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COMPLETELY STEREOCONTROLLED SYNTHESIS OF THE RIGHT FRAGMENT OF SALINOMYCIN, A POLYETHER ANTIBIOTIC, BY MEANS OF THE CHELATION-CONTROLLED GRIGNARD REACTION

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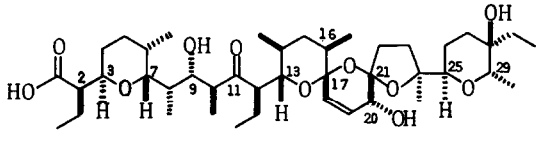
Summary In the course of our synthetic study of salinomycin (1), an ionophorous polyether antibiotic, the γ-lactone (2) corresponding to the C-21∼C-30 fragment (the right fragment) of 1 was synthesized from D-mannitol and ethyl L-lactate as chiral starting materials. The complete stereocontrol for the construction of new chiral centers has been achieved by means of the chelation-controlled Grignard reaction and the tetrahydropyran synthesis via the acid-catalyzed epoxide ring opening.

Salinomycin (1), isolated from Streptomyces albus,[1] is a typical ionophorous polyether antibiotic in use as an anticoccidial agent. The structure of 1 was determined by the X-ray analysis[2] and an elegant synthesis was achieved by Kishi.[3] As a target in our synthetic study of some macrolide and polyether antibiotics from sugars, mainly from D-glucose, by a common methodology, recently we also planned to synthesize 1 and wish to report here an almost completely stereocontrolled synthesis of the γ-lactone (2) corresponding to the C-21∼C-30 fragment of 1 (the right fragment), which was isolated from degradation products of 1 by alkaline treatment.[4,5]

In our synthetic plan of 2, emphasis has been placed to the following three points. 1) For the construction of two 1,2-diol systems at C-5∼C-6 and C-9∼C-10, the chelation-controlled Grignard reaction of acyclic α-alkoxyketones established by Still[7] was applied. 2) The tetrahydropyran ring was synthesized via the acid-catalyzed opening of an epoxide ring.[8] 3) The MPM (4-methoxybenzyl) protecting group for hydroxy function distinguishable from benzyl groups as well as other acid-sensitive protecting groups was applied.[9]



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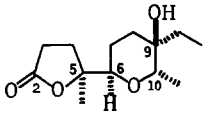

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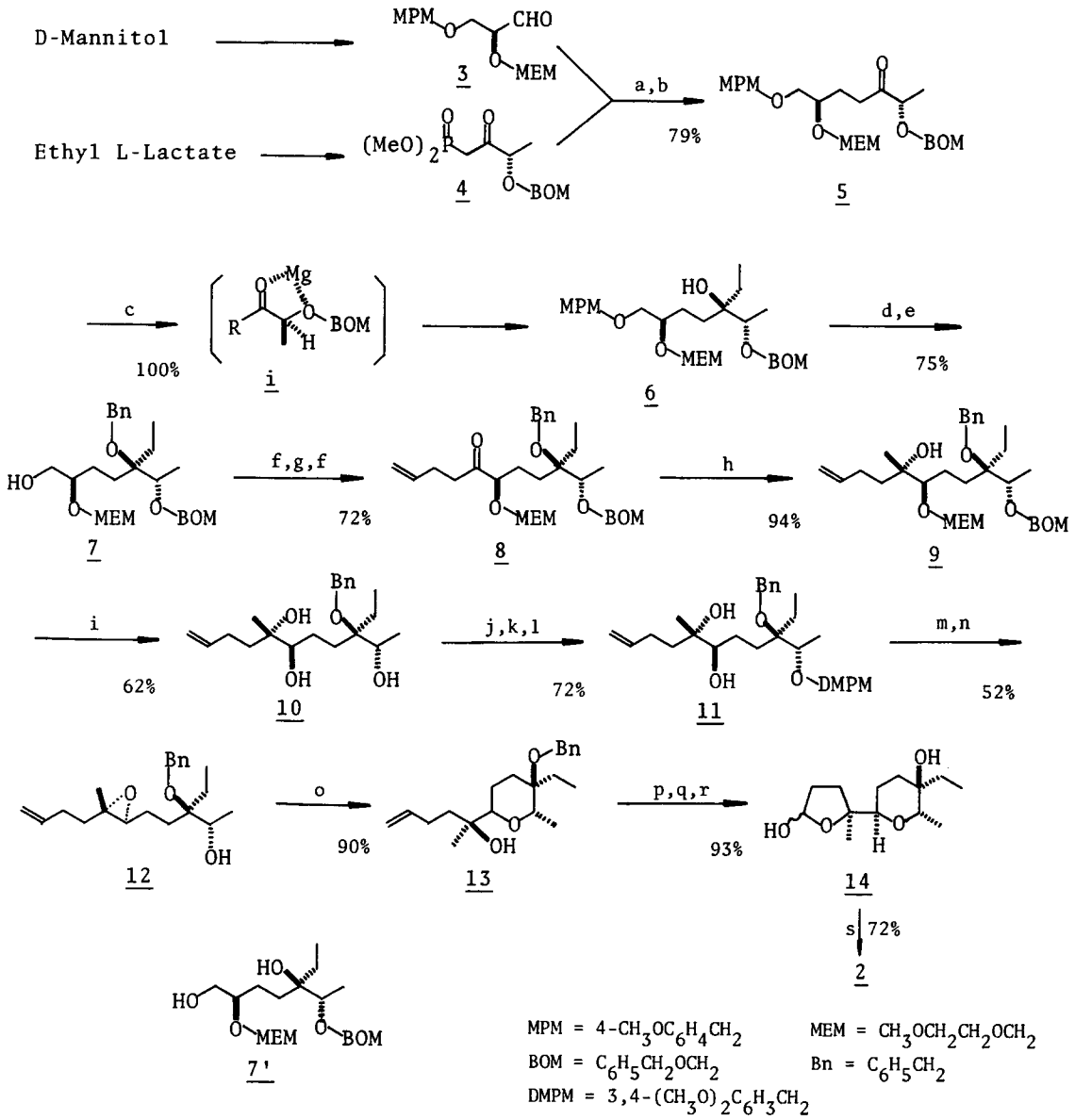
D-Mannitol and ethyl L-lactate were first chosen as the most convenient chiral starting materials. The Wittig-Horner reaction[10] between the aldehyde (3)[11] and the β-ketophosphonate (4)[12] prepared from D-mannitol and ethyl L-lactate, respectively, gave readily an enone (85%), which was reduced to the α-alkoxyketone (5) in 93% yield.

When a tetrahydrofuran solution of 5 was treated with a large excess of ethylmagnesium bromide (7.5 eq) at -78°C, a highly controlled reaction via a five-membered cyclic transition state (i) proceeded smoothly within 1.5 hr to give the alcohol (6) with erythro configuration in quantitative yield (stereoselection >100 : 1). After protection of the hydroxy group of 6 by benzylation (99%), the resulting ether was treated with DDQ (1.3 eq) to remove the MPM protecting group in the usual way [dichloromethane-water (20 : 1), room temperature, 2 hr].[9] Unfortunately debenzylation as well as deprotection of the MPM group occurred concomitantly to give a mixture of 7 (40%) and 7' (50%) because the tertiary benzyl ether was unusually sensitive to DDQ. Under low temperature (0 °C), the result was slightly improved (7, 54%; 7', 25%). In benzene at room temperature, a better result (7, 76%; 7', 24%) was obtained. The Swern oxidation[14] of 7 gave an aldehyde (90%), which was treated with excess 1-butenylmagnesium bromide in tetrahydrofuran. The resulting sencondary alcohol (96%) was again subjected to the Swern oxidation to give the second α-alkoxyketone (8, 83%).

The chelation-controlled Grignard reaction[7] of 8 with methylmagnesium bromide in tetrahydrofuran again proceeded quite smoothly to give the erythro alcohol (9) in 94% yield (stereoselection >100 : 1). In order to remove both the methoxyethoxymethyl (MEM) and benzyloxymethyl (BOM) protecting groups, 9 was treated with 4N-hydrochloric acid in tetrahydrofruan to give the triol (10, 62%), $[\alpha]_D^{21}$ +15° ($CHCl_3$, c = 2.44). The vicinal diol of 10 was protected as a p-methoxyphenylethylidene ketal (86%), the remaining secondary alcohol was protected with a DMPM (3,4-dimethoxybenzyl) group[15] (97%), and then the ketal was hydrolyzed with 1N-hydrochloric acid to recover the vicinal diol group giving 11, $[\alpha]_D^{22}$ +26° ($CHCl_3$, c = 1.96), in 86% yield. When 11 was treated with a slightly excess of mesyl chloride in the presence of triethylamine in toluene at 0°C, the secondary alcohol was only mesylated and then treatment with excess potassium carbonate at room temperature gave an epoxide, though only in 56% yield. Removal of the DMPM protection with DDQ[15] at 0°C proceeded quite smoothly to give the epoxyalcohol (12), $[\alpha]_D^{22}$ +6° ($CHCl_3$, c = 2.08), as a key intermediate to construct the substituted pyran ring, in 92% yield.

The crucial cyclization of 12 with an acid-catalyst of 10-camphorsulfonic acid (CSA) at 0 °C proceeded within 15 min with complete regio- and stereoselectivities giving the tetrahydropyran (13), $[\alpha]_D^{22}$ -5.0° ($CHCl_3$, c = 3.04), in 90% yield. Oxidation of 13 with a catalytic amount of osmium tetroxide in the presence of N-methylmorpholine N-oxide (NMO)[16] at room temperature for 30 min gave a triol in qunatitative yield, and the catalytic hydrogenation of the benzyl protection with Pd-black proceeded rather slowly but surely giving a tetraol in quantitative yield. Periodate oxidation of the vicinal diol group caused a spontaneous cyclization to the lactol (14, 93%). Finally, the title compound (2), $[\alpha]_D^{22}$ -31° ($CHCl_3$, c = 1.40), was obtained from 14 by the pydridinium chlorochromate (PCC) oxidation in the presence of powdered molecular sieves (3A) in 72% yield. This synthetic γ-lactone (2) was completely identical in its spectral data (IR, NMR, Mass) and specific optical rotation with the degradation product of natural salinomycin (1).



a) 4/NaH, THF, 0°C; b) H_2, Pd-C, EtOAc, rt; c) EtMgBr, THF, -78°C, 1.5h; d) NaH, BnBr, DMF-THF (1:3), 60°C; e) DDQ, C_6H_6-H_2O(10:1), rt, 2.0h; f) DMSO, $(COCl)_2$, CH_2Cl_2, -60°C; g) CH_2=$CHCH_2$-CH_2MgBr, THF, 0°C; h) MeMgBr, THF, -78°C; i) 4N-HCl-THF(1:3), 50°C; j) p-$MeOC_6H_4C(Me)(OMe)_2$, CSA, CH_2Cl_2, rt; k) NaH, DMPMCl, DMSO-THF(1:3), rt; l) 1N-HCl-THF(1:3), 50°C; m)1) MsCl, Et_3N, toluene, 0°C; 2) K_2CO_3, MeOH, rt; n) DDQ, CH_2Cl_2-H_2O(20:1), 0°C; o) CSA, CH_2Cl_2, 0°C; p) OsO_4, NMO, MeCOMe-H_2O(2:1), rt; q) H_2, Pd-black, EtOH, rt; r) $NaIO_4$, THF-H_2O(1:4), rt; s) PCC, molecular sieves(3A), CH_2Cl_2, rt.

The synthesis of 2 presented in this report required many steps, and 2 may not be the best intermediate to the right part (C-18∼C-30) in our synthetic plan of 1. Nevertheless, the synthesis of 2 has the following merits. 1) Every reaction is simple and requires no special conditions. 2) The stereoselectivities in the construction of new chiral centers at C-5, C-6, and C-9 are very high (>100 : 1). 3) Because 2 is available from the degradation products of 1, it is possible to confirm the structure of the synthetic 2 as an intermediate in a laborious synthesis of 1. Finally, a more convenient synthesis of the right part (C-18∼C-30) of 1 and connection with other parts (C-1∼C-17) already synthesized are in progress.

REFERENCES AND NOTES

1) Y. Miyazaki, M. Shibuya, H. Sugawara, O. Kawaguchi, C. Hirose, J. Nagatsu, and S. Esumi, J. Antibiot., 27, 814 (1974).

2) H. Kinashi, N. Otake, and H. Yonehara, Tetrahedron Lett., 4955 (1973).

3) Y. Kishi, S. Hatakeyama, and M. D. Lewis, Front. Chem. Plenary Keynote Lect. IUPAC Congr. 28th 1981, K. J. Laidler, Ed. (Pergamon, Oxford, 1982) pp 287-304.

4) H. Seto, Y. Miyazaki, K. Fujita, and N. Otake, Tetrahedron Lett., 2417 (1977).

5) This compound (2) was synthesized in the course of Kishi's total synthesis of 1[3] in a manner similar to the method for his lasalocid A synthesis.[6]

6) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, J. Am. Chem. Soc., 100, 2933 (1978).

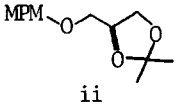
7) W. C. Still and J. H. McDonald, III, Tetrahedron Lett., 21, 1031 (1980).

8) K. C. Nicolaou, D. P. Papahatjis, D. A. Charemon, and R. E. Dolle, III, J. Am. Chem. Soc., 103, 6967 (1981). Cf. T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi, Tetrahedron Lett., 2741 (1978); T. Nakata and Y. Kishi, Ibid., 2745 (1978).

9) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., 23, 885 (1982); Y. Oikawa, T. Tanaka, K. Horita, and O. Yonemitsu, Ibid., 25, 5397 (1984).

10) J. Boutagy and R. Thomas, Chem. Rev., 74, 87 (1974).

11) The aldehyde (2) is a derivative of L-glyceraldehyde and readily prepared via ii by exchange of protecting groups.



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12) The β-ketophosphonate (4) was prepared from ethyl O-BOM-L-lactate and lithium dimethyl methylphosphonate.[13]

13) E. J. Corey and G. T. Kwiatkowski, J. Am. Chem. Soc., 88, 5654 (1966).

14) A. J. Mancuso, S. L. Huang, and D. Swern, J. Org. Chem., 43, 2480 (1978); A. J. Mancuso and D. Swern, Synthesis, 165 (1981).

15) Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., 25, 5393 (1984).

16) V. VanRheenen, R. C. Kelly, and D. Y. Cha, Tetrahedron Lett., 1973 (1976).

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