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Synthesis of new bridged tetrahydro-β-carbolines and *spiro*-fused quinuclidines

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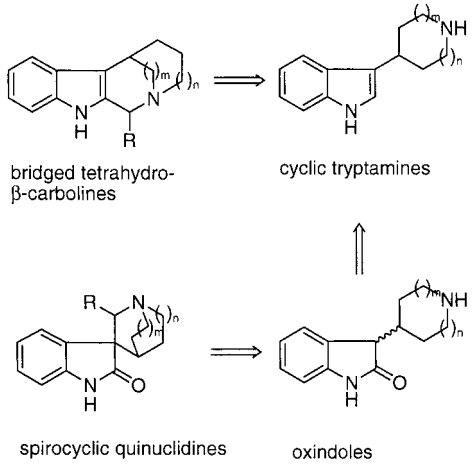
Abstract—Two series of chemically related, conformationally restricted ring systems were synthesized. Bridged tetrahydro-β-carbolines, designed as selective 5-HT receptor ligands, were formed via Pictet–Spengler condensation of cyclic tryptamine precursors. Oxidation of the indole 2-position of the precursors followed by condensation with aldehydes produced *spiro*-cyclic quinuclidines, containing important muscarine receptor pharmacophores. © 2001 Elsevier Science Ltd. All rights reserved.

Conformationally restricted analogs of receptor substrates have received much attention in medicinal chemistry. For instance, the serotonin and muscarinic cholinergic receptors are studied intensively by modification of their ligands. The introduction of rigidity in receptor ligands can result in discrimination between several receptor subtypes and thus contribute to the development of compounds that display specific therapeutic activity with reduced side effects.

Recognition of serotonin (5-hydroxytryptamine, 5-HT) by 5-HT receptors can be attributed partly to the orientation of the alkylamino sidechain. Some semi-rigid analogs of 5-substituted tryptamines have provided insight into the ligand recognition requirements for these receptor subtypes.[1–4] Tetrahydro-β-carbolines can be seen as 5-HT analogs, and their biological activity has been studied.[5,6] Introduction of a carbon-bridge across the piperidine part of the tetrahydro-β-carboline ring system as in Scheme 1 will result in increased rigidity and in particular the spatial arrangement of the substituent at C-1 will be influenced.

The muscarinic cholinergic class of receptors has proved to be sensitive for conformationally restricted ligands. In particular substituted quinuclidines exhibit selective muscarinic receptor binding properties[7–10] and we reasoned that quinuclidines containing a *spiro*-fused oxindole as shown in Scheme 1 are potential conformationally restricted muscarine analogs. These *spiro*-fused indoles contain the well-defined positions of pharmacophoric elements that are important for muscarinic receptor binding.[11] Although these oxindoles have a completely different structure, from a synthetic point of view they are closely related to the tetrahydro-β-carbolines discussed before.

As starting materials for the synthesis of conformationally restricted ligands for both receptor families, we have selected three tryptamines in which the aminoethyl side-chain is incorporated in a heterocyclic ring (Scheme 1). Application of the frequently used Pictet–Spengler condensation[12–14] to these tryptamine analogs will produce the anticipated tetrahydro-β-carbolines. Additionally, the desired *spiro*-fused compounds can be obtained from condensation reactions with aldehydes, when the indole 2-position is made unavailable for Pictet–Spengler condensation by oxidation. Examples of this type of reaction with 2-hydroxytryptamine in the synthesis of natural products



Scheme 1. m=1, 2; n=0, 1.

Keywords: Pictet–Spengler reaction; oxindoles; quinuclidines; *spiro*-compounds.

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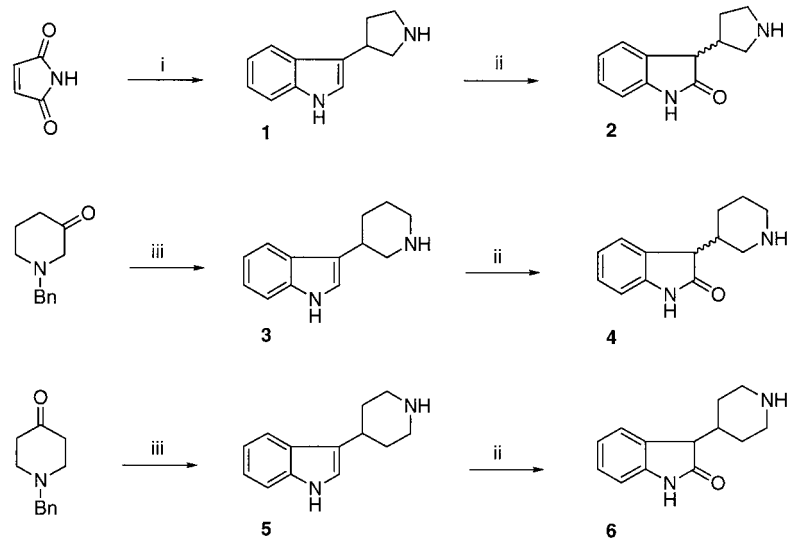


Scheme 2. (i) (a) Indole, HOAc, reflux, 12 h; (b) $LiAlH_4$, THF, reflux, 53% (two steps). (ii) DMSO, conc. HCl, rt, **2** (79%), **4** (79%), **6** (57%). (iii) (a) Indole, NaOMe, MeOH; (b) $Pd(OH)_2$/C, EtOH, HOAc, 40 psi, **3** (58%), **5** (74%) (two steps).

can be found in the literature.[15–17] Oxidative rearrangement of tetrahydro-β-carbolines offers an alternative route to *spiro*-fused oxindoles, but this will not be discussed here.

1. Synthesis

1.1. Tryptamine precursors

An efficient synthesis of 3-(3-indolyl)-pyrrolidines has recently been published.[18] Acid catalyzed condensation of maleimide with indole followed by lithium aluminum hydride reduction afforded cyclic tryptamine **1** (Scheme 2). Piperidine analog **3** was prepared in two steps by base catalyzed coupling of *N*-benzyl-3-piperidone[19] with indole following a literature procedure.[20–22] The symmetric 4-(3-indolyl)-piperidine **5** was prepared from commercially available *N*-benzyl-4-piperidone via the same procedure.

A simple and generally applicable method for selective oxidation of indoles at the 2-position was adapted for the preparation of oxindoles **2**, **4** and **6**.[23,24] The indole ring is protonated at the 3-position under strongly acidic conditions (i.e. conc. HCl), allowing addition of dimethyl sulfoxide to the 2-position and subsequent elimination of dimethyl sulfide. Following this procedure, the cyclic tryptamines **1**, **3** and **5** were oxidized to the corresponding 2-oxindoles **2**, **4** (both as mixtures of diastereomers) and **6**, respectively (Scheme 2). These oxindoles were only moderately stable and were used directly in the next cyclization step.

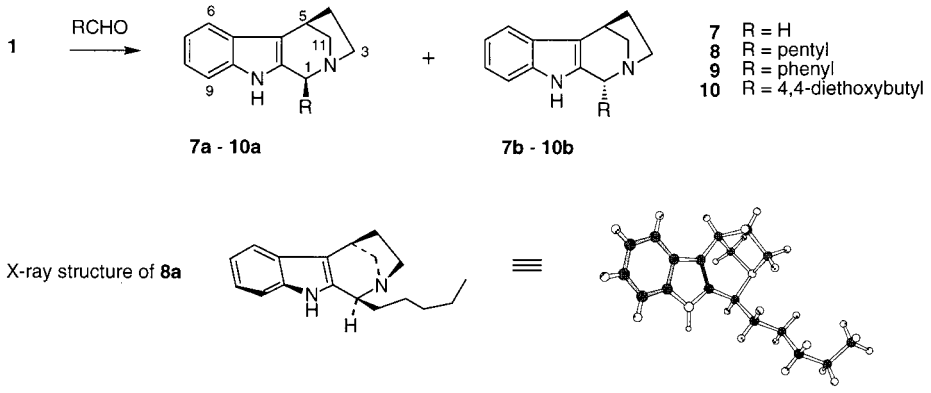
1.2. Pictet–Spengler condensations

The Pictet–Spengler reaction of aldehydes with the secondary amines **1**, **3** and **5** did not proceed under standard conditions such as trifluoroacetic acid in CH_2Cl_2 or reflux in benzene. In general, trifluoroacetic acid in refluxing ethanol (method A) or in toluene (method B) were most suitable with respect to the yield and reaction times (Table 1). To obtain the desired bridged tetrahydro-β-carbolines from acid labile aldehydes such as 5,5-diethoxypentanal, refluxing in toluene in the absence of an acid catalyst and prolonged reaction times were required. Reaction of pyrrolidine derivative **1** with some representative aldehydes gave ethano-bridged tetrahydro-β-carbolines **7–10** in acceptable yields as separable mixtures of diastereomers (Scheme 3). Depending on the volatility and stability of the aldehyde, 1.5–15 equiv. of this reagent were used. Little

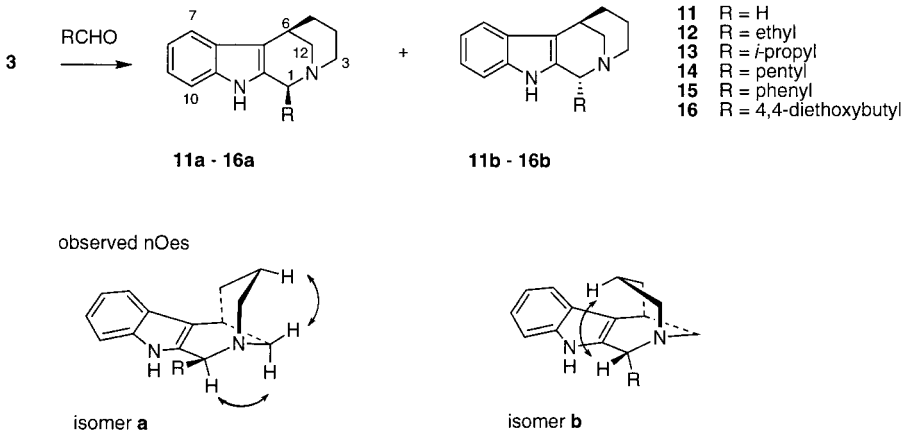
Table 1. Pictet–Spengler reactions of amines **1**, **3** and **5** with aldehydes as shown in Schemes 3–5

Precursor	Product	R	Ratio **a**:**b**[a]	Conditions[b]	Yield[c]
1	**7**	H	–	A	74
1	**8**	Pentyl	45:55	B	53
1	**9**	Phenyl	46:54	C	58
1	**10**	4,4-Diethoxybutyl	61:39	C	55
3	**11**	H	–	A	73
3	**12**	Ethyl	71:29	C	54
3	**13**	*i*-Propyl	50:50	B	15
3	**14**	Pentyl	70:30	C	64
3	**15**	Phenyl	95:5	B	58
3	**16**	4,4-Diethoxybutyl	67:33	C	73
5	**17**	Pentyl	–	B	3

[a] Ratio according to ^1H NMR spectra of the crude reaction mixtures.
[b] A: EtOH, TFA, reflux, 3 h; B: toluene, TFA, reflux, 6 h; C: toluene, reflux, 9 h.
[c] Isolated yields in % after separation of the diastereomers.



Scheme 3. Pictet–Spengler reactions with 3-(3-indolyl)pyrrolidine **1**.



Scheme 4. Pictet–Spengler reactions with 3-(3-indolyl)piperidine **3**.

preference for one of the diastereomers was observed, as is shown in Table 1. The structure of pentyl-substituted diastereomer **8a** was identified unequivocally by X-ray analysis.[25] All other isomers in this pyrrolidine series were characterized by comparison of their ^{1}H NMR spectra.

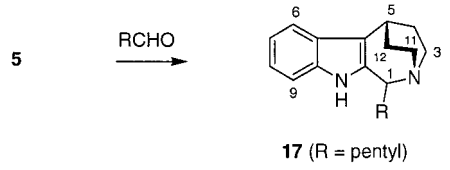
Exposure of piperidine derivative **3** to the reaction conditions described for **1** gave satisfactory results with most of the aldehydes.[26] The diastereoselectivity was somewhat better than in the pyrrolidine series. NOESY experiments established the *cis* or *trans* relationship of the propyl-bridge relative to the C-1 substituent in the two diastereomers **a** and **b** (Scheme 4). These experiments further showed that the *syn*-orientation of the C-1 substituent in isomer **a** forced the six-membered ring into a boat conformation, while without interference of the C-1 substituent the energetically favorable chair conformation as in **b** was adopted.

An additional methylene group between the indole nucleus and the secondary amine in tryptamine analog **5** will result in the formation of a β-carboline homolog after Pictet–Spengler condensation. Although a variety of reaction conditions were applied, merely slow decomposition of the starting materials was observed. Only from the reaction with hexanal, which required a large excess of aldehyde and long reaction times, was a small amount of the bridged indoloazepine **17** isolated (Scheme 5). The sluggishness of this condensation can be attributed to the formation of a seven-membered ring instead of a more favorable six-membered ring, which is normally formed during the Pictet–Spengler reaction. A second complication is the energetically disfavored conformation that the initially formed iminium salt has to adopt for cyclization.

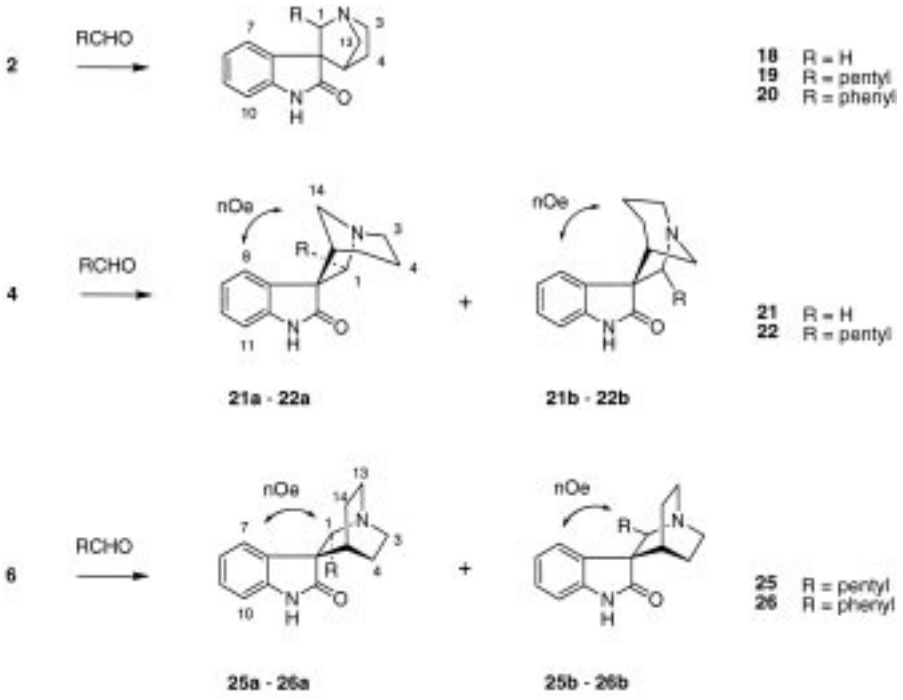
1.3. Oxindole *spiro*-cyclizations

Condensation reactions of the oxindoles **2**, **4** and **6** with representative aldehydes were investigated using a variety of both acidic and basic conditions. Pure acetic acid at 90°C or sodium acetate in methanol either at room temperature or reflux proved to be suitable, depending on the aldehyde. In general the acid catalyzed reactions gave somewhat higher yields.

Pyrrolidine substituted oxindole **2** was examined first. Instability of this compound is probably responsible for the low yields in the condensation reactions (Scheme 6). In principle four diastereomeric 1-azabicyclo[2.2.1]heptanes can be formed. In the reaction with formaldehyde,



Scheme 5. Pictet–Spengler reactions with 4-(3-indolyl)piperidine **5**.



Scheme 6. *spiro*-Cyclization reactions.

however, the formation of only one out of two possible isomers was observed (**18**, R=H), whereas in the case of hexanal and benzaldehyde, respectively, three and two diastereomers (**19**, R=pentyl and **20**, R=phenyl; Table 2) were formed. Low yields in combination with difficulties during separation of the isomers prevented complete structural assignment in this series.

Piperidyl substituted oxindole **4** gave better results in the cyclization reactions. The resulting diastereomeric azabicyclo[3.2.1]octanes **21a**,**b** and **22a**,**b** were separated using flash chromatography and fully characterized with 2D NMR spectroscopy. The unsubstituted *spiro*-compound **21** (R=H), obtained by reaction with one equivalent of formaldehyde, was formed as a 3:1 mixture of the two possible diastereomers. With hexanal, as an example for aliphatic aldehydes, longer reaction times and excess of aldehyde were required to obtain acceptable yields. Out of four possible diastereomers only the two 'ring'-isomers were formed; for steric reasons the R-substituent obviously prefers an *exo*-orientation in relation to the bicyclic ring system in both isomers, as was deduced from model studies.

Table 2. *spiro*-Cyclization reactions of amines **2**, **4** and **6** with aldehydes as shown in Scheme 6

Precursor	Product	R	Ratio **a**:**b**[a]	Conditions[b]	Yield[c]
2	**18**	H	1 isomer	A	6
2	**19**	Pentyl	3 isomers[d,e]	B	8
2	**20**	Phenyl	69:31[d]	B	6
4	**21**	H	76:24	A	81
4	**22**	Pentyl	63:37	A	57
4	**22**	Pentyl	55:45	B	57
4	**23**	Phenyl	–	A, B	0
6	**24**	H	–	A, B	0
6	**25**	Pentyl	21:79	A	47
6	**25**	Pentyl	36:64	B	61
6	**26**	Phenyl	–	A	0
6	**26**	Phenyl	36:64[d]	B	22

[a] Ratio according to ^{1}H NMR spectra of the crude reaction mixtures.
[b] A: HOAc, 90°C; B: NaOAc, MeOH.
[c] Isolated yields in % after separation of the diastereomers.
[d] Inseparable mixture.
[e] Ratio 50:5:45.

During NMR analysis in $CDCl_3$ it turned out that both pentyl-substituted diastereomers **22a** and **22b** were configurationally unstable, most likely as a result of trace amounts of acid in the $CDCl_3$. After one night at room temperature partial isomerization had taken place and this process could be completed by heating the NMR sample at 50°C for 6 h. Both pure isomers equilibrated to the same 63:37 isomer ratio under these conditions, which is exactly the same as was obtained from their synthesis in acetic acid. No such observation was made with the formaldehyde derived products **21**. To confirm the stability of **21a** and **21b**, both pure isomers were heated in acetic acid at 90°C. No isomerization was observed under these conditions and it took several hours at 110°C before some isomerization had taken place. Benzaldehyde was completely unreactive in the condensation reaction with **4**. With large amounts of reagent and prolonged reaction times the only process observed was decomposition of the starting material.

The *spiro*-cyclization of oxindole **6** with several aldehydes resulted in the formation of the indolo-quinuclidine (azabicyclo[2.2.2]octane) ring system (Scheme 6). Condensation of **6** with formaldehyde, which should lead to the parent ring system in this series, gave no product at all and only unidentified polymeric material was formed. The use of hexanal was more successful and the diastereomeric 1-azabicyclo[2.2.2]octanes **25a** and **25b** were obtained in reasonable yield after chromatographic separation (the yields are based on indolopiperidine **5**). Due to the

symmetry in the quinuclidine ring system only two diastereomers are possible and preference for the sterically favored diastereomer **25b** was observed. In contrast to the 1-azabicyclo[3.2.1]octanes **22a** and **22b**, the separate isomers **25a** and **25b** showed no isomerization when exposed to the same reaction conditions that were used for their formation. With benzaldehyde a moderate yield of the two inseparable isomers **26a** and **26b** was obtained. Structure analysis of these rigid *spiro*-structures was easily performed with NOE spectroscopy, as is shown in Scheme 6.

In summary, we demonstrated that cyclic tryptamine analogs are suitable precursors for the synthesis of a variety of new indole derived ring systems. Examples were presented for all of the six possible ring systems, and the scope and limitations of these condensation reactions were established.

2. Experimental

2.1. General information

All reagents and solvents were used as commercially available, unless indicated otherwise. Flash chromatography[27] refers to purification using the indicated eluents and Janssen Chimica silica gel 60 (0.030–0.075 mm). Infrared (IR) spectra were obtained from $CHCl_3$ solutions unless indicated otherwise, using a Bruker IFS 28 FT-spectrophotometer and wavelengths are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR; APT) spectra were determined in $CDCl_3$ using a Bruker ARX 400 (400, 100 MHz, respectively) spectrometer, unless indicated otherwise. Mass spectra and accurate mass measurements were performed on a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer using Fast Atom Bombardment (FAB) or Electron Impact (EI). A resolving power of 10,000 (10% valley definition) for high-resolution electron impact or FAB mass spectrometry was used.

2.1.1. 3-(2-Oxindol-3-yl)pyrrolidine (2). To a solution of 3-(3-indolyl)pyrrolidine **1**[18] (106 mg, 0.57 mmol) in dimethyl sulfoxide (1.5 mL, 21.1 mmol) aqueous hydrochloric acid (3.0 mL, 0.37 mol, 37%) was added dropwise. The mixture was stirred during 45 min at rt, and EtOAc (20 mL), EtOH (1 mL) and a saturated Na_2CO_3 solution (25 mL) were added at 0°C. The water layer was further basified with K_2CO_3, the layers were separated and the water layer extracted with EtOAc/5% EtOH (3×). When a third, yellow layer was being formed more water and K_2CO_3 were added. The combined organic layers were dried (Na_2SO_4) and evaporated giving oxindole **2** together with dimethyl sulfoxide. Due to its instability the product was not further purified: ^1H NMR ($CDCl_3$/5% CD_3OD) δ 8.59 (br s, 1H, H-1), 7.23 (d, J=7.8 Hz, 1H, H-4 or H-7), 7.16 (t, J=7.9 Hz, 1H, H-5 or H-6), 6.99 (t, J=7.8 Hz, 1H, H-5 or H-6), 6.84 (d, J=7.8 Hz, 1H, H-4 or H-7), 3.55–3.50 (m, 1H), 3.24–3.07 (m, 1H), 3.03–2.81 (m, 3H), 2.72–2.57 (m, 1H), 2.60 (s, $(CH_3)_2SO$), 1.72–1.58 (m, 1H).

2.1.2. 3-(2-Oxindol-3-yl)piperidine (4). To a mixture of 3-(2-indolyl-3-yl)piperidine **3**[19] (400 mg, 2.0 mmol) in dimethyl sulfoxide (1.5 mL, 20.0 mmol) aqueous hydrochloric acid (3.0 mL, 36.4 mmol, 37%) was added dropwise. The mixture was stirred during 30 min at rt, then water and an aqueous sodium bisulfite solution (3 mL) were added. The mixture was stirred during several minutes, saturated with K_2CO_3 and EtOAc/5% EtOH (5 mL) was added. The layers were separated and the water layer was extracted with EtOAc/5% EtOH (3×). The combined organic layers were dried (Na_2SO_4) and evaporated affording **4** (585 mg, 1.57 mmol, 79%), as two isomers according to the ^{13}C NMR spectrum. ^1H NMR δ 7.21–7.14 (m, 2H, H-6 or H-7), 6.96 (t, J=7.5 Hz, 1H, H-5), 6.84 (d, J=7.5 Hz, 1H, H-4), 3.31 (br s, 1H, H-3), 3.03 (br d, J=11.8 Hz, 1H, H-9_{eq} or H-11_{eq}), 2.97 (br d, J=12.2 Hz, 1H, H-9_{eq} or H-11_{eq}), 2.77–2.68 (m, 1H, H-9_{ax}, H-11_{ax}), 2.60 (s, $(CH_3)_2SO$), 2.51–2.43 (m, 1H), 2.27–2.18 (m, 1H), 1.70–1.58 (m, 2H), 1.51–1.39 (m, 1H); ^{13}C NMR δ 149.5 (C-2), 142.5 (C-7a), 128.1 (C-3a), 128.0 (C-3a), 127.6, 127.6, 124.5, 124.1, 121.6, 121.5, 109.5, 109.4, 49.9 (C-3), 49.7 (C-3), 49.5, 48.6, 46.3, 46.2, 40.7 ($(CH_3)_2SO$), 40.2 (C-8), 40.1 (C-8), 26.9 (C-13), 26.7 (C-13); IR ν 3436, 1706; HRMS (FAB) obs. mass 217.1360, calcd for $C_{13}H_{17}N_2O$ (M+1) 217.1341.

2.1.3. 4-(2-Oxindol-3-yl)piperidine (6). To a mixture of 4-(3-indolyl)piperidine **5** (2.07 g, 10.4 mmol) in dimethyl sulfoxide (1.4 mL, 20.0 mmol) hydrochloric acid (5.0 mL, 0.61 mol, 37%) was added dropwise. The mixture was stirred during 45 min at rt, then EtOAc (20 mL), EtOH (1 mL) and a saturated Na_2CO_3 solution (25 mL) were added at 0°C. The water layer was further basified with K_2CO_3, the layers were separated and the water layer extracted with EtOAc/5% EtOH (3×). The combined organic layers were dried (Na_2SO_4) and evaporated. The yellow oil thus obtained still contained dimethyl sulfoxide, but was used for the condensations. An analytical sample was prepared by flash chromatography (CH_2Cl_2/MeOH/concd NH_4OH 80:15:5) followed by crystallization from EtOAc, yielding **6** (1.29 g, 5.94 mmol, 57%) as a crystalline yellow compound: mp 149–151°C; ^1H NMR δ 7.22 (d, J=7.5 Hz, 1H, H-4 or H-7), 7.18 (t, J=7.7 Hz, 1H, H-5 or H-6), 6.98 (t, J=7.5 Hz, 1H, H-5 or H-6), 6.82 (t, J=7.7 Hz, 1H. H-4 or H-7), 3.34 (d, J=3.5 Hz, 1H, slow exchange with D, H-3), 3.08 (br d, J=12.5 Hz, 1H, H-10_{eq} or H-12_{eq}), 3.01 (br d, J=12.4 Hz, 1H, H-10_{eq} or H-12_{eq}), 2.58 (ddd, J=12.4 Hz, J=12.4 Hz, J=3.0 Hz, 1H, H-10_{ax} or H-12_{ax}), 2.25–2.18 (m, 2H, H-8, H-10_{ax} or H-12_{ax}), 1.67 (br d, J=12.7 Hz, 1H, H-9_{eq} or H-13_{eq}), 1.59 (dddd, J=12.4 Hz, J=12.4 Hz, J=12.4 Hz, J=4.2 Hz, 1H, H-9_{ax} or H-13_{ax}), 1.51 (br d, J=13.0 Hz, 1H, H-9_{eq} or 13_{eq}), 1.38 (dddd, J=12.4 Hz, J=12.4 Hz, J=12.4 Hz, J=4.2 Hz, 1H, H-9_{ax} or H-13_{ax}); IR ν 3436, 1708; HRMS (EI) obs. mass 216.1263, calcd for $C_{13}H_{16}N_2O$ 216.1263.

2.2. Pictet–Spengler condensations

2.2.1. General procedure A. A solution of the amine, trifluoroacetic acid (1 equiv.) and the aldehyde (1.5–4 equiv.) in EtOH was refluxed during 3 h. When formaldehyde was used as the aldehyde, methoxyamine hydrochloride (1.5–4 equiv.) and water (5 mL) were added and refluxing was continued for 2 h. The mixture was concentrated in vacuo and EtOAc and a saturated aqueous solution

of Na_2CO_3 were added. The layers were separated and the water layer was extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4) and evaporated.

2.2.2. General procedure B. To a solution of the amine and trifluoroacetic acid (1 equiv.) in refluxing toluene, the aldehyde (10 equiv.) was added in portions over a period of 2 h. The mixture was refluxed during 4 h, concentrated in vacuo and EtOAc and a saturated aqueous solution of Na_2CO_3 were added. The layers were separated and the water layer was extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4) and evaporated.

2.2.3. General procedure C. To a solution of the amine in refluxing toluene, the aldehyde (10 equiv.) was added over a period of 2 h. The mixture was refluxed during another 7 h, cooled to rt and concentrated in vacuo.

2.2.4. Pictet–Spengler reaction of 1 with formaldehyde (7). General procedure A was followed using **1** (500 mg, 2.16 mmol), trifluoroacetic acid (210 μL, 2.16 mmol), formalin (450 μL, 5.85 mmol, 36%) and methoxyamine hydrochloride (450 mg, 5.38 mmol). Crystallization from EtOAc gave **7** (403 mg, 2.0 mmol, 74%): mp 262–263°C (240°C subl.); ^{1}H NMR δ 7.96 (br s, 1H, H-10), 7.55–7.52 (m, 1H, H-6 or H-9), 7.30–7.27 (m, 1H, H-6 or H-9), 7.14–7.08 (m, 2H, H-7, H-8), 4.47 (d, J=16.7 Hz, 1H, H-1) 3.74 (d, J=16.7 Hz, 1H, H-1), 3.38–3.36 (m, 1H, H-5), 3.33 (ddd, J=12.6 Hz, J=10.0 Hz, J=3.6 Hz, 1H, H-3), 3.08 (dt, J=10.8 Hz, J=2.8 Hz, J=2.8 Hz, 1H, H-11), 2.88–2.80 (m, 1H, H-3), 2.14–2.00 (m, 2H, H-4); ^{13}C NMR δ 136.1 (C-9a), 129.1, 125.4, 121.0 (C-7 or C-8), 119.2 (C-7 or C-8), 117.9, 117.3 (C-6), 110.8 (C-9), 58.5 (C-11), 56.3 (C-1) 54.0 (C-3), 37.4 (C-4), 31.2 (C-5); IR ν 3435; HRMS (EI) obs. mass 198.1142, calcd for $C_{13}H_{14}N_2$ 198.1157.

2.2.5. Pictet–Spengler reaction of 1 with hexanal (8a and 8b). General procedure B was followed using **1** (1.01 g, 5.43 mmol), trifluoroacetic acid (415 μL, 5.39 mmol) and hexanal (3.22 mL, 26.9 mmol). According to ^{1}H NMR spectroscopy of the crude mixture the diastereomers had been formed in a ratio of **8a/8b**=45:55 and were separated by flash chromatography (PE/EtOAc 50:50 then PE/EtOAc/NEt_3 60:30:10). Both isomers were obtained as colorless crystals: **8a** (326 mg, 1.21 mmol, 22%) from EtOAc and **8b** (651 mg, 1.69 mmol, 31%) from EtOH as its 1:1 salt with fumaric acid.

8a: mp 151–152°C; ^{1}H NMR δ 7.72 (br s, 1H, H-10), 7.52 (d, J=6.5 Hz, 1H, H-6 or H-9), 7.30 (d, J=6.8 Hz, 1H, H-6 or H-9), 7.14–7.07 (m, 2H, H-7, H-8), 4.39 (dd, J=9.7 Hz, J=4.8 Hz, 1H, H-1), 3.32 (br s, 1H, H-5), 3.20 (d, J=10.7 Hz, 1H, H-11), 3.10–3.03 (m, 2H, H-11, H-3), 2.98–2.92 (m, 1H, H-3), 2.00–1.92 (m, 2H, H-4), 1.81–1.68 (m, 3H, H-12, H-14), 1.60–1.52 (m, 1H, H-12), 1.46–1.38 (m, 4H, H-13, H-15), 0.95 (t, J=7.0 Hz, 3H, H-16); ^{13}C NMR δ 135.7 (C-9a), 133.5 (C-5b), 125.3 (C-1a), 121.0, 119.4, 117.5, 116.7 (C-5a), 110.7, 62.4 (C-1), 60.6, 44.4, 35.8, 32.0 (C-5), 32.0, 31.8, 26.2, 22.5, 14.0 (C-16); IR ν 3436; HRMS (EI) obs. mass 268.1927, calcd for $C_{18}H_{24}N_2$ 268.1939.

8b: mp 151–152°C; ^{1}H NMR (d_6-DMSO) δ 10.90 (s, 1H, H-10), 7.50 (d, J=7.7 Hz, 1H, H-6 or H-9), 7.31 (d, J=8.0 Hz, 1H, H-6 or H-9), 7.05 (t, J=7.2 Hz, 1H, H-7 or H-8), 6.99 (t, J=7.2 Hz, 1H, H-7 or H-7 or H-8), 6.57 (s, 2H, $CHCO_2$), 4.11–4.08 (m, 1H, H-1), 3.58–3.51 (m, 1H, H-3), 3.51 (br s, 1H, H-5), 3.29 (d, J=10.6 Hz, 1H, H-11), 3.05–2.98 (m, 1H, H-3), 2.91 (d, J=10.6 Hz, 1H, H-11), 2.17–2.08 (m, 1H, H-4), 1.94–1.85 (m, 3H, H-4, H-12), 1.76–1.72 (m, 1H, H-13), 1.62–1.55 (m, 1H, H-13), 1.40–1.32 (m, 4H, H-14, H-15), 0.92 (t, J=6.7 Hz, 3H, H-16); ^{13}C NMR (d_6-DMSO) δ 167.2 ($CHCO_2$), 136.1, 134.7 ($CHCO_2$), 124.3, 120.8, 118.6, 117.3, 114.6, 111.2, 65.1 (C-1), 53.9 (C-3 or C-11), 52.5 (C-3 or C-11), 35.4, 34.2, 31.2 (C-5), 25.7, 22.0, 13.9 (H-16); IR ν 3436; HRMS (EI) obs. mass 268.1945, calcd for $C_{18}H_{24}N_2$ 268.1939.

2.2.6. Crystallographic data of 8a.[25] Monoclinic, $P2_1/c$, a=9.6605(9), b=15.995(2), c=10.291(2) Å, β=99.20(2)°, V=1569.7(5) Å^3, Z=4, D_x=1.14 g cm^{-3}, λ(CuKα)=1.5418 Å, μ(CuKα)=5.0 cm^{-1}, F(000)=584, room temperature. Final R=0.067 for 2113 observed reflections.

2.2.7. Pictet–Spengler reaction of 1 with benzaldehyde (9a and 9b). General procedure C was followed using **1** (981 mg, 5.27 mmol) and benzaldehyde (1.85 mL, 18.2 mmol). According to a ^{1}H NMR spectrum of the crude mixture the diastereomers had been formed in a ratio of **9a/9b**=46:54 and were separated by flash chromatography (PE/EtOAc 50:50 then PE/EtOAc/NEt_3 60:30:10). Both **9a** (382 g, 1.39 mmol, 26%) and **9b** (463 mg, 1.68 mmol, 32%) were obtained from EtOAc as crystals.

9a: mp 225–228°C; ^{1}H NMR δ 7.97 (br s, 1H, H-10), 7.61–7.58 (m, 1H, H-6), 7.38–7.35 (m, 5H, Ar–H), 7.24–7.22 (m, 1H, H-9), 7.15–7.11 (m, 2H, H-7, H-8), 5.68 (br s, 1H, H-1), 3.43 (br s, 1H, H-5), 3.31 (dd, J=10.7 Hz, J=2.7 Hz, 1H, H-11), 2.99–2.93 (m, 1H, H-3), 2.70–2.63 (m, 1H, H-3), 2.04–2.01 (m, 2H, H-4); IR ν 3436; HRMS (EI) obs. mass 274.1464, calcd for $C_{19}H_{18}N_2$ 274.1470.

9b: mp 214–215°C (170°C subl.); ^{1}H NMR (CD_3OD) δ 7.54 (d, J=7.0 Hz, 1H, H-6 or H-9), 7.39–7.30 (m, 3H Ar–H), 7.25–7.23 (m, 3H, H-6 or H-9, Ar–H), 7.08–7.00 (m, 2H, H-7, H-8), 5.04 (s, 1H, H-1), 3.52–3.50 (m, 1H, H-5), 3.43 (ddd, J=12.6 Hz, J=10.0 Hz, J=3.6 Hz, 1H, H-3), 3.30–3.27 (m, 1H, H-11), 3.17–3.10 (m, 1H, H-3), 2.54 (dd, J=11.0 Hz, J=2.9 Hz, 1H, H-11), 2.18–2.10 (m, 2H, H-4); ^{13}C NMR (CD_3OD) δ 138.3, 135.4, 134.4, 133.3, 132.0, 131.7, 126.2, 124.9, 122.4, 120.9, 114.7, 112.0, 72.6 (C-1), 57.7 (C-3 or C-11), 55.4 (C-3 or C-11), 40.3 (C-4), 35.7 (C-5); IR ν 3436; HRMS (EI) obs. mass 274.1465, calcd for $C_{19}H_{18}N_2$ 274.1470.

2.2.8. Pictet–Spengler reaction of 1 with 5,5-diethoxypentanal (10a and 10b). General procedure C was followed using **1** (36 mg, 0.19 mmol) and 5,5-diethoxypentanal (348 mg, 2.0 mmol). According to a ^{1}H NMR spectrum of the crude reaction mixture the diastereomers had been formed in a ratio of **10a/10b**=61:39. Separation by flash chromatography (PE/EtOAc 50:50 then PE/EtOAc/NEt_3 70:15:5) gave **10a** (23 mg, 0.07 mmol, 35%) and **10b** (13 mg, 0.04 mmol, 20%) as an oil.

10a: ^{1}H NMR δ 8.05 (br s, 1H, H-10), 7.51 (d, J=7.3 Hz,

1H, H-6 or H-9), 7.29 (d, *J*=7.3 Hz, 1H, H-6 or H-9) 7.12–7.07 (m, 2H, H-7, H-8), 4.58 (t, *J*=5.5 Hz, 1H, H-15), 4.49–4.41 (m, 1H, H-1), 3.74–3.62 (m, 2H, OCH_2CH_3), 3.60–3.47 (m, 2H OCH_2CH_3), 3.35 (br s, 1H, H-5), 3.22 (d, *J*=10.6 Hz, 1H. H-11), 2.71 (dd, *J*=10.6 Hz, *J*=2.7 Hz, 1H, H-11), 3.05–2.97 (m, 2H, H-3), 2.02–1.56 (m, 8H, H-4, H-12, H-13, H-14), 1.24 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.24 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.23 (t, *J*=7.1 Hz, 3H, OCH_2CH_3); IR ν 3436.

10b: ^{1}H NMR δ 8.08 (br s, 1H, H-10), 7.53 (d, *J*=7.3 Hz, 1H, H-6 or H-9), 7.28 (d, *J*=7.3 Hz, 1H, H-6 or H-9) 7.14–7.06 (m, 2H, H-7, H-8), 4.56 (t, *J*=5.1 Hz, 1H, H-15), 3.74–3.34 (m, 6H, H-1, H-3, OCH_2CH_3), 3.34 (br s, 1H, H-5), 3.17 (d, *J*=11.0 Hz, 1H, H-11), 2.83–2.76 (m, 1H, H-3), 2.71 (dd, *J*=11.0 Hz, *J*=2.7 Hz, 1H, H-11), 2.00–1.62 (m, 8H, H-4, H-12, H-13, H-14), 1.25 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.24 (t, *J*=7.1 Hz, 3H, OCH_2CH_3); IR ν 3436.

2.2.9. Pictet–Spengler reaction of 3 with formaldehyde (11). General procedure A was followed using **3** (40 mg, 0.20 mmol), trifluoroacetic acid (19 μL, 0.20 mmol), paraformaldehyde (9 mg, 0.30 mmol), EtOH (2 mL) and methoxyamine hydrochloride (41 mg, 0.50 mmol). Crystallization from EtOAc/PE gave **11** (31 mg, 0.15 mmol, 73%): mp 231–234°C; ^{1}H NMR δ 8.17 (br s, 1H, H-11), 7.49 (d, *J*=7.5 Hz, 1H, H-7 or H-10), 7.33 (d, *J*=7.8 Hz, 1H, H-7 or H-10), 7.17–7.09 (m, 2H, H-8, H-9), 4.44 (d, *J*=17.2 Hz, 1H, H-1), 3.78 (d, *J*=17.2 Hz, 1H, H-1), 3.24 (br d, 1H, *J*=13.2 Hz, H-12), 3.15 (ddd, *J*=13.7 Hz, *J*=13.7 Hz, *J*=3.8 Hz, 1H, H-3), 3.07–3.01 (m, 3H, H-3, H-6, H-12), 1.91–1.87 (m, 2H, H-5), 1.58–1.47 (m, 1H, H-4), 1.20 (br d, *J*=13.7 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$/5% CD_3OD) δ 136.0 (C-10a), 133.5 (C-6b), 126.0 (C-11a), 120.8 (C-7), 118.8 (C-9), 117.2 (C-8) 111.9 (C-6a), 110.7 (C-10), 55.1 (C-1 or C-12), 53.0 (C-1 or C-12), 49.4 (C-3), 28.1 (C-4), 25.8 (C-6), 18.3 (C-5); IR ν 3436; HRMS (EI) obs. mass 212.1315, calcd for $C_{14}H_{16}N_2$ 212.1313.

2.2.10. Pictet–Spengler reaction of 3 with propionaldehyde (12a and 12b). General procedure C was followed. Using **3** (50 mg, 0.25 mmol) and propionaldehyde (270 μL, 3.75 mmol) yielded an inseparable mixture of diastereomers (32.2 mg, 0.13 mmol, 54%) in a ratio of **12a/12b**=71:29 according to ^{1}H NMR spectroscopy: ^{1}H NMR (from the mixture) δ 7.94 (br s, 1H, H-11),7.88 (br s, 1H, H-11), 7.46 (d, *J*=7.1 Hz, 2H, H-7), 7.33 (d, *J*=7.3 Hz, 2H, H-10), 7.17–7.06 (m, 4H, H-8, H-9), 4.24–4.18 (m, 1H, H-1), 3.97–3.88 (m, 1H, H-1), 3.41–3.37 (m, 1H, H-12), 3.24–3.13 (m, 6H, H-3, H-6, H-12), 1.99–1.24 (m, 6H, H-4, H-5, H-13), 0.97 (t, *J*=6.8 Hz, 3H, H-14), 0.93 (t, *J*=6.8 Hz, 3H, H-14); ^{13}C NMR (from the mixture) δ 138.0, 136.2, 135.8, 126.5, 126.0, 121.9, 121.2, 120.1, 119.2, 119.1, 117.7, 113.0, 111.1, 110.6, 60.7 (C-1), 60.2 (C-12), 56.2 (C-12), 53.7 (C-3), 49.8 (C-3), 33.4 (C-6), 30.9, 28.7, 28.2, 26.3 (C-6), 25.1, 19.3, 18.6, 11.9 (C-14), 11.6 (C-14); IR ν 3436.

2.2.11. Pictet–Spengler reaction of 3 with *iso*-butyraldehyde (13a and 13b). General procedure B was followed. Using **3** (50 mg, 25 mmol) and *iso*-butyraldehyde (180 μL, 2.0 mmol) yielded an inseparable mixture of diastereomers (9.7 mg, 0.04 mmol, 15%) in a ratio of **13a/13b**=50:50 according to ^{1}H NMR spectroscopy of the crude mixture: ^{1}H NMR (representative parts of the spectrum) δ 8.06 (br s, 1H, H-11), 7.69 (d, *J*=7.8 Hz, 1H H-7), 7.62 (d, *J*=7.8 Hz, 1H, H-7).

2.2.12. Pictet–Spengler reaction of 3 with hexanal (14a and 14b). General procedure C was followed using **3** (40 mg, 0.20 mmol) and hexanal (340 μL, 2.82 mmol). Flash chromatography (EtOAc/PE/NEt_3 65:30:5) yielded **14a** (26.0 mg, 0.09 mmol, 46%) and **14b** (10 mg, 0.04 mmol, 18%), both as yellow oils.

14a: ^{1}H NMR δ 7.94 (br s, 1H, H-11), 7.46 (d, *J*=7.1 Hz, 1H, H-7), 7.33 (d, *J*=7.3 Hz, 1H, H-10), 7.17–7.06 (m, 2H, H-8, H-9), 4.33–4.28 (dd, *J*=6.6 Hz, *J*=4.3 Hz, 1H, H-1), 3.41–3.37 (m, 1H, H-12), 3.24–3.13 (m, 3H, H-3, H-12), 3.05 (br s, 1H, H-6), 1.97–1.08 (m, 12H, H-4, H-5, H-13, H-14, H-15, H-16), 0.97 (t, *J*=6.8 Hz, 3H, H-17); IR ν 3435.

14b: ^{1}H NMR δ 7.89 (br s, 1H, H-11), 7.49 (d, *J*=7.2 Hz, 1H, H-7), 7.34 (d, *J*=7.0 Hz, 1H, H-10), 7.19–7.03 (m, 2H, H-8, H-9), 3.79–3.76 (m, 1H, H-1), 3.25–3.12 (m, 3H, H-3, H-6, H-12), 3.10–2.96 (m, 2H, H-3, H-12), 1.91–1.18 (m, 11H, H-4, H-5, H-13, H-14, H-15, H-16), 1.16–1.11 (m, 1H, H-4), 0.98–0.79 (m, 3H, H-17); IR ν 3436.

2.2.13. Pictet–Spengler reaction of 3 with benzaldehyde (15a and 15b). General procedure B was followed using **3** (32 mg, 0.16 mmol), benzaldehyde (205 μL, 2.01 mmol) and trifluoroacetic acid (12 μL, 0.16 mmol). The diastereomers were formed in a ratio of **15a/15b**=95:5 as indicated by ^{1}H NMR spectroscopy of the crude reaction mixture. From this mixture only **15a** (38 mg, 0.09 mmol, 58%) was isolated as a solid.

15a: mp 208–209°C; ^{1}H NMR δ 7.90 (br s, 1H, H-11), 7.55 (d, *J*=7.3 Hz, 1H, H-7), 7.47–7.36 (m, 5H, Ar–H), 7.29 (d, *J*=7.4 Hz, 1H, H-10), 7.18–7.11 (m, 2H, H-8, H-9), 5.56 (s, 1H, H-1), 3.44 (d, *J*=12.6 Hz, 1H, H-12), 3.32 (d, *J*=12.6 Hz, 1H, H-12), 3.14 (br s, 1H, H-6), 2.70 (dt, *J*=14.0 Hz, *J*=3.5 Hz, 1H, H-3), 2.56–2.50 (m, 1H, H-3), 1.96–1.92 (m, 2H, H-5), 1.60–1.54 (m, 1H, H-4), 1.10–1.07 (m, 1H, H-4); ^{13}C NMR (CD_3OD) δ 138.2 (C-11a), 137.3 (C-6b), 135.2 (C-10), 130.9, 128.4, 128.0, 126.9, 121.3, 119.4, 118.0, 114.1, 110.9, 63.8 (C-1), 56.2 (C-12), 48.0 (C-3), 28.9 (C-4), 27.5 (C-6), 19.9 (C-5); IR ν 3436; HRMS (EI) obs. mass 288.1622, calcd for $C_{20}H_{20}N_2$ 288.1626.

15b: ^{1}H NMR δ 5.92 (s, 1H, H-6), 4.06 (d, *J*=12.6 Hz, 1H, H-12), 3.72 (d, *J*=12.6 Hz, 1H, H-12); the other signals could not be discerned from the crude reaction mixture.

2.2.14. Pictet–Spengler reaction of 3 with 5,5-diethoxypentanal (16a and 16b). General procedure C was followed using **3** (300 mg, 1.50 mmol) and 5,5-diethoxypentanal (3.71 g, 21.3 mmol). Flash chromatography (EtOAc/PE/NEt_3 65:30:5) yielded **16a** (258 mg, 0.72 mmol, 48%) and **16b** (132 mg, 0.38 mmol, 25%), both as yellow oils.

16a: ^{1}H NMR δ 7.99 (br s, 1H, H-11), 7.46 (d, *J*=7.6 Hz, 1H, H-7), 7.33 (d, *J*=6.5 Hz, 1H, H-10), 7.15–7.06 (m, 2H,

H-8, H-9), 4.59–4.48 (m, 1H, H-16), 4.31–4.27 (m, 1H, H-1), 3.73–3.60 (m, 2H, OCH_2CH_3), 3.57–3.48 (m, 2H, OCH_2CH_3), 3.37 (d, J=11.3 Hz, 1H, H-12), 3.19–3.14 (m, 2H, H-3, H-12), 3.04 (br s, 1H, H-6), 2.91 (dt, J=14.0 Hz, J=3.7 Hz, 1H, H-3), 1.96–1.76 (m, 8H, H-5, H-13, H-14, H-15), 1.42–1.36 (m, 1H, H-4), 1.35–1.16 (m, 7H, H-4, OCH_2CH_3); ^{13}C NMR δ 138.3 (C-10a), 135.5 (C-6b), 126.2 (C-11a), 120.9 (C-8), 119.1 (C-7), 117.5 (C-9), 112.1 (C-6a), 110.6 (C-10), 102.5 (C-16), 61.2 (OCH_2CH_3), 60.7 (OCH_2CH_3), 57.1 (C-1), 55.6 (C-12), 46.7 (C-3), 33.3 (C-15), 30.4 (C-13), 28.6 (C-14), 26.4 (C-6), 21.8 (C-5), 19.0 (C-4), 15.1 (OCH_2CH_3); IR ν 3492, 2360, 1458; HRMS (FAB) obs. mass 357.2543, calcd for $C_{22}H_{33}N_2O_2$ (M+1) 357.2542.

16b: ^{1}H NMR δ 8.04 (br s, 1H, H-11), 7.47 (d, J=7.6 Hz, 1H, H-7), 7.33 (d, J=7.9 Hz, 1H, H-10), 7.15–7.05 (m, 2H, H-8, H-9), 5.54–4.46 (m, 1H, H-16), 3.69–3.60 (m, 3H, H-1, OCH_2CH_3), 3.55–3.44 (m, 2H, OCH_2CH_3), 3.11 (dt, J=14.4 Hz, J=3.8 Hz, 1H, H-3), 3.10–3.08 (m, 2H, H-6, H-12), 2.97–2.95 (m, 2H, H-3, H-12), 1.89–1.44 (m, 8H, H-5, H-13, H-14, H-15), 1.39–1.35 (m, 1H, H-4), 1.27–1.11 (m, 7H, H-4, OCH_2CH_3); ^{13}C NMR δ 137.9 (C-10a), 135.7 (C-6b), 126.3 (C-11a), 121.1 (C-8), 119.2 (C-7), 117.7 (C-9), 112.2 (C-6a), 110.7 (C-10), 102.6 (C-16), 61.3 (OCH_2CH_3), 60.8 (OCH_2CH_3), 57.2 (C-1), 55.8 (C-12), 46.9 (C-3), 33.5 (C-15), 30.5 (C-4), 28.8 (C-13), 26.5 (C-6), 21.9 (C-14), 19.2 (C-5), 15.3 (OCH_2CH_3); IR ν 3492, 2360, 1458; HRMS (FAB) obs. mass 357.2559, calcd for $C_{22}H_{33}N_2O_2$ (M+1) 357.2542.

2.2.15. Pictet–Spengler reaction of 5 with hexanal (17). General procedure B was followed. To a solution of **5** (300 mg, 1.50 mmol) and trifluoroacetic acid (120 μL, 1.56 mmol) in toluene (10 mL), hexanal (3.60 mL, 30.0 mmol) was added in portions over a period of 5 days. Flash chromatography (PE/EtOAc 50:50 then PE/EtOAc/NEt_3 60:30:10) yielded **17** (12 mg, 0.04 mmol, 2.7%) as a yellow oil: ^{1}H NMR δ 8.07 (br s, 1H, H-10), 7.48 (d, J=7.0 Hz, 1H, H-6 or H-9), 7.30 (d, J=7.1 Hz, 1H, H-6 or H-9), 7.14–7.07 (m, 2H, H-7, H-8), 4.28–4.22 (m, 1H, H-1), 3.49–3.42 (m, 1H), 3.28 (br s, 1H, H-5), 3.23–3.16 (m, 1H), 3.10–2.96 (m, 2H), 2.06–1.88 (m, 4H), 1.87–1.75 (m, 2H), 1.68–1.62 (m, 1H), 1.59–1.46 (m, 1H), 1.43–1.35 (m, 4H), 0.97–0.87 (m, 3H, H-17); ^{13}C NMR δ 187.2 (C-10a), 135.8 (C-9a), 126.3 (C-5b), 121.0 (C-8), 119.1 (C-7), 119.0 (C-5a), 117.3 (C-6), 110.5 (C-9), 64.1 (C-1), 48.5, 40.0, 33.9, 31.9, 30.6, 29.2, 26.5, 24.3 (C-5), 22.5. 14.0 (C-17); IR ν 3437.

2.3. *spiro*-Cyclization reactions

2.3.1. General procedure A. The oxindole was freshly prepared from the corresponding amine according to the procedure described above prior to use. A solution of oxindole and aldehyde (1–5 equiv. based on the indole precursor) in acetic acid was stirred during the time and temperature indicated. The reaction mixture was concentrated in vacuo, then EtOAc and an aqueous saturated solution of K_2CO_3 were added. The layers were separated and the water layer was extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography afforded the pure diastereomers.

2.3.2. General procedure B. The oxindole was prepared prior to use from the corresponding amine according to the procedure described above. To a solution of this freshly prepared oxindole and NaOAc in MeOH, aldehyde (5 equiv. based on the indole precursor) was added. The reaction mixture was stirred during the time and temperature indicated and concentrated in vacuo. An aqueous saturated solution of K_2CO_3 and diethyl ether were added. The layers were separated and the water layer was extracted with diethyl ether (3×). The combined organic layers were washed with H_2O, dried (Na_2SO_4) and evaporated. Flash chromatography gave the pure diastereomers.

2.3.3. Condensation of 2 with formaldehyde (18). General procedure A was followed with **2** freshly prepared from **1** (100 mg, 0.54 mmol) and paraformaldehyde (16 mg, 0.54 mmol) in acetic acid (2 mL). The reaction mixture was stirred during 2 h at 90°C. Flash chromatography (CH_2Cl_2/MeOH/conc. NH_4OH 80:20:2) afforded **18** (7 mg, 0.03 mmol, 6%) as a glass: ^{1}H NMR δ 8.04 (br s, 1H, H-11), 7.53 (d, J=6.8 Hz, 1H, H-7), 7.30 (d, J=7.6 Hz, 1H, H-8 or H-9), 7.15–7.08 (m, 1H, H-8, H-9), 4.49 (d, J=16.6 Hz, 1H, H-1), 3.77 (d, J=16.6 Hz, 1H, H-1), 3.40–3.32 (m, 2H, H-3a, H-5), 3.09 (d, J=10.8 Hz, 1H, H-13a), 2.93 (dd, J=10.8 Hz, J=2.8 Hz, 1H, H-13), 2.88–2.81 (m, 1H, H-3 or H-4a), 2.14–2.01 (m, 2H, H-3 or H-4a, H-4); IR ν 3435, 1705.

2.3.4. Condensation of 2 with hexanal (19). General procedure B was followed using **2** freshly prepared from **1** (400 mg, 1.98 mmol) and hexanal (1.2 mL, 10 mmol). The mixture was stirred at rt during one night. In the crude reaction mixture three isomers could be discerned in a ratio of 50:5:45. Flash chromatography (EtOAc/PE/NEt_3 60:40:10) gave **19a** (23 mg, 0.08 mmol, 4%) and an inseparable mixture of **19b** and **19c** (25 mg, 0.09 mmol, 4.5%).

19a: ^{1}H NMR δ 8.64 (br s, 1H, H-11), 7.35 (d, J=7.6 Hz, 1H, H-7), 7.20 (t, J=7.6 Hz, 1H, H-8 or H-9), 7.00 (t, J=7.6 Hz, 1H, H-8 or H-9), 6.89 (d, J=7.6 Hz, 1H, H-10), 3.37 (br d, J=9.9 Hz, 1H, H-13), 3.08–2.92 (m, 3H, H-1, H-3), 2.59–2.56 (m, 2H, H-5, H-13), 2.47–2.42 (m, 1H), 1.56–1.47 (m, 1H), 1.40–1.27 (m, 3H), 1.25–1.00 (m, 4H), 0.91 (m, 1H), 0.72 (t, J=6.9 Hz, 3H, H-18); ^{13}C NMR δ 181.2 (C-12), 140.3 (C-11a), 131.8 (C-7a), 127.6, 124.5, 121.8, 109.4 (C-11), 76.8 (C-1), 59.9, 59.0, 54.9, 50.0 (C-5), 33.3, 31.5, 27.2, 23.0, 22.3, 13.8 (C-18); IR ν 3436, 1703.

19b: ^{1}H NMR (from the mixture) δ 9.10 (br s, 1H, H-11), 7.22–7.15 (m, 2H, H-7, H-8 or H-9), 6.99 (t, J=7.6 Hz, 1H, H-8 or H-9), 6.92 (d, J=7.6 Hz, 1H, H-10), 3.79 (br d, J=9.4 Hz, 1H, H-13), 3.42–3.38 (m. 1H, H-1), 3.10–3.03 (m, 1H), 2.89–2.82 (m, 1H), 2.67–2.66 (m, 1H, H-5), 2.62–2.53 (m, 2H, H-13), 1.65–1.60 (m, 1H), 1.49–1.41 (m, 1H), 1.30–1.00 (m, 6H), 0.91–0.87 (m, 1H), 0.70 (t, J=6.9 Hz, 3H, H-18); ^{13}C NMR δ 182.9 (C-12), 141.8 (C-11a), 128.2 (C-7a), 127.5, 126.9, 120.9, 109.9 (C-11), 71.0 (C-1), 59.9, 56.1, 54.9, 50.8 (C-5), 43.9, 31.4, 26.8, 25.4, 22.1, 13.7 (C-18); IR ν 3436, 1703.

19c: ^{1}H NMR (from the mixture) δ 8.02 (br s, 1H, H-11), 7.35 (d, J=7.6 Hz, 1H, H-7), 7.21 (d, J=7.6 Hz, 1H, H-8 or H-9), 7.00 (t, J=7.6 Hz, 1H, H-8 or H-9), 6.87 (d, J=7.6 Hz, 1H, H-10), 3.37 (br d, J=9.8 Hz, 1H, H-13), 3.08–2.96 (m, 3H, H-1, H-3, H-13), 2.58–2.56 (m, 2H, H-3, H-5), 2.47–2.41 (m, 1H), 1.63–0.98 (m, 7H), 0.94–0.75 (m, 2H), 0.73 (t, J=7.0 Hz, H-18); IR ν 3436, 1703.

2.3.5. Condensation of 2 with benzaldehyde (20). General procedure B was followed using **2** freshly prepared from **1** (149 mg, 0.80 mmol) and benzaldehyde (120 μL, 1.20 mmol). The mixture was stirred during one night at 55°C. The diastereomers were formed in a ratio of **20a**:**20b**=69:31 according to ^{1}H NMR spectroscopy. Flash chromatography (PE/EtOAc 50:50 then PE/EtOAc/NEt_3 60:25:15) gave an inseparable mixture of the two isomers **20a** and **20b** (14 mg, 0.005 mmol, 6%).

20a: ^{1}H NMR (from the mixture) δ 7.95 (br s, 1H, H-11), 7.47–6.93 (m, 8H, H-7, H-8, H-9, Ar–H), 6.83 (d, J=7.5 Hz, 1H, H-10), 4.23 (br s, 1H, H-1), 4.19 (br d, J=9.8 Hz, 1H, H-13), 3.31 (td, J=12.1 Hz, J=12.1 Hz, J=4.6 Hz, 1H, H-3a), 3.04–2.99 (m, 1H, H-3), 2.80 (d, J=4.1 Hz, 1H, H-5), 2.74–2.68 (m, 1H, H-13), 2.19–2.12 (m 1H, H-4a), 1.74–1.65 (m, 1H, H-4b); ^{13}C NMR (from the mixture) δ 178.9 (C-12), 141–109 (24 C's), 77.7 (C-1), 61.1 (C-3), 60.9 (C-6), 54.7 (C-3), 51.7 (C-5), 23.6 (C-4); IR ν 3437, 1705.

20b: ^{1}H NMR (from the mixture) δ 8.12 (br s, 1H, H-11), 7.47–6.93 (m, 5H, H-7, H-8 or H-9, Ar–H), 6.56 (t, J=7.6 Hz, 1H, H-8 or H-9), 6.39 (d, J=7.6 Hz, 1H, H-10), 4.45 (br s, 1H, H-1), 3.49 (br d, J=9.9 Hz, 1H, H-13), 3.17 (td, J=11.3 Hz, J=11.3 Hz, J=4.4 Hz, 1H, H-3), 3.06–3.04 (m, 1H,H-3), 2.74–2.68 (m, 2H, H-5, H-13), 2.59–2.53 (m, 1H, H-4), 1.49–1.46 (m, 1H, H-4); ^{13}C NMR (from the mixture) δ 178.9 (C-12), 141–109 (24C), 79.4 (C-1), 61.0 (C-3), 60.2 (C-6), 55.3 (C-3), 50.9 (C-5), 25.0 (C-4); IR ν 3437, 1705.

2.3.6. Condensation of 4 with formaldehyde (21a and 21b). General procedure A was followed using **4** prepared from **3** (67 mg, 0.36 mmol) and paraformaldehyde (11 mg, 0.37 mmol). After 2 h at 90°C the conversion was complete. According to the ^{1}H NMR spectrum of the crude reaction mixture two diastereomers in a ratio of 76:24 had been formed. Flash chromatography (EtOAc/EtOH/NEt_3 75:15:10) gave **21b** (21 mg, 0.07 mmol, 19%) as a glass. The other diastereomer **21a** (50 mg, 0.22 mmol, 62%) was crystallized from acetonitrile.

21a: mp 177–179°C; ^{1}H NMR δ 9.65 (br s, 1H, H-12), 7.32 (d, J=7.5 Hz, 1H, H-8), 7.16 (t, J=7.5 Hz, 1H, H-10), 6.95 (t, J=7.5 Hz, 1H, H-9), 6.83 (d, J=7.5 Hz, 1H, H-11), 3.56 (br d, J=13.1 Hz, 2H, H-1$_{endo}$, H-14$_{eq}$), 3.38 (d, J=13.1 Hz, 1H, H-1$_{exo}$), 3.29–2.98 (m, 4H, H-3, H-4$_{ax}$, H-14$_{ax}$), 2.17 (br s, 1H, H-6), 2.06–1.97 (m, 1H, H-5), 1.84–1.75 (m, 1H, H-5), 1.38–1.33 (m, 1H, H-4$_{eq}$); ^{13}C NMR δ 181.1 (C-13), 139.8 (C-11a), 136.6 (C-7a), 127.6 (C-10), 122.6 (C-8), 122.0 (C-9), 109.1 (C-11), 61.2 (C-1), 60.8 (C-7), 58.5 (C-3 or C-14), 56.0 (C-3 or C-14), 48.1 (C-6), 27.9 (C-5), 17.4 (C-4); IR ν 3437, 1708; HRMS (EI) obs. mass 228.1259, calcd for $C_{14}H_{16}N_2O$ 228.1263.

21b: ^{1}H NMR δ 9.16 (br s, 1H, H-12), 7.60 (d, J=7.5 Hz, 1H, H-8), 7.20 (t, J=7.5 Hz, 1H, H-10), 7.00 (t, J=7.5 Hz, 1H, H-9), 6.90 (d, J=7.5 Hz, 1H, H-11), 4.09 (br d, J=11.4 Hz, H-14$_{eq}$), 3.56 (d, J=13.0 Hz, 1H, H-1$_{endo}$), 3.18–3.01 (m, 3H, H-3, H-1$_{exo}$), 2.87 (d, J=11.4 Hz, 1H, H-14$_{ax}$), 2.61 (s, $(CH_3)_2SO$), 2.43–2.34 (m, 1H, H-4$_{ax}$), 2.17 (br s, 1H, H-6), 1.94–1.85 (m, 2H, H-5), 1.60–1.55 (m, 1H, H-4$_{eq}$); ^{13}C NMR δ 183.4 (C-13), 141.7 (C-11a), 130.3 (C-7a), 127.9 (C-10), 124.5 (C-8), 121.8 (C-9), 109.8 (C-11), 59.5, 59.2, 58.2, 55.5, 44.5 (C-6), 40.8 ($(CH_3)_2SO$) 26.9 (C-5), 18.2 (C-4); IR ν 3436, 1709; HRMS (EI) obs. mass 229.1345, calcd for $C_{14}H_{17}N_2O$ (M+1) 229.1341.

2.3.7. Condensation of 4 with hexanal (22). General procedure A was followed using **4** prepared from **3** (20 mg, 0.1 mmol) and hexanal (60 μL, 0.5 mmol). After stirring during 5 h at 90°C, a mixture of two diastereomers in a ratio of **22a**/**22b**=63:37 was formed according to ^{1}H NMR spectroscopy of the crude reaction mixture (see text). Alternatively the reaction could be performed following general procedure B, reacting **4** (55 mg, 0.15 mmol), NaOAc (20 mg, 0.25 mmol) and hexanal (60 μL, 0.5 mmol) during 6 h at 55°C. According to ^{1}H NMR spectroscopy of the crude reaction mixture two diastereomers in a ratio of **22a**/**22b**=55:45 had been formed. Flash chromatography (EtOAc/PE/NEt_3 65:30:5) gave **22a** (14 mg, 0.05 mmol, 31%) and **22b** (12 mg, 0.04 mmol 26%), both as a glass.

22a: ^{1}H NMR δ 7.86 (br s, 1H, H-12), 7.36 (d, J=7.6 Hz, 1H, H-8), 7.19 (t, J=7.6 Hz, H-10), 6.97 (t, J=7.6 Hz, 1H, H-9), 6.85 (d, J=7.6 Hz, 1H, H-11), 3.67–3.62 (m, 2H, H-1, H-14$_{eq}$), 3.20–3.09 (m, 2H, H-3), 3.04–2.93 (m, 2H, H-4$_{ax}$, H-14$_{ax}$), 2.21 (br d, J=2.9 Hz, 1H, H-6), 2.06–2.01 (m, 1H, H-5), 1.86–1.77 (m, 1H, H-5), 1.52–1.44 (m, 1H, H-15), 1.43–1.36 (m, 1H, H-4$_{eq}$), 1.34–1.23 (m, 2H, H-17), 1.18–0.99 (m, 4H, H-16, H-18) 0.98–0.86 (m, 1H, H-15), 0.76 (t, J=6.7 Hz, 3H, H-19); ^{13}C NMR δ 180.1 (C-13), 139.5 (C-11a), 132.5 (C-7a), 127.5 (C-10), 124.3 (C-8), 121.8 (C-9), 109.1 (C-11), 71.1 (C-1), 62.6 (C-7), 60.7 (C-14), 56.9 (C-3), 49.0 (C-6), 34.5 (C-15), 31.6 (C-16), 27.4 (C-5), 27.4 (C-17), 22.3 (C-18), 17.8 (C-4) 13.8 (C-19); IR ν 3437, 1708; HRMS (EI) obs. mass 298.2031, calcd for $C_{19}H_{26}N_2O$ 298.2045.

22b: ^{1}H NMR δ 7.84 (br s, 1H, H-12), 7.61 (d, J=7.6 Hz, 1H, H-8), 7.23 (t, J=7.6 Hz, 1H, H-10), 7.05 (t, J=7.6 Hz, 1H, H-9), 6.87 (d, J=7.6 Hz, 1H, H-11), 4.26 (br d, J=11.6 Hz, 1H, H-14$_{eq}$), 3.37–3.34 (m 1H, H-1), 3.04–2.93 (m, 1H, H-3$_{ax}$), (m 1H, H-3$_{eq}$), 2.83 (dd, J=11.6 Hz, J=1.5 Hz, 1H, H-14$_{ax}$), 2.43–2.32 (m, 1H, H-4$_{ax}$), 2.21 (br s, 1H, H-6), 1.97–1.92 (m, 2H, H-5), 1.80–1.72 (m, 1H, H-15), 1.62–1.51 (m, 1H, H-4$_{eq}$), 1.38–1.02 (m, 7H, H-15, H-16, H-18), 0.77 (t, J=6.8 Hz, 3H, H-19); ^{13}C NMR δ 180.1 (C-13), 140.7 (C-11a), 131.1 (C-7a), 127.7 (C-10), 124.5 (C-8), 122.0 (C-9), 109.2 (C-11), 72.5(C-1), 62.5 (C-7), 59.1 (C-14), 56.6 (C-3), 45.6 (C-6), 33.0 (C-15), 31.7 (C-16), 28.0 (C-17), 26.5 (C-5), 22.5 (C-18), 18.6 (C-4), 13.8 (C-19); IR ν 3437, 1708; HRMS (EI) obs, mass 298.2031, calcd for $C_{19}H_{26}N_2O$ 298.2045.

2.3.8. Condensation of 6 with hexanal (25a and 25b). General procedure B was followed using **6** prepared from

5 (400 mg, 2.0 mmol), NaOAc (492 mg, 6.0 mmol) and hexanal (1.25 mL, 10.0 mmol). Stirring the reaction mixture during 10 h at 65°C resulted in complete conversion. According to the ^{1}H NMR spectrum of the crude mixture the diastereomers had been formed in a ratio of **25a/25b**=36:64. Flash chromatography (EtOAc/PE/NEt_3 60:40:10) yielded both diastereomers **25a** (131 mg, 0.44 mmol, 22%) and **25b** (232 mg, 0.78 mmol, 39%) as a glass. Alternatively the reaction could be performed following general procedure A. Using **6** (20 mg, 0.1 mmol) and hexanal (25 μL, 0.2 mmol), after stirring during 8 h at 90°C, the diastereomers **25a/25b** (14 mg, 0.05 mmol, 47%) were formed in a ratio of 21:79 according to the ^{1}H NMR spectrum of the crude reaction mixture.

25a: ^{1}H NMR δ 8.30 (br s, 1H, H-11), 7.37 (d, J=7.4 Hz, 1H, H-7), 7.19 (t, J=7.4 Hz, 1H, H-9), 7.03 (t, J=7.4 Hz, 1H, H-8), 6.86 (d, J=7.4 Hz, 1H, H-10), 3.45–3.37 (m, 1H, H-13), 3.21–3.16 (m, 1H, H-3_{ar}), 3.15–3.05 (m, 3H, H-1, H-3), 2.81 (dd, J=11.0 Hz, J=12.2 Hz, 1H, H-13), 2.49–2.41 (m, 1H, H-14), 2.18–2.10 (m, 1H, H-4_{ar}) 1.85–1.77 (m, 1H, H-15a), 1.71 (br s, 1H, H-5), 1.52–1.44 (m, 2H, H-4, H-15), 1.35–1.27 (m, 1H, H-14), 1.19–1.01 (m, 5H, H-16, H-17, H-18), 0.98–0.88 (m, 1H, H-16), 0.72 (t, J=6.8 Hz, 3H, H-19); ^{13}C NMR δ 179.7 (C-12), 140.3 (C-10a), 134.9 (C-6a), 127.4 (C-7), 124.2 (C-8), 121.6 (C-9), 109.2 (C-10), 64.4 (C-1), 52.6 (C-6), 49.7 (C-3), 41.4 (C-13), 31.5 (C-16), 31.4 (C-5), 29.7 (C-15), 26.5 (C-17), 22.9 (C-4), 22.3 (C-18), 21.8 (C-14), 13.8 (C-19); IR ν 3436, 1702; HRMS (FAB) obs. mass 299.2117, calcd for $C_{19}H_{27}ON_2$ (M+1) 299.2123.

25b: ^{1}H NMR δ 7.88 (br s, 1H, H-11), 7.37 (d, J=7.6 Hz, 1H, H-7), 7.22 (t, J=7.6 Hz, 1H, H-9), 7.02 (t, J=7.6 Hz, 1H, H-8), 6.91 (d, J=7.6 Hz, 1H, H-10), 3.32 (t, J=7.3 Hz, 1H, H-1), 3.27–3.20 (m, 2H, H-3, H-13), 3.03–2.94 (m, 2H, H-3, H-13), 2.66–2.63 (m, 1H, H-14_a), 2.06–2.00 (m, 1H, H-4_{ar}), 1.69 (br s, 1H, H-5), 1.59–1.52 (m, 1H, H-15), 1.50–1.43 (m, 1H, H-14b), 1.39–1.30 (m, 3H, H-4, H-15, H-17), 1.10–0.82 (m, 4H, H-16, H-17, H-18), 0.72–0.65 (m, 4H, H-16, H-19); ^{13}C NMR δ 181.8 (C-12), 140.6 (C-10a), 129.6 (C-6a), 127.6 (C-8 or C-9), 126.6 (C-7 or C-10), 121.3 (C-7 or C-10), 109.9 (C-8 or C-9), 61.9 (C-1), 53.3 (C-6), 49.2 (C-3 or C-13), 41.6 (C-3 or C-13), 31.3 (C-18), 31.1 (C-5), 30.4 (C-15), 25.8 (C-16), 22.6 (C-4 or C-14), 22.1 (C-17), 20.4 (C-4 or C-14), 13.7 (C-19); IR ν 3435, 1704; HRMS (EI) obs. mass 298.2059, calcd for $C_{19}H_{26}N_2O$ 298.2045.

2.3.9. Condensation of 6 with benzaldehyde (26a and 26b). General procedure B was followed using **6** freshly prepared from **5** (200 mg, 1.0 mmol), NaOAc (246 mg, 3.0 mmol) and benzaldehyde (0.51 mL, 5.0 mmol). The reaction did not go to completion (44 h, 60–65°C). According to the ^{1}H NMR spectrum of the crude mixture two diastereomers had been formed in a ratio of **26a/26b**=36:64. Flash chromatography (EtOAc/PE/NEt_3 40:55:5) yielded an inseparable mixture of two diastereomers **26a/26b** (78 mg, 0.26 mmol, 22%) as a glass: ^{1}H NMR δ 9.40 (br s, 1H, H-11b), 9.28 (br s, 1H, H-11a), 7.55 (d, J=7.4 Hz, 1H, H-7a), 7.29–6.77 (m, 15H, Ar–Ha, Ar–Hb, H-8a, H-9a, H-10a, H-7b, H-9b), 6.65 (t, J=7.4 Hz, 1H, H-8b), 6.57 (d, J=7.4 Hz, 1H, H-10b), 4.86 (br s, 1H, H-1b) 4.64 (br s, 1H, H-1a), 3.75–3.70 (m, 1H, H-13a), 3.48–3.30 (m, 4H, H-3a, H-3b), 3.23–3.04 (m, 4H, H-13a, H-13b), 2.88–2.80 (m, 1H, H-14b), 2.35–2.30 (m, 2H, H-14a, H-4a), 2.02–1.92 (m, 1H, H-14b), 1.82 (br s, 2H, H-5a, H-5b), 1.64–1.58 (m, 1H, H-4a), 1.57–1.41 (m, 3H, H-14a, H-4b, H-14b); ^{13}C NMR δ 183.1 (C-12), 180.1 (C-12), 140.7, 140.6, 140.5, 139.2, 135.2, 130.3, 129.4, 129.1, 128.0, 127.9, 127.8, 127.4, 127.0, 126.6, 126.3, 126.2, 125.8, 125.3, 123.8, 121.8, 121.1, 115.5, 110.2, 110.0, 65.2 (C-1), 63.6 (C-6), 55.1 (C-6), 55.0 (C-6), 49.5, 49.3, 43.1 (2C), 31.9 (C-5), 31.6 (C-5), 22.8, 22.7, 22.3, 20.7; IR ν 3435, 1705.

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