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SYNTHESIS AND "ANOMERIZATION" OF *C*-GLYCOSYL COMPOUNDS RELATED TO SOME HETEROCYCLIC NATURAL PRODUCTS*

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ABSTRACT

Reaction of 2,3-*O*-isopropylidene-D-ribofuranose (**13**) with the stabilized Wittig reagents $Ph_3P{=}C(Me)CO_2Me$ (**14**) and $Ph_3P{=}C(Me)CN$ (**15**) gave olefinic products which, upon treatment with dilute base, afforded the corresponding anhydro sugars having the β-D-anomer configuration exclusively. Treatment of these kinetic products with a strong base did not affect the ester obtained from **14**, but the nitrile from **15** gave a β-to-α-anomer ratio at equilibrium of 4:1. Reaction of **13** with $Ph_3P{=}CHCOMe$ led directly to a 7:3 mixture of β- and α-D anomers, and this ratio was changed to 1:4 upon prolonged exposure to base. Treatment of 4,6-*O*-ethylidene-D-glucopyranose with the Wittig reagent $Ph_3P{=}CHCOCH_2CO_2Et$ led directly to a 1:1 mixture of the anomers of the anhydro sugar in which a β-keto ester residue is attached at the (original) anomeric center. This ratio of anomeric forms could not be changed by treatment with base, but the ethylidene-protecting group could be removed, and the resulting tetrol tritylated at the primary position.

INTRODUCTION

The *C*-glycosyl monosaccharides are derivatives of tetrahydrofurans or tetrahydropyrans, heterocyclic ring systems that are also encountered frequently in a wide variety of natural products. These natural products may, therefore, be regarded as elaborate *C*-glycosyl compounds and, hence, carbohydrate-based approaches to their syntheses seem justified. Nonactic acid[1] (**1**) and trichothecanes, such as **2** (ref. 2) are two such natural products, and we have been interested in adapting the methods of synthesis of *C*-glycosyl compounds to their preparation.

*Taken, in part, from the Ph.D. thesis of King Mo Sun, University of Maryland, 1981, and Robert D. Dave, University of Waterloo, 1982.

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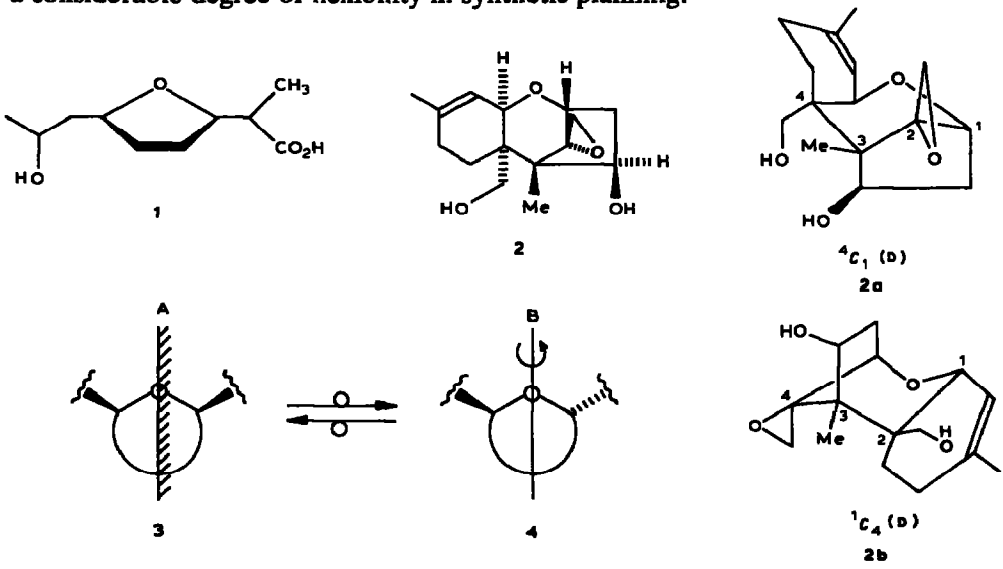
Preliminary communications related to these objectives have appeared[3,4] and, in this report, we describe some support studies which are of general interest.

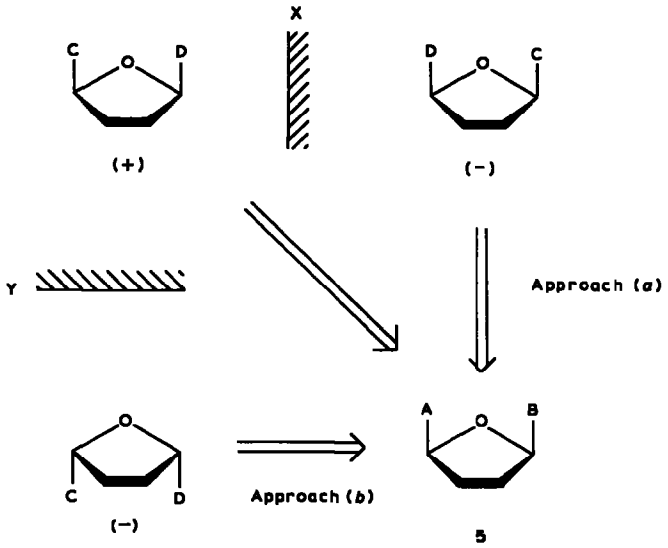
From the standpoint of *C*-glycosyl chemistry, the synthetic challenge for target compounds **1** or **2** is the local element of symmetry about the heterocyclic ring. Thus, if nonactic acid is represented as **3**, the local element of symmetry is seen to be a mirror plane (**A**) which bisects the molecule, whereas for the trichothecane **4**, there is a C_2 axis represented by **B**.

For a given heterocyclic ring system, equilibration of **3** and **4** is theoretically possible provided that appropriate functional elements are present, and this permits a considerable degree of flexibility in synthetic planning.



The possible interconversion of **3** and **4** is particularly relevant in the case of nonactic acid (**1**) since, in the macrotetrolide nonactin, both enantiomers occur in alternating sequence, as a result of which the macrocycle exhibits an S_4 symmetry and is optically inactive[5]. Ideally, the need for equal amounts of each enantiomer could be met by an enantiodivergent procedure in which the enantiomeric forms of **1** are derived from a single precursor. The considerations of symmetry in connection with **3** and **4** individually, and the ability to convert **3** into **4** (or vice versa), suggested two approaches to nonactic acid (see Scheme 1), which differ according to the mirror plane that is used to reflect the crucial key intermediate, represented as **5**. Thus, approach (*a*) utilizes the mirror plane **X** and would require the transformation of the functional groups, **A** and **B** into **C** and **D**, respectively, to give one enantiomer [designated arbitrarily as (+)], and into **D** and **C**, respectively, to give the (−) enantiomer. In approach (*b*), the mirror plane **Y** is used and the (+) enantiomer is obtained as mentioned before; however, the (−) enantiomer is now obtained by a double epimerization of the side chains.

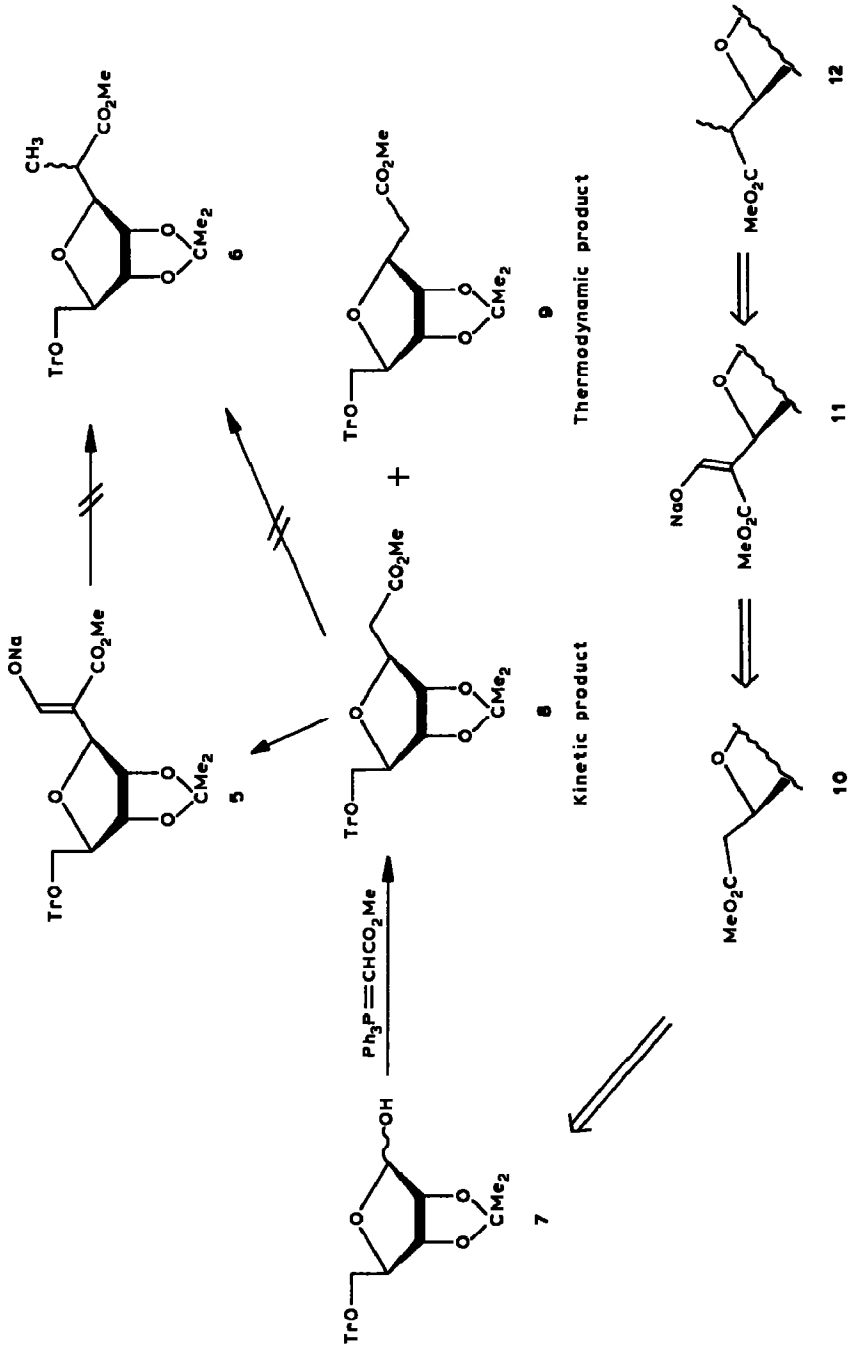
The first prerequisite for probing the application of this general plan was to

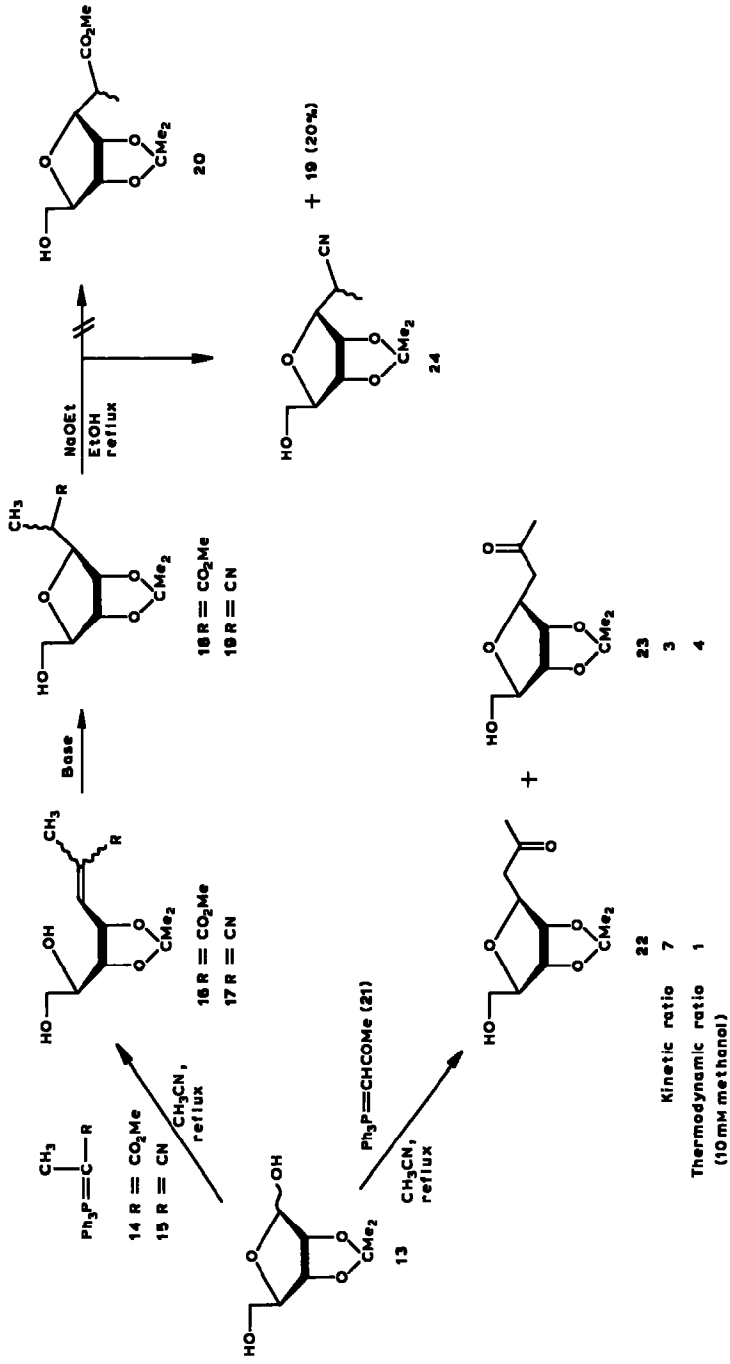


Scheme 1.

establish the feasibility of the proposed "anomerizations". Of particular significance, in this regard, was the detailed study reported by Ohuri *et al.*[6] who had shown that the isomers **8** and **9** could be obtained as kinetic and thermodynamic products, respectively, of Wittig reactions of 2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribofuranose (**7**). Indeed, **8** seemed an ideal precursor for our work, since Chu *et al.*[7] had reported the formation of the salt **5**, which indicated that a one-carbon unit could be attached to the activated methylene group of the side chain. These results seemed promising for approach (*a*) (Scheme 1), since the primary hydroxyl group of **7** would provide a ready access to ester **10**, to which the Chu *et al.* method[7] could be applied for the synthesis of the salt **11** from which the derivative **12** would be prepared. This approach was abandoned, however, when we found it impossible to obtain the methyl ester **6**, either from salt **5** or by direct alkylation of **8**.

In an alternative approach, 2,3-isopropylidene-D-ribofuranose[8] (**13**) was treated with the stabilized Wittig reagent (2-methoxycarbonylethylidene)triphenylphosphorane (**14**) in refluxing acetonitrile for 4 h to afford an isolable intermediate, presumed to be the (*E,Z*) mixture **16** in 95% yield. Brief treatment with dilute base gave a mixture of two compounds (in 3:1 ratio) which could be separated by column chromatography. Their structures as epimers of the β-D anomer **18** were established by their transformation into nonactic acid (**1**) and its 2-epimer[3]. Reaction of **13** with (2-cyanoethylidene)triphenylphosphorane (**15**) also gave an excellent yield of an isolable alkene **17**, which cyclized readily to give the anhydro sugar **19**. The reaction of **13** with acetonylidenetriphenylphosphorane (**21**), in acetonitrile at reflux for 2 h, led to the anomers **22** and **23** in the ratio 7:3 without any evidence for an unsaturated intermediate.


Ph3P=CHCO2Me
Kinetic product
Thermodynamic product


Ph3P=C(CH3)R
14 R = CO2Me
15 R = CN
CH3CN, reflux
16 R = CO2Me
17 R = CN
Base
18 R = CO2Me
19 R = CN
NaOEt
EtOH
reflux
20
+ 19 (20%)
24
Ph3P=CHCOMe (21)
CH3CN, reflux
22
23
Kinetic ratio 7 3
Thermodynamic ratio 1 4
(10 mM methanol)

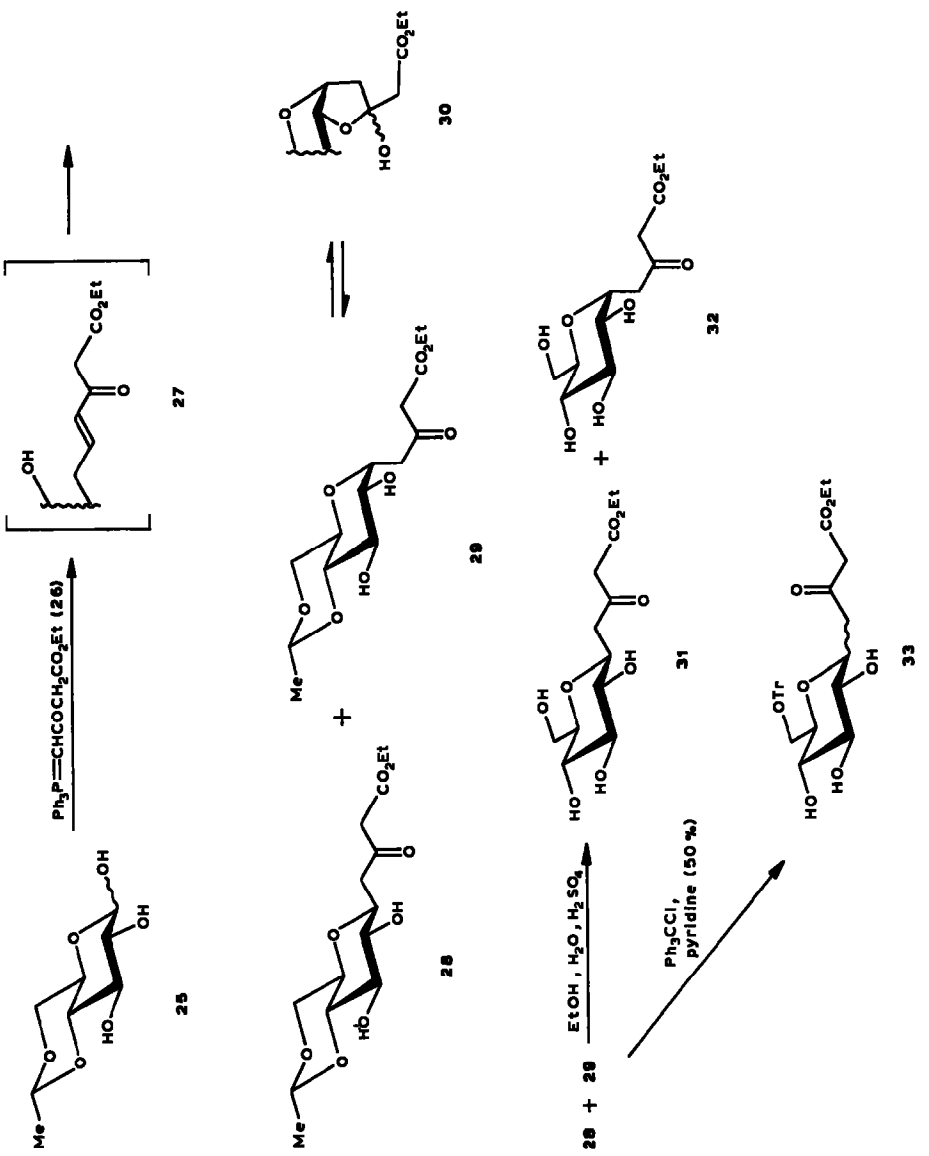
In light of the results from Moffatt's laboratory[6], the (major) products of kinetic control should be the α anomers, and the preliminary assignments of the (major) reaction products **18**, **19**, and **22** were made on this basis. Accordingly, prolonged treatment with base should effect equilibration, yielding the corresponding α anomers as the major products of thermodynamic control[6]. The availability of both anomers in each case would greatly facilitate the structural proof by the ^{13}C-n.m.r. techniques pioneered by Moffatt and associates[6] (*vide infra*).

In the case of **22** and **23**, the ratio (7:3) in which they were formed, could be changed to 1:4 by treating the mixture with 10mM sodium methoxide in methanol for 30 min. However, in the case of the ester **18**, treatment with 10mM methanolic sodium methoxide solution at room temperature for 16 h had no effect (t.l.c. and ^{1}H-n.m.r.), and even the drastic conditions of 0.3M methanolic sodium methoxide solution at reflux for 10 h failed to offer any formation of **20**. On the other hand, treatment of the nitrile **19** with 0.3M ethanolic sodium ethoxide solution at reflux for 4 h caused anomerization to afford a 4:1 mixture of **24** and **19**. The α anomers **24** could be separated from the β anomer **19**; however, separation of the epimers of each anomer was not achieved.

The aforementioned results indicated that the α and β anomers could be readily obtained in the case of the nitrile (**19** and **24**) and propanone derivatives (**22** and **23**), but not in the case of the ester **18**, thus delineating the possible choices of functional groups that could be utilized for the double epimerization outlined in approach (*b*) (Scheme 1). Thus, residue **D** could be $-CH(CH_3)CN$, but not $-CH(CH_3)CO_2R$, and residue **C** could be $-CH_2COMe$. This information was used for the final synthesis[3].

With respect to the trichothecene system **2**, the procedure to be adopted for a carbohydrate-based approach would depend on whether the molecule is represented in the $^4C_1$(D) (**2a**), or $^1C_4$(D) conformation (**2b**), and these considerations have been discussed elsewhere[4]. However, in either case, a *C*-α-D-glycopyranosyl derivative is needed that would provide access to an "annulated pyranose" having a bridged structure (**2a**) or a fused system (**2b**). A β-keto ester seemed to be an interesting candidate for these objectives.

Reaction of (ethoxycarbonylacetonylidene)triphenylphosphorane (**26**) with 4,6-*O*-ethylidene-D-glucopyranose[9] (**25**) in refluxing acetonitrile gave the expected *C*-glucopyranosyl compounds **28** and **29** without any evidence of intermediate **27**. Because of difficulties in removing triphenylphosphine oxide, only very small amounts of the pure products could be isolated, even after repeated, careful chromatography. However, t.l.c. indicated that the two components were present in approximately equal amounts. The optical rotation was +34.6° for the fastest-moving anomer (R_F 0.65) and −28.7° for the more polar (R_F 0.61). Since Hudson's rule of isorotation has been shown to be valid for *C*-glucopyranosyl compounds[10], the structures **28** and **29** were assigned to the α-D and β-D anomer, respectively. Support for these conclusions was provided by the ^{1}H-n.m.r. (600 MHz) spectra which, in the case of the β anomer **29** was easily interpreted. However, for the α


Ph3P=CHCOCH2CO2Et (26)
EtOH, H2O, H2SO4
Ph3CCl, pyridine (50 %)
25
27
28
29
30
31
32
33
28 + 29

anomer **28** the spectrum was exceedingly complex, a result which was ascribed to the presence of the hemicetal form **30** to an appreciable extent.

In view of the aforementioned difficulties with isolation, we found it best to treat the crude product from the Wittig reaction with acidic aqueous ethanol, the water being present to reduce the possibility of forming a mixed acetal from the α anomer **28**. The resulting tetrols (**31** and **32**) were readily separated from triphenylphosphine oxide by extraction into water. Evaporation of the aqueous phase and column chromatography of the residue afforded both compounds as oils, which gave acceptable elemental analyses. The optical rotations of +5.7 and +9.1° were consistent with the assignments of structures **31** and **32**, respectively. The high polarity of these tetrols presented a problem for further synthetic studies in view of their insolubility in organic solvents. This was overcome by tritylation, but the resulting compound **33**, indeed soluble in organic solvents, was obtained in a disappointingly low yield.

The stereoselectivity in the formation of **28** and **29** was low and, unlike in the case of **22** and **23**, the ratio in which they were formed could not be altered by equilibration, as the most acidic protons are undoubtedly the activated methylene group. Hence, retrocyclization of the pyrano ring is unlikely. Indeed, **28** and **29** were unchanged by prolonged treatment with sodium methoxide, and attempts to force the reaction led to decomposition.

The results obtained with the furanose system indicated the functional groups that could be used for the "anomerizations" required in approach (*b*) (Scheme 1), which led to the final synthesis of methyl (+)- and (−)-nonactates[3]. However, in the case of the pyranose system, the β-keto ester derivatives were not suitable as chirons[11] for trichothecenes, since it was not possible to increase the ratio of the desired α anomers. Therefore, an alternative procedure was adopted for the synthesis of the trichothecane skeleton[4].

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes with a Büchi 510 melting-point apparatus, and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. I.r. spectra were recorded with a Perkin–Elmer IR-298 spectrometer using NaCl cells and chloroform as solvent for solids or sodium chloride plates for films. ^{1}H-N.m.r. spectra were recorded with Varian EM-360A (60 MHz), Bruker WP-80 (80 MHz), Varian XL-100 (100 MHz), Varian HR-220 (220 MHz) spectrometers and a 600-MHz spectrometer on solutions in $CDCl_3$ (internal Me_4Si); coupling constants were obtained by measuring the spacings of the spectra judged to be first order. The progress of all reactions was monitored by t.l.c. on Silica gel 60 (HF-254, Merck) using the following solvent systems: ethyl acetate–light petroleum ether (*A* 1:4), dichloromethane–methanol (*B* 4:1, *C* 9:1, *D* 19:1, *E* 24:1, *F* 1:9, and *G* 1:4), and diethyl ether (*H*). The chromatograms were viewed under u.v. light and charred with

H_2SO_4. Flash column chromatography was performed in Kieselgel 60 (230–400 mesh, Merck). Elemental analyses were performed by Dr. F. Kasler (Department of Chemistry, University of Maryland) or by Guelph Chemical Laboratories (Guelph, Ontario, Canada).

Standard procedure for the reaction of furanose with stabilized Wittig reagents. — The furanose (1 equiv.) and Wittig reagent (1.5 equiv.) were dissolved in dry acetonitrile (1 g of sugar/50 mL). The solution was boiled under reflux and, when the reaction was complete (t.l.c.), the solvent was evaporated and the residue chromatographed.

*Reaction of 2,3-*O*-isopropylidene-*D*-ribofuranose* (**13**) *with (2-methoxycarbonylethylidene)triphenylphosphorane* (**13**) *and cyclization of the intermediate* **16** *into methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-2-*C*-methyl-*D*-glycero-*D*-allo- and -*D*-altro-heptonate* (**18**). — Under the standard Wittig reaction conditions, **13** (ref. 8) (250 mg, 1.32 mmol) and **16** (700 mg, 2 mmol) reacted to give **16** (325 mg, 95%), R_F 0.44 (*H*); $\nu_{max}^{CHCl_3}$ 3480 (OH), 1715, and 1662 (α,β-unsaturated ester) cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 1.44 (s, 6 H, $OCMe_2$), 1.95 (d, 3 H, H_3-8), 2.90–3.43 (br.s, 2 H, 2 OH), 3.68–4.01 (m, 7 H, H-5,6,7a,7b, CO_2CH_3), 4.00–4.87 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 6.0 Hz, H-4), and 6.66 (dd, 1 H, $J_{3,8}$ 0.7 Hz, H-3).

Anal. (h.r.m.s.): Calc. for $C_{11}H_{17}O_6$ ($M^+ - CH_3$): 245.1025. Found: 245.1043.

To a solution of **16** (130 mg, 0.5 mmol) in 1,4-dioxane, was added 2% methanolic KOH solution (1 mL). The mixture was stirred for 5 min at room temperature and then made neutral with 1% HCl. After removal of solvent under reduced pressure, the residue showed two components (t.l.c., *H*) which were separated by chromatography.

First component (31 mg, 24%): R_F 0.43 (*H*), $[\alpha]_D^{20}$ +10.9° (*c* 2.63, chloroform); $\nu_{max}^{CHCl_3}$ 3500 (OH) and 1730 (ester) cm^{-1}; ^{1}H-n.m.r. (220 MHz): δ 1.28 (d, 3 H, $J_{2,8}$ 7.0 Hz, H_3-8), 1.35 (s, 3 H, $OCCH_3$), 1.57 (s, 3 H, $OCCH_3$), 2.55 (br.s, 1 H, OH), 2.81 (quint., 1 H, $J_{2,3}$ 7.0 Hz, H-2), 3.67 (s, 3 H, CO_2CH_3), 3.25–3.83 (m, 2 H, H_2-7), 4.00 (m, 2 H, H-3,6), 4.65 (dd, 1 H, $J_{3,4}$ 3.8, $J_{4,5}$ 6.5 Hz, H-4), and 4.71 (dd, 1 H, $J_{5,6}$ 3.8 Hz, H-5); m.s.: *m/z* 245 ($M^+ - CH_3$), 229 ($M^+ - OCH_3$), and 213 ($M^+ - CH_3O_2$).

Second component (97 mg, 75%): R_F 0.38 (*H*), $[\alpha]_D^{20}$ −11.1° (*c* 0.90, chloroform); $\nu_{max}^{CHCl_3}$ 3470 (OH) and 1730 cm^{-1} (ester); ^{1}H-n.m.r. (220 MHz): δ 1.28 (d, 3 H, H_3-8), 1.38 (s, 3 H, $OCCH_3$), 1.57 (s, 3 H, $OCCH_3$), 2.68 (quint., 1 H, $J_{2,3}$ 7.0, $J_{2,8}$ 7.0 Hz, H-2), 3.10 (br.s, 1 H, OH), 3.77 (s, 3 H, CO_2CH_3), 3.61–3.89 (m, 2 H, H_2-7), 4.00–4.16 (m, 2 H, H-3,6), 4.51 (dd, 1 H, $J_{3,4}$ 4.2, $J_{4,5}$ 6.8 Hz, H-4), and 4.75 (dd, 1 H, $J_{5,6}$ 3.5 Hz, H-5).

Anal. (h.r.m.s.): Calc. for $C_{11}H_{17}O_6$ ($M^+ - CH_3$) 245.1025. Found: 245.1039.

(2-Cyanoethylidene)triphenylphosphorane (**15**). — A three-necked, 2-L, round-bottom flask, equipped with a condenser was charged with 2-hydroxypropanenitrile (100 g, 1.4 mol), dry pyridine (110 mL, 1.4 mol), and anhydrous diethyl ether (1 L). Thionyl chloride (83 g, 0.7 mol) was added slowly to the

ethereal solution over 0.5 h and, after being stirred for another 0.5 h, the solution was filtered under vacuum into a 2-L, 2-necked, round-bottom flask equipped with a condenser and drying tube. Thionyl bromide was added and the solution was boiled under reflux for 24 h, cooled, transferred to a dropping funnel, and added carefully to a vigorously stirred suspension of excess anhydrous $NaHCO_3$ in dry diethyl ether, at such a rate controlled evolution of CO_2 took place. After the addition was complete, the mixture was filtered, the solids were washed with diethyl ether (200 mL), and the filtrate was evaporated to dryness. The deep-red, crude product was distilled under vacuum (58–60°, 3.3 kPa) to give 2-bromopropanenitrile (46 g) as a colorless liquid. A portion (20 g, 0.15 mmol) of this material and triphenylphosphine (40 g, 0.15 mmol) were dissolved in dry toluene (200 mL) and the solution was refluxed for 12 h. The white solid formed was collected, washed well with anhydrous diethyl ether (3 × 50 mL) (55 g, 91.7%), recrystallized from dichloromethane–diethyl ether. To a solution of this salt (25 g, 63 mmol), in dry dichloromethane (250 mL), was added finely powdered anhydrous K_2CO_3 (20 g, 145 mmol) and the suspension was stirred vigorously for 4 h at room temperature. The solids were collected by filtration and washed with dry dichloromethane (3 × 50 mL). The filtrate and the washings were combined and the solvent was removed to give a yellow solid (19.9 g, 100%) which crystallized from diethyl ether–petroleum ether (30–60°), m.p. 168–169°; ^{1}H-n.m.r. (60 MHz): δ 1.72 (d, 3, J_{P,CH_3} 17.6 Hz, CH_3) and 7.2–8.05 [m, 15 H, J_{P,CH_3} $P(C_6H_5)_3$].

Anal. Calc. for $C_{21}H_{18}NP$: C, 80.00; H, 5.71; N, 4.40. Found: C, 79.60; H, 5.74; N, 4.32.

Reaction of **13** *with* **15** *and cyclization of the intermediate* **17** *into 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-2-*C*-methyl-*D*-glycero-*D*-allo- and -*D*-altro-heptononitrile* (**19**). — Reaction of **15** (1.2 g, 6.3 mmol) with **13** (3 g, 9.5 mmol) under the standard Wittig reaction procedure afforded **17**, R_F 0.27 (*H*); $\nu_{max}^{CHCl_3}$ 3420 (OH), 2215 (CN), and 1650 cm^{-1} (double bond); ^{1}H-n.m.r. (60 MHz): δ 1.40 (s, 3 H, OCCH_3), 1.50 (s, 3 H, OCCH_3), 2.00 (d, 3 H, $J_{3,8}$ 1.0 Hz, H_3-8), 3.48–3.91 (m, 5 H, H-5,7a,7b, 2 OH), 4.00–4.29 (m, 1 H, H-6), 4.86–5.10 (dd, 1 H, $J_{3,4}$ 5.5, $J_{4,5}$ 5.5 Hz, H-4), and 6.25–6.35 (dd, 1 H, H-3). A portion of **17** (500 mg, 2.2 mmol) was dissolved in methanol (25 mL) and a catalytic amount of sodium methoxide added. After stirring for 20 min at 25°, the reaction was quenched by addition of 1% methanolic HCl, the solvent evaporated, and the residue passed through a short chromatographic column. The product (500 mg, 100%) thus obtained was homogeneous on t.l.c. (*H*), but was shown to be a mixture of two compounds by ^{1}H-n.m.r., R_F 0.49 (*H*), 0.43 (*E*); $\nu_{max}^{CHCl_3}$ 3500 (OH) and 2253 cm^{-1} (CN).

First component: ^{1}H-n.m.r. (220 MHz): δ 1.39 (s, 3 H, OCCH_3), 1.40 (d, 3 H, $J_{2,8}$ 7.5 Hz, H_3-8), 1.57 (s, 3 H, $OCCH_3$), 2.72 (br.s, 1 H, OH), 3.12 (dq, 1 H, $J_{2,3}$ 5.5, $J_{2,8}$ 7.5 Hz, H-2), 3.69–3.80 (m, 1 H, H-7), 3.84–3.98 (m, 2 H, H-3,7), 4.19 (quint., 1 H, $J_{5,6}$ 3.5, $J_{6,7}$ 3.5 Hz, H-6), 4.68 (dd, 1 H, $J_{4,5}$ 6.6 Hz, H-4), and 4.02 (dd, 1 H, H-5).

Second component: ^{1}H-n.m.r. (220 MHz): δ 1.38 (s, 3 H, OCCH_3), 1.46 (d,

3 H, $J_{2,8}$ 7.5 Hz, H_3-8), 1.57 (s, 3 H, OCCH_3), 2.72 (br.s, 1 H, OH), 2.98 (dq, 1 H, $J_{2,3}$ 5.5 Hz, H-2), 3.69–3.80 (m, 1 H, H-7), 3.84–3.98 (m, 2 H, H-3,7), 4.19 (quint., 1 H, $J_{5,6}$ 3.5, $J_{6,7}$ 3.5 Hz, H-6), 4.53 (t, 1 H, $J_{3,4}$ 5.7, $J_{4,5}$ 5.7 Hz, H-4), and 4.82 (dd, 1 H, H-5); m.s.: *m/z* 213 ($M^+ + 1 - CH_3$), 212 ($M^+ - CH_3$), and 196 ($M^+ - OCH_3$).

Equilibration of compounds **19** *and* **24**. — The nitrile **19** (250 mg, 0.92 mmol; ratio of 2-epimers, 1:1) was dissolved in 0.3M sodium ethoxide in dry ethanol (25 mL) and the solution was boiled under reflux for 4 h, after which the reaction was quenched with 1% methanolic HCl. The crude syrup from evaporation was chromatographed (*E*) to give two homogeneous fractions, each of which contained two components (^{1}H-n.m.r.). The less polar component was identical to the starting material **19** and the more polar was the α anomer **24**, in the ratio 1:4.

α Anomer (**24**). R_F 0.34 (*E*), $\nu_{max}^{CHCl_3}$ 3500 (OH) and 2225 cm^{-1} (CN); ^{1}H-n.m.r. (1:1 mixture; 220 MHz): δ 1.34 and 1.38 (s, 3 H, OCCH_3), 1.50 and 1.40 (d, 3 H, $J_{2,8}$ 7.5 Hz, H_3-8), 1.53 and 1.56 (s, 3 H, OCCH_3), 2.04 and 2.30 (br.s, 1 H, OH), 3.02 (m, 1 H, H-2), 3.59–3.77 (m, 2 H, H_2-7), 4.03 and 4.08 (dd, 1 H, $J_{2,3}$ 9.0, $J_{3,4}$ 4.0 Hz, H-3), 4.15 and 4.20 (t, 1 H, $J_{6,7}$ 5.0 Hz, H-6), 4.73–4.80 (m, 1 H, H-5), 4.68 and 4.82 (dd, 1 H, $J_{4,5}$ 6.0 Hz, H-4).

Anal. (h.r.m.s.): Calc. for $C_{10}H_{14}NO_4$ ($M^+ - CH_3$): 212.0922. Found: 212.0921.

Reaction of **13** *with acetonylidenetriphenylphosphorane* (**21**). — Reaction of **13** (250 mg, 1.32 mmol) with **21** (700 mg, 2 mmol) under the standard Wittig reactions conditions was complete within 2 h. Although the product (280 mg, 97%) appeared homogeneous on t.l.c., ^{1}H-n.m.r. showed it to be a mixture of **22** and **23** in 7:3 ratio (integration of the isopropylidene methyl signals).

*4,7-Anhydro-1,3-dideoxy-5,6-*O*-isopropylidene-*D-altro*-oct-2-ulose* (**22**). R_F 0.34 (*H*); $\nu_{max}^{CHCl_3}$ 3420 (OH) and 1715 cm^{-1} (ester C=O); ^{1}H-n.m.r. (220 MHz): δ 1.33 (s, 3 H, OCCH_3), 1.49 (s, 3 H, OCCH_3), 2.20 (s, 3 H, H_3-1), 2.87 (d, 2 H, $J_{3,4}$ 6.0 Hz, H_2-3), 3.59 (d, 2 H, $J_{7,8}$ 5.6 Hz, H_2-8), 4.08 (t, 1 H, H-7), 4.37 (dt, 1 H, $J_{4,5}$ 3.4 Hz, H-4), 4.65 (d, 1 H, $J_{5,6}$ 6.3 Hz, H-6), and 4.75 (dd, 1 H, H-5).

*4,7-Anhydro-1,3-dideoxy-5,6-*D*-isopropylidene-*D*-allo-oct-2-ulose* (**23**). R_F 0.34 (*F*); $\nu_{max}^{CHCl_3}$ 3420 (OH) and 1715 cm^{-1} (ester); ^{1}H-n.m.r. (220 MHz): δ 1.34 (s, 3 H, OCCH_3), 1.54 (s, 3 H, OCCH_3), 2.20 (s, 3 H, H_3-1), 2.68–2.85 (m, 2 H, H_2-3), 3.13 (br.s, 1 H, OH), 3.63 (dd, 1 H, $J_{8a,8b}$ 12.0, $J_{7,8b}$ 3.9 Hz, H-8b), 3.76 (dd, 1 H, $J_{7,8a}$ 3.0 Hz, H-8a), 4.03 (ddd, 1 H, $J_{6,7}$ 4.0 Hz, H-7), 4.25 (ddd, 1 H, $J_{3,4}$ 7.0, $J_{3,4}$ 5.0, $J_{4,5}$ 4.8 Hz, H-4), 4.43 (dd, 1 H, $J_{5,6}$ 6.5 Hz, H-5), and 4.70 (dd, 1 H, H-6), m.s.: *m/z* 215 ($M^+ - CH_3$), 199 ($M^+ - OCH_3$), and 181 ($M^+ - OCH_3 - H_2O$).

Equilibration of compounds **22** *and* **23**. — A portion (230 mg, 0.92 mmol) of the isomeric uloses **22** and **23** was dissolved in methanol (50 mL), a catalytic amount of sodium methoxide added, and the solution stirred at room temperature. The ratio of **22** and **23** was determined periodically by removing an aliquot of the solution, neutralizing with 1% methanolic HCl, evaporation, and determination of the ^{1}H-n.m.r. spectrum. Integration of the isopropylidene methyl signals was used

to determine the ratio of the isomers. After 0.5 h, the ratio of **23** to **22** was 4:1 and remained unchanged thereafter.

Ethyl 5,9-anhydro-2,4-dideoxy-8,10-O-ethylidene-D-glycero-D-ido- (**28**) *and* -D-glycero-D-gulo-*dec-3-ulosonate* (**29**). — To a solution of triphenylphosphine (65 g, 0.28 mol) in benzene (250 mL), was added ethyl 4-bromo-3-oxobutanoate[12] (52 g, 0.33 mol) at such a rate that the temperature did not exceed 30°. After 18 h at room temperature, the precipitate was collected by filtration, washed with benzene, and dried (115 g, 97%). A portion of the salt (40 g, 95 mmol) was stirred vigorously in hot water (1.8 L), Na_2CO_3 (15 g, 0.14 mol) added, and the resulting suspension stirred at room temperature for 12 h. The solid material (**26**) was collected by filtration, washed with water, and dried under vacuum (27 g, 83%). 4,6-*O*-Ethylidene-D-glucopyranose[15] (**25**; 5 g, 14 mmol) was dissolved in acetonitrile (50 mL), the phosphorane **26** (8 g, 20 mmol) added, and the solution boiled under reflux for 72 h, when t.l.c. (*F*) indicated that the reaction was complete. The solvent was removed and the residue partitioned between dichloromethane and water. Evaporation of the organic extract afforded a brown syrup, a portion of which was purified by column chromatography for characterization. Two successive silica gel columns (93:7 dichloromethane–methanol) gave **29** (105 mg) and **28** (100 mg) as oils.

Compound **29**. R_F 0.65 (*F*), $[\alpha]_D^{22}$ +34.6° (*c* 2.23, chloroform); ν_{max}^{film} 3450 (OH), 1735 (ester C=O), and 1715 cm^{-1} (ketone C=O); ^{1}H-n.m.r. (600 MHz): δ 1.1–1.5 (m, 5 H, CH_3CH_2); the rest of the spectrum was too complex for definitive assignments to be made.

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 53.02; H, 6.82.

Compound **28**. $[\alpha]_D^{24}$ −28.9° (*c* 0.47, chloroform), R_F 0.61 (*F*); ν_{max}^{film} 3480 (OH), 1750 (ester C=O), and 1730 cm^{-1} (ketone C=O); ^{1}H-n.m.r. (600 MHz): δ 1.27 (t, 3 H, J_{CH_3,CH_2} 6.10 Hz, CH_3CH_2), 1.35 (d, 3 H, $J_{CH_3,CH}$ 4.28 Hz, CH_3CH), 2.75 (dd, 1 H, $J_{4,5}$ 7.35, $J_{4a,4b}$ 15.92 Hz, H-4a), 3.01 (dd, 1 H, $J_{4b,5}$ 3.67 Hz, H-4b), 3.23 (dd, 1 H, $J_{7,8}$ and $J_{8,9}$ 9.80 Hz, H-8), 3.32 (ddd, 1 H, $J_{9,10a}$ 9.80, $J_{9,10b}$ 3.68 Hz, H-9), 3.34 (dd, 1 H, $J_{6,7}$ 9.18 Hz, H-7), 3.42 (dd, 1 H, $J_{10a,10b}$ 9.80 Hz, H-10a), 3.48 (d, 1 H, $J_{2a,2b}$ 15.30 Hz, H-2a), 3.52 (d, 1 H, H-2b), 3.68 (dd, 1 H, $J_{5,6}$ 8.57 Hz, H-6), 3.83 (ddd, 1 H, H-5), 4.10 (dd, 1 H, H-10b), 4.19 (q, 2 H, CH_2CH_3), and 4.70 (q, 1 H, $CHCH_3$); the assignments for H-3 and H-4 may be reversed.

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 52.69; H, 6.96.

Ethyl 5,9-anhydro-2,4-dideoxy-D-glycero-D-ido- (**31**) *and* -D-glycero-D-gulo-*dec-3-ulosonate* **32**. — The crude reaction mixture containing **28** and **29** was dissolved in a mixture of ethanol (250 mL) and 5% (v/v) aqueous H_2SO_4 (24 mL), and the solution boiled under reflux for 4 h, when t.l.c. (*G*) indicated that the reaction was complete. The mixture was made neutral with $NaHCO_3$ and extracted with dichloromethane to remove triphenylphosphine oxide. The aqueous layer was evaporated to dryness and the residue leached repeatedly with ethanol. Evaporation of the ethanol solution gave a yellow oil (3.5 g, 82% from **25**). Column chromatography (*G*) afforded **31** as a clear oil, $[\alpha]_D^{23}$ +5.7° (*c* 0.42, methanol), R_F 0.50 (**G**); ν_{max}^{film} 3400 (OH) and 1720 cm^{-1} (ester and ketone C=O); ^{1}H-n.m.r. (60

MHz, D_2O, external Me_4Si): δ 1.25 (t, 3 H, J_{CH_3,CH_2} 6 Hz, CH_3CH_2), 2.1–3.7 (m, 9 H, H-5,6,7,8,9,10a,10b,4a,4b), and 4.0 (1, 2 H, CH_2CH_3).

Anal. Calc. for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 49.03; H, 6.80.

Further chromatography afforded **32**, a pale yellow oil, $[\alpha]_D^{23}$ +9.1° (*c* 0.47, methanol), R_F 0.20 (*G*); ν_{max}^{film} 3420 (OH) and 1715 cm^{-1} (ester and ketone C=O); ^{1}H-n.m.r. (60 MHz, D_2O, external Me_4Si): δ 1.25 (t, 3 H, J_{CH_3,CH_2} 6 Hz, CH_3CH_2), 2.1–3.7 (m, 9 H, H-5,6,7,8,9,10a,10b,4a,4b), and 4.0 (q, 2 H, CH_2CH_3).

Anal. Calc. for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 50.05; H, 7.14.

Ethyl 5,9-anhydro-2,4-dideoxy-10-O-triphenylmethyl-D-glycero-D-gulo-*and* D-ido-*dec-3-ulosonate* (**33**). — A mixture of the tetrols **31** and **32** (1.331 g, 4.60 mmol) was dissolved in dry pyridine (50 mL) and treated with chlorotriphenylmethane (1.40 g, 5.03 mmol) for two days at room temperature. The mixture was poured into water and extracted with dichloromethane. After washing, drying, concentration, and purification by column chromatography (*F*), a mixture was obtained as a clear oil (1.2 g, 50%), R_F 0.53 and 0.44 (*F*); ν_{max}^{film} 3400 (OH), 1740 (ester C=O), and 1720 cm^{-1} (ketone C=O); ^{1}H-n.m.r. (80 MHz): δ 1.15 (t, 3 H, J_{CH_3,CH_2} 7 Hz, CH_3CH_2), 2.5–3.0 (m, 2 H, H-4a,4b), 3.0–3.8 (m, 9 H, H-5,6,7,8,9,10a,10b,4a,4b), 3.8–4.4 (br.s, 3 H, 3 OH), 4.15 (q, 2 H, CH_2CH_3), and 7.1–7.6 (m, 15 H, arom.).

Anal. Calc. for $C_{31}H_{34}O_8$: C, 69.65; H, 6.41. Found: C, 69.38; H, 6.39.

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