126.1(11)	C(22′)—C(26′)—N(21)	116.8(10)
C(26″)—C(21″)—C(24)	120.8(12)	C(22″)—C(21″)—C(24)	121.5(11)
C(23″)—C(24′)—O(21)	122.5(15)	C(25″)—C(24″)—O(21)	118.8(14)
C(28′)—N(21)—C(26′)	108.6(11)		

Experimental Section

General Considerations. 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. Mass spectra were obtained on a Nermag R 10-G spectrometer. Rotations were measured on a Perkin-Elmer Model 241MC polarimeter. Elemental analyses were performed by the "Service Régional de Microanalyse", Université P. et M. Curie, Paris, France. The adsorbent used for column chromatography was Merck 60 GF_{254} silica gel. Tetrahydrofuran and ether were distilled from sodium/benzophenone under Ar and dichloromethane over calcium hydride before use. The ultrasonic bath used to perform ionic hydrogenation was a Bransonic 32 (150 W, 50 kHz).

X-ray Study of 7. Intensity data were collected at room temperature on a Nonius CAD4 diffractometer using Mo Kα

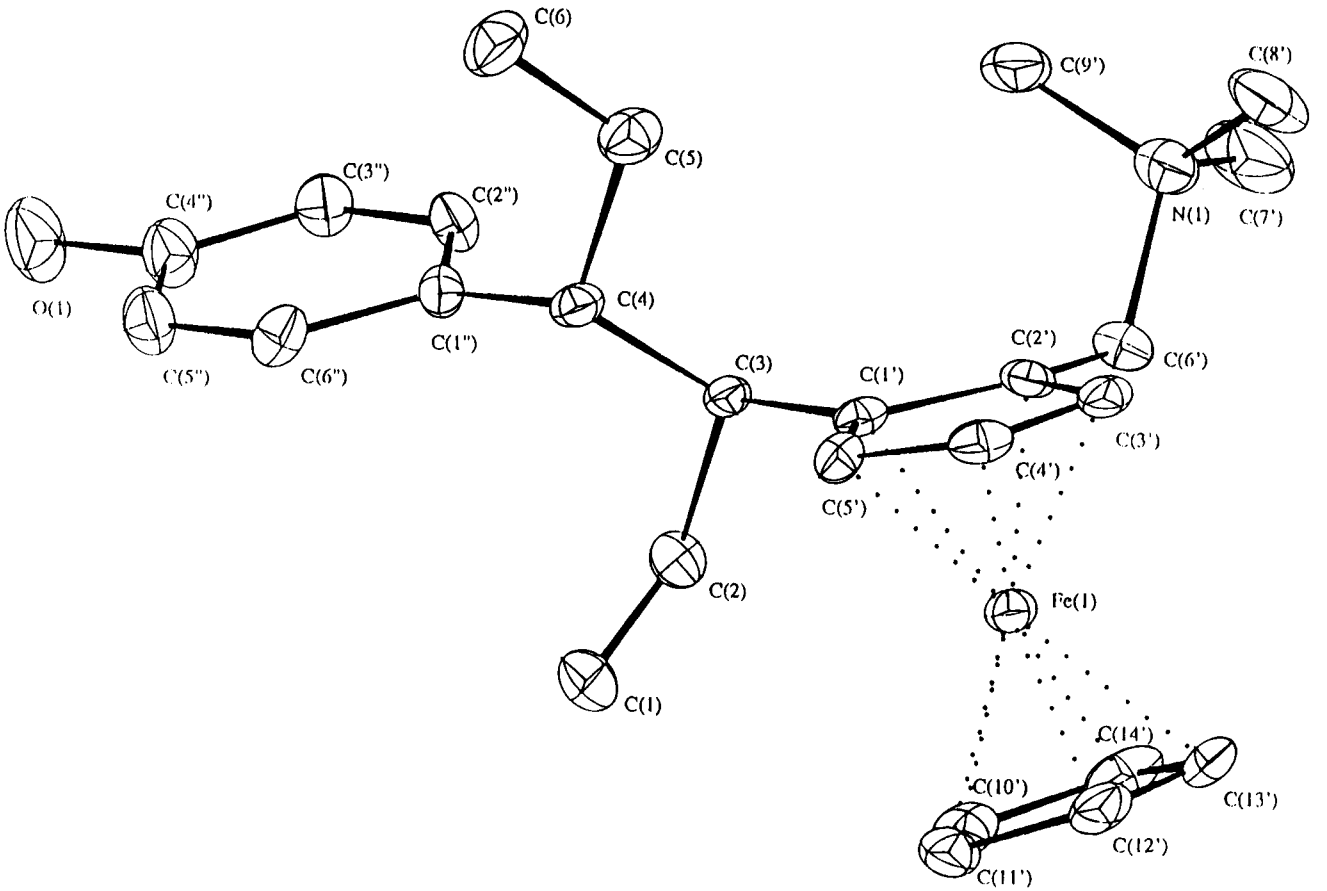

Figure 6. ORTEP plot of (p*S*,3*S*,4*R*)-**7** (molecule 1).

Table 5. Crystallographic Data for 8

chem formula	$C_{26}H_{36}ONFeI{\cdot}H_2O$
fw	580.3
cryst syst	monoclinic
space group	$P2_1/a$
Z	4
a, Å	10.180(2)
b, Å	15.429(2)
c, Å	17.517(3)
β, deg	104.53(1)
V, Å^3	2663(9)
F(000)	1184
ϱ(calcd), g cm^{-3}	1.44
μ(Mo Kα) cm^{-1}	17.3
diffractometer	CAD4
monochromator	graphite
radiation	Mo Kα (λ = 0.710 70 Å)
temp, °C	20
scan type	$\omega/2\theta$
scan range θ, deg	0.8 + 0.34 tan θ
2θ range, deg	3−50
no. of reflns collected	4671
no. of rflns used (criteria)	2265 ($I > 3\sigma(I)$)
R	0.037
R_w[a]	0.037
abs cor[b]	min 0.80, max 1.28
secondary extinctn cor	none
weighting scheme	unit weights
rms (shift/esd) (last ref)	0.54
least-squares params	396

[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 6. Fractional Parameters for $C_{26}H_{36}ONFeI{\cdot}H_2O$ (8)

atom	*x/a*	*y/b*	*z/c*	*U*(eq), Å^2
I(1)	0.12694(6)	0.36951(4)	0.37115(4)	0.0783
Fe(1)	0.5337(1)	0.57743(7)	0.82946(6)	0.0486
O(1)	0.1064(6)	0.1754(3)	0.6074(3)	0.0777
O(2)	0.4623(7)	0.2963(4)	0.4573(4)	0.1039
N(1)	0.2786(5)	0.5297(4)	0.5889(3)	0.0464
C(1)	0.2758(9)	0.5905(5)	0.9545(5)	0.0699
C(2)	0.2024(8)	0.6003(5)	0.8677(5)	0.0598
C(3)	0.2103(7)	0.5217(4)	0.8148(4)	0.0447
C(4)	0.1536(7)	0.4370(5)	0.8414(4)	0.0495
C(5)	0.0213(8)	0.4493(6)	0.8680(5)	0.0666
C(6)	−0.0177(8)	0.3686(7)	0.9051(5)	0.0725
C(1′)	0.3521(7)	0.5060(4)	0.8026(4)	0.0375
C(2′)	0.4012(6)	0.5252(4)	0.7340(4)	0.0397
C(3′)	0.5340(7)	0.4877(5)	0.7463(4)	0.0546
C(4′)	0.5674(7)	0.4481(5)	0.8208(5)	0.0549
C(5′)	0.4591(7)	0.4603(5)	0.8558(4)	0.0510
C(6′)	0.3303(7)	0.5798(5)	0.6656(4)	0.0505
C(7′)	0.1864(8)	0.4592(5)	0.5988(4)	0.0652
C(8′)	0.2018(8)	0.5908(5)	0.5278(4)	0.0669
C(9′)	0.3920(8)	0.4930(6)	0.5595(5)	0.0694
C(10′)	0.5224(9)	0.6958(5)	0.8815(6)	0.0733
C(11′)	0.547(1)	0.7057(6)	0.8105(6)	0.0761
C(12′)	0.670(1)	0.6645(8)	0.8108(7)	0.0855
C(13′)	0.7155(9)	0.6284(7)	0.8852(7)	0.0864
C(14′)	0.623(1)	0.6469(6)	0.9279(5)	0.0751
C(1″)	0.1370(6)	0.3665(5)	0.7790(4)	0.0429
C(2″)	0.0304(7)	0.3671(5)	0.7131(4)	0.0541
C(3″)	0.0156(8)	0.3033(5)	0.6559(4)	0.0601
C(4″)	0.1114(8)	0.2389(5)	0.6634(5)	0.0567
C(5″)	0.2160(8)	0.2360(5)	0.7295(5)	0.0627
C(6″)	0.2290(7)	0.2993(5)	0.7869(5)	0.0534

radiation. Accurate cell dimensions and orientation matrix were obtained from least-squares refinement of the setting 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 $P2_1$ with Z = 4 (with two independent formula units, one molecule of methanol, and half a molecule of acetone in the asymmetric unit). Complete crystal data and collection parameters are listed in Table 1. The usual corrections for Lorentz and polarization effects were applied.

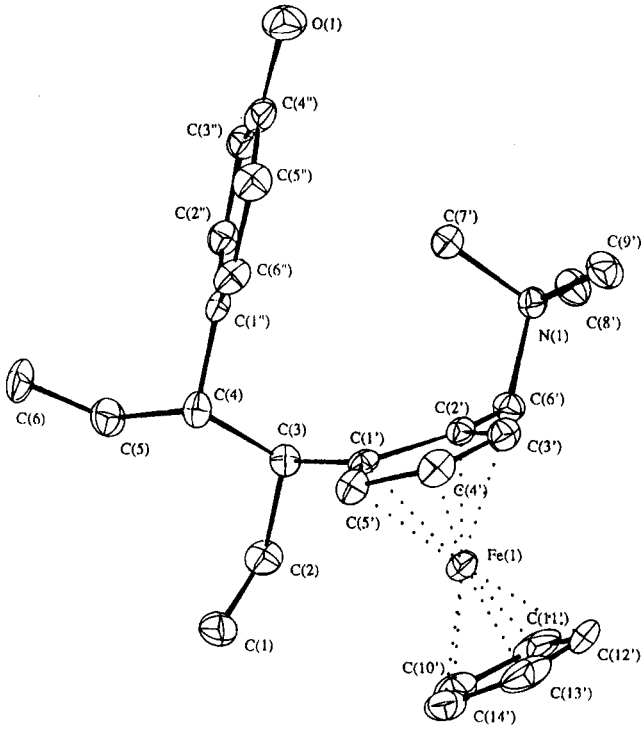

Figure 7. ORTEP plot of (p*S*,3*S*,4*S*)-**8**.

Table 7. Main Interatomic Distances (Å) and Bond Angles (deg) for $C_{26}H_{36}ONFeI\cdot H_2O$ (8)

Fe(1)—C(1′)	2.102(6)	Fe(1)—C(2′)	2.033(6)
Fe(1)—C(3′)	2.010(7)	Fe(1)—C(4′)	2.038(7)
Fe(1)—C(5′)	2.056(7)	Fe(1)—C(10′)	2.057(8)
Fe(1)—C(11′)	2.016(9)	Fe(1)—C(12′)	2.015(9)
Fe(1)—C(13′)	2.023(8)	Fe(1)—C(14′)	2.039(8)
O(1)—C(4″)	1.378(9)	N(1)—C(6′)	1.525(8)
N(1)—C(7′)	1.474(9)	N(1)—C(8′)	1.492(9)
N(1)—C(9′)	1.489(9)	C(1)—C(2)	1.52(1)
C(2)—C(3)	1.540(9)	C(3)—C(4)	1.548(9)
C(3)—C(1′)	1.530(9)	C(4)—C(5)	1.54(1)
C(4)—C(1″)	1.521(1)	C(5)—C(6)	1.50(1)
C(7′)—N(1)—C(6′)	111.5(5)	C(9′)—N(1)—C(6′)	111.8(5)
C(8′)—N(1)—C(7′)	108.4(6)	C(9′)—N(1)—C(8′)	107.7(6)
C(9′)—N(1)—C(7′)	109.4(6)	C(4)—C(3)—C(2)	113.8(6)
C(3)—C(2)—C(1)	115.9(6)	C(1′)—C(3)—C(4)	110.1(5)
C(1′)—C(3)—C(2)	113.7(6)	C(1″)—C(4)—C(3)	111.7(5)
C(5)—C(4)—C(3)	114.0(6)	C(6)—C(5)—C(4)	111.9(7)
C(1″)—C(4)—C(5)	110.9(6)	C(5′)—C(1′)—C(3)	125.3(6)
C(2′)—C(1′)—C(3)	128.3(6)	C(6′)—C(2′)—C(3′)	126.4(6)
C(6′)—C(2′)—C(1′)	125.8(6)	C(2′)—C(6′)—N(1)	114.2(6)
C(6″)—C(1″)—C(4)	121.0(6)	C(2″)—C(1″)—C(4)	121.5(7)
C(3″)—C(4′)—O(1)	123.2(7)	C(5″)—C(4″)—O(1′)	117.6(7)
C(8′)—N(1)—C(6′)	108.3(5)		

Computations were performed by using CRYSTALS[15] adapted to a Microvax-II computer. Scattering factors and corrections for anomalous dispersion were taken from ref 16. The structure was resolved by direct methods (SHELXS86[17]) and refined by least squares with anisotropic thermal parameters for all non-hydrogen atoms except the oxygen and carbon atoms of the organic solvent molecules (O(3) and C(10) for methanol; O(4), C(7), C(8), and C(9) for acetone). Hydrogen atoms were introduced as fixed contributors in theoretical positions (with U(iso) = 1.2U(eq) of the related carbon atom) and their coordinates recalculated after each refinement cycle. The structure was refined to R = 0.044 and R_w = 0.052 with use of 3954 reflections for 567 least-squares parameters.

X-ray Study of 8. The same procedure as for **7** was applied. This compound crystallizes in the monoclinic space group $P2_1/a$ with Z = 4 (with one formula unit and one hydrogen-bonded molecule of water in the asymmetric unit). Complete crystal data and collection parameters are listed in Table 2. Here, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located on a difference Fourier map. Their coordinates were refined with an overall variable isotropic thermal parameter. The structure was refined to R = 0.037 and R_w = 0.037 with use of 2265 reflections for 396 least-squares parameters.

***rac*-3-(2-((*N*,*N*-Dimethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexan-3-ol ((p*R**,3*R**,4*S**)-1 and (p*R**,3*S**,4*R**)-2).** 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 4-(4-methoxyphenyl)hexan-3-one in 15 mL of ether was added at −40 °C and the mixture was allowed to reach room temperature and stirred overnight. The solution was hydrolyzed and neutralized (Na_2CO_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_3N/hexane and dried to prevent the formation of tails). The two diastereomers (0.70 g; 31%) isolated were obtained as oils, yielding 0.30 g for the more polar isomer **1** and 0.40 g of the less polar isomer **2**. After a few days the products **1** and **2** crystallize spontaneously.

(p*R,3*R**,4*S**)-1.** ^{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 (m, 1), 2.50 (d, 1, J = 12.1), 3.77 (s, 3), 3.93 (dd, 1, J = 2.4, 1.4), 3.96 (d, 1, J = 12.0), 3.99 (dd, 1, J = 2.4, 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. Anal. Calcd for $C_{26}H_{35}O_2NFe$: 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**)-2.** ^{1}H NMR: δ 0.36 (t, 3, J = 7.3), 0.78 (t, 3, J = 7.3), 0.85 (m, 1), 1.17 (m, 1), 1.32 (m, 1), 1.95 (m, 1), 2.17 (s, 6), 2.71 (d, 1, J = 12.4), 2.77 (m, 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, 1.4), 4.15 (dd, 1, J = 2.4, 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. Anal. Calcd for $C_{26}H_{35}O_2NFe$: C, 69.48; H, 7.85; N, 3.11. Found: C, 69.53; H, 7.98; N, 2.97.

Optically Active 3-(2-((*N*,*N*-Dimethylamino)methyl)-ferrocenyl)-4-(4-methoxyphenyl)hexan-3-ol (1 and 2). The same procedure as for the racemic compound was used, except for the lithiated aminoferrocene, which is obtained optically enriched by treatment with butyllithium at −70 °C of the corresponding iodide enantiomer.

Reaction of Optically Active Lithiated Ferrocenic Compound (p*R* or p*S*) with 4-(4-methoxyphenyl)hexan-3-one. (a) To 1.4 g (3.8 mmol) of (p*S*)-1-(2-((*N*,*N*-dimethylamino)methyl)-2-iodoferrocene (ee = 68%) 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 4-(4-methoxyphenyl)hexan-3-one diluted in 30 mL of 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*)-**1**: $[\alpha]_D$ = −36.4° (c = 2.64, ethanol) (ee = 68%). (p*S*,3*R*,4*S*)-**2**: $[\alpha]_D$ = −35.4° (c = 2.60, ethanol) (ee = 68%).

(15) Watkin, D. J.; Carruthers, J. R.; Betteridge, P. W. *CRYSTALS User Guide*; Chemical Crystallography Laboratory, University of Oxford: Oxford, England, 1986.
(16) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.
(17) Sheldrick, G. M. SHELXS86, Program for Crystal Structure Solution; University of Göttingen, Göttingen, Germany, 1986.

(b) From 1.84 g (5.0 mmol) of (p*R*)-1-(2-((*N*,*N*-dimethylamino)methyl)-2-iodoferrocene (ee = 60%) and 1.4 g (6.8 mmol) of 4-(4-methoxyphenyl)hexan-3-one 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 **1** and 0.10 g of the less polar isomer **2**. (p*R*,3*R*,4*S*)-**1**: $[\alpha]_D = +39.7°$ (c = 2.9 EtOH) (ee = 60%). (p*R*,3*S*,4*R*)-**2**: $[\alpha]_D = +36.4°$ (c = 3.18, EtOH) (ee = 60%).

***rac*-3-(2-((*N*,*N*-Dimethylamino)methyl)ferrocenyl)-4-(4-methoxyphenyl)hexane (3 and 4). Ionic Hydrogenation.** In an ultrasonic bath at 0 °C, 0.42 g (0.93 mmol) of **1** dissolved in CH_2Cl_2 is placed in a Schlenk flask under a current of argon, to remove the hydrogen formed. $NaBH_4$ (0.07 g, 1.8 mmol) is added, followed by 0.3 mL (3.9 mmol) of trifluoroacetic acid. These additions have to be repeated each time that the bubble formation stops, for five cycles. Then the solution is poured in an ice–water bath to hydrolyze the excess of hydride, extracted by ether (3 × 20 mL) and neutralized (HCO_3Na). After the solvent is removed, the yellow oil is flash-chromatographed on silica gel (7730 F_{254} Merck; eluent 1:10 Et_3N/petroleum ether) to give 0.08 g of reduced product as an oil (20% yield) and 0.33 g of unreacted amino alcohol.

(p*S,3*S**,4*R**)-3.** ^1H NMR: δ 0.64 (t, 3, J = 7.3), 1.12 (t, 3. 7.5), 1.50 (m, 2), 1.7 (m, 2), 2.22 (s, 6), 2.56 (m, 1), 2.74 (m, 1), 2.96 (d, 1, J = 13.0), 3.31 (d, 1, J 13.0), 3.68 (dd, 1, J = 1.4, 2.4), 3.78 (s, 3), 4.00 (t, 1, J = 2.4), 4.03 (s, 5), 4.19 (dd, 1, J = 1.4, 2.4), 6.75 (d, 2, J = 6.5), 6.85 (d, 2, J = 6.5). ^{13}C NMR: δ 12.8, 13.3, 25.9, 26.1, 29.7, 42.4, 45.6, 51.8, 55.1, 58.3, 65.2, 67.7, 69.0, 82.9, 95.6, 112.8, 129.7, 135.8, 157.5. Anal. Calcd for $C_{26}H_{35}ONFe$: C, 72.05; H, 8.14; N, 3.23. Found: C, 72.09; H, 8.33; N, 3.14.

In the optically active series, the procedure was the same. (p*S*,3*S*,4*R*)-**3**: $[\alpha]_D = -6.2°$ (c = 1.4, EtOH) (ee = 60%). (p*R*, 3*R*,4*S*)-**3**: $[\alpha]_D = +9.2°$ (c = 1.2, EtOH) (ee = 68%).

In an ultrasonic bath at 0 °C, 0.32 g (0.71 mmol) of **2** dissolved in CH_2Cl_2 is placed in a Schlenk flask under a current of argon, to remove the hydrogen formed. $NaBH_4$ (0.15 g, 4 mmol) is added, followed by 1.1 mL (14 mmol) of trifluoroacetic acid. After 15 min another 0.08 g (2.1 mmol) of $NaBH_4$ is added, followed by 0.5 mL (6.5 mmol) of trifluoroacetic acid. Then the solution of poured in an ice–water bath to hydrolyze the excess hydride, extracted by ether (3 × 20 mL), and neutralized (HCO_3Na). After the solvent is removed, the yellow oil is flash-chromatographed on silica gel (7730 F_{254} Merck; eluent 1:10 Et_3N/petroleum ether) to give 0.25 g, (72% yield) of the reduced product as an oil. This compound could be obtained as a solid by further purification by thin-layer chromatography (7730 F_{254} Merck; eluent 1:10 Et_3N/petroleum ether).

(p*S,3*S**,4*S**)-4.** ^1H NMR δ 0.65 (t, 3, J = 7.2), 0.86 (t, 3, J = 7.5), 1.6 (m, 3), 1.84 (m, 1), 2.24 (s, 6), 2.55 (m, 1), 3.00 (d, 1, J = 12.6), 3.12 (m, 1), 3.68 (d, 1, J = 12.6), 3.81 (s, 3), 3.79 (t, 1, J = 2.4), 3.99 (dd, 1, J = 1.4, 2.4), 4.02 (s, 5), 4.17 (dd, 1, J = 1.4, 2.4), 6.81 (d, 2, J = 8.7), 7.08 (d, 2, J = 8.7). ^{13}C NMR: δ 12.6, 14.5, 20.5, 23.2, 45.2, 45.3, 49.9, 55.1, 58.4, 65.1, 68.3, 69, 70, 82.2, 94.9, 112.9, 129.7, 136.1, 157. MP: 80 °C. Anal. Calcd for $C_{26}H_{35}ONFe$: C, 72.05; H, 8.14; N, 3.23. Found: C, 71.84; H, 8.24; N, 3.22.

In the optically active series, the procedure was the same. (p*S*,3*S*,4*S*)-**4**: $[\alpha]_D = -24.9°$ (c = 0.62, EtOH) (ee = 60%). (p*R*, 3*R*,4*R*)-**4**: $[\alpha]_D = +35.7°$ (c = 0.28, EtOH) (ee = 68%).

***rac*-3-(2-((*N*,*N*,*N*-Trimethylammonio)methyl)ferrocenyl)-4-(4-hydroxyphenyl)hexane Iodide (7 and 8). General Procedure for the Deprotection of Methoxyphenyl Groups.** In a cold bath at −40 °C, 2 mmol of the methoxyphenyl compound is disolved in 5 mL of chloroform, and 0.5 mL (5.3 mmol) of BBr_3 is added with rapid stirring. The mixture is allowed to reach room temperature for 5 min; the solution turns dark brown. The mixture is cooled again before 30 mL of 10% aqueous ammonia is added ; this mixture is extracted with ether (3 × 15 mL) and neutralized ($NaHCO_3$). The crude oil obtained after evaporation is flash chromatographed on silica gel (7730 F_{254} Merck; eluent 1:4 Et_3N/ petroleum ether).

3-(2-((*N*,*N*-Dimethylamino)methyl)ferrocenyl)-4-(4-hydroxyphenyl)hexane (5 and 6). (p*S,3*S*,4*R**)-5.** ^1H NMR: δ 0.66 (t, 3, J = 7.1), 1.13 (t, 3, J = 7.2), 1.48 (m, 2), 1.78 (m, 2), 2.25 (s, 6), 2.42 (m, 1), 2.71 (m, 1), 2.73 (d, 1, J = 13.8), 3.04 (d, 1, 13.8), 3.79 (dd, 1, J = 1.4, 2.4), 4.00 (t, 1, J = 2.4), 4.01 (s, 5), 4.22 (dd, 1, J = 1.4, 2.4), 5.30 (broad, 1), 6.63 (d, 2, J = 8.5), 6.73 (d, 2, J = 8.5).

(p*S,3*S**,4*S**)-6.** ^1H NMR: δ 0.64 (t, 3, J = 7.2), 0.86 (t, 3, J = 7.4), 1.67 (m, 3), 1.88 (m, 1), 2.25 (s, 6), 2.53 (m, 1), 3.04 (m, 1), 3.11 (d, 1, J = 12.8), 3.60 (d, 1, J = 12.8), 3.77 (dd, 1, J = 1.4, 2.4), 3.99 (t, 1, J = 2.4), 4.01 (s, 5), 4.21 (dd, 1, J = 1.4, 2.4), 5.25 (broad, 1), 6.70 (d, 2, J = 8.5), 6.98 (d, 2, J = 8.5).

General Procedure for the Preparation of the Quaternary Ammonium Iodide Salts. The phenols described above (0.3 mmol) are dissolved in 1.5 mL of acetone previously distilled and dried over $MgSO_4$. Iodomethane (Prolabo) (0.1 mL, 1.6 mmol) is added and the mixture stored overnight at 4 °C. The precipitate is washed with ether, dried in vacuo, and suspended in 1.5 mL of acetone in which small amounts of 95% methanol are added until the solution turns clear. The solution is placed at 4 °C until the crystals appear: compound **7**, dec at 166 °C; compound **8**, dec at 152 °C.

Acknowledgment. This research was supported by CNRS-France and the Russian Academy of Sciences according to bilateral agreement No. 2–13 and by Grant No. 93-03-5827 from the Russian Fundamental Science Foundation.

Supplementary Material Available: Tables of bond angles, interatomic distances, and anisotropic thermal parameters for **7** and **8** (7 pages). Ordering information is given on any current masthead page.

OM9308304