The Nitrile Oxide–Isoxazoline Route to Higher-carbon Dialdoses

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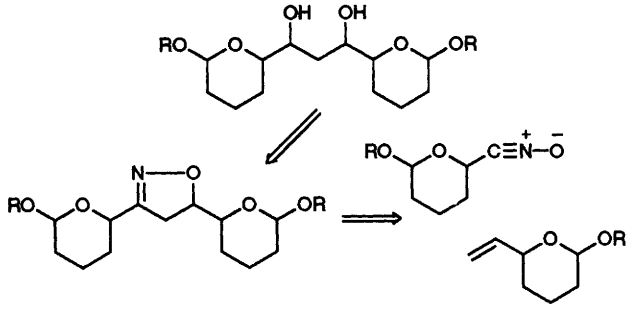
7-Deoxytrideca- and 6-deoxydodeca-dialdose derivatives are prepared by cycloaddition of D-galactose-derived nitrile oxide **2** to ω-unsaturated heptoses and hexoses and reductive hydrolytic cleavage of the resulting 2-isoxazolines.

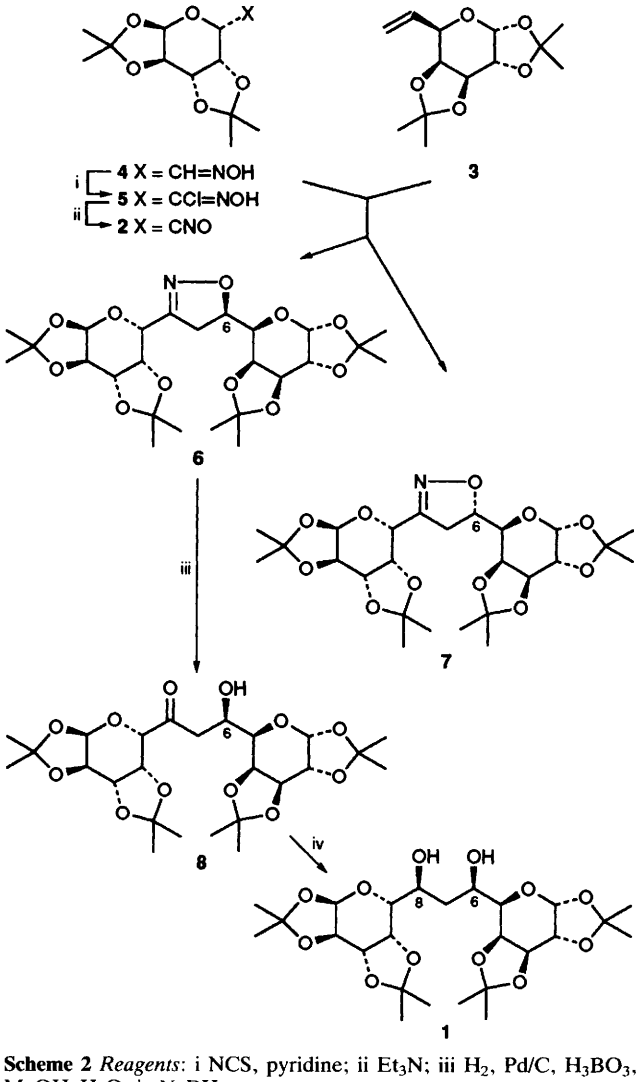
There is widespread interest in the higher-carbon monosaccharides present in antibiotics such as hikizimycin (anthelmycin)[1] and tunicamycin.[2] A variety of strategies for their synthesis have been developed,[3–5] most of which involve chain extension in one or more stages at the reducing end of hexoses to afford linear higher monoaldoses. In contrast, with the exception of the eleven-carbon tunicamine unit of tunicamycin,[6] little attention has been paid to higher-carbon dialdoses. We now describe a route from readily accessible precursors to higher dialdose derivatives, which is based on nitrile oxide–isoxazoline chemistry.[7] The synthetic approach, which is outlined for a tridecadialdose in Scheme 1, involves cycloaddition of a hexourononitrile oxide to an ω-unsaturated heptopyranose or hexofuranose and subsequent manipulation of the resulting 2-isoxazolines (4,5-dihydroisoxazoles).



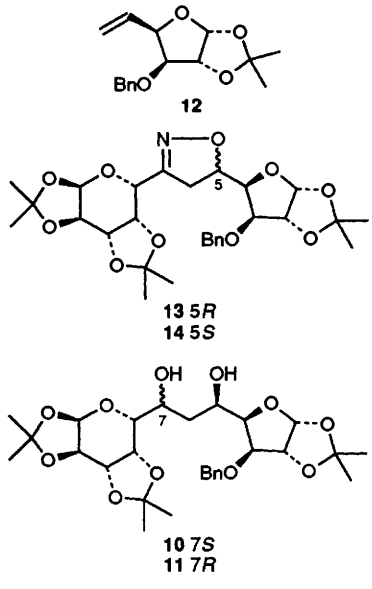
Scheme 1

Tridecadialdose derivative **1** was prepared (Scheme 2) from nitrile oxide **2** and alkene **3**[8] both of which are accessible from D-galactose. To minimise formation of furazan *N*-oxide dimer,[9] the nitrile oxide was generated *in situ* from the corresponding oxime **4** *via* hydroximoyl chloride **5** by initial treatment with *N*-chlorosuccinimide (NCS) followed by addition of triethylamine.[10] Chromatography of the reaction mixture afforded unconverted alkene and nitrile oxide dimers, followed by a pair of diastereoisomeric isoxazolines **6** and **7** in a combined yield of 40% (91% based on consumed alkene). The major product **6** was separated by crystallisation and its structure assigned by comparison of its ^{1}H and ^{13}C NMR parameters with those of previously reported isoxazolines prepared from the same alkene.[11] For adduct **6** the new asymmetric centre at C-6 has *R*-configuration† and the product ratio **6**:**7** was determined by ^{1}H NMR spectroscopy as 78:22. Neither of the other two possible regioisomeric cycloadducts, in which the oxygen of the nitrile oxide is attached to C-7 rather than C-6, were detected. The reaction is therefore regiospecific and diastereoselective in favour of adducts in which there is an *erythro* relationship between C-5 and C-6. Similar π-facial selectivity has been reported for cycloaddition of nitrile oxides to a wide variety of chiral allyl ethers[11,12] and is attributed[13] to the so called 'inside alkoxy effect'.

Isoxazoline **6** was converted in 72% yield to β-hydroxyketone **8** by reductive hydrolytic cleavage of the heterocyclic ring using hydrogen, palladium/charcoal and boric acid in methanol–water. The presence of the carbonyl group in the product is confirmed by an IR absorption at 1715 cm^{-1} and a characteristic ^{13}C NMR peak at δ 209.8. In the final stage



Scheme 2 *Reagents*: i NCS, pyridine; ii Et_3N; iii H_2, Pd/C, H_3BO_3, MeOH–H_2O; iv $NaBH_4$



12

13 5*R*
14 5*S*

10 7*S*
11 7*R*

compound **8** was reduced with sodium borohydride in ethanol–water to give as the principal product 7-deoxy-L-*erythro*-D-*gluco*-D-*glycero*-D-*galacto*-dialdose derivative **1** in 62% yield. The configuration at the newly created asymmetric centre C-8 was assigned by comparison of the ^{1}H NMR spectrum of the 1,3-diol and its isopropylidene derivative with those of similar 7-deoxynonose and decose derivatives.[5]

The dodecadialdose analogues **10** and **11** were prepared similarly by combination of nitrile oxide **2** and D-glucose-derived 5,6-hexenofuranose **12**. The cycloaddition step afforded an 85 : 15 diastereoisomeric mixture of adducts **13** and **14**. As expected, the major adduct **13** again has *R*-configuration† at the new chiral centre C-6. Hydrogenolysis of isoxazoline **13**, followed by reduction of the resulting β-hydroxyketone with sodium borohydride, afforded 6-deoxy-L-*erythro*-D-*gluco*-D-*gluco*- and 6-*deoxy*-L-*erythro*-D-*manno*-D-*gluco*-dodecadialdose derivatives **10** and **11**. In conclusion, the nitrile oxide–isoxazoline route can provide access from readily available precursors to a range of higher-carbon dialdose derivatives with control of stereochemistry.

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Footnote

† The structures of compounds **6** and **13** have been confirmed by X-ray crystallography, A. J. Blake, R. O. Gould, R. M. Paton and A. A. Young, unpublished observations.

References

1 M. Vuilhorgne, S. Ennifar, B. C. Das, J. W. Paschal, R. Nagarajan, E. W. Hagaman and E. J. Wenkert, *J. Org. Chem.*, 1977, **42**, 3289.
2 A. Takatsuki, K. Kawamura, M. Okina, J. Kodama, T. Ito and G. Tamura, *Agric. Biol. Chem.*, 1977, **41**, 2307.
3 For reviews of synthesis of higher monosaccharides see J. S. Brimacombe, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1989, vol. 4, Part C, p. 157; G. Casiraghi and G. Rassu, *Studies in Natural Products Chemistry*, 1992, vol. 11, p. 429.
4 N. Ikemoto and S. L. Schreiber, *J. Am. Chem. Soc.*, 1992, **114**, 2524; F. Emery and P. Vogel, *Tetrahedron Lett.*, 1993, **34**, 4209.
5 R. M. Paton and A. A. Young, *J. Chem. Soc., Chem. Commun.*, 1991, 132; K. E. McGhie and R. M. Paton, *Tetrahedron Lett.*, 1993, **34**, 2831.
6 S. Jarosz, *Carbohydr. Res.*, 1992, **224**, 73 and ref. therein; J. Ramza and A. Zamojski, *Carbohydr. Res.*, 1992, **228**, 205 and *Tetrahedron*, 1992, **29**, 6123; A. G. Meyers, D. Y. Gin and D. H. Rodger, *J. Am. Chem. Soc.*, 1993, **115**, 2036; R. Fernandez, C. Gasch, A. Gomez-Sanchez and J. E. Vilchez, *VIIth Eur. Carbohydr. Symp.*, Cracow, 1993, Abstr. A108; W. Kaspiesiuk and A. Benaszek, *VIIth Eur. Carbohydr. Symp.*, Cracow, 1993 Abs. A96 and A97.
7 For reviews of nitrile oxide–isoxazoline methodology see A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; D. P. Curran, *Adv. Cycloaddition*, 1988, **1**, 129; K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH Weinheim, 1988.
8 J. S. Brimacombe and A. K. M. S. Kabir, *Carbohydr. Res.*, 1986, **150**, 35.
9 C. Grundmann and P. Grünanger, in *The Nitrile Oxides*, Springer, 1971, ch. 4; P. Caramella and P. Grünanger, in *1,3-Dipolar Cycloaddition Chemistry*, ed A. Padwa, Wiley, New York, 1984, ch. 4, p. 287.
10 K. E. Larsen and K. B. G. Torssell, *Tetrahedron*, 1984, **40**, 2985.
11 A. J. Blake, R. O. Gould, R. M. Paton and A. A. Young, *J. Chem. Res.*, 1993, (*S*) 482, (*M*) 3173.
12 M. De Amici, C. De Micheli, A. Ortisi, G. Gatti, R. Gandolfi and L. Toma, *J. Org. Chem.*, 1989, **54**, 793; A. J. Blake, R. O. Gould, K. E. McGhie, R. M. Paton, D. Reed, I. H. Sadler and A. A. Young, *Carbohydr. Res.*, 1991, **216**, 461 and ref. therein; U. A. R. Al-Timari and L. Fisera, *Carbohydr. Res.*, 1991, **218**, 121.
13 K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe and F. R. Franczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880 and refs. therein.