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Divergent approach to imino sugar *C*-glycosides using imino glycals: application to the stereocontrolled synthesis of (+)-deoxoprosophylline

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Tri-*O*-acetyl imino glucal 2 is readily made and shown to undergo a variety of Lewis acid mediated carbon–carbon bond forming reactions at C-1 of the piperidine nucleus. In all the reactions studied, the β-anomer is predominant.

3,4,6-Tri-*O*-acetyl D-glucal **1** is an extremely useful starting material for the preparation of monosaccharides, oligosaccharides and other enantiomerically enriched organic molecules (Fig. 1). Significantly, as well as participating in simple addition reactions across the glycal double bond, the presence of a good leaving group at C-3 facilitates S_N' reactions allowing for the introduction of a wide variety of nucleophiles at C-1 of the sugar nucleus with concomitant migration of the double bond.[1] As part of our ongoing studies to devise general methods for the assembly of imino sugars, important inhibitors of the glycosidase enzymes,[2] we wondered whether an aza analogue of **1** such as tri-*O*-acetyl imino glucal **2** might behave similarly, and hence provide a convenient route to a diverse range of C-1 substituted imino sugars.[3] In this communication, we describe the successful preparation of **2** and demonstrate that it can be used in a number of C–C bond forming reactions at C-1 of the piperidine nucleus.

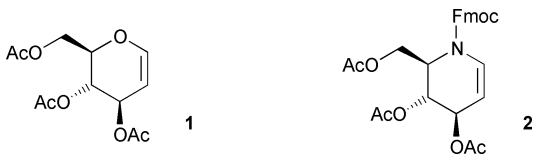
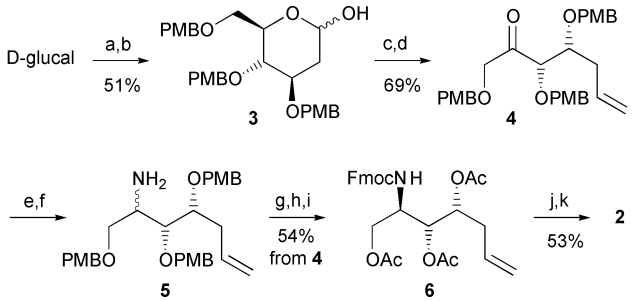


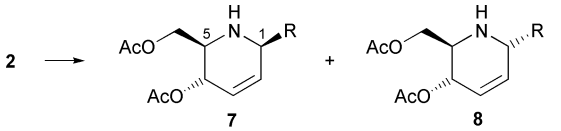
Fig. 1 3,4,6-Tri-*O*-acetyl D-glucal and 3,4,6-tri-*O*-acetyl imino D-glucal.

Imino glucal **2** was made from D-glucal as outlined in Scheme 1.†‡ Protection of the hydroxy groups as *p*-methoxybenzyl ethers followed by hydration of the double bond gave hemiacetal **3**. Wittig olefination with methylenetriphenylphosphorane followed by TPAP oxidation of the resulting secondary alcohol furnished ketone **4**, which was converted into amine **5** by reduction of the corresponding oxime. Using lithium aluminium hydride as reducing agent, this provided **5** as an inseparable 77 : 23 mixture of isomers in favour of the required (6*R*)-diastereoisomer. Whilst stereocontrolled reduction in favour of this diastereomer might be expected on the basis of literature precedent,[3,4] this assignment was later confirmed by an X-ray crystal structure of a derived imino sugar (*vide infra*). After the PMB ether protecting groups had been changed to acetates, triacetate **6** could be separated from its C-6 epimer by preparative MPLC. Completion of the synthesis of **2** was then achieved by ozonolytic cleavage of the terminal double bond of diastereomerically pure **6**, followed by dehydration of the resulting hemiacetal using oxalyl chloride.



Scheme 1 *Reagents and conditions*: (a) NaH, PMBCl, DMF; (b) $Hg(OAc)_2$, THF–H_2O then $NaBH_4$; (c) $Ph_3P{=}CH_2$, toluene; (d) TPAP, NMO, 4 Å sieves, CH_2Cl_2; (e) $HONH_2{\cdot}HCl$, pyridine, EtOH, 60 °C; (f) $LiAlH_4$, Et_2O, rt; (g) FmocCl, K_2CO_3, THF–H_2O (3 : 1); (h) CF_3CO_2H, CH_2Cl_2; (i) Ac_2O, pyridine, rt; (j) O_3, −78 °C, CH_2Cl_2 then Me_2S, rt; (k) $(COCl)_2$, Et_3N, DMF, CH_2Cl_2.

Imino glucal **2** participates in a wide variety of Lewis acid mediated C–C bond forming reactions by allylic displacement of the C-3 acetate group. Treatment of **2** with allyl trimethylsilane and $BF_3{\cdot}Et_2O$ at −50 °C provides, after Fmoc deprotection, piperidine **7a** in 78% yield along with small amount of the readily separable α-anomer **8a** (eqn. (1) and Table 1).‡



(1)

a: R = $CH_2CH{=}CH_2$; **b**: R = Et;
c: R = CH_2COPh; **d**: R = CH_2(1-cyclohexenyl)

Table 1 Lewis acid mediated additions to imino glycal **2**

Entry	Conditions[a,b]	β : α[c]	Products (% yield)[d]
1	$H_2C{=}CHCH_2SiMe_3$, $BF_3{\cdot}Et_2O$	79 : 21	**7a** (78); **8a** (18)
2	Et_2Zn, $BF_3.Et_2O$	67 : 33	**7b** (63); **8b** (27)
3	$H_2C{=}C(OSiMe_3)Ph$, $BF_3{\cdot}Et_2O$	62 : 38	**7c** (64); **8c** (31)
4	Methylenecyclohexane, $SnBr_4$	86 : 14	**7d** (80)

[a] All reactions performed using 1.0–1.5 equiv of Lewis acid and 1.2–1.5 equiv. of nucleophile in CH_2Cl_2 at the temperature indicated in the text. Reactions warmed to rt or 0 °C and quenched by addition of aq $NaHCO_3$. [b] Crude products treated with piperidine in CH_2Cl_2 for 1–2 h to remove the Fmoc group. [c] Ratio determined by ^1H NMR analysis prior to purification. [d] Isolated yields after silica gel chromatography.

Similarly, $BF_3{\cdot}Et_2O$ promoted addition of diethylzinc at −20 °C, and 1-phenyl-1-(trimethylsiloxy)ethylene at −45 °C, yield **7b** and **7c** respectively as the major products. Furthermore, Prins-type addition of methylenecyclohexane mediated by $SnBr_4$ at rt gives **7d** in excellent yield. In all these examples, the β-anomer was produced as the major product.§ Intriguingly, this facial selectivity is the reverse of that observed when the same nucleophiles are added to 3,4,6-tri-*O*-acetyl D-glucal **1** under comparable conditions.[5] Whilst the origin of this reversal is unclear at present, Craig has noted a similar trend studying Lewis acid mediated additions to 4-(arylsulfonyl)glycals and 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines.[6]

As a demonstration of the utility of this chemistry, we have applied it to the stereocontrolled synthesis of deoxoprosophylline **9**,[7] a reduction product of prosophylline, itself isolated from *Prosopis africana*.[8] Addition of 3-(trimethylsilyl)dodec-1-ene[7c]

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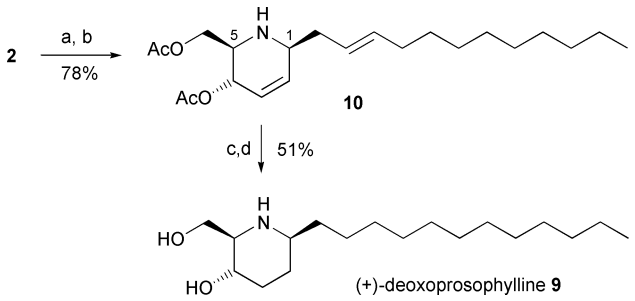
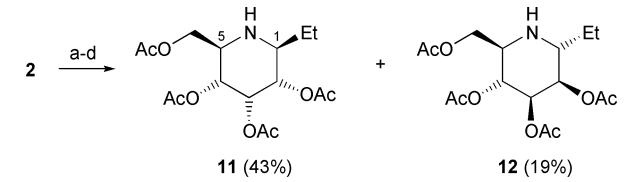
to **2** smoothly gave piperidine **10** in 78% yield, after Fmoc deprotection and chromatographic separation from traces of the minor α-anomer (Scheme 2).§ ^{1}H NMR analysis of the mixture prior to chromatography reveals that the addition of this silane occurs with very high levels of stereocontrol (β:α = 9:1). Hydrogenation of **10** followed by removal of the acetate groups provides (+)-deoxoprosophylline **9**, whose physical and spectroscopic data are in accordance with those previously described.‡



Scheme 2 *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, $H_2C{=}CHCH(SiMe_3)(CH_2)_8CH_3$, −60→0 °C, 3 h; (b) piperidine, CH_2Cl_2, rt, 1 h; (c) H_2, Pt/C, EtOH, 1.5 h; (d) LiOH, THF–H_2O, 2.5 h.

By combining the carbon–carbon bond forming reactions of imino glucal **2** with dihydroxylation chemistry, it is possible to make more highly oxygenated imino sugar *C*-glycosides. For example, **2** can be converted into readily separable piperidines **11** and **12** by ethylation, dihydroxylation, acetylation and Fmoc deprotection without recourse to chromatographic purification of any of the intermediates (Scheme 3).§ Dihydroxylation of both alkene intermediates (*i.e*. *N*-Fmoc protected forms of **7b** and **8b**), proceeds stereoselectively *anti*- to the ethyl group at C-1. The relative stereochemistry within **11** has been unambiguously established by X-ray crystallography (Fig. 2).¶ In addition to verifying the facial selectivity of the dihydroxylation, this crystallographic determination confirms our earlier stereochemical assignments. Since many other transformations of **1** are known, it is anticipated that imino glucal **2** (and its various stereoisomers) could find other applications in imino sugar synthesis. Work in this direction is ongoing in our laboratories.



Scheme 3 *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, Et_2Zn, CH_2Cl_2, −20 °C→rt; 2 h; (b) OsO_4 (cat.), *N*-methylmorpholine *N*-oxide, acetone–H_2O, 5 d; (c) Ac_2O, pyridine, 2 h; (d) piperidine, CH_2Cl_2, 1 h.

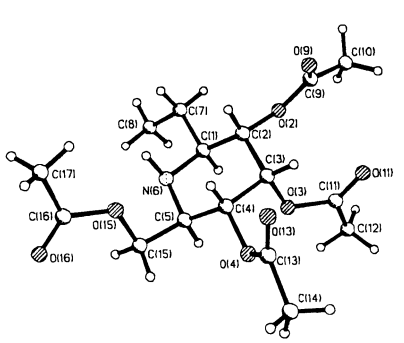


Fig. 2 X-Ray structure of one of the two independent molecules in **11**.

We are indebted to EPSRC and GlaxoSmithKline for financial support. We thank the EPSRC National Mass Spectrometry Centre for performing some of the mass spectrometry.

Notes and references

† All new compounds have been fully characterised using standard spectroscopic and analytical methods.

‡ *Selected physical and spectroscopic data:* **2**: mp 47–50 °C; δ_H (400 MHz; d_6-DMSO at 100 °C) 7.84 (2H, d, *J* 7.5 Hz), 7.60 (2H, d, *J* 7.5 Hz), 7.41 (2H, t, *J* 7.5 Hz), 7.32 (2H, t, *J* 7.5 Hz), 6.90 (1H, d, *J* 8.4 Hz), 5.13 (1H, m), 5.03 (1H, m), 4.92 (1H, m), 4.61 (1H, dd, *J* 10.6, 6.3 Hz), 4.53 (1H, dd, *J* 10.6, 6.0 Hz), 4.46 (1H, m), 4.33 (1H, br t, *J* 6.3), 4.15 (1H, dd, *J* 11.2, 7.2 Hz), 4.02 (1H, m), 1.98 (3H, s), 1.97 (3H, s), 1.96 (3H, s); Anal. Calc. for $C_{27}H_{27}NO_8$: C, 65.41; H, 5.43; N, 2.77%. Found: C, 65.71; H, 5.51; N, 2.84%. **7a**: δ_H (400 MHz; $CDCl_3$) 5.80–5.67 (2H, m), 5.63 (1H, m), 5.16–5.06 (3H, m), 4.18 (1H, dd, *J* 11.4, 2.9), 4.01 (1H, dd, *J* 11.4, 6.1 Hz), 3.46 (1H, m), 3.00 (1H, ddd, *J* 9.1, 6.1, 2.9 Hz), 2.41 (1H, br s), 2.20 (2H, t, *J* 7.0 Hz), 2.04 (3H, s), 2.02 (3H, s); Observed: 254.1386 (MH^+); $C_{13}H_{20}NO_4$ requires 254.1392. **9**: mp 84–85 °C (lit. mp 83 °C[7f]); $[\alpha]_D^{24}$+12.5 (*c* 0.24, $CHCl_3$) {lit. $[\alpha]_D^{20}$ +13 (*c* 0.22, $CHCl_3$)[7f]}.

§ Strong reciprocal NOE enhancements were observed between H-1 and H-5 in **7a–d**, **10** and **11**.

¶ *Crystallographic data for* **11**: X-ray diffraction studies on a colourless crystal grown from Et_2O–petrol (40–60) were performed at 293 K using a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods. $C_{16}H_{25}N_1O_8$, *M* = 359.37, orthorhombic, space group $P2_12_12_1$, *a* = 8.8915(4), *b* = 9.2151(3), *c* = 45.8131(19) Å, *U* = 3753.7(3) Å^3, Z = 8 (2 independent molecules), D_c = 1.272 Mg m^{-3}, μ = 0.102 mm^{-1}, *F*(000) = 1536, crystal size = 0.26 × 0.15 × 0.1 mm, Flack parameter 0.2(14). Of 16307 measured data, 5410 were unique (R_{int} = 0.0510) and 4108 observed ($I > 2\sigma(I)$]) to give R_1 = 0.0538 and wR_2 = 0.1252. C(28) in the second molecule was disordered into 2 orientations of 75 and 25%. The 25% hydrogens on C(28B) and C(27) were not allowed for in the refinement. All non-hydrogen atoms were refined with anisotropic displacement parameters; both NH protons were located from a Δ*F* map and allowed to refine isotropically subject to a distance constraint (N–H = 0.98 Å). All remaining hydrogen atoms bound to carbon were idealised and fixed. Structural refinements were by the full-matrix least-squares method on F^2. CCDC 173804. See http://www.rsc.org/suppdata/cc/b1/b110035a/ for crystallographic files in .cif or other electronic format.

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