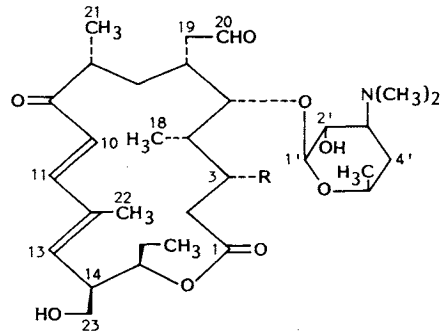
SYNTHESIS OF 3,4'-DIDEOXYMYCAMINOSYL TYLONOLIDE, A NOVEL TYPE OF MACROLIDE DERIVATIVE

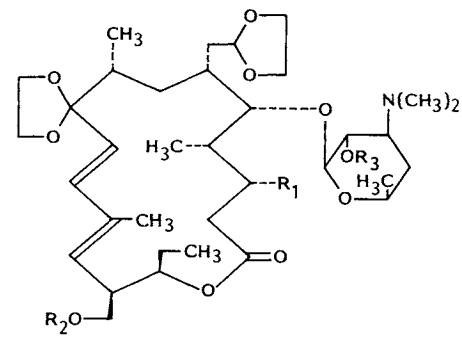
Sir:

Some macrolide antibiotics such as tylosin, josamycin, niddamycin, spiramycin I, and rosamicin have a hydroxyl (or acetoxyl) group at C-3 in the macrocyclic lactone. The role of the hydroxyl group in the therapeutic action of these drugs, however, has not been discussed. Based on the stereomodels, the hydroxyl group appears to have some interaction with the lactone-carbonyl, as well as to restrict the rotation of the sugar portion around the glycosidic bond at C-5 directly or through steric interaction with the C-4-methyl (or methoxyl) group. Moreover it is possible that biologically induced loss of water from the C-3 hydroxyl and one of the C-2 hydrogens could lead to the 2,3-unsaturated macrolide. Based on these considerations we have undertaken to remove the hydroxyl group. Here we describe the synthesis of 3,4'-dideoxymycaminosyl tylonolide (**2**) from 4'-deoxymycaminosyl tylonolide[1] (**1**), the latter being known to show weak to moderate antibacterial activity against Gram-negative bacteria.

Attempts at direct removal of the 3-OH group by radical reactions[2~4] or through displacement with a halogen atom proved unsuccessful, leading, in most cases, to 2,3-unsaturation compounds. Building positively on this result we chose to use the unsaturated compound as an intermediate in the preparation of the 3-deoxy derivative. The aldehyde and ketone groups of **1** were protected with a mixture of dry ethyleneglycol, tetramethyl orthocarbonate and camphorsulfonic acid in toluene-MeCN at room temperature to give the bis(1,3-dioxolane) **3** (82%), $[\alpha]_D^{20}$ −5° (*c* 1, $CHCl_3$). Silylation of **3** by treatment with dimethylthexylsilyl chloride (TDS-Cl) in the presence of imidazole in DMF (room temperature, 5 hours) followed by acetylation (Ac_2O in MeCN) gave the 2'-*O*-acetyl-23-*O*-TDS derivative **4** (81%), $[\alpha]_D^{20}$ −20° (*c* 1, $CHCl_3$); FAB-MS (*m/z*) 854 $(M+1)^+$. After mesylation of the 3-OH of **4** (MsCl-pyridine, 95%), the unstable product (**5**) was treated with K_2CO_3 in methanol (room temperature, 10 hours), whereupon the corresponding 2,3-unsaturation compound **6** (94%, $[\alpha]_D^{20}$ −20° (*c* 1, $CHCl_3$)) was obtained; ^1H NMR ($CDCl_3$) (prominent signals) δ 0.07 (6H, s, $Si(CH_3)_2$), 1.70 (3H, d, 22-CH_3), 2.27 (6H, s, $N(CH_3)_2$), 4.31 (1H, d, $J_{1',2'}=7.6$ Hz, 1'-H), 4.88 (1H, m, 15-H), 5.05 (1H, br s, 20-H), 5.29 (1H, d, 13-H), 5.48 (1H, d, $J_{10,11}=15.5$ Hz, 10-H), 5.58 (1H, d, $J_{2,3}=15.5$ Hz, 2-H), 6.26 (1H, d, 11-H), and 6.76 (1H, dd, $J_{3,4}=9.3$ Hz, 3-H). Subsequently selective reduction of the 2,3-double bond in the presence of intact 10,11- and 12,13-double bonds was attempted with several reducing agents. Among those tested,



1 R=OH
2 R=H



3 R_1=OH $R_2=R_3$=H

4 R_1=OH R_2 = $Si(CH_3)_2$—(TDS) R_3=Ac

5 $R_1=OSO_2CH_3$ R_2=TDS R_3=Ac

7 R_1=H R_2=TDS R_3=H

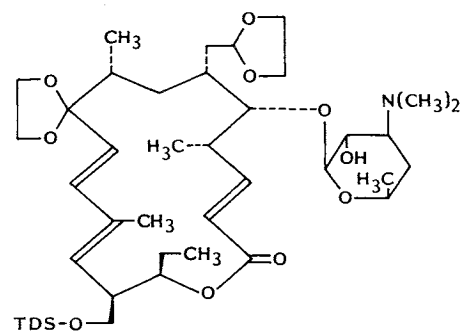


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Table 1. Antibacterial activity (MIC μg/ml) of **2** together with **1**, josamycin (JM), and erythromycin (EM).

Test organism[a]	**2**	**1**	JM	EM
Staphylococcus aureus FDA 209P JC-1	0.1	0.2	0.39	0.2
S. epidermidis IID 866	0.05	0.1	0.39	0.1
Streptococcus pyogenes Cook	0.2	0.2	0.39	0.05
S. pneumoniae IID 552	0.05	0.1	0.2	0.05
Enterococcus faecalis IID 682	0.39	0.78	1.56	0.1
Branhamella catarrhalis CAY 1267	0.1	0.2	1.56	0.2
Escherichia coli 0-1	3.13	6.25	>100	25
Citrobacter freundii NIH 10018-68	1.56	1.56	12.5	6.25
Shigella sonnei II 37148	3.13	6.25	>100	25
Salmonella enteritidis 1891	1.56	6.25	>100	25
Klebsiella pneumoniae ATCC 10031	0.39	0.78	6.25	3.13
Proteus vulgaris OX-19	3.13	25	>100	>100
Pseudomonas aeruginosa NCTC 10490	12.5	12.5	>100	>100

[a] Mueller-Hinton agar, inoculum size 10^6 cfu/ml, incubation 18 hours at 37°C.

di(*iso*-butyl)aluminum hydride, LAH, and $NaBH_4$-$NiCl_2$[5] were successful in producing the desired 3-deoxy derivative **7**, however, Raney nickel-hydrogen was most effective[†] in terms of yield (95%) and ease of purification, $[\alpha]_D^{20}$ −38° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) (selected resonances) δ 0.06 (6H, s, $Si(CH_3)_2$), 1.73 (3H, d, 22-CH_3), 2.27 (6H, s, $N(CH_3)_2$), 4.28 (1H, d, 1′-H), 4.92 (1H, m, 15-H), 5.01 (1H, br s, 20-H), 5.38 (1H, d, 13-H), 5.61 (1H, d, 10-H), and 6.38 (1H, d, 11-H). Removal of the protecting groups of **7** gave the desired product, 3,4′-dideoxymycaminosyl tylonolide (**2**), $[\alpha]_D^{19}$ −21° (*c* 1, $CHCl_3$); FAB-MS (*m/z*) 566 $(M+1)^+$; ^1H NMR ($CDCl_3$) (prominent signals) δ 0.94 (3H, t, 17-CH_3), 1.05 (3H, d, 18-H), 1.20 (3H, d, 6′-CH_3), 1.21 (3H, d, 21-CH_3), 1.85 (3H, d, 22-CH_3), 2.26 (6H, s, $N(CH_3)_2$), 4.19 (1H, d, 1′-H), 4.88 (1H, m, 15-H), 5.83 (1H, br d, 13-H), 6.35 (1H, d, 10-H), 7.30 (1H, d, 11-H), and 9.70 (2H, s, 20-H).

Compound **2** showed stronger antibacterial activity than **1** against typical pathogenic bacteria. The antibacterial activity of compounds **1** and **2** is compared to that of josamycin and erythromycin against some important strains in Table 1. This table shows that **2** exhibits somewhat stronger activity than those reference macrolide antibiotics, and moreover it was found to show strong activity against *Haemophilus influenzae* IID 985 (MIC: 0.78 μg/ml; erythromycin, 3.13 μg/ml). This result was extended to several clinically isolated strains of this pathogen, which is a common cause of infection in infants. Details other than described here involving energy-minimum conformations of **2** are now under study[††].

In conclusion, we have prepared, for the first time, a 3-deoxy derivative of macrolide antibiotic through selective reduction of the 2,3-double bond, and have shown that 3-deoxygenation leads to enhancement of antibacterial activity.

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† This study was performed by collaboration with Dr. T. MIYAKE of our laboratory.

†† Details will be published elsewhere.

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