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TOTAL SYNTHESIS OF TYLONOLIDE, AN AGLYCONE OF TYLOSIN

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Summary: The total synthesis of tylonolide, a 16-membered-ring aglycone of a macrolide antibiotic, tylosin, has been accomplished by coupling two segments of C1-C10 and C11-C17 portions, which are stereospecifically derived from D-glucose.

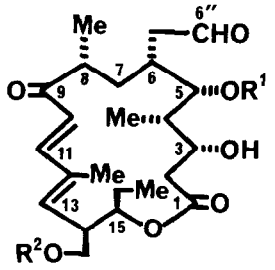
Josamycin (leucomycin A_3) and tylosin (1) constitute the medicinally important 16-membered-ring macrolide antibiotics. The first total synthesis of josamycin has previously been reported in these laboratories.[1] Herein, as an extension of the strategy, we report the first total synthesis of tylonolide (2a), an aglycone of tylosin (1).[2] The construction of the C1-C10 segment of 2a began with the preparation of the acetonide 4[3] ($[\alpha]_D$ -17°) from the previously described 3-C-methyl-D-glucoside 3[4] in 42% overall yield in 4 steps: (1) Ac_2O/H_2SO_4 20°; (2) MeONa/MeOH, 20°; (3) $Me_2CO/CuSO_4/H_2SO_4$, 35°; (4) aq. AcOH, 60°. Periodate oxidation ($NaIO_4$/90% MeOH, 20°, 1 h) of 4 followed by Wittig reaction ($[Ph_3PCH_2OCH_3]Cl$[5]/DMSO anion[6]/THF, 20°, 0.5 h) gave the enol ether, which was hydrolyzed with 90% AcOH to afford the aldehyde 5[3] (92%, $[\alpha]_D$ -15°). Reduction ($NaBH_4$/MeOH, 20°) of 5 followed by successive benzylation (BzlBr/NaH/DMF, 20°, 1 h) and hydrolysis (5% H_2SO_4/t-BuOH, 50°) afforded the 5-deoxyfuranose 6[3] (50%, $[\alpha]_D$ +43°). Reaction of 6 with Ph_3P=CHCOOMe (PhMe, 50°, 18 h) effected Wittig coupling to the *E*-unsaturated ester, which upon treatment with 2,2-dimethoxypropane (TsOH/DMF, 20°, 1 h) afforded the acetonide 7[3] (73%, $[\alpha]_D$ +13°). The introduction of an aldehyde equivalent into the C6 position[7] was effected by Michael addition as previously described.[1] Reaction of 7 with a reagent prepared from 1.5 equiv each of FAMSO[8] and BuLi (-78°, 2.5 h) gave the two adducts 8a and 8b (TLC, Rf 0.22 and 0.20, respectively, PhH-Me_2CO 4 : 1), which were separated by column chromatography to give 8a[3] (39%, $[\alpha]_D$ +25°) and 8b[3] (40%, $[\alpha]_D$ -8°). Since both adducts are converted into the same aldehyde 11 as described later on, the production of two adducts is found to be attributed to the asymmetry at C7, not at C6. Their C6 positions in question are considered to have the right configuration required for the synthesis (as depicted by 8a,b) from the similar possibility of forming a metal chelate to that previously described[1] and, finally, the successful completion of the synthesis presented below. Reaction of 8a with EtSH (BF_3-Et_2O, 20°, 18 h) produced the ethyl methyl dithioacetals 9a and 9b with lactonization: 9a[3] (35%, $[\alpha]_D$ +51°, Rf 0.28 on TLC with PhH-EtOAc 4 : 1); 9b[3] (37%, $[\alpha]_D$ +3°, Rf 0.25). The other 8b also gave the aforesaid dithioacetals 9a and 9b on the same procedure, indicating that the formation of the epimers 9a and 9b was attributable to the newly produced asymmetry at C7. Reduction of 9a and 9b with DIBAL (PhMe, -78°, 0.5 h) afforded the corresponding hemiacetals which were treated with Amberlyst 15 (H type) in MeOH (20°, 2 h) to give the methyl furanosides 10a and 10b, respectively: 10a[3] (80%, $[\alpha]_D$ +110°, Rf 0.35 on TLC with PhH-EtOAc 4 : 1); 10b[3] (80%, $[\alpha]_D$ +68°, Rf 0.32), each of which was shown to consist of only one anomer by the NMR. Benzylation (BzlBr/NaH/DMF, 20°, 4 h) of 10a followed by removal of the thioacetal group ($CdCO_3/HgCl_2$/80% Me_2CO, 20°, 1 h) afforded the labile aldehyde 11[3] (85%), which, on standing, was epimerized to the thermodynamically preferred *E*-isomer 11'[3]. Also,

10b gave the aforesaid 11 by the same procedure. The Wittig reaction of 11 with the previously described ylid 12[1] (PhMe, 60°, 90 h) occurred stereospecifically to give the Z-unsaturated ketone 13[1,3] (90%, $[\alpha]_D$ +1.5°). Reduction (3 atm H_2/Pd-black/MeOH, 20°) of 13 followed by successive catalytic oxidation[1] (O_2/Pt-black/$NaHCO_3$/H_2O, 80°) and esterification (CH_2N_2/Et_2O, 20°) gave the two epimers 14 and 15 (TLC, Rf 0.29 and 0.35, PhH-EtOAc 3 : 2), which were separated by column chromatography to give the 8R-epimer 14[3] (52%, $[\alpha]_D$ +90°) and the 8S-epimer 15[3] (27%, $[\alpha]_D$ +75°). These epimers were equilibrated with K_2CO_3 in MeOH (60°). This structural assignment is based on conversion of 14 into the naturally derived 26 (8R-epimer) as presented below.

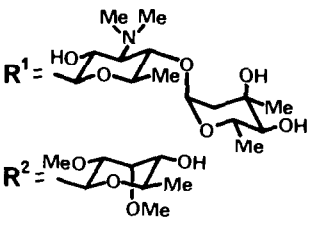
The C11-C17 segment for the synthesis was prepared in a stereochemically unambiguous manner starting with the branched D-allofuranose 16[3,9] which was easily available from D-glucose. Acetylation (Ac_2O/Py, 20°) of 16 gave the crystalline acetate 17[3] (95%, mp 67°, $[\alpha]_D$ +65°), which was converted into 18[3] [mp 117° (needles), $[\alpha]_D$ +53°] by a four-step sequence in 84% overall yield: (1) 90% AcOH, 50°; (2) $NaIO_4$/90% MeOH, 20°; (3) $Zn(BH_4)_2$/Et_2O, 0°; (4) TsCl/Py, 20°. Treatment of 18 with MeMgBr[10] (Li_2CuCl_4/THF, 50°, 4 h) afforded 19[3] (99%, $[\alpha]_D$ +72°). Hydrolysis of 19 (2.5% H_2SO_4/t-BuOH, 50°) followed by oxidation by Br_2 (70% dioxane, 20°, 48 h) to give the γ-lactone, which was treated with trityl chloride (Py, 20°) to give 20[3] (70%, mp 142°, $[\alpha]_D$ -10°). Reaction of 20 with MeLi (Et_2O, -78°, 2 h) to afford 21[3] (92%, $[\alpha]_D$ +8°), which was submitted to Wittig reaction (Ph_3P=CHCOOMe/PhMe, 80°, 72 h) to give 22[3] (76%, $[\alpha]_D$ +20°). Silylation (t-$BuMe_2SiCl$/imidazole/DMF, 60°, 20 h) followed by reduction ($LiAlH_4$/Et_2O, 20°) afforded 23[3] (93%, $[\alpha]_D$ +50°). Hydroboration[11] (BH_3-Me_2S/CH_2Cl_2, 20°, 72h; aq. EtOH/NaOH/H_2O_2, 20°, 2 h) of 23 gave the 1,2-diol which upon glycol cleavage ($NaIO_4$/90% MeOH, 0°) afforded an aldehyde. This was treated with MeONa (MeOH, 20°) to give the *E*-unsaturated aldehyde 24[3,12] (57% from 23, $[\alpha]_D$ +4°) with β-elimination, which was desilylated by Bu_4NF (THF, 20°) to give the aldehyde 25[3].

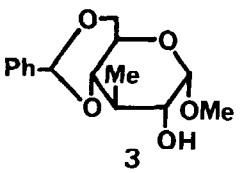
Thus, the epimer 14 was subjected to the aldol condensation with 25 (LDA/THF, -78° to 0°, 2 h) as previously described[1] to give the desired *E*,*E*-unsaturated ketone 26[3] (41%, $[\alpha]_D$ +66°, λ_{max}^{MeOH} 286 nm (ε 22200)). The other epimer 15 was not converted into 26 by the same procedure but into the 8S-epimer 27[3] ($[\alpha]_D$ +44°, Rf 0.54 and 0.49 for 26 and 27 on TLC with hexane-EtOAc 2 : 3). Synthetic 26 was identical in all respects with a sample of the same structure produced by an unambiguous series of transformations (outlined below) starting from a naturally derived aglycone 2a. Reduction ($NaBH_4$/MeOH, 0°) of 26 gave the C9-OH epimers 28a (48%, $[\alpha]_D$ +28°, Rf 0.38 on TLC with hexane-EtOAc 3 : 2) and 28b (42%, $[\alpha]_D$ +40°, Rf 0.34), which were saponified (0.2N KOH/aq. MeOH, 60°, 15 h) to afford the corresponding seco acids (~85%). The two acids were converted with 2,2'-dipyridyl disulfide (Ph_3P, 20°)[13] into the 2-pyridinethiol esters 29a[3] (Rf 0.63 on TLC, PhH-EtOAc 1 : 2) and 29b[3] (Rf 0.58) respectively, which were submitted to cyclization[14] (PhMe, 110°, 20 h) to afford the 16-membered-ring lactones 30a[3] (41%, mp ~94° (amorphous), $[\alpha]_D$ +37°, λ_{max}^{MeOH} 232 nm (ε 33900), Rf 0.35 on TLC with hexane-EtOAc 3 : 2) and 30b[3] (28%, mp 181° (needles), $[\alpha]_D$ +65°, λ_{max}^{MeOH} 231 nm (ε 32700), Rf 0.50), respectively. Selective oxidation (CrO_3/HMPT, 20°, 20 h) of 30a and 30b provided the desired aglycone 2a[3] (86%, mp 124° (needles), $[\alpha]_D$ +60°, λ_{max}^{MeOH} 282 nm (ε 21600)) identical in all respects with a naturally derived authentic sample. By this completion, the absolute configuration (especially at C14)[2b] of tylosin (1) was confirmed.

Authentic samples of 2a, 26 and 28a,b were derived from tylosin (1) as follows.



Tylosin (1)





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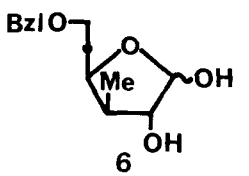

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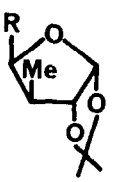
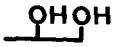
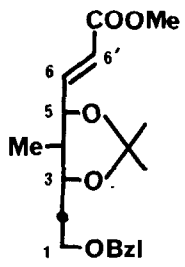


4: R = 

5: R = CH_2CHO



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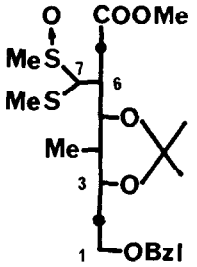
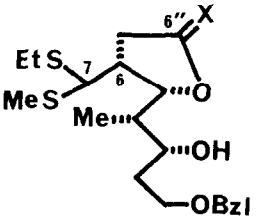
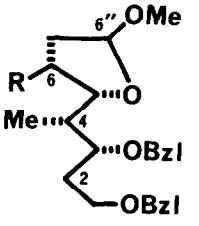


8a,b

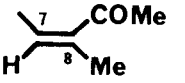


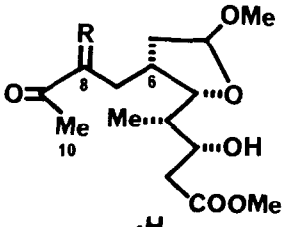
9a,b: X = O

10a,b: X = H, OMe



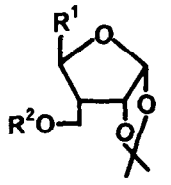
11: R = 

13: R = 



14: R = 

15: R = 

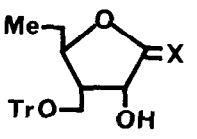


16: R^1 =  , R^2 = H

17: R^1 =  , R^2 = Ac

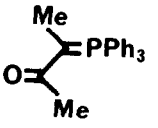
18: $R^1 = CH_2OTs$, R^2 = Ac

19: $R^1 = CH_2CH_3$, R^2 = H

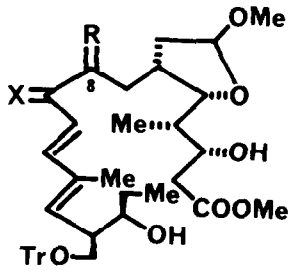


20: X = O

21: X = Me, OH



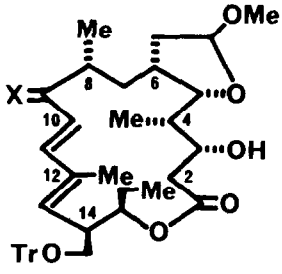
12



26: R =  , X = O

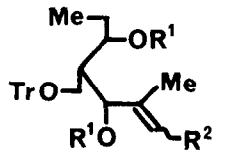
27: R =  , X = O

28a,b: R =  , X = H, OH



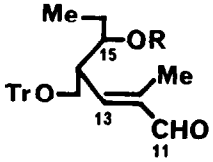
2a,b: X = O

30a,b: X = H, OH



22: R^1 = H, R^2 = COOMe

23: $R^1 = SiBu^tMe_2$, $R^2 = CH_2OH$



24: R = $SiBu^tMe_2$

25: R = H

Treatment of a tylonolide hemiacetal, which was prepared from 1, with Amberlyst 15 (H type) in MeOH (20°) gave the corresponding methyl furanosides,[2c] which were tritylated (TrCl/Py, 50°) to afford two anomers 2a[3] (65%, mp 124°, $[\alpha]_D$ +60°, Rf 0.56 on TLC with hexane-EtOAc 3 : 2) and 2b[3] (22%, mp ~85°, $[\alpha]_D$ 0°, $[\alpha]_{365}$ -83°, Rf 0.60). Reduction ($NaBH_4$/MeOH, 20°) of 2a to give 30a,b, followed by successive saponification (KOH/aq. MeOH, 60°, 15 h) and esterification (CH_2N_2/Et_2O, 20°) gave 28a (64%) and 28b (27%), which were selectively oxidized (MnO_2/CH_2Cl_2, 20°, 48 h) to afford a reference sample of 26 (79%). Treatment of 2a with K_2CO_3 in MeOH (70°, 20 h) resulted in epimerization at C8 to give directly a mixture of 26 (41%) and 27 (40%).

With the synthesis of 2a completed, the conversion into tylosin (1) can now be addressed.

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References and Notes:

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3) All compounds have been fully characterized by spectroscopic means and elemental compositions established by mass spectra and/or elemental analyses. Melting points were uncorrected. Optical rotations were done in $CHCl_3$ at *c* 1.00 (20°) unless stated otherwise. NMR (δ, ppm from TMS, and J in Hz) spectra were in $CDCl_3$ solution. Significant NMR spectral data are the following. 2a: 3.34(s, MeO), 5.02(m, H-6" & 15), 5.95(d, J=10.5, H-13), 6.35(d, J=16, H-10). 2b: 3.35(s, MeO), 4.93(d, J=6, H-6"), 5.02(dt, J=10 & 3, H-15). 4: 0.95(d, J=7.5, Me), 4.10(dd, J=9 & 4, H-4). 5: 4.60(dt, J=7 & 4, H-4), 9.73(sharp t, CHO). 7: 1.40(s, acetonide), 6.06(dd, J=13 & 2, H-6'), 6.81(dd, J=13 & 3, H-6). 8a: 0.84(d, J=7, Me-4), 2.38(s, MeS), 2.74(s, MeSO), 3.96(d, J=2, H-7). 8b: 0.88(d, J=7, Me-4), 2.26(s, MeS), 2.74(s, MeSO), 3.96(d, J=3, H-7). 9a: 1.26(t, J=7.4, MeCH$_2$S), 2.15(s, MeS). 9b: 1.26(t, J=7.4, MeCH$_2$S), 2.21(s, MeS). 10a: 2.05(s, MeS), 3.20(s, MeO). 10b: 2.01(s, MeS), 3.21(s, MeO). 11: 4.97(dd, J=6 & 3, H-6"), 9.53(d, J=3, CHO). 11': 4.91(t, J=3, H-6"), 9.46(d, J=3, CHO). 13: 2.23(s, Me-8), 6.51(dd, J=11 & 1, H-7). 14: 1.14(d, J=7, Me-8), 2.16(s, COMe), 3.72(s, COOMe). 15: 1.11(d, J=7, Me-8), 2.16(s, COMe), 3.72(s, COOMe). 18: 2.03(s, OAc), 2.42(s, Me of Ts). 20: 0.95(t, J=7, Me), 1.62(quintet, CH$_2$Me). 22: 2.03(s, vinyl Me), 3.60 (s, COOMe), 5.88(s, vinyl H). 24: -0.10 & 0.00(each s, Me$_2$Si), 1.13(s, t-BuSi), 1.75(s, Me-12), 6.40(d, J=11, H-13), 9.34(s, CHO). 25: 6.57(d, J=11, H-13), 9.33(s, CHO). 26: 0.94(d, J=6.5, Me-4), 1.15(d, J=7, Me-8), 6.13(d, J=10, H-13), 6.14(d, J=16, H-10). 27: 0.92(d, J=6.5, Me-4), 1.14(d, J=7, Me-8). 28a: 4.00(m, H-9), 5.59(dd, J=15.5 & 7, H-10), 5.65(d, J=10, H-13). 28b: 4.16(m, H-9), 5.61(dd, J=15.5 & 7, H-10), 5.63(d, J=8.5, H-13). 29a: 5.55 (dd, J=16 & 8, H-10), 5.63(d, J=10, H-13), 8.51(sharp m, SPy-H). 29b: 5.62(dd, J=16 & 7, H-10), 5.62(d, J=9.5, H-13), 8.59(sharp m, SPy-H). 30a: 4.27(dull dt, H-9), 4.99(m, H-6" & 15), 5.66(dd, J=16 & 9, H-10). 30b: 4.25(sharp m, H-9), 4.99(m, H-6" & 15), 5.77(dd, J=16 & 3.5, H-10).
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9) 16: Syrup, $[\alpha]_D$ +31° (*c* 2.0, $CHCl_3$), NMR: 4.74(apparent t, but dd, J=5 & 4, H-2), 5.76 (d, J=4, H-1); the p-bromobenzenesulfonate[3]: mp 109-110°, $[\alpha]_D$ +67°, NMR: 2.3(m, H-3), 3.6(m, H-4), 4.19(dd, J=10.5 & 9.5, H-3'a), 4.50(dd, J=9.5 & 4, H-3'b), 4.63(t, J≈4, H-2), 5.74 (d, J≈4, H-1). The NMR data were identical with those reported in a literature: A. Rosenthal and M. Sprinzl, *Can. J. Chem.*, 47, 4477 (1969).
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