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TOTAL SYNTHESIS OF ERYTHRONOLIDE B. 2.

SKELETON ASSEMBLY IN (C_5-C_9) + (C_3-C_4) + (C_1-C_2) + (C_{11}-C_{13}) SEQUENCE[1].

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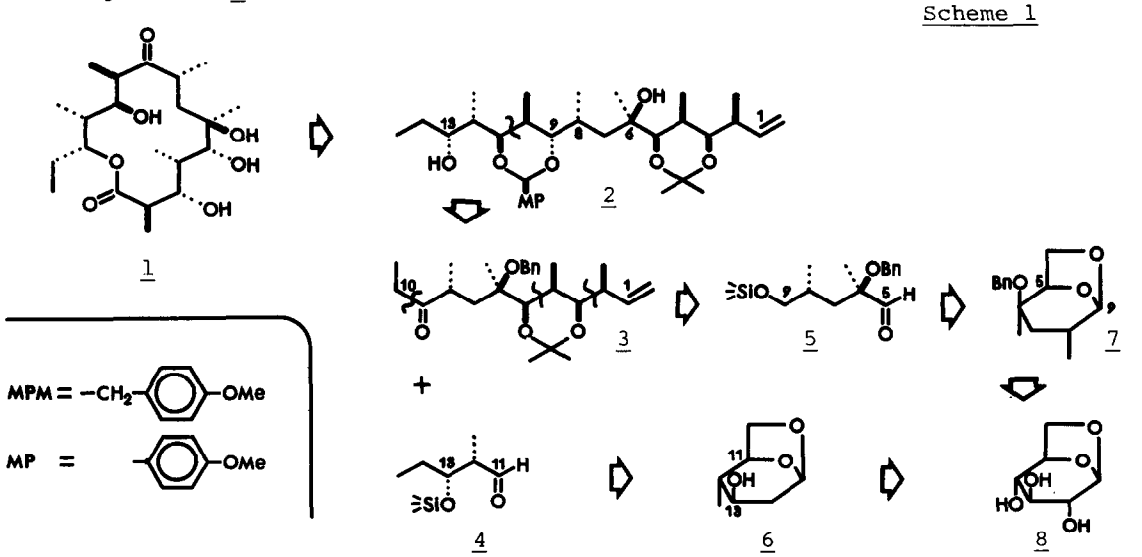
Abstract. Erythronolide B has been synthesized starting from levoglucosan.

In the preceding paper we reported the synthesis of erythronolide B (1) from levoglucosan[2]. The synthesis proceeded through assembly of C_1-C_6 and C_9-C_{13} segments and led to the seco-acid precursor 2 which was successfully transformed into erythronolide B (1). We now report an alternative synthesis of erythronolide B (1) through the same intermediate 2 using a carbohydrate-derived C_5-C_9 and C_{11}-C_{13} segments.

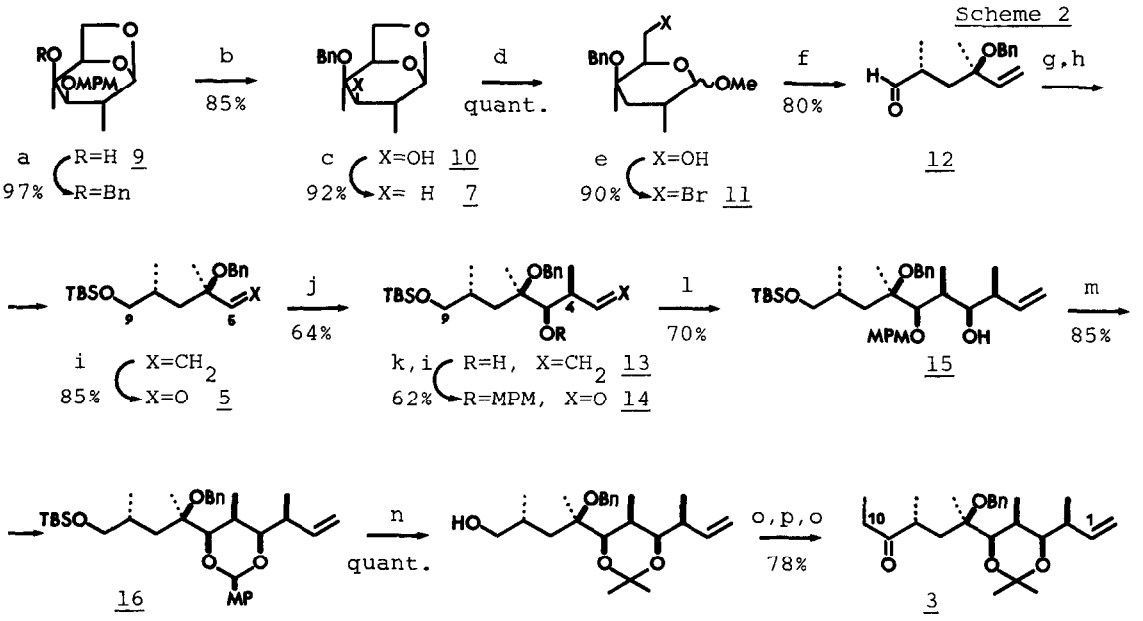
The common subtarget of the syntheses - seco-acid precursor 2 - can be obtained (Scheme 1) by aldol addition of C_1-C_{10} ketone 3 to C_{11}-C_{13} aldehyde 4 (cf.[3]). To produce the former, two consecutive crotylstannane additions to C_5-C_9 aldehyde 5 were proposed. Both C_5-C_9 (5) and C_{11}-C_{13} (4) segments can be obtained from levoglucosan 8.

Scheme 1



The C_1-C_{10} segment of erythronolide B was synthesized as follows (Scheme 2). Compound 9 was prepared from levoglucosan 8 in nine steps (36% overall yield) according to the described method[4]. Benzylation of 9 followed by selective MPM removal led to the alcohol 10 which was deoxygenated via its xanthate ester. The bicyclic derivative 7 so produced was transformed into the bromide 11 which was subjected to reductive elimination to afford the unsaturated aldehyde 12[5].

Scheme 2

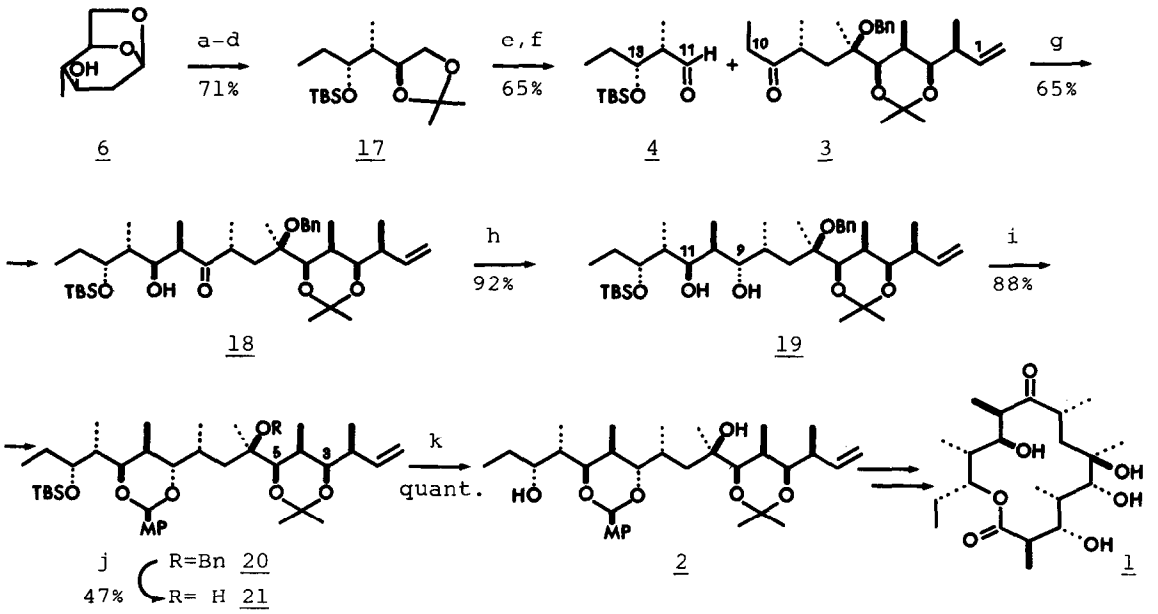


a.NaH,BnBr/DMF; b.DDQ/CH_2Cl_2-H_2O; c.NaH,CS_2,MeI/THF then Bu_3SnH,AIBN/$PhCH_3$,Δ; d.HCl/MeOH; e.CBr_4-Ph_3P/Py,60°; f.Zn/i-PrOH-H_2O(14:1),Δ; g.$LiAlH_4$/Et_2O; h.TBSCl, ImH/DMF; i.O_3/CH_2Cl_2-Py; j.$Bu_3SnCH_2CH{=}CHCH_3$,$MgBr_2$/CH_2Cl_2,20°; k.NaH,MPMCl/DMF; l.$Bu_3SnCH_2CH{=}CHCH_3$,$BF_3{\cdot}Et_2O$/CH_2Cl_2,-78°; m.DDQ,MS 3A°/CH_2Cl_2; n.DMP-Me_2CO,TsOH; o.$(COCl)_2$-DMSO,Et_3N/CH_2Cl_2; p.EtMgBr.

The aldehyde 12 was converted into the C_5-C_9 aldehyde 5[5] which, on $MgBr_2$--mediated crotylstannane addition, produces two homoallylic alcohols in moderate (4:1) selectivity[6]. The major product (13)[5], stereochemically corresponding to the C_4-C_9 segment of erythronolide B, was transformed into the aldehyde 14 which was subjected again to a crotylstannane addition reaction, but in the presence of $BF_3{\cdot}Et_2O$. The major homoallylic alcohol obtained proved to be the "Cram" product (15)[7], and the C_1-C_{10} ketone 3[5] derived from it posesses, at least, five chiral centres with the required configurations. At this stage of the synthesis the configuration at C_2 remained unknown and was proved later.

The C_{11}-C_{13} segment of erythronolide B (4) was obtained from the bicyclic acetal 6[8] as shown at Scheme 3.

Scheme 3



a.EtSH,HCl; b.Ra-Ni/EtOH; c.Me_2CO,$CuSO_4$; d.TBSOTf,Et_3N/CH_2Cl_2; e.$HS(CH_2)SH$, $BF_3 \cdot Et_2O/CH_2Cl_2$,-78°; f.$NaIO_4/THF-H_2O$; g.$LiN(SiMe_3)_2$/THF,-78°; h.$LiAlH(OBu\text{-}t)_3$; i.$MPCH(OMe)_2$,TsOH; j.DDQ/$CH_2Cl_2$-$H_2O$; k.$Bu_4NF$/THF.

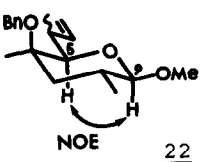
De-O-isopropylidenation of 17 was achieved by mercaptolysis and the resulting glycol was split by $NaIO_4$ to afford the C_{11}-C_{13} aldehyde 4[5] which was immediately introduced into reaction with the Li-enolate of C_1-C_{10} ketone 3. The aldols formed were separated by chromatography and the main diastereomer of the expected[3] structure 18[5] was reduced with $LiAlH(OBu\text{-}t)_3$ to yield the desired 9,11-*anti*-glycol 19[9] in 12:1 selectivity. Further transformation of 19 into 2 was carried out as follows. The p-methoxybenzylidene acetal 20[5], obtained as a single isomer at the acetal centre, on treatment with DDQ in wet CH_2Cl_2 undergoes rapid debenzylation to produce 21[5]. The high rate of the reaction in conjunction with unusual selectivity might arise through an intramolecular hydride transfer from benzyl to the sterically hindered dioxenium ion, generated from p-methoxybenzylidene acetal, as a result of conformational "rigidity" in 3,5:9,11-bis(cyclic)acetal of (9S)-dihydro seco-acid derivatives[10].

Desilylation of 21 provides the seco-acid precursor 2[5] which proved to be identical with that prepared by the independent route[2]. Transformation of 2 into erythronolide B (1) has been described in the preceding paper[2].

Adaptation of this strategy to erythronolide A synthesis as well as syntheses of erythromycins A and B are in progress now.

References and notes.

1. Presented at the VIth ICOS, Moscow, USSR, August 10-15, 1986; A-188, p.86.
2. Preceding paper in this issue.
3. S.Masamune, M.Hirama, S.Mori, S.A.Ali, D.S.Garvey, J.Amer.Chem.Soc., 103, 1568 (1981).
4. N.K.Kochetkov, A.F.Sviridov, M.S.Ermolenko, D.V.Yashunsky, Tetr.Lett., 25, 1605 (1984).
5. All new compounds were fully characterized by $[\alpha]_D$, ^{1}H-NMR, elemental analyses and (if crystalline) mp. Specific rotation (measured at 22 ± 2^o, c 1.0, $CHCl_3$) and representative ^{1}H-NMR (250 MHz, δ scale, J(Hz), $CDCl_3$) data for selected compounds are the following:
   5: +19.2°; 13: +8.6°; $J_{4,5}$=5; 3: +22.3°; $J_{3,4}=J_{4,5}$=2; 4: $J_{12,13}$=3.6; 18: +13.3°; $J_{10,11}$=2, $J_{11,12}$=10; 20: $J_{9,10}$=0, $J_{10,11}$=2.3; 21: $J_{3,4}=J_{4,5}=J_{10,11}$=2, $J_{9,10}$=0; 2: +7.1°; 0.78(d, J=7, Me-12), 1.00(t, J=7.3, Me-14), 1.01(d, J=6.5, Me-4), 1.05(d, J=6.3, Me-2), 1.11(d, J=6.5, Me-8), 1.20(s, Me-6), 1.21(d, J=6.5, Me-10), 1.42s and 1.43s(Me_2C), 1.67(ddq, $J_{3,4}=J_{4,5}$=2, H-4), 1.84(br.dq, $J_{9,10}$=0, $J_{10,11}$=2, H-10), 1.98(ddq, $J_{11,12}$=10, $J_{12,13}$=2, H-12), 2.33(m, $J_{1,2}$=8.2, $J_{2,3}$=9.5, H-2), 2.61(m, $J_{8,9}$=10.5, H-8), 3.31(br.d, H-9), 3.42(dd, H-3), 3.49(d, H-5), 3.65(ddd, $J_{13,14}$=5, $J_{13,14'}$=7.5, H-13), 4.17(dd, H-11), 5.05 m, 5.12 m (CH_2=), 5.61(ddd, H-1), 5.65(s, MPCH), 6.89m+7.41m (arom.).
6. The both isomers represent the products of chelate control as was shown by NMR (including NOE) investigations of the corresponding β-methylglycosides 22 which were obtained from chromatographically separated homoallylic alcohols in 4 steps (1.TBSOTf,Et_3N/CH_2Cl_2; 2.AcOH-H_2O-THF (3:1:5),50°; 3.$(COCl)_2$-DMSO,Et_3N/CH_2Cl_2; 4.HCl/MeOH.). At this stage of the synthesis the absolute configuration at C_4 in 13 remained unknown and was proved later[7].



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7. By NMR (including NOE) investigation of cyclic acetal 16.
8. Available from levoglucosan 8 in five steps and 40% overall yield: A.F.Sviridov, G.E.Berdimbetova, N.K.Kochetkov, Izv.Akad.Nauk SSSR, Ser.Khim., 1982, 2572.
9. By NMR (including NOE) investigation of cyclic acetal 20 and the corresponding acetal derived from 9,11-syn-isomer of 20.
10. This reaction was first observed with analogously protected (9S)-dihydroerythronolide A; unpublished results from this laboratory.

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