

STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF THE EZOMYCINS, THE
OCTOSYL ACIDS AND RELATED ANTIBIOTICS*

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Abstract - The ezomycins A, B and C, and the octosyl acids are nucleoside antibiotics endowed with an unprecedented structural feature, namely, a bicyclic trans-fused ring system which is part of a 3,7-anhydrooctose structure. Methods were explored for the construction of such bicyclic rings. Trans-fused perhydrofurofuran models, bicyclic 2-deoxy-3,7-anhydrooctosyl nucleosides and acyclic analogs related to the target molecules were synthesized by efficient regio- and stereocontrolled routes. Bicyclic lactones derived from carbohydrate precursors were also synthesized and their structures related to sesquiterpene α -methylene lactones.

INTRODUCTION

Over the past three decades or so, the important class of natural products, generally grouped under the title of nucleosides has provided us with a number of fascinating molecular structures (Ref.1). Research in this area has spanned several generations of scientific effort in different disciplines, and it has provided the fundamental basis for our present day understanding of a multitude of biological phenomena at the molecular level, in addition to giving us our deepest insights yet into the processes of life.

By today's standards, the nucleosides in general, are regarded as "small molecules", but from a synthetic viewpoint, their structures could, in many instances, be deceptively simple. As a group of compounds, they have few rivals in the vast realm of the natural products, with regard to diversity in biological function. In fact few classes of organic compounds can boast the potentially important biological activities associated with the nucleosides. Thus, it is remarkable that the range of activities cover among others, such important areas as antibiotic, antitumor, antiviral and antifungal action, not to mention the plethora of reported effects as specific and potent inhibitors or potentiators of enzymes vital to a number of biological processes in eukariotes, prokariotes, viruses and fungi. These important findings have not eluded the interest of the synthetic organic chemist over the years. Indeed, the great challenges of structure elucidation, and eventual total synthesis have been courageously confronted and admirably achieved. Without such contributions, the state of the art on other fronts would not have advanced to its present status, since such chemical studies have had a direct impact in providing an unbiased level of confidence for associating structure with biological activity. Perhaps equally important has been the enormous effort in chemical modification of existing structures and in the synthesis of other compounds based on logical biological rationales. Such a wealth of steadily accumulating chemical and biochemical knowledge will undoubtedly contribute significantly in rewriting new and exciting chapters in the molecular biology of the living cell and in shaping its future and destiny.

In examining the recent history of nucleoside antibiotics, one occasionally encounters the emergence of unique structures - such is the case with the ezomycins and the octosyl acids which have provided the stimulus for our recent studies directed at their total synthesis.

THE EZOMYCINS, OCTOSYL ACIDS AND THE HERBICIDINS

The ezomycins are a group of antifungal antibiotics active against a limited species of phytopathogenic fungi (Ref.2). They are produced by a strain of *Streptomyces* and individual components have been isolated by a combination of chromatographic techniques. The constitutional structures, including absolute stereochemistry, of the ezomycins have been determined by degradative (Ref.3-5) and spectroscopic (Ref.6) studies. To date, eight components have been isolated and characterized from the ezomycin complex (Ref. 3-5) and the structures of some representative members are in Fig. 1.

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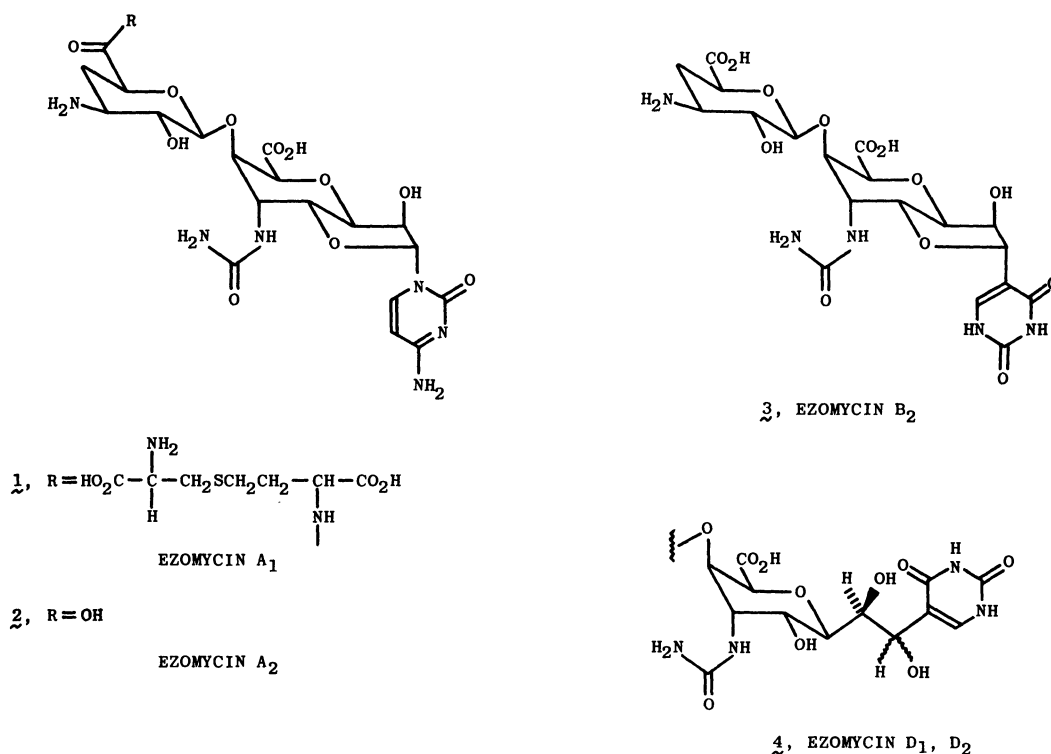


Fig. 1 The ezomycin group of antibiotics

The ezomycins are structurally related by the presence of a disaccharide unit consisting of two unique aminouronic acid residues, one of which has been named ezaminouronic acid. Beyond these common structural features, the individual ezomycin components can be paired with regard to structural genesis and each pair embodies distinct functional features that are germane to this group of compounds. With regard to their derivation from nucleosides in the classical sense, the three pairs of ezomycins can be classified as N-nucleosides (as in the A series 1, 2), C-nucleosides (as in the B, 3 and C series) and "acyclic" C-nucleosides (as in the D series, 4). The A, B and C series comprise a unique bicyclic trans-fused ring system which will be the main focus of our synthetic efforts. Ezomycins C₁ and C₂, not shown in Fig. 1, are in fact the "α-linked" C-nucleosides in the A and B series respectively. Ezomycin B₁ is a "β-linked" C-nucleoside corresponding to the A series. Ezomycin A₁, B₁, C₁ and D₁ components all contain the unusual amino acid L-cystathionine, which has been isolated and characterized (Ref.3-5), hence the common subscript.

The octosyl acids (Ref.7) have been isolated from a strain of *Streptomyces* that produces the polyoxins, which are nucleoside peptide antibiotics (Ref.8). The octosyl acids are structurally very similar to the ezomycin A series, but constitutionally they are much simpler (Fig.2).

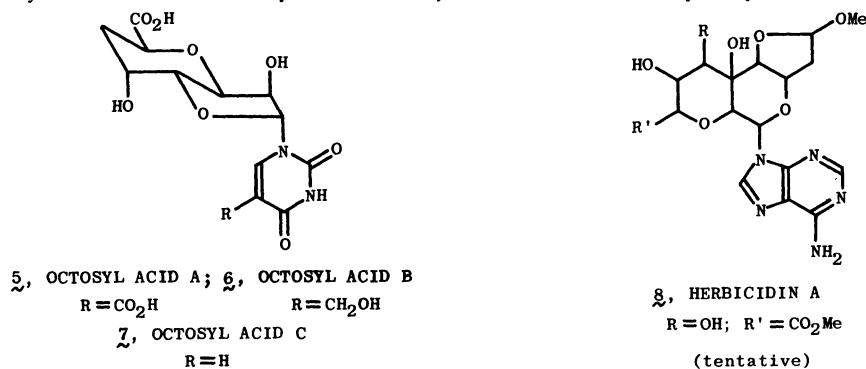


Fig. 2 The octosyl acids and the herbicidins

They share with the ezomycins A-C the common unique feature of a trans-fused bicyclic ring structure, but they are generically more closely related to the A components in that they are N-nucleosides. Degradative and spectroscopic studies (Ref.7) have established the structure of octosyl acid A as 1- β -(3,7-anhydro-6-deoxy-D-glycero-D-allo octofuranosyluronic acid)-5-carboxyuracil, **5**. The B component **6**, corresponds to the 5-hydroxymethyl derivative, while the C component **7** is simply the uracil analog. The biosynthesis of the octosyl acids has been studied (Ref.9). Recently, a group of nucleoside antibiotics active *in vivo* against *Xanthomonas oryzae* has been isolated and named the herbicidins (Ref.10). A tentative structure of herbicidin A **8** is shown in Fig. 2. The presence of a fused bicyclic ring system is reminiscent of the ezomycins and the octosyl acids although stereochemical details are not available as yet on this interesting structure. Otherwise, the gross structure of the herbicidins is significantly different from the ezomycins and the octosyl acids particularly with the presence of a tricyclic structure and an adenine nucleus. The biosynthesis of the ezomycins is thought to proceed by a pathway related to that of the octosyl acids (Ref.9). The formation of ezomycins B₂, C₂, D₁ and D₂ has been rationalized on the basis of a common biosynthetic intermediate shown in Fig. 3² (Ref.5), and is reminiscent of the biosynthetic route leading to pseudouridine (Ref.5).

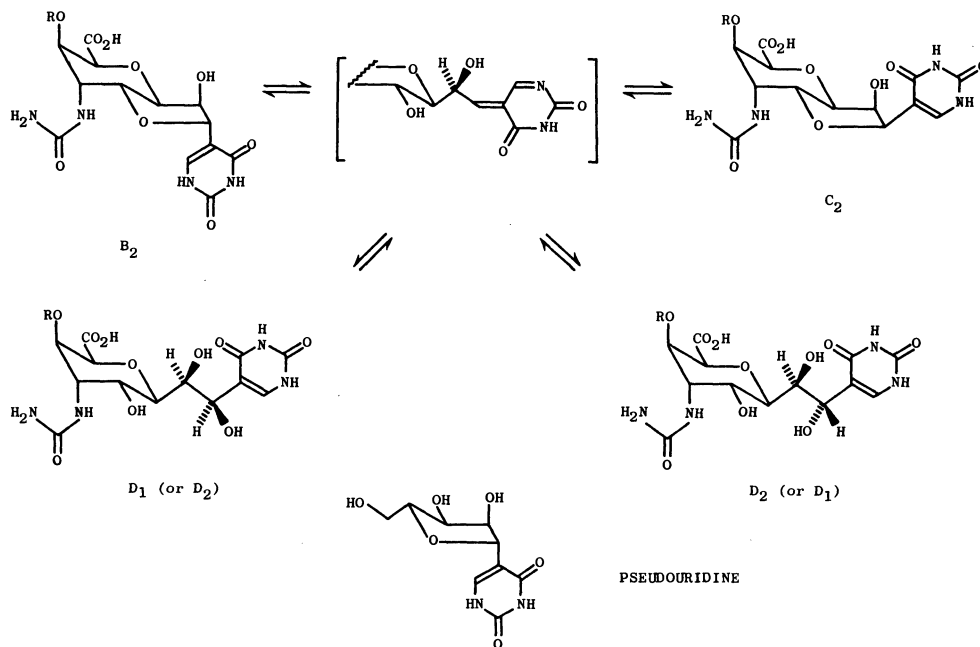


Fig. 3 Biosynthesis of ezomycins B₂, C₂, D₁, D₂

An attempt to construct the octosyl acid framework has been reported in the literature (Ref.10), and consisted in the intramolecular cyclization of malonyl ether **10** obtained from **2** by a sequence of reactions (Fig.4). The bicyclic system **11** was found to be extremely unstable to very dilute acid, giving the acyclic structure **12**.

SYNTHETIC STRATEGIES AND OBJECTIVES

Inspection of the structures of the ezomycins (A-C) and the octosyl acids reveals several structural features that require careful consideration in planning a synthetic strategy. Fig. 5 illustrates the ezomycin A₂ structure, shown in three perspectives. The "terpenoid" representation **2A** allows a better appreciation of the highly functionalized trans-fused perhydrofurofuran type ring system. This and other features are also seen in the more familiar expression **2B**, where idealized conformations are shown and the presence of a 3,7-anhydrooctose unit can be recognized. Expression **2C** places particular focus on the "cytidine" component and in this respect, it is interesting to compare the structures of the ezomycins and the octosyl acids with cyclic phosphates of nucleosides **13** (Ref.10).

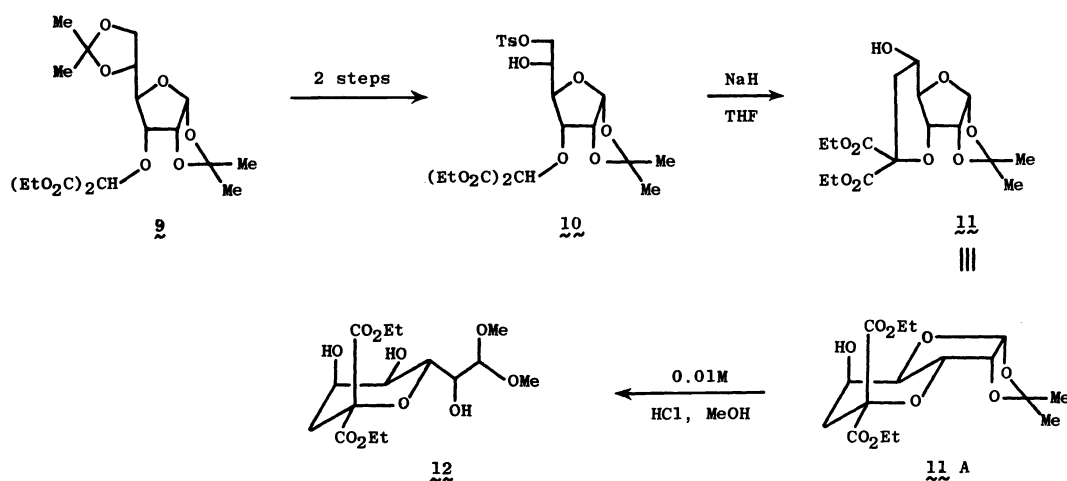


Fig. 4 The Anzai-Ito route to a bicyclic precursor to the octosyl acids

As previously remarked, taken as a representative member, the ezomycin A_2 structure contains unique features, never encountered in such a particular combination. Analysis of these structural features localizes the synthetic challenge around the formation of three strategic bonds involving glycosidic centers and the bicyclic trans-fused ring, as illustrated in expression 2A and 2B, Fig. 5. Retrosynthetic

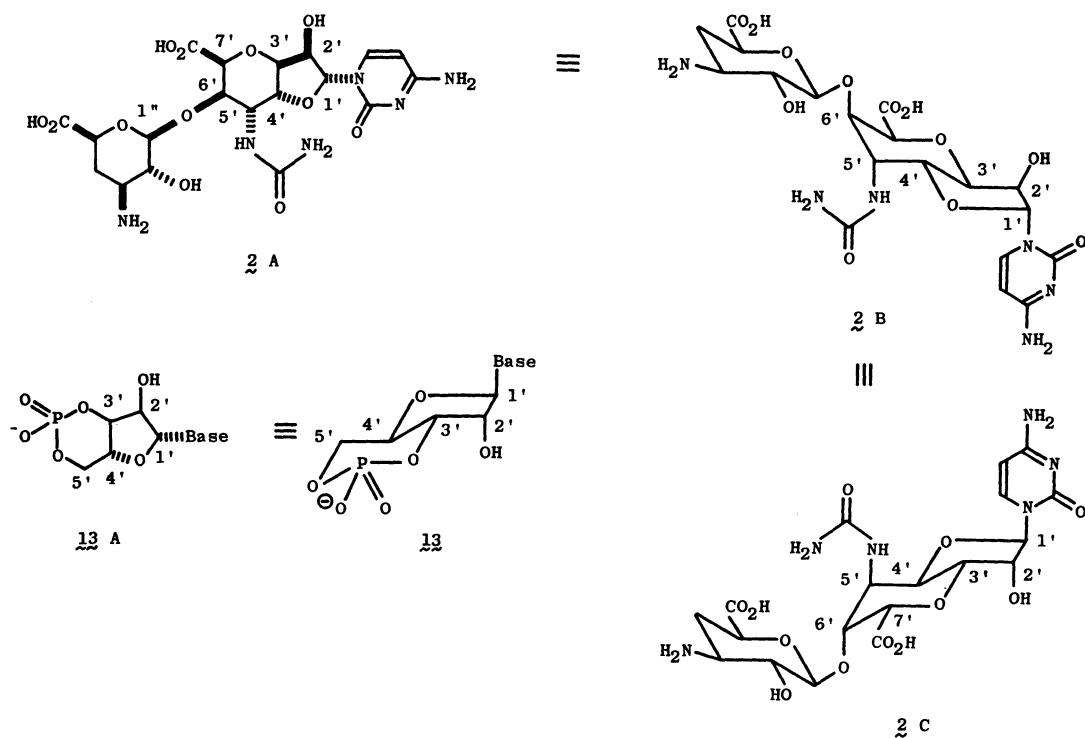


Fig. 5 Ezomycin A_2 perspectives

analysis reveals one of several synthetic plans that could be adopted. The C-glycosidic appendage (Ref.11) must have a 1,2-trans relationship and it must be functionalized directly or in latent form so as to accommodate the substituents ultimately to be found in the "furanose" portion of the targets. It was felt that the D-galactose structure provided the greatest degree of functional overlap with the existing chiral centers in the ezomycins and the octosyl acids and it was also amenable to subsequent peripheral chemical modification to produce the required functionality at predetermined centers. With these provisions in mind, we set out to achieve the four objectives summarized in Fig. 7 and 8. Objective I

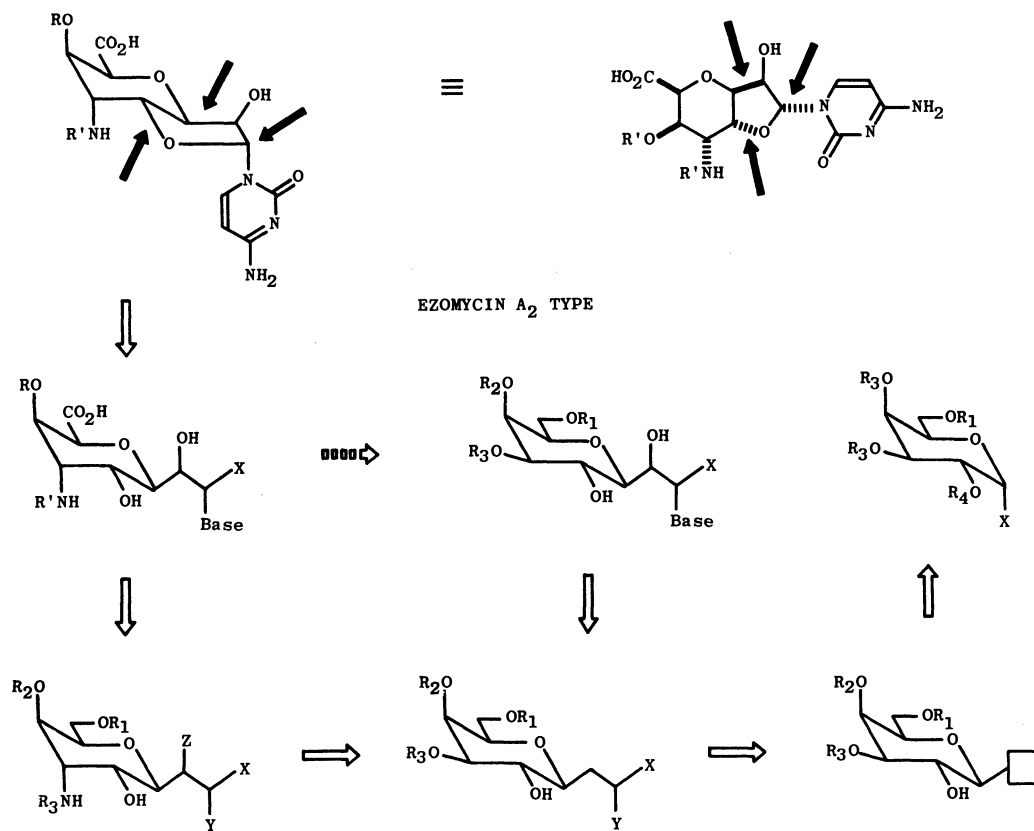
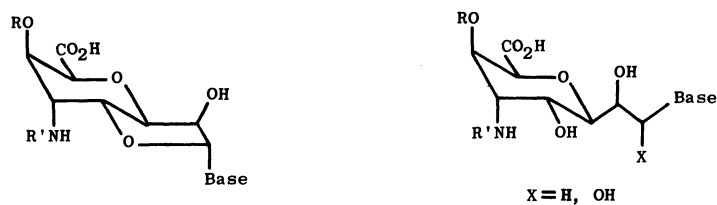


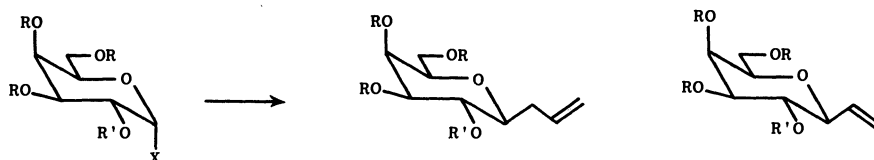
Fig. 6 Synthetic strategies

(Fig.7) consisted in the development of suitable C-glycosidation procedures. The C-allyl and C-vinyl glycosides were considered to be compatible with subsequent synthetic operations. The choice of substituents in the ring should make allowance for the C-2 hydroxyl group to be independently manipulated and eventually engaged in ring formation. Objective II (Fig.7) consisted in the introduction of vicinal and geminal functionality. In addition to consideration of regiocontrol, the nature of the group X would have to be such that it could be induced to act as a leaving group in a 5-membered ring forming reaction. The group Y was intended to be hydrogen (as a simple model), and a heterocyclic base (purine or pyrimidine). As dictated by the nature of the structures of the intended targets, the group Z would be a hydroxyl group. Objective III (Fig.8) addressed the crucial problem of effecting one or more ring forming reactions to produce bicyclic systems. In each case, intramolecular attack was perceived by the C-2 hydroxy group with X as a suitable leaving group. Thus, such cyclizations would individually lead to the model bicyclic system, a "deoxy" bicyclic system and a 2'-substituted one, the latter two containing a heterocyclic base. These structures are depicted in two perspectives to emphasize their conformational (carbohydrate type), as well as topological (terpenoid type) features. Objective IV (Fig.8) was construed as exploratory reactions aimed at acyclic analogs, in which purines and pyrimidines would be attached to a two carbon C-glycosidic appendage with various levels of oxidation.

TARGETS



OBJECTIVE I C-GLYCOSIDES



OBJECTIVE II FUNCTIONALIZATION

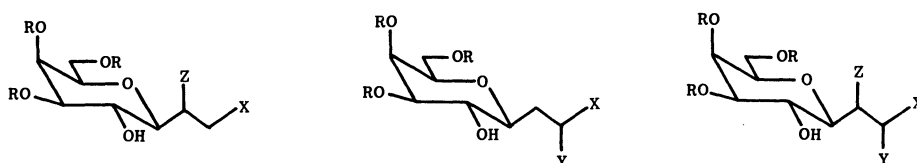
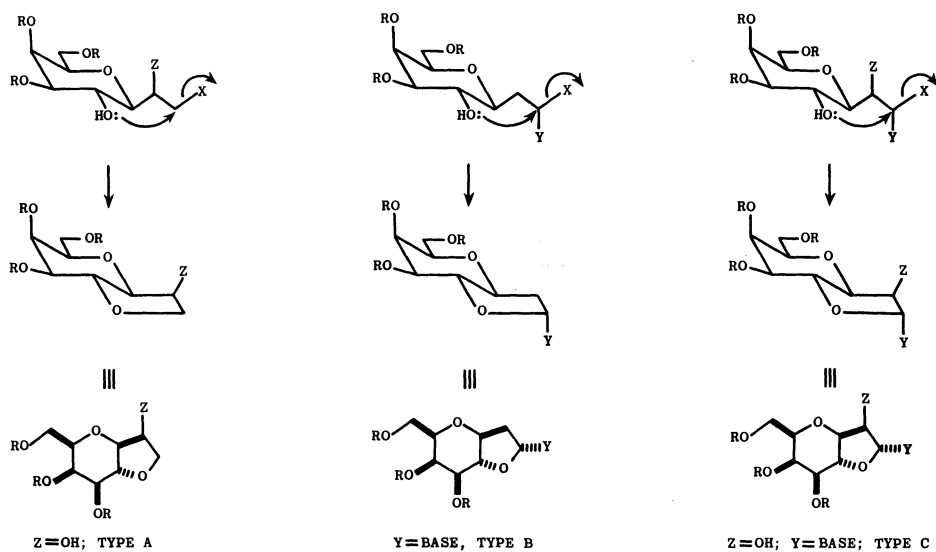


Fig. 7 Critical stages in the synthetic strategies

OBJECTIVE III —CYCLIZATION



OBJECTIVE IV —ACYCLIC ANALOGS



Fig. 8 Strategies for the formation of cyclic and acyclic analogs

Although these bicyclic structures are relatively simple, their attainment presents an interesting problem in logistics. There are in fact several modes of ring formation, and two direct ways of heterocyclization are illustrated in Fig. 9. Thus, internal cyclization

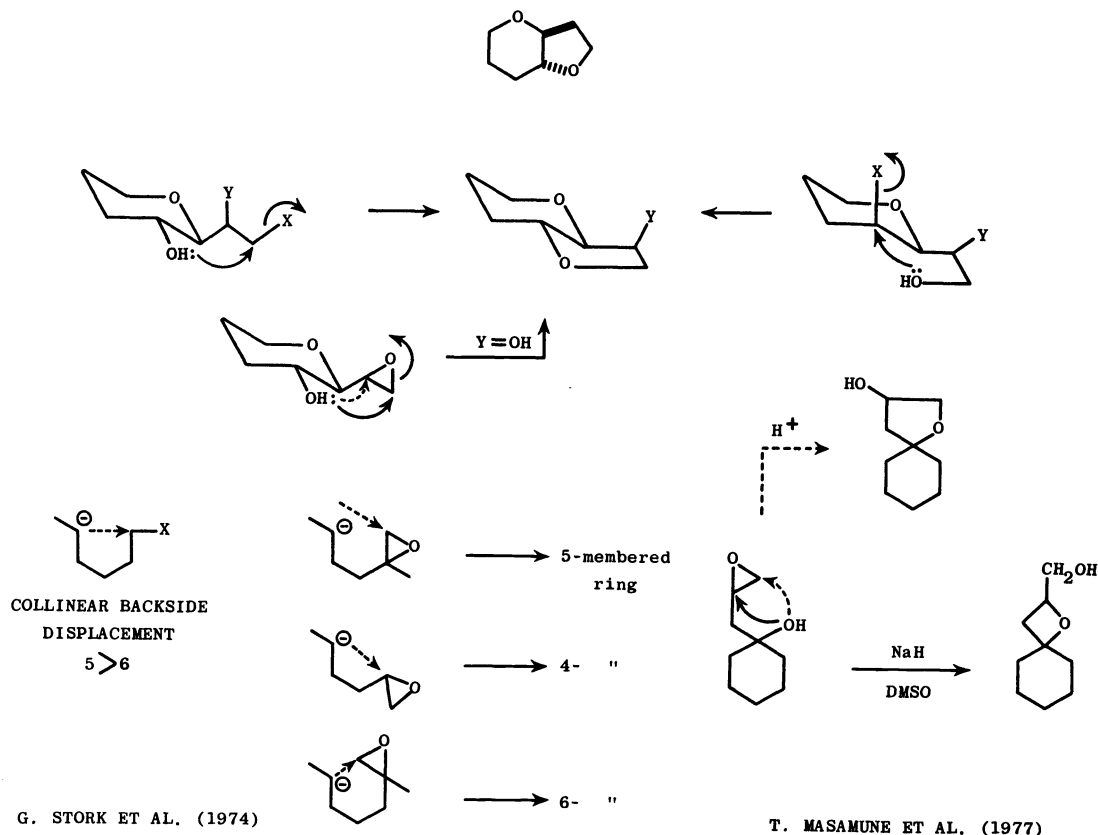


Fig. 9 The bicyclic system

would require a hydroxyl group on the terminus of the side-chain to attack C-2 of the pyranoid ring in an S_N2 type reaction. In the alternative external mode of cyclization, the leaving group is located on a peripheral carbon atom (side-chain). Clearly, the latter mode offers a better prospect for cyclization since it is known that other types of S_N2 reactions at C-2 in hexopyranose derivatives, particularly by oxygen nucleophiles are exceedingly difficult (Ref.12). Since in one of our objectives, the substituent in the five-membered ring is a hydroxyl group (C-2', nucleoside numbering), the epoxide function appeared to be a viable source.

Direct intramolecular displacement at carbon is well known to be subject to geometric constraints, among other things. Thus, it is known that a collinear backside displacement (as would be required in an S_N2 type C-C bond forming reaction) is favored to produce a five rather than a six-membered ring (Ref.13).

The situation is different in the case of intramolecular epoxynitrile cyclizations via suitably generated carbanions, where the formation of four and six-membered rings was favored provided that the substitution pattern of the epoxide derivative was not overly biased (Ref. 13). This has been explained by similar arguments invoking a more favorable alignment of charge with the proximal carbon atom of the epoxide. Heterocyclization of alkoxyepoxides also appears to be kinetically controlled, since an epoxypropyl cyclohexanol produces an oxetane rather than an oxolane derivative under basic conditions (Ref.14) (Fig.9). As expected however, acid catalyzed cyclization leads to the more stable spiro-oxolane structure. In our original plans, we had in fact considered acid-catalyzed intramolecular epoxide opening and closure as a viable approach to the construction of simple, trans-fused bicyclic ring systems related to our targets.

THE C-GLYCOSIDIC LINKAGE

The sequence of reactions leading to the desired C-glycosides is illustrated in Fig. 10.

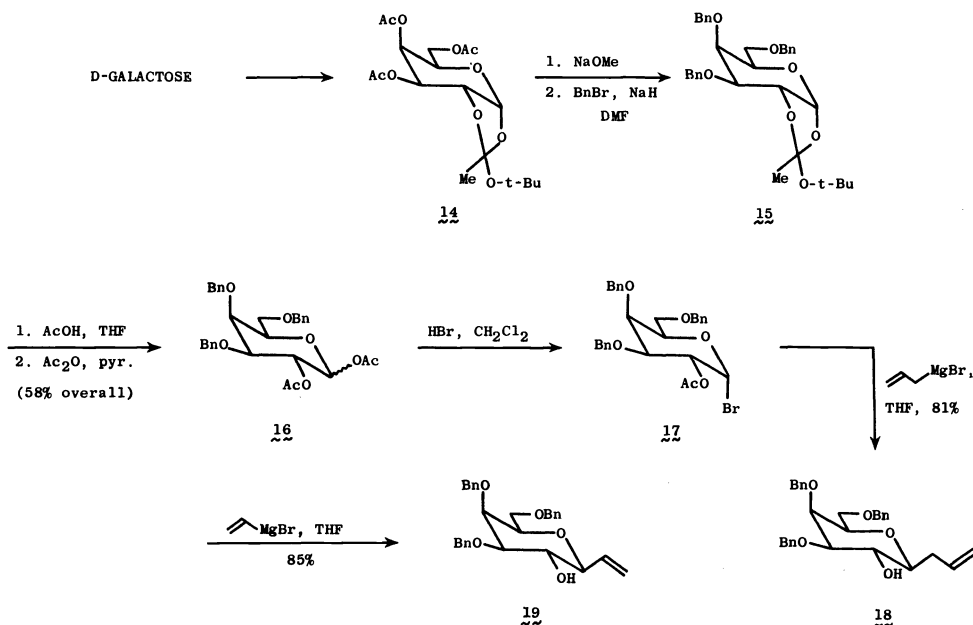


Fig. 10 Formation of C-glycosidic linkages

Previous experience in the reactions of O-protected glycosyl halides with organometallic reagents (Ref.11,15) and carbanions (Ref.16) has shown that C-glycosides can be obtained with regio- and stereocontrol. While the presence of a "participating" substituent at C-2 would, a priori, ensure the desired 1,2- trans configuration, the actual outcome may be different, since the intermediate 1,2-acyloxonium ion could give an acetal derivative (equivalent to a kinetic product). Indeed, such products were formed under certain conditions in the reaction of peracetylated glycosyl halides with carbanions (Ref.11,16). The required glycosyl halide derivative for our objectives was obtained in straightforward manner. Thus, D-galactose was converted into the orthoester derivative **14** by one of several efficient methods (Ref.17). Sequential deacetylation and benzylation afforded the tri-O-benzyl orthoester derivative **15** which was treated with aq. acetic acid and the product was acetylated to give a mixture of anomeric acetates (58% overall). The β -anomer **16** was obtained crystalline, but for the purposes of the synthesis, the mixture could be used as such. Thus, treatment with hydrogen bromide in the usual way produced the glycosyl bromide derivative **17**, which was treated individually with allyl and vinyl magnesium bromide in THF to give the C-allyl and C-vinyl glycosides **18** and **19**, respectively in over 80% yield. Their structures and anomeric configurations were ascertained by chemical and spectroscopic techniques. The mother liquors from the Grignard reaction appeared to contain small amounts of the corresponding α -D-C-glycosides.

THE BICYCLIC RING SYSTEM

Having an easy access to the anomerically pure C-glycosides **18** and **19**, we were now in position to prepare the corresponding epoxides and to study the feasibility of acid-catalyzed bicyclic ring formation. Treatment of **18** with m-chloroperbenzoic acid gave a mixture of epoxides **20** (n.m.r) (Fig. 11) which were characterized as the acetates **21**. When refluxed in dichloromethane in the presence of p-toluenesulfonic acid, the mixture of epoxides gave two bicyclic products in 90% yield. Chemical and spectroscopic studies revealed that the products were actually the bicyclic 6/5 systems shown in expression **22** (and **22A**), consisting of a mixture of epimers. Several derivatives (ex. **23**, **24**) were prepared and substantiated the presence of a primary hydroxyl group. Separation of epimeric products could be achieved at this stage. Debenzylation of the acetate derived from one of the isomers gave a crystalline derivative **25** of unknown absolute stereochemistry.

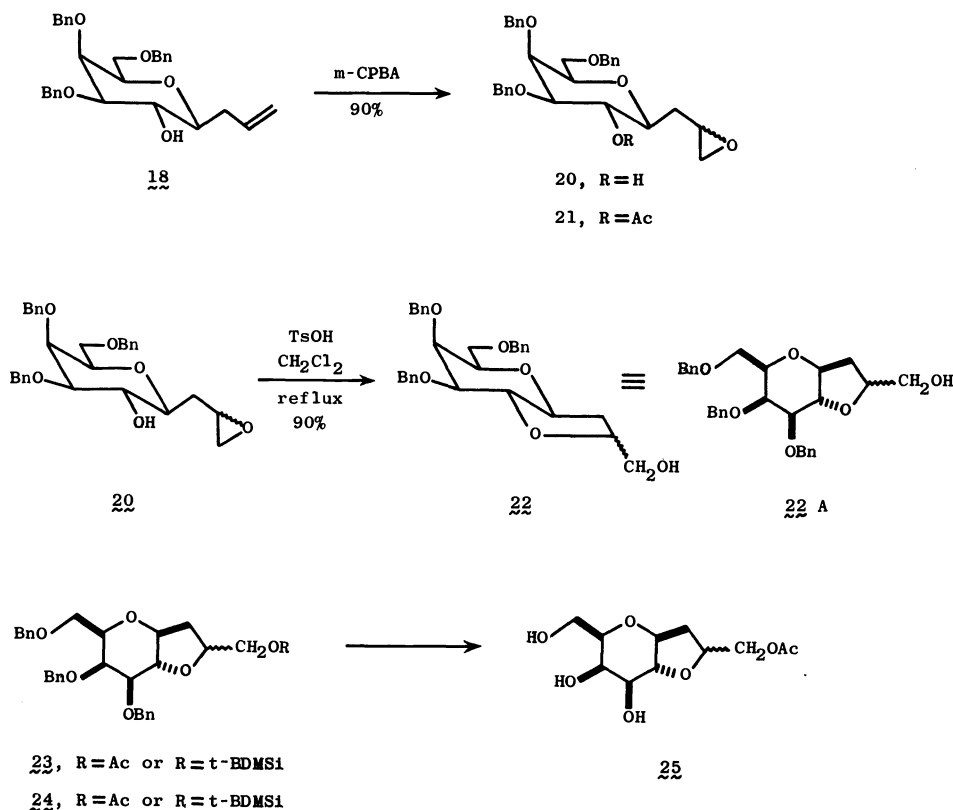


Fig. 11 Formation of a trans-fused bicyclic ring system - a model

Attention was then turned to the C-vinyl glycoside **19** (Fig.10) with the hope of achieving the construction of bicyclic system of type A, (Fig. 8). Epoxidation of **18** led in this case to a single epoxide **26**, whose structure could be conveniently studied (n.m.r) as the acetate derivative **27** (Fig.12). Refluxing a solution of **26** in dichloroethane containing a catalytic amount of camphorsulfonic acid gave a new product in 62% yield, which was formulated as **28**. The corresponding acetate **29** had properties (n.m.r) characteristic of a secondary ester. Hydrogenolysis over Pd/C gave the deprotected bicyclic anhydrooctitol **30** as a homogeneous colorless syrup. Thus, the simplest bicyclic system related to the ezomycin A-C series and the octosyl acids was constructed in an uneventful series of reactions. Other stereochemical and structural features being satisfied, there remained the question of establishing the stereochemical identity of the epoxide **26**, hence the product of ring opening, **30**. The stereochemistry of epoxidation of allylic alcohols with peracids and other agents is reasonably well understood and interpreted in terms of preferred geometries of the transition states, implicating the olefinic linkage, the reagent and the hydroxyl group (Ref.18). Examples of stereocontrolled epoxidations of homoallylic alcohols are less frequently encountered, although some examples in acyclic (Ref.19) and cyclic (Ref.20) systems are known. Epoxidation of **26** can be considered to occur via a stereocontrolled, intramolecular assistance of the homoallylic hydroxyl group (at C-2 in the sugar portion). Unlike the recorded examples, this system is conformationally flexible in the olefinic portion, hence one can consider two optimum transition states, each leading to a different epoxide (Fig.13). The idealized transition state depicted in expression **31** provides a favorable geometrical arrangement of atoms and allows a more efficient H-bonding with the terminally situated oxygen atom of the peracid (Ref.18b). Such a pathway will favor the formation of the epoxide with the proposed *S* configuration. The alternate transition state depicted in expression **34** appears to be less favorably disposed. Support for this hypothesis was obtained by chemical studies. Oxidation of **28**, with pyridinium chlorochromate (Ref.21) afforded a single ketone **32** in high yield. Inspection of molecular models reveals that hydride reduction could lead preferentially to the *R* alcohol **33**. This would have been the product of ring opening derived via transition state **34**.

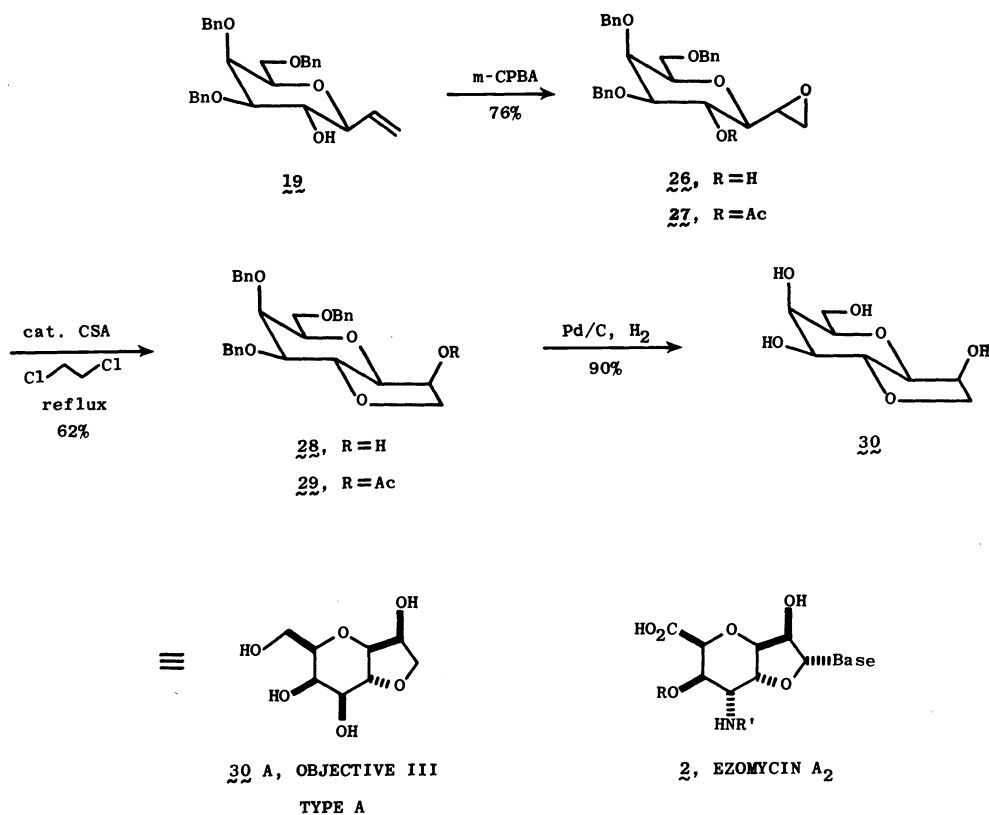


Fig. 12 Formation of the trans-fused bicyclic ring system present in the ezomycins and the octosyl acids

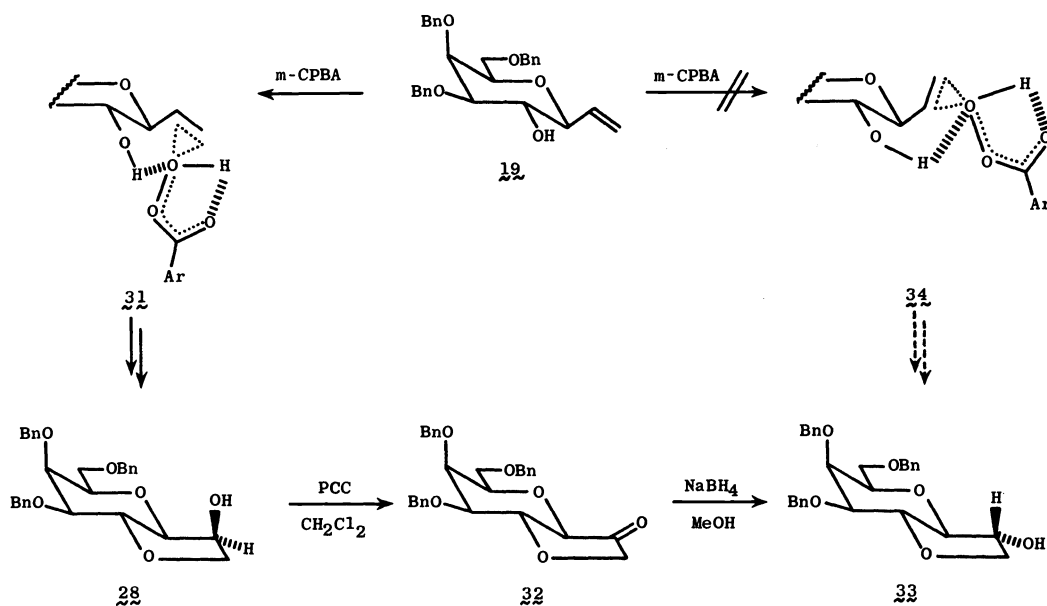


Fig. 13 Stereoselective epoxidation of the vinylic C-glycoside **19**

At this juncture, it is of interest to discuss the ring forming reaction itself, to examine the possible options, and to appreciate the nature of the corresponding bicyclic products (Fig.14). The relative ease of ring formation has been discussed by Baldwin in formulating

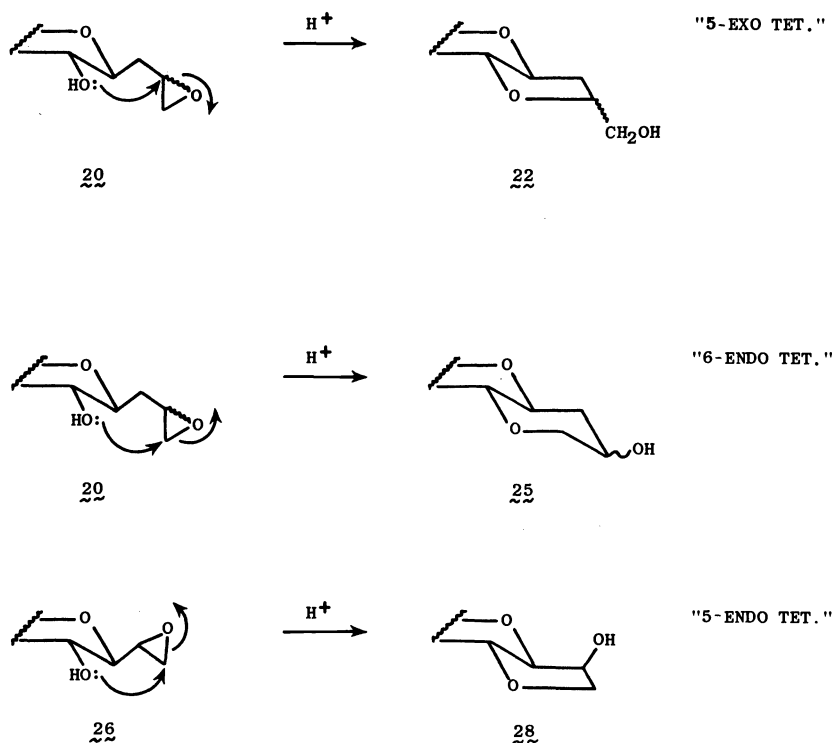


Fig. 14 Considerations of ring opening and closure

his useful rules (Ref.22). According to these rules, 5-and 6-endo-tetragonal ring closures are disfavored, while 3 to 7-exo-tetragonal closures are all favored processes. Although these generalizations apply to C-C bond formation and the presence of second row elements may present different geometric constraints, the general guidelines of the rules can be extended to the formation of oxygen-containing rings such as in our case. There are other reports which consider the operation of "statistical and geometrical" factors in controlling ring formation rather than adhering to the principle of collinearity (Ref.23). The formation of the bicyclic 6/6 system (Fig.14) should, a priori, be the thermodynamically more favored process in the treatment of **20** with acid. Yet, it appears that the more strained 6/5 system is produced by a process involving the equivalent of 5-exo-tetragonal transition state. The conversion **26** $\rightarrow$ **28** appears to involve a disfavored 5-endo-tetragonal transition state and it is of interest to note that during such reactions an intermediate product, possibly an oxetane, could be observed (t.l.c.). Such a product could arise from an alternate mode of epoxide opening at the secondary carbon atom of the epoxide and would constitute a 4-exo-tetragonal process which is favored according to the rules.

BICYCLIC OXYGENATED TERPENOID ANALOGS FROM CARBOHYDRATES - A PLANNED DIVERSION

We have previously recognized a structural element seldom appreciated in carbohydrate derivatives, namely, their potential relationship to simple terpenoids. In an intended diversion from our main synthetic theme, we describe studies aimed at the construction of bicyclic lactone structures corresponding to some naturally occurring and well known terpenoid trans-lactones. Sequential hydroxylation-oxidation, and esterification of the C-allyl glycoside **18** gave the C-glycosyl acetate derivative **35** in good overall yield (Fig.15).

Treatment of **35** with p-toluenesulfonic acid in benzene at reflux gave the bicyclic trans-lactone **36** in quantitative yield, which, upon debenzoylation afforded the lactone **37** in high yield. Expression **37A** depicts the structure of the product in terpenoid perspective. Fig. 16 illustrates steps leading to the methylenation of **36**, which involved standard methodolo-

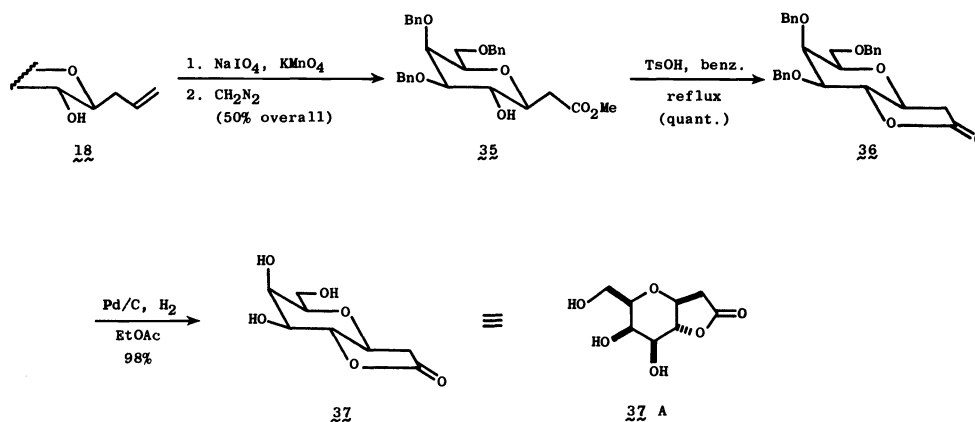
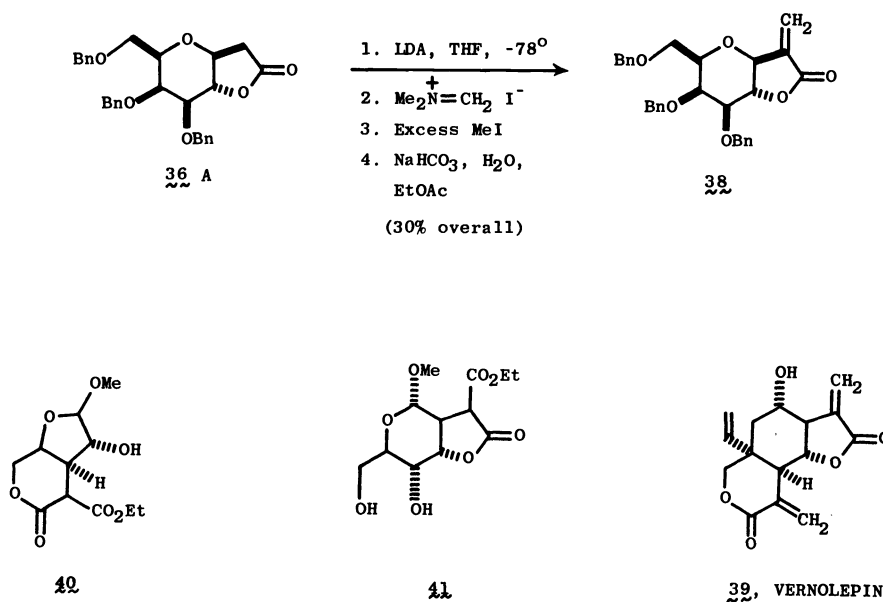


Fig. 15 Formation of trans-fused bicyclic lactones

gy. Thus, the anion generated by LDA at -78° was treated with dimethyl(methylene) ammonium iodide (Eschenmoser reagent) (Ref.24), the corresponding dimethylaminolactone derivative was N-methylated and subjected to fragmentation to give the α -methylene lactone derivative **38** in 30% overall yield (non-optimized). It is of interest at this point to comment on the somewhat peripheral, but nevertheless functionally relevant analogy with the structures of naturally occurring terpenoids as exemplified by vernolepin (Ref.25,26). In this context, it is also informative to draw attention to the much greater functional and stereochemical convergence found in the structures of two, readily available carbohydrate-derived lactones, obtained several years ago during our studies of regio- and stereocontrolled C-C bond forming reactions. As previously remarked (Ref.27), structure **40**, originally derived from D-xylose (Ref.28) shows overlap in the δ -lactone portion which further extends to two vicinal carbon atoms in vernolepin. Structure **41** on the other hand, obtained from methyl α -D-glucopyranoside in four steps (Ref.29) shows overlap with the trans-lactone portion of vernolepin. Both of these derivatives should be amenable to further elaboration to vernolepin or like structures since critical C-C bond forming reactions can be performed at sites presently occupying oxygen. Carbohydrates should therefore provide a viable source of the carbon backbone of terpenoid-like structures. Carbohydrate models of monocyclic α -methylene- γ -butyrolactones have been recently reported (Ref.30).

Fig. 16 Formation of a trans-fused bicyclic α -methylene lactone derivatives

ACYCLIC ANALOGS RELATED TO EZOMYCIN D

Preliminary studies were done in order to explore the feasibility of attaining two-carbon C-glycosyl appendages with or without a heterocyclic moiety, as in the structures of ezomycin D₁ and D₂. The C-allyl derivative **18** proved to be an ideal precursor to an aldehyde function, which could be subsequently transformed into another functionality. Thus, treatment of **18** with osmium tetroxide-periodate led directly to the aldehyde **42**, further characterized as the acetate **43** (Fig.17). It is of interest that **42** exists preponderantly if not exclusively in the free aldehyde form (n.m.r, i.r) rather than as the corresponding lactol, no doubt a reflection of the highly strained nature of such a bicyclic derivative. In fact, treatment of **42** with dilute methanolic hydrogen chloride, led to the formation of the corresponding dimethyl acetal, which under normal circumstances is the kinetic product in such reactions. The elusive glycoside derivative **45** could not be isolated, although it could be detected as a very minor component (t.l.c, n.m.r). As expected, the aldehyde **42** could be easily transformed into the corresponding diethyl dithioacetal derivative **46** in high yield. This proved to be a most versatile and useful chemical precursor to the intended nucleoside derivatives. Figures 18 and 19 illustrate preliminary studies aimed at the introduction of 2-carbon units containing adenine and uracil moieties at the anomeric carbon.

Thus, it was found that treatment of the acetate derivative **47**, (Fig.18) with chloromercuri N-benzoyladenine in the presence of cadmium carbonate in refluxing toluene, gave a good yield of the corresponding acyclic derivative **48**, presumably as a mixture of epimers. Acyclic nucleosides in the aldose series have been known for some time (Ref.31). Oxidation **48** with m-chloroperbenzoic acid then gave a mixture of sulfoxides **49**, which upon thermolysis in refluxing toluene, underwent elimination to give a good yield of the C-vinylc adenine nucleoside analog **50**. Attempts to epoxidize this mixture of E and Z olefins, gave instead the corresponding N-oxide.

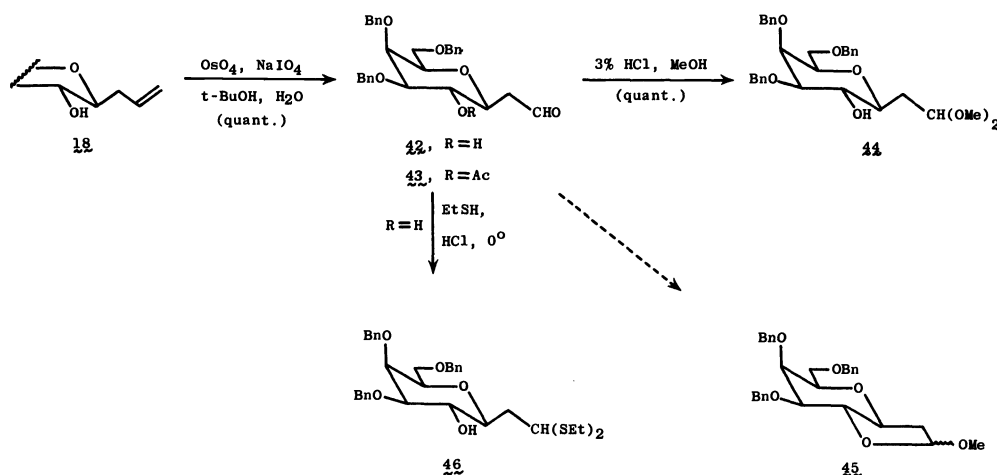


Fig. 17 Formation of acyclic C-glycoside derivatives

In a different study, the readily available epoxide **26** (Fig.12) was converted into a variety of 2-substituted derivatives. The methoxyethoxymethyl (MEM) derivative **51** (Ref.32) was treated with potassium adenide and gave the C-hydroxyethyl nucleoside derivative **52**, albeit in moderate yield (Fig.19). It is assumed that epoxide opening took place at the less hindered and more reactive primary position although no definitive proof was secured. It was also found that the methoxymethyl (MOM) derivative of the epoxide could be transformed into the acyclic 4-ethoxypyrimidinone nucleoside **53**, again in moderate yield. Preliminary studies showed that such a derivative could be induced to thermal dehydration in refluxing DMSO to give a mixture of olefins **54**. These however, could be obtained in better yield from **47** by a scheme similar to that shown in Fig. 18. Studies in this area are presently being pursued with the aim of obtaining substituted uracil analogs according to objective IV in our priorities.

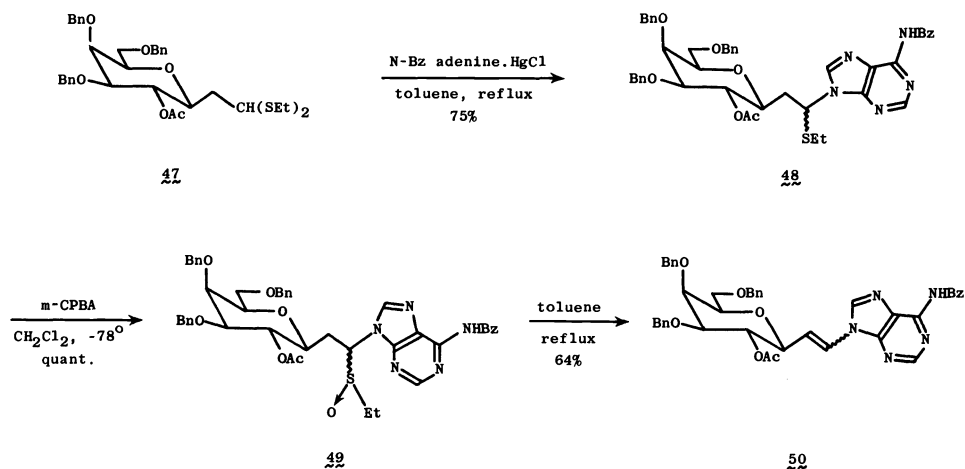


Fig. 18 Formation of acyclic adenine nucleoside analogs related to ezomycin D_1 and D_2

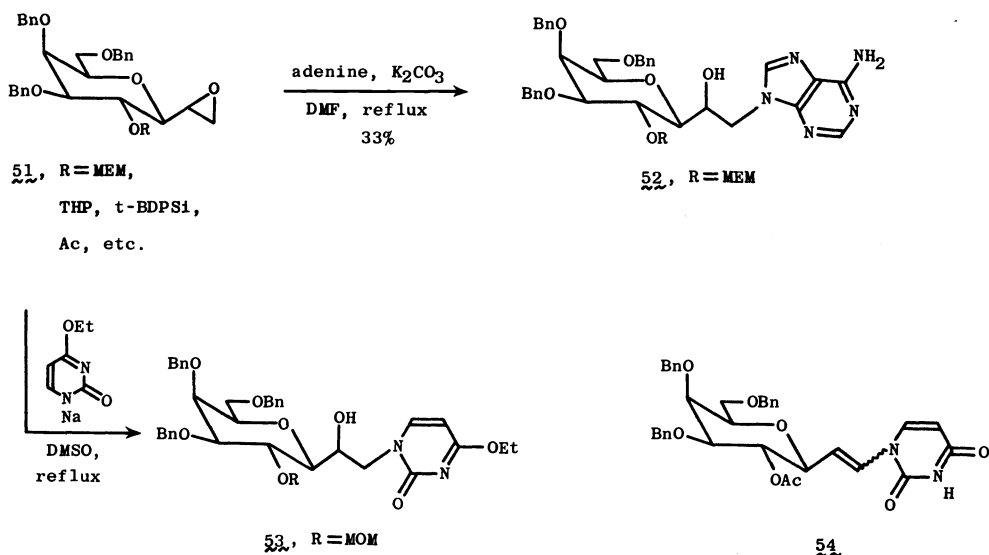


Fig. 19 Formation of acyclic adenine and uracil nucleoside analogs related to ezomycin D_1 , D_2

BICYCLIC TRANS-FUSED NUCLEOSIDE DERIVATIVES

Syntheses of nucleosides of this type are as yet unreported except for a unique chemical transglycosylation reaction in which octosyl acid A was first transformed into a "cytosine" analog **55**, and the latter subsequently converted into the corresponding adenine derivative **56** (Ref.33) (Fig.20).

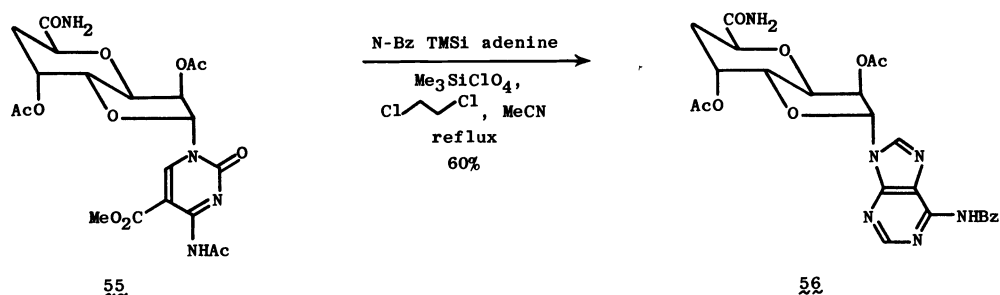


Fig. 20 Chemical transglycosylation of a cytosine analog of octosyl acid A according to Azuma and Isono (Ref. 33)

A 60% yield of the product with the 1,2-trans (natural) configuration was obtained, although it is possible that this is also the result of partial anomerization in the presence of trimethylsilyl perchlorate. This has proved to be a general reaction in the conversion of pyrimidine nucleosides into the corresponding purine analogs, although mixtures of anomers have been observed in these cases (Ref.34). We have developed efficient methodologies for the synthesis of bicyclic, trans-fused deoxyadenosine nucleosides (Fig.21). Thus, treatment of **46** with N-benzoyladenine and bromine in DMF solution, led directly to a 1:1 mixture of the bicyclic nucleoside derivatives in over 60% yield, which were de-N-benzoylated to give **57** and **58**. N.m.r and other physical criteria established their identities as "β"- and "α"-nucleosides respectively. It was thus possible to prepare the critical trans-fused bicyclic ring system and to incorporate the adenine moiety in one step from the readily available dithioacetal derivative. Acyclic nucleosides have been previously prepared from peracetylated 1-bromo-1-ethylthio aldoses (Ref.31). To the best of our knowledge, no cyclic nucleosides have been reported from such studies. The formation of cyclic nucleosides by our procedure should be applicable to other series as well and studies along these lines are under investigation in our laboratory.

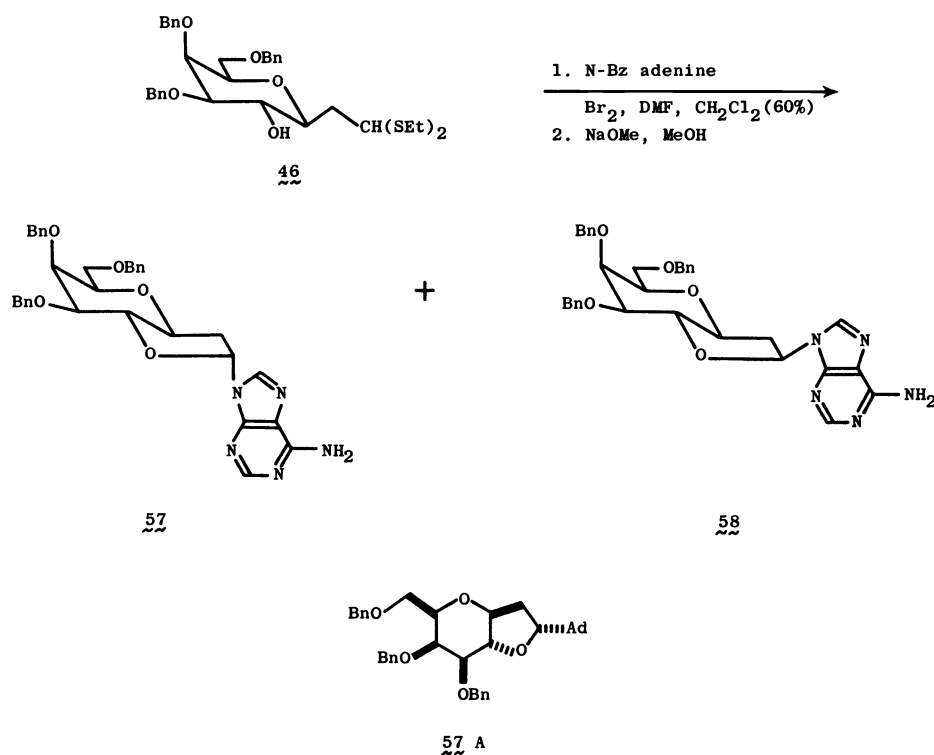


Fig. 21 Formation of trans-fused bicyclic adenine nucleoside analogs

Mechanistically, it is reasonable to assume the formation of sulfonium salts such as in expression 52 (Fig.22) which can evolve along two different pathways. Nucleophilic attack by N-benzoyladenine could take place and lead to 60, which, in turn could undergo intramolecular attack by the C-2 hydroxyl group to give the observed products. Alternatively, a thioglycoside 61 could initially be formed which could undergo *in situ* bromination and the resulting sulfonium salt, or glycosyl bromide derivative (Ref.35) could undergo displacement by the heterocyclic base via sulfonium ion 62. We can offer experimental support to the first possibility, although the second cannot be ruled out, since in another series, a related thioglycoside was found to undergo the same type of reaction in the presence of bromine and a heterocyclic base (Ref.36). The availability via another route of the acyclic analog 48 (Fig.18), provided a unique opportunity to explore the possible intermediacy of a "mixed acetal" in the cyclization reaction (Fig.23). Thus, deacetylation of 48 gave 63,

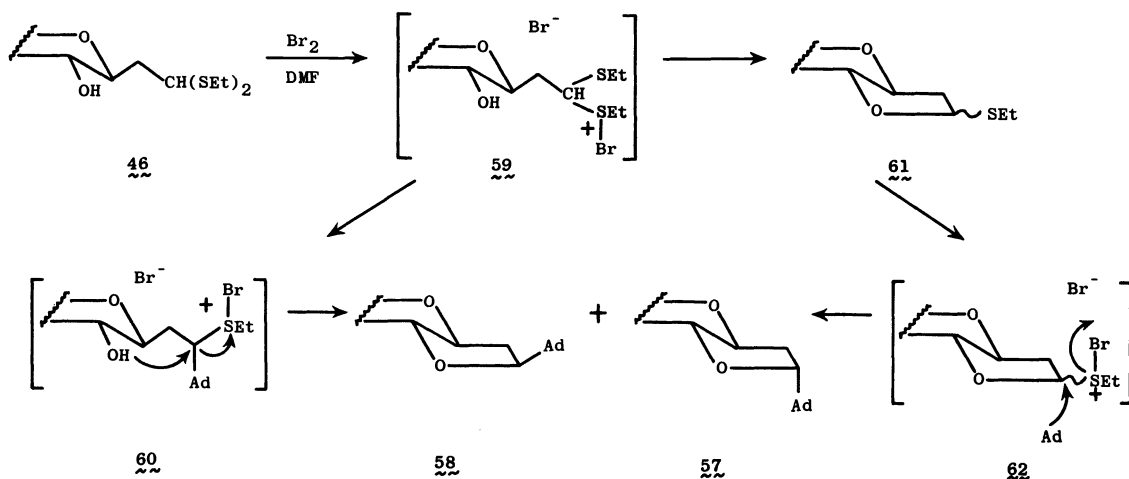


Fig. 22 Possible mechanistic pathways in the formation of the trans-fused bicyclic adenine nucleoside

which when treated with bromine in DMF, gave the nucleoside derivatives 57 and 58 in a ratio 1:1. In addition to providing an alternate synthetic approach to such bicyclic and related nucleoside derivatives, these results indirectly shed light on a possible mechanistic pathway. The original reaction (Fig.22) may in fact, proceed at least in part, by incorporation of the adenine moiety first, followed by intramolecular cyclization.

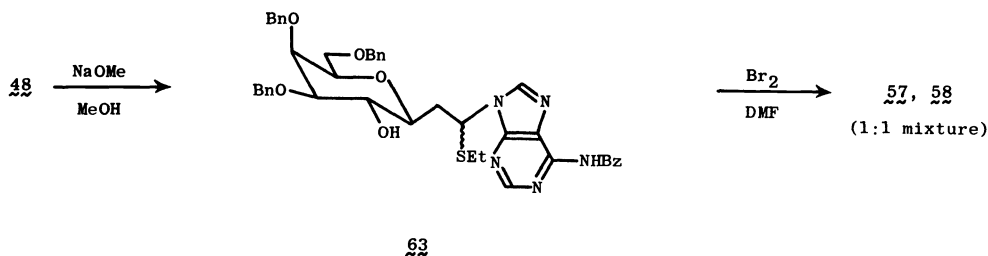


Fig. 23 Alternate preparation of a trans-fused bicyclic adenine nucleoside analog

In this regard, it should be noted that a synthesis of 2-deoxyadenosine reported by Pedersen and Fletcher (Ref.37) consisted in the treatment of 2-deoxy-D-erythro-pentose di-2-propyl dithioacetal with chloromercuriadenine. Although the yield was low (6.3% of β - and 8.1% of α -nucleosides), the potential utility of dithioacetals in such reactions was evident. Activation of the ethylthio group via formation of a sulfonium salt, and its subsequent reaction with the heterocyclic base in DMF solution offers distinct operational and mechanistic advantages over the chloromercuri procedure which takes place in heterogeneous medium. Hydrogenolysis of 57 in the presence of 20% palladium hydroxide on charcoal (Ref.38) in ethanol using cyclohexene as the source of hydrogen, led to the nucleoside derivative 64 (Fig.24). We have found debenzylation under conditions of catalytic transfer hydrogenation (Ref.39) to be practical with small quantities and preferable to the conventional method using hydrogen (Ref.36).

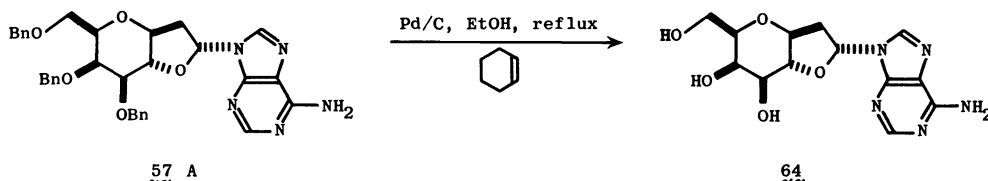


Fig. 24 Debzylolation via transfer hydrogenation -Formation of a trans-fused bicyclic adenine nucleoside

Unequivocal proof for the structure of 57 and its anomeric configuration was secured from X-ray crystallographic analysis (Fig.25).

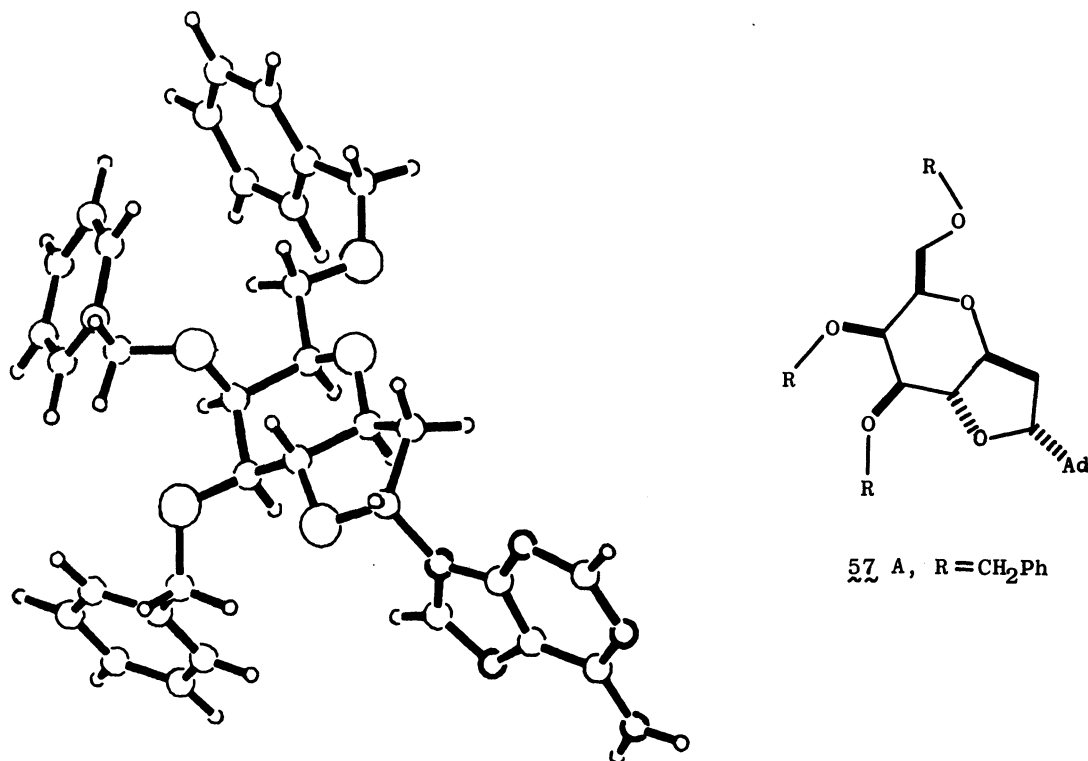


Fig. 25 Computer drawn three-dimensional structure of the bicyclic adenine nucleoside 57 (from X-ray diffraction data)

Finally, when the dithioacetal derivative **46** was treated with N-acetylcytosine mercury (Ref.40) in refluxing DMF, a 1:1 mixture of two nucleosides was obtained in low yield. Chemical and spectroscopic data revealed their identities as anomeric bicyclic 2'-deoxycytidine-type nucleosides. The β -anomer expressed as **65** is closely related to the bicyclic system of ezomycin A₁ and A₂ (Fig. 26). As indicated earlier, except for the deoxygenation at C-2', such a product is ideally suited for chemical manipulation to introduce the functionality at C-3 and C-6 required for attaining the ezomycin structure. Studies along these lines are presently in progress in our laboratories.

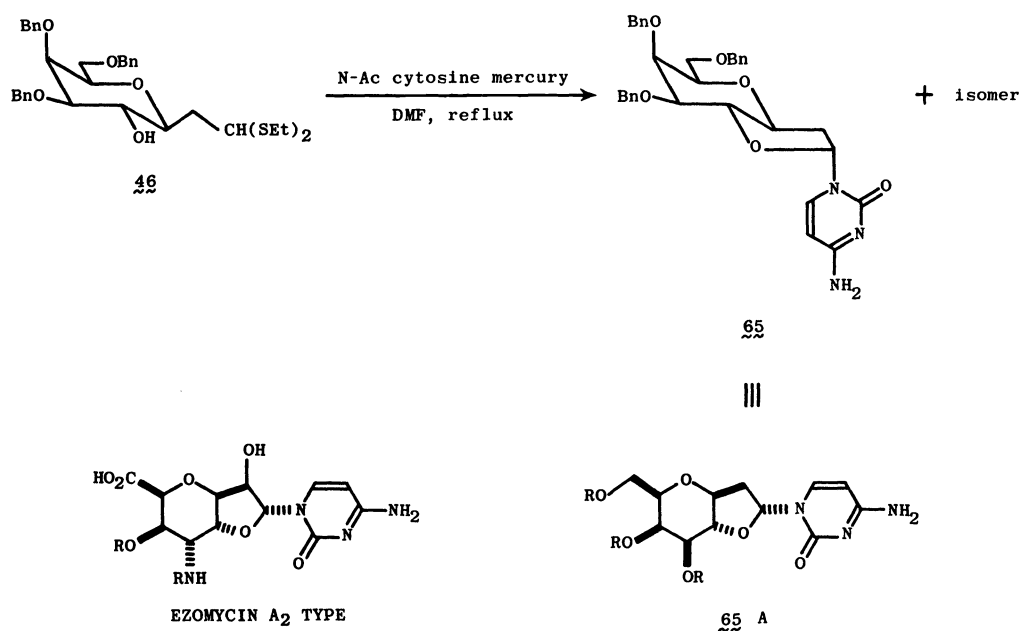


Fig. 26 Formation of a trans-fused bicyclic 2'-deoxycytidine analogs

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APPENDIX OF PHYSICAL CONSTANTS*

Compound	Pertinent data
<u>16</u>	mp 74-75°; $[\alpha]_D + 26.3^\circ$
<u>18</u>	symp; $[\alpha]_D + 42.3^\circ$; M^+ 474
<u>19</u>	symp; $[\alpha]_D + 6.9^\circ$; for the acetate derivative: 5.78 ppm (t, H-2, J=8Hz)
<u>22</u>	M^+ , 490
<u>23</u> isomer A; R=Ac	symp; $[\alpha]_D + 10.85^\circ$; M^+ 532
R=t-butyltrimethylsilyl	symp; $[\alpha]_D + 5.88^\circ$
<u>24</u> isomer B; R=Ac	symp; $[\alpha]_D + 7.0$; M^+ 532
R=t-butyltrimethylsilyl	symp; $[\alpha]_D - 3.29$
<u>25</u> from isomer A	mp 128-129°; $[\alpha]_D + 31.38^\circ$

* Optical rotations were measured in CHCl₃ unless otherwise mentioned; melting points are uncorrected. N.m.r. data obtained at 90 MHz in CDCl₃.

- 26 syrup; $[\alpha]_D + 4.6^\circ$
- 27 syrup; $M^+ 518$
- 28 syrup; $[\alpha]_D + 1.6^\circ$
- 29 syrup; $M^+ 518$
- 30 syrup; $[\alpha]_D + 4.48^\circ$
- 35 syrup; $[\alpha]_D + 25.9^\circ$; $\lambda_{\max}^{\text{film}} 1730 \text{ cm}^{-1}$
- 36 syrup; $[\alpha]_D + 43.65^\circ$; $M^+ 474$; $\lambda_{\max}^{\text{film}} 1780 \text{ cm}^{-1}$
- 37 syrup; $\lambda_{\max}^{\text{film}} 1775 \text{ cm}^{-1}$
- 38 syrup; 5.65 ppm; 6.15 ppm, $J=2.1 \text{ Hz}$ ($>=CH_2$); $\lambda_{\max}^{\text{film}} 1780 \text{ cm}^{-1}$
- 42 syrup; 10.1 ppm (CHO); $\lambda_{\max}^{\text{film}} 1710 \text{ cm}^{-1}$
- 43 syrup; 5.30 ppm (H-2, $J=10 \text{ Hz}$), 10.1 ppm (CHO)
- 44 syrup; $[\alpha]_D + 20.8^\circ$
- 46 syrup
- 48 syrup; $m/e 564$ ($M^+ - 41$); 504 ($M-60$), etc.
- 50 mp 102° ; $M^+ - H$ calcd. 728.2928; found 738.2896; $m/e 648$ ($M^+ - 91$) etc.
- 53 syrup; $M^+ 660$; 629 ($M^+ - 31$), etc.
- 57 mp 185° ; $[\alpha]_D + 26.92^\circ$; for N-benzoyl derivative; calcd. $M^+ - PhCH_2$ ($C_{34}H_{32}N_5O_6$) 606.2352; found: 606.2373.
- 58 syrup; $[\alpha]_D + 8.91^\circ$
- 64 mp $264-265^\circ$; $[\alpha]_D + 18.18^\circ$ (MeOH)
- 65 syrup; $M^+ 611$; $m/e 520$ ($M - 91$), etc; for the major isomer: 2.25 ppm (N-Ac); 6.12 ppm (d, H-5, $J_{5,6}=7\text{Hz}$); 7.1 ppm (m, H-1'); 7.62 ppm (d, H-6, $J_{6,5}=7\text{Hz}$).