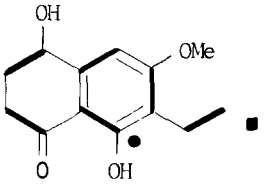
Tetrahedron Letters,Vol.23,No.49,pp 5103-5106,1982 0040-4039/82/495103-04$03.00/0
Printed in Great Britain

DEMONSTRATION OF AN ALTERNATIVE CHAIN FOLDING IN THE PYRANONAPHTHALENE FONSECIN[1]

James L Bloomer*, Thomas J Caggiano and Christopher A Smith
Department of Chemistry, Temple University
Philadelphia, Pennsylvania 19122

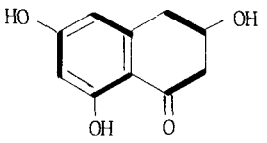
Summary Using recently reported heteronuclear long-range couplings for naphthalene the CMR spectrum of fonsecin has been assigned Acetate double-label experiments indicated a biosynthesis from a polyketide chain folding previously unreported for naphthalene ring formation

Naphthalenes represent a rather small class of natural product The acetate double label studies carried out to date on molecules containing the naphthalene moiety have yielded a wealth of anomalies, however The tetralone O-methylasparvenone has the relatively unusual snakelike folding shown in formula 1[2]. The carboxyl and methyl termini of a polyketide precursor are indicated by the dot and square labels, respectively

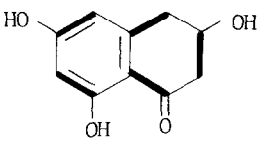


1

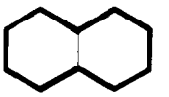
Another simple tetralone, scytalone, exhibits two sets of couplings between adjacent ^{13}C atoms when the acetate double label experiment is run, as shown in formulas 2 and 3[3] For purposes of discussion below, such a case may be represented as 4 to emphasize the "scrambling" effect of a symmetrical precursor The dimeric viomellein contains pyranonaphthalene and pyranonaphthoquinone moieties with chain foldings as shown by the acetate double-label result in 5[4]



2

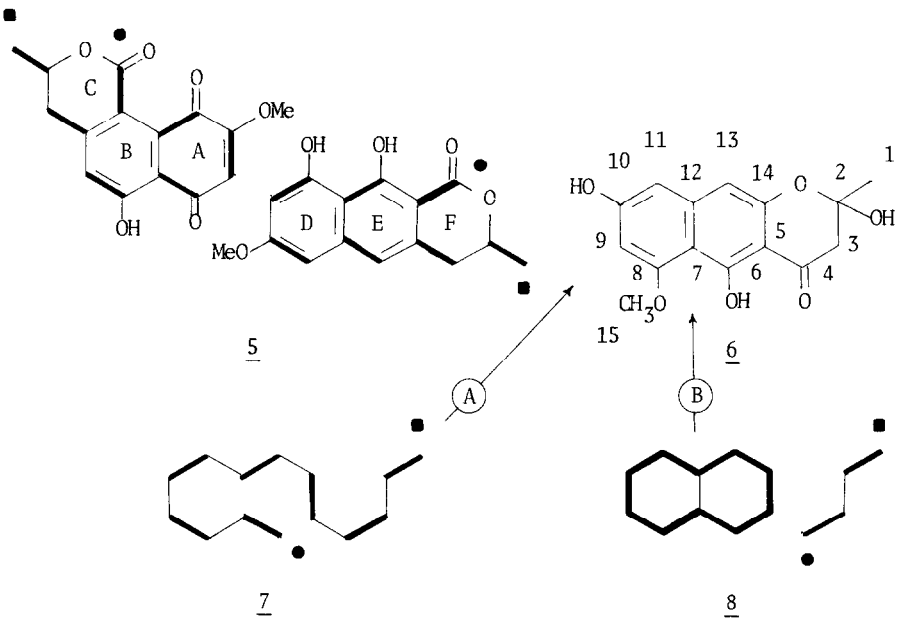


3



4

To our knowledge, the only other naphthalene-based metabolite to be studied by the double-label technique is mollisin, a naphthoquinone shown to be derived from two discrete polyketide chains[5]



5 6

7 8

We were interested in studying fonsecin 6, since the previous literature precedents suggested pathway A from skeletal form 7, which compares to O-methylasparvenone, or pathway B-involving attachment of a four-carbon unit to a simple naphthalene A bicyclic precursor of scytalone with its scrambled couplings could combine with a four-carbon unit as in 8

The polyketide nature of fonsecin was easily established. The feeding parameters were optimized for Aspergillus carbonarius NRRL-0-16-1[6] with sodium [1-^{14}C]-acetate, and subsequent acetate-[1-^{13}C] feeding labeled the even numbered carbons of fonsecin i e , a) the carbonyl carbon C-4, 198 1 b) the ketal carbon C-2, 100 7, and c) the phenolic and anisolic carbons, C-6,8,10,14 in the range 154.4-165 6

In order to assign the resonances unambiguously, we first constructed a theoretical profile of the CMR spectrum, based on earlier studies on monosubstituted[7] as well as disubstituted[8] naphthalenes In the case of the phenolic and anisolic carbons above, only C-6, 154 4, which was well upfield of the others, was clearly assignable Other peaks which were clearly assignable on the basis of the calculations were C-9, 97.1, and C-12, 144.2 In each case, an established peak was flanked by a pair of carbons the resonances of which were not easily assignable Thus the pivotal pairs are, for C-6, C-5 and C-7, for C-9, C-8 and C-10, and for C-12, C-11, and C-13. The latter two pairs were especially recalcitrant, as their separations were only 1.0 and 0.4 PPM respectively Solubility problems in our solvent system precluded use of paramagnetic shift reagents

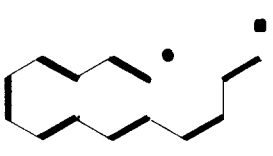
Within the fonsecin naphthalene ring, there are sets of carbons with very similar δ_C Fortunately, the benzene subsets differ in the number of protons attached to each ring (1 vs 2) Drastic expansion of the gated-decoupled experiment yielded a wealth of data on the long-range heteronuclear couplings for the fonsecin molecule. The long-range ^{1}H-^{13}C couplings were analyzed using the assumption that the magnitudes of the 2-,3-, and 4-bond couplings would be similar to those reported for naphthalene itself[9] As an example of the technique, expansion of the gated-decoupled spectrum changed the appearance of C-8 and C-10 from singlets to a doublet of doublets and a triplet, respectively The doublet of doublets would be expected to result from a combination of 2- and 4- bond couplings, however,two very similar 2- bond couplings would give an unresolved doublet of doublets which could appear as a triplet. The end result of the complete analysis is shown in Table I, along with the peaks enriched in the acetate single label experiment and the couplings observed in the sample enriched with acetate-1,2-^{13}C.

TABLE I

^{13}C nmr Spectrum of Fonsecin 6

δ_C	carbon	sodium-[1-^{13}C]-acetate peaks enriched	[sodium- 1,2-^{13}C]-acetate J ^{13}C-^{13}C in enriched sample
198 1	4	*	40
165.6	14	*	66
162 6	8	*	70
161.6	10	*	71
154 4	6	*	59
144.2	12	*	56
106 7	5		59
103 5	7		70
102 5	11		56
102.1	13		66
100 7	2	*	46
97 1	9		72
56 0	15		-0-
48 3	3		40
28.3	1		n.o.

These results are in clear disagreement with pathways for which there are literature precedent (Note 10). The present work, therefore, represents the first demonstration of the novel chain folding 9.



9

It is noteworthy that a number of technical difficulties were encountered in the isolation and feedings. In particular, the NMR experiments had to be run under reducing conditions in acetone-D6 solvent which had been treated with a saturated aqueous solution of sodium hydrosulfite A full account of detailed assignment techniques model studies and further metabolic experiments will be given later

This work was partially supported by National Science Foundation Grant No. CHE-76-05757

References and Notes

1. This should be considered as part XII in our series on microbial metabolites. For Part XI see J. L Bloomer and F. E. Kappler, J Chem. Soc. Perkin I, 1976, 1485.

2. T J. Simpson and D J. Stenzel, J Chem Soc. Chem Commun , 1981, 239

3. U Sankawa, H. Shimada, T Sato, T. Kinoshita, and K. Yamasaki, Tetrahedron Lett. 1977, 483 See also U Sankawa, H Shimada, and K Yamasaki, Tetrahedron Lett. 1978, 3375 Symbols for termini are not given since the primer unit of scytalone has not been ascertained

4 T J Simpson, J Chem. Soc Perkin I, 1977, 592. Viomellein is not a dimer in the strictest sense of the word, since the two halves (ABC and DEF) are not identical Its co-metabolite xanthomegnin is a true dimer consisting of two identical ABC units coupled similarly to viomellein Xanthomegnin was also studied and found to have couplings similar to the ABC unit of viomellein when the acetate double label experiment was run

5 M L Casey, R. C Paulick and H. W Whitlock, Jr., J Amer Chem. Soc., 1976, 98, 2636.

6. The same organism was used as in the original isolation studies, where it was referred to as Aspergillus fonsecaeus See O. L. Galmarini and F H Stodola, J. Org. Chem. 1965, 30, 112

7. P R Wells, D P Arnold, and D. Doddrell, J Chem Soc Perkin II, 1974, 1745.

8. J Seita, J Sandstrom, and T Drakenberg, Org. Mag. Res., 1978, 11, 239.

9. P E Hansen, Org. Mag. Res., 1979, 12, 109

10 The viomellein results do not apply, as there are carbon chains of one and three atoms attached to the naphthalene moiety of each half The mollisin work does not apply since there is no branching to indicate the possibility of multiple polyketide chains in fonsecin

(Received in USA 21 July 1982)