A Highly Efficient and Stereoselective Synthesis of Polyhydroxylated Pyrrolidines via Regioselective Asymmetric Aminohydroxylation (RAA) and Intramolecular Amidomercuration Reactions

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Dedicated to Professor Ray Lemieux for his many contributions to organic and carbohydrate chemistry.

Abstract: A new synthetic strategy, which allows a complete stereochemical control of all four chiral centers of two important polyhydroxylated pyrrolidines **8** and **9**, is described. The cornerstone of the present strategy is a successful implementation of the regioselective asymmetric aminohydroxylation (RAA) reaction of the designed achiral olefin **1** and the intramolecular stereoselective amidomercuration reaction of the δ-alkenylamide **4**, which were used for the introduction of the vicinal amino alcohol functionality and for the construction of the five membered ring in the targets respectively.

Key words: carbohydrate, glycosidase inhibitor, polyhydroxylated pyrrolidine, regioselective asymmetric aminohydroxylation reaction, intramolecular amidomercuration reaction

Glycosidases are believed to be involved in numerous important biological processes including intestinal digestion, catabolism and post-translational modification of glycoproteins and glycolipids, and carbohydrate recognition.[1] Glycosidases are also implicated in many serious diseases such as diabetes,[2] metastatic cancer,[3] malaria,[4] and viral infection.[5] Therefore, glycosidase inhibitors can not only have potential to control the above biological processes at will, but also provide a basis for the development of therapeutically useful agents for the treatment of those diseases.

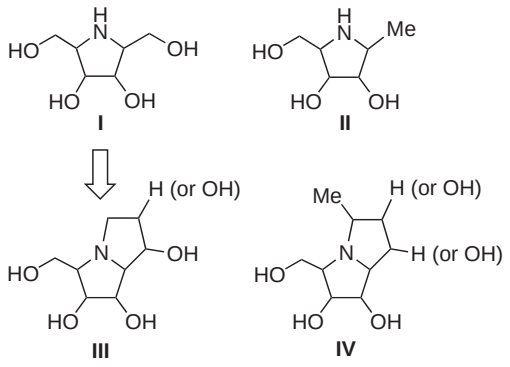

Figure 1

Glycosidases catalyze cleavage of the glycosidic bonds in carbohydrates and related molecules through cationic intermediates.[6] Certain polyhydroxylated pyrrolidines such as **I** and **II**, which closely resemble charge and shape of those intermediates under physiological conditions, have been shown to be potent inhibitors against glycosidases.[7] In addition, **I** and **II** (Figure 1) can serve as convenient intermediates for the synthesis of more complex nitrogen containing glycosidase inhibitors **III** (i.e., alexines and casuarines[8]) and **IV** (i.e., hyacinthacines[9]). Moreover, C_2-symmetrical derivatives of **I** have been utilized as chiral ligands and catalysts for a variety of chemical transformations.[10] Accordingly, a considerable amount of research effort has been put forth for the asymmetric synthesis of **I**[11,12] and **II**.[11,13] However, to the best of our knowledge, all reported synthetic methodologies required chiral materials at some point of synthesis, and some syntheses need rather lengthy routes. A truly asymmetric methodology, which is general, flexible, and divergent in terms of stereochemical manipulation and derivatization, lacks in the literature.

Any useful methodology for the synthesis of **I** and **II** should deal with the stereoselective introduction of the vicinal amino alcohol functionality as well as the stereoselective construction of the 5-membered ring containing a nitrogen atom. It was reasoned that the former could be derived from the RAA reaction of an appropriate olefin,[14] and the latter could form from the mercury(II)-mediated cyclization reaction of a δ-alkenylamide followed by the oxidative demercuration reaction.[15] Herein, we report a successful implementation of this strategy to the complete asymmetric synthesis of the polyhydroxylated pyrrolidines **8** and **9** as a respective representative of **I** and **II**.

Scheme 1 depicts our asymmetric synthesis of the polyhydroxylated pyrrolidines **8** and **9** starting from the achiral α,β-unsaturated ester **1**. The RAA reaction of **1** employing $(DHQD)_2PHAL$ ligand and *N*-bromoacetamide as a nitrogen source and oxidant produced the *syn*-aminoalcohol **2** with an excellent regio- (>20:1) and enantioselectivity (>99%). The 4-(*p*-methoxy)phenoxy (PMP) group of **1** plays dual role in our synthesis: its aryl-aryl stacking interaction with the aryl groups of the RAA catalyst can increase regio- and enantioselectivity of the RAA reaction of **1** (role as a catalyst binder),[16] and it can also act as a convenient alcohol protection group (role as a protection

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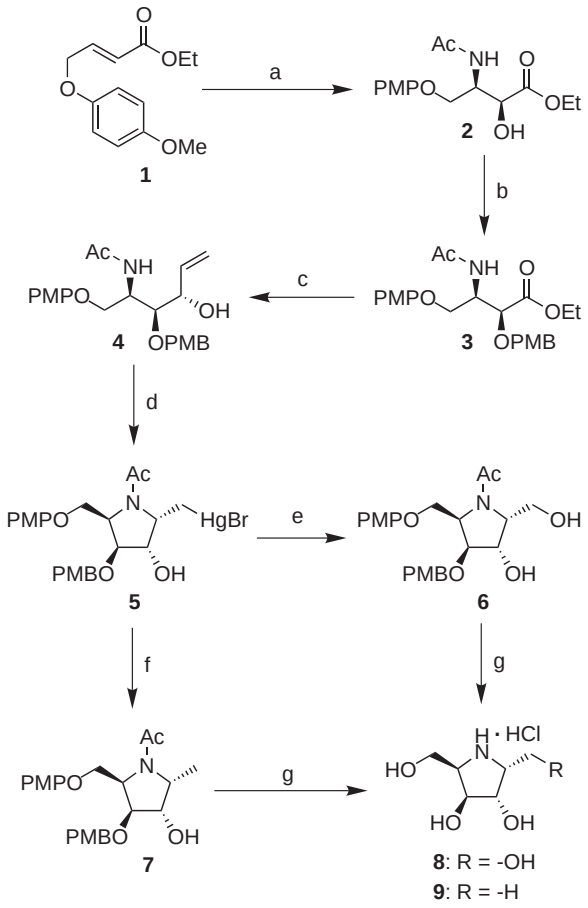
group).[17] Protection of the hydroxyl group of **2** by *p*-methoxybenzyl (PMB) chloride and sodium hydride gave the ester **3**. Partial reduction of the ester **3** by a slow addition of DIBAL at –78 °C, and reaction of the resulting aldehyde with vinylmagneium bromide at –50 °C generated the δ-alkenylamide **4** in a 5:1 diastereoselectivity.



Scheme 1 *Reagents and conditions*: (a) $K_2OsO_4{\cdot}2H_2O$ (5 mol%), $(DHQD)_2PHAL$ (6 mol%), LiOH, *N*-bromoacetamide, *t*-BuOH–H_2O 2:1, 4 °C, 8 h, 70%; (b) NaH, PMBCl, DMF, 0 °C, 10 h, 78%; (c) (i) DIBAL, CH_2Cl_2, –78 °C, 3 h, 90%, (ii) vinylmagnesium bromide, THF, –50°C, 1 h then r.t. 1 h, 74%; (d) $Hg(OAc)_2$, then $NaHCO_3$ and KBr; (e) O_2, $NaBH_4$, DMF, 44% for two steps; (f) $NaBH_4$, DMF, 80% for two steps; (g) (i) CAN, CH_3CN–H_2O 4:1, 4 °C, 10 min, (ii) 6 N HCl, reflux, 12 h, 86% for two steps (for **8**) and 89% for two steps (for **9**).

When exposed to $Hg(OAc)_2$ in THF, **4** smoothly underwent an intramolecular cyclization to give the organomercuric acetate, which upon addition of KBr transformed to the organomercuric bromide **5**. In the amidomercuration reaction of **4**, the *trans*-isomer (between the 2- and 5-substituents) formed predominantly in a >15:1 ratio. This as well as the structure and stereochemistry of **5** were established by converting the crude **5** to **8** and comparing with the literature data (see below). Although the exact cause for the preferential formation of the *trans*-isomer remains to be investigated further, the stereochemical outcome of the amidomercuration reaction of **4** can be rationalized by considering equilibrium among the chair conformers **4-I**, **4-II**, **4-III**, and **4-IV** of **4** (Figure 2). When subjected to the (kinetic) amidomercurization conditions,[15b–d] the conformers **4-I** and **4-III** should cyclize to the *trans*-isomer, whereas the conformers **4-II** and **4-IV** should lead to the *cis*-isomer. Then, stereochemistry of the amidomercuration reaction of **4** should reflect relative stability of these conformers under the reaction conditions, and thus the *trans*-isomer formed as a predominant product from the most stable conformer **4-I**, in which the α-(*p*-methoxyphenoxy)methyl group occupies an equatorial position and steric interactions between the substituents are least. Oxidative-demercuration reaction of **5** was effected by slowly adding O_2 and $NaBH_4$ to **5** in DMF, and gave the diol **6** as a major product with a small amount of the reduction product **7**. Deprotection of the PMP group of **6** by CAN and subsequent exhaustive acidic hydrolysis of the resulting triol furnished the C_2-symmetric polyhydroxylated pyrrolidine **8** as an HCl salt.[18]

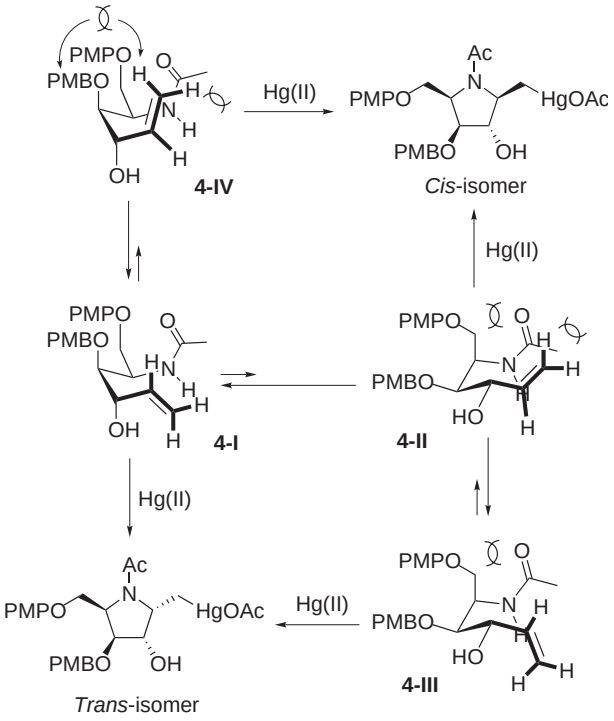


Figure 2

The organomercuric bromide **5** was also used as an intermediate for the synthesis of the other polyhydroxylated pyrrolidine target **9**. In the absence of oxygen, **5** underwent the reductive demercuration with $NaBH_4$ to give **7**. Deprotection of the PMP group followed by acidic hydrolysis converted **7** to the final product **9**.[18]

In summary, the polyhydroxylated pyrrolidines **8** and **9** were synthesized from the common starting olefin **1** in a highly efficient and stereoselective fashion through the RAA and intramolecular amidomercuration-oxidative demercuration reactions. Currently, we are in the final stage

of developing a methodology that allows stereoselective formation of the *cis*-isomer in the amidomercuration reaction (vide supra), and this work will be reported in due course.

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(18) The NMR data of **8** and **9** are consistent with those in the literatures (ref.[12j] for **8** and ref.[12m] for **9**). For **8**, ^{1}H NMR (500 MHz, D_2O) δ 3.73–3.77 (m, 2 H), 3.80–3.86 (m, 4 H), 4.20 (d, 2 H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, D_2O) δ 61.17, 66.58, 78.36. For **9**, ^{1}H NMR (500 MHz, D_2O) δ 1.27 (d, 3 H, *J* = 7.0 Hz), 3.75 (dd, 1 H, *J* = 7.5 Hz, 10.5 Hz), 3.77–3.87 (m, 3 H), 4.06 (d, 1 H, *J* = 3.5 Hz), 4.26 (d, 1 H, *J* = 3.5Hz).