C-Glycosyl Nucleosides. V.[1] Some Unexpected Observations on the Relative Stabilities of Compounds Containing Fused Five-Membered Rings with Epimerizable Substituents

Hiroshi Ohrui,[2a,b] Gordon H. Jones,[2a] John G. Moffatt,*[2a] Michael L. Maddox,[2c] Arild T. Christensen,[2d] and Susan K. Byram[2d]

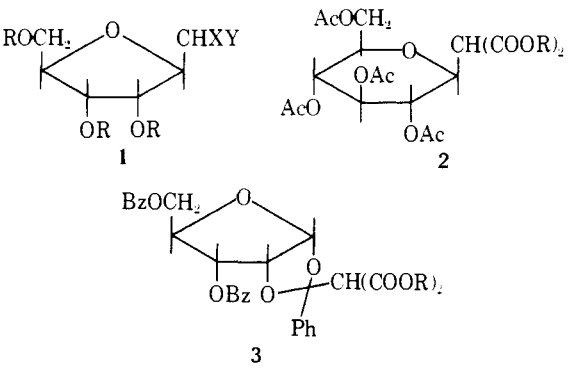
Contribution No. 111 from the Institute of Molecular Biology and Contribution No. 450 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304. *Received December 17, 1974*

Abstract: The reactions of a number of 2,3-*O*-isopropylidene sugars with stabilized ylides lead to the formation of furanosyl *C*-glycosides in high yield. By a combination of proton and ^{13}C NMR spectroscopy, it was shown that the predominant kinetic product in each case was the isomer in which the introduced group was in a trans relationship to the isopropylidene function. Base-catalyzed equilibration of these *C*-glycosides leads, unexpectedly, to the thermodynamically more stable isomer in which the C_1 substituent and the isopropylidene function are cis disposed. The correctness of these assignments is confirmed by X-ray crystallography of a suitable derivative. Several 2-(2,3-*O*-isopropylidene-D-aldofuranosyl) malonates have also been prepared by condensation of the appropriate aldofuranosyl halides with sodiomalonates. The kinetic and thermodynamic products have similarly been shown to have the malonate and isopropylidene functions oriented in a trans and cis fashion, respectively. Condensation of 2,3,5-tri-*O*-benzyl-D-ribose with carbomethoxymethylenetriphenylphosphorane leads to a mixture of cis and trans olefins which rapidly cyclize to furanosyl *C*-glycosides only upon treatment with base. Numerous examples of the value of ^{13}C NMR for structural assignments in carbohydrate chemistry are provided, and several interesting correlations based upon proton NMR are also discussed.

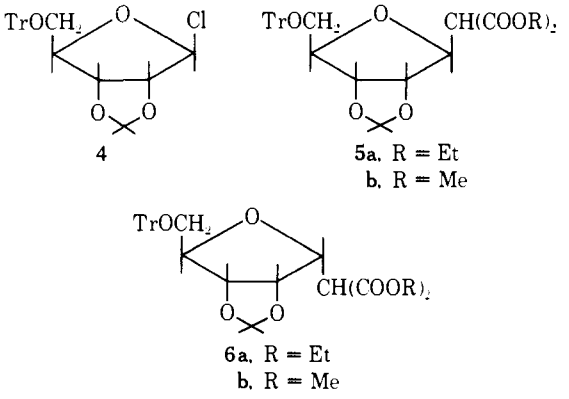
The natural occurrence of a number of *C*-glycosyl nucleosides [3]has led, in recent years, to considerable work directed toward the synthesis of such compounds. These efforts have included both the direct glycosidation of various heterocycles[4] and the elaboration of heterocycles from suitably functionalized anhydroalditols.[1,5] While the latter route can be considered to be the more versatile one, it, in turn, requires the development of synthetic routes to suitable functionalized anhydroalditols of general type **1**. This route has been adapted to synthesis of the naturally occurring nucleoside antibiotics showdomycin,[5a,b] pyrazomycin,[5c] formycin B,[5d] etc.

Syntheses of suitable anhydroalditols of type **1** have been achieved via transformations of the nitrile group in β-D-aldofuranosylcyanides,[5d,6] by ozonolysis of suitably substituted ribofuranosylbenzenes[5a] and by a multistep synthesis from glucose.[7] Only recently, however, has it proved possible to directly condense protected aldofuranosyl halides with stabilized carbanions. Thus Hanessian and Pernet[8a,b] have shown that condensation of, e.g., 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl halides with dialkyl sodiomalonates leads to moderate yields of the β-*C*-glycosides **2**. When the opportunity exists for anchiomeric participation by an acyl group at C_2, as in 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl halides[8b] or 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl halides, the preferred reaction involves alkylation of the intermediate acyloxonium ion to give 1,2-acetals such as **3**. The latter problem can be circumvented by using nonparticipating protecting groups at C_2. Thus successful condensations have been achieved between dialkyl sodiomalonates and 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl chloride[8c] or 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl bromide,[8b] although mixtures of *C*-glycosyl anomers were obtained.

For application to the synthesis of β-D-ribofuranosyl-*C*-glycosides, Ohrui and Fox[9] have also described the condensation of 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (**4**) with diethyl sodiomalonate leading to an anomeric[10] mixture of ribofuranosylmalonates **5**.[11] As a result of the presence of an acidic proton at C_2, these substances underwent "anomeric" equilibration via an acyclic intermediate upon prolonged reaction under basic conditions leading ultimately to one predominant isomer. This thermodynamically more stable isomer was considered to have the β-*C*-ribofuranosyl configuration (D-allo) largely because of decreased steric interactions between the malonyl and isopropylidene moieties. This assignment was supported by the fact that the thermodynamically more stable isomer gave, upon base-catalyzed reaction with urea, a ribofuranosylbarbituric acid salt, the NMR spectrum of which showed an anomeric proton (C_3H) as a singlet. Through the kindness of Dr. Malcolm Bramwell of Bruker Research, we have obtained the 270-MHz NMR spectrum of a sample obtained from Dr. Fox. From this spectrum it is clear that in fact $J_{3,4}$ = 3 Hz. Other features of the spectrum suggest, however, that the β configuration is correct.



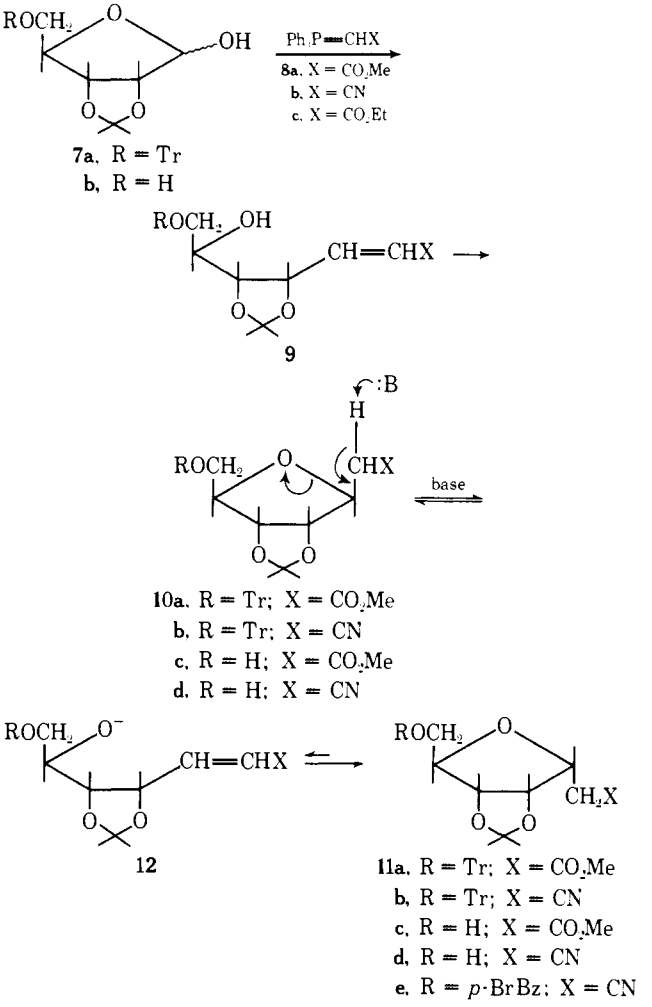
We too have been interested in the synthesis of functionalized anhydroalditols of the general types **1** or **5** and have directed our attention toward their synthesis via the reactions of protected furanoses (e.g., **7**) with stabilized phosphoranes (e.g., **8**). The reactions of several variously protected reducing sugars with phosphoranes have been investigated by Russian workers, and the results have been reviewed by Zhdanov et al.[12] In several cases these reactions led to both α- and β-furanosyl *C*-glycosides, and configura-



tions were assigned primarily on the basis of optical rotations.

Since our objective was the synthesis of β-D-ribofuranosyl *C*-glycosides, our initial investigation concerned the reaction of 2,3,-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (**7a**)[9] with carbomethoxymethylenetriphenylphosphorane (**8a**) in acetonitrile under reflux. After an overnight reaction, a mixture of the anomeric *C*-glycosides was isolated in essentially quantitative yield, and both pure isomers (**10a** and **11a**) could be isolated as analytically pure syrups by preparative thin layer chromatography (TLC). An examination of the proton NMR spectrum of the crude mixture showed a complete absence of vinyl protons, thus confirming that the initial reaction product (**9**) had undergone a spontaneous, Michael-type, ring closure to give an anomeric mixture of furanose *C*-glycosides in a ratio of 3:1, with the more polar (TLC) isomer predominating. If, however, the anomeric mixture was treated with methanolic sodium methoxide at room temperature, the ratio of the two products gradually changed until, after 16 hr, the less polar isomer predominated in a ratio of 5:2. From the above, it is clear that the kinetic product of this reaction undergoes base-catalyzed "anomerization" by way of the unsaturated alkoxide **12** which can recyclize in an equilibrium fashion ultimately leading to a thermodynamically more stable isomer.

By analogy with the assignments made previously in the closely related ethyl esters **5** prepared from the chloro sugar,[9] one might assume that the kinetic and thermodynamic products have the α and β configurations, respectively. The optical rotations of these pure compounds were, however, too similar to allow one to draw conclusions concerning configuration as had been done by Zhdanov et al.[12] in different series. The proton NMR spectra of the pure anomers (**10a, 11a**) (see Table II) were not immediately revealing with respect to assignment of configuration since, in both cases, $J_{3,4}$ (equivalent to $J_{1,2}$ in *O*-glycosides) was 3.5 Hz. Accordingly, we examined the ^{13}C NMR spectra of these compounds since it has been firmly established that the chemical shifts of individual carbon atoms are exquisitely sensitive to steric crowding, especially by vicinal oxygen substituents.[13] The chemical shifts of the methyl group, as well as of those of C_1 and C_2, are, e.g., found to occur at higher field in *cis*-2-methylcyclopentanol than in its trans isomer.[13a] This same shielding effect has also been observed in furanose sugars,[13b] compounds having a cis relationship of C_5 and C_3OH showing C_5 at higher field than the corresponding members with a trans configuration. The chemical shift of the anomeric carbon has also been recently used to distinguish between α- and β-furanosides in both *O*-glycosides[13c] and nucleosides,[13d] the signal of that isomer having a cis relationship between the aglycon and its C_2-hydroxyl appearing at higher field. The ^{13}C chemical shifts observed



for the pure isomers (**10a, 11a**) are recorded in Table I, the assignments for individual carbons being confirmed by both off-resonance and single frequency proton decoupling techniques.[14] The striking conclusion from a comparison of the spectra of these isomers is that C_2, C_3, and C_4 of the thermodynamically more stable isomer occur 3.8, 4.2, and 1.8 ppm, respectively, upfield of the same carbons in the kinetic product. This observation strongly suggests that, contrary to previous conclusions,[9] the kinetic product of this reaction is, in fact, the β isomer (**10a**), while the α anomer (**11a**) is the more thermodynamically stable product.

The sugar **7a** was also reacted with cyanomethylenetriphenylphosphorane (**8b**) under comparable conditions and gave an initial product in 92% yield that consisted of a 3:1 mixture of anomers with the more polar isomer predominating. Base-catalyzed equilibration of this mixture once again led to a gradual conversion of the more polar to the less polar isomer, the latter eventually predominating in a ratio of 3:1. The individual isomers could be readily separated by preparative TLC, the thermodynamic product in this case being obtained in crystalline form. Once again, the ^{13}C NMR spectra of the pure anomers showed that C_2, C_3, and C_4 of the thermodynamically more stable product appeared 3.34, 2.17, and 1.14 ppm, respectively, upfield from those in the kinetic product. It therefore appears that, in this case too, the initial kinetic product has the β configuration (**10b**), while the thermodynamic product has the α configuration (**11b**).

The reactions of 2,3-*O*-isopropylidene-D-ribose (**7b**)[15,16] with **8a** and **8b** followed a similar course. In these cases, it is possible to quantitatively follow the course of the reactions by gas–liquid chromatography, and it is interesting to note

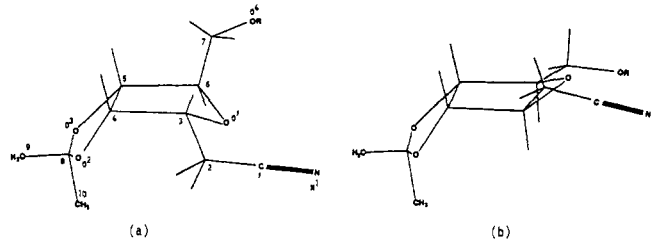


Figure 1. Preferred conformations: (a) 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*altro*-heptononitrile derivatives; (b) 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptononitrile derivatives.

that, in the absence of the 5-*O*-trityl substituent, the initial reaction products were 22:1 and ~50:1 mixtures with the β isomers (**10c, 10d**) predominating. These reactions thus appear to show greater stereoselectivity than those using 5-*O*-trityl substituents, where 3:1 mixtures (β/α) were obtained. As in the other cases, treatment of the pure β-*C*-glycosides (**10c** and **10d**) with sodium methoxide in methanol and benzene, respectively, led to anomeric equilibration favoring the α anomers (**11c, 11d**) in ratios of 3:1. No sign of the corresponding pyranose isomers was to be found, either during the initial reaction or following equilibration. It should be noted that the basicity of excess ylide (**8a,b**)[17] is sufficient to promote slow anomerization during the Wittig reaction itself. Thus a reaction between **7b** and **8b** was allowed to proceed under reflux in acetonitrile for 5 days rather than for 16 hr. Under these conditions, the conversion of the almost exclusive, initially formed β isomer (**10d**) to a 3:1 mixture in favor of the thermodynamically more stable α anomer (**11d**) was readily followed, and the latter compound was isolated in crystalline form in 65% yield. It also should be noted that many of the reactions reported here have not been optimized with respect to obtaining the maximal ratio of kinetic to thermodynamic products. Clearly, if one wishes to obtain the kinetic product in maximum yield, the reaction should be stopped as soon as the starting material has disappeared.

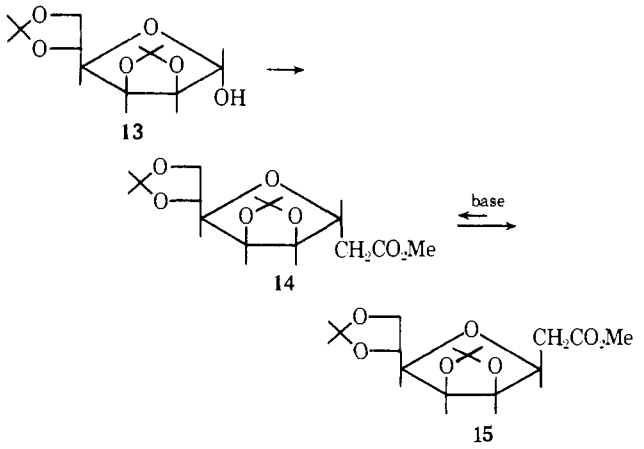
In order to provide a positive correlation between the 5-*O*-trityl (**10a,b**) and the 5-hydroxy (**10c,d**) series of compounds, their interconversion was examined. Thus treatment of the 5-hydroxy compounds (**10c, 10d, 11c,** and **11d**) with trityl chloride in pyridine at room temperature led to the isolation by preparative TLC of the corresponding 5-*O*-trityl derivatives (**10a, 10b, 11a,** and **11b**) in yields of 71–80% without any evidence of anomerization. In addition, detritylation of **10a, 10b, 11a,** and **11b** using an excess of *p*-toluenesulfonic acid monohydrate in a mixture of 2,2-dimethoxypropane and acetone gave the corresponding 5-hydroxy compounds (**10c, 10d, 11c,** and **11d**) in isolated yields of 75–80%. Once again, there was no indication of anomerization during these steps.

In an effort to provide a facile confirmation of the configurations as derived from ^{13}C NMR, we attempted the lactonization of **10c** via treatment with sodium methoxide in benzene in the hope that the intramolecular transesterification reaction might proceed faster than base-catalyzed anomerization. Three crystalline products were isolated from this reaction in yields of 35, 20, and 22% and, while none of these were still methyl esters, they were also not the desired lactone. By a combination of NMR spectroscopy and mass spectrometry, the first two compounds were shown to be dimers of the desired lactone, while the third was a trimer. Since the major dimer appeared to consist of one α- and one β-*C*-glycoside, this approach was not explored further.

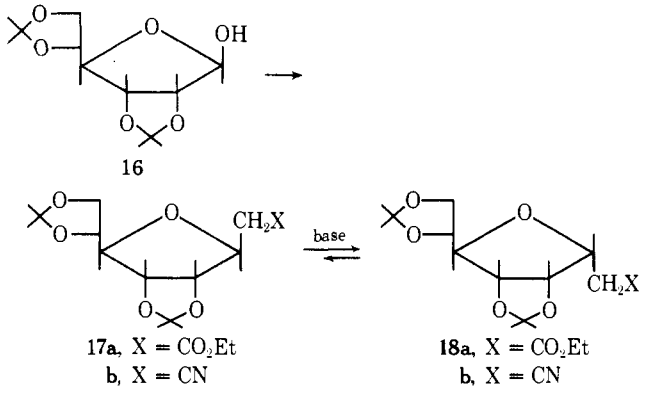
In order to ultimately confirm the assignments made above on the basis of ^{13}C NMR studies, several derivatives of 5-hydroxy compounds were prepared for X-ray crystallographic study. While the 5-*O*-*p*-bromobenzoyl derivative of **10d** was obtained in analytically and spectroscopically pure form, it could not be obtained in crystalline form, and likewise both the *p*-bromobenzoate and *p*-bromobenzenesulfonate of **10c** were only obtained as syrups. The 5-*O*-*p*-bromobenzoyl derivative (**11e**) of the thermodynamic product (**11d**) was, however, obtained in crystalline form, and it could be shown by both proton and ^{13}C NMR spectroscopy and by TLC that no anomerization accompanied the preparation of these derivatives. The X-ray structure of **11e** (see Experimental Section for details) provided the interatomic distances and bond angles shown in Table IV. The torsion angles C_3–C_4–C_5–C_6 and O_2–C_4–C_5–O_3 were shown to be 1.5 and 0.5°, respectively, and the fold angle between these planar portions of rings A and B was found to be 117°. Both the furanose ring oxygen (O_1) and the central isopropylidene carbon (C_8) were found to reside 0.47 and 0.48 Å below the planar moieties of rings A and B, respectively, leading to O_1-endo and C_8-endo envelope conformations for the two rings, as shown in Figure 1a. Least-squares plane calculations show that C_2 is disposed 0.81 Å below the plane described by C_3–C_4–C_5–C_6, while C_7 is 1.41 Å above that plane. This provides absolute evidence for the α configuration for **11e** and, taken together with the other transformations described above, allows definitive configurational assignments for both the tritylated and nontritylated derivatives **10** and **11** (X = CN).

As a further extension of the above studies, we have also reacted 2,3:5,6-di-*O*-isopropylidene-β-D-mannose (**13**)[18] with carbomethoxymethylenetriphenylphosphorane (**8a**) to give a 1:1 mixture of methyl 3,6-anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octonate (**14**) and its D-glycero-D-galacto isomer (**15**) in a combined yield of 90%. These isomers could be largely separated by chromatography on silicic acid to give samples of both pure isomers. Treatment of the crystalline, more polar isomer with sodium methoxide led to 80% epimerization to the thermodynamically more stable, less polar isomer, this conversion being readily followed by GLC. In the case of the crystalline, kinetic product it was possible to assign the α configuration (**14**) on the basis of its proton NMR spectrum since, with the aid of spin decoupling studies, $J_{3,4}$ was shown to be 0 Hz. This value is consistent only with a trans orientation of C_3H and C_4H (equivalent to C_1H and C_2H in simple glycosides).[19] Unfortunately a comparable assignment for the β isomer (**15**) could not be confirmed by proton NMR since the value $J_{3,4}$ = 2.5 Hz falls in an equivocal range.[19] The ^{13}C NMR spectra of **14** and **15,** however, provided convincing confirmation of the assignments based on proton NMR data. Thus, the thermodynamically more stable product showed chemical shifts for C_2, C_3, and C_4 that were respectively 2.9, 3.2, and 5.0 ppm upfield of those in the kinetic product. Thus, quite in analogy with the results in the 2,3-*O*-isopropylidene-D-ribofuranose series, the kinetic product (**14**) has its CH_2CO_2Me group oriented trans to the 4,5-*O*-isopropylidene group and, upon base treatment, this compound isomerizes to the more thermodynamically stable cis oriented β-*C*-glycoside (**15**).

The reaction of 2,3:5,6-di-*O*-isopropylidene-β-D-allofuranose (**16**)[20] with both **8b** and **8c** was also examined but, in these cases, analytically pure, but preparatively inseparable, mixtures of the anomeric products (**17, 18**) were obtained in quantitative yield. By GLC analysis and proton NMR spectroscopy, it could be shown that the expected two isomers were present with the one showing the shorter retention time predominating in ratios of 3:1 and 4:1, respectively. Treatment of both mixtures with sodium alkoxide at room

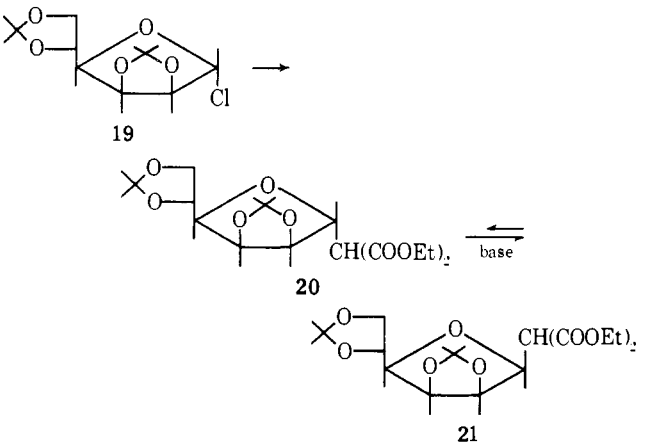


temperature led to the usual isomerization with the component of longer GLC retention time now predominating in ratios of 4:1 and 5:1, respectively. While individual isomers were not obtained in pure form in these cases, analysis of the ^{13}C NMR spectrum of the enriched mixtures confirmed that, as in the earlier examples, the kinetically favored products had the β configuration (**17a,b**) while the thermodynamic products were α (**18a,b**).



Since the above examples appear to lead to a consistent pattern regarding the kinetic and thermodynamic steric preferences for the reactions of 2,3-*O*-isopropylidenealdofuranoses with stabilized phosphoranes, we decided to reexamine the condensation reactions of sodiomalonates with several 2,3-*O*-isopropylidene glycofuranosyl halides. The reaction between 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (4) and diethyl sodiomalonate in the presence of sodium iodide was carried out as briefly described by Ohrui and Fox[9] giving two isomeric products in high yield. Chromatography of the mixture on silicic acid led to the isolation of the two pure isomers in yields of 80 and 10% with the less polar substance predominating. Examination of the ^{13}C NMR spectra of these products showed that, unlike the results from the Wittig reactions, the major product from this very basic reaction was the α anomer (**6a**) which showed (Table I) substantial upfield shifts of C_2, C_3, and C_4 relative to the comparable carbons in the minor β anomer (**5a**). The latter compound could, however, be shown to be the kinetic product since treatment of pure **5a** with sodium ethoxide at room temperature led to epimerization at C_3 giving a mixture of **6a** and **5a** in a ratio of 9:1, while comparable treatment of **6a** led to only minor equilibration. A similar reaction was also carried out between **4** and dimethyl sodiomalonate except that, in this case, a shorter reaction time (1 hr instead of 4 hr) was used. Under these conditions, a separable mixture of **6b** and **5b** was obtained in a ratio of 12:7 showing that, under these conditions, equilibration to the thermodynamic product (**6b**) was not yet complete. Treatment of **5b** with sodium methoxide led, as before, to equilibration to a 6:1 mixture of **6b** and **5b**. We are therefore led to the conclusion that, contrary to the presumption of Ohrui and Fox,[9] the sterically more hindered α isomers (**6a,b**), in which the malonate and isopropylidene moieties are cis disposed to one another, are in fact the thermodynamically more stable products.[21]

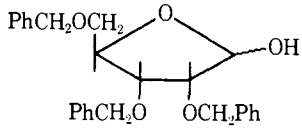
We have also examined the condensation of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride (**19**)[22] with diethyl sodiomalonate in the presence of sodium iodide, a reaction that has been described under somewhat different conditions by Hanessian and Pernet[8b] using the corresponding bromo sugar. This reaction gave, in 80% yield, a 9:1 mixture of two isomeric *C*-glycosides with the less polar isomer predominating. Once again, the ^{13}C NMR spectra of these products (**20, 21**) showed that the major isomer had, in fact, the β configuration (**21**), a conclusion that can in this case be confirmed by proton NMR, $J_{3,4}$ for **20** and **21** being 0 and 3 Hz, respectively. A similar assignment of configuration has also been made for the major product, on the basis of proton NMR and optical rotation.[8b] As in the case of the ribose series, it was possible to show that the minor isomer (**20**) is in fact the kinetic product since base treatment of pure **20** leads to over 80% conversion to **21** while similar treatment of pure **21** led to only minor isomerization. In contrast to this, Hanessian and Pernet have concluded that **21** is the direct product of an SN2 reaction and that "epimerization, if taking place at all, must be in favor of the minor α anomer because of the bulky isopropylidene groups".[8b]



Finally, since the presence of an adjacent isopropylidene function in an aldofuranose molecule appears to exert substantial steric control upon the configurations of *C*-glycosides prepared by the methods described in this paper, we have examined the role of other groups. Thus, the reaction between 2,3,5-tri-*O*-benzyl-D-ribofuranose (**22**)[23] with **6a** was carried out under reflux in acetonitrile under the same conditions used with other furanoses. Chromatography on silicic acid readily separated two isomeric products which were isolated as homogeneous syrups in yields of 54 and 36%. The NMR spectra of these compounds showed, however, that these were the cis (**23**) and trans (**24**) isomers of methyl 4,5,7-tri-*O*-benzyl-2,3-dideoxy-D-*ribo*-hept-2-enonate, the direct products of the Wittig reaction which had not undergone cyclization to furanose *C*-glycosides. The assignments of configuration to **23** and **24** were obvious from their proton NMR spectra, the values of $J_{2,3}$ being 11.5 and 14 Hz, respectively.[24]

Treatment of **23** and **24** with dilute sodium methoxide led to almost instantaneous cyclization to furanose *C*-glycosides (**25**). In the case of the trans olefin (**24**), the product

was a mixture of the β and α *C*-glycosides (**25a, 25b**) in a ratio of 3:2 as judged by proton and ^{13}C NMR (see Table I). Similar treatment of the cis olefin (**23**), however, gave only the pure β isomer (**25a**) in quantitative yield. The benzyl ethers (**25**) showed much less tendency to equilibrate in base than did their isopropylidene counterparts. Thus continuation of the treatment of **23** with sodium methoxide for 23 hr led to only about 25% epimerization of the initially formed pure β-*C*-glycoside (**25a**) to its α anomer (**25b**). Similar prolonged treatment of **24** led to a mixture of **25a** and **25b** in which the original ratio of 3:2 was changed to 2:1. It thus appears that, in the case of the benzyl ethers, equilibration is not nearly as facile and controlled as with the isopropylidene derivatives, and that there appears to be a slight thermodynamic preference for the β isomer (**25a**).



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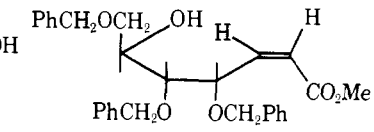

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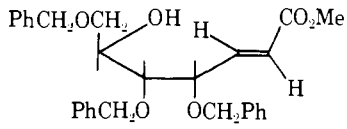

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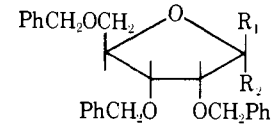
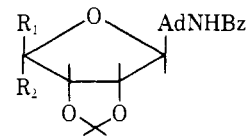


25a, $R_1 = CH_2CO_2Me$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_2CO_2Me$

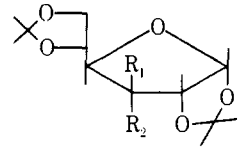
Clearly the presence of an isopropylidene group at O^2O^3 of the parent sugar plays a central role in promoting cyclization of the intermediate olefins of type **8**. An examination of the literature[25] provides many examples supporting the general contention that the presence of one five-membered ring strongly favors the formation of a second fused five-membered ring (i.e., oxa analogs of bicyclo[3.3.0]octane ring system). As examples, it is known that D-mannose 2,3-*O*-carbonate[26] and 3,6-anhydro-D-glucose[27] preferentially exist to an extent of greater than 99% in the furanose form, that acidic equilibration of methyl 3,6-anhydro-D-glucopyranoside leads predominantly to the furanoside isomer,[28] and that acetonation of methyl D-ribopyranoside gives methyl 2,3-*O*-isopropylidene-D-ribofuranoside as a major product.[29] The formation of only furanose *C*-glycosides (**10c,d, 11c,d**) from **7b** without any sign of their pyranose counterparts and the formation of only the acyclic products (**23, 24**) from the tribenzyl sugar (**22**) provide striking examples of this general tendency.

Several other examples of isopropylidene sugars which prefer to exist in a cis (endo) configuration are to be found in the literature. This we have previously shown that the 5′-ketonucleoside **26a** rapidly epimerizes at $C_{4'}$ giving **26b** upon chromatography on silicic acid,[30] and Kovâr and Baer[31] have reported the base-catalyzed epimerization of **27a** to the more stable isomer **27b**. Caution should be used, however, in attempting to predict the more stable configuration of compounds in which the epimerizable center is not immediately adjacent to the isopropylidene group. Thus, while the ketone **28a** has been shown to isomerize extensively to the seemingly more hindered endo compound **28b** during basic reactions,[32] base treatment of **29a** leads to 80% conversion to the exo isomer **29b**.[33] It should be pointed out that isomerizations of these sorts involving carbonyl sugars, or their equivalents, might well be examples of kinetically favored protonation rather than thermodynamic equilibria.

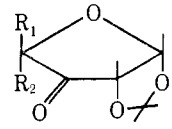
As described above, ^{13}C NMR spectroscopy proved to be the most effective method for the assignment of configuration to the kinetic and thermodynamically more stable products of the reactions studied. The ^{13}C NMR parameters for the various compounds examined are summarized in Table I, from which it can be seen that there is a very consistent pattern with C_2, C_3, and C_4 of the thermodynamic products appearing at higher field than those in the kinetic product. This indicates a cis orientation of C_2 and the 4,5-*O*-isopropylidene group in the thermodynamically more stable isomers and is supported by the X-ray structure of **11e**. In Table I we have also included ^{13}C chemical-shift data for several known reference compounds which support the general method, although the compounds are of a quite different nature. Thus, e.g., a comparison of the spectra of **13** and **16** shows the expected shielding of C_3, C_4, and C_5 in the former compound because of the cis relationship of C_5 and the 2,3-*O*-isopropylidene ring. Similarly, the spectra of the corresponding lactones, which are readily prepared by oxidation of **13** and **16**, show substantial shielding of C_4 and C_5 in the mannonolactone derivative for the same reason. In this case, however, we have been unable to distinguish between the signals for C_2 and C_3 in the manno isomer, but the maximum upfield shift of C_3 would appear to be only 0.3 ppm. From Table I it might also be noted that in *C*-glycosides derived from 2,3-*O*-isopropylidene-D-ribose and 2,3:5,6-di-*O*-isopropylidene-D-allose, there exists a correlation between the ^{13}C chemical shifts of the isopropylidene methyl groups and the anomeric configuration. Thus, in the "β" series, methyl signals appear at 25.5 ± 0.2 and 27.5 ± 0.2 ppm while, in the "α" anomers, they are at 24.9 ± 0.3 and 26.3 ± 0.2 ppm.

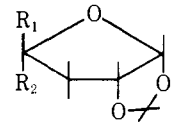


26a, $R_1 = COCH_3$; $R_2 = H$
b, $R_2 = COCH_3$; $R_1 = H$



27a, $R_1 = NO_2$; $R_2 = H$
b, $R_2 = NO_2$; $R_1 = H$





28a, $R_1 =$  ; $R_2 = H$

b, $R_1 = H$; $R_2 =$ 

29a, $R_1 = H$; $R_2 = CHO$
b, $R_1 = CHO$; $R_2 = H$

Further support for the assignments of configuration comes from an examination of proton NMR spectra. With the exception of the compounds **14** and **20**, derived from 2,3:5,6-di-*O*-isopropylidene-D-mannose, direct assignment of configuration based upon the magnitude of $J_{3,4}$ (equivalent to $J_{1,2}$ in *O*-glycosides) has not been possible, as shown in Tables II and III. Several other parameters do, however, lead to consistent patterns. Recently, Imbach et al.[34] have reported that the difference between the chemical shifts of the *gem*-dimethyl groups in a variety of 2,3-*O*-isopropylidene-β-D-ribofuranosyl nucleosides is always greater than 18 Hz, while the corresponding difference in an analogous series of α-D-nucleosides was less than 10 Hz. From Table II it can be seen that, while the chemical-shift differences in the present isopropylidene *C*-glycosides are not as great as those described by Imbach et al.[34] for *N*-glycosides, the kinetic products (β-D-ribo, β-D-allo) consistently show larger values of $\Delta\delta$ than do the thermodynamic products. In the case of the *C*-ribofuranosylmalonates (**5a, 6a; 5b, 6b**), the differences in chemical shift are only 0.5 Hz in deuteriochloroform, and the rule does not seem to apply in deuteriobenzene. Unfortunately, the isopropylidene methyl proton signals in the compounds derived from 2,3:5,6-di-*O*-isopro-

Table I. ^{13}C NMR Spectra (22.62 MHz) in $CDCl_3$[a]

Compd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	Isopropylidene Me	Isopropylidene Me	Isopropylidene C	Ester OC	Ester CC
5a	166.90 167.03	55.43	82.74	83.16	81.99	83.87	64.21		25.68	27.57	114.21	61.70	14.04
6a	166.90 167.91	53.45	80.27	81.63	83.26	83.42	64.66		25.00	26.24	112.61	61.70 61.40	14.11 14.01
5b	167.46 167.36	55.04	82.83	83.16	81.96	84.04	64.21		25.75	27.60	114.30	52.73	
6b	168.30 167.29	52.93	80.27	81.57	83.29	83.52	64.73		25.00	26.24	112.68	52.60 52.93	
10a	171.13	38.65	81.08	83.74	82.51	84.49	64.43		25.75	27.63	114.37	51.82	
11a	171.78	34.82	78.25	81.89	83.42	83.61	64.60		25.19	26.33	112.58	51.76	
10b	116.67	22.27	79.97	83.94	82.48	84.30	64.21		25.55	27.44	114.89		
11b	117.59	18.92	77.76	81.34	83.61	84.04	64.99		24.90	26.14	113.23		
10c	171.42	37.74	80.85	84.13	81.72	84.91	62.74		25.52	27.47	114.53	51.95	
11c	172.00	34.46	77.21	81.56	82.67	84.39	62.12		25.06	26.30	112.90	51.85	
10d	117.36	22.01	79.81	83.78	81.86	85.34	62.52		25.39	27.31	114.92		
11d	117.98	18.79	77.08	81.11	82.90	84.95	62.91		24.77	26.11	113.32		
10e	116.45	22.14	79.42	83.52	81.79	82.51	64.34		25.49	27.41	115.73		
11e	117.16	18.53	77.14	80.92	82.96	82.41	64.27		24.84	26.11	113.85		
13	101.30	85.60	79.78	80.36	73.37	66.64			24.51 25.19	25.88 26.79	109.20 112.78		
14	170.77	36.28	81.05	85.04	81.05	81.05	73.44	67.03	24.77 25.23	26.20 26.95	109.30 113.04	51.92	
15	171.52	33.35	77.86	81.14	80.85	81.73	73.18	66.97	24.71 25.32	25.78 26.95	109.17 112.68	51.76	
16	103.64	86.96	81.11	87.58	76.01	66.45			24.71 24.87	26.46 26.46	110.43 112.42		
17a	170.54	38.72	81.24	84.52	82.31	85.14	76.04	66.77	27.41 25.52	26.59 25.19	109.98 114.50	60.73	14.21
18a	171.32	34.62	77.83	81.60	82.44	84.72	74.93	67.07	26.66 26.27	25.00 25.00	110.11 112.68	60.60	14.21
17b	116.84	22.20	80.23	83.97	82.15	85.60	75.81	66.51	27.27 25.38	26.53 24.97	110.04 114.79		
18b	117.52	18.50	77.24	81.14	82.09	85.11	75.81	66.51	26.53 26.04	24.74 24.64	110.21 113.20		
20	166.71 167.10	53.25	83.06	84.43	80.98	81.96	73.37	67.03	24.67 25.45	25.78 26.89	109.39 113.20	61.87 61.93	14.04
21	166.81 167.62	52.21	79.52	81.01	80.59	81.76	73.11	66.87	24.81 25.29	26.27 26.95	109.26 112.91	61.64	13.98 14.11
25a	171.36	38.59	77.34	80.49	77.14	81.79	70.32					51.72	
25b[e]	172.23	35.11	76.46	77.86	79.65	80.10	70.22					51.53	
Manno-lactone[b]	173.67	76.23[d]	76.01[d]	78.32	72.76	66.51			25.16 25.94	26.82 26.98	109.98 114.53		
Allo-lactone[c]	173.80	75.23	76.36	82.83	74.48	65.31			24.06 25.62	26.17 26.76	110.69 113.59		

[a] Chemical shifts in parts per million downfield from Me_4Si. [b] 2,3:5,6-Di-*O*-isopropylidene-D-mannonolactone. [c] 2,3:5,6-Di-*O*-isopropylidene-D-allonolactone. [d] The designated assignments could be reversed. [e] Assignments are made from the spectrum of a mixture of **25a** and **25b**.

pylidene-D-mannose (**14, 15; 20, 21**) overlapped to the point that definitive assignments could not be made.

A further correlation arising from proton NMR spectra concerned the values of $J_{5,6}$ (corresponding to $J_{3,4}$ in *O*-glycosides) in the various *C*-glycosides derived from the D-ribose series. As can be seen from Table III, the kinetic products (β) consistently have values of $J_{5,6}$ = 4–5 Hz while, in the corresponding thermodynamic (α) products, $J_{5,6}$ = 0–1 Hz. From the X-ray crystal structure of **11e**, it can be seen that the isopropylidene furanose ring adopts a conformation in which C_3, C_4, C_5, and C_6 are essentially planar, and the ring oxygen is puckered into an endo oriented envelope (see Figure 1a). Examination of Dreiding models shows that such a conformation results in a dihedral angle between H_5 and H_6 of roughly 90°, which is consistent with the very small observed coupling constant. This conformation also tends to put the α-C_2-acetate substituent into a relatively unhindered pseudoequatorial conformation. If this same *O*-endo conformation is considered for the kinetically produced β-*C*-glycosides, both C_2 and C_7 are thrown into highly hindered pseudoaxial orientations. We therefore suggest that the β-*C*-glycosides (**5, 10**) adopt an alternate *O*-exo envelope conformation in which the steric interaction between these substituents is relieved. Models of this conformation (Figure 1b) show that the dihedral angle between C_5H and C_6H becomes roughly 160°, a figure that is quite compatible with the observed value of $J_{5,6}$ of 4–5 Hz. From Table II it can also be seen that the value of $J_{5,6}$ is essentially the same for both the β- (**21**) and α- (**20**) *C*-glycosides derived from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose. An examination of molecular models in this series shows that, while passage from an *O*-exo to an *O*-endo conformation leads to considerable movement of both C_5H and C_6H, the dihedral angles between these protons remains essentially the same. While a similar effect is apparent with the other mannose derivatives (**14, 15**), it is less striking. Also from Table II, it can be seen that, as with α and β nucleosides,[35] the chemical shifts of the "anomeric" proton (C_3H) are consistently downfield in those isomers with a cis orientation of C_2 and the C_4-oxygen (**6, 11, 21, 25b**) relative to those with a trans arrangement (**5, 10, 20, 25a**). Finally, it can be seen that the various α- and β-*C*-glycosides generally obey Hudson's rules,[36] the thermodynamically more stable α anomers in the D-ribose series (**10**) showing more positive rotations than their kinetic β anomers (**9**). In the mannose series, the kinetically controlled α-

Table II. 100-MHz Proton Magnetic Resonance Spectra[a]

Compd	Solvent	C_2H_a	C_2H_b	C_3H	C_4H	C_5H	C_6H	C_7H_a	C_7H_b	$\times^{CH_3}_{CH_3}$	Others
5a	C_6D_6	ca. 4.0		4.84 (dd)	4.98 (dd)	4.68 (dd)	4.23 (m)	3.32 (m)		1.11, 1.39 (s) ($\Delta\delta$ = 19.5)[b]	0.89 (t, 6, OCH_2CH_3), 3.92 (m, 4, OCH_2CH_3), 7.09, 7.57 (m, 15, Tr)
6a	C_6D_6	4.29 (d)		5.27 (dd)	5.08 (dd)	4.43 (d)	4.25 (dd)	3.20 (dd)	3.01 (dd)	1.07, 1.36 (s) ($\Delta\delta$ = 19.0)[b]	0.89, 0.98 (t, 3, OCH_2CH_3), 4.07 (q, 2), 3.93 (dq, 2) [OCH_2CH_3], 7.15, 7.51 (m, 15,Tr)
5b	C_6D_6	3.85 (d)		4.82 (dd)	4.98 (dd)	4.69 (dd)	4.21 (dt)	3.29 (m)		1.12, 1.39 (s) ($\Delta\delta$ = 19.0)[b]	3.26, 3.27 (s, 3, OCH_3), 7.1, 7.55 (m, 15, Tr)
6b	C_6D_6	4.34 (d)		5.28 (dd)	5.09 (dd)	4.46 (d)	4.27 (m)	3.21 (dd)	3.01 (dd)	1.08, 1.38 (s) ($\Delta\delta$ = 18.5)[b]	3.26, 3.42 (s, 3, OCH_3), 7.1, 7.55 (m, 15, Tr)
10a	$CDCl_3$	2.62 (dd)	2.78 (dd)	4.31 (dt)	4.63 (dd)	4.55 (dd)	4.13 (ddd)	3.26 (dd)	3.12 (dd)	1.31, 1.51 (s) ($\Delta\delta$ = 20 Hz)	3.64 (s, 3, OCH_3), 7.2, 7.4 (m, 15, Tr)
11a	$CDCl_3$	2.75 (d)		4.61 (dt)	4.82 (dd)	4.68 (d)	4.19 (t)	3.27 (dd)	3.09 (dd)	1.30, 1.47 (s) ($\Delta\delta$ = 17 Hz)	3.68 (s, 3, OCH_3), 7.3 (m, 15, Tr)
10b	$CDCl_3$	2.58 (dd)	2.77 (dd)	4.12 (m)	4.50 (dd)	4.65 (dd)	4.18 (m)	3.33 (dd)	3.21 (dd)	1.32, 1.51 (s) ($\Delta\delta$ = 19 Hz)	7.3 (m, 15, Tr)
11b	$CDCl_3$	2.67 (d)		4.50 (dt)	4.79 (dd)	4.71 (d)	4.22 (dd)	3.33 (dd)	3.11 (dd)	1.30, 1.47 (s) ($\Delta\delta$ = 17 Hz)	7.3 (m, 15, Tr)
10c	$CDCl_3$	2.56 (dd)	2.74 (dd)	4.24 (ddd)	4.48 (dd)	4.70 (dd)	4.03 (ddd)	3.60 (dd)	3.76 (dd)	1.32, 1.51 (s) ($\Delta\delta$ = 19 Hz)	3.05 (br s, 1, OH),[c] 3.68 (s, 3, OCH_3)
11c	$CDCl_3$	2.72 (d)		4.38 (dt)	4.78 (dd)	4.68 (d)	4.10 (t)	3.60 (d)		1.31, 1.46 (s) ($\Delta\delta$ = 15 Hz)	3.08 (br s, 1, OH),[c] 3.68 (s, 3, OCH_3)
10d	$CDCl_3$	2.67 (dd)[d]	2.85 (dd)[d]	4.1 (m)	4.49 (dd)	4.73 (dd)	4.1 (m)	3.63 (dd)[d]	3.80 (dd)[d]	1.33, 1.51 (s) ($\Delta\delta$ = 18 Hz)	2.86 (br t, 1, OH)
11d	$CDCl_3$	2.68 (d)		4.36 (dt)	4.77 (dd)	4.79 (d)	4.16 (dd)	3.65 (m)		1.33, 1.49 (s) ($\Delta\delta$ = 16 Hz)	2.96 (m, 1, OH)
10e	$CDCl_3$	2.60 (dd)	2.79 (dd)	4.11 (ddd)	4.56 (dd)	4.71 (dd)	4.23 (ddd)	4.46 (m)		1.32, 1.51 (s) ($\Delta\delta$ = 19 Hz)	7.53, 7.89 (d, 2, Ar)
11e	$CDCl_3$	2.71 (d)		4.40 (m)	4.40 (m)	4.40 (m)	4.40 (m)	4.80 (d)		1.34, 1.51 (s) ($\Delta\delta$ = 17 Hz)	
14	$CDCl_3$	2.40 (dd)	2.57 (dd)	4.47 (dd)	4.62 (d)	4.80 (dd)	3.78 (dd)	4.38 (ddd)		1.31, 1.34, 1.41, 1.47 (s)	3.67 (s, 3, OCH_3), 3.93 (dd, 1, C_8H_A), 4.11 (dd, 1, C_8H_B)
15	$CDCl_3$	2.65 (dd)	2.83 (dd)	3.93 (m)	4.76 (m)	4.76 (m)	3.50 (m)	4.38 (ddd)		1.30, 1.34, 1.41, 1.43 (s)	3.67 (s, 3, OCH_3), 4.05 (d, 2, C_8H_2)
20	$CDCl_3$	3.52 (d)		4.60 (d)	4.76 (m)	4.76 (m)	3.8–4.5 (m)			1.33, 1.33, 1.40, 1.47 (s)	1.25 (t, 6, OCH_2CH_3), 4.19 (q, 4, OCH_2CH_3), ca. 4.0 (m, C_8H_2)
21	$CDCl_3$	3.77 (d)		ca. 4.3 (m)	4.90 (dd)	4.74 (dd)	3.51 (dd)	ca. 4.0 (m)		1.27, 1.31, 1.36, 1.42 (s)	1.23 (t, 6, OCH_2CH_3), 4.18 (q, 4, OCH_2CH_3), ca. 4.0 (m, C_8H_2)
23	$CDCl_3$	5.95 (dd)		6.40 (dd)	5.38 (br d)	3.5–3.9 (m)					3.36 (d, 1, OH), 3.65 (s, 3, OCH_3), 4.5–4.9 (m, 6, OCH_2Ph),[e] 7.25 (m, 15, Ph)
24	$CDCl_3$	6.10 (dd)		7.02 (dd)	4.36 (m)	3.55–3.75 (m)					2.73 (br s, 1, OH), 3.68 (s, 3, OCH_3), 4.3–4.8 (m, 6, OCH_2Ph),[e] 7.25 (m, 15, Ph)
25a	$CDCl_3$	2.40 (dd)	2.59 (dd)	4.40 (m)	3.67 (dd)	3.89 (dd)	4.18 (dt)	3.45 (d)			3.60 (s, 3, OCH_3)

[a] Chemical shifts in parts per million from Me_4Si (δ = 0), by first-order analysis. [b] $\Delta\delta$ measured from $CDCl_3$ spectra. [c] In Me_2SO-d_6, the OH appeared as a triplet, δ = 4.81 ppm. [d] After addition of D_2O. [e] One CH_2 is equivalent, two are nonequivalent.

Table III. Coupling Constants (Hertz)

Compd	$J_{2a,2b}$	$J_{2a,3}$	$J_{2b,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7a}$	$J_{6,7b}$	$J_{7a,7b}$	$J_{7,8a}$	$J_{7,8b}$	$J_{8a,8b}$
5a		7.5		3.5	6.5	5	*a*	*a*	*a*			
6a		10.5		3.5	6	0	3.5	5	10			
5b		7.5		4	6.5	4.5	5	5	*a*			
6b		10.5		3.5	6	0	3.5	5	10			
10a	16	6	6	4	6	3.5	4	4.5	10			
11a	0	6.5	6.5	4	6	0	4.5	4.5	10			
10b	16	5.5	7	4.5	6.5	3.5	4	4	10			
11b	0	6.5	6.5	3.5	6	0	4	4	10.5			
10c	16	5	6.5	4.5	7	4	3.5	3.5	12			
11c	0	7	7	3.5	6	0	5	5	0			
10d	16	5	6	5	6.5	3.5	3.5	4.5	12			
11d	0	7	7	4	6	0	4.5	4.5	*a*			
10e	16	4.5	5	4.5	6	4	4	4	*a*			
11e	0	6.5	6.5	*a*	*a*	*a*	2	2	0			
14	16	7.5	7.5	0	6	3.5	7.5			4.5	5.5	15
15	16	6.5	6.5	*a*	*a*	*a*	7			5	5	0
20		9.5		0	*a*	3.5	6			*a*	*a*	*a*
21		10		3.5	6	3	7			*a*	*a*	*a*
23		11.5 ($J_{2,4}$ = 1 Hz)		9	1	*a*	*a*	*a*	*a*			
24		14 ($J_{2,4}$ = 1 Hz)		6.5	1	*a*	*a*	*a*	*a*			
25a	16	6.5	5.5	5	5	4	4	4	0			

[a] Unresolved.

C-glycosides (**14, 20**) show more positive rotations than their β counterparts (**15, 21**). In a number of cases, the differences in rotation between the isomer pairs is small but, in only one case, that of **10e** and **11e,** is Hudson's rule not obeyed.

Taken as a whole, the work presented in this paper appears to provide convincing evidence for the rather surprising steric course of the reactions described for the synthesis and equilibration of functionalized *C*-glycosides. Model building, with respect to both the nature of the products and the unsaturated intermediates (**8, 11**) presumably involved in ring closure and equilibration, suggests that the formation of *C*-nucleosides with a trans relationship between the "anomeric" substituent and the isopropylidene function should be favored. While this appears to be consistently true with respect to the kinetic products, it is difficult to rationalize the inescapable conclusion that the products with cis relationship are, in fact, of greater thermodynamic stability. By invoking specific *O*-exo and *O*-endo envelope conformations for the kinetic (β) and thermodynamic (α) *C*-glycosides derived from 2,3-*O*-isopropylidene-D-ribofuranose, major steric interactions are largely avoided, but one would still suggest that the β isomer is the least hindered. Based upon the results with the acyclic olefins (**23, 24**), it could be suggested that perhaps the major products of the Wittig reaction are the cis olefins which cyclize predominantly to the β-*C*-glycosides. There is, however, no definitive evidence to suggest that base-catalyzed equilibration proceeds via preferential formation of the trans isomer of **12**.

Ample evidence is to be found that 2,3-*O*-acetal derivatives of aldofuranoses containing equilibratable C_1 substituents (e.g., OH, OR, Cl, NH_2) prefer to adopt a 1,2-trans relationship. Thus, e.g., reducing sugars such as 2,3-*O*-benzylidene-D-ribofuranose[37] and 2,3:5,6-di-*O*-isopropylidene-D-allofuranose (**16**)[20] exist primarily in the β form, while 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**13**)[38] has the α configuration. Similarly, the proton NMR spectra of **6a** and **6b** show these substances to be at least 90% in the β configuration since, in both cases, the preponderant isomer had $J_{1,2}$ = 0 Hz. The furanosyl chlorides **4**[9] and **19**[22] have been shown to possess the β and α configurations, respectively, in spite of the fact that they were both prepared with apparent retention of configuration using reactions that normally proceed with inversion. In the case of *N*-glycosides, it has been shown that acetonation of D-ribopyranosylamines leads to 2,3-*O*-isopropylidene-D-ribofuranosylamine, which is predominantly in the β form in chloroform,[39] and several nucleosides prepared by either direct thermal condensation of **6b** or[40] from the chloro sugar **19**[41] have been found to have a 1,2-trans configuration.

The above trans relationships have, in general, been explained on purely steric grounds, the bicyclo[3.3.0] system tending to exist with the fewest possible large endo substituents.[25,42] More recent work on the equilibration of 1,3-dioxolanes has shown that, in the absence of very large substituents, 2-alkyl-4,5-*cis*-dialkyldioxolanes tend to prefer an all cis configuration.[43] While these dioxolanes are considerably less rigid than the bicyclo[3.3.0] system, we are considering, this nevertheless shows that stereochemical predictions in five-membered rings must be handled with great care. One possible difference between *C*-glycosides and other furanosyl derivatives is the absence of a dipole between C_1 and the polar substituent in the former case. Perhaps dipole interactions play a critical role in furanose derivatives in somewhat the same way as they do in pyranose rings, as exemplified by the well-known anomeric effect.[44] We are currently considering various ways of investigating this interesting question. The formation of a β-*C*-glycosylbarbituric acid upon base-catalyzed cyclization of the α precursor (**6a**)[9] is an apparent contradiction of the relative thermodynamic stabilities of the acyclic precursors. Whether this could be a consequence of unknown electronic effects accompanying the possible formation of a dianionic aglycon or of a preferential sterically controlled reaction of urea with only the equilibrated β isomer is difficult to understand and requires further study.

It has recently come to our attention that work is also underway in several other laboratories concerning the stereochemistry of epimerizable *C*-glycosides.[45] We are grateful to Drs. J. G. Buchanan and S. Hanessian for a brief discussion of their results, which appear to be in agreement with our own conclusions.

Tabulations of final positional and thermal parameters for the X-ray crystallographic study and ^{13}C chemical shifts for carbon atoms not included in Table I, e.g., trityl groups, benzyl ethers, etc., can be obtained by contacting the authors.

Table IV. Bond Lengths and Angles for Compound 11e

Bond lengths, Å[a,c]		Bond angles, deg[b,c]		Bond angles, deg[b,c]	
C(1)–N(1)	1.13	N(1)–C(1)–C(2)	179.2	O(2)–C(8)–O(3)	103.4
C(1)–C(2)	1.48	C(1)–C(2)–C(3)	112.0	O(2)–C(8)–C(9)	106.9
C(2)–C(3)	1.51	C(2)–C(3)–O(1)	109.7	O(3)–C(8)–C(10)	111.5
C(3)–C(4)	1.49	C(2)–C(3)–C(4)	115.5	O(2)–C(8)–C(10)	110.5
C(3)–O(1)	1.44	O(1)–C(3)–C(4)	106.7	O(3)–C(8)–C(9)	109.7
C(4)–C(5)	1.54	C(3)–C(4)–C(5)	103.9	C(9)–C(8)–C(10)	114.1
C(4)–O(2)	1.43	C(3)–C(4)–O(2)	112.5	C(5)–C(6)–O(1)	105.0
C(5)–C(6)	1.51	C(4)–C(5)–C(6)	105.9	C(3)–O(1)–C(6)	107.0
C(5)–O(3)	1.43	C(4)–O(2)–C(8)	108.6	C(6)–C(5)–O(3)	109.5
C(6)–C(7)	1.56	C(5)–C(4)–O(2)	103.5	O(1)–C(6)–C(7)	108.1
C(6)–O(1)	1.43	C(4)–C(5)–O(3)	104.9	C(5)–C(6)–C(7)	112.9
C(7)–O(4)	1.45	C(5)–O(3)–C(8)	107.9	C(6)–C(7)–O(4)	107.3
C(8)–O(2)	1.43				
C(8)–O(3)	1.42				
C(8)–C(9)	1.50				
C(8)–C(10)	1.51				

[a] Estimated standard deviations 0.01–0.02 Å. [b] Estimated standard deviations 0.8–1.0°. [c] See Figure 1a for numbering of atoms.

Experimental Section

General Methods. Column chromatography was performed using 70–230 mesh Merck silica gel. Thin layer chromatography (TLC) was done using 250 μ layers of silica gel GF 254 obtained from Analtech, Inc., Newark, Del., and preparative TLC using either 20 × 20 or 20 × 100 cm glass plates coated with a 1.0-mm layer of silica gel HF 254. Solvent systems used were (a) hexane–ethyl acetate (5:1, v/v), (b) hexane–ethyl acetate (3:1, v/v), (c) benzene–ethyl acetate (15:1, v/v), (d) benzene–ether (5:1, v/v), (e) petroleum ether (40–60°)–ethyl acetate (9:1, v/v), (f) chloroform–methanol (20:1, v/v) and (g) chloroform–methanol (10:1, v/v). Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using a Varian HA-100 spectrometer and ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra using a Bruker WH-90 instrument operating at 22.62 MHz. Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter and gas chromatographic analyses (GLC) were carried out with a Hewlett-Packard 402B instrument using nitrogen at a flow rate of 40 ml/min as carrier gas and a 1.8 m × 2.8 mm glass column containing 10% Carbowax on 80–100 Chromosorb. Retention times (R_T) are given in minutes. Some elemental analyses were obtained from Dr. A. Bernhardt, Elbach uber Engelskirchen, Germany, and other instrumental analyses were done by the staff of the analytical laboratories of Syntex Research, to whom we are particularly grateful.

X-Ray Crystallography. Unit cell parameters and intensity data were obtained with a Syntex $P2_1$ diffractometer using monochromatized Mo Kα radiation. Calculations were performed using the Syntex XTL system, and the solution of the structure was derived by the conventional heavy-atom method. The position of the bromine atom of **11e** was determined from a Patterson function, and subsequent Fourier synthesis, based upon the phase angles due to the bromine atom, located other atoms. The refinement was concluded by eight cycles of full matrix least-squares in which positional parameters of all atoms and anisotropic temperature factors of all atoms other than hydrogens were included. Atomic scattering factors are those of Cromer and Waber,[46] and anisotropic temperature factors fell in normally encountered ranges.

For the structure of **11e**, the crystals were orthorhombic, a = 5.775 (5), b = 11.878 (6), c = 25.007 (6), and were in space group $P2_12_12_1$; Z = 4, F (000) = 808. The calculated density was 1.53 g cm^{-3}, and the linear absorption coefficient was 25.7 cm^{-1} for Mo Kα. Of the 1347 reflections in the range $0 < 2\theta < 45$ that were measured using the ω scan technique, 1074 had an intensity greater than 1.96 times the standard deviation and were recorded as observed. The final R value for observed reflections was 0.046. Some slight deterioration of the crystal during data collection was suggested by a somewhat large value of B_{11} for the bromine atom.

Details of the final positional and thermal parameters are available from the authors.

Ethyl 3,6-Anhydro-2-deoxy-2-ethoxycarbonyl-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*- and -D-*altro*-heptonate (5a and 6a). Diethyl malonate (320 mg, 2 mmol) was added to a stirred suspension of sodium hydride (50% dispersion in oil, 96 mg, 2 mmol) in dry 1,2-dimethoxyethane (10 ml) at 0°. After 30 min at room temperature, **4** (902 mg, 2 mmol)[9] and sodium iodide (300 mg, 2 mmol) were added, and the mixture was heated under reflux for 4 hr. The cooled mixture was diluted with ether (100 ml), washed three times with saturated NH_4Cl solution and then with water, dried ($MgSO_4$), and concentrated to give 1.7 g of a syrup which was chromatographed on silica gel (100 g). Elution with benzene–ether (10:1) gave the pure D-altro epimer **6a** (900 mg) followed by a mixture of **5a** and **6a** (150 mg) that was further separated by preparative TLC using solvent g giving a further 19 mg of **6a** and 115 mg of the pure, more polar D-allo isomer (**5a**).

Compound **5a**: yield 10%; R_f 0.5 (solvent c); $[\alpha]^{20}$D 14° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{34}H_{38}O_8$ (574.64): C, 71.06; H, 6.66. Found: C, 70.81; H, 6.78.

Compound **6a**: yield 80%; R_f 0.6 (solvent c); $[\alpha]^{20}$D 35.6° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{34}H_{38}O_8$ (574.64): C, 71.06; H, 6.66. Found: C, 71.08; H, 6.84.

Epimerization of 5a by Base. A portion of 1 *N* sodium ethoxide (0.05 ml) was added to a solution of **5a** (50 mg) in absolute ethanol (5 ml). The solution was stored at 20° for 24 hr, diluted with ether (50 ml), washed with water and dried ($MgSO_4$). Evaporation of the solvents in vacuo gave a syrup (45 mg) which was shown by TLC and NMR to consist of **6a** and **5a** in a ratio of 9:1.

Methyl 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-2-methoxycarbonyl-7-*O*-trityl-D-*allo*- and -D-*altro*-heptonate (5b and 6b). Dimethyl malonate (264 mg, 2 mmol) was converted to the sodium salt as above and then reacted with **4** (700 mg, 1.55 mmol) and sodium iodide (100 mg, 0.67 mmol) under reflux for 1 hr. Following the usual work-up, the resulting syrup (1 g) was purified by preparative TLC using solvent a, giving an anomeric mixture of **6b** and **5b** (800 mg, 94%) in a ratio of 12:7 as shown by ^{1}H NMR. A portion (100 mg) of this mixture was separated by preparative TLC using solvent e, giving the two pure compounds **5b** and **6b** as viscous syrups.

Compound **5b**: R_f 0.25 (solvent a); $[\alpha]^{20}$D 9.3° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{32}H_{34}O_8$ (546.59): C, 70.31; H, 6.27. Found: C, 69.90; H, 6.38.

Compound **6b**: R_f 0.3 (solvent a); $[\alpha]^{20}$D 38.9° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{32}H_{34}O_8$ (546.59): C, 70.31; H, 6.27. Found: C, 70.07; H, 6.21.

Epimerization of 5b. A portion of 1 *N* sodium methoxide (0.2 ml) was added to a solution of the pure D-allo isomer (**5b**, 20 mg) in absolute methanol (2 ml). The mixture was stored at 20° for 4 hr and then worked up as usual giving a syrup (16 mg, 80%) which was shown by ^{1}H NMR to consist of **6b** and **5b** in a ratio of 6:1.

Methyl 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*- and -D-*altro*-heptonate (10a and 11a). A mixture of **7a**[9] (4.33 g, 10 mmol) and **8a** (6.68 g, 20 mmol) in acetonitrile (50 ml) was heated under reflux for 16 hr. The solvent was removed in vacuo and the residue chromatographed on silica gel (300 g) using solvent a, giving a colorless syrup (4.8 g, 98%) which was shown by ^{1}H NMR to consist of a mixture of **10a** and **11a** in a ratio of 3:1. A portion (300 mg) of the syrup was separated by preparative TLC

using solvent e, giving pure **10a** and its more polar D-altro isomer (**11a**) as colorless syrups.

Compound **10a**: R_f 0.35 (solvent e); $[\alpha]^{20}D$ 7.0° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{30}H_{32}O_6$ (488.56): C, 73.75; H, 6.60. Found: C, 73.72; H, 6.69.

Compound **11a**: R_f 0.4 (solvent e); $[\alpha]^{20}D$ 10.1° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{30}H_{32}O_6$ (488.56): C, 73.75; H, 6.60. Found: C, 73.72; H, 6.69.

Tritylation of 10c and 11c. A solution of trityl chloride (84 mg, 0.3 mmol) and **11c** (50 mg, 0.2 mmol) in dry pyridine (3 ml) was stirred at 20° for 16 hr and then concentrated in vacuo. The residue was purified by preparative TLC, using solvent c, giving **11a** (70 mg, 71%) as a colorless syrup.

In a similar fashion, **10a** was prepared in 72% yield by tritylation of **10c**. In both cases no epimerization at C_3 was observed, and the products were identical with those described above.

3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-and -D-*altro*-heptononitrile (10b and 11b). A solution of **7a** (4.33 g, 10 mmol) and **8b** (6 g, 20 mmol) in acetonitrile (75 ml) was heated under reflux for 16 hr. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (300 g) using ether, giving a 3:1 mixture (by ^1H NMR) of **10b** and **11b** as a colorless syrup (4.2 g, 92%). A portion of the syrup (300 mg) was separated by preparative TLC using solvent a, giving pure **11b** and the more polar D-allo isomer **10b**.

Compound **10b**: R_f 0.2 (solvent e); $[\alpha]^{20}D$ −5.5° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{29}H_{29}NO_4$ (455.53): C, 76.46; H, 6.42; N, 3.10. Found: C, 76.43; H, 6.55; N, 2.77.

Compound **11b**: mp 130° (from methanol); R_f 0.25 (solvent e); $[\alpha]^{20}D$ 9.8° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{29}H_{29}NO_4$ (455.53): C, 76.46; H, 6.42; N, 3.10. Found: C, 76.46; H, 6.35; N, 3.00.

The trityl derivatives **10b** (80%) and **11b** (75%) were also prepared from **10d** and **11d**, respectively, using the procedure described for the conversion of **11c** to **11a**.

Methyl 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*- and -D-*altro*-heptonate (10c and 11c). A solution of **7b**[15] (380 mg, 2 mmol) and **8a** (1 g, 3 mmol) in acetonitrile (10 ml) was heated under reflux for 4 hr. Examination of the reaction mixture by GLC showed the absence of starting material **5** and the formation of two new products in a ratio of 22:1. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (100 g) using ether, giving pure **10c** (450 mg, 91%) followed by a mixture of **10c** and **11c** (35 mg).

A solution of **10c** (246 mg, 1 mmol) and 1 *N* sodium methoxide (0.1 ml) in absolute methanol (10 ml) was heated under reflux for 3 days. Acetic acid (0.5 ml) was added, and the solvents were removed in vacuo, giving a syrup (250 mg). Analysis by GLC showed that the syrup consisted of a mixture of **10c** and **11c** in a ratio of 1:3. Separation by preparative TLC using solvent g afforded pure **10c** (60 mg, 24%) and the more polar **11c** (180 mg, 73%) as colorless syrups.

Compound **11c**: R_f 0.6 (solvent g); R_T = 14 min (210°); $[\alpha]^{20}D$ −6.6° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{11}H_{18}O_6$ (246.25): C, 53.65; H, 7.35. Found: C, 53.63; H, 7.44.

Compound **10c**: R_f 0.5 (solvent g); R_T = 19 min (210°); $[\alpha]^{20}D$ 5.4° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{11}H_{18}O_6$ (246.25): C, 53.65; H, 7.35. Found: C, 53.92; H, 7.58.

Detritylation of 10a and 11a. A solution of **10a** (244 mg, 0.5 mmol), 2,2-dimethoxypropane (10 ml), and *p*-toluenesulfonic acid monohydrate (475 mg, 2.5 mmol) in acetone (15 ml) was stirred at 20° for 5 hr. Sodium bicarbonate (1.5 g) was then added, and the reaction mixture was stirred for an additional 2 hr. The mixture was filtered and concentrated to a syrup which was purified by preparative TLC (solvent g), giving pure **10c** (96 mg, 78%). The absence of epimerization to **11c** during this reaction was confirmed using both TLC and GLC analyses.

In a similar fashion, **11c** was prepared in 80% yield from **11a**.

3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*- and D-*altro*-heptononitrile (10d and 11d). A mixture of **7b** (380 mg, 2 mmol)[15] and **8b** (1.2 g, 4 mmol) in acetonitrile (15 ml) was heated under reflux for 16 hr. GLC analysis showed the absence of **7b** and the formation of two new products (R_T = 18 min and R_T = 30 min at 210°) in a ratio of ca. 50:1. Purification by column chromatography on silica gel (100 g) using ether gave 410 mg (96%) of pure **10d** as a clear syrup.

In a separate experiment, the reaction mixture was heated under reflux for 3 days, at which time GLC analysis (210°) showed that the product consisted of a mixture of **10d** and **11d** in a ratio of 1:3. Chromatography on silica gel (50 g) using 2% methanol in chloroform gave **10d** (76 mg, 20%) and the more polar **11d** (347 mg, 65%) as homogeneous colorless syrups which, in the case of **11d**, crystallized spontaneously.

Compound **10d**: R_f 0.6 (solvent f); R_T = 18 min (210°); $[\alpha]^{20}D$ −25.2° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{10}H_{15}NO_4$ (213.23): C, 56.33; H, 7.10; N, 6.57. Found: C, 56.36; H, 7.25; N, 6.44.

Compound **11d**: mp 42–43°; R_f 0.5 (solvent f); R_T = 30 min (210°); $[\alpha]^{20}D$ 3.7° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{10}H_{15}NO_4$ (213.23): C, 56.33; H, 7.10; N, 6.57. Found: C, 56.39; H, 7.22; N, 6.40.

Compounds **10d** (80% yield) and **11d** (75% yield) were also obtained by detritylation of **10b** and **11b** using the method described for the conversion of **10a** to **10c**.

3,6-Anhydro-7-*O*-*p*-bromobenzoyl-2-deoxy-4,5-*O*-isopropylidene-D-*altro*-heptononitrile (11e). A solution of **11d** (213 mg, 1 mmol) and *p*-bromobenzoyl chloride (300 mg, 1.4 mmol) in pyridine (3 ml) was stirred at 0° for 1 hr and then at room temperature for 5 hr. It was then diluted with methylene chloride (50 ml) and washed successively with water, 3% sulfuric acid, aqueous sodium bicarbonate, and water. After drying ($MgSO_4$), evaporation of the solvent left 380 mg (96%) of crystalline **11e**. After recrystallization from methanol, **11e** had mp 136–137°; R_f 0.5 (solvent d); $[\alpha]^{20}D$ −3.5° (*c* 0.3, $CHCl_3$).

Anal. Calcd for $C_{17}H_{18}BrNO_5$ (396.26): C, 51.53; H, 4.58; N, 3.54; Br, 20.17. Found: C, 51.74; H, 4.68; N, 3.61; Br, 19.95.

3,6-Anhydro-7-*O*-*p*-bromobenzoyl-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptononitrile (10e). A reaction between **10d** (500 mg, 2.3 mmol) and *p*-bromobenzoyl chloride (700 mg, 3.2 mmol) in pyridine was carried out as described for **11e** above. Evaporation of the worked up product left 880 mg (95%) of **10e** as a TLC homogeneous syrup. An analytical sample was prepared by preparative TLC of a 150-mg sample using solvent d: R_f 0.5 (solvent d); $[\alpha]^{20}D$ 5.1° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{17}H_{18}BrNO_5$ (396.26): C, 51.53; H, 4.58; N, 3.54; Br, 20.17. Found: C, 51.80; H, 4.66; N, 3.37; Br, 20.03.

Methyl 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*- and -D-*glycero*-D-*galacto*-octonate (14 and 15). A solution of **13** (1.04 g, 4 mmol)[18] and **8a** (2.66 g, 8 mmol) in acetonitrile (50 ml) was heated under reflux for 16 hr. Analysis by GLC (210°) showed the absence of starting material and the formation of two products in almost equal amounts. Acetonitrile was removed in vacuo, and the residue was extracted with hot ether (200 ml). The ethereal solution was kept at 0° for 16 hr and the insoluble material removed by filtration and washed with cold ether. The combined filtrates were concentrated in vacuo to a syrup (1.5 g). Chromatography on silica gel (100 g) using solvent a gave pure **15** (500 mg, 40%), which crystallized spontaneously, a mixture of **14** and **15** (370 mg, 30%), and the pure more polar isomer **14** (250 mg, 20%).

Compound **14**: mp 59–60° (from hexane); R_f 0.27 (solvent b); $[\alpha]^{20}D$ −4.9° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{15}H_{24}O_7$ (316.34): C, 56.95; H, 7.65. Found: C, 56.68; H, 7.91.

Compound **15**: R_f 0.33 (solvent b); $[\alpha]^{20}D$ −5.7° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{15}H_{24}O_7$ (316.34): C, 56.95; H, 7.65. Found: C, 57.11; H, 7.80.

Epimerization of 14. A portion of 1 *N* sodium methoxide (0.01 ml) was added to a solution of **14** (5 mg) in absolute methanol (5 ml). The mixture was stored at 20° for 16 hr, at which time GLC analysis (210°) showed the presence of **14** and **15** in a ratio of 1:4.

Ethyl 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*allo*- and -D-*glycero*-D-*altro*-octonate (17a and 18a). A solution of **16**[20] (2.6 g, 10 mmol) and **8c** (7 g, 20 mmol) in acetonitrile (50 ml) was heated under reflux for 16 hr. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (250 g) using solvent d. Resolution of the two isomers was not achieved, and the product was isolated as a colorless syrup

(3.25 g, 98%) that was shown by proton and ^{13}C NMR to be a mixture of **17a** and **18a** in a ratio of 4:1 R_f 0.57 (solvent d).

Anal. Calcd for $C_{16}H_{26}O_7$ (330.37): C, 58.17; H, 7.93. Found: C, 58.23; H, 7.76.

In a separate experiment which was conducted for only 5 hr, the ratio of **17a** to **18a** was shown to be 7:1.

Equilibration of 17a. A portion of 1 *N* sodium ethoxide (0.1 ml) was added to a solution of a mixture of **17a** and **18a** (4:1, 30 mg) in absolute ethanol (10 ml). The mixture was stored at 20° for 16 hr and then worked up in the usual manner giving a syrup (24 mg, 80%) which was shown, by proton and ^{13}C NMR, to consist of a mixture of **17a** and **18a** in a ratio of 1:4.

3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*allo*- and -D-*glycero*-D-*altro*-octononitrile (17b and 18b). A solution of **16** (5.2 g, 20 mmol) and **8b** (12 g, 40 mmol) in acetonitrile (150 ml) was heated under reflux for 2 hr. GLC analysis (210°) indicated the disappearance of **16** (R_T = 11 min) and the formation of two products (R_T = 16 min and 18 min) in a ratio of 3:1. Acetonitrile was removed in vacuo and the residue chromatographed on silica gel (200 g) using solvent d, giving 5.5 g (100%) of a mixture of **17b** and **18b** (3:1 by GLC and NMR) as a colorless syrup that could not be resolved by TLC: R_f 0.5 (solvent d).

Anal. Calcd for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.43; H, 7.40; N, 4.88.

Equilibration of 17b. A 1 *N* sodium methoxide solution (0.05 ml) was added to a solution of a mixture of **17b** and **18b** (3:1, 30 mg) in benzene (15 ml), and the mixture was stored at 20° for 16 hr. Following the normal work-up, the product (21 mg, 70%) was shown by GLC to be a mixture of **17b** and **18b** in a ratio of 1:5.

Ethyl 3,6-Anhydro-2-deoxy-2-ethoxycarbonyl-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*- and -D-*glycero*-D-*galacto*-octonate (20 and 21). Sodium iodide (100 mg, 0.67 mmol) and **19** (279 mg, 1 mmol)[22] were added to a solution of diethyl sodiomalonate prepared from diethyl malonate (240 mg, 1.5 mmol) and sodium hydride in 1,2-dimethoxyethane (10 ml) as above, and the mixture was heated under reflux for 2 hr. Following the usual work-up, the product was purified by column chromatography on silica gel (10 g) using solvent e, giving a syrup (320 mg, 80%) consisting of **20** and **21** in a ratio of 1:9 as shown by ^1H NMR. Purification by preparative TLC using three developments with solvent c afforded pure **20** and its less polar epimer **21**.

Compound **20**: R_f 0.2 (solvent c); $[\alpha]^{20}D$ 17.9° (*c* 1.0, $CHCl_3$) [lit.[8b] $[\alpha]^{25}D$ 17° (*c* 3.6, $CHCl_3$)].

Anal. Calcd for $C_{19}H_{30}O_9$ (402.43): C, 56.71; H, 7.51. Found: C, 56.86; H, 7.86.

Compound **21**: R_f 0.1 (solvent c); $[\alpha]^{20}D$ −44.7° (*c* 1.0, $CHCl_3$) [lit.[8b] $[\alpha]^{25}D$ −45.4° (*c* 7.2, $CHCl_3$).

Anal. Calcd for $C_{19}H_{30}O_9$ (402.43): C, 56.71; H, 7.51. Found: C, 56.92; H, 7.82.

Epimerization of 20 and 21. A 1 *N* sodium ethoxide solution (0.05 ml) was added to a solution of pure **20** (50 mg) in absolute ethanol (5 ml). The mixture was stored at 20° for 24 hr and then worked up as usual giving a syrup (43 mg, 86%) which was shown by ^1H NMR to consist of **21** and **20** in a ratio of 5:1. Similar treatment of pure **21** gave the same mixture of **20** and **21**.

***cis*- and *trans*-4,5,7-Tri-*O*-benzyl-2,3-dideoxy-D-*ribo*-hept-2-enonate (23 and 24).** A solution of **22** (1.85 g, 5 mmol)[23] and **8a** (3.2 g, 10 mmol) in acetonitrile (50 ml) was heated under reflux for 6 hr. Acetonitrile was removed in vacuo, and the residue was dissolved in hot ether (100 ml). The ethereal solution was stored at 0° for 16 hr and the insoluble material removed by filtration and washed with cold ether. The combined filtrates were evaporated in vacuo, and the residue was chromatographed on silica gel (200 g) using solvent d giving 1.28 g (60%) of **23** and 860 mg (34%) of the more polar trans isomer (**24**) as homogeneous syrups.

Compound **23**: R_f 0.4 (solvent d); $[\alpha]^{20}D$ 34.9° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{29}H_{32}O_6$ (476.55); C, 73.09; H, 6.77. Found: C, 73.33; H, 6.94.

Compound **24**: R_f 0.3 (solvent d); $[\alpha]^{20}D$ 49.5° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{29}H_{32}O_6$ (476.55): C, 73.09; H, 6.77. Found: C, 73.40; H, 6.86.

Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-β-D-*allo*- and -β-D-*altro*-heptonate (25a and 25b). (a) A solution of the cis olefin **23** (100 mg) in methanolic sodium methoxide (0.5 ml of 0.1 *M*) was kept at room temperature for 10 min. The resulting yellow solution was diluted with ether and washed with 1 *M* aqueous sodium bisulfate and then water. Evaporation of the dried ($MgSO_4$) ether phase left 96 mg (96%) of pure **25a** as a clear syrup: $[\alpha]^{23}D$ −13.1° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{29}H_{32}O_6$ (476.55): C, 73.09; H, 6.77. Found: C, 73.14; H, 6.81.

(b) The pure trans olefin **24** was treated with sodium methoxide and worked up exactly as above, giving an inseparable 3:2 mixture of **25a** and **25b** in 98% yield. The relative proportions were apparent from the proton NMR spectrum of the mixture, which showed the C_2-methylene protons of **25a** and **25b** as well separated doublets of doublets at 2.40 and 2.59 ppm and at 2.66 and 2.85 ppm, respectively. The D-allo configuration of **25a** was apparent from the downfield positions of C_2, C_3, and C_4 in the ^{13}C NMR spectra relative to the same atoms in **25b**.

Anal. Calcd for $C_{29}H_{32}O_6$ (476.55): C, 73.09; H, 6.77. Found: C, 73.31; H, 6.78.

Equilibration of 25a and 25b. (a) A solution of **23** (100 mg) in methanolic sodium methoxide (0.5 ml of 0.1 *M*) was stored at room temperature for 23 hr and then worked up as above giving 100 mg (quantitative) of a mixture of **25a** and **25b** in a ratio of 3:1 (proton NMR).

(b) Treatment of **24** (193 mg) with sodium methoxide for 28 hr as above gave 190 mg (98%) of a mixture of **25a** and **25b** in a ratio of 2:1 (proton NMR).

Attempted Lactonization of 10c. A solution of **10c** (246 mg, 1 mmol) in benzene (100 ml) was heated for 18 hr under reflux in the presence of methanolic sodium methoxide (0.1 ml of 1.8 *M*) with periodic removal of a portion of the solvent by distillation. The cooled solution was then washed twice with water, dried, and evaporated. Crystallization of the residue from methanol gave 76 mg (35%) of a dimer with mp 237°: $[\alpha]^{23}D$ 28.2° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) complex with doubling of all signals (e.g., isopropylidene methyls at 1.30, 1.34, 1.57, 1.61 ppm); mass spectrum (70 eV), *m/e* 428 (M^+), 413 ($M^+ - CH_3$).

Anal. Calcd for $C_{20}H_{28}O_{10}$ (428.44): C, 56.07; H, 6.59. Found: C, 56.00; H, 6.58.

The mother liquors from the above dimer were separated into two pure compounds by chromatography on silica gel using ether. Crystallization of the less polar compound from methanol gave 43 mg (20%) of an isomeric dimer with mp 196–198°; NMR (C_6D_6) isopropylidene methyls at 1.10 and 1.34 ppm; mass spectrum (70 eV) *m/e* 428 (M^+), 413 ($M^+ - CH_3$). Crystallization of the more polar compound from methanol gave 47 mg (22%) of a trimer with mp 167–169°; NMR ($CDCl_3$) complex with isopropylidene methyls at 1.33, 1.48, and 1.54 ppm; mass spectrum (70 eV) *m/e* 642 (M^+), 627 ($M^+ - CH_3$).

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The Structure and Formation of Stable $C_2H_4O^{\cdot+}$ Ions[1]

C. C. Van de Sande[2] and F. W. McLafferty*

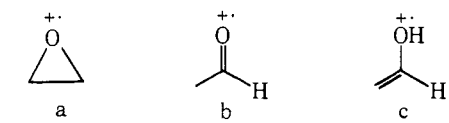
Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14850. *Received September 10, 1974*

Abstract: The $C_2H_4O^{\cdot+}$ isomeric ions $\overline{CH_2CH_2O}^{\cdot+}$ (a), $CH_3CH{=}O^{\cdot+}$ (b), and $CH_2{=}CHOH^{\cdot+}$ (c) are stable, with lifetimes of $>10^{-5}$ sec, and can be identified from their collisional activation (CA) spectra. The earlier assignments of structure c for $C_2H_4O^{\cdot+}$ ions generated from cyclic alcohols, alkyl vinyl ethers, and aliphatic epoxides are confirmed. Surprisingly, 2-haloethanols yield c through 1,2 elimination of HX. Ions c are also produced from glycerol and 1,4-butanediol. Both ions b and c are produced from 1,3-butanediol, and a and c are generated from 1,3-dioxolane.

Our knowledge of the formation and unimolecular decompositions of gaseous positive ions has been greatly enhanced by the development of new techniques for ion structure determination such as ion cyclotron resonance,[3] unimolecular metastable ion (MI),[4] and collisional activation (CA)[5] spectra. The latter appear to be especially advantageous, because they are insensitive to differences in ion internal energy, and because the substantial number of peaks in their spectra provide specificity for ion characterization.

Studies on $C_2H_5O^+$,[4a,5b] $C_3H_7O^+$,[5c] $C_2H_6N^+$, and $C_3H_8N^+$ [5d] ions indicate that structural inferences are particularly straightforward for even-electron ions containing a heteroatom; the isomers found to be stable (lifetimes $\geq 10^{-5}$ sec) are generally those predicted from physical organic principles. This observation prompted us to extend our investigations to odd-electron species; although these would be expected to be of lower stability,[6] the odd-electron $C_3H_6O^{\cdot+}$ ions corresponding to the keto and enol forms of acetone have been shown to be stable.[3b,7] In the present paper, the results of a CA study on $C_2H_4O^{\cdot+}$ ions (*m/e* 44) are presented. These ions are of considerable interest as they are important rearrangement products in the mass spectra of aliphatic aldehydes, cyclic alcohols, alkyl vinyl ethers, aliphatic epoxides, functionalized alcohols, and cyclic ethers.[6]

Based on ground-state chemistry, structures a, b, and c can be visualized for $C_2H_4O^{\cdot+}$ ions. In a recent independent



a b c

study of the molecular ions a and b, Pritchard[8] reviews the inconclusive nature of the previous structural investigations of these ions and reports MI spectral data that "reveal no reason to suppose" that a isomerizes to b, in contrast to previous postulates based on the similarity of their mass spectra. The reported[8] facile tautomerization b $\rightleftarrows$ c also is in contrast to the conclusions concerning the analogous $C_3H_6O^{\cdot+}$ ions.[3b,7]

Results and Discussion

Reference Ions. The CA spectra of $C_2H_4O^{\cdot+}$ ions from a variety of sources are given in Table I. Ions of structures a and b have been generated through ionization of ethylene