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Alternative and Expedient Asymmetric Syntheses of L-(+)-Noviose

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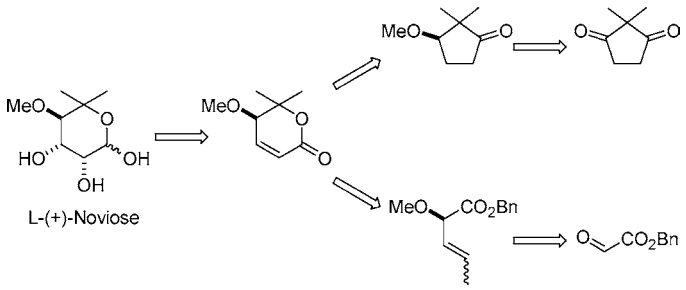
ABSTRACT



L-(+)-Noviose, the sugar component of the antibiotic novobiocin, was synthesized from readily available non-carbohydrate starting materials relying on stoichiometric and asymmetric processes by two independent methods, comprising six and nine steps, in 27 and 20% overall yields, respectively.

L-(+)-Noviose (**1**) is the sugar component of novobiocin (**2**) and coumermycin (**3**), two naturally occurring coumarin glycosides originally produced from a number of *Streptomyces* species (Figure 1).[1] Known for its antibiotic properties for many years, novobiocin has elicited considerable interest as a potential anticancer agent recently, due to its inhibitory effect on Hsp-90 (heat shock protein),[2] an important chaperone protein in a variety of physiologically important processes.[3] The relevance of coumarin antibiotics as inhibitors of DNA gyrase and topoisomerase IV has been amply documented.[4]

Although there are nearly 10 reported syntheses of (−)- or (+)-noviose, dating as far back as 1964,[5] the majority of these utilize carbohydrate precursors as starting materials that contain the C2−C3 *cis*-diol group at the outset.[5a−f,i−k] As such, the main challenge becomes the manipulation of existing functional groups in the starting aldose carbon framework by chain extension, cleavage, branching, and hydroxyl protection/deprotection protocols to achieve the

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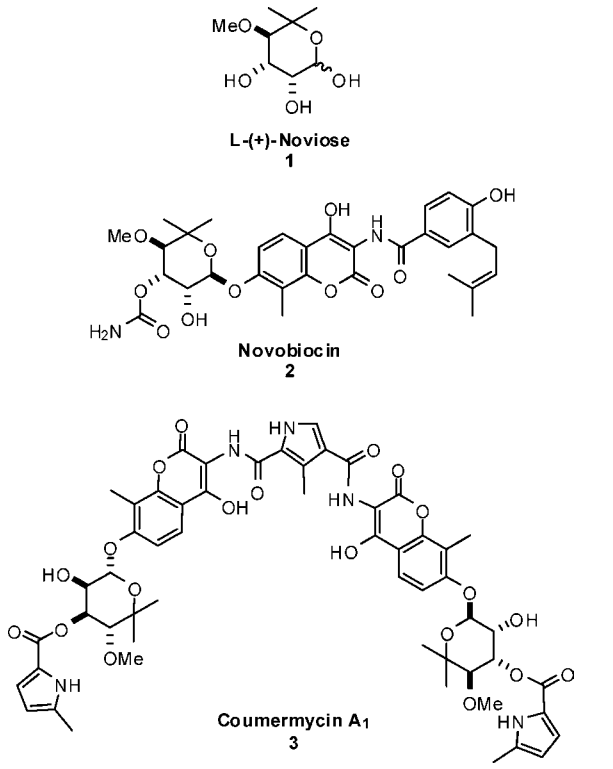


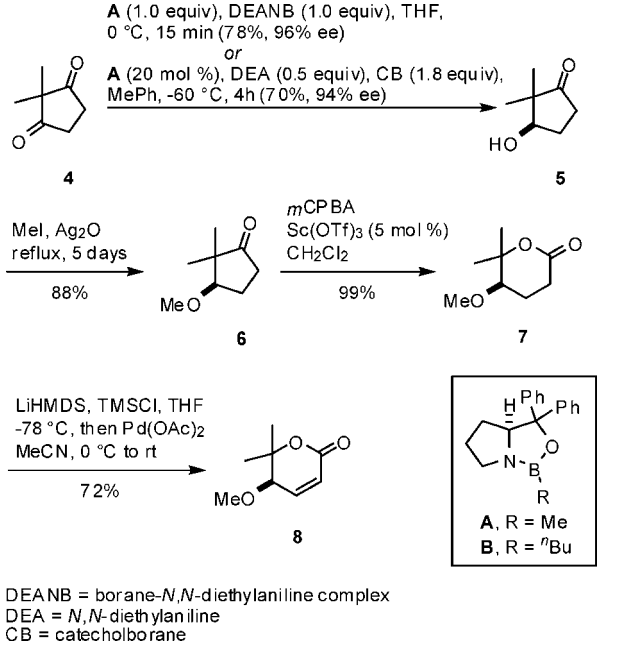
Figure 1. Structure of L-(+)-noviose and of antibiotics novobiocin and coumermycin A_1.

desired substitution and stereochemical pattern in the intended noviose. A chemoenzymatic route to unnatural (−)-noviose starts with *meso*-2,2-dimethylcyclopent-4-ene-1,3-diol which is desymmetrized via the monoacetate.[5g] In the most recent synthesis, (−)-pantolactone is utilized as a starting chiron already containing a *gem*-dimethyl substitution and the correctly configured C4 hydroxyl group of (−)-noviose.[5a]

In spite of these diverse approaches, the practical synthesis of noviose merits further attention especially involving principles of asymmetric C−C bond formation and catalysis from readily available non-carbohydrate starting materials. We describe herein two alternative and expedient routes to (−)- or (+)-noviose that can be adapted to the synthesis of unnatural analogues (Schemes 1−3). In both approaches, protection/deprotection manipulations are circumvented.

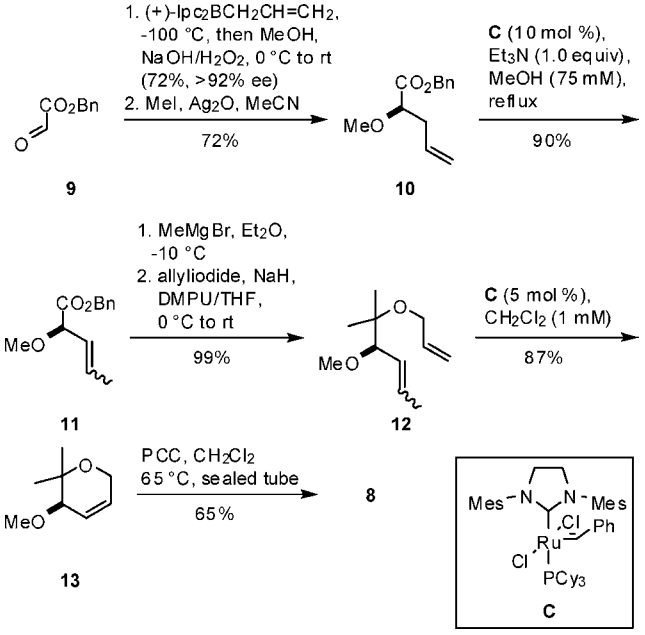
Central to the first approach (Scheme 1) is the enantioselective catalytic desymmetrization of the readily available

Scheme 1. Synthesis of Unsaturated Lactone **8**



2,2-dimethyl-1,3-cyclopentadione **4**.[6] Initially, stoichiometric (*S*)-*B*-Me-oxazaborolidine [(*S*)-*B*-Me-CBS, **A**][7] proved to be the requisite reagent in combination with equimolar BH_3−

Scheme 2. Alternative Synthesis of Unsaturated Lactone **8**



N,*N*-diethylaniline complex (DEANB) at 0 °C in THF for 10 min, providing the desired (*R*)-alcohol **5** (96% ee)[8] in

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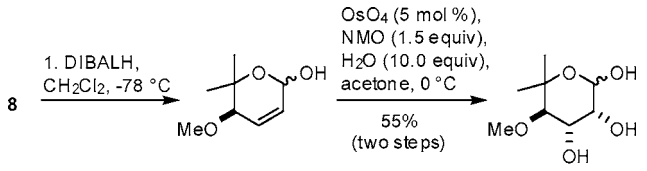
(7) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

Scheme 3. Final Steps toward L-(+)-Noviose



78% yield (Scheme 1).[9] Substoichiometric (50 mol %) or catalytic (20 mol %) (*S*)-*B*-Me-CBS was ineffective, often leading to non-reproducible enantioselectivity levels. Recently, Corey and co-workers reported the desymmetrization of diketone **1** with 10 mol % of (*S*)-*B*-^{n}Bu-CBS (**B**) in combination with catecholborane and in the presence of *N*,*N*-diethylaniline (DEA).[10] In the presence of 20 mol % of catalyst **A**, catecholborane, and diethylaniline, ketone **5** was obtained in 70% yield and the same enantioselectivity as reported by Corey (94%).[11]

Conversion to the methyl ether **6**[12] was followed by a $Sc(OTf)_3$-promoted Baeyer−Villiger reaction[13] to give the lactone **7**. A Saegusa oxidation[14] on the preformed trimethylsilyl enol ketene intermediate in the presence of $Pd(OAc)_2$ led the unsaturated lactone **8** in 63% yield for three steps.

We also describe an alternative method to the lactone **8** which relies on the venerable asymmetric Brown allylation reaction[15] (Scheme 2). Freshly distilled benzyl glyoxylate **9** was converted to the desired homoallylic alcohol intermediate in 72% yield and >92% ee following the Brown procedure[15] with preformed (+)-allyldiisopinocampheylborane [(+)-$(Ipc)_2BCH_2CH{=}CH_2$]. O-Methylation with MeI in the presence of Ag_2O in MeCN gave quantitatively the ether **10**. Application of the recently reported isomerization[16] of terminal double bonds to the 2-propenyl equivalent in the presence of 10 mol % of the second generation Grubbs' catalyst **C** and equimolar Et_3N in refluxing methanol gave **11** as a *cis*/*trans* mixture in excellent yield even on a gram scale.[17] After reaction of **11** with MeMgBr, the resulting *gem*-dimethyl tertiary alcohol was O-allylated to the diene **12** by treatment with allyl iodide and NaH in THF/DMPU in excellent yield for the two steps.[18] A ring closing metathesis reaction in the presence of 5 mol % of Grubbs' second generation catalyst[19] gave the α,β-unsaturated dihydropyran **13** in good yield. The metathesis reaction could be routinely run on multiples of 100 mg scale at substrate concentration of 1 mM. Next, we subjected the cyclic ether **13** to an allylic oxidation in the presence of pyridinium chlorochromate[20] to give the unsaturated lactone **8** in satisfactory yield.

With the unsaturated lactone **8** in hand, we were ready to perform the final dihydroxylation/reduction sequence (Scheme 3). Surprisingly, direct dihydroxylation[21] of lactone **8** under various conditions[22] resulted in low recovery of the diol, in contrast to several reports dealing with the dihydroxylation of related analogues.[23] We therefore decided to postpone the dihydroxylation reaction until after the reduction of **8** with DIBALH to an anomeric mixture of lactol intermediates **14**.

(8) Enantioselectivity was determined by ^{1}H NMR analysis of the Mosher ester derivatives at 700 MHz.

(9) For the use of DEANB or *N*,*N*-diethylaniline (DEA) in asymmetric reductions of ketones, see: (a) Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3883−3886. (b) Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2095−2100. (c) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1523−1526.

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(11) In the presence of 10 mol % of **A**, alcohol **5** was isolated in 82% ee, while 40 mol % of **A** provided **5** in 98% ee. Interestingly, a remarkable temperature effect was observed when the reduction was performed in a temperature range of −55 to 45 °C in the presence of 10 mol % of **A**, which afforded **5** in 94% ee (full details of the procedures are provided in the Supporting Information). For the effect of temperature on the enantioselectivity in CBS-catalyzed reduction, see: Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2003**, *68*, 10146−10151 and references therein.

(12) Mariano and co-workers prepared **6** in 57% yield by O-methylation of racemic 2,2-dimethyl-3-hydroxycyclopentanone with Ag_2O and MeI in DMF (Yoon, U. C.; Quillen, S. L.; Mariano, P. S.; Swanson, R.; Stavinoha, J. L.; Bay, E. *J. Am. Chem. Soc*. **1983**, *105*, 1218−1220). We observed that in the absence of DMF the reaction proceeded smoothly almost to completion with no side product formation.

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(15) (a) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404 and references therein. (b) Srebnik, M.; Rachamandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9−24. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 1−53.

(16) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481−5484.

(17) The concomitant formation of homocoupling side products was completely suppressed in the presence of equimolar Et_3N. See: Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089−1095.

(18) An O-allylation/RCM/allylic oxidation sequence was chosen in order to bypass the inefficient formation of acryl and crotonyl esters of the intermediate tertiary carbinol. Besides, the acrylate proved to be a poor substrate for the ring closing metathesis under various conditions and led mostly to decomposition. See: (a) Carda, M.; Castillo, E.; Rodriguez, S.; Uriel, S.; Marco, J. A. *Synlett* **1999**, 1639−1641. (b) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130−9136.

(19) (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (c) Louie, J.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 247−249. (d) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3012−3043.

(20) Bonadies, F.; Di Fabio, R. *J. Org. Chem.* **1984**, *49*, 1647−1649.

(21) For reviews regarding dihydroxylation methods, see: (a) Cha, J. K.; Kim, N.-S. *Chem. Rev*. **1995**, *95*, 1761−1795. (b) Kolb, H. C.; VanNieuwehnze, M. S.; Sharpless, B. K. *Chem. Rev*. **1994**, *94*, 2483−2547. (c) Schroeder, M. *Chem. Rev*. **1980**, *80*, 187−213.

(22) Among the others: $KMnO_4$ oxidation: (a) Mukaiyama, T.; Tabusa, F.; Suzuki, K. *Chem. Lett*. **1983**, 173−174. Stoichiometric OsO_4; cat. OsO_4, NMO (Upjohn conditions): (b) Van Rheenen, V.; Kelly, P. Y.; Cha, P. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976. $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$: (c) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem*. **1990**, *55*, 766−768. (d) Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Asymm*. **1993**, *4*, 133−141. Catalytic OsO_4, NMO, $PhB(OH)_2$ (Narasaka reaction): (e) Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett*. **1988**, 1721−1724. Simple ligands and additives for osmylation reactions, such as pyridine or citric acid, were also tested unsuccessfully; see ref 21b and: (f) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, B. K. *Adv. Synth. Catal*. **2002**, *344*, 421−433.

(23) See for example: (a) Zhao, G.-L.; Liao, W.-W.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 4929−4932. (b) Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem*. **2004**, *69*, 6294−6304. (c) Harris, J. M.; Keränen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res*. **2000**, *328*, 17−36.

Gratifyingly, catalytic dihydroxylation of **14** as a mixture of lactol anomers, performed in the presence of 10-fold molar excess of water, gave enantiopure L-(+)-noviose (**1)** in 55% yield starting from **8**.[24]

In conclusion, we have described a combination of catalytic and stoichiometric methods for two independent syntheses of (+)-noviose that do not require protecting groups. By means of a CBS-desymmetrization, L-(+)-noviose **1** was obtained in 27% overall yield and six steps from the readily available dione **4** on gram scale. In the second approach, **1** was synthesized in nine steps and 20% overall yield. Noteworthy, Corey's CBS and Brown's reagents are commercially available in both enantiomeric forms, allowing the expedient syntheses of L-(+)-noviose or its antipode.

(24) A minor amount of dihydroxylated lactone could also be isolated (20%).

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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