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Synthesis of statine employing a general *syn*-amino alcohol building block

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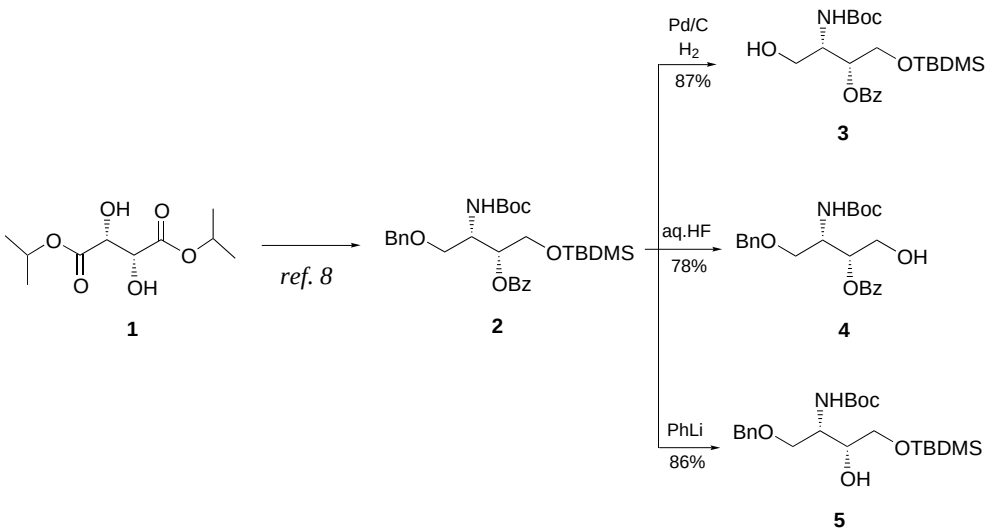
Abstract—An orthogonally protected *syn*-2-amino-1,3,4-butanetriol has been employed as a general *syn*-amino alcohol building block in the synthesis of statine. This synthesis demonstrates the utility of the building block in the synthesis of any *syn*-amino alcohol compound. © 2002 Elsevier Science Ltd. All rights reserved.

Amino alcohols are an important class of compounds. In addition to their use as chiral auxiliaries and ligands, the biological activities associated with this functional group have attracted intense interests among organic and medicinal chemists in these compounds.[1] Accordingly, several useful synthetic strategies have been developed. Take, for example, statine, the key component of the naturally occurring pepstatin, which is the prototype of the amino alcohols with the protease inhibitory activities.[2] A number of reported syntheses of statine attest the importance of amino alcohol compounds, while at the same time, highlight the critical issues in the synthesis of this important functional group.

Among the key issues in the synthesis of amino alcohol compounds are the stereo- and regiochemical controls. Various strategies have been devised to address these issues, including 1,2-asymmetric inductions,[3] chiral auxiliary-induced asymmetric aldol-type reactions,[4] catalytic asymmetric reactions,[5] and the chiron approach.[6] A rather conspicuous and seemingly surprising omission might be a synthesis based on the asymmetric aminohydroxylation strategy; however, the Sharpless



Scheme 1.

Keywords: statine; synthesis; *syn*-amino alcohol; building block.

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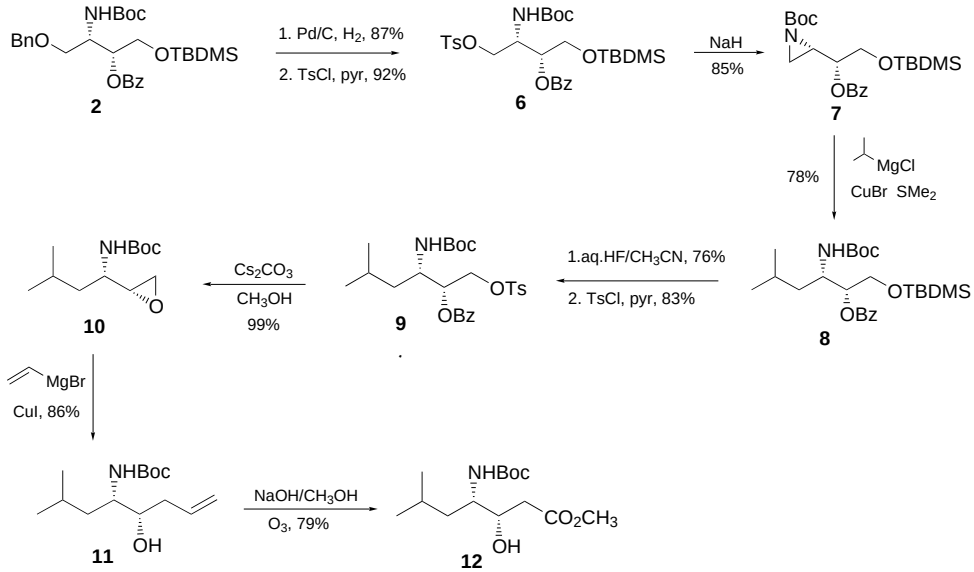

Scheme 2.

process has a problem of regiochemistry to overcome when applied on an isolated olefin substrate.[7]

Our interest in the amino alcohol synthesis has led us to propose *O*(1)-benzyl-*N*(2)-Boc-*O*(3)-benzoyl-*O*(4)-TBDMS-protected 2-amino-1,3,4-butanetriol (**2**) as a general building block for *syn*-amino alcohol compounds.[8] Unique features of this tartrate-derived four-carbon unit include: the *syn*-relative stereochemistry of the amino alcohol function—particularly so, originating from the *syn*-dihydroxy starting material[9]—as well as the rich functionalities and their orthogonal protections that would enable one to regioselectively transform the building block to the desired target molecules (Scheme 1). As a demonstration of the synthetic utility of the building block **2** for *syn*-amino alcohol compounds, a formal synthesis of statine has been undertaken, as presented herein.

The C(1)–C(4) of the building block, *O*(1)-Benzyl-*N*(2)-Boc-*O*(3)-benzoyl-*O*(4)-TBDMS-protected 2-amino-1,3,4-butanetriol (**2**), corresponds to the C(5)–C(2) of statine (statine numberings). Attachments of an isopropyl group and a carboxyl group at the C(1) and C(4) of the building block, respectively, would therefore accomplish the synthesis of statine (Scheme 2).

In order to attach the isopropyl group, the C(1)-hydroxyl group was selectively unveiled (H_2, Pd/C), which was then activated as tosylate (**6**). The carbon-chain extension was best accomplished first by converting the tosylate **6** to the *N*-Boc-aziridine **7**, which was then ring-opened using an isopropyl Grignard reagent in the presence of CuBr catalyst (to give **8**). For the one-carbon extension at the other end, an electrophilic site was similarly introduced at the C(4), i.e. by deprotection of the O(4) of **8** (aq. HF) followed by tosylation (to give **9**). While a nucleophilic substitution by cyanide anion would have been an easy choice for the required one-carbon extension, a reported difficulty in hydrolyzing the resulting nitrile forced us to opt for an alternative method.[10] Thus, after treating the tosylate **9** with Cs_2CO_3 in methanol to yield the corresponding epoxide (**10**), a two-carbon extension was carried out by a ring-opening of the epoxide **10** using a vinyl Grignard reagent-CuI to give **11**. The extra carbon was then cleaved off by ozonolyzing **11** in the presence of MeOH/NaOH to afford the desired *N*-Boc protected statine methyl ester **12**.[11]

In conclusion, we have employed *O*(1)-Benzyl-*N*(2)-Boc-*O*(3)-benzoyl-*O*(4)-TBDMS-protected 2-amino-1,3,4-butanetriol (**2**) as a building block in a formal synthesis of statine. Its orthogonal protecting groups enabled us to regioselectively transform the four-carbon unit to the desired target compound. The strategy employed in the present synthesis is generally applicable to other *syn*-amino alcohol compounds, demonstrating the utility of the compound **2** as a general building block for this important functional group.

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