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TOTAL SYNTHESIS OF (±)-ACETOMYCIN

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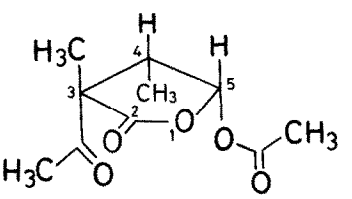
Summary; A stereocontrolled total synthesis of (±)-Acetomycin (**1**) is described. The acyloxy group was successfully introduced from sterically hindered α-side onto the γ-butyrolactone ring.

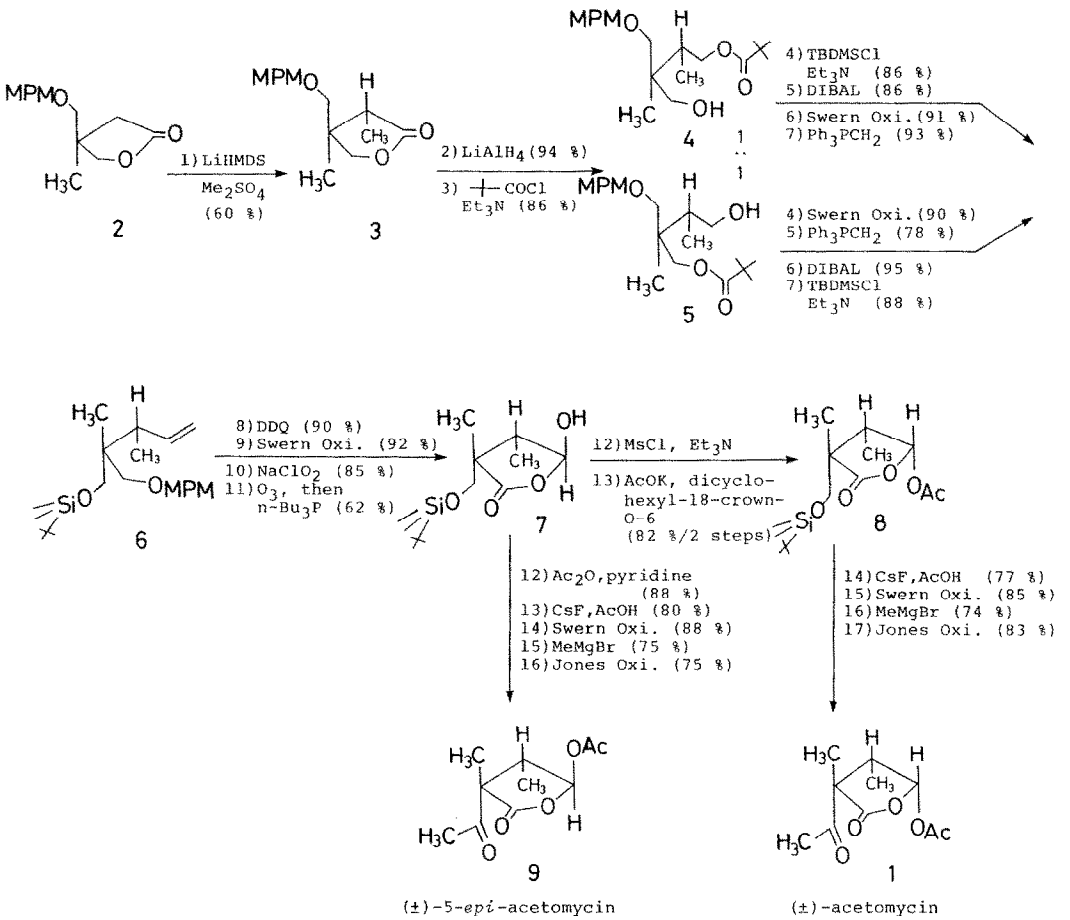
Acetomycin (**1**), isolated from *Streptomyces ramulosus sp.* by Prelog et al in 1958,[1] is a rather small but structurally unique γ-butyrolactone antibiotic. The absolute structure was determined in 1985 by X-ray analysis[2] and recently it was appeared to possess potent antitumor activity against HCT-8-human colon, L 1210 murine leukemia cell and human tumor stem cell.[3] In spite of the antitumor activity *in vitro* experiments, the very fast hydrolysis rate by esterase in metabolizing system[4] eliminates possibilities for clinical use as an antitumor drug. By this reason the total synthesis of **1** as well as syntheses of esterase resisted acetomycin derivatives are highly desirable. The synthesis, particularly construction of the consecutive three asymmetric centers on the ring, is attractive for synthetic organic chemists. Although the first total synthesis has recently been made by Tadano et al,[5] the problem to control the stereochemistry of acetoxy group present at the C-5[6] anomeric position on the sterically unfavourable α-side has still been remaining.[7]

Herein we would like to report the total synthesis of (±)-acetomycin under a stereocontrolled manner and also a success of stereoselective introduction of bulky acyloxy groups for syntheses of esterase inactive acetomycin derivatives.



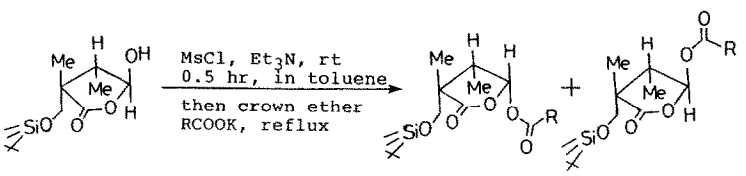
Acetomycin **1**

3,3-Disubstituted γ-butyrolactone **2** was available in 5 steps from allylmethylmalonate ester.[8] Stereoselective methylation of **2** was carried out at -78°C in THF by use of LiHMDS as a base and Me_2SO_4 for



alkylating reagent. The major stereoisomer **3** was obtained in 60 % yield after chromatographic separation from the other isomer,[9] and stereochemistry of the methyl group introduced at C-4[6] was found to be cis to the C-3[6] methyl group by NOE experiments. Unfortunately as it is opposite for the acetomycin structure, it needs to switch the relative stereochemistry between the C-4 methyl group and the C-3 stereocenter. This would be achieved by putting the hydroxymethyl group protecting with MPM in place of the hydroxymethyl group constituting the lactone ring. As shown in scheme above, the compound **6** was eventually attained in 49 % overall yield after several steps from **3**,[10] in which two diastereomeric hydroxymethyl groups were blocked by different protecting groups. After removal of the MPM group, the hydroxymethyl was oxidized to aldehyde followed by careful treatment with sodium chlorite giving rise to

carboxylic acid in 70 % yield. Subsequent ozonolysis proceeded cleanly to afford 7 as a single stereoisomer in 62 % yield which maintained a proper stereochemistry at the C-4 stereocenter but a wrong stereochemistry at the C-5 anomeric position on the newly produced lactone ring. Attempts to introduce the α-acetoxy functionality to yield **8** directly by employing a variety of protocols including Mitsunobu condition lead the undesired β-acetoxy stereoisomer **8'**.[11] However after mesylation of the hydroxy group in **7**, the crude reaction mixture was subjected to heat with a large excess of potassium acetate in the presence of dicyclohexyl-18-crown-O-6 in refluxing toluene for 30 min to give the desired product **8** in a ratio of 7.3:1 (α:β) with excellent chemical yield.[7,11] Under these conditions, high stereoselectivities and good chemical yields were achieved even when bulkier acyloxy groups were used. The results are shown in the Table below.



RCOOK	Crown* Ether	Time (min)	Yield (%)	Product Ratio (α : β)
H_3CCOOK	A	30	83	7.3 : 1
	B	30	82	3.5 : 1
PhCOOK	A	20	95	7.8 : 1
	B	20	69	3.5 : 1
Pr^iCOOK	A	10	79	2.3 : 1
Bu^tCOOK	A	10	60	2.8 : 1

* A;dicyclohexyl-18-crown-O-6, B;18-crown-O-6

The total synthesis was completed by straightfoward functional groups adjustment in the following 4 steps from **8**. Deprotection of the silyl group by heating with CsF in acetic acid at 60°C and followed by PCC oxidation afforded the aldehyde, which was lead to methyl ketone by treatment with methylmagnesium bromide at 0°C and succesive oxidation by Jones reagent to complete the total synthesis[12] in 40 % yield from **8**. 5-*epi*-Acetomycin **9** was also obtained from **7** as shown in the scheme.

Full details of syntheses and biological activities of the acetomycin derivatives having bulky acyloxy(RCOO) groups shown in the Table will be reported in due course.

References and Notes

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2) H.Uhr, A.Zeeck, W.Clegg, E.Egert, H.Fuhrer and H.H.Peter, J. Antibiot., **38**, 1684 (1985).

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4) S.W.Mamber, J.D.Mitulski, P.E.Borondy and J.B.Tunac, J. Antibiot., **40**, 77 (1987).

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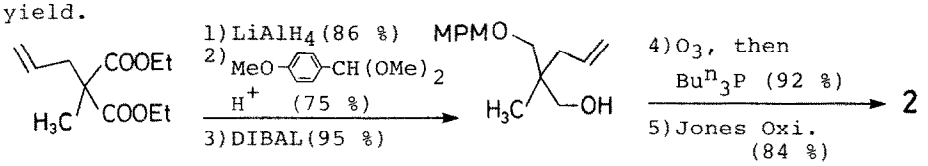
6) Original acetomycin ring numbering is used in this letter.

7) No stereoselectivity (α:β=1:1) was observed under Tadano's condition (AgOAc, Ac_2O, AcOH, 40 hrs in refluxing benzene) in ref. 5.

8) The synthetic way to the lactone **2** is shown below in 47 % overall yield.



MPM: *p*-methoxybenzyl

9) The two isomers were separable by silica gel chromatography, of which ratio was 3.5:1.

10) A shorter synthetic route to **6** from **3** *via* Wittig olefination (i,DIBAL, ii,Ph_3PCH_2, iii,TBSCl,imidazole) could not be adopted because of the low overall yield.

11) α -isomer **8**;^{1}H-NMR(400 MHz, in $CDCl_3$) δ =0.06(6H,s), 0.90(9H,s), 1.12 (3H,d,J=5.9), 1.25(3H,s), 2.13(3H,s), 2.50(1H,dq,J=5.9 and 6.2), 3.63 (1H,d,J=9.9), 3.81(1H,d,J=9.9), 6.56(1H,d,J=6.2).
β-isomer **8'**;^{1}H-NMR(400 MHz, in $CDCl_3$) δ =0.07(6H,s), 0.90(9H,s), 1.13 (3H,s), 1.18(3H,d,J=7.0), 2.13(3H,s), 2.26(1H,dq,J=7.0 and 7.3), 3.58 (1H,d,J=9.9), 3.65(1H,d,J=9.9), 6.33(1H,d,J=7.3).

12) Synthetic (±)-acetomycin **1**; mp 93-5°C, ^{1}H-NMR(400 MHz, in $CDCl_3$) δ =1.06(3H,d,J=7.3), 1.45(3H,s), 2.12(3H,s), 2.31(3H,s), 2.56(1H,dq, J=5.1 and 7.3), 6.59(1H,d,J=5.1), ^{13}C-NMR(100 MHz, in $CDCl_3$) δ =9.4, 20.6, 21.0, 28.9, 45.5, 56.8, 94.0, 168.6, 177.0, 203.3.

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