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

Sadagopan Raghavan *, Shaik Mustafa

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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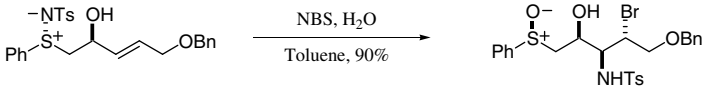
Abstract

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

* Corresponding author. Tel.: +91 040 27160123; fax: +91 040 27160512.
E-mail addresses: purush101@yahoo.com, sraghavan@iict.res.in (S. Raghavan).

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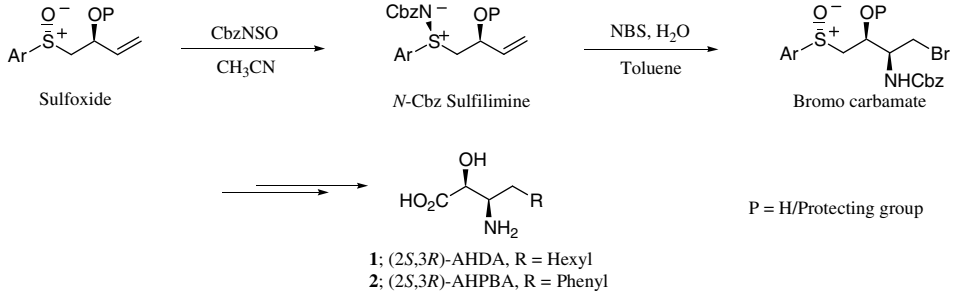


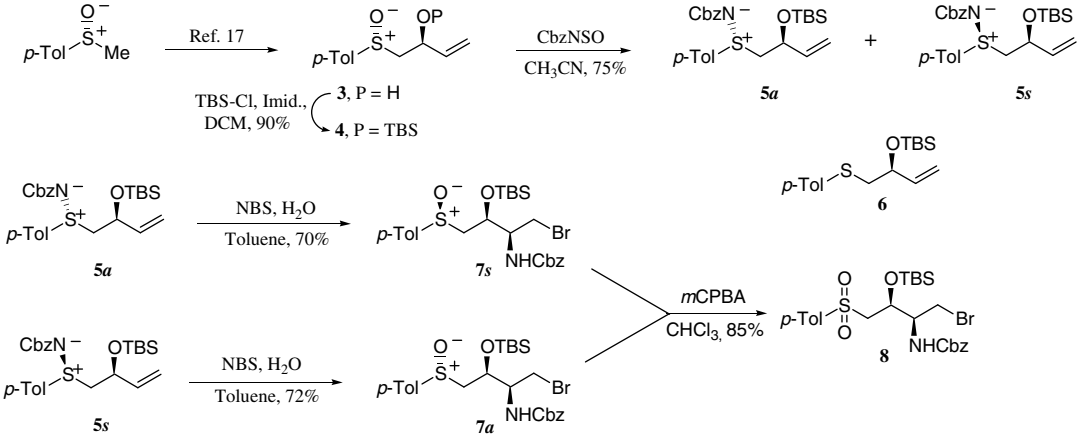
Scheme 1.

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.

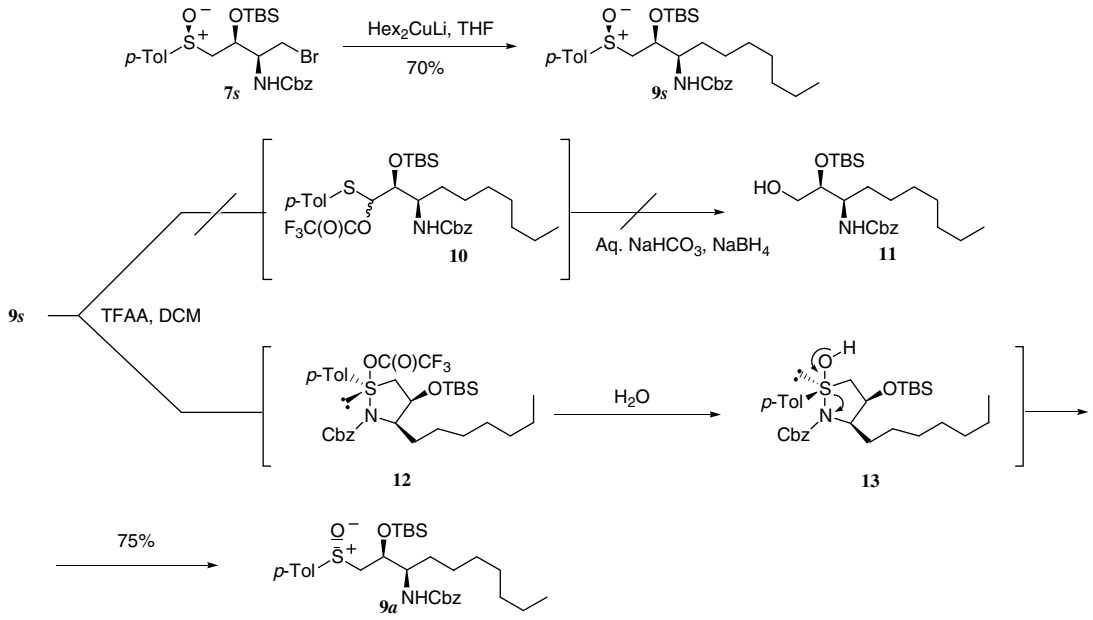
(2*S*,3*R*)-AHDA is an unusual amino acid constituent of microginin,[9] an ACE inhibitor, and several other linear peptides[10] isolated from the cyanobacterium *Microcystis aeruginosa*. (2*S*,3*R*)-AHPBA is a non-proteinogenic constituent of the dipeptide bestatin,[11] an aminopeptidase inhibitor, isolated 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.

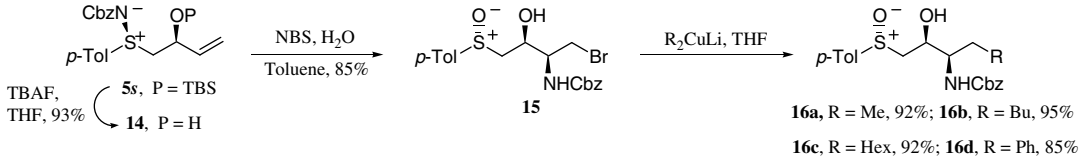
Further reactions were initially attempted on the bromocarbamate **7*s*** (though both **7*s*** and **7*a*** can be utilized). Thus, on treatment of **7*s*** with excess Hex_2CuLi in THF the chain elongated amino alcohol derivative **9*s*** was obtained in good yield (70%). Further elaboration to the 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.



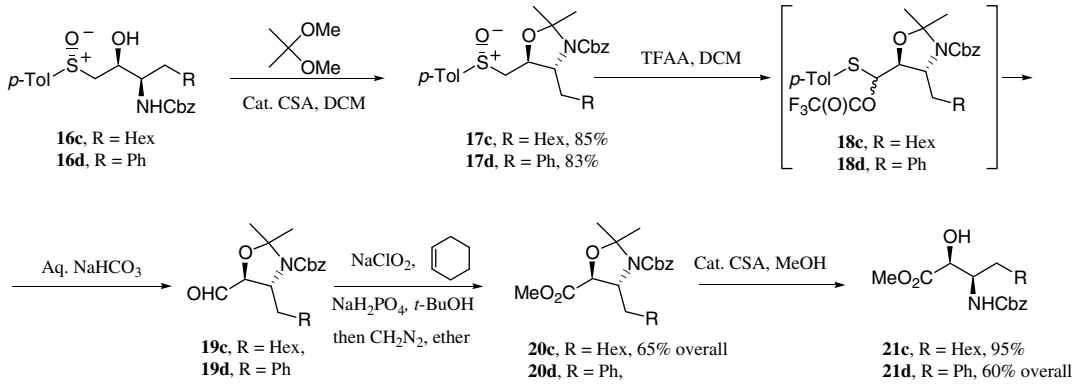
Scheme 3.



Scheme 4.

This unexpected result called for a revision of the synthetic strategy and further experiments were carried out with sulfilimine **5*s***. Deprotection of the silyl group in **5*s*** by treatment with *n*-tetrabutylammonium fluoride (TBAF) furnished the allyl alcohol **14** (93%, $[\alpha]_D^{25}$ −103 (*c* 2.25, $CHCl_3$)). The reaction of **14** with NBS proceeded regio- and stereoselectively to yield bromohydrin **15** (85%, $[\alpha]_D^{25}$ +11.3 (*c* 0.20, $CHCl_3$)), which served as the common advanced intermediate for the preparation of both AHDA and AHPBA. Thus, treatment with excess cuprate reagents in THF cleanly afforded the amino alcohol derivatives **16a–d** in 85–95% yields, Scheme 4.

This strategy obviates the necessity of starting from different (amino acid) precursors to synthesize 1,2-amino alcohols[5a,12b,c,15] and is versatile for its flexibility for the introduction of various carbon side chains and heteroatoms at a later stage in the synthesis on an advanced intermediate. Compound **16c** was transformed into AHDA as depicted in Scheme 5. The treatment of **16c** ($[\alpha]_D^{25}$ +10.7 (*c* 0.15, $CHCl_3$)) with excess 2,2-dimethoxypropane in the presence of cat. CSA yielded acetonide **17c** (85%, $[\alpha]_D^{25}$ +53.1 (*c* 1.3, $CHCl_3$)). Subjecting **17c** to TFAA led to formation of intermediate **18c** which without isolation was hydrolyzed by the treatment with aq satd $NaHCO_3$



Scheme 5.

to furnish aldehyde **19c**. Pinnick oxidation[23] afforded the acid which was characterized as its methyl ester **20c** (65% overall yield for 3 steps, $[\alpha]_D^{25}$ +6.5 (*c* 1, $CHCl_3$)). Deprotection of the acetonide furnished AHDA derivative **21c** (95%, $[\alpha]_D^{25}$ +12.5 (*c* 1.4, $CHCl_3$, 25% overall yield from **3** in 10 steps)). A similar sequence of reactions starting from **16d** gave AHPBA derivative **21d** (60% overall yield for 3 steps, $[\alpha]_D^{25}$ +80 (*c* 0.40, MeOH, 18.6% overall yield from **3** in 10 steps)) with spectral characteristics in excellent agreement to those reported in the literature.[24]

To summarize, *N*-Cbz sulfilimines were readily prepared from the corresponding sulfoxide with modest stereoselectivity. Further, it was used as an intramolecular nucleophile to oxidatively functionalize an alkene. Also, we have disclosed an efficient route to α-hydroxy-β-amino acid derivatives, a class of compounds with widely varying biological activities, starting from a common advanced intermediate.

Acknowledgements

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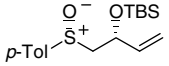
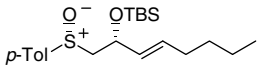
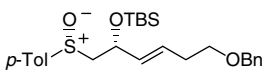
References and notes

1. Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.
2. Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 636.
3. Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Kiso, Y. *Chem. Commun.* **1989**, 1678.
4. Umemura, E.; Tsuchiya, T.; Umezawa, S. *J. Antibiot.* **1988**, *41*, 530.
5. (a) Sánchez-Obregon, R.; Salgado, F.; Ortiz, B.; Díaz, E.; Yuste, F.; Walls, F.; García Ruano, J. L. *Tetrahedron* **2007**, *63*, 10521 and references cited therein; (b) Raghavan, S.; Rasheed, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1371 and references cited therein.
6. Raghavan, S.; Naveen Kumar, Ch.; Tony, K. A.; Ramakrishna Reddy, S.; Ravi Kumar, K. *Tetrahedron Lett.* **2004**, *45*, 7231.
7. For the preparation of optically active sulfilimines from sulfoxides using *N*-sulfinyl-*p*-toluenesulfonamide see: (a) Yamgishi, F. G.; Rayner, D. R.; Zwicker, E. T.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 1916; (b) Christensen, B. W. *J. Chem. Soc. D* **1971**, 597; (c) Cram, D. J.; Day, J.; Rayner, D. R.; von Schriltz, D. M.; Duchamp, D. J.; Garwood, D. C. *J. Am. Chem. Soc.* **1970**, *92*, 7369; (d) Christensen, B. W.; Kjaer, A. *Chem. Commun.* **1969**, 934; (e) Johnson, C. R.; Rigau, J. J. *J. Org. Chem.* **1968**, *33*, 4340; (f) Using *N*,*N*′-bis(*p*-toluenesulfonyl)sulfur diimide see Ref. 7a. Using *p*-tosyl isocyanate see: (g) Garwood, D. C.; Jones, M. R.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 1925.
8. The β-hydroxy sulfoxides can be prepared readily from the keto sulfoxide by diastereoselective reduction following Solladie's protocol, see: (a) Solladie, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435; (b) Solladie, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912; (c) Carreno, M. C.; Garcia Ruano, J. L.; Martin, A.; Pedregal, C.; Rodrigues, J. H.; Rubio, A.; Sanchez, J.; Solladie, G. *J. Org. Chem.* **1990**, *55*, 2120.
9. Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501.
10. (a) Ishida, K.; Kato, T.; Murakami, M.; Watanabe, M.; Watanabe, M. F. *Tetrahedron* **2000**, *56*, 8643; (b) Ishida, K.; Matsuda, H.; Murakami, M. *Tetrahedron* **1998**, *54*, 13475.
11. Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *Antibiotics* **1976**, *26*, 100.
12. (a) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852; (b) Sugimura, H.; Miura, M.; Yamada, N. *Tetrahedron: Asymmetry* **1997**, *8*, 4089; (c) Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 903.
13. (a) Wee, A. G. H.; McLeod, D. D. *J. Org. Chem.* **2003**, *68*, 6268; (b) Jefford, C. W.; Mcnulty, J.; Lu, Z. H.; Wang, J. B. *Helv. Chim. Acta* **1996**, *79*, 1203; (c) Tuch, A.; Saniere, M.; Merrer, Y. L.; Depezay, J. *Tetrahedron: Asymmetry* **1996**, *7*, 2901.
14. Ha, H. J.; Ahn, Y.-G.; Woo, J.-S.; Lee, G. S.; Lee, W. K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1667.
15. Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 203–206.
16. (a) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 11303; (b) Shirode, N. M.; Rakeeb, A.; Deshmukh, A. S. *Tetrahedron* **2006**, *62*, 4615.
17. Wassermann, H. H.; Xia, M.; Peterson, A. K.; Jorgensen, M. R.; Curtis, E. A. *Tetrahedron Lett.* **1999**, *40*, 6163 and references cited therein.
18. Raghavan, S.; Joseph, S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 101.
19. (a) Weinreb, S. M.; Garigapati, R. S.; Gainor, J. A. *Heterocycles* **1984**, *21*, 309; (b) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7861.
20. The reaction of **4** with CbzNSO was attempted in different solvents to determine the stereoselectivity and acetonitrile was found to be the best in terms of yield and diastereoselectivity.

Reaction of sulfoxides with CbzNSO in different solvents

Entry	Sulfoxide	Solvent	Stereoselectivity inversion:retention	Yield (%)
1	**4**	DCM	1:1	50
2	**4**	THF	1:1	20
3	**4**	PhH	1:1	20
4		CH_3CN	3:2	75
5		CH_3CN	1:1	70
6		CH_3CN	1:1	70

21. The inversion of sulfur configuration is based on our earlier work using *N*-Ts sulfilimine as the intramolecular nucleophile, see Ref. 6. The *syn* disposition of the substituents at C2 and C3 in **7*a*** was proven by NOE studies on the acetonide derived from **15**.
22. The result obtained herein is in contrast to that reported by Garcia-Ruano and co-workers (Ref. 5a) who report recovery of the starting material from a *syn*-amino alcohol derivative.
23. Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
24. Herranz, R.; Castro-Pichel, J.; Garcia-Lopez, T. *Synthesis* **1989**, 703.