Studies in Biomimetic Alkaloid Syntheses. 8. Total Syntheses of the C-14 Epimeric Hydroxyvincadifformines, Tabersonine, a (Hydroxymethyl)-*D*-norvincadifformine, and the C-20 Epimeric Pandolines

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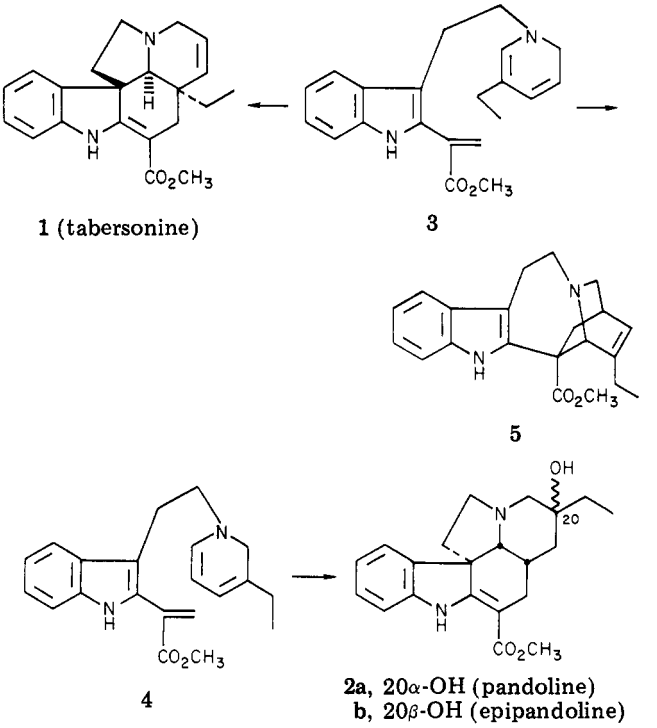
Condensation of methyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**6**) with 5-chloro-2-ethyl-4-hydroxypentanal lactol (**14**) yielded the 14α- and 14β-hydroxyvincadifformines (**8a,b**) in an epimeric ratio which was solvent dependent. On condensation of the indoloazepine **6** with 4,5-epoxy-2-ethylpentanal (**9**) the same compounds were formed together with a (hydroxymethyl)-*D*-norvincadifformine, **10**, as the major product. Dehydration of 14β-hydroxyvincadifformine (**8a**) readily gave tabersonine (**1**), while 14α-hydroxyvincadifformine (**8b**) could only be dehydrated by carbamate pyrolysis. The latter compound (**8b**) and the (hydroxymethyl)-*D*-norvincadifformine **10** could be converted to vincadifformine (**18**) through the chloromethyl derivative **16**. Condensation of the indoloazepine **6** with the epimeric 4,5-dichloro-2-ethylpentanals (**19**) also gave the (chloromethyl)-*D*-norvincadifformine **16** and 14β-chlorovincadifformine (**20**). Dehydrohalogenation of the latter compound provided a third sequence to tabersonine (**1**). A synthesis of the C-20 epimeric pandolines (**2a,b**) from 5-chloro-4-ethyl-4-hydroxypentanal lactol (**22**) similarly allowed control of the C-20 epimeric product ratio through its solvent dependence.

Tabersonine (**1**) and the C-20 epimeric pandolines (**2a,b**) are biogenetically derived from either of two respective postulated isomeric precursors, the dehydrosecodines **3** and **4**.[1,2] Formation of the pentacyclic alkaloids **1** and **2** is a consequence of intramolecular addition of the first dienamine double bond in the dehydrosecodines (**3**, **4**) to the indoloacrylate moiety. However, through an alternative intramolecular Diels–Alder reaction of the dienamine and acrylate functions, a dehydrosecodine can also be expected to cyclize to an isoquinuclidine product, i.e., catharanthine (**5**, Scheme I). Thus biomimetic syntheses specifically dircted at tabersonine (**1**) or at the pandolines (**2a,b**) are more advantageously based on dehydrosecodines in which the dienamine terminal double bond is masked. This report describes such syntheses.

Previously we had achieved syntheses of the C-20 epimeric pandolines (**2a,b**) by condensation of the indoloazepine **6** with 4-ethyl-4,5-epoxypentanal (**7**, Scheme II).[3] Extension of this reaction to syntheses of the C-14 epimeric hydroxyvincadifformines **8a,b** by use of 2-ethyl-4,5-epoxypentanal (**9**), however, is confronted by a problem in regioselective intramolecular opening of the epoxide function in intermediates derived from the epoxy aldehyde **9**. The decreased selectivity for attack at a primary vs. a secondary epoxide carbon (rather than primary vs. tertiary carbon, encountered in the pandoline synthesis) is aggravated by an intrinsic propensity for five- rather than six-membered-ring formation on intramolecular epoxide opening.[4] Thus, on condensation of the indoloazepine **6** with the epoxy aldehyde **9** in refluxing methanol a (hydroxymethyl)-*D*-norvincadifformine, **10**, was formed as the major product (68%), together with 14β-hydroxyvincadifformine (**8a**, 14%). At 0–20 °C in methanol only the five-membered-ring *D* product **10** was generated. However, almost equal amounts of the (hydroxymethyl)-*D*-norvincadifformine **10** and the hydroxyvincadifformine **8** ring systems were obtained in refluxing benzene, and the latter product consisted of a mixture of the C-14 epimeric alcohols **8a,b**, with the 14α-hydroxy epimer predominating.

These reactions proceed through initial formation of bridged indoloazepines **11a** followed by their intramolecular N-alkylation and fragmentation and final cyclization of the resulting secodine-type intermediates **12** and **13**.[5] The epimeric bridged indoloazepines **11a** could be identified by their characteristic UV chromophores (λ_{max} 230, 295, 328 nm) and color reactions with ceric ammonium sulfate on TLC (blue → green).[5] However, compounds **11a** were not rigorously characterized because of their spontaneous conversion to the final products **8** and **10** at room temperature.

Scheme I

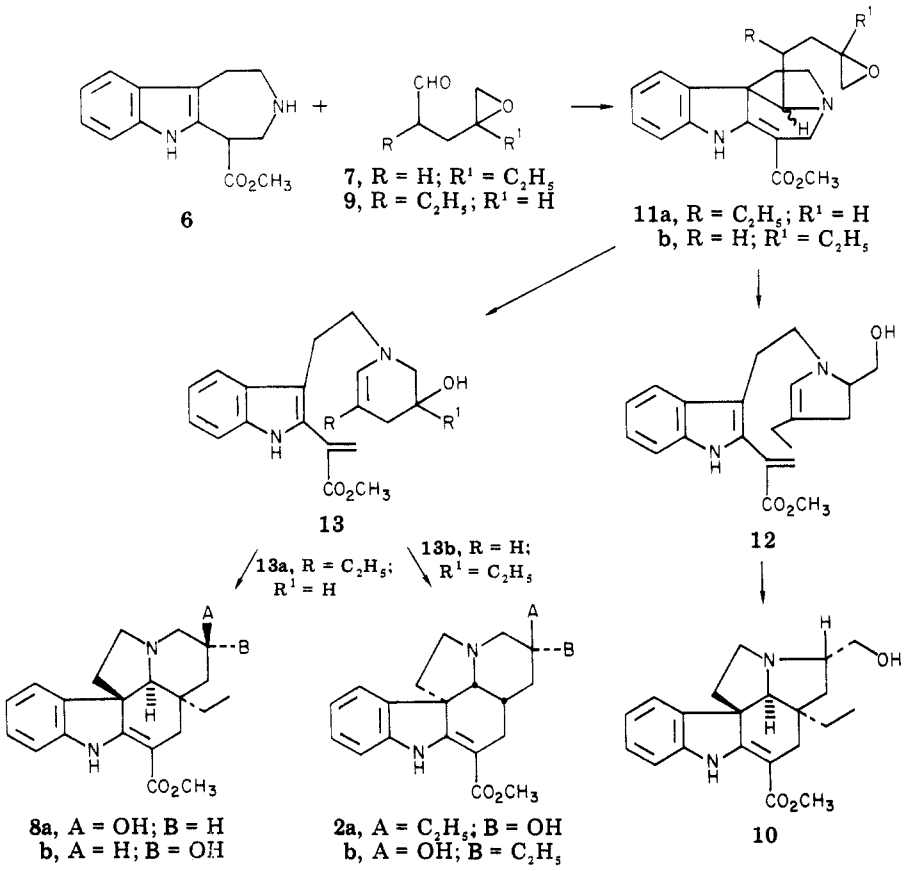


† This manuscript is dedicated to my mentor, Professor Gilbert Stork, on the occasion of his 60th birthday, in appreciation of the foundation he provided for many years of enjoyment in synthetic organic chemistry.

(1) E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962).
(2) A. I. Scott, *Acc. Chem. Res.*, **3**, 151 (1970); *Bioorg. Chem.*, **3**, 398 (1974).
(3) M. E. Kuehne, C. L. Kirkemo, T. H. Matsko, and J. C. Bohnert, *J. Org. Chem.* **45**, 3259 (1980).
(4) (a) G. Stork and J. F. Cohen, *J. Am. Chem. Soc.*, **96**, 5270 (1974); (b) R. Achini and W. Oppolzer, *Tetrahedron Lett.*, 369 (1975).
(5) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, D. Oliver-Smith, and L. Motyka, *J. Org. Chem.*, **46**, 2002 (1981).

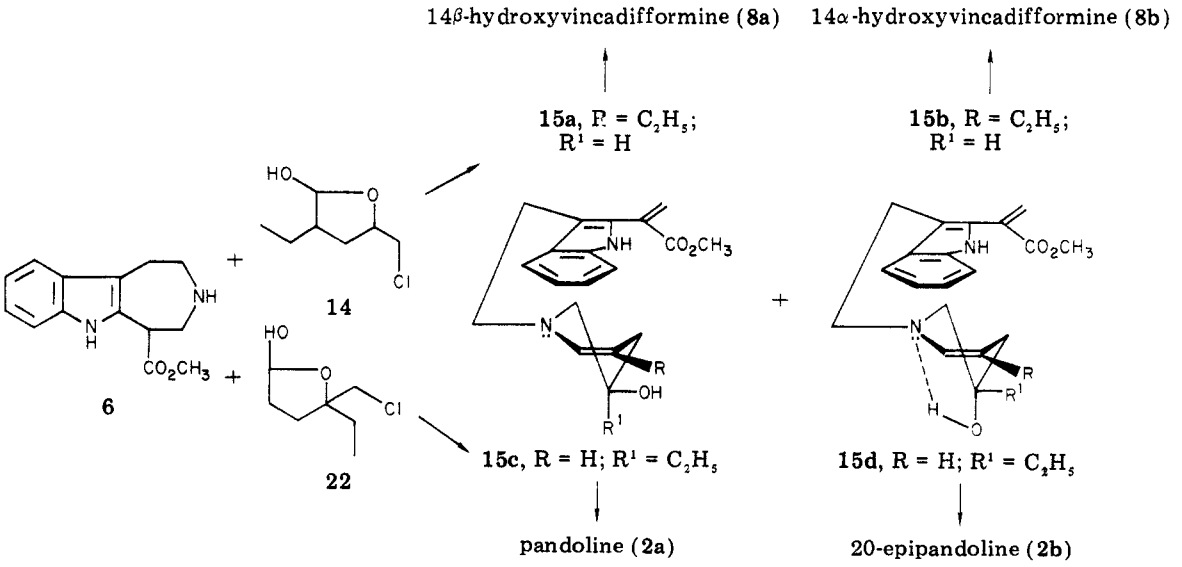
0022-3263/82/1947-1335$01.25/0

Scheme II[a]



[a] Racemic products are shown in the absolute stereochemistry of the natural products.

Scheme III



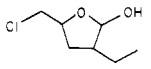
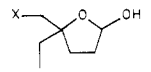
The structures and stereochemistry of the epimeric 14-hyroxyvincadifformines **8a,b** were secured by spectroscopic comparisons with the alcohols (and their acetate derivatives), obtained on hydroboration of tabersonine,[6] and they could be correlated with the chemical reactivities expected for such structures (below). The stereochemistry of the hydroxymethyl substituent indicated as α in **10** follows from an expected preferential addition of the indoloacrylate to the less hindered side of the hydroxymethyl-substituted pyrrolideine ring in the (hydroxymethyl)norsecodine **12**[7] and is consistent with a correlation of the hydroxymethyl product **10** with a 14α-substituted vincadifformine (see below).

In order to overcome the formation of the (hydroxymethyl)-*D*-norvincadifformine (**10**) product, obtained with the epoxy aldehyde **9**, we studied an alternative conden-

(6) C. Caron-Sigaut, L. Le Men-Olivier, G. Hugel, J. Lévy, and J. Le Men, *Tetrahedron*, **35**, 957 (1979). We thank Dr. J. Hannart of Omnichem for comparison samples of the 14-hydroxyvincadifformines derived from tabersonine.

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

Table I. Formation of Epimeric 14-Hydroxyvincadifformines (8a,b) and Pandolines (2a,b) from the Indoloazepine 6 and the Halo Lactols 14 or 22 and the Epoxides 9 or 7

aldehyde equivalent	solvent	temp, °C	time	isolated total yield, % (β/α-OH ratio)	HPLC ratio of vincadifformines, 14β-OH (8a)/ 14α-OH (8b)
 14	MeOH, TosOH	65	6 h	56 (3.2:1)	80/20
	MeOH, TosOH	20	4 d	incomplete reaction	~78/22
	diethylene glycol monoethyl ether, TosOH	130	6 h	61 (1:1.1)	50/50
	diethylene glycol monoethyl ether, benzoic acid	130	6 h	62 (1:1.2)	50/50
	diglyme, TosOH	130	6 h	83 (1:1.2)	50/50
	diglyme, benzoic acid	130	6 h	62 (1:1.2)	50/50
	benzene, TosOH	80	6 h	79 (1:1.6)	39/61
epoxide 9	MeOH	65	2 h	14 β-OH (8a) and 68 10	
epoxide 9	MeOH	0-20	24 h	only 10	
epoxide 9	C_6H_6	80	24 h	44 (1:1.2), 56 10	
aldehyde equivalent	solvent	temp, °C	time	isolated total yield, % (β/α-OH ratio)	pandolines 2a/2b
 22, X = Cl	MeOH	210	0.5 h	67	70/30
Cl	MeOH	65	48 h	73	63/37
Br	MeOH	65	2 h		63/37
Br	MeOH	20	24 h		50/50
Cl	C_6H_6	170	1.5 h		31/69
Cl	C_6H_6	80	48 h		23/77
Br	C_6H_6	47	72 h	63	33/67
Br	C_6H_6	20	7 d	57	36/64
epoxide 7	C_6H_6	47	4 d	61	31/69

sation of the indoloazepine 6 with the chloro lactols 14 (Scheme III). It was found that reaction with these halo aldehyde derivatives gave a mixture of epimeric 14-hydroxyvincadifformines (8a,b), where the relative proportion of epimers varied with the reaction solvent. in methanol, primarily the 14β-hydroxy product 8a was obtained while in benzene 14α-hydroxyvincadifformine 8b was favored (Table I).

These results are a consequence of stereoselective reactions of a hydroxysecodine intermediate 13a, where, in methanol, the hydroxyl group is solvated and therefore large and pseudoequatorial (conformation 15a), whereas the hydroxyl group is preferentially pseudoaxial, with hydrogen bonding to nitrogen (conformation 15b), when the hydroxysecodine 13a is generated in benzene. Intramolecular addition of the indoloacrylate moiety to the stereoelectronically favored and less encumbered face of the piperideine ring then leads to the observed preferential formation of the respective 14-hydroxyvincadifformines 8a or 8b in methanol vs. benzene.

The relative stereoselectivity was determined by isolation of products as well as by high-pressure liquid chromatography of reaction mixtures. These studies were complicated by formation of acetals derived from the starting lactols 14 and the 14-hydroxyvincadifformines (8a,b), with preferential derivatization of 14α-hydroxyvincadifformine (equatorial OH). Acid-catalyzed methanolysis of these acetals, which were generated particularly in reaction mixtures obtained with nonhydroxylic solvents, however, yielded the parent alcohols 8a,b.

It may be noted that the ratio of 14-hydroxyvincadifformine epimers (8a,b) showed the same solvent dependence in product mixtures derived from either the epoxy aldehyde 9 or from the chloro lactols 14, as expected for reactions passing through a common hydroxysecodine intermediate, 13a.

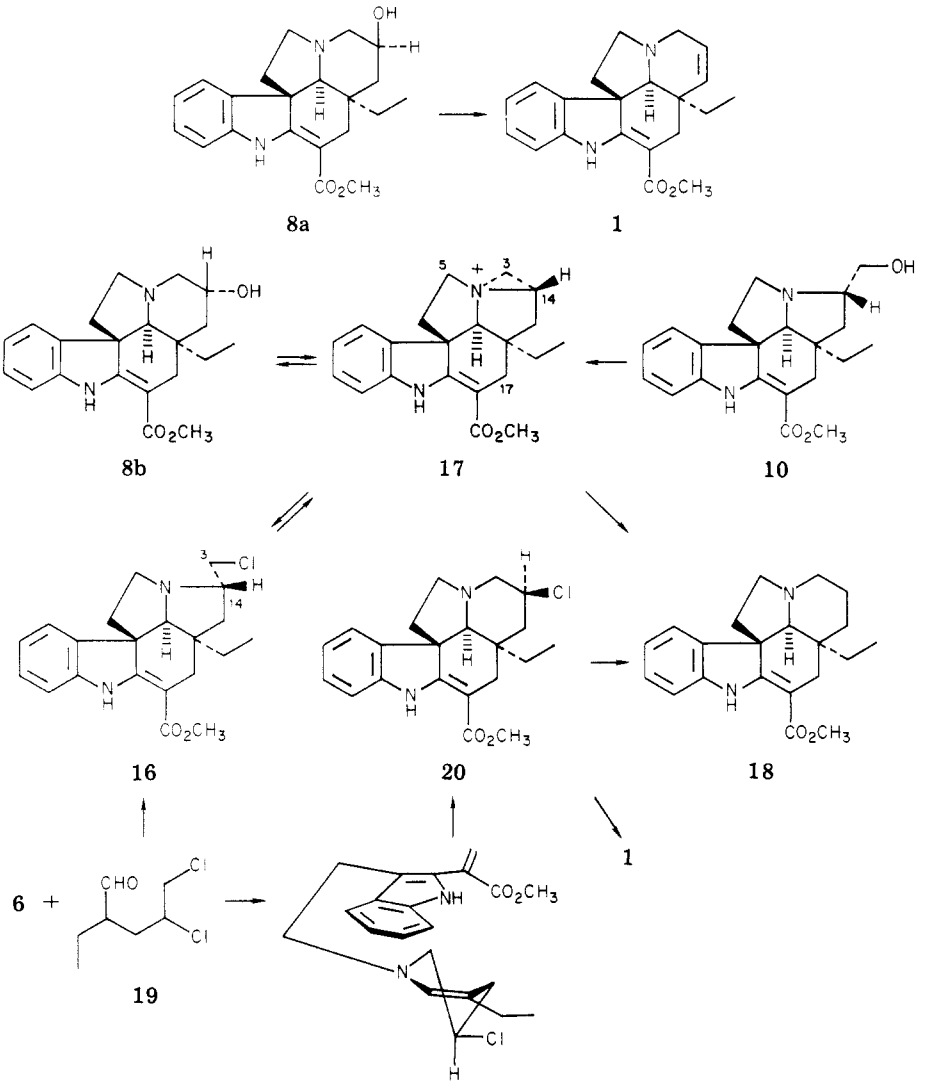
Dehydration of 14β-hydroxyvincadifformine (8a) to tabersonine (1) was readily accomplished in 68% yield by its treatment with triphenylphosphine and carbon tetrachloride in acetonitrile, with addition of triethylamine. On the other hand, no tabersonine (1) could be generated from the 14α-hydroxy epimer 8b under these conditions or in reactions with mesyl chloride or $POCl_3$ and base. Only the (chloromethyl)-*D*-norvincadifformine 16 was found (Scheme IV).

The structure of chloride 16 was assigned on the basis of its ^1H NMR spectrum, which showed a characteristic downfield shift of signals, relative to vincadifformine, with the region δ 2.0–3.0 now displaced to δ 3.0–3.8, a one-proton doublet at δ 2.77, and a downfield shift of the C-18 methyl group, all observed also with the corresponding hydroxy compound 10 and its acetate. A ^{13}C NMR proton off-resonance decoupling experiment revealed the C-3 chloromethyl group as a triplet at δ 52.0 and the C-14 methine carbon as a doublet at δ 7.97.[8] Hydrogenolysis of the chlorine substituent provided a product in which a methyl substituent could be seen as a doublet at δ 1.25 in the ^1H NMR spectrum.

The conversion of 14α-hydroxyvincadifformine (8b) to the (chloromethyl)-*D*-norvincadifformine 16 arises from a transannular displacement of an equatorial leaving group, with generation of an aziridium intermediate, 17, by a

(8) For the analogous methine in ibophyllidine a value of δ 75.6 was reported by F. Khuong-Huu, M. Cesario, J. Guilhem, and R. Goutarel, *Tetrahedron*, 32, 2539 (1976).

Scheme IV



process which is conformationally more favorable than the proton loss required for a generation of tabersonine (1). The same (chloromethyl)-*D*-norvincadifformine **16** was also obtained from the (hydroxymethyl)-*D*-norvincadifformine **10** on reaction with triphenylphosphine and CCl_4. This correlation of the two alcohols **8b** and **10** supports the above stereochemical assignment of the hydroxymethyl substituent in **10**.

When the (chloromethyl)-*D*-norvincadifformine **16** was heated in aqueous dimethylformamide, 14α-hydroxyvincadifformine (**8b**) was generated as the major product, together with very little of the (hydroxymethyl)-*D*-norvincadifformine **10**. Analogously, a reduction of the (chloromethyl)-*D*-norvincadifformine **16** with sodium borohydride in hot dimethylformamide gave vincadifformine (**18**). These last reactions demonstrate *selective unidirectional transformations of the five-membered ring D compounds* (***10***, ***16***) *into the aspidosperma alkaloid skeleton* (***8b***, ***18***) *while the specific reverse skeletal rearrangement was found on conversion of 14α-hydroxyvincadifformine* (***8b***) *to the chloride* ***16***. The opposing transformations may be ascribed to kinetic vs. thermodynamic control in opening of the aziridinium intermediate **17**, where a reversible reaction with chloride produces the five-membered ring D product **16**, but irreversible opening by water or hydride leads to six-membered ring D products **8b** and **18**.

Alternative modes of opening of aziridinium intermediates derived from 3-chloropiperidines, with dependence on the nature of the nucleophile, have been observed previously, but normally such intermediates are opened by chloride to yield 3-chloropiperidines and by hydroxide to yield primarily (hydroxymethyl)pyrrolidines.[9] A reversal of results is found with the present examples. Here the piperidine and aziridinium ring systems and their connecting transition states are deformed by cis fusion to a five-membered ring and by 1,3-diaxial repulsion of the C-5 and C-17 methylene substituents. These constraints deflect the equatorial nitrogen lone-pair orbital to the α face of the piperidine. Consequently, electrophilic attack on an aziridinium structure **17** stereoelectronically favors opening of the C-14 to N bond over the C-3 to N bond (kinetic control). As a corollary, the chloromethyl compound **16** requires more energy than a 14α-chlorovincadifformine to form the aziridinium intermediate **17** (thermodynamically controlled buildup of **16**). An analogous contraction of ring D in a vincadifformine derivative has also been observed on halogenation of the Δ^{14} double bond.[10,11]

(9) C. F. Hammer, S. R. Heller, and J. H. Craig, *Tetrahedron*, **28**, 239 (1972).

(10) N. Langlois and P. Potier, *Bull. Soc. Chim. Fr.* 144 (1978).

When the indoloazepine **6** was condensed with an epimeric mixture of 4,5-dichloro-2-ethylpentanals (**19**), the (chloromethyl)-*D*-norvincadifformine **16** (54%) and 14β-chlorovincadifformine (**20**, 18%) were formed in refluxing benzene. In some reactions the variable yield of the second product **20** was as high as 45%. With prolonged reactions the ratio of **16** to **20** gradually increased due to destruction of the latter compound (but not because of its conversion to **16**). When the isolated 14β-chloro compound **20** was heated with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), tabersonine (**1**) was formed in 42% yield. On reduction with tri-*n*-butyltin hydride the 14β-chloro derivative produced vincadifformine (**18**). However, this hydrogenolysis product was not generated on treatment of 14β-chlorovincadifformine (**20**) with $NaBH_4$ in hot dimethylformamide, and no 14-hydroxyvincadifformine was formed from **20** in hot aqueous dimethylformamide. These observations are in accord with expectations for the assigned 14-β-chloro stereochemistry and they can be contrasted with the results obtained with the (chloromethyl)-*D*-vincadifformine **16** and those expected for a related 14α-chlorovincadifformine.

The formation of 14β-chlorovincadifformine is directly derived from cyclization of an equatorially substituted chlorosecodine, **21**, whereas the (chloromethyl)-*D*-norvincadifformine **16** may be generated from the axial chloro epimer of **21**, followed by rearrangement of a subsequent 14α-chlorovincadifformine (equatorial Cl). Alternatively, **16** may be formed by cyclization of a (chloromethyl)-*D*-norsecodine.[7]

While elimination of a 14α substituent from vincadifformine by E_1- or E_2-type reactions can be expected to suffer from the competing intramolecular quaternization, with formation of an aziridium intermediate **17**, it was anticipated that a pyrolytic elimination reaction would allow the transformation of 14α- and 14β-hydroxyvincadifformines (**8a,b**) to tabersonine (**1**). Indeed, pyrolysis of a thiocarbamate derivative of the 14α-ol **8b** yielded tabersonine, but a low overall yield on derivatization and cracking indicated that such transformations of a 14-epimeric hydroxyvincadifformine mixture would not be preparatively advantageous over the preferential (but not exclusive) generation of 14β-hydrovincadifformine (**8a**) in methanol and its dehydration as described above.

A chlorolactol, **22**, was again a desirable synthon in assembly of pandoline (**2a**) and 20-epipandoline (**2b**) (Scheme III), since the previously used epoxy aldehyde **7** was relatively unstable and had to be employed in large excess in the condensation with the indoloazepine **6**. Syntheses of the pandolines from the chloro lactol **22** also showed solvent-dependent stereoselectivity, but, relative to the preceding 14-hydroxyvincadifformine syntheses, the selectivity was somewhat less pronounced. Competition between the geminal ethyl and the less solvated tertiary hydroxyl substituent for a pseudoequatorial orientation in the hydroxysecodines **15c** or **15d** (Scheme III) resulted in a 2:1 ratio of pandoline epimers **2a,b**, compared to a 4:1 ratio of the 14-hydroxyvincadifformine epimers **8a,b** from reactions in methanol. In contrast to the 14-hydroxyvincadifformine syntheses, these reactions did not lead to significant formation of pandoline-derived acetals, in accord with expectation for the more hindered tertiary alcohols **2a,b**.

The syntheses of 14-hydroxy- and 14-chlorovincadifformines, the pandolines, tabersonine, and the *D*-norvincadifformine derivatives demonstrate the versatility of such biomimetic syntheses, and they provide access to a variety of ring D functionalized or contracted aspidosperma alkaloids.

(11) G. Hugel, G. Massiot, J. Lévy, and J. Le Men, *Tetrahedron* **37**, 1369 (1981).

Experimental Section

Ethyl and Methyl 2-Ethyl-4-pentenoate.[12] A solution of 11.6 g (0.1 mol) of ethyl butyrate in 25 mL of tetrahydrofuran was added dropwise at −78 °C to lithium diisopropylamide prepared from 12.1 g (0.12 mol) of diisopropylamine and *n*-butyllithium (75 mL of a 1.6 M solution in hexane, 0.12 mol) in 200 mL of tetrahydrofuran at −78 °C. After 30 min at −78 °C, 14.5 g of allyl bromide (0.11 mol) was added. The reaction mixture was warmed to 20 °C over 45 min and then stirred at 20 °C for 45 min. After addition of 50 mL of saturated aqueous ammonium chloride and concentration under vacuum the residue was partitioned between 300 mL of ether and 100 mL of 20% aqueous HCl. The organic layer was washed with 20% aqueous HCl (4 × 75 mL), and the combined aqueous solutions were extracted with ether (3 × 100 mL). Washing of the combined organic solutions with saturated brine, drying over magnesium sulfate, concentration, and distillation gave 12.9 g (82%) of the title product: bp 84–88 °C (43 mm) (lit.[12] bp 165–168 °C); IR (film) ν_{max} 3080, 2960, 1730, 1640, 1150, 990, 910 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (t, 3 H), 1.34 (t, 3 H), 1.40–1.80 (m, 2 H), 2.0–2.6 (m, 3 H), 4.20 (q, 2 H), 5.10 (3 peaks, 2 H) 5.90 (m, 1 H); mass spectrum, *m/e* 156 (M^+). The corresponding methyl ester [bp 50–55 °C (25 mm)] was prepared analogously: NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.55 (q, 2 H), 2.35 (m, 3 H), 3.70 (s, 3 H), 5.10 (3 peaks, 2 H), 5.90 (m, 1 H).

Ethyl and Methyl 4,5-Epoxy-2-ethylpentanoate. At 0 °C 4.88 g (24 mmol) of 85% *m*-chloroperbenzoic acid was added to 3.12 g (20 mmol) of ethyl 2-ethyl-4-pentenoate in 40 ml of dichloromethane. After 2 h at 0 °C and 10 h at 20 °C the mixture was filtered and concentrated under vacuum, and the residue was dissolved in ether. The solution was washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), concentrated, and distilled to give 1.61 g (47%) of the title epoxide: bp 88–90 °C (3.5 mm), IR (film) ν_{max} 3050, 2970, 2940, 2880, 1730, 1460, 1375, 1180, 1030, 925 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.28 (t, 3 H), 1.40–2.04 (m, 4 H), 2.30–2.60 (m, 2 H), 2.68 (t, 1 H), 2.80–3.00 (m, 1 H), 4.10 (q, 2 H); mass spectrum, *m/e* 172 (M^+). The methyl ester was prepared analogously, giving 81% of product: bp 100 °C (25 mm); NMR δ 0.90 (t, 3 H), 1.4–2.0 (m, 4 H), 2.38–2.68 (m, 2 H), 2.75 (t, 1 H), 2.95 (m, 1 H), 3.74 (s, 3 H).

4,5-Epoxy-2-ethylpentanal (9). At −78 °C 14.0 mL of 1 M diisobutylaluminum hydride (14 mmol) in hexane was added dropwise to 2.19 g (13 mmol) of the preceding epoxy ethyl ester in 40 mL of dichloromethane. After the mixture was stirred at −78 °C for 30 min, 5 mL of saturated aqueous ammonium chloride and 100 mL of ether were added, and the mixture was warmed to 20 °C. Filtration, drying of the organic phase over sodium sulfate, and concentration gave 1.75 g of an oil which was flash distilled at 0.1 mm. The product (0.90 g, 56%) was collected at −78 °C: IR (film) ν_{max} 2970, 2930, 2880, 2710, 1725, 1420, 1370, 1230, 920, 850, 750, 710, cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, 3 H), 1.1–2.1 (m, 4 H), 2.3–2.6 (m, 2 H), 2.85 (t, 1 H), 3.05 (m, 1 H), 9.85 (d, 1 H).

2-Ethyl-4-pentenoic Acid.[13] Freshly distilled *n*-butyric acid (10.0 g, 114 mmol) was added dropwise to a THF solution of lithium diisopropylamide at −20 °C, prepared at −20 °C from 29.9 g (295 mmol) of diisopropylamine, 185 mL of 1.6 M *n*-butyllithium in hexane, and 500 mL of tetrahydrofuran (THF). Hexamethylphosphoramide (26.5 g, 148 mmol) was added to the colloidal suspension, and the mixture was warmed to 20 °C, stirred for 45 min, and cooled to 0 °C. Freshly distilled allyl bromide (18.0 g, 148 mmol) was added dropwise, and the reaction mixture was warmed to 20 °C. After the mixture was stirred for 4 h, 50

(12) B. Akermark, *Acta Chem. Scand.*, **16**, 599 (1962).

(13) K. Kunata, S. Tanaka, and K. Takahashi, *Chem. Pharm. Bull. Jpn.*, **24**, 538, (1976); prepared by a procedure analogous to that given for related acids by P. E. Pfeffer, L. S. Silbert, and J. M. Chiriuko, Jr., *J. Org. Chem.*, **37**, 451 (1972).

mL of saturated aqueous ammonium chloride was added, the mixture was concentrated under vacuum, and the residue was partitioned between 300 mL of ether and 100 mL of 20% aqueous HCl. The organic phase was washed with 20% HCl (4 × 75 mL), the combined aqueous portions were extracted with ether (3 × 100 mL), and the combined organic solutions were washed with saturated brine, dried ($MgSO_4$), and concentrated. Distillation of the residual product gave the product: 13.4 g (92%); bp 46–48 °C (0.1 mm) [lit.[13] bp 87–91 °C (6 mm)]; IR (film) ν_{max} 3400–2500, 3080, 2980, 2930, 2880, 1770, 1640, 1460, 1440, 1420, 1370, 1340, 1270, 1255, 1230, 995, 915, 775 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (t, 3 H), 1.64 (m, 2 H), 2.41 (m, 3 H) 5.07 (s, 1 H), 5.21 (s, 1 H), 5.95 (m, 1 H); mass spectrum, m/e 128 (M^+). A *p*-toluamide derivative had a melting point of 97–98 °C. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.24; H, 8.93; N, 6.24.

5-Chloro-2-ethyl-4-hydroxypentanoic Acid 1,4-Lactone. Chlorine gas was bubbled slowly for 15 min into a solution of 5.225 g (40.8 mmol) of 2-ethyl-4-pentenoic acid in 40 mL of dichloromethane at 0 °C. An IR spectrum of an aliquot then showed replacement of absorptions at 1700 and 1640 cm^{-1} by one at 1775 cm^{-1}. The reaction mixture was concentrated under vacuum, the residue dissolved in 60 mL of ether and washed with saturated $NaHCO_3$ solution, (2 × 25 mL), and the aqueous phase extracted with ether (2 × 25 mL). The combined ether solutions were washed with saturated brine, dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the residue on 100 g of silica gel (eluting with 3:2 hexane/ether) and distillation gave 5.76 g (87%) of product: bp 66–72 °C (0.01 mm); IR (film) ν_{max} 2970, 2940, 2885, 1775, 1460, 1430, 1355, 1340, 1315, 1265, 1245, 1175, 1030, 945, 780, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, J = 8 Hz, 3 H), 1.2–2.8 (m, 5 H), 3.6–3.7 (dd, J = 4Hz, 2 H), 4.4–4.8 (m, 1 H).

5-(Chloromethyl)-3-ethyl-2-hydroxytetrahydrofuran (14).[14] To 780 mg (4.79 mmol) of the preceding chloro lactone in 15 mL of dichloromethane, cooled to −78 °C, was added 5.26 mL of 1 M diisobutylaluminum hydride in hexane dropwise with stirring. After 30 min, 2.5 mL of saturated aqueous NH_4Cl solution was added, and the mixture was warmed to 20 °C, diluted with ether, and stirred for 15 min. Decantation and stirring of the residue twice with 50-mL portions of ether for 15 min, filtration of the combined organic solutions, washing with saturated brine, drying ($MgSO_4$), and concentration gave 785 mg of an oil. Chromatography on 30 g of silica gel, (eluting with 3:2 hexane/ether) provided 670 mg (85%) of an epimeric mixture of **14**: IR (film) ν_{max} 3400, 2960, 2930, 2870, 1460, 1430, 1150, 1015, 995, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, 3 H), 1.2–2.5 (m, 5 H), 3.5–3.8 (m, 2 H), 3.8–4.8 (m, 2 H), 5.27 (d, J = 2 Hz), 5.38 (d, d combined with preceding signal, 1 H); 2,4-dinitrophenylhydrazone, mp 142–143 °C. Anal. Calcd for $C_{13}H_{17}N_4O_5Cl$: C, 45.29; H, 4.97; N, 16.25; Cl, 10.29. Found: C, 45.07; H, 4.83; N, 16.19; Cl, 10.50.

14β- and 14α-Hydroxyvincadifformines (8a,b) and 14-(Hydroxymethyl)-*D*-norvincadifformine (10). (a) A solution of 495 mg (3.0 mmol) of the epimeric chloro lactols **14**, 488 mg (2.0 mmol) of the indoloazepine **6**, and 30 mg of *p*-toluenesulfonic acid in 10 mL of methanol was heated under nitrogen at gentle reflux for 24 h. TLC analysis showed no remaining indoloazepine at this point. Triethylamine (280 μL, 2.01 mmol) was added to the cooled solution and reflux continued for 12 h. Concentration under vacuum, solution in 25 mL of dichloromethane, washing with 5% ammonium hydroxide solution (3 × 5 mL), extraction of the combined aqueous layers with dichloromethane, washing of the combined organic solutions with brine, drying ($MgSO_4$), and concentration gave 885 mg of material which was chromatographed on 80 g of silica gel. Elution with 2% methanol in dichloromethane provided 305 mg (43%) of amorphous 14β-hydroxyvincadifformine (**8a**) and 75 mg (11%) of the amorphous 14α-hydroxy isomer (**8b**).

(b) When the addition of triethylamine was left out of the preceding procedure, 14β- and 14α-hydroxyvincadifformine (**8a,b**) were formed in 55% yield in a 14β/14α ratio 3.2, as determined by HPLC (Waters Assoc. Inc. μ-Bondapack CN column, ethyl acetate) and by isolation of the pure epimeric components by column chromatography, as described above. For determination of the ratio of 14β-/14α-hydroxyvincadifformines in this and the following reaction mixtures, hydrolysis of accompanying acetals, which had a TLC R_f of 0.95 (silica, 2% methanol in dichloromethane, CAS green changing to yellow), was accomplished by heating the mixture for 1 h in methanolic HCl.

(c) A solution of 561 mg (3.4 mmol) of the chloro lactols **14**, 488 mg (2.0 mmol) of the indoloazepine **6**, and 244 mg (2.0 mmol) of benzoic acid in 10 mL of benzene was refluxed under nitrogen for 24 h, when TLC showed complete reaction of the indoloazepine. After addition of 560 μL (4.0 mmol) of triethylamine and 12 h of reflux the reaction mixture was worked up as above to give 900 mg of crude products, chromatographed to 225 mg (34%) of the 14β-hydroxy epimer **8a** and 315 mg (47%) of the 14α-hydroxy epimer **8b**.

(d) A solution of 732 mg (3.0 mmol) of indoloazepine **6**, 576 mg (4.5 mmol) of the epoxypentanal **9**, and 30 mg of *p*-toluenesulfonic acid 15 mL of benzene was heated for 24 h under reflux with a water trap filled with molecular sieves. To the cooled mixture was added 304 mg of triethylamine, and heating at reflux was continued for 8 h. The mixture was then worked up as above to give 1.22 g of crude products, chromatographed on 50 g of silica gel to yield 125 mg (18%) of 14β-hydroxyvincadifformine (**8a**), 145 mg (22%) of 14α-hydroxyvincadifformine (**8b**), and 400 mg (56%) of the hydroxymethyl compound **10**, which was recrystallized from acetonitrile, mp 151–153 °C.

(e) A reaction of indoloazepine **6** with the epoxyaldehyde **9** in methanol at reflux for 2 h gave 68% of the crystalline hydroxymethyl product **10** and 14% of 14β-hydroxyvincadifformine (**8a**), while a reaction mixture held at 0–20 °C showed, by TLC, only the development of the former product.

(f) A reaction of the indoloazepine **6** with the epoxyaldehyde **9** in tetrahydrofuran at room temperature showed, by TLC, the initial formation of a bridged azepine intermediate, **11**, with R_f 0.19 [silica, ethyl acetate–ethanol (9:1), blue turning to green with CAS spray], as compared to R_f 0.11 for **6**. An isolated sample of this intermediate had UV λ_{max} (MeOH) 225, 295, and 327 nm. Concomitant formation of the final reaction products **8a,b** and **10** made purification of this intermediate impractical.

(g) After 1 h at 80 °C a solution of the (chloromethyl-*D*-norvincadifformine **16** in dimethylformamide containing some water showed, by TLC, primarily 14α-hydroxyvincadifformine (**8b**), traces of the hydroxymethyl compound **10**, and some material with R_f 0.

For 14β-hydroxyvincadifformine (**8a**): TLC R_f 0.43 (silica, 2% methanol in dichloromethane); NMR ($CDCl_3$) δ 8.95 (s, 1 H), 6.80–7.22 (m, 4 H), 3.90 (brs, 1 H), 3.77 (s, 3 H), 0.90–2.30 (m, 14 H), 0.60 (t, 3 H); IR ($CHCl_3$) ν_{max} 3600, 3380, 3005, 2970, 2940, 2880, 2800, 1670, 1610, 1475, 1440, 1380, 1315, 1305, 1275, 1270, 1255, 1195, 1180, 1165, 1155, 1045, 1015, 910 cm^{-1}; UV (EtOH) λ_{max} 230, 310, 332 nm; mass spectrum (80 eV), m/e (relative intensity) 355 (76) 336 (3), 354 (100), 323 (23), 141 (54), 140 (82); hydrochloride, amorphous. Anal. Calcd for $C_{21}H_{27}N_2O_3Cl$: C, 64.52; H, 6.96; N, 7.17. Found: C, 64.25, H, 7.07; N, 7.14.

Amorphous 14β-acetoxyvincadifformine was prepared in 73% yield by acetylation of the 14β-hydroxy compound with acetic anhydride in pyridine with 4-(dimethylamino)pyridine as a catalyst: TLC R_f 0.65 (silica; hexane–ethyl acetate, 3:2); IR ($CHCl_3$) ν_{max} 3490, 3030, 3010, 2970, 2950, 2880, 2790, 1725, 1670, 1610, 1475, 1465, 1440, 1380, 1310, 1290, 1280, 1250, 1180, 1165, 1155, 1130, 1110, 1045, 1025, 1015, 910 cm^{-1}; NMR ($CDCl_3$) δ 8.92 (brs, 1 H), 6.75–7.23 (m, 4 H), 4.96–5.11 (m, 1 H), 3.77 (s, 3 H), 2.30–3.50 (m, 6 H), 2.11 (s, 3 H), 0.90–2.20 (m, 6 H), 0.59 (m, 4 H); mass spectrum (80 eV), m/e (relative intensity) 397 (76), 396 (100), 365 (22), 336 (22), 183 (50), 182 (72).

For 14α-hydroxyvincadifformine (**8b**): TLC R_f 0.36 (silica, 2% methanol in dichloromethane); NMR ($CDCl_3$) δ 8.50 (s, 1 H) 6.75–7.25 (m, 4 H), 3.90–4.10 (m, 1 H), 3.76 (s, 3 H), 3.20–3.40 (m, 1 H), 0.80–3.00 (m, 11 H), 0.66–0.75 (m, 2 H), 0.62 (t, 3 H); IR ($CHCl_3$) ν_{max} 3600, 3380, 3015, 2930, 2790, 1670, 1610, 1475, 1460, 1435, 1385, 1315, 1290, 1280, 1255, 1190, 1165, 1155, 1120, 1040, 925 cm^{-1}; mass spectrum (80 eV), m/e (relative intensity) 355 (60), 354 (100), 336 (2), 323 (17), 141 (50), 140 (76); 3,5-dinitrobenzoate, mp 186–189 °C; amorphous hydrochloride. Anal. Calcd for $C_{21}H_{27}N_2O_3Cl$: C, 64.52; H, 6.96; N, 7.17. Found: C, 64.25; H, 7.07; N, 7.14.

(14) For a related procedure see K. Mori, *Tetrahedron*, 31, 3011 (1975).

Amorphous 14α-acetoxyvincadifformine was prepared in 71% yield by acetylation of the 14α-hydroxy compound: TLC R_f 0.74 (silica; hexane–ethyl acetate, 3:2); IR ($CHCl_3$) ν_{max} 3490, 3052, 3010, 2970, 2860, 2800, 1730, 1670, 1610, 1480, 1465, 1440, 1375, 1315, 1290, 1280, 1250, 1180, 1170, 1160, 1120, 1045, 1035, 1020, 980, 930, 915, 880, 855 cm^{-1}; NMR ($CDCl_3$) δ 8.93 (brs, 1 H), 6.78–7.20 (m, 4 H), 5.04–5.16 (m, 1 H), 3.76 (s, 3 H), 3.40–3.46 (m, 1 H), 2.02–2.94 (m, 6 H), 2.05 (s, 3 H), 1.72 (dd, J = 11 Hz, 1 H), 0.64–1.43 (m, 5 H), 0.59 (t, J = 7 Hz, 3 H); mass spectrum (80 eV), m/e (relative intensity) 397 (75), 396 (100), 365 (22), 336 (21), 183 (52), 182 (80).

The (hydroxymethyl)-*D*-norvincadifformine **10** was recrystallized from acetonitrile: mp 153–154 °C; TLC R_f 0.16 (silica, 2% methanol in dichloromethane); UV (methanol) λ_{max} 226, 298, 328 nm; IR (KBr) ν_{max} 3260 (br), 2980, 2970, 2950, 2910, 2860, 1685, 1605, 1480, 1475, 1470, 1435, 1400, 1380, 1315, 1295, 1275, 1250, 1210, 1205, 1190, 1165, 1110, 1060, 1050, 1035, 985, 960, 885, 870, 790, 745 cm^{-1}; NMR ($CDCl_3$) δ 9.04 (brs, 1 H), 6.80–7.34 (m, 4 H), 3.78 (s, 3 H), 2.96–3.72 (m, 7 H), 2.77 (d, J = 15 Hz, 1 H), 1.60–2.26 (m, 5 H), 0.95–1.40 (m, 2 H), 0.78 (t, J = Hz, 3 H); mass spectrum (80 eV), m/e (relative intensity) 355 (56), 354 (100), 323 (60), 214 (9), 156 (50), 141 (57), 140 (84). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.29; H, 7.42; N, 7.70.

The amorphous *O*-acetyl derivative was obtained in 66% yield: TLC R_f 0.40 (silica, 2% methanol in dichloromethane); IR ($CHCl_3$) ν_{max} 3400, 3030, 3010, 2970, 2960, 2890, 2860, 1735, 1670, 1610, 1480, 1465, 1440, 1370, 1315, 1290, 1275, 1250, 1190, 1160, 1120, 1070, 1040, 1020, 910 cm^{-1}; NMR ($CDCl_3$) δ 9.04 (brs, 1 H), 6.82–7.35 (m, 4 H), 4.11 (d, J = 6 Hz, 2 H) 3.78 (s, 3 H), 3.04–3.49 (m, 4 H), 2.77 (d, J = 15 Hz, 1 H), 2.10 (s, 3 H), 1.60–2.26 (m, 5 H), 0.95–1.40 (m, 2 H), 0.78 (t, J = 7 Hz, 3 H); mass spectrum (80 eV), m/e (relative intensity) 397 (67), 396 (94), 353 (2), 323 (29), 183 (55), 182 (100).

Tabersonine (1). (a)[15] A solution of 140 mg (0.40 mmol) of 14β-hydroxyvincadifformine (**8a**) and 125 mg (0.48 mmol) of triphenylphosphine in 0.5 mL of acetonitrile was heated at 80 °C for 5 min. Carbon tetrachloride (46 μL, 0.48 mmol) was added to the hot solution. After 5 min at 80 °C TLC showed mostly tabersonine (**1**) with R_f 0.85 (silica, 1% methanol in dichloromethane; CAS spray, blue) and a small amount of a product (?, Δ^3- or 14α-chlorovincadifformine) with R_f 0.89. Triethylamine (0.3 mL, 2.1 mmol) was added and heating of the reaction mixture continued for 45 min. The higher R_f product had then reacted completely. After cooling, the reaction mixture was diluted with 15 mL of dichloromethane and was washed three times with 5 mL of dilute ammonium hydroxide. Extraction of the aqueous solutions with 5 mL of dichloromethane, washing of the combined organic extracts with 5 mL of brine, drying (Na_2SO_4), and concentration under vacuum yielded 160 mg of material, which was slurried repeatedly with 9:1 ether–hexane at 0 °C and filtered. Concentration of the extracts and column chromatography of the 110 mg of residual material on 5 g of silica gel, eluting with 9:1 ether–hexane, gave 90 mg (68%) of amorphous tabersonine (**1**) which had chloroform solution IR, NMR, and UV spectra and a mass fragmentation pattern and TLC retention time identical with those obtained with *l*-tabersonine

(b)[16] A sample of 14α-hydroxyvincadifformine (**8b**) was converted with sodium hydride and dimethylthiocarbonyl chloride in dimethylformamide to its 14-thiocarbamate derivative in 48% yield. Without purification, this derivative (neat) was pyrolyzed at 150 °C for 1 h. TLC analysis then showed a multicomponent mixture of products including tabersonine.

(c) A solution of 25 mg (0.067 mmol) of 14β-chlorovincadifformine (**20**) in 0.5 mL of dry benzene and 50 mg (0.335 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was heated a reflux for 4 h. The reaction mixture, which then contained no starting material **20** by TLC analysis, was diluted with 10 mL of dichloromethane, washed twice with 2 mL of 10% ammonium hydroxide and 2 mL of brine, dried (Na_2SO_4), concentrated, and column chromatographed on 5 g of silica, eluting 9.5 mg (42% yield) of tabersonine, identified by spectroscopic and TLC comparison with the natural product.

Epimeric Methyl 4,5-Dichloro-2-ethylpentanoates. Under a nitrogen atmosphere 7.19 g (56.6 mmol) of oxalyl chloride was added to 2.42 g (18.9 mmol) of 2-ethyl-4-pentenoic acid at 0 °C. The reation mixture was stirred at 20 °C for 10 h, and excess oxalyl chloride was then removed under reduced pressure. The residual acid chloride [IR (film) λ_{max} 3100, 1800, 1640 cm^{-1}] was dissolved in 25 mL of dry dichloromethane and cooled to 0 °C. Chlorine was gently bubbled through the reaction mixture until a yellow color persisted. After 5 min at 20 °C the solvent was removed under reduced pressure, and the residue [IR (film) λ_{max} 1795 cm^{-1}] was slowly added to 25 mL of dry methanol at 0 °C. After the mixture was stirred at 20 °C for 2 h, the solvent was removed under reduced pressure, and the oily residue was dissolved in 50 mL of ether. The organic solution was washed three times with 10 mL of 50% aqueous $NaHCO_3$, twice with 10 mL of water, and once with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to 4.12 g of a yellow oil. The crude product was purified by chromatography on 150 g of silica (hexanes/ether, 3:2) to yield 3.04 g (76%) of the methyl esters: R_f 0.78 (silica; hexanes/ether, 3:2); IR (film) ν_{max} 2960, 2870, 1730, 1455, 1435, 1385, 1315, 1265, 1200, 1115, 980, 840, 800, 735 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, J = 6 Hz, 3 H), 1.20–2.80 (m, 5 H), 3.64 (s, 3 H), 3.64–4.16 (m, 3 H); mass spectrum (80 eV), m/e 212.

Epimeric 4,5-Dichloro-2-ethylpentanals (19). At −78 °C 8.5 mL of a 1 M solution of diisobutyl aluminum hydride in hexanes was added dropwise to a solution of 1.55 g (8.44 mmol) of methyl 4,5-dichloro-2-ethylpentanoates in 20 mL of dichloromethane. After the mixture was stirred at −78 °C for 30 min, 5 mL of saturated aqueous NH_4Cl solution was added, and the mixture was warmed to 20 °C, diluted with ether, and stirred for 15 min. Decantation and stirring of the residue with two 50-mL portions of ether, filtration of the combined organic solutions, washing with saturated brine, drying over $MgSO_4$, and concentration gave 1.67 g of a clear oil. Purification by chromatography on silica (hexanes–ether, 3:2) gave 1.51 g (98%) of the aldehyde **19**: R_f 0.76 (hexanes–ether, 3:2); IR (film) ν_{max} 2960, 2920, 2870, 2720, 1715, 1460, 1430, 1385, 1235, 1190, 1170, 780, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.90–1.10 (m, 3 H), 1.20–2.80 (m, 5 H), 3.48–4.32 (m, 3 H), 9.72 (d, J = 2 Hz, 1 H); 2,4-dinitrophenylhydrazone, mp 114–116 °C. Anal. Calcd for $C_{13}H_{16}N_4O_4Cl_2$: C, 42.99; H, 4.44; N, 15.43. Found: C, 42.85, H, 4.24; N, 15.44; Cl, 19.56.

14β-Chlorovincadifformine (20) and 14α-(Chloromethyl)-*D*-norvincadifformine (16). (a) After 12 h of reflux 1 mL of triethylamine was added to a solution of 300 mg (1.64 mmol) of the dichloro aldehyde **19**, 267 mg (1.09 mmol) of the indoloazepine **6**, and a small crystal of *p*-toluenesulfonic acid in 10 mL of benzene. Reflux was continued for 4 h, and the reaction mixtue was then cooled and diluted to 30 mL with dichloromethane. The mixture was washed with dilute ammonium hydroxide (3 × 10 mL), and the combined aqueous solutions were extracted with dichloromethane (3 × 5 mL). The combined organic solutions were washed with 10 mL of brine, dried ($MgSO_4$), and concentrated to yield 490 mg of a brown oil. TLC (silica; hexane/ethyl acetate, 4:1) showed two products (CAS blue) with R_f 0.72 for **20** and R_f 0.40 for **16**. Chromatography on 60 g of silica, eluting with hexanes/ethyl acetate (4:1), gave 66 mg (18%) of **20** and 200 mg (54%) of **16**, each as a clear oil.

In some experiments larger amounts of **20** were obtained, bringing the two products to a 1:1 ratio and the combined yield to 93%. On prolonged heating in benzene the isolated 14β-chlorovincadifformine (**20**) was gradually converted to unidentified polar material.

For 14α-(chloromethyl)-*D*-norvincadifformine (**16**): IR ($CHCl_3$) ν_{max} 3410, 3000, 2920, 1695, 1630, 1500, 1485, 1460, 1405, 1370, 1335, 1315, 1295, 1270, 1250, 1225, 1210, 1180, 1130, 1085, 1065, 1040, 930, 895, 820, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.79 (t, J = 7.3 Hz, 3 H), 1.00–1.37 (m, 2 H), 1.59–2.20 (m, 4 H), 2.77 (d, J = 15 Hz, 1 H), 3.05–3.67 (m, 4 H), 3.78 (s, 3 H), 6.82–7.32 (m, 4 H), 9.04 (brs, 1 H); off-resonance decoupled ^{13}C NMR ($CDCl_3$) δ 9.5 (q, C-18), 28.1 (dd, C-17), 30.5 (t, C-19), 39.0 (t, C-15), 42.3 (dd, C-6), 47.2 (s, C-20), 48.9 (dd, C-5), 51.0 (q, C-23), 52.0 (t, C-14), 57.7 (s, C-7), 68.0 (d, C-21), 79.7 (d, C-14), 90.3 (s, C-16), 109.3 (d, C-12), 121.0 (d, C-10), 122.6 (d, C-9), 128.2 (d, C-11), 136.6 (s, C-8), 143.5 (s, C-13), 163.8 (s, C-2), 168.8 (s, C-22); mass spectrum (80 eV), m/e (relative intensity) 375 (19), 374 (75), 373

(15) For an analogous procedure see R. Appel and H.-D Wihler, *Chem. Ber.*, **109**, 3446 (1976).

(16) M. S. Newman and F. W. Hetzel, *J. Org. Chem.*, **34**, 3604 (1969).

(56), 372 (100), 336 (9), 323 (1), 161 (28), 160 (69), 159 (66), 158 (87); UV (ethanol) λ_{max} 225, 298, 327 nm.

For 14β-chlorovincadifformine (**20**): IR ($CHCl_3$) ν_{max} 3380, 2990, 2965, 2900, 1680, 1615, 1470, 1445, 1380, 1315, 1280, 1255, 1185, 1140, 1095, 1050, 970, 930, 910, 885, 820, 760 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 0.62 (t, 3 H), 0.85–1.20 (m, 2 H), 1.22–1.34 (m, 1 H), 1.65–1.90 (2dd, 2 H), 2.04–2.20 (m, 2 H), 2.45–2.58 (m, 2 H), 2.60–2.75 (m, 1 H), 2.92–3.12 (m, 2 H), 3.37 (dd, 1 H), 3.78 (s, 3 H), 4.30 (m, 1 H), 6.78–7.28 (m, 4 H), 8.98 (s, 1 H); mass spectrum (80 eV), *m/e* (relative intensity) 375 (6), 374 (20), 373 (16), 372 (48), 336 (7), 323 (6), 161 (9), 160 (62), 159 (25), 158 (100); UV (ethanol) λ_{max} 225, 298, 332 nm.

(b) A mixture of 50 mg (0.14 mmol) of (hydroxymethyl)-*D*-norvincadifformine **10**, 39 mg (0.15 mmol) of triphenylphosphine, and 0.2 mL of chloroform was heated at 60 °C for 5 min. After addition of 15 μL (15.6 mmol) of carbon tetrachloride and continued heating for 45 min TLC (silica; hexanes-ethyl acetate, 4:1) showed formation of **16** with R_f 0.40 and loss of the alcohol **10**. The cooled mixture was diluted with 10 mL of dichloromethane, washed with dilute ammonium hydroxide (3 × 2 mL) and 5 mL of brine, dried (Na_2SO_4), and concentrated. The residue was slurried repeatedly with ether/hexanes (9:1) at 0 °C, and the filtered extracts were concentrated to 65 mg of residue, which was chromatographed on 5 g of silica with hexanes/ethyl acetate (4:1) to give 36 mg (68%) of **16**, identical in spectroscopic and TLC data with the product obtained above.

(c) By the same procedure, 120 mg (0.34 mmol) of 14α-hydroxyvincadifformine (**8b**) and 93 mg (0.36 mmol) of triphenylphosphine were heated initially in 0.5 mL of acetonitrile, followed by addition of 40 μL (42 mmol) of carbon tetrachloride and heating for 45 min to give 81 mg (64%) of the chloromethyl product **16**.

14α-Methyl-*D*-norvincadifformine. A solution of 35 mg (0.094 mmol) of the chloromethyl compound **16** in 1.5 mL of absolute ethanol was stirred at 55 °C under a hydrogen atmosphere with 35 mg of 5% Pd/C catalyst. A product with TLC R_f 0.15 (silica, 2% methanol in dichloromethane and exposure of the plate to NH_3 prior to development) gradually formed over 48 h. Filtration, concentration, solution of the residue in dichloromethane and washing twice with dilute ammonium hydroxide and brine gave a pale yellow oil which was column chromatographed on 5 g of silica. Elution with 2% methanol in dichloromethane yielded 12 mg of starting material **16** and 15 mg of dechlorinated product: IR ($CHCl_3$) ν_{max} 3440, 3380, 2970, 2920, 2880, 2860, 1650, 1610, 1480, 1465, 1440, 1380, 1315, 1290, 1275, 1250, 1205, 1185, 1160, 1115, 1090, 1040, 1015, 905 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (t, J = 7 Hz, 3 H), 1.00–1.20 (m, 1 H) 1.25 (d, J = 12 Hz, 3 H), 1.20–1.40 (m, 1 H), 1.56–2.22 (m, 5 H), 2.76 (d, J = 16 Hz, 1 H), 2.90–3.20 (m, 2 H), 3.30–3.41 (dt, 1 H), 3.49 (s, 1 H), 3.77 (s, 3 H), 6.80–7.40 (m, 4 H), 9.04 (s, 1 H); UV (ethanol) λ_{max} 228, 298, 330 nm.

Vincadifformine (18). (a) Triethylamine (100 μL) was added to a solution of 23 mg (0.62 mmol) of sodium borohydride in 0.2 mL of anhydrous dimethylformamide. After the mixture was stirred for 5 min at 20 °C under nitrogen, a solution of 115 mg (0.31 mmol) of (chloromethyl)-*D*-norvincadifformine **16** in 0.2 mL of dimethylformamide was added and the mixture heated at 80 °C for 4 h. TLC (silica; hexanes/ethyl acetate, 4:1) then showed loss of starting material and formation of vincadifformine with R_f 0.69 (CAS spray, blue) and a product with R_f 0.59 (CAS spray, blue-green). The reaction mixture was cooled, 10% aqueous HCl was added until effervescence ceased, and the mixture was then heated at 80 °C for 20 min. The cooled mixture was diluted with 5 mL of dichloromethane and washed with 5% aqueous ammonium hydroxide (2 × 2 mL). The aqueous washings were extracted with dichloromethane (2 × 2 mL), and the combined organic solutions were washed with 2 mL of brine, dried (Na_2SO_4), and concentrated to 110 mg. The residue was chromatographed on 15 g of silica, eluting with hexanes/ethyl acetate (4:1). The concentrated eluate (65 mg) was dissolved in ether, filtered, and concentrated to give 60 mg (57%) of vincadifformine (**18**), identified by comparison of its TLC and IR, NMR, and mass spectral data with those of a sample of the authentic alkaloid.

(b) A solution of 15 mg (0.04 mmol) of 14β-chlorovincadifformine, 53 μL (58 mg, 0.2 mmol) of tri-*n*-butyltin hydride, and a catalytic amount of azobis[isobutyronitrile] (<1 mg) in 0.4 mL of benzene was heated to reflux for 60 min. TLC analysis showed a complete conversion of starting material to vincadifformine. The reaction mixture was cooled and the solvent removed under vacuum. The oily residue was dissolved in 1 mL of acetonitrile and washed several times with 1-mL portions of hexane. On concentration of the acetonitrile fraction the oily residue crystallized slowly on standing under high vacuum to yield 9.5 mg (70.4%) of a light tan solid, mp 125–127 °C. After recrystallization from 95% EtOH the melting point was 125–126.5 °C, and the mixture melting point with authentic *dl*-vincadifformine was 125–127 °C.

5-Chloro-4-ethyl-4-hydroxypentanoic Acid 1,4-Lactone. At −78 °C chlorine was bubbled into a solution of 4.0 g (31.2 mmol) of 4-ethyl-4-pentenoic acid[17] and 4.5 mL (32.3 mmol) of triethylamine in 50 mL of dichloromethane until 2.9 g (41 mmol) of chlorine had been absorbed. After 5 min the solution was filtered and concentrated, and 100 mL of ether was added to the residue. Filtration, concentration, and distillation through a short-path apparatus gave 3.3 g (66%) of chloro lactone: bp 81–84 °C (0.02 mm); IR (film) ν_{max} 2960, 1785 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (s, 2 H), 2.80–2.00 (m, 4 H), 1.76 (q, 2 H), 0.95 (t, 3 H).

5-Bromo-4-ethyl-4-hydroxypentanoic Acid 1,4-Lactone. This was prepared analogously in 68% yield: bp 90–92 °C (0.05 mm); Ir (film) ν_{max} 2960, 1785 cm^{-1}; NMR ($CDCl_3$) δ 3.66 (s, 2 H), 2.84–2.54 (m, 2 H), 2.40–2.10 (m, 2 H), 1.92 (q, 2 H), 1.04 (t, 3 H).

Epimeric 5-(Chloromethyl)-5-ethyl-2-hydroxytetrahydrofurans (22). With rapid stirring, 67.5 mL of 1 M diisobutylaluminum hydride in hexane was added over 20 min to 10.0 g (61.5 mmol) of the above chloro lactone in 50 mL of dichloromethane at −78 °C. The reaction mixture was then poured into 300 mL of ether and 10 mL of water and stirred for 30 min. Filtration, washing of the residue with ethyl acetate, drying of the combined filtrates ($MgSO_4$), and concentration gave 9.0 g of oil which was distilled through an 8-cm column, giving 7.6 g (75%) of lactol: bp 60 °C (0.02 mm); IR (film) ν_{max} 3400, 2950 cm^{-1}; NMR ($CDCl_3$) δ 5.5 (d, 1 H), 4.50 and 4.40 (2 d, 1 H), 3.60 and 3.36 (2 s, 2 H), 2.10–1.30 (m, 6 H), 0.88 (2 t, 3 H).

Epimeric 5-(Bromomethyl)-5-ethyl-2-hydroxytetrahydrofurans (22a). These were prepared by the above procedure from the preceding bromo lactone in 51% yield: bp 70 °C (0.02 mm); IR (film) ν_{max} 3420, 2960 cm^{-1}; NMR ($CDCl_3$) δ 5.60 (d, 1 H), 4.22 and 4.10 (2 d, 1 H), 3.58 and 3.34 (2 s, 2 H), 2.30–1.52 (m, 6 H), 0.94 (2 t, 3 H); 2,4-dinitrophenylhydrazone derivative (recrystallized from 95% ethanol), mp 99–101 °C. Anal. Calcd for $C_{13}H_{17}N_4O_5Br$: C, 40.12; H, 4.40; N, 14.39; Br, 20.53. Found: C, 40.15; H, 4.34; N, 14.18; Br, 20.71.

Pandoline and 20-Epipandoline (2a,b). (a) A solution of 4.0 g (16.4 mmol) of the indoloazepine **6**, 3.4 g (21 mmol) of the chloro lactol **22**, and 100 mg of *p*-toluenesulfonic acid in 50 mL of anhydrous methanol was stirred at 20 °C under nitrogen for 24 h. TLC (silica, 2% methanol in dichloromethane, CAS spray) then showed traces of the indoloazepine (R_f 0.17, blue), predominantly two azepine-bridged intermediates (R_f 0.81, 0.33, blue turning to green) with UV λ_{max} (MeOH) 225, 295, and 328 nm, pandoline (**2a**; R_f 0.85, blue), and epipandoline (**2b**; R_f 0.64, blue). In ethyl acetate the following values were obtained: pandoline, R_f 0.90; epipandoline, R_f 0.80; bridged azepine intermediates, R_f 0.66, 0.11; indoloazepine **6**, R_f 0. Addition of 3 mL (21 mmol) of triethylamine and heating at reflux for 48 h resulted in complete conversion of the intermediates to pandoline and 20-epipandoline. The cooled reaction mixture was concentrated under vacuum and the residue partitioned between 100 mL of dichloromethane and 50 mL of water basified with sodium hydroxide. Extraction of the aqueous portion with dichloromethane (2 × 50 mL), filtration of the combined organic solutions through phase-separating paper and a 5 × 5 cm column of neutral, activity I alumina, elution with dichloromethane until all product had been removed, and concentration gave a mixture of pandoline and 20-epipandoline. The alkaloids were separated on a 5 × 30 cm column of neutral, activity I alumina, eluting 2.68 g (46%) of pandoline with 1:4 ethyl acetate/hexane and 1.55 g (27%) of 20-epipandoline with 1:1 ethyl

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acetate/hexane. The 63:37 isolated product ratio was matched by HPLC [Chromanetics Spherisorb ODS reverse-phase column, methanol/acetonitrile/H_2O, 0.01 M NH_4SO_4, 0.005 M $(NH_4)_2CO_3$ (2:1:1)] analysis of the crude reaction product. The alkaloids had physical constants corresponding to those of the products previously reported in our synthesis using the epoxy aldehyde 7.[3]

(b) From a reaction mixture sealed in glass and heated at 210 °C for 30 min after addition of triethylamine were isolated 42% of pandoline and 24% of 20-epipandoline (70:30 product ratio by HPLC).

(c) A reaction analogous to part a but using the bromo lactol **20a** and with refluxing for 2 h after addition of triethylamine gave a 63:37 ratio of pandoline to 20-epipandoline.

(d) A reaction at 20 °C for 24 h after addition of triethylamine gave equal amounts of pandoline and 20-epipandoline.

(e) When 0.64 g (3.1 mmol) of the bromo lactol **20a** and 0.50 g (2.05 mmol) of the indoloazepine **6** in 20 mL of benzene were stirred under nitrogen at 47 °C for 72 h, most of the azepine reacted, and traces of pandoline and 20-epipandoline formed. Addition of 1 mL of triethylamine, continued stirring at 47 °C for 72 h, and a workup as under a gave 173 mg (24%) of pandoline and 282 mg (39%) of 20-epipandoline. HPLC of the crude alkaloid mixture showed a 33:67 ratio.

(f) An analogous reaction mixture stirred at 20 °C for 7 days after addition of triethylamine gave 176 mg (24%) of pandoline and 238 mg (33%) of 20-epipandoline, with a 36:64 ratio of isomers in the crude reaction product.

(g) A solution of 950 mg (3.0 mmol) of the epoxy aldehyde **7** (at least 40% pure by NMR)[3] and 400 mg (1.6 mmol) of the indoloazepine **6** in 20 mL of benzene was held at 47 °C under nitrogen for 4 days and then worked up as under a to give 110 mg (19%) of pandoline and 244 mg (42%) of 20-epipandoline. The crude reaction product showed a 31:69 HPLC ratio of these alkaloids.

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Registry No. 1, 21217-98-1; **2a**, 73824-79-0; **2b**, 73805-38-6; **6**, 66859-22-1; **7**, 80641-93-6; **8a**, 80695-59-6; **8a**·HCl, 80695-60-9; **8a** acetate, 80695-61-0; **8b**, 80695-62-1; **8b**·HCl, 80695-63-2; **8b** 3,5-dinitrobenzoate, 80641-94-7; **8b** acetate, 80695-64-3; **8b** 14-thiocarbamate, 80641-95-8; **9**, 74129-84-3; **10**, 80779-26-6; **10** acetate, 80658-38-4; **11a**, 80665-38-9; **14**, 80642-07-5; **14** hydrazone, 80642-08-6; **16**, 80658-39-5; **18**, 18374-17-9; **19**, 80642-05-3; **19** hydrazone, 80642-06-4; **20**, 80641-96-9; **22**, 80641-97-0; **22a**, 80641-98-1; **22a** hydrazone, 80641-99-2; ethyl 2-ethyl-4-pentenoate, 80642-00-8; methyl 2-ethyl-4-pentenoate, 42998-02-7; ethyl 4,5-epoxy-2-ethylpentanoate, 80642-01-9; methyl 4,5-epoxy-2-ethylpentanoate, 74121-06-5; 2-ethyl-4-pentenoic acid, 1575-73-1; 2-ethyl-4-pentenoic acid *p*-toluamide derivative, 80642-02-0; 5-chloro-2-ethyl-4-hydroxypentanoic acid 1,4-lactone, 80642-03-1; methyl 4,5-dichloro-2-ethylpentanoate, 80642-04-2; 14α-methyl-*d*-norvincadifformine, 80658-40-8; 5-chloro-4-ethyl-4-hydroxypentanoic acid 1,4-lactone, 80642-09-7; 5-bromo-4-ethyl-4-hydroxypentanoic acid 1,4-lactone, 80642-10-0.

Notes

Chiral Intermediates from Aucubin as Synthons of Modified 11-Methylprostaglandins. Assignment of Correct Structures to Two Tetrahydrodideoxyaucubins

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Current interest in the field of prostaglandins is focused on obtaining optically active intermediates without resolution. To this end many important syntheses starting from natural chiral compounds with appropiate asymmetric centers have been carried out.[2,3] In particular, one industrial research group leaded by Ohno has recently patented an original conversion of aucubin **1**, the predominant naturally occuring iridoid glucoside, to 11-deoxy-11-α-(hydroxymethyl)prostaglandin F_2 and related compounds.[4] Furthermore, Berkowitz et al.[5] have carried out two syntheses of chiral prostaglandin intermediates from aucubin and asperuloside.

With our recent interest in the iridoid chemistry,[6] we have developed new routes[7] to prostaglandin synthons from aucubin, which is easily obtained from *Aucuba japonica* and *Eucommia ulmoides*.

Our approach is outlined in Scheme I, where we describe our procedure to obtain **8** and **9** which can be considered key intermediates in obtaining, by standard procedures, modified analogues of 11-methylprostaglandins.

Our starting material was the known dideoxytetraacetylaucubin **3**,[8] obtained by Li/NH_3 reduction at −40 °C of aucubin **1** and subsequent acetylation of **2**.

To obtain compounds **4** and **5**, we used a procedure described by Berkowitz[5] which in the case of dideoxytetraacetylaucubin turned out to be very efficient. The use of anhydrous Me_2SO yielded a bromohydrin-free mixture of bromo lactones **4** which were directly reduced (Zn/AcOH) without purification to compound **5** (95% overall yield).

The key step of the reduction of the double bond in compound **5** presented much difficulty, probably because of the bulky glucose moiety.

We obtained good results by sterespecific reduction in the following manner: compound **6** (α-methyl group epimer at C_8) was obtained by PtO_2 reduction in MeOH at

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