with anhydrous magnesium sulfate, filtered, and concentrated. Silica gel flash column chromatography (ethyl acetate–hexane, 1:6) gave **9** (169 mg, 89%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.37 (s, 9 H), 1.54 (s, 3 H), 1.62 (s, 3 H), 1.38–2.52 (m, 10 H), 3.30–3.77 (m, 2 H); ^{13}C NMR (25.4 MHz, $CDCl_3$) δ 19.0 (q), 22.6 (q), 22.6 (t), 22.7 (t), 28.5 (q), 31.3 (t), 39.1 (t), 39.4 (t), 47.1 (t), 70.1 (s), 78.2 (s), 121.5 (s), 137.7 (s), 153.5 (s); MS m/z (relative intensity) 265 (M^+, 10), 209 (100), 148 (31), 122 (52); IR (neat) 2950, 2870, 1690, 1392, 1250, 1175, 1135, 1100, 935, 870, 775; HRMS calcd for $C_{16}H_{27}NO_2$ 265.2042, found 265.2037.

1-Aza-1-(*tert*-butoxycarbonyl)spiro[4.4]nonan-6-one (10). To a solution of **9** (159 mg, 0.6 mmol) in methanol (8 mL) was bubbled with ozone at 0 °C. The reaction was followed by thin-layer chromatography until the starting material disappeared. The reaction was then quenched with dimethyl sulfide (1 mL). The reaction mixture was stirred at room temperature for 5 min and then concentrated. The residue was purified by silica gel flash column chromatography (ethyl acetate–hexane, 1:6) to give **10** (137 mg, 96%) as a colorless oil: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.61–2.69 (m, 10 H), 3.33–3.73 (m, 2 H); MS m/z (relative intensity) 239 (M^+, 29), 211 (21), 183 (38), 166 (13), 155 (38), 127 (100); IR (neat) 2965, 2870, 1745, 1685, 1389, 1175, 1145, 1098. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.50; H, 9.12; N, 5.73.

1-Aza-1-[2-[3,4-(methylenedioxy)phenyl]ethyl]spiro[4.4]nonan-6-one (14). To a solution of **10** (900 mg, 3.76 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 0.5 h. After neutralization with saturated sodium carbonate solution at 0 °C, the mixture was extracted with dichloromethane. The combined organic layer was dried with anhydrous magnesium sulfate and concentrated. The residue was then dissolved in acetonitrile (10 mL). To the solution was added a solution of **12** (2 g, 5.6 mmol) and diisopropylethylamine (2 mL, 1.46 g, 11.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 3 days. The solvent was then removed by a rotary evaperator. The residue was taken into dichloromethane solution. The organic layer was dried with anhydrous magnesium sulfate and then concentrated. Silica gel flash column chromatography (ethyl acetate–hexane, 1:1) gave **14** (778 mg, 2.71 mmol, 72%) as a yellow oil: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.50–2.30 (m, 10 H), 2.44–2.76 (m, 4 H), 2.80–3.24 (m, 2 H), 5.89 (s, 2 H), 6.48–6.77 (m, 2 H); ^{13}C NMR (25.4 MHz, $CDCl_3$) δ 18.2 (t), 21.8 (t), 32.1 (t), 35.6 (t), 35.9 (t), 37.3 (t), 51.7 (t), 68.3 (t), 73.6 (t), 100.4 (t), 107.7 (d), 108.8 (d), 121.0 (d), 133.8 (s), 145.3 (s), 147.0 (s), 221.5 (s); MS m/z (relative intensity) 287 (M^+, 15), 259 (100), 231 (15), 166 (23), 152 (35), 148 (46), 124 (69); IR (neat) 2960, 2880, 1735, 1622, 1495, 1445, 1247, 1180, 1100, 1045 935, 812, 733 cm^{-1}.

1-Aza-1-[2-(3,4-dimethoxyphenyl)ethyl]spiro[4.4]nonan-6-one (15). The same procedure as that for **14** was used. Compound **10** (195 mg, 0.76 mmol), **13** (100 mg, 1.9 mmol), and diisopropylethylamine (3 mL, 2.23 g, 17 mmol) reacted for 3 days to give **15** as a yellow oil (182 mg, 79%): ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.48–2.52 (m, 10 H), 2.52–2.88 (m, 4 H), 2.92–3.28 (m, 2 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 6.24–6.92 (m, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.9 (t), 21.5 (t), 31.6 (t), 35.3 (t), 35.5 (t), 36.9 (t), 51.4 (t), 51.5 (t), 55.3 (q), 73.4 (s), 110.7 (d), 111.6 (d), 120.0 (d), 132.6 (s), 146.8 (s), 148.2 (s), 221.6 (s); DEPT technique was used to determine the multiplicity; MS m/z (relative intensity) 303 (M^+, 10), 275 (78), 247 (14), 182 (14), 164 (100), 152 (29), 124 (50); IR (neat) 2950, 2825, 1730, 1600, 1511, 1460, 1425, 1260, 1234, 1138, 1030, 810, 768; HRMS calcd for $C_{18}H_{25}NO_3$ 303.1835, found 303.1841.

(*RS*)-2,3,5,6,8,9-Hexahydro-11,12-dimethoxy-4*H*-cyclopenta[*a*]pyrrolo[2,1-*b*][3]benzazepine (16). A mixture of **15** (504 mg, 1.66 mmol) and polyphosphoric acid (4 g) was stirred and heated at 60 °C for 20 h. The reaction mixture was then poured into a cold saturated sodium carbonate solution. The solution was then adjusted to basic (pH = 10) by sodium hydroxide solution and extracted with dichloromethane (3 × 40 mL). The organic layer was dried with anhydrous magnesium sulfate and concentrated. Silica gel flash column chromatography (dichloromethane–methanol, 9:1) gave the recovered starting material **15** (122 mg, 24%) and product **16** (240 mg, 56%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.45 (m, 1 H), 1.57–1.78 (m, 3 H), 1.82–1.95 (m, 2 H), 2.08–2.22 (m, 1 H), 2.27–2.40 (m, 1 H), 2.69–3.00 (m, 4 H), 3.18–3.35 (m, 1 H), 3.35–3.48 (m, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 5.65 (t, 1 H, J = 2.4 Hz), 6.51 (s, 1 H), 6.58 (s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.0 (t), 29.0 (t), 32.1 (t), 35.2 (t), 40.8 (t), 43.5 (t) 48.9 (t), 55.5 (q), 55.6 (q), 78.6 (s), 112.2 (d), 113.0 (d), 127.4 (s), 128.2 (d), 129.1 (s), 146.4 (s), 147.8 (s), 150.0 (s); MS m/z (relative intensity) 285 (M^+, 100), 270 (20); IR (neat) 2900, 1600, 1514, 1462, 1240, 1210, 1145, 1150, 1030 cm^{-1}; HRMS calcd for $C_{18}C_{23}NO_3$ 285.1729, found 285.1710. For the single-crystal X-ray analysis, a crystal of the HCl salt of **16** was obtained from recrystallization in ethyl acetate and dichloromethane and subjected to X-ray analysis. Crystal data of **16**, $[C_{18}H_{23}O_2NH]^+Cl^-$: M = 321.88, monoclinic, space group $P2_1/c$, a = 8.070 (2) Å, b = 8.3761 Å, c = 24.211 (6) Å, β = 92.49 (2)°, Z = 4, D_c = 1.31 g/cm^3. A total of 2521 independent reflections were measured of which 1870 were considered observed [$I > 2.5\sigma(I)$]. The structure was solved by the direct method to an R value 0.0466. All calculations were performed on a Micro Vax II based Nicolet SHELXTL PLUS system.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support.

Supplementary Material Available: X-ray data of the HCl salt of **16**, ^{1}H NMR spectra of compounds **7**, **8**, **9**, **10**, **14**, **15**, and **16**, and ^{13}C NMR spectra of compounds **9**, **14**, **15**, and **16** (17 pages). Ordering information is given on any current masthead page.

Total Syntheses of Tubotaiwine and 19,20-Dihydro-20-*epi*-akuammicine

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Starting from the indoloazepine **9**, the title products **2** and **7** were synthesized in seven steps in 27 and 22% overall yields, respectively.

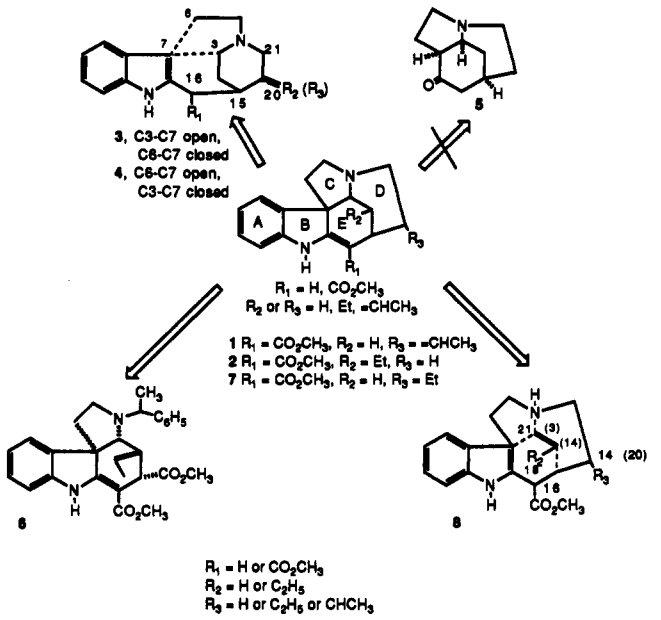
Introduction

Synthetic efforts leading to pentacyclic *Strychnos* alkaloids, represented by akuammicine (**1**) and tubotaiwine (**2**), have received less attention than those directed at other classes of indole or indoline alkaloids.[1,2] Nearly all of the studies that culminated in the former ring system utilized an oxidative cyclization of a stemmadenine-type

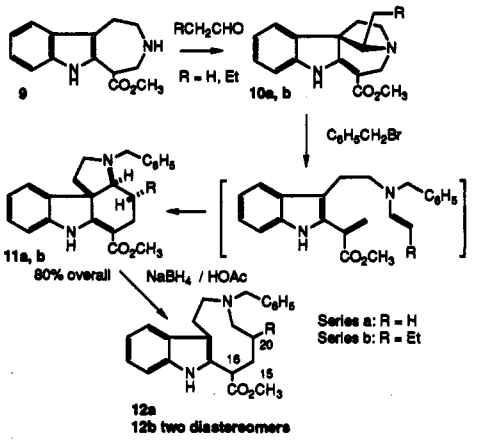
(1) Bosch, J.; Bonjoch, J. In Pentacyclic Strychnos Alkaloids. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed. Elsevier: Amsterdam, 1988; Vol. I, p 31.

0022-3263/91/1956-2696$02.50/0

Scheme I



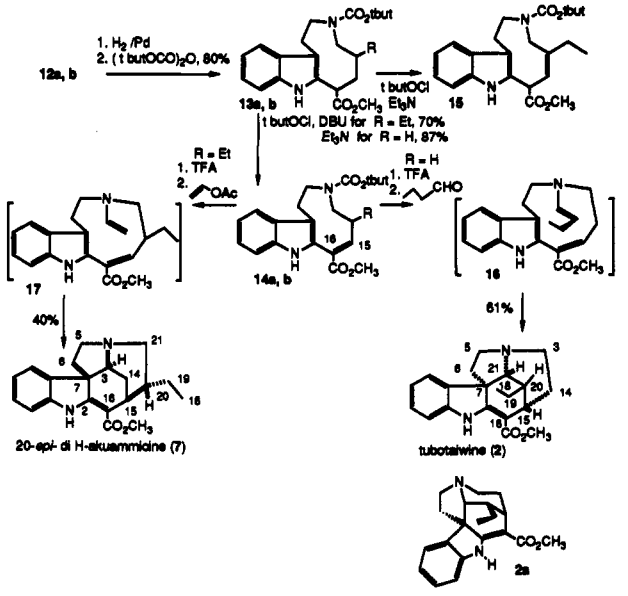
Scheme II



precursor **3** (Scheme I).[3] This strategy was also extended analogously to the C-seco compounds **4**,[4] with final introduction of a two-carbon bridge from N^b to the indole ring.[5] More recently, there has been a description of assembly of a DEC tricyclic ketone **5** (with the rings formed in that order). However, a final Fischer indole reaction did not give the desired regiochemistry in annelation of rings A and B.[6]

Alternatively, generation of a D-seco intermediate **6** by intramolecular Diels–Alder-type reaction of an indole 2-acrylate with an N^b-derived enamine (a concept used extensively in our group for construction of aspidosperma alkaloids)[7] provided the route for an enantioselective synthesis of the tubotaiwine (**2**) skeleton.[8]

Scheme III



Maximization of such secodine-type cyclization chemistry now allows us to present most efficacious syntheses of racemic tubotaiwine (**2**) and 19,20-dihydro-20-*epi*-akuammicine (**7**). In this strategy, an indoloazonine **8** is generated initially by way of secodine-type chemistry and then C18–C21 or C3–C14 segments are inserted, with simultaneous generation of rings C, D, and E by repetition of this indoloacrylate–enamine addition chemistry.

Condensation of the indoloazepine **9** with either acetaldehyde or with butyraldehyde provided the respective bridged azepines **10a** and **10b** as epimeric mixtures (Scheme II).[9] N^b-Benzylation of these compounds and treatment of the resulting quaternary salts with triethylamine resulted in fragmentation to transient indoloacrylate (*E*)-enamine intemediates and their stereospecific cyclization to the corresponding products **11a** and **11b**.[7] On treatment with sodium borohydride in hot acetic acid, these compounds underwent reductive ring cleavage to provide the indoloazonines **12a** and **12b**, respectively. While the latter product was formed as a 3:1 mixture of diastereomers, their convergence in the next step eradicated any inherent synthetic complication. The diastereomers of **12b** could, however, be chromatographically separated for characterization.

In the ^1H NMR spectra of all of these compounds **12a** and **12b** the C16 H signal is typically shifted downfield (to δ 5.6) due to interaction of that hydrogen with the N^b lone pair,[10] and consequently its isolation permitted more detailed structural studies on the diastereomers of **12b**. Thus, a relatively weaker nuclear Overhauser effect (NOE) interaction of the C16 H and C20 H in the major diastereomer of **12b** and a stronger NOE signal in the minor diastereomer suggest a cis assignment of methoxycarbonyl and ethyl substituents in the minor isomer.[11] It may be

(2) Cordell, G. A. *Heterocyclic Compounds: The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Vol. 25, Part 4, p 539.

(3) Cyclization of a D-ring lactam with $POCl_3$ was reported to furnish tubotaiwine (**2**) through an unusual spontaneous reduction: Dadson, B. A.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1969**, 665.

(4) The biogenetic numbering system used for all compounds is that of: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508. Lettering of the fused ring systems follows the same implied principle.

(5) (a) Amat, M.; Linares, A.; Muñoz, J.; Bosch, J. *Tetrahedron Lett.* **1988**, *29*, 6373. (b) Amat, M.; Linares, A.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 2293.

(6) Bonjoch, J.; Casamitjana, J.; Quirante, J.; Rodriguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267.

(7) For a summary of leading references, see: Kuehne, M. E., Marko, I. *The Alkaloids*; Brossi, A., Suffness, M., Eds. Academic Press: New York, 1990; Vol. 37, p 77.

(8) (a) Vercauteren, J.; Lavaud, C.; Lévy, J.; Massiot, G. *J. Org. Chem.* **1984**, *49*, 2278 (the same chemistry and generation of 15-carbomethoxy intermediates was developed in our laboratory by Dr. Richard Skeenan in 1982). (b) Henin, J.; Massiot, G.; Vercauteren, J.; Guilhem, J. *Tetrahedron Lett.* **1987**, *28*, 1271. (c) Legseir, B.; Henin, J.; Massiot, G.; Vercauteren, J. *Tetrahedron Lett.* **1987**, *28*, 3573.

(9) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002.

(10) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.

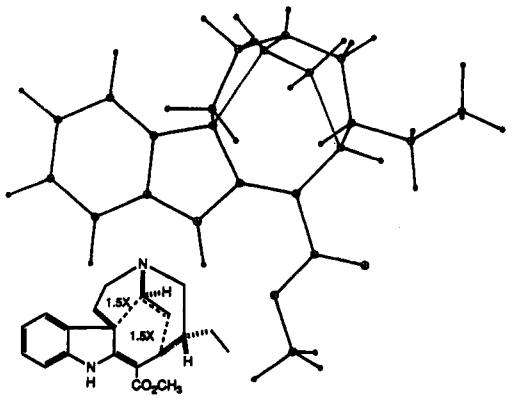


Figure 1.

noted that this isomer (C16 H–C20 H = 2.3 Å) is energetically less favored than the trans isomer of **12b** (C16 H–C20 H = 3.7 Å) by 2.8 kJ/mol, according to molecular modeling computation (MACROMODEL).

For introduction of a C15–C16 double bond and later enamine formation, N^b was debenzylated by hydrogenolysis and the resulting secondary amine function protected as a urethane (**13a**, **13b**) by reaction with di-*tert*-butyl dicarbonate (Scheme III). As expected, these products no longer displayed the downfield C16 H signals seen in the ^1H NMR spectra of the corresponding amines **12a** and **12b** and carbamate rotamers resulted in multiplicity of ^1H NMR signals.

Chlorination of the N^b-acylated indoloazonines **13a** and **13b** with *tert*-butyl hypochlorite and treatment of the resulting chloroindolenines with base then led to formation of the indoloacrylates **14a** and **14b** (Scheme III). While triethylamine could be used for generation of the unsubstituted product **14a**, it was found that extensive rearrangement to the β,γ-unsaturated ester **15** occurred on formation of the ethyl-substituted compound **14b** when triethylamine was used; but this deconjugation of the acrylate could be minimized through the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Cleavage of the carbamate function in the unsaturated esters **14a** and **14b** with trifluoroacetic acid and subsequent condensation of the resulting secondary amines, under basic conditions, with butyraldehyde or with vinyl acetate directly provided tubotaiwine (**2**) or 19,20-*epi*-akuammicine (**7**) from the respective reactions. The use of acetaldehyde in the latter case was less satisfactory, presumably due to its enhanced aldol condensation.

In both reaction sequences, a single (racemic) stereoisomer was obtained. In the synthesis of tubotaiwine (**2**), the equatorial ethyl orientation (with respect to ring D, see **2a**) could be expected on kinetic grounds from a Diels–Alder-like transition state **16** for addition of an (*E*)-enamine functionality to the indoloacrylate moiety. A thermodynamic derivation of the equatorial ethyl group seems less likely since reversible formation of the C7–C21 bond, required for epimerization at C20 through imonium–enamine tautomerism, is doubtful under the basic reaction conditions.

(11) Qualitatively, the C16 H signals of the major isomer (dd) and minor isomer (d) of **12b** are consistent with this assignment, considering modeling computations for energy-minimized conformations, which gave J = 7.3, 2.4 for the trans isomer and J = 10.6, 1.0 for the cis isomer. Measured values of J = 9.1, 1.0 for the minor (cis) isomer are a satisfactory match for the corresponding computed values, but with J = 12.6, 4.8, they are less close for the major (trans) diastereomer of **12b**, perhaps because of the presence of additional, higher energy conformers contributing to the NMR spectrum.

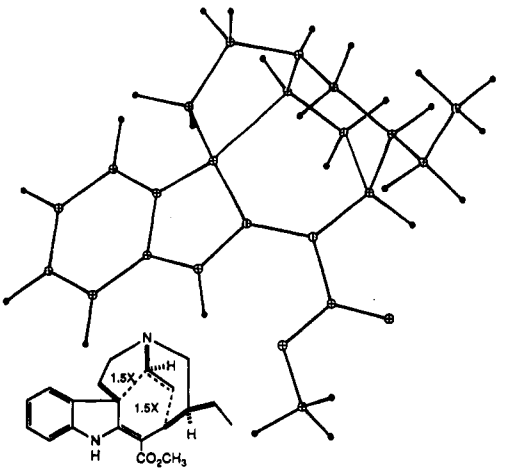


Figure 2.

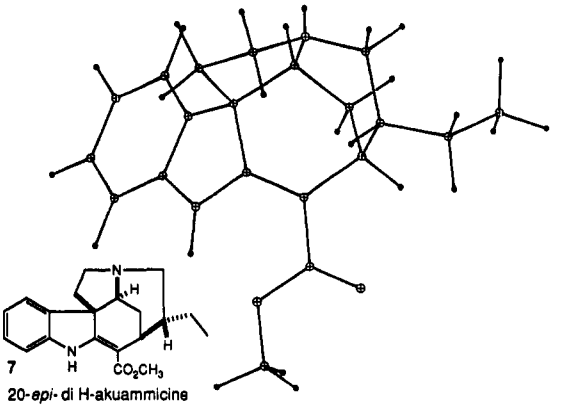


Figure 3.

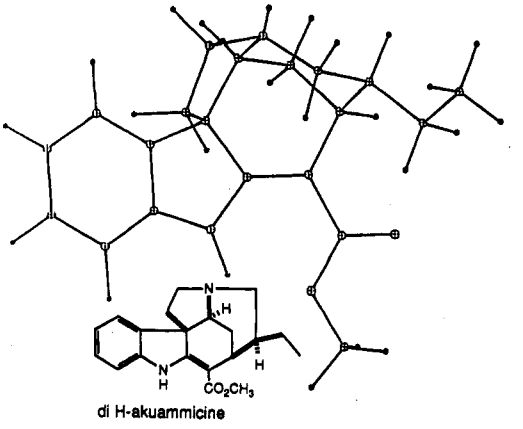


Figure 4.

More surprising was the stereochemical result obtained on formation of 19,20-dihydro-20-*epi*-akuammicine (**7**). Here, the enamine moiety added to the more substituted face of the indoloacrylate function and resulted in a product with a potential axial ethyl substituent on ring D. Nevertheless, molecular modeling calculations for the transition state of the reaction (**17**) indicated energy minimization at that configuration. When the developing C3–C7 and C14–C15 bonds in the transition state **17** were set at 1.5× the corresponding product bond lengths, the relative energy of the transition state leading to 20-*epi*-19,20-dihydroakuammicine (Figure 1) was calculated at 202 kJ/mol while that for the transition state leading to 19,20-dihydroakuammicine (Figure 2) was calculated at 229 kJ/mol. On the other hand, the relative energies of the corresponding products (Figure 3 and Figure 4), where ring

D is in a boat conformation for 20-*epi*-19,20-dihydroakuammicine (**7**) and in a chair conformation for 19,20-dihydroakuammicine, were calculated at 200 and 182 kJ/mol, respectively. ^1H NMR and ^{13}C NMR data for the product **7** differed from those published for its C20 epimer[5b] and are consistent with the indicated structure. Particularly, an NOE experiment revealed interaction of the 6β and the 20β hydrogens by irradiation at δ 2.45 and 1.73, respectively.

It should be noted that the two C20 epimers of dihydroakuammicine were reported to have been equilibrated by heating in methanol, leading to a 4:1 mixture favoring 19,20-dihydroakuammicine, starting from either C20 epimer (inversion at C3, C7, and C15).[12]

As seen from these two syntheses, this new approach to the *Strychnos* alkaloids is notably expeditious. Elaboration to more highly functionalized intermediates and products are readily visualized and their generation will be pursued further.

Experimental Section

General Methods. All reactions were started under a nitrogen atmosphere unless otherwise stated. Melting points were obtained on a Kofler micro hotstage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were obtained with Bruker 250- or 270-MHz instruments, and chemical shifts are expressed as parts per million (δ) downfield from tetramethylsilane unless otherwise stated. Mass spectra were obtained with a Finnigan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and hexafluorotriphenyl-*s*-triazine for higher molecular weight compounds. High-resolution mass spectra, providing accurate mass data, were obtained by electron-impact ionization and direct-probe sample insertion on a VG 70E-HF double-sector instrument and a VG 11-250 DEL based data system. IR spectra were obtained with a Nicolet 6000 FT instrument. Perkin-Elmer 402 and Lambda instruments were used for recording UV spectra. TLC data were obtained with Merck 60 PF 254 precoated silica gel on aluminum sheets. Indole derivatives were visualized with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid as a spray reagent, and other compounds were visualized by either UV or iodine vapor. Chromatography employed Baker 3405 60-200 mesh silica gel. Microanalyses were provided by Robertson Laboratories, Florham Park, NJ.

N^b-Benzyl-16-(methoxycarbonyl)-*D*-norcleavamine (12a). N^b-Benzyl-*D*-nordeethylvincadifformine (**11a**, 2.0 g, 5.6 mmol)[9] was dissolved in acetic acid (40 mL) and heated to 90 °C with an oil bath. Sodium borohydride (2.1 g, 56 mmol) was added in portions as quickly as possible. The mixture was immediately poured into a solution of ice–water and NH_4OH, and the basic mixture was extracted three times with dichloromethane. The organic phase was dried over sodium sulfate and then concentrated under vacuum to a residue. Crystallization with methanol gave 1.70 g (84%) of product: mp 126–127 °C; TLC (SiO_2, ether:hexane = 1:1) R_f 0.33 (CAS, blue); NMR ($CDCl_3$) δ 8.69 (s, 1 H), 7.48–7.25 (m, 7 H), 7.16–7.06 (m, 2 H), 5.51 (dd, 1 H, J = 12.0, 4.7 Hz) 3.84 (d, 1 H, J = 13.0 Hz), 3.78 (s, 3 H), 3.65 (d, 1 H, J = 13.0 Hz), 2.89–2.84 (m, 2 H), 2.64–2.37 (m, 4 H), 1.97 (m, 1 H), 1.75 (m, 1 H), 1.17–1.06 (m, 2 H); IR (KBr) ν_{max} 3459, 2919, 2844, 2805, 1718, 1459, 1159, 736 cm^{-1}; UV (ethanol) λ_{max} 291.8, 284.1, 224.8, 205.3 nm; MS *m/e* (relative intensity) 363 (8), 362 (M^+, 34) 211 (10), 182 (9), 160 (45), 146 (15), 144 (11), 143 (18), 134 (16), 91 (100), 86 (26), 84 (82), 65 (12), 51 (45). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.93; H, 7.30; N, 7.71.

N^b-Benzyl-16-(methoxycarbonyl)-14-ethyl-*D*-norcleavamine (12b). N^b-benzyl-*D*-norvincadifformine (**11b**,[9] 3.17 g, 8.16 mmol) was reduced with sodium borohydride (2.0 g, 53 mmol) according to the preceding procedure. The crude product was purified by flash chromatography on silica gel, eluting with ether hexane (2:3), to yield 2.5 g (79%) of two diastereomers in a ratio of 3:1.

For the major isomer: mp 107–108 °C; TLC (SiO_2, ether:hexane = 1:1) R_f = 0.48 (CAS, blue-green); NMR ($CDCl_3$) δ 8.78 (s, 1 H), 7.47–7.23 (m, 7 H), 7.14–7.05 (m, 2 H), 5.64 (dd, 1 H, J = 12.0, 4.6 Hz), 3.82 (d, 1 H, J = 12.9 Hz), 3.73 (s, 3 H), 3.61 (d, 1 H, J = 12.9 Hz), 2.87–2.82 (m, 2 H), 2.61 (m, 1 H), 2.46–2.31 (m, 3 H), 1.98 (m, 1 H), 1.55 (m, 1 H), 0.98 (m, 3 H), 0.66 (t, 3 H, J = 6.8 Hz); IR (KBr) ν_{max} 3396, 2923, 2908, 2846, 1713, 1461, 1450, 1338, 1294, 1165, 1149, 740, 731 cm^{-1}; UV (ethanol) λ_{max} 291.8, 284.1, 224.8, 203.7 nm; MS *m/e* (relative intensity) 391 (9), 390 (M^+, 35), 334 (6), 261 (11), 239 (7), 215 (14), 202 (16), 188 (6), 174 (9), 169 (14), 156 (12), 154 (11), 143 (9), 133 (21), 120 (9), 91 (100), 84 (33), 65 (11), 50 (21). Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.66; H, 7.67; N, 6.90.

For the minor isomer: TLC (SiO_2, ether:hexane = 1:1) R_f = 0.40 (CAS, blue-green); NMR ($CDCl_3$) δ 8.61 (s, 1 H), 7.43–7.03 (m, 9 H), 5.07 (d, 1 H, J = 8.9 Hz), 3.81 (s, 1 H), 3.76 (s, 3 H), 3.35 (d, 1 H, J = 14.0 Hz), 2.82–2.68 (m, 3 H), 2.37–2.27 (m, 4 H), 1.97–1.72 (m, 2 H), 1.26 (m, 1 H), 1.10 (m, 1 H), 0.84 (t, 3 H, J = 7.3 Hz); MS *m/e* (relative intensity) 391 (9), 390 (M^+, 32), 334 (4), 261 (9), 215 (12), 202 (12), 188 (6), 169 (11), 156 (8), 154 (8), 143 (6), 133 (14), 120 (6), 91 (100), 84 (10), 65 (10).

N-(*tert*-Butoxycarbonyl)-16-(methoxycarbonyl)-*D*-norcleavamine (13a). The N-benzyl cleavamine **12a** (0.5 g, 1.38 mmol) was dissolved in 20 mL of glacial acetic acid, and 0.2 g of 10% Pd/C was added under N_2. The reaction mixture was hydrogenated at 1 atm for 2 h. The mixture was then filtered through Celite and poured into a solution of ice–water and NH_4OH to basify. The product was extracted three times with dichloromethane, washed with brine, and dried over sodium sulfate. Concentration of the organic extracts gave a residue that was dissolved in 30 mL of dry dichloromethane. Triethylamine (0.21 mL, 1.5 mmol) was added, and the mixture was cooled to 0 °C with an ice bath. Di-*tert*-butyl dicarbonate (0.32 mL, 1.38 mmol) was added dropwise to the reaction mixture. After 0.5 h, the reaction was complete and the mixture was concentrated under vacuum. Flash chromatography on silica gel, eluting with ether hexane (1:1), yielded 0.418 g (81%) of product. TLC (SiO_2, ether:hexane = 2:1) R_f = 0.38 (CAS, brown with a light green center); NMR ($CDCl_3$) δ 8.67 (s, 1 H), 7.53 (t, 1 H, J = 6.6 Hz), 7.34 (d, 1 H, J = 7.6 Hz), 7.17–7.10 (m, 2 H), 4.17–3.80 (m, 3 H), 3.72 (2 s, 3 H), 3.25–2.85 (m, 2 H), 2.63 (m, 2 H), 2.06 (m, 2 H), 1.56 (s, 9 H), 1.30 (m, 1 H), 0.85 (m, 1 H); IR (KBr) ν_{max} 3428, 3417, 3389, 3369, 2939, 2929, 1738, 1729, 1691, 1462, 1412, 1366, 1163 cm^{-1}; UV (ethanol) λ_{max} 291.5, 284.0, 224.2, 200.1 nm; MS *m/e* (relative intensity) 272 (M^+, 3), 284 (10), 271 (3), 211 (8), 182 (3), 168 (3), 154 (3), 144 (5), 57 (100).

N-(*tert*-Butoxycarbonyl)-16-(methoxycarbonyl)-14-ethyl-*D*-norcleavamine (13b). The N-benzyl cleavamine **12b** (0.30 g, 0.769 mmol), was debenzylated and the secondary amine product converted to a carbamate according to the preceding procedure. The crude product was purified by flash chromatography on silica gel, eluting with ether/hexane (1:1), to yield 0.282 g (92%) of two diastereomers, as a white foam, in multiple fractions.

For the major isomer: TLC (SiO_2, ether:hexane = 2:1) R_f = 0.50 (CAS, brown); NMR ($CDCl_3$) δ 8.77 (s, 1 H), 7.52 (m, 1 H), 7.35 (m, 1 H), 7.23–7.07 (m, 2 H), 4.22 (m, 1 H), 4.19–3.75 (m, 3 H), 3.71 (2 s, 1 H), 3.20 (m, 1 H), 2.97 (m, 1 H), 2.62–2.48 (m, 2 H), 2.02–1.87 (m, 2 H), 1.56 (2 s, 9 H), 1.06 (q, 2 H), 0.71 (t, 3 H, J = 7.0 Hz); IR (KBr) ν_{max} 3416, 3400, 3387, 2972, 2965, 2928, 1737, 1730, 1691, 1478, 1462, 1441, 1414, 1367, 1339, 1308, 1249, 1238, 1167, 1118, 740 cm^{-1}; UV (ethanol) λ_{max} 291.5, 283.5, 223.5, 202.0 nm; MS *m/e* (relative intensity) 401 (10), 400 (M^+, 40), 344 (14), 312 (41), 301 (12), 299 (28), 240 (18), 239 (59), 202 (22), 170 (19), 169 (25), 168 (20), 167 (14), 156 (13), 154 (15), 144 (26), 57 (100).

For the minor isomer: TLC (SiO_2, ether:hexane = 2:1) R_f = 0.45 (CAS, pinkish brown); NMR ($CDCl_3$) δ 8.68 (s, 1 H), 7.49 (d, 1 H, J = 7.5 Hz), 7.30 (d, 1 H, J = 7.8 Hz), 7.18–7.06 (m, 2 H), 4.20–4.00 (m, 2 H), 3.77 (m, 1 H), 3.70 (s, 3 H), 3.35–3.29 (m, 1 H), 3.00 (m, 3 H), 2.80–2.50 (m, 1 H), 2.30–2.02 (m, 2 H), 1.57–1.22 (m, 11 H), 0.87 (m, 3 H); MS *m/e* (relative intensity) 400 (M^+, 9) 344 (20), 312 (53), 299 (19), 239 (30), 202 (9), 170 (6), 169 (9), 168 (6), 156 (7), 154 (7), 144 (25), 57 (100).

N-(*tert*-Butoxycarbonyl)-16-(methoxycarbonyl)-15,16-didehydro-*D*-norcleavamine (14a). A solution of the *t*-BOC-

(12) Scott, A. I.; Yeh, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 2273.

cleavamine **13a** (0.45 g, 1.21 mmol) in 100 mL of dichloromethane and 0.25 mL (1.80 mmol) of triethylamine was cooled to 0 °C. *tert*-Butyl hypochlorite (0.17 mL, 1.45 mmol) was added dropwise and the reaction mixture stirred for 10 min. The reaction mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum to give a white foam, which was used immediately in the next reaction. The chloroindolenine was heated at reflux in 50 mL of dry benzene with 0.42 mL (3.03 mmol) of triethylamine for 48 h. After being cooled, the reaction mixture was concentrated by rotary evaporator. Flash chromatography on silica gel, eluting with ether/hexane (2:1), gave 0.39 g (87%) of product: mp 177–178 °C; TLC (SiO_2, ether:hexane = 2:1) R_f = 0.28 (CAS, pinkish brown); NMR ($CDCl_3$) δ 8.05 (2 s, 1 H) 7.57 (t, 1 H), 7.40–7.10 (m, 4 H), 3.73 (s, 3 H), 3.45 (m, 4 H), 2.93 (m, 2 H), 2.22 (m, 2 H), 1.48–1.38 (2 s, 9 H); IR (KBr) ν_{max} 3332, 3327, 3317, 3303, 2972, 2945, 2939, 1721, 1688, 1667, 1464, 1439, 1414, 1366, 1272, 1249, 1242, 1171, 1142 cm^{-1}; UV (ethanol) λ_{max} 283.9, 222.9, 203.8 nm; MS *m/e* (relative intensity) 371 (23) 370 (M^+, 100), 314 (46), 295 (15), 282 (36), 269 (33), 240 (24), 237 (19), 228 (35), 214 (20), 211 (45), 209 (32), 194 (17), 180 (27), 167 (21), 57 (42). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.07; H, 7.08; N, 7.57. Found: C, 68.02; H, 7.16; N, 7.47.

***N*-(*tert*-Butoxycarbonyl)-16-(methoxycarbonyl)-14-ethyl-15,16-didehydro-*D*-norcleavamine (14b).** A solution of the *t*-BOC-cleavamine **13b** (0.30 g, 0.75 mmol) in 50 mL of dichloromethane and 0.13 mL (0.90 mmol) of triethylamine was cooled to 0 °C. *tert*-Butyl hypochlorite (0.10 mL, 0.83 mmol) was added and the reaction mixture stirred for 10 min. The mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum to give a white foam. This chloroindolenine was heated at reflux in 50 mL of dry benzene with 0.22 mL (1.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene for 4 h. After being cooled, the reaction mixture was concentrated by rotary evaporator. Flash chromatography on silica gel, eluting with ether/hexane (1:1), yielded 0.22 g (73%) of product: mp 201–203 °C: TLC (SiO_2, ether:hexane = 2:1) R_f = 0.34 (CAS, pinkish brown); NMR ($CDCl_3$) δ 8.04 (2 s, 1 H), 7.56 (t, 1 H, J = 7.8 Hz), 7.34 (d, 1 H J = 7.7 Hz), 7.23–7.05 (m, 3 H), 3.89–3.79 (m, 2 H), 3.73 (s, 3 H), 2.98–2.72 (m, 4 H), 2.20 (m, 1 H), 1.45 (2 s, 9 H), 1.26 (m, 2 H), 0.75 (t, 3 H, J = 7.4 Hz); IR (KBr) ν_{max} 3335, 2970, 2928, 1711, 1670, 1645, 1463, 1443, 1431, 1417, 1366, 1338, 1319, 1273, 1240, 1186, 1161, 1130, 736; UV (ethanol) λ_{max} 284.0, 222.9, 204.2 nm; MS *m/e* (relative intensity) 398 (M^+, 9), 342 (7), 310 (4), 297 (6), 240 (17), 239 (100), 209 (8), 194 (8), 180 (12), 167 (11), 153 (10), 84 (7), 57 (75). Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.03; H, 7.56; N,. 6.80.

(±)-Tubotaiwine (2). The *t*-BOC-acrylate **14a** (0.040 g, 0.108 mmol) was dissolved in 15 mL of dichloromethane. Trifluoroacetic acid (0.4 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. The mixture was then washed with 10% aqueous potassium carbonate and extracted three times with dichloromethane. The organic extracts were dried over sodium sulfate and concentrated to a residue by rotary evaporator. The residue was dissolved in 20 mL of dichloromethane and stirred with anhydrous potassium carbonate (0.216 mmol, 0.030 g). *n*-Butyraldehyde (0.13 mmol, 0.012 mL) was added dropwise to the reaction, and the mixture was stirred at room temperature. After 1 h, TLC showed the reaction to be complete. The mixture was washed with water, extracted three times with dichloromethane, dried over sodium sulfate, and concentrated. Flash chromatography on silica gel, eluting with CH_2Cl_2/MeOH (93:7), gave 0.0215 g (61%) of product. TLC (SiO_2, CH_2Cl_2:MeOH = 9:1) R_f = 0.28 (CAS, blue); 250-MHz ^1H NMR ($CDCl_3$) δ 8.85 (s, 1 H), 7.17–7.09 (m, 2 H), 6.89 (t, 1 H, J = 7.3 Hz), 6.81 (d, 1 H, J = 7.8 Hz), 3.94 (b s, 1 H), 3.77 (s 3 H), 3.10 (m, 3 H), 2.87 (m, 2 H), 2.53 (m, 1 H), 2.03 (m, 1 H), 1.86 (m, 3 H), 0.84 (m, 2 H), 0.70 (t, 3 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 169.8, 168.7, 143.6, 137.1, 127.5, 121.2, 119.6, 109.8, 95.7, 65.3, 55.0, 53.4, 51.2, 45.1, 43.3, 40.7, 30.4, 27.9, 23.6, 11.4; IR (thin film) ν_{max} 2955, 2945, 2927, 2874, 2856, 1676, 1603, 1463, 1435, 1236, 1203, 1151, 1098, cm^{-1}; UV (ethanol) λ_{max} 326.3, 297.0, 227.4, 202.4 nm; MS *m/e* (relative intensity) 324 (M^+, 23), 267 (9), 229 (19), 194 (10), 182 (9), 181 (11), 180 (23), 167 (26), 95 (42), 82 (10), 71 (100), 57 (12), 55 (20); M^+ calcd for $C_{20}H_{24}N_2O_2$ 324.18377, found 324.18378. The synthetic product was matched with a sample provided by Professor George Massiot by TLC, IR, and mass spectra and with corresponding published NMR values.[13]

19,20-Dihydro-20-*epi*-akuammicine (7). The *t*-BOC-acrylate **14b** (0.050 g, 0.126 mmol) was dissolved in 20 mL of dichloromethane and 2 mL of trifluoroacetic acid. This mixture was stirred at room temperature for ~1 h and then washed with 10% potassium carbonate to neutralize. The product was extracted three times with dichloromethane and the extract dried over sodium sulfate and concentrated to a residue by rotary evaporator. The residue was dissolved in 20 mL of chloroform, triethylamine (1.26 mmol, 0.18 mL), and vinyl acetate (1.26 mmol, 0.12 mL). After the solution was heated at reflux for 48 h, TLC showed the reaction to be complete. The mixture was washed with water and extracted three times with dichloromethane and the extract dried over sodium sulfate. Concentration by rotary evaporator gave a residue, which was purified by flash chromatography on silica gel. Elution with ethyl acetate/triethylamine (10:0.4) yielded 0.016 g (40%) of pure product. TLC (SiO_2, ethyl acetate:triethylamine = 10:0.4) R_f = 0.20 (CAS, blue); 250-MHz ^1H NMR ($CDCl_3$) δ 8.80 (s, 1 H), 7.20–7.11 (m, 2 H), 6.91–6.80 (m, 2 H), 3.99 (s, 1 H), 3.77 (s, 3 H), 3.15 (m, 1 H), 2.96 (m, 1 H), 2.77 (m, 2 H), 2.65 (m, 1 H), 2.45 (m, 1 H), 2.20 (m, 1 H), 1.96 (m, 1 H), 1.73 (m, 1 H), 1.46–1.30 (m, 2 H), 1.13 (m, 1 H), 0.96 (t, 3 H, J = 7.4 Hz); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 168.2, 168.0, 144.3, 135.9, 127.6, 120.8, 120.5, 109.5, 104.1, 59.6, 57.9, 53.9, 51.3, 50.8, 45.6, 38.3, 31.5, 28.0, 26.6, 11.6; IR (KBr) ν_{max} 3369, 2957, 2945, 1679, 1672, 1666, 1631, 1626, 1620, 1606, 1464, 1239, 1196, 1165, 1105 cm^{-1}; UV (ethanol) λ_{max} 327.4, 296.8, 226.5, 201.3 nm; MS *m/e* (relative intensity) 324 (M^+, 10), 255 (8), 225 (100), 214 (10), 194 (13), 180 (24), 167 (18), 123 (76), 110 (14), 99 (35), 94 (13), 84 (39), 57 (19). M^+ calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1844.

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Supplementary Material Available: NMR and IR spectra of the synthesized compounds (21 pages). Ordering information is given on any current masthead page.

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