# C-Glycosyl Nucleosides. VIII.[1] Synthesis of 3-Methylshowdomycin

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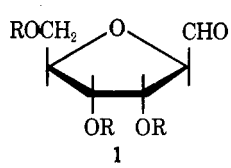
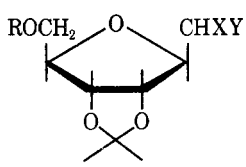
The preparation of 1-carbamoylethylidenedimethylphenylphosphorane (**10**) has been achieved by treatment of the corresponding phosphonium salt with either 1,5-diazabicyclo[4.3.0]non-5-ene or sodium hydride. The reaction of this ylide with methyl phenylglyoxylate leads to modest yields of 3-methyl-2-phenylmaleimide and methyl 3-methyl-2-phenylfumaramate. The reaction of **10** with methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate gives a 30% yield of crystalline 3-methyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)maleimide, which can be debenzylated with boron trichloride giving 3-methylshowdomycin. The condensation of triphenylphosphine with *N*-bromoacetylurea readily gives a phosphonium salt that can be converted to crystalline *N*-carbamoylcarbamoylmethylenetriphenylphosphorane (**20**). The condensation of **20** with methyl pyruvate gives methyl *N*-carbamoyl-2-methylfumaramate, while reaction with methyl phenylglyoxylate gives methyl *N*-carbamoyl-2-phenylfumaramate and 2-phenylmaleimide, the latter via thermal decarbamoylation.

In previous papers in this series we have outlined our general interest in the synthesis of *C*-glycosyl nucleosides. Much of this work has centered about the elaboration of *C*-β-D-ribofuranosyl heterocycles using derivatives of 2,5-anhydro-D-allose (**1**)[3] as starting materials. So far we have described routes for the preparation of maleimide,[4] pyrazole,[5,1] isoxazole,[6] and oxadiazole[1] *C*-glycosides using these generally useful starting materials. In addition, we have developed routes for the stereochemically controlled synthesis of other functionalized *C*-glycosides of general structure **2**[7] (X, Y = H, $CO_2Me$, CN) which open pathways to yet further heterocyclic systems.

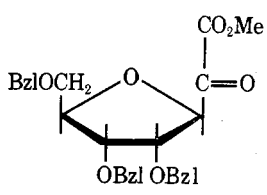



**1**




**2**

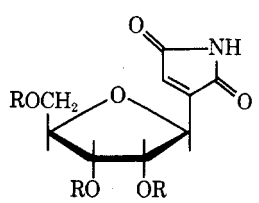
Included in the above work was a facile synthesis of the nucleoside antibiotic showdomycin (**5b**) via the reaction of methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*allo*-heptulosonate (**3**) with carbamoylmethylenetriphenylphosphorane (**4**) followed by debenzylation of the resulting maleimide (**5a**).[4]




**3**



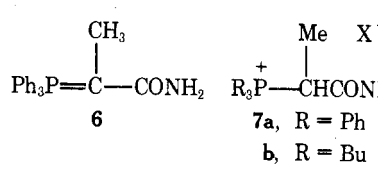

**4**




**5a**, R = Bzl
**b**, R = H

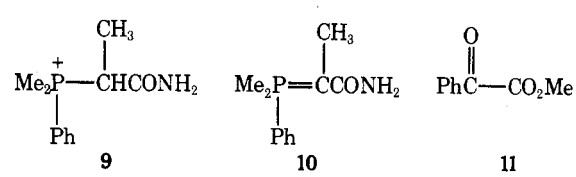
This synthetic route seems capable of extension to the preparation of showdomycin analogs bearing substituents at $C_3$ of the maleimide ring via the corresponding reactions of **3** with carbon-substituted derivatives of the phosphorane **4**. In this paper we describe the synthesis of 3-methyl-2-β-D-ribofuranosylmaleimide (3-methylshowdomycin, **15a**) via such a route.

The simplest appropriate phosphorane would be 1-carbamoylethylidenetriphenylphosphorane (**6**), but, as yet, the synthesis of this compound or its related phosphonium salt (**7a**) has eluded us. Thus, all our attempts to react 2-chloropropionamide[8] with triphenylphosphine in diverse solvents, or in the absence of solvent, at 100–150°, failed to yield the desired phosphonium salt. The comparable reaction using chloroacetamide, however, readily provides the phosphonium precursor of **4**.[9] On the other hand, the more reactive 2-bromopropionamide[10] reacted readily with triphenylphosphine in acetonitrile under nitrogen at 40–50°, giving triphenylphosphine oxide and hydrogen bromide. This reaction presumably proceeds by way of the enolphosphonium salt **8** in a way similar to that shown for more highly halogenated amides,[11] and reminiscent of the Perkow reaction.[12]

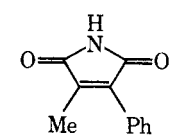



**6** **7a**, R = Ph **b**, R = Bu **8**

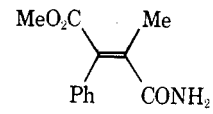
The above reaction could, however, be successfully accomplished using more highly nucleophilic phosphines. Thus 2-bromopropionamide reacted readily with tributylphosphine and with dimethylphenylphosphine in acetonitrile at 50–60° to form the corresponding crystalline phosphonium salts (**7b** and **9**) in yields of 44 and 81%, respectively. In view of the higher yield achieved in the preparation of **9**, the rest of our work has been done using that compound. The conversion of **9** to the ylide 1-carbamoylethylidenedimethylphenylphosphorane (**10**) has been in-




**9** **10** **11**




**12**



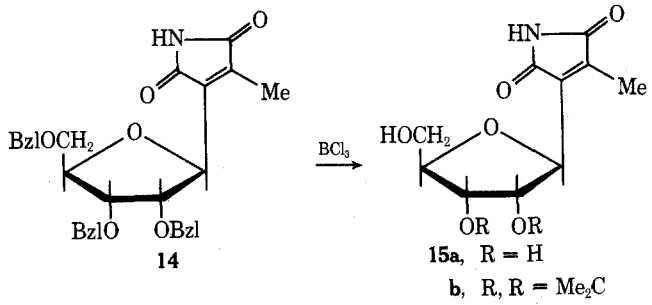

**13**

vestigated under a number of conditions. As expected, **10** was much less stable than **4** and its attempted preparation by treating **9** with aqueous sodium hydroxide led only to dimethylphenylphosphine oxide.[13] The ylide could, how-

ever, be generated by treatment of **9** with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) in a mixture of chloroform and dimethyl sulfoxide. Its formation was confirmed by its reaction at 65° with methyl phenylglyoxylate (**11**), which led to the isolation of crystalline 3-methyl-2-phenylmaleimide (**12**) and methyl 3-methyl-2-phenylfumaramate (**13**) in yields of 17 and 18%, respectively. The structures of these products were clear from their elemental analyses and NMR spectra. Variations in the reaction temperature and solvent did not improve the above yields. The formation of roughly equal amounts of **12** and **13** is quite consistent with what was observed earlier from the reaction of **4** and **10** and indicates little steric preference in the initial formation of **13** and its *Z* isomer.

Attempted direct extension of the above model to the desired reaction of **10** with the *C*-glycosyl keto ester **3** led to only traces of product with a TLC mobility close to that of **5a.** Because of this and the rather low yields of **12** and **13** obtained following generation of the ylide with DBN, we considered other methods for the conversion of **9** to **10** but were unsuccessful using sodamide or butyllithium in ether.[14] Treatment of **9** with slightly less than 1 equiv of sodium hydride in dimethyl sulfoxide at room temperature, however, led to the quite rapid formation of the ylide **10** as a yellow solution. Separately the keto ester **3** was prepared, as previously described,[4] by oxidation of an epimeric mixture of the corresponding hydroxy esters with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of dichloroacetic acid.[15] In view of the lability of **3**, this compound was added, without any purification, to the ylide solution above and allowed to react at room temperature. By TLC it could be shown that a fairly rapid reaction ensued with formation of dimethylphenylphosphine oxide and a nucleoside with the expected mobility just greater than that of **5a.** By chromatography of the products on a column of silicic acid crystalline 3-methyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)maleimide (**14**) was isolated in an overall yield of 30% from the mixed hydroxy esters. Debenzylation of **14** was readily achieved upon treatment with boron trichloride in methylene chloride at −78° for 2 hr. Following destruction of the excess boron trichloride with methanol and removal of the volatile methyl borate a crystalline residue was obtained. Direct recrystallization then gave pure 3-methyl-2-β-D-ribofuranosylmaleimide (3-methylshowdomycin, **15a**) in a yield of 81%.

**3** + **10** →




**14**

**15a**, R = H

**b**, R, R = $Me_2C$

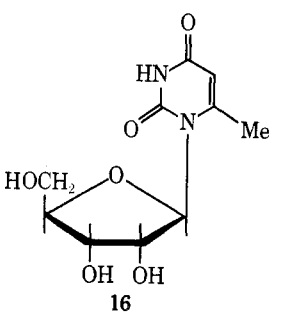
The $^1H$ NMR spectra of **15a** and of showdomycin (**5b**) are generally similar although $C_{2'}H$ and $C_{3'}H$ are deshielded by 0.17 and 0.16 ppm in **15a.** The most significant feature of the spectrum of **15a** is, of course, the absence of a vinyl proton at $C_3$ of the maleimide ring and the presence of a three-proton singlet at 1.99 ppm. The absence of $C_3H$ also leads to the appearance of $C_{1'}H$ as a doublet while that in showdomycin is a doublet of doublets due to allylic coupling. The mass spectrum of **15a** was quite typical of other *C*-glycosides[16] and showed major fragments corresponding to loss of water from the molecular ion, and cleavage of the sugar ring giving a B + 30 ion. To our surprise **15a** showed a negative rotation ($[\alpha]_D$ −39.5°) and a negative optical rotatory dispersion spectrum centered about 286 nm, while showdomycin is dextrorotatory[17] and shows a positive Cotton effect ($[\Phi]^{pk}_{309}$ 1000°, $[\Phi]_{288}$ 0°, $[\Phi]^{tr}_{254}$ −7,600°). We have previously shown[4] that no epimerization accompanies the preparation of **3** under the oxidative conditions used for its synthesis. Also, since only 0.87 molar equiv of sodium hydride was used relative to the crystalline phosphonium salt (**9**) during preparation of **10,** basic conditions which could lead to epimerization giving an α-nucleoside were avoided. While the rather large value of $J_{1',2'}$ (6.8 Hz) does not allow an assignment of anomeric configuration, the observed chemical shift of $C_{1'}H$ strongly suggests that **15a** has the desired β configuration. Thus, it is well known that in *N*-glycosides $C_{1'}H$ occurs roughly 0.5 ppm upfield in β-D-ribofuranosyl nucleosides relative to their α anomers.[18] The same is generally true for the known anomeric pairs of *C*-glycosyl nucleosides, $C_{1'}H$ in β-pseudouridine[19] and β-pyrazomycin[20] appearing 0.2–0.3 ppm upfield of the same proton in the α anomers. Since in $Me_2SO$-$d_6$–$D_2O$ $C_{1'}H$ of **15a** appears at 4.60 ppm, which is very close to that of showdomycin itself (4.53 ppm), it is quite unlikely that we are dealing with an α anomer. A very similar argument was used earlier in assigning the β configuration to showdomycin.[19a]

In an effort to provide unequivocal assignment of anomeric configuration, **15a** was converted in 96% yield into its 2′,3′-*O*-isopropylidene derivative (**15b**). Unfortunately the $^1H$ NMR spectra of **15b** in several solvents failed to resolve $C_{1'}H$ from $C_{2'}H$ and $C_{3'}H$ and hence it was not possible to observe a value of $J_{1',2'}$ sufficiently small to permit unequivocal assignment of the β configuration.[18] Several lines of supporting evidence were, however, available from an examination of the $^{13}C$ NMR spectra of **15b** and of 2′,3′-*O*-isopropylideneshowdomycin[17] prepared by the same route. Previous work has shown that the chemical shift of the anomeric carbon can be used to distinguish between α- and β-furanosides in *O*-glycosides,[21a] *N*-glycosides,[21b] and a few *C*-glycosides.[21c] In each case the isomer having the aglycone and the $C_{2'}$-oxygen function in a cis relationship (α-D-ribo) showed $C_{1'}$ at higher field. Recent work from this laboratory[7] has extended this work to a variety of *C*-glycosides with similar results, $C_1$ of the $C_1$–$C_2$ cis isomers appearing 2–4 ppm upfield of those in the trans counterparts. As expected,[22] the presence of the $C_3$-methyl group in **15b** led to significant α and β shifts of $C_2$ and $C_3$ relative to 2′,3′-*O*-isopropylideneshowdomycin while the other carbons had very similar chemical shifts (see Experimental Section). The cis $C_3$-methyl would also be expected to lead to a modest (several parts per million) upfield γ shift of $C_{1'}$ in **15b.** Based upon earlier work,[7,21c] if **15b** were to have an α configuration an additional upfield shift of 2–4 ppm would be observed owing to the cis relationship of $C_2$ and $C_{2'}$-OH. In fact, the chemical shift of $C_{1'}$ in **15b** (78.86 ppm) is only 1.5 ppm upfield of that in 2′,3′-*O*-isopropylideneshowdomycin, a fact which further supports the β configuration. The assignments for individual carbons were confirmed by both off-resonance and single-frequency decoupling techniques.[22]

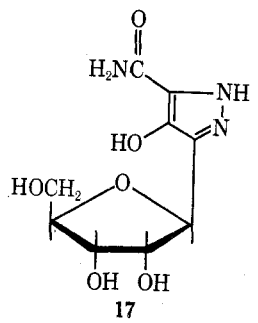
Still further confirmation comes from consideration of the $^{13}C$ and $^1H$ NMR signals of the isopropylidene function in **15b.** Thus the proton chemical shift difference between the isopropylidene methyl signals in **15b** was found to be 24 Hz, a figure that is compatible with a β configuration but far in excess of that for an α nucleoside.[23] Finally, we have recently pointed out that the $^{13}C$ chemical shifts for the methyl groups in the 2′,3′-*O*-isopropylidene derivatives of a

variety of C-glycosides appear at 25.5 ± 0.2 and 27.5 ± 0.2 ppm while those in the α anomers are at 24.9 ± 0.3 and 26.3 ± 0.2 ppm, respectively.[7] The observed figures for **15b** are 25.49 and 27.83 ppm, while those for 2′,3′-O-isopropylideneshowdomycin are 25.43 and 27.60 ppm, both in good agreement with the β configuration. The chemical shifts for the central isopropylidene carbon in a variety of C-glycosides are somewhat more variable but, after exclusion of one anomalous pair (compounds **10e** and **11e** in ref 22), occur at 114.20 ± 1.0 and 112.88 ± 0.5 ppm for the $C_1$-$C_2$-trans and $C_1$-$C_2$-cis isomers, respectively.[7] Once again, the observed values of 114.53 ppm for **15b** and of 114.92 ppm for 2′,3′-O-isopropylideneshowdomycin are compatible only with the β configuration. Taken together, the various NMR parameters of **15a** and **15b** would appear to provide convincing evidence that the β isomer expected from the method of synthesis is indeed present.

We interpret the inverted optical rotatory properties of **15a** as compared to showdomycin as an indication that the presence of the $C_3$-methyl group leads to an inversion of the normal anti glycosyl conformation. This situation is very similar to that shown by 6-methyluridine (**16**), which is known to have an opposite ORD spectrum to that of uridine or 5-methyluridine.[24] On the basis of NMR studies,[24b]




16

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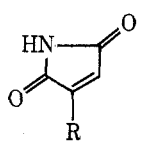
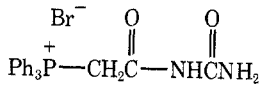



18a, R = Me
b, R = Ph

dipole moment measurements,[25] and X-ray crystallography,[26] 6-methyluridine, unlike its 5-methyl counterpart, has been shown to adopt the syn conformation, which is responsible for the optical effects referred to above. A similar syn conformation for 3-methylshowdomycin (**15**) would explain not only the observed optical properties but also the deshielding of $C_{2'}H$ and $C_{3'}H$ relative to the same protons in showdomycin, this same effect being noted in 6-methyluridine.[24b] It might also be pointed out that the antibiotic pyrazomycin (**17**), which is known to adopt a syn conformation in the crystal state,[27] also shows a negative Cotton effect in its circular dichroism spectrum.[20] Taken in concert, the above observations make us confident that 3-methylshowdomycin represents a further example of a nucleoside possessing a stable syn conformation.

A recent paper by Titani and Tsuruta[28] has discussed the various biological characteristics of showdomycin relative to those of the model compounds N-ethylmaleimide (NEM) and citraconimide **18a**). While marked similarities exist between showdomycin and NEM with respect to radiosensitization and reaction with thiols, citraconimide (**18a**), although a much closer structural analog, was much less active. 3-Methylshowdomycin is something of a structural hybrid of **5b** and **18** and it is interesting to note that, at least with respect to antibacterial activity, **15a** showed a marked reduction in activity with respect to showdomycin itself.[29]

Finally, we have briefly investigated the preparation of N-carbamoylcarbamoylmethylenetriphenylphosphorane (**20**), an ylide that appeared to offer a facile route to N-carbamoylmaleimides. The reaction of triphenylphosphine with N-bromoacetylurea[30] took place readily in acetonitrile at 50°, giving the crystalline phosphonium salt **19** in 75% yield. Treatment of **19** with aqueous sodium hydroxide led to the direct crystallization of the rather stable ylide **20** in almost quantitative yield. A reaction between **20** and methyl phenylglyoxylate (**11**) in chloroform under reflux gave, as its major product, a 35% yield of crystalline methyl N-carbamoyl-2-phenylfumaramate (**21a**) together with 15% of 2-phenylmaleimide (**18b**). The assignment of the E config-

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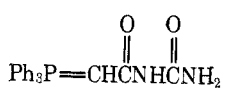
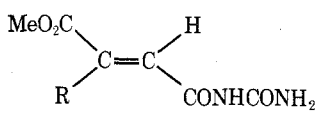



20




21a, R = Ph
b, R = Me

uration to **21a** is based largely upon analogy with the previously described reactions of **11** with **4** and **10**, the product with the Z configuration in each case undergoing spontaneous cyclization to a maleimide. In the present case the initially formed N-carbamoyl-2-phenylmaleimide appears to have undergone very mild thermal loss of the carbamoyl group giving **18b**, a reaction for which there is ample precedent.[31] A comparable reaction between **20** and methyl pyruvate in chloroform at room temperature led to the formation of only one significant product in addition to triphenylphosphine oxide. Separation of these compounds by chromatography on silicic acid was not complete but crystallization of the pure fractions gave methyl N-carbamoyl-2-methylfumaramate (**21b**) in 67% yield. Once again the E configuration is assumed because of the previously reported predominant formation of methyl 2-methylfumaramate from **4** and methyl pyruvate. Support for the configurations of both **21a** and **21b** comes from an examination of their NMR spectra.[32] Thus the single vinyl protons in **21a** and **21b** appear at 7.17 and at 6.95 ppm, respectively, in $Me_2SO$-$d_6$. These chemical shifts are very close to those that we have found for the related E compounds methyl 2-methylfumaramate (6.80 ppm) and methyl 2-phenylfumaramate (7.04 ppm) in $CDCl_3$[4] and that others have shown for dimethyl 2-methylfumarate (6.71 ppm).[33] They are quite different, however, from the chemical shift of the vinyl proton in dimethyl 2-methylmaleate (Z configuration, 5.77 ppm).[33] In general, the anisotropic effects of amide and ester functions are quite similar and differences in solvent would not be expected to lead to anything approaching chemical shift differences of 1 ppm. Hence we feel confident that the E stereochemistry of **21a,b** is correct and that, as with simple amides, formation of the Z amido esters leads to spontaneous cyclization to an N-substituted maleimide. In view of the ready decarbamoylation of N-carbamoylmaleimides mentioned above, the reaction of **3** and **20** has not been explored.

By extension of the above work to the preparation of other types of 2-substituted carbamoylmethylene ylides it would appear possible to develop syntheses of various 2,3-

substituted maleimides. In particular, the preparation of other 3-substituted derivatives of showdomycin would be of interest and is being considered.

## Experimental Section

**General Methods.** The general methods used are the same as those described previously.[4]

**Tri-*n*-butyl-1-carbamoylethylphosphonium Bromide (7b).** A mixture of 2-bromopropionamide (300 mg, 2 mmol)[10] and tributylphosphine (400 mg, 2 mmol) in acetonitrile (5 ml) was stirred under nitrogen at 60° for 6 hr and then at room temperature overnight. The solution was diluted with ethyl acetate (50 ml) and extracted with water (25 ml). The aqueous phase was evaporated to dryness and the residue was coevaporated with toluene, leaving a clear syrup that crystallized upon treatment with ether, giving 310 mg (44%) of **7b**: mp 126–128°; NMR ($CDCl_3$) 1.0 (m, 9, $CH_3$), 1.57 (dd, 3, $J_{H,H}$ = 8, $J_{P,H}$ = 18 Hz, $PCHCH_3$), 1.5 (m, 12, $CH_2$'s), 2.3 (m, 6, $PCH_2$), 4.90 ppm (dq, 1, $J_{H,H}$ = 8, $J_{P,H}$ = 12 Hz, PCHCO).

Anal. Calcd for $C_{15}H_{33}BrNOP$ (354.34): C, 50.85; H, 9.39; N, 3.95; Br, 22.55. Found: C, 50.97; H, 9.51; N, 3.81; Br, 22.37.

**1-Carbamoylethylidenedimethylphenylphosphonium Bromide (9).** Dimethylphenylphosphine (10.35 g, 75 mmol) was added dropwise under nitrogen to a solution of 2-bromopropionamide (11.4 g, 75 mmol) in acetonitrile (150 ml) at 50° and then held at 50° for 3 hr. The mixture was diluted with ethyl acetate and the resulting suspension was extracted with water. Following evaporation of the water the residue was coevaporated with toluene and crystallized twice from acetonitrile–ethyl acetate, giving 18.34 g (81%) of **9**: mp 188.5–190°; NMR ($Me_2SO$-$d_6$) 1.35 (dd, 3, $J_{H,H}$ = 7, $J_{P,H}$ = 18 Hz, $PCHCH_3$), 2.32 (dd, 6, $J_{PCH}$ = 14, $J_{H,PCH}$ = 2 Hz, $PMe_2$), 4.00 (m, 1, PCHCO), 7.55 (br s, 2, $CONH_2$), 7.6–8.1 (m, 5, Ar).

Anal. Calcd for $C_{11}H_{17}BrNOP$ (290.17): C, 45.53; H, 5.91; N, 4.83; Br, 27.54. Found: C, 45.58; H, 5.91; N, 4.58; Br, 27.35.

**Generation of Ylide 10 and Reaction with Methyl Phenylglyoxylate (11).** A solution of 1,5-diazabicyclo[4.3.0]non-5-ene in chloroform (0.5 ml of 1 *M*, 0.5 mmol) was added to a solution of the phosphonium salt (**9**, 160 mg, 0.55 mmol) in dimethyl sulfoxide (1 ml) and stored under nitrogen for 30 min. The resulting solution was added to a solution of **11** (82 mg, 0.5 mmol) in chloroform and heated at 65° for 20 min. The mixture was cooled, diluted with ethyl acetate, washed three times with water, dried, and evaporated, leaving a syrup. The latter was chromatographed on a 1.5 × 18 cm column of silicic acid using hexane–ether (2:1) which separated dimethylphenylphosphine oxide from two more polar products. The faster, fluorescent product (36 mg) was crystallized from chloroform–hexane giving 16 mg (17%) of 3-methyl-2-phenylmaleimide (**12**): mp 177–178.5°; $\lambda_{max}$ (MeOH) 223 nm ($\epsilon$ 18900), 252 (sh, 7900), 322 (4000); $\nu_{max}$ (KBr) 3225 (NH), 1710, 1770 $cm^{-1}$ (imide); NMR ($CDCl_3$) 2.14 (s, 3, $CH_3$), 7.45 ppm (m, 6, Ar and NH).

Anal. Calcd for $C_{11}H_9NO_2$ (187.20): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.57; H, 4.84; N, 7.35.

The most polar product (31 mg) was crystallized from chloroform–hexane, giving 20 mg (18%) of methyl 3-methyl-2-phenylfumaramate (**13**): mp 155–155.5°; $\lambda_{max}$ (MeOH) only broad end absorption with a shoulder ($\epsilon$ 6700) at 244 nm; $\nu_{max}$ (KBr) 3370 (NH), 1725 ($CO_2Me$), 1635, 1585 $cm^{-1}$ (CONH); NMR ($CDCl_3$) 2.19 (s, 3, $CH_3$), 3.75 (s, 3, $CO_2Me$), 5.0 and 5.3 (br s, 1, $NH_2$), 7.33 ppm (s, 5, Ar).

Anal. Calcd for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.96; H, 6.06; N, 6.30.

**3-Methyl-2-(2,3,5-tri-*O*-benzyl-$\beta$-D-ribofuranosyl)maleimide (14).** Dichloroacetic acid (0.205 ml, 2.5 mmol) was added to a stirred solution of a mixture of methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate and its D-glycero-D-altro isomer (2.25 g, 4.56 mmol)[4] and dicyclohexylcarbodiimide (2.6 g, 12.5 mmol) in dimethyl sulfoxide (25 ml) and benzene (25 ml) at 0°. The mixture was then stored at room temperature for 40 min and a solution of oxalic acid (950 mg, 7.5 mmol) in water (25 ml) was added portionwise. After stirring for 20 min the mixture was diluted with ethyl acetate (100 ml) and filtered. The organic phase was washed four times with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated to a syrup. The latter was dissolved in ethanol (25 ml), filtered, evaporated, and coevaporated three times with benzene (10 ml).

Separately, benzene-washed sodium hydride (240 mg, 10 mmol) was added in a drybox under nitrogen to a suspension of **9** (4.5 g, 11.5 mmol) in anhydrous dimethyl sulfoxide (12 ml) and stored at room temperature for 2 hr. The resulting yellow solution was then added to a solution of the keto ester **3** prepared as above in benzene (100 ml) and stirred at room temperature for 1.5 hr. The mixture was then diluted with benzene (200 ml), filtered, and washed four times with saturated aqueous sodium chloride and then with water, dried ($MgSO_4$), and evaporated, leaving 1.7 g of a syrup. This material was purified by preparative TLC using two developments with ether–hexane (1:1). Elution of the major band gave 710 mg (30%) of **14** as a TLC homogeneous crystalline product: mp 86–87° from ether–hexane; $\lambda_{max}$ (MeOH) 209 nm ($\epsilon$ 31100), 227 (sh, 14200); $[\alpha]^{23}D$ −6.0° (*c* 0.14, $CHCl_3$); NMR ($CDCl_3$) 1.94 (s, 3, $CH_3$), 3.51 (dd, 1, $J_{gem}$ = 12, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 3.69 (dd, 1, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.01 (dd, 1, $J_{2',3'} = J_{3',4'}$ = 5 Hz, $C_{3'}H$), 4.3 (m, 2, $C_{2'}H$, $C_{4'}H$), 4.45–4.75 (m, 6, $OCH_2Ar$), 4.91 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 7.3 ppm (m, 15, Ar).

Anal. Calcd for $C_{31}H_{31}NO_6$ (513.60): C, 72.50; H, 6.08; N, 2.73. Found: C, 72.46; H, 6.20; N, 2.82.

**3-Methyl-2-$\beta$-D-ribofuranosylmaleimide (15a).** A chilled solution of **14** (500 mg, 0.97 mmol) in methylene chloride (5 ml) was gradually added through a septum to a solution of boron trichloride (~4 g) in methylene chloride (40 ml) at −78°. After 2 hr at −78° the cooling bath was removed and a mixture of methanol and methylene chloride (1:1, 35 ml) was added dropwise. The solvents were then evaporated in vacuo and the residue was coevaporated four times with methanol (30 ml), leaving a crystalline residue. Recrystallization from acetone–benzene gave 190 mg (81%) of **15a**: mp 165–166°; $\lambda_{max}$ 223 nm ($\epsilon$ 14100); $[\alpha]^{23}D$ −39.5° (*c* 1.0, MeOH); ORD (MeOH) $[\Phi]^{pk}_{308}$ −4200°, $[\Phi]_{286}$ 0°, $[\Phi]^{pk}_{240}$ 6500°; mass spectrum (70 eV) *m/e* 244 ($M^+ + H$), 225 ($M^+ - H_2O$), 140 (base + $CH_2O$); NMR ($Me_2SO$-$d_6$–$D_2O$) 1.99 (s, 3, $CH_3$), 3.55 (m, 2, $C_{5'}H_2$), 3.81 (m, 1, $C_{4'}H$), 3.93 (dd, 1, $J_{2',3'}$ = 5, $J_{3',4'}$ = 3.5 Hz, $C_{3'}H$), 4.11 (dd, 1, $J_{1',2'}$ = 6.8 Hz, $C_{2'}H$), 4.60 ppm (d, 1, $C_{1'}H$).

Anal. Calcd for $C_{10}H_{13}NO_6$ (243.22): C, 49.38; H, 5.39; N, 5.76. Found: C, 49.54; H, 5.49; N, 5.94.

**2-(2,3-*O*-Isopropylidene-$\beta$-D-ribofuranosyl)-3-methylmaleimide (15b).** Perchloric acid (0.05 ml, 70%) was added to a solution of **15a** (45 mg, 0.185 mmol) in acetone (10 ml) and 2,2-dimethoxypropane (0.5 ml). After 15 min at room temperature the mixture was neutralized to pH 7 by careful addition of methanolic ammonia and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water and the organic phase was dried ($MgSO_4$) and evaporated. The residue was freed from acetone polymers by preparative TLC using chloroform–methanol (19:1), elution of the major band giving 50 mg (96%) of **15b** as a foam: $\lambda_{max}$ (MeOH) 223 nm ($\epsilon$ 14800); $[\alpha]^{23}D$ −72.3° (*c* 0.3, $CHCl_3$); $^1H$ NMR ($CDCl_3$–$D_2O$) 1.35 and 1.59 (s, 3, $CMe_2$), 2.05 (s, 3, $CH_3$), 3.67 (dd, 1, $J_{gem}$ = 12, $J_{4',5'a}$ = 2 Hz, $C_{5'a}H$), 3.85 (dd, 1, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.30 (ddd, 1, $J_{3',4'}$ = 2 Hz, $C_{4'}H$), 4.28–4.47 ppm (m, 3, $C_{1'}H$, $C_{2'}H$, $C_{3'}H$); $^{13}C$ NMR ($CDCl_3$) 8.77 ($C_3$ $CH_3$), 25.49 and 27.83 ($CMe_2$), 63.00 ($C_{5'}$), 78.86 ($C_{1'}$), 82.77 ($C_{3'}$), 84.04 ($C_{2'}$), 85.11 ($C_{4'}$), 114.53 ($CMe_2$), 136.96 ($C_3$), 142.72 ($C_2$), 170.38, and 170.84 ppm (C=O).

Anal. Calcd for $C_{13}H_{17}NO_6$ (283.29): C, 55.12; H, 6.05; N, 4.95. Found: C, 54.98; H, 6.30; N, 4.69.

**2',3'-*O*-Isopropylideneshowdomycin.** Showdomycin (100 mg, 0.44 mmol) was treated as above for **15b**. Following preparative TLC the product could be crystallized from ethyl acetate, giving 75 mg (64%) of 2',3'-*O*-isopropylideneshowdomycin with mp 138–139° (reported[17] mp 140.5–141°); $^1H$ NMR ($CDCl_3$) 1.37 and 1.59 (s, 3, $CMe_2$), 3.68 (dd, 1, $J_{gem}$ = 12, $J_{4',5'a}$ = 2.5 Hz, $C_{5'a}H$), 3.87 (dd, 1, $J_{4',5'b}$ = 2.5 Hz, $C_{5'b}H$), 4.27 (ddd, $J_{3',4'}$ = 2.5 Hz, $C_{4'}H$), 4.7–4.9 (m, 3, $C_{1'}H$, $C_{2'}H$, $C_{3'}H$), 6.62 ppm (s, 1, $C_3H$); $^{13}C$ NMR ($CDCl_3$) 25.43 and 27.60 ($CMe_2$), 62.87 ($C_{5'}$), 80.36 ($C_{1'}$), 82.35 ($C_{3'}$), 84.13 ($C_{2'}$), 85.37 ($C_{4'}$), 114.92 ($CMe_2$), 130.39 ($C_3$), 146.52 ($C_2$), 169.57 and 170.48 ppm (C=O).

***N*-Carbamoylcarbamoylmethyltriphenylphosphonium Bromide (19).** A solution of triphenylphosphine (26.2 g, 0.1 mol) and *N*-bromoacetylurea (18.1 g, 0.1 mol)[27] in acetonitrile (500 ml) was heated under nitrogen at 50° for 6 hr. Upon cooling to 0°, 33 g (75%) of crystalline **19** was obtained. An analytical sample from acetonitrile had mp 119–121°; $\nu_{max}$ (KBr) 3410, 3240, 3130, 1720, 1685, and 1580 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) 5.33 (d, 2, $J_{P,H}$ = 14 Hz, exchanges with $D_2O$, $^+PCH_2CO$), 7.22 (br s, 2, $CONH_2$), 7.5–8.0 (m, 15, Ar), 10.53 ppm (br s, 1 CONHCO).

Anal. Calcd for $C_{21}H_{20}BrN_2O_2P$ (443.31): C, 56.90; H, 4.55; N, 6.32; Br, 18.03. Found: C, 57.04; H, 4.59; N, 6.16; Br, 17.80.

***N*-Carbamoylcarbamoylmethylenetriphenylphosphorane (20).** A solution of the phosphonium salt **19** (22.15 g, 50 mmol) in water (4 l.) was cooled to 0° and to it was added 50 ml of 1 *N* sodium hydroxide (50 mmol). The resulting crystalline product was immediately collected by filtration and dried in vacuo over phos-

phorus pentoxide, giving 16.5 g (92%) of **20** that was suitable for direct use. A portion was recrystallized from chloroform–hexane: mp 190–192°; $\nu_{max}$ (KBr) 1685, 1590, 1580, 1560 $cm^{-1}$; NMR ($CDCl_3$) 3.10 (br s, 1, exchanged with $D_2O$, P=CH), 7.3–7.7 (m, 15, Ar), 8.17 ppm (br s, 2, $NH_2$).

Anal. Calcd for $C_{21}H_{19}N_2O_2P$ (362.38): C, 69.90; H, 5.28; N, 7.73. Found: C, 69.63; H, 5.25; N, 7.83.

**Reaction of 20 with Methyl Phenylglyoxylate (11).** A solution of **11** (330 mg, 2 mmol) and **20** (750 mg, 2 mmol) in chloroform (25 ml) was heated under reflux for 20 hr and then evaporated to dryness. The residue was chromatographed on a column of silicic acid using hexane–ether (2:1), which eluted unreacted **11** followed by 2-phenylmaleimide (**18b**). Crystallization from chloroform–hexane gave 52 mg (15%) of **18b** with mp 164° which was identical with an authentic sample[4] by TLC and NMR analysis. Continued elution with chloroform–ethyl acetate (1:1) gave triphenylphosphine oxide followed by a second material that was crystallized from chloroform–methanol giving 174 mg (35%) of **21a** as white plates that partially decomposed at 182–186° and melted at 193–196°, unchanged upon recrystallization: $\nu_{max}$ (KBr) 3480, 3360 (NH), 1712 (COOMe), 1630, 1570 $cm^{-1}$ (CONH); NMR ($Me_2SO$-$d_6$) 3.70 (s, 3, $CO_2Me$), 7.17 (s, 1, $C_3H$), 7.25 (m, 7, Ar, and $NH_2$), 10.43 ppm (br s, 1, NH).

Anal. Calcd for $C_{12}H_{12}N_2O_4$ (248.25): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.56; H, 4.94; N, 11.32.

**Methyl *N*-Carbamoyl-2-methylfumaramate (21b).** A solution of **20** (725 mg, 2 mmol) and methyl pyruvate (205 mg, 2 mmol) in anhydrous chloroform (25 ml) was stirred at room temperature for 20 hr and then evaporated to dryness. The residue was chromatographed on a 4 × 30 cm column of silicic acid using ethyl acetate–chloroform (1:1) which largely separated triphenylphosphine oxide from the slightly more polar product. Crystallization of the product from chloroform gave 248 mg (67%) of **21b** which started to decompose at 180° and melted at 183–185°: $\nu_{max}$ (KBr) 3420, 3365 (NH), 1730 ($CO_2Me$), 1685, 1575 $cm^{-1}$ (CONH); NMR ($Me_2SO$-$d_6$) 2.18 (d, 3, $J_{allylic}$ = 1.5 Hz, $CH_3$), 3.73 (s, 3, $CO_2Me$), 6.95 (q, 1, $J_{allylic}$ = 1.5 Hz, $C_3H$), 7.25, 7.65, and 10.45 ppm (br s, 1, NH).

Anal. Calcd for $C_7H_{10}N_2O_4$ (186.18): C, 45.16; H, 5.41; N, 15.05. Found: C, 45.41; H, 5.35; N, 15.10.

**Registry No.**—**7b,** 56629-80-2; **9,** 53296-04-1; **11,** 15206-55-0; **12,** 5109-46-6; **13,** 56629-73-3; **14,** 56629-74-4; **15a,** 56629-75-5; **15b,** 56629-76-6; **18b,** 34900-45-3; **19,** 53296-07-4; **20,** 53296-08-5; **21a,** 56629-77-7; **21b,** 56629-78-8; 2-bromopropionamide, 5875-25-2; tributylphosphine, 998-40-3; dimethylphenylphosphine, 672-66-2; 1,5-diazabicyclo[4.3.0]non-5-ene, 3001-72-7; methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*allo*-heptonate, 38821-09-9; methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-D-*glycero*-D-*altro*-heptonate, 38821-08-8; 2,2-dimethoxypropane, 77-76-9; 2′,3′-*O*-isopropylideneshowdomycin, 19254-15-0; triphenylphosphine, 603-35-0; *N*-bromoacetylurea, 6333-87-5.

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