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TETRAHEDRON

Biomimetic Construction of the Tetracyclic Ring System of Ngouniensine

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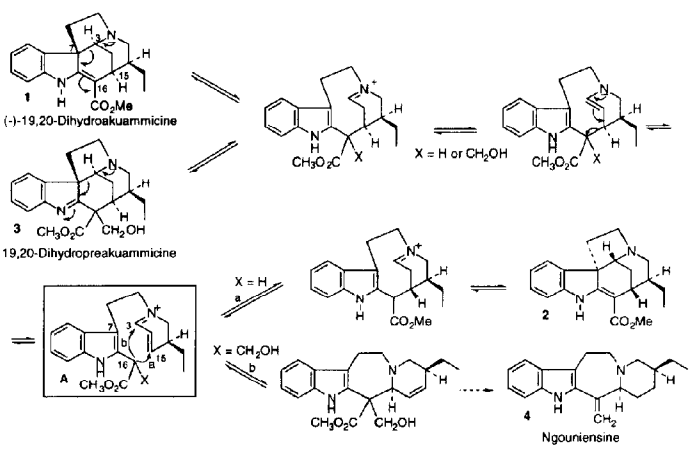
Abstract: 2-Cyanotetrahydropyridine **9**, bearing an indole-2-acetate moiety, was envisaged as a model synthetic equivalent of the dihydropyridinium cations **A**, which have been proposed as common biogenetic intermediates to both ngouniensine and *Strychnos* indole alkaloids. Lewis acid-promoted cyclization of the O-silyl ketene acetal derived from **9** led to the ngouniensine-type derivative **11**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: alkaloids, indoles, biomimetic reactions

INTRODUCTION

The biogenetic hypotheses have constituted the source of inspiration of a number of stereoselective biomimetic syntheses of natural products, which usually provide common synthetic entries to a variety of biogenetically related compounds.[1]



Scheme 1

The mechanism depicted in Scheme 1 has been proposed to explain the isomerization of (-)-19,20-dihydroakuammicine (**1**) to its diastereomer (**2**).[2,3] On the other hand, it has been

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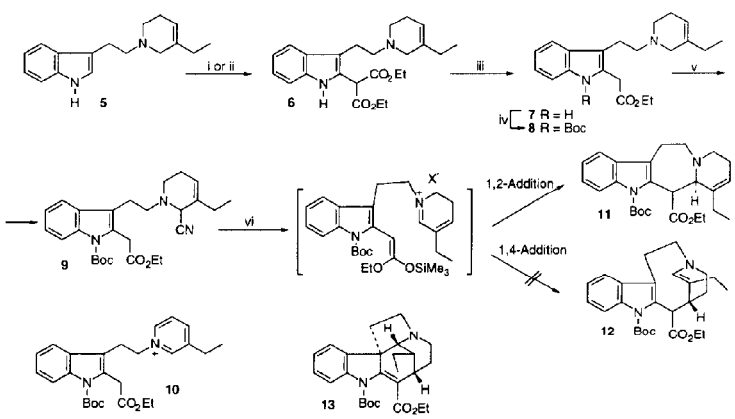
speculated that ngouniensine (**4**), the major alkaloid of *Strychnos ngouniensis*, may arise biogenetically from 19,20-dihydropreakuammicine (**3**), as outlined also in Scheme 1.[4] In both cases, a reverse Mannich fission of the C_3-C_7 bond, starting from the pentacyclic *Strychnos* structure, followed by cleavage of the C_{15}-C_{16} bond affords an open dihydropyridinium cation (**A**), which seems to be the crucial biogenetic intermediate. The feasibility of such an isomerization in the *Strychnos* field has been exploited by Kuehne in several syntheses of *Strychnos* alkaloids,[5] whereas the formation of C_3-C_{16} bond by intramolecular nucleophilic attack of C_{16} on the α position of a pyridinium cation has been employed in the preparation of tetracyclic derivatives with the ngouniensine skeleton.[6]

RESULTS AND DISCUSSION

In the context of our studies on the synthesis of the 2-vinyl indole alkaloid ngouniensine[7] and *Strychnos* indole[8] alkaloids we devised a common biomimetic approach to these alkaloids from 2-cyanotetrahydropyridine **9**, which can be envisaged as a model synthetic equivalent of the above key biogenetic dihydropyridinium intermediates **A**.[9] Intramolecular conjugate addition of the nucleophilic C_{16} carbon (bond formed C_{15}-C_{16}) would afford a nine-membered tetracyclic enamine, precursor of pentacyclic *Strychnos* alkaloids, whereas a 1,2-addition (bond formed C_3-C_{16}) would provide the tetracyclic ring system of ngouniensine.



Reagents and conditions: i) *t*-BuOCl, Et_3N, THF, then, $TlCH(CO_2Et)_2$; ii) *t*-BuOCl, Et_3N, THF, then, $LiCH(CO_2Et)_2$, $ZnCl_2$; iii) LiCl, $Et_3N.HCl$, DMA, 130 °C; iv) $(t\text{-BuOCO})_2O$, DMAP, MeCN; v) a. *m*-CPBA, CH_2Cl_2, K_2CO_3, b. TFAA, KCN, CH_2Cl_2, buffer pH = 4; vi) a. LDA, TMSCl, THF, b. $TiCl_4$, CH_2Cl_2.

Scheme 2

The target nitrile **9** was prepared from 3-(piperidylethyl)indole **5**,[10] as outlined in Scheme 2. The acetate moiety on the indole 2-position, required as the nucleophilic partner in the biomimetic ring closure, was introduced following Kuehne's method by chlorination of **5** with *tert*-butyl hypochlorite followed by treatment of the resulting chloroindolenine with either thallium diethyl malonate[11] or the less toxic lithium diethyl malonate and zinc chloride.[12] De-

ethoxycarbonylation of the resulting 2-indolemalonate **6** afforded the desired 2-indoleacetate **7** in good yields. Protection of the indole nucleus by treatment of **7** with di-*tert*-butyl dicarbonate and DMAP gave the *N*-Boc derivative **8**. The cyano group was regioselectively introduced at the piperidine 2 position by oxidative cyanation under modified Polonovski-Potier conditions.[13] Thus, oxidation of tetrahydropyridine **8** with *m*-CPBA followed by treatment of the corresponding *N*-oxide with TFAA and trapping of the resulting iminium salt with potassium cyanide in a one pot procedure afforded the 2-cyanotetrahydropyridine **9** in 60% yield.

The key cyclization was initially attempted by treatment of **9** with *p*-toluenesulfonic acid in refluxing benzene or with aqueous AcOH at 90 °C. Under these conditions a complex mixture of compounds was formed, from which only the pyridinium salt **10**[14] and the tetrahydropyridine **8** could be identified. This result can be rationalized by considering that the initially formed dihydropyridinium cation undergoes a disproportionation[15] instead of the desired cyclization. However, when a THF solution of compound **9** was treated with LDA and trimethylsilyl chloride, in order to form the corresponding *O*-silyl ketene acetal, and then the resulting crude mixture was dissolved in methylene chloride and treated with $TiCl_4$, the ngouniensine-type tetracycle **11** was formed in 63% overall yield as an almost equimolecular mixture of epimers at C_{16}. Compounds **11a** and **11b** were characterised by ^{1}H-NMR and ^{13}C-NMR spectroscopy, and the signals were unambiguously assigned with the aid of ^{1}H-^{1}H COSY and SFORD experiments. The ^{13}C-NMR chemical shifts of the methines α (δ ≈ 60 ppm) and γ (δ ≈ 124 ppm) carbons of the tetrahydropyridine ring precluded the possibility that the compound isolated was **12**.

The above result clearly demonstrates the feasibility of the biomimetic cyclization to tetracyclic ngouniensine-type systems (via b, Scheme 1). The alternative cyclization, by 1,4-addition to the dihydropyridinium cation, to the tetracyclic stemmadenine-type derivative **12** (or the corresponding pentacyclic *Strychnos* derivative **13**) was not observed. Probably, this result is not only a consequence of a preferential α-attack of the nucleophilic C_{16} carbon to the dihydropyridinium cation but also reveals the reversibility of the γ-attack, taking into account that the deactivating BOC group on the indole nitrogen may inhibit the subsequent cyclization to **13**.

EXPERIMENTAL SECTION

General. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-300 (^{1}H, 300 MHz; ^{13}C, 75.4 MHz) or Varian XL-200 (^{1}H, 200 MHz; ^{13}C, 50.2 MHz) instruments. Chemical shifts are expressed in parts per million (δ) relative to internal TMS. Mass spectra were determined on a VG 70-70 EQ-HF spectrometer. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.040-0.060 mm) or, when indicated, on Al_2O_3 (SDS, 0.05-0.2 mm). Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4.

3-[2-(3-Ethyl-1,2,5,6-tetrahydro-1-pyridyl)ethyl]indole (5). A solution of 1-[2-(3-indolyl)ethyl]-3-ethylpyridinium bromide (5.02 g, 15.0 mmol) in MeOH (50 ml) was treated with $NaBH_4$ (0.5 g, 13.5 mmol) and stirred for 1h at room temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. Flash chromatography (30:1 AcOEt-MeOH) afforded **5** (2.7 g; 72%). Amorphous solid. IR ($CHCl_3$, cm^{-1}) 3480, 1450; ^{1}H-NMR ($CDCl_3$) δ 8.10 (1H, bs), 7.62 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.17 (1H, t, *J* = 8.0 Hz), 7.11 (1H, t, *J* = 8.0 Hz), 7.01 (1H, s), 5.49 (1H, bs), 3.06 (2H, t, *J* = 6.2 Hz), 3.01 (2H, s), 2.80 (2H, t, *J* = 8.6 Hz), 2.65 (2H, t, *J* = 6.2 Hz), 2.24–2.19 (2H, m), 2.00 (2H, q, *J* = 7.2 Hz), 1.04 (3H, t, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 137.8 (C-3'), 136.4 (C-12a), 127.6 (C-7a), 121.8 (C-2), 121.6 (C-9), 119.1 (C-11), 118.8 (C-10), 117.8 (C-4'), 114.4 (C-7), 111.2 (C-12), 59.2 (C-2'), 55.8 (C-6'), 50.2 (CH_2N), 27.9 (CH_2In) , 25.9 (C-5'), 23.2 (CH_2CH_3), 12.2 (CH_2CH_3); EIMS: 254 (18), 144

(30), 124 (100). Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.07; H, 8.26; N, 11.66.

Diethyl 3-[2-(3-Ethyl-1,2,5,6-tetrahydro-1-pyridyl)ethyl]indole-2-malonate (6). Method A. To a solution of **5** (1 g, 4 mmol) in THF (30 ml) and Et_3N (0.5 ml) at –78 °C was added dropwise *t*-BuOCl (0.55 g, 0.6 ml, 5.1 mmol) dissolved in THF (3 ml) over a 10-min period. The chloroindolenine formation was monitored by TLC. When no starting material remained (30 min), the reaction mixture was concentrated under vacuum without heating. The residue was dissolved in THF (7 ml) and cannulated into a freshly prepared suspension of thallium diethyl malonate in THF at –78 °C. The mixture was stirred at –78 °C for 1h, warmed to 20 °C, and stirred for 1h. The mixture was filtered through a plug of Celite to remove the thallium salts, concentrated, and chromatographed (25:1 AcOEt-MeOH) to give **6** (1.10 g, 67%). Thallium diethyl malonate solution: TlOEt (125 mg, 355 µl, 5.1 mmol) was added to a solution of diethyl malonate (756 µl, 5.1 mmol) in THF (20 ml) and stirred at room temperature for 20 min. **Method B.** To a solution of **5** (1 g, 4 mmol) and Et_3N (0.54 ml) in THF (30 ml) at –78 °C was added *t*BuOCl (0.55 g, 0.6 ml, 5.1 mmol). After 20 min, a solution of $ZnCl_2$ (51 mg, 0.78 mmol; fused by flame-drying under reduced pressure) in THF (1 ml) was added dropwise. The reaction mixture was stirred for 5 min. Then, a solution of lithium diethyl malonate (4.67 mmol) was added dropwise, and the resulting solution was stirred for 1h at –78 °C and for 1h at room temperature. Water was added, and the aqueous layer was extracted with CH_2Cl_2. The product **6** was obtained in 75% yield after flash chromatography. Yellow oil. R_f = 0.2 (19:1 AcOEt-MeOH). CAS : yellow. IR ($CHCl_3$, cm^{-1}) 3440, 1730, 1450; ^{1}H-NMR ($CDCl_3$) δ 8.90 (1H, bs), 7.61 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.20 (1H, t, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 8.0 Hz), 5.46 (1H, bs), 5.02 (1H, bs), 4.21 (4H, t, *J* = 6.3 Hz), 3.06–2.92 (4H, m), 2.71–2.60 (4H, m), 2.28–2.14 (2H, m), 2.00 (2H, q, *J* = 8.0 Hz), 1.27 (6H, t, *J* = 6.3 Hz), 1.04 (3H, t, *J* = 8.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 167.3 (2C, CO_2), 137.6 (C-3'), 135.9 (C-12a), 127.5 (C-7a), 125.1 (C-2), 122.3 (C-9), 119.3 (C-10), 118.7 (C-11), 117.6 (C-4'), 113.2 (C-7), 111.2 (C-12), 62.2* (C-6'), 59.0* (C-2'), 55.8 (2C OCH_2), 50.2 (CH_2N), 49.2 (CHIn), 27.9 (CH_2In), 25.9 (C-5'), 22.2 (CH_2CH_3), 13.9 (2C OCH_2CH_3), 12.1 (CH_2CH_3); EIMS: 412 (40), 124 (100). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.87; H, 7.82; N, 6.79. Found: C, 69.61; H, 7.79; N, 6.95. Lithium diethyl malonate solution: diethyl malonate (747 mg, 4.67 mmol) was added to a solution of LDA, prepared from diisopropylamine (9 mmol) and BuLi (9 mmol) in THF (40 ml) at –78 °C.

Ethyl 3-[2-(3-Ethyl-1,2,5,6-tetrahydro-1-pyridyl)ethyl]indole-2-acetate (7). LiCl (434 mg, 10.3 mmol) and Et_3N.HCl were added to a flask containing a solution of **6** (5.3 g, 12.8 mmol) in *N,N*-dimethylacetamide (20 ml), and the mixture was heated at 130 °C for 10h and then cooled to room temperature. Brine (50 ml) and saturated NH_4OH (50 ml) were added to the reaction mixture, and the solution was extracted with AcOEt. Purification by flash chromatography rendered **7** (2.5 g, 61%). Yellow oil. R_f = 0.3 (25:1 AcOEt-MeOH). CAS: orange. IR ($CHCl_3$, cm^{-1}) 3460, 1720, 1460; ^{1}H-NMR ($CDCl_3$) δ 8.52 (1H, bs), 7.52 (1H, d, *J* = 8.0 Hz), 7.31 (1H, d, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 8.0 Hz), 4.98 (1H, m), 4.17 (2H, q, *J* = 6.0 Hz), 3.79 (2H, s), 3.01–2.92 (4H, m), 2.68–2.60 (4H, m), 2.24–2.18 (2H, m), 2.00 (2H, q, *J* = 7.5 Hz), 1.29 (3H, t, *J* = 6.0 Hz), 1.04 (3H, t, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 170.6 (CO_2), 137.7 (C-3'), 135.8 (C-12a), 128.1 (C-7a), 126.9 (C-2), 121.7 (C-9), 119.2 (C-10), 118.4 (C-11), 117.7 (C-4'), 111.6 (C-7), 110.8 (C-12), 61.2* (C-6'), 59.1* (C-2'), 55.8 (OCH_2CH_3), 50.2 (CH_2N), 31.9 (CH_2CO_2), 27.9 (CH_2In), 25.9 (C-5'), 22.2 (CH_2CH_3), 14.1 (OCH_2CH_3), 12.2 (CH_2CH_3); EIMS: 340 (85), 326 (100). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.34; H, 8.50; N, 8.36.

Ethyl 1-(*tert*-Butoxycarbonyl)-3-[2-(3-ethyl-1,2,5,6-tetrahydro-1-pyridyl)ethyl]indole-2-acetate (8). A mixture of **5** (2.5 g, 7.3 mmol), DMAP (164 mg, 1.3 mmol), and di-*tert*-butyl dicarbonate (3.9 g, 18.2 mmol) in CH_3CN (45 ml) was stirred at room temperature for 3h. Evaporation followed by flash chromatography (100:3 AcOEt-MeOH) gave **8** (3.1 g, 95%). Amorphous solid. R_f = 0.4 (25:1 AcOEt-MeOH). CAS: yellow. IR ($CHCl_3$, cm^{-1}) 1730, 1450, 1150; ^{1}H-NMR ($CDCl_3$) δ 8.08 (1H, d, *J* = 8.0 Hz),

7.51 (1H, d, J = 8.0 Hz), 7.28 (1H, t, J = 8.0 Hz), 7.20 (1H, t, J = 8.0 Hz), 5.47 (1H, bs), 4.15 (2H, q, J = 7.0 Hz), 4.05 (2H, s), 3.02–2.88 (4H, m), 2.62–2.53 (4H, m), 2.23–2.15 (2H, m), 1.98 (2H, q, J = 7.5 Hz), 1.66 (9H, s), 1.23 (3H, t, J = 7.0 Hz), 1.04 (3H, t, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 170.3 (CO_2), 150.5 (CON), 137.7 (C-3'), 135.9 (C-12a), 133.1 (C-2), 129.4 (C-7a), 124.9 (C-11), 122.4 (C-10), 118.9 (C-7), 118.3 (C-9), 117.7 (C-4'), 115.7 (C-12), 83.9 ($CO(CH_3)_3$), 60.8* (C-6'), 58.3* (C-2'), 55.8 (OCH_2CH_3) , 50.1 (CH_2N), 33.2 (CH_2CO_2), 28.2 ($3CH_3$), 28.1 (CH_2In), 25.9 (C-5'), 22.3 (CH_2CH_3), 14.1 (OCH_2CH_3), 12.2 (CH_2CH_3); EIMS: 440 (15), 124 (100). Anal. Calcd for $C_{26}H_{36}N_2O_4$: C, 70.88; H, 8.24; N, 6.36. Found: C, 70.97; H, 8.36; N, 6.51.

Ethyl 1-(*tert*-Butoxycarbonyl)-3[2-(2-cyano-3-ethyl-1,2,5,6-tetrahydro-1-pyridyl)ethyl]indole-2-acetate (9). A solution of *m*-CPBA (85%, 616 mg, 2.8 mmol) in anhydrous CH_2Cl_2 (20 ml) was slowly added to a stirred solution of **8** (1 g, 2.3 mmol) in CH_2Cl_2 (20 ml). The solution was stirred at 0 °C for 1h, K_2CO_3 (674 mg) was added, and the suspension was stirred for an additional 1h. The mixture was filtered over Celite, and the organic solution was dried, concentrated, and flash filtered through Al_2O_3 (49:1 AcOEt-MeOH) to give the N-oxide (700 mg, 67%), which was directly dissolved in CH_2Cl_2 (15 ml) and cooled to 0 °C. TFAA (0.45 ml, 3.14 mmol) was slowly added. After 15 min of stirring, an aqueous solution (10 ml) of KCN (204 mg, 3.14 mmol) was added, and the solution was buffered to pH = 4 by addition of citric acid. The mixture was stirred for 15 min, basified with K_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed with water, dried, concentrated, and flash filtered (Al_2O_3, 1:6 AcOEt-hexane) to give **7** (430 mg, 60%): Oil. R_f = 0.6 (2 : 3 AcOEt-hexane). CAS: orange. IR ($CHCl_3$, cm^{-1}) 2220, 1730, 1320; ^{1}H-NMR ($CDCl_3$) δ 8.10 (1H, d, J = 8.0 Hz), 7.58 (1H, d, J = 8.0 Hz), 7.32 (1H, t, J = 8.0 Hz), 7.23 (1H, t, J = 8.0 Hz), 5.65 (1H, m), 4.18 (2H, q, J = 7.0 Hz), 4.05 (2H, s), 4.07–4.00 (1H, m), 3.00–2.73 (5H, m), 2.55 (1H, td, J = 11.0, 3.1 Hz), 2.40–2.07 (4H, m), 2.63 (9H, s), 1.25 (3H, t, J = 7.0 Hz), 1.12 (3H, t, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 170.2 (CO_2), 150.0 (CON), 135.7 (C-12a), 132.9 (C-3'), 129.7 (C-2), 129.1 (C-7a), 124.1 (C-11), 122.5 (C-10), 122.3 (C-4'), 118.2 (C-9), 118.1 (C-7), 116.2 (CN), 115.7 (C-12), 83.9 ($OC(CH_3)_3$), 60.8 (C-6'), 55.4 (CH_2O), 54.9 (C-2'), 45.8 (CH_2N), 33.2 (CH_2CO_2), 28.1 ($3CH_3$, CH_2In), 26.5 (CH_2In), 25.3 (C-5'), 22.4 (CH_2CH_3), 14.1 (OCH_2CH_3), 11.6 (CH_2CH_3); HRMS calcd for $C_{26}H_{34}N_2O_4$ 465.2628. Found 465.2613.

6-Ethoxycarbonyl-7-ethyl-6,6a,9,10,12,13-hexahydropyrido[1',2':1,2]azepino[4,5-b]indole (11a,b). A solution of LDA (0.19 mmol) in THF (2 ml) was cooled at –78 °C, and a solution of nitrile **9** (75 mg, 0.16 mmol) was dropwise added. After 10 min the temperature was raised at 0 °C and maintained for 45 min. TMSCl (48 µl, 0.38 mmol) was added at –78 °C, then the solution was stirred at room temperature for 3h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (3 ml). A solution of $TiCl_4$ (160 µl, 1 M in CH_2Cl_2) was added at 0 °C. The reaction mixture was stirred overnight at room temperature. Evaporation and flash chromatography purification (2:3 AcOEt-hexane) gave **11a** (25 mg, 35%) and **11b** (20 mg, 28%). **11a**: Oil. R_f = 0.2 (2 :3 AcOEt - hexane); CAS: blue-green. IR ($CHCl_3$, cm^{-1}) 1730, 1450, 1380, 1240; ^{1}H-NMR ($CDCl_3$) δ 8.30 (1H, d, J = 7.0 Hz), 7.45 (1H, d, J = 7.0 Hz), 7.27 (1H, t, J = 7.0 Hz), 7.22 (1H, t, J = 7.0 Hz), 5.75 (1H, bs), 5.00 (1H, bs), 4.12 (2H, q, J = 7.0 Hz), 4.06 (1H, s), 3.50–1.45 (10H, m), 1.65 (9H, s), 1.29 (3H, t, J = 7.0 Hz), 1.10 (3H, t, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 170.2 (CO_2), 150.0 (NCO), 135.8 (C-4a), 133.0 (C-7), 129.7 (C-5a), 129.1 (C-13b), 124.7 (C-3), 122.9 (C-2), 120.7 (C-8), 118.1 (C-1), 118.0 (C-13a), 115.7 (C-4), 84.5 ($OC(CH_3)_3$), 61.3 (C-6a), 60.0 (C-10), 55.2 (OCH_2CH_3), 46.6 (C-6), 44.6 (C-12), 28.1 ($3CH_3$), 26.9 (CH_2CH_3), 21.9 (C-9), 20.8 (C-13), 13.9 (OCH_2CH_3), 12.1 (CH_2CH_3); EIMS: 438 (47), 381 (60), 351 (38), 337 (30). HRMS calcd for $C_{26}H_{34}N_2O_4$ 438.2518. Found 438.2506. **11b**: Oil. R_f = 0.15 (2:3 AcOEt-hexane); CAS: blue-green. IR ($CHCl_3$, cm^{-1}) 1730, 1410, 1330, 1210; ^{1}H-NMR ($CDCl_3$) δ 8.04 (1H, d, J = 7.0 Hz), 7.39 (1H, d, J = 7.0 Hz), 7.25 (1H, t, J = 7.0 Hz), 7.19 (1H, t, J = 7.0 Hz), 5.52 (1H, bs), 5.28 (1H, d, J = 4.5 Hz), 4.55 (1H, bs), 4.30–4.02 (2H, m), 3.41–3.31 (1H, m), 3.20–1.75 (8H, m), 2.40–2.21 (1H, m), 1.65 (9H, s), 1.29 (3H, t, J = 7.0 Hz), 1.10 (3H, t, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 170.2 (CO_2), 150.0 (NCO), 135.8 (C-4a), 133.0 (C-7), 129.7 (C-5a), 129.1 (C-13b), 123.9 (C-3), 122.4 (C-2), 120.8 (C-8), 118.1 (C-13a), 117.9 (C-1), 115.7 (C-4), 83.9 ($OC(CH_3)_3$), 61.1 (C-6a), 61.0 (C-10), 52.2 (OCH_2CH_3), 51.0 (C-12), 46.7 (C-6), 28.1 ($3CH_3$), 26.9 (CH_2CH_3), 23.9 (C-9), 23.3 (C-13), 14.1 (OCH_2CH_3), 12.6 (CH_2CH_3);

EIMS: 438 (25), 381 (30), 365 (10), 351 (25), 337 (25). HRMS calcd for $C_{26}H_{34}N_2O_4$ 438.2518. Found 438.2502.

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3. A similar mechanism could explain the formation in nature of *Strychnos* alkaloids both in racemic form (pseudoakuammicine, scholarine, vinervidine) and possessing an absolute configuration at C-15 opposite to that of (-)-secologanine [for instance (+)-20-epilochneridine and (+)-stricticine]. For a review, see: Bosch, J.; Bonjoch, J.; Amat, M. in *The Alkaloids*, Cordell, G. A., Ed.; Vol. 48, pp 75-189; Academic Press, Inc., New York, 1996.
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