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Preliminary communication

Synthesis of *trans*-fused perhydrofuropyrans and related α-methylene lactones: bicyclic ring-systems present in the ezomycins, the octosyl acids, and certain antitumor terpenoids*

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The ezomycins are a group of structurally related antifungal agents produced by a strain of *Streptomyces*[1]. Their chemical degradation has produced novel, bicyclic anhydro-octose uronic acid nucleosides[2] that are closely related to the octosyl acids[3], isolated from a fermentation broth of a polyoxin-producing micro-organism[4]. The structures of representative members, ezomycin A_2 (ref. 2) and octosyl acid A (ref. 3), are shown in Scheme 1**. Related compounds, such as ezomycin B_2 (ref. 2), are known that formally belong to the *C*-nucleoside category.

Clearly, the most unusual feature in these structures is the presence of a *trans*-fused, bicyclic (perhydrofuropyran) ring-system that can be considered to be part of a 3,7-anhydro-octose. Tentative structures proposed for herbicidin A and B also comprise a fused tetrahydrofuran ring as part of a tricyclic structure of as-yet-undetermined absolute configuration[5]. We now describe the synthesis of a 1,4:3,7-dianhydro-octitol, representing the *trans*-fused, bicyclic, carbon skeleton present in the ezomycins A_1, A_2, *etc.*, and in the octosyl acids. In terms of functional manipulations related to the target compounds (see Scheme 1), the D-*galacto* structure was considered to be the most suitable.

Scheme 2 shows the sequence of reactions that led to the dianhydro-octitol. The readily available orthoester derivative **1**, prepared according to the procedure of Ogawa and Matsui[6], was deacetylated and benzylated (NaH, $PhCH_2Br$, $HCONMe_2$, 0°), the product (**2**) was treated with aq. acetic acid in oxolane (THF), and the product was acetylated, to give a mixture of anomeric diacetates **3** (58% overall yield). The β anomer of **3** was isolated in crystalline form, m.p. 74–75° (hexane–EtOAc)§.

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**The conformations depicted in Schemes 1–3 represent idealized situations and are intended to provide a certain perspective.

§Crystalline compounds gave correct microanalyses. Rotations were recorded for solutions in chloroform, unless stated otherwise.

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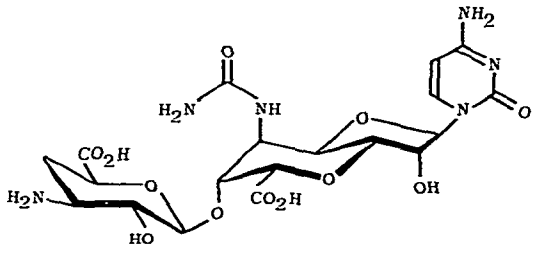
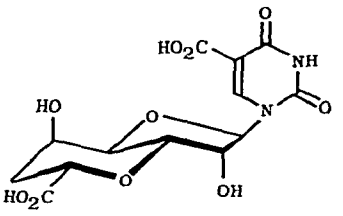
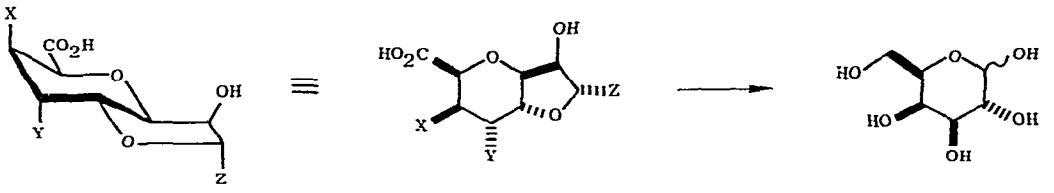


Ezomycin A_2



Octosyl acid A



Ezomycins: X=OH; Y=NH_2; Z=cytosin-1-yl

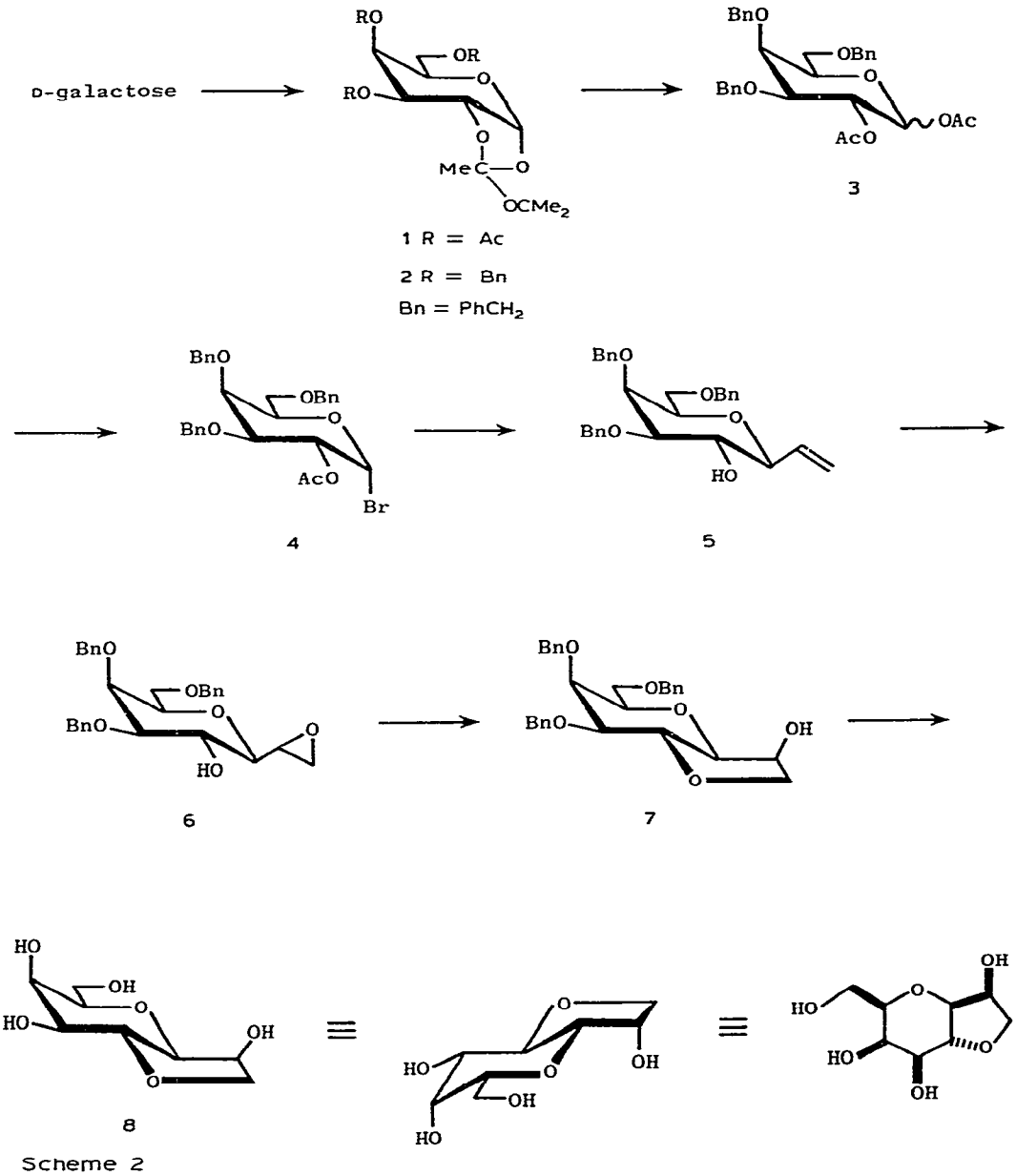
Octosyl acids: X=H; Y=OH; Z=uracil-1-yl

D-galactose

Scheme 1

Treatment of **3** in dichloromethane with a saturated solution of hydrogen bromide in glacial acetic acid during 30 min at 0° gave the bromide **4**, which was used, as such, in a critical, stereocontrolled, *C*-glycosylation reaction[7]. Treatment of **4** with freshly prepared vinylmagnesium bromide in dry THF, under N_2 at −78° and then for 1 h at 0°, gave, after chromatographic separation, the *C*-vinyl derivative **5** (85%, syrup); $[\alpha]_D$ +7°. The 1,2-*trans* configuration was established by n.m.r. studies on **5** and the corresponding, syrupy acetate. Epoxidation of the double bond in **5** with *m*-chloroperoxybenzoic acid in dichloromethane during 18 h at 25° gave epoxide **6** as the major product (75%) as a syrup; $[\alpha]_D$ +4.6°; M^+ 518 for the corresponding acetate derivative. Treatment of **6** (117 mg, 245 μmol) in dichloromethane (12 mL) with camphorsulfonic acid (12 mg) for 18 h under reflux led to the desired, bicyclic derivative **7** (61%); $[\alpha]_D$ +1.6°; M^+ 518 for the acetate derivative. Finally, debenzylation (H_2, Pd/C, MeOH) gave the dianhydro-octitol **8** as a syrup, $[\alpha]_D$ +4.48° (MeOH).

Concerning the stereochemistry of epoxidation of **5**, it may clearly be seen from molecular models that a hydroxyl-assisted process[8] could, *a priori*, lead to either of two possible epoxides, particularly as the system is of the homoallylic type and the alkenic side-chain can adopt one of two extreme orientations. The apparently exclusive formation of **6** may be rationalized on the basis of a more-favored transition-state, com-

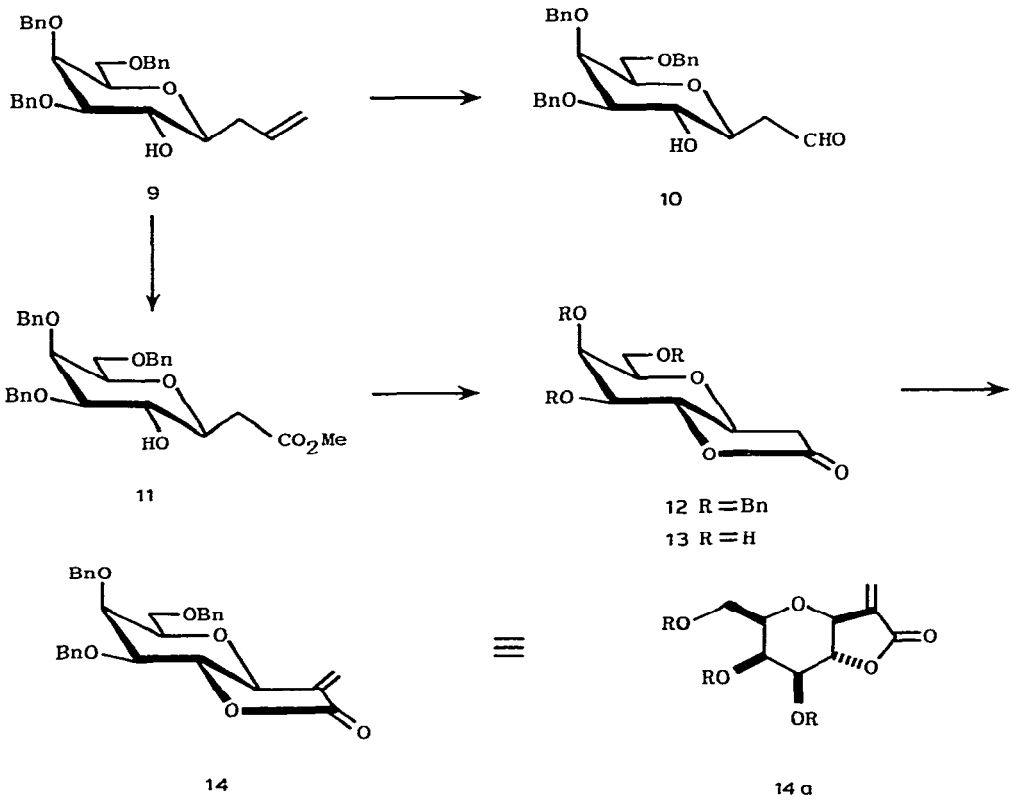


Scheme 2

pared to the alternative one[9]. Chemical support for this hypothesis was secured as follows. Oxidation of 7 with pyridinium chlorochromate[10] for 4 h gave the corresponding ketone (a syrup) which, on reduction with sodium borohydride, gave a single, new compound, epimeric at C-2*. The sense of chirality at C-2* is, therefore, related to that found in the ezomycins and the octosyl acids.

*Numbering at the five-membered ring. Study of molecular models revealed a more-favored attack of the reducing agent from the observed "β"-side.

In another study, aimed at the synthesis of bicyclic, terpenoid-like structures from carbohydrates[11], the *C*-allyl derivative **9**, prepared essentially as described for **5** (81%), was oxidized (OsO_4, $NaIO_4$, aq. *tert*-BuOH, 3 d at 25°; quant. yield) to the aldehyde **10**, which existed almost exclusively in the aldehydo form (i.r. and n.m.r. evidence). Treatment of **10** with 3% methanolic hydrogen chloride for 30 min at 25° gave the corresponding dimethyl acetal (~95%); $[\alpha]_D$ + 20.78°. Alternatively, oxidative cleavage[12] of **9** ($KMnO_4$, $NaIO_4$, aq. acetone), followed by esterification with diazomethane, gave the methyl ester derivative **11** (50%), $[\alpha]_D$ +25.86°. Treatment of **11** with a catalytic amount of TsOH (benzene, reflux, 2 h) afforded the lactone **12** (98%); $[\alpha]_D$ +43.65°; M^+ 474. Debenzylation of **12** (H_2, Pd/C, EtOAc) gave lactone **13**, in essentially quantitative yield, as a syrup; λ_{max}^{film} 1775 cm^{-1}. Introduction of the α-methylene functionality was achieved by treatment of the enolate derived from **12** (LDA, THF, –78°) with the Eschenmoser salt[13] ($Me_2N^+=CH_2I^-$) during 45 min at –40° and then 30 min at 25°, followed by refluxing a solution of the (dimethylamino)methyl intermediate in an excess of methyl iodide in 1,4-dioxane during 18 h, followed by elimination (aq. $NaHCO_3$, EtOAc 25°, 10 min) to give the α-methylene lactone deriva-



Scheme 3

tive **14** as a syrup (30% overall yield). Such functionality is present in the structures of a large number of *trans*-fused, bicyclic, antitumor agents[14], and formula **14a** places some of the functional and stereochemical features into the more-familiar, terpenoid perspective.

Finally, it should be noted that the geometric and stereoelectronic requirements for the formation of bicyclic lactones of the type herein described differ considerably from those involved in the formation of the dianhydro-octitol **7**. Intramolecular opening of epoxides by carbanionic centers[15] or hydroxyl groups[16] can be subject to several factors, including collinearity in an SN2 type of attack[15,16], the degree of substitution[15,17], the type of epoxide, and the reaction conditions. Thus, cyclobutane[15,17] and oxetane[16] ring-formation in preference to cyclopentane and oxolane (tetrahydrofuran) rings, respectively, has been observed under controlled, base-catalyzed conditions. These observations are also in agreement with the favored 4-*exo*-tetragonal, rather than the 5-*endo*-tetragonal, mode of ring-closure processes[18]. The situation, however, is different under acid catalysis, as exemplified by the reactions of certain epoxycyclohexanols[16] and carbohydrate epoxides[19] which lead to oxolane rings. The formation of **7** under acid-catalyzed conditions is to be expected, as the highly strained, bicyclic, oxetane structure, resulting from an alternative mode of intramolecular epoxide opening, would undergo spontaneous ring-expansion.

A bicyclic, *trans*-fused structure, derived from the intramolecular cyclization of a 3-malonyl ester in a furanose derivative, was recently reported[20] in an attempt to construct the octosyl acid skeleton. Unfortunately, these studies were impeded by the lability of the intermediate to further modification.

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