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Alkaloids from A*lstonia angustifolia*

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Abstract

Six new alkaloids, viz., alstolactone, affinisine oxindole, lagumicine, *N*(4)-demethylalstonerine, *N*(4)-demethylalstonerinal, and 10-methoxycathafoline *N*(4)-oxide, in addition to 36 other known alkaloids, were obtained from the leaf extract of *Alstonia angustifolia* var. *latifolia*. The structures of the new alkaloids were determined using NMR and MS analysis.

Keywords: *Alstonia* species; Apocynaceae; Indole alkaloids

1. Introduction

We previously reported the alkaloidal composition of the stem-bark and leaf extract, including the structures of a series of novel macroline indoles and oxindoles, of a Malayan *Alstonia* species which at the time we erroneously identified as *A. macrophylla* Wall (Kam et al., 1999, 2000). Since then we have investigated the alkaloidal content of an authentic sample of *A. macrophylla* which will be reported in due course. The later acquisition of samples of *A. macrophylla* prompted a careful reexamination of the earlier sample, which we now conclude to be that of *A. angustifolia* var. *latifolia* K. and G. The common tendency to confuse the latter with *A. macrophylla* Wall has been previously noted (Whitmore, 1973). We would like to report the full alkaloidal composition of this plant, including the isolation and structure determination of new alkaloids.

2. Results and discussion

The stem-bark extract of *A. angustifolia* var. *latifolia* yielded three new indoles, *viz*., alstonerinal (**1**), 10-methoxyaffinisine (**2**), and 10-methoxycathafoline (**3**), in addition to seven known alkaloids (Kam et al., 1999). The leaf extract provided a series of novel macroline oxindoles, including, isoalstonisine (**4**) and macrogentine (**5**) which represent the first examples of macroline oxindoles possessing the (*S*) configuration at the spirocarbon, the ring-opened macroline oxindoles, alstonoxines A (**6**) and B (**7**), the *N*(4)-formyl oxindole derivative, alstofoline (**8**), and two other macroline oxindoles *N*(1)-demethylalstonisine (**9**) and *N*(1)-demethylalstonal (**10**) (Kam and Choo, 2000). We now report the full alkaloidal composition, including the structures of an additional six new alkaloids, in addition to 29 known alkaloids from the leaf extract of this plant.

Alstolactone (**11**) was obtained as a light yellow oil, with $[\alpha]_D$ −10° (*c* 0.05, $CHCl_3$). The IR spectrum showed bands at 3390 and 1707 cm^{-1} due to NH and lactone carbonyl functions, respectively. The presence of a lactone function was confirmed by the observed resonance at δ 165.7 in the ^{13}C NMR spectrum. The ESI-MS spectrum showed a $[MH]^+$ at *m*/*z* 323, and HREIMS of **11** gave the formula $C_{20}H_{22}N_2O_2$. The UV spectrum showed absorption maxima at 216, 228, 284, and 293 nm typical of an indole chromophore. The ^1H NMR spectrum of **11** (Table 1) showed the presence of four aromatic hydrogens, a *N*(1)-Me, and an ethylidene side chain. The COSY spectrum indicated the presence of $NCHCH_2$ and $NCHCH_2$–$CHCHCH_2O$ fragments, which are characteristic of a macroline structure and correspond to the C(5)–C(6) and C(3)–C(14)–C(15)–C(16)–C(17) partial structures, respectively. The ^{13}C NMR spectrum showed a total of 20 carbon signals in agreement with the formula from HRMS. The NMR spectra accord well with that expected for a macroline indole with the exception of the signals due to the lactone and ethylidene side chain which are encountered for the first time as part of a macroline indole alkaloid. Comparison of the ^1H and ^{13}C NMR spectra with those

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Table 1
^{1}H NMR spectral data for **11**, **14**–**15** (400 MHz, $CDCl_3$)[a]

H	11	14	15
3	4.46 *br s*	4.23 *br s*	4.22 *br s*
5	3.50 *d* (7)	3.48 *br d* (7)	3.47 *br d* (7)
6	2.73 *d* (16)	2.70 *d* (16)	2.70 *d* (16)
	3.38 *dd* (16, 7)	3.26 *dd* (16, 7)	3.26 *dd* (16, 7)
9	7.52 *br d* (8)	7.44 *br d* (8)	7.44 *br d* (8)
10	7.15 *td* (8, 1)	7.09 *td* (8, 1)	7.09 *td* (8, 1)
11	7.24 *td* (8, 1)	7.20 *td* (8, 1)	7.20 *td* (8, 1)
12	7.33 *br d* (8)	7.33 *br d* (8)	7.33 *br d* (8)
14	1.68 *ddd* (14, 5, 3)	1.80 *m*	1.80 *m*
	2.21 *m*	2.10 *ddd* (12, 5, 3)	2.10 *ddd* (12, 5, 3)
15	2.90 *m*	2.73 *m*	2.73 *m*
16	2.21 *m*	1.91 *m*	1.91 *m*
17	4.32 *ddd* (12, 5, 2)	4.21 *ddd* (11, 4, 2)	4.24 *ddd* (11, 4, 2)
	5.04 *t* (12)	4.46 *t* (11)	4.51 *t* (11)
18	1.45 *d* (7)	2.09 *s*	2.17 *s*
19	7.11 *qd* (7, 1)	–	–
21	–	7.54 *s*	9.66 *s*
N(1)-Me	3.62 *s*	3.64 *s*	3.63 *s*

[a] Assignments based on COSY and HMQC.

of other macroline indoles (e.g., alstonerine), indicated that the major changes involved the fifth ring (ring E). In **11**, an unusually low field quartet of doublet was seen at δ 7.11 which was coupled to a methyl signal at δ 1.45. These signals have replaced those of the normal 18-methyl and the vinylic H(21) in a typical type-B macroline which appear as singlets at ca. δ 2.1 and 7.5, respectively (Kam et al., 1999, 2000). In the HMBC spectrum, a three-bond correlation is observed from the oxymethylene H(17) to the lactone carbonyl [C(21)], which fixes the position of the lactone carbonyl relative to C(17). Two additional three-bond correlations, viz., from H(15) and H(19) to the lactone carbonyl C(21) confirm the attachment of the ethylidene side chain at C(20), revealing ring E to incorporate a six-membered ring conjugated lactone. The geometry of the exocyclic double bond is determined to be *E*, from the observed shift of H(19) which is unusually deshielded at δ 7.11, as a consequence of the anisotropic influence of the lactone carbonyl function {maximum deshielding is expected for a *cis*-β-H (versus a *trans*-β-H) of a α, β-unsaturated carbonyl compound, as a consequence of the anisotropy of the carbonyl function, e.g., δ for the *cis*-β-H in methyl-*E*-crotonate is ca. 7.0} (Hesse et al., 1997; Ma et al., 1990; Nair et al., 1961; Roitman, 1983). This is the first example of a macroline indole which has incorporated a lactone function in ring E.

Compound (**12**) was obtained as a light yellow oil, with $[\alpha]_D$ −70° (*c* 0.06, $CHCl_3$). The IR spectrum showed bands at 3384 and 1712 cm^{-1} due to OH and a five-membered ring lactam function, respectively. The UV spectrum showed absorption maxima at 211, 233, 255, and 290 nm indicative of an oxindole chromophore. This latter observation, coupled with the IR band at 1712, and the observed carbon resonances at δ 181.4 and 56.4, due to oxindole carbonyl and the spirocyclic C(7), respectively, confirm the presence of an oxindole alkaloid. The ESI-MS showed the $[MH]^+$ peak at *m*/*z* 325, while HRFABMS gave the formula $C_{20}H_{24}N_2O_2$. The ^{13}C NMR spectrum gave a total of 20 carbon signals in agreement with the molecular formula from HRMS, while the ^{1}H NMR spectrum showed the presence of an unsubstituted aromatic moiety, a *N*(1)-Me, and an ethylidene side chain. The COSY spectrum yielded fragments consistent with a sarpagine carbon skeleton, viz., *N*CHCH$_2$, *N*CHCH$_2$CH, CHCH$_2$OH, and the ethylidene side chain. Moreover, the molecular formula indicates a DBE value of 10, which indicated a pentacyclic ring system. Assembly of the entire molecule based on the HMBC data revealed **12** to be the oxindole of the sarpagine alkaloid, affinisine, which was also present in the leaves. The configuration of the spirocyclic centre was determined to be (*R*) from the observed NOE interaction between H(9) and H(16). In addition, the reciprocal NOE observed between H(18) {methyl} and H(15) established the geometry of the 19,20-double bond as *E*. While there are many alkaloids of the sarpagine group, only a few of the corresponding oxindoles are known, among them chitosenine (Sakai et al., 1975) and voachalotine oxindole (Braekman et al., 1969). Affinisine oxindole (**12**) represents an addition to this small group of compounds.

Lagumicine (**13**) was obtained as a light yellowish oil, with $[\alpha]_D$ −552° (*c* 0.07, $CHCl_3$). The IR spectrum showed bands at 3364 and 1704 cm^{-1} due to *N*H/OH and various carbonyl functions, respectively while the UV spectrum showed absorption maxima at 234, 294, and 328 nm characteristic of a β-anilinoacrylate chromophore, and particularly characteristic of akuammicine derivatives (Sangster and Stuart, 1965). The ESI-MS spectrum showed a $[MH]^+$ at *m*/*z* 355 and HRFABMS measurements gave the formula $C_{20}H_{22}N_2O_4$. The ^{1}H NMR spectrum showed the presence of an unsubstituted indole chromophore, *N*H, a methyl ester, and a methyl ketone. The COSY spectrum indicated the presence of an isolated methylene adjacent to *N*(4), *N*CH$_2$CH$_2$, and *N*CHCH$_2$CH fragments, consistent with C(21), C(5)–C(6), and C(3)–C(14)–C(15), respectively, of a strychnan ring system. The ^{13}C NMR spectrum showed two carbonyl signals at δ 210.9 and 167.4, corresponding to the ketone C(19) and the conjugated ester carbonyl function. The resonance of the quaternary C(20) was significantly deshielded at δ 76.9 indicating hydroxy-substitution. Comparison of the NMR spectral data (Tables 2 and 3) with the other strychnan-type alkaloids indicated that **13** is the 11-demethoxy derivative of the known strychnan alkaloid, lagumidine (11-methoxy-19-oxo-20α-hydroxy-akuammicine) (Abe et al., 1994) which was also obtained. As in lagumidine, the observed NOEs between H(9)/H(3) and H(18)/H(15), CO_2Me established the relative configuration at C(20).

Table 2
^{1}H NMR spectral data for **12**–**13**, and **16** (400 MHz, $CDCl_3$)[a]

H	12	13	16
2	–	–	2.78 *s*
3	3.36 *dd* (10, 2)	4.06 *br s*	4.56 *d* (5)
5	3.31 *dd* (6, 3)	2.87 *dd* (12, 7)	3.31 *dd* (14, 6)
	–	3.17 *ddd* (13, 12, 7)	4.48 *m*
6	1.81 *d* (13)	2.00 *dd* (13, 7)	1.72 *dd* (16, 6)
	2.79 *dd* (13, 6)	2.98 *ddd* (13, 12, 7)	3.18 *ddd* (16, 14, 6)
9	7.37 *br d* (8)	7.20 *br d* (8)	6.61 *d* (1)
10	7.10 *td* (8, 1)	6.93 *td* (8, 1)	–
11	7.32 *td* (8, 1)	7.17 *td* (8, 1)	6.68 *dd* (8, 1)
12	6.84 *br d* (8)	6.83 *br d* (8)	6.58 *d* (8)
14	1.57 *ddd* (14, 10, 2)	1.28 *ddd* (13, 3, 2)	1.84 *dd* (14, 2)
	2.18 *ddd* (14, 4, 2)	2.88 *dt* (13, 3)	2.75 *m*
15	2.89 *br s*	3.10 *br s*	3.63 *br s*
16	2.05 *m*	–	2.99 *d* (3)
17	3.63 *m*	–	–
	3.63 *m*	–	–
18	1.61 *dt* (7, 2)	2.37 *s*	1.56 *dd* (7, 2)
19	5.32 *br q* (7)	–	5.60 *br q* (7)
21	3.78 *m*	2.84 *dd* (3, 1)	3.76 *m*
	3.78 *m*	3.21 *d* (13)	4.37 *br d* (14)
N(1)-Me	3.21 *s*	–	2.76 *s*
*N*H	–	8.97 *br s*	–
10-OMe	–	–	3.73 *s*
CO_2Me	–	3.70 *s*	3.81 *s*

[a] Assignments based on COSY and HMQC.

Table 3
^{13}C NMR spectral data for **11**–**16** (100 MHz, $CDCl_3$)[a]

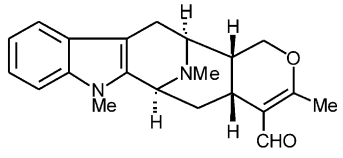
C	11	12	13	14	15	16
2	136.1	181.4	170.5	136.5	136.5	79.3
3	46.0	63.0	60.3	46.5	46.4	70.3
5	47.9	59.3	53.2	48.4	48.3	66.8
6	28.3	44.4	42.1	28.8	28.8	29.3
7	107.7	56.4	56.0	107.0	107.0	41.3
8	126.7	129.9	134.2	126.7	126.7	139.8
9	118.0	126.7	119.7	117.7	117.7	109.6
10	119.2	121.8	121.5	118.9	118.9	154.0
11	121.4	128.4	128.1	121.1	121.1	111.5
12	109.0	108.0	110.0	109.0	109.0	110.5
13	139.9	144.5	144.1	136.9	136.9	146.1
14	29.8	28.7	24.7	31.0	31.0	31.5
15	27.1	26.3	35.0	23.6	23.1	32.3
16	38.7	48.0	98.9	37.4	37.4	51.6
17	68.6	65.5	–	67.4	67.8	–
18	13.8	12.5	25.2	25.0	16.6	13.3
19	142.3	115.2	210.9	195.4	170.8	123.7
20	128.9	135.9	76.9	121.3	117.5	130.1
21	165.7	48.9	50.4	150.9	188.6	72.9
N(1)-Me	29.0	26.6	–	29.0	29.0	35.2
10-OMe	–	–	–	–	–	55.8
CO_2Me	–	–	51.0	–	–	51.9
CO_2Me	–	–	167.4	–	–	171.4

[a] Assignments based on HMQC and HMBC.

Compounds (**14**) and (**15**) coeluted during chromatography and proved resistant to further attempts at resolution by chromatography or fractional crystallization. The ESI-MS spectrum showed a $[MH]^+$ peak at *m*/*z* 323 corresponding to the formula $C_{20}H_{22}N_2O_2$. The NMR data indicated the presence of a mixture of type-A and -B macroline indoles, with the type-B isomer predominating by a 3.5-fold excess over the type-A isomer. The H(18) {methyl} and H(21) {aldehyde-H for **15**, vinylic-H for **14**} signals are clearly distinguishable in the ^{1}H NMR spectrum, while the signals of H(3), H(5) and H(17) are partially overlapped. The rest of the hydrogen resonances of the two isomers are coincident. In the ^{13}C NMR spectrum, the majority of the signals are coincident with the exception of C(18), C(19), C(20), and C(21). This behaviour has been observed previously in the case of the macroline indoles, alstonerine (type-B) and alstonerinal (type-A) (Kam et al., 1999), and in the case of the macroline oxindoles, *N*(1)-demethylalstonisine and *N*(1)-demethylalstonal (Kam and Choo, 2000). In the case of **14** and **15**, comparison of the NMR spectral data (Tables 1 and 3) with that of alstonerine and alstonerinal (Kam et al., 1999), indicated that **14** and **15** are the *N*(4)-demethyl derivatives of alstonerine and alstonerinal, respectively.

Compound (**16**) was readily shown to be the *N*(4)-oxide of 10-methoxycathafoline from the characteristic downfield shifts of H(3), H(5), and H(21) as well as the corresponding carbon shifts of C(3), C(5), and C(21), when compared to that of 10-methoxycathafoline (Kam et al., 1999). This was further confirmed by the mass spectrum and the ready reduction ($FeSO_4$) of **16** to 10-methoxycathafoline.

In addition to the above six new alkaloids, and the seven new macroline oxindoles recently reported (Kam and Choo, 2000), 29 other known alkaloids were also isolated from the leaf extract as detailed in the experimental section. The alkaloid composition of *A. angustifolia* var. *latifolia* from the present study, when compared to that of the Malayan *A. angustifolia* Wall previously determined (Ghedira et al., 1988; Kam, 1999), showed a distinct difference in the alkaloidal pattern, and provides a useful chemotaxonomic aid for distinguishing between the two. While macroline derivatives are common to both, the latter is nevertheless characterized by the presence of a significant number of bisindoles, which are conspicuously absent in the present sample.



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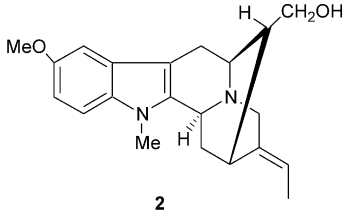

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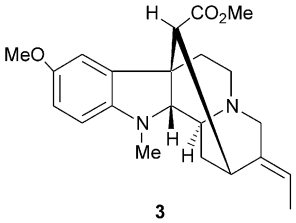

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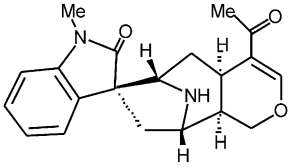

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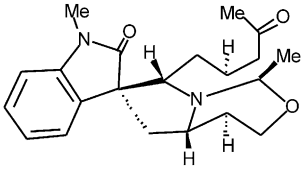

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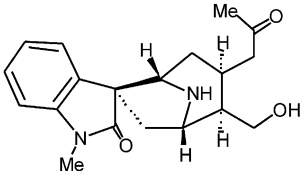

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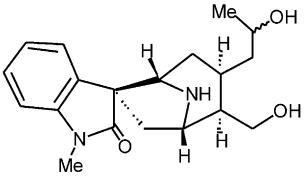

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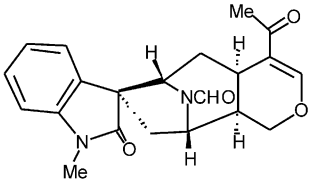

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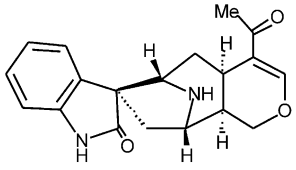

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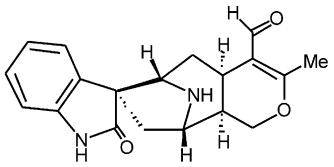

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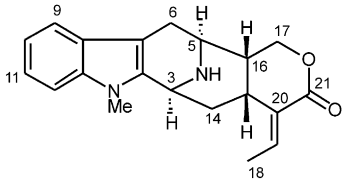

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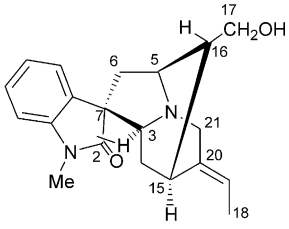

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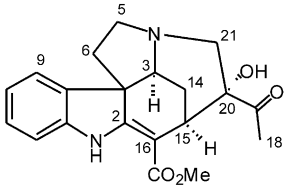

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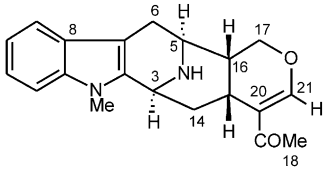

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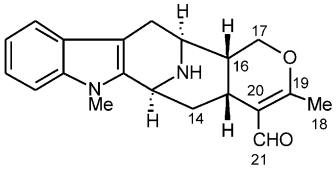

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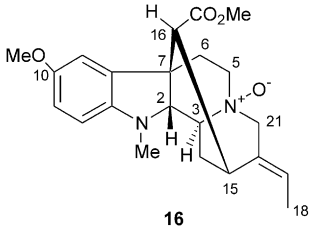

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3. Experimental

3.1. General

Optical rotations were determined on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrophotometer. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a Jeol JNM-LA 400 spectrometer at 400 and 100 MHz respectively. ESI-MS were obtained on a Perkin Elmer API 100 instrument. EIMS, HREIMS, and HRFABMS were obtained on a Jeol JMS-AX505H mass spectrometer, courtesy of Dr. K. Komiyama of the Kitasato Institute, Tokyo, Japan.

3.2. Plant material

Details of collection of plant material, identification, and deposition of specimens have been reported previously (Kam et al., 1999, 2000). The material was reexamined by Dr. K.M. Wong, Institute of Biological Sciences, University of Malaya, Kuala Lumpur, Malaysia, and the identity of the sample revised to that of *A. angustifolia* var. *latifolia*.

3.3. Extraction and isolation

Extraction of the ground material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as has been described in detail elsewhere (Kam et al., 1990). The alkaloids were isolated by initial column chromatography on silica gel using $CHCl_3$ with increasing proportions of MeOH (12 fractions), followed by rechromatography of appropriate partially resolved fractions using centrifugal TLC. Further fractionation of fraction 4 by two successive centrifugal TLC (Et_2O; 1% MeOH/Et_2O) gave **11**, **14** and **15**. Two successive centrifugal TLC of fraction 9 (2% MeOH/$CHCl_3$) yielded **12**, while **13** was obtained from fraction 10, following two successive centrifugal TLC (10% MeOH/EtOAc; 5% MeOH/EtOAc). Centrifugal TLC of fraction 12 (5% MeOH/$CHCl_3$) gave **16**. The yields (g kg^{-1}) of the alkaloids isolated from the leaves are as follows: alstonerinal **1** (0.002) (Kam et al., 1999), 10-methoxyaffinisine **2** (0.014) (Kam et al., 1999), 10-methoxycathafoline **3** (0.009) (Kam et al., 1999), isoalstonisine **4** (0.0016) (Kam and Choo, 2000), macrogentine **5** (0.0017) (Kam and Choo, 2000), alstonoxine A **6** (0.0023) (Kam and Choo, 2000), alstonoxine B **7** (0.0045) (Kam and Choo, 2000), alstofoline **8** (0.0044) (Kam and Choo, 2000), *N*(1)-demethylalstonisine **9** (0.0008) (Kam and Choo, 2000), *N*(1)-demethylalstonal **10** (0.0003) (Kam and Choo, 2000), alstolactone **11** (0.0011), affinisine oxindole **12** (0.0015), lagumicine **13** (0.0016), *N*(4)-demethylalstonerine **14** (0.0007), *N*(4)-demethylalstonerinal **15** (0.0003), 10-methoxycathafoline *N*(4)-oxide **16** (0.0015), alstonisine (0.082) (Ghedira et al., 1988; Kam and Choo, 2000; Wong et al., 1996), alstonal (0.035) (Wong et al., 1996), alstonerine (0.0063) (Ghedira et al., 1988; Kam et al., 1999), alstophylline (0.0014) (Ghedira et al., 1988), talcarpine (0.0013) (Naranjo et al., 1972; Wong et al., 1996], *N*(4)-methyl-*N*(4),21-*seco*talpinine (0.0016) (Naranjo et al., 1972), affinisine (0.043) (Clivio et al., 1991; Kam et al., 1999), normacusine B (0.0061) (Clivio et al., 1991), lochnerine (0.0028) (Poisson et al., 1957), alstoumerine (0.0023) (Atta-ur-Rahman et al., 1991), cathafoline (0.019) (Kam et al., 1999; Morfaux et al., 1990), cathafoline *N*(4)-oxide (0.0024) (Abe et al., 1994), strictamine (0.0076) (Schnoes et al., 1966; Subhadhirasakul et al., 1994), 11-methoxystrictamine (0.002) (Subhadhirasakul et al., 1994), 11-hydroxystrictamine (0.016) (Ghedira et al., 1988), vincorine (0.0046) (Das et al., 1974), vincamajine (0.0045) (Chatterjee et al., 1978; Morfaux et al., 1990), 10-methoxyvincamajine (0.0072) (Lewin et al., 1975), quebrachidine (0.011) (Burke et al., 1973), 16*R*,19*E*-isositsirikine (0.0024) (Kutney et al., 1966; Lounasmaa et al., 1994), sitsirikine (0.0034) (Brown et al., 1979; Kutney et al., 1966), 11-methoxyakuammicine (0.0026) (Cook et al., 1975), nor-*C*-fluorocurarine (0.0007) (Clivio et al., 1991), alstolagumine (0.0013) (Abe et al., 1994), lagumidine (0.0031) (Abe et al., 1994), and alstovine (0.0011) (Ravoa et al., 1982).

3.3.1. Alstolactone (**11**)

Light yellowish oil, $[\alpha]_D$ −10° ($CHCl_3$, *c* 0.05). UV (EtOH) λ_{max} (log ϵ) 216 (4.23), 228 (4.30), 284 (3.76), 293 (3.71) nm; IR (dry film) υ_{max} 3390, 1707 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 3; ESI-MS *m*/*z* 323 [MH]$^+$; HREIMS *m*/*z* 322.1688 (calcd for $C_{20}H_{22}N_2O_2$, 322.1681).

3.3.2. Affinisine oxindole (**12**)

Light yellowish oil, $[\alpha]_D$ −70° ($CHCl_3$, *c* 0.06). UV (EtOH) λ_{max} (log ϵ) 211 (4.31), 233 (3.82), 255 (3.87), 290 (3.35) nm; IR (dry film) υ_{max} 3384, 1712 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; FABMS *m*/*z* 325 [MH]$^+$; HRFABMS *m*/*z* 325.1916 (calcd for $C_{20}H_{24}N_2O_2$ + H, 325.1916).

3.3.3. Lagumicine (**13**)

Light yellowish oil, $[\alpha]_D$ −552° ($CHCl_3$, *c* 0.07). UV (EtOH) λ_{max} (log ϵ) 234 (3.79), 294 (3.71), 328 (3.85) nm; IR (dry film) υ_{max} 3364, 1704 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; ESI-MS *m*/*z* 355 [MH]$^+$; HRFABMS *m*/*z* 355.1653 (calcd for $C_{20}H_{22}N_2O_4$ + H, 355.1658).

3.3.4. N(4)-demethylalstonerine (14) and N(4)-demethylalstonerinal (15)

Were obtained as a mixture. ^{1}H and ^{13}C NMR data, see Tables 1 and 3; ESI-MS m/z 323 $[MH]^+$; HREIMS m/z 322.1687 (calcd for $C_{20}H_{22}N_2O_2$, 322.1681).

3.3.5. 10-Methoxycathafoline N(4)-oxide (16)

Light yellowish oil, $[\alpha]_D$ −32° ($CHCl_3$, c 0.14). UV (EtOH) λ_{max} (log ϵ) 208 (4.16), 249 (3.79), 311 (3.37) nm; IR (dry film) υ_{max} 3404, 1734 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; EIMS m/z 384 $[M]^+$ (13), 368 [M-16] (100), 194 (57), 117 (100), 97 (55), 69 (77), 57 (100), 44 (100).

3.3.6. Reduction of 10-methoxycathafoline N(4)-oxide (16)

Compound **16** (18 mg) was stirred in aqueous ferrous sulfate (2.5%, 2 ml) at 80 °C for 0.5 h. The mixture was then extracted with $CHCl_3$ and chromatography over SiO_2 gave the parent 10-methoxycathafoline (6.5 mg, 38%).

3.3.7. Oxidation of 10-methoxycathafoline to 10-methoxycathafoline N(4)-oxide (16)

*m*CPBA (20.3 mg) was added to a stirred solution of 10-methoxycathafoline (18.8 mg) in CH_2Cl_2 (3 ml) at 4 °C. After ca. 10 min, saturated Na_2CO_3 (10 ml) was added. The mixture was then extracted with CH_2Cl_2 and chromatography over SiO_2 gave 10-methoxycathafoline *N*-oxide (**16**) (13.8 mg, 70%).

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