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CHIRAL SYNTHESES OF THE ANTIBIOTICS ANISOMYCIN AND PENTENOMYCIN FROM CARBOHYDRATES[a]

Julien P. H. Verheyden, Anthony C. Richardson,[b,c] Ram S. Bhatt,[b] Barbara D. Grant,[b] William L. Fitch[b] and John G. Moffatt

Institute of Molecular Biology, Syntex Research, Palo Alto, California 94304, USA

Abstract - Syntheses of the natural, optically active forms of the antibiotics anisomycin and pentenomycin are described using simple glucose derivatives as chiral starting materials. The key step in the synthesis of anisomycin is the formation of a pyrrolidine ring embodying all three of the desired asymmetric centers *via* intramolecular nucleophilic displacement of a 3-*O*-tosyl function in an appropriately substituted 6-amino-6-deoxy-β-L-talofuranose derivative. Further elaboration involves the liberation of an aldehyde group by periodate oxidation of the 1,2-diol, Grignard coupling and removal of extraneous functions and blocking groups by several reductive steps.

The syntheses of pentenomycin, and its simpler analog 6-deoxypentenomycin, proceed *via* conversion of 3-benzyloxymethyl and 3-methyl derivatives of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose, respectively, into the respective 3-substituted methyl 2,3-cycloalkylidene-5-deoxy-D-*erythro*-pent-4-enofuranosides. Acidic hydrolysis of the latter gives the related 4-ketoaldehydes that undergo intramolecular aldol condensations to form the appropriately substituted 2-cyclopenten-1-ones that can be converted into the target compounds.

It is axiomatic in organic chemistry that the synthesis of an optically active product must make use of chiral substances, either as resolving agents or as synthetic intermediates. From the point of view of overall efficiency, the use of an appropriate chiral starting material is of particular attraction. This approach has found extensive use over the years, and syntheses of a great variety of optically active natural products have been described starting from readily available chiral substances such as amino acids and simple terpenes (Ref. 1). In spite of the fact that carbohydrates constitute one of Nature's richest sources of chirality, only in recent years have these substances found wide use as starting materials for asymmetric syntheses. This stems, to a considerable degree, from a long standing aversion on the part of many organic chemists to work with carbohydrates, which were considered to be mainly intractable syrups. With the advent of improved and more selective protecting groups and, in particular, the extensive application of contemporary instrumental analysis, carbohydrate chemistry is now enjoying a new image. As synthetic intermediates, carbohydrates are now becoming recognized as readily available, polyfunctional molecules containing several sites of predictably controllable asymmetry. In recent years this has led to the use of carbohydrate derivatives as intermediates in the synthesis of a number of optically active natural products of widely divergent structures. By way of example one can mention notable syntheses in the prostaglandin (Ref. 2a) and thromboxane (Refs. 2b-e) series, of biotin (Ref. 3), of the antifungal agents avenaciolide (Ref. 4) and isoavenaciolide (Ref. 5) and the imaginative approach to erythronolide devised by Hanessian and Rancourt (Ref. 6). In the present paper we further extend this general approach through a description of the syntheses of two optically active antibiotics, anisomycin (1) and pentenomycin (2), starting from D-glucose.

Anisomycin (1) was isolated from two strains of Streptomyces by Sobin and Tanner of Chas. Pfizer and Co. in 1954 (Ref. 7). Its gross structure was initially deduced by Beereboom *et al.* (Ref. 8), but the relative and absolute stereochemistry were subsequently modified on the

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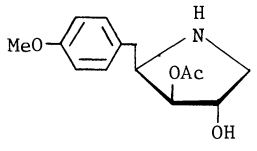
Note a. Contribution No. 137 from the Institute of Molecular Biology.
Note b. Syntex Postdoctoral Fellows.
Note c. On sabbatical leave from Queen Elizabeth College, University of London.



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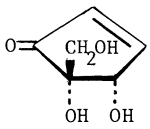

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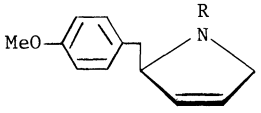
basis of ^{1}H-n.m.r. analysis (Ref. 9) and X-ray crystallography of a brominated derivative (Ref. 10) leading to the 2R,3S,4S configuration 1. Anisomycin has been found to have, at best, modest activity against bacteria (Ref. 11) but exhibits a remarkably selective inhibition of peptide chain elongation on 60S eukaryotic ribosomes (Ref. 12), making it a useful tool for molecular biology. Because of this mechanism of action, anisomycin exhibits selective and potent action against protozoa and certain fungal strains both *in vitro* (Ref. 11) and *in vivo* (Ref. 13). It has been shown to be clinically useful for the treatment of vaginal trichomoniasis (Ref. 14) and intestinal amebiasis (Ref. 15).

Several syntheses of racemic and optically active anisomycin have been reported, but each has depended upon random acylation steps followed by a separation of isomers. Thus D,L-anisomycin has been prepared from both D,L-tyrosine (Ref. 16) and 2-(4-methoxybenzoyl)pyrrole (Ref. 17) *via* multi-step conversions into suitable N-protected derivatives of the 3-pyrroline 3. Epoxidation of 3 followed by either solvolysis or hydrolysis and partial acetylation then led to N-protected derivatives of racemic anisomycin that could be deblocked. Wong *et al.* (Refs. 17, 18) have also prepared the (+) and (-) enantiomers of desacetyl-N-benzylanisomycin *via* a Grignard reaction on L-tartarimide and have converted these into (+) and (-) anisomycin by partial acetylation and hydrogenolysis. An alternative synthesis of (-) anisomycin has been described by Felner and Schenker (Ref. 19) starting from L-tartaric acid, which was converted in several steps into N-benzyloxycarbonyldesacetylanisomycin (4). Once again, the transformation of 4 into anisomycin required partial acetylation and separation of the desired 3-O-acetyl derivative.



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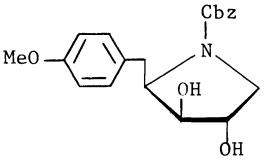

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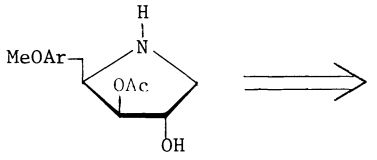
We considered that a completely selective synthesis of anisomycin could be devised in which the asymmetric carbons C-2, C-3, and C-4 were derived from C-3, C-4, and C-5 of hexoses of defined configuration. By application of retrosynthetic reasoning, anisomycin (1) could be selectively obtained from a monoacetylated triol derivative 5 by hydrogenolysis of the benzyl ether, benzyloxycarbonyl, and benzylic alcohol derivative functions. In turn, 5 would be derived from the pyrrolidine aldehyde 6, the stereochemistry of which originates in the 3,6-dideoxy-3,6-imino-L-idofuranose (7). The preparation of 3,6-iminohexofuranoses has previously been investigated by a number of workers (Ref. 20) and for our purpose would originate with 6-amino-6-deoxy-1,2-O-isopropylidene-3-O-tosyl-β-L-talofuranose (8).



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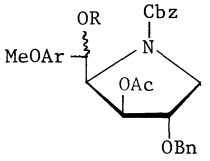

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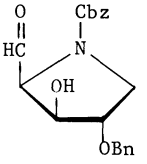

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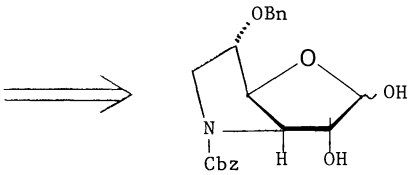

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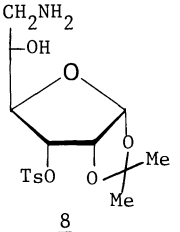

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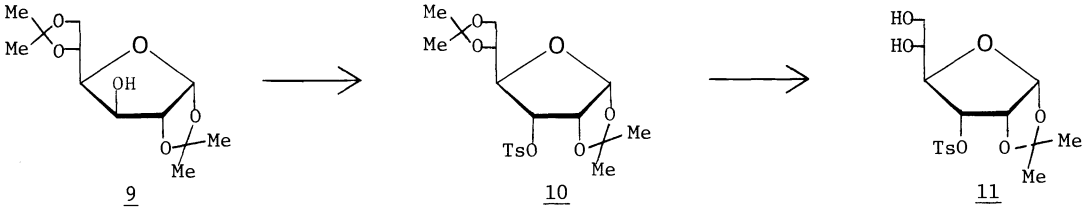
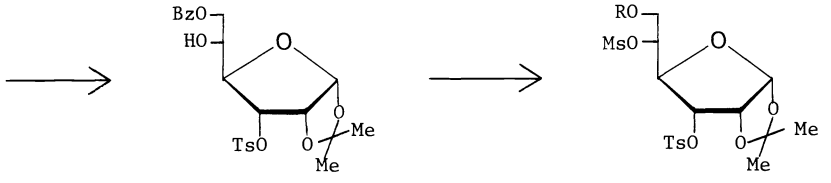
Our first objective was, therefore, the synthesis of 8. To this end 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (9) was converted in an overall yield of 80% into 1,2:5,6-di-O-isopropylidene-3-O-p-toluenesulfonyl-α-D-allofuranose (10, Ref. 21) via oxidation with ruthenium dioxide-sodium periodate (Refs. 22, 23) followed by borohydride reduction (Ref. 23) and tosylation. Selective hydrolysis of the 5,6-acetonide to give the diol 11 (88%) was achieved by careful treatment with 70% acetic acid at 60° for 2.5 h according to Brimacombe and Mofti (Ref. 20d). However, some care had to be taken with this step in order to avoid partial hydrolysis of the 1,2-acetonide. Thus, treatment of 10 with 70% acetic acid in aqueous dioxane at 100° for 15 min led to extensive formation of 3-O-p-toluenesulfonyl-D-allose that was isolated in crystalline form (68%) and was identical to the compound described by Christensen and Goodman (Ref. 24).

Selective benzoylation of the primary hydroxyl group of 11, gave crystalline 12 (69%), the location of the benzoate being apparent from the deshielding (1 p.p.m.) of H-6,6' in the ^{1}H-n.m.r. spectrum of 12 relative to that of 11. Subsequent treatment of 12 with methanesulfonyl chloride led, in 90% yield, to 6-O-benzoyl-1,2-O-isopropylidene-5-O-methanesulfonyl-3-O-p-toluenesulfonyl-α-D-allofuranose (13a). A potential alternative synthesis of 13a via conversion of 11 into the 5,6-dimesylate 13b followed by selective displacement of the primary mesylate with sodium benzoate in N,N-dimethylformamide was abandoned since there was concomitant formation of a somewhat less polar impurity.



9 10 11

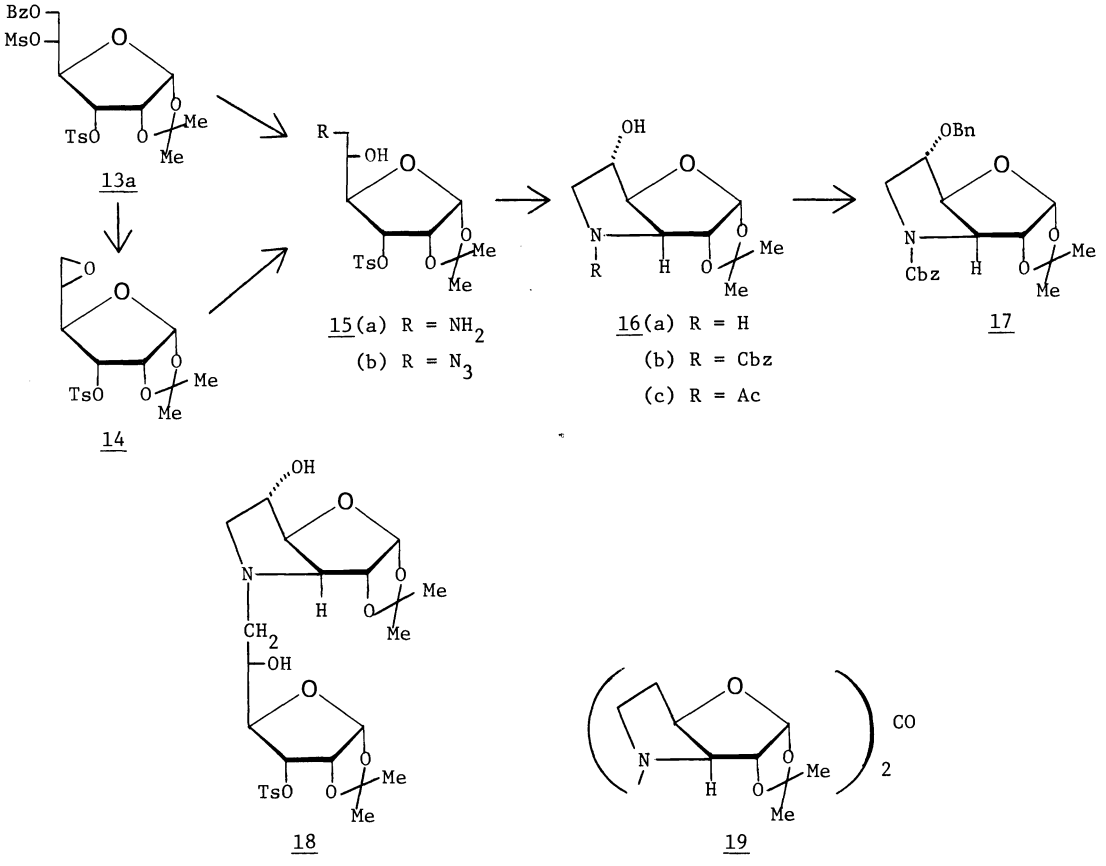


12 13(a) R = Bz (b) R = Ms

Our initial intention was to treat directly the 6-O-benzoyl-5-O-mesylate 13a with methanolic ammonia in order to generate the 6-amino-6-deoxy-β-L-talofuranose derivative 8 (15a) via the epoxide 14. In fact, small scale reactions of 13a with saturated methanolic ammonia at 105° for 64 h did indeed generate 8 (15a), but the latter was not isolated since, under the reaction conditions, it further underwent the desired intramolecular displacement of the 3-tosyl function. The crude reaction product was treated directly with benzyloxycarbonyl chloride and aqueous sodium carbonate giving crystalline N-benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-β-L-idofuranose (16b, 40%). The ^{1}H- and ^{13}C-n.m.r. spectral data for this compound supported the assigned structure but was complicated by a general broadening, or even doubling, of the signals for most of the sugar carbons and their appended protons. This is very likely the consequence of restricted rotation of the N-benzyloxycarbonyl group. A similar effect was noted previously for the closely related N-acetyl derivative 16c (Ref. 20d). As would be expected, upon running the n.m.r. spectra at 82° both the ^{1}H and ^{13}C resonances collapsed to sharp and readily analyzed signals.

In an effort to improve the yield of 16b, we attempted to modify the sequence in a stepwise manner. Thus, the mesylate 13a was briefly (2 min) treated with boiling methanolic sodium methoxide which led to the direct crystallization of the rather insoluble L-talo-5,6-epoxide 14 (91%). Formation of the epoxide was indicated by elemental analysis and was confirmed by ^{13}C-n.m.r. spectroscopy, which showed the typically large (∿20 p.p.m.) upfield shifts (Ref. 25) of the C-5 and C-6 signals relative to those of the same carbons in 11. Related upfield shifts of H-5,6,6' were also apparent. The facile crystallization of 14 allowed its preparation (overall yield 70%) from 11 without purification of any intermediates. Small scale reactions of 14 with methanolic ammonia at 105° followed by conversion of the crude product 16a into the benzyloxycarbonyl derivative led to the isolation of 16b in a maximum yield of 55%. However, on attempted scale-up the size of available stainless steel bombs necessitated the use of considerably more concentrated reaction mixtures. Under these conditions the formation of a second major product, somewhat less polar than 16b, was observed, the amount of this substance increasing with reaction concentration.

This by-product was isolated in crystalline form in yields of up to 53% and its ^{13}C-n.m.r. spectrum showed that it was dimeric in nature, signals for twelve sugar carbons, one tosyl group and two isopropylidene functions being clearly resolved. In addition, the mass spectrum showed fragments of up to m/e 542 (M^+-Me). This substance is thus assigned the structure 18.



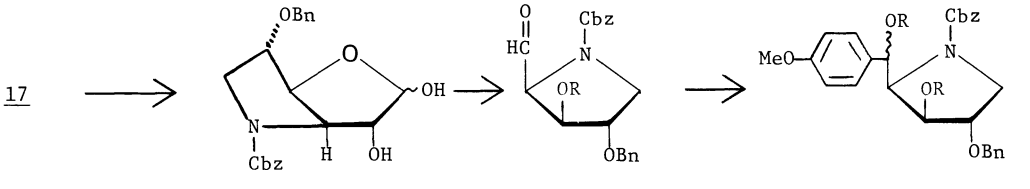
The formation of 18 was unexpected and could occur via attack of the 6-amino group of 15a upon the epoxide 14 giving a secondary amino tosylate followed by intramolecular displacement of the tosylate. Alternatively, the initial cyclization product 16a could open the unreacted epoxide 14 to form the same product. In either case, the amine functions in the intermediates 15a or 16a must undergo intermolecular nucleophilic reactions with the epoxide in the presence of a vast excess of ammonia. Since, as will be seen later, the conversion of 15a into 16a is a relatively slow step, one might anticipate that the concentration of 15a would be higher than that of 16a during the early stages of the reaction when unreacted epoxide is present. Hence we tend to favor the route to 18 involving initial opening of the epoxide by the amino group in 16a, its increased nucleophilicity relative to ammonia being related to its greater basicity.

In order to avoid the formation of the dimeric product 18 we turned to a more specific route to the key intermediate 15a. Thus, the epoxide 14 was reacted with sodium azide in N,N-dimethylformamide at 80° in the presence of ammonium chloride which led to the formation of crystalline 6-azido-6-deoxy-1,2-O-isopropylidene-3-O-p-toluenesulfonyl-β-L-talofuranose (15b, 84%). The expected introduction of the azido group at C-6 was confirmed by the fact that the ^{13}C signal, appearing at the high field position (53.90 p.p.m.) typical of azido substitution, was a triplet in the proton coupled spectrum. Reduction of the azide was readily effected by palladium catalyzed hydrogenation giving the crystalline 6-amino-L-talofuranose derivative 15a (8, 82%). Once again, reduction of the azide led to an expected upfield shift of the signal for C-6, which appeared as a triplet at 41.74 p.p.m. The conversion of 15a into the 3,6-imino sugar 16a could then be brought about by heating under reflux in ethanol for 18 h in the presence of sodium acetate. The imine 16a (62%) could be obtained in crystalline form, but its isolation was facilitated by prior conversion into the benzyloxycarbonyl derivative 16b. This process proved to be quite efficient, 16b being obtained in an overall yield of 73% from the epoxide 14 without purification of any intermediates.

In order to ensure that introduction of the acetyl group be restricted to HO-3 in the final product, it was necessary to protect the free hydroxyl group in 16b. Since this protecting group must be removed under non-basic conditions and be stable to acidic hydrolysis of the 1,2-O-isopropylidene function, the benzyl ether was the group of choice. Thus, 16b was treated with sodium hydroxide and benzyl bromide in N,N-dimethylformamide giving the desired 5-O-benzyl-N-benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-β-L-idopyranose (17, 98%). Unfortunately, since this compound (m.p. 83-84°) is difficult to crystallize, a facile chromatographic isolation is necessary. An attempt at high vacuum distillation led to a mixture of 17 and a dimeric substance considered to be the urea 19. The ^{13}C-n.m.r. spectrum of this substance showed the presence of only a single benzyl group and a doubling of the sugar carbon resonances, presumably, once again, an indication of restricted rotation since the molecule is symmetrical. A single carbonyl group appeared at 155.65 p.p.m., a position that is, perhaps, more typical of carbamates (154-158 p.p.m.) than ureas (160-164 p.p.m.) (Ref. 26). The fully protected molecule 17 can be obtained in an overall yield of 32% in twelve steps from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (9) with purification of only the intermediates 10, 11, 14, and 16b.

In order to transform the 3,6-iminofuranose 17 into the aldehydopyrrolidine necessary for introduction of the p-methoxyphenyl group in anisomycin, the 1,2-acetonide was first cleaved by treatment with 90% trifluoroacetic acid at room temperature for 4 h. This reaction was very clean and the diol 20 could readily be isolated (92%) by chromatography on silica gel. Whereas the ^{1}H-n.m.r. spectrum of this syrupy anomeric mixture was unrevealing, the ^{13}C-n.m.r. spectrum showed the α-anomer (C-1 at 98.57 p.p.m.) to preponderate over its β-counterpart (C-1 at 104.36 p.p.m.) in a ratio of ∿3:2 (Ref. 27). For most purposes it is unnecessary to purify 20, and the crude product can be oxidized directly with sodium periodate in a two phase, aqueous ether medium using tetraethylammonium acetate as a phase transfer catalyst (Ref. 28). T.l.c. of the ether soluble product of this oxidation gave two spots corresponding, presumably, to the desired pyrrolidine aldehyde 21a and its formate ester 21b. Upon stirring the moist ether solution with solid sodium hydrogen carbonate the mixture was converted entirely into the more polar component, an observation consistent with the hydrolysis of the formate ester. However, in view of the potential for epimerization of the aldehyde under alkaline conditions, we have preferred to directly use the mixture of 21a and 21b in the next step.

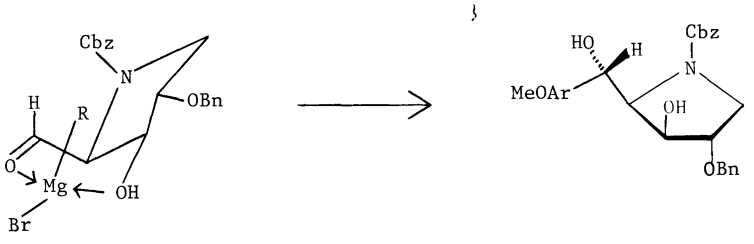
The reaction of mixed 21a and 21b with p-methoxyphenylmagnesium bromide in tetrahydrofuran at 0°-20° led to a complex mixture of multicolored spots on t.l.c. using visualization with ammonium molybdate-sulfuric acid. The majority of these spots were, however, also observed in both commercial or freshly prepared p-methoxyphenylmagnesium bromide. The major reaction product was readily recognized by its characteristic green color using the above spray. By chromatography on a column of silicic acid this product was isolated as a homogeneous syrup in a maximum overall yield of 54% from 17. This syrup gave an elemental analysis consistent with the desired product 22a, and both its ^{1}H- and ^{13}C-n.m.r. spectra suggested the presence of only a single product. It was possible to obtain a small portion of this substance in crystalline form (m.p. 84-85°), but no further crystalline material could be obtained from the mother liquors. Subsequently, it was shown that the Grignard reaction does lead to a mixture of epimers of the benzylic alcohol. This was demonstrated by treatment of crude 22a with acetic anhydride and pyridine, which very slowly led to a chromatographically separable mixture of diacetates. In one experiment the two epimeric diacetates 22b were obtained in a ratio of 5:1, whereas in other studies a more even distribution was indicated. Both isomers gave very sharp ^{13}C-n.m.r. spectra that were almost superimposable. Only the signals for the acetyl carbonyl group and the C-2a benzylic carbons could be differentiated, and even these signals were very similar, appearing at 169.70, 168.92, and 72.43 p.p.m. in the major isomer and at 169.41, 169.31, and 73.02 p.p.m. in the minor one. It is therefore perhaps not surprising that the epimeric diols were not resolved by n.m.r. spectroscopy.



20 21(a) R = H (b) R = CHO 22(a) R = H (b) R = Ac

Since the benzylic hydroxyl group in 22a will be removed during completion of the synthesis of anisomycin, a definition of its stereochemistry is not essential. However, previous work by others (Ref. 29) has shown that Grignard reactions on aldehydo and ketofuranoses are

generally quite stereoselective. In each case the major product can be rationalized by assuming that co-ordination of the magnesium to both the carbonyl and furanose ring oxygens leads to a selective orientation of the carbonyl group. Alkylation then occurs from the side distal to O-3. For the aldehyde 21a, the situation is more complex since co-ordination of the magnesium could occur to either HO-3 or the pyrrolidine nitrogen. If we assume the preferred formation of the less hindered six membered chain transition state involving the hydroxyl group (23), then transfer of the p-methoxybenzyl group to the front face of the carbonyl group would lead to the (S)-configuration as in 24. This interpretation is totally speculative at this time. Some tentative support comes from the fact that the crystalline isomer of 22a, the major diacetate 22b, and the deprotected molecule 26 all showed positive Cotton effects centered at ∿270 nm in their o.r.d. spectra. Based upon previous work on heterocyclic polyols (Ref. 30), a positive Cotton effect is characteristic of an (S)-configuration at the "benzylic" center.



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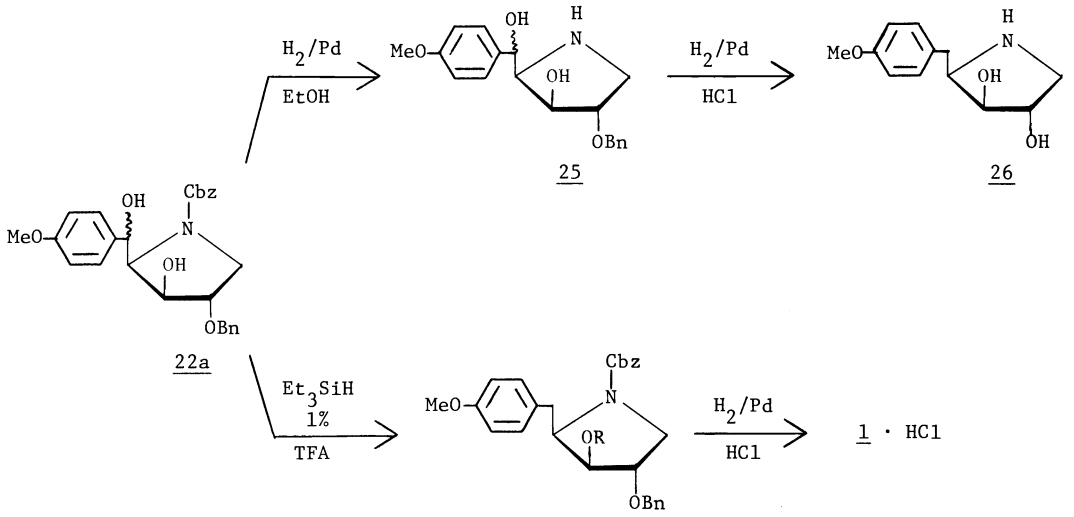
As a prelude to the synthesis of anisomycin itself, we examined the conditions necessary for the removal of the extraneous functions from 22a. It was anticipated that palladium catalyzed hydrogenation would lead to cleavage of the benzyl ether and benzyloxycarbonyl groups and to hydrogenolysis of the benzylic alcohol at C-2a giving the known desacetylanisomycin. In fact, treatment of 22a in ethanol with hydrogen at 60 p.s.i. in the presence of palladium on carbon or palladium hydroxide led only to quite rapid cleavage of the benzyloxycarbonyl group giving 25. When this hydrogenation was repeated in the presence of 4 equiv. of dilute hydrochloric acid a further transformation took place, but the product was considerably more polar than desacetylanisomycin. This material was isolated in a crystalline form, exhibiting a broad melting point, but both its ^{1}H- and ^{13}C-n.m.r. spectra showed little evidence of it being other than a single isomer. From these spectra it was clear that, under acidic conditions, the benzyl ether group had been removed in addition to the benzyloxycarbonyl but that the benzylic alcohol remained unaltered. The structure 26 was evident from the appearance of the carbinol proton signal at 4.92 p.p.m. (J 10 Hz) and the associated carbon as a doublet at 67.46 or 68.46 p.p.m. The hydrogenolysis of benzylic alcohols has been studied in some depth (Ref. 31), and the role of steric effects is recognized.

A solution to the above problem was found through the use of "ionic hydrogenation" (Ref. 32). It is known that benzylic alcohols, and certain other alcohols readily forming carbonium ions, can be hydrogenolyzed by treatment with triethylsilane and a moderately strong acid such as trifluoroacetic acid. Treatment of 22a with an excess of triethylsilane in trifluoroacetic acid led to excessive decomposition of the substrate. By gradual addition of 2% trifluoroacetic acid in methylene chloride to a solution of 22a and triethylsilane in methylene chloride at 0° a clean conversion into two less polar substances was effected. The major product, isolated (54%) by chromatography on silicic acid, was shown to be the desired deoxygenation product 27a still retaining the benzyl ether and benzyloxycarbonyl functions. Elemental analyses and the observed ^{1}H- and ^{13}C-n.m.r. spectra were in complete accord with the assigned structure, the signal for the benzylic methylene group now appearing at 32.87 p.p.m., a position compatible with those of other phenethyl derivatives but somewhat deshielded by the cis hydroxyl group (Ref. 33). The less polar product, isolated in 21% yield, proved to be the triethylsilyl ether 27b on the basis of elemental analysis, ^{1}H- and ^{13}C-n.m.r. and mass spectral data. This compound was surprisingly stable but could be hydrolyzed to regenerate 27a by treatment with 80% acetic acid at room temperature for 18 h. The overall yield of 27a was therefore quite acceptable.



27(a) R = H
(b) R = $SiEt_3$
(c) R = Ac

The ready availability of 27a then made the completion of the synthesis of anisomycin predictable. To this end, 27a was acetylated using acetic anhydride and pyridine to give the 3-acetate 27c which showed a small molecular ion in its mass spectrum and the expected signals and shifts characteristic of an acetate in its n.m.r. spectra. The acetylation was conveniently performed on the crude product of ionic hydrogenation, 27c being isolated in an overall yield of 70% from 22a. Catalytic reduction of 27c using a palladium on carbon catalyst in ethanol containing dilute hydrochloric acid proceeded readily at room temperature and led to the direct crystallization of anisomycin hydrochloride (1) with m.p. 187-188° (reported m.p. 188-189°) in 70% yield. The optical rotation {$[\alpha]_D$ +3.5° (c 0.6, MeOH)} compares very favorably with that (+3.9°) reported in the literature (Ref. 7). In addition, the hydrochloride could be converted into the free base form of anisomycin through treatment with lead carbonate, and once again its physical properties were in accordance with literature values. Both the ^1H- and ^{13}C-n.m.r. spectra of synthetic anisomycin hydrochloride were identical to those of an authentic sample obtained from Chas. Pfizer and Co. In addition, the biological activity of the synthetic material in inhibiting the growth of Trichomonas vaginalis and Candida albicans was identical to that of authentic anisomycin.

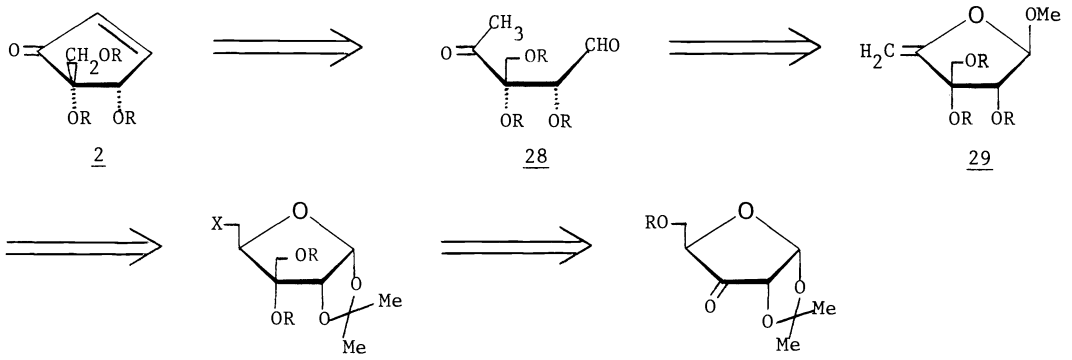
Two possibly attractive modifications of the later steps in the above synthetic scheme can also be mentioned. Thus, ionic hydrogenation of the crude mixed diacetates 22b could also be conducted under conditions similar to those used with 22a. From this reaction the 3-acetate 27c was isolated in analytically pure form in an overall yield of 65% from the diol 22a. Secondly, whereas the benzylic alcohol in 22a was resistant to catalytic hydrogenolysis, the corresponding benzylic acetate could be removed. Thus, palladium catalyzed hydrogenolysis of the mixed diacetates 22b in ethanol-dilute hydrochloric acid gave crystalline anisomycin (49%). Both of these modifications offer advantages in both yield and convenience.

Clearly, the synthetic route that has been developed for anisomycin can be readily adapted to the synthesis of a variety of ester and aryl modifications of the natural product. A number of such analogs have been prepared and will be described in detail elsewhere.

The second major goal in the present project was a stereospecific synthesis of the antibiotic pentenomycin (2). Isolation of pentenomycin I (1) and its 4-acetate (pentenomycin II) from Streptomyces eurythermus was described by Umino et al. from Tanabe Seiyaku Co., Ltd., in 1973 (Ref. 34). Its structure was elucidated by conventional chemical and spectroscopic methods (Ref. 35) and its absolute stereochemistry was defined as 4S,5S by X-ray analysis (Ref. 36). Pentenomycin I was found to have moderate activity against a variety of Gram-positive and negative bacteria including Neisseria gonorrhoeae. A number of structural modifications of the natural product have been described, several of which exhibit improved activity (Ref. 37), but we are unaware of any reports relating to its total synthesis.

Contemplation of retrosynthetic processes suggests that the cyclopent-2-enone system in 2 could be formed via an intramolecular aldol reaction on the ketoaldehyde 28 which can be

envisaged as the product of acidic hydrolysis of the 4,5-unsaturated furanoside 29. The latter type of compound is one with which we have had considerable prior experience, particularly in the nucleoside series (Ref. 38), and its preparation could be anticipated via an elimination reaction on a 5-iodo or 5-O-tosyl furanoside such as 30. The choice of the 1,2-O-isopropylidene function as a protecting group in 30 is based upon the steric control that this group is known to exert in the introduction of the branched chain at C-3 via alkylation of a ketone such as 31.



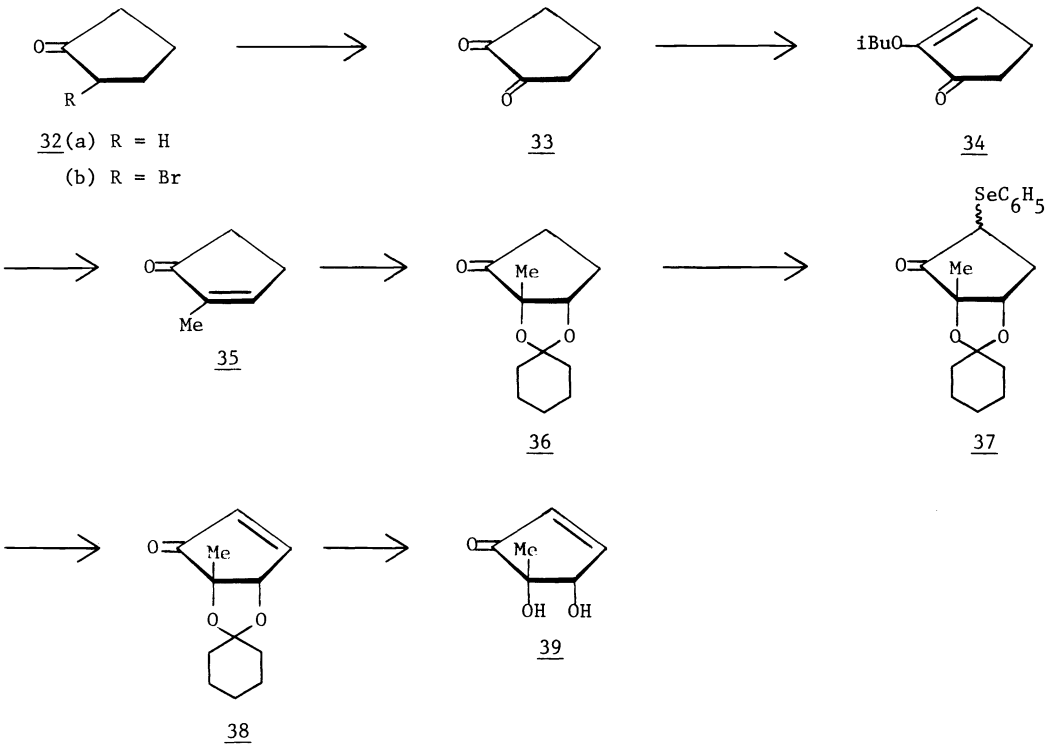
2 28 29

30 X = I, OTs 31

Therefore, our initial efforts were directed towards the synthesis of compounds related to 3-hydroxymethyl-1,2-O-isopropylidene-α-D-ribofuranose (30, R = H, X = I or OTs). The stereochemically controlled introduction of the hydroxymethyl function at C-3 of related allofuranose derivatives has been achieved by others (Ref. 39) via alkylation of ketones related to 31. However, our studies quickly showed that the preparation of suitably protected derivatives of compounds such as 30 was fraught with unexpected problems to be discussed later. As a result, we decided to approach initially the synthesis of the simpler 4(S),5(S)-dihydroxy-5-methyl-2-cyclopentene-1-one (39) or 6-deoxypentenomycin. Since we anticipated some potential problems during the latter steps of the projected synthesis, we first of all devised a relatively short synthesis of racemic 6-deoxypentenomycin (39) that is outlined in the sequence 32 → 39.

Thus, cyclopentanone (32a) was treated with bromine in acetic acid and the resulting 2-bromocyclopentanone (32b) was oxidized with aqueous ferric chloride to the rather unstable cyclopentane-1,2-dione (33) according to Acheson (Ref. 40). Since decomposition sometimes accompanied distillation of 33, it was preferable to convert the crude product directly into the enol isobutyl ether 34 according to Ansell and Ducker (Ref. 41). In this way, 34 was obtained in an overall yield of 42% from 32a. Treatment of 34 with methylmagnesium chloride followed by mild acidic hydrolysis and heating of the crude tertiary alcohol at 175° to effect dehydration led to 2-methylcyclopent-2-en-1-one (35, 84%). The use of thermal dehydration appeared to be preferable to the previously reported treatment with dilute hydrochloric acid, which led to some polymeric material (Ref. 41).

cis-Hydroxylation of the trisubstituted olefin 35 could be effected by reaction with a catalytic amount of osmium tetroxide in the presence of barium chlorate (Ref. 42). Osmium tetroxide and tert-butyl hydroperoxide (Ref. 43) also appeared to be effective. The crude diol was treated directly with 1,1-diethoxycyclohexane and a catalytic amount of perchloric acid giving analytically and spectroscopically pure cis-2,3-cyclohexylidenedioxy-2-methylcyclopentanone (36, 47% over the two steps). Introduction of the conjugated olefin was achieved via the selenoxide elimination method developed by Reich et al. (Ref. 44a) and Sharpless et al. (Ref. 44b). Thus, 36 was reacted with lithium di-isopropylamide and phenylselenyl bromide in tetrahydrofuran giving the crystalline 4-phenylseleno derivative 37 (73%). Treatment of 37 with hydrogen peroxide led to the selenoxide that underwent spontaneous elimination below 30° giving crystalline cis-4,5-cyclohexylidenedioxy-5-methyl-2-cyclopenten-1-one (38, 54%). The structure of this analytically pure compound was confirmed by its readily interpretable ^{1}H- and ^{13}C-n.m.r. spectra. Cleavage of the acetal function by treatment with 90% trifluoroacetic acid at room temperature then gave the desired D,L-6-deoxypentenomycin (39) that was chromatographically isolated as a low melting solid in 57% yield. Whereas 39 could be isolated by short path distillation (60°/1 mm Hg), on storage at room temperature it developed several impurities during two months.



32(a) R = H
(b) R = Br

33

34

35

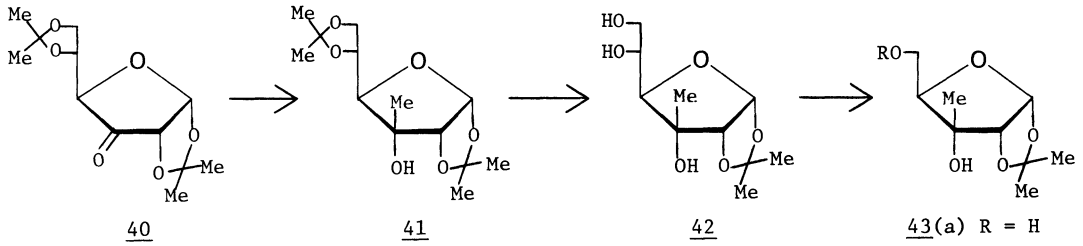
36

37

38

39

With reference samples of the racemic key substances 38 and 39 in hand, we then turned to the synthesis of the 4S,5S enantiomer. The stereochemistry of both asymmetric centers is, in fact, introduced in the very first step through the reaction of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (40), prepared as described in the anisomycin synthesis, with methylmagnesium bromide. As described previously (Ref. 45), the 1,2-O-alkylidene function renders the Grignard reaction highly stereoselective, and crystalline 1,2:5,6-di-O-isopropylidene-3-methyl-D-allofuranose (41) was obtained (74%). Selective cleavage of the 5,6-acetonide with 80% acetic acid gave, in 86% yield, the previously reported crystalline triol 42 (Ref. 45b) which was sequentially oxidized with sodium periodate and reduced with sodium borohydride to give 1,2-O-isopropylidene-3-methyl-α-D-ribofuranose (43a, 90%). The latter compound has previously been prepared by Horwitz et al. (Ref. 46) via a Grignard reaction on 1,2-O-isopropylidene-5-O-trityl-α-D-erythro-pentos-3-ulose. We have found it to be quite important to conduct the periodate oxidation step in a buffered medium, pH 6 borate buffer being convenient. If this precaution was not taken 43a was found to be contaminated with a second product of very similar mobility, this almost surely being the result of partial epimerization of the aldehyde arising from the periodate oxidation. Selective tosylation of the primary alcohol function in 43a was almost quantitative giving crystalline 1,2-O-isopropylidene-3-methyl-5-O-p-toluenesulfonyl-α-D-ribofuranose (43b). The sequence from 41 → 43b could be conveniently carried out in excellent yield without purification of any of the intermediates.

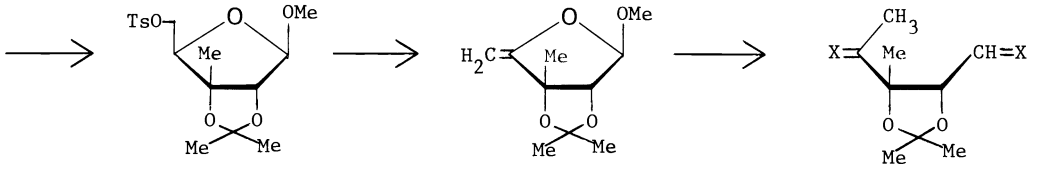


40

41

42

43(a) R = H
(b) R = Ts



44 45 46(a) X = O

(b) X = N-NHAr$(NO_2)_2$

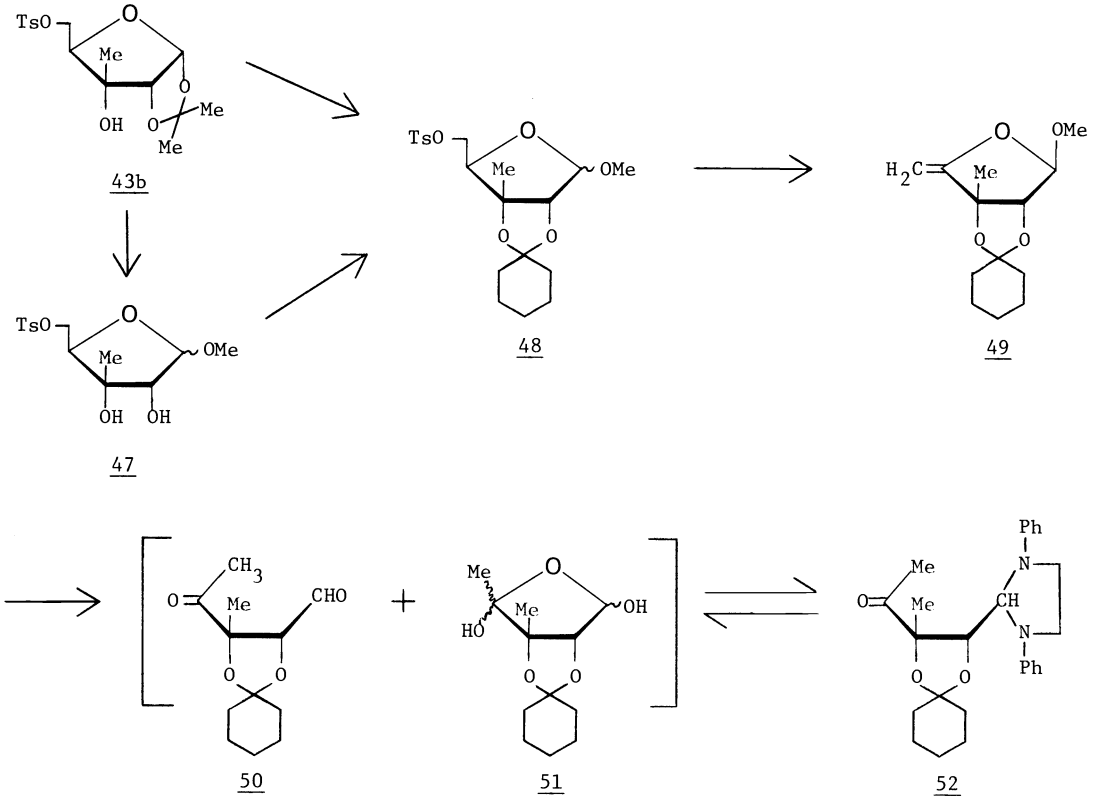
Isomerization of the 1,2-O-acetonide in 43b was achieved by treatment with a mixture of 2,2-dimethoxypropane and methanol in the presence of a catalytic amount of perchloric acid at 90° for 3 h. Following chromatography on silicic acid the pure β-glycoside 44 was obtained (81%). The less polar α-anomer of 44 was also obtained from this reaction and the anomeric configurations were determined by ^{1}H-n.m.r. spectroscopy; H-1 of the β-isomer afforded a singlet at 4.85 p.p.m. and H-1 of the α-anomer, a doublet ($J_{1,2}$ 2.5 Hz) at 4.93 p.p.m. The signals for the tertiary methyl groups also exhibited strikingly different chemical shifts appearing at 1.26 and 1.40 p.p.m. in the α- and β-anomers, respectively. Elimination of the tosyl group from 44 was readily achieved by treatment with potassium tert-butoxide in methyl sulfoxide at room temperature for 5 min. However, the resulting methyl 5-deoxy-2,3-O-isopropylidene-3-methyl-β-D-erythro-pent-4-enofuranoside (45) was very difficult to isolate in good yield due to its volatility and partial solubility in water. The ^{1}H-n.m.r. spectrum of 45 was typical of other exocyclic furanoside vinyl ethers (Ref. 38), H-5,5' appearing as a pair of doublets (J_{gem} 2 Hz) at 4.20 and 4.39 p.p.m. Whereas the physical difficulties in isolating 45 in adequate yield precluded its use for completion of the synthesis at hand, an attempt was made to confirm its desired hydrolysis to the ketoaldehyde 46a. Treatment of 45 with dilute acetic acid (pH 3-4) at 100° for 5 min gave several spots giving positive tests for carbonyl compounds with dinitrophenylhydrazine spray. The nature of this mixture will be discussed later, but it could be converted into a bis-2,4-dinitrophenylhydrazone (46b).

In order to decrease the volatility and water solubility of 45, it was desirable to prepare the related 2,3-O-cyclohexylidene derivative 49. The preparation of the 5-O-tosyl precursor 48 was achieved by two different routes. Firstly, the 1,2-acetonide 43b was subjected to methanolysis using methanolic hydrogen chloride in the presence of 15% of water. The added water was designed to suppress the formation of 44 via acetonide migration and was suggested by the work of Nutt et al. (Ref. 47). Under these conditions a ∿1:2 mixture of the α- and β-anomers of methyl 3-methyl-5-O-p-toluenesulfonyl-D-ribofuranoside (47) was obtained (85%). Each anomer could be obtained in crystalline form following chromatography on silicic acid and the configuration was apparent from consideration of the n.m.r. spectra and optical rotations. Treatment of the mixed anomers of 47 with 1,1-diethoxycyclohexane and perchloric acid in N,N-dimethylformamide at 70° under reduced pressure led to an 84% yield of the α- and β-anomers of the 2,3-O-cyclohexylidene derivative 48, in the same ratio of 1:2. Once again, each anomer could be obtained in crystalline form by chromatography. A shortened and more stereoselective synthesis of 48 was possible via direct treatment of the 1,2-acetonide 43b with 1,1-dimethoxycyclohexane, generated in situ from cyclohexanone and methyl orthoformate, and methanol in the presence of perchloric acid. Under these conditions the α- and β-anomers of 48 were isolated chromatographically in yields of 3% and 73%, respectively. A small amount (7%) of the 1,2-O-cyclohexylidene derivative corresponding to 43b was also isolated from this reaction.

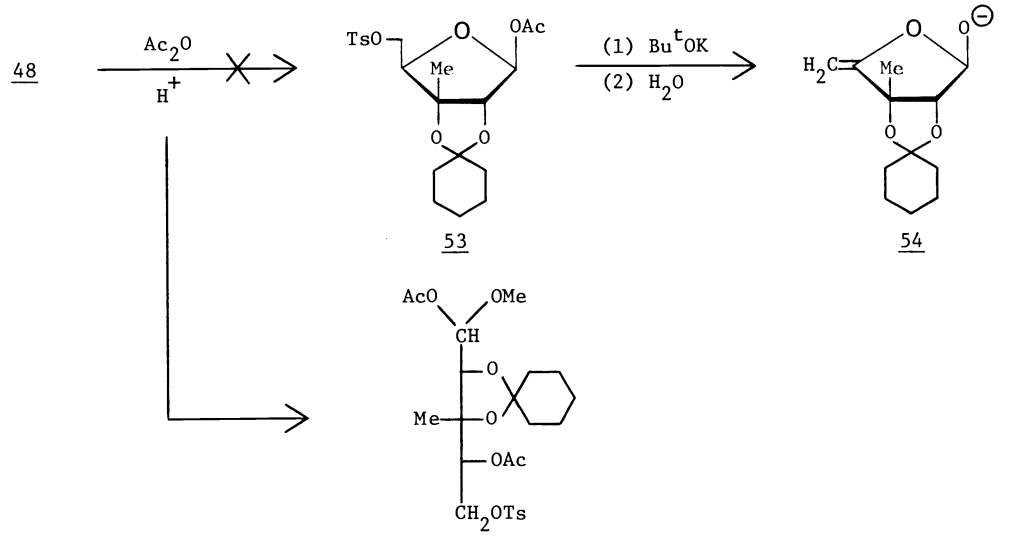
Conversion of 48 into the exocyclic vinyl ether 49 was readily accomplished by treatment with potassium tert-butoxide in methyl sulfoxide at 20° as described for 45. The formation of 49 and its chromatographic isolation were essentially quantitative and the product could also be purified by distillation (b.p. 80°/0.1 mm Hg). The ^{1}H-n.m.r. spectrum of 49 was similar to that of 45; H-5,5' gave doublets (J_{gem} 2 Hz) at 4.25 and 4.40 p.p.m. Hydrolysis of 49 proceeded readily with 80% acetic acid at 100° for 15 min or at 20° for 24 h giving one major and several minor products of greater polarity than the starting material. Purification by p.l.c. was only partially successful and the ^{1}H-n.m.r. spectrum of the crude product suggested the presence of a mixture of the desired ketoaldehyde 50 and the cyclic acetal 51 derived from the hydrate in ratios of ∿1:2 to 1:4. The aldehyde proton and the methyl group of 50 were apparent as a doublet (J 2 Hz) at 9.74 p.p.m. and a singlet at 2.13 p.p.m., respectively, whereas the methyl group of 51 gave a singlet at 1.99 p.p.m. in $CDCl_3$. Addition of N,N'-diphenylethylenediamine to the crude acidic hydrolysis mixture led to the isolation of the crystalline 1,3-diphenylimidazolidine derivative 52 (66%). The derivatization of aldehydes with this reagent is known (Ref. 48) and we have previously found that sensitive aldehydes can be regenerated from the 1,3-diphenylimidazolidines by mild acidic treatment (Ref. 49). Such regeneration by treatment of 52 with either p-toluenesulfonic acid monohydrate in acetone at room temperature or with Dowex 50 (H^+) resin in aqueous tetrahydrofuran led to a mixture of 50 and 51 that was qualitatively similar to the crude

ketoaldehyde by n.m.r. analysis.

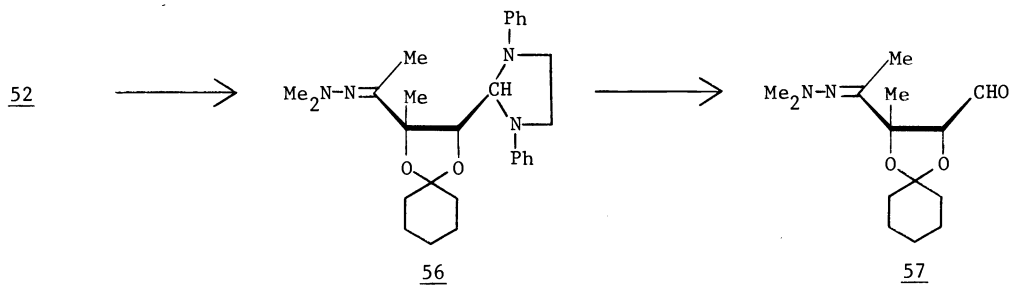
Since purification of 50 via the derivative 52 offered little advantage, we proceeded to investigate the critical intramolecular aldol closure (Ref. 50) to give the optically active form of 38. This reaction was investigated under a multitude of conditions using t.l.c. and g.l.c. comparison with racemic 38 for evaluation. Without elaboration, it can simply be stated that basic conditions (e.g. sodium or potassium hydroxide, lithium di-isopropylamide, potassium tert-butoxide, triethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene, and piperidinium acetate), acidic reagents (e.g. boron trifluoride, titanium tetrachloride, sulfuric acid, hydrogen chloride, p-toluenesulfonic acid), and certain more neutral reagents such as acetic anhydride and dicyclohexylcarbodi-imide-cupric chloride either failed to react or led to complex mixtures containing little, if any, of the desired product. In certain cases preliminary dehydration of 51 to 50 was attempted via azeotropic distillation with benzene, but no improvement was noted. In view of the many successful intramolecular aldol condensations that have been reported (Ref. 50), the present failures are somewhat surprising and, to say the least, frustrating.



In view of our failures to effect the aldol closure using preformed 50 and 51, we attempted an in situ generation of these species. It was our hope that acetolysis of 48 would lead to the 1-O-acetyl sugar 53 that could be treated first with anhydrous potassium tert-butoxide to generate the 4,5-olefin, and then with water to form the oxyanion 54. The latter would be in equilibrium with the enolic form of 50 and might undergo immediate cyclization. Unfortunately, treatment of 48 with acetic anhydride containing 0.5% sulfuric acid for only 1.5 min led to the formation of the acyclic diacetate 55 that was isolated (70%) as a ∿1:1 mixture of isomers. The structure of 55 was based upon its ^{1}H-n.m.r. spectrum, which showed the presence of one methoxyl group (3.36 and 3.43 p.p.m. in the two isomers) and two acetoxy functions (2.03 and 2.10 p.p.m.) in addition to the cyclohexylidene and tosyl groups. The H-1 resonated at 5.95 and 5.66 p.p.m. in the two isomers and in each case showed $J_{1,2}$ 7 Hz.



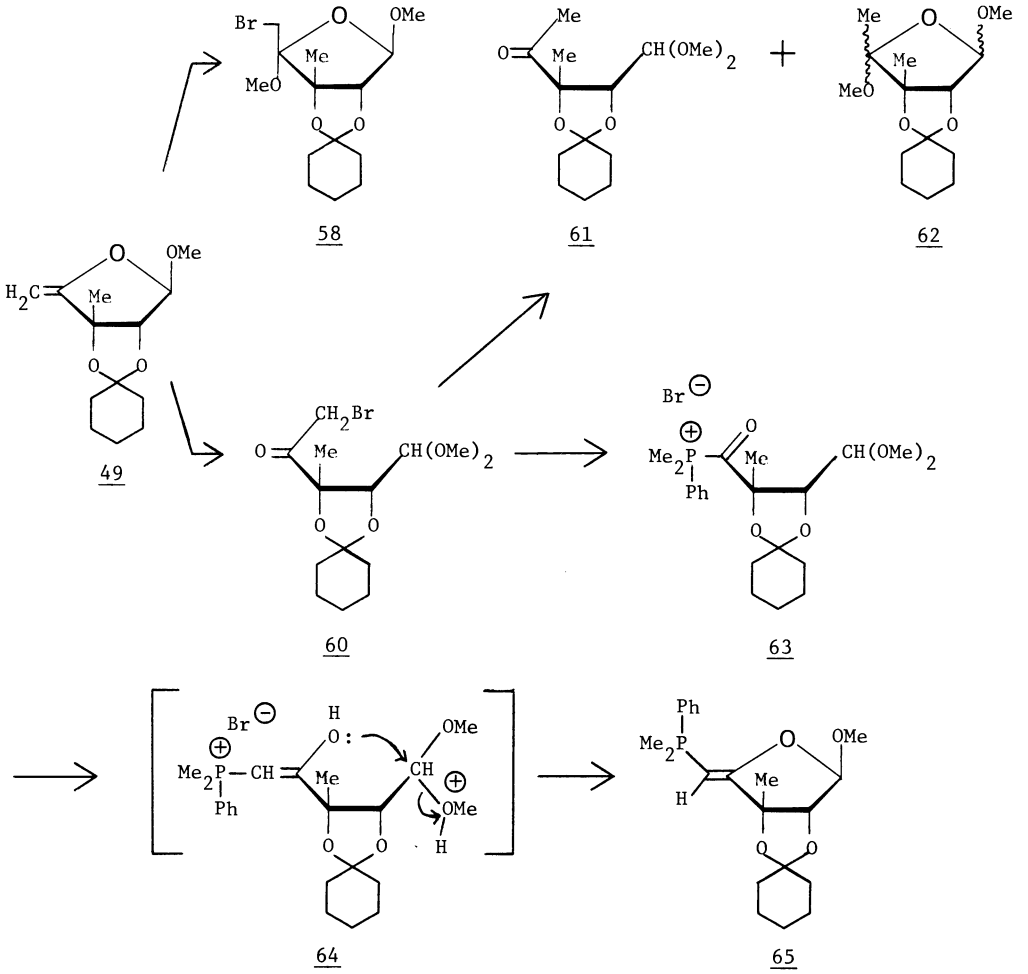
Since it seemed possible that the failure of the aldol cyclization was due to the formation of the very stable bishemiacetal 51, we considered another approach based upon the generation of a dimethylhydrazone-stabilized carbanion (Ref. 51). To this end the ketoimidazolidine 52 was reacted with 1,1-dimethylhydrazine to form the dimethylhydrazone 56. For reasons that are not clear, this reaction would only take place under forcing conditions, the best results being obtained in a sealed tube at 150° for 3 days. In this way 56 was obtained by p.l.c. (79%). Hydrolysis of the imidazolidine group was effected with an acidic ion exchange resin giving the desired aldehyde 57 as a hydrate (80%). Dehydration by azeotropic distillation with benzene over a molecular sieve led to the appearance of an aldehyde i.r. band at 1720 cm^{-1}. The mass spectrum of 57 also showed a strong molecular ion at m/e 268. Treatment of 57 with lithium di-isopropylamide in tetrahydrofuran, however, led to a complex mixture of products only a minor one of which had a t.l.c. mobility similar to that of the dimethylhydrazone of 38. This approach was not investigated further.



One further possibility for the preparation of the optically active form of 38 involved an intramolecular Wittig reaction. Previous work in our laboratory (Ref. 38) had shown that furanose vinyl ethers readily add the elements of MeOBr under mild conditions. Indeed, treatment of 49 with 1 equiv. of bromine in methanol at room temperature rapidly gave a mixture of products from which the desired methyl 5-bromo-2,3-O-cyclohexylidene-5-deoxy-4-methoxy-3-methyl-β-D-ribofuranoside (58) could be isolated in only 16% yield. The structure of this substance is entirely in accord with its mass spectrum (molecular ion at m/e 319, 321) and its ^1H- and ^{13}C-n.m.r. spectra. The ribo configuration for 58 is assigned by comparison of the ^{13}C-signal for C-4 to that previously reported (Ref. 38a) for a number of differently substituted derivatives of 5-iodo-5-deoxy-4-methoxyuridine and its α-L-lyxo isomer. In those compounds C-4' resonated at 102.9-106.2 p.p.m. in the ribo isomers and at 107.6-111.6 p.p.m. in the lyxo epimers. The β-shifts due to iodine and bromine are equal (Ref. 52) and one would anticipate a 4-5 p.p.m. downfield β-shift of the C-4 signal due to the Me-3 in 58. Hence C-4 in the ribo isomer 58 would be expected to appear at ∿109 p.p.m. whereas that in the α-L-lyxo isomer would be at ∿114 p.p.m. The observed value of 109.39 p.p.m. is therefore indicative of the ribo configuration as in 58. Also, the signal for the MeO-4 appeared at 49.28 p.p.m., a position very similar to that in the 4-methoxyuridines

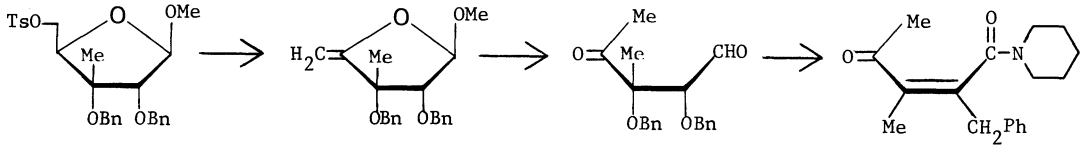
(49.12-49.51 p.p.m.) and somewhat different to that in the α-L-lyxo isomers (48.28-48.93 p.p.m.).

In an effort to increase the yield of 58, the reaction of 49 with bromine in methanol was repeated in the presence of a small excess of lead carbonate. A much simpler reaction mixture was then formed in which 58 was only a minor product isolated in 12% yield. The principal component was isolated (60%) and shown spectroscopically to be the acyclic bromoketone 5-bromo-2,3-O-cyclohexylidene-5-deoxy-3-methyl-D-erythro-4-pentosulose 1,1-dimethylacetal (60). The presence of both the bromoketone (37.71 and 203.05 p.p.m.) and the dimethylacetal (101.01, 55.75, and 55.14 p.p.m.) groups was apparent in the ^{13}C-n.m.r. spectrum. Attempts to convert 60 into a phosphonium salt with triphenylphosphine were unsuccessful, the debrominated products 61 (11%) and 62 (7%) being the only products isolated. Reductive dehalogenation of α-haloketones by phosphines is well known (Ref. 53). However, a similar reaction with the more nucleophilic dimethylphenylphosphine readily gave the desired phosphonium salt 63, in almost quantitative yield. Our objective was to hydrolyze the methyl glycoside under acidic conditions and then to generate the keto-stabilized phosphonium ylide with mild base, hoping that the latter would undergo an intramolecular Wittig reaction leading to 38. Once again, we were foiled since attempted cleavage of the acetal by treatment with 10% trifluoroacetic acid in methylene chloride at 20° for 10 min led to the isolation of the crystalline vinylphosphonium salt 65 (80%). This structure was apparent from the lack of any H-4 resonance and the appearance of a single vinyl proton signal at 5.18 p.p.m. showing a coupling of 13 Hz to phosphorus. In addition, the unsaturation was indicated by the appearance of the H-2 signal as a doublet of doublets showing $^{5}J_{H,P}$ 2 Hz. Presumably the formation of 65 is the result of acid catalyzed enolization of the ketone followed by nucleophilic displacement of a protonated methoxyl group in the intermediate 64. This approach was also abandoned.



To this point we were assuming that the presence of the 5-membered acetal grouping in 50 and related compounds would promote the closure of a second fused 5-membered ring (Ref. 54) during formation of 38. The failures recorded above led us to question this assumption.

Accordingly, the diol 47 was converted into the crystalline dibenzyl ether 66 (50%) using benzyl bromide and sodium hydride in N,N-dimethylformamide. Treatment of 66 with potassium tert-butoxide in the usual way generated the exocyclic vinyl ether 67 (72%). Hydrolysis of 67 with 80% acetic acid at 100° for 15 min gave the ketoaldehyde 68, that was largely purified by chromatography on silicic acid and dehydrated by azeotropic distillation with benzene. Quite unlike our attempts to effect aldol reactions with the cyclohexylidene ketoaldehyde 50, treatment of 68 with piperidinium acetate in benzene under reflux, conditions known to effect aldol closures of other γ-ketoaldehydes (Ref. 55), led to the formation of a major product isolated in an overall yield of 47% from 66. Analytical and spectroscopic data, however, showed this to bear no resemblance to the desired cyclopentenone. It had λ_{max} 284 nm (ε 6,400), was optically inactive, and had the molecular formula $C_{18}H_{23}NO_2$ by elemental analysis and mass spectrometry. An analysis of its ^{13}C- and ^{1}H- n.m.r. spectra indicated a number of unusual features including the incorporation of a molecule of piperidine and loss of one benzyl group. The remaining benzyl group would appear to be linked to carbon rather than oxygen since its methylene carbon signal appeared at 47.0 p.p.m. and those for its appended hydrogens at 2.97 and 3.38 p.p.m. rather than at the typical 75 and 4.5 p.p.m. of benzyl ethers. Although some features of the spectra are not yet completely reconciled, we tentatively suggest the rather bizarre structure 69 for this product. A mechanism can be provided to explain the formation of 69, but any further discussion will be postponed until the structure is on safer grounds (Note a).



66 67 68 69

Finally, in the face of all the adversities outlined above, we encountered evidence in support of the old adage that all things come to those who wait (and keep on trying). Thus, it was found that while we were unable to effect the desired aldol cyclization under conventional basic or acidic conditions, it could be accomplished thermally. Previous work by Cavill et al. (Ref. 56) showed that cyclization of 4-oxohexanal to 2-methylcyclopent-2-enone could be achieved by heating at 370° but not under normal aldol conditions. Treatment of 50 and 51 at various temperatures in sealed tubes indeed showed the formation of modest yields of the desired 38 after heating at 210-300°. A major improvement, however, was achieved by conducting these reactions in the presence of neutral alumina (Ref. 57). In early experiments the crude ketoaldehyde 50 was heated in a sealed tube at 180° for 6 min in the presence of a roughly equal weight of Woelm neutral alumina. Following chromatography of the products on silica gel, 4(S),5(S)-cyclohexylidenedioxy-5-methyl-2-cyclopenten-1-one (38) was isolated in an overall yield of 51% from the tosylate 48. On a larger scale it was found preferable to gradually heat the mixture of crude ketoaldehyde and alumina in a kugelrohr apparatus (Ref. 58) under a modest vacuum (20 mm Hg). Distillation of 38 took place at 100-120° and following redistillation the pure substance was obtained in a yield of 66% from 48. This material was in every way identical to the racemic sample prepared earlier except that it had $[\alpha]_D^{25}$ +45° (EtOH). Hydrolysis of the cyclohexylidene group was accomplished using 90% trifluoroacetic acid and gave optically active 6-deoxypentenomycin (39) with $[\alpha]_D^{23}$ +13° (EtOH) in 87% yield. It is interesting to note that 38 and 39 show in vitro antibacterial activities comparable, or even superior, to those of pentenomycin.

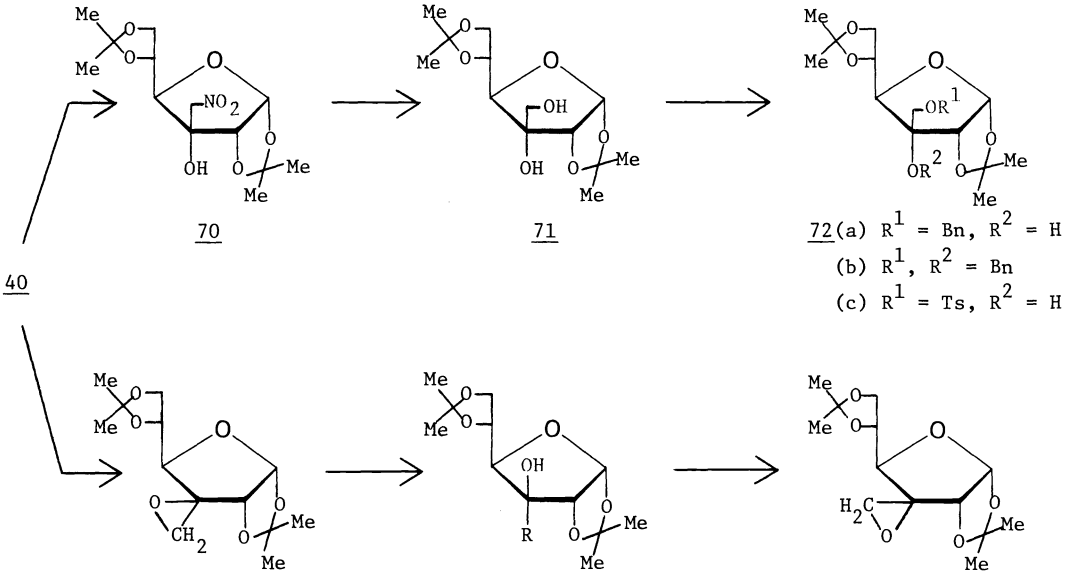
Armed with the successful preparation of the model compound 39, we then attacked the more difficult problem of the synthesis of pentenomycin. Clearly, the only fundamental change is the necessity of carrying a suitably protected hydroxymethyl group rather than Me-3 in the sequence outlined above. Several methods have been described for the stereochemically controlled synthesis of the desired starting material, 3-hydroxymethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (71, Refs. 39a,c). One of these (Ref. 39a) was attractive since it involved as its key intermediate 1,2:5,6-di-O-isopropylidene-3-nitromethyl-α-D-allofuranose (70), a compound that we have previously prepared in 85% yield by kinetically controlled reaction of 40 with nitromethane (Ref. 59). Oxidation of 70 with alkaline potassium permanganate at -12° according to Blackstock et al. (Ref. 39a) followed by immediate borohydride reduction of the resulting aldehyde gave the desired 71. However, the isolation of this compound required careful chromatography on silicic acid and the yields were capricious, ranging from 15-70%. The melting point observed for 71 (81.5-82.5°) was

Note a. We are very much indebted to Dr. M. L. Maddox and Professor E. J. Corey for much stimulating discussion concerning the structure and mechanism of formation of this compound.

somewhat higher than those (62-63° and 74°) reported previously (Ref. 39c) and is somewhat closer to that of the D-gluco isomer (m.p. 87-88.5°, Ref. 60). However, the ^{1}H-n.m.r. spectrum is in close agreement with that reported for the allo isomer (Refs. 39a,c) and subsequent transformations assure the configuration assigned.

In view of the requirement for stability during subsequent reactions under both acidic and basic conditions, the selection of a protecting group for the primary hydroxyl group in 71 was largely restricted to an ether. Our first choice was the benzyl ether, but considerable difficulty was encountered in effecting monobenzylation. Thus, treatment of 71 with benzyl bromide and a variety of bases led to the formation of considerable amounts of the dibenzyl ether 72b, as well as the desired 72a. The most selective result was obtained using 1.2 equiv. of benzyl bromide in the presence of powdered potassium hydroxide in dioxane, which gave 33% of the desired monoether 72a, and 15% of 72b. The use of an excess of benzyl bromide in the presence of sodium hydride led to the useless dibenzyl ether 72b in 76% yield. A solution to this problem was found in a two step process in which 71 was selectively converted into the crystalline primary tosylate 72c in 83% yield and thence to the monobenzyl ether 72a by treatment with sodium benzyloxide in N,N-dimethylformamide at room temperature. The latter step, which quite likely occurs via the allo epoxide 75, gave crystalline 72a (95%).

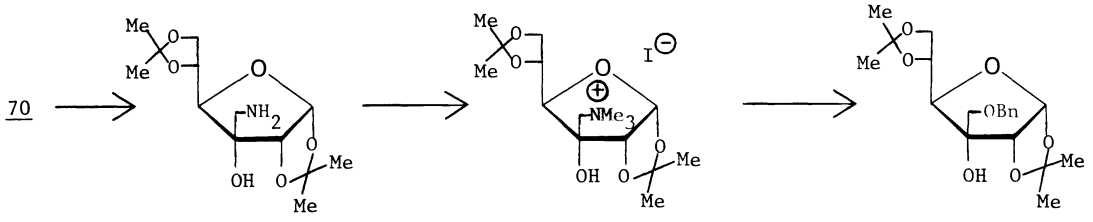
In spite of the efficient transformation of 71 into 72a described above, the variable yields and requisite chromatography during preparation of 71 made us seek an alternative route. One attractive possibility was the direct conversion of 40 into the allo epoxide 75 through reaction with methyl sulfoxonium methylide. We anticipated that the steric effect of the 1,2-acetonide would direct attack from the upper face leading to 75. However, to our surprise this reaction led in 48% yield to the gluco epoxide 73 that has previously been prepared via a different route by Funabashi et al. (Ref. 61). Verification of the gluco configuration was accomplished by reduction of 73 with lithium aluminum hydride, which gave crystalline 1,2:5,6-di-O-isopropylidene-3-methyl-α-D-glucofuranose (74a) that was identical to the compound described by Funabashi et al. (Ref. 61) and distinctly different from the allo isomer 41. Treatment of 73 with sodium benzyloxide gave 74b that was identical to 72a by t.l.c. but gave a distinguishable n.m.r. spectrum.



The route that eventually made the monobenzyl ether 72a readily available was also based upon the nitromethylallofuranose derivative 70. Reduction of the nitro group in 70 was readily achieved using a Raney nickel catalyst at a hydrogen pressure of 45 p.s.i. Under these conditions (Note a) crystalline 3-aminomethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (76) was obtained (95%). In our hands, the reduction of 70 using a palladium

Note a. These reduction conditions had previously been developed by Mr. T. Tompkins of this Laboratory as part of a different project.

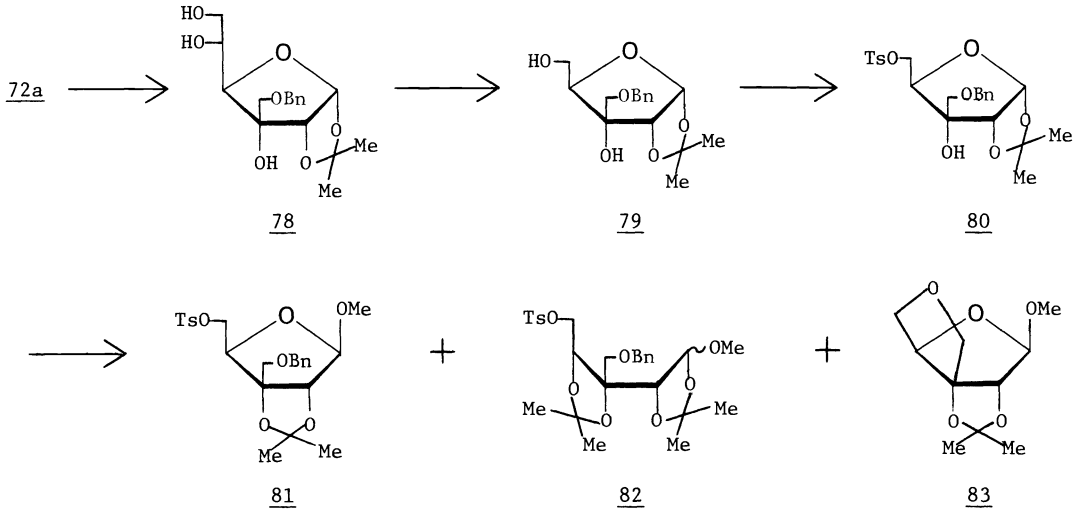
catalyst (Ref. 62) gave a less pure product. Treatment of 76 with an excess of methyl iodide in N,N-dimethylformamide in the presence of potassium carbonate led to the crystalline trimethylammonium derivative 77 (92%). Subsequent reaction of 77 with sodium benzyloxide in N,N-dimethylformamide at 55° gave crystalline 72a (86%) without need for chromatography. It appears as though the formation of 72a proceeds by direct displacement of trimethylamine from 77 rather than by intermediate formation of the allo epoxide 75. This conclusion is based solely upon our failure to accumulate 75 upon treating 77 with sodium hydride alone in N,N-dimethylformamide. The route described above is efficient and allows the preparation of crystalline 72b (overall yield 64%) from the ketone 40 without need for chromatography during any of the four steps.



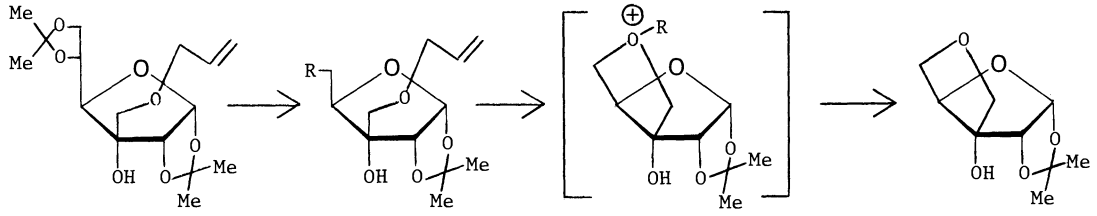
76 77 72a

With the ready availability of 72a, the subsequent synthetic steps generally followed those developed in the 6-deoxypentenomycin series. Selective cleavage of the 5,6-acetonide with 60% acetic acid at 20° for 35-40 h gave the crystalline diol 78 (95%). Periodate oxidation followed by direct reduction of the resulting aldehyde with sodium borohydride had to be done with some care since there was a marked tendency towards epimerization of the aldehyde if pH control was not maintained. Presumably the steric bulk of the benzyloxymethyl group has a distinct destabilizing effect on the cis oriented aldehyde group with the ribo configuration. By doing the periodate oxidation in pH 6 borate buffer, the formation of the C-4 epimer was completely suppressed and homogeneous 3-benzyloxymethyl-1,2-O-isopropylidene-α-D-ribofuranose (79) was isolated (95%). Although the absence of a proton at position 3 makes assignment of configuration difficult by ^{1}H-n.m.r. spectroscopy, the subsequent steps to be discussed allow unequivocal confirmation of the ribo structure.

Selective tosylation of 79 could be achieved in pyridine at 0° and crystalline 80 was isolated (83-94%). However, the tosylate was a sensitive molecule and storage in solution or as a syrup led to extensive degradation. Isomerization of the 1,2-acetonide to the 2,3-position with concomitant glycosidation was achieved by treatment of 80 with 2,2-dimethoxypropane and methanol in the presence of a catalytic amount of perchloric acid at 35° until the starting material had disappeared (36-44 h). These reaction mixtures became quite dark colored and gave a number of products (t.l.c.). By chromatography on silicic acid the major product (m.p. 58-59°) could be isolated (65%) and shown by ^{1}H-n.m.r. spectroscopy to be the desired methyl 3-benzyloxymethyl-2,3-O-isopropylidene-5-O-p-toluenesulfonyl-β-D-ribofuranoside (81), the β-configuration being apparent from the resonance of H-1 as a singlet at 4.91 p.p.m. Relatively little of the α-anomer of 81 appears to be formed under these conditions. Attempted use of either higher temperatures or more strongly acidic conditions led to a decrease in the amount of 81 present and the accumulation of larger amounts of by-products. The two major by-products were isolated and shown, primarily by n.m.r. spectroscopy, to have the structures 82 and 83. The acyclic derivative 82 is slightly less polar than 81 and its ^{1}H-n.m.r. spectrum in $CDCl_3$ shows the presence of a single methoxy group (3.33 p.p.m.), a tosyl group (methyl at 2.43 p.p.m.), a benzyl ether (CH_2 at 4.56 p.p.m.) and two isopropylidene functions as singlets at 1.31, 1.35 and 1.40 (6H) p.p.m. The much more significant tetrahydrofuran derivative 83, which was formed in up to 58% yield under more vigorous acidic conditions, also had a mobility slightly greater than that of 81. It was, however, non-u.v. absorbing and could readily be distilled in vacuo (120°/0.5 mm Hg). Its empirical formula was confirmed by elemental analysis and mass spectrometry and its structure was derived from its ^{1}H- and ^{13}C-n.m.r. spectra. Of particular importance was the presence of two methylene groups containing magnetically non-equivalent protons. One of these bore no adjacent hydrogens and gave a pair of doublets (J_{gem} 10 Hz) at 3.79 and 4.08 p.p.m. in $CDCl_3$, while the other showed additional coupling to H-4 and appeared as ABX patterns (J_{gem} 10 Hz) at 3.77 ($J_{4,5a}$ 3 Hz) and 3.92 p.p.m. ($J_{4,5b}$ 5 Hz). The pure β-configuration led to the resonance of H-1 as a singlet at 5.05 p.p.m. and other features of the spectrum were as expected. Similarly, the ^{13}C-spectrum showed the presence of two methylene groups with rather similar environments as triplets at 72.85 and 74.38 p.p.m.

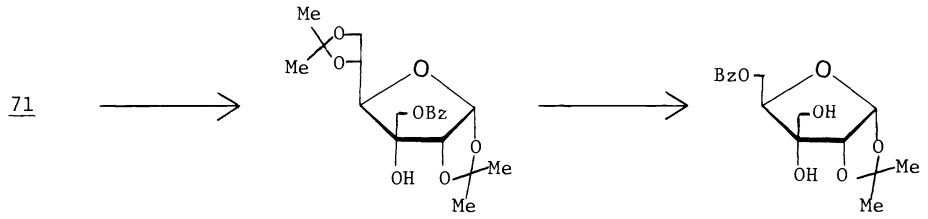


We had previously encountered the formation of a derivative related to 83 during attempts to use the allyl ether as a protecting group for the primary hydroxyl function in 71. It was found that selective formation of the monoallyl ether 84 was somewhat more facile than that of the monobenzyl derivative as described above. By treatment of 71 with allyl bromide and powdered potassium hydroxide in dioxane, pure 84 could be isolated in yields of up to 80%. The sequence of acidic hydrolysis, buffered periodate oxidation, and borohydride reduction essentially as described for the benzyl ether then gave 3-allyloxymethyl-1,2-O-isopropylidene-α-D-ribofuranose (85a, overall yield 90%). Attempted conversion of the primary hydroxyl group in 85a to an iodo function through reaction with methyltriphenoxyphosphonium iodide in N,N-dimethylformamide, a reaction that we have applied with much success to nucleosides (Ref. 63), failed completely to give the desired product 85b, and essentially the only new carbohydrate derivative formed proved to be the tetrahydrofuran 87. The latter compound has previously been characterized by Horwitz et al. (Ref. 46) as one of the major products arising from reaction of 1,2-O-isopropylidene-5-O-trityl-α-D-erythro-pentofuranos-3-ulose with diazomethane. Our product proved to be identical to a sample obtained from Dr. Horwitz, and our additional ^{13}C-n.m.r. data attest to the correctness of this structural assignment. The same compound was the major product when the 5-O-tosyl derivative 85c, which was obtained with some difficulty by treatment of 85a with tosyl chloride at 0° in the presence of 4-dimethylaminopyridine (Ref. 64), was reacted with sodium iodide in N,N-dimethylformamide at 40°. It would appear that the use of protecting groups such as the allyl or benzyl ether, that can form relatively stabilized carbonium ions, must be undertaken with great care when good leaving groups (tosyl or oxyphosphonium) are present at C-5. Collapse to 87 presumably involves oxonium intermediates such as 86. A related participation by a 3-benzyloxy function in intramolecular displacement of a 6-mesyl group in a glucose derivative has been reported by Brimacombe and Ching (Ref. 65).



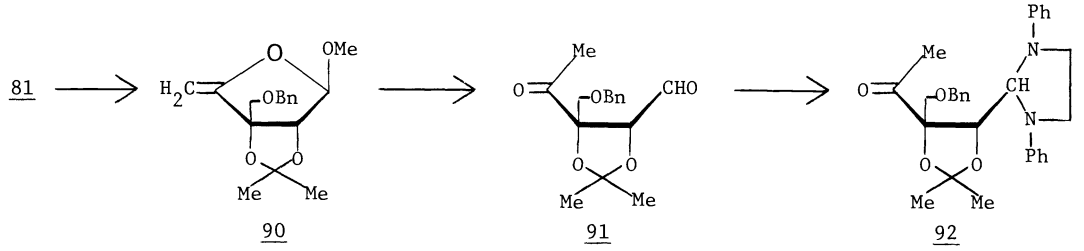
84 85(a) R = OH (b) R = I (c) R = OTs 86 R = Bn or Allyl 87

In passing, we might also mention that benzoylation of 71 led to the expected selective acylation of the primary hydroxyl group giving 88. However, hydrolysis of the 5,6-acetonide followed by periodate oxidation and borohydride reduction led exclusively to crystalline 5-O-benzoyl-3-hydroxymethyl-1,2-O-isopropylidene-α-D-ribofuranose (89) as judged by n.m.r. and mass spectral analysis. The formation of 89 is clearly the result of intramolecular benzoyl migration and offers further evidence of the proximity of CH_2OH-3 and HO-5 and hence of the ribo and allo configurations throughout this series.



88 89

However, as described earlier it was possible to prepare the key compound 81 in reasonable yield without serious participation by the 3-O-benzyloxymethyl group. Fortunately, it proved possible to convert 81 in yields of up to 78% into the desired exocyclic vinyl ether 90 by treatment with potassium tert-butoxide under the usual conditions. Varying amounts of 83 were also usually formed in this reaction but could, if desired, be easily removed by chromatography on silicic acid. The modest amounts of 83 observed are an indication, perhaps, that its formation is promoted by the presence of nucleophilic species leading to collapse of the oxonium ions analogous to 86. For most purposes it was not considered necessary to purify 90 and the crude product was directly hydrolyzed with 80% acetic acid at 100° for 15 min to generate the crude ketoaldehyde 91. As in the case of the deoxy compound 50, t.l.c. showed that crude 91 contained several spots but the crystalline 1,3-diphenylimidazolidine derivative 92 could be isolated in an overall yield of 50% from 81 without purification of intermediates.



90 91 92

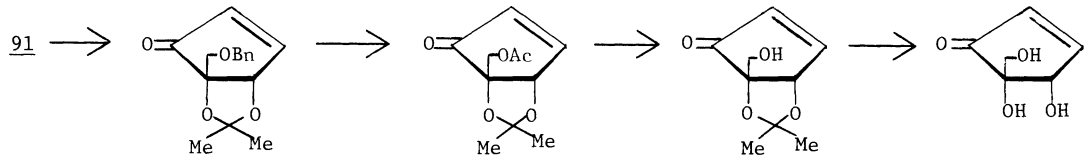
Unfortunately, the alumina catalyzed aldol cyclization of 91 to the cyclopentenone 93 did not proceed as efficiently as with the deoxy compound 50. The best results obtained resulted from heating crude 91 with roughly twice its weight of alumina at 100-180° at 30 mm Hg. Chromatography of the resulting distillate then gave analytically pure (4S,5S)-5-benzyloxymethyl-4,5-isopropylidenedioxy-2-cyclopentene-1-one (93) in overall yields of up to 48% from the tosylate 81. However, the yields of 93 were rather capricious and those in the overall 20-30% range were not uncommon. The structure of 93, which showed $[\alpha]_D^{23}$ -66° (c 0.5, EtOH), was apparent from its u.v. spectrum, which showed λ_{max} 208 nm (ε 7,200), and its ^{1}H-n.m.r. spectrum. The latter showed signals for the expected vinyl protons as a doublet (J 6 Hz) at 6.30 p.p.m. (H-2) and a doublet of doublets (J 6, 2.5 Hz) at 7.63 p.p.m. (H-3), H-4 as a doublet at 5.28 and H-5,5' as a pair of doublets (J_{gem} 11 Hz) at 3.68 and 3.90 p.p.m. in addition to the expected benzyl ether and isopropylidene signals.

We had previously ascertained that 6-deoxypentenomycin (39) was stable to treatment with an excess of boron trichloride in methylene chloride at -78° for 15 min since this was the method of choice for cleavage of the benzyl ether from 93. However, application of this reaction to 93 led to an intractable mixture of products. Accordingly, an alternative route for debenzylation was necessary and reductive methods were precluded by the presence of the enone system. An answer was found in acetolysis of the benzyl ether through treatment of 93 with acetic anhydride containing 0.7% sulfuric acid at -5° for 30 min (Ref. 66). This reaction led to the formation of two more polar products of very similar mobility from which the pure monoacetate 94, which retained the isopropylidene group, could be isolated in 38% yield by careful chromatography. The other major product, possibly the triacetate, was not obtained in pure form and was not examined further. Attempted removal of the acetate by treatment with methanolic ammonia, hydrogen chloride or sodium methoxide led to a mixture of products presumably due to reverse aldol cleavage of the liberated β-hydroxyketone. Accordingly, recourse had to be taken to enzymatic deacetylation, which was achieved upon vigorous stirring of a suspension of 94 in pH 7 phosphate buffer with the commercially available Type VII lipase from Candida cylindracea (Note a). Following chromatography on silicic acid the crystalline alcohol 95 (m.p. 63-66°) was obtained (50%). Subsequent hydrolysis of the acetonide could be accomplished with relatively little degradation by treatment of 95 with 90% trifluoroacetic acid at 20° for 30 min. The latter reaction gave the desired triol 2

Note a. Available from the Sigma Chemical Co., St. Louis, MO.

that was homogeneous (t.l.c.) and gave a ^{1}H-n.m.r. spectrum that was identical to that reported for natural pentenomycin I (Refs. 34, 35). By combining the latter two steps without intermediate purification of 95, 2 was obtained (overall yield 59%).

The observed optical rotation of the synthetic product was -27°, whereas that reported for the natural product is -32° (Ref. 34). At this point in the synthesis we were working with very small amounts of compound and this minor discrepancy does not appear to be significant. The synthetic product also showed a spectrum of microbiological activities that is qualitatively similar to that reported by Umino et al. (Ref. 34) with moderate inhibition of S. aureus and P. vulgaris.



93 94 95 2

Whereas the above synthesis is fairly lengthy and was replete with numerous unanticipated problems, it clearly confirms the absolute stereochemistry of pentenomycin I and provides the first synthesis of this natural antibiotic. The reported syntheses of 1 and 2 also provide further examples of the versatility of carbohydrate derivatives as intermediates in the synthesis of optically active natural products.

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