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SYNTHETIC STUDIES OF ERYTHROMYCINS. III.[1] TOTAL SYNTHESIS OF ERYTHRONOLIDE A THROUGH (9S)-9-DIHYDROERYTHRONOLIDE A

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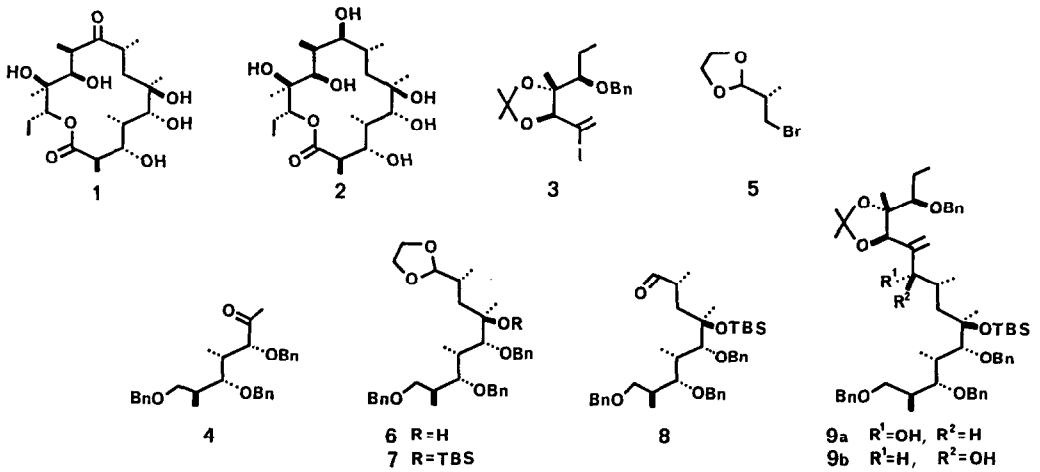
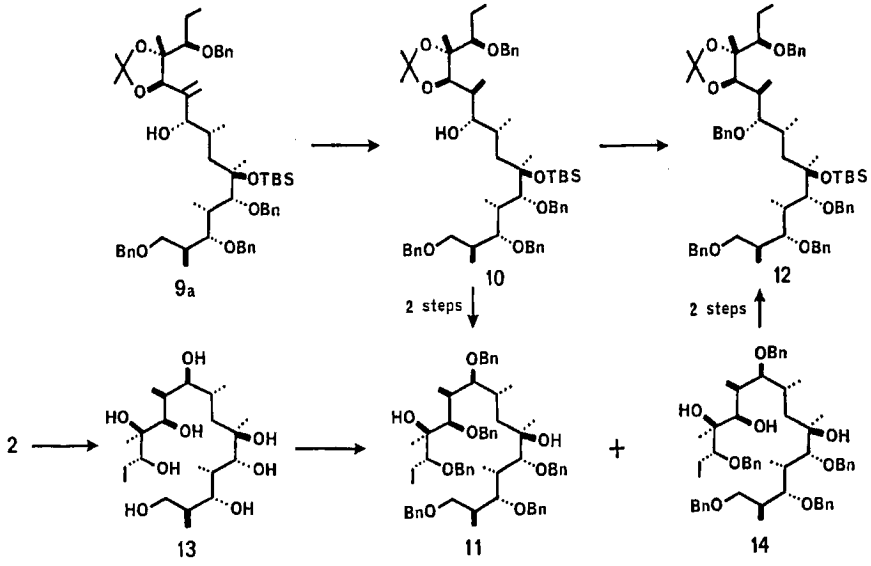
Summary: Erythronolide A (1) was enantiospecifically synthesized through (9S)-9-dihydroerythronolide A (2) from the chiral C-10-C-13, C-7-C-9, and C-1-C-6 synthetic segments, 3, 5, and 4, respectively. The overall yield of 1 from 4 was 1.84% in 21 steps.

In the preceding paper,[1] we described our synthetic strategy toward erythronolide A (1) and the synthesis of the C-10-C-13 synthetic segment 3, a requisite for the plan. In this paper, we will report a new enantiospecific total synthesis of erythronolide A (1) through (9S)-9-dihydroerythronolide A (2), which was derived from the major epimer 9a generated by the coupling of 3 with the new C-1-C-9 segment 8.[1] For the purpose of synthesizing 8 from the previously prepared C-1-C-6 segment 4,[2] an adequate chiral C-7-C-9 segment had first to be inquired. After many unsuccessful attempts, the most adaptable C-7-C-9 synthetic segment was



found to be (S)-(+)-2-(2-bromo-1-methylethyl)-1,3-dioxolane 5[3] ($[\alpha]_D$ +3°, $[\alpha]_{365}$ +11°), which was prepared from the known (R)-(-)-3-benzyloxy-2-methylpropanal[4] ($[\alpha]_D$ -28°) in three steps (1. $HOCH_2CH_2OH$, *p*-TSA, MeCN; 2. H_2/Pd, MeOH; 3. EtBr, Ph_3P, DEAD, THF) in 66% yield. The methyl ketone 4 was treated in ether with an excess of Grignard reagent prepared from 13 equiv of magnesium and 4.3 equiv of 5 to afford the alcohol 6[3,5] (79% isolated yield, $[\alpha]_D$ +3°, $[\alpha]_{365}$ +20° (c 0.64)) in a 9.9:1 epimeric excess. Thus obtained 6 was silylated (1.5 equiv

t-butyldimethylsilyl triflate, 2,6-lutidine, CH_2Cl_2, rt, 15h) to give 7[3] (89%, $[\alpha]_D$ 0°, $[\alpha]_{365}$ +8° (c 0.64)), whose ethylene acetal group was selectively cleaved ($SnCl_2$, acetone, 26°C, 19h) to provide the aldehyde 8 in 72% yield. A 1.9M etherial solution of 3[1] (3 equiv) was lithiated with 3 equiv of butyllithium (1.38M in hexane) at -100°C for 15 min under argon. To this solution was added a 0.3M etherial solution of 8 (1 equiv) and stirred at -100°C for 1h. Quench with saturated aqueous NH_4Cl followed by chromatographic isolation afforded the major coupling product 9a (*ca.* 50% yield[6] from 8) contaminated with a by-product,[7] and the pure minor one 9b[3] (10% yield from 8). The crude 9a was homogeneously hydrogenated (0.25 molar amount of $RhCl(PPh_3)_3$,[8] benzene, 50 atm H_2, 24°C, 5d) to give 10[3] (41% from 8, $[\alpha]_D$ -6.5°) in a 6.1:1 epimeric excess. The configuration of 10 was confirmed by the following fashion (Scheme 1). The product 10 was converted into 11[3] ($[\alpha]_D$ +7.2° (c 0.9)) in two steps

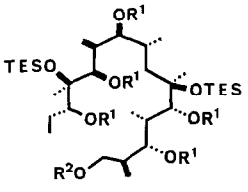


Scheme 1

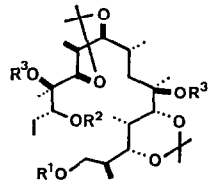
(1. 46% aq HF-MeCN (1:2), 24°C, 1h; 2. KOH (8 equiv), BnCl (4 equiv), DMF, 24°C, 5h) in 81% yield. Direct benzylation of 10 gave 12[3] (84%, $[\alpha]_D$ +10.2°). On the other hand, $LiAlH_4$ reduction (THF, 75°C, 36h) of the naturally derived 2[10] gave 13[3] (72%, $[\alpha]_D$ +17.1° (c 0.96, MeOH)), which was benzylated (BnCl, KOH, DMF, rt)[12] to afford 11[3] ($[\alpha]_D$ +7.1° (c 0.90)) and 14[3] ($[\alpha]_D$ +15.0°). O-Isopropylidenation of 14 followed by silylation provided 12[3] ($[\alpha]_D$ +10.4°). The synthetic 11 and 12 were spectroscopically and chromatographically identical with the corresponding materials produced by the aforesaid transformations starting from naturally derived 2. Consequently, the structures shown for 6, 7, 8, 9a, and 10 were determined and the *anti*-selectivity in homogeneous hydrogenation of the "Cram" product 9a was also confirmed.

Having thus prepared the intermediate 11, which contains the entire chiral sequence of (9*S*)-9-dihydroerythronolide A (2) in the proper absolute configuration, we turned our attention to the facile transformation of 11 into 2, which would be convertible to erythronolide A (1) through the 3,5-O-benzylidene-ketolactone 25. Triethylsilylation (triethylsilyl triflate (3 equiv), 2,6-lutidine (4 equiv), CH_2Cl_2, 23°C, 1.5h) of 11 afforded 15[3] (93%, $[\alpha]_D$ +19.4°), which was hydrogenolyzed (1 atm H_2, Pd-black, 20°C, 0.5h) to give 16

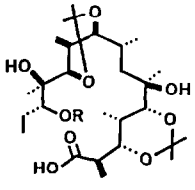
(92%). t-Butyldiphenylsilylation (TBDPSCl (4 equiv), imidazole (4 equiv), DMF, 25°C, 3h) of 16 followed by the selective O-isopropylidenation[13] (2-methoxypropene (5 equiv), PPTS (0.1 equiv), CH_2Cl_2, 25°C, 3h) of the silylation product 17 (82%) afforded the desired 3,5:9,11-diacetonide 18[3] (64% from 15, $[\alpha]_D$ +31.2°) and the 3,5:11,13-diacetonide (5%). Acetylation (Ac_2O (10 equiv), DMAP (0.1 equiv), Py, 60°C, 20h) of 18 followed by desilylation ($(n\text{-Bu})_4NF$ (6 equiv), THF, 60°C, 8h) of the acetate 19 (86%) gave 20[3] (70% from 18, $[\alpha]_D$ +29.8°). PDC oxidation (PDC (4 equiv), 3A molecular sieves, 22°C, 4h) of 20 followed by deacetylation (1M NaOH-dioxane(1:1), 23°C, 2h) of the acid 21 (85%) yielded the seco-acid 3,5:9,11-diacetonide 22 (82% from 20). Treatment (Ph_3P (1.5 equiv), $(2\text{-PyS})_2$ (1.5 equiv), THF, 23°C, 8h) of 22 afforded the 2-pyridinethiol ester (95%), which was subjected to lactonization by the modified Corey's method[14] (toluene, 110°C, 24h) to furnish 23[3] (65%, $[\alpha]_D$ +12.1° (c 0.66)). Exposure (24°C, 4h) of 23 to 50% aqueous acetic acid afforded quantitatively 2[3] (mp 203-206°C (acetone-hexane), $[\alpha]_D$ +9.5° (c 2.0, MeOH)), which proved to be identical in all respects with a sample of 2 (mp 203-206°C) prepared by the method of Jones and Rowley.[11] The overall yield of 2 from 11 was 21.1% in 11 steps. Selective 3,5-O-benzylidenation (dimethoxytoluene (5 equiv), CSA (0.1 equiv), CH_2Cl_2, 0°C, 24h) of 2 gave 24[3] (80%, mp 128-130°C (acetone-hexane), $[\alpha]_D$ +5.4°). Selective oxidation (PCC, 3A molecular sieves, 0°C, 0.5h) of 24 afforded 25[3] (80%, $[\alpha]_D$ -36.6° (MeOH), which was hydrogenolyzed with Pd-black (1 atm H_2, MeOH, 0.5h) to give 1[3] (82%, mp 170-172°C (acetone-hexane), $[\alpha]_D^{25}$ -36.7° (c 0.9, MeOH) (lit.[13] -37°)). The synthetic sample of 1 proved to be identical with naturally derived erythronolide A (mp 170-172°C (lit.[15] mp 172-173°C), $[\alpha]_D^{25}$ -37.3° (c 0.9, MeOH)) by spectroscopic means and mixture melting point measurement.



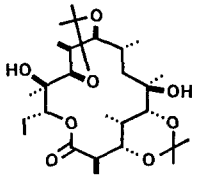
15 R^1=R^2=Bn
16 R^1=R^2=H
17 R^1=H, R^2=TBDPS



18 R^1=TBDPS, R^2=H, R^3=TES
19 R^1=TBDPS, R^2=Ac, R^3=TES
20 R^1=R^3=H, R^2=Ac



21 R = Ac
22 R = H



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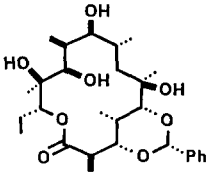

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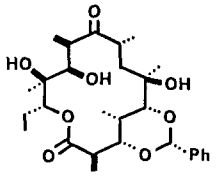

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References and Notes

1. Part II: M. Kinoshita, M. Arai, K. Tomooka, and M. Nakata, *Tetrahedron Lett.*, preceeding paper in this issue.
2. M. Kinoshita, N. Ohsawa, and S. Gomi, *Carbohydr. Res.*, 109, 5 (1982).
3. All compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were measured using a 0.5-dm tube, for solutions (c 1.0) in chloroform at 20°C, unless stated otherwise. Significant ^{1}H-NMR (90 MHz,* 250 MHz) spectral data [δ($CDCl_3$, TMS), J(Hz)] are the following. 5: (*) 1.09 (3H, d, J=6.5), 4.71 (1H, d, J=5.5). 6: (*) 0.9-1.3 (12H, m), 3.8-4.1 (4H, m). 7: (*) 0.89 (9H, s), 1.35 (3H, s). 9b: 0.88 (9H, s), 1.13 (3H, s), 1.30 (3H, s), 1.36 (3H, s), 1.43 (3H, s), 4.71 (1H, s), 5.16 (1H, s), 5.31 (1H, s). 10: 0.62 (3H, d, J=7.0), 0.89 (3H, d, J=7.0), 1.02 (3H, t, J=7.5), 1.03 (3H, d, J=7.3), 1.06 (3H, d, J=6.8). 11: 1.39 (1H, dd, J=5.0, 13.8), 1.88 (1H, dd, J=5.0, 13.8), 3.18 (1H, d, J=1.5), 3.30 (1H, dd, J=3.8, 7.5), 3.33 (1H, dd, J=5.3, 9.3), 3.43 (1H, dd, J=9.3, 9.3), 4.04 (1H, d, J=0.5). 12: 0.88 (9H, s), 1.21 (3H, s), 1.36 (6H, s), 1.46 (3H, s). 14: (*) 0.85-1.15 (21H, m), 4.35-4.8 (10H, m), 7.2-7.4 (25H, m). 15: 0.5-0.7 (12H, m). 18: 1.05 (9H, s), 1.17 (3H, s), 1.22 (3H, s), 1.27 (3H, s), 1.28 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 7.1-7.25 (6H, m), 7.35-7.55 (4H, m). 20: 2.09 (3H, s), 4.90 (1H, dd, J=3.3, 9.0). 23: 1.94 (1H, ddq, J=2.5, 7.5, 14.8), 2.75 (1H, dq, J=6.5, 10.8), 3.60 (1H, d, J=1.8), 3.97 (1H, d, J=1.5), 5.06 (1H, dd, J=2.5, 11.3). 24: 5.13 (1H, dd, J=2.3, 11.0), 5.65 (1H, s), 7.35-7.45 (3H, m), 7.45-7.55 (2H, m). 25: 2.85-3.1 (3H, m), 3.76 (1H, dd, J=5.0, 5.0), 3.83 (1H, dd, J=1.0, 10.3), 4.01 (1H, d, J=1.3), 4.88 (1H, dd, J=2.0, 10.3), 5.68 (1H, s). 2: 0.90 (3H, t, 3xH-15, J=7.3), 1.04 (3H, d, 4-Me, J=7.5), 1.05 (3H, s), 1.24 (3H, s), 1.24 (3H, d, 10-Me, J=7.3), 1.29 (6H, d, 2,8-Me, J=7.0), 2.79 (1H, dq, H-2, J=7.0, 10.3), 2.97 (1H, ddd, H-9, J=2.3, 9.0, 9.0), 3.48 (1H, dd, H-11, J=1.0, 4.3), 3.85 (1H, d, H-3, J=0, 10.3), 3.95 (1H, br-s, H-5), 4.64 (1H, dd, H-13, J=2.3, 10.3). 1: 0.85 (3H, t, 3xH-15, J=7.5), 1.01 (3H, d, 4-Me, J=7.3), 1.16 (3H, d, 10-Me, J=7.3), 1.17 (3H, s), 1.19 (3H, d, 2 or 8-Me, J=6.5), 1.24 (3H, d, 2 or 8-Me, J=6.5), 1.36 (3H, s), 2.6-2.8 (2H, m, H-2, 8), 3.07 (1H, br-q, H-10, J=0,7.3), 3.55-3.7 (2H, m, H-3, 5), 3.81 (1H, br-s, H-11, J=0), 5.04 (1H, dd, H-13, J=2.3, 10.8) [after addition of D_2O, the signals of H-5, 3, and 11 changed to 3.56 (d, J=2.5), 3.62 (d, J=0, 10.5), and 3.81 (d, J=1.0), respectively].
4. A. I. Meyers et al., *J. Am. Chem. Soc.*, 105, 5015 (1983). We prepared this aldehyde from methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate (Aldrich) in five steps (1. TrCl, Et_3N, DMAP, CH_2Cl_2, 20°C, 14h; 2. $LiAlH_4$, THF, 20°C, 4h; 3. NaH, BnBr, THF, 70°C, 1h; 4. Amberlyst 15, MeOH, 50°C, 2h; 5. $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78°C) in 74% yield.
5. The major isomer 6 was assumed to be the α-chelation controled addition product.
6. The yield of 9a was assumed based on the yield of 9b and on a ratio (5:1) of the corresponding separable desilylation products derived from the crude mixture of 9a and 9b.
7. This material is probably one of the by-products originated from 3.
8. Though, [Rh(NBD)(DIPHOS-4)]BF_4 [9] instead of the Wilkinson's catalyst was used under the same condition, neither of improvements in the isomeric ratio and in the reaction rate was observed.
9. D. A. Evans and M. M. Morrissey, *J. Am. Chem. Soc.*, 106, 3866 (1984), and references cited therein.
10. Lactone 2 was prepared by the known method [11] from natural erythromycin A. We wish to thank the Pfizer Taito Co., Ltd.(Japan) for the kind supply of natural erythromycin A.
11. P. H. Jones and E. K. Rowley, *J. Org. Chem.*, 33, 665 (1968).
12. When a mixture of 13 (1.69 g), BnCl (7.32 ml), KOH (7.11 g), and DMF (68 ml) was stirred at 22°C for 6.5h, 11 (2.24 g, 58.3%) was obtained accompanied by 14 (74 mg, 1.9%) and a mixture of partially benzylated products (1.12 g), while, treatment of a mixture of 13 (667 mg), BnCl (2.89 ml), KOH (2.82 g), and DMF (10 ml) in a sonicator (65W, 48 KHz) at room temperature for 3.5h, yielded 14 (436 mg, 28.8%), 11 (346 mg, 22.8%), and a mixture of partially benzylated products (844 mg).
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