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Synthesis of *C*-β-D-Ribofuranosyl Derivatives with a Highly Functionalized Two-Carbon Unit. Conversion to Certain Blocked Thiazole *C*-Nucleosides

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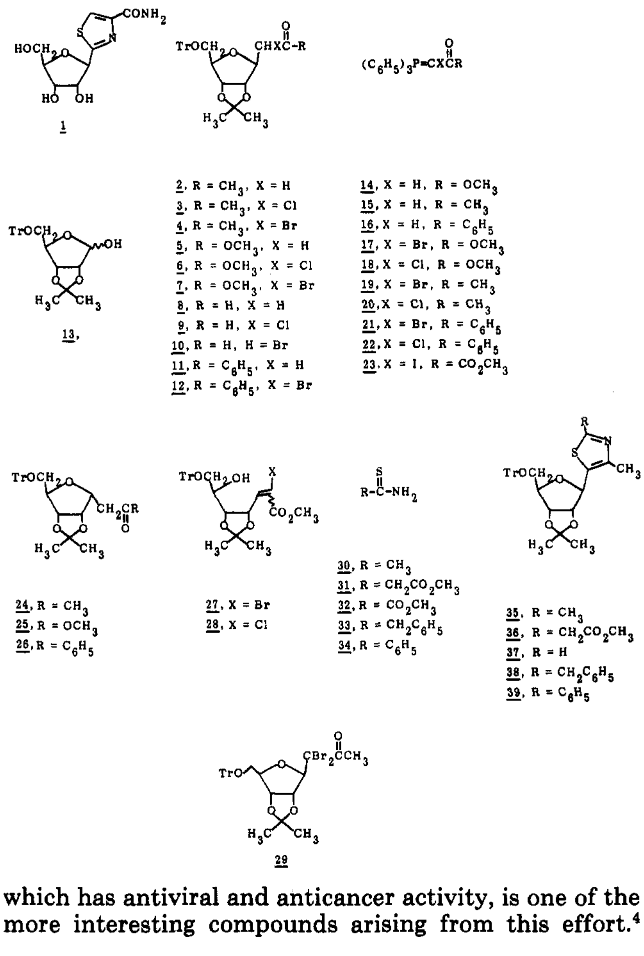
Condensation of halo ylides **17**–**20** with 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (**13**) produced exclusively the *C*-nucleoside precursors **3**, **4**, **6**, and **7**, all with the β configuration. With **17** and **18**, compounds postulated to be the ring-opened derivatives **27** and **28** were the major products formed initially. Treatment of **27** and **28** with a catalytic amount of DBU converted them rapidly to **6** and **7**. Treatment of **3**, **4**, **6**, and **7** with sodium methoxide did not result in the formation of any α isomers. Reduction of halo esters **6** and **7** with diisobutylaluminum hydride at low temperature afforded halo aldehydes **9** and **10**. Treatment of halo ketones **3** and **4** with various thioamides produced the blocked thiazole *C*-nucleosides **35**–**39**.

The biological activity shown by various *C*-nucleosides has provided the impetus for considerable synthetic effort.[2-5] The thiazole *C*-nucleoside tiazofurin (1, Chart I), which has antiviral and anticancer activity, is one of the more interesting compounds arising from this effort.[4]

Chart I



1

13,

2, R = CH_3, X = H
3, R = CH_3, X = Cl
4, R = CH_3, X = Br
5, R = OCH_3, X = H
6, R = OCH_3, X = Cl
7, R = OCH_3, X = Br
8, R = H, X = H
9, R = H, X = Cl
10, R = H, H = Br
11, R = C_6H_5, X = H
12, R = C_6H_5, X = Br

$(C_6H_5)_3P{=}CX\overset{O}{\overset{\|}{C}}R$

14, X = H, R = OCH_3
15, X = H, R = CH_3
16, X = H, R = C_6H_5
17, X = Br, R = OCH_3
18, X = Cl, R = OCH_3
19, X = Br, R = CH_3
20, X = Cl, R = CH_3
21, X = Br, R = C_6H_5
22, X = Cl, R = C_6H_5
23, X = I, R = CO_2CH_3

24, R = CH_3
25, R = OCH_3
26, R = C_6H_5

27, X = Br
28, X = Cl

$R{-}\overset{S}{\overset{\|}{C}}{-}NH_2$

30, R = CH_3
31, R = $CH_2CO_2CH_3$
32, R = CO_2CH_3
33, R = $CH_2C_6H_5$
34, R = C_6H_5

35, R = CH_3
36, R = $CH_2CO_2CH_3$
37, R = H
38, R = $CH_2C_6H_5$
39, R = C_6H_5

29

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(1) (a) Abstracted from the Ph.D. dissertation of M.C.C., The Ohio State University, 1979; *Diss. Abstr. B* **1980**, 3164–3165. (b) To whom correspondence should be addressed at the Southern Research Institute, P.O. Box 55305, Birmingham, AL 35255-5305.

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Although synthetic efforts have taken many forms, the most useful general approach seems to be the attachment of a highly functionalized one to three carbon unit to C-1 of a ribose derivative.[2a] This unit, ideally exclusively in the β configuration, is then elaborated to various heterocyclic ring systems. In this paper we report the syntheses of the C-1 C-functionalized β-D-ribofuranosyl compounds **3**, **4**, **6**, **7**, **9**, and **10**, which were obtained exclusively in the β configuration. As an example of their potential utility, we have converted **3** and **4** to several blocked thiazole *C*-nucleosides by condensation with certain thioamides.

Our synthetic approach was to condense 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (**13**)[6] with various ylides. This approach was initially reported in the condensation of **13** with ylide **14**,[7] which produced a mixture of the altro (α) and allo (β)[8] isomers of **5**[9]. We wanted to prepare the C-1 C derivatives **2**, **5**, and **11** and then halogenate them to produce the desired α-halo compounds. Condensation of **13** with **15**[10] afforded a 90% yield of a 1:1 α/β mixture of **2** and **24**. Condensation of **13** with **16**[10,11] was not nearly as facile, requiring a longer reaction time to achieve a 70–75% yield of a 1:1 α/β mixture of **11** and **26**. Separation of the diastereoisomers was achieved chromatographically.

Assignment of anomeric configurations for all compounds prepared was based mainly on ^{13}C NMR data[2t,9a,12] supplemented by ^{1}H NMR data.[13] The chemical shifts of the methyl carbons and the quaternary carbon of the isopropylidene group fall into the established regions for α and β anomers,[2t,9a] and the $\Delta\delta$ values for the methyls also fit the pattern established.[2t,12] Basic equilibration of **2**/**24** demonstrates the α isomer to predominate by a ratio of 4:1 at equilibrium. With **11**/**26** the equilibrium ratio favors **26** by a ca. 7:1 ratio. Earlier, it had been found that **5**/**25** equilibrates under basic conditions to a mixture favoring **25** by a 5:2 ratio.[9a] A rationalization for these results has been presented.[14]

Initially, we had hoped to prepare **7** and **12** by the halogenation of **5** and **11**. Examination of a variety of conditions, however, uncovered none that were satisfactory. We then attempted the condensation of ylides already containing the halogen with **13**. Ylides **17**–**22** are known compounds, prepared in one step from the appropriate unhalogenated ylides.[15–18] Literature reports, however, only present the condensation of these ylides with structurally simple or activated aldehydes.[11,15–18]

Condensation of **17** with **13** produced three products. Two of these were faster moving by TLC than **13** and quite similar in mobility, and the third, which was the major product, had a much lower mobility. After some experimentation, it was found that the addition of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the cooled reaction mixture caused the loss of this slower material with a concomitant increase in the amounts of the two faster-moving compounds. These two compounds were separated chromatographically, and both had the characteristics of the desired compound **7**. Examination of the ^{13}C NMR spectra indicated clearly that both compounds had the β configuration and thus were diastereomeric only at the carbon bearing bromine. Isolated yields of the two compounds were routinely 85–90%, with no trace of α isomers. We suggest that the slower moving material is probably **27**, the ring-opened form of **7**, which closes to form **7** in the presence of DBU.

Treatment of **13** with the chloro ylide **18** likewise produced three products, the one of slower chromatographic mobility (probably **28**) again being converted to the other two upon addition of DBU to the cooled reaction mixture. These two products, isolated as a 1:1 mixture in 85–90% yield, were the two diastereomeric β isomers **6**.

The course of the reaction of **13** with the bromo ylide **19** proved to be somewhat different than the ester ylides. After the disappearance of starting material, no band corresponding to a ring-opened compound comparable to **27** was seen, but rather two faster moving bands were seen, the more polar of which was rather broad. This latter band proved to be a roughly 1:1 mixture of the two diastereomeric β isomers **4**, which could be isolated in yields ranging from 40% to 48%.

The faster band, isolated in 15–20% yield, was identified as **29**. In the ^{1}H NMR **29** contained only a single set of isopropylidene methyl signals, and the acetyl methyl signal occurred at δ 2.62, approximately 0.2 ppm downfield from the two acetyl signals of the **4** mixture. Mass spectral evidence confirmed the identity of this compound.

The formation of **29** is apparently made possible by the decomposition of the bromo ylide **19**. Although the decomposition of this ylide is not mentioned in the literature, the iodo ylide **23** is unstable,[17,19] decomposing to iodine and other unspecified products upon attempted reaction with aldehydes. If **19** followed a similar decomposition pathway to yield bromine, bromination of **4** would produce **29**.

Condensation of **13** with **20** proceeded smoothly to produce a 3:2 mixture of the two diastereomeric β isomers **3**. Although some decomposition of **20** was noted, it was not significant during the time needed for complete loss of **13**. No dichloro compound corresponding to **29** was noted.

Attempted condensation of either benzoylhalomethylene ylide **21** or **22** with **13** under a variety of conditions resulted in decomposition of the ylide, **13**, or both.[20] Apparently

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(20) Efforts included utilization of a wide range of temperatures and concentrations in dichloromethane, acetonitrile, benzene, chloroform, toluene, and *N,N*-dimethylformamide. Direct fusion was also examined. Extensive decomposition of the ylide occurred above 50 °C, and at higher temperature this brought about decomposition of 13.

the decreased reactivity of **21** and **22** relative to **19** and **20** is sufficient to prevent reaction with **13** prior to decomposition.

In concurrent research, we developed a synthesis of aldehyde **8** by reduction of **5** with diisobutylaluminum hydride.[2t] Aldehyde **8** was then converted in several steps to bromo aldehyde **10**. Application of this reduction to esters **6** and **7** would produce halo aldehydes **9** and **10**, with **10** being produced in fewer steps than required by our other method. Utilization of the conditions employed successfully with **5**, however, resulted in overreduction of the ester and reductive dehalogenation. Good yields of both **9** (63%) and **10** (50%) were obtained by cooling both the solution of the ester and the diisobutylaluminum hydride to −100 to −90 °C followed by rapid addition of the hydride and quenching. Both **9** and **10** retained the β configuration exclusively during the reduction. The overall yield of **10** by this method is slightly greater than by our earlier method.

Attempted equilibration of **3**, **4**, **6**, **7**, **9**, and **10** in the same manner as with the esters **5** and **25** with methoxide in methanol[9a] resulted in no α isomer being formed. Both esters **6** and **7** were partially converted to the ring-opened compounds **27** and **28**. Under these conditions the bromo compounds decomposed significantly (ca. 50%) over 48 h at room temperature, while the chloro compounds did not reach this state of decomposition for at least 5 or 6 days. Thus, it appears that the size of the halogens increases the steric interactions in the α isomers to such an extent as to prevent their formation.

To illustrate the potential utility of the highly functionalized *C*-nucleoside precursors, we have prepared some blocked thiazole *C*-nucleosides by condensation of **3** and **4** with various thioamides. Utilizing conditions similar to those that we employed successfully with **10**,[2t] thiazoles **35**–**39** were prepared in 24–65% yields. For example, treatment of **4** with phenylthioacetamide (**33**) produced **38** in 60% yield. In general, under the conditions used, the bromo ketone **4** produced higher yields than the chloro ketone **3**, although the preparation of **36** was an exception. The reaction of methyl 2-thioxooxamate (**32**) with either **3** or **4** required quite vigorous conditions. The only thiazole product formed proved to be **37**, which exhibited a new thiazole ring proton at δ 8.66 in the ^1H NMR, as well as the absence of an ester signal in either the IR or NMR spectra. Apparently, under the conditions required to form a thiazole, decarbomethoxylation occurs. The ready loss of a carbomethoxy group in the 2-position of thiazole rings is well documented by initial conversion to carboxylic acid and then decarboxylation.[21] Examination of the ^1H and ^{13}C NMR spectra of the blocked thiazole *C*-nucleosides and application of the criteria mentioned earlier yields the information that all of the *C*-nucleosides are in the expected β configuration.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 sodium chloride spectrophotometer or a Perkin-Elmer 467 grating spectrophotometer. The spectra were calibrated against the polystyrene absorption peak at 1601 cm^{-1}. Only selected absorptions are given. ^1H NMR spectra were recorded on a Varian EM-360 and ^{13}C NMR spectra on a Bruker WP-80. Selected chemical shifts in $CDCl_3$ are reported in parts per million downfield from internal tetramethylsilane. Complete NMR data are available in the supplementary material. Mass spectra were measured on an AEI/MS9 spectrometer at 70 eV, and only selected fragmentations are given. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a 1-dm tube. Concentrations are given in g/100 mL. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Acetonitrile was predried over 4-Å molecular sieves, distilled from phosphorus pentoxide, and stored over 4-Å molecular sieves. Benzene was distilled from calcium hydride and stored over 4-Å molecular sieves. Hexamethylphosphoramide was distilled under reduced pressure from calcium hydride and stored frozen at −10 °C.

Thin-layer chromatography was performed with precoated TLC plates (silica gel F-254, 0.25-mm thickness) from EM Laboratories, Inc. Thick-layer chromatography was carried out on glass plates (20 × 20 cm) coated to a 2-mm thickness with 30 g of silica gel 60 PF-254 (EM Laboratories, Inc.) with 8 g of calcium sulfate as a binder. The solvent systems used (v/v) were as follows: A, 2:1 petroleum ether (30–60 °C)/ether; B, 1:1 petroleum ether (30–60 °C)/ether; C, 9:1 petroleum ether (30–60 °C)/ether; D, 95:5 chloroform/methanol; E, 4:1 chloroform/methanol.

4,7-Anhydro-1,3-dideoxy-5,6-*O*-isopropylidene-8-*O*-trityl-D-*allo*- and -*altro*-oct-2-ulose (2 and 24). To a solution of **13** (200 mg, 0.46 mmol) in 1 mL of toluene was added 1-(triphenylphosphoranylidene)-2-propanone (**15**; 180 mg, 0.56 mmol). The resultant light-yellow solution was heated at reflux for 3 h. TLC (solvent A) showed two new spots (R_f 0.45, 0.34) of approximately equal intensity. The solution was poured with stirring into 25 mL of solvent A and allowed to stand 1 h, during which time a precipitate separated. The solution was poured, with suction, through a plug of 5 g of silica gel. The silica was then washed two times with 10 mL of solvent A. The solution was reduced in vacuo to a slightly yellow, thick syrup consisting, by TLC, of the two new compounds. This syrup was purified further by thick-layer chromatography with two elutions in solvent A. The faster band, **24**, yielded 90 mg (41.5%) of product and the slower, **2**, 100 mg (46%) of product, for a net yield of 87.6%. Both pure compounds were colorless foams: IR (neat) cm^{-1} 1720; mass spectrum, calcd *m/e* 472.2249 (M^+), found *m/e* 472.2260, *m/e* 472 (M^+), 457 ($M^+ - CH_3$), 442 ($M^+ - 2CH_3$), 414 ($M^+ - C_3H_6O$), 395 ($M^+ - C_6H_5$), 243 (Tr^+). For **2**: $[\alpha]^{21}{}_D$ +2° (*c* 0.90, $CHCl_3$); ^1H NMR δ 1.31, 1.51 (2 s, 6, $C(CH_3)_2$), 2.14 ($COCH_3$), 2.73 (m, 2, CH_2CO); ^{13}C NMR δ 25.67, 27.55 ($C(CH_3)_2$), 30.71 ($COCH_3$), 47.52 (CH_2CO), 80.71, 82.35, 83.56, 84.66 (C_1–C_4), 114.39 ($C(CH_3)_2$), 206.03 (C=O). For **24**: $[\alpha]^{26}{}_D$ +3° (*c* 1.10, $CHCl_3$); ^1H NMR δ 1.28, 1.45 (2 s, 6, $C(CH_3)_2$), 2.15 (s, 3, $COCH_3$), 2.88 (m, 2, CH_2CO); ^{13}C NMR δ 25.06, 26.28 ($C(CH_3)_2$), 30.53 ($COCH_3$), 43.75 (CH_2CO), 77.68, 81.74, 83.20, 83.38 (C_1–C_4), 112.27 ($C(CH_3)_2$), 206.39 (C=O). Anal. Calcd for $C_{30}H_{32}O_5$ (**2** + **24** mixture): C, 76.24; H, 6.83. Found: C, 76.11; H, 6.87.

(3ξ)-4,7-Anhydro-1,3-dideoxy-3-chloro-5,6-*O*-isopropylidene-8-*O*-trityl-D-*allo*-oct-2-ulose (3). To a solution of **13** (1.00 g, 2.82 mmol) in 14 mL of toluene was added 1-chloro-1-(triphenylphosphoranylidene)-2-propanone (**20**; 1.99 g, 5.64 mmol) and the solution brought to reflux. After 3 h of reflux, the clear, yellow solution was poured into 75 mL of solvent A and allowed to stand for several hours. The solution was decanted from the precipitate and suction filtered through 25 g of silica gel. The silica was washed rapidly, with suction, four times with 25 mL of ether. The combined solutions were evaporated in vacuo to yield **3** as a light-yellow foam, homogeneous by TLC (R_f 0.68 in A). This material was sufficiently pure for further transformations. Analytical samples were prepared by thick-layer chromatography in solvent A. Despite multiple elutions, the diastereomers were not separated: IR 1720 cm^{-1}; $[\alpha]^{23}{}_D$ −6°, (*c* 6.20, $CHCl_3$); mass spectrum, calcd for $^{35}ClM^+$ *m/e* 506.1860, found *m/e* 506.1869, *m/e* 508, 506 (M^+), 493, 491 ($M^+ - CH_3$), 478, 476 ($M^+ - 2CH_3$), 470 ($M^+ - HCl$), 431, 429 ($M^+ - C_6H_5$); ^1H NMR δ 1.32, 1.51 (2 s, 6, $C(CH_3)_2$), 2.22, 2.33 (2 s, 3, $COCH_3$), 4.45 (m, 1, CHCl); ^{13}C NMR δ 25.61, 27.43, 27.73 ($C(CH_3)_2$), 26.58 ($COCH_3$), 62.20, 64.27 (CHCl), 114.27, 114.70 ($C(CH_3)_2$), 200.51, 202.27 (C=O). Anal. Calcd for $C_{30}H_{31}ClO_5$: C, 71.06; H, 6.16. Found: C, 70.95; H, 6.29.

(3ξ)-4,7-Anhydro-1,3-dideoxy-3-bromo-5,6-*O*-isopropylidene-8-*O*-trityl-D-*allo*-oct-2-ulose (4) and 4,7-Anhydro-1,3-dideoxy-3,3-dibromo-5,6-*O*-isopropylidene-8-*O*-

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[21] Meyer, R. In "The Chemistry of Heterocyclic Compounds"; Metzger, J. V., Ed.; Wiley: New York, 1979; Vol. 34, Chapter IV, Part 1.

trityl-D-*allo*-oct-2-ulose (29). To a solution of **13** (1.25 g, 2.90 mmol) in 6 mL of toluene was added 1-bromo-1-(triphenylphosphoranylidene)-2-propanone (**19**; 3.46 g, 8.7 mmol), and the solution was brought to reflux. After 1 h of reflux, the solution severely darkened, and a tarry residue appeared. After 3 h, the solution was cooled and poured into 100 mL of solvent A, and this solution was filtered with suction through 30 g of silica gel. The silica was then washed four times with 25 mL of ether. The combined solutions were reduced in vacuo, and the resultant thick, syrupy material was purified by thick-layer chromatography in solvent B. The three major bands in order of elution were the dibromide **29** (320 mg, 18%; R_f 0.85), the mono bromo ketone **4** (770 mg, 48%; R_f 0.78), and residual **13** (180 mg, 14%; R_f 0.55). The products were colorless foams. The isomers of **4** could not be separated.

4: IR 1730 cm^{-1}; $[\alpha]^{24}{}_D$ +1°, (*c* 1.10, $CHCl_3$) (both isomers); mass spectrum, calcd for $^{79}BrM^+$ *m/e* 550.1355, found *m/e* 550.1368, *m/e* 552, 550(M^+), 537, 535 ($M^+ - CH_3$), 522, 520 ($M^+ - 2CH_3$), 475, 473 ($M^+ - C_6H_5$), 471 ($M^+ - Br$), 243 (Tr^+); ^1H NMR δ 1.31, 1.34, 1.51, 1.54 (4 s, 6, $C(CH_3)_2$), 2.25, 2.35 (2 s, 3, $COCH_3$), 4.50 (m, 1, CHBr); ^{13}C NMR δ 25.52, 27.40, 27.71 ($C(\mathit{C}H_3)_2$), 26.13 ($CO\mathit{C}H_3$), 51.86, 54.59 (CHBr), 114.01, 114.49 ($\mathit{C}(CH_3)_2$), 199.69, 200.85 ($\mathit{C}OCH_3$). Anal. Calcd for $C_{30}H_{31}O_5Br$: C, 65.33; H, 5.67. Found: C, 65.33; H, 5.62.

29: IR 1720 cm^{-1}; $[\alpha]_D{}^{26}$ +5° (*c* 1.12, $CHCl_3$); mass spectrum, calcd for $^{79}Br^{81}BrM^+$ *m/e* 630.0441, found *m/e* 630.0457 (for brevity, only the central peak of the characteristic dibromo multiplets will be given), *m/e* 630 (M^+), 615 ($M^+ - CH_3$), 553 ($M^+ - C_6H_5$), 551, 549 ($M^+ - Br$), 243 (Tr^+); ^1H NMR δ 1.34, 1.54 (2 s, 6, $C(CH_3)_2$), 2.62 (s, 3, $COCH_3$); ^{13}C NMR δ 25.67, 27.55 ($C(\mathit{C}H_3)_2$), 24.33 ($CO\mathit{C}H_3$), 69.49 (CBr_2), 114.70 ($\mathit{C}(CH_3)_2$), 193.83 (C═O).

Methyl (2ξ)-3,6-Anhydro-2-deoxy-2-chloro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptonate (6). To a solution of **13** (390 mg, 0.9 mmol) in 2 mL of toluene was added methyl chloro(triphenylphosphoranylidene)acetate (**18**; 400 mg, 1.08 mmol), and the solution was heated to reflux. After 45 min, the light-yellow solution was cooled to room temperature. TLC (solvent A) showed no starting material, but three new bands were present at R_f 0.73, 0.67, and 0.37, with the two less polar bands being by far the more abundant. A trace of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added to the cooled reaction mixture, which was then stirred for ca. 1 min. TLC showed disappearance of the most polar compound while the less polar compounds remained. The solution was then poured into 75 mL of solvent A, and this solution was poured rapidly, with suction, through 25 g of silica gel. The silica was then washed three times with 25 mL of solvent B, and the combined solutions were evaporated in vacuo to a light-yellow foam, consisting of the two isomers of **6** (440 mg, 93.7%). These compounds can be separated, if desired, by thick-layer chromatography in solvent A, after two elutions. All data except rotations are for the mixture: IR 1760 cm^{-1}; faster isomer $[\alpha]_D{}^{28}$ +7° (*c* 2.66, $CHCl_3$), slower isomer $[\alpha]_D{}^{28}$ +8° (*c* 5.00, $CHCl_3$); mass spectrum, calcd *m/e* 522.5531, found for $^{35}ClM^+$ *m/e* 522.5542, *m/e* 524, 522 (M^+), 507 ($M^+ - CH_3$), 447 ($^{35}ClM^+ - C_6H_5$), 445 ($^{35}ClM^+ - C_6H_5$), 243 (Tr^+); ^1H NMR δ 1.32, 1.53 (2 s, 6, $C(CH_3)_2$), 3.67, 3.72 (2 s, 3, OCH_3), 4.45 (m, 1, CHCl); ^{13}C NMR δ 25.63, 27.43, 27,53 ($C(\mathit{C}H_3)_2$), 53.06 (OCH_3), 56.17, 56.95 (CHBr), 114.09, 114.43 ($\mathit{C}(CH_3)_2$), 167.88, 168.17 (C═O). Anal. Calcd for $C_{30}H_{31}ClO_6$ (both isomers): C, 68.89; H, 5.98. Found: C, 69.17; H, 6.29.

Methyl (2ξ)-3,6-Anhydro-2-deoxy-2-bromo-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptonate (7). To a solution of **13** (1.32 g, 3.05 mmol) in 4.5 mL of benzene was added methyl bromo(triphenylphosphoranylidene)acetate (**17**: 1.86 g, 4.5 mmol), and the solution was heated to reflux. After 7 h, TLC indicated the disappearance of **13** and the appearance of three new products with R_f 0.70, 0.60, and 0.40 (solvent A). The slowest moving material was by far the most intense by UV analysis. The reaction mixture was cooled to room temperature and 1 drop of DBU was added. After the mixture was stirred 1 min at room temperature, TLC indicated that only the faster moving two bands were present. The light-yellow reaction mixture was poured into 100 mL of solvent A and filtered, with suction, through 20 g of silica gel. The silica was washed four times with 25 mL of solvent B and the combined filtrates were evaporated to a thick, yellow syrup, containing 1.52 g (88%) of the two isomers of **7** in high purity. The isomers were separable by thick-layer chromatography in solvent A (two elutions). All data except rotations are for the mixture: IR (neat) 1755 cm^{-1}; faster isomer $[\alpha]_D{}^{26}$ −1° (*c* 1.75, $CHCl_3$), slower isomer $[\alpha]_D{}^{26}$ +20° (*c* 3.18, $CHCl_3$); mass spectrum calcd for $^{79}BrM^+$ *m/e* 566.4302, found for $^{79}BrM^+$ *m/e* 566.4314, *m/e* 568, 566 (M^+), 553, 551 ($M^+ - CH_3$), 538, 536 ($M^+ - 2CH_3$), 491, 489 ($M^+ - C_6H_5$), 243 (Tr^+); ^1H NMR δ 1.37, 1.56 (2 s, 6, $C(CH_3)_2$), 3.75 (s, 3, OCH_3), 4.55 (m, 1, CHBr); ^{13}C NMR δ 25.63, 25.68, 27.43 ($C(\mathit{C}H_3)_2$), 44.47, 44.59 (CHBr), 53.06, 53.09 (OCH_3), 113.94, 114.36 ($\mathit{C}(CH_3)_2$), 168.56, 168.22 (C═O). Anal. Calcd for $C_{30}H_{31}BrO_6$: C, 63.49; H, 5.51. Found (faster isomer): C, 63.31; H, 5.68. Found (slower isomer): C, 63.31; H, 5.56.

Reduction of the Esters 6 and 7 to the Aldehydes 9 and 10. Compounds **9** and **10** were made from the esters **6** and **7** by a procedure similar to that published for the ester **5**.[2t] Two dry 25-mL three-necked flasks were equipped with spin bars, two septa, and one nitrogen inlet each and filled with a nitrogen atmosphere. One flask was charged with a ca. 0.25 M solution of the ester in dry toluene. The other was charged with 2 equiv of 0.907 M diisobutylaluminum hydride (DIBAL-H) in heptane. Both flasks were cooled to −100 °C and allowed to stir. The DIBAL-H was rapidly transferred into the solution through a cannula by increasing the pressure of the nitrogen atmosphere. In each case the reaction was complete after 5 min. Excess DIBAL-H was quenched by the addition of excess dry methanol, also cooled to −90 °C. The reaction mixtures were then allowed to warm to room temperature, whereupon a gelatinous mass was observed. These masses were filtered off (Celite pad) and washed with ether. The resultant filtrates were evaporated in vacuo, placed on a thick-layer plate, and eluted with solvent B. In each case, the reaction mixture was complex, but the major band proved to be the expected aldehyde. Quantities and physical data for **9** and **10** are given below.

(2ξ)-3,6-Anhydro-2-deoxy-2-chloro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptose (9). Compound **6** (520 mg, 1 mmol) was dissolved in 4 mL of dry toluene and introduced to the reaction flask. The reagent flask was charged with 2 mL of DIBAL-H, and the reaction and workup were carried out as outlined. The yield was 310 mg (63%). The isomers (at C-2) could not be separated: IR 1740 (cm^{-1}; both diastereomers, $[\alpha]_D{}^{28}$ +1° (*c* 2.5, $CHCl_3$); mass spectrum, *m/e* 492.1703 ($^{35}ClM^+$), found *m/e* 492.1716, *m/e* 494, 492 (M^+), 479, 477 ($M^+ - CH_3$), 456 ($M^+ - HCl$), 417, 415 ($M^+ - C_6H_5$), 243 (Tr^+); ^1H NMR δ 1.32, 1.50 (2 s, 6, $C(Ch_3)_2$), 4.50 (m, 2, CHCl), 9.48, 9.59 (2 s, 1, CHO); ^{13}C NMR δ 25.59, 27.44, 27.53 ($C(\mathit{C}H_3)_2$), 62.36, 64.21 (CHCl), 114.43, 114.82 ($\mathit{C}(CH_3)_2$), 192.72, 194.23 (CHO). Although this compound was homogeneous by TLC, we were unable to obtain proper microanalytical data for it.

(2ξ)-3,6-Anhydro-2-deoxy-2-bromo-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptose (10). Compound **7** (640 mg, 1.13 mmol) was dissolved in 5 mL of dry toluene and injected into the reaction flask. The DIBAL-H (2 equiv) was added, and the reaction mixture was worked up as above. The isolated yield from the plate was 300 mg (50%). The compound was identical in every respect with an authentic sample.[2t] The isomers (at C-2) could not be separated.

2,5-Anhydro-1-*C*-benzoyl-1-deoxy-3,4-*O*-isopropylidene-6-*O*-trityl-D-*allo*- and -*altro*-hexofuranose (11 and 26). To a solution of **13** (490 mg, 1.13 mmol) in 2 mL of toluene was added 1-phenyl-2-(triphenylphosphoranylidene)ethanone (**16**; 520 mg, 1.36 mmol), and the solution was heated to reflux (the ylide did not completely dissolve). After 4.5 h, the mixture was poured with stirring into 50 mL of solvent A and allowed to stand 1 h. The solution was decanted from the precipitate, placed on a short chromatography column (30 g of 70–230 mesh silica gel), and eluted with solvent A. Evaporation of the eluent yielded a clear, colorless foam (510 mg, 84%) shown by TLC (R_f 0.75, 0.70) to consist of two compounds, **11** and **26**. Separation of these isomers required thick-layer chromatography with four elutions with solvent A. Thus, 230 mg of **26** and 260 mg of **11** were isolated as colorless foams: IR (neat) 1680 cm^{-1}; mass spectrum, *m/e* 519 ($M^+ - CH_3$), 504 ($M^+ - 2CH_3$), 486 ($M^+ - 2CH_3, H_2O$), 457 ($M^+ - C_6H_5$), 243 (Tr^+). For **11**: $[\alpha]_D{}^{26}$ −3° (*c* 1.30, $CHCl_3$); ^1H NMR δ 1.33, 1.54 (2 s, 6, $C(CH_3)_2$), 3.35 (m, 2, CH_2CO); ^{13}C NMR δ 25.73, 27.55 ($C(\mathit{C}H_3)_2$), 42.60 ($\mathit{C}H_2CO$), 81.08, 82.47, 83,81, 85.08 (C_1–C_4), 114.15 ($C(CH_3)_2$), 197.78 (C=O). For **26**: $[\alpha]_D^{26}$ −18° (*c* 1.21, $CHCl_3$); ^1H NMR δ 1.29, 1.48 (2 s, 6, $C(CH_3)_2$), 3.35 (m, 2, CH_2CO); ^{13}C NMR δ 25.12, 26.40 ($C(CH_3)_2$), 39.02 (CH_2CO), 78.16, 81.81, 83.20, 83.50 (C_1–C_4), 112.27 ($C(CH_3)_2$), 197.78 (C=O). Anal. Calcd for $C_{35}H_{34}O_5$ (**11** and **26** mixture): C, 78.62; H, 6.41. Found: C, 78.86; H, 6.61.

2,4-Dimethyl-5-*C*-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)thiazole (35). From 4. Compound **4** (140 mg, 0.25 mmol) was dissolved in 0.6 mL of HMPA with warming. Thioacetamide (**30**; 60 mg, 0.75 mmol) was added, and the flask was warmed to 70 °C. After 4 h, the starting material was gone as judged by TLC (solvent B), and one new spot was present at R_f 0.30 in solvent B. The reaction mixture was cooled and dissolved in 20 mL of ether. This solution was vigorously shaken with 100 mL of water and separated. The organic layer was then dried over magnesium sulfate, filtered, and evaporated in vacuo to yield 120 mg of a crude, yellowish syrup. This was purified by thick-layer chromatography in solvent B (two elutions) to yield 90 mg (65%) of the clear, colorless foam **35**.

From 3. Compound **3** (410 mg, 0.49 mmol) was dissolved in HMPA (0.55 mL), thioacetamide (**30**; 60 mg, 0.83 mmol) was added, and the flask was warmed to 70 °C. After 29 h, the reaction was halted. The reaction mixture was fairly complex, but there was one major spot at R_f 0.30 in solvent B. This compound was purified after extraction with 80 mL of ether and 50 mL of water, exactly as outlined above. The clear colorless foam (40 mg, 25%) was identical with the product obtained above: $[\alpha]_D^{20}$ −30° (*c* 1.05, $CHCl_3$); mass spectrum, calcd for M^+ *m/e* 527.2130, found *m/e* 527.2137, *m/e* 527 (M^+), 512 ($M^+ - CH_3$), 284 (M^+ − Tr), 243 (Tr^+); ^1H NMR δ 1.30, 1.57 (2 s, 6, $C(CH_3)_2$), 2.39 (s, 3, C_4CH_3), 2.58 (s, 3, C_2CH_3), 5.10 (d, 1, H-1′, $J_{1',2'}$ = 4.5 Hz); ^{13}C NMR δ 15.49 (C_4CH_3), 19.18 (C_2CH_3), 25.68, 27.67 ($C(CH_3)_2$), 114.87 ($C(CH_3)_2$), 164.14 (C_2). Anal. Calcd for $C_{32}H_{33}NO_4S$: C, 72.84; H, 6.30. Found: C, 72.61; H, 6.27.

2-(Carbomethoxymethylene)-4-methyl-5-*C*-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)thiazole (36). From 4. Compound **4** (500 mg, 0.91 mmol) was dissolved with warming in HMPA (4.5 mL), 2-(carbomethoxy)thioacetamide (**31**; 360 mg, 2.72 mmol) was added, and the solution was heated to 70 °C. After 12 h, starting **4** had disappeared, but a rather complex TLC remained, with a spot at R_f 0.27 (solvent B) being major. This solution was partitioned between 25 mL of ether and 100 mL of water and worked up as with **35**. The major band proved to be the expected **36** (160 mg, 30% yield), again a clear, colorless foam.

From 3. Compound **3** (240 mg, 0.47 mmol) was dissolved with warming in HMPA (1.00 mL), thioamide **31** (190 mg, 1.42 mmol) was added, and the solution warmed to 75 °C. After 30 h, the starting **3** had disappeared, and the solution was worked up as above after partitioning between 20 mL of ether and 100 mL of water. The compound (100 mg, 41%) isolated from the thick-layer plate was identical with that formed from **4**: IR 1740 cm^{-1}; $[\alpha]_D^{22}$ −4° (*c* 0.72, $CHCl_3$); mass spectrum, M^+ not seen for this compound, *m/e* 343 (M^+ − Tr + H), 243 (Tr^+); ^1H NMR δ 1.27, 1.55 (2 s, 6, $C(CH_3)_2$), 2.37 (s, 3, C_4CH_3), 3.58 (s, 3, OCH_3), 3.91 (s, 2, CH_2), 5.07 (d, 1, H-1′, $J_{1',2'}$ = 4.5 Hz); ^{13}C NMR δ 15.49 (C_4CH_3), 25.63, 27.62 ($C(CH_3)_2$), 38.89 (CH_2), 52.34 (OCH_3), 114.96 ($C(CH_3)_2$), 159.53 (C_2). Anal. Calcd for $C_{34}H_{35}O_6NS$: C, 69.72; H, 6.02; N, 2.39. Found: C, 69.51; H, 6.30; N, 2.53.

4-Methyl-5-*C*-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)thiazole (37). From 4. Compound **4** (500 mg, 0.91 mmol) was dissolved in 4.5 mL of HMPA, methyl monothiooxamate (**32**; 303 mg, 2.73 mmol) was added, and the solution was heated at 100 °C for 3 h. One new spot was present at R_f 0.45 in ether. The solution was partitioned between 25 mL of ether and 100 mL of water and worked up as with **35** and **36**. The product, a colorless foam, was isolated from the thick-layer plate in 25% yield (120 mg).

From 3. Compound **3** (250 mg, 0.49 mmol) was dissolved with warming in 1.0 mL of HMPA, thioamide **32** (180 mg, 1.47 mmol) was added, and the solution was heated at 110 °C for 8 h. The TLC of the resultant mixture was complex, but there was clearly one major spot. The solution was partitioned between 25 mL of ether and 100 mL of water and the product purified as before. The thiazole (60 mg, 24%) was identical with that obtained from **4**: $[\alpha]_D^{23}$ −18° (*c* 2.19, $CHCl_3$); mass spectrum, calcd for M^+ *m/e* 513.1974, found *m/e* 513.1987, *m/e* 513 (M^+), 498 ($M^+ - CH_3$), 436 ($M^+ - C_6H_5$), 243 (Tr^+); ^1H NMR δ 1.32, 1.60 (2 s, 6, $C(CH_3)_2$), 2.52 (s, 3, C_4CH_3), 5.18 (s, 1, H-1′, $J_{1',2'}$ = 5 Hz), 8.64 (s, 1, H-2); ^{13}C NMR δ 15.63 (C_4CH_3), 25.73, 27.72 ($C(CH_3)_2$), 115.06 ($C(CH_3)_2$, 151.08 (C_2). Anal. Calcd for $C_{31}H_{31}NO_4S$: C, 72.49; H, 6.08; N, 2.72. Found: C, 72.30; H, 6.19; N, 2.73.

2-Benzyl-4-methyl-5-*C*-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)thiazole (38). Compound **4** (200 mg, 0.36 mmol) was dissolved in 1.5 mL of HMPA with warming, (phenylthio)acetamide (**33**; 160 mg, 1.08 mmol) was added, and the solution was heated at 100 °C for 3 h, at which time TLC (solvent A) indicated disappearance of starting **4** and appearance of a new spot at R_f 0.20. The solution was worked up as usual, after partitioning between 20 mL of ether and 100 mL of water. The yield of **38** was 130 mg (60%): $[\alpha]_D^{20}$ −40° (*c* 0.97, $CHCl_3$); mass spectrum, *m/e* 603 (M^+), 588 ($M^+ - CH_3$), 360 (M^+ − Tr), 243 (Tr^+); ^1H NMR δ 1.30, 1.57 (2 s, 6, $C(CH_3)_2$), 2.43 (s, 3, C_4 CH_3), 4.23 (s, 2, CH_2), 5.07 (d, 1, H-1′, $J_{1',2'}$ = 5 Hz); ^{13}C NMR δ 15.54 (C_4 CH_3), 25.59, 27.62 ($C(CH_3)_2$), 39.96 (CH_2), 114.87 ($C(CH_3)_2$), 168.80 (C_2). Anal. Calcd for $C_{38}H_{37}NO_4S$: C, 75.59; H, 6.18; N, 2.32. Found: C, 75.59; H, 6.16; N, 2.17.

2-Phenyl-4-methyl-5-*C*-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)thiazole (39). From 4. Compound **4** (170 mg, 0.31 mmol) was dissolved in 0.6 mL of HMPA with warming, thiobenzamide **34** (130 mg, 0.93 mmol) was added, and the solution was heated to 120 °C. After 15 min, the reaction mixture had darkened somewhat, and after 1 h a new spot (R_f 0.52, solvent B) predominated in the complex TLC. The reaction was worked up as before, after partitioning between 20 mL of ether and 75 mL of water, to yield 100 mg (56%) of colorless foam.

From 3. Compound **3** (290 mg, 0.57 mmol) was dissolved in 1.4 mL of HMPA, thioamide **34** (240 mg, 1.72 mmol) was added, and the reaction mixture was warmed to 75 °C. After the mixture was heated for 22 h, starting material was gone and a new compound (R_f 0.52, solvent B) was noted by TLC. This reaction mixture was worked up exactly as in the preceding procedure. Once again, the reaction mixture was complex, but thick-layer chromatography in solvent B allowed the isolation of 120 mg (36%) of **39**: $[\alpha]_D^{22}$ −68° (*c* 0.43, $CHCl_3$); mass spectrum, no M^+ seen for this compound, *m/e* 346 (M^+ − Tr), 243 (Tr^+); ^1H NMR δ 1.34, 1.61 (2 s, 6, $C(CH_3)_2$), 2.51 (s, 3, C_4 CH_3), 5.15 (d, 1, H-1, $J_{1',2'}$ = 4.5 Hz); ^{13}C NMR δ 15.83 (C_4 CH_3), 25.73, 27.72 ($C(CH_3)_2$), 114.96 ($C(CH_3)_2$), 166.09 (C_2). Anal. Calcd for $C_{37}H_{35}NO_4S$: C, 75.35; H, 5.98; N, 2.38. Found: C, 75.51; H, 6.07; N, 2.16.

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Registry No. **2**, 86563-06-6; **3** (isomer 1), 86563-08-8; **3** (isomer 2), 86563-07-7; **4** (isomer 1), 86563-09-9; **4** (isomer 2), 86563-10-2; **6** (isomer 1), 86563-12-4; **6** (isomer 2), 86563-13-5; **7** (isomer 1), 86563-14-6; **7** (isomer 2), 86563-15-7; **9** (isomer 1), 86568-67-4; **9** (isomer 2), 86563-16-8; **10** (isomer 1), 86594-78-7; **10** (isomer 2), 86594-79-8; **11**, 86563-17-9; **13**, 55726-19-7; **15**, 1439-36-7; **16**, 859-65-4; **17**, 13504-77-3; **18**, 31459-98-0; **19**, 26487-95-6; **20**, 6161-37-1; **21**, 3201-60-3; **22**, 807-15-8; **24**, 86563-05-5; **26**, 86563-18-0; **27**, 86563-25-9; **28**, 86568-68-5; **29**, 86563-11-3; **30**, 62-55-5; **31**, 689-09-8; **32**, 86563-22-6; **33**, 645-54-5; **34**, 2227-79-4; **35**, 86563-19-1; **36**, 86563-20-4; **37**, 86563-21-5; **38**, 86563-23-7; **39**, 86563-24-8.

Supplementary Material Available: Tables I–IV containing complete ^1H and ^{13}C NMR data for all new compounds (4 pages). Ordering information is given on any current masthead page.