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Synthesis of an Azido Precursor to (2*S*,5*R*)-5-Hydroxylysine Using an Asymmetric Organocatalytic Chlorination/Reduction Sequence

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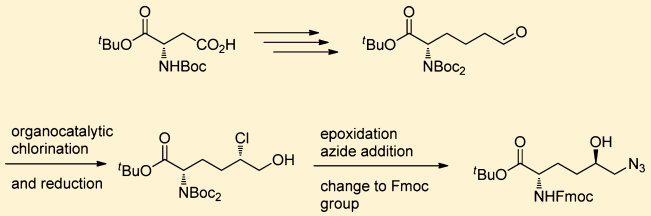
Supporting Information

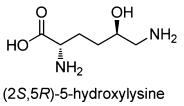
ABSTRACT: An efficient, robust, and scalable synthesis of an azido precursor to the modified amino acid (2*S*,5*R*)-5-hydroxylysine was developed on the basis of the use of a highly stereoselective organocatalytic α-chlorination-reduction protocol. The final Fmoc-protected (2*S*,5*R*)-6-azido-5-hydroxylysine derivative can be used in solid-phase peptide synthesis, providing access to proteins that contain large quantities of post-translationally modified lysine (e.g., collagens).



Collagen is by far the most abundant structural fibrous protein found in mammals. It plays an important role in the maintenance of the structural integrity of tissue and can be found in almost all organs in slightly different forms.[1] Certain proline and lysine residues in collagen are known to undergo post-translational modifications, such as hydroxylations, to give inter alia (2*S*,5*R*)-5-hydroxylysine, first discovered in protein hydrolysates.[2,3] Furthermore, hydroxylysine can also be glycosylated with either β-D-galactopyranosyl or α-D-glucopyranosyl-(1-2)-β-D-galactopyranosyl residues.[3,4] These post-translational modifications vary among the different collagen types but are believed to play a major role in a number of important processes, for example, in the regulation of collagen fibrillogenesis and the morphology of collagen.[5]

Many collagen and collagen-like proteins have also been shown to possess potential medicinal properties in various diseases.[6] Among these proteins, adiponectin is of particular interest because of its potential use as a drug candidate for the treatment of liver disease, hypertension, and obesity-related breast cancer.[7−9] In addition, an adiponectin-deficiency state has been identified in nonclinical models and was linked to the pathogenesis of type II diabetes.[10] Treatment with adiponectin to restore the circulating level in these deficiency states could be of therapeutic benefit. However, the biological activity of adiponectin was proven to depend on the post-translational modifications described above.[7] Therefore, recombinant-protein production is unlikely to result in a potential drug candidate. Furthermore, because of the structural complexity and heterogeneity of isolated adiponectin, no structure−activity relationship (SAR) studies using human adiponectin or fragments thereof have been reported to date. However, chemical synthesis provides the tools needed to synthesize enough material for biological evaluation and identification of a minimal structure capable of eliciting the desired pharmacological activity. As a first step toward the synthesis of adiponectin, a robust, reliable, high-yielding, and scalable synthesis of (2*S*,5*R*)-5-hydroxylysine suitable for subsequent glycosylation and incorporation into solid-phase peptide synthesis has to be developed.

The structure of naturally occurring (2*S*,5*R*)-5-hydroxylysine (Figure 1) was first determined in 1950,[11,12] and since then



(2*S*,5*R*)-5-hydroxylysine

Figure 1. (2*S*,5*R*)-5-Hydroxylysine.

several syntheses have been reported.[13] These approaches utilized either racemic synthesis with subsequent resolution[14,15] or chiral auxiliaries[16,17] to achieve stereoselectivity. In addition, Guichard and co-workers developed a substrate-directed asymmetric synthesis of 5-hydroxylysine.[18] However, to the best of our knowledge, there is no organocatalytic approach reported in the literature to synthesize (2*S*,5*R*)-5-hydroxylysine despite the fact that organocatalytic methodology has frequently been used as a powerful tool for the stereoselective synthesis of various bioactive compounds.[19]

In this report, we disclose a high-yielding, robust, and highly stereoselective organocatalytic approach to synthesize (2*S*,5*R*)-5-hydroxylysine using a MacMillan-type organocatalyst to perform the key step of the synthesis on a multigram scale. Our attention focused on the synthesis of azide **1** as a suitable precursor to 5-hydroxylysine for subsequent glycosylation and incorporation as a building block in solid-phase peptide synthesis. The azide at the ε-position serves as a protecting group for the amine during glycosylation and throughout solid-phase peptide synthesis and can be readily reduced to the corresponding amine upon completion of the synthesis.

It was decided to build the stereocenter at the 5-position of 5-hydroxylysine by means of a one-pot operation involving an

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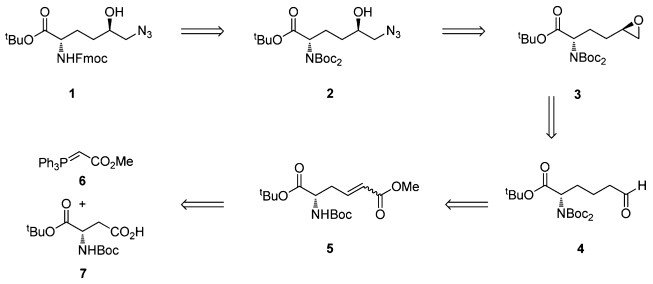
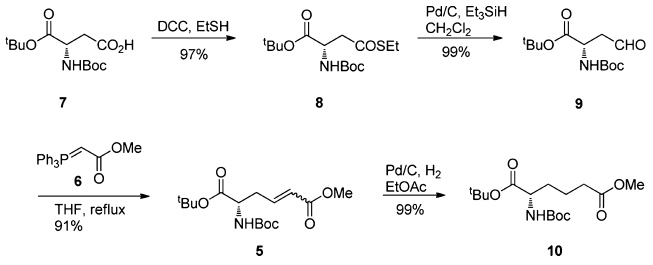
organocatalytic α-chlorination of aldehyde **4** followed by reduction to the corresponding alcohol and base-mediated epoxide formation to give **3**. After opening of the epoxide with NaN_3 to form **2**, the final steps include cleavage of the Boc group and installation of the Fmoc group to give (2*S*,5*R*)-6-azido-5-hydroxylysine **1** suitable for subsequent glycosylation and solid-phase peptide synthesis. Aldehyde **4**, in turn, could be synthesized by hydrogenation and reduction of methyl ester **5**, which is accessed by reduction of aspartic acid **7** to the corresponding aldehyde followed by Wittig reaction with methyl (triphenylphosphoranylidene)acetate **6** (Scheme 1).

Scheme 1. Retrosynthesis of (2*S*,5*R*)-6-Azido-5-hydroxylysine 1



The synthesis started with reduction of the free side-chain acid in aspartic acid **7** to the corresponding aldehyde **9**. Initial attempts to affect reduction of a mixed anhydride with sodium borohydride gave poor yields.[20] Therefore, we decided to first synthesize thioester **8** using DCC and ethanethiol and then reduce the thioester **8** with triethylsilane catalyzed by 10% Pd/C following a known procedure.[21] The desired aldehyde **9** was isolated in 96% yield over two steps and then used in a Wittig olefination with phosphorane **6**, affording an E/Z mixture of the corresponding unsaturated ester **5** in 91% yield.[21] Hydrogenolysis of **5** using hydrogen and 10% Pd/C as catalyst furnished the saturated ester **10** in quantitative yield (Scheme 2).[21]

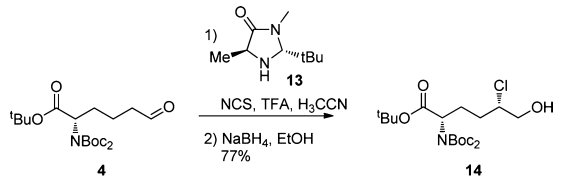
Scheme 2. Synthesis of Methyl Ester 10



To prevent cyclization at a later stage in the synthesis, a second Boc protecting group was next installed by treatment of **10** with Boc anhydride and DMAP in refluxing acetonitrile, affording the double-protected amine **11** in 98% yield (Scheme 3). The methyl ester was then reduced using sodium borohydride in ethanol,[22] and the corresponding alcohol **12** was then submitted to Swern oxidation, affording aldehyde **4** in 92% yield.

With aldehyde **4** in hand, we were ready to attempt the key one-pot stereoselective organocatalytic α-chlorination/reduction/epoxide formation sequence. This transformation was developed by MacMillan,[23] Jørgensen,[24] and Christmann[25,26] and has been applied to many different substrates with very good yields and selectivities. Therefore, in our initial attempts, we used the readily available imidazolidinone catalyst **13** (as the hydrochloride salt), developed by MacMillan,[27] with NCS as the halogen source. However, despite exploring different solvent systems and temperatures and varying amounts of catalyst and NCS, we were not able to synthesize the desired α-chlorinated product. Finally, the desired product was synthesized by using an in situ generated TFA salt of the catalyst. This was achieved by dissolving the hydrochloride salt in dichloromethane and washing with satd aqueous $NaHCO_3$ solution. The free amine (0.3 equiv) was then dissolved in acetonitrile, and an equimolar amount of TFA was added to the solution followed by NCS and aldehyde **4** at 0 °C. The progress of the reaction was monitored by ^1H NMR, and after completion of the reaction, $NaBH_4$ and ethanol were added. The resulting chloroalcohol **14** was isolated, and the stereoselectivity was determined by NMR and HPLC. Gratifyingly, only one diastereoisomer was isolated in 77% yield over these two steps[28] (Scheme 4).

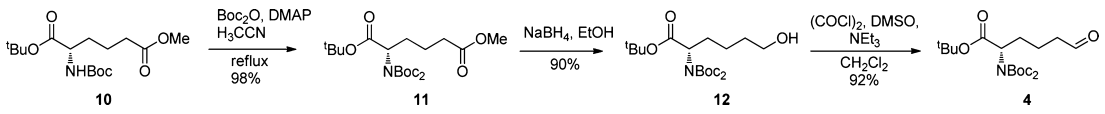
Scheme 4. Organocatalytic α-Chlorination/Reduction Sequence



Notably, the reaction time required strongly correlated with the amount of catalyst used for this transformation. Whereas the reaction was finished after 2 h using 0.3 equiv of the catalyst at 0 °C, the mixture had to be stirred for 10 h at this temperature if only 0.2 equiv of the catalyst was used and 48 h if only 0.14 equiv was used. However, it was possible to scale this reaction to 4 g of the corresponding starting aldehyde **4** without any loss of selectivity or yield. The ability to perform every reaction on a multigram scale was a necessary requirement to the synthetic route developed herein.

Having optimized the synthesis of **14** in two steps from aldehyde **4**, we next focused on the development of a three-step one-pot procedure to access the desired epoxide. Therefore, using the readily available chloroalcohol **14**, we attempted to find suitable conditions for the formation of the corresponding epoxide **3**. Unfortunately, the only product isolated using a variety of different conditions (e.g., Cs_2CO_3/EtOH, K_2CO_3/EtOH, NEt_3/DMF, KOH/EtOH/H_2O, and NaH/THF) was a

Scheme 3. Synthesis of Aldehyde 4



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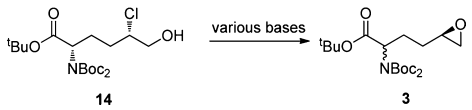
mixture of diastereoisomers formed by epimerization of the α-amino acid center upon treatment with base (Scheme 5). This

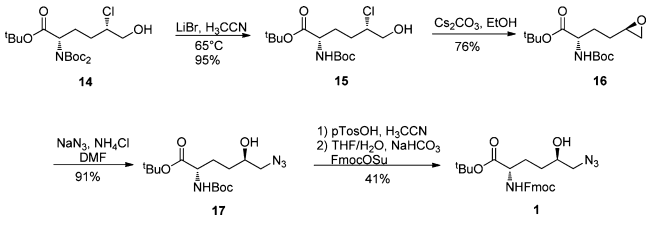
Scheme 5. Attempted Epoxidation of Chloroalcohol 14



phenomenon has been described for the basic hydrolysis of *N*,*N*-di-Boc-α-amino esters[29] and is due to the electron-withdrawing properties of the two *tert*-butyloxycarbonyl groups attached to the amino group in **14**.

Therefore, we had to revise our initial synthesis and remove one Boc group prior to epoxide formation. Use of mild reaction conditions, namely, LiBr in acetonitrile, developed by Martin and co-workers,[30] enabled selective cleavage of one of the Boc protecting groups, giving access to **15** in 95% yield. After removal of the Boc group, the acidity of the α-proton was no longer an issue, and epoxide **16** was formed using Cs_2CO_3 in ethanol in good yield (Scheme 6).

Scheme 6. Final Steps in the Synthesis of (2*S*,5*R*)-5-Hydroxylysine 1



Regioselective opening of epoxide **16** by treatment with sodium azide afforded azido alcohol **17** in high yield.[17] To use the modified lysine derivative in solid-phase peptide synthesis, the Boc group had to be replaced by a Fmoc protecting group. This was accomplished following a known procedure[31] using *para*-toluenesulfonic acid to cleave the carbamate followed by reaction with Fmoc-succinimide, yielding the desired (2*S*,5*R*)-6-azido-5-hydroxylysine **1** ready for subsequent glycosylation studies and solid-phase peptide synthesis. All of the spectroscopic and analytical data for **1** were in excellent agreement with that reported in the literature.[31]

In summary, we have developed a high-yielding, robust, multigram scale synthesis of (2*S*,5*R*)-6-azido-5-hydroxylysine (**1**) that is based on an organocatalytic α-chlorination/reduction sequence of an intermediate aldehyde. This highly selective method provides access to this post-translationally modified amino acid in an overall yield of 15% over 12 steps. The freely available imidazolidinone-organocatalyst **13** was readily transformed in situ into the active TFA salt, and use of 0.3 equiv of the TFA salt afforded the corresponding α-chloro aldehyde in only 2 h even on a multigram scale. Epoxide formation required cleavage of one of the *N*-Boc groups because of epimerization of the α-stereocenter under the basic conditions required for epoxide formation when two Boc groups were present. This new synthetic route gives access to sufficient amounts of (2*S*,5*R*)-6-azido-5-hydroxylysine **1** to carry out glycosylation studies and solid-phase peptide synthesis and will enable the synthesis of collagen-like protein sequences containing this important modified amino acid.

EXPERIMENTAL SECTION

General Methods. Dry solvents were used unless otherwise specified. All reactions were performed under an inert atmosphere maintained by a balloon of argon sealed with a rubber septum. Melting points are uncorrected. HPLC analysis was performed on a Phenomenex Gemini C_{18} column (5 μm, 4.60 × 150 mm) using a linear gradient (30−100% CH_3CN + 0.1% TFA, 25 min) and a flow rate of 1 mL/min (λ = 220, 264 nm).

***α-tert*-Butyl *β-S*-Ethyl-(*S*)-*N*-(*tert*-butoxycarbonyl)-thioaspartate (8).** To a stirred solution of aspartic acid (4.24 g, 14.7 mmol, 1.0 equiv) in abs dichloromethane (30 mL) were added DCC (3.60 g, 17.5 mmol, 1.19 equiv), ethanethiol (3.2 mL, 44.0 mmol, 3.0 equiv), and DMAP (0.18 g, 1.5 mmol, 0.10 equiv), and the suspension was stirred for 3 h at room temperature. The mixture was filtered, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica (hexanes/ethyl acetate 9:1) to give the desired thioester (4.75 g, 14.2 mmol, 97%) as a colorless oil that solidified upon standing. R_f = 0.44 (hexanes/ethyl acetate 9:1). $[\alpha]_D^{20}$ +39.9 (*c* 1.003, $CHCl_3$). mp 47−49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (d, *J* = 7.7 Hz, 1H), 4.44−4.36 (m, 1H), 3.31 (dd, *J* = 16.3, 4.6 Hz, 1H), 3.01 (dd, *J* = 16.2, 4.6 Hz, 1H), 2.95−2.80 (m, 2H), 1.44 (s, 9H), 1.43 (s, 9H), 1.23 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 169.9, 155.5, 82.5, 80.0, 51.1, 45.7, 28.4, 28.0, 23.6, 14.8. HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{28}NO_5S$, 334.1683; found, 334.1669. FT-IR: 2978, 2936, 1714, 1688, 1496, 1367, 1251, 1151, 1051, 1024, 991 cm^{-1}. The spectroscopic and analytical data for **8** were in good agreement with that reported in the literature.[21]

1-*tert*-Butyl (*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-oxobutanoate (9). To a stirred solution of the thioester (6.70 g, 20.1 mmol, 1.0 equiv) and Pd/C (0.043 g) in abs dichloromethane (50 mL) was added Et_3SiH (9.6 mL, 60.3 mmol, 3.0 equiv) quickly, and the mixture was stirred at 15−20 °C for 20 min. The mixture was filtered, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica (hexanes/ethyl acetate 85:15) to give the desired product (5.46 g, 20.0 mmol, 99%) as a colorless oil. R_f = 0.20 (hexanes/ethyl acetate 85:15). $[\alpha]_D^{20}$ −15.3 (*c* 1.500, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (d, *J* = 6.9 Hz, 1H), 4.48−4.40 (m, 1H), 2.97 (dd, *J* = 17.9 Hz, 4.9 Hz, 1H), 2.89 (dd, *J* = 17.8 Hz, 5.0 Hz, 1H), 1.41 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 170.0, 155.4, 82.6, 80.0, 49.4, 46.4, 28.3, 27.9. HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{13}H_{24}NO_5$, 274.1652; found, 274.1645. FT-IR: 2978, 2931, 1713, 1501, 1367, 1249, 1151, 1053, 847 cm^{-1}. The spectroscopic and analytical data for **9** were in good agreement with that reported in the literature.[21]

1-*tert*-Butyl 6-methyl (*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-hex-4-enedioate (5). To a stirred solution of the aldehyde (0.84 g, 3.1 mmol, 1.0 equiv) in abs THF (20 mL) was added the phosphorane (1.53 g, 4.6 mmol, 1.5 equiv), and the mixture was refluxed for 18 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica (hexanes/ethyl acetate 9:1) to give the desired product (0.92 g, 2.8 mmol, 91%) as a colorless solid. R_f = 0.26 (hexanes/ethyl acetate 9:1). $[\alpha]_D^{20}$ +3.3 (*c* 1.200, EtOH). mp 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87−6.80 (m, 1H), 5.90−5.84 (m, 1H), 5.12 (d, *J* = 7.0 Hz, 1H), 4.35−4.27 (m, 1H), 3.71 (s, 3H), 2.75−2.64 (m, 1H), 2.64−2.51 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 166.4, 155.2, 143.1, 124.3, 82.7, 80.1, 53.1, 51.7, 35.7, 28.4, 28.1. HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{16}H_{28}NO_6$, 330.1911; found, 330.1917. FT-IR: 2981, 1716, 1500, 1367, 1152, 1047, 847 cm^{-1}. The spectroscopic and analytical data for **5** were in good agreement with that reported in the literature.[21]

1-*tert*-Butyl 6-Methyl (*S*)-2-[*N*-(*tert*-butoxycarbonyl)amino]-hexanedioate (10). A solution of the enoate (4.69 g, 14.23 mmol, 1.0 equiv) and Pd/C (0.50 g) in EtOAc (40 mL) was stirred under an atmosphere of hydrogen (balloon) overnight. The mixture was filtered, and the solvent was removed under reduced pressure to give the desired product (4.7 g, 14.1 mmol, 99%) as a colorless oil. R_f = 0.17 (hexanes/ethyl acetate 9:1). $[\alpha]_D^{20}$ −6.4 (*c* 3.300, EtOAc). ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 5.05 (d, J = 7.6 Hz, 1H), 4.18−4.06 (m, 1H), 3.61 (s, 3H), 2.37−2.33 (m, 2H), 1.80−1.70 (m, 1H), 1.70−1.54 (m, 3H), 1.42 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 171.7, 155.4, 81.9, 79.6, 53.7, 51.6, 33.5, 32.3, 28.4, 28.0, 20.7. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{16}H_{30}NO_6$, 332.2068; found, 332.2066. FT-IR: 2917, 2341, 1710, 1500, 1366, 1149 cm^{-1}. The spectroscopic and analytical data for **10** were in good agreement with that reported in the literature.[21]

1-*tert*-Butyl 6-Methyl (*S*)-2-[*N*,*N*-di-(*tert*-butoxycarbonyl)-amino]hexanedioate (11). To a solution of the mono-Boc derivative (5.38 g, 16.2 mmol, 1.0 equiv) in abs acetonitrile (80 mL) was added DMAP (0.79 g, 6.5 mmol, 0.4 equiv) followed by Boc-anhydride (35.4 g, 162.4 mmol, 10.0 equiv), and the mixture was refluxed overnight. TLC showed that starting material was still present; therefore, another portion of Boc_2O was added, and the mixture was refluxed overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash chromatography on silica (hexanes/ethyl acetate 9:1) to give the desired product (6.87 g, 15.9 mmol, 98%) as an orange oil. R_f = 0.25 (hexanes/ethyl acetate 9:1). $[\alpha]_D^{20}$ −21.6 (c 1.000, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.71 (dd, J = 9.7, 5.2 Hz, 1H), 3.65 (s, 3H), 2.42−2.26 (m, 2H), 2.11−2.00 (m, 1H), 1.95−1.84 (m, 1H), 1.72−1.62 (m, 2H), 1.50 (s, 18H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 169.8, 152.6, 82.9, 81.4, 58.7, 51.6, 33.8, 28.8, 28.2, 28.1, 22.0. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{38}NO_8$, 432.2592; found, 432.2577. FT-IR: 2977, 2535, 2159, 1977, 1737, 1699, 1366, 1235, 849 cm^{-1}.

1-*tert*-Butyl (*S*)-2-[*N*,*N*-di-(*tert*-Butoxycarbonyl)amino]hexan-6-ol (12). To a solution of the methyl ester (5.24 g, 12.1 mmol, 1.0 equiv) in abs EtOH (80 mL) at 0 °C was added $NaBH_4$ (2.30 g, 60.7 mmol, 5.0 equiv) portionwise, and the mixture was stirred at room temperature overnight. The reaction was cautiously quenched by addition of water and satd aqueous NH_4Cl, ethyl acetate was added, and the mixture was washed with water and brine. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica (hexanes/ethyl acetate 3:1) to give the desired product (4.43 g, 10.9 mmol, 90%) as a colorless oil. R_f = 0.15 (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ −16.4 (c 1.000, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (dd, J = 9.5, 5.4 Hz, 1H), 3.62 (t, J = 6.5 Hz, 2H), 2.11−2.00 (m, 1H), 1.90−1.79 (m, 1H), 1.67−1.50 (m, 4H), 1.49 (s, 18H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 152.7, 82.9, 81.3, 62.7, 58.9, 32.4, 29.0, 28.1, 28.1, 22.7. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{20}H_{38}NO_7$, 404.2643; found, 404.2631. FT-IR: 2978, 2534, 2161, 1975, 1733, 1699, 1457, 1366, 1235, 1142, 850 cm^{-1}.

1-*tert*-Butyl (*S*)-2-[*N*,*N*-di-(*tert*-Butoxycarbonyl)amino]-6-oxohexaneoate (4). To a solution of DMSO (3.0 mL, 42.9 mmol, 4.0 equiv) in dichloromethane (35 mL) at −78 °C was added oxalyl chloride (1.81 mL, 21.4 mmol, 2.0 equiv) followed by the alcohol (4.33 g, 10.7 mmol, 1.0 equiv) dissolved in abs dichloromethane (20 mL). The mixture was stirred at −78 °C for 30 min, triethylamine (11.95 mL, 85.8 mmol, 8.0 equiv) was added, and the mixture was stirred at −45 °C for 1 h. The reaction was quenched by addition of satd aqueous NH_4Cl solution, the aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with water and brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica (hexanes/ethyl acetate 3:1) to give the desired product (4.05 g, 10.1 mmol, 92%) as a pale-yellow oil. R_f = 0.56 (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ −21.0 (c 1.000, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (t, J = 1.6 Hz, 1H), 4.70 (dd, J = 9.5, 5.3 Hz, 1H), 2.55−2.37 (m, 2H), 2.11−2.00 (m, 1H), 1.95−1.83 (m, 1H), 1.72−1.62 (m, 2H), 1.49 (s, 18H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 169.7, 152.6, 83.0, 81.5, 58.6, 43.5, 28.8, 28.1, 28.1, 19.2. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{20}H_{36}NO_7$, 402.2486; found, 402.2466. FT-IR: 2978, 2160, 1732, 1699, 1457, 1366, 1235, 1145, 1123, 850 cm^{-1}.

1-*tert*-Butyl (2*S*,5*S*)-6-Hydroxy-5-chloro-2-[(*N*,*N*-di-*tert*-butoxycarbonyl)amino]hexanoate (14). A solution of the hydrochloride salt of the catalyst (0.39 g, 1.9 mmol, 0.2 equiv) was dissolved in dichloromethane (5 mL) and washed with a satd solution of $NaHCO_3$ (5 mL), the aqueous phase was extracted with dichloromethane (3 × 5 mL), the combined organic layers were dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. To an ice-cold solution of the catalyst (0.32 g, 1.9 mmol, 0.2 equiv), TFA (0.15 mL, 1.9 mmol, 0.2 equiv) and NCS (1.53 g, 11.4 mmol, 1.2 equiv) in acetonitrile (12 mL) at 0 °C and the aldehyde (3.83 g. 9.5 mmol, 1.0 equiv) dissolved in acetonitrile (12 mL) were added, and the mixture was stirred for 10 h. (The progress of the reaction was monitored by ^{1}H NMR.) Then, $NaBH_4$ (1.08 g, 28.6 mmol, 3.0 equiv) and EtOH (3.0 mL) were added, and the mixture was stirred another 30 min at 0 °C. The mixture was extracted with diethyl ether, the combined organic layers were washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica (hexanes/ethyl acetate 3:1) to give the chloro alcohol (3.24 g, 7.4 mmol, 77%) as a colorless oil. R_f = 0.31 (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ −19.8 (c 1.000, $CHCl_3$). HPLC: t_R = 15.367 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.71 (dd, J = 5.0, 5.0 Hz, 1H), 4.08−4.01 (m, 1H), 3.77 (dd, J = 11.9, 4.0 Hz, 1H), 3.68 (dd, J = 12.0, 6.8 Hz, 1H), 2.24−2.05 (m, 3H), 1.91−1.81 (m, 1H), 1.77−1.65 (m, 1H), 1.50 (s, 18H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 152.6, 83.2, 81.6, 67.1, 64.4, 58.2, 31.2, 28.2, 28.1 26.2. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{20}H_{37}ClNO_7$, 438.2253; found, 438.2241. FT-IR: 2981, 2529, 2159, 2035, 1738, 1368, 1267, 1143, 801 cm^{-1}.

1-*tert*-Butyl (2*S*,5*S*)-6-Hydroxy-5-chloro-2-[(*N*-*tert*-butoxycarbonyl)amino]hexanoate (15). To a stirred solution of the alcohol (0.82 g, 1.9 mmol, 1.0 equiv) in acetonitrile (25 mL) was added LiBr (0.32 g, 3.7 mmol, 2.0 equiv), and the mixture was stirred at 70 °C overnight. The solvent was removed under reduced pressure, and the crude material was purified by flash chromatography on silica (hexanes/ethyl acetate 3:1) to give the desired product (0.59 g, 1.8 mmol, 94%) as a colorless oil. R_f = 0.27 (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ +1.9 (c 1.000, $CHCl_3$). HPLC: t_R = 10.933 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (d, J = 7.0 Hz, 1H), 4.24 − 4.15 (m, 1H), 4.08 − 3.98 (m, 1H), 3.75 (dd, J = 5.4, 5.4 Hz, 1H), 3.68 (dd, J = 6.1, 6.1 Hz, 1H), 2.30 (bs, 1H), 2.00−1.78 (m, 3H), 1.74−1.61 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 155.7, 82.4, 80.0, 67.0, 63.9, 53.3, 30.0, 28.4, 28.1. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{15}H_{29}ClNO_5$, 338.1729; found, 338.1743. FT-IR: 2979, 2492, 2160, 2035, 1977, 1699, 1520, 1452, 1394, 1267, 1249, 1154 cm^{-1}.

1-*tert*-Butyl (2*S*,5*R*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-hexane-5-oxiran (16). To a stirred solution of the alcohol (0.59 g, 1.8 mmol, 1.0 equiv) in ethanol (12 mL) was added Cs_2CO_3 (0.58 g, 1.8 mmol, 1.0 equiv), and the mixture was stirred at room temperature overnight. Water was added, the mixture was extracted with ethyl acetate, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica (hexanes/ethyl acetate 3:1) to give the product (0.38 g, 1.25 mmol, 71%) as a colorless oil. R_f = 0.40 (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ +17.1 (c 1.000, $CHCl_3$). HPLC: t_R = 11.275 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (d, J = 7.1 Hz, 1H), 4.23−4.13 (m, 1H), 2.94−2.88 (m, 1H), 2.74 (dd, J = 4.9, 4.1 Hz, 1H), 2.47 (dd, J = 5.0, 2.6 Hz, 1H), 2.01−1.90 (m, 1H), 1.75−1.65 (m, 1H), 1.65−1.53 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 155.5, 82.1, 79.8, 53.8, 51.8, 47.2, 29.4, 28.5, 28.4, 28.1. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{15}H_{28}NO_5$, 302.1962; found, 302.1962. FT-IR: 3360, 2977, 2932, 1711, 1517, 1453, 1393, 1366, 1247, 1153, 1049, 847 cm^{-1}.

1-*tert*-Butyl (2*S*,5*R*)-6-Azido-2-[*N*-(*tert*-butoxycarbonyl)-amino]-5-hydroxyhexanoate (17). To a stirred solution of the epoxide (0.38 g, 1.26 mmol, 1.0 equiv) in abs DMF (8 mL) were added sodium azide (0.82 g, 12.5 mmol, 10.0 equiv) and NH_4Cl (0.067 g, 1.26 mmol, 1.0 equiv), and the mixture was heated at 60 °C overnight. Water was added, the mixture was extracted with diethyl ether (2 × 10 mL), the combined organic phases were washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash

chromatography on silica (hexanes/ethyl acetate 3:1) to give the desired product (0.32 g, 0.93 mmol, 74%) as a colorless oil. R_f = 0.35 (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ +12.2 (*c* 1.000, $CHCl_3$). HPLC: t_R = 11.150 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (d, *J* = 6.8 Hz, 1H), 4.29−4.17 (m, 1H), 3.86−3.75 (m, 1H), 3.31 (dd, *J* = 12.8, 3.8 Hz, 1H), 3.25 (dd, *J* = 12.4, 6.7 Hz, 1H), 3.14−3.04 (m, 1H), 2.01−1.90 (m, 1H), 1.73−1.61 (m, 1H), 1.59−1.51 (m, 2H), 1.46 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 155.9, 82.3, 80.2, 70.6, 57.2, 53.5, 30.0, 29.8, 28.4, 28.1. HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{29}N_4O_5$, 345.2132; found, 345.2137. FT-IR: 3071, 2974, 2489, 2159, 2101, 1972, 1702, 1514, 1368, 1263, 1155 cm^{-1}. The spectroscopic and analytical data for **17** were in good agreement with that reported in the literature.[18]

1-*tert*-Butyl (2*S*,5*R*)-6-Azido-2-[((9*H*-fluoren-9-ylmethoxy)-carbonyl)amino]-5-hydroxy-hexanoate (1). To a stirred and cooled (0 °C) solution of the Boc-amine (2.27 g, 6.6 mmol, 1.0 equiv) in acetonitrile (30 mL) was added p-TsOH monohydrate (2.50 g, 13.1 mmol, 2.0 equiv), and the mixture was stirred for 2 h. The reaction was stirred for 6 h at ambient temperature and quenched with 1 M NH_4OH solution (200 mL), and the mixture extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica (ethyl acetate +0.5% NEt_3) to give the desired product (0.66 g, 2.7 mmol, 41%) as a colorless solid. R_f = 0.12 (ethyl acetate +0.1% NEt_3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83−3.75 (m, 1H), 3.42 (dd, *J* = 7.7, 4.0 Hz, 1H), 3.30 (dd, *J* = 12.4, 6.5 Hz, 1H), 3.23 (dd, *J* = 12.4, 4.9 Hz, 1H), 1.91−1.67 (m, 3H), 1.67−1.54 (m, 1H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 81.8, 69.9, 56.8, 54.1, 31.2, 30.6, 28.2. The amine (0.66 g, 2.7 mmol, 1.0 equiv) was then dissolved in THF (4 mL) and H_2O (4 mL), $NaHCO_3$ (0.45 g, 5.4 mmol, 2.0 equiv) was added followed by addition of FmocOSu (1.09 g, 3.2 mmol, 1.2 equiv) dissolved in the minimum amount of THF, and the mixture was stirred overnight at room temperature. THF was removed under reduced pressure, ethyl acetate was added, the mixture was washed with water and 1 M $KHSO_4$, the organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica (dichloromethane to dichloromethane/methanol 170:1) to give the desired product (1.26 g, 2.7 mmol, quant.) as a colorless oil. R_f = 0.13 (hexanes/ethyl acetate 3:1). $[\alpha]_D^{20}$ +7.5 (*c* 1.700, $CHCl_3$). HPLC: t_R = 15.558 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.35−7.26 (m, 2H), 5.51 (d, *J* = 7.7 Hz, 1H), 4.41 (d, *J* = 7.0 Hz, 2H), 4.32 (q, *J* = 6.6 Hz, 1H), 4.22 (t, *J* = 6.9 Hz, 1H), 3.85−3.76 (m, 1H), 3.33 (dd, *J* = 12.4, 3.7 Hz, 1H), 3.26 (dd, *J* = 12.3, 6.9 Hz, 1H), 2.67−2.60 (m, 1H), 2.08−1.96 (m, 1H), 1.79−1.67 (m, 1H), 1.59−1.51 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 156.3, 144.0, 143.9, 141.5, 127.9, 127.2, 125.2, 120.1, 82.7, 70.6, 67.2, 57.2, 53.9, 47.3, 29.8, 28.2. HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{25}H_{31}N_4O_5$, 467.2289; found, 467.2299. FT-IR: 3396, 2931, 2328, 2101, 1706, 1525, 1450, 1369, 1246, 1155, 741 cm^{-1}. The spectroscopic and analytical data for **1** were in good agreement with that reported in the literature.[31]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds and HPLC traces for compounds after organocatalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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