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THE CONVERSION OF METHYL PSEUDOMONATE C TO PSEUDOMONIC ACID A

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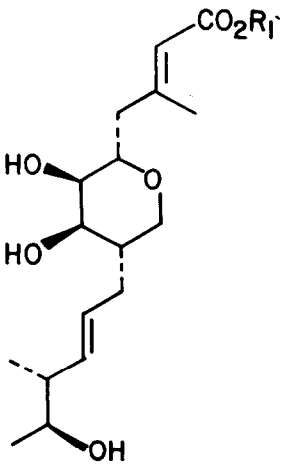
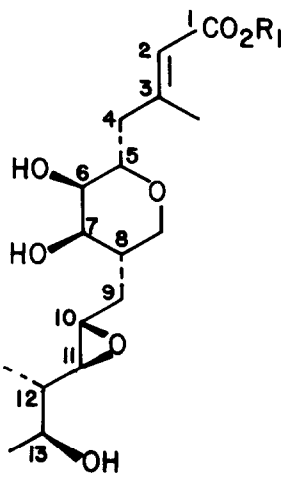
Summary: *A process for the conversion of methyl pseudomonate C to pseudomonic acid A with partial stereoselectivity is described.*

We have recently reported the total synthesis of the important antibiotic substance pseudomonic acid C (1a) through employment of a key alkoxyselenation reaction to convert a 3,4-dihydro-2H-pyran to a 2-alkoxy-5,6-dihydro-2H-pyran.[1] The reaction sequence consituted a





1a $R_1 = (CH_2)_8CO_2H$

1b $R_1 = (CH_2)_8CO_2Me$

1c $R_1 = C_2H_5$

2a $R_1 = (CH_2)_8CO_2H$

2b $R_1 = (CH_2)_8CO_2Me$

2c $R_1 = C_2H_5$

formal total synthesis of the related antibiotic pseudomonic acid A (2a) as well, for the conversion of methyl pseudomonate C (1b) to methyl pseudomonate A (2b) had been reported previously by Rogers, Clayton and O'Hanlon.[2] Thus, trimethylsilylation of the hydroxyl groups of 1b followed by m-chloroperbenzoic acid treatment and deprotection gave an hplc separable mixture of 2b and its isomer in a 1:2 ratio.

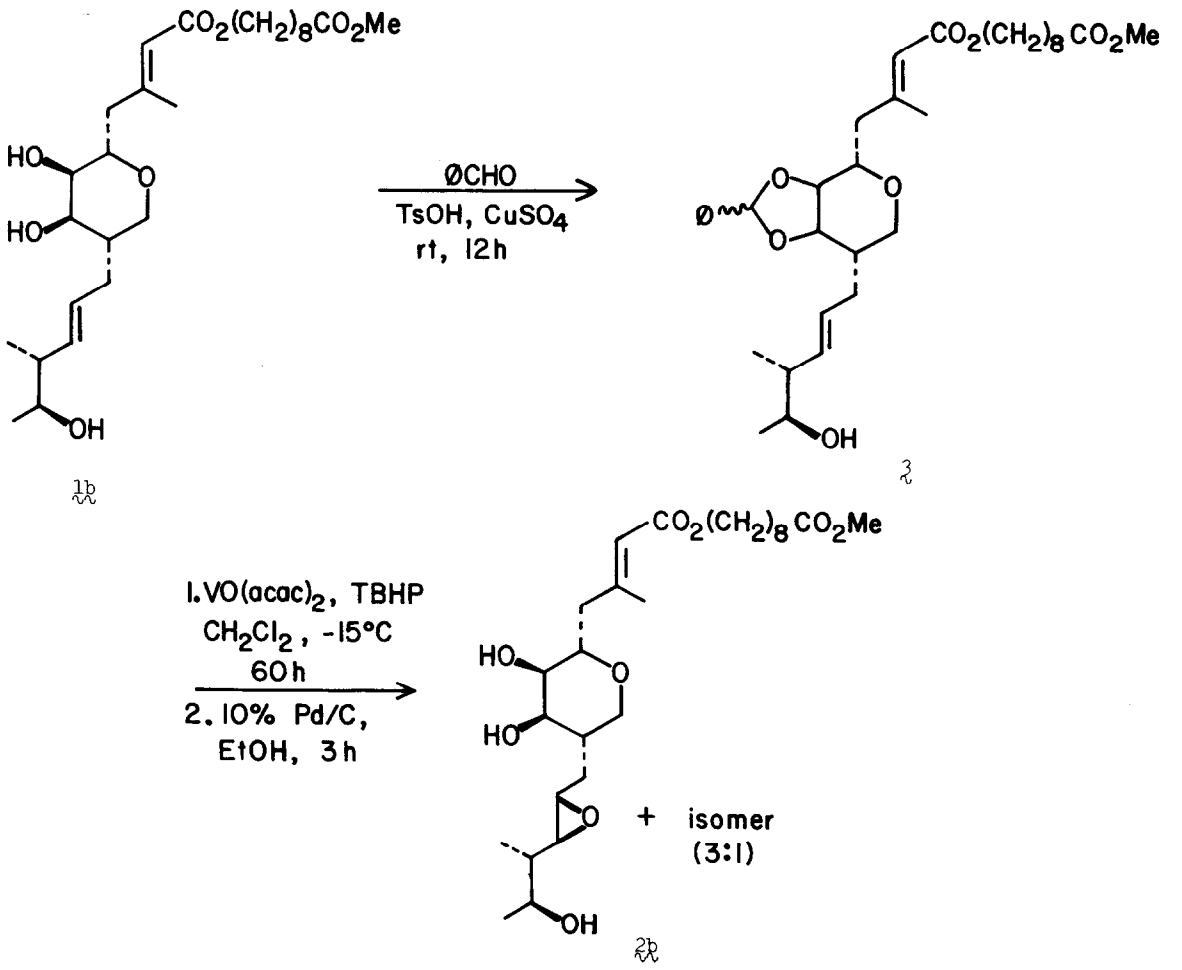
The conversion of 2b to 2a has been reported by us and can be effected by prior silylation of the hydroxyl groups to prevent intramolecular epoxide ring opening, then ester hydrolysis with potassium hydroxide/sodium bicarbonate followed by an acid workup (the pH of the hydrolysis mixture is adjusted to 4).[1]

We now describe in detail a somewhat more selective procedure for converting methyl pseudomonate acid C to pseudomonic acid A. We had first made the observation that direct epoxidation of methyl pseudomonate C without prior protection of the hydroxyl groups using MCPBA/$NaHCO_3$ in methylene chloride for one day at -15°C afforded some improvement in the ratio of 2b to its isomer over that obtained by Rogers. A 1:1 mixture was generated under these conditions.

To further enhance production of the correct isomer, we felt that use of the $VO(acac)_2$/TBHP system was called for.[3] A test reaction was first carried out on the more readily available ethyl monate C (1c). Thus, reaction of 1c with $VO(acac)_2$/TBHP in methylene chloride at 0°C for two days delivered a 1.5:1 mixture of ethyl monate A (2c) and its isomer. This somewhat disappointing ratio suggested that protection of the C_6, C_7-cis-diol unit would be required to optimize formation of the desired isomer. Diol protection would serve to stop competing complexation with the metal at these centers.[4]

Accordingly, the cis-diol of ethyl monate C was protected as its benzylidene acetal and the $VO(acac)_2$/TBHP epoxidation was carried out. By the criterion of ^1H NMR analysis (300 MHz), a 3:1 mixture of 2c and its isomer was produced in this case.

Application of the same strategy to methyl pseudomonate C was examined next.[5] Reaction of 1b with benzaldehyde in the presence of p-toluenesulfonic acid and copper sulfate in benzene gave 3. Epoxidation with the $VO(acac)_2$/TBHP system was carried out in methylene chloride at -15°C for 60 h (78%). Removal of the benzylidene protecting group by hydrogenolysis over 10% Pd/C in ethanol for 3 h provided methyl pseudomonate A and its isomer in a 3:1 ratio



(60%; some other minor impurities formed by overreduction were also present). The methyl pseudomonate A and its isomer could be separated easily by hplc on a μ-porasil column using 70% CH_2Cl_2/30% CH_3CN (containing 2% H_2O) as solvent.[6] The 300 MHz ^1H NMR spectrum of the synthetic material was identical to that of the methyl ester of the natural product. The hydrolysis of the methyl ester to the acid can be accomplished as detailed above.

The scheme reported herein thus offers a more stereoefficient route for the production of pseudomonic acid A from methyl pseudomonate C.

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2. J. P. Clayton, P. J. O'Hanlon and N. H. Rogers, Tetrahedron Lett., 881 (1980).
3. K. P. Sharpless and T. R. Verhoeven, Adrichimica Acta, 12, 63 (1979).
4. Formation of the desired epoxide isomer by use of the V^{+5}/TBHP system was anticipated on the basis of considerations similar to those offered by Kishi to explain the stereoselectivity encountered in the epoxidation of bis-homoallylic alcohols. T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. S.-Palmer and Y. Kishi, J. Am. Chem. Soc., 100, 2933 (1978). T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi, Tetrahedron Lett., 2741 (1978).
5. These studies have been carried out on both the natural and synthetic materials.
6. We thank Dr. N. H. Rogers for informing us of the hplc conditions required to separate these materials.

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