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Stereocontrolled synthesis of (+)-L-noviose using a versatile sugar building block

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Abstract

(+)-L-Noviose, the sugar moiety of the antibiotic novobiocin, has been synthesized diastereoselectively using a man-made sugar building block.

Keywords: antibiotics; carbohydrates; enantiocontrol; neighboring group effects; stereocontrol.

The antibiotic novobiocin **1** carries a sugar moiety which is responsible for its biological activity.[1] The sugar moiety was found to be removed under acidic conditions to give 4-*O*-methyl-5,5-dimethyl-L-lyxose, (+)-L-noviose[2] **2** (Fig. 1). Although this rare sugar has been synthesized[3] in both racemic and enantiomeric forms, only one procedure, namely, that by Pankau and Kreiser[3d,e] using a chiral building block[4] seemed to be the most practical so far. In relation to our recent project on sugar synthesis, we chose (+)-L-noviose **2** as a target to extend the synthetic applicability of our sugar building block[5,6] **3** which was originally designed for the diastereocontrolled construction of eight possible aldohexoses in both enantiomeric forms.[5,7] We wish to report here a new synthesis of (+)-L-noviose **2** starting from our sugar building block[5,6] (+)-**3** which was prepared from furfural in enantiomerically pure forms by employing either a chemical[5,8] or an enzymatic[6] procedure (Scheme 1).

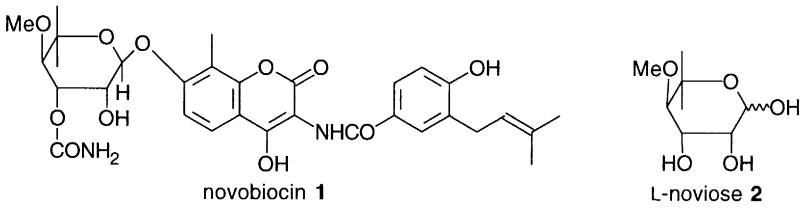

Fig. 1.

Owing to its biased structure, the building block (+)-**3** having a dioxabicyclo[3.2.1]octane framework allowed diastereoselective epoxidation from the convex face on reaction with alkaline hydrogen

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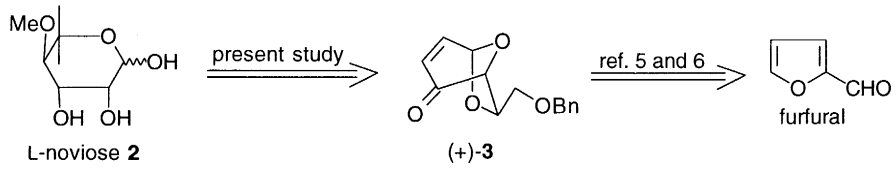
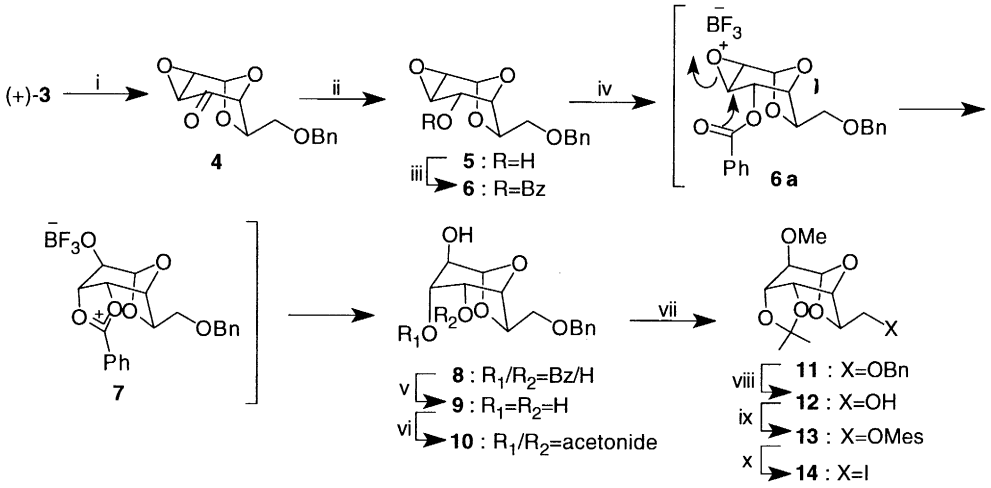


Scheme 1.

peroxide[8] to give the *exo*-epoxide **4** as a single product. Reduction of **4** with sodium borohydride-cerium(III) chloride[9] also took place diastereoselectively from the convex face to give the *endo*-alcohol **5**, $[\alpha]_D^{27}$ +17.7 (*c* 1.1, $CHCl_3$), as a single product. Benzoylation of **5** followed by treating the resulting benzoate **6**, $[\alpha]_D^{29}$ −18.2 (*c* 1.1, $CHCl_3$), with boron trifluoride etherate[10] in toluene brought about regio- and diastereoselective epoxy cleavage to give the monobenzoate mixture **8**. Without separation, the mixture was subjected to alkaline methanolysis to give the single triol **9** which allowed specific ketal formation to afford the crystalline hydroxy-acetonide **10**, mp 109–110°C, $[\alpha]_D^{29}$ −52.2 (*c* 1.1, $CHCl_3$), as the single product. The observed diastereoselective conversion of the epoxide **6** into the single triol **9** may be readily presumed by taking account of the participation of the benzoate group which produced the benzoate mixture **8** through **6a** and **7** as shown.

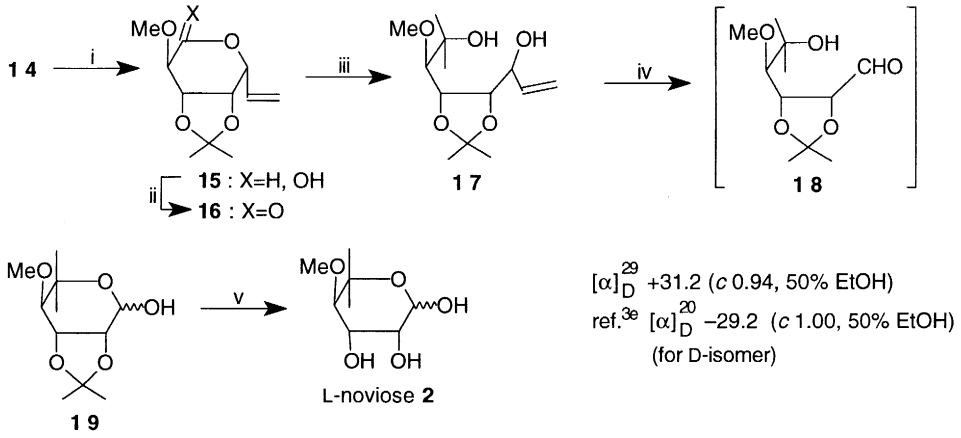
Having created three consecutive oxygen-bearing stereogenic centers, which are those required in the target molecule, the secondary alcohol **10** was first treated with methyl iodide under standard conditions to give the methyl ether **11**, $[\alpha]_D^{29}$ −53.9 (*c* 1.0, $CHCl_3$), whose benzyl functionality was then removed under hydrogenolysis conditions to give the crystalline primary alcohol **12**, mp 83–84°C, $[\alpha]_D^{27}$ −85.5 (*c* 1.0, $CHCl_3$). Mesylation of **12** followed by treating the resulting mesylate **13** with lithium iodide afforded the iodide **14**, $[\alpha]_D^{28}$ −47.8 (*c* 1.0, $CHCl_3$), without difficulty. Overall yield of **14** from (+)-**3** was 54% in 10 steps (Scheme 2).



Scheme 2. Reagents and conditions: (i) 30% H_2O_2, 0.5N NaOH, THF, 0°C. (ii) $NaBH_4$–$CeCl_3 \cdot 7H_2O$, MeOH, 0°C (82% for two steps). (iii) BzCl, pyridine, CH_2Cl_2 (96%). (iv) $BF_3 \cdot OEt_2$, toluene. (v) NaOMe, MeOH. (vi) $Me_2C(OMe)_2$, PPTS (cat.), toluene, reflux (84% for three steps). (vii) MeI, NaH, THF (99%). (viii) H_2, 10% Pd–C, MeOH (91%). (ix) MesCl, Et_3N, CH_2Cl_2. (x) LiI, THF, reflux (90% for two steps)

In order to attain the target molecule, the iodide **14** was treated with zinc in methanolic acetic acid to initiate reductive elimination to cleave the internal acetal functionality to give rise to the hemiacetal **15** as a mixture of epimers. Since an anhydro-sugar type internal acetal functionality requires rather severe conditions for its hydrolytic cleavage, the sugar building block **3** exerts its potential with respect

to this point. On oxidation with tetrapropylammonium perruthenate in the presence of *N*-morphorine *N*-oxide (TPAP–NMO),[5,11] **15** gave the δ-lactone **16**, mp 59–60°C, $[\alpha]_D^{29}$ +89.9 (*c* 1.1, $CHCl_3$), as colorless needles (Scheme 3). Treatment of **16** with an excess amount of methyllithium gave the acyclic diol **17**, $[\alpha]_D^{27}$ −51.7 (*c* 1.0, $CHCl_3$), whose extra two-carbon moiety was oxidatively removed under Lemieux–Johnson conditions[12] to give the hemiacetal **19** via the transient hydroxy-aldehyde **18**. Finally, **19** was acid-hydrolyzed in the presence of Dowex 50-W[13] to remove the acetonide protecting group to give rise to (+)-L-noviose **2**, mp 128–129°C, $[\alpha]_D^{29}$ +31.2 (*c* 0.94, 50% EtOH) [lit.[3e]: mp 128°C, $[\alpha]_D^{20}$ −29.2 (*c* 1.00, 50% EtOH) for D-enantiomer], as colorless crystals. Overall yield of **2** from **14** was 43%.



Scheme 3. Reagents and conditions: (i) Zn, AcOH:MeOH (1:10) (97%). (ii) TPAP–NMO, 4 Å sieves, CH_2Cl_2 (90%). (iii) MeLi, THF, 0°C (83%). (iv) OsO_4 (cat.), $NaIO_4$, 50% aq. THF. (v) Dowex 50-W, H_2O, 70°C (59% for two steps)

In summary, we have synthesized (+)-L-noviose **2** in 23% overall yield in 15 steps with complete diastereoselection from our sugar building block (+)-**3** on the basis of its inherent convex-face selectivity and high functionality.

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