Tetrahedron Letters No. 37, pp 3263 - 3266, 1974. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 5-ACETOXY-9-OXOTRIDECANOLACTONE. A MODEL FOR ERYTHRONOLIDE B

James D. White,* Siegfried N. Lodwig, Gary L. Trammell, and Michael P. Fleming

Department of Chemistry, Oregon State University
Corvallis, Oregon 97331

(Received in USA 8 July 1974; received in UK for publication 2 August 1974)

The fourteen-membered lactone ring of erythronolide B,[1] the aglycone of erythromycin B, contains a hydroxyl group at C-5 and a ketone function at C-9. As a model for the eventual total synthesis of erythronolide B, a route to 5-acetoxy-13-hydroxy-9-oxotridecanoic acid (15) has been developed, with the aim of effecting lactonization at the final stage of the macrolide synthesis.[2]

Recognizing that synthesis of a structure as stereochemically complex as erythronolide B will require a stable platform upon which to build the array of functionality in the proper configurational sense, we have elected to assemble the thirteen-carbon backbone from two cyclopentanoid and one propanoid unit. Alkylation of the potassio salt of cyclopentanone carboxylic ester[3] with 1,3-dibromopropane, followed by decarboxylation with 48% HBr (reflux, 2 hr), gave bromoketone 1 (1745 cm^{-1}; δ 3.42 (2 H, t, J=7 Hz)). Baeyer-Villiger oxidation of 1 with CF_3CO_3H,[4] buffered in CH_2Cl_2 with Na_2HPO_4 (1 hr at -3°, 3 hr at 25°), afforded the δ-lactone 2 (1740 cm^{-1}; δ 4.30 (1 H, m), 3.56 (2 H, t, J=7 Hz)) regio specifically and in excellent yield.[5] Bromolactone 2 was then used to alkylate the sodio salt of cyclopentanone carboxylic ester (prepared from the ester and sodium in refluxing toluene)[6] in toluene (reflux, 6 hr), with the resulting formation of ketoester 3 (1750, 1730 cm^{-1}) in 80% yield. After decarboxylation of 3 with 20% $HClO_4$ (reflux, 1.5 hr), ketolactone 4 (1740 cm^{-1}, δ 4.26 (1 H, m)) was obtained (88%) following chromatography on Florisil (ether eluent).

The δ-lactone carbonyl group in 4 provides the incipient, terminal hydroxyl group of 15 and, in order to differentiate functions at the chain termini, it became necessary to protect the cyclopentanone carbonyl of 4. This was conveniently achieved via transesterification and internal ketalization of 4 with $HC(OEt)_3$ in the presence of p-TsOH (EtOH, 25°, 19 hr), which led to 5 (1735 cm^{-1}; δ 4.14 (2 H, q), 3.8 (1 H, m), 3.50 (2 H, q)) in quantitative yield. The ester

group was reduced with $LiAlH_4$ (Et_2O, 0°), affording alcohol 6 (3500 cm^{-1}; δ 3.4-4.0 (5 H)), which was converted to its benzyl ether 7 (δ 4.50, 2 H, s) with benzyl bromide and NaH in glyme. The cyclopentanone carbonyl was then unmasked by hydrolysis with satd, aqueous tartaric acid in MeOH (25°, 2 hr), giving hydroxy-ketone 8 (3500, 1735 cm^{-1}; δ 7.35 (5 H), 4.54 (2 H, s), 3.47 (2 H, t, and 1 H, m) in an overall 64% yield from 6. Baeyer-Villiger oxidation of 8 with CF_3CO_3H (as for 1) afforded the δ-lactone 9, accompanied by its trifluoroacetate 10 (1780 cm^{-1}). Treatment of the crude product with KOH in aqueous MeOH, followed by acidification with conc HCl gave pure 9 (3440, 1733 cm^{-1}; δ 7.30 (5 H), 4.48 (2 H, s), 4.26 (1 H, m), 3.5 (2 H + 1 H) in 88% yield. The alcohol function of 9 underwent smooth oxidation with Collins' reagent[7] to produce keto-lactone 11 (1735, 1715 cm^{-1}) in 62% yield.

Saponification of 11 with 1 equiv of KOH in MeOH followed by benzylation of the dry potassium salt with benzyl bromide in DMF containing a catalytic amount of Et_3N produced 12, which was slowly converted to its acetate 13 (1733 cm^{-1}; δ 5.10 (2 H, s), 4.85 (1 H, m), 4.48 (2 H, s), 3.45 (2 H, t), 2.4 (6 H, m), 2.00 (3 H, s) with Ac_2O-pyridine (40°, 48 hr) (61% based on 11). The sluggishness of this acetylation may be attributable to an equilibrium between 12 and the more favorable hemiketal form 14. Hydrogenolysis of 13 over 10% Pd/C (EtOAc) furnished cleanly the hydroxy acid 15 (3200-2500, 1733, 1709 cm^{-1}; δ 8.24 (1 H, broad); 4.86 (1 H, m), 3.2 (2 H, m), 2.4 (6 H, m), 2.05 (3 H, s), which provided the focus for lactonization studies.

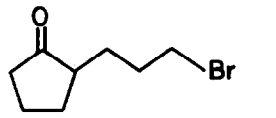
Exposure of 15 (0.01-0.02 M in benzene) to p-toluenesulfonyl chloride and Et_3N (1 equiv each), followed by preparative layer chromatography on silica with glyme gave the rather unstable lactone 16 (1735, 1710 cm^{-1}; δ 4.90 (1 H, m), 3.5 (2H, m), 2.45 (6 H, m), 2.04 (3 H, s); m/e 284)[8] in 52% yield. Alternatively, a milder procedure involving treatment of a benzene solution of 15 with 1,1'-carbonyldiimidazole,[9] followed by a catalytic quantity of sodium t-amylate in benzene, afforded 16 in 40% yield.[10,11]

The synthetic route to a 14-membered lactone described herein appears applicable to erythronolide as well as other macrolide systems. Our further efforts towards synthesis of macrocyclic lactones will be reported subsequently.

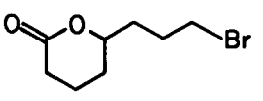
Acknowledgments. We are indebted to the National Science Foundation (GP-41510X) and to the National Institutes of Health (AI-10964) for financial support.

REFERENCES

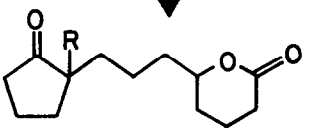
1. P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, O. Weaver, U. C. Quarck, R. R. Chauvette, and R. Monahan, J. Amer. Chem. Soc., 79, 6062 (1957).
2. Cf D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, Tetrahedron, 24, 2443 (1968); I. Vlattas, I. T. Harrison, L. Tokes, J. H. Fried, and A. D. Cross, J. Org. Chem., 33, 4176 (1968); H. L. Wehrmeister and D. Robertson, ibid., 33, 4173 (1968).
3. R. Mayer in "Newer Methods of Preparative Organic Chemistry", W. Foerst, Ed, Academic Press, New York, Vol II, 1963, p 101.
4. W. D. Emmons and G. B. Lucas, J. Amer. Chem. Soc., 77, 2287 (1955).
5. S. N. Lewis in "Oxidation", R. L. Augustine, Ed, Marcel Dekker Inc., New York, Vol I, 1969, p 213.
6. F. Elsinger, Org. Synth., 5, 76 (1973).
7. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).
8. Synthesis of the desacetoxy version of 16 along different lines has recently been reported (I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby, and S. Ueng, J. Org. Chem., 38, 1234 (1973).
9. H. A. Staab, Angew. Chem. Internatl. Edn., 1, 351 (1962).
10. Synthesis of the macrolide pyrenophorin successfully utilized a similar lactonization procedure (E. W. Colvin, T. A. Purcell, and R. A. Raphael, Chem. Commun., 1031 (1972)).
11. Satisfactory analytical data (combustion analysis or exact mass measurement) were obtained for compounds reported herein.



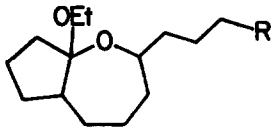
1



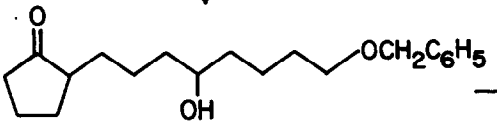
2



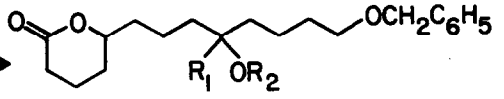
3, R = CO_2Me(Et)
4, R = H



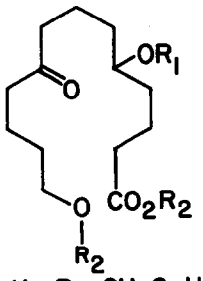
5, R = CO_2Et
6, R = CH_2OH
7, R = $CH_2OCH_2C_6H_5$



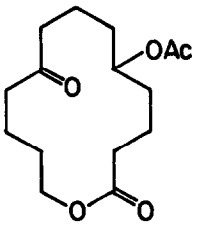
8



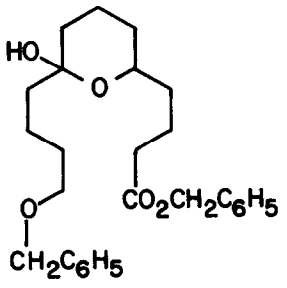
9, $R_1 = R_2 = H$
10, $R_1 = H$, $R_2 = COCF_3$
11, $R_1, R_2 = O$



12, $R_1 = H$, $R_2 = CH_2C_6H_5$
13, $R_1 = COCH_3$, $R_2 = CH_2C_6H_5$
15, $R_1 = COCH_3$, $R_2 = H$



16



14