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TOTAL SYNTHESIS OF CARBOMYCIN B AND JOSAMYCIN (LEUCOMYCIN A_3)

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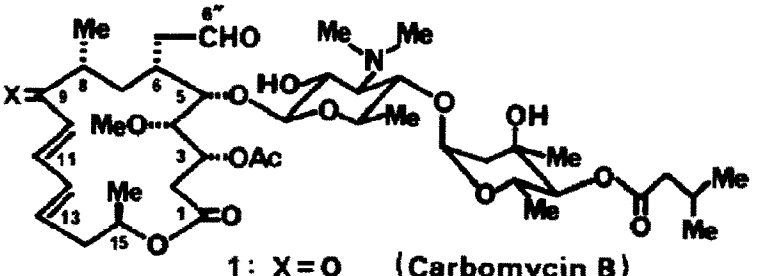
Summary: The stereospecific total synthesis of macrolide antibiotics, carbomycin B and josamycin (leucomycin A_3), is described. The key aglycone has been synthesized by coupling two segments of C1-C10 and C11-C16 portions, which are stereospecifically derived from D-glucose.

Carbomycin B (1, magnamycin B) and josamycin (2, leucomycin A_3) constitute members of medicinally important antibiotics. Herein we report the first total synthesis of carbomycin B (1) and josamycin (2) in the natural optically active form without need of resolution. Carbomycin B (1) has partially been synthesized from the naturally derived aglycone by the authors[1] and converted into 2.[2] The synthetic route to the key intermediate 3 is based on a convergent scheme involving the optically pure C1-C10 segment (13) and the previously described C11-C16 segment (15),[3] which are derived from D-glucose with a high degree of stereospecificity in multigram quantities, and on a modification of the sequence used in the total synthesis of a 16-membered lactone antibiotic A26771B.[4a] Our synthesis begins with the preparation of the starting acetonide 4[5,6] ($[\alpha]_D$ -45° (MeOH)) on a one-mol scale from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose[7] in 72% overall yield in five steps: (1) MeI/NaH, 20°; (2) 90% AcOH, 60°; (3) benzoyl chloride/Py, -10°; (4) TsCl/Py, 70°; (5) $LiAlH_4/Et_2O$, 20°. Hydrolysis (6N H_2SO_4, 20°, 3 h) of 4 gave the corresponding furanose which reacted with methoxycarbonylmethylenetriphenylphosphorane (MeOAc, 50°, 15 h) to afford the *E*-unsaturated ester 5[6] (75%, $[\alpha]_D$ -7°). Selective etherification (methoxy methyl chloride, N,N-diisopropylethylamine, $CHCl_3$, 28°, 3 days) followed by treatment with 2,2-dimethoxypropane (TsOH, DMF, 20°, 2 h) afforded the protected ester 6[6] (61%, $[\alpha]_D$ +35°). The introduction of an aldehyde equivalent into the C6 position[8] was effected by treatment of 6 (-78°, 2.5 h and 0°, 1 h) with a reagent prepared from 1.1 equiv each of methyl methylthiomethyl sulfoxide[9] in THF and butyllithium in hexane (0°, 20 min) to give a 79% yield of the adduct 7[6] ($[\alpha]_D$ +34°). Remarkably, the Michael addition was effectively stereospecific generating exclusively one of the two possible configurations at C6.[5a] Since the approach of the anion to the C6 position seems to be reasonably conducted from the less hindered side and assisted by the C5 oxygen and the ester carbonyl oxygen atoms, which can form a metal chelate with the lithiated reagent, the product 7 is considered to have the absolute configuration required for the synthesis (as depicted by 7).[10] The stereochemistry is completely verified by the successful completion of the synthesis presented below.

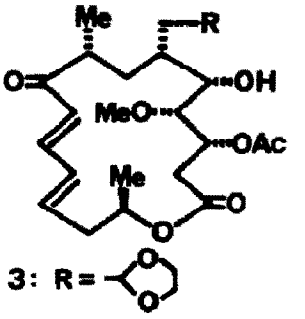
Reaction of 7 with EtSH (BF_3-Et_2O, 20°, 15 h) produced the ethyl methyl dithioacetal 8[6] (78%, $[\alpha]_D$ +30°) with lactonization. Reduction of 8 with diisobutylaluminium hydride (toluene, -78°, 30 min) afforded the corresponding hemiacetal (furanose-type) which was treated with Amberlyst 15 (H type) in methanol (20°, 3 h) to give the methyl furanoside-type 9[6] as only one anomer (72%, $[\alpha]_D$ +107°). Although the stereochemistry at the C6" is not defined, it is not

a critical point for the synthesis of 3. Benzylation of 9 (benzyl bromide, NaH, DMF, 20°, 2 h) followed by removal of the thioacetal group ($CdCO_3$, $HgCl_2$, aq. acetone, 20°, 2 h) afforded the labile aldehyde 10[6] (85%, $[\alpha]_D$ +90°), which was submitted to the Wittig reaction. The ylid 11[6] (plates from benzene, mp 177°, IR (KBr) 1510 cm^{-1}(C=O)) was prepared from 3-chloro-2-butanone by a three-step sequence in 64% overall yield: (1) NaI/acetone, 20°, 2 h; (2) Ph_3P/PhH, 20°, 15 h; (3) BuLi/THF, -78° to 48°, 1.5 h. The Wittig reaction of 10 (1 equiv) and 11 (3.2 equiv) in toluene (105°, 2 days) gave a homogeneous olefin 12[6] (91%, $[\alpha]_D$ +83°), the *Z*-stereochemistry of which was defined by comparison of the chemical shift (δ 6.64) of the vinylic proton with those (δ 6.40 and 7.02) of *Z*- and *E*-isomers of the corresponding benzyl furanoside-type of 12.[11] Reduction (3 atm H_2, Pd-black, aq. EtOH, 20°, 15 h) of 12 followed by successive catalytic oxidation (O_2, Pt-black, $NaHCO_3$, H_2O, pH 7, 85°, 3 h) of the resulting primary alcohol and esterification (CH_2N_2, Et_2O, 20°, 30 min) gave the two epimers 13 and 14 (on silica gel TLC, Rf 0.41 and 0.46, respectively, $CHCl_3$-acetone 3 : 1), which were readily separated by column chromatography to give the 8R-epimer 13[6] (44%, $[\alpha]_D$ +80°) and the 8S-epimer 14[6] (27%, $[\alpha]_D$ +78°) These epimers were equilibrated in aq. AcOH. This structural assignment is confirmed by the conversion of 13 into the naturally derived 16 (8R-epimer). The epimer 13 in THF was allowed to react with 3.2 equiv of lithium diisopropylamide (-78° to 0°, 30 min) and then treated with 2 equiv of the unsaturated aldehyde 15[3] in THF (0° to 20°, 1.5 h) to give, after chromatography, the desired *E*,*E*-unsaturated ketone 16[6] (67%, $[\alpha]_D$ +42°, λ_{max}^{MeOH} 279 nm (ε 15600)). The other epimer 14 was not converted into 16 by the same procedure but into the 8S-epimer 17.[6] ($[\alpha]_D$ +52°, Rf 0.36 and 0.41 for 16 and 17 on TLC, $CHCl_3$-acetone 2 : 1). Synthetic 16 was identical in all respects (IR, NMR, UV and mass spectra, $[\alpha]_D$ and TLC behavior) with a sample of the same structure produced by an unambiguous series of transformations (outlined below) starting from a naturally derived aglycone 21a. Reduction of 16 with $NaBH_4$ (MeOH, 20°, 1 h) gave a mixture (18) of the C9-OH epimers[6] (94%, $[\alpha]_D$ +71°, λ_{max}^{MeOH} 232 nm (ε 25200)), which was hydrolyzed (0.2N KOH, aq. MeOH, 20°, 6 h) to give the corresponding seco acid 19[6] (42%, IR ($CHCl_3$) 1710cm^{-1}(COOH) with concomitant formation of the 2,3-unsaturated acid (23%). Lactonization of 19 was accomplished by a modified Masamune's method[4] as follows. The acid 19 was converted with diethyl phosphorochloridate (Et_3N, THF, Ar, 20°, 2 h) and then thallium benzenethiolate (20°, 3 h) into the benzenethiol ester (NMR: δ 7.42 (SPh)), which was submitted to cyclization (Na_2HPO_4, CF_3COOAg, Drierite, benzene, Ar, 70°, 15 h) to afford the 16-membered-ring lactone 20[6] (17%, $[\alpha]_D$ +82°, λ_{max}^{MeOH} 232 nm (ε 15900)). Selective oxidation (6 equiv CrO_3, hexamethylphosphoric triamide, 20°, 1 h) of 20 provided the corresponding unsaturated ketone which was acetylated (Ac_2O, Py, 20°, 15 h) to give the labile aglycone 21a[6] (71%, mp 73° (amorphous), $[\alpha]_D$ +74°, λ_{max}^{MeOH} 277 nm (ε 15200)) identical in all respects with a naturally derived authentic sample.

Authentic 21a and also reference samples of intermediates 16 and 18 were derived from carbomycin B[1] (1) as follows. Carbomycin B (1) was partially hydrolyzed with acidic methanol (TsOH, 20°, 4 h) to give the demycarosyl dimethyl acetal, which was oxidized by m-chloroperbenzoic acid followed by treatment with acetic anhydride, according to a sequence used previously in the preparation of 3,[1] to afford the unique aglycone 23[6] (40%, mp 66°, $[\alpha]_D$ +39°, λ_{max}^{MeOH} 279 nm (ε 18600). Treatment of 23 with Amberlyst 15 (H type) (MeOH, 20°, 2 h) provided

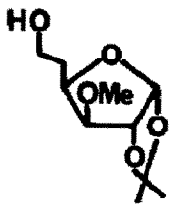


1: X = O (Carbomycin B)
2: X = OH / H (Josamycin)



3: R = O,O

23: R = $-CH(OMe)_2$



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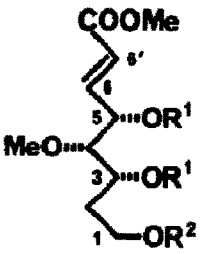
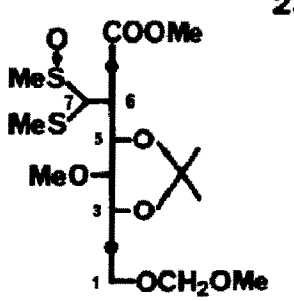


5: $R^1 = R^2 = H$

6: R^1 = acetonide
$R^2 = CH_2OMe$



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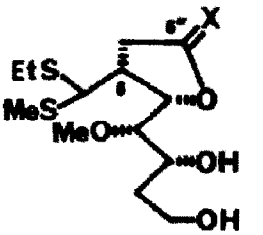
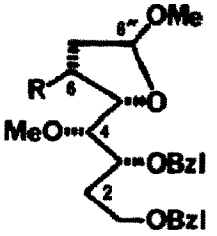
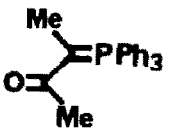


8: X = O

9: X = H, OMe



10: R = CHO



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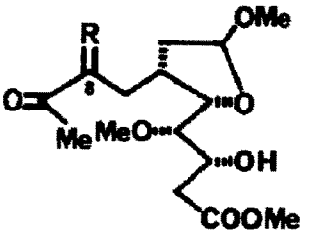
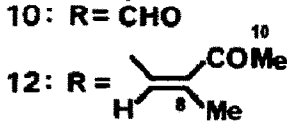
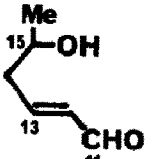




12: R =



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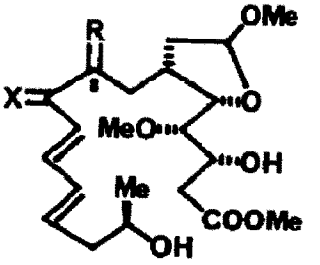
13: R = H / Me

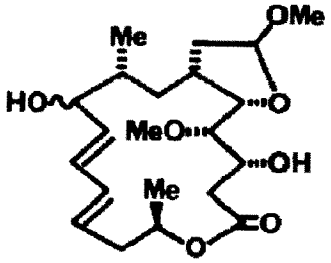
14: R = Me / H



16: R = H / Me , X = O

17: R = Me / H , X = O

18: R = H / Me , X = H, OH



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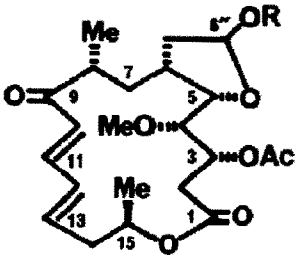

21a, b: R = Me

22: R = H

the methyl furanosides 21a and 21b (on TLC, Rf 0.42 and 0.35, PhH-EtOAc 1 : 1). The less pola anomer 21a[6] (32%) was rather unstable, whereas the other anomer 21b (15%, mp 182° (needles), $[\alpha]_D$ 0°) was stable. Reduction of 21a ($NaBH_4$, MeOH, 20°) followed by successive alkaline hydrolysis (0.2N KOH, aq. MeOH, 20°, 15 h) and esterification (CH_2N_2, Et_2O, 20°, 30 min) gave a sample of 18, which was selectively oxidized (MnO_2, CH_2Cl_2, 20°, 15 h) to afford a reference sample of 16. Direct alkaline hydrolysis of 21a followed by esterification resulted in epimerization at C8 to give a mixture of 16 and 17.

Acid hydrolysis (4% H_3PO_4 in 50% aq. THF, 40°, 6 h) of synthetic 21a afforded the hemiace 22[6] (90%, mp 88°, $[\alpha]_D$ +43°, λ_{max}^{MeOH} 278 nm (ε 16800)), which was treated with ethylene glycol (TsOH, CH_3CN, 20°, 6 h) to give the aglycone 3 [24%,[12] mp 75°, $[\alpha]_D$ +10°; the acetate (Ac_2O, P 45°, 14 h): mp 222°] identical with the previously described sample[1] by comparison of mp, mmp, spectra, $[\alpha]_D$, and TLC behavior. Since the aglycone 3 has already been transformed into carbomycin B (1) and josamycin (2, leucomycin A_3),[1,2] the synthesis of 3 constitutes the completion of the task.

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References and Notes:

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4) a) K. Tatsuta, A. Nakagawa, S. Maniwa and M. Kinoshita, *Tetrahedron Lett.*, in press.
b) S. Masamune, Y. Hayase, W. Schilling, W. K. Chan and G. S. Bates, *J. Am. Chem. Soc.*, 99 6756 (1977).
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6) All compounds have been fully characterized by spectroscopic means and elemental compositi established by mass spectra and/or elemental analyses. Melting points were uncorrected. Optical rotations were done in $CHCl_3$ at c 1.00 (20°C) unless stated otherwise. NMR (δ, pp from Me_4Si, and J in Hz) spectra were in $CDCl_3$ solution. Significant NMR spectral data ar the following. 3: 2.02(s, OAc), ~3.84(m, ethylene), 4.78(t, J=5, H-6"), 6.35(d, J=15, H-1 5: 6.18(dd, J=15.5 & 2, H-6'), 7.07(dd, J=15.5 & 4, H-6); 6: 1.49(s, acetonide); 7: 2.41(s SMe), 2.79(s, SOMe), 3.72(s, COOMe); 8: 1.30 & 1.32(each t, J=7, Me of SEt), 2.16 & 2.21(e s, SMe); 9: 3.32(s, MeO-6"), 3.54(s, MeO-4), 5.04(dd, J=5 & 1.5, H-6"); 10: 5.21(dd, J=5 & 1.5, H-6"), 9.51(d, J=3.5, CHO); 11: 1.65(d, J=15.5, MeC=P); 12: 1.71(d, J=1.5, Me), 2.28(Me); 13: 1.14(d, J=7, Me), 2.15(s, Me); 14: 1.12(d, J=7, Me), 2.15(s, Me); 16: 3.31(s, MeO 6"), 5.04(t, J=3.5, H-6"), 6.16(d, J=11.5, H-10); 17: 3.33(s, MeO-6"), 5.04(t, J=3.5, H-6" 6.16(d, J=12, H-10); 18: 3.34, 3.50, 3.71(each s, MeO X 3), 5.04(dd, J=5 & 2.5, H-6"); 20: 3.35, 3.54(each s, MeO X 2); 21a: 1.20, 1.28(each d, J~7, Me X 2), 2.07(s, OAc), 3.36, 3.5 (each s, MeO X 2), 6.31(d, J=15.5, H-10), 7.3(m, H-11); 21b: 1.21, 1.29(each d, J~7, Me X 3.35, 3.60(each s, MeO X 2), 6.34(d, J=15.5, H-10); 22: 3.53 & 3.56(each s, MeO-4); 23: 3. & 3.27(each s, $C(OMe)_2$), 4.41(t, J=5.5, H-6").
7) E. J. Hedgley, O. Meresz and W. G. Overend, *J. Chem. Soc.* (C), 1967, 888.
8) The numbering system, which matches with that of the aglycone, is employed in formulations
9) K. Ogura, M. Yamashita and G. Tsuchihashi, *Tetrahedron Lett.*, 1978, 1303.
10) These studies will be described in detail in the full paper.
11) The *Z*- and *E*-isomers of the benzyl furanoside of 12 (6"-OBzl) were derived from 8 by a similar procedure.
12) The hydroxyethyl furanoside (6"-OCH_2CH_2OH) of 22 was isolated as a by-product in 70% yield and recycled for the preparation of 3.

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