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Efficient stereodivergent synthesis of 1,4-dideoxy-1,4-iminohexitols from an (*S*)-glyceraldimine

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Abstract—A stereodivergent synthesis of 1,4-dideoxy-1,4-imino-D-mannitol **I** and D-allitol **III** from an (*S*)-glyceraldimine, which is easily prepared from D-mannitol, has been achieved with overall yields of 62 and 49%, respectively. The synthesis is based on the addition of vinylmagnesium bromide to *N*-benzylimine **1**, derived from readily available (*R*)-2,3-*O*-isopropylideneglyceraldehyde, followed by *N*-allylation or *N*-acryloylation, ring-closing metathesis and asymmetric dihydroxylation.
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Polyhydroxylated pyrrolidines and piperidines (known as azasugars) have attracted a great deal of attention in recent years due to their ability to mimic sugars and competitively and selectively inhibit glycosidases.[1] Glycosidase enzymes catalyse cleavage/formation of the glycosidic bonds in carbohydrates and related molecules[2] and the effect of these enzymes on the structure of cell-surface carbohydrates translates into important biological consequences for processes such as carbohydrate absorption from the wall of the small intestine,[3] tumour metastasis[4] and viral infections.[5] Such inhibitors are therefore regarded as promising chemotherapeutic agents against diabetes, metastatic cancer, malaria and AIDS.

1,4-Dideoxy-1,4-iminohexitols, which belong to the family of polyhydroxylated pyrrolidines, are among the most powerful glycosidase inhibitors.[6] For example, 1,4-dideoxy-1,4-imino-D-mannitol **I** is the archetypal azafuranose inhibitor of α-mannosidase and 1,4-dideoxy-1,4-imino-D-talitol **II** and 1,4-dideoxy-1,4-imino-L-allitol **IV** also show inhibitory activity towards α-mannosidases. In contrast, 1,4-dideoxy-1,4-imino-D-allitol **III**, the enantiomer of compound **IV**, was found to be an inhibitor of β-glucosidase and β-galactosidase and 1,4-dideoxy-1,4-imino-L-iditol **V** is a potent inhibitor of α-galactosidases (Fig. 1). It therefore seems that modification of the configuration on one or more stereogenic centres induces significant changes in their specificity or potency as glycosidase inhibitors. Moreover, most 1,4-dideoxy-1,4-iminohexitols that show biological activity have the hydroxy groups on the pyrrolidine ring in a *cis*-relative configuration.

The therapeutic importance of these compounds has led to a great deal of synthetic effort being directed towards their preparation.[7] The majority of the reported methodologies are based on the transformation of sugar derivatives and are often lengthy and involved. However, to the best of our knowledge, approaches that address the stereodivergent synthesis of 2,3-*cis*-1,4-dideoxy-1,4-iminohexitols have not been undertaken.

We previously reported[8] reactions involving nucleophilic attack of vinylmagnesium bromide on imines **1** and **2**, derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde and (*R*)-2,3-di-*O*-benzylglyceraldehyde, respectively. The reactions proceed in high yield and with excellent diastereoselectivity to give *anti*- and *syn*-aminodiol derivatives **3** and **4**, respectively (Scheme 1). These aminodiol derivatives have been successfully used as synthetic precursors in the stereodivergent synthesis of biologically important compounds with several chiral centres.[8b]

Keywords: Asymmetric synthesis; Imines; Asymmetric dihydroxylation; Ring-closing metathesis.
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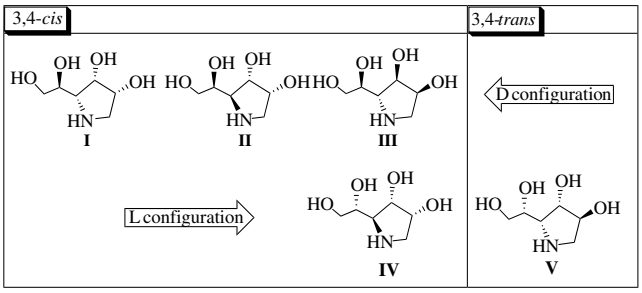
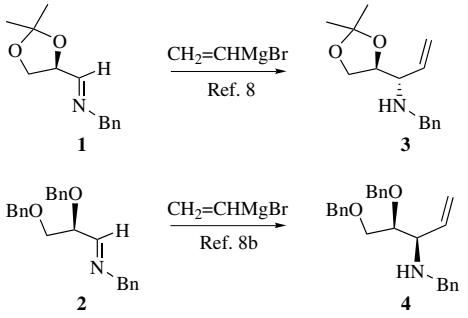
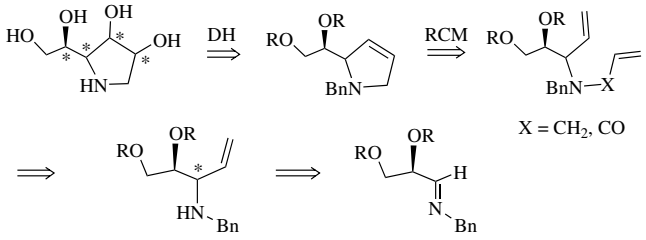


Figure 1. Structures of biologically active 1,4-dideoxy-1,4-iminohexitols.



Scheme 1. Addition of vinylmagnesium bromide to chiral imines derived from (*R*)-glyceraldehyde.



Scheme 2. Retrosynthetic analysis for the synthesis of 2,3-*cis*-1,4-dideoxy-1,4-iminohexitols from chiral imines derived from (*R*)-glyceraldehyde.

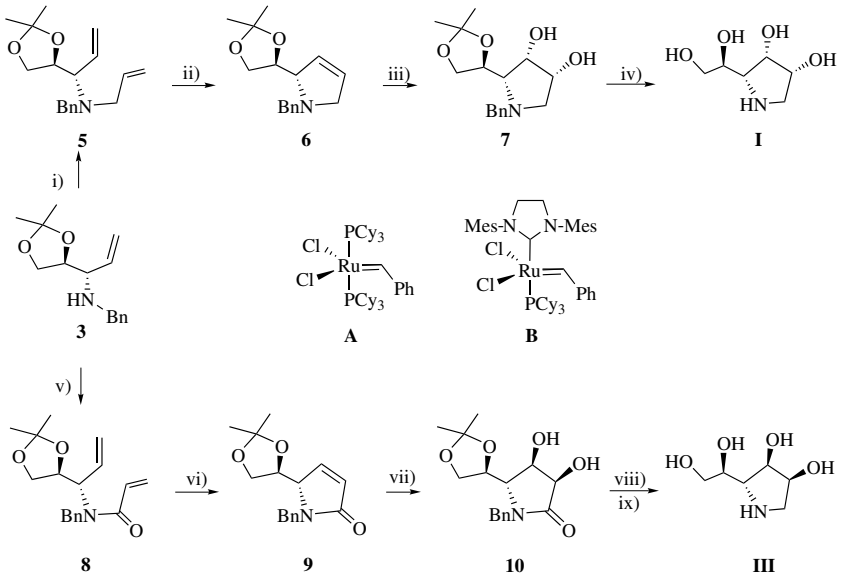
Ring-closing metathesis (RCM) reactions[9] have been widely used in the construction of five- or six-membered nitrogen-containing heterocycles from functionalised dienes. Moreover, in conjunction with dihydroxylation (DH) reactions,[10] RCM reactions have been successfully used for the construction of enantiopure polyhydroxylated alkaloids.[11] As depicted retrosynthetically in Scheme 2, 2,3-*cis*-1,4-dideoxy-1,4-iminohexitols can be prepared from readily available D-glyceraldimines. The synthesis is based on the following key steps: addition of vinylmagnesium bromide to *N*-benzylimines derived from D-glyceraldehyde, *N*-alkylation or acylation of the resulting aminodiol derivatives, ring-closing methathesis and stereoselective dihydroxylation of the intermediate dehydropyrrolidine.[12] We report in this communication our results obtained to date on applying the synthetic scheme outlined above. This route has allowed the efficient preparation of configurationally different 1,4-dideoxy-1,4-iminohexitols **I** and **III** from the same chiral starting material.

Enantiopure aminodiol **3** was prepared following our previously described procedure[8] by addition of vinylmagnesium bromide to (*S*)-glyceraldimine **1**, which is readily available on a multi-gram scale from the inexpensive D-mannitol.[13] 1,4-Dideoxy-1,4-imino-D-mannitol **I** and 1,4-dideoxy-1,4-imino-D-allitol **III** were obtained from *anti*-aminodiol derivative **3** as shown in Scheme 3.

Allylation of **3** with allyl bromide in the presence of NaH and DMF proceeded cleanly to give 1,6-diene **5** in excellent yield. Treatment of compound **5** with first generation Grubbs' catalyst **A**[14a] afforded dehydropyrrolidine **6** in 85% yield. The yield was increased (up to 98%) when the RCM reaction was carried out using the more active second generation Grubbs' catalyst **B**.[14b] These results are remarkable given that dienes containing free amino groups are not usually good substrates for ruthenium-catalysed RCM reactions.[15]

In the next step, an asymmetric *cis*-dihydroxylation reaction was assessed. First, catalytic dihydroxylation of **6** with osmium tetroxide was attempted in the presence of different co-oxidants such as *N*-methylmorpholine *N*-oxide (NMO) and $K_3Fe(CN)_6$. Extensive experimentation gave rise to complex mixtures of products under all the reaction conditions tested. The major compound was isolated and identified as the pyrrole resulting from aromatisation of **6**. This compound was obtained exclusively, albeit in a low yield, when the dihydroxylation reaction was carried with equimolar amounts of potassium permanganate, a classical alternative to osmium tetroxide. Sharpless[16] showed that DH reactions in the presence of cinchona alkaloid-based ligands are much faster than those in the absence of such systems and, on this basis, *cis*-hydroxylation of **6** using commercially available AD-mix was tested. The use of AD-mix-β in our reaction gave the desired diol **7** in a very highly diastereoselective manner (dr 10/1 from NMR analysis of the crude reaction mixture) and a single diastereomer was isolated in 85% yield by column chromatography. The use of AD-mix-α, on the other hand, gave rise to a diastereoselectivity of almost zero (mismatched pair).

Finally, *N*-debenzylation and acetonide deprotection in compound **7** was achieved in one step by catalytic hydrogenolysis with $Pd(OH)_2/C$ in the presence of HCl to give 1,4-dideoxy-1,4-imino-D-mannitol **I** as its HCl



Scheme 3. Synthesis of 1,4-dideoxy-1,4-imino-D-mannitol **I** and 1,4-dideoxy-1,4-imino-D-allitol **III**. Reagents and conditions: (i) allyl bromide, NaH, DMF, 0 °C → rt, 12 h, 93%; (ii) (a) 8% Grubbs' catalyst **A**, CH_2Cl_2, rt, 12 h, 85%; (b) 5% Grubbs' catalyst **B**, CH_2Cl_2, reflux, 24 h, 97%; (iii) AD-mix-β, $MeSO_2NH_2$, *tert*-butanol/H_2O (1:1), 0 °C → rt, 24 h, 85%; (iv) H_2, $Pd(OH)_2$/C, MeOH/HCl (100:1), rt, 12 h, ≈100%; (v) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C → rt, 3 h, 93%; (vi) (a) 8% Grubbs' catalyst **A**, CH_2Cl_2, reflux, 36 h, 85%; (b) 5% Grubbs' catalyst **B**, CH_2Cl_2, reflux, 36 h, 98%; (vii) 10% OsO_4, NMO, acetone/H_2O, rt, 48 h, 80%; (viii) $LiAlH_4$, THF, reflux, 3 h, 85%; (ix) H_2, $Pd(OH)_2$/C, MeOH/HCl (100:1), 98%.

salt, $[\alpha]_D^{25}$ −15.7° (*c* 1, H_2O) [lit.[17] $[\alpha]_D^{25}$ −16.3° (*c* 1, H_2O)] The spectral data of **I** are identical to those reported in the literature.[17] This synthetic process, which involves five steps from starting imine **1**, gave azasugar **I** in 62% overall yield.

Alternatively, aminodiol **3** was converted into 1,4-dideoxy-1,4-imino-D-allitol **III** by dihydroxylation of the intermediate unsaturated γ-lactam **9**. *N*-Acylation of compound **3** with acryloyl chloride followed by RCM of the resulting amide **8** gave intermediate **9** in excellent yield. Treatment of this compound with a catalytic amount of OsO_4 in the presence of NMO led to a highly diastereoselective dihydroxylation reaction that gave diol **10** together with a similar amount of a by-product. The by-product was isolated by column chromatography and identified as a cyclobutane derived from **9**. It was reasoned that this by-product could be formed through a photochemical reaction. The dihydroxylation was subsequently carried out in the absence of light and this change in the reaction conditions led to the exclusive formation of *cis*-diol **10** as a single diastereoisomer in 80% yield without contamination by the undesired by-product. In this case the dihydroxylation of **9** took place with complete facial selectivity—*syn* to the 1,3-dioxolane group. This stereochemical outcome is at first sight surprising but similar results have been reported for other five-membered rings.[7e,10b,18] Finally, reduction of the carbonyl group in compound **10** followed by one-step acetonide and benzyl deprotection provided 1,4-dideoxy-1,4-imino-D-allitol **III** as its HCl salt, $[\alpha]_D^{25}$ +28.5° (*c* 0.5, H_2O) [lit.[19] $[\alpha]_D^{25}$ +29.4° (*c* 0.53, H_2O)], in 49% overall yield from imine **1**. The NMR data and specific rotation are in good agreement with those reported in the literature.[19]

In conclusion, a very efficient diastereodivergent synthesis of 1,4-dideoxy-1,4-imino-D-mannitol **I** and 1,4-dideoxy-1,4-imino-D-allitol **III** from aminodiol derivative **3** has been developed. The key step in the stereodivergent synthesis is the asymmetric dihydroxylation reaction of 2,5-dihydro-1*H*-pyrrole **6** and 1,5-dihydropyrrol-2-one **9**, which were obtained by RCM of *N*-allyl and *N*-acryloyl derivatives of **3**, respectively. These synthetic routes can be adapted for the synthesis of other diastereoisomers of 2,3-*cis*-1,4-dideoxy-1,4-iminohexitols; for example, **II** could be synthesised starting from aminodiol **4**, obtained by the addition of vinylmagnesium bromide to (*S*)-2,3-di-*O*-benzylglyceraldehyde *N*-benzylimine. Similar azasugars with L-configuration could also be obtained using the corresponding imines derived from L-glyceraldehyde, which are readily available from L-mannonic γ-lactone.[20] This methodology is very flexible in terms of stereochemical manipulation, since the stereochemistry of up to three new stereogenic centres can be efficiently controlled. The extension of the work described here to the stereodivergent synthesis of 2,3-*trans*-1,4-dideoxy-1,4-iminohexitols and the synthesis of other related alkaloids with five- or six-membered rings is now in progress and detailed results will be published in due course.

Acknowledgements

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