Stereoselective Reactions of Alkenylpyranosides: The Effect of Double Bond Geometry on Conformation

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Abstract: For purposes of stereochemical analysis, alkenylpyranosides have been subdivided into *E* and *Z* versions of two classes differing by whether the double bond is or is not conjugated with an electron-withdrawing function (cf. ester). Ground-state solid-state conformations of three of the four permutants have been obtained by crystallographic means. Reactions of each of the various types of olefins with osmium tetraoxide have been investigated. Striking conformational differences between the four systems have been noted and interpreted. A strong correlation between these ground-state conformations in the crystalline state and the stereochemical outcome of the hydroxylation reaction have been found. Highly stereoselective routes to two of the three C_7,C_8 stereoisomers of *N*-acetylneuraminic acid have been developed.

Recently we described the first total synthesis of *N*-acetylneuraminic acid (Neu5Ac) from noncarbohydrate sources.[1,2] Our original synthesis reached racemic material. Subsequently a total synthesis of the required antipode (**1**) has been accomplished.[3] Our involvement in this family of compounds arose from consideration of the chemical issues posed by a total synthesis and from the remarkably broad range of functions that nature assigns to sialic acids.[4,5] New advances in the synthesis of sialic acid conjugates have been achieved.[2,3]

In this paper we focus on the question of control of stereochemistry at carbons 7 and 8 of Neu5Ac and stereoisomers thereof. The recognizability by neuraminidases and sialyltransferases of modified sialic acids, differing from natural compounds in their side-chain stereochemistry, is a matter of some interest.[6,7]

It will be recalled that in studies leading to the total synthesis of KDO[8] and in model studies directed at lincosamine,[9,10] the hydroxylations of enepyranosides **4** and **5** via their reactions with osmium tetraoxide were investigated. In each case the hydroxylation was essentially stereospecific. The relationship of side chain/ring stereochemistry produced in those osmylations was not that required for a synthesis of neuraminic acid (**1**).[11] It was in connection with the goal of reaching compound **1** that we investigated the osmylation of the *Z* enoate (**3**).[12] *In the event, a virtually stereospecific hydroxylation leading to compound 2 was realized. Compound 2 lent itself to transformation to Neu5Ac (1).* Thus the relative diastereofacial sense of hydroxylation of the double bond of substrate **3** is opposite to that of alkenyl types **4**[9] and **5**.[10b] In this paper we analyze the stereochemical issues associated with such reactions.

In our planning, which led to the synthesis of Neu5Ac (**1**), it was our conjecture that the reactive conformer of the *Z* enoate **3** might be of the type A (R′ = CO_2Me, Figure 1) in which the double bond would be antiplanar with the adjacent carbon–oxygen bond. Such a conformer would not suffer the attenuation of electronic availability associated with orthogonal conformer B, where the electronegative carbon–oxygen bond would overlap the π system of the double bond.[13] Given the presence of the electron-withdrawing ester linkage, avoidance of additional modes of depletion would seem to be important, particularly in the context of the osmylation.[14] Moreover, the anti form A might well be more stable than the synplanar form C in that potential steric and dipolar destabilizations in the latter are avoided in the former. It was further anticipated that attack of the osmylating agent on conformer A would occur from the α face of the double bond, which, as drawn, is opposite to the projection of the pyranose ring.

It is well to emphasize that the experimental realization of a prediction arising from a scientific proposal does not, per se, validate its underlying hypothesis. This nonconnectivity is particularly apparent in stereochemical issues where kinetically controlled products arise from a Curtin–Hammett conformer (cf. A, B, or C), which undergoes reaction in a particular sense (viz. α or β).[15a] Correspondence between prediction and outcome could in principle reflect the "correctness" or "incorrectness" of both the conformational and vectoral elements of the predictive argument. The field of osmium tetraoxide hydroxylations is one that warrants particular caution at the interpretive level. Thus a recent disclosure[15b] has questioned the central premise of the crucial electronic role of the allylic substituent. By this view, the primary effect of the allylic function arises from its steric interaction with the *E* or *Z* double bond.

Since compound **3** was obtained as a crystalline substance (mp 120–121 °C), it was of interest to establish its conformation, at least in the solid state. An ORTEP structure for this compound is given in Figure 2.[16] It will be recognized that the ORTEP drawing

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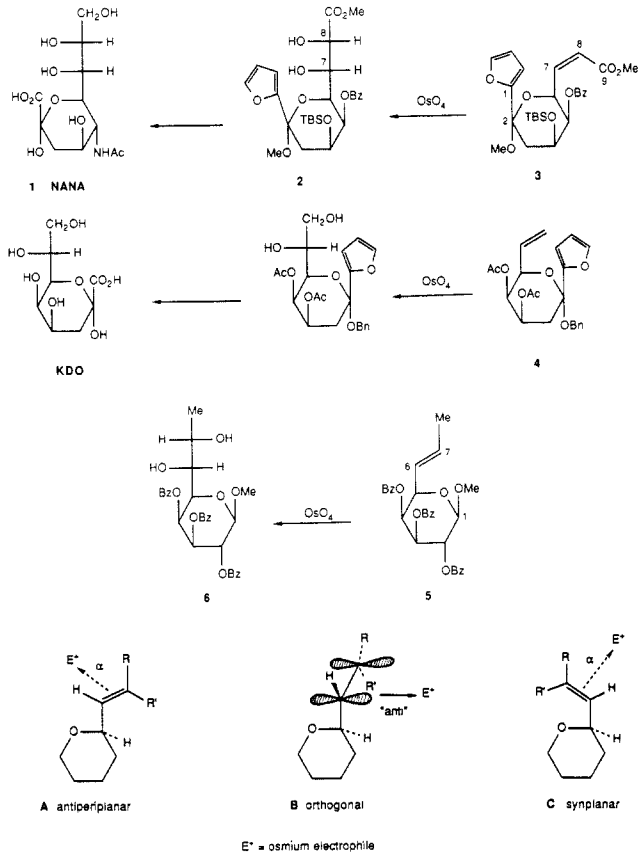

Figure 1.

of compound **3** corresponds to the conformation implied in structure A. The C_8–C_7–C_6–O dihedral angle is calculated to be 162°.[17] While the theoretical limitations associated with using ground-state conformations to predict the stereochemical outcome of reactions are appreciated,[15] the ORTEP figure of alkenylpyranoside **3** serves to rationalize the dramatically opposite result of the osmium tetraoxide oxidation of compound **3** relative to that of substrates **4** and **5**. The relationship between crystallographically determined ground-state conformers and the stereochemical outcome of the osmylation reactions will be further developed in the context of *E* enoate **8** (vide infra).

We next explored the outcome of varying the electronic nature of C_9 and the geometry of the C_7–C_8 double bond on the osmylation reaction. To evaluate these issues independently of any other structural changes, we focused on compounds **8**–**11**. In this fashion we could also hope to gain access to various C_7–C_8 stereoisomers of Neu5Ac.[7,8]

Aldehyde **7** of the original Neu5Ac synthesis was converted to *E* enoate **8** (61% yield) by a conventional Horner–Emmons reaction. Cycloaddition of the previously described diene **12**[9] and (*E*)-(benzyloxy)crotonaldehyde led eventually to ene pyranoside **9**.[18] The *Z* allylic alcohol **10** was obtained from *Z* enoate **3** by reduction with DIBAH (97%). Debenzoylation was avoided by reduction of **3** with lithium triethylborohydride wherein the *Z* benzoate alcohol **11** was obtained. Hydroxylation of these compounds was carried out under the same conditions (OsO_4–pyridine, −20 °C) as were previously used. The results are shown in Figure 3.

Most striking is the finding that the trans enoate ***8*** *reacts with very high facial selectivity (25:1) in an overall sense opposite to that of the cis enoate* ***3***. Thus the major product, **13a**, is one in which the configuration at C_7 is opposite to that of **2**, while the configuration at C_8 is the same. A strong clue as to the origin of the reversal is seen by examining the ground-state conformation of **8**. This is revealed in the ORTEP expression of an X-ray crystallographic determination of a single crystal of racemate **8**, mp 139–141 °C.[19] *Interestingly, the ground-state conformation is now synplanar* (C_8–C_7–C_6–*O dihedral angle*, −6.5°).[17] Presumed osmylation from the less hindered α face nicely serves to rationalize the observed result.

It will be recalled that in the *E* propenyl compound,[20] the olefin/pyranose relationship is only slightly (C_7–C_6–C_5–O, 106°) displaced from orthogonality. Indeed, in the preferred conformer of **5** the C_5 proton is virtually eclipsing the C_6–C_7 double bond (see Figure 2). Thus, three crystallographically determined versions of the three conformational types are now available. Compound **3** is of the antiperiplanar type, while compound **8** is synplanar. Arguments can be advanced to interpret the structural factors responsible for these major conformational differences.

In the relatively neutral olefin **5** the preferred ground-state conformation is one in which the smallest group (i.e., the C_5 hydrogen atom) eclipses the double bond[21] (see the ORTEP equivalent of conformer B, Figure 2). A comparable conformation in the case of the *E* enoate **8** would be disfavored in that it would occasion substantial and destabilizing overlap between the electron-withdrawing carbon–oxygen bond and the already electron-deficient π system. Apparently, a more favorable conformational possibility involves eclipsing the C_6–O bond with the C_7–C_8 double bond (see the ORTEP equivalent of conformer C; R = CO_2Me, **8** in Figure 2). However, the analogue of conformer C in the case of the *Z* enoate **3** (R′ = CO_2Me) would carry with

(16) The structure of **3** was determined by X-ray crystallography with a crystal that measured 0.50 × 0.50 × 0.50 mm. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Preliminary indications of the unit cell based on 25 randomly selected reflections revealed monoclinic symmetry with the following lattice parameters: a = 10.961 (5) Å, b = 11.409 (3) Å, and c = 23.042 (7) Å with β = 92.91°. The space group, on the basis of the observed systematic extinctions and absence of chirality, was assigned as $P2_1/c$ (14), Z = 4 with one molecule of composition $C_{27}H_{36}O_8Si$ forming the asymmetric unit. The volume was 2878 (1) Å^3, and the calculated density was 1.19 g/cm^3. There were 4512 reflections collected with $20 \leq 48°$, of those reflections 2993 (66%) with $I \geq 3\sigma(I)$ were adjudged observed. The structure was solved by using MULTAN 80. The phasing of 340 *E* values ≥ 1.74 resulted in an electron density map, which revealed 27 out of the 36 non-hydrogen atoms comprising the molecule. The remaining atoms were located by using the WTFOUR option in MULTAN 80. Hydrogen atoms were calculated by using SDP program HYDRO and added to the structure calculations. The following full-matrix refinement of the non-hydrogen atoms and addition of the hydrogen atoms to the structure factor calculations, without refinement of their positions resulted in convergence to a standard crystallographic unweighted residual of 0.056 and a weighted residual of 0.064. All intramolecular bond distances and angles are within normal ranges.

(17) Tables containing fractional coordinates, temperature factors, bond distances, tortional angles, and anisotropic factors for compounds **3** and **8** are available in the supplementary material.

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(19) The structure of compound **3** was determined by X-ray crystallography with a crystal that measured 0.50 × 0.50 × 0.50 mm. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Preliminary indications of the unit cell based on 25 randomly selected reflections revealed monoclinic symmetry with the following lattice parameters: a = 11.694 (3) Å, b = 11.858 (5) Å, and c = 21.119 (4) Å with β = 94.91°. The space group, on the basis of the observed systematic extinctions and absence of chirality was assigned as $P2_1/n$ (1014), Z = 4 with one molecule of composition $C_{27}H_{36}O_8Si$ forming the asymmetric unit. The volume was 2918 (1) Å^3, and the calculated density was 1.18 g/cm^3. There were 4542 reflections collected with $20 \leq 50°$; of those reflections 2945 (65%) with $I \geq 3\sigma(I)$ were adjudged observed. The structure was solved by using MULTAN 80. The phasing of 344 *E* values ≥ 1.77 resulted in an electron density map, which revealed 30 out of the 36 non-hydrogen atoms comprising the molecule. The remaining six carbon atoms, which were part of the TBS group, were located by using the WTFOUR option in MULTAN 80 after anisotropic refinement of the 30-atom fragment. This group showed disorder upon refinement. Therefore their positions were fixed and then refinement was attempted again. Hydrogen atoms were calculated by using SDP program HYDRO and added to the structure calculations. The following full-matrix refinement of the non-hydrogen atoms and addition of the hydrogen atoms to the structure factor calculations, without refinement of their positions, resulted in convergence to an unweighted residual of 0.119 and a weighted residual of 0.127. The failure of the *R* factor to converge at a lower value can be attributed to the initial difficulty in locating the carbons on the TBS and the subsequent disorder as revealed by attempted refinement procedures.

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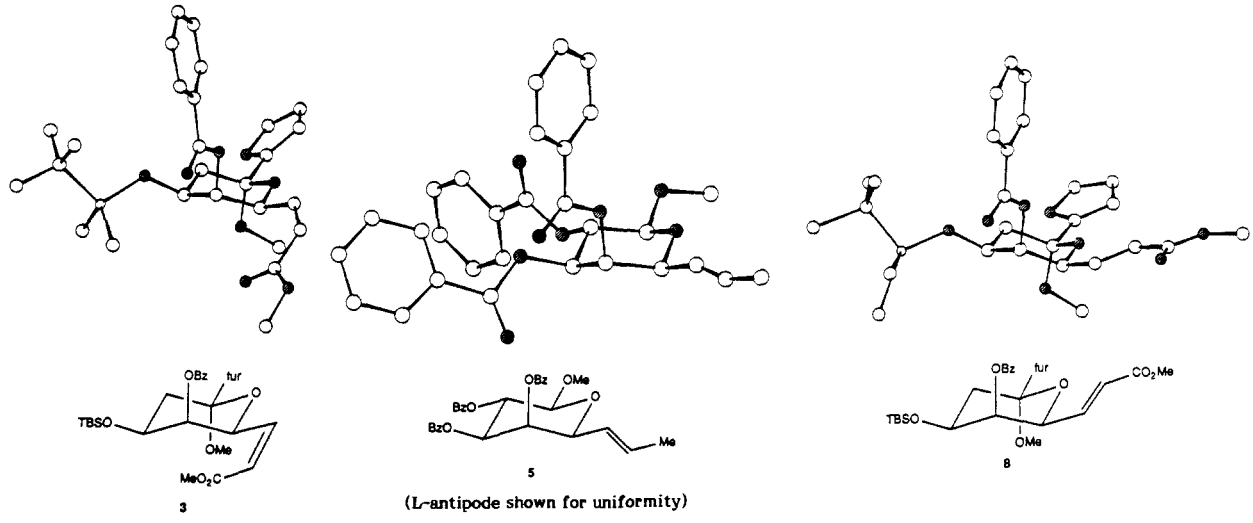

Figure 2.

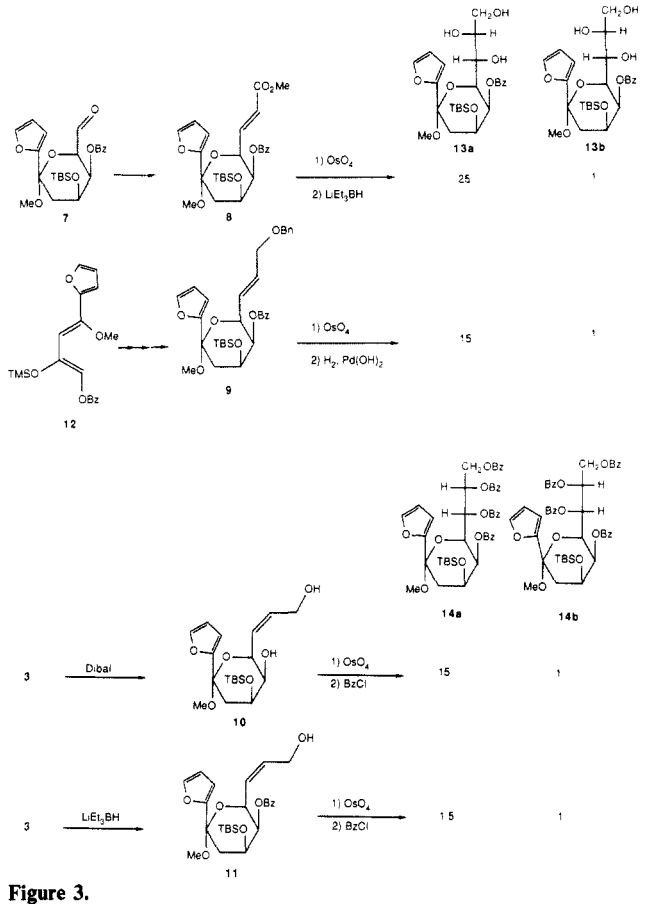

Figure 3.

it a very serious steric repulsion of the ester and oxygen functions. Interestingly, this *Z* isomer takes up an antiperiplanar conformation (see the ORTEP equivalent of conformer A in Figure 2). In this form the generally presumed advantage of eclipsing of one of the allylic bonds with the double bond[21] is forfeited. It seems quite likely that the advantage of the antiperiplanar conformation is that it maintains near orthogonality between the electron-deficient π system and the electron-withdrawing carbon–oxygen bond.

The osmylation results of the two enoates **3** and **8** are well accommodated by their ground-state conformations. In these conformations, the olefinic linkage is maximally nucleophilic in the sense previously proposed by Houk[22] and by our laboratory.[10] Less confidence is warranted in the case of neutral olefin **5**. The observed osmylation result may reflect the reaction of the ground state B-type conformer in accord with the empirical rules advanced by Kishi[23] (i.e., attack anti to the allylic oxygen). Alternatively, the reactive conformer may be of the C (inside alkoxy type)[22] wherein maximum double-bond nucleophilicity is maintained. Attack from the α face gives the observed result.

The availability of compounds **9–11** allowed for a finer probing of these effects. Some interesting results were obtained. The predominant sense of osmylation of compound **9**, bearing an (*E*)-(benzyloxy)methyl group, is the same as that of the *E* enoate **8** and the earlier compounds **4** and **5**. This result could arise from attack of the oxidant "anti" to the oxygen, on an orthogonal, B-type conformer (cf. Kishi rules).[23] An alternative possibility, which cannot be excluded, is that the reactive conformer more nearly resembles the synplanar C-type conformer, which would also give rise to the same product by reagent attack from the unhindered α face.

The results of the osmylations of *Z* allylic alcohols **10** and **11** are also striking. It is noted that in the case of diol **10**, the reaction is quite selective and *in the opposite direction to that of the Z enoate 3*. However, the need for caution in extrapolating from known cases is underscored in noting the sharp erosion of selectivity in the osmylation reaction of compound **11** relative to that of **10**. These results identify a significant role for the axial substituent at C_5. In retrospect this finding can best be rationalized in terms of orthogonal conformer B. Conceivably the bulky axial benzoate group partially shields attack in the "anti" sense. For the *Z* compounds, the alternative reactive conformer C, which would also be expected to have given the observed product, would be unlikely on steric grounds as discussed above.

Stereochemical Assignments and Correlations. The stereochemistry of **2** was initially ascertained by a crystallographic determination of its 7,8-bis(dinitrobenzoate) derivative, mp 114.5–115.5 °C. Moreover, diol **2** was converted without derivatization to racemic Neu5Ac. As previously described,[10] the stereochemistry of **6** was ascertained by a crystallographic determination of its 6,7-dibenzoyl derivative.

The minor product of the osmylation of *Z* allylic alcohol **11**, was correlated with compound **2**. Thus, reduction of **2** with lithium triethylborohydride, yielding **2b**, was followed by perbenzoylation to give **14b**. The relationships of **14a** and **14b** to **2** are thus securely established.

The stereochemistry of **13b**, the minor osmylation product of the *E* enoate **8** and *E* allylic ether **9**, was correlated with that of **2b**. Subjection of either compound to mild acid treatment afforded the corresponding "anhydro sugar" analogues **15** and **16**. Treatment of these compounds with sodium metaperiodate afforded the common aldehyde **17**. These experiments demonstrate

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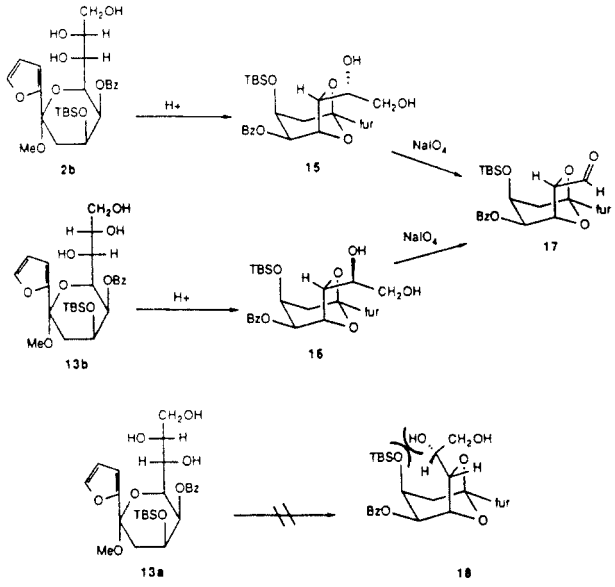

Figure 4.

that **13b** and **2b** have a common configuration at C_7, and differ at C_8. Interestingly, triol **13a** does not suffer cyclization upon comparable treatment with acid. The failure of **13a** to cyclize is eminently reasonable since such a reaction would produce compound **18** in which there would be a particularly serious repulsion between the glycolyl and OTBS groups.

In summary, highly stereoselective routes to three of the four C_7–C_8 permutants of *N*-acetylneuraminic acid are now available. Missing from our repertoire is the ability to selectively synthesize compounds of the type **13b**. By our current view, reaching such a compound via osmylation would require that an *E* isomer suffer osmylation from its α face via an antiperiplanar conformation.

At the more general level it would seem that insights gained here might well have broader implications in understanding conformational preferences of various allylic systems. With such insights can come a greater predictive capacity in acyclic stereoselection.

Experimental Section

All reactions were run in flame-dried glassware under dry nitrogen. Solvents were dried by using standard methods. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Spectral data were recorded on the following instruments: NMR, Bruker WM-250 (250 MHz) or a WM-500 (500 MHz); IR, Perkin-Elmer 1420; mass spectra, Hewlett-Packard 5985. Preparative column chromatography was carried out with silica gel 60 (E. Merck 9285, 230–400 mesh). Analytical data was obtained from Galbraith Laboratories Inc., Knoxville, TN. Copies of the original spectra and NMR spectral assignments are available in the Ph.D. Thesis of M. P. DeNinno, Yale University, 1987.

General Osmylation Procedure: Preparation of Diol 2. OsO_4 (1.26 mL of a 100 mg/mL solution in pyridine, 0.496 mmol) was added to a solution of enoate **3** (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 **2** (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 136–139 °C (hexanes/ethyl acetate); ^{1}H 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). Anal. C, H.

Preparation of *E* Enoate 8. (Carbomethoxymethylene)triphenylphosphorane (68 mg, 0.2 mmol) was added to a solution of aldehyde **7** (78 mg, 0.169 mmol) in methylene chloride (2 mL) at room temperature. After 2 h the solution was filtered through silica gel and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate/hexanes) to give 53 mg of trans enoate **8** (61%) and 19 mg of cis enoate **3** (not optimized): mp 139–140 °C (MeOH, H_2O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.95 (m, 2 H), 7.45 (m, 4 H), 6.95 (dd, 1 H, J = 15.6, 3.98 Hz), 6.55 (dd, 1 H, J = 3.35, 0.9 Hz), 6.43 (dd, 1 H, J = 3.26, 1.8 Hz), 6.25 (dd, 1 H, J = 15.6, 2.0 Hz), 5.5 (br d, 1 H, J = 3.2 Hz), 4.65 (m, 1 H), 4.44 (ddd, 1 H, J = 11.5, 5.1, 3.2 Hz), 3.7 (s, 3 H), 3.05 (s, 3 H), 2.36 (dd, 1 H, J = 13.0, 5.1 Hz), 2.1 (dd, 1 H, J = 13.0, 11.5 Hz), 0.76 (s, 9 H), 0.097 (s, 3 H), 0.085 (s, 3 H); IR ($CHCl_3$) 1725, 1275, 1170, 1130, 1045, 840, 715 cm^{-1}.

Preparation of Triols 13a/b. Compound **8** was osmylated by using the standard procedure to produce the corresponding diol (97%) as a 25:1 mixture of isomers. The ester was reduced with 6 equiv of $LiEt_3BH$ in THF at 0 °C for 1 h to give triols **13a/b**.

Compound **9** was osmylated by using the standard procedure to produce the corresponding diol (92%) as a 15:1 mixture of isomers. The benzyl group was removed by hydrogenolysis over $Pd(OH)_2/C$ to produce triols **13a/b** (96%). NMR data for **13a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02 (m, 2 H), 7.6 (m, 1 H), 7.5 (m, 3 H), 6.4 (m, 2 H), 5.3 (br d, 1 H, J = 3.0 Hz), 4.4 (m, 2 H), 4.2 (d, 1 H, J = 9.0 Hz), 3.8 (m, 5 H), 3.15 (s, 3 H), 2.7 (br s, 1 H), 2.42 (dd, 1 H, J = 13.0, 5.1 Hz), 2.2 (dd, 1 H, J = 13.0, 11.5 Hz), 0.7 (s, 9 H), 0.1 (s, 3 H), 0.05 (s, 3 H).

Preparation of Diol 10. DIBAH (0.58 mL of a 1 M solution in hexanes, 0.58 mmol) was added dropwise to a solution of cis enoate **3** (50 mg, 0.097 mmol) in CH_2Cl_2 (2 mL) at −78 °C. After 1 h the reaction was quenched by the addition of MeOH (100 μL) and brine (250 μL), and the solution was warmed to room temperature. The mixture was diluted with ether and filtered through silica gel. The filtrate was concentrated in vacuo, and the residue was flash chromatographed (30% ethyl acetate/hexanes) to afford 36 mg of diol **10** (97%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 (d, 1 H, J = 1.7 Hz), 6.46 (d, 1 H, J = 3.2 Hz), 6.34 (dd, 1 H, J = 3.2, 1.7 Hz), 5.94 (m, 2 H), 4.55 (br d, 1 H, J = 6.3 Hz), 4.42 (br dd, 1 H, J = 12.6, 6.3 Hz), 4.22 (m, 2 H), 3.06 (s, 3 H), 2.55 (br s, 1 H), 2.21 (dd, 1 H, J = 13.0, 5.2 Hz), 2.06 (br s, 1 H), 1.98 (dd, 1 H, J = 13.0, 11.3 Hz), 0.89 (s, 9 H), 0.13 (s, 6 H); IR ($CHCl_3$) 3550, 1165, 1090, 910, 840 cm^{-1}.

Preparation of Alcohol 11. $LiEt_3BH$ (0.2 mL of a 1 M solution in THF, 0.2 mmol) was added dropwise to a solution of cis enoate **3** (50 mg, 0.097 mmol) in THF (1 mL) at −78 °C. After 1 h the reaction was quenched by the addition of MeOH (100 μL), and the solution was warmed to room temperature. The mixture was diluted with ether and filtered through silica gel. The filtrate was concentrated in vacuo, and the residue was flash chromatographed (20% ethyl acetate/hexanes) to afford 28 mg of alcohol **11** (60%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03 (m, 2 H), 7.55 (m, 1 H), 7.4 (m, 3 H), 6.51 (dd, 1 H, J = 3.3, 0.7 Hz), 6.41 (dd, 1 H, J = 3.3, 1.8 Hz), 5.8 (m, 1 H), 5.62 (dd, 1 H, J = 11.5, 6.3 Hz), 5.44 (br d, 1 H, J = 3.1 Hz), 4.8 (d, 1 H, J = 6.3 Hz), 4.4 (ddd, 1 H, J = 11.5, 5.2, 3.1 Hz), 4.3 (m, 2 H), 3.1 (s, 3 H), 2.37 (dd, 1 H, J = 13.0, 5.2 Hz), 2.15 (dd, 1 H, J = 13.0, 11.5 Hz), 2.0 (t, 1 H, J = 6.3 Hz), 0.75 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); IR ($CHCl_3$) 3500, 1720, 1280, 1115, 1040, 840, 715 cm^{-1}.

Preparation of Tetrabenzoates 14a/b. Diol **10** was osmylated by the general procedure above. The crude osmylation product was perbenzoylated (BzCl/DMAP) to give tetrabenzoates **14a/b** as a 15:1 mixture of isomers (95%).

Alcohol **11** was osmylated by the general procedure above. The crude osmylation product was perbenzoylated (BzCl/DMAP) to give tetrabenzoates **14a/b** as a 1.5:1 mixture of isomers (97%). Analytical data for **14a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.95 (m, 8 H), 7.4 (m, 13 H), 6.69 (d, 1 H, J = 3.2 Hz), 6.46 (dd, 1 H, J = 3.2, 1.6 Hz), 6.18 (m, 1 H), 5.8 (dd, 1 H, J = 9.2, 3.0 Hz), 5.6 (br d, 1 H, J = 3.1 Hz), 4.95 (m, 2 H), 4.6 (dd, 1 H, J = 9.2, 1.5 Hz), 4.45 (ddd, 1 H, J = 11.4, 5.2, 3.1 Hz), 3.22 (s, 3 H), 2.4 (dd, 1 H, J = 13.0, 5.2 Hz), 2.17 (dd, 1 H, J = 13.0, 11.4 Hz), 0.7 (s, 9 H), 0.1 (s, 3 H), 0.04 (s, 3 H); IR ($CHCl_3$) 1730, 1270, 1120, 710 cm^{-1}.

Correlation Experiments. Preparation of 2b and 14b. $LiEt_3BH$ (1 mL of a 1 M solution in THF, 1 mmol) was added to a solution of ester **2** (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 MeOH followed by neutralization with acetic acid. The mixture was concentrated from MeOH several times under reduced pressure. The residue was filtered through silica gel, and the filtrate was concentrated in vacuo. The crude triol **2b** 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 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).

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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

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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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