C-Glycosyl Nucleosides. III.[1] A Facile Synthesis of the Nucleoside Antibiotic Showdomycin

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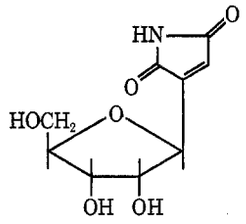
The reaction of 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose with sodium cyanide and hydrogen peroxide gives 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonamide (**6**) and its D-glycero-D-altro isomer (**5**). Methanolysis of these substances gives the corresponding methyl heptonates which can be oxidized using DMSO and DCC in the presence of dichloroacetic acid to methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (**9**). Reaction of this keto ester with carbamoylmethylenetriphenylphosphorane leads directly to the tribenzyl ether of showdomycin. Removal of the benzyl groups can be achieved either by boron trifluoride catalyzed acetolysis followed by acidic hydrolysis, or by treatment with boron trichloride at −78°. The showdomycin so obtained is identical with the natural product. Several model reactions are described to clarify the steric course of the reactions between α-keto esters and carbamoylmethylenetriphenylphosphorane.

The *C*-glycosyl nucleoside antibiotic showdomycin was first isolated from *Streptomyces showdoensis* by Nishimura, *et al.*[3] On the basis of spectroscopic studies, chemical transformations, and ultimately X-ray crystallographic examination, showdomycin was shown to be 2-(β-D-ribofuranosyl)maleimide (**1**).[4] Since the compound shows quite significant antibacterial[3] and antitumor[5] activities it has been the subject of numerous biochemical studies that have recently been reviewed.[6]

A synthesis of showdomycin has been briefly reported by Kalvoda, *et al.*,[7] involving, as the key intermediate, the keto ester **2** which was ingeniously prepared *via*



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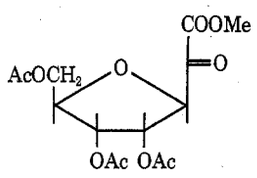


2

ozonolysis of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,4,6-trimethoxybenzene. As yet details and yields of this process have not been disclosed but the conversion of **2** into showdomycin required a six-step sequence.

In the accompanying paper[1] we have described efficient routes for the preparation of derivatives of 2,5-anhydro-D-allose in which the hydroxyl groups are protected as benzoyl or acetyl esters, benzyl ethers, or isopropylidene acetals. In this paper we describe the ready conversion of these compounds into keto esters similar to **2** and a much simplified, two-step conversion of one of these substances into showdomycin.

In conceiving a synthetic route to showdomycin one must bear in mind that, while this compound is very stable under acidic conditions, it is very labile in base,[3,4] owing, at least in part, to a rapid Michael type of addition of the 5′-hydroxyl group to the maleimide double bond.[4a] In view of this alkaline instability of the final product, and the necessity for a fairly vigorous acidic step during our proposed sequence, we decided to use benzyl ethers for protection of our sugar moiety.

The readily available 1,3-diphenyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazolidine (**3**) was therefore treated under reflux with Dowex 50 (H^+) resin in aqueous tetrahydrofuran to hydrolyze the imidazolidine ring and liberate 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (**4**) in 95% yield. The latter compound was previously liberated from **3** by treatment with *p*-toluenesulfonic acid monohydrate in a mixture of acetone and methylene chloride at room temperature, but under these conditions minor amounts of unreacted **3** were found in the final product.[1] Using the resin method the free aldehyde **4** was obtained as a chromatographically homogeneous syrup that was used directly in the next step (Scheme I).

In previous work on the synthesis of the nucleoside moiety of the polyoxin group of nucleoside antibiotics[8] and their analogs,[9] we have made extensive use of the cyanohydrin reaction as a means of homologating nucleoside 5′-aldehydes. In this work we have found that such cyanohydrins are frequently somewhat difficult to deal with because of their tendency to revert partially to the original aldehydes. To offset this we have shown that such cyanohydrin reactions can be made totally irreversible by immediate addition of hydrogen peroxide to the reaction mixture, thus giving the corresponding hydroxy amides. The same approach was used in the present work. Thus, the reaction of **4** with sodium cyanide and potassium carbonate was immediately followed by addition of hydrogen peroxide giving a roughly equal mixture of 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonamide (**6**) and its D-glycero-D-altro epimer (**5**) in a combined yield of 93%. By chromatography on a column of silicic acid the epimeric hydroxy amides could be quite readily separated, giving the pure, less polar and more polar isomers in yields of 45 and 39%, respectively. A definitive assignment of stereochemistry to these two isomers by chemical degradation does not appear to be too easy at this time. It is likely that such an assignment could be made on either the hydroxy amides or

(1) For part II, see H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **38**, 1836 (1973).

(2) Syntex Postdoctoral Fellow, 1971–1973.

(3) H. Nishimura, M. Mayama, Y. Komatsu, H. Kato, N. Shimaoka, and Y. Tanaka, *J. Antibiot., Ser. A*, **17**, 148 (1964).

(4) (a) Y. Nakagawa, H. Kano, Y. Tsukuda, and H. Koyama, *Tetrahedron Lett.*, 4105 (1967); (b) K. R. Darnall, L. B. Townsend, and R. K. Robins, *Proc. Nat. Acad. Sci.*, **57**, 548 (1967).

(5) S. Matsuura, O. Shiratori, and K. Katagiri, *J. Antibiot., Ser. A*, **17**, 234 (1964).

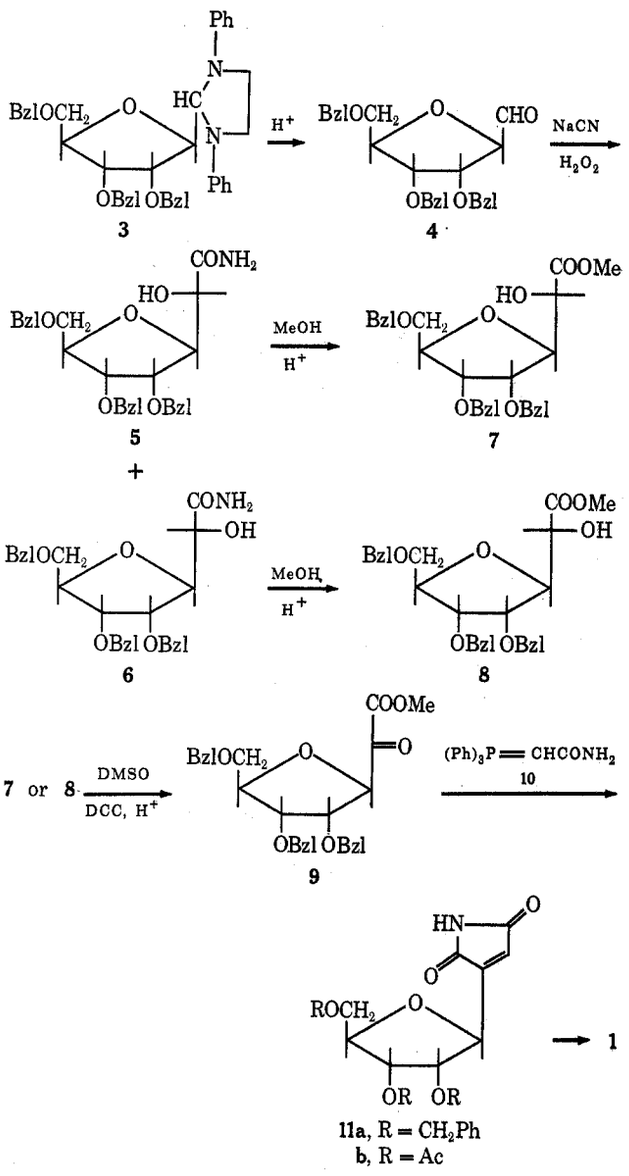
(6) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 393.

(7) L. Kalvoda, J. Farkaš, and F. Šorm, *Tetrahedron Lett.*, 2297 (1970).

(8) N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 3812 (1971).

(9) M. D. Edge, N. P. Damodaran, G. H. Jones, and J. G. Moffatt, unpublished work.

SCHEME I



the related hydroxy acids by circular dichroism[10] or other optical techniques, but such methods would presumably demand prior removal of the benzyl ether chromophore. Since for our present purpose a distinction between the two isomers is unnecessary, we have chosen to postpone this assignment of configuration until a later date.

Our original plan was to oxidize the hydroxy amides **5** and **6** to the corresponding keto amide and then to treat the latter with carbomethoxytriphenylphosphorane, giving a maleamic acid ester that could be cyclized to the maleimide **11a**. This route was, however, frustrated by the difficulties attending the oxidation of the hydroxy amides. The use of oxidants such as chromic oxide in acetic acid[11] led to complex mixtures, whereas mild methods such as the use of dimethyl sulfoxide and acetic anhydride[12] gave only the acetate ester of the hydroxy amide. The use of the DMSO–DCC oxidation reaction[13] is essentially precluded by the known reaction of amides with these agents.[14]

Because of these difficulties, each hydroxy amide (**5** and **6**) was then individually transformed into the corresponding hydroxy ester by treatment under reflux with anhydrous methanol in the presence of Dowex 50 (H^+) resin. In this way homogeneous methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate (**8**) and its D-glycero-D-altro epimer (**7**) were prepared in yields of 70–75%. While both **7** and **8** were analytically pure syrups, they could be readily differentiated by both tlc and by their nmr spectra. As has been the case in most of the intermediates in this work, the methylene protons of the benzyl ethers are superimposed upon most of the sugar protons and preclude a detailed analysis of this region. The methyl ester protons in **7** and **8** are, however, cleanly separated and permit a quantitative estimation of epimeric purity. It is interesting to note that the less polar hydroxy amide (**5** or **6**) gives rise to the more polar of the hydroxy esters (**7** or **8**). For the reasons cited above, the assignment of relative stereochemistry at C_2 in **7** and **8** must await further work.

Several different methods were examined for the oxidation of **7** and **8** to the keto ester methyl 3,-6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (**9**). By far the best results were obtained using the DMSO–DCC method with dichloroacetic acid as the proton source. By this method both **7** and **8** were converted essentially quantitatively to the keto ester **9** within 30 min at room temperature. Examination of the crude reaction mixture by tlc showed essentially a single carbohydrate containing spot together with some incompletely removed dicyclohexylurea and some *N*-dichloroacetyl-*N*,*N*′-dicyclohexylurea, both known by-products of the oxidation reaction using dichloroacetic acid.[13] The keto ester proved to be extremely labile and attempts to remove the by-products by either column or preparative thin layer chromatography on silicic acid led to partial decomposition. The oxidation step itself, however, appears to be quite clean and, since the urea-type by-products do not apparently interfere with subsequent steps, we routinely prepare **9** immediately prior to use and treat it without further purification.

Our previous work with nucleoside 5′-aldehydes[15] and with 5-ketohexofuranosyluronic acid derivatives as potential precursors to polyoxins[16] has taught us to be cautious of possible epimerization adjacent to the carbonyl group in such compounds. To convince ourselves that no such epimerization at C_3 had taken place during preparation of **9**, we directly reduce the carbonyl group in the normally worked up product using sodium borohydride in dimethoxyethane. The product from this reduction appeared by tlc to contain only the epimeric hydroxy esters **7** and **8** together with the re-

(10) (a) J. C. Craig and W. E. Pereira, *Tetrahedron*, **26**, 3457 (1970); (b) L. I. Katzin and E. Gulyas, *J. Amer. Chem. Soc.*, **92**, 1211 (1970).

(11) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 145.

(12) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967).

(13) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965). (b) For a review of these methods, see J. G. Moffatt in "Techniques and Applications in Organic Synthesis: Oxidation," Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., 1971, p 1.

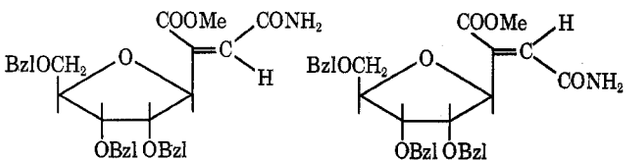
(14) U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3391 (1971).

(15) G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, CARB 16.

(16) Unpublished experiments of N. P. Damodaran, G. H. Jones, and J. G. Moffatt.

sidual urea products known to be present in the keto ester. The latter were removed by chromatography on silicic acid giving a tlc-pure mixture of **7** and **8** in an overall yield of 76% through the oxidation and reduction sequence. Examination of this mixture by nmr spectroscopy showed only signals corresponding to a mixture of **7** and **8** with the less polar isomer now predominating in a 3:1 ratio. This combination of tlc and nmr data would appear to allay any fear that epimerization of the labile keto ester **9** had taken place. The attempted selective reduction of **9** using sodium borohydride in methanol was not successful owing apparently to concomitant reduction of the ester grouping. The products of this reduction, or of the reduction of the hydroxy esters **7** and **8**, appeared as a pair of rather polar materials giving a positive test with the periodate–benzidine spray[17] for vicinal diols.

The keto ester **9** reacted very rapidly at room temperature with 1 equiv of carbamoylmethylenetriphenylphosphorane (**10**)[18] in chloroform to give a single major product with a polarity less than **9** together with considerable amounts of polar by-products. Chromatography of the mixture on a column of silicic acid led to the isolation of this crystalline product in an overall yield of 43% from the hydroxy esters **7** and **8**. The nmr and mass spectra of this substance clearly showed the disappearance of the methyl ester group and the presence of a single NH proton which was coupled to a vinyl proton. These results can be explained by spontaneous cyclization of an intermediate cis-oriented maleamic acid ester (**12**) to the corresponding maleimide (**11a**) which is the tribenzyl ether of showdomycin. Alternatively, the cyclization could take place at the level of the betaine precursor of **12** and for the



12 **13**

moment we cannot distinguish between these two possibilities.

Only traces of a more polar product with the mobility expected of the acyclic product (**12**) or its trans oriented isomer (**13**) could be found and no pure materials were isolated from the polar by-products which also contained triphenylphosphine oxide. It is not clear whether these by-products are the result of decomposition of the labile keto ester **9**, to a general nucleophilic instability of the maleimide ring,[19] or to further reactions of **11a** with the phosphorane **10**. Such reactions of imides with even highly stabilized phosphoranes are known[20] and model experiments (see below) have shown that the yields of maleimides from α-keto esters and **10** are markedly reduced if an excess of **10** is used. In addition, it could be shown by tlc that treatment of pure **11a** with **10** in chloroform led to fairly rapid conversion of **11a** into unidentified polar products.

(17) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).

(18) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 3874 (1959).

(19) For a review on cyclic imides, see M. K. Hargreaves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.*, **70**, 439 (1970).

(20) W. Flitsch and B. Müter, *Chem. Ber.*, **104**, 2847, 2852 (1971).

Completion of the synthesis of showdomycin then only required removal of the benzyl ether groups from **11a**. The usual approach *via* catalytic hydrogenolysis was not, however, feasible since the maleimide ring of showdomycin is rapidly reduced in the presence of palladium catalysts.[4] The alternative use of sodium in liquid ammonia is also precluded by the extreme base lability of showdomycin.[3,4b] Two solutions to this problem have been found. Our first approach involved the acetolysis of the benzyl ethers with acetic anhydride in the presence of boron trifluoride etherate at room temperature.[21] Under these conditions a fairly smooth reaction occurred giving what is considered to be 2′,3′,5′-tri-*O*-acetylshowdomycin (**11b**).[4a,7] Without purification, the latter was then subjected to treatment with 0.15 *M* methanolic hydrochloric acid at room temperature for 18 hr to remove the acetyl groups. Even on the very small scale upon which this reaction was conducted, crystalline showdomycin (**1**) was obtained in an overall yield of 33% from **11a**. The second, and more direct, approach was based on the well-established cleavage of carbohydrate methyl[22] and benzyl[23] ethers using boron trihalides. Treatment of **11a** with boron trichloride in methylene chloride at −78° followed by destruction of the excess reagent with methanol led quite smoothly to complete debenzylation. Subsequent chromatographic purification led to beautifully crystalline showdomycin in a yield of 69%. The synthetic product was physically and spectroscopically identical with an authentic sample of showdomycin[24] and also showed a spectrum of antibacterial activity identical with that of the natural product.[25] The above route thus appears to offer a direct and reasonably efficient route for the synthesis of showdomycin.

The spontaneous cyclization of the intermediate **12** (or of its betaine precursor) to the maleimide **11a** suggests that the reaction of carbamoylmethylenephosphoranes with α-keto esters might constitute a generally useful route for the preparation of substituted maleimides.[19] To check this the reaction of methyl pyruvate (**14a**) with **10** was examined under conditions similar to those used for preparing **11a**. The reaction proceeded rapidly at room temperature to give two major crystalline products in addition to triphenylphosphine oxide. The desired cyclized product, citraconimide (**17a**)[26] was only obtained in 9% yield while the major product, isolated in 53% yield, proved to be the acyclic methyl 2-methylfumaramate (**16a**) (Scheme II).[27]

There was no indication of the presence of the maleamate **15a**. The formation in this case of the fumaramate **16a** as the predominant product is clearly a consequence of steric factors. Thus when the substituent R in **14** is a small methyl group, the Wittig reac-

(21) Acetolysis of carbohydrate ethers with sulfuric acid and acetic anhydride has been described by R. Allerton and H. G. Fletcher, *J. Amer. Chem. Soc.*, **76**, 1757 (1954). Recently the very rapid acetolysis of a homoallylic benzyl ether using boron trifluoride has also been described by E. J. Corey and P. Grieco, *Tetrahedron Lett.*, 107 (1972).

(22) See, *e.g.*, T. G. Bonner, E. J. Bourne, and S. McNally, *J. Chem. Soc.*, 2929 (1960).

(23) H. Ohrui, H. Kuzuhara, and S. Emoto, *Tetrahedron Lett.*, 4267 (1971).

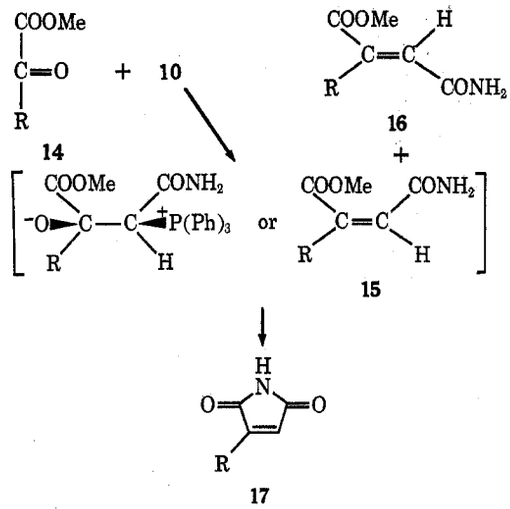
(24) We gratefully acknowledge receipt of a generous sample of showdomycin from Shionogi Research Laboratories, Osaka, Japan.

(25) The biological testing was done through the kind cooperation of Dr. K. Katagiri of Shionogi Research Laboratories.

(26) G. Ciamician and M. Dennstedt, *Gazz. Chim. Ital.*, **12**, 501 (1882).

(27) R. Anschütz, *Justus Liebigs Ann. Chem.*, **353**, 169 (1907).

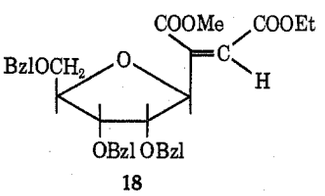
SCHEME II



a, R = CH_3; b, R = C_6H_5

tion proceeds so as to place the two bulkiest substituents (COOMe and $CONH_2$) in a stable trans relationship.[28] On the other hand, with the keto ester **9** the bulky, benzylated furan ring becomes the major steric influence and becomes oriented trans to the carbamoyl group. The resulting maleamate (**12**) then undergoes spontaneous cyclization to **11a**. Once again, it cannot be ruled out that cyclization occurs at the betaine level preceding actual formation of **12**. An intermediate course was taken in the reaction of **10** with methyl phenylglyoxalate (**14b**). This reaction, which was expectedly somewhat slower than the others and required brief heating in chloroform, led to roughly equal amounts of 2-phenylmaleimide (**17b**, 26%)[29] and the previously undescribed β-carbomethoxy-*cis*-cinnamamide (**16b**, 30%). In this case there is apparently little difference between the phenyl and carbomethoxy groups with regard to the steric control that they provide to the reaction.

The same type of steric control is clearly provided in the reaction of the acetylated keto ester **2** with carboethoxymethylenetriphenylphosphorane since the product of this reaction was shown to be a 10:1 mixture of isomers with the cis diester predominating.[7] The reaction of **9** with carboethoxytriphenylphosphorane also proceeded so as to give essentially a single isomer. By chromatography on silicic acid a homogeneous product, which by analogy with the results of the Czech workers[7] is considered to have the maleate structure **18**, was isolated in 65% yield. This product has not, however, been examined further.



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From the results above it is clear that the reaction of α-keto esters **14** with carbamoylmethylenetriphenylphosphorane provides a direct route to 2-substituted maleimides providing that the substituent R on **14** is reasonably bulky. The method would appear to offer an interesting route to analogs and homologs of showdomycin and we hope to describe our efforts in these directions at a later date.

(28) For a general discussion of the stereochemistry of the Wittig reaction, see J. Reucroft and P. Sammes, *Quart. Rev.*, **25**, 135 (1971).

(29) C. S. Rondestvedt and O. Vogl, *J. Amer. Chem. Soc.*, **77**, 2313 (1955).

Experimental Section

General Methods.—Thin layer chromatography was carried out using silica gel GF on glass plates obtained from Analtech, Inc., Newark, Del. Preparative tlc was done using 1.3-mm layers of Merck silica gel HF on 20 × 100 cm glass plates and column chromatography using Merck silica gel with 0.05–0.20-mm particles. Nmr spectra were determined using a Varian HA-100 spectrometer and are reported in parts per million downfield from an internal standard of tetramethylsilane. Mass spectra were obtained using an Atlas CH-4 spectrometer fitted with a direct inlet system. Elemental analyses and most physical measurements were obtained by the Analytical Laboratories of Syntex Research. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson and to Dr. L. Tökés for their cooperation with nmr and mass spectrometry.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-allose (4).—Dried Dowex 50 (H^+) resin (6.5 g) was added to a solution of 1,3-diphenyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)imidazolidine (**3**, 1.25 g, 2.0 mmol)[1] in a mixture of tetrahydrofuran (130 ml) and water (65 ml). The resulting mixture was stirred under reflux for 4 hr, the reaction being monitored by tlc using ether–hexane (2:1). Since some unreacted **3** persisted, the resin was removed by filtration and the filtrate was retreated with fresh Dowex 50 (H^+) resin as above. The mixture was then filtered and the resin was washed with tetrahydrofuran. The combined filtrates were evaporated and dried *in vacuo* leaving 821 mg (95%) of **4** that was chromatographically homogeneous and identical with the material previously described.[1]

3,6-Anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*altro*-heptonamide (6) and Its D-Glycero-D-altro Isomer (5).—A solution of sodium cyanide (1.5 g) and potassium carbonate (1.5 g) in water (20 ml) was added to a cooled (10°) solution of **4** (821 mg, 1.9 mmol) in dioxane (30 ml) and the mixture was then stirred at room temperature for 30 min. The solution was then cooled in ice and stirred while 30% hydrogen peroxide (5.5 ml) was added. After 1 hr the mixture was added to 500 ml of ice–water and the precipitate was collected, washed with cold water, and dried over phosphorus pentoxide giving 840 mg (93%) of a mixture of **5** and **6**. This material was chromatographed on a 4 × 50 cm column of silicic acid using ethyl acetate–chloroform (1:1) to effect a clean separation. The less polar isomer was crystallized from aqueous methanol giving 410 mg (45%) of **5** or **6** with mp 141.5–142°; $[\alpha]^{23}D$ 125.6° (*c* 0.18, $CHCl_3$); ν_{max} (KBr) 1650, 1640 cm^{-1} ($CONH_2$); nmr ($CDCl_3$), δ 3.4–4.8 (m, 13, sugar protons and $ArCH_2O$), 4.15 (br s, 1, C_2OH), 5.64 and 6.62 (br s, 1, $CONH_2$), 7.24 ppm (m, 15, Ar).

Anal. Calcd for $C_{28}H_{31}NO_6$ (477.57): C, 70.42; H, 6.54; N, 2.93. Found: C, 70.43; H, 6.31; N, 2.99.

The more polar isomer (355 mg, 39%) was obtained as a syrup that was homogeneous and free of the other isomer by tlc using $CHCl_3$–EtOAc (1:1) or ether–hexane (2:1) and that crystallized upon storage with mp 79–84° (it was, however, difficult to recrystallize from a solvent); $[\alpha]^{23}D$ 74.7° (*c* 0.11, $CHCl_3$); ν_{max} (KBr) 1660 cm^{-1} ($CONH_2$); nmr ($CDCl_3$) δ 3.51 (dd, 1, $J_{6,7a}$ = 2 Hz, J_{gem} = 10 Hz, C_{7a} H), 3.79 (dd, 1, $J_{6,7b}$ = 2.5 Hz, J_{gem} = 10 Hz, C_{7b} H), 3.9–4.8 (m, 11, C_2–C_6 H and $ArCH_2O$), 4.1 (br s, 1, C_2OH), 5.45 and 6.52 (br s, 1, $CONH_2$), 7.3 ppm (m, 15, Ar).

Anal. Calcd for $C_{28}H_{31}NO_6$ (477.57): C, 70.42; H, 6.54; N, 2.93. Found: C, 70.49; H, 6.64; N, 2.86.

Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate (8) and Its D-Glycero-D-altro Isomer (7).—Dried Dowex 50 (H^+) resin (2.5 g)[30] was added to a solution of the less polar hydroxy amide (**5** or **6**, 380 mg, 0.8 mmol) in dry methanol (20 ml) and the mixture was stirred under reflux, the reaction being monitored by tlc using EtOAc–$CHCl_3$ (1:1). After 6 hr a further portion of the resin (2.5 g) was added and after a total of 8 hr the resin was removed by filtration and washed with methanol. Evaporation of the solvent left a syrup that was purified by chromatography on a column of silicic acid using

(30) Freshly regenerated Dowex 50 (H^+) resin was carefully washed with methanol, then with ether, and dried in a vacuum oven at 40° for 24 hr.

ether–hexane (2:1) giving 277 mg (70%) of a homogeneous hydroxy ester (**7** or **8**) as a syrup: $[\alpha]^{23}D$ 40.9° (*c* 0.11, $CHCl_3$); nmr ($CDCl_3$) δ 3.3–4.7 (m, 13, sugar protons and $ArCH_2O$), 3.66 (s, 3, OMe), 7.27 ppm (s, 15, Ar).

Anal. Calcd for $C_{29}H_{32}O_7$ (492.58): C, 70.72; H, 6.55. Found: C, 70.76; H, 6.52.

The more polar hydroxy amide (290 mg, 0.6 mmol) was treated in the same way as above to give 215 mg (74%) of a hydroxy ester (**7** or **8**) that was homogeneous by tlc using ether–hexane (2:1) and was less polar than its isomer above: $[\alpha]^{23}D$ 20.3° (*c* 0.13, $CHCl_3$); nmr δ 3.3–4.7 (m, 13, sugar protons and $ArCH_2O$); 3.73 (s, 3, OMe), 7.27 ppm (s, 15, Ar).

Anal. Calcd for $C_{29}H_{32}O_7$ (492.58): C, 70.72; H, 6.55. Found: C, 70.29; H, 6.64.

Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (9).—Dichloroacetic acid (0.041 ml, 0.5 mmol) was added to an ice-cooled, stirred solution of **7**, **8**, or a mixture of these compounds (493 mg, 1 mmol) and dicyclohexylcarbodiimide (515 mg, 2.5 mmol) in a mixture of anhydrous dimethyl sulfoxide (5 ml) and benzene (5 ml). After 30 min at room temperature the mixture was cooled to 0° and a concentrated aqueous solution of oxalic acid (1.5 mmol) was added. The mixture was kept at room temperature for 20 min, diluted with ethyl acetate (50 ml), and filtered. The filtrate was washed five times with water and the organic phase was dried (Linde 4A Molecular Sieve) and evaporated to a syrup. The latter was dissolved in ethanol (5 ml) and a small amount of dicyclohexylurea was removed by filtration. Evaporation of the solution left the keto ester **9** as a syrup that was contaminated by minor amounts of dicyclohexylurea and *N*-dichloroacetyl-*N*,*N*′-dicyclohexylurea. Attempted purification of **9** by chromatography on silicic acid led to partial decomposition and accordingly the material was used directly in the next steps: ν_{max} (film) 1730 (sh), 1750 cm^{-1}, and no hydroxyl band.

Borohydride Reduction of 9.—Sodium borohydride (30 mg) was added to an ice-cooled solution of **9** (prepared from 0.2 mmol of a mixture of **7** and **8**) in 1,2-dimethoxyethane (1 ml) and the mixture was stirred at room temperature for 15 min. The mixture was diluted with chloroform (5 ml), washed four times with water, dried, and evaporated leaving a syrup. The latter was chromatographed on a column of silicic acid using ether–hexane (2:1) to remove residual urea by-products and gave 75 mg (76% overall from the hydroxy ester) of a mixture of **7** and **8** with the less polar isomer predominating in a 3:1 ratio. The nmr spectrum of this mixture was identical with that of a mixture of **7** and **8** and showed no evidence of other isomers.

A comparable reduction of **9** (or of a mixture of **7** and **8**) using sodium borohydride in methanol led to reduction of the ester grouping and gave two more polar products showing a positive test for vicinal diols with the periodate–benzidine spray.[17]

2-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)maleimide (11a).—A solution of carbamoylmethylenetriphenylphosphorane (**10**, 320 mg, 1 mmol)[18] and **9** (from 1 mmol of a mixture of **7** and **8**) in dry chloroform (15 ml) was stirred at room temperature for 30 min. The solvent was then evaporated and the residue was chromatographed on a 3.5 × 25 cm column of silicic acid using a gradient of 33 to 50% ether in hexane. Crystallization of the major product from ether–hexane gave 215 mg (43% from the hydroxy esters) of **11a** with mp 64–65°; $[\alpha]^{23}D$ 96° (*c* 0.55, $CHCl_3$); ν_{max} (KBr) 1775, 1720, 1635 cm^{-1}; nmr ($CDCl_3$) δ 3.51 (dd, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 3 Hz, $C_{5'a}$ H), 3.74 (dd, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 3 Hz, $C_{5'b}$ H), 3.9 (m, 2, $C_{2'}$ H and $C_{3'}$ H), 4.2–4.7 (m, 7, $ArCH_2$ and $C_{4'}$ H), 4.96 (dd, 1, $J_{1',2'} = J_{1',3}$ = 2 Hz, $C_{1'}$ H), 6.54 (dd, 1, $J_{1',3} = J_{3,NH}$ = 2 Hz, C_3 H), 7.25 (m, 15, Ar), 7.7 ppm (br s, 1, NH); ORD (MeOH) multiple Cotton effect $[\Phi]^{pk}_{220}$ 22,000°, $[\Phi]_{238}$ 0°, $[\Phi]^{tr}_{261}$ − 18,500°, $[\Phi]_{295}$ 0°, and $[\Phi]^{pk}_{308}$ 4500°; mass spectrum (70 eV, 150°) *m/e* 499 (M^+), 408 ($M - C_7H_7$).

Anal. Calcd for $C_{30}H_{29}NO_6$ (499.57): C, 72.13; H, 5.85; N, 2.80. Found: C, 72.59; H, 5.89; N, 2.84.

2-(β-D-Ribofuranosyl)maleimide (1) (Showdomycin). A.—A solution of boron trichloride (6.0 g, 50 mmol) in methylene chloride (20 ml) at −78° was added to a solution of **11a** (300 mg, 0.6 mmol) in methylene chloride (5 ml) and the mixture was stored at −78° for 30 hr and then at −50° for 2 hr. A mixture of methanol (25 ml) and methylene chloride (25 ml) at −78° was then added and the temperature was allowed to slowly rise to −20°. After storage overnight at −20° the solvents were evaporated *in vacuo* and the residue was coevaporated with methanol four times. The final residue was chromatographed on a 2 × 20 cm column of silicic acid using ethyl acetate–acetone (7:3). The major peak was crystallized from acetone–benzene giving 95 mg (69%) of **1** as colorless needles with mp 154.5–156° (lit. mp 153–154,[3] 152–153,[7] 160–161°[4a]). The melting point was not depressed upon admixture with an authentic sample of showdomycin[24] and the two samples showed identical spectroscopic and antibacterial[25] behavior.

B.—Boron trifluoride etherate (0.05 ml) was added to an ice-cooled solution of **11a** (25 mg) in acetic anhydride (0.5 ml). The resulting solution was stirred at 5° for 1 hr and then at room temperature for 18 hr with addition of a further portion of boron trifluoride (0.1 ml) after 6 hr. The mixture was then partitioned between water and chloroform and the organic phase was dried and evaporated to a syrup that contained the tri-*O*-acetate (**11b**). This was dissolved in methanol (10 ml) and a 3 *N* solution of hydrochloric acid in methanol (0.5 ml) was added. After storage at room temperature for 18 hr the solution was evaporated and the residue chromatographed on a column of silicic acid as described in A. Crystallization of the major peak from acetone–benzene gave 3.8 mg (33%) of **1** identical with that above.

Reaction of Methyl Pyruvate with Carbamoylmethylenetriphenylphosphorane (10).—A solution of **10** (319 mg, 1 mmol)[18] and methyl pyruvate (102 mg, 1 mmol) in dry chloroform (5 ml) was stirred at room temperature for 20 min and then evaporated to dryness. The residue was chromatographed on a 2 × 20 cm column of silicic acid using chloroform–ethyl acetate (1:1) giving three main fractions. Crystallization of the least polar compound gave 10 mg (9%) of citraconimide (**15**) with mp 109–110° (lit.[26] mp 109–110°); nmr ($CDCl_3$) δ 2.06 (d, 3, *J* = 2 Hz, CH_3), 6.3 (m, 1, CH), 7.7 ppm (br s, 1, NH). The second compound was triphenylphosphine oxide while the most polar fraction contained 75 mg (53%) of methyl 2-methylfumaramate (**16a**) with mp 118–119° from chloroform–hexane (lit.[27] mp 117°); λ^{MeOH}_{max} 221 nm (ε 10,000); ν_{max} (KBr) 1725, 1705, 1675, 1620 cm^{-1}; nmr ($CDCl_3$) δ 2.26 (d, 3, *J* = 2 Hz, CH_3), 3.79 (s, 3, COOMe), 5.80 (br s, 2, $CONH_2$), 6.80 ppm (m, 1, CH).

Reaction of Methyl Phenylglyoxalate (14b) with 10.—A solution of **10** (319 mg, 1 mmol)[18] and **14b** (164 mg, 1 mmol) in dry chloroform (3 ml) was heated under reflux for 30 min and then evaporated to a syrup which was chromatographed on a 3 × 25 cm column of silicic acid. Elution with hexane–ether (2:1) gave a little unreacted **14b**, followed by a substance that was crystallized from chloroform–hexane giving 45 mg (26%) of 2-phenylmaleimide with mp 166–168° (lit.[29] mp 167–168°); nmr ($CDCl_3$) δ 6.69 (s, 1, CH), 7.3–8 ppm (m, 5, Ar).

Elution with chloroform–ethyl acetate (1:1) gave triphenylphosphine oxide followed by a substance that was crystallized from chloroform–hexane giving 61 mg (30%) of β-carbomethoxy-*cis*-cinnamamide (**16b**) with mp 113.5–114.5°; λ^{MeOH}_{max} 278 nm (sh, ε 5200); ν_{max} (KBr) 1712, 1685, 1670, 1610 cm^{-1}; nmr ($CDCl_3$) δ 3.78 (s, 3, OMe), 5.2 and 5.6 (br s, 1, NH), 7.04 (s, 1, CH), 7.2–7.5 ppm (m, 5, Ar).

Anal. Calcd for $C_{11}H_{11}NO_3$ (205.22): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.31; H, 5.63; N, 6.75.

1-Methyl-4-ethyl 2-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)maleate (18).—Carboethoxymethylenetriphenylphosphorane (70 mg, 0.2 mmol) was added to a solution of **9** (from 0.2 mmol of a mixture of **7** and **8**) in chloroform (2 ml) and then stirred for 2.5 hr at room temperature. After evaporation of the solvent the residue was purified by chromatography on a 2 × 30 cm column of silicic acid using ether–hexane (1:1) giving 73 mg (65%) of **18** that was homogeneous by tlc: $[\alpha]^{23}D$ 6° (*c* 0.2, $CHCl_3$); $\nu^{CHCl_3}_{max}$ 1700, 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.23 (t, 3, *J* = 7 Hz, CH_2CH_3), 3.46 and 3.61 (dd, J_{gem} = 11 Hz, $J_{4',5'a} = J_{4',5'b}$ = 4 Hz, $C_{5'}$ H_2), 3.69 (s, 3, OCH_3), 3.8–4.3 (m, 2, $C_{3'}$ H and $C_{4'}$ H), 4.04 (dd, 1, $J_{1',2'} = J_{2',3'}$ = 4 Hz, $C_{2'}$ H), 4.14 (q, 2, *J* = 7 Hz, CH_2CH_3), 4.47, 4.50, and 4.55 (s, 2, OCH_2Ph), 4.73 (dd, 1, $J_{1',2'}$ = 4 Hz, $J_{allylic}$ = 2 Hz, $C_{1'}$ H), 6.27 (d, 1, $J_{allylic}$ = 2 Hz, CHCOOEt), 7.3 ppm (m, 15, Ar).

Anal. Calcd for $C_{33}H_{36}O_8$ (560.65): C, 70.70; H, 6.47. Found: C, 70.56; H, 6.41.

Registry No.—**1**, 16755-07-0; **3**, 38821-04-4; **4**, 37699-02-8; **5**, 38821-06-6; **6**, 38821-07-7; **7**, 38821-08-8; **8**, 38821-09-9; **9**, 38821-10-2; **10**, 38821-11-3; **11a**, 38821-12-4; **14b**, 15206-55-0; **16a**, 38821-13-5; **16b**, 38821-14-6; **18**, 38821-15-7; dichloroacetic acid, 79-43-6; methyl pyruvate, 600-22-6; carboethoxymethylenetriphenylphosphorane, 21382-83-2.