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A convenient synthesis of methyl *N*-acetyl-α-D-lividosaminide from D-glucal☆

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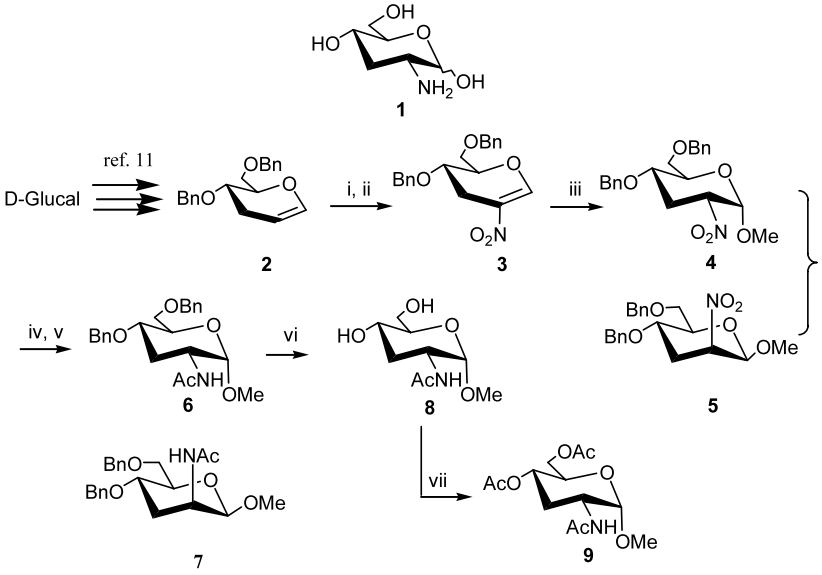
This paper is respectfully dedicated to Professor Dr. Richard R. Schmidt on the occasion of his 68th birthday

Abstract—Methyl *N*-acetyl-α-D-lividosaminide has been synthesised starting from 4,6-di-*O*-benzyl-D-glucal via a new nitro glucal derivative in six steps.

2-Aminosugars are integral components of several glycolipids[2] and glycoproteins.[3] Apart from this, they are used[4] as important building blocks in the synthesis of useful natural products. D-Lividosamine **1** (Scheme 1), a 2-aminosugar, is found[5] as a component of a few antibiotics such as lividomycins and 3′-deoxykanamycin. Also, it has been used[6] in the synthesis of thienamycin, an important penem antibiotic. In view of this, many routes to D-lividosamine or its derivatives have been reported in the literature, some



Scheme 1. *Reagents and conditions*: (i) Ac_2O, HNO_3, −33°C, 0.5 h; (ii) Et_3N, CH_2Cl_2, 0°C, 0.5 h, 72%; (iii) 0.1 M NaOMe in methanol, rt, 1 h, 85%; (iv) Raney-Ni (T_4)/H_2, EtOH, overnight; (v) Ac_2O/pyridine, 4 h, 65% (two steps); (vi) 20% $Pd(OH)_2$/C–H_2/THF, overnight; (vii) Ac_2O/pyridine, 4 h, 77% (two steps).

☆ Transformations in carbohydrate chemistry, Part 6. For Part 5, see Ref. 1.

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from carbohydrate[7] and some from non-carbohydrate precursors.[8] The amino functionality in lividosamine and its derivatives has been introduced by reducing functional groups such as an oxime[7a,c] and by replacing a leaving group by an amine equivalent such as azide[8c] or via a Michael reaction.[7d] Besides this, some synthetic methods have been developed[7b] for reductive removal of the oxygen functionality at C-3 while maintaining the amino or its equivalent functionality at C-2.

In recent years nitro sugars have been utilised[9] as important synthons in the synthesis of a variety of useful carbohydrate analogues. In particular, pioneering work by Schmidt et al.[10] has led to the synthesis of 2-amino-*O*- and *C*-glycosides and glycopeptides from 2-nitro-glycals. Since the nitro group is an excellent source of an amino functionality it is possible to start with an appropriately substituted glucal and synthesise a lividosamine derivative.

In this communication we wish to report a short synthesis of methyl *N*-acetyl-α-D-lividosaminide starting from D-glucal as shown in Scheme 1. Thus, nitration[10a] of 4,6-di-*O*-benzyl-glucal **2**, obtained from tri-*O*-acetyl glucal,[11] using acetic anhydride/nitric acid followed by Et_3N led to the formation of nitroglucal **3** in 72% yield whose glycosidation with MeOH in the presence of a catalytic amount of NaOMe yielded a mixture of two isomers **4** and **5** in a 2.5:1 ratio as revealed by ^1H NMR spectroscopic analysis.[12] For the major isomer, the anomeric proton appeared as a doublet at δ 5.23 with $J=3.6$ Hz whereas for the minor isomer it appeared as a broad singlet at δ 5.30. At this stage the two isomers were chromatographically inseparable and hence the mixture was reduced with platinised Raney-Ni(T_4)/H_2[13] and subsequently acetylated with acetic anhydride and pyridine. The two isomers could then be separated at this stage either by using a chromatotron or by recrystallisation from ethyl acetate/hexane. The minor isomer **7**, a viscous liquid isolated in 18% yield, showed a broad singlet for the anomeric hydrogen at δ 4.48 in its ^1H NMR spectrum. The structure of **7** was assigned on the basis of NOE experiments which indicated enhancements of peaks corresponding to H-1 and H-3′ (axial) when H-2 was irradiated clearly establishing a *cis*-relationship between the three hydrogens. The major isomer **6**, a crystalline solid isolated in 47% yield, could be readily debenzylated with $Pd(OH)_2/C$-H_2 in THF to obtain methyl *N*-acetyl-lividosaminide **8**, which was characterised[14] as methyl *N*-acetyl-4,6-di-*O*-acetyl-D-lividosaminide **9** obtained in a 77% yield over the two steps.

In conclusion, nitro sugar based chemistry has been readily utilised to prepare a D-lividosamine derivative staring from D-glucal. We expect this procedure to find use in organic synthesis.

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References

1. Rani, S.; Vankar, Y. D. *Tetrahedron Lett*. **2003**, *44*, 907.
2. (a) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev*. **1992**, *92*, 1167; (b) Deshpande, P. P.; Danishefsky, S. J. *Nature* **1997**, *387*, 164; (c) Vankar, Y. D.; Schmidt, R. R. *Chem. Soc. Rev*. **2000**, *29*, 201; (d) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem*. **1995**, *60*, 2160.
3. (a) Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev*. **2000**, *100*, 4495; (b) Wang, Z.-G.; Zhang, X. F.; Live, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 3652; (c) Davis, B. *Chem. Rev*. **2002**, *102*, 579; (d) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1191.
4. (a) Giannis, A. *Kontakte* **1994**, 37 and references cited therein; (b) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 1577.
5. (a) Mori, T.; Ichyansi, T.; Kondo, H.; Tokkunasa, T.; Oda, T.; Munakata, T. *J. Antibiot. Ser. A* **1971**, *24*, 339; (b) Konstantinova, N. V.; Lavrova, M. F.; Nesterova, T. P.; Potapova, N. P.; Ponomarenko, V. I.; Rozynov, B. V.; Brazhnikova, M. G.; Lapchinskaya, O. A.; Sinyagina, O. P. *Antibiot. Med. Biotekhnol*. **1985**, *30*, 729. (*Chem. Abs*. 104, 17418f).
6. Miyashita, M.; Chida, N.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun*. **1982**, 1354.
7. (a) Brewer, C. L.; Guthrie, R. D. *J. Chem. Soc., Perkin Trans. 1* **1974**, 657; (b) Hanessian, S.; Vatele, J.-M. *Tetrahedron Lett*. **1981**, *22*, 3579; (c) Rosenthal, A.; Catsoulacos, P. *Can. J. Chem*. **1969**, *47*, 2748; (d) Ravindran, B.; Deshpande, S. G.; Pathak, T. *Tetrahedron* **2001**, *57*, 1093 and references cited therein.
8. (a) de Guchteneere, E.; Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10603; (b) Jager, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199; (c) Fattori, D.; de Guchteneere, E.; Vogel, P. *Tetrahedron Lett*. **1989**, *30*, 7415.
9. (a) Holzapfel, C. W.; van der Merwe, T. L. *Tetrahedron Lett*. **1996**, *37*, 2307; (b) *Nitro Compounds*; Feuer, H.; Nielsen, A. T., Eds.; VCH: Weinheim, 1990; (c) Scheffler, G.; Justus, M.; Vasella, A.; Wessel, H. P. *Tetrahedron Lett*. **1999**, *40*, 5845; (d) Sakakibara, T.; Tokuda, K.; Hayakawa, T.; Seta, A. *Carbohydr. Res*. **2000**, *327*, 489.
10. (a) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem*. **1998**, 1609; (b) Winterfeldt, G. A.; Ito, Y.; Ogawa, T.; Schmidt, R. R. *Eur. J. Org. Chem*. **1999**, 1167; (c) Winterfeldt, G. A.; Das, J.; Schmidt, R. R. *Eur. J. Org. Chem*. **2000**, 3047; (d) Pachamuthu, K.; Gupta, A.; Das, J.; Schmidt, R. R.; Vankar, Y. D. *Eur. J. Org. Chem*. **2002**, 1479–1483; (e) Winterfeldt, G. A.; Schmidt, R. R. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 2654.
11. Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc*. **1970**, *92*, 6661.
12. **4,6-Di-*O*-benzyl-2,3-dideoxy-2-nitro-D-glucal 3**: $[\alpha]_D^{26}=+129.6$ (*c* 2.3, CH_2Cl_2); IR (CH_2Cl_2): 1555 cm^{-1}. ^1H NMR (400 MHz): δ 2.70–2.73 (dd, $J=16.3$, 6.8 Hz, 1H,

H-3), 2.95–3.0 (br dd, $J=16.3$, 5.4 Hz, 1H, H-3′), 3.67–3.71 (dd, $J=10.7$, 3.7 Hz, 1H, H-6), 3.72–3.76 (dd, $J=10.7$, 4.6 Hz, 1H, H-6′), 3.90–3.94 (m, 1H, H-4), 4.15–4.20 (m, 1H, H-5), 4.52–4.70 (m, 4H, 2× -OCH_2Ph), 7.24–7.40 (m, 10H, aromatic), 8.16 (s, 1H, H-1); ^{13}C NMR (100 MHz): δ 25.8, 67.6, 67.7, 71.3, 73.6, 78.4, 127.7–137.3 (m, aromatic), 129.1, 153.4. MSES$^+$: 373.3 $[M+NH_4]^+$. Anal. calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.59; H, 5.95; N, 3.94; found: C, 67.71; H, 5.98; N, 3.80%.

Methyl 4,6-di-*O*-benzyl-2,3-dideoxy-2-nitro-D-glucopyranoside 4: $[\alpha]_D^{26}=+87.4$ (*c* 1.9, CH_2Cl_2); IR (CH_2Cl_2): 1552 cm^{-1}. ^{1}H NMR (400 MHz): δ (mixture of isomers: 2.5:1), δ 2.02–2.14 (m, 1H, H-3, for *minor isomer*), 2.30–2.40 (q, $J=12.0$ Hz, 1H, H-3, for *α-isomer*), 2.57–2.62 (m, 1H, H-3′, for *α-isomer*), 2.70–2.80 (m, 1H, H-3′, for *minor isomer*), 3.40 (s, 3H, -OCH_3, for *α-isomer*), 3.43 (s, 3H, -OCH_3, for *minor isomer*), 3.62–3.86 (m, 4H, H-4, H-5, H-6, and H-6′, for both isomers), 4.40–4.80 (m, 5H, H-2 and 2× -OCH_2Ph, for both isomers), 5.23–5.24 (d, $J=3.6$ Hz, 1H, H-1, for *α-isomer*), 5.30 (br s, 1, H-1, for *minor isomer*), 7.21–7.33 (m, 10H, aromatic, for both isomers); ^{13}C NMR (100 MHz) (for both isomers): δ 27.1, 27.4, 55.2, 55.4, 68.0, 68.7, 68.9, 70.7, 70.8, 71.2, 71.3, 71.5, 73.3, 73.5, 80.3, 82.5, 96.1, 96.9, 127.5–128.4 (m, aromatic), 137.5, 137.7, 137.8, 138.1. MSES$^+$: 405 $[M+NH_4]^+$. Anal. calcd for $C_{21}H_{25}NO_6$ (387.42): C, 65.10; H, 6.50; N, 3.61; found: C, 64.97; H, 6.80; N, 3.55%.

Methyl 2-(acetylamino)-2,3-dideoxy-4,6-di-*O*-benzyl-α-D-ribo-hexopyranoside 6: $[\alpha]_D^{26}=+90.3$ (*c* 1.75, CH_2Cl_2); IR (CH_2Cl_2): 1653 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.55–1.64 (q, $J=11.5$ Hz, 1H, H-3), 1.97 (s, 3H, -NHAc), 2.31–2.36 (dt, $J=11.4$, 4.6 Hz, 1H, H-3′), 3.40 (s, 3H, -OCH_3), 3.57–3.63 (m, 1H, H-4), 3.67–3.71 (m, 3H, H-5, H-6, H-6′), 4.14–4.21 (ddd, $J=13.0$, 8.8, 4.2 Hz, 1H, H-2), 4.34–4.64 (m, 5H, 2× -OCH_2Ph and H-1), 5.71–5.74 (d, $J=9.0$ Hz, 1H, -NHAc), 7.18–7.34 (m, 10H, aromatic). ^{13}C NMR (100 MHz): δ 23.3, 30.8, 47.0, 54.6, 68.7, 70.7, 70.8, 71.5, 73.3, 97.1, 127.4–128.2 (m, aromatic), 137.9, 138.1, 169.3. Anal. calcd for $C_{23}H_{29}NO_5$ (399.48): C, 69.15; H, 7.31; N, 3.50; found: C, 69.20; H, 7.35; N, 3.57%. MSES$^+$: 422 $[M+Na]^+$.

Methyl 2-(acetylamino)-2,3-dideoxy-4,6-di-*O*-benzyl-β-D-arabino-hexopyranoside 7: $[\alpha]_D^{26}=+93.9$ (*c* 1.15, CH_2Cl_2). IR (CH_2Cl_2): 1653 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.86–1.91 (m, 1H, H-3), 1.95 (s, 3H, -NHAc), 2.17–2.22 (dt, $J=13.0$, 4.4 Hz, 1H, H-3′), 3.36 (s, 3H, -OCH_3), 3.62–3.68 (m, 1H, H-4), 3.71–3.83 (m, 3H, H-5, H-6, H-6′), 4.20–4.25 (br dt, $J=8.6$, 4.9 Hz, 1H, H-2), 4.33–4.65 (m, 4H, 2× -OCH_2Ph), 4.48 (br s, 1H, H-1), 6.14–6.16 (d, $J=8.8$ Hz, 1H, -NHAc), 7.20–7.34 (m, 10H, aromatic). ^{13}C NMR (100 MHz): δ 23.2, 29.0, 47.8, 54.7, 68.7, 70.7, 70.8, 73.5, 99.2, 127.6–128.3 (m, aromatic), 137.8, 137.9, 169.4. Anal. calcd for $C_{23}H_{29}NO_5$ (399.48): C, 69.15; H, 7.31; N, 3.50; found: C, 69.27; H, 7.33; N, 3.53%.

13. For the preparation of Raney-nickel, see: *Org. Synth.* **1955**, *Coll. Vol. 3*, 181.
14. The spectral data of this compound, mp 133–134°C (lit.[8a] 133–134°C, lit.[8b] 139°C) and $[\alpha]_D^{26}=+99.1$ (*c* 1.15, CH_2Cl_2) [lit.[8a] $[\alpha]_D^{25}=+90.0$ (*c* 0.17, MeOH), lit.[8b] $[\alpha]_D^{26}=+90.2$ (*c* 0.6, MeOH)] were comparable with the literature[8a,b] values.