Pergamon

Tetrahedron 54 (1998) 6135–6146

TETRAHEDRON

# Synthesis of the Brominated Marine Alkaloids (±)-Arborescidine A, B and C.

Brigitte E.A. Burm, Michaël M. Meijler, Jacco Korver, Martin J. Wanner and Gerrit-Jan Koomen*

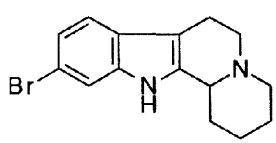
Amsterdam Institute of Molecular Studies, Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Received 23 February 1998; revised 1 April 1998; accepted 2 April 1998

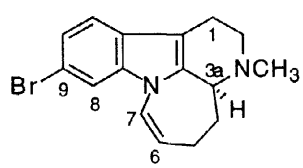
**Abstract:** A straightforward synthesis of the brominated marine alkaloids arborescidine A (**1**), B (**2**) and C (**3**), starting from 6-bromo-(*N*-methyl) trypatamine is described. An equilibrium, under both basic and acidic conditions was found to exist between the *trans*- and *cis*-isomers **3** and **4**. Spectral data indicated that the structure of isomer **4** does not correspond with the compound identified as arborescidine D recently isolated from the marine tunicate *Pseudodistoma arborescens*. 

## INTRODUCTION

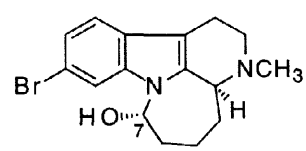
Bromoindoles and derivatives are common secondary metabolites of marine organisms, possibly functioning in their chemical defense mechanism against parasites. Several alkaloids having either 6-bromotryptophan or 6-bromotryptamine as the basic unit have been isolated from a variety of marine invertebrates including sponges, coelenterates and tunicates.[1] The occurrence of 6-bromoindoles has been reported since 1909 when 6,6'-dibromoindigotine was identified.[2] 6-Bromotryptamine itself has been found as a natural product in a number of marine organisms, e.g. in the tunicate *Didemnum candidum* [3] and also in *Lissoclinum* sp.[4] along with lissocline C, a brominated tetrahydro-β–carboline. Another group of well-known compounds possessing the brominated β–carboline structure, some of them based upon 6-bromotryptamine, are the eudistomines which were isolated from a Caribbean tunicate (*Eudistoma olivaceum*).



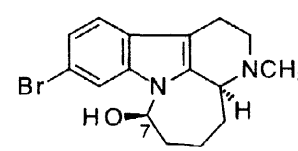

**1**




**2**




**3**

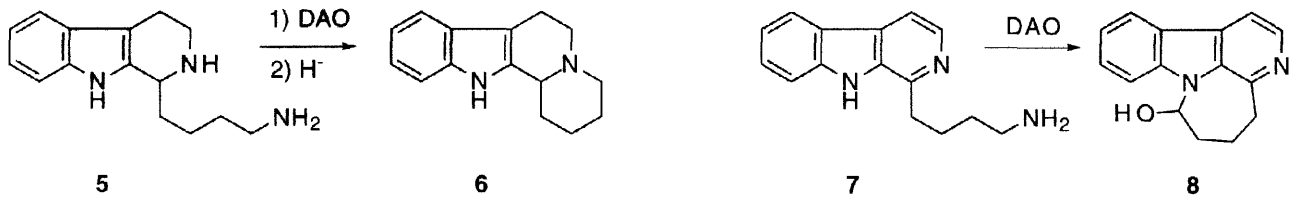



**4**

Recently[5] four new brominated alkaloids of the latter tetrahydro-β-carboline class were isolated from the marine tunicate *Pseudodistoma arborescens* and characterized as arborescidine A (**1**), B (**2**), C (**3**) and D (**4**).[6] Our interest arose in view of our previous work on oxidized analogs of nazlinine (**5**),[7] an alkaloid obtained from *Nitraria* plant extracts. Oxidative deamination of the primary amine function, using both enzymic (DAO) and chemical methods, resulted in an aldehyde which cyclized spontaneously (Scheme 1). Depending on the availability of the β–carboline-nitrogen atom, cyclization towards either an indoloquinolizidine **6** or an azepine ring system **8** occurred, starting from either nazlinine **5** or aromatized nazlinine **7**. Since these two ring systems

0040-4020/98/$19.00 
*PII:* S0040-4020(98)00306-8

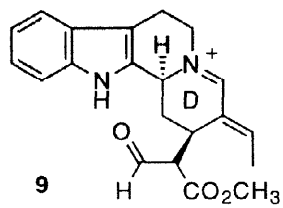
are also present in the arborescidines, arborescidine A being an indoloquinolizidine and B, C and D being azepines, we decided to synthesize these new biosynthetically related natural products.



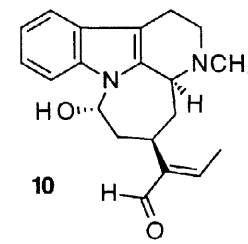

5 6 7 8

Scheme 1

Another example of the application of this biosynthetical ring conversion is found in the synthesis of akagerine (**10**). The perhydroazepine ring coupled to a tetrahydro-β–carboline moiety by a N(1)/ C(7) aminal bond, as present in arborescidine C (**3**) and D (**4**), is also part of the ring structure of akagerine (**10**). This alkaloid, isolated from *Strychnos* roots,[8] is thought to be linked biogenetically to dehydro-geissoschizine (**9**), an alkaloid that has the indoloquinolizidine structure. Transformation into the seven-membered ring could be achieved chemically by opening of ring D and cyclization of the aldehyde on the indole nitrogen atom. The first synthesis of akagerine (**10**) is based upon this interconversion and involves nucleophilic attack of the indole nitrogen on an activated carboxylic acid.[9] More examples of this azepine ring system are described in the synthesis of E-homoeburnane derivatives.[10]




9



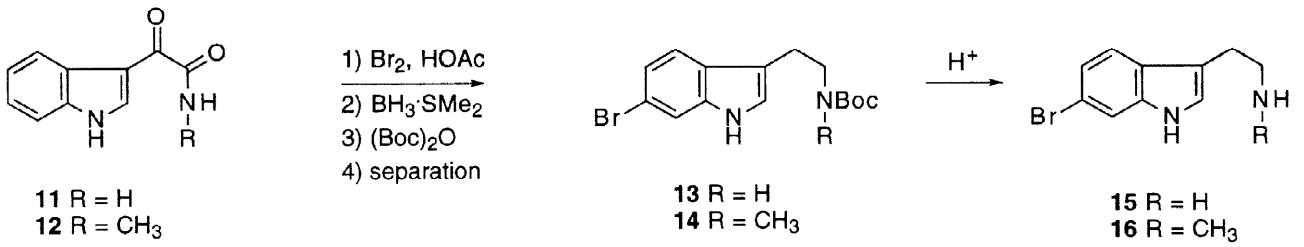

10

## RESULTS AND DISCUSSION

Our approach to the synthesis of the arborescidines started with the preparation of the 6-bromotryptamines **15** and **16** (Scheme 2). This new route towards brominated tryptamine derivatives combines an existing synthesis of tryptamines[11] and bromination of a suitable intermediate.[12] In order to brominate the indole moiety at the 6-position, reduction of the electron density in the 5-membered ring was a prerequisite and was effected *via* introduction of an α-keto-amide at the 3-position.[13] Bromination of **11** and **12**, employing elemental bromine in acetic acid gave a 1 : 1 mixture of the 5- and 6-bromo derivatives in good yield.

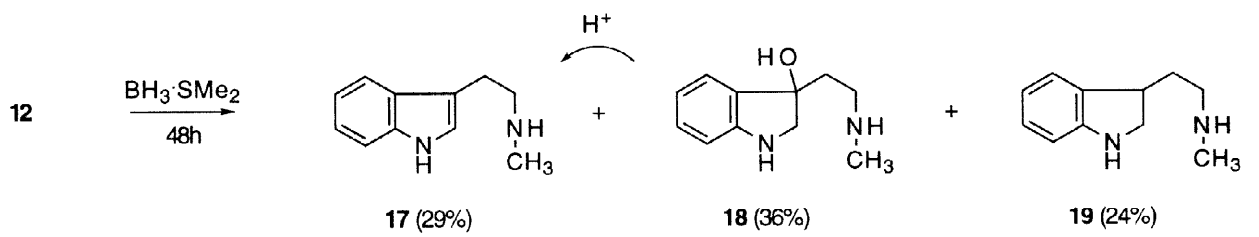
It was reported that the reduction of 6-bromo-3-glyoxylamide,[14] prepared from 6-bromoindole, using $LiAlH_4$ resulted in debromination. A wide variety of compounds, including glyoxylamides, can be reduced however employing borane-dimethylsulfide complex.[15] Compared to $LiAlH_4$ reductions, those mediated by $BH_3{\cdot}SMe_2$ are relatively slow. A dramatic increase in reaction rate could be achieved by distillation of dimethylsulfide from the reaction mixture.[15] Thus, reduction of the 5(6)-bromo glyoxylamides using $BH_3{\cdot}SMe_2$, produced the corresponding ethylamines in varying yields (40-60%). Separation of the resulting mixture of regio-isomers after conversion into the respective carbamates was readily effected by chromatography,

to afford the desired 6-bromo isomers **13** and **14**. Deprotection under acidic conditions gave the pure 6-bromotryptamines **15** and **16** as their crystalline hydrochlorides.



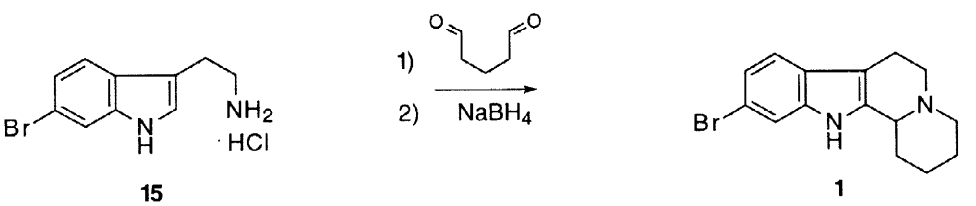

Scheme 2

When longer reaction times were used in the borane-mediated reduction of the glyoxylamides several side products were observed, which explains the variation in yield. A separate experiment was performed in which the glyoxylamide **12** was reacted with $BH_3{\cdot}SMe_2$ during two days (Scheme 3). Besides the expected *N*-methyltryptamine **17**, two products could be isolated by chromatography: indoline **18** and 2,3-dihydro-*N*-methyltryptamine **19**. Hydroboration of the indole 2-3 double bond followed by oxidation of the intermediate borane, which is probably accomplished by air-oxygen, resulted in the formation of alcohol **18**. Upon exposing the indoline **18** to hydrochloric acid, water-elimination occured and *N*-methyltryptamine **17** was formed. The low intensity of the molecular ion compared to that of the M-$H_2O$ fragment ion observed in the mass spectrum of **18** illustrates this instability. Since under acidic conditions indoline **18** is converted into tryptamine **17**, the yield of the reduction of the brominated glyoxylamides could be improved by stirring the reaction mixture during the work-up procedure with hydrochloric acid for several minutes.



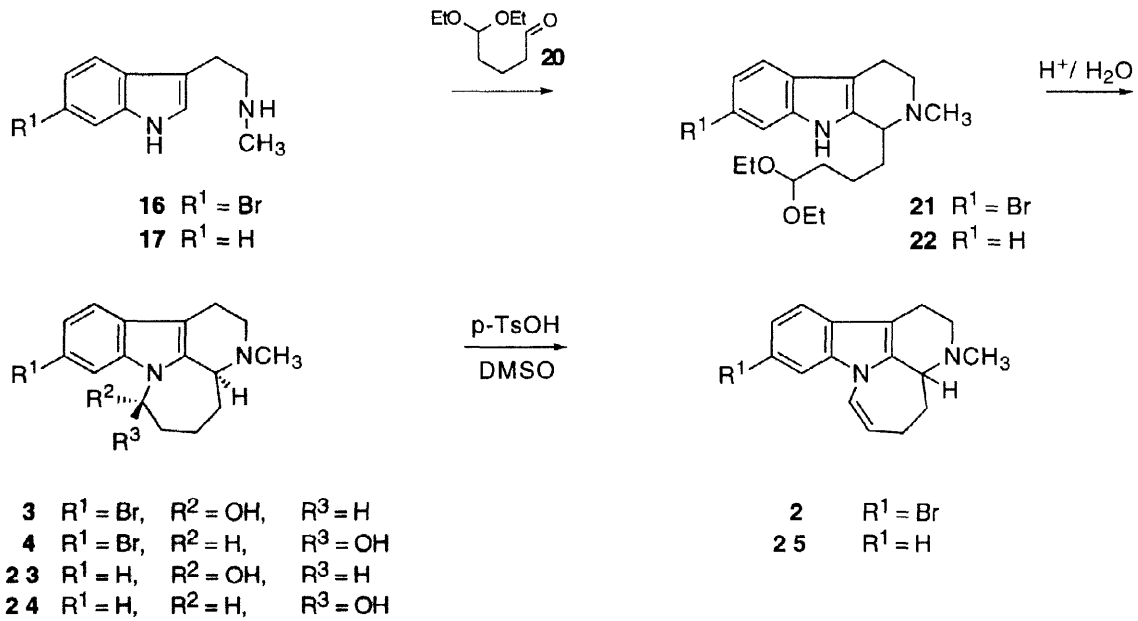

Scheme 3

With the required tryptamines in hand, the arborescidines could be synthesized straightforwardly employing the Pictet-Spengler condensation.[16] Reaction of 6-bromo-tryptamine hydrochloride **15** with glutaric aldehyde followed by one pot reduction of the resulting iminium salt with $NaBH_4$ led to the immediate formation of (±)-arborescidine A (**1**)[17] in moderate yield (Scheme 4).[18]




Scheme 4

The approach used for the synthesis of arborescidines B (**2**), C (**3**) and D (**4**) is based upon our strategy[7] previously described for azepine ring systems. The methyl substituent on the β-carboline-nitrogen atom prevents cyclization to the indoloquinolizidine structure instead leading to formation of the seven-membered ring. Non-acidic aprotic Pictet-Spengler condensation of 6-bromo-*N*-methyltryptamine **16** with 5,5-diethoxypentanal **20**[19] in refluxing toluene yielded acetal **21** in good yield (Scheme 5). Performing the Pictet-Spengler reaction under neutral conditions was required because of the susceptibility of the protected aldehyde to decomposition.




**16** $R^1$ = Br
**17** $R^1$ = H

**21** $R^1$ = Br
**22** $R^1$ = H

**3** $R^1$ = Br, $R^2$ = OH, $R^3$ = H
**4** $R^1$ = Br, $R^2$ = H, $R^3$ = OH
**23** $R^1$ = H, $R^2$ = OH, $R^3$ = H
**24** $R^1$ = H, $R^2$ = H, $R^3$ = OH

**2** $R^1$ = Br
**25** $R^1$ = H

Scheme 5

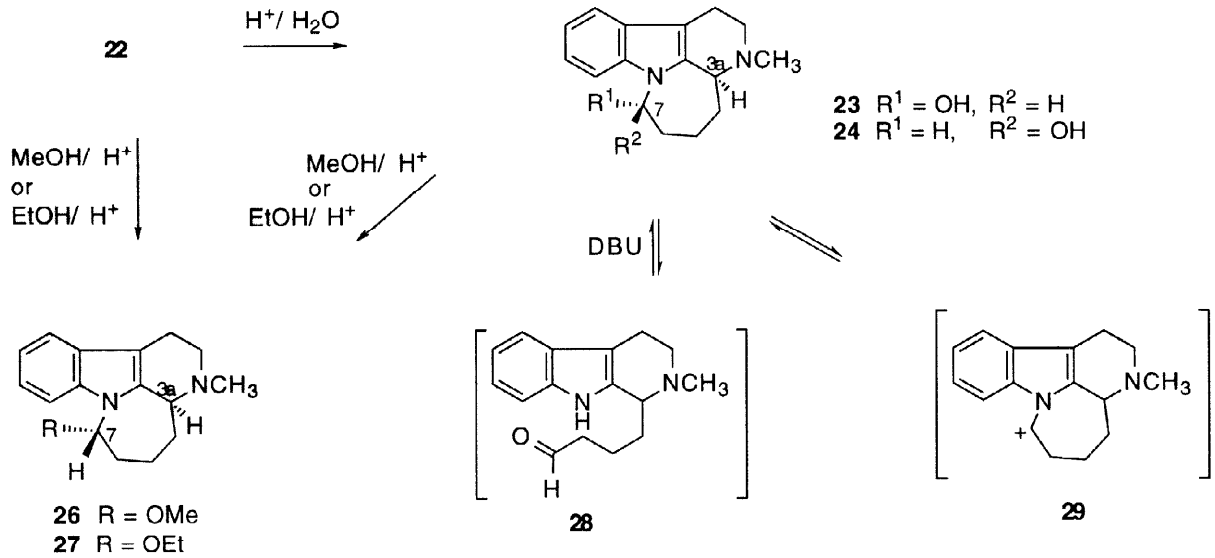
Deprotection of acetal **21** using aqueous TFA led to the simultaneous formation of the azepine ring structure as a mixture of the *trans*- (**3**) and *cis*-isomer (**4**) in an initial ratio of **3** : **4** = 4 : 1, as indicated by $^1$H-NMR spectroscopy. Prolonged reaction times (45 minutes) resulted in a thermodynamical equilibrium of **3** : **4** in a 10 : 1 ratio. The stereochemistry of **3** resp. **4** was established using different NMR techniques. Especially the chemical shift of H3a is characteristic for both diastereomers (3.64 and 3.38 ppm resp.). The *trans*- and *cis*-relations between H3a and H7 could clearly be distinguished in the NOESY spectrum; only in case of the *cis*-isomer **4** a cross peak was observed.

Isolation of the *trans*-isomer (±)-arborescidine C (**3**)[17] was readily effected by crystallization from methanol in good yield. To obtain the minor isomer (±)-arborescidine D (**4**) in pure form the reaction was only allowed to proceed for 15 minutes followed by crystallization from methanol. The spectral data of the synthesized **4** however were not in accord with the literature values[5] reported for (-)-arborescidine D. Spectral data (IR, MS, $^1$H and $^{13}$C NMR, $^1$H-$^1$H COSY, $^1$H-$^{13}$C COSY, NOESY) confirmed the structure of compound **4**. The major differences between arborescidine D and compound **4** are the proton shifts of H3a (3.13 resp. 3.38), H7 (5.65 resp. 6.08), H8 (6.63 resp. 7.57) and the m/z peaks in the mass spectrum (273/275 resp. 263/265). The fragment ions of high intensity at m/z 263 and 265, as seen in **4**, can be explained by benzylic/ β-cleavage from the molecular ion, a known process for tetrahydro-β-carbolines.[20] The compound isolated from the marine tunicate therefore probably has a structure different from the assigned **4**.

The enamine (±)-arborescidine B (**2**)[17] was readily synthesized from (±)-arborescidine C **3** (Scheme 5) upon heating with 1 equivalent *p*-TsOH in DMSO (Scheme 7). Several other solvents (e.g. THF and toluene) did not result in complete conversion due to lower boiling points or precipitation of the starting material as its *p*-TsOH salt. Preparation of the enamine (**3**) directly from the acetal (**21**) by heating under acidic non-protic conditions (TFA/ toluene) gave the desired product, however together with several unidentified side products.

Having synthesized arborescidine C (**3**) and its *cis*-isomer compound **4**, which apparently has a structure different from the natural arborescidine D, attention was focussed on the stability of both isomers in relation with the methods used for isolation of the natural products. The debromo analogs, synthesized *via* the described route (Scheme 5) were used for these studies, because they are easily accessible.

When either pure *trans*-(**23**) or *cis*-isomer (**24**) was subjected to aqueous TFA in both cases a 11 : 1 mixture of **23** and **24** was obtained eventually (Scheme 6). An acid catalyzed equilibration presumably involves $H_2O$ elimination/ addition *via* the carbocation **29** resulting in a mixture predominantly consisting of the thermodynamically more stable *trans*-isomer.




Scheme 6

Interestingly, ring closure of acetal **22** in the presence of methanol or ethanol instead of water, led to the isolation of (±)-*O*-methyl- and (±)-*O*-ethyldebromoarborescidine C **26** and **27** respectively. In contrast to the reaction with water resulting in alcohols **23** and **24**, no *cis*-isomers were detected after reaction with methanol or ethanol. The same products, **26** and **27**, could be obtained from reaction of (±)-debromo-arborescidine C (**23**) under the latter conditions. All these results indicate the intermediacy of carbocation **29** in the acidic equilibration between the *cis*- and *trans*-isomers.

Applying basic conditions (DBU/ THF) to pure **23** or **24** resulted in the formation of a mixture of **23** and **24** in a comparable ratio. Apparently under basic conditions an equilibration takes place, involving ring opening/ ring closure *via* aldehyde **28**, also in favor of the thermodynamically more stable *trans*-isomer.

These results support the finding that the compound named arborescidine D isolated from the marine tunicate has a structure different from the assigned **4**. Under acidic conditions such as extraction into a 1 M HCl

layer and chromatographic elution with EtOAc/ 2-butanone/ HCOOH/ $H_2O$, both used for isolation of the natural product, compound **4** as prepared by us is not stable. Equilibration to the *trans*-isomer (±)-arborescidine C (**3**) occurs immediately under both acidic and basic conditions as we have shown. Also the formation of arborescidine B (**2**) by water elimination from arborescidine C (**3**) cannot be excluded under these conditions.

## SUMMARY

Three new brominated alkaloids, arborescidine A (**1**), B (**2**), and C (**3**), which were isolated from the marine tunicate *Pseudodistoma arborescens*, were synthesized in racemic form starting from 6-bromo-(*N*-methyl) tryptamine and suitably functionalized $C_5$-fragments. It was shown by synthesis of **4** that the fourth brominated alkaloid arborescidine D has a structure different from the assigned **4**. Both under acidic and basic conditions (±)-arborescidine C (**3**) and **4** as well as their debromo-analogs reached a thermodynamical equilibrium in favor of the *trans*-isomers.

## EXPERIMENTAL SECTION

**General methods:** see ref. 21. In all HRMS data only $^{79}Br$ isotopes are quoted.

**2-[6-Bromo-1*H*-indol-3-yl]-*N*-*tert*-butyloxycarbonyl-ethanamine (13).** To a solution of 2-(1*H*-indol-3-yl)-2-oxo-ethanamide (**11**)[14] (7.27 g, 39 mmol) in acetic acid (200 mL), bromine (2.05 mL, 6.4 g, 40 mmol) was added dropwise at 15 °C. After 10 min of stirring the red solution turned cloudy and the mixture was stirred for another 30 min before transferring it to a 1L beaker. Water (500 mL) was added and the mixture was stirred thoroughly while the products precipitated as an off-white solid that was collected by filtration. After extensive washing with water, the solid was dissolved in ethyl acetate which was dried over $Na_2SO_4$ and concentrated *in vacuo*, yielding a white solid (9.52 g, 36 mmol, 92%). According to $^1$H-NMR this consisted of a 1:1 mixture of the 5-bromo- and 6-bromoisomers. The mixture was not separated, but used immediately in the next reaction.

The mixture of amides (9.3 g, 35 mmol) was evaporated once from THF before it was dissolved in THF (100 mL). The temperature was raised to 60 °C, then borane dimethylsulfide (10 mL of a 10.1 M solution in THF, 3 eq.) was added dropwise. The mixture was refluxed for 2 h and after cooling to rt an excess aqueous hydrogen chloride was added. The solution was stirred for another hour and the solvent was removed. Saturated $K_2CO_3$-solution was added and the product was extracted three times with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. This afforded a yellow syrup (5.9 g) which was not purified but immediately used for further reaction.

The mixture of amines (5.9 g) was dissolved in $CH_2Cl_2$ (200 mL). A solution of $(Boc)_2O$ (7.8 g, 36 mmol) in $CH_2Cl_2$ (10 mL) was added and the mixture was stirred at rt for 30 min. Concentration *in vacuo* afforded a syrup which was subjected to flash chromatography (PE/ EtOAc 75/ 25, ∅ 8 cm, 300 g silica), yielding the 5-bromo isomer (3.04 g, 8.99 mmol, 25%) and the 6-bromo isomer **13** (2.24 g, 6.61 mmol, 19%) as colorless glasses. **13**: $R_f$ (PE/ EtOAc 50/ 50) 0.40; $^1$H NMR ($CDCl_3$) δ 8.64 (br s, 1H), 7.50 (s, 1H), 7.43 (d, $J$ = 8.6 Hz, 1H), 7.18 (d, $J$ = 8.6 Hz, 1H), 6.92 (s, 3H), 4.72 (br s, 1H), 3.41 (m, 2H), 2.88 (m, 2H), 1.45 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 156.1, 137.1, 126.2, 122.6, 122.4, 119.9, 115.3, 114.1, 113.0, 79.3, 40.9, 28.3, 25.6; IR

($CHCl_3$) 3724, 3008, 2918, 1702, 1512 $cm^{-1}$.
The 5-bromo isomer of **13** was also characterized: $R_f$ (PE/ EtOAc 50/ 50) 0.35; $^1H$ NMR ($CDCl_3$) δ 8.48 (br s, 1H), 7.70 (d, $J$ = 1.7 Hz, 1H), 7.22 (m, 2H), 6.98 (s, 1H), 4.67 (br s, 1H), 3.48 (m, 2H), 2.88 (m, 2H), 1.44 (s, 9H); $^{13}C$ NMR ($CDCl_3$) δ 155.9, 134.9, 129.1, 124.7, 123.2, 121.2, 112.6, 112.5, 112.5 , 79.3, 40.9, 28.3, 25.5; IR ($CHCl_3$) 3743, 3323, 3012, 2932, 1703, 1510 $cm^{-1}$.

**2-[6-Bromo-1*H*-indol-3-yl]-*N*-methyl-*N*-*tert*-butyloxycarbonyl-ethanamine (14).** The procedure described for the synthesis of **13** was used starting with 2-(1*H*-indol-3-yl)-*N*-methyl-2-oxo-ethanamide (**12**)[14] (6.25 g, 31 mmol), yielding a white solid (7.84 g, 27.9 mmol, 90%) in a 1:1 ratio according to $^1H$-NMR.
The mixture of amides **14** (3.0 g, 10.7 mmol) was reduced using borane dimethylsulfide (15 mL of a 2.0 M solution in THF, 3 eq.) yielding a yellow syrup (1.5 g). To react the mixture of amines (1.5 g), $(Boc)_2O$ (2.38 g, 11 mmol) was used. Flash chromatography (PE/ EtOAc 75/ 25, ∅ 6 cm, 250 g silica), afforded the 5-bromo isomer (0.96 g, 2.72 mmol, 25%) and the 6-bromo isomer **14** (0.83 g, 2.35 mmol, 22%) as colorless glasses.
**14**: $R_f$ (PE/ EtOAc 50/ 50) 0.45; $^1H$ NMR ($CDCl_3$) δ 8.38 (br s, 1H), 7.49 (d, $J$ = 1.4 Hz, 1H), 7.46 (d, $J$ = 8.4 Hz, 1H), 7.20 (dd, $J$ = 8.4 Hz, $J$ = 1.4 Hz, 1H), 6.95 (s, 3H), 3.49 (m, 2H), 2.93 (m, 2H), 2.84 (s, 3H), 1.38 (br s, 9H); $^{13}C$ NMR ($CDCl_3$) δ 155.7, 137.0, 126.3, 122.4, 119.8, 115.3, 114.0, 113.3, 79.2, 49.3, 28.2, 27.9, 23.6; IR (KBr) 3687, 3618, 3019, 2400, 1684, 1521 $cm^{-1}$.
The 5-bromo isomer of **14** was also characterized: $R_f$ (PE/ EtOAc 50/ 50) 0.40; $^1H$ NMR ($d_6$-DMSO) δ 10.81 (br s, 1H), 7.49 (s, 1H), 7.10 (d, $J$ = 8.6 Hz, 1H), 6.96 (m, 2H), 3.18 (m, 2H), 2.63 (m, 2H), 2.56 (s, 3H), 1.10 (br s, 9H); $^{13}C$ NMR ($d_6$-DMSO) δ 154.9, 135.3, 129.5, 123.6, 120.8, 113.7, 111.5, 111.3, 78.3, 49.1, 28.4, 28.1, 23.5; IR (KBr) 3686, 3615, 3022, 2396, 1686, 1517 $cm^{-1}$.

**2-[6-Bromo-1*H*-indol-3-yl]-ethanamine hydrochloride (15·HCl).** To a solution of the **13** (2.24 g, 6.61 mmol) in ethanol (15 mL) an excess aqueous hydrogen chloride (25%) was added dropwise. The mixture was stirred at rt for 2 h and after removal of the solvent the residue was evaporated two more times from ethanol. The resulting solid was suspended in diethyl ether and stirred for 30 min. Filtration afforded **15·HCl** (1.69 g, 6.15 mmol, 93%): mp 214 - 216 °C; $^1H$ NMR ($D_2O$) δ 7.49 (d, $J$ = 1.7 Hz, 1H), 7.40 (d, $J$ = 8.4 Hz, 1H), 7.33 (dd, $J$ = 1.8, $J$ = 8.4 Hz, 1H), 7.29 (s, 1H), 3.30 (t, $J$ = 7.0 Hz, 2H), 3.10 (t, $J$ = 7.0 Hz, 2H); $^{13}C$ NMR ($D_2O$) δ 137.8, 130.1, 128.3, 127.3, 123.4, 116.3, 114.6, 111.5, 42.4, 25.5; IR (KBr) 3459, 2886, 1611, 1480, 1458 $cm^{-1}$; HRMS (EI) obs.mass 238.0112, calcd for $C_{10}H_{11}N_2Br$ 238.0106.

**2-[6-Bromo-1*H*-indol-3-yl]-*N*-methylethanamine hydrochloride (16·HCl).** The procedure described for the synthesis of **15·HCl** was used starting with **14** (0.83 g, 2.35 mmol) yielding **16·HCl** (0.65 g, 2.21 mmol, 94%): mp >240 °C (dec.); $^1H$ NMR ($D_2O$) δ 7.71 (d, $J$ = 1.6 Hz, 1H), 7.56 (d, $J$ = 8.5 Hz, 1H), 7.30 (m, 2H), 3.34 (t, $J$ = 6.9 Hz, 2H), 3.17 (t, $J$ = 6.9 Hz, 2H), 2.70 (s, 3H); $^{13}C$ NMR ($D_2O$) δ 139.9, 128.1, 127.7, 125.1, 122.4, 117.7, 117.4, 111.8, 51.9, 35.5, 24.7; IR (KBr) 3230, 3010, 1750, 1380 $cm^{-1}$. HRMS (EI) obs.mass 252.0275, calcd for $C_{11}H_{13}N_2Br$ 252.0262.

**Reduction of 12 with $BH_3$·$SMe_2$.** The amide **12** (200 mg, 1.0 mmol) was evaporated once from THF before it was dissolved in THF (100 mL). The temperature was raised to 60 °C, then borane dimethylsulfide (10 mL of a 10.1 M solution in THF, 3 eq.) was added dropwise. The mixture was refluxed for 48 h and after

cooling to rt an excess aqueous hydrogen chloride was added. The solution was stirred for another 5 min and the solvent was removed. Saturated $K_2CO_3$-solution was added and the product was extracted three times with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. This afforded a mixture of three compounds that could be separated using flash chromatography ($CH_2Cl_2$/ MeOH/ concd $NH_4OH$ 90/ 10/ 1). The products, *N*-methyltryptamine **17** (50 mg, 0.29 mmol, 29%), alcohol **18** (69 mg, 0.36 mmol, 36%) and 2,3-dihydro-*N*-methyltryptamine **19** (42 mg, 0.24 mmol, 24%), were isolated as oils. **19**: $R_f$ ($CH_2Cl_2$/ MeOH/ concd $NH_4OH$ 90/ 10/ 1) 0.30; $^1H$ NMR ($CD_3OD$) δ 7.22 (d, $J$ = 7.4 Hz, 1H), 7.08 (t, $J$ = 7.7 Hz, 1H), 6.75 (t, $J$ = 7.4 Hz, 1H), 6.68 (d, $J$ = 7.7 Hz, 1H), 3.47 (d, $J$ = 10.2 Hz, 1H), 3.47 (d, $J$ = 10.2 Hz, 1H), 2.75-2.71 (m, 1H), 2.66-2.60 (m, 1H), 2.37 (s, 3H), 2.16-2.08 (m, 1H), 2.00-1.93 (m, 1H); $^{13}C$ NMR ($CD_3OD$) δ 152.3, 134.4, 130.1, 124.3, 119.7, 111.9, 81.2, 60.6, 48.2, 39.5, 35.9; IR (KBr) 2914, 1675 $cm^{-1}$; HRMS (FAB) obs.mass 193.1359, calcd for $C_{11}H_{16}N_2O$ (M + 1) 193.1261; obs.mass 175.1236, calcd for $C_{11}H_{14}N_2$ (M + 1 - $H_2O$) 175.1157; *m/z* (% rel. int.) 193 (31), 175 (100).

**(±)-Arborescidine A (1).** To a solution of **15** (352 mg, 1.28 mmol) in water (250 mL), purged with $N_2$, aqueous glutaric aldehyde (25%, 0.8 mL, 2.21 mmol) was added at 0 °C over a period of 10 min. After stirring for 1 h at 0 - 5 °C the reaction mixture was stirred at rt for 2 weeks under $N_2$ atmosphere. At 0 °C, aqueous ethanol (95%, 100mL) was added followed by $NaBH_4$ (5.5 g, 0.15 mol) in portions. The solution was stirred at 0 °C for 1 h and then 8 h at rt. The reaction mixture was made alkaline by adding 6 M NaOH, extracted with $CH_2Cl_2$ and the organic layer was washed with brine and dried over $Na_2SO_4$. Concentration afforded a syrup that was subjected to flash chromatography (EtOAc/ $NEt_3$ 95/ 5), yielding **1** (80 mg, 0.26 mmol, 21%) as a yellow oil: $R_f$ (EtOAc/ $NEt_3$ 95/ 5) 0.36; $^1H$ NMR ($CDCl_3$) δ 7.84 (bs, 1H), 7.41 (s, 1H), 7.30 (d, $J$ = 8.4 Hz, 1H), 7.16 (d, $J$ = 8.4 Hz, 1H), 3.20 (br d, $J$ = 10.5 Hz, 1H), 3.08 - 2.93 (m, 3H), 2.67 - 2.58 (m, 2H), 2.41 - 2.35 (m, 1H), 2.08 - 2.03 (m, 1H), 1.90 - 1.87 (m, 1H), 1.74 - 1.71(m, 2H), 1.61 - 1.45 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ 136.6, 135.7, 126.3, 122.4, 119.2, 114.4, 113.6, 108.2, 59.9, 55.6, 53.3, 29.7, 25.6, 24.1, 21.3; IR ($CHCl_3$) 3402, 3166, 1621, 1584 $cm^{-1}$; HRMS (FAB) obs.mass 305.0649, calcd for $C_{15}H_{17}N_2Br$ (M+1) 305.0575; Anal. Calcd for $C_{15}H_{17}N_2Br$: C, 59.03; H, 5.61; N, 9.18; Br, 26.18. Found: C, 58.89; H, 5.58; N, 9.06; Br, 25.90.

**5,5-Diethoxypentanal (20).** A solution of aqueous glutaric aldehyde (50 wt%, 150 mL, 0.83 mol) in ethanol (99%, 1.6 L) was stirred with Dowex 50WX8 ($H^+$-form, 2.0 g) for 2 days at rt. Solid $NaHCO_3$ was added and after stirring for one hour the catalyst was removed by filtration. The resulting solution was concentrated *in vacuo* and the residue was destilled *in vacuo* from a small amount of $NaHCO_3$ using a 30 cm vigreux. The first fraction consisted of a mixture of glutaric aldehyde and cyclic acetal. The product **20** was obtained (second fraction) as a colourless oil (13.7 g, 0.078 mol, 9.4 %). Bp 42 - 45 °C/ 0.6 mbar; $^1H$ NMR ($CDCl_3$)[21] δ 9.76 (t, $J$ = 1.4 Hz, 1H), 4.48 (t, $J$ = 5.2 Hz, 1H), 3.76 - 3.41 (m, 4H), 2.47 (dt, $J$ = 1.4 Hz, $J$ = 7.0 Hz, 2H), 1.74 - 1.61 (m, 4H), 1.19 (t, $J$ = 7.0 Hz, 6H); $^{13}C$ NMR ($CDCl_3$)[22] δ 202.3, 102.5, 61.2, 43.5, 32.9, 17.3, 15.3; IR ($CHCl_3$) 1720 $cm^{-1}$.

**7-Bromo-1-(4,4-diethoxybutyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (21).** Extraction of **16·HCl** (830 mg, 2.88 mmol) with EtOAc from a saturated $K_2CO_3$ solution gave the free amine. A solution of the free amine **16** and 5,5-diethoxypentanal **20** (552 mg, 3.17 mmol, 1.1 eq.) in toluene (30 mL) was refluxed for 2 h.

Because 5,5-diethoxypentanal **20** dimerizes, an extra portion (360 mg, 2.07 mmol, 0.7 eq.) was added after 1 h. Evaporation of the solvent and flash chromatography (PE/ EtOAc/ $NEt_3$ 60/ 25/ 15) afforded **21** (1.09 g, 2.67 mmol, 93%) as a yellow oil: $R_f$ (PE/ EtOAc/ $NEt_3$ 60/ 25/ 15) 0.31; $^1H$ NMR ($CDCl_3$) δ 8.11 (bs, 1H), 7.44 (d, $J$ = 1.6 Hz, 1H), 7.32 (d, $J$ = 8.3 Hz, 1H), 7.17 (dd, $J$ = 1.7 Hz, $J$ = 8.3 Hz, 1H), 4.50 (t, $J$ = 5.5 Hz, 1H), 3.69 - 3.60 (m, 2H), 3.54 - 3.45 (m, 3H), 3.18 - 3.13 (m, 1H), 2.82 - 2.67 (m, 3H), 2.46 (s, 3H), 1.94 - 1.77 (m, 2H), 1.70 - 1.65 (m, 2H), 1.63 - 1.41 (m, 2H), 1.21 (t, $J$ = 7.0 Hz, 3H), 1.20 (t, $J$ = 7.1 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 136.3, 135.5, 126.0, 122.3, 119.1, 114.5, 113.5, 108.2, 102.7, 61.2, 61.1, 59.6, 49.3, 41.7, 33.1, 32.2, 20.5, 18.7, 15.3, 15.2; IR ($CHCl_3$) 3469, 2978, 1457, 1125, 1054 $cm^{-1}$; HRMS (EI) obs.mass 408.1395, calcd for $C_{20}H_{29}N_2O_2Br$ 408.1412.

**(±)-Arborescidine C (3).** To a solution of **21** (800 mg, 1.96 mmol) in THF (2 mL), aqueous TFA (15 mL 10% v/ v) was added. The mixture was stirred for 45 min at rt, made alkaline by adding saturated $Na_2CO_3$ solution and stirred for another 30 min. The product was extracted with ethyl acetate (3x). The combined organic layers were washed with water and brine, dried ($Na_2SO_4$) and evaporated. A mixture of (±)-arborescidine C (**3**) and its *cis*-isomer (**4**) (94%) in a ratio of 10 : 1 was obtained, according to $^1H$ NMR. Crystallization from MeOH yielded **3** (478 mg, 1.43 mmol, 73%) as white crystals: $R_f$ (EtOAc/ EtOH/ concd $NH_4OH$ 85/ 10/ 5) 0.55; mp 172 - 173 °C; $^1H$ NMR ($CDCl_3$) δ 7.46 (d, $J$ = 1.5 Hz, 1H), 7.30 (d, $J$ = 8.3 Hz, 1H), 7.18 (dd, $J$ = 1.5 Hz, $J$ = 8.3 Hz, 1H), 6.14 (dd, $J$ = 1.5 Hz, $J$ = 4.7 Hz, 1H), 3.64 (d, $J$ = 10.7 Hz, 1H), 3.05 - 3.01 (m, 1H), 2.75 - 2.68 (m, 3H), 2.52 (s, 3H), 2.38 - 2.27 (m, 2H), 2.18 - 2.11 (m, 1H), 1.87 - 1.82 (m, 1H), 1.70 - 1.61 (m, 1H), 1.51 - 1.41 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 138.1, 136.8, 125.5, 122.4, 119.3, 114.7, 111.5, 109.0, 76.6, 61.4, 50.7, 42.7, 34.1, 32.4, 21.1, 20.0; IR ($CHCl_3$) 3305, 2947, 2849, 1463 $cm^{-1}$; HRMS (EI) obs.mass 334.0681, calcd for $C_{16}H_{19}N_2OBr$ 334.0681; *m/ z* (% rel. int.) 336 (100), 335 (61), 334 (94), 333 (43), 291 (82), 265 (72), 263 (86). Anal. Calcd for $C_{16}H_{19}N_2OBr$: C, 57.32; H, 5.71; N, 8.36. Found: C, 57.59; H, 5.70; N, 8.30.

**Isomer 4.** The same procedure was used as described for **3** except that the reaction was stopped after 15 min. Stirring **21** (800 mg, 1.96 mmol) for 15 min gave a mixture of (±)-arborescidine C (**3**) and its *cis*-isomer (**4**) (548 mg, 1.64 mmol, 84%) in a ratio of 4 : 1, according to $^1H$ NMR. After crystallization from MeOH **4** was obtained as white crystals: $R_f$ (EtOAc/ EtOH/ concd $NH_4OH$ 85/ 10/ 5) 0.47; mp 173 - 174 °C; $^1H$ NMR ($CDCl_3$) δ 7.57 (d, $J$ = 1.5 Hz, 1H), 7.33 (d, $J$ = 8.3 Hz, 1H), 7.23 (dd, $J$ = 1.5 Hz, $J$ = 8.3 Hz, 1H), 6.08 (br d, $J$ = 5.9 Hz, 1H), 3.38 (br d, $J$ = 9.7 Hz, 1H), 3.18 - 3.14 (m, 1H), 2.97 - 2.88 (m, 1H), 2.76 - 2.62 (m, 2H), 2.45 (s, 3H), 2.36 - 2.34 (m, 1H), 2.20 - 2.09 (m, 3H), 1.85 - 1.80 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ 137.5, 137.3, 125.6, 122.9, 119.4, 115.1, 112.3, 108.1, 77.1, 60.3, 52.9, 41.1, 29.5, 28.6, 20.1, 19.2; IR ($CHCl_3$) 3312, 2943, 2851, 1462 $cm^{-1}$; HRMS (EI) obs.mass 334.0694, calcd for $C_{16}H_{19}N_2OBr$ 334.0681; *m/ z* (% rel. int.) 336 (80), 335 (47), 334 (80), 333 (34), 291 (61), 265 (89), 263 (100).

**(±)-Arborescidine B (2).** The same procedure was used as described for **25**. Using **3** (124 mg, 0.37 mmol) and *p*-TsOH (73 mg, 0.38 mmol) yielded **2** (97 mg, 0.31 mmol, 83%) as a yellow oil: $R_f$ (EtOAc/ EtOH/ concd $NH_4OH$ 85/ 10/ 5) 0.60; $^1H$ NMR ($CDCl_3$) δ 7.47 (d, $J$ = 1.5 Hz, 1H), 7.32 (d, $J$ = 8.3 Hz, 1H), 7.22 (dd, $J$ = 1.5 Hz, $J$ = 8.3 Hz,1H), 6.80 (dt, $J$ = 1.9 Hz, $J$ = 9.8 Hz, 1H), 5.12 - 5.07 (m, 1H), 3.39 (br d, $J$ = 10.1 Hz, 1H), 3.16 - 3.11 (m, 1H), 2.94 - 2.86 (m, 1H), 2.74 - 2.65 (m, 2H), 2.58 - 2.49 (m, 1H), 2.54 (s, 3H), 2.45 -

2.32 (m, 2H), 1.91 - 1.82 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 137.7, 136.8, 125.7, 123.2, 121.5, 119.2, 115.2, 112.3, 111.1, 109.2, 62.2, 52.5, 42.1, 29.7, 27.8, 20.4; IR ($CHCl_3$) 2914, 1675 cm$^{-1}$; **HRMS (FAB)** obs.mass 317.0674, calcd for $C_{16}H_{17}N_2Br$ (M+1) 317.0575.

**1-(4,4-Diethoxybutyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (22).** A solution of *N*-methyltryptamine **17** (2.69 g, 15.5 mmol) and 5,5-diethoxypentanal **20** (3.2 g, 18.4 mmol, 1.1 eq.) in toluene (100 mL) was refluxed for 2 h. Because 5,5-diethoxypentanal **20** dimerizes, an extra portion (830 mg, 4.77 mmol, 0.3 eq.) was added after 1 h. Evaporation of the solvent and flash chromatography (PE/ EtOAc/ $NEt_3$ 60/ 25/ 15) afforded **22** (4.95 g, 15.0 mmol, 97%) as a yellow oil: $R_f$ (PE/ EtOAc/ $NEt_3$ 60/ 25/ 15) 0.32; $^1$H NMR ($CDCl_3$) δ 7.98 (s, 1H), 7.50 - 7.48 (d, *J* = 7.6 Hz, 1H), 7.32 - 7.30 (d, *J* = 7.8 Hz, 1H), 7.16 - 7.07 (m, 2H), 4.51 (t, *J* = 5.5 Hz, 1H), 3.66 (m, 2H), 3.50 (m, 3H), 3.20 - 3.15 (m, 1H), 2.83 - 2.71 (m, 3H), 2.47 (s, 3H), 1.96 - 1.43 (m, 6H), 1.24 - 1.19 (m, 6H); $^{13}$C NMR ($CDCl_3$) δ 135.9, 134.8, 127.2, 121.3, 119.2, 118.0, 110.7, 108.2, 102.9, 61.2, 61.1, 59.8, 49.6, 41.9, 33.4, 32.6, 20.7, 18.9, 15.4, 15.3; IR ($CHCl_3$) 3473, 2975, 1455, 1126, 1054 cm$^{-1}$; HRMS (EI) obs.mass 330.2307, calcd for $C_{20}H_{30}N_2O_2$ 330.2307.

**(±)-Debromoarborescidine C (23).** The same procedure was used as described for **3**. Reacting **22** (1.29 g, 3.92 mmol) gave a mixture of (±)-debromo-arborescidine C (**23**) and its *cis*-isomer (**24**) in a ratio of 11 : 1, according to $^1$H NMR. After crystallization from MeOH **23** (667 mg, 2.61 mmol, 66%) was obtained as white crystals: $R_f$ (EtOAc/ EtOH/ concd $NH_4OH$ 85/ 10/ 5) 0.48; mp 146 - 147 °C; $^1$H NMR ($CDCl_3$) δ 7.45 (d, *J* = 7.1, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.14 - 7.06 (m, 2H), 6.12 (d, *J* = 3.4 Hz, 1H), 3.57 (br d, *J* = 10.3 Hz, 1H), 2.95 - 2.90 (m, 1H), 2.75 - 2.72 (m, 2H), 2.65 - 2.59 (m, 1H), 2.37 (s, 3H), 2.27 - 2.23 (m, 1H), 2.16 - 2.03 (m, 2H), 1.75 - 1.70 (m, 1H), 1.57 - 1.50 (m, 1H), 1.39 - 1.30 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 137.5, 136.1, 126.7, 121.2, 119.2, 118.2, 108.5, 108.4, 76.3, 61.1, 50.3, 42.5, 34.3, 31.8, 20.2, 20.2; IR ($CHCl_3$) 3615, 3017, 2945, 1467 cm$^{-1}$; HRMS (EI) obs.mass 256.1544, calcd for $C_{16}H_{20}N_2O$ 256.1576; Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.86; H, 7.87; N, 10.88.

**Debromo analog of isomer 4 (24).** The same procedure was used as described for **4** Reacting **22** (1.29 g, 3.92 mmol) gave a mixture of (±)-debromo-arborescidine C (**23**) and its *cis*-isomer (**24**) (0.97 g, 3.79 mmol, 96%) in a ratio of 2.5 : 1, according to $^1$H NMR. Subsequent crystallization from MeOH and EtOAc yielded the debromo analog of isomer **4** (**24**) as white crystals: $R_f$ (EtOAc/ EtOH/ concd $NH_4OH$ 85/ 10/ 5) 0.29; mp 151 - 152 °C; $^1$H NMR ($CDCl_3$) δ 7.48 (d, *J* = 7.7, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.09 (d, *J* = 5.8 Hz,1H), 3.61 (br s, 1H), 3.28 (br d, *J* = 10.5 Hz, 1H), 3.15 - 3.11 (m, 1H), 3.02 - 2.93 (m, 1H), 2.73 - 2.67 (m, 2H), 2.35 (s, 3H), 2.30 - 2.24 (m, 1H), 2.11 - 2.01 (m, 2H), 1.87 - 1.82 (m, 1H), 1.71 - 1.51 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 136.7, 136.5, 126.7, 121.6, 119.7, 118.1, 109.2, 107.9, 77.3, 60.5, 53.2, 41.3, 29.5, 28.1, 20.4, 19.3; IR ($CHCl_3$) 3315, 3009, 2944, 1469 cm$^{-1}$; HRMS (EI) obs.mass 256.1572, calcd for $C_{16}H_{20}N_2O$ 256.1576; Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.86; H, 7.71; N, 10.95.

**(±)-*O*-Methyldebromoarborescidine C (26).** A solution of **22** (155 mg, 0.61 mmol) in $H_2SO_4$/ MeOH (10 mL 20% v/ v) was stirred for 15 min at rt. After addition of a saturated $Na_2CO_3$ solution (10 mL) the product was extracted with ethyl acetate (3x). The combined organic layers were washed with water and brine, dried

($Na_2SO_4$) and evaporated. Flash chromatography (PE/ EtOAc/ $NEt_3$ 70/ 15/ 15) yielded **26** (149 mg, 0.55 mmol, 91%) as a slowly crystallizing yellow oil. Alternatively the same reaction could be performed starting from **23** (138 mg, 0.42 mmol) in which case also **26** (89 mg, 0.33 mmol, 79%) was obtained: $R_f$ (PE/ EtOAc/ $NEt_3$ 70/ 15/ 15) 0.24; mp 73-75 °C; $^1H$ NMR ($CDCl_3$) δ 7.49 (d, $J$ = 7.7 Hz, 1H), 7.35 (d, $J$ = 8.3 Hz, 1H), 7.18 (dt, $J$ = 1.1 Hz, $J$ = 8.3 Hz, 1H), 7.10 (t, $J$ = 7.7 Hz, 1H), 5.69 (dd, $J$ = 1.5 Hz, $J$ = 4.6 Hz, 1H), 3.59 (dd, $J$ = 1.1 Hz, $J$ = 11.2 Hz, 1H), 3.12 - 3.07 (m, 1H), 3.05 (s, 3H), 2.82 - 2.79 (m, 2H), 2.77 - 2.71 (m, 1H), 2.57 (s, 3H), 2.41 - 2.35 (m, 1H), 2.33 - 2.28 (m, 1H), 2.18 - 2.06 (m, 1H), 1.90 - 1.80 (m, 1H), 1.71 - 1.63 (m, 1H), 1.54 - 1.44 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 137.6, 137.4, 126.5, 121.2, 119.2, 118.2, 108.7, 108.4, 83.7, 61.5, 55.0, 51.0, 42.9, 33.8, 32.9, 20.9, 20.3; IR ($CHCl_3$) 3008, 2943, 1463 $cm^{-1}$; HRMS (EI) obs.mass 270.1742, calcd for $C_{17}H_{22}N_2O$ 270.1732.

**(±)-*O*-Ethyldebromoarborescidine C (27).** A solution of **22** (122 mg, 0.37 mmol) in $H_2SO_4$/ EtOH (10 mL 20% v/ v) was stirred for 30 min at rt. After addition of a saturated $Na_2CO_3$ solution (10 mL) the product was extracted with ethyl acetate (3x). The combined organic layers were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography ($CH_2Cl_2$/ MeOH 90/ 10) yielded **27** (95 mg, 0.33 mmol, 90%) as a slowly crystallizing yellow oil. Alternatively the same reaction could be performed starting from **23** (50 mg, 0.20 mmol) in which case also **27** (42 mg, 0.15 mmol, 74%) was obtained: $R_f$ ($CH_2Cl_2$/ MeOH 90/ 10) 0.56; mp 78 - 79 °C; $^1H$ NMR ($CDCl_3$) δ 7.52 (d, $J$ = 7.7 Hz, 1H), 7.36 (d, $J$ = 8.2 Hz, 1H), 7.20 (t, $J$ = 7.0 Hz, 1H), 7.12 (t, $J$ = 7.6 Hz, 1H), 5.82 (d, $J$ = 3.2 Hz,1H), 3.65 (d, $J$ = 10.1 Hz, 1H), 3.37 - 3.29 (m, 1H), 3.14 - 3.04 (m, 2H), 2.84 - 2.73 (m, 3H), 2.59 (s, 3H), 2.42 - 2.30 (m, 2H), 2.26 - 2.14 (m, 1H), 1.89 - 1.82 (m, 1H), 1.73 - 1.65 (m, 1H), 1.52 (dq, $J$ = 13.1 Hz, $J$ = 2.2 Hz, 1H), 1.11 (t, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 137.8, 137.5, 126.5, 121.9, 119.2, 118.2, 108.6, 108.5, 82.1, 62.8, 61.7, 51.1, 43.1, 34.1, 33.2, 21.1, 20.4, 14.9; IR ($CHCl_3$) 2944, 2875, 1464 $cm^{-1}$; HRMS (EI) obs.mass 284.1881, calcd for $C_{18}H_{24}N_2O$ 284.1889.

**(±)-Debromoarborescidine B (25).** A solution of **23** (215 mg, 0.76 mmol) and *p*-TsOH (130 mg, 0.76 mmol) in DMSO (5 mL) was stirred at 120 °C during 3 h. After cooling to rt the reaction mixture was poured into an aqueous $Na_2CO_3$ solution (50 mL 10%) and extracted three times with ether. The combined organic layers were washed with water (3x), dried ($MgSO_4$) and evaporated. Flash chromatography (EtOAc/ EtOH/ concd $NH_4OH$ 85/ 10/ 5) yielded **25** (140 mg, 0.59 mmol, 78%) as a white solid. Alternatively the same reaction could be performed starting from **27** (115 mg, 0.45 mmol) in which case also **25** (100 mg, 0.42 mmol, 94%) was obtained: $R_f$ (EtOAc/ EtOH/ concd $NH_4OH$ 85/ 10/ 5) 0.42; mp 102 - 103 °C; $^1H$ NMR ($CDCl_3$) δ 7.49 (d, $J$ = 7.6 Hz, 1H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.24 - 7.13 (m, 2H), 6.95 (dd, $J$ = 9.8 Hz, $J$ = 2.0 Hz, 1H), 5.09 - 5.05 (m, 1H), 3.42 (br d, $J$ = 10.3 Hz, 1H), 3.16 - 3.13 (m, 1H), 2.97 - 2.91 (m, 1H), 2.77 - 2.70 (m, 2H), 2.60 - 2.52 (m, 4H), 2.46 - 2.43 (m, 2H), 1.92 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 137.3, 136.2, 127.0, 122.0, 121.8, 120.2, 118.2, 110.1, 109.3, 109.1, 62.8, 52.9, 42.5, 30.0, 28.0, 20.7; IR ($CHCl_3$) 3006, 2909, 1674, 1464 $cm^{-1}$; HRMS (EI) obs.mass 238.1493, calcd for $C_{16}H_{18}N_2$ 238.1470.

## REFERENCES AND NOTES


1. (a) Bifulco, G.; Bruno, I.; Minale, L.; Riccio, R.; Calignano, A.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1294. (b) Schmidt, U.; Wild, J. *Angew. Chem.* **1984**, *98*, 996. (c) Raverty, W.D.; Thomson, R.H.; King, T.J. *J. Chem. Soc. Perkin Trans. I* **1977**, 1204. (d) Dellar, G.; Djura, P.; Sargent, M.V. *J. Chem. Soc. Perkin Trans. I* **1981**, 1679.
2. Friedländer, P. *Ber* **1909**, *42*, 765.
3. Searle, P.A.; Molinsky, T.F. *J. Org. Chem.* **1994**, *59*, 6600.
4. Fahy, E.; Potts, B.C.M.; Faulkner, D.J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564.
5. Chbani, M.; Païs, M.; Delauneux, J.-M.; Debitus, C. *J. Nat. Prod.* **1993**, *56*, 99.
6. Arborescidine A: 10-bromo-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine. Arborescidine B: 9-bromo-1,2,3,3a,4,5,6,7-hexahydro-3-methyl-3,7a-diazacyclohepta-[*jk*]fluorene. Arborescidine C and D: 9-bromo-1,2,3,3a,4,5,6,7-hexahydro-3-methyl-3,7a-diazacyclohepta-[*jk*]fluoren-7-ols.
7. Cheng, E.; Botzem, J.; Wanner, M.J.; Burm, B.E.A.; Koomen, G.-J. *Tetrahedron* **1996**, *52*, 6725.
8. Angenot, L; Dideberg, O.; Dupont, L. *Tetrahedron Lett.* **1975**, 1357.
9. Benson, W.; Winterfeldt, E. *Heterocycles* **1981**, *15*, 935.
10. (a) Maupérin, P.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1971**, 999. (b) Laronze, J.; Laronze, J.-Y.; Lévy, J.; Le Men, J. *Bull. Soc. Chim. France* **1977**, 1195.
11. (a) Alemany, A.; Fernandez Alvarez, E.; Nieto Lopez, O.; Rubio Herraez, M.E. *Bull. Soc. Chim. France* **1974**, 2883. (b) Benington, F.; Morin, R.D.; Clark Jr, L.C. *J. Org. Chem* .**1960**, *25*, 1542.
12. Hirano, S.; Akai, R.; Shinoda, Y.; Nakatsuka, S. *Heterocycles* **1995**, *41*, 255.
13. Grøn, C.; Christophersen, C. *Acta Chem. Scand. B 38* **1984**, *8*, 709.
14. In this approach the Fischer indole synthesis was employed for the synthesis of a separable mixture of 4-bromo and 6-bromoindole . Glyoxylation of 6-bromoindole gave 6-bromo-3-glyoxylamide which upon reduction with $LiAlH_4$ yielded largely debrominated products; Rinehart Jr, K.L.; Kobayashi, J.; Harbour, G.C.; Gilmore, J.; Mascal, M.; Holt, T.G.; Shield, L.S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378.
15. Brown, H.C.; Yong Moon Choi; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.
16. (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. See for a recent review: (b) Cox, E.D.; Cook, J.M. *Chem. Rev.* **1995**, *95*, 1797.
17. The synthetic (±)-arborescidine A (**1**), B (**2**) and C(**3**) were identical in all aspects (IR, MS, $^1H$ and $^{13}C$ NMR, except that a racemic mixture was obtained) with the natural alkaloids.[6]
18. Gribble, G.W. *J. Org. Chem.* **1972**, *37*, 9009.
19. Wanner, M.J.; Koomen, G.-J. *J. Org. Chem.* **1995**, *60*, 5634.
20. Mahboobi, S.; Wagner, W.; Burgemeister, T.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* **1994**, *327*, 463.
21. Wanner, M.J.; Koomen, G.-J. *J. Org. Chem.* **1994**, *59*, 7479.
22. Traces of acid in the $CDCl_3$ are removed by filtration over basic $Al_2O_3$.