Preparation and H(3) Isomerization of C(15)-Substituted Deplancheine Derivatives. Synthesis of Geissoschizol and Geissoschizine

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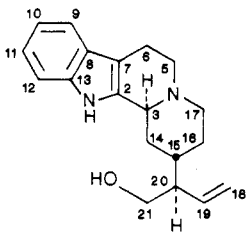
A series of indolo[2,3-*a*]quinolizidines have been prepared by the two-step scheme of nucleophile addition to 1-tryptophyl-3-acylpyridinium salts or their vinylogues and subsequent, acid-catalyzed cyclization. Acid-induced hydrolysis, decarboxylation, and reduction of the resultant vinylogous urethanes has opened an approach to antirhine and yielded C(15)-substituted deplancheine derivatives. Functional group manipulation of the latter has permitted the syntheses of geissoschizol and geissoschizine.

Indole alkaloids structurally based on the indolo[2,3-*a*]quinolizidine nucleus have been synthesized for some time by the reaction sequence illustrated in Scheme I.[1] Functional-group manipulations on several thus-prepared tetracycles now have opened a route toward antirhine (**1**) and led to syntheses of geissoschizol (**2**) and geissoschizine (**3**).



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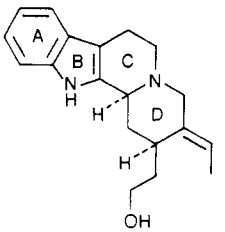

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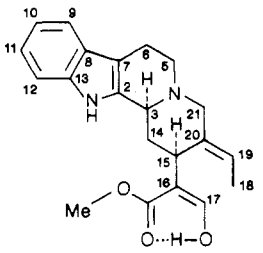

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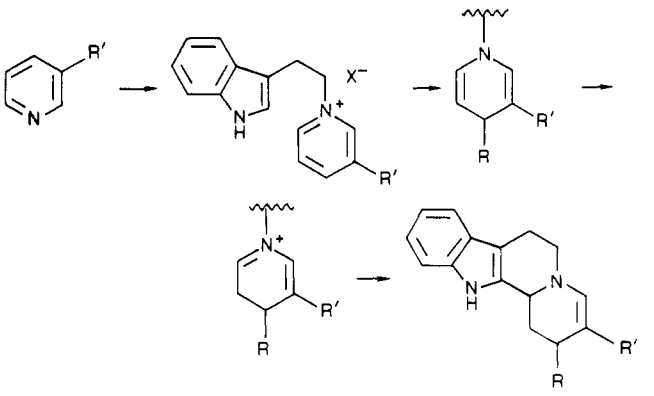
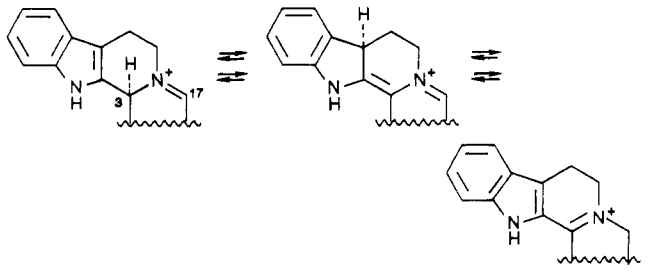
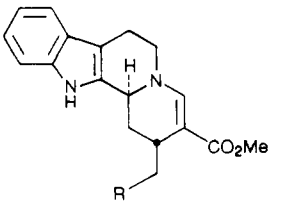
Antirhine Model. A recent application of Scheme I (starting with methyl nicotinate) has furnished readily tetracycle **4a**,[2] which now has been converted into alcohol **4b** on reduction with lithium aluminum hydride. The product appeared to be suited ideally for transformation into devinylantirhine (**5a**) on recognition of the fact of acid treatment of the vinylogous urethane (i.e. proton addition at the α-position, hydrolysis of the deconjugated ester, decarboxylation of the α-carboxyiminium salt, and protonation of the resultant enamine) and reduction of the resultant iminium salt with sodium borohydride yielding a decarbomethoxylated, dihydro piperidine unit.[3,4] Hydrolysis of tetracycle **4b** with methanolic barium hydroxide, decarboxylation of the resultant vinylogous carbamic acid in 0.1 N aqueous hydrochloric acid at room temperature, and borohydride reduction of the H(17)–N_b dehydro iminium salt resulted in the formation of devinylantirhine (**5a**). However, hydrolysis of vinylogous urethane **4b** in refluxing 4.0 N aqueous hydrochloric acid solution and subsequent borohydride reduction afforded 3-epidevinylantirhine (**5b**). Whereas these observations were precedented in the 18,19-dihydroantirhine series,[4] the isomerization of a H(17)–N_b dehydro iminum salt into one of H(3)–N_b dehydro structure, implicit in the last reaction sequence, is rare in unactivated cases. The isomerization under the harsher reaction condition can be explained most easily by invoking indole participation through its tau-

Scheme I

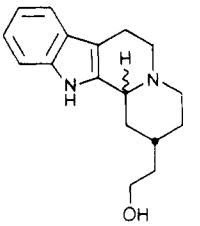


Scheme II





4a: R = CO_2Et
b: R = CH_2OH



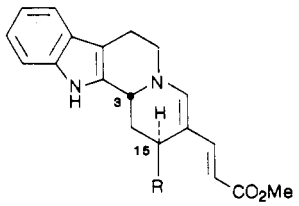
5a, H(3α)
b, H(3β)

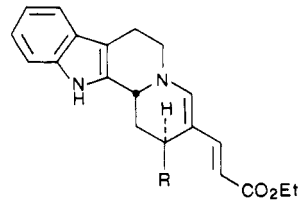
(1) (a) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. (b) Wenkert, E. *Heterocycles* **1984**, *21*, 325.
(2) Wenkert, E.; Angell, E. C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. St.; Shi, Y.-J.; Sultana, M.; Vankar, Y. D. *J. Org. Chem.* **1986**, *51*, 2995.
(3) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461.
(4) De Silva, K. T. D.; Smith, G. N.; Warren, K. E. H. *Chem. Commun.* **1971**, 905.

0022-3263/89/1954-1166$01.50/0

tomer (Scheme II).[5] The ready preparation of devinylantirhine (**5a**) from alcohol **4b** indicates that the alkaloid itself (**1**) can be reached from a starting compound **4**, whose C(15) substituent is a butenol moiety or its equivalent.[6]

Preparation of C(15)-Substituted Deplancheine Derivatives. A number of doubly vinylogous urethanes, related to compounds **4**, have become available in the recent past as a consequence of the use of methyl (or ethyl) β-(β-pyridyl)acrylate as the sequence-initiating pyridine in Scheme I. Thus, for example, tetracycle **6a** has been prepared by the N-alkylation of the methyl ester with tryptophyl bromide, treatment of the salt with dimethyl sodiomalonate, and acid-induced cyclization of the resultant 1,4-dihydropyridine and became an important intermediate en route to the yohimboid alkaloids.[9] Tetracycles **6b**,[2,10] **6c**,[2,10] **7b**, and **7c**[8] have been prepared by related chemistry and treatment of the thioethers **6c** and **7c** with Raney nickel now has yielded tetracycles **6d** and **7d**, respectively.





6a: R = $CH(CO_2Me)_2$
b: R = CCl_3
c: R = $CH(SMe)CO_2Et$
d: R = CH_2CO_2Et

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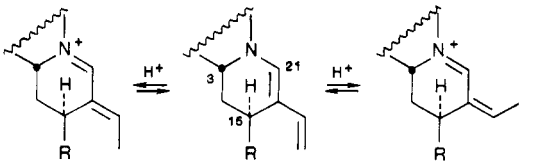
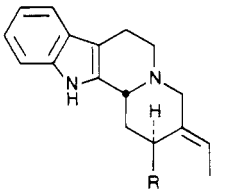
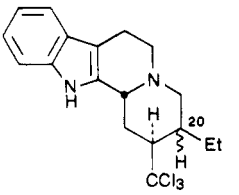
In analogy with the above **4b** → **5a** transformation acid-catalyzed hydrolysis and decarboxylation of chloride **6b**, followed by borohydride reduction, had yielded earlier 15-(trichloromethyl)deplancheine (**8a**),[2,10] a compound that now became also the product of the same degradation of chloride **7b**. When sodium cyanoborohydride was used as the reducing agent in the last step, a ca. 1:1 mixture of chlorides **9a** and **9b** was obtained. Acid-induced hydrolysis and didecarboxylation (i.e., of the malonic and vinylogous β-iminocarboxylic acid moieties) of ester **6a**, esterification with methanolic hydrogen chloride, and sodium borohydride reduction led to ester **8c**.[11] Identical treatments of ester **6d** and **7d** yielded the same product (**8c**).[12] The preparation of ester **8c** (deformyl-3-isogeissoschizine) constitutes a formal total synthesis of (±)-geissoschizine (**3**) in light of a previous conversion of the ester into the alkaloid by sequential mercuric acetate oxidation, zinc–acetic acid reduction and ester α-formylation.[13]

Scheme III







8a: R = CCl_3
b: R = $CHCl_2$
c: R = CH_2CO_2Me
d: R = CH_2CH_2OH

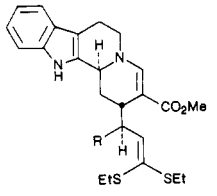
9a, H(20α)
b, H(20β)

The stereochemistry of the ethylidene unit of compounds **8a** and **8c** was as shown in the formulas and depended on a later tie-up of ester **8c** with geissoschizine (**3**), an alkaloid of known configuration. The exclusive formation of the *E* isomer of **8** in all cases of hydrolysis, decarboxylation, and reduction of trans H(3)–H(15) doubly vinylogous urethanes of type **6** (including a C(15)-unsubstituted example) can be explained readily, if it is assumed that an equilibrium between two iminium salts (Scheme III) is established just prior to the borohydride reduction. The cations would be expected to be composed of two half-chair piperideine rings in a *trans*-quinolizideine framework holding a quasi-axial C(15) substituent and maintaining the α,β-unsaturated iminium ion in coplanar form. In such a configuration the methyl group faces much less steric interference when oriented toward the quasi-equatorial H(15) than when oriented toward H(21).

15-(Trichloromethyl)deplancheine (**8a**) required conversion into a dichloromethyl compound of cis H(3)–H(15) constitution, in order to serve as an intermediate en route to the alkaloids of the pleiocarpamine and/or strictamine types. Reduction of trichloride **8a** with zinc in acetic acid yielded dichloride **8b**.[14] For reasons soon to become apparent the following modifications of the acetic ester side chain of ester **8c** were executed. Lithium aluminum hydride reduction of the ester gave known 3-isogeissoschizol (**8d**).[13,15] Condensation of the ester with methyl formate

(5) Wenkert, E.; Moeller, P. D. R.; Shi, Y.-J. *J. Org. Chem.* **1988**, *53*, 2383.

(6) The recent construction of ester i in connection with the synthesis of the alkaloid vallesiachotamine[7] and its transformation into alcohol ii on reduction with lithium aluminum hydride[8] makes such a starting material available.



i: R = CO_2Et
ii: R = CH_2OH

(7) Spitzner, D.; Zaubitzer, T.; Shi, Y.-J.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 2274.

(8) Wenkert, E.; Shi, Y.-J., unpublished observations.

(9) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 5370; **1982**, *104*, 6166.

(10) For improvement of the previous yield of this substance,[2] see the Experimental Section.

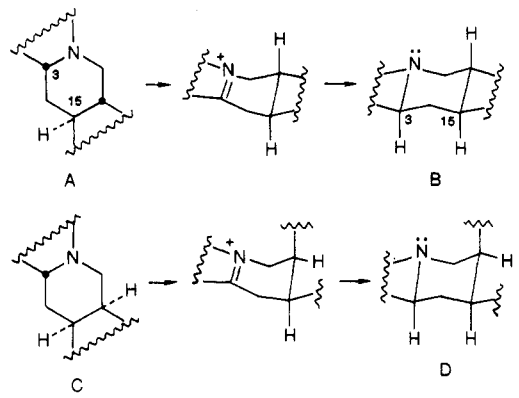
(11) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.* **1980**, *102*, 7971.

(12) For other examples of 6 → 8 transformations, see: (a) Besselièvre, R.; Cosson, B.-P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *63*. (b) Bosch, J.; Bennasar, M.-L.; Zulaica, E.; Feliz, M. *Ibid.* **1984**, 3119. (c) Alvarez, M.; Lavilla, R.; Bosch, J. *Ibid.* **1987**, 4457. (d) Bennasar, M.-L.; Zulaica, E.; Lopez, M.; Bosch, J. *Ibid.* **1988**, 2361.

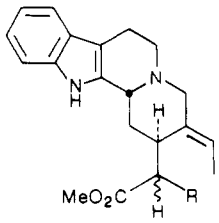
(13) Yamada, K.; Aoki, K.; Kato, T.; Uemura, D.; van Tamelen, E. E. *J. Chem. Soc., Chem. Commun.* **1974**, 908.

(14) When the reduction was carried out at 50 °C, but otherwise identically, it led to dichloride **8b** (23%), 15-methyldeplancheine (**8**, R = Me) (ca. 19%), and 15-(chloromethyl)deplancheine (**8**, R = CH_2Cl) (27%): mp 86–88 °C ($CHCl_3$–MeOH); UV λ_{max} 224 nm (log ε 4.31), 2.64 (3.80), $\lambda_{shoulder}$ 279 (3.77), 290 (3.66); IR (CH_2Cl_2) NH 3460 (m), CH 2740 (m), 2800 (m) cm^{-1}; ^1H NMR δ 1.68 (d, 3, *J* = 7 Hz, Me), 1.7–1.9 (m, 1, H-14), 2.4–3.4 (m, 8, methylenes, methines), 3.52 (d, 1, *J* = 12 Hz, H-3), 3.5–3.7 (m, 1, H-15), 3.7–3.8 (m, 1, H-16), 5.61 (q, 1, *J* = 7 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); ^{13}C NMR δ 13.1 (C-20), 21.5 (C-6), 32.1 (C-14), 37.5 (C-15), 44.1 (C-16), 52.2 (C-5), 54.8 (C-3), 60.1 (C-21), 108.7 (C-7), 110.6 (C-12), 118.2 (C-9), 119.3 (C-10), 121.5 (C-11), 126.9 (C-8), 129.2 (C-19), 131.2 (C-18), 133.2 (C-2), 134.7 (C-13); exact mass *m/e* 300.1392 (calcd for $C_{18}H_{21}{}^{35}ClN_2$ *m/e* 300.1390).

Scheme IV



under the influence of lithium diisopropylamide yielded aldehydo ester **10a** (in keto and enol forms), whose exposure to methanolic acid afforded acetal ester **10b**. Reduction of aldehyde **10a** with sodium borohydride in methanol solution afforded a C(16) epimer mixture of hydroxy esters **10c**. Compounds with these structures were reported recently to be indole alkaloids bhimberine (**10c**, α-H(16))[16] and rhazimanine (**10c**, β-H(16)).[17] However, spectral analysis of hydroxy esters **10c** and comparison of the data with those of two natural products showed the latter not to possess the **10c** configurations. Thus the infrared spectra of hydroxy esters **10c** revealed Wenkert–Bohlmann bands at 2740, 2800, and 2850 cm^{-1}, characteristic of an axial bridgehead hydrogen within a *trans*-quinolizidine skeleton and missing from the infrared spectra of the natural bases.[18] Further, the ^1H NMR spectra of esters **10c** exhibit the H(3) signal upfield of 3.8 ppm, characteristic of a *trans*-quinolizidine conformation, whereas the δ(H-3) values of 4.29 and 4.36 ppm of bhimberine and rhazimanine reflect a *cis*-quinolizidine structure.[19] Finally, esters **10c** possess δ(C-6) values of 21.5 and 22.6 ppm and δ(C-21) values of 60.2 and 59.8 ppm, indicative of *trans*-indoloquinolizidine orientations, whereas the two alkaloids show *cis*-indoloquinolizidine δ(C-6) values of 18.1 and 18.0 ppm and δ(C-21) values of 51.9 and 53.8 ppm.[20]



10a: R = CHO
b: R = $CH(OMe)_2$
c: R = CH_2OH

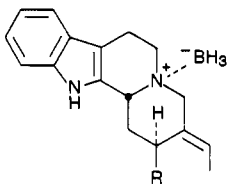
H(3) Isomerizations. Standard H(3) isomerization of indolo[2,3-*a*]quinolizidine-based indole alkaloids has depended mostly on oxidation–reduction processes, in which the oxidations involved reactions with mercuric acetate,[21] *tert*-butyl hypochlorite and subsequently acid,[22] or peracid and thereafter trifluoroacetic anhydride,[11] and the reductions were executed usually with methanolic sodium borohydride.[21] In this manner it has been possible to convert *pseudo* (A) and *epiallo* (C) isomers into *normal* (B) and *allo* (D) products, respectively, i.e. H(3)–H(15) trans compounds into H(3)–H(15) cis substances (Scheme IV).[21] These results can be justified on the basis of the reduction of the intermediate 3-dehydro salts proceeding via a transition state in which the incipient H(3)–C(3) bond and N_b-electron pair p orbital are aligned in a trans diaxial, coplanar array within a ring D chairlike conformation.

Ester **8c** could be oxidized with *tert*-butyl hypochlorite and the resultant β-chloroindolenine dehydrochlorinated with trifluoroacetic acid. Reduction of the 3-dehydro product with sodium borohydride in methanol reliberated ester **8c**. At first glance, this result was quite surprising, since it represented an iminium salt reduction leading to a H(3)–H(15) trans compound.[23]

Oxidation of chlorides **8a** and **8b** and esters **8c** and **10b** with *m*-chloroperbenzoic acid and dehydration with trifluoroacetic anhydride afforded 3-dehydro compounds, whose reduction with sodium borohydride in tetrahydrofuran yielded two products each. The major products of each reduction exhibited H(3) and C(6) NMR signals reminiscent of *cis*-quinolizidine conformations and hence of substances of the desired H(3)–H(15) cis configuration. However, further analysis showed these materials to be not even amines, but, instead, amine–borane complexes. The latter were fairly stable and hence separable on silica column chromatography, decomposing slowly in chloroform solution or protic solvents.[24] The stability of the complexes was illustrated best by the maintenance of the structure of the amine–borane subunit during the conversion of complex 11 (R = CH_2CO_2Me) into complex 11 (R = CH_2CH_2OH) by lithium aluminum hydride reduction. Exposure of the amine boranes to hydrochloric acid in acetone liberated the free amines, while treatment of the latter with borane–tetrahydrofuran complex in tetrahydrofuran regenerated the amine boranes. Thus borohydride reduction of the iminium salts in the aprotic solvent tetrahydrofuran had yielded amine boranes **11** and **12** in a ratio of ca. 4:1 (except for the products derived from chloride **8a**).[25] Furthermore, the borane unit of complexes **11** had imposed a positive charge on N_b, thus deshielding H(3) in the ^1H NMR spectrum, and a γ-shift on C(6), thus shielding the latter in the ^{13}C NMR spectrum. These effects caused early confusion in the determination of product structures in view of the interpretability of the NMR signals as reflecting free amines with *cis*-quinolizidine conformation. The presence of the borane unit,

(15) (a) Dastoor, N. J.; Gorman, A. A.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 213. (b) Rackur, G.; Winterfeldt, E. *Chem. Ber.* **1976**, *109*, 3837.
(16) Atta-ur-Rahman; Habib-ur-Rehman; Malik, S. *Heterocycles* **1986**, *24*, 703.
(17) Atta-ur-Rahman; Malik, S.; Habib-ur-Rehman *Phytochemistry* **1986**, *25*, 1731.
(18) (a) Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417; **1958**, *80*, 1613. (b) Bohlmann, F. *Angew. Chem.* **1957**, *69*, 641; *Chem. Ber.* **1958**, *91*, 2157.
(19) (a) Rosen, W. A.; Shoolery, J. N. *J. Am. Chem. Soc.* **1961**, *83*, 4816. (b) Wenkert, E.; Wickberg, B.; Leicht, C. L. *Ibid.* **1961**, *83*, 5037. (c) Wenkert, E.; Wickberg, B.; Leicht, C. L. *Tetrahedron Lett.* **1961**, 822. (d) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962**, *84*, 4914.
(20) Wenkert, E.; Chang, C-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645; **1982**, *104*, 6166.
(21) (a) Weisenborn, F. L.; Diassi, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 2022. (b) Wenkert, E.; Roychaudhuri, D. K. *J. Org. Chem.* **1956**, *21*, 1315. (c) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373 and ref 12 therein.
(22) Godtfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1956**, *10*, 1414.
(23) (a) Sodium borohydride reduction of *O*-acetyl-3-dehydro-**8d** in isopropyl alcohol has been reported to yield 3-isogeissoschizol acetate (*O*-acetyl-**8d**) (53%) and geissoschizol acetate (*O*-acetyl-**2**).[15b] (b) Zinc–acetic acid reduction of ester 3-dehydro-**8c** has led to esters **8c** (70%) and 3-iso-**8c** (8%), and a similar reduction of 3-dehydrogeissoschizol (3-dehydro-**8d**) has furnished 3-isogeissoschizol (**8d**) (31%) and geissoschizol (**2**) (27%).[13]
(24) Cf. Lane, C. F. *Aldrichimica Acta* **1973**, *6*, 51.
(25) For an example of amine borane formation on borohydride reduction of imines see the comment by A. Pelter and K. Smith ("Boron-Hydrogen Compounds") In Barton, D. H. R.; Ollis, W. D. *Comprehensive Organic Chemistry*; Pergamon Press: Oxford, 1979; Vol. 3, p 766 (A. Pelter and W. Paget, unpublished observations).

however, was confirmed by boron–hydrogen infrared absorption bands at 2280, 2340, 2380, and 2410 cm^{-1}, by the presence of a boron quartet ($^1J_{BH}$ = 114 Hz) at −12.0 ppm (with reference to the Et_2OBF_3 boron resonance) in the ^{11}B NMR spectrum of ester **11** (R = CH_2CO_2Me),[26] and by a quantitative boron determination via the elemental analysis of chloride **11** (R = CCl_3).



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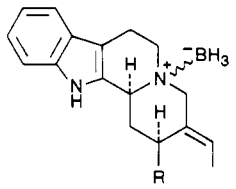

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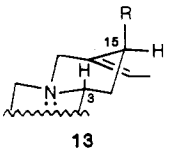
The ^1H and ^{13}C NMR spectral data of the C(15)-substituted deplancheine derivatives were conformationally most revealing. The H(3)–H(15) trans compounds **8a–d** possess the *trans*-quinolizidine conformation **13** on the basis of their C(3), C(6), and C(21) shifts of ca. 54.8, 21.4, and 60.0 ppm, respectively (compared with 60.0 ± 1.0, 21.5 ± 0.5, and 60.0 ± 1.0 ppm, respectively, for compounds of *normal* conformation (B)[20]), carbon 3 being shielded by a γ-effect from the axial C(15) substituent. The H(3) shift being upfield of 3.6 ppm (except for the δ(H-3) 4.38 ppm value of the trichloride **8a** due to the anisotropic deshielding by the chlorine facing H(3)) also is in accord with conformational structure **13**.[19] The amine boranes (**11**) of compounds **8a–d** maintain the conformation (**14**) of amines, as indicated by ca. 56.7, 19.0, and 65.0 ppm shifts for carbons 3, 6, and 21, respectively. Borane complexation thus causes deshielding of carbons 3 and 21 by a combination of a β-effect and imposition of a positive charge on N_b as well as mild shielding of carbon 6 due to a γ-effect from boron.



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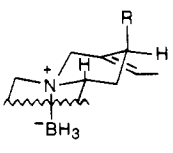

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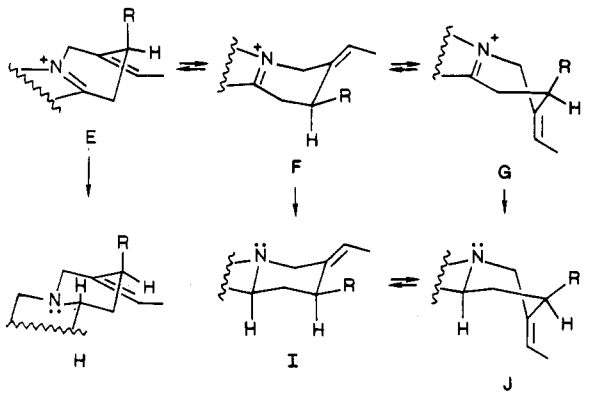
The conformational picture of the H(3)–H(15) cis compounds is more complex. Whereas chloride **15a** is a *trans*-quinolizidine in solution, ester **15c** and alcohol **2** appear to be *cis*-quinolizidines. The *trans*-quinolizidine form of chloride **15a** is substantiated by the compound's infrared absorption bands[18] at 2765, 2795, and 2835 cm^{-1} and its C(6) NMR shift of 21.4 ppm. Since the trichloromethyl group cannot adopt an equatorial orientation within a chairlike ring D because of the energetically unfavorable, nonbonded interaction of the olefinic methyl group with equatorial C(15) substituents, ring D must assume a boat (or quasi-boat) conformation. Hence chloride **15a** may be portrayed as in formula **16**.[27,28] The

Scheme V



ring D distortion may account for the anomalous δ(C-3) and δ(C-21) values. This *cis*-quinolizidine conformation for the H(3)–H(15) cis compounds **2** and **15c** was established by their lacking Wenkert–Bohlmann infrared absorption bands,[18] by the downfield position of their H(3) NMR signal (4.25 ppm)[19] as well as the low multiplicity of the latter (singlet) representative of the bridgehead hydrogen being equatorial to ring D,[30] and, finally, by the appearance of 53.3 and 18.0 ppm C(3) and C(6) signals in the ^{13}C NMR spectra (53.5 ± 0.5 and 16.5 ± 0.5 ppm resonances, respectively, being the expected carbon shifts of *cis*-quinolizidine-containing *pseudo* compounds (A)[20]). Since the ^{13}C NMR spectra of the two compounds are nearly identical (in all relevant positions) with those of several, naturally occurring, H(3)–H(15) cis, C(15)–substituted deplancheine derivatives—geissospermine,[31] usambarensine,[32] 5,6-didehydrousambarensine,[32] and 16-epiisositsirikine[33]—these alkaloids must have a *cis*-quinolizidine form in solution. By analogy with the conformation of geissospermine in the crystalline state[34] conformation **17** can be proposed for compounds **2** and **15c**.[31]

As indicated above, the oxidation–reduction sequence on H(3)–H(15) trans amines **8** and **10** led to trans–cis product mixtures containing mostly starting amines, in contrast to the formation of exclusively H(3)–H(15) cis products on borohydride reduction of 3-dehydro derivatives of *pseudo* (A) or *epiallo* (B) compounds (Scheme IV). This, at first glance, unusual result can be interpreted on the basis of the following arguments. The 3-dehydro oxidation products of amines **8** and **10** can adopt at least

(26) (a) Gaines, D. F.; Schaeffer, R. *J. Am. Chem. Soc.* **1964**, *86*, 1505. (b) Hertsch, C. W. *Inorg. Chem.* **1965**, *4*, 1019.

(27) It is noteworthy that geissoschizine (**3**) is a *trans*-quinolizidine in the crystalline state [Chiaroni, A.; Damak, M.; Ahond, A.; Riche, C. Abstr. 64, Journées de Chimie Organique, Orsay, France, September 7–9, 1977].

(28) The recorded[29] ^{13}C NMR spectral data and the following ^1H NMR spectral information on *O*-methylgeissoschizine (*O*-methyl-**3**) suggest that this alkaloid also may have conformation **16**: ^1H NMR δ 1.56 (d, 3, *J* = 7 Hz, Me), 1.90 (dm, 1, *J* = 12 Hz, H-14α), 2.34 (ddd, 1, *J* = 12, 12, 11 Hz, H-14β), 2.6–2.8 (m, 2 CH_2), 2.9–3.2 (m, 2, CH_2), 3.16 (d, 1, *J* = 12 Hz, H-21β), 3.44 (d, 1, *J* = 12 Hz, H-21α), 3.52 (br d, 1, *J* = 11 Hz, H-3), 3.71 (br d, 1, *J* = 12 Hz, H-5), 3.72 (s, 3, ester OMe), 3.82 (s, 3, ether OMe), 5.43 (q, 1, *J* = 7 Hz, H-19), 7.0–7.2 (m, 2, Ar Hs), 7.28 (d, 1, *J* = 7 Hz, H-9), 7.36 (s, 1, H-17), 7.47 (d, 1, *J* = 7 Hz, H-12).

(29) Damak, M.; Ahond, A.; Potier, P.; Janot, M.-M. *Tetrahedron Lett.* **1976**, 4731.

(30) Trager, W. F.; Lee, C. M.; Beckett, A. H. *Tetrahedron* **1967**, *23*, 365.

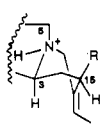
(31) Goutarel, R.; Païs, M.; Gottlieb, H.; Wenkert, E. *Tetrahedron Lett.* **1978**, 1235.

(32) Coune, C. A.; Angenot, L. J. G.; Denoël, J. *Phytochemistry* **1980**, *19*, 2009.

(33) Van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Planta Med.* **1983**, *47*, 83.

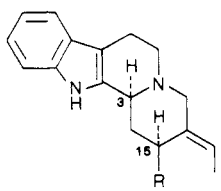
(34) Chiaroni, A.; Riche, C.; Païs, M.; Goutarel, R. *Tetrahedron Lett.* **1976**, 4729.

(35) It is difficult to propose a conformation for the amine boranes **12** (R = CH_2CO_2Me or CH_2CH_2OH) or the naturally occurring N_b-metho bases 5,6-didehydro-4-methylusambarensine[32] and diploceline[32] in view of the report of conformer iii representing usambarensine hydrobromide in the crystalline state.[36]

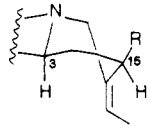


iii

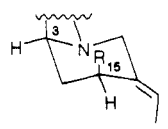
(36) Dideberg, P. O.; Dupont, L.; Angenot, L. *Acta Crystallogr.* **1975**, *B31*, 1571.



15a: R = CCl_3
b: R = $CHCl_2$
c: R = CH_2CO_2Me
d: R = $CH(CO_2Me)CH(OMe)_2$



16



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three conformations—E, F, and G (Scheme V). Borohydride reduction within the aforementioned stereoelectronic constraints would transform E (half-chair with axial C(15) substituent) into a trans product (H), F (half-chair with equatorial C(15) substituent) into a cis product (I ⇄ J), and G (half-boat) also into a cis product (J ⇄ I). Whereas E is the predominant conformer in solution, its reduction must be slower than that of its equilibrants in view of the steric interference of the axial hydride attack by the axial C(15) substituent. Thus a subtle balance is struck between the concentrations of the iminium ion conformers and the reduction rates, leading to the observed data.

Geissoschizol and Geissoschizine. While no difficulty was encountered in liberating trichloride **15a** from its amine borane, the dichloride **15b** proved to be unstable and decomposed on isolation from the product mixture of the reaction of its amine borane with aqueous hydrochloric acid in acetone. This reproducible but unpredicted behavior of dichloride **15b** blocked its use in the projected synthesis of alkaloids of the pleiocarpamine and/or strictamine types.

Reduction of ester **15c** with lithium aluminum hydride yielded (±)-geissoschizol (**2**).[37] Acid-catalyzed hydrolysis of acetal **15d** gave (±)-geissoschizine (**3**).[38]

Experimental Section

Melting points were determined on a Reichert micro hotstage and are uncorrected. Ultraviolet spectra were recorded on methanol solutions and infrared spectra on chloroform solutions. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions and ^{11}B NMR spectra of tetrahydrofuran (THF) solutions were obtained at 300, 75.5, and 96.2 MHz, respectively, in the Fourier transform mode. Complete ^1H and ^{13}C NMR spectral assignments of the reaction products were obtained by COSY NMR and ^{13}C–^1H correlated spectroscopies. The carbon shifts are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. All reactions were carried out under a nitrogen atmosphere, and all methylene chloride extracts of crude reaction mixtures were washed with brine and dried over anhydrous Na_2SO_4. Column chromatography was performed on 60–200 mesh, type H silica gel (Davison Chemical Co.). Medium-pressure chromatography was executed on Merck Lobar (A, B, or C) silica gel columns with the help of a Fluid Metering, Inc. Pump. The purity of all title compounds was shown to be >95% by ^1H and ^{13}C NMR spectral analyses.

Alcohol 4b. A mixture of 359 mg (0.98 mmol) of ester **4a** and 60 mg (1.6 mmol) of lithium aluminum hydride in 15 mL of anhydrous THF was stirred at 0 °C for 2 h. Hydrochloric acid (5 mL of 1 N) was added, and the mixture was extracted. Evaporation of the extract yielded 270 mg (85%) of colorless, crystalline alcohol **4b**: mp 166–168 °C (Et_2O–acetone); UV λ_{max} 222 nm (log ϵ 4.40), 291 (4.50); IR NH 3455 (m), OH 3280 (br w), C=O 1655 (s), 1610 (s), C=C 1590 (s) cm^{-1}; ^1H NMR δ 1.5–2.0 (m, 3, H-14, 2 H-20), 2.32 (br d, 1, J = 12 Hz, H-14), 2.7–3.0 (m, 2, 2 H-6), 3.0–3.1 (m, 1, H-15), 3.5–3.8 (m, 4, 2 H-5, OCH_2), 3.70 (s, 3, OMe), 4.55 (br d, 1, J = 11 Hz, H-3), 7.09 (t, 1, J = 7 Hz, H-11), 7.15 (t, 1, J = 7 Hz, H-10), 7.35 (d, 1, J = 7 Hz, H-9), 7.46 (d, 1, J = 7 Hz, H-12), 7.59 (s, 1, olefinic H); ^{13}C NMR δ 21.9 (C-6), 26.3 (C-15), 33.7 (C-14), 40.4 (C-20), 47.9 (C-3), 50.8 (OMe), 51.0 (C-5), 59.7 (C-21), 95.7 (C-16), 107.6 (C-7), 111.1 (C-9), 119.3 (C-10), 121.7 (C-11), 126.5 (C-8), 132.6 (C-2), 136.3 (C-13), 146.9 (C-17), 170.2 (C=O); MS m/e 326 (M^+, 45), 281 (base); exact mass 326.1611 (calcd for $C_{19}H_{22}O_3N_2$ 326.1628).

Devinylantirhine (5a). A solution of 130 mg (0.4 mmol) of alcohol **4b** in 10 mL of 1 N methanolic barium hydroxide was stirred at room temperature for 72 h and then diluted with 15 mL of water and 5 mL of ethyl acetate. Hydrochloric acid (3 mL of 1 N) was added to the aqueous layer, and the solution was stirred at room temperature for 48 h. The mixture was poured into 20 mL of saturated sodium bicarbonate solution and extracted. The extract was dried and evaporated, and the residue was dissolved in 10 mL of methanol. Sodium borohydride (50 mg, 1.3 mmol) was added slowly at 0 °C to the stirring solution, and the stirring was continued at this temperature for 1 h. The mixture was poured into 15 mL of aqueous sodium bicarbonate solution and extracted. The extract was washed, dried, and evaporated. Chromatography of the residue on neutral alumina (activity III) and elution with 50:1 chloroform–methanol afforded 30 mg (28%) of colorless, crystalline alcohol **5a**: mp 215–217 °C ($CHCl_3$–hexane); ^1H NMR (MeOH-d_4) δ 1.5–3.2 (m, 13, methylenes, CH), 3.61 (t, 2, J = 6 Hz, OCH_2), 3.94 (br s, 1, H-3), 6.95 (t, 1, J = 7 Hz, H-11), 7.02 (t, 1, J = 7 Hz, H-10), 7.27 (d, 1, J = 7 Hz, H-9), 7.36 (d, 1, J = 7 Hz, H-12); ^{13}C NMR (DMSO-d_6) δ 20.1 (C-6), 27.5 (C-15), 30.1 (C-16), 33.6 (C-14), 35.6 (C-20), 48.7 (C-17), 52.3 (C-5), 54.3 (C-3), 58.8 (C-21), 106.2 (C-7), 110.9 (C-12), 117.3 (C-9), 118.2 (C-10), 120.2 (C-11), 126.9 (C-8), 135.4 (C-2), 135.7 (C-13); MS m/e 270 (M^+, 83), 269 (base); exact mass 270.1721 (calcd for $C_{17}H_{22}ON_2$ 270.1730).

3-Epidevinylantirhine (5b). A suspension of 213 mg (0.65 mmol) of alcohol **5a** in 10 mL of a 4 N hydrochloric acid solution was stirred and refluxed for 5 h. The resultant solution was evaporated to dryness, and the residue was diluted with 6 mL of methanol. Sodium borohydride (60 mg, 1.6 mmol) was added slowly to the stirring solution at 0 °C, and stirring was continued at this temperature for 1 h. Workup as above and elution with 100:1 chloroform–methanol gave 55 mg (31%) of colorless, amorphous, solid alcohol **5b**: IR NH 3470 (m), OH 3270 (br w), CH 2850 (m), 2805 (w), 2750 (w), C=C 1620 (w) cm^{-1}; ^1H NMR (MeOH-d_4) δ 1.0–3.1 (m, 13, methylenes, CH), 3.18 (br d, 1, J = 11 Hz, H-3), 3.5–3.7 (m, 2, OCH_2), 6.95 (t, 1, J = 7 Hz, H-11), 7.02 (t, 1, J = 7 Hz, H-10), 7.24 (d, 1, J = 7 Hz, H-9), 7.34 (d, 1, J = 7 Hz, H-12); ^{13}C NMR (MeOH-d_4) δ 22.3 (C-6), 32.7 (C-15), 33.7 (C-16), 36.6 (C-14), 40.3 (C-20), 54.2 (C-5), 56.4 (C-17), 60.3 (C-3), 61.5 (C-21), 107.6 (C-7), 112.0 (C-12), 118.6 (C-9), 119.7 (C-10), 121.9 (C-11), 128.3 (C-8), 135.7 (C-2), 138.0 (C-13); MS m/e 270 (M^+, 82) 269 (base); exact mass 270.1712 (calcd for $C_{17}H_{22}ON_2$ 270.1730).

Vinylogous Urethanes 6 and 7. A stirring suspension of 1.50 g (2.71 mmol) of "dimers" (prepared by the interaction of methyl β-(1-tryptophyl-3-pyridyl)acrylate bromide with sodium hydride[2]) in 30 mL of chloroform and 30 mL of dry dimethyl sulfoxide was refluxed for 0.5 h, cooled to room temperature, and then diluted with 300 mL of methylene chloride. Trifluoroacetic acid (10 mL) was added, and the mixture was stirred at room temperature for 4 h. It then was washed twice with 100 mL of water each, saturated sodium bicarbonate solution, and brine, dried, and evaporated. Chromatography of the residue and elution with 6:1 hexane–ethyl acetate led to 1.49 g (65%) of urethane vinylogue **6b**, mp 150 °C dec, spectrally identical with an authentic sample.[2]

The same procedure, carried out on 4.50 g (7.0 mmol) of "dimers" (prepared by the interaction of ethyl β-(1-tryptopyl-3-pyridyl)acrylate bromide with sodium hydride[10]), yielded 4.29 g (70%) of colorless, solid urethane vinylogue **7b**: mp ca. 150 °C dec; ^1H NMR δ 1.27 (t, 3, J = 7 Hz, Me), 1.81 (ddd, 1, J = 14, 13, 5 Hz, H-14α), 2.7–3.8 (m, 6, 3 methylenes, CH), 4.1–4.3 (AB of ABX_3, 2, OCH_2), 5.22 (dd, 1, J = 13, 5 Hz, H-3), 5.66 (d, 1, J = 15 Hz, acrylate α-H), 7.00 (s, 1, olefinic NCH), 7.14 (t, 1, J = 7 Hz, H-11), 7.21 (t, 1, J = 7 Hz, H-10), 7.36 (d, 1, J = 7 Hz, H-9),

(37) For previous syntheses of this alkaloid see ref 13 and Hachmeister, B.; Thielke, D.; Winterfeldt, E. *Chem. Ber.* **1976**, *109*, 3825.

(38) For previous syntheses of this alkaloid see ref 13 and 37 and (a) Müller, J.; Winterfeldt, E. *Ibid.* **1978**, *111*, 1540. (b) Banks, B. J.; Calverley, M. J.; Edwards, P. D.; Harley-Mason, J. *Tetrahedron Lett.* **1981**, 1631. (c) Overman, L. E.; Robichaud, A. J. 194th Meeting of the American Chemical Society, 1987; Abstr. 148.

7.42 (d, 1, J = 15 Hz, acrylate β-H), 7.50 (d, 1, J = 7 Hz, H-12); exact mass m/e 438.0652 (calcd for $C_{21}H_{21}O_2N_2Cl_3$ m/e 438.0665).

After the addition of ethyl lithiomethylthioacetate to the pyridinium salt methyl β-(1-tryptopyl-3-pyridyl)acrylate bromide at −78 °C according to the procedure described in ref 2 the mixture was stirred at −78 °C for 2 h and then at −40 °C for another 2 h. It was diluted with 200 mL of methylene chloride, 5 mL of trifluoroacetic acid was added at 0 °C, and stirring was continued at this temperature for 3 h. Workup as before led to 46% of vinylogous urethane **6c**.

An aqueous Raney nickel slurry (12 mL of a 50% active nickel suspension; pH 10; Aldrich Chemical Co.) was washed three times each with 40 mL of water, methanol, and acetone. The suspension was refluxed in 50 mL of acetone for 0.5 h, and the solution was decanted. A solution of 1.15 g (2.6 mmol) of ester **6c** in 40 mL of methanol and 40 mL of acetone was added to the nickel residue, and the stirring suspension was refluxed for 1.5 h. It was filtered, the solid was washed three times with 20 mL of methanol each, and the combined filtrate and washings were evaporated. A solution of the residue in 300 mL of methylene chloride was washed with saturated ammonium chloride solution and brine, dried, and evaporated, yielding 1.02 g (99%) of colorless, crystalline ester **6d**: mp 192–193 °C (MeOH); UV λ_{max} 224 nm (log ϵ 4.45), 270 (3.80), 282 (3.74), 291 (3.67), 356 (4.62); IR NH 3468 (m), C=O 1725 (s), 1688 (s), C=O, C=C 1580 (s) cm^{-1}; ^{1}H NMR δ 1.33 (t, 3, Me), 1.82 (ddd, 1, J = 13, 12, 5 Hz, H-14α), 2.2–3.6 (m, 8, methylenes, CH), 3.72 (s, 3, OMe), 4.1–4.3 (AB of ABX_3, 2, OCH_2), 4.59 (br d, 1, J = 12 Hz, H-3), 5.46 (d, 1, J = 15 Hz, acrylate α-H), 6.61 (s, 1, olefinic NCH), 7.10 (t, 1, J = 7 Hz, H-11), 7.17 (t, 1, J = 7 Hz, H-10), 7.26 (d, 1, J = 15 Hz, acrylate β-H), 7.31 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12); ^{13}C NMR δ 14.2 (Me), 21.8 (C-6), 27.8 (C-15), 31.9 (C-14), 38.7 (C-16), 47.9 (C-3), 50.6 (C-5), 50.8 (OMe), 60.6 (OCH_2), 102.8 (C-18), 106.7 (C-20), 108.5 (C-7), 110.9 (C-12), 118.0 (C-9), 119.6 (C-10), 122.0 (C-11), 126.7 (C-8), 132.1 (C-2), 136.2 (C-13), 145.7 (C-19), 146.3 (C-21), 169.1 (C=O), 172.3 (ester C=O); MS m/e 394 (M$^+$, 73), 307 (base); exact mass 394.1879 (calcd for $C_{23}H_{26}O_4N_2$ 394.1891).

An aqueous Raney nickel slurry (11 mL of a 50% active nickel suspension; pH 10; Aldrich Chemical Co.) was treated as above and then caused to interact with 1.24 g (2.7 mmol) of ester **7c**.[8] The procedure yielded 1.06 g (95%) of colorless, crystalline ester **7d**: mp 171–172 °C (Et_2O); UV λ_{max} 222 nm (log ϵ 4.50), 266 (4.10), 355 (4.54), $\lambda_{shoulder}$ 289 (3.76); IR NH 3462 (m), C=O 1733 (s), 1685 (s), 1610 (s), C=C 1580 (s) cm^{-1}; ^{1}H NMR δ 1.30, 1.33 (t, 3 each, methyls), 1.82 (ddd, 1, J = 13, 11, 5 Hz, H-14α), 2.2–3.6 (m, 8, methylenes, CH), 4.1–4.3 (m, 4, 2 OCH_2, 4.60 (br d, 1, J = 11 Hz, H-3), 5.45 (d, 1, J = 15 Hz, acrylate α-H), 6.62 (s, 1, olefinic NCH), 7.10 (t, 1, J = 7 Hz, H-11), 7.17 (t, 1, J = 7 Hz, H-10), 7.26 (d, 1, J = 15 Hz, acrylate β-H), 7.31 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12); ^{13}C NMR δ 14.2 (Me), 14.4 (ester Me), 21.8 (C-6), 27.8 (C-14), 31.8 (C-15), 38.6 (C-16), 47.9 (C-3), 50.6 (C-5), 59.4 (OCH_2), 60.6 (ester OCH_2), 103.1 (C-18), 106.5 (C-20), 108.4 (C-7), 110.9 (C-12), 117.9 (C-9), 119.6 (C-10), 121.9 (C-11), 132.2 (C-2), 136.1 (C-13), 145.6 (C-18), 146.2 (C-21), 168.8 (C=O), 172.4 (ester C=O); MS m/e 408 (M$^+$, base), 321 (86); exact mass 408.2055 (calcd for $C_{24}H_{28}O_4N_2$ 408.2046).

H(3)–H(15) Trans C(15)-Substituted Deplancheine Derivatives. When the first, hydrolysis step of the **6b** → **8a** conversion[2] was changed as follows: a solution of 500 mg (1.4 mmol) of chloride **6b** in 23 mL of 4 N hydrochloric acid and 17 mL of ethanol being stirred and refluxed for 2h, the colorless, crystalline product **8a**[2] was isolated in 75% yield (338 mg). The same yield of chloride **8a** was obtained from a **7b** → **8a** transformation under the identical, modified reaction conditions.

A solution of 100 mg (0.23 mmol) of ester **6a** and 10 mL of 4 N hydrochloric acid in 5 mL of methanol was refluxed for 5 h and then evaporated to dryness under vacuum. A solution of the residue in 10 mL of methanol, saturated with hydrogen chloride gas, was kept at room temperature for 18 h and then was evaporated under vacuum to dryness. Sodium borohydride (40 mg, 1.1 mmol) was added slowly to a stirring solution of the residue in 15 mL of methanol at 0 °C, and the stirring was continued for 1 h. The solvent was evaporated under vacuum, and the residue was treated with 15 mL of water and extracted. The extract was washed with water and brine, dried, and evaporated. Thick-layer chromatography of the residue (69 mg) on silica gel and development with 4:1 benzene–acetone afforded 51 mg (69%) of colorless, crystalline ester **8c**:[13,38a,38b] mp 134–136 °C (MeOH) (lit.[13] mp 134–136 °C; lit.[38a] mp 134 °C); UV λ_{max} 226 nm (log ϵ 4.45), 282 (3.76), 290 (3.69); IR[38a] NH 3470 (m), CH 2850 (m), 2802 (w), 2740 (w), C=O 1725 (s), C=C 1620 (w) cm^{-1}; ^{1}H NMR δ[38a] 1.62 (d, 3, J = 7 Hz, Me), 1.80 (ddd, 1, J = 13, 11, 5 Hz, H-14α), 2.08 (br d, 1, J = 13 Hz, H-14β), 2.5–3.2 (m, 6, methylenes), 3.22 (br s, 2, 2 H-21), 3.4–3.5 (m, 1, H-15), 3.57 (br d, 1, J = 11 Hz, H-3), 3.72 (s, 3, OMe), 5.50 (q, 1, J = 7 Hz, H-19), 7.10 (t, 1, J = 7 Hz, H-11), 7.13 (t, 1, J = 7 Hz, H-10), 7.30 (d, 1, J = 7 Hz, H-9), 7.46 (d, 1, J = 7 Hz, H-12); ^{13}C NMR δ 12.4 (C-18), 21.4 (C-6), 30.7 (C-15), 33.9 (C-14), 36.5 (C-16), 51.5 (OMe), 52.4 (C-5), 54.7 (C-3), 59.6 (C-21), 108.2 (C-7), 110.6 (C-12), 117.8 (C-9), 119.0 (C-10), 121.1 (C-11), 121.6 (C-19), 127.1 (C-8), 134.1 (C-2), 134.9 (C-20), 135.9 (C-13), 172.6 (C=O); MS m/e 324 (M$^+$, base), 323 (80), 251 (47); exact mass 324.1835 (calcd for $C_{20}H_{24}O_2N_2$ 324.1835).

A stirring solution of 1.06 g (3.3 mmol) of ester **6d** and 40 mL of 4 N hydrochloric acid in 20 mL of ethanol was refluxed for 3 h and then evaporated to dryness under vacuum. A solution of the residue in 60 mL of methanolic 2 N hydrochloric acid was kept at room temperature for 15 h and then evaporated. Sodium borohydride (400 mg, 11 mmol) was added in portions to a stirring solution of the residue in 60 mL of methanol at 0 °C, and stirring was continued at this temperature for 1 h. Saturated sodium bicarbonate solution (80 mL) was added, and the mixture was extracted. The extract was washed with brine, dried, and evaporated. Chromatography of the residue on neutral alumina (activity III) and elution with 1:1 hexane–dichloromethane furnished 730 mg (84%) of ester **8c**, identical in all respects with the above sample. The identical procedure used on 376 mg (0.92 mmol) of ester **7d** led to 238 mg (80%) of ester **8c** also.

A stirring mixture of 20 mg (0.054 mmol) of chloride **8a** and 45 mg (0.69 mmol) of activated zinc powder in 1 mL of glacial acetic acid was kept at room temperature for 15 h, diluted with 15 mL of water, and decanted from the remaining solid. The latter was washed with water, and the combined decanted solution and washings were neutralized with saturated sodium bicarbonate solution. The mixture was extracted, and the separated zinc was washed with methylene chloride. The combined extract and washings were dried and evaporated. Medium-pressure liquid chromatography of the residue and elution with 6:1 hexane–ethyl acetate yielded 8 mg (40%) of crystalline, colorless dichloride **8b**: mp 75–77 °C; UV λ_{max} 226 nm (log ϵ 4.14), 282 (3.46), 290 (3.38); IR (CH_2Cl_2) NH 3440 (w), C=C 1592 (w) cm^{-1}; ^{1}H NMR δ 1.74 (d, 3, J = 7 Hz, Me), 1.88 (ddd, 1, J = 13, 11, 6 Hz, H-14α), 2.6–3.2 (m, 5, methylenes, CH), 3.18 (d, 1, J = 13 Hz, H-21β), 3.30 (d, 1, J = 13 Hz, H-21α), 3.44 (dd, 1, J = 10, 6 Hz, H-15), 3.58 (d, 1, J = 11 Hz, H-3), 5.77 (q, 1, J = 7 Hz, H-19), 6.16 (d, 1, J = 10 Hz, Cl_2CH), 7.0–7.5 (m, 4, Ar Hs); ^{13}C NMR δ 13.3 (C-20), 21.5 (C-6), 32.1 (C-14), 45.7 (C-15), 52.4 (C-5), 54.9 (C-3), 60.0 (C-21), 74.3 (C-16), 108.6 (C-7), 110.7 (C-12), 118.0 (C-9), 119.3 (C-10), 121.4 (C-11), 126.5 (C-19), 127.0 (C-8), 131.8 (C-18), 133.4 (C-2), 136.2 (C-13); MS m/e 334 (M$^+$, 45), 299 (base), 251 (47); exact mass 334.0989 (calcd for $C_{18}H_{20}N_2Cl_2$ 334.0986).

Trichlorides 9. A solution of 100 mg (1.59 mmol) of sodium cyanoborohydride and the dry, crude product of the hydrolysis and decarboxylation of 200 mg (0.46 mmol) of ester **7b** in 10 mL of glacial acetic acid was stirred at 0 °C for 5 min and then at room temperature for 0.5 h. The mixture was diluted with 25 mL of water and extracted with methylene chloride. The extract was washed with 10% sodium bicarbonate solution and brine, dried, and evaporated. Medium-pressure liquid chromatography of the residue and elution with 9:1 hexane–ethyl acetate gave 50 mg (29%) of amorphous, solid epiallo (C) chloride **9a**: UV λ_{max} 225 nm (log ϵ 4.04), 279 (3.49), 290 (3.40); IR (CH_2Cl_2) NH 3458 (m), CH 2849 (m), 2818 (w), 2770 (w) cm^{-1}; ^{1}H NMR δ 0.98 (t, 3, J = 7 Hz, Me), 1.70 (pent, 2, J = 7 Hz, 2 H-19), 2.1–3.2 (m, 10, methylenes, methines), 4.04 (d, 1, J = 10 Hz, H-3), 7.09 (t, 1, J = 7 Hz, H-11), 7.15 (t, 1, J = 7 Hz, H-10), 7.30 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12); ^{13}C NMR δ 12.0 (C-18), 20.5 (C-6), 27.1 (C-19), 29.8 (C-14), 39.0 (C-20), 52.6 (C-5), 53.5 (C-21), 54.6 (C-3), 56.3 (C-15), 105.0 (Cl_3C), 108.7 (C-7), 110.7 (C-12), 118.0 (C-9), 119.4 (C-10), 121.4 (C-11), 127.3 (C-8), 133.9 (C-2), 135.8 (C-13); MS m/e 370 (M$^+$, base), 369 (67), 341 (34), 253 (51), 225 (68), 170 (44); exact mass 370.0759 (calcd for $C_{18}H_{21}N_2Cl_3$ 370.0768).

Elution with 2:1 hexane–ethyl acetate afforded 46 mg (27%) of colorless, amorphous pseudo (A) chloride **9b**: UV λ_{max} 219 nm (log ϵ 4.11), 270 (3.45), 279 (3.42), 289 (3.29); IR (CH_2Cl_2) NH 3460 (m), C=C 1625 (w) cm^{-1}; ^1H NMR δ 0.98 (t, 3, J = 7 Hz, Me), 1.7–1.9 (m, 2, 2 H-19), 2.1–3.4 (m, 10, methylenes, methines), 4.65 (br s, 1, H-3), 7.11 (t, 1, J = 7 Hz, H-11), 7.17 (t, 1, J = 7 Hz, H-10), 7.37 (d, 1, J = 7 Hz, H-9), 7.48 (d, 1, J = 7 Hz, H-12); ^{13}C NMR δ 12.0 (C-18), 16.5 (C-6), 16.6 (C-19), 25.8 (C-14), 39.0 (C-20), 47.1 (C-21), 50.8 (C-5), 53.7 (C-3), 55.7 (C-15), 103.9 (Cl_3C), 108.0 (C-7), 111.1 (C-12), 118.0 (C-9), 119.6 (C-10), 121.7 (C-11), 127.3 (C-8), 130.7 (C-2), 135.7 (C-13).

3-Isogeissoschizol (8d). A mixture of 55 mg (0.17 mmol) of ester **8c** and 6.5 mg (0.17 mmol) of lithium aluminum hydride in 6 mL of anhydrous THF was stirred at 0 °C for 5 min and then at room temperature for 1 h. Hydrochloric acid (5 mL of 1 N) was added, and the mixture was poured into 20 mL of saturated sodium bicarbonate solution and thereafter extracted with methylene chloride. The extract was washed with brine, dried, and evaporated, yielding 46 mg (91%) of colorless, crystalline alcohol **8d**:[13] mp 197–199 °C (CH_2Cl_2–C_6H_{14}) (lit.[13] mp 202–204 °C dec); ^1H NMR δ 1.64 (d, 3, J = 7 Hz, Me), 1.6–3.3 (m, 12, methylenes, methines), 3.5–3.8 (m, 2, OCH_2), 5.48 (q, 1, J = 7 Hz, H-19), 7.08 (t, 1, J = 7 Hz, H-11), 7.13 (t, 1, J = 7 Hz, H-10), 7.30 (d, 1, J = 7 Hz, H-9), 7.45 (d, 1, J = 7 Hz, H-12); ^{13}C NMR δ (DMSO-d_6) 12.6 (C-18), 21.5 (C-6), 30.3 (C-15), 34.2 (C-14 or C-16), 34.7 (C-16 or C-14), 52.4 (C-5), 55.2 (C-3), 59.5 (C-21 or OCH_2), 59.8 (OCH_2 or C-21), 106.7 (C-7), 111.1 (C-12), 117.4 (C-9), 118.4 (C-10), 120.1 (C-11), 126.8 (C-8), 135.4 (C-2), 136.2 (C-20), 136.8 (C-13).

Acetal 10b. A solution of 0.27 mL (1.93 mmol) of diisopropylamine in 4 mL of anhydrous THF was treated with 1.28 mL of a 1.5 M hexane solution of n-butyllithium at −78 °C and after 5 min permitted to warm to 0 °C, at which temperature it was stirred for 0.5 h. A solution of 184 mg (0.57 mmol) of ester **8c** in 4 mL of dry THF was added to the recooled mixture at −78 °C, and stirring was continued for 1 h. Methyl formate (4 mL, 65.0 mmol) was added, and the mixture was brought to 0 °C. It was poured into 10 mL of water, the pH was adjusted to 12 by the addition of 10% sodium hydroxide solution, and the mixture was extracted with ether. Washing the extract with brine, drying, and evaporation led to the recovery of 85 mg (46%) of starting ester. The aqueous solution was acidified with citric acid and extracted with methylene chloride. The extract was dried and evaporated, yielding 58 mg (54%, based on consumed ester **8c**) of colorless, amorphous 3-isogeissoschizine (**10a**) (in keto and enol forms): UV absorption maxima at 226 and 273 nm; IR NH 3462 (m), C=O 1730 (s), 1714 (s), 1659 (s), C=C 1612 (s) cm^{-1}; exact mass m/e 352.1798 (calcd for $C_{21}H_{24}O_3N_2$ m/e 352.1787).

A solution of 233 mg (0.63 mmol) of 3-isogeissoschizine (**10a**) and 10 mL of acetyl chloride in 20 mL of dry methanol was kept at room temperature for 12 h and then evaporated under vacuum. A solution of the residue in 100 mL of methylene chloride was washed with saturated sodium bicarbonate solution and brine, dried, and evaporated, producing 235 mg (94%) of colorless, amorphous acetal **10b**:[11] IR NH 3463 (m), CH 2840 (m), 2802 (w), 2745 (w), C=O 1738 (s), C=C 1625 (w) cm^{-1}; ^1H NMR δ (major) 1.68 (d, 3, J = 7 Hz, Me), 2.04 (br d, 1, J = 14 Hz, H-14), 2.7–3.5 (m, 9, methylenes, methines), 3.31, 3.36 (s, 3 each, acetal OMe), 3.86 (s, 3, ester OMe), 4.35 (d, 1, J = 5 Hz, O_2CH), 5.62 (q, 1, J = 7 Hz, H-19), 7.05 (t, 1, J = 7 Hz, H-11), 7.12 (t, 1, J = 7 Hz, H-10), 7.39 (d, 2, J = 7 Hz, H-9, H-12); δ (minor) 1.61 (s, 3, J = 7 Hz, Me), 1.80 (ddd, 1, J = 13, 11, 5 Hz, H-14α), 2.5–3.8 (m, 9, methylenes, methines), 3.43, 3.50 (s, 3 each, acetal OMe), 3.62 (s, 3, ester OMe), 4.73 (d, 1, J = 6 Hz, O_2CH), 5.51 (q, 1, J = 7 Hz, H-19), 7.0–7.2 (m, 2, H-10, H-11), 7.30 (d, 2, J = 7 Hz, H-9, H-12); ^{13}C NMR δ (major) 12.9 (C-18), 21.1 (C-6), 33.2 (C-15), 32.7 (C-14), 49.8 (C-16), 51.2 (ester OMe), 52.0 (C-5), 54.7 (C-3), 54.9 (2 acetal OMe), 60.0 (C-21), 104.8 (C-17), 108.2 (C-7), 110.7 (C-12), 117.7 (C-9), 119.0 (C-10), 121.0 (C-11), 121.0 (C-19), 127.1 (C-8), 133.8 (C-2), 134.0 (C-20), 135.8 (C-13), 172.2 (C=O); exact mass m/e 398.2204 (calcd for $C_{23}H_{30}O_4N_2$ m/e 398.2205).

16,17-Dihydro-3-isogeissoschizine (10c). Sodium borohydride (86 mg, 2.3 mmol) was added in small portions to a stirring solution of 58 mg (0.17 mmol) of 3-isogeissoschizine (**10a**) and 0.1 mL of glacial acetic acid in 10 mL of methanol at 0 °C. Upon completion of the reaction, the mixture was poured into 20 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated, yielding 50 mg (86%) of colorless, amorphous ester **10c** (as two C(16) epimers): UV λ_{max} 226 nm (log ϵ 4.05), 273 (3.85), $\lambda_{shoulder}$ 290 (3.69); IR NH 3463 (m), OH 3260 (br. m), CH 2851 (m), 2800 (m), 2750 (w), C=O 1725 (s), C=C 1620 (m) cm^{-1}; ^1H NMR δ (major) 1.65 (d, 3, J = 7 Hz, Me), 1.6–4.2 (m, 13, methylenes, methines), 3.76 (s, 3, OMe), 5.60 (q, 1, J = 7 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); δ (minor) 1.57 (d, 3, J = 7 Hz, Me), 1.6–4.2 (m, 13, methylenes, methines), 3.53 (s, 3, OMe), 5.50 (q, 1, J = 7 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); ^{13}C NMR δ (major) 12.8 (C-18), 21.5 (C-6), 29.6 (C-15), 33.4 (C-14), 48.4 (C-16), 52.0 (OMe), 52.3 (C-5), 54.9 (C-3), 60.2 (C-21), 62.3 (C-17), 108.6 (C-7), 110.7 (C-12), 118.0 (C-9), 119.3 (C-10), 121.3 (C-11), 123.0 (C-19), 127.1 (C-8), 133.2 (C-20 or C-2), 133.8 (C-2 or C-20), 135.9 (C-13), 175.1 (C=O); δ (minor) 14.0 (C-18), 22.6 (C-6), 31.5 (C-15), 33.2 (C-14), 47.5 (C-16), 51.6 (OMe), 52.2 (C-5), 54.9 (C-3), 59.8 (C-21), 61.5 (C-17), 108.3 (C-7), 110.7 (C-12), 118.0 (C-9), 119.2 (C-10), 121.3 (C-11), 124.2 (C-19), 133.9 (C-2, C-20), 136.0 (C-13), 174.9 (C=O); MS m/e 354 (M^+, base), 353 (76), 323 (43), 252 (31), 184 (33), 169 (60), 156 (33); exact mass 354.1947 (calcd for $C_{21}H_{26}O_3N_2$ 354.1947).

Amine Boranes (11) of C(15)-Substituted Deplancheine Derivatives (8 and 10b). A solution of 0.10 mmol of amine (**8** or **10b**) in 5 mL of anhydrous THF and 0.20 mL of a 1 M tetrahydrofuran solution of borane–THF complex were mixed at 0 °C, and the mixture was stirred at this temperature for 0.5 h. It then was poured into 10 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated, yielding (95%) the following amine boranes.

Amine borane (11) of chloride **8a**: mp 130–132 °C; UV λ_{max} 225 nm (log ϵ 4.20), 277 (3.57), 290 (3.48); IR (CH_2Cl_2) NH 3460 (m), BH 2409 (m), 2378 (m), 2340 (m), 2280 (w) cm^{-1}; ^1H NMR δ 1.66 (dd, 3, J = 7, 1 Hz, Me), 2.20 (ddd, 1, J = 16, 11, 7 Hz, H-14), 2.8–3.6 (m, 5, methylenes, CH), 3.40 (d, 1, J = 15 Hz, H-21), 3.73 (dd, 1, J = 7, 2 Hz, H-15), 4.57 (br d, 1, J = 15 Hz, H-21), 4.82 (dd, 1, J = 11, 5 Hz, H-3), 6.02 (q, 1, J = 7 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); ^{13}C NMR δ 14.6 (Me), 18.8 (C-6), 30.0 (C-14), 50.0 (C-15), 52.0 (C-5), 56.7 (C-3), 64.3 (C-21), 103.2 (C-16), 103.4 (C-7), 111.1 (C-12), 117.8 (C-9), 118.6 (C-10), 120.8 (C-11), 125.4 (C-19), 126.0 (C-8), 134.0 (C-2), 134.7 (C-20), 135.9 (C-13). Anal. Calcd for $C_{28}H_{22}N_2Cl_3B$: C, 56.36; H, 5.78; B, 2.82. Found: C, 56.47; H, 5.74; B, 2.65.

Amine borane (11) of chloride **8b**: mp 210 °C dec; UV λ_{max} 225 nm (log ϵ 4.24), 281 (3.58), 290 (3.48); IR (CH_2Cl_2) NH 3462 (m), BH 2405 (m), 2380 (m), 2340 (m), 2280 (w) cm^{-1}; ^1H NMR δ 1.67 (d, 3, J = 6 Hz, Me), 1.9–3.6 (m, 7, methylenes, CH), 3.40 (d, 1, J = 15 Hz, H-21), 4.07 (d, 1, J = 15 Hz, H-21), 4.40 (dd, 1, J = 12, 4 Hz, H-3), 5.81 (q, 1, J = 6 Hz, H-19), 6.01 (d, 1, J = 9 Hz, Cl_2CH), 7.0–7.6 (m, 4, Ar Hs); ^{13}C NMR δ 13.1 (Me), 18.8 (C-6), 30.3 (C-14), 44.1 (C-15), 51.5 (C-5), 56.7 (C-3), 64.6 (C-21), 73.4 (C-16), 103.9 (C-7), 110.8 (C-12), 117.5 (C-9), 118.5 (C-10), 120.9 (C-11), 125.8 (C-20), 127.2 (C-8), 129.4 (C-19), 132.5 (C-2), 135.8 (C-13); MS m/e 334 [$(M - BH_3)^+$, 46], 299 (base), 251 (64), 169 (50), 156 (45); exact mass ($M^+ - BH_3$) 334.1006 (calcd for $C_{18}H_{20}N_2Cl_2$ 334.0986).

Amine borane (11) of ester **8c**: amorphous solid; UV λ_{max} 226 nm (log ϵ 4.45), 282 (3.76), 290 (3.67); IR NH 3460 (m), BH 2405 (m), 2378 (m), 2335 (m), 2280 (m), C=O 1725 (s), C=C 1620 (w) cm^{-1}; ^1H NMR δ 1.65 (d, 3, J = 7 Hz, Me), 1.8–3.4 (m, 9, methylenes, CH), 3.34 (d, 1, J = 15 Hz, H-21), 3.76 (s, 3, OMe), 4.10 (br d, 1, J = 7 Hz, H-21), 4.38 (dd, 1, J = 12, 4 Hz, H-3), 5.56 (q, 1, J = 7 Hz, H-19), 7.1–7.5 (m, 4, Ar Hs); ^{13}C NMR δ 12.7 (C-18), 19.2 (C-6), 30.1 (C-15), 34.6 (C-14), 36.0 (C-16), 49.4 (C-5), 51.7 (OMe), 56.6 (C-3), 65.0 (C-21), 104.6 (C-7), 110.9 (C-12), 118.0 (C-9), 119.4 (C-10), 121.6 (C-11), 126.3 (C-19), 130.0 (C-20), 132.9 (C-2), 135.9 (C-13), 171.9 (C=O); MS m/e 338 (M^+, 7), 337 (9), 324 (base), 323 (78), 251 (61), 170 (24), 156 (34); exact mass 338.2105 (calcd for $C_{20}H_{27}O_2N_2B$ 338.2166).

Amine borane (11) of alcohol **8d**: amorphous solid; UV λ_{max} 223 nm (log ϵ 4.44), 279 (3.77), 289 (3.68); IR (CH_2Cl_2) OH 3602 (w), NH 3455 (m), BH 2418 (m), 2375 (m), 2330 (m), 2280 (w) cm^{-1}; ^1H NMR δ 1.67 (dd, 3, J = 7, 1 Hz, Me), 1.6–3.4 (m, 9, methylenes, CH), 3.32 (d, 1, J = 15 Hz, H-21), 3.5–3.8 (m, 2, OCH_2), 4.14 (br d, 1, J = 15 Hz, H-21), 4.41 (dd, 1, J = 12, 5 Hz, H-3), 5.58 (q, 1, J = 7 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); ^{13}C NMR

δ 12.7 (C-18), 19.2 (C-6), 30.1 (C-15), 33.9 (C-16), 35.3 (C-14), 48.9 (C-5), 56.8 (C-3), 60.4 (C-17), 65.1 (C-21), 103.7 (C-7), 110.9 (C-12), 117.7 (C-9), 118.9 (C-10), 121.2 (C-11), 125.5 (C-19), 126.1 (C-8), 130.8 (C-20), 133.5 (C-2), 135.8 (C-13); exact mass (M^+ - H) *m/e* 309.2120 (calcd for $C_{19}H_{27}ON_2B$ *m/e* 309.1232).

A mixture of 110 mg (0.34 mmol) of the amine borane (**11**) of ester **8c** and 13 mg (0.34 mmol) of lithium aluminum hydride in 10 mL of dry THF was stirred at 0 °C for 5 min and then at room temperature for 1 h. It was poured into 20 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated. Chromatography of the residue on neutral alumina (activity III) and elution with 4:1 dichloromethane–ethyl acetate gave 78 mg (78%) of colorless, amorphous amine borane (**11**) of alcohol **8d**.

Amine borane (**11**) of acetal **10b**: amorphous solid; IR NH 3460 (m), BH 2420 (m), 2378 (m), 2340 (m), 2280 (m), C=O 1770 (s), C=C 1625 (w) cm^{-1}; ^1H NMR δ (major) 1.71 (d, 3, *J* = 7 Hz, Me), 1.6–3.6 (m, 8, methylenes, methines), 3.31, 3.37 (s, 3 each, 2 acetal OMe), 3.82 (s, 3 ester OMe), 4.08 (br d, 1, *J* = 15 Hz, H-21), 4.3–4.5 (m, 2, H-3, O_2CH), 5.61 (q, 1, *J* = 17 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); δ (minor) 1.63 (d, 3, *J* = 7 Hz, Me), 1.6–3.6 (m, 8, methylenes, methines), 3.45, 3.51 (s, 3 each, 2 acetal OMe), 3.62 (s, 3, ester OMe), 4.19 (br d, 1, *J* = 15 Hz, H-21), 4.3–4.5 (m, 1, H-3), 4.66 (d, 1, *J* = 7 Hz, O_2CH), 5.54 (q, 1, *J* = 7 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); ^{13}C NMR δ (major) 13.0 (C-18), 19.2 (C-6), 32.9 (C-14), 33.7 (C-15), 49.8 (C-16), 51.5 (ester OMe), 54.7 (2 acetal OMe), 56.6 (C-5), 56.8 (C-3), 65.9 (C-21), 104.3 (C-17), 105.7 (C-7), 110.9 (C-12), 118.0 (C-9), 119.3 (C-10), 121.5 (C-11), 126.7 (C-19), 127.3 (C-8), 129.2 (C-20), 132.9 (C-2), 135.9 (C-13), 171.1 (C=O); exact mass *m/e* 412.2546 (calcd for $C_{23}H_{33}O_4N_2B$ *m/e* 412.2531).

Decomposition of Amine Boranes 11. A solution of 2 mL of 4 N hydrochloric acid was added dropwise to a stirring solution of 0.20 mmol of amine borane **11** (of tetracycles **8** and **10b**) in 6 mL of acetone at 0 °C, and stirring was continued at this temperature for 1 h. The mixture was poured into 15 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated, leading to a 94% yield of amine (**8** and **10b**).

C(3)-Oxidation and Reductive Regeneration of Ester 8c. *tert*-Butyl hypochlorite (61 μL, 0.53 mmol) was added dropwise to a stirring solution of 173 mg (0.53 mmol) of ester **8c** and 77 μL of triethylamine in 10 mL of methylene chloride at −20 °C, and stirring was continued at this temperature for 0.5 h. The mixture was evaporated under vacuum, and a solution of the residue and 4 mL of trifluoroacetic acid in 20 mL of methylene chloride was kept at 0 °C for 5 min and then stirred at room temperature for 1 h. The mixture was evaporated under vacuum, leaving a residue whose TLC behavior showed it to be a polar material structurally dramatically different from starting ester and convertible into ester **15c** on borohydride reduction in THF. Sodium borohydride (50 mg, 1.32 mmol) was added in several portions to a stirring solution of the residue in 15 mL of methanol at 0 °C, and the stirring was continued for 1 h. The mixture was poured into 30 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated, yielding 147 mg (85%) of ester **8c**.

H(3)-Isomerizations. A solution of 0.50 mmol of *m*-chloroperbenzoic acid in 5 mL of anhydrous methylene chloride was added dropwise to a stirring solution of 0.50 mmol of amine (**8a–c**, **10b**) in 15 mL of dry methylene chloride at 0 °C, and stirring was continued at this temperature for 1 h. Solid sodium carbonate (15 mg) was added, and the mixture was stirred at 0 °C for 15 min and then filtered. Trifluoroacetic anhydride (0.5 mL) was added dropwise to the filtrate at −78 °C, and the mixture was stirred at this temperature for 2 h and thereafter at 0 °C for another 2 h. It was evaporated under vacuum, and the residue was dissolved in 15 mL of anhydrous THF. Sodium borohydride (50 mg) was added in several portions at 0 °C, and the mixture was stirred at this temperature for 1 h. It was poured into 30 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated. Medium-pressure liquid chromatography (elution with 10:1 to 5:1 hexane–ethyl acetate) was used for purification of the products.

Products of isomerization of chloride **8a**: amine borane of chloride **8a** (52%) and of chloride **15a** (2%). The low yield of the latter precluded its characterization.

Products of isomerization of chloride **8b**: amine borane of chloride **8b** (55%) and of amorphous chloride **15b** (17%); UV λ_{max} 224 nm (log ε 4.21), 279 (3.46), 281 (3.48), 290 (3.38); IR (CH_2Cl_2) NH 3460 (m), BH 2405 (m), 2380 (m), 2340 (m), 2280 (m) cm^{-1}; ^1H NMR δ 1.72 (d, 3, *J* = 6 Hz, Me), 2.2–3.5 (m, 8, methylenes, CH), 3.57 (br d, 1, *J* = 12 Hz, H-21), 4.20 (br s, 1, H-3), 5.25 (d, 1, *J* = 8 Hz, Cl_2CH), 5.85 (q, 1, *J* = 6 Hz, H-19), 7.0–7.5 (m, 4, Ar Hs); ^{13}C NMR δ 14.0 (C-18), 17.7 (C-6), 26.2 (C-14), 44.6 (C-15), 57.8 (C-5), 58.2 (C-3), 59.4 (C-21), 64.6 (C-16), 107.0 (C-7), 111.1 (C-12), 118.3 (C-9), 120.1 (C-10), 122.7 (C-11), 129.8 (C-20), 130.1 (C-2), 132.0 (C-19), 136.1 (C-13); MS *m/e* 334 (M^+ - BH_3, 5) 299 (4), 156 (20), 28 (base); exact mass (M^+ - BH_3) 334.1006 (calcd for $C_{18}H_{20}N_2Cl_2$ 334.1017).

Products of isomerization of ester **8c**: amine borane of ester **8c** (35%) and of ester **15c** (6%); mp 150 °C dec; UV λ_{max} 224 nm (log ε 4.15), 274 (3.69), 290 (3.56), $\lambda_{shoulder}$ 278 (4.68); IR NH 3460 (w), BH 2418 (w), 2380 (m), 2340 (m), 2280 (w), C=O 1725 (s), C=C 1598 (w) cm^{-1}; ^1H NMR δ 1.68 (dd, 3, *J* = 7, 1 Hz, Me), 1.8–2.1 (m, 2, 2 H-16), 2.21 (dt, 1, *J* = 15, 4 Hz, H-14), 3.12 (br d, 1, *J* = 12 Hz, H-21), 2.9–3.4 (m, 6, methylenes, CH), 3.68 (s, 3, OMe), 3.73 (br d, 1, *J* = 12 Hz, H-21), 4.37 (br s, 1, H-3), 5.56 (q, 1, *J* = 7 Hz, H-19), 7.12 (t, 1, *J* = 7 Hz, H-11), 7.19 (t, 1, *J* = 7 Hz, H-10), 7.35 (d, 1, *J* = 7 Hz, H-9), 7.48 (d, 1, *J* = 7 Hz, H-12); ^{13}C NMR δ 12.6 (C-18), 17.4 (C-6), 26.4 (C-14), 29.4 (C-15), 36.8 (C-16), 51.8 (OMe), 56.1 (C-21), 58.5 (C-5), 58.6 (C-3), 106.3 (C-7), 111.2 (C-12), 118.0 (C-9), 119.8 (C-10), 122.2 (C-11), 125.3 (C-19), 126.6 (C-8), 130.9 (C-20), 131.1 (C-2), 136.3 (C-13), 173.3 (C=O); MS *m/e* 337 [(M - H)$^+$, 15], 324 (base), 323 (79), 249 (55), 169 (53), 156 (47); exact mass (M - 1) 337.2085 (calcd for $C_{20}H_{26}O_2N_2B$ 337.2087).

Products of isomerization of ester **10b**: amine borane of ester **10b** (32%) and of amorphous ester **15d**; IR NH 3460 (w), BH 2410 (w), 2380 (m), 2340 (w), C=O 1730 (s) cm^{-1}; ^1H NMR δ (major isomer) 1.79 (d, 3, *J* = 7 Hz, Me), 3.25 (s, 6, 2 acetal methoxyls), 3.70 (s, 3, ester OMe), 4.06 (dd, 1, *J* = 9, 3 Hz, H-3), 4.47 (d, 1, *J* = 8 Hz, O_2CH), 5.82 (q, 1, *J* = 7 Hz, H-19), 7.0–7.6 (m, 4, Ar Hs); δ (minor isomer) 1.66 (d, 3, *J* = 7 Hz, Me), 3.37, 3.43 (s, 3 each, acetal methoxyls), 3.63 (s, 3, ester OMe), 4.38 (br s, 1, H-3), 4.70 (d, 1, *J* = 8 Hz, O_2CH), 5.61 (q, 1, *J* = 7 Hz, H-19), 7.0–7.6 (m, 4, Ar Hs).

H(3)–H(15) Cis C(15)-Substituted Deplancheine Derivatives. The liberation of free amines **15** from their amine boranes (**12**) followed the above procedure for the decomposition of amine boranes **11**.

Amine **15a**: amorphous solid; IR (CH_2Cl_2) NH 3460 (m), CH 2835 (m), 2795 (m), 2765 (w), C=C 1625 (w) cm^{-1}; ^1H NMR δ 1.85 (dd, 1, *J* = 7, 1 Hz, Me), 2.3–3.1 (m, 7, methylenes, CH), 3.45 (d, 1, *J* = 12 Hz, H-21), 3.8–4.1 (m, 3, H-21, H-3, H), 6.03 (q, 1, *J* = 7 Hz, H-19), 7.0–7.6 (m, 4, Ar Hs); ^{13}C NMR δ 15.5 (C-18), 21.6 (C-6), 32.3 (C-14), 49.0 (C-15), 51.1 (C-5), 54.8 (C-3), 59.4 (C-21), 103.9 (C-16), 109.3 (C-7), 110.6 (C-12), 118.2 (C-9), 119.4 (C-10), 121.6 (C-11), 126.9 (C-8), 130.6 (C-20), 132.2 (C-19), 133.7 (C-2), 136.1 (C-13); MS *m/e* 368 (M^+, 36), 333 (73), 251 (base); exact mass 368.0612 (calcd for $C_{18}H_{19}N_2Cl_3$ 368.0615).

Amine **15b**: On workup of its liberation from the amine borane state as well as in crude, unsolvated form it underwent rapid decomposition.

Amine **15c**:[13,37,38a] amorphous solid; UV λ_{max} 220 nm (log ε 4.44), 272 (3.80), 282 (3.76), 290 (3.63); IR (CH_2Cl_2) NH 3460 (w), C=O 1730 (s), C=C 1625 (w) cm^{-1}; ^1H NMR δ 1.62 (d, 3, *J* = 7 Hz, Me), 2.1–3.3 (m, 9, methylenes, CH), 2.99 (d, 1, *J* = 12 Hz, H-21), 3.55 (d, 1, *J* = 12 Hz, H-21), 3.66 (s, 3, OMe), 4.25 (br s, 1, H-3), 5.48 (q, 1, *J* = 7 Hz, H-19), 7.08 (t, 1, *J* = 7 Hz, H-11), 7.13 (t, 1, *J* = 7 Hz, H-10), 7.33 (d, 1, *J* = 7 Hz, H-9), 7.45 (d, 1, *J* = 7 Hz, H-12); ^{13}C NMR δ 12.5 (C-18), 17.8 (C-6), 30.6 (C-14), 31.3 (C-15), 37.1 (C-16), 51.2 (C-5), 51.6 (OMe), 52.9 (C-21), 53.1 (C-3), 107.4 (C-7), 110.9 (C-12), 117.8 (C-9), 119.2 (C-10), 120.2 (C-19), 121.2 (C-11), 127.5 (C-8), 133.8 (C-2), 135.8 (C-13 or C-20), 135.9 (C-20 or C-13), 173.8 (C=O); MS *m/e* 324 (M^+, 96), 323 (base), 251 (59), 170 (25), 169 (31), 156 (22).

Amine **15d**: amorphous solid; IR NH 3460 (w), C=O 1727 (s), C=C 1628 (w) cm^{-1}; ^1H NMR δ (major isomer) 1.35 (d, 3, *J* = 7 Hz, Me), 3.24, 3.29 (s, 3 each, acetal methoxyls), 3.69 (s, 3, ester OMe), 4.38 (d, 1, *J* = 8 Hz, O_2CH), 4.48 (br d, 1, *J* = 6 Hz, H-3), 5.63 (q, 1, *J* = 7 Hz, H-19), 7.0–7.3 (m, 4 Ar Hs); δ (minor isomer)

1.56 (d, 3, J = 7 Hz, Me), 3.07, 3.45 (s, 3 each, acetal methoxyls), 3.62 (s, 3, ester OMe), 4.65 (br s, 1, H-3), 4.72 (d, 1, J = 8 Hz, O_2CH), 5.63 (q, 1, J = 7 Hz, H-19), 7.0-7.4 (m, 4, Ar Hs).

Geissoschizol (2). The **8c** → **8d** conversion was repeated with 22 mg (0.068 mmol) of ester **15c** and 5 mg (0.13 mmol) of lithium aluminum hydride, yielding 19 mg (94%) of colorless, crystalline alcohol **2**: mp 99-103 °C (CH_2Cl_2-C_6H_{14}) (lit.[13] mp 190-194 °C dec); UV, IR, and ^1H NMR spectrally identical with literature data;[15a,39] ^{13}C NMR δ 12.8 (C-18), 18.1 (C-6), 31.5 (C-15), 32.5 (C-14), 35.6 (C-16), 51.0 (C-5), 53.4 (C-3), 53.9 (C-21), 61.4 (C-17), 107.1 (C-7), 110.9 (C-12), 117.9 (C-9), 119.3 (C-10), 120.9 (C-19), 121.3 (C-11), 127.3 (C-8), 133.9 (C-2), 135.9 (C-20 or C-13), 136.2 (C-13 or C-20).

Geissoschizine (3). A solution of 14 mg (0.035 mmol) of ester **15d** and 3 mL of a 4 N hydrochloric acid solution in 4 mL of THF was stirred at room temperature for 18 h. Enough saturated sodium bicarbonate solution was added to neutralize the solution, and the mixture was extracted with methylene chloride. The extract was washed with 5% sodium hydroxide solution and brine, dried, and evaporated, leading to the recovery of 5 mg (36%) of starting ester **15d**. The aqueous, alkaline solution was neutralized with citric acid and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated. Crystallization of the residue from chloroform yielded 5 mg (63%, based on consumed **15d**) of colorless, crystalline ester **3**: mp 185-188 °C ($CHCl_3$) (lit.[13] mp 187-189 °C); spectrally identical with literature data.[40,41]

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Synthetic Studies on the Lithiated Toluamide-Imine Cycloaddition Route to (±)-Corydalic Acid Methyl Ester[1]

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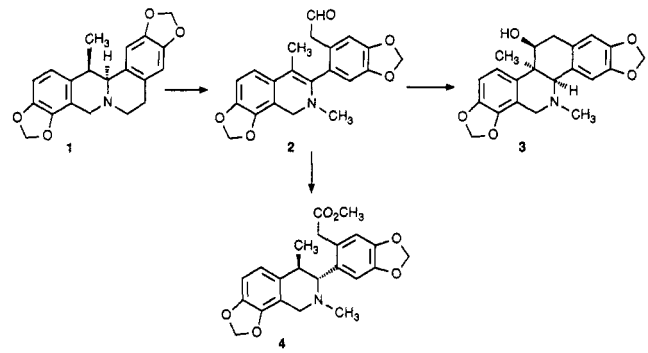
A total synthesis of (±)-corydalic acid methyl ester (**4**) was accomplished. Initial attempts to prepare the key intermediate **5** by condensation of lithiated toluamide **6** with benzaldimine **8** followed by trapping with iodomethane failed. This was apparently due to lack of deprotonation of the initial adduct **17** under the reaction conditions. However, condensation of the 6-ethyl *N,N*-diethylamide **14** with **8** stereospecifically afforded **5** after ring closure of the initially formed adduct **23**. The vinyl group of **5** was converted to the phenylacetic acid side chain, and subsequent reduction of the lactam furnished the racemic natural product **4**.

Corydalic acid methyl ester (**4**) is a tetrahydroisoquinoline alkaloid isolated along with protoberberine and benzo[*c*]phenanthridine alkaloids from *Corydalis incisa* Pers.[3] This alkaloid is presumably derived from aldehyde **2**, a hypothetical biosynthetic intermediate in the conversion of the tetrahydroprotoberberine alkaloids (e.g. tetrahydrocorysamine, **1**) to the benzo[*c*]phenanthridines (e.g. corynoline, **3**).[4] The development of a route to *trans*-3,4-disubstituted 3,4-dihydro-1(2*H*)-isoquinolones by cycloaddition of lithiated *o*-toluamides and benzaldimines followed by electrophilic trapping[5] prompted us to undertake a synthesis of (±)-corydalic acid methyl ester, utilizing this methodology.[6,7] Reported herein are the results of these investigations, which resulted in a stereospecific total synthesis of racemic **4**.

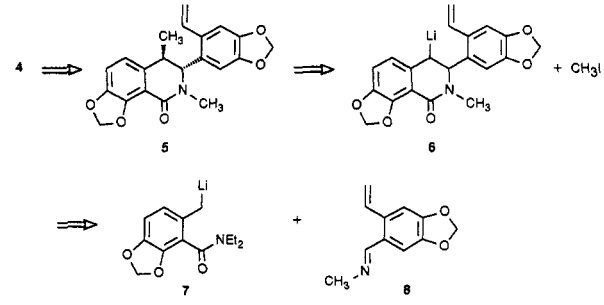
Results and Discussion

Our initial synthetic strategy (Scheme II) involved the preparation of key intermediate **5** by methylation of lithio derivative **6**, which would be available from condensation of lithiated toluamide **7** with benzaldimine **8** followed by

Scheme I



Scheme II



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