Aristolane Sesquiterpenes and Highly Brominated Indoles from the Marine Red Alga *Laurencia similis* (Rhodomelaceae)

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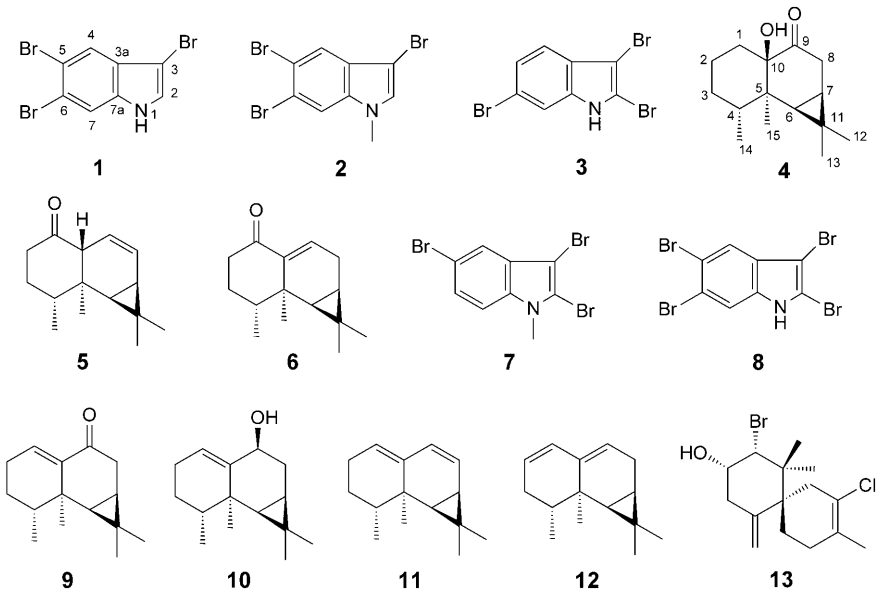
Three new polybrominated 1*H*-indoles, compounds **1**–**3**, and three new aristolane sesquiterpenes, compounds **4**–**6**, were isolated from the marine red alga *Laurencia similis*, together with seven known natural products. Their structures were elucidated on the basis of detailed spectroscopic and mass-spectrometric analyses, as well as by comparison with literature data.

Introduction. – Marine red algae of the genus *Laurencia* (Ceramiales, Rhodomelaceae) have been found to be a rich source of structurally unique secondary metabolites. The majority of these metabolites are characterized by the high degree of halogenation, the core structures mainly consisting of sesquiterpenes, diterpenes, triterpenes, and C_{15} acetogenins [1]. The secondary metabolites of the genus vary significantly with species and location. Although the ecological and biological roles of these metabolites have not been clearly elucidated yet, some metabolites have been reported to possess a variety of biological activities such as antifeedant [2], anthelmintic [3], antifouling [4], antimicrobial [4], and cytotoxic [5] properties.

In the course of our ongoing investigations toward biologically active compounds from Chinese marine algae, we examined *L. similis* collected off the coast of Sanya, Hainan island, China. To the best of our knowledge, only one study has been reported so far concerning the chemical constituents of *L. similis* [6]. From this species, we isolated and identified five new constituents, including three highly brominated simple 1*H*-indoles, compounds **1**–**3**, and two new aristolane[1]) sesquiterpenes, compounds **4** and **5**, as well as the known aristolane **6** [7][8], isolated herewith for the first time from a natural source. In addition, seven known compounds were obtained from *L. similis*: 2,3,5-tribromo-1-methyl-1*H*-indole (**7**) [9], 2,3,5,6-tetrabromo-1*H*-indole (**8**) [6][9], aristol-1(10)-en-9-one (**9**) [10], (9β)-aristol-1(10)-en-9-ol (**10**) [10], aristol-1(10),8-diene (**11**) [8][11], aristol-1,9-diene (**12**) [7][8], and elatol (**13**) [4]. Herein, we report the isolation and structure determination of the new constituents.

Results and Discussion. – The dried and powdered algal material was extracted with a mixture of $CHCl_3$/MeOH 1:1 (*v*/*v*). After solvent removal, the residue was further

[1]) Aristolane proper corresponds to (1a*R*,3a*R*,7*R*,7a*S*,7b*S*)-decahydro-1,1,7,7a-tetramethyl-1*H*-cyclopropa[*a*]naphthalene.



extracted with 95% aqueous EtOH. The concentrated extracts were combined and partitioned between H_2O and AcOEt, and the AcOEt-soluble fraction was purified by column chromatography (CC) on silica and *Sephadex LH-20* gel, as well as by preparative thin-layer chromatography (TLC), to yield compounds **1**–**13**.

Compound **1** was obtained as colorless crystals. Low-resolution EI-MS exhibited a characteristic molecular-ion cluster at *m*/*z* 357/355/353/351 in a ratio of 1 : 3 : 3 : 1, which clearly indicated the presence of three Br-atoms. The molecular formula was deduced as $C_8H_4Br_3N$ by positive HR-FAB-MS (*m*/*z* 353.7954 ($[M+H]^+$, $C_8H_5{}^{81}Br^{79}Br_2N^+$; calc. 353.7952)). The ^{13}C-NMR (DEPT) data (*Table 1*) indicated the presence of eight C-atoms, including three CH groups and five quaternary C-atoms. The ^{1}H-NMR spectrum (*Table 1*) exhibited four signals at δ(H) 7.22 (*d*, $J = 2.6$ Hz, H–C(2)), 7.84 (*s*, H–C(4)), 7.68 (*s*, H–C(7)), and 8.29 (br. *s*, NH). Detailed comparison with the reported NMR data of the known compounds **7** and **8** [6] [9] suggested that **1** possessed a tribromoindole skeleton. The ^{1}H,^{1}H-COSY spectrum showed a cross-peak between H–C(2) and H–N(1), which indicated that C(2) was connected to N(1). The two *singlet*s at δ(H) 7.84 (H–C(4)) and 7.68 (H–C(7)) confirmed that Br-atoms were attached to C(3), C(5), and C(6), respectively. The HMBC correlations (*Fig. 1*) from H–C(2) to C(3), C(3a), and C(7a), from H–C(4) to C(3), C(5), C(6), and C(7a), and from H–C(7) to C(5) and C(3a), respectively, confirmed that compound **1** corresponds to 3,5,6-tribromo-1*H*-indole.

Compound **2** was obtained as colorless crystals. Low-resolution EI-MS exhibited a characteristic molecular-ion cluster at *m*/*z* 371/369/367/365 in a ratio of 1 : 3 : 3 : 1, indicating three Br-atoms. The molecular formula was deduced as $C_9H_6Br_3N$ by positive HR-FAB-MS (*m*/*z* 367.8095 ($[M+H]^+$, $C_9H_7{}^{81}Br^{79}Br_2N^+$; calc. 367.8108)). The ^{13}C-NMR (DEPT) spectrum of **2** (*Table 1*) showed the presence of nine C-atoms, with one Me and three CH groups, as well as five quaternary C-atoms. The ^{1}H-NMR spec-

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1**–**3**. At 500 and 125 MHz, resp., in $CDCl_3$. Assignments were corroborated by ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments.

Position	**1**		**2**		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	7.22 (*d*, *J*=2.6)	125.2 (*d*)	7.06 (*s*)	129.5 (*d*)	–	110.6 (*s*)
3	–	91.0 (*s*)	–	88.7 (*s*)	–	94.7 (*s*)
3a	–	127.8 (*s*)	–	128.1 (*s*)	–	126.6 (*s*)
4	7.84 (*s*)	123.7 (*d*)	7.81 (*s*)	123.8 (*d*)	7.35 (*d*, *J*=8.5)	120.1 (*d*)
5	–	116.3 (*s*)	–	115.7 (*s*)	7.29 (*dd*, *J*=8.5, 1.5)	124.7 (*d*)
6	–	118.7 (*s*)	–	118.3 (*s*)	–	117.1 (*s*)
7	7.68 (*s*)	116.1 (*d*)	7.61 (*s*)	114.4 (*d*)	7.45 (*d*, *J*=1.5)	113.6 (*d*)
7a	–	134.9 (*s*)	–	136.0 (*s*)	–	136.2 (*s*)
NH	8.29 (br. *s*)	–	–	–	8.36 (br. *s*)	–
MeN	–	–	3.74 (*s*)	33.3 (*q*)	–	–

trum (*Table 1*) exhibited four *singlet*s at δ(H) 7.06 (H–C(2)), 7.81 (H–C(4)), 7.61 (H–C(7)), and 3.74 (Me(10)). Detailed comparison of the spectroscopic data of **1** and **2** suggested that **2** was an *N*-methylated tribromoindole. Whereas the ^{1}H,^{1}H-COSY spectrum of **2** showed no cross-peaks among the ^{1}H-NMR signals, the HMBC spectrum (*Fig. 1*) displayed correlations from H–C(2) to C(3), C(3a), and C(7a), from H–C(4) to C(3), C(5), C(6), and C(7a), from H–C(7) to C(5), C(6), and C(3a), and from H–C(10) to C(2) and C(7a), respectively. These data led to the establishment of the structure of compound **2** as 3,5,6-tribromo-1-methyl-1*H*-indole.

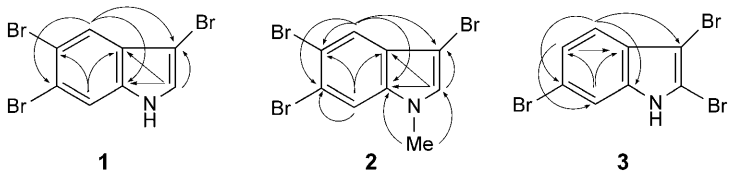


Fig. 1. *Selected HMBC correlations for* **1**–**3**

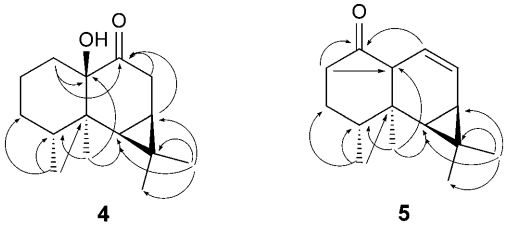
Compound **3** was obtained as colorless crystals. Low-resolution EI-MS exhibited a characteristic molecular-ion cluster at *m*/*z* 357/355/353/351 in a ratio of 1:3:3:1, which indicated the presence of three Br-atoms. The molecular formula was deduced as $C_8H_4Br_3N$ by positive HR-FAB-MS (*m*/*z* 353.7934 ($[M+H]^+$, $C_8H_5{}^{81}Br^{79}Br_2N^+$; calc. 353.7952)), just as for **1**. The ^{13}C-NMR (DEPT) spectrum of **3** (*Table 1*) showed the presence of eight C-atoms, with three CH groups and five quaternary C-atoms. The ^{1}H-NMR spectrum of **3** (*Table 1*) exhibited four signals at δ(H) 7.35 (*d*, *J*=8.5 Hz, H–C(4)), 7.45 (*d*, *J*=1.5 Hz, H–C(7)), 7.29 (*dd*, *J*=8.5, 1.5 Hz, H–C(5)), and 8.36 (br. *s*, NH). These signals, as well as the corresponding coupling constants, suggested the presence of a benzene ring with an *ABX* spin system. A comparison with the spectroscopic data of **1** and those of the known compound **7** indicated that **3** was either 2,3,5- or 2,3,6-tribromoindole. A strong HMBC correlation (*Fig. 1*) between the H–C(4) (δ(H) 7.35) and C(3) (δ(C) 94.7) suggested that one Br-atom was bonded to

C(6). The other HMBC correlations from H–C(4) to C(6) and C(7a), from H–C(5) to C(7) and C(3a), and from H–C(7) to C(5), C(6) and C(3a) confirmed that the structure of compound **3** corresponds to 2,3,6-tribromo-1*H*-indole.

Compound **4** was obtained as colorless crystals. The IR spectrum indicated the presence of OH (3476) and C=O (1702 cm^{-1}) groups. The molecular formula of **4** was determined as $C_{15}H_{24}O_2$, on the basis of positive HR-FAB-MS (*m/z* 259.1682 ($[M+Na]^+$, $C_{15}H_{24}NaO_2^+$; calc. 259.1673)). However, the ^{13}C-NMR (DEPT) spectrum, recorded in $CDCl_3$, revealed only 14 signals, corresponding to four Me, four CH_2, and three CH groups, as well as three quaternary C-atoms (*Table 2*). This was due to the fact that the signal of an additional, oxygenated quaternary C-atom was masked by the solvent signals ($CDCl_3$), as confirmed by recording the spectrum in CD_3OD (*Table 2*), where, indeed, an additional signal was observed at δ(C) 77.7.

The ^1H-NMR signals of **4** (*Table 2*) could be unequivocally assigned by HMQC experiments, which indicated the presence of an OH group at δ(H) 2.09 (br. *s*, 1 H), four Me groups at δ(H) 1.05 (*s*), 1.06 (*s*), 1.20 (*s*), and 0.94 (*d*), four CH_2 moieties in the range δ(H) 1.16–3.09, and three CH groups at δ(H) 0.80–1.51. The $^1H,^1H$-COSY correlations from CH_2(1) to CH_2(2), from CH_2(2) to CH_2(3), from CH_2(3) to H–C(4), and from H–C(4) to Me(14) clearly indicated a CH_2–CH_2–CH_2–CH–Me moiety in **4**. The second structural sequence, CH–CH–CH_2, was indicated by $^1H,^1H$-COSY correlations from H–C(6) to H–C(7), and from H–C(7) to CH_2(8). The observed key HMBC correlations (*Fig. 2*) between H–C(1) and both C(9) and C(10), between Me(14) and C(3), C(4), and C(5), between Me(15) and C(4), C(5), C(6), and C(10), and between H–C(7) and C(9) allowed us to connect the above two structural subunits. Furthermore, additional HMBC correlations between Me(12) and C(6), C(7), C(11), and C(13), and between Me(13) and C(6), C(7), C(11), and C(12), respectively, provided the planar structure of **4**.

The relative configuration of **4** was determined by a NOESY experiment and by analysis of coupling constants. In the NOESY spectrum, both Me H-atoms, Me(14) and Me(15), showed NOESY correlations with one H-atom of CH_2(1) (δ(H) 1.90–1.93), which suggested that the two Me groups were on the same side of the molecular plane. NOESY Correlation between H–C(6) and Me(15) further indicated that H–C(6) had the same orientation as Me(15). The coupling constant between H–C(6) and H–C(7) (J = 9.1 Hz) suggested a *cis* orientation [10][11], as also confirmed by an NOE. The 10-OH group should be *trans* relative to Me(14) and Me(15), since no NOE cross-peak was observed between them. Thus, based on the above evidence, the structure of compound **4** was established as (10β)-10-hydroxyaristolan-9-one.



4 **5**

Fig. 2. *Selected HMBC correlations for* **4** *and* **5**

Table 2. *^{1}H- and ^{13}C-NMR Data of* **4** *and* **5**. At 500 and 125 MHz, resp., in $CDCl_3$ (unless noted otherwise). Assignments were corroborated by ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments.

Position	**4**			**5**	
	δ(H)	δ(C)	δ(C)[a]	δ(H)	δ(C)
1	1.35–1.42 (*m*), 1.90–1.93 (*m*)	29.5 (*t*) –	30.8 (*t*)	– –	209.9 (*s*)
2	1.53–1.59 (*m*), 1.60–1.70 (*m*)	22.8 (*t*) –	24.1 (*t*)	2.29–2.42 (*m*) –	40.5 (*t*)
3	1.16–1.25 (*m*), 1.31–1.35 (*m*)	29.1 (*t*) –	30.3 (*t*)	1.65–1.73 (*m*), 1.90–1.98 (*m*)	31.4 (*t*)
4	1.43–1.51 (*m*)	34.8 (*d*)	36.3 (*d*)	1.92–2.00 (*m*)	40.1 (*d*)
5	–	46.8 (*s*)	48.0 (*s*)	–	39.1 (*s*)
6	0.80 (*d*, *J* = 9.1)	29.0 (*d*)	31.0 (*d*)	0.78 (*d*, *J* = 8.5)	35.1 (*d*)
7	1.32–1.33 (*m*)	22.9 (*d*)	24.8 (*d*)	1.23 (*dd*, *J* = 8.5, 5.6)	24.7 (*d*)
8	2.26 (*d*, *J* = 17.0), 3.09 (*dd*, *J* = 17.0, 9.0)	34.5 (*t*)	35.7 (*t*)	6.00–6.04 (*m*)	127.3 (*d*)
9	–	215.9 (*s*)	219.7 (*s*)	5.86 (*dd*, *J* = 10.1, 1.9)	118.8 (*d*)
10	–	n.d.[b])	77.7 (*s*)	2.58 (br. *s*)	54.7 (*d*)
11	–	21.0 (*s*)	21.6 (*s*)		26.1 (*s*)
12	1.05 (*s*)	16.8 (*q*)	17.3 (*q*)	1.01 (*s*)	16.0 (*q*)
13	1.06 (*s*)	30.6 (*q*)	31.0 (*q*)	1.16 (*s*)	30.5 (*q*)
14	0.94 (*d*, *J* = 6.7)	17.0 (*q*)	17.5 (*q*)	1.05 (*d*, *J* = 6.6)	15.5 (*q*)
15	1.20 (*s*)	18.4 (*q*)	18.8 (*q*)	0.56 (*s*)	15.9 (*q*)
OH	2.09 (br. *s*)	–	–		

[a]) In CD_3OD. [b]) Not detected due to solvent overlap.

Compound **5** was obtained as a colorless oil. Its IR spectrum indicated the presence of C=O (1720) and C=C (1631 cm^{-1}) functions, and the molecular formula was determined as $C_{15}H_{22}O$ by positive HR-FAB-MS (*m*/*z* 241.1564 ($[M+Na]^+$, $C_{15}H_{22}NaO^+$; calc. 241.1568)). The ^{13}C-NMR (DEPT) spectrum of **5** (*Table 2*) showed the presence of 15 C-atoms, corresponding to four Me, two CH_2, and six CH groups, as well as three quaternary C-atoms. The ^{1}H,^{1}H-COSY correlations from CH_2(2) to CH_2(3), from CH_2(3) to H–C(4), and from H–C(4) to Me(14) indicated a spin systems comprising a CH_2–CH_2–CH–Me unit. A second system was derived from correlations from H–C(6) to H–C(7), from H–C(7) to H–C(8), from H–C(8) to H–C(9), and from H–C(9) to H–C(10), in accord with the presence of a CH–CH–CH=CH–CH moiety. The HMBC correlations (*Fig. 2*) between CH_2(2) and C(1) and C(10), between H–C(9) and C(1), between Me(14) and C(3), C(4), and C(5), and between Me(15) and C(4), C(5), C(6), and C(10), respectively, established the connectivity of the above two sequences at C(1) and C(5). Additional HMBC correlations between Me(12) and C(6), C(7), C(11), and C(13), as well as between Me(13) and C(6), C(7), C(11), and C(12), allowed the establishment of the planar structure of **5**.

Based on biogenetic considerations, in combination with analysis of coupling constants and COSY experiments, the configurations at C(4), C(5), C(6), and C(7) of **5** were established to be identical with those in **4**. The coupling constant between H–C(6) and H–C(7) (*J* = 8.5 Hz) agreed with a *cis* orientation of H–C(6) and H–C(7)

[10][11]. The ^{1}H,^{1}H-COSY cross-peak between H–C(10) and Me(15) indicated a long-range *W*-type coupling, which suggested that H–C(10) and Me(15) were *trans*-oriented [12]. Notably, compound **5** differs from the known compound aristol-9-en-1-one only in the position of the C=C bond [7]. Thus, from the above data, the structure of **5** was determined as aristol-8-en-1-one.

Compound **6**, a colorless oil, was identified as aristol-9-en-1-one. Interestingly, this compound had been previously obtained synthetically by oxygenation of (1α)-aristol-9-en-1-ol with CrO_3, or by photooxygenation of calarene [7][8]. Our report shows for the first time that **6** is also a natural product.

Previous investigation toward the metabolites of the marine red alga species *L. similis* was less than other species, such as *L. obtusa*, *L. majuscula*, *L. nipponica*, and *L. okamurai*, within the genus *Laurencia*. To the best of our knowledge, only two species from this genus, *i.e.*, *L. similis* and *L. brongniartii*, have been reported to contain polybrominated indole metabolites. These may be produced *via* similar biogenetical pathways, indicating a close affinity between *L. similis* and *L. brongniartii*. Our results are unusual in the sense that both halogenated indole alkaloids and sesquiterpenes are co-occurring in *L. similis*, aristolane-type sesquiterpenes without halogen substitution being peculiar in the metabolites of the genus *Laurencia*.

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Experimental Part

General. Column chromatography (CC): silica gel (200–300 and 300–400 mesh; *Qingdao Haiyang Chemical Group, Co.*) or *Sephadex LH-20* (*Sigma*). TLC: precoated silica-gel plates *GF-254* (*Qingdao Haiyang*). Optical rotation: *Atago Polax-L* polarimeter. UV/VIS Spectra: *Beckman DU-640* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet Nexus-470* spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker Avance-500* spectrometer; at 500/125 MHz, resp.; δ in ppm, *J* in Hz. Low- and high-resolution FAB-MS: *VG Autospec-3000* mass spectrometer; in *m*/*z*.

Algal Material. The red alga *L. similis* was collected off the coast of Hainan island, P. R. China, in March 2006, and identified by Prof. *Lan-Ping Ding*, Institute of Oceanology, Chinese Academy of Sciences (IOCAS). A voucher specimen (06M04) was deposited at the Key Laboratory of Experimental Marine Biology of IOCAS.

Extraction and Isolation. The dried and powdered alga *L. similis* (487 g) was extracted with $CHCl_3$/MeOH 1:1. After solvent removal, the residue was further extracted with 95% aq. EtOH. The concentrated extracts were combined and partitioned between H_2O and AcOEt. The AcOEt-soluble fraction was purified by CC (SiO_2; petroleum ether (PE)/AcOEt gradient) to afford nine fractions: *Fr. I–Fr. IX*. *Fr. I* (eluted with PE) was further purified by prep. TLC (cyclohexane) to afford **7** (56.8 mg), and a mixture of **11** and **12** (31.7 mg). *Fr. II* (eluted with PE/AcOEt 100:1) was purified by prep. TLC (PE/AcOEt 100:1) to afford **2** (8.0 mg). *Fr. III* (eluted with PE/AcOEt 50:1) was further separated by CC (SiO_2 and *Sephadex LH-20*; $CHCl_3$/MeOH 1:1) followed by prep. TLC to afford **1** (8.8 mg), **3** (15.0 mg), **5** (29.8 mg), **6** (5.0 mg), **8** (56.0 mg), **9** (3.0 mg), **10** (103.8 mg), and **13** (8.7 mg). *Fr. VI* (eluted with PE/AcOEt 10:1) was further separated by CC (SiO_2 and *Sephadex LH-20*; $CHCl_3$/MeOH 1:1) followed by prep. TLC to afford **4** (6.5 mg).

*3,5,6-Tribromo-1*H-*indole* (**1**). Colorless crystals. M.p. 123–124°. UV ($CHCl_3$): 218 (5.15), 241 (4.64). IR (KBr): 3452, 1641, 1613, 1447, 1411, 1262, 1094, 1019, 799. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 357 (31)/355 (94)/353 (100)/351 (38) (M^+); 276 (29)/274 (58)/272 (33); 195 (44)/193 (47); 114 (33). HR-FAB-MS (pos.): 353.7954 ($[M+H]^+$, $C_8H_5{}^{81}Br^{79}Br_2N^+$; calc. 353.7952).

*3,5,6-Tribromo-1-methyl-1*H-*indole* (**2**). Colorless crystals. M.p. 166–168°. UV ($CHCl_3$): 218 (5.17), 240 (4.51). IR (KBr): 1649, 1607, 1512, 1462, 1417, 1259, 1122, 1082, 802. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 371 (31)/369 (95)/367 (100)/365 (37) (M^+); 356 (2)/354 (6)/352(6)/350 (2) ($[M-Me]^+$); 290 (10)/288 (21)/286 (11); 209 (41)/207 (44); 128 (46). HR-FAB-MS (pos.): 367.8095 ($[M+H]^+$, $C_9H_7{}^{81}Br^{79}Br_2N^+$; calc. 367.8108).

*2,3,6-Tribromo-1*H-*indole* (**3**). Colorless crystals. M.p. 105–107°. UV ($CHCl_3$): 216 (5.15), 240 (4.44). IR (KBr): 3380, 1701, 1611, 1503, 1435, 1220, 1048, 809. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 357 (30)/355 (92)/353 (100)/351 (34) (M^+); 276 (23)/274 (47)/272 (25); 195 (17)/193 (17); 114 (34). HR-FAB-MS (pos.): 353.7934 ($[M+H]^+$, $C_8H_5{}^{81}Br^{79}Br_2N^+$; calc. 353.7952).

(10β)-10-Hydroxyaristolan-9-one (**4**). Colorless crystals. M.p. 94–96°. $[\alpha]_D^{26} = +11.4$ ($c = 0.25$, $CHCl_3$). UV ($CHCl_3$): 210 (4.98), 239 (4.14). IR (KBr): 3476, 2959, 2936, 1702, 1091, 1014. ^{1}H- and ^{13}C-NMR: see *Table 2*. FAB-MS (pos.): 236 (M^+), 219 ($[M-H_2O+1]^+$). HR-FAB-MS (pos.): 259.1682 ($[M+Na]^+$, $C_{15}H_{24}NaO_2^+$; calc. 259.1673).

Aristol-8-en-1-one (**5**). Colorless oil. UV ($CHCl_3$): 212 (4.94), 240 (4.13). $[\alpha]_D^{26} = +46.0$ ($c = 1.07$, $CHCl_3$). IR (KBr): 2962, 2873, 1720, 1631, 1263, 1081, 1018. ^{1}H- and ^{13}C-NMR: see *Table 2*. FAB-MS (pos.): 218 (M^+), 175. HR-FAB-MS (pos.): 241.1564 ($[M+Na]^+$, $C_{15}H_{22}NaO^+$; calc. 241.1568).

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