Enantioselective synthesis of 2,6-dideoxy carbasugars based on a desymmetrizing hydroformylation–carbonyl ene cyclization process†

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A practical one-pot process involving a desymmetrizing hydroformylation with the aid of a chiral catalyst-directing group (CDG*), followed by a carbonyl ene cyclization provides a straightforward access to both enantiomers of the resulting cyclohexanediol; further divergent, highly selective and protecting group-free transformations furnish the carbocyclic analogues of four important 2,6-dideoxysugars.

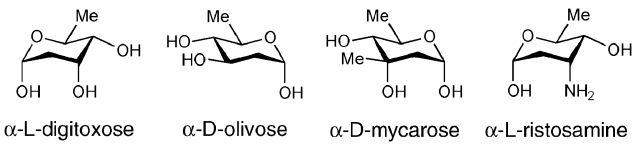
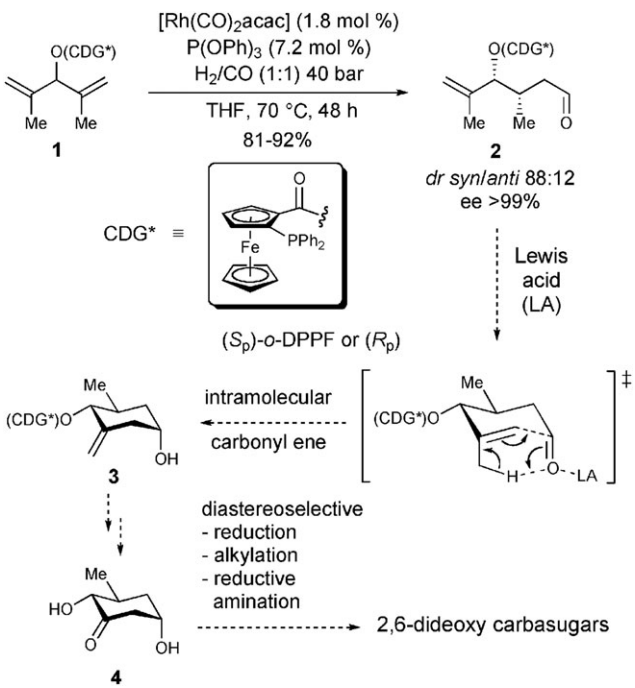


Fig. 1 Structure of selected 2,6-dideoxysugars.

The bioactivity of many naturally occurring antibiotics and antitumor agents is strongly depending on their glycosidic components.[1] Over the past years it has been demonstrated that the structure of the sugar moieties affects the compound's specificity, substrate binding and pharmacology.[2] Among the structural classes of the carbohydrates found in these natural products, the 2,6-dideoxy substitution pattern is the most frequently encountered, especially if one also includes branched and amino sugars.[3] For instance, the antibiotic kijanimicin[4] contains four 2,6-dideoxyhexose L-digitoxose components, the aureolic acid anticancer drug mithramycin[5] includes both D-olivose and methylated sugar D-mycarose, whereas the antibiotic ristocetin A[6] features L-ristosamine, a rare amino sugar (Fig. 1).

Recent efforts have focused on examining the structure–activity relationship by altering the natural product's glycosylation pattern.[7] One strategy has been to replace the original sugars with other natural analogues employing new chemoenzymatic technologies, leading in some cases to superior bioactivities.[8] An alternative approach would be the synthesis of chemically modified deoxysugar units.[9] For instance, the preparation of carbocyclic mimetics, so-called carbasugars,[10] would not only give the opportunity for further natural product modification but also furnish a tool to probe or inhibit the action of sugar-processing enzymes involved in the biosynthesis of these molecules. Carbasugars have become a precious and well-established tool in glycobiology. However, this field still suffers from the lack of efficient synthetic methods and to the best of our knowledge there is no synthesis of carbocyclic analogues of 2,6-dideoxysugars. We report herein the development of a straightforward and protecting group-free stereoselective synthesis of the carbon analogues of L-digitoxose, D-olivose, D-mycarose and L-ristosamine illustrating a new one-pot desymmetrizing hydroformylation–carbonyl ene cyclization approach.

We recently reported the first desymmetrizing hydroformylation of dialkenylcarbinols with the aid of a planar-chiral, catalyst-directing group, the *ortho*-(diphenylphosphanyl)ferrocenylcarbonyl (*o*-DPPF)[11] (Scheme 1). In the hydroformylation of **1** the *o*-DPPF function allows simultaneous diastereotopic alkene group and alkene face discrimination leading to aldehydes **2** in high yields and selectivity. Both optical antipodes are accessible this way, either starting from the (S_p)-*o*-DPPF ester or its (R_p) enantiomer. In the course of our investigations toward tandem processes, we anticipated that **2** could undergo a Lewis acid-catalyzed carbonyl ene cyclization.[12] This reaction should proceed through a highly



Scheme 1 Synthetic strategy based on a desymmetrizing hydroformylation with the aid of a chiral catalyst-directing group (CDG*) followed by a carbonyl ene cyclization.

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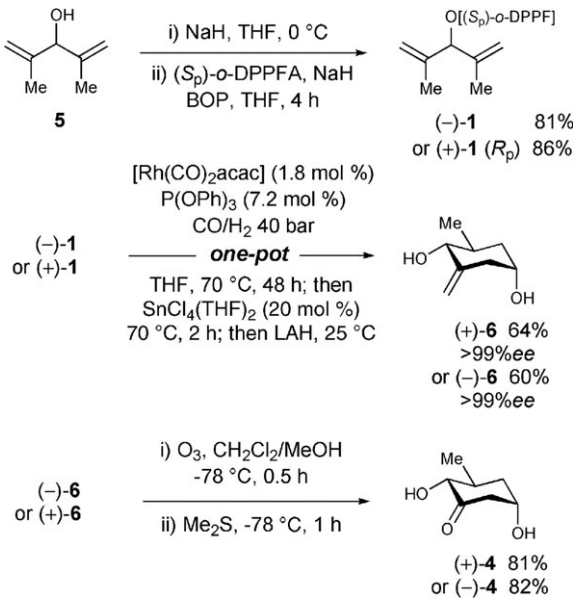
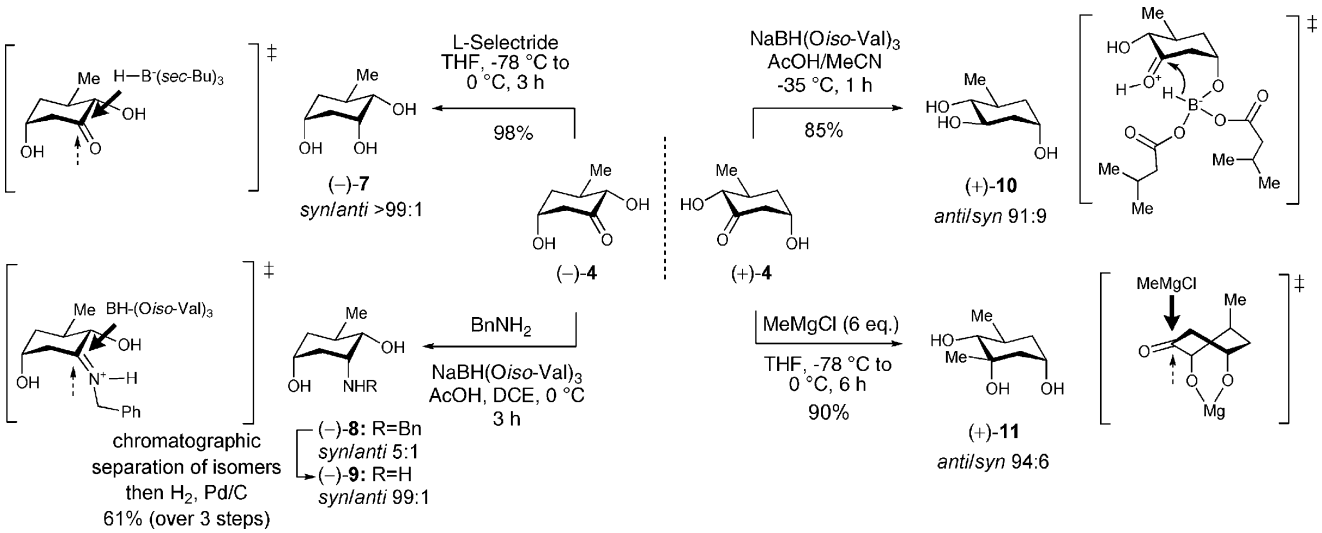
ordered bicyclic transition state providing homoallylic alcohol **3**. Moreover, this rearrangement might be conducted in a one-pot procedure,[13] setting directly from **1** the carbocyclic core of the carbasugars with three of the four desired stereocenters and an exocyclic double bond in a two-step catalytic process. After removal of the directing group, the olefin can be oxidatively cleaved to afford key intermediate ketone **4** which could be transformed easily into various 2,6-dideoxy carbasugars.

Our investigations started with the desymmetrizing hydroformylation of (−)-**1** and (+)-**1** furnishing aldehydes (−)-**2** and (+)-**2** in excellent yields and diastereoselectivity and in enantiomerically pure form (Scheme 2). Preliminary screening of Lewis acids showed that aldehydes **2** undergo smooth and highly diastereoselective carbonyl ene reactions upon treatment with 20 mol% $SnCl_4(THF)_2$ to furnish (+)-**3** and (−)-**3** as single enantiomers, respectively. To our delight the hydroformylation and ene reaction could be coupled in a practical one-pot process. Simple addition of the Lewis acid to the crude mixture of the hydroformylation furnished **3**. The *o*-DPPF esters were then cleaved in the same reaction vessel using lithium aluminium hydride. Through this short one-pot sequence, both enantiomers of carbocyclic diol **6** were readily obtained in good yields and as single stereoisomers. Cleavage of the alkene function of **6** through ozonolysis furnished the key intermediates dihydroxycyclohexanones (+)-**4** and (−)-**4**.



Scheme 2 Synthesis of both enantiomers of ketone **4**. BOP = (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate.

At this stage, we intentionally kept the free hydroxy groups for further functionalization. We envisioned that they would either not interfere or could act as directing groups to control the selectivity of the chosen reactions. Indeed, the direct reduction of (−)-**4** with L-Selectride afforded (−)-**7** through exclusive equatorial hydride addition in high yields (Scheme 3). Its *trans* counterpart was obtained by taking advantage of the directing effect of the free hydroxy groups using a bulky acyloxyborohydride reducing agent,[14] $NaBH(O\textit{iso}\text{-}Val)_3$,[15] to furnish (+)-**10** in excellent diastereoselectivity and yields. The high steric demand around the boron center favours prior coordination to the less hindered axial hydroxy group, delivering the hydride selectively from the lower face of the ketone.[16] The same reagent was employed for the reductive amination of (−)-**4** with benzylamine, affording (−)-**8** with good selectivity. The carbocyclic analog of L-ristosamine (−)-**9** was then obtained after separation of the diastereoisomers and hydrogenolysis in good overall yields over three steps. Finally the addition of an excess of methyl Grignard to (+)-**4** gave D-mycarose analog (+)-**11** in excellent diastereoselectivity and yields. A rational accounting for the selectivity is depicted in Scheme 3. Chelating coordination of the alkoxy functions in the 1,4-position to a magnesium center would induce a twist boat conformation, shielding the lower face of the molecule.



Scheme 3 Synthesis of carba-α-L-digitoxose (−)-**7**, carba-α-L-ristosamine (−)-**9**, carba-α-D-olivose (+)-**10** and carba-α-D-mycarose (+)-**11** and models for the observed selectivities.

In summary, we have illustrated through the asymmetric synthesis of four 2,6-dideoxy carbasugars an efficient approach to these important analogues. Key to success was a one-pot desymmetrizing hydroformylation–carbonyl ene cyclization with subsequent divergent functionalization of the intermediate dihydroxycyclohexanone through highly selective transformations, avoiding the use of protecting groups. Furthermore, this strategy represents a new example of the utility of reagent directing groups to control the selectivity in organic synthesis.

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