Structure, Synthesis, and Biological Activity of 14-Methoxy-1,2-dehydrocacalol Methyl Ether, a New Modified Furanoeremophilane Type Sesquiterpene from *Trichilia cuneata*

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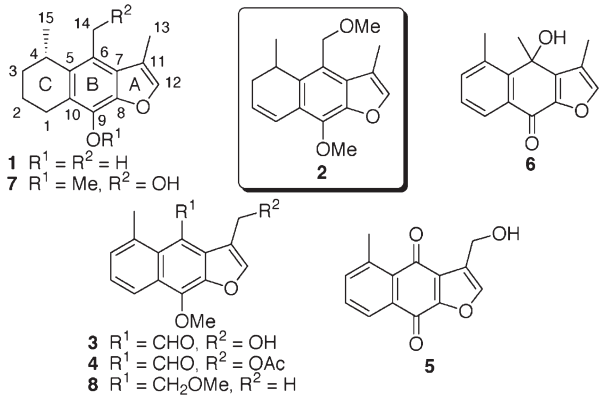
A new modified furanoeremophilane type sesquiterpene, (+)-14-methoxy-1,2-dehydrocacalol methyl ether (**2**), isolated from *Trichilia cuneata* exhibited inhibitory activity for mitochondrial lipid peroxidation. The first total synthesis of (±)-**2** and two related sesquiterpenes, (±)-14-hydroxycacalol methyl ether (**7**) and 14-methoxydehydrocacalohastine (**8**), has also been achieved.

Cacalia decomposita A. Gray,[2] a compositae widely distributed in the northern part of Mexico, is a shrub popularly known as matarique and maturin. Matarique is a medicinal plant complex of Mexico, the concoction of which is drunk for treating diabetes, kidney pain, and rheumatism; it can also be applied as a wash or cataplasm to treat wounds and skin ulcers.[3] Recently, in vivo bioassay-directed fractionation of an extract from the roots of *Cacalia decomposita* A. Gray revealed that a modified eremophilane cacalol (**1**), which has been shown to be the first representative of a new class of compounds (cacalol families) possessing the furotetralin ring system,[4] exhibits antihyperglycemic[5] and antimicrobial[6] activities. These stimulating findings prompted us to undertake studies on biologically active chemical constituents of *Trichilia cuneata*, one of shrubs composing the endemic medicinal plant complex in Mexico. In this paper, we preliminarily report structures and biological activities of 14-methoxy-1,2-dehydrocacalol methyl ether (**2**), a novel modified furanoeremophilane type sesquiterpene, and four known compounds **3**–**6**. We also report the first total synthesis of (±)-**2** and two related sesquiterpenes, (±)-14-hydroxycacalol methyl ether (**7**)[7] and 14-methoxydehydrocacalohastine (**8**),[8] via stepwise regioselective dehydrogenation of the C ring.



The methanol extract (10.9 g) of dried stem bark and leaves of *Trichilia cuneata*, which showed inhibition for mitochondrial and microsomal lipid peroxidation and weak antibacterial activities, was partitioned between $CHCl_3$ and H_2O. Purification of the $CHCl_3$ extract was repeated by column chromatography on silica gel. Further purification by a recycling preparative GPC (gel permeation chromatography) provided a novel compound **2** (2.5 mg, 0.023 wt % yield) along with four known compounds, maturin (**3**),[4b,d,9] maturin acetate (**4**),[4b,9,10] maturone (**5**),[4b,d] and cacalonol (**6**).[11]

The molecular formula of compound **2** was established as $C_{17}H_{20}O_3$ by EI-HRMS [m/z 272.1417 (M^+) + 0.5 mmu]. The ^{1}H NMR spectrum of **2** in $CDCl_3$ exhibited signals due to three sp^2 methine protons at δ 7.33, 6.92, and 5.91, aromatic and aliphatic methyl protons at δ 2.37 and 1.13, respectively, and two methoxy protons at δ 4.08 and 3.46 (Table 1). The 17 carbon signals observed in the ^{13}C NMR spectrum were characterized by a DEPT experiment, which suggested that **2** has seven sp^2 quaternary carbons, three sp^2 methines, one oxygenated methylene, two oxygenated methyls, one methine, one methylene, and two methyls. Complete ^{1}H and ^{13}C chemical shift assignments were made from the H–H COSY, HMQC, and HMBC spectral data, and the resulting structure **2** was also supported by NOEs observed between the diagnostic protons as shown in Figure 1. The absolute stereochemistry at C-4 position of the optically active compound **2**, $[\alpha]^{25}_D$ + 46.7 (c 0.125, $CHCl_3$), is deduced at present to be *S* configuration based on that of the biogenetically related sesquiterpene cacalol (**1**).[4j]

Table 1. ^{1}H and ^{13}C NMR and HMBC spectral data for compound **2** in $CDCl_3$[a]

Position	δ_C	δ_H	HMBC (H → C)
1	121.38	6.92 (dd, 9.7, 3.2)	C-3, 5, 10
2	124.7	5.91 (dddd, 9.7, 6.4, 2.4, 1.0)	C-3, 4, 10
3	30.7	2.56 (dddd, 17.1, 6.6, 3.2, 2.4)	C-2, 4, 15
		2.23 (ddd, 17.1, 6.4, 1.5)	C-1, 2, 4, 15
4	28.0	3.39 (br quintet, 7.1)	
5	136.6		
6	121.44		
7	129.3		
8	145.9		
9	140.7		
10	120.9		
11	116.5		
12	142.1	7.33 (q, 1.2)	C-7, 8, 11
13	10.1	2.37 (3H, d, 1.2)	C-7, 11, 12
14	66.8	4.66 (2H, s)	C-5, 6, 7, C-14–OMe
15	20.9	1.13 (3H, d, 7.1)	C-4, 5
C-9–OMe	60.8	4.08 (3H, s)	C-9
C-14–OMe	57.8	3.46 (3H, s)	C-14

[a]Proton resonance multiplicities and coupling constants (J in Hz) are given in parentheses.

In preliminary biological test, only two compounds (+)-**2** and **3** were evaluated as antioxidants because of available amounts. The new compound **2** was found to inhibit mitochondrial lipid peroxidation induced by Fe(III)–ADP/NADH (IC_{50}

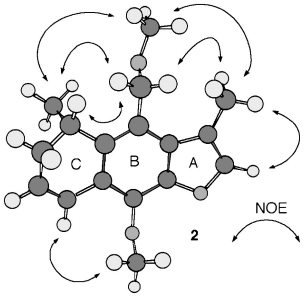
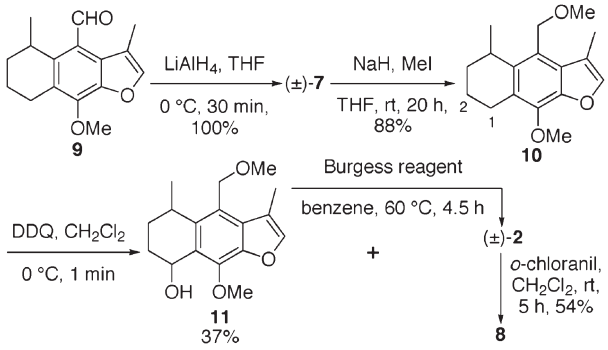


Figure 1. Diagnostic NOEs observed in NOESY spectrum of **2**.



Scheme 1. Total syntheses of (±)-**2**, (±)-**7**, and **8**.

$= 76.8\,\mu M$),[12] but the known compound **3** was not. This pharmacological property indicates that some of the effects of the endemic medicinal plant complex may be attributable to **2** and that this sesquiterpene may be useful as a lead compound in the field of medicinal chemistry. Therefore, we attempted the total synthesis of **2** in conjunction with confirmation of the structure elucidated by spectroscopic methods. We also synthesized the related compounds **7** and **8**, which were different from **2** in the oxidation stage at the C ring and might be expected to possess similar biological activities.

We have reported the total synthesis of some cacalol families including (±)-14-oxocacalol methyl ether (**9**)[13] (Scheme 1). Reduction of aldehyde **9** with $LiAlH_4$ gave (±)-14-hydroxycacalol methyl ether (**7**) in a quantitative yield. The spectral characteristics of synthetic **7**[14] were in good agreement with those reported for the natural product.[7] Methylation of **7** and subsequent oxidation of the resulting methyl ether **10** employing 1.1 equiv. of DDQ in CH_2Cl_2 at 0 °C for 1 min afforded regioselectively 1,2-dehydrogenated (±)-14-methoxy-1,2-dehydrocacalol methyl ether (**2**) in 39% yield along with compound **11**, which could be transformed into **2** by dehydration with the Burgess reagent[15] in 60% yield based on recovery of **11**. The spectral characteristics of synthetic (±)-**2** were consistent with those observed for the natural product (+)-**2**. 14-Methoxydehydrocacalohastine (**8**) was able to be derived from (±)-**2** by dehydrogenation with *o*-chloranil. The spectral characteristics of synthetic **8** were also identical to those of the natural product.[8]

In conclusion, we have determined the structure of 14-methoxy-1,2-dehydrocacalol methyl ether (**2**), a novel modified furanoeremophilane type sesquiterpene isolated from *Trichilia cuneata*, and accomplished the first total synthesis of (±)-**2** in addition to two related cacalol families (±)-**7** and **8**. We have also found that the new compound **2** possesses antioxidative activity. Further studies on biologically active chemical constituents of *Trichilia cuneata* are in progress and will be reported in due course.

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14 Synthetic (±)-**7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, q, J = 1.2 Hz), 4.96 (1H, d, J = 11.4 Hz), 4.91 (1H, d, J = 11.5 Hz), 4.10 (3H, s), 3.49–3.38 (1H, m), 3.06–2.94 (1H, m), 2.63 (1H, ddd, J = 18.2, 10.8, 7.3 Hz), 2.42 (3H, d, J = 1.2 Hz), 2.15 (1H, s), 1.97–1.70 (4H, m), 1.26 (3H, d, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 142.2, 141.6, 136.9, 127.9, 124.5, 123.9, 115.8, 59.9, 57.3, 29.8, 28.5, 23.9, 23.3, 16.7, 10.1. Synthetic (±)-**2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, q, J = 1.2 Hz), 6.92 (1H, dd, J = 9.8, 3.2 Hz), 5.92 (1H, ddd, J = 9.6, 6.5, 1.9 Hz), 4.65 (2H, s), 4.08 (3H, s), 3.47 (3H, s), 3.39 (1H, quintet, J = 7.0 Hz), 2.55 (1H, ddt, J = 17.1, 6.7, 2.8 Hz), 2.37 (3H, d, J = 1.0 Hz), 2.22 (1H, ddd, J = 17.1, 6.3, 1.2 Hz), 1.13 (3H, d, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 142.1, 140.5, 136.4, 129.2, 124.7, 121.3, 121.2, 120.8, 116.4, 66.7, 60.8, 57.9, 30.6, 27.8, 20.9, 10.0. Synthetic **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, t, J = 5.1 Hz), 7.48 (1H, q, J = 1.5 Hz), 7.31 (2H, d, J = 5.9 Hz), 5.03 (2H, s), 4.28 (3H, s), 3.55 (3H, s), 3.04 (3H, s), 2.52 (3H, d, J = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 142.6, 139.0, 134.3, 133.1, 131.0, 129.1, 126.4, 123.5, 120.6, 120.2, 116.1, 67.8, 61.0, 57.6, 23.9, 10.8.
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