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A novel type of spiroketalisation on pyranoses*

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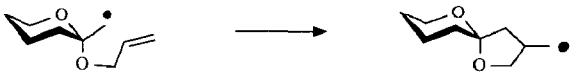
ABSTRACT

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**3**) was converted into allyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-iodo-α-D-*gluco*-2-heptulopyranoside (**4**) upon addition of allylic alcohol in the presence of *N*-iodosuccinimide. Treatment of **4** with tributyltin hydride triggered a stereoselective exo-Dig radical cyclisation, opening a novel route to the synthesis of the 1,6-dioxaspiro[4.5]decane ring system.

INTRODUCTION

The 1,6-dioxaspiro[4.5]decane ring system frequently occur in antibiotics and insect pheromones, and the importance of these compounds has triggered the development of a variety of synthesis strategies[1]. Acid-catalysed cyclisation of dihydroxyketones is the most common route employed and various processes that do not involve internal ketalisations have also been reported. However, an approach which involves the reaction **1**→**2** has not yet been considered.



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1-Methylene sugars are now readily available upon reaction of sugar lactones with Tebbe's reagent[2]. The iodonium ion-promoted addition of a primary alcohol at the anomeric C-2 centre of such "exo enol ethers' has been reported[3,4]. We now describe how this glycosylation reaction provides a novel route to methylated spiroketals.

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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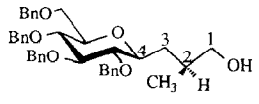
RESULTS AND DISCUSSION

N-Iodosuccinimide-promoted addition of allylic alcohol to 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol[2] (**3**) stereoselectively gave allyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-iodo-α-D-*gluco*-2-heptulopyranoside (**4**, 77%). The α configuration of **4** was inferred on the basis of a comparison of the chemical shift of the

resonance of H-4 ($CDCl_3$, δ 3.99–4.03, overlapped with the signal of H-3) with those of H-3 of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (δ 4.04, t) and the β anomer (δ < 3.7, not separated from the signals of the other non-anomeric ring hydrogens). Treatment of a refluxing solution of iodide **4** in benzene with tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) gave a single spiroketal **6** that resulted from a well-established kinetic exo-Dig radical cyclisation (**5**→**6**). The chemical shift (δ 4.0) of the H-3 resonance indicated that the stereochemical integrity of the anomeric centre had been preserved. On the basis of the chair-transition-state model[5,6], and taking into account anomeric effects, the formation of a single isomer is not unexpected.

The predicted *S* configuration at C-4′ in **6** was confirmed unambiguously as follows. Treatment of the spiroketal **6** with triethylsilane–BF_3·Et_2O–trifluoroacetic acid selectively[7] gave the crystalline *C*-glycoside **7** (60%). The β configuration of **7** was indicated by the $J_{4,5}$ value of 10.5 Hz. Swern oxidation[8] of **7** gave the aldehyde **8**, catalytic hydrogenolysis of which provided the bicyclic hemiacetal **9**. Acetylation of **9** gave the α,β-mixture **10**, the ^{1}H-n.m.r. spectrum of which contained signals for H-1 at δ 5.72 (d, $J_{1,2}$ 2.6 Hz) and 5.77 (d, $J_{1,2}$ 0.5 Hz). This clearly indicates Me-2 to be axial and the configuration at C-2 to be *S*. The observed *S* configuration at C-4′ of **6** supports the α-selectivity of the initial allylation of the exo-enol ether **3**. According to the Beckwith–Houk model[5,6], the β anomer of **4** would most probably cyclise to provide the *R* isomer at C-3. It is of interest to compare this stereospecific carbohydrate radical cyclisation with a related process (**11**→**12**) recently reported[9].



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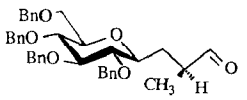

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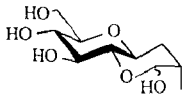

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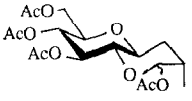

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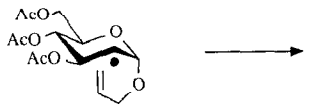

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The lack of selectivity (*R,S*-ratio 1:1) of this reaction may be due to the unfavorable location of the radical generated, which forces the allyl group to rotate from its favored orientation (exo-anomeric effect). Extension of the novel reaction reported above to substituted allylic alcohols is being studied.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi Model 510 capillary apparatus and are uncorrected. Optical rotations were measured at 20 $\pm 2°$ with a Perkin–Elmer Model 241 polarimeter. C.i. (ammonia)-mass spectra were obtained with a Nermag R10-10 spectrometer. Elemental analyses were performed at the University Pierre et Marie Curie (Paris VI) or at the "Service Central d'Analyse du Centre National de la Recherche Scientifique" (Vernaison). ^{1}H-N.m.r. spectra were recorded with Cameca 250 and Bruker AM-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). Reactions were monitored by t.l.c. on Silica Gel 60 F_{254} (Merck) and detection by charring with sulfuric acid. Flash-column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck).

Allyl 3,4,5,7-tetra-O-*benzyl-1-deoxy-1-iodo-α*-D-gluco-*2-heptulopyranoside* (**4**). — To a stirred suspension of *N*-iodosuccinimide (190 mg, 0.84 mmol) in dry dichloromethane (10 mL) was added, dropwise at $-78°$ under argon, a solution of **3**[2] (300 mg, 0.56 mmol) in dry dichloromethane (5 mL). The mixture was stirred for 1 h at $-78°$, allyl alcohol (1 mL) was added, and stirring was continued for 20 min at $-78°$. The

mixture was allowed to reach room temperature and then filtered through Celite, the solids were washed with dichloromethane, and the combined filtrate and washings were concentrated. Column chromatography (9:1 hexane–ethyl acetate) of the residue gave **4** (310 mg, 77%), isolated as a colourless syrup, $[\alpha]_D$ +49.5° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 7.30 (m, 20 H, 4 Ph), 6.00–5.85 (m, 1 H, $CH{=}CH_2$), 5.35–5.12 (2 dd, 2 H, $CH{=}CH_2$), 5.03–4.56 (m, 8 H, 4 CH_2Ph), 4.09–4.05 (m, 2 H, $OCH_2CH{=}CH_2$), 4.03–3.99 (m, 2 H, H-3,4), 3.83–3.65 (m, 4 H, H-5,6,7a,7b), 3.55 and 3.45 (2 d, 2 H, J_{gem} 10.6 Hz, CH_2I). Mass spectrum: *m/z* 738 (M^+ + 18).

Anal. Calc. for $C_{38}H_{41}IO_6$: C, 63.34; H, 5.73. Found: C, 63.23; H, 5.69.

*2,3,4,6-Tetra-*O*-benzyl-*α*-*D*-glucopyranosylspiro-2′-[(4′S)-4′-methyltetrahydrofuran]* (**6**). — To a stirred solution of **4** (113 mg, 157 μmol) in anhydrous benzene (8 mL) was added, dropwise during 1 h at 85°, under argon, a solution of tributylstannane (51 μL, 190 μmol) and a catalytic amount of AIBN in benzene (8 mL). Stirring was continued for 1 h, the solvent was evaporated, and a solution of the residue in dichloromethane was washed with aqueous 10% potassium fluoride for 2 h at room temperature. The aqueous phase was extracted three times with dichloromethane, and the combined organic extracts were dried ($MgSO_4$) and concentrated. Column chromatography (18:1 toluene–ether) of the residue gave **6** (72 mg, 77%), isolated as a colourless syrup, $[\alpha]_D$ +23° (*c* 1.1, chloroform). ^{1}H-N.m.r. data δ 7.3 (m, 20 H, 4 Ph), 5.0–4.5 (m, 8 H, 4 CH_2Ph), 4.1 (dd, 1 H, $J_{5'a,5'b}$ 9, $J_{4',5'a}$ 7 Hz, H-5′a), 4.0 (dd, 1 H, $J_{3,4}$ 9, $J_{2,3}$ 9.5 Hz, H-3), 3.9–3.8 (ddd, 1 H, $J_{5,6a}$ 3.5, $J_{5,6b}$ 2 Hz, H-5), 3.7 (m, 2 H, H-4,6a), 3.6 (dd, 1 H, $J_{6a,6b}$ 11 Hz, H-6b), 3.5 (d, 1 H, H-2), 3.4 (dd, 1 H, $J_{4',5'b}$ 8.5 Hz, H-5′b), 2.3 (m, 1 H, H-4′), 2.0 (dd, 1 H, $J_{3'a,4'}$ 9.5, $J_{3'a,3'b}$ 13 Hz, H-3′a), 1.5 (dd, 1 H, $J_{3'b,4'}$ 7.5 Hz, H-3′b), 1.0 (d, 3 H, *J* 7 Hz, Me). Mass spectrum: *m/z* 595 (MH^+), 612 (M^+ + 18).

Anal. Calc. for $C_{38}H_{42}O_6$: C, 76.75; H, 7.12. Found: C, 76.36; H, 7.35.

*4,8-Anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2-C-methyl-*D*-erythro-*L*-galacto-nonitol* (**7**). — To a stirred solution of **6** (150 mg, 0.25 mmol) in triethylsilane (0.2 mL, 1.3 mmol) was added, at 0° under argon, boron trifluoride etherate (0.15 mL, 1.3 mmol) and trifluoroacetic acid (50 μL, 0.56 mmol). The mixture was allowed to reach room temperature, then stirred for 30 min. Dichloromethane (0.5 mL) was added, the mixture was filtered through Celite, and the solvent was evaporated. Column chromatography (2:1 hexane–ethyl acetate) of the residue gave **7** (90 mg, 60%), m.p. 64–65°, $[\alpha]_D$ +1° (*c* 0.2, chloroform). ^{1}H-N.m.r. data: δ 7.40–7.30 (m, 20 H, 4 Ph), 5.00–4.50 (2 m, 8 H, 4 CH_2Ph), 4.23 (dd, 1 H, $J_{1a,2}$ 5.5, $J_{1a,1b}$ 10 Hz, H-1a), 4.13 (dd, 1 H, $J_{1b,2}$ 6 Hz, H-1b), 3.77–3.60 (m, 4 H, H-6,7,9a,9b), 3.40 (m, 1 H, H-8), 3.35 (m, 1 H, H-4), 3.30 (dd, 1 H, $J_{4,5}$ 10.5, $J_{5,6}$ 8.5 Hz, H-5), 2.20 (m, 1 H, H-2), 1.70–1.63 (m, 1 H, $J_{3a,3b}$ 9.5 Hz, H-3a), 1.57–1.50 (m, 1 H, H-3b), 1.0 (d, 3 H, *J* 7 Hz, Me). Mass spectrum: *m/z* 597 (MH^+), 614 (M^+ + 18).

Anal. Calc. for $C_{38}H_{44}O_6$: C, 76.49; H, 7.43. Found: C, 76.50; H, 7.50.

*4,8-Anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2-C-methyl-*D*-erythro-*L*-galacto-nonose* (**8**). — To a stirred solution of oxalyl chloride (0.2 mL, 2.3 mmol) in dry dichloromethane (34 mL) at −78° was added methyl sulfoxide (0.2 mL, 2.8 mmol). After 10 min, a solution of **7** (317 mg, 0.53 mmol) in dry dichloromethane (20 mL) was

added. After 15 min, the mixture was treated with triethylamine (11 mL), allowed to warm to 0°, and filtered through Celite, and the solvent was evaporated under reduced pressure. Column chromatography (5:1 hexane–ethyl acetate) of the residue gave **8** (315 mg, 90%), isolated as a colourless syrup, $[\alpha]_D$ −6° (*c* 0.3, chloroform). ^{1}H-N.m.r. data: δ 9.04 (d, 1 H, *J* 7 Hz, CHO), 7.38–7.09 (m, 20 H, 4 Ph), 4.88–4.48 (m, 8 H, 4 CH_2Ph), 3.66 (m, 4 H, from pyranose), 3.38–3.22 (m, 3 H, from pyranose), 2.53 (m, 1 H, H-2), 1.78 (d, 2 H, H-3a,3b), 1.06 (d, 3 H, *J* 7 Hz, Me). Mass spectrum: *m/z* 595 (MH^+), 612 (MH^+ + 18).

Anal. Calc. for $C_{38}H_{42}O_6$: C, 76.74; H, 7.12. Found: C, 76.66; 7.11.

*1,6,7,9-Tetra-*O*-acetyl-4,8-anhydro-2,3-dideoxy-2-*C*-methyl-α,β-*D*-erythro-*L*-galacto-nonopyranose* (**10**). — To a solution of **8** (90 mg, 0.15 mmol) in 1:1 methanol–ethyl acetate (4 mL) was added a catalytic amount of 5% Pd/C at room temperature under hydrogen. The mixture was stirred for 1 h, then filtered through Celite, and the solvent was evaporated to give **9** (35 mg, 100%) as a colourless syrup. Mass spectrum: *m/z* 234 (MH^+), 252 (M^+ + 18). To a solution of **9** (35 mg, 0.15 mmol) in dry pyridine (0.7 mL) was added acetic anhydride (0.2 mL) at room temperature. After 14 h, the mixture was filtered through Celite and concentrated under reduced pressure. Column chromatography (2:1 hexane–acetone) of the residue afforded **10** (42 mg, 70%), isolated as a colourless syrup (α,β-mixture). ^{1}H-N.m.r. data: δ 5.77 (d, $J_{1,2}$ 0.5 Hz, H-1), 5.72 (d, $J_{1,2}$ 2.5 Hz, H-1), 1.14 (d, *J* 7 Hz, Me-2), 1.07 (d, *J* 7 Hz, Me-2). Mass spectrum: *m/z* 420 (M^+ + 18).

Anal. Calc. for $C_{18}H_{26}O_{10}$: C, 53.73; H, 6.71. Found: C, 53.36; H, 6.91.

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