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Stereoselective synthesis of α-hydroxy-β-amino acid derivatives from β-hydroxy-γ,δ-unsaturated sulfilimine

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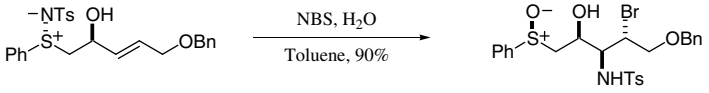
Abstract

The first report on the use of *N*-sulfinyl benzylcarbamate for the preparation of *N*-Cbz sulfilimine from the corresponding sulfoxide is reported. The sulfilimine moiety is utilized as an intramolecular nucleophile for the regio- and stereoselective heterofunctionalization of an alkene to furnish a bromo carbamate which is used as a key advanced intermediate in the synthesis of representative α-hydroxy-β-amino acid derivatives.

Keywords: *N*-Sulfinyl benzylcarbamate; Sulfoxide; *N*-Cbz sulfilimine; Bromo carbamate; (2*S*,3*R*)-AHDA; (2*S*,3*R*)-AHPBA

α-Hydroxy-β-amino acids are an important class of compounds that occur in diverse natural and synthetic molecules possessing significant biological activity; for example, paclitaxel,[1] the aminopeptidase inhibitor amastatin,[2] the renin inhibitor KRI-1314[3] and the anti-bacterial agent dideoxy-kanamycin.[4] Not surprisingly, much effort has been expended on the asymmetric synthesis of this structural unit.[5] Though relative stereocontrol in the synthesis of the amino alcohol subunit has been satisfactory, many of the reported methods suffer from limited practical utility because of the multi-step reaction sequences and demand for unusual reagents and synthetic intermediates. Therefore, it is of interest to develop new efficient routes, particularly one that employs a common advanced intermediate, for the synthesis of α-hydroxy-β-amino acids.

In 2004, we reported a novel method for the preparation of amino alcohol derivatives[6] from β-hydroxy/siloxy-γ,δ-unsaturated *N*-Ts sulfilimines. The synthetic methodology demonstrated the potential of the sulfilimine as an intramolecular nucleophile; however, the products bearing a *N*-Ts group could only be transformed into free NH-derivatives under harsh conditions (Eq. 1).



(1)

To fully exploit the potential of our methodology, it was imperative to prepare sulfilimines possessing protecting groups that are readily removable under mild conditions. To the best of our knowledge, only *N*-Ts sulfilimines have been prepared from the corresponding optically active sulfoxides either with retention or inversion of configuration.[7] We report herein for the first time, the synthesis of β-hydroxy-γ,δ-unsaturated *N*-Cbz sulfilimine from the

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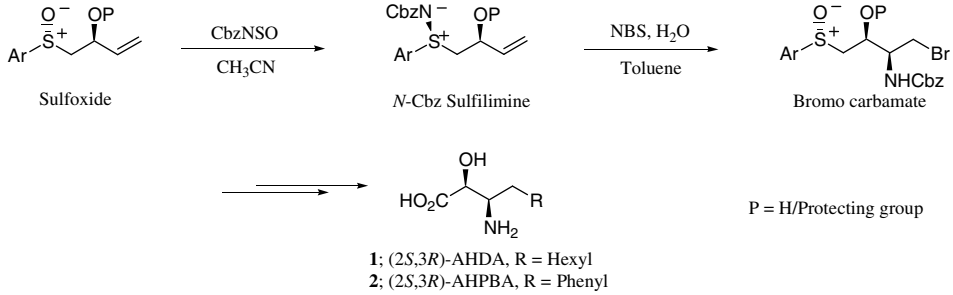


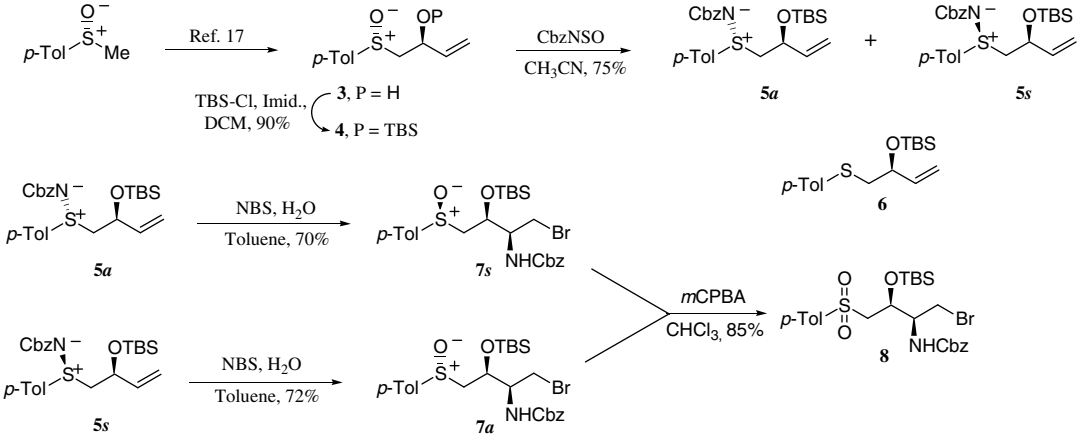
Scheme 1.

corresponding readily available sulfoxide,[8] its further conversion to a bromo carbamate en route to the synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid ((2*S*,3*R*)-AHDA) and (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid (2*S*,3*R*-AHPBA), Scheme 1.

(2*S*,3*R*)-AHDA is an unusual amino acid constituent of microginin,[9] an ACE inhibitor, and several other linear peptides[10] isolated from the cyanobacterium *Microcystis aeruginosa*. (2*S*,3*R*)-AHPBA is a non-proteinogenic constituent of the dipeptide bestatin,[11] an aminopeptidase inhibitor, isolated from *Streptomyces olivoreticuli*. The synthesis of AHDA has been reported by many groups using, (a) asymmetric functionalization of olefins[12] via asymmetric epoxidation/dihydroxylation, (b) a chiral pool strategy,[13] (c) Lewis acid-mediated nucleophilic addition of ketene acetals to non-racemic imines,[14] (d) conjugate addition of chiral amines to enoates[15] and other routes.[16] Likewise, the synthesis of (2*S*,3*R*)-AHPBA has been reported by many groups.[5b,17]

The synthesis of AHDA commenced from the β-hydroxy sulfoxide[18] **3**, obtained in two steps from (*R*)-methyl *p*-tolyl sulfoxide. Protection of **3** as its silyl ether **4** (90%, $[\alpha]_D^{25}$ +108.7 (*c* 0.67, $CHCl_3$)) by treatment with TBS–Cl followed by reaction with *N*-sulfinyl benzylcarbamate[19] (CbzNSO) in acetonitrile[20] afforded a 7:3 mixture of diastereomeric sulfilimines **5*s*** ($[\alpha]_D^{25}$ −17.5 (*c* 1, $CHCl_3$)) and **5*a*** ($[\alpha]_D^{25}$ +8.5 (*c* 0.35, $CHCl_3$)), respectively, in 75% yield along with the corresponding sulfide **6** (10% yield) that were separated by column chromatography on silica gel. The individual sulfilimines **5*a*** and **5*s*** were subjected to treatment with freshly recrystallized *N*-bromosuccinimide (NBS) to yield bromocarbamates **7*s*** (70%) and **7*a*** (72%), respectively. The reaction proceeded highly regio- and stereoselectively.[21] The oxidation of **7*s*** and **7*a*** using *m*CPBA yielded sulfone **8** (85%), thereby proving the stereoconvergency (at carbon) in the reactions of **5*a*** and **5*s***, Scheme 2.

Further reactions were initially attempted on the bromocarbamate **7*s*** (though both **7*s*** and **7*a*** can be utilized). Thus, on treatment of **7*s*** with excess Hex_2CuLi in THF the chain elongated amino alcohol derivative **9*s*** was obtained in good yield (70%). Further elaboration to the target required transformation of the sulfinyl moiety into a hydroxyl group. The treatment of **9*s*** with trifluoroacetic anhydride (TFAA) in DCM afforded a less polar product, assumed to be the Pummerer intermediate **10**, which without isolation was treated with aq satd $NaHCO_3$ solution and $NaBH_4$ in an attempt to obtain primary alcohol **11**. However, we only isolated the inverted sulfoxide **9*a*** as the sole product (75%). The reaction probably proceeds via sulfurane intermediate **12**, which is the less polar intermediate observed by TLC. Treatment with aq satd $NaHCO_3$ then leads to the displacement of the trifluoroacetate group with inversion of the sulfur configuration to yield intermediate **13** which then ring opens to afford the inverted sulfoxide **9*a***, Scheme 3.[22]



Scheme 2.