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SYNTHESIS OF CLADINOSE ANALOGUES OF CARBOMYCIN B

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Cladinose analogues (2 and 8) of carbomycin B have been synthesized by regio- and stereoselective introduction of cladinose instead of mycarose into the ethylene acetal (3) of demycarosylcarbomycin B. Their antimicrobial activities are also presented.

Macrolide antibiotics are important class of clinically useful chemotherapeutic agents and most of their structures contain basic and neutral sugar moieties.[1] However, there are significant differences between sugar moieties in 16- and 14-membered-ring macrolide antibiotics. For example, carbomycin B (1) and erythromycin, which are representative antibiotics of 16- and 14-membered-ring macrolides, contain mycarose and its O-methyl derivative, cladinose, as neutral sugars respectively.[1] It is apparent, therefore, that the synthesis of analogues in which the carbohydrate component is functionally and/or configurationally altered is of great biochemical and practical interest. We have recently synthesized carbomycin B (1) by regio- and stereoselective introduction of the disaccharide into the macrolide aglycone.[2]

We now wish to report a synthesis of new analogues (2 and 8) of carbomycin B by introduction of cladinose instead of mycarose into the demycarosylcarbomycin B (3), in order to obtain informations about the structure - activity relationships. This syntheis was achieved by using our method[3] for the synthesis of 2-deoxy-α-glycosides, including diaxial opening of glycals with alcohols in the presence of a brominating agent. The synthesis is the first success to exchange the sugar moiety of a macrolide antibiotic.

The key starting material 3, the ethylene acetal of demycarosylcarbomycin B, has already been prepared from carbomycin B in a high yield.[2] The other starting material 6, 1,5-anhydro-2,6-dideoxy-4-O-isovaleryl-3-C-methyl-3-O-methyl-L-*ribo*-hex-1-enitol, has been prepared from cladinose by our procedure[3] through 1,4-di-O-isovalerylcladinose (4). Treatment of cladinose with isovaleryl chloride in pyridine quantitatively gave the crystalline compound 4,[4] mp ∿50°C, $[\alpha]_D^{25}$ -34° (c 3.0, $CHCl_3$), which was partially hydrolyzed with dil. hydrochloric acid in dioxane (40°C, overnight) to yield 4-O-isovalerylcladinose (5)[4] as a syrup quantitatively, $[\alpha]_D^{21}$ -50° (c 1.0, $CHCl_3$). Treatment of 5 with p-toluenesulfonyl chloride and triethylamine in acetonitrile (r.t., 3 hrs) gave the glycal 6[4] as

a syrup (65% yield), $[\alpha]_D^{25}$ -184° (c 2.0, $CHCl_3$).

Reaction[2] of 6 with 1 equiv. of the acetal 3 and 1 equiv. of 1,3-dibromo-5,5-dimethylhydantoin in a mixture of acetonitrile and benzene (from -20°C to r.t., 4 hrs) afforded, after column chromatography on a silica gel (chloroform - acetone 5 : 1), a single condensation product and starting material 3 (recovery of 75% yield). Reprecipitation (ether - hexane) of the product afforded a solid of 7[4] (14% yield),[5] mp 110-113°C, $[\alpha]_D^{16}$ -24.5° (c 1.0, $CHCl_3$), λ_{max}^{MeOH} 279 nm (ε 23,000).

Proof of the structure of 7 was provided by ^{1}H- and ^{13}C-NMR spectra as described in the synthesis of carbomycin B.[2] The chemical shifts and coupling constants of H-1" and 2" in the ^{1}H-NMR were practically same as those (H-1 and 2) of alkyl 2-bromo-α-L-altropyranosides[3] which were converted to the corresponding α-glycosides of cladinose, and the signal due to C-4' in the ^{13}C-NMR was deshielded about 5 ppm in comparison with that of the starting acetal 3, supporting that 7 possesses an α-glycosidic linkage at the C-4'.

Deprotection[2] of 7 with 90% trifluoroacetic acid (5°C, 15 min) gave a solid of the aldehyde 8[4] (91.5% yield), mp 119-122°C, $[\alpha]_D^{16}$ -41° (c 1.0, $CHCl_3$), λ_{max}^{MeOH} 279 nm (ε 23,000).

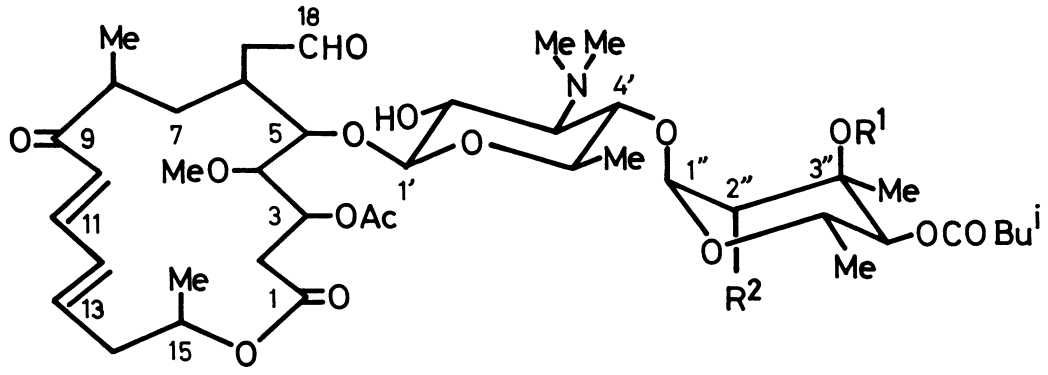
Debromination of 8 by use of tri-n-butylstannane (1.2 equiv) in benzene (60°C, 2 hrs under argon) with α,α'-azobisisobutyronitrile as catalyst gave a solid of the cladinose analogue (2)[4] of carbomycin B (89% yield), mp 115-118°C, $[\alpha]_D^{20}$ -46.5° (c 1.0, $CHCl_3$), λ_{max}^{MeOH} 279 nm (ε 23,000).

The compound 2 and carbomycin B (1) differ from one another only in the functional group at C-3". The antimicrobial spectra of 2 and 8 are given in Table 1 in comparison with those of carbomycin B (1) and 2"-bromocarbomycin B (9).[2] The synthesized 2 and 8 showed enhanced activities against Mycobacterium smegmatis.

Table 1. MIC (mcg/ml) of carbomycin B (1) and its analogues (2, 8 and 9).

Test organisms*	1	2	8	9
Staphylococcus aureus FDA 209P	1.56	1.56	1.56	3.12
Bacillus subtilis NRRL B-558	0.39	0.39	0.78	0.39
Escherichia coli NIHJ	100	50	100	50
Corynebacterium bovis 1810	0.39	<0.2	<0.2	0.2
Klebsiella pneumoniae PCI 602	50	100	100	25
Mycobacterium smegmatis ATCC 607**	25	6.25	3.12	50
Sarcina lutea PCI 1001	<0.2	<0.2	<0.2	0.2
Shigella dysenteriae JS 11910	6.25	12.5	12.5	6.25

* Agar dilution streak method (nutrient agar, 37°C, 17 hours). ** 48 hours.

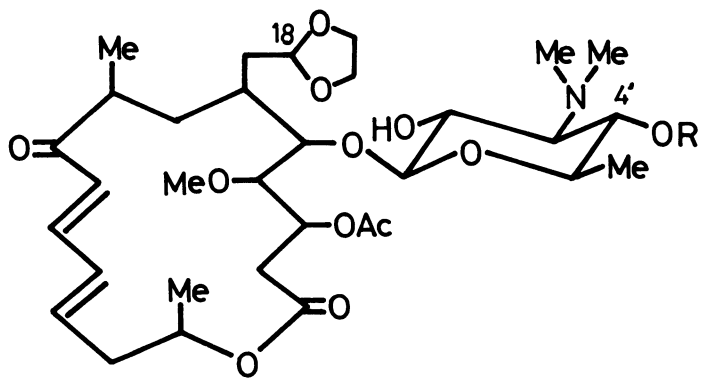


1 $R^1 = H$ $R^2 = H$ (Carbomycin B)

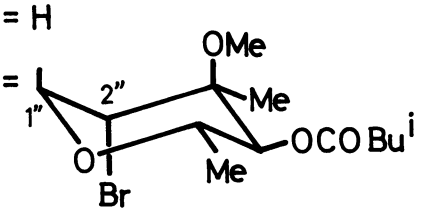
2 $R^1 = CH_3$ $R^2 = H$

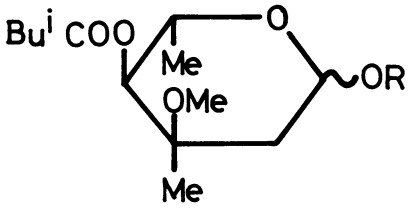
8 $R^1 = CH_3$ $R^2 = Br$

9 $R^1 = H$ $R^2 = Br$



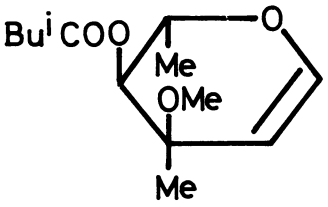
3 R = H

7 R = 



4 R = $COBu^i$

5 R = H



6

$Bu^i = CH_2CH(CH_3)_2$

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References and Notes

1) a) W. D. Celmer, Pure Appl. Chem. 28, 413 (1971). b) S. Ōmura and A. Nakagawa, J. Antibiotics 28, 401 (1975).

2) K. Tatsuta, A. Tanaka, K. Fujimoto, M. Kinoshita and S. Umezawa, J. Amer. Chem. Soc. in press.

3) K. Tatsuta, K. Fujimoto, M. Kinoshita and S. Umezawa, Carbohydr. Res. 54, 85 (1977).

4) All compounds gave satisfactory combustion analyses, IR, UV, NMR and mass spectra consistent with the reported structures. ^{1}H- and ^{13}C-NMR (δ, ppm from TMS) were in $CDCl_3$ solution, and melting points were uncorrected. Selected NMR spectral data are listed herein. 2: ^{1}H-NMR 2.20 (3H, s, AcO-3), 2.59 [6H, s, $N(CH_3)_2$-3'], 3.25 (3H, s, CH_3O-3"), 3.60 (3H, s, CH_3O-4), 9.55 (1H, s, CHO-18, which was accompanied by a little of a broad singlet at 9.63); ^{13}C-NMR 97.3 (C-1"), 103.3 (C-1'), 201.0 and 201.3 (C-18 and 9). 6: ^{1}H-NMR 1.01 (6H, d, J=6.5Hz, CH_3 of isovaleryl), 1.21 (3H, s, CH_3-3), 1.24 (3H, d, J_{5,CH_3}=6.5Hz, CH_3-5), ∿2.3 (3H, m, CH_2 and CH of isovaleryl), 3.32 (3H, s, CH_3O-3), 4.30 (1H, dq, H-5), 4.75 (1H, d, $J_{1,2}$=6Hz, H-2), 4.93 (1H, d, $J_{4,5}$=11Hz, H-4), 6.41 (1H, d, H-1). 7: ^{1}H-NMR 2.02 (3H, s, AcO-3), 2.54 [6H, s, $N(CH_3)_2$-3'], 3.25 (3H, s, CH_3O-3"), 3.60 (3H, s, CH_3O-4), 4.24 (1H, sharp d, $J_{1",2"}$=∿1Hz, H-2"), 5.16 (1H, sharp d, H-1"); ^{13}C-NMR 49.9 ($\underline{C}H_3O$-3"), 51.4 (C-2"), 64.5 and 64.1 (ethylene acetal), 101.9, 103.6 and 103.9 (C-1", 18 and 1'). 8: ^{1}H-NMR 4.23 (1H, sharp d, $J_{1",2"}$=∿1Hz, H-2"), 5.16 (1H, sharp d, H-1"), 9.55 (1H, s, CHO-18, which was accompanied by a little of a broad singlet at 9.63); ^{13}C-NMR 49.9 ($\underline{C}H_3O$-3"), 51.1 (C-2"), 102.1 (C-1"), 103.3 (C-1'), 200.8 (C-18).

5) Improvements of the yield will be sought in further experimentation. It should be noted, however, that the glycosylation was achieved without protection of C-2' hydroxyl and C-3' dimethylamino groups.

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