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SYNTHESIS OF A FUNCTIONALIZED D-GLUCOSE: A SYNTHON FOR THE CARBOMYCINS (MAGNAMYCINS)

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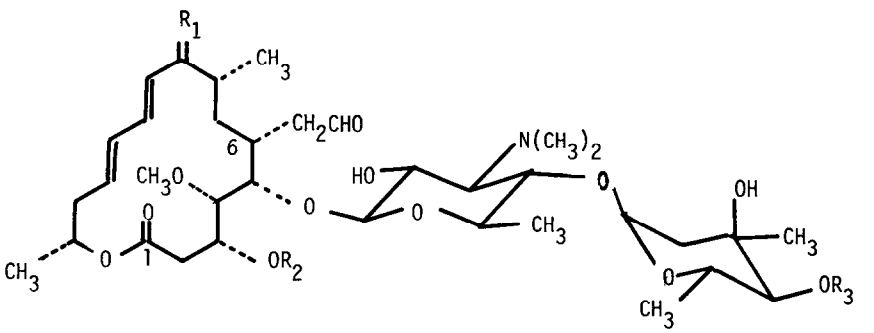
Abstract: D-Glucose has been converted into its functionalized derivative 7b a synthon (C_1-C_6) of the carbomycin macrolide antibiotics.

The 16-membered macrolides 1 are representative of a group of naturally occurring antibiotics which are active against gram positive organisms and certain *mycoplasm* strains.[1,2] As part of a program to synthesize members of this class, we report in this Letter a functionalized D-glucose which serves as the chiral C_1-C_6 synthon of the aglycone portion of these antibiotics.[3]



D-mycaminose L-mycarose

1a, R_1 = α-OH, R_2 = OAc, R_3 = i-valerate, leucomycin A_3

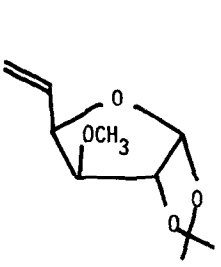
b, R_1 = O, R_2 = OAc, R_3 = i-valerate, carbomycin B

c, R_1 = O, R_2 = OH, R_3 = i-valerate, niddamycin

The olefin 2 was prepared by a four step sequence (82% yield) from diacetone glucose by modified literature procedures.[4] Hydroboration of olefin 2 (disiamylborane, 25°C, 18h; $NaOH/H_2O_2$, <20°C) provided the alcohol 3a[5] in 88% yield: bp 110°C (0.25 mm); $[\alpha]_D^{31}$-47.6° (c 1.01, $CHCl_3$); IR (neat) 3450 cm^{-1}; NMR ($CDCl_3$, 270 MHz): δ5.88 (1H, d, J = 4 Hz, C_1-H), 4.59 (1H, d, J = 4 Hz, C_2-H), 4.32 (1H, m, C_4-H), 3.76 (2H, m, $-CH_2OH$), 3.62 (1H, d, J = 3 Hz, C_3-H), 3.42 (3H, s, $-OCH_3$), 2.65 (1H, m, OH), 2.05-1.81 (2H, m, CH_2), and 1.50, 1.33 (2 x 3H, s, acetonide). The hydroxyl group was protected by allylation (NaH, THF reflux; allyl bromide, 25°C, 18h) to provide 3b in 94% yield: bp 89-90°C (0.15 mm); $[\alpha]_D^{31}$-41.9° (c 1.00, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ5.89-5.84 (1H, m), 5.87 (1H, d, J = 4 Hz), 5.30-5.14 (2H, m), 4.57 (1H, d, J = 4 Hz), 4.29 (1H, m), 3.98 (1H, d,d, J = 5 Hz, 1 Hz), 3.60-3.53 (4H, m), 3.40 (3H, s), 2.00-1.93 (2H, m) and 1.49, 1.32 (2 x 3H, s). The allyl protecting group could be cleaved with tris-triphenylphosphine rhodium chloride according to the procedure of Corey[6] to regenerate the alcohol 3a.

The acetonide group of 3b was removed (4% H_2SO_4:dioxane, 1:1 (V/V), 100°C, 2h) to afford the anomeric hemiacetals 4 (positive Fehlings test) as a viscous oil in 92% yield: IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ3.44 and 3.41 (3H, 1:2 ratio, OCH_3). As anticipated, the hemiacetal was quantitatively reconverted to 3b (2,2-dimethoxypropane, p-TsOH, 18h, reflux), precluding the direct formation of the dioxolane 7b (as its acetonide) from 4. Reduction of 4 ($NaBH_4$, C_2H_5OH, 25°C, 60h) provided the crude triol 5 (negative Fehlings and negative boron tests) in 100% yield: IR (neat) 3400 cm^{-1}.

The triol was transformed (C_6H_5CHO, H_2SO_4, CH_2Cl_2, 4Å molecular sieves, 2 days, 25°C) into a 7:1 mixture[7] (35% yield from 3b) of 7a: mp 63-64°C; IR ($CHCl_3$) 3550 cm^{-1}; $[\alpha]_D^{31}$+41.3° (c 1.83, $CHCl_3$); NMR ($CDCl_3$, 270 MHz) δ7.55-7.49 (2H, m), 7.39-7.28 (3H, m), 6.00-5.85 (1H, m), 5.61 (1H, s, benzylidene methine), 5.34-5.15 (2H, m), 4.10-3.94 (6H, m), 3.84-3.78 (1H, m), 3.71-3.57 (2H, m), 3.52 (3H, s), 3.12 (1H, s), 2.21-2.08 (1H, m), and 1.98-1.85 (1H, m) and 6: NMR ($CDCl_3$, 270 MHz) δ5.96 (1H, s) and 5.82 (1H, s) (benzylidene methines). Collins oxidation of alcohol 7a provided 5-deoxy-6-O-allyl-2,4-di-O-benzylidene-3-O-methyl-D-glucose 7b in 60% yield: mp 79-80°C; $[\alpha]_D^{25}$+63.4° (c 0.95, $CHCl_3$); IR ($CHCl_3$) 2860, 2750 and 1730 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ9.76 (1H, s, CHO), 7.60-7.26 (5H, m, phenyl), 5.99-5.89 (1H, m, -CH=), 5.66 (1H, s, benzylidene methine), 5.28-5.19 (2H, m, $=CH_2$), 4.32 (1H, d, J = 2 Hz, C_2-H), 4.12-4.05 (1H, m, C_4-H), 3.99 (2H, d, J = 6 Hz), 3.72-3.45 (2H, m, $-CH_2O-$),



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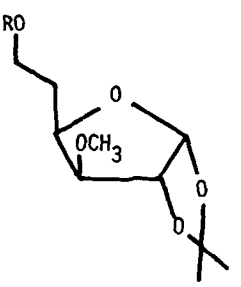
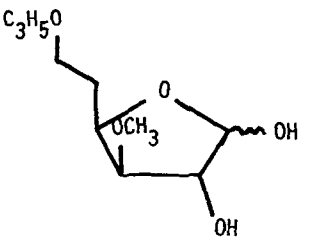


3a, R=H
b, R=C_3H_5



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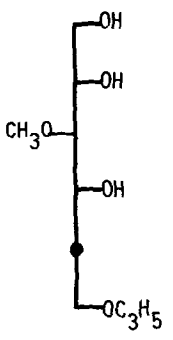

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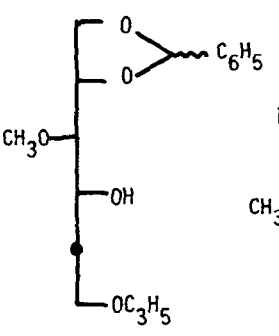

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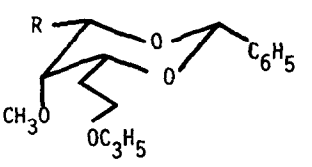

7a, R=CH_2OH
b, R=CHO

3.54 (1H, br.s, C<u>H</u>-OCH_3), 3.43 (3H, s, -OCH_3), 2.19-2.07 (1H, m), and 1.98-1.86 (1H, m).

(+)Deoxyglucose (<u>7b</u>) displays the correct absolute stereochemistry to serve as a chiral precursor of C_1-C_6 of the macrolide aglycones. Synthon <u>7b</u> will be utilized by further functionalization of the aldehyde carbon.

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REFERENCES:

1. K. Tatsua, A. Tanaka, K. Fujimoto, and M. Kinoshita, J. Am. Chem. Soc., 99, 5826 (1977).

2. S. Omura and A. Nakagawa, J. Antibiot., 28, 401 (1975).

3. We thank Professor K.C. Nicolaou, University of Pennsylvania, for a preprint of his work in this area.

4. J.S. Josan and F.W. Eastwood, Carbohyd. Res., 7, 161 (1968).

5. All new distilled and crystalline compounds gave correct combustion analyses.

6. E.J. Corey and J.W. Suggs, J. Org. Chem., 38, 3224 (1973).

7. Separated by flash chromatography, ethyl acetate-hexanes (3/1). W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).

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