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Enantiospecific synthesis of (−)-D-noviose from (−)-pantolactone☆

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Abstract—Noviose, the rare sugar moiety present in novobiocin, is an important antimicrobial and antitumor agent that has been shown to inhibit DNA gyrase and HSP90. An enantiospecific synthesis of D-(−)-noviose starting from commercially available (−)-pantolactone is reported.

Novobiocin is an antimicrobial agent produced by *Streptomyces* species[1] and was identified as a potent inhibitor of DNA gyrase which catalyzes the negative supercoiling of DNA in prokaryotes. Although novobiocin has been used clinically for the treatment of cancer for several years,[2] it was only recently shown to inhibit the 90 kDa heat-shock proteins (HSP90), which is an emerging target for the development of new cancer chemotherapeutics.[3,4] The noviose subunit of novobiocin is a unique sugar moiety that is found solely in the coumarmycin family of antibiotics and has been the target of several synthetic studies.[5] Except for the recent method reported by Blagg and co-workers,[5j] no existing procedure is capable of producing both (+)- and (−)-novioses. In this letter, we report a novel synthetic route to both enantiomers of noviose from pantolactones (Fig. 1).

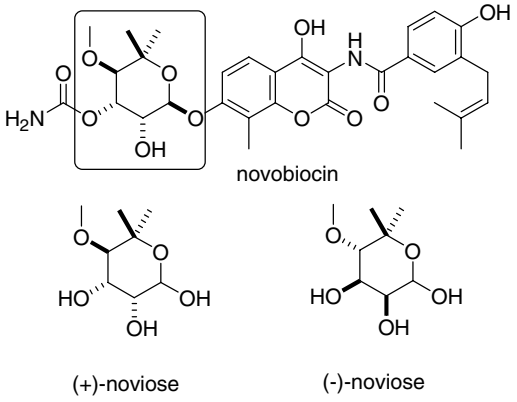

Figure 1. Structures of novobiocin and novioses.

Retrosynthetically, we envisioned (−)-noviose **1** to originate from cyclopentenone **2** via dihydroxylation of the double bond and Baeyer–Villiger (BV) oxidation of the corresponding ketone. It was proposed that ring-closing metathesis (RCM) could generate this α,β-unsaturated ketone from its acyclic precursor **3**, which in turn could be prepared from commercially available (−)-pantolactone **4** (Scheme 1).

Our synthesis began with the construction of the acyclic precursor **5** following literature procedures.[6] Swern oxidation of **5** followed by Grignard addition of vinylmagnesium bromide furnished diene **6** in excellent yield. We next subjected **6** to RCM using Grubbs' first generation catalyst to give a cyclopentene derivative, which upon oxidation with Jones reagent gave cyclopentenone **2**,[7] However, all efforts to dihydroxylate the double bond using OsO_4 failed (Scheme 2).

To circumvent this problem, we resorted to an alternative approach as described in Scheme 3. Thus, Luche reduction of cyclopentenone **2** gave the allylic alcohol with excellent diastereoselectivity, which was protected as the *tert*-butyldimethylsilylether to give compound **8**. The *syn*-stereochemistry of the alcohol with respect to the methoxy group is predictable based on hydride approach from the opposite side to the methoxy group (Scheme 3). Dihydroxylation of the alkene using a

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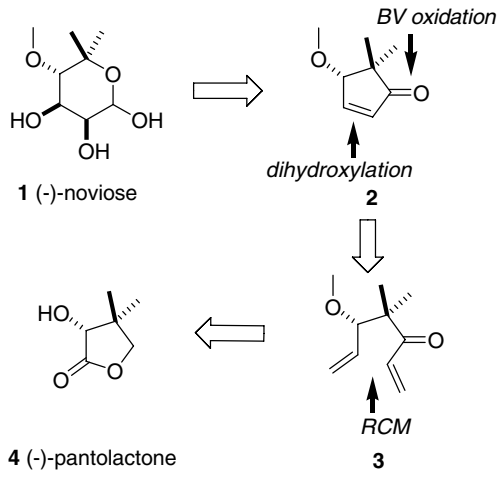
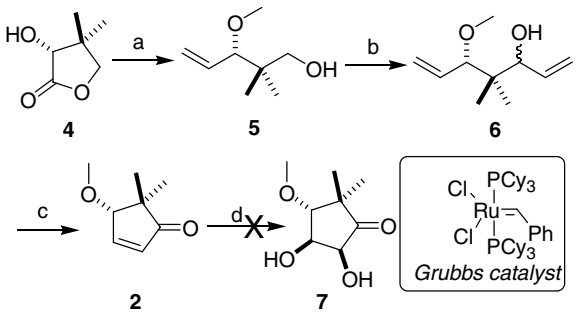
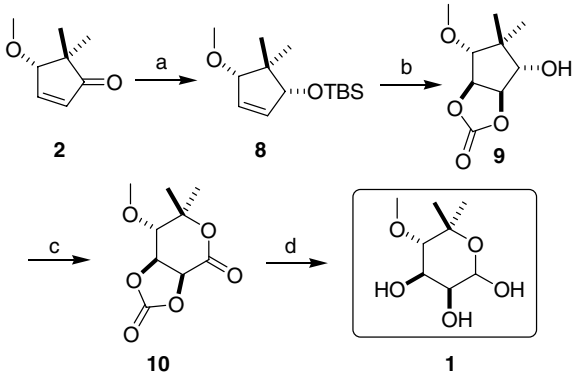


Scheme 1.



Scheme 2. Reagents and conditions: (a) Ref. 6, three steps; (b) (i) $(COCl_2)$, DMSO, Et_3N, −78 °C, 96%; (ii) $CH_2{=}CHMgBr$, 0 °C, 82%; (c) (i) 5 mol % Grubb's catalyst, rt, 91%; (ii) Jones' oxidation, 86%; (d) OsO_4, NMO.



Scheme 3. Reagents and conditions: (a) (i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, 0 °C, 96%; (ii) TBSCl, imid., 0 °C, 83%; (b) (i) OsO_4, NMO, acetone, H_2O, *t*-BuOH, rt, 89%; (ii) triphosgene, 0 °C to rt, 92%; (iii) TBAF, THF, 94%; (c) (i) Swern or PDC; (ii) *m*-CPBA, DCM, 3 days, rt, 90% for two steps; (d) DIBAL-H, −78 °C, 60% (Ref. 5e).

combination of osmium tetroxide and *N*-methylmorpholine-*N*-oxide followed by protection of the diol, and TBS deprotection furnished alcohol **9**. Oxidation of the hydroxy functional group (Swern or PDC), then Baeyer–Villiger oxidation of the resulting ketone with *m*-CPBA gave lactone **10**,[8] which had earlier been converted to the target compound, (−)-noviose **1**, in a single step using DIBAL-H reduction. The spectral data of synthetic **10** were compared with the reported data and were found to be identical, $[\alpha]_D$ +11.1 (*c* 0.45, $CHCl_3$), lit.[5e]: $[\alpha]_D$ +12.3 (*c* 1.44, $CHCl_3$). Similarly, (+)-noviose could be synthesized starting from commercially available (+)-pantolactone.

In conclusion, we have achieved the enantiospecific total synthesis of (−)-noviose from (−)-pantolactone via a short synthetic sequence. We are planning to generate analogues of noviose using this route, which may exhibit better biological profiles.

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7. Previously, (+)-dimethyl-4-hydroxy-2-cyclopentenone (a derivative of **2**) was synthesized prom (−)-pantolactone in 10 steps. Miyaoka, H.; Sagawa, S.; Nagaoka, H.; Yamada, Y.

Tetrahedron: Asymmetry **1995**, *6*, 587–594, We have prepared compound **2** in just 6 steps starting from pantolactone.

8. It was reported in the literature (Ref. 5e) that the other regio isomeric lactone also isolated from this reaction. However, in our hands we could not isolate the other isomer.