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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7983–7986

A synthesis of 2-fluoroglucal derivatives

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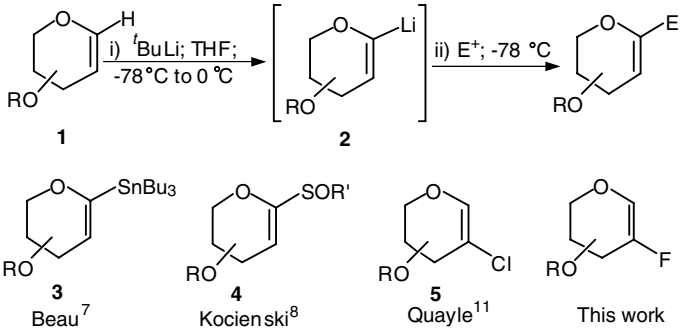
Received 26 July 2006; accepted 25 August 2006
Available online 26 September 2006

Abstract—3,4,6-Tri-*O*-methyl-D-glucal, readily prepared from 3,4,6-tri-*O*-acetyl-D-glucal, undergoes lithiation at −78 °C in THF with *t*-BuLi to afford a vinyl carbanion, which can be trapped with electrophiles in moderate overall yields. The palladium coupling and Dötz-type reactions of these intermediates are also described.

The synthesis of fluorosugars continues to be an active area of interest due to the marked effect of fluorine on their reactivity, their use as biological probes and as substrates for PET.[1] Most approaches to fluorinated carbohydrates[2] involve the displacement of an activated hydroxyl group with a nucleophilic fluoride reagent or by the direct displacement of hydroxyl groups with DAST.[3] Geminal difluorides have also been prepared, in a limited number of cases, by the reaction of ketonic substrates with this reagent. The paucity of synthetic methodology in this area led us to question whether fluorinated glycals could be usefully employed in the synthesis of fluorinated C-glycosides and if such intermediates could be prepared via Boeckman-type[4] metallation chemistry (Scheme 1).

Whilst direct deprotonation[4] of glycals **1** represents the most direct route to 2-lithioglycals **2** such reactions are often capricious, their outcome is often difficult to rationalise, being highly substrate dependent.[5] The metallation of commonly used protecting groups such as silyl ethers is frequently observed as a competing side reaction and it is not uncommon to employ large excesses of base (typically *t*-BuLi), which may compromise the efficiency of subsequent alkylation reactions.[6] In order to circumvent these problems, a variety of alternate procedures for the synthesis of **1** have been developed, most notable of which is the transmetallation of vinylstannanes **3** with butyl lithium as adumbrated by Beau and co-workers.[7] This route is unfortunately not without its drawbacks as the synthesis of the stannanes **3** can



Scheme 1. Preparation of lithiated glycals.

Keywords: Glycal; Metallation; Fluorosugar; Glucal; Lithiation; Fluorine.
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doi:10.1016/j.tetlet.2006.08.122

be highly inefficient. A major methodological advance, which addresses many of these issues, has recently been described by Kocienski and co-workers[8] and involves the alkyl lithium mediated Durst–Johnson fragmentation of glycal sulfoxides **4**.

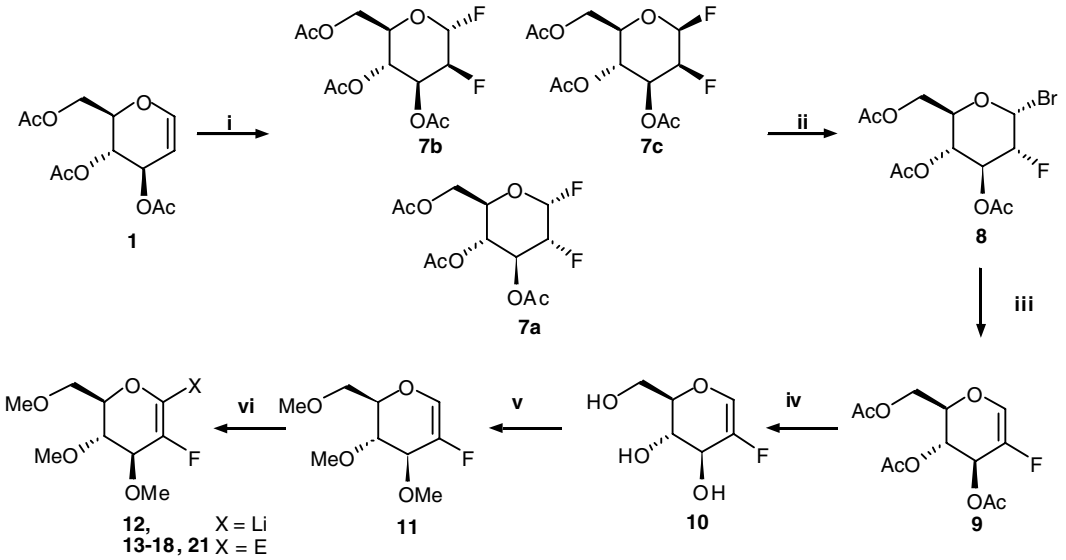
Based on the premise that fluorine exerts a weak *ortho*-directing effect in the metallation reactions of fluoroaromatics[9] and that the metallation of vinyl fluorides is reasonably well established[10] we wondered whether fluorinated glucals, for example **11**, would also undergo more facile deprotonation than the parent glucals affording vinyl carbanion **12** which could be utilised in the preparation of C-1 functionalised 2-fluoroglucals. This assumption is not without foundation as we have previously demonstrated that chloroglucals **5** undergo a facile lithiation at C-1 with *s*-BuLi or *t*-BuLi at −78 °C in THF.[11] In the event the synthesis of **11**, a model substrate for our metallation studies, was readily accomplished from commercially available tri-*O*-acetyl-D-glucal **6** in a five-step sequence using a modification of the route reported by Foster and co-workers.[12] In particular, the fluorination of tri-*O*-acetyl-D-glucal **1** was conveniently achieved using the methodology reported by Korytnyk et al.[13] (XeF_2, equiv: $BF_3{\cdot}OEt_2$, 0.2 equiv; benzene–ether, 1:1 v/v; 20 °C) and afforded 2-deoxy-2-fluoro-2-α-D-glucopyranosyl fluoride **7a** together with minor quantities of **7b** and **7c** (ca. 10%) in a 91% combined isolated yield. The use of XeF_2 offers a practical alterative to other fluorinating reagents commonly used for such reactions as it is a stable, crystalline solid (albeit with a relatively high vapour pressure) and can be employed in standard laboratory glassware. The direct conversion[1a,14] of **7a** to the α-bromide **8**[15] (HBr; HOAc–Ac_2O; 97%), elimination[12] of HBr (Et_3N; CH_3CN; 80 °C; 65%) and Zemplén deacylation (Na, cat; MeOH; 99%) to **10**[16] followed by permethylation[17a] (NaOH, 9 equiv; MeI, 12 equiv; DMSO; 20 °C; 69%) afforded the desired vinyl fluoride **11**[17b] in multi-gram quantities.

Gratifyingly, we found that the exposure of **11** to *t*-BuLi (1.5 equiv) in THF at −78 °C for 30 min afforded the lithiated glucal **12**, which underwent trapping reactions (Scheme 2) with a variety of electrophiles, again at −78 °C, in moderate overall yields (Table 1).[18] Although we have not, as yet, made an exhaustive study of these alkylation reactions, it is evident that enolizable ketones and non-enolizable aldehydes react with a similar efficiency and the reaction with α,β-unsaturated aldehydes and ketones appears to proceed via 1,2-addition. The stannylation of **12** (*n*-Bu_3SnCl, 1.5 equiv) afforded stannane **18**, which on treatment with molecular iodine (1.0 equiv) in CH_2Cl_2 at 20 °C generates iodide **19**. Iodide **19** proves to be an efficient partner in palladium-catalysed coupling reactions as exemplified by its participation in a Sonogashira reaction with phenylacetylene which proceeded cleanly to afford ene-yne **20** in a 72% isolated yield, Scheme 3.

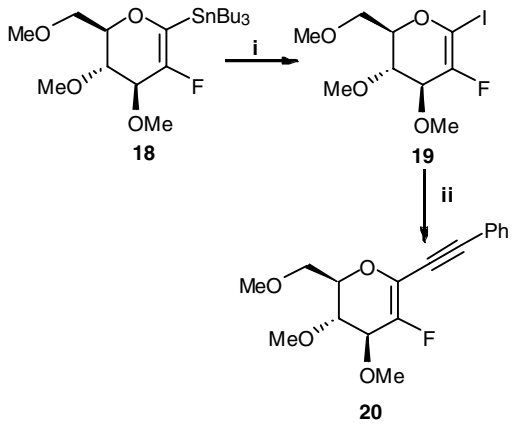
Table 1. Trapping of **12**[a]

Electrophile[b]	Product (yield, %)
c-$C_6H_{10}O$	**13** (41)
PhCHO	**14** (54)[c]
Ph_2CO	**15** (42)
Cinammaldehyde	**16** (53)[d]
4-Cholesten-3-one	**17** (52)[e]
Bu_3SnCl	**18** (55)
(a) $Cr(CO)_6$; (b) Et_3OBF_4	**21** (29)

[a] *t*-BuLi (1.5 equiv) added to **11** at −78 °C in THF and left at −78 °C for 30 min before trapping with an electrophile.
[b] Electrophile (1.5 equiv) reacted with **12** at −78 °C.
[c] Mixture (2:1) of diastereoisomers.
[d] Mixture (1:1) of diastereoisomers.
[e] Single diastereoisomer (*ex* 1,2-addition) after chromatography.

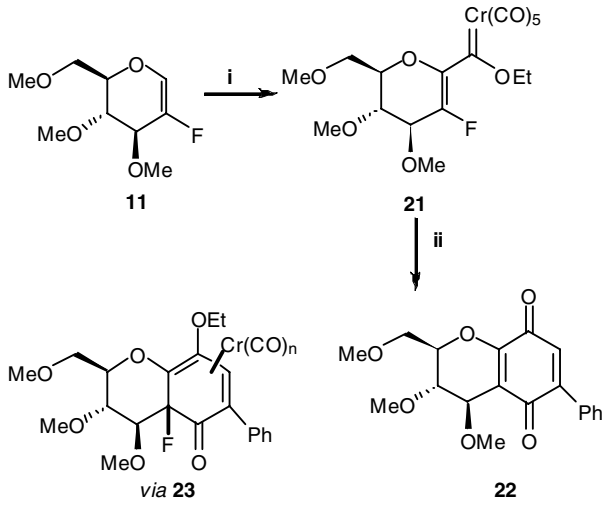


Scheme 2. Reagents and conditions: (i) XeF_2, 1.0 equiv; $BF_3{\cdot}OEt_2$, 0.1 equiv; PhH–Et_2O; 20 °C; 91%; (ii) HBr–HOAc, 45% w/v; Ac_2O; 97%; (iii) Et_3N; CH_3CN; 81 °C; 67%; (iv) Na, cat; MeOH; 99%; (v) MeI, 12 equiv; NaOH, 9 equiv; DMSO; 20 °C; 69%; (vi) (a) *t*-BuLi, 1.5 equiv; THF; −78 °C; (b) 'E^+'; THF; −78 °C.



Scheme 3. Reagents and conditions: (i) I_2, 1 equiv; CH_2Cl_2; 20 °C; 37%; (ii) $(Ph_3P)_2PdCl_2$, 6 mol %; CuI, 4 equiv; PhC≡CH, 5 equiv; Et_2NH, 1.0 equiv; CH_3CN, 81 °C; 72%.

Finally, interception of the vinyl anion **12** with chromium hexacarbonyl (1.02 equiv; THF; −78 °C to 20 °C) followed by the addition of Meerwein's reagent (1.02 equiv; 20 °C) afforded the carbene complex **21** in a 29% overall yield from **11**. The Dötz benzannulation reaction of **21** with phenyl acetylene (3 equiv) under dry state absorption conditions[19] (SiO_2; 90 °C) followed by an oxidative work-up (CAN) proved to be unusually inefficient and afforded quinone **22** in a low isolated yield (15%). However, application of standard thermolysis conditions (PhC≡CH, 5 equiv; THF; 80 °C) followed by an oxidative work-up (CAN) was more effective on this occasion affording quinone **22**[11b] in a 67% yield after chromatography, Scheme 4. This sequence exemplifies the dual role of fluorine as both an activating group in the initial metallation step of the glucal and as a nucleofuge in the aromatisation step of the Dötz reaction.[11b,20] We presume that the reduction of fluorodienone **23**, the presumed initial product



Scheme 4. Reagents and conditions: (i) (a) *t*-BuLi, 1.5 equiv; THF, −78 °C; (b) $Cr(CO)_6$, 1.02 equiv; THF; −78 °C to 20 °C; (c) Et_3OBF_4, 1.02 equiv; 20 °C; 29% (ii) (a) PhC≡CH, 5 equiv; THF; 80 °C; (b) CAN–HNO_3; 84%.

of the Dötz reaction, is mediated by a low-valent chromium species[21] and affords a hydroquinone, which on oxidation with CAN during work-up leads to the isolation of quinone **22**.

In conclusion, we have demonstrated that lithiation of 2-fluroglucals proceeds at a low temperature and that the vinyl anion produced undergoes capture with a variety of electrophiles. The synthesis of fluorinated hexoses by this route is a theme which is currently under further investigation.

Acknowledgments

The EPSRC and Syngenta are thanked for support of this work.

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18. *Representative experimental procedure*: To a solution of **11** (0.50 g; 2.5 mmol) in THF (10 mL) at −78 °C under nitrogen was added *t*-BuLi (2.2 mL of 1.7 M soln; 3.7 mmol) and benzophenone (0.67 g, 3.7 mmol) was added after after 30 min in THF (3 mL). After stirring at −78 °C for 10 min the reaction mixture was allowed to warm up to 20 °C and quenched (saturated aq NH_4Cl; 10 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic extracts dried ($MgSO_4$), concentrated in vacuo and the residue purified by column chromatography (SiO_2; EtOAc–petrol, 1:4) to afford **15** as a colourless oil. Yield 0.40 g; 42%; $[\alpha]_D^{24}$ +35.8 (*c* 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.21 (10H, m, Ar-H), 4.14–4.18 (1H, m, H-5), 3.99 (1H, dd, $J = 8$, 4 Hz, H-3), 3.62–3.66 (1H, m, H-4), 3.56 (1H, dd, $J = 10$, 6 Hz, H-6), 3.52–3.49 (3H, m, OMe, H-6), 3.45 (3H, s, OMe), 3.22 (3H, s, OMe) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −152.1 ppm; HRMS $C_{22}H_{25}FO_5$ requires 388.16859; found, 388.1690.
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