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THE OXIRANE RING OPENINGS OF THE DIANHYDRO SUGAR WITH HIGH REGIOSELECTIVITY AND ITS USE IN PREPARATION OF TWO CHIRAL SEGMENTS OF 6-DEOXYERYTHRONOLIDE B

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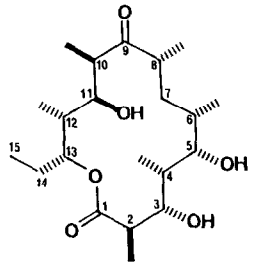
Summary: The oxirane ring of the dianhydro sugar **2** obtained from levoglucosan (1,6-anhydro-β-D-glucose) is opened regioselectively with organometallic carbon nucleophiles and its application to an asymmetric synthesis of the C_1-C_5 segment **9** together with the C_9-C_{15} unit **18** of 6-deoxyerythronolide B **1** is described.

Many monosaccharides and a large number of their derivatives are easily available and versatile compounds. They prove to be now an important source of chirality for the total synthesis of optically active natural products.[1] The structurally rigid and readily available levoglucosan **4** has been used recently in the synthesis of biologically active natural products.[2] Most recent report[3] that the 2,3-epoxide **2** was effectively opened trans-diaxially only with the reagent of the lithium anion of thioanisole as carbon nucleophiles prompted us to describe our own results, which provided a convenient method for the preparation of dialkyl alcohol **3** from **2** by reaction with organometallic reagents.



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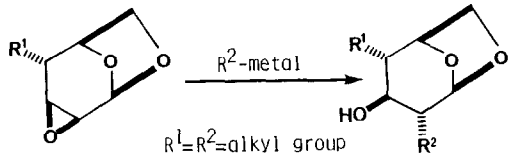
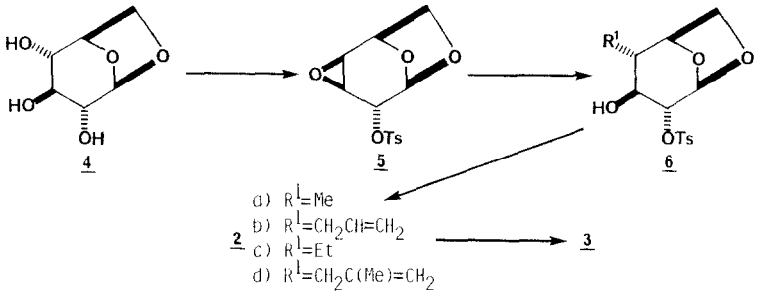


2 **3**

In connection with ongoing program directed toward utilization of levoglucosan **4** for synthesis of naturally occurring macrolide antibiotics, its application to the synthesis of two chiral segments of 6-deoxyerythronolide B **1** is described.



Levoglucosan **4**[4] was converted, via the ditosylate, into the 3,4-epoxytosylate **5**.[5] Compounds **2a** and **2b** were prepared in good yield by copper(I) induced reaction[2a,b] with methyl- or allylmagnesium chloride in THF, followed by treatment with sodium methoxide. A similar sequence for the preparation of **2c** and **2d** was applied to give rise to 62% yields respectively. Conversion of the 2,3-epoxide **2** into the dialkylated anhydro sugar **3** was achieved with a preferential trans-diaxial opening of oxirane ring and a wide variety of organometallic reagents were attempted before suitable conditions for the transformation were found. The reactions as shown in Table 1 were carried out either by using copper(I) catalyzed additions of Grignard reagents or by employing dimethylcopperlithium at 0°C in THF to afford **3** in acceptable yield.

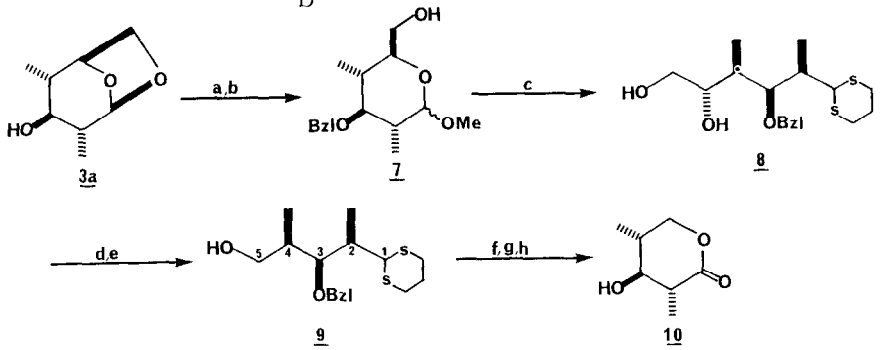
Table 1 Conversion of epoxide **2** to alcohol **3**[a)]

entry	R^1	R^2	organometallic reagent	yield(%)
a	Me	Me	Me_2CuLi	41
b	Me	CH_2=$CHCH_2$	CH_2=$CHCH_2MgBr$ /CuI	71[b)]
c	CH_2=$CHCH_2$	Me	MeMgI/CuI	70
d	CH_2=$CHCH_2$	CH_2=$CHCH_2$	CH_2=$CHCH_2MgCl$ /CuI	56
e	Et	CH_2=$CHCH_2$	CH_2=$CHCH_2MgBr$ /CuI	55
f	CH_2=$CMeCH_2$	Me	MeMgBr/CuI	45

a The reactions were performed at 0°C in THF unless indicated.
b The reaction was carried out at room temperature and the regioisomer (trans diequatrial opening) was isolated in 13% yield.

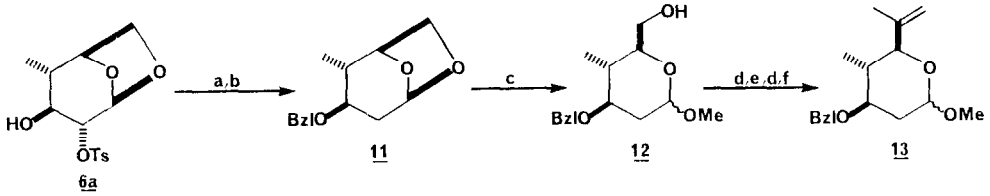
In the remaining paragraph, we will describe the synthesis of the optically active segments C_1-C_5 and C_9-C_{15} of 6-deoxyerythronolide B **1**, which is a macrolide antibiotic with ten asymmetric centers.[6]

Compounds 3a and 6a(R^1=Me) can be used in the preparation of two units 9 and 18 of 1 as follows. Benzylation of 3a ($PhCH_2Br/NaH/cat.n\text{-}Bu_4NI$, 94%) followed by anhydro ring opening (CSA/MeOH) gave smoothly acetal 7, which in turn was subjected to thioacetalization ($HS(CH_2)_3SH/BF_3\cdot Et_2O$) to furnish thioacetal 8 in 65% yield. Oxidative cleavage of 8 with lead tetraacetate and reduction with sodium borohydride led to the corresponding alcohol 9 in 63% yield. Thioacetal 9 obtained in this way was also converted to lactone 10 via the following functional group manipulation involving (I) $AgNO_3$/NCS (II) Jones oxidation (III) $H_2/Pd(OH)_2$-C. Lactone 10, which was obtained by Gerson[7] from part of (9S)-dihydroerythronolide A , had mp 88°C, and $[\alpha]_D$=-4.6° (MeOH)[lit.[7] mp 88-89°C, $[\alpha]_D$=-5.0°(MeOH)].



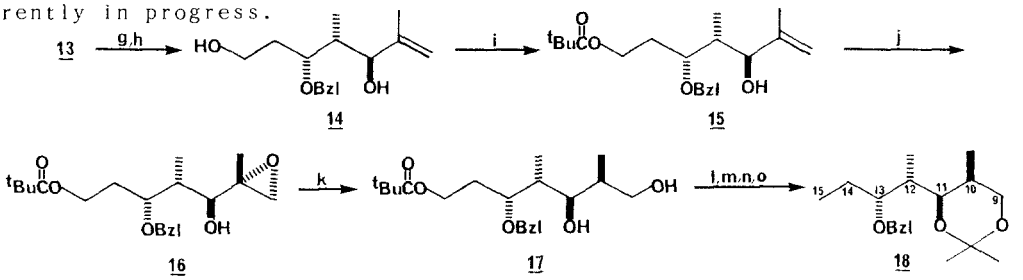
a) BzlBr/NaH/n-Bu_4NI(cat) b) MeOH/CSA c) $HS(CH_2)_3SH/BF_3\cdot Et_2O$ d) $Pb(OAc)_4/C_6H_6$
e) $NaBH_4$/MeOH f) $AgNO_3$/NCS g) Jones oxid. h) $H_2/Pd(OH)_2$-C/MeOH

Turning next to elaboration of the segment 18 , the anhydro benzyl ether 11 was easily prepared from 6a(R^1=Me) in two steps ((I) $LiBEt_3H$/THF, 80%[2c] (II) $C_6H_5CH_2Br/NaH/cat.n\text{-}Bu_4NI$, 94%). Subsequent ring opening of 11 ($MeOH/BF_3\cdot Et_2O$) gave an anomeric mixture of acetal 12 in quantitative yield. Transformation of 12 into 13 was performed by a conventional way in four steps ((I) PCC/MS4A[8], 80% (II) MeMgBr/THF, 83% (III) PCC/MS4A (IV) $Ph_3P{=}CH_2$/THF, 67% in two steps). Hydrolysis of 13 with 10% H_2SO_4 in THF and subsequent reduction with $LiAlH_4$ gave diol 14 in 76% yield. Concomitant protection of the primary hydroxyl group of 14 afforded 15 in 81% yield. Epoxidation[9] of the allylic alcohol 15 ($VO(acac)_2/TBHP/C_6H_6$) produced diastereomerically pure 16 in 79% yield. When epoxide 16 was allowed to react with $NaBH_3CN$[10] in the presence of $BF_3\cdot Et_2O$, a 33% yield of diol 17 was obtained with the desired stereochemistry at C-10 position.[11]



a) $LiBEt_3H$/THF b) BzlBr/NaH/n-Bu_4NI(cat) c) MeOH/$BF_3\cdot Et_2O$ d) PCC/MS4A
e) MeMgBr/THF f) $Ph_3P^+CH_3Br^-$/n-BuLi/THF

Finally, 17 was then converted to segment 18 by the following sequences shown below. The total synthesis directed toward 6-deoxyerythronolide B is currently in progress.



g) 10%H_2SO_4/THF h) $LiAlH_4$/THF i) ^tBuCOCl/Pyr. j) $VO(acac)_2$/TBHP/C_6H_6
k) $NaBH_3CN/BF_3{\cdot}Et_2O$/THF l) $Me_2C(OMe)_2$/CSA m) $LiAlH_4/Et_2O$ n) TsCl/Pyr. o) $LiBEt_3H$/THF

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