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HIGHLY STEREOSELECTIVE SYNTHESIS OF METHYNOLIDE, THE AGLYCONE OF THE 12-MEMBERED RING MACROLIDE METHYMYCIN, FROM D-GLUCOSE[1]

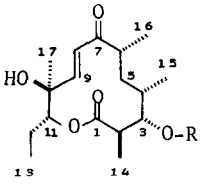
Yuji Oikawa, Tatsuyoshi Tanaka, and Osamu Yonemitsu*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

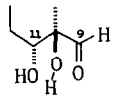
Summary A highly stereoselective and efficient synthesis of methynolide, the aglycone of 12-membered macrolide methymycin, was achieved from of C1-C8 and C9-C13 segments synthesized from D-glucose by employing some stereoselective reactions and benzyl-type protecting groups.

Stereocontrolled synthesis of macrolide and polyether antibiotics is one of the most attractive areas in current synthetic organic chemistry, and various new synthetic methodologies have been established through successful total syntheses of such complex compounds. Recently we planned to synthesize several representative antibiotics from D-glucose as a chiral starting material by a common methodology consisting mainly of the synthesis of three contiguous chiral centers[2] and the MPM (4-methoxybenzyl) protection.[3]

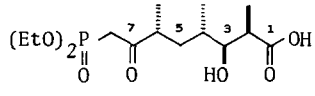
We report here a highly stereoselective synthesis of methynolide (**2**),[4] the aglycone of methymycin (**1**), to establish our synthetic methodology, which is directly applicable to syntheses of more complex antibiotics such as pikronolide, tylonolide and salinomycin.

Segmants i and ii were chosen as synthetic inetermediates from D-glucose. The coupling of C-1∼C-8 and C-9∼C-13 segments, already demonstrated in Masamune's first synthesis of **1**,[4b] is still most suitable, but it is worthwhile to develope a new method which can improve efficiency and selectivity in synthetic processes to **1** or **2**.





Segment i

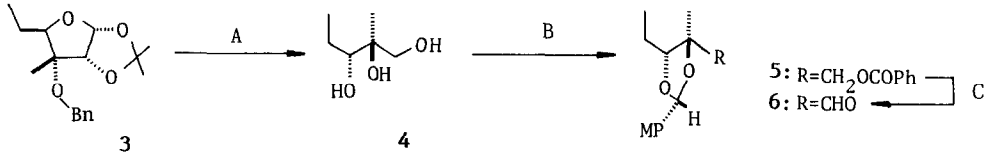


Segment ii

1: R=-(D)-Desosaminyl

2: R=H

As a synthetic equivalent of the segment i, the aldehyde (**6**) was synthesized as follows. The acetonide of **3**[5] was hydrolyzed, followed by $Pb(OAc)_4$ oxidation, $LiAlH_4$ reduction, and hydrogenolysis to give the triol (**4**), $[\alpha]_D^{15}$ + 3.0°.[6] After conversion to the monobenzoate,



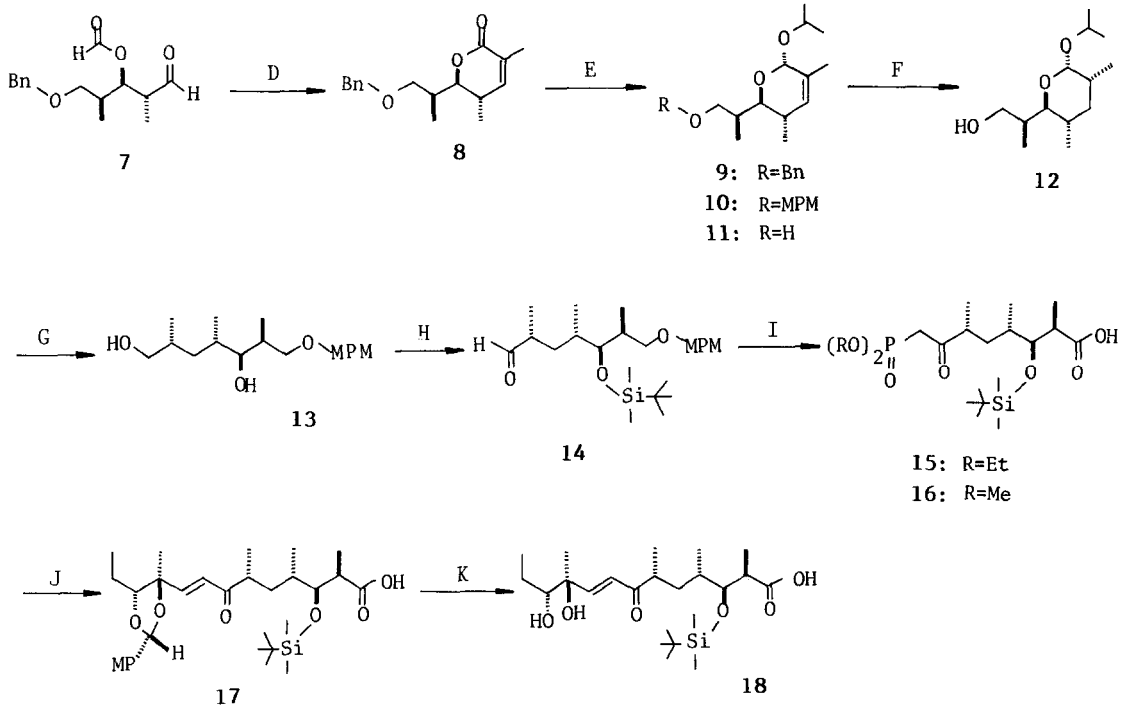
3 **4**

(A) 1) 4N-HCl, THF, 50°C or TFA, H_2O-THF, rt; 2) $Pb(OAc)_4$, C_6H_6; 3) $LiAlH_4$; 4) H_2, Pd-C (93%). (B) 1) PhCOCl; 2) MPMME, DDQ, CH_2Cl_2 (82%). (C) 1) KOH, MeOH-H_2O; 2) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2 (82%).

the remaining diol was protected as a 4-methoxybenzylidene acetal.[7] Kinetic acetalization with MPMME (4-methoxybenzyl methyl ether) and DDQ under neutral conditions[3b] gave **5** (97.5% stereoselectivity), which was hydrolyzed to the alcohol, $[\alpha]_D^{18}$ + 8.0°, and then Swern oxidation[8] easily gave the aldehyde of segment i (**6**).

The aldehyde (**7**), also derived from D-glucose with 96% stereoselectivity,[2c] was treated with a Wittig-Horner reagent[9] and then with K_2CO_3 to give the α,β-unsaturated lactone (**8**). In order to increase the selectivity of the reduction of the double bond, **8** was converted to the anomerically pure α-lactolide (**9**), $[\alpha]_D^{17}$ + 64.7°.[10] Catalytic reduction of **9** with Pd-C at 0°C gave **12** in 89% yield, but the stereoselectivity (5 : 1) was unsatisfactory. After detailed examinations of substrates and catalysts, the reduction of **11** with Rh-Al_2O_3 gave an excellent result, and **12**, $[\alpha]_D^{17}$ + 140°, with over 96% stereoselectivity was isolated in quantitative yield. The substrate (**11**) was synthesized from **10**, derived also from D-glucose, by DDQ oxidation.[3] Thus the introduction of all chiral centers of the segment ii was completed.

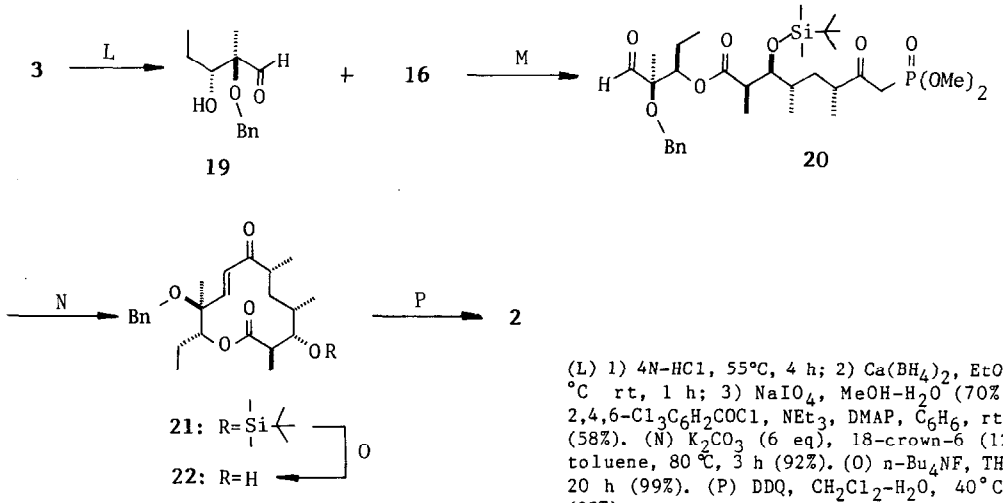
Conversion of **12** to the carboxylic ketophosphonate (**15**, segment ii) was carried out as follows. The hydroxy group of **12** was protected with MPM,[3] followed by acid-hydrolysis and $Ca(BH_4)_2$ reduction to give the diol (**13**), $[\alpha]_D^{18}$ - 14.5°. Four-steps conventional conversion of **13** gave **14**, which was treated with a phosphonate followed by immediate Swern oxidation to give a ketophosphonate (60%).[11] After removal of the MPM protection (81%), Jones oxidation of the resulting alcohol gave **15** (74%). The Witttig-Horner[12] coupling between **15** and **6** proceeded smoothly leading to the unsaturated ketone (**17**). Finally, the MP acetal protection was



(D) 1) $(MeO)_2P(O)CH(Me)CO_2Me$, NaH, -78~0°C; 2) K_2CO_3, MeOH (90%). (E) 1) $LiAlH_4$, -20°C; 2) i-PrOH, CSA (85%). (F) H_2, Rh-Al_2O_3, Et_2O (100%). (G) 1) NaH, MPMCl; 2) 0.4H-HCl, dioxane, 50°C; 3) $Ca(BH_4)_2$, EtOH (76%). (H) 1) PhCOCl, pyridine; 2) TBDMSCl, imidazole, DMF, 80 C; 3) KOH; 4) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2 (87%). (I) 1) $(EtO)_2P(O)CH_2Li$; 2) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2; 3) DDQ, CH_2Cl_2-H_2O; 4) CrO_3, H_2SO_4, acetone, 0°C (36%). (J) n-BuLi, 6, THF, 0°C rt, 13 h (59%). (K) 0.4N-HCl, DME, rt, 2 h (75%).

selectively removed without any detectable loss of the TBDMS protection to give the expected known seco-acid (**18**).[4b,g]

The following synthesis is much more efficient. As an alternative segment i, **19** was used. Only three steps conversion from **3** gave easily **19**, $[\alpha]_D^{12}$ + 82°. Esterification between **19** and **16**,[13] $[\alpha]_D^{12}$ + 13.8°, by the Yamaguchi method[14] gave **20**, though the reaction proceeded not so rapidly.[15] When 1 mM solution of **20** in toluene was treated with K_2CO_3 in the presence of 18-crown-6 at 80°C,[16] a smooth cyclization proceeded to yield the cyclic enone (**21**) in excellent yield,[17] $[\alpha]_D^{15}$ + 77°. After desilylation with the fluoride anion, the resulting benzyl methynolide (**22**), $[\alpha]_D^{16}$ + 61°, was treated with DDQ to remove the benzyl protection,[19] and methynolide (**2**) was isolated in excellent yield, mp 162.5-163.5°C (corrected), $[\alpha]_D^{16}$ + 72°.[20]



(L) 1) 4*N*-HCl, 55°C, 4 h; 2) $Ca(BH_4)_2$, EtOH, -10 °C rt, 1 h; 3) $NaIO_4$, MeOH-H_2O (70%). (M) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, DMAP, C_6H_6, rt, 20 h (58%). (N) K_2CO_3 (6 eq), 18-crown-6 (12 eq), toluene, 80 °C, 3 h (92%). (O) n-Bu_4NF, THF, rt, 20 h (99%). (P) DDQ, CH_2Cl_2-H_2O, 40°C, 8 h (95%).

There are two additional noteworthy features in this report. One is a high overall stereoselectivity of this synthesis from D-glucose. Stereoselectivities for the introduction of new chiral centers at the C-2, C-4, C-6, and C-10 were 96, 97, 96, and 100%, respectively, and hence the overall stereoselectivity was 89%. The other is that the methodology presented here is directly applicable to the synthesis of more complex antibiotics.

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6. All $[\alpha]_D$ were measured in $CHCl_3$.

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13. In analogy with **15**, **16** was synthesized from **14** using dimethyl lithiomethylphosphonate[11] instead of the diethyl ester.

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15. The esterification with DCC and DMAP also gave crude **20** in 70% yield, but it was difficult to remove impurities. Other esterification reagents gave only unsatisfactory results.

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17. In contrast with the cyclization of 16-membered macrolide rings, the 12-membered macrolactone cyclizations have been unsatisfactory.[4] The Aristoff[18]-Nicolaou[16a] method of intramolecular Wittig-Horner reactions may be most promising.

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19. The benzyl protection of tert. alcohols is rather easily removable by the DDQ oxidation.[1b]

20. **2**: δ (500 MHz) 0.90 (3H, t, J = 7.5 Hz, C-13), 1.01 (3H, d, J = 6.0 Hz, C-15), 1.15-1.40 (1H, m, C-5), 1.21 (3H, d, J = 7.0 Hz, C-16), 1.33 (3H, d, J = 7.0 Hz, C-14), 1.38 (3H, s, C-17), 1.50-1.60 (1H, m, C-4), 1.52 (1H, ddq, J = 11.0, 14.0, 7.5 Hz, C-12), 1.53 (1H, d, J = 6.0 Hz, C-3 OH), 1.63 (1H, t, J = 12.5 Hz, C-5), 1.94 (1H, ddq, J = 2.0, 14.0, 7.5 Hz, C-12), 2.04 (1H, s, C-10 OH), 2.56 (1H, dq, J = 3.0, 7.0 Hz, C-6), 2.62 (1H, dq, J = 10.0, 7.0 Hz, C-2), 3.57 (1H, dd, J = 6.0, 10.0 Hz, C-3), 4.78 (1H, dd, J = 2.0, 11.0 Hz, C-11), 6.33 (1H, d, J = 15.0 Hz, C-8), 6.59 (1H, d, J = 15.0 Hz, C-9). **20**: δ (270 MHz) 0.05 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 0.92 (3H, t, J = 7.5 Hz), 0.96 (3H, d, J = 6.0 Hz), 1.00-2.00 (5H, m), 1.11 (3H, d, J = 7.0 Hz), 1.16 (3H, d, J = 7.0 Hz), 1.35 (3H, s), 2.45-3.10 (2H, m), 3.10 (1H, d, J = 23 Hz), 3.11 (1H, d, J = 23 Hz), 3.75 (3H, d, J = 1.0 Hz), 3.83 (3H, d, J = 1.0 Hz), 3.85-3.92 (1H, m), 4.39 (1H, d, J = 12 Hz), 4.60 (1H, d, J = 12 Hz), 5.15 (1H, dd, J = 9.5, 4.0 Hz), 7.33 (5H, s), 9.60 (1H, s). m/z (FD) 643 (M^++1, 41%), 585 (25), 91 (100). **21**: δ 0.07 (3H, s), 0.08 (3H, s), 0.87 (3H, t, J = 7.5 Hz), 0.91 (9H, s), 0.94 (3H, d, J = 7.0 Hz), 1.12-1.56 (3H, m), 1.23 (3H, d, J = 7.0 Hz), 1.25 (3H, d, J = 7.0 Hz), 1.44 (3H, s), 1.66 (1H, t, J = 12.5 Hz), 2.00 (1H, ddq, J = 14.0, 2.5, 7.5 Hz), 2.43-2.66 (1H, m), 2.63 (1H, dq, J = 10.0, 7.0 Hz), 3.64 (1H, d, J = 10.0 Hz), 4.43 (1H, d, J = 11.5 Hz), 4.46 (1H, d, J = 11.5 Hz), 4.87 (1H, dd, J = 10.5, 2.5 Hz), 6.45 (1H, d, J = 16.0 Hz), 6.75 (1H, d, J = 16.0 Hz), 7.2-7.5 (5H, m). m/z (FD) 517 (M^++1, 11%), 461 (20), 459 (100).

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