Stereoselective synthesis of carbo- and heterocycles through desymmetrization reactions.

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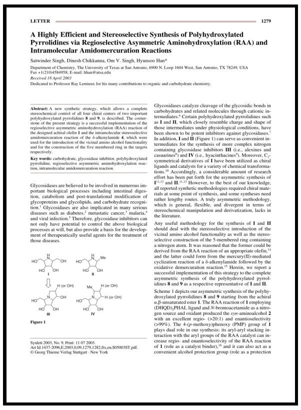

LETTER 1279

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

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Received 18 April 2003

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

Synlett 2003, No. 9, Print: 11 07 2003.
Art Id.1437-2096,E;2003,0,09,1279,1282,ftx,en;S05003ST.pdf.

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

Description: -
-Stereoselective synthesis of carbo- and heterocycles through desymmetrization reactions.
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Notes: Thesis (Ph.D.) -- University of Toronto, 2003.
This edition was published in 2003

Filesize: 36.43 MB

Tags: #Stereoselective #synthesis #of #pentasubstituted #1,3

Ni

Synthesis of amino polyols and amino sugars Petasis and coworkers reported the usage of unprotected carbohydrates as the carbonyl component in PBM reactions.

Catalytic Enantioselective Desymmetrization Reactions to All

Glycans have diverse physiological functions, ranging from energy storage and structural integrity to cell signalling and the regulation of intracellular processes. The use of pseudoephedrine as a practical chiral auxiliary for asym.

Enantioselective Synthesis of Carbo

While phenols are unreactive under our conditions, primary, secondary, and tertiary alkyl-substituted alcohols are all reactive in the copper-catalyzed cyclization. © 2007 · Doemling ·. Copper-assisted synthesis of five-membered O- heterocycles.

Stereoselective and Regioselective Synthesis of Heterocycles via Copper

Bonnesen, Radu Custelcean, Benjamin P. Desymmetrization Process by Mg II -Catalyzed Intramolecular Vinylogous Michael Reaction. In the first part of this chapter the development of a domino process using both rhodium and palladium catalysis is described.

Synthesis of rare sugar isomers through site

The catalytic system also converts methyl 2-isocyanobenzoate and amines into quinazolin-4-ones in excellent yields.

Rhodium and Palladium Catalysis in the Synthesis of Carbo

Journal of the American Chemical Society 2020, 142 1 , 214-221. Reaction rates do vary on a case-by-case basis.

Session: Heterocycles and Aromatics, Asymmetric Reactions and Syntheses and Total Synthesis of Complex Molecules

Ln II complexes are good reducing agents, which can be used in a wide variety of synthetically important reactions; when chiral ligands are used, many of these reactions are highly stereoselective. Reduction of the alkyl bromide to a terminal methyl group was observed as the major side reaction.

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