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Practical asymmetric synthesis of β-hydroxy γ-amino acids via complimentary aldol reactions

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ABSTRACT

Orthogonally protected chiral β-hydroxy-γ-amino acids can be accessed in >100 g quantities from readily available starting materials and reagents in three to four steps. These chiral synthons contain two adjacent stereocenters along with suitably protected functional groups (*O*-TBS, *N*-Boc) for downstream reactivity. Implementation of two existing aldol technologies allows rapid access to all possible stereoisomers of **1**. The guiding principles during reaction optimization were reaction scalability and operational efficiency. Conversion of the amino acids to a variety of chiral building blocks in one to two steps demonstrates their synthetic utility.

1. Introduction

Chiral β-hydroxy γ-amino acids are a class of non-proteinogenic amino acids present in many important biologically active natural products[1] (Fig. 1), including pepstatin,[2] bistramide A,[3] hapalosin,[4] and the didemnins.[5] Of particular interest to us was the utility of β-hydroxy γ-amino acids for diversity-oriented synthesis (DOS) in the context of developing new build/couple/pair pathways.[6,7] In the present study, we chose to focus on the synthesis of *O*-TBS-protected β-hydroxy-γ-amino acids **1a**,**b** (Fig. 2), which are low in molecular weight and contain handles for downstream chemistry. Anticipating the need for substantial quantities of the four amino acids for development of a number of DOS pathways, we selected chemical transformations that were scalable, robust, and general in scope. The enantioselective aldol[8] reaction fits all three criteria.

2. Results and discussion

After examining the literature regarding the enantioselective synthesis of chiral γ-amino acids,[9] we settled on a chiral oxazolidinone protocol pioneered by Evans for the synthesis of the 1,2-*syn* aldol[10] products **1a** and a norephedrine approach developed by Abiko for the 1,2-*anti* aldol[11] products **1b**. The commercial availability of both antipodes of each chiral auxiliary (**3a**,**b**) in large

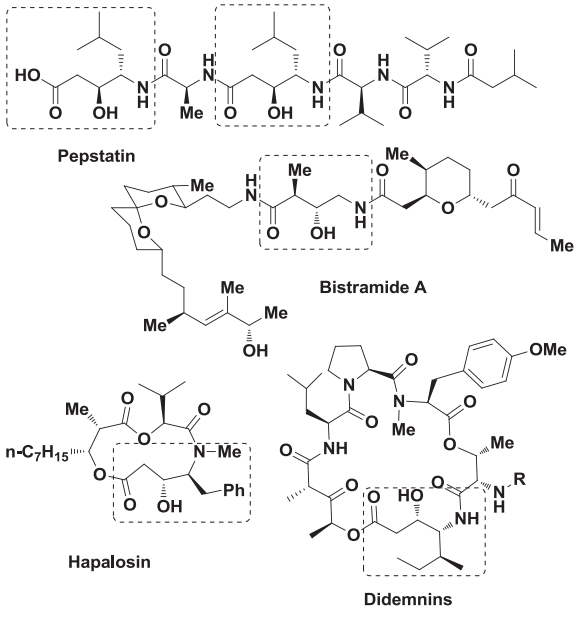

Fig. 1. Examples of natural products containing β-hydroxy-γ-amino acids.

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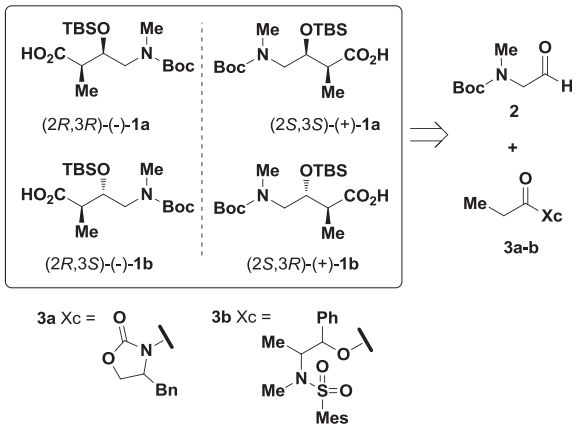
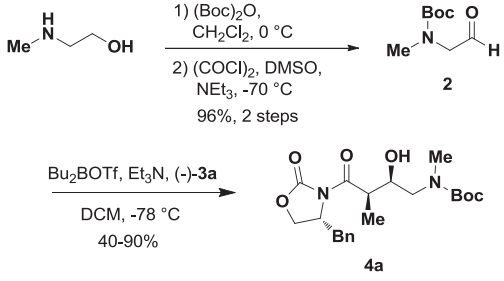


Fig. 2. Aldol approach to the full matrix of β-hydroxy-γ-amino acids **1a**,**b**.

quantities suggested that access to all stereoisomers of β-hydroxy-γ-amino acid **1** should be possible.

Kato and co-workers had reported the preparation of amino substituted acetaldehyde **2**[12] in two steps from relatively inexpensive 2-methylaminoethanol. Though this protocol was facile and was utilized for our preliminary studies, we replaced the reported Parikh–Doering oxidation with a Swern protocol (Scheme 1).[13] The change in oxidation conditions produced a cleaner reaction mixture from which the product could be isolated in 200 g scale and the overall unit cost to produce **2** was also reduced.[14] With access to substantial quantities of aldehyde **2** and auxiliaries, we proceeded with the development of the two aldol protocols.



Scheme 1. Aldehyde preparation and initial *syn*-aldol results.

Seminal work by Evans and co-workers with propionated chiral oxazolidinones has provided access to many 1,2-*syn* aldol products in high diastereomeric, and ultimately, enantiomeric excess. Although this procedure has been successfully utilized with a variety of aldehydes, we initially encountered unpredictable results when applying it to the reaction of aldehyde **2** and propionate **3a**. In our preliminary experiments, a solution of dibutylboron triflate in dichloromethane (1.0 M) was employed, which resulted in variable isolated yields (40–90%) of **4a**. As noted by Evans[15] and others,[16] the purity of the Lewis acid directly impacts the chemical yield, product purity, and diastereoselectivity. Examining other commercial sources of the Lewis acid led to a solution of dibutylboron triflate in toluene (1 M),[17] which was more stable to prolonged storage.[18] Replacing dichloromethane with toluene as the reaction solvent, however, led to slower reaction rates and lower yields. After examining a variety of solvent combinations, we arrived at a mixture of toluene and dichloromethane (1:1) as the optimal solvent pair. This solvent combination, along with the more reliable source of Lewis acid, provided more reproducible results and consistently higher yields (88–96%).

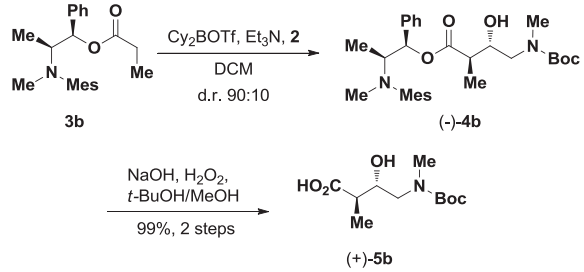
Having identified the critical variables for success of the aldol reaction on one-gram scale we next turned our attention to maximizing material throughput. Increasing reaction concentration and introducing the aldehyde neat, rather than as a solution, did not diminish yield or selectivity. The temperature of aldehyde addition could also be increased from −78 to 0 °C, which allowed for shorter reaction times without erosion of diastereoselectivity.[19,20]

Aware that the solvents and reagents used in both the aldol reaction and hydrolytic removal of the auxiliary were compatible, we contemplated if the two transformations could occur sequentially in a single flask operation. If successful, we would be able to avoid isolation of aldol adduct **4**, which required aqueous workup and silica gel chromatography.[21] Our initial attempts were plagued by sluggish hydrolysis reactions. We hypothesized that the immiscible solvent combination (PhMe/DCM/H_2O) was sequestering lithium peroxide from the substrate. Substituting methanol for aqueous buffer, followed by the addition of a 2:1 THF/H_2O_2 solution presumably increased the solubility of the nucleophile, thus allowing for a more reasonable hydrolysis rate. The optimized protocol (Scheme 2) provided hydroxy acid (−)-**5a** directly from propionate **3a** as a single isomer by chiral SFC in excellent yield after aqueous workup.[22] This one-pot procedure has been successfully utilized on preparative scale to routinely access >90 g[23] batches of either (−)-**5a** or (+)-**5a**.

Scheme 2. One-pot preparation of 1,2-*syn*-γ-amino acid **5a**.

We next turned our attention to the preparation of 1,2-*anti*-γ-amino acids **5b**. Many research programs have focused on the *anti*-aldol reaction.[24] Abiko and co-workers had demonstrated that norephedrine propionates **3b** could be utilized with dicyclohexylboron triflate to provide 1,2-*anti* aldol products in good diastereomeric excess and yield. Aspiring toward the goals of high chemical efficiency, selectivity, operational simplicity, and maximum material throughput, we initiated our studies with the Abiko protocol.

A survey of various sources of dicyclohexylboron triflate for this aldol reaction revealed the superiority of freshly prepared Lewis acid[25] over commercial supplies. The in-house prepared batch of dicyclohexylboron triflate was also less expensive and could be prepared in greater quantities (800 g scale) than was available from commercial vendors.[26] Optimization studies focused on the role of solvent used to introduce the Lewis acid. Initially a solution of dicyclohexylboron triflate in hexanes (1 M) was employed as reported by Abiko.[24d] Further studies revealed dichloromethane as a superior solvent for this reaction (Scheme 3). The *anti*-aldol reactions performed with a dichloromethane solution (1 M) of dicyclohexylboron triflate were faster, higher yielding, and more consistent. Concerned that this enhanced reactivity of the Lewis

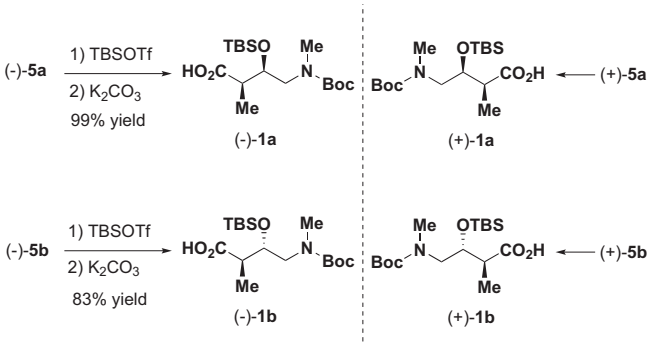


Scheme 3. Synthesis of 1,2-*anti*-γ-amino acids **5b**.

acid in dichloromethane would be coupled with instability, we studied the performance of aged solutions (>20 d) in the *anti*-selective aldol reaction and we were pleased to observe no erosion of yield or diastereoselectivity.

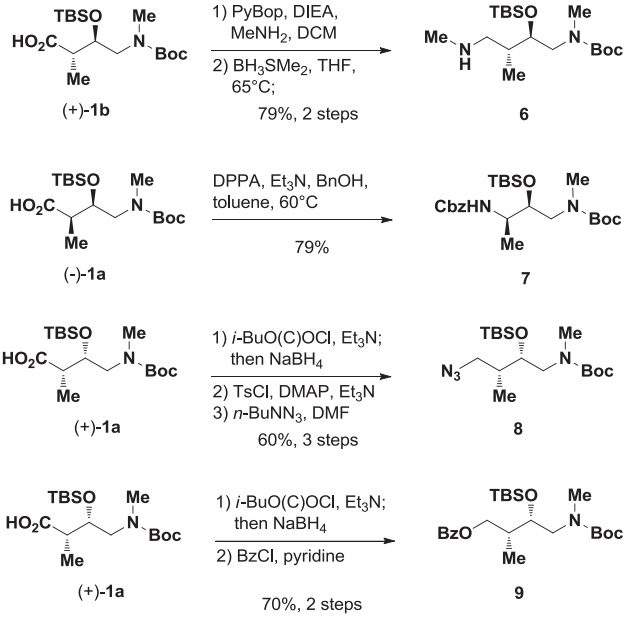
The hydrolysis of the ephedrine-based auxiliary was initially carried out with lithium hydroxide to provide acid (+)-**5b** contaminated with its C2-epimer (3–5%). Epimerization was suppressed (<1–2%) by conducting the hydrolysis with sodium hydroxide/hydrogen peroxide in a mixed *tert*-butanol/methanol solvent system (Scheme 3). Attempts to perform these two transformations sequentially in a single vessel, as was done in the *syn*-aldol reaction, were unsuccessful. The rate of hydrolysis during these experiments was too slow to be useful. Acceleration of the reaction rate by increasing temperature or changing solvent mixtures was unsuccessful as they were plagued with lower diastereomeric excesses. Fortunately, the two-vessel *anti*-aldol sequence was reliable and scalable. The chiral hydroxy acids (+)-**5b** and (−)-**5b** were obtained as colorless oils without need for silica gel chromatography in >100 g quantities per batch.[27]

Protection of the secondary alcohol as the *tert*-butyldimethylsilyl ether for downstream applications was the final task of our synthetic sequence (Scheme 4). Preliminary attempts utilized classical conditions involving *tert*-butyldimethylsilyl chloride and imidazole. These reactions were slow and unreliable on larger scale. A rapid scan of other silylating agents revealed that *tert*-butyldimethylsilyl triflate[28] as a superior reagent. The reaction was allowed to proceed to a bis-silylated species (ester/ether) followed by aqueous workup to remove residual triflic acid. Direct saponification of the silyl ester was accomplished with potassium carbonate in a binary mixture of THF/MeOH to provide amino acids (**1a**,**b**) in good yield (83–99%). This procedure is general for all stereoisomers, routinely providing >250 g of product per batch.



Scheme 4. Synthesis of γ-amino acids **1a**,**b**.

Confident in our ability to rapidly access large quantities of all stereoisomers of γ-amino acid **1**, we turned our attention to diversifying the carboxyl terminus. Converting the electrophilic carboxylate to a variety of masked amine or alcohol derivatives expands the utility of the chiral synthon (Scheme 5). Amidation of (+)-**1b** with methylamine followed by carbonyl reduction with borane methyl sulfide provided secondary amine **6** in two steps (79% yield). Alternatively, Curtius rearrangement of the acid (−)-**1a** provided protected amine **7** without stereochemical erosion in 79% yield. Chemoselective reduction of (+)-**1a** was accomplished via the mixed anhydride to provide the alcohol, which was converted to the corresponding tosylate and treated with tetra-*n*-butylammonium azide to provide compound **8** in 60% overall yield. The alcohol was also esterified with benzoyl chloride and pyridine to provide the orthogonally protected substrate **9**[29] in 70% yield from the acid. Introduction of these chemotypes did not greatly increase molecular weight or require lengthy synthetic sequences thus increasing their utility for downstream activities. The linear templates **6**–**9** have two stereocenters and three functional groups that are orthogonally protected for rapid access to a variety of chemotypes through appropriate functional group pairing strategies.



Scheme 5. Preparation of orthogonally protected chiral synthons.

3. Conclusion

The preparation of all possible stereoisomers of a versatile β-hydroxy γ-amino acid has been accomplished by two complementary aldol reactions. A one-pot protocol has been developed to access the 1,2-*syn* diastereomeric class (**1a**) in high yield and enantiomeric excess. Significant quantities (>90 g) of each stereoisomer have been prepared in single batches. Elaboration of these chiral acids to different orthogonally protected amines could be achieved in short order. The application of these chiral building blocks to a variety of build/couple/pair strategies for DOS has been reported[6,30] and is the focus of ongoing work.

4. Experimental section

4.1. General procedure

All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under vacuum (~0.5 mmHg) and purged with N_2 prior to use. Unless noted otherwise, reagents were introduced into the reaction vessels using syringe and septum techniques under a positive flow of N_2. Air- and/or moisture-sensitive solids were transferred in a glove bag. Unless otherwise noted, reactions were stirred with a Teflon™ covered magnet and carried out at room temperature (rt). Concentration refers to the removal of solvent under reduced pressure using a rotary evaporator. Silica gel flash column chromatography was performed using 60 Å (230–400 mesh ASTM) silica gel as the stationary phase on Teledyne ISCO Rf companion purification systems. Cerium ammonium molybdate was used as the primary thin layer chromatography (TLC) staining reagent. ^{1}H NMR spectra were collected on either a Bruker 300 MHz spectrometer or a Varian Inova 500 MHz spectrometer. All proton chemical shifts are reported in parts per million (ppm) with the solvent reference as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, hex=hextet, m=multiplet, br=broad), coupling constants (Hz), and integration. ^{13}C NMR (100 MHz) spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm with

the solvent reference as the internal standard ($CDCl_3$: 77.2 ppm). Melting points were reported uncorrected. Compound purity was determined by Waters Acquity HPLC analysis monitored at 210 nm. High resolution exact mass spectrometry was determined by Bruker Daltonics APEXIV 4.7 T Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Enantiomeric ratios were determined by chiral SFC. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. 29 Samson Ave. Madison, NJ 07940 and are reported in percent abundance.

4.2. Detailed synthetic protocols

*4.2.1. tert-Butyl methyl(2-oxoethyl)carbamate (**2**).* A flame-dried 3 L, 3-neck round bottom flask containing a mechanical stirrer (central port), internal temperature probe and addition funnel was charged with oxalyl chloride (176 mL, 2.01 mol) and CH_2Cl_2 (634 mL). The flask was cooled to −70 °C and DMSO (286 mL, 4.02 mol) was added over 2.5 h at a rate that maintained an internal temperature below −65 °C. The mixture was then stirred for an additional 15 min, after which *tert*-butyl 2-hydroxyethyl(methyl)carbamate[12] (235 g, 1.34 mol) in CH_2Cl_2 (700 mL) was added over 1 h, followed by slow addition of Et_3N (841 mL, 6.04 mol) over 30 min. Both of these reactants were added at a rate that did not cause an increase in internal temperature. After addition of the alcohol solution the reaction was cloudy. Upon initial addition of Et_3N the reaction became colorless/clear however at the end the reaction was milky white. The reaction was monitored by TLC (Hex/EtOAc 1:1) until the reaction was deemed complete (2.5 h additional, −70 °C). Saturated aqueous sodium bicarbonate solution (500 mL) was then introduced to quench the reaction at −78 °C. (Note: Quenching is fairly exothermic and thus should be done slowly.) The reaction was warmed to rt and the phases were separated. The combined organics were washed with water, dried over $MgSO_4$, and concentrated (upon concentration, some small amounts of precipitate (presumably Et_3N/HCl salt) were observed however this small amount did not impede distillation or effect final purity.) Distillation (87–89 °C, 3 mmHg) provided aldehyde **2** (200 g, 128 mmol) as a colorless oil, which matched all data reported by Kato and co-workers.[12]

*4.2.2. (2R,3R)-4-(tert-Butoxy-carbonyl(methyl)amino)-3-hydroxy-2-methylbutanoic acid (**5a**).* A jacketed 5 L, 3-neck round bottom flask was fitted with an overhead mechanical stirrer, internal temperature probe, and recirculating chiller. Under a positive flow of N_2, the reactor was charged with (*R*)-4-benzyl-3-propionyloxazolidin-2-one **3a** (86.0 g, 367 mmol) followed by CH_2Cl_2 (835 mL) and toluene (430 mL). The colorless solution was cooled to an internal temperature of −10 °C and degassed with nitrogen for 30 min. Dibutylboron triflate (405 mL, 405 mmol, 1 M in toluene) was added dropwise, maintaining an internal temperature below 0 °C. Next, triethylamine (66.5 mL, 478 mmol) was added dropwise and the resulting enolate solution was stirred at −5 °C for 90 min. Afterward, *tert*-butyl methyl(2-oxoethyl)carbamate **2** (68.0 mL, 404 mmol) was added dropwise, keeping the internal temperature below 0 °C. Upon complete addition, the light yellow solution was stirred at −5 °C for 90 min. The solution was cooled further to −10 °C and quenched by the slow addition of MeOH (428 mL) followed by a solution of THF/H_2O_2 (1.23 L, 2:1) that changed the yellow homogenous solution to a biphasic milky-white suspension. (Note: The initial rapid exotherm induced by the peroxide addition can be minimized by initial dropwise addition until no further exotherm is observed.) The reaction was stirred at −10 °C for 90 min at which time both layers became homogeneous. Solid lithium hydroxide (77.0 g, 1.84 mol) was then added to the biphasic mixture and the mixture was allowed to warm to ambient temperature over 12 h. Excess peroxides were reduced by the careful addition of solid Na_2SO_3 and organic solvents were removed in vacuo. The slurry was dissolved in dichloromethane and the organic layer was washed with aqueous NaOH (1.0 M, 1 L) and brine (100 mL). The aqueous layer was back extracted with CH_2Cl_2 (2×100 mL) to remove the oxazolidinone. The combined aqueous layers were cooled to 0 °C, agitated with a magnetic stir bar and then carefully acidified with concentrated HCl (12 M) to pH 4. The aqueous layer was extracted with EtOAc (3×600 mL). The combined organics were dried over $MgSO_4$ and concentrated to provide (2*R*,3*R*)-4-(*tert*-butoxycarbonyl(methyl)amino)-3-hydroxy-2-methylbutanoic acid (−)-**5a** (74.4 g, 301 mmol, 82% yield) as a colorless oil.[31] TLC: R_f=0.31 (10% MeOH in DCM). $[\alpha]_D^{20}$ −21.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 4.07 (dt, *J*=10, 5 Hz, 1H), 3.41 (br s, 1H), 3.22 (d, *J*=15 Hz, 1H), 2.91 (s, 3H), 2.62 (ddd, *J*=16, 10, 5 Hz, 1H), 1.45 (s, 9H), 1.25 (d, *J*=10 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 178.0, 80.6, 71.3, 53.1, 43.1, 36.1, 28.6, 11.6. HRMS (ESI) calcd for $C_{11}H_{21}NO_5Na$ $[M+Na]^+$: 270.1312. Found: 270.1312.

*4.2.3. (2S,3S)-(+)-**5a**.* $[\alpha]_D^{20}$ +16.8 (*c* 1.0, $CHCl_3$).

*4.2.4. 1-Phenyl-2-(N,2,4,6-tetramethylphenylsulfonamido)propyl-4-(tert-butoxycarbonyl(methyl)amino)-3-hydroxy-2-methylbutanoate (**4b**).* An oven dried, 3-L, 3-neck round bottom flask was equipped with mechanical stirrer and temperature probe. Under a positive flow of N_2, the vessel was charged with (1*R*,2*S*)-1-phenyl-2-(*N*,2,4,6-tetramethylphenylsulfonamido) propyl propionate (109 g, 270 mmol) and CH_2Cl_2 (932 mL). The reaction was cooled to −78 °C with constant agitation at which point Et_3N (112 mL, 810 mmol) was added dropwise (over ~10 min), maintaining an internal reaction temperature no greater than −65 °C. After 15 min of additional stirring, a solution of dicyclohexylboron triflate (1 M in CH_2Cl_2, 176 g, 540 mmol) was added dropwise (over ~30 min), maintaining an internal reaction temperature below −67 °C. The resulting yellow enolate reaction solution was stirred at −78 °C for 2 h additional. At this point *tert*-butyl methyl(2-oxoethyl)carbamate (68.1 mL, 405 mmol) was added dropwise at a rate so as to maintain an internal temperature below −67 °C (~15 min). The reaction mixture was stirred at −78 °C for 2 h and then was allowed to warm to 0 °C for 1 h. The reaction was quenched by the addition of MeOH (1.09 L) and pH 7 buffer (130 mL). Next aqueous H_2O_2 (130 mL, 1.5 mol, 35% by wt) was slowly added such that the internal reaction temperature did not exceed 20 °C. After the addition was completed, the mixture was allowed to warm to ambient temperature where it was stirred for 1 h. The resultant slurry was then concentrated in vacuo and the resulting oil was partitioned between water (550 mL) and CH_2Cl_2 (500 mL). The aqueous layer was extracted with CH_2Cl_2 (4×300 mL) and the combined organic layers were washed with water (100 mL) followed by brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed to yield 1-phenyl-2-(*N*,2,4,6-tetramethylphenylsulfonamido)propyl-4-(*tert*-butoxycarbonyl(methyl)amino)-3-hydroxy-2-methylbutanoate as a yellow oil. While the crude product was carried on to the next step without further purification, an analytical sample was obtained by chromatography on silica gel. (*S*,*R*,*R*,*S*)-(−)-**4b**: TLC: R_f=0.34 (30% EtOAc in hexanes). $[\alpha]_D^{20}$ −10.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.20 (d, *J*=7.4 Hz, 2H), 7.05 (d, *J*=7.5 Hz, 1H), 6.87 (s, 1H), 5.79 (d, *J*=5.3 Hz, 1H), 4.07 (s, 1H), 3.90 (s, 1H), 3.30 (s, 2H), 2.90 (s, 3H), 2.78 (s, 3H), 2.68–2.56 (m, 1H), 2.45 (s, 6H), 2.29 (s, 3H), 1.45 (s, 9H), 1.31 (d, *J*=6.8 Hz, 2H), 1.19 (d, *J*=7.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 173.8, 142.5, 140.6, 138.3, 132.9, 132.1, 128.6, 128.1, 126.5, 126.3, 80.2, 78.4, 73.1, 58.8, 55.9, 53.3, 47.3, 44.3, 36.3, 35.7, 28.6, 25.7, 24.2, 22.7, 20.9, 13.6, 12.3, 8.9. HRMS (ESI) calcd for $C_{21}H_{30}N_2O_6Na$ $[M+Na]^+$: 429.1996. Found: 429.2000.

*4.2.5. (R,S,S,R)-(+)-**4b**.* $[\alpha]_D^{20}$ +6.42 (*c* 1.0, $CHCl_3$).

*4.2.6. (2R,2S)-4-(tert-Butoxycarbonyl(methyl)amino)-3-hydroxy-2-methylbutanoic acid (**5b**).* A 3-neck round bottom flask was

equipped with an overhead stirrer, an internal temperature probe and an addition funnel. The vessel was charged with the crude 1-phenyl-2-(*N*,2,4,6-tetramethylphenylsulfonamido)propyl-4-(*tert*-butoxycarbonyl-(methyl)amino)-3-hydroxy-2-methyl-butanoate (202 g, 350 mmol, 1.0 equiv) and 1:1 *t*-BuOH/MeOH (4.5 L) was added and cooled to 0 °C. A solution of H_2O_2 (35% in water, 184 mL, 2101 mmol, 6.0 equiv) was added via addition funnel, followed by aqueous NaOH (1.0 M, 1051 mL, 1051 mmol, 3.0 equiv), which was added at such a rate that the internal temperature did not rise above 10 °C. The mixture was warmed to rt slowly and allowed to stir overnight. Additional H_2O_2 (40 mL) and aqueous NaOH (200 mL) solutions were added at 0 °C to drive the reaction to completion and the organic solvents were then removed in vacuo. The resulting aqueous layer was diluted with water (500 mL) and extracted with EtOAc (4×400 mL) to remove the auxiliary. The resulting aqueous layer was then acidified with 6 M HCl to pH 4 and extracted with EtOAc (5×500 mL). This second set of EtOAc extracts were combined, dried ($MgSO_4$), filtered, and concentrated. While the crude product was carried on to the next step without further purification, an analytical sample was obtained by chromatography on silica gel. (2*R*,3*S*)-(+)-**5b**: $[\alpha]_D^{20}$ +2.1 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 3.99 (s, 1H), 3.91 (dd, *J*=5.7, 11.4 Hz, 1H), 3.39 (m, 1H), 2.95 (s, 0.5×3H), 2.93 (s, 0.5×3H), 2.59 (dd, *J*=6.2, 12.0 Hz, 1H), 1.48 (s, 0.5×9H), 1.47 (s, 0.5×9H), 1.28 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 181.1, 158.2, 81.0, 72.6, 53.4, 43.8, 36.2, 28.7, 15.0. HRMS (ESI) calcd for $C_{11}H_{21}NO_5Na$ $[M+Na]^+$: 270.1312. Found: 270.1312.

*4.2.7. (2S,3R)-(−)-**5b**.* $[\alpha]_D^{20}$ −1.9 (*c* 1.0, $CHCl_3$).

*4.2.8. General reaction protocol for TBS protection. 4-(tert-Butoxycarbonyl(methyl)amino)-3-(tert-butyldimethylsilyloxy)-2-methyl butanoic acid (**1a**).* An oven dried, 5 L 3-neck round bottom flask equipped with magnetic stirrer and internal temperature probe was charged with 4-(*tert*-butoxycarbonyl (methyl)amino)-3-hydroxy-2-methylbutanoic acid **5a** (1.0 equiv), CH_2Cl_2 (concentration of **5a**=0.1 M and 2,6-lutidine (3.0–5.0 equiv)) under a positive flow of N_2. The reaction mixture was cooled to −78 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (2.2–3.0 equiv) was added dropwise over 20 min. The reaction mixture was stirred at −78 °C for 1 h, quenched with aqueous satd $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with aqueous satd NH_4Cl and brine, dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was dissolved in MeOH and THF and cooled to 0 °C. An aqueous solution of K_2CO_3 (1.5–2.2 equiv) was added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated to remove volatile solvents and the remaining aqueous layer was extracted with EtOAc. The organic layer was washed with 1 N HCl, then dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the crude product as a clear oil, which was co-evaporated with toluene to remove excess TBSOH and dried to provide the product **1a** as a clear oil.

Following the general reaction protocol (2*R*,3*R*)-**5a** (180 g, 728 mmol, 1.0 equiv) was reacted with TBSOTf (502 mL, 2.18 mol, 3.0 equiv) and 2,6-lutidine (424 mL, 3.64 mol, 5.0 equiv) in CH_2Cl_2 (3.5 L), and worked up with aqueous K_2CO_3 (151 g in 750 mL, 1090 mmol, 1.5 equiv) and MeOH (1475 mL) in THF (1475 mL) to provide pure product (2*R*,3*R*)-**1a** (260 g, 99%) as a clear oil. (2*R*,3*R*)-(−)-**1a**: TLC: R_f=0.70 (33% EtOAc in hexanes). $[\alpha]_D^{20}$ −29.1 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 4.32–4.22 (m, 1H), 3.55–3.33 (m, 1H), 3.09 (dd, *J*=6.7, 14.2 Hz, 1H), 2.89 (s, 3H), 2.69–2.41 (m, 1H), 1.47 (s, 9H), 1.23 (d, *J*=7.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 179.3, 156.1, 80.2, 71.6, 53.0, 43.3, 36.4, 26.1, 18.2, 10.8, −4.30, −4.63. HRMS (ESI) calcd for $C_{17}H_{25}NO_5SiNa$ $[M+Na]^+$: 384.2177. Found: 384.2173.

*4.2.9. (2S,3S)-(+)-**1a**.* $[\alpha]_D^{20}$ +23.3 (*c* 0.9, $CHCl_3$).

*4.2.10. (2R,3S)-(−)-**1b**.* Following the general reaction protocol (2*R*,3*S*)-**5b** (58.7 g, 237 mmol, 1.0 equiv) was reacted with TBSOTf (120 mL, 522 mmol, 2.2 equiv) and 2,6-lutidine (91 mL, 783 mmol, 3.3 equiv) in CH_2Cl_2 (950 mL), and worked up with aqueous K_2CO_3 (1.6 M, 325 mL, 522 mmol, 2.2 equiv) and MeOH (500 mL) in THF (500 mL) to provide pure product (*R*,*S*)-**1b** (74.1 g, 83%) as a colorless oil. (2*R*,3*S*)-(−)-**1b**: TLC: R_f=0.67 (33% EtOAc in hexanes). $[\alpha]_D^{20}$ −3.2 (*c* 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 4.17 (br s, 1H), 3.35 (dd, *J*=14.5, 6.0 Hz, 1H), 3.25 (br s, 1H), 2.90 (s, 3H), 2.66 (br s, 1H), 1.46 (s, 9H), 1.22 (d, *J*=7.0 Hz, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 176.8, 156.4, 80.3, 72.4, 52.9, 43.9, 36.7, 28.7, 26.0, 18.2, 12.8, −4.2, −4.7. HRMS (ESI) calcd for $C_{17}H_{25}NO_5SiNa$ $[M+Na]^+$: 384.2177. Found: 384.2167.

*4.2.11. (2S,3R)-(+)-**1b**.* $[\alpha]_D^{20}$ +3.7 (*c* 1.0, $CHCl_3$).

*4.2.12. tert-Butyl (2R,3R)-2-(tert-butyldimethylsilyl)oxy-3-(methyl-4-(methylamino)-butyl)(methyl)carbamate (**6**).* To a solution of (−)-(2*R*,3*R*)-4-(*tert*-butoxycarbonyl(methyl)amino)-3-(*tert*-butyldimethylsilyloxy)-2-methyl butanoic acid (−)-**1a** (4.49 g, 12.4 mmol), and DIEA (6.5 mL, 37 mmol, 3.0 equiv) in CH_2Cl_2 (96 mL) was added methylamine (7.45 mL, 14.9 mmol, 1.2 equiv). PyBop (6.46 g, 12.4 mmol, 1.0 equiv) was added at once and the mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and satd aqueous NH_4Cl, the phases separated, and the organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification was accomplished via silica gel chromatography to yield 11.7 g (94%) of *tert*-butyl (2*R*,3*S*)-2-(*tert*-butyldimethylsilyl)oxy-3-methyl-4-(methylamino)-4-(oxobutyl)(methyl)carbamate **S1** as an oil. ^1H NMR (500 MHz, $CDCl_3$, 50 °C) δ 6.69 (s, 0.5×1H), 6.38 (s, 0.5×1H), 4.01 (br s, 1H), 3.32 (dd, *J*=6.5, 14.2 Hz, 1H), 3.20 (dd, *J*=6.1, 14.1 Hz, 1H), 2.88 (s, 3H), 2.78 (d, *J*=4.8 Hz, 3H), 2.41 (qd, *J*=3.5, 7.2 Hz, 1H), 1.46 (s, 9H), 1.21 (d, *J*=7.3 Hz, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 174.7, 138.0, 80.0, 72.8, 53.7, 45.0, 36.8, 28.7, 26.2, 21.6, 18.2, 15.6, −4.1, −4.6.

To a chilled (0 °C) solution of amide **S1** (4.37 g, 11.7 mmol) in THF (100 mL) was added dropwise BH_3/SMe_2 (5.5 mL, 58.3 mmol, 5 equiv). The reaction mixture was warmed to rt then the flask was fitted with a reflux condenser and the reaction mixture was heated in a 65 °C oil bath for 24 h. The mixture was cooled in an ice bath and quenched with MeOH. The mixture was concentrated, the residue was dissolved in MeOH (80 mL) and a satd aqueous solution of Rochelle's salt (50 mL) was added. The mixture was heated in a 90 °C oil bath for 48 h, then cooled to rt and concentrated. The residue was diluted with EtOAc and water, the aqueous phase extracted with EtOAc and the combined organics were washed with brine, dried ($MgSO_4$) and the solvent evaporated to yield *tert*-butyl (2*R*,3*R*)-2-(*tert*-butyldimethylsilyl)oxy-3-(methyl-4-(methylamino)-butyl)(-methyl)carbamate (**6**) as a colorless oil (3.55 g, 84%). ^1H NMR (500 MHz, DMSO, 120 °C) δ 3.97 (dt, *J*=3.9, 7.7 Hz, 1H), 3.28 (dd, *J*=4.4, 14.1 Hz, 1H), 3.10 (dd, *J*=7.8, 14.1 Hz, 1H), 2.84 (s, 3H), 2.64 (dd, *J*=5.4, 11.9 Hz, 1H), 2.41 (dd, *J*=7.9, 11.9 Hz, 1H), 2.36 (s, 3H), 1.89–1.78 (m, 1H), 1.43 (s, 9H), 0.94 (d, *J*=6.9 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 156.4, 73.8, 72.9, 54.9, 54.0, 52.1, 37.0, 28.7, 26.1, 18.2, 14.6, 13.9, −4.4. HRMS (ESI) calcd for $C_{18}H_{40}N_2O_3Si$ [M+H]+: 361.2886. Found: 361.2888.

*4.2.13. tert-Butyl ((2S,3R)-3-((benzyloxy)carbonyl)amino-2-(tert-butyldimethylsilyl)oxy-butyl)(methyl)carbamate (**7**).* To a solution of 4-(*tert*-butoxycarbonyl(methyl)amino)-3-(*tert*-butyldimethylsilyl-oxy)-2-methyl butanoic acid (+)-**1a** (1.15 g, 3.18 mmol) in toluene (32 mL) were added Et_3N (0.62 mL, 4.5 mmol) and DPPA (0.83 mL, 3.8 mmol). The mixture was heated to 60 °C for 3 h, then benzyl alcohol (1.65 mL, 15.9 mmol) was added and the mixture heated to reflux

overnight. The mixture was cooled and concentrated and the residue diluted with EtOAc, washed with H_2O, dried ($MgSO_4$), and the solvent evaporated. Purification was accomplished with chromatography on silica gel to provide *tert*-butyl ((2*S*,3*R*)-3-((benzyloxy)carbonyl)amino-2-(*tert*-butyldimethylsilyl)oxy-butyl)(methyl)carbamate (**7**) as a clear resin (1.18 g, 79%). $[\alpha]_D^{20}$ +4.4 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, DMSO) δ 7.38–7.28 (m, 5H), 6.24 (br s, 1H), 5.17–4.92 (m, 2H), 4.02 (br s, 1H), 3.61 (br s, 1H), 3.33 (dd, *J*=5.9, 14.3 Hz, 1H), 3.08 (dd, *J*=7.0, 14.0 Hz, 1H), 2.83 (s, 3H), 1.43 (s, 9H), 1.08 (d, *J*=6.6 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 154.7, 154.4, 136.7, 127.4, 127.0, 126.8, 78.1, 71.7, 64.7, 49.0, 34.6, 27.5, 25.2, 17.0, 13.6, −5.4. HRMS (ESI) calcd for $C_{17}H_{35}NO_5SiNa$ $[M+Na]^+$: 489.2761. Found: 489.2753.

*4.2.14. tert-Butyl-((2S,3R)-4-azido-2-((tert-butyldimethylsilyl)oxy)-3-methylbutyl)(methyl)carbamate (**8**).* To a solution of **1a** (500 mg, 1.25 mmol) in dry THF (14 mL) under N_2 and chilled to 0 °C was added Et_3N (0.23 mL, 1.7 mmol) followed by isobutyl chloroformate (0.16 mL, 1.7 mmol). The resultant suspension was stirred at ambient temperature for 2 h, then cooled to 0 °C and a solution of $NaBH_4$ (314 mg, 8.30 mmol) in water (6 mL) was added dropwise. The mixture was stirred for 2 h, warming slowly to ambient temperature. The reaction mixture was then diluted with water and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water, brine, dried (Na_2SO_4), and the solvent was evaporated. To a solution of this alcohol (362 mg, 1.04 mmol) in dry CH_2Cl_2 (10 mL) under N_2 and chilled to 0 °C was added *p*-toluenesulfonyl chloride (218 mg, 1.15 mmol) followed by Et_3N (0.44 mL, 3.1 mmol) then DMAP (13 mg, 0.10 mmol). The reaction mixture was stirred for 16 h then was quenched with water, the phases separated and the aqueous phase was washed with CH_2Cl_2. The combined organic phases were washed with satd aqueous $NaHCO_3$ (2×), then satd aqueous NH_4Cl (2×), water, brine, dried (Na_2SO_4), and the solvent evaporated to provide **S2**, which was carried on to the next step without further purification.

Tetrabutylammonium azide (567 mg, 1.99 mmol) was added to a solution of tosylate **S2** (500 mg, 0.997 mmol) in dry DMF (10 mL) under nitrogen. The reaction mixture was stirred until LC–MS indicated the disappearance of starting material. The reaction mixture was diluted with water and EtOAc and the phases separated. The aqueous phase was washed with EtOAc and the combined organics were washed with water and brine, dried (Na_2SO_4) and the solvent evaporated. Purification was accomplished via silica gel chromatography (EtOAc/hexanes) to yield *tert*-Butyl-((2S,3R)-4-azido-2-((*tert*-butyldimethylsilyl)oxy)-3-methylbutyl)(methyl)carbamate (**8**) as a colorless oil (224 mg, 0.601 mmol, 60% yield). $[\alpha]_D^{20}$ +15.5 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, DMSO, 80 °C) δ 3.99 (t, *J*=5.2 Hz, 1H), 3.42–3.17 (m, 3H), 3.06 (dd, *J*=6.1, 13.8 Hz, 1H), 2.82 (s, 3H), 1.78 (dd, *J*=6.6, 11.9 Hz, 1H), 1.42 (s, 9H), 0.92 (d, *J*=6.9 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 154.4, 78.3, 69.8, 53.3, 51.2, 35.8, 35.1, 27.7, 25.3, 17.2, 11.0, −4.9, −5.4. HRMS (ESI) calcd for $C_{17}H_{36}N_4O_3SiNa$ $[M+Na]^+$: 373.2635. Found: 373.2631.

*4.2.15. (2S,3S)-4-((tert-Butoxycarbonyl)(methyl)amino)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutyl benzoate (**9**).* To a solution of acid **1b** (1.42 g, 3.93 mmol) in dry THF (20 mL) under N_2 was added Et_3N (1.1 mL, 7.9 mmol) at 0 °C followed by isobutyl chloroformate (0.668 mL, 5.11 mmol). The resultant suspension was stirred at rt for 2 h and then chilled to 0 °C. A solution of $NaBH_4$ (892 mg, 23.6 mmol) in H_2O (17 mL) was added dropwise and the mixture was stirred for 2 h, warming slowly to rt. The reaction mixture was then diluted with H_2O and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with H_2O, brine, dried (Na_2SO_4), and the solvent was evaporated to yield **S3**, which was carried on crude to provide benzoate **9**.

To a solution of crude alcohol **S3** in dry CH_2Cl_2 (20 mL) under N_2 was added pyridine (6.4 mL) then benzoyl chloride (2.3 mL, 20 mmol). The reaction mixture was stirred overnight (16 h) then diluted with CH_2Cl_2 and 0.1 N HCl. The phases were separated and the aqueous was washed with CH_2Cl_2. The combined organics were washed with 0.1 N HCl, H_2O, brine, dried (Na_2SO_4), and the solvent evaporated. Purification was accomplished via silica gel chromatography (EtOAc/hexanes) to yield (2S,3S)-4-((*tert*-butoxycarbonyl)(methyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylbutyl benzoate (**9**) (1.24 g, 70%) as a colorless oil. $[\alpha]_D^{20}$+5.6 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, DMSO, 80 °C) δ 7.97 (d, *J*=7.5 Hz, 2H), 7.63 (t, *J*=7.2 Hz, 1H), 7.50 (t, *J*=7.5 Hz, 2H), 4.24 (d, *J*=6.9 Hz, 2H), 4.15 (t, *J*=6.0 Hz, 1H), 3.36 (dd, *J*=6.4, 14.0 Hz, 1H), 3.19 (dd, *J*=6.5, 14.0 Hz, 1H), 2.85 (s, 3H), 2.08 (dd, *J*=6.7, 13.0 Hz, 1H), 1.41 (s, 9H), 1.00 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, DMSO, 80 °C) δ 165.2, 154.5, 132.7, 129.6, 128.5, 128.2, 78.3, 69.2, 65.8, 51.4, 35.1, 27.7, 25.3, 18.4, 17.3, 9.8, −4.9, −5.5. HRMS (ESI) calcd for $C_{24}H_{41}NO_5SiNa$ $[M+Na]^+$: 474.2652. Found: 474.2652.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.06.043.

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21. After aqueous workup the aldol adduct (−)-**4a** was isolated as a colorless oil (>95% by HPLC), which could be carried forward to the subsequent hydrolysis. Alternatively, silica gel chromatography provided the adduct as a white solid from which we obtained single crystals for X-ray analysis. CCDC 828856 contains the supplementary crystallographic data for (−)-**4a**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
22. Absolute stereochemical assignment for (+)-**5a** was confirmed by X-ray crystallography. Purity was >95% by HPLC and er 99:1 by SFC. CCDC 828857 contains the supplementary crystallographic data for (+)-**5a**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
23. The total volume of the reaction after the addition of all reagents and solvents dictated the scale of the reaction. In house capabilities were initially limited to a 5-L jacketed round bottom flask. We have since transferred this protocol to a contract research organization where it has been routinely performed on >500 g scale.
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