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SYNTHETIC STUDIES OF ERYTHROMYCINS. II.[1] ENANTIOSPECIFIC SYNTHESIS OF A C-10-C-13 SEGMENT OF ERYTHRONOLIDE A FROM D-RIBOSE

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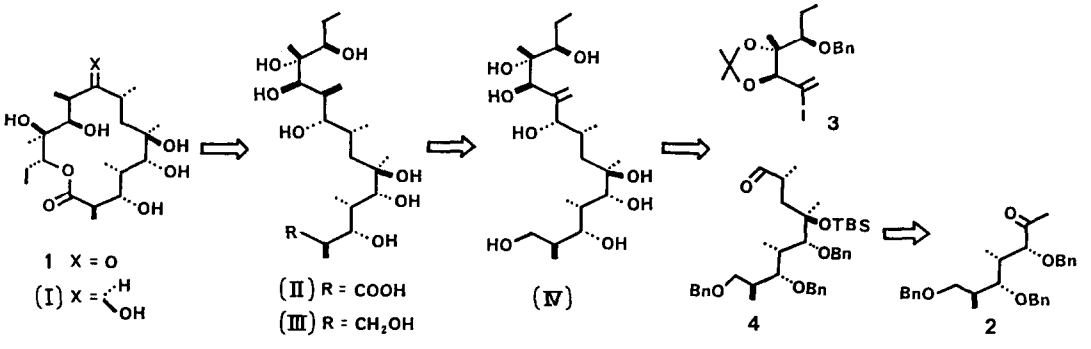
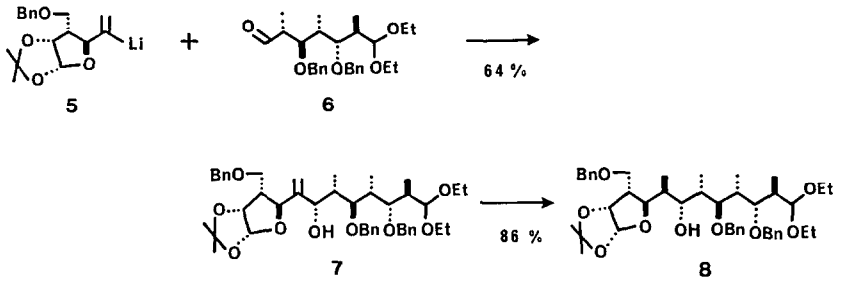
Summary: (3*R*,4*R*,5*R*)-5-O-Benzyl-2-iodo-3,4-O-isopropylidene-4-methyl-1-heptene-3,4,5-triol 3, a C-10-C-13 synthetic segment of erythronolide A (1) was enantiospecifically synthesized in sixteen steps and 8.3% overall yield from D-ribose.

The successful total synthesis of erythronolide A (1), aglycone of the medicinally important 14-membered macrolide antibiotic erythromycin A, has recently been achieved by two Harvard groups,[2,3] one of which succeeded during the final stages of their conquest of erythromycin A itself.[3] Other synthetic efforts have been announced.[4] In the studies directed toward the enantiospecific synthesis of 1, the C-1-C-6 segment 2 of 1 was synthesized from D-glucose,[1] being considered to be practically viable and also well suited for a



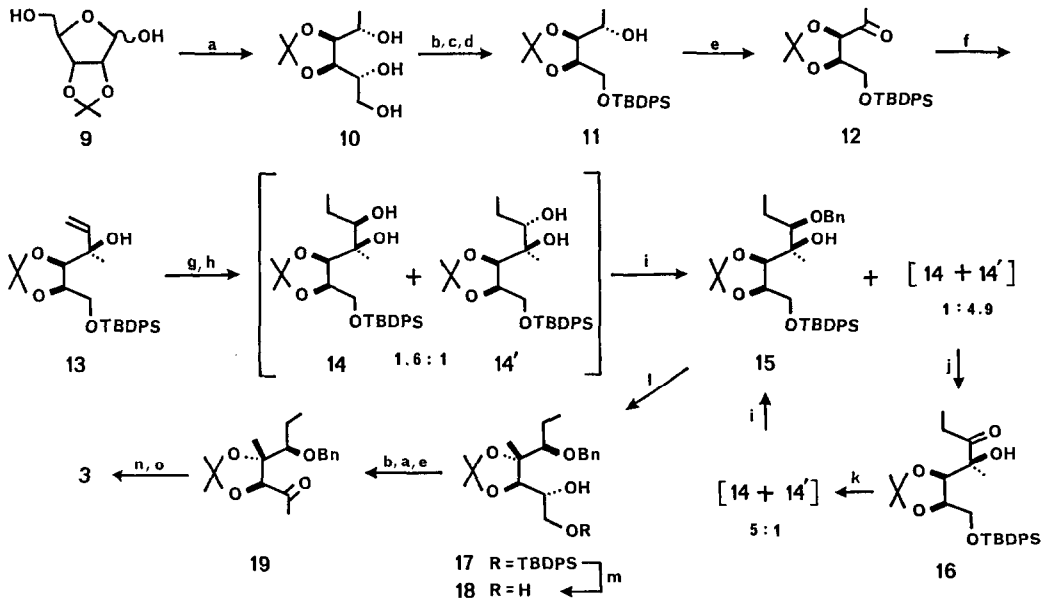
Scheme 1

stereoselective coupling reaction with a second chiral synthetic segment (Scheme 1). Recently, it has been found[5] that addition reaction of the chiral vinyllithium compound 5 to the chiral aldehyde 6 afforded predominantly the "Cram" product 7, which was subsequently hydrogenated with Wilkinson's catalyst to give solely the *anti*-epimer 8, a synthetic precursor of the aliphatic segment of rifamycin W (Scheme 2). This result suggested a retrosynthesis of erythronolide A (1) which led to the new synthetic segments, 3 and 4, corresponding to the C-10-C-13 and C-1-C-9 portions of 1, through (9*S*)-9-dihydroerythronolide A[6] (I) and the acyclic (II), (III), and (IV) (Scheme 1). The 3,5:9,11-bis(cyclic acetal) derivative of the (9*S*)-seco-acid (II) has been shown to be an excellent substrate[3] for the cyclization to 14-membered macrolactone such as (I). This report will describe the enantiospecific synthesis of the segment 3 from D-ribose, which served to realize our synthetic plan of 1.



Scheme 2

The acetonide 9[7] was obtained in good yield (83%) from D-ribose by the modified O-isopropylidenation (acetone, 2,2-dimethoxypropane, concd H_2SO_4, 0°C, 3h; 5°C, 20h). Treatment of 9 with an excess of methylmagnesium iodide gave 10[8] as a sole product (73%, mp 72-73°C, $[\alpha]_D$ +28°), which was transformed in three steps into 11[8,9] (81.5%, $[\alpha]_D$ +8°, $[\alpha]_{365}$ +29°). PCC oxidation of 11 afforded the methyl ketone 12[8] (95%, $[\alpha]_D$ +49°, IR($CHCl_3$) ν_{max} 1712 cm^{-1}). The ketone 12 was treated with an excess of vinylmagnesium bromide in THF to give a 77:1 mixture in favor of the (2*R*)-epimer 13[8,10] which was isolable by column chromatography (silica-gel, 10:1 hexane-ethyl acetate) in isomerically pure form (94%, $[\alpha]_D$ +33°). Ozonolysis of 13 followed by addition of ethylmagnesium bromide to the resulting aldehyde gave a *ca.* 1.6:1 mixture of the desired 14[11] and its epimer 14' in 63.5% yield. Since the chromatographic separation of 14 and 14' was quite difficult, the isomeric ratio was assumed



(a) 10 equiv MeMgI, ether, rt, 3h; (b) $NaIO_4$, aq acetone, rt, 2h; (c) $LiAlH_4$, THF, rt, 2h; (d) 1.2 equiv TBDPSCl, imidasole, DMF, rt, 1h; (e) PCC, 3A molecular sieves,

CH_2Cl_2, rt, 2h; (f) 10 equiv CH_2=ChMgBr, THF, rt, 2h; (g) O_3, CH_2Cl_2, -78°C; Me_2S, -78°C rt; (h) 8 equiv EtMgBr, ether, rt, 1.5h; (i) 2.2 equiv NaH, 1.5 equiv BnBr, THF, rt, 4h; (j) DMSO, DCC, TFA, py, PhH, rt, 5h; (k) $LiAlH_4$, ether, -78°C, 2h: (l) 0.5 mol. equiv $FeCl_3$, acetone, 29°C, 1h; (m) $(n\text{-}Bu)_4NF$, THF; (n) $NH_2NH_2 \cdot H_2O$, Et_3N, EtOH, 70°C, 1h; (o) I_2, tetramethylguanidine, PhMe, 0°C, 0.5h.

based on the isolated yields of the separable products formed by desilylation of the epimeric mixture. Direct O-benzylation of the mixture afforded fortunately only one isomeric O-benzyl derivative 15[8,11] (55%, $[\alpha]_D$ +8°) corresponding to the desired (3*R*)-epimer 14, and a 4.9:1 mixture of 14' and 14 was recovered in 28% yield. The unchanged epimeric mixture in favor of the (3*S*)-epimer 14' was converted into the ketone 16[8] (90%, $[\alpha]_D$ 0°, $[\alpha]_{365}$ -18°, IR($CHCl_3$) ν_{max} 3440, 1713 cm^{-1}) by DMSO oxidation. $LiAlH_4$ reduction of 16 gave a 5:1 epimeric mixture in excess of 14, which was again benzylated to afford 15 in 55% yield from 16; the total yield of 15 from 13 amounted to 43.8%. Brief exposure of 15 to 0.5 molar equiv of $FeCl_3$ in acetone (1h, 29°C) led to the isomeric acetonide 17[8] (95%, $[\alpha]_D$ -18°), which was desilylated to give 18[8] (92%, $[\alpha]_D$ -45°). The product 18 was then transformed in three steps into the methyl ketone 19[8] (89%, $[\alpha]_D$ 0°, $[\alpha]_{365}$ +25°, IR($CHCl_3$) ν_{max} 1720 cm^{-1}), which was converted through its hydrazone[12] into the vinyl iodide 3[8] (55%, $[\alpha]_D$ 0°, $[\alpha]_{365}$ -11°), according to the improved procedure of Barton et al.[13]

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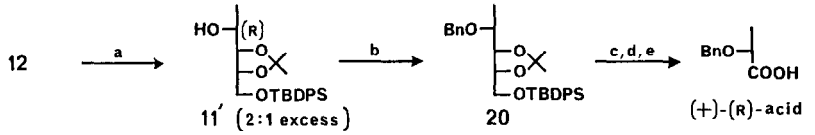
8. All compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Optical rotations(c 1.0, $CHCl_3$) were done using a 0.2 dm tube at 20°C. Significant ^{1}H-NMR(90 MHz) spectral data [δ($CDCl_3$, TMS), J(Hz)] are the following. 10: 1.32 (3H, d, J=6.0), 1.35 (3H, s), 1.39

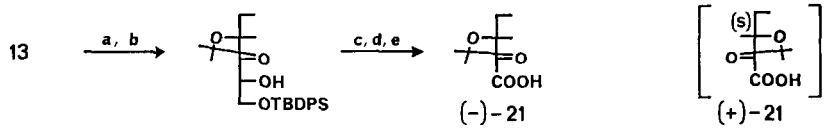
(3H, s). 11: 1.07 (9H, s), 1.28 (3H, s), 1.30 (3H, s), 1.34 (3H, d, J=7.0), 7.30-7.80 (10H, m). 12: 1.03 (9H, s), 1.37 (3H, s), 1.57 (3H, s), 2.27 (3H, s). 13: 1.06 (9H, s), 1.30 (3H, s), 1.35 (3H, s), 1.37 (3H, d, $J_{1,OH}$=1.8), 5.12 (1H, dd, J=1.8, 10.5), 5.52 (1H, dd, J=1.8, 17.7), 6.36 (1H, dd, J=10.5, 17.7). 15: 1.08 (12H, br s), 1.29 (6H, s), 1.39 (3H, s), 4.72 (2H, s), 7.20-8.00 (15H, m). 16: 1.06 (3H, t, J=7.5), 1.08 (9H, s), 1.27 (3H, s), 1.36 (6H, s), 2.69 (2H, q, J=7.5). 17: 1.06 (3H, t, J=7.4), 1.08 (9H, s), 1.25 (3H, s), 1.31 (3H, s), 1.36 (3H, s), 4.67 (2H, s), 7.25-7.85 (15H, m). 18: 1.10 (3H, t, J=7.5), 1.23 (3H, s), 1.30 (3H, s), 1.40 (3H, s), 3.34 (1H, t, J=5.5), 4.53 and 4.76 (2H, ABq, J=10.8), 7.39 (5H, s). 19: 1.00 (3H, t, J=7.0), 1.14 (3H, s), 1.35 (3H, s), 1.53 (3H, s), 2.23 (3H, s), 3.38 (1H, dd, J=4.8, 8.8), 4.51 (1H, s). 3: 1.04 (3H, t, J=7.5), 1.28 (3H, s), 1.38 (3H, s), 1.52 (3H, s), 1.55-1.90 (2H, m), 3.56 (1H, t, J=6.0), 4.52 (1H, s), 4.72 (2H, s), 6.10 (1H, s like), 6.63 (1H, s like), 7.37 (5H, s). 11': 1.08 (9H, s), 1.27 (3H, d, J=6.0), 1.35 (3H, s), 1.43 (3H, s), 7.30-7.80 (10H, m).

9. Since the attempts of 2-O-benzylation of 11 for the purpose of straightforward determination of its (2*S*)-configuration was unsuccessful, the epimer 11'[8] ($[\alpha]_D$ 0°, $[\alpha]_{365}$ +15°) was prepared in 57.3% yield by $LiAlH_4$ reduction of 12 along with 11 (28.2%). The 2-O-benzyl derivative 20 obtained from 11' could be transformed into (+)-(*R*)-O-benzyllactic acid ($[\alpha]_{546}$ +85°(c 2.3, benzene)), which was proved to be the enantiomer of the reported (-)-(*S*)-O-benzyllactic acid ($[\alpha]_{546}$ -78.6° (c 2.3, benzene); K. Steiner, U. Graf, and E. Hardegger, *Helv. Chim. Acta*, 54, 845 (1971)) by the ^{1}H-NMR spectrum and the positive sign of the optical rotation.



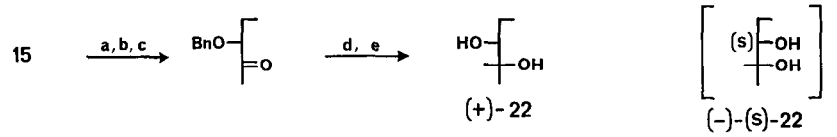
(a) $LiAlH_4$, ether, -78°C; (b) 1.5 equiv NaH, 1.5 equiv BnBr, THF, rt, 8h; (c) $(n\text{-}Bu)_4NF$, THF; (d) 75% AcOH, 80°C, 11h; (e) 1. $NaIO_4$, aq acetone, 2. CrO_3-AcOH-Py

10. The (2*R*)-configuration of 13 was confirmed by the following manner:



(a) H_2/Pd, MeOH; (b) $ZnBr_2$, CH_2Cl_2; (c) $(n\text{-}Bu)_4NF$, THF; (d) $NaIO_4$; (e) KIO
The ^{1}H-NMR spectra of (-)-21 ($[\alpha]_D$ -27°(c 0.84, $CHCl_3$)) and the authentic (+)-21 ($[\alpha]_D$ +26° (c 0.84, $CHCl_3$)); M. Kinoshita, H. Hamazaki, and M. Awamura, *Bull. Chem. Soc. Jpn.*, 51, 3595 (1978)) were superimposable.

11. The (3*R*)-configuration of 15(14) was confirmed by the following manner:



(a) $(n\text{-}Bu)_4NF$; (b) 50% AcOH, 110°C, 2h; (c) $NaIO_4$; (d) MeMgI, ether: (e) H_2/Pd, t-BuOH
The product (+)-22 ($[\alpha]_D$ +27°(c 1.1, ether)) was proved to be the enantiomer of the reported (-)-(*S*)-22 ($[\alpha]_D^{28}$ -32.6°(c 1.1, ether); D. G. Manwaring, R. W. Rikards, and R. M. Smith, *Tetrahedron Lett.*, 1970, 1029) by the positive sign of the optical rotation.

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