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Mono and difunctionalisation of chiral ferrocenyl bis-acetals. X-Ray crystal structure of bis-1,1′-[(2*S*, 4*S*)-(hydroxymethyl)-2-dioxane1,3]-ferrocene[1]

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Abstract

The chiral 1,1′-bis-acetals, bis-1,1′-[(2*S*, 4*S*)-(hydroxymethyl)-2-dioxane1,3]-ferrocene (**3**) and 1,1′-bis-1,1′-[(2*S*, 4*S*)-(methoxymethyl)-2-dioxane1,3]-ferrocene (**4**) were synthesized. (**3**) was crystallographically characterised. The ortholithiation of (**4**) was studied in various conditions. Fair yields of monosubstituted compounds could be obtained with a complete regioselectivity in favor of the 2 position but the diastereoselectivities were moderate (up to 35%). Some disubstituted compounds can be isolated but in low yields (up to 8%). The regioselectivity is complete in favor of the 2,2′-disubstituted isomer. Only the diastereoisomer with two opposite planar chiralities is observed.

Keywords: Iron; Ferrocene; Regioselectivity; Diastereoselectivity; Chirality

1. Introduction

Owing to their use in many fields for example organic synthesis, supramolecular chemistry, materials chemistry or catalysis, ferrocenes with planar chirality are of high interest [1]. A number of years ago, the procedure reported by Ugi and coworkers concerning the diastereoselective ortholithiation of (*R*)-*N*,*N*-dimethyl-1-ferrocenyl ethyl amine (92% of diastereoisomeric excess) became the method of choice for introducing planar chirality on a ferrocene ([2]a,b). More recently, many new efficient methods have been reported. Most of them used ferrocene derivatives which possess a chiral group bearing heteroatom acting as a directing group for diastereoselective ortholithiation. Various chiral directing groups were described such as an amine ([2]c), an acetal [3], a sulfoxide [4] or an oxazoline [5]. Only very recently were 'direct methods' described which use an achiral ferrocene derivative but a chiral base [6] for the ortholithiation, sometimes with very high enantioselectivities (up to 99% ee) ([6]b).

The enantioselective synthesis of C_2-symmetric-tetrasubstituted ferrocene derivatives with planar chirality only recently started to attract more attention, despite the attractive structure of this type of compound. Most of the reported methods for their synthesis followed the diastereoselective ortholithiation strategy applied to ferrocenes bearing one chiral directing group on each cyclopentadienyl ring. This chiral directing group may be an amino group [7], an oxazoline [8]. Only very recently was reported enantioselective syntheses of C_2-symmetric-tetrasubstituted ferrocenes from 1,1′-ferrocenecarboxaldehyde with a bis-aminoalkoxide as an intermediate [9] or from an 1,1′-ferrocenyl diamides with *n*BuLi/sparteine [10]. Nevertheless, C_2-symmetric

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[1] Dedicated to Professor Michael Bruce on the occasion of his 60th birthday in recoginition of his important contribution to organometallic chemistry.

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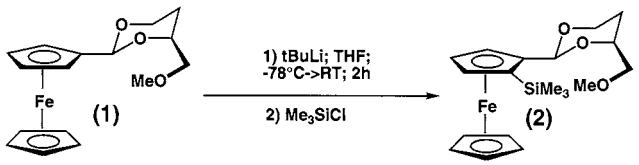


Scheme 1.

tetrasubstituted ferrocene have already found successful application to asymmetric catalysis, namely to palladium-catalyzed asymmetric cross coupling (ee up to 93%) ([7]a) and to asymmetric allylic substitution (ee up to 99%) [11].

In 1993, Kagan et al. showed that the monoacetal (**1**) (see Scheme 1) ([3]a) allows the synthesis of various 2-substituted ferrocenecarboxaldehydes with good yields and in an essentially enantiomerically pure form. Our idea was to consider the corresponding bis-acetal (**4**) with one acetal group on each cyclopentadienyl ring as starting materials to obtain C_2-symmetric 2,2′-disubstituted 1,1′-ferrocenedicarboxaldehyde. This type of molecule, owing to the large reactivity of the aldehyde function, can be an intermediate in the synthesis of numerous compounds of great interest in various fields of chemistry. Here we report the synthesis of chiral bis acetal bis-1,1′-[(2*S*, 4*S*)-(hydroxymethyl)-2-dioxane1,3]-ferrocene (**3**) and bis-1,1′-[(2*S*, 4*S*)-(methoxymethyl)-2-dioxane1,3]-ferrocene (**4**) and our results with regard to the reactivity and stereochemistry of the mono- and dilithiation of (**4**) under various conditions (see Scheme 3). (**3**) was identified by X-ray analysis.

2. Results and discussion

2.1. Synthesis of the acetals (3) and (4)

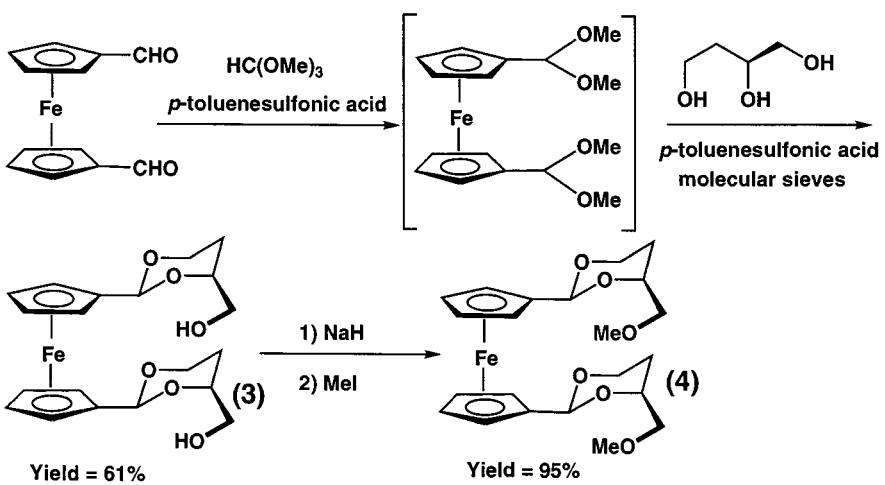
The synthesis of (**3**) was similar to that used by Kagan et al. to obtain (**1**) (see Scheme 2**).** 1,1′-ferrocenecarboxaldehyde is heated in neat trimethylorthoformate in the presence of a catalytic amount of paratoluenesulfonic acid to obtain the bis dimethylacetal. Transacetalization of the crude bis-acetal is carried out in chloroform in the presence of commercially available (*S*)-(−)-1,2,4-butanetriol and a catalytic amount of paratoluenesulfonic acid. The desired bis-acetal is obtained as a mixture of diastereoisomers. After recrystallisation in toluene, pure (**3**) is obtained as a single diastereoisomer. (**4**) is synthesized from (**3**) by deprotonation of the hydroxy group using NaH followed by alkylation with iodomethane.

2.2. X-ray crystal structure of (3)

The molecular structure of (**3**) shown in Fig. 1, is essentially as expected and confirms the formulation of the complex. Bond lengths and angles are collected in Table 1. As this complex is enantiomerically pure and crystallizes in the noncentrosymmetric $P2_12_12_1$ space group, its absolute configuration was determined by refining the Flack enantiopole parameter x [12], which is defined as

$$F_0^2 = (1-x)F(h)^2 + xF(-h)^2$$

x is then the fractional contribution of $F(-h)$ to the observed structure amplitude, and it is sensitive to the polarity of the structure. The x value, 0.01(3), agrees with the absolute configuration expected from the synthetic route for the C(14) and C(64) atoms. The two acetal carbon C(11) and C(61) are asymmetric and they have the same absolute configuration S. It is worth



Scheme 2.

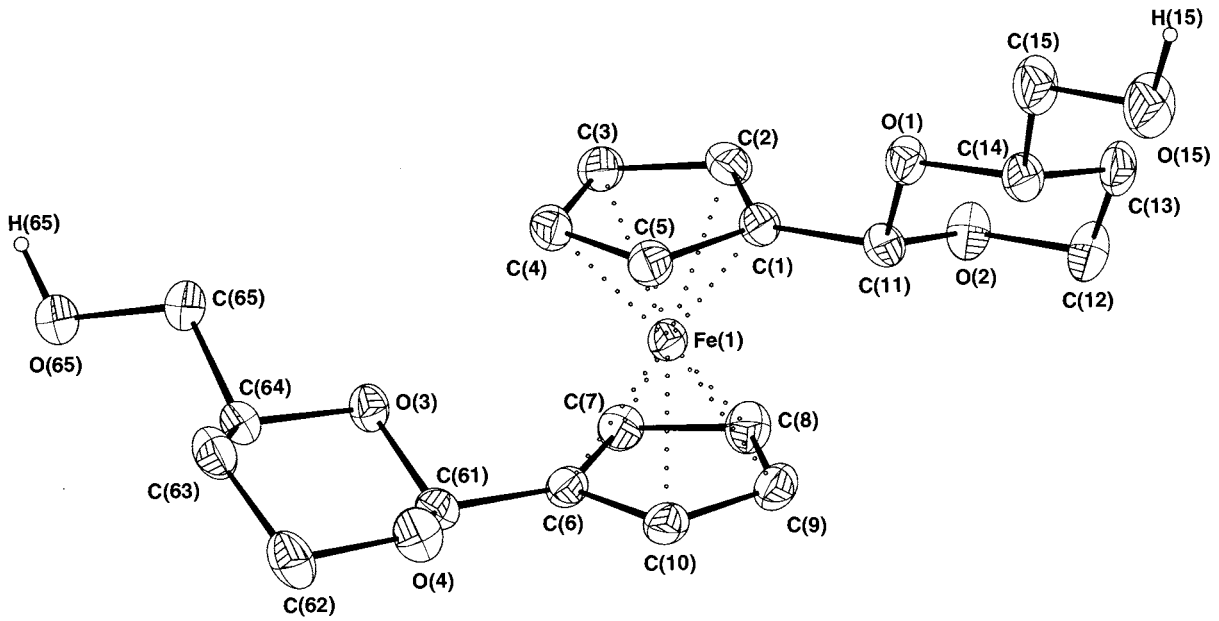


Fig. 1. Cameron view of the molecule with ellipsoids plotted at the 50% probability level. Hydrogen atom but those attached to the hydroxy group have been omitted for clarity.

pointing out that this *S* configuration is identical to the one we recently reported for a ferrocenophane acetal complex [13] and confirms the configuration of the acetal carbon and the planar chirality which was established by Kagan et al. ([3]a).

Table 1
Bond lengths (Å) and bond angles (°) with e.s.d.s in parentheses.

O(1)–C(11)	1.426(6)	C(1)–C(11)	1.485(7)
O(1)–C(14)	1.440(6)	C(6)–C(61)	1.461(7)
O(2)–C(11)	1.390(7)	C(7)–C(8)	1.405(7)
O(2)–C(12)	1.429(7)	C(8)–C(9)	1.432(8)
O(3)–C(61)	1.409(6)	C(9)–C(10)	1.398(8)
O(3)–C(64)	1.432(6)	C(12)–C(13)	1.507(9)
O(4)–C(61)	1.410(6)	C(13)–C(14)	1.511(9)
O(4)–C(62)	1.437(8)	C(14)–C(15)	1.491(8)
O(15)–C(15)	1.417(8)	C(62)–C(63)	1.504(9)
O(65)–C(65)	1.409(7)	C(63)–C(64)	1.508(8)
		C(64)–C(65)	1.504(7)
O(15)–H(15)	0.99(4)	O(65)–H(65)	0.94(4)
O(15)···O(65)	2.753(6)	O(65)···O(1)	2.771(5)
O(65)···H(15)	1.80(4)	O(1)···H(65)	1.85(4)
C(11)–O(1)–C(14)	111.8(4)	O(1)–C(14)–C(13)	108.7(4)
C(11)–O(2)–C(12)	111.2(4)	O(1)–C(14)–C(15)	107.3(4)
C(61)–O(3)–C(64)	113.0(4)	C(13)–C(14)–C(15)	114.5(5)
C(61)–O(4)–C(62)	110.9(4)	O(15)–C(15)–C(14)	106.2(5)
C(2)–C(1)–C(11)	126.7(5)	O(3)–C(61)–O(4)	112.1(4)
C(5)–C(1)–C(11)	125.1(5)	O(3)–C(61)–C(6)	109.6(4)
C(7)–C(6)–C(61)	127.3(4)	O(4)–C(61)–C(6)	110.0(4)
C(10)–C(6)–C(61)	125.9(5)	O(4)–C(62)–C(63)	109.8(5)
C(6)–C(10)–C(9)	108.8(5)	C(62)–C(63)–C(64)	109.5(5)
O(1)–C(11)–O(2)	111.6(4)	O(3)–C(64)–C(63)	109.7(4)
O(1)–C(11)–C(1)	108.1(4)	O(3)–C(64)–C(65)	104.9(4)
O(2)–C(11)–C(1)	109.4(4)	C(63)–C(64)–C(65)	113.6(5)
O(2)–C(12)–C(13)	110.6(4)	O(65)–C(65)–C(64)	108.1(4)
C(12)–C(13)–C(14)	110.6(5)		
O(15)–H(15)···O(65)	161(6)	O(65)–H(65)···O(1)	145(2)

The ferrocene moiety reveals the expected geometry with no unusual bond lengths or angles. The two Cp rings which are eclipsed, are virtually parallel making a dihedral angle of 0.6°.

The two dioxane rings have a slightly distorted chair conformation. The four atoms, O(1), O(2), C(12), C(14) or O(3), O(4), C(62), C(64) are coplanar while atoms C(11) or C(61) lie 0.648 or 0.625 Å below and C(61) or C(62) 0.639 or 0.664 Å above these planes, respectively. The arrangement of these two dioxane rings with respect to the Cp rings are different. The dioxane attached to C(1) makes a dihedral angle of 48.1° with the corresponding Cp ring whereas the other dioxane is roughly coplanar with the Cp ring making a dihedral angle of only 10.2°. This difference may be related to the occurrence of intermolecular hydrogen bonds which engage the O(1) atom of the first dioxane ring.

One of the interesting feature of the structure is indeed the occurrence of a complex system of inter-

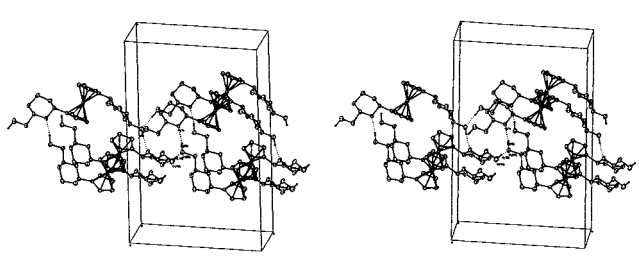


Fig. 2. Stereoview of the packing showing intermolecular hydrogen bonding. Dotted lines indicate O–H···OH and O–H···O hydrogen bonds. For clarity, only half of the packing is represented.

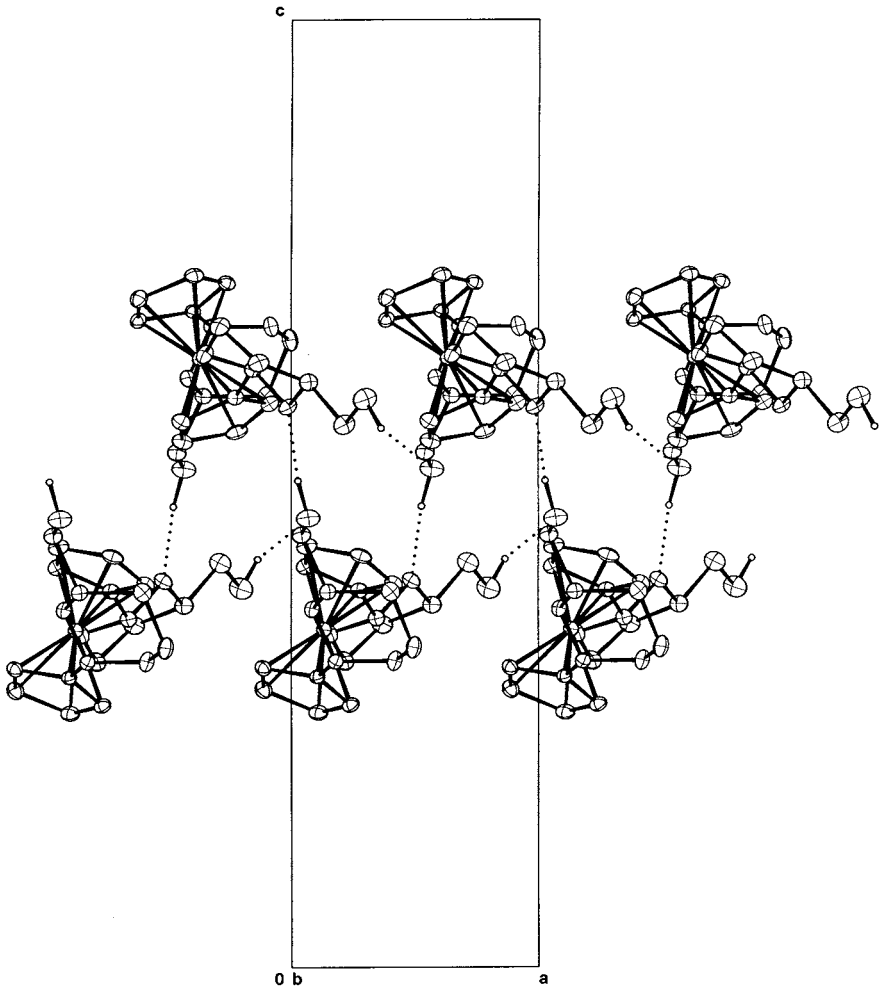


Fig. 3. Packing diagram viewed down the b axis and showing the wave-like layer built by the intermolecular hydrogen bonds.

molecular hydrogen bonds between the molecules to form a two-dimensional network (Fig. 2). One of the hydroxy group O(65) acts as both a donor and an acceptor for intermolecular hydrogen bonds whereas the other hydroxy O(15) acts as only a donor. Moreover, the oxygen atom O(1) of one of the 1,3-dioxane ring is also an intermolecular hydrogen-bond acceptor. Firstly, molecules are linked by O–H···OH hydrogen bonds via unit cell translations to form infinite chain in the diagonal xy direction [O(15)···O(65)$\{x-1,1+y,z\}$ 2.753(6) Å]. Secondly, two chains related by the symmetry operator $1/2+x,1/2-y,-z$ are also linked by O–H···O hydrogen bonds which develop between the hydroxy group O(65) and one of the 1,3-dioxane ring [O(65)···O(1) $\{1/2+x,1/2-y,-z\}$, 2.771(5) Å]. This second link between chains results in the build up of wave-like layers which develop perpendicular to the c direction (Fig. 3).

2.3. Deprotonation of (4)

The deprotonation of (**4**) was studied in different conditions by characterization of the reaction mixture after electrophilic quenching of the lithiated intermediates by Bu_3SnCl to give (**5a**) and (**6a**) or Me_3SiCl to yield (**5b**) and (**6b**) (see Table 2 and Scheme 3).

The yields of the monosubstituted bisacetals (**5**) formed by deprotonation with tBuLi was not higher than 22% (entry 1, Table 2) despite many attempts in various conditions. The yields of disubstituted bisacetals (**6**) were even lower. We supposed that the approach to the ferrocenyl protons was very hindered by the two large acetal groups. Using a less bulky base might be a way to deprotonate (**4**) more efficiently. The yields of (**5**) when MeLi was employed as base were increased (up to 69%, isolated yield) but not the yields of (**6**) (entries 6–9, Table 2). With 1 equiv. of MeLi, no deprotonation occurred. The deprotonation started only when more than 1 equiv. of MeLi was used (entries 6, 7, 8, Table 2).

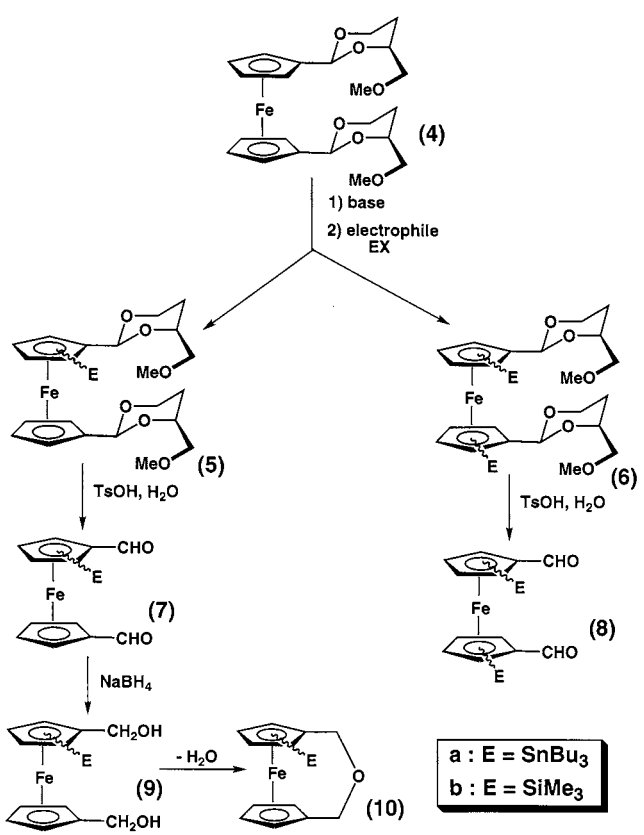
In every case, (**5**) ((**5a**) or (**5b**)) is a mixture, in various proportions, of only two diasteroisomers, amongst the four possible ones which can be synthesized by monofunctionalisation of (**4**) in a 2 or 3 position. The hydrolysis of each mixture of diastereoisomers ((**5a**) or (**5b**)) provides only one alde-

Table 2
Functionalisation of the bis-acetal (**4**)

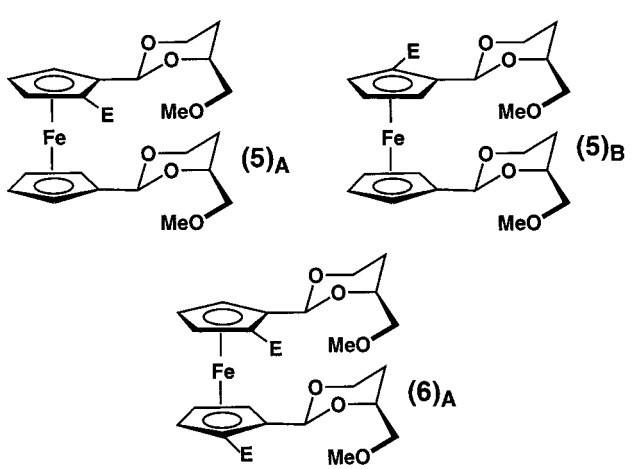
Entry	Conditions for the deprotonation step	Electrophile	Yield in (**5**)[a] (de, major isomer[b])	Yield in (**6**)[a]
1	2.1 eq. tBuLi in Et_2O; −78°C then RT, 2 h	Bu_3SnCl	(**5a**) 22% (19%, S)	(**6a**) 8%
2	2.1 eq. TBuLi in THF; −78°C then RT, 2 h	Bu_3SnCl	(**5a**) 0%[c]	(**6a**) 0%[c]
3	4.2 eq. TBuLi in Et_2O; −78°C then RT, 2h	Bu_3SnCl	(**5a**) 0%[d]	(**6a**) 0%[d]
4	2.1 eq. TBuLi in Et_2O; reflux, 15 h	Bu_3SnCl	(**5a**) 0%[e]	(**6a**) 0%[e]
5	1.05 eq. tBuLi in Et_2O; −78°C then RT, 2 h	Bu_3SnCl	(**5a**) 0%[c]	(**6a**) 0%[c]
6	2.1 eq. MeLi in Et_2O; −78°C then RT, 2 h	Bu_3SnCl	(**5a**) 69% (34%, R)	(**6a**) 5%
7	1.6 eq. MeLi in Et_2O; −78°C then RT, 2 h	Bu_3SnCl	(**5a**) 44% (33%, R)	(**6a**) 2%
8	1.05 eq. MeLi in Et_2O; −78°C then RT, 2 h	Bu_3SnCl	(**5a**) 0%[c]	(**6a**) 0%[c]
9	2.1 eq. MeLi in Et_2O; −78°C then RT, 2 h	Me_3SiCl	(**5b**) 64% (36%, R)	(**6b**) 5%[f]

[a] Isolated yields.
[b] The given configuration is related to the planar chirality.
[c] Starting materials recovered.
[d] Not isolated from a complex mixture.
[e] Starting materials completely decomposed.
[f] Isolated only after hydrolysis to the dialdehyde **(6b).**

hyde ((**7a**) or (**7b**)). If the functionalisation occurred in a 2 position, the ^{1}H-NMR spectrum must show for the H on the disubstituted cyclopentadienyl ring, a triplet with a coupling constant of ca. 2.5 Hz, and two doublets of doublets with one coupling constant of ca. 2.5 Hz and the other one of ca. 1.3 Hz [14]. If the functionalisation occurred in a 3 position, the ^{1}H-NMR spectrum must show for the H on the disubstituted cyclopentadienyl ring, a triplet with a coupling constant of ca. 1.3 Hz, and two similar doublets of doublets. The first case is observed, for (**7a**) and (**7b**), so they are the 2-substituted 1,1′-ferrocenecarboxaldehydes and therefore (**5**) is a mixture of $(\mathbf{5})_A$ and $(\mathbf{5})_B$ (see Scheme 4). Furthermore, (*S*)-2-(trimethylsilyl)-1,1′-ferrocenecarboxaldehyde has already been synthesized by another pathway [13] and all the physical data (except rotarory power) are the same for (*S*)-2-(trimethylsilyl)-1,1′-ferrocenecarboxaldehyde and (**7b**), confirming the 2-substitution in (**7b**). The integration of the different acetal signals in the ^{1}H-NMR spectrum of (**5a**) or (**5b**) gave us the diastereoisomeric excess of the different mixtures of diastereoisomers. In the case of (**7b**), the value and the sign of the rotarory power gave the enantiomeric excess of (**7b**) and the absolute configuration of the major enantiomer. So, we can identify $(\mathbf{5b})_A$ and $(\mathbf{5b})_B$. Making the very logical hypothesis that the stereoselectivity of the functionalisation is made at the lithiation step and therefore does not depend of the electrophile, $(\mathbf{5a})_A$ and $(\mathbf{5a})_B$ were identified. The measurement of the ee of (**7b**) was not precise because it is difficult to obtain it



Scheme 3.



Scheme 4.

Table 3

de of (**5b**) by integration of the acetal signals (%)	ee of (**7b**)by measurement of $[\alpha]_D$ (%)	ee of (**9b**) by measurement of $[\alpha]_D$ (%)	ee of (**9b**) using $Eu(hfc)_3$ (%)	ee of (**10b**) by measurement of $[\alpha]_D$
36	ca. 25	ca. 25	35	31

very pure. Therefore, we decided to reduce (**7b**) into (**9b**) (see Scheme 3) and afterwards to transform (**9b**) into (**10b**). The corresponding diol and ferrocenophane are known in an enantiomerically pure form [13], so the measurement of the rotarory power of (**9b**) and (**10b**) can give values of the ee of (**7b**). Furthermore, the diol have been resolved in ^{1}H-NMR using $Eu(hfc)_3$ as a chiral chemical shift reagent. The measurement of the rotarory power of (**10b**) is not very precise because of the low value of $[\alpha]_D$ (36.2) and it is even worse for (**9b**) ($[\alpha]_D = +8.17$ ($CHCl_3$, $c = 0.93$)). The data concerning the diastereoisomeric excess of (**5b**) and the enantiomeric excess of (**7b**), (**9b**) and (**10b**) are collected in Table 3. All this data are well related and support our hypothesis. With *t*BuLi (Table 2, entry 1), the major diastereoisomer have a S configuration like the aldehydes (**2**) obtained by deprotonation of (**1**) (see Scheme 1) but the selectivity is much lower (19% instead of more than 98%). Moreover, using MeLi, the diastereoselectivity is also low (de = 35%) but the major diastereoisomer have now a *R* configuration, although the deprotonation of (**1**) yields mainly the S diastereoisomer (de = 50%, see Table 4). (**3**) and (**1**) do not react in a similar way.

In any of the cases examined, the yields of tetrasubstituted (**6**) (see Scheme 3) are low ($< 8\%$), even with an excess of MeLi, but only one diastereoisomer was observed amongst the ten possible compounds which can be obtained by a double deprotonation in a 2 or 3 position. The ^{1}H-NMR spectrum of (**6a**) shows that the two Cp rings and the two acetal functions are not equivalent, so there is no C_2 axis in this molecule. After hydrolysis, (**6a**) yields only one disubstituted 1,1′-ferrocenedicarboxaldehyde (**8a**). The ^{1}H-NMR spectrum of this compound shows the equivalence of the Cp rings and of the two aldehyde functions, therefore (**8a**) must be the 2,2′ or 3,3′ functionalised compound, ruling out all stereoisomers with one functionalisation in a 2 position and the other one in a 3 position. Furthermore, the signal for one H on the cyclopentadienyl ring is a triplet with a coupling constant of 2.5 Hz, indicating that this hydrogen atom have two neighboring hydrogen atoms in a 2 position related to it [14]. So each Cp ring of (**8a**) is 1,2 disubstituted, therefore each Cp ring of (**6a**) is also 1,2 disubstitued. (**6a**) is $(\mathbf{6a})_A$ (see Scheme 4) and (**8a**) is the *meso* 2,2′-disubstituted 1,1′-ferrocenedicarboxaldehyde. When Me_3SiCl was used as an electrophile, the dialdehyde (**8b**) was isolated. According to its ^{1}H-NMR spectrum, (**8b**) is a 2,2′-disubstituted 1,1′-ferrocenedicarboxaldehyde which is not the *dl* diastereoisomer (the (*R*,*R*)-2,2′-bis (trimethylsilyl) 1,1′-ferrocenecarboxaldehyde was synthesized by an other route (see Scheme 5); the structure and stereochemistry of this compound was confirmed by X-ray crystal analysis [9]). Once again, (**8b**) is the *meso* diastereoisomer. Finally, the *meso* structure of (**8a**) and (**8b**) was confirmed by their rotatory power which was found to be 0.

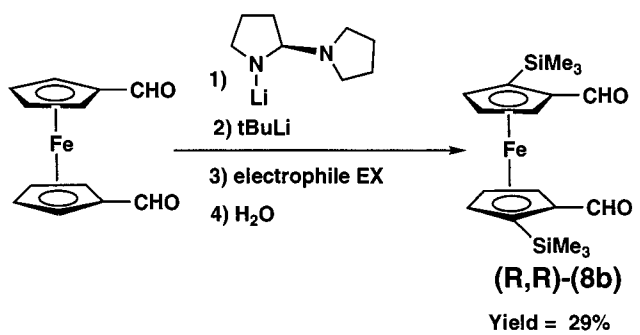
Table 4
Trimethylsilylation of the monoacetal (**1**)

Entry	Base	Yield in (10) (%)	de of (10), major isomer[a]
1	tBuLi	93	>98%, S[b]
2	MeLi	12	50%, S

[a] In the experimental conditions described in ref. ([3]a) the given configuration is related to the planar chirality.
[b] From reference ([3]a).

2.4. Conclusion

The reactivity of (**3**) is not directly related to that of (**1**). The two acetal groups do not act independently. They are close enough to interact together with the *t*BuLi or MeLi delivering a completely new system. But, unfortunately, although the regioselectivities are very high in all cases, the diastereoselectivity of the synthesis of (**5**) is quite low (19% with *t*BuLi; 35% with MeLi). Furthermore, the yields of the disubstituted (**6**) are very low and only the achiral *meso* stereoisomer which is not useful for the synthesis of chiral tetrasubstituted ferrocenes can be observed. But it is worth to point out that the difunctionalisation of (4) occurs with a perfect regio and diastereoselectivity.



Scheme 5.

3. Experimental section

3.1. General procedure and reagent syntheses

All of the reactions were carried out in the absence of air using standard Schlenk techniques and vacuum-line manipulations. Chlorotrimethylsilane and iodomethane was distilled on calcium hydride and stored on 3–4 Å molecular sieves. Bu_3SnCl was distilled under reduced pressure on carborandum and kept on 3–4 Å molecular sieves. 1,1′-ferrocenedicarbaldehyde was synthesized according to ref. [15]. Other compounds were used as commercial samples. All solvents were dried before use. Thin layer chromatography was carried out on Merck Kieselgel $60F_{254}$ precoated silicagel plates. Preparative flash chromatography was performed on Merck Kieselgel. Instrumentation: Bruker AM250 (^1H, ^{13}C), Hewlett-Packard HP MSD 7590 (GC/MS), Enraf-Nonius CAD4 (X-ray). Elemental analyses were performed by the Service d'Analyse du Laboratoire de Chimie de Coordination, Toulouse (France).

3.2. Synthesis of bis-1,1′-[(2S, 4S)-(hydroxymethyl)-2-dioxane-1,3]-ferrocene (3)

A mass of 6.0 g (24.6 mmol) of 1,1′-ferrocenedicarboxaldehyde was heated overnight at 80°C in 100 ml of trimethyl orthoformate together with 0.5 g (2.63 mmol) of paratoluenesulfonic acid monohydrate. Anhydrous potassium carbonate was then added and the mixture was stirred one more hour at 80°C. After cooling, the solution was diluted with ether, then filtered on celite. After evaporation of the solvents, a brown oil was obtained.

To a solution of 6.0 g (56 mmol) of (*S*)-(−)-1,2,4-butanetriol in 30 ml of chloroform, was added 4 Å molecular sieves and 0.5 g (2.63 mmol) of paratoluenesulfonic acid monohydrate. After 5 min stirring at r.t., was added a solution of the brown oil in 30 ml of chloroform and the mixture was heated at 60°C overnight. Anhydrous potassium carbonate was then added and the mixture was cooled down back to r.t. The mixture was then filtered on celite, which was washed by several fractions of dichloromethane. The organic solution was evaporated with a rotavapor to yield a brown oil. The crude materials was chromatographed on silicagel with ethyl acetate to yield 6.27 g of a yellow solid (61%). ^1H–NMR (δ (ppm), $CDCl_3$): 5.40 (s, 2H, O–C<u>H</u>–O), 4.30 (t, $J = 1.8$ Hz, 4H, Cp), 4.23–4.08 (m, 6H, 4H on Cp and 2H –C<u>H</u>–O), 4.0–3.85 (m, 4H, C<u>H</u>–O), 3.63 (m, 4H, –C<u>H</u>$_2$–O), 2.72 (s, 2H, –OH), 1.78 (br. qd., $J(CH_{2gem}) = 13$ Hz and 5.1 Hz, 2H, –C<u>H</u>$_2$–), 1.41 (dd, $J(CH_{2gem}) = 13$ Hz, and $J = 1.2$ Hz, 2H, –C<u>H</u>$_2$–).^{13}C–NMR (δ (ppm), $CDCl_3$): 99.97 (O–CH–O), 86.31, 77.37, 68.67, 68.64, 67.77, 67.60, 66.46, 65.58, 26.78(–CH_2–C<u>H</u>$_2$–CH).$[\alpha]_D = -18.7$($CHCl_3$, $c = 0.60$) MS (IE, 70 eV) m/e: 418 (M, 33%), 75 (73%), 57 (64%), 45 (77%), 43 (50%), 31 (100%). Anal. Found: C, 57.51; H, 6.44. $C_{20}H_{26}FeO_6$ Calc.: C, 57.44; H, 6.27.

3.3. X-ray crystal determination of (3)

The data were collected at r.t. (293 K) on a Stoe Imaging Plate Diffraction System (IPDS). The crystal-to-detector distance was 60 mm. 143 exposures (4 min. per exposure) were obtained with $0 < \varphi < 200°$ and with the crystals rotated through 1.4° in φ. Coverage of the unique set was over 99% complete to at least 28° in θ. Crystal decay was monitored by measuring 200 reflections per image. The final unit cell parameters were obtained by the least-squares refinement of 2000 reflections. Only statistical fluctuations were observed in the intensity monitors over the course of the data collection. Owing to the rather low μx value, 0.16, no absorption correction was considered.

The structure was solved by direct methods (SIR92) [16] and refined by least-squares procedures on F_o. H atoms were located on difference Fouriers maps, but those attached to C atoms were introduced in calculation in idealized positions(d(CH) = 0.96 Å) and their atomic coordinates were recalculated after each cycle. They were given isotropic thermal parameters 20% higher than those of the carbon to which they are attached. The coordinates of the H atoms attached to the O atoms were refined with a fixed isotropic thermal parameter of 0.07. Least-squares refinements were carried out by minimizing the function $\Sigma w(|F_o| - |F_c|)^2$, where F_o and F_c are the observed and calculated structure factors. The weighting scheme used in the last refinement cycles was $w = w'[1 - \{(\Delta F/6\sigma(F_o)\}^2]^2$ where $w' = 1/\Sigma_1^n A_r T_r(x)$ with three coefficients A_r for the Chebyshev polynomial $A_r T_r(x)$ where x was $F_c/F_c(\max)$ [17]. Models reached convergence with $R = \Sigma(||F_o| - |F_c||)/\Sigma(|F_o|)$ and $Rw = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2]^{1/2}$, having values listed in Table 4. Criteria for a satisfactory complete analysis were the ratios of rms shift to standard deviation less than 0.1 and no significant features in final difference maps. Details of data collection and refinement are given in Table 5.

The calculations were carried out with the CRYSTALS package programs [18] running on a PC. The drawing of the molecule was realized with the help of CAMERON [19].

3.3.1. Supplementary materials available

The fractional atomic coordinates and the anisotropic thermal parameters for non hydrogen atoms have been deposited at the Cambridge Crystallographic Data Center.

Table 5
Crystal data

Crystal parameters	
Compound	$C_{20}H_{26}O_6Fe$
Formula weight (g)	418.27
Shape (color)	Box (yellow)
Size (mm)	0.23, 0.20, 0.19
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	5.8730(4)
b (Å)	14.363(2)
c (Å)	22.592(1)
β (°)	93.66(1)
V (Å^3)	1905.7(4)
Z	4
F(000)	881
ρ_{calcd} (g cm^{-3})	1.458
μ(Mo–K$_\alpha$) (cm^{-1})	8.212
Data collection	
Diffractometer	IPDS Stoe
Monochromator	Graphite
Radiation	Mo–K$_\alpha$ ($\lambda = 0.71073$)
Scan mode	φ
Detector distance (mm)	60
φ Range (°)	$0 < \varphi < 200.2$
φ Incr. (°)	1.4
Exposure time (min)	4
2θ range (°)	$10.0 < 2\theta < 56.1$
No. of reflections collected	7190
No. of unique reflections (R_{int})	4423(0.063)
Reflections used ($I > 2\sigma(I)$)	2706
Refinement	
R	0.0512
Rw	0.0575
Weighting scheme	Chebyshev
Coefficient Ar	3.60, −2.11, 2.56
GOF	1.090
$(\Delta/\sigma)_{max}$	0.0262
$\Delta\rho_{min}/\Delta\rho_{max}$	−0.563/0.466
Flack's parameter	0.01(3)
Ls parameters	252

3.4. Synthesis of bis-1,1′-[(2S, 4S)-(methoxymethyl)-2-dioxane-1,3]-ferrocene (4)

In a schlenk tube, 330 mg of a 60% dispersion of NaH in mineral oil (8.33 mmol) was washed with two portions of dry cyclohexane. Then 5 ml of dry THF was added. To the hydride suspension, cooled down to 0°C, was added a solution of 1 g of bisacetal **(3)** in 30 ml of dry THF. After 30 min stirring at 0°C, was added 0.54 ml (8.82 mmol) of iodomethane. After one night stirring at r.t., the excess of hydride was destroyed by addition of ethanol followed by water. The solution was extracted with ether, washed with water and dried on magnesium sulfate. After evaporation of the solvent with a rotavapor, the crude materials was chromatographed on silicagel with ether and finally precipitated by dissolution in ether followed by a slow addition of pentane yield 1.02 g of an orange oil(2.28 mmol, 95%).

^{1}H-NMR (δ (ppm), $CDCl_3$): 5.38 (s, 2H, O–C$\underline{H}$–O), 4.29 (m, 4H, Cp), 4.19 (ddd, $J = 10.2$ Hz, 5.0 and 1.0 Hz, 2H, C$\underline{H}$–O), 4.10 (t, $J = 1.8$ Hz, 4H, Cp), 3.98 (m, 2H, C$\underline{H}$–O), 3.88 (ddd, $J = 11.3$, 10.2 and 2.6 Hz, 2H, C$\underline{H}$–O), 3.51 (dd, $J = 11$ and 6.2 Hz, 2H, C$\underline{H}_2$–OMe), 3.38 (dd, $J = 10.2$ and 4.8 Hz, 2H, C$\underline{H}_2$–OMe, ABX with H with δ at 3.51 and 3.98 ppm), 3.39 (s, 6H, C$\underline{H}_3$), 1.74 (br dq, $J =$ ca. 12 Hz (with H at 3.98, 3.88 and 1.45 ppm) and 5.1 Hz (with H at 4.19 ppm), 2H, C$\underline{H}_2$), 1.45 (br. d, $J(CH_{2gem}) = 11.3$ Hz, 2H, C$\underline{H}_2$).^{13}C-NMR (δ (ppm), $CDCl_3$): 99.87(O–$\underline{C}$H–O), 86.22, 75.86, 75.54, 68.76, 67.46, 66.59, 59.28(O–$\underline{C}H_3$), 27.92(–CH_2–$\underline{C}H_2$–CH). $[\alpha]_D = -49.0$ ($CHCl_3$, $c = 0.45$) GC-MS (IE, 70 eV) m/e: 448 (10%), 447 (36%), 446 (M, 100%), 149 (12%), 135 (10%), 121 (14%), 185 (12%). Anal. Found: C, 59.22; H, 7.29. $C_{22}H_{30}FeO_6$. Calc.: C, 59.20; H, 6.77.

3.5. Functionalisation of (4) (general procedure): synthesis of (5a) and (6a)

A mass of 0.15 g (0.33 mmol) of bisacetal (**4**) was dissolved in 10 ml of dry ether in a schlenk tube, then the solution was cooled down to −78°C. 470 μl of a 1.5 M solution of t-BuLi in pentane (7.1 mmol, 2.1 eq.) was added and the mixture was stirred 15 min. at −78°C, then 2 h at r.t. A yellow precipitate appeared. The mixture was cooled down again to −78°C and tributyltin chloride (4 eq.) was added. After 15 min. stirring at −78°C, the mixture was allowed to come back at r.t. After 1 h stirring at r.t., the excess of electrophile was destroyed by addition of 0.5 ml of isopropylamine first, afterwards by water. The solution was extracted with ether, washed with water, dried on magnesium sulfate, evaporated to yield an orange oil which was chromatographed on silicagel with a cyclohexane/ ether mixture, to yield 31 mg of (**6a**) (8%), 167 mg of (**5a**) (69%) as a mixture of diastereoisomer (ratio $(\mathbf{5a})_A/(\mathbf{5a})_B = 1.5$; de = 19%) and 14 mg of 1,1′-ferrocenedicarboxaldehyde (12%).

(**5a**):^{1}H-NMR (δ (ppm), $CDCl_3$): 5.40 (s, 1H $(\mathbf{5a})_A$, O–CH–O), 5.39 (s, 1H $(\mathbf{5a})_B$, O–CH–O), 5.37 (s, 1H $(\mathbf{5a})_B$, O–CH–O), 5.28 (s, 1H $(\mathbf{5a})_A$, O–CH–O), 4.48 (m, 1H $(\mathbf{5a})_A + (\mathbf{5a})_B$, Cp), 4.32–4.07 (m., 5H $(\mathbf{5a})_A + (\mathbf{5a})_B$), 4.03–3.78 (m 7H $(\mathbf{5a})_A + (\mathbf{5a})_B$), 3.67–3.29 (m, 10H $(\mathbf{5a})_A + (\mathbf{5a})_B$), 1.75 (m, 2H $(\mathbf{5a})_A + (\mathbf{5a})_B$, –CH–), 1.52 (m, 6H $(\mathbf{5a})_A + (\mathbf{5a})_B$, $SnBu_3$), 1.34 (m, 8H $(\mathbf{5a})_A + (\mathbf{5a})_B$, $SnBu_3$ + –CH–), 1.00 (m, 6H $(\mathbf{5a})_A + (\mathbf{5a})_B$, $SnBu_3$), 0.89 (m, 9H $(\mathbf{5a})_A + (\mathbf{5a})_B$, $Sn(CH_2)_3C\underline{H}_3$). Anal. Found: C, 55.67; H, 7.96. $C_{34}H_{56}FeO_6Sn$ Calc.: C, 55.58; H, 7.62.

(**6a**): ^{1}H-NMR (δ (ppm), $CDCl_3$): 5.33 (s, 1H, O–CH–O), 5.26 (s, 1H, O–CH–O), 4.47 (dd, $J = 2.2$ and 1.1 Hz, 1H, C_5H_3), 4.45 (dd, $J = 2.2$ and 1.1 Hz, 1H,

C_5H_3), 4.19 (m, 2H, 1H C_5H_3 and 1H CH–O), 4.12 (m, 2H, 1H C_5H_3 and 1H, CH–O), 3.89 (m, 6H, 2H C_5H_3 and 4H CH–O), 3.50 (dd, $J = 9.9$ and 5.5 Hz, 2H, –CH–O), 3.36 (m, 8H, 2×3H OCH_3 (s, 3H each at 3.37 and 3.35 ppm) and 2H $-CH_2-O$), 1.75–0.8 (m, 58H, 4H –CH– and 54H $-Sn\underline{Bu}_3$). ^{13}C-NMR (δ (ppm), $CDCl_3$): 100.98 (O–CH–O), 100.90 (O–CH–O), 91.02, 90.85, 76.28, 76.12, 75.82, 75.75, 75.39, 72.00, 71.79, 69.75, 69.64, 68.71, 68.34, 66.57, 66.39, 59.43 (OCH_3), 59.29 (OCH_3), 29.31 ($Sn\underline{Bu}_3$), 28.57 (O–$CH_2\underline{C}H_2$–CH–O), 28.30 (O–$CH_2\underline{C}H_2$–CH–O), 27.57 ($Sn\underline{Bu}_3$), 13.72, ($Sn\underline{Bu}_3$), 10.68 ($Sn(CH_2)_3\underline{C}H_3$).

3.6. Synthesis of (5b) and (6b)

Experimental conditions similar to Section 3.3 with MeLi as a base and Me_3SiCl as an electrophile. Yield = 64%; ratio $(\mathbf{5b})_A/(\mathbf{5b})_B = 1/2.1$; de = 36%

(**5b**): ^{1}H-NMR (δ (ppm), $CDCl_3$): 5.44 (s, 1H $(\mathbf{5b})_A$, O–CH–O), 5.42 (s, 1H $(\mathbf{5b})_B$, O–CH–O), 5.41 (s, 1H $(\mathbf{5b})_B$, O–CH–O), 5.37 (s, 1H $(\mathbf{5b})_A$, O–CH–O), 4.56 (m, 1H $(\mathbf{5b})_A + (\mathbf{5b})_B$, Cp), 4.27 (m, 3H $(\mathbf{5b})_A + (\mathbf{5b})_B$), 4.20–3.78 (m, 9H $(\mathbf{5b})_A + (\mathbf{5b})_B$), 3.60–3.25 (m, 10H $(\mathbf{5b})_A + (\mathbf{5b})_B$, 2H–$OCH_3$ and 2H–O–CH), 1.72 (m, 2H $(\mathbf{5b})_A + (\mathbf{5b})_B$, –CH–), 1.45 (m, 2H $(\mathbf{5b})_A + (\mathbf{5b})_B$, –CH–), 0.25 (s, 9H $(\mathbf{5b})_A$, $SiMe_3$), 0.23 (s, 9H $(\mathbf{5b})_B$, $SiMe_3$).

3.7. Hydrolysis of the bisacetal: synthesis of (7) and (8)

In a schlenk tube to a solution of bisacetal in dichloromethane (ca. 0.15 mol l^{-1}) was added 0.7 eq. of paratoluenesulfonic acid monohydrate and ca. 130 eq. of deoxygenated water. The mixture was stirred 90 min at 60°C. After cooling, the solution was diluted with ether, washed with water, dried on sodium sulfate and evaporated to yield the dialdehyde which was purified by flash chromatography on silicagel using a cyclohexane/ether mixture.

(**7a**): Yield = 83% ^{1}H-NMR (δ (ppm), $CDCl_3$): 9.90 (s, 1H, CHO), 9.87 (s, 1H, CHO), 4.96 (dd, $J = 2.5$ and 1.1 Hz, 1H, C_5H_3), 4.82 (m, 1H, C_5H_4), 4.79 (t, $J = 2.5$ Hz, 1H, C_5H_3), 4.77 (m, 1H, C_5H_4), 4.59 (m, 1H, C_5H_4), 4.52 (m, 1H, C_5H_4), 4.48 (m, 1H, C_5H_3), 1.50 (m, 6H, $SnBu_3$), 1.29 (m, 6H, $SnBu_3$), 1.05 (m, 6H, $SnBu_3$), 0.87 (t, $J = 7.1$ Hz, 9H, $SnBu_3$). ^{13}C-NMR (δ (ppm), $CDCl_3$): 194.50 (CHO), 192.88 (CHO), 84.89, 80.84, 79.60, 76.45, 76.36, 74.94, 74.02, 73.97, 70.61, 70.30, 29.11 ($SnBu_3$), 27.30 ($SnBu_3$), 13.65 ($SnBu_3$), 10.81 ($SnBu_3$).

(**7b**): Yield = 92%. Same physical data than for the product described in ref. [13].

(**8a**): Yield = 54%. ^{1}H-NMR (δ (ppm), $CDCl_3$): 9.88 (s, 2H, CHO), 4.86 (m, 2H, Cp), 4.70 (t, $J = 2.4$ Hz, 2H, Cp), 4.55 (m, 2H, Cp), 1.75–0.75 (m, 54H, –$SnBu_3$).^{13}C-NMR (δ (ppm), $CDCl_3$): 194.24 (CHO), 84.36, 80.57, 76.67, 74.65, 73.81, 29.22 ($SnBu_3$), 27.38 ($SnBu_3$), 13.69 ($SnBu_3$), 10.94 ($SnBu_3$). $[\alpha]_D = 0.0$ ($CHCl_3$, $c = 0.15$)

(**8b**): Obtained from an impure (**4b**). (**6b**) was purified by preparative layer chromatography on silicagel with a cyclohexane/ether mixture. ^{1}H-NMR (δ (ppm), $CDCl_3$): 9.96 (s, 2H, CHO), 5.00 (m, 2H, Cp), 4.76 (t, $J = 2.2$ Hz, 2H, Cp), 4.59 (m, 2H, Cp), 0.32 (s, 18H, $SiMe_3$). GC-MS: m/e: 388 (M + 2, 12%), 387 (M + 1, 32%), 386 (M, 100%), 371 (46%), 32 (26%). $[\alpha]_D = 0.0$ ($CHCl_3$, $c = 0.12$)

3.8. Reduction of the bisaldehyde (7b): synthesis of (9b)

In a Schlenk tube under argon, to a solution of dialdehyde (**7b**) in methanol (ca. 0.05 mol l^{-1}), cooled at 0°C, was added a solution of $NaBH_4$ (15 eq.) in aqueous 2N sodium hydroxide solution. The mixture was stirred overnight at r.t., then the methanol was evaporated with a high vacuum pump. The organic phase was extracted with ether, washed with water, dried on magnesium sulfate and evaporated. The crude product was purified by flash chromatography on silicagel to yield pure (**9b**) (79% yield).

(**9b**)**:** Same physical data than for the product described in ref. [13] except $[\alpha]_D = -2.04$ ($CHCl_3$, $c = 0.93$): ee = 25%; (*R*)-(**7b**) was the major enantiomer ($[\alpha]_D = +8.17$ ($CHCl_3$, $c = 0.93$) for (*S*)-(**7b**) [13]).

3.9. Synthesis of the β-oxa-trimethyleneferrocene (10b)

Under argon, to a solution of diol (ca. 0.01 mol l^{-1}) in 30 ml of freshly distilled benzene were added molecular sieves 4 Å then 1 eq. of tosyl chloride. The mixture was heated at 50°C. After 1.5 h the reaction was completed and anhydrous sodium carbonate was added after cooling. The solvent was evaporated and the crude product was purified by flash chromatography on silicagel to yield (**10b**) (68% yield).

(**8b**): Same physical data than for the product described in ref. [13] except $[\alpha]_D = -10.9$ ($CHCl_3$, $c = 0.57$) ee = ca. 30%; (*R*)-(**8b**) was the major enantiomer ($[\alpha]_D = +36.2$ ($CHCl_3$, $c = 0.55$) for (*S*)-(**7b**) [13]).

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