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TOTAL SYNTHESIS OF ERYTHRONOLIDE B. 1.

SKELETON ASSEMBLY IN (C_9-C_{13}) + (C_7-C_8) + (C_1-C_6) SEQUENCE[1].

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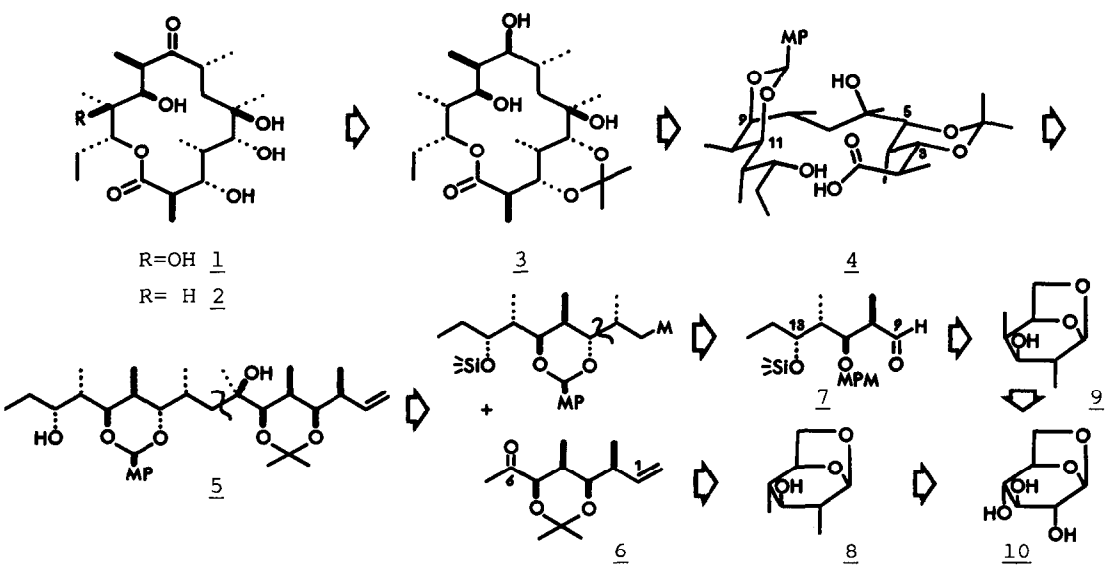
Abstract. Erythronolide B has been synthesized starting from levoglucosan.

Erythronolides A (1) and B (2) represent two basic aglycones of macrolide antibiotics produced by Streptomyces erythreus. Erythronolide B has earlier been synthesized by Corey[2] from achiral starting materials. In this and the following papers[3] we report two different syntheses of erythronolide B from 1,6-anhydro-β--D-glucose (levoglucosan).

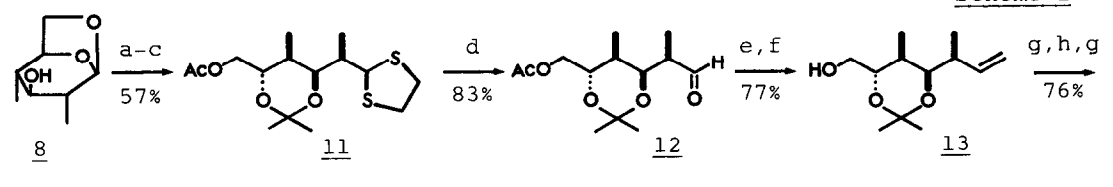
The strategy of the syntheses is based on utilization of 3,5:9,11-bis-(cyclic)acetal derivative of (9S)-dihydro seco-acid (4), conformationally arranged for efficient lactonization[4] (Scheme 1). This one, in its masked form 5 serves as a common subtarget in both the syntheses described. In this synthesis structure 5 was transformed to C_1-C_6 (6) and C_9-C_{13} (7) segments stereochemically correlated with bicyclic acetals 8 and 9 respectively. Some syntheses of these compounds from levoglucosan 10 have earlier been elaborated[5-7].

Scheme 1



The bicyclic acetal 8 was converted into the open-chain derivative 11[8] without isolation of intermediates (Scheme 2). Dithiolane carbonyl protection has some advantages, particularly in hydrolysis step, and ensured about 2-fold increase in total yield of the aldehyde 12, compared with dithiane derivative. Methylenation of 12 followed by deacetylation gave the alcohol 13[9] which was transformed into the ketone 14. The 1,3-dioxane ring in 14 adopts boat conformation, and smooth isomerization under mild conditions occurs to yield the C_1-C_6 segment 6[8] with chair ring conformation.

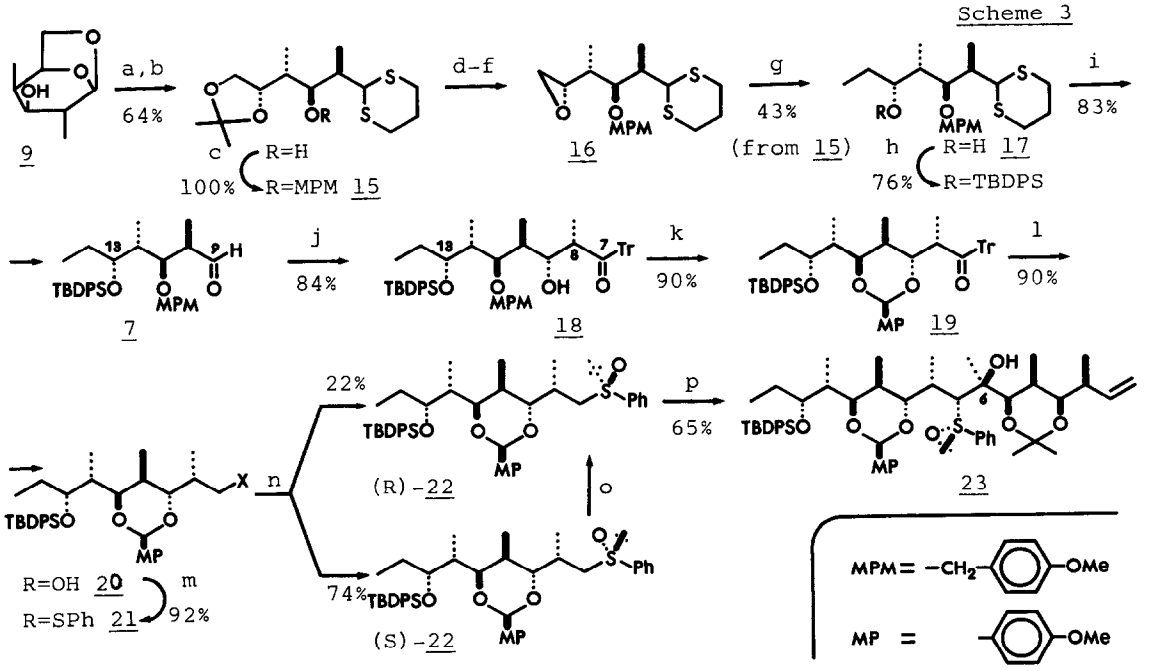
Scheme 2



a.$HS(CH_2)_2SH,BF_3\cdot Et_2O/CH_2Cl_2$; b.$Ac_2O$-Py; c.DMP-$Me_2CO$,TsOH; d.$HgCl_2$-$CaCO_3$/MeCN-$H_2O$; e.$Ph_3P{=}CH_2/C_6H_6,\Delta$; f.MeONa/MeOH; g.$(COCl)_2$, DMSO,$Et_3N/CH_2Cl_2$; h.MeMgCl; i.$K_2CO_3$/MeOH.

To obtain the C_9-C_{13} segment 7 the bicyclic acetal 9 was converted into the selectively protected dithiane derivative 15 (Scheme 3). After mild acid hydro-

Scheme 3



a.$HS(CH_2)_3SH,BF_3\cdot Et_2O/CH_2Cl_2$; b.DMP-$Me_2CO$,TsOH; c.NaH,MPMCl/DMF; d.AcOH-H_2O,50°; e.TsCl-Py; f.K_2CO_3/MeOH,-15°; g.MeMgCl,CuCl·Me_2S/THF; h.t-$BuPh_2SiClO_4$,Et_3N/CH_2Cl_2 i.$HgCl_2$-$CdCO_3$/Me_2CO-H_2O; j.C_2H_5COTr-BuLi/THF,-78°; k.DDQ,MS 3A°/CH_2Cl_2; l.$LiBHEt_3$ m.Ph_2S_2-Bu_3P/Py; n.MCPBA/AcOEt,-40°; o.TFAA,collidine/THF;+H_2O; p.LDA/THF,-78°,+6

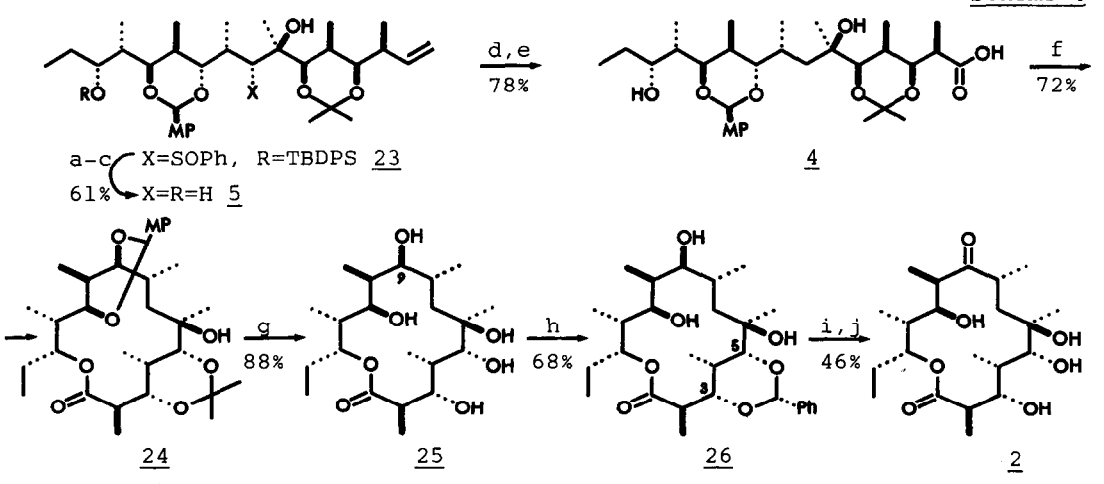
lysis of 15 the resulting glycol was transformed into extremely labile oxirane 16 which was immediately subjected to CuCl-catalyzed oxirane ring opening with MeMgCl. Silylation of the alcohol obtained (17) by TBDPS perchlorate (produced *in situ* from t-$BuPh_2SiH$ and $TrClO_4$[10]) followed by dithioacetal hydrolysis provides the C_9-C_{13} aldehyde 7[8].

The two-carbon chain elongation of C_9-C_{13} to C_7-C_{13} segment was best carried out by addition of Li-enolate of ethyl trityl ketone[11] to the aldehyde 7 affording the desired aldol 18[8] as a sole product. Treatment of this MPM ether with DDQ led to the p-methoxybenzylidene acetal 19[8] as a single (and the only required) isomer at the acetal centre. The trityl ketone 19 was reductively split[11] to the alcohol 20 which was converted into sulfide 21[8]. Oxidation of 21 with MCPBA gave an easily separable mixture of (R)- and (S)-sulfoxides 22[12] (22% and 74% respectively).

Only minor (R)-22 was found to join with C_1-C_6 ketone 6 to afford two products in >7:1 ratio. Since all attempts to change the selectivity of the sulfide 21 oxidation in favour of the desired (R)-22 were unsuccessful, we have elaborated a new convenient method of sulfoxide isomerization. Thus, treatment of (S)-22 with trifluoroacetic anhydride (1.2 eq., 2,4,6-collidine 3 eq./THF,-78°, 20 min) followed by addition of aqueous THF gave a mixture of (R)- and (S)-22 in 77:23 ratio. In this way (by oxidation, separation and isomerization of the undesired (S)-isomer) the sulfide 21 was converted into the (R)-sulfoxide 22 in high total yield.

The main product of coupling of (R)-22 with 6 was obtained in 88% yield based on consumed (R)-22. It should have, as expected[13,14], the "natural" C_6 configuration (23) and this was confirmed later. Labile adduct 23 was immediately deoxy-

Scheme 4



a.TFAA,NaI/Me_2CO; b.Na/NH_3 liq.; c.Bu_4NF/THF; d.O_3; e.MCPBA/THF, phosphate buffer(pH 7); f.2,2'-dithiobis(4-t-Bu-1-i-Pr-imidazole),Ph_3P/$PhCH_3$,Δ,C=10^{-3} M; g.TFA-H_2O-MeCN (4:1:4); h.$PhCH(OEt)_2$,CSA/CH_2Cl_2,-10°; i.PCC,MS 3A°/CH_2Cl_2, 0°; j.AcOH-H_2O (4:1),50°.

genated[15] to sulfide (Scheme 4) which was subjected to desulfurization by Na/NH_3 and, finally, to desilylation to furnish the desired seco-acid precursor 5[8]. Thus obtained 5 was converted into the seco-acid 4 which was subjected to lactonization by a modified thiol ester method[16] to produce the lactone 24 in excellent yield.

Unfortunately, all attempts to remove p-methoxybenzylidene acetal protection selectively to produce 3 failed. Therefore both the acetal moieties were cleaved. The resulting 25[8] proved to be identical with (9S)-dihydroerythronolide B prepared by reduction of the authentic 2 with $NaBH_4$ (cf.[4]). Selective 3,5-O-benzylidenation of 25 (cf.[17]) gave 26 which was subjected to oxidation followed by hydrolysis to afford erythronolide B (2). Synthetic 2[8] was found to be identical in all respects (^{1}H-NMR, $[\alpha]_D$, mp, mmp and chromatographic mobility) with the natural erythronolide B[18].

Adaptation of this strategy to the synthesis of erythronolide A (1) as well as syntheses of erythromycins A and B are in progress in this laboratory.

References and notes.

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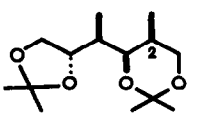
8. Specific rotation (measured at 22 ± 2^o, c 1.0, $CHCl_3$), mp and representative ^{1}H-NMR (250 MHz, δ scale, J(Hz), $CDCl_3$) data for selected compounds are the following: 6: $+40.2^o$; 7: -32.4^o, 83-3.5°; 18: -4.4^o, 155-5.5°, $J_{8,9}<1, J_{9,10}=10$; 21: $+28.0^o$, 119.5-20°; (R)-22: $+105.7^o$, 100.5-1°; (S)-22: -24.5^o, 106.5-7°; 5: $+7.2^o$; 25: $+6.0^o$(MeOH), 181-2°; 2: -65.8^o(MeOH), 224°, ^{1}H-NMR(C_5D_5N-CD_3OD): 0.82t, 1.01d, 1.19d, 1.23d, 1.62s(Me-groups at C-14,-8,-10,-12 and -6 respect.) 1.45d (6H, Me-2 and Me-4), 1.41m, 1.67m(CH_2-14), 1.76m, 2.31dd(CH_2-7), 1.80 ddq ($J_{12,13}=0.5$,H-12), 2.60br.q (H-4), 3.00dq ($J_{2,3}=10.4$,H-2), 3.11ddq ($J_{7,8}=1.5$,H-8), 3.15dq ($J_{10,11}=1.5$,H-10), 4.12br.d (H-3), 4.13d ($J_{4,5}=2.5$,H-5), 4.42dd ($J_{11,12}=10$,H-11), 5.84br.dd (J=4.5,J=10,H-13).
9. The retention of C_2 configuration in 8→13 conversion was confirmed by ^{1}H-NMR spectroscopy of 27 obtained from the acetate of 13 in 3 steps(1.O_3, 2.$LiAlH_4$, 3.DMP,TsOH).



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18. Sample of natural 2 (isolated from industrial mother liquor after erythromycin A crystallization) has $[\alpha]_D$ -65.7^o, mp 224° (from EtOH).

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