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Synthesis of 2,3-*cis* Stereomeric Emetamines *via Reissert* Compounds

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Summary. Alkylation of *Reissert* compounds with certain benzoquinolizinone derivatives followed by hydrolytic cleavage afforded the core of the title compounds in a two step sequence. Finally, the lactam intermediates were reduced with *DIBAH* giving the target compounds, the structural and stereochemical assignments of which were achieved by ^{13}C NMR spectroscopy.

Keywords. Alkaloids; Benzo[*a*]quinolizinones; *cis*-Emetamines; *Reissert* compounds.

Introduction

Emetamine (**1**) belongs to the group of emetine alkaloids, the main components of the well known drug ipecac which represents the dried roots of either *Cephaelis ipecacuanha* or *Cephaelis acuminata* belonging to the plant family of Rubiaceae [1, 2]. Another important source for emetine alkaloids is *Alangium lamarckii*, Alangiaceae.

Ipecac has been used in therapy since the 16th century, especially as an emetic and expectorant [3], later on it has been administered against amebic dysentery. Today, its application as an expectorant in treatment of bronchitis is obsolet because of the possible serious side actions, only standardized tinctures or syrups [3] are yet used as emetics especially for emergencies resulting from drug overdose and poisening. In the same sense, emetamine (**1**) in combination with the other emetine alkaloids has been used to prevent drug overdoses by adding it to oral pharmaceuticals in a specified amount, which causes no emesis, if the medicament is ingested normally, but if overdosed, emesis does occur [4].

In contrast to emetine [5, 6], very little is known about the pharmacological potential of emetamine (**1**) concerning the pure compound. Until now, only a single publication is available reporting several properties *e.g.* the dilation of the coronary vessels or its lethal dose; furthermore, depending from the doses the blood pressure and the respiration are depressed [7]. Obviously, current investigations concerning the pharmacodynamical and pharmacokinetical properties of emetamine are lacking. The low natural occurrence (*ca.* 0.005%, [8]) and, consequently, the restricted availability of the pure alkaloid may be a possible reason for it. From this view efficient synthesis accesses of the alkaloid were desirable.

Until now two synthesis routes to emetamine (**1**) have been published. For the first time it has been prepared by dehydrogenation of emetine under retention of the *trans* configurations concerning both the fusion of rings B and C and the attachment of the substituents at C2 and C3 [9]. The main features of the second pathway were the reaction of a benzo[*a*]quinolizidinylacetic acid with a 2-methoxyphenethylamine affording the corresponding amide followed by its cyclization according to *Bischler-Napieralski* [10, 11].

In a preceding paper we reported the synthesis of benzo[*a*]quinolizidinones **5**, **6**, **12**, and **13**, which – in comparison to the emetine-alkaloids – exhibited an unnatural *cis*-configuration concerning both the attachment of the substituents at C2 and C3 and

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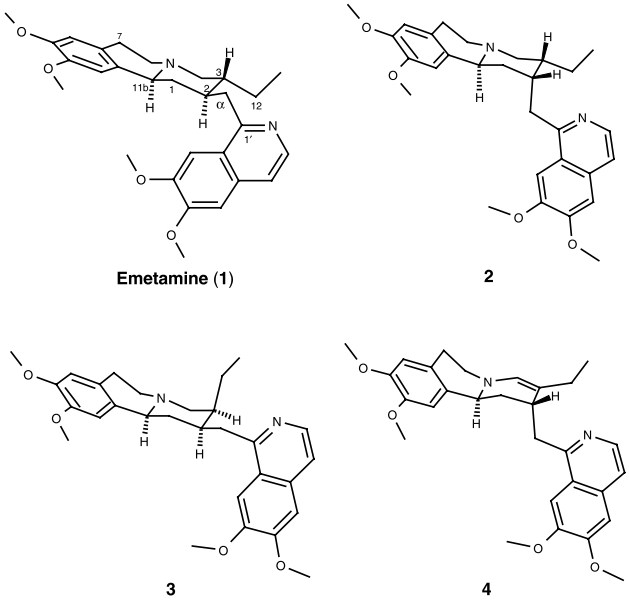


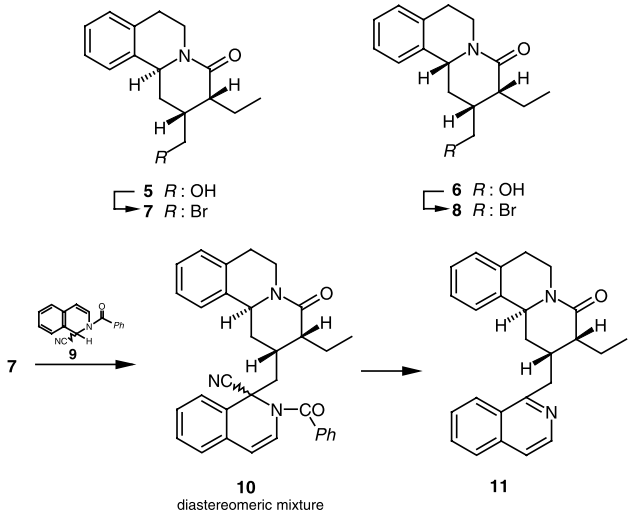
Fig. 1. Stereochemistry of emetamine (**1**) and related target compounds **2**–**4**

additionally, in the compounds **6** and **13**, the fusion of the rings B and C [12]. We assumed these compounds to be suitable synthons for the approach to unnatural, hitherto unknown emetamines **2** and **3** using our strategy *via Reissert* compounds. Herein we like to report the outcome of these investigations.

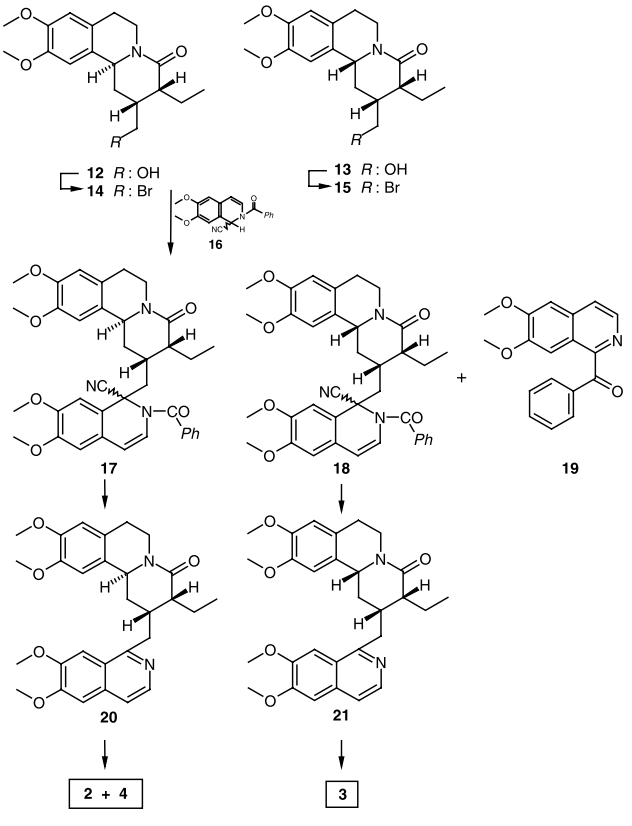
Results and Discussion

Initially, the principle of our pathway was tested in a model reaction (Scheme 1). Thus, after transforming the unsubsituted epimeric 2,3-*cis*-configured carbinols **5** and **6** [12] to the corresponding bromides **7** and **8**, the (*2R*,*3R*,*11bS*)-epimer **7** was reacted with the *Reissert* compound **9** of isoquinoline affording a diastereomeric mixture of the alkylation product **10**. This could be readily hydrolized to the diastereomeric pure parent compound **11** exhibiting the same configuration at the C-atoms mentioned in the educt **7** (Scheme 1).

Similarly the dimethoxy educts both the (*11bS*)- as well as the (*11bR*)-epimer **12** and **13** were transformed to the bromides **14** and **15** which on reaction with the dimethoxy-*Reissert* compound **16** provided the expected intermediates **17** and **18** each as a diastereomeric mixture. The latter was easily separable giving the pure diastereomers **18a** and **18b**. Furthermore, a small amount of 1-benzoyl-6,7-dimethoxyisoquinoline (**19**) could be detected by TLC. The hydrolytic cleavage of **17** and **18** afforded in excellent yields the pure diastereomeric lactames **20** and **21** with restored isoquinoline moieties. Finally, their reduction with *DIBAH* gave the diastereomeric title compounds **2** and **3**, the former being accompanied with the same amout of the $\Delta^{3,4}$-dehydroemetamine **4**.



Scheme 1



Scheme 2

The stereochemistry of the target compounds **2** and **3** as well as of the dehydroproduct **4** could be deduced from those of the known educts **12** and **13**. In addition, the NMR spectra of the natural emetamine (**1**) turned out to be also very helpful for a full stereomeric characterization of the title compounds. Because corresponding data were lacking in the literature, an analytical sample of **1** was prepared from natural emetine according to Ref. [9] giving a mass spectrum which was full in line with that previously published [13] (see Exp.).

Following the presented synthesis route, the bromination of the educts **5**, **6**, **12**, and **13** to the halogenides **7**, **8**, **14**, and **15** proceeded with retention of the configurations at the atoms C2, C3, and C11b as established by their consistent ^{13}C NMR values. The same was true for the *Reissert* compounds **10**, **17**, and **18** with the exception of the noticeable diamagnetic shifts of the δ-values of C2 obviously caused by the adjacent *N*-benzoyl and nitrile functions. Since the latter generated a new chiral center at C1′, the aforementioned *Reissert* compounds accumulated as diastereomeric mixtures, thus each exhibiting double peaks in the ^{13}C NMR spectra (see Exp.).

The rebuilding of the isoquinoline moiety affording the emetaminone derivatives **11**, **20**, and **21** slightly redeshielded, as expected, the C2 atom ($\delta\sim$3 ppm), otherwise the rest of the shifts of the crucial atoms, *e.g.* C1, C3, C6, C7, and C11b were found in the range of those of the precursors.

The final transformation of the lactams **20** and **21** to the target amines **2** and **3** differently took place concerning the stereochemistry. Thus, the reduction of **20** was found proceeding under retention, but that of **21** under complete inversion of the configurations at atoms C2, C3, and C11b with respect to the educt, corresponding to relative configurations (*2S,3R,11bS*) or (*2R,3S,11bR*) for **2**, and (*2R,3S,11bS*) or (*2S, 3R,11bR*) for **3**, *i.e.* being equivalent with 2a/3e and 2e/3a positions of the substituents at atoms C2 and C3. These assignments could be definitely deduced from the ^{13}C NMR spectra. Thus, the δ-values of C11b, C4, and Cα in **2** showed a marked upfield shift in comparison to those of the natural 2,3-*trans*-configured emetamine (**1**) ($\delta = 57.39$, 57.40, and 31.23 *versus* 62.49, 61.41, and 38.82 ppm) caused by an axial positioned C2 substituent and the thereby resulting γ-effect. In **3** the shifts of C2, C11b, and Cα are in the same range as those of the natural emetamine (**1**) ($\delta = 41.38$, 63.20, and 38.99 *versus* 41.65, 62.49, and 38.82 ppm), *i.e. trans* fusion of the rings B and C and equatorial attachment of Cα. In contrast, the axial position of the ethyl substituent caused the expected upfield shift of C1 and C12 ($\delta = 33.72$ and 18.11 *versus* 37.75 and 23.96 ppm).

Concerning the stereochemistry of the concomitant product **4** the C2 substituent should be positioned pseudoaxially (ψ-a) due to the 1,2-allylic strain ($A^{1,2}$) in the dehydrogenated C ring [14–16]. Aditionally, the favored ψ-a position was confirmed by the similar chemical shifts of C2 in comparison to that of **2** ($\delta = 36.27$ *versus* 35.00 ppm). In contrast, the δ-values of C1 and C11b exhibited a noted upfield shift ($\delta = 31.16$ and 51.17 *versus* 34.49 and 57.39 ppm). No adequate explanation for this result could be given because – with the exeption of strained oligocyclic alkenes as *e.g.* bornene [17] – no detailed ^{13}C NMR investigations especially focused on non-bridged cyclohexenes or on related compounds containing the cyclohexene core were available. However, the shifts observed were in good accordance with those of a similar, B/C *trans* configured $\Delta^{3,4}$-benzoquinolizidine derivative reported in the literature ($\delta = 30.7$ and 51.9 ppm) [18].

Conclusions

A short route to 2,3-*cis* configured emetamines **2** and **3** has been opened starting from the recently synthesized stereomeric benzo[*a*]quinolizin-4-ones **5**, **6**, **12**, and **13**. These were reacted with isoquinoline *Reissert* compounds **9** and **16** providing the key intermediates of the title compounds **17** and **18**. The approach presented should permit the preparation of substantial quantities of the target substances needed for systematic biological tests.

Experimental

Melting points are measured with a Büchi Melting Point B-545. IR: Perkin Elmer FT-IR Paragon 1000 and Jasco FT-IR 410. NMR: Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz, $CDCl_3$, *TMS* as internal reference); MS (70 eV): Hewlett Packard MS-Engine. Elemental analyses: Heraeus CHN-Rapid; the results are in good agreement with the calculated values. Thin layer chromatography (TLC): aluminum sheets Kieselgel 60 F_{254} (Merck), thickness of layer 0.2 mm. Flash chromatography (FC): ICN-SiliTech 32–36, 60 A. NaH (60% dispersion in mineral oil); isoquinoline and dimethoxyisoquinoline *Reissert* compounds **9** and **16** were prepared according to Ref. [19]. Di*iso*butylaluminumhydrid (*DIBAH*): 45% solution in toluene.

Emetamine (**1**)
A suspension of 576 mg (1.04 mmol) emetine dihydrochloride hydrate (Fluka) and 1.1 g (10.4 mmol) Na_2CO_3 in 20 cm^3 $CHCl_3$ was stirred for 15 h at ambient temperature. Then the $CHCl_3$ phase was decanted and the solid washed with the same solvent. After evaporating the combined organic phases *in vacuo* 118 mg 10% palladium on charcoal was added to the oily residue and the mixture was heated for 15 min at 180–190°C under N_2. The cold mixture was treated with *Et*OH and then the catalyst was filtered off by a glass frit. After removing the solvent *in vacuo* the reddish oily residue was purified by FC (*Et*OAc:*Me*OH:ethyldimethylamine = 19:1: 0.5). Yield 91 mg (18%; Ref. [9]: 11%); TLC (see FC): $R_f = 0.45$ (emetine: $R_f = 0.35$); MS (EI): m/z (%) = 476 ($M^{+\cdot}$, 13), 461 ($M^{+\cdot}$ – CH_3, 10), 287 (28), 272 (100), 258 (50), 244 (78), 203 (90); ^{1}H NMR ($CDCl_3$): $\delta = 8.38$ (d, $J = 5.9$ Hz, 3′-H), 7.40 (d, $J = 5.5$ Hz, 4′-H), 7.37, 7.08, 6.52, and 6.29 (each s, each 1H, 8-H, 11-H, 5′-H, 8′-H), 4.02, 3.99, 3.80, and 3.59 (each s, 4 OCH_3), 3.66 (dd, $J = 13.7/3.1$ Hz, 1H, α-CH_2), 3.16–3.06 and 3.01–2.89 (each m, 2H + 3H, 4-H, 7-H, 6-H, 11b-H, α-CH_2), 2.60 and 2.44 (each m, each 1H, 7-H, 6-H), 2.10–1.94 (m, 4H, 4-H, 2-H, 1-H_a, 12-H_a), 1.74–1.66 and 1.37–1.25 (each m, 2 + 1H, 3-H, 1-H_b, 12-H_b), 1.03 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 158.64$ (C-1′), 152.55, 149.89, 147.41, and 147.02 (C-9, C-10, C-6′, C-7′), 141.01 (C-3′), 133.15, 130.08, 126.57, and 123.44 (C-7a, C-11a, C-4a′, C-8a′), 118.08 (C-4′), 111.49, 108.34, 105.41, and 103.92 (C-8, C-11, C-5′, C-8′), 62.49 (C-11b), 61.41 (C-4), 56.00 (2 OCH_3), 55.82 and 55.74 (each OCH_3), 52.61 (C-6), 42.58 (C-3), 41.65 (C-2), 38.82 (Cα), 37.75 (C-1), 29.10 (C-7), 23.96 (C-12), 11.48 (C-13) ppm.

General Procedure for the Synthesis of the Bromides ***7***, ***8***, ***14***, *and* ***15***
A solution of the carbinol **5**, **6**, **12**, or **13**, CBr_4, and Ph_3P in dry CH_3CN or CH_2Cl_2 was stirred at ambient temperature for 15 min. After removing the solvent *in vacuo*, the residue was taken up in few cm^3 $CHCl_3$ and purified by FC (*n*-hexane:*Et*OAc = 1:1).

(2R,3R,11bS/2S,3S,11bR)-2-Bromomethyl-3-ethyl-1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-one
(**7**, $C_{16}H_{20}NOBr$)
Starting from 505 mg (1.9 mmol) **5**, 646 mg (1.9 mmol) CBr_4, 511 mg (1.9 mmol) Ph_3P, 10 cm^3 CH_3CN; first *n*-hexane was used as eluent followed by the solvent mixture mentioned; yield: 492 mg (79%) oil; TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.60$; (educt **5**: $R_f = 0.10$); MS (EI): m/z (%) = 323 ($M^{+\cdot}$, 100), 322 ($M^{+\cdot}$-1, 93), 321 ($M^{+\cdot}$, 100), 320 ($M^{+\cdot}$-1, 78), 242 (32), 200 (70), 173 (52), 132 (98); ^{1}H NMR ($CDCl_3$): $\delta = 7.25$–7.13 (m, 4 arom H), 4.80–4.74 (m, 2H, 6-H and 11b-H), 3.62 and 3.33 (each dd, $J = 10.3/4.5$ and 11.7/10.6 Hz, each 1H, CH_2Br), 3.02–2.94 (m, 2H, 1-H and 7-H), 2.86 and 2.74 (each dt, $J = 11.9/3.6$ and 15.8/3.2 Hz, 2H, 6-H and 7-H), 2.55–2.48 (m, 2-H), 2.40 (dt, $J = 9.5/5.5$ Hz, 3-H), 2.23–2.13 and 1.43–1.31 (each m, each 1H, CH_2), 1.92 (ddd, $J = 13.8/11.0/2.9$ Hz, 1H, 1-H), 1.04 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.82$ (CO), 137.25 and 134.98 (C-7a and C-11a), 128.98, 126.77, 126.54, and 124.42 (4 arom C), 52.25 (C-11b), 46.71 (C-3), 40.12 (C-6), 34.61 (C-2), 32.41 (C-1), 31.71 (CH_2Br), 28.71 (C-7), 20.40 (CH_2), 12.12 (CH_3) ppm.

(2R,3R,11bR/2S,3S,11bS)-2-Bromomethyl-3-ethyl-1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-one
(**8**, $C_{16}H_{20}NOBr$)
Starting from 505 mg (1.9 mmol) **6**, reagents and work-up as given under **7**; yield: 492 mg (79%) oil; TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.50$; ^{1}H NMR ($CDCl_3$): $\delta =$ 7.26–7.15 (m, 4 arom H), 4.81–4.77 (m, 1H, 6-H), 4.69 (dd, $J = 11.4/5.1$ Hz, 11b-H), 3.47 and 3.32 (each dd, $J = 10.1/6.1$ and 10.1/8.2 Hz, CH_2Br), 2.93–2.90 (m, 2H, 6-H and 7-H), 2.81–2.76 (m, 1H, 7-H), 2.64–2.53 (m, 3H, 1-H, 2-H, and 3-H), 1.74–1.66 (m, 1H, 1-H), 1.61–1.54 (m, CH_2), 1.06 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 171.16$ (CO), 136.82 and 134.88 (C-7a and C-11a), 128.99, 126.93, 126.67, and 125.07 (4 arom C), 55.66 (C-11b), 45.41 (C-3), 39.43 (C-6), 37.67 (C-2), 35.14 (CH_2Br), 32.99 (C-1), 29.12 (C-7), 20.22 (CH_2), 13.03 (CH_3) ppm.

(2R,3R,11bS/2S,3S,11bR)-2-Bromomethyl-3-ethyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-one (**14**, $C_{18}H_{24}NO_3Br$)
Starting from 846 mg (2.65 mmol) **12**, 880 mg (2.65 mmol) CBr_4, 696 mg (2.65 mmol) Ph_3P, 8 cm^3 CH_2Cl_2; treatment of the colourless oil with Et_2O gave an amorphous solid; yield: 820 mg (81%); mp 112–113°C; TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.40$ (R_f educt 0.1, Ph_3PO 0.25, Ph_3P and CBr_4 each 0.9); IR (KBr): $\bar{\nu} = 1640$ (CO), 658/536 (C-Br) cm^{-1}; MS (EI): m/z (%) = 383 ($M^{+\cdot}$, 43), 382 ($M^{+\cdot}$-1, 42), 381 ($M^{+\cdot}$, 41), 380 ($M^{+\cdot}$-1, 39), 352 (33), 350 (30), 272 (41), 258 (30), 191 (100), 176 (23); ^{1}H NMR ($CDCl_3$): $\delta = 6.70$ and 6.22 (each s, arom 11-H and 8-H), 4.82 (ddd, $J = 12.3/5.0/2.6$ Hz, 1H, 6-H), 4.70 (dd, $J = 10.2/5.4$ Hz, 11b-H), 3.89 and 3.87 (each s, each OCH_3), 3.62 and 3.33 (each dd, $J = 10.4/4.5$ Hz, CH_2Br), 2.98–2.88 (m, 2H, 1-H and 7-H), 2.81 (dt, $J = 12.0/3.4$ Hz, 1H, 6-H), 2.60 (m, 1H, 7-H), 2.53–2.46 (m, 2-H), 2.39 (dt, $J = 9.3/5.5$ Hz, 3-H), 2.22–2.11 and 1.43–1.32 (each m, each 1H, CH_2), 1.93 (ddd, $J = 13.5/10.4/3.1$ Hz, 1H, 1-H), 1.04 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.82$ (CO), 147.97 (C-9), 147.77 (C-10), 129.06 (C-7a), 127.29 (C-11a), 111.66 (C-8), 107.79 (C-11), 56.19 and 55.89 (2 OCH_3), 52.20 (C-11b), 46.80 (C-2), 40.34 (C-6), 34.74 (C-3), 32.38 (C-1), 31.98 (CH_2Br), 28.26 (C-7), 20.44 (CH_2), 12.19 (CH_3) ppm.

(2R,3R,11bR/2S,3S,11bS)-2-Bromomethyl-3-ethyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-one (**15**, $C_{18}H_{24}NO_3Br$)
Starting from 2.14 g (6.70 mmol) **13**, 2.22 g (6.70 mmol) CBr_4, 1.89 g (6.70 mmol) Ph_3P, 20 cm^3 CH_2Cl_2; treatment of the colourless oil with Et_2O gave an amorphous solid; yield: 2.30 g (90%); mp 118–119°C; TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.30$ (R_f of the byproducts see under **14**); IR (KBr): $\bar{\nu} = 1639$ (CO), 647 (C-Br) cm^{-1}; MS (EI): m/z (%) = 383

($M^{+\bullet}$, 20), 382 ($M^{+\bullet}$-1, 21), 381 ($M^{+\bullet}$, 19), 380 ($M^{+\bullet}$-1, 15), 352 (15), 350 (10), 303 (21), 261 (25), 191 (100), 176 (23); ^{1}H NMR ($CDCl_3$): $\delta = 6.68$ and 6.64 (each s, arom 11-H and 8-H), 4.86–4.79 (m, 1H, 6-H), 4.63 (dd, $J = 11.1/5.1$ Hz, 11b-H), 3.89 and 3.87 (each s, each OCH_3), 3.47 and 3.32 (each dd, $J = 10.3/5.7$ and $10.1/8.3$ Hz, CH_2Br), 2.90–2.80 (m, 2H, 6-H and 7-H), 2.70–2.50 (m, 4H, 7-H, 2-H, 3-H, and 1-H), 1.72–1.61 (m, 1H, 1-H), 1.61–1.53 (m, CH_2), 1.05 (t, $J = 7.5$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 171.07$ (CO), 148.02 (C-9), 147.85 (C-10), 128.58 (C-7a), 127.09 (C-11a), 111.61 (C-8), 108.38 (C-11), 56.21 and 55.90 (each OCH_3), 55.39 (C-11b), 45.32 (C-2), 39.49 (C-6), 37.58 (C-3), 35.08 (CH_2Br), 33.04 (C-1), 28.61 (C-7), 20.16 (CH_2), 12.98 (CH_3) ppm.

*General Procedure for the Alkylation of the Reissert compounds **9** and **16***

A solution of the *Reissert* compound in dry *DMF* was stirred for 20–30 min under Ar or N_2 and then it was treated with NaH. After the colour of the mixture had changed to dark red, a solution of the bromide **7**, **8**, **14**, or **15** in dry *DMF* was added and stirring was continued at ambient temperature for another h under inert gas atmosphere. The mixture was cautiously poured into a mixture of *Et*OAc and H_2O and then the aqueous layer was extracted with *Et*OAc. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residual *DMF* was removed in high *vacuo* at 80°C. The remaining crude product was purified by FC.

(1RS,2S,3R,11bS/1RS,2R,3S,11bR)-2-Benzoyl-1-(3-ethyl-4-oxo-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-2-ylmethyl)-1,2-dihydroisoquinoline-1-carbonitrile (**10**, $C_{33}H_{31}N_3O_2$, *diastereomeric mixture*)

Starting from 816 mg (3.1 mmol) **9**/10 cm^3 *DMF*, 125 mg (3.1 mmol) NaH, 505 mg (1.57 mmol) **7**/1 cm^3 *DMF*, 50 cm^3 *Et*OAc/100 cm^3 H_2O, 3×100 cm^3 *Et*OAc; FC: First the excess educt **9** was eluated with *n*-hexane:*Et*OAc = 3:1, then the product with *n*-hexane:*Et*OAc = 1:1. Yield: 526 mg (67%) glassy foam; TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.40$ (educt **9**: $R_f = 0.70$); IR (film): $\bar{\nu} = 2244$ (CN), 1674, 1643, and 1635 (CO) cm^{-1}; MS (EI): m/z (%) = 501 ($M^{+\bullet}$, 1), 370 (31), 198 (100), 143 (84), 105 (94); ^{1}H NMR ($CDCl_3$): $\delta = 7.85$–7.07 (m, 13 arom H), 6.53, 6.50, 5.83, 5.80 (each d, each $J = 7.9$ Hz, each 0.5H, 3′-H and 4′-H), 5.04 and 4.65 (each dd, $J = 10.7/5.6$ and $11.2/5.7$, each 0.5H, 11b-H), 4.86–4.76 (m, 1H, 6-H), 3.19 (dt, $J = 13.5/5.0$ Hz, 0.5H, 1-H), 3.02–2.65 (m, 3H, 7-H and 6-H), 2.54–2.42 (m, 2H), 2.38–2.32 (m, 1H), 2.15–1.96 (m, 2.5H), 1.84 and 1.69–1.62 (each m, each 0.5H, 1-H), 1.33–1.25 and 1.07–0.99 (each m, each 0.5H), 0.85 and 0.49 (each t, $J = 7.2$ and 7.4 Hz, each 1.5H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.49$, 170.46, 169.64, 169.41, 137.82, 137.70, 134.84, 134.81, 133.06, 132.93, 132.32, 132.27, 129.99, 129.91, 129.72 (2C), 129.57 (2C), 129.20, 129.10 (2C), 129.00 (2C), 128.81 (3C), 128.71, 127.97, 127.83, 127.16, 126.86 (2C), 126.72 (2C), 126.67 (2C), 126.54 (2C), 125.67, 125.48, 125.03, 124.47, 118.64 (CN), 117.95 (CN), 107.54, 107.00, 60.00, 59.54, 53.29/53.18 (C-11b), 48.53/48.29 (C-3), 40.03/39.92 (C-6), 34.12/33.97 (C-1), 33.97/33.13 (C-2), 28.99 (2 C-7), 28.91/27.92 (Cα), 20.27/19.92 (C-12), 12.15/11.37 (C-13) ppm.

(1RS,2S,3R,11bS/1RS,2R,3S,11bR)-2-Benzoyl-1-(3-ethyl-9,10-dimethoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-2-ylmethyl)-6,7-dimethoxy-1,2-dihydroisoquinoline-1-carbonitrile (**17**, $C_{37}H_{39}N_3O_6$, *diastereomeric mixture*)

Starting form 4.27 g (13.3 mmol) **16**/35 cm^3 *DMF*, 534 mg (13.3 mmol) NaH, 2.55 g (6.67 mmol) **14**/13 cm^3 *DMF*, 200 cm^3 *Et*OAc/1000 cm^3 H_2O, 3×200 cm^3 *Et*OAc; FC: First the excess educt **16** and the byproducts were eluated with *n*-hexane:*Et*OAc = 1:1, then the product was obtained with *Et*OAc. Yield: 2.97 g (72%); TLC (*n*-hexane:*Et*OAc = 1:1 (or *Et*OAc)): $R_f = 0.11$ (0.56) (educt **16**: $R_f = 0.53$ (0.85); 1-cyano-6,7-dimethoxyisoquinoline: $R_f = 0.39$ (0.71); 1-benzoyl-6,7-dimethoxyisoquinoline **19**: $R_f = 0.47$ (0.78)); IR (KBr): $\bar{\nu} = 2239$ (CN), 1673/1641 (CO) cm^{-1}; MS (EI): m/z (%) = 490 (38), 459 (2), 258 (100), 203 (43), 105 (19), 77 (15); ^{1}H NMR ($CDCl_3$): $\delta = 7.65$–7.42 (m, 5 arom H), 7.31, 7.22, and 6.78 (each s, each 0.5H), 6.63 (s, 1H), 6.58, 6.57, and 6.46 (each s, each 0.5H), 6.43, 6.41, 5.77, and 5.72 (each d, $J = 5.8$, 5.9, 7.9 and 7.9 Hz, each 0.5H), 4.94 (dd, $J = 9.6/5.6$ Hz, 0.5H), 4.88–4.81 (m, 1H), 3.97, 3.90, 3.87, 3.85, 3.84, 3.83, and 3.77 (each s, 4 OCH_3), 2.97–2.81 and 2.80–2.68 (each m, each 1.5H), 2.61–2.55 (m, 1H), 2.48–2.31 (m, 2.5H), 2.18–2.09, 2.08–2.00, and 2.00–1.92 (each m, each 1H), 1.72–1.65, 1.29–1.22, and 1.15–1.08 (each m, each 0.5H), 0.85 and 0.61 (each t, each $J = 7.4$ Hz, each 1.5H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.55$ (CO), 170.38 (CO), 169.65 (CO), 169.35 (CO), 150.05 (2C), 149.37 (2C), 148.78 (2C), 147.77 (2C), 133.18, 132.96, 132.18, 132.08, 129.61 (2C), 129.36 (2C), 129.30 (2C), 128.72 (4C), 127.05, 126.95, 125.19, 125.06, 122.26 (2C), 121.48, 119.88, 118.83, 118.22, 111.62 (2C), 110.87, 110.22, 108.53, 108.47, 108.20, 107.81, 107.65, 106.97, 59.61, 59.32, 56.62 (2C), 56.30 (2C), 56.13 (2C), 55.87 (2C), 53.31/52.79 (C-11b), 48.34/48.34 (C-3), 40.24/39.88 (C-6), 34.20/34.20 (C-2), 32.86/32.60 (C-1), 28.91/28.06 (C-7), 28.44/28.44 (Cα), 20.20/19.99 (C-12), 12.03/11.70 (C-13) ppm.

(1RS,2S,3R,11bR/1RS,2R,3S,11bS)-2-Benzoyl-1-(3-ethyl-9,10-dimethoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-2-ylmethyl)-6,7-dimethoxy-1,2-dihydroisoquinoline-1-carbonitrile (**18**, $C_{37}H_{39}N_3O_6$, *diastereomeric mixture*)

Starting from 2.18 g (6.8 mmol) **16**/22 cm^3 *DMF*, 273 mg (6.8 mmol) NaH, 1.3 g (3.4 mmol) **15**/13 cm^3 *DMF*, 100 cm^3 *Et*OAc/400 cm^3 H_2O, 3×100 cm^3 *Et*OAc; FC: First the excess educt **16** and the byproducts were eluated with *n*-hexane:*Et*OAc = 1:1, then the product was obtained with *Et*OAc. Diastereomer **18a** shortly crystallized from the eluat, diastereomer **18b** could be obtained from the mother liquor. Total yield: 1.25 (59%) colourless crystals; TLC (*n*-hexane:*Et*OAc = 1:1 (or *Et*OAc)): $R_f = 0.15$ (0.45) (educt **16**: $R_f = 0.60$ (0.80); 1-cyano-6,7-dimethoxyisoquinoline: $R_f =$ 0.38 (0.70); 1-benzoyl-6,7-dimethoxyisoquinoline **19**: $R_f =$

2150.48 (0.75)); IR (KBr): $\bar{\nu} = 2239$ (CN), 1671/1641 (CO) cm^{-1}; MS (EI): m/z (%) = 490 (20), 459 (6), 258 (17), 203 (100), 131 (32), 105 (48), 77 (35).

18a: ^1H NMR ($CDCl_3$): $\delta = 7.56–7.52$ (m, 3 arom H), 7.46–7.42 (m, 2 arom H), 7.26, 6.62, 6.60, and 6.48 (each s, each 1H, 4 arom H), 6.39 and 5.72 (each d, $J = 7.8$ and 7.9 Hz, 3-H and 4-H), 4.84–4.76 (m, 1H), 4.48 (dd, $J = 10.7/5.2$ Hz, 11b-H), 3.96, 3.91, 3.86, and 3.80 (4s, 4 OCH_3), 2.83–2.74 (2 m, each 1H), 2.63 (m, 1H), 2.43–2.29 (m, 5H), 1.60–1.40 (m, 3H), 0.93 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 171.54$ (CO), 169.59 (CO), 149.95, 149.33, 147.91, 147.84, 133.23, 131.98, 129.26 (2C), 128.93, 128.68 (2C), 126.91, 124.93, 122.22, 121.26, 118.21, 111.57, 110.00, 108.34 (2C), 107.41, 59.59, 56.47, 56.11, 56.03, 55.92, 55.67 (C-11b), 47.19 (C-3), 40.31 (Cα), 39.26 (C-6), 34.30 (C-1), 30.85 (C-2), 28.66 (C-7), 20.81 (C-12), 12.88 (C-13) ppm.

18b: ^1H NMR ($CDCl_3$): $\delta = 7.63–7.44$ (m, 6 arom H), 6.62, 6.59, and 6.47 (each s, each 1 arom H), 6.44 and 5.69 (each d, $J = 7.9$ and 8.1 Hz, 3-H and 4-H), 4.81–4.72 (m, 1H), 4.44 (dd, $J = 11.2/5.1$ Hz, 11b-H), 3.96, 3.91, 3.85 and 3.82 (4s, 4 OCH_3), 2.86–2.14 (m, 8H), 1.43–1.35 (m, 3H), 0.88 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.22$ (CO), 169.40 (CO), 150.11, 149.09, 147.90, 147.84, 133.12, 131.96, 129.31 (2C), 128.67 (2C), 127.76, 126.78, 125.30, 122.35, 120.27, 118.36, 111.58, 110.44, 108.37, 107.98, 106.56, 59.61, 56.39, 56.01, 55.63, 55.36, 54.75 (C-11b), 47.40 (C-3), 40.42 (Cα), 39.45 (C-6), 33.99 (C-1), 30.36 (C-2), 28.58 (C-7), 20.71 (C-12), 12.87 (C-13) ppm.

(2R,3R,11bS)-3-Ethyl-2-isoquinolin-1-ylmethyl-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-4-one (**11**, $C_{25}H_{26}N_2O$)

A suspension of 526 mg (1.05 mmol) of the diastereomeric mixture **10** in 15 cm^3 *Me*OH and 0.95 g (2 mmol) 12% KOH was stirred at ambient temperature until the reaction was complete (about 1 h, TLC monitoring). After removing the solvent *in vacuo*, the residue was dissolved in 20 cm^3 H_2O. The solution was acidified with 2*N* HCl and washed with 3×20 cm^3 *Et*OAc. The aqueous layer was rendered alkaline with 50% KOH and extracted with 3×30 cm^3 of the same solvent. The combined organic extracts were washed with 1*N* NaOH, dried (Na_2SO_4), and concentrated *in vacuo* giving a colourless residue, which crystallized from *n*-hexane (15 h). Yield: 313 mg (81%) colourless crystals; mp 133–134°C; TLC (*n*-hexane:*Et*OAc = 1:1): $R_f = 0.2$ (educt: $R_f = 0.4$); IR (film): $\bar{\nu} = 1632$ (CO) cm^{-1}; MS (EI): m/z (%) = 370 ($M^{+\bullet}$, 35), 198 (100), 143 (83) 130 (42); ^1H NMR ($CDCl_3$): $\delta = 8.46$ (d, $J = 5.6$ Hz, 3′-H), 8.15 and 7.86 (each d, $J = 8.4/8.0$ Hz, each 1 arom H), 7.70–7.55 and 7.14–7.05 (each m, each 3 arom H), 6.82 (d, $J = 7.7$ Hz, 1 arom H), 5.19 (dd, $J = 10.9/5.7$ Hz, 11b-H), 4.94–4.86 (m, 1H, 6-H), 3.63 and 3.14 (each dd, $J = 14.2/4.3$ and 14.1/11.9 Hz, CH_2), 3.01–2.97 (m, 2H, 6-H and 7-H), 2.92–2.87 and 2.79–2.74 each m, each 1H), 2.44–2.34 (m, 2H), 2.29 (dt, $J = 13.5/5.1$ Hz, 1H, 1-H), 1.77–1.60 (m, 2H), 1.18 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.96$ (CO), 160.07 (C-1′), 141.76 (C-3′), 138.25, 136.37, 134.97, 129.95, 128.83, 127.64, 127.29, 127.11, 126.36, 126.25, 124.79, 124.39, 119.63, 52.73 (C-11b), 47.79 (C-3), 40.05 (C-6), 32.84 (C-1), 32.49 (Cα), 32.49 (C-2), 28.93 (C-7), 20.76 (C-12), 12.74 (C-13) ppm.

*General Procedure for the Synthesis of the Diastereomeric 4-Oxoemetamines **20** and **21***

A mixture of the *Reissert* compound **17** or **18**, *Me*OH, and 12% KOH was heated at 70°C for 1 h. After removing the solvent *in vacuo*, the residue was taken up in a small quantity of $CHCl_3$, and purified by FC (*Et*OAc:*Me*OH = 9:1).

(2S,3R,11bS / 2R,3S,11bR)-2-(6,7-Dimethoxyisoquinolin-1-ylmethyl)-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-4-one (**20**, $C_{29}H_{34}N_2O_5$)

Starting from 1.1 g (1.77 mol) **17**, 55 cm^3 *Me*OH, 2.86 cm^3 (26.4 mmol) KOH. Yield: 800 mg (92%) colourless oil, which on treatment with Et_2O gave a colourless amorphous solid; mp 169–172°C; TLC (see FC): $R_f = 0.32$ (educt: $R_f = 0.64$); IR (KBr): $\bar{\nu} = 1633$ (CO) cm^{-1}; MS (EI): m/z (%) = 490 ($M^{+\bullet}$, 48), 459 (8), 286 (17), 258 (100), 203 (38), 190 (40); ^1H NMR ($CDCl_3$): $\delta = 8.35$ and 7.45 (each d, each $J = 5.6$ Hz, 3′-H and 4′-H), 7.33, 7.10, 6.59 and 6.31 (each s, each 1H, 5′-H, 8′-H, 8-H, and 11-H), 5.16 (dd, $J = 10.3/5.6$ Hz, 11b-H), 4.97–4.89 (m, 1H, 6-H), 4.04, 4.02, 3.83, and 3.67 (each s, each OCH_3), 3.53 and 3.06 (each dd, $J = 14.0/4.2$ and 13.9/12.2 Hz, each 1H, α-CH_2), 2.98–2.88 (m, 2H), 2.69–2.61 (m, 1H), 2.46–2.34 (m, 2H), 2.23 (dt, $J = 13.5/5.2$ Hz, 1H), 1.77–1.64 (m, 2H), 1.19 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.87$ (CO), 157.48, 152.66, 150.19, 147.65, 147.52, 140.71, 133.23, 130.03, 127.22, 122.87, 118.49, 111.55, 107.95, 105.55, 103.16, 56.04 (2 OCH_3), 55.60 (OCH_3), 55.84 (OCH_3), 52.52 (C-11b), 47.70 (C-3), 40.21 (C-7), 32.98 (C-1), 32.73 (Cα), 32.02 (C-2), 28.46 (C-7), 20.58 (C-12), 12.56 (C-13) ppm.

(2S,3R,11bR/2R,3S,11bS)-2-(6,7-Dimethoxyisoquinolin-1-ylmethyl)-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-4-one (**21**, $C_{29}H_{34}N_2O_5$)

Starting from 123 mg (0.23 mol) **18**, 5 cm^3 *Me*OH, 0.4 cm^3 (3.7 mmol) KOH. Yield: 101 mg (90%) colourless oil; TLC (see FC): $R_f = 0.35$ (educt: $R_f = 0.66$); IR (film): $\bar{\nu} = 1632$ (CO) cm^{-1}; MS (EI): m/z (%) = 490 ($M^{+\bullet}$, 15), 459 (9), 286 (10), 258 (19), 203 (100), 190 (8), 97 (10); ^1H NMR ($CDCl_3$): $\delta = 8.36$ and 7.42 (each d, $J = 5.6$ and 5.4 Hz, 3′-H and 4′-H), 7.20, 7.08, 6.56, and 6.50 (each s, each 1H, 5′-H, 8′-H, 8-H, and 11-H), 4.85–4.81 (m, 1H, 6-H), 4.54 (dd, $J = 10.3/5.8$ Hz, 11b-H), 4.03, 4.02, 3.82, and 3.75 (each s, each OCH_3), 3.35 and 3.10 (each dd, $J = 14.5/4.7$ and 14.5/9.9 Hz, each 1H, α-CH_2), 2.99–2.89 (m, 2-H), 2.91–2.78 and 2.66–2.62 (each m, 2H and 1H, 7-H and 6-H), 2.56 (dt, $J = 8.1/5.1$ Hz, 3-H), 2.44 (dt, $J = 13.6/4.9$ Hz, 1H, 1-H), 1.90–1.69 (m, 1-H and CH_2), 1.09 (t, $J = 7.3$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 172.20$ (CO), 156.86, 152.57, 150.02, 147.72, 147.61, 140.76, 133.10, 129.32, 126.89, 123.09, 118.37, 111.44, 108.33, 105.51, 103.00, 56.03 (3 OCH_3), 55.80 (OCH_3), 55.66 (C-11b), 46.74 (C-3), 39.72 (C-6), 36.50 (Cα), 33.94 (C-2), 33.14 (C-1), 28.68 (C-7), 20.79 (C-12), 13.14 (C-13) ppm.

(2S,3R,11bS/2R,3S,11bR)-2-(6,7-Dimethoxyisoquinolin-1-ylmethyl)-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine (**2**, $C_{29}H_{36}N_2O_4$) *and (2S,11bS/2R,11bR)-2-(6,7-dimethoxyisoquinolin-1-ylmethyl)-3-ethyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2H-benzoquinolizine* (**4**, $C_{29}H_{34}N_2O_4$)

To a solution of 5.35 cm^3 (16.9 mmol) *DIBAH* was dropwise added a solution of 500 mg (1.0 mmol) **20** in 15 cm^3 dry monoglyme under N_2, ice cooling, and stirring. After removing the ice bath stirring was continued for 1 h. The mixture was cautiously diluted with 20 cm^3 *Me*OH and the solid formed was extracted with 3×20 cm^3 of the same solvent. The combined *Me*OH extracts were concentrated *in vacuo* and the residue was separated by FC (SiO_2, *Et*OAc:*Me*OH:ethyldimethylamine = 18:3:0.1). Yield: 140 mg (29%) colourless, fine needles; mp 187°C (Et_2O); TLC: a) (eluent see FC): $R_f = 0.43$ (byproduct **4** (see below): $R_f = 0.22$, detection: spraying with a saturated solution of I_2 in $CHCl_3$, then temporary heating gave citreous spots, or yellow fluorescence in UV ($\lambda = 365$ nm); b) (*Et*OAc:*Me*OH = 18:2): $R_f = 0.10$ (educt **20**: $R_f = 0.40$, detection: *Dragendorff*'s reagent); MS (EI): m/z (%) = 476 ($M^{+\bullet}$, 57), 461 ($M^{+\bullet} - CH_3$, 35), 287 (43), 272 (100), 258 (57), 244 (96), 230 (25), 203 (12); ^{1}H NMR ($CDCl_3$): $\delta = 8.37$ (d, $J = 5.5$ Hz, 3′-H), 7.43 (s, 1 arom H), 7.42 (d, $J = 5.5$ Hz, 4′-H), 7.10, 6.53, and 6.19 (each s, each 1 arom H), 4.03, 3.99, 3.81, and 3.61 (each s, each OCH_3), 3.82 (m, 11b-H), 3.37 (m, α-CH_2), 3.14–3.07 (m, 1H, 7-H), 3.03–2.99 (m, 1H, 6-H), 2.89 ((dd), 1H, 4-H), 2.66–2.54 (m, 4H, 2-H, 4-H, 6-H, and 7-H), 2.10–2.06 and 1.73–1.69 (each m, 2H, 3-H and 1-H), 1.63–1.47 (m, CH_2), 1.40 (m, 1H, 1-H), 1.12 (t, $J = 7.3$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 159.47$ (C-1′), 152.64, 150.03, 147.21, and 147.04 (C-9, C-10, C-6′, C-7′), 140.99 (C-3′), 133.30, 130.31, 126.74, and 123.34 (C-7a, C-11a, C-4a′, and C-8a′), 118.19 (C-4′), 111.43, 108.26, 105.56, and 103.80 (C-8, C-11, C-5′, and C-8′), 57.39 (C-4 and C-11b), 56.09, 55.94, 55.84, and 55.60 (4 OCH_3), 52.35 (C-6), 41.21 (C-3), 36.27 (C-2), 34.49 (C-1), 31.23 (Cα), 29.26, (C-7), 23.95 (C-12), 12.11 (C-13) ppm.

4 (byproduct of **2**): Yield: 170.9 mg (35%) amorph solid; MS (CI): m/z (%) = 475 ($M^{+\bullet}$ +1, 50), 272 (100), 204 (65); ^{1}H NMR ($CDCl_3$): $\delta = 8.40$ (d, $J = 5.7$ Hz, 3′-H), 7.48 (s, 1 arom H), 7.44 (d, $J = 5.6$ Hz, 4′-H), 7.10, 6.55, and 6.53 (each s, each 1 arom H), 5.88 (s, 4-H), 4.17 ((dd), 11b-H), 4.04, 3.99, 3.83, and 3.69 (each s, each OCH_3), 3.75–3.70 and 3.21–3.14 (each m, 1 + 2H, α-CH_2 and 6-H), 3.08 (dt, $J = 11.0/3.6$ Hz, 1H, 6-H), 3.01–2.96 and 2.84–2.79 (each m, each 1H, 7-H and 2-H), 2.65–2.60 ((dt), 1H, 7-H), 2.28 (q, $J = 7.9$ Hz, 12-CH_2), 2.06–2.02 and 1.53–1.45 (each m, each 1H, 1-H), 1.15 (t, $J = 7.32$ Hz, 13-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 157.68$ (C-1′), 151.64, 148.96, 146.22, and 146.16 (C-9, C-10, C-6′, and C-7′), 139.93 (C-3′), 132.18, 128.62, 125.86, and 122.38 (C-7a/C-11a/C-4a′/C-8a′), 131.60 (C-4), 117.28 (C-4′), 114.58 (C-3), 110.35, 107.50, 104.42, and 102.74 (C-8/C-11/C5′/C-8′), 55.05, 54.82, 54.79, and 54.43 (4 OCH_3), 51.17 (C-11b), 48.35 (C-6), 39.26 (Cα), 35.00 (C-2), 31.16 (C-1), 28.77 (C-7), 24.61 (C-12), 12.69 (C-13) ppm.

(2R,3S,11bS/2S,3R,11bR)-2-(6,7-Dimethoxyisoquinolin-1-ylmethyl)-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine (**3**, $C_{29}H_{36}N_2O_4$)

To a solution of 230 mg (0.5 mmol) **21** in 20 cm^3 monoglyme cooled to 0°C and flushed with N_2 for 15 min was added 2.56 cm^3 *DIBAH*. After removing the ice bath the mixture was stirred for 1 h at ambient temperature and thereafter cautiously poured into a mixture of 2 *N* NaOH and *Et*OAc (each 50 cm^3). The aqueous layer was extracted with 3×50 cm^3 of *Et*OAc. The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by FC (*Et*OAc:*Me*OH:ethyldimethylamine = 18:2:0.1). Yield: 135 mg (57%) yellowish, foaming oil, giving a glassy solid; mp 95°C; TLC (see FC): $R_f = 0.60$ (educt: $R_f = 0.30$); MS (EI): m/z (%) = 476 ($M^{+\bullet}$, 29), 461 ($M^{+\bullet} - CH_3$, 23), 441 (13), 287 (30), 274 (44), 272 (100), 244 (62), 203 (29); ^{1}H NMR ($CDCl_3$): $\delta = 8.37$ (d, $J = 5.8$ Hz, 3′-H), 7.42 (d, $J = 5.7$ Hz, 4′-H), 7.37, 7.09, 6.55, and 6.49 (each s, each 1H, 8-H, 11-H, 5′-H, 8′-H), 4.04, 4.01, 3.82, and 3.71 (each s, 4 OCH_3), 3.27 and 3.18 (each dd, $J = 13.8$, 5.9 and 13.6, 8.4 Hz, each 1H, α-CH_2), 3.08 (m, 7-H_a), 3.00–2.94 (m, 1-H_a and 11b-H), 2.85 (dd, $J = 11.0$, 6.0 Hz, 6-H_a), 2.57 (dd, $J = 15.7$, 3.4 Hz, 7-H_b), 2.49–2.38 (m, 6-H_b and 2-H), 2.32–2.29 and 2.08–2.04 (each m, 1-H_b and 4-H_a), 1.88–1.75 (m, 12-H_a), 1.62–1.49 (m, 4-H_b, 12-H_b, 3-H), 0.92 (t, $J = 7.4$ Hz, C-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 158.69$ (C-1′), 152.55, 149.87, 147.38, and 147.09 (C-9, C-10, C-6′, C-7′), 141.05 (C-3′), 133.19, 130.50, 126.97, and 123.28 (C-7a, C-11a, C-4a′, C-8a′), 118.05 (C-4′), 111.60, 108.21, 105.44, and 103.86 (C-8, C-11, C-5′, C-8′), 63.20 (C-11b), 59.02 (C-4), 55.97 and 55.86 (each 2 OCH_3), 53.05 (C-6), 41.38 (C-2), 40.21 (C-3), 38.99 (Cα), 33.72 (C-1), 29.31 (C-7), 18.11 (C-12), 12.61 (C-13) ppm.

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