with 20% ethyl acetate/hexanes and filtered through silica gel to remove excess DMAP. The filtrate was concentrated and flash chromatographed (10% ethyl acetate/hexanes) to yield 120 mg of tetrabenzoate **14b** (80%) as a colorless glass, which was identical with the minor tetrabenzoate obtained from the osmylation of **10** and **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (m, 8 H), 7.35 (m, 13 H), 6.48 (dd, 1 H, J = 3.2, 0.7 Hz), 6.37 (dd, 1 H, J = 3.2, 1.8 Hz), 6.08 (t, 1 H, J = 5.2 Hz), 5.94 (dt, 1 H, J = 6.3, 4.3 Hz), 5.74 (br d, 1 H, J = 2.9 Hz), 5.0 (dd, 1 H, J = 12.2, 3.8 Hz), 4.6 (dd, 1 H, J = 12.2, 6.3 Hz), 4.4 (dd, 1 H, J = 5.8, 1.0 Hz), 4.37 (ddd, 1 H, J = 11.4, 4.9, 3.4 Hz), 2.96 (s, 3 H), 2.32 (dd, 1 H, J = 13.0, 4.9 Hz), 2.08 (dd, 1 H, J = 13.0, 11.4 Hz), 0.72 (s, 9 H), 0.056 (s, 3 H), 0.043 (s, 3 H); IR ($CHCl_3$) 1730, 1265, 1110, 910, 712 cm^{-1}; MS (20 eV) 777 (2.8, M^+ - *tert*-butyl). Anal. C, H.

Preparation of Anhydro Sugars 15 and 16 and Aldehyde 17. Camphorsulfonic acid was added to a solution of triol **2b** in CH_2Cl_2 at room temperature. After 1 h the solution was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to give diol **15** (100%). A solution of the crude diol in 10:1 THF/H_2O was treated with 2 equiv $NaIO_4$. After 2 h the mixture was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% ethyl acetate/hexanes) to afford pure aldehyde **17** (90%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.88 (d, 1 H, J = 1.5 Hz), 8.08 (m, 2 H), 7.6 (m, 1 H), 7.48 (m, 4 H), 6.62 (d, 1 H, J = 3.4 Hz), 6.43 (dd, 1 H, J = 3.4, 1.8 Hz), 5.25 (m, 2 H), 4.80 (d, 1 H, 3.8 Hz), 4.67 (br s, 1 H), 2.6 (dd, 1 H, J = 13.8, 4.3 Hz), 2.5 (dd, 1 H, J = 13.8, 1.6 Hz), 0.84 (s, 9 H), 0.06 (s, 3 H), -0.16 (s, 3 H); IR ($CHCl_3$) 1720, 1270, 1120, 840, 715 cm^{-1}; MS (20 eV) 443 (0.4, M^+ - Me), 429 (2.7, M^+ - CHO), 401 (100, M^+ - *tert*-butyl).

Camphorsulfonic acid was added to a solution of triol **13b** in CH_2Cl_2 at room temperature. After 1 h the solution was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to give diol **16** (100%). A solution of the crude diol in 10:1 THF/H_2O was treated with 2 equiv $NaIO_4$. After 2 h the mixture was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% ethyl acetate/hexanes) to afford pure aldehyde **17** (88%), which was identical with the aldehyde prepared from **14b** (see above).

Acknowledgment. This work was supported by PHS Grant AI 16943. A fellowship from the Corn Refiners Association, Inc. to M.P.D. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which is supported by NSF/Chemistry Division Grant CHE 7916210.

Registry No. 2, 102650-47-5; **2b**, 102650-48-6; **3**, 102682-12-2; **7**, 114273-48-2; **8**, 114375-29-0; **9**, 114273-49-3; **10**, 114273-51-7; **11**, 114273-52-8; **13a**, 114375-32-5; **13b**, 114375-33-6; **14a**, 114375-35-8; **1b**, 102650-49-7; **15**, 114273-53-9; **16**, 114375-36-9; **17**, 114273-54-0; Ph_3P=CHCOOMe, 2605-67-6; (8*R**)-methyl 9,12-anhydro-7,10,11-trideoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-DL-*glycero*-DL-*galacto*-dodeco-9,11-dien-8-ulo-8,4-pyranosidonic acid methyl ester 5-benoate, 114375-30-3; (8*R**)-methyl 9,12-anhydro-7,10,11-trideoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-DL-*glycero*-DL-*ido*-dodeco-9,11-dien-8-ulo-8,4-pyranosidonic acid methyl ester 5-benzoate, 114375-31-4; methyl 1,4-anhydro-2,3,6-trideoxy-7-*O*-[(1,1-dimethylethyl)dimethylsilyl]-12-*O*-(phenylmethyl)-DL-*glycero*-α-LD-*manno*-dodeco-1,3-dien-5-ulo-5,9-pyranoside 8-benzoate, 114273-50-6; methyl 1,4-anhydro-2,3,6-trideoxy-7-*O*-[(1,1-dimethylethyl)dimethylsilyl]-12-*O*-(phenylmethyl)-DL-*glycero*-β-LD-*gulo*-dodeco-1,3-dien-5-ulo-5,9-pyranoside 8-benzoate, 114375-34-7.

Supplementary Material Available: ORTEP drawings and tables containing fractional coordinates, temperature factors, bond distances, fractional angles, and anisotropic temperature factors for compounds **3** and **8** (16 pages). Ordering information is given on any current masthead page.

Stereoselective Total Syntheses of the Naturally Occurring Enantiomers of *N*-Acetylneuraminic Acid and 3-Deoxy-D-*manno*-2-octulosonic Acid. A New and Stereospecific Approach to Sialo and 3-Deoxy-D-*manno*-2-octulosonic Acid Conjugates

Samuel J. Danishefsky,* Michael P. DeNinno, and Shu-hui Chen

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received August 28, 1987*

Abstract: The total syntheses of the title compounds have been achieved. A critical element of these syntheses was the concept of using a furan ring as a surrogate for a carboxylic acid. The furyl diene **22** reacted with the *R* and *S* enantiomers of 2-(phenylseleno)propionaldehyde (see compounds **9R** and **9S**) with high regiospecificity under catalysis by boron trifluoride etherate. Another useful consequence of the furan surrogate was its ability to promote exchange reactions of an anomeric methoxyl group with a variety of primary "sugar alcohols" (see reactions of compound **33** with alcohols **62-64**). Upon oxidation of the furan to the corresponding C_1 methyl ester, a fully synthetic route to sialic acid conjugates has been developed (see compounds **65-67**). An important finding that was crucial for the total syntheses of the naturally occurring antipodes was a very high diastereofacial selectivity, in the Cram-Felkin sense, manifested in Lewis acid catalyzed cyclocondensation reactions of aldehydes **9R** and **9S**. Since these compounds are available in two steps from the naturally occurring lactic esters, the total syntheses of the naturally occurring enantiomers was a straightforward matter.

Background of the Problem and Synthetic Planning. The elucidation of the roles of neuraminic or sialic acids in moderating a range of biological properties and functions is an increasingly important area of biochemical research.[1,2] The acids are encountered in glycosidic linkages at the nonreducing end of a variety of biooligomers. For instance, sialoconjugation has implications in influencing the physical characteristics of oligosaccharides (**2**) and glycoproteins (**3**). Moreover, the extent of sialylation has an apparent effect in masking the antigenicity of many macromolecules. Not the least interesting involvement of neuraminic acids is their presence in glycosphingolipids such as gangliosides (**4**).[3]

(1) *Sialic Acids: Chemistry, Metabolism and Function in Cell Biology Monographs*; Schauer, R., Ed.; Springer-Verlag: New York, 1982; Vol. 10.
(2) Schauer, R. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 131.
(3) (a) *Glycolipids* in *New Comprehensive Biochemistry*, Wiegandt, H., Ed.; Elsevier: New York, 1985; Vol. 10, pp 199-260. (b) *Ganglioside Structure, Function, and Biomedical Potential*: Leeden, R. W. et al., Eds.; Plenum: New York, 1984.

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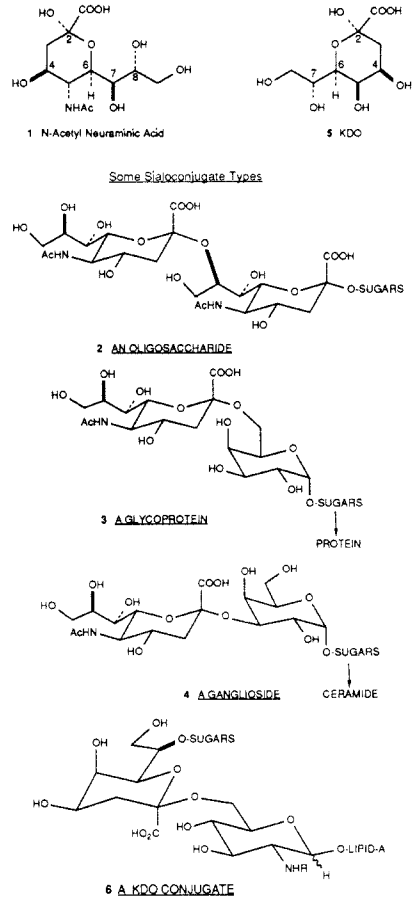
Chart I

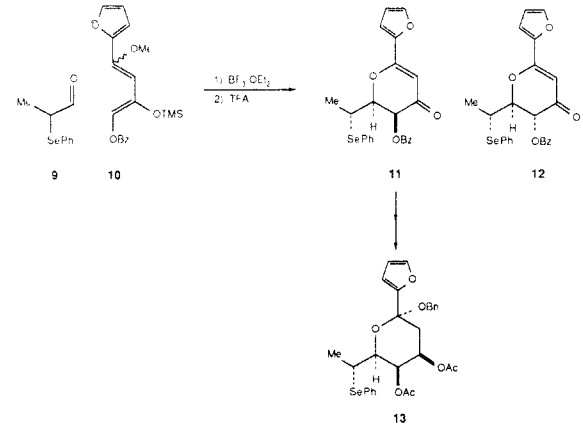


Ganglioside levels are relevant to the binding capacity of various membranes. The single most common neuraminic acid is the *N*-acetyl derivative Neu5Ac (**1**).

A compound with a significant resemblance to **1** is the ketose 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **5**).[4,5] However, according to present knowledge, the biological roles of the two compounds are strikingly different. KDO seems to be restricted to the realm of Gram-negative bacteria, whereas sialic acids are found throughout the mammalian domain. The primary role of KDO is that of providing a structural connecting link between the lipid A and core polysaccharide regions in the membrane structures of these microorganisms (cf. structure **6**).

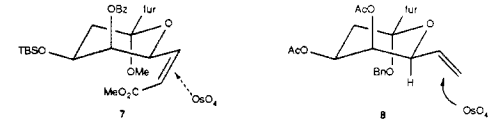
Our interest in *N*-acetylneuraminic acid (Neu5Ac, **1**) and 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **5**) initially arose from a broader involvement in the synthesis of polyoxygenated natural products including complex monosaccharides. We have recently described the total syntheses of both compounds from noncarbohydrate precursors.[6-8] One of the challenges in each of these constructions lay in exercising control of the stereochemistry of the side chains (C_7 and C_8 in **1** and C_7 in **5**). Eventually it was shown that these goals could be achieved via precursors **7** and **8**, respectively. In each instance osmium tetraoxide hydroxylation

Scheme I



occurred with very high selectivity in a fashion that was required for the goal system.

It will be recognized that for this result to have pertained, the overall stereochemical sense of the osmylation reaction would have to be different in the two cases. Elsewhere we have brought evidence to bear that this striking result arises from the differing conformations of the two substrates.[9] In the case of **7**, the reactive conformer seems to be one where the double bond is anti to the carbon–oxygen bond of the pyran. In the KDO precursor **8**, the result is consistent with the hydroxylation having occurred anti to the pyranoid oxygen atom, in the conformer shown.[10] The ground-state conformation of **7**, at least in the crystalline state, is known. The one for **8** is surmised from the crystal structure of a closely related compound.[9] For purposes of sharpening the contrast in the osmylation reaction of the two compounds, racemate **8** is shown in the absolute configuration which would actually lead to *ent*-KDO.

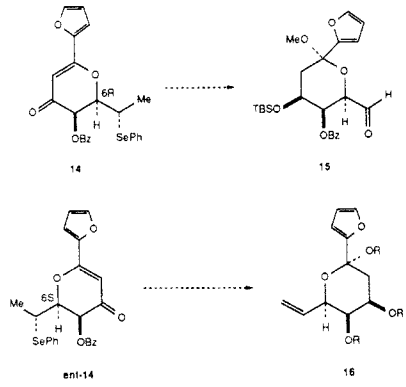


Of course, each of these two syntheses suffered from a major shortcoming in that the products were produced as racemates. *In the research described herein, total syntheses of the naturally occurring enantiomers of Neu5Ac (**1**) and KDO (**5**) have been achieved.* In the cases at hand, synthetic access to the "natural enantiomers" seemed to be a particularly worthy pursuit. As noted above, the interest in these materials arises not primarily from the free compounds themselves but from their glycosidically linked conjugates (cf. oligosaccharides, glycolipids, glycoproteins). Since the species entering into "sialoconjugation" are chiral, the prospect of joining a single enantiomeric substrate to a racemic "sialylating" agent was not promising. Moreover, as will be discussed below (vide infra), it was not our intention to use the final natural product as the sialyl or KDO "donors" but to take advantage of synthetic intermediates on the way to the final products for this purpose. With this in mind, we sought to orient both syntheses to produce the desired antipode at early stages.

Given the fact that in our earlier studies[6-9] the racemic compounds **7** and **8** were shown to be viable precursors for control of the relative stereochemical issues required to reach **1** and **5**, respectively, it seemed reasonable to focus our pursuits on reaching enantiomerically pure versions of these enepyranosides. It will be noted that though **1** and **5** each belong to the broad class of D sugars (see C_8 in **1** and C_7 in **5**), *the configurations of the two pyranose rings as defined by C_6 are opposite.* Thus, in structure **1**, C_6 is *R*, while in structure **5**, it is *S*. This difference, then, must be reflected in the enantiomeric versions of precursors, **7** and **8** used in the syntheses of **1** and **5**, respectively.

(4) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323.
(5) Anderson, L.; Unger, F. M. *Bacterial Lipopolysaccharides: Structure, Synthesis and Biological Activities*; ACS Symposium Series No. 231; American Chemical Society: Washington, DC.
(6) Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280.
(7) (a) Danishefsky, S. J.; DeNinno, M. P. *J. Org. Chem.* **1986**, *51*, 2615. (b) For previous syntheses of Neu5Ac, see: Ledeen, R. W.; Yu, R. K. In *Biological Roles of Sialic Acid*; Rosenberg, A., Schengrund, C. L., Eds.; Plenum: New York, 1976, pp 1–57. Benzing-Nguyen, L.; Perry, M. B. *J. Org. Chem.* **1978**, *43*, 551. Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 1205. Auge, C.; David, S.; Gautheron, C. *Tetrahedron Lett.* **1984**, *25*, 4663. Bednarski, M. D.; Chenault, H. K.; Simon, E. S.; Whitesides, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 1283.
(8) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.
(9) DeNinno, M. P.; Danishefsky, S. J., manuscript submitted for publication.
(10) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943.

Scheme II

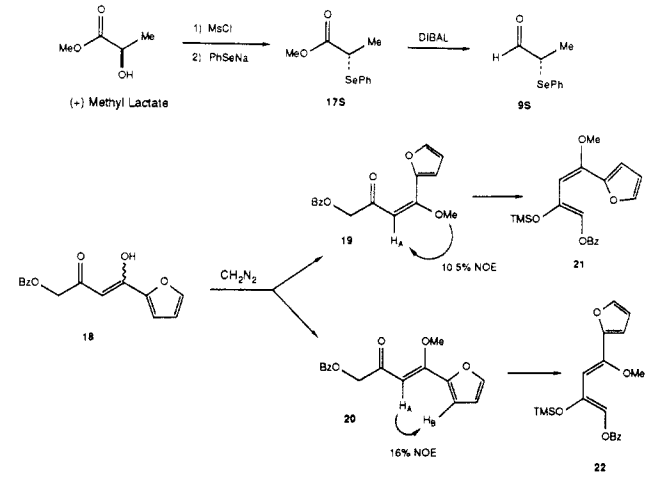


An important clue as to how this objective might be accomplished arose during the course of the synthesis of racemic KDO.[6] In that effort we utilized the racemic phenylseleno aldehyde **9** as a viable synthetic equivalent of acrolein. Cycloaddition of dienes **10** with **9** gave a mixture of cis (**11**) and trans (**12**) isomers, with the former predominating, though only in a ratio of 2.5:1 (Scheme I). *The observation that formed the basis of the effort described below was that each of these compounds is formed as a single diastereomer.* In other words, the stereogenic center bearing the phenylseleno grouping provided very powerful communication in determining the outcome of the emerging center at C_6. The nature of this stereochemical relationship became clear through a single crystal X-ray structure of compound **13**,[6] from which we could learn that the overall sense of the cyclocondensation reaction leading to **11** had occurred in accordance with the Cram–Felkin formulations.[11] While the stereochemical connectivity in the trans compound **12** was not rigorously shown, it was assumed that it had also been fashioned by a cyclocondensation reaction, which had occurred in the Cram–Felkin sense. *Therefore, given access to the appropriate enantiomers of compound **9**, strict Cram–Felkin diastereofacial connectivity could be exploited to produce pyranose rings of the absolute configurations required to reach the natural products.* In our envisioned scheme, the chirality at the selenium-bearing carbon would be forfeited in the transformations leading to olefinic intermediates **7** and **8**. However, this forfeiture would occur after the chiral imprint of the seleno-bearing center had been conveyed in fashioning the dissymmetric pyranose ring. From the pyranose ring, stereochemical information would be transmitted back to the unsaturated side chains of enantiomerically pure versions of **7** and **8** to produce the desired products.

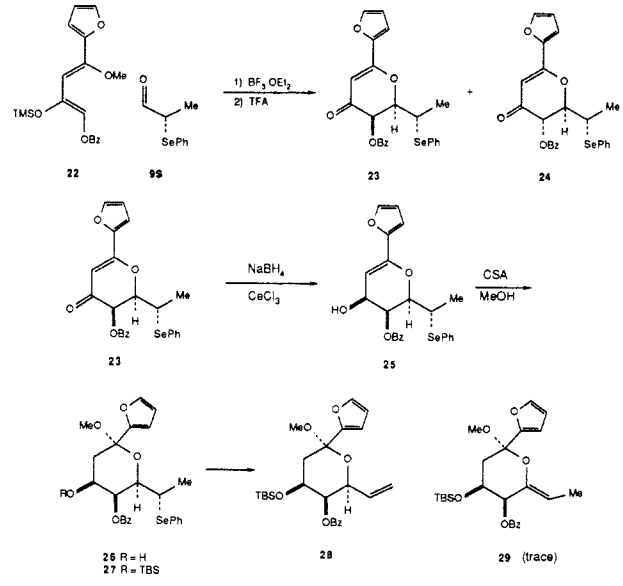
At approximately the time of this planning exercise, Hopkins[12] had reported a synthesis of **9** via chemistry that started with lactic acid. Given the availability of both antipodes of lactic acid and the well-defined configurational connectivity of the Hopkins sequence, either configurational version of aldehyde **9** should thus be available. For the synthesis of Neu5Ac it was necessary that 6*R* pyranose **14** be converted to aldehyde **15**. For KDO, the 6*S* pyranose (*ent*-**14**) would require conversion to a vinyl compound of the type **16** (Scheme II). With these compounds in hand, it would then be possible to retrace the steps that had been demonstrated to be viable in the synthesis of the racemates.[6,7]

Total Synthesis of Neu5Ac. Via the general procedure of Hopkins, (*R*)-methyl lactate was converted in two steps to the *S* seleno ester **17** (Scheme III). Reduction of the ester with diisobutylaluminum hydride gave (*S*)-seleno aldehyde (**9S**). When this compound was prepared in modest scale (less than 1 g) the aldehyde could be obtained relatively pure. In larger runs, it was more convenient to generate the aldehyde in crude form. Under this treatment, the aldehyde was contaminated to some extent by starting ester **17**.

Scheme III



Scheme IV



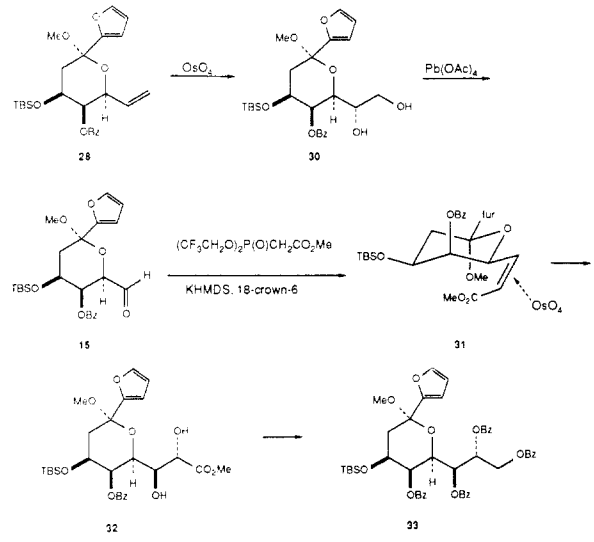
We now turn to consideration of the cyclocondensation reaction of aldehyde **9S** with an appropriate furyl diene. The reasoning that led to the use of such unusual dienes was already set forth in some detail.[6] In previous investigations in the racemic series, the diene that was used was a 1:1 mixture of the 1*E* (**21**) and 1*Z* (**22**) compounds (see diene **10**). In the interim it was discovered that of these two geometric diastereomers, it is only isomer **22** that effectively undergoes the reaction. Each of these dienes was prepared from the corresponding enones, **19** and **20**. In the present study, these substances were obtained in homogeneous form upon silica gel chromatography of the product arising from the action of the previously described enone, **18**, with diazomethane. Enone **19** led to the pure *E*-diene, **21**, while enone **20** led to the pure *Z*-diene, **22**. The configurations of the two enones, and hence of the two dienes, could be assigned on the basis of nuclear Overhauser effect (NOE) experiments. The reasons for the dramatically different performances of the two dienes in the coupling reaction are not at all clear.

After some considerable experimentation, it was possible to achieve a substantial improvement in the cis/trans ratio of the pyrones (cf. **12** and **13**) available through the cyclocondensation reaction. When methylene chloride was used as the solvent with $BF_3{\cdot}OEt_2$ at −78 °C, a 5:1 mixture of cis (**23**) and trans (**24**) dihydropyrones was obtained (Scheme IV). Optical purities in the range of 95% of **23** were realized when an aqueous workup procedure for the isolation of **9S** was avoided. Apparently aqueous treatment led to partial racemization of this labile selenoaldehyde. In the optimum protocol for avoiding racemization, reduction of **17** with diisobutylaluminum hydride was immediately followed

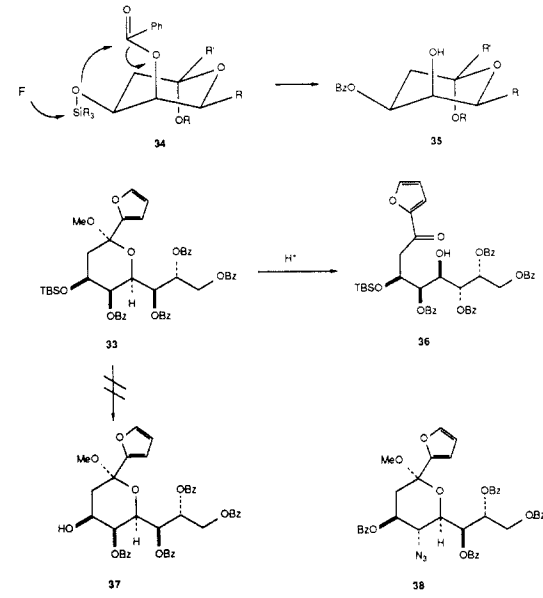
(11) Cram, D. J.; AbdElhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (c) Ahn, N. J. *Top. Curr. Chem.* **1980**, *88*, 145.

(12) Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 417.

Scheme V



Scheme VI



by addition of $BF_3 \cdot OEt_2$ and *Z*-diene **22**.

Reduction of the keto function with sodium borohydride in the presence of cerium(III) chloride[13] afforded the alcohol **25**. Addition of methanol to the double bond was easily accomplished through the action of camphorsulfonic acid (CSA) to afford the axial glycoside **26**. This type of reaction, previously demonstrated during the course of our racemate syntheses, is clearly a consequence of the stabilizing effect of the furan linkage on incipient cationoid character at C_2. The alcohol was smoothly converted to the OTBS ether **27**. The stage was set for oxidative elimination of the phenylseleno function. This was accomplished by treatment of **27** with hydrogen peroxide. Compound **28** was obtained in 81% yield from **23**. The presence of a trace of the trisubstituted olefin **29** was also noted.

Osmium tetraoxide hydroxylation of **28** afforded diol **30** (Scheme V). This is a stereospecific reaction. Factors which define the sense of this reaction have been considered elsewhere.[9] Here we note that the enantiomer of **30** (see compound **51**) is a critical intermediate in the KDO synthesis. For purposes of synthesizing Neu5Ac, this specificity was not exploitable. Indeed, the diol function in **30** was cleaved with $Pb(OAc)_4$, affording aldehyde **15**. As in the synthesis of racemic Neu5Ac, **15** was condensed with the Still phosphonate[14] to afford an 80% yield of *Z* enoate **31** (admixed with less than 5% of the *E* isomer). In the case at hand, compound **31** served as a convenient point to improve optical purity (>98% ee) via recrystallization.

It was hoped that osmium tetraoxide would attack compound **31** via the conformer shown, with attack of the electrophile from the face of the double bond which is anti to the pyranose. As described previously, the ground-state conformation of **31**, as revealed by an X-ray crystallographic determination, corresponds quite closely to that shown. In the event, hydroxylation proceeded with high selectivity (ca. 20:1) to give a 90% yield of the desired **32**. The structure of the racemic version of **31** had earlier been established by crystallographic determination of its bis(3,5-dinitrobenzoate) derivative.[9] Success in reducing the ester function of **32** was attained through the action of lithium triethylborohydride. Upon perbenzoylation, the tetrabenzoate **33** was in hand (80% from **31**).

It was not by accident that compound **33** came "equipped" with a TBS protecting group at its C_4 hydroxyl function. It was anticipated that desilylation would trigger a benzoyl migration from the C_5 oxygen to the C_4 hydroxyl (see generalized transformation of **34** → **35**, Scheme VI).[15] Thus the lone axially bound oxygen atom would emerge as a free hydroxyl group. Such an outcome could be exploited. Thus displacement of an activated derivative of **35**, with inversion, by a suitable nitrogen-based nucleophile could provide the opportunity for introduction of the 5-NAc group. Unfortunately, the opening phase of this plan could not be reduced to practice. Attempted desilylation at C_4 with tetra-*n*-butylammonium fluoride led only to extensive decomposition. Attempted formation of compound **37** by desilylation under acidic conditions led to the formation of **36**.

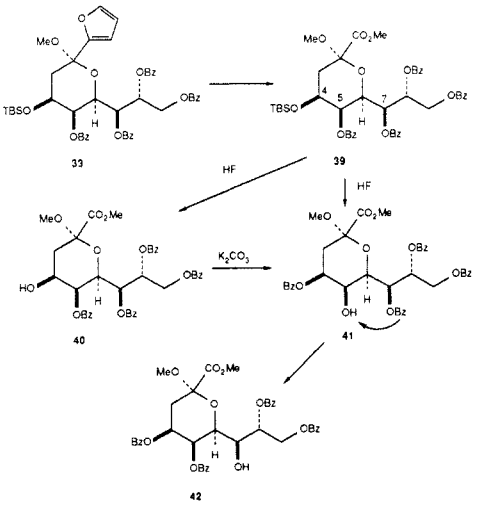
The vinylogous ortho ester like anomeric center was seen to be a serious source of instability in compound **33**. Accordingly, it was decided to convert the furan grouping to a carboxyl level group prior to desilylation. This change of tactic was to have an adverse effect on our plans for sialoconjugate synthesis. In those plans it was assumed that a variety of nucleophiles under protic or Lewis acid conditions might displace the anomeric methoxyl group. The furyl group, with its tendency to stabilize electron deficient character at C_2 would be crucial for this capability (vide infra). The incompatibility of the furan residue with the late stages of the Neu5Ac synthesis meant that compound **38** was not a viable possibility by total synthesis. Therefore, any new complex alcohol would have to be introduced at the stage of compound **33**. This in turn meant that a significant fraction of the sialoconjugate synthesis would have to be carried out in a complex setting where the moiety to be conjugated was already present (i.e., on a di- or oligosaccharide). An example of the difficulties engendered by this situation will be described later.

With a view to the immediate goal of a total synthesis of the parent compound **1**, only a slight change of tactic was required. Compound **33** was oxidized with ruthenium tetraoxide in the presence of excess sodium bicarbonate as buffer.[16] Reaction appeared to be complete after one minute. Workup followed by diazomethane treatment afforded methyl ester **39** in 90% yield (Scheme VII). At this stage the system was sufficiently stable to allow for removal of the TBS protecting group with HF in methanol. The major product (60%) that arose from this treatment was the expected 4-hydroxy compound **40**. The other (ca. 30%) was compound **41**, bearing the equatorial benzoyloxy group at C_4 with a free hydroxyl at C_5.[16] Reaction of **40** with potassium carbonate also triggered benzoyl migration to produce additional amounts of **41**. In addition to recovered **40** there was also obtained **42**, which is the result of still another benzoyl transfer from C_7 to C_5. Compound **42** appears to be the most stable tetrabenzoate in the series, presumably reflecting the fact that the C_7 oxygen center is the most hindered among the C_4, C_5, C_7,

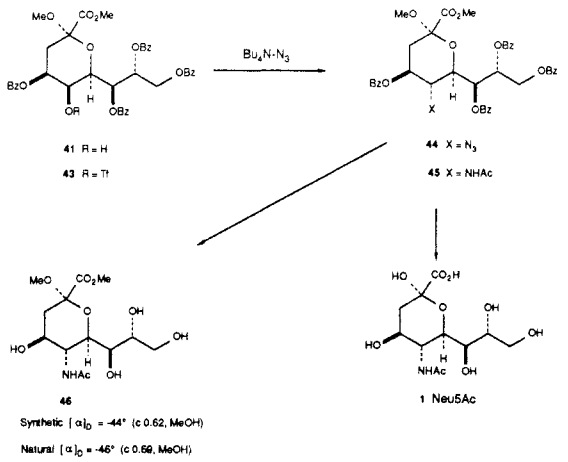
(13) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(14) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(15) For references on acyl migrations in carbohydrates, see: (a) Albert, R.; Dax, K.; Stutz, A. E.; Weidmann, H. *J. Carbohydr. Chem.* **1983**, *2*, 279. (b) Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 100. (c) Capon, B. *Q. Rev., Chem. Soc.* **1964**, *18*, 45.

(16) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

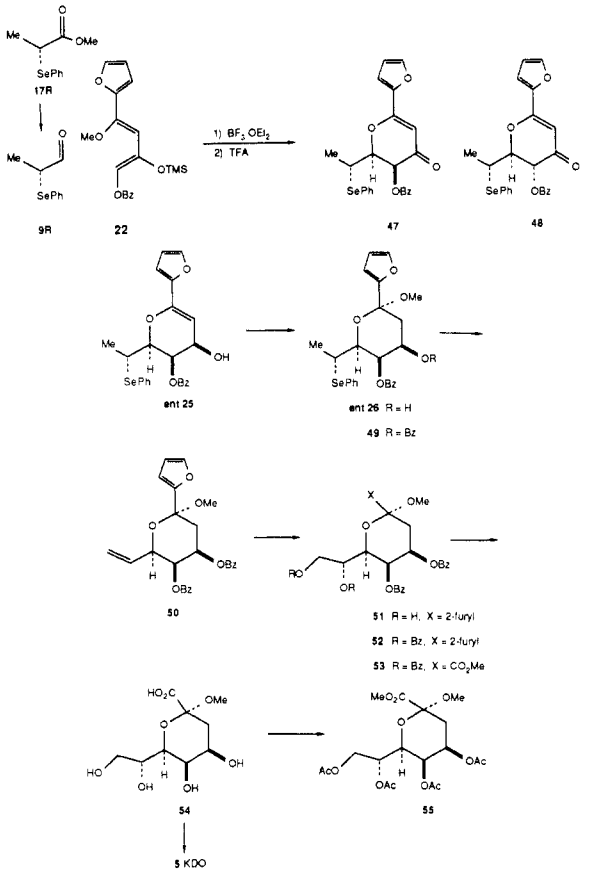
Scheme VII



Scheme VIII



Scheme IX



C_8, and C_9 "quintet". The overall minimum yield of desired **41** by this methodology was ca. 65%. Additional amounts could be obtained by further recycling of **40**.

The best procedure for installing the C_5 nitrogen atom involved activation of the C_5 hydroxyl of **41** as its corresponding triflate, **43**, via reaction with triflic anhydride. Compound **43** reacted smoothly with tetra-*n*-butylammonium azide to give an 86% overall yield of azidotetrabenzoate **44** (Scheme VIII). Reductive acetylation, leading to compound **45** (90%), was achieved by a two-step sequence: (i) reduction of the azide function with hydrogen and Lindlar catalyst; (ii) acetylation with acetic anhydride. To establish the correctness of our various structural assignments, a sample of compound **45** was synthesized from **1** by reaction with methanol followed by perbenzoylation.[17] The compounds were identical by spectroscopic (IR, NMR, 500 MHz) and chromatographic comparisons.

Fully synthetic **45** was debenzoylated and reesterified with diazomethane to give compound **46**. This intermediate was convenient for evaluating the optical purity of our synthetic material by polarimetric means. The data shown below indicate a very close correspondence. Finally, treatment of **45** first with aqueous sodium hydroxide, followed by reaction with Dowex 50W-X8 H^+ resin in aqueous THF under reflux afforded the fully synthetic Neu5Ac, **1**. The correspondence of this material with an authentic sample was established by the identity of their 500-MHz NMR spectra. The first total synthesis of **1** from noncarbohydrate sources had been concluded.

Total Synthesis of KDO. With the results of the Neu5Ac total synthesis in hand, and with the background of our previous investigations in the synthesis of the racemic version of **5**, the groundwork for a synthesis of the naturally occurring (7*R*) enantiomer of KDO[19] was secure. A minor change was instituted in this program relative to that utilized in the racemic series. In that work we had utilized benzyl glycosides (cf. compound **16**). Since in the synthesis of **1** it had been shown that methyl glycosides function quite well and can be readily cleaved at a strategic stage, methyl rather than benzyl glycosides were used in the 7*R* KDO synthesis.

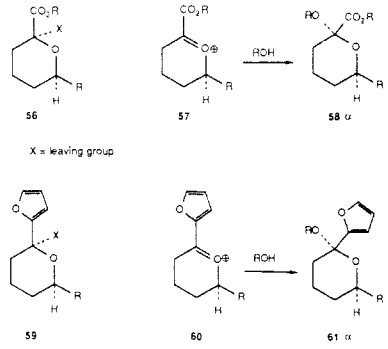
The synthesis started with the *S* enantiomer of methyl lactate. This was converted to the seleno ester **17R** and thence (vide supra) to the crude aldehyde **9R** (Scheme IX). The aldehyde reacted with the pure 1*Z*-diene **22** to afford a (76% overall yield from **17S**) 5:1 mixture of cis/trans dihydropyrones **47** and **48** (the enantiomers of **23** and **24**, respectively). Reduction of the major product **47** with sodium borohydride and purification by silica gel chromatography afforded *ent*-**25**. Addition of methanol to the "glycal"-like double bond occurred in a stereospecific fashion, leading to *ent*-**26** and thence after perbenzoylation, **49**. Oxidative elimination (93%), as above, afforded the vinylic compound **50**. Osmium tetraoxide hydroxylation of the double bond proceeded smoothly to give diol **51** (i.e., *ent*-**30**), which upon benzoylation afforded tetrabenzoate **52**. Oxidation with ruthenium tetraoxide followed by esterification with diazomethane afforded a 95% yield of **53**. Cleavage of the four benzoates and hydrolysis of the methyl ester afforded methyl KDO α-methyl glycoside **54**. Deprotection with 6 N HCl afforded fully synthetic, optically active KDO (**5**) itself, characterized as its crystalline ammonium salt. Also, esterification of **54** followed by peracylation afforded **55**, whose NMR spectrum was identical with that of an authentic sample prepared by Pearson during the course of his synthesis of **5**-*rac*.[6] The first total synthesis of the naturally occurring 7*R* KDO from

(17) Although acid catalyzed acyl migrations are known, the presence of compound **41** did not appear until after the workup of the reaction mixture (see the Experimental Section).

(18) Kuhn, R.; Lutz, P.; MacDonald, D. L. *Chem. Ber.* **1966**, *99*, 611.

(19) For previous syntheses of KDO, see ref 4 and: (a) Schmidt, R. R.; Betz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 430. (b) Collins, P. M.; Overend, W. G.; Shing, T. *J. Chem. Soc., Chem. Commun.* **1981**, 1139.

Scheme X



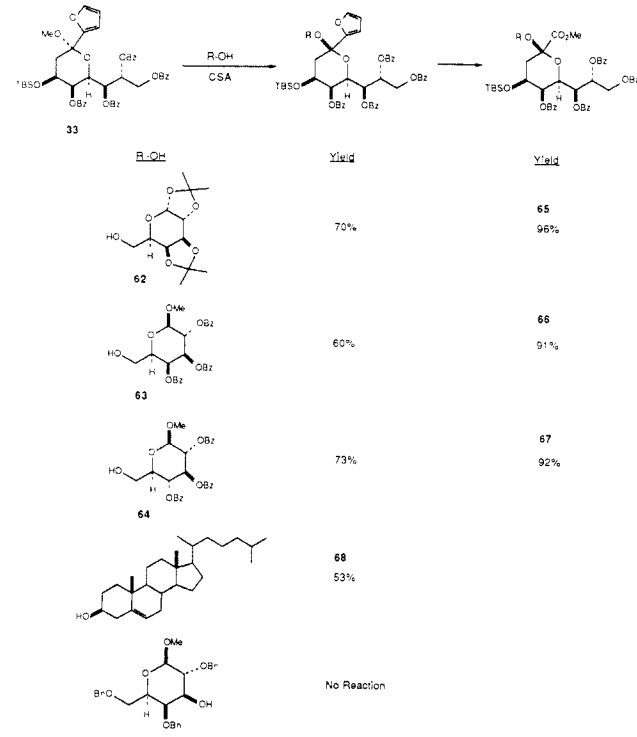
noncarbohydrate sources was thus achieved.

A New Route to Sialic Acid and KDO Conjugates. At the outset, one of our prime considerations in undertaking the synthesis of the naturally occurring enantiomer of **1** was the hope to use the chemistry that was being developed to construct sialic acid conjugates of a type that are found in natural oligomeric systems. One of the most important challenges in carbohydrate research is that of realizing improvements in the fashioning of the glycosidic bond. The importance of this goal arises from the fact that, along with the peptide and internucleotide linkages, the glycosidic bond is a widely encountered connecting linkage in biooligomers. Happily, major progress has been achieved in the gross fashioning of the glycosidic bond and in the control of stereochemistry at the anomeric center produced through glycosidation.[20] A more difficult problem arises in establishing the glycosidic attachment to sialic acids.[21a-c] The complexity associated with ordinary glycosidation is compounded in this case by three factors. First, the presence of the carboxyl-equivalent substituent at the anomeric carbon carries with it additional steric hindrance. Furthermore, the electron-withdrawing capacity of the carbonyl center undoubtedly attenuates the oxonium character of systems such as **57**. Finally, the absence of a substituent at C_3 can serve to complicate the problem of exercising stereochemical control in the conversion of **56** → **58**α (Scheme X). In naturally occurring sialic acid conjugates, the glycosidic bond is apparently universally equatorial (α).[21] The electron-withdrawing character of the carbonyl group is likely to complicate the process of thermodynamic equilibration at the anomeric carbon (via a species related to **57**).

We conjectured about the possibility that the furan surrogate, which played a crucial role in the synthesis of **1** *itself, could provide a helpful margin of reactivity for the sialylation.* The logic of the plan is implied in the projected transformation **59** → **61**α, which would occur through the agency of the stabilized **60**. It was also foreseen that increased accessibility to **60** could facilitate the possibility of obtaining **61** in its thermodynamically more stable equatorial form (**61**α). It was further hoped that the leaving group (X) in **59** might correspond to a simple methyl glycoside such as is available from the synthesis (vide supra).

It was our original plan to use compound **38** for the trans glycosylation. However, as described, we could not gain access

Scheme XI



to azido furyl glycoside **38** via total synthesis since the transformation **33** → **37** failed. Thus we were obliged to return to compound **33**, which lacked the C_5 nitrogen functionality.

Indeed, the methyl ether linkages α to the furyl function proved to be an adequate glycosylation group. This important finding is summarized in the reactions of **33** with three representative primary sugar alcohols, **62**–**64** (Scheme XI). In the presence of catalytic quantities of the simple acid, CSA, in benzene at room temperature, exchange took place. Furthermore, in each case only a single stereoisomer was produced. In one instance (compound **80**, vide infra) it was rigorously shown spectroscopically that the glycoside linkage was of the natural equatorial configuration. Since the glycosides derived from compounds **62**–**64** evidenced very similar spectroscopic properties, it is safely assumed that they are all linked the same way. Thus, all the glycosides produced by this method were of the natural configuration. Whether this is the consequence of thermodynamic or kinetic control remains to be clarified. Ruthenate oxidation of these compounds, as above, followed by esterification (diazomethane) provided the corresponding methyl esters **65**–**67**, respectively.

Another interesting trans-glycosidation reaction of **33** was achieved with cholesterol. Compound **68** was obtained in 53% yield, as a single anomer. In this case, oxidative conversion to the corresponding anomeric carbomethoxy system was not attempted due to the presence of the double bond in the steroid. We note that cholesteryl ketosides of **1** have been claimed to have useful immunomodulation properties.[22] This successful reaction with cholesterol demonstrates that the exchange process is possible with secondary as well as primary alcohols. At the present writing, however, attempted trans glycosidations with compound **33** and several pyranose systems bearing secondary alcohols, with a variety differential protection arrangements, have been unsuccessful. If the furan-based method is to become of general utility, major improvements in its extension to secondary "sugar alcohols" will be necessary.

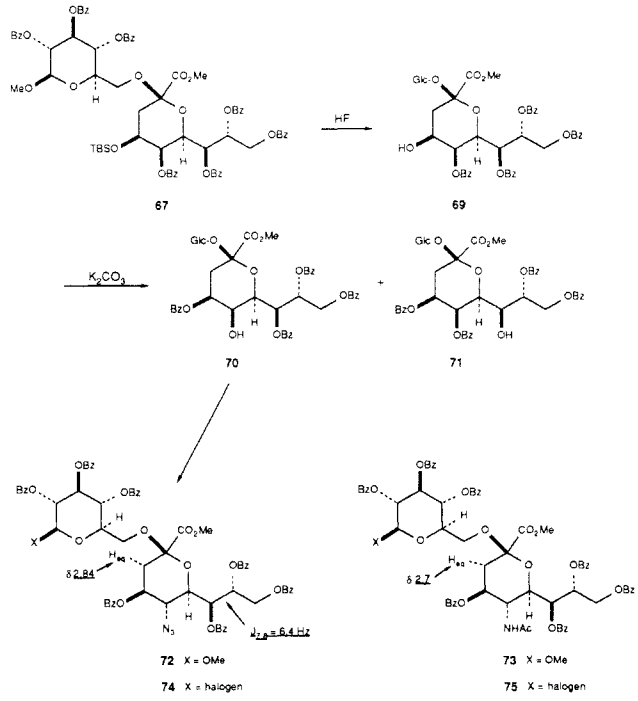
We have investigated the possibility of elaborating compound **67** in the direction of a sialodisaccharide and have shown this to be feasible. Reaction of **67** with HF in methanol did in fact remove the single TBS group, affording equatorial alcohol **69** in 92% yield (Scheme XII). However, benzoyl migration did not

(20) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (b) Nicolaou, K. C.; Dolle, R. E.; Paphatjis, D. P.; Randall, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 4189.

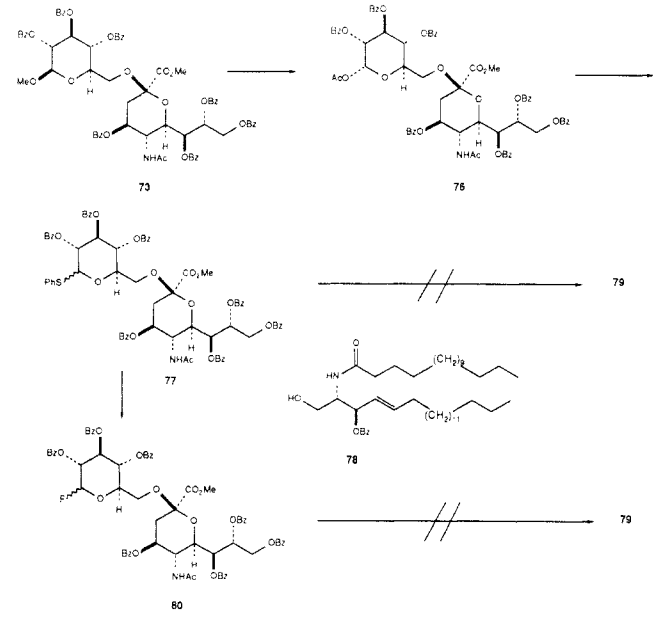
(21) For the synthesis of Neu5Ac conjugates, see: (a) (by enzymatic methods) Sabesan, S.; Paulson, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2068. (b) (From sialic acid glycosyl halides) Ogawa, T.; Sugimoto, M. *Carbohydr. Res.* **1985**, *135*, C5. Kitajima, T.; Sugimoto, M.; Nukada, T.; Ogawa, T. *Carbohydr. Res.* **1984**, *127*, C1. Paulsen, H.; Von Deessen, U. *Carbohydr. Res.* **1986**, *146*, 147. Paulsen, H.; Von Deessen, U.; Tietz, H. *Carbohydr. Res.* **1985**, *137*, 63. Paulsen, H.; Tietz, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 128. Paulsen, H.; Tietz, H. *Carbohydr. Res.* **1984**, *125*, 47. Furuhata, K.; Anazawa, K.; Itoh, M.; Shitori, Y.; Ogura, H. *Chem. Pharm. Bull.* **1986**, *34*, 2725. Ogura, H.; Furuhata, K.; Itoh, M.; Shitori, Y. *Carbohydr. Res.* **1986**, *158*, 37. Brandstetter, H. H.; Zbiral, E. *Monatsh. Chem.* **1983**, *114*, 1247. Kunz, H.; Waldmann, H. *J. Chem. Soc., Chem. Commun.* **1985**, 638. Pozsgay, V.; Jennings, J.; Kaspar, D. L. *J. Carbohydr. Chem.* **1987**, *6*, 41. (c) (From 2,3-dehydroneuraminic acid) Okamoto, K.; Kondo, T.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 5233. Okamoto, K.; Kondo, T.; Goto, T. *Chem. Lett.* **1986**, 1449.

(22) Ogura, H.; Furuhata, K.; Fujita, H.; Ito, M.; Yoshimura, S.; Shidori, Y. Jpn. Kokai Tokyo Koho 61, 243, 096.

Scheme XII



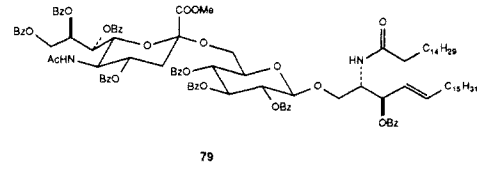
Scheme XIII



occur as smoothly as was the case with the methyl glycoside (see **40** → **41**). The desired benzoyl migration could be induced by treatment of **69** with potassium carbonate in methylene chloride. Unfortunately, the migration, leading to isomeric alcohol **70** was rapidly followed by another migration producing the unwanted isomer **71**. Although the problem of $C_7 \rightarrow C_5$ migration had been encountered earlier with the axial methyl glycoside (see **40** → **41** → **42**), it was more serious in the case of the complex equatorial glycoside. It was necessary to discontinue formation of **70** when the consumption of **69** was only half complete. After **69** was recycled and recovered under the conditions described above, the yield of **70** reached ca. 50%.

We now applied the technology developed in the case of the methyl ketoside (see compound **41**) to the more elaborate disaccharide system **70**. Reaction of **70** with triflic anhydride and displacement with tetrabutylammonium azide afforded, in nearly quantitative yield, the azido ketoside **72**. Reduction followed by acylation afforded a 92% yield of **73**. At this stage the NMR analysis in conjunction with previous correlations sufficed to establish that the stereochemistry of the ketosidic anomeric center is indeed that shown and corresponds to the natural series for sialic acid conjugates.[23] Given our earlier enantiospecific synthesis of glucose (albeit demonstrated for the L enantiomer),[24] *the claim of a totally synthetic route to this complex sialodisaccharide from noncarbohydrate sources can now be registered.*

With the completion of this subgoal, work was directed toward completion of the synthesis of a simple ganglioside. We set as our target the fully protected system **79**.[25] To reach this compound, the introduction of a ceramide derivative into the anomeric center of the glucose residue of **72** or **73** had to be accomplished.



The synthesis of simple glycosphingolipids has been extensively studied.[26] The standard procedure involves the coupling of a glycosyl bromide with a 3-*O*-benzoyl ceramide under $Hg(CN)_2/HgBr_2$ catalysis. However, this method often requires harsh conditions to promote reaction. For example, Shapiro reported that the coupling of a galactosyl bromide and ceramide under $Hg(CN)_2/HgBr_2$ catalysis required 40 °C for 12 h to isolate a 55% yield of glycospinogolipid.[27] Ogawa and co-workers have completed the only synthesis of complete gangliosides.[28a] The attachment of a sialoconjugate to a ceramide residue had been achieved via trichloroacetimidate activation,[28b] though often in poor yield and with poor anomeric stereoselectivity.[28c]

Our first task in accomplishing the synthesis of **79** involved replacing the methyl glycoside with a useful leaving group. At the outset we felt that azide **74** would be a superior donor for the glycosidation reaction since it lacked the possible local buffering effect of an acetamido function.[29] Surprisingly, attempted hydrolysis of the methyl glycoside in **72** failed under a variety of conditions (H_2O, Dowex 50W-X8 resin; 2 N HCl; 4 N H_2SO_4). This molecule proved to be remarkably stable.

Success in replacing the methyl glycoside was achieved with the *N*-acetyl derivative **73**. Treatment of this compound with acetic anhydride in the presence of sulfuric and acetic acid afforded the anomeric acetate **76** in 85% yield (Scheme XIII). However, attempted conversion of **76** to the corresponding anomeric bromide[30a] or chloride[30b] (**75**, X = Br or Cl) was unsuccessful. It was reasoned that a thiophenyl glycoside would be a worthy target since it would be amenable to purification and could be selectively activated. Accordingly, **76** was treated with 30 equiv of TMSSPh and 15 equiv of TMSOTf[31] at room temperature to afford a mixture of thiophenyl glycosides **77** in 89% yield. Treating a mixture of **77** and the ceramide **78**[32] with *N*-bromosuccinimide

(23) The chemical shift for the C_3 equatorial proton in **71** and **72** and the J_{7-8} coupling constants in **71** are within the normal limits for α-linked disaccharides: (a) Dabrowski, U.; Friebolin, H.; Brossmer, R.; Supp, M. *Tetrahedron Lett.* **1979**, 4637. (b) Paulsen, H.; Tietz, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 927.

(24) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060.

(25) Kochetkov, N. K.; Smirnova, G. P.; Chekareva, N. V. *Biochim. Biophys. Acta* **1976**, *424*, 274.

(26) (a) Gigg, R. *Chem. Phys. Lipids* **1980**, *26*, 287. (b) Schmidt, R. R.; Klager, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 65.

(27) Shapiro, D.; Flowers, H. M. *J. Am. Chem. Soc.* **1961**, *83*, 3327.

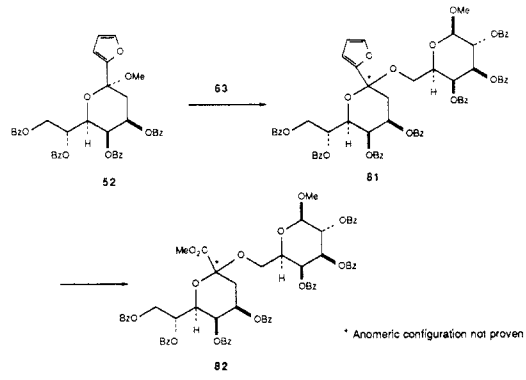
(28) (a) Sugimoto, M.; Numata, M.; Koike, K.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *156*, C1. (b) Numata, M.; Sugimoto, M.; Koike, K.; Ogawa, T. *Carbohydr. Res.* **1987**, *163*, 209. (c) For some very recent successes in this type of glycosylation, see: Schmidt, R. R.; Zimmerman, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 725. Schmidt, R. R.; Bar, T.; Apell, H. J. *Ibid.* **1987**, *26*, 793.

(29) It has been our experience that the reactivity of an anomeric oxygen function toward protic and Lewis acids is attenuated in sugars containing an acetamido group.

(30) (a) Treatment of **76** with HBr in an attempt to prepare the glycosyl bromide led only to recovered starting material. (b) Attempted preparations of the glycosyl chloride (Cl_2HCOCH_3, $ZnBr_2$) gave a complex mixture of products.

(31) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430.

Scheme XIV



gave no coupling product (cf. **79**). Apparently the NBS had reacted with the ceramide.

In an attempt to avoid this unwanted occurrence, the activation method of Garegg was attempted.[33] It had been shown that the methyl triflate–methyl disulfide complex is a very selective reagent, which only alkylates thio groups. However, using the Garegg conditions on our system led only to decomposition. A last effort was put forth by synthesizing the fluoro glycoside **80**. It was prepared by reacting of **77** with NBS and DAST[34] in 70% yield. Treatment of **80** with silver triflate and stannous chloride followed by the addition of ceramide **78** gave several minor products, none of which contained identifiable amounts of **79**. To bring this scheme to fruition, on the amounts of material available to us, would require marked major improvements in the technology of appending ceramide residues to complex saccharides. The quest for such improvement represents a worthy goal for future exploration.[28c]

The use of the furan surrogate to promote the formation of KDO glycosides[35] was also investigated and shown to be successful.[36] Thus, reaction of tetrabenzoate **52** with the protected galactose **63** under the now standard trans glycosylation conditions, afforded the anomeric furyl disaccharide **81** in 40% yield (Scheme XIV). The stereochemistry of this compound at the ketosidic center is in fact not rigorously known. The validity of an otherwise inviting analogy with the compounds derived from **33** is open to question since the relative stereochemistry of the two interlocked sugars differ in going from the presialoconjugate series to the pre-KDO conjugate system, **81**. Oxidation of **81** and esterification under the usual conditions afforded a 75% yield of the protected KDO conjugate, **82**, whose stereochemistry at the anomeric center is also not firmly established.

Prospects. Several important goals have been achieved herein. Expeditious total syntheses of **1** and **5** have been accomplished. The concept of the "furan surrogate" has been shown to be useful not only for the synthesis of the parent systems but also for the construction of sialo and KDO conjugates. A simple methyl glycoside suffices as an anomeric leaving group in this chemistry (see compounds **33** and **52**). Moreover the sialic acid glycosides are produced stereospecifically in the natural α (equatorial) configuration at the ketosidic bond.

While encouraging, these results underscore the need for advances in several areas. First, it would be helpful if the *C*-furylglycosyl compounds could be constructed by simple methods from readily available carbohydrates rather than by total synthesis. Second, it will be crucial to extend the coupling reaction of substrates such as **33** and **52** to encompass secondary alcohols on various strategic hexose and pentose carbon centers. Finally, for the synthesis of gangliosides, significant improvements in the construction of ceramide glycosides, particularly in systems bearing sialic acid residues, will be required. These goals will be of continuing interest in our laboratory.

Experimental Section

General Experimental Procedures. THF and diethyl ether were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from P_2O_5. Benzene was distilled from calcium hydride. All reactions requiring anhydrous conditions were run in flame-dried glassware under nitrogen or argon atmosphere. Spectra were recorded on the following instruments: IR, Perkin-Elmer 1420; MS, Hewlett-Packard 5985; NMR, 90 MHz, Varian EM390, 250 MHz, Bruker WM250, 500 MHz, Bruker WM500. High-resolution mass spectra were recorded on a Kratos MS 80RFA by Dan Pentek of the Yale University Instrumentation Center. Preparative column chromatography was carried out on silica gel 60 (E. Merck 9285, 230–400 mesh). Thin-layer chromatographic analyses were performed on E. Merck precoated silica gel 60 F-254 plates (0.25 mm). Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN. Original copies of the spectra and assignments are found in the Ph.D. Thesis of M. P. DeNinno, Yale University, 1987.

Enones 19/20. A mixture of diketone **18**[6] (7.1 g, 26.0 mmol) in ether (50 mL) was treated with ethereal diazomethane (ca. 75 mmol in 160 mL of ether) at 0 °C. After 1 h the solution was concentrated, and the oily residue was flash chromatographed (25–30% EtOAc/hexanes) to afford 3.4 g of the faster eluting enone **19** and 3.6 g of the slower eluting enone **20**. NMR data for **19**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.1 (m, 2 H), 7.55 (m, 5 H), 6.5 (dd, 1 H, J = 3.2, 0.8 Hz), 5.65 (s, 1 H), 4.95 (s, 2 H), 3.85 (s, 3 H). NOE data for **19** (see text) Irradiation of H_A showed a 14.3% enhancement of the methoxy protons and no enhancement of H_B. Likewise, irradiation of the methoxy group gave a 10.5% enhancement of H_A. NMR data for enone **20** (see text): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.1 (m, 2 H), 7.5 (m, 4 H), 7.18 (dd, 1 H, J = 3.2, 0.8 Hz), 6.5 (dd, 1 H, J = 3.2, 1.0 Hz), 6.12 (s, 1 H), 4.97 (s, 2 H), 4.0 (s, 3 H). NOE data for **20** (see text): Irradiation of H_A showed a 16% enhancement of H_B and no enhancement of the methoxy protons. Irradiation of the methoxy protons gave no NOE enhancement of H_B.

Dienes 21/22. A solution of pure enone (1 equiv) and triethylamine (5 equiv) in ether was treated with trimethylsilyl triflate (1.5 equiv) at 0 °C. After 5 min the ice bath was removed, and the solution was allowed to warm to room temperature. After 30 min the solution was poured into $NaHCO_3$ solution. The mixture was extracted with ether two times, and the combined ethereal layers were dried (K_2CO_3) and concentrated in vacuo for several hours to ensure removal of residual triethylamine. NMR data for diene **22**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.9 (m, 2 H), 7.2 (m, 5 H), 6.2 (m, 2 H), 5.5 (s, 1 H), 3.5 (s, 3 H), 0.0 (s, 9 H). NMR data for diene **21**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.9 (m, 2 H), 7.2 (m, 4 H), 7.0 (s, 1 H), 6.2 (m, 2 H), 6.0 (s, 1 H), 3.4 (s, 3 H), 0.0 (s, 9 H).

Dihydropyrones 23/24. Dibal (18.9 mL, 18.9 mmol) was added dropwise to a solution of seleno ester **17** (4.0 g, 16.5 mmol) in a 3:1 mixture of methylene chloride/hexanes (200 mL) at −78 °C. After 45 min, DMF (2.5 mL, 33 mmol) was added. After 5 min at −78 °C, the solution was warmed to 0 °C for 5 min and then recooled to −78 °C. $BF_3{\cdot}OEt_2$ (6.08 mL, 50 mmol) was then added followed by the slow (30 min) addition of diene **22** (3.6 g, 10 mmol). After 30 min the reaction was quenched with $NaHCO_3$ solution and warmed to room temperature. The mixture was extracted with methylene chloride (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude mixture was purified by flash chromatography (30% EtOAc/hexanes) to afford a mixture of aldol products, which were dissolved in methylene chloride (25 mL) and treated with trifluoroacetic acid (4 mL) at room temperature. After 1 h, the solution was washed with $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (16–20% EtOAc/hexanes) afforded first 0.6 g (13%) trans pyrone **24**, followed by 2.94 g (63% based on diene) of cis pyrone **23**. **23**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.0 (m, 2 H), 7.4 (m, 9 H), 6.97 (d, 1 H, J = 3.5 Hz), 6.56 (dd, 1 H, J = 3.5, 1.8 Hz), 6.04 (m, 2 H), 4.56 (dd, 1 H, J = 8.9, 2.0 Hz), 3.50 (dq, 1 H, J = 8.9, 7.1 Hz), 1.67 (d, 3 H, J = 7.1 Hz); IR ($CHCl_3$) 1733, 1664, 1620, 1539, 1470, 1259 cm^{-1}; MS (20 eV) 468 (1.0, M$^+$), 311 (2.0); $[\alpha]_D$ +77.9° (*c* 4.5, $CHCl_3$). Anal. C, H. ent-**23**: $[\alpha]_D$ −78.86° (*c* 2.0, $CHCl_3$).

Alcohol 26. Ceric chloride heptahydrate (3.2 g, 8.56 mmol) was added to a solution of dihydropyrone **23** (4.0 g, 8.56 mmol) in CH_2Cl_2 (75 mL)

(32) Compound **78** was prepared in 12 steps from D-galactose by the procedure of Kiso: Kiso, M.; Nakamura, A.; Tomita, Y.; Hasegawa, A. *Carbohydr. Res.* **1986**, *158*, 101.

(33) Fugedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9.

(34) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189.

(35) Both α and β glycosides of KDO have been isolated, see ref 4 and: Christian, R.; Schulz, G.; Waldstatten, P.; Unger, F. M. *Tetrahedron Lett.* **1984**, *25*, 3433.

(36) For recent syntheses of KDO conjugates, see: (a) Paulsen, H.; Schuller, M. *Liebigs Ann. Chem.* **1987**, 249. (b) Paulsen, H.; Stiem, M.; Unger, F. M. *Liebigs Ann. Chem.* **1987**, 273. (c) Paulsen, H.; Hayauchi, Y.; Unger, F. M. *Liebigs Ann. Chem.* **1984**, 1288. (d) Paquet, F.; Sinay, P. *J. Am. Chem. Soc.* **1984**, *106*, 8313.

and absolute ethanol (75 mL) at room temperature. The solution was cooled to −78 °C, and $NaBH_4$ (8.56 mL of a 1 M solution in ethanol) was added via syringe pump over 1 h. After being stirred for an additional 30 min, the solution was warmed to −20 °C and quenched by the careful addition of pH 7 phosphate buffer (60 mL). The mixture was extracted with Et_2O (2 × 100 mL) and EtOAc (100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was filtered through a plug of silica gel and used immediately in the next reaction.

Camphorsulfonic acid (50 mg) was added to a solution of the crude glycal **25** in methanol (10 mL), trimethyl orthoformate (5 mL), and benzene (70 mL) at 25 °C. After 3 h (the reaction was monitored by TLC, 5% acetone/methylene chloride) the solution was diluted with ether and washed with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was flash chromatographed (16% ethyl acetate/hexanes) to afford 3.86 g of **26** (90%) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 8.0 (m, 2 H), 7.5 (m, 6 H), 7.15 (m, 3 H), 6.49 (d, 1 H, J = 3.2 Hz), 6.4 (dd, 1 H, J = 3.2, 1.0 Hz), 5.97 (br d, 1 H, J = 3.0 Hz), 4.5 (qd, 1 H, J = 12.2, 4.6, 3.6, 3.0 Hz), 3.86 (dd, 1 H, J = 9.5, 1.0 Hz), 3.48 (m, 1 H), 3.0 (s, 3 H), 2.5 (d, 1 H, J = 3.6 Hz), 2.46 (dd, 1 H, J = 12.2, 4.6 Hz), 1.95 (dd, 1 H, J = 12.2, 12.2 Hz), 1.63 (d, 3 H, J = 7.0 Hz); IR ($CHCl_3$) 3600, 1715, 1280, 1165, 720 cm^{-1}; MS (20 eV) 502 (M^+, 17.4), 471 (M^+ − OMe, 0.7), 345 (M^+ − SePh, 26.7); $[\alpha]_D$ −36.6° (c 3.0, $CHCl_3$). Anal. C, H. ent-**26**: $[\alpha]_D$ +36.5° (c 2.4, $CHCl_3$).

TBS Ether 27. *tert*-Butyldimethylsilyl triflate (2.52 mL, 11 mmol) was added to a solution of alcohol **26** (3.66 g, 7.31 mmol) and 2,6-lutidine (4.2 mL, 36.0 mmol) in CH_2Cl_2 (60 mL) at −78 °C. After 1 h the reaction was quenched by the addition of triethylamine (5 mL) followed by saturated $NaHCO_3$ (50 mL). The mixture was extracted with ether (3 × 100 mL), and the combined ethereal layers were dried (K_2CO_3) and concentrated in vacuo. The residue was flash chromatographed (5% ethyl acetate/hexanes) to give 4.2 g of **27** (93%) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 8.01 (m, 2 H), 7.55 (m, 9 H), 6.5 (dd, 1 H, J = 3.2, 1.0 Hz), 6.4 (dd, 1 H, J = 3.2, 1.8 Hz), 5.9 (br d, 1 H, J = 3 Hz), 4.35 (ddd, 1 H, J = 11.4, 5.1, 3.3 Hz), 3.9 (dd, 1 H, J = 8.4, 0.9 Hz), 3.4 (q, 1 H, J = 6.9 Hz), 3.0 (s, 3 H), 2.3 (dd, 1 H, J = 13.0, 5.1 Hz), 2.1 (dd, 1 H, J = 13.0, 11.4 Hz), 1.6 (d, 3 H, J = 6.9 Hz), 0.78 (s, 9 H), 0.12 (s, 6 H); IR ($CHCl_3$) 1720, 1275, 1165, 1110, 840, 710 cm^{-1}; MS (20 eV) 615 (1.5, M^+), 584 (0.9), 558 (18, M^+ − *tert*-butyl). Anal. C, H.

Enepyranoside 28. Hydrogen peroxide (30%, 4.5 mL) was added to a solution of selenide **27** (4.2 g, 6.83 mmol) and pyridine (2.7 mL, 34 mmol) in THF (60 mL) at room temperature. The mixture was stirred for 4 h, diluted with ether, and washed with $NaHCO_3$ and NaCl solution. The solution was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (4% ether/hexanes) to afford 3.0 g of olefin **28** (96%) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 8.0 (m, 2 H), 7.45 (m, 4 H), 6.54 (dd, 1 H, J = 3.2, 1.0 Hz), 6.41 (dd, 1 H, J = 3.2, 1.8 Hz), 5.9 (ddd, 1 H, J = 17.2, 10.6, 5.3 Hz), 5.48 (m, 2 H), 5.2 (br d, 1 H, J = 10.6 Hz), 4.42 (m, 2 H), 3.07 (s, 3 H), 2.35 (dd, 1 H, J = 13.0, 5.3 Hz), 2.11 (dd, 1 H, J = 13.0, 11.0 Hz), 0.76 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); IR ($CHCl_3$) 1720, 1280, 1165, 1115, 1045, 845, 715 cm^{-1}; MS (20 eV) 443 (0.1, M^+ − Me), 427 (0.7, M^+ − OMe), 401 (34.0, M^+ − *tert*-butyl); $[\alpha]_D$ −54.2° (c 3.4, $CHCl_3$). Anal. C, H.

Diol 30. Osmium tetraoxide (61 mg, 0.24 mmol) as a solution in THF was added to a solution of alkene **28** (2.2 g, 4.8 mmol) and NMO (1.03 g, 10 mmol) in 20:1 THF/H_2O (40 mL). After 2 h the mixture was treated with Florisil (2 g) and $NaHSO_3$ (250 mg) and stirred at room temperature for 1 h. The solution was dried with $MgSO_4$, diluted with ether, and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (30–40% EtOAc/hexanes) to afford 2.22 g of diol **30** (94%) as a colorless foam: ^1H NMR (250 MHz, $CDCl_3$) δ 8.05 (m, 2 H), 7.6 (m, 1 H), 7.42 (m, 3 H), 6.38 (m, 2 H), 5.38 (br d, 1 H, J = 3.0 Hz), 4.41 (ddd, 1 H, J = 11.4, 5.2, 3.2 Hz), 4.1 (d, 1 H, J = 5.2 Hz), 3.9 (m, 2 H), 3.7 (m, 2 H), 3.06 (s, 3 H), 2.4 (dd, 1 H, J = 13.0, 5.2 Hz), 2.2 (m, 2 H), 0.75 (s, 9 H), 0.1 (s, 3 H), 0.04 (s, 3 H); IR ($CHCl_3$) 3590, 3460, 1700, 1285, 1120, 1040, 910, 840, 715 cm^{-1}; MS (20 eV) 461 (0.6, M^+ − OMe), 435 (39.0, M^+ − *tert*-butyl); $[\alpha]_D$ −85.1° (c 3.4, $CHCl_3$). Anal. C, H.

Aldehyde 15. $NaHCO_3$ (200 mg) was added to a solution of $Pb(OAc)_4$ (1.7 g, 3.46 mmol) in CH_2Cl_2 (40 mL) at 0 °C. Diol **30** (1.7 g, 3.46 mmol) was added dropwise as a solution in CH_2Cl_2. After 10 min, the mixture was filtered through Celite and concentrated in vacuo. The residue was purified by filtration through a plug of silica gel. The filtrate was concentrated, and the crude aldehyde was used directly in the next reaction.

Enoate 31. KHMDS (5.27 mL of a 0.5 M solution in toluene, 3.46 mmol) was added to a solution of bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate[14] (0.734 μL, 3.46 mmol) and 18-crown-6/acetonitrile complex (5.3 g, 17.5 mmol) in THF (60 mL) at −78 °C. After 15 min, the crude aldehyde **15** from above was added. The reaction was quenched after 30 min by the addition of saturated NH_4Cl (30 mL). The mixture was extracted with ether (3 × 50 mL). The combined ethereal layers were washed with water and brine and dried ($MgSO_4$). Concentration in vacuo and flash chromatography of the residue (5% ethyl acetate/hexanes) afforded 1.27 g (71% from **30**) of pure *Z* enoate **31** as a white solid; recrystallization afforded optically pure material: mp 126–128 °C (hexanes/ether); ^1H NMR (250 MHz, $CDCl_3$) δ 8.02 (m, 2 H), 7.52 (m, 1 H), 7.40 (m, 4 H), 6.5 (dd, 1 H, J = 3.3, 1.0 Hz), 6.41 (dd, 1 H, J = 3.3, 1.8 Hz), 6.33 (dd, 1 H, J = 11.7, 7.25 Hz), 5.9 (dd, 1 H, J = 11.7, 1.6 Hz), 5.7 (br s, 1 H), 5.6 (dt, 1 H, J = 7.25, 1.6 Hz), 4.5 (ddd, 1 H, J = 11.5, 5.1, 3.2 Hz), 3.78 (s, 3 H), 3.08 (s, 3 H), 2.35 (dd, 1 H, J = 13.0, 5.1 Hz), 2.14 (dd, 1 H, J = 13.0, 11.5 Hz), 0.76 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); IR ($CHCl_3$) 1725, 1275 cm^{-1}; MS (20 eV) 459 (11.4, M^+ − *tert*-butyl); $[\alpha]_D$ +70.7° (c 1.02, $CHCl_3$). Anal. C, H.

Diol 32. OsO_4 (1.26 mL of a 100 mg/mL solution in pyridine, 0.496 mmol) was added to a solution of enoate **31** (213 mg, 0.413 mmol) in pyridine (2 mL) at −25 °C over 15 min. The brown solution was kept at −25 °C for 1 h and then warmed to room temperature. The osmate ester was reduced by adding THF (5 mL), H_2O (0.25 mL), Florisil (2 g), and solid $NaHSO_3$ (0.5 g). The mixture was stirred vigorously at room temperature. When the reduction was complete (as judged by TLC, ~24 h), the mixture was filtered through silica gel with copious washings (EtOAc). Concentration of the filtrate afforded 209 mg of diol (92%) as a colorless foam, which was used without further purification. The ratio of diols was ≥18:1 as determined by 250-MHz NMR: mp 128–129.5 °C (hexanes/ethyl acetate); ^1H NMR (250 MHz, $CDCl_3$) δ 8.0 (m, 2 H), 7.51 (m, 1 H), 7.41 (m, 3 H), 6.49 (dd, 1 H, J = 3.3, 0.72 Hz), 6.41 (dd, 1 H, J = 3.3, 1.77 Hz), 5.59 (br d, 1 H, J = 3.0 Hz), 4.4 (m, 2 H), 4.15 (m, 2 H), 3.84 (s, 3 H), 3.15 (br d, 1 H, J = 8.5 Hz), 3.1 (s, 3 H), 2.78 (br d, 1 H, J = 4.3 Hz), 2.33 (dd, 1 H, J = 13.0, 5.1 Hz), 2.16 (dd, 1 H, J = 13.0, 11.4 Hz), 0.75 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); IR ($CHCl_3$) 3600, 1735, 1280, 1175, 1115, 720 cm^{-1}; MS (20 eV) 493 (8.0, M^+ − *tert*-butyl); $[\alpha]_D$ −27.9° (c 1.05, $CHCl_3$). Anal. C, H.

Tetrabenzoate 33. $LiEt_3BH$ (1 mL of a 1 M solution in THF, 1 mmol) was added to a solution of ester **32** (92 mg, 0.167 mmol) in THF (3 mL) at −78 °C. After the addition was complete, the mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched by the slow addition of a 10:1 mixture of NH_4Cl/HOAc. The boron complex was extracted with EtOAc (3 × 20 mL). The complex was broken up by sequential evaporations from MeOH. The crude mixture was dissolved in CH_2Cl_2, and DMAP (245 mg, 2.0 mmol) was added. The solution was cooled to 0 °C and treated with benzoyl chloride (195 μL, 1.67 mmol). After 15 min the solution was warmed to room temperature and stirred for 8 h. The reaction was quenched by the addition of MeOH (100 μL) and concentrated in vacuo. The residue was diluted with 20% ethyl acetate/hexanes and filtered through silica gel to remove excess DMAP. The filtrate was concentrated and flash chromatographed (10% ethyl acetate/hexanes) to yield 115 mg tetrabenzoate **33** (80%) as a colorless glass: ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (m, 8 H), 7.35 (m, 13 H), 6.48 (dd, 1 H, J = 3.2, 0.7 Hz), 6.37 (dd, 1 H, J = 3.2, 1.8 Hz), 6.08 (t, 1 H, J = 5.2 Hz), 5.94 (dt, 1 H, J = 6.3, 4.3 Hz), 5.74 (br d, 1 H, J = 2.9 Hz), 5.0 (dd, 1 H, J = 12.2, 3.8 Hz), 4.6 (dd, 1 H, J = 12.2, 6.3 Hz), 4.4 (dd, 1 H, J = 5.8, 1.0 Hz), 4.37 (ddd, 1 H, J = 11.4, 4.9, 3.4 Hz), 2.96 (s, 3 H), 2.32 (dd, 1 H, J = 13.0, 4.9 Hz), 2.08 (dd, 1 H, J = 13.0, 11.4 Hz), 0.72 (s, 9 H), 0.056 (s, 3 H), 0.043 (s, 3 H); IR ($CHCl_3$) 1730, 1265, 1110, 910, 712 cm^{-1}; MS (20 eV) 777 (2.8, M^+ − *tert*-butyl); $[\alpha]_D$ +33.06° (c 1.8, $CHCl_3$). Anal. C, H.

Methyl Ester 39. $RuO_2 \cdot H_2O$ (20 mg) was added to a solution of $NaIO_4$ (151 mg, 0.73 mmol) in a CCl_4 (2 mL)/H_2O (2 mL)/CH_3CN (3 mL) solvent system at room temperature. After 20 min, the solution was light green, and solid $NaHCO_3$ (1 g, 0.012 mol) was added followed by 1 mL of water. After 5 min, the light orange mixture was treated with a solution of the furan compound **33** (102 mg, 0.122 mmol) in CH_3CN. The solution immediately turned black, and after 1 min, enough $NaIO_4$ was added to turn the color dark green (~50 mg). The mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The aqueous layer was acidified (HCl) and reextracted (EtOAc). The combined organic layers were washed with saturated $NaHSO_3/Na_2SO_3$, dried (Na_2SO_4), and concentrated in vacuo. The crude acid was dissolved in ether (5 mL) and treated with diazomethane. Concentration and filtration through silica gel (16% ethyl acetate/hexanes eluant) afforded 90 mg of methyl ester **39** (90%), which was homogeneous by TLC and NMR analyses and used without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 7.9–7.15 (m, 20 H), 6.04 (dd, 1 H, J = 5.6, 4.5 Hz), 5.9 (dt, 1 H, J = 5.8, 3.3 Hz), 5.69 (dd, 1 H, J = 3.0, 1.0 Hz), 5.0 (dd,

1 H, J = 12.3, 3.3 Hz), 4.51 (dd, 1 H, J = 12.3, 5.8 Hz), 4.28 (m, 2 H), 3.82 (s, 3 H), 3.25 (s, 3 H), 2.08 (m, 2 H), 0.70 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); IR ($CHCl_3$) 1730, 1270, 1110, 715 cm^{-1}; MS (20 eV) 769 (5.0, M^+ – *tert*-butyl); $[\alpha]_D$ +37.4° (*c* 1.82, $CHCl_3$).

Alcohols 40/41. HF (~15 drops of a 48% solution in H_2O) was added to a solution of silyl ether **39** (66 mg, 0.08 mmol) in MeOH (4 mL). The mixture was heated to 45 °C for 4 h, cooled to 0 °C, and quenched with triethylamine (0.5 mL) followed by saturated $NaHCO_3$ (5 mL). The product was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was flash chromatographed (30% ethyl acetate/hexanes then 50% ethyl acetate/hexanes) to give 17 mg of axial alcohol **41** (30%) and 34.6 mg of equatorial alcohol **40** (62%). The equatorial alcohol was dissolved in CH_2Cl_2 (1 mL) and treated with finely ground K_2CO_3 (50 mg) at room temperature. After 5 h the mixture was filtered and concentrated, and the residue was chromatographed (30% ethyl acetate/hexanes) to afford an additional 20 mg of axial alcohol **41** for a combined yield of 37 mg (65%). **41**: ^1H NMR (250 MHz, $CDCl_3$) δ 8.02 (m, 8 H), 7.5 (m, 12 H), 6.14 (dd, 1 H, J = 5.9, 4.7 Hz), 5.95 (dt, 1 H, J = 6.6, 4.2 Hz), 5.47 (ddd, 1 H, J = 11.24, 5.7, 2.7 Hz), 5.02 (dd, 1 H, J = 12.2, 3.76 Hz), 4.62 (dd, 1 H, J = 12.2, 6.3 Hz), 4.5 (m, 1 H), 4.21 (d, 1 H, J = 6.1 Hz), 3.74 (s, 3 H), 3.18 (s, 3 H), 2.55 (br s, 1 H), 2.32 (m, 2 H); IR ($CHCl_3$) 3600, 1725, 1265, 1110, 715 cm^{-1}; MS (20 eV); $[\alpha]_D$ +9.14° (*c* 1.97, $CHCl_3$).

Azide 44. Triflic anhydride (17.5 μL, 0.1 mmol) was added to a solution of alcohol **41** (37 mg, 0.052 mmol) and pyridine (42 μL, 0.52 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 10 min the solution was warmed to room temperature and allowed to stir for 1 h. The reaction was quenched by the addition of saturated $NaHCO_3$ (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was filtered through silica gel (20% ethyl acetate/hexanes eluant) to give 41 mg of crude product. The triflate was dissolved in benzene (1 mL) and added to a solution of tetra-*n*-butylammonium azide (74 mg, 0.26 mmol) in benzene (1 mL) at room temperature. After 10 min the mixture was concentrated, and the residue was purified by flash chromatography (20% ethyl acetate/hexanes) to afford 33 mg of azide **44** (86% from **41**): ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (m, 2 H), 8.0 (m, 6 H), 7.7–7.38 (m, 12 H), 6.19 (d, 1 H, J = 8 Hz), 5.95 (m, 1 H), 5.51 (dt, 1 H, J = 10.6, 4.9 Hz), 5.14 (dd, 1 H, J = 12.6, 2.05 Hz), 4.54 (dd, 1 H, J = 12.6, 5.5 Hz), 3.97 (d, 1 H, J = 10, 6 Hz), 3.83 (s, 3 H), 3.56 (dd, 1 H, J = 10.0, 10.0 Hz), 3.2 (s, 3 H), 2.74 (dd, 1 H, J = 12.5, 4.9 Hz), 1.82 (dd, 1 H, J = 12.5, 12.5 Hz); IR ($CHCl_3$) 2110, 1725, 1265, 1105, 710 cm^{-1}; $[\alpha]_D$ +91.0° (*c* 5.13, $CHCl_3$).

Acetamide 45. Lindlar catalyst ($Pd/CaCO_3$, poisoned with lead, ~10 mg) was added to a solution of azide **44** (20 mg, 0.027 mmol) in ethyl acetate (1 mL) and methanol (0.5 mL). The flask was fitted with a balloon of hydrogen, and the flask was evacuated under aspirator pressure and filled with H_2 three times. After being stirred for 5 h at room temperature, the mixture was filtered through Celite and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and treated with DMAP (25 mg, 0.2 mmol) followed by acetic anhydride (13 μL, 0.135 mmol). After 8 h the solution was concentrated and chromatographed (40% ethyl acetate/hexanes) to give 19 mg of acetamide **45** (94%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (m, 2 H), 8.02 (m, 2 H), 7.95 (m, 4 H), 7.62–7.35 (m, 12 H), 5.95 (dd, 1 H, J = 4.9, 1.3 Hz), 5.9 (m, 1 H), 5.58 (m, 1 H), 5.5 (br d, 1 H, J = 9.2 Hz), 5.25 (dd, 1 H, J = 12.4, 2.8 Hz), 4.58 (dd, 1 H, J = 12.4, 7.16 Hz), 4.32 (m, 2 H), 3.84 (s, 3 H), 3.31 (s, 3 H), 2.64 (dd, 1 H, J = 12.8, 4.9 Hz), 2.04 (dd, 1 H, J = 12.8, 11.4 Hz), 1.81 (s, 3 H); IR ($CHCl_3$) 1725, 1275, 1110, 715 cm^{-1}.

Neu5Ac (1). NaOH (1 mL of a 1 N solution) was added to a solution of tetrabenzoate **45** (10 mg) in THF (2 mL), and the mixture was heated to 50 °C for 2 h. The solution was cooled and acidified with Dowex HCR-S acid resin. The mixture was heated to 50 °C for 8 h, cooled, filtered, and concentrated in vacuo (water removed by concentration from benzene). The residue was dissolved in water and filtered to remove benzoic acid. The 500-MHz NMR spectrum of this material was identical with the spectrum of an authentic sample.

Tetrol 46. A solution of **45** (24 mg, 32 μmol) in 4:1 THF/1 N NaOH was heated to reflux for 1 h. The mixture was cooled and acidified with Dowex 50W-X-8 acid resin. The solution was filtered and concentrated in vacuo. The crude product was dissolved in THF and treated with excess CH_2N_2. The solution was concentrated, and the residue was purified by flash chromatography (20% MeOH/methylene chloride) to afford 8.5 mg of tetrol **46** (98%). This material was identical with that prepared by literature methods, $[\alpha]_D$ –44.2° (*c* 0.62, MeOH) [Lit. $[\alpha]_D$ –46.0° (*c* 0.69, MeOH)].

Dibenzoate 49. A solution of alcohol *ent*-**26** (2.71 g, 5.41 mmol) and pyridine (8 mL) in CH_2Cl_2 (160 mL) was treated with benzoyl chloride (3.2 mL, 25 mmol) at 0 °C. The solution was warmed to room temperature. After 10 h the reaction was quenched by the addition of MeOH (2 mL). The mixture was poured into $NaHCO_3$ solution and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford 4.43 g of **49** (96%) and was used without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 8.05 (m, 2 H), 7.90 (m, 2 H), 7.25–7.67 (m, 12 H), 6.58 (d, 1 H, J = 3.22 Hz), 6.47 (m, 1 H), 6.33 (d, 1 H, J = 2.76 Hz), 5.80 (m, 1 H), 4.06 (dd, 1 H, J = 9.02–9.07 Hz), 3.47 (m, 1 H), 3.08 (s, 3 H), 2.64 (dd, 1 H, J = 12.64, 5.05 Hz), 2.32 (t, 1 H), 1.68 (d, 1 H, J = Hz 6.99); IR 3100–3066, 2960, 2830, 1719, 1588, 1440, 1268, 1160 cm^{-1}; MS 105 (100.0), 124 (3.5), 165 (3.2), 174 (6.3), 191 (7.5), 267 (10.5), 295 (5.4), 449 (12.5), 606 (2.8); $[\alpha]_D$ 37.59° (*c* 1.4, $CHCl_3$).

Enepyranoside 50. A solution of selenide **49** (55 mg, 0.091 mmol) in THF (4 mL) containing 10 equiv of pyridine was treated with H_2O_2 (1 mL of a 30% solution, 8.5 mmol) at 0 °C. The solution was warmed to room temperature. After 4 h the mixture was diluted with ether and washed with $NaHCO_3$ solution and brine. The solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to afford 38 mg of enepyranoside **50** (93%): ^1H NMR (250 MHz, $CDCl_3$) δ 8.0 (m, 2 H), 7.83 (m, 2 H), 7.24–7.6 (m, 7 H), 6.56 (dd, 1 H, J = 3.24, 0.87 Hz), 6.40 (m, 1 H), 5.85 (m, 3 H), 5.49 (m, 1 H), 5.22 (dd, 1 H, J = 10.6, 1.4 Hz), 4.60 (m, 1 H), 3.10 (s, 3 H), 2.62 (m, 1 H), 2.32 (m, 1 H); IR ($CHCl_3$) 3025, 3004, 2954, 1702, 1595, 1437, 1351, 1258, 1109, 894 cm^{-1}; MS 105 (100.0), 124 (31.0), 148 (19.3), 165 (35.4), 173 (41.7), 204 (14.8), 221 (11.0), 295 (6.0), 326 (3.1), 417 (10.1); $[\alpha]_D$ +109.1° (*c* 1.25, $CHCl_3$).

Tetrabenzoate 52. OsO_4 (32 mg, as a solution in THF; 0.13 mmol) and NMO (215 mg, 1.9 mmol) were added to a solution of olefin **50** (287 mg, 0.6 mmol) in THF (35 mL) at room temperature. After 12 h the mixture was treated with Florisil (1.5 g) and $NaHSO_3$ (800 mg). After 1 h the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The crude diol was dissolved in CH_2Cl_2 (30 mL) and treated with pyridine (1.8 mL) and benzoyl chloride (0.543 mL, 3.2 mmol). Catalytic DMAP was added, and the solution was allowed to stir for 48 h, quenched with MeOH (1 mL), and poured into $NaHCO_3$ solution. The mixture was extracted with ether (3 × 20 mL). The combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to afford 278 mg of tetrabenzoate **52** as a light yellow oil (70%): ^1H NMR (250 MHz, $CDCl_3$) δ 7.95–8.1 (m, 6 H), 7.83 (m, 2 H), 7.25–7.67 (m, 13 H), 6.59 (m, 1 H), 6.46 (dd, 1 H, J = 3.23, 1.83 Hz), 5.94 (s, 1 H), 5.88 (m, 1 H), 5.77 (m, 1 H), 4.92 (dd, 1 H, J = 12.3, 2.40 Hz), 4.72 (m, 2 H), 3.09 (s, 3 H), 2.70 (dd, 1 H, J = 5.35, 2.36 Hz), 2.41 (t, 1 H); IR ($CHCl_3$) 3060, 3006–2823, 1715, 1597, 1447, 1267, 1107 cm^{-1}; $[\alpha]_D$ –30.53° (*c* 1.44, $CHCl_3$).

Methyl Ester 53. $RuO_2 \cdot H_2O$ (7.2 mg) was added to a solution of $NaIO_4$ (93 mg, 0.43 mmol) in 3:2:2 $CH_3CN/CCl_4/H_2O$ (3.5 mL) at room temperature. After 30 min solid $NaHCO_3$ (300 mg) was added. Furyl compound **52** (30 mg, 0.043 mmol) was added as a solution in CH_3CN. The mixture immediately turned black, and enough $NaIO_4$ was added to turn the solution green. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with $NaHSO_3$ until colorless and dried (Na_2SO_4). The solution was concentrated in vacuo, and the residue was dissolved in Et_2O (5 mL). The crude acid was treated with excess CH_2N_2. The solution was concentrated, and the residue was purified by flash chromatography (35% ethyl acetate/hexanes) to afford 28 mg of the title compound **53** (94%) as a colorless foam: ^1H NMR (250 MHz, $CDCl_3$) δ 8.05 (m, 4 H), 7.95 (m, 2 H), 7.79 (m, 2 H), 7.25–7.65 (m, 12 H), 5.89 (d, 1 H, J = 2.36 Hz), 5.78 (m, 2 H), 4.90 (dd, 1 H, J = 12.4, 2.35 Hz), 4.60 (dd, 1 H, J = 9.68, 1.15 Hz), 4.72 (dd, 1 H, J = 12.3, 4.04 Hz), 3.89 (s, 3 H), 3.33 (s, 3 H), 2.42 (m, 2 H); IR ($CHCl_3$) 1728, 1599, 1448, 1265, 1160, 1103 cm^{-1}; MS 105.1 (100.0), 153.2 (1.0), 257.0 (2.8), 406.2 (1.7), 623.7 (1.8); $[\alpha]_D$ –32.15° (*c* 0.79, $CHCl_3$).

Tetraacetate 55. Sodium methoxide (catalytic was added to a solution of tetrabenzoate **53** (42.1 mg, 0.061 mmol) in 2:1 MeOH/THF (3 mL). The solution was heated to reflux for 3 h, cooled, and acidified with Dowex 50W H^+ resin. The mixture was filtered and concentrated in vacuo. The solid residue was washed with ether to remove excess methyl benzoate. The crude product was dissolved in MeOH and treated with excess diazomethane. The solution was concentrated to give the crude tetrol, which was peracetylated (Ac_2O, pyridine, DMAP) to give after chromatographic purification (35% ethyl acetate/hexanes) tetraacetate **55** (16 mg): ^1H NMR (250 MHz, $CDCl_3$) δ 5.3 (m, 3 H), 4.60 (dd, 1 H, J = 12.3, 2.3 Hz), 4.19 (dd, 1 H, J = 12.4, 3.9 Hz), 4.10 (dd, 1 H, J = 9.8, 0.9 Hz), 3.83 (s, 3 H), 3.27 (s, 3 H), 2.15 (m, 2 H), 2.09 (s, 3 H), 2.08 (s, 3 H), 2.01 (s, 3 H), 1.98 (s, 3 H); IR ($CHCl_3$) 3020–3000, 1750, 1440, 1370, 1250–1210, 1170, 1090, 1050 cm^{-1}; MS 153.1, 195.1, 217.1, 255.1, 375.1; $[\alpha]_D$ +79.1° (*c* 0.23, $CHCl_3$).

KDO (5). Sodium methoxide (catalytic) was added to a solution of tetrabenzoate **53** (200 mg, 0.29 mmol) in 2:1 MeOH/THF (8 mL). The solution was heated to reflux for 3 h, cooled, and acidified with Dowex 50W H^+ resin. The mixture was filtered and concentrated in vacuo. The solid residue was washed with ether to remove excess methyl benzoate. The crude tetrol acid was dissolved in THF (4 mL) and treated with 10 drops of 6 N HCl. The solution was allowed to reflux for 16 h, cooled, and neutralized with Dowex-SBR basic resin. The mixture was filtered (with methanol washings) and concentrated in vacuo to afford KDO. Treatment of the above compound with methanolic ammonia afforded KDO ammonium salt as a white solid, whose NMR (250 MHz) and chromatographic properties were identical with those of an authentic sample.

General Glycosidation Procedure. A mixture of the glycosyl donor (1 equiv) and alcohol (2.5 equiv) was dried by concentration from benzene. Benzene was added to give a 0.5 M solution of the glycosyl donor, followed by 4-Å molecular sieves. Camphorsulfonic acid was added (5 mol %), and the solution was allowed to stir at room temperature for 5 h. The reaction was decanted into ether, washed with $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (20% → 30% → 80% EtOAc/hexanes) to afford pure glycoside along with recovered starting materials.

General Oxidation Procedure. RuO_4 was prepared by adding RuO_2 (hydrate) (20 mol %) to a solution of $NaIO_4$ (8 equiv) in 3:2:3 $CH_3CN/CCl_4/H_2O$. After 15 min, solid $NaHCO_3$ (50 equiv) was added, and the mixture was stirred for 5 min. The furyl compound was then added as a solution in CH_3CN. The solution turned black immediately, and enough $NaIO_4$ was added to turn the color light green. The mixture was poured into water and extracted with EtOAc (three times). The aqueous phase was acidified and reextracted with EtOAc. The combined organic layers were washed with $NaHSO_3/Na_2SO_3$ solution until colorless, dried (Na_2SO_4), and concentrated in vacuo. The crude acid was taken up in ether and treated with excess diazomethane. The solution was concentrated, and the residual was filtered through a plug of silica gel (30% EtOAc/hexanes eluant) to afford pure methyl ester.

Disaccharide 65. The reaction of **33** with alcohol **62** following the general glycosidation procedure afforded the disaccharide (70%); following the general oxidation procedure afforded methyl ester **65** (96%): ^{1}H NMR (500 MHz) δ 7.9 (m, 8 H), 7.5–7.3 (m, 12 H), 6.05 (dd, 1 H, J = 5.5, 4.2 Hz), 5.9 (m, 1 H), 5.75 (br d, 1 H, J = 3.1 Hz), 5.56 (d, 1 H, J = 5.0 Hz), 5.04 (dd, 1 H, J = 12.4, 2.6 Hz), 4.68 (m, 2 H), 4.57 (dd, 1 H, J = 5.6, 1.2 Hz), 4.39 (m, 3 H), 4.08 (t, 1 H, J = 8.8 Hz), 3.86 (t, 1 H, J = 8.8 Hz), 3.81 (s, 3 H), 3.63 (dd, 1 H, J = 9.0, 6.3 Hz), 2.26 (m, 2 H), 1.71 (s, 3 H), 1.64 (s, 3 H), 1.51 (s, 3 H), 1.46 (s, 3 H), 0.88 (s, 9 H), 0.21 (s, 3 H), 0.18 (s, 3 H); IR ($CHCl_3$) 1730, 1270, 1110, 1075, 715 cm^{-1}; $[\alpha]_D$ +10.33° (c 1.5, $CHCl_3$).

Disaccharide 66. The reaction of **33** with alcohol **63** following the general glycosidation procedure afforded the disaccharide (60%); following the general oxidation procedure afforded methyl ester **66** (91%): ^{1}H NMR (500 MHz) δ 8.1–7.95 (m, 14 H), 7.5–7.3 (m, 21 H), 6.09 (d, 1 H, J = 3.4 Hz), 5.89 (dd, 1 H, J = 5.94, 5.0 Hz), 5.8 (dd, 1 H, J = 10.4, 7.9 Hz), 5.68 (m, 1 H), 5.64 (dd, 1 H, J = 10.4, 3.4 Hz), 5.6 (br d, 1 H, J = 2.9 Hz), 4.7 (d, 1 H, J = 7.9 Hz), 4.55 (dd, 1 H, J = 12.4, 2.8 Hz), 4.35 (ddd, 1 H, J = 11.5, 5.1, 2.9 Hz), 4.28 (dd, 1 H, J = 12.4, 6.75 Hz), 4.22 (t, 1 H, J = 7.3 Hz), 4.08 (dd, 1 H, J = 6.1, 1.0 Hz), 3.86 (s, 3 H), 3.8 (m, 2 H), 3.62 (s, 3 H), 2.24 (dd, 1 H, J = 13.0, 5.1 Hz), 2.16 (dd, 1 H, J = 13.0, 11.5 Hz), 0.87 (s, 9 H), 0.26 (s, 3 H), 0.2 (s, 3 H); IR ($CHCl_3$) 1730, 1270, 1100, 715 cm^{-1}; $[\alpha]_D$ +95.0° (c 0.8, $CHCl_3$).

Disaccharide 67. The reaction of **33** with alcohol **64** via the general glycosidation procedure afforded the disaccharide (74 %); following the general oxidation procedure afforded methyl ester **67** (91%): ^{1}H NMR (500 MHz) δ 8.1–7.8 (m, 14 H), 7.6–7.15 (m, 21 H), 6.0 (t, 1 H, J = 4.3 Hz), 5.86 (m, 1 H), 5.8 (t, 1 H, J = 9.1 Hz), 5.68 (br d, 1 H, J = 2.7 Hz), 5.58 (t, 1 H, J = 9.8 Hz), 5.36 (dt, 1 H, J = 7.8, 1.0 Hz), 4.95 (dt, 1 H, J = 12.3, 3.0 Hz), 4.6 (d, 1 H, J = 7.8 Hz), 4.52 (dd, 1 H, J = 11.3, 6.6 Hz), 4.46 (d, 1 H, J = 5.0 Hz), 4.38 (ddd, 1 H, J = 11.4, 5.1, 2.7 Hz), 3.94 (m, 2 H), 3.76 (dd, 1 H, J = 11.3, 4.6 Hz), 3.5 (s, 3 H), 3.4 (s, 3 H), 2.15 (dd, 1 H, J = 13.0, 5.1 Hz), 2.10 (dd, 1 H, J = 13.0, 11.5 Hz), 0.74 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H); IR ($CHCl_3$) 1735, 1270, 1110, 1100, 1075, 1030, 715 cm^{-1}; $[\alpha]_D$ +33.3° (c 1.2, $CHCl_3$).

Compound 68. The reaction of **33** with cholesterol via the general glycosidation procedure gave glycoside **68** (53%): ^{1}H NMR (500 MHz) δ 8.0 (m, 8 H), 7.6–7.3 (m, 13 H), 6.4 (dd, 1 H, J = 3.25, 0.9 Hz), 6.36 (dd, 1 H, J = 3.25, 1.7 Hz), 6.07 (dd, 1 H, J = 7.0, 3.1 Hz), 5.89 (m, 1 H), 5.7 (br d, 1 H, J = 3.1 Hz), 5.03 (dd, 1 H, J = 12.0, 4.5 Hz), 4.84 (br d, 1 H, J = 5.2 Hz), 4.67 (dd, 1 H, J = 12.0, 6.5 Hz), 4.60 (dd, 1 H, J = 6.9, 1.2 Hz), 3.2 (m, 1 H), 2.38 (dd, 1 H, J = 13.1, 4.8 Hz), 2.07 (dd, 1 H, J = 13.1, 12.0 Hz), 2.0 (m, 1 H), 1.8 (m, 2 H), 1.6–1.0 (m, 25 H), 0.9 (m, 12 H), 0.73 (s, 9 H), 0.65 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H); IR ($CHCl_3$) 1730, 1270, 1110, 715 cm^{-1}; $[\alpha]_D$ +17.5° (c 1.6, $CHCl_3$).

Equatorial Alcohol 69. A solution of TBS ether **67** (500 mg, 0.385 mmol) in methanol (15 mL) was treated with 500 μL of 48% HF. The mixture was heated to reflux. After 3 h, the solution was cooled, poured into $NaHCO_3$ solution, and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue (40% EtOAc/hexanes) afforded 420 mg of equatorial alcohol **69** (92%) as a colorless glass: ^{1}H NMR (500 MHz) δ 8.0–7.8 (m, 14 H), 7.6–7.15 (m, 21 H), 6.04 (t, 1 H, J = 5.08 Hz), 5.85 (m, 1 H), 5.83 (t, 1 H, J = 9.6 Hz), 5.71 (br d, 1 H, J = 2.7 Hz), 5.57 (t, 1 H, J = 9.6 Hz), 5.41 (dd, 1 H, J = 9.6, 7.9 Hz), 4.97 (dd, 1 H, J = 12.4, 3.1 Hz), 4.64 (d, 1 H, J = 7.8 Hz), 4.55 (dd, 1 H, J = 12.4, 6.6 Hz), 4.46 (dd, 1 H, J = 5.3, 0.9 Hz), 4.3 (m, 1 H), 3.96 (m, 1 H), 3.89 (dd, 1 H, J = 10.8, 3.8 Hz), 3.71 (dd, 1 H, J = 10.8, 3.8 Hz), 3.51 (s, 3 H), 3.48 (s, 3 H), 2.12 (dd, 1 H, J = 13.1, 5.0 Hz), 1.9 (dd, 1 H, J = 13.1, 11.9 Hz), 1.9 (d, 1 H, J = 3.5 Hz); IR ($CHCl_3$) 3600, 1730, 1110, 1100, 715 cm^{-1}; $[\alpha]_D$ +40.1° (c 1.55, $CHCl_3$).

Axial Alcohol 70. K_2CO_3 (finely ground) was added to a solution of equatorial alcohol **69** (50 mg, 0.042 mmol) in benzene (1 mL). The mixture was heated to ~45 °C. To optimize recovery, the reaction was stopped after 50% conversion. The mixture was filtered and concentrated in vacuo. Flash chromatography (4% EtOAc/methylene chloride) afforded 15 mg of axial alcohol **70** along with 25 mg of recovered starting material. Resubmission of the recovered equatorial alcohol to the reaction conditions afforded an additional 10 mg of **70** for a total of 25 mg (50%): ^{1}H NMR (500 MHz) δ 8.1–7.3 (m, 35 H), 6.08 (dd, 1 H, J = 6.6, 3.85 Hz), 5.88 (q, 1 H, J = 3.6 Hz), 5.8 (t, 1 H, J = 9.6 Hz), 5.5 (t, 1 H, J = 9.6 Hz), 5.38 (dd, 1 H, J = 9.6, 7.8 Hz), 5.34 (m, 1 H), 4.9 (dd, 1 H, J = 12.3, 3.4 Hz), 4.64 (dd, 1 H, J = 12.3, 7.0 Hz), 4.62 (d, 1 H, J = 7.8 Hz), 4.5 (m, 1 H),4.31 (d, 1 H, J = 6.7 Hz), 3.9 (m, 1 H), 3.82 (dd, 1 H, J = 11.0, 3.6 Hz), 3.75 (dd, 1 H, J = 11.0, 4.9 Hz), 3.49 (s, 3 H), 3.47 (s, 3 H), 2.52 (d, 1 H, J = 5.0 Hz), 2.3 (t, 1 H, J = 13.0 Hz), 2.23 (dd, 1 H, J = 13.0, 5.3 Hz); IR ($CHCl_3$) 3600, 1730, 1270, 1110, 720 cm^{-1}; $[\alpha]_D$ +15.5° (c 1.2, $CHCl_3$).

Azide 72. A solution of axial alcohol **70** (91 mg, 0.077 mmol) in CH_2Cl_2 (2 mL) was treated with triflic anhydride (20 μL, 0.12 mmol) and pyridine (40 μL, 0.5 mmol) at 0 °C. The solution was allowed to warm to room temperature. After 1 h, the reaction was quenched with $NaHCO_3$, extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Filtration through a plug of silica gel (30% EtOAc/hexanes eluant) afforded the crude product. The crude triflate was dissolved in benzene (1 mL) and treated with tetrabutylammonium azide (~50 mg). After 10 min at room temperature, the solution was concentrated and flash chromatographed (40% EtOAc/hexanes) to give 86.6 mg of azide **72** (93% from **70**): ^{1}H NMR (500 MHz) δ 8.2–7.3 (m, 35 H), 6.15 (dd, 1 H, J = 6.44, 1.4 Hz), 5.95 (dt, 1 H, J = 2.7, 2.6 Hz), 5.78 (t, 1 H, J = 9.5 Hz), 5.39 (m, 3 H), 5.12 (dd, 1 H, J = 12.5, 2.6 Hz), 4.56 (dd, 1 H, J = 12.5, 6.1 Hz), 4.48 (d, 1 H, J = 7.8 Hz), 4.15 (dd, 1 H, J = 10.4, 1.4 Hz), 3.81 (m, 3 H), 3.61 (s, 3 H), 3.55 (t, 1 H, J = 10.1 Hz), 3.44 (s, 3 H), 2.84 (dd, 1 H, J = 13.0, 5.0 Hz), 1.82 (dd, 1 H, J = 13.0, 11.4 Hz); IR ($CHCl_3$) 2120, 1730, 1265, 1110, 715 cm^{-1}; $[\alpha]_D$ +56.3° (c 0.8, $CHCl_3$).

Acetamide 73. A solution of azide **72** (54 mg, 44.6 μmol) in 3:1 EtOAc/MeOH (500 μL) over Lindlar catalyst was fitted with a balloon of hydrogen. The solvent was degassed and filled with hydrogen three times. After 8 h, the solution was filtered through Celite and concentrated. The crude product was dissolved in methylene chloride (1.0 mL), treated with DMAP (50 mg) and Ac_2O (50 μL), and stirred overnight. The reaction was concentrated and flash chromatographed (40% EtOAc/hexanes) to afford 47 mg of acetamide **73** (87%): ^{1}H NMR (500 MHz) δ 8.2–7.3 (m, 35 H), 5.9 (m, 1 H), 5.87 (t, 1 H, J = 9.6 Hz), 5.66 (m, 1 H), 5.64 (d, 1 H, J = 9.6 Hz), 5.44 (dd, 1 H, J = 9.8, 7.8 Hz), 5.4 (m, 1 H), 5.3 (dd, 1 H, J = 12.5, 2.7 Hz), 4.67 (d, 1 H, J = 7.8 Hz), 4.59 (dd, 1 H, J = 12.5, 7.7 Hz), 4.42 (m, 2 H), 4.05 (dd, 1 H, J = 9.9, 3.3 Hz), 3.99 (dt, 1 H, J = 9.7, 3.3 Hz), 3.84 (dd, 1 H, J = 10.9, 3.8 Hz), 3.59 (s, 3 H), 3.53 (s, 3 H), 2.68 (dd, 1 H, J = 13.0, 5.0 Hz), 2.04 (dd, 1 H, J = 13.0, 11.5 Hz), 1.8 (s, 3 H); IR ($CHCl_3$) 1730, 1270, 1115, 720 cm^{-1}; $[\alpha]_D$ +38.9° (c 0.55, $CHCl_3$).

Compound 76. A solution of methyl glycoside **73** (47 mg, 38 μmol) in methylene chloride (1 mL) was treated with acetic anhydride (500 μL), acetic acid (250 μL), and H_2SO_4 (200 μL of a 5% solution in acetic acid). After being stirred at room temperature for 6 h, the mixture was poured into $NaHCO_3$ solution (20 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was flash chromatographed (40% ethyl acetate/hexanes) to afford 40 mg of the axial anomeric acetate **76** (85%): ^{1}H NMR (500 MHz) δ 8.0 (m, 14 H), 7.4

(m, 21 H), 6.6 (d, 1 H, J = 3.7 Hz), 6.12 (t, 1 H, J = 9.9 Hz), 6.0 (d, 1 H, J = 9.9 Hz), 5.96 (dd, 1 H, J = 4.5, 1.0 Hz), 5.9 (m, 1 H), 5.78 (t, 1 H, J = 10.0 Hz), 5.52 (dd, 1 H, J = 11.5, 2.0 Hz), 4.45 (t, 1 H, J = 11.1 Hz), 4.35 (dt, 1 H, J = 10.2, 3.25 Hz), 4.01 (dd, 1 H, J = 11.2, 3.0 Hz), 3.8 (dd, 1 H, J = 11.2, 3.5 Hz), 3.62 (s, 3 H), 2.72 (dd, 1 H, J = 13.1, 4.9 Hz), 2.11 (s, 3 H), 2.05 (dd, 1 H, J = 13.1, 11.5 Hz), 1.85 (s, 3 H).

Disaccharide 82. Via the general procedure, the reaction of **52** with alcohol **63** afforded disaccharide **81** (41%) with 39% recovery of starting material. Following the general oxidation procedure afforded methyl ester **82** (75%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.0 (m, 7 H), 7.8 (m, 7 H), 7.2–7.6 (m, 21 H), 5.90 (m, 2 H), 5.78 (m, 3 H), 5.60 (dd, 1 H, J = 10.4, 3.2 Hz), 5.27 (m, 1 H), 4.81 (d, 1 H, J = 9.8 Hz), 4.70 (d, 1 H, J = 7.9 Hz), 4.53 (dd, 1 H, J = 12.2, 5.2 Hz), 4.28 (m, 1 H), 3.97 (m, 1 H), 3.81 (m, 1 H), 3.66 (s, 3 H), 3.59 (s, 3 H), 2.43 (m, 2 H).

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Registry No. 1, 19342-33-7; **5**, 10149-14-1; **5**·NH_3, 90461-30-6; **9R**, 94292-14-5; **15**, 114027-47-3; **17**, 113892-48-1; **18**, 113892-49-2; **19**, 92622-29-2; **20**, 92622-30-5; **21**, 113892-50-5; **22**, 113892-51-6; **23**, 113974-03-1; **24**, 113974-04-2; **25**, 113974-05-3; *ent*-**25**, 113974-15-5; **26**, 113924-25-7; *ent*-**26**, 113924-27-9; **27**, 113892-52-7; **28**, 113892-53-8; **30**, 113892-54-9; **31**, 113974-06-4; **32**, 113974-07-5; **33**, 114027-54-2; **39**, 113974-08-6; **40**, 113974-09-7; **41**, 113974-10-0; **42**, 113892-55-0; **43**, 113892-56-1; **44**, 113974-11-1; **45**, 113974-12-2; **46**, 6730-43-4; **47**, 113974-13-3; **48**, 114031-35-5; **49**, 113892-57-2; **50**, 113892-58-3; **52**, 113892-59-4; **53**, 113974-14-4; **55**, 73650-02-9; **62**, 4064-06-6; **63**, 53182-61-9; **64**, 88037-32-5; **65**, 113892-60-7; **65** (furyl precursor), 113892-74-3; **66**, 113892-61-8; **66** (furyl precursor), 113892-75-4; **67**, 113892-62-9; **67** (furyl precursor), 113892-76-5; **68**, 113924-26-8; **69**, 113892-63-0; **70**, 113892-64-1; **70** (triflate derivative), 113892-77-6; **71**, 113892-65-2; **72**, 113892-66-3; **73**, 113892-67-4; **76**, 113892-68-5; α-**77**, 113892-69-6; β-**77**, 113892-78-7; **78**, 113892-70-9; α-**80**, 113892-71-0; β-**80**, 113892-79-8; **81**, 113892-72-1; **82**, 113892-73-2; $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 88738-78-7; cholesterol, 57-88-5.

Substituent Effects and the Wittig Mechanism: The Case for Stereospecific Oxaphosphetane Decomposition

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Abstract: A search for reversible Wittig reactions of the ylides **a**–**d** has been made by using the method of independent oxaphosphetane generation. Four pairs of diastereomeric oxaphosphetanes have been synthesized, and those corresponding to the Wittig reactions of **b**–**d** with tertiary aldehyde **18** decompose to alkenes with >98% stereospecificity. In the case of ylide **a**, the oxaphosphetane **20a**-*trans* also decomposes without detectable reversal or loss of stereochemistry. The isomer **19a**-*cis* is the only system studied that undergoes measurable equilibration. The kinetic selectivity of $Et_3P{=}CHCH_3$ favors **19a** by a ratio of ca. 3:1. A variety of phosphorus ylides have been studied in the Wittig reaction. Depending on phosphorus substituents, a range of *kinetic* cis or trans selectivity is observed. Although the one example of extensive Wittig reversal (**19a**-*cis*) is associated with a trans-selective empirical result, there is no connection with retro-Wittig reaction in several other examples of *E*-olefin-selective Wittig reactions.

The first systematic attempts to explain Wittig reaction stereochemistry placed emphasis on reversibility in the step leading to the initial adduct.[1,2] Although the adduct proved to be an oxaphosphetane[3] and not a betaine as suggested in the early rationales, the notion that adduct stereochemistry need not correspond to olefin Z/E ratios was widely accepted. The reversibility argument was invoked for E alkene selective Wittig reactions (for example, those of carbonyl-stabilized ylides, presumed thermodynamic control). Conversely, Z-selective Wittig reactions of nonstabilized $Ph_3P{=}CHR$ were assumed to involve relatively minor reversal (kinetic control), and moderated ylides were believed to occupy a middle ground between these extremes.[1,2]

Few of the above assumptions have been tested, but some important studies have partially clarified the situation. Schlosser and Christmann (1967) demonstrated that $Ph_3P{=}CHCH_3$-PhCHO adducts decompose with good stereospecificity and minor, but significant, Wittig reversal, judging from crossover experiments.[2] Although independent proof of adduct stereochemistry in the $Ph_3P{=}CHR$ series was based only on evaluation of NMR J values, a syn-cycloreversion mechanism for the olefin-forming step was correctly assumed, a proposal that has subsequently been confirmed in related systems by X-ray analysis of a β-hydroxyphosphonium salt obtained by acid quenching of the low-temperature adduct.[4]

Deoxygenation of epoxides by phosphines has often been cited to support arguments for Wittig reversal.[5] Although the mechanisms may be related, the conditions are harsh, and the extrapolation to typical Wittig conditions is difficult at best. The first method for unequivocal generation of Wittig adducts of known stereochemistry under more representative conditions was reported by Jones and Trippett (1966), who also demonstrated the conversion of **1**/**2** into stilbenes upon treatment with base.[6] Most of the experiments were done under protic conditions, which favored loss of stereochemistry, and formation of crossover

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