Enantioselective Synthesis of *Epi*-Emetine Analogues: Control of the Facial Selectivity in a Three-Component Domino *Knoevenagel*-Hetero-*Diels-Alder* Reaction*

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The domino *Knoevenagel*-hetero-*Diels-Alder* reaction of the aldehyde *rac*-**8**, *Meldrum's* acid **2** and enol ether **3** leads to the cycloadduct *rac*-**17** as the main product which in a second domino process was transformed into the benzoisoquinolizidine *rac*-**18** by solvolysis, hydrogenolysis, condensation and hydrogenation; *rac*-**18** was used as a substrate for the synthesis of the two diastereomeric epi-emetine analogues **9** and **10** with > 96% *ee* (**9**) and 80% *ee* (**10**), respectively, by condensation with the phenylethylamine **23**, *Bischler-Napieralski* reaction and "enantioselective" hydrogenation using the chiral catalyst (*R,R*)-**26**.

Key words: Alkaloids, Bischler-Napieralski Reaction, Enantioselective Hydrogenation, Domino Reactions, Iminium Ions, Multicomponent Reactions

Introduction

The domino-*Knoevenagel*-hetero-*Diels-Alder* reaction is a highly potent synthetic method to prepare dihydropyrans which can act as valuable intermediates in the total syntheses of natural products [1]. In this reaction an aldehyde is condensed with a 1,3-dicarbonyl compound to give a reactive 1-oxa-1,3-butadiene which can undergo a hetero-*Diels-Alder* reaction with inverse electron demand employing either an enol ether or an alkene as dienophile. The reaction can be performed as a two-, three- or four- component process [2]. In those cases where the Diels-Alder-reaction proceeds in an intramolecular mode, high facial selectivity is observed. In contrast, a low facial selectivity is usually found for reactions with an intermolecular *Diels-Alder*-step. Recently we have used the domino *Knoevenagel*-hetero-*Diels-Alder* reaction in the enantioselective synthesis of the indole alkaloids hirsutin, dihydrocorynanthein and dihydroantirhin [3], as well as the Ipecacuanha alkaloid emetine and the Alangium alkaloid tubulosine [4]. In addition, two new concepts in combinatorial chemistry were developed using this approach [5, 6]. One of these concepts deals with stereochemical diversity. Thus, we were able to prepare 12 out of 16 possible stereoisomers of emetine **7** [6].

In the synthesis towards emetine **7** the enantiopure aldehyde **1** was condensed with *Meldrum's* acid **2** to give the 1-oxa-1,3-butadiene **4** which underwent a hetero *Diels-Alder* reaction with the enol ether **3**. As products the two diasteromeric cycloadducts **5** and **6** were obtained as a 1:1 mixture. Thus, it seems that the stereogenic center in **1** and **4**, respectively, does not effect a facial differentiation. Another explanation for the lack of selectivity in the *Diels-Alder* reaction would be the coexistence of the two conformers **4a** and **4b** which both might undergo a facial selective cycloaddition. Thus, one could assume that the attack of the enol ether **3** occurs at the (*E*)-oxabutadiene moiety in both **4a** and **4b** from below as the less hindered side to give **5** and **6**. High 1,3-diastereoselective induction should therefore be expected if one stabilizes or destabilizes one of the conformers **4a** and **4b**. Thus, the introduction of a bulky substituent at C-8 in **4** should destabilize the conformer **4b**.

Here we describe the synthesis of the aldehyde *rac*-**8** and its use in the stereoselective domino-*Knoevenagel*-hetero-*Diels-Alder* reaction with *Meldrum's* acid **2** and the enol ether **3** to give a benzoquinolizidine *rac*-**18**,

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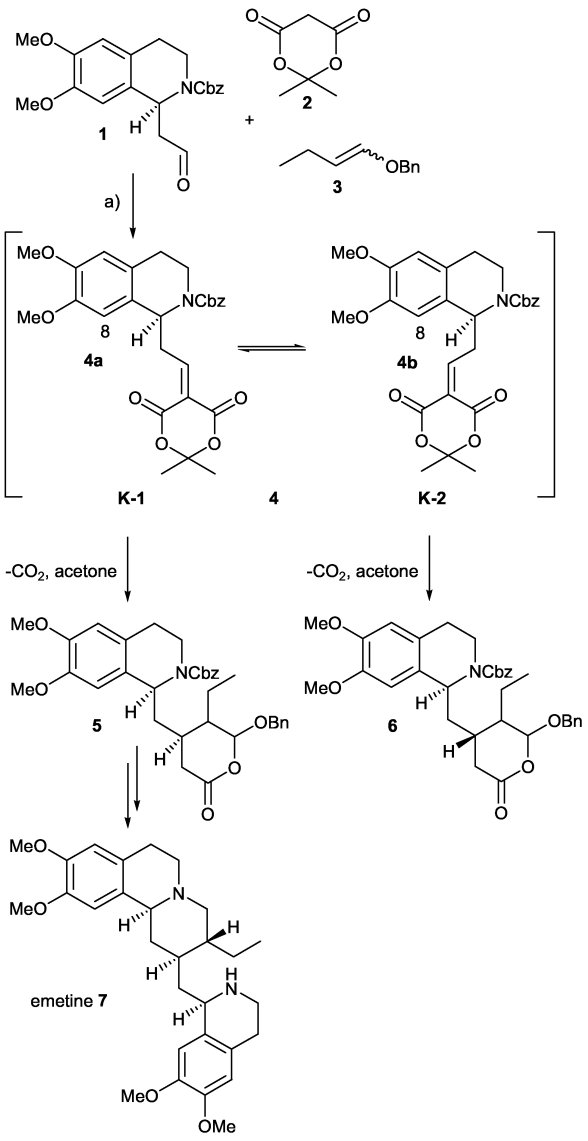
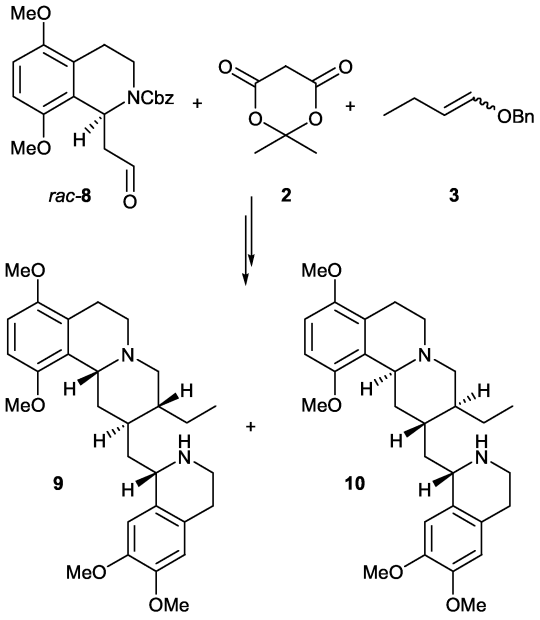


Scheme 1. Facial selectivity in the three component domino *Knoevenagel*-hetero-*Diels-Alder* process of **1**, **2** and **3**; a) 1.2 eq. **2**, 4.0 eq. **3**, EDDA, toluene, 12 h, 60 °C, ultrasonic bath, 86%.

which was transformed into the epi-emetine analogues **9** and **10**.

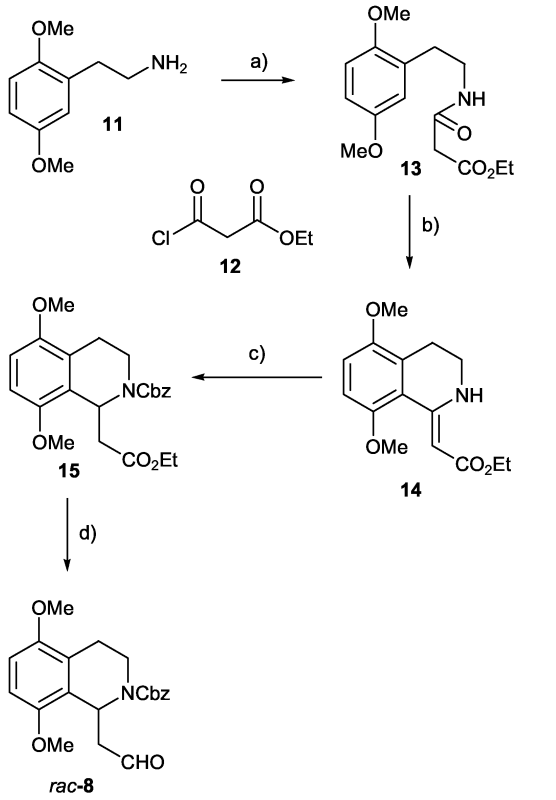
Results and Discussion

The aldehyde *rac*-**8** was synthesised starting from the known (2,5-dimethoxyphenyl)ethylamine **11** [7]. Condensation of crude **11** with the acid chloride **12** in CH_2Cl_2 in the presence of a base led to the amide **13**, which in a consecutive *Bischler-Napieralski* reaction using P_4O_{10} in refluxing toluene afforded the isoquinoline derivative **14**. Heterogenous hydrogenation of the enamine moiety in **14** using Pd/C as a catalyst in acetic acid/methanol with nearly quantitative yield was followed by protection of the formed secondary amine with benzyl chloroformate (CbzCl). Reduction of the ester moiety in protected **15** with diisobutyl aluminum hydride (DIBAL) finally led to the desired aldehyde *rac*-**8** in 70% yield, which was used in the following domino reaction.



Scheme 2. Synthesis of epi-emetine analogues **10** and **11**.

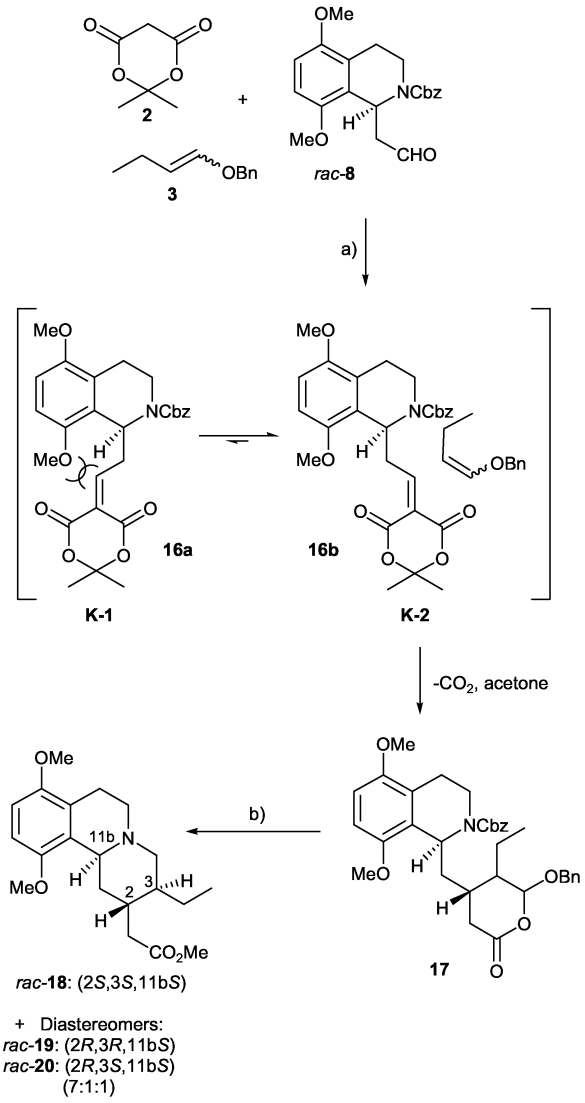
The domino *Knoevenagel*-hetero-*Diels-Alder* reaction of aldehyde *rac*-**8**, *Meldrum's* acid **2** and enol ether **3** was performed in the presence of a catalytic amount of ethylene diammonium diacetate (EDDA). At first the 1-oxa-1,3-butadiene **16** is obtained in situ, which in contrast to **4** should mainly exist as conformer K-2, since K-1 is destabilised due to the steric interaction of the methoxy and the alkylidene 1,3-dicarbonyl group. If one now assumes that the attack of the dienophile **3** at the major conformer K-2 of **16** occurs from below as the less hindered side one would obtain **17** with a 1,3-trans orientation. Since the enol ether **3** is used as a distereomeric mixture and the *exo/endo*-selectivity in the cycloaddition is low, as already mentioned, **17** is obtained as a mixture of diastereomers, which were not separated. Crude **17** was stirred in methanol with K_2CO_3, moleculare sieves and a catalytic amount of Pd/C in methanol for 60 min



Scheme 3. Synthesis of the aldehyde *rac*-**8**: a) 1.2 eq. **12** in Et_2O, 1.2 eq. K_2CO_3 in H_2O, 1 h, 0 °C, 61%; b) 10 eq. P_4O_{10}, toluene, 70 min, reflux, 59%; c) 1. Pd/C, H_2 (4.1 bar), acetic acid/methanol, 70 min, 25 °C, 99%; 2. 1.3 eq. CbzCl, 2.0 eq. NEt_3, CH_2Cl_2, 3 h, 25 °C, 67%; d) 1.2 eq. DIBAL, toluene, 80 min, −78 °C, 70%.

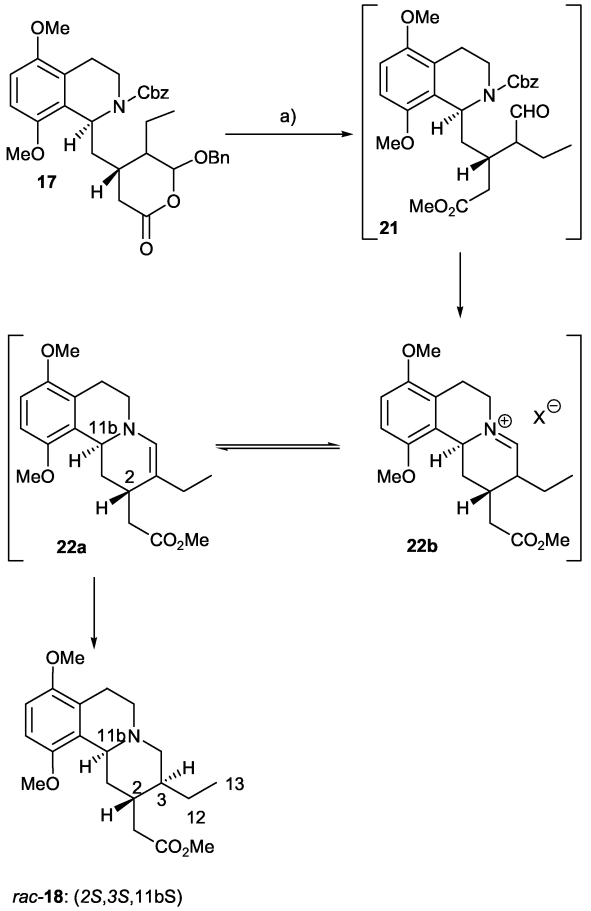
and afterwards a hydrogen atmosphere was applied and stirring was continued for another 5.5 h to give the diasteromeric benzoquinolizidines *rac*-**18**, *rac*-**19** and *rac*-**20** in a ratio of 7:1:1. The diastereomers were separated by column chromatography.

For the transformation we propose the following sequence: In the first step the lactone moiety in **17** is attacked by methoxide to give a methyl ester and a hemiacetal which looses benzyl alcohol providing the aldehyde **21**. Hydrogenolytic removal of the Cbz protecting group leads to the corresponding secondary amine which reacts with the aldehyde moiety to afford either an iminium ion **22b** or an enamine **22a**; both moieties would be hydrogenated under the reaction conditions. The formation of *rac*-**18** as the major diastereomer in the process corresponds well with our assumption of a destabilisation of conformer K-1 of **16** due to steric interaction.



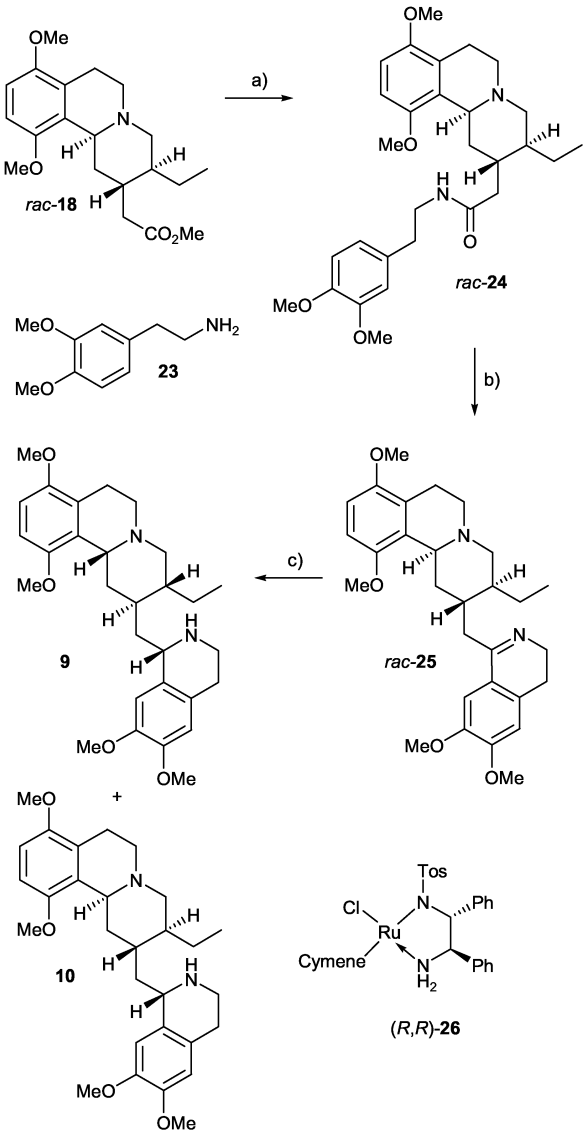
Scheme 4. Control of the facial selectivity during the *Diels-Alder* reaction and synthesis of benzoquinolizidines *rac*-**18**, *rac*-**19** and *rac*-**20**; a) 1.2 eq. **2**, 5.0 eq. **3**, EDDA, toluene, 5.5 h, 60 °C, ultrasonic bath; b) 0.5 eq K_2CO_3, Pd/C, MeOH, 60 min; H_2 (1 bar), 5.5 h, 25 °C, 40%, based on *rac*-**8**.

For the synthesis of *epi*-emetine analogues **9** and **10** the benzoquinolizidine **18** was treated with the phenylethylamine **23** and trimethylaluminium to give the amide **24** [8] which could then directly be transformed into the desired imine **25** using $POCl_3$. As final step in the synthesis of *epi*-emetine analogues **9** and **10**, the imine moiety in **25** was hydrogenated using a catalytic transfer hydrogenation with triethyl ammonium formate and the chiral catalyst (*R*,*R*)-**26** [9]. In



rac-**18**: (2*S*,3*S*,11b*S*)

Scheme 5. Formation of the benzoquinolizidine *rac*-**18** from *rac*-**17** by a domino process involving solvolysis, hydrogenolysis, condensation and hydrogenation; a) 1.2 eq. **2**, 5.0 eq. **3**, EDDA, toluene, 5.5 h, 60 °C, ultrasonic bath.

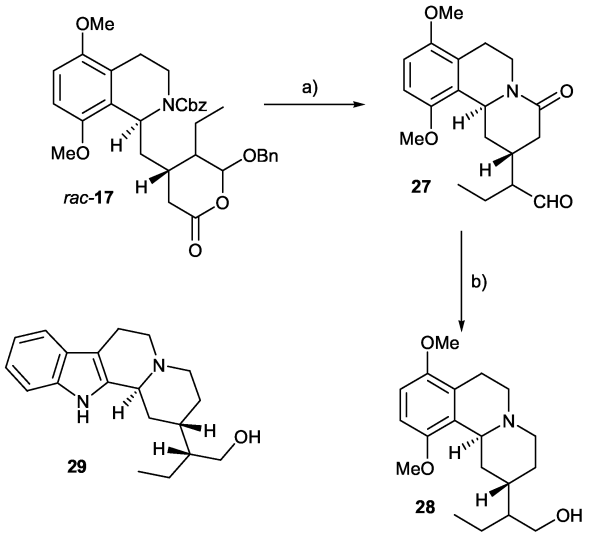


Scheme 6. Enantioselective synthesis of the epi-emetine analogues **9** and **10**; a) 3 eq. $AlMe_3$, 3 eq. **23**, CH_2Cl_2, 3.5 h, reflux, 57%; b) $POCl_3$, benzene, 65 min, reflux, 78%; c) 10mol% (*R*,*R*)-**26**, HCO_2H/NEt_3, DMF, 25 °C, 50 min, 60%.

this reaction a fourth stereogenic center is introduced in a catalyst controlled manner with a selectivity of $>$ 98:2 for **9** and 90:10 for **10**. Since the imine **25** exists as a racemic mixture, the enantiopure diastereomer **9** (*ee* $>$ 96%) and the enantiomer-enriched diastereomer **10** (*ee* = 80%) are formed as a 1:1 mixture, which was seperated by column chromatography. Using *S*,*S*-**26** as the catalyst would allow to get the enantiomer of **10** also with *ee* $>$ 96%.

The described domino-*Knoevenagel*-hetero-*Diels-Alder* process did not only allow the syntheses of *epi*-emetine analogues **9** and **10**, but also gives access to so far unknown benzoquinolizidine alkaloids such as **28**.

Reaction of the cycloadduct *rac*-**17** under a hydrogen atmosphere in methanol in the presence of a catalytic amount of Pd/C led to the lactam **27** in 12% yield over two steps in a non-optimized reaction. In this transformation, first the Cbz-protecting group is removed by hydrogenolysis to furnish the corresponding secondary amine which then attacks the lactone moiety in an intramolecular fashion to give the lactam and a hemiacetal, which looses benzyl alcohol affording **27**. Reduction of **27** with $LiAlH_4$ in THF yields the



Scheme 7. Synthesis of dihydroantirhin resembling alkaloid **28**; a) Pd/C, H_2 (1 bar), MeOH, 4 h, 25 °C, 12% over two steps; b) 10 eq. $LiAlH_4$, THF, 4.5 h, 25 °C, 44%.

alkaloid **28**, which resembles the vallesiachotamine alkaloid dihydroantirhin **29**.

Conclusion

The three component domino-*Knoevenagel*-hetero-*Diels-Alder* reaction of the aldehyde *rac*-**8**, *Meldrum's* acid **2** and the enol ether **3** followed by another domino process consisting of solvolysis, hydrogenolysis, condensation and hydrogenation allows a very short entry to the *epi*-emetine analogues **9** and **10**. The introduction of a bulky substituent at position C-8 of the aldehyde *rac*-**8** controls the facial selectivity of the *Diels-Alder* reaction and therefore allows a selective synthesis of one stereoisomer. In addition, the so far unknown benzoquinolizidine alkaloid **28** which resembles the vallesiachotamine alkaloid **29** can be obtained using this approach. The described procedure underlines the potency of domino processes and clearly also allows the preparation of analogues which might have interesting pharmacological properties.

Experimental Section

N-(2-(2,5-Dimethoxyphenyl)ethyl)-malonic acid ethylester amide (**13**)

To a well stirred two layer-system of crude amine **11** [6] (10.3 g, 56.8 mmol) in diethyl ether (100 cm^3) and potassium carbonate (9.4 g, 68.2 mmol) in water (100 cm^3) a solution of malonic acid ethylester chloride **12** (10.3 g, 68.2 mmol) was added dropwise at 0 °C and the mixture was stirred for further 1.5 h at this temperature. The layers were seperated and the aqueous layer was extracted with dichloromethane (3×150 cm^3). The combined extracts were dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure to give a brown oil. Flash chromatography (silica gel; eluent: Et_2O) gave **13** as a pale brown oil (10.3 g, 61%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 291.0 nm (3.605), 225.5(3.943) 196.0(4.636). – IR (KBr): ν = 3304, 2940 (C-H), 2835 (OMe), 1739 (ester), 1652 (amide), 1465 (CH_2), 869 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, $^3J = 7.1$ Hz, 3 H, -CH_2CH_3), 2.81 (t, $^3J = 6.9$ Hz, 2 H, 2-H), 3.26 (s, 2 H, -CH_2CO_2Et), 3.52 (m, 2 H, 1-H), 3.76 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 4.19 (q, $^3J = 7.1$ Hz, 2 H, -CH_2CH_3), 6.73 (m, 3 H, Ar-H), 7.12 (bs, 1 H, NH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ= 13.97 (-CH_2CH_3), 30.13 (C-2), 39.84 (-CH_2CO_2Et), 41.36 (C-1), 55.59 (OMe), 55.74 (OMe), 61.37 (-CH_2CH_3), 111.1 C-4'), 112.0 (C-6'), 116.6 (C-3'), 128.2 (C-1'), 151.6 (C-2'), 153.4 (C-5'), 164.9 (-CONHR), 169.3 (-CO_2Et). – MS (70 eV, EI): m/z (%) = 295.3 (20) [M^+], 164.1 (100) [$C_{10}H_{12}O_2^+$]; $C_{15}H_{21}NO_5$ (295.33): calcd. 295.1420; found 295.1420.

(5,8-Dimethoxy-3,4-dihydro-2H-isoquinolin-1-yliden)-acetic acid ethyl ester (**14**)

To a hot solution of malonic ester **13** (10.2 g, 34.5 mmol) in toluene P_4O_{10} (50 g, 352 mmol) was added in three portions within 10 min. The suspension was kept for further 60 min under reflux with vigorous stirring (mechanical stirrer). The suspension was filtered and the solid was dissolved in ice-water. The filtrate was extracted with 1N HCl (300 cm^3) and the combined aqueous layers were neutralized with K_2CO_3. After extraction of the aqueous layer with ethyl acetate (4×300 cm^3) the organic layer was dried over sodium sulfate and filtered. The solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography (silica gel, eluent: Et_2O). The product **14** was obtained as a pale yellow solid (5.60 g, 59%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 345.0 nm (4.120), 257.5(3.855), 229.5(4.323). – IR (KBr): ν = 3303, 2940 (C-H), 2834 (OMe), 1640 (ester), 1570 (amide), 1476 cm^{-1} (CH_2). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, $^3J = 7.1$ Hz, 3 H, -CH_2CH_3), 2.84 (t, $^3J = 6.0$ Hz, 2 H, 4-H), 3.31 (m, 2 H, 3-H), 3.80 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 4.15 (q, $^3J = 7.1$ Hz, 2 H, -CH_2CH_3), 5.70 (s, 1 H, 1'-H), 6.80 (d, $^3J = 9.2$ Hz, 1 H, 7-H), 6.88 (d, $^3J = 9.2$ Hz, 1 H, 6-H), 9.32 (bs, 1 H, NH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.71 (-CH_2CH_3), 23.14 (C-4), 38.03 (C-3), 55.99 (OMe), 56.06 (OMe), 58.51 (-CH_2CH_3), 82.60 (C-1'), 110.1 (C-7), 112.4 (C-6), 120.1 (C-8a),

128.2 (C-4a), 149.8 (C-1), 152.3 (C-5), 154.0 (C-8), 169.3 (-*C*O_2Et). – MS (70 eV, EI): m/z (%) = 277.1(44) [M^+], 190.1(100) [$C_{11}H_{12}NO_2^+$]; $C_{15}H_{19}NO_4$ (277.31): calcd. 277.1314; found 277.1314.

N-Carbobenzyloxy-(5,8-dimethoxy-3,4-dihydro-2H-isoquinolin-1-yl)-acetic acid ethyl ester (**15**)

1. (5,8-Dimethoxy-3,4-dihydro-2H-isoquinolin-1-yl)-acetic acid ethyl ester: A suspension of α,β-unsaturated ester **14** (5.58 g, 34.5 mmol) and 10% palladium on charcoal (10 mol%) in ethanol (80 cm^3) and acetic acid (60 cm^3) was shaken under a hydrogen atmosphere (4.1 bar) for 70 min. The reaction mixture was filtered and ethanol was removed under reduced pressure. The residue was diluted with water (150 cm^3), neutralized with solid K_2CO_3 and extracted with diethyl ether (3×200 cm^3). The solution was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure to give **15** as a yellow solid (5.52 g, 98%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 287.5 nm (3.565), 197.0(4.626). – IR (KBr): δ = 3320, 2930 (C-H), 2837 (OMe), 1724 (ester), 1478 cm^{-1} (CH_2). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, ^3J = 7.1 Hz, 3 H, -CH_2CH_3), 2.44 (bs, 1 H, NH) 2.66 (m, 2 H, $2 \times$ 4-H), 2.68 (dd, ^2J = 16.0 Hz, ^3J = 10.2 Hz, 1 H, 1'-H_A), 2.89 (dd, ^2J = 16.0 Hz, ^3J = 2.9 Hz, 1 H, 1'-H_B), 3.06 (m, 2 H, $2 \times$ 3-H), 3.77 (s, 6 H, 2$\times$ OMe), 4.60 (dd, ^3J = 10.2, 2.9 Hz, 1 H, 1-H), 6.62 (d, ^3J = 9.2 Hz, 1 H, 7-H), 6.67 (d, ^3J = 9.2 Hz, 1 H, 6-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.26 (-CH_2CH_3), 23.58 (C-4), 37.10 (C-3 or C-1'), 37.70 (C-3 or C-1'), 55.41 (OMe), 55.60 (OMe), 60.29 (-*C*H_2CH$_3$), 107.0 (C-7), 107.6 (C-6), 125.6 (C-8a), 127.8 (C-4a), 149.9 (C-5), 151.3 (C-8), 172.8 (-*C*O_2Et). – MS (70 eV, EI): m/z (%) = 279.2(8) [M^+], 192.1(100) [$C_{11}H_{14}NO_2^+$]; $C_{15}H_{19}NO_4$ (279.33): calcd. 279.1471; found 279.1471.

*2. N-Carbobenzyloxy-(5,8-dimethoxy-3,4-dihydro-2H-isoquinolin-1-yl)-acetic acid ethyl ester **(15)**:* Benzyl chloroformate (3.65 cm^3, 25.6 mmol) was added dropwise to a solution of the above mentioned ester (5.50 g, 19.7 mmol) and NEt_3 (5.46 cm^3, 39.4 mmol) in CH_2Cl_2 (60 cm^3) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and afterwards diluted with CH_2Cl_2 (200 cm^3). The organic layer was washed with 1N HCl (100 cm^3) and dried over sodium sulfate. After filtration the solvent was removed under reduced pressure to yield the crude product, which was purified by column chromatography (silica gel, eluent: ethyl acetate/pentane; 2:1). The protected ester **15** was obtained as a pale yellow solid (5.40 g, 67%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 288.0 nm (3.596). – IR (KBr): ν = 2958(C-H), 2835 (OMe), 1737 (ester), 1681 (carbamate), 1481 cm^{-1} (CH_2). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 (m_C, 3 H, -CH_2CH_3), 2.50 – 3.47 (m, 6 H, 2 $\times$ 1'-H, $2 \times$ 3-H $2 \times$ 4-H), 3.77 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.88 – 4.50 (m, 3 H, 1-H, -CH_2CH_3), 5.14 (s, 2 H, -CH_2Ph), 5.84 (m_c, 1 H, 1-H), 6.67 (s, 2 H, 5-H, 8-H), 7.30 – 7.45 (m, 5 H, Ph-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.10 (-CH_2CH_3), 22.18, 22.61 (C-4), 36.14, 36.70 (C-1' or C-3), 38.39, 38.69 (C-3 or C-1'), 48.08 (C-1), 55.49 (OMe), 55.58 (OMe), 60.45 (-*C*H_2CH$_3$), 67.03, 67.10 (-*C*H_2Ph), 107.4 (C-7), 108.3 (C-6), 124.6 (C-8a), 126.3 (C-4a), 127.8 (Ph), 128.3 (Ph), 128.4 (Ph), 149.3, 149.6 (C-5), 151.0, 151.1 (C-8), 155.1, 155.2 (–N*C*O_2CH$_2$Ph), 170.8, 171.0 (-*C*O_2Et). – MS (70 eV, EI): m/z (%) = 413.2(8) [M^+], 326.2(64) [$C_{19}H_{20}NO_4^+$], 278.2(20) [$C_{15}H_{20}NO_4^+$], 91.1(100) [$C_7H_7^+$]; $C_{23}H_{27}NO_6$ (413.46): calcd. 413.1838; found 413.1838.

*N-Carbobenzyloxy-(5,8-dimethoxy-3,4-dihydro-2H-isoquinolin-1-yl)-acetaldehyde **(rac-8)***

To a stirred solution of the protected ester **15** (5.40 g, 13.1 mmol) in toluene (65 cm^3) diisobutyl aluminium hydride (1.5 M in toluene, 10.4 cm^3, 15.7 mmol) was added dropwise at −78 °C. The reaction mixture was kept at this temperature for 80 min and subsequently diluted with ethyl acetate (10 cm^3); after the solution had reached room temperature it was washed with water (50 cm^3). The aqueous layer was extracted with ethyl acetate (4×100 cm^3) and the combined organic layers were dried over sodium sulfate and filtered. After removal of the solvent under reduced pressure the crude product was subjected to column chromatography (silica gel; eluent: ethyl acetate/pentane, 1:2) to yield in the aldehyde *rac*-**8** as a colourless oil (3.34 g, 70%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 289.0 nm (3.364). – IR (KBr): ν = 2958 (C-H), 2835 (OMe), 1737 (ester), 1681 (carbamate), 1481 (CH_2). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 – 3.35 (m, 5 H, 1'-H_A, $2 \times$ 3-H $2 \times$ 4-H), 3.77 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 4.09 – 4.46 (m, 1 H, 1'-H_B), 5.14 (s, 2 H, -CH_2Ph), 5.84 (m_c, 1 H, 1-H), 6.67 (s, 2 H, 5-H, 8-H), 7.30 – 7.45 (m, 5 H, Ph-H), 9.81 (m_c, 1 H, -C*H*O). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.15, 22.47 (C-4), 36.56, 37.07 (C-3), 46.27 (C-1), 48.30 (C-1'), 55.33 (OMe), 55.58 (OMe), 60.45 (-*C*H_2CH$_3$), 67.28, 67.49 (-*C*H_2Ph), 107.4, 107.6 (C-7), 108.3 (C-6), 124.1 (C-8a), 125.5 (C-4a), 127.8, 128.0 (Ph), 128.1, 128.1 (Ph), 128.5 (Ph), 149.3, 149.6 (C-5), 151.0, 151.1 (C-8), 155.1, 155.3 (–N*C*O_2CH$_2$Ph), 200.8, 201.4 (*C*HO). – MS (70 eV, EI): m/z (%) = 369.2(8) [M^+], 326.2(20) [$C_{19}H_{20}NO_4^+$], 91.1(100) [$C_7H_7^+$]; $C_{21}H_{23}NO_5$ (369.41): calcd. 369.1576; found 369.1576.

N-Carbobenzyloxy-1-(2-benzoxy-3-ethyl-6-oxo-tetrahydropyran-4-ylmethyl)-5,8-dimethoxy-3,4-dihydro-2H-isoquinoline (**17**)

A suspension of aldehyde **8** (500 mg, 1.35 mmol), Meldrum's acid **2** (234 mg, 1.62 mmol) and (*E,Z*)-butenylbenzyl ether **3** (1.10 g, 6.77 mmol) as well as a catalytic amount

of ethylene diammonium diacetate in toluene (6.7 cm^3) in a closed flask was put into a ultrasonic bath for 5.5 h at 60 °C. The product mixture was purified by column chromatography (silica gel, eluent: toluene:acetone, 10:1) to give the isoquinoline **17** as a colourless oil (790 mg, quant.). The mixture of several diastereomers was converted to the corresponding benzoquinolizidines without further purification. MS (dCI, NH_3): m/z (%) = 574.5(24) $[M+H]^+$, 591.5(100) $[M+NH_3]^+$.

Cyclisation of the domino Knoevenagel-hetero-Diels Alder-reaction product

A suspension of dry potassium carbonate (94 mg, 0.68 mmol), palladium on charcoal (100 mg, 10%) and molecular sieves (3 Å) in methanol (5 cm^3) was stirred for 10 min and a solution of isoquinoline **17** (780 mg, 1.36 mmol) in methanol (12 cm^3) was added. The suspension was stirred for 60 min and then for further 5.5 h under a hydrogen atmosphere. The reaction mixture was filtered over a small amount of silica gel using methanol. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (silica gel, eluent: CH_2Cl_2/MeOH, 40:1) to yield in diastereomers *rac*-**18**, *rac*-**19** and *rac*-**20** (7:1:1) (189 mg, 40%).

rac-2,3(S,S)-11b(S)-(3-Ethyl-8,11-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-yl)- acetic acid methyl ester (**18**)

UV/vis (CH_3CN): λ_{max} (lg ε) = 198.0 nm (4.618), 288.0(3.534). – IR (Film): ν = 2952 (C-H), 2833 (OMe), 2872, 2804, 2779, 1737 (C=O), 1463 (CH_2), 1359 cm^{-1} (CH_3). – ^{1}H NMR (500 MHz, C_6D_6): δ = 0.87 (t, 3 H, ^3J = 7.5 Hz, 13-H), 1.18 (m_c, 1 H, 3-H), 1.53 (m_c, 1 H, 12-H), 1.73 (m_c, 1 H, 12-H), 1.79 (ddd, ^2J = 13.3 Hz, ^3J = 11.2,4.5 Hz,1 H, 1-H_{ax}), 2.33 (ddd, ^2J = 10.7 Hz, ^3J = 10.7,3.5 Hz, 1 H, 6-H_{ax}), 2.37 (m_c, 1 H, 2-H), 2.51 (dd, ^2J = 15.5 Hz, ^3J = 7.5 Hz, 1 H, 4-H_A), 2.52 (m_c, 1 H, α-H), 2.56 – 2.65 (m, 3 H, 1-H_{eq}, 6-H_{eq}, 4-H_B), 2.69 (dd, ^2J = 15.5 Hz, ^3J = 7.7 Hz, 1 H, α-H), 2.88 (m_c, 1 H, 7-H_A), 2.97 (m_c, 1 H, 7-H_B), 3.40 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.64 (m_c, 1 H, 11b-H), 6.42 (d, ^3J = 9.1 Hz 1 H, 9-H), 6.44 (d, ^3J = 9.1 Hz 1 H, 10-H). – ^{13}C NMR (125 MHz, C_6D_6): δ = 12.67 (C-13), 25.74 (C-7), 26.75 (C-12), 30.76 (C-1), 34.78 (C-2), 38.27 (C- α), 40.83 (C-3), 50.87 (C-6), 50.91 (OMe), 55.03 (OMe), 55.18 (OMe), 55.72 (C-4), 56.84 (C-11b), 107.4 (C-9), 108.2 (C-10), 127.1 (C-11a), 129.3 (C-7a), 151.5 (C-11), 151.8 (C-8), 173.1 (*C*O_2Me). – MS (70 eV, EI): m/z (%) = 347.2(94) [M^+], 332.4(32) [M^+–CH_3], 316.3(48) [M^+–OMe], 274.3(44) [M^+–CO_2Me-CH_3], 246.3(100) [$C_{15}H_{20}NO_2^+$], 205.2(84) [$C_{12}H_{15}NO_2^+$], 191.2(80) [$C_{11}H_{13}NO_2^+$]; $C_{20}H_{29}NO_4$ (347.45): calcd. 347.2097; found 347.2097.

rac-2,3(R,R)-11b(S)-(3-Ethyl-8,11-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-yl)-acetic acid methyl ester (**19**)

UV (CH_3CN): λ_{max} (lg ε) = 198.5 nm (4.638), 288.0(3.560). – IR (Film): ν = 2954 (C-H), 2831 (OMe), 2872, 2802, 2774, 1737 (C=O), 1465 (CH_2), 1359 cm^{-1} (CH_3). – ^{1}H NMR (300 MHz, C_6D_6): δ = 0.90 (t, 3 H, ^3J = 7.5 Hz, 13-H), 1.31 (m_z, 1 H, 3-H), 1.70 (m_z, 1 H, 2 H, 12-H), 1.84 (ddd, ^2J = 13.8 Hz, ^3J = 11.2,4.5 Hz, 1 H, 1-H_{ax}), 2.28 (ddd, ^2J = 10.8 Hz, ^3J = 10.8,3.7 Hz,1 H, 6-H_{ax}), 2.48 – 2.56 (m, 1 H, 4-H), 2.56 (m_z, 1 H, 6-H_{eq}), 2.69 (dd, ^2J = 12.2 Hz, ^3J = 3.3 Hz, 1 H, 4-H), 2.81 – 3.08 (m, 6 H, 2 × α-H, 1-H, 2-H, 2 × 7-H), 3.39, 3.42, 3.48 (s, 3× OMe), 3.64 (m_z, 1 H, 11b-H), 6.44 (s, 2 H, 9-H, 10-H). – ^{13}C NMR (125 MHz, C_6D_6): δ = 12.59 (C-13), 25.90 (C-7), 26.65 (C-12), 28.55 (C-1), 34.85 (C-2), 38.95 (C-3), 50.95 (C-6), 51.81 (C-α), 54.84 (OMe), 55.11 (OMe), 55.18 (OMe), 56.05 (C-4), 57.32 (C-11b), 107.5 (C-9), 108.4 (C-10), 127.3 (C-11a), 129.1 (C-7a), 151.5 (C-11), 151.8 (C-8), 169.4 (*C*O_2Me). – MS (70 eV, EI): m/z (%) = 347.2(74) [M^+], 332.4(40) [M^+–CH_3], 316.3(18) [M^+–OMe], 274.3(50) [M^+–CO_2Me–CH_3], 246.3(100) [$C_{15}H_{20}NO_2^+$], 205.2(90) [$C_{12}H_{15}NO_2^+$], 191.2(70) [$C_{11}H_{13}NO_2^+$]; $C_{20}H_{29}NO_4$ (347.45): calcd. 347.2097; found 347.2097.

rac-2,3(R,S)-11b(S)-(3-Ethyl-8,11-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-yl)-acetic acid methyl ester (**20**)

UV/vis (CH_3CN): λ_{max} (lg ε) = 198.0 nm (4.630), 288.0(3.551). – IR (Film): ν = 2955 (C-H), 2835 (OMe), 2873, 2810, 2775, 1740 (C=O), 1463 (CH_2), 1359 cm^{-1} (CH_3). – ^{1}H NMR (500 MHz, C_6D_6): δ = 0.86 (t, 3 H, ^3J = 7.5 Hz, 13-H), 1.22 (m_c, 1 H, 12-H), 1.27 (ddd, ^2J = 12.3 Hz, ^3J = 12.3,10.5 Hz,1 H, 1-H_{ax}), 1.42 (m_c, 1 H, 3-H), 1.69 (m_c, 1 H, 12-H), 2.19 (m_c, 2 H, α-H), 2.36 (ddd, ^2J = 11.1 Hz, ^3J = 11.1,3.4 Hz, 1 H, 6-H_{ax}), 2.44 (dd, ^2J = 11.8 Hz, ^3J = 2.8 Hz,1 H, 4-H_A), 2.48 (m_c, 1 H, 2-H), 2.62 (ddd, ^2J = 11.1 Hz, ^3J = 5.3,2.6 Hz,1 H, 6-H_{eq}), 2.82 – 2.94 (m, 2 H, 1-H, 7-H_A), 2.87 (dd, ^2J = 11.8 Hz, ^3J = 2.2 Hz,1 H, 4-H_B), 3.01 (m_c, 1 H, 7-H_B), 3.38, 3.39, 3.41 (s, 3× OMe), 3.60 (m_c, 1 H, 11b-H), 6.43, (d, ^3J = 9.0 Hz, 1 H, 9-H or 10-H), 6.45 (d, ^3J = 9.0 Hz, 1 H, 9-H or 10-H). – ^{13}C NMR (125 MHz, C_6D_6): δ = 12.82 (C-13), 18.62 (C-12), 26.25 (C-7), 32.44 (C-1), 38.58 (C-2), 38.61 (C-α), 39.84 (C-3), 50.83 (OMe), 50.94 (C-6), 55.04 (OMe), 55.20 (OMe), 58.83 (C-4), 62.50 (C-11b), 107.5 (C-9), 108.3 (C-10), 127.2 (C-11a), 129.4 (C-7a), 151.8 (C-11), 151.8 (C-8), 172.9 (*C*O_2Me). – MS (70 eV, EI): m/z (%) = 347.4(56) [M^+], 316.3(20) [M^+–OMe], 274.3(30) [M^+–CO_2Me–CH_3], 246.3(50) [$C_{15}H_{20}NO_2^+$], 205.2(100)

$[C_{12}H_{15}NO_2^+]$, 191.2(60) $[C_{11}H_{13}NO_2^+]$: calcd. 347.2097; found 347.2097.

rac-2,3(S,S)-11b(S)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(3-ethyl-8,11-dimethoxy-1,3,4,7,11b-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-yl)-acetamide (**24**)

A solution of homoveratryl amine **23** (140 mg, 0.78 mmol) and trimethyl aluminium (2M in hexane, 0.39 cm^3, 0.78 mmol) in dichloromethane (0.70 cm^3) was stirred for 1 h at 25 °C and a solution of the methyl ester **18** (90.0 mg, 0.26 mmol) in dichloromethane (0.60 cm^3) was added dropwise and stirring was continued for further 3.5 h under reflux. The reaction was cautiously quenched with saturated aqueous NaCl solution (10 cm^3) and extracted with ethyl acetate (4×50 cm^3). The combined organic layers were dried over sodium sulphate, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: CH_2Cl_2/MeOH, 20:1) to give the acetamide **24** as a colourless foam (81 mg, 61%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 200.5 nm (4.916), 227.5 (4.196), 285.5 (3.754). – IR (KBr): ν = 3299 (NH), 2933 (C-H), 2832 (OMe), 1644 ($CONR_2$), 1515 ($CONR_2$), 1359 cm^{-1} (CH_3). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 7.5 Hz, 3 H, 13-H), 1.21 (m_c, 1 H, 3-H), 1.49 (m_c,1 H, 12-H), 1.57 – 1.77 (m, 2 H, 1-H_{ax}, 12-H), 2.10 – 2.25 (m, 2 H, 1-H_{eq}, 2-H), 2.41 (m_c, 2 H, $2 \times \alpha$-H), 2.49 (ddd, $^2J = 10.9$ Hz, $^3J = 8.7, 3.9$ Hz, 1 H, 6-H_{ax}), 2.59 – 2.90 (m, 7 H, $2 \times 2'$-H, $2 \times$ 4-H, 6- H_{eq}, $2 \times$ 7-H), 3.45 (m_c, 1 H, 1'-H), 3.53 – 3.68 (m, 2 H, 1'-H, 11b-H), 3.65 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 5.62 (m, 1 H, NH), 6.59 (s, 2 H, 9-H, 10-H), 6.66 (s, 1 H, 8-H or 11-H), 6.67 – 6.74 (m, 2 H, 2"-H, 6"-H), 6.78 (d, ^3J = 8.5 Hz, 1 H, 5"-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.48 (C-13) 24.62 (C-7), 26.53 (C-12), 29.61 (C-1), 34.66 (C-2), 35.41 (C-2'), 40.13 (C-3), 40.58 (C-α), 40.80 (C-1'), 49.97 (C-6), 54.83 (C-4), 55.32, 55.41, 55.59, 55.80, 55.86 (4× OMe, C-11b), 107.3 (C-9), 107.9 (C-10), 111.3 (C-2"), 111.9 (C-5"), 120.6 (C-6"), 126.2 (C-11a), 128.4 (C-7a), 131.9 (C-1"), 147.6, 149.0 (C-3", C-4"), 150.7, 151.2 (C-8, C-11), 172.5 (*C*ONH). – MS (70 eV, EI): m/z (%) = 496.3(34) [M^+], 465.3(100) [M^+–OCH_3], 274.2(30) [M^+–$C_{11}H_{13}NO_2$], 205.1(24) [M^+-$C_{12}H_{15}NO_2$], 191.1(72) $[C_{11}H_{13}NO_2^+]$; $C_{29}H_{40}N_2O_5$ (496.64): calcd. 496.2937; found 496.2937.

rac-2,3(S,S)-11b(S)-2-(6,7-Dimethoxy-3,4-dihydro-isoquinolin-1-ylmethyl)-3-ethyl-8,11-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinoline (**25**)

To a solution of the amide **24** (65.0 mg, 131 μmol) in benzene (3.50 cm^3) phosphorus oxychloride (0.27 g, 1.74 mmol) was added under reflux and stirring was continued for 65 min at the same temperature. The solvent was removed and the residue was solved in dichloromethane (5.00 cm^3). The organic layer was extracted with 1*N* sodium hydroxide solution (5.00 cm^3) and the aqueous layer was extracted with dichloromethane (3×10 cm^3). The combined organic layers were dried over sodium sulphate, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: CH_2Cl_2/MeOH 10:1) to give the imine **25** as a yellow powder (49 mg, 78%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 197.5 nm (4.720), 296.0(3.886), 356.5(3.408). – IR (KBr): ν = 3422, 2935 (C-H), 2833 (OMe), 1561 (C=N), 1463 cm^{-1} (CH_2). – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.5 Hz, 3 H, 13-H), 1.43 (m_c, 1 H, 12-H), 1.65 (m_c,1 H, 12-H), 1.83 (m_c, 1 H, 3-H), 2.02 (ddd, ^2J = 15.4 Hz, ^3J = 11.0, 6.0 Hz, 1 H, 1-H_{ax}), 2.28 – 2.40 (m, 2 H, 1-H_{eq}, 2-H), 2.68 (m_c, 2 H, $2 \times \alpha$-H), 2.76 (dd, ^2J = 12.7 Hz, ^3J = 8.0 Hz, 1 H, 4-H_A), 2.91 – 3.28 (m, 6 H, 4-H_B, 4'-H_A, $2 \times$ 6-H, $2 \times$ 7-H), 3.44 (s, 3 H, OMe), 3.60 (m_c, 1 H, 11b-H), 3.65 (m_c, 1 H, 3'-H_A), 3.65 (m_c, 1 H, 3'-H_A), 3.75 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 4.51 (m_c, 1 H, 4'-H_B), 6.60 (d, ^3J = 8.0 Hz, 1 H, 9-H or 10-H), 6.67 (d, ^3J = 8.0 Hz, 1 H, 9-H or 10-H), 6.75 (s, 1 H, 5'-H), 7.10 (s, 1 H, 8'-H). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.78 (C-13), 21.34 (C-4'), 25.76 (C-7 or C-12), 25.79 (C-7 or C-12), 28.45 (C-1), 33.63 (C-2), 37.20 (C-α), 37.35 (C-3), 45.83 (C-3'), 47.25 (C-6), 51.92 (C-11b), 54.12 (C-4), 55.00, 55.54, 56.02, 56.34 (4× OMe), 108.4 (C-9), 108.6 (C-10), 108.7 (C-5'), 110.3 (C-8'), 121.6 (C-7a or C-11a), 122.6 (C-7a or C-11a), 131.5 (C-4'a), 147.8 (C-6' or C-7'), 149.9 (C-6' or C-7'), 150.7 (C-8 or C-11), 151.6 (C-8 or C-11). – MS (70 eV, EI): m/z (%) = 478.3(76) [M^+], 286.3(28) [M^+–$C_{11}H_{14}NO_2$], 273.3(65) [M^+-$C_{12}H_{17}NO_2$], 244.3(100) [M^+-$C_{13}H_{18}NO_2$], 205.1(22) $[C_{12}H_{15}NO_2^+]$; $C_{29}H_{38}N_2O_4$ (478.62): calcd. 478.2832; found 478.2832.

Asymmetric catalytic transfer hydrogenation of the imine **25**

A solution of dichloro-(*p*-cymene)-ruthenium(II) dimer (7.4 mg, 18.8 μmol), 1,2(*R,R*)-*N*-tosyl-1,2-diphenylethyl diamine (5.8 mg, 9.4 μmol) and triethyl amine (5.2 μcm^3, 37.6 μmol) in dimethyl formamide (0.36 cm^3) was stirred in a sealed flask under an argon atmosphere at 80 °C for 60 min. The warm solution was added to a solution of imine **25** (45 mg, 94.1 μmol) in dimethyl formamide (0.4 cm^3), cooled down to 0 °C and a mixture of formic acid/triethyl amine (5:2, 45 μcm^3) was added dropwise. The solution was allowed to reach 25 °C and after 50 min of stirring it was diluted with ethyl acetate, and the reaction was quenched by addition of saturated aqueous K_2CO_3 solution and water. The aqueous layer was extracted with dichloromethane (4×20 cm^3) and the combined organic layers were dried over sodium sulphate, filtered and the solvent was removed under reduced pressure. The crude product was purified by

column chromatography (silica gel, eluent: CH_2Cl_2/MeOH 10:1) to give the diastereomers **9** (> 96% *ee*) and **10** (80% *ee*) as yellow oils (27 mg, 60%).

1(S)-2,3(S,R)-11b(R)-2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl)-3-ethyl-8,11-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinoline (**9**)

$[\alpha]_D^{20} = +28.3^\circ$ (c = 0.60 in $CHCl_3$). – UV/vis (CH_3CN): λ_{max} (lg ε) = 200.0 nm (4.836), 287.0(3.824). – IR (KBr): ν = 3332, 2932 (C-H), 2832 (OMe), 1463 cm^{-1} (CH_2). – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.5 Hz, 3 H, 13-H), 1.38 (m_z, 1 H), 1.54 (m_z, 1 H), 1.69 – 1.83 (m, 3 H), 1.86 – 1.98 (m, 2 H), 2.12 (ddd, ^2J = 13.9 Hz, ^3J = 8.9, 3.3 Hz, 1 H), 2.28 (m_z, 1 H), 2.49 (ddd, ^2J = 10.7 Hz, ^3J = 9.8, 3.7 Hz, 1 H), 2.64 (m_z, 1 H), 2.69 – 2.80 (m, 4 H), 2.87 (ddd, ^2J = 10.9 Hz, ^3J = 4.8, 4.8 Hz, 1 H), 2.97 (dd, ^2J = 12.6 Hz, ^3J = 3.9 Hz, 1 H), 3.00 (m_z, 1 H), 3.24 (m_z, 1 H), 3.66 (m_z, 1 H), 3.69, 3.74 (s, 2 × OMe), 3.84 (s 6 H, 2 × OMe), 3.93 (m_z, 1 H), 6.57 (s, 1 H) 6.60 (s, 3 H). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 12.88 (C-13), 25.17 (C-12), 26.88 (C-4' or C-7), 29.55 (C-4' or C-7), 31.13 (C-1), 34.98 (C-2), 39.99 (C-3), 40.29 (C-α or C-3'), 40.69 (C-α or C-3'), 49.83 (C-6), 52.67 (C-1'), 54.13 (C-11b), 55.28 (C-4), 55.33, 55.64, 55.83, 56.06 (4× OMe), 107.2, 107.7, 109.7, 111,7 (C-5', C-8, C-8', C-11), 126.6, 127.2, 129.3, 132.4 (C-4'a, C-7a, C-8'a, C-11a), 147.1, 147.3, 150.9, 151.2 (C-6', C-7', C-8, C-11). – MS (70 eV, EI): m/z (%) = 480.4(40) [M^+], 449.4(70) [M^+–OMe], 286.1(40) [M^+–$C_{11}H_{12}NO_2$], 272.3(100) [M^+–$C_{12}H_{17}NO_2$], 192.2(60) [$C_{11}H_{14}NO_2^+$]; $C_{29}H_{40}N_2O_4$ (480.64): calcd. 480.2988; found 480.2988.

1(S)-2,3(R,S)-11b(S)-2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinolin-1-yl-methyl)-3-ethyl-8,11-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-α]isoquinoline (**10**)

$[\alpha]_D^{20} = -14.8^\circ$ (c = 0.40 in $CHCl_3$). – UV/vis (CH_3CN): λ_{max} (lg ε) = 200.0 nm (4.824), 287.0(3.786). – IR (KBr): ν = 3332, 2934 (C-H), 2832 (OMe), 1463 cm^{-1} (CH_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.5 Hz, 3 H, 13-H), 1.17 (m_z, 1 H), 1.54 (m_z, 1 H), 1.63 (ddd, ^2J = 14.3 Hz, ^3J = 11.5, 3.1 Hz, 1 H), 1.70 (m_z, 1 H), 1.77 (ddd, ^2J = 14.1 Hz, ^3J = 11.0, 4.1 Hz, 1 H), 1.94 (m_z, 1 H), 2.34 (ddd, ^2J = 14.2 Hz, ^3J = 12.2, 2.2 Hz, 1 H), 2.43 (m_z, 1 H), 2.58 (ddd, ^2J = 14.1 Hz, ^3J = 11.0, 4.1 Hz, 1 H), 2.63 – 2.84 (m, 5 H), 2.90 – 3.02 (m 3 H), 3.20 (ddd, ^2J = 14.2 Hz, ^3J = 12.2, 2.2 Hz, 1 H), 3.71, 3.75, 3.81, 3.84 (s, 4 × OMe), 3.92 (m_z, 1 H), 4.20 (m_z, 1 H), 6.57 (s, 1 H), 6.62 (s, 2 H), 6.76 (s, 1 H). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 12.70 (C-13), 24.67 (C-12), 26.85 (C-4' or C-7), 27.02 (C-4' or C-7), 29.37 (C-1), 34.01 (C-2), 40.05 (C-α or C-3'), 40.17 (C-α or C-3'), 42.40 (C-3), 49.37 (C-6), 52.48 (C-1'), 54.72 (C-11b), 54.89 (C-4), 55.20, 55.58, 55.78, 55.90 (4× OMe), 107.2, 107.5, 109.4, 111.6 (C-5', C-8, C-8', C-11), 126.3, 126.9, 128.7 132.4 (C-4'a, C-7a, C-8'a, C-11a), 147.1 147.3, 150.6, 151.3 (C-6', C-7', C-8, C-11). – MS (70 eV, EI): m/z (%) = 480.4(40) [M^+], 449.4(58) [M^+–OMe], 288.1(40) [M^+–$C_{11}H_{14}NO_2$], 272.3(100) [M^+–$C_{12}H_{17}NO_2$], 192.2(60) [$C_{11}H_{14}NO_2^+$]; $C_{29}H_{40}N_2O_4$ (480.64): calcd. 480.2988; found 480.2988.

2-(8,11-Dimethoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-yl)-butyraldehyde (**27**)

A suspension of **17** (800 mg, 1.33 μmol) and a catalytic amount of Pd/C in MeOH (10.0 cm^3) was stirred under a H_2-atmosphere for 4.0 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: toluene/acetone, 10:1). The title compound was obtained as a mixture of diastereomers (50 mg, 12%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 197.5 nm (4.713), 288.5(3.639). – IR (KBr): ν = 3423, 2936 (C-H), 2837 (OMe), 1720 (CHO), 1632 (R_2NCOR), 858 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 – 0.97 (m, 3 H), 1.49 – 1.80 (m, 3 H), 2.01 – 2.73 (m, 6 H), 2.74 – 3.07 (m, 2 H), 3.72 – 3.81 (m, 6 H), 4.69 – 4.99 (m, 2 H), 6.65 – 6.70 (m, 2 H), 9.60 – 9.67 (m, 1 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.29, 11.37, 11.41 (C-4'), 18.89, 19.12, 19.66 (C-3'), 22.62, 22.72, 23.54 (C-7), 28.99, 29.40, 31.03 (C-2), 32.72, 33.58, 33.80 (C-3), 35.16, 35.60 (C-1), 37.94, 38.19 (C-6), 49.74, 49.91, 54.35 (C-11b), 55.37, 55.73 (OMe), 57.15, 57.37, 57.96 (C-2'), 108.1, 108.2, 108.2, 108.3, 108.4 (C-9 and C-10), 125.7, 125.7, 125.8, 125.9, 126.0, 126.3 (C-7a, C-11a), 168.6, 170.4, 170.5 (C-4), 203.9, 204.1 (C-1'). – MS (70 eV, EI): m/z (%) = 331.2(24) [M^+], 258.1(100) [$C_{15}H_{16}NO_3^+$], 191.1[$C_{11}H_{13}NO_2^+$]; $C_{19}H_{25}NO_4$ (331.41); calcd. 331.1784; found 331.1784.

2-(8,11-Dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]-isoquinolin-2-yl)-butanol (**28**)

To a stirred suspension of lithium aluminium hydride (29 mg, 0.75 mmol) in tetrahydrofuran (1 cm^3) at −50 °C a solution of the aldehyde **27** (25 mg, 75.4 μmol) in tetrahydrofuran (2 cm^3) was added dropwise. The reaction mixture was stirred for 4.5 h at 25 °C and quenched with water (0.03 cm^3). After stirring for 10 min an aqueous sodium hydroxide solution (0.03 cm^3, 15%) was added, stirring was continued for 10 min and water (0.07 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 (silica gel; eluent: CH_2Cl_2/MeOH; 10:1). The title compound was obtained as a yellow oil (8 mg, 44%).

UV/vis (CH_3CN): λ_{max} (lg ε) = 201.0 nm (4.555), 282.5(3.496), 286.0(3.499). – IR (film): ν = 3384 cm^{-1} (OH), 2930 (C-H), 2873 (OMe), 1464 (CH_2), 1361 (CH_3), 856. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 – 0.97 (m, 3 H), 1.21 – 2.19 (m, 8 H), 2.40 – 2.40 (m, 7 H), 2.74 – 3.07 (m, 2 H), 3.60 – 4.10 (m, 9 H), 6.60 – 6.65 (m, 2 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.14, 11.26, (C-4'), 16.27, 20.51, 21.39 (C-3'), 25.59, 25.86, 25.97 (C-7), 29.32, 30.54, 33.34 (C-3), 40.71 (C-1), 40.91, 42.59 (C-2), 45.94, 46.01 (C-4), 48.51, 58.78 (C-2'), 52.31 (C-6), 55.30 – 55.88 (OMe), 58.86 (C-11b), 64.34, 65.25, 65.36 (C-1'), 106.9 – 108.0 (C-9, C-10), 127.0 – 128.5 (C-7a, C-11a), 150.7 – 151.2 (C-8, C-11). – MS (70 eV, EI): m/z (%) = 319.3(5) [M^+], 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) [$C_{10}H_{10}NO_2^+$].

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