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Stabilized Zwitterionic Derivatives From The Reaction Of 16-Chloro-1-dehydrovincadifformine With Sodium Alkoxides

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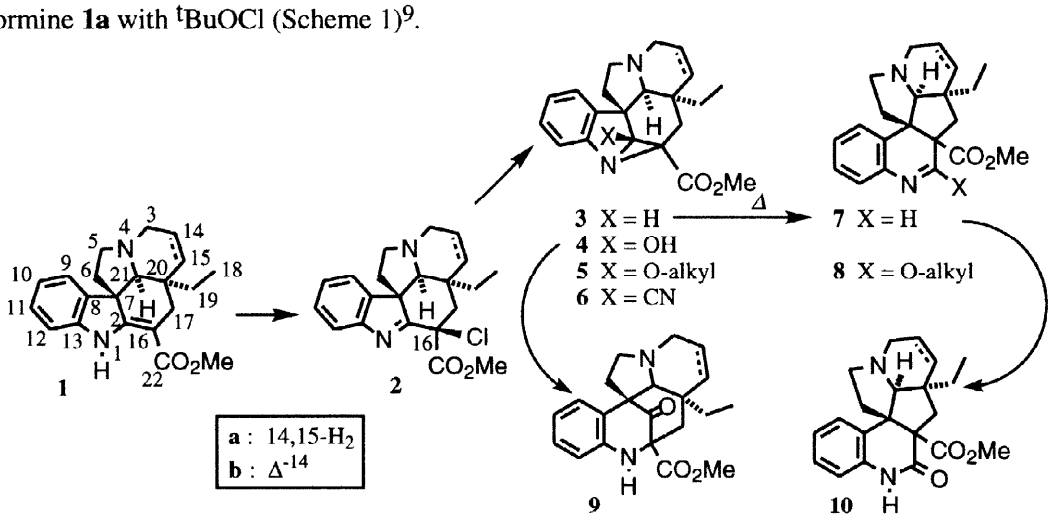
Abstract: Treatment of 16-chloro-1-dehydrovincadifformine **2a** and 16-chloro-1-dehydrotabersonine **2b** with sodium methoxide respectively yielded the 16-methoxyindolenines **11a** *vs* **11b**, and the two betaines **12a** *vs* **12b** and **14a** *vs* **14b**. Sodium ethoxide gave similar results, except for the absence of the 16-ethoxyindolenines. The structures of all derivatives were ascertained by their spectroscopic data, by chemical correlations, and by transformations to compound **26**, whose racemate was prepared by total synthesis. In contrast with previously described reactions of **2a,b** in alcohols, the formation of the internally bolted zwitterionic derivatives **12-15** under the influence of alkoxides appears here to govern the reaction pathways.

INTRODUCTION

Several years ago we reported the first syntheses of 16-*X* -1-dehydrovincadifformines and of 16-*X* -1-dehydrotabersonines (*X* = Cl (**2a,b**)[1], OAc[2], OH[3], NO[4]). Since that time these highly reactive 16-substituted indolenines in the *aspidosperma* series have been widely used by us[5] and others[6] along partial and total syntheses of related natural and unnatural products. In particular, with in hand short total syntheses of the parent alkaloids (±)-vincadifformine **1a**[7] and (±)-tabersonine **1b**[8], these transformations gave us an entry to a number of alkaloids with various rearranged skeletons. Among them, the *melodinus* skeleton (*cf* tetrahydromeloscandine **10b**) was constructed[5b] through thermal rearrangement of the hexacyclic aziridine **3**, that was obtained by reduction of 16-chloro-1-dehydrovincadifformine **2a**, resulting itself from the reaction of vincadifformine **1a** with ^{t}BuOCl (Scheme 1)[9].



Scheme 1

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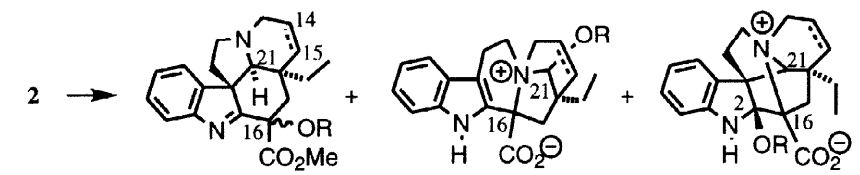
In the event, the reductive step in the synthesis of **3** from **2a** resulted in obtention of an imine (**7**), that had to be oxidized in order to generate quinolone **10**. In order to avoid the last oxidation step it seemed obvious to consider the 2-alkoxyaziridine **5** as a possible intermediate, that might rearrange to iminoether **8** with the right oxidation level. Obtention of quinolone **9**[10]through acidic treatment of **2a** gave indeed an indication that an intermediate 2-hydroxyaziridine (**4**) might be generated from **2a.** Moreover, under conditions used by De Kimpe[11] in the transformation of a β–chloroimine into a 2-cyanoazetidine, the 16-chloroindolenine **2a** gave the cyanoaziridine **6a** in low yield[12].

RESULTS AND DISCUSSION

While numerous attempts at reacting **2a** with MeONa in aprotic solvents (THF, toluene, xylene) were fruitless, treatment of **2a** with MeONa in methanol for 12 days at rt yielded compounds **11a** (21%), **12a** (47%), and **14a** (2.5%), along with some starting material (4.5%) (Scheme 2). In refluxing methanol for 24 h, the yield of **12a** decreased to 6%, while that of **11a** and more significantly that of **14a** increased.



a : 14,15-H_2
b : Δ^{-14}

11 R = Me

12 R = Me
13 R = Et

14 R = Me
15 R = Et

Scheme 2

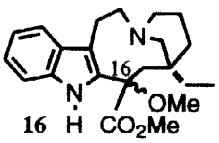
Comparable results were obtained upon treating **2a** with EtONa in ethanol, yielding **13a**, and **15a**, and also upon treating **2b** with the same alkoxides, yielding **11b**, **12b** and **14b** (MeONa) on one hand, and **13b** and **15b** (EtONa) on the other (Table 1). In some runs with EtOH/EtONa, ethyl 16-chloro-1-dehydrovincadifforminate **2a** (Me = Et), was isolated with yields ranging from 6 to 20%.

Starting materials	Solvent	Conditions	Isolated compounds		
2a	MeOH	MeONa, rt, 12 days	**11a** (21%)	**12a** (47%)	**14a** (2.5%)
2a	MeOH	MeONa, reflx, 24h	**11a** (28%)	**12a** (6%)	**14a** (26%)
2b	MeOH	MeONa, rt, 4 days	**11b** (79%)	**12b** (5%)	**14b** (1.5%)
2b	MeOH	NaOH, reflx, 2h	**11b** (21%)	**12b** (26%)	**14b** (27%)
2a	EtOH	EtONa, rt, 48h, reflx 1h	-	**13a** (1.5%)	**15a** (26%)
2a	EtOH	EtONa, rt, 7 days	-	**13a** (1.5%)	**15a** (43%)
2a	EtOH	EtONa, reflx 1h30	-	-	**15a** (11%)
2b	EtOH	EtONa, 35°C, 48h	-	**13b** (6%)	**15b** (10%)

Table 1

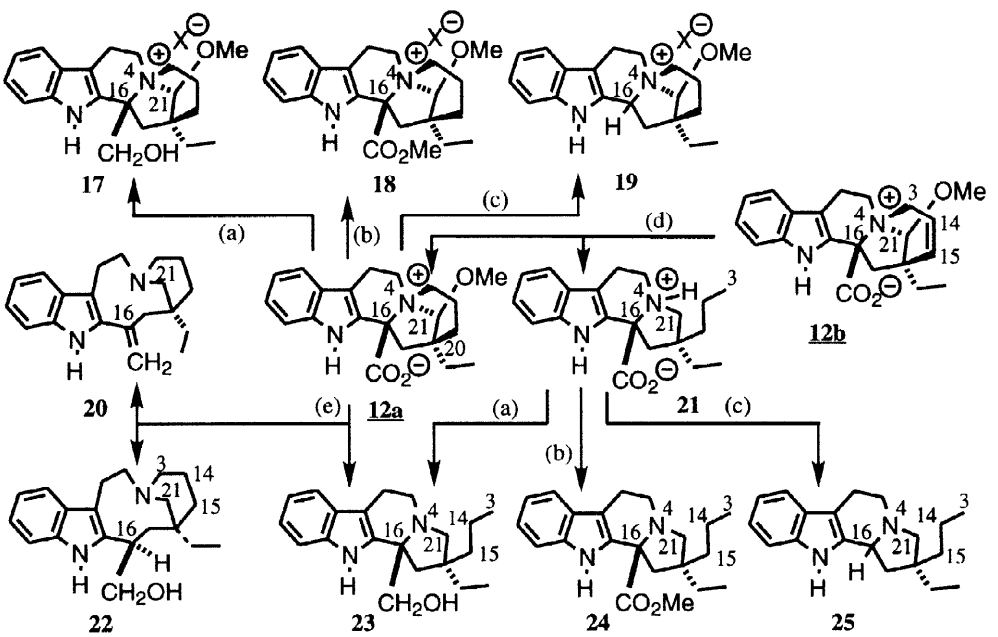
Compounds 11

The structures of indolenines **11a,b** were based on their UV (indolenines), mass, and ^{1}H and ^{13}C NMR spectra, and further confirmed by the reduction ($NaBH_3CN$, MeOH) of **11a** to indole **16.**



Compounds 12, 13

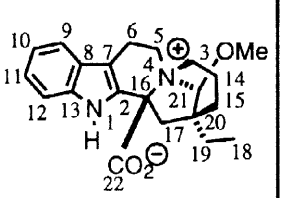
Although they appeared to possess both a carbonyl and a methoxy group, retention of a methyl ester in compounds **12a,b** was questionable, with regard to an IR absorption around 1645 cm^{-1}, and to the ^{13}C C=O and OMe signals at 166.9 and 62.1 - 62.2 ppm, respectively. The following chemical tranformations actually demonstrated a betainic structure (Scheme 3). Reduction of **12a** with $LiAlH_4$ in THF gave the quaternary alcohol **17**; while diazomethane in CH_2Cl_2 was effectless, heating **12a** with methyl iodide ($CHCl_3$, sealed tube) yielded the methyl ester **18**. **12a** was decarboxylated to **19** upon heating in aqueous acidic solution. All three compounds **17-19** were indolic and had retained the initial methoxy group, in favour of a quaternary aminoketal. Reduction of **12a** with $LiAlH_4$ in refluxing N-methylmorpholine resulted in isolation of three indolic non quaternary products, namely the novel 16-methylene-quebrachamine (**20**), vincadinol (**22**)[13], and indole **23**, bearing an ethyl and a propyl side chain. Compounds **20** and **22** had then suffered cleavage of one N-4 - C-16 bond so that reduction of the aminoketal could now ensue. The origin of the propyl chain in **23** from an Emde-like reduction was demonstrated through catalytic hydrogenation of **12b** (PtO_2, MeOH), giving **12a** and acid **21**. Acid **21** was reduced ($LiAlH_4$, THF) to the previously obtained alcohol **23**, while treatment with MeI gave the ester **24** and decarboxylation gave **25**.



a) LAH, THF, rt; b) CH_3I, 55°C, sealed tube; c) aqueous HCl, Δ; d) PtO_2, Na_2CO_3, MeOH, H_2; e) LAH, N-methylmorpholine, Δ.

Scheme 3

The NMR spectra of **12a,b**, of their derivatives, and of **13a,b** agreed with the depicted structures (Schemes 2,3). In particular, HMQC and HMBC experiments allowed attributions of all carbons and protons in **12a** (table 2).



12a

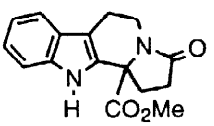
^{1}H	ppm	HMBC correlations	^{1}H	ppm	HMBC correlations
H-1	10.01	C-2, C-7, C-8, C-13	H-15	1.64	C-14, C-17, C-20
H-3	4.40	C-14, C-21	H'-15	1.32	C-14, C-17, C-20
H'-3	3.40	C-14	H-17	3.10	C-15, C-16, C-20, C-21, C-22
H-5	4.53	C-6, C-21	H'-17	2.24	C-2, C-15, C-16, C-20, C-22
H'-5	3.23	C-6, C-7, C-16	H-19	1.32	C-15, C-17, C-18, C-20, C-21
H-6	3.03	C-2, C-5, C-7, C-8	H'-19	1.11	C-15, C-17, C-18, C-20, C-21
H'-6	2.96	C-2, C-5, C-7	H-21	4.40	C-15, H_3CO-
H-14	2.05	C-17, C-20	H_3CO	3.68	C-21

Table 2

Concerning the two newly asymmetric centers in **12a**, C-16 can only accomodate the depicted configuration, while that of C-21 is deduced from the observation of NOE effect (5%) between H-21 and H-6α in **19**.

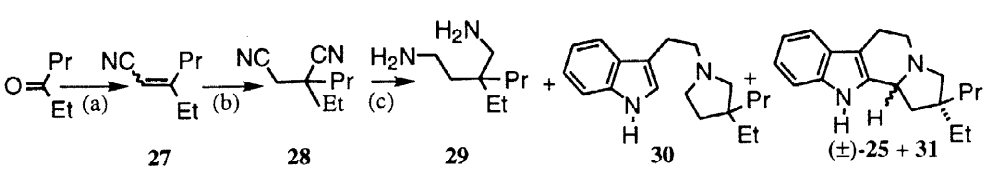
The correlation of **12a** with vincadinol (**22**) left little doubt about its structure. Nevertheless the synthesis of compound **25** was considered, in order to ascertain the N-4 - C-16 bond.

Thus, compound **26** was prepared[14] from tryptamine and dimethyl 2-oxoglutarate, but all attempts at alkylations α to the lactam group failed, due to difficulties in protecting the indolic NH.



26

We next turned to our synthesis of tetrahydro-ß-carbolines through reductive cyclization of nitriles[15]. To this effect, 2-ethyl-2-propylsuccinonitrile **28** was prepared in two steps from 3-hexanone through treatment with acetonitrile[16] followed by reaction[17] of **27** with KCN and NH_4Cl in aqueous DMF (Scheme 4). Hydrogenation of **28** (Pd-C, AcOH) in the presence of tryptamine gave diamine **29**, the bicyclic indole **30**, and a very low yield of a diastereomeric mixture from which the less polar component was shown to be identical with **25**, except for rotation. Parallel work in the laboratory has indeed shown that highly crowded nitriles cyclize with difficulty into amines under such reductive conditions.



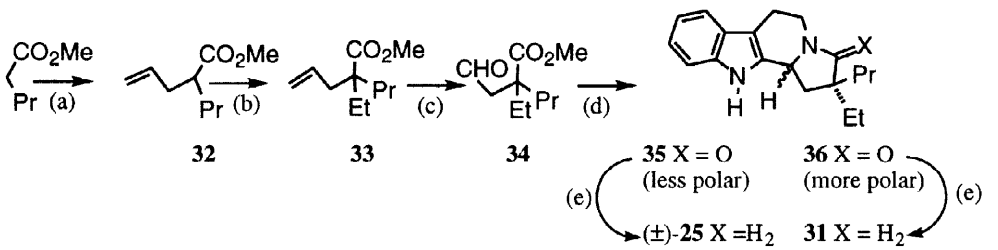
27 **28** **29** **30** (±)-**25** + **31**

a) KOH, CH_3CN, Δ; b) KCN, NH_4Cl, DMF-H_2O, Δ; c) tryptamine, AcOH, Pd-C, H_2.

Scheme 4

A more efficient synthesis was performed (Scheme 5) upon alkylating methyl pentanoate with allyl bromide (->**32**) and then with ethyl iodide (->**33**, 63% for the two steps) under Schlessinger's condition[18].

Ozonolysis of **33** then gave the aldehyde **34** (75%), which was reacted with tryptamine (AcOH, reflux) to yield compounds **35**, less polar, and **36**, more polar (47 : 53, 90%), which were separated. Reduction of **35** and of **36** with $LiAlH_4$ gave (±)-**25** (70%), and **31** (78%), respectively.

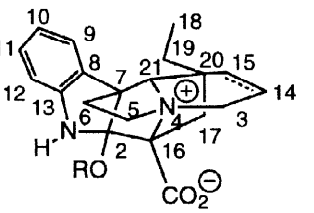


a) LDA, THF, allyl bromide, -78°C; b) LDA, THF, C_2H_5I, -78°C; c) CH_2Cl_2, O_3, -78°C, Ph_3P; d) tryptamine, AcOH, Δ; e) LAH, THF, rt.

Scheme 5

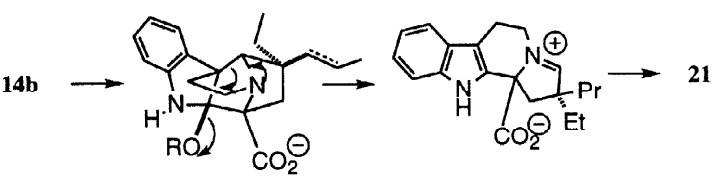
Compounds 14, 15

Like **12a,b** and **13a,b**, these polar compounds, had suffered quaternisation through formation of a N-4 - C-16 bond, as demonstrated by the ^3J couplings (HMBC) of H-21, H's-3 and H's-5 with C-16. Their indolinic UV spectrum, and the presence of an alkoxy group on C-2 (*ca* 100 ppm) appealed for the depicted structures, which were consistent with all the NMR data. When hydrogenated (PtO_2, MeOH), compound **14b** gave **14a** and, more interestingly, acid **21** (Scheme 3), thus establishing the configuration of C-16 in this last derivative.



	14,15	R
14a	H_2	OMe
14b	Δ	OMe
15a	H_2	OEt
15b	Δ	OEt

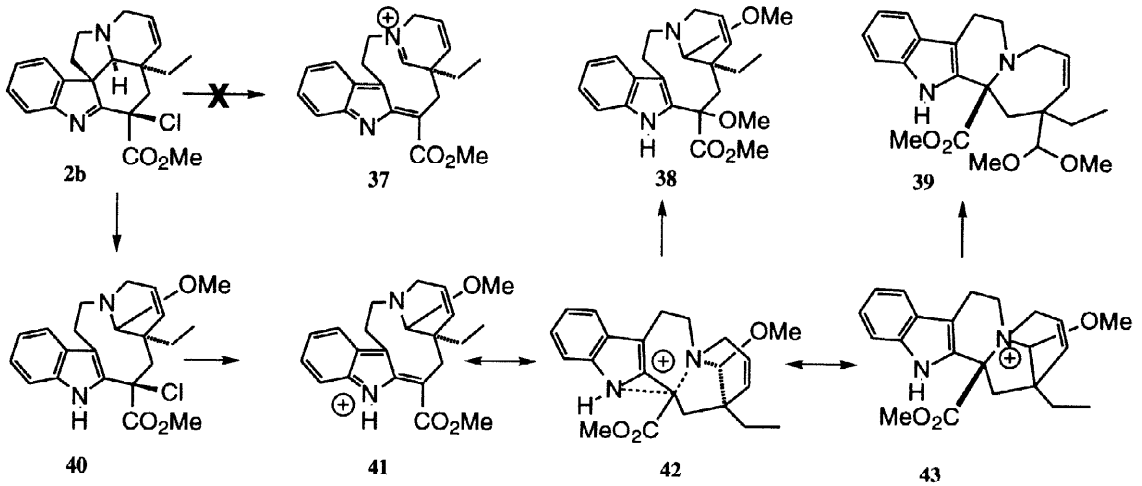
Formation of **21** from **14b** results from an Emde scission of the 3,4 bond, hydrogenation of the 14,15 double bond, Grob's fragmentation along breakage of the 7, 21 bond and departure of methanol, and finally hydrogenation of the resulting N-4 - C-21 iminium (Scheme 6).



Scheme 6

Discussion

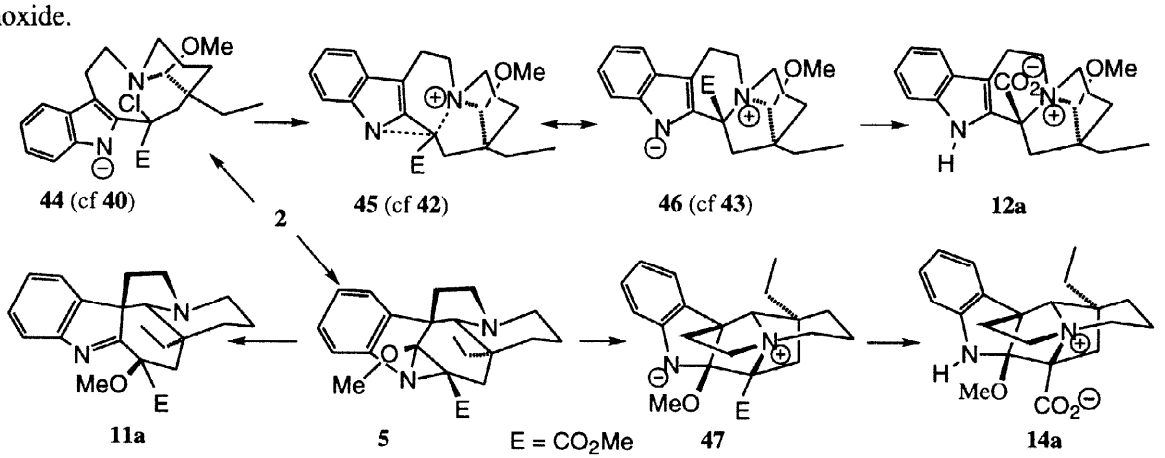
The structures of the compounds **11-15** resulting from the treatment of chloroindolenines **2a,b** with alkoxides strikingly differ from those of compounds **38**, **39** obtained upon reaction of **2b** with boiling methanol[1] (Scheme 7).



Scheme 7

Formation of the last two derivatives had been interpreted by the fragmentation of **2b** to the quinoïd intermediate **37**. However formation of this highly strained (if ever possibly existing) species appears largely unlikely, and we rather now suggest a direct attack of methanol onto C-21, leading to **40**. Only after formation of that aminal is the fragmentation to the quinoïd intermediate **41** possible (more likely to exist in the form of the less strained mesomeric **42**, **43**), further yielding **38** and **39**.

Scheme 8 depicts possible pathways for the formation of the compounds obtained in the present study, as exemplified by derivatives **11a**, **12a**, and **14a** resulting from the reaction of 16-chloro-1-dehydrovincadifformine (**2a**) with sodium methoxide (E = CO_2Me or CO_2^-). Direct attack of methoxide onto **2a** would generate **44** leading to **12a** *via* **45** and **46** along a process similar to that of the formation of **43** (Scheme 7). However, while the quaternary salt **43** or its equivalent was further opened by methanol to the ketal **39**, here formation of the related compound **12a** in the form of a betaine prevents it from further opening by methoxide.



Scheme 8

Although the initially targeted compound **5** was not isolated, it is thought to account for the formation of **14a** *via* **47**. Here again, the highly strained framework of **14a** is electrostatically bolted by the zwitterionic structure. The close proximity of N-4 to C-16 in **44** and **5**[19] allows the cyclizations to **12a** and **14a**

respectively. Formation of **11a** is thought to proceed from the rearrangement of **5**, either through an intramolecular [1,2] shift of the methoxide, or by an attack and elimination process. Interessingly enough, **11a** was the sole derivative that had retained the methoxycarbonyl group, while its formation is accounted for by the rearrangement of a neutral species. In contrast, **12a** and **14a** both arise from an N-1 anion, which might be related with the observed saponification.

EXPERIMENTAL

Melting points were determined on a Reichert melting point apparatus and were uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter: $[\alpha]_D$ (solvent, c $g.L^{-1}$). UV spectra (nm) were recorded on a Varian 634 spectrophotometer; IR spectra (ν cm^{-1}) on a Bomem FTIR apparatus. ^1H and ^{13}C NMR spectra ($CDCl_3$) were measured on a Bruker AC 300 apparatus at 300 MHz and 75 MHz respectively with TMS as internal standard; the chemical shifts are expressed in ppm downfield and coupling constants in Hz; the following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet or multiple protons signal (m) and broad (b); labelled assignments may be interchanged. Electronic impact mass spectra (EIMS), fast atom bombardment mass spectra (FABMS, with glycerol or glycerol/LiCl as matrix), chemical ionisation (CIMS); high resolution mass spectra (HREIMS) and (HRFABMS) were recorded on a VG Autospec spectrometer.

Monitoring of reactions were carried out using Merck TLC aluminium sheets (Kieselgel 60 PF 254). Preparative TLC (Kieselgel 60 PF 254) and column chromatography (Kieselgel 60 70-230 mesh) were performed with indicated eluents. The isolated compounds are described following less to more polar range. Methanol and ethanol were distilled from sodium; tetrahydrofuran and diethylether from calcium hydride.

Rearrangement of 16-chloro-1-dehydrovincadifformine 2a and of 16-chloro-1-dehydrotabersonine 2b with sodium alkoxides. General procedure. The starting material was added to a freshly prepared solution of alkoxide (15-20 mL of alcohol per mmole, 4 eq of sodium) in a dried flask, under N_2. The mixture was stirred at room temperature, or sligthly heated, or refluxed until the major part of the starting material was transformed. Then, alcohol was removed *in vacuo*, water was added (30 mL per mmole) and the solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by column chromatography or preparative TLC.

Reaction of 2a with sodium methoxide in methanol. a) 2a (360 mg, 0.97 mmole) was added to a sodium ethoxide solution (MeOH : 19 mL, sodium : 208 mg). The mixture was stirred at rt during 12 days. After work-up, the residue was purified by column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH 49:1, 47:3, then 42:8); 4 compounds were obtained: starting material **2a** (16 mg, 4.5%), **11a** (74 mg, 21%), **12a** (162 mg, 47%), **14a** (9 mg, 2.5%). **11a**: $[\alpha]_D$ -263.3 (MeOH, c 6.3); UV: 269, 224; IR (film): 2940, 2775, 1745; EIMS: 369 (30) $[M+H]^+$, 368 (80) $[M^{+\cdot}]$, 353 (58), 337 (73), 309 (65), 155 (100), 124 (94); HREIMS: calc. for $C_{22}H_{28}N_2O_3$: 368.2100, found: 368.2107; ^1H NMR: 7,62 (dd, 1H, 7.8, 0.9, H-12), 7.35 (dd, 1H, 7.8, 0.9, H-9), 7.27 (td, 1H, 7.8, 0.9, H-11), 7.23 (td, 1H, 7.8 , 0.9, H-10), 3.88 (s, 3H, CH_3OCO-16), 3.50 (s, 3H, CH_3O-16), 3.18 (m, 2H, H-5, H-3), 2.93 (d, 1H, 14.0, H-17), 2.65 (m, 2H, H'-5, H-6), 2.44 (s, 1H, H-21), 2.22 (td, 1H, 11.2, 2.2, H'-3), 2.17 (dd, 1H, 14.0, 1.3, H'-17), 1.85 (m, 1H, H-14),(m, 1H, H'-6), 1.53 (m, 2H, H'-14, H-15), 1.07 (td, 1H, 14.4, 5.4, H'-15), 0.85 (m, 1H, H-19), 0.68-0.53 (m, 4H, H'-19, H_3-18); ^{13}C NMR: 183.3 (C-2), 172.9 (C-22), 152.6 (C-13), 147.7 (C-8), 127.5

(C-11), 126.6 (C-10), 121.8 (C-12), 120.8 (C-9), 82.3 (C-16), 77.9 (C-21), 61.2 (C-7), 54.1 (C-5), 53.7 (CH_3O), 52.3 ($\underline{C}H_3OCO$), 51.7 (C-3), 38.4 (C-17), 36.6 (C-20), 35.7 (C-6), 33.1 (C-15), 28.9 (C-19), 22.0 (C-14), 6.8 (C-18). **12a**: mp 181-183°C (MeOH-Et_2O); $[\alpha]_D$ +115.9 (MeOH, c 3.5); UV: 291, 283, 275, 222; IR (film): 3300-3100, 2965, 2860, 1645, 1455; FABMS (glycerol): 355.2 (100) $[M+H]^+$, 311.2 (75), (glycerol/LiCl): 361.1 (96) $[M+Li]^+$, 311.2 (64), 279.2 (100); HRFABMS: calc. for $C_{21}H_{27}N_2O_3$: 355.2022, found: 355.2102; ^1H NMR: 10.01 (s, 1H, H-1), 7.44 (dd, 1H, 7.7, 0.9, H-9), 7.38 (dd, 1H, 7.7, 0.9, H-12), 7.08 (td, 1H, 7.7, 0.9, H-11), 7.02 (td, 1H, 7.7, 0.9, H-10), 4.53 (dt, 1H, 13.0, 5.9, H-5), 4.40 (s + m, 2H, H-21, H-3), 3.68 (s, 3H, CH_3O-21), 3.40 (td + bs, >2H, 11.3, 4.1, H'-3, H_2O), 3.23 (dd, 1H, 13.0, 4.0, H'-5), 3.10 (d, 1H, 15.7, H-17), 3.03 (m, 1H, H-6), 2.93 (td, 1H, 13.5, 5.8, H'-6), 2.24 (d, 1H, 15.7, H'-17), 2.05 (m, 1H, H-14), 1.64 (m, 2H, H'-14, H-15), 1.32 (m, 2H, H'-15, H-19), 1.11 (dq, 1H, 15.0, 7.4, H'-19), 0.72 (t, 3H, 7.4, H_3-18); ^{13}C NMR: 166.9 (C-22), 137.2 (C-13), 134.6 (C-2), 125.3 (C-8), 122.4 (C-11), 119.5 (C-10), 117.6 (C-9), 112.1 (C-12), 101.4 (C-7), 98.8 (C-21), 72.1 (C-16), 62.1 (CH_3O), 54.8 (C-3), 52.4 (C-5), 43.3 (C-20), 41.7 (C-17), 29.5 (C-19), 25.1 (C-15), 18.5 (C-14), 17.1 (C-6), 8.0 (C-18). **14a**: $[\alpha]_D$ +158.2 (MeOH, c 3.6); UV: 299, 242, 208; IR (film): 3500-3100, 2965, 2930, 1620, 1470; FABMS (glycerol): 355.5 (100) $[M+H]^+$, 279.3 (96); (glycerol/LiCl): 361.4 (100) $[M+Li]^+$, 279.3 (53); HRFABMS: calc. for $C_{21}H_{27}O_3N_2$: 355.2022, found: 355.1983. ^1H NMR: 7.14 (t, 1H, 7.3, H-11), 7.12 (d, 1H, 7.3, H-12), 7.01 (s, 1H, H-1), 6.75 (d, 1H, 7.3, H-12), 6.67 (t, 1H, 7.3, H-10), 4.90 (dt, 1H, 11.4, 7.3, H-5), 4.70 (dd, 1H, 12.0, 5.5, H-3), 4.07 (bs, >2H, H_2O), 3.60 (s, 1H, H-21), 3.62-3.38 (m, 2H, H'-5, H'-3), 3.18 (s, 3H, CH_3O-2), 2.93 (d, 1H, 13.5, H-17), 2.57 (dt, 1H, 9.9, 9.0, H-6), 2.17 (d, 1H, 13.5, H'-17), 2.20-2.00 (m, 2H, H'-6, H-14), 1.82 (m, 1H, H'-14), 1.67 (m, 1H, H-15), 1.45 (m, 1H, H'-15), 1.04 (m, 2H, H_2-19), 0.52 (t, 3H, 7.4, H_3-18); ^{13}C NMR: 167.6 (C-22), 151.8 (C-13), 130.2 (C-11), 123.2 (C-9), 121.4 (C-8), 118.0 (C-10), 108.3 (C-12), 101.2 (C-2), 97.1 (C-16), 82.1 (C-21), 63.5 (C-7), 58.8 (C-5), 56.4 (C-3), 52.7 (CH_3O), 42.3 (C-20), 37.8 (C-17), 32.3 (C-15), 27.6 (C-6), 36.3 (C-19), 18.8 (C-14), 8.7 (C-18). **b) 2a** (100 mg, 0.27 mmole) was added to sodium methoxide (4 eq) in MeOH (5 mL), then heated at reflux (24h). TLC (CH_2Cl_2/MeOH 94:6), allowed separation of starting material **2a** (1 mg), **11a** (28 mg, 28%), **12a** (5.5 mg, 6%) and **14a** (25 mg, 26%).

Reaction of 2b with sodium methoxide in methanol. a) 2b (216 mg, 0.58 mmole), was left in a solution of sodium methoxide (4 eq, 10 mL) at rt (4 days) and the following compounds were isolated (TLC, CH_2Cl_2/MeOH 94:6) : starting material **2b** (13 mg, 6%), **11b** (170 mg, 79%), **12b** (10 mg, 5%) and **14b** (3 mg, 1.5%). **11b**: mp 147-148°C (MeOH), $[\alpha]_D$ -221.9 (MeOH, c 5.0); UV: 268, 234; IR (film): 2960, 2775, 1745; EIMS: 366 (52) $[M^{+\cdot}]$, 351 (15), 335 (20), 153 (100), 121 (40); HREIMS: calc. for $C_{22}H_{26}N_2O_3$: 366.1943, found: 366.1946; ^1H NMR: 7.62 (d, 1H, 8.0, H-12), 7.35 (dd, 1H, 8.0, 0.9, H-9), 7.31 (td, 1H, 8.0, 0.9, H-11), 7.23 (td, 1H, 8.0, 0.9, H-10), 5.73 (ddd, 1H, 9.9, 4.8, 1.8, H-14), 5.42 (dt, 1H, 9.9, 2.2, H-15), 3.90 (s, 3H, CH_3OCO-16), 3.56 (ddd, 1H, 15.7, 4.8, 1.8, H-3), 3.45 (s, 3H, CH_3O-16), 3.33 (dd, 1H, 7.7, 6.7, H-5), 3.03 (bd, 1H, 15.7, H'-3), 2.90 (d, 1H, 14.0, H-17), 2.86 (m, 1H, H-6), 2.82 (s, 1H, H-21), 2.76 (m, 1H, H'-5), 2.36 (dd, 1H, 14.0, 1.4, H'-17), 1.68 (dd, 1H, 11.7, 4.5, H'-6), 1.08 (dq, 1H, 13.5, 7.7, H-19), 0.93 (dq, 1H, 13.5, 7.7, H'-19), 0.50 (t, 3H, 7.7, H_3-18); ^{13}C NMR: 181.7 (C-2), 172.3 (C-22), 152.4 (C-13), 147.2 (C-8), 133.3 (C-15), 127.4 (C-11),126.6 (C-10), 125.2 (C-14), 121.6 (C-12), 120.7 (C-9), 81.2 (C-16), 72.4 (C-21), 60.2 (C-7), 53.5 (CH_3O), 53.5 (C-5), 52.1 ($\underline{C}H_3OCO$), 51.5 (C-3), 42.9 (C-17), 40.1 (C-20), 35.1 (C-6), 27.5 (C-19), 7.9 (C-18). **12b**: $[\alpha]_D$ +248.8 (MeOH, c 4.8); UV: 290, 280, 272, 221; IR (film): 3500-3200, 2970, 2930, 2860, 1645, 1455, 1330; FABMS (glycerol): 353.1 (62) $[M+H]^+$, 309.1 (100); HRFABMS: calc. for $C_{21}H_{25}N_2O_3$: 353.1865, found: 353.2029; ^1H NMR: 9.65 (s, 1H, H-1), [a]7.42 (d, 8.0, H-9), [a]7.40 (d, 1H, 8.0, H-12), 7.13 (t, 1H, 8.0, H-11), 7.06 (t, 1H, 8.0, H-10), 5.73 (bd, 1H, 8.2, H-15), 5.62 (m, 1H, H-3), 5.58 (m, 1H, H-14), 4.63 (s, 1H, H-21), 4.42 (dt, 1H, 11.4, 7.3, H-5), 3.78 (s + m, 4H,

CH_3O-21, H'-3), 3.55 (d, 1H, 13.0, H-17), 3.34 (dt, 1H, 11.4, 2.5, H'-5), 3.08 (m, 2H, H_2-6), 2.73 (bs, >1H, H_2O), 2.12 (d, 1H, 13.0, H'-17), 1.48 (dq, 1H, 13.9, 6.7, H-19), 1.28 (dq, 1H, 13.9, 6.7, H'-19), 0.85 (t, 3H, 6.7, H_3-18); ^{13}C NMR: 166.9 (C-22), 137.1 (C-13), 135.0 (C-2), 129.8 (C-15), 125.4 (C-8), 122.7 (C-11), 119.7 (C-10, C-14), 117.8 (C-9), 112.1 (C-12), 100.7 (C-7), 97.9 (C-21), 75.5 (C-16), 62.2 (CH_3O), 58.1 (C-3), 53.9 (C-5), 47.2 (C-17), 44.1 (C-20), 26.5 (C-19), 17.3 (C-6), 7.9 (C-18). **14b**: $[\alpha]_D$ +172.2 (MeOH, c 4.3); UV: 303, 242, 207; IR (film): 3500-3200, 3055, 2970, 1620, 1465, 1385; FABMS (glycerol/LiCl): 359 (100) $[M+Li]^+$, 327 (10), 277 (35); HRFABMS: calc. for $C_{21}H_{25}N_2O_3$: 353.1865, found: 353.1956; ^1H NMR: 7.18 (td, 1H, 7.6, 0.9, H-11), 7.12 (d, 1H, 7.6, H-9), 6.77 (d, 1H, 7.6, H-12), 6.72 (s + m, 2H, H-1, H-10), 6.19 (dd, 1H, 9.0, 2.7, H-15), 5.72 (bd, 9.0, H-14), 5.35 (m, 1H, H-5), 5.30 (m, 1H, H-3), 4.05 (dd, 1H, 18.0, 4.0, H'-3), 3.52 (s + m, 2H, H-21, H'-5), 3.38 (bs, >2H, H_2O), 3.22 (s, 3H, CH_3O-2), 3.06 (d, 1H, 14.4, H-17), 2.54 (dt, 1H, 11.3, 9.0, H-6), 2.36 (m, 1H, H'-6), 2.30 (d, 1H, 14.4, H'-17), 1.20 (m, 2H, H_2-19), 0.54 (t, 3H, 7.7, H_3-18); ^{13}C NMR: 166.5 (C-22), 151.7 (C-13), 141.9 (C-15), 130.7 (C-11), 123.2 (C-9), 122.7 (C-14), 120.5 (C-8), 118.5 (C-10), 108.5 (C-12), [a]99.4 (C-2), [a]99.0 (C-16), 81.4 (C-21), 63.5 (C-7), 60.2 (C-5), 58.6 (C-3), 52.5 (CH_3O), 44.6 (C-17), 43.4 (C-20), 28.8 (C-19), 24.2(C-6), 9.3 (C-18). **b) 2b** (180 mg, 0.48 mmole), was heated at reflux in MeOH (10 mL) and aqueous NaOH 40% (0,23 mL) for 2h. After work-up and TLC (CH_2Cl_2/MeOH 92:8): starting material **2b** (13 mg, 7%), **11b** (38 mg, 21%), **12b** (45 mg, 26%) and **14b** (47 mg, 27%) were isolated.

Reaction of 2a with sodium ethoxide in ethanol. a) 2a (300 mg, 0.81 mmole) was added to a solution of sodium ethoxide in EtOH (4 eq, 12 mL), at rt (48h) then heated at reflux (1h) affording after TLC (CH_2Cl_2/MeOH 94:6): **2a** (ethyl 16-chloro-1-dehydrovincadifforminate, Me = Et) (19 mg, 6.5%), **13a** (4.5 mg, 1.5%) and **15a** (76 mg, 26%). **2a** (ethyl 16-chloro-1-dehydrovincadifforminate, Me = Et): $[\alpha]_D$ -223.6 (MeOH, c 7.3); UV: 283, 228; IR (film): 2960-2940, 2785, 1740, 1450; EIMS: 388 (26) $[M^{+\cdot}, {}^{37}Cl]$, 386 (60) $[M^{+\cdot}, {}^{35}Cl]$, 350 (43), 321 (54), 280 (49), 124 (100); ^1H NMR: 7.58 (dd, 1H, 8.0, 0.9, H-12), 7.35-7.20 (m, 3H, H-9, H-11, H-10), 4.43 (m, 2H, $CH_3C\underline{H}_2OCO$), 3.25 (m, 2H, H-3, H-5), 3.21 (d, 1H, 13.5, H-17), 3.10 (dt, 1H, 11.0, 7.6, H'-5), 2.85 (dd, 1H, 13.5, 1.0, H'-17), 2.62 (ddd, 1H, 12.0, 7.6, 6.7, H-6), 2.43 (s, 1H, H-21), 2.18 (td, 1H, 12.2, 2.3, H'-3), 1.85 (m, 1H, H-14), 1.76 (dd, 1H, 12.0, 4.9, H'-6), 1.53 (m, 2H, H'-14, H-15), 1.40 (t, 3H, 7.7, $C\underline{H}_3CH_2OCO$), 1.08 (td, 1H, 13.9, 6.7, H'-15), 0.70 (m, 1H, H-19), 0.56 (m, 4H, H'-19, H_3-18). **13a**: $[\alpha]_D$ +63.1 (MeOH, c 5.9); UV: 291, 283, 274, 221; IR (film): 3400-3200, 2970, 2930, 2860, 1645, 1455; FABMS (glycerol): 391 (41) $[M+Na]^+$, 369 (85) $[M+H]^+$, 325 (90), 295 (77), 279 (52), 124 (100); HRFABMS: calc. for $C_{22}H_{29}N_2O_3$: 369.2178, found: 369.2156; ^1H NMR: 9.06 (bs, 1H, H-1), 7.40 (d, 1H, 7.7, H-9), 7.33 (t, 1H, 7.7, H-12), 7.18 (t, 1H, 7.7, H-11), 7.10 (t, 1H, 7.7, H-10), 4.68-4.52 (s + m, 3H, H-21, H-3, H-5), 4.07 + 3.83 (2m, 2H, $CH_3C\underline{H}_2O$-21), 3.52 (td, 1H, 11.6, 4.3, H'-3), 3.32 (bdd, 1H, 13.0, 5.3, H'-5), 3.19 (d, 1H, 13.9, H-17), 3.06 (dt,1H, 17.1, 5.3, H-6), 3.01 (ddd, 1H, 17.1, 12.2, 5.3, H'-6), 2.29 (d,1H, 13.9, H'-17), 2.20-1.95 (m + bs, >2H, H-14, H_2O), 1.76 (m, 2H, H'-14, H-15), 1.65-1.40 (m, 2H, H'-15, H-19), 1.37 (t, 3H, 7.0, $C\underline{H}_3CH_2O$-21), 1.26 (m, 1H, H'-19), 0.83 (t, 3H, 7.0, H_3-18). **15a**: $[\alpha]_D$ +132.1 (MeOH, c 5.4); UV: 300, 242, 211; IR (film): 3500-3200, 2970, 2935, 1620, 1470, 1390; FABMS (glycerol/LiCl): 375.2 (100) $[M+Li]^+$, 279.2 (47); HRFABMS: calc. for $C_{22}H_{29}N_2O_3$: 369.2178, found: 369.2187; ^1H NMR: 7.17 (td, 1H, 7.5, 0.9, H-11), 7.10 (d, 1H, 7.5, H-9), 6.75 (d, 1H, 7.5, H-12), 6.72 (t, 1H, 7.5, H-10), 6.50 (bs, 1H, H-1), 5.07 (dt, 1H, 11.6, 8.4, H-5), 4.87 (ddd, 1H, 12.2, 6.0, 2.0, H-3), 3.79 (dq, 1H, 8.6, 7.7, $CH_3C\underline{H}_2O$-2), 3.33 (s, 1H, H-21), 3.30 (m, 1H, H'-5), 3.20 (m, 1H, H'-3), 3.11 (dq, 1H, 8.6, 7.7, $CH_3C\underline{H}_2O$-2), 2.94 (d, 1H, 14.0, H-17), 2.43 (dt, 9.4, 8.4, H-6), 2.23 (d, 1H, 14.0, H'-17), 2.17 (m, 2H, H-14, H'-6), 1.80 (m, 1H, H'-14), 1.60 (td, 1H, 14.0, 4.9, H-15), 1.48 (m, 1H, H'-15), 1.10 (t, 3H, 7.7, $C\underline{H}_3CH_2O$-2), 1.05 (m, 2H, H_2-19), 0.53 (t, 3H, 7.7, H_3-18); ^{13}C NMR: 167.4 (C-22), 151.5 (C-13), 130.4 (C-11), 123.1 (C-9), 121.0 (C-8), 118.2 (C-

10), 108.1 (C-12), 100.6 (C-2), 97.7 (C-16), 82.5 (C-21), 63.6 (C-7), 60.5 ($CH_3\underline{C}H_2O$), 59.0 (C-5), 57.0 (C-3), 42.5 (C-20), 37.6 (C-17), 32.5 (C-15), 28.0 (C-6), 26.3 (C-19), 18.8 (C-14), 14.8 ($\underline{C}H_3CH_2O$), 8.6 (C-18). **b) 2a** (85 mg, 0.23 mmole), in an ethanolic solution of sodium ethoxide at rt (7 days) yielded **2a** (ethyl 16-chloro-1-dehydrovincadifforminate, Me = Et) (5 mg, 6%), **13a** (1 mg, <1.5%) and **15a** (37 mg, 43%). **c) 2a** (300 mg, 0.80 mmole), refluxed in an ethanolic solution of sodium ethoxide (1h30) yielded **2a** (ethyl 16-chloro-1-dehydrovincadifforminate, Me = Et) (60 mg, 20%) and **15a** (33 mg, 11%).

Reaction of 2b with sodium ethoxide in ethanol. 2b (300 mg, 0.81 mmole), in an ethanolic solution of sodium ethoxide (12 mL, 4 eq) was heated at 35°C (48h), and afforded after work-up and TLC (3 runs using CH_2Cl_2/MeOH 94:6): **13b** (18 mg, 6%) and **15b** (29 mg, 10%). **13b**: $[\alpha]_D$ +243.1 (MeOH, c 6.1); UV: 290, 282, 273, 221; IR (film): 3400-3150, 2970, 2935, 2865, 1645, 1450, 1330; FABMS (glycerol): 367 (45) $[M+H]^+$, 323 (75), 293 (100), 277 (64); HRFABMS: calc. for $C_{22}H_{27}N_2O_3$: 367.2022, found: 367.2025; ^1H NMR: 9.07 (s, 1H, H-1), 7.42 (d, 1H, 7.7, H-9), 7.35 (d, 1H, 7.7, H-12), 7.17 (t, 1H, 7.7, H-11), 7.08 (t, 1H, 7.7, H-10), 5.84 (m, 2H, H-15, H-3), 5.64 (bd, 1H, 9.9, H-14), 4.72 (s, 1H, H-21), 4.47 (td, 1H, 12.2, 5.8, H'-3), 4.11 (dq, 1H, 8.8, 6.8, $CH_3C\underline{H}_2O$-21), 3.90 (dq, 1H, 8.8, 6.8, $CH_3C\underline{H}_2$ O-21), 3.86 (bd, 1H, 12.0, H-5), 3.61 (d, 1H, 13.5, H-17), 3.41 (bdt, 1H, 12.2, 3.2, H'-5), 3.11 (m, 2H, H_2-6), 2.14 (d, 1H, 13.5, H'-17), 2.04 (bs, ≥2H, H_2O), 1.55 (dq, 1H, 7.7, 5.8, H-19), 1.35 (t + m, 4H, 7.5, $C\underline{H}_3CH_2O$-21, H'-19), 0.91 (t, 3H, 7.5, H_3-18); ^{13}C NMR: 167.0 (C-22), 137.1 (C-13), 135.0 (C-2), 129.8 (C-15), 125.3 (C-8), 122.7 (C-11), [a]119.7 (C-10), [a]119.6 (C-14), 117.8 (C-9), 112.0 (C-12), 100.6 (C-7), 96.8 (C-21), 75.3 (C-16), 70.9 ($CH_3\underline{C}H_2O$), 59.1 (C-3), 53.8 (C-5), 47.2 (C-17), 44.0 (C-20), 28.5 (C-19), 17.4 (C-6), 15.7 ($\underline{C}H_3CH_2O$), 7.9 (C-18). **15b**: $[\alpha]_D$ +179.9 (MeOH, c 3.9); UV: 301, 242, 207; IR (film): 3400-3100, 2975, 2930, 1625, 1470, 1380; FABMS (glycerol): 389 (35) $[M+Na]^+$, 367 (100) $[M+H]^+$, 322 (42), 277 (68); HRFABMS: calc. for $C_{22}H_{27}N_2O_3$: 367.2022, found: 367.2011; ^1H NMR: 7.19 (td, 1H, 7.7, 1.0, H-11), 7.11 (d, 1H, 7.7, H-9), 6.74 (d, 1H, 7.7, H-12), 6.72 (t, 1H, 7.7, H-10), 6.62 (s, 1H, H-1), 6.18 (dd, 9.6, 2.2, H-15), 5.72 (ddd, 1H, 9.4, 3.7, 2.2, H-14), 5.44 (dt, 19.0, 2.3, H-3), 5.33 (dt, 1H, 11.9, 8.4, H-5), 4.07 (dd, 19.0, 3.7, H'-3), 3.78 (dq, 1H, 9.1, 7.2, $CH_3C\underline{H}_2O$-2), 3.53 (s + m, 2H, H-21, H'-5), 3.12 (dq, 1H, 9.1, 7.2, $CH_3C\underline{H}_2O$-2), 3.05 (d, 1H, 13.7, H-17), 2.56 (dt, 1H, 11.1, 8.8, H-6), 2.34 (m, 1H, H'-6), 2.32 (d, 1H, 13.7, H'-17), 1.19 (m, 2H, H_2-19), 1.12 (t, 3H, 7.2, $C\underline{H}_3CH_2O$-2), 0.53 (t, 3H, 7.4, H_3-18); ^{13}C NMR: 166.6 (C-22), 151.8 (C-13), 141.7 (C-15), 130.6 (C-11), 123.2 (C-9), 122.9 (C-14), 120.7 (C-8), 118.3(C-10), 108.5 (C-12), [a]99.2 (C-2), [a]98.8 (C-16), 81.2 (C-21), 63.6 (C-7), 60.4 ($CH_3\underline{C}H_2O$), 60.1 (C-5), 58.5 (C-3), 44.7 (C-17), 43.2 (C-20), 29.0 (C-19), 24.2 (C-6), 14.9 ($\underline{C}H_3CH_2O$), 9.3 (C18).

Reduction of indolenine 11a with $NaBH_3CN$. $NaBH_3CN$ (150 mg) was added to a solution of **11a** (50 mg, 0,13 mmole) in MeOH (3 mL) over 30 min, at rt. The mixture was stirred for 30 min, then diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried, filtered and concentrated *in vacuo*. Separation by TLC (CH_2Cl_2/MeOH 94:6) afforded starting material **11a** (24 mg, 48%) and indole **16** (14 mg, 28%): $[\alpha]_D$ +7.8 (MeOH, c 6.9); UV: 291, 284, 277, 222; IR (film): 3420, 2935, 2795, 1720; EIMS: 370 (40) $[M^+\cdot]$, 353 (27), 338 (40), 310 (23), 155 (100), 124 (70); HREIMS: calc. for $C_{22}H_{30}N_2O_3$: 370.2256, found: 370.2265; ^1H NMR: 10.25 (s, 1H, H-1), 7.56 (d, 1H, 8.0, H-9), 7.40 (d, 1H, 8.0, H-12), 7.20 (td, 1H, 8.0, 0.9, H-11), 7.11 (td, 1H, 8.0, 0.9, H-10), 3.93 (s, 3H, CH_3OCO-16), 3.42 (m, 2H, H-17, H-21), 3.15 (m, 2H, H-3, H-5), 3.00 (s, 3H, CH_3O-16), 2.95 (m, 1H, H'-5), 2.68 (m, 1H, H'-3), 2.26 (d, 1H, 14.4, H'-17), 2.04 (m, 1H, H-6), 1.85 (m, 1H, H-14), 1.68 (m, 1H, H'-6), 1.50 (m, 1H, H-15), 1.36 (m, 2H, H'-14, H'-21), 1.20 (dq, 1H, 13.5, 6.8, H-19), 0.97 (m, 1H, H'-15), 0.76 (m, 1H, H'-19), 0.67(t, 3H, 7.2, H_3-18); ^{13}C NMR: 176.0 (C-22), 134.4 (C-13), 129.9 (C-2), 127.5 (C-8), 121.9 (C-11), 118.9 (C-9, C-10), 115.2 (C-7), 111.2 (C-12), 81.7 (C-16), 59.1 (C-21), 54.9 (C-

3), 53.5 (C-5), 52.6 ($\underline{C}H_3OCO$, $\underline{C}H_3O$), 44.5 (C-7), 37.7 (C-20), 36.8 (C-15), 28.6 (C-6, C-19), 23.2 (C-14), 7.2, (C-18).

Reduction of 12a with $LiAlH_4$. $LiAlH_4$ (300 mg) was slowly added (30 min) to a stirred solution of **12a** (75 mg, 0.21 mmole) in THF (20 mL). After 4h at rt the mixture was diluted with THF (20 mL) then THF/H_2O: 4/1, filtered on a funnel loaded with $MgSO_4$ and Celite®, then washed with THF (40 mL). The residue (68 mg) was purified by TLC (CH_2Cl_2/MeOH 86:14) to provide alcohol **17** (44 mg, 58%): mp 185-187° (MeOH/Et_2O); $[\alpha]_D$ + 46.5 (MeOH, c 8.3); UV: 290, 281, 270, 222; IR(film): 3500-3100, 2940, 2865, 1460; FABMS (glycerol): 341.3 (100) [M^+], 309.2 (6); HRFABMS: calc. for $C_{21}H_{29}N_2O_2$: 341.2229, found: 341.2220; ^1H NMR: 11.62 (s, 1H, H-1), 7.61 (d,1H, 7.9, H-12), 7.40 (d, 1H, 7.9, H-9), 7.18 (t, 1H, 7.9, H-11), 7.08 (t, 1H, 7.9, H-10), 5.62 (bs, 1H, $\underline{H}OCH_2$-16), 4.49 (s, 1H, H-21), 4.37 + 4.22 (AB, 2H, 13.5, $HOC\underline{H}_2$-16), 4.10 (dt, 1H, 12.6, 5.7, H-5), 3.78 (dd, 1H, 13.6, 5.2, H-3), 3.70 (s, 3H, CH_3O-21), 3.37 (m, 1H, H'-3), 3.20 (dd, 1H, 12.6, 5.5, H'-5), 2.98 (dd, 1H, 16.2, 5.7, H-6), 2.83 (ddd, 16.2, 11.8, 5.7, H'-6), 2.36 (d, 1H, 13.9, H-17), 1.98 (d, 1H, 13.9, H'-17), 1.70 (m, 3H, H-14, H_2-15), 1.28 (m, 2H, H'-14, H-19), 1.20 (m, 1H, H'-19), 0.72 (t, 3H, 7.4, H_3-18); ^{13}C NMR :137.6 (C-13), 132.3 (C-2), 124.9 (C-8), 122.5 (C-11), 119.4 (C-10), 117.8 (C-9), 112.8 (C-12), 104.0 (C-7), 99.1 (C-21), 71.2 (C-16), 63.3 (CH_2OH), 62.3 (CH_3O), 53.9 (C-5), 53.6 (C-3), 43.2 (C-20), 39.0 (C-17), 29.5 (C-19), 24.8 (C-15), 18.7 (C-14), 17.0 (C-6), 8.0 (C-18).

Methylation of 12a. A solution of **12a** (30 mg, 0.085 mmole) in $CHCl_3$ (3 mL) and iodomethane (0.1 mL) was heated (55°C) for 3h in a sealed tube. Concentration *in vacuo* followed by purification (TLC, CH_2Cl_2/MeOH 94:6) yielded starting material **12a** (6 mg, 20%) and indole **18** (13 mg, 41%): mp 180-182°C (MeOH); $[\alpha]_D$ +49.3 (MeOH, c 5.2); UV: 292, 284, 276, 220; IR (film): 3440, 3170, 2960, 1740, 1455; FABMS (glycerol): 369.2 (100) [M^+], 311.2 (12); HRFABMS: calc. for $C_{22}H_{29}N_2O_3$: 369.2178, found: 369.2236; ^1H NMR: 10.28 (s, 1H, H-1), 7.87 (d, 1H, 7.9, H-12), 7.48 (d, 1H, 7.9, H-9), 7.19 (td, 1H, 7.9, 0.9, H-11), 7.12 (td, 1H, 7.9, 0.9, H-10), 4.62 (s, 1H, H-21), 4.23 (td, 1H, 12.6, 5.6, H-5), 4.01 (s, 3H, CH_3OCO-16), 3.97 (m, 1H, H-3), 3.92 (s + m, 5H, CH_3O-21, H'-3, H-6), 3.34 (dd, 1H, 12.6, 5.6, H'-5), 3.13 (td, 1H, 12.6, 5.6, H'-6), 3.09 (d, 1H, 13.9, H-17), 2.80 (d, 1H, 13.9, H'-17), 1.90 (m, 2H, H-14, H-15), 1.65 (m, 1H, H'-14), 1.51 (m, 1H, H'-15), 1.43 (dq, 1H, 14.4, 7.7, H-19), 1.27 (dq, 1H, 14.4, 7.7, H'-19), 0.81(t, 3H, 7.7, H_3-18); ^{13}C NMR: 166.5 (C-22), 137.8 (C-13), 127.9 (C-2), 124.4 (C-8), 123.9 (C-11), 120.4 (C-10), 118.2 (C-9), 113.4 (C-12), 103.6 (C-7), 100.6 (C-21), 70.1 (C-16), 63.6 (CH_3O), 55.6 (C-3), 55.2 ($\underline{C}H_3OCO$), 53.6 (C-5), 43.7 (C-20), 40.9 (C-17), 29.1 (C-19), 25.0 (C-15), ^{a}18.5 (C-14), ^{a}17.2 (C-6), 8.2 (C-18).

Decarboxylation of 12a. A solution of **12a** (32 mg, 0.09 mmole) in aqueous HCl (36%, 1 mL) was heated at reflux for 20 min. The mixture was diluted with iced-water (20 mL), basified by ammonia and extracted (CH_2Cl_2, 30 mL). The residue was purified by TLC (CH_2Cl_2/MeOH 88:12) to afford indole **19** (22 mg, 78%): $[\alpha]_D$ +106.4 (MeOH, c 6.6); UV: 288, 281, 273, 220; IR (film): 3390, 3155, 2965, 1460; FABMS (glycerol): 313 (25), 312 (100) $[M+H]^+$, 311 (5), 156 (13); HRFABMS: calc. for $C_{20}H_{27}N_2O$: 311.2123 (100), found: 311.2124; ^1H NMR: 10.90 (s, 1H, H-1), 7.61 (d, 1H, 7.7, H-12), 7.39 (d, 1H, 7.7, H-9), 7.18 (t, 1H, 7.7, H-11), 7.08 (t, 1H, 7.7, H-10), 4.99 (dd, 1H, 9.0, 4.4, H-16), 4.19 (s, 1H, H-21), 3.70 (s, 3H, CH_3O-21), 3.50-3.25 (m, 3H, H-3, H_2-5), 3.13 (m, 1H, H'-3), 2.98 (bd, 1H, 13.4, H-6), 2.78 (bt, 1H, 13.4, H'-6), 2.58 (dd, 1H, 14.4, 9.9, H-17), 1.80 (dd, 1H, 14.4, 4.4, H'-17), 1.73-1.50 (m, 3H, H_2-14, H-15), 1.32 (dq, 1H, 14.0, 7.0, H-19), 1.15 (m, 2H, H'-15, H'-19), 0.73 (t, 3H, 7.2, H_3-18); ^{13}C NMR: 137.3 (C-13), 131.6 (C-2), 124.9 (C-8), 122.5 (C-11), 119.6 (C-10), 118.2 (C-9), 112.3 (C-12), 102.2 (C-7), 97.8 (C-21), 62.3 (CH_3O), 59.8 (C-16), 57.1 (C-3), 53.9 (C-5), 43.7 (C-20), 37.0 (C-17), 29.1 (C-19), 24.2 (C-15), 17.5 (C-14), 16.7 (C-6), 8.0 (C-18).

Reduction of 12a with $LiAlH_4$ in N-methylmorpholine. $LiAlH_4$ (200 mg) was added to a solution of **12a** (50 mg, 0.14 mmole) in distilled N-methylmorpholine (10 mL). The mixture was heated at reflux for 20h and worked-up as for **12a** → **17**. Separation by TLC (CH_2Cl_2/MeOH 94:6) afforded **20** (9 mg, 22%), **22** (6 mg, 13.5%) and **23** (6 mg, 13.5%). **20**: $[\alpha]_D$ +94.9 (EtOH, c 2.9); UV: 290, 282, 222; IR (film): 3400, 2920, 2850, 2785, 1670, 1460; EIMS: 294 (63) [$M^{+\cdot}$], 279 (43), 275 (87), 251 (75), 170 (64), 168 (54), 124 (100); HREIMS: calc. for $C_{20}H_{26}N_2$: 294.2096, found: 294.2060; ^1H NMR: 7.73 (bs, 1H, H-1), a7.50 (d, 1H, 7.7, H-9), a7.29 (dd, 1H, 7.7, 0.9, H-12), 7.12 (td, 1H, 7.7, 0.9, H-11), 7.07 (1H, 7.7, 0.9, H-10), 5.28 (d, 2H, 7.9, CH_2=16), 3.08 (dt, 1H, 11.8, 2.0), 2.96 (ddd, 1H, 14.4, 10.4, 5.4), 2.84 (dt, 1H, 14.4, 3.8), 2.71 (d, 1H, 12.1), 2.52 (m, 1H), 2.42 (m, 2H), 2.27 (td, 1H, 12.6, 3.8), 2.23 (d, 1H, 12.6), 1.72-1.40 (m, 4H), 1.33 (m, 1H), 1.25-1.05 (m, 2H, H_2-19), 0.90 (t, 3H, H_3-18). (+)-vincadinol (**22**): $[\alpha]_D$ +134.7 (EtOH, c 3.4, lit. +150,0[13]), UV: 292, 284, 276, 227; IR (film): 3450-3200, 2930, 2790, 1460; EIMS: 312 (40) [$M^{+\cdot}$], 282 (35), 281 (100), 187 (32), 124 (100), 110 (34); HREIMS: calc. for $C_{20}H_{26}N_2O$: 312.2202, found: 312.2197; ^1H NMR: 8.93 (s, 1H, H-1), 7.49 (d, 1H, 7.7, H-9), 7.30 (dd, 1H, 7.7, 0.9, H-12), 7.08 (td, 1H, 7.7, 0.9, H-11), 7.03 (td, 1H, 7.7, 0.9, H-10), 3.99 (m, 2H, HOC$\underline{H}_2$-16), 3.29 (td, 1H, 12.6, 2.2, H-21), 3.00 (m, 1H, H-16), 2.78 (m, 2H, H_2-5), 2.47 (ddd, 1H, 11.2, 5.4, 1.8, H-6), 2.45-2.20 (m, 3H, H_2-3, H'-6), 2.10 (dd, 1H, 13.5, 5.4, H-17), 1.52 (d + m, 2H, 12.6, H'-21, H-14), 1.39 (dd, 1H, 13.5, 5.4, H'-17), 1.35-1.08 (m, 5H, H_2-15, H'-14, H_2-19), 0.88 (t, 3H, 7.7, H_3-18); ^{13}C NMR: 141.5 (C-2), 135.0 (C-13), 128.0 (C-8), 120.3 (C-11), 118.5 (C-10), 117.3 (C-9), 110.5 (C-12), 109.2 (C-7), 67.5 (CH_2OH), 56.9 (C-21), 55.2 (C-3), 53.1 (C-5), 37.6 (C-20), 35.6 (C-17), 34.1 (C-15), 33.6 (C-16), 31.0 (C-19), 22.5 (C-14), 22.0 (C-6), 7.6 (C-18). **23**: $[\alpha]_D$ +62.4 (MeOH, c 7.0); UV: 290, 282, 273, 225; IR (film): 3400, 3295, 2945, 2860, 1455; EIMS: 312 (2) [$M^{+\cdot}$], 311 (3), 297 (3), 282 (37), 281 (100); HREIMS: calc. for $C_{20}H_{28}N_2O$: 312.2202 found: 312.2201; ^1H NMR: 7.76 (s, 1H, H-1), 7.48 (d, 1H, 7.9, H-9), 7.32 (d, 1H, 7.9, H-12), 7.16 (td, 1H, 7.9, 0.9, H-11), 7.10 (td, 1H, 7.9, 0.9, H-10), 3.62 + 3.56 (AB, 2H, 9.9, HOC$\underline{H}_2$-16), 3.11 (m, 2H, H_2-5), 3.02 (m, 1H, H-6), 2.77 (AB, 2H, 8.1, H_2-21), 2.52 (dt, 1H, 14.4, 5.4, H'-6), 2.40 -2.00 (bs, 1H, $\underline{H}OCH_2$-16), 2.21 (d, 1H, 13.0, H-17), 1.83 (d, 1H, 13.0, H'-17), 1.50 (m, 2H, H_2-15), 1.28 (m, 2H, H_2-14), 1.12 (m, 2H, H_2-19), 0.93 (t, 3H, 7.7, H_3-3), 0.65 (t, 3H, 7.7, H_3-18); ^{13}C NMR: 136.0 (C-13, C-2), 127.1 (C-8), 121.7 (C-11), 119.4 (C-10), 118.3 (C-9), 110.7 (C-12), 107.0 (C-7), 65.6 (CH_2OH), 64.2 (C-16), 60.2 (C-21), 44.4 (C-5), 42.2 (C-20), 41.6 (C-17), 40.4 (C-15), 31.3 (C-19), 17.6 (C-6), 15.7 (C-14), 14.8 (C-3), 9.0 (C-18).

Catalytic hydrogenation of indole 12b. A mixture of indole **12b** (50 mg, 0.14 mmole), Na_2CO_3 (5 mg) and PtO_2 (6 mg) in MeOH (2 mL) was hydrogenated for 22h. The filtrate was concentrated *in vacuo* and the residue was purified by TLC (Et_2O/MeOH 85:15) to afford **12a** (6 mg, 12%) and secoindole **21** (30 mg, 63%): $[\alpha]_D$ +53.3 (MeOH, c 2.3). UV: 290, 281, 274, 224; IR (film): 3220, 3060, 2960, 2870, 1630, 1565, 1455; EIMS: 282 (78) $[M-44]^+$, 281 (100) $[M-45]^+$, 251 (41), 237 (44), 208 (31), 184 (70), 156 (23), 144 (13); FABMS (glycerol): 327.2 (6) $[M+H]^+$, 281.2 (100); ^1H NMR: 9.88 (s, 1H, H-1), 7.40 (d, 2H, 8.0, H-9, H-12), 7.17 (td, 1H, 8.0, 0.9, H-11), 7.07 (td, 1H, 8.0, 0.9, H-10), 3.52 (d, 1H, 11.7, H-21), 3.50-3.30 (m, 2H, H_2-5), 2.87 (d, 1H, 11.7, H'-21), 2.82 (m, 1H, H-6), 2.73 (m, 1H, H'-6), 2.51 (d, 1H, 14.0, H-17), 2.27 (d, 1H, 14.0, H'-17), 1.60-1.35 (m, 2H, H_2-15), 1.35-1.00 (m, 4H, H_2-14, H_2-19), 0.90 (t, 3H, 7.2, H_3-3), 0.65 (t, 3H, 7.2, H_3-18); ^{13}C NMR: 171.4 (C-22), 136.7 (C-13), 130.5 (C-2), 125.4 (C-8), 122.3 (C-11), 119.4 (C-10), 117.9 (C-9), 111.5 (C-12), 103.7 (C-7), 72.2 (C-16), 59.3 (C-21), 47.6 (C-17), 45.6 (C-5), 43.5 (C-20), 38.5 (C-15), 30.0 (C-19), 17.2 (C-14), 15.5 (C-6), 14.2 (C-3), 8.4 (C-18).

Catalytic hydrogenation of indole 12b followed by reduction with $LiAlH_4$. 12b (50 mg, 0.14 mmole), was hydrogenated (PtO_2: 6 mg, Na_2CO_3: 5 mg, MeOH: 2 mL) for 22h. After filtration and evaporation, $LiAlH_4$ (250

mg) was added to a stirred solution of the crude residue in dry THF (15 mL). After 0.5 h, work-up followed by purification (TLC, CH_2Cl_2/MeOH 93:7) yielded **23** (29 mg, 60%) and **17** (4 mg, 8%).

Methylation of secoindole 21. Iodomethane (0.05 mL) was added to a solution of compound **21** (12 mg, 0.04 mmole) in $CHCl_3$/MeOH 9/1 (1 mL). Heating in a sealed tube (55°C, 4 h) followed by evaporation of the solvents and purification by TLC (CH_2Cl_2/MeOH 95:5) yielded starting material **21** (6 mg, 50%) and **24** (4 mg, 33%): $[\alpha]_D$ +0.8 (MeOH, c 3.6); UV: 292, 284, 276, 222; IR (film): 3385, 2955, 2930, 2870, 1735, 1460; EIMS: 340 (6) [$M^{+\cdot}$], 298 (14), 283 (100), 282 (82), 281 (78), 251 (20), 237 (30), 223 (28), 208 (29), 154 (20), 141 (18); HREIMS: calc. for $C_{21}H_{28}N_2O_2$: 340.2151, found: 340.2150; ^{1}H NMR: 8.16 (s, 1H, H-1), 7.51 (d, 1H, 7.8, H-9), 7.35 (d, 1H, 7.8, H-12), 7.18 (t, 1H, 7.8, H-11), 7.10 (t, 1H, 7.8, H-10), 3.76 (s, 3H, CH_3OCO), 3.31 (m, 2H, H_2-5), 2.96 (m, 1H, H-6), 2.91 (d, 1H, 8.1, H-21), 2.73 (d,1H, 8.1, H'-21), 2.53 (dd, 1H, 16.2, 4.3, H'-6), 2.40 (d, 1H, 13.5, H-17), 2.06 (d, 1H, 13.5, H'-17), 1.70-1.40 (m, 3H, H-14, H_2-15), 1.28 (m, 1H, H'-14), 1.16 (q, 2H, 7.3, H_2-19), 0.93 (t, 3H, 7.4, H_3-3), 0.70 (t, 3H, 7.3, H_3-18).

Decarboxylation of secoindole 21. A solution of **21** (13 mg, 0.04 mmole) in aqueous HCl (36%, 1 mL) was refluxed for 20 min. After work-up (as for **12a** → **19**), purification by TLC (CH_2Cl_2/MeOH 92:8) provided **25** (6 mg, 53 %): $[\alpha]_D$ +69.6 (MeOH, c 3.8); UV: 291, 283, 273, 225; IR (film): 3405, 3150, 3060; 2955, 2860, 1455; EIMS: 283 (13), 282 (62) [$M^{+\cdot}$], 281 (100), 253 (7), 239 (8), 184 (58), 156 (30), HREIMS: calc. for $C_{19}H_{26}N_2$: 282.2096, found: 282.2103; ^{1}H NMR: 8.05 (s, 1H, H-1), 7.46 (dd, 1H, 7.2, 1.3, H-9), 7.26 (dd, 1H, 7.2, 1.3, H-12), 7.11 (td, 1H, 7.2, 1.3, H-11), 7.06 (td, 1H, 7.2, 1.3, H-10), 4.19 (dd, 1H, 7.2, 5.4, H-16), 3.25 (m, 1H, H-5), 3.05-2.85 (m, 2H, H'-5, H-6), 2.74 (AB, 1H, 9.0, H-21), 2.68 (AB + m, 2H, 9.0, H'-21, H'-6), 2.03 (dd, 1H, 12.6, 7.7, H-17), 1.52 (dd, 1H, 12.6, 5.9, H'-17), 1.55-1.35 (m, 2H, H_2-15), 1.35-1.17 (q + m, 4H, 7.4, H_2-19, H_2-14), 0.94 (t, 3H, 7.2, H_3-3), 0.70 (t, 3H, 7.7, H_3-18); ^{13}C NMR: ^{a}136.0 (C-13), ^{a}135.5 (C-2), 127.4 (C-8), 121.2 (C-11), 119.2 (C-10), 118.0 (C-9), 110.7 (C-12), 107.2 (C-7), 60.9 (C-21), 57.1 (C-16), 46.2 (C-5), 44.5 (C-20), 41.8 (C-17), 40.5 (C-15), 31.3 (C-19), 17.7 (C-6, C-14), 14.8 (C-3), 9.1 (C-18).

Catalytic hydrogenation of indoline 14b. A mixture of **14b** (21 mg, 0.06 mmole), PtO_2 (4.5 mg) and Na_2CO_3 (2 mg) in MeOH (2 mL) was hydrogenated for 22h to yield after purification (TLC, CH_2Cl_2/MeOH 86:14) **21** (7 mg, 33%) and **14a** (4 mg, 19%).

1-cyano-2-ethylpentenes 27a,b. Powdered KOH 85% (1.32 g, 20 mmoles) was added to a solution of 3-hexanone (2 g, 20 mmoles) in anhydrous acetonitrile (28 mL) and the stirred mixture was refluxed for 15h under N_2. The solvent was removed *in vacuo*, the residue was treated with iced water (40 mL) and extracted with Et_2O (90 mL), then purified by column chromatography (hexane → hexane/CH_2Cl_2 1:1) to afford a mixture of **27a** and **27b** (1.59 g, 64%), **27a/27b**: 1.1:1 (measured by ^{1}H NMR): IR (film): 2970, 2940, 2875, 2216, 1625, 1465; EIMS: 123 (100) [$M^{+\cdot}$], 108 (14); EIMS: calc. for $C_8H_{11}N$: 123.1048, found: 123.1054; ^{1}H NMR: 5.03 + 4.99 (2s, 1H, H-1), 2.33 (m, 2H, H_2-3), 2.12 (m, 2H, H_2-1'), 1.45 (m, 2H, H_2-4), 1.02 (m, 3H, H_3-5), 0.77 (m, 3H, H_3-2'); ^{13}C NMR: 170.1 + 169.9 (C-2), 116.6 + 116.4 (CN), 93.6 + 93.5 (C-1), 37.3 + 36.3 (C-3), 28.4 + 27.4 (C-1'), 20.7 + 19.8 (C-4), 13.1 + 13.0 (C-5), 12.0 + 10.9 (C-2').

2-ethyl-2-propylsuccinonitrile 28. KCN (1.59 g, 2 eq) and NH_4Cl (0.98 g, 1.5 eq) were added to a solution of **27a,b** (1.50 g, 12.2 mmoles) in DMF/H_2O 9:1 (50 mL) and the stirred mixture was heated at 120°C (20h) under N_2. The solvent was removed *in vacuo*, and water was added (50 mL). Extraction with CH_2Cl_2 (60 mL) and purification as above provided **28** (1.40 g, 76%): IR (film), 2970, 2940, 2880, 2550, 1435; CIMS (CH_4): 151 (3) [M+H]$^+$; ^{1}H NMR: 2.72 (s, 2H, H_2-3), 1.95-1.60 (m, 4H, H_2-1', H_2-1''), 1.52 (m, 2H, H_2-2''), 1.13 (t, 3H, 7.4, H_3-

3"), 1.03 (t, 3H, 7.4, H_3-2'); ^{13}C NMR: 120.8 (C-1), 115.0 (C-4), 39.8 (C-2), 38.4 (C-3), 29.9 (C-1"), 25.1 (C-1'), 18.1 (C-2"), 13.8 (C-3"), 8.9 (C-2').

Hydrogenation of 28 in the presence of tryptamine. A mixture of **28** (245 mg, 1.63 mmole), tryptamine (314 mg, 1.2 eq) and Pd/C 10% (44 mg, 0.025 eq) in AcOH (6 mL) was hydrogenated over 6 days. The concentrated filtrate was roughly purified by column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH 9:1), then the main fraction was purified by TLC (CH_2Cl_2/MeOH 92:8) providing (±)-**25** (6.5 mg, 1.4%), identical to (+)-**25** except optical rotation, (±)-**31** (6 mg, 1.3%) and (±)-**30** (10 mg, 2.2%). (±)-**31**: UV: 291, 282, 275, 224; IR (film): 3410, 3055, 2940, 2930, 1460; EIMS: 282 (71) [$M^{+\cdot}$], 281 (100) 239 (26), 184 (67), 154 (14); HREIMS: calc. for $C_{19}H_{26}N_2$: 282.2096, found: 282.2120; ^1H NMR: 7.75 (s, 1H, H-1), 7.48 (dd, 1H, 7.2, 1.0, H-9), 7.31 (dd, 1H, 7.2, 1.0, H-12), 7.13 (td, 1H, 7.2, 1.0, H-11), 7.07 (td, 1H, 7.2, 1.0, H-10), 4.18 (dd, 1H, 6.7, 5.4, H-16), 3.27 (m, 1H, H-5), 3.05-2.85 (m, 2H, H'-5, H-6), 2.72 (d, 1H, 13.5, H-21), 2.65-2.55 (d + m, 2H, 13.5, H'-21, H'-6), 2.06 (dd, 1H, 12.6, 8.1, H-17), 1.62 (dd, 1H, 12.6, 6.0, H'-17), 1.54 (m, 2H, H_2-19), 1.30-1.10 (m, 4H, H_2-14, H_2-15), 0.87 (t, 3H, 7.5, H_3-3), 0.79 (t, 3H, 6.8, H_3-18). (±)-**30**: UV: 291, 281, 275, 224; IR (film): 3365, 2960, 2900, 2870, 2795, 1610, 1460; EIMS: 284 (17) [$M^{+\cdot}$], 154 (100), 144 (32), 138 (81), 130 (32), 124 (84); ^1H NMR: 8.06 (bs, 1H, H-1), [a]7.62 (d, 1H, 8.0, H-9), [a]7.35 (d, 1H, 8.0, H-12), 7.18 (t, 1H, 8.0, H-11), 7.11 (t, 1H, 8.0, H-10), 7.03 (d, 1H, 1.8, H-2), 3.02 (m, 2H), 2.84 (m, 2H), 2.76 (t, 2H, 7.4), 1.65 (t, 2H, 7.4), 1.53-1.33 (m, 4H), 1.33-1.15 (m, 4H), 0.92 (t, 3H, 7.2, H_3-3), 0.84 (t, 3H, 7.4, H_3-18).

Methyl 2-allylpentanoate 32. Under Ar atmosphere, BuLi 2.5M (12.0 mL, 30 mmoles) was added to a solution of diisopropylamine (3.95 mL, 30 mmoles) in anhydrous THF (25 ml) at 0°C. The stirred solution was left 20 min at rt, then cooled to -78°C. Methyl pentanoate (3.30 mL, 25 mmoles) was intoduced dropwise; 30 min later, a mixture of allyl bromide (2.6 mL, 30 mmoles) and *N,N'*-dimethylpropyleneurea [DMPU] (0.91 mL, 7.5 mmoles, 0.3 eq) was slowly added and the reaction was left for 3h at -78°C. The mixture was concentrated *in vacuo* at rt, then diluted with iced acidic water (H_2O/HCl 19:1). After extraction (Et_2O, 60 mL), then evaporation of the organic layers (*in vacuo*, rt), purification of the residue by column chromatography (hexane → hexane/CH_2Cl_2 1:1) afforded **32** (3.15 g, 80%): IR (film): 3080, 2960, 2935, 2870, 1740, 1440; ^1H NMR: 5.73 (m, 1H, H_2-3'=2'-H), 5.05 (bdd, 1H, 14.8, 1.4, H_{tr}-3'=2'-H), 5.01 (bd, 1H, 9.0, 1.4, H_{cis}-3'=2'-H), 3.66 (s, 3H, CH_3O-1), 2.45 (m, 1H, H-2), 2.33 (m, 1H, H-1'), 2.22 (m, 1H, H'-1'), 1.60 (m, 1H, H-3), 1.45 (m, 1H, H'-3), 1.30 (m, 2H, H_2-4), 0.89 (t, 3H, 7.2, H_3-5); ^{13}C NMR: 175.9 (C-1), 135.4 (C-2'), 116.4 (C-3'), 51.1 (CH_3O), 45.0 (C-2), 36.4 (C-1'), 33.9 (C-3), 20.4 (C-4), 13.7 (C-5).

Methyl 2-allyl-2-ethylpentanoate 33. A solution of ethyl iodide (2.25 mL, 1.5 eq) and DMPU (1.58 mL, 0.7 eq) was slowly added to a mixture of **32** (2.9 g, 18.6 mmoles) and lithium diisopropylamide (1.3 eq) at -78°C. Purification by column chromatography (eluent as above) yielded **33** (3.42 g, 78%): IR (film): 3075, 2965, 2875, 1730, 1460; ^1H NMR: 5.63 (m, 1H, H_2-3'=2'-H), 5.05 (m, 2H, H_2-3'=2'-H), 3.64 (s, 3H, CH_3O-1), 2.29 (dt, 2H, 7.6, 2.0, H_2-1'), 1.65-1.35 (m, 4H, H_2-3, H_2-4), 1.17 (m, 2H, H_2-1"), 0.85 (t, 3H, 7.4, H_3-5), 0.75 (t, 3H, 7.4, H_3-2"); ^{13}C NMR: 177.1 (C-1), 133.(C-2'), 117.3 (C-3'), 51.3 (CH_3O), 49.5 (C-2), 37.8 (C-3), 36.9 (C-1'), 27.4 (C-1"), 17.2 (C-4), 14.4 (C-5), 8.3 (C-2").

Methyl 2-ethyl-2-formylmethylpentanoate 34. A stirred solution of **33** (0.92 g, 5.0 mmoles), in CH_2Cl_2 (100 mL), cooled at -78°C, was ozonized until the color turned to pale blue. A stream of N_2 was bubbled for 20 min at -40°C, then Ph_3P (1.44 g, 5,5 mmoles) was added. The mixture was left 3h at -40°C, and the temperature slowly raised to 0°C. Evaporation of the solvent then distillation *in vacuo* afforded **34** (0.72 g, 77%): IR(film): 2965, 2880, 1730; CIMS (NH_3): 203 (100) $[M+NH_3]^+$, 187 (59), 186 (58), 171 (30), 157 (28), 143 (50); ^1H

NMR: 9.76 (t, 1H, 2.2, H-2'=O), 3.70 (s, 3H, CH_3O-1), 2.65 (d, 2H, 2.2, H_2-1'), 1.73 (m, 2H, H_2-1"), 1.63 (m, 2H, H_2-3),1.22 (m, 2H, H_2-4), 0.90 (t, 3H, 7.4, H_3-5), 0.85 (t, 3H, 7.4, H_3-2"); ^{13}C NMR: 201.1 (C-2'), 176.1 (C-1), 51.7 (CH_3O), 47.8 (C-2), 47.2 (C-1'), 37.9 (C-3), 28.7 (C-1"), 17.3 (C-4), 14.2 (C-5), 8.3 (C-2").

Reaction of 34 with tryptamine. A solution of **34** (0.67 g, 3.6 mmoles) and tryptamine (0.63 g, 1,2 eq) in AcOH (6 mL) was heated at reflux for 1h under N_2 atmosphere. The mixture was diluted with iced water then basified with ammonia and extracted (CH_2Cl_2: 60 mL). Purification of the residue needed 2 successive TLC separations (hexane/AcOEt 3:1) to yield (±)-**35** (0.420 g, 42%) and (±)-**36** (0.485 g, 47.5%). (±)-**35**: UV: 327, 312, 290, 282, 273, 222; IR (film): 3300-3200, 2960, 2925, 2870, 1665; EIMS: 297 (23) $[M+H]^+$, 296 (100) $[M^{+\cdot}]$, 295 (63), 267 (7), 253 (6), 239 (8), 169 (18), 156(9), 143 (16); HREIMS: calc. for $C_{19}H_{24}N_2O$: 296.1888, found: 296.1886; ^1H NMR: 8.28 (s, 1H, H-1), 7.48 (d, 1H, 7.6, H-9), 7.35 (d, 1H, 7.6, H-12), 7.18 (t, 1H, 7.6, H-11), 7.12 (t, 3H, 7.6, H-10), 4.86 (bt, 1H, 7.7, H-16), 4.55 (m, 1H, H-5), 3.05 (dt, 1H, 12.0, 8.0, H'-5), 2.82 (m, 2H, H_2-6), 2.36 (dd, 1H, 12.6, 7.9, H-17), 1.93 (dd, 1H, 12.6, 7.9, H'-17), 1.64-1.48 (m, 4H, H_2-15, H_2-19), 1.48-1.28 (m, 2H, H_2-14), 0.94 (t, 3H, 7.2, H_3-3), 0.72 (t, 3H, 7.4, H_3-18); ^{13}C NMR: 176.8 (C-21), 136.3 (C-13), 133.8 (C-2), 126.9 (C-8), 122.0 (C-11), 119.7 (C-10), 118 3 (C-9), 111.0 (C-12), 108.0 (C-7), 51.6 (C-16), 49.7 (C-20), 39.5 (C-5), 37.8 (C-17), 35.0 (C-15), 29.5 (C-19), 21.2 (C-6), 17.9 (C-14), 14.6 (C-3), 8.4 (C-18). (±)-**36**: UV: 327, 312, 291, 282, 273, 222; IR (film): 3330-3200, 2960, 2930, 2870, 1665; EIMS: 297 (32) $[M+H]^+$, 296 (100) $[M^{+\cdot}]$, 295 (77), 265 (17), 251 (20), 239 (14), 169 (36), 143 (33); HREIMS: calc. for $C_{19}H_{24}N_2O$: 296.1888, found: 296.1894 ; ^1H NMR: 8.16 (s, 1H, H-1), 7.50 (d, 1H, 7.6, H-9), 7.34 (d, 1H, 7.6, H-12), 7.19 (t, 1H, 7.6, H-11), 7.12 (t, 1H, 7.6, H-10), 4.84 (bt, 1H, 7.9, H-16), 4.54 (m, 1H, H-5), 3.03 (m, 1H, H'-5), 2.81 (m, 2H, H_2-6), 2.37 (dd, 1H, 12.5, 7.7, H-17), 1.82 (dd, 1H, 12.5, 7.7, H'-17), 1.64 (m, 2H, H_2-19), 1.44 (m, 2H, H_2-15), 1.13 (m, 2H, H_2-14), 0.97 (t, 3H, 7.4, H_3-3), 0.80 (t, 3H, 7.4, H_3-18); ^{13}C NMR: 176.9 (C-21), 136.3 (C-13), 133.8 (C-2), 126.8 (C-8), 121.9 (C-11), 119.6 (C-10), 118.2 (C-9), 111.0 (C-12), 107.7 (C-7), 51.7 (C-16), 49.7 (C-20), 39.4 (C-5), 37.7 (C-17), 35.0 (C-15), 29.4 (C-19), 21.2 (C-6), 17.8 (C-14), 14.4 (C-3), 8.3 (C-18).

Reduction of (±)-35 with $LiAlH_4$. A solution of (±)-**35** (84 mg, 0.28 mmole) in anhydrous THF (2 mL) was added to a filtered solution of $LiAlH_4$ (0.5 g) in THF (20 mL). The mixture was stirred for 21h at rt then treated as for **12a** → **17**. Purification of the residue by TLC (CH_2Cl_2/MeOH 94:6) yielded starting material (±)-**35** (13 mg, 16%) and (±)-**25** (56 mg, 70%).

Reduction of (±)-36 with $LiAlH_4$. The same procedure applied to (±)-**36** (51 mg, 0.17 mmole) for 26h afforded (±)-**36** (3 mg, 6%) and (±)-**31** (38 mg, 77%); mp : 234-236°C (MeOH); UV, IR, MS and ^1H NMR are identical with those of (±)-**31**; ^{13}C NMR: 136.0 (C-13), 135.4 (C-2), 127.3 (C-8), 121.3 (C-11), 119.3 (C-10), 118.0 (C-9), 110.8 (C-12), 107.2 (C-7), 60.8 (C-21), 57.0 (C-16), 46.4 (C-5), 44.5 (C-20), 41.9 (C-17), 40.7 (C-15), 30.4 (C-19), ^{a}18.0 (C-6), ^{a}17.9 (C-14), 14.7 (C-3), 8.9 (C-18).

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