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TOTAL SYNTHESIS OF (-)-ACETOMYCIN

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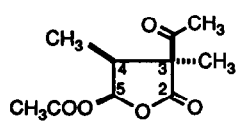
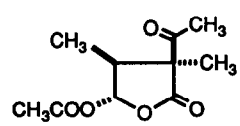
Summary : Enantiospecific total synthesis of the titled antibiotic (**1**) has been completed. The pentasubstituted tetrahydrofuran (**3**), efficiently obtained from D-glucose, was used as an enantiomerically pure starting material.

In recent reports from this laboratory, we have demonstrated the efficacy of the ortho ester Claisen (Johnson-Claisen) rearrangement protocol, performing by using carbohydrate-derived enantiomerically pure substrates, for the highly stereoselective carbon-carbon bond forming reaction.[1] A particular worth of this protocol is the realization of stereoselective introduction of a quaternary carbon atom into the framework with a defined configuration. The utility of the Claisen rearrangement product was embodied through the transformation of one rearrangement product into some natural products such as (+)-asteltoxin.[2] Along this synthetic concept directed toward natural product synthesis, we herein disclose the first total synthesis of an antibiotic,(-)-acetomycin (**1**), beginning with one of the Claisen rearrangement products.

Acetomycin (**1**) was initially isolated from *Streptomyces ramulosus sp. nov.* by Prelog *et al.* in 1958.[3] They determined the constitution of the antibiotic by chemical degradations and spectral analyses (IR and UV).[4] Later, they investigated the biosynthesis of acetomycin revealing that the carbon framework of **1** derives from acetates, a L-methionine, and D-glucose.[5] However, the detailed structure of this antibiotic remained unclear for one and half decade. In 1984, Zeeck and coworkers reinvestigated the structure of **1**, and they determined its relative stereostructure by the ^{1}H and ^{13}C NMR spectral analyses. At the same time, they established the absolute configuration of **1** as depicted below by the X-ray crystallography of a bromine-containing derivative of **1**.[6] This highly oxygenated γ-lactone derivative **1** exhibits marginal inhibitory effects (*in vitro*) on Gram-positive bacteria, some fungi, and protozoae.[3,6] Furthermore, this antibiotic was recently found to be an antitumor agent (*in vitro*) against HCT-8 human colon adenocarcinoma cells, L1210 murine leukemia cells, and human tumor stem cells.[7] These pharmacological effects inhering in **1** prompted us to synthesize this rather small molecular-size but highly functionalized antibiotic **1**, which possesses three contiguous stereogenic centers including a quaternary carbon, and its stereocongener such as 5-*epi*-acetomycin (**2**) for elucidation of a structure-pharmacological activity relationship.[8] Further structural characteristic is that three functional groups (a methyl ketone, a γ-lactone, and an acetylated hemiacetal hydroxyl group) consist in different oxidation states, and this structural surrounding makes the total synthesis of **1** a formidable one.

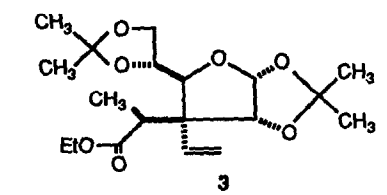


(-)-Acetomycin 1



(+)-5-*epi*-Acetomycin 2

For a reliable construction of the carbon-framework, we started the total synthesis of **1** with our previously reported D-glucose-derived tetrahydrofuran derivative (**3**).[9] The stereochemically defined quaternary carbon center in **3**, which was introduced by means of the ortho ester Claisen rearrangement, would be C-3 of **1**. And the methyl group adjacent to the ester functionality in **3** corresponds to the methyl group at C-4 of **1**. Along this retrosynthetic perspective, the synthon **3** was first modified to the diol (**4**) by the reported procedure[9] [1) $LiAlH_4$, 2) BzlBr, NaH, and 3) 50% aqueous AcOH]. The side chains functionalization of **4** for conversion to trimethyl derivative (**6**),[10] via the bis(diethyldithio acetal) derivative (**5**),[10] was achieved in a combined yield of 40% by the following sequential reactions: 1) ozonolysis in CH_2Cl_2; then reductive work-up with Ph_3P; 2) glycol cleavage with $NaIO_4$ in aqueous MeOH; 3) EtSH in CH_2Cl_2 in the presence of $BF_3{\cdot}Et_2O$ at 0 °C; and 4) Raney Ni in boiling EtOH. The benzyl group in **5** was removed under the desulfurization conditions, so the liberated hydroxyl group in **6** was protected to be the benzyl ether (**7**)[10] [BzlBr, NaH, DMF, 70% yield]. Unexpectedly, acidic hydrolysis for removal of the isopropylidene group in **7** was troublesome. Among a number of reaction conditions screened,[11] hydrolysis with $(COOH)_2$ (dihydrate, 20 wt% for **7**) in aqueous THF at 50 °C for 3 days gave the optimal result giving the desired **8**[10] as a mixture of hemiacetals in 79% yield along with 21% recovery of **7**. Glycol cleavage of **8** followed by hydride reduction gave an acyclic diol (**9**)[10] in 85% yield [1) $NaIO_4$ in aqueous MeOH, and 2) $NaBH_4$ in EtOH followed by aqueous H_2O_2 work-up]. The uneventful protection-deprotection manipulation from **9** afforded a primary alcohol derivative (**12**),[10] via the pivaloyl ester (**10**)[10] and the MOM ether (**11**)[10] [1) pivaloyl chloride in pyridine and CH_2Cl_2 (82% yield), 2) MOMCl, $Et(i\text{-}Pr)_2N$ in CH_2Cl_2 (93%) and 3) atmosperic H_2, 10% Pd/C in EtOH (97%)]. As a temporary aldehyde equivalent, the primary hydroxyl group in **12** was converted to a vinyl group by oxidation followed by Wittig ethylenation in a combined yield of 72% [1) pyridinium dichromate in CH_2Cl_2 in the presence of molecular sieves (MS), and 2) $CH_2{=}PPh_3$ in THF at 0 °C]. The ester functionality of thus obtained vinyl derivative (**13**)[10,12] was then reduced with $LiAlH_4$ in THF to give a primary alcohol (**14**)[10] in 91% yield. Oxidation of the primary hydroxyl group of **14** to a carboxylic acid was achieved smoothly with Jones reagent in acetone at 0 °C giving **15**,[10] which was immediately ozonolyzed in CH_2Cl_2 at -78 °C to generate an aldehyde group. After reductive work-up of the reaction mixture with Ph_3P, the γ-hydroxylated γ-lactones (**16**-α, β)[10] were obtained as an inseparable diastereomeric mixture on the hemiacetal carbon in a combined yield of 89% for two steps. The ratio of the diastereomers was estimated to be 6 to 1 by the ^1H NMR spectral analysis, however, the configuration of each diastereomer was not determined. The mixture was treated with mesyl chloride (3 mol equiv.) in the presence of excess Et_3N in benzene afforded the presumable mesylate, which was unstable on SiO_2 for purification, and the reaction mixture was then stirred in the presence of AcOH, Ac_2O and AcOAg for 40 h. As a result, the acetylated products (**17**-α,β)[10] were obtained as an inseparable diastereomeric mixture in 50% yield[13] (the mixture **16**-α,β was also recovered in 8% yield). Fortunately, the diastereomeric mixture **17**-α,β was mostly separated by SiO_2 chromatography after deprotection of the MOM groups (TMSBr in CH_2Cl_2 in the presence of MS at -30 °C). Each diastereomer (**18**-α[10] or **18**-β[10,14]) was obtained in an equal ratio (43% and 43% yields, respectively, and the mixture **17**-α,β was recovered in 3%). Finally, both **18**-β and **18**-α were oxidized with pyridinium chlorochromate in CH_2Cl_2 in the presence of MS to afford acetomycin (**1**) and 5-*epi*-acetomycin (**2**)[15] in 72% and 78% yields, respectively. The physical properties (mp, mixed mp, and TLC behavior) and the spectral data (^1H and ^{13}C NMR spectra) of the synthetic **1** coincided with those of natural acetomycin. Furthermore, the levorotatory property of the synthetic **1**[[α]$_D$-133° (c 0.42, EtOH)] confirmed the absolute stereochemistry of natural **1** [[α]$_D$-157° (c1.25, EtOH)] reported by Zeeck's group.[6]



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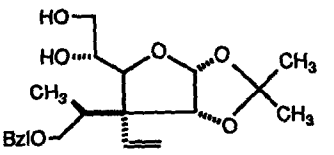

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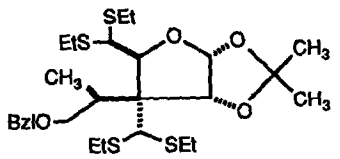
Bzl : $CH_2C_6H_5$



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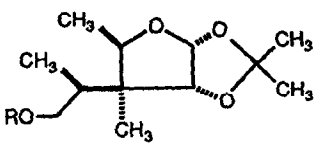
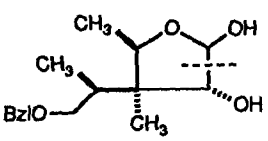


6 R = H
7 R = Bzl



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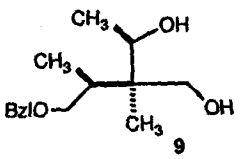

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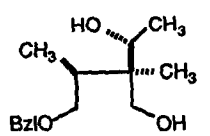
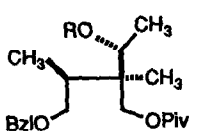
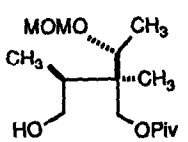




10 R = H
11 R = MOM



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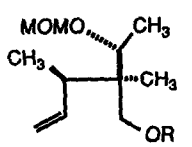
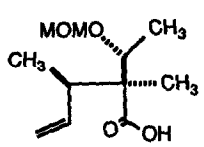


13 R = Piv
14 R = H

Piv : $C(=O)C(CH_3)_3$ MOM : CH_2OCH_3



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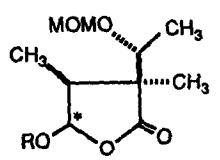
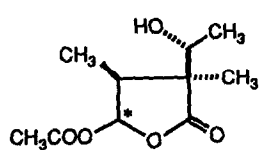


16-α,β R = H
17-α,β R = $C(=O)CH_3$



18-α,β

* α = ····· OR
β = —— OR

In conclusion, we have achieved the first total syntheses of antibiotic acetomycin and its 5-epimer as pure enantiomers. These syntheses substantiate the applicability of the Claisen rearrangement product 3 for natural product synthesis.

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8. The alcohols obtained by reduction of the methyl ketone at C-3 in **1** lose the biological activity (see ref.6).

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10. All new compounds are fully characterized by the spectral means (^{1}H NMR and IR). Satisfactory combustion analyses (C,H) were given for compounds **6** through **14**, and **2**.

11. The following conditions were examined: 1) 60% aqueous trifluoroacetic acid, 5 ° C (63% yield of **8**); 2) 1:1 4 N HCl:THF, 5 °C (45%); and 3) $(COOH)_2$ (8 wt%) in aqueous THF, reflux (49%).

12. Ozonolysis of **13** followed by $NaBH_4$ reduction regenerated **12** as a sole isolated product in 70% yield. This result verified that no epimerization at C-4 occurred during the aldehyde formation of **12** by PDC.

13. Acetylations of the mixture **16**-α,β under the following conditions resulted in the formation of **17**-α as a sole product: 1) Ac_2O in pyridine at r. t. (62% yield from **14**); 2) Ac_2O in the presence of AcONa at 80 °C for 40 min (88%). Acidic acetylation (1% H_2SO_4 in Ac_2O) gave a complex mixture. Acetylation under Mitsunobu conditions (Ph_3P, AcOH, DEAD) in THF at r.t. resulted in a quantitative recovery of the starting material.

14. Compound **18**-β was obtained independently by $NaBH_3CN$ reduction of **1** (see, ref.6). The spectral data (^{1}H and ^{13}C NMR and IR) of the synthetic **18**-β was well matched with those reported in the literature.

15. 5-*epi*-Acetomycin (2): TLC Rf 0.39 (AcOEt/hexane 1:2); mp 69.0-69.5 °C; [α] $_D^{25}$ +79.5 ° (c 0.36, EtOH); IR ($CHCl_3$) 3020, 1785, 1710, 1510, 1420, 1380, 1360, 1330, 1225 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13 (3H, d, J=7.3 Hz), 1.60 (3H, s), 2.16 (3H, s), 2.27 (3H, s), 2.38 (1H, dq, J=6.2 and 7.3 Hz), 6.36 (1H, d, J=6.2 Hz); ^{13}C NMR (100 MHz,$CDCl_3$) δ 204.0, 173.8, 169.1, 97.8, 60.6, 46.7, 28.9, 20.8, 20.1, 11.2. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.37; H, 6.47.

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