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$LaCl_3 \cdot 7H_2O$/NaI/benzyl alcohol: a novel reagent system for regioselective hydration of glycals: application in the synthesis of 1,6-dideoxynojirimycin☆

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Abstract—Glycals can be readily hydrated using the $LaCl_3 \cdot 7H_2O$/NaI/$PhCH_2OH$ reagent system. In one case, having an *exo* methylene group, such hydration gives an intermediate which is readily converted into 1,6-dideoxynojirimycin, a potential enzyme inhibitor. © 2003 Elsevier Science Ltd. All rights reserved.

2-Deoxysugars are an integral part of several biologically important natural products such as anthracyclin antibiotics,[2] aureolic acids,[3] avermectins,[4] orthosomycins[5] and cardiac glycosides.[6] Recently 2-deoxyglucose has been proposed as a potent drug against ageing.[7] Furthermore, both 2-deoxy-*O*-glycosides **I**[8], as well as 1-hydroxy-2-deoxysugars **II**[9,14a] (Fig. 1) function as important building blocks in organic synthesis. Both of these types of compounds have been obtained from glycals and a few reagents have been developed for the direct addition of alcohols to glycals without a competing Ferrier reaction.[10] These include the use of MeOH·HCl,[11a] Ph_3PBr_2,[11b] the cation exchange resin $AG50WX_2$[11c] and BCl_3 (or BBr_3).[11d] More recently from our group, ceric ammonium nitrate[12] and subsequently from Yadav's group,[13] $CeCl_3 \cdot 7H_2O$/NaI were also found to be useful reagents for this purpose. One can, in principle, convert a 2-deoxy-*O*-glycoside **I** (Fig. 1) into a 1-hydroxy-2-deoxy-sugar **II**, by the hydrolysis of the appropriate *O*-glycoside **I**, at the anomeric carbon. However, there are only a few methods in the literature[14] which permit the direct hydration of glycals to **II**. A recent report in this area by Piancatelli et al.[15] using $Hg(OAc)_2/NaBH_4$ led us to investigate whether any other reagent would permit such a transformation especially since mercury salts are toxic in nature and there is current emphasis on green chemistry.[16]

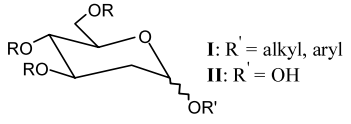

Figure 1.

In this paper we wish to report $LaCl_3 \cdot 7H_2O$/NaI/$PhCH_2OH$ as a new reagent system for the regioselective hydration of glycals. This combination was arrived at after much experimentation. Initially, we attempted to use $LaCl_3 \cdot 7H_2O$[17] in the hope that the water of hydration would participate in addition to glycals under the influence of $LaCl_3$ as the Lewis acid. However, under these conditions there was no reaction at all and the glycals were recovered unchanged. Since the NaI/$CeCl_3 \cdot 7H_2O$ combination has been reported[13,18] to be a reactive reagent system for a number of useful transformations, we performed reactions with $LaCl_3 \cdot 7H_2O$ along with a molar equivalent of NaI but again the glycals were found to be unreactive. In an attempt to compare the reactivity of $LaCl_3 \cdot 7H_2O$ with $CeCl_3 \cdot 7H_2O$, and to assess subsequent anomeric selectivity, we reacted tri-*O*-acetyl glucal with $LaCl_3 \cdot 7H_2O$/NaI in methanol. We expected the formation of 2-deoxy-*O*-glycoside **I** (R = Ac, R^1 = Me) analogous to the results reported with $CeCl_3 \cdot 7H_2O$.[13] However, the present reaction was slow and after 30 h at 40°C, to our surprise, one of the products was **II** (R = Ac, R^1 = H) in 45% yield along with the corresponding Ferrier product in 42% yield. Screening several alcohols indicated that a combination of $LaCl_3 \cdot 7H_2O$/NaI/$PhCH_2OH$ in a 1:1:1 ratio was ideal for the optimum hydration of the glycals without the formation of any *O*-glycoside or Ferrier

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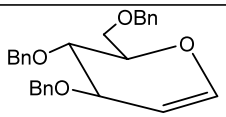
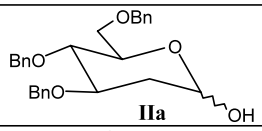
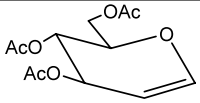
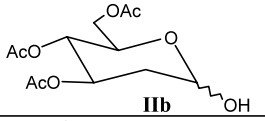
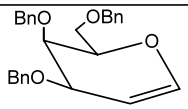
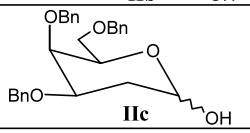
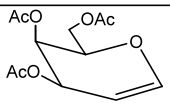
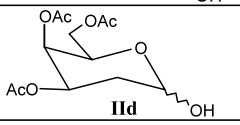
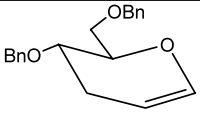
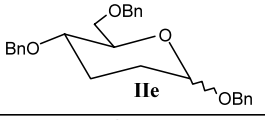
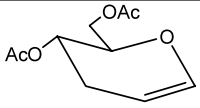
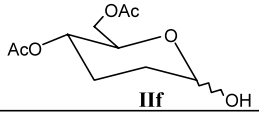
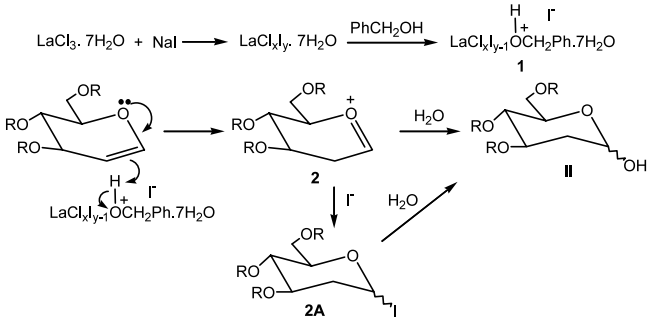
Table 1. Hydration of glycals with $LaCl_3{\cdot}7H_2O$/NaI/$PhCH_2OH$

S.No.	Glycal	Product	Time (h)	% Yield
1		 **IIa**	1.5	88[15]
2		 **IIb**	2	87[15]
3		 **IIc**	2	82[15]
4		 **IId**	4	79[15]
5		 **IIe**	1.5	88[19]
6		 **IIf**	8	93[19]

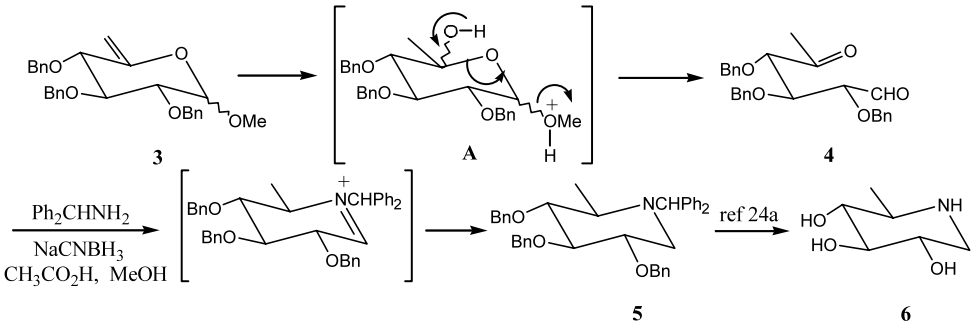
product. Both acetyl as well as benzyl protected glycals gave the hydrated products in good to excellent yields. Our results are summarised in Table 1. Furthermore, the reaction using a catalytic amount of $PhCH_2OH$ instead of 1 equiv. proceeded very slowly taking almost 48 h for completion with the formation of about 10% of the Ferrier product. Surprisingly,[20] the reaction of 3-deoxy-4,6-di-*O*-benzyl glucal under the present conditions gave addition of benzyl alcohol rather than water. At this stage nothing is clear as far as the mechanism of this reaction is concerned but it appears that a species such as **1**, may be formed, as shown in Scheme 1, which acts as a source of a proton leading to the formation of the oxonium ion **2**, when reacting with a glycal, which in turn is trapped by H_2O forming **II**. Alternatively,[21] an iodide ion can add to **2**, forming the 1-iodo-2-deoxy-sugar **2A**, which is then hydrolysed by water forming **II**. We have no evidence for either of the mechanisms which are mere speculation only.

The current resurgence of interest in glycobiology[22] has led to the synthesis of a variety of azasugars as possible drugs[23] by way of inhibiting carbohydrate processing enzymes. In this connection, the synthesis of 1,6-dideoxynojirimycin **6** (Scheme 2), a potential enzyme inhibitor, has been reported in the literature.[24] It occurred to us that a substrate like **3**[25] (Scheme 2) could be hydrated in an analogous manner to a glycal leading to the corresponding keto-aldehyde **4**[26] which could be condensed with an appropriately protected amine leading to **5**, which has been converted[24a] into 1,6-dideoxynojirimycin **6**. Indeed, it was found that hydration of **3** using the present reagent system gave **4**, in 84% yield in 3 h which, was condensed with benzhydrylamine in the presence of $NaCNBH_3$ in acetic acid/methanol mixture to give the expected[27] 2,3,4-tri-*O*-benzyl-1,6-dideoxynojirimycin derivative **5**[28] in 68% yield. This compound can be hydrogenolysed to 1,6-dideoxynojirimycin **6**, as reported.[24a] Since the reaction medium is acidic, formation of the intermediate **A** (a hemiacetal) followed by the loss of MeOH should readily occur. Alternatively, La(III) ions could coordinate with –OMe to facilitate its removal.

In summary, we have developed a new reagent system which is mild and non-toxic for the hydration of glycals which has been utilised in the formation of an azasugar **6**, a potential enzyme inhibitor, in good yield. We expect that this reagent system, as well as the synthesis of **5**, will find further use in organic synthesis.



Scheme 1.



Scheme 2.

General experimental procedure

To a solution of 0.1 mmol of a glycal in 2 mL of acetonitrile, was added lanthanum chloride heptahydrate (37 mg, 0.1 mmol), sodium iodide (15 mg, 0.1 mmol) and benzyl alcohol (11 mg, 0.1 mmol). The mixture was then stirred at 40°C and the reaction progress was monitored by TLC. Once the TLC showed complete consumption of glycal, the solvent was evaporated from the reaction mixture. The residue was dissolved in ethyl acetate (15 mL) and washed with a saturated solution of sodium thiosulfate (15 mL), water (20 mL×3) and brine (20 mL) and then dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product which was purified by column chromatography using hexane:ethyl acetate.

Acknowledgements

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References

1. Reddy, B. G.; Vankar, Y. D. *Tetrahedron Lett*. **2003**, *44*, 4765.
2. (a) Kelly, T. R. *Annu. Rep. Med. Chem*. **1979**, *14*, 288–298; (b) Andrews, F. L.; Larsen, D. S. *Tetrahedron Lett*. **1994**, *35*, 8693–8696.
3. Remers, W. R. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979.
4. Fisher, M. H.; Mrozik, H. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: New York, 1984; pp. 553–606.
5. Wright, D. E. *Tetrahedron* **1979**, *35*, 1207–1237.
6. Henderson, F. G. In *Digitalis*; Fish, C.; Surawicz, B., Eds.; Grune and Stratton: New York, 1969; pp. 3–21.
7. Lane, M. A.; Ingram, D. K.; Roth, G. S. *Sci. Am*. August **2002**, 24–29.
8. (a) Hanessian, S. Total Synthesis of Natural Products: 'The Chiron Approach' Pergamon Press: Oxford, 1983; pp. 40–183; (b) Grisebach, H. *Adv. Carbohydr. Chem. Biochem*. **1978**, *35*, 81–126.
9. (a) Muller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett*. **1994**, *35*, 4763–4766; (b) Leasage, S.; Perlin, A. S. *Can. J. Chem*. **1978**, *56*, 2889–2896.
10. (a) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem*. **1969**, *24*, 199–266; (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570–575.
11. (a) Hadfield, A. F.; Sartorelli, A. C. *Carbohydr. Res*. **1982**, *101*, 197–208; (b) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem*. **1990**, *55*, 5812–5813; (c) Sabesan, S.; Neira, S. *J. Org. Chem*. **1991**, *56*, 5468–5472; (d) Toshima, K.; Nagai, H.; Ushiski, Y.; Matsumura, S. *Synlett* **1998**, 1007–1009.
12. Pachamuthu, K.; Vankar, Y. D. *J. Org. Chem*. **2001**, *66*, 7511–7513.
13. Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Satyanarayana, M. *Tetrahedron Lett*. **2002**, *43*, 7009–7012.
14. (a) Wild, R.; Schmidt, R. R. *Liebigs Ann*. **1995**, 755–764; (b) Barnes, N. J.; Probert, M. A.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 431–438; (c) Costantino, V.; Imperatore, C.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett*. **2000**, *41*, 9177–9180; (d) Nieschalk, J.; O'Hagen, D. *J. Fluorine Chem*. **1998**, *91*, 159–163; (e) Bartolozzi, A.; Capozzi, G.; Menichetti, S.; Nativi, C. *Org. Lett*. **2000**, *2*, 251–253.
15. Bettelli, E.; Cherubini, P.; D'Andrea, P.; Passacantilli, P.; Piancatelli, G. *Tetrahedron* **1998**, *54*, 6011–6018.
16. Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res*. **2002**, *35*, 686–694.
17. For some reactions using $LaCl_3{\cdot}7H_2O$, see: (a) Sasai, A.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett*. **1993**, *34*, 851–854; (b) Lu, J.; Bai, Y. J.; Wang, Z. I.; Yang, B. Q.; Ma, H. R. *Tetrahedron Lett*. **2000**, *41*, 9075–9078.
18. Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem*. **2000**, *65*, 2830–2833 and references cited therein.
19. Physical data: **1,4,6-tri-*O*-benzyl-2,3-dideoxy-D-*arabino*-hexopyranose**, **IIe**: $[\alpha]_D = +73.7$ (*c* 1.9, CH_2Cl_2). IR (neat) ν_{max}: 1025, 1221 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.45–2.20 (m, 4H, H-2, H-2′, H-3, H-3′), 3.52–3.60 (m, 1H, H-4), 3.66–3.81 (m, 2H, H-6, H-6′), 3.83–3.87 (m, 1H, H-5), 4.38–4.74 (m, 6H, 3×CH_2Ph), 4.90–4.94 (m, 1H, H-1), 7.21–7.36 (m, 15H, 3×$CH_2C_6H_5$). ^{13}C NMR (100 MHz, α/β anomers): δ 24.05, 27.09, 28.89, 29.81, 68.54, 69.18, 69.79, 70.11, 70.77, 71.07, 72.80, 72.86, 73.39, 78.08, 127.48, 127.52, 127.59, 127.65, 127.75, 127.83, 127.96, 128.25, 128.28, 137.76, 138.01, 138.23, 138.32, 138.37, 138.47. MS (*m*/*z*): 441 (M+Na^+), 442,

326, 272, 91. Anal. calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.42; H, 7.18. **4,6-Di-*O*-acetyl-2,3-dideoxy-D-*arabino*-hexopyranose**, **IIf**: $[\alpha]_D = +75.7$ (*c* 0.7, CH_2Cl_2). IR (neat) ν_{max}: 3467, 1745, 1729 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.41–2.26 (m, 4H, H-2, H-2′, H-3, H-3′), 2.06 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 4.12–4.24 (m, 3H, H-5, H-6, H-6′), 4.66–4.88 (m, 1H, H-4), 5.31 (s, 1H, H-1). ^{13}C NMR (100 MHz, α/β anomers): δ 20.79, 21.00, 21.04, 23.12, 26.87, 28.74, 29.62, 30.95, 63.25, 63.29, 67.22, 67.87, 68.53, 75.06, 85.34, 90.85, 95.82, 170.11, 171.04. MS (*m*/*z*): 250 ($M+NH_4^+$): 250. Anal. calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.65; H, 6.89.

20. This reaction has been repeated several times but no addition of water was observed and on each occasion product **IIe** was obtained (Table 1). This result is undoubtedly very surprising but at present we have no explanation for its formation.
21. We thank the referee for suggesting the possibility of iodo sugar formation followed by hydrolysis.
22. (a) McAuliffe, J. C.; Hindsgaul, O. *Chemistry & Industry* **1997**, 170, 3rd March; (b) Kobata, A. *Acc. Chem. Res.* **1993**, *26*, 319–324.
23. (a) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–554; (b) Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5280–5291; (c) Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A., Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187–6196.
24. (a) Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482–7484; (b) Di, J.; Rajanikanth, B.; Szarek, W. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2151–2152; (c) Pistia, G.; Hollingsworth, R. I. *Carbohydr. Res.* **2000**, *328*, 467–472; (d) Bordier, A.; Compain, P.; Martin, O. R.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 47–51; (e) Defoin, A.; Sarazin, H.; Streith, J. *Helv. Chim. Acta* **1996**, *79*, 560–567.
25. Das, S. K.; Mallet, J.-M.; Sinay, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 493–496.
26. Spectral data for the keto aldehyde **4**: $[\alpha]_D = -19.3$ (*c* 2.7, CH_2Cl_2). IR (neat) ν_{max}: 3441, 1729 cm^{-1}. ^1H NMR ($CDCl_3$ 400 MHz): δ 2.09 (s, 3H, $COCH_3$), 3.91 (d, 1H, H-2, $J = 5.2$ Hz), 4.07 (d, 1H, H-4, $J = 3.2$ Hz), 4.09–4.12 (m, 1H, H-3), 4.48–4.76 (m, 6H, $3\times CH_2Ph$), 7.18–7.37 (m, 15H, $3\times CH_2C_6H_5$), 9.74 (s, 1H, CHO). ^{13}C NMR (100 MHz, relevant and important peaks only): δ 27.93 (CH_3), 200.24 (-CO-CH_3) and 210.51 (-CHO). MS (*m*/*z*): 455 ($M+Na^+$), 406, 341, 306, 118, 102, 91. Anal. calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.81; H, 6.49.
27. Condensation of benzhydrylamine was performed as per a procedure reported in Ref. 24a (vide supra).
28. Minor products formed during this reaction were not obtained in pure form and hence could not be characterised.