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Note

Alkyl and cyclopropyl sugars: approaches to branched-chain D-glucofuranose derivatives*

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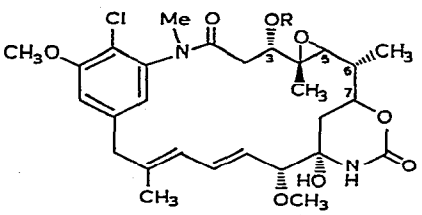
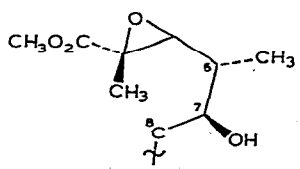
A problem of considerable concern to organic chemists is the stereospecific construction of functionalized acyclic compounds bearing multiple, contiguous asymmetric centers. The issue is particularly germane to the natural-products chemist interested in total synthesis, as portions of the biologically active macrolide antibiotics[1], ansamycins[2], and maytansinoids[3] display such structural features in enantiomerically pure form. Newly developed methods of kinetic stereoselection in the aldol[4] or halolactonization[5] reactions have addressed this objective, but still must rely on a classical resolution to produce chiral substances. One alternative strategy is to use modified carbohydrates as optically active starting materials. This approach, employed successfully in a number of recently completed total syntheses[6], has proven to be an extremely efficient and attractive one.

Our own research towards an enantioselective synthesis of maytansine (**1**) first led us to consider sugars as a potential source of the chiral C-3–C-8 unit in **1**, with particular focus on the *5S,6R,7S* branching point in the macrocycle[7]. The chemistry of new methyl and cyclopropyl monosaccharides that we have prepared is the subject of this Note.



1
R = OC–CH(CH3)–N(CH3)–COCH3
maytansine



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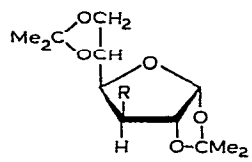

3 R = OH
4 R = CH3

*Part III in the series "Ansa Macrolide Synthesis"; for Part II see ref. 7.

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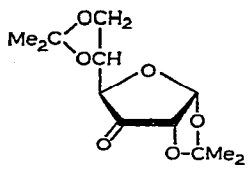
DISCUSSION

We chose to work with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) both for its low cost and ready availability (Pfanstiehl Laboratories, Waukegan, Illinois) and because replacement of the 3-hydroxyl substituent by a methyl group, as in **4**, would generate chirality at C-2–C-4 of the sugar precisely corresponding to C-5–C-7 of **2**. A number of strategies might be envisaged for construction of a C-3–C-8 synthon for maytansine from **4**; however, the paucity of methods for preparing *C*-branched deoxyglycosides[8] caused us first to focus our efforts on this more-general objective.

The photoreduction of acetates and benzoates in hexamethylphosphoric triamide[9] has recently been applied to the high-yield synthesis of deoxy sugars[10]. Ketone **5** (ref. 11) reacted with methyllithium or methylmagnesium bromide in oxolane to furnish 1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**6**) in 65% yield[12]. Deoxygenation of the corresponding acetate **7** in 19:1 hexamethylphosphoric triamide–water through quartz at 254 nm afforded a readily separated, 1:1 mixture of the original alcohol **6** and a single, methyl-substituted, 3-deoxy sugar formulated as the isomer **8**. This assignment was based on n.m.r. spectroscopy, which showed H-2 to be coupled to adjacent *cis*-protons at C-1 ($J_{1,2}$ = 3 Hz) and C-3 ($J_{2,3}$ = 3.5 Hz)[13]. This result was consistent with capture of a rapidly interconverting, radical-intermediate[9c] from the less hindered, "upper" face of the oxolane ring.



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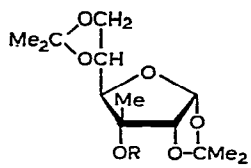
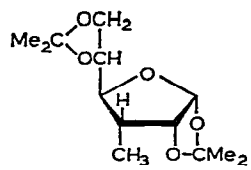


6 R = H
7 R = Ac

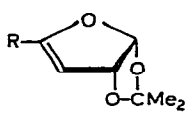


8

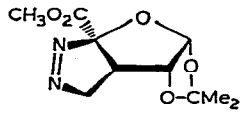
We next investigated a variety of conjugate additions to the α,β-unsaturated ester **9** (ref. 14), but were unable to effect the desired methylation of **9** at C-3 by either dimethylcopperlithium[15] or methylcopper–boron trifluoride etherate[16]. An interesting photochemical alkylation of enones by alcohols, acetals, or orthoformates has been applied to the synthesis of branched-chain sugars by Fraser-Reid and coworkers[17]. However irradiation of **9** in methanol or methanol–acetonitrile at 350 nm (Rayonet Reactor) yielded a complex mixture.

In sharp contrast to these results was the ease whereby **9** combined with ethereal diazomethane. A single pyrazoline, formulated as **10**, could routinely be isolated in 68–73% yield. Photolysis of **10** in 1,2-dimethoxyethane converted it into the crystalline cyclopropane **11**. Although reductive cleavage[18] of **11** was expected to afford a 3-methylated 3-deoxy sugar, exposure of **11** to an excess of lithium in liquid ammonia furnished only the amide **12** and alcohol **13**, together with starting material. The corresponding acid (**14**) was inert to metal–amine solutions and, upon catalytic hydrogenation (palladium-on-carbon, ethanol, room temperature, 3 atm),

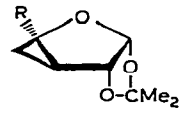
produced the alcohol **13**. We have not yet surmised a satisfactory explanation for the resistance of these cyclopropyl sugars toward reductive opening.



9 R = CO_2Me
17 R = CO_2H
18 R = $COCH_3$



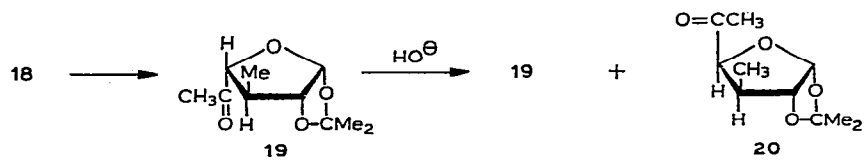
10



11 R = CO_2Me
12 R = $CONH_2$
13 R = CH_2OH
14 R = CO_2H
15 R = CH_2OSnBu_3
16 R = $CH{-}OSnBu_3$

An oxidative cleavage of cyclopropylcarbinyl stannyl ethers has been reported[19], which was tested on **15**. Photolysis in the presence of di-*tert*-butyl peroxide (pentane, —78→20°) did produce a new methylated furanoid carboxaldehyde, presumably through the intermediacy of a stannyloxy radical **16**, but never in preparatively useful yields.

The best synthetic route to a glycofuranose 3-*C*-methylated on the "upper" face consisted of the 1,4-addition of dimethylcopperlithium to the α,β-unsaturated ketone **18**, readily available[20] in two steps from **9**. The enhanced reactivity of conjugated ketones over esters proved to be a critical factor in this successful conjugate addition[15,21]. Unlike the enoate **9**, enone **18** was completely consumed within 15 min at —5° to afford **19** as the exclusive, kinetic product. The 3,4-*trans* arrangement of **19** was supported by the observed $J_{3,4}$ coupling-constant of 1.5 Hz. Equilibration of **19** in sodium methoxide–methanol at 20° led to a 1 : 1.7 mixture of the 4-epimeric ketones **19** and **20**. The new isomer **20**, having correct relative and absolute stereochemistry for the maytansine fragment **2**, had $J_{3,4}$ = 3 Hz. Both structural assignments were consistent with couplings observed in a closely related series of *cis*- and *trans*-3-deoxy-3,4-disubstituted glucofuranose derivatives[14].



18 → **19** (+ $HO^{\ominus}$) + **20**

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover Unimelt instrument and are uncorrected. N.m.r. spectra of solutions in chloroform-*d* were recorded on a Varian A-60A or EM-390 spectrometer relative to an internal standard of tetramethylsilane. I.r. spectra were determined with a Perkin–Elmer 137 spectrophotometer. Mass spectra were recorded with a computerized AEI MS-902 instrument.

Unless otherwise noted, all reactions were performed under nitrogen in flame-

dried or oven-dried (overnight at 105°) glassware. All air- and moisture-sensitive solutions were transferred or dispensed by using oven-dried hypodermic syringes. Ethereal solvents were distilled under nitrogen from lithium aluminum hydride. All reagents were commercial products and were used as supplied.

3-O-Acetyl-1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-allofuranose (**7**). — A mixture of the alcohol[12] **6** (0.38 g, 1.38 mmol) and dry pyridine (3 mL) containing a trace of 4-*N*,*N*-dimethylaminopyridine was treated with acetic anhydride (0.6 mL, 3.5 mmol), kept for 24 h at room temperature, and then poured into ice–chloroform. The organic layer was washed successively with 5% hydrochloric acid, saturated sodium hydrogencarbonate, and brine, dried (magnesium sulfate) and evaporated to afford 376 mg (86%) of **7**, m.p. 75–76°; n.m.r. ($CDCl_3$): δ 5.71 (d, J 4 Hz, H-1), 4.80 (d, H-2), 4.0–4.15 (m, 4H), 2.03 (s, 3H), 1.50, 1.48, 1.34, and 1.30 (4s, 15H); *m/e* 301 ($M^+ - CH_3$, 35%), 215 (11%), and 43 (100%).

Anal. Calc. for $C_{15}H_{23}O_7$: C, 57.13; H, 7.35. Found: C, 57.10; H, 7.37.

Photoreduction of **7**: *3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-allofuranose* (**8**). — A solution of **7** (53 mg, 0.167 mmol) in 19:1 hexamethylphosphoric triamide–water (12 mL) was placed in a quartz tube fitted with a stopcock and flushed with nitrogen. The tube was lowered into a Rayonet Reactor fitted with sixteen low-pressure 253.7-nm lamps, and irradiated for 9 h at 20–30°. The mixture was then transferred to a large separatory funnel and diluted with ether (300 mL) and aqueous sodium chloride (200 mL). The organic phase was washed exhaustively with brine, and then dried and evaporated to furnish 46 mg (86% recovery) of a mixture that by n.m.r. analysis was a 1:1 mixture of the known[12] alcohol **6** plus a new deoxy sugar **8**. These could be readily separated by column chromatography (3:2 ethyl acetate–hexane) to afford **8** as an oil; n.m.r. ($CDCl_3$): δ 5.75 (d, J 3 Hz, H-1), 4.53 (dd, J 3, 3.5 Hz, H-2), 1.22 (d, 3H, J 7 Hz, methyl).

Reaction of diazomethane with 3-deoxy-1,2-O-isopropylidene-α-D-glycero-pent-3-enfuranuronic acid methyl ester (**9**). — To a solution of **9** (0.90 g, 4.5 mmol) in dry ether (40 mL) was added 3 mL of ethereal diazomethane[22]. The flask was stoppered, wrapped in aluminum foil, and kept at 20°. More diazomethane (2 mL) was added once every day (5–7 days) until all **9** was consumed. Evaporation of the solvent and column chromatography of the residue afforded 0.75–0.80 g (68–73%) of the pyrazole **10**; m.p. 81–84° (dec); $[\alpha]_D^{20}$ +312° (*c* 0.5, chloroform); R_F 0.32 (3:2 hexane–ether); $\lambda_{max}^{CH_2Cl_2}$ 5.68, 5.75, and 6.41 μm; n.m.r. ($CDCl_3$): δ 4.71, 4.80 (ABX, 2H), 5.72 (d, 1H, J 3 Hz), 4.31 (d, 1H, J 3 Hz), 3.83 (s, 3H), 2.93 (dd, 1H, J 3.9 Hz), 1.59, and 1.32 (2s, 6H); *m/e* 243 (M + 1, 8%), 227 (21%), 185 (12%), and 97 (100%).

Anal. Calc. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.82. Found: C, 49.61; H, 5.90.

Methyl 3,4-C-Cyclopropyl-3-deoxy-1,2-O-isopropylidene-β-L-arabino-pentofuranuronate (**11**). — A dry solution (0.08M) of **10** (0.5 g, 2.06 mmol) in 1,2-dimethoxyethane in a Pyrex test tube was deaerated in a stream of argon for 15 min and then strapped to a water-cooled immersion well and irradiated with a Hanovia medium-pressure mercury lamp for 2 h. The solution was evaporated and the residue purified

by column chromatography on silica gel. Elution with 3:1 ether–hexane afforded 0.295 g (67%) of crystalline **11**; m.p. 57–58°, $[\alpha]_D^{20}$ +104° (*c* 0.51, chloroform); R_F 0.6 (3:2 ether–hexane); n.m.r. ($CDCl_3$): δ 5.62 (d, 1H, *J* 4 Hz), 4.77 (d, 1H, *J* 4 Hz), 3.80 (s, 3H), 2.22 (dd, 1H, *J* 4, 10.5 Hz), 1.60 (m, 1H, cyclopropane), 1.53, 1.41 (2s, 6H), and 0.85 (m, 1H, cyclopropane); *m/e* 199 ($M^+ - CH_3$, 3%), 156 (8%), and 97 (100%).

Anal. Calc. for $C_{10}H_{14}O_5$: C, 56.06; H, 6.58. Found: C, 56.10; H, 6.61.

Saponification of **11**: *3,4-C-Cyclopropyl-3-deoxy-1,2-O-isopropylidene-β-*L-arabino-*pentofuranuronic acid* (**14**). — A solution of **11** (0.154 g, 0.72 mmol) in oxolane (5 mL) was treated dropwise with M sodium hydroxide (1.5 mL, 1.5 equiv). After 2 h at 20°; the solvent was evaporated under diminished pressure, the residue acidified to pH 2 with 5% hydrochloric acid and the solution extracted repeatedly with chloroform. The combined extracts were dried and evaporated to furnish 0.130 g (90%) of **14**, m.p. 103–104°, $[\alpha]_D^{20}$ +112° (*c* 0.5, chloroform); λ_{max}^{film} 3.25 and 5.83 μm; n.m.r. ($CDCl_3$): δ 5.67 (d, 1H, *J* 4 Hz), 4.80 (d, 1H, *J* 4 Hz), 2.41 (dd, 1H, *J* 4, 10 Hz), 1.70 (m, 1H), 1.55, 1.39 (2s, 6H), and 0.92 (m, 1H, cyclopropane).

Reaction of methyllithium with **17**: *3,6-dideoxy-1,2-O-isopropylidene-α-*D-glycero-*hex-3-enos-5-ulose* (**18**). — A solution (1.45M) of methyllithium (Ventron) in ether, (0.95 mL, 1.4 mmol) was added dropwise at −5° to a solution of the carboxylic acid[14] **17** (0.130 g, 0.70 mmol) in ether (8 mL). After 90 min at room temperature, ice (5 g) was added and the mixture acidified with 0.1M hydrochloric acid to pH 5. The ether layer was separated, and then combined with five subsequent chloroform extracts. Evaporation of the dried extract afforded **18** as an oil contaminated with a small quantity of the corresponding dimethyl tertiary carbinol. The enone **18** was rather unstable and was, therefore, not further purified; λ_{max}^{film} 5.90 and 6.18 μm; n.m.r. ($CDCl_3$): δ 6.17 (d, 1H, *J* 6 Hz), 6.02 (d, 1H, *J* 2), 5.39 (dd, 1H, *J* 2 and 6 Hz), 2.32 (s, 3H), and 1.43 (s, 6H).

Conjugate addition of dimethylcopperlithium to **18**: *3,6-Dideoxy-1,2-O-isopropylidene-3-C-methyl-β-*L-arabino-*hexos-5-ulose* (**19**). — Methyllithium (0.81 mL, 1.18 mmol) was added dropwise to a suspension at −5° of flame-dried cuprous iodide (Fisher, "purified" grade, 0.112 g, 0.59 mmol) in dry ether (6 mL) and after 5 min, an ethereal solution (5 mL) of the enone **18** (0.10 g, 0.54 mmol) was added dropwise. T.l.c. after 10 min indicated the absence of starting material. The mixture was hydrolyzed with 10% ammonium chloride (3 mL), and the aqueous layer drawn off and extracted 5 more times with chloroform. The combined organic layers were washed once with brine, dried, and evaporated. Column chromatography on silica gel produced the pure ketone **19** as an oil (21% yield from acid **17**); $[\alpha]_D^{20}$ +8.8° (*c* 0.15, chloroform); R_F 0.54 (4:1 hexane–ethyl acetate); λ_{max}^{film} 5.81, 8.30, 8.61, 9.05, 9.46, and 9.95 μm; n.m.r. ($CDCl_3$): δ 5.91 (d, *J* 3.5 Hz, H-1), 4.32 (d, *J* 3.5 Hz, H-2), 3.98 (d, *J* 1.5 Hz, H-4), 2.92 (dq, *J* 1.5 and 7.5 Hz, H-3), 2.31 (s, 3H), 1.41, 1.25 (2s, 6H), and 1.12 (d, 3H, *J* 7.5 Hz, methyl); *m/e* 200 (M^+, 0.4%), 185 ($M^+ - CH_3$, 6%), 157 (16%), 43 (100%).

Base-catalyzed equilibration of **19**: *3,6-Dideoxy-1,2-O-isopropylidene-3-C-*

methyl-α-D-xylo-hexos-5-ulose (**20**). — The kinetically produced isomer **19** (22 mg, 0.11 mmol) was dissolved in dry methanol (3 mL) and sodium hydride (dispersion, ~5 mg) was added. The solution (pH 10) was kept for 24 h at room temperature and then acidified to pH 5. The mixture was evaporated under diminished pressure and the residue extracted three times with chloroform. The combined extracts were dried and evaporated to afford 20 mg of **19** and **20** in 1 : 1.7 ratio. The new isomer (**20**) had the following n.m.r. characteristics ($CDCl_3$): δ 5.95 (d, J 4 Hz, H-1), 4.79 (d, J 4 Hz, H-2), 4.39 (d, J 3 Hz, H-4), 2.66 (dq, J 3 and 7 Hz, H-3), 2.21 (s, 3H), 1.50, 1.31 (2s, 6H), and 0.82 (d, 3H, J 7 Hz, methyl).

ACKNOWLEDGMENTS

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