Tetrahedron Letters No. 25, pp 2327 - 2330. 0040-4039/79/0615-2327$02.00/0

SYNTHESIS OF 16-MEMBERED RING MACROLIDE ANTIBIOTICS I. STEREOSELECTIVE CONSTRUCTION OF THE "RIGHT WING" OF THE CARBOMYCINS AND LEUCOMYCINS FROM D-GLUCOSE

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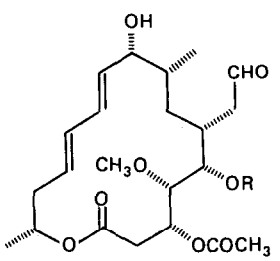
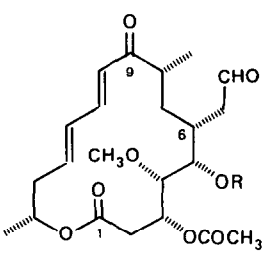
Summary. D-Glucose was converted to a backbone chain containing the appropriate functionalities and correct stereochemistry for the construction of the C1-C9 fragment of the 16-membered ring macrolide antibiotics carbomycin A and B and leucomycin A_3.

Leucomycin A_3 and carbomycins A and B (magnamycins A and B) shown below are members of the clinically important 16-membered ring class of macrolide antibiotics.[1] We wish to report a highly efficient synthesis of the "right wing" segment (C1-C9) of these substances from D-glucose. Our synthetic plan called for the construction of the Michael acceptor 6 (Scheme I) corresponding to the C1-C6 fragment of these 16-membered ring macrolides. The α,β-unsaturated ester 6 was then to be utilized for building up the complete "right wing" (C1-C9) as the aldehyde 9, onto which the "left wing" will be attached. Both the construction of 6 and the successful 1,4 addition of cuprate reagents to this acceptor have now been realized and are reported herein.



LEUCOMYCIN A_3



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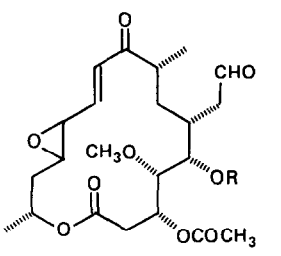
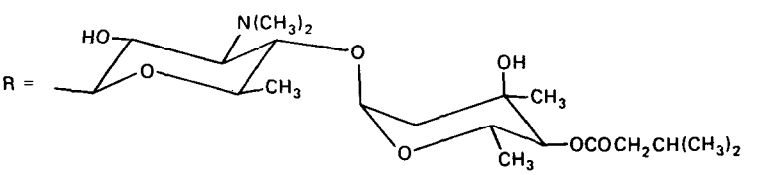
(MAGNAMYCIN B)



CARBOMYCIN A
(MAGNAMYCIN A)

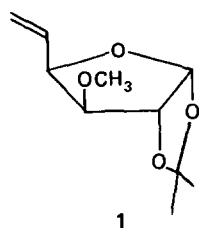


Intermediate 1, easily derived from D-glucose[2], was converted to the primary alcohol 2[3] [86% yield; IR (CCl_4) νmax 3470cm^{-1} (OH); $[\alpha]_D^{23^o}$ -44.53 (CH_3OH); Rf 0.40 (silica, 2.5% CH_3OH in ether)] by hydroboration with diisoamylborane in THF (0-25°C). Oxidation of this alcohol with Jones reagent in acetone at 0°C followed by esterification (CH_2N_2) led to the methyl ester 3[3] [82% yield; IR (CCl_4) νmax 1740cm^{-1} (ester); $[\alpha]_D^{23^o}$ -45.89 (CH_3OH); Rf 0.26 (ether-petroleum ether, 1:1)]. Removal of the acetonide from 3 at 80°C with amberlite IR-120 (H^+) in aqueous solution furnished the lactol 4[3] [78% yield, mixture of epimers; IR ($CHCl_3$) νmax 3410 (OH), 1730cm^{-1} (ester); $[\alpha]_D^{23^o}$ -16.19 (CH_3OH); Rf 0.26 (2.5% CH_3OH in ether)]. Condensation of the lactol 4 with (carbethoxymethylene)-triphenylphosphorane in toluene solution (25°C, 16h) resulted in the formation of the crystalline α,β-unsaturated ester 5[3] [(86% yield; m.p. 48-49°C; IR ($CHCl_3$) νmax 3460 (OH), 1740, 1720 (esters), 1660cm^{-1} (olefin); $[\alpha]_D^{23^o}$ -8.74 (CH_3OH); Rf 0.37 (2.5% CH_3OH in ether)]. The acetonide 6[3] [IR ($CHCl_3$) νmax 1740, 1720 (esters), 1660cm^{-1} (olefin); $[\alpha]_D^{23^o}$ +18.45 (CH_3OH); Rf 0.12 (ether-petroleum ether, 1:1)] was obtained in 95% yield by exposure of the diol 5 to excess dimethoxyacetone in benzene in the presence of catalytic amounts of camphorsulfonic acid (25°C, 0.5h).

The α,β-unsaturated ester 6 now readily available in large quantities contains the appropriate functionalities and correct stereochemistry for elaboration to the 16-membered ring macrolide antibiotics leucomycin A_3 and carbomycins A and B. To this end we have demonstrated that 6 reacts smoothly and in a highly stereoselective manner with lithium di(2-methylallyl) cuprate[4] in ether at -78°C (2h) to afford the olefin 7[3] [(85% yield; IR (CCl_4) νmax 1740 (esters), 1640cm^{-1} (olefin); $[\alpha]_D^{23^o}$ +5.09 (CH_3OH); Rf 0.28 (ether-petroleum ether, 1:1)]. The 360MHz ^{1}H NMR and the ^{13}C NMR spectra of this compound were consistent with a major isomer at C6 contaminated with less than 5% of its epimer at that center. Careful hydroboration of 7 (diisoamyl borane or borane in THF, 0-25°C) produced the primary alcohol 8 [two epimers at C8; 80%, ca 2.5:1; IR (CCl_4) νmax 3470 (OH), 1740cm^{-1} (esters); Rf 0.35, 0.41 (20% ethylacetate in ether)]. Each epimer of 8 was then oxidized to the corresponding aldehyde 9 [85% yield; IR (CCl_4) νmax 2800 (aldehyde), 1740cm^{-1} (esters, aldehyde); Rf 0.16 (ether-petroleum-ether 1:1)] with pyridinium chlorochromate in CH_2Cl_2 at 25°C.

An x-ray diffraction analysis on a crystalline derivative in this series is planned and is expected to reveal the stereochemistries of C6 and C8. These centers, however, are of little consequence, since a proper choice of the cuprate reagent in the elaboration of 6 could allow for A) the possible interchange of destinies for the two generated side chains, thus defining the desired stereochemistry at C6, and B) the introduction of the correct C8 stereocenter, which is, however, epimerizable at a later stage.

The construction of the "left wing" of these 16-membered ring macrolide antibiotics and their eventual total synthesis is now in progress in our laboratories.



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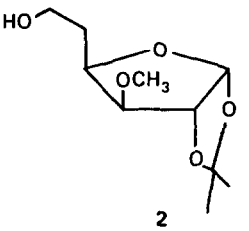

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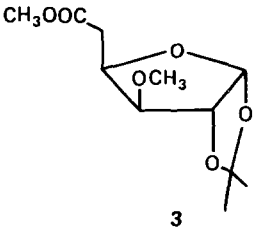

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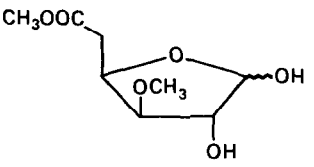

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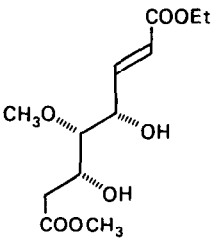

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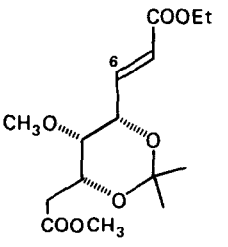

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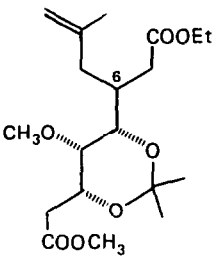

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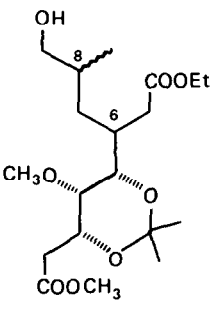

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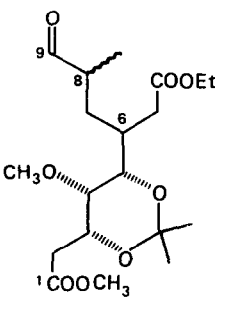

9

Scheme I. Synthesis of the "right wing" (C_1–C_9) of the leucomycins and carbomycins.

Acknowledgement

The 360MHz ^{1}H NMR spectra were recorded at the Middle Atlantic Regional NMR Facility (NIH No PR542) at the University of Pennsylvania directed by Dr. G. McDonald. The work was financially supported by Merck Sharp and Dohme, USA, Grünenthal Chemie, West Germany and the University of Pennsylvania.

References and Footnotes

1. (a) K. Tatsuta, A. Tanaka, K. Fujimoto, M. Kinoshita, S. Umezawa, J. Amer. Chem. Soc., 99, 5826 (1977); (b) S. Omura and A. Makagawa, J. Antibiot., 28, 401 (1975) and references cited therein.
2. (a) J. S. Josan, F. L. Eastwood, Carbohyd. Res., 7, 161 (1968); (b) J. K. Jones, J. L. Thompson, Can. J. Chem., 35, 955 (1957).
3. ^{1}H NMR Spectral data (360MHz, $CDCl_3$): 2: τ 4.09 (d, J=6Hz, 1H, O-CH-O-acetonide), 5.40 (d, J=4.2Hz, 1H, CH-O-acetonide), 5.63 (m, 1H, CH-O), 6.19 (m, 2H, CH_2OH), 6.35 (d, J=3Hz, 1H, CH-OCH_3), 6.57 (s, 3H, OCH_3), 7.93 (s, 1H, OH), 8.05 (m, 2H, CH_2), 8.51 and 8.69 (singlets, 3H each, acetonide-CH_3); 3: τ 4.09 (d, J=4.2Hz, 1H, O-CH-O-acetonide), 5.40 (d, 4.2Hz, 1H, CH-O-acetonide), 5.43 (dt, J=6.0, 3.6Hz, 1H, CH-O), 6.20 (d, 3.6Hz, 1H, CH-OCH_3), 6.29 (s, 3H, $COOCH_3$), 6.60 (s, 3H, OCH_3), 7.24 (d, J=6.0Hz, 2H, CH_2COOCH_3), 8.49 and 8.67 (singlets, 3H each, acetonide-CH_3); 4 (two anomers): τ 4.55 (d, J=4.2Hz) and 4.85 (s) (1H, O-CH-OH), 5.30 (m, 1H, CH-O-), 5.73 (s) and 5.84 (m) (1H, CH-OH), 6.21 (m, 1H, CH-OCH_3), 6.30 and 6.31 (singlets, 3H, $COOCH_3$), 6.52 and 6.55 (singlets, 3H, OCH_3), 7.20 (dd, J=7.2Hz) and 7.37 (d, J=2Hz) (2H, CH_2COOCH_3); 5: τ 2.97 (dd, J=16, 5Hz, 1H, CH=CHCOOEt), 3.80 (dd, J=16, 2Hz, CH=CHCOOEt), 5.44 (m, 1H, C5-H), 5.80 (q, J=7.2Hz, 3H, OCH_2CH_3, OH), 6.28 (s, 3H, $COOCH_3$), 6.48 (s, 3H, OCH_3), 6.78 (m, 2H, C3-H, OH), 7.07 (d = J=6.0Hz, 1H, CH-OCH_3), 7.29 (dd, J=15.5, 7.2Hz, 1H, CH_2COOEt), 7.40 (dd, J=15.5, 4.8Hz, 1H, CH_2COOEt), 8.80 (t, J=7.2Hz, 3H, CH_2CH_3); 6: τ 3.00 (dd, J=16, 5Hz, 1H, CH=CHCOOEt), 3.81 (dd, J=16, 2Hz, 1H, CH=CHCOOEt), 5.41 (d, J=2.4Hz, 1H, C5-H), 5.61 (dt, J=6.5, 2.4Hz, 1H, C3-H), 5.79 (q, J=7.2Hz, 2H, OCH_2CH_3), 6.28 (s, 3H, $COOCH_3$), 6.60 (s, 3H, OCH_3), 6.82 (s, 1H, CH-OCH_3), 7.25 and 7.34 (ddoublets, J=15.5, 7.2Hz, 1H each, CH_2COOEt), 8.50 and 8.51 (singlets, 3H each, acetonide-CH_3), 8.71 (t, J=7.2Hz, 3H, CH_2CH_3); 7: τ 5.25 and 5.31 (singlets, 1H each, $=CH_2$), 5.89 (q, J=7.2, 2H, OCH_2CH_3), 6.20 (dd, J=7.2, 1.2Hz, 1H, C5-H), 6.32 (s, 3H, $COOCH_3$), 6.52 (s, 3H, OCH_3), 6.82 (s, 1H, C3-H), 7.34 (d, J=7.2Hz, 2H, CH_2COOCH_3), 7.50 (m, 3H, C6-H, CH_2-C=, CH_2COOEt), 7.68 (dd, J=15, 4.8Hz, 1H, CH_2COOEt), 7.98 (dd, J=15, 11Hz, 1H, CH_2-C=), 8.28 (bs, 3H, CH_3-C=), 8.60 and 8.62 (s, 3H each, acetonide-CH_3), 8.75 (t, J=7.2Hz, 3H, CH_2CH_3).
4. (a) H. O. House, W. F. Fischer, Jr., J. Org. Chem., 34, 3615 (1969); (b) D. Seyferth, M. A. Weiner, J. Org. Chem., 26, 4797 (1961).

(Received in USA 22 February 1979)