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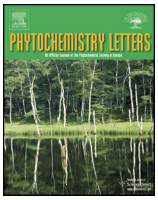

Novel cadinane-related sesquiterpenes from *Nectandra amazonum*

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ABSTRACT

Two novel cadinane-type sesquiterpenes (**1**–**2**) were isolated from *n*-hexane-soluble sub-extract from leaves of *Nectandra amazonum* NEES. (Lauraceae) along with two known stigmastane-related sterols, which were structurally characterized by spectroscopic techniques (NMR, MS) and DFT molecular modeling. Additionally, from the less polar fraction, four known cadinane-type sesquiterpenoids were also identified by GC/MS analyses.

1. Introduction

Lauraceae family is gathered into 67 genera (including more than 2700 species) and mainly distributed in tropical and subtropical regions such as America and Malasia (Lorea-Hernández, 2002; Chanderbali et al., 2001). This family keeps up a huge economic importance for wood, food, seasoning, and essential oil supplies (Marques, 2001; Chanderbali et al., 2001). Several metabolites, such as aporphine and benzylisoquinoline alkaloids, furofuran lignans, dihydrobenzofuran and bicyclo[3.2.1]octane neolignans, diarylpropanes, pyrones, and sesquiterpenes, among others (Pagotto et al., 1998), have been isolated from Lauraceae plants as well as some species have exhibited great potential on antitumoral, vermifugal, antibacterial, antifungal, antioxidant, cytotoxic, and insecticide activities, among others (Cicció et al., 2009; Garcez et al., 2010; Zschocke et al., 2000). *Nectandra* plants are especially abundant in neotropical regions with 114 species (Rohwer, 1993). It has been demonstrated that some *Nectandra* plants have potential antitumoral, antioxidant, antiinflammatory, febrifuge, and hypotensive activities (Le Quesne et al., 1980; Silva-Filho et al., 2004; Moreno et al., 2007) which are attributed to the presence of alkaloids and neolignans in crude extracts of *Nectandra*, suggesting good potential as chemotherapeutics (Silva-Filho et al., 2004). Only two previous studies illustrate the isolation of two furofuran lignans (Barbosa-Filho et al., 1989) and ten neolignans (Coy and Cuca, 2009) from *Nectandra amazonum* NEES. Thus, as part of our research on Colombian Lauraceae plants, a phytochemical exploration on *n*-hexane-soluble sub-extract led to the isolation of two novel cadinane-type sesquiterpenes (**1**–**2**), along with two ubiquitous stigmastane-type sterols (**3–4**), whose structures were established on the basis of the spectroscopic means and by spectroscopic comparison with data in the literature. In addition, four cadinane-sesquiterpenes (**5–8**) were also identified into an oily fraction by GC–MS analyses.

2. Results and discussion

Repeated chromatography of the *n*-hexane-soluble sub-extract from *N. amazonum* leaves-derived EtOH extract yielded two new cadinane-related sesquiterpenes (**1**–**2**), along with two known sterols (**3**–**4**), whose chemical structures (Fig. 1) were established by analyses of spectroscopic data (1D and 2D NMR, MS) in comparison with spectroscopic data in the literature. The interesting structural features of the new compounds **1**–**2** are then described on the basis of spectroscopic analyses

The molecular formula of compound **1** was assigned as $C_{15}H_{24}$ by HRESIMS analysis ($[M+H]^+$ m/z 205.1977, calcd for $C_{15}H_{25}$, 205.1956). IR spectrum indicated the absence of functional groups. The ^1H NMR spectrum (see Table 1) revealed a typical profile of cyclic hydrocarbon, showing the signals for four methyl groups, i.e., a methyl group attached to sp^3 carbon [δ_H 0.86 (3H, d, 6.2 Hz)],

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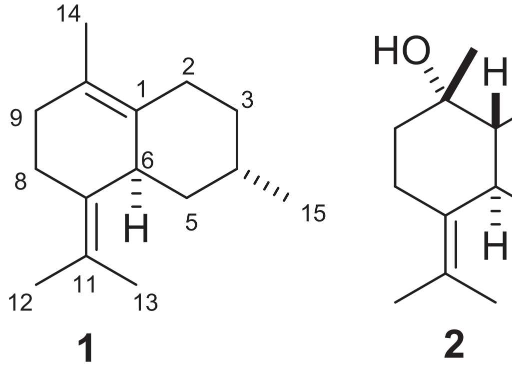

Fig. 1. Structures of cadinane-type sesquiterpenes **1**–**2**.

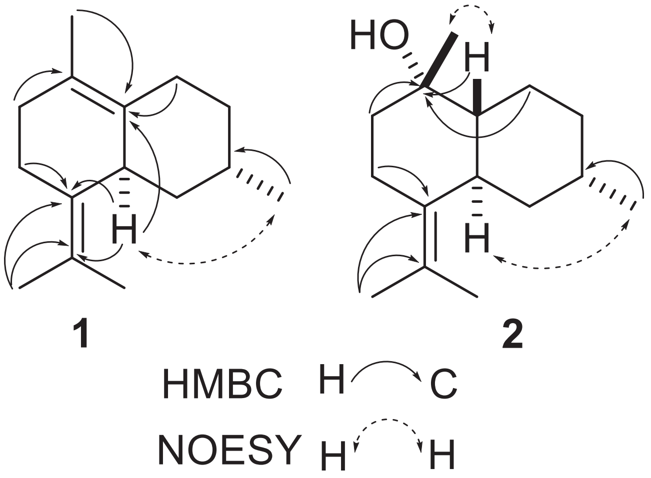

Fig. 2. Selected key HMBC and NOESY correlations of compounds **1**–**2**.

and three methyl groups attached to sp^2 carbons [δ_H 2.11 (3H, s), 2.16 (3H, s), 1.69 (3H, s)], a double double doublet signal [δ_H 2.60 (1H, ddd, 13.5, 3.5, 3.2 Hz)]. The ^{13}C NMR spectrum (see Table 1) and DEPT experiments revealed the presence of 15 carbon signals assigned to four methyl groups (δ_C 22.8, 18.3, 22.2, 19.7), five methylenes (δ_C 21.1, 24.5, 37.3, 37.4, 37.5), two methine groups (δ_C 31.6, 39.8), four olefinic quaternary carbons (δ_C 145.6, 122.6, 121.0, 118.5). The HMQC spectrum established the connectivities between C and H signals whose spectroscopic information was used to establish the core structure as a cadinane-related sesquiterpene (Narita et al., 2007; Liu et al., 2007) and confirmed by HMBC data (Fig. 2). The HMBC spectrum of **1** showed a long-range correlation between H$_3$-14 methyl protons [δ_H 1.69 (3H, s)] and C-1 and C-10 olefinic carbons (δ_C 145.6; 121.0), which were also correlated with H$_2$-9 and H$_2$-2 methylene protons [δ_H 1.91 (2H, m); 2.60 (1H, ddd, 13.5, 3.5, 3.2 Hz); 1.65 (1H, m)], indicating the first double bond position. On the other hand, both H$_3$-12 and H$_3$-13 methyl protons [δ_H 2.16(3H, s); 2.11 (3H, s)], H-6 methine proton [δ_H 1.53 (1H, m)], and H$_2$-8 methylene protons [δ_H 1.97 (1H, m)] were correlated with C-7 and C-11 olefinic carbons (δ_C 122.6; 118.5), revealing the second double bond location. Through the long-range correlation between H$_3$-15 methyl protons [δ_H 0.86 (3H, d, 6.2 Hz)] and C-3, C-4, and C-5 aliphatic carbons (δ_C 37.4, 31.6, 37.5) was located C-5 methyl group. The relative configuration of **1** was derived from analysis of data from a NOESY experiment. The key NOESY correlation between H-6 and H$_3$-15 indicated these protons are situated in the same plane in a *pseudo*-1,3-diaxial orientation (Fig. 2), and the NOESY correlation between H-6 and H-2$_{ax}$ [δ_H 1.65 (1H, m)] indicated a chair-conformed B ring. Thereby, structure **1** was determined to be *rel*-(4*S*,6*S*)-cadina-1(10),7(11)-diene.

Compound **2** has the molecular formula $C_{15}H_{26}O$, as deduced from HRESIMS analysis ([M+H]$^+$ *m*/*z* 223.2081, calcd for $C_{15}H_{27}O$, 223.2062). IR spectrum showed an absorption band at 3461 cm^{-1} due to a hydroxyl group. The ^{1}H NMR spectrum of **2** (Table 1) exhibited a similar signal pattern to that of **1** except for the presence of a methine proton [δ_H 1.32 (1H, m)]. The ^{13}C NMR spectrum of **2** (Table 1) was also similar to that of **1**, except for the presence of a carbinol carbon (δ_C 74.5) and methine carbon (δ_C 42.8) instead two olefinic carbons. The ^{1}H and ^{13}C NMR data of **2** was in agreement with the reported data for sesquiterpene-related molecules (Duh et al., 2002; Narita et al., 2007; Borg-Karlson and Norin, 1981). Key HMBC correlations were used to determine the structure of **2**. H$_3$-12 and H$_3$-13 methyl protons [δ_H 1.96 (3H, s); 1.83 (3H, s)], H-6 methine proton [δ_H 2.05 (1H, m)], and H$_2$-8 methylene protons [δ_H 1.97 (1H, m)] exhibited long-range correlation with C-7 and C-11 olefinic carbons (δ_C 144.5; 117.4), indicating the double bond location. Position of carbinol carbon

Table 1
^{1}H and ^{13}C NMR chemical shifts[a] (δ) of compounds **1**–**2** (400 MHz ^{1}H, 100 MHz ^{13}C, CDCl$_3$).

	1			**2**		
	δ_C (ppm)	Type	δ_H (ppm), mult. (J = Hz)	δ_C (ppm)	Type	δ_H (ppm), mult. (J = Hz)
1	145.6	C	–	42.8	CH	1.32 (1H, m)
2	24.5	CH$_2$	a, 2.60, ddd (13.5, 3.5, 3.2) b, 1.65, m	20.8	CH$_2$	a, 1.82, m b, 1.40, m
3	37.4	CH$_2$	a, 1.74, m b, 0.86, m	39.9	CH$_2$	a, 1.57, m b, 1.60, m
4	31.6	CH	1.37, m	32.7	CH	1.44, m
5	37.5	CH$_2$	a, 0.80, m b, 2.02, m	37.5	CH$_2$	a, 0.75, m b, 1.85, m
6	39.8	CH	1.53, m	28.0	CH	2.05, m
7	122.6	C	–	144.5	C	–
8	21.1	CH$_2$	1.97, m	24.8	CH$_2$	1.41, m
9	37.3	CH$_2$	1.91, m	39.4	CH$_2$	a, 1.80, m b, 1.67, m
10	121.0	C	–	74.5	C	–
11	118.5	C	–	117.4	C	–
12	22.8	CH$_3$	2.16, s	22.7	CH$_3$	1.96, s
13	18.3	CH$_3$	2.11, s	19.7	CH$_3$	1.83, s
14	22.2	CH$_3$	1.69, s	22.6	CH$_3$	1.24, s
15	19.7	CH$_3$	0.86, d (6.2)	23.5	CH$_3$	0.88, d (7.0)

[a] Assignments made by ^{1}H–^{1}H COSY, HMBC, and HMQC experiments.