

Salvimultine, a New Noricetexane Diterpene from the Roots of *Salvia multicaulis*

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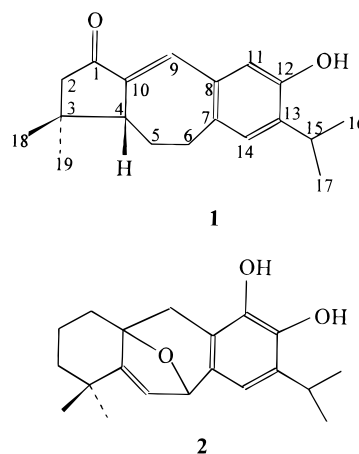
A new noricetexane diterpene, salvimultine, has been isolated from the polar fractions of *Salvia multicaulis*. Its structure was established as 1(10)-seco-2(10)-cyclo-icetexane by using 1D and 2D NMR spectral methods, including COSY, HETCOR, COLOC, and NOESY experiments as well as HRMS.

In previous studies with the roots of *Salvia multicaulis* Vahl^{1,2} (Labiatae) we have isolated 11 new and 21 known terpenoids. Four of the new compounds were unsaturated norbiatane diterpenes, which showed significant activity against *Mycobacterium tuberculosis*.¹ We now report a new compound, salvimultine (**1**), with a noricetexane structure from the polar fractions of the root extract. A literature survey revealed the presence of icetexane-type diterpenes in various *Salvia* species, including *S. bellotaeflora*,³ *S. canariensis*,⁴ *S. fruticulosa*,⁵ *S. candicans*,⁶ and *S. aspera*.⁷ However, this is the first reported isolation of a noricetexane diterpenoid from nature.

The structure of salvimultine (**1**) was assigned by extensive NMR studies (spin decoupling, COSY, HETCOR, COLOC, and NOESY) and by HRMS. The molecular formula, C₁₉H₂₄O₂, derived from its HRMS, indicates eight degrees unsaturation, three of which were accounted for by the tricyclic ring system, one by the carbonyl group, and the remaining four by double bonds. The UV spectrum shows the presence of a conjugated system with absorptions at 352 and 308 nm. The IR spectrum supports this conjugation with bands at 1737 (sh), 1720, and 1700 cm⁻¹, as well as bands for an aromatic system at 1582 and 1510 cm⁻¹. The ¹³C NMR spectrum also shows the presence of a carbonyl carbon (δ 200.7). The ¹H NMR spectrum exhibits signals for two aromatic protons *para* to each other, a vinyl proton, and two methine (H-4 and H-15), three methylene, and four methyl groups (Table 1). The ¹³C NMR (APT) spectrum shows 18 signals for 19 carbon atoms, with a very strong signal at δ 22.4 that could be due to two methyl groups. A HETCOR experiment showed the expected direct correlations between carbons and protons (Table 1). Spin-decoupling experiments indicated the sequence between C-4 and C-6, as well as the relationship between C-4 and C-9. One of the three methylene groups resonates at δ_C 23.5 (C-5) and δ_H 1.60 [(1H, ddd, *J* = 13, 14, 14 Hz, H-5α) and 2.10 (1H, ddd, *J* = 4, 8, 13, H-5β)]. A second methylene resonates at δ_C 29.9 (C-6) and δ_H 2.82 [(1H, ddd, *J* = 8, 14, 14 Hz, H-6α) and 1.45 (1H, td, *J* = 14, 14 Hz, H-6β)]. The methine group resonates at δ_C 47.6 (C-4) and δ_H 2.50 (1H, ddd, *J* = 1.5, 4, 14 Hz, H-4β). When the latter signal (δ 2.50) was irradiated, the signals at δ 2.10 (H-5β) and 1.60 (H-5α) became double doublets (*J* = 8, 13 Hz and *J* = 13, 14 Hz, respectively). The signal at δ 6.65 (1H, d, *J* = 1.5 Hz, H-9; vinyl proton) also collapsed to a sharp singlet

showing a *W*-like relation with the methine proton at C-4, indicating the β position of H-4. This was confirmed by a NOESY experiment, which showed the interaction of H-4β with H-6β, as well as Me-18. When the signal at δ 2.10 (H-5β) was irradiated, the signals at δ 1.60 (H-5α) and 2.82 (H-6α) became double doublets (*J* = 14, 14 Hz and *J* = 4, 14 Hz, respectively), and the signal at δ 2.50 (H-4β) also became a double doublet (*J* = 1.5, 14 Hz). Irradiation of the signals at C-6 (H-6α and H-6β) showed the relationship between the two H-6 protons as well as with C-5 protons. The third methylene group, which resonates at δ_C 53.3 and δ_H 2.37 (2H, d, *J* = 10 Hz), did not change upon irradiation, supporting placement of this methylene between the carbonyl (C-1) and the quaternary (C-3) carbon. The COSY experiment (Table 1) supported these assignments.

The structure of the molecule was further confirmed by HETCOR and COLOC experiments. The carbon at C-1 (δ 200.7) showed correlations with H-2 (δ 2.37) and H-4 (δ 2.50) (two and three bonds away, respectively), and C-2 correlated with H-18 (δ 0.91) and H-19 (δ 1.17). Carbons at C-7, C-9, and C-13 correlated with δ 6.99 (H-11) (all three bonds away). C-13 also correlated with δ 1.24 (Me-16 and Me-17), while a COLOC experiment showed C-10 (δ 156.9) to be correlated with H-4β (δ 2.50) and H-5β (δ 2.10), and C-14 to be correlated with H-6α (δ 2.82). A Dreiding-model study supported the suggested structure. Thus, salvimultine (**1**) was deduced to be 1(10)-seco-2(10)-cyclo-icetexane. The diterpene icetexane derivatives such as salviasperanol (**2**), isolated from *S. aspera* have 20 carbon atoms as shown by NMR,⁷ while compound **1** has 19 carbon atoms.



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Table 1. NMR Data of Salvimultine (**1**)^a

position	¹³ C	¹ H	COSY	COLOC	NOESY
1	200.7 s			H-2, H-4	
2	53.3 t	2.37 d		Me-18, Me-19	
3	36.5 s				
4β	47.6 d	2.50 ddd	5α, 5β, 9		H-6β, Me-18
5α	23.5 t	1.60 ddd	4β, 5β, 6α, 6β		
5β		2.10 ddd	4β, 5α, 6α, 6β		
6α	29.9 t	2.82 ddd	5α, 5β, 6β		
6β		1.45 ddd	5α, 5β, 6α		H-14
7	129.7 s			H-11	
8	152.2 s				
9	119.2 d	6.65 d	4β	H-11	H-11
10	156.9 s			H-4, H-5β	
11	127.1 d	6.99 s			H-9
12	156.9 s			H-14	
13	139.2 s			H-11, Me-16, Me-17	
14	111.1 d	7.32 s		H-6α	H-6β
15	27.2 d	3.27 sept			
16	22.4 q	1.24 d			
17	22.4 q	1.24 d			
18	20.3 q	0.91 s			
19	29.1 q	1.17 s			

^a *J*(Hz): 2α,2β = 10; 4β,5β = 4; 4β,5α = 14; 4β, 9 = 1.5; 5α,5β = 13; 5α,6β = 14; 5β,6α = 8; 6α,6β = 14.

Experimental Section

General Experimental Procedures. The UV spectrum was recorded on a Shimadzu 1601 spectrophotometer. The IR spectrum was obtained on a Perkin-Elmer 983 spectrophotometer. ¹H (200 MHz) and ¹³C NMR (50.32 MHz) spectra were recorded on a Bruker AC 200L instrument. The mass spectrum was run on a VG ZabSpec instrument. Column chromatography was carried out on Si gel 60 (230–400 mesh).

Plant Material. The roots of *S. multicaulis* were collected from southern Turkey (Adana, Armutluk) and identified by Prof. Dr. Neriman Özhatay (Istanbul). A voucher specimen (ISTE 68325) is deposited in the Herbarium of Faculty of Pharmacy, University of Istanbul.

Extraction and Isolation. The dried and powdered roots of the plant (600 g) were extracted with acetone in a Soxhlet, filtered, and evaporated to dryness in vacuo. The residue was fractionated on a Si gel column eluting with petroleum ether, followed by a gradient of EtOAc up to 100% and then with EtOH. Compound **1** was obtained from the combined fractions of EtOAc–EtOH (7:3). The yield of salvimultine (**1**) was 15 mg. TLC on Si gel plates (E. Merck) in CH₂Cl₂–MeOH (95:5) and in CHCl₃ showed *R_f* values of 0.47 and 0.36, respectively.

Salvimultine (1): light yellow needles, mp 132 °C (uncorrected) [α]_D +27.4° (*c* 1.6, CHCl₃); UV (MeOH) λ_{\max} (log ϵ) 352 (2.7), 308 (3.8), 239 (sh), 225 (3.4) nm; IR (CHCl₃) ν_{\max} , 3390,

1737 (sh), 1720, 1700, 1660 (sh), 1640, 1582, 1510, 1460, 1430, 1310, 1260, 1240, 1190, 1160, 1085, 1040, 1000, 900, 760 cm⁻¹; ¹H and ¹³C NMR (CDCl₃), given in Table 1; EIMS *m/z* 284 [M]⁺ (100), 269 [M – Me]⁺ (70), 256 [M – CO]⁺ (12), 228 (45), 213 (30), 200 (18), 186 (37), 157 (30), 82 (42); HRMS *m/z* 284.1762 [M]⁺ (calcd for C₁₉H₂₄O₂, 284.1776).

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References and Notes

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