(2C), 138.929, 146.184. **5a**: ^{1}H NMR δ 1.20-1.90 (m), 1.97 (d, br, 1 H), 2.12 (q, br, 2 H), 2.55 (m, 1 H), 3.95 (s, br 1 H), 4.90-5.10 (m, 1 H), 5.75-5.90 (m, 1 H), 7.10-7.40 (m, aromatic); ^{13}C NMR δ 27.446, 31.012, 31.940, 33.664, 34.017, 41.087, 44.088, 67.725, 114.474, 125.888, 126.752 (2C), 128.259 (2C), 138.782, 147.177.

Cyclization of the Radical Derived from 5a. The cyclization was carried out as described above for **5b**. The products were isolated by column chromatography on silica gel with hexane as the solvent. The low recovery may be due to the volatility of the products. Analysis of the product mixture on column A (140 °C, 4 min; 8 °C per min to 200 °C; 200 °C, 16 min) revealed three volatile products. The isolated yield of the cyclic products was 29% and the starting alcohol recovered amounted to 47%. Major product (2α,4aβ,5α,7aβ)-5-methyl-2-phenylbicyclo[4.3.0]nonane (**8a**, retention time 10.14 min, 82%): ^{1}H NMR, inter alia, δ 1.05 (d, J = 7.5 Hz); ^{13}C NMR (assignments by INEPT experiment) δ 18.85 (*C*H$_3$), 23.61 (*C*H$_2$), 31.19 (*C*H$_2$), 31.76 (*C*H$_2$), 33.16 (*C*H$_2$), 36.63 (*C*H), 37.49 (*C*H$_2$), 39.37 (*C*H), 40.07 (*C*H), 41.71 (*C*H), 125.56, 126.72 (2C), 128.19, 148.10; HRMS 214.1755 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721). Minor product (2α,4aβ,5β,7aβ)-5-methyl-2-phenylbicyclo[4.3.0]nonane (**9a**, retention time 9.53 min, 11%): ^{1}H NMR δ 0.96 (d, J = 7 Hz, *C*H$_3$); ^{13}C NMR δ 19.51 (*C*H$_3$); HRMS, m/z 214.1730 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721). Another product (retention time 9.82 min, 4%) having a CH$_3$ signal at δ 17.84 has not been identified.

Cyclization of the Radical Derived from 4a. The cyclic products were obtained in 21% yield; the starting alcohol recovery was 50%. ^{13}C NMR of major (retention time 9.67 min, 63%) product ((2α,4aα,5α,7aα)-5-methyl-2-phenylbicyclo[4.3.0]nonane, **13a**): ^{1}H NMR, inter alia, δ 0.962 (d, J = 7 Hz); ^{13}C NMR δ 22.71 (*C*H$_3$), 27.97 (*C*H$_2$), 29.33 (*C*H$_2$), 31.87 (*C*H$_2$), 33.17 (*C*H$_2$), 35.21 (*C*H$_2$), 37.18 (*C*H), 38.65 (*C*H), 39.48 (*C*H), 46.18 (*C*H); HRMS, m/z 214.1713 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721); minor (retention time 10.16 min, 31%) product ((2α,4aα,5β,7aα)-5-methyl-2-phenylbicyclo[4.3.0]nonane, **14a**): ^{1}H NMR, inter alia, δ 0.940 (d, J = 7 Hz); ^{13}C NMR δ 15.54 (*C*H$_3$), 22.57 (*C*H$_2$), 26.71 (*C*H$_2$), 30.53 (*C*H$_2$), 33.02 (*C*H$_2$), 35.76 (*C*H$_2$), 38.44 (*C*H), 38.70 (*C*H), 40.48 (*C*H), 43.14 (*C*H); HRMS, m/z 214.1731 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721). Another hydrocarbon with no CH$_3$ group (5%) was not identified.

Zn/TMSCl-Mediated Cyclization of 2b. Activated Zn was prepared according to the literature[15] from 2.73 g of anhydrous $ZnCl_2$ and to this were added 0.42 g (2 mM) of **2b** (97.5% pure) dissolved in 8 mL of freshly distilled THF, 1.53 mL (12 mM) of chlorotrimethylsilane, and 0.70 mL of distilled 2,6-lutidine. The mixture was refluxed for 18 h. Unreacted Zn was filtered off with the aid of Celite and 20 mL of saturated sodium bicarbonate and 50 mL of ether were added. The aqueous layer was separated and was repeatedly extracted. The organic layers was washed with brine, dried, and concentrated. Analysis on column B (100 °C, 5 min; 10 °C per min to 200 °C; 200 °C, 20 min) indicated complete absence of starting ketone. The three peaks at 15.75 min (23%), 16.03 min (65%), and 16.38 min (12%) were identified as a mixture of at least four silyl ether components: three of exact molecular composition $C_{17}H_{34}OSi$ (282.2379) and one of composition $C_{17}H_{32}OSi$ (280.2222) by GC-HRMS.

The mixture of silyl ethers was treated with tetrabutylammonium fluoride in THF, and the desilylated products were readily separated by column chromatography. The first fraction was identified as a mixture of **2b** and **3b** presumably formed by the desilylation of silylenol ethers of the ketone **2b**. The second component was identifed as the 1,5-trans cyclization product **16** and the third fraction as the 1,5-cis product **17**. The last fraction (17%) was readily identified as a ketone-reduction product **4b** by comparison of GC retention time and NMR spectra with those of an authentic sample. The yield of cyclization products under these conditions was about 20%. The ratio of 1,5-trans ((2α,4aα,5α,7aα)-2-*tert*-butyl-4a-hydroxy-5-methylbicyclo[4.3.0]nonane, **16**) to 1,5-cis ((2α,4aα,5β,7aα)-2-*tert*-butyl-4a-hydroxy-5-methylbicyclo[4.3.0]nonane, **17**) isomers was determined as 75:25 by the mass of the isolated compounds. More than 50% of the ketone was recovered as the silyl enol ethers. **16**: ^{1}H NMR δ 0.85 (s, 9 H), 0.93 (d, J = 7.50 Hz, 3 H), 1.10-2.10 (m, 14 H); ^{13}C NMR δ 16.692, 22.552, 25.123, 25.342, 27.516 (3C), 29.743, 32.300 (quaternary), 35.768, 41.387, 42.233, 42.288, 78.444; HRMS, m/z 210.1997 (M$^+$, calcd for $C_{14}H_{26}O$ 210.1984). **17**: ^{1}H NMR δ 0.85 (s, 9 H), 0.89 (d, J = 6.50 Hz, 3 H), 1.10-2.05 (m, 14 H); ^{13}C NMR δ 12.838, 22.080, 24.178, 25.283, 27.573 (3C), 28.277, 28.399, 32.188 (quaternary), 41.658, 45.151, 45.633, 77.911; HRMS, m/z 210.1997 (M$^+$, calcd for $C_{14}H_{26}O$ 210.1984).

Cyclization of 3b. For comparison of spectral data an authentic sample of (2α,4aβ,5α,7aβ)-2-*tert*-butyl-4a-hydroxy-5-methylbicyclo[4.3.0]-nonane (**15**) was prepared by cyclization of **3b** using activated Zn as described earlier.[10b,15] As in the case of **2b**, the product was invariably contaminated with the silyl enol ethers of the starting ketone. In our hands, the yield of the expected products was only about 46% based on the amount of unrecovered ketone. **15**: ^{1}H NMR δ 0.83 (s, 9 H), 0.98 (d, J = 6.5 Hz, 3 H), 1.15-2.10 (m); ^{13}C NMR δ 15.886 (*C*H$_3$), 21.311 (*C*H$_2$), 27.180 (3 C, *C*H$_3$), 30.250 (*C*H$_2$), 30.263 (*C*H$_2$), 30.298 (*C*), 32.251 (*C*H$_2$), 32.705 (*C*H$_2$), 43.444 (*C*H), 46.727 (*C*H), 48.840 (*C*H), 81.922 (*C*HOH).

Total Syntheses of (+)-Geissoschizine, (±)-Geissoschizine, and (±)-(*Z*)-Isositsirikine. Stereocontrolled Synthesis of Exocyclic Double Bonds by Stereospecific Iminium Ion-Vinylsilane Cyclizations

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Abstract: (+)-Geissoschizine (**1**) was prepared in an efficient and stereocontrolled fashion in 11 steps and 7.5% overall yield from (*S*)-tryptophanamide (**20**). Key steps are the stereoselective 1,4-addition of cuprate **13a** to tetracyclic intermediate **8**, which establishes the C-3/C-15 stereorelationship of the product alkaloid, and cyclization of the (*E*)-vinylsilane iminium cation intermediate **4** (R^1 = H, R^2 = CH$_3$) to form the indoloquinolizidine ring system and elaborate the (*E*)-ethylidene side chain. The related cyclization of a (*Z*)-vinylsilane iminium ion intermediate (**4**, R^1 = CH$_3$, R^2 = H) is a key step in the stereocontrolled synthesis of the (19*Z*)-isositsirikines (**2**).

Geissoschizine (**1**), a pivotal early intermediate in the biosynthesis of polycyclic indole alkaloids of the *Corynantheine-Yohimbine*, *Strychnos*, *Aspidosperma*, and *Iboga* groups, was first isolated from hydrochloric acid cleavage of the dimeric indole

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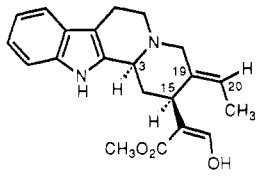
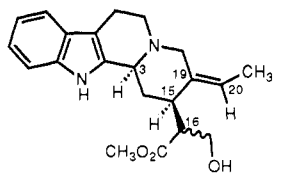


Geissoschizine (1)



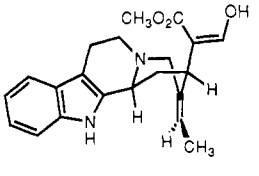
(19*Z*)-Isositsirikine (2)

alkaloid geissospermine.[1,2] Subsequently isolated from a variety of plant species, geissoschizine was structurally characterized in 1959 by the Rapoport[3] and Janot[4] groups. A variety of evidence demonstrates that geissoschizine adopts a D-ring boat conformation.[5] This conformation (see Figure 1) relieves the nonbonded interactions that would exist between the equatorial C-15 side chain and the ethylidene group (an $A^{1,3}$ interaction[6]) if geissoschizine existed in a D-ring chair conformation. Analysis of ^1H NMR[5c] and ^{13}C NMR[5d] data suggests that in solution geissoschizine possesses a cis C/D ring junction (see Figure 1), while the *trans*-quinolizidine conformation is preferred in the crystal.[7]

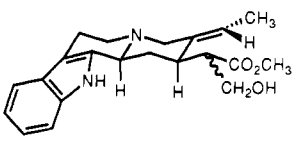
The isolation of related *Corynanthe* alkaloids containing the rare (*Z*)-ethylidene stereochemistry, the two C-16 epimers of (19*Z*)-isositsirikine (2), has recently been described.[8,9] Cytotoxic activity for the 16*S* isomer was reported initially by Cordell;[9a] however this activity was not verified by subsequent investigators.[9b,10] As expected, the (19*Z*)-isositsirikines exist in normal D-ring chair conformations (see Figure 1), since destabilizing allylic interactions with an equatorial C-15 substituent are not present in this stereoisomer.[11]

A number of syntheses of racemic geissoschizine have been reported[1] since the original total synthesis accomplishment in this area by the van Tamelen group.[12] Notable enantioselective syntheses of (+)-geissoschizine[13] and the (19*Z*)-isositsirikines[10] have been reported recently by Winterfeldt and co-workers.

Since geissoschizine is not readily available currently from natural sources, convenient access to synthetic samples of (+)-geissoschizine would facilitate ongoing biosynthetic studies in the indole alkaloid area.[2,14] For this reason, and also because the stereochemical problems posed by geissoschizine have not yet been met by a direct synthesis strategy that does *not* involve either epimerization at C-3 or $Z \rightarrow E$ isomerization of the ethylidene group, we undertook the total synthesis of (+)-geissoschizine. In this paper we report that (+)-geissoschizine can be prepared in a practical fashion from (*S*)-tryptophanamide by using a stereospecific[15] iminium ion–vinylsilane cyclization to assemble the (*E*)-ethylideneindoloquinolizidine ring system.[16]



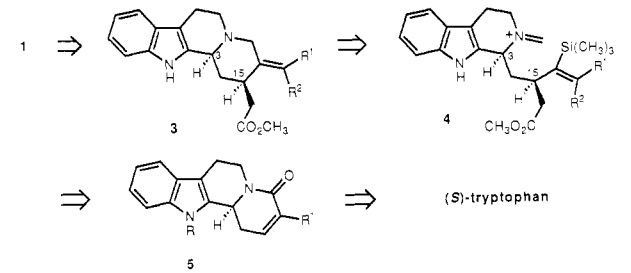
Geissoschizine (1)



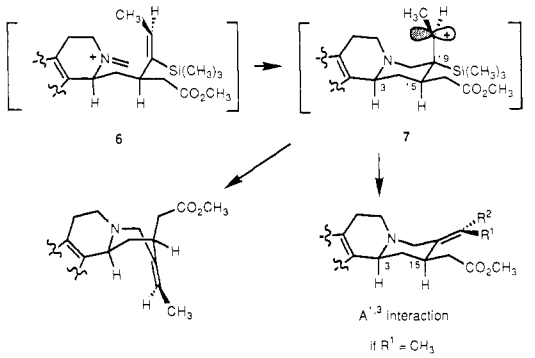
(19*Z*)-Isositsirikine (2)

Figure 1. Preferred solution conformations.

Scheme I



Scheme II



Results and Discussion

Synthesis Plan. Our general strategy is outlined in Scheme I and incorporated, as a key step, stereocontrolled formation of the ethylidene side chain by stereospecific[15] cyclization of an (*E*)- or (*Z*)-vinylsilane iminium cation (**4** → **3**). The required C-3/C-15 stereorelationship[17] would evolve from stereoelectronically favored axial addition[18] of a 1-(trimethylsilyl)-1-propenyl nucleophile from the α face to tetracyclic vinyl lactam intermediate **5**. Precedent[19]

(1) For comprehensive reviews of structural and synthetic studies up to mid-1984, see: Szántay, C.; Blaskó, C.; Honty, K.; Dörnyei, G. *Alkaloids (New York)* **1986**, *27*, 131 and earlier reviews in this series. (b) See also: Brown, R. T. In *Indoles. The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter 4.

(2) For a recent summary of biosynthetic relationships, see: Herbert, R. B. In *Indoles. The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter 1.

(3) (a) Rapoport, H.; Onak, T. P.; Hughes, N. A.; Reinecke, M. G. *J. Am. Chem. Soc.* **1958**, *80*, 1601. (b) Rapoport, H.; Windgassen, R. J.; Hughes, N. A.; Onak, T. P. *Ibid.* **1960**, *82*, 4404.

(4) (a) Janot, M. M. *Tetrahedron* **1961**, *14*, 113. (b) Puisieux, F.; Goutarel, R.; Janot, M. M.; LeHir, A. *C. R. Seances Acad. Sci., Ser. 2* **1959**, *249*, 1369.

(5) (a) Rakur, G.; Winterfeldt, E. *Chem. Ber.* **1976**, *109*, 3837. (b) Damak, M.; Ahound, A.; Potier, P.; Janot, M. M. *Tetrahedron Lett.* **1976**, 4731. (c) Höfle, G.; Heinstein, P.; Stöckigt, J.; Zenk, M. H. *Planta Med.* **1980**, *40*, 126. (d) Goutarel, R.; Pais, M.; Gottlieb, H. E.; Wenkert, E. *Tetrahedron Lett.* **1978**, 1235.

(6) For a review, see: Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(7) Chiaroni, A.; Damak, M.; Ahoud, A.; Riche, C. *Journées de Chimie Organique*, Orsay, 7–9 September 19778 Abstract No. 64 cited in ref 5d.

(8) Kutney, J. P.; Brown, R. T. *Tetrahedron* **1966**, *22*, 321.

(9) (a) Mukhopadhyay, S.; El-Sayed, A.; Handy, C. A.; Cordell, G. A. *J. Nat. Prod.* **1983**, *46*, 409. (b) Kohl, W.; Witte, B.; Sheldrick, W. S.; Höfle, G. *Planta Med.* **1984**, *48*, 242.

(10) Winterfeldt, E.; Freund, R. *Liebigs Ann. Chem.* **1986**, 1262.

(11) Kan, C.; Kan, S.-K.; Lounasmaa, M.; Husson, H.-P. *Acta Chem. Scand. B* **1981**, *35*, 269.

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

(13) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winerfeldt, E. *Liebigs Ann. Chem.* **1985**, 1752.

(14) The difficulty in obtaining (+)-geissoschizine from natural sources was brought to our attention by Professor A. I. Scott.

(15) We use stereospecific and stereoselective in the sense discussed by Zimmerman and House, see: House, H. O. *Modern Synthetic Reactions: 2nd ed.*; Benjamin: Menlo Par, CA, 1972; pp 307–398 and ref 40a,b therein.

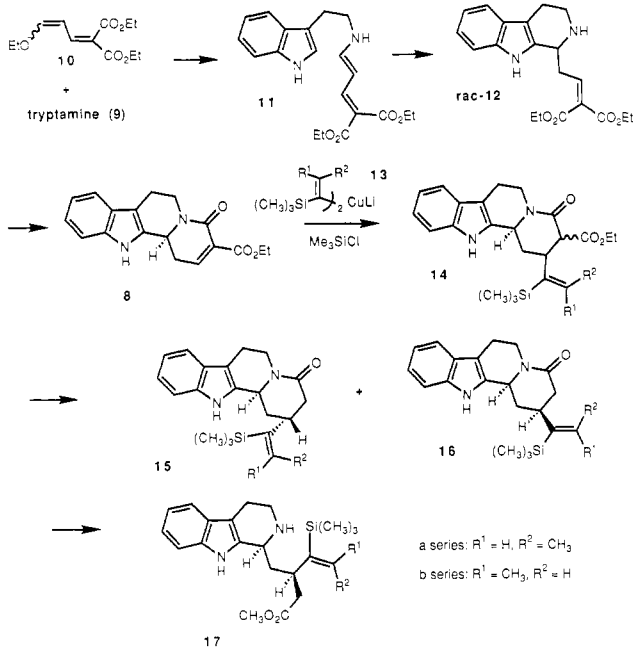
(16) For an earlier use of this strategy in a simpler total synthesis context, see: Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297. (b) For a recent review of cyclization reactions of vinylsilanes, see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

(17) To simplify discussion, the numbering system of geissoschizine will be utilized for all synthesis intermediates in the Results and Discussion section and in the schemes. The proper IUPAC names and numbering systems for these intermediates are employed in the Experimental Section of this paper.

(18) For a close precedent, see: Ficini, J.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1979**, *101*, 1318.

(19) For enantioselective preparations of (3*S*)-indoloquinolizidines from (*S*)-tryptophan intermediates, see inter alia: (a) Akimoto, H.; Okamura, K.; Yui, M.; Shioiri, T.; Kuramoto, M.; Kikugawa, U.; Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *22*, 2614. (b) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535. (c) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1147. (d) Massiot, G.; Mulamba, T.; Levy, J. *Bull. Soc. Chim. Fr.* 1982, 241. (e) Harrison, D. M.; Sharma, B. B. *Tetrahedron Lett.* **1986**, *27*, 521. (f) Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, M.; Kodato, S.-I.; Une, T.; Taniguchi, M.; Hino, T. *Ibid.* **1986**, *27*, 3235.

Scheme III



suggested that this latter indoloquinolizidine might be prepared with the required 3*S* absolute configuration by Pictet–Spengler cyclization of an appropriate intermediate derived from (*S*)-tryptophan.

An additional stereochemical problem arises in the key cyclization step when the vinylsilane has the *E* configuration. The fact that nucleophilic addition to iminium cations occurs preferentially with antarafacial orientation of the entering nucleophile and the developing electron pair on nitrogen[20] suggests that quinolizidines will be formed in a *single* cis conformation from cylization of a piperidine-derived iminium ion.[21] For the case at hand, this stereochemical feature is illustrated in Scheme II for the conversion of **6** → **7**.[22] In contrast to iminium ion–vinylsilane cyclizations studied earlier,[16] loss of the Me_3Si group from **7** to afford the (*E*)-ethylidene product in a chair piperidine conformation would be inhibited by developing $A^{1,3}$ interactions. A chair → boat conformational interconversion of ring D prior to loss of the Me_3Si group could obviate this difficulty.[23] Nonetheless, the impediment to loss of the Me_3Si group which is occasioned by the presence of the C-15[17] side chain could compromise the stereospecificity of the iminium ion–vinylsilane cyclization if the barrier to loss of the Me_3Si group were now comparable to that of rotation of the C-19/C-20 bond of the β-silyl cation intermediate **7**.[24,25] An examination of the degree of stereospecificity of iminium ion–vinylsilane cyclizations in this demanding context was viewed from the outset as a significant component of this synthesis endeavor.

Preparation of Racemic Cyclization Precursors. The basic synthesis sequence was worked out initially with racemic intermediates. Our early studies demonstrated that the known[18] α,β-unsaturated lactam **5** (R = CH_2Ph, R^1 = H) or the analogous thiolactam would not serve as useful substrates for 1,4-addition of vinyl cuprate nucleophiles.[26] We then turned to a more reactive Michael acceptor, the α-carbethoxy α,β-unsaturated lactam **8**, which was assembled in three steps from tryptamine (**9**) and the readily available[27] alkoxy diene ester **10** (see Scheme III). Condensation of these components in EtOH at room temperature afforded crystalline **11** in 95% yield as a single stereoisomer. Pictet–Spengler cyclization[28] of this intermediate with 3–5 equiv of trifluoroacetic acid in CH_2Cl_2 at room temperature gave the labile tetrahydro-β-carboline *rac*-**12**[29] in 77% yield after recrystallization. Lactam formation was best effected by heating this tricyclic intermediate in ethyl acetate, providing the tetracyclic lactam *rac*-**8** in 99% crude yield. Although this reactive intermediate could be purified by rapid chromatography on silica gel, the crude product was sufficiently pure to be employed directly in the subsequent cuprate-coupling step.

After examining a number of cuprate reagents, we found that the desired 1,4-addition to **8** was best accomplished under the influence of Me_3SiCl catalysis[30] with the lower order homocuprate prepared from (*Z*)-1-bromo-1-(trimethylsilyl)-1-propene[31] and CuI. In this way, *rac*-**8** and **13a** were combined to provide *rac*-**14a**, as a mixture of stereoisomers, in 75% yield (see Scheme III). The high (≥93%) facial stereoselectivity of the conjugate addition under these conditions was determined after removal of the carbethoxy substituent. Decarbalkoxylation of **14a** was accomplished by treatment of *rac*-**14a** with aqueous $Ba(OH)_2$[32] to produce, after acidification, the corresponding acid, which underwent smooth decarboxylation at 80 °C in toluene. Analysis of this crystalline product by capillary GC indicated that three products had been produced in a ratio of 91.5:7.0:1.5. Purification of this mixture on silica gel provided the major product, *rac*-**15a**, in 57% overall yield from *rac*-**8**. The minor product was subsequently shown (vide infra) to be *rac*-**15b**, which presumably resulted from a small contaminant of the *E* stereoisomer in the starting vinyl bromide. We were unable to isolate the third stereoisomer, which comprised 7% of the crude product mixture, in pure form. It is tentatively assigned as **16a**, the product which would arise from the addition of **13a** to **8** from the β-face.

In a similar fashion, *rac*-**8** was coupled with cuprate **13b**[31] and the resulting crude product decarbalkoxylated to provide *rac*-**15b**, *rac*-**16b**, and *rac*-**15a** in a ratio of 95:4:1. Separation of this mixture on silica gel provided the major stereoisomer, *rac*-**15b**, in 66% overall yield from *rac*-**8**. In this case we were able to isolate the product resulting from addition of cuprate **13b** to *rac*-**8** from the β-face. The 300-MHz ^1H NMR spectrum of this isomer showed the methine hydrogen α to the lactam nitrogen as a doublet of doublets (J = 11.5 and 4.5 Hz), consistent with **16b** adopting a *trans*-quinolizidine conformation with the C-15 side chain

(20) See, e.g.: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Series Ed.; Pergamon: New York, 1983, Chapter 2.

(21) This stereoelectronic preference for forming a single cis conformation of the cyclization product should be true for all cyclizations of piperidine-derived iminium ions containing a tethered nucleophile at C-2.

(22) To simplify the discussion we have depicted cyclization of the vinylsilane in only one of the two possible orientations, the one that leads to the $SiMe_3$ group occupying an equatorial position in the initial cyclization product.

(23) The developing $A^{1,3}$ interaction would also be absent in the other *cis*-quinolizidine conformation. However, this conformation would have a destabilizing 1,3-diaxial interaction of the C-3 (indole) and C-15 (acetic acid) side chains. The severity of this interaction is presumably responsible for geissoschizine adopting a D-ring boat conformation.

(24) This barrier could be on the order of 20 kcal/mol. For $H_3SiCH_2CH_2^+$ ab initio MO calculations (MP3/6-31G*) find the bisected structure (maximal C–Si hyperconjugation) to be 30 kcal/mol more stable than the eclipsed structure.[25a] In solution (97% aqueous CF_3CH_2OH) an antiperiplanar Me_3Si group is reported to accelerate the formation of a cyclohexyl-β-silyl cation by 2×10^{10} from the hyperconjugative interaction.[25b]

(25) (a) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496. (b) Lambert, J. B.; Wang, G.; Finzel, R. B.; Teramura, D. H. *Ibid.* **1987**, *109*, 7838.

(26) Conjugate addition of nucleophiles to α,β-unsaturated lactams is typically difficult. For the successful addition of organocuprates to *N*-tosyl α,β-unsaturated lactams, see: Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657.

(27) Windholz, T. B.; Peterson, L. H.; Kent, G. J. *J. Org. Chem.* **1963**, *28*, 1443.

(28) For a related cyclization of a vinylogous carbamate, see: Kirkpatrick, A.; Maclaren, J. A. *Aust. J. Chem.* **1977**, *30*, 2045.

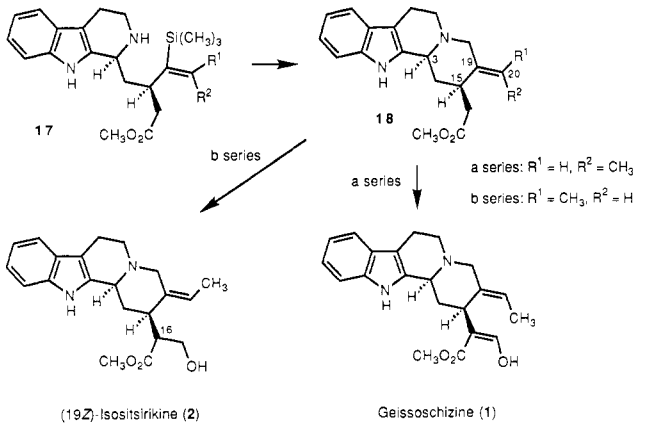
(29) The compound numbers for racemic compounds will be prefixed with rac. This prefix will not be used in the schemes if the compound was also prepared in nonracemic form.

(30) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305. Corey: E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. Alexakis, A., Berln, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

(31) (a) The addition to enones of cuprate **13b** has been described: Kroft, E. R.; Smith, A. B., III *J. Am. Chem. Soc.* **1982**, *104*, 2659. (b) The vinylsilane bromides were prepared as described by Zweiffel: Zweiffel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739. (c) Zweiffel, G.; On, H. P. *Synthesis* **1980**, 803.

(32) Grieco, P. A., Noguez, J. A., Masaki, Y. *J. Org. Chem.* **1977**, *42*, 495.

Scheme IV



equatorial. In comparison, the major product **15b** shows a broad doublet of doublets (J = 5 and 1 Hz) for this hydrogen, suggesting that **15b** adopts a *cis*-quinolizidine conformation. Structural assignments for *rac*-**15a** and *rac*-**15b** were subsequently confirmed (vide infra) by conversion of these intermediates to (±)-geissoschizine (**1**) and the (±)-(19*Z*)-isositsirikines (**2**), respectively.

Methanolysis of amides **15** to provide the cyclization substrates *rac*-**17a** and *rac*-**17b** was accomplished in good yield via the corresponding imidate salts.[33] Under optimized conditions, *rac*-**15a** was treated with 2 equiv of freshly prepared trimethyloxonium tetrafluoroborate[34] in the presence of 2 equiv of 2,6-di-*tert*-butylpyridine at room temperature. Hydrolysis of the resulting imidate salt at 0 °C with aqueous Na_2CO_3 provided the (*E*)-vinylsilane ester *rac*-**17a** in 82% yield, together with 12% of the starting lactam *rac*-**15a**. Amino ester *rac*-**17a** was very prone to cyclization to regenerate the starting lactam, and for this reason *rac*-**17a** was used immediately in the next step. Omission of the 2,6-di-*tert*-butylpyridine resulted in the recovery of up to 50% of the starting lactam and the formation of ~20% of the corresponding protodesilylated lactam. We attribute the formation of both products to the presence of HBF_4, a presumed contaminant of our oxonium salt, which is selectively scavenged by 2,6-di-*tert*-butylpyridine.[35] Under similar optimized conditions, *rac*-**15b** was converted to the (*Z*)-vinylsilane ester *rac*-**17b** in 78% yield (87% based on consumed *rac*-**15b**).

Cyclization To Form (±)-Geissoschizine and the (±)-(19*Z*)-Isositsirikines. With use of our standard cyclization conditions,[16] the (*Z*)-vinylsilane ester *rac*-**17b** was exposed to an excess of paraformaldehyde and 0.95 equiv of camphorsulfonic acid at 50 °C in several solvents (acetonitrile, MeOH, MeOH–H_2O) to provide (±)-(19*Z*)-methyl geissoschizoate (**18b**) in excellent yield (see Scheme IV). Analysis of the crude cyclization product by 500-MHz ^1H NMR and capillary GC failed to detect methyl geissoschizoate (**18a**), confirming that the cyclization occurred with complete (>98%) retention of double bond stereochemistry. The cyclization was fastest in acetonitrile; however, the unprotected indole nitrogen was converted to the *N*-hydroxymethyl derivative to a small extent in this solvent. An essentially quantitative yield of *rac*-**18b** was obtained when a 1:1 mixture of MeOH and H_2O was used as solvent. Conversion of *rac*-**18b** to the two C-16 epimers of racemic (19*Z*)-isositsirikine was accomplished by formylation and $NaBH_4$ reduction, as described by Winterfeldt.[10] Separation on silica gel provided crystalline samples of each (19*Z*)-isositsirikine isomer, which showed ^1H NMR properties indistinguishable from those reported.[9,10]

In contrast to the high stereospecificity of the cyclization of the (*Z*)-vinylsilane ester **17b**, the formaldiminium ion derived from the *E* stereoisomer *rac*-**17a** underwent cyclization at 50 °C in acetonitrile to provide a 1.7:1 mixture of racemic methyl geissoschizoate (**18a**) and the *Z* stereoisomer **18b**. Careful monitoring of this reaction by capillary GC demonstrated that $E \rightarrow Z$ isomerization of the ethylidene group was not occurring subsequent to cyclization, while quenching the cyclization reaction at 65% conversion and reisolation of the starting amino ester confirmed that the starting (*E*)-vinylsilane ester suffered no stereomutation under the reaction conditions.

Table I. Cyclization of **17a** To Form Methyl Geissoschizoate **18a** and **18b**[a]

entry	solvent	additive	product ratio,[b] **18a**:**18b**
1	CH_3CN		1.7:1
2	CH_3CN	Bu_4NBr (5 equiv)	2.0:1[c]
3	EtOH		2.7:1[c]
4	MeOH		4.5:1[c]
5	MeOH	Bu_4NBr (5 equiv)	3.4:1[d,e]
6	MeOH	NaF (5 equiv)	7:1[c,e]
7	CH_3CN–H_2O (1:1)		9:1
8	CH_3OH–H_2O (1:1)		8.5:1
9	H_2O		9.1:1[c,f]

[a] Cyclizations were done at 50 °C with 30 equiv of paraformaldehyde and 0.9 equiv of camphorsulfonic acid at a substrate concentration of 0.25 M. The cyclization was complete within 3 h in CH_3CN and took up to 24 h in H_2O. [b] By capillary GC analysis. [c] Reaction temperature was raised to 75 °C after ~20 h. [d] Reaction conducted at 65 °C. [e] Reaction was not clean; other unidentified products were also formed. [f] Formalin was employed instead of paraformaldehyde.

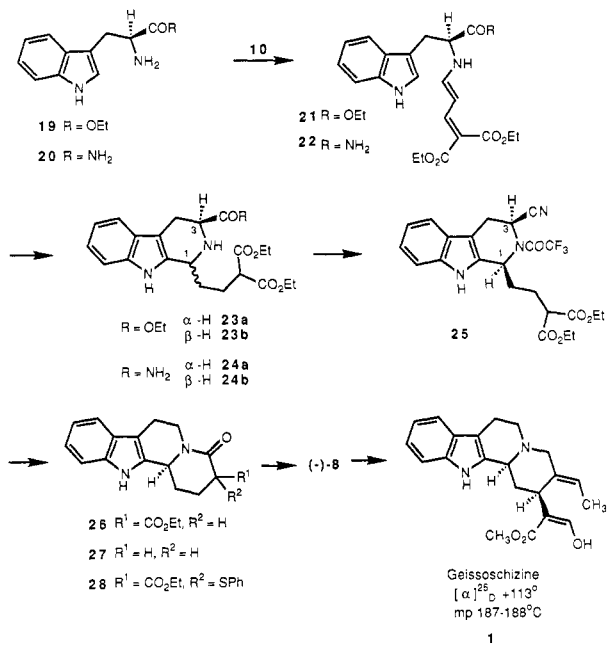
Since cyclizations of (*E*)-vinylsilane analogues of **17a** lacking the acetic acid side chain occur with complete[16] retention of configuration, the developing allylic interactions between the vinylic methyl group and the C-15 side chain of methyl geissoschizoate must be responsible for the loss of stereochemistry in the cyclization of **17a**. We assume that rotation of the C-19/C-20 bond of β-silyl cation intermediate **7** (see Scheme II) is now competitive with loss of the Me_3Si group (vide supra). On the basis of the reasonable assumption[36] that loss of the silyl group from a β-silyl cation involves transfer of this group to a nucleophile, we investigated cyclizations in solvents more silylphilic than acetonitrile. Results of these experiments are presented in Table I and show a clear trend of higher retention of stereochemistry in more nucleophilic solvents. Addition of *n*-Bu_4NBr (entry 5) had little effect on the cyclization in methanol, while the addition of the more silylphilic halide salt NaF (entry 6) did increase the stereospecificity of the reaction.

The cyclization of *rac*-**17a** was most conveniently conducted on a preparative scale in 1:1 MeOH–H_2O and provided racemic methyl geissoschizoate (*rac*-**18a**) in 80% yield after purification on silica gel. Formylation of *rac*-**18a**, as described by Winterfeldt,[37] provided (±)-geissoschizine (mp 189–190 °C) which was indistinguishable from an authentic sample kindly provided by Professor E.Winterfeldt.

Enantioselective Synthesis of (+)-Geissoschizine. An efficient enantioselective synthesis of (+)-geissoschizine along these lines would be possible if a convenient route to the S enantiomer of the key tetracyclic intermediate **8** were developed. Toward this end, we initially examined Pictet–Spengler cyclization[19,28] of the dienamine diester **21**, which was prepared from the reaction of (*S*)-tryptophan ethyl ester with **10** in the presence of tetramethylguanidine (see Scheme V).[38] Cyclization of **21** with trifluoroacetic acid in CH_2Cl_2 at room temperature, followed by reduction of the alkylidene malonate with $NaBH_4$ in EtOH, afforded a separable 2:1 mixture of tetrahydro-β-carbolines **23a** and **23b**. Conducting the cyclization initially at lower temperature (−50 °C → 0 °C) did not improve the yield of **23a**.[39] The lability

(33) See, e.g.: Deslongchamps, P.; Dube, S.; Lebreux, C.; Patterson, D. R.; Taillefer, R. J. *Can. J. Chem.* **1975**, *53*, 2791.
(34) Meerwein, H. *Org. Synth.* **1966**, *46*, 120.
(35) This additive was suggested to us by Professor S. Danishefsky.
(36) See, e.g.: Fleming, I. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds., Pergamon: Oxford, 1979; Vol. 3, p 539.
(37) Winterfeldt, E.; Hachmeister, B.; Thielke, D. *Chem. Ber.* **1976**, *109*, 3825.
(38) For the use of this catalyst to prepare a related intermediate, see: Maclaren, J. A. *Aust. J. Chem.* **1977**, *30*, 2045.

Scheme V



of the alkylidene malonate functionality in the initial cyclization product made chromatographic separation at this point extremely difficult, so we chose to remove this group prior to analysis or product isolation.

Massiot[19c] has reported that Pictet–Spengler cyclizations of iminium cations derived from tryptophanamide (**20**) can be more stereoselective than those of comparable derivatives of tryptophan esters. Thus, we prepared tryptophanamide derivative **22** (as a single stereoisomer in 73% yield from **20** and **10**) and examined its cyclization under acidic conditions. Best results were obtained with trifluoroacetic acid (3 equiv) in CH_2Cl_2 at room temperature, and the reaction provided, after $NaBH_4$ reduction, the *cis*- and *trans*-tetrahydro-β-carbolines **24a** (mp 143–144 °C) and **24b** (mp 141.5–142.5 °C) in a 5.1:1 ratio and 70% yield. Since these diastereomers were highly crystalline and could be separated on a large scale by chromatography, this sequence provided convenient access to diastereomerically pure **24a** on a 10-g scale (40% overall yield from **20**). Stereochemical assignments for the tetrahydro-β-carboline stereoisomers **23** and **24** were initially made on the basis of ^{13}C NMR shifts[40] and were subsequently confirmed in the case of **24a** by conversion to (+)-geissoschizine.

Dehydration of **24a** with trifluoroacetic anhydride[41] afforded the nitrile trifluoroacetamide **25** in 91% yield. After examining a number of reduction conditions for removal of the nitrile moiety, we found that this conversion, as well as cyclization to provide the tetracyclic intermediate **26**, could be accomplished in 90% yield by treatment of **25** with 2 equiv of KBH_4 in refluxing ethanol. This new conversion should be of general utility for the preparation of optically active indoloquinolizidines from tryptophan-derived tetrahydro-β-carbolines. At this stage the enantiomeric purity of our intermediates was determined by conversion[42] of **26** to the known (*S*)-indoloquinolizidine **27**. Comparison of the optical rotation of our sample, $[\alpha]^{25}_D$ −239° (*c* 1.1, $CHCl_3$), with the rotation reported by Meyers[43] ($[\alpha]^{25}_D$ −232° (*c* 1.1, $CHCl_3$)), for a sample believed to have an enantiomeric excess (ee) of 96%, indicates that our sample of **26** has an ee of 99%.

Conversion of **26** to the key tetracyclic intermediate **8** was accomplished by sulfenylation[44] of the lithium salt of **26** at −55 °C with benzenethiosulfonate to provide **28**. Oxidation of sulfide **28**[45] with *m*-(chloroperoxy)benzoic acid at −78 °C followed by elimination of benzenesulfenic acid at 80 °C provided optically active (*S*)-**8** in 73% yield from **26**. As a result of the facile reaction of the alkylidene malonate functionality of **8** with nucleophiles, it was essential that the crude product mixture formed in the elimination step *not* be concentrated to dryness but applied as a solution to silica gel for rapid chromatographic purification. The sequence summarized in Scheme V provides access to indoloquinolizidine **8** of high enantiomeric purity (99% by rotation criteria) in six steps and 24% overall yield from (*S*)-tryptophanamide.

Elaboration of (*S*)-**8** to (+)-geissoschizine was readily accomplished by using the sequence optimized during our studies in the racemic series. Synthetic (+)-geissoschizine (**1**) was isolated as a colorless solid: mp 187–188 °C, $[\alpha]^{25}_D$ + 113° (*c* 0.43, EtOH); natural[4b] (+)-geissoschizine $[\alpha]^{25}_D$ +114° (EtOH).

Conclusion

A practical sequence for the preparation of enantiomerically pure (+)-geissoschizine has been developed. The synthesis involves only 11 chemical steps and proceeds in 7.5% overall yield from (*S*)-tryptophanamide. Notably this sequence does *not* resort at any stage to the use of protecting groups.

This synthesis is the first of (+)- or (±)-geissoschizine that *directly* establishes the correct C-3/C-15 stereorelationship (formed with >13:1 stereocontrol) as well as the *E* stereochemistry of the ethylidene side chain (formed with 9:1 stereocontrol).[49] A related strategy which proceeded with slightly higher levels of stereocontrol was also utilized to prepare the racemic (19*Z*)-isositsirikines (**2**).

This synthetic endeavor demonstrates that stereospecific[15] iminium ion–vinylsilane cyclizations can be employed as key steps in the synthesis of indoloquinolizidine alkaloides containing either the (19*E*)- or (19*Z*)-ethylidene side chain. The successful conversion of **17a** to methyl geissoschizoate (**18a**) indicates that cyclizations of this type occur with useful (although reduced) stereospecificity[15] if the chair conformer of the alkylidene products is destabilized by allylic ($A^{1,3}$) interactions. Tetracyclic intermediate **8**, which is available in 24% yield and 99% enantiomeric purity from (*S*)-tryptophanamide, should be a useful intermediate for the asymmetric synthesis of other alkaloids containing the indoloquinolizidine ring system.

Experimental Section[46]

(±)-3-[2′-((5′-Oxo-5′-ethoxy-4′-(ethoxycarbonyl)penta-1′,3′-dienyl)-amino)ethyl]-1*H*-indole (11). Tryptamine (**9**, 5.00 g, 31.2 mmol) was added to a solutionof **10**[27] (7.56 g, 31.2 mmol) and freshly distilled EtOH (250 mL). The resulting solution was deoxygenated (3×) and maintained under argon at room temperature for 28 h. Concentration of the reaction mixture followed by purification of the residue by flash chromatography (230–400-mesh silica gel; 1:1 ethyl acetate–hexane) gave 10.6 g (95%) of chromatographically pure **11**, an orange glass, as a single stereoisomer: mp 44–48 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.64 (br s, indole NH), 7.61 (d, *J* = 12.5 Hz, *CH*=C(CO_2Et)), 7.54 (d, *J* = 7.7 Hz, 1 H, aromatic), 7.05–7.23 (m, 3 H, aromatic), 6.97 (d, *J* = 2.2 Hz, C-2 H),

(39) For a recent study of temperature effects in cyclizations of this type, see: Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1987**, *28*, 5177.

(40) Sandrin, J.; Soerens, D.; Cook, J. M. *Heterocycles* **1976**, *4*, 1249. Bailey, P. D.; Hollinshead, S. P. *J. Chem. Soc., Chem. Commun.* **1985**, 1575.

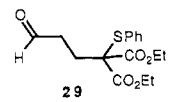
(41) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813.

(42) Yamanaka, E.; Nakayama, K.; Yanagisima, N.; Nagaashima, K.; Yamauchi, M.; Sakai, S. I. *Chem. Pharm. Bull.* **1980**, *28*(8), 2527.

(43) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108.

(44) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405. Trost, B. M.; McDougal, P. G.; Haller, K. J. *J. Am. Chem. Soc.* **1984**, *106*, 383.

(45) We also investigated the direct preparation of this intermediate from (*S*)-tryptophanamide and ethyl 2-(carbethoxy)-5-oxo-2-(phenylthio)pentanoate (**29**); a general sequence which would have precedent from earlier



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studies of Massiot.[19e] However, Pictet–Spengler cyclizations of **29** and **20** proceeded in only modest yield (~40%) and stereoselectivity (~4:1). Details of this sequence will appear in the forthcoming Ph.D. thesis of A. J. Robichaud.

(46) General experimental details have been described: Fisher, M.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

6.86 (br t, J = 12.4 Hz, NHC*H*=CH), 6.20 (t, J = 12.6 Hz, CH=C*H*=CH), 5.33 (br s, NH), 4.15–4.33 (m, 4 H, OCH_2CH$_3$), 3.44 (q, J = 6.4 Hz, 2 H, CH_2NH), 2.99 (t, J = 6.4 Hz, 2 H, CH_2CH_2NH), 1.22–1.39 (m, 6 H, OCH$_2$CH_3); IR ($CHCl_3$) 3478, 3427, 3018, 1693, 1606, 1566, 1212 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 300 (4.48); MS (CI), m/z 357 (MH$^+$), 311, 144, 143; MS (EI), m/z 356.1760 (15, 356.1736 calcd for $C_{20}H_{24}N_2O_4$), 143 (87), 131 (57), 130 (100).

(±)-Ethyl 2-(Ethoxycarbonyl)-4-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)butenoate (*rac*-12). A solution of the N_b-substituted tryptamine **11** (16.6 g, 46.6 mmol) and dry CH_2Cl_2 (500 mL) was deoxygenated (3×) and cooled to 0 °C and freshly distilled trifluoroacetic acid (26.5 g, 230 mmol) was added dropwise. After 20 min at 0 °C, the solution was allowed to warm to room temperature and was washed with H_2O (300 mL) and brine (300 mL), dried ($MgSO_4$), and concentrated to yield 16.4 g (99%) of crude *rac*-**12** as a pale yellow solid. Crystallization from warm ethyl acetate–hexane gave 12.7 g (77%) of pure *rac*-**12** as a pale yellow solid: mp 156–157 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.68 (br s, indole NH), 7.06–7.42 (m, 4 H, aromatic), 7.40 (d, J = 12.2 Hz, C*H*=C(CO$_2$Et)), 5.01 (br s, NH), 4.23–4.32 (m, 4 H, OCH$_2$), 4.19 (dd, J = 7.1, 2.3 Hz, C-1 H), 3.28–3.51 (m, 2 H, C-4 H), 3.14–3.28 (m, 2 H, C-3 H), 2.95–3.09 (m, 2 H, CH_2CH=), 1.20–1.32 (m, 6 H, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 164.0, 143.8, 137.3, 132.5, 128.3, 126.6, 123.4, 120.5, 119.0, 112.4, 107.9, 62.8, 62.4, 52.3, 41.5, 33.2, 18.9, 14.5; IR ($CHCl_3$) 3295, 2990, 1723, 1673, 1455, 1379, 1261, 1202, 835 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 288 (sh, 3.73), 280 (3.82), 268 (3.75), 263 (sh, 3.75), 222 (4.49); MS (CI), m/z 357 (MH$^+$), 171, 161; MS (EI), m/z 356.1746 (356.1736 calcd for $C_{20}H_{24}N_2O_4$), 167 (60), 143 (100), 115 (28).

(±)-Ethyl 4-Oxo-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine-3-carboxylate (*rac*-8). A solution of *rac*-**12** (1.95 g, 5.47 mmol) and dry ethyl acetate (500 mL) was deoxygenated (3×). This solution was heated to reflux under argon for 30 min and concentrated to give 1.68 g (99%) of nearly pure (by ^{1}H NMR analysis) *rac*-**8** as a yellow-orange powdery solid: mp 240–242 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$–DMSO-d_6) δ 10.16 (br s, indole NH), 7.41 (d, J = 7.7 Hz, 1 H, aromatic), 7.29 (dd, J = 6.9, 2.1 Hz, C-2 H), 7.26 (d, J = 7.7 Hz, 1 H, aromatic), 6.95–7.09 (m, 2 H, aromatic), 4.95 (dd, J = 12.8, 3.5 Hz, C-6 H$_{eq}$), 4.78 (dd, J =13.4, 4.3 Hz, C-12b H), 4.20 (q, 2 H, J = 6.8 Hz, CH_2O), 3.07 (ddd, J = 18.1, 6.8, 4.5 Hz, C-1 H$_{eq}$), 2.59–2.91 (m, 3 H, C-6 H$_{ax}$ and 2 C-7 H), 2.31 (ddd, J = 18.1, 13.5, 2.2 Hz, C-1 H$_{ax}$), 1.25 (t, 3 H, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, DMSO-d_6) δ 165.1, 162.0, 144.8, 137.2, 132.8, 130.3, 126.8, 122.3, 119.8, 118.7, 111.7, 108.9, 61.8, 51.6, 39.4, 31.7, 21.4, 14.7, 14.5; IR (KBr) 3283, 2983, 1737, 1646, 1610, 1425, 1248, 1105, 741 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 288 (sh, 3.96), 276 (4.09), 268 (4.09), 222 (4.58); MS (CI), m/z 311 (MH$^+$), 309, 89, 70; MS (EI), m/z 310.1298 (18, 310.1317 calcd for $C_{18}H_{18}N_2O_3$), 237 (80), 170 (64), 169 (100).

(±)-Ethyl 4-Oxo-2-[(*E*)-1-(trimethylsilyl)-1-propenyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (*rac*-14a). A solution of *sec*-BuLi (21.5 mL of a 1.20 M solution in cyclohexane, 25.8 mmol) was added dropwise at −78 °C to a solution of (*E*)-1-bromo-1-(trimethylsilyl)-1-propene **13a** (5.11 g, 26.5 mmol) and dry THF (26 mL), and the resulting solution was maintained at −55 °C for 1 h. The reaction was then cooled to −78 °C and this pale green solution was added, via a cannula, to a suspension of freshly recrystallized CuI[47] (2.40 g, 12.6 mmol) and dry THF (50 mL) at −78 °C. After stirring for 10 min, the resulting black slurry was warmed to −55 °C and maintained at that temperature for 35 min. The reaction mixture was then cooled to −78 °C and freshly distilled trimethylsilyl chloride[30] (3.2 mL, 25 mmol) was added and the resulting black, homogeneous solution was maintained at −60 °C for 30 min. After cooling to −78 °C, a solution of the tetracycle *rac*-**8** (1.56 g, 5.04 mmol) in dry THF (30 mL) was added over 20 min. The resulting dark red solution was maintained at −78 °C for 15 min, −60 °C for 15 min, −45 °C for 1 h, and then −20 °C for 1.5 h, whereupon it was quenched with a solution of saturated aqueous NH_4Cl (80 mL) and concentrated aqueous NH_4OH (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic extracts were washed with 10% aqueous NH_4OH (2 × 200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the crude product (HF254 TLC-grade silica gel; 1.5% MeOH–98.5% CH_2Cl_2) gave 1.61 g (75%) of *rac*-**14a**, a mixture of diastereomers, as a pale yellow solid. A crystalline sample was prepared by recrystallization from ethyl acetate. *rac*-**14a**: mp 221–222.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (br s, indole NH), 7.43 (d, J = 7.5 Hz, 1 H, aromatic), 7.30 (d, J = 7.5 Hz, 1 H, aromatic), 7.0–7.18 (m, 2 H, aromatic), 5.94 (q, J = 6.7 Hz, 1 H, C=C*H*CH$_3$), 4.94 (bd, J = 4.7 Hz, C-6 H$_{eq}$), 4.85 (dd, J = 10.8, 3.7 Hz, C-12b H), 3.85–4.08 (m, 2 H, OCH_2CH$_3$), 3.52 (d, J = 12.2 Hz C-3 H), 3.33 (dt, J = 12.2, 3.5 Hz, C-2 H$_{eq}$), 2.88–3.03 (m, 2 H, C-7 H), 2.65 (br d, J = 12.0 Hz, C-6 H$_{ax}$), 2.36 (dt, J = 13.3, 6.4 Hz, C-1 H$_{ax}$), 2.17 (dt, J = 13.9, 3.0 Hz, C-1 H$_{eq}$), 1.50 (d, J = 6.7 Hz, 3 H, C=CHCH_3), 1.08 (J = 7.1 Hz, 3 H, OCH$_2$CH_3), 0.12 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.2, 163.1, 142.3, 139.8, 137.6, 134.2, 128.9, 123.3, 121.0, 119.5, 112.4, 112.3, 61.9, 56.3, 44.1, 36.3, 33.0, 22.2, 16.0, 15.1, 2.04; IR (KBr) 3388, 3291, 2953, 1732, 1624, 1446, 1250, 1177, 838, 743 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 288 (sh, 3.68), 280 (3.77), 268 (sh, 3.68), 262 (sh, 3.61), 223 (4.49); MS (CI), m/z 425 (MH$^+$), 89, 73; MS (EI), m/z 424.2166 (39, 424.2182 calcd for $C_{24}H_{32}N_2O_3Si$), 351 (100), 309 (56), 73 (80). Anal. Calcd for $C_{24}H_{32}N_2O_3Si$: C, 67.89; H, 7.60; N, 6.60. Found: C, 67.98; H, 7.64; N, 6.57.

(±)-Ethyl 4-Oxo-2-[(*Z*)-1-(trimethylsilyl)-1-propenyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (*rac*-14b). According to the procedure used for the preparation of *rac*-**14a**, *rac*-**8** (1.50 g, 4.83 mmol) was allowed to react with the cuprate reagent prepared from (*Z*)-1-bromo-1-(trimethylsilyl)-1-propene **13b** (4.90 g, 25.3 mmol). Purification of the crude product by flash chromatography (HF254 TLC grade silica gel; 1.5% MeOH–98.5% CH_2Cl_2) gave 1.60 g (78%) of *rac*-**14b**, a mixture of diastereomers, as a pale yellow solid. A crystalline sample was prepared by recrystallization from ethyl acetate. *rac*-**14b**: mp 243–244 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (br s, indole NH), 7.51 (d, J = 7.6 Hz, 1 H, aromatic), 7.35 (d, J = 8.0 Hz, 1 H, aromatic), 7.20 (dt, J = 7.6, 1.1 Hz, 1 H, aromatic), 7.14 (dt, J = 7.9, 0.96 Hz, 1 H, aromatic), 6.11 (dq, J = 6.8, 0.71 Hz, 1 H, C=C*H*CH$_3$), 5.09 (dd, J = 12.2, 3.7 Hz, C-6 H$_{eq}$), 4.76 (dd, J = 7.0, 5.8 Hz, C-12b H), 4.08–4.18 (m, 2 H, OCH_2CH$_3$), 3.61 (d, J = 6.6 Hz, C-3 H), 2.99–3.03 (m, C-2 H$_{eq}$), 2.96 (ddd, J = 14.6, 4.7, 2.5 Hz, C-7 H), 2.89 (dt, J = 12.1, 3.4 Hz, C-6 H$_{ax}$), 2.75 (d, J = 15.1, C-7 H), 2.22 (ddd, J = 13.9, 7.4, 4.1 Hz, C-1 H$_{eq}$), 2.09 (ddd, J = 14.0, 7.4, 5.8 Hz, C-1 H$_{ax}$), 1.82 (d, J = 7.0 Hz, 3 H, C=CHCH_3), 1.19 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 0.22 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 167.1, 140.5, 138.0, 136.7, 133.1, 127.8, 122.9, 120.6, 119.0, 111.6, 111.3, 62.0, 54.6, 52.4, 42.0, 38.8, 32.8, 21.6, 18.7, 14.8, 1.2; IR (KBr) 3309, 2953, 1738, 1617, 1445, 1324, 1305, 1249, 1159, 1034, 849, 838, 747 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 289 (sh, 3.79), 280 (3.89), 268 (sh, 3.84), 262 (sh, 3.77), 224 (4.59); MS (CI), m/z 425 (MH$^+$), 89, 81, 71; MS (EI), m/z 424.2173 (60, 424.2182 calcd for $C_{24}H_{32}N_2O_3Si$), 351 (75), 237 (63), 169 (62), 73 (100). Anal. Calcd for $C_{24}H_{32}N_2O_3Si$: C, 67.89; H, 7.60; N, 6.60. Found: C, 67.91; H, 7.64; N, 6.59.

(±)- and (2*S*,12b*S*)-4-Oxo-2-[(*E*)-1-(trimethylsilyl)-1-propenyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (*rac*-15a and (−)-15a). The general procedure of Grieco[32] was followed. A solution of tetracycle *rac*-**14a** (817 mg, 1.92 mmol) and EtOH (33 mL) was heated at 55 °C and a solution of Ba(OH)$_2$·8H$_2$O (3.53 g, 11.2 mmol) in EtOH–H_2O (100 mL, 1:2) was added over 15 min. The resulting heterogeneous mixture was stirred vigorously at reflux for 3.5 h and then was cooled to ~5 °C, diluted with brine (100 mL), and acidified with 5% aqueous HCl. The aqueous phase was extracted with ethyl acetate (3 × 250 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield a yellow solid which was presumed to be the corresponding carboxylic acid. This solid was taken up in dry toluene (100 mL) and heated at 80 °C for 1 h. Concentration yielded a tan solid, which was purified by flash chromatography (HF254 TLC-grade silica gel; 2% MeOH–98% CH_2Cl_2) to give 522 mg (76%) of pure *rac*-**15a** as a colorless crystalline solid and 51 mg (11%) of a mixture of *rac*-**15a**, *rac*-**16a**, and *rac*-**15b**. Capillary GC analysis[48] of the crude product mixture showed that this reaction sequence afforded a 91.5:7.0:1.5 ratio of *rac*-**15a**:*rac*-**16b**:*rac*-**15b**. An analytically pure sample of *rac*-**15a** was prepared by recrystallization from ethyl acetate: mp 234–235 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (br s, indole NH), 7.50 (d, J = 7.5 Hz, 1 H, aromatic), 7.34 (d, J = 8.0 Hz, 1 H, aromatic), 7.17 (t, J = 7.3 Hz, 1 H, aromatic), 7.13 (t, J = 7.3 Hz, 1 H, aromatic), 5.93 (q, J = 6.5 Hz, 1 H, C=C*H*CH$_3$), 5.03 (dd, J = 12.3, 5.3 Hz, C-6 H$_{eq}$), 4.99 (br dd, J = 4.6, 1.0 Hz, C-12b H), 3.07 (tdd, J = 13.6, 5.4, 2.5 Hz, C-7 H$_{eq}$), 2.96 (dt, J = 12.2, 4.1 Hz, 2 H, C-3$_{cis}$ H and C-6 H$_{ax}$), 2.71 (dd, J = 15.1, 4.1 Hz, C-7 H$_{ax}$), 2.53 (dd, J = 16.7, 12.6 Hz, C-3$_{trans}$ H), 2.30-2.42 (m, 2 H, C-1 H), 2.20 (ddd, J = 13.9, 5.2, 2.4 Hz, C-2 H), 1.56 (dd, J = 6.7, 1.5 Hz, 3 H, C=CHCH_3), 0.15 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 143.2, 137.5, 136.6, 133.8, 128.2, 122.7, 120.5, 118.9, 111.7, 54.8, 43.3, 39.4, 33.2, 32.6, 21.6, 15.4, 1.54; IR (KBr) 3406, 3270, 2953, 1620, 1468, 1443, 1303, 1264, 1249, 853, 835, 754, 736 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 288 (sh, 3.77),

(47) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.

(48) Capillary GC analysis was performed with a Hewlett-Packard 5880A series gas chromatograph employing a 30 m × 0.25 mm DB-5 column with temperature programming from 70 to 280 °C.

(49) **Note Added in Proof**: An efficient stereocontrolled synthesis of (±)-geissoschizine was recently reported from Martin's laboratories: Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925.

280 (3.85), 269 (sh, 3.75), 262 (3.66), 223 (4.56); MS (CI, isobutane), m/z 353 (MH^+), 351, 81, 71; MS (EI), m/z 352.1983 (9, 352.1971 calcd for $C_{21}H_{28}N_2OSi$), 237 (60), 169 (29), 73 (100). Anal. Calcd for $C_{21}H_{28}N_2OSi$: C, 71.54; H, 8.00; N, 7.95. Found: C, 71.59; H, 8.04; N, 7.86.

Reaction of (*S*)-**8** with **13a** as described for the preparation of *rac*-**14a**, followed by decarboalkoxylation and purification as described above, provided (−)-**15a** in comparable yield: $[\alpha]^{25}_D$ −72.8° (*c* 0.46, MeOH).

(±)-4-Oxo-2-[(*Z*)-1-(trimethylsilyl)-1-propenyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (*rac*-15b). According to the procedure used for the preparation of *rac*-**15a**, *rac*-**14b** (1.15 g, 2.70 mmol) was decarbalkoxylated and purified by flash chromatography (HF254 TLC-grade silica gel; 2.5% MeOH–97.5% CH_2Cl_2) to give 812 mg (85%) of *rac*-**15b** as a colorless crystalline solid and 68 mg of a mixture of diastereomers *rac*-**15b**, *rac*-**16b**, and *rac*-**15a**. Capillary GC analysis[48] of the crude product mixture showed that this reaction sequence provided a 95:4:1 ratio of *rac*-**15b**:*rac*-**15a**:*rac*-**16b**.

An analytically pure sample of *rac*-**15b** was prepared by recrystallization from ethyl acetate: mp 244–245 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, indole NH), 7.50 (d, J = 7.7 Hz, 1 H, aromatic), 7.35 (d, J = 8.0 Hz, 1 H, aromatic), 7.19 (t, J = 7.7 Hz, 1 H, aromatic), 7.13 (t, J = 7.3 Hz, 1 H, aromatic), 6.09 (dq, J = 6.5, 6.3 Hz, 1 H, C=C*H*CH_3), 5.14 (dd, J = 12.3, 4.4 Hz, C-6 H_{eq}), 4.73 (br t, J = 6.5 Hz, C-12b H), 2.92 (ddt, J = 14.3, 4.3, 2.4 Hz, C-7 H), 2.85 (dt, J = 12.0, 3.3 Hz, C-6 H_{ax}), 2.72–2.80 (m, 2 H, C-7 H and C-2 H_{eq}), 2.57 (dd, J = 17.4, 5.6 Hz, C-3 H_{ax}), 2.50 (dd, J = 17.4, 5.1 Hz, C-3 H_{eq}), 2.16–2.23 (m, C-1 H_{eq}), 2.05 (app ddd, J = 13.4, 8.6, 3.8 Hz, C-1 H_{ax}), 1.83 (d, J = 6.9 Hz, 3 H, C=CHC*H*$_3$), 0.22 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 141.5, 136.8, 133.8, 127.9, 122.7, 120.5, 118.9, 111.6, 110.9, 52.0, 41.2, 38.7, 35.1, 33.9, 21.7, 18.6, 1.21; IR (KBr) 3254, 2950, 2918, 2856, 1616, 1471, 1447, 1416, 1352, 1324, 1302, 1266, 1249, 1235, 837, 742 cm^{-1}; UV (MeOH) λ_{max} (log ε) 288 (sh, 3.83), 280 (3.91), 268 (sh, 3.84), 262 (sh, 3.78), 223 (4.61); MS (CI), m/z 353 (MH^+), 352, 351, 297; MS (EI), m/z 352.1974 (32, 352.1971 calcd for $C_{21}H_{28}N_2OSi$), 237 (100), 169 (36), 73 (44). Anal. Calcd for $C_{21}H_{28}N_2OSi$: C, 71.54; H, 8.00; N, 7.95. Found: C, 71.51; H, 8.01; N, 7.90.

A chromatographically pure sample of *rac*-**16b** was obtained by preparative TLC (silica gel, 1% MeOH–99% CH_2Cl_2, three elutions). *rac*-**16b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (br s, indole NH), 7.52 (d, J = 7.5 Hz, 1 H, aromatic), 7.34 (d, J = 7.6 Hz, 1 H, aromatic), 7.10–7.23 (m, 2 H, aromatic), 6.12 (q, J = 6.6 Hz, 1 H, C=C*H*CH_3), 5.17 (d, J = 8.2 Hz, C-6 H_{eq}), 4.80 (dd, J = 11.4, 4.5 Hz, C-12b H), 2.58–2.98 (m, 6 H, C-3 H, C-7 H, C-6 H_{ax}, C-2 H_{ax}), 2.36 (dt, J = 12.7, 2.2 Hz, C-1 H_{eq}), 2.20 (dd, J = 17.6, 13.0 Hz, C-1 H_{ax}), 1.81 (d, J = 6.9 Hz, C=CHC*H*$_3$), 0.23 (s, 9 H, $Si(CH_3)_3$).

(±)- and (2*S*,12b*S*)-Methyl 2,3,4,9-Tetrahydro-β-[(*E*)-1-(trimethylsilyl)-1-propenyl]-1*H*-pyrido[3,4-*b*]indole-1-butanoate (*rac*-17a and (−)-17a). A solution of 2,6-di-*tert*-butylpyridine (0.13 mL, 0.57 mmol), *rac*-**15a** (100 mg, 0.28 mmol), freshly prepared trimethyloxonium tetrafluoroborate[34] (84.0 mg, 0.57 mmol), and dry CH_2Cl_2 (2.0 mL) was maintained at room temperature for 3 h and then concentrated to yield a tan solid. This solid was taken up in CH_3CN (1.5 mL), cooled to 0 °C, and 20% aqueous Na_2CO_3 (2 mL) was added. The ice bath was removed and the reaction mixture was stirred vigorously for 20 min. The aqueous portion was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (HF254 TLC-grade silica gel; 2.5% MeOH–0.3% Et_3N–97.2% CH_2Cl_2) gave 90 mg (82%) of chromatographically pure *rac*-**17a** as a pale yellow semisolid and 12.3 mg (12%) of recovered *rac*-**15a** as a white solid. *rac*-**17a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (br s, indole NH), 7.48 (d, J = 7.6 Hz, 1 H, aromatic), 7.39 (d, J = 7.9 Hz, 1 H, aromatic), 7.06–7.10 (m, 2 H, aromatic), 6.02 (q, J = 6.7 Hz, 1 H, C=C*H*CH_3), 3.92 (brt, J = 6.3 Hz, N-2 H), 3.70 (s, 3 H, OCH_3), 3.58 (app ddd, J = 14.1, 8.1, 6.0 Hz, C-1 H), 3.32 (dt, J = 12.6, 4.8 Hz, 1 H), 3.04 (app ddd, J = 12.9, 7.7, 5.5 Hz, 1 H), 2.71–2.85 (m, 2 H), 2.65 (dd, J = 15.7, 8.7 Hz, 1 H), 2.45 (dd, J = 15.7, 6.0 Hz, 1 H), 1.98 (app dt, J = 14.0, 6.0 Hz, 1 H), 1.82–1.92 (m, 2 H), 1.81 (d, J = 6.8 Hz, 3 H, C=CHC*H*$_3$), 0.17 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 145.2, 137.5, 136.7, 128.3, 122.1, 120.0, 118.6, 111.6, 52.4, 52.3, 43.2, 41.2, 40.4, 35.6, 23.3, 16.1, 1.49; IR (neat) 3359, 2951, 2845, 1720, 1438, 1300, 1248, 1163, 837 cm^{-1}.

By use of an identical procedure, (−)-**17a** was prepared in comparable yield: $[\alpha]^{25}_D$ −63.9° (*c* 0.74, MeOH).

(±)-Methyl 2,3,4,9-Tetrahydro-β-[(*Z*)-1-(trimethylsilyl)-1-propenyl]-1*H*-pyrido[3,4-*b*]indole-1-butanoate (*rac*-17b). According to the procedure used for the preparation of *rac*-**17a**, *rac*-**15b** (183 mg, 0.52 mmol) was hydrolyzed to give, after flash chromatography of the residue (HF254 TLC-grade silica gel; 2.5% MeOH–0.3% Et_3N–97.2% CH_2Cl_2), 156 mg (78%) of chromatographically pure *rac*-**17b** as a pale yellow semisolid and 19.3 mg (10%) of recovered starting material *rac*-**15b** as a white solid. *rac*-**17b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (br s, indole NH), 7.46 (d, J = 7.6 Hz, 1 H, aromatic), 7.36 (d, J = 7.8 Hz, 1 H, aromatic), 7.03–7.19 (m, 2 H, aromatic), 6.26 (q, J = 6.9 Hz, 1 H, C=C*H*CH_3), 3.99 (bt, J = 6.1 Hz, N-2 H), 3.67 (s, 3 H, OCH_3), 3.32 (app dt, J = 12.7, 4.7 Hz, C-1 H), 2.94–3.11 (m, 2 H), 2.63–2.80 (m, 2 H), 2.50 (dd, J = 7.1, 1.6 Hz, 2 H), 1.82–1.92 (m, 3 H), 1.80 (d, J = 6.9 Hz, 3 H, C=CHC*H*$_3$), 0.20 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 143.5, 137.6, 137.5, 136.5, 128.2, 122.0, 119.9, 118.6, 111.5, 109.4, 54.7, 54.6, 45.8, 44.1, 43.3, 41.4, 25.9, 21.1, 3.71; IR (neat) 3398, 2951, 2844, 1725, 1437, 1300, 1248, 1157, 843, 757, 743 cm^{-1}.

(±)-Methyl Geissoschizoate and (3*S*,15*R*)-Methyl Geissoschizoate (*rac*-18a and 18a). A mixture of paraformaldehyde (656 mg, 22.0 mmol), *rac*-**17a** (274 mg, 0.71 mmol), camphorsulphonic acid (149 mg, 0.64 mmol), and MeOH–H_2O (20 mL, 1:1) was heated at 50 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with 5% aqueous NaOH (40 mL). The aqueous portion was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried (K_2CO_3) and concentrated. Purification of the residue by flash chromatography (HF254 TLC-grade silica gel; 1% MeOH–0.3% Et_3N–98.7% CH_2Cl_2) gave 185 mg (80%) of chromatographically pure racemic methyl geissoschizoate (*rac*-**18a**) as a pale yellow semisolid. In addition, 27.1 mg (12%) of *rac*-**18b** was isolated as a pale yellow solid: mp 67–68.5 °C dec. *rac*-**18a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br s, indole NH), 7.49 (d, J = 7.7 Hz, 1 H, aromatic), 7.36 (d, J = 7.9 Hz, aromatic), 7.16 (dt, J = 7.5, 1.1 Hz, 1 H, aromatic), 7.11 (dt, J = 7.6, 1.0 Hz, 1 H, aromatic), 5.48 (q, J = 6.8 Hz, 1 H, C=C*H*CH_3), 4.28 (br s, C-3 H), 3.70 (s, 3 H, OCH_3), 3.55 (d, J = 12.2 Hz, C-21 H), 3.27 (app ddd, J = 13.0, 5.8, 1.2 Hz, C-5 H_β), 3.10–3.18 (m, 2 H, C-5 H_α and C-15 H), 2.98–3.08 (m, C-6 H_β), 2.95 (d, J = 12.3 Hz, C-21 H), 2.64 (ddd, J = 15.7, 3.5, 1.6 Hz, C-6 H_α), 2.31 (dt, J = 14.3, 3.7 Hz, C-14 H), 2.10–2.22 (m, 3 H, C-14 H and 2 C-16 H), 1.65 (dd, J = 6.8, 1.4 Hz, 3 H, C=CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 136.9, 136.7, 134.5, 128.5, 122.2, 121.4, 120.2, 118.7, 111.8, 108.5, 54.2, 54.1, 52.3, 52.1, 38.2, 32.0, 31.6 18.9, 13.3; IR ($CHCl_3$) 3472, 3363, 3010, 2928, 1718, 1449, 1439, 1316, 1141, 1110, 1010, 909 cm^{-1}; MS (CI), m/z 325 (MH^+), 324, 323; MS (EI), m/z 324.1832 (100, 324.1838 calcd for $C_{20}H_{24}N_2O_2$), 323 (70), 251 (74), 169 (66).

An identical sequence starting with (−)-**17a** yielded (3*S*,15*R*)-**18a** in comparable yield as a low-melting solid.

(±)-(19*Z*)-Methyl Geissoschizoate (*rac*-18b). According to the procedure used for the preparation of *rac*-**18a**, amino ester *rac*-**17b** (40 mg, 0.10 mmol) was cyclized and the crude product purified by flash chromatography (HF254 TLC-grade silica gel; 1% MeOH–0.3% Et_3N–98.7% CH_2Cl_2), to give 33.7 mg (100%) of chromatographically pure (±)-(19*Z*)-methyl geissoschizoate (*rac*-**17b**) as a pale yellow solid: mp 67–68.5 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (br s, indole NH), 7.46 (d, J = 7.6 Hz, 1 H, aromatic), 7.30 (d, J = 7.9 Hz, 1 H, aromatic), 7.03–7.18 (m, 2 H, aromatic), 5.24 (q, J = 6.4 Hz, 1 H, C=C*H*CH_3), 3.90 (d, J = 12.3 Hz, C-21 H_β), 3.75 (s, 3 H, OCH_3), 3.56 (bd, J = 11.0 Hz, C-3 H), 3.16 (m, C-5 H_β), 3.01 (m, C-6 H_β), 2.76 (d, J = 11.7 Hz, C-21 H_α), 2.65–2.85 (m, 4 H, C-5 H_α, C-6 H_α and 2 C-16 H), 2.33 (app dd, J = 17.2, 10.1 Hz, C-15 H), 2.26 (app dt, J = 12.4, 3.2 Hz, C-14 H_α), 1.72 (d, J = 6.7 Hz, 3 H, C=CHC*H*$_3$), 1.39 (app q, J = 11.9 Hz, C-14 H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 136.7, 136.5, 134.9, 122.0, 120.0, 118.8, 117.2, 111.4, 108.8, 60.2, 56.0, 53.1, 52.4, 38.7, 37.4, 22.3, 13.8; IR ($CHCl_3$) 3475, 3353, 3021, 2953, 2920, 2853, 2808, 2756, 1732, 1459, 1439, 1323, 1047, 1010, 909 cm^{-1}; MS (CI), m/z 325 (MH^+), 324, 75, 71; MS (EI), m/z 324.1822 (100, 324.1838 calcd for $C_{20}H_{24}N_2O_2$), 323 (69), 185 (82), 169 (77).

(±)-Geissoschizine and (+)-Geissoschizine (*rac*-1 and (+)-1). Formylation of methyl geissoschizoate (*rac*-**18a**, 110 mg, 0.34 mmol) following the procedure of Winterfeldt[37] provided, after recrystallization from EtOH, 63.0 mg (53%, 87% yield based on consumed starting material) of pure (±)-geissoschizine (**1**) as colorless crystals: mp 189–190 °C (lit.[37] mp 187–189 °C). Spectral (500-MHz ^{1}H NMR, ^{13}C NMR,[5d] MS) properties of this material were indistinguishable from those reported,[5] and synthetic (±)-**1** was also indistinguishable, by TLC comparisons (in three solvent systems), with an authentic sample of geissoschizine provided by E. Winterfeldt.

In an identical fashion, (3*S*,15*R*)-methyl geissoschizoate (**18a**) was converted to (+)-geissoschizine (**1**): mp 188–189 °C (lit.[3b] mp 180–182 °C, lit.[4b] mp 194–196 °C); $[\alpha]^{25}_D$ +113° (*c* 0.43, EtOH) (lit.[4b] $[\alpha]^{21}_D$ +115° (EtOH).

(±)-(19*Z*)-Isositsirikine (*rac*-2). According to the general procedure of Winterfeldt,[10] *rac*-**18b** was formylated and reduced with $NaBH_4$. Separation by preparative TLC (silica gel, 3.5% MeOH–96.5% CH_2Cl_2,

three elutions) provided pure samples of the two C-16 diastereomers of (±)-(19*Z*)-isositsirikine. Spectral (500-MHz ^{1}H NMR, MS, UV) properties of these isomers were consistent with those reported[8-10] for the two (±)-(19*Z*)-isositsirikine diastereomers. High R_f isomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 136.8, 135.6, 134.8, 127.9, 122.1, 120.0, 118.8, 118.0, 111.5, 108.7, 61.2, 60.2, 56.3, 53.2, 52.8, 48.9, 41.3, 33.68 22.2, 13.9; IR ($CHCl_3$) 3350, 2955, 2875, 2809, 1725, 1450, 1378, 1205, 1047 cm^{-1}. Low R_f isomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 136.7, 134.7, 128.0, 122.2, 120.1, 119.5, 118.8, 111.6, 108.8, 63.1, 59.1, 55.1, 52.8, 52.7, 49.6, 41.6, 34.8, 30.4, 21.7, 13.9.

(*S*)-3-[2′-Carbamoyl-2′-((5′-oxo-5′-ethoxy-4′-(ethoxycarbonyl)penta-1′,3′-dienyl)amino)ethyl]-1*H*-indole (22). Freshly distilled tetramethylguanidine (9.80 g, 85.1 mmol) was added to a solution of (*S*)-(−)-tryptophanamide (**20**, 17.0 g, 85.1 mmol) and dry DMF (1 L) at 0 °C. After 20 min the alkoxy diene dioate **10** (22.4 g, 92% pure by capillary GC[48] analysis, 85.1 mmol) was added slowly. The orange solution was maintained at 0 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was quenched by addition of 1 M aqueous $NaHCO_3$ (500 mL). The aqueous layer was extracted with ethyl acetate (2 × 500 mL) and saturated with NaCl and extracted again with ethyl acetate (2 × 500 mL). The combined organic extracts were washed with 1 M aqueous $NaHCO_3$ (500 mL), H_2O (2 × 500 mL), and brine (500 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (230–400-mesh silica gel; 1–2% MeOH in ethyl acetate) gave 24.8 g (73%) of **22**, a yellow crystalline solid, as a single stereoisomer: mp 67–69 °C; $[\alpha]^{25}_D$ −30.7° (*c* 0.68, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (br s, indole NH), 7.62 (d, *J* = 7.9 Hz, 1 H, aromatic), 7.51 (d, *J* = 12.2 Hz, C*H*=C(CO_2Et)), 7.38 (d, *J* = 8.0 Hz, 1 H, aromatic), 7.22 (t, *J* = 7.6 Hz, 1 H, aromatic), 7.15 (t, *J* = 7.4 Hz, 1 H, aromatic), 7.06 (d, *J* = 2.1 Hz, C-2 H), 6.83 (br t, *J* = 10.5 Hz, NHC*H*=), 6.19 (t, *J* = 12.6 Hz, CH=C*H*=CH), 5.80 (br s, CONH), 5.63 (t, *J* = 7.9 Hz, NH), 5.55 (br s, CONH), 4.15–4.30 (m, 4 H OCH_2CH_3), 4.16 (q, *J* = 6.3 Hz, CH_2CH(NH)), 3.32 (dd, *J* = 14.8, 5.6 Hz, 1 H, CH_2CH(NH)), 3.24 (dd, *J* = 14.7, 6.7 Hz, 1 H, CH_2CH-(NH)), 1.25–1.35 (m, 6 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 172.0, 168.1, 167.8, 154.0, 136.8, 127.8, 124.5, 122.7, 120.2, 119.1, 112.3, 109.6, 61.2, 61.1, 15.0, 14.9; IR (KBr) 3330, 1683, 1677, 1615, 1561, 1327, 1175, 1068, 744 cm^{-1}; UV (EtOH) λ_{max} (log ε) 222 (4.55), 282 (3.88), 290 (sh, 3.83), 366 (4.59); MS (CI), *m/z* 400 (MH^+), 355, 354, 186, 168; MS (EI), *m/z* 399.1777 (36, 399.1794 calcd for $C_{21}H_{25}N_3O_5$), 373 (60), 308 (49), 186 (100).

(1*S*,3*S*)- and (1*R*,3*S*)-Ethyl 2,3,4,9-Tetrahydro-3-carbamoyl-α-(ethoxycarbonyl)-1*H*-pyrido[3,4-*b*]indole-1-butanoate (24a and 24b). A solution of **22** (11.0 g, 27.5 mmol) and dry CH_2Cl_2 (1.4 L) was deoxygenated (3×) and cooled to 0 °C and freshly distilled trifluoroacetic acid (9.40 g, 82.6 mmol) was added dropwise. After 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.8 L) and diluted with H_2O (500 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL), and the combined organic extracts were washed with brine (0.8 L), dried (Na_2SO4), and concentrated to yield 11.0 g (100%) of the crude cyclization product (a 5:1 mixture of cis and trans diastereomers, by ^{1}H NMR analysis) as a pale yellow solid.

Without purification, this solid was dissolved in dry EtOH (1.6 L) and $NaBH_4$ (2.10 g, 55.0 mmol) was added portionwise and the resulting mixture was stirred for 4.5 h at room temperature. After concentration of the reaction mixture to approximately 0.8 L, it was quenched with H_2O (0.8 L). The aqueous solution was extracted with ethyl acetate (3 × 0.8 L), and the combined organic extracts were washed with brine (0.8 L), dried (Na_2SO_4), and concentrated. This sequence was conducted two times on this scale to afford 19.9 g of crude product as an orange solid. Preliminary purification by flash chromatography (230–400-mesh silica gel; 2.5–7% MeOH in CH_2Cl_2) afforded 15.4 g (70%) of a mixture of **24a** and **24b** (~5:1 by ^{1}H NMR analysis). Separation of this mixture by preparative HPLC (Waters Prep LC 500; 5% EtOH–95% CH_2Cl_2; 250 mL/min) afforded 11.9 g (54%) of the pure cis diastereomer **24a** and 2.92 g of a 16:1 mixture of the trans and cis diastereomers. Recrystallization of each of these fractions from ethyl acetate–hexane afforded analytically samples of the cis diastereomer as colorless needles (mp 143–144 °C) and the trans diastereomer as a colorless crystalline solid (mp 141.5–142.5 °C). Cis diastereomer **24a**: $[\alpha]^{25}_D$ −107.6° (*c* 0.50, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, indole NH), 7.50 (d, *J* = 7.7 Hz, 1 H, aromatic), 7.35 (d, *J* = 8.0 Hz, 1 H, aromatic), 7.17, (dt, *J* = 7.5, 1.1 Hz, 1 H, aromatic), 7.10 (dt, *J* = 7.6, 0.9 Hz, 1 H, aromatic), 7.04 (br d, *J* = 3.4 Hz, CONH), 5.87 (br d, *J* = 3.3 Hz, CONH), 4.16–4.28 (m, 5 H, OCH_2CH_3 and NH), 3.62 (dd, *J* = 11.3, 4.7 Hz, C-3 H_{ax}), 3.46 (t, *J* = 7.0 Hz, C-1 H_{ax}), 3.29 (ddd, *J* = 15.6, 4.7, 2.0 Hz, C-4 H_{eq}), 2.76 (ddd, *J* = 15.6, 11.4, 2.6 Hz, C-4 H_{ax}), 1.97–2.15 (m, 4 H), 1.72–1.81 (m, 1 H), 1.22–1.37 (m, 6 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 170.14, 170.07, 136.8, 135.9, 127.9, 122.6, 120.3, 118.9, 111.7, 109.9, 62.4, 58.4, 54.1, 52.1, 32.1, 25.9, 25.2, 14.8, 14.7; IR (KBr) 3350, 3290, 2982, 2907, 1744, 1725, 1671, 1453, 1370, 1300, 1227, 1158, 1027, 743 cm^{-1}; UV (EtOH) λ_{max} (log ε) 225 (4.54), 283 (3.82), 290 (sh, 3.70); MS (CI), *m/z* 402 (MH^+), 339, 173, 161; MS (EI), *m/z* 401.1943 (21, 401.1950 calcd for $C_{21}H_{27}N_3O_5$), 214 (100), 169 (49), 69 (90). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.92; H, 6.82; N, 10.41.

Trans diastereomer **24b**: $[\alpha]^{25}_D$ −27.9° (*c* 0.70, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (br s, indole NH), 7.50 (d, *J* = 7.4 Hz, 1 H, aromatic), 7.32 (d, *J* = 8.0 Hz, 1 H, aromatic), 7.17 (t, *J* = 7.1 Hz, 1 H, aromatic), 7.10 (t, *J* = 7.5 Hz, 1 H, aromatic), 7.07 (br s, CONH), 5.59 (br s, CONH), 4.18–4.29 (m, 4 H, OCH_2CH_3), 4.06 (dd, *J* = 9.6, 4.1 Hz, NH), 3.71 (dd, *J* = 9.9, 4.8 Hz, C-3 H_{ax}), 3.47 (t, *J* = 7.3 Hz, C-1 H_{eq}), 3.23 (dd, *J* = 15.9, 4.8 Hz, C-4 H_{eq}), 2.83 (ddd, *J* = 15.9, 9.9, 1.2 Hz, C-4 H_{ax}), 2.27–2.37 (m, 1 H), 2.02–2.15 (m, 1 H), 1.71–1.88 (m, 3 H), 1.23–1.33 (m, 6 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 170.3, 170.2, 136.6, 136.3, 127.7, 122.4, 120.1, 118.8, 111.5, 108.8, 62.3, 53.1, 52.2 51.9, 32.6, 26.6, 24.8, 14.7; IR (KBR) 3387, 3305, 3295, 2982, 2937, 1725, 1671, 1453, 1371, 1303, 1255, 1184, 1156, 1025, 744 cm^{-1}; UV (EtOH) λ_{max} (log ε) 226 (4.60), 283 (3.93), 290 (sh, 3.87); MS (CI), *m/z* 402 (MH^+), 85, 81, 71; MS (EI), *m/z* 401.1958 (41, 401.1950 calcd for $C_{21}H_{27}N_3O_5$), 242 (35), 214 (100), 169 (91). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.92; H, 6.80; N, 10.39.

(1*S*,3*S*)-Ethyl 2,3,4,9-Tetrahydro-3-cyano-2-(trifluoroacetyl)-α-(ethoxycarbonyl)-1*H*-pyrido[3,4-*b*]indole-1-butanoate (25). The general procedure of Campagna and Casini[41] was followed. To a solution of the *cis*-1,3-tetrahydro-β-carboline **24a** (5.00 g, 12.4 mmol) and dry dioxane (100 mL) were added freshly distilled trifluoroacetic anhydride (3.92 g, 18.7 mmol) and dry pyridine (2.46 g, 31.1 mmol) at room temperature. After 7 h, additional trifluoroacetic anhydride (3.92 g, 18.7 mmol) and dry pyridine (2.46 g, 18.7 mmol) were added, and after 14 h the solution was quenched by addition of 1 M aqueous $NaHCO_3$ (250 mL). The aqueous layer was extracted with ethyl acetate (3 × 200 mL), and the combined organic extracts were washed with brine (250 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (230–400-mesh silica gel; 2–3% MeOH in CH_2Cl_2) yielded 5.38 g (91%) of **25** as a colorless crystalline solid: mp 51–53 °C; $[\alpha]^{25}_D$ +36.8° (*c* 1.1, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of amide conformational isomers) δ 8.92 (br s, indole NH), 8.84 (br s, indole NH), 7.41–7.52 (m, 2 H, aromatic), 7.23–7.29 (m, 1 H, aromatic), 7.15–7.20 (m, 1 H, aromatic), 6.21 (dd, *J* = 4.9, 3.0 Hz), 5.54–5.58 (m), 5.42 (dd, *J* = 5.6, 1.5 Hz), 5.10–5.13 (m), 4.15–4.33 (m, 4 H, OCH_2CH_3), 3.54 (t, *J* = 6.5 Hz), 3.45 (dd, *J* = 7.5, 5.7 Hz), 3.20–3.39 (m), 2.63–2.72 (m), 2.18–2.40 (m), 1.23–1.36 (m, 6 H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 169.9, 137.2, 131.3, 131.0, 126.5, 126.4, 123.8, 123.6, 121.0, 120.9, 119.1, 118.9, 118.8, 117.8, 117.7, 115.4, 112.3, 112.2, 104.6, 103.9, 62.9, 62.7, 62.6, 62.5, 54.13, 54.11, 52.5, 52.1, 51.9, 42.94, 42.91, 42.88, 39.3, 35.6, 33.3, 27.5, 26.6, 26.4, 25.9, 14.7, 14.6; IR (KBr) 3354, 3018, 2987, 2967, 1746, 1737, 1708, 1434, 1303, 1257, 1217, 1202, 1180, 1146, 1062, 747 cm^{-1}; UV (EtOH) λ_{max} (log ε) 222 (4.59), 272 (4.02), 275 (sh, 4.01), 289 (3.85); MS (CI), *m/z* 480 (MH^+); MS (EI), *m/z* 479.1668 (21, 479.1667 calcd for $C_{23}H_{24}N_3O_5F_3$), 305 (16), 292 (100), 169 (18). Anal. Calcd for $C_{23}H_{24}N_3O_5F_3$: C, 57.62; H, 5.05; N, 8.76. Found: C, 57.69; H, 5.06; N, 8.72.

(12b*S*)-Ethyl 4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine-3-carboxylate (26). A solution of the nitrile **25** (5.30 g, 11.0 mmol) and dry EtOH (0.6 L) was deoxygenated and purged with argon. To this solution was added KBH_4 (3.10 g, 57.5 mmol) and the resulting mixture was stirred at mild reflux. After 2 the reaction mixture was allowed to cool to room temperature and was concentrated to approximately 300 mL and then quenched by addition of H_2O (300 mL) and brine (300 mL). The aqueous layer was extracted with ethyl acetate (3 × 300 mL), and the combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (230–400-mesh silica gel; 3–5% MeOH in CH_2Cl_2) gave 3.10 g (90%) of **26** (a ~1:1 mixture of C-3 diastereomers) as a pale yellow solid. Recrystallization from ethyl acetate–hexane gave an analytical sample of **26** as a colorless crystalline solid: mp 200–201.5 °C; $[\alpha]^{25}_D$ −149° (*c* 0.94, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (br s, indole NH), 7.94 (br s, indole NH), 7.51 (d, *J* = 7.8 Hz, 1 H, aromatic), 7.35 (d, *J* = 7.8 Hz, 1 H, aromatic), 7.20 (t, *J* = 7.5 Hz, 1 H, aromatic), 7.14 (t, *J* = 7.4 Hz, 1 H, aromatic), 5.12–5.21 (m, 1 H), 4.79–4.92 (m, 1 H), 4.18–4.32 (m, OCH_2CH_3), 4.14 (q, *J* = 7.1 Hz, OCH_2CH_3), 3.58 (dd, *J* = 5.3, 3.4 Hz), 3.44 (dd, *J* = 11.2, 6.4 Hz), 2.75–2.96 (m), 2.49–2.57 (m), 2.33–2.51 (m), 2.16–2.32 (m), 2.02–2.15 (m), 1.77–1.86 (m), 1.32 (t, *J* = 7.2 Hz, OCH_2CH_3), 1.20 (t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 171.4, 166.1, 166.0, 137.0, 136.9, 133.5, 133.4, 127.4, 127.3, 122.8, 122.7, 120.4, 120.3, 119.0, 111.74, 111.70, 110.0, 109.9, 62.2, 62.1, 55.1, 55.0, 49.1, 41.5,

41.2, 28.2, 26.4, 23.9, 23.6, 21.7, 21.6, 14.7, 14.6; IR (KBr) 3303, 3272, 1734, 1623, 1470, 1437, 1324, 1306, 1159, 1094, 742 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 224 (4.53), 282 (3.90), 290 (3.82); MS (CI), m/z 313 (MH^+), 311.241; ms (EI), m/z 312.1486 (100, 312.1474 calcd for $C_{18}H_{20}N_2O_3$), 239 (78), 237 (51), 184 (80). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.13; H, 6.49; N, 8.94.

(12b*S*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (27). A solution of the ester **26** (100 mg, 0.32 mmol), lithium chloride (27 mg, 0.64 mmol), H_2O (~7 μL), and dimethyl sulfoxide (2.0 mL) was heated at 160 °C for 3.5 h.[42] The reaction mixture was cooled and concentrated in vacuo and the residue was partitioned between H_2O and $CHCl_3$. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3× 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and purification of the residue by flash chromatography (HF 254 TLC-grade silica; 3% MeOH–CH_2Cl_2) gave 56 mg (73%) of **27** as a yellow solid. Recrystallization from MeOH afforded pure **27** as pale yellow needles: mp 247–248.5 °C; lit.[19e] mp 250 °C; $[\alpha]^{25}_D$ −239° (*c* 1.12, $CHCl_3$); lit.[43] $[\alpha]^{25}_D$ −232° (*c* 1.02, $CHCl_3$).

(12b*S*)-Ethyl 4-Oxo-3-(phenylthio)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-3-carboxylate (28). To a solution of 0.50 M lithium diisopropylamide (0.50 mL, 0.25 mmol, in THF) and dry THF (1.0 mL) at −78 °C under argon was added a solution of the tetracycle **26** (79.2 mg, 0.25 mmol) and dry THF (1.5 mL), and the resulting solution was maintained at −78 °C for 10 min and then at 0 °C for 20 min. The reaction mixture was then cooled to −45 °C and a solution of benzenethiosulfonate[44] (62.0 mg, 0.25 mmol) and dry THF (1.5 mL) was added dropwise over 10 min. The resulting cloudy mixture was stirred for 2 h and then quenched by addition of saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 30 mL), and the combined organic extracts were washed with 1 M aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by radial chromatography[46] (GF 254 silica gel, 2-mm plate; 0.5% MeOH–0.2% Et_3N–99.3% CH_2Cl_2) afforded 102 mg (98%) of chromatographically pure **28** (a mixture of diastereomers) as a pale yellow solid, which was suitable for use in the next step. For characterization purposes these diastereomers were separated by preparative TLC (silica gel, 1% MeOH–99% CH_2Cl_2, three elutions). Diastereomer A: mp 220–221 °C (from ethyl acetate); $[\alpha]^{25}_D$ −73.0° (*c* 0.20, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (br s, indole NH), 7.64 (d, *J* = 7.0 Hz, 2 H, aromatic), 7.51 (d, *J* = 7.7 Hz, 1 H, aromatic), 7.40 (d, *J* = 7.3 Hz, 1 H, aromatic), 7.29–7.42 (m, 3 H, aromatic), 7.18 (t, *J* = 7.2 Hz, 1 H, aromatic), 7.13 (t, *J* = 7.2 Hz, 1 H, aromatic), 5.20 (dd, *J* = 11.4, 4.0 Hz, C-6 H_{eq}), 4.62 (dd, *J* = 11.6, 4.3 Hz, C-12$_b$ H_{ax}), 4.13 (q, *J* = 7.1 Hz, OCH_2CH_3), 2.73–2.92 (m, 3 H, C-6 H_{ax} and C-7 H), 2.30–2.40 (m, 2 H), 2.04–2.13 (m, 1 H), 1.72–1.84 (m, 1 H), 1.15 (t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 166.1, 138.2, 136.9, 133.1, 131.1, 130.4, 129.3, 127.4, 123.0, 120.7, 119.2, 111.6, 110.4, 63.1, 60.7, 55.1, 41.8, 31.5, 27.4, 21.6, 14.6. Diastereomer B: $[\alpha]^{24}_D$ −8.4° (*c* 0.34, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (br s, indole NH), 7.55 (d, *J* = 7.0 Hz, 2 H, aromatic), 7.52 (d, *J* = 7.7 Hz, 1 H, aromatic), 7.35 (d, *J* = 8.0 Hz, 1 H, aromatic), 7.19–7.33 (m, 4 H, aromatic), 7.15 (t, *J* = 7.4 Hz, 1 H, aromatic), 5.13 (m, 1 H, C-6 H_{eq}), 4.88 (br t, *J* = 7.2 Hz, C-12$_b$ H_{ax}), 4.22–4.32 (m, 2 H, OCH_2CH_3), 2.83–2.96 (m, 2 H, C-7 H), 2.72–2.81 (m, C-6 H_{eq}), 2.45 (ddd, *J* = 13.9, 10.1, 3.8 Hz, 1 H), 2.20–2.35 (m, 2 H), 1.9 (ddd, *J* = 13.8, 6.6, 3.6 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 165.6, 137.7, 136.8, 133.2, 131.1, 130.2, 129.3, 127.6, 123.0, 120.7, 119.1, 111.7, 110.8, 63.2, 62.5, 54.8, 42.2, 294, 25.6, 21.6, 14.8. Mixture of diastereomers: $[\alpha]^{25}_D$ −50.9° (*c* 0.84, EtOH); IR (KBr) 3330, 3296, 3059, 2979, 2920, 2849, 1727, 1624, 1438, 1304, 1220, 1188, 1025, 741, 692 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 224 (4.60), 274 (3.97), 290 (sh, 3.84); MS (CI), m/z 421 (MH^+), 314, 313, 311, 111; MS (EI), m/z 420.1489 (0.5%, 420.1507 calcd for $C_{24}H_{24}N_3O_3S$), 265 (100%), 184 (21%), 169 (22%). Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66. Found: C, 67.80; H, 5.82; N, 6.55.

(12b*S*)-Ethyl 4-Oxo-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]-quinolizine-3-carboxylate (8). To a solution of the sulfide **28** (305 mg, 0.720 mmol) and dry CH_2Cl_2 (20 mL) at −78 °C was added a solution of *m*-chloroperbenzoic acid (197 mg, ~70%, 0.80 mmol) and dry CH_2Cl_2 (10 mL). The cloudy mixture was stirred for 1.5 h at −78 °C and then warmed to −30 °C. After 15 min at −30 °C, freshly distilled Et_3N (147 mg, 1.45 mmol) was added and the cloudy reaction mixture immediately became homogeneous. The resulting solution was then warmed to 0 °C and quenched by pouring into a separatory funnel containing 1 M aqueous $NaHCO_3$ (50 mL) and ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (2 × 50 mL), and the combined organic extracts were washed with 1 M aqueous $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated to a volume of approximately 50 mL. This solution was heated at 80 °C for 45 min and then allowed to cool to room temperature. Concentration of this solution to ~10 mL and immediate flash chromatography (230–400-mesh silica gel, activity IV, 12 g; 24 mm i.d. column; 3:2 ethyl acetate–hexane) yielded 164 mg (74%) of chromatographically pure (−)-**8** as a pale orange glass: mp 233–235 °C. Due to the instability of this intermediate, it must be used immediately if optimum results in the cuprate coupling sequence are to be obtained. Chromatographically purified (−)-**8** showed melting points which ranged from 198 to 233 °C in various runs.

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The Trifulvathiane System

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Abstract: Permethylated monofulvathiane, difulvathiane, and trifulvathiane were synthesized by reacting *s*-trithiane with *N*-butyllithium and 1, 2, or 3 equiv, respectively, of the tetraphenylborate of either 4,5-dimethyl-1,3-dithia-2-imminium or the 4,5-dimethyl-1,3-dithia-2-methylthiolium ions. The MNDO calculated ionization potentials of the fulvathianes support the prediction that they should be as easy to oxidize as tetrathiafulvalene, but cyclic voltammetry (CV) shows significant shifts in the solution redox potentials. EPR solution spectra of the radical ions were obtained.

The synthesis of interesting organic one-electron donors and acceptors in the last 30 years has concentrated on flat (or almost flat) molecules of D_{2h} symmetry (or C_i symmetry approaching D_{2h} symmetry). Thus, high conductivity compounds, or quasi-

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