Kopsifolines A – F: a New Structural Class of Monoterpenoid Indole Alkaloids from *Kopsia*

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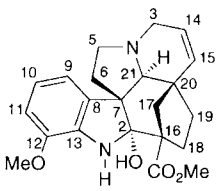
Six new indole alkaloids, named kopsifolines A – F (**1** – **6**), with an unprecedented hexacyclic carbon skeleton, constituting a new structural group of monoterpenoid indole alkaloids, were obtained from the leaf extract of a Malayan *Kopsia* species, and their structures were established by spectroscopic analysis.

Introduction. – The genus *Kopsia* is rich in indole alkaloids and has provided many new biologically active alkaloids with novel carbon skeletons [1 – 13]. In continuation of our studies on the Malaysian members of this genus [1 – 11], we would like to report the structures of a group of novel indole alkaloids named kopsifolines A – F (**1** – **6**), which are characterized by an unprecedented carbon skeleton, isolated for the first time from a Malayan *Kopsia* species [14].



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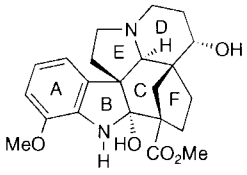

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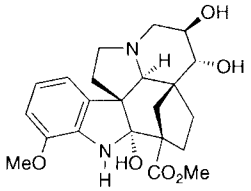

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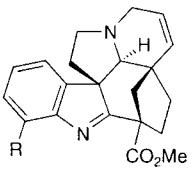
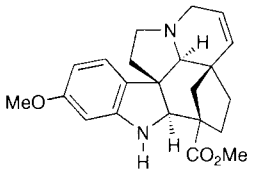


4 R = H
5 R = MeO



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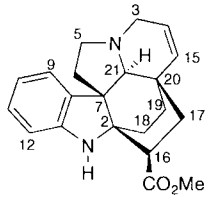

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Results and Discussion. – The kopsifolines A – F (**1** – **6**) represent a new structural class of monoterpenoid indole alkaloids. They were isolated together from the same source, and for the first time. All six compounds occur only in the leaf extract of a hitherto unencountered Malayan *Kopsia* species, which has been identified as *K. fruticosa* (Ker) A. DC.

Kopsifoline A (**1**) was obtained as a colorless oil, with an $[\alpha]_D$ value of -11 ($c = 0.43$, $CHCl_3$). The UV spectrum was characteristic of a dihydroindole chromophore, with absorption maxima at 213, 248, and 296 nm ($\log \varepsilon = 4.26$, 3.93, and 3.51, resp.), and the IR spectrum showed bands at 3369 (broad) and 1710 cm^{-1} due to NH/OH and ester C=O functions, respectively. The EI mass spectrum of **1** showed the molecular-ion peak at *m/z* 382, which analyzed for $C_{22}H_{26}N_2O_4$, requiring eleven degrees of unsaturation. The ^{13}C-NMR spectrum (*Table 1*) showed a total of 22 separate C-resonances (two Me, six CH_2, six CH, and eight quaternary C-atoms), in agreement with the molecular formula. The ^{1}H-NMR spectrum of **1** (*Table 2*) showed the presence of two MeO groups (belonging to an aromatic system and an ester COOMe group, resp.), three contiguous aromatic H-atoms, two olefinic H-atoms, an indole NH and an OH function. The aromatic MeO substituent was deduced to be at C(12) from examination of the aromatic C-resonances and from the HMBC spectrum. The ^{13}C-NMR spectrum of **1**, in particular the nonaromatic portion of the molecule, showed a general similarity to that of the aspidofractinine compound venalstonine (**7**) [15], except for changes involving C(2), C(16), C(17), C(20), and C(21).

Table 1. *100-MHz ^{13}C-NMR Spectral Data for Compounds* **1**–**6**. Assignments (trivial atom numbering, see structural representations) were made by means of COSY and HMBC experiments. Solvent: $CDCl_3$; δ in ppm.

	1	**2**	**3**	**4**	**5**	**6**
C(2)	97.1	97.4	97.1	187.7	186.7	74.2
C(3)	53.0	47.2	54.2	46.9	46.9	52.9
C(5)	53.9	53.3	53.2	50.9	50.9	54.7
C(6)	34.8	31.9	34.7	34.7	34.7	45.7
C(7)	56.2	61.1	61.5	63.0	63.2	55.6
C(8)	138.6	137.5	136.9	147.0	149.2	138.6
C(9)	114.7	114.6	114.4	121.6	113.9	118.3
C(10)	119.4	119.7	119.8	125.8	127.2	114.5
C(11)	109.4	109.5	109.8	127.5	110.2	143.5
C(12)	143.0	143.1	142.8	120.3	142.4	110.0
C(13)	135.9	135.9	135.8	154.3	150.9	143.5
C(14)	125.4	31.0	69.7	125.2	125.1	125.1
C(15)	132.8	73.4	75.0	132.5	132.5	133.5
C(16)	60.0	56.4	55.9	56.5	56.5	55.3
C(17)	38.1	35.2	32.7	43.4	44.1	41.0
C(18)	29.5	29.5	27.7	39.0	39.0	26.3
C(19)	35.1	34.2	33.9	35.0	35.0	35.1
C(20)	44.8	46.8	45.1	42.3	42.4	46.5
C(21)	75.6	70.0	71.3	69.1	69.2	75.2
MeO	52.0	52.0	52.0	52.6	52.4	52.1
C=O	176.3	176.1	176.6	172.2	172.5	176.6
12-OMe	55.3	55.3	55.3	–	55.7	–
11-OMe	–	–	–	–	–	55.3

The COSY spectrum of **1** also revealed virtually the same partial structures as those present in an aspidofractinine skeleton, such as, *e.g.*, venalstonine (**7**), which was also isolated. Thus, in common with aspidofractinine compounds, the following fragments were identified: $NCH_2CH{=}CH$, NCH_2CH_2, CH_2CH_2, and an isolated methine group. However, whereas an additional CH_2CH fragment is present in the aspidofractinines, in

Table 2. *400-MHz ^{1}H-NMR Spectral Data for Compounds* **1**–**6**. Assignments (trivial atom numbering, see structural representations) were made by means of COSY and HMBC experiments. Solvent: $CDCl_3$; δ in ppm, J in Hz.

	1	**2**	**3**	**4**	**5**	**6**
H–C(2)	–	–	–	–	–	3.98 (*s*)
CH_2(3)	2.83 (*dt*, *J* = 16, 2), 3.53 (*ddd*, *J* = 16, 5, 2)	2.45 (*td*, *J* = 13, 2), 2.96 (*ddd*, *J* = 13, 5, 2)	2.62 (*dd*, *J* = 12, 2), 2.99 (*m*)	3.42 (*dd*, *J* = 17, 4), 3.59 (br. *d*, *J* = 17)	3.41 (*ddd*, *J* = 17, 4, 2), 3.58 (br. *d*, *J* = 17)	2.87 (br. *d*, *J* = 16), 3.54 (*dd*, *J* = 16, 4)
CH_2(5)	2.38 (*ddd*, *J* = 12, 8, 7), 3.24 (*t*, *J* = 8)	2.35 (*q*, *J* = 9), 3.12 (*t*, *J* = 9)	2.37 (*q*, *J* = 8), 2.99 (*m*)	3.31 (*m*), 3.36 (*td*, *J* = 8, 6)	3.32 (*m*), 3.34 (*td*, *J* = 8, 6)	2.42 (*ddd*, *J* = 12, 7, 6), 3.26 (br. *t*, *J* = 7)
CH_2(6)	1.40 (*dd*, *J* = 13, 7), 3.05 (*ddd*, *J* = 13, 12, 8)	1.34 (*m*), 3.02 (*dt*, *J* = 13, 9)	1.33 (*dd*, *J* = 12, 8), 2.99 (*m*)	2.14 (*m*), 2.61 (*m*)	2.08 (*m*), 2.59 (*m*)	1.95 (*dd*, *J* = 12, 6), 2.21 (*td*, *J* = 12, 7)
H–C(9)	6.75 (*dd*, *J* = 8, 1)	6.80 (br. *d*, *J* = 8)	6.74 (br. *d*, *J* = 8)	7.48 (br. *d*, *J* = 8)	7.10 (br. *d*, *J* = 8)	6.68 (*d*, *J* = 6)
H–C(10)	6.69 (*t*, *J* = 8)	6.71 (*t*, *J* = 8)	6.65 (*t*, *J* = 8)	7.30 (*td*, *J* = 8, 2)	7.17 (*t*, *J* = 8)	6.75 (*dd*, *J* = 6, 3)
H–C(11)	6.65 (*dd*, *J* = 8, 1)	6.65 (br. *d*, *J* = 8)	6.60 (br. *d*, *J* = 8)	7.20 (*td*, *J* = 8, 2)	6.86 (*dd*, *J* = 8, 2)	–
H–C(12)	–	–	–	7.57 (*dd*, *J* = 8, 2)	–	6.67 (*d*, *J* = 3)
H–C(14)[a])	5.72 (*ddd*, *J* = 10, 5, 2)	1.75 (*dq*, *J* = 13, 2), 1.99 (*tdd*, *J* = 13, 5, 2)	3.70 (br. *s*)	5.77 (*ddd*, *J* = 10, 4, 2)	5.76 (*ddd*, *J* = 10, 4, 2)	5.75 (*ddd*, *J* = 10, 4, 2)
H–C(15)	5.47 (*dt*, *J* = 10, 2)	3.67 (br. *s*)	3.45 (*d*, *J* = 2)	5.64 (*dt*, *J* = 10, 2)	5.64 (*dt*, *J* = 10, 2)	5.52 (*dt*, *J* = 10, 2)
CH_2(17)	1.86 (*dd*, *J* = 13, 1), 2.23 (*dd*, *J* = 13, 1)	1.54 (br. *d*, *J* = 12), 2.35 (br. *d*, *J* = 12)	1.60 (br. *d*, *J* = 13), 2.47 (br. *d*, *J* = 13)	1.78 (*dd*, *J* = 13, 2), 2.63 (br. *d*, *J* = 13)	1.76 (*dd*, *J* = 12, 2), 2.60 (br. *d*, *J* = 12)	1.84 (*dd*, *J* = 12, 1), 1.99 (br. *d*, *J* = 12)
CH_2(18)	1.71 (*m*), 1.71 (*m*)	1.58 (*m*), 1.58 (*m*)	1.51 (*m*), 1.51 (*m*)	2.13 (*dddd*, *J* = 12, 9, 3, 2), 2.43 (*td*, *J* = 12, 8)	2.19 (*ddt*, *J* = 12, 9, 2), 2.44 (*td*, *J* = 12, 8)	1.58 (*m*), 1.76 (*m*)
CH_2(19)	1.26 (*m*), 1.52 (*m*)	1.34 (*m*), 1.58 (*m*)	1.25 (*m*), 1.51 (*m*)	1.20 (*m*), 1.69 (*m*)	1.16 (*dddd*, *J* = 14, 9, 8, 2), 1.70 (*m*)	1.30 (*m*), 1.58 (*m*)
H–C(21)	2.48 (br. *s*)	2.70 (br. *s*)	2.68 (br. *s*)	2.78 (br. *s*)	2.76 (br. *s*)	2.51 (br. *s*)
MeOOC	3.75 (*s*)	3.74 (*s*)	3.69 (*s*)	3.79 (*s*)	3.75 (*s*)	3.73 (*s*)
12-OMe	3.82 (*s*)	3.83 (*s*)	3.77 (*s*)	–	3.97 (*s*)	–
11-OMe	–	–	–	–	–	3.83 (*s*)
NH	5.98 (br. *s*)	5.93 (br. *s*)	5.82 (br. *s*)	–	–	4.47 (br. *s*)
2-OH	2.99 (br. *s*)	–	–	–	–	–

[a]) In compound **2**, a CH_2(14) group is present with two diastereotopic H-atoms.

1 and its congeners **2**–**6**, this fragment, which corresponds to CH(16)–CH_2(17) is conspicuously absent in the kopsifolines, being replaced instead with an isolated methylene group and an additional quaternary center. These differences suggest a structure bearing some resemblance to the aspidofractinines, but, at the same time, distinguished by a significant departure from the aspidofractinine skeleton. This feature was revealed on careful examination of the HMBC spectrum of **1**, which showed the following long-range (^3J) correlations: H–C(19) to C(16), H–C(17) to C(18), and H–C(18) to the ester C=O group. These correlations represent a clear departure from that normally observed in aspidofractinine compounds, and clearly indicate that in kopsifoline A (**1**) (as well as in **2**–**6**), a novel carbon skeleton is present in which C(18) is now linked to C(16) instead of C(2) (see the *Figure*).

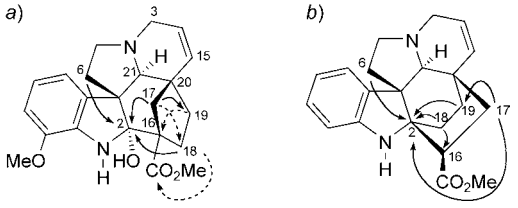


Fig. 1. *Selected HMBC correlations observed for* a) *kopsifoline A* (**1**) *and* b) *venalstonine* (**7**). The correlations marked with dashed arrows have been observed exclusively for the novel type of indole alkaloid, but not for the structurally different compound **7**.

The presence of a 2-OH group was indicated by the ^{13}C-NMR signal for C(2) at δ_C 97.1, downfield-shifted due to the vicinal OH and NH groups. This assignment was also supported by the following correlations observed in the HMBC spectrum: from H–C(6), H–C(17), H–C(18), and H–C(21) to C(2). The configuration at C(21) was similar to that in aspidofractinine compounds, as deduced from the observed NOE enhancement of the H–C(9) and H_α–C(19) resonances upon irradiation of H–C(21). This result also confirmed the orientation of the C(17)H_2 bridge in the bicyclo[3.2.1]octane fragment constituting rings C and F. The orientation of the C(2)–OH substituent was deduced to be α due to the observed NOE enhancement of the H_β–C(17) resonance on irradiation of H_β–C(6).

Kopsifoline B (**2**) was obtained as a colorless oil, with an $[\alpha]_D$ value of – 46 (c = 0.66, $CHCl_3$). The IR and UV spectra were similar to those of **1**. The mass spectrum of **2** showed the molecular-ion peak at m/z 400, which analyzed for $C_{22}H_{28}N_2O_5$, with an MS base peak at m/z 382 (loss of H_2O). Based on the ^{1}H- and ^{13}C-NMR spectra (*Tables 2* and *1*), compound **2** was lacking the C(14)=C(15) double bond. Instead, an oxymethine function was present (δ_H 3.67 for H–C(15), δ_C 73.4 for C(15)). This was also supported by the replacement of the NCH_2CH=CH fragment of **1** by a NCH_2CH_2CHOH fragment in **2**, as revealed by COSY and HMQC experiments. The orientation of the C(15)–OH function was determined from the NOESY spectrum, which showed interactions between H–C(15) and H_α–C(17), indicating an α-OH substituent.

Kopsifoline C (**3**), a colorless oil, with $[\alpha]_D = +87$ ($c = 0.08$, $CHCl_3$), showed a molecular ion at m/z 416 in the mass spectrum, which analyzed for $C_{22}H_{28}N_2O_6$, differing from **2** by an additional OH group at C(14). As in **2**, the mass spectrum of **3**

showed a base peak at *m/z* 398 due to loss of one H_2O molecule. The ^{1}H- and ^{13}C-NMR spectral data were generally similar to those of **2**, except for the resonances due to ring D, which was shown to incorporate two oxymethines (δ_C 69.7, 75.0) associated with a 1,2-diol function. The corresponding ^{1}H-NMR resonances were observed at δ_H 3.70 and 3.45, assigned to H–C(14) and H–C(15), respectively. The configurations at C(14) and C(15) were established from the pertinent ^3J coupling constant, and from the NOESY spectrum. A ^3J value of 2 Hz indicated that H–C(14) and H–C(15) are not *trans*-diaxially disposed. The NOESY spectrum showed correlations between H_β–C(15) and H_α–C(17), and between H_α–C(14) and CH_2(3), consistent with both H–C(14) and H–C(15) being oriented equatorially in a six-membered ring.

Kopsidine D (**4**) was obtained as a light yellowish oil, with an $[\alpha]_D$ value of – 27 ($c = 0.09$, $CHCl_3$). The UV spectrum was characteristic of an indolenine chromophore, with absorption maxima at 224, 249, and 280 nm ($\log \varepsilon = 4.15$, 3.68, and 3.56, resp.), and the IR spectrum showed an ester C=O band at 1726 cm^{-1}. Additional confirmation for the indolenine chromophore was provided by resonances for two quaternary C-atoms at δ_C 187.7 and 63.0, assigned to C(2) and C(7), respectively. The EI mass spectrum of **4** showed a molecular ion at *m/z* 334, which analyzed for $C_{21}H_{22}N_2O_2$. The ^{13}C-NMR spectrum (*Table 1*) showed the presence of one Me, six CH_2, and seven CH groups, and seven quaternary C-atoms. The ^{1}H-NMR spectrum of **4** (*Table 2*) showed the presence of four aromatic H-atoms, a COOMe group, and two olefinic H-atoms, as confirmed by the ester C=O resonance at δ_C 172.2, and the olefinic resonances at δ_C 125.2 and 132.5. The COSY spectrum showed similar partial structures as in **1**, while the HMBC spectrum showed the same distinct correlations as for compounds **1**–**3**, indicating the presence of a similar ring system. Kopsifoline D (**4**), thus, represents a variation of the prototype structure (as represented by **1**) in which the principal change has occurred in the indole portion (dehydration to an indolenine chromophore).

Kopsifoline E (**5**) was obtained as a light yellow oil, with an $[\alpha]_D$ value of + 84 ($c =$ 0.15, $CHCl_3$). The UV (230, 253, 309 nm) and IR (1727 cm^{-1}) spectra were similar to those of **4**, consistent with a substituted indolenine chromophore and a COOMe function, but the EI mass spectrum showed a molecular ion at *m/z* 364, which analyzed for $C_{22}H_{24}N_2O_3$, formally differing from **4** by a CH_2O group. As in **4**, the observed quaternary C-atom resonances at δ_C 186.7 and 63.2, corresponding to C(2) and C(7), respectively, confirmed the presence of an indolenine chromophore. The ^{1}H-NMR spectrum (*Table 2*) showed the presence of three aromatic H-atoms, one COOMe group, two olefinic H-atoms, and an aromatic MeO substituent at C(12), as derived from the coupling pattern of the aromatic H- and C-atom resonances. The NMR spectral data of **5** were essentially similar to those of **4**, except for changes caused by the additional MeO substituent.

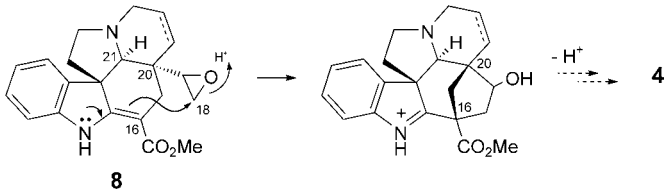
Kopsifoline F (**6**), a colorless oil, with an $[\alpha]_D$ value of – 112 ($c = 0.07$, $CHCl_3$), showed an $[M+H]^+$ signal at *m/z* 367 in its ESI and FAB mass spectra. HR-FAB-MS Measurements led to the formula $C_{22}H_{26}N_2O_3$. The UV and IR spectra of **6** were similar to those of **1**–**3**. The ^{1}H-NMR spectrum (*Table 2*) showed the presence of three aromatic H-atoms, a COOMe group, two olefinic H-atoms, and an aromatic MeO substituent, as in **1**. However, the coupling pattern of the aromatic H-atoms were different, indicating MeO substitution at position 10 or 11. The MeO substituent was finally placed at position 11 from examination of the HMBC spectrum (three-bond

correlations from H–C(6), H–C(10), H–C(12), and H–C(21) to C(8)). Another major difference was found in the ^{13}C-NMR spectrum, which showed C(2) to be a methine group at δ_C 74.2, the corresponding H–C(2) signal being observed at δ_H 3.98 (*s*). Thus, in contrast to compounds **1**–**3**, the 2-OH group was replaced by a H-atom, which was also consistent with the HMBC data (three-bond correlations from H–C(17) and H–C(18) to C(2)). Irradiation of H–C(2) did not cause any enhancement of the H–C(6) or H–C(17) resonances, which is consistent with an α-H–C(2), as shown in **6**.

The kopsifolines represent a new family of indole alkaloids with an unprecedented carbon skeleton, in which C(18) is not linked to C(2), but to C(16), unlike in aspidofractinine compounds. These compounds have been found for the first time[1]), and have been isolated from the same single source. The plant has been identified as *K. fruticosa*, although, perplexingly, another group of new compounds with a novel quinoline-type carbon skeleton (mersinines A and B, and mersiloscine), entirely different from the kopsifolines, have been isolated from material collected in a vastly different location, but which has also been identified as *K. fruticosa* [2].

A possible biogenetic pathway to the kopsifolines (*e.g.*, **4**) from an aspidosperma-type precursor (such as **8**) *via* an intramolecular epoxide-ring opening, resulting in bond-formation between C(16) and C(18), is shown in the *Scheme.*

Scheme. *Proposed Biogenesis of Kopsifoline D* (**4**) *from the Aspidosperma-Type Precursor* **8**



Experimental Part

General. Optical rotations were determined on a *JASCO DIP-370* digital polarimeter or an *Atago Polax-D* polarimeter. IR Spectra were recorded on a *Perkin-Elmer 1600* or a *Perkin-Elmer RX1* FT-IR spectrophotometer. UV Spectra were obtained on a *Shimadzu UV-3101PC* spectrophotometer; λ_{max} in nm, log ε. ^{1}H- and ^{13}C-NMR Spectra were recorded in $CDCl_3$, using $SiMe_4$ as an internal standard, on a *JEOL JNM-LA-400* spectrometer at 400 and 100 MHz, resp.; δ in ppm, *J* in Hz. ESI Mass spectra were obtained on a *Perkin-Elmer API-100* instrument. EI, HR-EI (*Micromass 70E*), and HR-FAB mass spectra (*VG Autospec*) were obtained courtesy of Prof. *G. Pattenden*, School of Chemistry, University of Nottingham, UK; in *m*/*z* (rel. %).

Plant Material. The plants were collected in Kuala Lumpur, Malaysia, in November 1996, and were identified by Dr. *D. Middleton*, Rijksherbarium, University of Leiden, Leiden, The Netherlands. Herbarium voucher specimens (K-651) have been deposited at the Herbarium, University of Malaya, Kuala Lumpur, Malaysia, and at Leiden, The Netherlands.

Extraction and Isolation. Extraction of the ground leaf material was carried out by partitioning the conc. EtOH extract with dilute acid, as described in detail elsewhere [16]. The alkaloids were isolated by initial column chromatography (SiO_2; $CHCl_3$ with increasing amounts of MeOH), followed by a second chromatographic purification of appropriate, partially resolved fractions by means of centrifugal thin-layer chromatog-

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[1]) We have described a kopsifoline-type partial structure in the novel bisindole tenuiphylline isolated from *K. tenuis* [7].

raphy ($CHCl_3$/MeOH 50:1, NH_3-sat. $CHCl_3$/MeOH 50:1, Et_2O/hexane 1:1, Et_2O/MeOH 50:1, NH_3-sat. Et_2O, and NH_3-sat. Et_2O/MeOH 100:3). The yields (in mg kg^{-1}) of the alkaloids were as follows: **1** (367), **2** (11), **3** (1.0), **4** (1.6), **5** (2.5), and **6** (1.0).

*Methyl (1*R,*4*R,*5*R,*13*R,*20*S*)-5-Hydroxy-8-methoxy-6,16-diazahexacyclo[11.6.1.1^{1,4}.0^{5,13}.0^{7,12}.0^{16,20}]henicosa-7(12),8,10,18-tetraene-4-carboxylate* (*Kopsifoline A*; **1**). Colorless oil. $[\alpha]_D = -11$ ($c = 0.43$, $CHCl_3$). UV (EtOH): 213 (4.26), 248 (3.93), 296 (3.51). IR (dry film): 3369, 1710. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. EI-MS: 382 (100, M^+), 364 (93), 334 (23), 305 (21), 283 (91), 207 (30), 192 (81), 94 (28); HR-EI-MS: 382.1889 (M^+, $C_{22}H_{26}N_2O_4^+$; calc.: 382.1893).

*Methyl (1*S,*4*R,*5*R,*13*R,*19*S,*20*S*)-5,19-Dihydroxy-8-methoxy-6,16-diazahexacyclo[11.6.1.1^{1,4}.0^{5,13}.0^{7,12}.0^{16,20}]henicosa-7(12),8,10-triene-4-carboxylate* (*Kopsifoline B*; **2**). Colorless oil. $[\alpha]_D = -46$ ($c = 0.66$, $CHCl_3$). UV (EtOH): 213 (4.00), 248 (3.88), 295 (3.44). IR (dry film): 3360, 1710. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. EI-MS: 400 (17, M^+), 382 (100, $[M - H_2O]^+$), 352 (38), 323 (8), 268 (12), 225 (11), 179 (8), 127 (9), 51 (12). HR-EI-MS: 400.2005 (M^+, $C_{22}H_{28}N_2O_5^+$; calc.: 400.1998).

*Methyl (1*S,*4*R,*5*R,*13*R,*18*R,*19*S,*20*S*)-5,18,19-Trihydroxy-8-methoxy-6,16-diazahexacyclo[11.6.1.1^{1,4}.0^{5,13}.0^{7,12}.0^{16,20}]henicosa-7(12),8,10-triene-4-carboxylate* (*Kopsifoline C*; **3**). Colorless oil. $[\alpha]_D = +87$ ($c = 0.08$, $CHCl_3$). UV (EtOH): 214 (4.35), 248 (3.72), 294 (3.33). IR (dry film): 3370, 1710. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. EI-MS: 416 (6, M^+), 398 (100, $[M - H_2O]^+$), 326 (23), 297 (32), 200 (13), 169 (11), 149 (22), 57 (16). HR-EI-MS: 416.1919 (M^+, $C_{22}H_{28}N_2O_6^+$; calc.: 416.1947).

*Methyl (1*R,*4*R,*13*R,*20*S*)-6,16-Diazahexacyclo[11.6.1.1^{1,4}.0^{5,13}.0^{7,12}.0^{16,20}]henicosa-5,7(12),8,10,18-pentaene-4-carboxylate* (*Kopsifoline D*; **4**). Light yellowish oil. $[\alpha]_D = -27$ ($c = 0.09$, $CHCl_3$). UV (EtOH): 224 (4.15), 249 (3.68), 280 (3.56). IR (dry film): 1726. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. EI-MS: 334 (100, M^+), 275 (18), 248 (15), 183 (15), 170 (22), 125 (19), 51 (48). HR-EI-MS: 334.1678 (M^+, $C_{21}H_{22}N_2O_2^+$, calc.: 334.1681).

*Methyl (1*R,*4*R,*13*R,*20*S*)-8-Methoxy-6,16-diazahexacyclo[11.6.1.1^{1,4}.0^{5,13}.0^{7,12}.0^{16,20}]henicosa-5,7(12),8,10,18-pentaene-4-carboxylate* (*Kopsifoline E*; **5**). Light yellowish oil. $[\alpha]_D = +84$ ($c = 0.15$, $CHCl_3$). UV (EtOH): 230 (4.05), 253 (3.63), 309 (3.56). IR (dry film): 1727. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. EI-MS: 364 (100, M^+), 333 (14), 305 (18), 265 (8), 200 (71), 152 (8), 99 (7), 57 (8). HR-EI-MS: 364.1780 (M^+, $C_{22}H_{24}N_2O_3^+$, calc.: 364.1787).

*Methyl (1*R,*4*R,*5*R,*13*S,*20*S*)-8-Methoxy-6,16-diazahexacyclo[11.6.1.1^{1,4}.0^{5,13}.0^{7,12}.0^{16,20}]henicosa-7(12),8,10,18-tetraene-4-carboxylate* (*Kopsifoline F*; **6**). Colorless oil. $[\alpha]_D = -112$ ($c = 0.07$, $CHCl_3$). UV (EtOH): 212 (4.56), 248 (3.99), 295 (3.57). IR (dry film): 3378, 1722. ^{1}H- and ^{13}C-NMR: see *Tables 2* and *1*, resp. ESI-MS: 367 ($[M + H]^+$). HR-FAB-MS: 367.2014 ($[M + H]^+$, $[C_{22}H_{26}N_2O_3 + H]^+$; calc.: 367.2022).

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