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Ipobscurines C and D: macrolactam-type indole alkaloids from the seeds of *Ipomoea obscura*☆

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Abstract

Separation of the methanolic seed extract of *Ipomoea obscura* afforded five indole alkaloids, three of them (ipobscurines B-D) being new natural products of a unique structural type characterized as serotonin hydroxycinnamic acid amide-type conjugates with a second phenylpropanoid moiety forming an ether with the 5-OH position of the indole nucleus. Due to an oxidative phenolic coupling between the two phenylpropanoid moieties of the supposed precursor ipobscurine B two 21-membered macrolactams with a phenol ether partial structure are formed: the *trans–cis* isomers ipobscurines C and D. Their structures were established on the basis of spectral data. Moreover, total synthesis of the racemic *erythro*- and *threo*-ipobscurine B 4′,4″-dimethyl ethers and the comparison with the corresponding derivative of natural (−)-ipobscurine B proved an *erythro* configuration of the latter.

Keywords: *Ipomoea obscura*; Convolvulaceae; Indole alkaloids; Serotonin; Hydroxycinnamic acid amide-type conjugates; Ipobscurines; Neolignans

1. Introduction

The largest convolvulaceous genus *Ipomoea* comprises species which are phytochemically characterised by the occurrence of different types of alkaloids in the seeds. The accumulation of ergoline alkaloids in a remarkable amount of species is well-known since they were discovered 40 years ago at the same time in *Turbina corymbosa* (L.) Raf. [syn.: *Rivea corymbosa* (L.) H. Hall.] as well as in *I. tricolor* Cav. (syn.: *I. violacea* auct., non L.) (Hofmann and Tscherter, 1960; Hofmann, 1961; Amor-Prats and Harborne, 1993). However, species of the subgenus Quamoclit show other structural types: members of the section Calonyction accumulate indolizidine alkaloids (Gourley et al., 1969; Dawidar et al., 1977), whereas members of the section Mina show pyrrolizidine alkaloids (Jenett-Siems et al., 1993, 1998). In both cases the special structures are unique in the plant kingdom.

We now report on the isolation and structure determination of a novel type of *Ipomoea* seed alkaloids from *I. obscura* (L.) Ker-Gawl., a very common and widespread paleotropic perennial herb, belonging to the subgenus Eriospermum, section Erpipomoea. Five serotonin hydroxycinnamic acid amide (HCA)-type conjugates could be characterized; three of them represent novel natural compounds of a unique structural type.

2. Results and discussion

TLC examination of the methanolic seed extract of *I. obscura* revealed the presence of several compounds giving a positive reaction with van Urk's reagent with typical blue spots indicating a C-3-substituted indole moiety (Mayer and Eich, 1975). Separation by column chromatography led to the isolation of five compounds. On the basis of spectroscopic analyses two of them turned out to be N_b-(*p*-coumaroyl)serotonin (ipobscurine A) and its 5-*O*-β-D-glucopyranoside, simple serotonin hydroxycinnamic acid amides already known as constituents of safflower seeds (*Carthamus tinctorius* L.,

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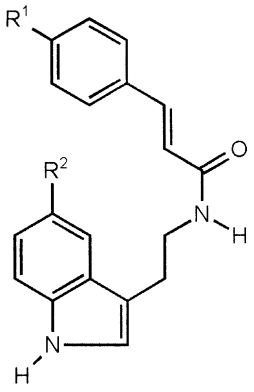
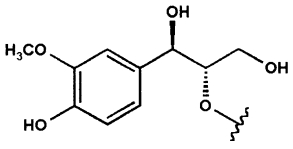
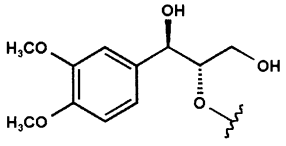
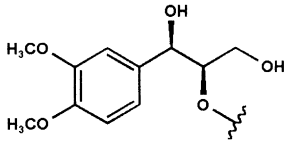
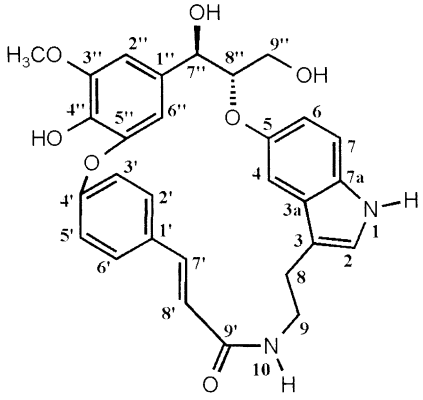
Asteraceae) (Sakamura et al., 1978, 1980). Compounds **1**–**3** were found to be new natural products of a more complex structure and named, respectively, ipobscurines B–D.

Using FAB MS measurements, the molecular mass of **1** could be determined as 518. In combination with ^{1}H and ^{13}C NMR spectra a molecular composition of $C_{29}H_{30}N_2O_7$ could be assumed. The ^{1}H NMR spectrum displayed characteristic signals of a serotonin and a *p*-coumaroyl moiety as in ipobscurine A but in addition a 1,2,4-tri-substituted aromatic system could be observed. Furthermore, the spectrum showed one methoxy group, two hydroxymethine groups at δ 5.06 (1H, *dd*, $J = 4.0$, 4.5 Hz) and δ 4.43 (1H, *dt*, $J = 4.0$, 4.5 Hz) as well as one hydroxymethylene group (δ 3.58, 1H, *m* and δ 3.90, 1H, *dd*, $J = 11.5$, 4.5 Hz). These data hinted to the presence of a second phenylpropanoid moiety, namely 7,8-dihydroxy-dihydroconiferyl alcohol. The positions of the methoxy group as well as the linkage of the additional phenylpropane residue were determined by NOE experiments. Irradiation in the methoxy signal led to an enhancement of the signal of H-2″, whereas irradiation in the hydroxymethine signal at δ 4.43 caused positive NOEs at H-4 and H-6. The small coupling constant of 4.0 Hz between the two hydroxymethine protons indicated that **1** existed as the *erythro* isomer (Barata et al., 1978; Zacchino and Badano, 1988). This was confirmed by synthesis of both forms—

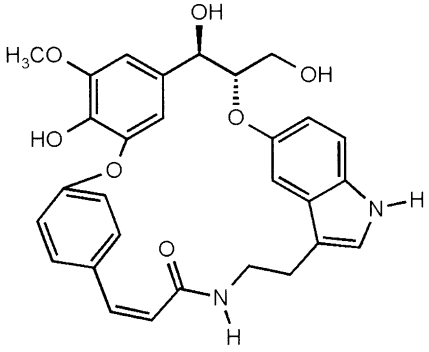


	R^1	R^2
1	OH	
6a	OCH_3	
6b	OCH_3	



2

(biogenetic numbering)



3

erythro (**6a**) and *threo* (**6b**)— of the dimethyl ether of **1** (Fig. 1). The spectroscopic data of synthetic *rac*. *N*-[2-[5-*erythro*-[2-[(3,4-dimethoxyphenyl)-2-hydroxy-1-hydroxymethyl]ethoxy]indol-3-yl]ethyl]-4-methoxycinnamoyl amide (**6a**) were identical with those of the dimethyl ether of natural **1**. In conclusion **1** represents the (−)-*erythro* isomer; we propose ipobscurine B as trivial name for this novel serotonin–HCA conjugate.

Compound **2** displayed a molecular ion peak at *m*/*z* 516 in the EIMS spectrum, corresponding to a molecular formula of $C_{29}H_{28}N_2O_7$ (HREIMS). ^1H and ^{13}C NMR spectra were quite similar to those of **1** revealing the presence of a 1,2,3,5-tetra-substituted instead of a 1,2,4-tri-substituted aromatic system. These data suggested the existence of an ether bridge between C-4′ and C-5″, formed by an oxidative phenolic coupling. In the NOESY spectrum of **2**, cross-peaks between H-6 and H-8″ revealed the attachment of the arylglycerol moiety at position 5 of the indole ring. The position of the methoxy group could be deduced from NOESY correlations to H-2″ (δ 6.79 *d*, $J = 1.5$ Hz). Further correlations were observed between H-2′/6′ and the olefinic protons of a *trans*-double bond at δ 7.09 (*d*, $J = 15.5$ Hz, H-7′) and δ 5.68 (*d*, $J = 15.5$ Hz, H-8′), revealing the presence of a *p*-substituted cinnamic acid derivative. Finally, correlations between H-6″ and the hydroxy group at C-7″ as well as between the hydroxy groups at C-7″ and C-9″ were also detected. Thus **2**, which we named ipobscurine C, represents a macrocyclic serotonin–HCA conjugate.

Compound **3** showed the same molecular ion peak as **2** in the EIMS spectrum. Regarding the ^1H NMR spectrum, the only striking difference compared to **2** was the coupling constant $J = 12.5$ Hz between H-7′ and H-8′ instead of $J = 15.5$ Hz. This pointed to a *cis*-configuration of the 7,8-double bond. Thus, **3**, which we named ipobscurine D, had to be the *Z*-isomer of **2**.

The ipobscurines A–D are only present in mature or—in smaller concentrations—in almost mature seeds. Neither flowers and undeveloped fruits (diameter 3–7 mm) nor epigeal vegetative material and roots show any ipobscurine. These compounds are synthesized apparently in the late phase of the seed development since the first small concentrations can be detected in elder

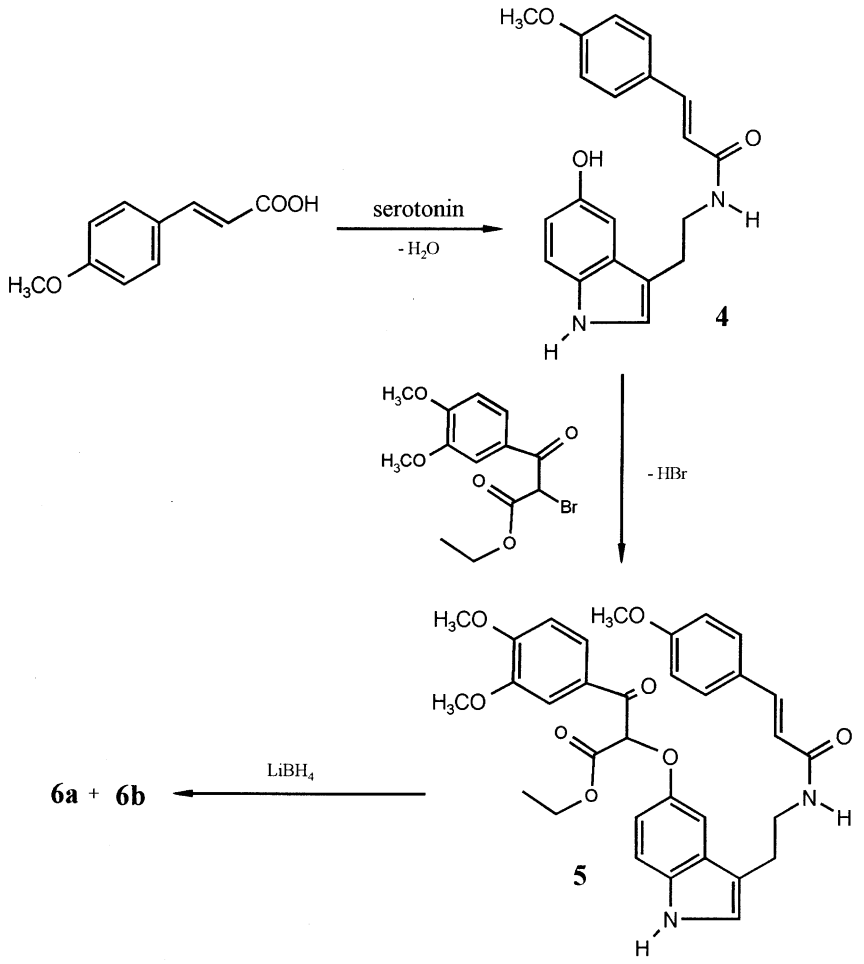


Fig. 1. Synthesis of *rac*. *N*-[2-[5-*erythro*- and *threo*-[2-[(3,4-dimethoxyphenyl)-2-hydroxy-1-hydroxymethyl]ethoxy]indol-3-yl]ethyl]-4-methoxycinnamoyl amide (**6a**/**6b**) from 4-methoxycinnamic acid.

though immature fruits (diameter: 10 mm). The ipobscurines A and B were found in any of the provenances collected in the Asian wild (Sri Lanka/6 prov.; Bali/Java (Indonesia)/2 prov.) with 0.054–0.104% (dry wt.) for ipobscurine A and up to 0.062% for B, respectively. The Asian provenances belong to the cream or white blooming form of *I. obscura var. obscura* with or without purple, red or brown centre.

Ipobscurine C in seeds from the wild was only determinable in one provenance of Sri Lanka (0.047%). However, mature seeds obtained by cultivation in the greenhouse from seeds originally collected on Java also contained this macrocyclic lactam. In this latter case the A:B:C relation was 0.136:0.011:0.079%. Ipobscurine D was only present as a minor component.

Seeds harvested in the greenhouse originating from three different locations of Tanzania contained only very low concentrations of ipobscurine B. Ipobscurine C was not detectable. Their content of ipobscurine A has been 0.043, 0.057, and 0.061%, respectively. These African provenances represented the orange-yellow blooming form of *I. obscura* var. *obscura*. The main components of the seeds (Asian and African origin) are caffeic acid derivatives of the chlorogenic acid type (0.8–1.6%).

Since no *threo*-configurated compound could be detected and **1** is present together with **2**/**3**, we assume that ipobscurine B (**1**) is the precursor of the macrolactams (Fig. 2). Comparison of the coupling constants between H-7″ and H-8″ of **1**, **2**, and **3** ($J = 4.0$ Hz, $J < 3.0$ Hz, and $J = 3.0$ Hz, respectively) clearly demonstrates that all isolated ipobscurines belong to the *erythro* series (Barata et al., 1978; Zacchino and Badano, 1988). Determination of the absolute configuration by using the method of Mosher failed (Ohtani et al., 1991), thus further investigations concerning this problem are necessary. The fact that compound **2** was only present in two provenances analyzed, is a strong indicator that **2** cannot be an artefact of **1** since all samples were treated in the same manner.

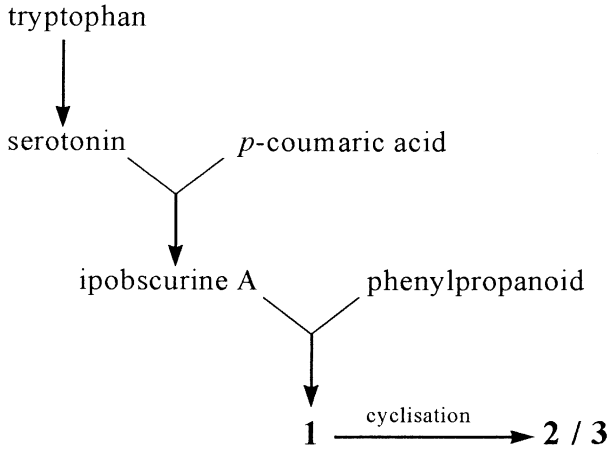


Fig. 2. Proposed biosynthesis of the ipobscurines.

Though our group has investigated numerous convolvulaceous species from many genera over the years ipobscurines were not detected in any other case. Compounds arising from the amide formation between serotonin and a hydroxycinnamic acid (e.g. *p*-coumaric acid, ferulic acid) have been observed beside *Carthamus tinctorius* (see Introduction) in two other asteraceous species: *Centaurea moschata* L. (Sarker et al., 1997) and *C. cyanus* L. (Sarker et al., 2001). Moreover, a cyclization of such a conjugate between the side-chain of the hydroxycinnamic acid moiety and the indole nucleus in the positions 4 and 5 of the latter could be observed in safflower seeds forming the phenol ether serotobenine (Sato et al., 1985).

However, none of these asteraceous species contains serotonin hydroxycinnamic acid amides with a second phenylpropanoid moiety like the ipobscurines B–D. The phenol ether partial structure between the 5-hydroxyindole nucleus of ipobscurine A and the second phenylpropanoid moiety forming ipobscurine B is somehow comparable with certain dimeric phenylpropanoid partial structures of lignin (Nimz, 1975) or 8.*O*.4′-neolignans (Zacchino and Badano, 1988; Wang et al., 1998). Ipobscurine C should be the cyclic derivative of its supposed precursor B formed by oxidative phenol coupling between the arylglycerol and the *p*-coumaroyl moieties originating a diaryl ether substructure (C-5″–O–C-4′) with the result of a unique 21-membered macrolactam.

Macrocyclic alkaloids with similar neolignan substructures are known based on spermine as the amine component, e.g. chaenorhine from *Chaenorhinum origanifolium* (L.) Willk. et Lge., Scrophulariaceae (Bernhard et al., 1973). However, in contrast to the polyamine spermine presenting two amino groups for the amide type conjugation with two phenylpropanoid acids or a corresponding neolignan, serotonin shows only one amino group. But in this case the phenolic hydroxy group at C-5 of the indole nucleus presents the possibility of another conjugation with a second phenylpropanoid moiety thus forming a phenol ether linkage with an arylglycerol.

3. Experimental

3.1. General

For fractionation silica gel 60 (230–400 mesh) or Sephadex LH-20 were utilized. Preparative high performance liquid chromatography (HPLC) was performed on a Pharmacia LKB instrument on a Superpac Pep-S C-2/C-18 (5 μm) reversed-phase column. Melting points (uncorrected) were obtained on a Kofler apparatus and

Table 1
^{1}H NMR and ^{13}C NMR data of **1**–**3**[a] (biogenetic numbering according to formula **2**)

	1[b]		**2**[c]		**3**[d]
	δ_H	δ_C	δ_H	δ_C	δ_H
1	9.70 *br s*		10.74 *s*		
2	7.09 *d* (2.5)	124.1	7.12 *d* (2.0)	125.3	7.12 *br s*
3		113.2		111.5	
3a		127.7		127.2	
4	7.26 *d* (2.5)	105.6	6.92 *d* (2.0)	105.8	6.99 *d* (2.0)
5		153.7		152.4	
6	6.82 *dd* (8.5, 2.5)	114.5	6.37 *dd* (9.0, 2.0)	112.0	6.54 *dd* (8.5, 2.0)
7	7.22 *d* (8.5)	112.5	7.28 *d* (9.0)	111.7	7.04 *d* (8.5)
7a		133.3		130.7	
8	2.90 *t* (7.5)	26.5	2.65 *m* 2.85 *m*	27.7	2.86 *m*
9	3.58 *m*	40.9	3.25 *m* 3.44 *m*	41.8	3.48 *m* 3.70 *m*
10	7.54 *t* (5.5)		7.46 *br t* (7.5)		
1′		129.0		133.7	
2′/6′	7.39 *d* (9.0)	130.2	6.53 *d* (8.5)	127.8	6.94 *d* (8.5)
3′/5′	6.84 *d* (9.0)	116.6	6.70 *d* (8.5)	118.4	6.40 *d* (8.5)
4′		159.8		158.7	
7′	7.51 *d* (15.5)	140.5	7.09 *d* (15.5)	138.6	6.63 *d* (12.5)
8′	6.52 *d* (15.5)	119.6	5.68 *d* (15.5)	122.2	5.89 *d* (12.5)
9′		167.2		167.5	
1″		134.6		132.4	
2″	7.13 *d* (2.0)	111.7	6.79 *d* (1.5)	110.3[e]	7.10 *d* (1.5)
3″		148.1[e]		148.5	
4″		146.6[e]		136.7	
5″	6.78 *d* (8.5)	115.3		144.6	
6″	6.92 *dd* (8.5, 2.0)	120.4	6.55 *br s*	106.9[e]	6.56 *br s*
7″	5.06 *dd* (4.0, 4.5)	73.2	4.79 *br d* (5.5)	70.8	4.91 *d* (3.0)
8″	4.43 *td* (4.0, 4.5)	85.7	4.06 *br t* (5.5)	85.1	4.32 *ddd* (6.0, 5.5, 3.0)
9″	3.58 *m* 3.90 *dd* (11.5, 4.5)	61.8	3.40 *m* 3.65 *m*	59.7	3.79 *m* 3.90 *m*
OCH_3	3.77 *s*	56.3	3.89 *s*	56.0	3.94 *s*
4′-OH	8.80 *br s*				
4″-OH	7.60 *s*		8.78 *s*		
7″-OH	4.65 *d* (4.5)		5.26 *d* (5.5)		
9″-OH	4.12 *t* (4.5)		4.68 *t* (5.5)		

[a] Chemical shifts are reported in ppm relative to TMS. *J*-Values are given in parentheses in Hz.
[b] Acetone-d_6.
[c] DMSO-d_6.
[d] CD_3OD.
[e] Values within the same column may be interchanged.

optical rotations were measured with a Perkin Elmer 241 MC. EIMS and HR-EIMS were recorded on a Varian MAT 711 (80 eV), FAB MS on a Varian MAT CH_5DF. ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, and NOESY spectra were obtained on a Bruker AC 300 MHz or a Bruker AMX 400 MHz spectrometer (TMS as int. standard).

3.2. Plant material

For the isolation of the compounds **1** – **3** plant material of *I. obscura* var. *obscura* grown from seeds collected in the wild near Surabaya, Java, was harvested in the greenhouse of the Institut für Pharmazie, Freie Universität Berlin. Herbarium specimens are deposited there.

3.3. Extraction and isolation

Ground seeds (500 g) were first defatted for 8 h with petrol in a Soxhlet apparatus. The dried material was then extracted with 3 × 2 l MeOH at room temp. The solvent was evaporated under reduced pressure at 40 °C, the residue (50 g) redissolved in 2% aq. tartaric acid and extracted with EtOAc (5 × 800 ml). After evaporation of the organic solvent, the residue was subjected to CC over Sephadex LH-20 and eluted with MeOH. Fractions containing van Urk positive compounds were combined and further separated by CC on silica gel with Me_2CO–cyclohexane (60:40). Fractions 31–57 contained pure **1** (150 mg). Fractions 58–109 were further purified by preparative reversed-phase HPLC MeOH–H_2O (30:70, flow rate = 5.0 ml/min) to afford **3** (5 mg). Frac-

tions 110–200 were purified by CC on silica gel $CHCl_3$–MeOH (85:15) and yielded pure **2** (100 mg).

*3.3.1. N-[2-[5-[2-[(4-Hydroxy-3-methoxyphenyl)-2-hydroxy-1-hydroxymethyl]ethoxy]indol-3-yl]ethyl]-4-hydroxycinnamoyl amide (ipobscurine B) (**1**)*

Yellow solid. $[\alpha]_D^{20}$ −35° (MeOH; *c* 0.28); ^{1}H NMR (400 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (100 MHz, Me_2CO-d_6): see Table 1; (+)-FAB MS (80 eV): *m*/*z* 519 $[M+H]^+$; (−)-FAB MS (80 eV): *m*/*z* 517 $[M-H]^-$.

*3.3.2. 4,5″-Epoxy-N-[2-[5-[2-[(4-hydroxy-3-methoxyphenyl)-2-hydroxy-1-hydroxymethyl]ethoxy]indol-3-yl]-ethyl]-cinnamoyl amide (ipobscurine C) (**2**)*

White crystals. $[\alpha]_D^{20}$ −44° ($CHCl_3$; *c* 0.16); mp 193–195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) see Table 1; ^{13}C NMR (75 MHz, DMSO-d_6) see Table 1; EIMS (80 eV): *m*/*z* (rel. int.) 516 $[M]^+$ (4), 498 (61), 482 (28), 468 (100), 439 (24), 422 (20), 411 (26), 185 (47), 159 (78), 147 (21), 146 (45); HREIMS: *m*/*z* 516.1896 (calc. for $C_{29}H_{28}N_2O_7$ 516.1897).

*3.3.3. 4,5″-Epoxy-N-[2-[5-[2-[(4-hydroxy-3-methoxyphenyl)-2-hydroxy-1-hydroxymethyl]ethoxy]indol-3-yl]-ethyl]-(Z)-cinnamoyl amide (ipobscurine D) (**3**)*

Yellow solid. Mp 245–247° C; ^{1}H NMR (400 MHz, CD_3OD) see Table 1; EIMS (80 eV): *m*/*z* (rel. int.): 516 $[M]^+$ (2), 498 (100), 482 (10), 468 (91), 451 (15), 439 (4), 422 (8), 411 (2), 185 (26), 159 (33), 147 (12), 146 (18); HREIMS: *m*/*z* 516.1901 (calc. for $C_{29}H_{28}N_2O_7$ 516.1897).

*3.4. Synthesis of rac. N-[2-[5-erythro- and threo-[2-[(3,4-dimethoxyphenyl)-2-hydroxy-1-hydroxy-methyl]-ethoxy]indol-3-yl]ethyl]-4-methoxycinnamoyl amide (rac. erythro- and threo-ipobscurine B 4′,4″-dimethyl ether) (**6a**/**6b**)*

*3.4.1. N_b-(4-Methoxycinnamoyl)-serotonin (**4**)*

A soln. of 3.5 g of 4-methoxycinnamic acid in 200 ml THF was stirred with 6 ml of ethyl chloroformate and 6 ml triethylamine for 10 min. After addition of 8.1 g serotonin creatinine sulfate monohydrate and 18 ml triethylamine, the mixture was again stirred for 24 h at room temp. Then, H_2O was added and the aq. phase extracted with EtOAc. After evaporation of the organic solvent, the residue was purified by CC on silica gel with EtOAc–cyclohexane (9:1) to yield 2.9 g of **4**.

Colourless crystals. Mp 160–162 °C. ^{1}H NMR (300 MHz, Me_2CO-d_6): δ 2.91 (2H, *t*, *J* = 7.5 Hz, H-8), 3.58 (2H, *dt*, *J* = 6.0, 7.5 Hz, H-9), 3.83 (3H, *s*, OCH_3), 6.54 (1H, *d*, *J* = 15.5 Hz, H-8′), 6.70 (1H, *dd*, *J* = 2.5, 8.5 Hz, H-6), 6.95 (2H, *d*, *J* = 9.0 Hz, H-3′/H-5′), 7.02 (1H, *d*, *J* = 2.5 Hz, H-4), 7.10 (1H, *d*, *J* = 2.0 Hz, H-2), 7.20 (1H, *d*, *J* = 8.5 Hz, H-7), 7.29 (1H, *t*, *J* = 6.0 Hz, N_{10}-H), 7.50 (2H, *d*, *J* = 9.0 Hz, H-2′/H-6′), 7.51 (1H, *d*, *J* = 15.5 Hz, H-7′), 7.69 (1H, *s*, 5-OH), 9.76 (1H, *br s*, N_1-H); EIMS (80 eV): *m*/*z* (rel. int.): 336 $[M]^+$ (2), 178 (3), 161 (20), 159 (100), 146 (30).

*3.4.2. Ethyl 2-[5-[3-[2-[2-(4-methoxyphenyl)-ethenyl]carbonylamino]ethyl]indolyloxy]-3-(3,4-dimethoxyphenyl)-3-oxo-propanate (**5**)*

One gram of **4** was dissolved in 50 ml acetonitrile and boiled with 2.0 g K_2CO_3 and 0.2 g dibenzo-18-crown-6 for 30 min. After cooling to room temp. a soln. of 1.5 g ethyl 2-bromo-3-(3,4-dimethoxyphenyl)-3-oxo-propanate (Pearl and Gratzl, 1962) in 20 ml acetonitrile was added dropwise within 1 h. After 3 h the filtered soln. was evaporated and the residue purified by means of CC on silica gel with cyclohexane–EtOAc (7:3) to yield 1.3 g of **5**.

White solid. ^{1}H NMR (300 MHz, Me_2CO-d_6): δ 1.24 (3H, *t*, *J* = 7.0 Hz, H-2‴), 2.95 (2H, *t*, *J* = 7.0 Hz, H-8), 3.62 (2H, *t*, *J* = 7.0 Hz, H-9), 3.83 (3H, *s*, OCH_3), 3.85 (3H, *s*, OCH_3), 3.92 (3H, *s*, OCH_3), 4.27 (2H, *q*, *J* = 7.0 Hz, H-1‴), 6.11 (1H, *s*, H-8″), 6.58 (1H, *d*, *J* = 16.0 Hz, H-8′), 6.87 (1H, *dd*, *J* = 2.0, 9.0 Hz, H-6), 6.94 (2H, *d*, *J* = 9.0 Hz, H-3′/H-5′), 7.24 (2H, *m*, H-2/H-4), 7.34 (5H, *m*, H-7, H-2′/H-6′, H-3″, N_{10}-H), 7.55 (1H, *d*, *J* = 16.0 Hz, H-7′), 7.83 (2H, *m*, H-2″/H-6″), 10.39 (1H, *br s*, N_1-H); EIMS (80 eV): *m*/*z* (rel. int.): 586 $[M]^+$ (1), 568 (2), 409 (6), 391 (11), 252 (11), 165 (100), 161 (37), 159 (43), 146 (16).

*3.4.3. Rac. N-[2-[5-erythro- and threo-[2-[(3,4-Dimethoxyphenyl)-2-hydroxy-1-hydroxymethyl]ethoxy]-indol-3-yl]ethyl]-4-methoxycinnamoyl amide (rac. erythro- and threo-ipobscurine B 4′,4″-dimethyl ether) (**6a**/**6b**)*

One gram of **5** was dissolved in 100 ml THF and stirred with 200 mg $LiBH_4$ for 2 h. Then, H_2O was added and the aq. phase extracted with EtOAc. After evaporation of the organic solvent, the residue was purified by CC on silica gel with $CHCl_3$–MeOH (98:2) to yield 140 mg of the *rac. erythro*- **6a** and 90 mg of the *rac. threo*- **6b**.

6a: White solid. ^{1}H NMR (300 MHz, Me_2CO-d_6): δ 2.92 (2H, *t*, *J* = 7.5 Hz, H-8), 3.58 (3H, *m*, H-9/H-9″a), 3.77 (3H, *s*, OCH_3), 3.78 (3H, *s*, OCH_3), 3.83 (3H, *s*, OCH_3), 3.88 (1H, *dd*, *J* = 5.0, 11.5 Hz, H-9″b), 4.45 (1H, *m*, H-8″), 5.09 (1H, *d*, *J* = 4.0 Hz, H-7″), 6.55 (1H, *d*, *J* = 16.0 Hz, H-8′), 6.84 (1H, *dd*, *J* = 2.5, 9.0 Hz, H-6), 6.94 (2H, *d*, *J* = 9.0 Hz, H-3′/H-5′), 7.02 (1H, *dd*, *J* = 2.0, 8.5 Hz, H-6″), 7.13 (1H, *d*, *J* = 2.0 Hz, H-2″), 7.15 (1H, *d*, *J* = 2.0 Hz, H-2), 7.24 (1H, *d*, *J* = 9.0 Hz, H-7), 7.35 (1H, *d*, *J* = 2.5 Hz, H-4), 7.45 (1H, *br s*, N_{10}-H), 7.51 (1H, *d*, *J* = 16.0 Hz, H-7′), 7.52 (2H, *d*, *J* = 9.0 Hz, H-2′/H-6′), 9.86 (1H, *br s*, N_1-H); ^{13}C NMR (75 MHz, acetone-d_6): δ 26.7 (*t*, C-8), 40.8 (*t*, C-9), 55.6 (*q*, 4′-OCH_3), 56.0 (*q*, 4″-OCH_3), 56.1 (*q*, 3″-OCH_3), 61.6 (*t*, C-9″), 72.8 (*d*, C-7″), 85.4 (*d*, C-8″), 105.3 (*d*, C-4), 111.9 (*d*, C-2″),

112.6 (*d*, C-7), 113.1 (*s*, C-3), 114.3 (*d*, C-6), 115.0 (*d*, C-3′/C-5′), 119.9 (*d*, C-6″), 120.4 (*d*, C-8′), 124.0 (*d*, C-2), 128.7 (*s*, C-3a), 129.0 (*d*, C-5″), 130.0 (*s*, C-1′), 130.0 (*d*, C-2′/C-6′), 133.2 (*s*, C-7a), 135.8 (*s*, C-1″), 139.9 (*d*, C-7′), 149.4 (*s*, C-4″), 149.9 (*s*, C-3″), 153.5 (*s*, C-5), 161.7 (*s*, C-4′), 166.7 (*s*, C-9′); EIMS (80 eV): *m*/*z* (rel. int.): 528 $[M-H_2O]^+$ (2), 498 (25), 408 (2), 321 (40), 165 (16), 161 (50), 159 (100), 146 (26); HREIMS: *m*/*z* 528.2263 (calc. for $C_{31}H_{32}N_2O_6$ 528.2260).

6b: White solid. ^{1}H NMR (300 MHz, Me_2CO-d_6): δ 2.92 (2H, *t*, *J* = 7.5 Hz, H-8), 3.58 (3H, *m*, H-9/H-9″a), 3.77 (3H, *s*, OCH_3), 3.78 (3H, *s*, OCH_3), 3.83 (3H, *s*, OCH_3), 3.94 (1H, *dd*, *J* = 5.0, 10.5 Hz, H-9″b), 4.38 (1H, *m*, H-8″), 4.99 (1H, *d*, *J* = 5.5 Hz, H-7″), 6.55 (1H, *d*, *J* = 16.0 Hz, H-8′), 6.76 (1H, *dd*, *J* = 2.5, 9.0 Hz, H-6), 6.94 (2H, *d*, *J* = 9.0 Hz, H-3′/H-5′), 7.02 (1H, *dd*, *J* = 2.0, 8.5 Hz, H-6″), 7.13 (1H, *d*, *J* = 2.0 Hz, H-2″), 7.17 (1H, *d*, *J* = 2.0 Hz, H-2), 7.21 (1H, *d*, *J* = 9.0 Hz, H-7), 7.35 (1H, *d*, *J* = 2.5 Hz, H-4), 7.46 (1H, *br s*, N_{10}-H), 7.50 (1H, *d*, *J* = 16.0 Hz, H-7′), 7.51 (2H, *d*, *J* = 9.0 Hz, H-2′/H-6′), 9.85 (1H, *br s*, N_1-H); ^{13}C NMR (75 MHz, acetone-d_6): δ 26.5 (*t*, C-8), 40.7 (*t*, C-9), 55.6 (*q*, 4′-OCH_3), 56.0 (*q*, 4″-OCH_3), 56.1 (*q*, 3″-OCH_3), 62.1 (*t*, C-9″), 74.2 (*d*, C-7″), 85.5 (*d*, C-8″), 106.1 (*d*, C-4), 111.9 (*d*, C-2″), 112.5 (*d*, C-7), 113.1 (*s*, C-3), 114.7 (*d*, C-6), 115.0 (*d*, C-3′/C-5′), 120.2 (*d*, C-6″), 120.5 (*d*, C-8′), 124.1 (*d*, C-2), 128.9 (*s*, C-3a), 128.8 (*d*, C-5″), 130.0 (*s*, C-1′), 130.0 (*d*, C-2′/C-6′), 133.3 (*s*, C-7a), 136.1 (*s*, C-1″), 139.8 (*d*, C-7′), 149.5 (*s*, C-4″), 150.0 (*s*, C-3″), 153.3 (*s*, C-5), 161.7 (*s*, C-4′), 166.5 (*s*, C-9′); EIMS (80 eV): *m*/*z* (rel. int.): 546 $[M]^+$ (0.5), 528 $[M-H_2O]^+$ (2), 498 (25), 408 (2), 321 (40), 165 (16), 161 (50), 159 (100), 146 (26); HREIMS: *m*/*z* 528.2266 (calc. for $C_{31}H_{32}N_2O_6$ 528.2260).

3.5. Semisynthesis of (−)-erythro-ipobscurine B 4′,4″-dimethyl ether [(−)-**6a**]

Forty milligrams of **1** were dissolved in 25 ml MeCOEt and refluxed with 500 mg K_2CO_3 and 0.2 ml dimethyl sulfate for 1 h to yield 28 mg (−)-ipobscurine B 4′,4″-dimethyl ether. Its spectroscopic data were identical with those of **6a**.

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References

Amor-Prats, D., Harborne, J.B., 1993. New sources of ergoline alkaloids within the genus *Ipomoea*. Biochem. Syst. Ecol. 21, 455–462.

Barata, L.E.S., Baker, P.M., Gottlieb, O.R., Ruveda, E.A., 1978. Neolignans of *Virola surinamensis*. Phytochemistry 17, 783–786.

Bernhard, H.O., Kompis, I., Johne, S., Gröger, D., Hesse, M., Schmid, H., 1973. Chaenorhin, ein macrocyclisches Spermin-Alkaloid. Helv. Chim. Acta 56, 1266–1303.

Dawidar, A.M., Winternitz, F., Johns, S.R., 1977. Structure of ipomine, a new alkaloid from *Ipomoea muricata* Jacq. Tetrahedron 33, 1733–1734.

Gourley, J.M., Heacock, R.A., McInnes, A.G., Nikolin, B., Smith, D.G., 1969. The structure of ipalbine, a new hexahydroindolizine alkaloid, isolated from *Ipomoea alba* L. J. Chem. Soc., Chem. Commun. 709–710.

Hofmann, A., 1961. Die Wirkstoffe der mexikanischen Zauberdroge "Ololiuqui". Planta Med. 9, 354–367.

Hofmann, A., Tscherter, H., 1960. Isolation of lysergic acid alkaloids from the Mexican magic drug Ololiuqui (*Rivea corymbosa*). Experientia 16, 414.

Jenett-Siems, K., Kaloga, M., Eich, E., 1993. Ipangulines, the first pyrrolizidine alkaloids from the Convolvulaceae. Phytochemistry 34, 437–440.

Jenett-Siems, K., Schimming, T., Kaloga, M., Eich, E., Siems, K., Gupta, M.P., Witte, L., Hartmann, T., 1998. Pyrrolizidine alkaloids of *Ipomoea hederifolia* and related species. Phytochemistry 47, 1551–1560.

Mayer, K., Eich, E., 1975. Zur C-17-Oxidation von Clavinalkaloiden mit primärer alkoholischer Hydroxylgruppe. Arch. Pharm. (Weinheim, Ger.) 308, 819–824.

Nimz, H., 1975. Beech lignin. Draft of a constitution scheme. Angew. Chem. 86, 336–344.

Ohtani, I., Kusumi, T., Kashman, Y., Kakisawa, H., 1991. High-field FT NMR application of Mosher's method. The absolute configurations of marine terpenoids. J. Am. Chem. Soc. 113, 4092–4096.

Pearl, I.A., Gratzl, J., 1962. Lignin and related products. XVI. Synthesis of lignin model compounds of the phenylglycerol β-ether and related series. J. Org. Chem. 27, 2111–2114.

Sakamura, S., Terayama, Y., Kawakatsu, S., Ichihara, A., Saito, H., 1978. Conjugated serotonins related to carthartic activity in safflower seeds (*Carthamus tinctorius* L.). Agric. Biol. Chem. 42, 1805–1806.

Sakamura, S., Terayama, Y., Kawakatsu, S., Ichihara, A., Saito, H., 1980. Conjugated serotonins and phenolic constituents in safflower seed (*Carthamus tinctorius* L.). Agric. Biol. Chem. 44, 2951–2954.

Sarker, S.D., Savchenko, T., Whiting, P., Sik, V., Dinan, L., 1997. Moschamine, *cis*-moschamine, moschamindole and moschamindolol: four novel indole alkaloids from *Centaurea moschata*. Nat. Prod. Lett. 9, 189–194.

Sarker, S.D., Laird, A., Nahar, L., Kumarasamy, Y., Jaspars, M., 2001. Indole alkaloids from the seeds of *Centaurea cyanus*. Phytochemistry 57, 1273–1276.

Sato, H., Kawagishi, H., Nishimura, T., Yoneyama, S., Yoshimoto, Y., Sakamura, S., Furusaki, A., Katsuragi, S., Matsumoto, T., 1985. Serotobenine, a novel phenolic amide from safflower seeds. Agric. Biol. Chem. 49, 2969–2974.

Wang, C.Z., De, Q.Y., 1998. Lignan and acetylenic glycosides from *Aster auriculatus*. Phytochemistry 48, 711–717.

Zacchino, S.A., Badano, H., 1988. Enantioselective synthesis and absolute configuration assignment of *erythro*-(3,4,5-trimethoxy-7-hydroxy-1′-allyl-2′,6′-dimethoxy)-8.*O*.4′-neolignan, isolated from mace (*Myristica fragrans*). J. Nat. Prod. 51, 1261–1265.