angle, we were led to an investigation of the inversion process for bicyclo[1.1.0]butane. We found that this process involved a non-least-motion movement of the substituents on C1 and C3 of the hydrocarbon skeleton.

Acknowledgment. We are indebted to the National Science Foundation for grants that supported this investigation.

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Supplementary Material Available: Positional and thermal parameters and their estimated standard deviations and observed and calculated structure factors are provided for the X-ray structure determinations of 1, 2, and 3 (23 pages). Ordering information is given on any current masthead page.

Annulated Pyranosides. 4.[1a] Routes to Cyclohexano and Cyclopentano Pyranosides from Carbohydrate α-Enones[1b]

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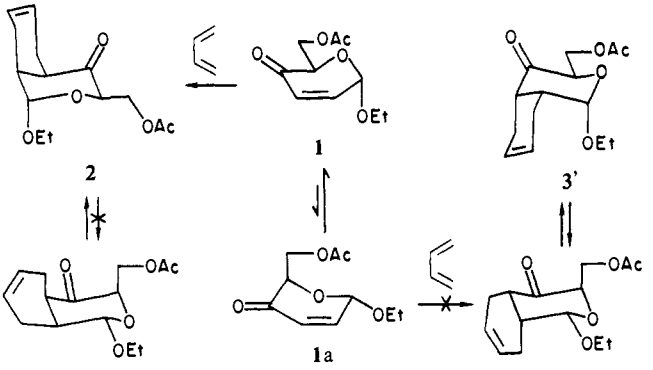
Abstract: Diels–Alder addition of butadiene to ethyl 6-*O*-acetyl-2,3-dideoxyhex-2-enopyranosid-4-ulose proceeds at low temperature in excellent yield when catalyzed by aluminum trichloride. Addition is exclusively from the β-face leading to the product having a 2,3-dideoxy α-D-*lyxo* configuration. The system is conformationally immobile, and reduction of the carbonyl group occurs from the α-face of the pyranoside ring (i.e., exo to the oxa-*cis*-decalin surface), giving a single alcohol, endo to the bicyclic system, which is so hindered that even benzylation required lengthy reaction times. Various attempts to contract the cyclohexenyl ring are described. Failure was met in all cases with the cyclohexenyl pyranosides. However, when the sugar ring was contracted first, the resulting cyclohexenyl furanose underwent cyclohexane to cyclopentane conversion via oxidative cleavage followed by a Dieckmann cyclization.

In a recent communication[5] we outlined a route to the enantiomers of chrysanthemumdicarboxylic acid in which the cyclopropyl moiety was mounted upon a pyranoside template. Because of their prevalence among natural products, cyclopentano and cyclohexano systems are of particular interest. Stork's early synthesis of prostaglandin[6] and recent alternative approaches to these important compounds by Ferrier[7] and Horton[8] indicate methodology for cyclopentanes from sugars, as do reports from Vasella's laboratory.[9] With regard to six-membered rings, routes utilizing dicarbonyl sugars have been developed by Kiely[10] and Ferrier.[11]

It is interesting to note that these[6-11] routes to carbocyclic systems utilize acyclic sugar derivatives, some by cyclization,[6,7,10,11] others by cycloaddition.[8,9] Thus the sugar moiety serves as an agent for "chirality transfer"[12] to the carbocycle. We have been concerned with the use of the carbohydrate ring system not only for "chirality transfer" but also as a device for eliciting highly stereocontrolled reactions. The role of the anomeric effect in producing a reliable, conformationally biased template,[13] well-known to carbohydrate chemists,[14] is now fully appreciated,[15,16] and we wish to take advantage of this powerful force. We have been investigating the preparation of "annulated sugars"[17,18] in

Scheme I



(1) (a) For parts 1, 2, and 3 see ref 17, 5, and 18, respectively. (b) Taken in part from: Anderson, R. C.; Primeau, J. L. Ph.D. Theses, University of Waterloo, 1978 and 1982, respectively. For a preliminary account of this work see ref 17.

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(4) University of Maryland. Address correspondence to this author at Paul M. Gross Laboratory, Department of Chemistry, Duke University, Durham, NC 27706.

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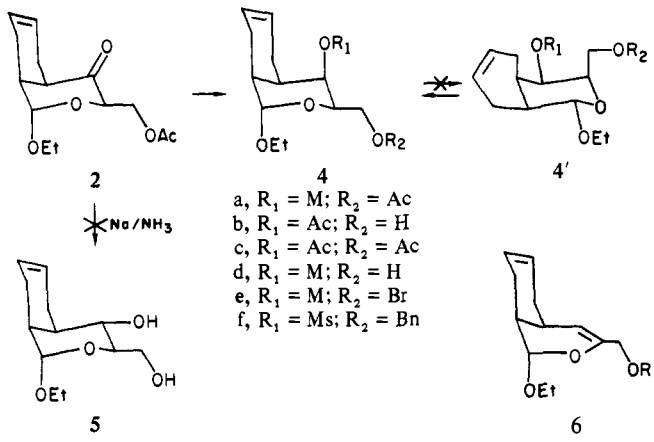
Scheme II



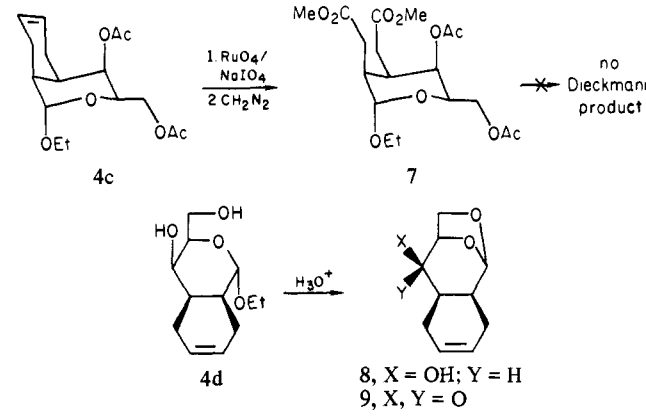
the expectation that the sugar ring would bias the conformation of the entire assembly, thereby enabling stereocontrolled processes not only on the sugar moiety itself but on the annulus as well. Some of our results have been published in preliminary form[17] and in this paper we give full details.

We[19] and others[20] have developed ready routes to carbohydrate α-enones (hexenopyranosiduloses), for example, **1**, and some of them have proved valuable for syntheses of modified saccharides, including branched-chain sugars and amino sugars.[21] We are, therefore, interested in the use of these derivatives as dienophiles and chose first to examine the reactivity of **1a** with butadiene. While our work was in progress Jones[22] and Hutchinson[23] reported thermal additions of butadiene to comparable enones; however, heating **1a** with butadiene under a variety of conditions[24] led only to degradation. The low-temperature, Lewis-acid-catalyzed process pioneered by Yates and Eaton[25] was therefore examined. When the prescribed catalytic amounts of aluminum chloride were used, the reaction was slow and gave many side products; however, when 1.5–6 molar equiv were employed, the reaction went smoothly with yields ranging from 80 to 90%, depending on the scale.

The reaction gave a single adduct whose 220-MHz ^{1}H NMR spectrum showed H-1 as a doublet, $J_{1,2}$ = 2.3 Hz, that could be accomodated either by structure **2** or **3** (Scheme I). However, our previous work on 4-keto sugars had shown that upon reduction of the carbonyl, $J_{1,2}$ would collapse to a singlet in the former but remain a doublet with the latter.[26] Accordingly, the Diels–Alder adduct was reduced with sodium borohydride, whereupon two products were obtained that were shown to be the monoacetates **4a** and **4b**, since acetylation gave the same diacetate **4c**. Reduction of the Diels–Alder adduct with lithium aluminum hydride gave the diol **4d**. In the 220-MHz spectrum of the derived diacetate **4c**, the anomeric proton appears as a singlet, thereby confirming the diequatorial relationship of H-1 and H-2, and the stereochemistry of the Diels–Alder adduct shown in Scheme II.

In assigning the configuration of C-4 of alcohol **4a**, we relied on the fact that H-4 is a singlet that would be more easily reconciled with a cis-H-4/H-5 relationship. These considerations reveal an interesting circumstance relating to these bicyclic systems which, being oxa-*cis*-decalins, might experience some conformational mobility. However **2'** is clearly less favorable than **2** because of the 1,3-diaxial interactions. Reduction from the exo surface of **2** then fully rationalizes the formation of **4a**.

Scheme III



However, **4a** itself might be conformationally mobile, and if only the nonbonded interactions were considered, **4a'** with one less axial substituent on the pyranoside ring would seem to be preferable. For **4a'**, the expected value of $J_{1,2}$ would be ~8 Hz. *The fact that H-1 appears as a singlet at 220 MHz means that **4a** cannot be present, even to the extent of 10%.* The fact that the ethoxy group is axial in **4** suggests that the anomeric effect controls not only the stereochemistry of *formation* of the "annulated pyranoside" (**2**) but its subsequent reactions.

In order to obtain the epimeric C-4 alcohol, **5**, we tried to reduce ketone **2** with dissolving metals. However the results obtained from these experiments were not encouraging. In an alternative approach we set out to invert the C-4 configuration of **4**. Treatment of the diol **4d** with benzyl bromide at room temperature gave the 6-*O*-benzyl derivative **4e**; the failure to give the di-*O*-benzyl derivative is in keeping with the hindered nature of the C-4 alcohol. The sulfonate **4f** was then prepared; but all attempts to displace the sulfonate with an oxy anion failed. Instead the enol ether **6** was obtained.

We now wished to contract the cyclohexyl ring of **4** in order to obtain a *cyclopentano* pyranose, and toward this end it was necessary to cleave the double bond in **4c**. However, treatment with ozone or the Lemieux–Johnson reagent[27] led to several products. Finally success was had with a $RuO_2/NaIO_4$ system,[28] and the related diester **7** was obtained directly in 35% overall yield. Efforts to improve upon this yield were not pursued since **7** failed to undergo the Dieckmann cyclization (Scheme III). Under a wide variety of conditions,[29] the starting material either remained unchanged or was decomposed. A variety of procedures for thallium-mediated ring contractions as described by Taylor and McKillop[30] were applied to **2** and **4**, but generally, complex mixtures of substances were obtained.

As was noted above, the more congested conformer **4a** is perferred, and it is therefore not surprising that the ozonolysis of **4c** and the Dieckmann cyclization of **2** should fail since the intermediates would experience even greater congestion of the β-face of the pyranoside ring.

Since we could not contract the *carbocyclic* ring of **4**, we set out to contract the heterocyclic ring. Examination of models

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(28) Pelletier, S. W.; Iyer, K. N.; Chang, C. W. J. *J. Org. Chem.* **1970**, *35*, 3535.
(29) Conditions tried included NaH/C_6H_6/reflux, Na/C_6H_6/reflux, $NaOMe/C_6H_6$/reflux, and NaH/DMF/60 °C.
(30) McKillop, A.; Hung, J. D.; Kienzle, F.; Bigham, E.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3635. Taylor, E. C.; Robey, R. L.; Lui, K. T.; Favre, B.; Bozimo, H. T.; Conley, R. A.; Chiang, C. S.; McKillop, A.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 3037.

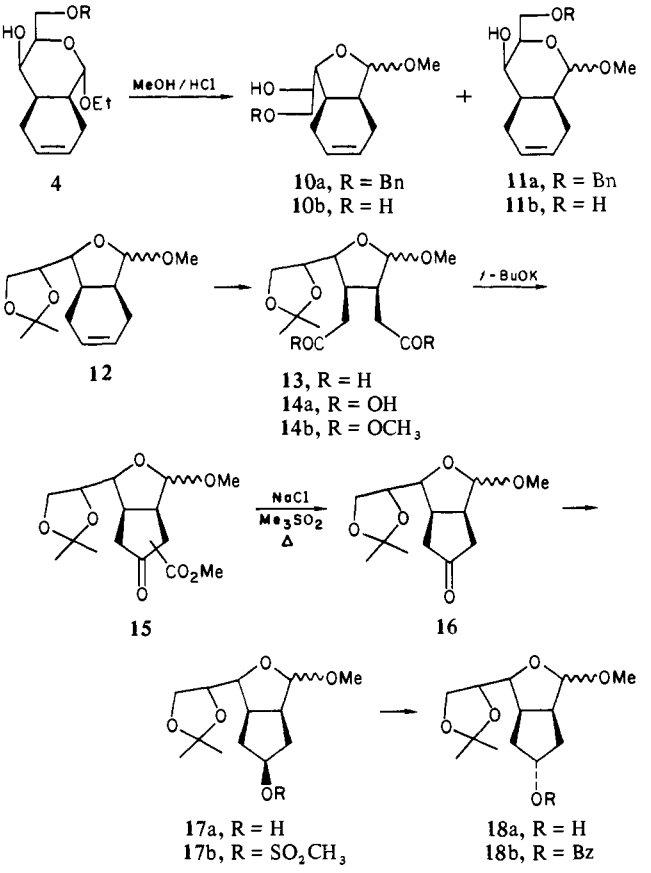
indicated that a furanose ring should experience fewer nonbonded interactions than the pyranoside, and we, therefore, believed that upon hydrolytic cleavage of the glycoside, the lactol ring would contract spontaneously to a five-membered ring. In fact, hydrolysis of **4d** with dilute acid give a product whose molecular ion showed that it was not the desired furanoside **10b**, but rather an anhydro sugar, whose structure was established as being **8** by oxidation with pyridinium chlorochromate, whereupon ketone **9**, rather than an aldehyde, was obtained. We therefore treated the 6-*O*-benzyl ether **4e** with methanolic hydrogen chloride, the course of the reaction being monitored by a polarimeter. After 5 h, equilibrium had been attained, and two substances, **10** and **11** were isolated in 6:1 ratios by preparative layer chromatography. The structural assignments follow from the fact that treatment of corresponding debenzylated materials **10b** and **11b** with sodium metaperiodate caused changes (TLC) only in the former.

The same methyl glycosides (**10b + 11b**) were obtained as an inseparable mixture when the diol **4d** was treated with methanolic hydrogen chloride. Upon reaction with dimethoxypropane and *p*-toluenesulfonic acid, the 5,6-*O*-ispropylidene derivative **12** was isolated in 74% yield.

The ring contraction of **12** was now studied. As with **4c**, ozonolysis failed to give the dialdehyde **13**; however, the Lemieux–Johnson reaction[27] gave the diacid **14a**, which afforded the corresponding diester **14b** in 33% overall yield. The ester (**14b**) underwent the Dieckmann cyclization to give a rich mixture of β-keto esters **15**, judging from the number of methoxyl singlets in the NMR. Decarbomethoxylation was successfully carried out with the Krapcho procedures,[31] giving the anomeric mixture of cyclopentanones corresponding to the α,β-furanosides of **16**. Reduction of ketone **16** with lithium aluminum hydride gave a 25:1 mixture (GLC) of alcohols, the major isomer being consistent with the endo product **17a**. The epimeric alcohol **18a** could be obtained by treating the sulfonate **17b** with sodium benzoate, followed by methanolysis (Scheme IV).

This study illustrates that reactions can be carried out with high stereoselectivities either on the pyranosides or the cycloalkyl ring, and that events in one ring may be strongly influenced by the topology of the other. Thus contraction of the cyclohexenyl ring succeeded with the furanoside **12**, but not the pyranoside **7**. Further studies on these systems are proceeding and will be reported in due course.

Scheme IV

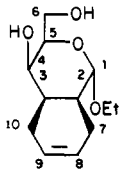


Experimental Section

General. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were performed by Dr. F. Kasler, University of Maryland, Department of Chemistry or at the Microanalysis Laboratory, Toronto, Ontario, Canada. Nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ (TMS) with one of the following spectrometers: Varian T-60, Perkin-Elmer R-12B, Varian HR-220, Varian XL-100, Varian XL-200, Bruker WP-80, and Bruker WH-400. Coupling constants were obtained by measuring the spacings of spectra judged to be first order. Infrared (IR) spectra were determined on a Beckmann Model IR-10 or Perkin-Elmer Model 298 spectrometer with either sodium chloride blanks for neat Syrups or 0.1-mm sodium chloride cells and chloroform as solvent. Low-resolution mass spectra were determined with one of the following spectrometers: Varian MAT-CM7 or Hitachi/Perkin-Elmer RMH-2. High-resolution mass spectra (HRMS) were determined either with a VG 7070F or a VG Micromass 7070H.

Gas–liquid chromatography (GLC) was performed on a Hewlett-Packard Model 5730 with an Ultrabond-packed coiled-steel column (6 ft × $^1/_8$ in.), or on a Varian Model 3760 with a 3% OV-101 on Chromasorb-W (HP80/100) packed glass column (200 cm × 2 mm). The progress of all reactions was monitored by thin-layer chromatography (TLC) which was performed on aluminum sheets precoated with Silica Gel-60 (HF-254) to a thickness of 0.2 nm (E. Merck, No. 5539). Unless otherwise stated, the following solvent systems were used to develop the plates: A, ethyl acetate–petroleum ether (1:4) (30–60 °C); B, ethyl acetate–petroleum ether (1:1) (30–60 °C); C, methanol–methylene chloride (1:9); D, diethyl ether; E, ethyl acetate. The chromatographs were viewed under an ultraviolet light, sprayed with concentrated sulfuric acid, and briefly heated to a temperature >100 °C under a hot-air gun. For column chromotography, E. Merck silica gel (0.063–60.20 mm, 70–230 mesh ASTM) was used. Preparative thick-layer chromotography (PTLC) was done on glass plates (20 × 20 cm) coated with Silica Gel-60 (F-254, E. Merck) to a depth of 2.0 mm.

For the purposes of NMR interpretation the numbering schemes shown below have been adopted.



Ethyl 6-*O*-Acetyl-2,3-*C*-(2-butene-1,4-diyl)-2,3-dideoxy-α-D-*lyxo*-hexopyranosid-4-ulose (2). The α-enone **4**[19] (200.3 mg, 0.935 mmol) was dissolved in dry methylene chloride (40 mL), the solution was cooled to −78 °C under argon, and 1,3-butadiene (10 mL) was added. Aluminum chloride (800 mg, 5.99 mmol) was then added with stirring, and the temperature of the reaction mixture was raised to −40 °C. After 2.5 h, when TLC (solvent A) indicated that the reaction was complete, the mixture was poured into a cold (0 °C) saturated aqueous sodium bicarbonate solution (100 mL). The solution was extracted twice with methylene chloride (2 × 100 mL) that was then washed with water (2 × 100 mL), dried over sodium sulfate, and evaporated to give an oily residue. Purification by column chromatography (solvent A) gave **2** (203.1 mg, 81%) as an oil that displayed the following characteristics: TLC R_f 0.62 (solvent A); $[\alpha]_D$ +144° (*c* 6.26 in $CHCl_3$); IR (neat) ν_{max} 1740 (br), 1440, 1370, 1230, 1130, 1060 cm^{-1}; MS, *m/e* 268 (M^+), 223 (M^+ − OEt), 213; ^1H NMR (220 MHz) δ 1.30 (t, 3, OCH_2CH_3), 1.91–2.27 (m, 4, H-7,7′-10,10′), 2.06 (s, 3, OAc), 2.49 (m, 1, H-2), 3.15 (m, 1, H-3), 3.65 (dq, 1, J_{gem} = 10 Hz, $OCH_AH_BCH_3$), 3.88 (dq, 1, $OCH_AH_BCH_3$), 4.23–4.55 (m, 3, H-5,6,6′), 4.80 (d, 1, $J_{1,2}$ = 2.0 Hz, H-1), 5.67 (s br, 2, H-8.9); HRMS calcd for M^+ 268.1311, found 268.1306 (Δppm = 2), calcd for M^+ − OEt 223.0971, found 223.0968 (Δppm = 1).

Ethyl 4,6-Di-*O*-acetyl-2,3-*C*-(butene-1,4-diyl)-2,3-dideoxy-α-D-talopyranoside (4c). The Diels–Alder adduct **2** (193.6 mg, 0.722 mmol) was dissolved in absolute ethanol (10 mL), and sodium borohydride (100 mg, 2.6 mmol) was added with stirring. The mixture was stirred at room

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temperature for 0.5 h at which time acetic acid was added dropwise until the evolution of hydrogen ceased. The reaction mixture was then diluted with methylene chloride (30 mL) and processed in the usual manner to yield an oil (163.1 mg, 83%), which appeared as two components **4** (a + b) on TLC. The mixture on MS analysis showed the following: *m/e* 225 (M^+ – OEt), 224 (M^+ – 1 – OEt), 146, 117, 96. A portion of the mixture, 80 mg, was dissolved in acetic anhydride and pyridine (1:2, 12 mL) and left to stand at room temperature 48 h. The reaction mixture was cooled to 0 °C and methanol (5 mL) was carefully added. Evaporation of the resultant solution and processing of the residue in the usual manner afforded the diacetate **4c** as an oil (78 mg, 84%) that displayed the following characteristics: TLC R_f 0.50 (solvent *A*); ^{1}H NMR (220 MHz), δ 1.27 (t, 3, OCH_2CH_3), 2.00 (s, 3, OAc), 2.07 (s, 3, OAc), 2.01–2.54 (m, 6, H-2,3,7a,7b,10a,10b), 3.55 (dq, 1, $OCH_AH_BCH_3$), 3.75 (dq, 1, $OCH_AH_BCH_3$), 4.00–4.27 (m, 3, H-5,6a,6b), 4.68 (s, 1, H-1), 5.16 (s, 1, H-4), 5.36–5.86 (m, 2, H-8,9).

Ethyl 2,3-*C*-(2-Butene-1,4-diyl)-2,3-dideoxy-α-D-talopyranoside (4d). The Diels–Alder adduct **2** (1.01 g, 3.77 mmol) was dissolved in dry THF (10 mL) and cooled (0 °C), and lithium aluminum hydride (150 mg, 3.97 mmol) was added. The reaction mixture was stirred at room temperature for 0.5 h at which time saturated ammonium chloride was added dropwise (until hydrogen evolution ceased). The resulting solution was diluted with water (30 mL) and extracted several times with diethyl ether (3 × 50 mL). The organic fractions were combined, dried over sodium sulfate, and evaporated to give **4d** (695 mg, 80%) as an oil. After purification by PTLC (solvent A) compound **4d** displayed the following characteristics: TLC R_f 0.26 (solvent A); $[\alpha]^{23}_D$ +126° (*c* 5.86 in $CHCl_3$); IR (neat) ν_{max} 3440 (OH), 1660, 1430, 1372, 1340, 1125, 1055, 965, 745 cm^{-1}; MS, *m/e* 228 (M^+), 183 (M^+ – OEt), 182 (M^+ – 1 – OEt), 146, 133; ^{1}H NMR (220 MHz) δ 1.17 (t, 3, OCH_2CH_3), 1.82–2.18 (m), 2.18–2.64 (m), 3.34–3.59 (m), 3.59–4.09 (m), 4.66 (s, 1, H-1), 5.75 (m, 2, H-8,9); HRMS calcd for M^+ 228.1362, found 228.1366 (Δppm = 2), calcd for M^+ – OEt 183.1022, found 183.1018 (Δppm = 2).

Ethyl 6-*O*-Benzyl-2,3-*C*-(2-butene-1,4-diyl)-2,3-dideoxy-α-D-talopyranoside (4e). The diol **4d** (625.8 mg, 2.74 mmol) was dissolved in dry 1,2-dimethoxyethane (20 mL), and sodium hydride (excess) was slowly added with stirring. The reaction mixture was stirred at room temperature under argon for 5 min at which time benzyl bromide (0.326 mL, 2.74 mmol) was added. After stirring for a further 4 h, methanol was carefully added to the reaction mixture followed by methylene chloride (100 mL), and the solution was processed in the usual manner to give **4e** (586.2 mg, 67%) as an oil. After purification by PTLC (solvent B), compound **4e** displayed the following characteristics: TLC R_f 0.35 (solvent B); GLC 20.0 min (190 °C); $[\alpha]^{23}_D$ + 61.4° (*c* 5.97 in $CHCl_3$); IR (neat) ν_{max} 3480 (OH), 1450, 1370, 1125, 1000, 968, 742 cm^{-1}; MS, *m/e* 273 (M^+ – OEt), 272 (M^+ – 1 – OEt), 180; ^{1}H NMR (220 MHz) δ 1.25 (t, 3, OCH_2CH_3), 2.00–2.23 (m), 2.23–2.59 (m), 3.36–3.63 (dq, 2, OCH_2CH_3), 3.63–3.91 (m), 3.91–4.09 (m), 4.59 (s, 2, $PhCH_2$), 4.69 (s, 1, H-1), 5.79 (s, 2, H-8,9).

Ethyl 6-*O*-Benzyl-2,3-*C*-(2-butene-1,4-diyl)-2,3-dideoxy-4-*O*-(methylsulfonyl)-α-D-talopyranoside(4f). The alcohol **4e** (558.7 mg, 1.76 mmol) was dissolved in dry pyridine (10 mL), and methanesulfonyl chloride (1.3 mL) was added. The reaction mixture was stirred at room temperature for 7 h, and then it was diluted with methylene chloride (50 mL) and processed in the usual manner to yield the sulfonate **4f** (648 mg, 93%) as an oil. After purification by PTLC (solvent A) compound **4f** displayed the following characteristics: TLC R_f 0.21 (solvent B); $[\alpha]^{23}_D$ +32.8° (*c* 4.38 in $CHCl_3$); IR (neat) ν_{max} 1450, 1330, 1165, 910, 478 cm^{-1}; MS, *m/e* 396 (M^+), 350, 349, 258; ^{1}H NMR (60 MHz) δ 1.22 (t, 3, OCH_2CH_3), 1.80–2.70 (m, 6, H-2,3,7,7′,10,10′), 2.98 (s, 3, SO_2CH_3), 3.30–4.30 (m, 5, H-5,6,6′, OCH_2CH_3), 4.58 (s, 2, $PhCH_2$), 4.68 (s, 1, H-1), 4.95 (m, 1, H-4), 5.70 (s, 2, H-8,9), 7.32 (s, 5, $PhCH_2$).

Ethyl 6-*O*-Benyl-2,3-*C*-(2-butene-1,4-diyl)-2,3,4-trideoxy-β-L-*erythro*-hex-4-enopyranoside (6). The sulfonate **4f** (120 mg, 0.303 mmol) was dissolved in dry DMF (15 mL), sodium benzoate (130 mg, 0.907 mmol) was added, and the reaction mixture was heated with stirring under argon at 120 °C for 24 h. Usual workup afforded an oil (73 mg) that, as evidenced by TLC, GLC, and ^{1}H NMR, was neither unreacted **4f** nor a benzoate. The structure **6** was assigned on the basis of the following data: TLC R_f 0.84 (solvent A); GLC 11.25 min (190 °C); IR ν_{max} 1630, 1450, 1320, 1275, 1140, 1068, 1022 980 cm^{-1}; MS, *m/e* 300 (M^+), 284, 255 (M^+ – OEt), 226; ^{1}H NMR (60 MHz) δ 1.20 (t, OCH_2CH_3), 1.90–3.00 (m), 3.38–4.00 (m), 4.61 (s, 2, $PhCH_2$), 4.73 (s, 1, H-1), 5.51 (s, br, 1, H-4), 5.70 (s, 2, H-8,9), 7.38 (s, 5, $PhCH_2$).

Ethyl 4,6-*O*-Diacetyl-2,3-*C*-bis[(methoxycarbonyl)methyl]-2,3-dideoxy-α-D-talopyranoside (7). A solution of the diacetate **4c** (2.2 g, 7.05 mmol) in acetone (100 mL) was added to a mixture of sodium metaperiodate (5.5 g, 25.7 mmol), water (100 mL), acetone (100 mL), and ruthenium dioxide (100 mg) and stirred vigorously. After 1 h further amounts of sodium metaperiodate (2.2 g, 10.2 mmol), water (40 mL), and acetone (80 mL) were added, and stirring was continued for another 3 h. The reaction mixture was then diluted with methylene chloride (300 mL) which was subsequently separated from the aqueous phase and extracted with a saturated sodium bicarbonate solution. After neutralization of the bicarbonate solution with 6 N hdyrochloric acid, the aqueous phase was extracted with methylene chloride which was then dried over sodium sulfate and evaporated.

The residue obtained was dissolved in diethyl ether (15 mL), and diazomethane was added dropwise until a yellow color persisted. Acetic acid was then carefully added until the evolution of nitrogen ceased. The reaction mixture was diluted with diethyl ether (15 mL), washed with a saturated sodium bicarbonate solution (10 mL), dried over sodium sulfate, and evaporated to give **7** as an oil (1.0 g, 35%) that was predominately one spot on TLC (R_f 0.33, solvent A). Compound **7** displayed the following characteristics: MS, *m/e* 359 (M^+ – OEt), 358 (M^+ – HOEt), 330, 329, 270; ^{1}H NMR (60 MHz) δ 1.20 (t, 3, OCH_2CH_3), 2.00 (s, 3, OAc), 2.10 (s, 3, OAc), 2.0–2.6 (m, 4, $2(CH_2CO_2CH_3)$), 3.69 (s), 6, $2(CO_2CH_3)$, 3.3–4.3 (m, 5, H-5,6,6′,OCH_2CH_3), 4.8 (s, br, 1, H-1), 5.1 (m, 1, H-4).

Attempted Dieckmann Cyclization of 7. The diester 7 (165.3 mg, 0.409 mmol) was dissolved in dry benzene (15 mL), sodium hydride (200 mg, 50% oil, 4.16 mmol) was added, and the reaction mixture was refluxed under argon for 5 h. After the careful addition of water (until hydrogen evolution ceased), the reaction mixture was diluted with methylene chloride (50 mL) and processed in the usual manner. However, as evidenced by TLC and ^{1}H NMR, the predominant material was unreacted **7**.

Other conditions that also left **7** unchanged were: (b) benzene/Na/reflux 8 h; (c) benzene/NaOMe/reflux 5 h; (d) DMF/NaH/60 °C/18 h.

1,6-Anhydro-2,3-*C*-(2-butene-1,4-diyl)-2,3-dideoxy-B-D-talopyranose (8). The diol **4d** (0.175 g, 0.8 mmol) was dissolved in dry benzene (10 mL), and a catalytic amount of *p*-toluenesulfonic acid monohydrate was added. The solution was stirred at room temperature for 12 h at which time TLC analysis indicated the complete consumption of the starting material and the formation of a major product, **8**. Standard processing followed by silica gel chromatography (solvent B) afforded **8** as a clear syrup (0.126 g, 90%), which displayed the following characteristics: TLC (R_f 0.61 (solvent A); $[\alpha]^{23}_D$ + 155° (*c* 1.05 in $CHCl_3$); IR (neat) ν_{max} 3450, 2930, 2885, 1450, 1100, 1040, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) (60 MHz) δ 1.90–2.30 (m, 6), 3.30–4.30 (m, 4), 4.72 (s, 1, H-1), 5.75 (br s, 2, H-8,9); HRMS calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0940 (Δppm = 1.7). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.96; H, 7.87.

1,6-Anhydro-2,3-*C*-(2-butene-1,4-diyl)-2,3-dideoxy-β-D-*lyxo*-hexopyranosid-4-ulose (9). To a solution of (0.102 g, 0.6 mmol) in methylene chloride (10 mL) were added Celite (0.5 g), sodium acetate (0.5 g, 5.9 mmol), and pyridinium chlorochromate[32] (0.5 g, 2.3 mmol). The solution was stirred at room temperature for 24 h. The reaction mixture was processed by dilution with diethyl ether (25 mL) followed by passage through a pad of Florisil, whereby **9** was obtained as a clear syrup that displayed the following characteristics: TLC R_f 0.61 (solvent A); $[\alpha]^{23}_D$ 138° (*c* 0.9 in $CHCl_3$); IR (neat) ν_{max} 2930, 2880, 1735, 1110, 1050, 910, 690; ^{1}H NMR (60 MHz) δ 1.90–2.35 (m, 5), 2.90 (m, 1), 4.00–4.40 (m, 2), 4.70–5.00 (m, 2), 5.20 (s, 1, H-1), 5.70 (br s, 2, H-8,9).

Methyl 2,3-*C*-(2-Butene-1,4-diyl)-2,3-dideoxy-α,β-D-talofuranoside (10b) and -α,β-talopyranoside (11b). (a) The 6-*O*-benzyl ether **4e** (0.15 g, 0.5 mmol) was dissolved in dry methanol (10 mL), and 6% methanolic hydrogen chloride (10 mL) was added. The solution was stirred at room temperature for 90 min, at which time the solution was neutralized with solid barium carbonate, filtered, and evaporated to yield a clear oil (0.13 g, 91%), which appeared as two components on TLC. The major component **10a** (90 mg) was isolated by PTLC (solvent C). A portion (50 mg, 0.16 mmol) was dissolved in dry dimethoxyethane (10 mL), and ammonia (10 mL) was condensed into the reaction solution. Fine slivers of sodium were added until the blue coloration persisted, at which time excess ammonium chloride was added and all the solvents were removed in a nitrogen stream. The resulting salts were extracted with ethyl acetate to yield a clear oil **10b** (0.029 g, 79%) (R_f 0.3, solvent C), which displayed the following data: ^{1}H NMR (220 MHz) ($CDCl_3$) δ 1.82–2.77 (m, 8, H-2, 3,7,7′,10,10′, CH_2OH, RCHO*H*), 3.36 (s, 3, OCH_3), 3.55–3.64 (m, 1, H-4), 3.66–3.73 (m, 2, H-6,6′), 3.85 (dd, 1, H-5), 4.61 (s, 1, H-1), 5.64 (m, 2, H-8,9); ^{1}H NMR (220 MHz) (C_6D_6) δ 1.61–2.50 (m, 7), 2.70 (m, 1), 3.02 (s, 3, OCH_3), 3.48 (m, 1, H-4), 3.65 (m, 2, H-6, 6′) 3.75 (dd, 1, H-5), 4.28 (s, 1, H-1), 5.48 (m, 2, H-8,9). A portion (5 mg, 0.02 mmol) of **10b** was dissolved in methanol (1.5 mL) containing 3 drops of water. Sodium metaperiodate (0.05 g, 0.2 mmol) was added,

(32) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

and the solution was stirred at room temperature. After 1 h TLC indicated that all of the starting material had been consumed.

The minor component from the PTLC **11a** (20 mg, 0.06 mmol) was debenzylated similarly to afford a diol **11b** (0.012 g, 86%) (R_f 0.3, solvent C), which displayed the following ^{1}H NMR data: ^{1}H NMR (220 MHz) ($CDCl_3$) δ 1.9–2.8 (m, 8, H-2,3,7,7′,10,10′, CH_2OH), 3.36 (s, 3, OCH_3), 3.73–4.00 (m, 4, H-4, H-5, H-6, H-6′), 4.57 (s, 1, H-1), 5.77 (s, 2, H-8,9); ^{1}H NMR (220 MHz) (C_6D_6) δ 1.82–2.27 (m, 4), 2.36–2.64 (m, 2), 2.80 (br s, 2), 3.20 (s, 3, OCH_3), 3.68–4.0 (m, 4, H-4,5,6,6′), 4.39 (s, 1, H-1), 5.50 (m, 2, H-8,9). A portion (0.005 g, 0.02 mmol) was dissolved in 1.5 mL of methanol and 3 drops of water. Sodium metaperiodate (0.05 g, 0.2 mmol) was added, and the solution was stirred at room temperature. After 24 h TLC indicated that no reaction had occurred.

(b) The diol **4d** (3.7 g, 1.62 mmol) was dissolved in 1% methanolic hydrogen chloride (150 mL), the solution was stirred at room temperature, and the progress of the reaction was monitored by a polarimeter. When the optical rotation had obtained a constant value (~5 h), the reaction mixture was neutralized with solid sodium bicarbonate, filtered, and evaporated to yield a pale yellow syrup, which was freed from small quantitites of sodium bicarbonate by methylene chloride extraction. The syrup (3.0 g, 86%), although homogeneous on TLC (R_f 0.3 (E)), was shown by ^{1}H NMR to consist of **10b** and **11b** in a 6:1 ratio. The syrup displayed the following characteristics: TLC R_f 0.3 (solvent C); IR (neat) ν_{max} 3600 (OH), 2900, 1040, 660 cm^{-1}; ^{1}H NMR (100 MHz) ($CDCl_3$) δ 1.8–2.5 (m, 5), 2.74 (m, 1), 3.0 (br s, 2, RCHOH, CH_2OH), 3.4 (s, 3, OCH_3), 3.55–3.95 (m, 4, H-4,5,6,6′), 4.60 (s, 0.2, H-1 **11b**), 4.63 (s, 1, H-1 **10b**), 5.00 (d, 0.1, H-1 (β)), 5.6–5.8 (m, 2, H-8,9); ^{1}H NMR (100 MHz) (C_6D_6) δ 1.6–2.7 (m, 8, H-2,3,7,7′,10,10′,CHRO*H*, CH_2O*H*), 3.0 (s, 3, OCH_3 **10b**), 3.17 (s, 0.3, OCH_3 **11b**), 3.5–3.75 (m, 4, H-4, H-5, H-6, H-6′), 4.3 (s, 1, H-1), 5.45–5.6 (m, 2, H-8,9); MS, *m/e* 214 (M^+), 183 ($M^+ - OCH_3$).

Methyl 5,6-*O*-Isopropylidine-2,3-*C*-(2-butene-1,4-diyl)-2,3-dideoxy-α,β-D-talofuranoside (12). The mixture of methanolysis products from part b above (2.4 g, 11.2 mmol) was dissolved in dry methylene chloride (50 mL) and 2,2-dimethoxypropane (10 mL, 81 mmol), and a trace of *p*-toluenesulfonic acid monohydrate was added. The reaction solution was stirred for 12 h, at which time the solution was washed with sodium bicarbonate solution and water and then dried. There was obtained a light amber oil that displayed on TLC a major product, R_f 0.6 (solvent C), and some minor products. The major product, **12** (2.12 g, 74%), isolated by silica gel chromatography, displayed the following characteristics: TLC R_f 0.6 (solvent C); $[\alpha]^{23}_D$ +192° (*c* 1.5 in $CHCl_3$); IR (neat) ν_{max} 2890, 1390, 1370, 1045, 660 cm^{-1}; ^{1}H NMR (220 MHz) ($CDCl_3$) δ 1.39 (s, 3, $C(CH_3)_2$), 1.45 (s, 3, $C(CH_3)_2$), 1.70–2.60 (m, 6, H-2,3,7,7′,10,10′), 3.39 (s, 3, OCH_3), 3.86 (m, 2, H-6,6′), 4.03 (dd, 1, $J_{3,4}$ = 8 Hz, $J_{4,5}$ = 7 Hz, H-4), 4.18 (ddd, 1, H-5), 4.64 (s, 1, H-1 (α)), 5.0 (d, 0, 1, H-1 (β)), 5.55–5.8 (m, 2, H-8,9); ^{1}H NMR (100 MHz) (C_6D_6) δ 1.36 (s, 3, $C(CH_3)_2$), 1.46 (s, 3, $C(CH_3)_2$), 1.75–2.4 (m, 5), 2.5–2.8 (m, 1), 3.25 (s, 3, OCH_3), 3.75–4.25 (m, 4, H-4,5,6,6′), 4.5 (s, 1, H-1 (α)), 4.84 (d, 0.1, H-1 (β)), 5.5–5.8 (m, 2, H-8,9); MS, *m/e* 254 (M^+), 239 ($M^+ - CH_3$), 223 ($M^+ - OCH_3$); Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.26; H, 8.95.

Methyl 5,6-*O*-Isopropylidene-2,3-bis[(methoxycarbonyl)methylene]-2,3-dideoxy-α,β-D-talofuranoside (14b). (a) The olefin **12** (0.51 g, 2.0 mmol) was dissolved in 75 mL of 2:1 acetone/water. To this solution was added sodium metaperiodate (5 g, 23.4 mmol) and a trace of ruthenium dioxide. The resulting suspension was stirred vigorously for 18 h, at which time the reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate (3 × 75 mL). The combined ethyl acetate fractions were washed with saturated aqueous sodium chloride (3 × 20 mL), dried over anhydrous magnesium sulfate, and evaporated to yield the crude dicarboxylic acid, **14a** (250 mg), which displayed the following characterisitics: TLC R_f 0.08 (solvent C); IR (neat) ν_{max} 3300 (v br), 2920, 1720 (br), 1205, 1145, 1045, 745 cm^{-1}; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 1.32 (s, 3, $C(CH_3)_2$), 1.40 (s, 3, $C(CH_3)_2$), 2.10–3.0 (m, 6, H-2,3,7,7′,10,10′), 3.30 (s, 3, OCH_3), 3.70–4.30 (m, 4, H-4,5,6,6′), 4.68 (s, 1, H-1 (α)), 4.90 (br s, 0.1, H-1 (β)), 9.4 (br s, 2, CO_2H).

(b) The olefin **12** (0.7 g, 2.76 mmol) was dissolved in 225 mL of a 1:2 mixture of acetone and phosphate buffer (pH 4). To this solution was added sodium metaperiodate (6 g, 28 mmol) and potassium permanganate (0.044 g, 2.78 mmol), and the resulting suspension was stirred vigorously for 11 h. At this time the reaction mixture was processed as described in part a to yield a clear syrup (320 mg) that displayed characteristics analogous to those described in part a for crude **14a**.

The crude diacid **14a** from either experiment (300 mg) was dissolved in methanol (10 mL), and a solution of diazomethane in diethyl ether was added slowly until the characteristic yellow color of the diazomethane persisted. The reaction solution was quenched with acetic acid and evaporated to yield a pale yellow syrup. Silica gel chromatography of this syrup (solvent A) gave **14b** as clear syrup (0.215, 33%) that displayed the following characteristics: TLC R_f 0.36 (solvent A); IR (neat) ν_{max} 2960, 1745, 1440, 1380, 1375, 1255, 2115, 1090, 1050 cm^{-1}; ^{1}H NMR (60 MHz) ($CDCl_3$), δ 1.35 (s, 3, $C(CH_3)_2$, 1.40 (s, 3, $C(CH_3)_2$), 2.00–2.90 (m, 6, H-2,3,7,7′,10,10′), 3.30 (s, 3, OCH_3), 3.65 (s, 6, CO_2Me), 3.70–4.20 (m, 4, H-4,5,6,6′), 4.68 (s, 1, H-1 (α)), 4.90 (d, 0.1, H-1 (β)); MS, *m/e* 331 ($M^+ - CH_3$), 315 ($M^+ - OCH_3$); HRMS calcd for $C_{15}H_{23}O_8$ 331.1393; found 331.1376 (Δ ppm = 5.1).

Dieckmann Cyclization of Diester (14b). The diester **14b** (0.3 g, 0.88 mmol) was dissolved in dry benzene (75 mL), potassium *tert*-butoxide (1.0 g, 8.9 mmol) was added under argon, and the solution was stirred at room temperature for 4 h, at which time TLC indicated the complete disappearance of **14b** and the formation of a new product, R_f 0.34 (solvent A). The reaction mixture was diluted with diethyl ether (75 mL), and 5% hydrochloric acid was added until the aqueous layer remained acidic. The organic fraction was collected, dried over anhydrous magnesium sulfate, and evaporated to yield **15** as an amber oil (0.2 g, 76%), displaying the following characteristics: TLC R_f 0.34 (solvent A); IR (neat) ν_{max} 2920 (1760, 1735, 1680, 1640 cm^{-1} β-keto ester), 1450, 1380, 1245, 1050 cm^{-1}; ^{1}H NMR (100 MHz) ($CDCl_3$) displayed two singlets of three protons each at δ 1.36 and 1.40 due to 5,6-*O*-isopropylidene, multiple singlets with total integration of three protons centered around δ 3.4 due to OCH_3, multiple singlets with total integration of three protons centered around δ 3.8 due to CO_2*Me*, and multiple absorptions with a total integration of one proton centered around δ 5.0 due to H-1; more detailed interpretation of the NMR spectrum was impossible owing to the many isomers of **15**; MS, *m/e* 299 (M^+, $- CH_3$), 283 ($M^+ - OCH_3$).

Methyl 5,6-*O*-Isopropylidene-2,3-*C*-(2-oxopropane-1,3-diyl)-2,3-dideoxy-α,β-D-talofuranoside (16). The ketoester **15** (0.140 g, 0.45 mmol) was dissolved in redistilled dimethyl sulfoxide (10 mL) and sodium chloride (0.026 g, 0.45 mmol), 5 drops of water were added, and the reaction mixture was heated to 120–125 °C under an argon atmosphere. After 4 h, the reaction mixture was poured into water and extracted with water. Processing in the usual way yielded **16** (0.082 g, 72%) as an amber oil. After silica gel chromatography (solvent A), **16** displayed the following charactersitics: TLC R_f 0.30 (solvent A); IR (neat) ν_{max} 2980, 2910, 1750 (cyclopentanone), 1375, 1215, 1150, 1040, 990, 850 cm^{-1}; ^{1}H NMR (220 MHz) ($CDCl_3$) δ 1.39 (s, 3, $C(CH_3)_2$), 1.45 (s, 3, $C(CH_3)_2$), 2.11 (dd, 1) 2.24–2.89 (m, 3), 2.93 (m, 2), 3.36 (s, 3, OCH_3 (β)), 3.42 (s, 3, OCH_3 (α)), 3.84 (m, 2, H-6,6′), 4.08 (dd, 1, $J_{3,4}$ = $J_{4,5}$ = 6 Mz, H-4), 4.27 (dd, 1, H-5), 4.93 (s, 1, H-1); ^{13}C NMR (80 MHz) ($CDCl_3$) δ 25.20 ($C(CH_3)_2$), 26.72 ($C(CH_3)_2$), 39.78, 39.96 (C-7,9), 42.76 (C-3), 47.49 (C-2), 54.90 (OCH_3), 65.40 (C-6), 78.53 (C-4), 86.73 (C-5), 109.26, 109.99 (C-1, $C(CH_3)_2$), 181.77 (C-8); MS, *m/e* 256 (M^+), 241 ($M^+ - CH_3$), 225 ($M^+ - OCH_3$); HRMS calcd for $C_{13}H_{20}O_5$ (M^+) 256.1311, obsd 256.1272 (Δppm = 15).

Methyl 5,6-*O*-Isopropylidene-2,3-*C*-((2*S*)-2-hydroxypropane-1,3-diyl)-2,3-dideoxy-α,β-D-talofuranoside (17a). The ketone **16** (0.085 g, 0.33 mmol) was dissolved in dry dimethoxyethane (20 mL) and cooled to −40 °C. Lithium aluminum hydride (0.004 g, 0.11 mmol) was added, and the solution was stirred at −40 °C for 1 h, at which time the reaction mixture was quenched with hydrated sodium sulfate. After diluting with methylene chloride (40 mL), the reaction mixture was filtered and evporated to yield a clear syrup that consisted of **17a** with <2% of **18a**. The syrup (0.071 g, 83%) displayed the following characteristics: TLC R_f 0.11 (solvent A); GLC retention times, 5.0 min. (**17a**), 5.25 min. (**18a**), ultra bond, 70 °C/4 min, 8 °C/min to 250 °C; IR (neat) 3450, 1375, 1210, 1065, 980 cm^{-1}; ^{1}H NMR (100 MHz) ($CDCl_3$) δ 1.35 (s, 3, $C(CH_3)_2$), 1.45 (s, 3, $C(CH_3)_2$), 1.50–1.82 (m, 4), 1.88–2.80 (m, 4), 3.35 (s, 3, OCH_3), 3.50–3.75 (m, 1, H-4), 3.90–4.31 (m, 3, H-5,6,6′), 4.88 (s, 1, H-1); ^{13}C NMR (80 MHz) ($CDCl_3$) δ 25.08 ($C(CH_3)_2$), 26.59 ($C(CH_3)_2$), 39.10, 41.59 (C-7,9), 42.51 (C-3), 49.91 (C-2), 54.53 (OCH_3), 65.89 (C-6), 74.02 (C-8), 78.76 (C-4), 89.57 (C-5), 109.55 (C-1), 111.68 ($C(CH_3)_2$); MS, *m/e* 243 ($M^+ - CH_3$), 227 ($M^+ - OCH_3$), 226 ($M^+ - 1 - OCH_3$), HRMS calcd for $C_{11}H_{16}O_4$ ($M^+ - CH_3 - OCH_3$) 212.1049, found 212.1056 (Δppm = 3.6).

Methyl 5,6-*O*-Isopropylidene-2,3-*C*-((2*R*)-2-hydroxypropane-1,3-diyl)-2,3-dideoxy-α,β-D-talofuranoside (18a). The mixture of **17a** and **18a** (0.0715 g, 0.28 mmol) was dissolved in dry methylene chloride (5 mL) and cooled to 0 °C. Pyridine (10 mL) and methanesulfonyl chloride (0.5 mL, 6.5 mmol) were added and the reaction solution was stirred at 0 °C for 3 h. Standard processing of the reaction mixture yielded the sulfonate **17b**, predominantly, as a somewhat unstable amber oil (0.0841 g, 90%), which displayed the following characteristics: TLC R_f 0.19 (solvent A); ^{1}H NMR (100 MHz) ($CDCl_3$) δ 1.35 (s, 3, $C(CH_3)_2$), 1.45 (s, 3, $C(CH_3)_2$), 1.77–2.75 (m, 6, H-2,3,7,7′,9,9′), 3.00 (s, 3, SO_2*Me*), 3.37 (s, 3, OCH_3), 3.50–3.75 (m, 1, H-4), 3.80–4.25 (m, 3, H-5,6,6′), 4.88 (s, 1, H-1), 5.05 (m, 1, H-8). The sulfonate **17b** was dissolved in dry dimethylformamide (20 mL), sodium benzoate (0.5 g, 3.5 mmol) was

added, and the resultant suspension was stirred at 75 °C under argon. After 9 h, the reaction mixture was poured into water, extracted with diethyl ether, and processed in the usual way to yield the benzoate mixture as a pale yellow oil (0.087 g, 89%): chromatographic purification PTLC (solvent A); IR (neat), ν_{max} 2970, 1725, 1450, 1270, 710 cm^{-1}; ^1H NMR (100 MHz) ($CDCl_3$) δ 1.38 (s, 3, $C(CH_3)_2$), 1.5 (s, 3, $C(CH_3)$), 1.70–2.4 (m, 4), 2.50–2.75 (m, 1), 2.77–3.10 (m, 1), 3.40 (s, 3, OCH_3), 3.58–4.38 (m, 4, H-4,5,6,6'), 4.88 (s, 1, H-1), 5.55 (m, 1, H-8), 7.50, 8.05 (2m, 5, O_2CPh); ^{13}C NMR (80 MHz) ($CDCl_3$) δ 25.32 ($C(CH_3)_2$), 26.85 ($C(CH_3)_2$), 36.07, 39.22 (C-7,9), 42.81 (C-3), 50.56 (C-2), 54.66 (OCH_3), 66.00 (C-6), 78.07 (C-8), 79.10 (C-4), 89.41 (C-5), 128.49, 129.66, 130.61 (O_2CPh), 166.17 (O_2CPh); MS, *m/e* 347 ($M^+ - CH_3$), 331 ($M^+ - OCH_3$).

The benzoate **18b** (0.010 g, 0.03 mmol) was dissolved in dry methanol (10 mL), a trace of sodium methoxide was added and the solution was stirred at room temperature for 18 h. The reaction solution was evaporated and the resulting salts extracted with methylene chloride. The extract was evaporated to yield a clear syrup that contained as the major product a 25:1 mixture of **18a** and **17a**. This syrup displayed the following characteristics: TLC R_f 0.11 (solvent A); GLC retention time 5.0 min (**17a**), 5.25 min (**18a**), ultra bond, 70 °C/4 min, 8 °C/min up to 250 °C; ^1H NMR (80 MHz), ($CDCl_3$) δ 1.35 (s, 3, $C(CH_3)_2$), 1.45 (s, 3, $C(CH_3)_2$), 1.50–2.10 (m, 5), 2.20–2.95 (m, 3), 3.35 (s, 3, OCH_3), 3.50–4.50 (m, 4, H-4,5,6,6'), 4.79 (s, 1, H-1); ^{13}C NMR (80 MHz) ($CDCl_3$) δ 25.20 ($C(CH_3)_2$), 26.81 ($C(CH_3)_2$), 39.02, 42.10 (C-7,9), 42.68 (C-3), 49.93 (C-2), 54.54 (OCH_3), 66.02 (C-6), 74.22 (C-8), 79.12 (C-4), 89.51 (C-5), 109.71 (C-1), 111.24 ($C(CH_3)_2$).

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Oxygen Chiral Phosphate in Uridylyl(3′→5′)adenosine by Oxidation of a Phosphite Intermediate: Synthesis and Absolute Configuration†

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Abstract: Coupling of 2′,5′-silylated uridine and 2′,3′-silylated N^6-benzoyladenosine with dichloromethoxyphosphine furnished dinucleoside monophosphite triesters. Oxidation of these intermediates with $[^{17}O,^{18}O]H_2O$ and iodine afforded the diastereoisomeric phosphate triesters of fully protected $[^{17}O,^{18}O]$UpA having the oxygen labels in the P=O group. The diastereoisomeric mixture of major and minor components was separated by column chromatography. Stereospecific cleavage of the phosphate protecting group by thiophenolate followed by desilylation with $(Bu)_4NF$ yielded the oxygen chiral isotopomers of $[^{17}O,^{18}O]$UpA. The incorporation of ^{17}O was demonstrated by ^{17}O NMR spectroscopy and of ^{18}O by ^{31}P NMR spectroscopy. Hydrolysis of the major isotopomer with nuclease P1 in $[^{17}O,^{18}O]H_2O$ with inversion of configuration at phosphorus yielded $[^{16}O,^{17}O,^{18}O]$AMP. This was converted into the isotopomers of the respective cyclic 3′,5′-phosphate with inversion of configuration. Methylation of the latter followed by ^{31}P NMR spectroscopy established the absolute isotopic configuration of the $[^{16}O,^{17}O,^{18}O]$AMP as S_p. The absolute configurations of the diastereoisomeric triesters from the phosphite oxidation are therefore assigned as S_p for the major isomer and R_p for the minor isomer. Consequently, the resulting deprotected isotopomers of $[^{17}O,^{18}O]$UpA have the opposite R_p and S_p configurations, respectively. Methylation of (R_p)-$[^{17}O,^{18}O]$UpA gave two diastereoisomeric triesters whose absolute configurations were established by inspection of the ^{18}O isotope shifts on phosphorus in the ^{31}P NMR spectrum. An unknown absolute isotopic configuration of $[^{18}O]$UpA can now be determined by methylation and subsequent ^{31}P NMR spectroscopy.

The elucidation of the stereochemical course of action of many nucleotide and polynucleotide processing enzymes has been accomplished to a large extent by the use of phosphorothioate analogues.[2-5] More recently, considerable advances have been made in the study of this type of reaction by the use of some or all of the three stable isotopes of oxygen, ^{16}O, ^{17}O, and ^{18}O, for the synthesis of stereospecifically labeled phosphate esters.[6-8] Syntheses of oxygen chiral $[^{16}O,^{17}O,^{18}O]$phosphate monoesters and their configurational assignments have been described by Lowe et al.[6] and by Knowles and associates,[7] and these compounds have since been used for a wide variety of mechanistic studies in the realm of phosphoryl transfer reactions. Interest in this field has also recently centered around the introduction of oxygen isotopes by the stereospecific replacement of sulfur by ^{17}O or ^{18}O.[9]

The analysis of the chirality of oxygen chiral nucleoside monophosphates has been facilitated by the development of a method[10] that depends on the different effects of ^{17}O and ^{18}O in ^{31}P NMR spectroscopy.[11-13] More specifically, a 5′-$[^{16}O,^{17}O,^{18}O]$nucleotide[10a] (which can be obtained by stereospecific enzymic cleavage of an oxygen chiral dinucleoside monophosphate in oxygen isotope enriched water[14]) is converted into the respective

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