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Application of Ferrocenylalkyl Chiral Auxiliaries to Syntheses of Indolenine Alkaloids: Enantioselective Syntheses of Vincadifformine, *ψ*- and 20-*epi*-*ψ*-Vincadifformines, Tabersonine, Ibophyllidine, and Mossambine

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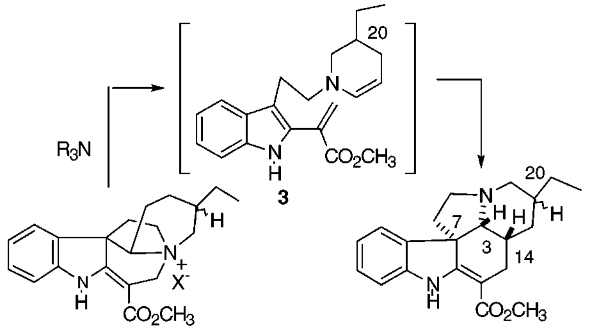
Condensations of the chiral *N*-ferrocenylethylindoloazepines **4a**,**b**, with the aldehydes **5**, **13**, **19**, **29**, and **32**, led to tetracyclic vinylogous urethanes **6a**,**b** and **7**, **14a** and **14b**, **21a**,**c** and **21b**,**d**, **30a** and **31a**, and **30b** and **31b**. Respectively, 6:1, 5:1, 3:1, 1.7:1, and 2:1 diastereomeric selections provided intermediates which, on cleavage of the chiral auxiliary N-substituent and subsequent elaboration of ring D of the *Aspidosperma* and *Strychnos* alkaloids, provided enantiomerically pure (−)-*ψ*- and (−)-*epi*-*ψ*-vincadifformines (**1**, **2**), (+)-ibophyllidine (**12**), (+)- and (−)-vincadifformine (**16a**, **16b**), (−)-tabersonine (**27**), and (−)-mossambine (**41**).

The present enantioselective alkaloid syntheses were undertaken in order to ascertain the practical limits of chiral *N*-ferrocenylethyl enamine substituents for achieving enantioselective intramolecular Diels−Alder reactions of the isosecodine type, using methodology by which we had synthesized a variety of racemic *Aspidosperma*, *Iboga*, and *Strychnos* alkaloids.

Application of our biomimetic isosecodine chemistry to syntheses of the racemic *ψ*- and 20-*epi*-*ψ*-vincadifformines (**1**, **2**) had allowed the identification and assignment of relative stereochemistry of the natural, nonracemic alkaloid mixture.[1] The racemic alkaloids were formed in a 4:1 ratio from the transient enamine acrylate (isosecodine) intermediate **3** (Scheme 1) and corresponded to the 4:1 ratio of natural occurrence. For an enantioselective synthesis of these alkaloids, extension of this strategy to an intermediate (**3**) with a defined absolute stereochemistry at C-20 would result in a 4:1 mixture of diastereomers with opposite absolute configurations at C-3, C-7, and C-14. To generate the two *ψ*- and 20-*epi*-*ψ*-vincadifformine (**1**, **2**) diastereomers with the same absolute stereochemistry at C-3, C-7, and C-14, and differing in absolute stereochemistry at C-20, an alternative synthetic path was required. With the discovery of complete enantioselectivity (at C-3, C-7, C-14) in the reaction of the ferrocenylethyl-substituted indoloazepines **4a** with an aldehyde precursor to vinblastine,[2] it seemed that this approach could also provide enantioselective access to the two *ψ*-vincadifformine epimers **1** and **2** (Scheme 2). While either enantiomer of the indoloazepines **4a**,**4b** is available,[2] the enantiomer **4a** leading to the *ent*-(−)-*ψ*-vincadifformines was chosen for this study.

Scheme 1



1, 20 αEt + **2**, β Et
4 : 1

A reaction of the indoloazepines **4a** with 4-(methoxycarbonyl)hexanal (**5**) was not as highly enantioselective as our earlier example,[2] providing the C-3, C-7, and C-14 enantiomeric pairs **6** and **7** in a 6:1 ratio. No stereoselectivity was found at the side chain chiral center, with the separable C-20 *S* (**6a**) and C-20 *R* (**6b**) epimers isolated in equal amounts from the major enantiomeric product. Heating of these tetracyclic compounds **6a** or **6b** in acetic acid at 110 °C for 10 min resulted in cleavage of the chiral auxiliary substituent, epimerization at C-3 and C-7, and cyclization of the transient secondary amino esters.

Under these conditions, the chiral auxiliary substituent was converted to the corresponding vinylferrocene.[2] However, when heated to 70 °C in acetic acid, the tetracyclic intermediates **6a**,**b** provided mostly the chiral ferrocenylethyl acetate **8** (for reuse in synthesis of the indoloazepines **4a**)[2] and a mixture of secondary amines **9**, derived from incomplete epimerization at C-3 and C-7.

The lactam products **10a** and **10b** were converted to thiolactams **11a** and **11b** with phosphorus pentasulfide, and these products were desulfurized with Raney nickel to provide (−)-*ψ*-vincadifformine (*ent*-**1**) and (−)-*epi*-*ψ*-vincadifformine (*ent*-**2**) in >99% ee.[3] These products can thus be obtained in four steps (16% and 14% overall yields) from the racemic aldehyde **5** and the indoloazepines **4**, with one chromatographic separation of diastereomers. Use of a single enantiomer of the aldehyde **5**[4] would allow

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[1] Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.

[2] Kuehne, M. E.; Bandarage, U. K. *J. Org. Chem.* **1996**, *61*, 1175.

[3] For ee determination by NMR chiral shift, see: Sullivan, G. R. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1978; p 287.

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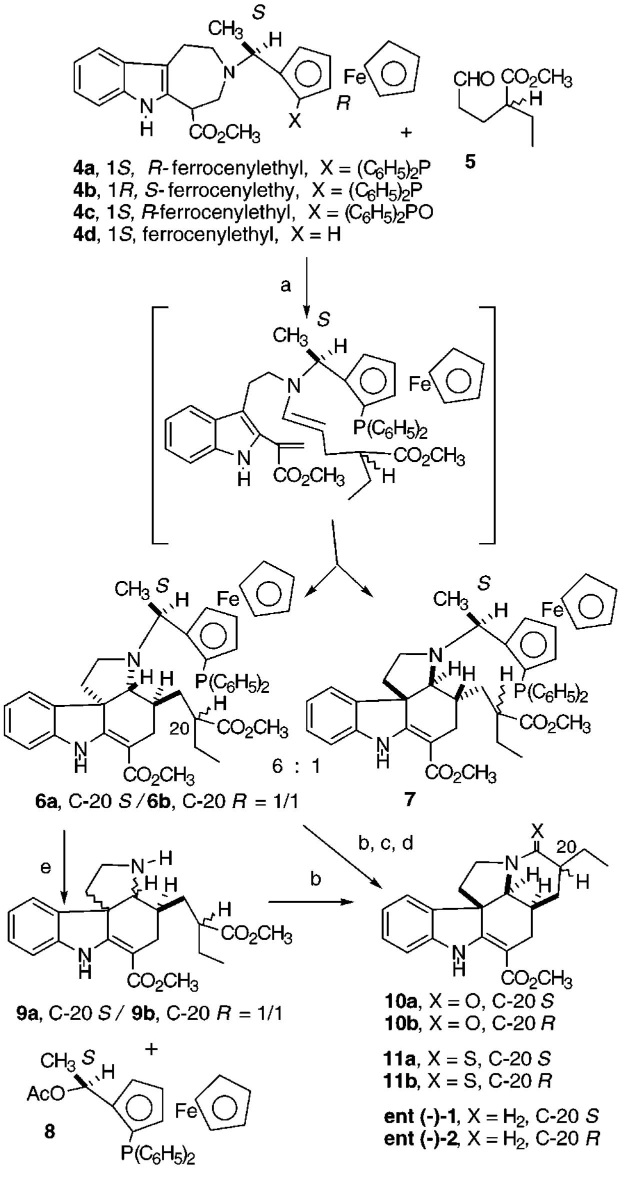
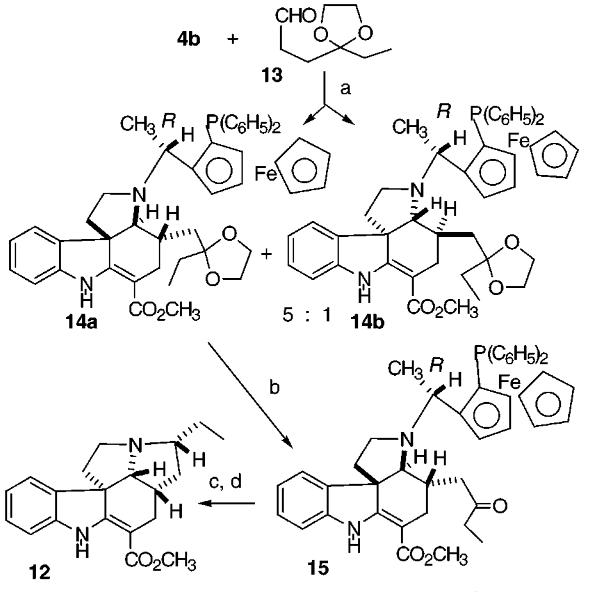
Scheme 2



a. C_6H_6, reflux, 71%; b. HOAc, 100 °C, 94%, 91%; c. P_4S_{10}, rt, 76%, 64%; d. R Ni, 76%, 78%; e. HOAc, 70 °C.

Scheme 3



a. C_6H_6, reflux, 90%; b. 10% HCl, 99%; c. HOAc, 70 °C; d. H_2 / Pd, 60% for c + d.

the enantioselective synthesis of either product **1** or **2** in 30% overall yield.

Comparison of the optical rotation of natural "ψ-vincadifformine" ($[\alpha]_D = +430$, apparently somewhat impure),[5] which was shown to consist of a 4:1 mixture of ψ- and *epi*-ψ-vincadifformines,[1] with the optical rotation values obtained for the two synthetic *ent* products above ($[\alpha]_D = -506$ and -450, respectively), allows one to conclude that the natural isomers have the same absolute configuration at C-3, C-7, and C-14 and are epimeric at C-20. Consequently, they do not arise from cyclization of a common isosecodine, according to the synthetic process of Scheme 1, which would give a 4:1 mixture of (impure) isomers with $[\alpha]_D < +300$. The natural products are thus more likely formed by a dehydrosecodine cyclization, followed by a subsequent reduction with generation of the C-20 chiral center.

A synthesis of (+)-ibophyllidine (**12**) by the same general strategy for achieving enantioselection provided a reaction sequence unencumbered by the formation of a C-20 (1:1) enantiomeric pair of tetracyclic intermediates that was encountered in the preceding syntheses of the ψ-vincadifformines (**1**, **2**). Condensation of the indoloazepines **4b** with 4,4-(ethylenedioxy)hexanal (**13**)[6] furnished a 5:1 diastereomeric mixture of tetracyclic ketals **14a** and **14b** (Scheme 3). While the aldehyde in this reaction is γ-disubstituted, analogous to the aldehyde used in the vinblastine synthesis, which had resulted in a single enantiofacial 4 + 2 cyclization reaction,[2] the enantioselection was now actually decreased somewhat relative to that found in the above-described synthesis of the ψ-vincadifformines (**1**, **2**). Ketal hydrolysis of the major tetracyclic product **14a** was followed by cleavage of the chiral auxiliary substituent of the ketone **15** in acetic acid at 70 °C. Epimerization at C-3 and C-7 and cyclization to a pentacyclic enamine and its hydrogenation followed the sequence developed for the corresponding racemic compound[6,7] and provided (+)-ibophyllidine (**12**) in 60% yield and > 98% ee.

For further exploration of this new methodology, a synthesis of vincadifformine (**16**, Scheme 8) offered the opportunity to determine if a β-disubstituted enamine intermediate is compatible with the enantioselection induced by the chiral ferrocenylethyl N-substituent. We had previously found that racemic tetracyclic esters **17a**,**b** were formed without selection for *E* and *Z* enamine intermediates by either the condensation of the N-benzylated indoloazepine **18** with the aldehyde ester **19** at 110 °C[8] or by fragmentation of the quaternary bridged

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(4) See Kuehne and Bornmann (Kuehne, M. E.; Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407) for a synthesis of the racemic aldehyde **5** and for methodology, which could provide an enantioselective synthesis of that aldehyde or an equivalent synthon.

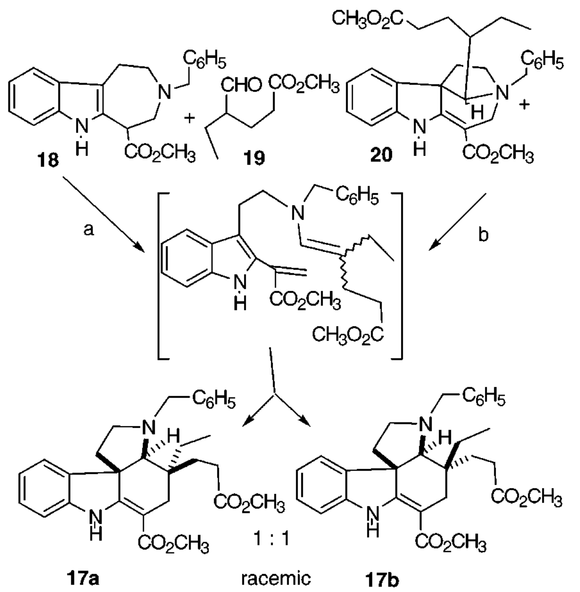
(5) (a) Zeches, M.; Debray, M. M.; Ledouble, G.; LeMen-Olivier, L.; LeMen, J. *Phytochemistry* **1975**, *14*, 1122. (b) LeMen, J.; Caron-Sigant, C.; Hugel, G.; LeMen-Olivier, L.; Lévy, J. *Helv. Chim. Acta* **1978**, *61*, 566. (c) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708.

(6) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443.

(7) Kuehne, M. E.; Pitner, J. B. *J. Org. Chem.* **1989**, *54*, 4553.

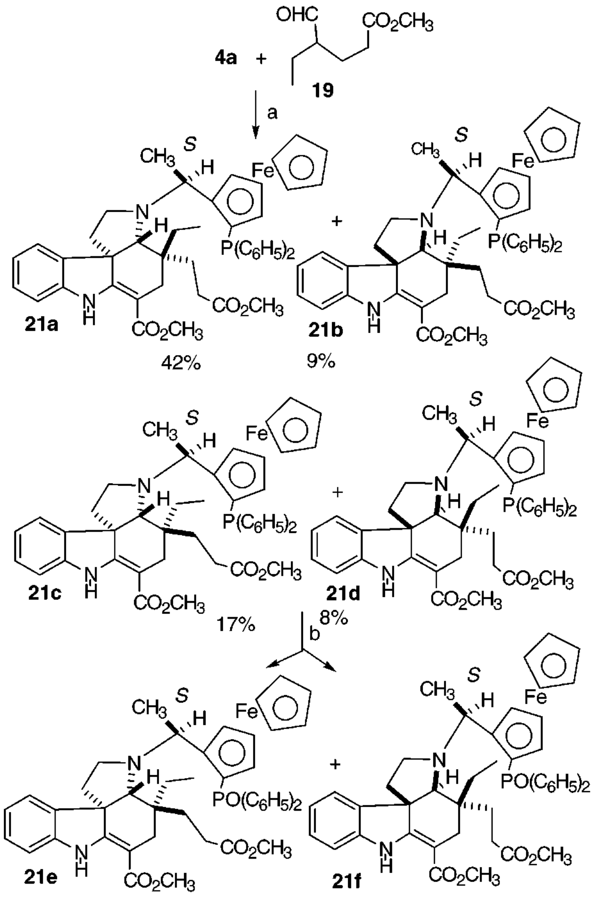
(8) Kuehne, M. E.; Kuehne, S. E. *J. Org. Chem.* **1993**, *58*, 4147.

Scheme 4



a. toluene, reflux; b. $[(CH_3)_2CH]_2NC_2H_5$, $CHCl_3$, reflux

Scheme 5

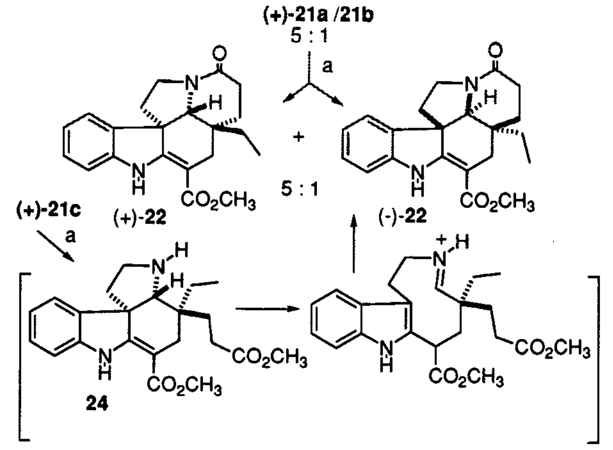


a. C_6H_6, reflux, 76%; b. H_2O_2, 0 °C, 98%

indoloazepines **20** (Scheme 4).[9] Analogous results were reported for a related reaction sequence.[10a]

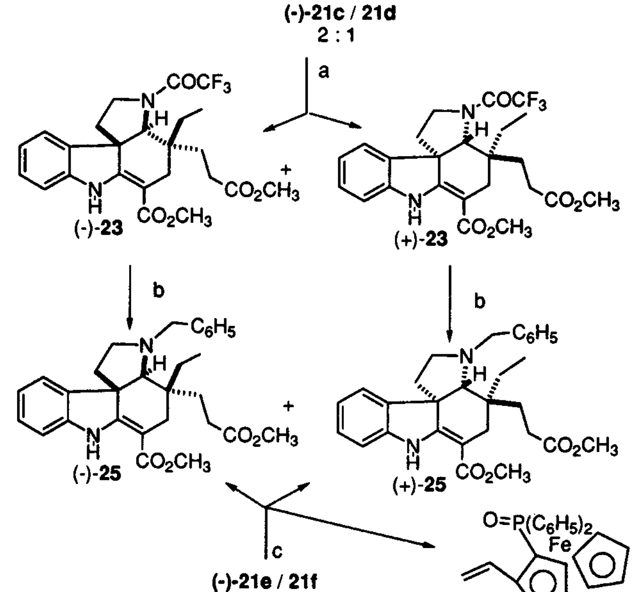
When the indoloazepines **4a** and 2-ethyl-4-(methoxycarbonyl)butanal (**19**) were heated at 80 °C in benzene, four tetracyclic products (+)-**21a**−**d** were formed in 76% yield and isolated as two product pairs: (+)-**21a**,**b** and (+)-**21c**,**d** (Scheme 5). The *Z*-enamine-derived products (+)-**21a**,**b** predominated over the *E*-enamine-derived products (+)-**21c**,**d** (51%:25%, vide infra) while the C-7*S*, C-21*R* tetracyles (+)-**21a**,**c** predominated over the C-7*R*, C-21*S* tetracycles (+)-**21b**,**d** (59%:17%). Maximum selection for *Z* vs *E* enamine reaction was found in the major enantioselected products (+)-**21a** > **21c**, while the minor enantioselected products (+)-**21b** and (+)-**21d** were formed in equal amounts analogous to the formation of racemic products.

Scheme 6



a. HOAc, 100 °C

Scheme 7



a. F_3CCO_2H, $(F_3CO)_2O$; b. $C_6H_5CH_2Br$, K_2CO_3; c. $C_6H_5CH_2Br$, LiI, THF/ tol. reflux.

In contrast to the lack of *E*/*Z*-enamine selectivity found with the closely analogous reaction of the *N*-benzylindoloazepine **18** with the aldehyde **19** in refluxing toluene, the preferential formation of *Z*-enamine intermediates in the present reaction, in refluxing benzene, may be in part the result of a selectivity allowed by a lower reaction temperature and interaction between the enamine nitrogen and the ester carbonyl group. As the *N*-benzyl compound **18** failed to react (fragment) at the

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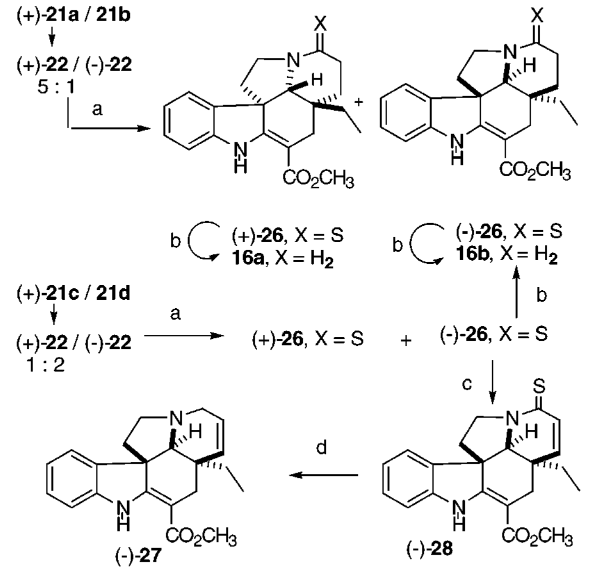
[9] Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002.

[10] (a) Kalaus, Gy.; Greiner, I.; Peredy-Kajtar, M.; Brlik, J.; Szabo, L. Szantay, Cs. *J. Org. Chem.* **1993**, *58*, 1434; (b) **1993**, *58*, 6076.

Scheme 8



a. P_2S_5; b. R Ni; c. $CH_3C_6H_4SOCl$, $EtN(i\text{-}Pr)_2$; d. CH_3I, $NaBH_4$

lower reaction temperature of the ferrocenyl analogue **4a** and, conversely, because that compound undergoes destructive decomposition at the higher reaction temperature of the benzyl compound **18**, it was not possible to verify the temperature dependence of *E*- *vs* *Z*-enamine formation. Since mono-trans-substituted enamine intermediates had been found to give higher enantioselectivity (vide supra and ref 2), a *Z*-alkyl enamine substituent seems detrimental to enantioselectivity (**21c**/**21d**, 2:1) while a *Z* substituent, which can complex with the enamine nitrogen, allows better enantioselectivity (**21a**/**21b** 5:1).

Structural assignments to the four products (+)-**21a**−**d** were derived from the following experiments: The chromatographically less polar fraction (+)-**21a**,**b** (5:1) was heated in acetic acid at 100 °C for 10 min, resulting in cleavage of the ferrocenylethyl substituent and cyclization of the amino ester derived from (+)-**21a** to form the lactam (+)-**22** and correspondingly cyclization of (+)-**21b** to the enantiomeric lactam (−)-**22**. An enantiomeric mixture of the same lactam products (unique TLC, NMR) was also obtained from the more polar fraction of tetracylic product (+)-**21c**,**d** (2:1). This partially racemic product showed a reversed sign and decreased magnitude of rotation relative to the product derive from the esters (+)-**21a**,**b**. Here, cyclization requires an initial acid-catalyzed epimerization at C-3a and C-11b of the secondary amine intermediate **24**.

To circumvent the ambiguity arising from the foregoing epimerization on cleavage of the chiral auxiliary substituent in acid, which could accommodate an exchange of structures **21b** and **21c**, a mixture of *ent* tetracycles (−)-**21c**,**d** (2:1) was treated with trifluoroacetic acid and trifluoroacetic anhydride. A partially racemic single diastereomer of the trifluoroacetamide **23** was formed and this was treated with moist potassium carbonate and benzyl bromide (Scheme 7). The resulting diastereomerically unique, partially racemic *N*-benzyl tetracylic ester (−)-**25** matched in NMR spectra the corresponding racemic compound obtained previously by a different synthesis.[9]

An alternative strategy, for conversion of the tetracyles (−)-**21c**,**d** to the *N*-benzyl esters (−)- and (+)-**25**, avoided all acid treatment. The phosphines (−)-**21c**,**d** were oxidized with hydrogen peroxide, and the resulting phosphine oxides (−)-**21e**,**f** (compare *ent* **21e**,**f**, Scheme 5) were then N-benzylated in refluxing toluene, resulting in formation of ferrocenylethylene phosphine oxide **8a** and the partially racemic *N*-benzyl tetracycle (−)-**25** (Scheme 7).

On reaction of the enantiomeric mixture of 3-oxovincadifformine (+/−)-**22** with phosphorus pentasulfide, in THF at room temperature, the corresponding thiolactams (+/−)-**26** were formed in 87% yield (Scheme 8). Reductive desulfurization of the thiolactam mixture with R/Ni provided (+)-vincadifformine (**16a**) in 87% yield and 67% ee (as determined by NMR, vide infra). Crystallization of the major thiolactam enantiomer (+)-**26** and its reduction gave (+)-vincadifformine (**16a**) in >98% ee.

Treatment of the chromatographically more polar 2:1 mixture of tetracyclic products (+)-**21c**,**d** with acetic acid at 100 °C provided an enantiomeric mixture of lactams (−/+)-**22** in 97% yield. Formation of the corresponding thiolactams (−/+)-**26** and their reduction then gave (−)-vincadifformine (**16b**) in 33% ee. The enantiomeric product ratios **16a**/**16b** in these reaction sequences was determined by titration with Eu(hfc)$_3$ and analysis of the resulting ^{1}H NMR shift spectra.[3]

To obtain (−)-vincadifformine (**16b**) with more favorable chiral induction, the aldehyde **19** was condensed with the enantiomeric indoloazepines **4b**. The major, less polar chromatographic fraction of tetracyclic products (−)-**21a**,**b**, on thiolactam formation, crystallization, and reduction, furnished (−)-vincadifformine (**16b**) in 98% ee, with yields of intermediates and product in good agreement with the enantiomeric reaction sequence starting from the indoloazepines **4a**.

A synthesis of (−)-tabersonine (**27**, Scheme 8) was then obtained by reaction of the intermediate thiolactam (−)-**26** with *p*-toluenesulfinyl chloride and *N*,*N*-diisopropyl-*N*-ethylamine (40% yield), followed by S-methylation of the resulting unsaturated thiolactam (−)-**28** and reduction with sodium borohydride (48% yield, ee> 98%).[10a]

We had previously reported alternative enantioselective syntheses of vincadifformine and tabersonine.[11] They were based on the reaction of a mannitol-derived chiral, cyclic enamine−indoloacrylate intermediate, which avoided the formation of C-20 diastereomeric intermediates in the intramolecular Diels−Alder reaction step, and enantioselectivity was complete. In comparison, the present route with formation of C-20 diastereomeric products, and only partial enantioselectivity, suffers an obvious strategic disadvantage. However, now the more readily available racemic aldehyde **19** provides a shorter path to vincadifformine-type alkaloids, where enantioselectivity and diastereoselectivity might be improved by variation of the recoverable chiral auxiliary that is attached to nitrogen in the indoloazepine precursors **4a**,**b**.

For a fourth exploration of enantioselectivity in cyclization of ferrocenylethyl enamine indoloacrylates, we applied this methodology to a synthesis of the Strychnan-type alkaloid mossambine.[12a,b,13] Here, condensation of

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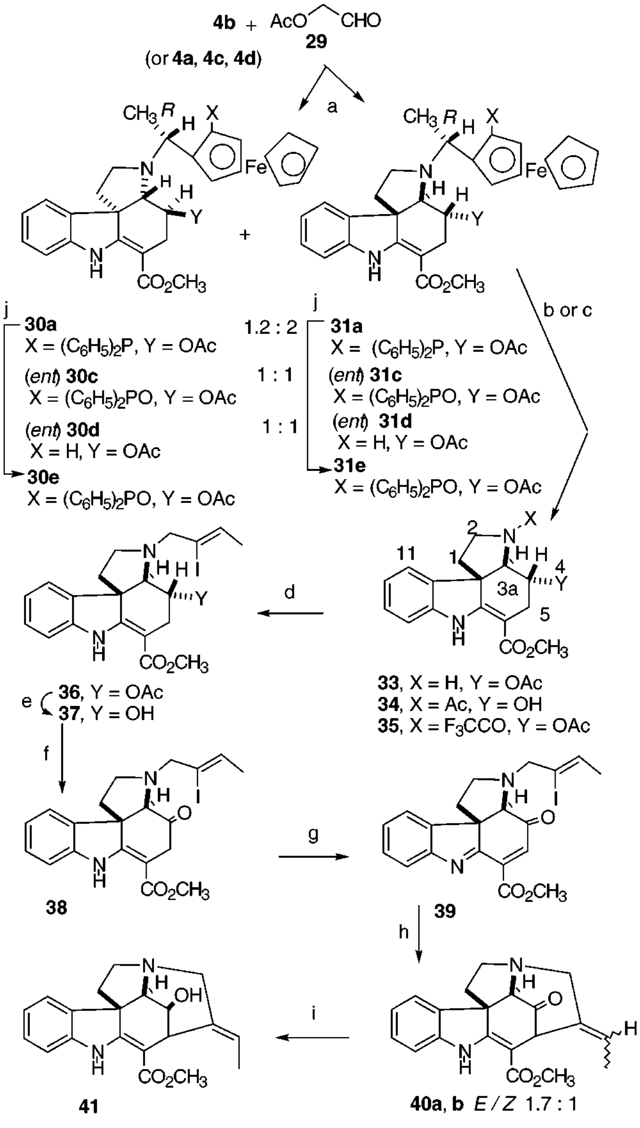
(11) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924.

(12) (a) Stauffacher, D. *Helv. Chim. Acta* **1961**, *44*, 2006. (b) Monseur, X.; Goutarel, R.; LeMen, J.; Wilson, J.; Budzikiewicz, H.; Djerassi, C. *Bull. Soc. Chim. Fr.* **1962**, 1088.

Scheme 9

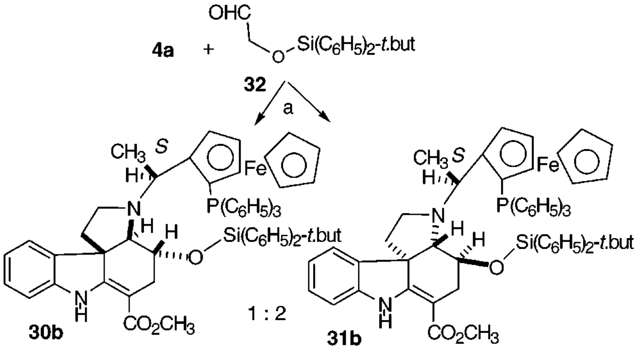


a. C_6H_6, refl. 81-90%; b. F_3CCO_2H, rt, 66% **35**, 20% **33**; c. F_3CCO_2H,$(F_3CCO)_2O$, 92% **35**; d. 1-bromo-2-iodobut-2-en, K_2CO_3, THF, refl. 71% from **33**, 93% from **35**; e. K_2CO_3, MeOH, refl. 96%; f. $(F_3CCO)_2O$, DMSO, Et_3N, 85%; g. *t*-ButOCl, Et_3N, 100% ; h. hv, AIBN, Bu_3SnH, 44%; i. $NaBH_4$, $CeCl_3$, 60%; j. H_2O_2, 81%.

the indoloazepines **4b** with acetoxyacetaldehyde (**29**) resulted in a 90% yield of the diastereomeric tetracycles **30a** and **31a**, which were formed in a 0.6:1 ratio (Scheme 9). An attempt to increase this ratio to that found with the monoalkyl-substituted enamines (vide supra) by use of the corresponding diphenyl-*tert*-butylsiloxy-substituted acetaldehyde **32** provided only a marginal increment in diastereoselection (**30b**/**31b** 1:2, Scheme 10). On the other hand, either oxidation of the diphenylphosphinyl substituent (**4c**), or removal of that substituent (**4d**) from the chiral auxiliary, destroyed the enantioselectivity of the intramolecular Diels–Alder reaction.

Cleavage of the chiral auxiliary substituent from the major tetracyclic product **31a** with acetic acid resulted in a 1:1 mixture of the expected secondary amine **33** and the acetamide alcohol **34**. To avoid this acyl migration, cleavage of the auxiliary substituent was carried out in trifluoroacetic acid. This resulted in formation of the trifluoroacetamide acetate **35** as the major product and the amine acetate **33** as a minor product. The two products showed the same negative sign of rotation, indicating that the spirocyclic center had not been inverted (through protonation of the vinylogous acrylate, cleavage to an indole–iminium salt and alterfacial cyclization). Both products showed the C-3a hydrogen as an NMR singlet, indicating a near 90° angle with respect to the hydrogen at C-4, which is also observed in the above tetracyclic analogues, and both products gave NOE coupling of the C-11 aromatic hydrogen to the C-3a hydrogen and to a C-2 hydrogen, indicating the maintenance of the original tetracyclic skeleton. The expected downfield shift of hydrogens α to N in the trifluoroacetamide **35**, relative to those in the amine **33**, was also accompanied by a pronounced downfield shift of the C-4 ^1H signal (at δ 5.46 for **35** rather than at δ 4.88 for **33**).

Scheme 10



a. C_6H_6, refl. 86%

Alkylation of either tetracyclic product **33** or **35** with (*Z*)-1-bromo-2-iodo-2-butene in the presence of potassium carbonate (nonanhydrous) furnished the tertiary amine **36**. The in situ hydrolysis and alkylation of the trifluoroacetamide **35** proved advantageous, since its basic hydrolysis resulted in a low yield of the isolated amine **33**.

Hydrolysis of the acetate function of the alkylation product **36** and Swern oxidation of the resultant alcohol **37** to the ketone **38** was followed by its oxidation to the imino ketone **39**. This compound was sensitive to racemization, in contrast to its precursor **38**. Consequently, the following reaction with tributyltin hydride could not be carried out at the usual elevated temperature. However, a photochemical radical cyclization of the vinyl iodide **39** provided a 1.7:1 *E*:*Z* mixture of pentacyclic ketones. Reduction of the major ketone product **40a** with sodium borohydride and ceric chloride then yielded mossambine **41**, corresponding to the natural enantiomer.

Experimental Section

(3a*R*,4*S*,11b*S* and 3a*S*,4*R*,11b*R*)-Methyl 3-[1(*S*)-[(*R*)-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-[(S and R)-2-(methoxycarbonyl)butyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (6a,b and 7a,b). A solution of the (*S*)-(+)-ferrocenylethylindoloazepine (*S*)-**4a**[2] (0.5 g, 0.78 mmol) and methyl 2-ethyl-5-oxopentanoate (**5**)[4] (0.136 g, 0.85 mmol) in dry benzene (5 mL) was heated at reflux for 6 h. The benzene was evaporated under reduced

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(13) For establishment of relative stereochemistry by synthesis of the racemate, see: Kuehne, M. E.; Wang, T. *J. Org. Chem.* **1996**, *61*, 7873.

pressure. The residue was dissolved in dry methanol/CH_2Cl_2 (1:10, 50 mL), and $NaBH_4$ (0.1 g) was added with stirring to reduce excess aldehyde, which contaminated the product. The mixture was stirred at room temperature for 15 min, and water (50 mL) was added. The aqueous phase was extracted with ether (3 × 25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by low-pressure flash chromatography (silica gel/ether/hexane, 1:1) gave the major enantiomeric type of diastereomers **6a** (0.19 g, 31%) and **6b** (0.18 g, 30%) and an inseparable mixture of minor enantiomeric type diastereomers **7a** and **7b** (0.06 g, 10%, TLC R_f = 0.53, silica, ether/hexane, 1:1).

For the less polar isomer **6a**: $[\alpha]^{25}_{D}$ +411 (c 0.62, $CHCl_3$); mp 95 °C (decomp); TLC R_f = 0.47 (silica gel, hexane/ether, 1:1, CAS blue to purple); UV (EtOH) λ_{max} 216, 232, 300, 330 nm; IR (KBr) ν_{max} 3370, 3049, 2958, 2944, 2866, 1725, 1666, 1594, 1476, 1463, 1437, 1371, 1293, 1267, 1240, 1180, 1096, 1037, 890, 814, 736, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.50 (m, 1 H), 0.64 (t, J = 7.4 Hz, 3 H), 0.74−0.93 (m, 2 H), 0.80−1.10 (m, 2 H)0.1.22−1.72 (m, 7 H), 1.75 (d, J = 6.9 Hz, 3 H), 2.10 (m, 1 H), 2.29 (d, J = 15 Hz, 1 H), 2.35 (m, 1 H), 2.75−2.85 (m, 1 H), 3.70 (s, 6 H), 3.84 (s, 5 H), 4.15 (s, 1 H), 4.44 (m, 2 H), 4.53 (s, 1 H), 6.73 (d, J = 7.7 Hz, 1 H), 6.79 (d, J = 4.3 Hz, 2 H), 6.98−7.10 (m, 4 H), 7.21 (t, J = 7 Hz, 2 H), 7.36 (m, 3 H), 7.66 (m, 2 H), 8.89 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.82, 18.49, 20.17, 26.21, 32.13, 38.11, 39.84, 44.24, 48.41, 50.61, 51.18, 52.12, 52.21, 55.42, 67.04, 69.02, 69.43, 69.59 (5C), 70.95, 74.82, 89.61, 98.48, 98.71, 108.81, 120.24, 122.69, 127.32, 127.38, 127.58, 127.62, 127.87, 127.93, 128.96, 132.28, 132.43, 135.28, 135.46, 137.54, 139.00, 140.19, 140.25, 142.76, 164.58, 168.90, 176.39; mass spectrum (CI), m/z (rel intensity) 781 (M + 1, 61), 425 (17), 411 (21), 398 (16), 397 (100), 396 (93), 383 (10), 268 (13), 267 (23), 266 (42). Anal. Calcd for $C_{46}H_{49}N_2O_4$-PFe: C, 70.77; H, 6.32; N, 3.56; P, 3.97; Fe, 7.15. Found: C, 69.99; H, 6.13; N, 3.42; P, 3.52; Fe, 7.55.

For the more polar diastereomer **6b**: $[\alpha]^{25}_{D}$ = +445 (c 0.94, $CHCl_3$); mp 115 °C (decomp); TLC R_f = 0.38 (silica gel,hexane/ether, 1:1, CAS blue to purple); UV (EtOH) λ_{max} 214, 230, 300, 330 nm; IR (KBr) ν_{max} 3383, 3048, 2966, 2943, 2872, 1727, 1674, 1598, 1475, 1451, 1422, 1381, 1287, 1270, 1240, 1187, 1111, 1035, 906, 818, 735, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.60−0.85 (m, including 3 H triplet at δ 0.73, J = 7.3 Hz, 4 H), 1.19−1.60 (m, 7 H), 1.66 (d, J = 6.8 Hz, 3 H), 2.00−2.10 (m, 2 H), 2.75−2.90 (m, 3 H), 3.44 (s, 3 H), 3.63 (s, 3 H), 3.78 (s, 5 H), 4.12 (s, 1 H), 4.33 (s, 1 H), 4.41 (m, 2 H), 6.65−6.80 (m, 4 H), 6.90−7.35 (m, 8 H), 7.60 (m, 2 H), 8.76 (s,1 H); ^{13}C NMR ($CDCl_3$) δ 11.83, 18.50, 20.19, 26.23, 32.16, 38.08, 38.13, 44.26, 48.45, 50.62, 51.20, 52.16, 52.25, 55.45, 67.07, 69.05, 69.45, 69.54 (5C), 69.61, 89.65, 98.53, 98.75, 108.83, 120.26, 122.71, 127.35, 127.40, 127.60, 127.65, 127.89, 127.96, 128.98, 132.31, 132.45, 135.30, 135.48, 137.57, 139.02, 139.09, 140.27, 140.25, 164.60, 168.93, 176.41; mass spectrum (CI), m/z (rel intensity) 781 (M^+ + 1, 10), 438 (11), 410 (14), 398 (25), 397 (100), 396 (76), 212 (25). Anal. Calcd for $C_{46}H_{49}N_2O_4PFe$: C, 70.77; H, 6.32; N, 3.56; P, 3.97; Fe, 7.15. Found: C, 70.77; H, 6.58; N, 3.50; P, 3.60; Fe, 6.73.

(−)-21-Oxopseudovincadifformine (10a). A solution of the less polar diastereomer **6a** (0.93 g, 1.19 mmol) in glacial acetic acid (15 mL) was heated at 100 °C for 10 min. The mixture was then poured into crushed ice (5 g) and basified with 15% NH_4OH in brine (25 mL) to produce a yellow precipitate, which was extracted with ether (4 × 25 mL). The ether extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (silica gel, 5% methanol in CH_2Cl_2) gave 21-oxopseudovincadifformine **10a** (0.411 g, 94%) as a single product. The ferrocenyl moiety was completely converted to the vinylferrocene **8**,[2] and PPFOAC was not recovered under these conditions. However, while removal of the ferrocenylethyl moeity at 70 °C produced a considerable amount of PPFOAC,[2] a mixture of tetracyclic amines (cis and trans) was produced and the lactam **10a** was formed only as a minor product under these conditions. For **10a**: $[\alpha]^{25}_{D}$ = −224 (c 0.7, $CHCl_3$); TLC R_f = 0.42, (silica gel, 5% methanol in CH_2Cl_2, CAS blue). ^{1}H NMR and ^{13}C NMR data matched those reported for the racemic compound.[1]

(−)-21-Oxo-20-*epi*-pseudovincadifformine (10b). Cleavage of the more polar isomer **6b** (0.41 g, 0.525 mmol) in glacial actic acid (5 mL), according to the preceding procedure, gave 21-oxo-20-*epi*-pseudovincadifformine **10b** (0.17 g, 91%): $[\alpha]^{25}_{D}$ −215 (c 0.5, $CHCl_3$). ^{1}H NMR and ^{13}C NMR data matched those reported for the racemic compound.[1]

(−)-21-Thioxopseudovincadifformine (11a). A mixture of the lactam **10a** (0.40 g, 1.13 mmol) and P_4S_{10} (0.80 g, 1.8 mmol), in dry THF (75 mL), was stirred at room temparature for 24 h under nitrogen. After addition of CH_2Cl_2 (100 mL) and brine (100 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried, filtered, and concentrated. Purification by flash chromatography (silica, ether/hexane (1:1)) gave 21-thiooxopseudovincadifformine **11a** (0.318 g, 76%): $[\alpha]^{25}_{D}$ = − 50 (c 0.5, $CHCl_3$). ^{1}H NMR and ^{13}C NMR data matched those reported for the racemic compound.[4,10b]

(−)-21-Thioxo-20-*epi*-pseudovincadifformine (11b). Operating as described in the preparation of the epimer **11a**, starting from the lactam **10b** (0.44 g, 1.24 mmol) with P_4S_{10} (0.88 g) in THF (75 mL), gave the product **11b** (0.292 g, 64%): $[\alpha]^{25}_{D}$ = −71 (c 0.56, $CHCl_3$). ^{1}H NMR and ^{13}C NMR data matched those reported for the racemic compound.[4,10b]

(−)-Pseudovincadifformine (1). A mixture of the thiolactam **11a** (0.125 g, 0.067 mmol) and about 2 g of Raney nickel in ethanol (10 mL) was stirred for 6 h at room temparature and filtered. The Raney nickel was washed with CH_2Cl_2 (3 × 10 mL), and the combined filtrate was concentrated. Purification by flash chromatography (silica/ether/hexane) gave pseudovincadifformine **1** (0.087 g, 76%): $[\alpha]^{25}_{D}$ − 506 (c 0.62, EtOH, >98% ee); lit.[5] $[\alpha]^{25}_{D}$ −503 (EtOH). ^{1}H NMR and ^{13}C NMR data matched those reported for the racemic compound.[1,4,10b]

(−)-20-*epi*-Pseudovincadifformine (2). Operating as described in the preparation of the epimer **1**, starting from the thiolactam **11b** (0.025 g, 0.067 mmol), gave *epi*-pseudovincadifformine **2** (0.018 g, 78%): $[\alpha]^{25}_{D}$ = −450 (c 0.3, EtOH, >98% ee); lit. $[\alpha]^{25}_{D}$ −433 (c 0.7, EtOH).[5] ^{1}H NMR and ^{13}C NMR data matched those reported for the racemic compound.[1,4,10b]

(3a*S*,4*R*,11b*R* and 3a*R*,4*S*,11b*S*)-Methyl 3-[1(*R*)-[(*S*)-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-[1-(2,5-dioxalanyl)butyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (14a,b). A solution of the indoloazepines (−)-**4b**[2] (1.00 g, 1.56 mmol) and 4,4-(ethylenedioxy)hexanal (**13**,[6] 500 mg, 3.16 mmol) in dry benzene (10 mL) was heated at reflux for 18 h. The benzene was removed by rotary evaporation to give an orange oil. This oil was dissolved in a methanol/dichloromethane mixture (30 mL, 3:1), and sodium borohydride was added in small portions to reduce the excess aldehyde. The mixture was partitioned between water and ether (150 mL), and the ether extract was washed with water and dried over magnesium sulfate. The ethereal extract was concentrated by rotary evaporation to give an orange oil. ^{1}H NMR analysis of the crude product showed that this reaction gave a 5:1 ratio of diastereomers (67% de). This oil was applied to a flash silica column and eluted with a hexane/ether mixture (2:1) to give the minor diasteromer (−)-**14b**, contaminated with the reduced aldehyde, and the major diastereomer (−)-**14a** (948 mg, 75% yield).

For the major diastereomer **14a**: yellow foam, $[\alpha]^{25}_{D}$ −403° (c 0.14, $CHCl_3$); TLC R_f 0.19 (slica gel, hexane/ether 2:1); IR (NaCl) ν_{max} 3391, 2973, 2943, 2879, 1674, 1610, 1478, 1465, 1435, 1369, 1294, 1279, 1247, 1213, 1203, 1109, 1069, 1001, 946, 821, 749, 698, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.78 (t, J = 7.40 Hz, 3 H), 0.89−0.94 (m, 1 H), 1.24 (dd, J = 4.65, 11.58 Hz, 1 H), 1.43−1.53 (m, 3 H), 1.67 (dd, J = 3.35, 5.85 Hz, 1 H), 1.72 (d, J = 6.97 Hz, 3 H), 1.72 (dd, J = 5.11, 12.08 Hz), 2.33 (br d, J = 15 Hz, 1 H), 2.68−2.72 (m, 1 H), 2.83 (dd, J = 6.59 Hz, 1 H), 2.89 (s, 1 H), 3.56 (dd, J = 6.29 Hz, 1 H), 3.60−3.73 (m, 4 H), 3.65 (s, 3 H), 3.82 (s, 5 H), 4.10 (s, 1 H), 4.33 (dd, J = 2.36 Hz, 1 H), 4.41 (q, J = 5.25 Hz, 1 H), 4.55 (d, J = 1.01 Hz, 1 H), 6.66 (d, J = 2.28 Hz, 1 H), 6.69−6.74 (m, 2 H), 7.01 7.05 (m, 4 H), 7.23 (dd, J = 1.75, 7.75 Hz, 2 H), 7.31−7.33 (m, 3 H), 7.60−7.64 (m, 2 H), 8.76 (br s, 1 H); ^{13}C NMR

(CDCl$_3$) δ 17.97, 18.19, 22.68, 29.63, 31.60, 35.86, 36.07, 41.02, 59.31, 50.76, 55.45, 64.31, 64.57, 68.19, 68.93, 69.06, 69.65, 69.82, 69.86, 70.04, 70.45, 71.10, 71.51, 75.03, 75.11, 91.18, 99.09, 99.31, 108.34, 111.77, 120.21, 122.54, 127.52, 127.74, 127.99, 128.06, 129.07, 132.55, 132.69, 135.35, 135.53, 137.80, 139.02, 139.08, 139.99, 140.05, 143.07, 164.68, 169.37; MS *m/z* (rel intensity) 780 (M$^+$, 0.6), 426 (2), 425 (5), 413 (1), 412 (3), 411 (2), 410 (4), 399 (3), 398 (20), 397 (65), 396 (58), 395 (24), 394 (3), 384 (9), 383 (6), 332 (3), 331 (14), 330 (3), 329 (7), 319 (7), 288 (10), 284 (5), 283 (17), 276 (3), 275 (8), 264 (3), 257 (2), 256 (4), 252 (8), 251 (4), 242 (4), 228 (7), 226 (6), 183 (15), 176 (13), 171 (6), 170 (8), 169 (4), 168 (6), 167 (9), 166 (6), 165 (14), 159 (7), 157 (7), 154 (7), 153 (6), 152 (7), 149 (14), 129 (62), 121 (13), 115 (5), 101 (87), 69 (11), 57 (18).

For the minor diastereomer **14b**: TLC R_f 0.30 (slica gel, hexane/ether 2:1); ^{1}H NMR (CDCl$_3$) δ (visible peaks only) 2.06 (br d, J = 15.26 Hz, 1 H), 2.33 (dd, J = 6.24, 8.46 Hz, 1 H), 2.52−2.53 (m, 1 H), 2.74−2.79 (m, 1 H), 3.68 (s, 3 H), 3.92 (s, 5 H), 4.31 (dd, J = 2.42 Hz, 1 H), 4.54 (s, 1 H), 6.74 (d, J = 7.60 Hz, 1 H), 6.74 (d, J = 7.60 Hz, 1 H), 6.84 (dd, J = 7.43 Hz, 1 H), 7.05−7.13 (m, 6 H), 7.36−7.38 (m, 4 H), 7.56 (ddd, J = 1.98, 7.75, 9.66 Hz, 2 H), 8.83 (s, 1 H).

(3a*S*,4*R*,11b*R*)-Methyl 3-[1(*R*)-[(*S*)-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-[1-(2-oxobutyl)]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (15). To a solution of the ketal (−)-**14a** (400 mg, 0.512 mmol) in THF/MeOH (12 mL, 1:1) at room temperature was added an aqueous hydrochloric acid solution (6 mL, 10%). This solution was allowed to stir at ambient temperature for 4 h and then neutralized with an aqueous NaOH solution (10%) and extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate, and concentrated by rotary evaporation to give a yellow foam. This foam was applied to a flash silica column and eluted with a hexane/ether mixture (1:1) to give the title compound (350 mg, 99%) as a yellow foam: $[\alpha]^{25}_{D}$ −347 (c 0.10, CHCl$_3$); TLC R_f 0.41 (SiO$_2$, hexane/ether 2:1, CAS blue to purple); IR (NaCl) ν_{max} 3380, 3054, 2978, 2934, 2859, 1715, 1675, 1653, 1609, 1540, 1477, 1465, 1436, 1371, 1293, 1278, 1247, 1202, 1109, 1049, 822, 742, 699, 668 cm^{-1} ; ^{1}H NMR (CDCl$_3$) δ 0.89 (t, J = 7.32 Hz, 3 H), 1.35−1.42 (dd, J = 10.73, 16.47 Hz), 1.68−1.74 (m, 1 H), 1.79 (d, J = 6.98 Hz, 3 H), 1.96−2.07 (m, 3 H), 2.19 (dd, J = 3.46, 7.07 Hz, 1 H), 2.26 (dd, J = 1.62, 15.50 Hz, 1 H), 2.71 (s, 1 H), 2.85−2.89 (m, 1 H), 2.90−2.95 (m, 1 H), 3.66 (s, 3 H), 3.81 (s, 5 H), 4.29 (d, J = 1.39 Hz, 1 H), 4.53 (s, 1 H), 4.53 (q, J = 3.86 Hz, 1 H), 4.63 (d, J = 0.99 Hz, 1 H), 6.64 (d, J = 7.29 Hz, 1 H), 6.74 (d, J = 7.68 Hz, 1 H), 6.80 (dd, J = 7.51 Hz), 6.85−6.88 (m, 2 H), 7.00 (dd, J = 7.43 Hz, 1 H), 7.11−7.16 (m, 3 H), 7.36−7.38 (m, 3 H), 7.66−7.69 (m, 2 H), 8.91 (s, 1 H); ^{13}C NMR (CDCl$_3$) δ 20.00, 20.21, 21.50, 35.30, 35.65, 36.18, 39.96, 40.11, 42.34, 46.18, 50.52, 50.71, 55.18, 65.95, 66.09, 68.35, 68.87, 69.00, 69.56, 70.38, 70.51, 71.33, 71.58, 74.90, 74.99, 90.33, 96.99, 97.23, 108.82, 120.21, 122.73, 127.38, 127.55, 127.60, 128.01, 129.13, 132.06, 132.21, 132.35, 135.42, 135.60, 137.10, 139.42, 140.56, 140.62, 142.85, 164.42, 169.09, 210.62.

(+)-Ibophyllidine (12). A solution of the amino ketone (−)-**15** (70 mg, 0.102 mmol) in acetic acid (2 mL) was heated to 70 °C for 10 min. This orange solution was quenched with ice, basified with 15% ammonium hydroxide solution, and extracted with CH$_2$Cl$_2$. The organic layer was washed with an aqueous HCl solution (3 × 3 mL, 10%). The acid extract was basified with a sodium hydroxide solution (10%), extracted with toluene, and dried over magnesium sulfate. The toluene was removed by rotary evaporation, and the residual oil was dissolved in acetic acid (1 mL) containing 10% Pd/C (20 mg). This mixture was allowed to stir at room temperature for 4 days under hydrogen at atmospheric pressure. The catalyst was filtered off under suction and washed with hot methanol. The acidic solution was added to ice and then basified with ammonium hydroxide solution (15%). Subsequent extraction with CH$_2$Cl$_2$, drying over magnesium sulfate, and rotary evaporation gave a white foam, which was separated by PLC (SiO$_2$, ethyl acetate:ethanol 3:1) to give (+)-ibophyllidine (20 mg, 60% yield, in over 98% ee, by chiral shift titration). Addition of up to five times the required amount of Eu(hfc)$_3$ for complexation of a sample of (+)-ibophyllidine showed only a single enantiomer at δ 3.85 (vide infra). A ^{13}C NMR spetrum matched that of a racemic sample:[6] $[\alpha]^{25}_{D}$ +141 (c 0.1, CHCl$_3$), lit.[14,15] $[\alpha]^{25}_{D}$ +134, +259 (CHCl$_3$); TLC R_f 0.35 (SiO$_2$, ethyl acetate/ethanol, 4:1, CAS blue to purple); ^{1}H NMR (CDCl$_3$) δ 1.03 (t, J = 7.42 Hz, 3 H), 1.26−1.32 (m, 1 H), 1.43−1.59 (m, 1 H), 1.81 (dd, J = 11.22, 15.20 Hz, 1 H), 1.85−1.94 (m, 1 H), 2.00−2.06 (m, 1 H), 2.14−2.20 (m, 2 H), 2.24−2.29 (m, 1 H), 2.80 (q, J = 9.62 Hz, 1 H), 3.12 (dd, J = 5.04, 13.58 Hz, 1 H), 3.14−3.19 (m, 1 H), 3.21−3.23 (m, 1 H), 3.50 (d, J = 8.63 Hz, 1 H), 3.76 (s, 3 H), 6.82 (d, J = 7.66 Hz, 1 H), 6.93 (ddd, J = 1.00, 7.58, 8.34 Hz, 1 H), 7.14 (ddd, J = 1.18, 7.64, 8.81 Hz, 1 H), 7.52 (d, J = 7.58 Hz, 1 H), 9.12 (s, 1 H).

(3a*R*,11b*S*)- and (3a*S*,11b*R*)-Methyl 3-[1-(*S*)-[(*R*)-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-(*R* and *S*)-ethyl-4-[2-(methoxycarbonyl)ethyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (21a,b and 21c,d; (+)-Diastereomers). A solution of the indoloazepine **4a** (2.0 g, 3.05 mmol) and methyl 4-formylhexanoate (**19**,[9] 2.0 g, 12.51 mmol) in dry benzene (6 mL) was heated under reflux for 24 h. The benzene was evaporated under reduced pressure. The residue was dissolved in dry methanol/CH$_2$Cl$_2$ (1:10, 50 mL), and NaBH$_4$ (0.2 g) was added in small portions with stirring to reduce excess aldehyde, which contaminated the product. The mixture was stirred at room temperature for 15 min, and water (15 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 60 mL), and the extract was dried over MgSO$_4$, filtered, and concentrated under reduced pressure to give a yellow foam. The crude product was purified by column chromatography (silica, ether/hexane, 1:2) to give an inseparable mixture of less polar diastereomers (+)-**21a** and (+)-**21b**, in a 5:1 ratio, as a yellow foam (1.21 g, 51%). Further elution gave an inseparable mixture of the more polar diastereomers (+)-**21c** and (+)-**21d**, in a 2:1 ratio, as a yellow foam (0.6 g, 25%).

For the less polar isomers (+)-**21a**,**b**: $[\alpha]^{25}_{D}$ +360 (c 0.10, CHCl$_3$); mp 110−111 °C (decomp); TLC R_f = 0.48, (silica gel, hexane/ether, 1:2, CAS blue to purple); UV (EtOH) λ_{max} 216, 226, 302, 332 nm; IR (KBr) ν_{max} 3380, 3052, 2972, 2953, 2875, 1736, 1679, 1610, 1478, 1465, 1434, 1377, 1288, 1271, 1248, 1211, 1157, 1107, 1049, 1002, 821, 743, 698 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ −0.30 to −0.20 (m, 1 H), 0.1−0.2 (m, 1 H), 0.22 (t, J = 7.9 Hz, 3 H), 1.27−1.30 (m, 1 H), 1.37−1.39 (m, 1 H), 1.83 (d, J = 6.9 Hz, 3 H), 1.95−2.00 (m, 1 H), 2.02 (d, J = 15.1 Hz, 1 H), 2.16 (d, 1 H, J = 15.3 Hz, 1 H), 2.26−2.32 (m, 1 H), 2.51 (s, 1 H), 2.71−2.74 (m, 1 H), 2.92−2.98 (m, 1 H), 3.01−3.08 (m, 1 H), 3.67 (s, 3 H), 3.74 (s, 5 H), 3.81 (s, 3 H), 4.40 (s, 1 H), 4.57−4.59 (m, 1 H), 4.70 (s, 1 H), 4.76 (s, 1 H), 6.07 (d, J = 7.7 Hz, 1 H), 6.50 (t, J = 7.1 Hz, 2 H), 6.70−6.71 (m, 2 H), 6.81 (t, J = 7.3 Hz, 1 H), 6.92 (t, J = 7.3 Hz, 2 H), 7.12 (t, J = 7.1 Hz, 2 H), 7.35−7.39 (m, 2 H), 7.68 (m, 2 H), 8.86 (s, 1 H); ^{13}C NMR (CDCl$_3$) (visible peaks only) δ 24.01, 25.64, 28.05, 29.53, 29.55, 30.23, 38.86, 42.06, 50.60, 51.39, 57.26, 69.81, 70.78, 70.79, 71.88, 71.91, 89.08, 108.44, 119.80, 124.34, 126.85, 127.09, 127.97, 129.16, 132.12, 132.26, 135.67, 135.85, 136.31, 140.24, 142.74, 168.78, 175.49; mass spectrum (CI), m/z (rel intensity) 781 (M + 1, 52), 566 (16), 412 (17), 398 (76), 397 (35), 396 (100), 212 (22), 199 (25), 127 (10), 111 (10), 89 (13), 71 (16), 69 (10), 59 (31). Anal. Calcd for $C_{46}H_{49}N_2O_4PFe$: C, 70.77; H, 6.32; N, 3.56; P, 3.97. Found: C, 70.37; H, 6.51; N, 3.27; P, 3.78.

For the more polar diastereomers (+)-**21c** and **21d**: $[\alpha]^{25}_{D}$ +256 (c 0.10, CHCl$_3$); mp 73−74 °C (decomp); TLC Rf = 0.33, (silica gel, hexane/ether, 1:2, CAS blue to purple); UV (EtOH) λ_{max} 216, 226, 302, 332 nm; IR (KBr) ν_{max} 3380, 3053, 2948, 2877, 1737, 1679, 1642, 1602, 1478, 1465, 1434, 1384, 1286, 1247, 1205, 1186, 1119, 1106, 1049, 1026, 1001, 970, 821, 743, 699 cm^{-1}; ^{1}H NMR (CDCl$_3$) (major peaks for major diastereomer) δ 0.52−0.60 (m, 1 H), 0.11−0.17 (m, 1 H), 0.94 (t, J = 7.17 Hz, 3 H), 1.84 (d, J = 7.0 Hz, 3 H), 3.41 (s, 3 H), 3.67 (s,

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3 H), 3.71 (s, 5 H), 4.37 (s, 1 H), 4.60 (m, 1 H), 4.68 (s, 1 H), 4.75 (s, 1 H), 6.07 (d, *J* = 7.3 Hz, 1 H), 7.64−7.67 (m, 2 H), 8.83 (s, 1 H); ^{1}H NMR (CDCl$_3$) (major peaks for minor diastereomer) δ 1.13 (t, *J* = 7.50 Hz, 3 H), 1.68 (d, *J* = 6.5 Hz, 3 H), 3.49 (s, 3 H), 3.70 (s, 3 H), 4.01 (s, 5 H), 7.53−7.56 (m, 1H), 8.83 (1 H); mass spectrum (CI), *m/z* (rel intensity) 781 (M + 1, 28), 566 (33), 413 (12), 411 (23), 397 (100), 396 (89), 394 (13), 212 (12), 180 (12), 70 (12).

(3a*S*,11b*R*)- and (3a*R*,11b*S*)-Methyl 3-[(*R*)-[(*S*)-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-(*R* and *S*)-ethyl-4-[2-(methoxycarbonyl)ethyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (21a, 21b and 21c, 21d, (−)-Diastereomers). By the above procedure, starting with (−)-ferrocenyl azepine **4b** and aldehyde **19**, the title compounds were obtained with similar yield and diastereomeric ratio. For the less polar diastereomers (−)-**21a** and **21b**: $[\alpha]^{25}_D$ −361 (*c* 0.10, CHCl$_3$); mp 110−111 °C (decomp); TLC R_f = 0.48 (silica gel, hexane/ether, 1:2, CAS blue to purple). For the more polar diastereomers (−)-**21c** and **21d**: $[\alpha]^{25}_D$ −225 (*c* 0.10, CHCl$_3$); mp 73−74 °C (decomp); TLC R_f = 0.33, (silica gel, hexane/ether, 1:2, CAS blue to purple).

(+)-3-Oxovincadifformine (22). (a) A solution of the amines (+)-**21a** and **21b** (1.09 g, 1.39 mmol) in glacial acetic acid (16 mL) was heated at 100 °C for 10 min. The dark orange mixture was then poured into crushed ice (5 g) and basified with 15% NH$_4$OH in brine (25 mL) to produce a yellow precipitate, which was extracted with ether (3 × 50 mL). The ether extracts were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, methanol/CH$_2$Cl$_2$ 1:19) gave mostly (+)-3-oxovincadifformine (+)-**22** (0.48 g, 97%) as a white foam: mp = 214−215 °C (decomp); $[\alpha]^{25}_D$ = +178 (*c* 0.1, CHCl$_3$); TLC R_f = 0.51 (silica gel, 5% methanol in CH$_2$Cl$_2$, CAS blue); ^{1}H NMR (CDCl$_3$) δ 0.69 (t, *J* = 7.4 Hz, 3 H), 0.98 (q, *J* = 7.4 Hz, 2 H), 1.32−1.40 (m, 1 H), 1.71 (s, 1 H), 1.82 (dd, *J* = 6.4, 12.3 Hz, 1 H), 1.91 (d, *J* = 15.5 Hz, 1 H), 1.95−2.02 (m, 2 H), 2.28−2.36 (m, 1 H), 2.38 (dt, *J* = 4.32, 15.5 Hz, 1 H), 2.63 (dd, *J* = 0.28, 1.73 Hz, 1 H), 3.41 (dt, *J* = 5.54, 12.1 Hz, 1 H), 3.77 (s, 1 H), 4.15 (dd,*J* = 7.69, 11.71 Hz, 1 H), 6.86 (d, *J* = 7.7 Hz, 1 H), 6.91 (t, *J* = 7.5 Hz, 1 H), 7.16−7.21 (m, 2 H), 8.98 (s, 1 H).

(b) Cleavage of the more polar diastereomers (−)-**21c** amd **21d** (0.50 g, 0.64 mmol, vide supra) in glacial acetic acid (5 mL), similar to that (+)-**21a** and **21b**, produced mostly (+)-3-oxovincadifformine (+)-**22** (0.208 g, 95%): mp 200−205 °C; $[\alpha]^{25}_D$ +96 (*c* 0.1, CHCl$_3$).

(−)-3-Oxovincadifformine (22). (a) Cleavage of the more polar diastereomers (+)-**21c** and **21d** (0.50 g, 0.64 mmol) in glacial acetic acid (5 mL), similar to that for (+)-**21a** and **21b**, produced mostly (−)-3-oxovincadifformine (−)-**22** (0.208 g, 95%): mp 200−205 °C; $[\alpha]^{25}_D$ −95 (*c* 0.1, CHCl$_3$).

(b) Cleavage of less polar diastereomers (−)- **21a** and **21b** (0.50 g, 0.64 mmol) in glacial acetic acid (5 mL), similar to that for (+)-**21a** and **21b** produced mostly (−)-3-oxovincadifformine (−)-**22** (0.208 g, 95%): mp 214−215 °C; $[\alpha]^{25}_D$ −180 (*c* 0.1, CHCl$_3$).

(+)-3-Thioxovincadifformine (26). A 5:1 mixture of (+)-**22**/(−)-**22** (0.34 g, 0.96 mmol) and P$_4$S$_{10}$ (0.76 g, 1.71 mmol) in dry THF (65 mL) was stirred at room temperature for 19 h under nitrogen. Then water (50 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, ether/hexane 1:2) to give (+)-**26** (0.312 g, 88%) as a white solid. The white solid was dissolved in a mixture of hexane/ether/CH$_2$Cl$_2$ (1:2:0.25, 10 mL) with gentle heating and left at −12 °C for 12 h. The precipitated white crystals were filtered and dried at room temperature (0. 07 g). This product was found to be racemic material, $[\alpha]^{25}_D$ = 0 (*c* 0.1, CHCl$_3$), mp = 185−187 °C. The mother liquor was concentrated under reduced pressure to produce white solid, which was enriched with optically pure enantiomer (+)-**26** (0.24 g, 68%); $[\alpha]^{25}_D$ = +50 (*c* 0.2, CHCl$_3$); mp = 150−152 °C; TLC R_f = 0.43 (silica gel, hexane/ether, 1:2, CAS blue to purple); UV (EtOH) λ_{max} 200, 230, 274, 296, 328 nm; IR (KBr) ν_{max} 3380, 3052, 2972, 2875, 1736, 1679, 1610, 1478, 1466, 1435, 1377, 1289, 1271, 1248, 1211, 1158, 1107, 1049, 1002, 821, 743, 698 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.71 (t, *J* = 7.3 Hz, 3 H), 0.96−1.16 (m, 2 H), 1.18−1.21 (m, 1 H), 1.83 (d, *J* = 15.6 Hz, 1 H), 1.96 (dd, *J* = 6.1, 12.6 Hz, 1 H), 2.02 (dt, *J* = 3.5 13.4 Hz, 1 H), 2.08−2.13 (m, 1 H), 2.55 (dt, *J* = 3.4, 13.9 Hz, 1 H), 2.73 (dd, *J* = 1.5, 15.7 Hz, 1 H), 3.12 (dt, *J* = 3.9, 5.4 Hz, 1 H), 3.39 (s, 1 H), 3.70−3.77 (m, 1 H), 3.78 (s, 3 H), 4.61 (dd, *J* = 7.94, 13.1 Hz, 1 H), 6.88 (t, *J* = 7.8 Hz, 1 H), 6.92 (t, *J* = 7.5 Hz, 1 H), 7.19−7.24 (m, 2 H), 8.99 (br s, 1 H); ^{13}C NMR (CDCl$_3$) δ 7.07, 27.38, 29.49, 30.16, 38.84, 40.21, 41.25, 49.47, 50.94, 51.17, 56.42, 70.30, 91.10, 109.63, 121.06, 121.44, 128.68, 135.00, 142.75, 162.90, 168.05.

(−)-3-Thioxovincadifformine (26). Operating as described in the preparation of (+)-**26**, starting from 5:1 (−)-**22**/(+)-**22** (0.44 g, 1.24 mmol) with P$_4$S$_{10}$ (0.88 g) in THF (75 mL) gave (−)-**26** (0.383 g, 84%). The enantiomerically pure product was obtained as described for its enantiomer (vide supra); $[\alpha]^{25}_D$ = −50 (*c* 0.12, CHCl$_3$).

(−)-Vincadifformine (16b). (a) A mixture of enantiomerically pure thiolactam (−)-**26** (0.050 g, 0.135 mmol) and about 2 g of Raney nickel in ethanol (2 mL) was stirred for 16 h at room temperature and filtered. The Raney nickel was washed with CH$_2$Cl$_2$ (3 × 10 mL), and the combined filtrate was concentrated. Purification by flash chromatography (silica, ether/hexane 1:1) gave vincadifformine (−)-**16b** (0.039 g, 87%): $[\alpha]^{25}_D$ −556 (*c* 0.14, EtOH, >98% ee, vide infra); lit.[11] $[\alpha]^{25}_D$ −564 (*c* 0.14, EtOH); mp = 98−99 °C; ^{1}H NMR (CDCl$_3$) δ 0.58 (t, *J* = 7.1 Hz, 3 H), 0.61−0.64 (m, 1 H), 0.98−1.20 (m, 1 H) 1.28−1.31 (m, 1 H), 1.71−1.79 (m, 1 H), 1.80 (br d, *J* = 4.1 Hz, 1 H), 1.82 (m, 2 H), 2.05−2.06 (m, 1 H), 2.28 (d, *J* = 15.3 Hz, 1 H), 2.41−2.45 (m, 2 H), 2.52−2.56 (m, 1 H), 2.73 (d, *J* = 15.1 Hz, 1 H), 2.92 (t, *J* = 7.0 Hz, 1 H), 3.12 (br d, *J* = 8.9 Hz, 1 H), 3.76 (s, 3 H), 6.79 (d, *J* = 7.2 Hz, 1 H), 6.85 (t, *J* = 7.4 Hz, 1 H), 7.12 (t, *J* = 7.7 Hz, 1 H) 8.89 (br s, 1 H).

(b) Starting from the more polar tetracyclic ferrocenylethyl diastereomers (+)-**21c** and **21d** (cleavage, formation of thiolactam, desulfurization) produced (−)-**16b** with 33% enantiomeric excess: $[\alpha]^{25}_D$ = −125 (*c* 0.3, CHCl$_3$). Here recrystallization was not applied at the thioxovincadifformine stage.

(+)-Vincadifformine (16a). (a) Operating as described in the preparation of (−)-**16b**, starting from unrecrystallized 3-thiooxovincadifformine (+)-**26** (0.05 g, 0.135 mmol), gave **16a** (0.038 g, 87%): $[\alpha]^{25}_D$ = + 440 (*c* 0.3, CHCl$_3$, >80% ee, vide infra); lit.[11] $[\alpha]^{25}_D$ +542 (*c* 0.04, EtOH).

(b) Starting from the more polar diastereomers (−)- **21c** and **21d** (cleavage, formation of thiolactam, desulfurization) produced **16a** with 33% enantiomeric excess, $[\alpha]^{25}_D$ = +124 (*c* 0.3, CHCl$_3$). Recrystallization was not applied at the thiooxovincadifformine stage.

(3a*S*,11b*R*)- and (3a*R*,11b*S*)-Methyl 3-(Trifluoroacetyl)-2,3,3a,4,5,7-hexahydro-4-(*R* and *S*)-ethyl-4-[2-(methoxycarbonyl)ethyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates ((−)-23). To a solution of 0.172 g (0.22 mmol) of the ferrocenylethyl tetracycles (−)-**21c** and **21d**, 2/1, low R_f, $[\alpha]_D$ = −256 (*c* 0.32, CHCl$_3$)) in 5 mL of anhydrous CH$_2$Cl$_2$, cooled to 0 °C, was added, under nitrogen, 47 μL (0.33 mmol) of TFAA, followed by 1 mL of trifluoroacetic acid. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for an additional 30 min. Then, the volatile components were evaporated at reduced pressure. The resulting residue was diluted with CH$_2$Cl$_2$ and neutralized by stirring with solid potassium carbonate. After filteration, the filtrate was concentrated at room temperature under reduced pressure. The residue was subjected to flash chromatography on silica gel and eluted with acetone/ethyl acetate, 1:8, to yield 0.091 g (86%) of partially racemic trifluoroacetamide (−)-**23**: TLC R_f = 0.58 (silica gel, acetone, CAS blue); $[\alpha]_D$ −99 (*c* 0.83, CHCl$_3$); UV (EtOH) λ_{max} 208, 230, 300, 330 nm; IR (KBr) ν_{max} 3373, 2953, 1735, 1681, 1611, 1468, 1438, 1384, 1254, 1203, 1134, 1060, 835, 799, 750, 721 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.94 (1 H, s), 7.35 (1 H, d, *J* = 7.4 Hz), 7.24 (1 H, dd, *J* = 7.7 and 7.7 Hz), 6.97 (1 H, dd, *J* = 7.4 and 7.4 Hz), 6.88 (1 H, d, *J* = 7.7 Hz), 3.80 (1 H, s), 3.79 (3 H, s), 3.56 (3 H, s), 3.47 (1 H, br s), 3.36 (1 H, br s), 2.50 (1 H, d, *J* = 16.2 Hz) 2.27 (1 H, d, *J*

= 16.2 Hz), 2.18 (1 H, m), 2.09 (1 H, m), 1.99 (2 H, m), 1.66 (1 H, m), 1.58 (1 H, m), 1.40 (1 H, m), 1.14 (1 H, m), 0.97 (3 H, t, *J* = 7.3 Hz); mass spectrum (CI) *m*/*z* (rel intensity) 481 (M^+ + 1, 0.5), 480 (M^+, 0.1), 449 (0.4), 385 (37), 353 (16), 170 (31), 115 (63), 99 (70), 60 (100). This trifluoroacetamide was shown to be a mixture of enantiomeric isomers by ^{1}H NMR shift studies using a gradual addition of a 0.1 M solution of Eu(hfc)$_3$ in *d*-chloroform. The ester methyl proton signal at δ 3.79 was split to give signals at δ 4.11 and 4.04. The indole proton signal at δ 8.94 was split to give signals at δ 9.32 and 9.28. The ratio between the integral of the split signals was ca. 2:1.

(3a*S*,11b*R*)- and (3a*R*,11b*S*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-(*R* and *S*)-ethyl-4-[2-(methoxycarbonyl)ethyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (25). (a)To a solution of 0.125 g (0.16 mmol) of the ferrocenylethyl tetracycles (−)-**21c** and **21d**, low R_f, $[\alpha]_D$ = −256 (*c* 0.32, CHCl$_3$) in 10 mL of acetone, cooled to 0 °C, was added 0.23 mL (30% w/w, 2.3 mmol) of hydrogen peroxide. The solution was allowed to warm to room temperature in 30 min. The excess hydrogen peroxide was reduced by the addition of 10 mL of aqueous sodium thiosulfate solution. The resulting mixture was extracted with ether. The organic layers were combined, washed with brine, and dried with sodium sulfate. Concentration under vacuum gave the corresponding phosphine oxide compounds **21e** and **21f** as a yellow foam (0.127 g, 100%): $[\alpha]_D$ −157 (*c* 0.1, CHCl$_3$).

The crude phosphine oxide product was suspended with benzyl bromide (39 μL, 0.32 mmol) and lithium iodide (0.022 g, 0.16 mmol) in THF−toluene (10 mL, 1:1). The mixture was heated at reflux for 4 h and then cooled to room temperature, diluted with ether, and washed with water. The ether extracts were dried over sodium sulfate and concentrated by rotary evaporation. The residue was applied to silica gel and eluted with ethyl ether/hexane (1:2) to afford the benzyl compound (−)-**25** (0.035 g, 46%): $[\alpha]_D$ − 72.5 (*c* 0.15, CHCl$_3$). The proton NMR data matched those given below. Further elution with ether/hexane (1:1) gave the ferrocenylethylene phosphine oxide **8a**,[16] $[\alpha]^{25}_D$ +364 (*c* 0.79, CHCl$_3$), followed by unreacted starting phosphine oxides **21e**,**f**. The ^{13}C and ^{1}H NMR spectra of the ferrocenylethylene **8a** matched those reported.[16]

(b) A mixture of the above trifluoroacetamide (−)-**23** (58 mg, 0.12 mmol), benzyl bromide (22 μL, 0.18 mmol), water (6 μL, 0.34 mmol), and potassium carbonate (0.082 g, 0.59 mmol) in dry THF (5 mL) was heated at reflux overnight under nitrogen. After cooling, and filtration of the inorganic materials, the filtrate was concentrated. The residue was separated by chromatography on silica gel, eluting with ethyl ether/hexane (1:1) to give the benzyl compound (−)-**25** (0.025 g, 44%). Further elution with acetone/ethyl acetate (1:1) gave the starting trifluoroacetamide (0.030 g). For the partially racemic benzyl compound (−)-**25**: TLC R_f = 0.31 (silica gel, ethyl ether/hexane, 1:1, CAS blue faded to yellow); $[\alpha]_D$ − 73 (*c* 0.2, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 8.92 (1 H, s), 7.46 (1 H, d, *J* = 7.5 Hz), 7.36 (1 H, dd, *J* = 7.2 and 7.7 Hz), 7.28 (1 H, dd, *J* = 7.2 and 7.4 Hz), 7.16 (1 H, dd, *J* = 7.6 and 7.6 Hz), 7.01 (1 H, d, 7.3 Hz), 6.88 (1 H, dd, *J* = 7.2 and 7.6 Hz), 4.27 (1 H, d, *J* = 13.5 Hz), 3.78 (3 H, s), 3.73 (1 H, d, *J* = 13.5 Hz), 3.53 (3 H, s), 2.98 (1 H, dd, *J* = 6.6 and 9.4 Hz), 2.94 (1 H, d, *J* = 1.2 Hz), 2.46 (1 H, dd, *J* = 1.2 and 15.5 Hz), 2.24 (1 H, d, *J* = 15.5 Hz), 2.14−2.05 (3 H, m), 1.92 (1 H, m), 1.78 (1 H, m), 1.63 (1 H, dd, *J* = 5.0 and 12.1 Hz), 1.26 (1 H, m), 1.16 (1 H, m), 0.99 (3 H, t, *J* = 7.5 Hz). These values matched those previously reported for the racemic compound, which was obtained by alternative synthesis.[8,10]

(−)-Tabersonine (27). Operating as described in the preparation of racemic tabersonine[10] but starting from enatiomerically pure (−)-3-oxovincadifformine ((−)-**22a**, 0.10 g, 0.27 mmol) gave (−)-tabersonine (**27**, 0.017 g, 19%): $[\alpha]^{25}_D$ = −248 (*c* 0.09, CHCl$_3$, >98% ee, vide infra); reported $[\alpha]^{25}_D$ −240 (*c* 0.15, EtOH);[11] ^{1}H NMR (CDCl$_3$) δ 0.62 (t, *J* = 7.4 Hz, 3 H), 0.84−0.88 (m, 1 H), 0.96−1.20 (m, 1 H) 1.79 (dd, *J* = 3.8, 11.6 Hz, 1 H), 2.05−2.10 (m, 1 H), 2.44 (d, 1 H), 2.54 (dd, *J* = 1.8, 15.1 Hz, 1 H), 2.68 (s, 1 H), 2.69−2.73 (m, 1 H), 3.03−3.20 (m, 1 H), 3.44 (dd, *J* = 1.3, 4.7 Hz, 1 H), 3.76 (s, 3 H), 5.70 (ddd, *J* = 1.5, 4.7, 9.9 Hz, 1 H), 5.78 (ddd, *J* = 1.5, 4.7, 9.9 Hz, 1 H), 6.81 (d, *J* = 7.7 Hz, 1 H), 6.86 (m, 1 H), 7.13 (dd, *J* = 7.7 Hz, 1 H), 7.23 (d, *J* = 7.4 Hz, 1 H) 8.98 (br s,1 H).

Determination of Enantiomeric Purity. Enantiomeric excesses (ee) of all synthesized natural products were determined by the chiral shift method using Eu(hfc)$_3$.[3] **(a) ψ-Vincadifformine.** The methyl ester singlet at δ 3.76 of racemic ψ-vincadifformine was split into two broad singlets when the racemic alkaloid and Eu(hfc)$_3$ (1:0.2) were complexed. The same singlet of enantiomerically pure material was not split when it was complexed with Eu(hfc)$_3$ at the same concentration or even higher concentrations.

(b) Ibophyllidine. Eu(hfc)$_3$ (0.01 M) was added to ibophyllidine samples (0.06 M). The first addition to a racemic ibophyllidine sample caused complexation and splitting of the methyl ester singlet, which was shifted to δ 3.78 for (−)-ibophyllidine and to δ 3.79 for (+)-ibophyllidine. When uncomplexed, the methyl ester singlet is found at δ 3.76. Addition of up to five times the required amount of Eu(hfc)$_3$ for complexation of a sample of (+)-ibophyllidine showed only a single enantiomer at δ 3.85.

(c) Vincadifformine. A vincadifformine to Eu(hfc)$_3$ 1:0.1 molar ratio was used. The methyl ester singlet of racemic vincadifformine at δ 3.76 when uncomplexed was split to give signals at δ 4.33 for the (+) enantiomer and at δ 4.21 for the (−) enantiomer.

Methyl3-[1(*S*)-[(*R*)-2-(Diphenylphosphinyl)ferrocenyl]ethyl]-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5ζ-carboxylates (4c). To a solution of (+)-ferrocenylethylindoloazepines **4a** (1.00 g, 1.56 mmol) in acetone (18 mL) was added dropwise hydrogen peroxide (30%, 1.26 mL, 11.1 mmol). After 30 min of stirring at room temperature, aqueous sodium thiosulfate was added to decompose an excess of the hydrogen peroxide. The reaction mixture was extracted with ether. The combined extracts were washed with water, dried over MgSO$_4$, and concentrated under reduced pressure. Purification of the residue by short-column chromatography on alumina, eluting with ethyl acetate, gave the title phosphine oxide (0.95 g, 93%) as an inseparable mixture of isomers: TLC R_f = 0.33, 0.40 (silica gel, EtOAc, CAS green); mp 147−150 °C; $[\alpha]_D$ +266 (*c* 0.35, CHCl$_3$); UV (EtOH) λ_{max} 212, 226, 266 nm; IR (KBr) ν_{max} 3374, 3185, 3066, 2959, 1728, 1602, 1457, 1437, 1250, 1180, 1146, 1117, 1072, 1000, 838, 750, 702 cm^{-1}; ^{1} H NMR (CDCl$_3$) δ 8.53, 8.51 (1 H, 2s), 7.83−7.76 (2 H, m), 7.67−7.53 (2 H, m), 7.48−7.42 (3 H, m), 7.39−7.27 (1 H, m), 7.23−7.19 (1 H, m), 7.12−6.94 (5 H, m), 4.73−4.68 (1 H, m), 4.52−4.43 (1 H, m), 4.37−4.31 (1 H, m), 4.15−3.97 (2 H, m), 5.15, 4.14 (5 H, 2s), 3.77, 3.72 (3 H, 2s), 3.29−1.97 (6 H, m), 1.32−1.23 (3 H, m); mass spectrum (EI) *m*/*z* (rel intensity) 657 (M^+ + 1, 37), 656 (M^+, 100), 413 (ferrocenyl, 28), 347 (14), 245 (23), 244 (indoloazepinyl, 32), 242 (51), 202 (45), 154 (68).

(3a*R*,4*R*,11b*R*)- and (3a*S*,4*S*,11b*S*)-Methyl 3-[1(*S*)-[[*R*]-2-(Diphenylphosphinyl)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-acetoxy-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (30c and 31c). A solution of the above ferrocenylethylindoloazepine phosphine oxide (**4c**, 0.450 g, 0.685 mmol) and acetoxyacetaldehyde (**29**, 1.43 N in CH$_2$Cl$_2$, 0.60 mL, 0.86 mmol) in dry benzene (4.5 mL) was heated at reflux for 12 h. The solvent was removed by rotary evaporation, and the residue was chromatographed on silica gel and eluted by EtOAc/hexane (1:1 to 2:1) to give tetracycle **30c** (0.224 g) and **31c** (0.233 g) as yellow solids; total yield 90%. For **30c**: TLC R_f = 0.38 (silica gel, EtOAc/hexane, 2:1, CAS blue to brown); mp 152−154 °C dec (ethyl ether/hexane); $[\alpha]_D$ +282 (*c* 0.22, CHCl$_3$); UV (EtOH) λ_{max} 210, 300, 328 nm; IR (KBr) ν_{max} 3374, 3065, 2983, 2952, 1731, 1679, 1610, 1438, 1247, 1193, 1117, 912, 729, 701 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.92 (1 H, s), 7.95−7.92 (2 H, m), 7.87−7.83 (2 H, m), 7.52 (3 H, br s), 7.40 (3 H, t, *J* = 2.3 Hz), 7.14 (1 H, t, *J* = 7.6 Hz), 7.07 (1 H, d, *J* = 7,4 Hz), 6.86 (1 H, t, *J* = 7.4 Hz), 6.78 (1 H, d, *J* = 7.7 Hz), 4.93 (1 H, q, *J* = 6.9 Hz), 4.56 (1 H, s), 4.38 (1 H, d, *J* = 2.0 Hz),

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4.20−4.09 (3 H, m), 4.13 (5 H, s), 3.70 (3 H, s), 3.24 (1 H, s), 2.88 (2 H, br d, $J = 6.1$ Hz), 2.46 (1 H, br d, $J = 14.6$ Hz), 1.74 (3 H, s), 1.69 (3 H, d, $J = 6.9$ Hz), 1.38−1.24 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 168.93, 168.03, 163.00, 143.15, 136.97, 135.62, 134.92, 134.78, 134.05, 131.30, 131.23, 131.15, 131.04, 128.35, 128.13, 127.77, 122.60, 120.48, 109.07, 97.62, 97.53, 88.25, 73.32, 73.12, 70.91, 70.32, 70.24, 70.04, 69.95, 69.90, 64.20, 55.27, 51.52, 50.82, 50.41, 39.31, 30.86, 22.83, 21.14, 13.74; mass spectrum (EI) *m/z* (rel intensity) 455 ($M^+ - Ph_2PO - CH_3CO$, 4), 414 (20), 413 (ferrocenyl, 49), 412 (72), 347 (17), 326 (3), 121 (60), 84 (100). Anal. Calcd for $C_{42}H_{41}N_2O_5PFe\cdot 0.5H_2O$: C, 67.29; H, 5.60; N, 3.74; P, 4.13; Fe, 7.45. Found: C, 67.09; H, 5.62; N, 3.52; P, 4.18; Fe, 7.27.

For **31c**: TLC $R_f = 0.22$ (silica gel, EtOAc/hexane, 2:1, CAS blue); mp 156−158 °C dec (ethyl ether/hexane); $[\alpha]_D - 6.3$ (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} 210, 300, 328 nm; IR (KBr) ν_{max} 3586, 3378, 3065, 2990, 2824, 1747, 1682, 1596, 1437, 1371, 1247, 1204, 1039, 911, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.84 (1 H, s), 7.73 (2 H, dd, $J = 7.2$ and 11.6 Hz), 7.53−7.43 (5 H, m), 7.37 (1 H, dd, $J = 6.9$ and 7.4 Hz), 7.29 (2 H, m), 7.12 (2 H, dd, $J = 6.9$ and 7.4 Hz), 6.84 (1 H, dd, $J = 7.4$ and 7.4 Hz), 6.75 (1 H, d, $J = 7.7$ Hz), 5.32 (1 H, s), 5.22 (1 H, q, $J = 6.5$ Hz), 4.63 (1 H, s), 4.36 (1 H, d, $J = 1.8$ Hz), 4.21 (1 H, m), 4.16 (5 H, s), 3.95 (1 H, s), 3.68 (3 H, s), 3.33 (1 H, s), 2.80 (1 H, m), 2.33 (1 H, br d, $J = 12.4$ Hz), 2.27 (1 H, dd, $J = 6.6$ and 8.3 Hz), 1.77 (3 H, s), 1.62 (3 H, d, $J = 6.5$ Hz), 1.31 (1 H, dd, $J = 4.3$ and 11.5 Hz), 1.10 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 170.65, 169.05, 163.24, 143.30, 137.56, 136.88, 136.04, 135.48, 134.65, 131.78, 131.70, 131.33, 131.08, 127.91, 127.81, 127.70, 122.26, 120.23, 109.07, 96.19, 96.12, 89.65, 73.94, 73.82, 71.52, 70.93, 70.39, 70.03, 69.70, 69.10, 66.10, 60.32, 54.60, 50.79, 49.45, 42.46, 39.99, 22.58, 21.46, 20.98, 14.16, 9.71; mass spectrum (EI) *m/z* (rel intensity) 413 (ferrocenyl, 37), 412 (100), 347 (9), 328 (21), 269 (33), 215 (33), 1665 (22), 72 (29). Anal. Calcd for $C_{42}H_{41}N_2O_5PFe\cdot 0.5H_2O$: C, 67.29; H, 5.60; N, 3.74; P, 4.13; Fe, 7.45. Found: C, 67.12; H, 5.62; N, 3.54; P, 4.15; Fe, 7.10.

(3a*R*,4*R*,11b*R*)- and (3a*S*,4*S*,11b*S*)-Methyl 3-[1(*S*)-[[*R*]-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-(*tert*-butyldiphenylsilyloxy)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (30b and 31b). A solution of ferrocenylindoloazepine **4a** (0.320 g, 0.50 mmol) and silyloxy aldehyde **32** (0.179 g, 0.60 mmol) in dry benzene (3.2 mL) was heated at reflux for 20 h. After evaporation of the solvent under reduced pressure, the resulting residue was dissolved in a mixture of dry CH_2Cl_2 (2 mL) and dry MeOH (2 mL). To this mixture was added $NaBH_4$ (0.05 g) with stirring to reduce excess aldehyde. The reaction mixture was stirred at room temperature for 15 min, and then water (25 mL) was added. The aqueous phase was extracted with ether (3 × 10 mL), and the extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with ether/hexane (1:2) to give an inseparable mixture of diastereoisomers of **30b** and **31b** (0.396 g, 86%) in a 1:2 ratio, on the basis of indole NH singlets in the ^{1}H NMR spectrum: TLC $R_f = 0.62$ (silica gel, ether/hexane, 1:1, CAS brown); mp 136−139 °C dec (ethyl ether/hexane); $[\alpha]_D$ +148 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} 224, 300, 328 nm; IR (KBr) ν_{max} 3383, 3073, 2931, 2856, 1675, 1610, 1466, 1436, 1289, 1276, 1247, 1198, 1111, 909, 822, 738, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.05, 9.02 (1 H, 2s), 7.72 (1 H, m), 7.61 (1 H, m), 7.52 (2 H, m), 7.44 (4 H, m), 7.39 (4 H, m), 7.34 (2 H, m), 7.25 (3 H,), 7.15 (2 H, m), 7.08 (3 H, m), 6.88 (1 H, m), 6.83 (1 H, m), 4.33 (1 H, m), 3.95 (1 H, br s), 3.88 (1 H, br s), 3.81 (1 H, s), 3.79 (5 H, s), 3.66 (2 H, s), 3.59 (3 H, s), 3.48 (1 H, m), 3.35 (1 H, s), 2.90 (1 H, m), 2.84 (1 H, m), 1.34 (3 H, d, $J = 6.7$ Hz), 1.27 (2 H, m), 0.73 (9 H, s); mass spectrum (EI) *m/z* (rel intensity) 397 (ferrocenyl, 6), 396 (14), 288 (tetracyclyl-*t*-BuPh$_2$SiO, 4), 268 (17), 242 (39), 232 (59), 199 (100), 135 (45).

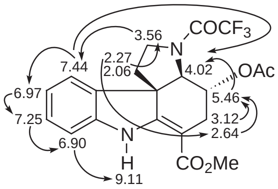
(3a*S*,4*S*,11b*S*)- and (3a*R*,4*R*,11b*R*)-Methyl 3-[1(*R*)-[[*S*]-2-(Diphenylphosphinyl)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-acetoxy-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (30a, 31a) and Phosphine Oxides (30e, 31e). A solution of ferrocenylindoloazepine **4b** (0.400 g, 0.624 mmol) and acetoxyacetaldehyde (**29**, 1.43 N in CH_2Cl_2, 0.55 mL, 0.78 mmol) in dry benzene (4 mL) was heated at reflux for 12 h. The solvent was removed by distillation under vacuum. The resulting residue (**30a**, **31a**) was dissolved in acetone (7 mL), and hydrogen peroxide (40%, 0.25 mL, 2.94 mmol) was added dropwise. After 30 min of stirring at room temperature, aqueous $Na_2S_2O_3$ was added to decompose an excess of hydrogen peroxide. The reaction mixture was extracted with ether, dried ($MgSO_4$), and purified by chromatography on silica gel (EtOAc/hexane 1:1 to 2:1) to afford tetracycle **31e** (0.234 g) and its diastereoisomer **30e** (0.140 g) successively; total yield 81%. For **31e**: TLC $R_f = 0.38$ (silica gel, EtOAc/hexane, 2:1, CAS blue to brown); mp 152−154 °C dec (ethyl ether/hexane); $[\alpha]_D$ −286 (*c* 0.32, $CHCl_3$). This tetracycle has identical spectroscopica data with its enantiomer **31c**. Anal. Calcd for $C_{42}H_{41}N_2O_5PFe\cdot 0.5H_2O$: C, 67.29; H, 5.60; N, 3.74; P, 4.13. Found: C, 67.41; H, 5.58; N, 3.62; P, 4.01.

For **30e**: TLC $R_f = 0.22$ (silica gel, EtOAc/hexane, 2:1, CAS blue); mp 156−158 °C dec (ethyl ether/hexane); $[\alpha]_D$ +6.9 (*c* 0.28, $CHCl_3$). This tetracycle has identical spectroscopica data with its enantiomer **30c**. Anal. Calcd for $C_{42}H_{41}N_2O_5PFe\cdot 0.5H_2O$: C, 67.29; H, 5.60; N, 3.74; P, 4.13. Found: C, 67.50; H, 5.62; N, 3.60; P, 4.12.

(3a*R*,4*R*,11b*R*)-Methyl 3-(Trifluoroacetoxy)-2,3,3a,4,5,7-hexahydro-4-acetoxy-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (35). To a solution of the tetracycle **31e** (3.0 g, 4.05 mmol) in dry CH_2Cl_2 (30 mL), at 0 °C under nitrogen, was added dropwise trifluoroacetic acid (3 mL). The reaction mixture was allowed to warm to room temperature and stirred for 6 h; then the volatile component was evaporated at reduced pressure. The residue was diluted with CH_2Cl_2, potassium carbonate was added, and the mixture was stirred for 15 min to neutralize any residual acid and filtered. The filtrate was concentrated at room temperature under reduced pressure. The resulting residue was subjected to chromatography on silica gel and eluted with MeOH/EtOAc (1:20) to give trifluoroacetamide **35** (1.10 g, 64%) and the corresponding free amine **33** (0.226 g, 17%). The ratio was determined as ca. 3:1 by ^{1}H NMR. For trifluoroacetamide **35**: TLC $R_f = 0.40$ (silica gel, methanol/ethyl acetate, 1:10, CAS blue), $R_f = 0.55$ (silica gel, acetone); $[\alpha]_D$ −144 (*c* 0.3, $CHCl_3$); UV (EtOH) λ_{max} 238, 298, 328 nm; IR (KBr) ν_{max} 3376, 3018, 2953, 1733, 1682, 1612, 1469, 1440, 1251, 1205, 1136, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.11 (1 H, s), 7.44 (1 H, d, $J = 7.4$ Hz), 7.25 (1 H, dd, $J = 7.7$ and 7.9 Hz), 6.97 (1 H, dd, $J = 7.5$ and 7.5 Hz), 6.90 (1 H, d, $J = 7.8$ Hz), 5.46 (1 H, s), 4.02 (1 H, s), 3.79 (3 H, s), 3.59−3.53 (2 H, m), 3.12 (1 H, d, $J = 16.8$ Hz), 2.64 (1 H, d, $J = 15.6$ Hz), 2.27 (1 H, m), 2.06 (1 H, m), 1.90 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.10, 168.24, 162.59 (q, $J = 36.3$ Hz), 160.12, 143.09, 133.81, 129.20, 122.33, 121.58, 116.39 (q, $J = 289.8$ Hz), 109.73, 89.36, 69.69, 65.35, 54.27, 43.85, 40.20, 30.83, 24.00, 20.88; mass spectrum (EI) *m/z* (rel intensity) 424 (M^+, 1), 328 (7), 296 (10), 268 (19), 214 (37), 167 (34), 154 (38), 69 (100).

For the free amine **33**: TLC $R_f = 0.33$ (silica gel, methanol/ethyl acetate, 1:10, CAS blue); $[\alpha]_D$ −225 (*c* 0.1, $CHCl_3$); UV (EtOH) λ_{max} 240, 298, 326 nm; IR (KBr) ν_{max} 3374, 2961, 2925, 2854, 1731, 1683, 1610, 1467, 1438, 1246, 1204, 1133, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.06 (1 H, s), 7.22−7.17 (2 H, m), 6.91 (1 H, dd, $J = 6.7$ and 7.7 Hz), 6.87 (1 H, d, $J = 8.1$ Hz), 4.88 (1 H, s), 3.78 (3 H, s), 3.63 (1 H, s), 3.24 (1 H, m), 3.16 (1 H, dd, $J = 7.1$ and 9.3 Hz), 2.96 (1 H, dd, $J = 3.2$ and 16.1 Hz), 2.55 (1 H, dd, $J = 2.5$ and 16.0 Hz), 2.02 (1 H, m), 1.86 (3 H, s), 1.81 (1 H, dd, $J = 5.2$ and 12.1 Hz); ^{13}C NMR ($CDCl_3$) δ 170.68, 169.17, 163.84, 143.34, 136.47, 128.07, 122.04, 120.82, 109.35, 88.74, 74.15, 65.15, 54.83, 44.78, 42.14, 30.90, 23.77, 21.29; mass spectrum (EI) *m/z* (rel intensity) 328 (M^+, 10), 268 ($M^+ -$ AcOH, 69), 215 (52), 195 (39), 168 (36), 154 (54), 114 (31), 72 (100).

Cleavage of Ferrocenylethyl Group with TFA−CH_2Cl_2 and TFAA. To a solution of tetracycle **31e** (0.020 g, 0.027 mmol) in 5 mL of dry CH_2Cl_2, cooled at 0 °C, was added TFAA (3.8 μL, 0.0405 mmol) under nitrogen, followed by 1 mL of trifluoroacetic acid. The mixture was allowed to warm to room



NOESY of trifluoroacetamide **35**

temperature and stirred for an additional 4 h. Workup and purification, as above, gave the trifluoroacetamide **35** (0.011 g, 92%).

(3a*R*,4*R*,11b*R*)-Methyl 3-((*Z*-2-Iodobut-2-en-1-yl)-2,3,3a,4,5,7-hexahydro-4-acetoxy-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (36). A mixture of trifluroacetamide **35** (1.33 g, 3.14 mmol), (*Z*)-1-bromo-2-iodobut-2-ene (1.59 g, 6.09 mmol) and potassium carbonate (2.73 g, 19.8 mmol) in THF (10 mL) was heated at reflux overnight under nitrogen. After filteration of the inorganic materials, the filtrate was concentrated and chromatographed on silica gel (1:2 ethyl ether:hexane) to yield the title compound **36** (1.46 g, 92%): TLC R_f = 0.40 (silica gel, ethyl ether/hexane, 2:1, CAS blue to gray); mp 164−166 °C (EtOH); $[\alpha]_D$ −252 (*c* 0.5, CHCl$_3$); UV (EtOH) λ_{max} 208, 240, 300, 328 nm; IR (KBr) ν_{max} 3376, 2947, 2801, 1728, 1681, 1612, 1479, 1466, 1438, 1372, 1248, 1201, 1143, 1090, 1034, 752 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.01 (1 H, s), 7.18 (1 H, dd, *J* = 7.7 and 8.0 Hz), 7.15 (1 H, d, *J* = 7.4 Hz), 6.90 (1 H, dd, *J* = 7.4 and 8.0 Hz), 6.85 (1 H, d, *J* = 7.7 Hz), 5.96 (1 H, q, *J* = 6.2 Hz), 5.05 (1 H, s), 4.03 (1 H, d, *J* = 13.8 Hz), 3.78 (3 H, s), 3.53 (1 H, d, *J* = 13.8 Hz), 3.14 (1 H, s), 3.00 (2 H, m), 2.68 (2 H, m), 2.09 (1 H, m), 1.84 (3 H, s), 1.81 (3 H, d, *J* = 6.2 Hz), 1.75 (1 H, dd, *J* = 4.7 and 8.5 Hz).

Preparation of Alkylation Product 36 from the Amine 33. The free amine (0.040 g, 0.12 mmol) was subjected to the above alkylation conditions in reagent-pure THF to produce the alkylation product (0.058 g, 94%). This product had identical spectroscopica data to the product prepared by alkylation of the trifluoroacetamide, but a relatively low optical rotation: $[\alpha]_D$ −230 (*c* 0.5, CHCl$_3$).

Alkylation Reaction of Trifuoroacetamide 35. A mixture of trifuoroacetamide **35** (44 mg, 0.104 mmol), (*Z*)-1-bromo-2-iodobut-2-ene (0.041 g, 0.156 mmol) and *dry* potassium carbonate (0.070 g, 0.507 mmol) in dry THF (5 mL) was heated at reflux for 4 h under nitrogen. There was no reaction, as monitored by TLC. Water (~2 μL, 0.104 mmol) was added. The reaction mixture was heated for another 2 h. The desired alkylation product was seen to appear in the TLC; neither free amine **33** nor alcohol from hydrolysis of acetate was detected. More water (8 μL, 4 equiv) was added, and refluxing was continued for 24 h. Workup and purification as above yielded the alkylated amine **36** (0.049 g, 93%). To test the stability of the acetate group, compound **36** (0.010 g) and potassium carbonate (0.015 g) were heated at reflux in a H$_2$O−THF (5 mL, 1:10) mixture for 30 min. No corresponding alcohol was detected in TLC. On heateng at reflux in 1:1 H$_2$O−THF for 1 h, the acetate cleavage product **37** was detected by TLC.

(3a*R*,4*R*,11b*R*)-Methyl 3-((*Z*)-2-Iodobut-2-en-1-yl)-2,3,3a,4,5,7-hexahydro-4-hydroxy-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (37). A mixture of acetate **36** (0.785 g, 1.55 mmol), potassium carbonate (0.226 g, 1.64 mmol) in methanol (25 mL), and water (1.6 mL) was heated at reflux for 30 min. The reaction mixture was cooled and concentrated. To the residue was added 50 mL of water. After extracting with 3 × 50 mL of dichloromethane, drying (MgSO$_4$), and concentration, the residue was purified on a flash column (SiO$_2$), eluting with 4:1 diethyl ether:hexane, to afford alcohol **37** (0.691 g, 96%): TLC R_f = 0.30 (silica gel, ethyl ether/hexane, 5:1, CAS blue); mp 172−174 °C (EtOH); $[\alpha]_D$ −314 (*c* 0.1, CHCl$_3$); UV (EtOH) λ_{max} 214, 300, 328 nm; IR (KBr) ν_{max} 3388, 2918, 2854, 1674, 1609, 1466, 1438, 1284, 1249, 1199, 1120, 747 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.04 (1 H, s), 7.18 (2 H, m), 6.90 (1 H, t, *J* = 7.0 Hz), 6.85 (1 H, d, *J* = 7.8 Hz), 5.94 (1 H, q, *J* = 6.1 Hz), 4.11 (1 H, br s), 3.82 (1 H, d, *J* = 13.8 Hz), 3.78 (3 H, s), 3.54 (1 H, d, *J* = 13.8 Hz), 3.11 (1 H, s), 3.04−2.95 (2 H, m), 2.73−2.63 (2 H, m), 2.08 (1 H, m), 1.82 (1 H, d, *J* = 6.2 Hz), 1.73 (1 H, dd, *J* = 4.7 and 12.1 Hz).

(3a*R*,11b*R*)-Methyl 3-((*Z*)-2-Iodobut-2-en-1-yl)-2,3,3a,4,5,7-hexahydro-4-oxo-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (38). To a solution of DMSO (0.31 mL, 4.4 mmol) in dichloromethane (30 mL) at −70 °C was added dropwise trifluoroacetic anhydride (0.60 mL, 4.3 mmol). After the solution was stirred for 20 min, alcohol **37** (0.663 g, 1.42 mmol) in dichloromethane (15 mL) was added at −70 °C. Stirring was continued at the same temperature for 1 h before addition of triethylamine (2.01 mL, 14.23 mmol). After being stirred for 2 h, the reaction mixture was gradually warmed to room temperature. The mixture was diluted with 100 mL of dichloromethane, washed with saturated aqueous sodium bicarbonate, and dried (MgSO$_4$). Purification of the evaporated residue by flash column (2:1 hexane:ethyl ether) gave ketone **38** (0.561 g, 85%): TLC R_f = 0.43 (silica gel, ethyl ether/hexane, 1:1, CAS greenish blue); mp 132−134 °C (ether/hexane); $[\alpha]_D$ −538 (*c* 0.24, CHCl$_3$); UV (EtOH) λ_{max} 240, 298, 332 nm; IR (KBr) ν_{max} 3365, 2983, 2952, 2858, 1717, 1682, 1610, 1479, 1467, 1437, 1244, 1210, 1137, 749 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.14 (1 H, s), 7.45 (1 H, d, *J* = 7.4 Hz), 7.19 (1 H, dd, *J* = 7.4 and 7.6 Hz), 6.93 (1 H, dd, *J* = 7.6 and 7.7 Hz), 6.82 (1 H, d, *J* = 7.7 Hz), 5.95 (1 H, q, *J* = 6.4 Hz), 3.77 (1 H, d, *J* = 14.0 Hz), 3.74 (3 H, s), 3.72 (1 H, dd, *J* = 1.1 and 14.0 Hz), 3.52 (1 H, d, *J* = 17.2 Hz), 3.22 (1 H, d, *J* = 1.1 Hz), 3.05−3.01 (2 H, m), 2.55 (1 H, dt, *J* = 8.6 and 12.6 Hz), 2.04 (1 H, ddd, *J* = 2.9, 12.6 and 12.6 Hz), 1.80 (3 H, d, *J* = 6.4 Hz).

(3a*R*,11b*R*)-Methyl 3-((*Z*)-2-Iodobut-2-en-1-yl)-2,3,3a,4-tetrahydro-4-oxo-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (39). To a solution of the ketone **38** (0.419 g, 0.903 mmol) and triethylamine (0.176 mL, 1.26 mmol) in dichlorometham e (30 mL) at 0 °C was added dropwise *tert*-butyl hypochlorite (0.129 mL, 1.08 mmol). The reaction mixture was stirred at 0 °C for 10 min and then brought to room temperature, diluted with 50 mL of dichloromethane, and washed with brine. After drying (MgSO$_4$) and evaporation under vacuum, the residue was subjected to silica gel chromatography, eluting with 1:1 ether: hexane, to yield imino ketone **39** (0.417 g, 100%): TLC R_f = 0.38 (silica gel, ethyl ether/hexane, 3:1, CAS blue faded to greenish yellow); $[\alpha]_D$ +112 (*c* 0.4, CHCl$_3$); IR (KBr) ν_{max} 2950, 1733, 1684, 1609, 1406, 1437, 1244, 751 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.97 (1 H, d, *J* = 7.4 Hz), 7.82 (1 H, d, *J* = 7.7 Hz), 7.42 (1 H, m), 7.33 (1 H, m), 6.84 (1 H, s), 6.01 (1 H, q, *J* = 6.4 Hz), 4.24 (1 H, d, *J* = 13.9 Hz), 3.99 (3 H, s), 3.97 (1 H, d, *J* = 13.9 Hz), 3.49 (1 H, s), 3.35 (1 H, m), 2.91 (1 H, m), 2.43 (1 H, m), 2.02 (1 H, m), 1.79 (3 H, d, *J* = 6.4 Hz).

Epimerization Studies on Imino Ketone 39. Imino ketone **39** (0.012 g, $[\alpha]_D$ +112) was heated at reflux in dry benzene (7 mL) for 12 h. After removal of the solvent, the imino ketone showed $[\alpha]_D$ +71 (*c* 0.4, CHCl$_3$). Prolonged heating (64 h) induced decomposition of the imino ketone, and a 30% yield of imino ketone was recovered after flash chromatography. It showed $[\alpha]_D$ +12 (*c* 0.1, CHCl$_3$).

(−)-(18,19(*E* and *Z*))-14-Oxoakuammicine (40a, 40b). A mixture of imino ketone **39** (0.034 mg, 0.074 mmol), tributyl tinhydride (0.022 mL, 0.081 mmol), and AIBN (0.008 g) in dry benzene (7 mL) was degassed with argon and then irradiated with a Pen-Ray Ps-1 UV lamp at room temperature for 1 h. The solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 75:25:0.5 ethyl acetate:hexane: triethylamine, to afford a *Z*/*E* mixture in a ratio of 1:1.7 as determined by ^{1}H NMR (11 mg, 44%). After crystallization of the mixture from methanol, a 9:1 mixture was obtained with the desired *E*-isomer enriched. One more crystallization from methanol yielded pure *E*-**40a**: TLC R_f = 0.41 (silica gel, ethyl acetate/hexane/triethylamine, 9:1:0.5, CAS blue); mp 214−216 °C; $[\alpha]_D$ −774 (*c* 0.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 9.09 (1 H, s), 7.17−7.14 (2 H, m), 6.90 (1 H, dd, *J* = 7.6 and 7.6 Hz), 6.79 (1 H, d, *J* = 8.1 Hz), 5.57 (1 H, qt, *J* = 1.8 and 7.0 Hz), 4.22 (1 H, s), 3.85 (1 H, d, *J* = 2.4 Hz), 3.80 (3 H, s), 3.74 (1 H, dd, *J* = 1.7 and 15.3 Hz),3.41 (1 H, m), 3.28 (1 H, m), 3.20 (1 H, d, *J* = 15.3 Hz), 3.06 (1 H, m), 2.04 (1 H, m), 1.63 (3 H, dt, *J* = 1.6 and 7.0 Hz).

(−)-Mossambine (41). To a stirred mixture of ketone (−)-**40a** (0.007 g, 0.022 mmol) and $CeCl_3 \cdot 7H_2O$ (0.011 g, 0.030 mmol) in methanol (1.5 mL) and THF (1.5 mL), cooled in an ice bath, was added sodium borohydride (0.020 g, 0.53 mmol) by portions. The reaction mixture was allowed to warm to room temperature, and saturated aqueous sodium biscarbonate (15 mL) was added. Extraction with 4 × 10 mL of chloroform, followed by drying ($MgSO_4$) and evaporation, gave the crude product, which was purified by column chromatography (eluted with 70:30:0.5 ethyl acetate:methanol:triethylamine) to afford the α/β-hydroxy mixture in a ratio of 1:5 as determined by ^{1}H NMR. Crystallization of the mixture from methanol gave (−)-mossambine (**41**) as white crystals (4.5 mg, 60%): TLC $R_f = 0.24$ (silica gel, ethyl acetate/methanol, 1:1, CAS blue); mp 219−211 °C; $[\alpha]_D$ −494 (c 0.05, $CHCl_3$), reported −482;[13] UV (EtOH) λ_{max} 206, 298, 330 nm; IR (KBr) ν_{max} 3366, 2925, 2861, 1670, 1603, 1464, 1463, 1235, 1200, 1104, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.83 (1 H, s), 7.19 (1 H, d, $J = 7.3$ Hz), 7.15 (1 H, dd, $J = 7.7$ and 7.7 Hz), 6.91 (1 H, dd, $J = 7.4$ and 7.5 Hz), 6.81 (1 H, d, $J = 7.7$ Hz), 5.75 (1 H, q, $J = 6.6$ Hz), 3.95 (1 H, d, $J = 3.2$ Hz), 3.86 (1 H, br s), 3.77 (3 H, s), 3.73 (1 H, t, $J = 3.1$ Hz), 3.51 (1 H, d, $J = 13.1$ Hz), 3.16 (1 H, d, $J = 12.8$ Hz), 3.00 (1 H, dd, $J = 7.1$ and 14.7 Hz), 2.94−2.89 (2 H, m), 2.45 (1 H, br s), 1.87 (1 H, dd, $J = 6.9$ and 12.6 Hz), 1.79 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.54, 167.88, 144.49, 135.47, 132.03, 127.88, 124.05, 121.26, 120.00, 109.76, 97.91, 70.41, 65.23, 58.56, 54.63, 53.95, 51.17, 44.62, 36.26, 12.65; mass spectrum (EI) m/z (rel intensity) 339 ($M^+ + 1$, 8), 338 (M^+, 19), 321 ($M^+ - OH$, 1), 279 ($M^+ - CO_2Me$, 5), 252 (9), 206 (10), 149 (54), 121 (100).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **6a**, **6b**, **10b**, **11a**, **11b**, **14a**, **14b**, **15**, **16a**, **21a−f**, **30a**, and **31a** and ^{1}H NMR spectra for compounds **1**, **2**, **10a**, **12**, **22**, **25**, **27**, **28**, and **33**/**34** (45 pages). Spectra of other intermediates in the mossambine synthesis match those of corresponding racemic compounds. They are available from the previous publication.[13] This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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