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STEREOSELECTIVE SYNTHESIS OF THE MIDDLE (C10-C17) AND RIGHT (C18-C30) SEGMENTS, AND THEIR COUPLING TO COMPLETE A FORMAL SYNTHESIS OF THE POLYETHER ANTIBIOTIC SALINOMYCIN[1]

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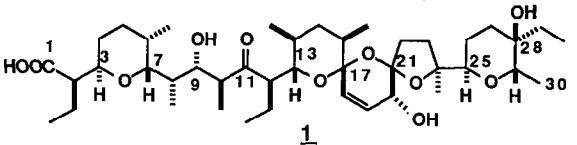
Summary The middle (C10-C17) and right (C18-C30) segments of the polyether antibiotic salinomycin were stereoselectively synthesized from D-glucose, D-mannitol, and ethyl L-lactate. Coupling of the two segments followed by construction of the bisketal ring system gave the C10-C30 segment, which was already converted to salinomycin by Kishi.

Highly stereocontrolled synthesis of complex natural products such as polyether ionophore and macrolide antibiotics is one of challenging subjects for modern synthetic organic chemists to establish new synthetic methodologies. For the past few years, we also have engaged in the synthetic work of a series of such complex natural products by a common methodology starting from D-glucose. In the macrolide series, we recently reported highly stereoselective syntheses of aglycons such as methynolide,[2] pikronolide,[3] and tylonolide,[4] pointing out that suitable selection of protecting groups as well as stereoselective reactions was extremely important. As the first extension to the polyether series, we now report a stereoselective formal synthesis of salinomycin (**1**),[5] describing the synthesis of the middle (C10-C17)[8] (**2**) and right (C18-C30) segments (**3**) from D-glucose, D-mannitol, and ethyl L-lactate, and their coupling to afford the C10-C30 segment (**4**).[9]



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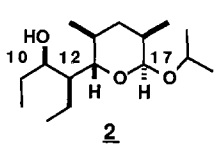

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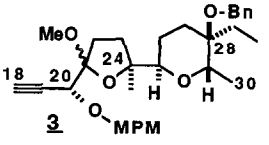

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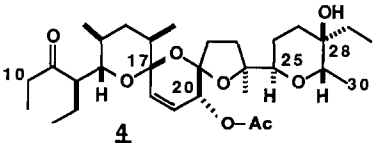

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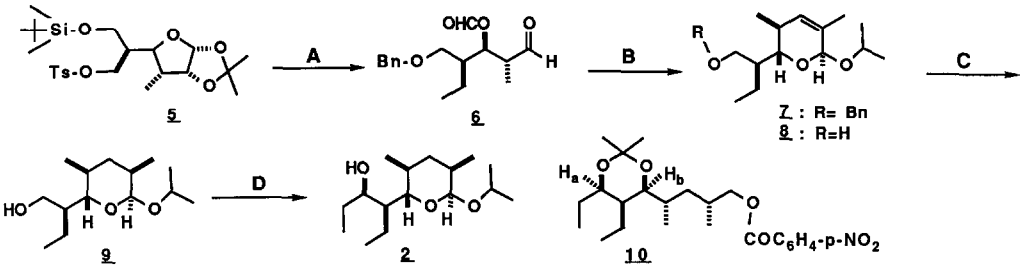
Because the middle segment (**2**) is identical with the Prelog-Djerassi lactonic acid[10] with respect to configuration of four chiral centers at C12, C13, C14, and C16, the method developed for the synthesis of macrolide aglycons[2,3,4] was directly applicable to the synthesis of 2. Five step conversion [methylation with CuI-MeLi, removal of the TBDMS protection, benzylation, hydrolysis, and $NaIO_4$ oxidation] of **5**[11] derived from D-glucose gave the aldehyde (**6**). The Wittig-Horner reaction of **6** followed by treatment with K_2CO_3 readily gave an α,β-unsaturated lactone, which was converted to **7** via DIBAH reduction and isopropylation. Catalytic hydrogenation of **7** with Raney Ni and then with Rh-Al_2O_3 gave **9** (13 : 1 stereoselection).[12] Swern oxidation of **9** followed by treatment with EtMgBr in ether at -50°C gave only the Cram adduct (**2**) in excellent yield.[13]

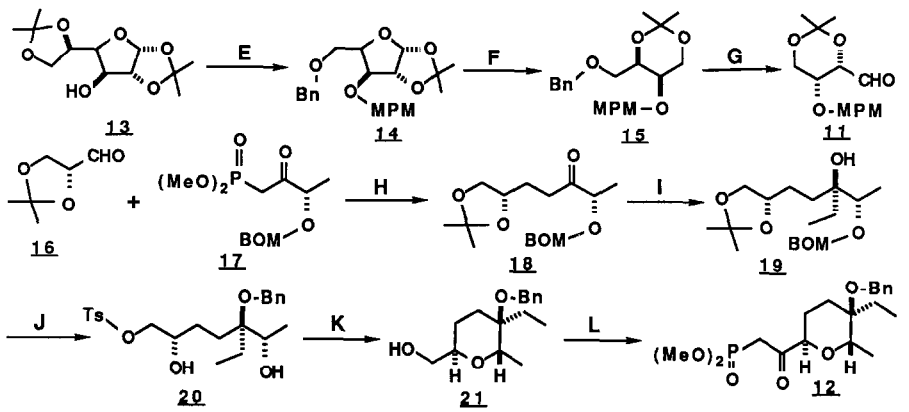
The right segment (**3**) was synthesized from **11** and **12**. Diacetoneglucose (**13**) was converted to **11** as follows. Five consecutive reactions [MPM protection[18b,19] of **13**, partial hydrolysis of acetonides, $NaIO_4$ oxidation, $NaBH_4$ reduction, and benzylation] readily gave **14**, which was converted to **15** in the usual way. Finally, selective removal of the benzyl protection with



(A) 1) CuI, MeLi, Et_2O, -25°C, r.t, 100%; 2) 1N-HCl, MeOH, r.t., 89%; 3) Bn-Cl, NaH, DMSO-THF (3:1), 90%; 4) 4N-HCl, THF, 45°C, 98%; 5) $NaIO_4$, THF-MeOH, r.t., 99%. (B) 1) $(MeO)_2P(O)CHMeCO_2Me$, NaH, THF, -78~-15°C, 2) K_2CO_3, MeOH, r.t., 74% (overall); 3) DIBAH, toluene, -80°C; 4) CSA, Me_2CHOH, r.t., 91% (overall). (C) 1) Raney Ni (W-2), EtOH; 2) Rh-Al_2O_3, EtOH, r.t., 82% (overall). (D) 1) DMSO, $(COCl)_2$, Et_3N, 100%; 2) EtMgBr, Et_2O, -50°C, 89%.

Raney-Ni[18] followed by Swern oxidation gave **11**.

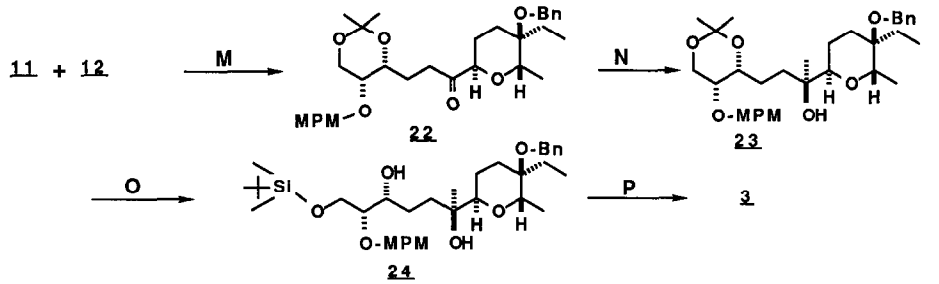
Another synthon (**12**) was synthesized from **16** and **17**.[16] Wittig-Horner coupling followed by reduction gave **18**, which was then treated with EtMgBr in THF at -93°C. A chelation controlled reaction[16,20] proceeded to give quantitatively **19**, which was then converted to **20** in the usual way. Treatment of **20** with a large excess of NaH in DMSO-THF (1 : 1) gave directly the expected tetrahydropyran (**21**).[21] Final conversion of **21** into **12** was carried out via an ester.



(E) 1) MPM-Cl, NaH, DMSO-THF, r.t., 100%; 2) 2%-H_2SO_4, MeOH, r.t., 94%; 3) $NaIO_4$, MeOH-H_2O, r.t.; 4) $NaBH_4$, 96% (overall); 5) Bn-Cl, NaH, DMSO-THF, 82%. (F) 1) 4N-HCl, THF, 55°C, 64%; 2) $NaIO_4$, THF, MeOH-H_2O, r.t., 100%; 3) LAH, THF, 0°C, 74%; 4) $(MeO)_2CMe_2$, CSA, acetone, 96%. (G) 1) Raney Ni (W-2), EtOH, r.t., 87%; 2) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, 100%. (H) 1) NaH, DMSO-THF, 0°C, 94%; 2) Pd-C, H_2, AcOEt, r.t., 98%. (I) EtMgBr, THF, -93°C, 100%. (J) Bn-Br, NaH, DMF, r.t., 100%; 2) 4N-HCl, THF, 50°C, 85%; 3) Ts-Cl, pyridine, r.t., 59%. (K) NaH, DMSO-THF, r.t., 68%. (L) 1) CrO_3, H_2SO_4, acetone, 0°C; 2) CH_2N_2; 3) $(MeO)_2P(O)Me$, n-BuLi, THF, -93°C, 64% (overall).

Wittig-Horner coupling of **11** and **12** followed by reduction gave quantitatively **22**, which was treated with MeLi in ether at -93°C. The chelation controlled reaction again occurred to give **23** with an excelllent stereoselectivity (33 : 1).[23] After removal of the acetonide protection, the primary alcohol was protected with a TBDMS group to give **24**. Swern oxidation of the secondary alcohol led to form a hemiacetal accompanied by removal of the TBDMS group. After conversion of the hemiacetal into a methyl acetal, the remaining primary alcohol was oxidized to an aldehyde, which was readily converted to **3**[24] via a dichloroolefin.[25]

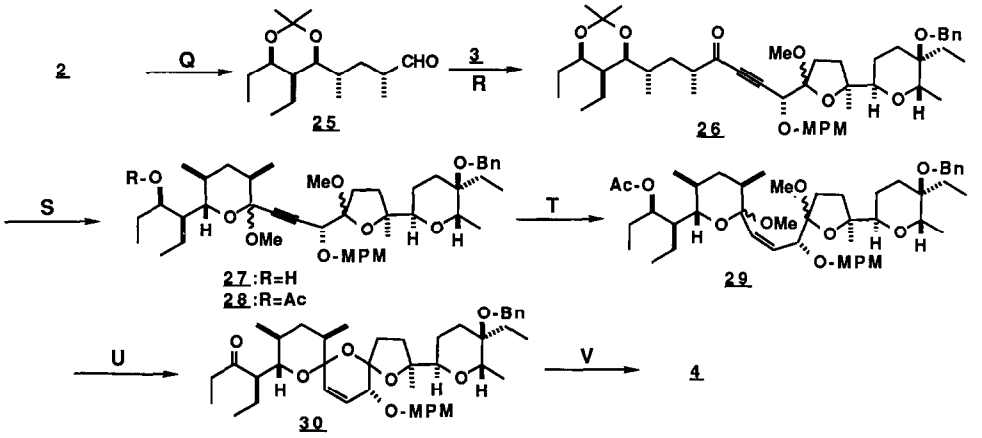
Compound **2** was first converted to the aldehyde (**25**) and then coupled with **3** in the presence of n-BuLi at -78 °C to give an acetylene-alcohol, which was readily oxidized to the ynone (**26**). Treatment of **26** with a catalytic amount of CSA in MeOH gave a mixture of four diastereoisomeric bisketals (**27**), which were separable into each isomer after conversion to



(M) 1) NaH, DMSO-THF, 0°C, 100%; 2) Pd-C, H_2, AcOEt, 98%. (N) MeLi, Et_2O, -93°C, 87%. (O) 1) 1N-HCl, THF, r.t., 96%; 2) TBDMS-Cl, imidazole, CH_2Cl_2, r.t., 95%. (P) 1) DMSO, $(COCl)_2$, Et_3N, 96%; 2) CSA, MeOH, r.t., 99%; 3) DMSO, $(COCl)_2$, Et_3N, 97%; 4) Ph_3P, $PhHgCBrCl_2$, PhH, 89%; 5) n-BuLi, THF, -78°C, 94%.

the monoacetates (**28**).[26] Since the four isomers of **28** showed quite different reactivities in reduction with Lindler catalyst, better results were obtained when each isomer was reduced separately,[27] and the combined yield of a mixture of Z-olefins (**29**) was 67%.

When the mixture (**29**) was treated with 80% AcOH, bisspiro-ketalization proceeded quite smoothly. After removal of the acetyl protection, the resulting alcohol was oxidized with PCC to give the ketone (**30**) as a mixture of three diastereoisomers (1.8 : 1.4 : 1.0). Treatment of **30** with DDQ resulted in the removal of the benzyl protection for the tertiary alcohol[2,3] as well as the MPM group.[18,19] After acetylation of the secondary alcohol of the resulting diol, the acid-catalyzed isomerization with CSA in CH_2Cl_2 at room temperature gave the title compound (**4**) with 17-epi configuration[28] as the sole product, whose spectral data were completely identical to those of the authentic sample derived from natural salinomycin (**1**). Since **4** was converted to **1** after condensation with the left (C1-C9) segment[29] by Kishi,[7] a formal synthesis of 1 has now been achieved. A highly improved total synthesis of 1 has also been effected and will be reported soon.



(Q) 1) 1N-HCl, THF, 50°C; 2) LAH, THF; 3) CSA, $Me_2C(OMe)_2$; 4) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 44% (overall). (R) 1) n-BuLi, THF, -78°C, 82-92%; 2) MnO_2, CH_2Cl_2, 100%. (S) CSA, MeOH, 85%. (T) Lindler catalyst, H_2, MeOH(AcOH), 67%. (U) 1) 80% AcOH, 69%; 2) KOH, aq MeOH, 60~70°C, 100%; 3) PCC, molecular sieves, CH_2Cl_2, 81%. (V) 1) DDQ, CH_2Cl_2-H_2O(10 : 1); 2) Ac_2O, Et_3N, DMAP, CH_2Cl_2; 3) CSA, CH_2Cl_2, 42% (overall).

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5) Salinomycin (1), isolated from Streptomyces albus,[6] is a very important anticoccidial agent in the poultry industry, and a marvelous total synthesis was achieved by Kishi.[7]
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8) Unless otherwise noted, the numbering is based on that of salinomycin (1).
9) The C10-C30 segment (**4**) is a retro-aldol and isomerization product of the 20-O-acetyl-1-ester derivative of 1 as well as a key intermediate in Kishi's synthesis.[7]
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12) In the hydrogenation with Raney Ni debenzylation occurred first to give **8**, followed by reduction of the double bond to give **9**. Hydrogenation of isolated **8** with Rh-Al_2O_3 gave **9** with 57 : 1 stereoselection.
13) Configuration of the hydroxy group of 2 was determined after conversion to **10**, in which 8% NOE was observed between H_a and H_b.
14) A synthetic equivalent of **3**[15a] was also synthesized from a C21-C30 segment,[16] an alkaline degradation product of **1**,[17] and will be reported soon.
15) Since in Kishi's total synthesis of 1 introduction of the C20 chiral center was in uncontrol of stereochemistry, the desired product with the correct C20 configuration was minor and the undesired product was converted to the desired one after repeated recycles, though its efficiency was not so good.[7]
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20) Cf. W. C. Still and J. H. McDonald III, Tetrahedron Lett., **21**, 1031 (1980); W. C. Still and J. A. Schneider, Ibid., **21**, 1035 (1980).
21) This reaction can be explained in terms of initial formation of an epoxide followed by a base-catalyzed recyclization to a tetrahydropyran ring.[22] Treatment of **20** with K_2CO_3 in MeOH gave the epoxide, which was converted to **21** by treatment with CSA in CH_2Cl_2 in the usual way, but a side reaction forming a tetrahydrofuran derivative was unavoidable.
22) Cf. L. A. Reed, III, Y. Ito, S. Masamune, and K. B. Sharpless, J. Am. Chem. Soc., **104**, 6468 (1982).
23) Under all other conditions, only poor results were so far obtained, e. g., in THF with MeLi **23** was minor (stereoselectivity 1 : 2.3) and no reaction occurred with MeMgBr or Me_2CuLi at -93°C.
24) This compound was almost 1 : 1 mixture with respect to the C21 acetal position.
25) D. Seyferth, H. D. Simmons, and G. Singh, J. Organomet. Chem., **3**, 337 (1965); D. Seyferth, J. K. Heeren, G. Singh, S. O. Grim, and W. B. Hughes, Ibid., 5, 267 (1966).
26) **28a**, **28b**, **28c**, and **28d** were isolated in the ratio of 3.8 : 3.2 : 1.4 : 1.0. Configurations at the bisketal positions were variable in the presence of a trace of acid.
27) Reduction conditions: For **28a**; Lindler catalyst (a large amount), MeOH, room temperature, 8.5 h (78%). For **28b**; Lindler catalyst (a large amount), MeOH-AcOH, 50°C, 7.5 h (72%). For **28d**; Lindler catalyst (a catalytic amount), MeOH, 30 min (100%). No reduction of **28c** occurred.
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29) The left (C1-C10) segment has been synthesized from D-glucose in this laboratory and will be reported soon.

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