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A New Efficient Route to Chiral 1,3-Disubstituted Ferrocenes: Application to the Syntheses of (R_p)- and (S_p)-17α-[(3′-formylferrocenyl)ethynyl]estradiol

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Abstract: Starting from (2*S*,4*S*)-2-ferrocenyl-4-(methoxymethyl)-1,3-dioxane (**4**), use of the stereogenic *ortho*-directing menthyl *para*-tolyl sulfoxide group, which occupies the 2′ position in the ferrocenyl ring and redirects subsequent lithiation to the 3′ position, allowed the synthesis of optically pure (S_p)-1-formyl-3-iodoferrocene (**8**), that was characterized by single-crystal X-ray diffraction. Combination of this method with a protection–deprotection strategy, using trimethylsilyl as a temporary blocking group, yielded (R_p)-1-formyl-3-iodoferrocene (**13**). Separate Sonogashira coupling of each of the enantiomeric iodoformylferrocenes **8** and **13** with 17α-ethynyl-estradiol produced (R_p)-17α-[(3′-formylferrocenyl)ethynyl]estradiol (**14**) and (S_p)-17α-[(3′-formylferrocenyl)ethynyl]estradiol (**15**), respectively.

Keywords: bioorganic chemistry · chirality · ethynylestradiol · ferrocenes · organometallics

Introduction

Planar chiral ferrocene derivatives have played an important role in asymmetric synthesis.[1] For several years, the use of ferrocenes in bioorganometallic chemistry has been growing rapidly, and several promising applications have been developed.[2] For instance, ferrocene derivatives exhibit a cytotoxic activity that can be used to kill malignant cells.[3] We have shown that ferrocifens, the analogues of tamoxifen, obtained by replacing one of the phenyl groups by a ferrocenyl moiety, exhibit an antiproliferative effect against hormone-dependent and hormone-independent breast cancers.[4] Another example is ferroquine, a chloroquine analogue, which is active against malaria strains resistant to chloroquine.[5] Moreover, these compounds can be used as precursors for radiopharmaceuticals containing technetium or rhenium in ligand exchange reactions.[6] Additionally, ferrocenes have shown great promise in the labelling of peptide nucleic acids (PNA) for the detection of biomolecules.[7] However, when planar chiral ferrocenes are used, not only must the synthetic method be efficient, simple and versatile, but the compounds must also be optically pure.

Most of the known planar chiral ferrocenyl compounds are 1,2-disubstituted derivatives prepared by diastereoselective *ortho*-lithiation and subsequent reaction with an appropriate electrophile. The most important strategy adopted to achieve this diastereoselective lithiation is the use of stereogenic *ortho*-directing groups developed initially by Ugi et al., for example compound **1** (see below).[8] Subsequently, Kagan et al. showed that the chiral methoxymethyl-1,3-dioxane moiety in **2** allows efficient ortho functionalization of formylferrocene.[9]

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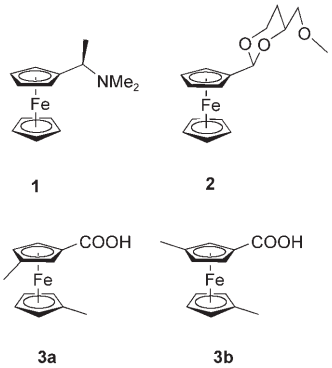
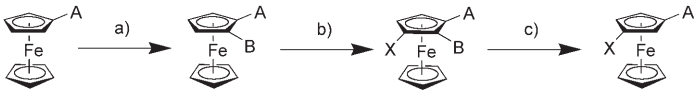


This strategy has been now extended to other organometallic compounds.[10] In contrast to 1,2-disubstituted compounds, there are very few examples of enantiomerically pure 1,3-disubstituted ferrocene derivatives. The first representative of this type was 3,1′-dimethylferrocenecarboxylic acid obtained, along with 2,1′-dimethyl-ferrocenecarboxylic acid, from the lithiation of 1,1′-dimethylferrocene followed by addition of CO_2.[11] The enantiomers (**3a** and **3b**) were separated by resolution of the racemate by using cinchonidine and quinidine. Lithiation of isopropylferrocene, in the presence of (−)-sparteine as an inducing reagent, produced 3,1′-disubstituted isopropylferrocenes in very low enantiomeric excess.[12] At present, to our knowledge, there is no convenient method available yet for the preparation of enantiopure 1,3-disubstituted ferrocenes. A number of other 1,3-disubstituted compounds have been prepared by the reaction of $FeCl_2$ with appropriately disubstituted cyclopentadienides, but only as racemates.[13] Recently, racemate 1-tolylthio-3-bromoferrocene has been obtained with excellent regioselectivity from the lithiation of tolylthioferrocene route.[14]

We now describe a new and useful strategy to prepare, separately, both 1,3-planar chiral enantiomers in their optically pure form. The concept is based on the use of an additional stereogenic *ortho*-directing group temporarily introduced at the 2-position (Scheme 1). For instance, attaching a *p*-tolyl sulfoxide group (B) should direct the lithiation to the 3-position.[1b,c,15]

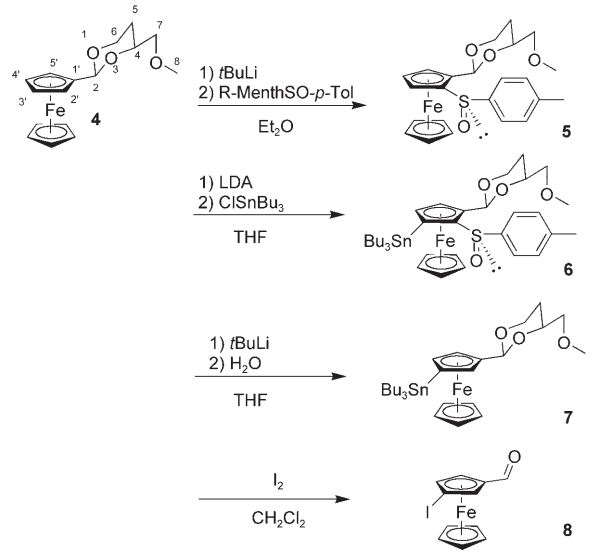


Scheme 1. Conceptual route to chiral 1,3-disubstituted ferrocenes: a) introduction of second *ortho*-directing group B; b) functionalization; c) elimination.

(S_p)- and (R_p)-1-formyl-3-iodoferrocene have been prepared by using this synthetic strategy. The coupling of these two enantiomers, separately, with 17α-ethynyl-estradiol, following the Sonogashira coupling reaction, produced (R_p)-17α-[(3′-formylferrocenyl)ethynyl]estradiol (**14**) and (S_p)-17α-[(3′-formylferrocenyl)ethynyl]estradiol (**15**), respectively.

Results and Discussion

(S_p)-1-Formyl-3-iodoferrocene (8): (S_p)-1-Formyl-3-iodoferrocene (**8**) can be prepared from (2*S*,4*S*)-2-ferrocenyl-4-(methoxymethyl)-1,3-dioxane (**4**).[16] Thus, as depicted in Scheme 2, the methoxymethyldioxanyl moiety exclusively stabilizes the lithium intermediate at the 2′ position when **4** was treated with *t*BuLi at −78 °C.[9] Addition of menthyl (*R*)-*p*-toluenesulfinate at low temperature gave product **5** in 55% yield. It is important to use the (*R*)-sulfinate rather than the racemate because the *S* enantiomer does not stabilize the lithium intermediate at the 3′ position, as is required for the next step. Now, the preferred site of lithiation is controlled by the strongly *ortho*-directing sulfoxide group, and so addition of LDA to a THF solution of **5** at low temperature (−78 °C), leads to deprotonation only at the 3′ position. Subsequent reaction with chlorotributyltin produced the 1′,2′,3′-trisubstituted chiral ferrocene **6**.



Scheme 2. Synthetic route to (S_p)-3-iodoferrocenecarboxaldehyde, **8**.

It is important to introduce the tributyltin group at the 3′ position instead of carrying out a direct iodination. Since the procedure for removal of the sulfoxide involves the attack of *t*BuLi on the sulfur atom,[1b,c] then, if an iodo substituent were to be already present, it would also be eliminated; by contrast, the tributyltin group is resistant to such treatment. Hence, addition of *t*BuLi to a THF solution of **6** at −78 °C produced **7** which was readily identified by the NMR coupling constants between protons H-2′, H-4′ and H-5′. Thus, H-4′ and H-5′ each appeared as a doublet of doublets with $^3J_{H,H}=2.2$ and $^4J_{H,H}=1.1$ Hz, while H-2′ gave rise to a triplet resonance with $^4J_{H,H}=1.1$ Hz. Finally, addition of iodine to a dichloromethane solution of tin compound **7** yielded (S_p)-1-formyl-3-iodoferrocene (**8**). The simultaneous removal of the methoxymethyldioxanyl substituent may be explained by the in situ formation of HI from iodotributyltin. The molecular structure of **8** was confirmed by a single crystal X-ray diffraction study as depicted in Figure 1 along with selected bond lengths and angles.

(R_p)-1-Formyl-3-iodoferrocene (13): Interestingly, we found that (R_p)-1-formyl-3-iodoferrocene (**13**) can also be prepared from (2*S*,4*S*)-2-ferrocenyl-4-(methoxymethyl)-1,3-dioxane (**4**). As we have shown in a previous paper,[17] it is possible to temporarily block the 2′ position with a trimethylsilyl group and thus force the subsequent directed lithiation to occur at the 5′ position. The synthetic pathway depicted in Scheme 3 shows the expected initial lithiation of **4**

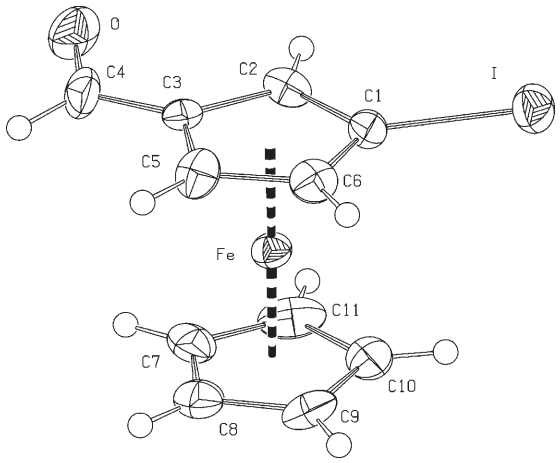
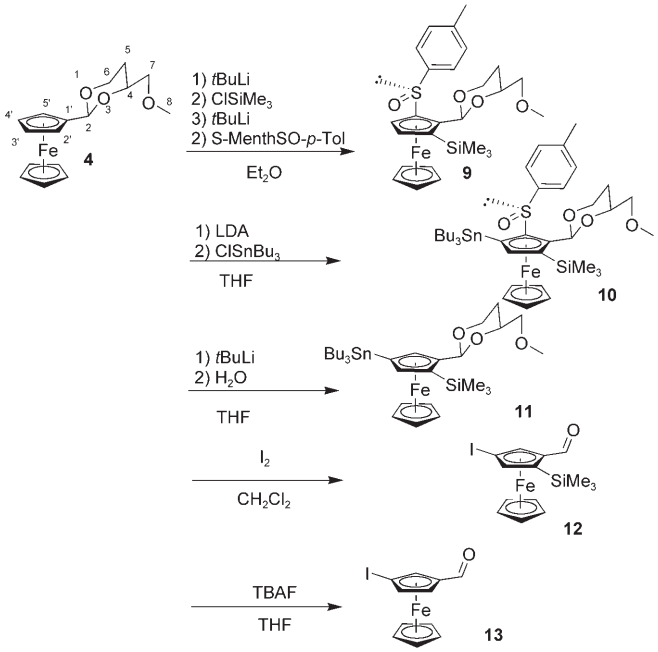


Figure 1. Molecular structure of **8**. Selected bond lengths [Å] and angles [°]: C1–C2 1.433(11), C2–C3 1.437(11), C1–I 2.083(7), C1–C6 1.425(13), C4–O 1.207(11), C8–C9 1.409(12); C2-C1-C6 108.0(7), C2-C3-C5 107.4(7), C3-C4-O 123.4(8).

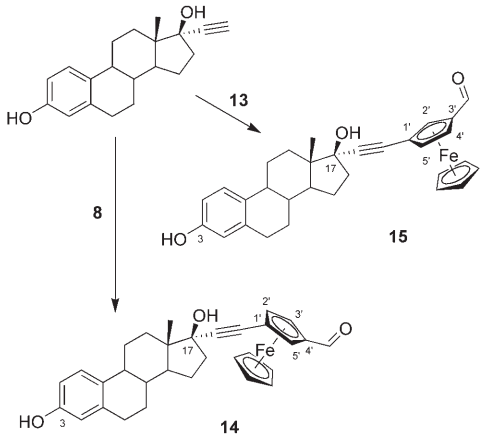


Scheme 3. Synthetic route to (R_p)-3-iodoferrocenecarboxaldehyde, **13**.

at −78 °C at the 2′ site; treatment with chlorotrimethylsilane gave the 2′-trimethylsilyl compound. After removal of unreacted chlorotrimethylsilane and solvent under reduced pressure, the crude oil obtained was redissolved in diethyl ether and *t*BuLi was again added. After stirring for one hour at room temperature, and cooling again to −78 °C, menthyl (*S*)-*p*-toluenesulfinate was added to give the trisubstituted ferrocene **9** in 30 % overall yield. In this case, deprotonation of **9** by LDA occurred only at the 4′ position, adjacent to the sulfoxide group, and treatment with chlorotributyltin produced the tetrasubstituted ferrocene **10** in 62 % yield. As before, the sulfoxide group must be removed prior to transformation to the iodo compound. Addition of *t*BuLi at −78 °C in THF gave **11**, which in turn reacted with iodine to yield the iodo compound **12**. Finally, removal of the trimethysilyl group with TBAF furnished (R_p)-1-formyl-3-iodoferrocene (**13**).

(R_p)- and (S_p)-17α-[(3′-Formylferrocenyl)ethynyl]estradiol (14) and (15): Having both enantiomers, **8** and **13**, optically pure and separately prepared, it is now possible to label ethynylestradiol with these organometallic groups. We found that, for this purpose, the Sonogashira cross-coupling reaction with diisopropylamine as the solvent is suitable.[18] Thus, when **8** or **13** was heated with 17α-ethynylestradiol in the presence of copper(II) acetate monohydrate and [$PdCl_2$-(PPh_3)$_2$] as catalysts, the coupled products (R_p)- and (S_p)-17α-[(3′-formylferrocenyl)ethynyl]estradiol (**14**) or (**15**) were obtained in 90 and 60 % yield, respectively (Scheme 4).

Compounds **14** and **15** are characterized by the presence of a formyl group on the Cp ring at the position farthest from C-17 of estradiol and may provide more insight to elucidate the affinity of modified hormones towards a specific receptor. Moreover, we have previously demonstrated the feasibility of transforming ferrocenes bearing a carbonyl group on the Cp ring into the corresponding technetium or



Scheme 4. Coupling reactions of **8** and **13** with 17α-ethynylestradiol: diisopropylamine, 5 % [$PdCl_2(PPh_3)_2$], 10 % $Cu(OAc)_2 \cdot H_2O$, reflux, 2 h.

rhenium tricarbonyl complexes[6d] and **14** and **15** may be used as precursors of their potential Tc and Re analogues.

Conclusion

In conclusion, we have adumbrated in this paper a convenient strategy to prepare both enantiomers of 1,3-disubstituted ferrocenes as optically pure forms. It is possible to prepare (S_p) and (R_p)-1-formyl-3-iodo-ferrocenes by using a combination of suitable *ortho*-directing substituents, such as methoxymethyldioxane and *p*-tolylsulfoxide, as well as trimethylsilyl as a temporary blocking group. The success in obtaining these two pure enantiomers allows the prepara-

tion of enantiopure ethynylestradiol complexes which pave the way for new bioorganometallic chemistry studies.

Experimental Section

Anhydrous THF and diethyl ether were distilled from sodium/benzophenone. *n*BuLi, *t*BuLi, LDA, and diisopropylamine were purchased from Acros. Flash chromatography was performed on silica gel Merck 60 (40–63 μm). Infrared spectra were recorded on an IR-FT BOMEM Michelson-100 spectrometer. ^{1}H- and ^{13}C NMR spectra were recorded on 300 and 400 MHz Bruker spectrometers. Mass spectrometry was performed with a Nermag R 10-10C spectrometer. High resolution mass spectrometry (HRMS) was performed on a JEOL MS 700 instrument. Melting points were measured with a Kofler device. Elemental analyses were performed by the Service de Microanalyse I.C.S.N., Gif sur Yvette, France.

(2*S*,4*S*,S_p)-4-Methoxymethyl-2-α-[2′-((*R*)-*p*-toluenesulfoxo)ferrocenyl]-3,1-dioxane (5): Ferrocene dioxane **4** (1.10 g, 3.48 mmol) was dissolved under argon in distilled diethyl ether (15 mL). The mixture was cooled to −78 °C, then *t*BuLi (3.02 mL, 4.52 mmol) was added dropwise. The cooling bath was removed and the mixture was stirred for 1 h at room temperature. The mixture was cooled to −78 °C and menthyl (*R*)-*p*-toluenesulfinate (1.30 g, 4.5 mmol) in THF (7 mL) was added dropwise. The mixture was stirred at this temperature for 30 min. The cooling bath was removed and the mixture was stirred at room temperature for 2 h more. A classical work up was performed. The crude oil was purified by chromatography on silica gel with dichloromethane/diethyl ether 8:2 yielding **5** as a red oil (1.082 g, 55 %). $[\alpha]_D^{25} = -314.5°$ ($c = 6.0\ g\,L^{-1}$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (br d, $J = 13.3$ Hz, 1H, H5eq), 1.78 (dq, $J = 5.1$, 12.2 Hz, 1H, H5ax), 2.32 (s, 3H, CH_3 tol), 3.37 (s, 3H, H8), 3.36 (dd, $J = 4.3$, 9.8 Hz, 1H, H7), 3.48 (dd, $J = 6.2$, 16.5 Hz, 1H, H7), 3.93 (td, $J = 2.6$, 14.3 Hz, 1H, H6eq), 4.03 (m, 1H, H4), 4.25 (d, 1H, $J = 3.9$ Hz, H6ax), 4.28 (t, $J = 2.6$ Hz, 1H, H4′), 4.42 (s, 5H, Cp), 4.48 (m, 2H, H3′, H5′), 5.58 (s, 1H, H2), 7.16 (d, $J = 8.1$ Hz, 2H, Har), 7.59 ppm (d, $J = 8.1$ Hz, 2H, Har); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3 tol), 27.8 (C5), 59.3 (C8), 64.5 (C4′), 66.8 (C6), 68.8 (C5′, C3′), 71.0 (Cp), 75.4 (C7), 76.1 (C4), 86.6 (C1′), 93.6 (C2′), 98.9 (C2), 124.7, 129.4, 140.4, 144.0 ppm; elemental analysis calcd (%) for $C_{23}H_{26}FeO_4S + {}^1/_2$pentane: C 62.45, H 6.68; found: C 62.52, H 6.41.

(2*S*,4*S*,S_p)-4-Methoxymethyl-2-α-[2′-((*R*)-*p*-toluenesulfoxo)-3-tributyltinferrocenyl]-3,1-dioxane (6):[19] Compound **5** (300 mg, 0.66 mmol) was dissolved in THF (4 mL) under argon. The solution was cooled to −78 °C, and then LDA (0.403 mL, 0.73 mmol) was added dropwise. The mixture was stirred at this temperature for 1 h and chlorotributyltin (0.215 mL, 0.79 mmol) was added. The mixture was stirred for 30 min and cooled to room temperature and stirring for two hours more. An aqueous solution of NaOH (1 M, 10 mL) was added to end the reaction and a classical work up had been performed. The crude oil was purified on silica gel with pentane/diethyl ether 8:2 → 6:4 giving red oil (418 mg, 85 %). $[\alpha]_D^{25} = -103.6°$ ($c = 15.0\ g\,L^{-1}$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, $J = 7.2$ Hz, 9H, CH_3-($SnBu_3$)), 0.92 (t, $J = 7.3$ Hz, 6H, -CH_2-Sn), 1.25 (q, $J = 5.6$ Hz, 6H, -CH_2-($SnBu_3$)), 1.38 (m, 8H, CH_2-CH_3, H5eq), 1.71 (dq, $J = 7.1$, 11.8 Hz, 1H, H5ax), 2.32 (s, 3H, CH_3 tol), 3.27 (dd, $J = 4.7$, 10.3 Hz, 1H, H7), 3.31 (s, 3H, H8), 3.35 (dd, $J = 5.6$, 10.2 Hz, 1H, H7), 3.86 (m, 2H, H6eq, H4), 4.22 (m, 1H, H6ax), 4.23 (d, $J = 2.2$ Hz, 1H, H4′), 4.36 (s, 5H, Cp), 4.73 (d, $J = 2.5$ Hz, 1H, H5′), 5.45 (s, 1H, H2), 7.13 (d, $J = 8.1$ Hz, 2H, Har), 7.47 ppm (d, $J = 8.1$ Hz, 2H, Har); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9 (CH_2 $SnBu_3$), 13.8 (CH_3 $SnBu_3$), 21.3 (CH_3 tol), 27.6 (CH_2 $SnBu_3$), 27.9 (C5), 29.3 (CH_2 $SnBu_3$), 59.3 (C8), 66.8 (C6), 67.6 (C3′), 70.8 (Cp), 71.9 (C4′), 75.3 (C7), 75.9 (C5′), 76.0 (C4), 89.4 (C1′), 94.9 (C2′), 99.1 (C2), 126.4, 129.1, 140.1, 144.2 ppm; elemental analysis calcd (%) for $C_{35}H_{52}FeO_4SSn$: C 56.55, H 7.05; found: C 56.44, H 7.15.

(2*S*,4*S*,S_p)-4-Methoxymethyl-2-α-[3′-tributyltin-ferrocenyl]-3,1-dioxane (7): Compound **6** (300 mg, 0.403 mmol) was dissolved under argon in THF (4 mL). At −78 °C *t*BuLi (0.296 mL, 0.444 mmol) was added dropwise into the mixture. After stirring at this temperature for 30 min, water was added and the cooling bath was removed. After 30 min, a classical work up was performed and the crude oil was purified on silica gel with dichloromethane giving the expected product as a red oil quantitatively. $[\alpha]_D^{25} = -26.1°$ ($c = 8.0\ g\,L^{-1}$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, $J = 7.3$ Hz, 9H, CH_3 $SnBu_3$), 1.00 (m, 6H, Sn-CH_2-), 1.35 (q, $J = 6.9$ Hz, 6H, CH_2 $SnBu_3$), 1.52 (m, 7H, H5eq, CH_2 ($SnBu_3$)), 1.79 (dq, $J = 5.1$, 12.2 Hz, 1H, H5ax), 3.43 (dd, $J = 4.7$, 10.3 Hz, 1H, H7), 3.44 (s, 3H, H8), 3.55 (dd, $J = 6.0$, 10.4 Hz, 1H, H7), 3.91 (td, $J = 2.6$, 14.1 Hz, 1H, H6eq), 3.96 (dd, $J = 1.1$, 2.2 Hz, 1H, H4′), 4.01 (m, 1H, H4), 4.11 (s, 5H, Cp), 4.21 (t, $J = 1.1$ Hz, 1H, H2′), 4.25 (dd, $J = 6.2$, 10.2 Hz, 1H, H6ax), 4.48 (dd, $J = 1.1$, 2.4 Hz, 1H, H5′), 5.42 ppm (s, 1H, H2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.3 (CH_2 $SnBu_3$), 13.8 (CH_3 $SnBu_3$), 27.5 (CH_2 $SnBu_3$), 28.2 (C5), 29.3 (CH_2 $SnBu_3$), 59.5 (C8), 66.8 (C6), 69.2 (Cp), 69.4 (C4′), 73.1 (C2′), 74.5 (C5′), 75.8 (C4), 76.2 (C3′), 88.5 (C1′), 100.5 ppm (C2); elemental analysis calcd (%) for $C_{28}H_{46}FeO_3Sn$: C 55.57, H 7.66; found: C 55.74, H 7.69.

(S_p)-3-Iodoferrocenylcarboxaldehyde (8): Compound **7** (201 mg, 0.34 mmol) was dissolved in dichloromethane (30 mL). Iodine (173 mg, 0.68 mmol) was added and the mixture was stirred overnight. An aqueous saturated solution of $Na_2S_2O_3$ was added (20 mL) following by a classical work up. The crude oil was purified by filtration on silica gel with dichloromethane as eluent giving the good product as red crystals quantitatively. $[\alpha]_D^{25} = -150°$ ($c = 2.0\ g\,L^{-1}$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.30 (s, 5H, Cp), 4.79 (dd, $J = 1.3$, 2.6 Hz, 1H, H5′), 4.83 (dd, $J = 1.1$, 2.4 Hz, 1H, H4′), 5.05 (t, $J = 1.1$ Hz, 1H, H2′), 9.87 ppm (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.6 (C3′), 70.5 (C4′), 72.6 (Cp), 75.8 (C5′), 79.7 (C2′), 79.9 (C1′), 192.3 ppm (CHO); IR ($CHCl_3$): $\tilde{\nu}$ = 1669.2, 1686.2 cm^{-1} (CO); elemental analysis calcd (%) for $C_{11}H_9FeIO + {}^1/_2Et_2O$: C 41.42, H 3.74; found: C 41.92, H 3.38.

(2*S*,4*S*,R_p)-4-Methoxymethyl-2-α-[5′-((*S*)-*p*-toluenesulfoxo)-2′-trimethylsilyl-ferrocenyl]-3,1-dioxane (9):[19] Compound **4** (600 mg, 1.9 mmol) was dissolved under argon in diethyl ether (9 mL). At −78 °C, *t*BuLi (1.39 mL, 2.1 mmol) was added dropwise. The cooling bath was removed and the mixture was stirred for 1 h at room temperature. Then the mixture was cooled to −78 °C and chlorotrimethylsilane (1.52 mL, 2.28 mmol) was added. The mixture was stirred at room temperature for 1 h and then the solvent removed under reduced pressure. The crude oil was dissolved in diethyl ether (9 mL) under argon. *t*BuLi (1.52 mL, 2.28 mmol) was added dropwise at −78 °C and the mixture was stirred at room temperature for 1 h before cooled again to −78 °C. Menthyl (*S*)-*para*-toluenesulfinate (780 mg, 4 mmol), dissolved in THF (3 mL), was added dropwise to the mixture. The cooling bath was removed and the mixture was stirred for 3 h more. A classical work up was performed and the crude oil was purified on silica gel with pentane/diethyl ether 7:3 giving a viscous orange oil (385 mg, 30 %). $[\alpha]_D^{25} = +146.2°$ ($c = 6.0\ g\,L^{-1}$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.24 (s, 9H, $SiMe_3$), 1.45 (d, $J = 11.9$ Hz, 1H, H5eq), 1.65 (dq, $J = 5.0$, 12.3 Hz, 1H, H5ax), 2.32 (s, 3H, CH_3 tol), 3.32 (m, 1H, H7), 3.32 (s, 3H, H8), 3.38 (m, 1H, H3), 3.88 (dt, $J = 2.67$, 11.6 Hz, 1H, H6eq), 3.94 (m, 1H, H4), 4.23 (ddd, $J = 1.1$, 11.3, 16.3 Hz, 1H, H6ax), 4.22 (d, $J = 2.5$ Hz, 1H, H3′), 4.40 (s, 5H, Cp), 4.79 (d, 1H, $J = 2.5$ Hz, H4′), 5.51 (s, 1H, H2), 7.17 (d, $J = 7.9$ Hz, 2H, Har), 7.58 ppm (d, $J = 8.2$ Hz, 2H, Har); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.6 ($SiMe_3$), 21.4 (CH_3 tol), 27.8 (C5), 59.2 (C8), 66.4 (C6), 71.7 (Cp), 74.1 (C2′), 75.0 (C3′), 75.4 (C7), 75.9 (C4′ and C4), 90.3 (C1′), 96.0 (C5′), 99.9, 125.12, 129.3, 140.2, 144.8 ppm; elemental analysis calcd (%) for $C_{26}H_{34}FeO_4SSi$: C 59.31, H 6.51; found: C 59.35, H 6.34.

(2*S*,4*S*,R_p)-4-Methoxymethyl-2-α-[5′-((*S*)-*p*-toluenesulfoxo)-4′-tributyltin-2′-trimethylsilyl-ferrocenyl]-3,1-dioxane (10):[19] Compound **9** (200 mg, 0.38 mmol) was dissolved in THF (2.4 mL) under argon. At −78 °C, lithiumdiisopropylamine (0.253 mL, 0.46 mmol) was added and the mixture was stirred at this temperature for 1 h. Chlorotributyltin (0.134 mL, 0.50 mmol) was added and the mixture was stirred for 30 min at this temperature and 2 h at room temperature. Aqueous NaOH (10 mL, 1 M) was added to the mixture following by a classical work up. The crude oil was purified on silica gel with dichloromethane as eluent yielding an orange viscous oil (190 mg, 62 %). $[\alpha]_D^{25} = +5.6$ ($c = 12\ g\,L^{-1}$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.28 (s, 9H, $SiMe_3$), 0.86 (t, $J = 7.2$ Hz, 9H, CH_3 ($SnBu_3$)), 0.91 (m, 6H, CH_2 ($SnBu_3$)), 1.27 (q, $J = 6.8$ Hz, 6H, Sn-CH_2),

1.39 (m, 8H, CH_2 ($SnBu_3$), H5), 2.33 (s, 3H, CH_3 (tol)), 3.21 (dd, J=4.78, 10.2 Hz, 1H, H7), 3.32 (s, 3H, H8), 3.33 (dd, J=4.6, 10.1 Hz, 1H, H7), 3.73 (dd, J=2.4, 11.4 Hz, 1H, H6eq), 3.81 (m, 1H, H4), 4.08 (dd, J=4.7, 11.5 Hz, 1H, H6ax), 4.12 (s, 1H, H4), 4.33 (s, 5H, Cp), 5.43 (s, 1H, H2), 7.13 (d, J=7.9 Hz, 2H, Har), 7.46 ppm (d, J=8.2 Hz, 2H, Har); ^{13}C NMR (75 MHz, $CDCl_3$): δ=0.6 ($SiMe_3$), 12.3 (CH_2-Sn), 13.8 (CH_3 ($SnBu_3$)), 21.3 (CH_3 (tol)), 27.6 (CH_2 ($SnBu_3$)), 29.4 (CH_2 ($SnBu_3$)), 59.3 (C1′), 65.9 (C5), 66.2 (C6), 69.9 (C4′), 70.9 (Cp), 74.9 (C7), 75.5 (C4), 82.2 (C3′), 92.3 (C1′), 96.3 (C5′), 99.9 (C2), 126.7, 129.0, 140.0, 144.8 ppm; elemental analysis calcd (%) for $C_{33}H_{50}FeO_2SSiSn$: C 55.55, H 7.06; found: C 56.23, H 7.12.

(2*S*,4*S*,*R*$_P$)-4-Methoxymethyl-2-α-[4′-tributyltin-2′-trimethylsilyl-ferrocenyl]-3,1-dioxane (11):[19] Compound **10** (190 mg, 0.233 mmol) was dissolved under argon in THF (2 mL). At −78°C *t*BuLi (0.186 mL, 0.28 mmol) was added dropwise to the mixture. After stirring at this temperature for 30 min, water was added and the cooling bath was removed. After 30 min, a classical work up was performed and the crude oil was purified on silica gel with dichloromethane giving the expected product quantitatively as a red oil. $[\alpha]_D^{25}$=−5.43° (c=15.0 g L^{-1}, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.22 (s, 9H, $SiMe_3$), 0.93 (t, J=7.14 Hz, 9H, CH_3 ($SnBu_3$)), 1.01 (m, 6H, CH_2 ($SnBu_3$)), 1.36 (q, J=6.9 Hz, 6H, CH_2-Sn), 1.59 (m, 8H, CH_2 ($SnBu_3$)), 1.79 (dq, J=5.1, 12.4 Hz, 1H, H5ax), 3.3 (s, 3H, H8), 3.4 (dd, J=4.7, 9.9 Hz, 1H, H7), 3.51 (dd, 1H, J=5.8, 9.8 Hz, H7), 3.85 (dd, $J_{H,H}$=1.3, $J_{H,Sn}$=4.1 Hz, 1H, H3′), 3.91 (td, J=1.5, 13.7 Hz, 1H, H6eq), 3.97 (m, 1H, H4), 4.06 (s, 5H, Cp), 4.28 (dd, J=3.9, 11.5 Hz, 1H, H6ax), 4.46 (dd, $J_{H,H}$=1.3, $J_{H,Sn}$=4.1 Hz, 1H, H5′), 5.53 ppm (s, 1H, H2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=0.4 ($SiMe_3$), 10.4 (CH_2-Sn), 13.8 (CH_3 ($SnBu_3$)), 27.5 (CH_2 ($SnBu_3$)), 28.3 (C5), 29.1 (CH_2 ($SnBu_3$)), 59.2 (C8), 66.9 (C6), 69.03 (Cp), 70.9 (C2′), 72.8 (C4′), 75.6 (C7), 75.8 (C4), 76.1 (C5′), 81.4 (C3′), 92.3 (C1′), 101.3 ppm (C2); elemental analysis calcd (%) for $C_{31}H_{54}FeO_3SiSn$: C 54.96, H 8.03; found: C 55.71, H 8.14.

(*R*$_P$)-4′-Iodo-2′-trimethylsilyl-ferrocenecarboxaldehyde 12:[19] Compound **11** (160 mg, 0.24 mmol) was dissolved in dichloromethane (20 mL), under air. Iodine (120 mg, 0.48 mmol) was added and the mixture was stirred overnight. A saturated aqueous solution of $Na_2S_2O_3$ (20 mL) was added to neutralize iodine and a classical work up was performed. The crude oil was purified on silica gel with dichloromethane giving product **12** (88 mg, 90%). $[\alpha]_D^{25}$=−104.3° (c=2.0 g L^{-1}, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.31 (s, 9H, $SiMe_3$), 4.28 (s, 5H, Cp), 4.72 (d, J=1.2 Hz, 1H, H3′), 5.20 (d, J=1.2 Hz, 1H, H5′), 9.94 ppm (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.1 ($SiMe_3$), 42.8 (C3′), 72.8 (Cp), 76.5 (C2′), 79.6 (C4′), 83.9 (C1′), 85.82 (C5′), 193.0 ppm (CHO); IR ($CHCl_3$): $\tilde{\nu}$=1677.6 cm^{-1} (CO); elemental analysis calcd (%) for $C_{14}H_{17}FeIOSi$: C 40.80, H 4.16; found: C 41.77, H 4.63.

(*R*$_P$)-3-Iodoferrocenylcarboxaldehyde (13): Compound **12** (88 mg, 0.21 mmol) was dissolved in THF (3 mL) under argon. TBAF (1 M in THF, 0.43 mL, 0.43 mmol) was added dropwise and the mixture was stirred 30 min. A classical work up was performed. The crude oil was purified by filtration on silica gel with dichloromethane giving quantitatively the good product as red crystals. $[\alpha]_D^{25}$=+149° (c=2.0 g L^{-1}, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.30 (s, 5H, Cp), 4.79 (dd, J=1.3, 2.6 Hz, 1H, H5′), 4.83 (dd, 1H, J=1.1, 2.4 Hz, H3′), 5.05 (t, J=1.1 Hz, 1H, H2′), 9.8 ppm (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ=41.6 (C3′), 70.5 (C2′), 72.6 (Cp), 75.9 (C5′), 79.7 (C4′), 79.9 (C1′), 192.3 ppm (CHO); IR ($CHCl_3$): $\tilde{\nu}$=1669.2, 1686.2 cm^{-1} (CO); elemental analysis calcd (%) for $C_{11}H_9FeIO$: C 38.87, H 2.67; found: C 39.54, H 2.74.

(*R*$_P$)-17α-[(3′-Formyl-ferrocenyl)ethynyl]estradiol (14): Compound **8** (100 mg, 0.294 mmol) and ethynylestradiol (121 mg, 0.294 mmol) were dissolved under argon in degassed diisopropylamine (5.2 mL). Cuprous diacetate monohydrate (3 mg, 0.0147 mmol) and dichlorobis(triphenylphosphine)palladium (10 mg, 0.0147 mmol) were added. The mixture was heated under reflux for 2 h and cooled to room temperature. Dichloromethane (20 mL) was added to the mixture which was filtered through Celite and evaporated under reduced pressure. The crude product was dissolved in dichloromethane (30 mL) and the organic phase was washed with HCl (1×10 mL, 5%) and with water (3×10 mL). The organic phase was dried on $MgSO_4$ and evaporated under reduced pressure. The crude product was purified on silica gel with dichloromethane/diethyl ether 10:0 → 8:2 giving the expected product as a red solid (120 mg, 90%). $[\alpha]_D^{25}$=+96.7° (c=3 g L^{-1}, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (s, 3H, Me13), 1.81 (m, 14H), 2.83 (m, 2H, H6), 4.31 (s, 5H, Cp), 4.82 (m, 2H, H4′, H5′), 5.04 (t, J=1.1 Hz, 1H, H2′), 5.56 (s, 1H, Ph-OH), 6.58 (d, J=2.1 Hz, 1H, H4), 6.65 (dd, J=2.4, 8.4 Hz, 1H, H2), 7.17 (d, J=8.4 Hz, 1H, H1), 9.89 ppm (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.9, 23.00, 26.5, 27.4, 29.7, 33.2, 39.1, 39.5, 43.9, 47.6, 50.0, 70.1 (C4′), 71.5 (Cp), 72.5 (C5′), 76.4 (C2′), 79.3 (C19), 80.5 (C3′), 82.4 (C20), 90.9 (C1′), 112.9, 115.4, 126.7, 132.2, 138.2, 153.7, 192.2 ppm (CHO); IR ($CHCl_3$): $\tilde{\nu}$=1671.8 cm^{-1} (CO); HRMS: calcd for $C_{31}H_{33}O_3Fe$: 509.1780; found: 509.1777.

(*S*$_p$)-17α-[(3′-Formyl-ferrocenyl)ethynyl]estradiol (15): Compound **13** (50 mg, 0.147 mmol) and ethynylestradiol (60 mg, 0.147 mmol) were dissolved under argon in degassed diisopropylamine (2.6 mL). Cuprous diacetate monohydrate (1.5 mg, 0.0075 mmol) and dichlorobis(triphenylphosphine)palladium (5.15 mg, 0.0075 mmol) were added. The mixture was heated under reflux for 2 h and cooled to room temperature. Dichloromethane (10 mL) was added to the mixture which was filtered through celite and evaporated under reduced pressure. The crude product was dissolved in dichloromethane (15 mL) and the organic phase was washed with HCl (1×5 mL, 5%) and water (3×5 mL). The organic phase was dried on $MgSO_4$ and evaporated under reduced pressure. The crude product was purified on silica gel with dichloromethane/diethyl ether 10:0 → 8:2 giving the expected product (37 mg, 60%). $[\alpha]_D^{25}$=−110.7° (c=8 g L^{-1}, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (s, 3H, Me18), 1.81 (m, 14H,), 2.83 (m, 2H, H6), 4.31 (s, 5H, Cp), 4.82 (m, 2H, H4′, H5′), 5.04 (t, J=1.1 Hz, 1H, H2′), 5.56 (s, 1H, Ph-OH), 6.58 (d, J=2.10 Hz, 1H, H4), 6.65 (dd, J=2.4, 8.4 Hz, 1H, H2), 7.17 (d, J=8.4 Hz, 1H, H1), 9.89 ppm (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.9, 23.0, 26.5, 27.4, 29.7, 33.2, 39.2, 39.5, 43.9, 47.7, 50.0, 70.1 (C4′), 71.5 (Cp), 72.6 (C5′), 76.2 (C2′), 79.5 (C19), 80.5 (C3′), 82.4 (C20), 90.9 (C1′), 112.8, 115.4, 126.6, 132.4, 138.3, 153.6, 193.0 ppm (CHO); HRMS: *m*/*z*: calcd for $C_{31}H_{33}O_3Fe$: 509.1780; found: 509.1774.

Crystal data for compound 8: Crystal suitable for X-ray diffraction was obtained by slow evaporation of diethyl ether solution of the complex: $C_{11}H_9FeIO$, M=339.93, orthorhombic, space group $P2_12_12_1$, red crystal, a=5.708(1), b=11.641(1), c=16.075(2) Å, V=1068.1(2) Å^3, ρ_{calcd}=2.114 g cm^{-3}, Z=4, μ=4.263 mm^{-1}, F(000)=648. Data were collected on a Nonius KappaCCD diffractometer (graphite $Mo_{K\alpha}$ radiation, 0.71073 Å) at 173 K. 3083 unique reflections collected with ($2.16 < \theta < 30.05°$), 1836 data with $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXS97) and refined anisotropically on F^2 by using the SHELXL97 procedure. Hydrogen atoms were included by using a riding model (SHELXL97). Absorption was semi empirically corrected with the use of SORTAV software (R. H. Blessing, *Crystallogr. Rev.* **1987**, *1*, 3–58).

Final results: $R1(F^2)$=0.0378, $wR2(F^2)$=0.1306, GoF=0.856, 127 parameters, largest difference peak=1.063 e Å^{-3}.

CCDC-272861 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/.

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