New Ferrocenyl Chiral Auxiliary Substituents for Amines. Applications to Syntheses of Mossambine and Vinblastine

Martin E. Kuehne,* Wenning Dai, and Yun-Long Li

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

mkuehne@zoo.uvm.edu

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(+)−(*R*)-1,2-(α-(*R*)-Mesyloxy-*β*-dimethyltetramethylene)-ferrocene was synthesized and used as a chiral auxiliary for N-alkylation of methyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*] indole-5-*ξ*−carboxylates. Condensation with aldehydes then provided tetracyclic products in a diastereomeric ratio of at least 97:3. Gentle cleavage in acetic acid removed the chiral auxiliary to give the corresponding secondary amines in >99% ee. Thus, key intermediates leading to mossambine and vinblastine could be synthesized with high enantioselectivity. The enantioselectivity greatly exceeds that found with other chiral N-auxiliaries developed in our studies.

In our long-standing program of syntheses of indole and indoline alkaloids, based on a biomimetic secodine-type reaction, we required a chiral auxiliary amine substituent that would provide enantioselectivity in this (reverse electron demand) Diels−Alder reaction step (Figure 1). To that end, we had developed a ferrocenylethyl chiral auxiliary **1** as the first chiral moiety that could be introduced onto an amine function at an advanced stage of a synthetic sequence and that could be subsequently removed with recovery.[1] While this chiral substituent provided complete enantioselectivity for our vinblastine synthesis,[1,2] it was less effective in other analogous reactions. Ratios of 5 or 6:1 of diastereomeric intermediates **2** were obtained in syntheses of vincadifformine, *ψ*-vincadifformine, and ibophyllidine.[3] The poorest result was found in the synthesis of mossambine, where the acetoxy-substituted enamine intermediate gave only a 1.2:1 ratio of diastereomeric Diels−Alder products.[3]

Molecular modeling of potential chiral N^b-substituents suggested that diastereoselectivity would be increased in the Diels−Alder step by increasing the size of the ferrocenyl ethyl substituent (i.e., larger than methyl) and by increasing its rigidity. Consequently, the ferrocenodimethylcyclohexyl mesylate **3** was synthesized and found to provide excellent diastereoselectivity for the Diels−Alder-type reaction step.

In the development of this reagent we first examined the ferrocenocyclohexene derivative **4** where an element of rigidity, but no steric bulk, is introduced relative to the ferrocenylethyl system **1**. While we had found only a 2:1 diastereoselectivity in the reaction of the indoloazepine derived from a ferrocenylethyl reagent **5** lacking a diphenylphosphine substituent, the corresponding ferrocenocyclohexene derived indoloazepines **6a,b**, obtained from reagent **4**, now provided a 7−9:1 ratio (NMR estimates) of chromatographically inseparable diastereomeric products **7** and **8** (Scheme 1), with the aldehyde

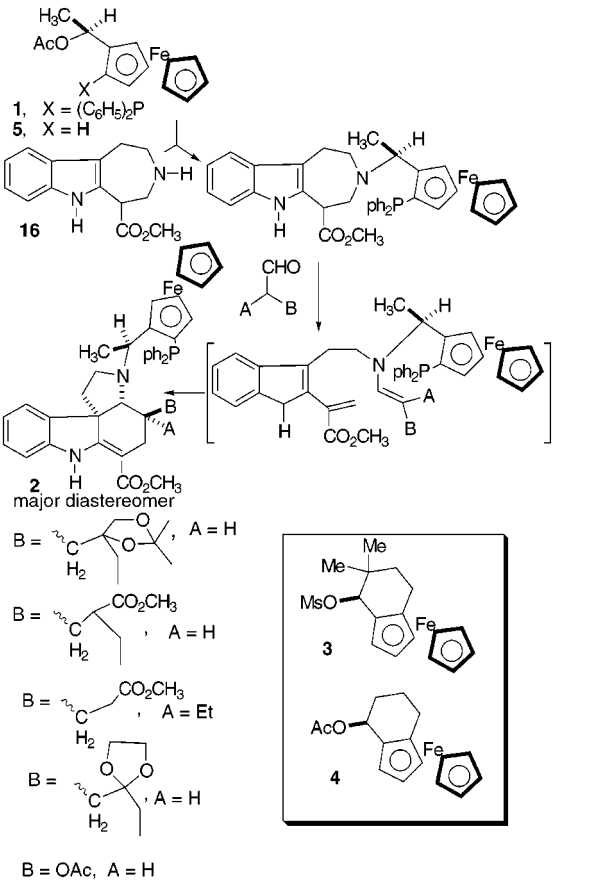

Figure 1. The new chiral auxiliary **3** is readily prepared, linked to, and removed from amines. It gives much better chiral induction than reagents **1**, **4**, or **5**.

9 used in the vinblastine synthesis. (Note: The homo chiral α-naphthylethyl substituent gave only a 4:1 ratio of diastereomers.[2]) The ferrocenocyclohexene reagent **4** was obtained by acetylation of 1,2-(α-*endo*-hydroxytetramethylene)-ferrocene.[4]

(1) Kuehne, M. E.; Bandarage, U. K. *J. Org. Chem.* **1996**, *61*, 1175.
(2) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513.
(3) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y.-L.; Wang, T. *J. Org. Chem.* **1998**, *63*, 2172.
(4) Hill, E. A.; Richards, J. H. *J. Am. Chem. Soc.* **1961**, *83*, 4216.

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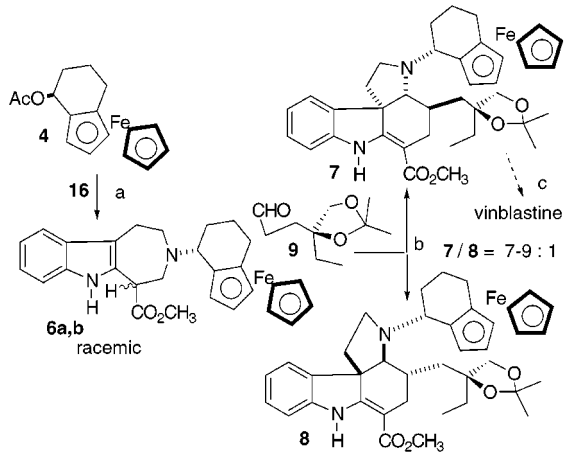
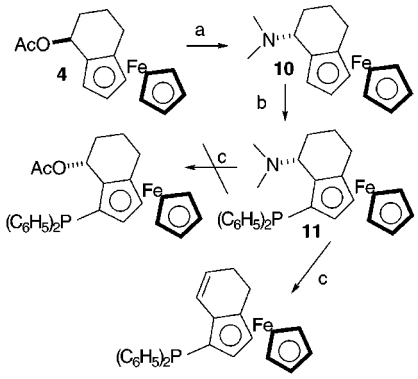
Scheme 1



[a] *t*-BuOH, 80 °C, 6 h, 24%. [b]Dry benzene, 4 h refl, 68%. [c]Analogous to refs **1**, **2**.

Scheme 2



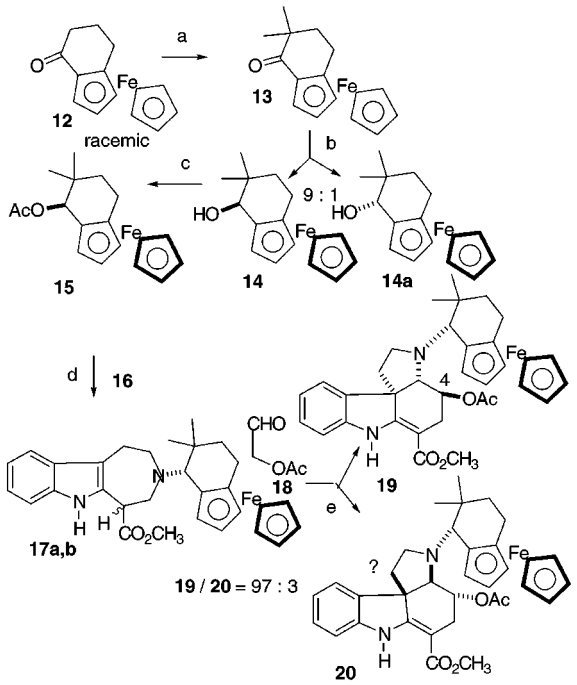
[a] Me_2NH, MeOH, Et_3N, 24 h, 80 °C, 98%. [b]BuLi, Et_2O, rt, 20 min; Ph_2PCl, Et_2O, refl, 4 h, 96%. [c]Δ, HOAc.

Since the presence of a diphenylphosphine substituent in reagent **1** had resulted in complete diastereoselectivity in the Diels–Alder reaction of the enamine derived from the aldehyde **9**,[1] introduction of this substituent into the reagent **4** was attempted. For that (Scheme 2), the acetate function was replaced by dimethylamine (98%) and the product **10** was treated with *n*-butyllithium, followed by chlorodiphenylphosphine (96%).

While the phosphine substituent could thus be introduced in excellent yield, subsequent regeneration of an acetate from the dimethylamine product **11** could not be achieved on heating in acetic acid due to a preferential elimination reaction, with formation of a cyclohexene derivative.

To block this elimination pathway, and at the same time to also achieve increased substitution bulk α to the functional center of the chiral auxiliary, the precursor cyclohexenone **12**[5] was dimethylated (Scheme 3) with KH and methyl iodide (95%), and the resulting dimethyl ketone **13** was reduced, quantitatively, with lithium aluminum hydride to the endo alcohol **14** and its exo epimer **14a** in a ratio of 9:1 in analogy to reduction of the ferrocenocyclohexenone **12**.[4] An acetate derivative **15** was formed from the major alcohol **14** with acetic

Scheme 3



[a] KH, THF, rt 50 min; MeI, rt 1 h, 95%. [b]LAH, Et_2O, 90 min, 100%. [c]Ac_2O, pyridine, 20 h, 87%. [d]Et_3N, EtOH, refl 19 h, 29%. [e] Dry benzene, refl 22 h, 76%.

anhydride (85%). While the acetate **15** was sluggish in its reaction with the indoloazepine **16** (29% yield), a corresponding mesylate **3** (nonracemic, Scheme 5) was later found to give an excellent yield (97%) of the epimeric ester *N*-alkylation products **(+)-17a,b**.

The new chiral auxiliary **15** was then tested in comparison with our initial chiral auxiliary **1** in its least favorable reaction. Thus, the condensation of its derived indoloazepines **17a,b** with 2-acetoxyacetaldehyde (**18**) gave essentially only one tetracyclic acetate **19**. A minor product, which could not be chromatographically separated from the main product **19** for characterization and which was formed in a 3:97 ratio (by NMR and HPLC), is tentatively assigned the diastereomeric tetracyclic structure **20** (Scheme 3).[6] Thus, increasing steric bulk and rigidity at the center for attachment to the amine had made an additional diphenylphosphine substituent on the ferrocene moiety unnecessary for good diastereoselectivity.

For generation of the nonracemic reagent **3**, the ketone **12** was resolved by its reaction with the anion derived from *n*-butyllithium and (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (Scheme 4) or its enantiomer.[7] Exo addition to the racemic ketone, in accord with the results of a reaction of the homo chiral ketone with phenyllithium,[8] provided the diastereomeric carbinols **21a** and **21b** (100%). (The enantiomers **21c,d** were obtained by addition of the (−)-(*R*)-reagent.) Chromatographic separation

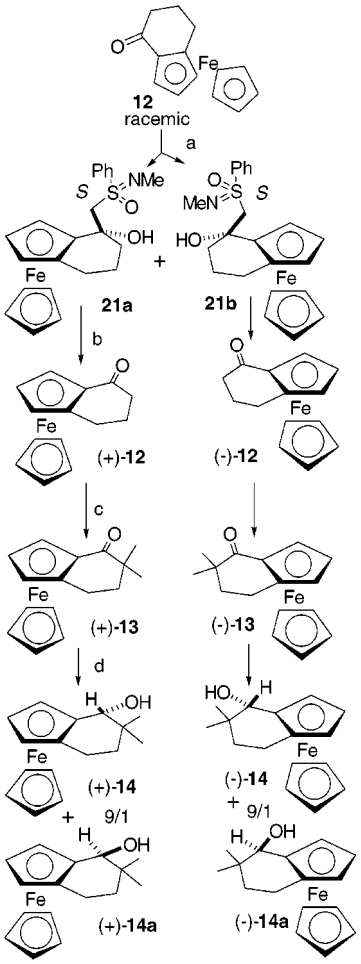
(5) Rinehart, K. L.; Curby, R. J., Jr.; Gustafson, D. H.; Harrison, K. G.; Bozak, R. E.; Bublitz, D. E. *J. Am. Chem. Soc.* **1962**, *84*, 3262.

(6) While our previous syntheses of mossambine had given no indication of tetracyclic C-4 epimeric acetoxy products (93% yield: Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, *61*, 7873. 81–90%: ref 3, for this reaction step), the small (3%) amount of minor product from the present reaction suggests that a 4-*epi*-acetoxy **19** structure should also be considered in place of structure **20**.

(7) (a) Johnson, C. R.; Zeller, J. R. *Tetrahedron* **1984**, *40*, 1225. (b) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3.

(8) Schlögl, K.; Fried, M.; Falk, H. *Monatsh. Chem.* **1964**, *95*, 576.

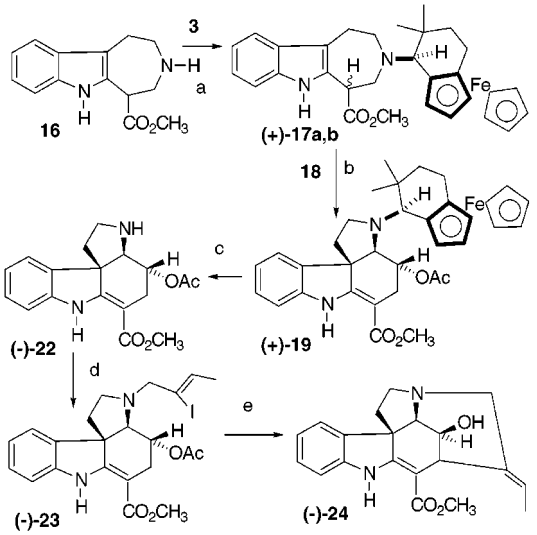
Scheme 4



[a] (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine, BuLi, THF, 0 °C; THF, −78 to −20 °C, 3 h, 100%. [b] Dry toluene, refl, 14 h, 100% [c] KH, THF, rt 50 min; MeI, rt. 1 h, 95%. [d] LAH, Et_2O, 90 min, 100%.

of the two diastereomeric alcohol products **21a** and **21b** and pyrolysis gave the respective enantiomeric ketone products **(+)-12** and **(−)-12** in quantitative yields. The absolute configuration of the former, obtained (albeit less pure) by alternative routes,[8,9] had been established.[10] Methylation of these separate products, followed by reduction of the resulting dimethyl ketones **(+)-13** and **(−)-13** with lithium aluminum hydride, led to the enantiomeric alcohols **(+)-14** and **(−)-14** and their hydroxy epimers **(+)-14a** and **(−)-14a** in a ratio of 9:1 in accord with the reduction of of the ketone **(+)-12**.[10b] A reaction of the alcohol **(+)-14** with mesyl chloride for formation of the nonracemic reagent **(+)-3**, its condensation with the indoloazepine **16** (Scheme 5), and a subsequent reaction of the product **(+)-17a,b** with 2-acetoxyacetaldehyde (**18**), following the above sequence of reactions of the racemic compounds, provided the enantiomerically pure (ee > 99%) tetracyclic acetate **(+)-19** in 76% yield, after chromatography. Enantiomeric purity was checked by chiral HPLC comparison with the racemic product, which was obtained, above, with the same yield and which showed baseline separation of the enantiomers. Again, a minor (3%) uncharacterized component, which

Scheme 5



[a] **(+)-14**, MsCl, Et_3N, CH_2Cl_2, 10 °C, 3 h; isopropanol, −78 to 10 °C, 14 h, 97%. [b] Acetoxyacetaldehyde, dry benzene, refl 22 h, 76%. [c] HOAc, rt, 22 h, 98%. [d] (*Z*)-1-Br-2-l-but-2-ene, K_2CO_3, THF, refl 14 h, 70%. [e] Ref 3.

could be a diastereomer, was also detected in the homo chiral product **(+)-19**.

Removal of the chiral auxiliary substituent in acetic acid at room temperature (98%) and alkylation of the secondary amine product **(−)-22** with (*Z*)-1-bromo-2-iodobut-2-ene gave the key intermediate **(−)-23** (70%, ee > 99%) for cyclization to mossambine **(−)-24**.[3]

Conclusion. The ferrocenodimethylcyclohexenol **14**, through its mesylate, is a new chiral auxiliary for N-alkylation. It can be introduced and later removed under very mild conditions. Its chiral induction in the studied intramolecular Diels−Alder reactions was excellent, even in an example where an earlier ferrocenyl analogue had given us only marginal selectivity.

For the generation of this new reagent, a quantitative resolution of its ferrocenocyclohexenone precursor **12** was developed. Previous methodology had been tedious and provided the enantiomers of **12**, which have been key compounds in several studies,[11,12] in lower yield and purity.[8, 9]

As a corollary, the enantiomeric synthesis of mossambine, through the reagent **14**, derived from the ketone **12,** now also provides a chemical definition of the absolute configuration of this class of dialkylferrocenes.[12]

Experimental Section

(±)−(3a*R,4*R**,11b*S**)- and (3a*S**,4*S**,11b*S**)-Methyl 3-(2,3-(*S**)-Ferroceno-1(*R**)-cyclohexyl)-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-isopropylidinedioxy)]-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (7 and 8).** To a solution of 1,2-(α-*endo*-hydroxytetramethylene)-ferrocene[4] (0.718 g, 2.80 mmol) in dry pyridine (3.57 mL) at 0 °C was added acetic anhydride (3.57 mL). The solution was stirred at 0 °C for 20 min, then warmed to room temperature with stirring for 20 h. The mixture was cooled to 0 °C. MeOH (1 mL) was added, and the mixture stirred for 15 min. It was then poured into water (10 mL) and extracted with ether (3 × 13 mL). The combined ether extracts were washed with 5% HCl (2 × 5 mL), 10% $NaHCO_3$ solution (2 × 5 mL), water (10 mL), and brine

(9) Thomson, J. B. *Tetrahedron Lett.* **1959**, *6*, 26.
(10) (a) Schlögl, K.; Falk, H. *Angew. Chem.* **1964**, *76*, 570; (b) Falk, H.; Schlögl, K. *Monatsh. Chem.* **1965**, *96*, 265, 1081.
(11) Lehner, H.; Schlögl, K. *Monatsh. Chem.* **1970**, *101*, 895.
(12) Schlögl, K. *Fortschr. Chem. Forsch.* **1966**, *6*, 479.

(10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc, 10:1) to give 0.620 g (74%) of the acetate **4** as a red liquid. ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 1 H), 1.82 (m, 1 H), 1.94−2.00 (m, 2 H), 2.17 (s, 3 H), 2.25 (m, 1 H), 2.63 (m, 1 H), 4.03−4.13 (m, 8 H), 5.49 (m, 1 H).

A solution of the acetate **4** (78 mg, 0.26 mmol), indoloazepine **16** (155 mg, 0.64 mmol), and dry triethylamine (73 μL) in dry *t*-BuOH (2 mL) was heated at 80 °C for 6 h and then concentrated under reduced presssure. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (3 × 5 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was chromatographed on activity I alumina (hexane/EtOAc, 6:1) to give 30 mg (24%) of the (±)-methyl 3-(2,3-(*S**)-ferroceno-1(*R**)-cyclohexyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-ζ-carboxylates (**6a,b**). TLC R_f = 0.39 (hexane/EtOAc, 5:2, CAS yellow-blue).

A solution of the ferrocenocyclohexylindoloazepines **6a,b** (30 mg, 0.062 mmol) and 4-(*S*)-ethyl-4,5-dihydroxypentanal acetonide **9**[2] (22 mg, 0.12 mmol) in dry benzene (2 mL) was heated at reflux for 4 h.The solvent was then evaporated under reduced pressure. The residue was dissolved in dry MeOH (1.5 mL), and $NaBH_4$ (11 mg, 0.29 mmol) was added, with stirring, to reduce excess aldehyde, which contaminated the product. After the mixture was stirred at room temperature for 15 min, water (4 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL), and the combined extracts were dried over Na_2SO_4. Concenration and chromatography (eluting solvent: hexane/EtOAc, 6:1) afforded an inseparable mixture of diastereomers **7** and **8** as a yellow solid (27 mg, 68%) in a 7−9:1 ratio, on the basis of the overlapped NH signals in the ^{1}H NMR spectrum. TLC R_f = 0.37 (hexane/EtOAc, 5:2, CAS blue); UV (EtOH) λ_{max} 210, 300, 330; IR (KBr) ν_{max} 3381, 2931, 2856, 1677, 1610, 1466, 1437, 1369, 1293, 1278, 1244, 1204, 1126, 1105, 1053, 912, 806, 734 cm^{-1}; MS *m*/*z* (rel intensity) 650 (M^+, 3), 239 (18).

1,2-(α-*exo*-Dimethylaminotetramethylene)-5-(diphenylphospheno)-ferrocene (11). A solution of the endo acetate **4** (1.30 g, 4.36 mmol) and dimethylamine (2 M in MeOH, 25 mL, 50 mmol) and triethylamine (1.22 mL, 8.72 mmol) in dry MeOH (10 mL) was heated at 80 °C for 24 h. Then the mixture was concentrated under reduced pressure and chromatographed on alumina (CH_2Cl_2) to give 1,2-(α-*exo*-dimethylaminotetramethylene)-ferrocene (**10**, 1.20 g, 98%) as a red liquid. TLC R_f = 0.29 (hexane/Et_2O, 5:2, CAS blue); IR (KBr) ν_{max} 3091, 2930, 2855, 2818, 2774, 1451, 1440, 1354, 1338, 1267, 1186, 1155, 1133, 1105, 1053, 1025, 1018, 999, 948, 876, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 1 H), 1.97−2.19 (m, 3 H), 2.25 (m, 1 H), 2.28 (s, 6 H), 2.60 (m, 1 H), 4.12∼4.19 (m, 7 H, including 5 H s at 4.08), 4.17 (m, 1 H), 4.42 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.2, 22.5, 25.1, 40.5, 61.5, 65.3, 65.5, 66.1, 69.6, 85.6, 86.4; MS (CI,CH_4) *m*/*z* (rel intensity) 285 (M^+ + 2, 1), 239 (4), 123 (10), 119 (6).

Butyllithium (1.6 M in hexane, 3.14 mL, 5.02 mmol) was added to a solution of the amine **10** (546 mg, 1.93 mmol) in 15 mL of dry ether, at room temperature, over 20 min. The mixture was stirred at room temperature for 1.5 h and chlorodiphenylphosphine (0.88 mL, 4.90 mmol) in 7 mL of dry ether was added with heating at gentle reflux in the course of 45 min. After 4 h of reflux, 10 mL of 10% $NaHCO_3$ was slowly added with cooling in an ice-bath. The separated organic layer and benzene extracts obtained from extraction of the aqueous phase were combined, washed with water (2 × 5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under vacuum. Chromatography of the red oil on silica gel (hexane/EtOAc, 6:1) gave the title product **11** as orange crystals (864 mg, 96%). TLC R_f = 0.52 (hexane/EtOAc, 5:2, yellow); IR (KBr) ν_{max} 3069, 3052, 2930, 2854, 2816, 2773, 1727, 1585, 1476, 1434, 1360, 1324, 1269, 1199, 1179, 1154, 1140, 1107, 1093, 1070, 1054, 1024, 1002, 951, 909, 872, 816, 741, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 1 H), 1.63 (s, 6 H), 1.84 (m, 2 H), 1.94 (m, 1 H), 2.24 (m, 1 H), 2.50 (br d 1 H), 3.72 (s, 1 H), 3.88 (s, 5 H), 4.20 (s, 1 H), 4.32 (dd, J = 6.5 and 8.0 Hz, 1 H), 7.21 (m, 3 H), 7.32 (m, 3 H), 7.38 (m, 2 H), 7.61 m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.7, 22.4, 25.4, 39.5, 59.5, 67.1, 69.7, 70.9, 89.7, 92.1, 92.4, 127.4, 127.5, 127.6, 127.7, 128.3, 132.8, 133.0, 134.9, 135.1; MS (CI, CH_4) *m*/*z* (rel intensity) 468 (M^+ + 1, 25), 467 (M^+, 100), 424 (12), 423 (31), 283 (2), 282 (2), 239 (10), 238 (9), 185 (2).

(±)−(3a*S,4*S**,11b*S**)- and (3a*R**,4*R**,11b*R**)-Methyl 3-(2,3-(*S**)-Ferroceno-6,6-dimethyl-1(*R**)-cyclohexyl)-2,2,-3a,4,5,7-hexahydro-4-acetoxy-1*H*-pyrrolo[2.3-*d*]carbazole-6-carboxylate (19 and 20).** The racemic endo alcohol **14** (0.589 g, 2.074 mmol) was converted to its acetate derivative **15** (0.584 g, 87%) by the procedure given for the didemethyl analogue **4**. The red oil, chromatographed on silica gel (hexane/EtOAc, 7:1), had TLC R_f = 0.51 (hexane/EtOAc, 5:1, yellow); IR (KBr) ν_{max} 3095, 2959, 2979, 2850, 1731, 1443, 1388, 1370, 1244, 1106, 1017, 978, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3 H), 1.03 (s, 3 H), 1.38 (ddd, J = 1.8, 2.7, 5.0 Hz, 1 H), 2.08 (dt, J = 5.2, 12.6 Hz, 1 H), 2.19 (s, 3 H), 2.30 (dt, J = 5.2, 12.6 Hz, 1 H), 2.55 (ddd, J = 2.5, 5.2, 15.9 Hz, 1 H), 4.04 (m, 1 H), 4.06 (m, 1 H), 4.11 (s, 5H), 4.12 (s, 1 H), 5.05 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.8, 23.9, 25.9, 32.1, 33.8, 64.4, 66.6, 67.0, 69.0, 73.4, 85.8, 86.3, 107.6; MS (CI, CH_4) *m*/*z*(rel intensity) 328 (M^+ + 2, 1), 327 (M^+ + 1, 4), 326 (M^+, 23), 269 (3), 268 (15), 267 (100).

A solution of the acetate **15** (0.518 g, 1.59 mmol), the indoloazepine **16** (1.564 g, 6.41 mmol), and triethylamine (0.91 mL) in dry ethanol (5 mL), was heated at reflux for 19 h and then concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (15 mL) and washed with water (2 × 6 mL). The organic layer was dried over Na_2SO_4, concentrated, and chromatographed on silica gel (hexane/EtOAc, 11:1) to give the (±)-methyl 3-(2,3-(*S**)-ferroceno-6,6-dimethyl-1(*R**)-cyclohexyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-ζ-carboxylates (**17a,b**, 237 mg, 29%) as an orange solid, mp 78−99 °C (diastereomeric mixture). TLC R_f = 0.40 (hexane/EtOAc, 5:2, yellow, CAS green); UV (EtOH) λ_{max} 242, 284 nm; IR (KBr) ν_{max} 3401, 3089, 2958, 2919, 2847, 1729, 1463, 1338, 1260, 1103, 1027, 910, 801, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.71 (s, 3 H), 1.10 (m, 3 H), 1.51 (m, 5 H), 2.01 (dt, J = 5.2, 12.5 Hz, 1 H), 2.34 (m, 1 H), 2.45∼2.52 (m, 2 H), 2.86 (m, 2 H), 2.95−3.05 (m, 1 H), 3.39 (m, 1 H), 3.61 (m, 1 H), 3.71 (s, 3 H), 3.86 (s, 1 H), 3.95 (s, 1 H), 4.01 (s, 5 H), 4.06 (s, 1 H), 4.12 (m, 2 H), 7.08∼7.16 (m, 2 H), 7.26∼7.53 (m, 2 H), 7.85, 8.80 (2s, 1 H); MS (CI, CH_4) *m*/*z* (rel intensity) 511 (M^+ + 1, 6), 510 (M^+, 4), 269 (21), 268 (45), 267 (100), 246 (4), 245 (13), 244 (7), 243 (3).

A solution of the racemic indoloazepine derivatives **17a**,**b** (31 mg, 0.062 mmol) and acetoxyacetaldehyde **18** (1.43 N in CH_2Cl_2, 0.112 mL, 0.160 mmol) in dry benzene (2 mL) was heated at reflux for 22 h. The solvent was removed under vacuum and the residue chromatographed on silica gel (hexane/EtOAc, 18:1) to provide, as a yellow solid, the racemic product **19** including, as a minor component, the presumed diastereomer **20** (27.9 mg, 76%) in a ratio of 29:1 on the basis of the NH NMR signals and HPLC. No mp, dec > 170 °C; TLC R_f = 0.53 (hexane/EtOAc, 5:2, yellow, CAS blue); UV (EtOH) λ_{max} 240, 298, 328 nm; IR (KBr)$_{max}$ 3381, 3084, 2952, 2912, 2846, 1728, 1681, 1611, 1467, 1437, 1374, 1273, 1243, 1198, 1131, 1094, 1027, 998, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 3 H), 1.25 (m, 2 H), 1.27 (s, 3 H), 1.48∼1.51 (m, 1 H), 1.63 (m, 1 H), 1.92 (s, 3 H), 2.01 (m, 1 H), 2.13 (m, 1 H), 2.36 (m, 1 H), 2.49 (m, 1 H), 2.78 (dd, J = 2.1, 16.0 Hz, 1 H), 3.07∼3.20 (m, 3 H), 3.69 (d, J = 1.5 Hz, 1 H), 3.82 (s, 3 H), 3.95 (s, 1 H), 4.06∼4.13 (m, 7 H), 4.96 (s, 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 6.94 (t, J = 7.4 Hz, 1 H), 7.20 (t, J = 7.6 Hz, 1 H), 7.33 (d, J = 7.3 Hz, 1 H), 9.09 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.2, 21.5, 21.9, 22.6, 24.8, 25.3, 29.8, 31.6, 34.7, 39.4, 39.5, 44.3, 51.0, 55.7, 61.8, 66.8, 69.7, 71.3, 71.7, 88.2, 109.4, 120.9, 122.5, 128.1, 136.8, 143.4, 164.1, 168.9, 170.7; MS (CI, CH_4) *m*/*z* (rel intensity) 595 (M^+ + 1, 2), 594 (M^+, 2), 328 (3), 269 (6), 268 (14), 267 (51), 255 (3), 254 (7), 253 (30), 237 (2), 225 (3), 209 (1).

Resolution of 1,2-(α-Ketotetramethylene)-ferrocene ((±)-12) Through (+)-(*S*)-*N*,*S*-Dimethyl-*S*-Phenylsulfoximine Adducts 21a and 21b. To a solution of (+)−(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (0.118 mL, 0.792 mmoL, ∼2 equiv) in dry THF (5 mL) at 0 °C was added a solution of *n*-butyllithum in hexane (1.6 M, 0.490 mL, ∼2 equiv). After 15 min of stirring, the mixture was cooled to −78 °C, and

racemic ferrocenyl ketone **(±)-12**[5] (100 mg, 0.394 mmol) in dry THF (1 mL) was then added dropwise over 10 min. The mixture was stirred for an additional 3 h, while being allowed to warm to −20 °C, at which temperature saturated ammonium chloride (3.25 mL) was added. The mixture was diluted with water (15 mL) and extracted with ether (3 × 25 mL). The ether phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was subjected to chromatography on silica gel and eluted with ethyl acetate/hexane (1:6) to give two diastereoisomers: **21a** (83 mg, 50%) as crystals, and **21b** (83 mg, 50%) as a yellow foam. The total yield was 100%. For **21a**: TLC $R_f = 0.59$ (silica gel, hexane/ethyl acetate, 5:4, yellow); mp 141−142 °C dec; $[\alpha]^{25}_D = +275$ (c 0.35, $CHCl_3$); IR (KBr) ν_{max} 3269, 3091, 2937, 2874, 1582, 1477, 1445, 1413, 1243, 1220, 1209, 1149, 1106, 1082, 1071, 999, 883, 818, 773, 741, 692, 576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (m, 2 H), 7.60−7.52 (m, 3 H), 6.91 (br s, 1 H), 4.19 (s, 5 H), 4.07 (s, 1 H), 4.02 (s, 1 H), 3.96 (t, $J = 2.3$ Hz, 1 H), 3.34 (d, $J = 14.0$ Hz, 1 H), 3.15 (d, $J = 14$ Hz, 1 H), 2.71−2.61 (m, 5 H including 3 H, s), 2.41 (1 H, m), 2.28 (1 H, 2 t, $J = 5.6$ Hz), 2.09 (1 H, m), 1.68 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 139.01, 132.97, 129.47, 128.92, 92.87, 85.68, 71.68, 69.79, 65.91, 65.75, 64.01, 62.24, 35.97, 28.78, 24.16, 21.11; MS (CI, isobutane) *m/z* (rel intensity) 424 ($M^+ + 1$, 18), 423 (M, 34), 254 (29), 170 (100), 154 (3), 106 (2), 77 (2). Anal. Calcd for $C_{22}H_{25}O_2NSFe$: C, 62.42; H, 5.95; N, 3.31; S, 7.57; Fe, 13.19. Found: C, 62.32; H, 5.83; N, 3.22; S, 7.66; Fe, 12.80.

For **21b**: TLC $R_f = 0.44$ (silica gel, hexane/ethyl acetate, 5:4, yellow); mp 93−94 °C; $[\alpha]^{25}_D = -57$ (c 0.41, $CHCl_3$); IR (KBr) ν_{max} 3253, 3090, 2934, 2875, 1582, 1475, 1466, 1445, 1240, 1144, 1106, 1083, 999, 879, 817, 773, 743, 693, 572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.59−7.51 (m, 3 H), 6.11 (br s, 1 H), 4.27 (d, $J = 1.0$ Hz, 1 H) 4.15 (s, 5 H), 4.10 (s, 1 H), 4.01 (t, $J = 2.4$ Hz, 1 H), 3.46 (d, $J = 14.3$ Hz, 1 H), 3.35 (d, $J = 14.3$ Hz, 1 H), 2.73 (s, 3 H), 2.62 (m, 1 H), 2.26−2.17 (m, 2 H), 1.94 (m, 1 H), 1.85 (m, 1 H), 1.36 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 139.82, 132.70, 129.25, 128.78, 92.67, 85.53, 70.27, 69.61, 65.78, 65.66, 65.36, 63.44, 36.94, 29.04, 23.88, 20.25; MS (CI, isobutane) *m/z* (rel intensity) 424 ($M^+ + 1$, 13), 423 (M^+, 23), 255 (28), 170 (100), 156 (7). Anal. Calcd for $C_{22}H_{25}O_2NSFe$: C, 62.42; H, 5.95; N, 3.31; S, 7.57; Fe, 13.19. Found: C, 62.40; H, 5.87; N, 3.22; S, 7.48; Fe, 12.76.

Resolution of 1,2-(α-Ketotetramethylene)-ferrocene ((±)-12) Through (−)-(*R*)-*N*,*S*-Dimethyl-*S*-Phenylsulfoximine Adducts 21c and 21d. Following the above procedure, the reaction of racemic ferrocenyl ketone **(±)-12** with (−)-(*R*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine gave two diastereoisomers: **21c** (50%) as crystals, and **21d** (50%) as a yellow foam. The total yield was 100%. For **21c**: TLC $R_f = 0.59$ (silica gel, hexane/ethyl acetate, 5:4, yellow); mp 142−143 °C dec; $[\alpha]^{25}_D = -281$ (c 0.45, $CHCl_3$); IR (KBr) ν_{max} 3272, 3091, 2934, 2874, 1582, 1478, 1445, 1243, 1219, 1208, 1149, 1106, 1082, 1071, 812, 879, 773, 741, 692, 576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (m, 2 H), 7.59−7.51 (m, 3 H), 6.91 (br s, 1 H), 4.19 (s, 5 H), 4.06 (s, 1 H), 4.02 (s, 1 H), 3.95 (t, $J = 2.3$ Hz, 1 H), 3.33 (d, $J = 14.0$ Hz, 1 H), 3.15 (d, $J = 14.0$ Hz, 1 H), 2.72−2.61 (m, 5 H, including 3 H, s), 2.41 (m, 1 H), 2.27 (2 t, $J = 5.5$ and 5.5 Hz, 1 H), 2.08 (m, 1 H), 1.68 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.94, 132.93, 129.42, 128.86, 92.82, 85.61, 71.62, 69.73, 65.86, 65.71, 63.93, 62.20, 35.91, 28.74, 24.11, 21.06; MS (CI, isobutane) *m/z* (rel intensity) 424 ($M^+ + 1$, 100), 423 (M^+, 93), 270 (11), 254 (92), 170 (98); Anal. Calcd for $C_{22}H_{25}O_2NSFe$: C, 62.42; H, 5.95; N, 3.31; S, 7.57; Fe, 13.19. Found: C, 62.36; H, 5.89; N, 3.20; S, 7.51; Fe, 12.95.

For **21d**: TLC $R_f = 0.44$ (silica gel, hexane/ethyl acetate, 5:4, yellow); mp 142−143 °C; $[\alpha]^{25}_D = +57$ (c 0.41, $CHCl_3$); IR (KBr) ν_{max} 3253, 3090, 2934, 2875, 1582, 1478, 1467, 1445, 1240, 1144, 1106, 1083, 999, 879, 817, 773, 743, 693, 572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.60−7.52 (m, 3 H), 6.09 (br s, 1 H), 4.27 (d, $J = 1.0$ Hz, 1 H), 4.16 (s, 5 H), 4.10 (s, 1 H), 4.02 (t, $J = 2.4$ Hz, 1 H), 3.46 (d, $J = 14.3$ Hz, 1 H), 3.35 (d, $J = 14.3$ Hz, 1 H), 2.73 (s, 3 H), 2.62 (m, 1 H), 2.27−2.17 (m, 2 H), 1.94 (qd, $J = 7.2$ and 2.6 Hz, 1 H), 1.85 (m, 1 H), 1.37 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 139.82, 132.70, 129.25, 128.78, 92.67, 85.53, 70.27, 69.61, 65.78, 65.66, 65.36, 63.44, 36.94, 29.04, 23.88, 20.25; mass spectrum (CI, isobutane) *m/z* (rel intensity) 424 ($M^+ + 1$, 100), 423 (M^+, 37), 339 (25), 270 (11), 254 (58), 170 (65); Anal. Calcd for $C_{22}H_{25}O_2NSFe$: C, 62.42; H, 5.95; N, 3.31; S, 7.57; Fe, 13.19. Found: C, 62.35; H, 6.02; N, 3.17; S, 7.43; Fe, 12.63.

(+)-(*R*)-1,2-(α-Ketotetramethylene)-ferrocene ((+)-12). A solution of adduct **21a** (4.11 g, 9.70 mmoL) in dry toluene (120 mL) was heated at reflux overnight, then purified by flash chromatography on silica gel (elution with ethyl acetate/hexane 2:5) to afford ketone **(+)-12** (2.46 g, 100%) as orange-red crystals: mp 80−82 °C, (lit. 78−80 °C,[8] 83−85 °C[9]); $[\alpha]^{25}_D = +668$ (c 0.72, $CHCl_3$), (lit $[\alpha]^{15}_D = +585$,[8] +550[9] (c 0.3, $CHCl_3$)); ^1H NMR ($CDCl_3$) δ 4.83 (m, 1 H), 4.47 (s, 1 H), 4.45 (m, 1 H), 4.18 (s, 5 H), 2.65 (m, 2 H), 2.43 (m, 1 H), 2.33 (m, 1 H), 2.19 (m,1 H), 2.10 (m, 1 H).

Following the same procedure, adduct **21d** was converted to compound **(+)-12** (100%).

(−)-(*S*)-1,2-(α-Ketotetramethylene)-ferrocene ((−)-12). A solution of adduct **21b** (3.64 g, 8.59 mmol) in dry toluene (100 mL) was heated at reflux overnight, then purified by flash chromatography on silica gel (elution with ethyl acetate/hexane 2:5) to afford ketone (−)-**12** (2.16 g, 100%) as a orange-red crystals: mp 82−83 °C, (lit.[7] 76−79 °C[8]); $[\alpha]^{25}_D = -683$ (c 0.43, $CHCl_3$), (lit.[8] $[\alpha]^{20}_D = -580$ (c 0.5, EtOH)); 100% ee, on the basis of a chiral shift experiment (using a 0.1M solution of Eu(hfc)$_3$, [tris(3-heptafluoropropyl-hydroxymethylene)-*d*-camphorato]europium(III) in $CDCl_3$ as chiral shift reagent); ^1H NMR data matched data for **(+)-12**.

Following the same procedure, adduct **21c** was converted to compound **(−)-12** (100%).

(+)−(*R*)-1,2-(α-Keto-*β*-dimethyltetramethylene)-ferrocene ((+)-13). A 100-mL round-bottom flask was equipped with a magnetic stirring bar. The flask was charged with KH (5.80 g, 35 wt % dispersion in mineral oil, 51 mmol). Dry THF (20 mL) was injected, followed by dropwise addition of ketone **(+)-12** (3.02 g, 12 mmol) in dry THF (10 mL) over 10 min at room temperature. After the mixture was stirred for an additional 40 min, methyl iodide (17.0 mL, 273 mmol) was added dropwise over a 15 min period. The mixture was stirred at room temperature for 1 h, followed by treatment with water (2 mL) at 0 °C. The aqueous layer was extracted with ether (2 × 30 mL). The combined ether layers were washed with brine (10 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate, 7:1) to afford the dimethylated product **(+)-13** (3.26 g, 98%) as an orange solid: TLC $R_f = 0.57$ (silica gel, hexane/ethyl acetate, 5:2); mp 89−90 °C; $[\alpha]^{25}_D = +554$ (c 0.34, $CHCl_3$); IR (KBr) ν_{max} 3095, 2962, 1669, 1472, 1381, 1360, 1345, 1331, 1266, 1106, 1036, 953, 817, 683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81 (m, 1 H), 4.43 (m, 2 H), 4.20 (s, 5 H), 2.52 (m, 2 H), 2.34 (m, 1 H), 1.81 (m, 1 H), 1.29 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.19, 91.37, 74.32, 70.72, 70.00, 69.73, 65.94, 42.80, 38.21, 25.19, 23.80, 20.79; MS (CI,CH_4) *m/z* (rel intensity) 283 ($M^+ + 1$, 100), 282 (M, 25), 267 (7). Anal. Calcd for $C_{16}H_{18}OFe$: C, 68.11; H, 6.43. Found: C, 68.15; H, 6.49.

(−)-(*S*)-1,2-(α-Keto-*β*-dimethyltetramethylene)-ferrocene ((−)-13). Following the above procedure, the reaction of ketone **(−)-12** with methyl iodide gave the dimethylated product **(−)-13** (98%): $[\alpha]^{25}_D = -554$ (c 0.40, $CHCl_3$). Anal. Calcd for $C_{16}H_{18}OFe$: C, 68.11; H, 6.43. Found: C, 68.01; H, 6.48.

Racemic 1,2-(α-Keto-*β*-dimethyltetramethylene)-ferrocene (13). Following the same procedure with the racemic ketone **12** gave a 95% yield of the dimethylation product. Its TLC and ^1H NMR data matched those of the separate enantiomers described above.

(+)−(*R*)-1,2-(α-(*R*)-Hydroxy-*β*-dimethyltetramethylene)-ferrocene ((+)-14) and (+)−(*R*)-1,2-(α-(*S*)-Hydroxy-*β*-dimethyltetramethylene)-ferrocene ((+)-14a). To a solution of dimethyl ketone **(+)-13** (1.59 g, 5.63 mmol) in Et_2O (15 mL) at 0 °C was added LAH (0.260 g, 6.85 mmol). The mixture was stirred in an ice−water bath for 90 min, followed by addition of water (0.9 mL) at 0 °C, with stirring for 0.5 h, then

stirring was continued at room temperature for an additional 2h. The mixture was filtered, and the filtrate was diluted with Et_2O (20 mL). The ether phase was washed with brine (5 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was separated by chromatography on silica gel (hexane/ethyl acetate, 12:1 to 7:1) to give the less polar product **(+)-14** (1.45 g, 90%) as a deep red oil (endo alcohol) and the more polar product **(+)-14a** (0.172 g, 10%) as a yellow solid (exo alcohol). For **(+)-14**: TLC $R_f = 0.63$ (silica gel, hexane/ethyl acetate, 5:2, yellow); $[\alpha]^{25}_D = +64$ (c 0.55, $CHCl_3$); IR (KBr) ν_{max} 3528, 3092, 2952, 2923, 2872, 1648, 1448, 1387, 1363, 1106, 1041, 1013, 982, 818, 661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.17 (m, 5 H), 4.15 (s, 1 H), 4.09 (s, 2 H), 3.55 (d, $J = 6.7$ Hz, 1 H), 2.40 (m, 1 H), 2.19−2.26 (m, 2 H), 1.94 (dt, $J = 5.3$ and 12.3 Hz, 1 H), 1.28 (m, 1 H), 1.12 (s, 3 H), 0.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 94.35, 86.46, 69.86, 68.69, 66.59, 65.74, 65.10, 34.72, 31.30, 25.83, 24.00, 21.64; MS (CI, isobutane) *m/z* (rel intensity) 285 (M^++1, 14), 284 (M^+, 53), 268 (20), 267 (100). Anal. Calcd for $C_{16}H_{20}OFe$: C, 67.62; H, 7.09. Found: C, 67.50; H, 7.33.

For **(+)-14a**: TLC $R_f = 0.47$ (silica gel, hexane/ethyl acetate, 5:2); mp 53−55 °C; $[\alpha]^{25}_D = +111$ (c 0.50, $CHCl_3$); IR (KBr) ν_{max} 3364, 3099, 2952, 2908, 2850, 1766, 1700, 1648, 1475, 1450, 1411, 1382, 1364, 1272, 1251, 1134, 1105, 1045, 1029, 1013, 994, 832, 805, 677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.72 (br s, 1 H), 4.39 (s, 1 H), 4.00 (s, 7 H), 2.42 (dd, $J = 4.1$ and 15.6 Hz, 1 H), 2.32 (m, 1 H), 1.90 (dt, $J = 5.5$ and 12.7 Hz, 1 H), 1.55 (m, 1 H), 1.43 (br s, 1 H), 1.11 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 87.18, 84.21, 76.76, 69.65, 66.21, 65.41, 65.01, 36.14, 35.42, 27.98, 21.44, 17.21; MS (CI, isobutane) *m/z* (rel intensity) 285 (M^+ + 1, 18), 284 (M^+, 71), 267 (100), 131 (2), 59 (17). Anal. Calcd for $C_{16}H_{20}OFe$: C, 67.62; H, 7.09. Found: C, 67.45; H, 7.23.

When the same procedure was followed, enantiomeric ketone **(−)-13** was reduced by LAH to the endo alcohol **(−)-14** (90%) and the exo alcohol (−)-**14a** (10%). For **(−)-14**: $[\alpha]^{25}_D = -65$ (c 0.52, $CHCl_3$). For (−)-**14a**: mp 54−56 °C; $[\alpha]^{25}_D = -111$ (c 0.52, $CHCl_3$).

Racemic 1,2-(α-*endo*- and *exo*-Hydroxy-*β*-dimethyltetramethylene)-ferrocene (14 and 14a). Reduction of the racemic ketone **13** with LAH, by the above procedure, provided the racemic endo alcohol **14** as a red oil (90%) and the exo alcohol **14a** as a yellow solid (10%). TLC and NMR data matched those of the separate enantiomers given above.

Methyl 3-(2,3-(*R*)-Ferroceno-6,6-dimethyl-1(*S*)-cyclohexyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-*ξ*-carboxylates ((+)-17a,b). To a stirred solution of the endo alcohol **(+)-14** (1.05 g, 3.70 mmol) and triethylamine (1.41 mL) in CH_2Cl_2 (8 mL), at −78 °C under nitrogen, was added a solution of mesyl chloride (0.640 mL, 8.27 mmol) in CH_2Cl_2 (6 mL). After the addition, the temperature of the reaction mixture was raised to 10 °C over 3 h. The yellow slurry was then injected, over 5 min, with cooling in a dry ice/acetone bath, into a solution of the indolozepine **16** (1.05 g, 4.31 mmol, 1.16 equiv) in 2-propanol (41 mL) at −78 °C. After the mixture was stirred overnight at 10 °C, the volatile components were evaporated at reduced pressure (temperature of the bath < 50 °C). The residue was diluted with Et_2O (35 mL). The organic phase was washed with brine (10 mL) and concentrated under reduced pressure to give the crude product **(+)-17a,b** (1.82 g, 97%) as a chromatographically inseparable mixture of C-5 epimeric esters. This orange solid crude product was used in subsequent reactions. A small portion of the crude product was purified by flash column chromatography on silica gel, with eluant (hexane/ethyl acetate 10:1). Mp of diastereomeric mixture 82−94 °C. TLC $R_f = 0.40$ (silica gel, hexane/ethyl acetate, 5:2, yellow, CAS green); $[\alpha]^{25}_D = +232$ (c 0.36, $CHCl_3$); UV (EtOH) λ_{max} 242, 284 nm; IR (KBr) ν_{max} 3401, 2958, 2919, 2847, 1729, 1463, 1338, 1260, 1103, 1027, 801, 739 cm^{-1}; MS (CI, isobutane) *m/z* (rel intensity) 511 (M^++1, 6), 510 (M^+, 4), 267 (100), 245 (13), 147 (7), 83 (11), 71 (19); EI HRMS calcd $C_{30}H_{34}N_2O_2Fe$ (M^+) 510.1969, found 510.1970.

(3a*R*,4*R*,11b*R*)-Methyl 3-(2,3-(*R*)-Ferroceno-6,6-dimethyl-1(*S*)-cyclohexyl)-2,3,3a,4,5,7-hexahydro-4-acetoxy-1*H*-pyrrolo[2.3-*d*]carbazole-6-carboxylate ((+)-19). A solution of ferrocenylindoloazepine **(+)-17a,b** (31 mg, 0.062 mmol) and acetoxyacetaldehyde (1.43 N in CH_2Cl_2, 0.112 mL, 0.160 mmol) in dry benzene (2 mL) was heated at reflux for 22 h. The solvent was removed under reduced pressure. The crude product was subjected to chromatography on silica gel (hexane/ethyl acetate 18:1) to provide the title compound **(+)-19** (28 mg, 76%) as a yellow solid, > 99.5% ee on the basis of a chiral HPLC experiment: 250 × 4.6 mm Chiracel OD column, 2-propanol/hexane, 1:9, flow rate 0.80 mL/min, retention time 8.29 min; no **(−)-19** detected but 0.5% detectable in a test mixture with **(+)-19**; racemic **19** retention times, 8.29 and 10.36 min. The product, crystallized from ether−hexane, decomposed at 174−178 °C. TLC $R_f = 0.53$ (silica gel, hexane/ethyl acetate, 5:2, yellow, CAS blue); $[\alpha]^{25}_D = +6$ (c 0.32, $CHCl_3$); UV (EtOH) λ_{max} 240, 298, 328 nm; IR (KBr) ν_{max} 3381, 3084, 2952, 2912, 2846, 1728, 1681, 1611, 1467, 1437, 1374, 1273, 1243, 1198, 1131, 1094, 1027, 998, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.09 (s, 1 H), 7.33 (d, $J = 7.4$ Hz, 1 H), 7.20 (t, $J = 7.6$ Hz, 1 H), 6.94 (t, $J = 7.6$ Hz, 1 H), 6.88 (d, $J = 7.8$ Hz, 1 H), 5.32 (s, 1 H), 4.95 (s, 1 H), 4.14 (s, 5 H), 4.09−4.07 (2 H, m), 3.96 (1 H, s), 3.82 (3 H, s), 3.69 (1 H, d, $J = 1.3$ Hz), 3.20−3.08 (m, 3 H), 2.79 (dd, $J = 1.8$ and 16.0 Hz, 1 H), 2.48 (m, 1 H), 2.37 (m, 1 H), 2.12 (m, 1 H), 2.01 (m, H), 1.92 (s, 3 H), 1.63 (m, 1 H), 1.49 (dd, $J = 4.2$ and 13.0 Hz, 1 H), 1.27 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.70, 168.83, 164.04, 143.32, 136.72, 128.02, 122.42, 120.89, 109.32, 88.11, 86.37, 85.35, 71.61, 71.22, 69.80, 66.78, 65.28, 65.17, 61.77, 55.70, 50.94, 44.28, 39.48, 39.34, 29.75, 24.73, 21.88, 21.43, 21.14, 14.06; MS (CI, isobutane) *m/z* (rel intensity) 595 (M^+ + 1, 4), 594 (M^+, 21), 156 (11), 147 (23), 91 (10), 83 (100), 69 (96); EI HRMS calcd $C_{34}H_{38}N_2O_4Fe$ (M^++1) 595.2259, (M^+) 594.2181, found 595.2189, 594.2176.

(3a*R*,4*R*,11b*R*)-Methyl 2,3,3a,4,5,7-Hexahydro-4-acetoxy-1*H*-pyrrolo[2.3-*d*]carbazole-6-carboxylate ((−)-22). The tetracycle **(+)-19** (0.205 g, 0.345 mmol) was dissolved in acetic acid (1.5 mL) and stirred under nitrogen at room temperature for 22 h. The reaction mixture was cooled to 0 °C and added to concentrated ammonium hydroxide (7 mL), which was already cooled by addition of crushed ice. The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with brine (6 mL) and concentrated under reduced pressure. The resulting residue was subjected to chromatography on silica gel (2% MeOH in CH_2Cl_2) to provide the title product **(−)-22** as a colorless oil (111 mg, 98%). TLC $R_f = 0.38$ (silica gel, 10% MeOH in CH_2Cl_2, CAS blue to yellow); UV (EtOH) λ_{max} 234, 300, 326 nm; $[\alpha]^{25}_D = -425$ (c 0.13, $CHCl_3$), reported[3] $[\alpha]^{25}_D = -225$ (c 0.1, $CHCl_3$); ^1H NMR δ 9.07 (s, 1 H), 7.21−7.17 (m, 2 H), 6.92−6.86 (m, 2 H), 4.89 (m, 1 H), 3.77 (s, 3 H), 3.64 (s, 1 H), 3.24 (1 H, m), 3.16 (1 H, m), 2.99−2.94 (1 H, m), 2.55 (1 H, dd, $J = 2.5$ and 16.2 Hz), 2.05−2.01 (m, 1 H), 1.86 (s, 3 H), 1.83 (m, 1 H); MS (CI, isobutane) *m/z* (rel intensity) 329 (M^++1, 100), 328 (M^+, 13), 269 (34), 268 (M^+ − AcOH, 19), 223 (13), 117 (25), 107 (95); EI HRMS calcd $C_{18}H_{20}N_2O_4$ (M^++1) 329.1501, (M^+) 328.1423, found 329.1453, 328.1437.

(3a*R*,4*R*,11b*R*)-Methyl 3-(Z-2-Iodobut-2-en-1-yl)-2,2,-3a,4,5,7-hexahydro-4-acetoxy-1*H*-pyrrolo[2.3-*d*]carbazole-6-carboxylate ((−)-23). A mixture of secondary amine **(−)-22** (68 mg, 0.207 mmol), (*Z*)-1-bromo-2-iodobut-2-ene (81 mg, 0.310, ∼1.5 equiv), and potassium carbonate (139 mg, 1.01 mmol) in reagent-pure THF (10 mL) was heated at reflux overnight under nitrogen. After filtration of the inorganic materials, the filtrate was concentrated under reduced pressure and chromatographed on silica gel (hexane/ethyl acetate 3:1) to yield the title compound **(−)-23** (74 mg, 70%) as a white foam. TLC $R_f = 0.57$ (silica gel, ethyl ether/hexane, 2:1, CAS blue to gray); $[\alpha]^{25}_D = -267$ (c 0.58 $CHCl_3$), reported[3] $[\alpha]^{25}_D = -252$ (c 0.5 $CHCl_3$); UV (EtOH) λ_{max} 208, 238, 300, 328 nm; IR (KBr) ν_{max} 3382, 2947, 2802, 1733, 1687, 1611, 1479, 1466, 1435, 1245, 1206, 1092, 916, 741 cm^{-1}. An ^1H NMR spectrum matched that previously reported.[3]

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Supporting Information Available: ^{1}H NMR spectra for compounds **4, 7/8, 10, 11, (+)-13, (+)-14, (+)-14a, 15, 17a,b, 19 (20), (+)-19, 21a, 21b, (−)-22**; ^{13}C NMR spectra for **10, 11, (+)-13, (+)-14, (+)-14a, (15), 19, (+)-19, 21a, 21b**; IR spectra for compounds **7/8, 10, 11, (+)-13, (+)-14, (+)-14a, 15, 17a,b, 19, 21a, 21b**; and chiral HPLC graphs for racemic **19** and **(+)-19**. This information is available free of charge via the Internet at http://pubs.acs.org.

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