Tetrahedron Letters,Vol.24,No.34,pp 3635-3638,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

STEREOCONTROLLED SYNTHESIS OF A SEGMENT HAVING SIX CONSECUTIVE CHIRAL CENTERS FOR THE SYNTHESIS OF ERYTHROMYCIN A FROM D-GLUCOSE[1)]

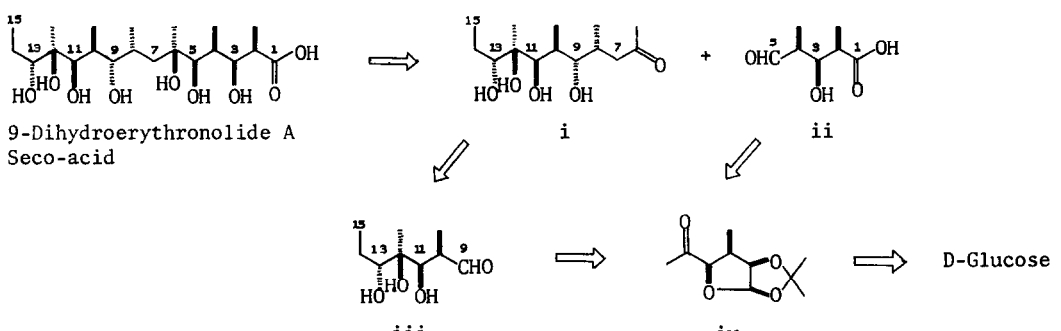
Yuji Oikawa,* Takao Nishi, and Osamu Yonemitsu
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Abstract In order to synthesize erythromycin A from D-glucose as a chiral starting material, the left-hand segment of 9-dihydroerythronolide A having six consecutive chiral centers was synthesized by means of some stereoselective reactions in acyclic systems and MPM protection.

In recent years, much attention has been given to the stereocontrolled synthesis of macrolide and ionophore antibiotics in connection with the establishment of new synthetic methodologies. Stereochemical control in acyclic systems[2)] is essential for the total synthesis of such complex molecules other than that in cyclic systems leading to many elegant syntheses of polycyclic compounds such as steroids, alkaloids, terpenes, etc.

It is also very important how to choose the most suitable protecting groups especially for many hydroxy groups. For example, in order to synthesize erythromycin A, we have to protect hydroxy groups so as to be differentiated from each other. Particularly, the protecting group for the hydroxy group at C-13 is important because it must be removed selectively prior to the macro-lactonization.[3)] Recently, we reported a new protecting group, MPM (p-methoxybenzyl), for hydroxy function, which can be selectively removed by DDQ oxidation under neutral conditions, and showed its versatility especially in sugar chemistry.[4)] We report here a synthesis of the left-hand segment i having six consecutive chiral centers of 9-dihydroerythronolide A from D-glucose[5)] by means of some stereoselective reactions in acyclic systems and the MPM protection. Needless to say, D-glucose is one of the most easily available chiral starting materials.

The total synthesis of the aglycone erythronolide A and erythromycin A itself has been achieved by Corey[6)] and Woodward[3)] groups respectively. Stork[7)] reported recently a simpler synthesis of the chiral sequence of erythronolide A. Our retrosynthesis is shown in Scheme 1, and iv was expected to be the common key chiral intermediate for both the segments i and ii.[1)]

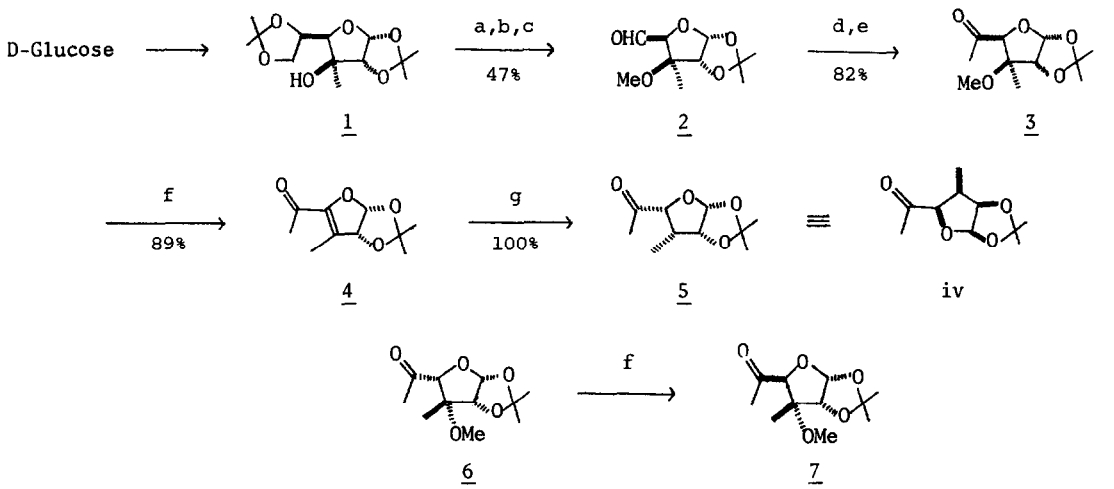


Scheme 1.

Synthesis of C-10 ∿ C-12 Fragment

The alcohol (1)[8] readily available from D-glucose was converted to the ketone (3) in the sequence of conventional reactions in 39% overall yield as follows. Methylation of 1 with MeI (89%), selective hydrolysis with 2% H_2SO_4 (87%), and oxidative cleavage with $Pb(OAc)_4$ gave the aldehyde (2)(61%), mp 72-72.5°C. The Grignard reaction of 2 with MeMgI gave a 4:1 mixture of alcohols (90%), which was oxidized with PCC to give the ketone (3)(91%), mp 53-53.5°C, $[\alpha]_D^{18}$ -107°.† Anti-elimination of MeOH from 3 occurred quite smoothly to give the enone (4) by treatment with K_2CO_3, though the isomeric ketone (6) derived also from D-glucose gave only more stable another isomeric ketone (7) under similar conditions.

Catalytic reduction of 4 at ordinary pressure in EtOAc gave an oil of the single ketone (5), $[\alpha]_D^{17}$+4.2°. Addition of hydrogen occurred exclusively from the β-side of 4 because of the steric hinderance of the α-side.[9]

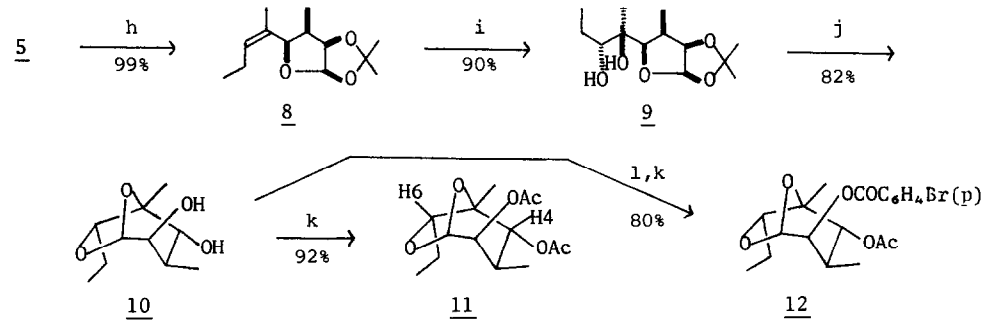


a: MeI/NaH/DMSO, b: 2%H_2SO_4/MeOH, c: $Pb(OAc)_4$/PhH, d: MeMgI/Et_2O, e: PCC/mol.sieve/CH_2Cl_2, f: K_2CO_3/MeOH, g: Pd-C/H_2/EtOAc

Scheme 2.

Synthesis of C-10 ∿ C-15 Fragment

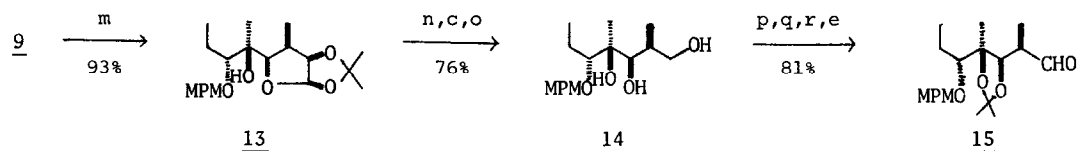
The Wittig reaction of 5 occurred stereoselectively to afford the sole olefin (8),[10] which was osmylated to give the diol (9) again with excellent stereoselection (23:1). Purification of 9 by silica gel chromatography gave colorless needles, mp 131.5-132°C, $[\alpha]_D^{18}$ -18°. The stereochemical structure of 9 was established as follows. Cleavage of the acetonide group with TsOH-H_2O in CH_2Cl_2 gave the dihydroxyacetal (10), mp 180-181.5°C, $[\alpha]_D^{11}$ +49°, which was converted to the diacetate (11). In the pmr spectrum, the long-range coupling (1.5 Hz) due to the W-configuration between H-4 (δ 5.02) and H-6 (δ 3.53) was clearly observed. Among four possible isomers only 11 has such a W-arrangement of the 4σ-bonds between H-4 and H-6. Therefore, the stereostructure of 8 as well as 9 was necessarily determined. These structures were finally confirmed by the X-ray analysis of the p-bromobenzoate (12), mp 137-137.5°C, derived from 10.



h: Ph_3P=CHEt/THF, i: OsO_4/NMMO-H_2O/Me_2CO-H_2O, j: TsOH-H_2O/CH_2Cl_2,
k: Ac_2O/DMAP-Et_3N/CH_2Cl_2, l: 4-BrC_6H_4COCl/Py/CH_2Cl_2

Scheme 3.

Compound 9 was converted to the aldehyde (15) in 57% overall yield as shown in Scheme 4. MPM protection of the secondary alcohol of 9, followed by seven conventional steps, hydrolysis of the acetonide, $Pb(OAc)_4$ oxidation (87%), $LiAlH_4$ reduction (87%), benzoylation (95%), acetonide protection of the diol group (94%), removal of the benzoyl group (100%), and final oxidation with PCC gave 15 (91%) as a colorless oil, $[\alpha]_D^{11}$ -7.0°.[11]



MPM: 4-$MeOC_6H_4CH_2$

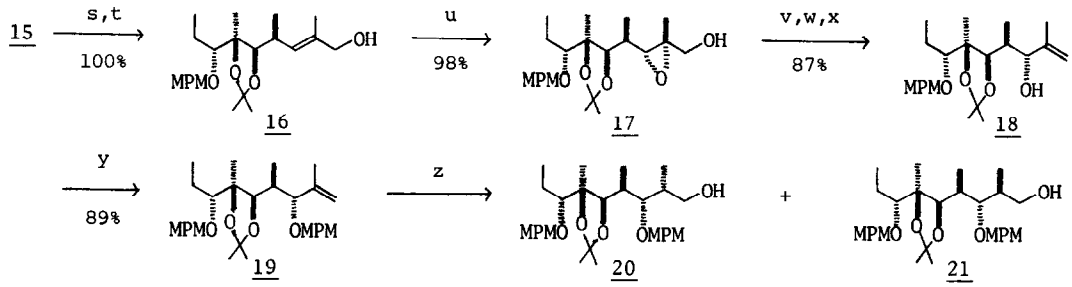
m: MPMCl/NaH/DMF, n: 4N-HCl/THF, o: $LiAlH_4$/Et_2O, p: PhCOCl/Py/CH_2Cl_2,
q: $Me_2C(OMe)_2$/TsOH/Me_2CO, r: 1N-KOH/MeOH

Scheme 4.

Synthesis of C-7 ∿ C-15 Fragment

The Wittig reaction of 15, followed by $LiAlH_4$ reduction gave selectively the sole allylic alcohol (16). Epoxidation of 16 with m-chloroperbenzoic acid at -15 ∿ -10°C in CH_2Cl_2 occurred exclusively from the α-side[12] to afford the threo epoxide alcohol (17; oil).[13] Treatment of 17 with MsCl gave the O-mesylate (92%), which was converted to the iodide (98%), and then treated with Zn-Cu couple in refluxing EtOH to give the allyl alcohol (18)(oil, 96%).[14]

After protection of the hydroxy group of 18 with MPMCl, hydroboration of the resultant 19 was examined. No reaction occurred under usual conditions (BH_3 in THF), but treatment with BH_3 in CH_2Cl_2 prepared in situ from Bu_4NBH_4 and MeI at room temperature[15] gave a mixture of the expected alcohol (20)(10.8%) and the isomer (21)(16.3%), though both the yield and stereoselectivity are still very unsatisfactory. Compound 20, which is basically identical to the segment i because 20 has all of the six consecutive chiral centers, was easily purified by

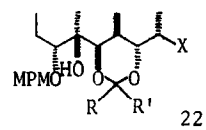


s: $Ph_3P{=}C(Me)CO_2Et$/EDC, t: $LiAlH_4$/THF, u: mcpba/CH_2Cl_2, v: MsCl/Et_3N/PhH, w: NaI/Me_2CO, x: Zn-Cu/EtOH, y: MPMCl/NaH/DMSO, z: Bu_4NBH_4/MeI/CH_2Cl_2

Scheme 5.

silica gel chromatography as a colorless oil, and its ir, nmr, and mass spectra were completely identical to those of the degradation product of natural erythromycin A, which will be reported soon.

We are now synthesizing variously protected segment i as exemplified by 22, because it is difficult to predict how to protect many hydroxy groups to get a seco-acid which have a favorable conformation for the lactonization[2] to erythromycin A.



22

X=OHC;$EtO_2CCH_2CH_2$
R,R'=Me;Ph;2,4,6-$Me_3C_6H_2$

Acknowledgement We are grateful to Dr. M. Kido, Otsuka Pharmaceutical Co. Ltd., for his X-ray analysis.

References and Notes

1) Chiral Synthesis of Polyketide-derived Natural Products. 2. Part 1; Y. Oikawa, T. Nishi, H. Itaya, and O. Yonemitsu, Tetrahedron Lett., 24, 1987 (1983).
2) For reviews: Y. Kishi, Aldrichimica Acta, 13 (2), 23 (1980); D. A. Evans, ibid., 15 (2), 23 (1982); S. Masamune and W. Choy, ibid., 15 (3), 47 (1982); P. A. Bartlett, Tetrahedron, 36, 3 (1980).
3) R. B. Woodward, et al., J. Am. Chem. Soc., 1981, 103, 3210, 3213, 3215.
4) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., 23, 885, 889 (1982).
5) An approach to erythronolide A from D-glucose: S. Hanessian, G. Rancourt, Y. Guindon, Can. J. Chem., 56, 1843 (1978).
6) E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, J. R. Falck, J. Am. Chem. Soc., 1979, 101, 7131.
7) G. Stork, I. Paterson, and A. S. Tracey, J. Am. Chem. Soc., 1982, 104, 4686.
8) M. Funabashi, H. Sato, and J. Yoshimura, Bull. Chem. Soc. Japan, 49, 788 (1976).
9) Cf. K. N. Slessor and A. S. Tracey, Can. J. Chem., 47, 3989 (1969).
10) Yield based on the consumed starting material (5). The gross yield was 51% with 48.3% recovery of 5.
11) $\delta(CDCl_3)$: 1.03(3H, t, J=7.0 Hz), 1.16 (3H, s), 1.20 (3H, d, J=7.0), 1.34, 1.41 (3H each, s), 1.50-1.82 (2H, m), 2.70 (1H, 2dq, J=2.5, 7.0, 7.5), 3.30 (1H, dd, J=5.0, 7.0), 3.80 (3H, s), 4.26 (1H, d, J=6.0), 4.46, 4.56 (2H, q, J=11), 6.86 (1H, d, J=8.5), 7.23 (1H, d, J=8.5), 9.45 (1H, d, J=2.5).
12) Cf. M. R. Johnson and Y. Kishi, Tetrahedron Lett., 4347 (1979).
13) $\delta(CDCl_3)$: 1.00 (3H, t, J=8.0 Hz), 1.06 (3H, d, J=7.0), 1.23 (3H, s), 1.26 (3H, s), 1.36, 1.44 (3H each, s), 1.6-1.9 (3H, m), 2.92 (1H, d, J=10), 3.39 (1H, dd, J=5.0, 7.0), 3.58, 3.63 (2H, ABq, J=10), 3.79 (3H, s), 4.03 (1H, d, J=5.5), 4.54, 4.66 (2H, ABq, J=11), 6.84 (2H, d, J=9.0), 7.30 (2H, d, J=9.0).
14) Cf. E. W. Logusch, Tetrahedron Lett., 3365 (1979); A. Yasuda, H. Yamamoto, and H. Nozaki, ibid., 2621 (1976).
15) A. Brandström, U. Junggren, and B. Lamm, Tetrahedron Lett., 3173 (1972).

† All $[\alpha]_D$ were measured in chloroform.

(Received in Japan 7 May 1983)