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Conoliferine and isoconoliferine, structurally novel alkaloid-lignan conjugates from *Tabernaemontana corymbosa*

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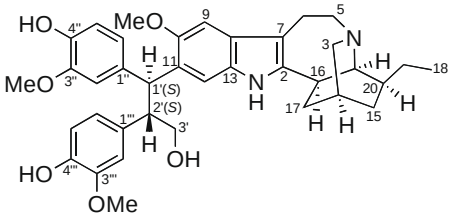
ABSTRACT

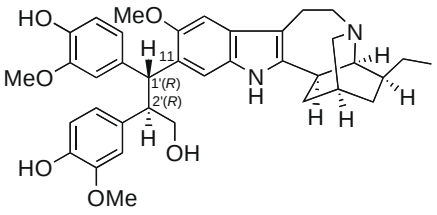
Conoliferine and isoconoliferine were isolated from *Tabernaemontana corymbosa* as an unresolvable mixture of (1′*S*, 2′*S*)- and (1′*R*, 2′*R*)-diastereomers. These novel natural products are constituted from the union of an iboga alkaloid, ibogaine, and a lignan moiety, and represent the first instance of such an alkaloid-lignan conjugate. The structure was determined by spectroscopic methods, including the extensive use of NOE experiments for assignment of stereochemistry.

Plants of the genus *Tabernaemontana* are rich sources of structurally novel, as well as biologically active, indole and bisindole alkaloids.[1–4] In recent years a number of alkaloids of unusual structures have been reported from plants of this genus. The Malayan *T. corymbosa* for instance has provided several new alkaloids that are characterized by novel molecular skeletons such as the hexacyclic alkaloid, tronoharine,[5] the pentacyclic indole, tronocarpine[6] and the indole-derived quinolinic alkaloid, voastrictine.[7] The same plant also yielded a number of new indole and bisindole alkaloids,[8–17] including several vobasinyl-iboga bisindoles, which reverse multidrug-resistance in vincristine-resistant KB cells.[8] We recently reported the structure of conolutinine, a hexacyclic indole characterized by a novel ring system incorporating a diazaspirocenter and fused oxadiazepine-tetrahydrofuran rings, which was isolated from a different sample of *T. corymbosa*.[18] We now report the isolation of conoliferine (**1a**) and isoconoliferine (**1b**), the first examples of alkaloid-lignan conjugates, which were isolated from the stem bark extract of the same plant.

The conoliferines (**1a** and **1b**) were obtained as a mixture of the 1′(*S*), 2′(*S*)- and 1′(*R*), 2′(*R*)-diastereomers, which was intractable to further resolution by chromatography. This was revealed by the ^{1}H NMR spectrum which showed the presence of an approximately 1:1 mixture of the two diastereomers (Table 1). The UV spectrum showed absorption maxima characteristic of an indole chromophore (229, 287, and 301 nm) but with an additional band at 208 nm, due possibly to the presence of additional phenolic moieties. The IR spectrum showed bands due to OH (3534 cm^{-1}) and NH (3414 cm^{-1}) functions. The EI mass spectrum did not show the expected molecular ion at *m*/*z* 612. Instead, the highest mass fragment ion was detected at *m*/*z* 445 ($C_{28}H_{33}N_2O_3$, base peak), which corresponds to loss of a $C_9H_{11}O_3$ fragment. When the mass spectrum was obtained using LSIMS, the MH$^+$ peak was observed at *m*/*z* 613, which was analyzed for $C_{37}H_{44}N_2O_6$ + H, requiring 17 degrees of unsaturation.[19] The fragment peak observed at *m*/*z* 445 in EIMS was also detected in LSIMS as an intense peak (54%).



1a



1b

The presence of a diastereomeric mixture was not easily noticeable at first due to extensive overlap (complete coincidence) of most of the signals for both the diastereomers in the ^{1}H and ^{13}C

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Table 1
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data of conoliferine (**1a**) and isoconoliferine (**1b**) in $CDCl_3$[a]

Position	1a		1b	
	δ_C	δ_H	δ_C	δ_H
2	141.7	—	141.7	—
3a	49.42[b]	3.00 (m)	49.45[b]	3.00 (m)
3b		3.00 (m)	—	3.00 (m)
5a	53.83[c]	3.05 (m)	53.92[c]	3.05 (m)
5b		3.31 (m)		3.31 (m)
6a	20.04[d]	2.48 (m)	20.09[d]	2.48 (m)
6b		3.20 (m)		3.20 (m)
7	107.4	—	107.4	—
8	129.11[e]	—	129.22[e]	—
9	98.5	6.71 (s)	98.5	6.71 (s)
10	151.0	—	151.0	—
11	126.56[f]	—	126.67[f]	—
12	109.43[g]	7.04 (s)[q]	109.57[g]	7.05 (s)[q]
13	126.9		126.9	
14	25.8	1.79 (m)	25.8	1.79 (m)
15a	31.4	1.16 (m)	31.4	1.16 (m)
15b		1.76 (m)		1.76 (m)
16	40.2	2.80 (m)	40.2	2.80 (m)
17a	33.7	1.51 (m)	33.7	1.51 (m)
17b		1.96 (m)		1.96 (m)
18	11.5	0.86 (t, 7 Hz)	11.5	0.86 (t, 7 Hz)
19a	27.19[h]	1.45 (m)	27.24[h]	1.45 (m)
19b		1.57 (m)		1.57 (m)
20	41.3	1.51 (m)	41.3	1.51 (m)
21	57.21[i]	2.78 (br s)	57.26[i]	2.78 (br s)
10-OMe	55.71[j]	3.789 (s)	55.74[j]	3.793 (s)
NH	—	7.41 (br s)	—	7.41 (br s)
1′	44.0	4.86 (d, 11.5 Hz)[r]	44.0	4.89 (d, 11.5 Hz)[r]
2′	50.85[k]	3.65 (m)	50.95[k]	3.65 (m)
3′a	66.1	3.60 (m)	66.1	3.60 (m)
3′b		3.68 (m)		3.68 (m)
1″	135.8	—	135.8	—
2″	111.5	6.96 (d, 2 Hz)[s]	111.5	6.97 (d, 2 Hz)[s]
3″	146.40[l,w]	—	146.42[l,w]	—
4″	143.61[x]	—	143.61[x]	—
5″	114.38[m]	6.74 (m)	114.44[m]	6.74 (m)
6″	120.03[n]	6.93 dd (dd, 8, 2 Hz)	120.12[n]	6.93 (dd, 8, 2 Hz)
3″-OMe	55.2[y]	3.74 (s)[z]	55.2[y]	3.74 (s)[z]
1‴	133.2	—	133.2	—
2‴	111.19[o]	6.77 (d, 2 Hz)[t]	111.24[o]	6.79 (d, 2 Hz)[t]
3‴	146.48[w]	—	146.48[w]	—
4‴	143.69[x]	—	143.69[x]	—
5‴	114.21[p]	6.68 (d, 8 Hz)[u]	114.24[p]	6.70 (d, 8 Hz)[u]
6‴	121.09	6.73 (m)	121.09	6.73 (m)
3‴-OMe	55.4[y]	3.84 (s)[v,z]	55.4[y]	3.85 (s)[v,z]

[a] Assignments based on COSY, HMQC, and HMBC.
[b–v] Assignments (across rows) are interchangeable.
[w–z] Assignments (down columns) are interchangeable.

NMR spectra (Table 1). In addition, signals that were not completely coincident showed very similar chemical shifts (average $\Delta\nu$ for all paired ^{1}H and ^{13}C signals is 0.01 and 0.07 ppm, respectively) and were therefore not distinguishable. When variable temperature NMR studies were carried out (^{1}H NMR, benzene-d_6, rt to 70 °C; toluene-d_8, rt to 100 °C), the ^{1}H NMR spectrum was essentially unchanged without any signs of coalescence at the higher temperatures applied. The ^{13}C NMR data accounted for 37 carbon resonances (22 are coincident and 15 appeared as paired signals), of which 20 showed a close correspondence to those of ibogaine (**2**). The ^{1}H NMR data also showed a striking similarity with those of ibogaine except for the presence of some additional signals in the aromatic as well as in the deshielded up-field regions. The absence of the doublet signal due to H(11) and the appearance of H(12) as a singlet instead of a doublet were also noted when the ^{1}H NMR data of **1** were compared with those of ibogaine (**2**), suggesting that the ibogaine unit is substituted at C(11).

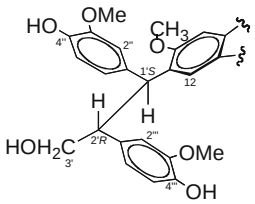
Subtraction of the ibogaine unit from the molecular formula of **1** revealed that the ibogaine unit is substituted at C(11) with a $C_{17}H_{19}O_5$ fragment. Examination of the ^{1}H and ^{13}C NMR spectra with the aid of COSY and HMQC data showed that this $C_{17}H_{19}O_5$ fragment is made up of six aromatic methines, two aromatic quaternary carbons, four oxygenated aromatic carbons, two sp^3 methines, an oxygenated sp^3 methylene, two aromatic OMe groups, and two OH groups. The presence of the 12 aromatic carbons suggested the presence of two highly oxygenated aromatic rings, bearing two OMe and two OH groups.

In addition to the partial structures usually present in ibogaine, the COSY data showed two sets of aromatic AB doublets (*ortho* coupling) and two sets of one-H aromatic doublets (*meta* coupling), suggesting the presence of two phenyl rings with disubstitution at the *meta* and *para* positions. In addition, the HMBC data (Fig. 1) revealed that the two phenyl rings correspond to two identical 4-hydroxy-3-methoxyphenyl units. The COSY, HMQC, and HMBC data also disclosed the $CHCHCH_2OH$ partial structure, which corresponds to the C(1′)–C(2′)–C(3′) fragment. The attachment from C(1′) of the $CHCHCH_2OH$ fragment to the indole C(11) was indicated by the observed three-bond correlations from H(1′) to C(10) and C(12) as well as a two-bond correlation from H(1′) to C(11) in the HMBC spectrum. On the other hand, three-bond correlations from H(2″) and H(6″) to C(1′) and a two-bond correlation from H(1′) to C(1″) allowed connection of one of the two phenolic rings to C(1′), while three-bond correlations from H(2‴) and H(6‴) to C(2′) as well as from H(3′) to C(1‴) indicated connection of the other phenolic ring to C(2′). The $C_{17}H_{19}O_5$ fragment linked to the ibogaine unit at C(11) is therefore 1,2-bis-(4-hydroxy-3-methoxyphenyl)-3-hydroxypropyl, a moiety present in a number of naturally occurring lignans.[20–27]

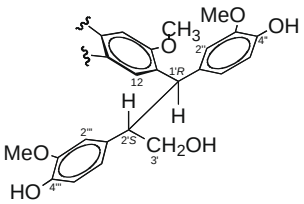
The structure is also consistent with the observed mass spectral fragments. The *m*/*z* 445 and 309 peaks can now be attributed to fragments arising from scission of the C(1′)–C(2′) and C(1′)–C(11) bonds, respectively. A search of the literature revealed that the 1,2-bis-(4-hydroxy-3-methoxyphenyl)-3-hydroxypropyl moiety in lignans is usually linked at C(1′) to OH,[20–24] OMe,[25] OCH_2CH_3[26], or *O*-monosaccharide[27] groups. In the case of **1**, this lignan moiety is for the first time substituted at C(1′) with a monoterpene indole alkaloid via a carbon–carbon bond.

The large coupling constant observed between H(1′) and H(2′) (^3J = 11.5 Hz) indicated that the preferred conformation adopted about the C(1′) and C(2′) bond is one that places the two vicinal hydrogens at C(1′) and C(2′) *anti* to one another. This may be due to the presence of a phenolic and an ibogaine moiety at C(1′) and another phenolic unit at C(2′), which apparently results in steric hindrance to free rotation about the C(1′)–C(2′) bond.

This was further supported by the NOEs observed between H(1′)/H(3′), H(2‴), H(6‴), H(2′)/H(2″), H(6″), and by the absence of an NOE between H(1′)/H(2′), observations that require both H(1′) and H(2′) to be disposed *anti* with respect to each other (Fig. 1). A key NOE is that observed between H(3′) and H(12) which indicated that the indole moiety and the CH_2OH unit must be on the same side with respect to the C(1′)–C(2′) bond, which is consistent with structures **1a** and **1b**, but which rules out the alternative stereoisomers, **1c** and **1d**. The observation of the H(1′)/H(12) NOE in addition to the H(3′)/H(12) NOE (Fig. 1) suggested that free rotation about the C(1′)–C(11) bond may also be restricted.



1c 1′(*S*), 2′(*R*)



1d 1′(*R*), 2′(*S*)

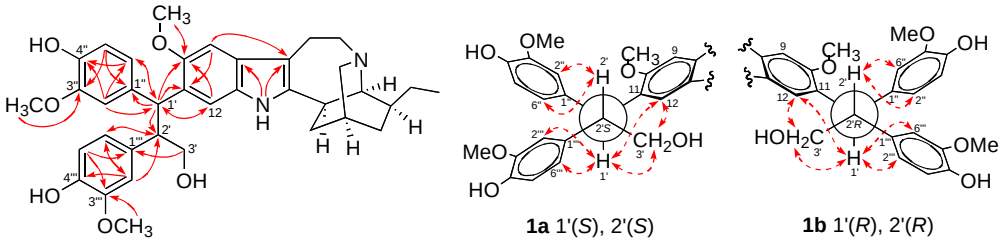
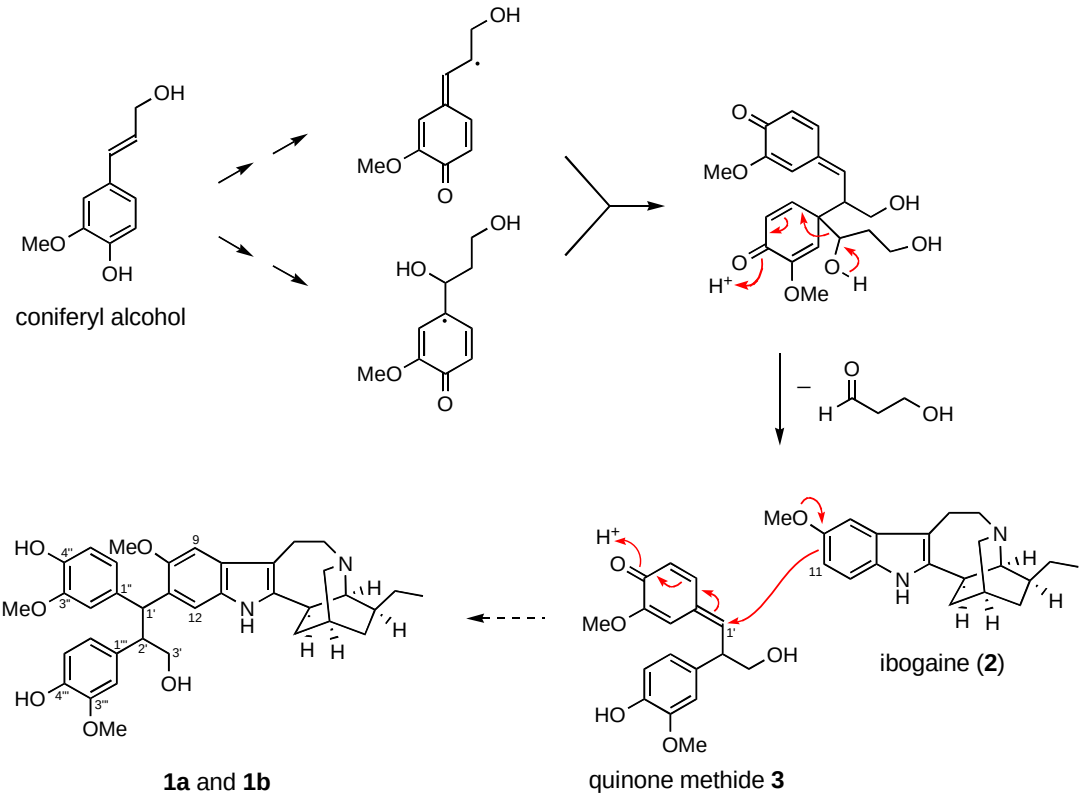


Figure 1. Selected HMBCs and NOEs of **1** (= HMBC; = NOE).



Scheme 1. A possible pathway to **1**.

These observations therefore allow the configurations at C(1′) and C(2′) to be assigned as either 1′(*S*), 2′(*S*) or 1′(*R*), 2′(*R*), since the 1′(*S*), 2′(*R*) and 1′(*R*), 2′(*S*) diastereomers are ruled out by the observed H(3′)/H(12) NOE. The iboga-lignan conjugate isolated is therefore constituted from a non-resolvable, approximately equimolar mixture of the diastereomers **1a** and **1b**, and represents the first example of a monoterpene indole alkaloid linked to a lignan.

A possible pathway to **1** is shown in Scheme 1 involving nucleophilic attack on the quinone methide **3** (in turn derived from phenolic oxidative coupling of two units of coniferyl alcohol followed by expulsion of a molecule of 3-hydroxypropanal[22]) by the activated C(11) of the ibogaine indole ring.

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