The hydrochloride salt was obtained by adding HCl saturated ether to an ether solution of the azepine. Filtration and recrystallization (ethanol) afforded the hydrochloride salt as pale yellow crystals, mp 195–197 °C dec: NMR (Me_2SO-d_6) δ 7.00–7.54 (m, 4 H), 4.78 (br s, 1 H), 3.92 (dd, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.38–3.48 (m, 2 H), 2.94–3.24 (m, 3 H); IR (KBr) ν_{max} 2953, 2642, 2623, 2527, 1740, 1462, 1207, 762 cm^{-1}; UV (ethanol) λ_{max} 235, 279 nm. Anal. Calcd for $C_{13}H_{19}N_2O_2Cl$: C, 61.12; H, 6.50; N, 9.50; Cl, 12.03. Found: C, 61.02; H, 6.37; N, 9.26; Cl, 11.92.

Methyl 3-[(Benzyloxy)carbonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (20). Benzyl chloroformate (0.77 g, 4.51 mmol) was added to a solution of the indoloazepine **1a** (1.0 g, 4.1 mmol) in CH_2Cl_2 (100 mL), containing solid Na_2CO_3. After 5 min, TLC (SiO_2, ether) showed that the starting material had reacted completely and the presence of a single product with R_f 0.69 (CAS, green). The reaction mixture was washed with saturated $NaHCO_3$ (50 mL) and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (SiO_2, 3 × 30 cm column, ether) gave 1.2 g (83%) of the benzylurethane derivative of **1a** after recrystallization from ether, mp 158–159 °C: NMR ($CDCl_3$) δ 8.40, 8.49 (2 br s, 3:2, 1 H), 7.20–7.45 (m, 9 H), 5.13–5.29 (m, 2 H), 4.06–4.23 (m, 3 H), 3.83–3.65 (m, 2 H), 3.72, 3.66 (2 s, 3:2, 3 H), 3.01–3.13 (m, 2 H); IR (KBr) ν_{max} 3311, 2908, 1743, 1671, 1297, 1199 cm^{-1}; UV (ethanol) λ_{max} 233, 284, 292 nm; MS, *m/z* (relative intensity) 378 (16), 346 (44), 255 (41), 214 (25), 91 (100). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.85; N, 7.40. Found: C, 69.67; H, 6.14; N, 7.11.

Sodium hydride (1.2 equiv) was added to the benzylurethane derivative of **1a** (700 mg, 1.85 mmol) in 50 mL of dimethylformamide and the mixture was stirred at 0 °C for 30 min under N_2. Methyl iodide (0.32 g, 2.2 mmol) was added dropwise and the mixture was stirred at 0 °C under N_2 for an additional 30 min. TLC (SiO_2, 1:1 ether:pentane) of the reaction mixture showed two major products with R_f 0.81 (CAS, purple) and R_f 0.76 (CAS, blue), at least three minor products, and unreacted starting material. Water (300 mL) was added to the reaction mixture and the suspension was extracted with ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure, and the two major products and unreacted starting material were separated by chromatography (SiO_2, 1:1 ether:pentane, 3 × 30 cm column). The product that eluted first was crystallized from ether and pentane to give 180 mg (25%) of the dimethyl[(benzyloxy)carbonyl]indoloazepine **20**, mp 107–109 °C: NMR ($CDCl_3$) δ 7.12–7.53 (m, 9 H), 5.11–5.20 (m, 2 H), 4.24 (m, 1 H), 3.97–4.05 (m, 1 H), 3.72–3.79 (m, 2 H), 3.55, 3.54 (2 s, 2:1, 3 H), 3.51, 3.52 (2 s, 2:1, 3 H), 3.12–3.18 (m, 2 H), 1.59, 1.53 (2 s, 2:1, 3 H); IR (KBr) ν_{max} 2949, 1731, 1697, 1262, 1131 cm^{-1}; UV (ethanol) λ_{max} 237, 286 nm; MS, *m/z* (relative intensity) 406 (M^+, 23), 347 (12), 283 (10), 230 (49), 182 (13), 168 (12), 91 (100), 65 (14). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.21; N, 6.89. Found: C, 70.95; H, 6.43; N, 6.71.

Continued elution gave 116 mg (15%) of the C-5 monomethylation product as a colorless oil: NMR ($CDCl_3$) δ 8.37, 8.31 (2 s, 3:2, 1 H), 7.07–7.52 (m, 9 H), 5.10–5.23 (m, 2 H), 4.07–4.15 (m, 2 H), 3.71–3.85 (m, 2 H), 3.67, 3.68 (2s, 3:2, 3 H), 3.03–3.16 (m, 2 H), 1.61, 1.54 (2 s, 3:2, 3 H); IR (KBr) ν_{max} 3354, 2948, 1731, 1698, 1683, 1423, 1215 cm^{-1}; UV (ethanol) λ_{max} 237, 286 nm; MS, *m/z* (relative intensity) 392 (M^+, 17), 301 (11), 269 (10), 257 (5), 242 (7), 230 (10), 168 (14), 91 (100).

Studies in Biomimetic Alkaloid Syntheses. 12. Enantioselective Total Syntheses of (-)- and (+)-Vincadifformine and of (-)-Tabersonine

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The (-) and (+) enantiomers of vincadifformine (**1**) were obtained with ≥98% ee and ≥97% ee, respectively (before purification), from the two enantiomers of epichlorohydrin. This synthetic scheme is based on generation and cyclization of the enantiomeric (hydroxymethyl)norsecodine intermediates **3a,b**. By an alternative synthetic route, passing through (14*S*)-14-hydroxy-$\Delta^{20,21}$-secodine (**14**), (-)-tabersonine (**18b**) was obtained with ≥99% ee.

Aspidosperma alkaloids are found naturally in either of the two possible enantiomeric senses (i.e., as antipodes of the spiro center C7), and their prime representative, vincadifformine (**1**), occurs separately in both enantiomeric forms,[1,2] as well as in form of the racemic natural product.[3] This chiral diversity is of interest in view of a probable proximate achiral precursor, which is responsible for formation of the aspidosperma alkaloid skeleton.

According to the Wenkert–Scott biogenetic hypotheses, a $\Delta^{20,21}$-secodine (**2**) was postulated as the key intermediate in the formation of these pentacyclic alkaloids.[4] Incorporation of isotopically, specifically labeled precursors and establishment of isotopic label distribution in the final alkaloid products supported a secologanin pathway,[4] plausibly passing through an undetected $\Delta^{20,21}$-secodine (**2**) intermediate. This biogenetic proposal was strengthened further by synthetic generation of the transient secodine intermediate **2** through two alternative independent routes and consequent biomimetic cyclization of the secondine **2** in high yield to racemic vincadifformine (**1**).[5,6]

Lack of chirality in the $\Delta^{20,21}$-secodine (**2**) and its instantaneous cyclization to racemic vincadifformine (**1**) pose a challenge, if one hopes to utilize the efficacious secodine

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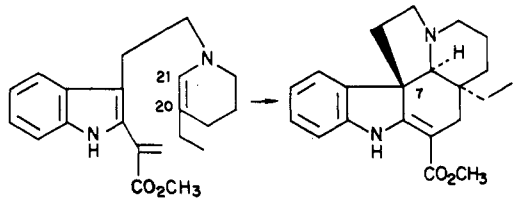
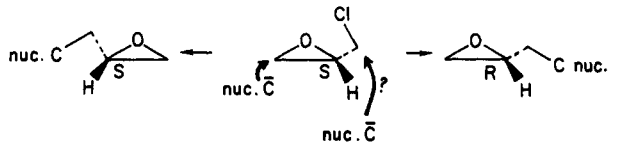


cyclization chemistry for an enantioselective synthesis of vincadifformine (1). One of our approaches to such asymmetric syntheses is the following one, based on chiral modification of the cyclic enamine portion of a secodine-type precursor.

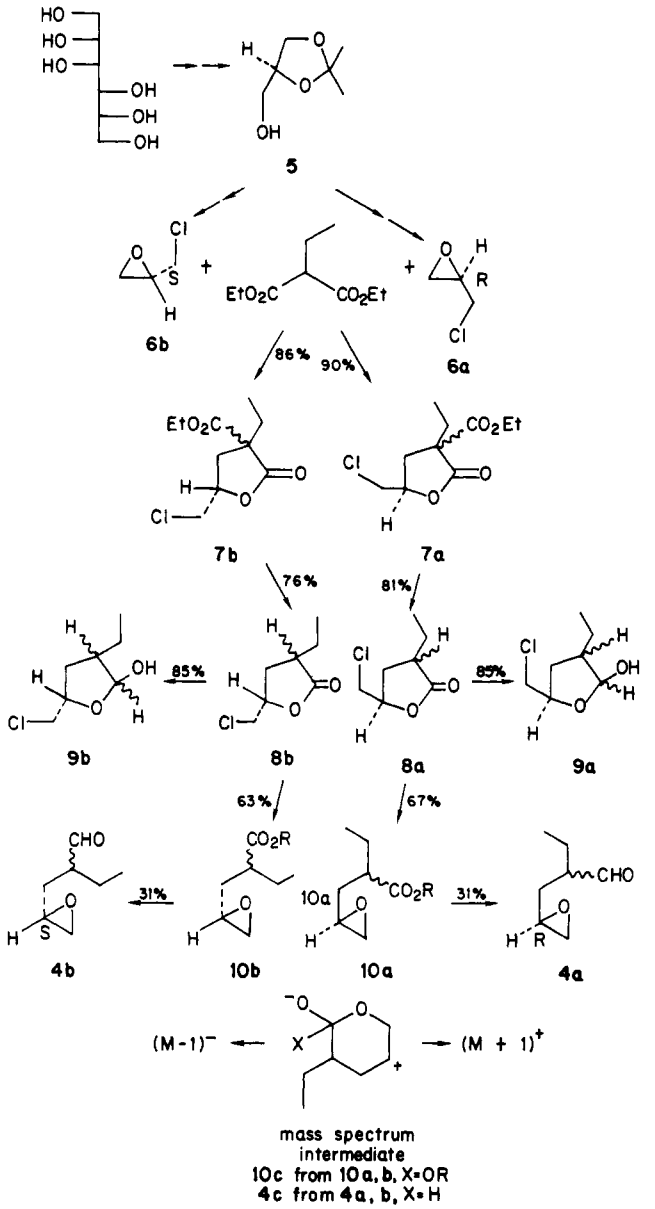
In order to maximize the desired enantioselectivity, we required a secodine reactant in which the enamine moiety would have an inherent stereodirecting substituent, resulting in high diastereoselectivity, in the racemic mode, for its intramolecular reaction with the acrylate function. From our syntheses of the ibophyllidines,[7] ψ-vincadifformines,[8] and pandolines,[8,9] we had learned that substituted five-membered cyclic enamines provided much greater diastereoselectivity in secodine-type cyclizations than similar six-membered cyclic enamine intermediates. We, therefore, focused our approach on the generation of a chiral hydroxymethyl-substituted pyrrolideine intermediate **3** (in Scheme II). The synthetic reaction scheme described in this report was studied first with racemic compounds and then it was specifically carried to generation of each enantiomer of the (hydroxymethyl)norsecodine (i.e., **3a** and **3b**).

For syntheses of the chiral (hydroxymethyl)norsecodines **3a,b** we required epoxy aldehydes **4a,b** in which the epoxide bearing secondary carbon is enantiomerically pure, while the tertiary center adjacent to the aldehyde function is not of stereochemical consequence, since it becomes trigonal in the subsequent norsecodine intermediates **3a,b**. Considering assembly of these epoxy aldehydes **4a,b**, our attention was drawn to the chiral glycerol acetonide **5**, which can be obtained by lead tetraacetate cleavage of mannitol bisacetonide and which had been converted selectively to either enantiomer of chiral epichlorohydrin (**6a,b**).[10] While the opening of these chiral epoxides with oxygen nucleophiles had been studied,[11] their use as chiral building blocks in carbon alkylations remained to be established. Of concern was, of course, the potential for some duality of reaction paths, which might lead to partial racemization by initial attack at both ends of the epichlorohydrin.



Unwilling to compromise on the enantiomeric purity of the alkylation product, we required an alkylation which would allow a chemical distinction between the two possible modes of reaction and which would permit separation of a unique product. This was achieved through use of ethyl diethylmalonate anion as the nucleophile for epoxide opening of the epichlorohydrins **6a,b** (Scheme I). Here, the resulting alkoxide does not form a new epoxide but is trapped as a chloromethyl lactone. The specifically generated chloromethyl lactones **7a,b** can then be distinguished and separated, on purification, from any product derived from chloride displacement.

Scheme I



Decarbethoxylation of the lactone esters **7a,b** provided C-2 epimeric mixtures of the respective lactones **8a,b**. While reduction of these lactones with diisobutylaluminum hydride gave chloromethyl lactols **9a,b** in 85% yield,[9] attempts at conversion of those products to the epoxy aldehydes **4a,b** were not fruitful and resulted either in recovery or destruction of the lactols.

However, opening of the lactones **8a,b** with sodium alkoxides provided the epoxy esters **10a,b**. Subsequent reduction with diisobutylaluminum hydride in dichloromethane now generated the desired aldehyde epoxides **4a,b**. Unfortunately, these reductions were not very selective for the ester function. Even with variations of solvents (CH_2Cl_2, THF, 1,2-dimethoxyethane) one could not reproducibly obtain the pure epoxy aldehydes **4a,b** in

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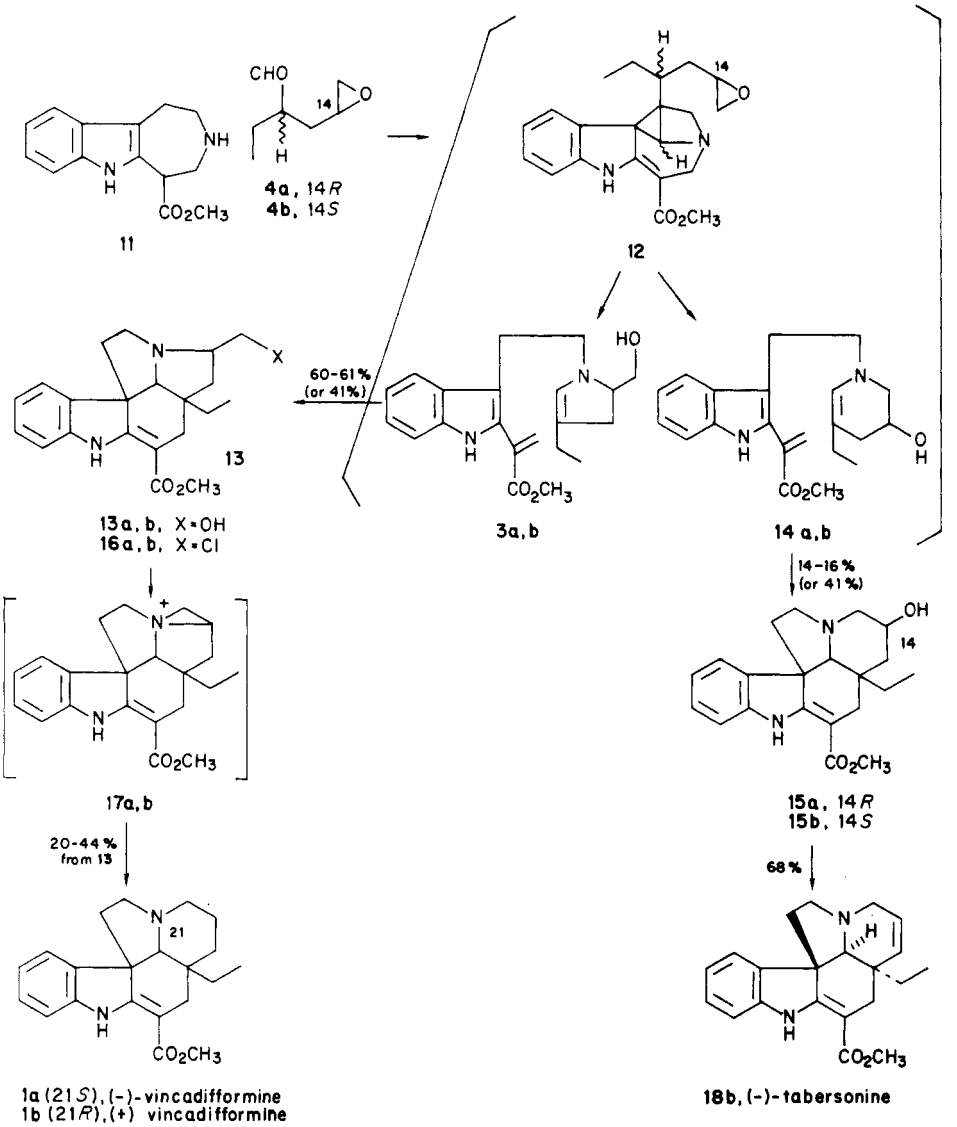
Scheme II



yields above 31%. This reduction step thus constitutes the weakest link in the chain of reactions of this synthetic scheme. Use of the butyl, rather than a lower alkyl ester, was found to help in separation of the aldehyde product **4a,b** from unreacted ester **10a,b**.

Before continuing with the synthetic reaction scheme, one may note the unusual mass spectra of compounds **10a,b** and **4a,b**. Neither contained a molecular ion in the electron impact spectrum, but the M + 1 peaks were the parent peaks (100%) for the epoxy ethyl esters **10a,b** and the epoxy aldehydes **4a,b**. The aldehydes **4a,b** (but not the esters **10a,b**) also showed a substantial M - 1 (37%) peak in the electron impact spectrum. On chemical ionization with methane, the ethyl esters **10a,b** again gave the now normal M + 1 peak in the positive ion spectrum, while a negative ion spectrum showed a prominent M - 1 peak. These findings may be rationalized in terms of structures **10c** and **4c** which could explain the unusually facile acceptance or loss of a proton.

On condensation of the respective chiral aldehydes **4a,b** with the indoloazepine **11**, the bridged azepines **12** were formed (Scheme II). Through intramolecular N-alkylation and fragmentation reactions the latter intermediates rearranged primarily to the goal chiral (hydroxymethyl)-norsecodines **3a,b**. Spontaneous cyclization of these likely,[5,6,9] transient intermediates provided the respective enantiomeric (hydroxymethyl)norvincadifformines **13a,b**.

In this intramolecular epoxide opening some 14-hydroxysecodines **14** were also formed, but the resultant 14-hydroxyvincadifformines **15** could be readily removed from the major product **13** by chromatography (or crystallization in the racemic case). It may be noted that while the (hydroxymethyl)norsecodine **3** reacts with complete diastereoselectivity, the reaction of the hydroxysecodine **14** may be less stereoselective and its epimeric product ratio can be changed with variations of solvents.[9] Although variations of the absolute configuration of the 14-hydroxyvincadifformine ring skeleton (**15**), by variation of solvents, are thus also possible, they are not of practical significance for maximization of the yield of enantiomerically pure vincadifformine (**1**), derived from the present reaction scheme.

For completion of the enantioselective syntheses of (-)- and (+)-vincadifformine (**1a,b**), a modification of previously described reactions (with racemic intermediates) was used.[9] The respective (hydroxymethyl)norvincadifformines **13a,b** were converted to the respective chloromethyl compounds **16a,b** with carbon tetrachloride and triphenylphosphine, and these products were then brought to cyclization in pyridine. Reduction of the resultant aziridinium salts **17a,b** with sodium borohydride in pyridine gave (-)- and (+)-vincadifformine, respectively, from the two

enantiomeric series of reactions.

The enantiomeric purity of the crude reduction products, before crystallization, was found to be ≳98% ee for (−)-vincadifformine and ≳97% ee for (+)-vincadifformine. The enantiomeric excess was determined by NMR chiral shift studies by using tris[3-[(heptafluoropropyl)-hydroxymethylene]-*d*-camphorato]europium(III), Eu(hfc)$_3$,[12] with a 0.1 M ratio of reagent to alkaloid. The racemic vincadifformine methyl ester singlet 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.

For the same crude reaction products the (less reliable) optical rotation values were respectively only 1.6% and 3.9% lower than the value obtained with the crystallized, analytically pure product. Like the NMR chiral shift results, this supports as assignment of high enantiomeric selectivity for the main-line synthetic sequence, which was not perturbed by enantiomeric enrichment at intermediate stages.

When the (hydroxymethyl)norsecodine **3** was generated in methanol, in the presence of an acid catalyst (boric acid), one found minimal formation of a 14-hydroxysecodine (**14**) intermediate, and under those conditions, this minor intermediate **14** cyclized to give a 14-axial-hydroxyvincadifformine (**15**) with high diastereoselectivity.[9] In the absence of an acid catalyst, in methanol, the ratio of products **13**:**15** approached unity, and each was still formed with high diastereoselectivity. Since tabersonine (**18**) can be obtained by dehydration of the axial alcohol **15**, this second reaction path then gives an enantiomeric synthetic access to tabersonine (**18**). Examination of the product of this sequence, passing through the (14*S*)-14-hydroxysecodine (**14b**), by the NMR chiral shift technique and by rotation measurement, showed that (−)-tabersonine (**18b**) was also formed with high enantiomeric selectivity. Again, only one enantiomer was actually seen in this instance by the chiral shift technique, indicating that (−)-tabersonine was formed in ≳99% ee.

Experimental Section

For general methods, see preceding paper. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

2-Carbethoxy-2-ethyl-4-(chloromethyl)butyrolactone (7).[13] Racemic. To a solution of 3.9 g (0.10 mol) of potassium in 100 mL of *tert*-butyl alcohol under nitrogen was added 38 mL (0.20 mol) of diethyl ethylmalonate over 15 min at 20 °C, followed by 8.6 mL (0.11 mol) of epichlorohydrin, over 5 min. The mixture was heated at reflux for 12 h and cooled, and the white slurry was acidified with ethanolic HCl. After concentration under vacuum and partitioning between water and ether, the organic extracts were washed with water and saturated brine. Concentration and distillation gave recovered malonate, bp 47–55 °C (0.4 mm), followed by 22.8 g (97%) of the lactone: IR (neat) ν_{max} 2971, 2936, 2880, 1774, 1724, 1457, 1365, 1245, 1175, 1097, 1027 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (d of t, 3 H), 1.28 (d of t, 3 H), 1.80–2.50 (m, 3 H), 2.75 (m, 1 H), 3.73 (m, 2 H), 4.24 (m, 2 H), 4.65–4.85 (m, 1 H); mass spectrum, *m*/*z* (relative intensity) 237 (28), 235 (100), 206 (21), 189 (39), 185 (21), 175 (23), 155 (28), 147 (23), 127 (25), 111 (45). Anal. Calcd for $C_{10}H_{15}O_4Cl$: C, 51.18; H, 6.44. Found: C, 51.01; H, 6.53.

4*S* and 4*R*. From 50 mL of *tert*-butyl alcohol, 1.96 g (0.05 mol) of potassium, 19 mL (0.10 mol) of diethyl ethylmalonate, 4.65 g (0.05 mol) of (*S*)-epichlorohydrin,[10] 10.1 g (86%), bp 103–111 °C (0.4–0.2 mm), of the 4*S* lactone **7b**, was obtained. Analogously, from the (*R*)-epichlorohydrin,[10] the 4*R* lactone **7a** was formed. [A poor yield was obtained with 1 equiv of the malonic ester. The extra equivalent of malonic ester was recovered on distillation. A poor yield was obtained with sodium ethoxide in ethanol.]

Table I. Comparison of Reductions of Alternative Esters 8 by This Procedure

ester 8	% aldehyde 4 in distilled product	real yield of aldehyde 4, %
methyl	54	13
ethyl	75	31
isopropyl	66	29
n-butyl	95	31
n-hexyl	35 (+ *n*-hexanol)	30
β-methoxyethyl at −78 to −20 °C	0	0

4-(Chloromethyl)-2-ethylbutyrolactone (8).[14] Racemic. A solution of 22.8 g (0.097 mol) of the racemic lactone ester **7** in 80 mL of acetic acid and 40 mL of concentrated hydrochloric acid was heated at reflux for 4 h. Concentration under vacuum, addition of toluene, concentration under vacuum, and distillation at 91–111 °C (0.8–2.5 mm) gave 12.5 g (80%) of product: IR (neat) ν_{max} 2957, 2929, 2873, 1767, 1457, 1357, 1344, 1175, 1027, 943 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (d of t, 3 H), 1.40–2.80 (m, 5 H), 3.70 (d of t, 2 H), 4.55–4.80 (m, 1 H); mass spectrum, *m*/*z* (relative intensity) 165 (30), 163 (73), 136 (16), 134 (52), 127 (16), 113 (100). Anal. Calcd for $C_7H_{11}O_2Cl$: C, 51.71; H, 6.82; Cl, 21.81. Found: C, 51.47; H, 6.91; Cl, 21.67.

(4*R* and 4*S*)-8a,b. Analogously, on half-scale reactions, the 4*R* and 4*S* lactone esters **7a,b** gave respectively 81% and 76% of **8a,b**, enantiomeric at C4.

4-(Carbalkoxy)-1-hexene Oxides 10. (a) Ethyl Ester. A solution of 12.55 g (0.077 mol) of the racemic chloromethyl lactone **8**, dissolved in 10 mL of absolute ethanol, was added to a solution of 1.84 g (0.080 mol) of sodium in 50 mL of absolute ethanol, causing precipitation of sodium chloride. After 15 min the mixture was concentrated under vacuum and partitioned between water and ether. The ether extracts were washed with water and saturated brine, dried (sodium sulfate), concentrated, and distilled at 41–44 °C (0.1 mm) to give 9.85 g (74%) of epoxy ester **10**: IR (neat) ν_{max} 3042, 2964, 2929, 2873, 1725, 1457, 1372, 1260, 1175, 1020, 914, 844 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (d of t, 3 H), 1.24 (d of t, 3 H), 1.50–1.75 (m, 3 H), 1.80–1.95 (m, 1 H), 2.43 (m, 2 H), 2.72 (m, 1 H), 2.91 (m, 1 H), 4.13 (q, 2 H); electron impact mass spectrum, *m*/*z* (relative intensity) 173 (M + 1, 100), 155 (15), 144 (10), 143 (10), 128 (7), 127 (79), 114 (26), 113 (14), 111 (8), 99 (35), 98 (10), 85 (45), 83 (10), 81 (40), 72 (11), 69 (18), 67 (12), 57 (18). CH_4 chemical ionization spectrum, (+) ions, *m*/*z* (relative intensity) 173 (78), 143 (1), 128 (8), 127 (100), 99 (85), 71 (5), 69 (6); (−) ions, *m*/*z* (relative intensity) 171 (10), 157 (3), 156 (3), 155 (29), 145 (12), 144 (5), 143 (3), 142 (12), 126 (14), 125 (4), 115 (7), 114 (12), 113 (8), 86 (5), 85 (70), 82 (22), 81 (100). This compound was previously prepared by a different reaction.[9] Analogously, 2.40 g of the 2*S* epoxide **10b**, bp 37–38 °C (0.14 mm), was prepared in 63% yield and 2.88 g of the 2*R* epoxide **10a**, bp 38–45 °C (0.14 mm), was obtained in 67% yield from the respective enantiomeric lactones **8**. Using equivalent procedures with substitution of other alcohols for ethanol, the following other esters were prepared.

(b) Methyl ester: 72%; bp 30–32 °C (0.1 mm); IR (neat) ν_{max} 3044, 2959, 2930, 2873, 1728, 1429, 1365, 1258, 1187, 1166, 1087, 988, 838 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (d of t, 3 H), 1.50–2.00 (m, 4 H), 2.48 (m, 2 H), 2.75 (m, 1 H), 2.94 (m, 1 H), 3.72 (s, 3 H). This compound was previously prepared by a different reaction.[9]

(c) Isopropyl ester: 65%; bp 43–45 °C (0.05 mm); IR (neat) ν_{max} 3042, 2971, 2929, 2873, 1725, 1457, 1372, 1260, 1175, 1105, 964, 830 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (d of t, 3 H), 1.25 (d, 6 H), 1.50–1.80 (m, 3 H), 1.85–2.00 (m, 1 H), 2.48 (m, 2 H), 2.75 (m, 1 H), 2.94 (m, 1 H), 5.05 (m, 1 H).

(d) *n*-Butyl ester: 66%; bp 53–62 °C (0.08 mm); IR (neat) ν_{max} 3042, 2957, 2929, 2866, 1725, 1457, 1386, 1358, 1260, 1224, 1175, 1133, 837^{-1}; NMR ($CDCl_3$) δ 0.93 (m, 6 H), 1.30–1.50 (m, 2 H), 1.50–1.80 (m, 5 H), 1.85–2.00 (m, 1 H), 2.47 (m, 2 H), 2.75 (m, 1 H), 2.94 (m, 1 H), 4.10 (d of t, 2 H).

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(14) For method, see: Cardellach, J.; Estopa, C.; Font, J.; Moreno-Manas, M.; Ortuno, R. M.; Sanchez-Ferrando, F.; Valle, S.; Villamajo, L. *Tetrahedron* **1982**, *38*, 2377.

(e) *n*-Hexyl ester: 70%; bp 75–95 °C (0.06 mm); IR (neat) ν_{max} 3042, 2957, 2929, 2866, 2852, 1725, 1457, 1365, 1260, 1168, 1133, 985, 914, 844 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (m, 6 H), 1.20–1.40 (m, 6 H), 1.50–1.80 (m, 6 H), 1.85–2.00 (m, 1 H), 2.48 (m, 2 H), 2.75 (m, 1 H), 2.94 (m, 1 H), 4.10 (t, 2 H).

(f) β-Methoxyethyl ester: 70%; bp 72–82 °C (0.15 mm); IR (neat) ν_{max} 3042, 2957, 2929, 2893, 2816, 2739, 1725, 1450, 1379, 1260, 1175, 1126, 1027, 957, 914, 844 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (d of t, 3 H), 1.50–1.80 (m, 3 H), 1.85–2.00 (m, 1 H), 2.40–2.60 (m, 2 H), 2.75 (m, 1 H), 2.95 (m, 1 H), 3.39 (s, 3 H), 3.60 (d of t, 2 H), 4.28 (d of t, 2 H).

4-Formyl-1-hexene Oxide (4). Preparation of this compound, by reduction of the ethyl ester **10**, was reported previously.[9] It has been found that the product was contaminated by starting ester, lactone, and alcoholic products. Extensive reinvestigation of the Dibal-H reduction of **10** showed poor selectivity for the ester relative to the epoxide function. With oxygenated solvents (tetrahydrofuran and 1,2-dimethyoxyethane at −75 to 0 °C) very little aldehyde was produced. Hexane showed no advantage over dichloromethane. When more than a 20% excess of Dibal was used, complete reduction of the ester was found but then extensive reduction of the epoxide group occurred. For optimum separation of aldehyde product from unreacted ester, *n*-butyl ester was used.

Typical Procedure Used To Obtain the Tabulated Results. To a solution of 2.0 g (0.01 mol) of the *n*-butyl epoxy ester **8** in 30 mL of dichloromethane at −78 °C was added 12 mL (0.012 mol) of 1 M diisobutylaluminum hydride (Dibal-H) in dichloromethane over 10 min. The mixture was stirred for 90 min, 10 mL of aqueous saturated ammonium chloride was added, and the mixture was allowed to warm to 20 °C. Filtration through Celite, drying of the organic phase (Na_2SO_4), concentration, and chromatography of the residue on 50 g of silica, eluting with 5% ethyl acetate in hexanes, gave a mixture of aldehyde and ester in the initial fractions. Flash distillation with bp <24 °C (0.1 mm) and collection of product at −70 °C gave 900 mg (31%) of **4**, of >95% purity by NMR integration of the aldehyde proton: IR (neat) ν_{max} 3042, 2957, 2930, 2873, 2711, 1717, 1457, 1408, 1379, 1253, 1126, 907, 837, 767 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (d of t, 3 H), 1.45–2.10 (m, 4 h), 2.46 (m, 2 H), 2.77 (m, 1 H), 2.95 (m, 1 H), 9.68 (d, 1 H); mass spectrum, *m/z* (relative intensity) 129 (M^+ + 1, 100), 127 (37), 113 (72), 111 (29), 99 (39), 97 (11).

14-(Hydroxymethyl)norvincadifformine (13) and 14β-Hydroxyvincadifformine (15). (a) A solution of 6 mg (0.1 mmol) of boric acid, 160 mg (80% purity, 1.00 mmol) of the racemic epoxy aldehyde **4**, and 268 mg (1.10 mmol) of the indoloazepine **11** in 5 mL of methanol was stirred at 20 °C for 2 days. Cooling and filtration gave 170 mg (48%) of the (hydroxymethyl)norvincadifformine **13**, mp 153–155 °C.[9] Concentration of the filtrate and chromatography of the residue on a 40-g silica gel column, eluting with 2% ethanol in chloroform, gave 50 mg (14%) of 14β-hydroxyvincadifformine (**15**) followed by an additional 44 mg (12%) of the (hydroxymethyl)norvincadifformine **13**.

For 14α-(hydroxymethyl)norvincadifformine (13): IR ($CHCl_3$) ν_{max} 3387, 2957, 2880, 1668, 1605, 1478, 1457, 1436, 1372, 1288, 1246, 1203, 1112 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.79 (t, 3 H), 0.95–1.13 (m, 1 H), 1.24–1.43 (m, 1 H), 1.60–2.25 (m, 6 H), 2.78 (d, 1 H), 3.03 (m, 1 H), 3.10–3.75 (m, 5 H), 3.78 (s, 3 H), 6.80–7.30 (m, 4 H), 9.04 (br s, 1 H); mass spectrum, *m/z* (relative intensity) 355 (7), 354 (M^+, 29), 323 (7), 206 (2), 180 (3), 168 (3), 167 (3), 154 (3), 145 (5), 141 (11), 140 (100), 108 (2), 94 (2), 84 (2), 80 (2).

For 14β-hydroxyvincadifformine (15): NMR values as reported,[9] except for printing error: the δ 0.90–2.30 should read δ 0.90–3.30; mass spectrum, *m/z* (relative intensity) 355 (9), 354 (M^+, 29), 257 (11), 141 (9), 140 (100), 129 (15).

(b) Using the same reaction procedures with 142 mg (90% purity, 1.00 mmol) of the *R* epoxy aldehyde **4a**, no precipitation of the corresponding product **13a** was found. Chromatography of the entire concentrated reaction mixture on 80 g of silica gel, eluting with 2% ethanol in chloroform, gave 58 mg (16%) of the 14-hydroxyvincadifformine (**15a**) and 220 mg (61%) of amorphous (hydroxymethyl)norvincadifformine **13a**, $[\alpha]^{24}_D$ −305° (*c* 0.14, ethanol), minimum value on nonpurified product.

(c) Repetition of the condensation reaction, at 20 °C in methanol without boric acid catalysis,[9] using well-purified indoloazepine **11**, gave lower yields of the (hydroxymethyl)norvincadifformine **13** and increased yields of the 14β-hydroxyvincadifformine (**15**). Thus, a solution of 422 mg (3.00 mmol, 90% pure) of the *S* epoxy aldehyde **4b** and 733 mg (3.00 mmol) of the indoloazepine **11** in 15 mL of methanol was stirred at 20 °C for 2 days. Concentration and chromatography of the residue on 100 g of silica gel, eluting with 2% methanol in dichloromethane, gave 436 mg (41%) of a crude 14β-hydroxyvincadifformine (**15b**) fraction. Elution with 3% methanol in dichloromethane then produced 440 mg (41%) of the amorphous (hydroxymethyl)-norvincadifformine fraction. When 300 mg of the latter was subjected to centrifugal chromatography on a 2-mm silica plate, eluting with 10% ethanol in chloroform, 158 mg of amorphous product **13b** was obtained with $[\alpha]^{25}_D$ +310° (*c* 0.10, ethanol), minimum value on nonpurified product.

(−)-Tabersonine (18b). Using the previous procedure of dehydration of 14β-hydroxyvincadifformine with triphenylphosphine and carbon tetrachloride in acetonitrile[9] with the above **15b** fraction gave (−)-tabersonine (**18b**), showing for the unpurified product a methyl signal at δ 4.85 on addition of 0.5 M $Eu(hfc)_3$ shift reagent and no signal at δ 6.43. This methyl ester signal appears at δ 3.70 for tabersonine without added shift reagent and a 1:1 ratio of signals was found at δ 4.85 and 6.43 with 0.5 M shift reagent and at δ 4.05 and 4.18 with 0.1 M shift reagent added to racemic tabersonine.[15] An optical rotation of $[\alpha]^{27}_D$ −219° (*c* 0.15, ethanol) was obtained for the unpurified free base, compared with $[\alpha]^{27}_D$ −240° (*c* 0.15, ethanol) for the natural product and an $[\alpha]^{27}_D$ −346° (*c* 0.03, methanol) for the unpurified synthetic hydrochloride compared with $[\alpha]^{28}_D$ −333° (*c* 0.03, methanol) and $[\alpha]^{28}_D$ −304° (*c* 0.1, methanol) [lit.[16] $[\alpha]_D$ −310° (*c* 0.1, methanol) for the hydrochloride of the natural product].

Vincadifformine 1. (a) Racemic. A solution of 1 mL of chloroform, 0.5 mL of carbon tetrachloride, and 100 mg (0.28 mmol) of the (hydroxymethyl)norvincadifformine **13** was heated to 50 °C, and 154 mg (0.56 mmol) of triphenylphosphine was added. After 3 h at 70 °C the cooled mixture was diluted with dichloromethane, washed twice with cold, 10% aqueous ammonium hydroxide, water, and saturated brine, and dried (Na_2SO_4). Concentration under vacuum and chromatography on a 20-g silica gel column, eluting with 20% ethyl acetate in hexanes, gave 85 mg (81%) of an amorphous chloride **16**: IR ($CHCl_3$) ν_{max} 3387, 2957, 2915, 2880, 2852, 1668, 1605, 1478, 1464, 1436, 1372, 1288, 1246, 1203, 1112 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (t, 3 H), 1.05 (m, 1 H), 1.30 (m, 1 H), 1.55–1.70 (m, 3 H), 2.00–2.20 (m, 3 H), 2.78 (d, 1 H), 3.10 (m, 1 H), 3.20–3.50 (m, 3 H), 3.62 (m, 1 H), 3.78 (s, 3 H), 6.80–7.30 (m, 4 H), 9.04 (br s, 1 H); mass spectrum, *m/z* (relative intensity) 374 (4), 372 (11), 277 (6), 160 (29), 158 (100), 149 (9), 146 (10), 129 (10).

A mixture of 3 mL of pyridine, 120 mg (0.32 mmol) of the (chloromethyl)norvincadifformine **16**, and 15 mg (0.40 mmol) of sodium borohydride was heated under nitrogen at 70 °C for 2.5 h. Concentration under vacuum and vacuum evaporation of two 10-mL portions of toluene was followed by chromatography of the residue through 20 g of silica gel, eluting with 10% ethyl acetate in hexanes, to provide 60 mg (55%) of racemice vincadifformine, crystallized from acetonitrile to mp 121–123 °C (lit.[3,5] mp 124–125 °C); IR ($CHCl_3$) ν_{max} 3373, 2957, 2929, 2859, 2774, 2703, 1668, 1605, 1471, 1457, 1429, 1372, 1288, 1274, 1254, 1231, 1182, 1154, 1119, 1105, 1041 cm^{-1}; NMR ($CDCl_3$) δ 0.60 (m, 3 H), 0.85–1.05 (m, 1 H), 1.18–1.35 (m, 1 H), 1.50–1.60 (m, 3 H), 1.65–1.95 (m, 2 H), 1.99–2.12 (m, 1 H), 2.22, 2.32 (d of d, 1 H), 2.35–2.50 (m, 2 H), 2.50–2.62 (m, 1 H), 2.73 (d, 1 H), 2.92 (t, 1 H), 3.08–3.18 (br d, 1 H), 3.77 (s, 3 H), 6.77–7.21 (m, 4 H), 8.89 (br s, 1 H); mass spectrum, *m/z* (relative intensity) 339 (4), 338 (M^+, 21), 180 (3), 167 (5), 154 (3), 153 (4), 125 (8), 124 (100).

(b) From 100 mg (0.28 mmol) of (+)-(hydroxymethyl)norvincadifformine **13b**, using the above procedure, 62 mg (60%) of the chloride **16b** was obtained $[\alpha]^{25}_D$ +440° (*c* 0.1, $CHCl_3$). This product, 50 mg (0.13 mmol), was subjected to rearrangement and reduction to provide 26 mg (58%) of (+)-vincadifformine, mp

(15) Racemic tabersonine was prepared for comparison by the alternative route given in ref 9.

(16) Janot, M. M.; Pourrat, H.; LeMen, J. *Bull. Soc. Chim. Fr.* **1954**, 707.

88–93 °C, $[\alpha]^{24}_D$ +542° (c 0.04, ethanol), ee ≳97%, by NMR chiral shift (below).

From 590 mg (1.7 mmol) of (−)-(hydroxymethyl)norvincadifformine **13a**, 360 mg (57%) of the chloride **16a** was obtained, $[\alpha]^{24}_D$ −370° (c 0.1, ethanol). Rearrangement and reduction of 350 mg (0.939 mmol) of this product gave 155 mg (49%) of total solid vincadifformine product with $[\alpha]^{24}_D$ −555° (c 0.14, ethanol), ee ≳98% by NMR chiral shift (below). Recrystallizations from ethanol and aqueous methanol provided an analytical sample with mp 98–99 °C: $[\alpha]^{24}_D$ −564° (c 0.14, ethanol). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.62; H, 8.02; N, 8.19.

A sample of natural vincadifformine, recrystallized from ethanol, had mp 98–99 °C and $[\alpha]^{24}_D$ −563° (c 0.15, ethanol) and gave no depression on mixture melting point with the synthetic product.

For determination of enatiomeric excesses (ee) by the NMR chiral shift method, 0.1 molar ratios of $Eu(hfc)_3$ to vincadifformine were used. The methyl ester singlet at δ 3.76, when not complexed, is split into signals at δ 4.33 for the (+) enantiomer and δ 4.21 for the (−) enantiomer, when the racemic compound is complexed. In order to evaluate the asymmetric efficacy of the synthesis, the ee values were obtained for the respective total uncrystallized vincadifformine product. In each enantiomeric series only one enantiomeric ester peak could actually be seen and the 97% and 98% ee values are conservatively derived from assignment of base-line noise to a conceivable minor enantiomer.

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3,4,9,9a-Tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one Derivatives. 2.[1] Unusual Results from Eschweiler–Clarke Methylation

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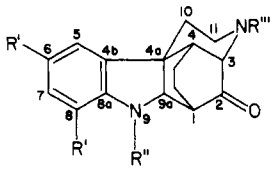
The N-methylation of 3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (1) under Eschweiler–Clarke reaction conditions using excess formaldehyde gave 3,4,9,9a-tetrahydro-6,8,9,12-tetramethyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (**1b**). When an equivalent amount of formaldehyde was used, the main products were 3,4,9,9a-tetrahydro-12-methyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (**1c**) and 1,3,4,9a-tetrahydro-12-methyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazole-9(2*H*)-carboxaldehyde (**1d**).

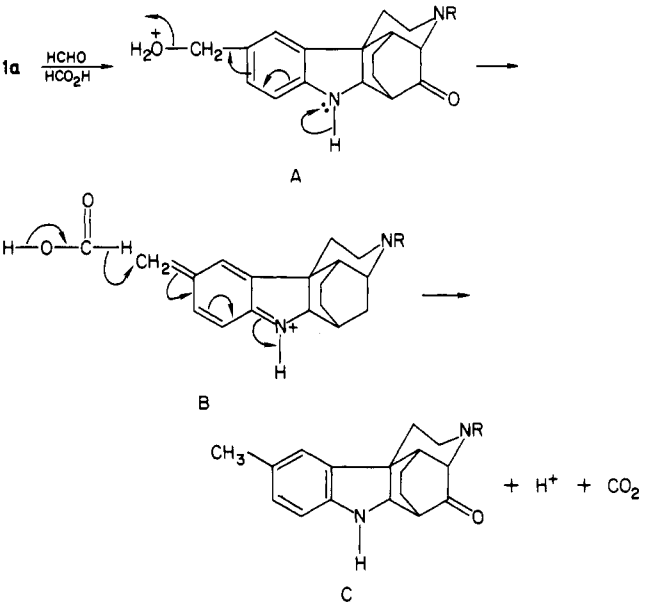
In an earlier paper,[1] we have reported the synthesis of 3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (**1a**) and its hexacyclic derivatives. We now describe some unusual methylation results using a typical Eschweiler–Clarke procedure.[2]



1a, R′=R″=R‴=H
1b, R′=R″=R‴=CH_3
1c, R′=R″=H; R‴=CH_3
1d, R′=H; R″=CHO; R‴=CH_3
1e, R′=H; R″=R‴=CH_3
1f, R′=H; R″=$CONHCH_3$; R‴=CH_3

Refluxing a solution of **1a** with excess formaldehyde in 90% aqueous formic acid gave 3,4,9,9a-tetrahydro-6,8,9,12-tetramethyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (**1b**) as the sole isolable product. Analytical and spectral data are in full agreement with structure **1b** (see Experimental Section).

Mechanistically, a quinoid-like intermediate (B) can be proposed, which is reduced in situ to give C. A similar mechanism would operate for the introduction of the second (ortho) nuclear methyl group. Electron availability on the aniline nitrogen[3,4] is apparently necessary for the



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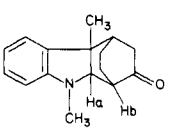
(2) (a) Icke, R. N.; Wisegarver, B. B. *Org. Synth.* **1946**, *25*, 89. (b) Eschweiler, W. *Chem. Ber.* **1905**, *38*, 880. (c) Decker, H.; Becker, P. *Liebigs Ann. Chem.* **1913**, *395*, 343; (d) **1913**, *395*, 360. (e) Decker, H.; Becker, P. *Chem. Ber.* **1912**, *45*, 2404. (f) Werner, E. A. *J. Chem. Soc.* **1917**, *111*, 844. (g) Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571. (h) Wagner, E. C. *J. Am. Chem. Soc.* **1933**, *55*, 724. (i) Kametani, T.; Noguchi, I.; Saito, K. *J. Heterocycl. Chem.* **1969** *6*(6), 869.

(3) In a partly similar structure Cranwell and Saxton (Cranwell, P. A.; Saxton, J. E. *Tetrahedron* **1964**, *20*, 877) report NCH_3 at δ 2.77 and Ha as a doublet ($J_{a,b}$ = 4.5 Hz) at δ 3.40. In the parent compound **1a**[1] this proton (H-9a) resonates at δ 3.75. It is obvious that the neighboring *N*-methyl group causes considerable shielding.



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