An Alternative Enantioselective Generation of Intermediates in the Total Synthesis of Vinblastine: Enantioselection in Secodine-Type Reactions Induced by α-Ferrocenylethyl *N*-Substituents

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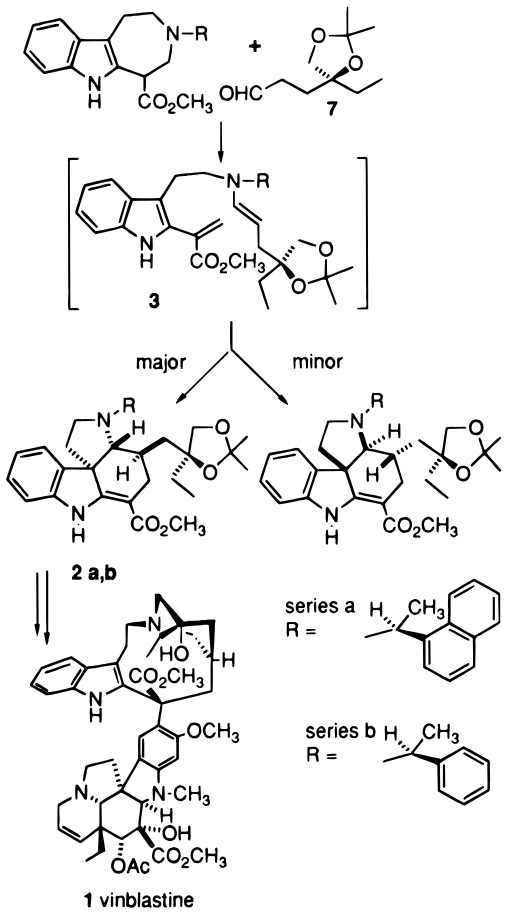
In 1991, we reported enantioselective total syntheses of vinblastine (**1**, 22% overall yield).[1] The tetracyclic intermediates (**2a**,**b**, Scheme 1) required for these syntheses were obtained, respectively, as a 4:1 mixture of two diastereomers from an intramolecular Diels−Alder, secodine-type, cyclization reaction with an N^b-(1(*S*)-(α-naphthyl)ethyl) substituent on the transient enamine **3** and as a 3:1 mixture of two diastereomers with a corresponding 1(*S*)-phenethyl N^b-substituent. While these chiral benzylic-type N^b-substituents provided workable solutions for completion of enantioselective syntheses of vinblastine, a better diastereoosectivity in the secodine-type cyclization step was obviously of interest.

Consequently, alternative chiral N^b-substituents were considered for the enamine intermediate **3** in the intramolecular Diels−Alder reaction. Desirable features for such an N^b-substituent are, first, the ability to introduce it at a late stage in the the synthesis of the secodine-type intermediate **3** and, second, the ability to remove it with preservation of its chirality after the intramolecular Diels−Alder-type reaction for a reuse in the synthesis. Neither of these requirements was met by the above chiral benzylic-type substituents, nor were they known for any other chiral auxiliaries attached to a basic nitrogen.

However, the remarkable chemistry of α-ferrocenylethyl derivatives seemed to offer the possibility of satisfying both of our desired synthetic requirements,[2−5] provided that good chiral induction would also be found in the intramolecular Diels−Alder-type step. Nucleophilic substitution, with retention of absolute stereochemistry,[3,4] had been demonstrated in the reactions of α-ferrocenylethyl acetate with ammonia or secondary amines and in conversions of (α-ferrocenylethyl)ammonium iodide to the corresponding alcohol, methyl ether, or acetate.[5]

The compatibility of α-ferrocenylethyl *N*-substituents with our synthetic strategy for generation of the tetracyclic D-*nor*-aspidosperma alkaloid skeleton **2** was demonstrated by alkylation of the N^b-*H*-indoloazepine **4**[6] with (*S*)-α-ferrocenylethyl acetate (**5a**) (Scheme 2),[5] and reaction of the resulting tertiary amine **6a** with 4-ethyl-4,5-dihydroxypentanal acetonide (**7**).[1] An inseparable 2:1 (by NMR) diastereomeric mixture of the tetracyclic

Scheme 1



products **2c** and **2d** was obtained in 71% yield from this condensation. The diastereomeric product ratio was thus less favorable than that obtained with the chiral α-phenethyl N^b-substituent. However, when the indoloazepine **4** was alkylated with the 2-diphenylphosphenyl-substituted (*S*)-α-ferrocenylethyl acetate **5b**[7] and its product **6b** was condensed with the aldehyde **7**, a 77% yield of the tetracyclic product **2e** was obtained as a single diastereomer! In contrast to analogous reactions of the *N*-benzylindoloazepine with aldehydes,[8] which required 110 °C (refluxing toluene), this reaction could be accomplished at 80 °C (refluxing benzene)—a fortunate observation, since extensive decomposition occurred at higher temperature with the α-ferrocenylethyl derivative.

For continuation of the vinblastine synthesis, the ferrocenyl substituent could now be removed from the tetracycle **2e**. Acetolysis in acetic acid provided the enantiomerically pure α-(acetoxyethyl)ferrocene **5b** and a 7:1 mixture of tetracyclic 3a*S*,4*S*,11b*R* and 3a*R*,4*S*,-11b*S* diastereomers **8a** and **9a**, which were readily separated by chromatography. Partial epimerization at the C/E ring juncture had occurred in the acetic acid medium by reversible protonation of the aminoacrylate function, with formation of an indole−imonium intermediate, which could undergo alterfacial recyclization. The enantiomeric relationship at centers 3a and 11b in compounds **8a** and **9a** was indicated by their opposite optical rotations (+367° for **8a** and −386° for **9a**) and,

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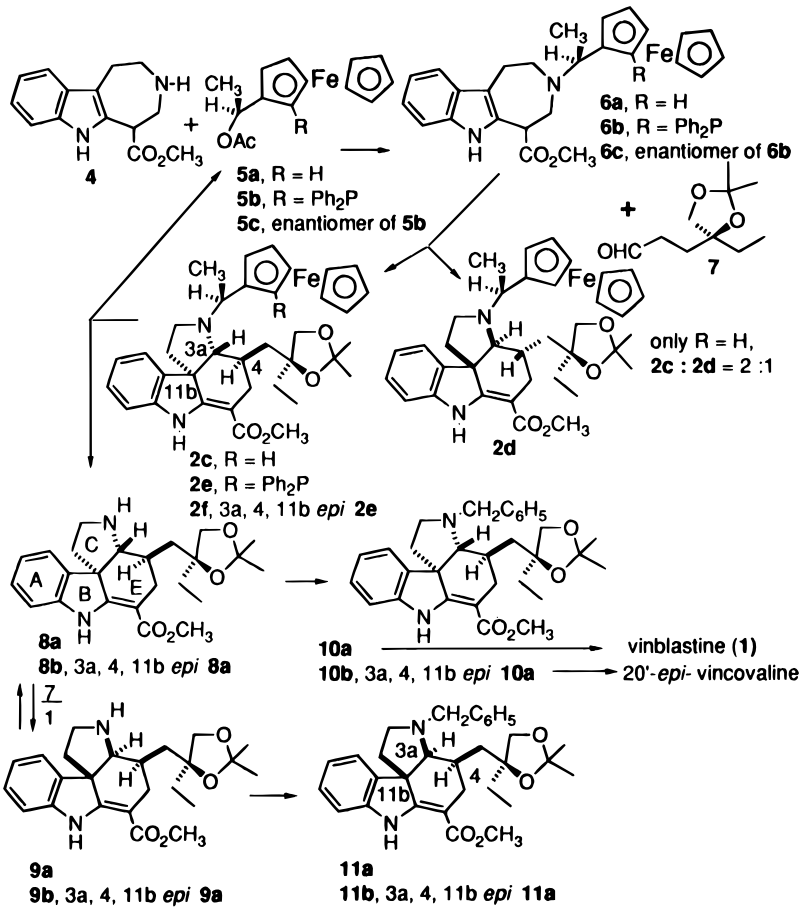
Scheme 2



together with 3a,4 *trans* H coupling for **8a** (^{1}H NMR: 3a-H, δ 3.45) with $J = 0$ Hz and 3a,4 *cis* H coupling for **9a** (^{1}H NMR 3a-H, δ 3.75) with $J = 4.5$ Hz,[9] showed that epimerization had not occurred at C-4. When the separate diastereomer **8a** was heated in acetic acid, a 7:1 equilibrated mixture of the epimers **8a** and **9a** was also formed.

Benzylation of the separate secondary amines **8a** and **9a** with benzyl bromide provided the corresponding tertiary amines **10a** and **11a**. On heating of these compounds in acetic acid for 15 min, no epimerization was found, but on prolonged heating they decomposed with destruction of the aminoacrylate functionality.

In order to avoid the partial epimerization of the secondary amine **8a**, N^b-quaternization of the ferrocenylethyl precusor **2e** with benzyl bromide and subsequent acetolysis was attempted. But, for such a sequence, the more alkylatable phosphine substituent is an impediment to N^b-alkylation and also to subsequent recovery of the chiral auxiliary **5b**.

The same reaction sequence could also be carried out starting with the enantiomer **5c** of the (diphenylphosphenyl)ferrocene **5b**. Formation, once again, of only one enantiomeric tetracyclic intermediate **2f** showed that the intramolecular Diels−Alder reaction step is not affected by the chirality of the enamine substituent, but that it is controlled by the chirality of the ferrocenyl substituent on nitrogen.

Our use of the 3a,4,11b diastereomeric mixture of the tetracyclic *N*-benzylamine **10a** for completion of a vinblastine synthesis has already been described.[1] The need for separation of the diastereomers is now eliminated with the enantioselective generation of the tetracycle **10a**. Introduction of the chiral ferrocenyl auxiliary at the indoloazepine stage of the synthesis, its subsequent recovery, and the excellent chiral induction in the intramolecular Diels−Alder reaction step greatly improve the otherwise satisfactory synthesis of vinblastine (**1**). Starting with the enantiomer of the aldehyde **7**,[1] condensations with the ferrocenylindoloazepines **6b** and **6c** provide, respectively, enantioselective routes to the alkaloids leurosidine and vincovaline.[1]

This study demonstrates the alkylation of a nonchiral amine intermediate with a chiral ferrocenylalkyl acetate and subsequent recovery of that chiral auxiliary for reuse after a reaction step benefiting from chiral induction. While cyclic, chiral induction processes, with recovery of the chiral auxiliary, have been developed for many reactions (i.e., α-alkylation of aldehydes, ketones, or acid derivatives) this objective had not been reached in chiral functionalization of amines with maintenance of their basicities.

Experimental Section

Methyl 3-(1(*S*)-Ferrocenylethyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-ξ-carboxylate (6a). A solution of (*S*)-(+)-1-ferrocenylethyl acetate **5a**[5] (1.10 g, 4.04 mmol), indoloazepine **4**[6] (1.50 g, 6.06 mmol), and triethylamine (1.12 mL, 8.08 mmol) in absolute ethanol (15 mL) was heated at reflux for 2 h and concentrated under reduced pressure. Workup and purification, similar to that for compound **6b** (below), gave the products **6a** (1.46 g, 79%) as two inseparable isomers: $[\alpha]^{25}_D$ +37° (*c* 2.8, $CHCl_3$); mp 82 °C; TLC $R_f = 0.50$ (silica gel, hexane/ether, 2:1,

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CAS green); UV (EtOH) λ_{max} 210, 228, 282, 292 nm; IR (KBr) ν_{max} 3399, 3092, 3055, 2972, 2903, 2830, 1729, 1619, 1463, 1453, 1434, 1371, 1336, 1286, 1238, 1211, 1163, 1105, 1042, 1001, 910, 819, 7341 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26−1.30 (m, 1 H), 1.41 and 1.43 (2 × d, J = 6.3, 8.2 Hz, 3 H), 2.49−2.94 (m, 5 H), 3.18 and 3.31 (2 × dd, J = 6.4, 12.9, 5.6, 12.8 Hz, 1 H), 3.66 and 3.74 (2 × s, 3 H), 3.76−4.22 (m, including 5 H singlet at δ 4.13, 1 H), 7.03−7.11 (m, 2 H), 7.24 (d, J = 9.1 Hz, 2 H), 7.42−7.45 (m, 1 H), 8.01 and 8.12 (2 × s, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.1, 16.9, 25.9, 26.0, 47.3, 47.5, 52.1, 52.2, 53.9, 54.8, 55.6, 62.2, 62.3, 66.1, 66.7, 66.8, 67.0, 67.8, 67.9, 68.3, 68.6, 68.7, 68.8, 69.9, 88.8, 88.9, 110.6, 114.1, 114.2, 118.0, 119.0, 119.1, 121.3, 128.7, 128.7, 132.4, 132.5, 134.9, 172.3, 172.3; mass spectrum. (CI) m/z (rel intensity) 457 (M + 1, 24), 456 (M^+, 9), 245 (11), 244 (13), 230 (35), 229 (13), 228 (21), 214 (19), 213 (100), 212 (87), 138 (9), 121 (8). Anal. Calcd for $C_{26}H_{28}N_2O_2Fe$: C, 68.43; H, 6.18; N, 6.14. Found: C, 68.08; H, 6.50; N, 5.81.

Methyl 3-[1(*S*)-[(*R*)-2-(Diphenylphospheno)ferrocenyl]-ethyl]-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-*ζ*-carboxylate (6b). A solution of 1(*S*)-[(*R*)-2-(diphenylphospheno)-ferrocenyl]ethyl acetate (PPFOAc) **5b**,[7] (4.5 g, 9.86 mmol), indoloazepine **4**[6] (3.61 g, 14.79 mmol), and triethylamine (2.75 mL, 19.72 mmol) in absolute ethanol (35 mL) was heated at reflux for 2 h and concentrated under reduced pressure. The residue was dissolved in dichloromethane (25 mL) and washed with water (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated, and the residue was subjected to chromatography on activity I alumina. Less polar minor byproducts (*R*)-1-(diphenylphospheno)-2-vinylferrocene (0.164 g, see analytical data below) and 1(*S*)-ethoxy-[(*R*)-2-(diphenylphospheno)ferrocenyl]ethane (0.064 g)[10] were first eluted with ether/hexane, 1:10, and a dark yellow, polar band was then eluted with ether/hexane/MeOH, 75:23:2, to give **6b** (4.65 g, 74%) as inseparable isomers in a 1:1.5 ratio: $[\alpha]^{25}_D$ +238° (*c* 0.24, $CHCl_3$); mp 103−105 °C; TLC R_f = 0.43, 0.51 (silica gel, hexane/ether, 1:1, CAS brown); UV (EtOH) λ_{max} 196, 226, 282, 294 nm; IR (KBr) ν_{max} 3429, 3049, 2970, 2924, 2898, 2820, 1725, 1615, 1574, 1457, 1424, 1365, 1332, 1306, 1266, 1227, 1155, 1096, 991, 919, 882, 742, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36, 1.40 (2 × d, J = 6.8, 6.4 Hz, 3 H), 1.95−3.10 (m, 5 H), 3.25, 3.35 (2 × d, J = 12.4, 9.4, 1H), 3.69, 3.79 (2 × s, 3 H), 3.92−4.00 (m, including 5 H singlets at δ 3.94, 3.95, 6 H), 4.35 (m, 1 H), 4.45−4.48 (m, 1 H), 6.95−7.15 (m, 4 H), 7.20−7.45 (m, 8 H), 7.55−7.70 (m, 5 H), 8.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.3, 11.9, 24.1, 24.9, 45.4, 46.1, 47.9, 51.2, 52.1, 52.2, 53.4, 54.5, 56.8, 60.6, 60.7, 60.8, 61.0, 68.6, 68.7, 69.6, 69.7 (5 C), 69.8, 69.9, 71.9, 72.0, 72.1, 96.3, 97.1, 110.6, 113.3, 113.5, 117.6, 118.8, 118.9, 120.9, 127.5, 127.6, 127.7, 127.9, 128.0, 128.2, 128.3, 128.8, 128.9, 132.2, 132.4, 132.5, 132.6, 132.8, 134.3, 134.4, 135.1, 135.1, 135.4, 135.5, 138.1, 138.5, 139.9, 140.0, 140.3, 173.3, 173.5; mass spectrum (EI) m/z (rel intensity) 640 (M^+, 20), 398 (19), 397 (71), 286 (18), 243 (13), 242 (92), 215 (17), 214 (14), 213 (20), 212 (100), 210 (27), 202 (22), 183 (13), 182 (18), 181 (14).

Methyl 3-[1(*R*)-[(*S*)-2-(Diphenylphospheno)ferrocenyl]-ethyl]-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-*ξ*-carboxylate (6c). By the above procedure, starting with a solution of 1(*S*)-[(*R*)-2-(diphenylphospheno)ferrocenyl]ethyl acetate (PPFOAc) (**5c**), the title product was obtained with $[\alpha]^{25}_D$ −240° (*c* 2.8, $CHCl_3$); mp 103−105 °C; TLC R_f = 0.43, 0.51 (silica gel, hexane/ether, 1:1, detection with ceric ammonium sulfate [CAS], brown). Anal. Calcd for $C_{38}H_{37}N_2O_2PFe$: C, 71.25; H, 5.82; N, 4.37; P, 4.83; Fe, 8.72. Found: C, 70.86; H, 6.06; N, 4.46; P, 4.74; Fe, 8.64.

(3a*S*,4*S*,11b*R*)- and (3a*R*,4*R*,11b*S*)-Methyl 3-(1(*S*)-Ferrocenylethyl)-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (2c and 2d). A solution of ferrocenylindoloazepine **6a** (0.20 g, 0.438 mmol) and 4(*S*)-ethyl-4,5-dihydroxypentanal acetonide (**7**)[1] (0.101 g, 0.542 mmol) in dry benzene (2 mL) was heated at reflux for 4 h, and the solvent was then evaporated under reduced pressure. The residue was dissolved in dry methanol (10 mL), and $NaBH_4$ (0.05 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 (25 mL) was added. The aqueous phase was extracted with ether (3 × 20 mL) and the extract dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ether/hexane, 1:1) to give an inseparable mixture of diastereoisomers **2c**, **2d** (0.194 g, 71%) in a 1:2 ratio, on the basis of OCH_3 singlets in the ^{1}HNMR spectrum: TLC R_f = 0.60 (silica gel, hexane/ether, 2:1, detection with ceric ammonium sulfate [CAS], blue to purple); UV (EtOH) λ_{max} 216, 228, 300, 330 nm; IR (KBr) ν_{max} 3384, 3093, 2977, 2936, 1677, 1610, 1478, 1465, 1437, 1379, 1368, 1294, 1279, 1249, 1204, 1127, 1106, 1052, 1000, 911, 818, 733 cm^{-1}; mass spectrum (CI), m/z (rel intensity) 626 (M + 2, 15), 626 (M + 1, 34), 230 (70), 214 (13), 213 (100), 212 (48), 138 (18), 121 (8).

(3a*S*,4*S*,11b*R*)-Methyl 3-[1(*S*)-[(*R*)-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (2e). A solution of (+)-ferrocenylindoloazepine **6b** (4.00 g, 6.24mmol) and 4(*S*)-ethyl-4,5-dihydroxypentanal acetonide (**7**)[1] (1.40 g, 7.49 mmol) in dry benzene (20 mL) was heated at reflux for 12 h, and the solvent was then evaporated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (10 mL) and dry methanol (75 mL), and $NaBH_4$ (0.5 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 (250 mL) was added. The aqueous phase was extracted with ether (3 × 100 mL) and the extract dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ether/hexane, 1:2) to give **2e** (3.6 g, 71%) as a yellow foam: $[\alpha]^{25}_D$ +367° (*c* 0.06, $CHCl_3$); mp 92−95 °C dec; TLC R_f = 0.45 (silica gel, hexane/ether, 1:1, CAS blue to brown); UV (EtOH) λ_{max} 216, 230, 300, 330 nm; IR (KBr) ν_{max} 3391, 3069, 3053, 2980, 2938, 2875, 1677, 1610, 1478, 1465, 1435, 1378, 1368, 1345, 1292, 1280, 1247, 1208, 1148, 1126, 1110, 1047, 1000, 910, 865, 822, 735, 698, 647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (d, J = 12 Hz, 1 H), 0.74−0.82 (m, 1 H), 0.93 (t, J = 7.4 Hz, 3 H), 1.04 (s, 3 H), 1.32 (s, 3 H), 1.36−1.44 (m, 1 H), 1.57 (q, J = 7.5 Hz, 2 H), 1.66−1.72 (m, 1 H), 1.79 (d, J = 7.0 Hz, 3 H), 2.04 (dd, J = 3, 15 Hz, 1 H), 2.58 (d, J = 15 Hz, 1 H), 2.68 (s, 1 H), 2.75−2.80 (m, 1 H), 2.92 (t, J = 7.4 Hz, 1 H), 3.03 (d, J = 8.5 Hz, 1 H), 3.59 (d, J = 8.5 Hz, 1 H), 3.71 (s, 3 H), 3.82 (s, 5 H), 4.29 (s, 1 H), 4.46−4.52 (m, 1 H), 4.53 (s, 1 H), 4.60 (s, 1 H), 6.56 (d, J = 7.3 Hz, 1 H), 6.72−6.76 (m, 2 H), 6.90 (t, J = 7.4 Hz, 2 H), 7.02 (t J = 7.3 Hz, 1 H), 7.08−7.16 (m, 3 H), 7.39 (bs, 3 H), 7.65−7.69 (m, 2 H), 8.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.4, 26.0, 27.3, 29.3, 35.8, 37.1, 41.6, 46.4, 50.5, 51.3, 55.2, 68.0, 69.1, 69.6, 69.7, 69.8 (5C), 71.4, 72.9, 74.9, 75.0, 83.2, 91.1, 97.4, 97.7, 108.8, 119.9, 122.6, 127.3, 127.7, 127.7, 128.0, 128.1, 129.2, 132.1, 132.2, 135.5, 135.6, 137.3, 137.7, 139.6, 139.7, 140.5, 140.6, 143.1, 164.4, 169.4; mass spectrum (CI) m/z (rel intensity) 809 (M + 1, 3), 594 (3), 439 (2), 425 (5), 412 (3), 398 (16), 397 (79), 396 (100), 331(11), 288 (12), 283 (6), 252 (5), 213 (12), 165 (5), 164 (7), 120 (18), 56 (14). Anal. Calcd for $C_{48}H_{53}N_2O_4PFe$: C, 71.28; H, 6.61; N, 3.46; P, 3.97; Fe, 7.15. Found: C, 70.95; H, 6.74; N, 3.42; P, 3.93; Fe, 6.96.

(3a*S*,4*S*,11b*R*)-Methyl 3-[1(*R*)-[(*S*)-2-(Diphenylphospheno)ferrocenyl]ethyl]-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (2f). A solution of the (−)-indoloazepine **6c** (1.00 g, 1.52 mmol) and (4*S*)-4-ethyl-4,5-dihydroxypentanal acetonide (**7**)[1] (0.426 g, 2.28 mmol) in dry benzene (10 mL) was heated under reflux for 12 h. The benzene was evaporated under reduced pressure. The residue was dissolved in dry methanol (50 mL), and $NaBH_4$ (0.2 g) was added with stirring to reduce excess aldehyde, which was inseparable by chromatography. The mixture was stirred at room temperature for 15 min, and water (100 mL) was added. The mixture was extracted with ether (3 × 25 mL) and the extract dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silical gel (ether/hexane, 1:1) to give the tetracycle **2f** (0.968 g, 77%) as a yellow foam: $[\alpha]^{25}_D$ −396° (*c* 0.35, $CHCl_3$); mp 95−98 °C dec; TLC R_f = 0.31 (silica gel, hexane/ether, 1:1, CAS blue to purple); UV (EtOH) λ_{max} 214, 230, 300, 330 nm; IR (KBr) ν_{max} 3385, 3053, 2979, 2938, 2875, 1677, 1610, 1478, 1465, 1435, 1378, 1368, 1294, 1279, 1212, 1202, 1109, 1051, 1000, 821, 741, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, J = 7.4 Hz, 3 H), 0.85−0.87 (m, 2 H), 1.14 (s, 3 H), 1.25−1.60 (m, including 3 H singlet at δ 1.36, 6 H), 1.70−1.85 (m, including

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3 H doublet at δ 1.78, J = 6.9 Hz, 4 H), 2.02 (d, J = 15.3 Hz, 1 H), 2.79 (m, 1 H), 2.94 (t, J = 7.8 Hz, 1 H), 3.13 (s, 1 H), 3.39 (d, J = 8.5 Hz, 1 H), 3.67 (d, J = 8.5 Hz, 1 H), 3.79 (s, 3 H), 3.87 (s, 5 H), 4.15 (s, 1 H), 4.37 (s, 1 H), 4.48 (m, 1 H), 4.64 (s, 1 H), 6.73 (d, J = 7.7 Hz, 1 H), 6.76 (t, J = 7.4 Hz, 1 H), 6.83 (d, J = 7.3 Hz, 1 H), 6.95−7.15 (m, 4 H), 7.30 (t, J = 7.3 Hz, 2 H), 7.37 (m, 3 H), 7.65−7.68 (m, 2 H), 6.71−7.69 (m, 2 H), 8.80 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.5, 17.2, 22.9, 26.7, 27.3, 29.3, 35.8, 38.2, 41.2, 49.8, 50.7, 52.9, 55.6, 67.7, 68.9, 69.5, 69.6, 69.7 (5 C), 73.5, 75.0, 83.7, 90.4, 99.2, 108.3, 108.9, 120.3, 122.5, 127.4, 127.7, 127.8, 127.9, 127.9, 128.0, 129.0, 132.5, 132.7, 135.3, 135.5, 137.7, 139.9, 140.0, 142.8, 142.8, 165.5, 169.0; mass spectrum (CI), m/z (rel intensity) 809 (M + 1, 2), 439 (2), 412 (3), 397(14), 396 (100), 212 (9), 171 (21), 157 (3), 129 (32), 111 (69). Anal. Calcd for $C_{48}H_{53}N_2O_4PFe$: C, 71.28; H, 6.61; N, 3.46; P, 3.97; Fe, 7.15. Found: C, 71.18; H, 6.65; N, 3.32; P, 3.27; Fe, 6.80.

Removal of Chiral Ferrocenyl Auxiliary. Formation of Amines 8a,b and 9a,b. 1. A solution of the tetracycle **2e** or **2f** (0.808 g, 1 mmol) in glacial acetic acid (15 mL) was heated at 70 °C for 15 min. The mixture was then poured into crushed ice and basified with 15% NH_4OH in brine (25 mL) to produce a yellow precipitate. Glacial acetic acid was slowly added until the solution became slightly acidic, and the mixture was vigorously shaken in a separatory funnel. The yellow precipitate (**5c**) was filtered, and the clear filtrate was basified with 15% NH_4OH in brine (25 mL) to produce a white precipitate, which was extracted with ether (3 × 25 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed on silica gel, eluting with 5% methanol in CH_2Cl_2, to give *trans* epimer **8a** or **8b** (0.306 g, 74%) and *cis* epimer **9a** or **9b** (0.058 g, 14%). The yellow precipitate (**5c**) was dissolved in CH_2Cl_2 (25 mL), dried over Na_2SO_4, and concentrated to give a residue (0.98 g). This residue mainly contained PPFOAC. Further purification of this residue by flash chromatography produced an inseparable mixture of PPFOH and PPFOAC. Consequently, the residue was directly used to synthesize chiral indoloazapine **6c**.

For the *trans* epimer (3a*R*,4*R*,11b*S*)-methyl 2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (**8a**): $[\alpha]^{25}_D$ +367° (*c* 0.32, $CHCl_3$); TLC R_f = 0.29 (silica gel, 5% methanol in CH_2Cl_2, CAS blue to purple); UV (EtOH) λ_{max} 214, 228, 300, 328 nm; IR (KBr) ν_{max} 3381, 3054, 2980, 2936, 2877, 1677, 1610, 1478, 1466, 1437, 1379, 1369, 1284, 1248, 1204, 1107, 1051, 911, 868, 786, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.65 (t, J = 7.5 Hz, 3 H), 0.94 (dd, J = 5.3, 14 Hz, 1 H), 1.17−1.32 (m, including 2 × 3 H singlet at δ 1.20 and 1.23, 7 H), 1.44−1.52 (m, 2 H), 1.68−1.87 (m, 3 H), 2.26 (dd, J = 3.4, 15.3 Hz, 1 H), 2.28 (dd, J = 1.3, 15.3 Hz, 1 H), 2.98−3.02 (m, 2 H), 3.39 (d, J = 8.4 Hz, 1 H), 3.45 (s, 1 H), 3.59 (d, J = 8.4 Hz, 1 H), 3.60 (s, 3 H), 6.73 (d, J = 7.7 Hz, 1 H), 6.77 (t, J = 7.5, 1 H), 7.04 (t, J = 7.6 Hz, 1 H), 7.12 (d, J = 7.3 Hz, 1 H), 8.94 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.6, 24.1, 26.9, 27.1, 29.9, 36.5, 38.9, 45.1, 45.6, 50.8, 55.6, 68.7, 72.7, 83.8, 90.9, 109.0, 109.1, 120.6, 121.7, 127.8, 137.5, 143.2, 165.7, 168.9; mass spectrum (EI) m/z (rel intensity) 413 (9), 412 (M$^+$, 11), 284 (14), 283 (100), 228 (30), 223 (8), 215 (19), 214 (9), 169 (9), 168 (33), 167(18), 154 (22), 144 (9), 140 (14), 129 (27), 72 (10), 71 (18), 69 (15), 69 (19), 59 (25), 57 (17), 56 (10), 55 (13).

For the *trans* epimer (3a*S*,4*S*,11b*R*)-methyl 2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (**8b**): $[\alpha]^{25}_D$ −326° (*c* 0.5, $CHCl_3$); TLC R_f = 0.5 (silica gel, 10% methanol in CH_2Cl_2, CAS blue to purple); UV (EtOH) λ_{max} 206, 228, 300, 328 nm; IR (KBr) ν_{max} 3384, 3055, 2982, 2943, 2877, 1677, 1611, 1482, 1466, 1439, 1380, 1371, 1286, 1250, 1206, 1122, 1106, 1057, 912, 881, 786, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (t, J = 7.50 Hz, 3 H), 0.83 (s, 3 H), 1.13−1.20 (m, including 3 H singlet at δ 1.17, 4 H), 1.45−1.49 (m, 1 H), 1.60−1.71 (m, 1 H), 1.71−1.95 (m, 4 H), 2.33−2.50 (m, 3 H), 3.05 (m, 2 H), 3.38 (d, J = 8.5 Hz, 1 H), 3.63 (d, J = 8.5 Hz, 1 H), 3.68 (s, 3 H), 3.88 (s, 1 H), 3.75−3.95 (m, including 3 H singlet at δ 3.79, 7 H), 6.73 (d, J = 7.7 Hz, 1 H), 6.78 (t, J = 7.5 Hz, 1 H), 7.05 (t, J = 7.5 Hz, 1 H), 7.15 (d, J = 7.3 Hz, 1 H), 8.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.6, 24.4, 26.2, 26.9, 29.6, 44.8, 45.1, 50.7, 53.3, 55.3, 65.9, 73.3, 83.6, 90.5, 108.8, 109.1, 120.5, 121.8, 127.6, 137.6, 143.0, 165.9, 168.7; mass spectrum (EI) m/z (rel intensity) 413 (8), 412 (M$^+$, 18), 284 (15), 283 (100), 228 (38), 223 (8), 215 (18), 194 (10), 180 (10), 168 (45), 154 (17), 144 (18), 140 (18), 129(19), 86 (9).

For the *cis* epimer (3a*S*,4*R*,11b*R*)-methyl 2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]-carbazole-6-carboxylate (**9a**): $[\alpha]^{25}_D$ −386° (*c* 0.33, $CHCl_3$); TLC R_f = 0.31 (silica gel, 10% methanol in CH_2Cl_2, CAS blue); UV (EtOH) λ_{max} 210, 228, 298, 328 nm; IR (KBr) ν_{max} 3380, 3055, 2979, 2938, 2879, 1677, 1610, 1478, 1465, 1437, 1380, 1369, 1307, 1284, 1247, 1202, 1156, 1107, 1051, 911, 880, 783, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.4 Hz, 3 H), 1.33−1.35 (m, including 2 × 3 H singlet at δ1.27 and 1.29, 7 H), 1.42−1.60 (m, 3 H), 1.73−1.81 (m, 2 H), 1.83−2.01 (m, 2 H), 2.24 (bs, 1 H), 2.57 (d, J = 15 Hz, 1 H), 3.01−3.03 (m, 2 H), 3.67 (s, 2 H), 3.68 (s, 3 H), 3.75 (d, J = 4.5 Hz, 1 H), 6.73 (d, J = 7.7 Hz, 1 H), 6.79 (t, J = 7.4 Hz, 1 H), 7.07 (t, J = 7.7 Hz, 1 H), 7.12 (d, J = 7.1 Hz, 1 H), 8.84 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.7, 25.2, 27.1, 27.3, 30.8, 36.5, 37.9, 44.9, 45.7, 50.9, 53.4, 57.1, 63.3, 72.4, 83.9, 95.4, 109.0, 109.2, 120.5, 121.6, 127.8, 137.4, 143.5, 165.7, 168.4; mass spectrum (EI) m/z (rel intensity) 413 (10), 412 (M$^+$, 15), 284 (14), 283 (100), 228 (27), 215 (10), 168 (16), 167 (13), 154 (14), 140 (8), 129 (13), 71 (13), 69 (9), 68 (11), 59 (14), 57 (16), 55b (15).

For the *cis* epimer (3a*R*,4*S*,11b*S*)-methyl 2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]-carbazole-6-carboxylate (**9b**): $[\alpha]^{25}_D$ +265° (*c* 0.17, $CHCl_3$); TLC R_f = 0.6 (silica gel, 10% methanol in CH_2Cl_2, CAS blue); UV (EtOH) λ_{max} 214, 230 298, 326 nm; IR (KBr) ν_{max} 3378, 2989, 2942, 2877, 1680, 1612, 1478, 1466, 1439, 1380, 1369, 1312, 1285, 1266, 1205, 1106, 1055, 911, 880, 783, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 7.5 Hz, 3 H), 1.33 (s, 3 H), 1.34 (s, 3 H), 1.36−1.57 (m, 4 H), 1.71−1.74 (m, 1 H), 1.81−1.88 (m, 2 H), 2.02−2.08 (m, 1 H), 2.30 (d, J = 14 Hz, 1 H), 2.99−3.25 (m, 2 H), 3.57 (d, J = 8.4 Hz, 1 H), 3.69 (s, 3 H), 3.77 (d, J = 4.2 Hz, 1 H), 3.80 (d, J = 8.4 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 6.83 (t, J = 7.6 Hz, 1 H), 7.09 (t, J = 7.6 Hz, 1 H), 7.19 (d, J = 7.5 Hz, 1 H), 8.84 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.1, 25.0, 26.8, 27.1, 27.5, 30.0, 37.3, 38.3, 44.2, 45.1, 50.8, 56.6, 61.8, 73.2, 84.0, 95.3, 109.1, 120.4, 121.9, 127.8, 137.6, 143.5, 165.8, 168.3; mass spectrum (EI) m/z (rel intensity) 413 (5.5), 412 (M$^+$, 16), 284 (16), 283 (100), 228 (34), 223 (7), 215 (24), 198 (10), 196 (12), 182 (10), 180 (11), 173 (7), 167 (43), 154 (20), 144 (21), 140 (24), 129 (40), 113 (27), 110 (17), 95 (28), 86 (9).

2. Phenyl chloroformate (0.067 g, 0.43 mmol) was added to a stirred solution of the ferrocenylindoloazepine (+)-**6b** (0.05 g, 0.078 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The soluton was stirred for 36 h under nitrogen and then washed with 10% NaOH (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with ether/hexane, 1:1, to give the indoloazepine phenylcarbamate (0.018 mg, 64%) and (*R*)-1-(diphenylphosphinyl)-2-vinylferrocene (0.021 g, 68%). A ^{1}H NMR spectrum of the indoloazepine derivative was identical with that of an authentic sample. For the vinylphosphinylferrocene: $[\alpha]^{25}_D$ −42° (*c* 0.8, $CHCl_3$); TLC R_f = 0.73 (silica gel, ether/hexane, 1:9); mp 132−133 °C; IR (KBr) ν_{max} 3069, 3052, 3028, 2960, 2922, 2851, 1634, 1618, 1585, 1477, 1433, 1404, 1261, 1168, 1106, 1038, 1026, 1003, 899, 819, 742, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 1 H), 3.94 (s, 5 H), 4.26 (t, J = 2.40 Hz, 1 H), 4.65 (m, 1H), 4.96 (dd, J = 1.2, 10.8 Hz, 1 H), 5.31 (dt, J = 1.1, 17.3 Hz, 1 H), 6.66 (ddd, J = 2.5, 10.8, 17.3 Hz, 1 H), 7.05−7.08 (m, 2 H), 7.15−7.18 (m, 3 H), 7.30−7.32 (m, 3 H), 7.47−7.49 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 67.6 (d), 70.0 (s), 70.3 (s, 5C), 72.0 (d), 75.8 (d), 86.9 (d), 112.3 (s), 127.7 (s), 128.0, 128.1, 128.2, 129.1 (s), 132.1 (d), 133.3 (d), 135.2 (d), 137.2 (d), 139.8 (d); mass spectrum (EI) m/z (relative intensity) 397 (29), 396 (M$^+$, 100), 395 (21), 331 (27), 329 (13), 176 (21), 165 (26), 288 (22), 275 (18), 252 (20), 196 (16), 183 (15), 152 (14), 133 (12), 121 (37), 120 (11), 107 (10), 95 (10). Anal. Calcd for $C_{24}H_{21}PFe$: C, 72.75; H, 5.34; P, 7.82; Fe, 14.09. Found: C, 72.45; H, 5.43; P, 7.56; Fe, 14.45.

However, removal of the ferrocenyl auxiliary by this method was unsuccessful with the tetracycle **2e**.

(3a*R*,4*R*,11b*S*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (10a) and (3a*S*,4*S*,11b*R*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (10b). Benzyl bromide (0.05 g, 0.29 mmol) was added to a stirred solution of the *trans* epimer **8a** or **8b** (0.11 g, 0.266 mmol) and triethylamine (0.076 mL, 0.54 mmol) in acetone (3 mL), and powdered anhydrous K_2CO_3 (0.2 g) was then added. The

mixture was stirred at room temperature for 6 h and filtered, and the solid was washed with CH_2Cl_2 (3 × 10 mL). The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel, eluting with ether/hexane, 1:1, to give the benzylated tetracycle **10a** or **10b** (0.096 g, 72%) as a viscous oil.

For **10a**: $[\alpha]^{25}_D$ +316° (*c* 0.26, $CHCl_3$); TLC R_f = 0.59 (silica gel, ether/hexane, 2:1, CAS blue to purple); UV (EtOH) λ_{max} 212, 228, 302, 326 nm; IR (KBr) ν_{max} 3383, 3058, 3028, 2980, 2935, 2835, 2858, 2793, 1678, 1611, 1477, 1465, 1437, 1379, 1368, 1344, 1280, 1249, 1209, 1126, 1104, 1048, 912, 744, 701, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (t, *J* = 7.40 Hz, 3 H), 0.85 (dd, *J* = 7.6, 15 Hz, 1 H), 1.27 (s, 3 H), 1.31−1.34 (m, including 3 H singlet at δ 1.34, 4 H), 1.50−1.67 (m, 3 H), 1.99−2.13 (m, 2 H), 2.54−2.63 (m, 2 H), 2.77 (d, *J* = 15 Hz, 1 H), 2.86−2.89 (m, 1 H), 2.96 (s, 1 H), 3.47 (d, *J* = 8.3 Hz, 1 H), 3.66−3.69 (m, 2 H), 3.76 (s, 3 H), 4.20 (d, *J* = 13.3 Hz, 1 H), 6.80−6.85 (m, 2 H), 7.03 (d, *J* = 7.3 Hz, 1 H), 7.13 (t, *J* = 7.6, 1 H), 7.26 (t, *J* = 7.1 Hz, 1 H), 7.34 (t, *J* = 7.1 Hz, 2 H), 7.40 (d, *J* = 7.4 Hz, 2 H), 8.94 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.7, 24.0, 26.9, 27.2, 29.8, 38.0, 43.2, 50.7, 50.8, 55.1, 58.4, 73.0, 74.4, 84.1, 91.6, 109.1, 109.2, 120.4, 122.0, 127.0, 127.8, 128.3, 128.7, 137.7, 143.1, 169.2; mass spectrum (EI) *m*/*z* (rel intensity) 502 (M^+, 10), 374 (18), 373 (26), 288 (15), 277 (16), 228 (12), 168 (13), 167 (15), 129 (18), 120 (5), 91 (100), 71 (13), 59 (14), 57 (12), 55 (10).

For **10b**: $[\alpha]^{25}_D$ −323° (*c* 0.63, $CHCl_3$); TLC R_f = 0.32 (silica gel, ether/hexane, 1:1, CAS blue to purple); UV (EtOH) λ_{max} 210, 226, 300, 326 nm; IR (KBr) ν_{max} 3382, 3058, 3028, 2979, 2966, 2931, 2857, 2792, 1677, 1610, 1478, 1465, 1437, 1379, 1368, 1345, 1280, 1250, 1204, 1148, 1125, 1104, 1054, 744, 701, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, *J* = 7.40 Hz, 3 H), 1.02 (s, 3 H), 1.12−1.34 (m, including 3 H singlet at δ 1.29, 5 H), 1.54−1.74 (m, 3 H), 1.97−2.02 (m, 1 H), 2.52−2.68 (m, 3 H), 2.86−2.89 (m, 1 H), 3.30 (s, 1 H), 3.44 (d, *J* = 8.5 Hz, 1 H), 3.66−3.76 (m, 2 H), 3.77 (s, 3 H), 6.78−6.83 (m, 2 H) 6.98 (d, *J* = 7.3 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 7.27 (d, *J* = 7.1 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 2 H), 7.43 (d, *J* = 7.5 Hz, 2 H), 8.93 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.7, 26.8, 27.1, 29.7, 34.8, 38.3, 42.9, 50.5, 50.9, 55.1, 58.1, 72.3, 73.6, 84.1, 91.0, 108.8, 109.2, 120.5, 122.2, 126.9, 127.7, 128.2, 128.9, 137.9, 139.4, 143.0, 166.0, 169.1; mass spectrum (EI) *m*/*z* (relative intensity) 502 (M^+, 4), 374 (32), 288 (16), 277 (11), 228 (14), 214 (6), 180 (6), 168 (13), 167 (8), 154 (7), 129 (13), 120 (6), 92 (9), 91 (100). The spectroscopic data matched those of the racemic compound.[1]

(3a*S*,4*R*, 11b*R*)-Methyl 3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[(2*S*)-2-ethyl-2,3-(isopropylidenedioxy)]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (11a). Benzylation of 50 mg of the amine **9a**, according to the procedure given for benzylation of the amine **8a**, gave 43 mg (71%) of the title product: $[\alpha]^{25}_D$ −256° (*c* 0.34, $CHCl_3$); TLC R_f = 0.59 (silica gel, ether/hexane, 2:1, CAS blue); UV (EtOH) λ_{max} 214, 226, 300, 328 nm; IR (KBr) ν_{max} 3386, 3059, 3028, 2979, 2944, 2799, 1678, 1611, 1494, 1478, 1466, 1437, 1379, 1368, 1278, 1247, 1211, 1198, 1115, 1046, 911, 880, 734, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (t, *J* = 7.4 Hz, 3 H), 1.23 (s, 3 H), 1.29 (s, 3 H), 1.41−1.54 (m, 3 H), 1.61 (dd, *J* = 5.1, 12.1 Hz, 1 H), 1.67 (dd, *J* = 7.1, 15 Hz, 1 H), 2.01−2.02 (m, 1 H), 2.11−2.16 (m, 2 H), 2.52−2.53 (m, 1 H), 2.73 (dd, *J* = 1.3, 17 Hz), 2.91−2.94 (m, 1 H), 3.36 (d, *J* = 5 Hz, 1 H), 3.61 (d, *J* = 8.4 Hz, 1 H), 3.68−3.71 (m, including 3 H singlet at δ 3.69, 5 H), 4.34 (d, *J* = 13.9 Hz, 1 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 6.79 (t, *J* = 7.5, 1 H), 6.96 (d, *J* = 7.3 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.18 (m, 1 H), 7.27 (t, *J* = 7.6 Hz, 2 H), 7.40 (d, *J* = 7.4 Hz, 2 H), 8.81 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.94, 25.39, 27.05, 27.36, 31.00, 36.20, 40.18, 42.02, 50.90, 52.20, 58.10, 61.94, 69.29, 72.78, 84.12, 95.34, 109.11, 109.28, 120.44, 122.54, 126.91, 127.83, 128.33, 137.20, 139.80, 143.39, 164.59, 168.49; mass spectrum (EI) *m*/*z* (rel intensity) 502 (M^+, 1), 374 (4), 373 (5), 230 (9), 168 (3), 167 (9), 149 (16), 129 (43), 122 (14), 119 (24), 118 (15), 111 (9), 106 (14), 105 (22), 91 (100), 86 (21), 85 (10), 84 (26), 83 (22), 77 (25), 72 (11), 71 (26), 69 (11), 67 (10), 65 (11), 59 (20), 57 (29), 55 (20), 51 (60).

Epimerization Studies. The secondary amine *trans* epimer **8b** (0.01 g, 0.024 mmol) was heated in glacial acetic acid (0.5 mL) at 90 °C for 2 h. The mixture was cooled to room temperature, basified with 15% NH_4OH in brine, and extracted with ether (3 × 5 mL). The ether layer was dried over sodium sulfate and concentrated. ^1H NMR analysis of the crude mixture showed a 1:7 ratio of *cis* epimer **9b** to *trans* epimer **8b**. However, heating of the N^b benzylated *trans* epimer **10b** or the *cis* epimer **11b** in acetic acid for 15 min gave unchanged starting materials, and epimerization was not observed under this condition, whereas longer heating (2−3 h) gave a mixture of highly polar, unidentified products.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **2c**−**f**, **5a**−**c**, **6a**−**c**, **8a**,**b**−**11a** (27 pages). 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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