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Asymmetric syntheses of polysubstituted homoprolines and homoprolinols

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Dedicated to the memory of our colleague and friend Kristína Csatayová BSc. MSc. D.Phil. (1983–2015)

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ABSTRACT

Complementary protocols for the diastereoselective *syn*- and *anti*-dihydroxylations of enantiopure dihydropyrrole scaffolds were used as the key steps in the asymmetric syntheses of several polysubstituted homoprolines and homoprolinols. The requisite dihydropyrroles were prepared in three steps from commercially available sorbic acid via either hydroamination or aminohydroxylation of the corresponding *tert*-butyl ester, followed by ring-closing metathesis. Subsequent olefinic oxidation and deprotection gave access to the corresponding enantiopure homoprolines [(2*S*,3*S*,4*R*)-dihydroxyhomoproline, (2*S*,3*R*,4*R*)-dihydroxyhomoproline and (*S*,*S*,*S*)-3-amino-4-hydroxy-homoproline], enantiopure α-hydroxy-homoprolines [3,6-dideoxy-3,6-imino-D-allonic acid and 3,6-dideoxy-3,6-imino-D-gulonic acid] and enantiopure homoprolinols [1,4-dideoxy-1,4-imino-L-allitol and (*S*,*S*,*S*)-3-amino-4-hydroxyhomoprolinol] as single diastereoisomers in good overall yields.

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1. Introduction

Polyhydroxylated pyrrolidines are known to exhibit potent and specific inhibitory activity toward carbohydrate processing enzymes,[1] and have been reported as highly promising candidates for the treatment of disorders such as diabetes, cancer and HIV.[2] For example, 1,4-dideoxy-1,4-imino-D-lyxitol **1** is a strong competitive inhibitor of α-galactosidase,[3] and (+)-DGDP **2** and (+)-DMDP **5** are known inhibitors of several galactosidase and glucosidase enzymes.[4] Amino substituted pyrrolidines have also been utilised in glycosidase inhibition studies:[5] 2-aminomethyl pyrrolidine **4**, for example, has been shown to be a more potent inhibitor of α-mannosidase than **3**,[6] and (+)-ADMDP **6** [i.e., the 1-deoxy-1-amino-analogue of (+)-DMDP **5**] has also been shown to display significantly enhanced selectivity and potency towards the inhibition of glucosidases (Fig. 1).[7] Due to the potent biological activities displayed by polyhydroxylated pyrrolidines, and their deoxyamino analogues, these classes of compounds have provided the targets for numerous synthetic investigations.[8]

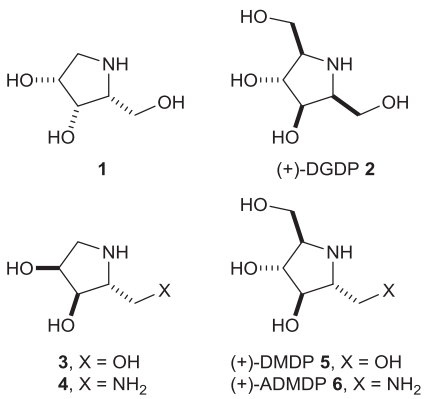

Fig. 1. Biologically active polyhydroxylated pyrrolidines and their deoxyamino analogues.

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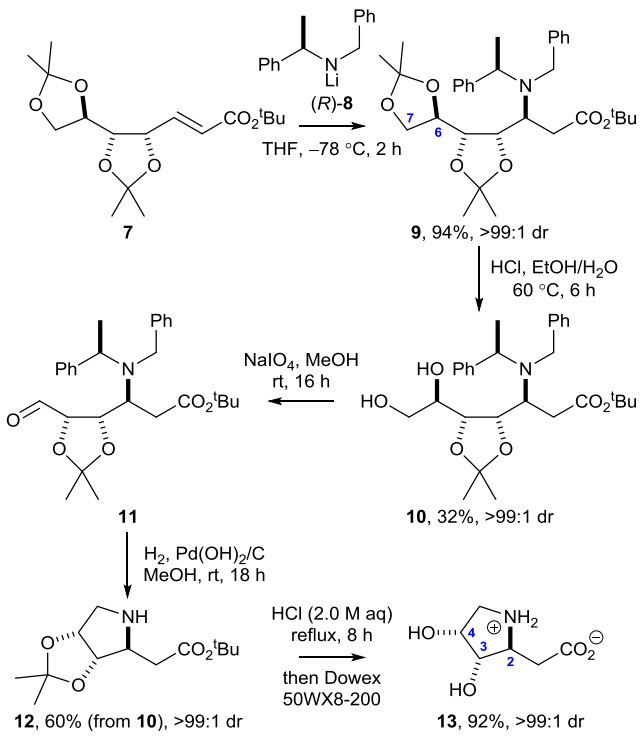
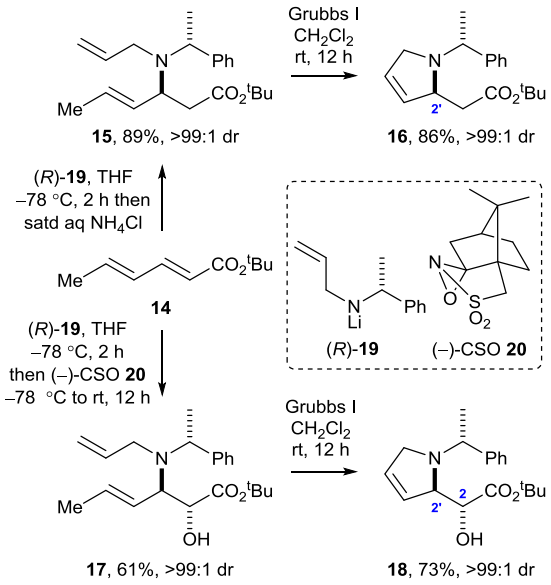
As part of our research programme directed towards the synthesis of functionalised azacyclic scaffolds,[9] we have recently reported the syntheses of some 3,4-dihydroxyhomoprolines[10] from the corresponding D-pentoses. For example, the doubly diastereoselective conjugate addition[11] of lithium amide (*R*)-**8** to α,β-unsaturated ester **7** (which was derived from D-ribose) gave β-amino ester **9** in 94% yield as a single diastereoisomer (>99:1 dr). Subsequent deprotection of the primary acetonide group within **9**, followed by oxidative cleavage of the C(6)–C(7) bond within diol **10** gave the corresponding aldehyde **11**. Hydrogenolytic N-deprotection of **11** and concomitant intramolecular reductive amination gave pyrrolidine **12** in 60% yield (from **10**) and >99:1 dr. Global deprotection of **12** upon treatment with aqueous HCl gave (2*S*,3*S*,4*R*)-dihydroxyhomoproline **13** in 92% yield and >99:1 dr, after purification via ion exchange chromatography on Dowex 50WX8-200 resin (Scheme 1). Herein, we report complementary methodology for the synthesis of polyhydroxylated homoprolines and their derivatives, as well as the corresponding deoxyamino analogues, using diastereoselective olefinic oxidations of enantiopure dihydropyrroles as the key step.



Scheme 1.

2. Results and discussion

The requisite enantiopure dihydropyrroles **16**[12] and **18** were prepared via either hydroamination or aminohydroxylation of dienyl ester **14** using our diastereoselective lithium amide conjugate addition methodology,[13] followed by ring-closing metathesis. Conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)-amide **19**[14] to dienyl ester **14** (which was prepared in 80% yield from sorbic acid) gave the known β-amino ester **15**[12] in 89% isolated yield and >99:1 dr. Meanwhile, conjugate addition of (*R*)-**19** to dienyl ester **14** followed by oxidation of the intermediate lithium (*Z*)-β-amino enolate[15] with (–)-camphorsulfonyloxaziridine [(–)-CSO] **20** gave α-hydroxy-β-amino ester **17** in 61% yield and >99:1 dr, in addition to β-amino ester **15** which was isolated in 10% yield and >99:1 dr.[12] The stereochemical outcome of the aminohydroxylation reaction was initially assigned by analogy to the well-established outcome of this aminohydroxylation protocol,[13,16,17] and was later confirmed unambiguously by single crystal X-ray diffraction analyses of several derivatives. Subsequent ring-closing metathesis of **15** and **17** upon treatment with Grubbs I catalyst gave dihydropyrroles **16**[12] and **18**, which were isolated as single diastereoisomers (>99:1 dr) in 86 and 73% yield, respectively (Scheme 2). The relative configuration within **16** was confirmed by single crystal X-ray diffraction analysis of the corresponding hydrochloride salt **16**·HCl,[18] and the absolute (2′*S*,α*R*)-configuration of **16** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment (Fig. 2); this analysis therefore also confirmed the assigned configuration within β-amino ester **15**. With samples of **16** and **18** in hand, the olefinic oxidation of these substrates was investigated using the following two diastereodivergent approaches: (i) *syn*-dihydroxylation with OsO_4 under Upjohn conditions,[19] and (ii) overall *anti*-dihydroxylation via epoxidation followed by hydrolytic epoxide ring-opening.[20,21]



Scheme 2.

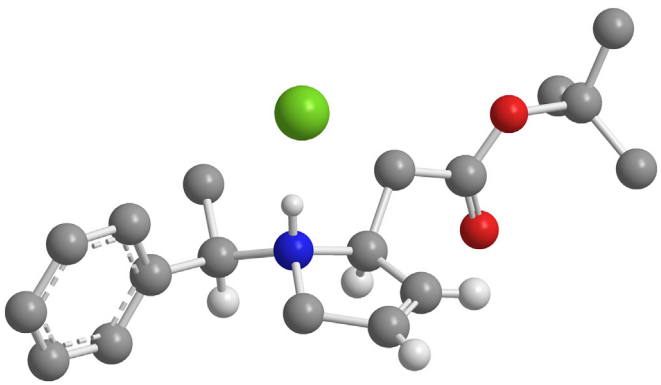


Fig. 2. X-ray crystal structure of (2′*S*,α*R*)-**16**·HCl (selected H atoms are omitted for clarity).

2.1. *syn*-Dihydroxylation of dihydropyrroles 16 and 18

Using the protocol originally reported by the Upjohn company,[19] treatment of **16** (X=H) with 0.1 equiv of OsO_4 and 4.0 equiv of NMO gave a 32:25:44 mixture of starting material **16**, pyrrole **21** and *cis*-diol **22**, respectively, although chromatographic purification of the crude reaction mixture only allowed the isolation of pyrrole **21**[22] in

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