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Synthesis of Bioactive 2-Aza-Analogues of Ipecac and Alangium Alkaloids

Michael Kölzer,[a] Kerstin Weitzel,[b] H. Ulrich Göringer,[b] Eckhard Thines,[c] and Till Opatz*[a]

Polycyclic alkaloids with potent eukaryotic cytotoxicity have been isolated from the tropical shrubs *Cephaelis ipecacuanha* and *Alangium lamarckii*.[1,2] Their skeleton features an invariable benzoquinolizidine core, which is linked to a bi- or tricyclic unit by a methylene bridge (Figure 1).

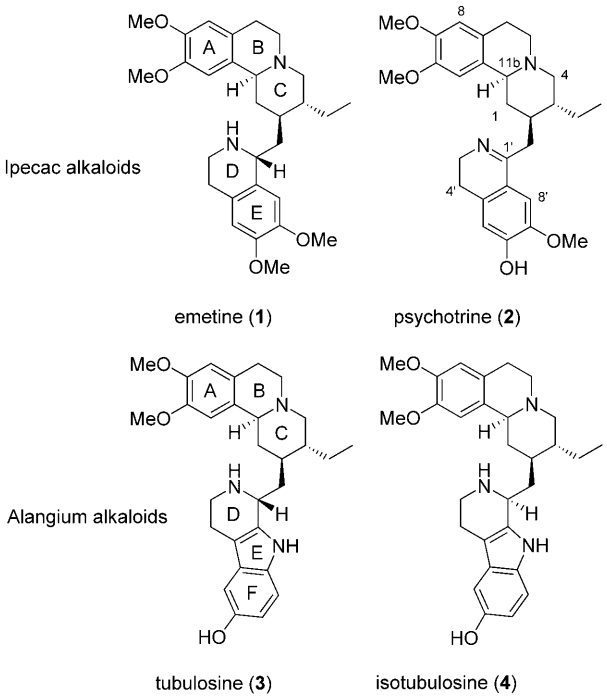
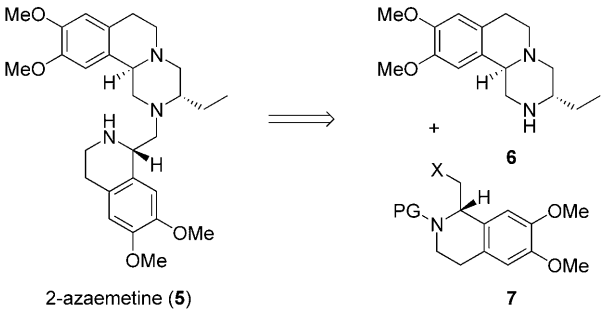


Figure 1. Structures of some ipecac and alangium alkaloids.

Due to their striking bioactivity,[3–5] the ipecac alkaloid emetine (**1**) and its synthetic derivative dehydroemetine have been used for the treatment of protozoal infections, such as amebiasis, trypanosomiasis and bilharziasis, which pose a constant threat to inhabitants of tropical areas.[6,7] In addition, emetine (**1**) has recently become an attractive anticancer and antiviral target.[8–10] However, these alkaloids have severe side effects; their therapeutic window is small, and safer alternatives are needed. Herein, we describe a short and versatile synthesis of functional emetine mimetics, which facilitates the establishment of structure–activity relationships.[11–13]

Replacement of methine carbon C2 in the ABC-ring system of the ipecac and alangium alkaloids by nitrogen should yield analogues resembling their natural counterparts with respect to their preferred conformation and charge distribution at physiological pH. At neutral pH, the diethylenetriamine portion of the aza-analogues will be protonated at both termini, that is, at the same positions as the natural products.[14] Furthermore, the possibility of attaching different DE- or DEF-ring systems to the aza-analogous ABC-ring building block in a C–N bond formation should permit the preparation of a broad variety of analogues in a combinatorial search for drugs with favorable properties (Scheme 1).



Scheme 1. Retrosynthetic analysis of 2-azaemetine.

For the synthesis of the crucial pyrazinoisoquinoline building block **6**, (*S*)-2-aminobutyric acid (**8**) was nosylated and coupled to homoveratrylamine. N-Allylation of the sulfonamide followed by dihydroxylation and periodate cleavage gave a reactive aldehyde. Upon treatment with $POCl_3$, the aldehyde converted to the protected tricycle **10** in a Speckamp cyclization with virtually complete diastereoselectivity.[15,16] Denosylation with thiolate[17] and reduction of amide **11** resulted in the secondary amine **6**. Surprisingly, all attempts to link **6** to a suitable DE-ring system by means of an N-alkylation or a reductive amination were unsuccessful. In contrast, reaction with *N*-chloroacetyl homoveratrylamine followed by a Bischler–Napieralski cyclization produces the desired dihydroisoquinoline **13**, which is the 2-aza-analogue of *O*-methylpsychotrine. Catalytic hydrogenation of the imine resulted in a 2:1 mixture of 2-azaemetine (**5**) and 2-azaisoemetine (**14**), while reduction with $NaCNBH_3$ gave a 7:1 selectivity in favor of the natural diastereomer (Scheme 2).[18,19] Attempts to prepare either amine **5** or **14** by enantioselective reduction of imine **13** failed, presumably due to the chelating properties of reactant and/or product.

[a] *Dr. M. Kölzer, Prof. Dr. T. Opatz*
Institute for Organic Chemistry, University of Mainz
Duesbergweg 10-14, 55128 Mainz (Germany)
Fax: (+49) 6131-3922338
E-mail: opatz@uni-mainz.de

[b] *K. Weitzel, Prof. Dr. H. U. Göringer*
Genetics, Darmstadt University of Technology
Schnittspahnstrasse 10, 64287 Darmstadt (Germany)

[c] *Dr. E. Thines*
Institute for Biotechnology and Drug Research (IBWF)
Erwin Schrödinger-Str. 56, 67663 Kaiserslautern (Germany)

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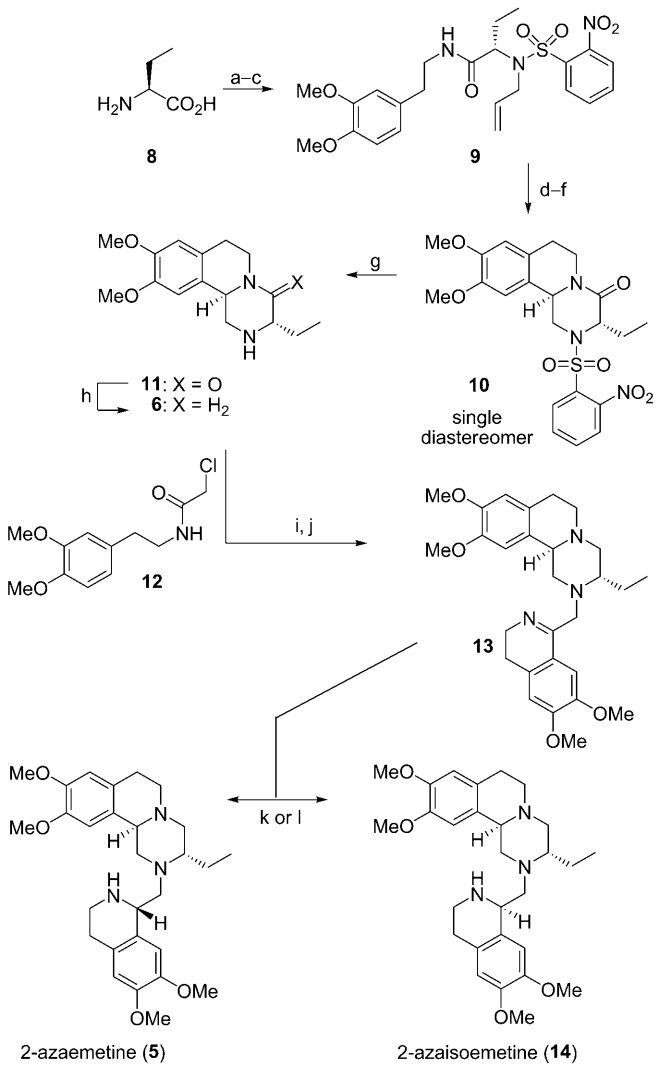
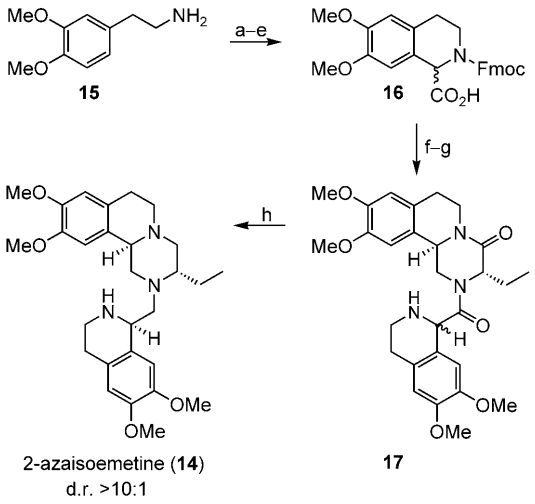


Scheme 2. Preparation of 2-azaemetine **5**. *Reagents and conditions*: a) 2-$NO_2C_6H_4SO_2Cl$, aq NaOH, CH_2Cl_2, RT, 12 h, then reflux, 3 h; b) EDC·HCl, homoveratrylamine, 1-hydroxybenzotriazole, THF, 3.5 h; c) allyl bromide, K_2CO_3, $BnNEt_3Cl$, MeCN, RT, 2.5 h, then 50 °C, 2 h, 63% (three steps); d) $K_2OsO_2(OH)_4$, $(DHQD)_2$-PHAL, $K_3[Fe(CN)_6]$, *t*BuOH/H_2O (1:1), 0 °C, 3.5 h; e) $NaIO_4$, THF/H_2O (1:2), 1.5 h; f) $POCl_3$, CH_2Cl_2, 14 h, 79% (three steps); g) 2-mercaptoethanol, DBU, DMF, 50 °C, 2 h, 97%; h) $LiAlH_4$, THF, 50 °C, 2 h, 89%; i) $EtNiPr_2$, DMF, 90 °C, 14 h; j) $POCl_3$, toluene, reflux, 45 min, 49% (two steps); k) $NaCNBH_3$, AcOH, EtOH, 60 °C, 2 h, 76% (product ratio: **5**/**14**; 7:1); l) H_2, Pd/C, THF, 20 bar, 4 d, 56% (product ratio: **5**/**14**; 2:1). EDC, 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide; $(DHQD)_2$-PHAL, hydroquinidine 1,4-phthalazinediyl diether; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

For the preparation of **14**, the Fmoc-protected tetrahydroisoquinoline-1-carboxylic acid *rac*-**16** obtained in five steps from homoveratrylamine was used as the coupling component for the northern half of the compound.[20–22] Acylation of amine **11** was achieved according to a modified Steglich protocol.[23] After removal of the Fmoc group, double reduction yielded **14** with high diastereoselectivity. Apparently, the configurationally labile C1′ had epimerized to the thermodynamically favored form during the last steps (Scheme 3).

The preparation of 2-azadeoxytubulosine **21** was achieved according to the same sequence used for the preparation of **5**.

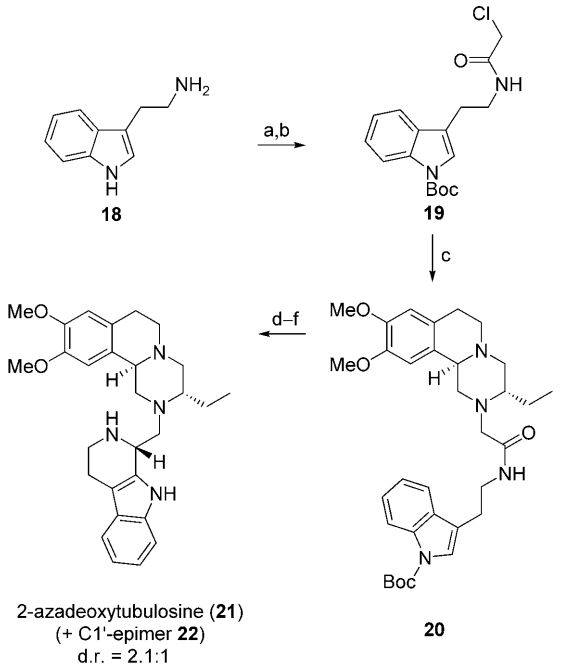


Scheme 3. Synthesis of 2-azaisoemetine **14** with a diasteromeric ratio (d.r.) of >10:1. *Reagents and conditions*: a) EtO_2CCOCl, Et_2O, 0 °C→25 °C, 1.75 h; b) $POCl_3$, toluene/EtOH (10:1), reflux, 3 h; c) H_2, Pd/C, EtOH, 1 bar, 12 h; d) LiOH, THF/H_2O (3:1), 45 min; e) Fmoc-OSu, $NaHCO_3$, H_2O/1,4-dioxane (1:1), 45 min, 39% (five steps); f) **11**, DIC, DMAP, CH_2Cl_2, 0 °C→25 °C, 1.5 h; g) Et_2NH, MeCN, 45 min, 69% (two steps); h) $LiAlH_4$, THF, microwave, 65 °C, 15 min, 97%. Fmoc-OSu, *N*-(9-fluorenylmethoxycarbonyloxy) succinimide; Fmoc, 9-fluorenylmethoxycarbonyl; DIC, *N*,*N*′-diisopropylcarbodiimide; DMAP, 4-(dimethylamino)pyridine.

Boc-protected *N*-chloroacetyltryptamine **19** was used for the N-alkylation of **6**. After deprotection and Bischler–Napieralski-cyclization, reduction of the resulting dihydrocarboline with $NaCNBH_3$ gave a 2.1:1 mixture of **21** and its C1′-epimer **22** (2-azadeoxyisotubulosine; Scheme 4).[24]

After separation of the diastereomeric pairs **5**/**14** and **21**/**22** by preparative HPLC, biological evaluation of the pure compounds was performed using different cellular test systems. The antiprotozoal activity was assayed using noninfective (insect stage) and infective (blood stage) African trypanosomes (*Trypanosoma brucei brucei*, strain Lister 427). The cytotoxicity against mammalian cells was determined using L-1210 and colo 320 cell lines. The results are summarized in Figure 2 and Table 1.

While compounds **5** and **21** were about six to sevenfold less potent than emetine (**1**), they were about tenfold more active than their C1′-epimers in the *T. b. brucei* assay. The same holds true for the cytotoxicity, which roughly parallels the antitrypanosomal activity.[25,26] However, compared to emetine, which was used as a positive control, the 2-aza-analogue **5** exhibits an improved potency/toxicity ratio (Table 1). In all tested cases, infective stage trypanosomes were about twice as sensitive than noninfective parasites; this is probably due to the different surface structure of the parasite at the noninfective stage. Importantly, onset of growth arrest coincides with the development of a severe and characteristic morphological alteration in which the normally elongated parasite cell bodies retract from the anterior end, thereby generating a rounded, tadpole-like cell shape. Identical morphological characteristics were also identified with **5**- and **21**-treated *Leishmania tarentolae* cells,[27] indicating that the same, or at least a similar, growth inhibition



Scheme 4. Synthesis of 2-azadeoxytubulosine **21** and the C1′-epimer **22** with a diasteromeric ratio (d.r.) of 2.1:1. *Reagents and conditions*: a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C, 45 min; b) $(Boc)_2O$, DMAP, CH_2Cl_2, 0 °C→25 °C, 45 min, 75% (two steps); c) **6**, Et*Ni*Pr_2, BaO, MeCN, microwave, 100 °C, 45 min, 81%; d) TFA, Me_2S, 0 °C→25 °C, 12 h; e) $POCl_3$, toluene, reflux, 1 h; f) $NaCNBH_3$, AcOH, EtOH/THF (50:3), 12 h 51% (three steps). Boc, *tert*-butoxycarbonyl; TFA, trifluoroacetic acid.

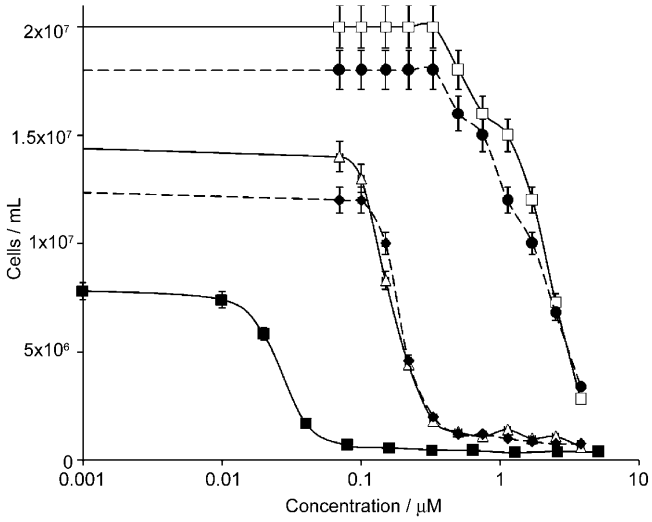


Figure 2. Antitrypanosomal activity against the insect stage of *T. b. brucei* (strain Lister 427). **1**, ■; **5**, △; **14**, □; **21**, ◆; **22**, ●.

mechanism operates in different protozoan parasites. Remarkably, the morphotype induced by compounds **5** and **21** resembles the tadpole-like phenotype of a transdominant trypanosome mutant reported by Lamb et al.[28] Thus, the two compounds can be used as small-molecule modulators or "chemical genetic" tools to illuminate trypanosome morphogenetics.

Table 1. Cytotoxicity against African trypanosomes and mammalian cancer cell lines.[a]

Compd	LC_{50} (*T. b. brucei*) [μM]		LC_{50} [μM]	
	noninfective	infective	L-1210	Colo 320
1	0.03	0.015	0.04	0.1
5	0.18	0.08	0.4	2
14	2.1	1.0	2	5
21	0.2	0.1	0.3	0.3
22	2.0	1.0	5	5
23	>1.3	nd[b]	>25	>25

[a] All values determined at least in triplicate. Standard deviations vary between 3–5%. [b] Not determined.

The assignment of the configuration of the newly formed stereocenter at C1′ in compounds **5**, **14**, **21**, and **22** was performed based on one-dimensional NMR and NOESY data. In each diastereomeric pair, one compound showed a significant upfield shift of both the methoxy group in position 10 and the hydrogen in position 11, indicative of an anisotropic shielding by the E- or EF-ring system. This has also been observed for the natural series.[1,24,29,30] While azaemetines **5** and **14** behaved in a similar manner to their natural counterparts with respect to the chemical shift, line shape, and coupling pattern of the H-1′ resonances, nuclear Overhauser effect (NOE) data indicated an unusual behavior for compounds **21** and **22**. As in the natural series, one of the compounds (**21**) showed the downfield shifts in the A-ring observed for the iso-series, but failed to show the characteristic triplet for the H1′ signal. However, its diastereomer **22** gave the doublet, which is characteristic for tubulosine (**3**), but did not show any anisotropic shielding by the A-ring. NOESY spectra recorded in $CDCl_3$ revealed a remarkable and unexpected proximity of the indole NH proton to the axial proton in position 11b for **21** and **22**. This is in contrast to the corresponding data for compounds **5** and **14**, as well as to the crystal structure of tubulosine (**3**),[31] in which the DEF-ring system points towards the opposite face of the ABC tricycle. Thus, NOE contacts and coupling constants of H1′, as well as the anisotropic shielding, are interchanged when switching form the natural to the 2-aza-series. A possible explanation for the unusual conformational preference of the alangium-alkaloid-derived 2-aza-analogues could be the formation of a hydrogen bond between the indole NH and N2.[32,33] Based on the full set of NOE data and molecular modeling experiments, the configuration of **21** and **22** can be unambiguously assigned; the results are in accordance with their biological activity (Figure 3).[12,25]

To investigate the relevance of the southern half of the molecules for their bioactivity, the truncated compound **23** was prepared by condensation of Fmoc-L-pipecolic acid with ABC building block **11** followed by deprotection and reduction (Scheme 5).

Again, epimerization of the newly introduced stereocenter was observed, which in this case led to a nearly equimolar mixture of C1′-epimers. Remarkably, this mixture was neither active against trypanosomes nor cytotoxic. Thus it can be as-

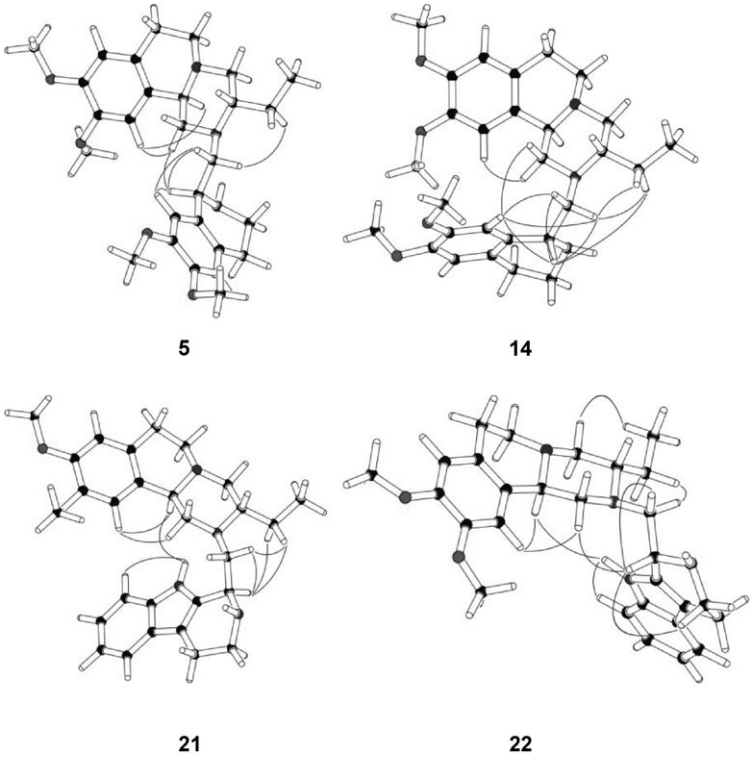
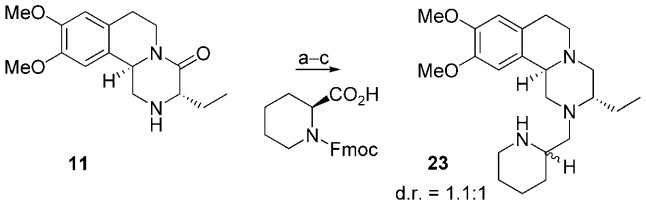


Figure 3. Energy-minimized (MD/MM2) models of 2-azaemetine (**5**), 2-azaisoemetine (**14**), 2-azadeoxytubulosine (**21**) and 2-azadeoxyisotubulosine (**22**) showing relevant NOE contacts.



Scheme 5. Synthesis of the truncated analogue **23** with a diasteromeric ratio (d.r.) of 1.1:1. *Reagents and conditions*: a) Fmoc-L-pipecolic acid (structure shown), DIC, DMAP, CH_2Cl_2, 0 °C→25 °C, 85 min; b) Et_2NH, MeCN, 45 min; c) $LiAlH_4$, THF, 55 °C, 2 h, 65% (three steps).

sumed that the E-ring of the ipecac alkaloids and the EF-ring system of the alangium alkaloids are required for their bioactivity.

In conclusion, the presented 2-aza-analogues show the characteristic structure–activity relationships of the natural series. Although they are less active than their natural counterparts, mimetic **5** shows an improved potency/toxicity ratio compared with the benchmark compound emetine (**1**). The modular assembly of the presented mimetics allowed, for the first time, the determination of the role of the aromatic ring(s) in the southern half of the scaffold, and this information will simplify the identification of further key elements of the pharmacophore.

Experimental Section

(*S*)-2-[Allyl-(2-nitrobenzenesulfonyl)amino]-*N*-[2-(3,4-dimethoxyphenyl)ethyl]butyramide (9)

Compound **8** (500 mg, 3.6 mmol) and NaOH (427 mg, 10.7 mmol, 3 equiv) were dissolved in distilled H_2O (8 mL). After 5 min, a solution of 2-nitrobenzenesulfonyl chloride (867 mg, 3.9 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) was added slowly (20 min) with vigorous stirring. After 12 h stirring at RT, the reaction mixture was heated to reflux for a further 3 h. After separation of the organic layer, the aqueous phase was acidified to pH 2 by addition of 7% H_2SO_4 and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine (2×10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. (*S*)-2-(2-Nitrobenzenesulfonylamino)butyric acid was obtained as a yellow oil that crystallized into colorless needles (740 mg, 2.6 mmol, 71%): $R_f = 0.45$ (EtOAc + 1% AcOH); mp: 132–133 °C; $[\alpha]_D^{23} = -164.6$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$–7.85 (m, 1H, H3′), 7.68–7.63 (m, 1H, H6′), 7.56–7.50 (m, 2H, H4′, H5′), 6.52 (d, $J = 8.0$ Hz, 1H, SO_2NH), 3.78 (dt, $J_d = 5.1$ Hz, $J_t = 7.9$ Hz, 1H, NCHCO), 1.73 (mc, 1H, CH_3CH_2-a), 1.65 (mc, 1H, CH_3CH_2-b), 0.74 ppm (t, $J = 7.4$ Hz, 3H, CH_3CH_2); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): $\delta = 172.4$ (CO), 147.3 (C2′), 133.9 (C4′), 133.4 (C1′), 132.4 (C5′), 129.9 (C6′), 124.1 (C3′), 57.2 (NCHCO), 25.2 (CH_3CH_2), 10.0 ppm (CH_3CH_2); IR (KBr): $\tilde{\nu} =$ 3486, 3333, 2932, 1712, 1632, 1535,1453, 1360, 1169, 1125, 1065, 789, 731 cm^{-1}; MS (ESI): *m/z* (%): 311.1 (100) $[M+Na]^+$; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{10}H_{12}N_2O_6S$: 311.0308, found: 311.0299; Anal. calcd for $C_{10}H_{12}N_2O_6S$: C 41.66, H 4.20, N 9.72, S 11.12, found: C 41.66, H 4.24, N 9.78, S 11.19.

The butyric acid intermediate (2.24 g, 7.8 mmol), HOBt·H_2O (1.31 g, 8.6 mmol, 1.1 equiv) and homoveratrylamine (1.55 g, 8.6 mmol, 1.1 equiv) were suspended in dry THF (30 mL). Under stirring, EDC·HCl (1.64 g, 8.6 mmol, 1.1 equiv)[34] was added and the mixture was stirred for 5 h. The reaction mixture was concentrated in vacuo, and the yellow oily residue was partitioned between EtOAc (100 mL) and 1 N HCl (100 mL). After the addition of further EtOAc (100 mL), the aqueous phase was removed. The organic layer was washed with 1 N HCl (3×35 mL) and saturated aq $NaHCO_3$ (3× 35 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. (*S*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(2-nitrobenzenesulfonylamino)butyramide was obtained as a viscous yellow oil that solidified to a yellow glass (3.31 g, 7.3 mmol, 94%): $R_f = 0.44$ (EtOAc + 3% AcOH); $[\alpha]_D^{22} = -59.3$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.10$–8.05 (m, 1H, H6′), 7.89–7.86 (m, 1H, H3′), 7.74 (mc, 2H, H4′, H5′), 6.80 (d, $J = 7.9$ Hz, 1H, H5″), 6.70 (dd, $J = 10.0$, 2.0, Hz, 2H, H2″, H6″), 6.40 (br t, $J = 5.7$ Hz, 1H, NHCO), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.79 (dt, $J_d = 3.3$, $J_t = 7.6$ Hz, 1H, NCHCO), 3.46 (mc, 1H, $ArCH_2CH_2$-a), 3.36 (dtd, $J_d = 13.1$, 5.6 Hz, $J_t = 7.2$ Hz, 1H, $ArCH_2CH_2$-b), 2.70 (mc, 2H, $ArCH_2$), 1.76 (mc, 1H, CH_3CH_2-a), 1.64 (ddd, $J = 14.8$, 11.1, 3.7 Hz, 1H, CH_3CH_2-b), 0.77 ppm (t, $J = 7.4$ Hz, 3H, CH_3CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 170.2$ (CO), 149.3 (C3″), 148.0 (2C, C2′, C4″), 134.1 (C4′), 133.5 (C1′), 133.0 (C5′), 131.0 (2C, C6′,C1″), 125.7 (C3′), 120.9 (C6″), 112.1 (C2″), 111.7 (C5″), 59.5 (NCHCO), 56.1 (OCH_3), 56.0 (OCH_3), 41.0 (NCH_2CH_2), 35.4 ($ArCH_2$), 26.3 (CH_3CH_2), 9.6 ppm (CH_3CH_2); IR (KBr): $\tilde{\nu} = 3342$, 3156, 1665, 1543, 1517, 1467, 1367, 1265, 1236, 1160, 1142, 1027 cm^{-1}; MS (ESI): *m/z* (%): 490.2 (28) $[M+K]^+$, 474.2 (100) $[M+Na]^+$, 469.2 (21) $[M+NH_4]^+$, 452.2 (97) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}N_3O_7S$: 452.1491,

found: 452.1508; Anal. calcd for $C_{20}H_{25}N_3O_7S$: C 53.20, H 5.58, N 9.31, S 7.10, found: C 53.07, H 5.58, N 9.21, S 7.23.

Using an adapted protocol by Albanese et al.,[35] the butyramide intermediate (2.91 g, 6.44 mmol) was dissolved in dry MeCN (30 mL), and finely powdered K_2CO_3 (1.78 g, 12.89 mmol), allyl bromide (1.68 mL, 19.33 mmol) and benzyltriethylammonium chloride (147 mg, 10 mol%) were added. The mixture was stirred for 2.5 h and then warmed to 50 °C until TLC indicated complete conversion (120 min). The yellow reaction mixture was partitioned between Et_2O (30 mL) and H_2O (20 mL). The organic layer was washed with H_2O (15 mL) and the combined aqueous layers were extracted into EtOAc (3×20 mL). The combined organic layers were washed with H_2O (3×15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Compound **9** was obtained as a yellow oil of sufficient purity (3.00 g, 6.1 mmol, 95%): R_f = 0.35 (cyclohexane/EtOAc, 1:1); $[\alpha]_D^{22}$ = −32.5 (c = 0.5, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (dd, J = 7.7, 1.5 Hz, 1H, H6′), 7.69 (mc, 2H, H4′, H5′), 7.61 (dd, J = 7.6, 1.5 Hz, 1H, H3′), 6.81 (d, J = 8.1 Hz, 1H, H5″), 6.73 (m, 2H, H2″, H6″), 6.50 (br t, J = 5.5 Hz, 1H, NHCO), 5.64 (ddt, J_t = 6.5, J_d = 17.0, 10.1 Hz, 1H, =CH), 5.17 (ddd, J = 17.0, 2.5, 1.4 Hz, 1H, =CH_2-*syn*), 5.04 (ddd, J = 10.1, 2.5, 1.4 Hz, 1H, =CH_2-*anti*), 4.13 (t, J = 7.5 Hz, 1H, NCHCO), 4.09 (ddt, J_d = 16.2, 6.5, J_t = 1.4 Hz, 1H, All-CH_2-a), 3.91 (ddt, J_d = 16.2, 6.5, J_t = 1.4 Hz, 1H, All-CH_2-b), 3.87 (s, 3H, OCH_3), 3.86 (s, 1H, OCH_3), 3.44 (pseudo-q, J = ~7 Hz, 2H, $ArCH_2CH_2$), 2.73 (br t, J = ~7 Hz, 1H, $ArCH_2$), 2.01 (d-pseudo-quin, J_d = 14.8 Hz, J_{quin} = ~7 Hz, 1H, CH_3CH_2-a), 1.61 (d-pseudo-quin, J_d = 14.8 Hz, J_{quin} = ~7 Hz, 1H, CH_3CH_2-b), 0.73 ppm (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.5 (CO), 149.2 (C3″), 148.0 (C2′), 147.9 (C4″), 133.9 (2C, allyl=CH, C4′), 133.8 (C1′), 131.9 (C5′), 131.6 (C6′), 131.3 (C1″), 124.3 (C3′), 120.9 (C6″), 118. 9 (allyl = CH_2), 112.1 (C2″), 111.7 (C5″), 61.5 (NCHCO), 56.1 (OCH_3), 56.0 (OCH_3), 47.9 (allyl-CH_2), 41.1 (NCH_2CH_2), 35.2 ($ArCH_2$), 22.4 (CH_3CH_2), 10.7 ppm (CH_3CH_2); IR (NaCl): $\tilde{\nu}$ = 2937, 1675, 1545, 1516, 1466, 1372, 1263, 1237, 1158, 1028 cm^{-1}; MS (ESI): *m/z* (%): 514.2 (81) $[M+Na]^+$, 492.2 (70) $[M+H]^+$, 468.3 (100), 428.3 (78); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{29}N_3O_7S$: 492.1804, found: 492.1814; Anal. calcd for $C_{23}H_{29}N_3O_7S$: C 56.20, H 5.95, N 8.55, S 6.52, found: C 56.31, H 5.95, N 8.41, S 6.34.

(3*S*,11b*R*)-3-Ethyl-9,10-dimethoxy-2-(2-nitrobenzenesulfonyl)-1,2,3,6,7,11 b-hexahydro-pyrazino[2,1-a]-isoquinolin-4-one (10)

According to an adapted protocol by Sharpless et al.,[36,37] *N*-allyl sulfonamide **9** (8.80 g, 17.90 mmol) was dissolved in *t*BuOH (50 mL) and added under stirring to a solution of finely powdered K_2CO_3 (7.43 g, 53.70 mmol) and freshly ground $K_3[Fe(CN)_6]$ (13.56 g, 41.20 mmol) in H_2O (50 mL). The mixture was cooled to 0 °C and $(DHQD)_2$-PHAL (139.50 mg, 1 mol%) and $K_2OsO_2(OH)_4$ (26.40 mg, 0.4 mol%) were added. The mixture was stirred at 0 °C until TLC indicated complete conversion. (12 h). The reaction was quenched by the addition of solid Na_2SO_3 (9 g, 71.6 mmol) and stirred for 45 min at RT. The mixture was partitioned between EtOAc (45 mL) and H_2O (45 mL), and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with 0.5 N HCl (25 mL), brine (25 mL), saturated aq $NaHCO_3$ (25 mL), again with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (EtOAc) gave (2′*RS*,2*S*)-2-[2,3-dihydroxypropyl-(2-nitrobenzenesulfonyl)amino]-*N*-[2-(3,4-dimethoxyphenyl)ethyl]butyramide a pale yellow foam (8.65 g, 16.47 mmol, 92%): R_f = 0.18 (EtOAc); $[\alpha]_D^{22}$ = −35 (c = 1, $CHCl_3$); ^{1}H NMR, COSY, TOCSY, NOESY, HSQC, HMBC (500 MHz, $CDCl_3$; 2:1 mixture of diastereomers A and B): δ = 8.02 (ddd, J = 5.7, 4.1, 1.7 Hz, 1H, H6′), 7.73 (mc, 2H, H4′, H5′), 7.63 (ddd, J = 7.4, 5.7, 1.7 Hz, 1H, H3′), 6.83 (dd, J = 8.0, 3.8 Hz, 1H, H5″), 6.79–6.73 (m, 2H, H2″, H6″), 6.60 (br t, J = 5.1 Hz, 1H, $NHCO^A$), 6.36 (br t, J = 5.6 Hz, 1H, $NHCO^B$), 4.16 (t, J = 7.6 Hz, 1H, $NCHCO^B$), 4.12 (t, J = 7.8 Hz, 1H, $NCHCO^A$), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.75 (ddt, J_d = 14.9, 3.7 Hz, J_t = 7.4 Hz, 1H, *CH*OH), 3.69–3.56 (m, 3H, NCH_2-a, $HOCH_2$-a, $ArCH_2CH_2$-a), 3.55–3.46 (m, 2H, $HOCH_2$-b, $ArCH_2CH_2$-b), 3.32 (dd, J = 15.5, 3.3 Hz, 1H, NCH_2-a^A), 3.21 (dd, J = 15.7, 7.9 Hz, 1H, NCH_2-b^B), 2.80 (t, J = 6.4 Hz, 2H, $ArCH_2$), 2.47 (br s, 2H, OH^A), 2.16 (br s, 2H, OH^B), 1.99 (mc, 1H, CH_3CH_2-a), 1.65 ppm (mc, 1H, CH_3CH_2-b); ^{13}C NMR, HSQC, HMBC (125.8 MHz, $CDCl_3$): δ = 171 (NCO), 149.19 ($C3''^B$), 149.18 ($C3''^A$), 148.15 ($C2'^A$), 148.11 ($C2'^B$), 147.91 ($C4''^B$), 147.89 ($C4''^A$), 134.3 ($C4'^A$), 134.2 ($C4'^B$) 132.8 ($C1'^B$), 132.5 ($C1'^A$), 132.1 ($C5'^B$), 132.0 ($C5'^A$), 131.5 ($C6'^A$), 131.3 ($C6'^B$), 131.1 ($C1''^A$), 131.0 ($C1''^B$), 124.48 ($C3'^B$), 124.43 ($C3'^A$), 120.93 ($C6''^B$), 120.88 ($C6''^A$), 112.1 (C2″), 111.66 ($C5''^A$), 111.61 ($C5''^B$), 71.7 ($CHOH^A$), 70.0 ($CHOH^B$), 64.6 (CH_2OH^B), 63.5 (CH_2OH^A), 61.79 (NCHCO), 56.1 (OCH_3), 56.0 (OCH_3), 48.8 (NCH_2^B), 47.7 (NCH_2^B), 41.3 ($ArCH_2CH_2$), 35.1 ($ArCH_2^A$), 35.0 ($ArCH_2^B$), 22.4 ($CH_3CH_2^B$), 21.9 ($CH_3CH_2^A$), 10.6 ($CH_3CH_2^A$), 10.2 ppm ($CH_3CH_2^B$); IR (NaCl): $\tilde{\nu}$ = 3355, 3094, 2939, 2838, 1657, 1591, 1544, 1516, 1466, 1373, 1263, 1237, 1159, 1028, 852, 736 cm^{-1}; MS (ESI): *m/z* (%): 548.17 (100) $[M+Na]^+$; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{31}N_3O_9S$: 548.1679, found: 548.1691; Anal. calcd for $C_{23}H_{31}N_3O_9S$: C 52.56, H 6.06, N 7.98, S 6.21, found: C 52.63, H 6.06, N 7.95, S 5.96.

The dihydroxylated intermediate (2.80 g, 5.33 mmol) was dissolved in THF (20 mL). After addition of H_2O (40 mL) and finely powdered $NaIO_4$ (1.48 g, 6.93 mmol), the mixture was stirred until TLC indicated complete conversion (90 min). The mixture was partitioned between H_2O (10 mL) and EtOAc (20 mL), and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic layers were washed with H_2O (15 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The sensitive aldehyde, (*S*)-2-[*N*-(2-oxoethyl-(2-nitrobenzenesulfonyl)amino]-*N*-[2-(3,4-dimethoxyphenyl)ethyl]butyramide, was obtained as a pale yellow foam (2.58 g, 5.22 mmol, 98%): R_f = 0.53 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.42 (s, 1H, CHO), 8.01 (dd, J = 7.5, 1.8 Hz, 1H, H6′), 7.72 (mc, 2H, H4′, H5′), 7.65 (mc, 1H, H3′), 6.81 (d, J = 8.7 Hz, 1H, H5″), 6.74 (m, 2H, H2′, H6′), 6.41 (br t, J = 5.6 Hz, NHCO), 4.33–4.09 (m, 3H, CH_2CHO, NCHCO), 3.86 (s, 6H, OCH_3), 3.45 (mc, 2H, $ArCH_2CH_2$), 2.74 (t, J = 7.0 Hz, 1H, $ArCH_2$), 1.83 (mc, 1H, CH_3CH_2-a), 1.51 (d-pseudo-quin, J_d = 14.5 Hz, J_{quin} = 7.3 Hz, 1H, CH_3CH_2-b), 0.73 ppm (t, J = 7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 196.9 (CHO), 169.3 (NCO), 149.13 (C3″), 147.9 (C4″), 147.82 (C2′), 134.4 (C4′), 133.1 (C1′), 132.2 (C5′), 131.5 (C6′), 131.1 (C1″), 124.5 (C3′), 120.8 (C6″), 112.1 (C2″), 111.6 (C5″), 61.3 (NCHCO), 56.1 (OCH_3), 56.0 (OCH_3), 53.3 (CH_2CHO), 41.0 ($ArCH_2CH_2$), 35.0 ($ArCH_2$), 23.0 (CH_3CH_2), 10.2 ppm (CH_3CH_2); IR (NaCl): $\tilde{\nu}$ = 3355, 3094, 2938, 2837, 1733, 1671, 1591, 1544, 1516, 1465, 1372, 1354, 1263, 1237, 1160, 1028 cm^{-1}. The product was of sufficient purity and slowly decomposed upon standing.

The aldehyde intermediate (2.41 g, 4.88 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and freshly distilled $POCl_3$ (900 μL, 9.77 mmol) was added.[16,38] The yellow mixture slowly turned brown and stirring was continued until TLC indicated complete conversion (2 h). Besides the main cyclization product (R_f = 0.19; EtOAc/petroleum ether/CH_2Cl_2, 2:2:3), a side product was detected (R_f = 0.37; EtOAc/petroleum ether/CH_2Cl_2, 2:2:3). Excess $POCl_3$ and solvent were removed by distillation (125 °C). The residue was partitioned between EtOAc (15 mL) and saturated aq $NaHCO_3$ (20 mL), and the aqueous phase was extracted with EtOAc (3×10 mL). The organic

phase was separated and dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark yellow viscous oil. Purification by column chromatography (silica; EtOAc/petroleum ether/CH_2Cl_2, 2:2:3) gave compound **10** as a yellow foam (2.04 g, 4.3 mmol, 88%): *ee* > 94% (see Supporting Information); $[\alpha]_D^{25} = -55.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): $\delta = 7.97–7.93$ (m, 1H, H6′), 7.57–7.70 (m, 3H, H3′, H4′, H5′), 6.67 (s, 1H, H11), 6.56 (s, 1H, H8), 4.86 (dd, $J = 7.8$, 3.5 Hz, 1H, H11b), 4.73–4.77 (m, 1H, H6-a), 4.40 (t, $J = 6.1$ Hz, 1H, H3), 4.12 (dd, $J = 12.6$, 3.7 Hz, 1H, H1-a), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.30 (dd, $J = 12.6$, 8.10 Hz, 1H, H1-b), 2.87 (dt, $J_t = 12.9$ Hz, $J_d = 2.2$, 1H, H6-b), 2.80 (br, dt, $J_t = 11.8$ Hz, $J_d = 2.2$ Hz, 1H, H7-a), 2.55–2.65 (m, 1H, H7-b), 2.00–2.10 (m, 2H, CH_3CH_2), 0.93 ppm (t, $J = 7.5$ Hz, 3H, CH_3CH_2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): $\delta = 167.4$ (CO), 148.5 (C9), 148.2 (C10), 148.05 (C2′), 134.1 (C4′), 132.3 (C1′), 131.9 (C5′), 131.0 (C6′), 127.80 (C7a), 124.5 (C3′), 123.8 (C11a), 111.72 (C8), 108.78 (C11), 61.0 (C3), 56.2 (OCH_3), 56.0 (OCH_3), 54.3 (C11b), 48.9 (C1), 39.7 (C6), 28.31 (C7), 26.9 (CH_3CH_2), 9.7 ppm (CH_3CH_2); IR (NaCl): $\tilde{\nu} = 2936$, 1660, 1542, 1519, 1465, 1438, 1362, 1266, 1229, 1168, 1138, 852, 740 cm^{-1}; MS (FD): *m/z* (%): 475.2 (100) $[M]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_3O_7S$: 476.1491, found: 476.1498; Anal. calcd for $C_{22}H_{25}N_3O_7S$: C 55.57, H 5.30, N 8.84, S 6.74, found: C 55.59, H 5.26, N 8.73, S 6.84.

The minor product was the corresponding dihydropyrazinone, 1-[2-(3,4-dimethoxyphenyl)ethyl]-3-ethyl-4-(2-nitrobenzenesulfonyl)-3,4-dihydro-1*H*-pyrazin-2-one, which was isolated as a yellow oil (209 mg, 0.44 mmol, 9%): $[\alpha]_D^{22} = +298.9$ ($c = 1$, $CHCl_3$); ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): $\delta = 7.97–7.94$ (m, 1H, H6′), 7.72–7.61 (m, 3H, H3′, H4′, H5′), 6.71 (d, $J = 8.1$ Hz, 1H, H5″), 6.64–6.59 (m, 2H, H2″, H6″), 6.04 (dd, $J = 5.5$ Hz, 1.7 Hz, 1H, H5), 5.68 (d, $J = 5.5$ Hz, 1H, H6), 4.49 (ddd, $J = 8.9$, 6.0, 1.8 Hz, 1H, H3), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.61 (t, $J = 7.5$ Hz, 2H, NCH_2), 2.61 (m, 2H, NCH_2CH_2), 1.66 (mc, 2H, CH_3CH_2), 0.98 ppm (t, $J = 7.4$ Hz, 3H, CH_3CH_2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): $\delta = 164.2$ (C2), 149.1 (C2′), 148.2 (C3″), 147.9 (C4″), 134.3 (C4′), 132 (C1′), 131.9 (C5′), 130.8 (C6′), 130.2 (C1″), 124.5 (C3′), 120.9 (C6″), 118.7 (C6), 111.9 (C2″), 111.4 (C5″), 106.6 (C5), 60.7 (C3), 56.03 (OCH_3), 55.98 (OCH_3), 47.6 (NCH_2), 34.2 (NCH_2CH_2), 23.8 (CH_3CH_2), 10.0 ppm (CH_3CH_2); IR (NaCl): $\tilde{\nu} = 2985$, 2933, 1679, 1591, 1545, 1516, 1456, 1411, 1371, 1264, 1238, 1181, 1142, 1029, 852, 745 cm^{-1}; MS (ESI): *m/z* (%): 498.1 (100) $[M+Na]^+$; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{22}H_{25}N_3O_7S$: 498.1311, found: 498.1326.

(3*S*,11b*R*)-3-Ethyl-9,10-dimethoxy-1,2,3,6,7,11b-hexahydropyrazino[2,1-a]isoquinolin-4-one (11)

Cyclized sulfonamide **10** (1.9 g, 4.0 mmol) was dissolved in dry DMF (20 mL) under rigorous exclusion of air. Under stirring, 2-mercaptoethanol (2.8 mL, 40 mmol, 10 equiv) and DBU (2.99 mL, 20 mmol, 5 equiv) were added.[17,39] The mixture was stirred at 50 °C until TLC indicated complete conversion (2 h). The solvent was removed in vacuo and the remaining yellow oil was purified by column chromatography (silica; EtOAc/petroleum ether/CH_2Cl_2, 8:5:1). The resulting viscous oil crystallized within several months into fine yellow needles (1.13 g, 3.9 mmol, 97%): $R_f = 0.23$ (EtOAc/petroleum ether/Et_2NH, 8:5:1); mp: 97 °C; $[\alpha]_D^{22} = -212.4$ ($c = 0{,}5$, $CHCl_3$); ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): $\delta = 6.63$ (s, 1H, H11), 6.57 (s, 1H, H8), 4.88 (ddd, $J = 12.5$, 4.9, 2.2 Hz, 1H, H6-a), 4.74 (dd, $J = 10.4$, 4.3 Hz, 1H, H11b), 3.86 (s, 1H, OCH_3), 3.85 (s, 1H, OCH_3), 3.69 (dd, $J = 12.6$, 4.6 Hz, 1H, H1-a), 3.39 (dd, $J = 8.0$, 3.6 Hz, 1H, H3), 2.96–2.83 (m, 2H, H7-a, H1-b), 2.82–2.76 (m, 1H, H6-b), 2.62 (br dt, $J_d = \sim 15$ Hz, $J_t = \sim 3$, Hz, 1H, H7-b), 2.07 (mc, 1H, CH_3CH_2-a), 1.82 (br s, NH), 1.74 (mc, 1H, CH_3CH_2-b), 1.01 ppm (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): $\delta = 169.5$ (CO), 147.9 (C9), 147.8 (C10), 127.5 (C7a), 126.3 (C11a), 111.8 (C8), 107.9 (C11), 60.5 (C3), 57.0 (C11b), 56.2 (OCH_3), 55.8 (OCH_3), 50.1 (C1), 39.0 (C6), 28.4 (C7), 25.8 (CH_3CH_2), 10.2 ppm (CH_3CH_2); IR (NaCl): $\tilde{\nu} = 3457$, 3316, 2961, 2933, 2854, 1630, 1515, 1463, 1436, 1360, 1319, 1292, 1258, 1227, 1113, 1009, 848, 771 cm^{-1}; MS (ESI): *m/z* (%): 291.2 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{22}N_2O_3$: 291.1709, found: 291.1701.

(3*S*,11b*R*)-3-Ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrazino[2,1-a]isoquinoline (6)

The secondary amine **11** (2.0 g, 6.9 mmol) was dissolved in dry THF (15 mL) and $LiAlH_4$ (2 M in THF, 17 mL, 34.5 mmol, 5 equiv) was added.[40] The grey suspension was stirred for 2 h at 50 °C. After cooling to RT, the reaction was quenched by the addition of 2 N aq NaOH (10 mL) at 0 °C, and the colorless precipitate (insoluble aluminum salts) was removed by filtration. The filter cake was washed with EtOAc (25 mL) and the organic layer was washed with H_2O (15 mL). The combined aqueous layers were extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting yellow oil was purified by column chromatography (silica; EtOAc/petroleum ether/Et_2NH, 5:5:1) to give compound **6** as a yellow oil (1.69 g, 6.1 mmol, 89%): $R_f = 0.22$ (EtOAc/petroleum ether/Et_2NH, 5:5:1); $[\alpha]_D^{23} = -51.3$ ($c = 0.3$, $CDCl_3$); ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): $\delta = 6.61$ (s, 1H, H11), 6.59 (s, 1H, H8), 3.84 (OCH_3), 3.83 (OCH_3), 3.54 (dd, $J = 11.6$, 2.6 Hz, 1H, H1-a), 3.21–3.05 (m, 2H, H11b, H7-a), 2.98–2.90 (m, 2H, H4-a, H6-a), 2.88–2.79 (m, 1H, H3), 2.74 (dd, $J = 11.6$, 10.3 Hz, 1H, H1-b), 2.62 (dd, $J = 16.0$, 4.1 Hz, 1H, H7-b), 2.54 (td, $J_t = 11.5$, $J_d = 4.1$ Hz, 1H, H6-b), 2.10 (t, $J = 10.6$ Hz, 1H, H4-b), 1.43 (mc, 2H, CH_3CH_2), 0.97 ppm (t, $J = 7.5$ Hz, 3H, CH_3CH_2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): $\delta = 147.6$ (C10), 147.1 (C9), 127.2, 127.1 (C7a, C11a), 111.8 (C8), 107.7 (C11), 62.5 (C11b), 61.3 (C4), 56.3 (OCH_3), 56.3 (C3), 56.2 (OCH_3), 52.3 (C6), 50.7 (C1), 29.0 (C7), 27.1 (CH_3CH_2), 10.3 ppm (CH_3CH_2); IR (NaCl): $\tilde{\nu} = 3457$, 3317, 2962, 2933, 2854, 1630, 1515, 1463, 1436, 1360, 1318, 1291, 1257, 1226, 1113, 1009, 848, 771 cm^{-1}; MS (ESI): *m/z* (%): 277.2 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{24}N_2O_2$: 277.1916, found: 277.1927.

2-Chloro-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (12)

Homoveratrylamine (931 μL, 5.52 mmol) and *N*,*N*-dimethylaniline (1.12 mL, 8.85 mmol, 1.6 equiv) were dissolved in dry CH_2Cl_2 (34 mL) and the resulting solution was cooled to 0 °C. Under stirring, a solution of chloroacetyl chloride (0.46 mL, 5.8 mmol, 1.05 equiv) in dry CH_2Cl_2 (15 mL) was added.[41] The mixture was stirred until TLC indicated complete conversion (2 h). The mixture was partitioned between 1 N aq HCl (20 mL) and CH_2Cl_2 (15 mL), and the organic layer was separated and washed with 1 N aq HCl (3×10 mL) and brine (15 mL). After drying (Na_2SO_4), the organic layer was filtered and concentrated in vacuo to give **12** as a green–grey solid (1.39 g, 5.41 mmol, 98%): $R_f = 0.49$ (petroleum ether/EtOAc, 1:1); mp: 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.82$ (d, $J = 8.1$ Hz, 1H, H5), 6.76–6.69 (m, 2H, H2, H6), 6.64 (br s, 1H, NH), 4.03 (s, 2H, CH_2Cl), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.54 (td, $J_t = 7.0$ Hz, $J_d = 5.9$ Hz, 2H, $ArCH_2CH_2$), 2.79 ppm (t, $J = 7.0$ Hz, 2H, $ArCH_2CH_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 166.0$ (CO), 149.3 (C3), 148.0 (C4), 131.0 (C1), 120.8 (C6), 112.9 (C2), 111.7 (C5), 56.04 (OCH_3), 55.98 (OCH_3), 42.7 (CH_2Cl), 41.2 ($ArCH_2CH_2$), 35.1 ppm ($ArCH_2CH_2$); IR (NaCl): $\tilde{\nu} = 3424$, 3313, 3282, 3082, 3000, 2940, 1662, 1642, 1589, 1555, 1518, 1464, 1419, 1262, 1238, 1158, 1139, 1027,

1037, 808 cm^{-1}; MS (ESI): *m/z* (%): 258.10 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{16}ClNO_3$: 258.0891, found: 258.0890.

(3*S*,11b*R*)-2-(6,7-Dimethoxy-3,4-dihydro-isoquinolin-1-yl-methyl)-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrazino[2,1-a]isoquinoline (13)

Amine **6** (350 mg, 1.27 mmol) was dissolved in dry DMF (4 mL) and the resulting solution was degassed by ultrasonication under argon for 15 min. After addition of $EtNiPr_2$ (572 mg, 4.43 mmol, 3.5 equiv) and stirring for 5 min at 0 °C, a solution of amide **12** (326 mg, 1.27 mmol, 1 equiv) in DMF (1 mL) was added. The mixture was stirred for 14 h at 90 °C. When TLC indicated complete conversion of the amine, the solvent was removed in vacuo. The crude was codistilled with toluene repeated and dried in vacuo prior to further purification. Column chromatography (silica; EtOAc/EtOH, 5:1) gave (3*S*,11b*R*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-[3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrazino[2,1-a]isoquinolin-2-yl]acetamide) as a brown oil (439 mg, 0.88 mmol, 70%): R_f = 0.18 (EtOAc/EtOH, 5:1); $[\alpha]_D^{20} = -2.8$ (c = 0.5, $CHCl_3$); ^{1}H NMR, COSY, TOCSY, NOESY, HSQC, HMBC (500 MHz, $CDCl_3$): δ = 7.48 (t, J = 5.7 Hz, 1H, NH), 6.78–6.73 (m, 3H, H2′, H5′, H6′), 6.59 (s, 1H, H8), 6.45 (s, 1H, H11), 3.86 (s, 3H, OCH_3-4′), 3.84 (s, 3H, OCH_3-9), 3.83 (s, 3H, OCH_3-3′), 3.74 (s, 3H, OCH_3-10), 3.59 (mc, 2H, $ArCH_2CH_2$), 3.37 (d, J = 17.3 Hz, 1H, NCH_2CO-a), 3.15 (dd, J = 11.2, 2.7 Hz, 1H, H1-a), 3.06–3.01 (m, 2H, H7-a, H11b), 2.96–2.88 (m, 2H, H6-a, H4-a), 2.85 (d, J = 17.3 Hz, 1H, NCH_2CO-b), 2.82 (t, J = 6.9 Hz, 2H, $ArCH_2$), 2.62 (dd, 15.8, 3.7 Hz, 1H, H7-b), 2.50–2.41 (m, 2H, H6-b, H3), 2.35 (t, J = 11 Hz, 1H, H1-b), 2.05 (dd, J = 11.4, 10.2 Hz, 1H, H4-b), 1.50 (d-pseudo-quin, J_d = 14.7 Hz, J_{quin} = ~7 Hz, 1H, CH_3CH_2-a), 1.61 (d-pseudo-quin, J_d = 14.7 Hz, J_{quin} = ~7 Hz, 1H, CH_3CH_2-b), 0.84 ppm (t, J = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 171.5 (CO), 149.3 (C4′), 148 (C9), 147.9 (C3′), 147.4 (C10), 131.3 (C1′), 127.2 (C7a), 126.9 (C11a), 120.7 (C6′), 112.0, 111.9 (C2′, C5′), 111.5 (C8), 107.6 (C11), 61.54 (C11b), 61.45(C3), 60.11 (C4), 59.3 (C1), 57.3 (NCH_2), 56.3 (OCH_3), 56.00 (OCH_3), 55.99 (OCH_3), 55.9 (OCH_3), 51.9 (C6), 40.1 ($ArCH_2CH_2$), 35.3 ($ArCH_2CH_2$), 29.0 (C7), 24.2 (CH_3CH_2), 10.1 ppm (CH_3CH_2); IR (NaCl): $\tilde{\nu}$ = 3456, 3333, 3097, 2975, 2932, 2874, 1712, 1593, 1536, 1453, 1422, 1360, 1291, 1266, 1169, 1125, 1065, 1009, 905, 789, 743, 731, 654, 597, 560, 501 cm^{-1}; MS (ESI): *m/z* (%): 498.30 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{39}N_3O_5$: 498.2962, found: 498.2955.

The above intermediate (190 mg, 0.38 mmol) was dissolved in dry toluene (8 mL) and treated with freshly distilled $POCl_3$ (105 μL, 1.15 mmol, 3 equiv) under stirring.[38] The yellow reaction mixture was heated to reflux under rigorous exclusion of moisture until TLC indicated complete conversion (45 min). Most of the toluene and the $POCl_3$ were removed by distillation, and the remaining viscous brown residue was suspended in warm dioxane (7.5 mL). The suspension was ultrasonicated and ice (35 g) was added. After basification with 4 N aq NaOH, the product was extracted with EtOAc (6×10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Fast purification by column chromatography (silica; EtOAc/EtOH, 1:1) gave imine **13** as a viscous brown oil (127.6 mg, 0.27 mmol, 70%): R_f = 0.17 (EtOAc/EtOH, 1:1); $[\alpha]_D^{25} = +8.3$ (c = 0.2, $CDCl_3$); ^{1}H NMR, COSY, HSQC, HMBC (400 MHz, $CDCl_3$): δ = 7.81 (s, 1H, H8′), 6.70 (s, 1H, H5′), 6.55 (s, 1H, H8), 6.34 (s, 1H, H11), 4.29 (d, J = 13.0 Hz, 1H, NCH_2C=N-a), 3.92 (s, 3H, OCH_3-6′), 3.90 (s, 3H, OCH_3-7′), 3.81 (s, 3H, OCH_3-9), 3.71 (s, 3H, OCH_3-10), 3.70 (s, 2H, CH_2-3′), 3.27 (dd, J = 11.1, 2.4 Hz, 1H, H1-a), 3.18–3.03 (m, 3H, 1H, NCH_2C=N-b, H7-a, H11b), 3.02–2.92 (m, 2H, H4-a, H6-a), 2.70–2.57 (m, 3H, H4′-a, H4′-b, H7-b), 2.53–2.41 (m, 2H, H3, H6-b), 2.31 (t, J = 10.6 Hz, 1H, H4-b), 2.21 (t, J = 11.1 Hz, 1H, H1-b), 1.92 (tdd, J_t = 7.1 Hz, J_d = 14.7, 2.7 Hz, 1H, CH_3CH_2-a), 1.52 (d-pseudo-quin, J_d = 15.0 Hz, J_{quin} = ~7 Hz, 1H, CH_3CH_2-b), 1.01 ppm (t, J = 7.5 Hz, 3H, CH_3CH_2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 164.9 (C1′), 151.1 (C6′), 147.7 (C9), 147.4 (C7′), 147.1 (C10), 131.5 (C4a′), 127.4 (C11a), 127.1 (C7a), 121.7 (C8a′), 111.9 (C8), 110.4 (C8′), 110.0 (C5′), 107.8 (C11), 62.3 (C3), 61.5 (C11b), 60.1 (C4), 57.0 (C1), 56.3 (OCH_3), 56.1 (OCH_3), 55.94 (OCH_3), 55.91 (OCH_3), 51.8 (C6), 47.3 (C3′), 28.9 (C7), 25.9 (C4′), 24.0 (CH_3CH_2), 10.3 ppm (CH_3CH_2); IR (ATR): $\tilde{\nu}$ = 2925, 2853, 1727, 1605, 1512, 1462, 1353, 1268, 1210, 1154, 1029, 857, 809, 732 cm^{-1}; MS (ESI): *m/z* (%): 480.28 (100) $[M+H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{37}N_3O_4$: 480.2862, found: 480.2849.

2-Azaemetine (5) and 2-Azaisoemetine (14)

Procedure A: A solution of imine **13** (19.2 mg, 42 μmol) and $NaCNBH_3$ (6.5 mg, 0.104 mmol, 2.5 equiv) in dry THF (400 μL) was treated with AcOH (7.2 μL, 0.126 mmol, 3 equiv) and dry EtOH (123 μL, 2.1 mmol, 50 equiv). The mixture was first stirred at 60 °C for 2 h, and then at RT for a further 3 h. The reaction was stopped by addition of saturated aq citric acid (2 mL) to destroy borane complexes. The mixture was heated to 100 °C by microwave irradiation (CEM Discover, air cooling, IR temperature control, maximum power 150 W, maximum pressure 15 bar). Since TLC still indicated incomplete hydrolysis, the procedure was repeated. Finally, the mixture was stirred for 12 h at 60 °C and basified to pH 12–14 by addition of 4 N aq NaOH. The product was extracted with EtOAc (3×10 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography (silica; EtOAc/EtOH, 1:1) gave the light sensitive compound **5** (**5**/**14**, d.r. = 7:1) as a yellow oil (14.6 mg, 30 μmol, 76%): R_f = 0.21 (EtOAc/EtOH, 1:1).

Procedure B: A mixture of amide **17** (11 mg, 22 μmol) and solid $LiAlH_4$ (8 mg, 220 μmol, 10 equiv) in dry THF (100 μL) was heated to 65 °C for 15 min by microwave irradiation (CEM Discover, air cooling, IR temperature control, maximum power 150 W, maximum pressure 15 bar). After cooling to RT and pressure equilibration, cold 4 N aq NaOH (2 mL) was added under ice cooling. The mixture was stirred for 30 min, diluted with THF (2 mL), and the insoluble aluminum salts were filtered off. The filter cake was washed with THF (10 mL) and EtOAc (15 mL). The aqueous phase was extracted with EtOAc (2×5 mL). The combined organic layers (including THF) were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Fast purification by column chromatography (silica; EtOAc/EtOH, 1:1) gave compound **5** (**5**/**14**, d.r. = 1:10) as a yellowish oil (10.1 mg, 20.97 μmol, 97%).

Procedure C: A solution of imine **13** (105 mg, 0.24 mmol) in THF (8 mL) was treated with Pd/C (10%, 10 mg), and the suspension was stirred for 28 h under H_2. The mixture was filtered over Celite, and the remainder was washed with a warm mixture of EtOAc (200 mL) and EtOH (20 mL). The filtrate was concentrated in vacuo to give the crude product as a brown oil. Purification by column chromatography (silica; EtOAc/EtOH, 1:1) gave several fractions (total weight 73.8 mg). One fraction (22.0 mg) contained the epimer **5** and amine **6**. Separation of both components was effected by preparative TLC (pyridine/toluene/Et_2NH, 4:6:1; **5** R_f = 0.43, amine **6** R_f = 0.25) to give pure **5** (6.4 mg) and **6** (8.9 mg). Another fraction (34.0 mg) contained the epimeric product mixture (**5** and **14**) in a 1:1.8 ratio (NMR): Yield: 73.8 mg (after column chromatography, 0.15 mmol, 70%, impure; after prep TLC and HPLC: 21%,

see below); UV (diastereomeric mixture, MeCN): λ (log ε) = 285 (3.44), 225 nm (sh, 3.87). The diastereomers were separated from the 1:1.8 mixture by prep RP-HPLC (mobile Phase: MeCN/phosphate buffer 25 mM, pH 7, 60:40). From a portion of the product (27.0 mg), five fractions were obtained and analyzed by NMR: Fraction 1, 4.99 mg, pure **5**; Fraction 2, 3.40 mg, 1:4.5 mixture of **5**/**14**; Fraction 3, 6.02 mg, pure **14**; Fraction 4, 3.27 mg, pure **14**; Fraction 5,3.91 mg, unidentified side products. The amount of pure **5** obtained was 4.99 mg (5.58 mg total); the amount of pure **14** obtained was 9.29 mg (12.0 mg total); the combined yield of **5** and **14** was 17.6 mg. The total yield from **13** was 21%.

Procedure D: A solution of imine **13** (10 mg, 21 μmol) in dry THF (0.4 mL) was treated with Pd/C (10%, 1 mg), and the suspension was stirred for 4 d at RT under H_2 pressure (20 bar). The mixture was filtered over Celite, and the remainder was washed with a warm mixture of EtOAc (20 mL) and EtOH (10 mL). The combined filtrates were concentrated in vacuo and the crude product was purified by column chromatography (silica; EtOAc/EtOH, 1:1). A diastereomeric mixture of **5** and **14** (2:1) was obtained as a yellow oil (5.9 mg, 12.3 μmol, 56%).

(1′*S*,3*S*,11b*R*)-2-[(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrazino[2,1-*a*]isoquinoline (5): $[\alpha]_D^{27} = -3.7$ ($c = 0.5$, $CDCl_3$); ^{1}H NMR, COSY, TOCSY, NOESY, HSQC, HMBC (400 MHz, $CDCl_3$): $\delta =$ 6.74 (s, 1H, H11), 6.62 (s, 1H, H5′), 6.60, (s, 1H, H8), 6.60 (s, 1H, H8′), 4.37 (br d, $J = 9.6$ Hz, 1H, H1′), 3.86 ($2\times OCH_3$), 3.85 ($2\times OCH_3$), 3.66 (mc, 1H, H1-a), 3.34 (d, $J = 9.8$ Hz, 1H, H11b), 3.21–3.06 (m, 4H, NCH_2-a, CH_2-3′, H7-a), 3.02–2.91 (m, 3H, H4-a, H6-a, H4′-a), 2.74 (t, $J = 4.2$ Hz, H4′-b), 2.64 (br d, $J = 15.8$ Hz, H7-b), 2.55–2.43 (m, 2H, H6-b, H3), 2.35–2.29 (m, 3H, NCH_2-b, H1-b, H4-b), 2.22 (t, $J =$ 10.8 Hz, 1H, NH), 1.73 (tdd, $J_t = 15.3$ Hz, $J_d = 7.5$, 2.5 Hz, 1H, CH_3CH_2-a), 1.34 (mc, 1H, CH_3CH_2-b), 0.92 ppm (t, $J = 7.5$ Hz, 3H, CH_3CH_2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): $\delta = 147.99$ (C9*), 147.89 (C10*), 147.59 (C6′*), 147.49 (C7′*), 127.5 (C8a′*), 127.3 (C4a′*), 127.2 (C11a*), 127.0 (C7a*), 111.9 (C8, C5′), 109.7 (C8′), 108.3 (C11), 61.4 (11b), 61.0 (C3), 60.2 (C4), 57.08 (NCH_2), 57.05 (C1), 56.6 (OCH_3), 56.3 (OCH_3), 56.01 (OCH_3), 55.99 (OCH_3), 51.6 (C6), 50.8 (C1′), 38.7 (C3′), 29.2 (C7), 28.6 (C4′), 24.4 (CH_3CH_2), 10.2 ppm (CH_3CH_2); * assignment uncertain; IR (ATR): $\tilde{\nu} = 3420$, 2925, 2853, 1663, 1610, 1516, 1463, 1357, 1330, 1258, 1225, 1114, 1033, 859, 772 cm^{-1}; MS (ESI): *m/z* (%): 482.30 (100) $[M+H]^+$, 483.31 (20) $[M+2H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{40}N_3O_4$: 482.3019, found: 482.3010.

(1′*R*,3*S*,11b*R*)-2-[(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]-3-ethyl-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrazino[2,1-*a*]isoquinoline (14): $[\alpha]_D^{27} = -13.4$ ($c = 0.45$, $CDCl_3$); ^{1}H NMR, COSY, NOESY, HSQC, HMBC (400 MHz, $CDCl_3$): $\delta = 6.84$ (s, 1H, H8′), 6.59 (s, 1H, H5′), 6.56 (s, 1H, H8), 6.28 (s, 1H, H11), 4.09 (t, $J = 5.4$ Hz, 1H, H1′), 3.84 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.36–3.25 (m, 3H, H3′-a, NCH_2-a, H1-a), 3.19 (d, $J = 10.2$ Hz, H11b), 3.13–3.05 (m, 1H, H7-a), 3.04–2.92 (m, 3H, H3′-b, H4-a, H6-a), 2.85–2.76 (m, 1H, H4′-a), 2.72 (t, $J =$ 4.2 Hz, H4′-b), 2.63 (br d, $J = 5.8$ Hz, H7-b), 2.61 (m, 1H, NCH_2-b), 2.51–2.42 (m, 2H, H3, H6-b), 2.28–2.18 (m, 3H, H1-b, H4-b, NH), 1.82 (d-pseudo-quin, $J_d = 15.1$ Hz, $J_{quin} = \sim 7$ Hz, 1H, CH_3CH_2-a), 1.45–1.30 (m, 1H, CH_3CH_2-b), 0.94 ppm (t, $J = 7.5$ Hz, 3H, CH_3CH_2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): $\delta = 147.8$ (C9*), 147.6 (C10*), 147.5 (C6′*), 147.4 (C7′*), 130.0 (C8a′), 127.7 (C4a′), 127.6 (C11a), 127.1 (C7a), 112.0 (C8, C5′), 109.5 (C8′), 107.7 (C11), 62.5 (C3), 61.5 (C11b), 60.3 (C4), 59.5 (C1), 58.3 (NCH_2), 56.3 (OCH_3), 56.2 (OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 54.6 (C1′), 52.0 (C6), 41.8 (C3′), 29.8 (C4′), 29.0 (C7), 24.8 (CH_3CH_2), 10.5 ppm (CH_3CH_2); * assignment uncertain; IR (ATR): $\tilde{\nu} = 3432$, 2927, 2823, 1665, 1610, 1515, 1463, 1355, 1331, 1256, 1225, 1160, 1114, 1028, 857, 773 cm^{-1}; MS (ESI): *m/z* (%): 482.30 (100) $[M+H]^+$, 483.31 (10) $[M+2H]^+$; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{40}N_3O_4$: 482.3019, found: 482.3010.

Supporting information, containing general methods, all remaining experimental procedures, growth curves, microscopy images and NMR spectra of all compounds, is available on the WWW under *http://dx.doi.org/10.1002/cmdc.201000230*.

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