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NOVEL TRIOXYGENATED CARYOPHYLLENES FROM INULA SPIRAEFOLIA

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Summary: The identification of two novel isomeric trioxygenated caryophyllenes from the plant species Inula Spiraefolia is reported.

As a continuation of our study concerning constituents of Yugoslav plant species, a chloroform extract of the powdered Inula Spiraefolia[1,2] (the whole plant) was chromatographed on a silica gel column. Two sesquiterpenes (1 and 2) were isolated as consecutive fractions from the C_6H_6/Et_2O (8.5/1.5) eluate in form of viscous colourless oils. Compounds 1 and 2 exhibited identical molecular formulas ($C_{17}H_{24}O_4$) and very similar spectra (Table 1).

Table 1. Spectral data of 1 (I: R=Ac, R'=H) and 2 (I: R=H, R'=Ac)

	1 $[\alpha]_D^{14^\circ}(CHCl_3)=-37.2$		2 $[\alpha]_D^{14^\circ}(CHCl_3)=-30.7$		
MS, m/z (%)	292(M, 2.5), 274(M-18, 0.5), 264(M-28, 1.9), 250(M-42, 4.9), 232(M-60, 5.3), 219(M-CH_2OAc, 7.6), 43(100)		292(M, 0.9), 274(M-18, 0.3), 261(M-CH_2OH, 5.9), 250(M-42, 0.9), 232(M-60, 8.9), 43(100)		
IR, $\nu_{max}^{CCl_4}$, cm^{-1}	3450(OH), 1750, 1245(OAc), 1695(α,β-unsat. C=O)		3400(OH), 1745, 12445(OAc) 1695(α,β-unsat. C=O)		
^1H 60 MHz NMR ($CDCl_3$), δ[a] (LIS)[b]	ca. 5.85, 1H, m brd.	(47.5)	ca. 5.85, 1H, m brd.	(17.5)	5-H
	4.97, 1H, s brd.	(12)	4.95, 1H, s brd.	(16)	12-H
	4.93, 1H, s brd.	(8.5)	4.85, 1H, s brd.	(10)	12'-H
	4.18, 2H, s brd.[c]	(81,100)	4.64, 2H, AB, J=-12	(43.5,34)	15-CH_2
	4.14, 2H, s brd.[c]	(31)	3.63, 2H, s brd.	(100,93)	14-CH_2
	ca. 2.87, 2H, ABC	(43)	ca. 2.87, 2H, ABC	(62.5)	8-CH_2
	2.05, 3H, s	(23)	2.03, 3H, s	(30.5)	OAc
	1.92, 2H, d, J=9.5	(14)	1.91, 2H, d, J=9.5	-	10-CH_2
	1.12, 3H, s	(14.5)	1.08, 3H, s	(46)	13-CH_3

a) In ppm, referenced to internal TMS. b) LIS = Eu(fod)$_3$ induced shifts, calculated using the previously reported method (ref. 3); the LIS of the proton attached to the main binding site, i.e. 15-H and 14-H in 1 and 2 respectively, was used as intramolecular standard as 100 units. c) The assignments may be interchanged.

The spectral data of 1 and 2 indicated trioxygenated caryophyllene derivatives, i.e. isomeric keto diol monoacetates (see I), as possible structures for the isolated

compounds. The relationship between 1 and 2 was unambiguously established by acetylation and also hydrogenation of these compounds. Thus, upon treatment with Ac_2O/Py both compounds afforded identical diacetates (3, Table 2).

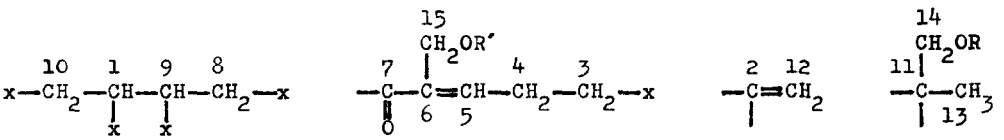
Table 2. Spectral data of diacetate 3 (I: R=R′=Ac), viscous oil $[\alpha]_D^{14^\circ}(CHCl_3)=-17.3$

MS, m/z (%)	334(M, 2.3), 306(M-28, 0.6), 292(M-42, 0.8), 274(M-60, 4.1), 261(M-CH_2OAc, 2.5), 214(M-2x60, 11.5), 43(100)	
IR, ν_{max}^{film}, cm^{-1}	1750, 1240(OAc), 1697(α,β-unsat. C=O)	
^1H 500 MHz NMR ($CDCl_3$), δ[a], J(Hz)	5.76, 1H, dxd (6,12)	5-H ← b
	4.88, 1H, s brd.	12-H
	4.84, 1H, s brd.	12′-H
	4.66, 1H, dxt (-12,≤1,≤1)	15-H ←
	4.45, 1H, d (-12)	15′-H
	4.04, 2H, AB, Δδ(AB)=0.04 (-11)	14-H, 14′-H
	2.75, 2H, ABX, Δδ(AB)=0.03, J(AB)=-19, J(AX)=9.5, J(BX)=4	8-H, 8′-H ← c
	2.44, 1H, q (9.5)	1-H
	ca. 2.38, 1H, m brd.	4-H ←
	ca. 2.32, 2H, m brd.	3-H, 3′-H
	2.17, 1H, m ($w_{\frac{1}{2}}$=26)	4′-H ←
	2.00, 1H, dxt (4,9.5,9.5)	9-H ←
	1.72, 2H, ABX, Δδ(AB)≤0.01	10-H, 10′-H ← d
	1.05, 3H, s	13-CH_3
	2.03, 1.94, 2x3H	2xOAc
^{13}C 25.2 MHz NMR[e] ($CDCl_3$) δ[a]	194.7 (s, C-7), 171.3, 170.4 (2xs, 2x$\underline{C}OOCH_3$), 149.9 (s, C-2), 136.8, 136.7 (s,t, C-5, C-6), 110.9 (t, C-12), 68.4 (t, C-14), 66.0 (t, C-15), 49.7 (d, C-1), 45.5 (t, C-8), 37.7, 37.0 (C-10, C-11)[f], 32.6, 26.8 (2xt, C-3, C-4), 25.2 (q, C-13), 21.0, 20.9 (2xq, 2x$\underline{C}H_3COO$)	

a) In ppm, referenced to internal TMS. b) 15-H-{5-H}: dxt(-12,≤1,≤1)→dxd(-12,≤1); 4-H-{5-H}: m brd.→m (still very complex, due to the additional strong couplings to the adjacent 3-CH_2); 4′-H-{5-H}: m($w_{\frac{1}{2}}$=26)→dxt(-12,~4,~4), revealing J(4′,5)=6 and also J(4,5)=12. c) 9-H-{8-CH_2}: dxt(4,9.5,9.5)→d(9.5). d) 1-H-{10-CH_2}: q(9.5)→d(9.5). e) Most of the assignments are based on the off-resonance and the published data regarding various caryophyllenes (ref. 4a,b,d). f) Multiplicity of δ 37.7 and 37.0 dubious (most possibly s and t).

At the same time, hydrogenation of 1 and 3 (H_2/PtO_2/EtOH at room temperature and atm. pressure) resulted in almost quantitative conversion to a bicyclic keto acetate (4, M.280, $C_{17}H_{28}O_3$) exhibiting following functionality: sat. C=O (1720 cm^{-1}), +CH_2OAc (1750, 1240 cm^{-1}, δ4.08, 2H, s and 2.08, 3H, s), +CH_3 (δ 1.10, 3H, s) and 2xCH-CH_3 (δ 0.81, 0.91, 2xd, J=6.5). Under the same conditions compound 2 yielded the corresponding keto alcohol (5, M.238, $C_{15}H_{26}O_2$). The spectral data of 5, apart from those associated with +CH_2OH moiety (3480, 1050 cm^{-1}, δ3.64, 2H, s) are almost analogous to those of 4. The hydrogenation experiment confirmed also the number of double bonds (and rings), as well as the allylic nature of the CH_2CR' moiety.

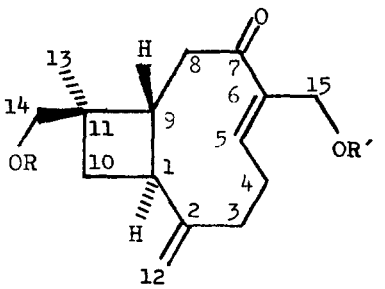
In order to obtain unambiguous proof regarding the proposed structure I, which is unique, as far as the oxygenation pattern is concerned, and at the same time derive the stereochemistry of these molecules, the ^{1}H 500 MHz NMR study of diacetate 3 was undertaken. By the aid of spin decoupling the complete spectrum of compound 3 was assigned (Table 2). These data, together with the evidence quoted so far, enabled identification of the following structural units:



A B C D

x = carbons bearing no protons; 1(R=Ac, R′=H), 2(R=H, R′=Ac); 3(R=R′=Ac).

The interrelations of various groups of protons in A and B are based on the observed ^{1}H (500 MHz) chemical shifts and splitting patterns, and most of them are verified by the decoupling experiments (Table 2). The geminal relationship of CH_3 and CH_2OR groups (D) follows from the fact that (since units A, B and C contain twelve skeletal carbons) only one quaternery carbon (C-11) is available to be connected to these groups. This fits also to a relatively high LIS value, observed for the methyl protons in 2 (Table 1), which demonstrates its vicinity to the main lanthanide binding site, i.e. CH_2OH. The enolizable character of 8-CH_2 (A), as shown by a disappearance of its signal from the ^{1}H 60 MHz NMR spectrum upon exchange with $D_2O/NaOD$[5], demonstrated attachment of this methylene group to the carbonyl (C-7, B). Moreover, a relatively large absolute value of the geminal coupling concerning 8- and 8′-H (19 Hz), which is typical for the methylene adjacent to the carbonyl (i.e. CH_2 with both protons on one side of the π-orbital)[6], provides an additional proof for the proposed 7-8 connection. From the all hypothetical structures that could be constructed from the available units (AB, C and D), only structure I is in accordance with the spectral data.



I

1 (R=Ac, R′=H)
2 (R=H, R′=Ac)
3 (R=R′=Ac)

The NMR data concerning 5-H, 4-CH_2, 1-H and 9-H in diacetate 3, are in accordance with the stereochemistry analogous to this of the recently identified caryophyllenes,[4] i.e. the trans fusion of the cyclobutane to the nine-membered ring, as well as the trans configuration of the endocyclic double bond. At the same time, a comparison of the ^{13}C chemical shifts of C-14 (CH_2OAc) and C-13 (CH_3) to those of the geminal methyls in various caryophyllenes,[4a,b,d] after correction for the influence of the acetoxy group,[7] indicated cis C-14, 9-H geometry (as denoted in I).

It should be also noted that no caryophyllene derivative was among constituents of the previously studied Inula Spiraefolia.[1] At the same time, neither of the compounds isolated from that plant has yet been detected in the plant of Yugoslav origin, whose investigation is still in progress.

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References and Notes

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