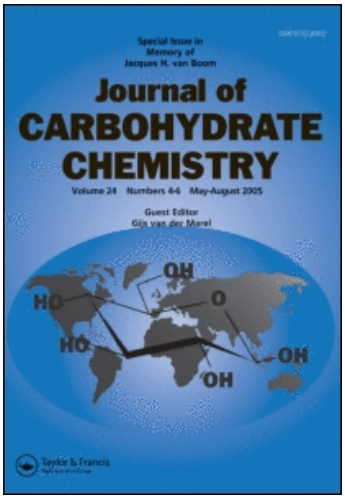

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Chain-Elongation of Dialdoses Containing the α-Galactopyranosyl Group by a Wittig Reaction with 2-Thiazolylmethylenetriphenylphosphorane. The Thiazole Route to Long-Chain Alkene Sugars

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CHAIN-ELONGATION OF DIALDOSES CONTAINING THE α-GALACTOPYRANOSYL GROUP BY A WITTIG REACTION WITH 2-THIAZOLYLMETHYLENETRIPHENYLPHOSPHORANE. THE THIAZOLE ROUTE TO LONG-CHAIN ALKENE SUGARS

Alessandro Dondoni,* Giancarlo Fantin, Marco Fogagnolo, and Pedro Merino

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, Ferrara, Italy

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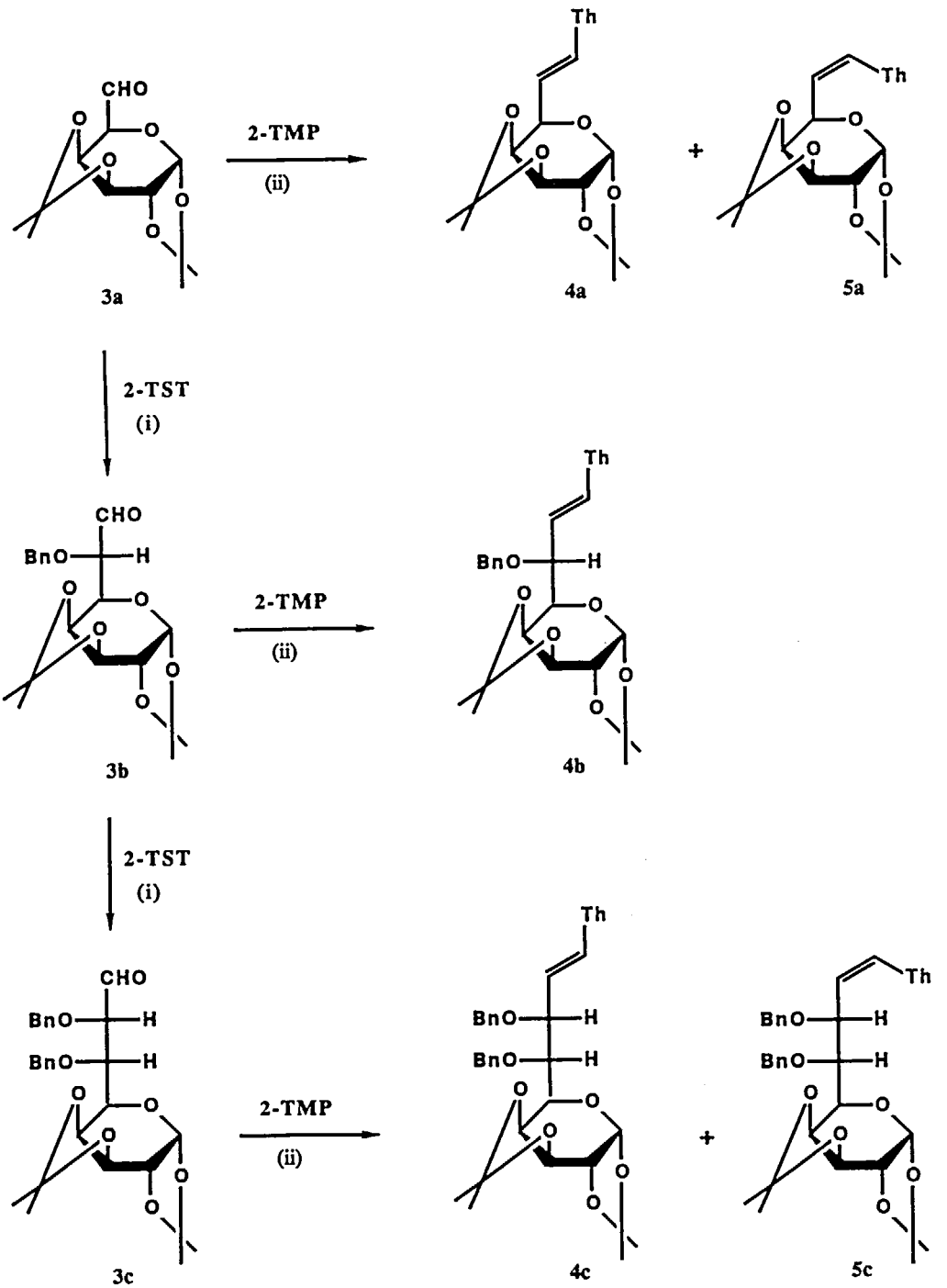
ABSTRACT

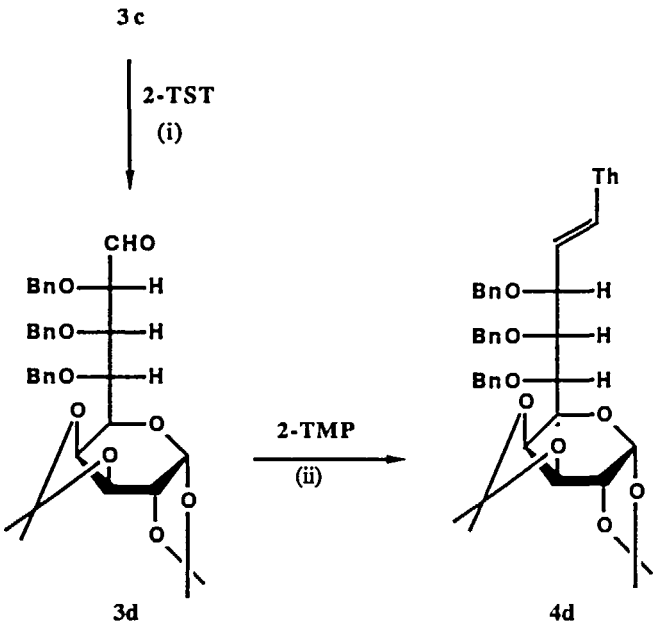
1,2:3,4-Di-*O*-Isopropylidene-α-D-galactohexodialdo-1,5-pyranose and its C-7, C-8, and C-9 homologues react with the title phosphorane in toluene at room temperature to give the corresponding olefins in good yield and variable *E/Z* selectivity depending on the dialdose employed. The highest numbered terminus of these thiazole-masked alkene sugars is transformed into a dideoxy undecadialdose by a one-pot reduction of the ethylenic double bond and deblocking of the formyl group from the thiazole ring.

INTRODUCTION

The construction of stereochemically defined polyhydroxyalkyl chains attached to a furanose or pyranose moiety is an operation of considerable importance in natural products synthesis. For instance, Danishefsky and co-workers have described[1] a new synthetic protocol directed toward the glycidic part of various biologically active compounds starting from dialdoses via an iterative cyclocondensation sequence.



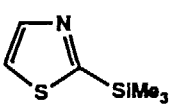
SCHEME I



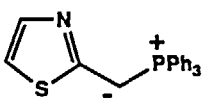
(i) : a, 2-TST-addition ; b, O-benzylation; c, CHO-deblocking
(ii) : Wittig with 2-TMP

SCHEME I (continued)

Recently, we have reported new methodology for the stereoselective side-chain elongation of dialdoses which exploits 2-trimethylsilylthiazole (2-TST) (1) as a synthetic equivalent to the formyl anion synthon.[2] Key steps involve employing the stereoselective addition of 1 to the aldehyde carbonyl and the release of the formyl group from the thiazole ring in the resulting adduct (Thiazole Route).[3] Thus, the repetition of this thiazole-addition-unmasking sequence over four consecutive cycles transforms the protected α-D-galactohexodialdo-1,5-pyranose (**3a**) into the three higher homologues **3b-3d** in good chemical yields and high diastereoselectivity[4] (Scheme I).



1 (2-TST)



2 (2-TMP)

Having sufficiently demonstrated the synthetic utility of 2-TST (**1**) as one-carbon homologating reagent, we are exploring the use of various 2-substituted thiazoles as equivalents to aldehyde synthons[5] for the multi-carbon chain-lengthening of polyalkoxyaldehydes into higher sugars.[6] We describe here the two-carbon homologation of dialdoses **3a-3d** by Wittig olefination with the readily available 2-thiazolylmethylenetriphenylphosphorane[7](2-TMP) (**2**). This provides a new entry to protected long-chain alkene-sugars, a class of versatile intermediates to branched-chain monosaccharides and rare sugars[8] and precursors to biologically active compounds.[9]

RESULTS AND DISCUSSION

The phosphorane **2** is generated in toluene from the appropriate phosphonium chloride and one equivalent of potassium *tert*-butoxide[10] and then reacts with dialdoses **3a-3d** at room temperature over an appropriate time interval (ca. 16 h) to give the corresponding alkene(s) in good yield, but variable *E*/*Z* selectivity, depending on the dialdose employed (Table and Scheme I). In fact, the reactions with **3a** and **3c** give mixtures of *E*- and *Z*-alkenes **4** and **5** in ca. 1 : 2 ratio, whereas those with **3b** and **3d** afford exclusively the *E*-isomer **4**. The configuration about the double bond in alkene sugars **4** and **5** was readily assigned from their ^{1}H NMR spectra. The

TABLE. Reactions of 2-TMP (**2**) with Dialdoses **3a-3d** in Toluene at r.t.

Dialdose	Alkene(s)	*E* : *Z* (%)[a]	Yield(%)[b]
(3a)	**(4a), (5a)**	28 : 72	80
(3b)	**(4b)**	≥95	92
(3c)	**(4c), (5c)**	35 : 65	80
(3d)	**(4d)**	≥95	78

[a] Determined on the crude reaction mixture by ^{1}H NMR. [b] Isolated yield.

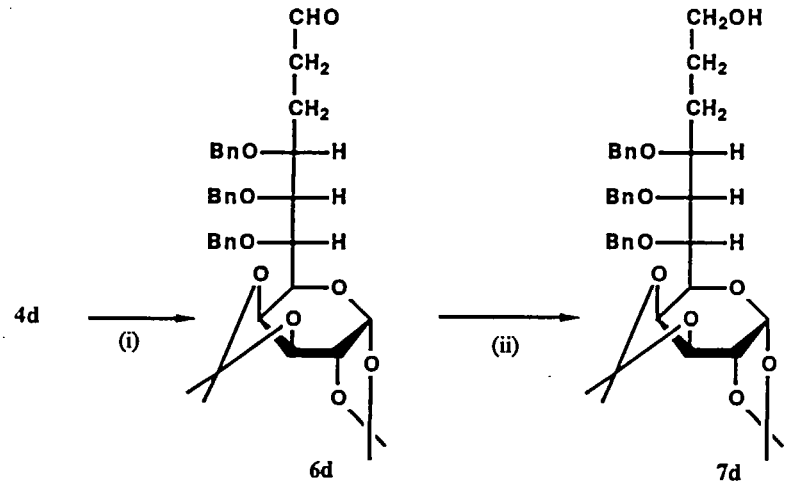
E-isomers **4a** and **4d** show larger *J*-values for the ethylenic protons (ca. 16 Hz) than do the *Z*- isomers **5a** and **5d** (ca. 11 Hz). Hence, the *E/Z* selectivity of the Wittig olefination[11] of dialdoses **3** with the phosphorane **2** appears to be quite sensitive to the length of the aldehyde side-chain.[12] While the explanation of this result is open to conjecture, the phosphorane **2** appears to be an effective reagent for the installation of an ethylenic bond in the side-chain of dialdopyranoses. We have recently described the application of the same strategy to a dialdofuranose having a protected α-amino group in the side-chain aldehyde.[13] The resulting thiazole-masked alkene sugars[14] may serve as precursors to various carbon linked disaccharides throught the numerous elaborations of the double bond[15] which should be feasible in the presence of an effective stable equivalent of the formyl group such as the thiazole ring.[16]

As expected on the basis of earlier work,[7] the aldehyde release in thiazole-alkene sugars occurs with the concomitant reduction of the double bond. In fact, the application of the one-pot formyl deblocking sequence[2,3] to **4d**, i.e. *N*-methylation, $NaBH_4$-reduction, and Hg^{++}-assisted hydrolysis (Scheme II), affords the corresponding dideoxy undecadialdose **6d** which by further reduction with sodium borohydride, is characterized as the undecitol **7d**. Hence, a new methodology for the conversion of dialdoses to dideoxy homologues with two more carbon atoms appears to be at hand. We have recently applied this methodology to a concise synthesis of L-(-)-rhodinose from ethyl lactate.[17]

In conclusion the combination of one- and two-carbon chain-elongation methodologies employing 2-TST (**1**) and 2-TMP (**2**) as equivalents to aldehyde synthons, transforms the readily available C-6 dialdose **3a** into a series of higher homologues up to the C-11 term. This provides further evidence of the synthetic potential of the Thiazole Route to higher-carbon sugars.

EXPERIMENTAL

General Methods. Melting points are uncorrected. ^1H NMR spectra were recorded in chloroform-*d* solution on a 80 MHz Bruker WP-80 or on a 300 MHz Varian Gemini-300 spectrometer. Chemical shifts are given in parts per million downfield from tetramethylsilane. IR spectra were obtained on a Perkin-Elmer Model 297 grating spectrometer. Optical rotations were measured at ca. 22 °C using a



(i) : a, MeI / MeCN ; b, $NaBH_4$ / MeOH; c, $HgCl_2$ / H_2O
(ii) : $NaBH_4$ / MeOH

SCHEME II

Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed on a 1106 Microanalyzer (Carlo Erba). All experiments were carried out under N_2 in freshly distilled and dried solvents. Thin-layer chromatography (TLC) on glass-slides precoated with silica gel (Merck Kiesel gel 60 F254) and preparative chromatography on columns of silica gel (Merck 70-230 mesh) were performed using mixtures of petroleum ether - ethyl acetate as eluents.

2-Thiazolylmethylenetriphenylphosphorane (2-TMP) (**2**) was prepared as described;[7] 1,2:3,4-di-*O*-isopropylidene-α-D-galactohexodialdo-1,5-pyranose (**3a**) was prepared according to the literature procedure;[18] dialdoses **3b-3d** were obtained by homologation of **3a** using 2-trimethylsilylthiazole (2-TST) (**1**) as described.[2,4]

Wittig Reaction of 2-TMP (2) with Dialdoses 3a-3d. General procedure. To a stirred suspension of 2-thiazolylmethylenetriphenylphosphonium chloride[7](0.574 g, 1.45 mmol) in anhydrous (Na wires) toluene (20 mL) was added potassium *tert*-butoxide (0.16 g, 1.45 mmol) . After 2-3 h at room temperature the mixture becomes yellow orange. To this mixture, a solution of the dialdose **3** (1.3 mmol) in toluene (10 mL) was added dropwise and stirring was continued for ca. 16 h.

The reaction mixture was filtered through Celite, the solvent was removed under reduced pressure and the residue was chromatographed to give the *E*-alkene **4** and eventually the *Z*-isomer **5**.

6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-7-(2-thiazolyl)-α-D-galacto-hept-6-ene-1,5-pyranose E-(4a), (0.1 g, 23%) : mp 105-107° C (from petroleum ether-diethyl ether); $[\alpha]_D$ = -163.5° (c 0.58, $CHCl_3$); ^1H NMR (300 MHz) δ 1.33 (s, 3 H), 1.37 (s, 3 H), 1.47 (s, 3 H), 1.55 (s, 3 H), 4.33 (dd, 1 H, J = 8.5 Hz, J = 2.1 Hz), 4.37 (dd, 1 H, J = 4.9 Hz, J = 2.1 Hz), 4.51 (m, 1 H), 4.68 (dd, 1 H, J = 10.3 Hz, J = 2.5 Hz), 5.64 (d, 1 H, J = 4.9 Hz), 6.63 (dd, 1 H, J = 16.1 Hz, J = 5.7 Hz) 6.97 (ddd, 1 H, J = 16.1 Hz, J = 1.5 Hz, J = 0.7 Hz), 7.23 (dd, 1 H, J = 3.2 Hz, J = 0.7 Hz), 7.78 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{16}H_{21}O_5NS$: C, 56.63; H, 6.24; N, 4.13. Found : C, 56.71; H, 6.20; N, 4.05.

Z-(5a), (0.25 g, 57 %) : mp 89-9° C (from petroleum ether-diethyl ether); $[\alpha]_D$ = -154.4° (c 1.24, $CHCl_3$); ^1H NMR (300 MHz) δ 1.35 (s, 3 H), 1.37 (s, 3 H), 1.53 (s, 3 H), 1.57 (s, 3 H), 4.39 (dd, 1 H, J = 4.9 Hz, J = 2.5 Hz), 4.68 (m, 2 H), 5.61 (d, 1 H, J = 4.9 Hz), 5.74 (br d, 1 H, J = 7.0 Hz), 6.20 (dd, 1 H, J = 11.7 Hz, J = 7.7 Hz), 6.67 (dd, 1 H, J =11.7 Hz, J = 1.2 Hz), 7.31 (d, 1 H, J = 3.2 Hz), 7.81 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{16}H_{21}O_5NS$: C, 56.63; H, 6.24; N, 4.13. Found : C, 56.86; H, 6.18; N, 4.03.

6-*O*-Benzyl-7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8-(2-thiazolyl)-D-glycero-α-D-galacto-oct-7-ene-1,5-pyranose E-(4b), (0.55 g , 92 %) : mp 80-82° C (from petroleum ether-diethyl ether); $[\alpha]_D$ = -96.9° (c 1.23, CH_2Cl_2); ^1H NMR (80 MHz) δ 1.29 (s, 3 H), 1.37 (s, 3 H), 1.46 (s, 3 H), 1.48 (s, 3 H), 3.70 -4.80 (m, 7 H), 5.51 (d, 1 H, J = 5.0 Hz), 6.62 (dd, 1 H, J = 16.2 Hz, J = 5.8 Hz), 7.01 (d, 1 H, J = 16.2 Hz), 7.16-7.41 (m, 6 H), 7.77 (d, 1 H, J = 3.2 Hz).

Anal Calcd for $C_{24}H_{29}O_6NS$: C, 62.73; H, 6.36; N, 3.05. Found : C, 62.66; H, 6.41; N, 2.97.

6,7-Di-*O*-benzyl-8,9-dideoxy-1,2:3,4-di-*O*-isopropylidene-9-(2-thiazolyl)-D-erythro-α-D-galacto-non-8-ene-1,5-pyranose E-(4c), (0.21 g, 28 %) : syrup; $[\alpha]_D$ = -18.1° (*c* 0.22, $CHCl_3$); ^1H NMR (80MHz) δ 1.20 (s, 6 H), 1.34 (s, 3 H), 1.47(s, 3 H), 3.65 (m, 1 H), 4.0-5.12 (m, 9 H), 5.50 (d, 1 H, J = 5.0 Hz), 6.66 (dd, 1 H, J = 16.0 Hz, J = 7.4 Hz), 7.0 (d, 1 H, J = 16.0 Hz), 7.25 (m, 11 H), 7.71 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{32}H_{37}O_7NS$: C, 66.31; H, 6.43; N, 2.42. Found : C, 66.15; H, 6.31; N, 2.32.

Z-(5c), (0.39 g, 52 %): syrup; $[\alpha]_D$= -50.2° (c 3.06, $CHCl_3$); ^1H NMR (300 MHz) δ 1.20 (s, 3 H), 1.31 (s, 3 H), 1.35 (s, 3 H), 1.44 (s, 3 H), 4.04 (br s, 1 H), 4.21 (dd, 1 H, *J* = 5.0 Hz, *J* = 2.4 Hz), 4.78-4.44 (m, 6 H), 4.98 (d, 1 H, *J* = 11 Hz), 5.42 (d, 1 H, *J* = 4.9 Hz), 5.59 (d, 1 H, *J* = 9.6 Hz), 6.26 (dd, 1 H, *J* = 12.1 Hz, *J* = 9.6 Hz), 6.82 (d, 1 H, *J* = 12.1 Hz), 7.18-7.44 (m, 11 H), 7.79 (d, 1 H, *J* = 3.2 Hz).

Anal. Calcd for $C_{32}H_{37}O_7NS$: C, 66.31; H, 6.43; N, 2.42. Found: C, 66.18; H, 6.48; N, 2.46

6,7,8-Tri-*O*-benzyl-9,10-dideoxy-1,2:3,4-di-*O*-isopropylidene-10-(2-thiazolyl)-D-ribo-α-D-galacto-dec-9-ene-1,5-pyranose E-(4d), (0.71 g, 78 %) : syrup; ^1H NMR (80 MHz) δ 1.27 (s, 3 H), 1.32 (s, 3 H), 1.37 (s, 3 H), 1.47 (s, 3 H), 3.85-4.75 (m, 13 H), 5.50 (d, 1 H, *J* = 5.1 Hz), 6.70 (dd, 1 H, *J* = 5.2 Hz, *J* = 16.2 Hz), 7.0 (d, 1 H, *J* = 16.2 Hz), 7.30 (m, 16 H), 7.76 (d, 1 H, *J* = 3.2 Hz). Compound **4d** was used as obtained for the next synthetic step, without further purification.

Conversion of Vinylthiazole *E*-(4d) into the Dideoxy Undecadialdose (6d). A solution of **4d** (0.3 g, 0.45 mmol) and methyl iodide (0.56 g, 4 mmol) in acetonitrile (30 mL) was refluxed for 18 h. The solvent was removed under vacuum and the crude *N*-methylthiazolium salt was dissolved in methanol (30 mL). After cooling the solution at -10° C, sodium borohydride was added portionwise and the mixture stirred for 20 min at room temperature. The mixture was quenched with acetone (0.5 mL), the solvent was partially evaporated under vacuum and, after addition of brine (10 mL), the residue was extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The resulting crude thiazolidine was dissolved in acetonitrile (3 mL) and added to a stirred solution of $HgCl_2$ (0.15 g, 0.54 mmol) in a 4:1 acetonitrile-water mixture (20 mL). After 15 min, the reaction mixture was filtered through Celite, the solvent was partially evaporated under reduced pressure, brine (10 mL) was added to the residue and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed in vacuo, and the residue was chromatographed (silica gel, 1:1, petroleum ether-diethyl ether) to give 0.17 g (62 %) of **6,7,8-tri-*O*-benzyl-9,10-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-ribo-α-D-galacto-undecadialdo-1,5-pyranose (6d)**: oil; IR (CH_2Cl_2) 1730 cm^{-1}; ^1H NMR δ 1.27 (s, 3 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 1.95-2.45 (m, 4 H), 3.75-4.85 (m, 13 H), 5.50 (d, 1 H, *J* = 5.0 Hz), 7.30 (m, 15 H), 9.62 (t, 1 H, *J* = 2.1 Hz). This compound was not purified.

Reduction of Dideoxy Undecadialdose (6d) to Undecitol (7d). The dialdose **6d** (0.15 g, 0.24 mmol) was dissolved in methanol (10 mL) at room temperature and sodium borohydride (0.01 g, 0.26 mmol) was added portionwise. After 15 min, acetone (0.5 mL) was added and the solution was concentrated in vacuo. A saturated solution of NH_4Cl (10 mL) was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was chromatographed (silica gel, 1:1 ethyl acetate-petroleum ether) to give 0.13 g (90 %) of **6,7,8-tri-*O*-benzyl-9,10-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-ribo-α-D-galacto-undeculo-1,5-pyranose (7d)**: sticky oil; $[\alpha]_D$ = -27.6° (c 1.72, $CHCl_3$); IR (film) 3450, 1500, 1460 cm^{-1}; ^1H NMR (300 MHz) δ 1.28 (s, 3 H), 1.33 (s, 3 H), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.58-2.02 (m, 5 H), 3.56 (m, 2 H), 3.85 (m, 1 H), 3.95-4.17 (m, 3 H), 4.28 (dd, 1 H, J = 5.1 Hz, J = 2.2 Hz), 4.40-4.85 (m, 8 H), 5.52 (d, 1 H, J = 5.0 Hz), 7.32 (m, 15 H).

Anal. Calcd for $C_{38}H_{48}O_9$: C, 70.35; H, 7.46. Found : C, 70.28; H, 7.40.

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9. See for instance ref. 1 for the synthesis of lincosamine, 3-deoxy-manno-2-octulosonic acid (KDO), and *N*-acetylneuraminic acid (NANA).

10. The olefination of **3c** produced occasionally considerable amounts of unidentified by-products whose formation however was totally suppressed by the use of a slight defect of potassium tert-butoxide or by employing preformed and isolated 2-TMP as described (ref. 7).

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14. By virtue of the thiazolyl-formyl group equivalence (ref. 2-4), polyhydroxyalkyl- and polyhydroxyalkenylthiazoles are considered as 'thiazole-sugars'.

15. Results from studies on addition (hydroxylation, oxyamination, epoxidation, etc.) and cycloaddition reactions will be published in due course.

16. The thiazole ring is stable toward hydrolysis in both acid and base and toward oxidation and reduction. See: J. V. Metzger, *The Chemistry of Heterocyclic Compounds. Thiazole and its Derivatives,* Vol. 34; Wiley: New York, 1979, Part. 1.

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