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A STEREOSELECTIVE TOTAL SYNTHESIS OF (9S)-9-DIHYDROERYTHRONOLIDE A FROM D-GLUCOSE[1]

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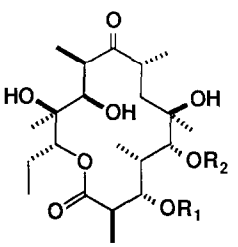
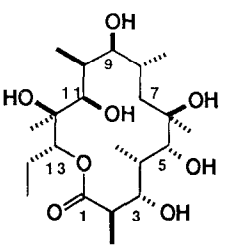
Summary A rather facile stereoselective total synthesis of (9S)-9-dihydroerythronolide A starting from D-glucose was achieved via coupling of C1-C6 and C7-C15 segments and subsequent macrolactonization.

The well known macrolide antibiotic erythromycin A (**1**) has been an attractive synthetic target for modern synthetic chemists, because of its complex chemical structure as well as important biological activity, and many new synthetic methodologies have been developed.[2] As part of our synthetic studies of macrolide and polyether antibiotics by a common methodology,[3] we report here a rather facile total synthesis of 9-dihydroerythronolide A (**3**)[7] by use of some stereoselective reactions and suitable protecting groups. Two segments **4** (C7-C15)[8] and **5** (C1-C6) were first chosen as synthetic intermediates in one of our various synthetic approaches to **1**, **2**, and **3**.



1:R_1=L-Cladinosyl
R_2=D-Desosaminyl
2:R_1,R_2=H



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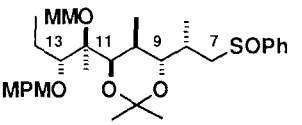

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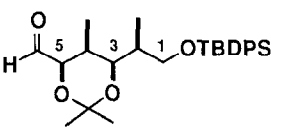
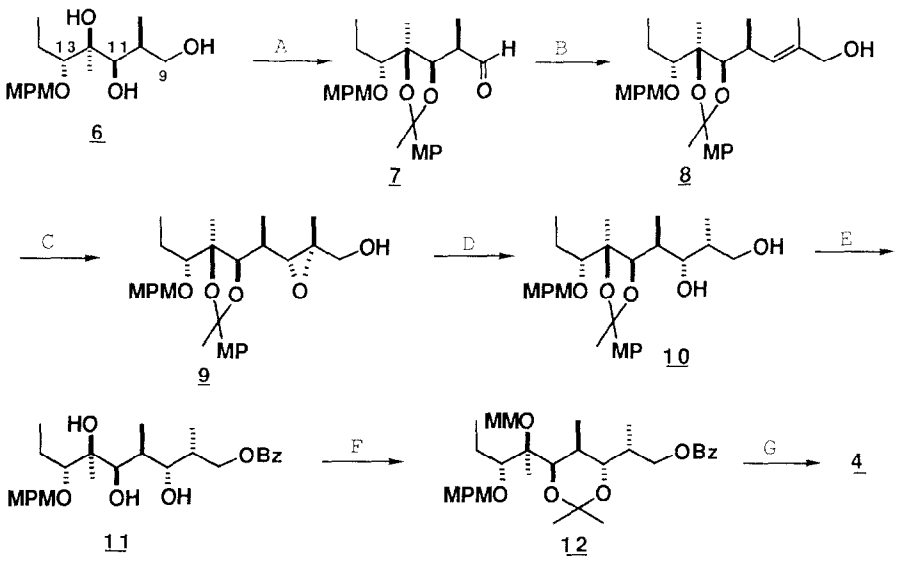


5

MPM : p-MeO-$C_6H_4CH_2$
TBDPS : t-BuPh_2Si

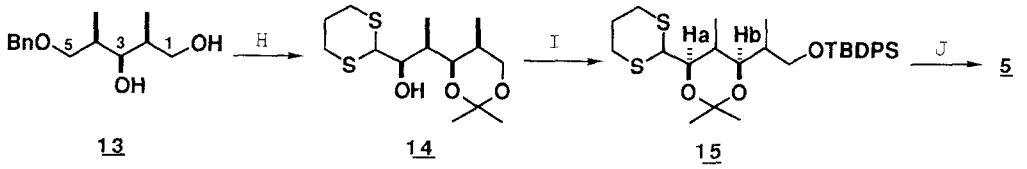
The triol (**6**)[9] derived from D-glucose was first converted to a monobenzoate, and then the remaining diol was protected with a p-methoxyphenylethylidene group.[10] After hydrolysis of the benzoate, Swern oxidation[11] readily gave the aldehyde (**7**), which was subjected to the Wittig reaction, followed by reduction to give the (E)-allyl alcohol (**8**). m-CPBA oxidation of **8** at -10 °C gave the epoxide (**9**) with 8 : 1 stereoselectivity. The regio- and stereoselective reductive opening of the epoxide ring was one of crucial steps in this total synthesis, and only the desired alcohol (**10**) was obtained in high yield by treatment with a large excess of $NaBH_3CN$ in the presence of $BF_3{\cdot}OEt_2$ in refluxing THF.[12,13] Benzoyl protection of the primary alcohol of **10** followed by selective removal of the ketal protection gave the triol (**11**). When **11** was treated with 2-methoxypropene in the presence of a catalytic amount of PPTS at room temperature,[2a] the expected kinetic product, 9,11-O-isopropylidene compound,[16] was isolated



(A) 1) BzCl, Py, CH_2Cl_2, rt, 100%; 2) p-$MeOC_6H_4CMe(OMe)_2$, CSA, rt, 95%; 3) 1N-KOH, MeOH, rt, 98%; 4) $(COCl)_2$, DMSO, Et_3N, 100%. (B) 1) $Ph_3P{=}CMeCO_2Et$, EDC, reflux, 100%; 2) $LiAlH_4$, Et_2O, 0 °C, 94%. (C) m-CPBA, CH_2Cl_2, -15～-10 °C, 95%. (D) $NaBH_3CN$ (12 eq), $BF_3{\cdot}OEt_2$ (6 eq), THF, reflux, 89%. (E) 1) BzCl, Py, CH_2Cl_2, rt, 84%; 2) 4N-HCl, THF, rt, 84%. (F) 1) $CH_2{=}C(Me)OMe$, PPTS, CH_2Cl_2, rt, 89%; 2) MMCl, i-Pr_2EtN, CH_2Cl_2, 45°C, 100%. (G) 1) 1N-NaOH, dioxane, 65～75 °C, 100%; 2) TsCl, Et_3N, DMAP, CH_2Cl_2, reflux, 100%; 3) PhSNa, EtOH-DMF, reflux, 90%; 4) $NaIO_4$, MeOH-H_2O, rt, 97%.

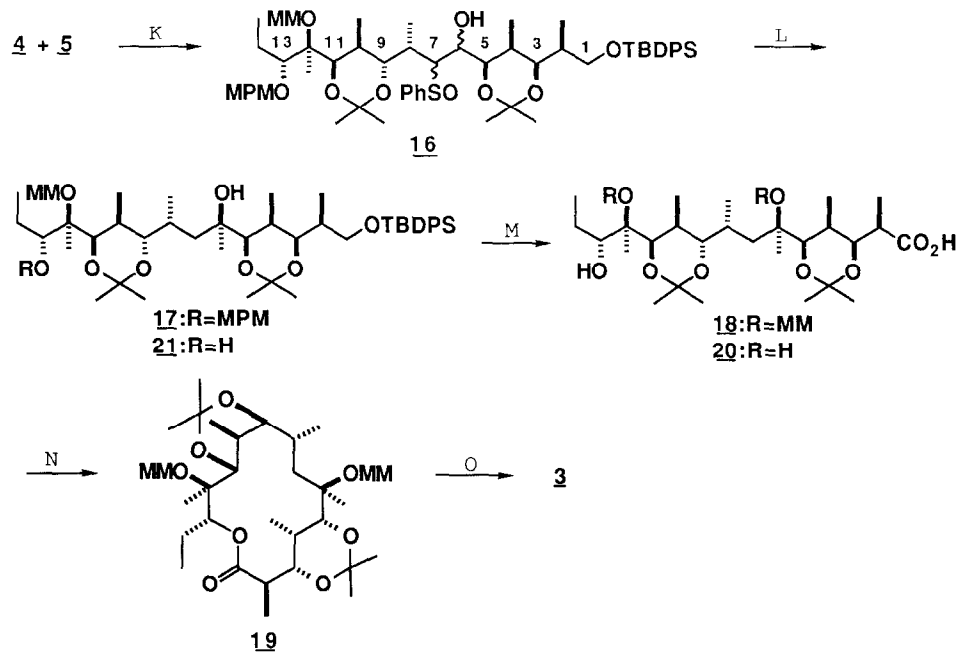
in high yield. MM protection of the remaining tertiary alcohol readily gave **12**, which was converted to the C7-C15 segment (**4**) via treatment of a tosylate with PhSNa in excellent yield.[17,18]

The diol (**13**)[19] derived also from D-glucose was protected as an acetonide, then removal of the Bn group followed by PCC oxidation gave the aldehyde, which was treated with the carbanion of 1,3-dithiane, and a stereoisomeric mixture (4.6 : 1) mainly consisting of the Cram adduct (**14**) was obtained. The acetonide group of **14** was removed, then the resulting primary alcohol was protected with a TBDPS group, and protection of the remaining diol gave **15**, whose configuration was confirmed by observation of the NOE (8%) between an acetonide methyl group and each of Ha and Hb in the NMR spectrum. Finally, treatment of **15** with MeI[20] gave the C1-C6 segment (**5**) in high yield.[21]



(H) 1) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt; 2) 10%Pd-C, H_2, EtOH, 96% (overall); 3) PCC, molecular sieves, CH_2Cl_2, rt, 82%; 4) 1,3-dithiane, n-BuLi, THF, -75～-70°C, 86%. (I) 1) $TsOH{\cdot}H_2O$, MeOH, rt, 92%; 2) TBDPSCl, imidazole, DMF, rt, 93%; 3) $CH_2{=}C(Me)OMe$, PPTS, rt, 95%. (J) MeI, $NaHCO_3$, 90%MeCN, 70°C, 88%.

Coupling of 5 and **4** (2 eq) in the presence of LDA (2 eq) at -80∼-70 °C proceeded quite smoothly to give a stereoisomeric mixture of **16** in high yield.[23] Desulfurization with Raney Ni and subsequent Swern oxidation[11] readily gave the 6-keto compound, which was treated with a large excess of MeLi in THF at -85 °C. The Cram addition (non-chelation) took place rather rapidly to give **17** in excellent yield (7.2 : 1 stereoselectivity).[24] Thus all chiral centers required for **3** were constructed. Four step conversion of **17** [MM protection of C6-OH group, desilylation with F^-, Jones oxidation of the resulting primary alcohol, and final removal of the MPM protection by catalytic reduction or DDQ oxidation[25]] gave the fully protected (except 1-CO_2H and 13-OH) seco-acid (**18**) in good yield. Macrolactonization of **18** was achieved only by Yamaguchi's method[26] at rather high concentration of DMAP. When a 2 mM toluene solution of a mixed anhydride, prepared from **18** and 2,4,6-trichlorobenzoyl chloride in the presence of Et_3N, was added dropwise to an equal volume of refluxing 50 mM toluene solution of DMAP (25 eq) over a period of 39 h, the expected lactone (**19**) was isolated in 27% yield.[27,28] Removal of the protecting groups of **19** with 50% AcOH readily gave the title compound (**3**).[29] More efficient syntheses of 2 and 3 will be reported later.



(K) LDA, THF, -80∼-70°C, 1.5h, 85%. (L) 1) Raney Ni (W-2), EtOH, rt, 83%; 2) $(COCl)_2$, DMSO, Et_3N, 92%; 3) MeLi (15 eq), THF, -85°C, 1h, 95%. (M) 1) MMCl, i-Pr_2EtN, CH_2Cl_2, 50∼55°C, 100%; 2) n-Bu_4NF, THF, 55∼60°C, 94%; 3) 2.67M Jones reagent, Me_2CO, -17°C, 78%; 4) 10%Pd-C, H_2, EtOH, 55°C, 99%. (N) i) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, ii) DMAP (25 eq), toluene, reflux, 39h, 27%. (O) 50%AcOH, rt, 91%.

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17) cf. a) G. Stork, I. Paterson, and F. K. C. Lee, J. Am. Chem. Soc., 104, 4686 (1982); b) I. Paterson, Tetrahedron Lett., **24**, 1311 (1983).

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23) Most of excess **4** was recovered (86%). Coupling between **4** and the 6-methylketone derived from **5**[17a] gave only poor results in <20% yield.

24) Treatment of the ketone with MeLi (10 eq) in the presence of HMPA (40 eq) in ether at -86 °C for 1 h also gave **17** in 95% yield with 5.6 : 1 stereoselectivity. On the other hand, in the absence of HMPA, the chelation controlled addition of MeLi in ether occurred quite smoothly to give the C6 epimer of **17** in quantitative yield with 5 : 1 stereoselctivity. When the ketone was treated with MeMgI in ether or with $MeCeCl_2$ in THF, no reaction occurred.

25) a) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., **23**, 885 (1982); b) K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, and O. Yonemitsu, Tetrahedron, 42, 3021 (1986).

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27) In this macrolactonization, concentration of DMAP was very important. Yields of **19** in various concentrations of DMAP are as follws [final mM of DMAP (% yield of **19**)]: 25 mM (27%); 9.5 mM (14%); 6 mM (13%); 3 mM (0%).

28) As pointed out by Stork,[2e] an axial methyl group of 9,11-acetonide protection hindered this lactonization. Actually we could not obtain **19** by the modified Corey method,[2b] and also **20** gave only a trace of lactonization product, which was, however, obtained in 63% yield by highly reactive Yamaguchi's method[26] at high concentration of DMAP.

29) **3**, **18**, **19**, and a 6-O-MM derivative of **21** were identical with the respective authentic samples derived from natural erythromycin A in terms of IR, NMR, and MS spectra.

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