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PREPARATION AND USE OF LITHIATED GLYCALS: VINYLIC DEPROTONATION VERSUS TIN-LITHIUM EXCHANGE FROM 1-TRIBUTYLSTANNYL GLYCALS[1]

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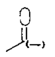
Summary *Methods for preparing glycals lithiated at the C-1 atom by either direct vinylic deprotonation or by tin-lithium exchange from the corresponding 1-tri-n-butylstannyl glycals are described. Alkylation of these lithiated anions with various electrophiles leads to products of potential interest for further synthetic manipulations.*

Useful synthetic equivalents of the acyl anion **1** can be readily produced by direct α-lithiation of simple vinyl ethers 2[2] or cyclic analogues 3[3]. In the cyclic example, extention of this lithiation process to polyfunctional substrates such as glycals **4** could afford a particularly interesting development of this procedure in the construction of fragments of natural products.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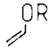
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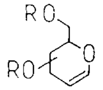
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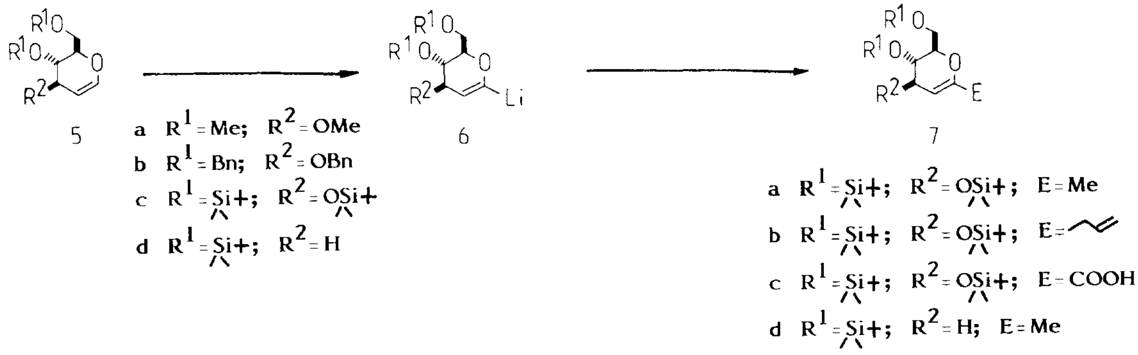
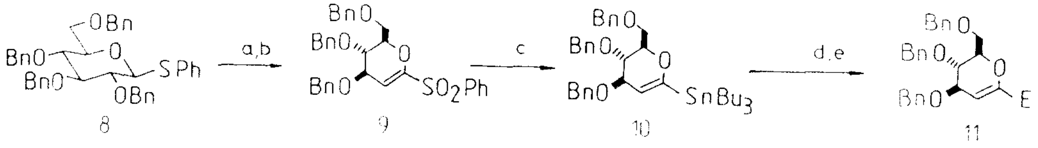
Initial attempts at deprotonation of glycals 5a-c[4,5] under conditions described by Riobé[3b] (nBuLi,



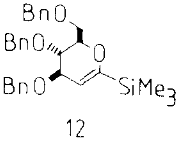
THF, 0°C then 25°C, 1 h) gave unsatisfactory results, even though a reasonable amount of the lithiated species **6c** (85%) was obtained from 3,4,6-tri-O-t-butyldimethylsilyl-D-glucal **5c** by treatment with nBuLi (1.5 equiv., 0°C then 25°C, 1 h) in hexanes with THF (1 equiv.) as was demonstrated by deuteriation experiments. Clean conversion of the glycals **5c,d** to their lithiated species **6c,d** following Boekman[3c] (t-BuLi, 1.5 equiv., -78°C then 0°C, 2 h) occurred as was shown by reacting the intermediates with D_2O (-78°C).

Further reaction of the anionic species **6c** with methyl iodide, allyl iodide or carbon dioxide (-78°C) gave the corresponding alkylated products **7a** (86%), **7b** (70%) and **7c** (60%). Similarly, the 3-deoxy glycal **5d**[4] afforded, after vinylic deprotonation and methyl iodide treatment, the methylated adduct **7d** (85%).

Extension of this direct α-lithiation to the more practical tri-O-benzyl-D-glucal **5b** proved to be inadequate. In order to overcome this difficulty we opted for another more flexible route to the lithiated anion via the 1-tri-n-butylstannyl derivatives[8] as outlined below.



a) mCPBA, 2.2 equiv., $NaHCO_3$, CH_2Cl_2, RT; b) nBuLi, THF, -78°C; c) nBu_3SnH, 2.5 equiv., AIBN, toluene, reflux; d) nBuli, 1.1 equiv., -78°C, 5 min; e) electrophile, -78°C then NH_4Cl.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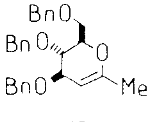
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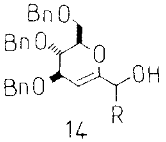
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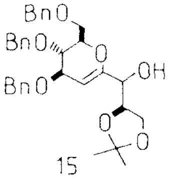
a R = Ph
b R = C_5H_{11}
c R = $CH(Me)_2$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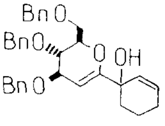
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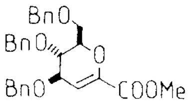
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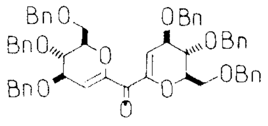
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Oxidation (mCPBA, $NaHCO_3$, CH_2Cl_2, 0-25°C) of phenyl tetra-O-benzyl-1-thio-β-D-glucopyranoside **8**[9] furnished the corresponding phenylsulfone (94%). Base catalyzed elimination (nBuLi, THF, -78°C) of benzyl alcohol gave the known[10] vinylic phenylsulfone **9**, $[\alpha]_D$ -58°, mp 83° (92%, 60% overall yield from D-glucose). Tri-n-butyltin hydride treatment (nBu_3SnH, 2.5 equiv., AIBN, toluene, reflux) afforded the vinylic tri-n-butyl stannane **10**[11] $[\alpha]_D$ -9.5° (77%) together with the starting sulfone **9** (21%). This type of stannylation, previously observed with phenylthio uracil derivatives[12], was recently reported using 2-(alkylsulfonyl)benzothiazole and simple vinyl sulfones[13]. Tin-lithium exchange (nBuLi, THF, -78°C, 5 min) with the vinylic stannane **10** and treatment of the lithiated species[14] with chlorotrimethylsilane or methyl iodide gave the adducts **12**, $[\alpha]_D$ -9° (93%), and **13**, $[\alpha]_D$ -1° (76%), respectively. Similarly, the reaction with benzaldehyde, n-hexanal, isobutyraldehyde and 1,2-O-isopropylidene-D-glyceraldehyde gave the corresponding diastereoisomeric alcohols **14a** (89%), **14b** (62%), **14c** (93%), and **15** (49%). Diastereofacial selectivity was low (isomeric ratio from 1:1 to 2:1) in every case. The reaction with 2-cyclohexenone afforded exclusively the product of the 1,2-addition **16** (77%, isomeric ratio, 1:1) and alkylation with dimethyl carbonate gave the methyl ester **17**, $[\alpha]_D$ -14° (36%) along with the bis-adduct **18**, $[\alpha]_D$ -17° (50%).

We are currently trying out different methods for preparing polyfunctional units of various natural products through regiocontrolled functionalization of these 1-substituted glycals.

References and Notes

1. This work was presented at the Xth International Symposium on Carbohydrate Chemistry, Abstract Th3, (vinylic deprotonation), Sydney (Australia) July, 1980, and at the XIIIth International Carbohydrate Symposium, Abstract A69, (1-tri-n-butylstannyl glycals), Ithaca, New York, August, 1986.
2. (a) U. Schöllkopf and P. Hänssle, Justus Liebigs Ann. Chem., 763, 208 (1972); (b) J.E. Baldwin, G.A. Höfle and O.W. Lever, Jr., J. Am. Chem. Soc., 96, 7125 (1974); (c) C.G. Chavdarian and C.H. Heathcock, J. Am. Chem. Soc., 97, 3822 (1975).
3. (a) M. Schlosser, B. Schaub, B. Spahic and G. Sleiter, Helv. Chim. Acta, 56, 228 (1973); (b) O. Riobé, A. Lebouc and J. Delaunay, C. R. Acad. Sci., Ser. C, 284, 281 (1977); (c) R.K. Boeckman, Jr. and K.J. Bruza, Tetrahedron Lett., 4187 (1977); Tetrahedron, 37, 3997 (1981); (d) P. Kocienski and C. Yeates, Tetrahedron Lett., 24, 3905 (1983).
4. Glycal **5c** ($[\alpha]_D$ -29°) was prepared from commercial tri-O-acetyl-D-glucal **a** by (i) MeONa, MeOH, 0°C, (ii) t-butyldimethylsilyl chloride (TBDMSCl), imidazole, DMF, 25°C, 2 h then 45°C, 10 h (87%); glycal **5d** ($[\alpha]_D$ +78°) was prepared from **a** by (i) $BF_3.Et_2O$, MeOH, PhH[6], (ii) $LiAlH_4$ dioxane, reflux, 5 h (75%)[7], (iii) TBDMSCl, imidazole, DMF, 10 min, 25°C (87%).
5. All new compounds gave satisfactory analytical and spectral data. Optical rotations were measured for solutions in chloroform. ^{1}H-N.m.r. spectroscopy was performed for $CDCl_3$ solutions at 300 MHz with a Brucker AM-300 WB spectrometer.
6. R.J. Ferrier and N. Prasad, J. Chem. Soc., C, 570 (1969).
7. B. Frazer-Reid and B. Radatus, J. Am. Chem. Soc., 92 (1970) 6661; O. Achmatowicz and B. Szechner, Tetrahedron Lett., 1205 (1972).
8. We demonstrated that anomeric stannylated 2-deoxy-D-glucopyranosides are good precursors of anomeric lithiated reagents: P. Lesimple, J.-M. Beau and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 894 (1985).
9. P.J. Pfäffli, S.H. Hixson and L. Anderson, Carbohydr. Res., 23, 195 (1972).
10. Vinylic sulfone 9 was already isolated as a by-product: R.J. Ferrier, R.H. Furneaux and P.C. Tyler, Carbohydr. Res., 58, 397 (1977).
11. Selected ^{1}H-n.m.r. data: **10**: δ 4.24 (ddd, 1 H, $J_{3,5}$ 1.6, $J_{2,3}$ 2.3, $J_{3,4}$ 5.8 Hz, H-3); 4.85 (d, 1 H, $J_{2,3}$ 2.3 Hz, H-2). ^{117,119}Sn Satellites for H-2; $J_{Sn,2}$ 26.4 Hz.

12: δ 0.13 (s, 9 H, Me_3Si); 4.19 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 6.2 Hz, H-3); 5.05 (d, 1 H, $J_{2,3}$ 2.5 Hz, H-2).

13: δ 1.80 (m, 3 H, J <1 and 1.2 Hz, Me); 4.15 (m, 1 H, $J_{3,Me}$ 1.2, $J_{2,3}$ 3.0, $J_{3,4}$ 5.8 Hz, H-3); 4.67 (m, 1 H, $J_{2,Me}$ < 1, $J_{2,3}$ 3.0 Hz, H-2).

14a: Major isomer: δ 4.17 (dd, 1 H, $J_{2,3}$ 3.1, $J_{3,4}$ 5.0 Hz, H-3); 5.03 (d, 1 H, $J_{2,3}$ 3.1 Hz, H-2); minor isomer: δ 4.22 (dd, 1 H, $J_{2,3}$ 2.9, $J_{3,4}$ 5.8 Hz, H-3); 5.05 (d, 1 H, $J_{2,3}$ 2.9 Hz, H-2).

14b: One isomer: δ 4.14 (dd, 1 H, $J_{2,3}$ 3.1, $J_{3,4}$ 5.2 Hz, H-3); 4.97 (d, 1 H, $J_{2,3}$ 3.1 Hz, H-2); other isomer: δ 4.22 (dd, $J_{2,3}$ 2.9, $J_{3,4}$ 5.8 Hz, H-3); 4.95 (d, 1 H, $J_{2,3}$ 2.9 Hz, H-2).

14c: Major isomer: δ 4.21 (dd, 1 H, $J_{2,3}$ 3.2, $J_{3,4}$ 6.2 Hz, H-3); 4.96 (d, 1 H, $J_{2,3}$ 3.2 Hz, H-2); minor isomer: δ 4.25 (dd, 1 H, $J_{2,3}$ 2.8, $J_{3,4}$ 6.2 Hz, H-3); 4.94 (d, 1 H, $J_{2,3}$ 2.8 Hz, H-2).

15: Major isomer: δ 4.18 (dd, 1 H, $J_{2,3}$ 3.1, $J_{3,4}$ 5.2 Hz, H-3); 5.14 (d, 1 H, $J_{2,3}$ 3.1 Hz, H-2); minor isomer: δ 4.24 (dd, 1 H, $J_{2,3}$ 2.8, $J_{3,4}$ ~6 Hz, H-3); 5.11 (d, 1 H, $J_{2,3}$ 2.8 Hz, H-2).

16: One isomer: δ 4.17 (dd, 1 H, $J_{2,3}$ 3.2, $J_{3,4}$ 5.5 Hz, H-3); 5.03 (d, 1 H, $J_{2,3}$ 3.2 Hz, H-2); other isomer: δ 4.22 (dd, 1 H, $J_{2,3}$ 2.9, $J_{3,4}$ 6.0 Hz, H-3); 4.99 (d, 1 H, $J_{2,3}$ 2.9 Hz, H-2).

17: δ 3.81 (s, 3 H, Me); 4.28 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 6.1 Hz, H-3); 6.11 (d, 1 H, $J_{2,3}$ 3.0 Hz, H-2).

18: δ 4.31 (dd, 2 H, $J_{2,3}$ 3.0, $J_{3,4}$ 6.4 Hz, 2 H-3); 6.11 (d, 2 H, $J_{2,3}$ 3.0 Hz, 2 H-2).

12. H. Tanaka, H. Hayakawa, K. Obi and T. Miyasaka, Tetrahedron Lett., 26, 6229 (1985).
13. Y. Watanabe, Y. Ueno, T. Araki, T. Endo and M. Okawara, Tetrahedron Lett., 27, 215 (1986).
14. Direct reductive desulfonylation of vinylic phenylsulfone **9** by lithium naphthalenide (LN, THF, -78°)[15] is also possible leading to the lithiated species **11** (E = Li). This process was not selected however as notable amounts (30 to 40%) of glycal **5b** were always formed together with the 1-alkylated glycal.
15. J.-M. Beau and P. Sinaÿ, Tetrahedron Lett., 26, 6185 (1985).
16. Alkylation of 3,4,6-tri-O-t-butyldimethylsilyl-D-glucal **5c** by vinylic deprotonation and subsequent synthetic transformations appeared in print after this work was completed: K.C. Nicolaou, C.-K. Hwang and M.E. Duggan, J. Chem. Soc., Chem. Commun., 925 (1986); S. Hanessian, M. Martin and R.C. Desai, J. Chem. Soc., Chem. Commun., 926 (1986). Professor R.R. Schmidt has kindly informed us of a similar work being done in his group (cf. 17, work on direct lithiation at C-2 of 1-phenylsulfinyl glucals).
17. R.R. Schmidt and J. Kast, Tetrahedron Lett., 27, 4007 (1986).

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