Pergamon

Tetrahedron Letters, Vol. 36, No. 32, pp. 5815-5818, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01104-8

Template-directed Intramolecular *C*-Glycosidation. Total Synthesis of 2,3-Dideoxy-D-*manno*-2-octulopyranosonic Acid

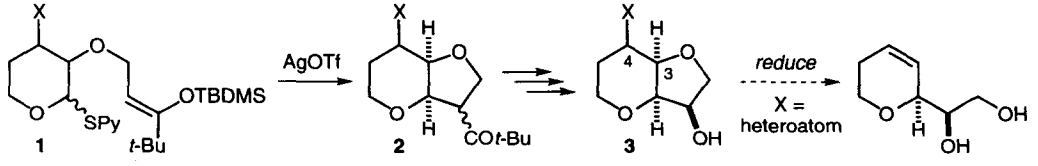
Donald Craig,*[a] Mark W. Pennington[a] and Peter Warner[b]

[a]Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, U.K.

[b]ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

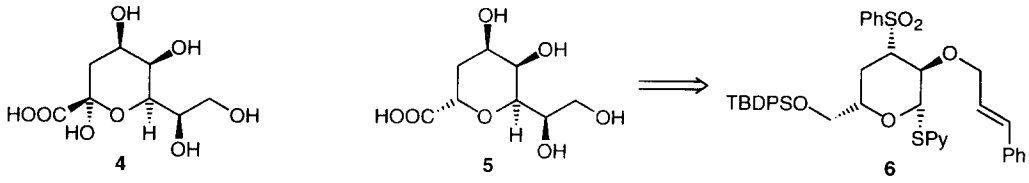
Abstract: The total synthesis of the KDO-inhibitor 2,3-dideoxy-D-*manno*-2-octulopyranosonic acid (2-deoxy-KDO) starting from TBDPS-protected (*S*)-glycidol and 3,3-dimethoxy-1-(phenylsulfonyl)-propane is described. The key steps are silver(I) trifluoromethylsulfonate-mediated cyclisation of the cinnamyl ether **6**, and Na(Hg)-induced reductive ring-opening of the bicyclic alcohol **15**.

As part of an ongoing programme to develop stereoselective intramolecular *C*-glycosidation reactions via cation-induced cyclisation reactions,[1,2] we recently reported[3] the silver trifluoromethylsulfonate-mediated reaction of the enol ether-containing thioglycosides **1** (X=H). Only cis-fused bicyclic ketotetrahydrofurans **2** were formed, with the stereoselectivity at the position α- to the ketone varying according to the stereochemical relationship between the thiopyridyl leaving group at the anomeric position and the nucleophilic enol ether side-chain in **1**. The products **2** could further be transformed via an enol ether formation–ozonolysis–reduction sequence to give alcohols **3** (X=H) with complete selectivity at the newly-formed carbinol stereocentre (Scheme 1). It occurred to us that if the C3–O bond in **3** could be cleaved, the overall transformation from the initial thioglycoside would be one of highly stereoselective delivery of a nucleophilic 1,2-ethanediol fragment to the anomeric position, and that this might provide an effective route to higher-order sugars.[4] We reasoned that analogues of **3** possessing a heteroatomic X group would be amenable to reductive ring-opening to generate a dihydropyran, and that the C3–C4 double bond in the product would allow introduction of the required diol functionality by a vicinal dihydroxylation procedure.



Scheme 1

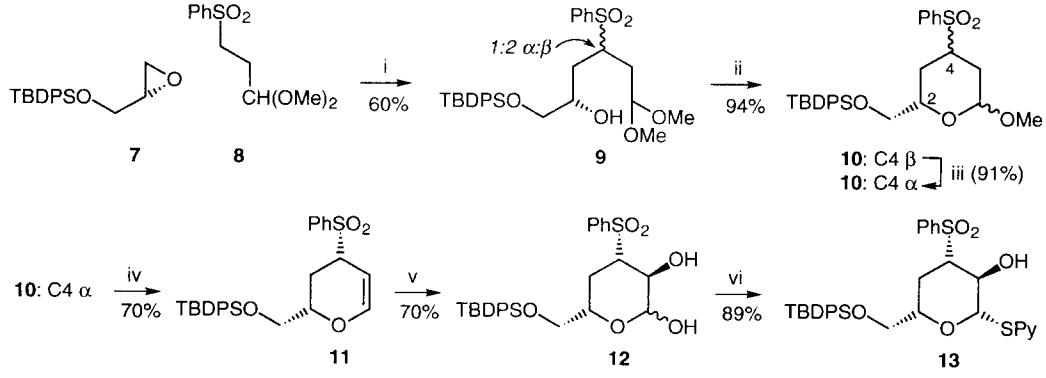
The higher-order sugar 3-deoxy-D-*manno*-2-octulosonic acid (KDO) **4** is a key structural element in cell walls of gram-negative bacteria, and inhibitors of its biosynthesis, or of its incorporation into the cell wall are being sought as potential anti-bacterial therapies.[5] We report herein the synthesis of the potent KDO inhibitor



2,3-dideoxy-D-*manno*-2-octulopyranosonic acid **5**,[6] using as the key step the cation-mediated intramolecular *C*-glycosidation of the thioglycosidic cinnamyl ether **6**.

The synthetic route started with commercially available[7] (*S*)-glycidol and 3,3-dimethoxy-1-(phenylsulfonyl)propane **8**.[8] Treatment of the *tert*-butyldiphenylsilyl ether **7** of (*S*)-glycidol with two equivalents of lithiated **8** in THF in the presence of TMEDA as co-solvent gave the adducts **9**[9] together with recovered sulfone **8** upon proton quench and simple extractive work-up. Exposure of the mixture of **9** and unreacted **8** to catalytic acid gave the methyl glycosides **10** as a mixture of isomers epimeric at the sulfone α-position and at the anomeric centre. Acetal **8** was inert under these conditions and could easily be separated at this stage.

Our *C*-glycosidation strategy relied on installation of the ether tether in **6** on the β-face of the pyran template so as to direct the internal nucleophile to that face. Therefore, it was necessary to have the bulky sulfone group on the α-face of the ring. In the event, treatment of the four-component mixture of **10** with potassium *tert*-butoxide–*tert*-butanol in THF effected smooth conversion to a *two*-component mixture of isomers with equatorial C2 and C4 substituents, differing only in terms of the configuration at the anomeric centre. Elimination of the elements of methanol from **10** using excess iodotrimethylsilane–hexamethyldisilazane[10] followed by treatment of the resulting single diastereomeric glycal **11** with *meta*-chloroperbenzoic acid gave diols **12** upon mildly basic methanolysis prior to work-up.[11] Treatment of **12** with 2,2'-dipyridyldisulfide–tri-*n*-butylphosphine as described previously[1-3,12] gave the hydroxythioglycoside **13** as a single, all-equatorial diastereomer in good yield.[13] The synthesis of **13** from **7** and **8** is summarised in Scheme 2.

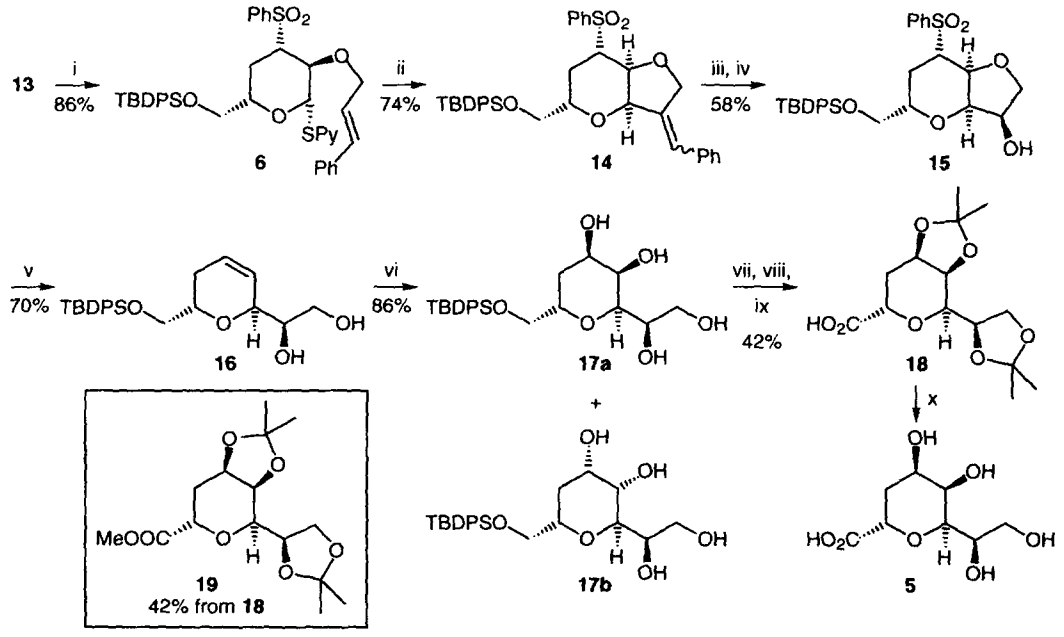


(i) Add *n*-BuLi to **8**, THF, TMEDA, -78°C; add **7**, -78°C→rt, then H^+; (ii) TFA, CH_2Cl_2, rt, 4 h; (iii) *t*-BuOK (0.5 eq), *t*-BuOH (20 eq), THF, rt, 1 h; (iv) TMSCl (6 eq), NaI (6 eq), MeCN, rt, 40 min, then add HMDS (10 eq); (v) *m*-CPBA (1.7 eq), wet ether, rt, 16 h, then Et_3N (2 eq), MeOH, rt, 15 min; (vi) PySSPy (1.2 eq), *n*-Bu_3P (1.1 eq), CH_2Cl_2, -78°C→rt, then rt, 30 min.

Scheme 2

By direct analogy with our earlier work,[3] we sought to *O*-alkylate the free hydroxyl group in **13** by phase-transfer-catalysed[14] conjugate addition to 2,2-dimethyl-4-penten-3-one. However, under a wide range of conditions, at best trace (≤ 5%) amounts of the desired adduct were formed. We reasoned that the hindered nature of the C5 –OH group was such as to disfavour its reversible addition to the enone acceptor. In a modification of the original sequence, alcohol **13** was subjected to cinnamylation using phase-transfer conditions, giving the ether **6** in good yield. Treatment of **6** with excess silver(I) trifluoromethylsulfonate in

dichloromethane, followed by the addition of DBU after consumption of the starting material gave directly the cis-fused bicyclic *C*-glycoside **14** as a ca. 5:1 mixture of geometric isomers.[15] Ozonolysis of the exocyclic double bond in **14** followed by reduction of the crude, hygroscopic ketone gave exclusively the β-configured alcohol **15**. In order to cleave the bicyclic *C*-glycoside to the desired functionalised dihydropyran nucleus, **15** was exposed to sodium amalgam under buffered conditions, providing the diol **16** in good yield. Syn-dihydroxylation of **16** gave a ca. 1:2.5 mixture of diastereomeric tetraols **17a** and **17b**, which was most easily separated after formation of the corresponding bisacetonides. Removal of the silyl protecting group from the minor diastereomer proceeded uneventfully, and oxidation of the product alcohol using ruthenium tetroxide generated in situ gave the acid **18**. Finally, deprotection of the acetonide groups gave the target 2-deoxy-KDO **5**. The ^{1}H nmr spectrum of **5** was very similar to, but not identical with that reported for the derived ammonium salt.[6] The identity of synthetic **5** was confirmed by sequential diazomethane-mediated esterification and bisacetonide formation to give **19**, which had ^{1}H and ^{13}C nmr characteristics identical with those reported.[16,17] The completion of the synthesis of **5** is depicted in Scheme 3.



(i) Aliquat® 336, PhCH=CHCH$_2$Br, CH_2Cl_2, 50% aq NaOH, rt, 15 min; (ii) add **6** to $AgOSO_2CF_3$, 4Å molecular sieves, CH_2Cl_2, rt, 20 min, then add DBU (5 eq); (iii) O_3, CH_2Cl_2, -78°C, 10 min, then PPh_3 (1 eq), -78°C→rt, then rt, 16 h; (iv) $NaBH_4$ (3 eq), MeOH, 0°C, 1 h; (v) 6% Na(Hg) (4 eq, 30 min, then 8 eq, 15 min, then 8 eq, 15 min), Na_2HPO_4 (1.25 eq), MeOH, 0°C; (vi) OsO_4 (0.01 eq), NMO (1.5 eq), 9:1 acetone–H_2O, rt, 30 h; (vii) $CuSO_4$ (1 eq), H_2SO_4 (cat.), acetone, rt, 15 min; (viii) *n*-Bu_4NF (1.5 eq), THF, rt, 30 min; (ix) $NaIO_4$ (3 eq), $RuO_2{\cdot}H_2O$ (0.2 eq), 3:2:2 H_2O–MeCN–CCl_4, rt, 30 min; (x) 9:1 TFA–H_2O, rt, 1 h.

Scheme 3

In summary, we have demonstrated that cation-mediated intramolecular *C*-glycosidation is an effective and selective strategy for the elaboration of higher-order sugars from simple, non-glycosidic precursors. We are currently exploring the utility of sulfonylglycals such as **11** in *inter*molecular *C*-glycosidation processes, and we are actively developing the cinnamyl function as an intramolecular nucleophile in pyrrolidine-forming reactions. The results of these studies will be reported in due course.

ACKNOWLEDGEMENTS

We thank the SERC/EPSRC and ZENECA Pharmaceuticals[18] (CASE Studentship to M. W. P.) for financial support of this research. We gratefully acknowledge the SERC Mass Spectrometry Service Centre, University College of Swansea for providing high-resolution mass spectra.

REFERENCES AND NOTES

1. Formation of six-membered bicyclic *C*-glycosides: Craig, D.; Munasinghe, V. R. N. *Tetrahedron Lett.* **1992**, *33*, 663.
2. Formation of bicyclic ketooxetanes via intramolecular *C*-glycosidation: Craig, D.; Munasinghe, V. R. N. *J. Chem. Soc., Chem. Commun.* **1993**, 901.
3. Craig, D.; Pennington, M. W.; Warner, P. *Tetrahedron Lett.* **1993**, *34*, 8539.
4. For leading references on higher-order sugar synthesis, see: Marshall, J. A.; Beaudoin, S. *J. Org. Chem.* **1994**, *59*, 6614, reference 1.
5. For a review, see: Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323.
6. For a recent synthesis of 2-deoxy-KDO, and leading references, see: Lopez-Hereira, F. J.; Sarabia-Garcia, F.; Pino-Gonzalez, M. J. *Tetrahedron Lett.* **1994**, *35*, 6709. For references to KDO synthesis, see: Gao, J.; Härter, R.; Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1994**, *59*, 3714, reference 2.
7. Aldrich Chemical Co. Ltd.
8. Compound **8** was easily made in 82% overall yield by triethylamine-catalysed conjugate addition of thiophenol to acrolein, followed by acetalisation (trimethyl orthoformate–K-10 montmorillonite clay) and oxidation of the thioether to the sulfone. All yields cited herein are of isolated, purified materials which gave satisfactory ^{1}H, ^{13}C nmr and ir spectra, and which showed low-resolution ms and either elemental combustion analysis or high-resolution ms characteristics in accord with the assigned structures.
9. The stereochemistry of the major diastereomer of **9** was assigned by analogy with that of the crystalline unsaturated adduct derived from reaction of lithiated 3-benzyloxy-1-(phenylsulfonyl)-2-propene with racemic *tert*-butyl-protected glycidol: Pennington, M. W., Ph.D. thesis, University of London, 1995.
10. Paquette, L. A.; Oplinger, J. A. *J. Org. Chem.* **1988**, *53*, 2953.
11. Significant amounts (ca. 30% of oxidised product) of the *meta*-chlorobenzoate anomeric ester of **12** were formed; these were cleaved efficiently to **12** by treatment of the crude product with triethylamine–methanol.
12. Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289.
13. Nmr data for **13** (octulose numbering): δ_H (500 MHz, $CDCl_3$) *inter alia* 5.24 (1H, d, J 9.5 Hz, H-6), 3.91 (1H, t, J 9.5 Hz, H-5), 3.73 (1H, dd, J 10, 4.5 Hz, H-1), 3.75-3.68 (1H, m, H-2), 3.57 (1H, dd, J 9.5, 4.5 Hz, H-1), 3.45-3.39 (1H, m, H-4), 2.21 (1H, ddd, J 13, 4, 1.5 Hz, H-3_{eq}), 1.72-1.64 (1H, m, H-3_{ax}), 1.60 (1H, br s, -O*H*), 0.99 (9H, s, *t*-Bu); δ_C (125.9 MHz, $CDCl_3$) *inter alia* 85.8 (C-6), 77.6 (C-5), 68.8 (C-2 or C-4), 67.0 (C-4 or C-2), 65.8 (C-1), 27.7 (C-3), 26.8 (C(CH_3)$_3$), 19.2 (C(CH$_3$)$_3$).
14. For phase-transfer-catalysed alkylation reactions of hindered secondary alcohols with *tert*-butyl bromoacetate, see: Burke, S. D.; Lee, K. C.; Santafianos, D. *Tetrahedron Lett.* **1991**, *32*, 3957.
15. We have not assigned the major and minor geometric isomers of bicycle **14**.
16 Luthman, K.; Orbe, M.; Waglund, T.; Claesson, A. *J. Org. Chem.* **1987**, *52*, 3777
17. Nmr data for **19** (octulose numbering): δ_H (500 MHz, $CDCl_3$) 4.59 (1H, dt, J 8, 3 Hz, H-4), 4.55 (1H, dd J 11.5, 6 Hz, H-2), 4.34 (1H, dd J 8, 1.5 Hz, H-5), 4.23-4.20 (2H, m, H-7, H-8), 4.12-4.09 (1H, m, H-8), 3.75 (3H, s, OCH_3), 3.51-3.45 (1H, m, H-6), 2.30 (1H, ddd, J 15, 6, 3.5 Hz, H-3_{eq}), 1.86 (1H, ddd, J 14.5, 11.5, 2.5 Hz, H-3_{ax}), 1.49 (3H, s, CCH_3), 1.42, (3H, s, CCH_3), 1.38 (3H, s, CCH_3), 1.36 (3H, s, CCH_3); δ_C (125.9 MHz, $CDCl_3$) 173.4 (C-1), 109.4 (C(CH$_3$)$_2$), 109.3 (C(CH$_3$)$_2$), 72.8 (C-6), 72.2 (C-5), 69.7 (C-4), 68.3 (C-2), 67.2 (C-8), 52.0 (OCH_3), 26.7 (C-3), 27.0 (CCH_3), 26.2 (CCH_3), 25.1 (CCH_3), 24.9 (CCH_3).
18. ZENECA in the U. K. is part of ZENECA Limited.

(*Received in UK* 5 *May* 1995; *revised* 9 *June* 1995; *accepted* 16 *June* 1995)