with the structure and the data published. Unless otherwise indicated new compounds were fully characterized by all the usual spectroscopy methods and confirmed by microanalysis.

Registry No. **1a**, 591-50-4; **1b**, 615-37-2; **1e**, 583-55-1; **2b**, 624-31-7; **2c**, 35779-04-5; **2d**, 637-87-6; **2e**, 589-87-7; **2f**, 352-34-1; **2g**, 33527-94-5; **2h**, 28896-49-3; **2i**, 622-50-4; **2j**, 126063-08-9; **3a**, 615-42-9; **4a**, 624-38-4; **5b**, 32704-08-8; **5c**, 126063-03-4; **5e**, 126063-04-5; **5f**, 126063-06-7; **6b**, 32704-10-2; **6d**, 126082-46-0; **6e**, 126063-05-6; **6f**, 126063-07-8; C_6H_6, 71-43-2; C_6H_5Me, 108-88-3; C_6H_5t-Bu, 98-06-6; C_6H_5Cl, 108-90-7; C_6H_5Br, 108-86-1; C_6H_5F, 462-06-6; C_6H_5OAc, 122-79-2; $C_6H_5OC_6H_5$, 101-84-8; C_6H_5NHAc, 103-84-4; $C_6H_5NHC(O)CF_3$, 404-24-0; $C_6H_5CO_2Et$, 93-89-0; C_6H_5CHO, 100-52-7; C_6H_5Ac, 98-86-2; C_6H_5CN, 100-47-0; $2\text{-}O_2NC_6H_4OMe$, 91-23-6; $4\text{-}O_2NC_6H_4OMe$, 100-17-4; $4\text{-}O_2NC_6H_4NHAc$, 104-04-1; $3,4\text{-}I_2C_6H_3Br$, 21521-54-0; I_4C_6HF, 126063-09-0; $3\text{-}IC_6H_4CO_2Et$, 58313-23-8; $3\text{-}IC_6H_4CHO$, 696-41-3; $3\text{-}IC_6H_4Ac$, 14452-30-3; $3\text{-}IC_6H_4CN$, 69113-59-3; 4-iodo-2-nitroanisole, 52692-09-8; 2-iodo-4-nitroanisole, 5399-03-1; 2-iodo-4-nitroacetanilide, 19591-18-5.

Diels–Alder Reactions of Dieno-Pyranosides. Anomeric vs Allylic Stereoselection‡

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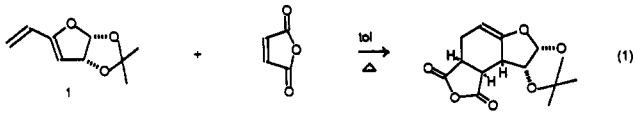
A series of carbohydrate-derived dienes with different patterns of substitution on the pyranose ring were synthesized and their Diels–Alder reactions investigated. The diene moiety was incorporated into the pyranose ring by oxidation of 4-*O*-methanesulfonate esters of sugar derivatives to enals, followed by Wittig alkenation. This new class of dienes underwent cycloaddition with maleimide or its *N*-phenyl derivative to give annulated pyranosides. The Diels–Alder reactions were highly stereoselective, giving single products in some cases. Structural analysis of the reaction products was carried out by NMR spectroscopy and X-ray crystallography. The results indicated a strong preference for the formation of the products resulting from addition of the dienophile to the face of the diene opposite the anomeric center. In cases where the anomeric and allylic substituents on the diene occupied opposite faces, addition of the dienophile occurred predominantly from the face opposite the more remote anomeric center. This result was contrary to expectations based on the reported effects of allylic groups on the diastereofacial selectivity of Diels–Alder reactions.

Introduction

Diels–Alder reactions of carbohydrate derivatives constitute a useful methodology for the synthesis of carbocyclic compounds in optically active form. In recent studies, Diels–Alder adducts obtained from sugar substrates have been used as intermediates in approaches to complex natural products that contain cycloalkyl rings, for example, the aureolic acid antibiotic olivin,[1] the antibiotic actinobolin,[2] the diterpene forskolin,[3] and prostaglandins.[4] While carbohydrate derivatives have functioned both as dienes and dienophiles in the Diels–Alder reaction, in most applications, the dienophile has been derived from the carbohydrate. The first examples of the synthesis of carbocyclic compounds with carbohydrate-derived dienes were reported from the laboratories of Fraser-Reid.[5] Dieno-furanoside **1** and related systems underwent cycloaddition to maleic anhydride, giving annulated furanosides in high stereoselectivity (eq 1). In spite of these promising

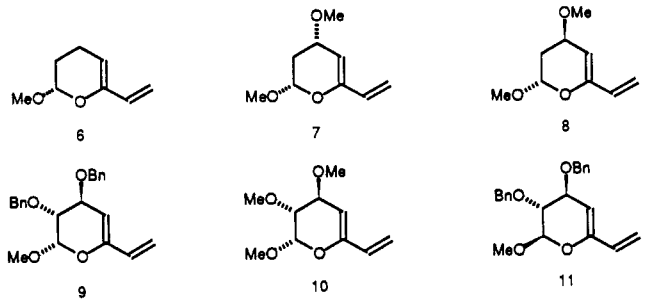


(1)

results, only a few other examples of carbohydrate-derived dienes have been reported.

In a recent communication[6] from our laboratory, we described the synthesis and Diels–Alder reactions of

Table I. Dieno-Pyranosides



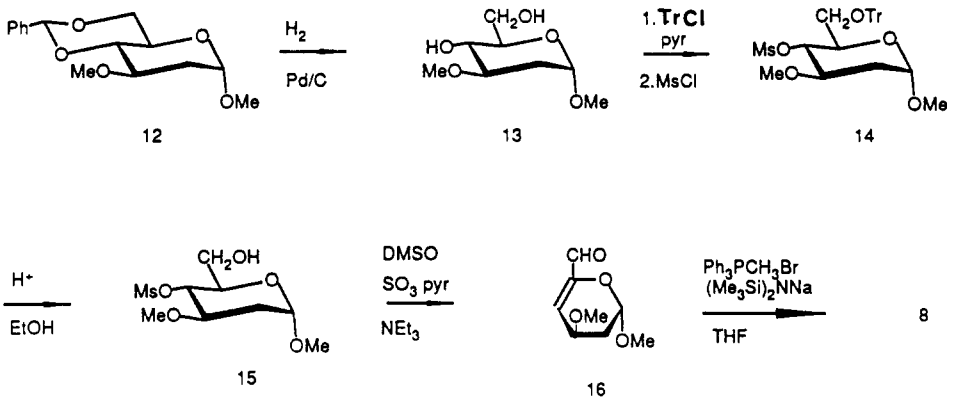
analogous six-membered dieno-pyranosides **2**, the prototypes of a new class of dienes which contain a pyranose ring. Since the publication of our results, structurally related dieno-pyranosides in which the diene moiety occurs at a different position have also been reported.[7,8] In

‡ Taken in part from the Ph.D. thesis of J. H. Buzby, Villanova University, 1987; *Diss. Abstr. Int. B* **1987**, DA8720636.

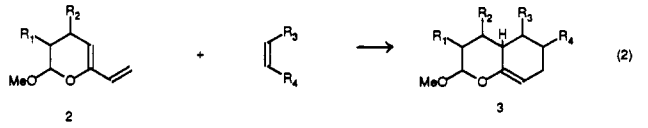
(1) Franck, R. W.; John, T. V. *J. Org. Chem.* **1983**, *48*, 3269.
(2) Rahman, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576.
(3) Mukhopadhyay, A.; Ali, S. M.; Husain, M.; Suryawanshi, S. N.; Bhakuni, D. S. *Tetrahedron Lett.* **1989**, *30*, 1853.
(4) Horton, D.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135.
(5) Sun, K. M.; Fraser-Reid, B.; Tam, T. F. *J. Am. Chem. Soc.* **1982**, *104*, 367. Sun, K. M.; Giuliano, R. M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4774.
(6) Giuliano, R. M.; Buzby, J. *Carbohydr. Res.* **1986**, *158*, c1.
(7) Lopez, J. C.; Lameignere, E.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1988**, 706.
(8) Lipshutz, B. H.; Nguyen, S. L.; Elworthy, T. R. *Tetrahedron* **1988**, *44*, 3355.

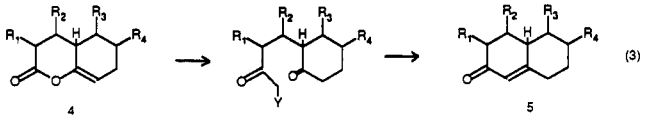
0022-3263/90/1955-3555$02.50/0

Scheme I



undertaking our investigation, we considered that a versatile route to annulated pyranosides of general structure **3** could be developed by Diels–Alder reactions of **2** (eq 2),



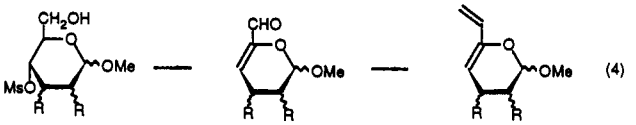


and that functionalized decalones **5** might be derivable from **3** by oxidation to enol lactone **4**, followed by nucleophilic ring opening–ring closure (eq 3).[9] In order to pursue either of these objectives, it is first necessary to ascertain the factors that control the stereoselectivity of the Diels–Alder reactions of **2**. Three new stereocenters are generated in the cycloaddition, and we need to know the effects that substituents on the pyranose ring will exert on the stereoselectivity of additions to the diene system. Accordingly, dieno-pyranosides with different patterns of ring substitution were synthesized and their Diels–Alder reactions investigated.

The dieno-pyranosides chosen for this study are shown in Table I. Given the depth of the existing methodology for the preparation of carbohydrates in their pyranose form, many variations of general structure **2** are possible. In selecting these dienes, we considered the feasibility of synthesis from readily available monosaccharides and the pattern of substitution at the C-1, C-2, and C-3 positions on the pyranose ring. Diene **6** was chosen because we wished to determine the stereodirecting effects of the anomeric substituent independent of other groups on the diene. Dienes **7** and **8** differ only in configuration at the allylic, C-3 position and were chosen to probe the relative magnitudes of the effects of allylic vs anomeric substituents on diastereofacial selectivity. Dienes **9** and **10** were selected in order that the effect of additional ring substitution might be determined. Both **9** and **10** possess the same configurations at C-1 and C-3 as **8**, but are also substituted at the C-2 position. Diene **11**, a β-methyl glycoside, differs from **9** only in the stereochemistry of the anomeric center.

Results

The dienes were all prepared from the corresponding α,β-unsaturated aldehydes (enals) by the Wittig reaction (eq 4). The enals were obtained by treatment of 4-*O*-



methanesulfonate esters of suitably protected sugar derivatives with sulfur trioxide–pyridine complex in DMSO, under conditions described by Perlin for the oxidation of partially acetylated sugars.[10] The syntheses of dienes **6** and **7**, and the enal used to prepare diene **9**, have been described in previous publications from our laboratory.[6,11] The synthesis of dieno-pyranoside **8** is shown in Scheme I.

Hydrogenolysis of methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**12**)[12] gave diol **13** which was converted to hydroxy mesylate **15** in three steps as shown. Treatment of **15** with sulfur trioxide–pyridine complex resulted in simultaneous oxidation and elimination to give enal **16**. Chromium-based oxidants were also examined for this transformation and found to be less efficient. The direct oxidation of **13** to **16** was also attempted without success. Wittig alkenation of **16** using sodium hexamethyldisilazide and methyl triphenylphosphonium bromide in THF gave dieno-pyranoside **8** in 12% overall yield from diol **13**. Dieno-pyranosides **10** and **11** were synthesized from methyl α- and β-D-glucopyranoside, respectively, using analogous reaction sequences.[13] For compounds that contain benzyl ether protecting groups, e.g., **9** and **11**, removal of the 4,6-*O*-benzylidene group was achieved by treatment with *p*-toluenesulfonic acid in refluxing ethanol. The sequence leading from **13** to **8** is general and was used to prepare all of the dienes in this study.

Diels–Alder reactions of the dieno-pyranosides were attempted with several dienophiles in benzene, at room temperature and reflux temperature, using different mole ratios of dienophile. The choice of benzene as solvent was suggested by previous work with carbohydrate dienes.[5] In the recent work of Overman,[14] and Franck and Tripathy,[15] on the Diels–Alder reactions of semicyclic dienes, solvent effects were not observed with dienes substituted at the allylic site with methoxy or trialkylsilyloxy groups. In view

(9) Henrick, C. A.; Bohme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926. Becker, K. R. *Tetrahedron* **1980**, *36*, 1717.

(10) Cree, G. M.; Mackie, D. W.; Perlin, A. S. *Can. J. Chem.* **1969**, *47*, 511.

(11) Giuliano, R. M.; Buzby, J. *J. Carbohydr. Chem.* **1987**, *6*, 541.

(12) Charon, D.; Szabo, L. *Carbohydr. Res.* **1974**, *34*, 271.

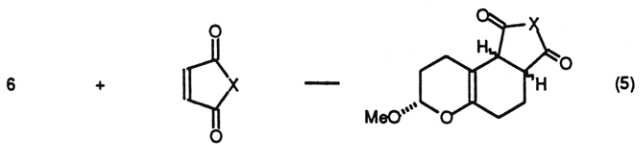
(13) Dennison, J. C., McGilvra, D. I. *J. Chem. Soc.* **1951**, 1616.

(14) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.

(15) Tripathy, R. Ph.D. Thesis, Hunter College, 1989.

of these results, one would not expect solvent effects to be significant for the Diels–Alder reactions of the dienes used in this study because the hydroxyl groups are all protected. Dienophiles which did not react included acrolein, acrylonitrile, α-chloroacrylonitrile, 2(5*H*)-furanone, thiophen-2-one, nitroethylene, and 2-nitropropylene. The sensitivity of the dienes to acid precluded the use of Lewis acid catalysts. The best yields of cycloadducts were obtained using excess maleimide or its *N*-phenyl derivative in refluxing benzene. Cycloadducts were separated from excess dienophile by column chromatography on Florisil; crystalline products were obtained in some cases. Results of the Diels–Alder reactions are summarized in Table II for five of the six dieno-pyranosides. Assignment of structure to the Diels–Alder adducts was made on the basis of NMR spectroscopy and X-ray crystallography. Vicinal proton coupling constants were useful in determining both the facial selectivity of addition (from $J_{3,4}$ in the cycloadducts) and the endo/exo selectivity (from $J_{4,9}$). Large differences in chemical shifts were observed for pyranoid ring protons in the products resulting from α-face vs β-face addition to dieno-pyranosides with substituents at C-2. Our initial assignments of stereochemistry in the cycloadducts, made on the basis of NMR methods, were corroborated by X-ray crystallographic analysis of one of the Diels–Alder adducts, compound **22**.

All of the dienes underwent the Diels–Alder reaction to give annulated pyranosides with the general structure **3**, except for **6**, which gave a rearranged cycloadduct as a near-equal mixture of stereoisomers which could not be separated (eq 5).[6] Because the stereocenter at C-4 was

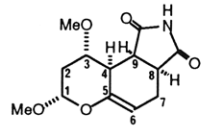
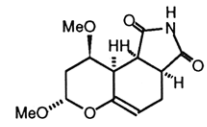
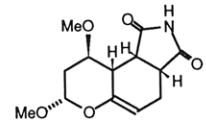
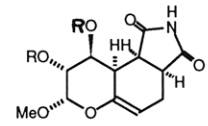
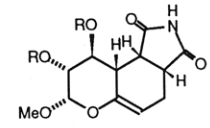
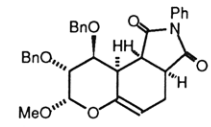
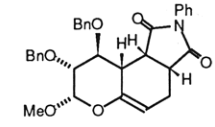
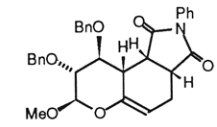


(5)

destroyed in the rearrangement, the facial selectivity of the addition to **6** could not be determined. The presence of a single anomeric configuration is indicated in the ^1H NMR and ^{13}C NMR spectra of the product, suggesting that the mixture of diastereomers results from a lack of either facial or endo/exo selectivity in the cycloaddition. In either case this experiment is anomalous when compared with all others examined. In the case of diene **7**, recorded in entry 1, treatment with maleimide gave a single adduct (**17**) in 53% yield after purification. The structure of **17** was assigned on the basis of its NMR spectrum recorded at 200 MHz ($J_{3,4}$ = 10.1 Hz; $J_{4,9}$ = 6.2 Hz).[6] The configurations of the new stereocenters generated at C-4 and C-9 in the product are those which result from cycloaddition to the β-face of **7**, in the endo mode.

Under identical conditions dieno-pyranoside **8** (entry 2) gave a mixture in which the major component (**18**) was the product resulting from β-face addition of maleimide in the endo mode. The adducts could not be separated; however, key resonances in the ^1H NMR spectra of the mixture were sufficiently resolved to allow assignments of product stereochemistry to the major isomer. Except for the smaller $J_{3,4}$ value, the ^1H NMR spectrum of **18** was very similar to that obtained for **17**. Dienes **9** and **10** (entries 3 and 4) both gave β-face endo adducts as the major products when treated with maleimide. The major and minor isomers produced in the reaction of **10** could be separated, but assignment of structure to these adducts

Table II

entry	diene	β-face adduct	α-face adduct	ratio
1.	7	 **17**		
2.	8	 **18**	 **19**	4.1:1
3.	9	 **20a** (R=Bn) **20b** (R=Me)	 **21a** (R=Bn) **21b** (R=Me)	4.7:1
4.	10			3.0:1
5.	9	 **22**	 **23**	6.4:1
6.	11		 **24**	

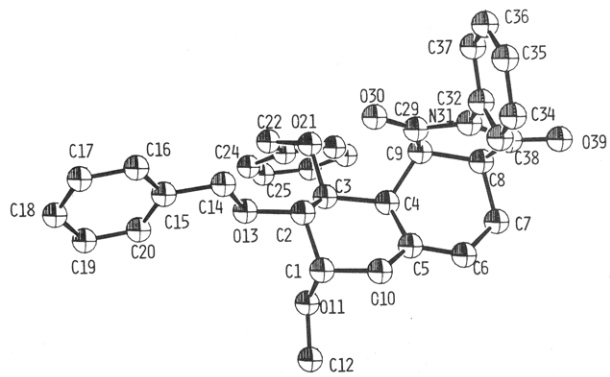


Figure 1. Computer-generated drawing of **22** derived from the X-ray coordinates with hydrogens omitted for clarity.

by NMR methods alone proved to be more difficult owing to the overlap of key resonances, even at 400 MHz. While extensive decoupling experiments enabled us to measure the critical *J* values, we were unable to make unambiguous assignments of stereochemistry on the sole basis of the NMR spectra. Fortunately, treatment of **9** with *N*-phenylmaleimide (entry 5) gave a mixture from which the major component **22** could be separated from the minor adduct **23** and crystallized. The structure of **22** obtained by X-ray crystallographic analysis is shown in Figure 1. The figure shows an all-cis relationship between H-3, H-4, and H-9, and a dihedral angle for H-3 and H-4 of 30°. The cyclohexene ring of **22** is in the boat conformation and the pyranoid ring occupies the twist-boat form with C-2 and C-1 lying above and below the plane formed by the ring oxygen, vinylic carbon, and the C-3 and C-4 carbons. As in the case of **17**, the configurations of the newly formed stereocenters are those which result from β-face addition

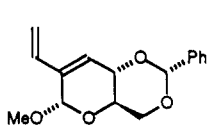
to the diene, in the endo mode.

The ^1H NMR spectra of **22** and **23** provided an additional feature which proved useful in assigning structures to other Diels–Alder adducts. An unexpectedly large difference in the chemical shifts of the H-2 resonances was observed in the spectra of the major (β-endo) and minor (α-endo) adducts. The H-2 resonance occurred at δ 4.29 in **22** and at δ 3.57 in **23**, while the region between δ 3.2 and 4.2 ppm was devoid of peaks in the spectrum of **22**. Downfield shifts of the H-2 resonances were also observed in the spectra of **20a** and **20b**, relative to the shifts for these protons in the minor products **21a** and **21b**, the spectra of which were most consistent with expected products of α-face addition in the endo mode. The downfield shift of the H-2 resonance may be a result of deshielding of H-2 by the imide carbonyl at C-9 which is in close proximity.

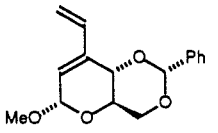
Diene **11**, the β-anomer of **9**, gave a single cycloadduct when treated with *N*-phenylmaleimide (entry 6). The ^1H NMR spectrum of the product exhibited values for $J_{3,4}$ and $J_{4,9}$ of 10.7 Hz and 6.3 Hz, respectively. The large $J_{3,4}$ value implies a trans-diaxial relationship between these two hydrogens that would exist in the two possible adducts resulting from addition to the α-face, but not in those produced by addition to the opposite, β-face. The value of 6.2 Hz for $J_{4,9}$ suggests a cis relationship for these two hydrogens which would result from cycloaddition in the endo mode. Further comparisons of the NMR spectra of **24** with those obtained for **22** and **23** support the assignment of **24** as the α-endo adduct.

Discussion

Although four possible products are possible for the Diels–Alder reactions of the dieno-pyranosides, only two were formed with dienes **8**, **9**, and **10**, while dienes **7** and **11** gave a single cycloadduct. In all cases, only products resulting from addition in the endo mode were obtained, consistent with other results in the literature.[7,8] The stereoselectivities observed in the Diels–Alder reactions in this study, as well as those reported[7,8] for **25** and **26**,

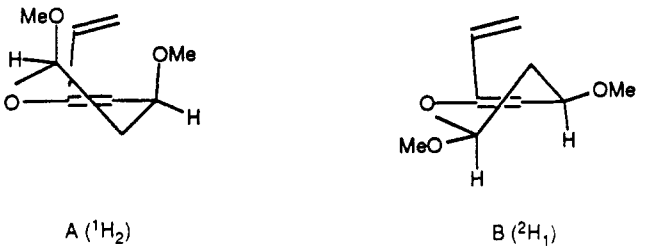


25



26

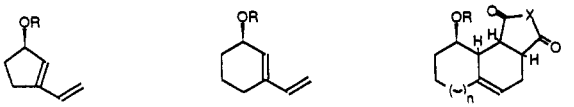
indicated a strong preference for addition of the dienophile to the face of the diene opposite the anomeric substituent. The exclusive preference for β-face addition to **7**, and for α-face addition to **11**, might have been predicted from a consideration of steric effects alone since the allylic group at C-3 and the anomeric substituent both occupy the same face in each case: α in **7** and β in **11**. The preference for addition to the β-face of dienes **8**, **9**, and **10**, however, was somewhat surprising. We predicted that the stereocenter at C-3 would have a greater effect on the facial selectivity of the cycloaddition because C-3 is attached to the diene terminus, while the anomeric and C-2 positions are remote. The effect of allylic substituents, particularly hydroxyl or ether groups, on the stereoselectivity of organic reactions has received much attention in recent literature, and the effects that such groups exert on diastereofacial selectivity have been well-documented for many examples of Diels–Alder reactions.[16] Unfortunately, nearly all of the studies



A ($^1H_2$) B ($^2H_1$)

Figure 2. Half-chair conformations of **7**.

have treated only acyclic dienes, which can undergo free rotation of the allylic group. Two recent studies that include examples of semicyclic dienes have been described by Overman, Hehre, and co-workers,[14] and by Franck and Tripathy.[15] In the Overman study, it was observed that cycloaddition to dienes of general structure **27** occurred predominantly from the face of the diene opposite the allylic substituent. This anti selectivity was ascribed to



27 R=H,Me,R'$_3$Si 28 anti n=0,1 X=O,NPh

unfavorable electrostatic interactions that develop in the transition state leading to the alternate, syn product. In the study of Franck and Tripathy, anti selectivity was also observed in nearly all cycloadditions to semicyclic dienes **28**; however, the importance of electrostatic effects was questioned. It was argued that the antiselectivity observed in cycloadditions to semicyclic dienes, and to the dieno-pyranosides of this study as well, results mainly from steric effects. For the dieno-pyranosides, our results indicate that although the allylic substituent has an effect on the stereochemistry of the Diels–Alder reaction in these systems, it is the anomeric substituent that is most important in determining the facial selectivity of addition. Some idea of the relative magnitudes of the stereodirecting effects of allylic and anomeric groups in the dieno-pyranosides is indicated by the results recorded in entries 2, 3, 4, and 5 in Table II. In these cases, the allylic and anomeric groups occupy opposite faces of the diene. Surprisingly, dieno-pyranoside **8** (entry 2) underwent addition preferentially syn to the allylic group, in contrast to the systems reported by Overman and Franck. Likewise, **9** and **10** (entries 3–5) gave adducts that result from syn addition to the allylic group as the major products. The major products in all cases examined were those resulting from addition to the face of the diene opposite the anomeric substituent.

In considering the basis for the facial selectivity observed in the Diels–Alder reactions of the dieno-pyranosides, we agree with the suggestion of Lopez, Lameignere, and Lukacs[7] that addition takes place from the face opposite the anomeric center because of unfavorable steric effects in the transition state for syn addition. Anomeric stereoselectivity is well-known for other reactions of carbohydrate derivatives in their pyranose form, for example, nucleophilic additions to pyranosid-3-uloses[17] and Claisen rearrangements.[18] In the analysis of the Diels–Alder reactions described in this study, a question of conformation for the dieno-pyranosides arises. In the two half-chair conformations that these systems would be expected to adopt,

(16) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257. Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800. McDougal, P. G.; Rico, J. G.; VanDerveer, D. *J. Org. Chem.* **1986**, *51*, 4494.

(17) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69.

(18) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347.

the anomeric substituent will be pseudo-axial in one conformer and pseudo-equatorial in the other. The two half-chair forms are shown in Figure 2 for dieno-pyranoside **7**. Conformer A ($^1H_2$), in which the anomeric methoxy group is pseudo-axial, is favored by the anomeric effect over conformer B ($^2H_1$), but is destabilized by the 1,3-diaxial orientation of the C-1 and C-3 substituents. Analysis of the ^{1}H NMR spectrum of the diene strongly suggests that **7** exists in conformer A. The value of 2.4 Hz for $J_{1,2e}$ and $J_{1,2a}$ implies gauche relationships between the anomeric proton and the protons attached to C-2, and is more consistent with conformer A. Molecular mechanics calculations also indicate that conformer A is favored for **7**, with slight distortion of the ring toward the sofa form in which C-2 lies nearer to the plane established by the ring oxygen, C-3, C-4, and C-5. An energy difference of 1.6 kcal/mol was calculated for the two conformers. While these data do not rule out the possibility that **7** reacts via conformer B, or some other distorted form, they do suggest a favored conformation for the diene in its ground state. With respect to the stereoselectivity of the Diels–Alder reaction, the exclusive preference for addition of the dienophile to the β-face of **7** also seems more consistent with conformer A, since the α-face is more sterically hindered in A than in B. NMR data and MM2 calculations obtained for dienes **8**, **9**, and **10** both suggest the $^1H_2$ conformer for the ground state. For diene **11**, the β-anomer of **9**, the $J_{1,2}$ and $J_{2,3}$ values of 7.4 and 9.4 Hz are consistent with the $^2H_1$ conformer.

In summary, a new class of carbohydrate-derived dienes were synthesized and their Diels–Alder reactions investigated. The best yields of cycloadducts were obtained with maleimide and its *N*-phenyl derivative in refluxing benzene. A new route to annulated pyranosides was developed using this methodology. The stereoselectivities observed in the Diels–Alder reactions of the dieno-pyranosides indicated a strong preference for addition of the dienophile to the face of the diene opposite the anomeric substituent. The allylic groups on the dienes had a smaller effect on the facial selectivity of the cycloaddition than was predicted from current theories of allylic stereoselection. Adducts resulting from syn addition to the allylic substituents were the major products in some cases, in contrast to results obtained for other, less highly substituted dienes reported in the recent literature.

Experimental Section

General Procedure. Melting points were determined on a Thomas–Hoover apparatus and they are reported uncorrected. Infrared spectra were recorded on an Analect FX-6160 spectrometer. Only the strongest and structurally most significant peaks are reported. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer at 200 and 50.3 MHz, respectively. Chemical shifts were recorded relative to tetramethylsilane (0.0) for ^{1}H resonances and deuteriochloroform (76.91) for ^{13}C resonances. Coupling data for ^{13}C NMR spectra were obtained using a gated decoupling two-pulse sequence with an acquisition time of 0.5 s and a delay of 0.75 s. Mass spectra were recorded at the University of Pennsylvania on a VG-7070H spectrometer, under CI conditions with either isobutane or ammonia. HPLC was performed on Beckman Ultrasphere ODS columns.

The progress of reactions was monitored by thin layer chromatography using aluminum-supported plates of silica gel 60 (0.2 mm, F-254, E. Merck). Components were detected by observation under short-wavelength ultraviolet light or spraying with 5% sulfuric acid–ethanol or a solution of ammonium molybdate and ceric sulfate in 10% sulfuric acid, followed by heating. Flash chromatography was performed on silica gel 60 (230–400 mesh) or Florisil (60–100 mesh). Chloroform was dried by passing through a column of basic alumina (Woelm, activity 1). Methanol was dried by distillation from magnesium; pyridine was dried by distillation from barium oxide; benzene was dried by distillation from sodium–benzophenone ketyl; triethylamine was dried by distillation from barium oxide.

X-ray Crystallography. Suitable crystals of **22** ($C_{32}H_{31}NO_6$) for X-ray diffraction studies formed from ethyl acetate–petroleum ether with space group symmetry $P2_12_12_1$ and cell constants of a = 10.046 (1) Å, b = 11.580 (1) Å, and c = 23.622 (1) Å for Z = 4 and a calculated density of 1.270 g/cm^3. Of the 2122 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 1944 were observed ($I > 3sI$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis, and refined using full-matrix least-squares techniques.[21] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.051. No abnormally short intermolecular contacts were noted. Tables I, II, and III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **22** from the final X-ray coordinates.

Molecular Mechanics Calculations. The 1984 version of MM2 was provided by QCPE.[19] Chemical structures were built with MACROMODEL[20] (Version 2.0) and converted into MM2 input. Energy minimization was conducted using standard defaults.

Methyl 2-Deoxy-3-*O*-methyl-α-D-*arabino*-hexopyranoside (13). In a 500-mL, round-bottomed flask equipped with a source of hydrogen (balloon) was added methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**12**: 12.63 g, 47 mmol), methanol (250 mL), 10% palladium/carbon (1.5 g), and glacial acetic acid (5 drops). The mixture was stirred under hydrogen at 1 atm pressure (760 mmHg) for 2.5 h, filtered through a pad of Celite, and evaporated under reduced pressure to give 8.37 g (93%) of **13** as a colorless syrup: R_f 0.36, ethyl acetate; $[\alpha]_D$ +88.3° (*c* 1.0, $CHCl_3$); IR (cm^{-1}, film) 3435–3400 (OH); ^{1}H NMR ($CDCl_3$) δ 4.85 (dd, 1 H, $J_{1,2eq}$ = 1.1 Hz, H-1), 3.86 (ABq, 2 H, $J_{6,6}$ = 12 Hz H-6,6), 3.65–3.47 (m, 3 H, H-3, H-4, H-5), 3.41 (s, OCH_3), 3.33 (s, OCH_3), 2.30 (dddd, 1 H, $J_{2eq,3}$ = 13.1 Hz, $J_{1,2eq}$ = 1.1 Hz, H-2eq), 1.51 (dddd, 1 H, $J_{2,2}$ = 13.6 Hz, $J_{2ax,1}$ = 3.8 Hz, H-2ax); ^{13}C NMR ($CDCl_3$) δ 98.6 (C-1), 78.1, 71.0, 62.5 (C-6), 56.5 (OCH_3), 54.6 (OCH_3), 33.6 (C-2). Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 49.90; H, 8.36.

Methyl 2-Deoxy-3-*O*-methyl-4-*O*-methanesulfonyl-6-*O*-triphenylmethyl-α-D-*arabino*-hexopyranoside (14). To a solution of **13** (8.0 g 41.7 mmol) in dry pyridine (250 mL) was added triphenylmethyl chloride (22.0 g, 79 mmol). The reaction mixture was stirred at room temperature for 5 days and then transferred to a 500-mL funnel containing ether (150 mL). The organic layer was washed with 5% HCl (2 × 250 mL), saturated $NaHCO_3$ (2 × 100 mL), and water (2 × 50 mL), dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield 16.31 g of crude methyl 2-deoxy-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-*arabino*-hexopyranoside as a viscous syrup: R_f 0.6, ethyl acetate. A sample from a previous run was purified by flash chromatography to give crystalline product: mp 118–120 °C; $[\alpha]_D$ +15.3° (*c* 1, $CHCl_3$); IR (cm^{-1}, film) 3450–3401 (OH), 3096–3004, 2996–2835, 1590 (C=C); ^{1}H NMR ($CDCl_3$) δ 7.50–7.25 (m, 15 H, Ph-H), 4.84 (dd, 1 H, $J_{1,2eq}$ = 1.1 Hz, H-1), 3.70 (dd, 1 H, H-5), 3.55–3.42 (m, 2 H, H-3, H-4), 3.40 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3), 2.23 (dddd, 1 H, $J_{2eq,3}$ = 13.1 Hz, $J_{1,2eq}$ = 1.1 Hz, H-2eq), 1.53 (dddd, 1 H, $J_{2,2}$ = 13.6 Hz, $J_{2ax,1}$ = 3.8 Hz, $J_{2ax,3}$ = 9.4 Hz, H-2ax); ^{13}C NMR ($CDCl_3$) δ 143.7 (Ph), 128.6 (Ph), 127.7 (Ph), 126.9 (Ph), 98.3 (C-1), 86.8 (Ph_3CO), 78.0 (C-3/C-4/C-5), 72.4 (C-3/C-4/C-5), 70.1 (C-3/C-4/C-5), 64.4 (C-6), 56.8 (OCH_3), 54.5 (OCH_3), 33.7 (C-2). Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63, H,

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(20) MACROMODEL is available from W. C. Still, Department of Chemistry, Columbia University, New York, NY 10027.

(21) The following library of crystallographic programs was used: SHELXS-86, G. M. Sheldrick, University of Gottingen, Gottingen, West Germany, 1986. ORTEP-II: C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN, 1970. SDP Plus V1.1, Y. Okaya, B. A. Frenz, and associates, College Station, TX, 1984.

6.96. Found: C, 74.60; H, 6.94.

Into a 500-mL round-bottomed flask equipped with a magnetic stirrer, ice bath, addition funnel, and drying tube was placed a solution of the trityl ether (16.31 g, 37.66 mmol) in dry pyridine (250 mL). After cooling, a solution of methanesulfonyl chloride (3.50 mL, 450 mmol) in dry chloroform (23 mL) was added dropwise. The reaction mixture was stirred at room temperature for 24 h and then transferred to a 1000-mL separatory funnel containing ether (400 mL). The organic layer was washed with 5% aqueous HCl (2 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and water (2 × 100 mL), dried (Na_2SO_4), and evaporated to give crude mesylate which was purified by flash chromatography to give 15.38 g (73%) of **14** as a white solid: R_f 0.63, ethyl acetate; mp 133–139 °C; $[\alpha]_D$ 21.7° (*c* 1.0, $CHCl_3$); IR (cm^{-1}, film) 3090–3040, 2919–2829, 1334 ($S(=O)_2$); ^1H NMR ($CDCl_3$) δ 7.45–7.29 (m, 15 H, Ph-H), 4.89 (dd, 1 H, $J_{1,2eq}$ = 1.1 Hz, H-1), 4.50 (dd, 1 H, $J_{3,4}$ = 5.0 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 3.98–3.70 (m, 2 H, H-3, H-5), 3.42 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 3.20 (dd, 2 H, $J_{6,6}$ = 10 Hz, $J_{6,5}$ = 4.8 Hz, H-6,6), 3.16 (s, 3 H, SCH_3), 2.40 (dddd, 1 H, $J_{2,2eq}$ = 13.1 Hz, $J_{2eq,1}$ = 1.1 Hz, H-2eq), 1.62 (dddd, 1 H, $J_{2,2}$ = 13.5 Hz, $J_{2ax,1}$ = 3.6 Hz, H-2ax); ^{13}C NMR ($CDCl_3$) 143.7 (Ph), 128.5 (Ph), 127.5 (Ph), 127.1 (Ph), 126.9 (Ph), 98.0 (C-1), 86.8 (Ph_3CO), 75.6, 69.8, 60.3 (C-6), 56.2 (OCH_3), 54.8 (OCH_3), 38.1 (SCH_3), 34.3 (C-2). Anal. Calcd for $C_{28}H_{32}O_7S$: C, 65.61; H, 6.29. Found: C, 65.69; H, 6.26.

Methyl 2-Deoxy-4-*O*-methanesulfonyl-3-*O*-methyl-α-D-*arabino*-hexopyranoside (15). A solution of **14** (10.0 g, 19.5 mmol) and *p*-toluenesulfonic acid (100 mg) in ethanol (250 mL) was stirred at 85 °C for 24 h. The solution was transferred to a 1000-mL separatory funnel containing chloroform (400 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 150 mL) and water (1 × 100 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by flash chromatography to give **15** as a white solid: yield, 2.6 g (55%); R_f 0.48, ethyl acetate; mp 108–112 °C; $[\alpha]_D$ +62.6° (*c* 1, $CHCl_3$); IR (cm^{-1}, film) 3545–3400 (OH), 2939–2836, 1340 ($S(=O)_2$); ^1H NMR ($CDCl_3$) α 4.78 (dd, 1 H, $J_{1,2ax}$ = 3.6 Hz, $J_{1,2eq}$ = 1.2 Hz, H-1), 4.47 (dd, 1 H, H-4), 4.00–3.60 (m, 4 H, H-3, H-5, H-6,6′), 3.38 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 3.14 (s, 3 H, SCH_3), 2.40 (dddd, 1 H, $J_{2,2}$ = 13.1 Hz, $J_{1,2eq}$ = 1.1 Hz, H-2eq), 1.60 (dddd, 1 H, $J_{2ax,3}$ = 10 Hz, $J_{2ax,1}$ = 3.6 Hz, $J_{2ax,2eq}$ = 13.1 Hz, H-2ax); ^{13}C NMR ($CDCl_3$) δ 98.0 (C-1), 79.1 (C-3/C-4/C-5), 75.4 (C-3/C-4/C-5), 69.8 (C-3/C-4/C-5), 60.6 (C-6), 56.2 (OCH_3), 54.8 (OCH_3), 38.1 (SCH_3), 34.3 (C-2). Anal. Calcd for $C_9H_{18}O_7S$: C, 39.99; H, 6.71. Found: C, 39.85; H, 6.69.

Methyl 2,4-Dideoxy-3-*O*-methyl-α-L-*glycero*-hex-4-enodialdo-1,5-pyranoside (16). In a 100-mL, round-bottomed flask equipped with a magnetic stirrer and drying tube was added methyl 2-deoxy-4-*O*-methanesulfonyl-3-*O*-methyl-α-D-*arabino*-hexopyranoside (0.71 g, 2.0 mmol), dry DMSO (18 mL), and dry triethylamine (5 mL, 35.8 mmol). The mixture was stirred rapidly for 2 h after which sulfur trioxide–pyridine complex (2.0 g, 12.56 mmol) in dry DMSO (10 mL) was added. After stirring at room temperature for 1 h, the solution was transferred to a 500-mL separatory containing chloroform (150 mL) and washed with saturated aqueous tartaric acid solution (2 × 100 mL), saturated aqueous sodium hydrogen carbonate solution (2 × 100 mL), and water (2 × 100 mL, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel to give syrupy **16**: yield, 0.30 g (58%); R_f 0.38, 1:3 ethyl acetate–petroleum ether; $[\alpha]_D$ +176.5° (*c* 1, $CHCl_3$); IR (cm^{-1}, film): 3081, 2729 (CHO), 1701 (C=O), 1638 (C=C); ^1H NMR ($CDCl_3$) δ 9.22 (s, 1 H, CHO), 6.10 (d, 1 H, H-4), 5.17 (dd, 1 H, $J_{1,2eq}$ = 3.8 Hz, H-1), 4.23 (m, 1 H, H-3), 3.50 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 2.24 (m, 1 H, H-2eq), 1.90 (dddd, 1 H, $J_{2ax,2eq}$ = 13.3 Hz, $J_{2ax,3}$ = 8.7 Hz, H-2ax); ^{13}C NMR ($CDCl_3$) δ 187.0 (C-6), 149.6 (C-5), 121.1 (C-4), 99.7 (C-1), 68.9 (C-3), 56.6 (OCH_3), 56.3 (OCH_3), 31.9 (C-2). Exact mass calculated for $C_8H_{12}O_4$: 172.0735; found 172.0748.

Methyl 2,4,6,7-Tetradeoxy-3-*O*-methyl-α-L-*glycero*-hepta-4,6-dienopyranoside (8). A 100-mL, three-necked flask equipped with a magnetic stirrer and a Firestone valve was charged with sodium hexamethyldisilazide (0.53 g, 2.89 mmol) and dry tetrahydrofuran (25 mL). After the mixture was stirred for 10 min, a solution of methyl triphenylphosphonium bromide (0.88 g, 2.46 mmol) and **16** (0.32 g, 1.86 mmol) in dry tetrahydrofuran (20 mL) was added, and the reaction mixture was stirred under an atmosphere of nitrogen for 30 min at room temperature. The solution was then transferred to a 250-mL separatory funnel containing 30–60° petroleum ether (100 mL) and washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated carefully under reduced pressure to a volume of 10 mL. The crude product was purified by flash chromatography on Florisil to give **8** as a colorless liquid: yield 0.16 g (50%); R_f 0.91, 1:3 ethyl acetate–petroleum ether; $[\alpha]_D$ +133.7° (*c* 1, $CHCl_3$); IR (cm^{-1}, film) 3081, 1650 (C=C); ^1H NMR ($CDCl_3$) δ 6.10 (dd, 1 H, H-6), 5.64 (dd, 1 H, $J_{7,6}$ = 18.1 Hz, H-7), 5.15 (dd, 1 H, $J_{7',6}$ = 11.7 Hz, $J_{7',7}$ = 1.1 Hz, H-7′), 5.12 (d, 1 H, H-4), 5.03 (d, 1 H, $J_{1,2}$ 3.8 = Hz, H-1), 3.96 (m, 1 H, H-3), 3.55 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 2.0–1.8 (m, 2 H, H-2ax, H-2eq); ^{13}C NMR ($CDCl_3$) δ 132 (C-6), 114 (C-7), 102.1 (C-4), 98.7 (C-1), 69.7 (C-3), 56.3 (OCH_3), 56.1 (OCH_3) 32.7 (C-2). Exact mass calculated for $C_9H_{14}O_3$: 170.0943, found 170.0940.

Methyl 2,3-Di-*O*-benzyl-4,6,7-trideoxy-β-L-*threo*-hepta-4,6-dienopyranoside (9). Diene **9** was prepared by Wittig alkenation of methyl 2,3-di-*O*-benzyl-β-L-*threo*-hex-4-enodialdo-1,5-pyranoside[11] using the conditions described above for the preparation of **8**. From 1.37 g of the aldehyde, there was obtained 0.66 g (48%) of diene **9** after purification by column chromatography on Florisil: R_f 0.86, 1:4 ethyl acetate–petroleum ether; $[\alpha]_D$ +126.1° (*c* 0.62, $CDCl_3$); IR (cm^{-1}, film) 3090–3035, 2923, 2877, 1655, 1600; ^1H NMR ($CDCl_3$) δ 7.33 (bs, 10 H, Ph-H), 6.07 (dd, 1 H, H-6), 5.60 (dd, 1 H, $J_{7,6}$ 17.0 Hz, H-7), 5.13 (d, 1 H, $J_{7'6}$ = 10.8 Hz, $J_{7,7'}$ = 1.76 Hz, H-7′), 4.96 (d, 1 H, H-4), 4.91 (d, 1 H, H-1), 4.78 (ABq, 2 H, J = 13.8 Hz, OCH_2Ph), 4.63 (s, 2 H, OCH_2Ph), 4.28 (dd, 1 H, $J_{3,4}$ = 3.1 Hz, H-3), 3.79 (dd, 1 H, $J_{2,3}$ = 6.8 Hz, $J_{2,1}$ = 2.4 Hz, H-2), 3.50 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 148.2 (C-5), 138.2 (Ph), 138.0 (Ph), 131.2 (C-6), 128.4 (Ph), 128.0 (Ph), 127.8 (Ph), 127.7 (Ph), 127.6 (Ph), 115.0 (C-7), 102.4 (C-4), 99.2 (C-1), 76.2 (C-2/C-3), 73.8 (C-2/C-3), 73.1 (OCH_2Ph), 71.4 (OCH_2Ph), 56.5 (OCH_3). Exact mass calculated for $C_{22}H_{25}O_4$: 353.1753, found 353.1743.

Methyl 4,6,7-Trideoxy-2,3-di-*O*-methyl-β-L-*threo*-hepta-4,6-dienopyranoside (10). Diene **10** was prepared by a reaction sequence identical with that used for the synthesis of **9**, except for the substitution of a methylation in place of a benzylation step. Compound **10** was obtained in 49% yield from the aldehyde after purification by column chromatography on Florisil: R_f 0.72, 1:1 ethyl acetate–petroleum ether; $[\alpha]_D$ +158.7° (*c* 0.45, $CHCl_3$); IR (cm^{-1}, film) 2920–2821, 1650, 1598; ^1H NMR ($CDCl_3$) δ 6.09 (dd, 1 H, H-6), 5.62 (d, 1 H, $J_{6,7}$ = 17.1 Hz, H-7), 5.16 (d, 1 H, $J_{6,7'}$ = 10.8 Hz, H-7′), 5.03 (d, 1 H, $J_{1,2}$ = 2.4 Hz, H-1), 4.98 (d, 1 H, H-4), 4.02 (dd, 1 H, $J_{3,2}$ = 6.7 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 3.56 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 3.45 (m, 1 H, H-2), 3.45 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 148.1 (C-5), 130.9 (C-6), 114.9 (C-7), 101.4 (C-4), 98.3 (C-1), 78.0 (C-2/C-3), 74.8 (C-2/C-3), 58.6 (OCH_3), 56.4 (OCH_3), 56.3 (OCH_3). Exact mass calculated for $C_{10}H_{16}O_4$: 200.1049, found 200.1027.

Methyl 2,3-Di-*O*-benzyl-4,6,7-trideoxy-α-L-*threo*-hepta-4,6-dienopyranoside (11). Diene **11** was prepared from the methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside[13] by a reaction sequence analogous to that used for the synthesis of **9**. Wittig alkenation of the aldehyde gave **11** in 38% yield after purification by column chromatography on Florisil: R_f 0.8, 1:3 ethyl acetate–petroleum ether; $[\alpha]_D$ +6.15° (*c* 0.1, $CHCl_3$); IR (cm^{-1}, film) 3088–3029, 2929–2860, 1661; ^1H NMR ($CDCl_3$) δ 7.49–7.23 (m, 10 H, Ph-H), 6.06 (dd, 1 H, H-6), 5.61 (dd, 1 H, $J_{7,6}$ = 16.5 Hz, H-7), 5.19 (dd, 1 H, $J_{7'6}$ = 11.0 Hz, $J_{7,7'}$ = 2.0 Hz, H-7′), 4.96 (d, 1 H, H-4), 4.91 (d, 1 H, H-1), 4.78 (ABq, 2 H, J = 11.1 Hz, OCH_2Ph), 4.70 (ABq, 2 H, J = 9.9 Hz, OCH_2Ph), 4.11 (dd, 1 H, $J_{3,4}$ = 3.1 Hz, H-3), 3.74 (dd, 1 H, $J_{2,3}$ = 7.0 Hz, $J_{2,1}$ = 7.4 Hz, H-2), 3.56 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 148.5 (C-5), 138.0 (Ph), 137.5 (Ph), 132.1 (Ph), 131.9 (Ph), 131.7 (Ph), 131.1 (C-6), 130.5 (Ph), 130.3 (Ph), 128.5 (Ph), 128.3 (Ph), 127.9 (Ph), 127.7 (Ph), 127.6 (Ph), 115.4 (C-7), 102.1 (C-4/C-1), 101.3 (C-1/C-4), 77.1 (C2/C3), 73.6 ($PhCH_2O$), 73.1 (C2/C3), 70.8 ($PhCH_2O$), 56.8 (OCH_3). Exact mass calculated for $C_{22}H_{25}O_4$: 353.1753, found 353.1747.

(2*S*,4*R*,4a*R*,5*R*,6*S*)-4a,5,6,7-Tetrahydro-2,4-dimethoxy-5,6-chromandicarboxamide (18) and (2*S*,4*R*,4a*S*,5*S*,6*R*)-4a,5,6,7-Tetrahydro-2,4-dimethoxy-5,6-chromandicarboximide (19). A solution of methyl 2,4,6,7-tetradeoxy-3-*O*-methyl-β-L-*glycero*-hepta-4,6-dienopyranoside (**8**: 0.3 g, 0.84 mmol) and

maleimide (0.22 g, 1.27 mmol) in dry benzene (25 mL) was stirred under reflux in an atmosphere of nitrogen for 12 h. Solvent was evaporated under reduced pressure to leave a solid which was purified by column chromatography on Florisil using 1:1 ethyl acetate–petroleum ether (R_f 0.34). Compounds **18** and **19** were obtained as an inseparable mixture in 75% yield. The ratio of major (**18**) to minor (**19**) adduct was determined by ^{1}H NMR spectral integration to be 4.1:1: IR (cm^{-1}, film) 3215 (N–H), 3084, 1717 (C=O), 1655 (C=C); ^{1}H NMR (**18**, $CDCl_3$) δ 8.20 (bs, 1 H, N-H), 4.99 (ddd, 1 H, $J_{6,7eq}$ = 7.1 Hz, $J_{6,7ax}$ = 3.3 Hz, $J_{6,4}$ = 3.0 Hz, H-6), 4.81 (ddd, 1 H, $J_{3,2eq}$ = 4.6 Hz, $J_{3,2ax}$ = 11.2 Hz, $J_{3,4}$ = 8.7 Hz, H-3), 4.68 (dd, 1 H, $J_{1,2ax}$ = 2.6 Hz, $J_{1,2eq}$ = 2.6 Hz, H-1), 3.39 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 2.84 (dd, 1 H, $J_{9,4}$ = 6.8 Hz, $J_{9,8}$ = 8.9 Hz, H-9), 2.46 (ddd, 1 H, $J_{7a,7e}$ = 16.4 Hz, H-7ax), 2.24 (ddd, 1 H, $J_{8,7eq}$ = 1.9 Hz, $J_{8,7a}$ = 7.2 Hz, H-8), 2.2 (m, 1 H, H-4), 2.16 (ddd, 1 H, $J_{2ax,2eq}$ = 10.4 Hz, H-2eq), 1.61 (dddd, 1 H, H-7eq), 1.31 (ddd, 1 H, H-2a); ^{13}C NMR (**18**, $CDCl_3$) δ 180.6 (C=O), 178.5 (C=O), 150.9 (C-5), 101.2 (C-6), 99.6 (C-1), 69.8 (C-3), 56.8 (OCH_3), 55.8 (OCH_3), 41.6 (C-4), 41.3 (C-8/C-9), 40.6 (C-8/C-9), 34.1 (C-2), 23.7 (C-7). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.36; H, 6.38; N, 5.21.

(2*S*,3*R*,4*S*,4a*R*,5*R*,6*S*)-3,4-Bis(benzyloxy)-4a,5,6,7-tetrahydro-2-methoxy-5,6-chromandicarboximide (20a) and (2*S*,3*R*,4*S*,4a*S*,5*S*,6*R*)-3,4-Bis(benzyloxy)-4a,5,6,7-tetrahydro-2-methoxy-5,6-chromandicarboximide (21a). Under the conditions described for the Diels–Alder reaction of diene **8**, methyl 2,3-di-*O*-benzyl-4,6,7-trideoxy-β-L-*threo*-hepta-4,6-dienopyranoside (**9**: 0.74 g, 2.1 mmol) was treated with maleimide (3.4 g, 35 mmol) in benzene (40 mL). After 14 h, the mixture was evaporated and the crude product was purified by column chromatography on Florisil using 1:1 ethyl acetate–petroleum ether (R_f 0.61). A mixture of **20a** and **21a** was obtained as a white amorphous solid: yield, 0.29 g (31%). The ratio of **20a** to **21a** was estimated to be 4.88:1 by HPLC and 4.65:1 by ^{1}H NMR spectral integration: IR (cm^{-1}, film) 3240 (N–H), 3090–3038, 2930, 2860, 1780 (C=O), 1715 (C=O), 1615 (C=C); ^{1}H NMR (**20a**, $CDCl_3$) δ 9.14 (s, 1 H, N–H), 7.6–7.0 (m, 10 H, Ph-H), 5.14 (m, 1 H, $J_{6,4}$ = 1.8 Hz, H-6), 4.78 (ABq, 2 H, J = 11.8 Hz, OCH_2Ph), 4.77 (d, 1 H, H1), 4.59 (ABq, 2 H, J = 11.1 Hz, OCH_2Ph), 4.44 (dd, 1 H, $J_{3,4}$ = 6.1 Hz, H3), 4.27 (dd, 1 H, $J_{2,3}$ = 7.2 Hz, $J_{2,1}$ = 2.3 Hz, H-2), 3.23 (s, 3 H, OCH_3), 3.04 (m, 1 H, H-9), 2.90 (m, 1 H, $J_{4,9}$ = 7.0 Hz, $J_{4,3}$ = 6.7 Hz, H-4), 2.59 (ddd, 1 H, $J_{7ax,6}$ = 6.7 Hz, H-7ax), 2.34 (ddd, 1 H, $J_{8,9}$ = 8.7 Hz, $J_{8,7ax}$ = 1.9 Hz, H-8), 1.76 (dddd, 1 H, $J_{7eq,8}$ = 7.9 Hz, $J_{7eq,6}$ = 3.6 Hz, $J_{7eq,4}$ = 1.5 Hz, H-7eq); ^{13}C NMR (**20a**, C_6D_6) δ 180.6 (C=O), 180.5 (C=O), 150.5 (C5), 139.7 (Ph), 139.6 (Ph), 129.1 (Ph), 128.7 (Ph), 128.3 (Ph), 127.9 (Ph), 127.5 (Ph), 101.7 (C-6), 101.2 (C-1), 76.7 (C2/C3), 75.5 (C2/C3), 74.1 (OCH_2Ph), 73.4 (OCH_2Ph), 56.7 (OCH_3), 42.4 (C-8/C-9), 41.3 (C-8/C-9), 35.9 (C4), 23.1 (C-7). Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.13. Found: C, 69.13; H, 6.16; N, 3.29.

(2*S*,3*R*,4*S*,4a*R*,5*R*,6*S*)-4a,5,6,7-Tetrahydro-2,3,4-tri-*O*-methoxy-5,6-chromandicarboximide (20b) and (2*S*,3*R*,4*S*,4a*R*,5*R*,6*S*)-4a,5,6,7-Tetrahydro-2,3,4-tri-*O*-methoxy-5,6-chromandicarboximide (21b). A mixture of methyl 4,6,7-trideoxy-2,3-di-*O*-methyl-β-L-*threo*-hepta-4,6-dienopyranoside (**10**: 0.864 g, 4.12 mmol) and maleimide (2.54 g, 26 mmol) in benzene (30 mL) was treated under the aforementioned conditions to give 0.39 g (31%) of a mixture of adducts **20b** and **21b** as a white amorphous solid after column chromatography on Florisil (R_f 0.22, 1:1 ethyl acetate–petroleum ether). A second chromatography gave the separate adducts in a 3:1 ratio of **20b** to **21b**. Analytical data for the major adduct **20b** are as follows: $[\alpha]_D$ +42.8° (*c* 0.15, benzene); IR (cm^{-1}, film) 3259 (N–H), 3028, 2957, 2932, 1772 (C=O), 1718 (C=O), 1653 (C=C); ^{1}H NMR (C_6D_6) δ 7.35 (s, 1 H, N–H), 5.16 (ddd, 1 H, $J_{6,4}$ = 2.2 Hz, H-6), 4.70 (d, 1 H, H-1), 3.92 (dd, 1 H, $J_{3,4}$ = 9.9 Hz, $J_{3,2}$ = 5.9 Hz, H-3), 3.71 (dd, 1 H, $J_{2,3}$ = 5.9 Hz, $J_{2,1}$ = 2.3 Hz, H-2), 3.37 (s, 3 H, OCH_3), 3.24 (s, 3 H, OCH_3), 3.08 (s, 3 H, OCH_3), 2.92–2.80 (m, 1 H, H-4), 2.69 (dd, 1 H, $J_{9,8}$ = 8.8 Hz, $J_{9,4}$ = 8.8 Hz, H-9), 2.60 (dddd, 1 H, $J_{7ax,6}$ = 2.0 Hz, $J_{7ax,4}$ = 1.1 Hz, H-7ax), 2.16 (ddd, 1 H, $J_{8,9}$ = 8.9 Hz, $J_{8,7ax}$ = 8.9 Hz, $J_{8,7eq}$ = 1.9 Hz, H-8), 1.69 (dddd, 1 H, $J_{7eq,7ax}$ = 11.3 Hz, $J_{7eq,6}$ = 7.1 Hz, $J_{7eq,8}$ = 3.3 Hz, $J_{7eq,4}$ = 0.7 Hz, H-7eq); ^{13}C NMR (C_6D_6) δ 179.8 (C=O), 178.5 (C=O), 149.5 (C-5), 102.2 (C-1/C-6), 100.7 (C-1/C-6), 77.3 (C-2/C-3), 76.8 (C-2/C-3), 59.1 (OCH_3), 57.7 (OCH_3), 56.3 (OCH_3), 41.1 (C-9), 40.1 (C-8), 34.3 (C-4), 21.5 (C-7). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44. Found: C, 56.64; H, 6.44.

NMR data for the minor adduct **21b** are as follows: ^{1}H NMR (C_6D_6) δ 7.29 (s, 1 H, N–H), 5.08 (dd, 1 H, $J_{3,2}$ = 9.7 Hz, $J_{3,4}$ = 8.5 Hz, H-3), 5.00 (ddd, 1 H, $J_{6,4}$ = 2.8 Hz, H-6), 4.69 (d, 1 H, $J_{1,2}$ = 2.4 Hz, H-1), 3.76 (s, 3 H, OCH_3), 3.17 (s, 3 H, OCH_3), 3.15 (m, 1 H, H-2), 3.13 (s, 3 H, OCH_3), 2.79 (dd, 1 H, $J_{9,8}$ = 9.0 Hz, $J_{9,4}$ = 7.0 Hz, H-9), 2.52 (ddd, 1 H, $J_{7ax,8}$ = 7.3 Hz, $J_{7ax,6}$ = 2.0 Hz, H-7ax), 2.40–2.20 (m, 2 H, H-4, H-8), 1.62 (dddd, 1 H, $J_{7ax,7eq}$ = 15.5 Hz, $J_{7eq,6}$ = 7.1 Hz, $J_{7eq,8}$ = 3.0 Hz, $J_{7eq,4}$ = 3.0 Hz, H-7eq); ^{13}C NMR (C_6D_6) δ 177.5 (C=O), 170.2 (C=O), 149.9 (C-5), 99.6 (C-1/C-6), 97.9 (C-1/C-6), 83.5 (C-3), 73.9 (C-2), 60.7 (OCH_3), 57.8 (OCH_3), 55.4 (OCH_3), 41.7 (C-9), 41.1 (C-4), 40.4 (C-8), 23.2 (C-7).

***N*-Phenyl-(2*S*,3*R*,4*S*,4a*R*,5*R*,6*S*)-3,4-bis(benzyloxy)-4a,5,6,7-tetrahydro-2-methoxy-5,6-chromandicarboxamide (22) and *N*-Phenyl-(2*S*,3*R*,4*S*,4a*S*,5*S*,6*R*)-3,4-bis(benzyloxy)-4a,5,6,7-tetrahydro-2-methoxy-5,6-chromandicarboximide (23).** Dieno-pyranoside **9** (0.6 g, 1.7 mmol) was reacted with *N*-phenylmaleimide (3.0 g, 16 mmol) in benzene (40 mL) under the conditions described above for 30 h. Solvent was removed under reduced pressure and the crude product was purified by column chromatography on Florisil (1:4 ethyl acetate–petroleum ether) to give the major adduct **22** (0.45 g) as a crystalline solid (R_f 0.32) and the minor adduct **23** (0.02 g) as a syrup (R_f 0.38) in a combined yield of 53%. In the crude product, the ratio of **22** to **23** was determined to be 6.38:1 by NMR spectral integration. Analytical data for **22** are given below: mp 148–150 °C; $[\alpha]_D$ +116.0° (*c* 0.99, benzene); IR (cm^{-1}, film) 3059, 3025, 2910, 2850, 1950, 1800, 1775 (C=O), 1720 (C=O); ^{1}H NMR (C_6D_6) δ 7.40–7.25 (m, 4 H, Ph-H), 7.25–6.90 (m, 11 H, Ph-H), 5.21 (ddd, 1 H, $J_{6,4}$ = 2.0 Hz, $J_{6,7eq}$ = 3.7 Hz, $J_{6,7ax}$ = 6.5 Hz, H-6), 4.78 (d, 1 H, $J_{1,2}$ = 2.5 Hz, H-1), 4.66 (ABq, 2 H, OCH_2Ph), 4.51 (ABq, 2 H, OCH_2Ph), 4.48 (dd, 1 H, $J_{3,4}$ = 7.0 Hz, $J_{3,2}$ = 7.0 Hz, H-3), 4.29 (dd, 1 H, $J_{2,3}$ = 7.1 Hz, $J_{2,1}$ = 2.5 Hz, H-2), 3.22 (s, 3 H, OCH_3), 3.14 (dd, 1 H, $J_{9,8}$ = 9.1 Hz, $J_{9,4}$ = 7.4 Hz, H-9), 2.99 (dddd, 1 H, $J_{4,6}$ = 1.9 Hz, $J_{4,7eq}$ = 1.9 Hz, H-4), 2.70 (dddd, 1 H, $J_{7ax,4}$ = 0.6 Hz, $J_{7ax,8}$ = 2.2 Hz, $J_{7ax,7eq}$ = 16.3 Hz, H-7ax), 2.36 (ddd, 1 H, $J_{8,7eq}$ = 7.8 Hz), 1.85 (dddd, 1 H, H-7eq); ^{13}C NMR (C_6D_6) δ 177.9 (C=O), 176.7 (C=O), 150.7 (C-5), 139.5 (Ph), 128.9 (Ph), 128.5 (Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 127.9 (Ph), 127.5 (Ph), 127.4 (Ph), 126.9 (Ph), 101.0 (C-1/C-6), 100.9 (C-1/C-6), 76.6 (C-3), 75.2 (C-2), 73.8 (OCH_2Ph), 73.2 (OCH_2Ph), 56.5 (OCH_3), 41.0 (C-8/C-9), 40.0 (C-8/C-9), 36.0 (C-4), 23.6 (C-7). Anal. Calcd for $C_{32}H_{31}NO_6$: C, 73.13; H, 5.95; N, 2.66. Found: C, 72.83; H, 5.85; N, 2.65.

NMR data for the minor adduct **23** is as follows: ^{1}H NMR (C_6D_6) δ 7.60–7.44 (m, 3 H, Ph-H), 7.44–7.00 (m, 12 H, Ph-H), 5.50 (dd, 1 H, H-3), 5.21 (ABq), 2 H, OCH_2Ph), 5.11 (ddd, 1 H, H-6), 4.67 (d, 1 H, H-1), 4.46 (ABq, 2 H, OCH_2Ph), 3.57 (dd, 1 H, $J_{2,1}$ = 2.4 Hz, $J_{2,3}$ = 9.7 Hz, H-2), 3.01 (s, 3 H, OCH_3), 2.97 (dd, 1 H, H-9), 2.69 (ddd, 1 H, $J_{7ax,6}$ = 7.5 Hz, H-7ax), 2.52 (dddd, 1 H, $J_{4,6}$ = 2.9 Hz, $J_{4,9}$ = 7.5 Hz, $J_{4,3}$ = 8.3 Hz, H-4), 2.39 (ddd, 1 H, $J_{8,7ax}$ = 2.2 Hz, $J_{8,9}$ = 9.0 Hz, H-8), 1.66 (dddd, 1 H, $J_{7eq,4}$ = 3.1 Hz, $J_{7eq,6}$ = 3.1 Hz, $J_{7eq,8}$ = 6.3 Hz, $J_{7eq,7ax}$ = 15.1 Hz, H-7eq); ^{13}C NMR (C_6D_6) δ 177.8 (C=O), 176.0 (C=O), 149.8 (C-5), 140.5 (Ph), 139.1 (Ph), 100.3 (C-1/C-6), 98.5 (C-1/C-6), 82.0 (C-3), 75.6 (OCH_2Ph), 73.4 (C-2), 72.9 (OCH_2Ph), 55.8 (OCH_3), 41.0 (C-4/C-8/C-9), 40.8 (C-4/C-8/C-9), 40.4 (C-4/C-8/C-9), 23.4 (C-7).

***N*-Phenyl-(2*R*,3*R*,4*S*,4a*S*,5*S*,6*R*)-3,4-bis(benzyloxy)-4a,5,6,7-tetrahydro-2-methoxy-5,6-chromandicarboximide (24).** A solution of methyl 2,3-di-*O*-benzyl-4,6,7-trideoxy-α-L-*threo*-hepta-4,6-dienopyranoside (**11**: 0.16 g, 0.94 mmol) and *N*-phenylmaleimide (0.34 g, 3.5 mmol) in benzene (25 mL) was stirred under reflux for 12 h. The solvent was evaporated and the crude product was purified by column chromatography on Florisil (1:3 ethyl acetate–petroleum ether, R_f 0.49) to give 0.19 g (67%) of a single crystalline cycloadduct (**24**): mp 70–75 °C; $[\alpha]_D$ –94.9° (*c* 1.0, benzene); IR (cm^{-1}, film) 3085, 3009, 2943, 1770 (C=O); ^{1}H NMR (C_6D_6) δ 7.40–7.25 (m, 4 H, Ph-H), 7.25–6.90 (m, 11 H, Ph-H), 5.27 (ABq, 2 H, OCH_2Ph), 5.10 (ddd, 1 H, $J_{6,4}$ = 1.8 Hz, $J_{6,7eq}$ = 3.6 Hz, $J_{6,7ax}$ = 6.5 Hz, H-6), 4.95 (dd, 1 H, $J_{3,4}$ = 10.7 Hz, $J_{3,2}$ = 9.7 Hz, H-3), 4.81 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1), 4.67 (ABq, 2 H, OCH_2Ph), 3.66 (dd, 1 H, H-2), 3.07 (dd, 1 H, $J_{9,4}$ = 6.2 Hz, $J_{9,8}$ = 8.9 Hz, H-9), 2.61 (dddd, $J_{7ax,4}$ = 1.4 Hz, $J_{7ax,6}$ = 6.8 Hz, $J_{7ax,8}$ = 2.2 Hz, $J_{7ax,7eq}$ = 16.3 Hz, H-7ax), 2.39 (ddd, $J_{8,7eq}$ = 8.0 Hz, H-8), 2.19 (dddd, 1 H, H-4), 1.64 (m, 1 H, H-7eq);

^{13}C NMR (C_6D_6) δ 177.9 (C=O), 176.3 (C=O), 151.1 (C-5), 140.1 (Ph), 128.9 (Ph), 128.4 (Ph), 127.9 (Ph), 127.4 (Ph), 127.1 (Ph), 126.8 (Ph), 125.5 (Ph), 104.6 (C-1/C-6), 102.4 (C-1/C-6), 85.8, 74.9 (OCH_2Ph), 74.5 (OCH_2Ph), 72.8, 55.0 (OCH_3), 40.4, 40.1, 39.9, 24.1. Exact mass calculated for $C_{32}H_{31}NO_6$ + H: 526.2232, found 526.2275.

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Registry No. **7**, 110519-50-1; **8**, 126257-10-1; **9**, 126257-11-2; **9** aldehyde precursor, 116013-32-2; **10**, 126257-12-3; **10** aldehyde precursor, 126257-20-3; **11**, 126257-13-4; **11** aldehyde precursor, 126373-52-2; **12**, 126373-46-4; **13**, 99371-27-4; **13** 6-*O*-trityl derivative, 126257-19-0; **14**, 126257-14-5; **15**, 126257-15-6; **16**, 126257-16-7; **17**, 110519-52-3; **18**, 126373-47-5; **19**, 126373-48-6; **20a**, 126257-17-8; **20b**, 126257-21-4; **21a**, 126373-49-7; **21b**, 126373-53-3; **22**, 126257-18-9; **23**, 126373-50-0; **24**, 126373-51-1; $Me(Ph)_3P^+Br^-$, 1779-49-3; methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside, 31873-34-4; maleimide, 541-59-3; *N*-phenylmaleimide, 941-69-5.

Supplementary Material Available: Tables of fractional coordinates and temperature factors, bond distances in angstroms, and bond angles in degrees (4 pages). Ordering information is given on any current masthead page.

Synthesis of Fluoro Nitro Ethers by Michael Addition Reactions to Activated β,β-Difluoroolefins

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The ferric chloride catalyzed reaction of isobutyryl chloride with 1,1-difluoroethylene gave 1-chloro-1,1-difluoro-4-methyl-3-pentanone (**1**), which was oxidized with *m*-chloroperbenzoic acid to isopropyl 3-chloro-3,3-difluoropropionate (**2**). β,β-Difluoroolefins 1,1-difluoro-4-methyl-1-penten-3-one (**3**) and isopropyl 3,3-difluoroacrylate (**4**) were prepared by dehydrohalogenation of **1** and **2** with amine bases. Unlike their non-fluorinated analogues, **3** and **4** gave no stable Michael adducts with the salts of nitroalkanes, but with β-nitroalcohols such as 2,2-dinitropropanol (**7**), fluorodinitroethanol (**10**), and 2-fluoro-2-nitropropane-1,3-diol (**13**), the corresponding fluoro nitro ethers were obtained in high yields. Reaction of sodium azide with **1**, **2**, and 2-chloro-2,2-difluoroacetophenone gave 1-azido-1,1-difluoro-4-methyl-3-pentanone (**17**), isopropyl 3-azido-3,3-difluoropropionate (**18**), and 2-azido-2,2-difluoroacetophenone (**19**).

The study of the Michael reactions of β,β-difluorovinyl ketones or acrylic acid derivatatives has been limited because of the inaccessibility of these olefins.[1] Reported synthetic routes to 3,3-difluoroacrylic acid are the zinc-mediated reduction of 2,3-dichloro-3,3-difluoropropionic acid[2] and the reaction of carbon dioxide with (2,2-difluorovinyl)lithium.[3] Although, ethyl 3,3-difluoroacrylate was prepared by cautious dehydrohalogenation of ethyl 3-bromo-3,3-difluoropropionate, dehydrochlorination of the corresponding chloro derivative failed because of disproportionation leading to ethyl 3,3,3-trifluoropropionate.[4] The presence of the β-fluoro groups increased the reactivity of the olefin toward addition of fluoride ion.[1,5]

Nitro-group functionalized ethers are of interest for use in propellant and explosives mixtures.[6] In the case of non-fluorine-containing systems, these ethers cannot generally be synthesized by a base-catalyzed Michael addition of β-nitro alcohols to activated olefins. The explanation for failure of this reaction may be found in the low nucleophilicity of the alkoxide ion[7] and its instability toward the reverse Henry reaction resulting in deformylation.[8] The effect of β-fluoro groups on this addition has not been studied. This report describes a facile synthesis of isopropyl 2,2-difluorovinyl ketone and isopropyl 3,3-difluoroacrylate and some unusual addition reactions of these olefins with nitronate anions and β-nitro alcohols.

Scheme I[a]

$CH_2{=}CF_2 + RCOCl \rightarrow \underset{\mathbf{1}}{CF_2ClCH_2C(O)R}$

$\mathbf{1} + MCPBA \rightarrow \underset{\mathbf{2}}{CF_2ClCH_2C(O)OR}$

$\mathbf{1} + Et_3N \rightarrow \underset{\mathbf{3}}{CF_2{=}CHC(O)R}$

$\mathbf{2} + Et_3N \rightarrow \underset{\mathbf{4}}{CF_2{=}CHC(O)OR}$

[a] R = $CHMe_2$.

Results and Discussion

Synthesis of Isopropyl 3,3-Difluoroacrylate. The Friedel–Crafts acylation of fluoro-substituted ethylenes with acid chlorides has been used to prepare 2-chloro-2-fluoroethyl alkyl ketones.[9] We have extended this method to the ferric chloride catalyzed reaction of isobutyryl chloride with 1,1-difluoroethylene, which gave 1-chloro-1,1-difluoro-4-methyl-3-pentanone (**1**) in 41% yield.

Oxidation of **1** with *m*-chloroperbenzoic acid gave isopropyl 3-chloro-3,3-difluoropropionate (**2**) in 33% yield. Although two products, 2-chloro-2,2-difluoroethyl isobutyrate and **2**, are possible in this oxidation, only **2** was observed. A regiospecific oxidation[10] may have occurred,

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(10) A regiospecific reaction was claimed for similar oxidation use for the preparation of 3-fluoroacrylates. See ref 4.

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