Pergamon

Tetrahedron Letters 40 (1999) 5191–5192

TETRAHEDRON
LETTERS

Improved Double Epimerisation of (D)-Glucose into (D)-Gulose and the Synthesis of (D)-Xylo-imidazolopiperidinose.

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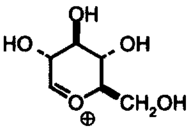
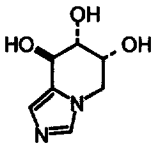
Received 12 March 1999; accepted 19 May 1999

Abstract: Rhodium/alumina catalysed cis-hydrogenation of the known enol-acetate **7** proceeded quantitatively and with complete stereoselectivity leading to the D-gulose derivative **8**. Several reaction steps permitted transformation of **8** into the target D-xylo-imidazolopiperidinose *ent*-**4** molecule, *i.e.* the enantiomer of the already known imidazolo-sugar **4**. © 1999 Published by Elsevier Science Ltd. All rights reserved.

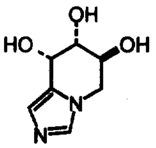
Cyclic half-chair carboxonium ions are nowadays the accepted intermediates during glycosidase-induced hydrolysis of pyranose type oligo- and polysaccharides. The geometry of these half-chair carboxonium ions, *e.g.* **1**, is very close to the postulated transition state which leads to them. Half-chair sugar-amidines which were prepared by Wong [1] and by Ganem [2] proved to be among the most potent artificial glycosidase inhibitors. We prepared half-chair piperidinose derivatives by incorporating an imidazole ring, *e.g.* the D-arabino-aminosugar **2** [3] a compound which turned out to be a good and selective inhibitor of human liver α-mannosidase [4]. In the meantime we also prepared the L-lyxo **3** [5] and the L-xylo **4** [6] stereoisomers of **2**. Similarly, Vasella prepared several triazole- [7] and tetrazole-sugar derivatives [8]. Eventually, nagstatine **5**, a naturally occurring imidazolosugar, was isolated, and proven to be an inhibitor of N-acetylaminoglucosaminidase [9]. To the best of our knowledge **5** is the only imidazole-sugar found so far in nature whose N-protonated form corresponds to the postulated half-chair cyclic carboxonium ion.



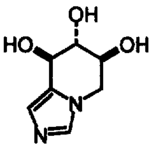
D-gluco
1



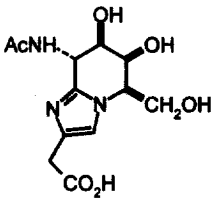
D-arabino
2



L-lyxo
3



L-xylo
4



5

We describe herein the hemi-synthesis of the D-xylo-imidazolopiperidinose *ent*-**4**, which required a twofold configurational inversion of D-glucose-diacetonide **6** into the known 3-O-benzyl-D-gulose derivative **9** [10] according to a novel catalytic hydrogenation methodology. The critical cis-hydrogenation of **7** - which led mostly to hydrogenolysis of the acetoxy group with palladium [10] - was achieved successfully over a rhodium catalyst, the crystalline stereoisomer **8** being formed as the only reaction product (96% after crystallization). Reaction of **8** with sodium methanolate in THF using PTC conditions (NBu_4I) gave the corresponding

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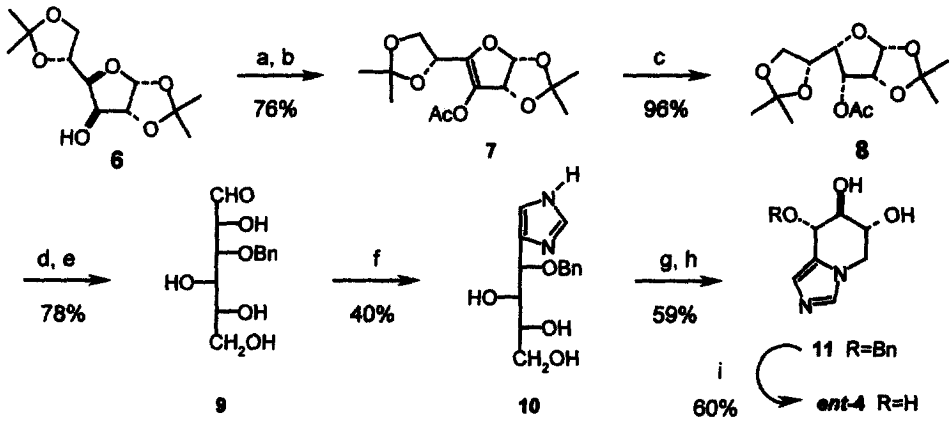
PII: S0040-4039(99)01003-5

alcoholate, to which benzyl bromide was added to yield the expected O-benzyl derivative. Removal of the acetonide protection groups (Dowex ®) gave the desired D-gulose derivative **9**. Condensation of the latter with formamidine according to a method we described previously [11], led in moderate yield to the imidazole derivative **10**. Ditosylation in pyridine at -10 °C of this latter compound occurred both at the remote nitrogen atom, and selectively at the primary alcohol function. The expected crude ditosyl derivative dissolved slowly in sodium hydroxide at 60 °C and led to bicyclic compound **11**. Hydrogenolysis of benzyl ether **11** led to the target molecule ***ent*-4** which showed all the physical characteristics of **4** except for the optical rotation which is of opposite sign: ***ent*-4** ($[\alpha]_D$ = - 68); **4** ($[\alpha]_D$ = + 63) [6].



a) PCC, CH_2Cl_2, 45 °C, 4h; b) Ac_2O, pyridine, 80 °C, 6h; c) H_2, 50 bar, Rh(5%)/Al_2O_3, AcOEt, rt, 5 mn; d) 1. MeONa, NBu_4I, THF, rt, 45 mn, 2. NaH, BnBr, THF, 45 °C, 2h; e) Dowex ® (5x28), H_2O/EtOH (5:5), 75 °C, 4h; f) formamidinium acetate, NH_3, 45 bar, 80 °C, 48h; g) TsCl (2.8 eq), pyridine, -10 °C, 4h; h) NaOH (1M), 60 °C, 16h; i) H_2, 1 bar, Pd(5%)/C, AcOEt, rt, 1h.

Acknowledgements. The support of the *Centre National de la Recherche Scientifique* (*UPRES-A* 7015) is gratefully acknowledged. We also wish to thank the French Ministry of Higher Education for a PhD-grant to H.S. and the department of catalysis of NOVARTIS in Basle for the catalytic hydrogenation procedure of compound **11**.

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