Tetrahedron Letters, Vol.31, No.40, pp 5765-5768, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A STEREOCONTROLLED APPROACH TO 3-DEOXY-D-MANNO-2-OCTULOSONIC ACID CONTAINING DISACCHARIDES [1]

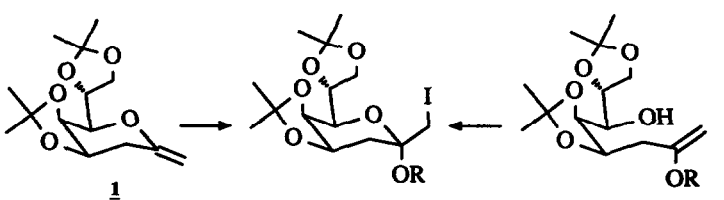
Arnaud Haudrechy and Pierre Sinaÿ *
Ecole Normale Supérieure, Laboratoire de Chimie, UA 1110,
24 Rue Lhomond,75231 Paris Cédex 05, France

Summary: The development of a synthetic approach to KDO containing disaccharides based on stereocontrolled iodocyclization of an enol ether is detailed.

3-Deoxy-D-manno-2-octulosonic acid (KDO) occurs as a characteristic component of enterobacterial lipopolysaccharides (LPS) and has also been found in several acidic exopolysaccharides (K antigens), both located at the cell surface of Gram-negative bacteria [2]. The incorporation of KDO appears to be a vital step in growth of the bacteria. Therefore the synthetic chemistry involving KDO has become of increasing interest.

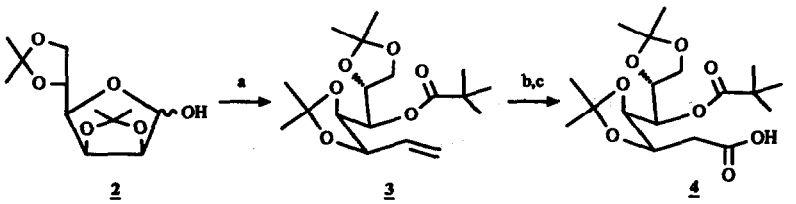
The synthesis of KDO-containing oligosaccharides has largely been approached so far by conventional glycosylation procedures [3] involving either methyl 3-deoxy-4,5,7,8-tetra-*O*-acetyl-α-D-manno-octulopyranosonate chloride, bromide, fluoride or the corresponding glycal. Anomerically selective O-alkylation has also been described [4]. Other solutions to this synthetic problem involve the use of a furan ring as a surrogate for the carboxylic acid residue of KDO [5] and the intramolecular oximercuration-demercuration of an appropriate acyclic precursor [6]. We would like to present a new solution, where the key step is a stereospecific intramolecular iodocyclization of a complex enol ether [7].

We first considered the "exo-glycal" **1** [8] as a possible candidate for iodonium mediated glycosylation of "sugar alcohols". This approach was disappointing [9], so that the development of the intramolecular version was a logical issue and indeed proved a successful stratagem:



1

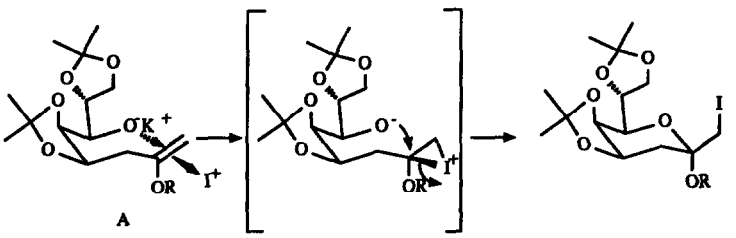
The carboxylic acid **4**, a general precursor of the KDO unit, was first prepared in three steps from known [10] 2,3-5,6-di-*O*-isopropylidene-D-mannose **2**. Wittig reaction followed by "in situ" pivaloylation (a, $Ph_3P{=}CH_2$, THF, HMPA then pivaloyl chloride) gave the derivative **3** (71%) [11], $[\alpha]_D$ -22°. Hydroboration (b, 9-BBN then NaOH, H_2O_2 [12]), followed by oxidation (c, $RuCl_3$, $NaIO_4$, CH_3CN-CCl_4-H_2O [13]) gave the carboxylic acid **4** (91%).



2 3 4

The carboxylic acid 4 was immediately esterified (a, ROH, DCC, DMAP, 1h, room temperature) with two "sugar alcohols", methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside [14] and 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose [10] (Scheme 1); 5a and 5b were obtained (86% and 88%). Methylenation of the ester group (b, Tebbe's reagent, pyridine, 30min, -78°C [15]) gave derivatives 6a and 6b (81% and 87%). Depivaloylation (c, $LiAlH_4$, THF, 1h, room temperature) gave the complex enol ethers 7a and 7b (93% and 90%). The key iodocyclization (d, tBuOK, I_2, 1h, -78°C [7]) gave the α-glycosides 8a and 8b as only detectable isomers in 92% and 90% yield.

The remarkable stereoselectivity of the cyclization reaction may be rationalized in assuming (i) a chair product like $^5C_2$(D) conformation for the transition state and (ii) a conformational preference of 7 as A:

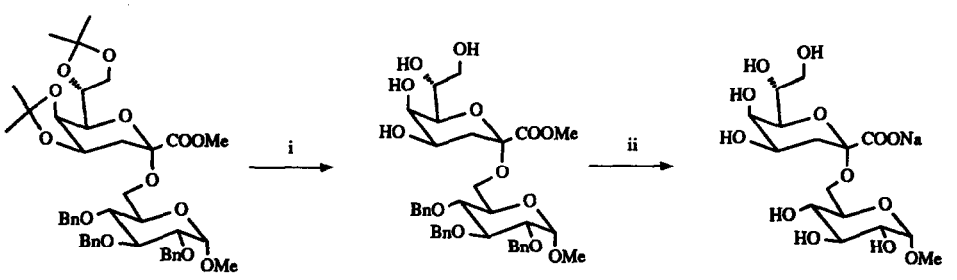


A

α-configuration of 8a and 8b was assigned from the characteristic chemical shift of H-4 [16].

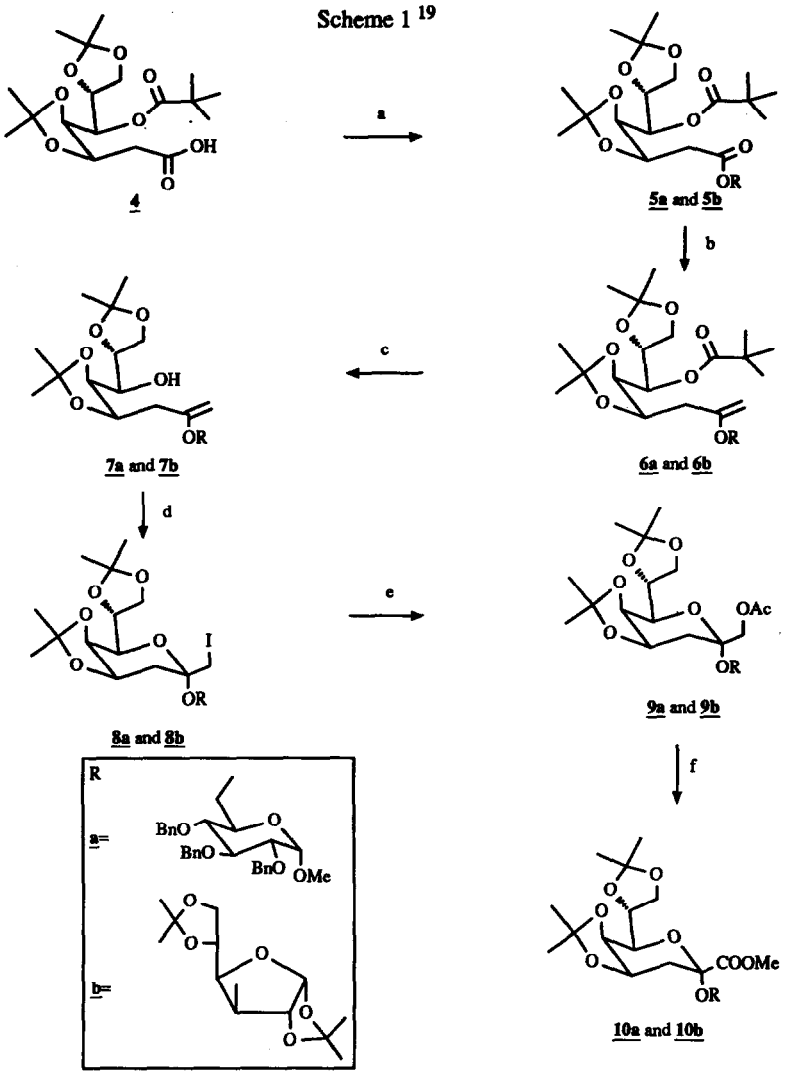
The CH_2I-appendage was modified as follows: nucleophilic displacement under drastic conditions (e, CsOAc, HMPA, 36h, 140°C) gave the acetates 9a and 9b (68% and 84%), which were easily converted into 10a and 10b (f, MeONa, MeOH, 2h, room temperature, then $(COCl)_2$, DMSO, Et_3N, -78°C [17], then $NaClO_2$, H_2O_2 30%, CH_3CN, 12h, room temperature [18], then CH_2N_2, 0°C, 67% and 62%).

Compound 10a was converted (i, CF_3COOH, MeOH, H_2O, 48h, room temperature) into 11a (90%), which, after catalytic hydrogenolysis (ii, H_2, Pd/C) and saponification (NaOH), provided the known KDO-disaccharide 12a [6]:



10a 11a 12a

Scheme 1 [19]



References and Notes

1. Part of this work was presented at the *5th European Symposium on Carbohydrates* (Eurocarb V), Prague, August 1989, A-141 and at *Journées de Chimie Organique* (JCO 89), Palaiseau, September 1989, A-233.

2. F.M. Unger, *Adv. Carbohydr. Chem. Biochem.*, *38*, 323 (1981).

3. P. Waldstätten, R. Christian, P. Kosma, C. Kratky, G. Schultz, H. Paulsen and F.M. Unger, *ACS Symp. Ser.*, *231*, 121 (1983); H. Paulsen, Y. Hayaushi and F.M. Unger, *Carbohydr. Res.*, *111*, C5 (1983); H. Paulsen, Y. Hayaushi and F.M. Unger, *Liebigs Ann. Chem.*, 1270 and 1288 (1984); P. Kosma, R. Christian, G. Schultz and F.M. Unger, *Carbohydr. Res.*, *141*, 239 (1985); H. Paulsen, M. Stiem and F.M. Unger, *Tetrahedron Lett.*, 1135 (1986); H. Paulsen and M. Schüller, *Liebigs Ann. Chem.*, 249 (1987); H. Paulsen, M. Stiem and F.M. Unger, *ibid.*, 273 (1987); M. Kiso, M. Fujita, E. Hayashi, A. Hasegawa and F.M. Unger, *J. Carbohydr. Chem.*, 6, 691 (1987); M. Imoto, N. Kusunose, Y. Matsuura, S. Kusumoto and T.

Shiba, *Tetrahedron Lett.*, 6277 (1987); M. Kiso, M. Tanahashi, A. Hasegawa and F.M. Unger, *Carbohydr. Res.*, *163*, 279 (1987); P. Kosma, J. Gass, G. Schultz, R. Christian and F.M. Unger, *Carbohydr. Res.*, *167*, 39 (1987); M. Kiso, M. Fujita, M. Tanahashi, Y. Fujishima, Y. Ogawa, A. Hasegawa and F.M. Unger, *Carbohydr. Res.*, *177*, 51 (1988); S. Kusumoto, N. Kusunose, T. Kamikawa and T. Shiba, *Tetrahedron Lett.*, 6325 (1988); K. Ikeda, S. Akamatsu and K. Achiwa, *Carbohydr. Res.*, *189*, C1 (1989); P. Kosma, G. Schultz, F.M. Unger and H. Brade, *Carbohydr. Res.*, *190*, 191 (1989); M. Kiso, M. Fujita, Y. Ogawa, H. Ishida and A. Hasegawa, *Carbohydr. Res.*, *196*, 59 (1990).

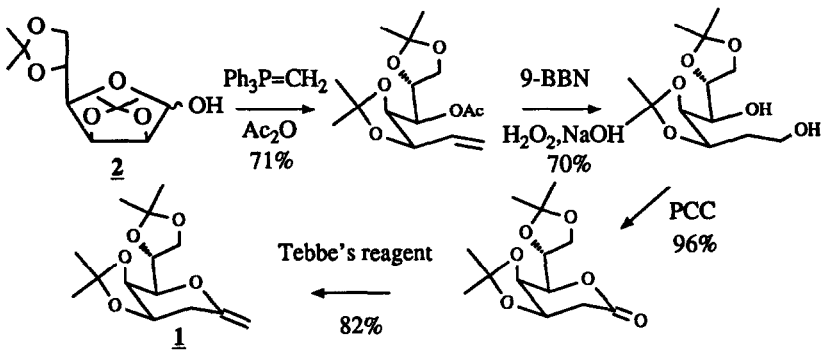
4. R.R. Schmidt and A. Esswein, *Angew. Chem. Int. Ed. Engl.*, *27*, 1178 (1988); A. Esswein, H. Rembold and R.R. Schmidt, *Carbohydr. Res.*, *200*, 287 (1990).

5. S.J. Danishefsky, M.P. DeNinno and S. Chen, *J. Am. Chem. Soc.*, *110*, 3929 (1988).

6. F. Paquet and P. Sinaÿ, *J. Am. Chem. Soc.*, *106*, 8313 (1984).

7. While this work was in progress, a similar reaction has independently been reported: A.G.M. Barrett, B.C.B. Bezuidenhout, A.F. Gasiecki, A.R. Howell and M.A. Russell, *J. Am. Chem. Soc.*, *111*, 1392 (1989).

8. The compound **1**, $[\alpha]_D$ +2°, has been prepared from 2,3-5,6-di-*O*-isopropylidene-D-mannose **2**[10] as follows:



9. We found in a model study that NIS mediated addition reaction on fully benzylated 1-methylene--D-glucose occured only with reactive alcohols. See also: D. Noort, G.H. Veeneman, G.J.P.H. Boons, G.A. van der Marel, G.J. Mulder, J.H. van Boom, *Synlett*, 205 (1990).

10. O.T. Schmidt, *Methods Carbohydr. Chem.*, *2*, 318 (1963).

11. All new compounds had satisfactory microanalytical and spectral properties. Optical rotations were measured for solutions in chloroform at 20°C, unless otherwise stated.

12. T.V. RajanBabu and G.S. Reddy, *J. Org. Chem.*, *51*, 5458 (1986).

13. P.H.J. Carlsen, T. Katsuki, V.S. Martin and K.B. Sharpless, *J. Org. Chem.*, *46*, 3936 (1981).

14. A. Lipták, I. Jodál and P. Nánási, *Carbohydr. Res.*, *44*, 1 (1975).

15. F.N. Tebbe, G.W. Parshall and G.S. Reddy, *J. Am. Chem. Soc.*, *100*, 3611 (1978).

16. **8a**: δ 4.45 (ddd, $J_{5,4}$ 2.5, $J_{3a,4}$ 11.5, $J_{3e,4}$ 3.5 Hz); **8b**: δ 4.49 (ddd, $J_{5,4}$ 3.5, $J_{3a,4}$ 11.5, $J_{3e,4}$ 3Hz).

17. A.J. Mancuso and D. Swern, *Synthesis*, 165 (1981).

18. E. Dalcanale and F. Montanari, *J. Org. Chem.*, *51*, 567 (1986).

19. **5a**: $[\alpha]_D$ +11°; **5b**: $[\alpha]_D$ -14°; **6a**: $[\alpha]_D$ +6°; **6b**: $[\alpha]_D$ -23°; **7a**: $[\alpha]_D$ +44° (c 0.9, pyridine); **7b**: $[\alpha]_D$ -13°; **8a**: $[\alpha]_D$ +12°; **8b**: $[\alpha]_D$ +5°; **9a**: $[\alpha]_D$ +26°; **9b**: $[\alpha]_D$ -2°; **10a**: $[\alpha]_D$ +51°, m.p. 101°C (from hexane); **10b**: $[\alpha]_D$ +1°; **11a**: $[\alpha]_D$ +38°, m.p. 100°C (from hexane).

(Received in France 3 August 1990)