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Asymmetric syntheses of dihydroxyhomoprolines via doubly diastereoselective lithium amide conjugate addition reactions

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ABSTRACT

The asymmetric syntheses of novel dihydroxyhomoprolines have been achieved using the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a set of four chiral α,β-unsaturated esters (derived from D-pentoses) as one of the key steps. A full account of the diastereoselectivity observed in these conjugate additions is presented and the stereochemical outcomes of these reactions have been established unambiguously via a combination of hydrogenolytic chemical correlation and single crystal X-ray diffraction analyses. A tandem hydrogenolysis/intramolecular reductive amination reaction was then used to create the corresponding enantiopure pyrrolidines, providing access to (2′*S*,3′*S*,4′*R*)-dihydroxyhomoproline and (2′*S*,3′*R*,4′*S*)-dihydroxyhomoproline after deprotection.

1. Introduction

Polyhydroxylated pyrrolidines are challenging targets for synthetic chemists due to the presence of dense oxygen functionality and multiple contiguous stereogenic centres within these molecular scaffolds. Of the eight possible stereoisomers of 3,4-dihydroxyproline, only three have been isolated from natural sources:[1] in 1969 (*S*,*S*,*S*)-**1** was isolated from the cell wall hydrolysates of the diatom *Navicula pelicullosa*,[2] in 1980 (2*S*,3*R*,4*R*)-**2** was isolated from the acid hydrolysates of the toxic mushroom *Amanita virosa*,[3] and in 1994 (2*S*,3*R*,4*S*)-**3** was identified as the sixth residue in the repeating decapeptide sequence of Mefp1, an adhesive protein produced by the marine mussel *Mytilus edulis*.[4] These compounds have been shown to display potent activity as glycosidase inhibitors,[5] and are also of interest due to their roles in peptide structure and function.[6] Many elegant syntheses of the 3,4-dihydroxyproline motif have been reported,[7] although relatively few investigations have focussed on the β-amino acid congeners.[8,9] The parent β-amino acid, β-homoproline **4**, and derivatives such as tetrazole **5**, have shown utility as effective organocatalysts.[10] The conformational behaviour[11] of β-homoproline **4** and the secondary structure of its oligomers[12] has also been studied, and a range of derivatives of **4** have been found to display significant biological activity[13] including in peptidomimetic studies.[14] However, despite the interesting features of this class of cyclic β-amino acids, the dihydroxy analogues **6** have not previously been the targets of any synthetic endeavours (Fig. 1).

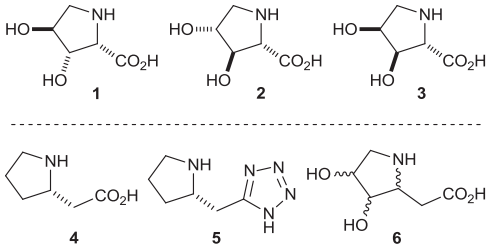

Fig. 1. The structures of naturally occurring dihydroxyprolines **1**–**3**, β-homoproline **4**, tetrazole derivative **5** and dihydroxyhomoprolines **6**.

As part of our long-term goal directed towards the ab initio asymmetric syntheses of pyrrolidines and piperidines (including unnatural aminosugars and amino acids),[15] we envisaged that β-amino esters **9**, derived from conjugate addition of an enantiopure lithium amide reagent **7**[16–20] to enantiopure α,β-unsaturated esters **8**, would be useful templates for elaboration to a range of densely functionalised azacycles, including dihydroxyhomoprolines **6**. It was anticipated that selective deprotection of the primary acetonide functionality within **9** followed by oxidative cleavage of the C(6)–C(7) bond within the resultant diol would then give the corresponding aldehyde **10**. Application of a tandem hydrogenolysis/intramolecular reductive amination protocol[21] would

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then effect both the removal of the *N*-benzyl and *N*-α-methylbenzyl groups within **10**, as well as reduction of the intermediate imine resulting from cyclisation of the C(3)-amino group onto the aldehyde functionality to give the corresponding pyrrolidines **11**. Global deprotection of **11** upon treatment with acid would then finally reveal the target dihydroxyhomoproline **6** (Fig. 2).

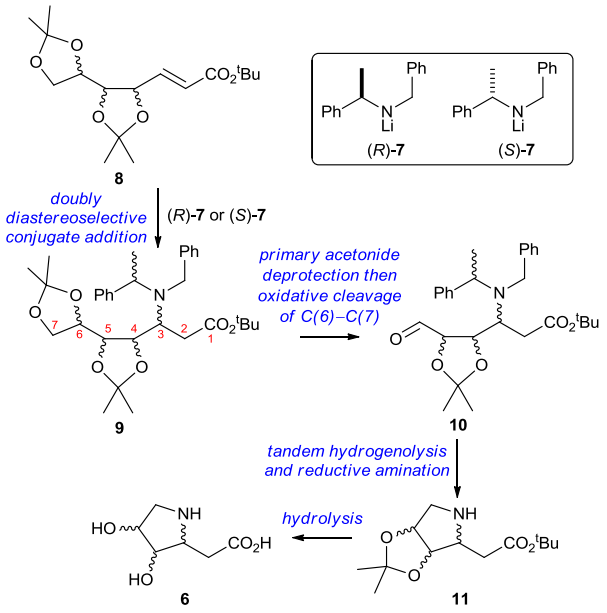

Fig. 2. Proposed synthetic strategy towards dihydroxyhomoprolines **6**.

2. Results and discussion

We have previously investigated the effects of double asymmetric induction[22] upon conjugate addition of enantiopure lithium amides to some enantiopure α,β-unsaturated esters.[18] These studies prompted us to investigate further the origin of diastereoselectivity in these systems and we have recently reported a full account of the effects of double asymmetric induction upon conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **7**[20,23] to *trans*- and *cis*-dioxolane containing α,β-unsaturated esters **12** and **14**, which culminated in the production of models to rationalise the outcomes of these reactions.[24] In the case of *trans*-dioxolane containing α,β-unsaturated esters, such as **12**, reactive conformations similar to **12A** were proposed to account for the observed diastereoselectivity where the lithium amide reagent approaches the *Si* face[25] of the α,β-unsaturated ester. In the case of *cis*-dioxolane containing α,β-unsaturated esters, such as **14**, the competitive formation of β,γ-unsaturated esters (such as **16**), due to deprotonation of the substrate at the γ-position by the basic lithium amide reagent, complicates the assessment of the reaction diastereoselectivity. We therefore reasoned that this γ-deprotonation pathway proceeds via a similar reactive conformation to that of conjugate addition and considered the 'facial selectivity' of both conjugate addition and γ-deprotonation. These data were found to be consistent with approach of the lithium amide reagent on the *Re* face[25] of the α,β-unsaturated ester in conformations similar to **14A**, **14B** or **14C** (Fig. 3).

Given this precedent, we proposed to investigate fully the effects of double asymmetric induction upon the conjugate addition of the antipodes of **7** to a range of four D-pentose derived α,β-unsaturated esters **8**. In order to determine the inherent substrate control provided by the α,β-unsaturated esters **8**, the conjugate additions of the achiral lithium amides lithium *N*-isopropyl-*N*-benzylamide **17** and lithium *N*,*N*-dibenzylamide **18** were performed first. The stereochemical outcomes of the corresponding doubly

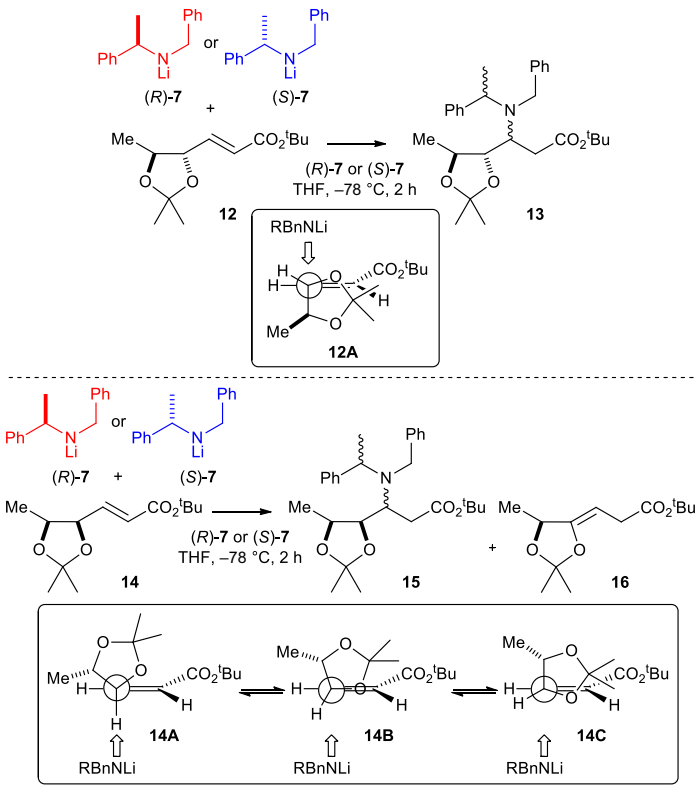

Fig. 3. Models to account for the diastereoselectivity observed upon conjugate addition of lithium amides to *trans*- and *cis*-dioxolane containing α,β-unsaturated esters **12** and **14**.

diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **7** could then be predicted prior to their investigation (Fig. 4). The stereochemical outcomes of these conjugate addition reactions were, in each case, established unambiguously by a series of hydrogenolytic/reductive alkylation experiments and single crystal X-ray diffraction analyses.

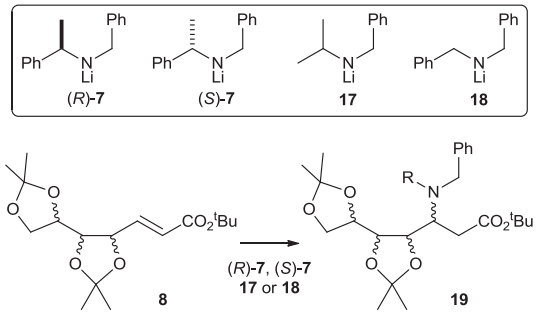

Fig. 4. Investigations into the doubly diastereoselective conjugate additions of the antipodes of lithium amide **7** to α,β-unsaturated esters **8**.

2.1. Doubly diastereoselective conjugate additions to D-pentose derived α,β-unsaturated esters

α,β-Unsaturated esters **20**–**23** were synthesised from the naturally occurring pentose sugars D-arabinose, D-xylose, D-ribose and D-lyxose. Wittig reaction of the requisite (unprotected) pentose with *tert*-butyl 2-(triphenylphosphoranylidene)acetate was expected to provide the corresponding tetraols,[26] within which the free hydroxyl groups could easily be protected with isopropylidene groups. Thus, in the case of α,β-unsaturated ester **20**, subjection of