Pergamon

Tetrahedron Letters 39 (1998) 2089–2090

TETRAHEDRON LETTERS

Enantioselective Total Synthesis of (-)-D-Noviose

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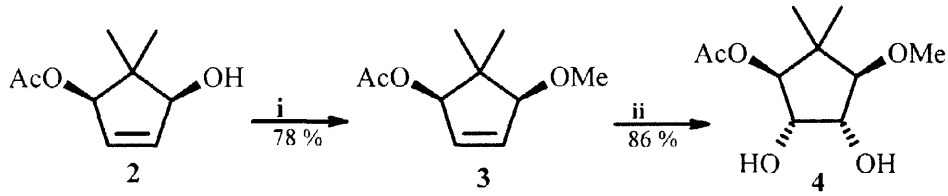
Received 12 January 1998; accepted 30 January 1998

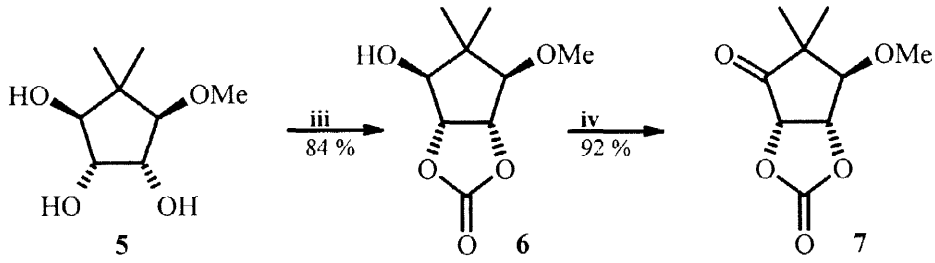
Abstract: Noviose (**1**), the sugar moiety of the antibiotic Novobiocin[1], has been synthesized enantioselectively from the readily available[2] chiral building block **2** in seven steps.

In contrast to reported syntheses of noviose (**1**) from the past, which either lead to racemic material[3] or start with natural sugar derivatives[4,5], we present here an enantioselective approach to the target molecule, that has to be classified as total synthesis. The shortness of our route and the cheap availability[2] established for both antipodes of building block **2** are outstanding features, providing access to the native (+)-L-noviose and its (-)-D-enantiomer, as well. The latter has not been obtainable, until now.



Scheme 1: i) CH_2N_2, $BF_3{\cdot}Et_2O$, Et_2O, 0 °C ii) OsO_4, NMO, acetone/water (8/1), 0 °C

Building block (-)-**2** is transformed to methyl ether **3** by formal carbene insertion into the OH-bond of the allylic alcohol using diazomethane in etheral solution catalyzed by BF_3-etherate[6]. *cis*-Hydroxylation of **3** with catalytic amounts of osmium tetroxide and NMO as co-oxidant[7] stereoselectively leads to α-diol **4** due to the direct influence of two substituents on the ß-face of the molecule.



Scheme 2: iii) $CO(OCCl_3)_2$, pyridine, CH_2Cl_2, - 70 °C iv) PDC, CH_2Cl_2, 20 °C

After saponification of the acetate function in **4**, which is quantitatively achieved by aqueous KOH in methanol, the *syn*-located *vic.* hydroxyls of the resulting triol **5** are protected as cyclic carbonate utilizing triphosgene and pyridine as reagents[8]. The resulting bicyclic cyclopentanol **6** then is submitted to oxidation with pyridinium dichromate (PDC) in dichloromethane[9] to give **7** in high yield.

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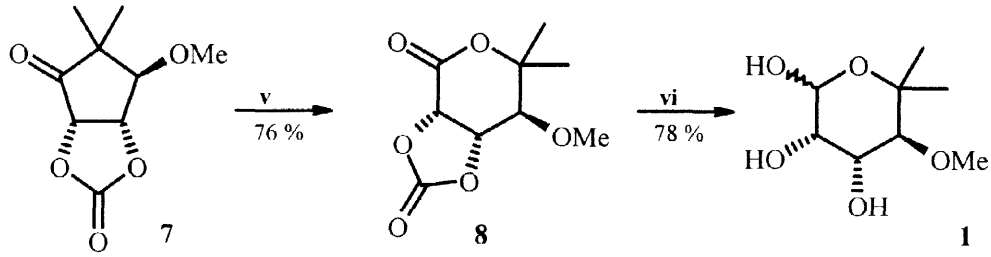
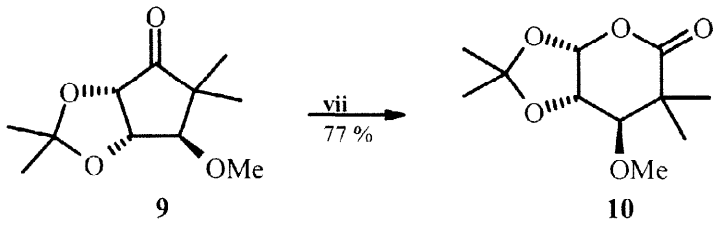
0040-4039/98/$19.00
PII: S0040-4039(98)00295-0

In this way protected ketone **7** turned out a suitable substrate for Baeyer-Villiger rearrangement leading to the corresponding noviolactone **8** with high regioselectivity, whereas the isomeric lactone **10** is produced as a side product only, in about 20 % yield.



Scheme 3: v) MCPBA, CH_2Cl_2, rt vi) DIBAH, CH_2Cl_2, - 78 °C

The total synthesis is completed by reduction of lactone **8** with DIBAH at low temperature[10], which directly leads to the (-)-D-enantiomer of noviose in a single step. The synthetic noviose after recrystallization from cyclohexane/ethyl acetate is formed in 31 % yield over seven steps, and displays m.p. 128 °C [Lit[11]: 128-130 °C] and a surprisingly high optical rotation of $[\alpha]_D^{20}$ = -29.2° (in 50 % ethanol, c = 1.00) [Lit.: +38[11], +22.6[12], +20.8[5], +19.9[1], +19.35[4]].



Scheme 4: vii) MCPBA, CH_2Cl_2, rt

Alternatively, we have investigated quite a few different protective groups for the *vic.* hydroxyls, e.g. isopropylidene acetal **9**, but in all cases failed, since only the wrong regioisomers like **10** could be isolated. These observations came unexpected to us, but there are precedents in very recent literature[13]. On the other hand acyclic ester groups like benzoates undergo immediate β elimination forming conjugated ketones.

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