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AN INVESTIGATION OF THE MECHANISM OF THE PEDERIN TO PEDERENAL TRANSFORMATION.

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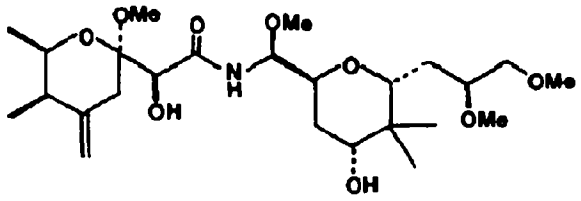
Summary: The mechanism of the acid catalyzed conversion of pederin (1) and pedaldehyde (3) into pederenal (2) is investigated by isotopic labeling using model hydroxyaldehyde 5.

Pederin (1), whose structure has been established by two independent x-ray crystallographic studies,[1] is a potent antimetabolite produced by beetles of the genus Paederus. Degradation of 1 under acidic conditions cleaves the aza-acetal moiety and gives rise to the α,β-unsaturated aldehyde pederenal (2),[2,3] an apparent dehydration product of the expected pedaldehyde (3). The surprising ease of this dehydration, which led initially to a misassignment of the pederin structure,[2] has never been fully rationalized. In connection with a recently completed synthesis of 3,[4,5] we have investigated the mechanism of this facile dehydration.



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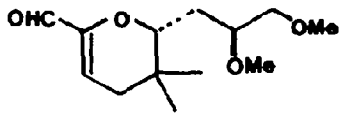

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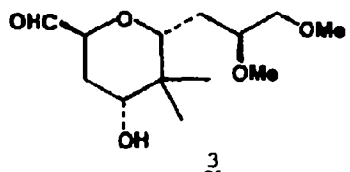

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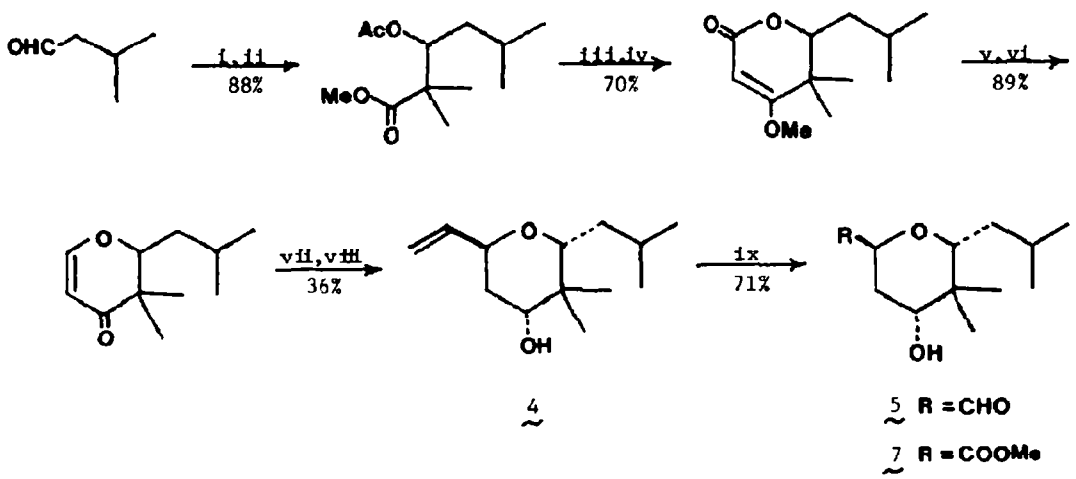
Scheme I outlines the synthesis of hydroxyaldehyde 5, chosen as a convenient model of pedaldehyde in our initial work.[5,6] Heating of 5 in a two phase system composed of hexane and 1N H_2SO_4[2] for 8 hr produced a 1:1 mixture of unchanged 5 and its dehydration product 6. Under these conditions 1 or 3 require ca. 4 hr for complete conversion to 2. The difference in rates might result simply from a lower solubility of 5 in the acidic phase.

A key role of the aldehyde group in these transformations is suggested by the failure of either the corresponding vinylic alcohol 4 (and its p-toluenesulfonyl or acetyl derivatives) or methyl ester 7 to dehydrate under similar conditions. Further information was provided by a

study of the conversion of 5 to 6 in deuterated solvent.

SCHEME I



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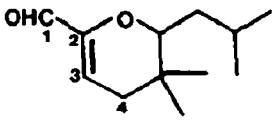
5 R = CHO

7 R = COOMe

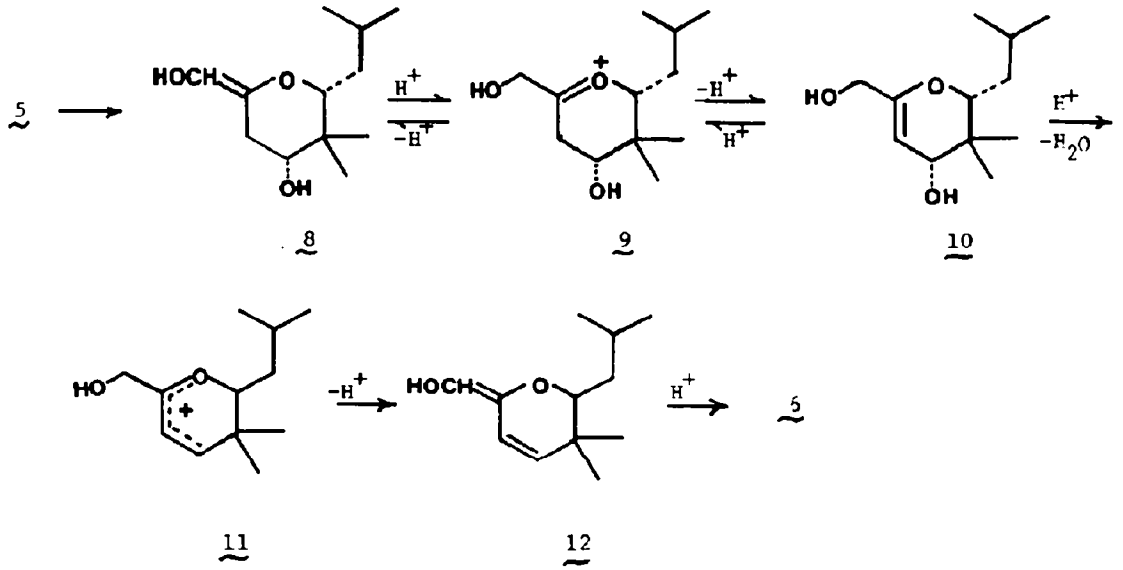
(i) MeO_2CCMe_2Li (ii) Ac_2O,pyr (iii) 2 $(i\text{-pr})_2NLi$ (iv) Me_2SO_4, K_2CO_3 (v) $(i\text{-Bu})_2AlH$ (vi) H_3O^+ (vii) $(\quad)_2CuLi$ (viii) $LiAlH_4$, separation of epimers (ix) O_3, Ph_3P

Substituting D_2O for H_2O in the above experiment yielded a sample of 6 in which deuteration had occurred at C-1 (~95%), C-3 (~80%), and C-4 (~100%, one deuterium) as determined by ^1H NMR and mass spectral analysis. Two control experiments indicated that the isotopic exchanges come about as a result of the transformation itself. Recovered 5 was found to be undeuterated at these positions, and unlabeled 6, when exposed to the same experimental conditions, showed no exchange at C-1 and C-4 and less than 20% exchange at C-3.



6

SCHEME II



Scheme II outlines a mechanism which is consistent with these observations. In this pathway, enolization of the aldehyde produces an ene-diol derivative, 8, which upon protonation in the appropriate direction yields oxonium ion 9. Deprotonation of 9 can occur to give the endocyclic enol ether 10, in which the hydroxyl group is highly activated. Thus, protonation and departure of hydroxyl produces 11, in which the positive charge is stabilized by delocalization over several atoms. Since 11 has neopentyl cation character, one might anticipate rearrangemen of the carbon skeleton at this point. However, either of the resulting tertiary cations would appear to be less stable than the delocalized precursor. A more likely fate for 11, therefore, is deprotonation to 12, which is simply the enol of 6.

Complete isotopic exchange of one proton at C-4 of 6 is a necessary consequence of the fin step in this proposed pathway when the reaction is carried out in D_2O. The high levels of deuterium incorporation at C-1 and C-3 imply that oxonium ion 9 is formed reversibly from both 8 a 10. Isotopic exchange at C-1 is difficult to rationalize by any other mechanism.[7]

Evidence that pederin (1) and pedaldehyde (3) react via a corresponding series of intermediates was provided by the production of pederenal (2) bearing a similar pattern of deuterium incorporation when 1 or 3 were dehydrated in the presence of D_2O.

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REFERENCES AND NOTES

1. (a) A. Furusaki, T. Watanabe, T. Matsumoto, M. Yanagiya, Tetrahedron Lett., 6301 (1968); (b) A.B. Corradi, A. Mangia, M. Nardelli, C. Pelizzi, Gazz. Chim. Ital., 101, 591 (1971).
2. (a) C. Cardani, D. Ghiringhelli, R. Mondelli, A. Quilico, Tetrahedron Lett., 2537 (1965); (b) Gazz. Chim. Ital. 96, 3 (1966).
3. Pederenal is also produced by acid treatment of pseudopederin,[2] dihydropederin,[2] dihydropseudopederin,[2] meropederoic acid,[2] and meropederin acetal.[8]
4. J. Meinwald, Pure Appl. Chem., 49, 1275 (1977).
5. The experimental details of this work will be published elsewhere.
6. Satisfactory ^{1}H NMR, IR, and MS data have been obtained for all intermediates in this sequence.
7. An alternative path from 9 to 12 would involve ring opening to an acyclic trihydroxyketone, loss of the β-hydroxyl group to form a conjugated enone, and reclosure to yield 12. This seems unattractive, since dehydration of the acyclic intermediate would have to produce only cis-enone to make reclosure possible.
8. C. Cardani, D. Ghiringhelli, R. Mondelli, A. Selva, Gazz. Chim. Ital., 103, 247 (1973).

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