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APPROACHES TO THE TOTAL SYNTHESIS OF NATURAL PRODUCTS FROM CARBOHYDRATES

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Abstract - Carbohydrates provide useful starting materials for the synthesis of polyfunctional, chiral natural products. The complex macrolide aglycon, erythronolide A, which has 10 asymmetric carbon atoms, substituted with hydroxyl and *C*-methyl groups can be considered as two functionalized acyclic segments (C-1—C-6 and C-9—C-15), bridged by a two-carbon unit (C-7—C-8) bearing a *C*-methyl group. Approaches to the synthesis of these two segments from D-glucose are described, based on the systematic, stereocontrolled introduction of functional groups, and the efficient utilization of common synthetic intermediates.

INTRODUCTION

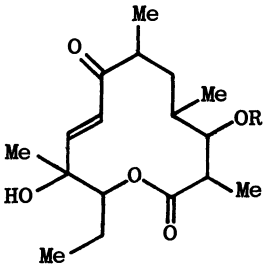
With the advent of sophisticated instrumental techniques, newer isolation methods, and micro-scale physico-chemical analyses, truly remarkable progress has been made in the structure elucidation of complex, naturally-occurring compounds, many of which are of therapeutic interest. The unveiling of novel structures by these methods has fostered new developments in synthetic organic chemistry, and it has provided the organic chemist with ever-increasing challenges. The past two or three decades have witnessed an accelerating growth in this area, highlighted by many outstanding achievements in the pursuit of formidable synthetic objectives (Ref. 1). The unique structural and stereochemical features in many of these substances have necessitated the development of ingeneous synthetic schemes, which have been ultimately tested in the laboratory. As a result, many tailor-made reagents have been discovered, and have found wide applications. In this context, even unsuccessful synthetic ventures have contributed to the development of new preparative methods. Indeed, the chemical literature is rich in a multitude of elegant reactions, describing individual transformations.

The pursuit of a given synthetic goal has been characterized by the highly individualized nature of the various synthetic approaches as a result of the application of widely different concepts and designs. The proper selection of starting material, could therefore essentially dictate the synthetic strategy, and possibly its outcome. The carbohydrates constitute an abundant and relatively inexpensive source of chiral carbon compounds, and they are readily available in a variety of chain lengths and configurations. Through chemical manipulation, these compounds can be transformed into versatile synthetic intermediates, that bear functional groups and chiral centers of a predetermined nature, and are amenable to elaboration into the structural framework of many natural products. It is thus possible to utilize carbohydrates, or fragments derived therefrom, to construct chiral, acyclic, heterocyclic or carbocyclic compounds, in such a manner so as to situate some, or all of the functional groups and chiral centers in the target molecule at the outset (Ref. 2). A long-standing research program in our laboratory has been based on the recognition of hidden "sugar" components in the carbon skeletal framework of certain natural products. With due consideration being given to the elements of practicality and efficacy, this aspect of the utility of carbohydrates in organic synthesis could be viewed in a much wider perspective. The seldom used "carbohydrate precursor" approach to total synthesis has now been extended to the challenging problem of macrolide synthesis (Ref. 3).

*Professor Hanessian was unable to attend the Symposium to present the lecture personally.

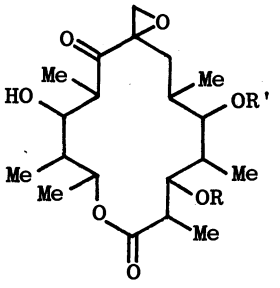
THE MACROLIDE ANTIBIOTICS

The macrolide antibiotics (Ref. 4) are a group of glycosidically-bound 12-, 14-, and 16-membered macrocyclic lactones derived from various Actinomycetes (Ref. 5). Many of these therapeutically important substances are commercially produced. Their constitutional structures, which are endowed with unique functional and configurational features, have been elegantly elucidated by chemical and physico-chemical methods (Ref. 6). From chemical degradation data and biosynthetic considerations (Ref. 7), a configurational model was developed (Ref. 8) that ingeneously demonstrated the close chiral relationships in the macrolide antibiotics, and predicted configurational assignments. Figure 1 illustrates the structures of three macrolide antibiotics, namely



METHYMYCIN

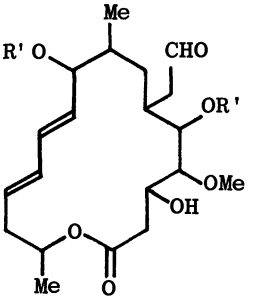
R = desosaminyl



OLEANDOMYCIN

R = oleandrosyl

R'=desosaminyl



SPIRAMYCIN

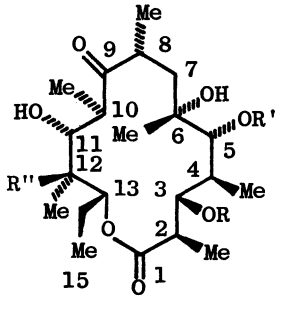
R' = mycarosyl-
mycaminosyl

Fig. 1 Examples of macrolide antibiotics

methymycin, oleandomycin and spiramycin, representing 12-, 14-, and 16-membered aglycons respectively. Interestingly, methymycin is the only example of a 12-membered macrolide. Although the structures and biogenesis of the macrolide antibiotics have been known for some years, efforts directed toward their total synthesis have been curtailed, most likely due to the difficulties encountered in the construction of the uniquely functionalized carbon chains, and the lack of suitable macrolactonization methods. The latter problem has been recently solved with the discovery of mild lactonization procedures (Ref. 9, 10), that are also applicable to the aglycon portions of the macrolide antibiotics. Another landmark accomplishment in this area has been the first, total synthesis of a macrolide antibiotic, methymycin, by Masamune and coworkers (Ref. 11). The pursuit of equally, if not more formidable synthetic objectives in this series, will undoubtedly be among the most challenging endeavours in the near future.

THE ERYTHRONOLIDES

Erythromycin is a mixture of three closely related antibiotics, elaborated by *S. erythreus*. The major component, erythromycin A, was the first to be isolated and its structure assigned (Ref. 12, 13). Its complete structure and stereochemistry was determined by X-ray crystallographic analysis (Ref. 14). Figure 2 shows the structures of erythromycin A and B, and of erythronolide A



R = cladinosyl;

R'=desosaminyl

Erythromycin A, R" = OH

Erythromycin B, R" = H

Erythronolide A, R = OH

Erythronolide B, R = H

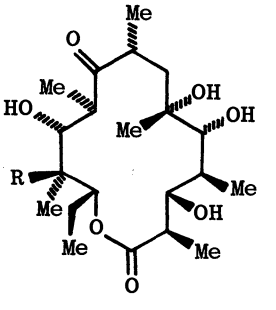


Fig. 2 Structures of the erythronolides and the erythromycins

and B, the respective aglycon portions of these antibiotics. Although the structures and absolute configuration of these molecules were established beyond doubt by the mid-sixties, aspects pertaining to their conformations in solution were yet to be deciphered. This intriguing problem was solved mainly due to the pioneering studies of Celmer (Ref. 15), Perun (Ref. 16) and their coworkers. Figure 3 depicts the preferred conformation of erythronolide B in

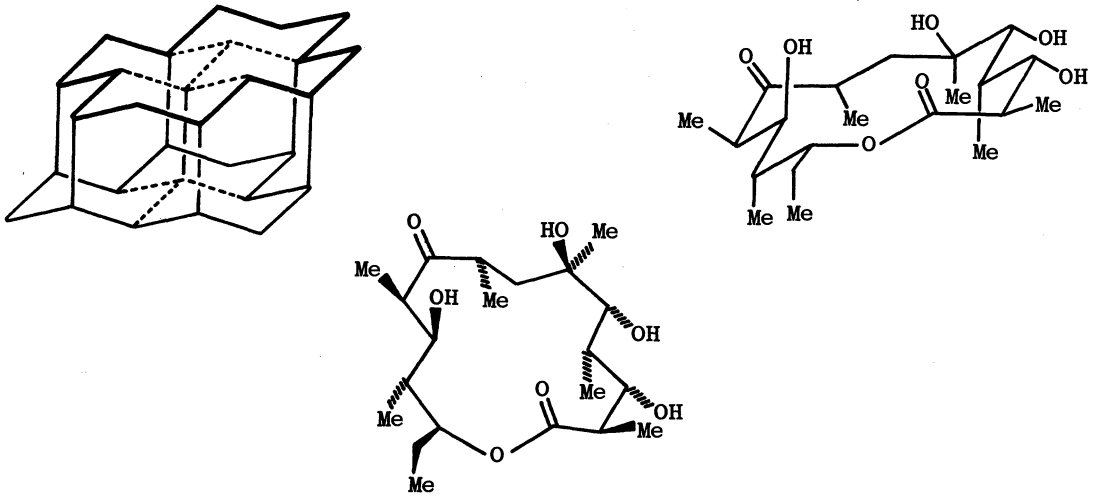


Fig. 3 Conformational models of erythronolide B.

dilute solution as proposed by Perun and coworkers (Ref. 16), based on careful nuclear magnetic resonance spectral data analysis.

The presently accepted conformation for the erythronolides is the result of further refinements of the ingeneously perceived "diamond lattice" conformation, originally proposed for 14-membered cyclic hydrocarbons (Ref. 17), and later applied to the macrolides (Ref. 15, 18). It may be pertinent to point out that because of the phenomenon of pseudorotation in these large rings, the various functional groups tend to adopt "apparent" spatial orientations depending on the arbitrary conformation that is selected. Configurational correlations between different pictorial structural representations of the erythronolides (and of other functionalized, chiral macrocyclic compounds), could therefore be misleading, and may result in the erroneous transposition of some functional groups (compare Fig. 2, 3).

SYNTHETIC STUDIES

The total synthesis of the erythronolides constitutes one of the many challenging problems that are of current interest in synthetic organic chemistry.

Erythronolide A and B contain each, 10 asymmetric centers, comprising several vicinally situated alternating, *C*-methyl and hydroxyl groups. Erythronolide A, contains two tertiary carbon atoms at C-6 and C-12 (Fig. 2). The formidable task of chemically assembling the carbon skeleton of the erythronolides can be considerably simplified, with the recognition of the sequence of chiral centers, as two functionalized, acyclic, carbohydrate-derived chains. This can be best visualized by a consideration of the extended-chain form of erythronolide A for example, where it can be recognized that C-1—C-6, and C-9—C-15 have the L-*ido* and D-*gluco* stereochemistry respectively (Fig. 4). In the alternate hypothetical expression, the chain is partially "folded" to illustrate the configurational relation of C-1—C-6 and C-9—C-15 of the original molecule, to two proposed synthetic carbohydrate precursors I and II having the L-*ido* and D-*gluco* stereochemistry respectively.

Precursors I and II thus comprise eight of the ten chiral centers in erythronolide A, and contain the desired sequence of functional groups. The anomeric carbon atoms, are, respectively, the sites of the lactone and C-9 carbonyl groups in the original molecule. Consideration of these structures reveals that C-2 and C-10, and C-3 and C-11 have the same substituents, namely *C*-methyl

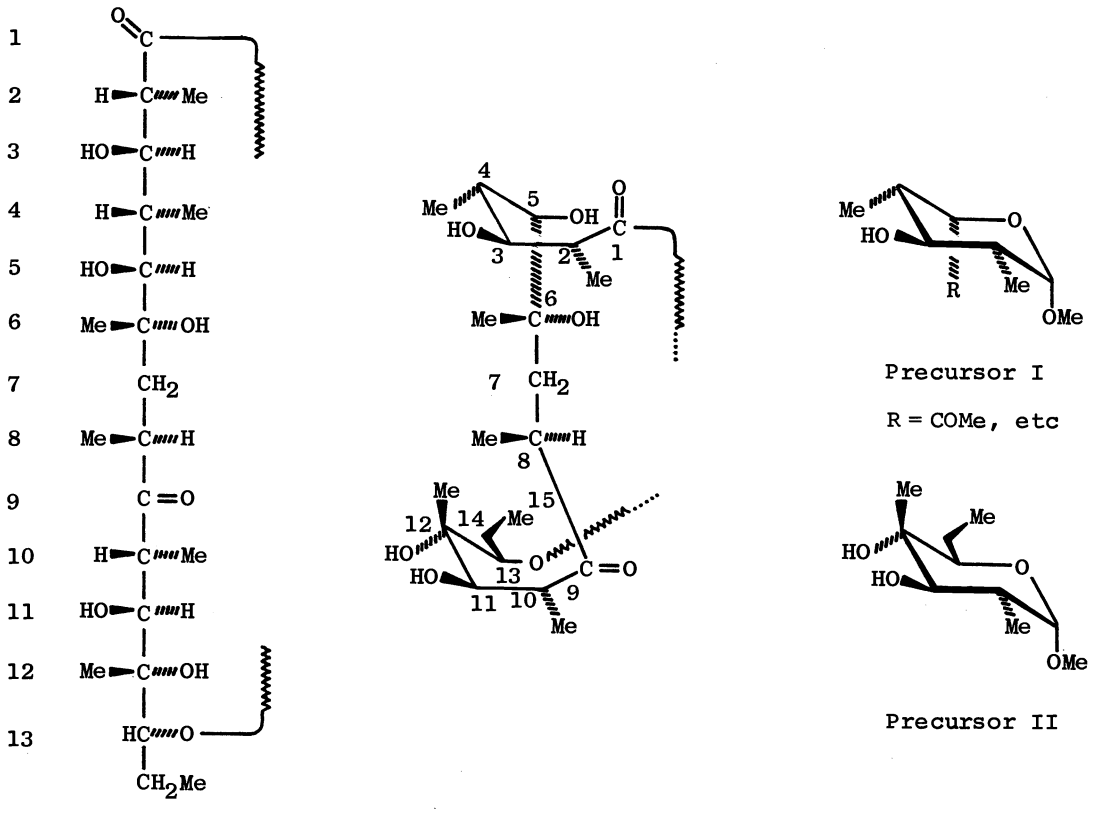


Fig. 4 "Extended" chain (left) and "folded" chain (middle) forms of erythronolide A. - Chemical precursors (I and II) to the C-1—C-6 and C-9—C-15 segments of erythronolide A (right).

and hydroxyl respectively. In planning a synthetic stratagem leading to the two precursors I and II, it was considered highly desirable to utilize readily available and cheap starting materials. In the broader context of the synthesis of erythronolide A from these precursors, it was also important to devise schemes that would utilize common intermediates, so as to render the multistep sequence as efficient as possible. Our synthetic plan for the synthesis of the two precursors starts with D-glucose, and is based on the systematic and stereocontrolled introduction of appropriate functional groups. Since the C-3 hydroxyl group in each compound can be considered as being part of the original sugar, and the *C*-ethyl group in II can be elaborated from the terminal carbon atoms of a compound having the D-*gluco* configuration, the crucial synthetic problems consist in the regio- and stereospecific incorporation of *C*-methyl branch points in both compounds, and in the establishment of an L-*ido* stereochemistry in precursor I (C-1—C-6 segment of erythronolide A). Figure 5 illustrates the basic synthetic plan for the preparation of precursors I and II. A common 4-uloside intermediate, in which C-2 and C-3 have the required functionalities and correct chirality was envisaged for the elaboration of both precursors. Stereoselective *C*-methylation at C-4 and further chain extension at C-6 would lead to the desired precursor II (representing C-9—C-15 of erythronolide A). On the other hand, oxidation of C-6 in the branched-chain intermediate, followed by base-catalyzed β-elimination would lead to a 4,5-unsaturated derivative, which would be expected to undergo a *cis* hydrogenation either catalytically or by chemical means, to give preponderantly, if not exclusively, precursor I, having the L-*ido* stereochemistry, based on related precedents reported in the literature (Ref. 19).

Branched-chain sugars in which the *C*-methyl group is attached to a ring carbon atom bearing a hydroxyl group (Type A, Me-C-OH) can be relatively easily prepared from appropriate glycosulose derivatives and organometallic reagents (Ref. 20, 21). On the other hand, branched-chain sugars in which the *C*-methyl group replaces a hydroxyl group on a ring carbon atom (Type B, Me-C-H), are not as readily accessible (Ref. 22). The situation is further complicated

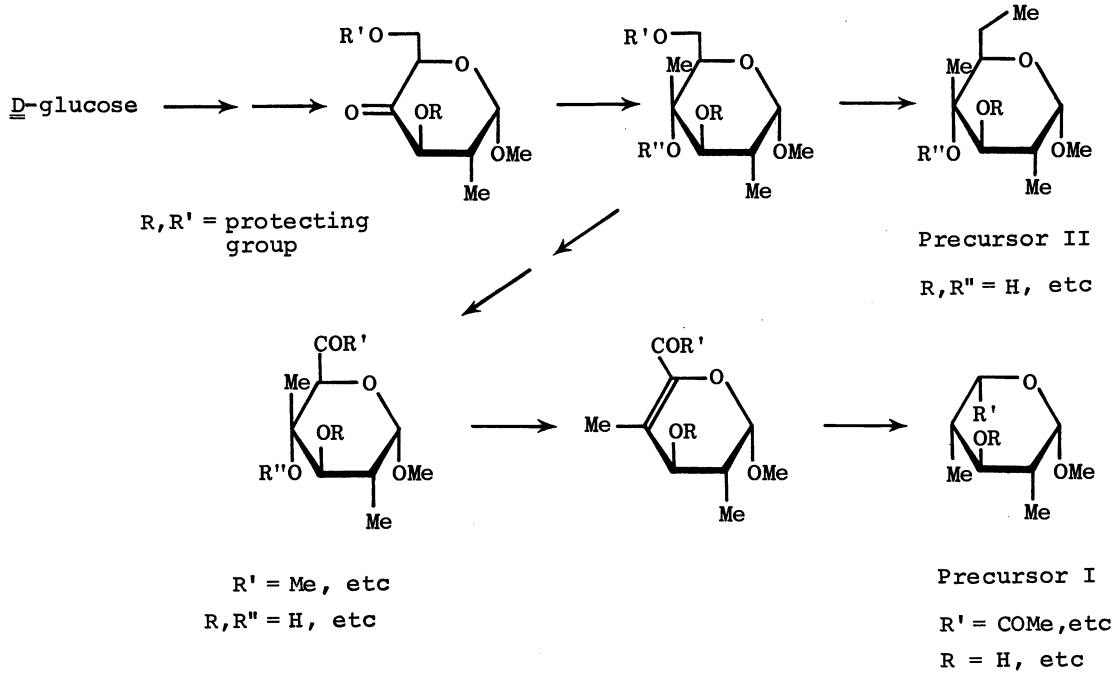


Fig. 5 Synthetic plan for the preparation of chemical precursors to erythronolide A.

when the introduction of these *C*-methyl groups should also take place stereospecifically, in order to accomodate the desired chirality at the branch point. Thus, it can be seen that in precursor I for example, no less than two *C*-methyl groups of Type B have to be introduced. Furthermore, these groups have equatorial orientations - a stereochemical subtlety that can be better appreciated if it is recalled that direct access to this type of orientation has, to the best of our knowledge, no precedent in the carbohydrate series. The opening of an epoxide ring in a conformationally-biased derivative with nucleophiles, including carbanions (Ref. 22), is regiospecific, but leads to products with axially disposed groups. For example, treatment of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside with methylmagnesium chloride gives a 2-*C*-methyl derivative with the D-*altro* configuration, and in only moderate yield, after chromatographic purification. (Ref. 23). An alternate method involves treatment of the above mentioned epoxide with sodium methylsulfinylmethide (dimsyl sodium), followed by desulfurization of the resulting sulfoxide derivative with Raney - nickel (Ref. 24). A method for the indirect introduction of the 2-*C*-methyl substituent in the D-*gluco* series, consists in the treatment of an appropriately substituted 2-hexosulose derivative with methylenetriphenylphosphorane, followed by stereoselective catalytic reduction of the *C*-methylene derivative (Ref. 25). The synthesis of macrolide antibiotics from *C*-methyl sugars has been alluded to (Ref. 25).

The incorporation of equatorial *C*-methyl and hydroxyl groups at C-2 and C-3 respectively in compounds leading to precursors I and II, was expected to take place via a fundamental, thermodynamically controlled transformation in synthetic organic chemistry, namely the base-catalyzed epimerization of α-substituted ketones. We based our prediction on the premise that an axial *C*-methyl group situated at C-2 of a derivative in the D-*altro* series for example, could be induced to epimerize, once the axial C-3 hydroxyl group was oxidized to a carbonyl group. The same principle was expected to be operative in the introduction of an equatorial hydroxyl at C-3, Fig. 6. The incorporation of the remaining functional groups, and the establishment of the correct chirality at the ring carbon atoms (C-4, C-5) were based on well-known reactions, previously reported in other series. The synthetic plan outlined in Fig. 5 was then executed as described below.

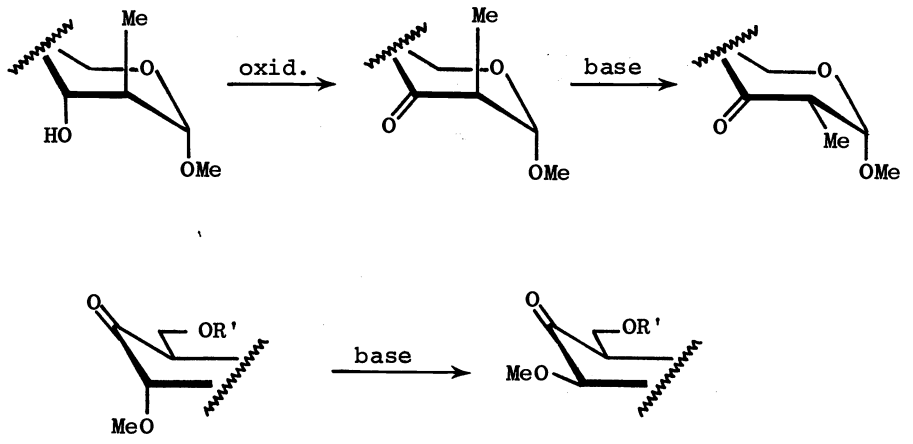


Fig. 6 Base-catalyzed epimerizations leading to equatorially disposed *C*-methyl and *O*-methyl groups.

Approaches to precursors I and II via a common synthetic pathway. The introduction of the *C*-methyl group located at C-2 in both precursors was accomplished by treatment of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside 1 (Ref. 26) with lithium dimethylcuprate in ether (Ref. 27, 28), which gave crystalline methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-altropyranoside 2 in 65% yield (Fig. 7). Additional material could also be obtained by chromatography of the mother liquors. Treatment of 2 with methylsulfoxide-acetic anhydride gave the crystalline 3-uloside derivative 3 in over 95% yield. Upon treatment of 3 with a solution of sodium methoxide in methanol, essentially complete epimerization took place to give the C-2 epimeric, crystalline derivative 4 in 85% yield. The peaks due to the *C*-methyl and anomeric proton in the p.m.r. spectrum of compound 4 were shifted upfield and downfield respectively, compared to the same peaks in the spectrum of 3. In this manner, the first chiral center in precursors I and II was introduced in three steps from 1 and in good overall yield. Reduction of the carbonyl function in 4 with sodium borohydride in a mixture of methanol and DMF, gave the corresponding axial alcohol almost exclusively. It is of interest that similar reduction of 3, led preponderantly to 2, indicating that epimerization did not take place under these conditions. Methylation of the axial alcohol resulting from the reduction of 4 with methyl iodide in the presence of sodium hydride in the usual manner, gave the crystalline 3-*O*-methyl derivative 5 in 80% overall yield. The acetal group was then cleaved under hydrogenolytic conditions, and the resulting product was treated with trityl chloride in pyridine to give the crystalline 6-*O*-trityl derivative 6 in 83% overall yield. Inversion of configuration at C-3 in 6, as would be required for precursors I and II, was accomplished by an oxidation-epimerization sequence as previously described. Oxidation of 6 with 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDAC.HCl) in methylsulfoxide (Ref. 29,30), in the presence of pyridinium trifluoroacetate, or with pyridinium chlorochromate in dichloromethane (Ref. 31), gave methyl 2-deoxy-2-*C*-methyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-*ribo*-hex-4-pyranuloside, 7 in quantitative yield. Oxidations of primary and secondary hydroxyl groups by the above mentioned methods has been found to proceed easily and in high yields in several carbohydrate derivatives and merits attention. When compound 7 was treated with methanolic sodium methoxide, essentially complete epimerization took place at C-3 to give the highly crystalline derivative 8. The chemical shifts and multiplicities of H-3 and H-5 in the p.m.r spectrum of compound 8 were clearly changed compared to the same proton signals in the epimeric 7. A change could also be seen in the chemical shift of the respective C-3 methoxyl groups. Compound 8 incorporates two chiral centers, (C-2, C-3) bearing the required functional groups of the desired precursors I and II. The elaboration of the remaining functional groups leading to II, followed a predicted route utilizing 8 as a common intermediate. Thus, treatment of the uloside derivative with methyl lithium in ether led to a mixture of two products (quant.), in which 9 and 10 were the major and minor components respectively,

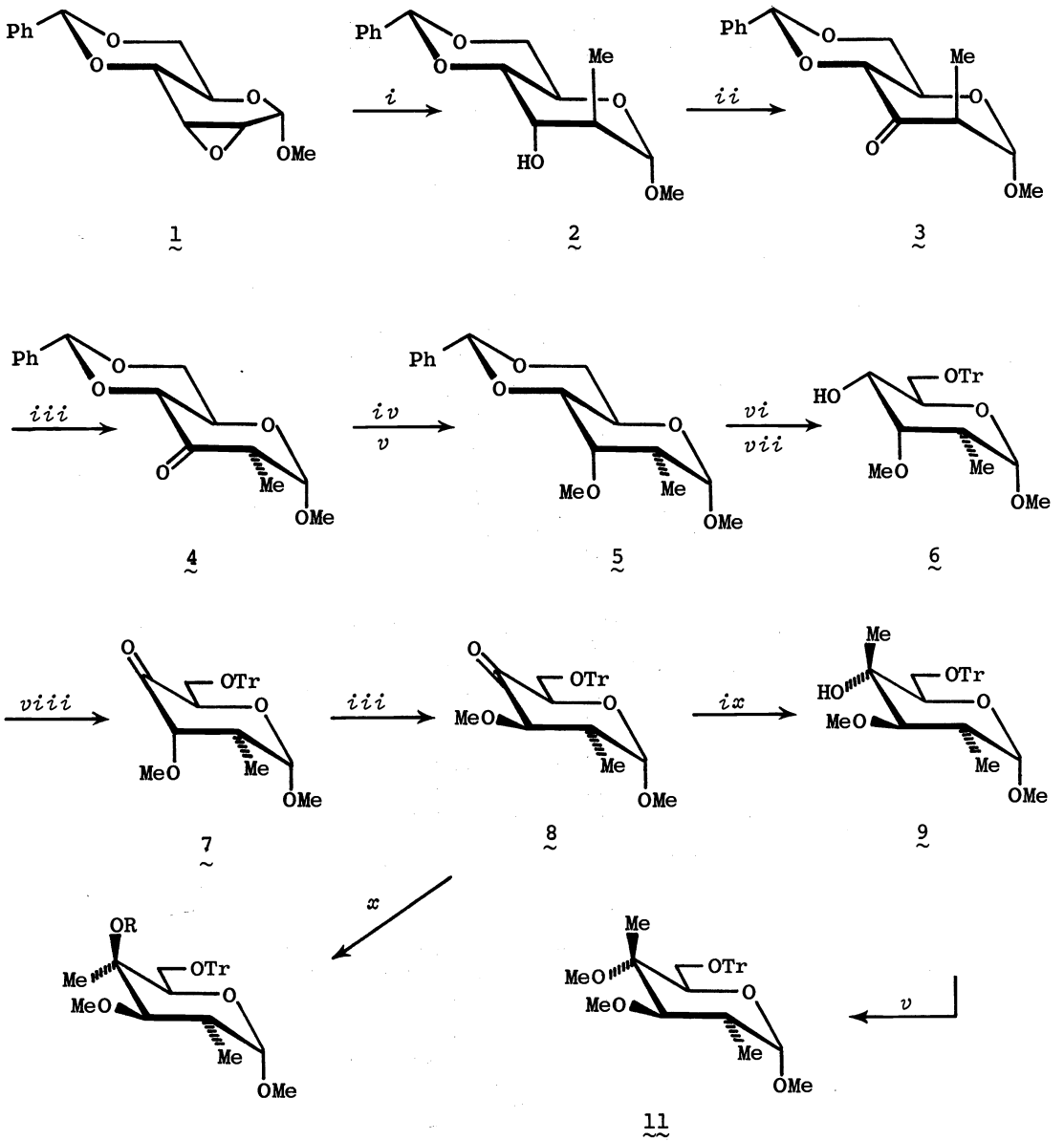


Fig. 7 Synthetic pathway leading to precursors I and II via common intermediates. Broken and solid lines are meant to show the chiral relation of the ring carbon atoms bearing new functional groups to the corresponding chiral centers in erythronolide A (compare Fig. 4). Reagents. *i)* Me_2CuLi. *ii)* DMSO-Ac_2O. *iii)* NaOMe, MeOH. *iv)* $NaBH_4$, DMF MeOH. *v)* MeI, NaH, DMF. *vi)* $Pd(OH)_2$-C, H_2. *vii)* TrCl, pyr. *viii)* DMSO - EDAC·HCl. *ix)* MeLi. *x)* MeMgBr.

and could be easily separated by chromatography. Such separations were, however, unnecessary, since methylation of the mixture of 9 and 10 gave the corresponding 4-*O*-methyl derivatives 11 and 12, from which the preponderant isomer, methyl 2-deoxy-2,4-di-*C*-methyl-3,4-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside 11, could be easily obtained as beautiful crystals by fractional crystallization. Interestingly, treatment of 8 with methylmagnesium bromide gave a mixture of epimeric *C*-methyl derivatives, in which the D-*galacto* isomer 10 predominated. Similar results have been reported in the case of the 2,3-di-*O*-methyl analog of 8 (Ref. 32); however, it was claimed

that the reaction with methyl lithium was stereospecific, leading to a product having the D-*gluco* configuration. As described later, the crystalline isomer 11 and the mother liquors containing additional amounts of 11, and the epimeric 12, were individually used in the synthesis of precursor II and I respectively, thus rendering the synthetic pathway both practical and efficient.

The easily accessible intermediate 11, contains all the chiral and functional (except at C-6) centers of precursor II. Its conversion into the latter, hence, to a segment encompassing the C-9—C-15 portion of erythronolide A, necessitates detritylation, followed by deoxygenation of the primary hydroxyl function and the incorporation of a terminal *C*-ethyl group. Thus hydrogenolysis of 11 led to 13 in almost quantitative yield, and the latter was converted in high yield to the important intermediate 14 using a Collins oxidation (Ref. 33) (Fig. 8). The p.m.r spectrum of the 6-*aldehydo* derivative 14 was

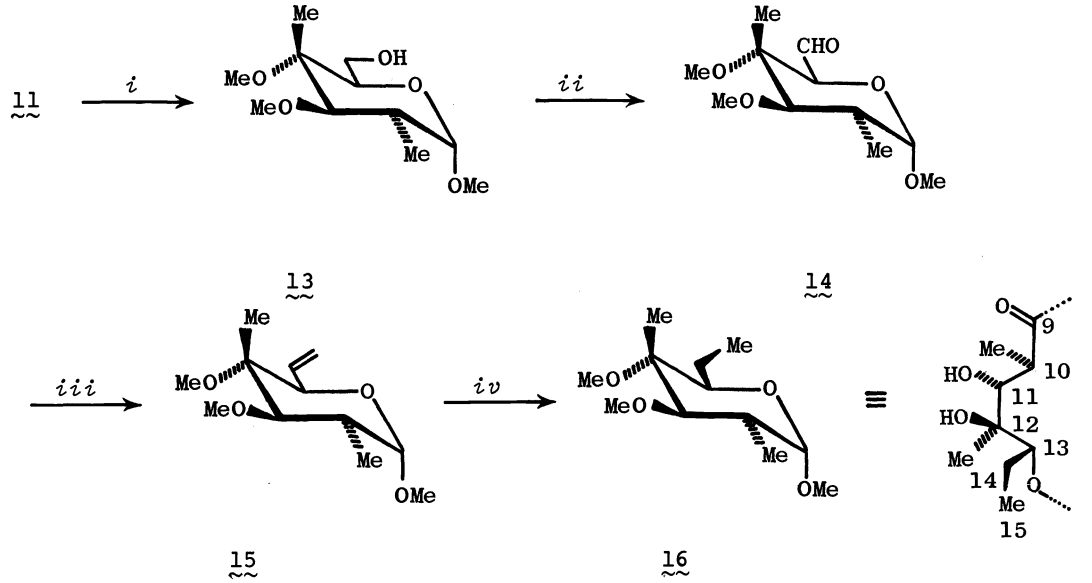


Fig. 8 Synthetic pathway leading to precursor II. Reagents. *i)* $Pd(OH)_2$, C/H_2; *ii)* CrO_3-pyr.; *iii)* $Ph_3P{=}CH_2$; *iv)* $Pd/C,H_2$

clearly resolved, and agreed with the proposed structure. Treatment of 14 with methylenetriphenylphosphorane gave the corresponding terminal olefinic derivative 15, which was characterized by p.m.r spectral analysis and by mass spectrometry. Catalytic reduction of the double bond led to compound 16 in high yield. The latter represents the 3,4-dimethyl ether of precursor II and its relationship to erythronolide A can be seen in the partial structure (C-9-C-15) in Fig. 8. In this manner, the pure, crystalline, axial *C*-methyl isomer 11, resulting from the sequence shown in Fig. 7 could be channelled to the synthesis of precursor II.

Initially, our synthetic plan for the elaboration of precursor I, called for the introduction of appropriate chirality and functionality at C-4 and C-5 by a sequence involving the stereoselective reduction of a 4,5-unsaturated derivative. Provided that all the functional groups were present at the outset, and that the chirality at C-2, C-3 was already established (as in structures 9 and 10), such a sequence would lead to the desired L-*ido* stereochemistry. Pursueing such an approach, compounds 9 and 10 were individually converted into the corresponding uronic acid derivatives (Fig. 9). Thus, detritylation of 9 with palladium hydroxide-on-charcoal (Ref. 34), followed by oxidation of the resulting alcohol 17 with potassium permanganate, afforded the crystalline uronic acid derivative 18 in high yield, which was converted into the corresponding methyl ester 19, with diazomethane. As the esterification of the tertiary hydroxyl group in 19 was found to be sluggish with various carboxylic and sulfonic acid derivatives, it was decided to attempt a sequential esterification-elimination reaction with thionyl chloride. Treatment of 19 with thionyl chloride in a mixture of pyridine and chloroform, effected elimination easily, to give an unsaturated derivative. This substance

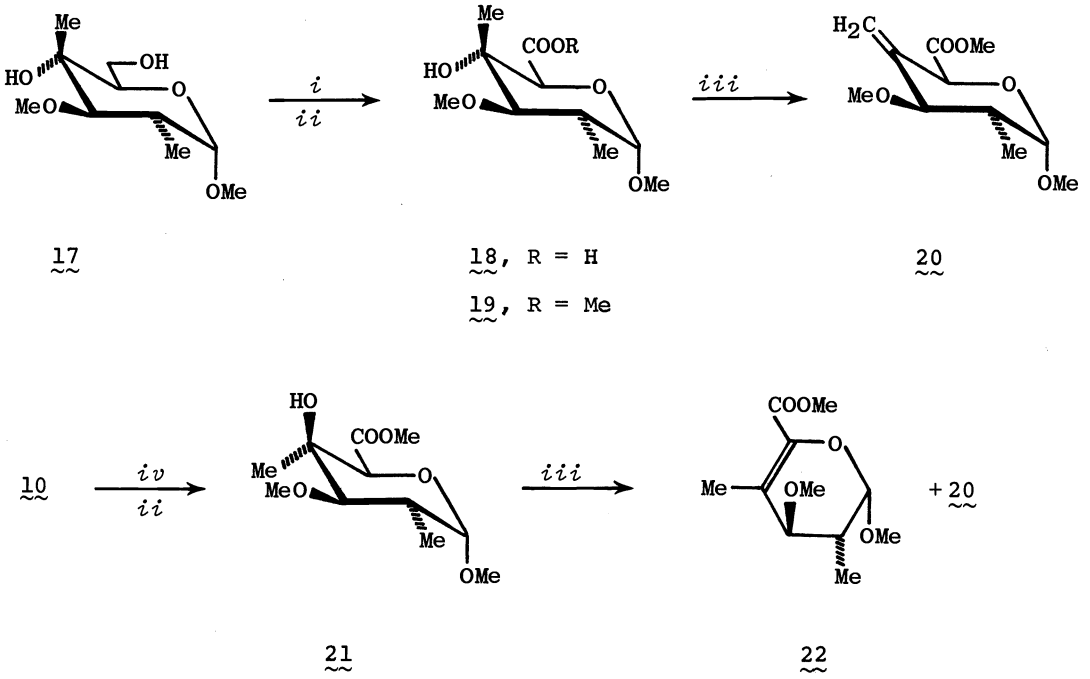


Fig. 9 Attempted β-elimination of C-4 epimeric hexopyranuronate derivatives. Reagents. *i)* $KMnO_4$; *ii)* CH_2N_2; *iii)* $SOCl_2$, pyr.; *iv)* CrO_3-H_2SO_4.

did not absorb in the ultraviolet light region, indicating the absence of an α,β-unsaturated ester function. The structure of the product was established as that of the exocyclic olefinic derivative 20, based on p.m.r spectral data. It was therefore evident that elimination had occurred by abstraction of a proton from the *C*-methyl function at C-4, rather than from that on C-5. Since the stereochemical course of β-elimination reactions of this type are susceptible to orientational effects (Ref. 35), the same reaction was attempted with the C-4 epimeric uronate derivative, 21, in which a *trans*-periplanar arrangement of groups exists between H-5 and the C-4 hydroxyl group, favorable for a diaxial β-elimination. In this case, hydrogenolytic removal of the trityl group was not necessary, as it was found that 10 could be converted into the corresponding methyl ester derivative 21 by sequential oxidation with chromic acid, followed by esterification with diazomethane. Interestingly oxidation of 17 with chromic acid was sluggish and led to secondary products. Treatment of 21 with thionyl chloride in a mixture of pyridine and chloroform gave a mixture of unsaturated products, that could be separated by chromatography. These were obtained as syrups in a ratio of approximately 1 : 3, and assigned the exocyclic and endocyclic olefinic structures 20 and 22 respectively. Several attempts to effect acid or base-catalyzed transformations of the seemingly less stable exocyclic olefinic derivative 20 into the conjugated isomer 22 were only partially successful. Such experiments led to mixtures containing varying amounts of 20 and 22, as evidenced by p.m.r spectral analysis. Rhoads and coworkers (Ref. 36) have studied the tautomeric equilibria in several cyclic systems and have shown that while conjugative interactions of the double bond with the ester function in methyl 1-cyclohexenecarboxylate are important, and stabilizing (ΔG°_{100} = +2.2 Kcal/mol), the introduction of a methyl group at the β-carbon atom reduces the free energy change by 1.35 Kcal/mol. This decrease in free energy is attributed to a *cis* steric destabilization energy of the coplanar methyl and ester groups in the conjugated isomer. The formation of the exocyclic olefinic derivative 20 from the treatment of 19 with thionyl chloride, can be explained based on the preferential proton abstraction from the *C*-methyl group, since in one of its rotamers, a *trans*-periplanar arrangement exists between one of the hydrogen atoms on the methyl group, and the chlorosulfite ester group, Fig. 10(A). A similar stereochemical course can be operative in the case of the C-4 epimeric derivative (B); however the process may be somewhat less favored compared to the diaxial β-elimination, involving the C-5 hydrogen and the chlorosulfite group. Equilibration between 20 and 22 under the reaction conditions did not take place as evidenced by simulated tests.

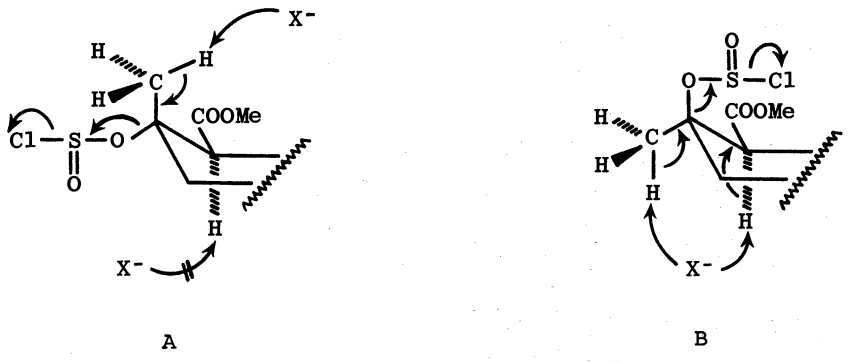


Fig. 10 *Trans*-periplanar arrangement of hydrogen atoms on the *C*-methyl group (A) and C-5 (B) with respect to the chlorosulfite ester group at C-4.

Access to compound 22 and to precursor I was gained by a sequence based on the same general strategy as outlined in Fig. 9, but utilizing compounds containing an aldehyde or ketone function at C-6, rather than an ester function. It is known that enol-acetal forming β-eliminations in 6-*aldehydo* derivatives of pyranosides is a facile process, particularly when the leaving group is an ester function (Ref. 19, 37). In contrast, isopropylidene and various ether groups are not eliminated, and it is possible to isolate the corresponding *aldehydo* derivatives (Ref. 19).

The mother liquors resulting from the crystallization of compound 11 (already used for the preparation of precursor II), containing the epimeric derivative 12, as well as additional amounts of 11, were detritylated to a mixture containing compounds 13 and 23. Oxidation of the mixture with the Collins reagent gave the 6-*aldehydo* derivatives 24 in high yield. Attempts to effect β-elimination of the methoxyl group situated at C-4 in 24, under a variety of base-catalyzed conditions, led to the formation of mixtures (Fig.11). However,

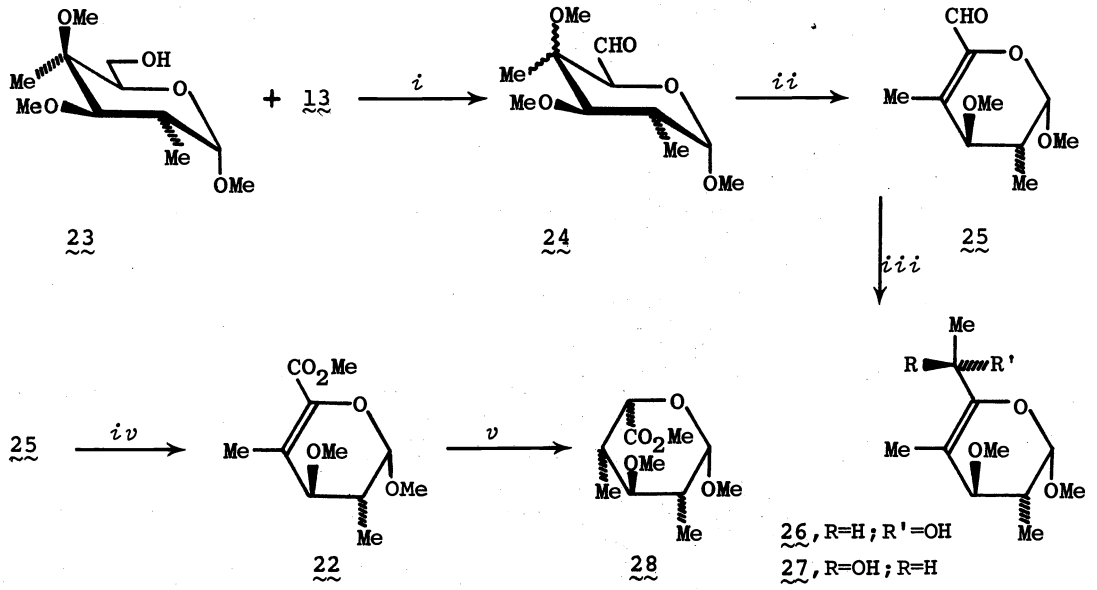


Fig. 11 Synthetic pathway leading to precursor I - terminally functionalized intermediates. Reagents: *i)* CrO_3-pyr.; *ii)* $Ca(OH)_2$; *iii)* MeLi; *iv)* MnO_2, NaCN, AcOH, MeOH; *v)* Pd-C, H_2.

elimination was found to take place in dilute aqueous calcium hydroxide solution to give the syrupy methyl 6-*aldehydo*-2,4-dideoxy-2,4-di-*C*-methyl-3-*O*-methyl-β-L-*threo*-hex-4-enopyranoside 25 in high yield. P.m.r and mass spectral data were in accord with this structure. Treatment of 25 with methyl lithium gave a 1:1 mixture of the C-6 epimeric alcohols 26 and 27 in good yield. These allylic alcohols however, proved to be relatively unstable, and preliminary attempts to effect catalytic or chemical reduction of the double bond led to mixtures. However, oxidation and esterification of 25 in the presence of active manganese dioxide, sodium cyanide, acetic acid and methanol (Ref. 38) gave an excellent yield of the methyl ester derivative 22. Catalytic reduction of this compound gave, almost exclusively, a product, 28, having the desired L-*ido* stereochemistry, as evidenced by p.m.r. spectroscopy.

Treatment of the C-4 epimeric mixture of 6-*aldehydo* derivatives 24 with methyl lithium, followed by oxidation of the resulting mixture of alcohols with the Collins reagent gave an excellent yield of the methyl ketone derivatives 29 (Fig. 12). Model experiments showed that the treatment of 29 with $NaOCD_3$-CD_3OD effected virtually total and rapid exchange of the C-7 methyl hydrogen atoms (p.m.r), which was followed by a slower disappearance of the hydrogen atom situated at C-5.

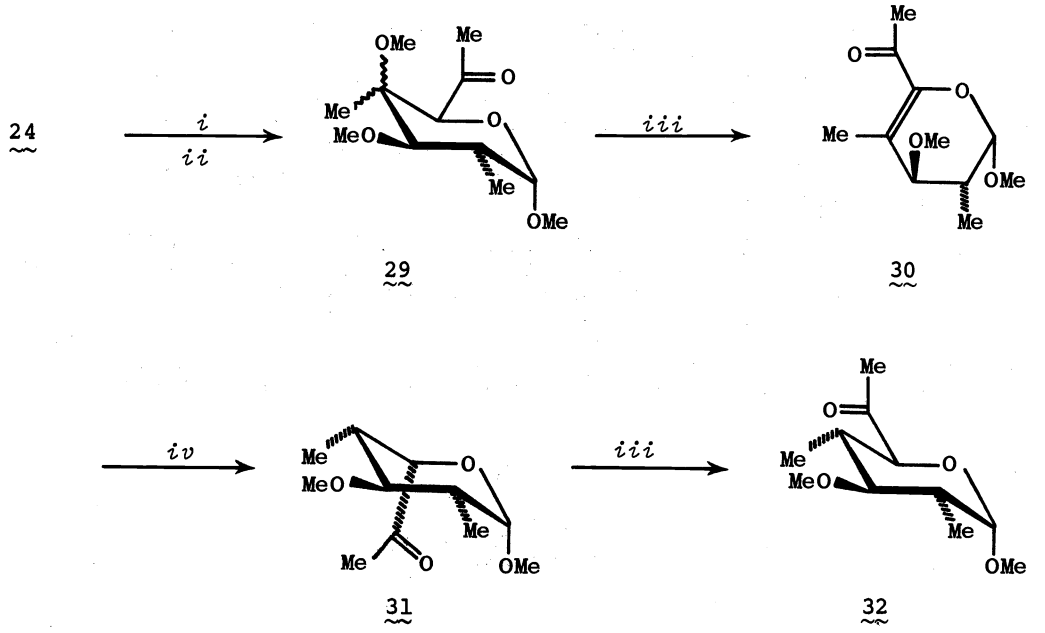


Fig. 12 Synthetic pathway leading to precursor I. Reagents. *i)* MeLi; *ii)* CrO_3-pyr.; *iii)* NaOMe, MeOH; *iv)* Pd/C,H_2;

Chromatographic monitoring of the reaction confirmed, as expected, the presence of an olefinic product resulting from a β-elimination reaction. In a preparative experiment, compound 29 was treated with a solution of sodium methoxide in methanol at reflux, to give an excellent yield of the 4,5-unsaturated derivative 30. Hydrogenation of the latter in the presence of palladium-on-charcoal in methanol gave almost exclusively a product, 31, to which we assign the desired L-*ido*, rather than the alternative D-*galacto* stereochemistry, based on very convincing p.m.r. spectral data and chemical transformations. Although several *O*-substituted derivatives of L-idopyranose have been suggested to exist almost exclusively in the *1C*(L) conformation in solution (Ref. 19, 39), our p.m.r. data suggest the predominance of a *C1*(L) conformation for compound 31. In the alternative *1C* conformation, there would exist a severe 1,3-diaxial interaction between the methyl groups situated on C-2 and C-4. When compound 31 was treated with sodium methoxide in methanol, it was converted into the thermodynamically more stable D-*gluco* epimer 32, which further substantiates the structure of 31.

Compounds 28 and 31 are thus the 3-*O*-methyl ethers of precursor I (Fig. 4, where R=CO_2CH_3 or R = $COCH_3$) and their functional and configurational relationships to the C-1—C-6 segment of erythronolide A is shown in Fig. 13.

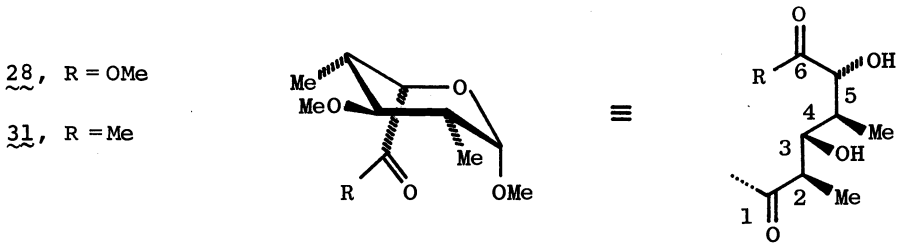


Fig. 13 Functional and configurational correlations between compounds 28 and 31 (representing precursor I) and the C-1–C-6 segment of erythronolide A.

CONCLUSION

Based on the recognition of carbohydrate-like sequences in the structure of erythronolide A, a synthetic route to carbohydrate-derived intermediates, represented by precursors I and II, has been developed. These compounds constitute fully chiral and functionalized segments of erythronolide A, and are therefore extremely useful in a program directed toward its total synthesis. Their relationship to the target molecule is illustrated in Fig. 14.

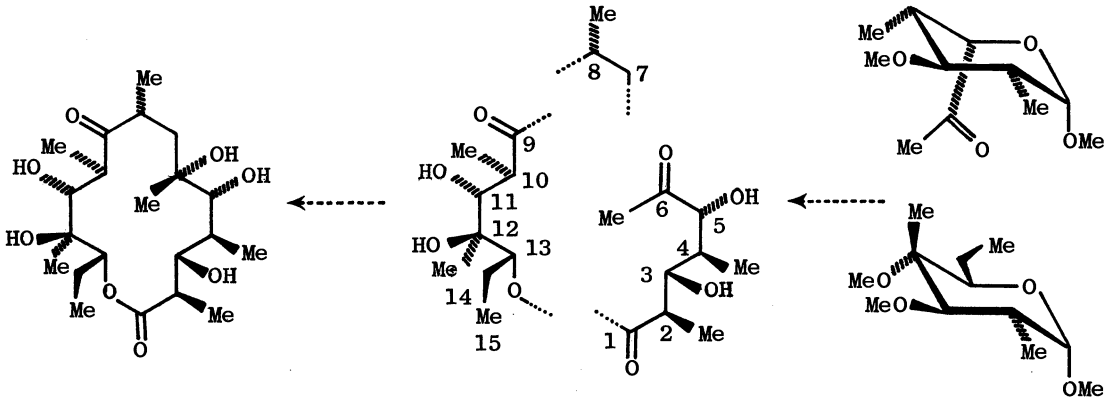


Fig. 14 Structures of carbohydrate-derived intermediates (right) and their depiction as acyclic segments of erythronolide A. The bridging two-carbon unit bearing the C-8 methyl group is shown separately (center). Erythronolide A (left) is depicted in a conformation patterned after that of crystalline erythromycin A.

They have been prepared from D-glucose, via a common synthetic pathway, in a reasonable number of high yielding steps, that for the most part, require no chromatographic separations, and are adaptable to large scale operations.

Eight of the ten chiral centers in erythronolide A, all of which bear the required functional groups, are present in precursors I and II. Thus the synthetic conquest of a structure that was once remarked as being "quite hopelessly complex" (Ref. 40), because of the propensity of functional groups and its plethora of asymmetric centers, can now be viewed with chiral optimism. The carbohydrate-precursor approach to total synthesis as illustrated here, can, in fact, be integrated into the synthetic blueprints of a variety of other macrolides, as well as equally, if not more challenging structures.

With regard to the synthesis of erythronolide A, and ultimately erythromycin A, via the carbohydrate-precursor route, there remain several crucial problems ahead, namely: a. the bridging of the two segments through C-6(7) of precursor I and C-1 of precursor II; b. the control of stereochemistry at the newly created asymmetric carbon atoms C-6 and C-8; c. the final lactonization of an acyclic macrolide precursor, and, d. the all-important glycosylation reactions.

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