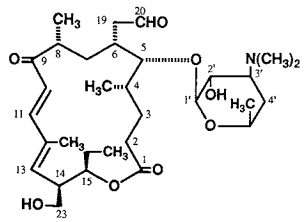
SYNTHESIS OF 2-C-METHYL DERIVATIVES OF 3,4'-DIDEOXYMYCAMINOSYLTYLONOLIDE, A NOVEL TYPE OF 16-MEMBERED MACROLIDE ANTIBIOTIC

Sir:

Recently we reported[1,2] the synthesis of 3-deoxy derivatives of 5-*O*-mycaminosyltylonolide and its 4'-deoxy analog, and the new-type of compounds showed stronger antibacterial activities than those for the respective parent compound against pathogenic bacteria including *Haemophilus influenzae* IID 985. To investigate whether much more active substances would result, we decided to attach an alkyl group at the C-2 position of the macrolactone ring. We thought that such derivation might stabilize the macrolactone ring *in vivo*, giving drugs of long duration in human blood. Here we describe the synthesis of 2-C-methyl derivatives of 3,4'-dideoxymycaminosyltylonolide[1] (**1**).



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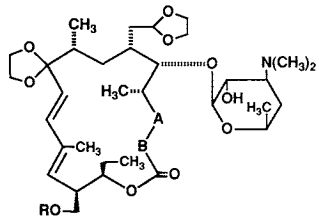
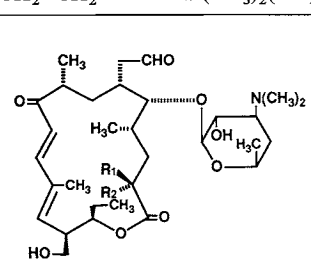


	A–B	R
2	HC=CH (*trans*)	H
3	HC=CH (*trans*)	$Si(CH_3)_2(tBu)$
4	CH_2–CH_2	$Si(CH_3)_2(tBu)$



5 R_1=H, R_2=CH_3
6 R_1=CH_3, R_2=H

The key step in this synthesis is to introduce a methyl group with the other parts of the molecule of **1** intact. After many fruitless experiments involving protection of the 2'-hydroxyl group, we concluded that the quantity and basicity strength of the reagent used for activating the C-2 position are the most important. The synthesis was started from 3-deoxy-5-*O*-(4-deoxymycaminosyl)-2,3-didehydrotylonolide 9,20-bis(ethylene acetal)[2] (**2**). After silylation of **2**, the 23-*O*-(*tert*-butyldimethylsilyl) derivative (**3**) was selectively hydrogenated (at the 2,3-double bond) as described previously[1,2] (Raney nickel-H_2 in MeOH, quantitative yield) to give **4**. The 3-deoxy derivative **4** having a free 2'-OH was dissolved in THF and treated (−70°C, 30 minutes) with excess lithium diisopropylamide (10 molar equivalents for **4**; prepared by reacting equimolar amounts of diisopropylamine and butyllithium in hexane). The resulting 2-*C*,2'-*O*-dilithio intermediate was then reacted (−20°C→0°C) with methyl iodide by monitoring with thin layer chromatography. A mixture of two 2-C-methyl derivatives was produced in good yield without methylation of the 2'-hydroxyl and 3'-dimethylamino groups (quarternization). Usual deprotection of the products followed by chromatography gave (2*R* and 2*S*)-3,4'-dideoxy-2-*C*-methylmycaminosyltylonolides (**5** and **6**) in a ratio of ~2:1 (total yield based on **4** was 62%). 2*R*-Isomer (**5**): Rf 0.20 (TLC with $CHCl_3$-MeOH-aq 28% NH_3, 20:1:0.5), $[\alpha]_D^{20}$ +2° (*c* 1, $CHCl_3$); FAB-MS (*m/z*) 580 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.94 (3H, t, J=6.8 Hz, 17-CH_3), 1.08 (3H, d, J=6.7 Hz, 18-CH_3) ~1.2 (a mixture of three 3H d, J=6~7.5 Hz; 2-, 21-, and 6'-CH_3), 2.27 (6H, s, $N(CH_3)_2$), 4.14 (1H, d, J=7.3 Hz, 1'-H), 5.85 (1H, d, J=10.4 Hz, 13-H), 6.32 (1H, d, J=15.8 Hz, 10-H), 7.18 (1H, d, 11-H), and 9.71 (1H, s, 20-H). 2*S*-Isomer (**6**): Rf 0.26 (TLC with $CHCl_3$-MeOH-aq 28% NH_3, 20:1:0.5), $[\alpha]_D^{20}$ +15°C (*c* 1, $CHCl_3$); FAB-MS (*m/z*) 580 $(M+1)^+$, ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz, 17-CH_3), 0.98 (3H, d, J=6.7 Hz, 2-CH_3), 1.02 (3H, d, J=6.7 Hz, 18-CH_3), 1.20 (3H, d, J=6.1 Hz, 6'-CH_3), 1.23 (3H, d, J=6.7 Hz, 21-CH_3), 2.26 (6H, s, $N(CH_3)_2$), 4.23 (1H, d, J=7.3 Hz, 1'-H), 5.75 (1H, d, J=11 Hz, 13-H), 6.37 (1H, d, J=15.8 Hz, 10-H), 7.18 (1H, d, 11-H), and 9.70 (1H, s, 20-H).

Configurations at C-2 of **5** and **6** were presumed to be *R* and *S*, respectively, based on the NOE measurements (by ROESY). Compound **6** showed

Table 1. Antibacterial activity (MIC μg/ml) of **5** and **6** together with **1**.

Test organism[a]	**5**	**6**	**1**
Staphylococcus aureus FDA 209P JC-1	0.05	0.39	0.1
S. epidermidis IID 866	0.05	0.39	0.1
Streptococcus pyogenes Cook	0.1	0.78	0.2
S. pneumoniae IID 552	0.05	0.39	0.1
Enterococcus faecalis IID 682	0.2	1.56	0.39
Corynebacterium diphteriae A-7	0.1	1.56	0.2
Mycobacterium smegmatis ATCC 607	0.78	>25	3.13
Branhamella catarrhalis CAY 1267	0.2	1.56	0.39
Escherichia coli O-1	6.25	12.5	6.25
Citrobacter freundii NIH 10018-68	3.13	6.25	3.13
Shigella sonnei II 37148	6.25	12.5	6.25
Salmonella enteritidis 1891	1.56	3.13	3.13
Klebsiella pneumoniae ATCC 10031	0.78	1.56	1.56
Proteus vulgaris OX-19	12.5	12.5	6.25
Pseudomonas aeruginosa NCTC 10490	>25	>25	25

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

NOE between both 2-H ~ 18-CH_3 and 2-CH_3 ~ 4-H, and **5**, only between 2-H ~ 18-CH_3. As C-4 of **1** has *S* configuration, 2*S*,4*S* structure of **6** satisfies the above result. If **6** has 2*R*,4*S* structure, it is sterically difficult 2- and 4-methyls come close to 4-H and 2-H, respectively. Details involving the other minor results will be described elsewhere.

Compound **5** showed slightly enhanced antibacterial activity compared with that of **1** against typical pathogenic bacteria, but **6** was much less active (Table 1). This result shows that the 2-C-methyl orientation in the molecule is an important factor for the activity. Other biological experiments are now under study.

In conclusion, we have prepared, for the first time, 2-C-methyl derivatives of a 16-membered macrolide antibiotic. The absolute configuration at C-2 of **5** is proposed to be the same (that is 2*R*) with that[3] of 14-membered macrolide antibiotics such as erythromycin.

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References

1) KAGEYAMA, S.; T. TSUCHIYA, S. UMEZAWA & T. TAKEUCHI: Synthesis of 3,4'-dideoxymycaminosyl tylonolide, a novel type of macrolide derivative. J. Antibiotics 45: 144~146, 1992
2) KAGEYAMA, S.; T. TSUCHIYA, S. UMEZAWA & M. ORITA: Synthesis of 3-deoxy-5-*O*-mycaminosyltylonolide and 3-deoxy-5-*O*-(4-deoxymycaminosyl)-tylonolide. Bull. Chem. Soc. Jpn. 65: 3405~3411, 1992
3) NAKAGAWA, A. & S. ŌMURA: Structure and stereochemistry of macrolides. *In* Macrolide Antibiotics, *Ed.*, S. ŌMURA, pp. 64~67, Academic Press, Inc., 1984