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Stereoselective Synthesis of *anti*-*N*-Protected 3-Amino-1,2-epoxides by Nucleophilic Addition to *N*-*tert*-Butanesulfinyl Imine of a Glyceraldehyde Synthon†

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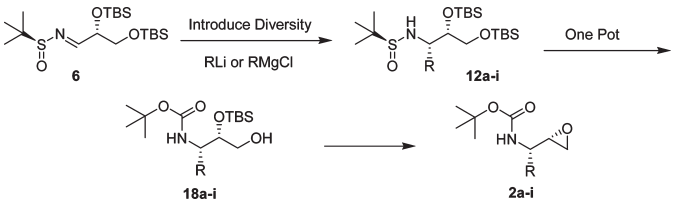
Received April 3, 2009



A di-*O*-TBS protected glyceraldehyde synthon was condensed with Ellman's reagent to form a bench-stable *N*-*tert*-butanesulfinyl imine **6**, which served as a common intermediate for the stereoselective introduction of various R groups. The Ellman adducts were converted to useful multifunctional intermediates **18a**−**i** in one pot. The alcohols **18a**−**i** were efficiently elaborated to both known and novel *anti*-*N*-protected-3-amino-1,2-epoxides in two steps. Compound **2a** is a key intermediate toward HIV protease inhibitors.

Introduction

The hydroxyethylamine (HEA) isostere is a common structural motif present in several approved HIV protease inhibitors, such as Amprenavir **1** (Scheme 1).[1] *anti*-*N*-BOC-3-Amino-1,2-epoxides are commonly used as key intermediates toward these important drugs.[2] Many of the published syntheses of these *N*-BOC-amino epoxides rely on either *N*-BOC protected amino acids or their derivatives. These routes are very efficient and cost-effective for the synthesis of a single targeted epoxide as an intermediate toward an active pharmaceutical ingredient. However, from a medicinal chemistry perspective, these amino-acid-based routes are hampered by a few shortcomings. The main disadvantage of these routes is the early introduction of P1 molecular diversity.[3] The P1 group is introduced at the first step of the synthetic sequence when an amino acid or its derivative is used to synthesize a 3-amino-1,2-epoxide. The early introduction of diversity limits both the speed and efficiency for the synthesis of new analogues.

Another shortcoming of these amino-acid-based routes is the potential for racemization of α chiral esters or activated acid intermediates.[4] Additionally, several of these routes use potentially hazardous reagents, such as diazomethane.[5] Chemists[2] have also utilized *N*,*N*-dibenzyl amino aldehydes[6] (**4** in Scheme 1) in order to achieve the desired 2,3-*anti* relationship of the *N*-protected amino epoxides. Again, with this strategy, the P1 diversity is introduced at the first step of the synthetic sequence and is usually applied to amino acid inputs.

Results and Discussion

The powerful, flexible, and practical sulfinyl imine chemistry pioneered by Davis[7] and extended by Ellman[8] and others[9]

† This manuscript is dedicated to Professor Yoshito Kishi.

(1) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541–558.

(2) (a) Izawa, K.; Onishi, T. *Chem. Rev.* **2006**, *106*, 2811–2827 and references therein. (b) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203–2229 and references therein .

(3) For a Perspective on protease inhibitors and standard nomenclature, see: Leung, D.; Abbenante, G.; Fairlie, D., P. *J. Med. Chem.* **2000**, *43*, 305–341.

(4) Wang, D.; Schwinden, M., D.; Radesca, L.; Patel, B.; Kronenthal, D.; Huang, M.; Nugent, W., A. *J. Org. Chem.* **2004**, *69*, 1629–1633.

(5) Albeck, A.; Persky, R. *Tetrahedron* **1994**, *50*, 6333–6346.

(6) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531–1546.

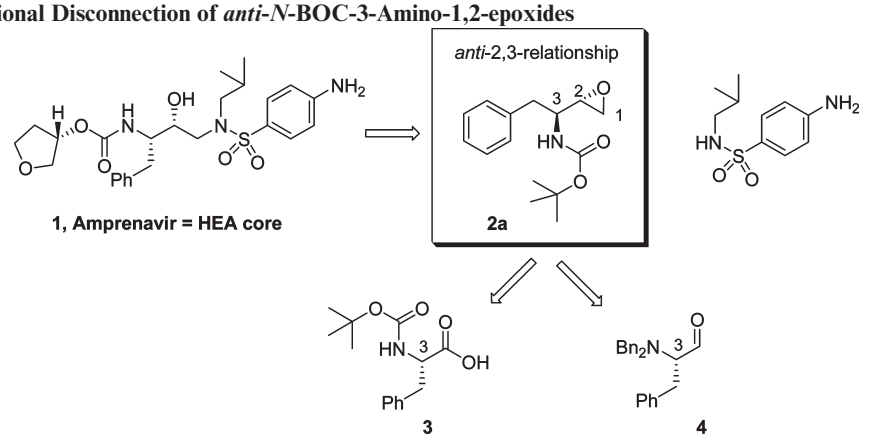
(7) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993–9003.

(8) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. and references therein. *Acc. Chem. Res.* **2002**, *35*, 984–995. (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93–104 and references therein .

(9) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186.

DOI: 10.1021/jo900643b Published on Web 07/08/2009

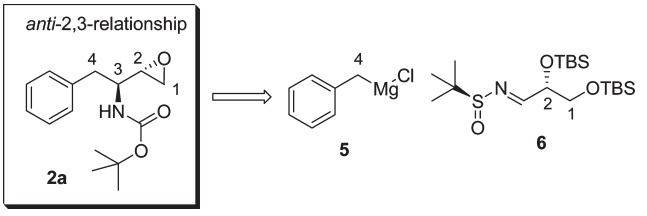
SCHEME 1. Conventional Disconnection of *anti*-*N*-BOC-3-Amino-1,2-epoxides



seemed to be a perfect solution for our medicinal chemistry focused diversity problem. We decided to frame shift the key disconnection of the epoxide **2a** over to the formation of the C.3−C.4 carbon−carbon bond instead of the more conventional C.1−C.2 carbon−carbon bond disconnection (Scheme 2).[10] In doing so, we have gained a few key advantages. First, we delayed the introduction of our P1 diversity. Second, we released ourselves from the necessity of starting with an amino-acid-based input. Third, we mitigated the problem of epimerization of a stereocenter α to a carbonyl. Application of an Ellman *tert*-butylsulfinyl imine disconnection to epoxide **2a** gives di-*O*-TBS protected imine **6** and an organometallic reagent **5**, many of which are commercially available.

Our initial synthetic challenge was to produce multigram quantities of a glyceraldehyde synthon for the formation of the *tert*-butylsulfinyl imine **6**. Both antipodes of glyceraldehyde acetonide or related acetals[11] are widely used intermediates in the field of synthetic organic chemistry.[12] However, we found the acidic hydrolysis conditions required to remove the acetonide diol protecting group[13] to be incompatible with the standard acidic hydrolysis conditions commonly used to remove the chiral sulfinyl group. Therefore, we decided to synthesize a glyceraldehyde equivalent that has the diol functional group protected as two silyl ethers instead of a acetal. Corey and co-workers[14] have shown that allylic 4-methoxybenzoates are excellent substrates for the Sharpless asymmetric dihydroxylation[15] reaction (AD) in terms of yield and enantiomeric purity. The required allylic benzoate is readily prepared from commercially available allyl alcohol and 4-methoxybenzoyl chloride on a mole scale (Scheme 3). The desired absolute stereochemistry was established using the commercially

SCHEME 2. *tert*-Butylsulfinyl Imine Disconnection of 2a



available $(DHQ)_2PHAL$ ligand in the Sharpless AD reaction. The solid diol **8** was produced in greater than 85% yield with a 95−98% ee and then protected with 2.2 equiv of TBSOTf and TEA in DCM to give di-*O*-TBS ether **9** in good yield. The 4-methoxybenzoate was reductively removed with Dibal-H in DCM to give the di-*O*-TBS protected primary alcohol **10**. The primary alcohol **10** could be stored for months on the benchtop without loss of optical purity. The 2,3-di-*O*-TBS glyceraldehyde synthon **11**[16] could be produced in good yield by either Dess−Martin[17] or Swern[18] oxidation conditions without epimerization of the α-silyloxy stereocenter or *β*-elimination.

The condensation of Ellman's *tert*-butylsulfinamide reagent with the glyceraldehyde synthon **11** and subsequent nucleophilic addition of organolithium or Grignard reagents were our next challenges. The Ellman laboratory has formed the *N*-*tert*-butanesulfinyl imines of protected lactals without epimerization at the α-stereocenter.[19] Moreover, they observed excellent stereoselective addition of either EtMgBr or PhMgBr in THF with TMEDA at −78 °C in good yields. The *anti* addition product, which was consistent with both the Felkin−Ahn[20] and Cornforth[21] models, was formed in a

(10) For a conceptually similar reaction with *N*-benzylimine of glyceraldehyde acetonide, see: (a) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **1997**, *53*, 1411–1416. (b) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. *Tetrahedron* **2002**, *58*, 341–354. (c) For a review on additions of organometallic reagents to imines, see: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.

(11) (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585–587 and references therein . (b) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D., E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056–4058.

(12) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447–488.

(13) Greene, T. W.; Wuts, P. G., M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, NY, 1999.

(14) Corey, E. J.; Guzman-Perez, A; Noe, M., C. *J. Am. Chem. Soc.* **1995**, *117*, 10805–10816.

(15) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(16) (a) For the synthesis of **11** from D-mannitol, see: Jurczak, J.; Bauer, T.; Chmielewski, M. *Carbohydr. Res.* **1987**, *164*, 493–498. (b) For a route to di-OBn glyceraldehyde, see: Schreiber, S. L.; Satake, K. *Tetrahedron Lett.* **1986**, *27*, 2575–2578.

(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

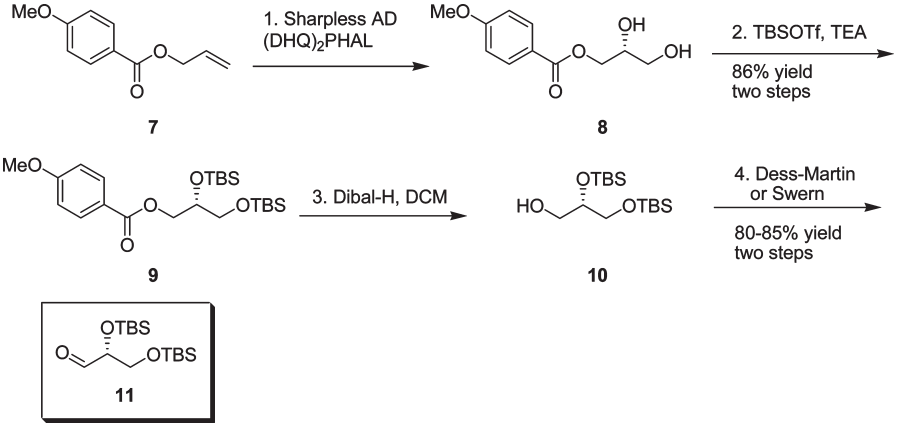
(18) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(19) (a) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948–9957. These authors added 2.0 equiv of a Grignard to the sulfinyl imine. We added the sulfinyl imine to 4 equiv of Grignard . For other examples of sulfinyl imine formation from an α-oxygenated aldehyde, see: (b) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051–2054. (c) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772–8778. (d) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2003**, *9*, 1495–1498.

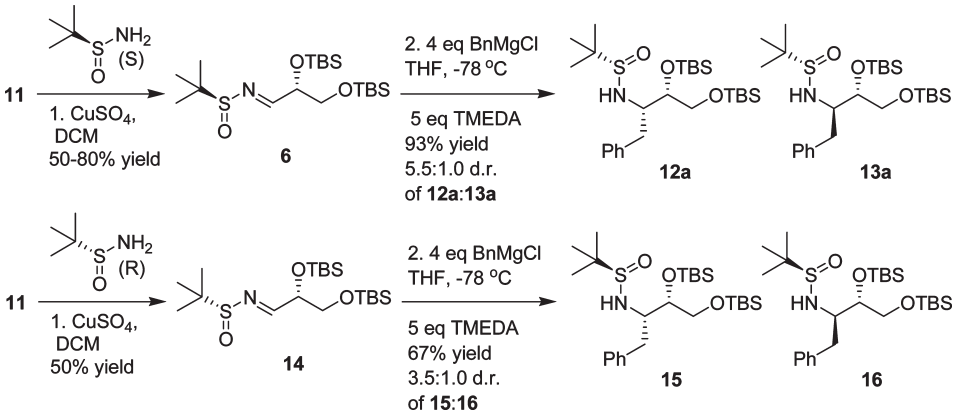
(20) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162.

(21) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761–1765.

SCHEME 3. Gram-Scale Synthesis of Glyceraldehyde Synthon 11



SCHEME 4. Synthesis of Common Intermediate 6 and Stereoselective Addition of BnMgCl



98:2 ratio. Freshly prepared aldehyde **11** was subjected to $CuSO_4$-promoted[22] imine formation with (*S*)-(−)-*tert*-butylsulfinamide in DCM to give good yields (50−80%) of the di-*O*-TBS protected *N*-*tert*-butanesulfinyl imine **6** (Scheme 4). We found it necessary to purify the crude mixture by silica gel chromatography in order to prevent decomposition of the product. We did not observe any epimerization of the α-silyloxy stereocenter during the formation of this imine. The chiral auxiliary nicely provided a convenient handle for simple 1D NMR analysis of the diastereomeric purity of **6** or **14**. If the α-silyloxy stereocenter of the labile aldehyde **11** were to epimerize, then we could detect it by NMR. In fact, we synthesized the enantiomer of **14** (**ent-14**), obtained ^{1}H and ^{13}C NMR spectra of a 1:1 mixture of **ent-14** to **6**, and clearly observed doubling of carbon peaks. We also formed **6** using 2.5 equiv of $Ti(OEt)_4$ in THF at room temperature for 2−14 h followed by addition to quickly stirred brine and EtOAc with a filtration through Celite.[23] In our hands, the titanium-mediated process gave comparable yields (50−70%) but resulted in somewhat difficult product isolation due to formation of titanium dioxide emulsions. Ultimately, we decided that the operational simplicity of the $CuSO_4$-promoted procedure was easier to perform than the titanium-mediated methods.

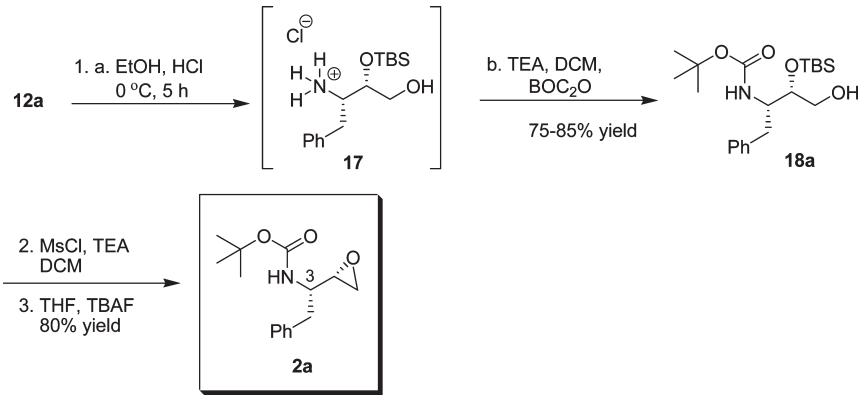
Following Ellman's optimized conditions,[19] we subjected **6** to excess BnMgCl in THF with TMEDA at −78 °C to obtain a 5.5:1.0 ratio of diastereomers in a 93% yield.[24] Analysis of the crude reaction mixture in order to determine the diastereomeric ratio of products in a proper fashion was found to be very difficult. After much effort, we simply could not discover an analytical reverse phase HPLC method that would provide adequate resolution of the peaks. The products are very nonpolar and are retained on a reverse phase column until 100% acetonitrile is used as the mobile phase, resulting in broad peak shapes and poor resolution. The major diastereomer **12a** (higher R_f) was isolated in a 80% yield after silica gel chromatography. The minor diastereomer **13a** (lower R_f) was easily separated from the major diastereomer (ΔR_f = 0.25). Subsequent experiments proved that the major diastereomer **12a** has the desired 2,3-*anti* configuration for further elaboration to *anti*-*N*-BOC 3-amino-1,2-epoxides **2a**. To determine the effect of the chirality on the sulfur atom toward the diastereofacial selectivity of nucleophilic addition, the diastereomeric di-*O*-TBS

(22) See refs 8 and 19.

(23) For representative example of Ti-mediated processes, see: (a) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910–6911. (b) Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. J. *Org. Lett.* **2008**, *10*, 841–844. (c) Denolf, B.; Leemans, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 3211–3217. (d) Denolf, B.; Mangelinckx, S.; Trnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129–3132. (e) Reference 19 .

(24) The diasteromeric ratio was determined by the mass balance of isolated pure diasteromers. The ratio was confirmed by reverse phase HPLC analysis (integration at 215 nm) of the resulting diols after treatment of the crude reaction mixture to excess TBAF in THF for 24 h. Analysis of the crude reaction mixture gave unsatisfactory results because the products are very nonpolar and are not eluted until 100% acetonitrile is used as the mobile phase, resulting in broad peak shapes and poor resolution.

SCHEME 5. Deprotection to Multifunctional Intermediate 18 and Synthesis of *anti-N*-BOC-3-Amino-1,2-epoxides 2a



protected *N-tert*-butanesulfinyl imine **14** was synthesized by the condensation of aldehyde **11** with (*R*)-(+)-*tert*-butylsulfinamide. The same conditions of excess BnMgCl in THF with TMEDA at −78 °C were used on substrate **14** to give a 3.5:1.0 dr of **15** to **16** in a 67% yield. Interestingly, both diastereomeric di-*O*-TBS protected *N-tert*-butanesulfinyl imines **6** and **14** gave the 2,3-*anti* product as the major product, albeit in slightly different ratios. Under the conditions of excess BnMgCl in THF with TMEDA at −78 °C,[25] the α-OTBS stereocenter is the major stereochemical determinate toward the diastereofacial selectivity of nucleophilic addition to the sulfinyl imines **6** and **14**. The temperature, solvent, concentration, solvent ratio of mixed solvents, and chelating additives such as TMEDA all have an impact on the diastereoselectivity of nucleophilic addition to sulfinyl imines **6** and **14**. It is important to follow the conditions of THF (as the only or primary solvent), temperature, and TMEDA closely, otherwise the diastereoselectivity may erode or even favor the opposite diastereomer. Under Ellman's conditions, the (*S*)-(−)-*tert*-butylsulfinamide is a matched case that reinforces the Felkin−Ahn or Cornforth models. The (*R*)-(+)-*tert*-butylsulfinamide resulted in a mismatched diastereofacial bias.

Efficient functional group manipulations of the Felkin−Ahn addition product **12a** toward useful multifunctional intermediates, including the desired *anti-N*-BOC 3-amino-1,2-epoxides **2a**, remained as our last synthetic challenge before going into rapid production of P1 analogue epoxides. The *N*-sulfinyl imine addition product **12a** has three functional groups that are potentially labile to acidic hydrolysis conditions: the sulfinyl group, the primary TBS ether, and the secondary TBS ether. Careful analyses of the reaction rates were required to achieve the desired deprotections. The sulfinyl group was the first functional group to be removed when **12a** was exposed to ≥4 equiv of HCl (4 N in 1,4-dioxane) in EtOH at 0 °C (Scheme 5).

Under these reaction conditions, the sulfinyl group was completely removed to give the primary amine between 15 and 60 min, according to analytical HPLC/MS analysis. The deprotected primary amine was instantly protonated in the acidic EtOH. This proton transfer event had an advantageous effect toward selective TBS ether ethanolysis. Once the primary amine is protonated, the resulting positive charge decreased the rate of adjacent secondary TBS deprotection. The qualitative rate of ethanolysis of the primary TBS was found to be independent of both the equivalence of HCl and the protonation state of the primary amine. We were able to exploit these rate differences and observed nearly complete chemoselective hydrolysis of both the sulfinyl group and the primary TBS ether in the presence of the secondary TBS ether to give the unisolated intermediate **17** after 5 h of HCl treatment at 0 °C.[26] The amino alcohol **17** is a useful and multifunctional molecule. The primary amine of **17** was conveniently protected as a BOC carbamate in 75−85% yield by adding excess TEA followed by DCM and BOC_2O. The versatile intermediate **18a** was converted to *anti-N*-BOC 3-amino-1,2-epoxides **2a** by activation of the primary alcohol with MsCl and TEA in DCM. The crude mesylate was immediately subjected to excess TBAF to give the desired epoxide **2a** in 80% yield for the two steps. The experimental data for **2a** matches that from the literature[27] and therefore proves the configuration of the C.3 stereocenter set during the addition of BnMgCl to imine **6**. Analytical supercritical fluid chromatography (SFC) using a chiral column (ADH) along with commercially available **2a** and **ent-2a** (the 2*R*,3*R*-epoxide) as standards showed that synthetic **2a** was in fact the 2*S*,3*S*-epoxide. Moreover, the enantiomeric excess of synthetic **2a** is greater than 95%.

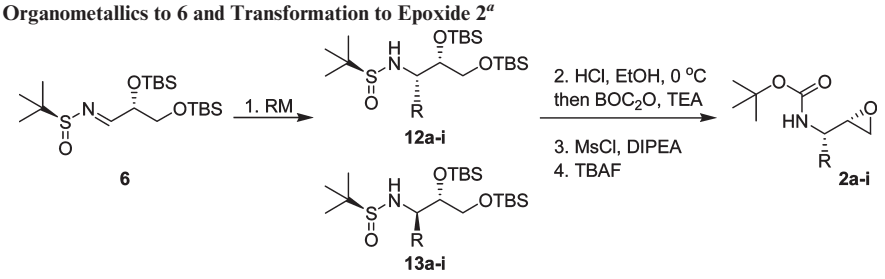
A paradigm of medicinal chemistry is to synthesize high quality new chemical species in high purity in a short period of time. One way to help accomplish this goal is to stockpile a common intermediate and introduce diversity as late into the synthesis of new analogues as possible. With the required chemistry in place, we started to make analogues of *anti-N*-BOC 3-amino-1,2-epoxides. Various organometallic reagents were added into the common intermediate **6** under the same conditions of THF/TMEDA at −78 °C to give good yields of single diastereomers **12a**−**i** after silica gel column chromatography (Table 1). All of the organometallic reagents that were added to sulfinyl imine **6** gave the Felkin−Ahn diastereomer **12** as the major product except

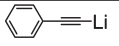
(25) We found that minor changes to Ellman's conditions gave rise to different diastereomeric ratios. From a practical point of view, these changes were not significant for our purposes. In every case, the desired diastereomer was the higher R_f product. Moreover, the minor product was easily separated by chromatography.

(26) For a review on selective deprotection of silyl ethers, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1069.

(27) (a) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615–4625. (b) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635–3645. (c) Ojima, I.; Wang, H.; Wang, T.; Ng, E. W. *Tetrahedron Lett.* **1998**, *39*, 923–9126. (d) Reference 4.

TABLE 1. Addition of Organometallics to 6 and Transformation to Epoxide 2[a]



entry	R-M	compound	Yield **12** (%)	d.r.[b] (**12** anti : **13** syn)	Yield[c] **2** (%)
1	BnMgCl	a	80	5.5 : 1.0	80
2	vinylMgCl	b	33	1.0 : 1.4	59[d]
3	PhLi	c	90	>9.0 : 1.0	43
4	*n*-BuLi	d	80	5.5 : 1.0	58
5	allylMgCl	e	61	6.0 : 1.0	59
6	*tert*-BuLi	f	48	>9.0 : 1.0	80
7	i-PrLi	g	92	>9.0 : 1.0	39
8	MeLi	h	56	1.5 : 1.0	50
9	MeMgCl[e]	h	46	2.9 : 1.0	-
10		i	81	5.0 :1.0	58

[a]All addition reactions were conducted in 4 equiv of RM in THF with 5 equiv of TMEDA at −78 °C. [b]Ratios were determined by mass balance of material except for entry 10, which was determined by analysis of crude ^{1}H NMR. After many attempts, we could not create a satisfactory analytical reverse-phase HPLC method to analyze the crude reaction mixtures for dr determination. [c]Yield of **2a**−**i** over three steps. [d]Yield for diastereomer **20** not **2b**. [e]Reaction conducted at −45 °C.

for vinylmagnesium chloride. The *syn*-2,3 diastereomer **13b**, which is consistent with a chelation-controlled transition state, was obtained in a slight excess when vinylmagnesium chloride was added to the imine **6** under the standard conditions of THF with TMEDA. The diasteromeric ratio of **12** to **13** was excellent (> 9:1) for the addition of phenyl lithium, *tert*-butyl lithium, and isopropyl lithium (entries 3, 6, and 7).

For these three organolithium reagents, none of the minor diastereomers **13c**, **13f**, and **13g** were detected by either thin layer chromatography (the products and starting imine stained very well and in all cases the diastereomers **12** and **13** had a R_f difference of 0.25) or during silica gel chromatography. The diastereoselectivity of MeLi addition to imine **6** was poor. The diastereoselectivity in favor of the desired Felkin−Ahn product **12h** was slightly enhanced by switching from MeLi to MeMgCl. The rate of addition of MeMgCl to imine **6** was much slower than the rate with MeLi, which completely consumed the imine **6** in less than 1 h at −78 °C. In fact, the addition of MeMgCl required elevated temperature (−45 °C) for 48 h and the imine was not completely consumed. The remaining entries in Table 1 gave good diastereomeric ratios of **12** to **13**. In all cases, the desired a*nti*-2,3 addition product **12** was the higher R_f diastereomer. Moreover, the minor diastereomer **13** (lower R_f) was easily separated from the major diastereomer **12** (ΔR_f = 0.25) by silica gel chromatography. The optimized conditions for the elaboration to the key coupling epoxide **2a** were successfully used for all of the sulfinyl imine addition products **12a**−**i**. This demonstrated the generality of our acidic ethanolysis conditions. The α-chiral center is prone to racemization in some of the literature routes toward *anti*-*N*-BOC 3-amino-1,2-epoxides, such as **2a**.[28] Our method circumvents this problem of unwanted racemization. The epoxide **2c**[29] has appeared in the literature. Our method seems to be well suited for making aryl P1 epoxides such as **2c**.

Stereochemical proofs were conducted for all the epoxides **2** that were not previously known in the literature and for epoxides **2g**[30] and **2h**[31] that were previously published compounds (Scheme 6). This was accomplished by converting the

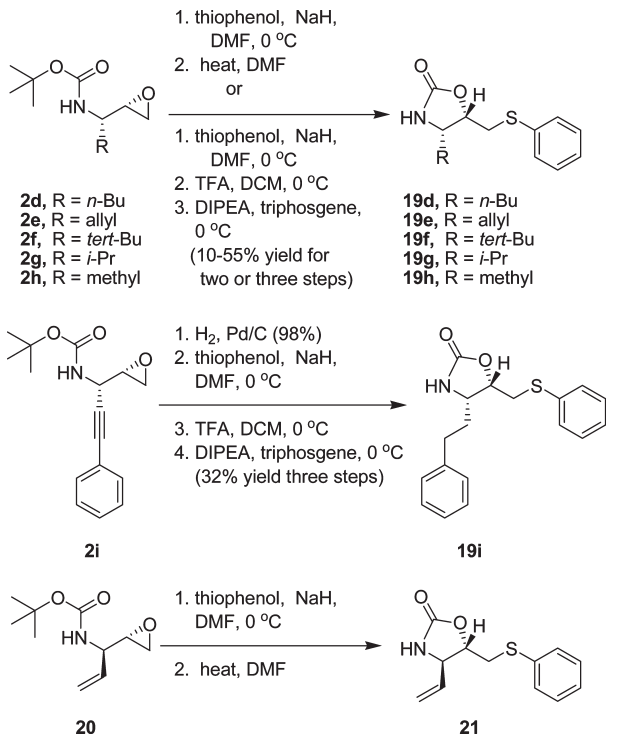
(28) See ref 4.

(29) To our knowledge, **2c** has not been synthesized starting from phenylglycine. However, **2c** has been synthesized from other starting materials: (a) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M., D.; Galvez, J., A. *Tetrahedron* **1999**, *55*, 14145–14160. (b) Reference 31b and 31c.

(30) (a) Rotella, D. P. *Tetrahedron Lett*. **1995**, *36*, 5453–5456. (b) Reference 27b.

(31) (a) Reference 30a. (b) Castejon, P.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron* **1996**, *52*, 7063–7086. (c) Castejon, P.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett*. **1995**, *36*, 3019–3022. (d) Reference 27b .

SCHEME 6. Conversion of Epoxides to Oxazolidinones; Stereochemistry Determined by COSY and NOESY



epoxides **2** to oxazolidinones[32] **19** where the cyclic structures would allow for 2D NMR experiments (COSY and NOESY) to clearly establish the relative stereochemistry of the heterocyclic ring. The epoxides **2** were regioselectively opened at the primary carbon by the action of thiophenol and sodium hydride in DMF. The desired oxazolidinones were then formed by heating the thiophenol addition adducts or removing the BOC group followed by treatment with triphosgene.

Conclusions

In summary, a di-OTBS protected glyceraldehyde synthon **11** was synthesized using a Sharpless AD reaction in order to establish the absolute stereochemistry in high optical purity. This aldehyde was condensed with Ellman's (*S*)-(−)-*tert*-butylsulfinamide reagent to form a bench-stable sulfinyl imine **6** on a multigram scale. The sulfinyl imine **6** served as a common intermediate for the stereoselective addition of various organometallic reagents in good yield. The α-silyloxy stereocenter of **6** controlled the diastereofacial selectivity of nucleophilic addition and is consistent with a Felkin−Ahn or Cornforth model. The (*S*)-(−)-*tert*-butylsulfinyl imine **6** provided a matched stereodifferentiation, whereas the (*R*)-(+)-*tert*-butylsulfinyl imine **14** gave a mismatched result. The organometallic addition products were efficiently converted to *anti-N*-BOC 3-amino-1,2-epoxides in three steps. These *anti-N*-BOC 3-amino-1,2-epoxides are key intermediates toward many commercial syntheses of HIV protease inhibitors. Novel *anti-N*-BOC 3-amino-1,2-epoxides could be used to synthesize a novel HIV protease inhibitor.

(32) (a) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487–1492. (b) Barrett, A. G. M.; Seefeld, M. A.; White, A., J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677–2685.

Experimental Section

(*R*)-2,3-Dihydroxypropyl 4-Methoxybenzoate (8). *Note*: the product of this reaction is thermally and hydrolytically sensitive. Perform all workup procedures below 30 °C and removal of solvents on a rotary evaporator below 40 °C. To a 2.0 L round-bottom flask containing potassium hexacyanoferrate(III) (68.988 g, 187.29 mmol) was added water (300 mL), and the mixture was allowed to stir at 23 °C for 5 min. At this time, potassium carbonate (25.885 g, 187.29 mmol) and $(DHQ)_2$-PHAL (0.48633 g, 0.62431 mmol) were added in one portion. The mixture was allowed to stir for 15 min in order to allow all of the salts to completely dissolve. At this point, *tert*-butanol (200 mL) was added, and the flask was placed in a 0 °C bath and allowed to stir for 10 min before the addition of potassium osmate dihydrate (0.23003 g, 0.62431 mmol) in one portion. The allyl 4-methoxybenzoate (12.000 g, 62.431 mmol) was added in *tert*-butanol (100 mL), and the internal temperature of the reaction was determined to be 8 °C. The reaction was allowed to stir for 2 h (the internal temp ranged from 3 to 8 °C during the reaction) and then quenched by the addition of sodium thiosulfate (118.45 g, 749.18 mmol). The quenched reaction was allowed to stir in the cooling bath for 10 min, then the bath was removed, and the quenched reaction was allowed to stir for 10 more min before it was poured into EtOAc (300 mL) and water (200 mL). The aq layer was extracted with EtOAc (3 × 200 mL). The combined organics were washed with brine and dried with sodium sulfate. The dried solution was passed through a short plug of silica gel and concentrated to give 14.000 g of a white solid in a 99% yield. $R_f = 0.30$ in EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.60−3.80 (m, 2 H), 3.88 (s, 3 H), 4.00−4.13 (m, 1 H), 4.35−4.55 (m, 2 H), 6.92 (d, $J = 8.80$ Hz, 2 H), 8.00 (d, $J = 8.80$ Hz, 2 H).

(*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)propyl 4-Methoxybenzoate (9). To a 1.0 L round-bottom flask containing (*R*)-2,3-dihydroxypropyl 4-methoxybenzoate (4.800 g, 21.2 mmol) was added DCM (100 mL), and the mixture was allowed to stir at 0 °C for 5 min. At this time, TEA (8.87 mL, 63.7 mmol) was added, and the reaction was allowed to stir for 5 min before the dropwise addition of *tert*-butyldimethylsilyl triflate (10.2 mL, 44.6 mmol) via a syringe. The reaction was allowed to stir for 1 h and then quenched by pouring into HCl (0.1 N, 100 mL). The aq layer was extracted with DCM (2 × 75 mL). The combined organics were washed with HCl (0.1 N, 2 × 150 mL), sodium bicarbonate (1 × 150 mL, sat), and brine and dried with sodium sulfate. The dried solution was passed through a plug of silica gel to and concentrated to give 9.20 g of **9** as a colorless oil in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.04−0.14 (m, 12 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 3.64 (d, $J = 5.87$ Hz, 2 H), 3.87 (s, 3 H), 4.03 (dd, $J = 5.67$, 4.50 Hz, 1 H), 4.25 (dd, $J = 6.0$, 6.00 Hz, 1 H), 4.41 (dd, $J = 11.35$, 3.91 Hz, 1 H), 6.93 (d, $J = 8.61$ Hz, 2 H), 8.01 (d, $J = 8.41$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.4, −4.8, −4.6, 18.0, 18.3, 25.7, 25.9, 55.3, 64.8, 66.3, 71.3, 113.5, 122.7, 131.6, 163.2, 166.2; HRMS (TOF) calcd for [$C_{23}H_{42}O_5Si_2$ + H] 455.2644, found 455.2643, error = −0.13 ppm. $R_f = 0.75$ in 20% EtOAc in hexanes, UV active and stains white to anisaldehyde stain. $[\alpha]^{34.0}_D = -15.0$ ($c = 4.84$ in $CHCl_3$). FTIR (thin film) 2955, 2930, 1719, 1607, 1512, 1257, 1168, 1101, 836, 777 cm^{-1}.

(*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)propan-1-ol (10). To a 3.0 L round-bottom flask containing (*S*)-2,3-bis(*tert*-butyldimethylsilyloxy)propyl 4-methoxybenzoate (26.5000 g, 58.3 mmol) was added DCM (300 mL), and the mixture was allowed to stir at −78 °C for 15 min. At this time, DIBAL-H (1.0 M in hexanes) (117 mL, 117 mmol) was added via syringe over 20 min. The reaction was allowed to stir an additional 30 min, when TLC indicated that all starting material was consumed, and then quenched by the addition of methanol (7.09 mL, 175 mmol) via syringe. The quenched reaction was allowed to stir for 5 min, and

then potassium sodium tartrate (411 g, 1457 mmol) in 250 mL of water was added. The reaction was allowed to warm to 23 °C and stirred for 2 h when the layers nicely separated. The aq layer was extracted with DCM (3 × 150 mL). The combined organics were washed with brine and dried with sodium sulfate over the weekend. The dried solution was filtered and concentrated to give 28 g of crude oil. This oil was passed through a plug of silica gel and eluted with 30% EtOAc in hexanes (four 1.0 L fractions, product in fractions 2 and 3) to remove the 4-methoxy benzyl alcohol byproduct (R_f = 0.10 in 20% EtOAc in hexanes, stains red to anisaldehyde, and is UV active) and give 18.40 g of primary alcohol **10** in 98% yield. Product R_f = 0.50 in 20% EtOAc in hexanes, not UV active, faint gray to anisaldehyde stain. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.03−0.20 (m, 12 H) 0.81−0.95 (m, 18 H) 3.45−3.84 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.51, −5.46, −4.8, −4.7, 18.0, 18.3, 25.8, 25.9, 64.8, 64.9, 72.5; HRMS (TOF) calcd for [$C_{15}H_{36}O_3Si_2$ + H] 321.2276, found 321.2276, error = 0.06 ppm. R_f = 0.50 in 20% EtOAc in hexanes, UV active and faint gray to anisaldehyde. $[\alpha]^{34.5}_D$ = −13.0 (c = 2.2 in $CHCl_3$). FTIR (thin film) 3445, 2956, 2929, 2858, 1473, 1256, 1093, 836, 777 cm^{-1}.

(*R*)-2,3-Bis(*tert*-butyldimethylsilyloxy)propanal (11). To a 500 mL round-bottom flask containing (*S*)-2,3-bis(*tert*-butyldimethylsilyloxy)propan-1-ol **10** (4.70 g, 14.7 mmol) was added DCM (100 mL), and the mixture was allowed to stir at 23 °C for 2 min. At this time, sodium bicarbonate (3.69 g, 44.0 mmol) and Dess−Martin periodinane (7.46 g, 17.6 mmol) were added in one portion, and the reaction was allowed to stir for 1.5 h. The reaction was quenched by the addition of sodium thiosulfate (6.95 g, 44.0 mmol) in one portion followed by sodium bicarbonate (satd 250 mL) and diethyl ether (250 mL). The quenched reaction was allowed to stir for 45 min and then the clear layers were separated. The organic layer was washed with sodium bicarbonate (2 × 250 mL), water (1 × 250 mL) and brine (1 × 100 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated to give 5.00 g of a colorless oil. R_f = 0.80 in 20% EtOAc in hexanes, not UV active, stains pink/orange to anisaldehyde. The aq layers were back extracted with ether (2 × 125 mL). The combined back extractions were washed with brine, dried with magnesium sulfate, filtered, and concentrated to give less than 200 mg of oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.06 (s, 3 H), 0.06 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 0.92 (s, 9 H), 3.81 (d, J = 5.26 Hz, 2 H), 4.06 (dt, J = 5.33, 1.32 Hz, 1 H), 9.66 (d, J = 1.32 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.50, −5.47, −4.84, −4.80, 18.26, 18.28, 25.74, 25.81, 64.64, 78.85, 203.22; HRMS (TOF) calcd for [$C_{15}H_{34}O_3Si_2$ + H] 319.2119, found 319.2134, error = 4.54 ppm. R_f = 0.80 in 20% EtOAc in hexanes, not UV, stains pink/orange to anisaldehyde. $[\alpha]^{31.5}_D$ = +6.0 (c = 2.67 in $CHCl_3$). FTIR (thin film) 2957, 2930, 2859, 1740, 1473, 1254, 1115, 978, 836, 779 cm^{-1}.

(*S*,*E*)-*N*-((*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)propylidene)-2-methylpropane-2-sulfinamide (6). To a 500 mL round-bottom flask containing (*R*)-2,3-bis(*tert*-butyldimethylsilyloxy)propanal **11**(4.670 g, 14.7 mmol) was added DCM (100 mL), and the mixture was allowed to stir at 23 °C for 2 min. At this time, (*S*)-2-methylpropane-2-sulfinamide (2.13 g, 17.6 mmol) and copper(II) sulfate (5.85 g, 36.6 mmol) were added, and the reaction was allowed to stir for 24 h. At this time TLC showed that all of the aldehyde was consumed. The crude reaction mixture was filtered through a plug of Celite in order to remove the solid copper salt. The organic layer was concentrated to give 7.50 g of oil, which was subjected to a 330 g Isco column (10−35% EtOAc in hexanes) to give 4.90 g of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.05 (s, 6 H), 0.08 (s, 3 H), 0.09 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.20 (s, 9 H), 3.67−3.81 (m, 2 H), 4.43−4.53 (m, 1 H), 7.98 (d, J = 4.33 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.54, −5.49, −4.84, −4.78, 18.09, 18.28, 22.27, 25.65, 25.80, 56.59, 66.03, 75.32, 169.52; HRMS (TOF) calcd for [$C_{19}H_{43}NO_3Si_2$ + H] 422.2575, found 422.2581, error = 1.45 ppm. R_f = 0.50 in 20% EtOAc in hexanes, UV active and stains yellow to anisaldehyde. $[\alpha]^{34.4}_D$ = +166.0 (c = 3.2 in $CHCl_3$). FTIR (thin film) 2956, 2930, 2859, 1625, 1473, 1254, 1142, 1091, 835, 779 cm^{-1}.

(*R*,*E*)-*N*-((*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)propylidene)-2-methylpropane-2-sulfinamide (14). The same procedure used to synthesize compound **6** was followed, and 2.1 g of a colorless oil was isolated (50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.03−0.11 (m, 12 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.21 (s, 9 H), 3.74−3.78 (m, 2 H), 4.44−4.53 (m, 1 H), 7.99 (d, J = 3.95 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.43, −5.41, −4.83, −4.71, 18.19, 18.31, 22.39, 25.71, 25.78, 56.78, 65.93, 75.44, 169.48; HRMS (TOF) calcd for [$C_{19}H_{43}NO_3Si_2$ + H] 422.2575 found 422.2589, error = 3.25 ppm. R_f = 0.30 in 10% EtOAc in hexanes, UV active and stains pink to anisaldehyde. $[\alpha]^{34.4}_D$ = −112.0 (c = 2.35 in $CHCl_3$). FTIR (thin film) 2956, 2930, 2859, 1627, 1473, 1256, 1091, 836, 778 cm^{-1}.

General Procedure for the Grignard or Organolithium Addition to *N*-*tert*-Butanesulfinyl Imine 6 or 14. To a 1.0 L round-bottom flask containing the Grignard reagent (in THF) (24.9 mL, 49.8 mmol) was added THF (100 mL), and the mixture was allowed to stir at −78 °C for 15 min. At this time, TMEDA (9.39 mL, 62.2 mmol) was added via syringe, and the reaction was allowed to stir for 30 min prior to the addition of sulfinyl imine (5.25 g, 12.4 mmol) in THF (15 mL) dropwise over 15 min. The reaction was allowed to stir for 5 h and then quenched by the addition of ammonium chloride (satd 150 mL). The aq layer was extracted with EtOAc (3 × 100 mL). The combined organics were washed with brine, dried with sodium sulfate, filtered, and concentrated to give 7 g of a crude oil. The crude oil was subjected to a 330 g Isco column (10 to 35%EtOAc in hexanes) to give pure single diastereomeric product.

(*S*)-*N*-((2*S*,3*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-phenylbutan-2-yl)-2-methylpropane-2-sulfinamide (12a). Higher R_f spot is the major diastereomer. The material was subjected to high vacuum overnight to give 5.07 g of clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08−0.12 (m, 9H), 0.17 (s, 3H), 0.93 −0.55 (m, 27H), 2.59−2.67 (m, 1H), 2.88−2.94 (m, 1H), 3.53−3.59 (m, 2H), 3.63−3.69 (m, 1H), 3.74−3.82 (m, 1H), 4.13−4.19 (m, 1H), 7.13−7.17 (m, 3H), 7.22−7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.4, −4.5, −4.2, 18.1, 18.3, 22.3, 25.9, 25.9, 35.1, 55.7, 60.7, 64.3, 75.6, 125.9, 128.1, 129.5, 139.4; HRMS (TOF) calcd for [$C_{26}H_{51}NO_3SSi_2$ + H] 514.3201, found 514.3187, error = −2.68 ppm. R_f = 0.40 in 20% EtOAc in hexanes, UV active and stains purple to anisaldehyde. $[\alpha]^{34.4}_D$ = −24.0 (c = 3.16 in $CHCl_3$). FTIR (thin film) 2954, 2930, 2858, 1472, 1254, 1127, 1076, 837, 779, 698 cm^{-1}.

General Procedure for Deprotection of 12 to Primary Alcohols 18: *tert*-Butyl (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-1-phenylbutan-2-ylcarbamate (18a). To a 1.0 L round-bottom flask containing **12** (9.73 mmol) was added EtOH (50 mL), and the mixture was allowed to stir at 0 °C for 10 min. At this time, HCl (4.0 M in 1,4-dioxane) (9.73 mL, 38.9 mmol) was added in one portion. After 5 h LC/MS showed complete removal of sulfinyl and primary silyl ether, TEA (6.78 mL, 48.6 mmol) and DCM (20 mL) were added, and the reaction was removed from the ice bath. After 10 min, BOC_2O (3.19 g, 14.6 mmol) was added in one portion, and the reaction was allowed to stir for 14 h. The bulk of the solvent was removed, and then the residue was dissolved in EtOAc (300 mL). The organic layer was washed with ammonium chloride (3 × 100 mL), sodium bicarbonate, and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated to give **18a** as an oil. The crude product was subjected to a 330 g Isco column (20% to 45% EtOAc in hexanes) to give 3.40 g of colorless oil (88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm −0.00 (s, 3 H), 0.01 (s, 3 H),

0.03 (s, 1 H), 0.84 (s, 9 H), 1.25 (s, 9 H), 2.44−2.73 (m, 2 H), 2.91 (dd, J = 13.74, 4.38 Hz, 1 H), 3.42−3.70 (m, 3 H), 3.79−4.03 (m, 1 H), 4.63 (d, J = 8.77 Hz, 1 H), 6.96−7.32 (m, 5 H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.4, 18.1, 25.4, 28.4, 36.5, 54.0, 63.6, 73.9, 79.4, 126.7, 128.4, 129.1, 138.3, 155.9.; HRMS (TOF) calcd for [$C_{21}H_{37}NO4Si$ + H] 396.2565, found 396.2573, error = 1.98 ppm. R_f = 0.25 in 20% EtOAc in hexanes, UV active and stains white to anisaldehyde stain.

Representative Procedure for Conversion of Primary Alcohols 18 to Epoxides 2: *tert*-Butyl (*S*)-1-((*S*)-Oxiran-2-yl)-2-phenylethylcarbamate (2a). To a 250 mL round-bottom flask containing *tert*-butyl (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-1-phenylbutan-2-ylcarbamate **18a** (310.00 mg, 784 μmol) was added DCM (5 mL), and the mixture was allowed to stir at 0 °C for 10 min. At this time, DIPEA (411 μL, 2351 μmol) and Ms-Cl (0.5 M in DCM) (1567 μL, 784 μmol) were added via syringe. The reaction was allowed to stir for 1 h and then poured into ammonium chloride (satd 75 mL) and extracted with DCM (4 × 35 mL). The combined organics were washed with brine, dried with sodium sulfate, passed though a short plug of silica gel, and concentrated to give 370.00 mg of colorless oil. R_f = 0.20 in 20% EtOAc in hexanes (slightly lower than starting primary alcohol) UV active and stains white/pink to anisaldehyde). The material was taken directly into the epoxide forming reaction.

To a 150 mL round-bottom flask containing the mesylate (290.00 mg, 612.20 μmol) was added THF (10 mL), and the mixture was allowed to stir at 0 °C for 10 min. At this time, TBAF (192.08 mg, 734.64 μmol) was added in one portion, and the reaction was allowed to stir for 14 h before it was transferred to a separatory funnel with EtOAc (100 mL). The organic layer was washed with water (100 mL). The aq layer was back extracted with EtOAc (50 mL). The dried solution was filtered and concentrated to give a white solid that was subjected to a 40 g Isco column (15 to 45% EtOAc in hexanes) to give 130 mg of a white solid (80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.73−3.00 (m, 5H), 3.69 (br s, 1H), 4.49 (br s, 1H), 7.21−7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 46.8, 52.5, 53.2, 79.6, 126.6, 128.5 129.4, 136.7, 155.2; HRMS (ESI) calcd for [$C_{15}H_{21}NO_3$ + Na] 286.1414, found 286.1420. R_f = 0.40 in 30% EtOAc in hexanes, UV active and stains yellow/brown to anisaldehyde stain, cospots with commercially available material. $[\alpha]^{34.3}_D$ = +6.0 (c = 1.0 in $CHCl_3$). FTIR (KBr pellet) 3378, 2982, 1680, 1524, 1170, 928, 702 cm^{-1}. Mp = 121−123 °C, lit = 122−124 °C.[27b]

Acknowledgment. We gratefully acknowledge and thank Drs. Jason Tedrow, Filisity Vounatsos, and Kenneth McRae and Mr. Bobby Riahi for helpful discussions, technical assistance, and large scale syntheses. The authors thank Drs. Randy Jensen, Steven Sukits, and Christopher Wilde for conducting 2D NMR experiments, Steven Notari for the development of analytical HPLC methods, Zheng Hua for chiral SFC, and Dr. Paul Schnier for high resolution mass spectra. We thank Dr. Ted Judd and Frenel DeMorin for helpful discussions.

Supporting Information Available: General experimental information and complete synthetic details and characterization for compounds **7**, **13a**, **15**, **16**, **12b**, **13b**, **12a**−**i**, **18a**, **20**, **2c**−**i**, **19i**, **19d**, **19e**, **19f**, and **21**; copies of ^{1}H NMR and ^{13}C NMR; copies of 2D NMR experiments (COSY and NOESY) for compound **19d**. This material is available free of charge via the Internet at http://pubs.acs.org.