Enantioselective Total Syntheses of the *Ipecacuanha* Alkaloid Emetine, the *Alangium* Alkaloid Tubulosine and a Novel Benzoquinolizidine Alkaloid by Using a Domino Process

Lutz F. Tietze,*[a] Nils Rackelmann,[a] and I. Müller[b]

Dedicated to Prof. Johann Mulzer on the occasion of his 60th birthday

Abstract: The first enantioselective syntheses of the *Ipecacuanha* alkaloid emetine (**1**) and the *Alangium* alkaloid tubulosine (**2**) is described employing a domino Knoevenagel/hetero-Diels–Alder reaction and an enantioselective catalytic transfer hydrogenation of imines as key steps. Thus, hydrogenation of the imine **15** with the catalyst (*R*,*R*)-**16** gives the tetrahydroisoquinoline **14** with 95% *ee* which was transformed into the aldehyde (1*S*)-**7**. The three-component domino reaction of (1*S*)-**7** with **6** and **8** led to **19**, which in a second domino process was treated with K_2CO_3 in methanol followed by a hydrogenation to give the benzoquinolizidine **4** together with the diastereomers **22** and **23** in a overall yield of 66%. Further transformation of **4** with the amines **3** and **5** yielded enantiopure emetine (**1**) and tubulosine (**2**), respectively. In addition, starting from **19** the novel benzoquinolizidine alkaloid **34** was synthesised; this compound resembles the vallesiachotamine alkaloid dihydroantirhin **31**, which has not been isolated so far but probably must also exist in nature.

Keywords: alkaloids · asymmetric catalysis · domino reactions · hydrogenation · imines · natural products

Introduction

The *Ipecacuanha* alkaloid emetine (**1**) and the *Alangium* alkaloid tubulosine (**2**) belong to the group of tetrahydroisoquinoline alkaloids that are formed in nature from dopamine and the monoterpene secologanin. Emetine (**1**) was isolated from *Radix Ipecacuanha* and the roots of *Psychotria Ipecacuanha* and *Cephalis acuminata*[1] and possesses multifold interesting biological activity. It shows antiprotozoic properties[2] and activity in the treatment of lymphatic leukaemia;[3] furthermore, it used to be applied as an emetic. Nowadays, emetine (**1**) is not used as a drug anymore due to its considerable toxicity. Tubulosine (**2**) was isolated from the dried fruits of *Alangium lamarckii*[4] and the sap of *Pogonopus speciosus*.[5] It is remarkably active against several cancer cell lines[5,6] and has been studied for various other biological activities, such as inhibition of protein biosynthesis[7] and HIV reverse transcriptase inhibitory activities.[8]

Here we describe the first enantioselective total syntheses of **1**[9] and **2**[9e,10] by means of a three-component domino process[11] that combines a Knoevenagel reaction and a cycloaddition followed by a solvolysis, a condensation and a hydrogenation.[12] The stereogenic centres C-11b and C-1′ in **1** and **2** were introduced by an enantioselective transfer hydrogenation of the corresponding imines by using a chiral ruthenium catalyst. This type of catalyst-controlled hydrogenation has recently been used by us for a stereochemical combinatoric as a new approach in combinatorial chemistry.[13]

Results

The retrosynthesis of **1** and **2** leads to the amines **3** and **5**, respectively and the benzoquinolizidine **4**, which can be obtained starting from the isoquinolineacetaldehyde (1*S*)-**7**, Meldrum's acid **6** and the enol ether **8** (Scheme 1). An important aspect of modern syntheses is the formation of enantiopure products, whereby the first stereogenic centre should be introduced by a catalytic process. This was achieved upon the synthesis of (1*S*)-**7**. For this purpose racemic

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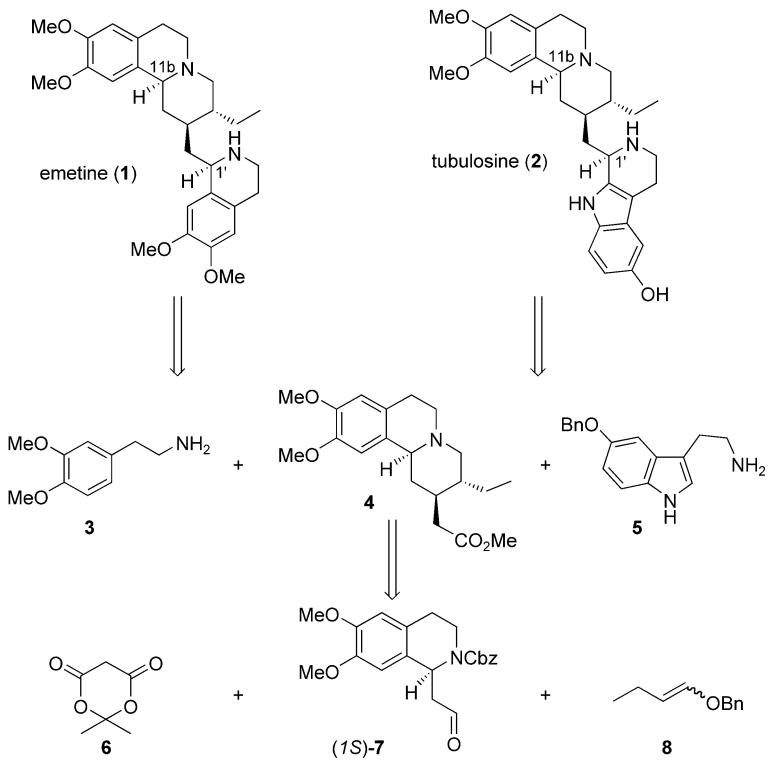
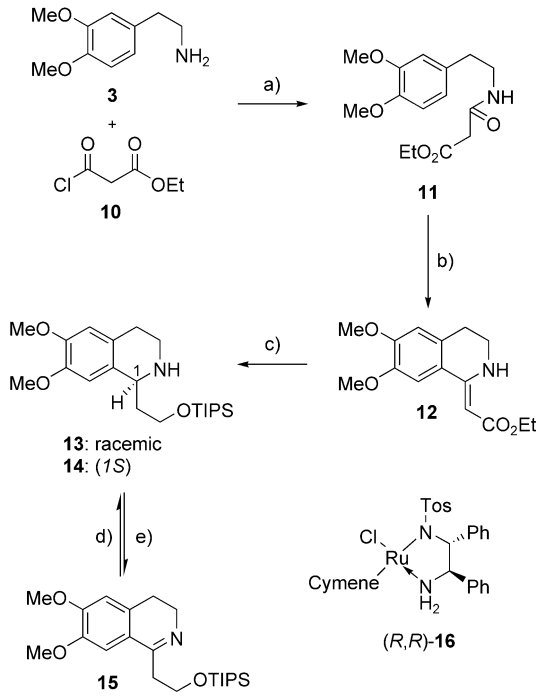


Scheme 1. Retrosyntheses of emetine (**1**) and tubulosine (**2**).

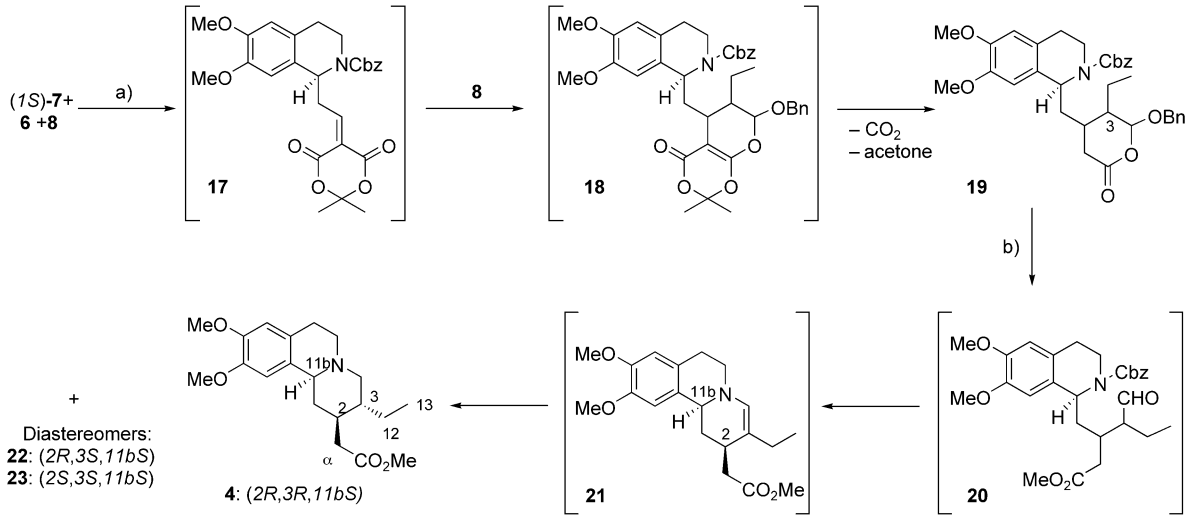
tetrahydroisoquinoline **13** was prepared; this compound is easily accessible by a Bischler–Napieralski reaction of **11**, which in turn was obtained from **3** and **10**. Consecutive reduction of the formed vinylogous urethane **12** and TIPS protection gave **13** (Scheme 2). Compound **13** was then oxidised with $KMnO_4$ at −7 °C[14] to give the imine **15** with an overall yield of 55 % (6 steps from the starting materials **3** and **10**). Transfer hydrogenation with triethylammonium formate in the presence of the chiral Ru catalyst (*R*,*R*)-**16** developed by Noyori[15] provided the tetrahydroisoquinoline (1*S*)-**14** in a yield of 93 % and 95 % *ee*.

Protection of the secondary amino moiety with CbzCl, deprotection of the TIPS group and oxidation of the formed primary hydroxy group led to the aldehyde (1*S*)-**7** (56 % yield from (1*S*-**14**)). The domino reaction of (1*S*)-**7**, Meldrum's acid **6** and enol ether **8** was performed in the presence of a catalytic amount of ethylene diammonium diacetate (Scheme 3). At first the 1-oxa-1,3-butadiene **17** is formed, which gives **18** in a hetero-Diels–Alder reaction with inverse electron demand; under the reaction conditions **18** looses CO_2 and acetone to yield **19** as the final product. Due to the electron-withdrawing carbonyl group at the oxabutadiene moiety in **17**, resulting in a lowering of its LUMO energy, the cycloaddition with the enol ether **8** takes place around 60 °C or below. Compound **19** is usually not isolated, but treated with K_2CO_3/MeOH and a catalytic amount of Pd/C in methanol. After stirring for 50 min, a hydrogen atmosphere is applied and the mixture stirred for another two hours at room temperature to give the benzoquinolizidine **4**, with the correct stereochemistry at all stereogenic centres as in emetine (**1**), together with the two diastereomers **22** and **23** in a ratio of (1.5:1.0:1.8) (**22**:**4**:**23**) and an overall yield of 66 % based on (1*S*)-**7**.

The diastereomers can easily be separated by column chromatography and the relative configuration of the diastereomers **4** and **22** was identified by crystal structure analysis.[16–18] For the transformation we propose the following sequence: In the first step the lactone moiety in **19** is attacked by methoxide to give a methyl ester and a hemiacetal, which looses benzylalcohol providing the corresponding aldehyde **20**. Hydrogenolytic removal of the Cbz protecting group leads to the corresponding secondary amine, which reacts with the aldehyde to afford either an iminium ion or an enamine **21**; both moieties are hydrogenated under the reaction conditions. The formation of the three diastereomers in the process is, on the one hand, probably due to the flexibility of the oxabutadiene moiety in **17**, which can exist in the two different conformations **17a** and **17b**



Scheme 2. Enantioselective synthesis of the tetrahydroisoquinoline (1*S*)-**14**: a) K_2CO_3, Et_2O/H_2O, 1.5 h, 91 %; b) P_4O_{10}, toluene, 110 °C, 70 min, 83 %; c) 1. H_2 (4 bar), Pd/C, EtOH/HOAc, 80 min, 93 %; 2. $LiAlH_4$, THF, RT, 4 h, 92 %; 3. TIPSCl, imidazole, DMAP, DMF, RT, 18 h, 94 %; d) 2.5 mol % (*R*,*R*)-**16**, HCO_2H/NEt_3, DMF, RT, 120 min, 93 %, 95 % *ee*; e) $KMnO_4$, CH_3CN, −7 °C, 70 min, 90 %.

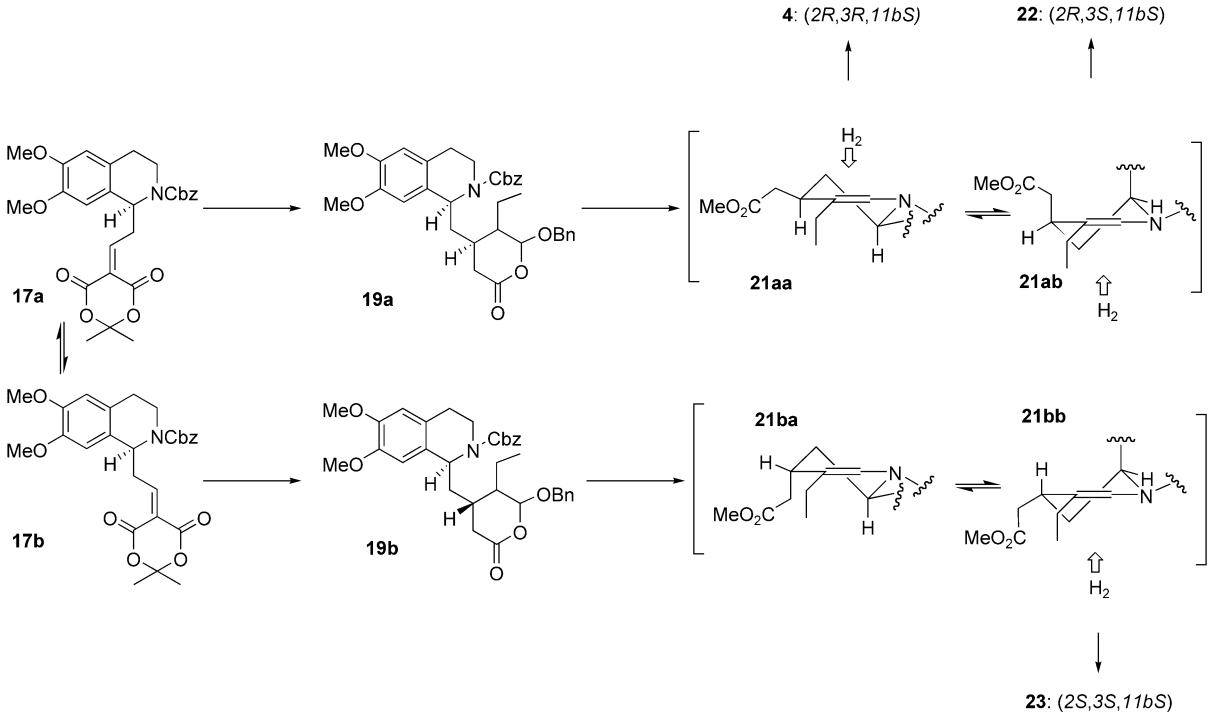


Scheme 3. Domino process and synthesis of the benzoquinolizidine **4**: a) [EDDA], benzene, 60 °C, ultra sonic, 17 h, 86 %; b) 1. 0.5 equiv K_2CO_3, MeOH; 2. Pd/C, H_2, 77 %.

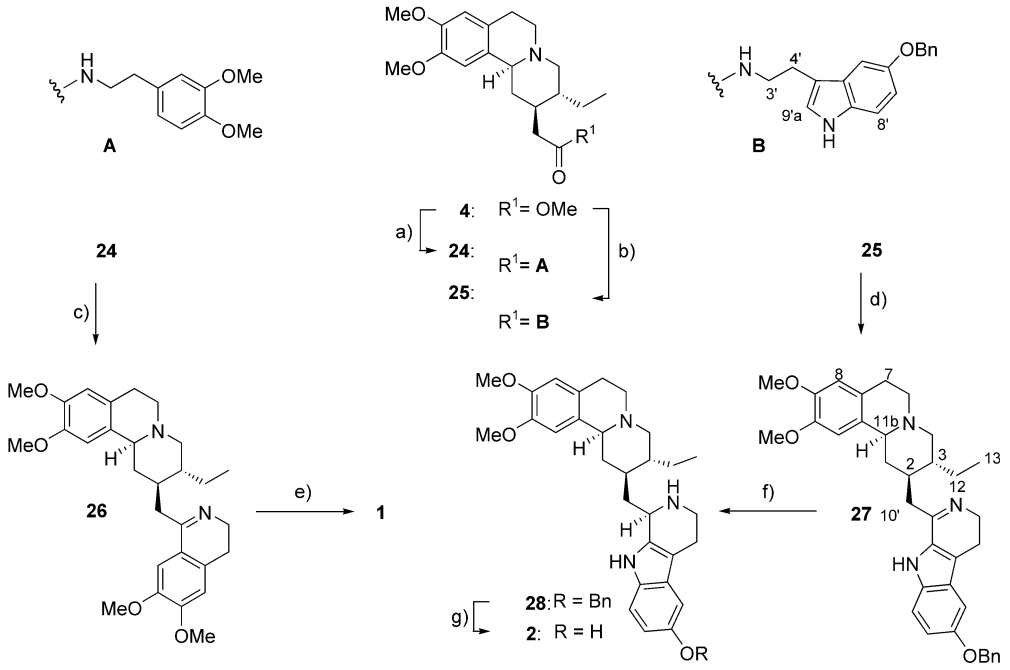
(Scheme 4). Since we assume that the attack of the enol ether takes place in both forms from below, as the less hindered site, two diastereomers **19a** and **19b** with the opposite configuration at C-4 would be formed. In addition, the hydrogenation of the intermediate enamine **21a** and **21b** seems to be selective only in the case of **21b** to give **23**; thus, the hydrogenation takes place preferably via the conformation **21bb** under stereoelectronic control. For the diastereomer **21a** the two conformations **21aa** and **21ab** seem to be equally involved in the transition structure, which is astounding. However, one can not exclude, that here the formation of the enamine **21a** is slow compared to the hydrogenation of the corresponding primarily formed iminium ion. Since the stereogenic centre C-3 in **19** is not formed selectively in the Diels–Alder reaction a mixture would result. That iminium ions can be intermediates in such a hydrogenation process has been shown by us in the synthesis of indole alkaloids using a similar process.[12a,c]

For the synthesis of emetine (**1**), the benzoquinolizidine **4** was treated with the phenylethylamine **3** and trimethylaluminium to give the amide **24**,[19] which could then directly be transformed into the desired imine **26** by using $POCl_3$ (Scheme 5). The final step towards emetine (**1**) was the transfer hydrogenation with (*S*,*S*)-**16**; this allowed the introduction of the fourth stereogenic centre with a *ds* > 98:1.[20]

In a similar approach, the alkaloid tubulosine (**2**) was synthesised by reaction of the benzoquinolizidine **4** with *O*-benzylseretonine **5**. However, using trimethylaluminum as in



Scheme 4. Diels–Alder and biomimetic solvolysis, condensation and hydrogenation sequence.



Scheme 5. Syntheses of emetine (**1**) and tubulosine (**2**): a) 1. **3**, $AlMe_3$, 1.0 h; 2. **4**, 4.5 h, reflux, 78%; b) **4** and **5**, 2-hydroxypyridine, 170°C, 3.25 h, 73%; c) $POCl_3$, benzene, reflux, 45 min, 82%; d) $POCl_3$, benzene, reflux, 85 min, 49%; e) 10 mol% (S,S)-**16**, HCO_2H/NEt_3, DMF, RT, 71%, >95% *ee*; f) 10 mol% (S,S)-**16**, HCO_2H/NEt_3, DMF, RT, 73%, >95% *ee*; g) Pd/C, H_2, MeOH, RT, 95 min, 67%.

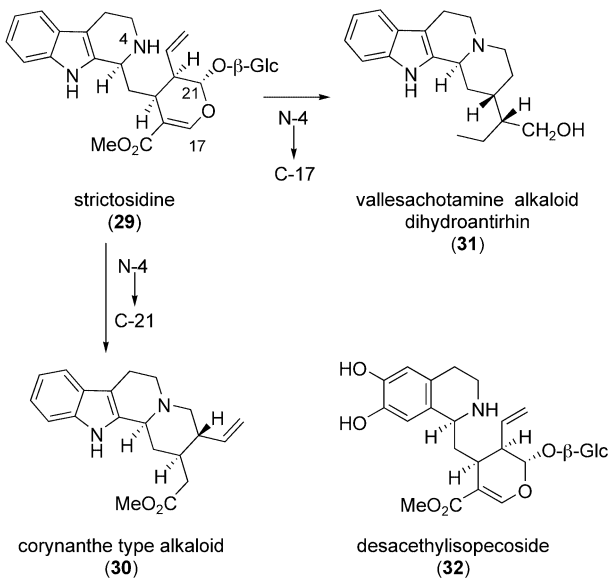
the reaction of **3** and **4** only low yields were obtained. Fortunately, reaction of **4** with **5** in the presence of 2-hydroxypyridine allowed the synthesis of the amide **25** in 73% yield. The formation of the imine **27** from **25** by using $POCl_3$ gave a lower yield as in the case of **24**; however, this is quite understandable since the Bischler–Napieralski reaction conditions are quite harsh and less suitable for the indole moiety. A Pictet–Spengler reaction would also have been possible,[21] but in this reaction the configuration of the newly formed stereogenic centre cannot be controlled and a selective oxidation to give the desired imine **27** seemed less likely. In contrast, the hydrogenation of the imine again using the catalyst (*S*,*S*)-**16** in the presence of triethylammonium formate gave the tetrahydro-β-carboline **28** in a high yield of 78% and excellent selectivity, with a *ds* of >98:1. Cleavage of the benzyl ether by hydrogenolysis with Pd/C as a catalyst provided tubulosine (**2**) in high purity.

Whereas the published spectroscopic data for emetine (**1**) and those of the synthesised product are in complete agreement, it should be mentioned that the NMR data of our synthesised tubulosine (**2**) did not match with published spectroscopical data.[22] We therefore compared our data with those obtained from natural tubulosine (**2**).[23] Here the ^1H and ^{13}C NMR data and the rotation value were in complete agreement.

The described domino Knoevenagel/hetero-Diels–Alder process did not only allow the enantioselective syntheses of emetine (**1**) and tubulosine (**2**) as well as related compounds, but it also gives access to so far unknown benzoquinolizidine alkaloids as **34**.

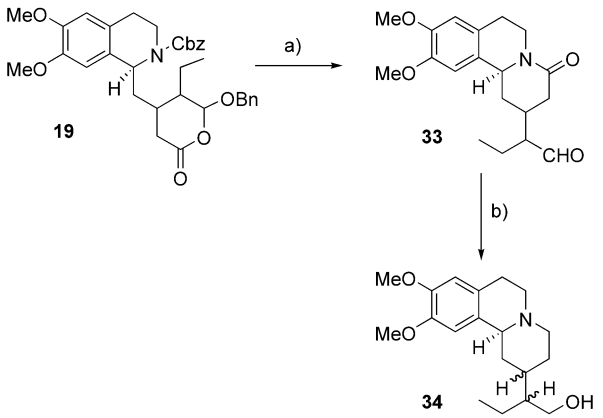
In the series of the biosynthetic early indole alkaloids, we can differentiate between corynanthe **30** and the vallesiachotamine alkaloids, for example, dihydroantirhin **31**. The former is formed from strictosidine **29** by a N-4→C-21 condensation, whereas the latter is obtained by a N-4→C-17 condensation after enzymatic cleavage of the glucosidic bond (Scheme 6).[24] A similar process could be envisaged for the transformation of desacetylisopecoside **32**, which is the natural precursor of emetine **1**. However, the corresponding alkaloids have so far not been found in nature.

In contrast, they are easily accessible synthetically from the same intermediate **19** used in the preparation of emetine (**1**). Reaction of the cycloadduct **19** under a hydrogen atmosphere in methanol in the presence of a catalytic amount



Scheme 6. Biosyntheses of indole alkaloids.

of Pd/C led to the lactam **33** in 81% yield (Scheme 7). In this transformation, first the Cbz-protecting group is removed by hydrogenolysis to give the corresponding secondary amine, which then attacks the lactone moiety in an intramolecular fashion to yield a lactam and a hemiacetal; finally the hemiacetal looses benzyl alcohol affording **33**. Reduction of **33** with $LiAlH_4$ in THF yields the alkaloid **34** as a mixture of diastereomers with 95% *ee*; **34** resembles the vallesiachotamine alkaloid dihydroantirhin **31**.



Scheme 7. Synthesis of a new benzoquinolizidine alkaloid **34**: a) H_2, Pd/C, MeOH, 4.5 h, RT, 81%; b) $LiAlH_4$, THF, 4.5 h, RT, 99%.

Conclusion

The three-component domino Knoevenagel/hetero-Diels–Alder reaction of the enantiopure aldehyde (1*S*)-**7**, Meldrum's acid **6** and the enol ether **8**, followed by another domino process consisting of solvolysis, hydrogenolysis, condensation and hydrogenation, allows a very short enantioselective entry to the *Ipecacuanha* alkaloid emetine (**1**) and the *Alangium* alkaloid tubulosine (**2**). In addition, so far unknown benzoquinolizidine alkaloids, which resemble the vallesiachotamine alkaloid dihydroantirhin and which probably also exist in nature, can be obtained using this approach. The described procedure underlines the potency of domino processes and clearly also allows the preparation of analogues that might have better pharmacological properties.

Experimental Section

Ethyl ester amide of *N*-[2-(3,4-dimethoxyphenyl)ethyl]malonic acid (11):[25] A solution of malonic acid ethyl ester chloride **10** (40 g, 0.27 mol) in diethyl ether (200 cm^3) was added dropwise to a well-stirred two-layer system of homoveratryl amine **3** (40.1 g, 0.22 mol) in diethyl ether (240 cm^3) and potassium carbonate (36.7 g, 0.27 mol) in water (367 cm^3) at 0 °C; the mixture was stirred for a further 1.5 h at this temperature. The layers were separated and the aqueous layer was extracted with dichloromethane (3×300 cm^3). The combined extracts were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure to give the amide (59.5 g, 91%) as a yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.27$ (t, ^3J(H,H) = 7.0 Hz, 3H; CH_3), 2.79 (t, ^3J(H,H) = 7.0 Hz, 2H; $ArCH_2CH_2$) 3.28 (s, 2H; $O_2CCH_2CO_2$), 3.53 (q, ^3J(H,H) = 6.5 Hz, 2H; CH_2CH_2NH), 3.86 (s, 3H; OMe), 3.88 (s, 3H; OMe), 4.14 (q, ^3J(H,H) = 7.0 Hz, 2H; OCH_2CH_3), 6.73–6.84 (m, 3H; Ar-H), 7.17 ppm (br s, 1H; NH).

Ethyl ester of (6,7-dimethoxy-3,4-dihydro-2*H*-isoquinoline-1-ylidene)acetic acid (12: Bischler–Napieralski reaction):[25] Phosphorus pentoxide (180 g, 1.43 mol) was added over a period of 30 min in portions of 60 g to a heavily stirred solution (mechanical stirrer) of the amide **11** (30 g, 0.10 mol) in toluene (600 cm^3) at 110 °C. Overall the suspension was stirred for 70 min under reflux and afterwards the reaction mixture was cooled down to 0 °C. Ice water (1000 cm^3) was added, the layers were separated and the organic layer extracted with 2 N HCl solution (1×200 cm^3). The combined aqueous layers were neutralised with potassium carbonate and extracted with diethyl ether (5×300 cm^3). The organic phase was dried over sodium sulphate, filtered and the solvents was evaporated under reduced pressure. The crude product was purified by column chromatography on silica using ethyl acetate as eluent to give the ethyl ester as a yellow solid (23.1 g, 83%) ^{1}H NMR (200 MHz, C_6D_6, 25 °C, TMS): $\delta=$ 1.19 (t, ^3J(H,H) = 7.0 Hz, 3H; CH_3), 2.22 (t, 2H; ^3J(H,H) = 6.0 Hz, $ArCH_2$-CH_2), 2.76 (dt, ^3J(H,H) = 6.0, 3.0 Hz, 2H; CH_2CH_2NH), 3.21 (s, 3H; OMe), 3.27 (s, 3H; OMe), 4.30 (q, ^3J(H,H) = 7.0 Hz, 2H; OCH_2CH_3), 5.56 (s, 1H; $R_2C{=}CHR$), 6.14 (s, 1H; Ar-H), 7.07 (s, 1H; Ar-H), 9.12 ppm (br s, 1H; NH).

Ethyl ester of (6,7-dimethoxy-3,4-dihydro-2*H*-isoquinoline-1-yl)acetic acid:[25] A suspension of **12** (13.5 g, 49.0 mmol) and palladium on charcoal (1.5 g, 10%) in ethanol (80 cm^3) and acetic acid (60 cm^3) was shaken under a hydrogen atmosphere (4.1 bar) for 80 min. The reaction mixture was filtered and the ethanol was removed under reduced pressure. The residue was diluted with water (150 cm^3), neutralised with potassium carbonat and extracted with diethyl ether (3×200 cm^3). The solution was dried over sodium sulfate and filtered and the solvent was removed under reduced pressure to give the title compound as a yellow solid (12.7 g, 93%) ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.19$ (t, ^3J(H,H) = 7.0 Hz, 3H; CH_3), 2.36 (s, 1H; NH), 2.75 (dd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 6.0 Hz, 2H; $CHCH_2CO_2Et$), 2.69–2.90 (m, 2H; $ArCH_2CH_2$), 3.01 (dddd, ^3J(H,H) = 6.0, 6.0, 6.0, 6.0 Hz, 2H; CH_2CH_2NH), 3.84 (s, 3H; OMe), 3.85 (s, 3H; OMe), 4.18 (q, ^3J(H,H) = 7.0 Hz, 2H; OCH_2CH_3), 4.40 (dd, ^3J(H,H) = 9.0, 4.5 Hz, 1H; $ArCHRNH$), 6.58 ppm (s, 2H; Ar-H).

***rac*-*O*-Triisopropylsilyl-2-(6,7-dimethoxy-3,4-dihydro-2*H*-isoquinoline-1-yl)ethanol (13)**:

2-(6,7-Dimethoxy-3,4-dihydro-2H-isoquinoline-1-yl)-ethanol: A solution of the ester (11.0 g, 39.4 mmol) in tetrahydrofuran (100 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (3.36 g, 88.6 mmmol) in tetrahydrofuran (400 cm^3) at 0 °C. The reaction mixture was stirred for 4 h at 25 °C and quenched with water (3.4 cm^3), followed by 10 min of stirring, addition of an aqueous sodium hydroxide solution (3.4 cm^3, 15%), 10 min of stirring and again addition of water (10.2 cm^3). The formed precipitate was removed by filtration and washed with tetrahydrofuran (400 cm^3). The alcohol was obtained as a yellow solid after removal of the solvent under reduced pressure (8.61 g, 92%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): $\delta=1.89$ (m, 1H; CH_2CH_2OH), 2.06 (m, 1H; CH_2CH_2OH), 2.74 (m, 2H; $ArCH_2CH_2$), 3.02 (ddd, ^2J(H,H) = 13.0 Hz, ^3J(H,H) = 5.5, 5.5 Hz, 1H; $ArCH_2CH_2$), 3.21 (ddd, ^2J(H,H) = 13.0 Hz, ^3J(H,H) = 8.5, 8.5 Hz, 1H; $ArCH_2CH_2$), 3.83 (s, 3H; OMe), 3.85 (s, 3H; OMe), 3.80–3.98 (m, 2H; CH_2CH_2OH), 4.19 (dd, ^3J(H,H) = 9.5, 4.0 Hz, 1H; 1-H), 6.53 (s, 1H; Ar-H), 6.57 ppm (s, 1H; Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta=$ 28.64 (C-4), 35.99 (C-2′), 39.36 (C-3), 55.66 (OMe), 55.80 (OMe), 56.30 (C-1), 62.48 (C-1′), 109.0 (C-5), 111.7 (C-8), 126.8 (C-8a), 129.2 (C-4a), 147.2 (C-7), 147.4 ppm (C-6); UV/Vis (acetonitrile): λ_{max} ($\lg\varepsilon$) = 202.0 (4.576), 283.0 (3.549), 286.0 nm (3.551); IR (KBr): $\tilde{\nu}=$ 3250 (NH), 2957 (C-H), 2863 (OMe), 1464 (CH_2) 1359 (CH_3), 858 cm^{-1} (arom-H); MS (70eV, EI): *m*/*z* (%): 237.1365 (5) [M^+] ($C_{13}H_{19}NO_3$ requires 237.1365), 192.1 (100) [$M^+-CH_2CH_2OH$].

*Compound **13***: Triiso-propylsilylchloride (19.5 g, 101 mmol) was added dropwise to a stirred solution of the unprotected alcohol (20.0 g, 84.3 mmol), imidzole (6.89 g, 101 mmol) and a catalytic amount of 4-dimethylaminopyridine in dimethylformamide (150 cm^3) and stirred for 18 h at 25 °C. The reaction was quenched with saturated aqueous sodium hydrogen carbonate solution (400 cm^3) and water (400 cm^3). The aqueous layer was extracted with diethyl ether (4×300 cm^3), the combined organic layers were dried over sodium sulphate and filtered, and the solvent was

removed under reduced pressure to provide the crude product, which was purified by column chromatography on silica using ethyl acetate/methanol (4:1) as eluent to give **13** as an orange oil (31.2 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 1.00–1.14 (m, 21H; 3× *i*Pr's), 1.88–2.08 (m, 2H; CH_2CH$_2$O), 2.58 (brs, 1H; NH), 2.68 (t, ^3J(H,H) = 6.0 Hz, 1H; 3-H) 2.97 (dt, ^3J(H,H) = 13.0, 6.0 Hz, 1H; 4-H), 3.16 (dt, ^3J(H,H) = 13.0, 6.0 Hz, 1H; 4-H), 3.82 (s, 3H; OMe), 3.84 (s, 3H; OMe), 3.81–3.94 (m, 2H; CH$_2$CH_2O), 4.13 (dd, ^3J(H,H) = 9.0, 4.0 Hz, 1H; 1-H), 6.52 (s, 1H; Ar-H), 6.58 ppm (s, 1H; Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 11.88 (*i*Pr-CH$_3$), 18.00 (*i*Pr-CH), 29.21 (C-4), 38.75 (C-2′), 40.43 (C-3), 53.39 (C-1), 55.87 (OMe), 55.90 (OMe), 61.40 (C-1′), 109.2 (C-5), 111.8 (C-8), 127.1 (C-8a), 131.1 (C-4a), 147.1 (C-7), 147.2 ppm (C-6); UV/Vis (acetonitrile): λ_{max} (lg ε) = 201.5 (4.606), 283.5 (3.589), 286.5 nm (3.590); IR (film): $\tilde{\nu}$ = 3334 (NH), 2941 (C-H), 2865 (OMe), 1699, (C=O), 1463 (CH$_2$) 1380 (CH$_3$), 855 cm^{-1} (arom-H); MS (70 eV, EI): *m*/*z* (%): 393.2699 (15) [M^+] ($C_{22}H_{39}NO_3Si$ requires 393.2699), 350 (4) [$M^+-C_3H_7$], 218 (3) [M^+-OSi(C$_3$H$_7$)$_3$], 192 (100) [$C_{11}H_{14}NO_2^+$].

***O*-Triisopropylsilyl-2-(6,7-dimethoxy-3,4-dihydro-isoquinoline-1-yl)ethanol (15)**: Potassium permanganate (23.3 g, 147 mmol) was added in small portions over a period of 15 min to a stirred solution of **13** (27.6 g, 70.2 mmol) in acetonitrile (650 cm^3) at −7°C. The suspension was stirred further for 70 min at −5°C and afterwards diluted with ice cooled diethyl ether (2.5 dm^3). The organic layer was extracted with equal amounts of a saturated aqueous sodium chloride solution until the violet colour of potassium permanganate had disappeared from the organic layer. The solution was dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure. The pale yellow oil **15** (24.7 g, 90%) was used for the next reaction without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 0.90–1.12 (m, 21H; 3×*i*Pr's), 2.56 (t, ^3J(H,H) = 7.5 Hz, 2H; CH_2CH$_2$O), 2.93 (t, ^3J(H,H) = 7.0 Hz, 2H; 3-H), 3.57 (t, ^3J(H,H) = 7.0 Hz, 2H; 4-H), 3.86 (s, 3H; OMe), 3.88 (s, 3H; OMe), 4.03 (t, ^3J(H,H) = 7.5 Hz, 2H; CH$_2$CH_2O), 6.64 (s, 1H; Ar-H), 7.04 ppm (s, 1H; Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 11.91 (*i*Pr-CH$_3$), 17.96 (*i*Pr-CH), 25.77 (C-4), 38.98 (C-2′), 46.88 (C-3), 55.92 (OMe), 56.12 (OMe), 62.08 (C-1′), 108.9 (C-5), 110.1 (C-8), 122.4 (C-8a), 131.2 (C-4a), 147.4 (C-7), 150.6 (C-6), 165.0 ppm (C-1); UV/Vis (acetonitrile): λ_{max} (lg ε) = 224.0 (4.346), 270.0 (3.827), 302.5 nm (3.747); IR (film): $\tilde{\nu}_{max}$ = 2940 (C-H), 2865 (OMe), 1605 (C=N), 1463 (CH$_2$), 1357 (CH$_3$), 859 cm^{-1} (arom-H); MS (70 eV, EI): *m*/*z* (%): 391 (36) [M^+], 348 (100) [$M^+-C_3H_7$], 306 (7) [$M^+-(C_3H_7)_2$], 262 (9) [$M^+-(C_3H_7)_3$], 216 (3) [M^+-OSi(C$_3$H$_7$)$_3$].

1-(S)-*O*-Triisopropylsilyl-2-(6,7-dimethoxy-3,4-dihydro-2*H*-isoquinoline-1-yl)ethanol ((1*S*)-14): A solution of dichloro(*p*-cymene)ruthenium(II) dimer (403 mg, 0.66 mmol), 1,2-(*R*,*R*)-*N*-tosyl-1,2-diphenylethyldiamine (530 mg, 1.45 mmol) and triethylamine (0.366 cm^3, 2.63 mmol) in dimethylformamide (6.10 cm^3) was stirred in a closed flask under a argon atmosphere at 80°C for 60 min. This warm solution was added to a solution of **15** (21.5 g, 55.0 mmol) in dimethylformamide (103 cm^3), cooled down to 0°C and a mixture of formic acid/triethylamine (5:2, 27.5 cm^3) was added dropwise. The solution was allowed to reach 25°C and after 2 h of stirring the reaction was diluted with ethyl acetate and quenched with saturated aqueous potassium carbonate solution and water. The aqueous layer was extracted with ethyl acetate (4×200 cm^3), the combined organic layers were dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate/triethylamine (100:1) as a eluent to give (1*S*)-**14** as a slightly brown oil (20.2 g, 93%, 95% *ee*). $[\alpha]_D^{20}$ = −12.9 (*c* = 0.58 in $CHCl_3$) HPLC; the spectroscopic data (except optical rotation) are in agreement with those of compound **13**.

1-(S)-*N*-Carbobenzyloxy-(6,7-dimethoxy-3,4-dihydro-2*H*-isoquinoline-1-yl)-ethanal ((1*S*)-7):

1-(S)-N-Carbobenzyloxy-O-Triisopropylsilyl-2-(6,7-dimethoxy-3,4-dihydro-2H-isoquinoline-1-yl)ethanol: Carbobenzyloxychloride (9.45 g, 55.4 mmol) was added dropwise to a well-stirred two-layer system of (1*S*)-**14** (19.8 g, 50.3 mmol) in dichloromethane (213 cm^3) and saturated aqueous sodium hydrogen carbonate solution (213 cm^3), and the reaction mixture was stirred for 3.5 h under reflux. The layers were separated and the aqueous layer was extracted with dichloromethane (3×200 cm^3). The combined organic layers were dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure to give the crude Cbz-protected amine which was used for the next reaction without purification.

Tetrabutyl ammonium fluoride (30 g, 95.1 mmol) was added in small portion over a period of 10 min to a solution of the crude material (26.8 g, 50.8 mmol) in tetrahydrofuran (400 cm^3). Overall the reaction was stirred 70 min at 25°C. The reaction mixture was absorbed on silica and purified by column chromatography on silica by using ethyl acetate as the eluent to give the alcohol as a yellow foam (11.6 g, 62% over two steps). $[\alpha]_D^{20}$ = 82.9 (*c* = 0.73 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): δ = 1.78 (m, 1H; CH_2CH$_2$O), 2.13 (m, 1H; CH_2CH$_2$O), 2.64 (dt, ^2J(H,H) = 16.0 Hz, ^3J(H,H) = 3.5 Hz, 1H; 3-H), 2.90 (m, 1H; 4-H), 3.19 (m, 1H; 4-H), 3.48–3.71 (m, 3H; CH$_2$CH_2O, 3-H), 3.84 (s, 6H; OMe), 4.18 (m, 1H; 1-H), 5.28 (m, 2H; Cbz), 6.58 (s, 1H; Ar-H), 6.65 (s, 1H; Ar-H), 7.37 ppm (m, 5H; Cbz); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C): δ = 28.21 (C-4), 38.14 (C-2′), 38.14 (C-3), 50.76 (C-1), 55.85 (OMe), 55.97 (OMe), 58.38 (C-1′), 67.59 (Cbz), 109.5 (C-5), 111.2 (C-8), 125.5 (C-4a), 127.8–129.0 (Ph), 129.0 (C-8a), 136.4 (Ph), 147.6 (C-5), 147.7 (C-6), 156.7 ppm (Cbz); UV/Vis (acetonitrile): λ_{max} (lg ε) = 191.0 (4.844), 202.0 (4.844), 203.5 (4.841), 253.5 (2.880), 285.0 nm (3.567); IR (film): $\tilde{\nu}$ = 2938 (C-H), 2836 (OMe), 1694 (Cbz), 1612 (C=O), 1434 (CH$_2$), 1357 (CH$_3$), 857 cm^{-1} (iso-arom-H); MS (70 eV, EI): *m*/*z* (%): 371.1733 (10) [M^+] ($C_{21}H_{25}NO_5$ requires 371.1733), 326.2 (65) [M^+-CH$_2$CH$_2$OH], 282.2 (80) [$M^+-C_7H_7+H_2$], 91.1 (100) [$C_7H_7^+$].

Compound (1S)-7: A solution of the alcohol (10.0 g, 26.9 mmol) in dichloromethane (60 cm^3) was added dropwise to a suspension of Dess–Martin periodinane (14.9 g, 35.0 mmol) in dichloromethane (106 cm^3) and stirred for 60 min at 0°C. The reaction mixture was diluted with diethyl ether (950 cm^3) and extracted with 1N sodium hydroxide solution (2×230 cm^3) and saturated sodium chloride solution (200 cm^3). The organic layer was dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica using toluene/acetone (10:1) as a eluent to give the aldehyde (1*S*)-**7** as a colourless foam (8.94 g, 90%). $[\alpha]_D^{20}$ = 74.2 (c 0.60 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 2.65 (dt, ^2J(H,H) = 16.0 Hz, ^3J(H,H) = 4.0 Hz, 1H; 3-H), 2.83–2.88 (m, 3H; 3-H, CH_2CH$_2$O), 3.33 (m, 1H; 4-H), 3.85 (s, 6H; OMe), 4.12 (m, 1H; 4-H), 5.16 (m, 2H; Cbz), 5.65 (m, 1H; 1-H), 6.60 (s, 1H; Ar-H), 6.64 (s, 1H; Ar-H), 7.36 (m, 5H; Cbz), 9.80 ppm (m, 1H; CHO); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C): δ = 27.90 (C-4), 38.40 (C-2′), 49.85 (C-1), 51.10 (C-3), 55.90 (OMe), 56.02 (OMe), 67.50 (Cbz), 109.4 (C-5), 111.5 (C-8), 126.1 (C-4a), 126.2 (C-8a), 127.8–129.0 (Ph), 136.4 (Ph), 147.8 (C-5), 148.1 (C-6), 155.4 (Cbz), 199.9 ppm (C-1′); UV/Vis (acetonitrile): λ_{max} (lg ε) = 204.0 (4.735), 285.0 nm (3.623); IR (film): $\tilde{\nu}$ = 2936 (C-H), 2835 (OMe), 1721 (Cbz), 1612 (C=O), 1429 (CH$_2$), 1357 (CH$_3$), 860 (iso-arom-H), 736, 698 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 369.1576 (5) [M^+] ($C_{21}H_{23}NO_5$ requires 369.1576), 326.1 [M^+-CH$_2$CHO] 91.1 (100) [$C_7H_7^+$].

Domino Knoevenagel/hetero-Diels–Alder reaction

1-(*S*)-*N*-Carbobenzyloxy-1-(2-benzoxy-3-ethyl-6-oxo-tetrahydropyran-4-ylmethyl)-6,7-dimethoxy-3,4-dihydro-2*H*-isoquinoline (19): A suspension of (1*S*)-**7** (8.50 g, 23.0 mmol), Meldrum's acid **6** (3.98 g, 27.6 mmol) and (*E*,*Z*)-butenylbenzyl ether **8** (13.9 g, 85.4 mmol) as well as a catalytic amount of ethylene diammonium diacetate in benzene (20 cm^3) in a closed flask was put into a ultra sonic bath for 14 h at 60°C. The product mixture was purified by column chromatography on silica gel using toluene/acetone (10:1) as a eluent to give the isoquinoline **19** as a colourless foam (11.4 g, 86%). The mixture of several diastereomers was converted in the following reaction to the corresponding benzoquinolizidines without any further purification. MS (DCI, NH_3): *m*/*z* (%): 574.5 (16) [M^++H], 591.5 (100) [M^++NH_3].

Cyclisation of the domino product 19: A suspension of dry potassium carbonate (1.25 g, 9.06 mmol), palladium on charcoal (1.25 g, 10%) and molecular sieves (3 A) in methanol (40 cm^3) was stirred for 10 min and a solution of isoquinoline **19** (10.4 g, 18.1 mmol) in methanol (200 cm^3) was added. The suspension was stirred for 50 min and then for further 5 h under a hydrogen atmosphere. The reaction mixture was filtered over a small amount of silica using methanol as eluent and the filtrate was absorbed on silica. Consecutive column chromatography on silica with ethyl acetate/methanol (4:1) and then toluene/acetone (6:1) as eluents gave the diastereomeric benzoquinolizidines **4**, **22** and **23**.[16]

Methyl ester of 2,3-(*R*,*R*)-11b-(*S*)-(3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-α]isoquinoline-2-yl)acetic acid (4): (840 mg, 13.3%, yellow solid), $[\alpha]_D^{20} = -22.4$ ($c = 1.04$ in $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 25°C, TMS): $\delta = 0.81$ (t, $^3J(H,H) = 7.5$ Hz, 3H; 13-H), 0.95–1.05 (m, 1H; 12-H), 1.41–1.52 (m, 3H; 1-H, 3-H, 12-H), 1.80 (m, 1H; 10′-H), 1.92 (dd, $^2J(H,H) = 15.5$ Hz, $^3J(H,H) = 15.5$ Hz, 1H; 4-H_{ax}), 2.01 (dd, $^2J(H,H) = 22.0$ Hz, $^2J(H,H) = 12.0$ Hz, 1H; 10′-H), 2.35–2.48 (m, 4H; 1-H, 2-H, 6-H, 7-H), 2.73–2.81 (m, 1H; 6-H), 2.93 (dd, $^2J(H,H) = 15.5$ Hz, $^3J(H,H) = 5.5$ Hz, 1H; 4-H_{eq}), 3.10–3.14 (m, 2H; 7-H, 11b-H), 3.34 (s, 3H; OMe), 3.42 (s, 3H; OMe), 3.44 (s, 3H; OMe), 6.45 (s, 1H; 8-H), 6.77 ppm (s, 1H; 11-H); ^{13}C NMR (75 MHz, C_6D_6, 25°C): $\delta = 11.20$ (C-13), 23.75 (C-12), 30.00 (C-7), 38.85 (C-1), 38.52 (C-3), 38.24 (*C*-10′), 41.79 (C-2), 50.93 (OMe), 52.77 (C-4), 55.64 (OMe), 56.00 (OMe), 61.43 (C-6), 63,00 (C-11b), 110.1 (C-8), 112.8 (C-11), 127.4 (C-11a), 130.8 (C-7a), 148.5 (C-10), 148.8 (C-9), 172.9 ppm (carboxylic-C); UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 201.0 (4.618), 283.0 (3.560), 285.5 nm (3.562); IR (film): $\tilde{\nu} = 2916$ (C-H), 2829 (OMe), 2791, 2752, 1733 (C=O), 1468 (CH_2), 1369 (CH_3), 852 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 347.2097 (100) [M^+] ($C_{20}H_{29}NO_4$ requires 347.2097), 332.3 (37) [$M^+ - CH_3$], 316.3 (12) [$M^+ - OMe$], 274.3 (28) [$M^+ - CO_2Me - CH_3$], 246.3 (80) [$C_{15}H_{20}NO_2^+$], 205.2 (53) [$C_{12}H_{15}NO_2^+$], 191.2 (81) [$C_{11}H_{13}NO_2^+$].

Methyl ester of 2,3-(*R*,*S*)-11b-(*S*)-(3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-α]isoquinoline-2-yl)acetic acid (22): (1.455 g, 23.1%, yellow oil), $[\alpha]_D^{20} = -57.9$ ($c = 0.61$ in $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 25°C, TMS): $\delta = 0.81$ (t, $^3J(H,H) = 7.5$ Hz, 3H; 13-H), 0.95–1.05 (m, 1H; 12-H), 1.41–1.52 (m, 3H; 1-H, 3-H, 12-H), 1.80 (m, 1H; 10′-H), 1.92 (dd, $^2J(H,H) = 15.5$ Hz, $^3J(H,H) = 15.5$ Hz, 1H; 4-H_{ax}), 2.01 (dd, $^2J(H,H) = 22.0$ Hz, $^3J(H,H) = 12.0$ Hz, 1H; 10′-H), 2.35–2.48 (m, 4H; 1-H, 2-H, 6-H, 7-H), 2.73–2.81 (m, 1H; 6-H), 2.93 (dd, $^2J(H,H) = 15.5$ Hz, $^3J(H,H) = 5.5$ Hz, 1H; 4-H_{eq}), 3.10–3.14 (m, 2H; 7-H, 11b-H), 3.34 (s, 3H; OMe), 3.42 (s, 3H; OMe), 3.44 (s, 3H; OMe), 6.45 (s, 1H; 8-H), 6.77 ppm (s, 1H; 11-H); ^{13}C NMR (75 MHz; C_6D_6): $\delta = 11.20$ (C-13), 23.75 (C-12), 30.00 (C-7), 38.85 (C-1), 38.52 (C-3), 38.24 (*C*-10′), 41.79 (C-2), 50.93 (OMe), 52.77 (C-4), 55.64 (OMe), 56.00 (OMe), 61.43 (C-6), 63,00 (C-11b), 110.1 (C-8), 112.8 (C-11), 127.4 (C-11a), 130.8 (C-7a), 148.5 (C-10), 148.8 (C-9), 172.9 ppm (carboxylic-C); UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 201.0 (4.618), 283.0 (3.560), 285.5 nm (3.562); IR (film): $\tilde{\nu} = 2916$ (C-H), 2829 (OMe), 2791, 2752, 1733 (C=O), 1468 (CH_2), 1369 (CH_3), 852 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 347.2097 (100) [M^+] ($C_{20}H_{29}NO_4$ requires 347.2097), 332.3 (37) [$M^+ - CH_3$], 316.3 (12) [$M^+ - OMe$], 274.3 (28) [$M^+ - CO_2Me - CH_3$], 246.3 (80) [$C_{15}H_{20}NO_2^+$], 205.2 (53) $C_{12}H_{15}NO_2^+$], 191.2 (81) [$C_{11}H_{13}NO_2^+$].

Methyl ester of 2,3-(*S*,*S*)-11b-(*S*)-(3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-α]isoquinoline-2-yl)acetic acid (23): (1.839 mg, 29.1%, yellow oil), $[\alpha]_D^{20} = -81.5$ ($c = 0.46$ in $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 25°C, TMS): $\delta = 0.88$ (t, 3H; $^3J(H,H) = 7.5$ Hz, 13-H), 1.26 (m, 1H; 3-H), 1.54–1.80 (m, 2H; 12-H), 1.88 (ddd, $^2J(H,H) = 13.5$ Hz, $^3J(H,H) = 4.0$, 4.0 Hz,1H; 1-H_{eq}), 2.04 (ddd, $^2J(H,H) = 13.5$ Hz, $^3J(H,H) = 10.0$, 4.5 Hz, 1H; 1-H_{ax}) 2.22 (m, 1H; 2-H), 2.28–2.45 (m, 3H; 10′-H, 10′-H, 7-H) 2.57 (t, $^3J(H,H) = 4.0$ Hz, 2H; 4-H), 2.53 (dd, $^2J(H,H) = 12.5$ Hz, $^3J(H,H) = 4.0$ Hz, 1H; 6-H), 2.71 (ddd, $^2J(H,H) = 12.5$ Hz, $^3J(H,H) = 6.0$, 1.0 Hz, 1H; 6-H), 3.04 (ddd, $^2J(H,H) = 17.0$ Hz, $^3J(H,H) = 13.0$, 6.5 Hz, 1H; 7-H), 3.41–3.46 (m, 1H; 11b-H), 3.39 (s, 3H; OMe), 3.44 (s, 3H; OMe), 6.43 (s, 1H; 8-H), 6.77 ppm (s, 1H; 11-H); ^{13}C NMR (75 MHz, C_6D_6, 25°C): $\delta = 12.32$ (C-13), 25.65 (C-12), 28.44 (C-7), 32.68 (C-1), 33.72 (C-2), 37.92 (*C*-10′), 40.76 (C-3), 50.97 (OMe), 53.09 (C-6), 54.35 (C-6), 54.35 (C-4), 55.61 (OMe), 55.65 (OMe), 58.20 (C-11b), 109.8 (C-8), 112.8 (C-1), 127.3 (C-11a), 130.1 (C-7a), 148.6 (C-10), 148.7 (C-9), 173.0 ppm (carboxylic-C); UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 201.5 (4.601), 286.0 nm (3.587); IR (film): $\tilde{\nu} = 2935$ (C-H), 2835 (OMe), 2873, 2804, 2753, 1735 (C=O), 1463 (CH_2), 1358 (CH_3), 855 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 347.2097 (100) [M^+] ($C_{20}H_{29}NO_4$ requires 347.2097), 332.4 (42) [$M^+ - CH_3$], 316.3 (12) [$M^+ - OMe$], 274.3 (24) [$M^+ - CO_2Me - CH_3$], 246.3 (85) [$C_{15}H_{20}NO_2^+$], 205.2 (52) [$C_{12}H_{15}NO_2^+$], 191.2 (63) [$C_{11}H_{13}NO_2^+$].

2,3-(*R*,*R*)-11b-(*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(3-ethyl-9,10-dimethoxy-1,3,4,7,11b-hexahydro-2*H*-pyrido[2,1-α]isoquinoline-2-yl)acetamide (24): A solution of homoveratryl amine **3** (1.77 g, 9.79 mmol) and trimethyl aluminium (2M in toluene, 4.89 cm^3, 9.79 mmol) in dichloromethane (5.44 cm^3) was stirred for 1 h at 25°C and a solution of **4** (680 mg, 1.96 mmol) in dichloromethane (4 cm^3) was added dropwise; stirring was continued for further 4.5 h under reflux. The reaction was cautiously quenched with water (50 cm^3) and extracted with ethyl acetate (4× 100 cm^3). The combined organic layers were dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane/methanol (20:1) as eluent to give the acetamide **24** as a colourless foam (760 mg, 78%) $[\alpha]_D^{20} = 32.1$ ($c = 0.77$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.88$ (t, $^3J(H,H) = 7.5$ Hz, 3H; 13-H), 1.10–1.20 (m, 2H; 1-H_{ax}, 12-H), 1.36–1.42 (m, 1H; 3-H), 1.57–1.62 (m,1H; 12-H), 1.74 (dd, $^2J(H,H) = 14.4$ Hz, $^3J(H,H) = 9.6$ Hz, 1H; 10′-H), 1.88 (m, 1H; 2-H), 2.07 (dd, $^2J(H,H) = 11.2$, $^3J(H,H) = 11.2$ Hz, 1H; 4-H_{ax}), 2.36 (ddd, $^2J(H,H) = 12.8$ Hz, $^3J(H,H) = 3.2$, 3.2 Hz, 1H; 1-H_{eq}), 2.48 (ddd, $^2J(H,H) = 11.8$ Hz, $^3J(H,H) = 11.8$ and 4.1 Hz, 1H; 6-H_{ax}), 2.57 (dd, $^2J(H,H) = 14.4$ Hz $^3J(H,H) = 3.9$ Hz, 1H; 10′-H), 2.61 (m, 1H; 7-H), 2.70–2.76 (m, 1H; 4′-H), 2.78–2.84 (m, 1H; 4′-H), 2.96 (ddd, $^2J(H,H) = 11.8$ Hz, $^3J(H,H) = 5.6$, 1.6 Hz, 1H; 6-H_{eq}), 3.05 (dd, $^2J(H,H) = 11.6$ Hz, $^3J(H,H) = 4.4$ Hz ,1H; 4-H_{eq}), 3.07–3.13 (m, 2H; 7-H, 11b-H), 3.42–3.50 (m, 1H; 3′-H), 3.56–3.62 (m, 1H; 3′-H), 3.77 (s, 3H; OMe), 3.80 (s, 3H; OMe), 3.82 (s, 3H; OMe), 3.83 (s, 3H; OMe), 5.58 (m, 1H; NH), 6.55 (s,1H; 8-H or 11-H), 6.66 (s, 1H; 8-H or 11-H), 6.77 (d, $^3J(H,H) = 8.0$ Hz, 1H; 8′-H), 6.68–6.73 ppm (m, 2H; 5′-H, 8′a-H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 11.05$ (C-13) 23.40 (C-12), 29.04 (C-7), 35.50 (C-4′), 37.60 (C-1), 37.99 (C-2), 40.73 (C-10′), 41.12 (C-3′), 41.67 (C-3), 52.18 (C-6), 55.65 (OMe), 55.68 (OMe), 55.75 (OMe), 55.87 (OMe), 60.90 (C-4), 62.23 (C-11b), 108.0 (C-5′), 111.2, 111.3, 111.6 (C-2′, C-8, C-11), 120.4 (C-8a′), 126.5, 129.7, 131.1 (C-4a′, C-7a, C-11a), 147.0, 147.3, 147.5, 148.9 (C-6′, C-7′, C-9, C-10), 172.3 ppm (amide); UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 201.0 (4.427), 229.0 (3.700), 281.5 nm (3.273); IR (film): $\tilde{\nu} = 3283$ (NH), 2936 (C-H), 2834 (OMe), 1634 ($CONR_2$), 1518 ($CONR_2$), 1369 (CH_3), 858 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 496.2937 (29) [M^+] ($C_{29}H_{40}N_2O_5$ requires 496.2937), 481.3 (38) [$M^+ - CH_3$], 274.2 (42) [$M^+ - C_{11}H_{13}NO_2$], 205.1 (22) [$M^+ - C_{12}H_{15}NO_2$], 191.1 (72) [$C_{11}H_{13}NO_2^+$].

2,3-(*R*,*R*)-11b-(*S*)-Dehydroemetine (26): Phosphorus oxychloride (2.23 g, 14.5 mmol) was added to a solution of the amide **24** (555 mg, 1.12 mmol) in benzene (30.5 cm^3) under reflux and stirring was continued for 45 min at the same temperature. The solvent was removed and the residue was dissolved in dichloromethane. The organic layer was extracted with 1N sodium hydroxide solution (55 cm^3) and the aqueous layer was extracted with dichloromethane (3×50 cm^3). The combined organic layers were dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with dichloromethane/methanol (10:1) as eluent to give dehydroemetine **26** as a yellow foam (439 mg, 82%). $[\alpha]_D^{20} = 36.5$ ($c = 0.37$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 0.98$ (t, $^3J(H,H) = 7.5$ Hz, 3H; 13-H), 1.12–1.30 (m, 2H; 1-H_{ax}, H-12), 1.50–1.62 (m, 1H; 3-H), 1.76–1.90 (m, 2H; 2-H, 12-H), 2.06 (1H, dd, *J* 11.2 and 11.2, 4-H_{ax}), 2.24 (ddd, $^2J(H,H) = 12.8$, $^3J(H,H) = 3.2$, 3.2 Hz, 1H; 1-H_{eq}), 2.37 (dd, $^2J(H,H) = 14.4$ Hz, $^3J(H,H) = 10.2$ Hz, 1H; 10′-H), 2.46 (ddd, 1H, $^2J(H,H) = 11.8$, $^3J(H,H) = 11.8$, 4.1 Hz, 6-H_{ax}), 2.59 (m, 1H; 7-H), 2.65 (t, $^3J(H,H) = 7.5$ Hz, 2H; 4′-H), 2.90–3.21 (m, 5H; 10′-H, 4-H_{eq}, 6-H_{eq}, 7-H, 11b-H), 3.52–3.84 (m, 2H; 3′-H, 3′-H), 3.79 (s, 3H; OMe), 3.82 (s, 3H; OMe), 3.90 (s, 3H; OMe), 3.93 (s, 3H; OMe), 6.49 (s, 1H; 8-H or 11-H), 6.54 (s, 1H; 8-H or 11-H), 6.73 (d, $^3J(H,H) = 8.0$ Hz, 1H; 5′-H), 7.02 ppm (s, 1H; 8′-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C): $\delta = 11.25$ (C-13) 23.72 (C-12), 26.07 (C-4′), 28.89 (C-7), 37.23 (C-1), 39.17 (C-2), 39.50 (C-10′), 42.15 (C-3), 46.77 (C-3′), 52.39 (C-6), 55.68 (OMe), 55.74 (OMe), 55.95 (OMe), 56.14 (OMe), 61.10 (C-4), 62.42 (C-11b), 108.0, 108.9, 110.3, 111.3 (C-5′, C-8′, C-8, C-11), 122.2, 126.4, 129.5, 131.4 (C-4′a, C-8′a, C-7a, C-11a), 146.9, 147.3, 147.5, (C-7′, C-9, C-10), 150.9 (C-6′) 166.3 ppm (C-1′); UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 201.0 (4.412), 224.0 (4.172), 276.0 nm (3.655); IR (film): $\tilde{\nu} = 3417$, 2935 (C-H), 2831 (OMe), 1570 (C=N), 1463 (CH_2), 854 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 478.2832 (100) [M^+] ($C_{29}H_{38}N_2O_4$ requires 478.2832), 463.2 (8) [$M^+ - CH_3$], 286.3 (28) [$M^+ - C_{11}H_{14}NO_2$], 272.3 (65) [$M^+ - C_{12}H_{16}NO_2$], 244.3 (87) [$M^+ - C_{13}H_{18}NO_2$], 206.1 (22) [$C_{12}H_{16}NO_2^+$].

Emetine (1): A solution of dichloro(*p*-cymene)ruthenium(II) dimer (6.4 mg, 10.5 μmol), 1,2-(*S*,*S*)-*N*-tosyl-1,2-diphenylethyldiamine (8.4 mg, 23.0 μmol) and triethylamine (4.2 mg, 41.8 μmol) in dimethylformamide (0.1 cm^3) was stirred in a sealed flask under a argon atmosphere at 80°C for 60 min. The warm solution was added to a solution of dehydroemetine **26** (100 mg, 209 μmol) in dimethylformamide (0.4 cm^3), cooled down

to 0 °C and a mixture of formic acid/triethylamine (5:2, 0.105 cm^3) was added dropwise. The solution was allowed to reach 25 °C; after 40 min of stirring it was diluted with ethyl acetate and the reaction was quenched by addition of saturated aqueous potassium carbonate solution and water. The aqueous layer was extracted with dichloromethane (4× 20 cm^3); the combined organic layers were dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica using dichloromethane/methanol (10:1) as eluent to give emetine (**1**) as a colourless foam (71 mg, 71 %, >98:2 *ds*), $[\alpha]_D^{20} = -45.3$ ($c = 0.40$ in $CHCl_3$) ($[\alpha]_D^{25} = -46.0$ ($c = 0.42$ in $CHCl_3$));[20] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.91$ (t, $^3J(H,H) = 7.5$ Hz, 3H; 12-H), 1.08–1.32 (m, 2H; 1-H_{ax}, 12-H), 1.38–1.52 (m, 2H; 10′-H, 3-H), 1.59–1.75 (m, 2H; 2-H, H-12), 2.06–2.10 (m, 1H; 10′-H), 2.12 (dd, $^2J(H,H) = 11.2$ Hz, $^3J(H,H) = 11.2$ Hz, 1H; 4-H_{ax}), 2.52 (ddd, $^2J(H,H) = 11.8$ Hz, $^3J(H,H) = 11.8$, 4.1 Hz, 1H;, 6-H_{ax}), 2.58–2.78 (m, 4H; 2×4′-H, 1-H_{eq}, 7-H), 2.95–3.32 (m, 6H; 2×3′-H, 4-H_{eq}, 6-H, 7-H, 11b-H), 3.81 (s, 3H; OMe), 3.83 (s, 3H; OMe), 3.85 (s, 3H; OMe), 3.87 (s, 3H; OMe), 4.12 (m, 1H; 1′-H), 6.51 (s, 1H; 8-H or 11-H), 6.58 (s, 1H; 8-H or 11-H), 6.60 (d, $^3J(H,H) = 8.0$ Hz, 1H; 5′-H), 7.78 ppm (s, 1H; 8′-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 11.15$ (C-13), 23.55 (C-12), 29.01 (C-4′), 29.21 (C-7), 36.74 (C-2), 36.85 (C-1), 40.07 (C-3′), 40.68 (C-10′), 41.69 (C-3), 51.77 (C-1′), 52.24 (C-6), 55.77 (OMe), 55.80 (OMe), 55.90 (OMe), 56.20 (OMe), 61.33 (C-4), 62.38 (C-11b), 108.6, 109.1, 111.4, 111.7 (C-5′, C-8′, C-8, C-11), 126.7, 126.8, 130.1, 131.5 (C-4a′, C-8a′, C-7a, C-11a), 147.1, 147.3, 147.3, 147.4 ppm (C-6′, C-7′, C-9, C-10); UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 201.0 (4.874), 286.0 nm (3.847); IR (film): $\tilde{\nu} = 3331$, 2935 (C-H), 2833 (OMe), 1463 (CH_2), 860 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 480.2988 (100), $[M^+]$ ($C_{29}H_{40}N_2O_4$ requires 480.2988), 465.2 (8) $[M^+ - CH_3]$, 288.1 (32) $[M^+ - C_{11}H_{14}NO_2]$, 272.1 (20) $[M^+ - C_{12}H_{17}NO_2]$, 192.0 (100) $[C_{11}H_{14}NO_2^+]$.

2,3-(*R*,*R*)-11b-(*S*)-*N*-[2-(5-Benzyloxy-1*H*-indol-3-yl)-ethyl]-2-(3-ethyl-9,10-dimethoxy-1,3,4,6,7,7a,11a,11b-octahydro-2*H*-pyrido[2,1-α]isoquinolin-2-yl)acetamide (25): A heterogeneous mixture of benzoquinolizidine **4** (200 mg, 580 μmol), *O*-benzylserotonine **5** (230 mg, 860 μmol) and 2-hydroxypyridine (82 mg, 860 μmol) was stirred for 3.25 h at 170 °C under an argon atmosphere in a sealed flask. The solution was cooled to 25 °C and the resulting solid was dissolved in CH_2Cl_2 and absorbed on silica gel. Column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) gave the amide **25** as a dark yellow foam (246 mg, 73 %), $[\alpha]_D^{20} = -30.0$ ($c = 0.4$ in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 8.13$ (brs, 1H, indol-NH), 7.47 (d, $^3J(H,H) = 8.0$ Hz, 2H; benzyl), 7.38 (dd, $^3J(H,H) = 7.6$, 7.6 Hz, 2H; benzyl), 7.31 (dd, $^3J(H,H) = 7.6$, 7.6 Hz, 1H; benzyl), 7.22 (d, $^3J(H,H) = 8.4$ Hz, 1H; 8′-H), 7.12 (d, $^3J(H,H) = 2.2$ Hz, 1H; 9′a-H), 6.96 (d, $^3J(H,H) = 2.0$ Hz, 1H; 5′-H), 6.93 (dd, $^3J(H,H) = 8.4$, 2.2 Hz, 1H; 7′-H), 6.66 (s, 1H; 8-H or 11-H), 6.57 (s, 1H; 8-H or 11-H), 5.60 (t, $^3J(H,H) = 5.8$ Hz, 1H; amide-NH), 5.09 (s, 2H; CH_2-benzyl), 3.83 (s, 3H; OMe), 3.76 (s, 3H; OMe), 3.66 (m, 1H; 3′-H), 3.55 (m, 1H; 3′-H), 3.02–3.18 (m, 3H; 4-H, 7-H, 11b-H), 2.87–3.02 (m, 3H; 4′-H, 4′-H, 6-H), 2.63 (m, 1H; 7-H), 2.45–2.57 (m, 2H, 6-H, 10′-H), 2.35 (ddd, $^2J(H,H) = 13.5$ Hz, $^3J(H,H) = 3.1$, 3.1 Hz, 1H; 1-H), 2.09 (dd, $^2J(H,H) = 11.2$ Hz, $^3J(H,H) = 11.2$ Hz, 1H; 4-H), 1.89 (m, 1H; 2-H), 1.73 (dd, $^2J(H,H) = 13.9$ Hz, $^3J(H,H) = 9.7$ Hz, 1H; 10′-H), 1.59 (m, 1H, 12-H), 1.42 (m, 1H, 3-H), 1.05–1.32 (m, 2H, 1-H, 12-H), 0.89 ppm (t, $^3J(H,H) = 7.7$ Hz, 3H; 13-H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 172.3$ (C-amide), 153.0 (C-6′), 147.5 (C-9 or C-10), 147.1 (C-9 or C-10), 137.4 (C-benzyl), 131.7 (C-11a), 129.4 (C-4′a), 128.4 (C-benzyl), 127.7 (C-benzyl) 127.5 (C-benzyl), 127.4 (C-7a), 123.0 (C-9′a), 112.8 (C-7′), 112.2 (C-4′a), 112.0 (C-8′), 111.4 (C-8), 108.5 (C-11), 102.0 (C-5′), 70.89 (C-benzyl), 62.29 (C-11b), 60.80 (C-4), 56.14, 55.71 (C-OMe), 52.18 (C-6), 41.3 (C-3), 40.95 (C-3′), 39.49 (C-10′), 37.88 (C-2), 37.23 (C-1), 28.83 (C-7), 25.48 (C-4′), 23.34 (C-12), 10.98 ppm (C-13); IR (KBr): $\tilde{\nu} = 3375$ (NH), 2932 (C-H), 2859 (OMe), 1647 ($CONR_2$), 1513 ($CONR_2$), 1366 (CH_3), 858 cm^{-1}; UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 281.5 (3.962), 200.0 nm (4.875); MS (70 eV, EI): *m*/*z* (%): 581.3254 (18) $[M^+]$ ($C_{36}H_{41}N_3O_3$ requires 581.3254), 490.4 (100) $[M^+ - C_7H_7]$, 272.3 (42) $[C_{17}H_{22}NO_2^+]$, 246.3 (58) $[C_{16}H_{16}NO_2^+]$, 191.1 (38) $[C_{11}H_{13}NO_2^+]$, 91.1 (50) $[C_7H_7^+]$.

2,3-(*R*,*R*)-11b-(*S*)-*O*-Benzyl-dehydrotubulosine (27): Phosphorus oxychloride (316 mg, 2.06 mmol) was added dropwise to a solution of amide **25** (240 mg, 413 μmol) in benzene (13 cm^3), and the reaction mixture was stirred under reflux for 85 min. The workup was carried out similarly as described for dehydroemetine **26**. The obtained organic layer was treated with silica and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica using CH_2Cl_2/MeOH (10:1) as eluent to give dehydrotubulosine (**27**) as a bright yellow foam (114 mg, 49 %; 15 % of starting material was recovered). $[\alpha]_D^{20} = +15.1$($c = 0.45$ in chloroform); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): $\delta = 7.47$ (d, $^3J(H,H) = 8.0$ Hz, 2H; benzyl), 7.38 (dd, $^3J(H,H) = 7.6$, 7.6 Hz, 2H; benzyl), 7.31–7.36 (m, 2H; benzyl, 8′-H), 7.04 (dd, $^3J(H,H) = 8.8$, 2.2 Hz, 1H; 7′-H), 7.01 (d, $^3J(H,H) = 2.2$ Hz, 1H; 5′-H), 6.47 (s, 1H; 8-H or 11-H), 6.38 (s, 1H; 8-H or 11-H), 5.09 (s, 2H; CH_2-benzyl), 3.92 (m, 1H; 3′-H), 3.85 (m, 1H; 3′-H), 3.76 (s, 3H; OMe), 3.51 (s, 3H; OMe), 3.25 (m, 1H; 11b-H), 3.20–3.21 (m, 3H; 4-H, 7-H, 10′-H), 3.08 (m, 1H; 6-H), 2.92 (t, $^3J(H,H) = 8.3$ Hz, 2H; 4′-H), 2.61–2.71 (m, 2H; 7-H, 10′-H), 2.58 (ddd, $^2J(H,H) = 10.3$ Hz, $^3J(H,H) = 10.3$, 3.5 Hz, 1H; 6-H), 2.30 (m, 1H; 1-H), 2.19 (dd, $^2J(H,H) = 10.9$ Hz, $^3J(H,H) = 10.9$ Hz, 1H; 4-H), 2.10 m, 1H; 2-H), 1.67–1.78 (m, 2H, 3-H, 12-H), 1.40 (m, 1H, 1-H), 1.23 (m, 1H; 12-H), 0.90 ppm (t, $^3J(H,H) = 7.3$ Hz, 3H; 13-H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 164.2$ (C-1′), 153.9 (C-6′), 147.4 (C-10), 147.0 (C-9), 141.8 (C-9′a), 137.0 (benzyl), 129.0 (C-11a), 128.5 (benzyl), 128.4 (C-8′a), 127.9 (benzyl), 127.5 (benzyl), 125.7 (C-7a), 125.1 (C-5′a), 120.2 (C-4′a), 118.3 (C-8′), 113.8 (C-8), 111.1 (C-11), 107.8 (C-7′), 101.6 (C-5′), 70.58 (benzyl), 62.19 (C-11b), 60.54 (C-4), 55.67, 55.52 (C-OMe), 52.17 (C-6), 46.03 (C-3′), 41.68 (C-3), 39.74 (C-10′), 37.78 (C-1), 36.56 (C-2), 28.37 (C-7), 23.51 (C-12), 19.44 (C-4′), 10.99 ppm (C-13); IR (KBr): $\tilde{\nu} = 3417$, 2933 (C-H), 2831 (OMe), 1547 (C=N), 1463 (CH_2), 854 cm^{-1}; UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 364.0 (3.841), 320.0 (4.089), 292.5 (3.912), 202.0 nm (4.793); MS (70 eV, EI): *m*/*z* (%): 565.3304 (20) $[M^+]$ ($C_{36}H_{43}N_3O_3$ requires 565.3304), 290.3 (64) $[C_{19}H_{18}N_2O^+]$, 199.2 (64) $[C_{12}H_{11}N_2O^+]$, 106.1 (80) $[C_7H_6O^+]$, 91.1 (48) $[C_7H_7^+]$.

***O*-Benzyltubulosine (28)**: By using the procedure for the synthesis of emetine (**1**), compound **27** (90.0 mg, 160 μmol) was converted into the protected tubulosine **28** after 80 min of stirring. Column chromatography on silica gel using CH_2Cl_2/MeOH (10:1) as eluent gave **28** as a yellow foam(70 mg, 78 %, >98:2 *ds*) $[\alpha]_D^{20} = -13.4$($c = 0.5$ in chloroform); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): ?$\delta = 7.73$ (brs, 1H, indol-NH), 7.47 (d, $^3J(H,H) = 8.0$ Hz, 2H; benzyl), 7.38 (dd, $^3J(H,H) = 7.6$, 7.6 Hz, 2H; benzyl), 7.31 (dd, $^3J(H,H) = 7.6$, 7.6 Hz, 1H; benzyl), 7.20 (d, $^3J(H,H) = 8.0$ Hz 1H; 8′-H), 7.03 (d, $^3J(H,H) = 2.2$ Hz, 1H; 5′-H), 7.01 (dd, $^3J(H,H) = 8.8$, 2.2 Hz, 1H; 7′-H,), 6.73 (s, 1H; 8-H or 11-H), 6.59 (s, 1H; 8-H or 11-H), 5.10 (s, 2H; CH_2-benzyl), 4.27 (m, 1H; 1′-H), 3.85 (s, 3H; OMe), 3.82 (s, 3H; OMe), 3.39 (ddd, $^2J(H,H) = 13.2$ Hz, $^3J(H,H) = 4.5$, 4.5 Hz, 1H; 3′-H), 3.05–3.22 (m, 4H; 3′-H, 4-H, 7-H, 11b-H), 3.01 (m, 1H; 6-H), 2.57–2.78(m, 4H; 1-H, 4′-H, 4′-H, 7-H), 2.52 (ddd, $^2J(H,H) = 11.4$ Hz, $^3J(H,H) = 11.3$, 4.0 Hz, 1H; 6-H), 2.11 (dd, $^2J(H,H) = 11.3$ Hz, $^3J(H,H) = 11.3$ Hz, 1H; 4-H), 2.04 (dd, $^2J(H,H) = 11.3$ Hz, $^3J(H,H) = 11.3$ Hz, 1H; 10′-H), 1.75 (m, 1H; 2-H), 1.64 (m, 1H; 12H), 1.51 (m, 1H; 10′-H), 1.45 (m, 1H; 3H), 1.23 (ddd, $^2J(H,H) = 11.5$ Hz, $^3J(H,H) = 11.5$, 11.5 Hz, 1H; 1-H), 1.14 (m, 1H; 12-H), 0.90 ppm (t, $^3J(H,H) = 7.7$ Hz, 3H, 13-H); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): $\delta = 153.1$ (C-6′), 147.4 (C-10), 147.1 (C-9), 137.7 (benzyl), 137.4 (C-9′a), 130.9 (C-11a), 129.9 (C-8′a), 128.4 (benzyl), 127.8 (C-5′a), 127.63 (benzyl), 127.5 (benzyl), 126.7 (C-7a), 111.8 (C-8), 111.4 (C-8′), 108.5 (C-11), 108.4 (C-7′), 101.9 (C-5′), 70.90 (CH_2-benzyl), 62.36 (C-11b), 61.23 (C-4), 56.15, 55.70 (OMe), 52.35 (C-6), 49.30 (C-1′), 41.99 (C-3), 41.56 (C-3′), 38.54 (C-10′), 36.75 (C-1), 36.29 (C-2), 29.02 (C-7), 23.41 (C-12), 22.68 (C-4′), 11.08 ppm (C-13); IR (KBr): $\tilde{\nu} = 3382$, 2935 (C-H), 2836 (OMe), 1453 (CH_2), 860 cm^{-1}; UV/Vis (acetonitrile): λ_{max} ($\lg \varepsilon$) = 283.0 (4.054), 200.0 nm (4.844); MS (70 eV, EI): *m*/*z* (%): 563.3148 (54) $[M^+]$ ($C_{36}H_{43}N_3O_4$ requires 563.3148), 290.3 (64) $[C_{19}H_{18}N_2O^+]$, 199.2 (68) $[C_{12}H_{11}N_2O^+]$, 91.1 (50) $[C_7H_7^+]$.

Tubulosine (2): A suspension of compound **28** (45 mg, 79 μmol) and Pd/C (10 %, 54 % water, 20 mg) in MeOH (2.5 cm^3) was stirred under a hydrogen atmosphere (1 bar) for 95 min. The catalyst was removed by filtration over silica gel using CH_2Cl_2/MeOH (5:1) as eluent. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (5:1) as eluent again. Compound **2** was obtained as a amorphous white powder (25 mg, 67 %). $[\alpha]_D^{20} = -60.7$($c = 0.3$ in pyridine), ($[\alpha]_D^{27} = -63.9$($c = 2.0$ in pyridine))[26] ^{1}H NMR (600 MHz, [D$_6$]DMSO, 35 °C): $\delta = 10.22$ (brs, 1H; Indol-NH), 8.39 (brs, 1H; OH), 7.02 (dd, $^3J(H,H) = 8.4$, $^5J(H,H) = 2.0$ Hz, 1H; 8′-H), 6.81 (s, 1H; 8-H or 11-H), 6.65 (d, $^4J(H,H) = 2.0$ Hz, 1H; 5′-H), 6.64 (s, 1H; 8-H or 11-H), 6.49 (ddd, $^3J(H,H) = 8.4$, $^4J(H,H) = 2.0$ Hz, 2.0 Hz, 1H; 7′-H), 4.11 (m, 1H; 1′-H), 3.71, 3.70 (s, 3H; OMe), 3.10

(ddd, ^2J(H,H) = 12.5 Hz, ^3J(H,H) = 5.3, 5.3 Hz, 1H; 3′-H), 2.86–3.00 (m, 5H, 3′-H, 4-H, 6-H, 7-H, 11b-H), 2.45–2.62 (m, 4H, 1-H, 4′-H, 4′H, 7-H,), 2.34 (m, 1H, 6H), 1.98 (dd, ^2J(H,H) = 11.2 Hz, ^3J(H,H) = 11.2 Hz, 1H; 4-H), 1.81 (dd, ^2J(H,H) = 12.0 Hz, ^3J(H,H) = 12.0 Hz, 1H; 10′-H), 1.50–1.68 (m, 3H; 2-H, 10′-H, 12-H), 1.24 (m, 1H; 3-H), 1.09 (m, 1H; 12-H), 1.04 ppm (ddd, ^2J(H,H) = 12.0 Hz, ^3J(H,H) = 12.0, 12.0 Hz, 1H, 1-H); ^{13}C NMR (150 MHz, [D$_6$]DMSO, 35 °C): δ = 150.2 (C-6′), 147.4 (C-10), 147.1 (C-9), 138.2 (C-9′a), 130.6 (C-11a), 130.1 (C-8′a), 127.9 (C-5′a), 126.9 (C-7′a), 112.1 (C-8), 111.0 (C-8′), 110.2 (C-7′), 109.6 (C-11), 106.4 (C-4′a), 101.8 (C-5′a), 62.33 (C-11b), 61.15 (C-4), 55.99, 55.48 (OMe), 52.01 (C-6), 48.72 (C-1′), 41.67 (C-3), 41.45 (C-3′), 37.79 (C-10′), 36.53 (C-1), 36.16 (C-2), 28.96 (C-7), 23.03 (C-12), 22.35 (C-4′), 11.00 ppm (C-13); IR (KBr): $\tilde{\nu}$ = 3380, 2933 (C-H), 1463 cm^{-1} (CH_2); UV/Vis (acetonitrile): λ_{max} (lg ε) = 282.5 (3.971), 225.0 (4.371), 200.5 nm (4.710); MS (70 eV, EI): *m*/*z* (%): 475.2835 (100) [M^+] ($C_{29}H_{37}N_3O_3$ requires 475.2835), 272.3 (42) [$C_{17}H_{22}NO_2^+$], 201.2 (62) [$C_{12}H_{13}N_2O^+$], 187.2 (58) [$C_{11}H_{11}N_2O^+$].

2-(9,10-Dimethoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-α]isoquinoline-2-yl)butyraldehyde (33): A suspension of **19** (500 mg, 870 μmol) and a catalytic amount of Pd/C in MeOH (6.0 cm^3) was stirred under a hydrogen atmosphere for 4.5 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude product was purified on silica gel using toluene/acetone (6:1) as eluent. Compound **33** was obtained as a mixture of diastereomers (233 mg, 81%, colourless oil). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.81–0.98 (m, 3H; $CHCH_2CH_3$), 1.34–1.79 (m, 2H; $CHCH_2CH_3$), 1.96–2.52 (m, 6H; 1-H, 2-H, $CHCH_2CH_3$, 7-H), 2.58–2.66 (m, 1H; 11b-H), 2.72–3.02 (m, 2H; 6-H), 3.78–3.88 (m, 6H; OMe), 4.58–4.84 (m, 2H; 3-H) 6.56–6.60 (m, 2H; 8-H, 11-H), 10.18–10.26 ppm (m, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 10.83, 10.97, 11.60, 12.00 ($CHCH_2CH_3$), 18.64, 18.81, 19.02, 19.53 ($CHCH_2CH_3$) 28.00, 28.38, 30.86, 30.86, 31.81 (C-1), 28.09, 28.60, 30.02, 31.00 (C-2), 34.41, 35.63, 35.74, 35.93 (C-7), 36.40, 39.46, 39.50, 41.09 (C-3), 54.20, 54.40, 55.84, 56.04 (C-6), 56.10 (OMe), 56.12 (OMe), 56.16, 56.19, 57.05, 57.40 (C-11b), 107.29, 107.31, 108.1, 108.1 (C-8) 111.4, 111.5, 111.7, 111.9 (C-11), 127.0, 127.1, 127.5, 127.9 (C-7a), 128.3, 128.4, 128.5, 128.6 (C-11a), 147.5, 147.7, 147.9, 148.0 (C-9, C-10), 168.0, 168.3, 168.6 (lactam-C), 203.6, 203.7, 203.8, 204.1 ppm (carbonyl-C); UV/Vis (acetonitrile): λ_{max} (lg ε) = 204.5 (4.645), 285.0 nm (3.568); IR (film): $\tilde{\nu}$ = 2934 (C-H), 2876 (OMe), 1719 (CHO), 1638 ($CONR_2$), 1464 (CH_2), 1359 (CH_3), 858 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 331.1784 (29) [M^+] ($C_{19}H_{25}NO_4$ requires 331.1784), 303.3 (8) [M^+−CO], 258.2 (100) [M^+ −CO−3CH_3], 244.2 (8) [M^+−CO−3CH_3−CH_2], 205.2 (7) [$C_{12}H_{15}NO_2^+$], 192.2 (72) [$C_{11}H_{14}NO_2^+$], 176.1 (5) [$C_{10}H_{10}NO_2^+$].

2-(9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-α]isoquinoline-2-yl)butyralcohol (34): A solution of the aldehyde **33** (230 mg, 6.94 mmol) in tetrahydrofuran (10 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (263 mg, 6.94 mmol) in tetrahydrofuran (20 cm^3) at −50 °C. The reaction mixture was stirred for 4.5 h at 25 °C and quenched with water (0.26 cm^3). After stirring for 10 min, an aqueous sodium hydroxide solution (0.26 cm^3, 15%) was added, stirring was continued for 10 min and water (0.78 cm^3) was added again. The formed precipitate was removed by filtration and washed with tetrahydrofuran (20 cm^3). The combined filtrates were evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (4:1) as eluent. Compound **34** was obtained as two fractions each of them containing two diastereomers; fraction 1 (146 mg, 65%), fraction 2 (75 mg, 34%);

Fraction 1: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.78–1.02 (m, 3H, $CHCH_2CH_3$), 1.12–1.88 (m, 8H, 1-H, 2-H, 3-H, $CHCH_2CH_3$, $CHCH_2CH_3$), 2.05–2.71 (m, 5H, 4-H, 6-H, OH), 2.89–3.21 (m, 3H, 7-H, 11b-H), 3.54–3.71 (m, 2H, $CHCH_2OH$), 3.82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.55 (s, 1H, 8-H), 6.68 ppm (s, 1H, 11-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 12.23, 12.28 (C-4′), 20.27, 20.79 (C-3′), 27.83, 28.24 (C-3), 29.00, 29.61 (C-7), 34.84, 35.18 (C-1), 36.88, 36.99 (C-2), 47.11, 47.17 (C-2′), 52.24 (C-4), 55.73, 56.04 (OMe), 56.62, 56.67 (C-5), 62.36, 62.40, (C-1'), 62.90 (C-11b), 108.16 (C-8), 111.4 (C-11), 126.5 (C-7a), 130.0 (C-11a), 147.1 (C-9), 147.4 ppm (C-10); UV/Vis (acetonitrile): λ_{max} (lg ε) = 201.0 (4.555), 282.5 (3.496), 286.0 nm (3.499); IR (film): $\tilde{\nu}$ = 3384 (OH), 2930 (C-H), 2873 (OMe), 1464 (CH_2), 1361 (CH_3), 856 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 319.2147 (59) [M^+] ($C_{13}H_{16}NO_3$ requires 319.2147), 288.4 (14) [M^+−OMe], 246.3 (100) [$C_{15}H_{20}NO_2^+$], 218.3 (48) [$C_{13}H_{16}NO_2^+$], 205.2 (76) [$C_{12}H_{15}NO_2^+$], 191.2 (34) [$C_{11}H_{13}NO_2^+$] 176.2 (14) [$C_{10}H_{10}NO_2^+$].

Fraction 2: ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.78–1.98 (m, 3H, $CHCH_2CH_3$), 1.06–1.78 (m, 7H, 1-H_2, 2-H, 3-H, $CHCH_2CH_3$),1.81–2.18 (m, 2H, $CHCH_2CH_3$, OH), 2.21–2.78 (m, 4H, 4-H_2, 6-H_2), 2.82–3.16 (m, 3H, 7-H_2, 11b-H), 3.52–3.74 (m, 2H, $CHCH_2OH$), 3.82 (s, 6H, OMe), 6.55 (s, 1H, 8-H), 6.69, 6.71 ppm (s, 1H, 11-H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 11.44, 11.57 (C-4'), 20.41, 20.95 (C-3'), 25.00 (C-3), 28.77, 29.61 (C-7), 30.86, 31.27 (C-2), 31.81, 31.96 (C-1), 43,75 (C-2'), 47.69, 47.85 (C-4), 51.42, 52.32 (C-6), 55.72, 55.82, 55.92 (OMe), 56.85, 56.91 (C-11b), 62.11, 62.22 (C-1'), 108.2, 108.5 (C-8), 111.7, 111.7 (C-1), 126.7, 126.8 (C-7a), 128.6, 128.7 (C-11a), 147.3 ppm (C-9, C-10); UV/Vis (acetonitrile): λ_{max} (lg ε) = 201.5 (4.556), 286.0 nm (3.506); IR (film): $\tilde{\nu}$ = 3361 (OH), 2927 (C-H), 2855 (OMe), 1463 (CH_2), 1356 (CH_3), 855 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 319.2147 (59) [M^+] ($C_{13}H_{16}NO_3$ requires 319.2147), 288.4 (12) [M^+−OMe], 246.3 (100) [$C_{15}H_{20}NO_2^+$], 218.3 (45) [$C_{13}H_{16}NO_2^+$], 205.2 (72) [$C_{12}H_{15}NO_2^+$], 191.2 (38) [$C_{11}H_{13}NO_2^+$] 176.2 (14) [$C_{10}H_{10}NO_2^+$].

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[16] X-ray crystallography: Crystals were mounted on a glass fibre in rapidly cooled perfluoropolyether. Data collection was performed at 133(2) K on a four-circle diffractometer equipped with a Stoe fine-focus sealed tube X-ray generator (graphite monochromated $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å), a Siemens CCD area detector and Huber goniometer. Structures were solved by direct methods using SHELXS-97[17] and refined against F^2 on all data by full-matrix least-squares with the program SHELXL-97.[18] Non-hydrogen atoms were refined anisotropically, hydrogen atoms were included at geometrically calculated positions and refined using a riding model with isotropic displacement parameters constrained to multiple U_{eq} values of the attached atoms. Crystal data of compound **4**: $C_{20}H_{29}NO_4$, $M_r = 347.44\ g\,mol^{-1}$, orthorhombic, space group $P2_12_12_1$, $a = 8.0175(16)$, $b = 13.628(3)$, $c = 17.375(4)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1898.5(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.216\ Mg\,m^{-3}$, $F(000) = 752$, $\mu = 0.084\ mm^{-1}$, 14949 reflections measured, 2Θ range from 1.90 to 24.71° ($0 \le h \le 9$, $0 \le k \le 16$, $0 \le l \le 20$), 1868 independent reflections (99.9% of the unique data), data/restraints/parameters = 1868/0/230, $R1 = 0.0363$ [reflections with $I > 2\sigma(I)$], $wR2 = 0.0889$ (all data), goodness-of-fit on $F^2 = 1.095$, largest electron difference density peak and hole = 0.148 and −0.161 e Å^{-3}, absolute structure parameter = −1.0(15). Crystal data of compound **22**: $C_{20}H_{29}NO_4$, M = 347.44 g mol^{-1}, orthorhombic, space group $P2_12_12_1$, $a = 5.5259(11)$, $b = 14.402(3)$, $c = 23.554(5)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1874.5(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.231\ Mg\,m^{-3}$, $F(000) = 752$, $\mu = 0.085\ mm^{-1}$, 12539 reflections measured, 2Θ range from 2.83 to 27.52° ($0 \le h \le 7$, $0 \le k \le 18$, $0 \le l \le 30$), 2497 independent reflections (99.6% of the unique data), data/restraints/parameters = 2497/0/230, $R1 = 0.0358$ [reflections with $I > 2\sigma(I)$], $wR2 = 0.0950$ (all data), goodness-of-fit on $F^2 = 1.058$, largest electron difference density peak and hole = 0.224 and −0.162 e Å^{-3}, absolute structure parameter = −0.2(13). CCDC-226496 (**4**) and CCDC-226497 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

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