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A Versatile Approach to *N*-Boc-statine and *N*-Boc-norstatine Based on the Reduction of 1-Trialkylsilyl Acetylenic Ketones. Strong Remote Effect of the C(1) Substituent on the Stereoselectivity

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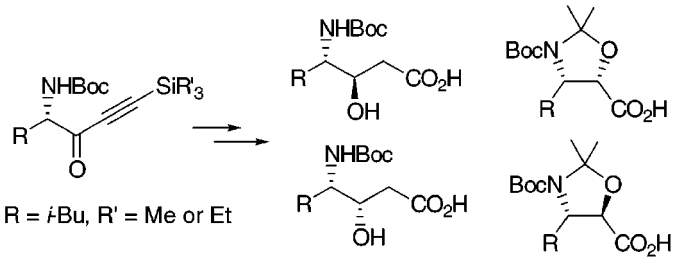
ABSTRACT



An efficient, unified approach to chiral, protected β-hydroxy γ-amino and α-hydroxy β-amino acids derived from Boc-L-leucine has been accomplished on the basis of the oxazaborolidine-controlled, stereoselective reduction of 1-trialkylsilyl acetylenic ketones; stereoselectivity in the reduction step has shown strong dependence upon C(1) substitution.

In recent years, *syn*-β-hydroxy γ-amino acids (**1**) have received much attention since compounds as statine (**1**, R = *i*-Bu) or cyclohexylstatine (**1**, R = cyclohexylmethyl) became key components of peptidomimetic protease inhibitors.[1] Interestingly, the *syn* (*threo*) relative configuration of the amino and hydroxy groups in **1**, which mimics the tetrahedral transition state for peptide bond hydrolysis, has been found to be essential for their bioactivity. However, several members of the corresponding diastereomeric *anti* (*erythro)* series (**2**) are also of natural occurrence.[2] Representative exemples of those substructures can be found in the bioactive depsipeptides didemnins A−C[3] and hapalosin[4] inter alia. On the other hand, both *syn*- and *anti*-α-hydroxy β-amino acid units (**3** and **4**) are constituents of many natural products including paclitaxel (taxol), the immunological response modifier bestatin, several biologically active metabolites isolated from lithistid sponges,[5] and a number of protease inhibitors.[6] Thus, for example, norstatine (**3**, R = *i*-Bu) is present in KRI-1230, a human renin inhibitor peptide,[6b] whereas its enantiomer has been found in the natural peptide amastatine.[6c]

(1) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.
(2) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 10419 and references therein.
(3) Hossain, H. B.; van der Helm, D.; Antel, J.; Sheldrick, G. M.; Sanduja, S. K.; Weinheimer, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4118; Banaigs, B.; Jeanty, G.; Francisco, C.; Jouin, P.; Poncet, J.; Heitz, A.; Cave, A.; Prome, J. C.; Wahl, M.; Lafargue, F. *Tetrahedron* **1989**, *45*, 181. For nordidemnin B, a closely related natural product, see: Jouin, P.; Poncet, J.; Dufour, M.; Pantaloni, A.; Castro, B. *J. Org. Chem.* **1989**, *54*, 617.
(4) Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1994**, *59*, 7219.
(5) Bewley, C. A.; Faulkner, D. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2163.
(6) (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (b) Iizuka, K.; Kamijo, T.; Kubota, T.; Akahane, K.; Umeyama, Y.; Kiso, Y. *J. Med. Chem.* **1988**, *31*, 701. (c) Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T.; Umezawa *J. Antiobiot.* **1978**, *31*, 636.

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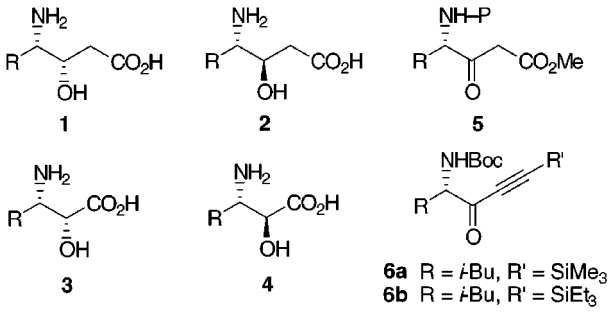
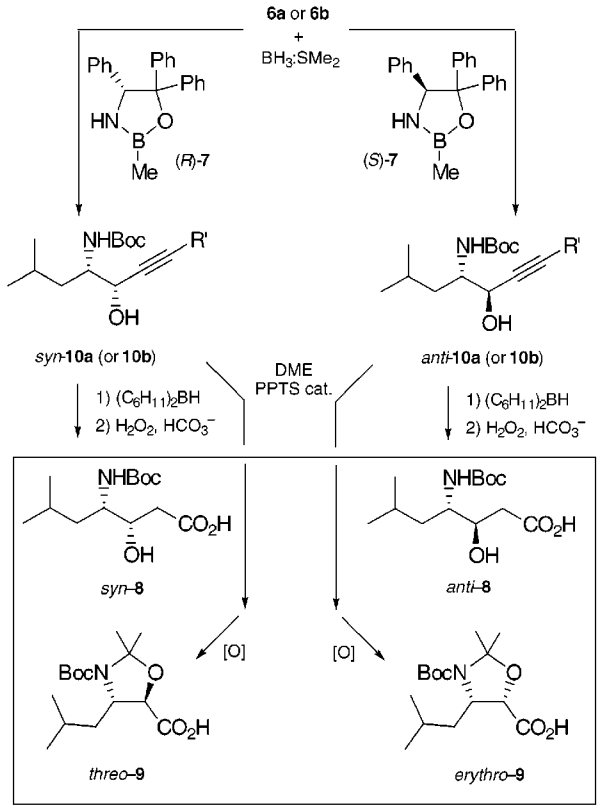


The importance of amino acids **1**−**4** has fueled intensive search for synthetic approaches, both in academic and industrial laboratories, over the past decade.[6,7] As the result of this effort, there are now suitable methods for the preparation of some of these compounds in reasonable yields and stereoselectivities,[8] but there is not a general and unified route to all of them.

In particular, several groups have reported the reduction of suitable chiral α-amino ketones (such as **5**) to obtain **1** or **2**, with modest to good diastereoselectivities for a number of amine protecting groups and achiral reducing agents,[9] the *anti* isomer generally prevailing.[10] Taking advantage of our previous experience in the reduction of acetylenic ketones with BH_3:SMe_2 in the presence of oxazaborolidines (*R*)- or (*S*)-**7**,[11] we envisaged that a single ketone (either **6a** or **6b**) derived from Boc-L-leucine could be a potentially versatile gateway to *N*-Boc-statine (*syn*-**8**) and protected *N*-Boc-norstatine (*threo*-**9**) as well as to their respective diastereomers *anti*-**8** and *erythro*-**9**, as outlined in Scheme 1.

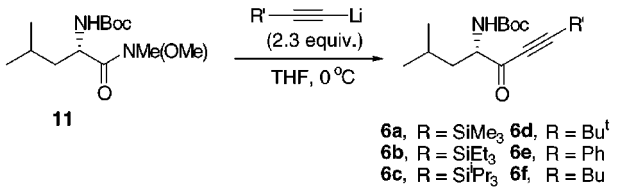
Scheme 1



According to this strategy and bearing in mind that Boc-D-leucine is also commercially available, a judicious combination of the starting leucine, the proper configuration of the oxazaborolidine **7**, and the final treatment (hydroboration/oxidation against oxidative cleavage of the triple bond) could ultimately allow us to obtain any of the eight possible stereoisomers of **8** and **9**. Herein, we wish to report our findings in this connection.

A series of acetylenic ketones derived from Boc-L-leucine were synthesized in 70−85% yield[12] by reaction of Weinreb amide **11** with different lithium acetylides,[13] in order to investigate their performance in oxazaborolidine-mediated reductions (Scheme 2). Besides the aforementioned 1-trialkylsilyl acetylenic ketones, a number of other 1-substituted-1-alkyn-3-ones (**6d**−**f**) were included since the corresponding propargylic alcohols are also amenable to transformation into protected amino acids **9** by oxidative cleavage of the triple bond.

Scheme 2



Reductions of **6** were performed by slow addition (∼20 min) of the ketone (1 mmol) to a solution of BH_3:SMe_2 (1.2 mmol) in THF (2 mL) with 0.2−1.0 mmol of (*R*)- or (*S*)-**7** under Ar at 0 °C. We were gratified to observe that, as shown in Table 1, when R′ was a bulky, quaternary substituent (ketones **6a**−**d**), the oxazaborolidine **7** largely overcame the intrinsic facial bias of the carbonyl group of **6**; good to

Table 1. Reduction of Ketones **6** with BH_3:SMe_2 in the Presence of Oxazaborolidines **7**

entry	ketone	catalyst	yield[a]	*syn*-**10**/*anti*-**10** ratio[a,b]
1	**6a**	(*R*)-**7**	85% (60%)	9:1(9:1)
2		(*S*)-**7**	85% (76%)	1:33.5 (1:32)
3	**6b**	(*R*)-**7**	90% (55%)	24:1 (23:1)
4		(*S*)-**7**	80% (60%)	1:>50 (1:>50)
5	**6c**	(*R*)-**7**	75%	13.4:1
6		(*S*)-**7**	80%	1:>50
7	**6d**	(*R*)-**7**	80%	13.3:1
8		(*S*)-**7**	76%	1:50
9	**6e**	(*R*)-**7**	78%	5:1
10		(*S*)-**7**	75%	1:6.2
11	**6f**	(*R*)-**7**	99%	1.2:1
12		(*S*)-**7**	81%	1:1.8

[a]Within parentheses values using 0.2 mmol of oxazaborolidine.
[b]Determined by HPLC, ^{1}H NMR and/or ^{19}F NMR analysis of the corresponding Mosher esters.

excellent diastereoselectivities were obtained even in the mismatched cases. In sharp contrast, reduction of ketones with lower steric requeriments on C(1), such as **6e**−**f**, was much more disappointing. For the sake of comparison, reductions of **6** with $NaBH_4$ (MeOH, 0 °C) were also performed, leading to a mixture of diastereomeric amino alcohols **10** (from 1.5:1 to 3.5:1 *anti*/*syn* ratio) in all cases.

According to the mechanism proposed by Corey et al.,[14] this remarkable effect of the C(1) substituent, R′, on the stereoselectivity was unexpected since it is distant from the oxazaborolidine ring, avoiding any repulsive interaction with the *B*-Me group; the stereoselectivity observed for analogous oxazaborolidine-mediated reductions is usually explained in this way. However, a closer analysis of molecular models reveals that an "*endo*" arrangement, as in **12**, may be disfavored, since the rigid linear nature of the triple bond puts the SiR'_3 and the α-phenyl group in close proximity; the *i*-Bu group and the Boc-amino moiety (shown as a ball in Figure 1) are then pushed near to the borane−oxazaborolidine complex, destabilizing that arrangement. This repulsive interaction becomes more important when R′ is bulky, encouraging the pathway that proceeds via "*exo*" complex **13**.

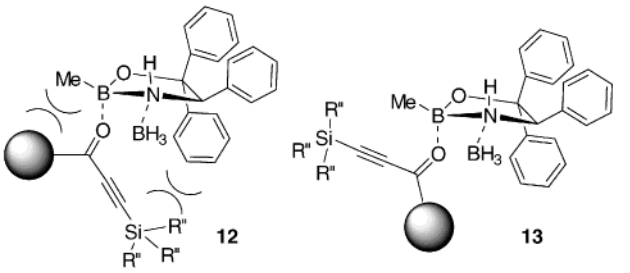


Figure 1. Complexes of ketones **6a**−**c** with (*R*)-**7**.

To assess this assumption, a series of ab initio 3-21G calculations[15] have been undertaken. In our preliminary results for the BH_3−**6a**−(*R*)-**7** complex, the arrangement of the most stable *exo* conformation (which would lead to *syn*-**10a**) is ca. 1.85 kcal mol^{-1} more stable than the *endo* conformation of lowest energy (Figure 2, **13a** and **12a** respectively), in agreement with the experimental results.

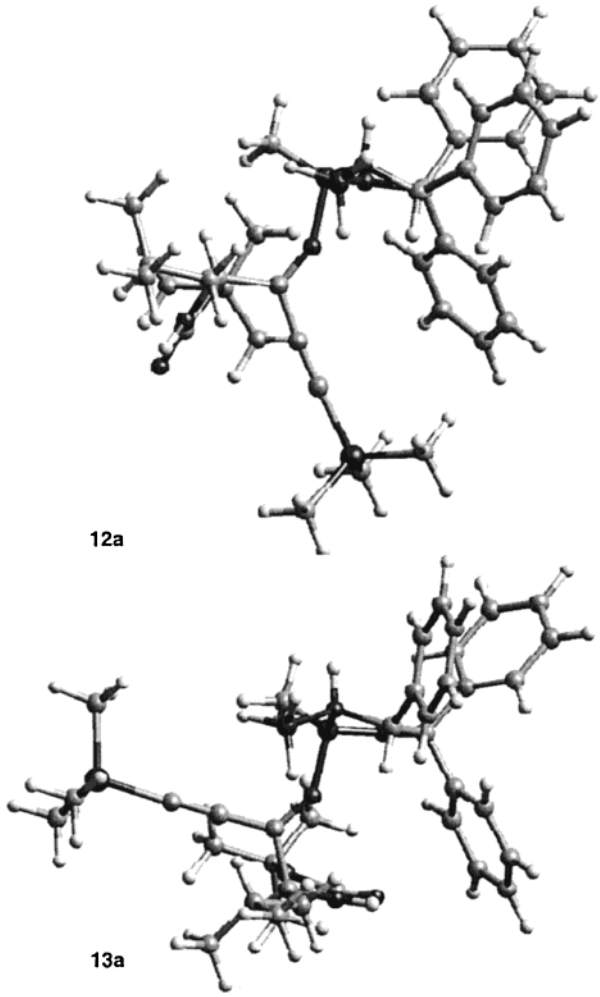


Figure 2. Ab initio 3-21G geometries for BH_3−**6a**−(*R*)-**7** complexes.

Having in hand stereochemically enriched amino alcohols **10**, we undertook their transformation into acids **8** and **9** (see Scheme 3). Thus, hydroboration[16] of *syn*-**10a** (or *syn*-**10b**) with dicyclohexylborane followed by oxidative workup afforded protected statine (*syn*-**8**). In a similar way, *anti*-**8** was obtained from *anti*-**10a** or *anti*-**10b**.

On the other hand, treatment of amino alcohols **10** with 2,2-dimethoxypropane and a catalytic amount of PPTS provided a mixture of oxazolidines **14** from which the minor

(7) For a review on syntheses of β-amino acids, see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. For a discussion of the synthetic approaches to β-hydroxy γ-amino acids, see: Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1996**, *52*, 7063. See also: Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1996**, *7*, 243.

(8) For example, see: Merino, P.; Castillo, E.; Franco, S.; Merchán, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301. See also: Jost, S.; Gimbert, Y.; Greene, A. E.; Fotiadu, F. J. *J. Org. Chem.* **1997**, *62*, 6672.

(9) For example, see: Harris, B. C.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 3489. Good results have been also reported with bulky *N*,*N*-dibenzyl-protected compunds, but the deprotection step was troublesome: Reetz, M. T.; Drewes, M. W.; Matthews, B. R.; Lennick, K. *Chem. Commun.* **1989**, 1474. See also: Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292 and references therein.

(10) For a review on the synthesis of diastereomeric amino alcohols, see: Tramontini, M. *Synthesis* **1982**, 605. See also ref 9.

(11) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021. Bach, J.; Garcia, J. *Tetrahedron Lett.* **1998**, *39*, 6761. Bach, J.; Galobardes, M.; Garcia, J.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 6765.

(12) Compound **6c** was obtained in only 30% yield.

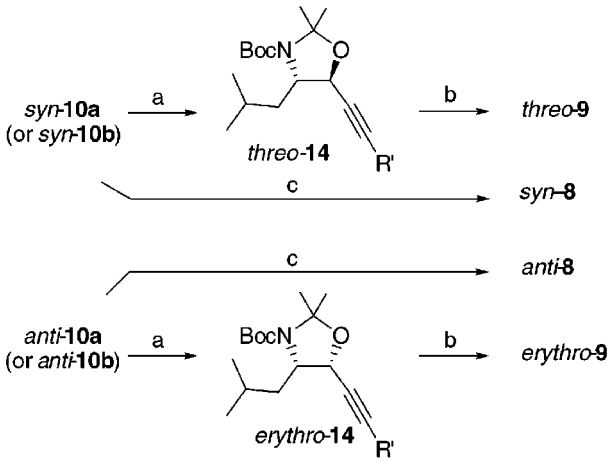
(13) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972.

(14) For a review on oxazaborolidine-mediated reductions, see: Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986. Remote repulsive interactions with the *B*-alkyl group in the reduction of α,β-ynones have been reported: Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938.

(15) All ab initio calculations were carried out using the GAUSSIAN-94 (rev. E.1) series of programs (Gaussian, Inc., Pittsburgh, PA, 1995).

(16) Midland, M. M.; Lee, P. E. *J. Org. Chem.* **1981**, *46*, 3933.

Scheme 3



Reaction conditions: (a) DME (10 equiv.), PPTS (0.3 equiv.), toluene, 90 °C, 4 h, 86–92%; (b) $RuCl_3.H_2O$ (0.2 equiv.), $NaIO_4$ (4 equiv.), $CCl_4/CH_3CN/H_2O$ 2:2:3, 3 h, rt, 84–99%; (c) Dicyclohexylborane (4 equiv.), 0 °C to rt, THF, 2 h, followed by H_2O_2 in aq. $NaHCO_3$ and then AcOH, 72–99%.

stereoisomer could be removed[17] by flash chromatography. Finally, protected α-hydroxy β-amino acids **9** were readily obtained by Ru-mediated oxidation[18] of the triple bond.

In summary, we have demonstrated that all the stereoisomers of the 4-(*N*-*tert*-butoxycarbonylamino)-3-hydroxy-6-methylheptanoic acid (**8**) as well as of the protected 3-(*N*-*tert*-butoxycarbonylamino)-2-hydroxy-5-methylhexanoic acid (**9**) can be efficiently prepared from the appropiate enantiomer of Boc-leucine with the aid of oxazaborolidines (*R*)- or (*S*)-**7**. It is likely that this strategy can be applied to prepare a variety of other protected β-hydroxy γ-amino and α-hydroxy β-amino acids. Work is in progress in this connection.

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Supporting Information Available: General experimental procedures and spectroscopic data for compounds **6a**, *anti*-**8**, *threo*-**9**, *anti*-**10a**, and *erythro*-**14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Samples of stereochemically pure alcohols **10** were available by deprotection (aqueous MeOH, catalytic *p*-TsOH, rt) of pure oxazolidines **14**.

(18) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.