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TOTAL SYNTHESIS OF TYLONOLIDE, THE AGLYCONE OF THE 16-MEMBERED RING MACROLIDE TYLOSIN, FROM D-GLUCOSE. SELECTIVE APPLICATION OF MPM AND DMPM PROTECTING GROUPS FOR HYDROXY FUNCTIONS[1]

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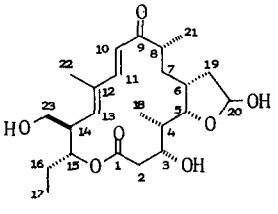
Summary Segments i (C11-C17) and ii (C1-C10), synthesized from D-glucose by employing some stereoselective reactions and benzyl-type protecting groups, were esterified and cyclized to the 16-membered enone, which was readily converted to tylonolide, the aglycone of tylosin.

Tylosin is a typical 16-membered ring macrolide antibiotic that is important not only as a therapeutic agent but also as a target molecule in modern synthetic organic chemistry. In connection with our synthetic study of macrolide and polyether antibiotics from D-glucose by a common methodology consisting of stereocontrolled reactions and the MPM (4-methoxybenzyl) protection,[2] a highly stereoselective and efficient synthesis of methynolide, the aglycone of the 12-membered ring macrolide methymycin, was recently achieved.[1] This methodology has been successfully applied to the total synthesis of tylonolide (**1**),[3] the aglycone of tylosin. The general synthetic strategy consists of condensation and cyclization of segments i (**2**) and ii (**3**), and selectivity between DMPM (3,4-dimethoxybenzyl) and MPM protecting groups in the deprotection with DDQ[2c,e] is crucial in the final stage of the synthesis of **1**.



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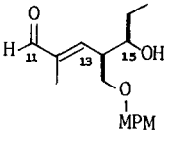

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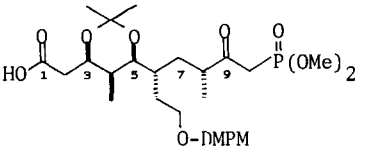
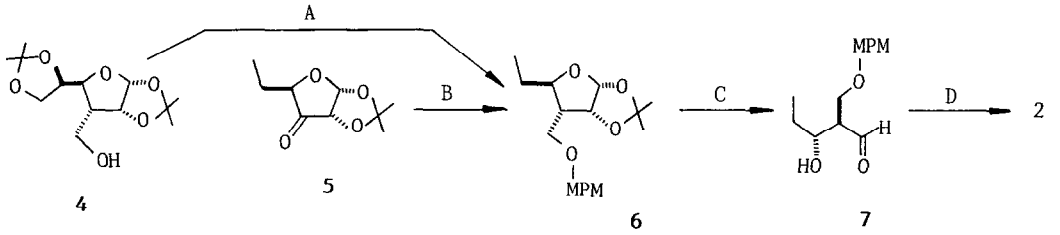


3

Segment i (**2**) was easily synthesized from glucose via the known alcohol (**4**).[4] The alcohol (**4**) was first protected with MPM,[2a] and the 5,6-side chain[5] was reduced to give **6**, which was also synthesized from glucose via **5**.[1] After hydrolysis of the acetonide group of **6**, the

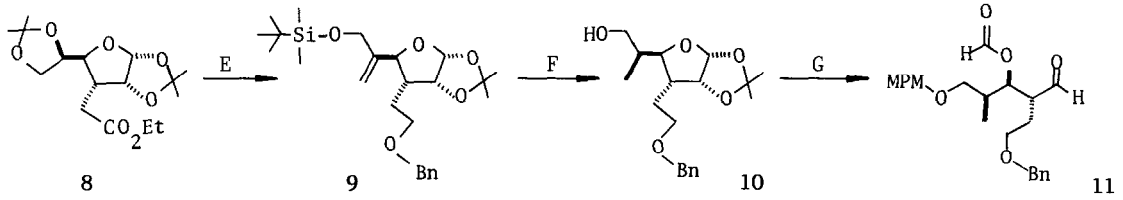


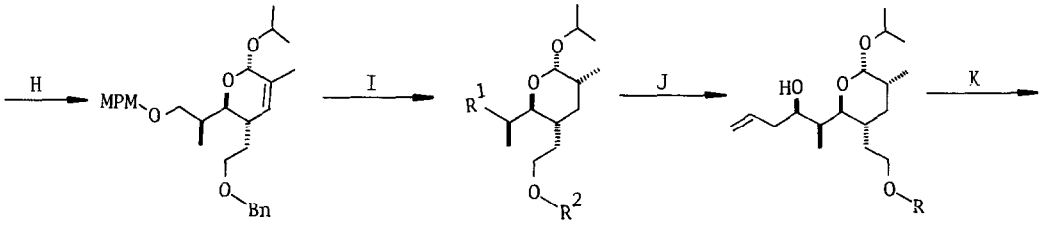
4 **5** **6** **7**

(A) 1) NaH, MPMCl, (93%); 2) 2%-H_2SO_4, MeOH, rt (96%); 3) TsCl, NaI (80%); 4) H_2, Pd-C (100%). (B) 1) $Ph_3P{=}CH_2$ (82%); 2) BH_3, THF; H_2O_2, NaOH (55%); 3) NaH, MPMCl (80%). (C) 1) 4.5N-HCl, THF, 50 °C (72%); 2) $Ca(BH_4)_2$, EtOH (86%); 3) $NaIO_4$, MeOH-H_2O (95%). (D) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, 60°C (91%); 2) $LiAlH_4$, THF (97%); 3) MnO_2, CH_2Cl_2 (96%).

resulting hemiacetal group was reduced with $Ca(BH_4)_2$,[6] followed by treatment with $NaIO_4$ to give **7**, $[\alpha]_D^{15}$ + 6.9°.[7] The Wittig reaction of **7** with a stable ylid gave the expected E-ester, which was reduced with $LiAlH_4$, followed by oxidation with MnO_2 leading easily to the segment i (**2**) in excellent yield.

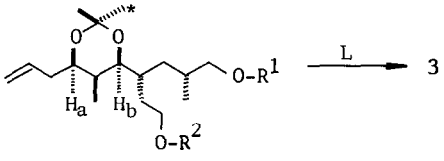
Segment ii (**3**) has a more complex structure. However, since the stereochemical configurations at C-4∼C-8 are identical to those at C-2∼C-6 of methynolide, the methodology employed in the synthesis of the segment ii of methynolide[1] can be applied to the synthesis of **3**. Compound **8**[8] easily available from glucose was converted to **9** via a series of six conventional reactions. Catalytic reduction of **9** with various catalysts easily gave a dihydro compound, but this reduction was not practically useful because of poor stereoselectivity (2.5∼3.0 : 1). Another route via hydroboration proceeded with an excellent stereoselectivity (16 : 1) to give **10**, $[\alpha]_D^{20}$ + 68°, which has three consecutive chiral centers corresponding to the C-4∼C-6 of **1**. The chiral center at the C-8 was constructed via the aldehyde (**11**) and the acetal (**12**) to give **13**, $[\alpha]_D^{16}$ + 97°,[9] by a method similar to that described in the construction of the C-6 chiral center of methynolide.[1]





13: R^1=CH_2OMPM, R^2=H
14: R^1=CH_2OH, R^2=TBDMS
15: R^1=CHO, R^2=TBDMS

16: R=TBDMS
18: R=DMPM

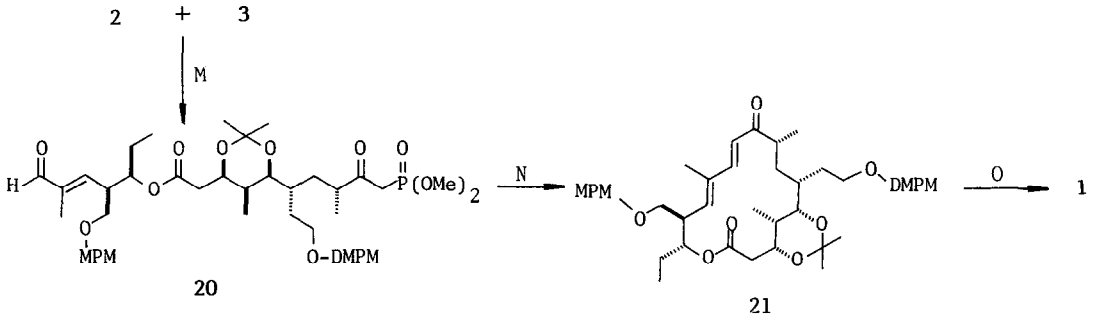


17: R^1=R^2=COC_6H_4-NO_2-p
19: R^1=H, R^2=DMPM

(E) 1) $LiAlH_4$; 2) NaH, BnCl (92%, overall); 3) 2%-H_2SO_4, MeOH, rt (92%); 4) TBDMSCl, imidazole, CH_2Cl_2 (95%); 5) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, - 60 °C (95%); 6) $Ph_3P=CH_2$, THF (92%). (F) 1) BH_3, THF, - 30°C; H_2O_2, NaOH (87%); 2) TsCl, pyridine; 3) $LiAlH_4$, Et_2O (88%, overall). (G) 1) NaH, MPMCl (92%); 2) 4N-H_2SO_4, dioxane, 60°C (68%); 3) $NaIO_4$, MeOH-H_2O (95%). (H) 1) $(MeO)_2P(O)CH(Me)CO_2Me$, NaH, THF, - 80∼0 °C; 2) K_2CO_3, MeOH (68%, overall); 3) DIBAH, toluene, - 78°C; 4) CSA, i-PrOH (93%, overall). (I) 1) H_2, Raney Ni, EtOH (81%); 2) TBDMSCl, imidazole, CH_2Cl_2 (95%); 3) H_2, Pd-C (96.5%) or DDQ, CH_2Cl_2-H_2O (94%); 4) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, - 60 °C (100%). (J) 1) $CH_2=CHCH_2I$, $CrCl_2$, 0°C (78%); 2) n-Bu_4NF, THF (98%); 3) NaH, DMPMCl (70%). (K) 1) 1N-HCl, THF, 50°C; 2) $Ca(BH_4)_2$, EtOH (90%, overall); 3) $Me_2C(OMe)_2$, CSA, C_6H_6 (86%). (L) 1) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, - 60 °C; 2) $MeP(O)(OMe)_2$, n-BuLi, THF, - 78°C; 3) PDC, DMF (60%, overall); 4) $KMnO_4$, $NaIO_4$, Me_2CO-H_2O (83%).

The final chiral center at the C-3 was introduced by the Cram addition[10] of a Grignard reagent to the aldehyde (**15**). The primary alcohol of **13** was protected with a TBDMS (t-butyldimethylsilyl) group, and the MPM group was removed to give **14**, which was readily oxidized to the aldehyde (**15**). When **15** was treated with CH_2=$CHCH_2MgBr$ at - 90°C, a stereo-mixture (6.7 : 1) mainly containing the Cram adduct (**16**; 90%) was isolated. A better stereoselectivity (10 : 1) was obtained by the reaction with CH_2=$CHCH_2I$ in the presence of $CrCl_2$.[11] The structure of **16** was confirmed after conversion to **17**, in which NOE between the methyl group* and H_a and H_b were observed to be 13 and 14%, respectively. Thus the introduction of all chiral centers of the segment ii (**3**) was completed. The silyl protection of **16** was replaced by the DMPM group[2c] to give **18**, which was converted to **3** via **19** in almost the same manner as described in the preceding paper.[1] Thus **19** readily prepared from **18** was oxidized and condensed with a phosphonate,[12] followed by immediate PDC (pydridinium dichromate) oxidation[13] to give the ketophosphonate. Finally, the terminal olefin was oxidized under Lemieux-von-Rudloff conditions[14] to give the segment ii (**3**), $[\alpha]_D^{26.5}$ - 5.6°.

Esterification between **2** and **3** proceeded by the usual treatment with DCC, but the Yamaguchi method[15] gave a better result. The resulting ester (**20**), $[\alpha]_D^{26}$ + 2.8°, was subjected to the Aristoff-Nicolaou cyclization[3c,16] at 100°C for 12 hr to give the 16-membered enone (**21**), $[\alpha]_D^{26}$ + 6.2°, in acceptable yield. Four steps conversion of **21** into tylonolide (**1**) as follows. Selective deprotection of the DMPM group[2c] with DDQ at 0°C gave the primary alcohol, which was converted to the aldehyde by the PDC oxidation,[13] and then acid-treatment to remove the isopropylidene protection gave the hemiacetal compound. Finally, the MPM protection was removed by re-treatment with DDQ under usual conditions[2a] to give tylonolide (**1**; mp 103°C), which was completely identical in its spectral data (IR, NMR, Mass) with **1** derived from natural tylosin.[17,18] In this total synthesis, stereoselectivities for the construction of new chiral centers at the C-3, C-4, C-6, C-8, and C-14 were 91, 94, 100, 87, and 100%, respectively.[19]



(M) 1) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, THF, DMAP, C_6H_6, rt, 1 h (66%). (N) K_2CO_3 (6eq), 18-crown-6 (12eq), toluene, 100°C, 12 h (59%). (O) 1) DDQ (1.2eq), CH_2Cl_2-H_2O, 0°C (75%); 2) PDC, CH_2Cl_2 (94%); 3) 1N-HCl, THF, rt (90%); 4) DDQ, CH_2Cl_2-H_2O, rt (70%).

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18. The synthetic tylonolide (**1**) is a 3.3:1 isomeric (equilibrium) mixture with respect to the hemiacetal position. When a $CDCl_3$ solution of **1** derived from the natural tylosin by Grieco's method C[17a] [6:1 mixture, mp 155-156°C (lit.[17a] mp 102.5-103.5°C or 157.5-158.5°C)] was allowed to stand in a NMR tube, isomerization probably with a trace of acid occurred to give a 3:1 mixture.

19. **1**: δ (500 MHz): 0.95 (3H, t, J = 7 Hz, C-17), 1.02 (3H, d, J = 7 Hz, C-21), 1.05 (1H, ddd, J = 4, 12, 16 Hz, C-7), 1.23 (3H, d, J = 7 Hz, C-18), 1.60-1.73 (3H, m, C-7(1H), C-16(2H)), 1.55 (1H, dq, J = 7, 10 Hz, C-4), 1.80-1.95 (1H, m, C-19), 1.80 (3H, s, C-22), 1.94 (1H, dd, J = 2, 17 Hz, C-2), 2.01-2.07 (1H, m, C-6), 2.19 (0.23H, dd, J = 6, 13 Hz, C-19), 2.27 (0.77H, dd, J = 6, 13 Hz, C-19), 2.45-2.65 (1H, m, C-8), 2.57 (1H, dd, J = 11, 17 Hz, C-2), 2.88 (1H, ddt, J = 5, 6, 10 Hz, C-14), 3.67 (1H, dd, J = 2, 11 Hz, C-3), 3.68-3.77 (2H, m, C-23), 3.80 (0.23H, dd, J = 4, 10 Hz, C-5), 4.12 (0.77H, dd, J = 4, 10 Hz, C-5), 4.93 (1H, dt, J = 2, 10 Hz, C-15), 5.42 (0.23H, d, J = 6 Hz, C-20), 5.50 (0.77H, dd, J = 4, 6 Hz, C-20), 5.80 (1H, d, J = 10 Hz, C-13), 6.33 (0.77H, d, J = 15 Hz, C-10), 6.37 (0.23H, d, J = 15 Hz, C-10), 7.22 (1H, d, J = 15 Hz, C-11). **20**: δ (270 MHz) 0.84 (3H, d, J = 7.0 Hz), 0.86 (3H, t, J = 7.5 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.10-2.00 (8H, m), 1.36 (3H, s), 1.41 (3H, s), 1.78 (3H, s), 2.21 (1H, dd, J = 15.0, 4.0 Hz), 2.51 (1H, dd, J = 15.0, 9.0 Hz), 2.85-3.25 (2H, m), 3.13 (2H, d, J = 22.0 Hz), 3.38-3.60 (4H, m), 3.63-4.05 (2H, m), 3.74 (3H, d, J = 1.0 Hz), 3.80 (6H, s), 3.87 (3H, s), 3.88 (3H, s), 4.32-4.45 (4H, m), 5.21 (1H, m), 6.45 (1H, d, J = 10.0 Hz), 6.80-6.95 (5H, m), 7.20 (2H, d, J = 9.0 Hz), 9.44 (1H, s). **21**: δ 0.83 (3H, d, J = 6.5 Hz), 0.88 (3H, t, J = 7.0 Hz), 1.10-2.20 (8H, m), 1.13 (3H, d, J = 6.5 Hz), 1.38 (3H, s), 1.43 (3H, s), 1.82 (3H, s), 2.34 (2H, t, J = 5.0 Hz), 2.80-3.10 (3H, m), 3.40 (2H, t, J = 6.5 Hz), 3.46 (2H, d, J = 5.0 Hz), 3.81 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 3.90-4.20 (2H, m), 4.35-4.50 (4H, m), 4.99 (1H, dt, J = 4.0, 7.5 Hz), 5.81 (1H, d, J = 11.0 Hz), 6.17 (1H, d, J = 16.0 Hz), 6.80-6.95 (5H, m), 7.17 (1H, d, J = 16.0 Hz), 7.20 (2H, d, J = 9.0 Hz). m/z (FD) 736 (M^+, 100%).

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