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STEREO-CONTROLLED SYNTHESIS OF ERYTHRONOLIDES A AND B FROM 1,6-ANHYDRO-β-D-GLUCOPYRANOSE (LEVOGLUCOSAN). SKELETON ASSEMBLY IN (C_9 - C_{13}) + (C_7 - C_8) + (C_1 - C_6) SEQUENCE

N.K.Kochetkov*, A.F.Sviridov, M.S.Ermolenko, D.V.Yashunsky, and V.S.Borodkin

N.D.Zelinsky Institute of organic Chemistry, Academy of Sciences of the USSR, Moscow, USSR

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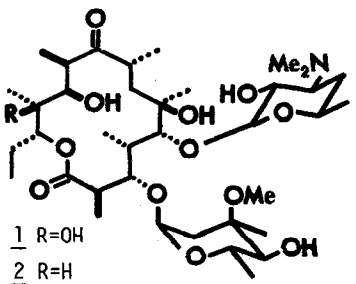
Abstract: Stereospecific syntheses of erythronolides A and B have been accomplished starting from 1,6-anhydro-β-D-glucopyranose (levoglucosan) in a uniform synthetic sequence.

The macrolide antibiotics, erythromycin A 1 and erythromycin B 2, are two basic components of the erythromycin complex produced by Streptomyces erythreus[1]. In the last decade erythromycins have proved highly attractive as objects of synthesis due to their structural complexity, the possibility of revealing useful, in a practical sense, analogues, as well as the common nature of problems of synthesis of macrolide antibiotics and other natural compounds of polyketide origin. To date total syntheses of erythromycin A (1)[2-4], the aglycones of erythromycin A (3)[5-8] and erythromycin B (4)[9], have been accomplished and efficient methods have been found for the solution of many synthetic problems in the chemistry of macrolide antibiotics.

In this paper we wish to report the synthesis of two basic aglycones of erythromycins A and B, erythronolides A (3) and B (4) by skeleton assembly in the (C_9 - C_{13}) + (C_7 - C_8) + + (C_1 - C_6) sequence.

It was proposed (see retrosynthetic scheme) to carry out the synthesis of the target aglycones 3 and 4 via (9S)-dihydro derivatives 5 and 6, the hydroxyl group at C-9 in which can be selectively oxidised[9,10]. This would allow to make use, at the step of lactonization, of 3,5:9,11-bis(cyclo)acetal derivatives 7 and 8 to ensure conformational arrangement of the carbon chain of the seco-acid required for efficient macrolactonization[2,7]. Traditional acetonide was used as a protection for the 3,5-glycol system and p-methoxybenzylidene acetal as a protection for 9,11-glycol. Particular attention was paid to creation of the configuration of the acetal centre of the p-methoxybenzylidene acetal, as specified in the Scheme; with

Retrosynthetic scheme



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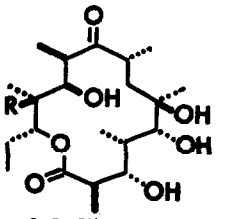

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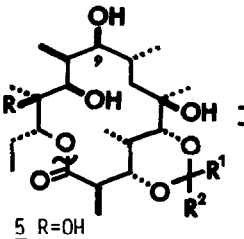

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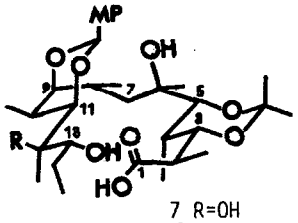

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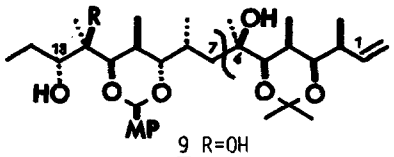
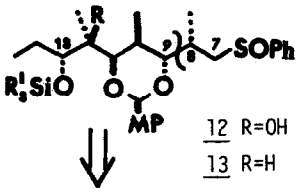
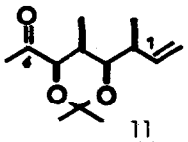
8 R=H



9 R=OH
10 R=H



12 R=OH
13 R=H



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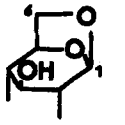

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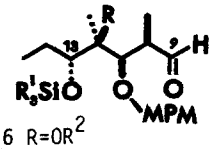
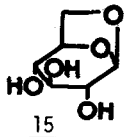


16 R=OR^2
17 R=H

18 R=OH
19 R=H



15

the other configuration of this centre,steric hindrance between the MP-group and the hydroxyl at C-6 would preclude the arrangement of the carbon chain required for macrolactonization of 7(cf., however[6]).

Olefins 9 and 10 serve as precursors of seco-acids 7 and 8. Synthesis of derivatives of this type can be performed by addition of an anion generated from sulfoxides 12 or 13 to ketone 11, which is a common C_1 - C_6 segment of erythronolides A and B. In turn, the chelate-controlled syn-selective addition of the C_7 - C_8 segment to the C_9 - C_{13} segments of erythronolides A and B (aldehydes 16 and 17 respectively) yields sulfoxides 12 and 13. Structures 16 and 17 stereochemically correlate with thebicyclic derivatives 18 and 19, while the C_1 - C_6 segments correlates with the bicyclic derivative 14. In our previous reports[11-13] it was shown that thestructures 14, 18, and 19, can be prepared through stereoselective conversions of levoglucosan 15.

Thus, the total synthesis of erythronolides A and B according to this scheme involves as its first step the preparation of the C_1 - C_6 segment (methyl ketone 11) and the C_9 - C_{13} segments of erythronolide A (aldehyde 16) and erythronolide B (aldehyde 17).

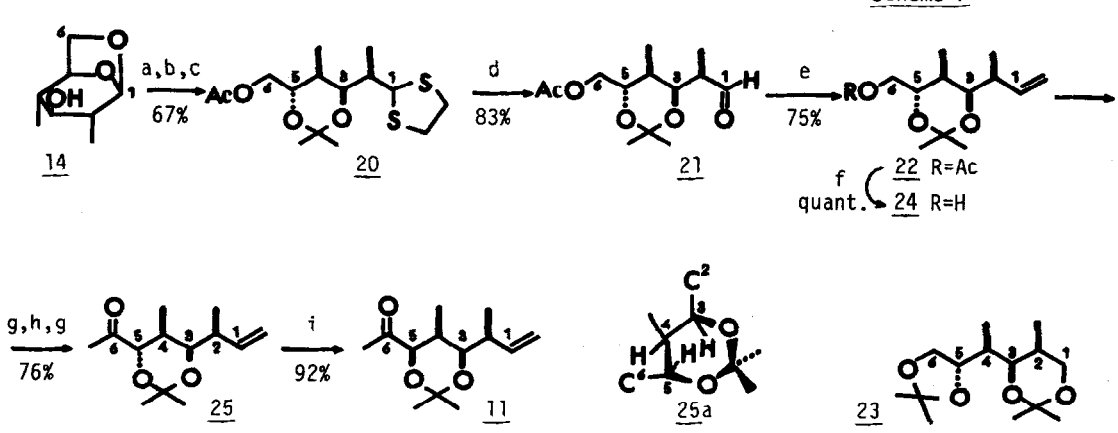
Synthesis of C_1 - C_6 segments of erythronolides A and B (methyl ketone 11)

Bicyclic derivative 14, which can be synthesized in five steps from levoglucosan in 54% total yield[11], served as the starting material for the synthesis of the C_1 - C_6 segment of erythronolides A and B (see Scheme 1). Derivative 14 was successively subjected to mercaptolysis, selective acetylation followed by isopropylidenation to give 20, hydrolysis of the latter under the action of $HgCl_2$-$CaCO_3$ in aqueous acetonitrile at room temperature yielded aldehyde 21. It should be emphasized that dithiolane carbonyl protection in 20 has some advantages, particularly in hydrolysis step, and ensures two-fold increase in total yield of aldehyde 21, as compared with dithiane carbonyl protection.

Reaction of aldehyde 21 with $Ph_3P{=}CH_2$ (1,5 equiv) in boiling benzene gave a mixture of olefin 22 and its deacetylated derivative 24; directed treatment of the mixture with MeONa gave the unsaturated alcohol in high yield. In order to prove the retention of configuration of C-2 in methylene derivative 22, which was prepared from -configurationally unstable aldehyde, a sample of 22 was converted by the standart procedure to bis-acetonide 23. The coupling constants, $J_{1a,2}$ = 2,7 Hz, $J_{1e,2}$ = 1,7 Hz and $J_{2,3}$ = 2,3 Hz, in the ^{1}H-NMR spectrum of 23, proved unambiguously that the configuration of C-2 was unaffected upon conversion of 14 into 22.

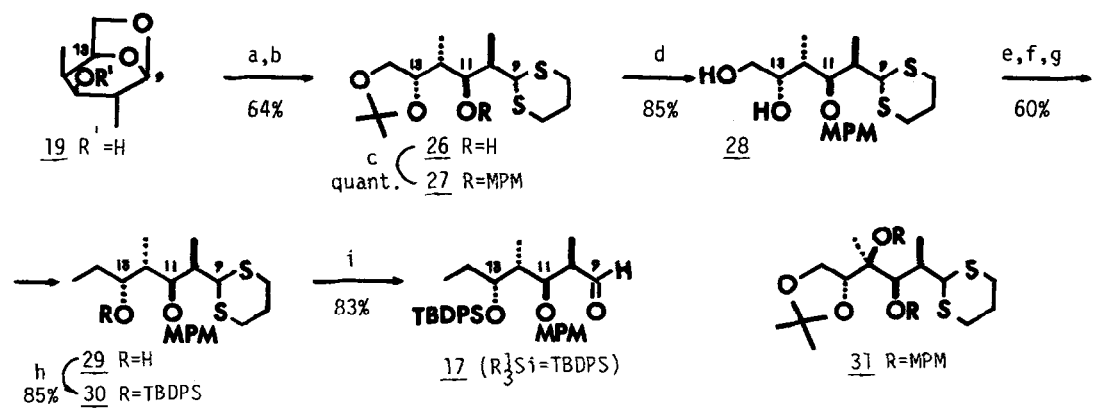
Swern oxidation[14] of alcohol 24 followed by addition of MeMgCl to the resulting aldehyde and subsequent oxidation of intermediate alcohol under the same conditions[14] gave ketone 25. The coupling constants, $J_{3,4}$ = 4 Hz, $J_{4,5}$ = 7 Hz, in the ^{1}H-NMR spectrum of 25 and n.O.e. between the axial Me group (resonating at lower fields) of the O-isopropylidene moiety and H-3 show that the 1,3-dioxane ring in 25 adopts the unfavourable boat or a distorted boat conformation 25a (Scheme 1). In fact, mild alkaline isomerization of ketone 25 at C-5 proceeds in almost quantitative yield to give thermodynamically more stable ketone 11 (cf.,[15]) with the chair ring conformation of the dioxane ring ($J_{3,4}$ = $J_{4,5}$ = 2,2 Hz; n.O.e. between H-3, H-5, axial Me group of O-isopropylidene moiety).

Scheme 1



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.$Ph_3P{=}CH_2/C_6H_6$, Δ; f.MeONa/MeOH; g.$(COCl)_2$,DMSO,$Et_3N/CH_2Cl_2$; h.MeMgCl; i.$K_2CO_3$/MeOH.

Scheme 2



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,Δ; e.TsCl-Py; f.K_2CO_3/MeOH; g.MeMgCl-CuCl·Me_2S/THF; h.TBDPS-OClO$_3$,Et_3N/CH_2Cl_2; i.$HgCl_2$-$CdCO_3$/Me_2CO-H_2O,Δ.

Ketone 11 represents the properly protected and functionalized C_1 - C_6 segment of erythronolides A and B.

Synthesis of C_9 - C_{13} segments of erythronolides A and B (aldehydes 16 and 17)

As a starting material in the synthesis of aldehyde 17 (R'_3Si=TBDPS), the C_9 - C_{13} segment of erythronolide B, was used the bicyclic derivative 19 (R=H) which has been synthesized[12] by deoxygenation of the xanthate ester of the respective tertiary alcohol or by hydrozirconation of the respective 4-C-methylene derivative followed by protolysis. Mercaptolysis of 19 and subsequent acetonation gave predominantly the dioxolane derivative 26 and the free hydroxyl group was protected as MPM-ether 27. Mild acid hydrolysis of 27 gave diol 28, which was converted[16] into the hydroxyl derivative 29 by successive tosylation of 28, formation of the α-oxide, and opening of the latter with MeMgCl in the presence of a copper(I) salt. It should be pointed out that the above intermediates are extremely labile, and all operations were carried out without isolation of individual compounds and in a very short time.

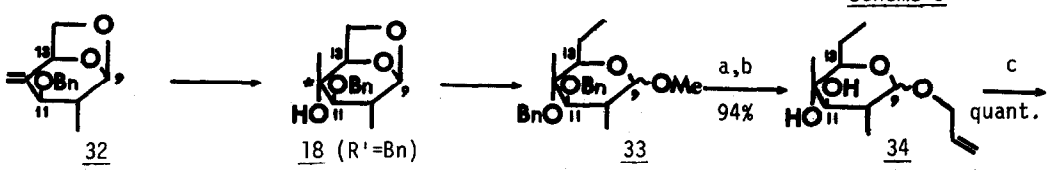
Protection of the hydroxyl group in 29 as tert-butyldiphenylsilyl (TBDPS) ether was accomplished by treatment with tert-butyldiphenylsilyl perchlorate (generated in situ from TPDPSiH and $TrClO_4$ [17], and the resulting thioacetal 30 was subjected to Hg^{2+} -assisted hydrolysis to give aldehyde 17(R'_3Si=TBDPS) representing the C_9 - C_{13} segment of erythronolide B. It is noteworthy that tert-butyldimethylsilyl ether (TBS) protection gave an analogue of aldehyde 17 (R'_3Si=TBS) in about half the yield.

The C_9 - C_{13} segment of erythronolide A (aldehyde 16 (R'_3Si=R^2=TBS)) was prepared starting from the bicyclic derivative 18 (R^1=Bn). Synthesis of compound 18 and further conversions into methyl glycosides 33 have been reported by as elsewhere[13]. In the present work we employed a highly improved preparation of derivative 18 (R^1=Bn) starting from methylene derivative 32. This involves stereospecific hydroxylation of 32 with OsO_4 - N-oxide-N-methyl morpholine[18] and conversion of the resultant diol into the desired alcohol 18 via an oxirane ring closure/ring opening sequence (see Experimental). Hg^{2+}-assisted hydrolysis of the dithiane derivative 31(prepared from 18 in a synthetic sequence similar to that for transformation 19⟶30) into the corresponding aldehyde resulted unfortunately in formation of furanose derivative due to deprotection of the tertiary hydroxyl, hence this route was abandoned. As a consequence, we chose a more reliable method to transform the bicyclic structure 18(R^1=Bn) into aldehyde 16 (R'_3Si=R^2=TBS).

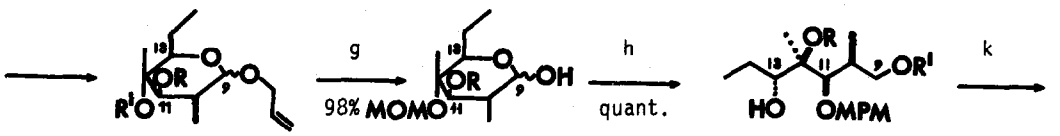
Initially, compound 18(R^1=Bn) was transformed[13] to a mixture of methyl glycosides 33[13]. Next, methyl glycosides 33 were subjected to debenzylation and, further, transglycosylation with allyl alcohol in the presence of catalytic amounts of pyridinium p-toluenesulfonate(PPTS) (Scheme 3) to afford a mixture of unprotected allyl glycosides 34. To facilitate control over conversions by spectral and chromatographic methods the synthesis of the segment was initially performed with the individual allyl α-glycoside (α-34).

Selective acetylation of α-34 with Ac_2O in pyridine afforded monoacetyl derivative α-35 in quantitative yield. Conversion of α-35 in methoxymethyl (MOM) ether α-36 followed by deacetylation proceeded also in quantitative yields to give monosubstituted derivative α-37, which, after alkylation with p-methoxybenzyl chloride, provided a strategically important

Scheme 3



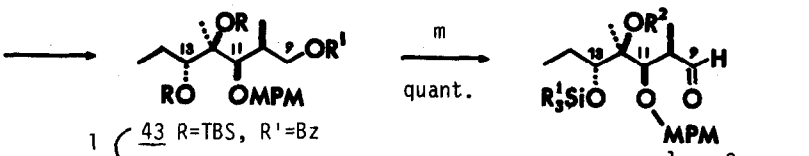
32 18 (R'=Bn) 33 34



d 35 R=Ac, R'=H
e 36 R=Ac, R'=MOM
f 37 R=H, R'=MOM
38 R=MPM, R'=MOM 96.5% from 35

39

i 40 R=MOM, R'=H
j 41 R=MOM, R'=Bz
42 R=H, R'=Bz



l 43 R=TBS, R'=Bz
44 R=TBS, R'=H quant.from 41

16 (R^1_3Si=R^2=TBS)

a.Ra-Ni/EtOH,Δ; b.allOH,PPTS,Δ; c.Ac_2O-Py,Δ; d.MOM-Cl,i-Pr_2NEt/CH_2Cl_2,Δ; e.NaOMe/MeOH; f.NaH-MPMCl/DMF; g.1.t-BuOK/DMSO; 2.$Hg(OAc)_2/Me_2CO$-H_2O; h.$NaBH_4$/EtOH-H_2O; i.BzCl/Py; j.HCl-THF,Δ; k.TBSOTf,Et_3N/CH_2Cl_2,Δ; l.NaOH/MeOH-H_2O; m.DMSO-$(COCl)_2$,Et_3N/CH_2Cl_2.

11-O-MPM protection. The resulting selectively protected allyl glycoside α-38 was converted by the known method[19] to the free monosaccharide 39, which was reduced with $NaBH_4$ in aqueous ethanol to give in quantitative yield the selectively protected tetrol 40. As individual steps have high yields and are free from by-products the transformation 34→40 can be performed starting from a mixture of anomeric allyl glycosides without recourse to chromatography, thus greatly facilitating the preparation of large amounts of 40.

The tetrol 40 was then to be converted to the C_9 - C_{13} segment of erythronolide A. At first this step of the synthesis was proposed to employ an aldehyde with all hydroxyl groups selectively protected. To this effect, tetrol 40 was subjected to benzoylation at its primary hydroxyl group, the resulting monobenzoate 41 was subjected to silylation (TBSOTf, Et_3N/CH_2Cl_2), then the benzoyl group was removed and the free primary hydroxyl group was oxidised[14]. The prepared aldehyde 16(R^1_3Si=TBS,R^2=MOM) was used for creation of the carbon chain of seco-acid 7; however, the MOM-protection of the tertiary hydroxyl group caused unexpected difficulties in one of the later steps, and so we had to dispense with this protection.

Mild acid hydrolysis removed MOM-protection from benzoate 41 to give diol 42, which was subjected to stepwise silylation at the secondary hydroxyl group, and then, under more drastic conditions, at the tertiary one. The attempt undertaken to perform one-step bis-silylation of diol 42 was unsuccessful. Debenzoylation of the bis-TBS ether 43 gave monohydroxyl derivative 44 in quantitative yield starting from 41. Swern oxidation[14] of 44 gave aldehyde 16 (R^1_3Si=R^2=TBS) representing the C_9 - C_{13} segment of erythronolide A.

Synthesis of C_7 - C_{13} segments of erythronolides A and B

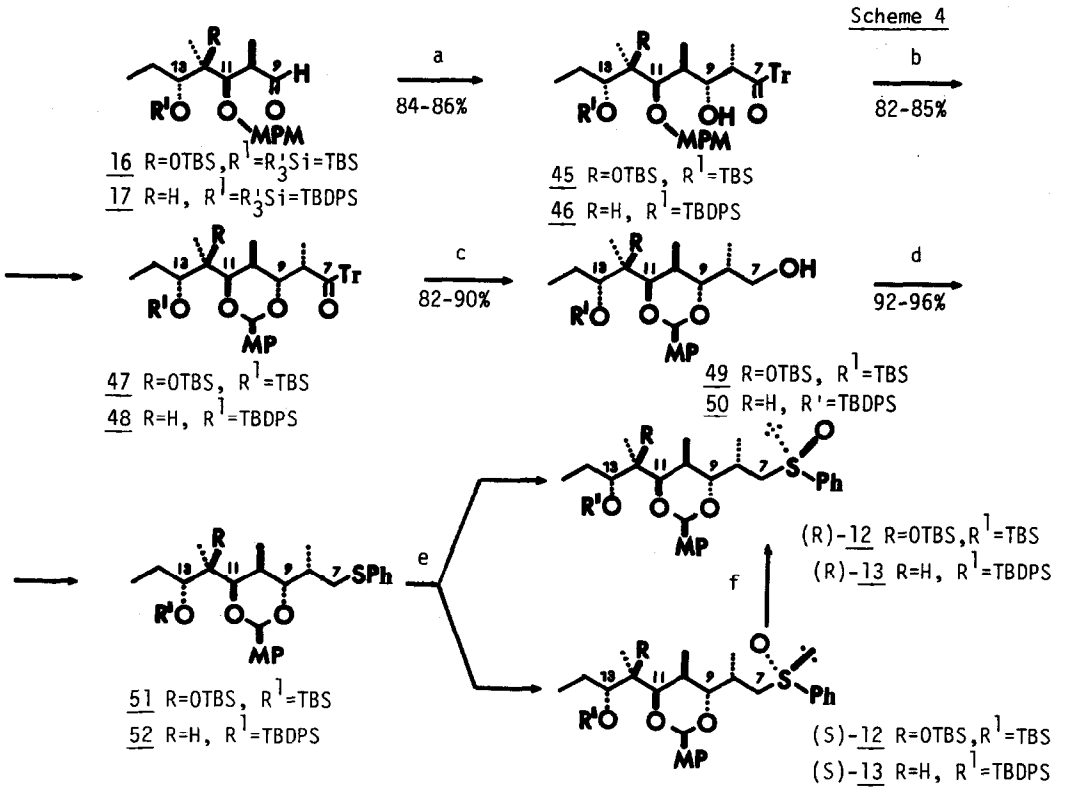
Next step in the synthesis was the stereoselective coupling of the two-carbon C_7 - C_8 segment with C_9 - C_{13} segments of erythronolides A and B, 16 and 17, to give the C_7 - C_{13} segments required for further coupling with the C_1 - C_6 segment. This step of the synthesis is most important since it involves creation of two new chiral centres, C-8 and C-9, in the absence of cyclic stereocontrol of the reactions, the latter operating in creation of stereochemistry of the segments 11, 16, and 17. A study of several syn-selective aldol and crotyl-metal reagents showed that this problem can be solved most effectively through addition of lithium (Z)-enolate of ethyl trityl ketone 20 to aldehydes 16 and 17, which affords the desired (8,9-syn-9,10-anti)-aldols 45 and 46 as the sole products (Scheme 4).

According to available data the aldol 45 or 46 is the product of the kinetically controlled reversible reaction; the rate of equilibration of this reaction increases highly with temperature. So, even a short heating of the reaction mixture prior to hydrolysis (as, e.g., for several seconds sampling for TLC) gave an altogether different result than that obtained if the reaction was quenched at -78°C. Heating shifts the equilibrium towards predominant formation of the other product, probably non-chelate (8,9-syn-9,10-syn)-aldol.

(8,9-syn-9,10-anti)-Structure of the adducts 45 and 46 is evident from the coupling constants $J_{8,9}$ = 10 Hz, $J_{9,10}$ = 1 Hz in the ^{1}H-NMR spectra and is in full agreement with the known data on addition of lithium (Z)-enolates of ketones to ß-alkoxy aldehydes[21].

Treatment of aldol 45 (and 46) with DDQ[22] readily gave high yield of 9,11-O-p-methoxybenzylidene derivative 47 (and 48) as a single (and only that required, see above) isomer at

Scheme 4



16 R=OTBS, $R^1=R'_3Si$=TBS
17 R=H, $R^1=R'_3Si$=TBDPS

45 R=OTBS, R^1=TBS
46 R=H, R^1=TBDPS

47 R=OTBS, R^1=TBS
48 R=H, R^1=TBDPS

49 R=OTBS, R^1=TBS
50 R=H, R'=TBDPS

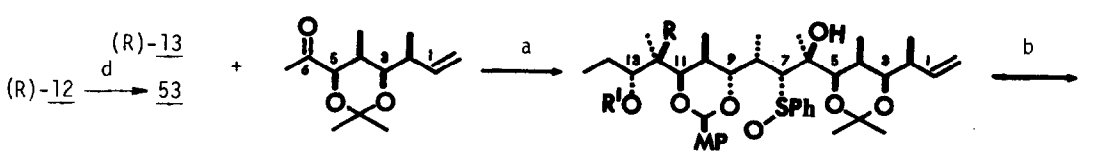
51 R=OTBS, R^1=TBS
52 R=H, R^1=TBDPS

(R)-12 R=OTBS, R^1=TBS
(R)-13 R=H, R^1=TBDPS

(S)-12 R=OTBS, R^1=TBS
(S)-13 R=H, R^1=TBDPS

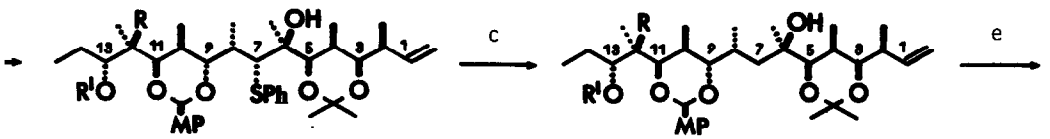
a.n-BuLi-EtCOTr(20)/THF,-78°; b.DDQ/CH_2Cl_2,MS 3Å; c $LiBHEt_3$/THF; d.Ph_2S_2-n-Bu_3P/Py; e.MCPBA/EtOAc,-40°; f.TFAA-2,4,6-collidine/THF,-60°, then THF-H_2O.

Scheme 5



54 R=OH, R^1=H
55 R=H, R^1=TBDPS

Scheme 5 (continuation)



56 R=OH, R'=H

57 R=H, R'=TBDPS

c

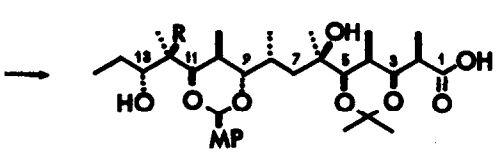
9 R=OH, R'=H

58 R=H, R'=TBDPS

10 R=R'=H

e

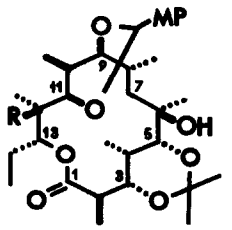
d



7 R=OH

8 R=H

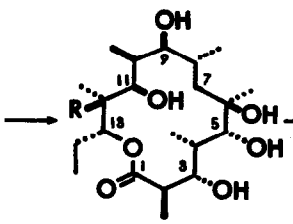
f



59 R=OH

60 R=H

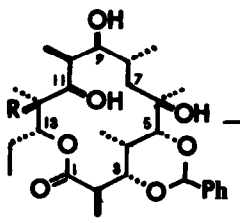
g



61 R=OH

62 R=H

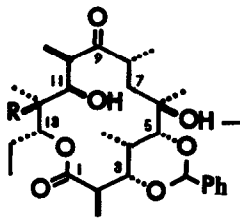
h



5 R=OH

6 R=H

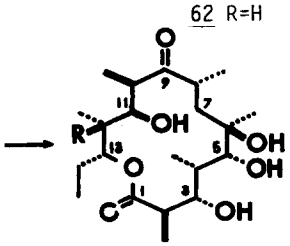
i



63 R=OH

64 R=H

j



3 R=OH

4 R=H

a. LDA/THF,-78°; b.NaI-TFAA/Me_2CO; c.Na-NH_3/Et_2O; d.n-$Bu_4NF \cdot 3H_2O$/THF,Δ; e.1.O_3/CH_2Cl_2-Py; 2.MCPBA/THF--pH 7; f.bis-(1-isopropyl-4tert-butylimidazolyl--2-sulfide) - Ph_3P/$PhCH_3$,Δ,C 10^{-3}; g.TFA-MeCN-H_2O; h.$PhCH(OMe)_2$-CSA/CH_2Cl_2; i.PCC/CH_2Cl_2-MS 3A; j.H_2-Pd/ /MeOH (63 → 3); AcOH-H_2O,Δ (64 → 4).

the acetal centre. Thus, MPM-protection ensured simplicity and selectivity of these conversions[22].

The coupling constants ($J_{9,10}$ = 0.5 Hz, $J_{10,11}$ = 2 Hz) in the ^{1}H-NMR spectra of 47 and 48, and n.O.e. between the acetal proton and H-11 evidence in favour of the suggested confiration of the acetal centre and a slightly distorted chair conformation of the 1,3-dioxane ring.

Reductive splitting of the trityl ketones 47 and 48 with $LiBHEt_3$[20] gave alcohols 49 and 50, which under the action of the Ph_2S_2-Bu_3P system[23] were readily converted into phenyl sulfides 51 and 52. Oxidation of 51 and 52 with MCPBA gave an easily separable mixture of the required sulfoxides 12 and 13, representing the C_7 - C_{13} segments of erythronolides A and B respectively. The prepared sulfoxides of each series, which are isomers at the sulfur atom, were separated by chromatography; the configuration of the sulfur atom was assigned on the basis of the specific rotation of individual compounds (cf.[24]).

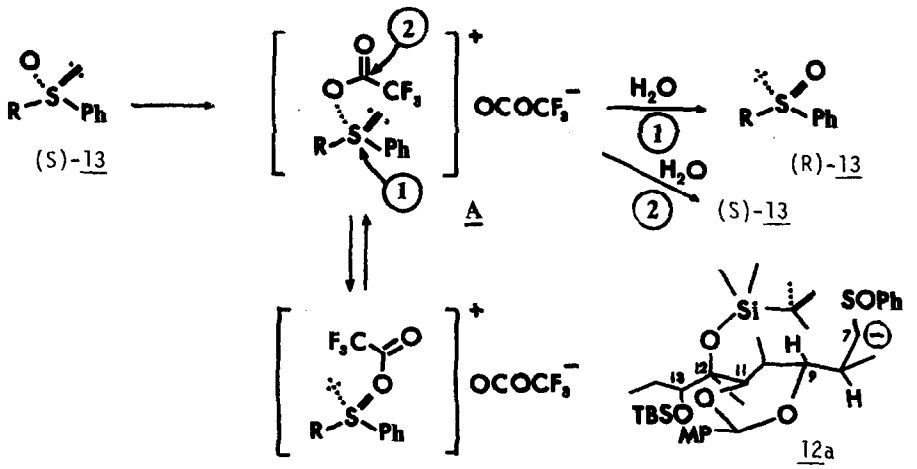
Coupling of C_1 - C_6 and C_7 - C_{13} segments, synthesis of seco-acids of erythronolides A and B, macrolactonization, synthesis of erythronolides A and B

Coupling of the C_1 - C_6 and C_7 - C_{13} segments of erythronolides A and B should result in creation of the tertiary chiral centre C-6, and some preliminary studies concerning addition of metallic compounds to methyl ketone 11 and literature analogies[15] allowed us to expect the reaction to proceed in the desire direction.

The pure isomers, (R)- and (S)-sulfoxides 13 (the C_7 - C_{13} segment of erythronolide B) were lithiated and coupled separately with methyl ketone 11. As it turned out, minor (R)-sulfoxide gave a mixture of two products in 7:1 ratio, whereas major (S)-isomer 13 did not react at all. Analysis of the literature data concerning the reactions of sulfoxides of this type[25] does not provide satisfactory explanation for such a dramatic difference in the behaviour of the (R)- and (S)-isomer 13. So, we had find a new approach which would allow to synthesize the required reactive (R)-sulfoxide 13 in higher yield.

Since all attempts to change the selectively of oxidation of sulfoxide 52 in favour of the desired (R)-isomer were unsuccessful, we have elaborated a smooth and convenient method of sulfoxide isonerization. Thus, treatment of (S)-13 with TFAA (THF, 2,4,6-collidine 3 eq., -78°C, 20 min) followed by addition of water gave a mixture (R)- and (S)-13 in 77:23 ratio. The reaction proceeds evidently via formation of the trifluoroacetoxysulfonium ion A, which is subjected to attack by H_2O at the sulfur atom to give the isomeric sulfoxide. The presence of (S)-13 in the reaction mixture can be rationalised by either a) an attack of H_2O on carbonyl of the trifluoroacetoxy moiety, or b) racemization of the sulfoxonium ion A via formation of a symmetrical tetracoordinated sulfurane.

In this way (oxidation, separation, and isomerization of the (S)-isomer) sulfide 52 was converted in high overall yield to (R)-sulfoxide 13. The reaction of the latter with ketone 11 gave two products with high selectivity. The main coupling product 55 was obtained in 88% yield (based on consumed (R)-13).



This should have, as expected on the basis of literature data[15,21], the required configuration of the C-6 centre and this was confirmed later by the structure of the macrolactones derived therefrom and also by an independent synthesis of a derivative of the seco-acid of erythronolide B 10 from a segment possessing the authentic configuration of this centre[26].

The coupling product 55 proved to be highly labile compound and so it was immediately deoxygenated to sulfide 57[27]. Desulfuration of 57 with 2 eq. Na in liquid NH_3 at -78°C using ether as cosolvent gave compound 58 in a good yield which was subjected to desilylation to afford 10, which is the precursor of (9S)-dihydroerythronolide B seco-acid.

By similar treatment the isomeric sulfoxides 12 (the C_7 - C_{13} segment of erythronolide A) were separated and (S)-sulfoxide was isomerized into a mixture of (R)- and (S)-12 in 75 and 22% yield, respectively. As earlier, the configuration of the sulfur atom was assigned on the basis of the specific rotation of the individual isomers[24].

An attempt to assemble the anion of sulfoxide (R)-12 (the C_7 - C_{13} segment of erythronolide A) with methyl ketone 11 (the C_1 - C_6 segment) under the conditions specified above was unsuccessful. An analysis of space molecular models of the carbon chain conformation of sulfoxide (R)-12, which is consistent with its ^{1}H-NMR spectrum, led to the suggestion that the absence of addition products may be due to steric overcrowding at the reaction centre caused, on the one hand, by the methyl group at C-8 and, on the other hand, by the 12-O-TBS moiety, as shown on structure 12a. Therefore sulfoxide (R)-12 was desilylated and the trianion of the resulting sulfoxide 53 reacted with methyl ketone 11. The reaction mixture contained, together with an excess of ketone 11, the unreacted sulfoxide 53 and the adduct 54 in ~1:1 ratio, as well as traces of two more products. However, chromatographic separation gave the adduct 54 in only 23% yield or, with respect to the reacted sulfoxide 53(45%), this amounts to total 41% yield. Taking into account the observed selectivity of the reaction and the degree of conversion of 53, the only feasible explanation for the low yield of adduct 54 may be decomposition of 54 during chromatography. The lability of adduct 54 seems to be essentially hig-

her than that of 55 (see above). Deoxygenation[27] of sulfoxide 54 gave sulfide 56, which was converted, like 57, to the key intermediate 9, the precursor of (9S)-dihydroerythronolide A seco-acid.

Further conversions of derivative 9 and 10 to the selectively protected bis-(cyclo)-acetal derivatives of the seco-acids of (9S)-dihydroerythronolides A (7) and B (8) was accomplished by ozonolysis of the double bond followed by oxidation of the resulting aldehydes with MCPBA in the presence of the phosphate buffer. The obtained derivatives of the seco-acids 7 and 8 were converted to activated thiol esters and subjected to lactonization (Scheme5) by Corey's modified method[28], i.e. by boiling of highly dilute solutions ($C = 10^{-3}$ M, 8 h for erythronolide B and 20 h for erythronolide A).

The macrolides 59 and 60, obtained in excellent yield (72% in both cases) were subjected to acid hydrolysis (TFA-CH_3CN-H_2O) to afford (9S)-dihydroerythronolides A (61) and B (62) which proved to be identical in all respects (^{1}H-NMR, $[\alpha]_D$, mp and chromatographic mobility) with those obtained from the natural erythromycin A[29] and B[30].

Conversion of the dihydro-derivative 61 into erythronolide A via selective benzylidenation of the 3,5-diol moiety in 5, oxidation of the hydroxyl group at C-9, and hydrogenolysis of the acetal has been published elsewhere[6].

In a similar way, (9S)-dihydroerythronolide B 62 via the 3,5-O-benzylidene derivative 6, oxidation of the hydroxyl group at C-9 (64) followed by removal of acetal protection, was converted in high total yield into erythronolide B 4 which proved to be identical in all respects with the natural sample.

Thus, a highly efficient unified scheme of synthesis of erythronolides A and B starting from levoglucosan by the coupling of segments in (C_9 - C_{13}) + (C_7 - C_8) + (C_1 - C_6) sequence has been achieved.

EXPERIMENTAL

Melting points were measured in a capillary and are uncorrected. Specific rotations were measured with a JASCO DIP-360 polarimeter for solutions in chloroform unless otherwise stated. ^{1}H-NMR Spectra were recorded on a Bruker WM-250 instrument with samples in $CDCl_3$ unless otherwise stated. Signals in the ^{1}H-NMR spectra were assigned by using sequential, selective spin-decoupling experiments performed by the difference mode.

All reactions with air- and moisture-sensitive compounds were conducted under positive argon pressure in an oven- or flame-dried glassware connected and evacuated hot prior filling with argon.

Reactions were monitored by TLC on silica gel plates (Merck). The components were detected by the plates with 5% H_2SO_4 in MeOH followed by heating to 200°C. Extractive work-up involved dilution of a reaction mixture with an appropriate solvent (normally $CHCl_3$ or Et_2O) and washing with either 1 N HCl to remove basic concomitants or with $NaHCO_3$ solution to remove acidic ones followed by washing with water, brine, and drying by filtering the solutions through a pad of anh. Na_2SO_4. Finally, the solutions were concentrated by rotary evaporation (bath temperature ca. 40°C).

Reaction mixtures were separated by medium pressure liquid chromatography on silica gel Silpearl (25-40um) in the isocratic mode. Detection was monitored by a Knauer 88.00 refractometer.

Solvents were distilled under argon from a proper drying agent (CaH_2, $LiAlH_4$).

Dithioacetal 20. To a solution of 3.967 g (25.08 mmol) of 14 and 3.543 g (37.62 mmol, 1.5 eq., 3.155 ml) of 1,2ethanedithiol in 25 ml of CH_2Cl_2 was added 10.678 g (75.23 mmol, 3 eq., 9.285 ml) of $BF_3 \cdot OEt_2$. The mixture was kept at RT for 2 h, cooled to -40°C, and then 23.8 g (301 mmol, 12 eq., 24.4 ml) of pyridine and 12.8g(125.4 mmol, 5 eq., 11.8 ml) of Ac_2O were added. The mixture was kept at -10°C for 2 h and quenched with 5 ml of MeOH. After extractive work-up the residue (R_f 0.57, EtOAc) was dissolved in 40 ml acetone-DMP (1:1) mixture and 0.5 g of $TsOH \cdot H_2O$ was added to the solution. The mixture was kept at RT for 30 min, neutralized with solid $NaHCO_3$ and evaporated.After extractive work-up the residue was chromatographed (heptane-EtOAc 4:1) to give 20 (4.75 g, 56.6%), syrup, $|\alpha|_D$ -29° (C1.0); ^{1}H-NMR:δ 0.97 (3H, d: 6.8 Hz, Me-4), 1.12 (3H, d: 6.5 Hz, Me-2), 1.35 and 1.37 (6H, 2s. $-OCMe_2O$), 1.83 (1H, ddq: 6.8, 4.4, 7 Hz, H-4), 2.07 (1H, ddq: 3.3, 9.5, 6.5 Hz, H-2), 2.10 (3H, s, MeCOO-6), 3.20 (4H, m, $-SCH_2CH_2S-$), 3.50 (1H, ddd: 7, 7, 3 Hz, H-5), 3.58 (1H, dd: 9.5, 4.4 Hz, H-3), 4.07 (1H, dd: 3, 12 Hz, H-6), 4.17 (1H, dd: 7, 12 Hz, H-6'), 4.68 (1H, d: 3.3 Hz, H-1).

Aldehyde 21. A suspension of 4.81 g (14.38 mmol) of 20, 14.39g(143.39 mmol, 10 eq.) of $CaCO_3$ and 19.52 g (71.9 mmol, 5 eq.) of $HgCl_2$ in 75 ml of MeCN-H_2O (4:1) was stirred at RT for 84 h. The precipitate was filtered off through a celite and the filtrate was extracted with ether. The extract was washed with water, brine, dried, and evaporated. Chromatography of the residue (hexane-EtOAc 4:1) gave 0.36 g of 20 (7.5%) and 2.80 g of 21 (77% with respect to consumed 20), syrup, $|\alpha|_D$ +35.4° (C 1.0); ^{1}H-NMR:δ 0.87 (3H, d: 7 Hz, Me-4), 1.16 (3H, d: 7 Hz, Me-2), 1.35 (6H, s, $-OCMe_2O-$), 2.07 (3H, s, MeCOO-6), 1.90 (1H, ddq: 5, 8, 7 Hz, H.4), 2.62 (1H, ddq: 2, 10, 7 Hz, H-2), 3.50 (1H, ddd: 3, 7.2, 8 Hz, H-5), 3.95 (1H, dd: 10, 5 Hz, H-3), 4.03 (1H, dd: 12, 7.2 Hz, H-6), 4.16 (1H, dd: 12, 3 Hz, H-6'), 9.68 (1H, d: 2 Hz, H-1).

Compounds 22 and 24. To a stirred suspension of 6.43 g (18 mmol, 2.5 eq.) of methyltriphenylphosphonium bromide in 35 ml of PhH was added 10.8 ml of 1.32 N solution of n-BuLi in hexane (14.2 mmol, 2 eq.). The mixture was stirred at RT for 10 min, heated to boiling and a solution of 1.836 g (7.107 mmol) of 21 in 10 ml of PhH was added. The mixture was refluxed for 10 min. After cooling an excess of phosphorane was decomposed with 0.5 ml of acetone.

Because two products 22, R_f 0.64 and 24, R_f 0.38 (heptane-ether 2:1) in approximately 3:2 ratio were detected in the crude reaction mixture, 40 ml of MeOH and 0.5 ml of 2 N MeONa were added to complete deacetylation. After 30 min water was added and the mixture was subjected to extractive work-up. Chromatographic purification of the residue (pentane-ether 1:1) gave 1.182 g (77.6%) of 24, syrup, $|\alpha|_D$ -17.2° (C 1.0); ^{1}H-NMR:δ 0.92 (3H, d: 7 Hz, Me-4), 1.05 (3H, d: 7 Hz, Me-2). 1.35 and 1.38 (6H, 2s, $-OCMe_2O-$), 1.74 (1H, ddq: 7, 4.6, 7 Hz, H-4), 1.98 (1H, m, OH-6), 2.32 (1H, dddq: 10.7, 8, 1, 7 Hz, H-2), 3.42 (1H, ddd: 3, 7, 7 Hz, H-5), 3.47 (1H, dd: 10.7, 4.6 Hz, H-3), 3.54 (1H, dd: 11.7, 3 Hz, H-6), 3.63 (1H, dd:

11.7, H-6'), 5.03 (1H, dd: 10.7, 2 Hz, H-1'cis), 5.11 (1H, ddd: 2, 1, 17.5 Hz, H-1'trans). 5.56 (1H, ddd: 10.7, 17.5, 8 Hz, H-1).

The analytic sample of 22 was isolated as a syrup, $|\alpha|_D$ 0° (c 1.0); ^{1}H-NMR:δ 0.95 (3H, d: 6.8 Hz, Me-4), 1.00 (3H, d: 6.7 Hz, Me-2), 1.36 and 1.37 (6H, 2s, -OCMe$_2$O-), 1.71 (1H, ddq: 4.5, 11, 6.8 Hz, H-4), 2.08 (3H, s, MeCOO-6), 2.32 (1H, dddq: 8, 1.5, 10.8, 6.7 Hz, H-2), 3.50 (1H, dd: 10.8, 4.5 Hz, H-3). 3.52 (1H, ddd: 22, 8, 3 Hz, H-5), 4.02 (1H, dd: 12, 8 Hz, H-6), 4.15 (1H, dd: 3, 12 Hz, H-6'), 5.03 (1H, dd: 2, 10.7 Hz, H-1'cis), 5.11 (1H, dd: 2, 17.5 Hz, H-1'trans), 5.65 (1H, ddd: 8, 10.7, 17.5 Hz, H-1).

Methyl ketone 25. To 17 ml of stirred 0.64 M $(COCl)_2$ solution in CH_2Cl_2 (10.88 mmol, 1.28 eq.) was added 8.5 ml of 2.38 M solution of DMSO in CH_2Cl_2 (20.23 mmol, 2.38 eq.) over 10 min at -60°C. The mixture was stirred at this temperature for 10 min and then a solution of 1.82 g (8.493 mmol) of 24 in 15 ml of CH_2Cl_2 was added over 5 min. After an additional 15 min 4.36 g (43 mmol, 3.93 eq., 6 ml) of Et_3N was added; the reaction mixture was warmed to -5°C and 60 ml of 1 N HCl was added. After exreactive work-up the residue (intermediate aldehyde, R_f 0.47 benzene-ether 9:1) was dissolved in 10 ml of THF. The solution was cooled to -70°C and 6 ml of 1.95 g MeMgCl solution in THF (11.7 mmol, 1.38 eq.) was added. The mixture was warmed to RT and after additional 30 min was quenched with sat. NH_4Cl soln. The precipitate was filtered off and the solution was evaporated to dryness. The residue was oxidized according the procedure described above with the same amounts of reagents. Chromatography (hexane-EtOAc 11:1) gave ketone 25, 1.262 g (65.7% with respect to consumed alcohol 24), syrup, $|\alpha|_D$ -73.2° (C 1.0); ^{1}H-NMR:δ 1.03 (6H, 2d: 6.8 Hz, Me-2 and 4), 1.37 and 1.39 (6H, 2s, -OCMe$_2$O-), 2.09 (1H, ddq: 4, 7, 6.8 Hz, H-4), 2.31 (1H, m: 10.5 , 8.2, 6.8 Hz, H-2), 2.33 (3H, s, Me-6), 3.50 (1H, dd: 4, 10.5 Hz, H-3), 3.71 (1H, d: 7 Hz, H-5), 5.03 (1H, dd: 2, 10 Hz, H-1'cis), 5.11 (1H, ddd: 1, 2, 17 Hz, H-1'trans), 5.63 (1H, ddd: 8.2, 10, 17 Hz, H-1). The n.O.e. between acetyl moiety methyl group protons (1.39 ppm) and H-3 (3.71 ppm) in 25 was observed.

Methyl ketone 11. To a solution of 0.4955 g (508 μmol) of methyl ketone 25 in 5 ml of MeOH was added 0.2 g (1.45 mmol, 2.85 eq.) of K_2CO_3. The mixture was stirred at RT for 1 h, diluted with water and subjected to extractive work-up followed by chromatography (hexane-EtOAc 11:1) to give 0.47 g (95%) of 11, syrup, $|\alpha|_D$ +40.2° (C 1.0); ^{1}H-NMR:δ 0.80 (3H, d: 6.5 Hz, Me-4), 1.03 (3H, d: 6.5 Hz, Me-2). 1.41 (3H, s, Me-ax of -OCMe$_2$O-), 1.49 (3H, s, Me-eq of -OCMe$_2$O-), 2.00 (1H, ddq: 2.2, 2.2, 6.5 Hz, H-4), 2.18 (3H, s, Me-6), 2.28 (1H, dddq: 0.5, 6.5, 8.5, 10 Hz, H-2), 3.51 (1H, dd: 2.2, 10 Hz, H-3), 4.24 (1H, d: 2.2 Hz, H-5), 5.04 (1H, dd: 2, 10 Hz, H-1'cis), 5.10 (1H, ddd: 0.5, 2, 17 Hz, H-1'trans), 5.60 (1H, ddd: 8.5, 10, 17 Hz, H-1).

Bis-acetonide 23. A solution of 37 mg (144 μmol) of 22, 0.3 ml of Py and 0.2 ml of 0.05% solution of Sudan IV in 25 ml of CH_2Cl_2 was ozonized at -70°C until the solution became colourless. An excess of ozone was removed by passing argon through the solution (5 min), 1 ml of Me_2S was added and the mixture was warmed to RT in 1 h. The solution was evaporated and the residue was dissolved in a mixture of 5 ml of ether and 5 ml of CH_2Cl_2, an excess of a

solution of $LiAlH_4$ in THF was added, the mixture was stirred for 30 min and quenched by successive addition of 0.25 ml of H_2O, 0.25 ml of 15% NaOH soln and 0.75 ml of H_2O. The precipitate was separated by filtration through a pad of anh. Na_2SO_4 and the solution was evaporated. The residue was dissolved in a mixture of 3 ml of acetone and 0.5 ml of DMP, 2 mg of $TsOH \cdot H_2O$ was added, and the resulting solution was kept at RT for 30 min. An excess of Et_3N was added and the solution was evaporated. Chromatography of the residue (heptane-EtOAc 4:1) gave 21 mg (56%) of 23, syrup, $|\alpha|_D$ +12° (C 1.0); ^{1}H-NMR:δ 0.85 (3H, d: 6.6 Hz, Me-4), 1.14 (3H, d: 6.9 Hz, Me-2), 1.38 and 1.42 (12H, 2s, $-OCMe_2O-$), 1.73 (1H, dddq: 2.7, 1.7, 2.3, 6.9 Hz, H-2), 1.91 (1H, ddq: 6.6, 8.8, 6.6 Hz, H-4), 3.58 (1H, dd: 1.7, 11.3 Hz. H-1 eq), 3.60 (1H, dd, H-6'), 3.64 (1H, dd: 2.3, 8.8 Hz, H-3), 3.92 and 3.95 (2H, m, AB system of H-5, H-6), 4.08 (1H, dd: 2.7, 11.3 Hz. H-1 ax).

1,3-Propylenedithioacetal 26. To a solution of 7.32 g (46.27 mmol) of 19 and 7.51 g (69.4 mmol 1.5 eq., 6.95 ml) of 1,3-propanedithiol in 46 ml of CH_2Cl_2 was added 19.7 g (138.8 mmol, 3 eq., 17.1 ml) of $BF_3 \cdot OEt_2$. The mixture was kept at RT for 12 h, cooled to -20°C and quenched with NH_3 gas. The solvent was evaporated, the residue was dissolved in 75 ml acetone-DMP (2:1) and 1 g of $TsOH \cdot H_2O$ was added. After 1 h the mixture was neutralized with sat. $NaHCO_3$ soln. and evaporated. Chromatography of the residue (step wise gradient benzene-EtOAc 0→25%) gave 9.34 g (66%) of 26, syrup, $|\alpha|_D$ -4.5° (C 2.0); ^{1}H-NMR:δ 0.88 and 1.10 (6H, 2d: 6.7 Hz, Me-10 and Me-12), 1.34 and 1.41 (6H, 2s, $-OCMe_2O-$), 1.82 (1H, ddq: 4.5, 9, 6.7 Hz, H-12), 2.00 (1H, ddq: 2.5, 6.7, 6.7 Hz, H-10), 2.05-2.18 (2H, m, $SCH_2\underline{CH_2}CH_2S$), 2.62 (1H, d: 4 Hz, OH-11), 2.83-2.92 (4H, m, $S\underline{CH_2}CH_2\underline{CH_2}S$), 3.71 (1H, t: 7 Hz, H-14), 3.91 (1H, ddd: 2.5, 4, 9 Hz, H-11), 4.06 (1H, dd: 6.7, 7 Hz, H-14'), 4.17 (1H, d: 6.7 Hz, H-9), 4.31 (1H, ddd: 4.5, 6, 6.7 Hz, H-13).

MPM-ether 27. To a stirred suspension of 1.1 g (46 mmol, 2 eq.) of NaH in 23 ml of DMF was added a solution of 7.06 g (23 mmol) of 26 in 23 ml of DMF, the mixture was stirred at RT for 5 min and then 4.33 g (27.6 mmol, 1.2 eq., 3.75 ml) of p-methoxybenzyl chloride was added dropwise. The mixture was stirred for 1 h, an excess of NaH was decomposed with MeOH (2 ml). Extractive (Et_2O) work-up followed by chromatography (heptane-ether 5:1) gave 8.55 g (87%) of 27, syrup, $|\alpha|_D$ -0.5° (C 2.0); ^{1}H-NMR:δ 0.93 and 1.12 (6H, 2d: 7 Hz, Me-10 and Me-12), 1.35 and 1.44 (6H, 2 s, $-OCMe_2O-$), 1.70-1.90 (2H, m, H-10 and H-12), 2.08 (2H, m, $SCH_2\underline{CH_2}CH_2S$), 3.65 (1H, t: 7.6 Hz, H-11), 3.80 (3H, s, $MeOC_6H_4CH_2O$-11), 3.81 (1H, dd: 7, 7.8 Hz, H-14), 4.01 (1H, dd: 7, 8 Hz, H-14'), 4.02 (1H, d: 8.5 Hz, H-9), 4.33 (1H, dd: 7, 4 Hz, H-13), 4.62 and 4.75 (2H, 2d: 11 Hz, AB-system of $MeOC_6H_4\underline{CH_2}O$-11), 6.90 and 7.30 (4H, 2m, $MeOC_{\underline{6}}\underline{H_4}CH_2O$-11).

Diol 28. A solution of 7.70 g (18.0 mmol) of 27 in 50 ml of 80% AcOH was heated at 60°C for 1.5 h and evaporated. Extractive work-up followed by chromatography (EtOAc) gave 5.25 g (75%) of 28, syrup, $|\alpha|_D$ +7.5° (C 2.0); ^{1}H-NMR:δ 1.02 (3H, d: 7 Hz, Me-12), 1.23 (3H, d: 7 Hz, Me-10), 1.88 (1H, ddq: 1.6, 5, 7 Hz, H-12), 2.10 (2H, m, $SCH_2\underline{CH_2}CH_2S$), 2.20 (1H, tq: 6, 7 Hz, H-10), 2.86 (4H, m, $S\underline{CH_2}CH_2\underline{CH_2}S$), 3.52 (1H, dd: 4.3, 11.7 Hz, H-14), 3.65 (1H, dd: 8, 11.7 Hz, H-14'), 3.74 (1H, dd: 5, 6 Hz, H-11), 3.80 (3H, s, $MeOC_6H_4CH_2O$-11), 4.04 (1H, ddd: 1.6, 4.3, 8 Hz, H-13). 4.08 (1H, d: 6 Hz, H-9), 4.58 and 4.68 (2H, 2d: 10.5 Hz, AB system $MeOC_6H_4\underline{CH_2}O$-11), 6.87 and 7.27 (4H, 2m, $MeOC_{\underline{6}}\underline{H_4}CH_2O$-11).

Alcohol 29. To a solution of 5.25 g (13.58 mmol) of 28 in 25 ml of Py was added 2.72 g (14.26 mmol, 1.05 eq.) of TsCl and the solution was stirred at RT for 5 h. After extractive work-up the residue (monotosylate) was dissolved in 50 ml of dry MeOH, cooled to -15°C and 2.82 g (20.37 mmol, 1.5 eq.) of K_2CO_3 was added. The mixture was stirred for 4 h, poured into water, extracted with $CHCl_3$. The extract was washed with water, brine, dried and evaporated to dryness. The residue oxirane was dissolved in 20 ml of THF, the solution was added at -40°C to a stirred suspension prepared by addition of 14 ml of 1.95 M MeMgCl soln in THF (27.3 mmol, 3 eq.) to 0.438 g (2.72 mmol, 20 mol%) of $CuCl \cdot Me_2S$ in 6 ml of THF. The mixture was warmed to 0°C in 30 min and quenched with 3 ml of sat. NH_4Cl soln, the precipitate was separated by filtration through a pad of anh. Na_2SO_4, the solvent was evaporated. Chromatography of the residue (benzene-ether 9:1) gave 2.966 g (56.7%) of 29, syrup, $|\alpha|_D$ +8.5° (C 1.0); ^{1}H-NMR: δ 0.95 (3H, t: 7.3 Hz, Me-14), 1.02 (3H, d: 7 Hz, Me-12), 1.23 (3H, d: 7 Hz, Me-10), 1.39 (1H, ddq: 8, 7.3 Hz, H-14), 1.81 (1H, ddq: 1.6, 4.5, 7 Hz, H-12), 2.09 (2H, SCH_2-CH_2CH_2S-), 2.22 (1H, ddq: 5.5, 6.5, 7 Hz, H-10), 2.86 (4H, m, $-SCH_2CH_2CH_2S-$), 2.98 (1H, m OH-13), 3.72 (1H, dd: 4.5, 6.5 Hz, H-11), 3.80 (3H, s, $MeOC_6H_4CH_2O$-11), 3.86 (1H, br.d: 8 Hz, H-13), 4.05 (1H, d: 5.5 Hz, H-9), 4.58 and 4.67 (2H, 2d: 10.5 Hz, AB system of $MeOC_6H_4CH_2O$-11), 6.86 and 7.28 (4H, 2m, $MeOC_6H_4CH_2O$-11).

TBDPS-Ether 30. To a stirred suspension of 0.6039 g (1.762 mmol, 1.4 eq.) of tritylium perchlorate in 2 ml of CH_2Cl_2 was added at 0°C a solution of 0.454 g (1.888 mmol, 1.5 eq.) of tert-butyldiphenylsilane (prepared by reduction of the corresponding chloride by $LiAlH_4$ in ether) in 2 ml of CH_2Cl_2. The mixture was heated to RT, 0.382 g (3.776 mmol, 3 eq.) of Et_3N and a solution of 0.484 g (0.259 mmol) of 29 in 4 ml of CH_2Cl_2 was successively added. The mixture was stirred for 5 min, neutralized with sat. $NaHCO_3$ soln, and subjected to extractive work-up followed by chromatography (heptane-EtOAc 20:1) to give 0.593 g (75.6%) of 30, m.p. 118-118.5°C (hexane), $|\alpha|_D$ +53.2° (C 1.0); ^{1}H-NMR: δ 0.58 (3H, t: 7.5 Hz, Me-14), 0.92 (3H, d: 7 Hz, Me-12), 1.09 (3H, d: 7 Hz, Me-10), 1.10 (9H, s, t-$BuPh_2SiO$-13). 1.40-1.60 (2H, m, H-14 and H-14'), 1.74 (1H, ddq: 1, 9.5, 7 Hz, H-12), 1.89 (1H, ddq: 1.8, 10, 7 Hz, H-10), 2.08 (2H, m, $-SCH_2CH_2CH_2S-$), 3.81 (3H, s, $MeOC_6H_4CH_2O$-11), 3.97 (1H, d: 10 Hz, H-9), 4.07 (1H, ddd: 1, 5, 9 Hz, H-13), 4.19 (1H, dd: 1.8, 9.5 Hz, H-11), 4.32 and 4.59 (2H, 2d: 12.5 Hz, AB system of $MeOC_6H_4CH_2O$-11), 6.81, 7.02, 7.32, 7.62, and 7.72 (14H, 5m, t-$BuPh_2SiO$-13, $MeOC_6H_4CH_2O$-11). Found: C, 69.35; H, 8.12. Calc. for $C_{36}H_{50}O_3S_2Si$: C, 69.40; H, 8.09%.

Aldehyde 17. To a solution of 3.80 g (6.1 mmol) of 30 in 10 ml of acetone-water (9:1) was added 5.258 g (30.5 mmol, 5 eq.) of $CdCO_3$ and 4.968 g (18.3 mmol, 3 eq.) of $HgCl_2$. The mixture was refluxed with stirring for 6 h. The precipitate was filtered off and the filtrate was subjected to extractive work-up followed by chromatography (heptane-ether 19:1) to yield 2.685 g (83%) of 17, m.p. 83-83.5°C (pentane), $|\alpha|_D$ -32.4° (C 1.0); ^{1}H-NMR: δ 0.60 (3H, t: 7.5 Hz, Me-14), 1.00 and 1.14 (6H, 2d: 7 Hz, Me-10 and Me-12), 1.11 (9H, s, t-$BuPh_2SiO$-13), 1.55 (2H, m, H-14 and H-14'), 1.79 (1H, ddq: 1, 9.5, 7 Hz, H-12), 2.56 (1H, dq: 1.8, 7 Hz, H-10), 3.80 (3H, s, $MeOC_6H_4CH_2O$-11), 3.94 and 4.08 (2H, 2d: 10 Hz, AB system of $MeOC_6H_4CH_2O$-

-11), 4.13 (1H, dd: 1.8, 9.5 Hz, H-11), 4.13 (1H, ddd: 1, 5.5, 8.8 Hz, H-13), 6.75-7.75 (14H, m, t-BuPh$_2$SiO-13 and MeOC$_6$H$_4$CH$_2$O-11), 9.85 (1H, s, H-9). Found: C, 74.32; H, 8.35. Calc. for $C_{33}H_{44}O_4Si$: C, 74.39; H, 8.32%.

1,6-Anhydro-3-O-benzyl-2-deoxy-2,4-di-C-methyl-β-D-glucopyranose (18). To a solution of 35.4 g (143.8 mmol) of olefin 32[13] and 42 g (310.6 mmol, 2.15 eq.) of N-methylmorpholine N-oxide in 360 ml of acetone-water (8:1) was added 0.395 g (1.55 mmol, 1 mol%) of OsO_4. The mixture was stirred at RT for 40 h, concentrated to 100 ml volume, diluted with 200 ml of $CHCl_3$, washed with 200 ml of 10% aqueous KOH, the aqueous phase was extracted with $CHCl_3$ (3 x 100 ml), the extract was washed with water, 1 N HCl, brine, dried, and evaporated to dryness. The residue diol, R_f 0.06; starting methylene, R_f 0.69 (PhH-Et_2O 3:1) was dissolved in 200 ml of dry Py. 32.8 g (172.56 mmol, 1.2 eq.) of TsCl then was added and the mixture was stirred at RT for 6 h. After extractive work-up the solution was evaporated to dryness, the residue (monotosylate, R_f 0.43) was dissolved in 200 ml of dry MeOH and 28 g (200 mmol, 1.4 eq.) of K_2CO_3 was added. The mixture was stirred at RT for 15 min, diluted with 200 ml of water and extracted with $CHCl_3$. The extract was washed with brine, dried, evaporated to dryness, and the residue oxirane was dissolved in 80 ml of Et_2O. The solution was slowey added to a stirred suspension of 1.9 g (50 mmol, 1.4 eq.) of $LiAlH_4$ in 150 ml of ether. The mixture was stirred at RT for 1 h, quenched by successive addition 1.9 ml of water,1.9 ml of 15% solution of NaOH, and 5.7 ml of water. The precipitate was separated by filtration, filter cake was washed with Et_2O and the combined filtrates were evaporated to dryness to give syropy alcohol 18 (38.0 g, 100%, cf.[13]).

Allyl 2,6-dideoxy-2,4,6-tri-C-methyl-α,β-D-glucopyranoside 34. A solution of 9.725 g (25.221 mmol) of 33[13] in 400 ml of EtOH was refluxed for 1 h with 160 g Ra-Ni. The catalyst was removed by filtration and washed with EtOH. The combined solutions were evaporated to dryness. The residue was dissolved in a little $CHCl_3$ and passed through a pad of SiO_2 and anh. Na_2SO_4. Pure diol was eluted with Et_2O. Ether was evaporated and the residue (4.759 g, 23.299 mmol) was dissolved in 47.5 ml (698.96 mmol, 30 eq.) of allyl alcohol, 0.586 g (10 mol%) of PPTS was added and mixture was refluxed with Dean-Stark trap for 5 h. The mixture was evaporated and the residue was subjected to flash chromatography on silica with $CHCl_3$-EtOAc (10→50%) gradient to give 5.08 g (93.9%) of 34. A portion of the α- and β-32 mixture was separated by column chromatography (hexane-EtOAc 2:1) to give α and β anomers in 2:1 ratio. α-(34), syrup, $[\alpha]_D$ +186.4° (C 1.0); ^{1}H-NMR:δ 1.02 (3H, t: 7.3 Hz, Me-14), 1.04 (3H, d: 6.9 Hz, Me-10), 1.14 (3H, s, Me-12), 1.42 (1H, m: 7.3, 10 Hz, H-14), 1.73 (1H, m: 2, 7.3 Hz, H-14'), 1.79 (1H, m: 3.8, 11, 6.9 Hz, H-10), 1.90 and 2.20 (2H, 2 br.s, OH-11 and OH-12), 3.46 (1H, dd: 2, 10 Hz, H-13), 3.61 (1H, d: 11 Hz, H-11), 3.92 and 4.17 (2H, m, CH_2=CHCH_2O--9), 4.67 (1H, d: 3.8 Hz, H-9), 5.18 and 5.30 (2H, m, CH_2=CHCH_2O-9), 5.90 (1H, m, CH_2=CHCH_2--O-9); β-34, syrup, $[\alpha]_D$ -1.8° (C 1.0); ^{1}H-NMR:δ 1.00 (3H, t: 7.5 Hz, Me-14), 1.04 (3H, d: 6.5 Hz, Me-10), 1.15 (3H, s, Me-12), 1.48 (1H, m: 10.5, 7.5 Hz, H-14), 1.60 (1H, m: 9, 11, 6.5 Hz, H-10), 1.71 (1H, m: 2, 7.5 Hz, H-14'), 2.56 and 2.85 (2H, 2 br.s, OH-11 and OH-12), 2.95 (1H, dd: 2, 10.5 Hz, H-13), 3.14 (1H, d: 11 Hz, H-11), 4.07 and 4.35 (2H, m, CH_2=CHCH_2O-9), 4.11 (1H, d: 9 Hz, H-9), 5.19 and 5.28 (2H, m, CH_2=CHCH_2O-9), 5.92 (1H, m,

CH_2=CHCH_2O-9).

Allyl 3-O-acetyl-2,6-dideoxy-2,4,6-tri-C-methyl-α-D-glucopyranoside 35. To a solution of 0.31 g (1.346 mmol) of α-(34) in 5 ml of Py was added 1 ml of Ac_2O. The mixture was heated at 50°C for 2 h, quenched with 1 ml of MeOH. Extractive work-up followed by chromatography (hexane-EtOAc 3:2) gave 0.366 g (100%) of 35, syrup, $|\alpha|_D$ +200.4° (C 1.0); ^{1}H-NMR: δ 0.94 (3H, d: 6 Hz, Me-10), 1.02 (3H, t: 7.5 Hz, Me-14), 1.12 (3H, s, Me-12), 1.39 (1H, m: 7.5, 10.5 Hz, H-14), 1.81 (1H, m: 2, 7.5 Hz, H-14'), 1.98 (1H, m: 3.7, 11.6, 6 Hz, H-10), 2.14 (3H, s, MeCOO-11), 2.42 (1H, br.s, OH.12), 3.52 (1H, dd: 2, 10.5 Hz, H-13), 3.92 and 4.19 (2H, CH_2=CHCH_2O-9), 4.71 (1H, d: 3.7 Hz, H-9), 4.93 (1H, d: 11.6 Hz, H-11), 5.29 and 5.30 (2H, m, CH_2=CHCH_2O-9), 5.89 (1H, m, CH_2=CHCH_2O-9).

Allyl 3-O-acetyl-4-methoxymethyl-2,6-dideoxy-2,4,6-tri-C-methyl-α-D-glucopyranoside 36. To a solution of 346 mg (1.274 mmol) of 35 and 665 mg (3.822 mmol, 3 eq., 494 μl) of i-Pr_2NEt in 3 ml of CH_2Cl_2 was added 280 μl (3,822 mmol, 3 eq., 307 mg) of MOM-Cl. The mixture was heated at 50°C for 2.5 h. Extractive work-up followed by chromatography (hexane-EtOAc 2:1) gave 0.3945 g (100%) of 36, syrup, $|\alpha|_D$ +118.8° (C 1.0); ^{1}H-NMR: δ 0.90 (3H, d: 7 Hz, Me-10), 1.01 (3H, t: 7.5 Hz, Me-14), 1.23 (3H, s, Me-12), 1.36 (1H, m: 10.5, 7.5 Hz, H-14), 1.74 (1H, m: 1.5, 7.5 Hz, H-14'), 1.93 (1H, m: 3.5, 11, 7 Hz, H-10), 2.09 (3H, s, MeCOO-11), 3.31 (3H, s, MeOCH_2O-12), 3.65 (1H, dd: 1.5, 10.5 Hz, H-13), 3.92 and 4.18 (2H, m, CH_2=CHCH_2O-9), 4.54 and 4.66 (2H, 2d: 8 Hz, AB system of MeOCH_2O-12), 4.67 (1H, d: 3.5 Hz, H-9), 5.18 and 5.30 (2H, m, CH_2=CHCH_2O-9), 5.25 (1H, d: 11 Hz, H-11), 5.89 (1H, m, CH_2=CHCH_2O-9).

Allyl 4-O-methoxymethyl-2,6dideoxy-2,4,6-tri-C-methyl-α-D-glucopyranoside 37. To a solution of 374 mg (1.182 mmol) of 36 in 5 ml of dry MeOH was added 0.5 ml of 1 N MeONa solution in MeOH. The mixture was heated at 50°C for 3 h then evaporated to dryness. Extractive work-up followed by chromatography (hexane-EtOAc 4:1) gave 324 mg (100%) of 37, syrup, $|\alpha|_D$ +94.6° (C 1.0); ^{1}H-NMR: δ 1.00 (3H, z: 7.5 Hz, Me-14), 1.06 (3H, d: 6.8 Hz, Me-10), 1.15 (3H, s, Me-12), 1.34 (1H, m: 7.5, 10.5 Hz, H-10), 3.45 (3H, s, MeOCH_2O-12), 3.50 (1H, dd: 2, 10.5Hz, H-13), 3.60 (1H, dd:, 11, 2.5 Hz, H-11), 3.94 and 4.19 (2H, m, CH_2=CHCH_2O-9), 4.32 (1H, d: 2.5 Hz, OH-11), 4.55 and 4.90 (2H, 2d: 8 Hz, AB system of MeOCH_2O-12), 4.65 (1H, d: 4 Hz, H-9), 5.19 and 5.31 (2H, m, CH_2=CHCH_2O-9), 5.92 (1H, m, CH_2=CHCH_2O-9).

Allyl 3-O-(p-methoxybenzyl)-4-O-methoxymethyl-2,6-dideoxy-2,4,6-tri-C-methyl-α-D-glucopyranoside 38. To a stirred suspension of 125 mg (5.2 mmol, 4.44 eq.) of NaH in 3.5 ml of DMF was added a solution of 322 mg (1.174 mmol) of 37 in 2 ml of DMF. After 30 min 0.318 ml (1.761 mmol, 1.5 eq., 375.7 mg) of MPM-Cl was added. The mixture was stirred, an excess of NaH was decomposed with MeOH. Extractive work-up followed by chromatography (hexane-EtOAc 4:1) gave 447 mg (96.5%) of 38, syrup, $|\alpha|_D$ +134.0° (C 1.0); ^{1}H-NMR: δ 1.02 (3H, t: 7.5 Hz, Me-14), 1.05 (3H, d: 7 Hz, Me-10), 1.27 (3H, s, Me-12), 1.38 (1H, m: 7.5, 10.5 Hz, H-14), 1.61 (1H, m: 7.5, 1.9 Hz, H-14'), 1.87 (1H, m: 3.5, 11, 7 Hz, H-10), 3.38 (3H, s, MeOCH_2O-12), 3.43 (1H, dd: 1.9, 10.5 Hz, H-13), 3.58 (1H, d: 11 Hz, H-11), 3.81 (3H, s, MeOC_6H_4CH_2O-11), 3.92 and 4.19 (2H, m, CH_2=CHCH_2O-9), 4.54 and 4.66 (2H, 2d: 11 Hz, AB system of MeOC_6H_4CH_2O-11), 4.64 (1H, d: 3.5 Hz, H-9), 4.72 and 5.03 (2H, m , CH_2=CHCH_2O-9), 5.92 (1H, m, CH_2=CHCH_2O-9), 6.87 and 7.28 (4H, m, MeOC_6H_4CH_2O-11).

2,6-Dideoxy-3-O-(p-methoxybenzyl)-4-O-methoxymethyl-2,4,6-tri-C-methyl-D-glucopyranose 39. A stirred mixture of 447 mg (1.133 mmol) of 38 and 160 mg (1.426 mmol, 1.26 eq.) of tert-BuOK in 2.3 ml of DMSO was heated at 50°C for 2 h, diluted with water, extracted with Et_2O. The extract was evaporated, the residue was dissolved in 5 ml of acetone-water (9:1) and 397 mg (1.246 mmol, 1.1 eq.) of $Hg(OAc)_2$ was added. The mixture was kept at RT for 12 h, evaporated to dryness, diluted with brine, extracted with $CHCl_3$. The extract was evaporated and the residue was passed through a pad of SiO_2 and anh. Na_2SO_4, with hexane-EtOAc (10→→40%) gradient to remove inorganics. The collected fractions were evaporated and chromatography of the residue (hexane-EtOAc 3:2) gave 393 mg (98%) of 39. According to the ^{1}H-NMR spectrum 4.68 (1H, d: 11 Hz, H-9β), 5.02 (1H, d: 7.5 Hz, H-9α) α - and β -39 ratio was as 1:1.

Diol 40. To a stirred solution of 881 mg (2.486 mmol) of 39 in 10 ml of EtOH-H_2O (9:1) was added 486 mg (12.8 mmol, 10.3 eq.) of $NaBH_4$ in portions of 30 mg for 50 h. The mixture was diluted with water, quenched with AcOH and extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated. The residue was passed through a pad of SiO_2 with benzene-EtOAc (15 → 30%) gradient to remove inorganics. The collected fractions were evaporated and chromatography of the residue (EtOAc) gave 886 mg (100%) of 40, syrup, $|\alpha|_D$ +9.0° (C 1.0); ^{1}H-NMR (+D_2O):δ 1.00 (3H, t: 7.5 Hz, Me-14), 1.02 (3H, d: 7 Hz, Me-10), 1.29 (1H, m, H-14), 1.35 (3H, s, Me-12), 1.62 (1H, m: 2, 7.5 Hz, H-14'), 2.20 (1H, m: 2.4, 5.5, 7 Hz, H-10), 3.38 (3H, s, $\underline{Me}OCH_2O$-12), 3.43 (1H, dd: 5.5, 11 Hz, H-9), 3.53 (1H, dd: 2, 10.5 Hz, H-13), 3.57 (1H, dd: 5.5, 11 Hz, H-9'), 3.78 (3H, s, $\underline{Me}OC_6H_4CH_2O$-11), 3.79 (1H, d: 2.4 Hz, H-11), 4.54, 4.73, and 4.58 (4H, 2d and s, $MeOC\underline{H}_2O$-12 and $MeOC_6H_4C\underline{H}_2O$-11), 6.85 and 7.23 (4H, m, $MeOC_6\underline{H}_4CH_2O$-12).

Benzoate 41. To a solution of 1.043 g (2.926 mmol) of 40 in 15 ml of CH_2Cl_2 was added 947 μl (11.704 mmol, 4 eq., 926 mg) of Py and 679 μl (5.852 mmol, 2 eq., 823 mg) of BzCl. The mixture was stirred at RT for 1 h, quenched with water and subjected to extractive work-up followed by chromatography (hexane-EtOAc 3:2) to give 1.347 g (100%) of 41, syrup, $|\alpha|_D$ +42.5° (C 1.0); ^{1}H-NMR (+D_2O):δ 1.01 (3H, t: 7.6 Hz, Me-14), 1.16 (3H, d: 7 Hz, Me-10), 1.30 (1H, m, H-14), 1.38 (3H, s, Me-12), 1.62 (1H, m: 1.7, 7.5 Hz, H-14'), 2.48 (1H, ddq: 7, 2, 7 Hz, H-10), 3.38 (3H, s, $\underline{Me}OCH_2O$-12), 3.51 (1H, dd: 1.7, 10.5 Hz, H-13), 3.73 (1H, d: 2 Hz, H-11), 3.77 (3H, s, $\underline{Me}OC_6H_4CH_2O$-11), 4.23 (2H, d: 7 Hz, H-9 and H-9'), 4.60, 4.68, and 4.78 (4H, 2d and s, $MeOC_6H_4C\underline{H}_2O$-11 and $MeOC\underline{H}_2$-12), 6.48 and 7.23 (4H, m, $MeOC_6\underline{H}_4CH_2O$-11), 7.45, 7.55, and 8.03 (5H, m, PhCOO-9).

Bis-(O-TBS)-ether 44. A solution of 1.15g(2.497 mmol) of 41 in 45 ml of THF-1 N HCl (2:1) was heated at 60°C for 3 h. The mixture was neutralized with solid $NaHCO_3$, evaporated to dryness, diluted with water and extracted with $CHCl_3$. The extract was dried, evaporated and the residue (42) was dissolved in 10 ml of CH_2Cl_2. To the solution 1.39 ml (10 mmol, 4 eq., 1.01 g) of Et_3N and 0.8 ml (3.5 mmol, 1.4 eq., 0.925 g) of TBSOTf were successively added at 0°C. The mixture was warmed to RT for 10-min and stirred for additional 10 min. Addition of sat. $NaHCO_3$ solution followed by extractive work-up gave an oily residue which was dissolved in 10 ml CH_2Cl_2 and treated with 2.5 ml (17.9 mmol, 7.1 eq., 1.82 g) of Et_3N and 1.6

ml (6.96 mmol, 2.8 eq., 1.85 g) of TBSOTf for 17 h at 100°C in a sealed tube. After the reaction mixture was quenched with sat.$NaHCO_3$ soln extractive work-up was performed, and the residue (43) was dissolved in a mixture of 45 ml of MeOH and 5 ml of 15% aqueous NaOH. The solution was refluxed for 1 h then MeOH was removed by evaporation. Extractive work-up followed by chromatography (hexane-EtOAc 4:1) gave 1.35 g (100%) of 44, syrup, $|\alpha|_D$ +27.5° (C 1.0); ^{1}H-NMR:δ 0.09 and 0.17 (12H, 2s, t-BuMe_2SiO-12 and 13), 0.90 and 0.93 (18H, 2s, t-$BuMe_2$SiO-12 and 13), 0.97 (3H, d: 7 Hz, Me-10), 0.99 (3H, t: 7.5 Hz, Me-14), 1.32 (3H, s, Me-12), 1.55 (1H, m: 7.5 Hz, H-14), 1.68 (1H, m: 2.4, 7.5 Hz, H-14'), 1.88 (1H, m: 2.4, 7, 7 Hz, H-10), 3.44 (2H, d: 7 Hz, H-9 and H-9'), 3.55 (1H, dd: 2.4, 7.5 Hz, H-13), 3.57 (1H, d: 2.4 Hz, H-11), 3.82 (3H, s, $MeOC_6H_4CH_2O$-11), 4.53 and 4.77 (2H, 2d:11.3 Hz, AB system of $MeOC_6H_4CH_2O$-11), 6.88 and 7.28 (4H, m, $MeOC_6H_4CH_2O$-11).

Aldehyde 16. Swern[14] oxidation of alcohol 44 was performed as it was described for derivative 25 to give quantitative yield of the desired 16 after chromatography (hexane-EtOAc 24:1), syrup, $|\alpha|_D$ +8.7° (C 1.0); ^{1}H-NMR:δ 0.05, 0.07, and 0.11 (12H, 3s, t-BuMe_2SiO-12 and 13), 0.86 and 0.91 (18 , 2s, t-$BuMe_2$SiO-12 and 13), 0.98 (3H, t: 7.5 Hz, Me-14), 1.21 (3H, d: 7.8 Hz, Me-10), 1.25 (3H, s, Me-12), 1.43 (1H, m: 7.5 Hz, H-14), 1.72 (1H, m: 2.3, 7.5 Hz, H-14'), 2.77 (1H, m: 3.7, 1.5, 7.8 Hz, H-10), 3.63 (1H, dd: 2.3, 7.5 Hz, H-13), 3.82 (3H, s, $MeOC_6H_4CH_2O$-11), 3.92 (1H, d: 3.7 Hz, H-11), 4.35 and 4.42 (2H, 2d: 11 Hz, AB system of $MeOC_6H_4CH_2O$-11), 6.85 and 7.22 (4H, m, $MeOC_6H_4CH_2O$-11), 9.68 (1H, d: 1.5 Hz, H-9).

Tritylketone 45. To a stirred of 797 mg (2.653 mmol, 1.32 eq.) of TrCOEt in 10 ml THF 3.6 ml of 0.7 N n-BuLi soln in hexane (2.55 mmol, 1.27 eq.) was added at -78°C. The mixture was stirred at this temperature for 1 h and then a solution of 1.08 g (2.004 mmol) of aldehyde 16 in 8 ml of THF was added. The mixture was stirred for additional 1 h, quenched at -78°C with sat. NH_4Cl soln. Extractive work-up followed by chromatography (hexane-EtOAc 23:2) gave 1.449 g (86%) of 45, syrup, $|\alpha|_D$ +7.0° (C 0.8); ^{1}H-NMR:δ 0.015, 0.03, and 0.12 (12H, 3s, t-BuMe_2SiO-12 and 13), 0.53 and 0.75 (6H, 2d: 7 Hz, Me-8 and 10), 0.86 and 0.91 (18H, 2s, t-$BuMe_2$SiO-12 and 13), 0.95 (3H, t: 7.5 Hz, Me-14), 1.20 (3H, s, Me-12), 1.45 and 1.58 (2H, m, H-14 and 14'), 1.75 (1H, m, H-10), 2.82 (1H, br.d: 10 Hz, H-9), 3.18 (1H, br.q: 7 Hz, H-8), 3.30 (1H, s, OH-9), 3.47 (1H, dd: 1.9, 8 Hz, H-13), 3.81 (3H, s, $MeOC_6H_4CH_2O$-11), 3.84 (1H, br.s, H-11), 4.31 and 4.58 (2H, 2d: 11 Hz, AB system of $MeOC_6H_4CH_2O$-11), 6.92 and 7.25 (19H, m, $MeOC_6H_4CH_2O$-11 and Ph_3CO-8).

Tritylketone 46. This was obtained according to the procedure described for tritylketone 45 in 84.3% yield, m.p. 155.5-156° (pentane), $|\alpha|_D$ -4.4° (C 1.0); ^{1}H-NMR:δ 0.43 (3H, d: 7 Hz, Me-12), 0.54 (3H, t: 7.5 Hz, Me-14), 0.71 (3H, d: 7 Hz, Me-10), 0.82 (3H, d: 7 Hz, Me-8), 1.07 (9H, s, t-$BuPh_2$SiO-13), 1.20-1.70 (4H, m, H-10, 12, 14, and 14'), 3.19 (1H, dq: 1, 7 Hz, H-8), 3.32 (1H, br.d: 10 Hz, H-9), 3.47 (3H, s, $MeOC_6H_4CH_2O$-11), 4.00 (1H, br.dd: 4, 10 Hz, H-13), 4.10 (1H, dd: 1, 10 Hz, H-11), 6.80-7.70 (29 H, m, t-BuPh_2SiO-13, $MeOC_6H_4CH_2O$-11, and Ph_3CO-8). Found: C, 79.25; H, 7.71. Calc. for $C_{55}H_{64}O_5Si$: C, 79.28; H,7.74%.

MP-Acetal 47. To a stirred solution of 1.449 g (1.726 mmol) of 45 in 15 ml of dry CH_2Cl_2 was added 3g of powdered molecular sieves (3 Å) and 411 mg (1.812 mmol, 1.05 eq.) of DDQ. The mixture was stirred at RT for 3 min, passed through a celite pad, washed with brine,

dried,evaporated; chromatography of the residue (hexane-Et_2O 23:2) gave 1.184 g (82%) of 47, syrup, $|\alpha|_D$ +4.7° (C 0.7); ^{1}H-NMR: δ -0.155, -0.08, and 0.055 (12H, 3s, t-BuMe$_2$SiO-12 and 13), 0.75 and 0.96 (6H, d: 6.7 Hz, Me-8 and 10), 0.80 and 0.91 (18H, 2s, t-BuMe$_2$SiO-12 and 13), 0.93 (3H, t: 7.5 Hz, Me-14), 1.19 (3H, s, Me-12), 3.22 (1H, dd: 2.7, 4.5 Hz, H-14), 3.58 (1H, d: 1.5 Hz, H.11), 3.80 (3H, s, MeOC$_6$H$_4$CH), 4.07 (1H, d: 9 Hz, H-9), 5.23 (1H, s, MeOC$_6$H$_4$CH), 6.86, 7.15, and 7.30 (19H, 3m, MeOC$_6$H$_4$CH, Ph_3CO-8).

MP-Acetal 48. This was obtained according to the procedure described for 47 in 85% yield, m.p. 182-182.5° (pentane), $|\alpha|_D$ -11.6° (C 1.0); ^{1}H-NMR: δ 0.41 (3H, t: 7.5 Hz, Me-14), 0.54 (3H, d: 7 Hz, Me.12), 0.81 (3H, d: 6.5 Hz, Me-8), 1.00 (9H, s, t-BuPh$_2$SiO-13), 1.18 (3H, d: 6.7 Hz, Me-10), 1.35 (2H, m, H-14, H-14'), 1.53 (1H, dq: 2, 6.7 Hz, H-10), 1.68 (1H, ddq: 1.5, 10, 7 Hz, H-12), 3.80 (3H, s, MeOC$_6$H$_4$CH), 3.81 (1H, dd: 2, 10 Hz, H-11), 4.05 (1H, ddd: 1.5, 4.5, 10 Hz, H-13), 4.22 and 4.31 (2H, dq and d: 10.5, 6.5 Hz, AB system of H-8 and H-9), 5.18 (1H,s, MeOC$_6$H$_4$CH), 6.80-7.60 (29H, m, t-BuPh$_2$SiO-13, MeOC$_6$H$_4$CH, and Ph_3CO-8). Found: C, 79.41; H, 7.48. Calc. for $C_{55}H_{62}O_5Si$: C, 79.48; H, 7.52%.

Alcohol 49. To a solution of 1.184 g (1.415 mmol) of 47 in 10 ml of THF was added 20 ml of 1 N LiBHEt$_3$ soln in THF (20 mmol, 7 eq.). The reaction mixture was kept at RT for 5 days, then quenched by successive addition, of 18.4 ml of 15% aqueous NaOH and 18.4 ml of 30% aqueous H_2O_2 at 0°C. Additional stirring for 2 h at RT followed by extractive work-up and chromatography (hexane-EtOAc 4:1) gave 689 mg (82%) of 49, syrup, $|\alpha|_D$ -20.3° (C 1.0); ^{1}H-NMR (+D_2O): δ -0.075, -0.025, 0.09, and 0.10 (12H, 4s, t-BuMe$_2$SiO-12 and 13), 0.82 and 0.94 (18H, 2s, t-BuMe$_2$SiO-12 and 13), 0.98 (3H, t: 7.5 Hz, Me-14), 1.11 and 1.28 (6H, 2d: 7 Hz,Me--8 and 10), 1.28 (3H, s,Me-12), 1.48-1.72 (2H, m, H-14 and 14'). 1.81 (1H, m, H-10), 2.52 (1H, m, H^8), 3.41 (1H, dd: 10, 2.5 Hz, H-13), 3.52 (1H, dd: 1, 10.5 Hz,H-9), 3.62 (2H, m, H-7 and 7'), 3.82 (3H, s, MeOC$_6$H$_4$CH), 4.05 (1H, d: 2 Hz, H-11) 5.66 (1H, s, MeOC$_6$H$_4$CH), 6.90 and 7.45 (4H, 2m, MeOC$_6$H$_4$CH).

Alcohol 50. This was obtained according to the procedure described for alcohol 49 in 90% yield, syrup; ^{1}H-NMR (+D_2O): δ 0.55 (3H, t: 7.4 Hz, Me-14), 0.93 (3H, d: 6.6 Hz, Me-12), 1.06 (12H, s and d: 6.5 Hz, Me-8 and t-BuPh$_2$SiO-13), 1.18 (3H, d: 6.5 Hz, Me-10), 1.46 (2H, m, H-14 and 14'), 1.72 (1H, ddq: 1, 10, 6.6 Hz, H-12), 1.86 (1H, br.dq: 2, 6.5 Hz, H-10), 2.36 (1H, m: 4.5, 10, 6.5 Hz, H-8), 3.57 (1H, dd: 5, 10.5 Hz, H-7), 3.56 (1H, br.d: 10 Hz, H-9), 3.67 (1H, dd: 4, 10.5 Hz, H-7'), 3.83 (3H, s, MeOC$_6$H$_4$CH), 4.05 (1H, dd: 2, 10 Hz, H-11), 4.14 (1H, ddd: 1, 5, 9 Hz, H-13), 5.12 (1H, s, MeOC$_6$H$_4$CH), 6.84-7.70 (14H, m, t-BuPh$_2$SiO-13 and MeOC$_6$H$_4$CH). N.O.e. measurements showed spatial proximity between the ortho-protons of the aromatic ring of the acetal moiety and the proton H-9, the protons of the Me moeties at C-8 and C-10.

Sulfide 51. To a solution of 497 mg (0.833 mmol) of 49 in 5 ml of pyridine was added 363 mg (1.665 mmol, 2 eq.) of Ph_2S_2 and 518 µl (2.08 mmol, 2.5 eq., 421 mg) of n-Bu_3P. The mixture was kept under argon at RT for 22 h, quenched with water, subjected to extractive work-up followedby chromatography (hexane-EtOAc 9:1) to give 550 mg (96%) of 51, syrup, $|\alpha|_D$ +7.8° (C 1.0); ^{1}H-NMR: δ -0.09, -0.025, 0.08, and 0.10 (12H, 4s, t-BuMe$_2$SiO-12 and 13), 0.83 and 0.94 (18H, 2s, t-BuMe$_2$SiO-12 and 13), 0.96 (3H, t: 7.5 Hz, Me-14), 1.21 and 1.25 (6H,

d: 7 Hz, Me-8 and 10), 1.42 (1H, m: 2, 7.5 Hz, H-14), 1.60 (2H, m, H-10 and 14'), 2.66 (1H, m, H-8), 2.76 (1H, dd: 3.2, 12.5 Hz, H-7), 3.05 (1H, dd: 3.2, 12.5 Hz, H-7'), 3.34 (1H, dd: 2, 8 Hz, H-13), 3.82 (3H, s, MeOC$_6$H$_4$CH), 3.49 (1H, br.d: 10 Hz, H-9), 3.94 (1H, d: 2 Hz, H-11), 5.60 (1H, s, MeOC$_6$H$_4$CH), 6.90 and 7.30 (9H, 2m, MeOC$_6$H$_4$CH and PhS-7).

Sulfide 52. This was obtained according to the procedure described for sulfide 51 in 92% yield, m.p. 119.5-120°, $[\alpha]_D$ +28° (C 1.0); ^{1}H-NMR: δ 0.51 (3H, t: 7 Hz, Me-14), 0.90 (3H, d: 6.9 Hz, Me-12), 1.05 (9H, s, t-BuPh$_2$SiO-13). 1.14 (3H, d: 6.4 Hz, Me-8), 1.16 (3H, d: 6.5 Hz, Me-10), 1.30-1.56 (2H, m, H-14 and 14'), 1.71 (1H, ddq: 1.6, 10.4, 6.9 Hz, H-12), 1.82 (1H, dq: 2, 6.5 Hz, H-10), 2.40 (1H, dddq: 3.1, 8.5, 11, 6.4 Hz, H-8), 2.68 (1H, dd: 8.5, 13 Hz, H-7), 3.13 (1H, dd: 3.1, 13 Hz, H-7'), 3.46 (1H, d: 11 Hz, H-9), 3.81 (3H, s, MeOC$_6$H$_4$CH), 3.95 (1H, dd: 2, 10.4 Hz, H-11), 4.07 (1H, ddd: 1.6, 5.2, 7 Hz, H-13), 4.79 (1H, s, MeOC$_6$H$_4$CH), 6.80-7.50 (19H, m, t-BuPh$_2$SiO-13, PhS-7, and MeOC$_6$H$_4$CH). Found: C, 74.01; H, 7.33. Calc. for $C_{42}H_{54}O_4SiS$: C, 73.85; H, 7.97%.

(R)- And (S)-sulfoxide 12. To a solution of 18 mg (26.1 μmol) of 51 in 1 ml of EtOAc was added 5 mg (27.4 μmol, 1.05 eq.) of 85% MCPBA at -40°C. The mixture was stirred for 10 min, quenched with sat. $NaHCO_3$ soln, followed by extractive work-up and chromatography (hexane-EtOAc 2:1) to give (R)-12, 6 mg (33%), syrup, $[\alpha]_D$ +108° (C 0.5); (S)-12, 12 mg (65%), syrup, $[\alpha]_D$ -19.6° (C 1.0); ^{1}H-NMR for (R)-12: δ -0.07, -0.02, 0.07, and 0.09 (12H, 4s, t-BuMe$_2$SiO--12 and 13), 0.85 and 0.96 (18H, 2s, t-BuMe$_2$SiO-12 and 13), 1.02 (3H, t: 7.5 Hz, Me-14), 1.23 (3H, d: 7 Hz, Me-10), 1.28 (3H, s, Me-12), 1.37 (3H, d: 6.5 Hz, Me-8), 1.52-1.80 (3H, m, H-10, 14, and 14'), 2.34 (1H, dd: 11, 13 Hz, H-7), 2.71 (1H, dd:2, 13 Hz, H-7'), 3.05 (1H, m, H-8), 3.32 (1H, dd: 2, 8 Hz, H-13), 3.33 (1H, br.s: 10 Hz, H-9), 3.82 (3H, s, MeOC$_6$H$_4$CH), 4.07 (1H d: 2 Hz, H.11), 5.68 (1H, s, MeOC$_6$H$_4$CH), 6.90 and 7.43 (4H, 2m, MeOC$_6$H$_4$CH), 7.52 and 7.63 (5H, 2m, PhSO-7). ^{1}H-NMR for (S)-12: δ -0.11, -0.02, 0.08, and 0.10 (2H, 4s, t-BuMe$_2$SiO-12 and 13), 0.815 and 0.93 (18H, 2s, t-BuMe$_2$SiO-12 and 13), 0.98 (3H, t: 7.5 Hz, Me-14), 1.22 (3H, d: 7 Hz, Me-10), 1.27 (3H, s, Me-12), 1.29 (3H, d: 6 Hz, Me-8), 1.54 (2H, m, H-14 and 14'), 1.64 (1H, m, H-10), 2.62 (2H, m, H-7 and 8), 2.81 (1H, dd: 9, 13.5 Hz, H-7'), 3.33 (1H, dd: 2, 8 Hz, H-13), 3.48 (1H, dd: 2, 8.5 Hz, H-9), 3.78 (1H, d: 2.5 Hz, H-11), 3.82 (3H, s, MeOC$_6$H$_4$CH), 5.59 (1H, s, MeOC$_6$H$_4$CH), 6.90 and 7.42 (4H, 2m, MeOC$_6$H$_4$CH), 7.55 (5H, m, PhSO-7).

Isomerization of (S)-12 into (R)-12. To a solution of 12 mg (17 μmol) of (S)-12 in 0.5 ml of THF was added 8 μl (61.2 μmol, 3.6 eq., 7.4 mg) of 2,4,6-collidine. The solution was cooled to -60°C and a solution of 2.9 μl (20.4 μmol, 1.2 eq., 4.3 mg) of TFAA in 200 μl of THF was added . The mixture was stirred at -60°C for 20 min, 500 μl of THF-H_2O (4:1) was added, the resulting mixture was heated to RT, diluted with $CHCl_3$, dried and evaporated; chromatography of the residue (hexane-EtOAc 2:1) gave 9 mg (75%) of (R)-12 and 2.6 mg (21.7%) of (S)-12.

(R)- And (S)-sulfoxide 13. These were obtained according the procedure described for sulfoxides 12 affording (R)-13 in 21.8% yield, m.p. 100.5-101°, $[\alpha]_D$+ 105° (C 1.0) and (S)-13 in 74% yield, m.p. 106.5-107°, $[\alpha]_D$ -24.5° (C 1.0); ^{1}H-NMR for (R)-13: δ 0.50 (3H, t: 7 Hz, Me-14), 0.89 (3H, d: 7 Hz, Me-12), 1.10 (9H, s, t-BuPh$_2$SiO-13), 1.12 (3H, d: 6.5 Hz, Me-8), 1.25 (3H, d: 7 Hz, Me-10), 1.25-1.70 (4H, m, H.10, 14, and 14'), 2.50 (1H, dd: 10, 13 Hz, H-7),

2.80 (1H, dd: 2.5, 13 Hz, H-7'), 2.91 (1H, m: 2.5, 10, 10.5 Hz, H-8), 3.38 1H, d: 10.5 Hz, H-9), 3.82 (3H, s, MeOC$_6$H$_4$CH), 4.07 (1H, ddd: 1.2, 5, 9 Hz, H-13), 4.04 (1H, dd: 2.5, 10 Hz, H-11), 4.82 (1H, s, MeOC$_6$H$_4$CH), 6.80-7.70 (19H, m, PhSO-7, MeOC$_6$H$_4$CH, and t-BuPh$_2$SiO-13). Found: C, 72.05; H, 7.81. Calc. for $C_{42}H_{54}O_5SiS$: C, 72.16; H, 7.79%. ^{1}H-NMR for (S)-13:δ 0.50 (3H, t: 7 Hz, Me-14), 0.83 (3H, d: 7 Hz, Me-12), 1.08 (9H, s, t-BuPh$_2$SiO-13), 1.16 (6H, t: 7 Hz, Me-8 and 10). 1.20-1.80 (4H, m, H-10, 12, 14, and 14'), 2.66 (1H, m, H-8), 2.81, 2.82, and 2.83 (2H, 3s, H-7 and 7'), 3.52 (1H, br.d: 1, 10 Hz, H-9), 3.82 (3H, s, MeOC$_6$H$_4$CH), 3.93 (1H, dd: 2.5, 10.5 Hz, H-11), 4.07 (1H, ddd: 1.5, 5, 8 Hz, H-13), 4.95 (1H, s, MeOC$_6$H$_4$CH), 6.80-7.70 (19H, m, PhSO-7, MeOC$_6$H$_4$CH, and t-BuPh$_2$SiO-13). Found: C, 72.11; H, 7.82. Calc. for $C_{42}H_{54}O_5SiS$: C, 72.16; H, 7.79%.

Isomerization of (S)-13 into (R)-13 was carried out according to the above procedure to give (R)-13 in 76.5% and (S)-13 in 23.5% yield, respectively.

Compound 53. A solution of 15 mg (21.3 μmol) of (R)-12 and 67 mg (212 μmol, 5 eq.) of $(n\text{-Bu})_4NF\cdot 3H_2O$ in 1 ml of THF was heated at 100°C for 30 h. The mixture was cooled, diluted with $CHCl_3$, washed with water, brine, dried and evaporated; chromatography of the residue (EtOAc) gave 10.1 mg (100%) of 53, syrup, $|\alpha|_D$ +118.5° (C 1.0); ^{1}H-NMR:δ 1.06 (3H, t: 7.5 Hz, Me-14), 1.12 (3H, s, Me-12), 1.28 (1H, m, H-14), 1.34 and 1.43 (6H, 2d: 6.7 Hz, Me-8 and 10), 1.70-1.90 (3H, m, H-10, 14', and OH-12(13)), 2.43 (1H, dd: 10, 13 Hz, H-7), 3.02 (1H, br.s, OH-13(12)), 3.30 (1H, br.d: 11 Hz, H-13), 3.42 (1H, br.d: 10.5 Hz, H-9), 3.81 (3H, s, MeOC$_6$H$_4$CH), 4.26 (1H, d: 2 Hz, H-11), 5.73 (1H, s, MeOC$_6$H$_4$CH), 6.92 and 7.41 (4H, m, MeOC$_6$H$_4$CH), 7.55 and 7.65 (5H, m, PhSO-7).

Compound 56. To the stirred LDA soln, prepared from 42 μl (302.77 μmol, 3.7 eq., 30.6 mg) of i-Pr$_2$NH and 337 μl of 0.85 N n-BuLi in hexane (286 μmol, 1.4 eq.) in 1 ml of dry THF (-40°C, 1 h), a soln of 33 mg (69.24 μmol) of 53 in 0.7 ml of dry THF was added dropwise over 10 min at -60°C. After 1 h a soln of 46 mg (204.5 μmol, 2.5 eq.) of ketone 11 in 0.5 ml of dry THF was added at -78°C. After additional 2h the reaction was quenched with 2 ml of sat. NH_4Cl soln at this temperature. Extractive work-up followed by chromatography (EtOAc) gave the coupling product 54, 11 mg (22.6%, 41.4% with respect to consumed 53), which was immediately dissolved in 0.5 ml of acetone and an excess of NaI and a solution of 5 μl (35.4 μmol, 2.3 eq., 7.4 mg) of TFAA in 50 μl of acetone were successively added at 0°C. The mixture was stirred for 5 min, quenched with sat. $NaHCO_3$ soln, extracted with $CHCl_3$. The extract was washed with sat. $Na_2S_2O_3$ soln, brine, dried and evaporated and chromatography of the residue (hexane-EtOAc 2:1) gave 9 mg (84%) of 56, syrup, $|\alpha|_D$ +31.1° (C 0.7); ^{1}H-NMR: δ 0.91, 1.00, 1.05, and 1.25 (12H, 4d: 6.5 Hz, Me-2, 4, 8, and 10), 1.01 (3H, t: 7.5 Hz, Me-14), 1.26 and 1.38 (6H, 2s, Me-6 and 12), 1.45 and 1.48 (6H, 2s,-OCMe$_2$O-), 3.26 (2H, d: 3 Hz, H-7, 7'), 3.34 (2H, m, H-3 and 13), 3.81 (3H, s, MeOC$_6$H$_4$CH), 4.02 (1H, br.d: 10 Hz, H-9), 4.15 and 4.34 (2H, 2d: 2 Hz, H-5 and 11), 4.88 and 5.02 (2H, 2m, H-1'cis and 1'trans), 5.27 (1H, m, H-1), 5.65 (1H, s, MeOC$_6$H$_4$CH), 6.80-7.50 (9H, m, PhS-7 and MeOC$_6$H$_4$CH).

Compound 55. The coupling of (R)-13 and 11 was carried according to the procedure described for preparation of compound 56. Desired 55 along with its C_6-epimer were isolated after chromatography (hexane-EtOAc 5:1) in 64.7% and 8.9% yields respectively. Because of high lability

no data on specific rotation of 55 are available; ^{1}H-NMR:δ 0.29 (3H, d: 7 Hz, Me-10), 0.40 (3H, t: 6.5 Hz, Me-14), 0.85 (1H, m, H-12), 0.95 (3H, d: 6.5 Hz, Me-12), 1.03 (3H, d 6.5 Hz, Me-2), 1.12 (3H, d: 7 Hz, Me-4), 1.15 (9H, s, t-BuPh$_2$SiO-13), 1.17 (3H, d: 7 Hz, Me-8), 1.22-1.48 (2H, m, H-14 and 14'), 1.45 and 1.46 (6H, 2s, -OCMe$_2$O-), 1.46 (1H, m, H-10), 1.77 (3H, s, Me-6), 1.80 (1H, m, H-4), 2.36 (1H, m, H-4), 2.36 (1H, ddq: 9, 10, 6.5 Hz, H-2), 2.89 (1H, br.s, H-7), 2.98 (1H, m, H-8), 3.45 (1H, dd: 1.5, 10 Hz, H-3), 3.77 (1H, d: 10 Hz, H-9), 3.82 (3H, s, MeOC$_6$H$_4$CH), 3.85 (1H, dd: 2, 10 Hz, H-11), 3.95 (1H, ddd: 1.4, 5, 9 Hz, H-13), 3.97 (1H, d: 2 Hz, H-5), 4.80 (1H, s, MeOC$_6$H$_4$CH), 5.70 (1H, dd: 2, 10 Hz, H-1'cis), 5.13 (1H, dd: 2, 17 Hz, H-1'trans), 5.58 (1H, ddd: 9, 10, 17 Hz, H-1), 6.80-7.80 (19H, m, PhSO-7, MeOC$_6$H$_4$CH, and t-BuPh$_2$SiO-13).

Sulfide 57. This was obtained from 55 according to the procedure described for compound 56 in 90.1% yield, syrup, $[\alpha]_D$ +25.9° (C1.02); ^{1}H-NMR:δ 0.49 (3H, t, 7.3 Hz, Me-14), 0.92 (3H, d: 7 Hz, Me-12), 0.97 (3H, d: 6.5 Hz, Me-4), 1.00 (3H, d: 6.5 Hz, Me-2), 1.04 (9H, s, t-BuPh$_2$SiO-13), 1.22 (3H, d 7 Hz, Me-10), 1.25 (3H, d: 7 Hz, Me 8), 1.36 (3H, s, Me-6), 1.46 and 1.51 (6H, 2s,-OCMe$_2$O-), 1.29 and 1.47 (2H, 2m, H-14 and 14'), 1.61 (1H, m, H-4), 1.80 (1H, m, H-2), 2.04 (1H, br.dq: 0.5, 2, 7 Hz, H-10), 2.27 (1H, m, 8.5, 10, 6.5 Hz, H-2), 2.68 (1H, s, OH-6), 2.79 (1H, m, H-8), 3.40 (1H, dd: 2, 10 Hz, H-3), 3.45 (1H, d: 3 Hz, H-7), 3.83 (3H, s, MeOC$_6$H$_4$CH), 4.10 (1H, d: 10.5 Hz, H-9), 4.20 (1H, ddd: 1.5, 5, 9 Hz, H-13), 4.20 (1H, d: 2 Hz, H-5), 4.22 (1H, dd: 2, 10 Hz, H-11), 4.87 (1H, dd: 10, 2 Hz, H-1'cis), 5.03 (1H, dd: 17, 2 Hz, H-1'trans), 5.30 (1H, ddd: 8.5, 10, 17 Hz, H-1), 5.32 (1H, s, MeOC$_6$H$_4$CH), 6.80-7.70 (19H, m, PhS-7, MeOC$_6$H$_4$CH, and t-BuPh$_2$SiO-13).

Compound 9. 3 Mg (130 μmol, 10 eq.) of Na-metal was dissolved in 2 ml of NH_3(liq.) and a solution of 9 mg (13.1 μmol) of 56 in 1 ml of dry Et_2O was added to this at -78°C. The mixture was stirred at -78°C for 1 h and quenched with solid NH_4Cl. Cooling bath was removed and liquid ammonia was allowed to evaporate. The residue was washed with $CHCl_3$ on a sintered glass filter. Washings were dried with Na_2SO_4 and evaporated. Chromatography of the residue (hexane-EtOAc 2:1) gave 6 mg (78%) of 9, syrup, $[\alpha]_D$ +17.0° (C 0.5); ^{1}H-NMR (+D_2O):δ 0.98 (3H, d: 7 Hz, Me-4), 1.04 (3H, t: 7.5 Hz, Me-14), 1.04 (3H, d: 6 Hz, Me-2), 1.07 and 1.21 (6H, 2s, Me-6 and 12), 1.10 (3H, d: 7 Hz, Me-8), 1.34 (1H, m, H-14), 1.41 and 1.43 (6H, 2s, -OCMe$_2$O-), 1.45 (3H, d: 7 Hz, Me-10), 1.60 (2H, m, H-7 and 7'), 1.65 (1H, m, H-4), 1.74 (1H, m, H-14'), 1.97 (1H, m, H-10), 2.33 (1H, m, H-2), 2.63 (1H, m, H-8), 3.27 (1H, d: 11 Hz, H-9), 3.28 (1H, dd: 1.5, 11 Hz, H-13), 3.42 (1H, dd: 2, 10 Hz, H-3), 3.49 (1H, d: 2 Hz, H-5), 3.81 (3H, s, MeOC$_6$H$_4$CH), 4.35 (1H, d: 2 Hz, H-11), 5.05 and 5.72 (2H, 2m, H-1'cis and 1'trans 5.60 (1H, m, H-1), 5.72 (1H, s, MeOC$_6$H$_4$CH), 6.90 and 7.40 (4H, 2m, MeOC$_6$H$_4$CH).

Compound 58. This was prepared from 57 according to the procedure described 9 in 69.1% yield, syrup, $[\alpha]_D$ +14.2° (C 1.0); ^{1}H-NMR:δ 0.50 (3H, t: 7.2 Hz, Me-14), 0.90 (3H, d: 7 Hz, Me-12), 1.03 (3H, d: 7Hz, Me-4), 1.06 (9H, s, t-BuPhSiO-13), 1.07 (3H, d: 7 Hz, Me-2), 1.10 (3H, d: 6.4 Hz, Me-8), 1.17 (3H, d: 7 Hz, Me-10), 1.25 (3H, s, Me-6), 1.45 and 1.47 (6H, 2s, -OCMe$_2$O-), 1.75 (1H, m, H-12), 1.91 (1H, m, H-10), 2.26 (1H, s, OH-6), 2.36 (1H, m, H-2), 2.56 (1H, m, H-8), 3.26 (1H, br.d: 11 Hz, H-9), 3.45 (1H, dd: 1.8, 9.5 Hz, H-3), 3.54 (1H, d: 2 Hz, H-5), 3.83 (3H, s, MeOC$_6$H$_4$CH), 4.16 (1H, ddd: 1.5, 5, 9.5 Hz, H-13), 4.27 (1H, dd: 2, 10 Hz, H-11),

5.04 (1H, dd: 10, 2 Hz, H-1'cis), 5.12 (1H, dd: 16.5, 2 Hz, H-1'trans), 5.61 (1H, ddd: 8.5, 10, 16.5 Hz, H-1), 6.80-7.70 (14H, m, $MeOC_6H_4CH$ and t-$BuPh_2SiO$-13).

Compound 10. A solution of 264 mg (329 μmol) of 58 and 962 mg (3.049 mmol, 9.62 eq.) of $(n\text{-}Bu)_4NF\cdot 3H_2O$ in 3 ml of THF was heated at 80°C for 20 h. The solution was concentrated in vacuo, the residue was dissolved in $CHCl_3$, washed with brine, dried and evaporated; chromatography of the residue (hexane-EtOAc 3:1) gave 182 mg (98%) of 10, syrup, $|\alpha|_D$ +7.2° (C 1.0); ^{1}H-NMR:δ 0.78 (3H, d: 7 Hz, Me-12), 1.00 (3H, t: 7.3 Hz, Me-14), 1.01 (3H, d: 6.5 Hz, Me-4), 1.05 (3H, d: 6.3 Hz, Me-2), 1.10 (3H, d: 6.5 Hz, Me-8), 1.20 (3H, s, Me-6), 1.21 (3H, d: 6.5 Hz, Me-10), 1.42 and 1.43 (6H, 2s,-$OCMe_2O$-), 1.67 (1H, tq: 2, 6.5 Hz, H-4), 1.84 (1H, br.dq: 2, 6.5 Hz, H-10), 1.98 (1H, ddq: 2, 10, 7 Hz, H-12), 2.33 (1H, ddq: 8.2, 9.5, 6.3 Hz, H-2), 2.61 (1H, ddq: 1.5, 10.5, 6.5 Hz, H-8), 3.31 (1H, br.d: 10.5 Hz, H-9), 3.42 (1H, dd: 2, 9.5 Hz, H-3), 3.49 (1H, d: 2 Hz, H-5), 3.65 (1H, ddd: 5, 7.5, 2 Hz, H-13), 4.17 (1H, dd: 2, 10 Hz, H-11), 5.05 (1H, dd: 10, 2 Hz, H-1'cis), 5.12 (1H, br.dd: 16.5, 2 Hz, H-1'trans), 5.61 (1H, ddd: 8.2, 10, 16.5 Hz, H-1), 5.65 (1H, s, $MeOC_6H_4C\underline{H}$), 6.89 and 7.41 (4H, 2m, $MeOC_6\underline{H}_4CH$).

Compound 7. A solution of 46 mg (79.48 μmol) of 9, 0.6 ml of Py, and 0.2 ml of 0.05% Sudan IV solution in CH_2Cl_2 in 65 ml of CH_2Cl_2 was ozonized at -78°C until the solution became colourless. An excess of ozone was removed by passage of argon for 5 min at -78°C then 0.5 ml of Me_2S was added. The solution was warmed to RT, washed with 1 N HCl, water, brine, dried and evaporated. The residue was dissolved in 5 ml of THF pH 7.0 phosphate buffer (10:1) and 32 mg (158.96 μmol, 2 eq.) of 85% MCPBA was added. The mixture was stirred at RT for 30 min, quenched with sat. $NaHCO_3$ soln, extracted with $CHCl_3$. The extract was washed with sat. $Na_2S_2O_3$ soln, 1 N HCl, brine, dried and evaporated. The residue was passed a pad of SiO_2, in hexane-EtOAc (50 → 100%) gradient to give 42 mg (88.6%) of 7, syrup, $|\alpha|_D$ +5.8° (C 1.0): ^{1}H-NMR:δ 1.04, 1.12, 1.28, and 1.45 (12H, 4d, Me-2, 4, 8, and 10), 1.03 (3H, t: 7.5 Hz, Me-14), 1.08 and 1.22 (6H, 2s, Me-6 and 12), 1.44 and 1.45 (6H, 2s, -$OCMe_2O$-), 1.60, 1.75, and 1.95 (6H, 3m, H-4, 7, 7', 10, 14 and 14'), 2.60 (1H, m, H-8), 2.68 (1H, dq: 7, 10 Hz, H-2), 3.28 (1H, br.d: 11 Hz, H-9), 3.35 (1H, dd: 2, 10 Hz, H-3), 3.62 (1H, d: 2 Hz, H-5), 3.81 (3H, s, $\underline{Me}OC_6H_4CH$), 4.31 (1H, d: 2 Hz, H-11), 5.82 (1H, s, $MeOC_6H_4C\underline{H}$), 6.90 and 7.42 (4H, 2m, ($MeOC_6\underline{H}_4CH$).

Compound 8. This was obtained from 10 according to the procedure described for 7 in 77.5% yield, syrup, $|\alpha|_D$ -62° (C 1.0); ^{1}H-NMR: δ 0.76 (3H, d: 7 Hz, Me-12), 0.97 (3H, t: 7 Hz, Me--14), 1.02 (3H, d: 6.5 Hz, Me-10(4)), 1.21 (3H, d: 6.5 Hz, Me-8), 1.22 (3H, d: 6.5 Hz, Me-4 (10)), 1.24 (3H, s, Me-6), 1.27 (3H, d: 6.5 Hz, Me-2), 1.43 and 1.56 (2H, 2m, H-14) and 14'), 1.45 and 1.48 (6H, 2s, -$OCMe_2O$-), 1.70-1.80 (2H, m, H-4 and 10), 1.85 (1H, ddq: 2, 8.5, 7 Hz, H-12), 2.56 (1H, m, H-8), 2.66 (1H, dq: 10, 6.5 Hz, H-2), 2.32 (1H, br.d: 10.5 Hz, H-9), 3.81 (3H, s, $\underline{Me}OC_6H_4CH$), 3.89 (1H, d: 2 Hz, H-5), 3.90 (1H, dd: 2, 10 Hz, H-3), 3.91 (1H, dd: 2, 8.5 Hz, H-11), 3.95 (1H, ddd: 2, 4.5, 9 Hz, H-13), 5.62 (1H, s, $MeOC_6H_4C\underline{H}$), 6.90 and 7.42 (4H, 2m, $MeOC_6\underline{H}_4CH$).

Compound 59. A solution of 42 mg (70.4 μmol) of 7, 92 mg (351.9 μmol, 5 eq) of Ph_3P and 202 mg (351.9 μmol, 5 eq.) of bis-(1-isopropyl-4-tert-butylimidazolyl-2-sulfide) in 70 ml of dry $PhCH_3$

was refluxed under argon for 20 h. Then the solution was evaporated and 50 ml of EtOAc-hexane (1:10) was added. The precipitate was separated with hexane. The combined solutions were evaporated to dryness, the residue was dissolved in 4 ml acetone-water (3:1), an excess of $CaCO_3$ and $Hg(OCOCF_3)_2$ were added to the stirred solution. The mixture was stirred for 5 min, sat. $NaHCO_3$ soln was added, and the resulting solution was extracted with $CHCl_3$. The extract was washed with brine, dried and evaporated; chromatography of the residue (hexane-EtOAc 3:2) gave 29 mg (71.2%) of 59, m.p. 232-233°C (hexane-EtOAc 4:1), $|\alpha|_D$ 0°(C 1.0); ^{1}H-NMR: δ 0.84 (3H, t: 7.5 Hz, Me-14), 1.02, 1.22, 1.24, and 1.40 (12H, 4d, Me-2, 4, 8, and 10), 1.15 and 1.25 (6H, 2s, Me-6 and 12), 1.48 and 1.53 (6H, 2s, $-OCMe_2O-$), 1.60 and 1.90 (6H, 2m, H-4, 7, 7', 10, 14, and 14'), 2.20 (1H, br.s, OH-6), 2.46 (1H, m, H-8), 2.70 (1H, s, OH-12), 2.78 (1H, dq: 11, 6.5 Hz, H-2), 3.32 (1H, br.d: 11.5 Hz, h-9), 3.70 (1H, d: 1.9 Hz, H-11), 3.82 (3H, s, $MeOC_6H_4CH$), 3.88 (1H, dd: 1, 11 Hz, H-3), 4.04 (1H, d: 1 Hz, H-5), 5.16 (1H, dd: 2, 11.5 Hz, H-13), 5.78 (1H, s, $MeOC_6H_4CH$), 6.92 and 7.52 (4H, 2m, $MeOC_6H_4CH$). Found: C, 66.32; H, 8.80. Calc. for $C_{32}H_{50}O_9$: C, 66.41; H, 8.71%.

Compound 60. a) To a solution of 144 mg (248 μmol) of 8 in 3.5 ml of THF was added 403.6 mg (1.55 mmol, 6.25 eq.) of Ph_3P and 220.31 mg (1.55 mmol, 6.25 eq.) of $(PyS)_2$. The mixture was kept at RT for 30 min, diluted with dry $PhCH_3$ (100 ml), refluxed for 20 h under argon and then evaporated. Chromatography of the residue (hexane-EtOAc 4:1) gave 30 mg (21.5%) of 60, m.p. 103-104°C (pentane), $|\alpha|_D$ -1° (C 1.0).

b) To a solution of 13 mg (22.38 μmol) of 8 in 22 ml of dry $PhCH_3$ was added 29 mg (111.8 μmol, 5 eq.) of Ph_3P and 44 mg (111.8 μmol, 5 eq.) of bis-(1-isopropyl-4-tert-butylimidazolyl-2-sulfide). The mixture was refluxed under argon for 10 h and then evaporated. Chromatography of the residue (hexane-EtOAc 4:1) gave 9.0 mg (71.5%)of 60. ^{1}H-NMR: δ 0.87 (3H, t: 7.3 Hz, Me-14), 0.88 and 1.02 (6H, 2d, Me-10 and 12), 1.21 (3H, d: 6.5 Hz, Me-2), 1.23 (3H, d: 6.5 Hz, Me-4), 1.25 (3H, s, Me-6), 1.26 (3H, d: 6 Hz, Me-8), 1.48 and 1.53 (6H, 2s, $-OCMe_2O-$), 1.30-1.50 (2H, m, H-7 and 7'), 1.46 (1H, m, H-14), 1.60-1.80 (4H, m, H-4, 10, 12, and 14'), 2.23 (1H, br.s, OH-6), 2.51 (1H, dddq: 2, 10.5, 6 Hz, H-8), 2.78 (1H, dq: 10.5, 6.5 Hz, H-2), 3.35 (1H, d: 10.5 Hz, H-9), 3.66 (1H, dd: 1.5, 9.1 Hz, H-11), 3.90 (1H, dd: 1, 10.5 Hz, H-3), 3.80 (3H, s, $MeOC_6H_4CH$), 4.06 (1H, d: 1.2 Hz, H-5), 5.47 (1H, ddd: 0.9, 4.5, 10 Hz, H-13), 5.69 (1H, s, $MeOC_6H_4CH$), 6.89 and 7.50 (4H, 2m, $MeOC_6H_4CH$), Found: C, 68.21; H, 8.91. Calc. for $C_{32}H_{50}O_8$: C, 68.30; H, 8.96%.

(9S)-Dihydroerythronolide A 61. A solution of 29 mg (50.1 μmol) of 59 in 2.25 ml of MeCN-TFA-H_2O (4:4:1) was kept at RT for 10 min. The mixture was neutralized with solid $NaHCO_3$, diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried and evaporated. Chromatography of the residue (EtOAc) gave 19.7 mg (93.5%) of 61, m.p. 202-204°C (hexane-acetone), $|\alpha|_D$ +8.4° (C 1.0) (cf.[29]).

(9S)-Dihydroerythronolide B 62. A solution of 293 mg (520.7 μmol) of 60 in 11.25 ml MeCN-TFA-H_2O (4:4:1) was kept at RT for 5 min. The mixture was neutralized with solid $NaHCO_3$, diluted with $CHCl_3$, washed with water, brine, dried and evaporated. Chromatography pf the residue ($CHCl_3$-MeOH 30:1) gave 185 mg (88%) of 62, m.p. 181.5-182°C (ether), $|\alpha|_D$ +6.1° (C 1.0, methanol) (cf.[30]).

(9S)-Dihydro-3,5-benzylideneerythronolide B 6. To a suspension of 451 mg (1.115 mmol) of 62 in 10 ml of CH_2Cl_2 was added 1.0 mg (5.6 mmol, 5 eq.) of benzylidene diethylacetal. The mixture was cooled to -10°C and 28 mg (120 μmol. 10 mol.%) of (±)-camphor-10-sulfonic acid was added. The mixture was stirred for 5.5 h at -10°C and neutralized with $NaHCO_3$ solution. Extractive work-up followed by chromatography (hexane-EtOAc 3:2) gave 264 mg (48%) of 6, 46 mg (10%) of unchanged 62, and besides other mono- and bis-acetal derivatives. These were hydrolyzed (MeCN-TFA-H_2O 4:4:1, 30 h, RT) to give 87 mg (19.3%) of 62. Thus, corrected total yield of 6, m.p. 235.5-236°C (hexane), $|\alpha|_D$ +2.3° (C 1.0), was 67.9% with respect to consumed 62; ^{1}H-NMR (+D_2O):δ 0.93 (3H, t: 7.5 Hz, Me-14), 0.85, 1.11, 1.15, 1.28, and 1.36 (15H, 5d, Me-2, 4, 8, 10, and 12), 1.31 (3H, s, Me-6), 2.91 (1H, dq: 11, 6.5 Hz, H-2), 3.12 (1H, dd: 2, 10 Hz, H-9), 3.70 (1H, br.d: 9.5 Hz, H-11), 3.83 (1H, dd:1, 11 Hz, H-3), 4.00 (1H, d: 1 Hz, H-5), 5.32 (1H, ddd: 1.2, 4.5 Hz, H-13), 5.68 (1H, s, PhC<u>H</u>), 7.40 and 7.52 (5H, 2m, <u>Ph</u>CH). Found: C, 68.15; H, 9.05. Calc. for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00%.

3,5-O-Benzylideneerythronolide B 64. To a stirred solution of 236 mg (479 μmol) of 6 in 5 ml of CH_2Cl_2 was added 0.5 g of powdery molecular sieves (3 A), the mixture was cooled to 0° and 310 mg (1.44 mmol. 3 eq.) of PCC was added. After 30 min the mixture was diluted with ether, passed with the same solvent through a pad of SiO_2, to remove inorganics. The washings were evaporated. Chromatography of the residue (hexane-EtOAc 2:1) gave 167 mg (71%) of 64, m.p. 94-94.5°C (pentane-ether), $|\alpha|_D$ -41° (C 1.0); ^{1}H-NMR:δ 0.92, 1.08, 1.22, and 1.30 (15H, 4d: 7 Hz, Me-2, 4, 8, 10, and 12), 0.93 (3H, t: 7 Hz, Me.14), 1.33 (3H, s, Me-6), 1.55, 1.80 2.14 (6H, 3m, H-4, 7, 7', 12, 14, and 14'), 2.30 (1H, br.s, OH-6), 2.75-3.05 (3H, m, H-2, 8, and 10), 3.91 (1H, dd: 1.5, 10.5 Hz, H-3), 3.93 (1H, m, H-11), 4.06 (1H, d: 1.5 Hz, H-5), 5.35 (1H, ddd:, 1.5, 4.5, 9.5 Hz, H-13), 5.71 (1H, s, PhC<u>H</u>), 7.40 and 7.53 (5H, 2m, <u>Ph</u>CH). Found: C, 68.39; H, 8.58. Calc. for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63%.

Erythronolide B 4. A solution of 28 mg (57 μmol) of 64 in 1 ml of 80% AcOH was heated at 50°C for 3 h. The mixture was neutralized with $NaHCO_3$ solution, extracted with EtOAc, the extract was washed with brine, dried and evaporated. Chromatography of the residue ($CHCl_3$-MeOH 20:1) gave 15 mg (65%) of 4, m.p. 223-224°C (ethanol), $|\alpha|_D$ -65.8° (C 1.01, MeOH) (cf.[31]). Synthesized erythronolide B proved to be identical in all respects to the natural sample, isolated from mother liquor after crystallization of erythromycin A. Samples of derivatives 60 and 62, obtained from natural erythronolide B, also proved to be identical.

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