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A SESQUITERPENE DIMER FROM *XYLOPIA AROMATICA*

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Key Word Index—*Xylopia aromatica*; Annonaceae; sesquiterpene dimer.

Abstract—A new guaiane dimer has been isolated from the leaves of *Xylopia aromatica*. The natural product, whose IUPAC name is [11α,12β,13α,21β]-7-hydroxy-16-oxo-17-isopropylidene-1α,5,5,9β,14α,20-hexamethyl-6-oxaheptacyclo[10.9.1.$0^{2,10}$.$0^{4,7}$.$0^{12,21}$.$0^{13,19}$]docosa-2(10),3,19-triene, seems to have been formed by cycloaddition of two cyclopentadiene precursors, and contains an unusual hemiacetal oxetane ring. The structure was elucidated mainly by 1D and 2D NMR techniques; NOESY spectra were instrumental in the determination of stereochemistry.

INTRODUCTION

We have been interested for several years in the genus *Xylopia*, and in particular *X. aromatica*, which contains several different classes of natural products, including alkaloids, acetogenins, and diterpenes [1–6]. We have recently reported on the isolation of labdane dimers from the bark of this plant [7], and in the present paper, we report on the structure elucidation of an unusual guaiane dimer from its leaves.

RESULTS

The natural product gave 30 lines in the ^{13}C NMR spectrum; this, together with the presence of several methyl signals in the ^{1}H NMR spectrum, suggested a triterpene or a sesquiterpene dimer. The structure was determined primarily by the use of NMR spectroscopy, and in the following we give a schematic account of the steps taken and the type of information obtained. Firstly, proton signals were observed in the 1D spectrum at 600 MHz and their connectivity established by a COSY experiment. This process was greatly helped by the 1D ^{13}C spectrum, together with a one-bond correlation map (using the HMQC technique) which indicates which two hydrogens belong to the same methylene group. Thus we could identify two chains of protonated carbons: the first extending from C-9 through C-10 and C-1 up to C-3, and the second including C-9′, C-10′ and C-15′. Several singlets (methyl groups, the olefinic methine) and an isolated methylene, C-6, were also present. An unusual feature of the molecule was the 3′ methylene, with very shielded protons, a quite deshielded carbon, and an unusual geminal coupling constant ($^{2}J_{HH} = 8$ Hz). This seemed to indicate a strained CH_2 group, with a relative large HCH angle.

In a second step, these molecular fragments were associated with non-protonated carbons through an HMBC experiment. Thus these carbons could be located adjacent to the previously identified sequences, and the fragments "glued" together. Confirmation for the planar structure of **1** was provided by long-range HH correlations, identified in the COSY spectrum.

The last step involved the determination of the relative stereochemistry. For this, a crucial source of information was the detection of the through-space interactions observed in NOESY spectra. In order to resolve potential ambiguities with proton signals with similar chemical shifts, ^{1}H spectra (1D, COSY and NOESY) were also performed for a C_6D_6 solution (Table 2). The results shown in **1** were determined as follows:

1. Both H-2 and H-3 have NOE interactions with one of the protons on the bridge methylene, H-3′b. This indicates that they are both on the *exo* (we will assume this to be the β) side of the norbornene moiety. The coupling constant between these two methines is 8.5 Hz, in agreement with a *cis* relationship [8]. Also, the chemical shift of C-3, δ 55.89, is similar to that of the bridge methylene in 1-methylnorbornene (55.0 ppm), showing the

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Table 1. ^{13}C NMR data*

C	δ_C	^{13}C–^1H correlations One bond	Long-range
1	57.81	1.80	3.23 (6β), 2.72 (9α), 2.19 (9β), 1.07 (15)
2	51.82	2.35	1.33 (3′a)
3	61.26	2.74	1.43 (14), 1.33 (3′a), 1.40 (14′)
4	136.22†		2.74 (3), 3.23 (6β), 1.43 (14)
5	137.74†		2.60 (6α), 3.23 (6β), 1.43 (14)
6	28.25	3.23, 2.60	
7	133.11		3.23 (6β), 2.19 (9β), 1.84 (12), 1.96 (13)
8	205.88		3.23 (6β), 2.72 (9α), 2.19 (9β), 1.84 (12), 1.96 (13)
9	50.74	2.72, 2.19	1.07 (15)
10	41.28	1.38	2.72 (9α), 2.19 (9β), 1.43 (14), 1.07 (15)
11	140.50		3.23 (6β), 1.84 (12), 1.96 (13)
12	22.56	1.84	
13	22.97	1.96	
14	13.75	1.43	
15	21.92	1.07	2.19 (9β)
1′	132.31		2.84 (2′), 1.26 (3′b and/or 15′), 2.75 (10′), 1.40 (14′)
2′	48.13	2.84	1.33 (3′a), 1.26 (3′b)
3′	55.89	1.33, 1.26	1.40 (14′)
4′	55.13		1.33 (3′a), 1.26 (3′b), 5.57 (6′), 1.40 (14′)
5′	150.98		1.26 (3′b), 5.57 (6′), 2.10 (9′α), 1.69 (9′β), 2.75 (10′)
6′	112.61	5.57	
7′	153.40		5.57 (6′), 2.10 (9′α), 1.69 (9′β), 1.44, 1.41 (12′, 13′)
8′	103.18		5.57 (6′), 2.10 (9′α), 1.69 (9′β), 1.26 (15′)
9′	38.93	2.10, 1.69	2.75 (10′), 1.26 (15′)
10′	33.46	2.75	2.10 (9′α), 1.69 (9′β), 1.26 (15′)
11′	85.17		5.57 (6′), 1.44, 1.41 (12′, 13′)
12′	24.76‡	1.44	1.41 (13′)
13′	27.50‡	1.41	1.44 (12′)
14′	18.31	1.40	
15′	19.03	1.26	2.10 (9′α), 1.69 (9′β), 2.75 (10′)

* In $CDCl_3$.
† ‡ May be interchanged.

absence of the γ-effect that *exo*-substituents would introduce [9].

2. $^3J_{1,2} = 3.5$ Hz, suggesting a *trans* relationship between these protons. This is confirmed by the presence of a NOE interaction between H-1 and H-10′, which is only possible if both are pointing towards the *endo* (α) face of the molecule.
3. $^3J_{1,10} = 10$ and $^3J_{9\alpha,10} = 11.5$ Hz; the NOE cross-peak is weak for the former pair of protons and undetectable for the latter. This suggests that both are in a *ca trans*-diaxial relationship. This is confirmed by the NOE interactions between 1, 6α and 9α, indicating all three are on the same (α) face of the molecule, and that they are all pseudo-axial. Conversely, the NOE sequence 12-6β-14 shows that 6β is pseudoequatorial, roughly in the plane of the 7–11 and 4–5 double bonds. 6β and 9β are deshielded by more than 0.5 ppm relative to their α counterparts, as expected for protons approximately coplanar with the adjacent sp^2 systems.
4. Turning to the "primed" half of the molecule, we have already shown that H-10′ is on the α side; $^3J_{9',10'}$ values and NOE interactions then establish the identity of the 9′-hydrogens. We cannot determine with any certainty the stereochemistry at the 8′ centre. Since this unusual oxetane-ring hemiacetal is potentially in equilibrium with its epimer, we would only suggest that the OH is more likely to be located on the more crowded *endo* (α) side.

While we have used a guaiane numbering system for **1** in the Tables, the IUPAC name for the natural product is [11α,12β,13α,21β]-7-hydroxy-16-oxo-17-isopropylidene-1α,5,5,9β,14α,20-hexamethyl-6-oxaheptacyclo[10.9.1.$0^{2,10}$.$0^{4,7}$.$0^{12,21}$.$0^{13,19}$]docosa-2(10),3,19-triene.

DISCUSSION

Natural product **1** is the expected product of cycloaddition of cyclopentadienes **2** and **3**, in which the proximal ketone and alcohol functions have further closed to an unusual oxetane hemiacetal (interestingly, the two largest fragments in the mass spectrum of **1** result from the loss of a hydrogen from each of the two monomers, respectively). The latter two

Table 2. ^{1}H NMR data

H	δ_H*	δ_H†	multiplicity‡§	NOE correlations
1	1.80	1.77	*bd*, 10(10)	2, 3, 6α, 9α, 10, 15, 2′, 10′
2	2.35	2.17	*ddd*, 8.5, 4.5, 3.5	1, 3, 10, 15, 2′, 3′b
3	2.74	2.57	*dd*, 8.5, 2.5(10)	1, 2, 14, 3′b, 12′, 13′
6α	2.60	2.63	*bd*, 15	1, 6β, 9α
6β	3.23	3.26	*d*, 15	6α, 12, 14
9α	2.72	2.63	*t*, 11.5	1, 6α, 9β, 15
9β	2.19	2.36	*dd*, 11.5, 2	2, 9α,10, 15
10	1.38	1.49	*m*	1, 2, 9β, 15
12	1.84	1.66	*d*, 1.5(6a)	6β, 13, 14
13	1.96	2.11	*d*, 2(6b)	12
14	1.43	1.44	*t*, 1(1, 3)	3, 6β, 12
15	1.07	0.93	*d*, 6.5	1, 2, 9α, 9β, 10, 2′
2′	2.84	2.64	*ddd*, 4.5, 2, 1.5	1, 2, 15, 3′a, 3′b, 15′
3′a‖	1.33	1.25	*dd*, 8, 2	2′, 3′b, 13′
3′b‖	1.26	1.06	*dd*, 8, 1.5	2, 3, 2′, 3′a
6′	5.57	5.43	*s*	12′, 13′
9′α	2.10	2.07	*dd*, 13.5, 5.5	9′β, 10′, 15′
9′β	1.69	1.68	*dd*, 13.5, 13	9′α, 15′
10′	2.75	2.68	*dqd*, 13, 7, 5.5	1, 9′α, 15′
12′	1.44¶	1.28¶	*s*	3, 6′
13′	1.41¶	1.27¶	*s*	3, 6′
14′	1.40	1.35	*s*	6′
15′	1.26	1.03	*d*, 7	2′, 9′α, 9′β, 10′

* In $CDCl_3$.

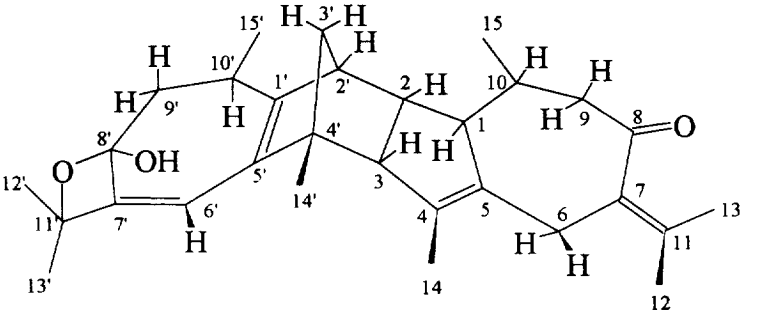
† In C_6D_6.

‡ The coupling partner has been specified, in parenthesis, where not obvious.

§ Small coupling interactions (<0.5 Hz) are deduced from the COSY spectrum, for the following proton pairs: 9α, 14; 3,6′; 3,2′; 2′,6′; 3′a,14′; 3′b,14′.

‖ 3′a and 3′b are *syn* to the non-primed and primed halves of the molecule, respectively.

¶ May be interchanged.



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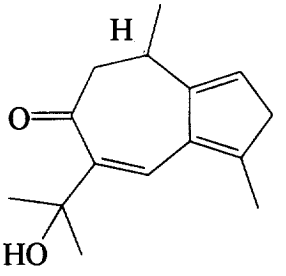

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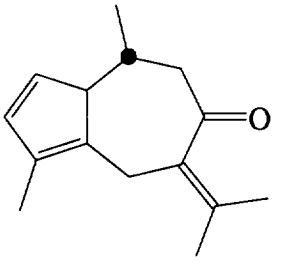

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structures are almost identical, with a guaiane skeleton and the same stereochemistry at the chiral centre; they only differ in the double bond pattern of the cyclopentane ring and in the oxidation level of the isopropylidene moiety. It is not inconceivable that they derive from a same precursor and that some of the chemical processes involved in the formation of **1**, e.g. the Diels-Alder reaction, are thermal.

The formation of terpenoid dimers by a cycloaddition reaction is not unprecedented. We have previously isolated diterpene dimers in *Xylopia* sp. [10], and guaianolide dimers containing a norbornene core have been reported in the Asteraceae [11–12]. To the best of our knowledge, however, the carbon skeleton of **1** is novel.

EXPERIMENTAL

NMR: 600.1 and 150.9 MHz for ^1H and ^{13}C, respectively. All chemical shifts are reported in ppm downfield from internal TMS, and coupling constants in Hz. Unless otherwise indicated, data refer to $CDCl_3$ solutions. NOESY spectra were recorded with a mixing time of 0.7 sec.

CC and flash CC: Silica gel 60 (Merck), 70–230 mesh (CC) or 230–400 mesh (flash CC). All solvents were analytical grade, from Merck.

Leaves of *Xylopia aromatica* (Lamarck) Martius were collected in Coqueiral, Minas Gerais, Brazil, in March 1994. A voucher is deposited at the Herbarium of the Instituto de Botanica of the Secretaria do Meio Ambiente of the State of São Paulo (SP 142.360). 500 g of dried and ground leaves were extracted with hexane (3 × 2 l) at room temp. The extract was concentrated (13.59 g) and partitioned between hexane and MeOH–H_2O (9:1). The hexane phase, after evaporation of the solvent (6.64 g), was filtered through a silica gel column (100 g), eluted with hexane, followed by CH_2Cl_2, $CHCl_3$, EtOAc and MeOH. The CH_2Cl_2 fraction (2.23 g) was chromatographed through a silica gel column (50 g), eluted with a gradient of hexane–EtOAc–MeOH; frs 7 and 8 out of 23 (468 mg) were pooled and rechromatographed in a similar way. Frs 10 to 12 out of 30 (211 mg) were pooled and submitted to flash CC over silica (30 g), eluting with CH_2Cl_2–EtOAc (96:4), to give 21 mg of the sesquiterpene dimer **1** as colourless crystals, mp 157–158° (CH_2Cl_2, uncorr.), $[\alpha]_D^{21}$ −17.8° ($CHCl_3$; *c* 0.01). MS (DCI, CH_4) *m/z* (rel. int.): 448.2926 [M^+, calc. for $C_{30}H_{40}O_3$ 448.2977] (14), 447.2850 [calc. for $C_{30}H_{39}O_3$ 447.2899] (49), 431.2931 [calc. for $C_{30}H_{39}O_2$ 431.2950] (25), 407.2570 [calc. for $C_{27}H_{35}O_3$ 407.2586] (20), 231.1354 [calc. for $C_{15}H_{19}O_2$ 231.1385] (87), 215.1392 [calc. for $C_{15}H_{19}O$ 215.1436] (100), 191.1039 [calc. for $C_{12}H_{15}O_2$ 191.1072] (33), 173.0924 [calc. for $C_{12}H_{13}O$ 173.0966] (22).

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