Branched-chain Sugars. Part 7.[1] A Route to Sugars with Two-carbon Branches using 1-Methoxyvinyl-lithium

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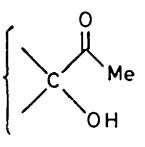
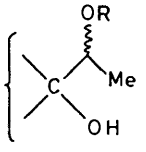
1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (11) reacted with 1-methoxyvinyl-lithium in tetrahydrofuran–n-pentane at −60 °C to give a crystalline adduct identified as 1,2:5,6-di-*O*-isopropylidene-3-*C*-(1-methoxyvinyl)-α-D-allofuranose (12). The sugar derivatives (13), (14), (16), and (18), which contain a variety of two-carbon branches, were readily derived from the adduct (12).

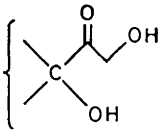
A NUMBER of sugar components of antibiotic substances contain two-carbon branches such as (1), (2), (3), or (4) at a tertiary alcoholic centre.[2] For example, the *C*-acetyl function (1) is present in one of the sugar components (5) of flambamycin,[3] while aldgarose [4] (6) (from



(1)



(2) R = H
(4) R = Me



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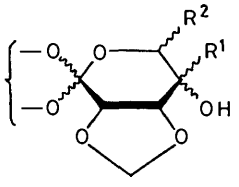
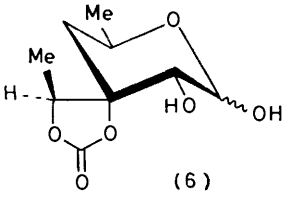


(5) R^1 = COMe; R^2 = Me
(8) R^1 = CHMe(OMe); R^2 = H



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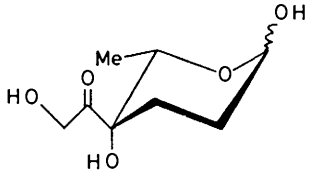

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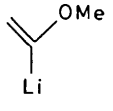

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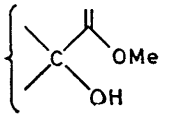


(10)

aldgamycin [5]), pillarose [6] (7) (from pillaromycin A [7]), and a sugar component (8) of everninomicins B [8] and D [9] contain the functionalities (2), (3), and (4), respectively. Related functionalities also occur in the anthracycline antibiotics quinocycline A and B and isoquinocycline A and B,[10] as well as in avilamycins A and C.[11] Hitherto, the introduction of such branched-chain functionalities into sugars has relied upon the addition of vinyl [12] and acetylene [13] organometallic reagents or metallated 1,3-dithian and its derivatives [14] (acyl anion equivalents) to appropriately protected keto-sugars. The functionality (3) has recently been introduced [15] into corticoid hormones (*e.g.* oestrone methyl ether) by using 1-methoxyvinyl-lithium [16] (9) as a masked acylating agent. Since the resulting adduct (10) can be transformed into such functionalities as (1)—(4) by simple operations, it seemed appropriate to explore the possible use of 1-methoxyvinyl-lithium (9) in the synthesis of sugars containing a two-carbon branch. We now report the details of our preliminary investigation [17] of the reaction of (9) with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (11), while some reactions with hexopyranosiduloses and the synthesis of a derivative of pillarose (7) are described in Part 8.[18]

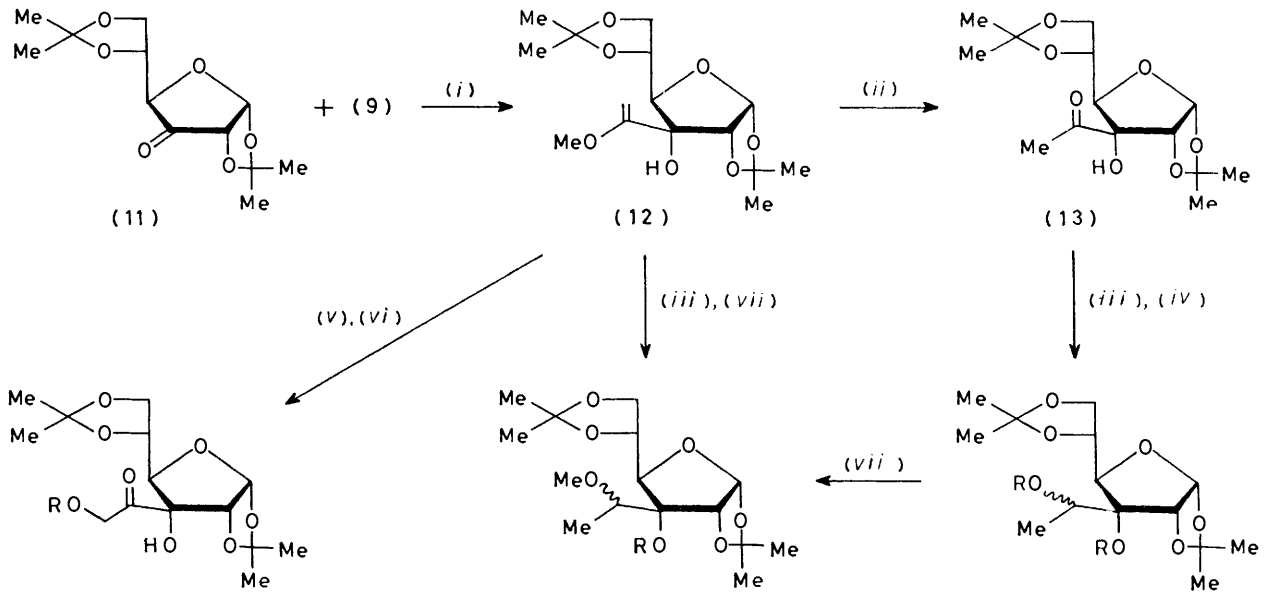
RESULTS AND DISCUSSION

The keto-sugar [19] (11) reacted with an excess of 1-methoxyvinyl-lithium [16] in tetrahydrofuran–n-pentane at −60 °C to yield the crystalline adduct (12) (39%), $\nu_{max.}$ 1 625 cm^{-1} (C=C), which was smoothly hydrolysed (0.02M-hydrochloric acid in aqueous 1,4-dioxan) to the *C*-acetyl derivative (13). Although (12) and (13) could not be distinguished by t.l.c. [possibly due to hydrolysis of (12) on the chromatogram], the outcome of the reaction was readily discerned on examination of the crude product by either i.r. spectroscopy (appearance of the carbonyl absorption at 1 710 cm^{-1}) or ^{1}H n.m.r. spectroscopy (appearance of the *C*-acetyl group at δ 2.44). Catalytic hydrogenation of the *C*-acetyl derivative (13) gave a crystalline 3-*C*-(1-hydroxyethyl) derivative (14), which afforded the 3,3^1-cyclic carbonate (15) on carbonylation with phosgene in pyridine. The physical constants of (14) and (15) were in close agreement with those of derivatives prepared by Horton and co-workers [13] *via* ethynylation of the keto-sugar (11). Since their work established the D-*allo*-configuration for (14) and (15), it follows that the adduct (12) has the D-*allo*-configuration. The configuration at C-3^1 of (14) and (15) remains to be determined. There is ample precedent to suggest that 1-methoxyvinyl-lithium, like other organometallic reagents,[20] would add to the carbonyl group of (11) from the *exo*-direction with respect to the trioxabicyclo-[3.3.0]octane ring-system.

When the adduct (12) was oxidised with *m*-chloroperbenzoic acid in wet ether or, preferably, with osmium tetraoxide in pyridine, it was converted into the *C*-glycoloyl derivative (16), which gave the monoacetate (17) on acetylation. The stereochemistry at C-3 is necessarily controlled by that of the initial adduct, so that (16) can be assigned the D-*allo*-configuration.

Catalytic hydrogenation of the adduct (12) produced roughly equal amounts of the epimeric 3-*C*-(1-methoxyethyl) derivatives (18a and b). Both C-3[1] epimers were obtained crystalline after chromatography on silica gel and sublimation. Methylation of (18a and b) gave the corresponding dimethylated derivatives (19a and b), each having a distinctive ^{1}H n.m.r. spectrum and optical rotation. The diol (14) gave the dimethylated derivative (19a) on methylation, thereby relating, but not defining, the stereochemistry at C-3[1] of these compounds.

The foregoing transformations demonstrate that 1-methoxyvinyl-lithium (9) is effective as a masked acylating agent in the synthesis of sugars containing a functionalized side-chain. A notable advantage over other procedures [12-14] is that the initial adduct can be easily diverted to all the two-carbon, branched-chain functionalities so far encountered in antibiotic sugars.[2] One slight drawback is that isolation or purification of such enol ethers as (12) cannot be accomplished by chromatography over silica gel, which catalyses their hydrolysis to the corresponding *C*-acetyl derivative in the presence of adventitious water. However, as we show in Part 8,[18] we experienced no difficulty in effecting transformations on impure methoxyvinyl adducts.



Reagents: (*i*) THF–C_5H_{12} at −60 °C; (*ii*) H_3O^+; (*iii*) H_2–Pt; (*iv*) $COCl_2$-pyridine; (*v*) *m*-$ClC_6H_4CO_3H$–Et_2O–H_2O or OsO_4–pyridine; (*vi*) Ac_2O–pyridine; (*vii*) MeI–NaH–DMF

EXPERIMENTAL

T.l.c. was performed on Kieselgel G; spots were located with vanillin–sulphuric acid.[21] I.r. spectra were recorded for Nujol mulls or liquid films on a Perkin-Elmer Infracord spectrophotometer. N.m.r. spectra were measured with a Brucker Spectrospin (90 MHz) spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. Optical rotations were measured at ambient temperature with a Perkin-Elmer 141 automatic polarimeter. Light petroleum refers to the fraction having b.p. 60—80 °C.

1,2:5,6-*Di*-O-*isopropylidene*-3-C-(1-*methoxyvinyl*)-α-D-*allofuranose* (12).—To a stirred solution containing 1-methoxyvinyl-lithium [16] (22 mmol) in tetrahydrofuran–n-pentane at −60 °C under nitrogen was added dropwise the keto-sugar [19] (11) (2.04 g, 7.9 mmol) in tetrahydrofuran (40 ml), and, on complete addition, the reaction mixture was stirred at this temperature for 30 min before it was allowed to warm to 0 °C over 30 min. It was then quenched with a saturated solution of ammonium chloride, the aqueous solution was extracted several times with ether, and the combined ethereal extracts were dried ($MgSO_4$) and concentrated. Recrystallisation of the residue from chloroform–light petroleum gave the *enol ether* (12) (0.98 g, 39%), m.p. 157—158 °C; $[\alpha]_D$ +62° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 1 625 (C=C) and 3 460 cm^{-1} (OH) (Found: C, 56.9; H, 7.9. $C_{15}H_{24}O_7$ requires C, 56.9; H, 7.6%); δ 1.31, 1.35, 1.41, and 1.58 (12 H, s, 2 × CMe_2), 3.55 (3 H, s, OMe), 3.78—4.26 (3 H, complex m and C=CH_2), 4.43 (1 H, d, $J_{1,2}$ 4 Hz, H-2), 4.58 (1 H, d, $J_{4,5}$ 3 Hz, H-4), and 5.81 (1 H, d, H-1).

3-C-*Acetyl*-1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose* (13).—The enol ether (12) (0.55 g) in 1,4-dioxan (20 ml) was hydrolysed with 0.02M-hydrochloric acid (40 ml) at room temperature for 2 h, after which the solution was extracted

with chloroform (3 × 100 ml) and the combined organic extracts were washed with a saturated solution of sodium hydrogencarbonate and dried ($MgSO_4$). Removal of the solvent left a crystalline residue, which was purified by chromatography on silica gel [eluant methylene chloride–acetone (20 : 1)]. Recrystallisation from ether–n-hexane gave the C-*acetyl derivative* (13) (0.50 g, 95%), m.p. 86—87.5°; $[\alpha]_D$ +32° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 1 710 (C=O) and 3 440 cm^{-1} (OH) (Found: C, 55.9; H, 7.2. $C_{14}H_{22}O_7$ requires C, 55.6; H, 7.3%); δ 1.32, 1.38, 1.45, and 1.60 (12 H, s, 2 × CMe_2), 2.44 (3 H, s, COMe), 3.62—4.20 (4 H, overlapping m, H-4—H-6), 4.38 (1 H, d, $J_{1,2}$ 3.5 Hz, H-2), and 5.93 (1 H, d, H-1).

3-C-(1-*Hydroxyethyl*)-1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose* (14).—A solution of the *C*-acetyl derivative (13) (0.35 g) in methanol (35 ml) containing Adams catalyst (0.35 g) was shaken under a slight overpressure of hydrogen at room temperature until the uptake of hydrogen had ceased. Removal of the catalyst and solvent gave the 3-C-*hydroxyethyl derivative* (14) (0.25 g, 71%), m.p. 118—119 °C (from ether–n-hexane); $[\alpha]_D$ +25.5° (*c* 1 in $CHCl_3$) {lit.[13] m.p. 119—119.5 °C, $[\alpha]_D$ +26.8° (*c* 1.7 in $CHCl_3$)}.

Carbonylation of (14), as described by Horton *et al.*,[13] gave 3,3[1]-*O*-carbonyl-3-*C*-(1-hydroxyethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (15), m.p. 207—208 °C (from ether–light petroleum); $[\alpha]_D$ +26° (*c* 1 in $CHCl_3$) {lit.,[13] m.p. 205—205.5 °C, $[\alpha]_D$ +25.4° (*c* 1.3 in $CHCl_3$)}.

3-C-*Glycoloyl*-1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose* (16).—(*a*) *Using* m-*chloroperbenzoic acid*. A stirred solution of the enol ether (12) (2.5 g) in wet ether (110 ml) was treated at room temperature with *m*-chloroperbenzoic acid (1.38 g) for 5 h; a further quantity (0.6 g) of the peracid was then added and stirring was continued overnight, after which t.l.c. [methylene chloride–acetone (20 : 1)] revealed the presence of three products in the reaction mixture. The ethereal solution was washed in turn with saturated solutions of sodium hydrogencarbonate and sodium chloride, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel [eluant methylene chloride–acetone (20 : 1)] gave two unidentified components (0.396 g and 0.012 g, respectively) followed by the 3-C-*glycoloyl derivative* (16) (0.85 g, 34%), m.p. 97—98 °C (from chloroform–n-hexane); $[\alpha]_D$ +29° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 1 710 (C=O) and 3 440 cm^{-1} (OH) (Found: C, 52.6; H, 7.2. $C_{14}H_{22}O_8$ requires C, 52.8; H, 6.9%); δ 1.28, 1.38, 1.44, and 1.60 (12 H, s, 2 × CMe_2), 4.43 (1 H, d, $J_{1,2}$ 4 Hz, H-2), and 6.00 (1 H, d, H-1).

(b) *Using osmium tetraoxide*. To a stirred solution of the enol ether (12) (0.238 g) in dry pyridine (20 ml) was added a solution of osmium tetraoxide (0.191 g) in pyridine (20 ml) and stirring was continued for 18 h at room temperature. The osmate ester was then reduced by shaking vigorously with a solution of sodium metabisulphite (8 g) in pyridine–water (120 ml, 5 : 1 v/v) for 3 h, and the resulting solution was extracted with chloroform (5 × 50 ml). The combined chloroform extracts were washed with dilute hydrochloric acid and a solution of sodium hydrogencarbonate, and dried ($MgSO_4$). Removal of the solvent gave the 3-C-*glycoloyl derivative* (16) (0.164 g, 68%), m.p. and mixed m.p. 98—99 °C; $[\alpha]_D$ +29.5° (*c* 0.9 in $CHCl_3$), which was identical (n.m.r. and i.r. spectra) with that prepared in (a).

3-C-(O-*Acetylglycoloyl*)-1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose* (17).—Acetylation of the 3-*C*-glycoloyl derivative (16) with acetic anhydride in pyridine in the usual way gave the *monoacetate* (17) (78%), m.p. 120—121 °C (from ether–n-hexane); $[\alpha]_D$ +7° (*c* 0.9 in $CHCl_3$) (Found: C, 53.3; H, 6.4. $C_{16}H_{24}O_9$ requires C, 53.3; H, 6.7%); δ 1.31, 1.34, 1.43, and 1.57 (12 H, s, 2 × CMe_2), 2.13 (3 H, s, OAc), 4.47 (1 H, d, $J_{1,2}$ 4 Hz, H-2), 5.29 (2 H, s, CH_2OAc), and 5.98 (1 H, d, H-1).

1,2:5,6-*Di*-O-*isopropylidene*-3-C-[(1R *and* 1S)-1-*methoxyethyl*]-α-D-*allofuranoses* (18a) *and* (18b).—A solution of the enol ether (12) (0.45 g) in dry methanol (20 ml) containing Adams catalyst (0.45 g) was shaken at room temperature under a slight overpressure of hydrogen until the uptake of hydrogen had ceased; t.l.c. [methylene chloride–acetone (20 : 1)] then showed the presence of two products. Removal of the catalyst and solvent, followed by chromatography on silica gel, gave first (18a) (0.17 g, 37.5%), m.p. 83—85 °C (after sublimation at *ca.* 80 °C and 15 mmHg); $[\alpha]_D$ +3° (*c* 1 in $CHCl_3$) (Found: C, 56.6; H, 8.4. $C_{15}H_{26}O_7$ requires C, 56.6; H, 8.2%); δ 1.28 (3 H, d, *J* 6 Hz, *Me*CH), 1.38, 1.44, and 1.58 (12 H, s, integrated ratio 2 : 1 : 1, 2 × CMe_2), 3.31 (3 H, s, OMe), 3.62—4.40 (5 H, overlapping m, H-3[1]—H-6), 4.47 (1 H, d, $J_{1,2}$ 3.5 Hz, H-2), and 5.69 (1 H, d, H-1). Continued elution gave (18b) (0.14 g, 31%), m.p. 66—68 °C (after sublimation at *ca.* 60 °C and 0.5 mmHg); $[\alpha]_D$ +29° (*c* 1 in $CHCl_3$) (Found: C, 56.8; H, 8.4%); δ 1.21 (3 H, d, *J* 6 Hz, *Me*CH), 1.36, 1.46, and 1.60 (12 H, s, integrated ratio 2 : 1 : 1, 2 × CMe_2), 3.44 (3 H, s, OMe), 3.61 (1 H, q, H-3[1]), 3.80—4.37 (4 H, overlapping m, H-4—H-6), 4.44 (1 H, d, $J_{1,2}$ 3.5 Hz, H-2), and 5.68 (1 H, d, H-1).

The Epimeric 1,2:5,6-*Di*-O-*isopropylidene*-3-C-(1-*methoxyethyl*)-3-O-*methyl*-α-D-*allofuranoses* (19a) *and* (19b).—To a cooled (0 °C) and stirred solution of (18a) (0.32 g) in *NN*-dimethylformamide (10 ml) was added sodium hydride (0.24 g) followed by methyl iodide (1 ml) during 10 min. Stirring was continued until t.l.c. [methylene chloride–acetone (20 : 1)] indicated that all the starting material had reacted, whereupon the reaction mixture was worked-up in the usual way [22] to give, after chromatography on silica gel, the *dimethylated derivative* (19a) (0.22 g, 66%), b.p. 110 °C (bath) at 0.2 mmHg; $[\alpha]_D$ +10° (*c* 1.3 in $CHCl_3$) (Found: C, 57.5; H, 8.6. $C_{16}H_{28}O_7$ requires C, 57.8; H, 8.4%); δ 1.22 (3 H, d, *J* 6 Hz, *Me*CH), 1.36, 1.42, and 1.58 (12 H, s, integrated ratio 2 : 1 : 1, 2 × CMe_2), 3.32 and 3.48 (6 H, s, 2 × OMe), 3.64—4.31 (5 H, overlapping m, H-3[1]—H-6), 4.75 (1 H, d, $J_{1,2}$ 3.5 Hz, H-2), and 5.62 (1 H, d, H-1).

Similar methylation of the diol (14) and distillation afforded a *dimethylated derivative* (81%), $[\alpha]_D$ +8° (*c* 1 in $CHCl_3$), whose n.m.r. and i.r. spectra were indistinguishable from those of (19a).

Methylation of (18b) and chromatography on silica gel gave the *dimethylated derivative* (19b) (67%), b.p. (bath) 108 °C at 0.2 mmHg; $[\alpha]_D$ +48° (*c* 0.92 in $CHCl_3$) (Found: C, 57.8; H, 8.5%); δ 1.31 (3 H, d, *J* 6 Hz, *Me*CH), 1.35, 1.43, and 1.58 (12 H, s, integrated ratio 2 : 1 : 1, 2 × CMe_2), 3.38 and 3.53 (6 H, s, 2 × OMe), 3.69 (1 H, q, H-3[1]), 3.77—4.42 (4 H, overlapping m, H-4—H-6), 4.48 (1 H, d, $J_{1,2}$ 4 Hz, H-2), and 5.65 (1 H, d, H-1).

We thank the University of Dundee for financial support (to A. M. M.) and J. A. Chudek for recording the ^1H n.m.r. spectra.

[9/329 *Received*, 28*th February*, 1979]

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