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BIOSYNTHETIC STUDIES WITH CARBON-13: THE FT-^{13}C NMR SPECTRA OF THE SESQUITERPENOID CORIOLINS

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The coriolins (I, II, III) are structurally unique tricyclic sesquiterpene antibiotics which possess useful biological properties including antibacterial and anti-tumor activity.[1] The coriolins bear a formal structural relationship to another recently described sesquiterpene fungal metabolite, hirsutic acid C(V),[2] the structure of which was rigorously established by X-ray crystallography. The biosynthesis of hirsutic acid was recently reported.[3]

The most reasonable biosynthetic pathway to the coriolins begins with the cyclization of all trans-farnesyl pyrophosphate to humulene (VI).[4] From humulene to the tricyclic coriolin metabolites three possible cyclization routes, which differ only in type and degree of concertedness of the cyclization, could be considered. Each of the proposed pathways, a, b, and c, involves the initial protonation of humulene at C-10 followed by formation of the C-2 and C-3 bond. The resulting C-3 cationic species could then react further by one of these pathways to give after a series of Wagner-Meerwein shifts the coriolin ring system.

The correct pathway can be determined without recourse to elaborate degradative experiments from the ^{13}C nmr spectra of coriolin biosynthesized from 1,2-^{13}C-acetate as a precursor.

Coriolus consors (ATCC 11574) was fermented according to Umezawa's method.[1] The ^{13}C-enriched 5-dihydrocoriolin C (IV) was isolated as the triacetate VII which is more stable and soluble than, and more easily separated from, other co-metabolites.[6]

In the FT-^{13}C nmr spectrum of the labeled coriolin derivative 20 of the carbon signals appeared with characteristic satellites caused by ^{13}C-^{13}C spin-spin coupling. The assignment of all the carbon chemical shifts and the 10 ^{13}C-^{13}C couplings was made with the aid of the off-resonance decoupled spectrum of the unlabeled metabolite which yielded the individual

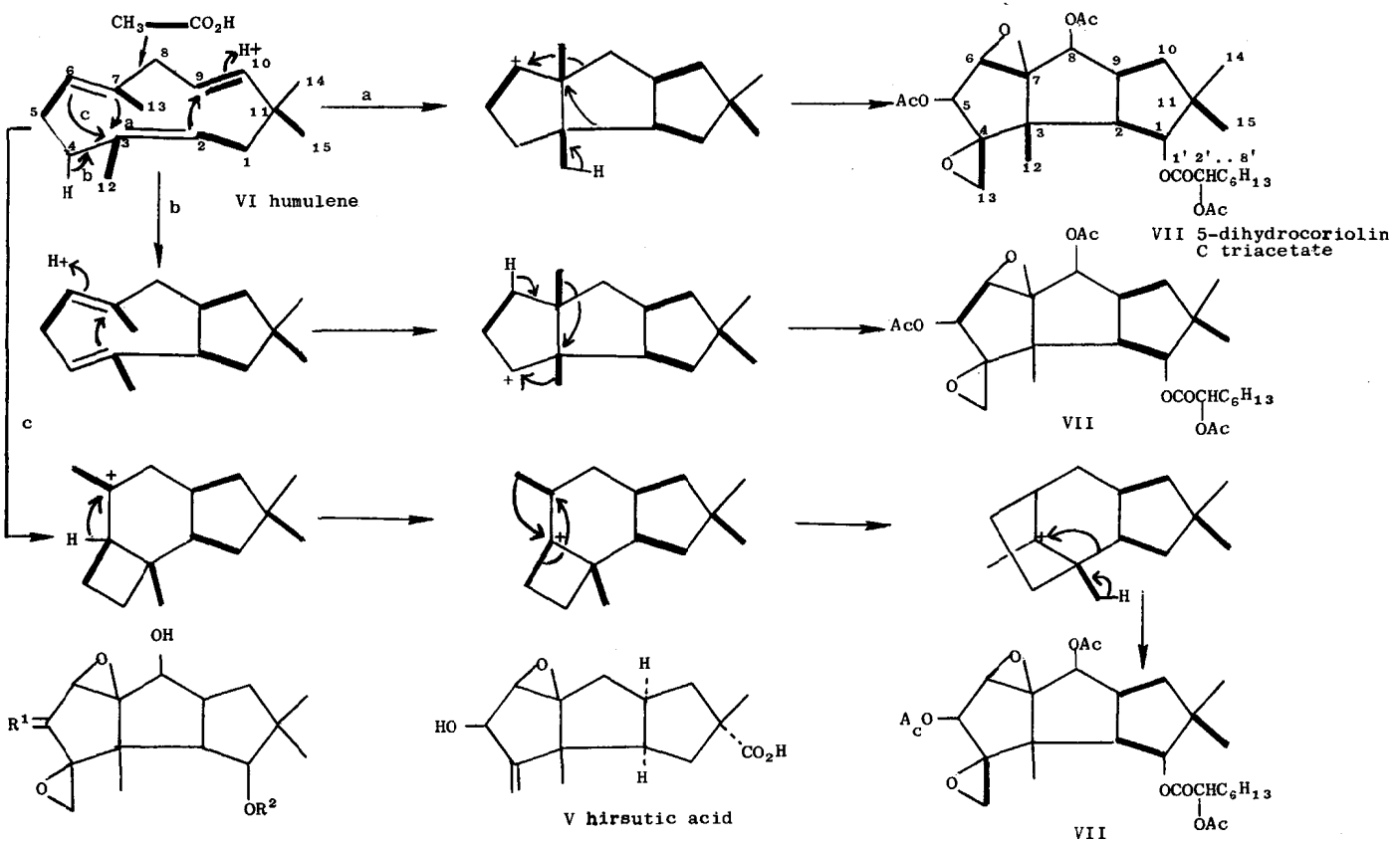
multiplicities as singlet, doublet, triplet or quartet carbons. Dihydrocoriolin C has 24 possible ^{13}C-^{13}C coupling combinations which were classified into couplings between quartet and triplet; quartet and singlet carbons, etc., as shown in Table 1. The individual carbons in each coupling combination were further identified as saturated, oxygenated or trigonal. Each carbon type has a characteristic range of chemical shifts and ^{13}C-^{13}C coupling constants that helped in its assignment.[7] For example, the only ^{13}C-^{13}C coupling observed between a quartet and triplet carbon in the labeled metabolite must originate from the saturated C-8' and C-7' carbons. Of the two ^{13}C-^{13}C couplings observed between doublet and singlet carbons, one was identified as that between the oxygenated C-6 and C-7 epoxide carbons (J=26 Hz). The small coupling constant is characteristic of epoxide carbons. The other ^{13}C-^{13}C coupling between a doublet and singlet carbon was identified as that between C-1' and C-2'. It was identified by the large coupling constant (65 Hz) and downfield position (170 ppm) which is expected for a trigonal carbon. This approach afforded the chemical shift assignments and the 10 ^{13}C-^{13}C couplings of the labeled metabolite.

The data, which are shown in Table 2, clearly establish that dihydrocoriolin C biosynthesis proceeds through pathway a. This is the only route with 1,2-^{13}C-acetate as a substrate that retains the six carbon-carbon couplings in the tricyclic moiety in the positions indicated in Table 2.

Additional feeding experiments conducted with 2-^{13}C-mevalonic acid, 1-^{13}C-acetate and 2-^{13}C-acetate were consistent with biosynthetic pathway a.

Table 1 The 24 ^{13}C-^{13}C Coupling Possibilities in Dihydrocoriolin C

Multiplicities	C-C Bond Units					
q-t	8'- 7'					
q-s	12 - 3 ,	14 - 11 ,	15 - 11			
t-t	3'- 4' ,	4'- 5' ,	5'- 6' ,	6'- 7'		
t-d	10 - 9 ,	3'- 2'				
t-s	10 - 11 ,	13 - 4 (-O-)(-O-)				
d-d	1 - 2 , (OH)	2 - 9 ,	5 - 6 , (OH)(-O-)	8 - 9 (OH)		
d-s	1 - 11 ,	2 - 3 ,	5 - 4 , (OH)(-O-)	6 - 7 , (-O-)(-O-)	8 - 7 , (OH)(-O-)	2'- 1' (OH)(=O)
s-s	3 - 4 , (-O-)	3 - 7 (-O-)				



I R^1 = O, R^2 = H

II R^1 OH, H, R^2 = COC_7H_{15}

III R^1 = O, R^2 = $COCHOHC_6H_{13}$

IV R^1 OH, H, R^2 = $COCHOHC_6H_{13}$

Darkened lines show ^{13}C—^{13}C coupling.

Table 2 Carbon Chemical Shifts and Coupling Constants of Dihydrocoriolin C Triacetate

Position $\delta c^{\dagger,\ddagger,\ddagger}$	J (Hz)	Position $\delta c^{\dagger,\ddagger,\ddagger}$	J (Hz)
C_1 (80.8,d,Δ)§ - C_2 (51.0,d,●)	42	C_{14} (26.5,●*)	
C_3 (47.1,s,Δ) - C_{12} (13.1,q,●)	38	$C_{1'}$ (170.0,s,Δ) - $C_{2'}$ (72.4,d,●)	65
C_4 (64.5,s,Δ) - C_{13} (44.9,t,●)	30	$C_{3'}$ (31.3,t,Δ) - $C_{4'}$ (25.2,t,●)	34
C_5 (71.7,d,●*)§		$C_{5'}$ (28.8,t,Δ) - $C_{6'}$ (31.5,t,●)	35
C_6 (60.9,d,Δ) - C_7 (73.5,s,●)	26	$C_{7'}$ (22.5,t,Δ) - $C_{8'}$ (14.0,q,●)	34
C_8 (72.7,d,●*)§		$\underline{C}H_3CO$ (20.5,20.5,20.9)	
C_9 (41.3,d,Δ) - C_{10} (37.6,t,●)	33	$CH_3\underline{C}O$ (170.0,170.5,170.8)	
C_{11} (43.9,s,Δ) - C_{15} (21.4,q,●)	34		

† Measured in $CDCl_3$ solution, in ppm downfield from internal TMS.
‡ q, quartet; t, triplet; d, doublet; s, singlet.
‡ 90% enriched 1,2-^{13}C-acetate, 2-^{13}C-acetate (●), 1-^{13}C-acetate (Δ), and 2-^{13}C-mevalonate (*) were used.
§ Assigned by selective decoupling.

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