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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. © 2000 Elsevier Science Ltd. All rights reserved.

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

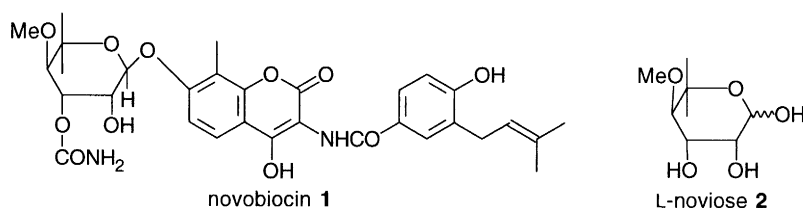
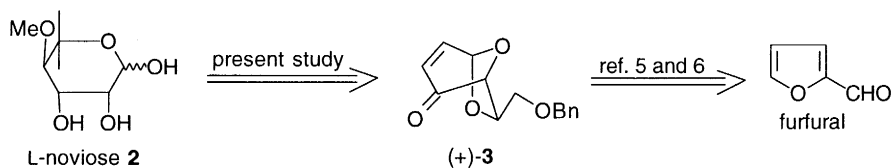


Fig. 1.

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

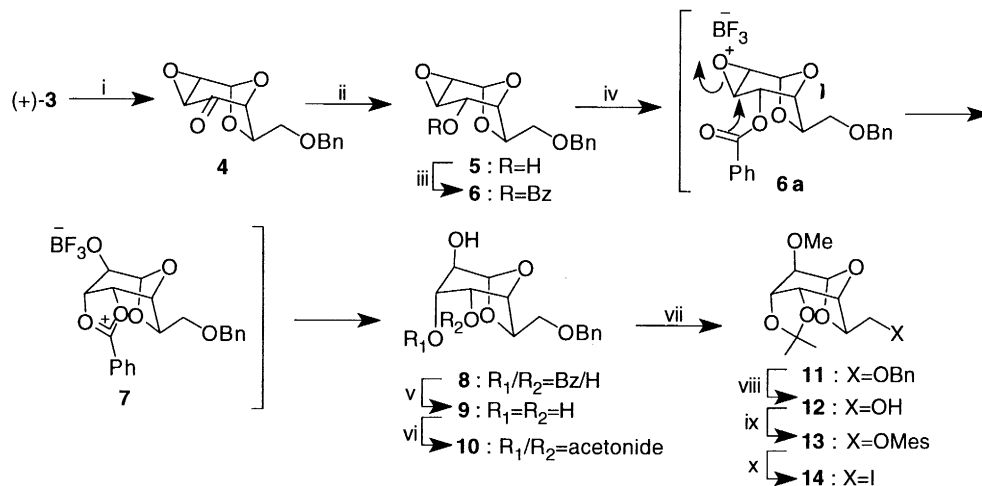
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Scheme 1.

peroxide<sup>8</sup> to give the *exo*-epoxide **4** as a single product. Reduction of **4** with sodium borohydride-cerium(III) chloride<sup>9</sup> also took place diastereoselectively from the convex face to give the *endo*-alcohol **5**,  $[\alpha]_D^{27} +17.7$  (*c* 1.1,  $\text{CHCl}_3$ ), as a single product. Benzoylation of **5** followed by treating the resulting benzoate **6**,  $[\alpha]_D^{29} -18.2$  (*c* 1.1,  $\text{CHCl}_3$ ), with boron trifluoride etherate<sup>10</sup> 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,  $\text{CHCl}_3$ ), 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.

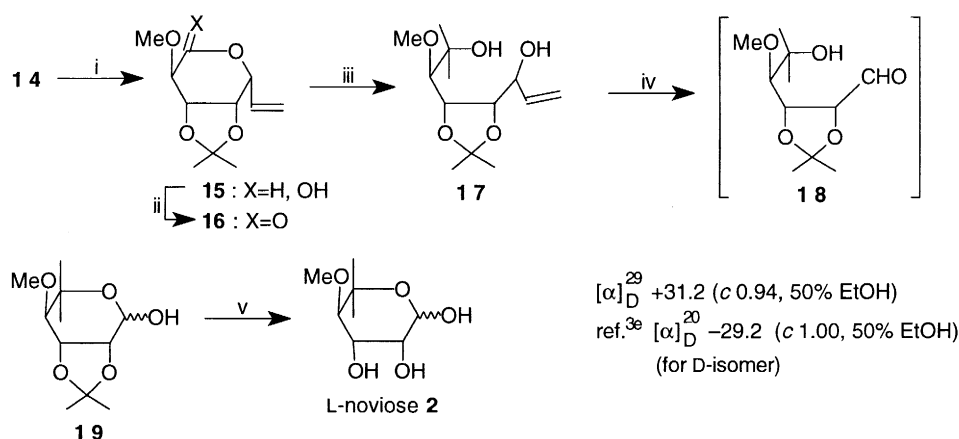
Having created three consecutive oxygen-bearing stereogenic centers, which are those required in the target molecule, the secondary alcohol **10** was first treated with methyl iodide under standard conditions to give the methyl ether **11**,  $[\alpha]_D^{29} -53.9$  (*c* 1.0,  $\text{CHCl}_3$ ), whose 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,  $\text{CHCl}_3$ ). 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,  $\text{CHCl}_3$ ), without difficulty. Overall yield of **14** from (+)-**3** was 54% in 10 steps (Scheme 2).



Scheme 2. Reagents and conditions: (i) 30%  $\text{H}_2\text{O}_2$ , 0.5N NaOH, THF, 0°C. (ii)  $\text{NaBH}_4\text{-CeCl}_3\cdot 7\text{H}_2\text{O}$ , MeOH, 0°C (82% for two steps). (iii) BzCl, pyridine,  $\text{CH}_2\text{Cl}_2$  (96%). (iv)  $\text{BF}_3\cdot\text{OEt}_2$ , toluene. (v) NaOMe, MeOH. (vi)  $\text{Me}_2\text{C}(\text{OMe})_2$ , PPTS (cat.), toluene, reflux (84% for three steps). (vii) MeI, NaH, THF (99%). (viii)  $\text{H}_2$ , 10% Pd-C, MeOH (91%). (ix) MesCl,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ . (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*-morpholine *N*-oxide (TPAP–NMO),<sup>5,11</sup> **15** gave the  $\delta$ -lactone **16**, mp 59–60°C,  $[\alpha]_{\text{D}}^{29} +89.9$  (*c* 1.1, CHCl<sub>3</sub>), as colorless needles (Scheme 3). Treatment of **16** with an excess amount of methyllithium gave the acyclic diol **17**,  $[\alpha]_{\text{D}}^{27} -51.7$  (*c* 1.0, CHCl<sub>3</sub>), whose extra two-carbon moiety was oxidatively removed under Lemieux–Johnson conditions<sup>12</sup> to give the hemiacetal **19** via the transient hydroxy-aldehyde **18**. Finally, **19** was acid-hydrolyzed in the presence of Dowex 50-W<sup>13</sup> to remove the acetonide protecting group to give rise to (+)-*L*-noviose **2**, mp 128–129°C,  $[\alpha]_{\text{D}}^{29} +31.2$  (*c* 0.94, 50% EtOH) [lit.<sup>3e</sup>: mp 128°C,  $[\alpha]_{\text{D}}^{20} -29.2$  (*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<sub>2</sub>Cl<sub>2</sub> (90%). (iii) MeLi, THF, 0°C (83%). (iv) OsO<sub>4</sub> (cat.), NaIO<sub>4</sub>, 50% aq. THF. (v) Dowex 50-W, H<sub>2</sub>O, 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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