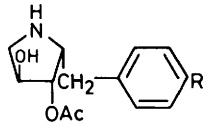
A New Synthesis of (−)-Anisomycin and its Demethoxy Analogue from D-Ribose[1]

J. Grant Buchanan,* Keith A. MacLean, and Richard H. Wightman
Department of Chemistry, Heriot-Watt University, Edinburgh EH14 4AS
Hans Paulsen
Institut für Organische Chemie und Biochemie der Universität Hamburg, D-2000 Hamburg 13, Federal Republic of Germany

2,3-*O*-Isopropylidene-D-ribose (**7**) reacted with *p*-methoxybenzylmagnesium chloride in tetrahydrofuran to give the D-*allo*triol (**6a**) (77%). Periodate oxidation of compound (**6a**) followed by reaction with hydroxylamine hydrochloride in pyridine gave (*E,Z*)-5-deoxy-2,3-*O*-isopropylidene-5-(*p*-methoxyphenyl)-L-ribose oxime (**18a**) which was converted into the nitrile methanesulphonate (**19a**) with methanesulphonyl chloride in pyridine. Reduction of the nitrile (**19a**) with lithium aluminium hydride gave (2*R*,3*S*,4*R*)-3,4-isopropylidenedioxy-2-(*p*-methoxybenzyl)pyrrolidine (**2a**) [45% from (**6a**)], which was converted into the epoxide (**24a**) (68%) *via* the bromo acetates (**28a**) and (**29a**). Regioselective opening of the epoxide ring in compound (**24a**) with acidic allyl alcohol gave the allyl ether (**30a**) (63%) which was converted into the *N*-benzyl 3-acetoxy compound (**31a**) (77%). Removal of the allyl and benzyl groups, by treatment with palladium–charcoal under acidic conditions followed by hydrogenolysis, gave (−)-anisomycin (**1a**) (86%).

A similar series of reactions afforded demethoxyanisomycin (**1b**) which showed antibiotic activity against *Trichomonas vaginalis* [about one sixth the activity of anisomycin (**1a**)].

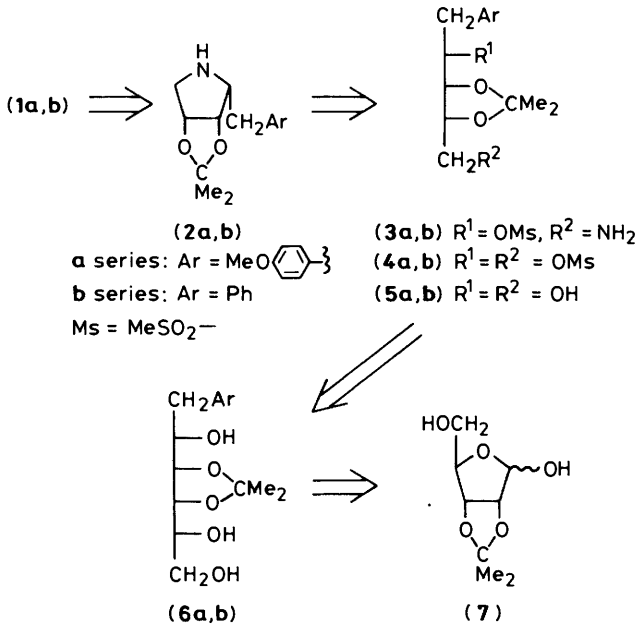
The antibiotic anisomycin (**1a**) was first isolated in 1954, by Sobin and Tanner,[2] from two *Streptomyces* species (*S. grisoleus* and *S. roseochromogenes*) and has since been obtained from a third species (*Streptomyces* sp. No. 638).[3] It exhibits marked activity against protozoa and certain fungi,[4] acting as an inhibitor of protein synthesis.[4,5] The main structural features were elucidated in 1965[6] and the relative stereochemistry determined later by *X*-ray crystallography[7] and ^{1}H n.m.r. spectrometry.[8] By chemical correlation with L-tyrosine the absolute configuration (**1a**) of anisomycin was established in 1968.[9]



(**1**) **a**; R = OMe
b; R = H

Early syntheses of anisomycin were non-stereoselective and proceeded in poor overall yield.[10] Moffatt and his colleagues[11] have developed an efficient chiral synthesis of anisomycin from D-glucose and, most recently, Schumacher and Hall[12] have reported a highly efficient and stereoselective synthesis of the racemate and two analogues, including the racemic demethoxy compound (**1b**). We now describe a new enantio- and stereoselective synthesis of (−)-anisomycin (**1a**) and its demethoxy analogue (**1b**) from D-ribose.[1]

The first general plan for the synthesis is shown in Scheme 1. It was envisaged that anisomycin (**1a**) could be obtained by elaboration of the pyrrolidine (**2a**), derived by cyclisation of the amino mesylate (**3a**).[13] The dimesylate (**4a**) of the diol (**5a**) should be a suitable precursor of (**3a**), either by reaction with ammonia or with azide ion followed by reduction.[13] The diol (**5a**) could be obtained by degradation of the triol (**6a**), the product to be expected from the reaction of 2,3-*O*-isopropylidene-D-ribose (**7**) with *p*-methoxybenzylmagnesium chloride. The necessary D-*allo* stereochemistry in triol (**6a**) should follow from earlier work on the reaction of (**7**) with ethynylmagnesium bromide.[14] Since our objectives included the synthesis of analogues of anisomycin, we conducted some of our trial

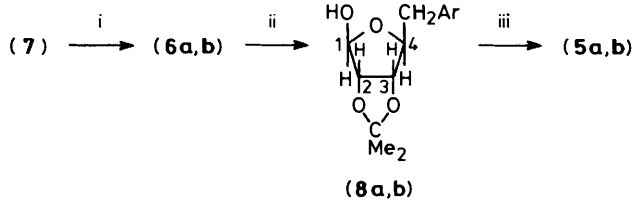


Scheme 1.

experiments in the demethoxy series (**b** series, Scheme 1), where it was found that some of the intermediates crystallised more readily and gave simplified ^{1}H n.m.r. spectra.

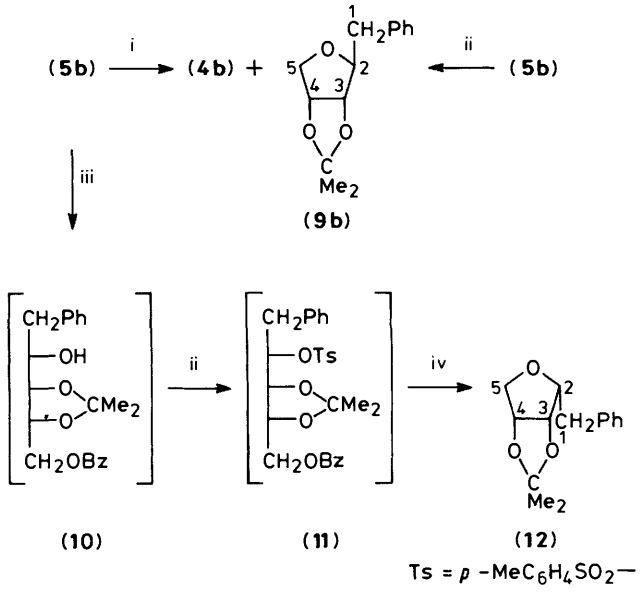
Grignard reagents derived from benzyl, and particularly *p*-methoxybenzyl, halides tend to undergo Wurtz-type coupling with unchanged benzyl halide when prepared in the normal way. This was avoided[15,16] by slow addition of the chloride to a well stirred suspension of magnesium in tetrahydrofuran (THF), which was preferred to ether for the subsequent reactions with compound (**7**). Treatment of the furanose (**7**)[17] with a large excess of the appropriate Grignard reagent gave the required triols (**6a**) (77%) and (**6b**) (70%). In each case only one stereoisomer could be isolated and was shown to have the D-*allo* configuration, as follows. When the triols (**6a**) and (**6b**)

were oxidised by periodate the corresponding hemiacetals (**8a,b**) were produced (Scheme 2). The ^{1}H n.m.r. spectra of compounds



Scheme 2. *Reagents:* i, $ArCH_2MgCl$, THF; ii, $NaIO_4$; iii, $NaBH_4$

(**8a**) and (**8b**) were very similar and strongly suggested a *trans* arrangement of protons at C-1, C-2 and at C-3, C-4 since the coupling constants were zero in each case. The hemiacetals were reduced, by means of sodium borohydride, to the corresponding diols (**5a**) and (**5b**). The D-*ribo* stereochemistry of (**5b**) was confirmed in detail (Scheme 3). Reaction of diol (**5b**) with an



Scheme 3. *Reagents:* i, excess of $MeSO_2Cl$, C_5H_5N; ii, TsCl, C_5H_5N; iii, BzCl (1 mol equiv.), C_5H_5N; iv, KOH, MeOH

excess of methanesulphonyl chloride in pyridine, by inverse addition, gave the bis(methanesulphonate) (**4b**) as the major product (74%) together with the anhydride (**9b**) (11%) arising by cyclisation of the first formed primary sulphonate. The same anhydride (**9b**) was produced from diol (**5b**) in 75% yield using toluene-*p*-sulphonyl chloride in pyridine. The epimeric anhydride (**12**) was obtained (69%) from diol (**5b**) by way of the monobenzoate (**10**) and toluene -*p*-sulphonate (**11**) (Scheme 3).

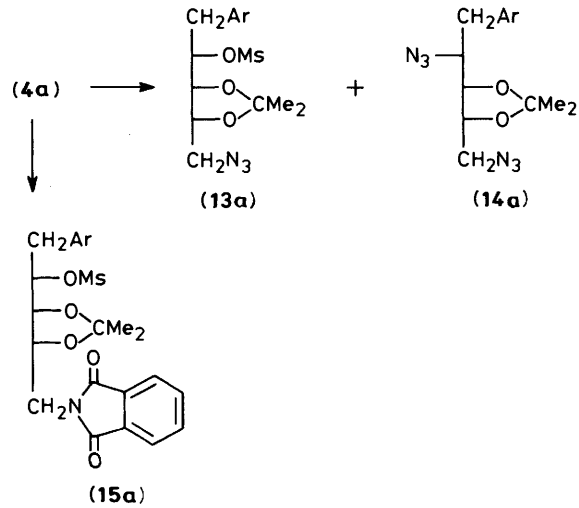
Since the anhydrides (**9b**) and (**12**) were prepared in a stereocontrolled manner from diol (**5b**) their structures reflect the configuration of compound (**5b**). In tetrahydrofurans of this type the ^{13}C chemical shifts of the isopropylidene group [18–21] and the three carbon atoms C-1—C-3 [18,19] are at higher field in the all-*cis* isomer than in its epimer. From the Table it can be seen that these conditions are fulfilled, in the case of compounds (**9b**) and (**12**), for C-1 and the isopropylidene groups; the signals for C-2—C-4 were not assigned individually. The D-*ribo* configuration in diol (**5b**) is thus established and it follows that triol (**6b**) has the D-*allo* configuration, as expected.[14]

The dimesylates (**4a**) and (**4b**) were surprisingly unreactive

Table. ^{13}C N.m.r. data for compounds (**9b**) and (**12**) (δ values in $CDCl_3$; 50.32 MHz)

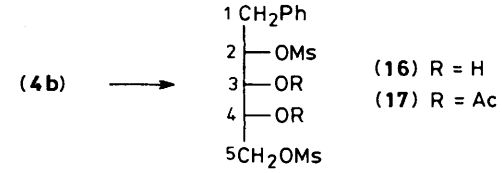
Compound	C-1	Isopropylidene: Acetal	Isopropylidene: Me_2	C-2—C-4	C-5	Ph
(**9b**)	37.17	112.85	25.15, 26.67	80.97, 84.22, 85.16	72.02	126.51, 128.54 (× 2), 129.12 (× 2), 137.56
(**12**)	34.85	112.04	25.06, 26.17	80.82, 81.12, 83.68	72.87	126.27, 128.34 (× 2), 129.28 (× 2), 138.57

towards ammonia and benzylamine. At room temperature starting materials were recovered and when the reaction mixtures with benzylamine were heated a complex mixture of products resulted, probably due to 1,2-elimination. Aryl participation at C-2 is also a possibility,[22] but this was not proved. Similar results were obtained using sodium azide in dimethylformamide (DMF). When dimesylate (**4a**) was treated with potassium azide in refluxing benzene containing 1,4,7,10,13,16-hexaoxacyclo-octadecane (18-crown-6) both mono- (**13a**) and di-azide (**14a**) were produced in poor yield and characterised by ^{1}H n.m.r. spectrometry (Scheme 4). The most



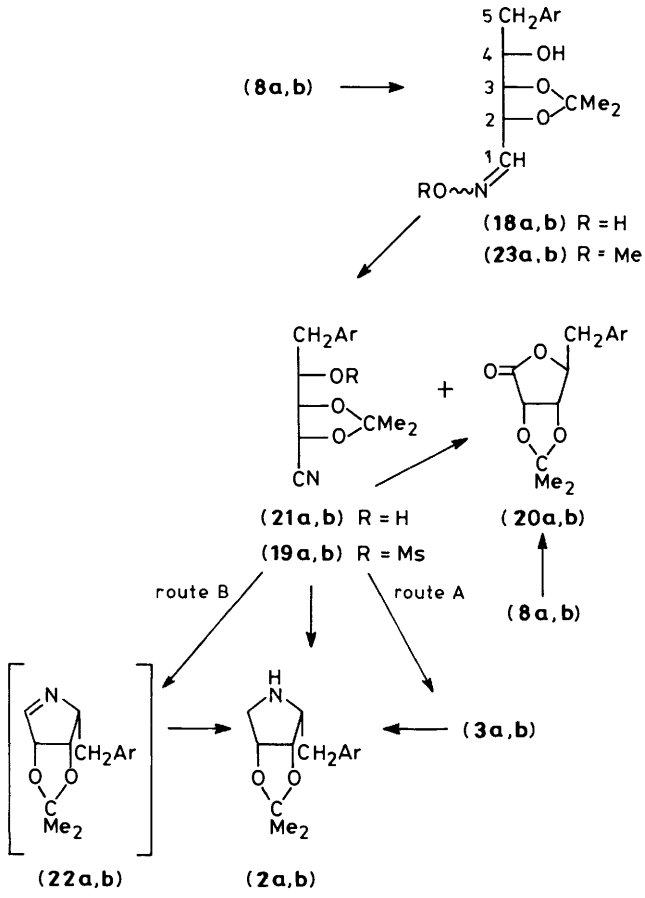
Scheme 4.

satisfactory displacement (58% yield) was with potassium phthalimide and 18-crown-6 in refluxing benzene to give the phthalimide (**15a**). Examination of molecular models of the dimesylates (**4a**) and (**4b**) indicates considerable hindrance either to the incoming nucleophile or to the departing group for displacement at C-5, due to the isopropylidene methyl groups. Removal of the isopropylidene group in compound (**4b**) by acidic hydrolysis gave the crystalline diol (**16**). Although diol



(**16**) and its diacetate (**17**) readily underwent displacement reactions with ammonia and azide ion the stereochemical outcome is less predictable because of the formation of epoxides or acetoxonium-ion intermediates involving C-4 and C-3. The formation of the 5-phthalimido derivative (**15a**) was the most encouraging part of this phase and could no doubt have been exploited but a new approach had by then borne fruit.

The hemiacetals (**8a,b**) were potential intermediates for the introduction of a nitrogen atom. Treatment of compounds (**8a**) and (**8b**) with hydroxylamine hydrochloride in pyridine gave the corresponding oximes (**18a**) and (**18b**) in very high yield as mixtures of *E* and *Z* isomers (~4:1) (Scheme 5).[23] ^{1}H N.m.r.

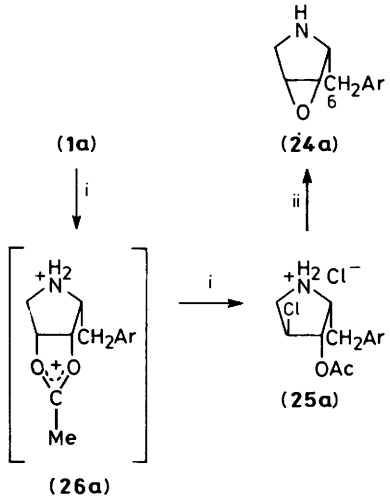


Scheme 5.

spectra showed that only the acyclic oximes were present, the signals for 1-H appearing at low field; no furanosylhydroxylamines were detected. It is well known, and there are many carbohydrate examples,[24] that oximes may be dehydrated to give nitriles using an acid chloride in pyridine. It was envisaged that oximes (**18a,b**) could be converted into the nitrile mesylates (**19a,b**) in one step, thus simultaneously incorporating a leaving group into the molecule. When oxime (**18b**) was added to an excess of methanesulphonyl chloride in pyridine the crystalline nitrile (**19b**) was isolated as the major product together with a small amount of the lactone (**20b**) which probably arose from nitrile (**21b**) through intramolecular attack by the hydroxyl group on the nitrile group.[25] The nitrile mesylate (**19a**) was prepared similarly. The unpurified nitriles (**19a,b**), when treated with lithium aluminium hydride in ether, gave the pyrrolidines (**2a,b**), isolated as their crystalline hydrochlorides, in 48 and 42% overall yield respectively, from the hemiacetals (**8a,b**). The ring-closure step, with inversion of configuration, probably involves either the amines (**3a,b**) (route A) or pyrrolines (**22a,b**) (route B) as intermediates.

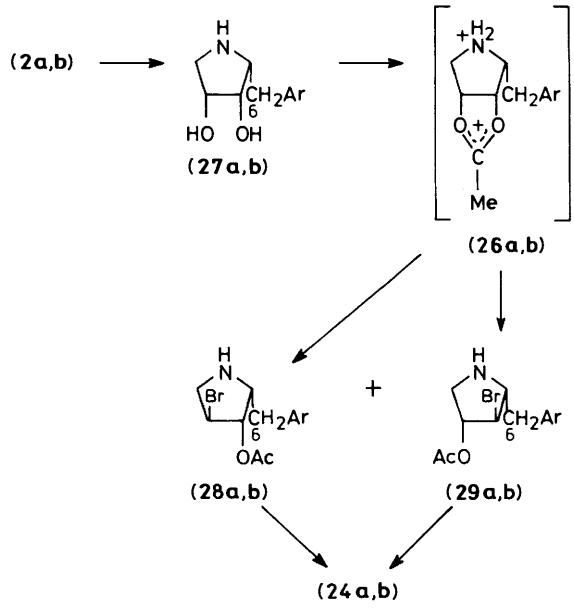
Some unsuccessful attempts were made to achieve reductive amination of the hemiacetals (**8a, b**) using ammonium acetate and sodium cyanoborohydride.[26] We were also unable to convert the oximes (**18a,b**) or the methoximes (**23a,b**) into the corresponding amines using a variety of reducing agents.

With the pyrrolidines (**2a,b**) in hand we had then to complete the manipulation of oxy-substituents on the pyrrolidine ring. The epoxide (**24a**) is a degradation product of anisomycin,[6] by way of the acetoxy chloro compound (**25a**) with the acetoxonium ion (**26a**) as a probable intermediate (Scheme 6).



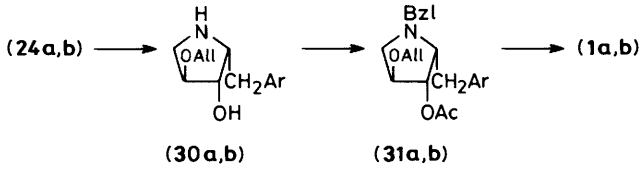
Scheme 6. *Reagents:* i, PCl_5 or $SOCl_2$; ii, KOH

The epoxide (**24a**) has already been used as an intermediate in earlier syntheses of anisomycin.[10a–c,12] The isopropylidene compounds (**2a,b**) were easily converted by acidic hydrolysis into the diols (**27a,b**) (Scheme 7). Treatment of the diols with



Scheme 7.

hydrogen bromide in acetic acid[27] gave the bromo acetates (**28a,b**) and (**29a,b**). After several unsuccessful attempts to convert the esters (**28a,b**) and (**29a,b**) into anisomycin derivatives *via* the acetoxonium ions (**26a,b**) we concentrated on the epoxides (**24a,b**). The mixture of bromo acetates (**28a**) and (**29a**) was easily converted, by aqueous methanolic KOH, into the epoxide (**24a**), identical with a sample prepared from natural anisomycin;[6] the epoxide (**24b**) was prepared similarly. It is known that in the absence of an *N*-substituent the epoxide (**24a**) undergoes regioselective ring opening at C-4 with nucleophiles.[6,10,12] The epoxides (**24a,b**) reacted cleanly with allyl alcohol under acidic condtions to give the allyl ethers (**30a,b**) in over 60% yield (Scheme 8). The ether (**30a**) was *N*-benzylated



Scheme 8.

with benzyl bromide and triethylamine and the product was acetylated to give the anisomycin derivative (**31a**) in 77% yield. The allyl ether grouping was removed by isomerisation in the presence of palladium–charcoal[28] and acidic methanolysis of the resulting propenyl ether; hydrogenation using the same catalyst then removed the *N*-benzyl group to give anisomycin (**1a**) (86%), indistinguishable from an authentic sample. In similar fashion the allyl ether (**30b**) of the phenyl analogue was converted into demethoxyanisomycin (**1b**) in 68% overall yield.

Tests for antibiotic activity were carried out at Pfizer Central Research, Sandwich, by courtesy of Dr. K. Richardson. Tests against four isolates of *Trichomonas vaginalis* showed that synthetic (−)-anisomycin (**1a**) was indistinguishable from anisomycin isolated from natural sources. Demethoxyanisomycin (**1b**) showed about one sixth of the activity, in agreement with Hall and his co-workers[12,29] who have studied a number of racemic analogues.

Experimental

I.r. spectra were measured for KBr discs or for films, using Perkin-Elmer 137, 157G, or 257 spectrophotometers. N.m.r. spectra were recorded on the following spectrometers: Perkin-Elmer R12B (60 MHz), Perkin-Elmer R32 (90 MHz), JEOL MH100 (100 MHz), Bruker WP200SY (200 MHz), Bruker WH270 (270 MHz), and Bruker WM400 (400 MHz) with tetramethylsilane as internal standard. Specific rotations refer to room temperature (20—25 °C) and were measured using a Bendix NPL 143D automatic polarimeter with a path length of 1 cm.

Evaporations were carried out under reduced pressure (rotary evaporator). Light petroleum refers to the fraction of b.p. 30—60 °C. Column chromatography was carried out using silica gel (Merck 7734 or equivalent). For t.l.c., compounds were detected using *p*-anisaldehyde–sulphuric acid in ethanol,[30] followed by heating on an electric plate.

1-*Deoxy*-3,4-O-*isopropylidene*-1-*phenyl*-D-*allitol* (**6b**).—A solution of benzyl chloride (150 g) in dry THF (600 ml) was added dropwise to a vigorously stirred suspension of Mg turnings (40 g) in THF, the temperature being maintained just below the boiling point. [Generally the reaction was initiated by addition of the benzyl chloride solution (20 ml) and a few grains of iodine to the unstirred Mg suspension. When the mixture was heated, a vigorous reaction ensued and the solution became grey-green in colour]. The solution of Grignard reagent was allowed to cool to room temperature and a solution of 2,3-*O*-isopropylidene-D-ribose (**7**)[17] (22 g) in dry THF (440 ml) was added dropwise during 10 min. The mixture was stirred for 1 h after which water (50 ml) was added slowly. The resultant heterogeneous mixture was filtered through a glass wool plug, to remove excess of Mg, into a slurry of NH_4Cl (140 g) in water. After being vigorously shaken the organic phase was decanted and the aqueous slurry was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness and the residue was chromatographed on silica. Dichloromethane eluted all of the non-carbohydrate by-products. Ether eluted, first, some unchanged (**7**) (1 g, 4%) followed by the *allitol* (**6b**) (23 g, 70%), m.p. 93 °C (from ether-light petroleum); $[\alpha]_D$ +5.4° (*c* 1.7 in $CHCl_3$); $\nu_{max.}$(KBr) 3 340 cm^{-1} (OH); δ (100 MHz; $CDCl_3/D_2O$) 1.30 and 1.38 (2 × 3 H, 2 s, CMe_2), 2.60 (1 H, m, 1-H_a), 3.08 (1 H, d, 1-H_b), 3.3—4.1 (6 H, m), and 7.14 (5 H, s, Ph) (Found: C, 63.8; H, 7.8. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85%).

1-*Deoxy*-3,4-O-*isopropylidene*-1-(p-*methoxyphenyl*)-D-*allitol* (**6a**).—A solution of *p*-methoxybenzyl chloride (90 ml), prepared from *p*-methoxybenzyl alcohol and ethereal HCl,[31] without distillation, in dry THF (400 ml) was added, in a similar fashion to the previous experiment, to a suspension of Mg turnings (25 g) in dry THF (130 ml). After the addition of compound (**7**) (15 g) dissolved in THF (300 ml) and work-up as for (**6b**) the *allitol* (**6a**) was obtained as a syrup (19 g, 77%) after column chromatography; $[\alpha]_D$ +0.9° (*c* 1.1 in $CHCl_3$); $\nu_{max.}$(film) 3 380 cm^{-1} (OH); δ [100 MHz; $(CD_3)_2CO$–D_2O] 1.22 and 1.33 (2 × 3 H, 2 s, CMe_2), 2.53 (1 H, m, 1-H_a), 2.90 (1 H, d, $J_{1a,1b}$ 12 Hz, 1-H_b), 3.3—4.2 (6 H, m), 3.62 (3 H, s, OMe), and 6.57—7.03 (4 H, 2 d, arom. A_2B_2) (Found: C, 62.2; H, 7.4. $C_{16}H_{24}O_6$ requires C, 61.5; H, 7.7%).

5-*Deoxy*-2,3-O-*isopropylidene*-5-*phenyl*-β-L-*ribofuranose* (**8b**).—A solution of the triol (**6b**) (20 g) in ethanol (500 ml) was added to $NaIO_4$ (25 g) in water (250 ml). The resulting solution was stirred for 30 min, filtered to remove $NaIO_3$, and the filtrate was extracted with ether. The organic phase was dried ($MgSO_4$) and evaporated to give a syrup which crystallised from ether–light petroleum to give the *hemiacetal* (**8b**) (13.5 g, 76%), m.p. 68 °C; $[\alpha]_D$ −10.1° (*c* 1.5 in $CHCl_3$); $\nu_{max.}$(KBr) 3 420 cm^{-1} (OH); δ (90 MHz; $CDCl_3$) 1.27 and 1.45 (2 × 3 H, 2 s, CMe_2), 2.87 (1 H, dd, $J_{5a,5b}$ 14.2, $J_{5a,4}$ 8.2 Hz, 5-H_a), 3.06 (1 H, dd, $J_{5b,4}$ 7.8 Hz, 5-H_b), 3.55 (1 H, d, OH), 4.50 (1 H, t, 4-H), 4.65 (2 H, s, 2- and 3-H), 5.42 (1 H, d, $J_{1,OH}$ 2.8 Hz, 1-H), and 7.25 (5 H, s, Ph) (Found: C, 67.1; H, 7.2. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.25%).

5-*Deoxy*-2,3-O-*isopropylidene*-5-(p-*methoxyphenyl*)-β-L-*ribofuranose* (**8a**).—A solution of the triol (**6a**) (3 g) in ethanol (70 ml) was added to $NaIO_4$ (3.5 g) in water (35 ml) and treated as for triol (**6b**). This yielded the *hemiacetal* (**8a**) (2.5 g, 93%), m.p. 106 °C; $[\alpha]_D$ −8.9° (*c* 1.2 in $CHCl_3$); $\nu_{max.}$(KBr) 3 400 cm^{-1} (OH); δ (100 MHz; $CDCl_3$) 1.28 and 1.44 (2 × 3 H, 2 s, CMe_2), 2.90 (1 H, dd, $J_{5a,5b}$ 15, $J_{5a,4}$ 9 Hz, 5-H_a), 2.98 (1 H, dd, $J_{5b,4}$ 7.5 Hz, 5-H_b), 3.36 (1 H, d, OH), 3.76 (3 H, s, OMe), 4.42 (1 H, dd, 4-H), 4.64 (2 H, s, 2- and 3-H), 5.42 (1 H, d, $J_{1,OH}$ 2 Hz, 1-H), and 6.84 and 7.12 (4 H, 2 d, arom. A_2B_2) (Found: C, 64.1; H, 7.1. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%).

1-*Deoxy*-3,4-O-*isopropylidene*-1-*phenyl*-D-*ribitol* (**5b**).—A mixture of compound (**8b**) (2.0 g) and $NaBH_4$ (600 mg) in

ethanol (30 ml) was stirred for 1 h. The solution wsa added to dichloromethane (600 ml) and washed with saturated aqueous NH_4Cl. The aqueous layer was extracted with dichloromethane, and the combined organic phases were dried ($MgSO_4$) and evaporated to give the *diol* (**5b**) as a chromatographically homogeneous syrup (1.9 g, 94%) which gelled on attempted crystallisation. For analysis a solid sample was prepared from ether–light petroleum, m.p. 51 °C; $[\alpha]_D$ −1.7° (*c* 1.4 in $CHCl_3$); $\nu_{max.}$(KBr) 3 300 cm^{-1} (OH); δ (100 MHz; $CDCl_3$–D_2O) 1.33 and 1.42 (2 × 3 H, 2 s, CMe_2), 2.6 (1 H, m, 1-H_a), 3.08 (1 H, dd, $J_{1b.2}$ 1.5, $J_{1b.1a}$ 15 Hz, 1-H_b), 3.57 (1 H, dd, $J_{5a.4}$ 6, $J_{5a.5b}$ 13 Hz, 5-H_a), 3.64 (1 H, dd, $J_{5b.4}$ 7 Hz, 5-H_b), 3.90 (2 H, m, 2- and 3-H), 4.15 (1 H, m, 4-H), and 7.19 (5 H, s, Ph) (Found: C, 66.6; H, 8.0. $C_{14}H_{20}O_4$ requires C, 66.65; H, 8.0%).

1-*Deoxy*-3,4-O-*isopropylidene*-1-(p-*methoxyphenyl*)-D-*ribitol* (**5a**).—A mixture of compound (**8a**) (3.5 g) and $NaBH_4$ (1 g) was stirred in ethanol (75 ml) for 1 h. The product was isolated as for (**8b**) above to give a pure syrup (3 g, 85%) which crystallised from benzene–light petroleum to give the *diol* (**5a**), m.p. 75 °C; $[\alpha]_D$ −4.6° (*c* 1.5 in $CHCl_3$); $\nu_{max.}$(KBr) 3 480 cm^{-1} (OH); δ [100 MHz; $(CD_3)_2CO$–D_2O] 1.26 and 1.36 (2 × 3 H, 2 s, CMe_2), 2.51 (1 H, dd, $J_{1a.2}$ 7.8, $J_{1a.1b}$ 15.6 Hz, 1-H_a), 2.90 (1 H, d, 1-H_b), 3.4—4.3 (5 H, m), 3.69 (3 H, s, OMe), and 6.70 and 7.06 (4 H, 2 d, arom. A_2B_2) (Found: C, 63.85; H, 8.0. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85%).

1-*Deoxy*-3,4-O-*isopropylidene*-2,5-*di*-O-*methylsulphonyl*-1-*phenyl*-D-*ribitol* (**4b**) *and* 2,5-*Anhydro*-1-*deoxy*-3,4-O-*isopropylidene*-1-*phenyl*-D-*ribitol* (**9b**).—A solution of the diol (**5b**) (1.5 g) in pyridine (20 ml) was added dropwise during 20 min to a stirred solution of methanesulphonyl chloride (3 ml, 6.45 mol equiv.) in pyridine (15 ml). After 5 min excess of reagent was decomposed by dropwise addition of water (~5 ml) and after addition of more water (25 ml) the product was isolated with ether. The resulting syrup crystallised from ethanol—light petroleum to give the *disulphonate* (**4b**) (1.8 g, 74%), m.p. 73 °C; $[\alpha]_D$ +42.2° (*c* 1.3 in $CHCl_3$); $\nu_{max.}$(KBr) 1 330 and 1 170 cm^{-1} (SO_2Me); δ (90 MHz; $CDCl_3$) 1.33 and 1.53 (2 × 3 H, 2 s, CMe_2), 2.22 (3 H, s, 2-$MeSO_2O$), 3.09 (3 H, s, 5-$MeSO_2O$), 3.17 (2 H, m, 1-H_2), 4.1—4.6 (4 H, m), 5.13 (1 H, q, *J* ~ 6 Hz, 2-H), and 7.36 (5 H, s, Ph) (Found: C, 47.2; H, 6.0; S, 15.3. $C_{16}H_{24}O_8S_2$ requires C, 47.05; H, 5.9; S, 15.7%).

The mother liquors from the crystallisation of the disulphonate (**4b**) were evaporated and the residue was chromatographed on silica. Dichloromethane eluted the *anhydroribitol* (**9b**) as a syrup (150 mg, 11%) which crystallised from ethanol–light petroleum at 20 °C; m.p. 34 °C; $[\alpha]_D$ −67.7° (*c* 0.6 in $CHCl_3$); δ (100 MHz; $CDCl_3$) 1.30 and 1.46 (2 × 3 H, 2 s, CMe_2), 2.70 (2 H, m, 1-H_2), 3.86 (2 H, m, 5-H_2), 4.24 (1 H, dt, $J_{2.1}$ 8.1, $J_{2.3}$ 1.8 Hz, 2-H), 4.44 (1 H, dd, $J_{3.4}$ 7.0 Hz, 3-H), 4.72 (1 H, m, 4-H), and 7.18 (5 H, s, Ph) (Found: C, 71.7; H, 7.7. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%).

The same anhydroribitol (**9b**) resulted when the diol (**5b**) (100 mg) in pyridine (5 ml) was treated with toluene-*p*-sulphonyl chloride (450 mg, ~6 mol equiv.) overnight at room temperature. Excess of acid chloride was hydrolysed with water (0.5 ml) and the product was isolated with ether. The resulting syrup was chromatographed on silica as before to give compound (**9b**) as a syrup (70 mg, 75%) indistinguishable (t.l.c., ^1H n.m.r., i.r.) from the sample prepared above.

1-*Deoxy*-3,4-O-*isopropylidene*-1-(p-*methoxyphenyl*)-2,5-*di*-O-*methylsulphonyl*-D-*ribitol* (**4a**) *and* 2,5-*Anhydro*-1-*deoxy*-3,4-O-*isopropylidene*-1-(p-*methoxyphenyl*)-D-*ribitol* (**9a**).—A solution of the diol (**5a**) (1.5 g) in pyridine (25 ml) was added dropwise during 20 min to a solution of methanesulphonyl chloride (3.75 g, 6.15 mol equiv.) in pyridine (25 ml). The product was isolated as for (**4b**) above; it crystallised from ethanol to give the *disulphonate* (**4a**) (2 g, 86%), m.p. 87 °C; $[\alpha]_D$ +35.4° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$(KBr) 1 340 and 1 165 cm^{-1} (SO_2Me); δ (60 MHz; $CDCl_3$) 1.30 and 1.50 (2 × 3 H, 2 s, CMe_2), 2.76 (3 H, s, 2-$MeSO_2O$), 3.04 (3 H, s, 5-$MeSO_2O$), 3.1 (2 H, m, 1-H_2), 3.67 (3 H, s, OMe), 4.0—4.5 (4 H, m), 5.07 (1 H, m, 2-H), and 6.83 and 7.24 (4 H, 2 d, arom. A_2B_2) (Found: C, 46.9; H, 6.1. $C_{17}H_{26}O_9S_2$ requires C, 46.6; H, 6.0%).

The mother liquors from the crystallisation of the disulphonate (**4a**) were evaporated and the residue was chromatographed on silica. Elution with dichloromethane afforded the *anhydroribitol* (**9a**) as a chromatographically pure syrup (100 mg, 7%); $\nu_{max.}$(film) 2 930, 1 610, 1 510, 1 380, 1 245, 1 035, 855, and 720 cm^{-1}; δ (60 MHz; $CDCl_3$) 1.40 and 1.48 (2 × 3 H, 2 s, CMe_2), 2.72 (2 H, m, 1-H_2), 3.80 (3 H, s, OMe), 3.94 (2 H, d, $J_{5.4}$ 3 Hz, 5-H_2), 4.38 (1 H, dt, $J_{2.1}$ 8, $J_{2.3}$ 2 Hz, 2-H), 4.50 (1 H, dd, $J_{3.4}$ 7.5 Hz, 3-H), 4.84 (1 H, m, 4-H), and 6.80—7.26 (4 H, 2 d, arom. A_2B_2).

2,5-*Anhydro*-1-*deoxy*-3,4-O-*isopropylidene*-1-*phenyl*-D-*arabinitol* (**12**).—A solution of the diol (**5b**) (225 mg) in pyridine (8 ml) containing benzoyl chloride (240 mg, 1.9 mol equiv.) was stirred for 20 min and the excess of benzoyl chloride was destroyed by the addition of water. The crude benzoate (**10**) was isolated with ether and treated with a solution of toluene-*p*-sulphonyl chloride (750 mg, 4.4 mol equiv.) in pyridine (4 ml). The mixture was kept at 50 °C overnight, when aqueous methanol containing KOH (5 g) was added. After 30 min the product was isolated with ether and the residue obtained after evaporation was subjected to chromatography on silica. Dichloromethane eluted the *anhydroarabinitol* (**12**) as a syrup (145 mg, 69%) which crystallised from light petroleum, m.p. 36 °C; $[\alpha]_D$ −79.1° (*c* 4.4 in $CHCl_3$); δ (100 MHz; $CDCl_3$) 1.32 and 1.52 (2 × 3 H, 2 s, CMe_2), 2.98 (2 H, m, 1-H_2), 3.38 (1 H, dd, $J_{5a.5b}$ 12.6, $J_{5a.4}$ 4.2 Hz, 5-H_a), 3.52 (1 H, m, 2-H), 3.96 (1 H, d, 5-H_b), 4.42 (1 H, dd, $J_{3.4}$ 7.0, $J_{2.3}$ 4.0 Hz, 3-H), 4.66 (1 H, dd, 4-H), and 7.22 (5 H, s, Ph) (Found: C, 71.5; H, 7.75. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%).

Reaction of 1-*Deoxy*-3,4-O-*isopropylidene*-2,5-*di*-O-*methylsulphonyl*-1-(p-*methoxyphenyl*)-D-*ribitol* (**4a**) *with Potassium Azide*.—The disulphonate (**4a**) (150 mg) was dissolved in benzene (2 ml) containing potassium azide (30 mg, 1 mol equiv.) and 18-crown-6 (180 mg) and heated under reflux for 12 h. After filtration the filtrate was subjected to chromatography on silica. Elution with light petroleum–ether yielded first the diazide (**14a**) as a syrup (32 mg, 28%); $\nu_{max.}$(film) 2 100 cm^{-1} (N_3); δ (60 MHz; $CDCl_3$) 1.33 and 1.55 (2 × 3 H, 2 s, CMe_2), 2.8—3.1 (2 H, m, 1-H_2), 3.1—3.7 (3 H, m, 2-H and 5-H_2), 3.77 (3 H, s, OMe), 4.0—4.5 (2 H, m, 3- and 4-H), and 6.85 and 7.15 (4 H, 2 d, arom. A_2B_2).

Further elution afforded the monoazide (**13a**) as a syrup (22 mg, 16%); $\nu_{max.}$(film) 2 100 (N_3), 1 350 and 1 170 cm^{-1} (OSO_2Me); δ (60 MHz; $CDCl_3$) 1.25 and 1.43 (2 × 3 H, 2 s, CMe_2), 2.57 (3 H, s, SO_2Me), 2.8—3.1 (2 H, m, 1-H_2), 3.29 (2 H, d, 5-H_2), 3.70 (3 H, s, OMe), 3.7—4.4 (2 H, m, 3- and 4-H), 4.85 (1 H, m, 2-H), and 6.67 and 7.14 (4 H, 2 d, arom. A_2B_2).

1,5-*Dideoxy*-3,4-O-*isopropylidene*-1-(p-*methoxyphenyl*)-2-O-*methylsulphonyl*-5-*phthalimido*-D-*ribitol* (**15a**).—The disulphonate (**4a**) (70 mg) was dissolved in benzene (2 ml) containing potassium phthalimide (90 mg, 3 mol equiv) and 18-crown-6 (170 mg) and the mixture was heated under reflux for 48 h. After filtration the filtrate was chromatographed on silica. Elution with light petroleum–ether gave the *phthalimide* (**15a**) (45 mg, 58%), m.p. 134 °C (from ethanol–light petroleum); $[\alpha]_D$ +43.7° (*c* 1.2 in $CHCl_3$); $\nu_{max.}$(KBr) 1 775 and 1 715 (C=O), 1 340 and 1 170 cm^{-1} (OSO_2Me); δ (60 MHz; $CDCl_3$) 1.28 and 1.61 (2 × 3

H, 2 s, CMe_2), 3.07 (3 H, s, SO_2Me), 3.0—3.35 (2 H, m, 1-H_2), 3.82 (3 H, s, OMe), 3.8—4.8 (4 H, m), 5.2 (1 H, m, 2-H), 6.75 and 7.33 (4 H, 2 d, arom. A_2B_2), and 7.80 (4 H, m, phthalimido arom.) (Found: C, 58.8; H, 5.7; N, 2.8. $C_{24}H_{27}NO_8S$ requires C, 58.9; H, 5.6; N, 2.9%).

1-*Deoxy*-2,5-*di*-O-*methylsulphonyl*-1-*phenyl*-D-*ribitol* (**16**).—A solution of the disulphonate (**4b**) (1.75 g) in ethanol (10 ml) and water (5 ml) containing toluene-*p*-sulphonic acid monohydrate (250 mg) was heated under reflux for 2 h. The reaction mixture was added to $CHCl_3$ (200 ml) and saturated aqueous $NaHCO_3$ (30 ml). The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to give the *diol* (**16**) which was recrystallised from ethanol (1.4 g, 89%), m.p. 126 °C; $[\alpha]_D$ −28.3° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$(KBr) 3 475 and 3 400 (OH), 1 325 and 1 160 cm^{-1} (OSO_2Me); δ [90 MHz; $(CD_3)_2CO$] 2.41 (3 H, s, 2-$MeSO_2O$), 3.12 (3 H, s, 5-$MeSO_2O$), 3.18 (2 H, m, 1-H_2), 3.97 (1 H, m, 4-H), 4.10 (1 H, dd, $J_{3,4}$ 8, $J_{3,2}$ 2 Hz, 3-H), 4.36 (1 H, dd, $J_{5a,5b}$ 11, $J_{5a,4}$ 5 Hz, 5-H_a), 4.59 (1 H, dd, $J_{5b,4}$ 3 Hz, 5-H_b), 5.17 (1 H, ddd, $J_{2,1a}$ 5, $J_{2,1b}$ 7 Hz, 2-H), and 7.21 (5 H, s, Ph) (Found: C, 42.3; H, 5.4; S, 17.5. $C_{13}H_{20}O_8S_2$ requires C, 42.4; H, 5.5; S, 17.4%).

3,4-*Di*-O-*acetyl*-1-*deoxy*-2,5-*di*-O-*methylsulphonyl*-1-*phenyl*-D-*ribitol* (**17**).—The diol (**16**) (400 mg) was treated with acetic anhydride (3 ml) in pyridine (9 ml) for 1 h at room temperature. The product was isolated with ether to give the *diacetate* (**17**) (458 mg, 93%), m.p. 98 °C (from ethanol–light petroleum); $\nu_{max.}$(KBr) 1 730 (CO), 1 350 and 1 170 cm^{-1} (OSO_2Me); δ (270 MHz; $CDCl_3$) 2.19 and 2.20 (2 × 3 H, 2 s, COMe), 2.30 and 3.09 (2 × 3 H, 2 s, SO_2Me), 3.03 (1 H, dd, $J_{1a,1b}$ 14.3, $J_{1a,2}$ 10 Hz, 1-H_a), 3.18 (1 H, dd, $J_{1b,2}$ 3.6 Hz, 1-H_b), 4.45 (1 H, dd, $J_{5a,5b}$ 10.8, $J_{5a,4}$ 6.2 Hz, 5-H_a), 4.66 (1 H, dd, $J_{5b,4}$ 2.4 Hz, 5-H_b), 5.04 (1 H, ddd, $J_{2,3}$ 2.6 Hz, 2-H), 5.31 (1 H, dd, $J_{3,4}$ 5.1 Hz, 3-H), 5.49 (1 H, ddd, 4-H), and 7.32 (5 H, m, Ph) (Found: C, 45.2; H, 5.4; S, 14.3. $C_{17}H_{24}O_{10}S_2$ requires C, 45.1; H, 5.35; S, 14.2%).

(E,Z)-5-*Deoxy*-2,3-O-*isopropylidene*-5-*phenyl*-L-*ribose Oxime* (**18b**).—The hemiacetal (**8b**) (4.8 g) was dissolved in pyridine (90 ml) containing hydroxylamine hydrochloride (2.4 g) and the mixture was stirred for 3 h. The product was isolated with ether and the residue obtained after evaporation of the extract was re-extracted with hot n-heptane. On evaporation the *oxime* (**18b**) was obtained as a syrup (4.8 g, 94%); $[\alpha]_D$ −13.3° (*c* 0.9 in $CHCl_3$); $\nu_{max.}$(film) 3 340 cm^{-1} (OH); δ (90 MHz; $CDCl_3$–D_2O) 1.38 and 1.53 (2 × 3 H, 2 s, CMe_2), 2.5—3.2 (2 H, m, 5-H_2), 3.7—4.3 (3 H, m), 4.76 [0.8 H, dd, $J_{2,1}$ 7.5, $J_{2,3}$ 5.8 Hz, 2-H (*E* isomer)], 5.38 [0.2 H, t, $J_{2,1}$ and $J_{2,3}$ 5.8 Hz, 2-H (*Z* isomer)], 6.89 [0.2 H, d, $J_{1,2}$ 6Hz, 1-H (*Z* isomer)], 7.31 (5 H, s, Ph), and 7.53 [0.8 H, d, $J_{1,2}$ 8 Hz, 1-H (*E* isomer)] (Found: C, 62.6; H, 7.25; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2; N, 5.3%).

(E,Z)-5-*Deoxy*-2,3-O-*isopropylidene*-5-(p-*methoxyphenyl*)-L-*ribose Oxime* (**18a**).—The hemiacetal (**8a**) (2.1 g) in pyridine (40 ml) containing hydroxylamine hydrochloride (770 mg) was treated as for (**18b**) to yield the *oxime* (**18a**) as a syrup (2.2 g, 99%); $[\alpha]_D$ −12.5° (*c* 2.2 in $CHCl_3$); $\nu_{max.}$(film) 3 360 cm^{-1} (OH); δ (60 MHz; $CDCl_3$–D_2O) 1.36, 1.49, and 1.51 (6 H, 3 s, CMe_2), 2.4—3.0 (2 H, m, 5-H_2), 3.6—4.3 (3 H, m), 3.75 (3 H, s, OMe), 4.73 [0.8 H, dd, $J_{1,2}$ 7.5, $J_{2,3}$ 5.5 Hz, 2-H (*E* isomer)], 5.24 [0.2 H, t, 2-H (*Z* isomer)], 6.75—7.30 [4.2 H, m, arom. A_2B_2 and 1-H (*Z* isomer)], and 7.49 [0.8 H, d, $J_{1,2}$ 8 Hz, 1-H (*E* isomer)] (Found: C, 61.1; H, 7.2; N, 4.6. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.2; N, 4.7%).

5-*Deoxy*-2,3-O-*isopropylidene*-5-*phenyl*-L-*ribonolactone* (**20b**).—Pyridinium chlorochromate (PCC)[32] (250 mg) was added to a boiling solution of the acetal (**8b**) (100 mg) in benzene (2 ml) and the mixture was refluxed for 4 h. The benzene solution was decanted from the gummy residue which was further extracted with hot benzene. Evaporation of the combined extracts yielded a brown residue which was dissolved in ether and the solution was filtered through a short column of silica gel which was then washed with more ether. After evaporation the residue crystallised from ether–light petroleum to give the *lactone* (**20b**) (77 mg, 78%), m.p. 139 °C; $[\alpha]_D$ +58.8° (*c* 2.0 in $CHCl_3$); $\nu_{max.}$(KBr) 1 775 cm^{-1} (C=O); δ (100 MHz; $CDCl_3$) 1.27 and 1.38 (2 × 3 H, 2 s, CMe_2), 2.88 (1 H, dd, $J_{5a,5b}$ 16.5, $J_{5a,4}$ 6 Hz, 5-H_a), 3.00 (1 H, dd, $J_{5b,4}$ 6 Hz, 5-H_b), 3.84 (1 H, d, $J_{2,3}$ 6 Hz, 3-H), 4.47 (1 H, d, 2-H), 4.75 (1 H, t, 4-H), and 6.9—7.3 (5 H, s, Ph) (Found: C, 67.85, H, 6.4. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%).

5-*Deoxy*-2,3-O-*isopropylidene*-5-(p-*methoxyphenyl*)-L-*ribonolactone* (**20a**).—The hemiacetal (**8a**) (250 mg) in benzene (4 ml) was treated with PCC (650 mg) as for (**20b**) above. The residue was chromatographed on silica. Light petroleum–ether eluted the *lactone* (**20a**) as a syrup (205 mg, 83%), $[\alpha]_D$ +32.5° (*c* 1.4 in $CHCl_3$); $\nu_{max.}$(film) 1 770 cm^{-1} (CO); δ (100 MHz; $CDCl_3$) 1.30 and 1.39 (2 × 3 H, 2 s, CMe_2), 2.85 (1 H, dd, $J_{5a,5b}$ 16, $J_{5a,4}$ 5 Hz 5-H_a) 2.93 (1 H, dd, $J_{5b,4}$ 6.5 Hz, 5-H_b), 3.72 (3 H, s, OMe), 3.81 (1 H, d, $J_{3,2}$ 6.5 Hz, 3-H), 4.47 (1 H, d, 2-H), 4.75 (1 H, t, 4-H), and 6.72 and 7.04 (4 H, 2 d, arom. A_2B_2) (Found: C, 64.7; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%).

5-*Deoxy*-2,3-O-*isopropylidene*-4-O-*methylsulphonyl*-5-*phenyl*-L-*ribononitrile* (**19b**).—A solution of the oxime (**18b**) (4.8 g) in pyridine (50 ml) was added during 1 h to a vigorously stirred solution of methanesulphonyl chloride (15 ml, 10.7 mol equiv.) in pyridine (35 ml). After a further 1 h at 60 °C the mixture was treated with water, carefully at first, and the product was isolated, with ether, as a syrup (5.2 g, 88%) which was suitable for further reactions.

Chromatography of part of the product on silica, and elution with light petroleum–ether, gave first the pure *nitrile* (**19b**), m.p. 95 °C (from light petroleum); $[\alpha]_D$ +73.6° (*c* 1.4 in $CHCl_3$); $\nu_{max.}$(KBr) 2 110vw (CN), 1 355 and 1 170 cm^{-1} (OSO_2Me); δ (90 MHz; $CDCl_3$) 1.33 and 1.58 (2 × 3 H, 2 s, CMe_2), 2.59 (3 H, s, SO_2Me), 3.03 (1 H, dd, $J_{5a,5b}$ 15, $J_{5a,4}$ 7 Hz, 5-H_a), 3.38 (1 H, dd, $J_{5b,4}$ 4 Hz, 5-H_b), 4.19 (1 H, dd, $J_{3,2}$ 5, $J_{3,4}$ 7 Hz, 3-H), 4.84 (1 H, d, 2-H), 5.02 (1 H, dt, 4-H), and 7.31 (5 H, s, Ph) (Found: C, 55.4; H, 5.9; N, 4.3; S, 9.8. $C_{15}H_{19}NO_5S$ requires C, 55.4; H, 5.9; N, 4.3; S, 9.8%).

Light petroleum–ether also eluted a small amount of the lactone (**20b**), indistinguishable from an authentic sample.

5-*Deoxy*-2,3-O-*isopropylidene*-4-O-*methylsulphonyl*-5-(p-*methoxyphenyl*)-L-*ribononitrile* (**19a**).—A solution of the oxime (**18a**) (1 g) in pyridine (10 ml) was added to a solution of methanesulphonyl chloride (2.7 ml, 10.3 mol equiv.) in pyridine (6 ml) as for oxime (**18b**). After isolation the crude product (1.1 g, 91%) was suitable for the next reaction. A sample was purified by chromatography on silica. Elution with light petroleum–ether gave first the *nitrile* (**19a**) as a syrup, $[\alpha]_D$ +54.9° (*c* 3.0 in $CHCl_3$); δ (90 MHz; $CDCl_3$) 1.39 and 1.62 (2 × 3 H, 2 s, CMe_2), 2.71 (3 H, s, SO_2Me), 3.03 (1 H, dd, $J_{5a,5b}$ 14, $J_{5a,4}$ 7 Hz, 5-H_a), 3.38 (1 H, dd, $J_{5b,4}$ 3.5 Hz, 5-H_b), 3.81 (3 H, s, OMe), 4.20 (1 H, dd, $J_{3,2}$ 5.5, $J_{3,4}$ 7 Hz, 3-H), 4.89 (1 H, d, 2-H), 5.06 (1 H, ddd, 4-H), and 6.90 and 7.30 (4 H, 2 d, arom. A_2B_2) (Found: C, 55.0; H, 6.3; N, 4.4. $C_{16}H_{21}NO_6S$ requires C, 54.1; H, 5.9; N, 3.9%).

Further elution gave a small amount of the lactone (**20a**) indistinguishable from an authentic sample.

(2R,3S,4R)-2-*Benzyl*-3,4-*isopropylidenedioxypyrrolidine* (**2b**).—The crude nitrile (**19b**) (5.2 g) was dissolved in ether (250 ml) and lithium aluminium hydride (2.2 g) was added. The

mixture was stirred vigorously for 2 h. Ethyl acetate (25 ml) was then added and the mixture was stirred for a further 1 h. Water was added carefully until a semi-solid precipitate formed. The clear ether layer was decanted and the solids were washed with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in ether and extracted with 1M-hydrochloric acid, and the aqueous layer, containing the hydrochloride of the pyrrolidine (**2b**), was immediately basified with KOH pellets. The alkaline solution was extracted with ether, and the extract was dried ($MgSO_4$) and evaporated to give the pyrrolidine (**2b**) as a syrup. An ethereal solution of compound (**2b**) was treated with ethereal hydrogen chloride to give the *hydrochloride* which was recrystallised from acetone–light petroleum (2.2 g, 51%), m.p. 270 °C; $[\alpha]_D$ +8.7° (*c* 2.3 in water); $\nu_{max.}$(KBr) 2 890 and 2 715 cm^{-1} ($\overset{+}{N}H_2$); δ (100 MHz; D_2O) 1.29 and 1.74 (2 × 3 H, 2 s, CMe_2), 3.09—3.75 (5 H, m), 4.48 (1 H, dd, $J_{3,4}$ 4.5, $J_{3,2}$ 3 Hz, 3-H), 4.78 (1 H, dd, 4-H), and 7.30 (5 H, m, Ph) (Found: C, 62.15; H, 7.2; N, 5.2. $C_{14}H_{20}ClNO_2$ requires C, 62.3; H, 7.5; N, 5.2%).

(2R,3S,4R)-3,4-*Isopropylidenedioxy*-2-(p-*methoxybenzyl*)-*pyrrolidine* (**2a**).—The crude nitrile (**19a**) (980 mg) was dissolved in ether (50 ml) and lithium aluminium hydride (420 mg) was added. The mixture was treated as described for the nitrile (**19b**) to yield the pyrrolidine (**2a**) as its *hydrochloride*, after recrystallisation from acetone–light petroleum (450 mg, 54%), m.p. 220 °C; $[\alpha]_D$ +11.2° (*c* 1.2 in water); $\nu_{max.}$(KBr) 2 890, 2 730, and 2 580 cm^{-1} ($\overset{+}{N}H_2$); δ (100 MHz; D_2O) 1.42 and 1.63 (2 × 3 H, 2 s, CMe_2), 2.9—3.9 (5 H, m), 3.84 (3 H, s, OMe), 4.9 (2 H, m), and 7.06 and 7.36 (4 H, 2 d, arom. A_2B_2) (Found: C, 59.7; H, 7.3; Cl, 12.3; N, 4.7. $C_{15}H_{22}ClNO_3$ requires C, 60.1; H, 7.3; Cl, 11.85; N, 4.7%).

(2R,3S,4R)-2-*Benzyl*-3,4-*dihydroxypyrrolidine* (**27b**).—A solution of acetonide (**2b**) (100 mg) in methanol (5 ml) and 1M-HCl (2 ml) was boiled under reflux for 3 h. The mixture was evaporated to dryness and the residue was recrystallised from ethanol–ether to give the diol (**27b**) as its *hydrochloride*, m.p. ~255 °C (decomp.); $[\alpha]_D$ +38.2° (*c* 1.8 in water); $\nu_{max.}$(KBr) 3 410 and 3 210 (OH), and 2 890 cm^{-1} ($\overset{+}{N}H_2$); δ (400 MHz; D_2O) 2.94 (1 H, dd, $J_{6a.2}$ 9.0, $J_{6a.6b}$ 14.2 Hz, 6-H_a), 3.06 (1 H, dd, $J_{5a.4}$ 8.0, $J_{5a.5b}$ 12.0 Hz, 5-H_a), 3.16 (1 H, dd, $J_{6b.2}$ 6.2 Hz, 6-H_b), 3.42 (1 H, dd, $J_{5b.4}$ 8.0 Hz, 5-H_b), 3.78 (1 H, ddd, $J_{2.3}$ 3.2 Hz, 2-H), 4.11 (1 H, dd, $J_{3.4}$ 4.0 Hz, 3-H), 4.41 (1 H, dt, 4-H), and 7.22—7.36 (5 H, m, Ph) (Found: C, 57.3; H, 7.0; N, 5.8. $C_{11}H_{16}ClNO_2$ requires C, 57.5; H, 7.0; N, 6.1%).

(2R,3S,4R)-3,4-*Dihydroxy*-2-(p-*methoxybenzyl*)*pyrrolidine* (**27a**).—The acetonide (**2a**) was treated as for (**2b**) above to give the diol (**27a**) as its *hydrochloride*, m.p. ~240 °C (decomp.); $[\alpha]_D$ +29.2° (*c* 1.0 in water); $\nu_{max.}$(KBr) 3 410 and 3 220 (OH), and 2 900 cm^{-1} ($\overset{+}{N}H_2$); δ (400 MHz; D_2O) 2.87 (1 H, dd, $J_{6a.2}$ 9.4, $J_{6a.6b}$ 15.0 Hz, 6-H_a), 3.03 (1 H, dd, $J_{5a.5b}$ 12.5, $J_{5a.4}$ 8.5 Hz, 5-H_a), 3.06 (1 H, dd, $J_{6b.2}$ 6.7 Hz, 6-H_b), 3.38 (1 H, dd, $J_{5b.4}$ 8.5 Hz, 5-H_b), 3.68 (1 H, m, 2-H), 3.69 (3 H, s, OMe), 4.07 (1 H, dd, $J_{3.2}$ 4.2, $J_{3.4}$ 2.9 Hz, 3-H), 4.38 (1 H, dt, 4-H), and 6.86 and 7.19 (4 H, 2 dd, arom. A_2B_2) (Found: C, 55.15; H, 6.95; Cl, 13.3; N, 5.4. $C_{12}H_{18}ClNO_3$ requires C, 55.5; H, 6.9; Cl, 13.65; N, 5.4%).

Reaction of Compound (**27b**) *with* HBr *in Glacial Acetic Acid*.—The diol (**27b**), as its hydrochloride (300 mg), was treated with HBr in glacial acetic acid (45% w/v; 10 ml), at 50 °C for 1 h (lower temperatures and longer reaction times may be used). Solid $NaHCO_3$ was added until the pH of the solution was >2. Further neutralisation was carried out with an aqueous slurry of $NaHCO_3$ and finally with aqueous $NaHCO_3$ solution. Extraction with ether, drying ($MgSO_4$), and evaporation afforded the bromo acetates (**28b**) and (**29b**) as a syrup, $\nu_{max.}$(film) 3 320 (NH) and 1 730 cm^{-1} (CO); δ (400 MHz; $CDCl_3$–CD_3OD) (**28b**): 2.15 (3 H, s, COMe), 2.78—2.93 (2 H, m, 6-H_2), 3.15—3.27 (1 H, d, $J_{5a.5b}$ 13.2 Hz, 5-H_a) 3.73 (1 H, dd, $J_{5b.4}$ 6.0 Hz, 5-H_b), 3.82 (1 H, m, 2-H), 4.21 (1 H, m, 4-H), 5.18 (1 H, brs, 3-H), and 7.13—7.38 (5 H, m, Ph). For (**29b**) (*inter alia*): 2.05 (3 H, s, COMe), 2.96 (1 H, d, $J_{6a.6b}$ 13.8, $J_{6a.2}$ ~ 0 Hz, 6-H_a), 3.11 (1 H, dd, $J_{6b.2}$ 5.6 Hz, 6-H_b), and 5.27 (1 H, m, 3-H).

(2R,3S,4R)-2-*Benzyl*-3,4-*epoxypyrrolidine* (**24b**).—The diol (**27b**), as its hydrochloride (300 mg), was treated with HBr in acetic acid as above. After the reaction most of the HBr was removed by means of a stream of N_2. After 1 h the solution was evaporated to dryness, the residue was dissolved in methanol (5 ml), the solution was treated with KOH (5 g) in water (5 ml). After 10 min the product was isolated with ether and the final crystalline residue was recrystallised from light petroleum at 20 °C to give the *epoxide* (**24b**) (160 mg, 70%), m.p. 60 °C; $[\alpha]_D$ −82.5° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$(KBr) 3 200 cm^{-1} (NH); δ (400 MHz; $CDCl_3$–CD_3OD) 2.75 (1 H, br d, $J_{5a.5b}$ 13.6 Hz, 5-H_a), 2.79 (1 H, dd, $J_{6a.6b}$ 13.2, $J_{6a.2}$ 8.8 Hz, 6-H_a), 2.96 (1 H, dd, $J_{6b.2}$ 5.6 Hz, 6-H_b) 3.17 (1 H, m, 2-H), 3.19 (1 H, d, 5-H_b), 3.38 (1 H, br d, J ~ 2 Hz, 3- or 4-H), 3.57 (1 H, d, J 2.6 Hz, 4- or 3-H), and 7.20—7.43 (5 H, m, Ph) (Found: C, 74.7; H, 7.5; N, 7.8. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%).

(2R,3S,4R)-3,4-*Epoxy*-2-(p-*methoxybenzyl*)*pyrrolidine* (**24a**).—The hydrochloride salt of the diol (**27a**) (150 mg) was treated with HBr in glacial acetic acid (45% w/v; 8 ml) at <15 °C for 3—5 h. Excess of HBr was removed by passage of N_2 and the solution was evaporated to give a syrup which was dissolved in methanol (5 ml) and treated with KOH (5 g) in water (5 ml) for 10 min. The product was isolated with ether and the final residue was crystallised from light petroleum to give the epoxide (**24a**) (80 mg, 68%), m.p. 79 °C (lit.,[6] 78—79 °C), indistinguishable (t.l.c., ^1H n.m.r.) from a sample prepared[6] from natural anisomycin (**1a**); $\nu_{max.}$(KBr) 3 250 cm^{-1} (NH); δ (400 MHz; $CDCl_3$) 1.54 (1 H, br s, NH), 2.71 (1 H, d, $J_{5a.5b}$ 13.4 Hz, 5-H_a), 2.75 (1 H, dd, $J_{6a.6b}$ 13.0, $J_{6a.2}$ 9.0 Hz, 6-H_a), 2.91 (1 H, dd, $J_{6b.2}$ 5.6 Hz, 6-H_b), 3.12 (1 H, m, 2-H), 3.17 (1 H, d, 5-H_b), 3.38 and 3.57 (2 H, 2 d, $J_{3.4}$ 2.8 Hz, 3- and 4-H), 3.79 (3 H, s, OMe), and 6.83 and 7.25 (4 H, 2 d, arom. A_2B_2).

(2R,3S,4S)-4-*Allyloxy*-2-*benzyl*-3-*hydroxypyrrolidine* (**30b**).—The epoxide (**24b**) (50 mg) was added to a mixture of allyl alcohol (2.5 ml), chloroform (7.5 ml), and perchloric acid (70%; 190 mg) and the mixture was heated in an oil-bath at 60 °C for 36—48 h. After dilution with ether (100 ml) the organic phase was extracted with 1M-HCl. The aqueous solution was basified with KOH and the pH was adjusted to ~9. Ether extraction, drying ($MgSO_4$), and evaporation afforded the *allyl ether* (**30b**) (44 mg, 67%), m.p. 147 °C (from ether–light petroleum): $[\alpha]_D$ −36.7° (*c* 0.6 in $CHCl_3$); $\nu_{max.}$(KBr) 3 280 and 3 020 cm^{-1} (OH and NH); δ (100 MHz; $CDCl_3$) 2.24 (2 H, br, NH and OH), 2.54—2.93 (3 H, m, 6-H_2 and 5-H_a), 3.12—3.48 (2 H, m, 5-H_b and 2-H), 3.66—4.00 (4 H, m, 3-H, 4-H, and OCH_2), 4.93—5.27 (2 H, m, $=CH_2$), 5.7 (1 H, m, CH=), and 7.14 (5 H, s, Ph) (Found: 71.4; H, 8.1; N, 6.0. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%).

(2R,3S,4S)-4-*Allyloxy*-3-*hydroxy*-2-(p-*methoxybenzyl*)-*pyrrolidine* (**30a**).—A mixture of the epoxide (**24a**) (78 mg), allyl alcohol (3.5 ml), chloroform (10 ml), and perchloric acid (70%; 250 mg) was treated as for epoxide (**24b**) to yield the *allyl ether* (**30a**) (63 mg, 63%), m.p. 135 °C (from ether–light petroleum); $[\alpha]_D$ −41.6° (*c* 1.1 in $CHCl_3$); $\nu_{max.}$(KBr) 3 280 and 2 020 cm^{-1}

(NH and OH); δ (100 MHz; $CDCl_3$) 2.09 (2 H, br, NH and OH), 2.57—2.93 (3 H, m, 6-H_2 and 5-H_a), 3.12—3.45 (2 H, m, 5-H_b and 2-H), 3.75 (3 H, s, OMe), 3.63—4.00 (4 H, m, 3-H, 4-H, and OCH_2), 5.00—5.33 (2 H, m, $=CH_2$), 5.8 (1 H, m, CH=), and 6.75 and 7.08 (4 H, 2 d, arom. A_2B_2) (Found: C, 68.1; H, 8.0; N, 5.3. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.0; N, 5.3%).

(2R,3S,4S)-3-*Acetoxy*-4-*allyloxy*-1-*benzyl*-2-(p-*methoxybenzyl*)*pyrrolidine* (**31a**).—The allyl ether (**30a**) (55 mg) was dissolved in chloroform (5 ml) containing benzyl bromide (0.15 ml) and triethylamine (0.15 ml) and the solution was stirred for 2 h. Acetic anhydride (1.5 ml) was added and the solution was then stirred at 60 °C for 5 h. After evaporation to dryness the residual *acetate* (**31a**) was obtained as a syrup (64 mg, 77%) after chromatography on silica and elution with light petroleum–ether; $[\alpha]_D$ −101.3° (*c* 1.2 in $CHCl_3$); $\nu_{max.}$ 1 735 cm^{-1} (CO); δ (100 MHz; $CDCl_3$) 2.06 (3 H, s, COMe), 2.14—2.36 (1 H, dd, 5-H_a), 2.66—3.42 (5 H, m, 6-H_2, 5-H_b, and NCH_2Ph), 3.57—4.09 (4 H, m, 2-H, 4-H, and OCH_2), 3.72 (3 H, s, OMe), 4.78—5.24 (3 H, m, 3-H and $=CH_2$), 5.70 (1 H, m, CH=), 6.70 and 6.98 (4 H, 2 d, arom. A_2B_2), and 7.23 (5 H, s, Ph) (Found: M^+, 395.2063. $C_{24}H_{29}NO_4$ requires *M*, 395.2095. Found: $[M + H]^+$ 396.2151. $C_{24}H_{30}NO_4$ requires *m/z*, 396.2173).

(2R,3S,4S)-3-*Acetoxy*-4-*hydroxy*-2-(p-*methoxybenzyl*)*pyrrolidine* [*Anisomycin* (**1a**)].—A solution of the allyl ether (**31a**) (25 mg) in methanol (3 ml) containing 2M-HCl (0.075 ml) was stirred vigorously with palladium–charcoal (10%; 30 mg) for 48 h at reflux. The flask was connected to a hydrogenator and the mixture was stirred for 3 h under a H_2 atmosphere. After filtration of the mixture and evaporation of the filtrate, anisomycin (**1a**) was obtained as its hydrochloride (18 mg, 86%) after crystallisation from ethanol–ether. The hydrochloride was dissolved in saturated aqueous $NaHCO_3$ and immediately extracted with chloroform. The organic phase was dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from ether–light petroleum gave anisomycin (**1a**), m.p. 138 °C (lit.,[6] 140 °C), indistinguishable from an authentic sample [t.l.c., mixed m.p. (140 °C), ^1H n.m.r.]; δ (400 MHz; $CDCl_3$) 2.19 (3 H, s, COMe), 2.55 (2 H, br s, NH and OH), 2.75 (1 H, dd, $J_{5a,5b}$ 11.6, $J_{5a.4}$ 4.8 Hz, 5-H_a), 2.77 (1 H, dd, $J_{6a.6b}$ 13.8, $J_{6a.2}$ 8.2 Hz, 6-H_a), 2.83 (1 H, dd, $J_{6b.2}$ 6.4 Hz, 6-H_b), 3.42 (1 H, dd, $J_{5b.4}$ 6.4 Hz, 5-H_b), 3.53 (1 H, ddd, $J_{2.3}$ 4.8 Hz, 2-H), 3.78 (3 H, s, OMe), 4.19 (1 H, ddd, $J_{4.3}$ 1.6 Hz, 4-H), 4.73 (1 H, dd, 3-H), and 6.79 and 7.16 (4 H, 2 d, *J* 8 Hz, arom. A_2B_2).

(2R,3S,4S)-3-*Acetoxy*-2-*benzyl*-4-*hydroxypyrrolidine* (*Demethoxyanisomycin*) (**1b**).—The allyl ether (**30b**) (30 mg) was dissolved in chloroform (3 ml) and treated, as for (**30a**), with benzyl bromide (0.1 ml), triethylamine (0.1 ml), and finally acetic anhydride (1 ml) to yield crude ester (**31b**). This was then treated with palladium–charcoal (10%; 60 mg) in methanol containing 2M-HCl (0.05 ml) as above to yield *demethoxyanisomycin* (**1b**) as its hydrochloride (24 mg, 68%), m.p. 242 °C (from ethanol–ether); $\nu_{max.}$(KBr) 3 300 (OH), 2 895 ($\overset{+}{N}H_2$), 1 740 (CO), 1 210, 1 070, and 710 cm^{-1}; δ (200 MHz; D_2O) 2.05 (3 H, s, COMe), 2.95 (1 H, dd, $J_{6a.6b}$ 14.8, $J_{6a.2}$ 9.3 Hz, 6-H), 3.05 (1 H, dd, $J_{6b.2}$ 7.0 Hz, 6-H_b), 3.15 (1 H, d, $J_{5a.5b}$ 13.5 Hz, 5-H_a), 3.55 (1 H, dd, $J_{5b.4}$ 4.6 Hz, 5-H_b), 4.13 (1 H, ddd, $J_{2.3}$ 3.5 Hz, 2-H), 4.38 (1 H, d, $J_{4.3} \sim 0$ Hz, 4-H), 4.98 (1 H, br d, 3-H), and 7.08—7.43 (5 H, m, Ph) (Found: C, 56.8; H, 6.6; N, 5.2. $C_{13}H_{18}ClNO_3$ requires C, 57.5; H, 6.7; N, 5.15%).

Acknowledgements

We thank the S.E.R.C. (Studentship to K. A. M.) and the Nuffield Foundation (One-Year Science Research Fellowship to R. H. W.) for financial support, and Dr. K. Richardson (Pfizer Central Research, Sandwich) for providing the biological data and for a generous gift of natural anisomycin.

References

1 Preliminary communication, J. G. Buchanan, K. A. MacLean, H. Paulsen, and R. H. Wightman, *J. Chem. Soc., Chem. Commun.*, 1983, 486.
2 B. A. Sobin and F. W. Tanner, Jr., *J. Am. Chem. Soc.*, 1954, **76**, 4053.
3 S. Ishida, O Yamada, F. Futatsuya, K. Ito, H. Yamamoto, and K. Munakata, Proceedings of the First International Congress of IAMS, 1974, vol. 3, p. 641.
4 A. Jiménez and D. Vázquez, in 'Antibiotics,' ed. F. E. Hahn, Springer Verlag, Berlin, 1979, p. 1, and references therein.
5 A. P. Grollman, *J. Biol. Chem.*, 1967, **242**, 3226.
6 J. J. Beereboom, K. Butler, F. C. Pennington, and I. A. Solomons, *J. Org. Chem.*, 1965, **30**, 2334.
7 J. P. Schaefer and P. J. Wheatley, *Chem. Commun.*, 1967, 578; *J. Org. Chem.*, 1968, **33**, 166.
8 K. Butler, *J. Org. Chem.*, 1968, **33**, 2136.
9 C. M. Wong, *Can. J. Chem.*, 1968, **46**, 1101.
10 (*a*) C. M. Wong, J. Buccini, and J. Te Raa, *Can. J. Chem.*, 1968, **46**, 3091; (*b*) C. M. Wong, J. Buccini, I. Chang, J. Te Raa, and R. Schwenk, *ibid.*, 1969, **47**, 2421; (*c*) S. Oida and E. Ohki, *Chem. Pharm. Bull.*, 1968, **16**, 2086; 1969, **17**, 1405; (*d*) I. Felner and K. Schenker, *Helv. Chim. Acta*, 1970, **53**, 754.
11 J. P. H. Verheyden, A. C. Richardson, R. S. Bhatt, B. D. Grant, W. L. Fitch, and J. G. Moffatt, *Pure Appl. Chem.*, 1978, **50**, 1363.
12 D. P. Schumacher and S. S. Hall, *J. Am. Chem. Soc.*, 1982, **104**, 6076.
13 A. Gateau, A.-M. Sepulchre, A. Gaudemer, and S. D. Géro, *Carbohydr. Res.*, 1972, **24**, 478.
14 J. G. Buchanan, A. D. Dunn, and A. R. Edgar, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1191.
15 W. G. Young and S. Siegel, *J. Am. Chem. Soc.*, 1944, **66**, 354.
16 M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, *J. Am. Chem. Soc.*, 1948, **70**, 2296.
17 N. A. Hughes and P. R. H. Speakman, *Carbohydr. Res.*, 1965, **1**, 171.
18 H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, 1975, **97**, 4602.
19 G. Trummlitz, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, 1975, **40**, 3352.
20 J. A. Secrist III, *J. Org. Chem.*, 1978, **43**, 2925.
21 J. G. Buchanan, A. R. Edgar, D. I. Rawson, P. Shahidi, and R. H. Wightman, *Carbohydr. Res.*, 1982, **100**, 75.
22 C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer, in 'Carbonium Ions,' eds. G. A. Olah and P. v. R. Schleyer, Wiley-Interscience, New York, 1972, vol. III, pp. 1347—1483.
23 P. Finch and Z. Merchant, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1682.
24 V. Deulofeu, *Adv. Carbohydr. Chem.*, 1949, **4**, 119.
25 P. W. Austin, J. G. Buchanan, and R. M. Saunders, *J. Chem. Soc. C*, 1967, 372.
26 R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.
27 B. T. Golding, D. R. Hall, and S. Sakrikar, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1214.
28 R. Boss and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 558.
29 S. S. Hall, D. Loebenberg, and D. P. Schumacher, *J. Med. Chem.*, 1983, **26**, 469.
30 E. Stahl and U. Kaltenbach, *J. Chromatogr.*, 1961, **5**, 166.
31 R. L. Shriner and C. J. Hull, *J. Org. Chem.*, 1945, **10**, 228.
32 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.

Received 1*st November* 1984; *Paper* 4/1863