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A HIGHLY STEREOSELECTIVE OSMIUM TETROXIDE-CATALYZED HYDROXYLATION OF γ-HYDROXY α,β-UNSATURATED ESTERS

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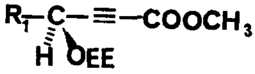
Abstract: The hydroxylation of α,β-unsaturated esters catalyzed by osmium-tetroxide leads to 3,4-dihydroxy-γ-lactones of predictable stereochemistry.

We report here on the remarkable stereoselectivity encountered in the osmium tetroxide hydroxylation of E α,β-unsaturated esters bearing a γ-hydroxyl function.



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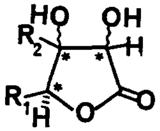

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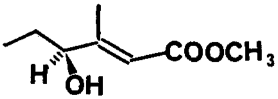
In the case where $R_2 = CH_3$, that transformation would lead to a sequence of alternating secondary, tertiary and secondary carbinols (cf. starred centers in 2) which is, an occasional structural feature, inter alia, of a number of macrolides (e.g. erythromycin).

Addition of dimethyllithiocuprate to the ethoxyethyl-protected hydroxy acetylenic ester 1[1] (-78°C → room temperature; tetrahydrofuran) gave the E ester 3 after removal of the protecting group. Hydroxylation catalyzed by osmium tetroxide[2] (aqueous acetone, N-methylmorpholine oxide; room temperature; sodium bisulfite work up) afforded a single crystalline dihydroxylactone, mp 73-74°C, in 73% yield. NMR (CDCl$_3$, 200 MHz): δ 1.12 (3H, t J = 7 Hz), 1.24 (3H, s), 1.72 (2H, m), 4.20 (1H, dd, J = 9, 4 Hz), 4.60 (s, 1H). The necessarily trans diol was established to be 4 by a single crystal x-ray determination.



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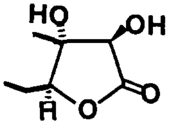

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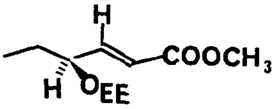
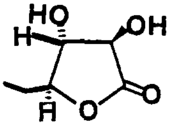
The specific formation of a single diol is of considerable interest since there exists, to our knowledge, no convincing case in which the stereochemistry of an osmium tetroxide hydroxylation is clearly the result of coordination to a neighboring hydroxyl group[3]. That it is not the free hydroxyl of 3 which is responsible for the observed stereochemistry is strongly suggested by the fact that its ethoxyethyl derivative leads to the identical lactone 4 upon removal of the protecting group after hydroxylation.

In deciding on a possible model for hydroxy (alkoxy) esters which could rationalize these results, two further facts need be considered:

1) Replacement of the β-methyl group of 3 by a hydrogen does not affect the stereoselectivity: the structure of the dihydroxylactone, mp 64-65.5°C, NMR: δ 1.02 (3H, t, J = 7 Hz), 1.79 (2H, m), 4.08 - 4.46 (3H, m) thus obtained was demonstrated to be 5 by single crystal x-ray determination.





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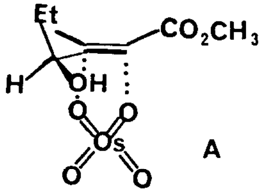
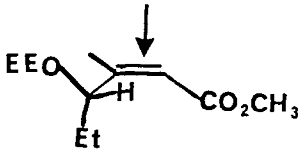
2) There is a considerable effect of the electron withdrawing ester group in enhancing stereoselectivity: the same hydroxylation conditions with the isopropenyl analog of 3 (carbomethoxy replaced by hydrogen) showed considerably less stereoselectivity.

We suggest that a transition state A in which the carbon-oxygen bond is near the plane of the conjugated double bond is compatible with the observed stereochemical course of the hydroxylation reaction. Possibly, this conformation results from a favorable interaction between the p-orbitals of the double bond and an unshared pair on the γ-oxygen. Such an interaction could be due to the electron withdrawing carbomethoxy function.[4] Approach of the osmium reagent would be least hindered between the hydrogen and oxygen functions, thus leading to the observed stereochemistry of 4.[5,6]



A



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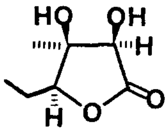

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A corollary of this suggestion is that hydroxylation of the Z-ester isomer of 3 should now make a transition state like A less favorable than one (B) in which it is now, for steric reasons, the smallest group (H) which eclipses the conjugated double bond. The isomer obtained from that reaction was indeed the dihydroxylactone 6 which again results from approach of osmium tetroxide between the OR and H in B. Assignment of the stereochemistry of 6 follows from comparison with the dihydroxylactones derived from the osmium tetroxide-catalyzed hydroxylation of the butenolide 7.[7] This gave a mixture of dihydroxylactones 6 (identical with the product from the Z-ester) and 8, in a ratio of ∼ 1:7 in favor of the latter. Assignment of the structures shown here follows from the determination of nuclear overhauser effects. The percentage NOE observed are indicated on the structure of 6 and 8.

There are four possible relative arrangements that can be obtained from the contiguous addition of a tertiary and a secondary carbinol center at the site of the double bond of a lactone such as 7. The reaction described here represents a stereospecific construction of two of these (cf 4 and 6) and a moderately stereoselective route to another (cf. 8).

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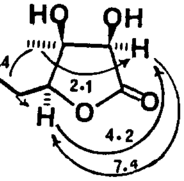

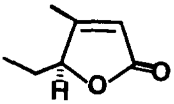

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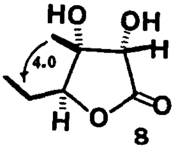

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Acknowledgments: We wish to express our sincere appreciation to Professor Paul Williard of Brown University for carrying out the x-ray structure determinations on dihydroxylactones 4 and 5, and to Dr. John Snyder of this department for carrying out the NOE experiments on dihydroxylactones 6 and 8. We thank the National Science Foundation and the National Institutes of Health for their support of our work.

References and Notes

1. E.J. Corey and J.A. Katzenellenbogen, J. Am. Chem. Soc., 91, 1851 (1961); J.M. Siddall, M. Bishop and J.H. Fried, ibid., 1853 (1969).

2. V. VanRheenen, R.C. Kelly and D. Y. Cha, Tetrahedron Lett., 1973 (1976).

3. Among many examples of hydroxylation trans a) to hydroxyl groups: Th. Posternak and H. Friedli, Helv. Chim. Acta, 36, 251 (1953) or b) to an ether: C.L. Stevens, J.B. Filippi and K.G. Taylor, J. Org. Chem., 31, 1292 (1966). For a contrary model involving hydroxyl coordination, see K. Kon and S. Isoe, Tetrahedron Lett., 3399 (1980) and A.B. Smith, III and D. Boschelli, J. Org. Chem., 48, 1217 (1983). It is not entirely clear, however, that these cases do not simply reflect steric factors.

4. Cf. J. Lessard, J.K. Sanders and M. T. Phan Viet, Tetrahedron Lett., 2059, 1982. We thank Professor Barry Trost for drawing our attention to this paper.

5. Of course, if there is more than one hydroxyl or alkoxy group in the vicinity of the conjugated double bond, the stereochemical results may not easily be anticipated. One such case has been described by T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham and F.J. Walker, J. Org. Chem., 47, 1373 (1982). The selectivity in that case was less pronounced, but in the same direction as we observed in the synthesis of 5.

6. Professor Y. Kishi has studied the osmium tetroxide hydroxylation of a variety of allylic carbinols which differ from those we now report in not having an ester conjugated with the olefin, as well as by having a hydrogen rather than a methyl at the double bond end proximate to the allylic CO bond. He suggests that a different transition state model best explains the hydroxylation results in these structural types. We thank him for letting us see a copy of his paper in advance of publication.

7. Cf. R. Lukes, M. Moll, A. Zobacova and J. Jary, Coll. Czech. Commun., 27, 500 (1962).

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