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Stereodivergent approach to both *syn*- and *anti*-isomers of γ-amino-β-hydroxy acids: (3*S*,4*S*)- and (3*R*,4*S*)-AHPPA derivatives

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ABSTRACT

A stereodivergent approach employing an *N*-hydroxymethyl group has been utilized to produce both diastereomeric derivatives of (3*S*,4*S*)-AHPPA **3** and (3*R*,4*S*)-AHPPA **4**, via an intramolecular conjugate addition and an intramolecular epoxidation, respectively. The selectivity of the intramolecular conjugate addition was more than 10:1 while that of the intramolecular epoxidation was more than 1:20.

1. Introduction

γ-Amino-β-hydroxy acids are frequent motifs found in a number of natural and synthetic compounds with various biological activities. As a result, the stereoselective syntheses of these compounds have attracted a lot of attention.[1] Among others, both the *syn*- and *anti*-isomers of 4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) are of natural occurrence as key constituents of pharmaceutically important molecules. Compound (3*S*,4*S*)-AHPPA **1** is a common constituent of many biologically active compounds such as the ahpatinins, tasiamide B, thalassospiramide B, and other protease inhibitors (Fig. 1).[2] Meanwhile, *N*-methyl-(3*R*,4*S*)-AHPPA **2** is an amino acid constituent of hapalosin, which has multidrug-resistance reversing activity in cancer cells.[3]

Due to their potential biological activities, considerable effort toward the asymmetric synthesis of AHPPA derivatives has been expended, most of which employ separate routes to obtain each diastereomer of AHPPAs.[4,5]

Thus, it would be interesting and useful to develop an efficient and stereodivergent route to give both *syn*- and *anti*-stereoisomers of the γ-amino-β-hydroxy acid units from a common starting compound.[6] We have demonstrated that the *N*-hydroxymethyl group can be used as an internal nucleophile for the β-hydroxyl group of (−)-statine and the β-amino group of (−)-3-aminodeoxystatine[7] as well as a configurational stabilizer of α-amino aldehydes.[8] We have also reported that the *N*-hydroxymethyl group can be utilized to accomplish *anti*-selective epoxidation via functional group transformation.[9] Herein, we report a stereodivergent and stereoselective synthetic methodology for both the *syn*- and *anti*-stereoisomers of AHPPA derivatives **3** and **4** via intramolecular conjugate addition and epoxidation, respectively.

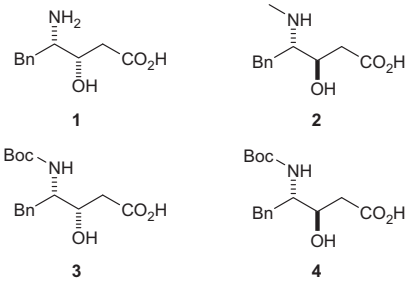

Figure 1. (3*S*,4*S*)-AHPPA, (3*R*,4*S*)-AHPPA, and their derivatives.

2. Results and discussion

The key intermediate **5** for our stereodivergent approach, containing the *N*-hydroxymethyl group, was derived from *N*-Boc-L-phenylalanine in three steps by following a reported procedure.[7,8] The preparation of the *syn*-isomer, an *N*-Boc derivative of (3*S*,4*S*)-AHPPA **3**, was first started by the intramolecular conjugate addition of **5** (Scheme 1). In terms of selectivity, this showed a preference for *trans*-oxazolidine **6** over the corresponding *cis*-isomer with several bases. The best selectivity of more than 10:1, as determined by GC, was attained with 1.0 equiv of K_2CO_3 as a base at 1.0 M concentration. Other bases such as TEA, $NaHCO_3$, and DBU showed 1.7:1, 2.1:1, and 4.3:1 diastereoselectivity, respectively. In addition, higher concentrations of base lowered the yield, causing partial hydrolysis of ester **6** to give the corresponding carboxylic acid as a by-product.

Orthogonal deprotection of the *N*,*O*-acetal group of **6** in the presence of other protecting groups was difficult under acidic or basic hydrolysis conditions. Therefore, we turned our attention to oxidative cleavage conditions and the *N*,*O*-methylene group of **6** was selectively converted into the *O*-formyl group of **7** via

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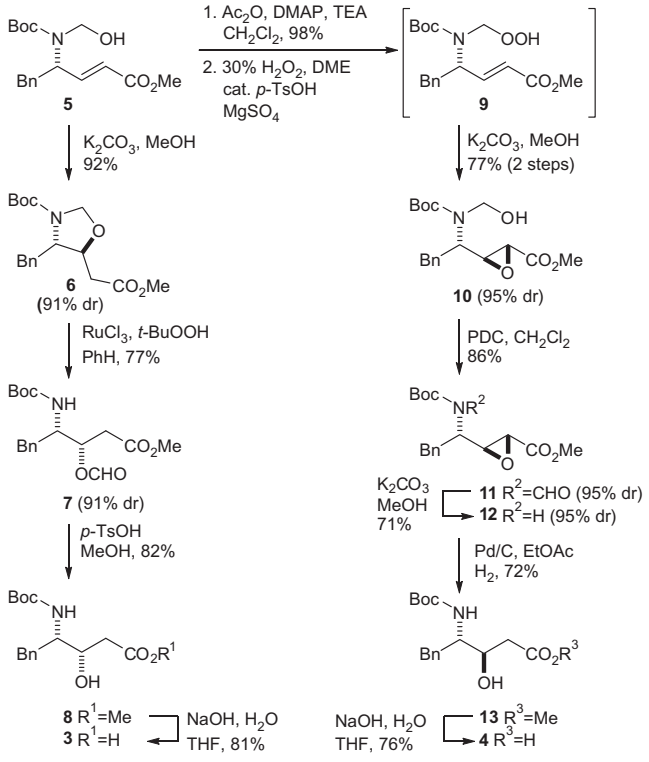
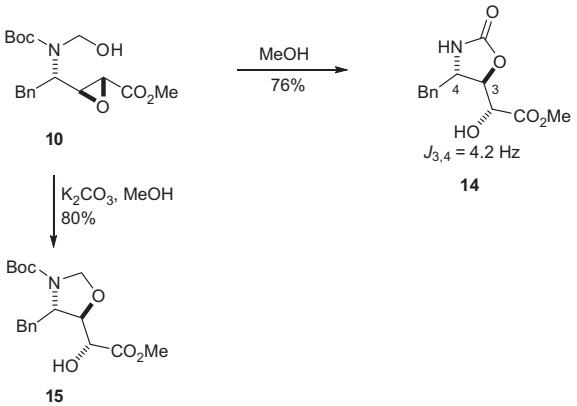
Ru-catalyzed oxidation[10] along with the corresponding oxazolidinone[11] as a by-product in a ratio of ca. 4:1 (^{1}H NMR). A diastereomeric mixture of **7** (*syn*-isomer) and its *anti*-isomer (not shown) was not separable by column chromatography, but **8** (*syn*-isomer) was isolable from its *anti*-isomer (not shown). Thus, **8** could be obtained as a single diastereomer after removing the *O*-formyl group under acidic conditions, followed by column chromatography separation. The synthesis of *N*-Boc-(3*S*,4*S*)-AHPPA **3** was completed with the basic hydrolysis of methyl ester **8**. The physical properties (melting point, specific rotation) and spectroscopic data of **3** matched those in the literature.[6b,12]

A complementary pathway for the preparation of the *anti*-isomer, an *N*-Boc derivative of (3*R*,4*S*)-AHPPA **4**, is also shown in Scheme 1. Starting from the common intermediate **5**, *anti*-selective intramolecular epoxidation was employed to result in the opposite configuration of the β-hydroxyl group. After acetylation of the *N*-hydroxymethyl group of **5**, the *N*-hydroperoxymethyl group of **9** was introduced by treating the resulting acetate from **5** with aqueous H_2O_2 under acidic conditions for 4 h in the presence of $MgSO_4$. Without work-up of the resulting reaction mixture, the epoxidation reaction was achieved within 30 min at room temperature by the sequential addition of MeOH and K_2CO_3. It should be noted that the epoxidation was very fast even under mild basic conditions, probably because of the intramolecular nature of the reaction. The *N*-hydroxymethyl group of **10** was removed via PDC oxidation followed by methanolysis of **11**. Thus, epoxide **12** was obtained in 48% yield after five reactions from **5**. The diastereoselectivity of the intramolecular epoxidation was determined at the stage of **12**, because the diastereomeric mixtures of **10** and **11** could not be well separated on the ^{1}H NMR spectra. The ratio of **12** (*anti*-epoxide) and its *syn*-epoxide (not shown) was more than 20:1 by ^{1}H NMR, indicating that the in situ intramolecular epoxidation reaction gave the *anti*-epoxide with high selectivity. The epoxidation selectivity did not depend much on the concentration of hydroperoxide **9**. However, the yields of the epoxidation decreased as the concentration of hydroperoxide **9** increased. This could be explained by the resulting epoxide **10** reacting further to give oxazolidinone **14** which was presumably produced by in situ intramolecular attack of the Boc group onto the epoxide ring in higher concentrations (Scheme 2).[9] The ^{1}H NMR analysis of **14** showed a $J_{3,4}$ value of 4.2 Hz, which can be used as an additional evidence for the *anti*-selective intramolecular epoxidation.[11,12]



Scheme 1. Synthesis of *N*-Boc-(3*S*,4*S*)-AHPPA **3** and *N*-Boc-(3*R*,4*S*)-AHPPA **4**.

A diastereomeric mixture of epoxide **12** (*anti*-isomer) and its *syn*-epoxide (not shown) was then reduced regioselectively via Pd-catalyzed hydrogenation to give the corresponding diastereomeric amino alcohol isomers,[13] from which the major *anti*-diastereomer **13** could be isolated from its *syn*-isomer by column chromatography (Scheme 1). Initially, we tried to convert the epoxide group of **10** directly into the β-hydroxyl group before removal of the *N*-hydroxymethyl group of **10**. However, those trials were unsuccessful due to the instability of **10**. Under the catalytic hydrogenation conditions, **10** was cyclized to afford **14** as mentioned earlier (Scheme 2). After the removal of the *N*-hydroxymethyl group of **10**, however, **12** was stable enough to undergo regioselective reduction. Previously, the *N*-hydroxymethyl group was easily removed under mild acidic or basic conditions.[8,9] In the presence of an epoxide however, **10** was transformed into oxazolidine **15** under mild basic conditions via intramolecular attack of the *N*-hydroxymethyl group at the epoxide, while oxazolidinone **14** was produced under mild acidic or even neutral conditions. In the reduction of the epoxide of **12** into the alcohol of **13**, the Pd catalyst was most effective under 10 atm of H_2 gas among the reducing reagents investigated; an Rh catalyst reduced the phenyl ring of **12**, a Pt catalyst was not effective at all, while regioselective reduction with SmI_2 resulted in the partial elimination of the hydroxyl group of **13** to give the corresponding α,β-unsaturated ester (not shown). A low yield of **13** (43%) was obtained with the Pd catalyst under 1 atm of H_2 gas and some starting epoxide **12** was also recovered (38%). Finally, the synthesis of *N*-Boc-(3*R*,4*S*)-AHPPA **4** was completed with basic hydrolysis of methyl ester **13** as described above. The physical properties (melting point, specific rotation) and spectroscopic data of **4** matched those in the literature.[6b,12]



Scheme 2. Facile cyclization of **10** into **14** or **15**.

3. Conclusion

In conclusion, we have established a stereodivergent and stereoselective synthetic method to obtain both *syn*- and *anti* derivatives of 4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA), **3** and **4**, from a readily available and common starting compound, γ-amino-α,β-unsaturated ester **5**. The intramolecular conjugate addition of the *N*-hydroxymethyl group of unsaturated ester **5**

resulted in the *syn*-selectivity of the β-hydroxyl group, whereas the complementary *anti*-selectivity of the β-hydroxyl group was established from the intramolecular epoxidation of the *N*-hydroperoxymethyl group of unsaturated ester **9**. Thus, both (3*S*,4*S*)-AHPPA and (3*R*,4*S*)-AHPPA diastereomers were obtained as their Boc protected forms in 47% (4 steps) and 25% (7 steps) yields from **5**, respectively. We hope that the method could provide a versatile approach for the synthesis of either diastereomer of γ-amino-β-hydroxy acids found in natural products.

4. Experimental

4.1. General

Materials were obtained from commercial suppliers and were used without further purification. Methylene chloride was distilled from calcium hydride immediately prior to use. Likewise benzene was distilled from sodium benzophenone ketyl. Air or moisture sensitive reactions were conducted under nitrogen atmosphere using oven-dried glassware and the standard syringe/septa technique. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm) followed by visualization with a molybdenum stain solution. Column chromatography was performed on Silica Gel 60 (70–230 mesh). ^{1}H NMR spectra were measured at 300 MHz in $CDCl_3$ unless otherwise stated and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hz). Gas chromatographic analyses were done with a capillary column (30 m × 0.25 mm). High resolution mass spectra were obtained with a JEOL JMS-AX505WA gas chromatography–mass spectrometer.

4.2. Synthesis of *N*-Boc-(3*S*,4*S*)-AHPPA 3 [(3*S*,4*S*)-*N*-*tert*-buthoxycarbonyl-4-amino-3-hydroxy-5-phenylpentanoic acid]

4.2.1. Methyl (2*E*,4*S*)-4-(*N*-*tert*-butoxycarbonyl-*N*-hydroxymethyl)amino-5-phenylpent-2-enoate 5

To a solution of (4*S*)-4-benzyl-3-(*tert*-butoxycarbonyl)-5-hydroxyoxazolidine[8a] (1.66 g, 5.95 mmol) in benzene (100 mL) was added methyl (triphenylphosphoranylidene)acetate (2.39 g, 7.14 mmol). The mixture was heated at reflux for 2 h. The resulting mixture was partitioned between H_2O (2 × 100 mL) and Et_2O (2 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give **5** (2.00 g, 94%) as a colorless oil. R_f = 0.29 (2:1 hexane/EtOAc); $[\alpha]_D^{19} = -36.7$ (*c* 1.74, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.42 (s, 9H), 2.87–3.12 (m, 2H), 3.74 (s, 3H), 4.47–4.61 (m, 1H), 4.77–4.83 (m, 2H), 5.97 (d, 1H, *J* = 15.9), 7.01 (dd, 1H, *J* = 15.9, and 5.0), 7.19–7.32 (m, 5H); ^{13}C NMR δ 27.7, 38.3, 51.1, 58.6, 69.6, 80.5, 121.1, 126.1, 128.0, 128.8, 137.3, 147.1, 154.8, 166.2.

4.2.2. Methyl (4*S*,5*S*)-(4-benzyl-3-*tert*-butoxycarbonyl-oxazolidin-5-yl)acetate 6

To a solution of **5** (574 mg, 1.71 mmol) in MeOH (1.7 mL) was added K_2CO_3 (237 mg, 1.71 mmol) at room temperature and the mixture was stirred for 30 min. Then a cold aq solution of 1 M HCl (3 mL) was added to the resulting solution and the mixture was partitioned between H_2O (2 × 20 mL) and Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give a mixture of **6** and its *cis*-isomer (527 mg, 92%) as a colorless oil in a ratio of more than 10:1. Data for **6** (*trans*-isomer): R_f = 0.35 (2:1 hexane/EtOAc); ^{1}H NMR (60 °C) δ 1.47 (s, 9H), 2.22 (dd 1H, *J* = 15.5, and 5.4), 2.45 (dd, 1H, *J* = 15.5, and 7.7), 2.80 (dd, 1H, *J* = 13.3, and 8.2), 3.12 (dd, 1H, *J* = 13.3, and 3.9), 3.59 (s, 3H), 3.84–3.89 (m, 1H), 4.30–4.35 (m, 1H), 4.59 (d, 1H, *J* = 4.2), 5.05 (m, 1H), 7.18–7.31 (m, 5H); ^{13}C NMR δ 28.3, 38.0, 38.8, 51.8, 60.8, 77.9, 78.7, 80.5, 126.6, 128.6, 129.4, 137.0, 152.8, 170.5; HRMS(CI) calcd for $C_{18}H_{26}NO_5$ (M^+-H) 336.1811, found 336.1811.

4.2.3. Methyl (3*S*,4*S*)-3-*O*-formyl-4-(*tert*-butoxycarbonyl)-amino-5-phenylpentanoate 7

To a mixture of **6** and its *cis*-isomer (78 mg, 0.23 mmol) in benzene (5 mL) was added $RuCl_3$ monohydrate (4.82 mg, 0.02 mmol) and a 5 M solution of TBHP in decane (1.88 mL, 9.32 mmol). The reaction mixture was stirred for 7 h at room temperature and then partitioned between H_2O (2 × 20 mL) and Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane/EtOAc) to give the formate **7** containing its *anti*-isomer (63 mg, 77%) in a ratio of more than 10:1 and the corresponding oxazolidinone[11] (16 mg, 19%) as a colorless oil. Data for **7** (*syn*-isomer): ^{1}H NMR δ 1.37 (s, 9H), 2.60–2.83 (m, 4H), 3.65 (s, 3H), 4.11–4.19 (m, 1H), 4.70 (br d, 1H, *J* = 10.1), 5.33–5.40 (m, 1H), 7.17–7.32 (m, 5H), 8.11 (s, 1H); ^{13}C NMR δ 28.2, 36.6, 38.8, 52.0, 53.7, 71.0, 79.8, 126.8, 128.6, 129.1, 136.8, 155.5, 160.1, 170.3; HRMS(CI) calcd for $C_{18}H_{26}NO_6$ (M^++H) 352.1760, found 352.1761.

4.2.4. Methyl (3*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-amino-3-hydroxy-5-phenylpentanoate 8

To a diastereomeric mixture of formate **7** and its *anti*-isomer (71 mg, 0.20 mmol) in MeOH (4 mL) was added *p*-TsOH (38 mg, 0.20 mmol). The mixture was stirred for 1 h at room temperature. The resulting mixture was partitioned between H_2O (2 × 10 mL) and Et_2O (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give **8** (54 mg, 82%) as a white solid. R_f = 0.26 (2:1 hexane/EtOAc); mp 92–94 °C {lit.[4a] mp 97–98 °C}; $[\alpha]_D^{20} = -36.5$ (*c* 0.1, CH_3OH) {lit.[4a] $[\alpha]_D^{20} = -36$ (*c* 1.0, CH_3OH)}; ^{1}H NMR δ 1.41 (s, 9H), 2.39 (dd, 1H, *J* = 17.0, and 2.6), 2.60 (dd, 1H, *J* = 17.0, and 10.1), 2.92 (d, 2H, *J* = 7.7), 3.44 (d, 1H, *J* = 2.8), 3.68 (s, 3H), 3.72–3.77 (m, 1H), 3.94–4.02 (m, 1H), 4.95 (d, 1H, *J* = 9.3), 7.12–7.35 (m, 5H); ^{13}C NMR δ 28.3, 38.3, 38.6, 51.9, 55.3, 66.9, 79.5, 126.4, 128.5, 129.4, 138.1, 155.8, 174.0; HRMS calcd for $C_{17}H_{26}NO_5$ (M^++H) 324.1811, found 324.1810.

4.2.5. (3*S*,4*S*)-*N*-*tert*-Buthoxycarbonyl-4-amino-3-hydroxy-5-phenylpentanoic acid 3

To a solution of **8** (186 mg, 0.53 mmol) in THF (5 mL) and H_2O (5 mL) was added NaOH (128 mg, 3.2 mmol). The mixture was stirred for 1 h at room temperature. Then a cold aq solution of 1 M HCl (5 mL) was added to the resulting solution and the mixture was partitioned between H_2O (2 × 20 mL) and EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The solid residue was purified with SiO_2 column chromatography (95:5:1 CH_2Cl_2/MeOH/AcOH) to give **3** (133 mg, 81%) as a white solid. R_f = 0.22 (95:5:1 CH_2Cl_2/MeOH/AcOH); mp 147–149 °C {lit.[12] mp 148–148.5 °C}; $[\alpha]_D^{20} = -36.8$ (*c* 0.05, CH_3OH) {lit.[12] $[\alpha]_D^{20} = -37.0$ (*c* 1.1, CH_3OH)}; ^{1}H NMR (CD_3OD, 50 °C) δ 1.35 (s, 9H), 2.35–2.49 (m, 2H), 2.72 (dd, 1H, *J* = 13.6, and 9.0), 2.88 (dd, 1H, *J* = 13.6, and 6.0), 3.74–3.79 (m, 1H), 4.03–4.12 (m, 1H), 7.13–7.24 (m, 5H); ^{13}C NMR (CD_3OD) δ 28.7, 38.8, 40.0, 57.3, 69.9, 80.1, 127.2, 129.3, 130.4, 140.1, 158.2, 175.5; IR (KBr) 3378, 2980, 1692, 1680 cm^{-1}; HRMS(CI) calcd for $C_{16}H_{24}NO_5$ (M^++H) 310.1653, found 310.1654.

4.3. Synthesis of *N*-Boc-(3*R*,4*S*)-AHPPA 4 [(3*R*,4*S*)-*N*-*tert*-buthoxycarbonyl-4-amino-3-hydroxy-5-phenylpentanoic acid]

4.3.1. Methyl (2*R*,3*S*)-3-[(*S*)-1-(*N*-*tert*-butoxycarbonyl-*N*-hydroxymethyl)amino)-2-phenylethyl]-oxirane-2-carboxylate 10

To a solution of **5** (1.92 g, 5.72 mmol) in CH_2Cl_2 (80 mL) was added Ac_2O (1.75 g, 17.2 mmol), TEA (1.74 g, 17.2 mmol), and DMAP (140 mg, 1.14 mmol). The mixture was stirred for 1 h at room temperature. The resulting mixture was partitioned between H_2O (2 × 40 mL) and Et_2O (2 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane/EtOAc) to give the corresponding acetate (2.11 g, 98%) as a colorless oil. R_f = 0.51 (2:1 hexane/EtOAc); $[\alpha]_D^{19} = -34.9$ (*c* 0.32, $CHCl_3$); ^{1}H NMR δ 1.43 (s, 9H), 1.99 (s, 3H), 2.99 (dd, 1H, *J* = 13.7, and 6.6), 3.01–3.19 (m, 1H), 3.74 (s, 3H), 4.55–4.95 (m, 1H), 5.04 (d, 1H, *J* = 10.9), 5.28 (br d, 1H, *J* = 10.9), 5.89 (dd, 1H, *J* = 15.9, and 1.7), 7.01 (dd, 1H, *J* = 15.9, and 5.3), 7.10–7.36 (m, 5H); ^{13}C NMR δ 20.5, 27.7, 38.3, 51.1, 59.1, 69.6, 80.5, 121.1, 126.1, 128.0, 128.8, 137.3, 147.1, 154.8, 166.2, 170.7; Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.59; H, 7.31; N, 3.58. To a solution of the above acetate (849 mg, 2.25 mmol) in DME (30 mL) was added 30% aq H_2O_2 (1.79 g, 16.0 mmol), *p*-TsOH (25 mg, 0.23 mmol), and $MgSO_4$ (100 mg). The reaction mixture was stirred for 4 h at room temperature. After filtration of $MgSO_4$ from the resulting mixture, MeOH (17 mL), and K_2CO_3 (933 mg, 6.75 mmol) were added in sequence to the filtrate. The resulting mixture was stirred at room temperature and the reaction was complete within 30 min. The resulting mixture was partitioned between H_2O (2 × 30 mL) and Et_2O (2 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give a mixture of **10** and its *syn*-isomer (611 mg, 77%) as a colorless oil in a ratio of more than 20:1. Data for **10** (*anti*-isomer): ^{1}H NMR (benzene-d_6, 75 °C) δ 1.29 (s, 9H), 2.81 (dd, 1H, *J* = 14.1, and 5.3), 2.87–3.00 (m, 1H), 3.29 (s, 3H), 3.45 (d, 1H, *J* = 1.8), 3.57–3.65 (m, 1H), 3.72–3.85 (m, 1H), 4.26–4.40 (m, 1H), 4.45–4.62 (m, 1H), 6.96–7.11 (m, 5H); ^{13}C NMR (benzene-d_6) δ 28.9, 37.4, 52.2, 53.2, 60.3, 61.1, 71.8, 81.4, 127.4, 129.3, 130.1, 138.7, 155.6, 169.3; IR (KBr) 3433, 1715, 1675 cm^{-1}. Compound **10** was rather reactive and cyclized during storage at room temperature.[9] Therefore, an elemental analysis of **10** was not carried out. Rotational isomerism of **10** blurred some of the NMR peaks.

4.3.2. Methyl (2*R*,3*S*)-3-[(*S*)-1-(*N*-*tert*-butoxycarbonylamino)-2-phenylethyl]-oxirane-2-carboxylate 12

To a solution of **10** and its *syn*-isomer (1.10 g, 3.13 mmol) in CH_2Cl_2 (50 mL) was added PDC (1.61 g, 4.27 mmol). The mixture was stirred overnight at room temperature. The resulting mixture was partitioned between H_2O (2 × 40 mL) and Et_2O (2 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane/EtOAc) to give a mixture of **11** and its *syn*-isomer (939 mg, 86%) as a colorless oil in a ratio of more than 20:1. Data for **11** (*anti*-isomer): ^{1}H NMR δ 1.45 (br s, 9H), 3.15 (dd, 1H, *J* = 13.8, and 5.6), 3.33 (d, 1H, *J* = 1.8), 3.36 (dd, 1H, *J* = 13.8, and 11.0), 3.78 (s, 3H), 3.73–3.89 (m, 1H), 4.23–4.44 (m, 1H), 7.07–7.32 (m, 5H), 9.00 (s, 1H); ^{13}C NMR δ 27.6, 35.3, 51.7, 52.2, 55.1, 57.7, 84.6, 126.6, 128.2, 128.8, 136.1, 151.4, 162.6, 168.3; Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.53; H, 6.72; N, 3.84. To a solution of **11** and its *syn*-isomer (644 mg, 1.84 mmol) in MeOH (10 mL) was added K_2CO_3 (255 mg, 1.84 mmol). The mixture was stirred for 0.5 h at room temperature. Then, a cold aq solution of 1 M HCl (5 mL) was added to the resulting solution and the mixture was partitioned between H_2O (2 × 20 mL) and Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane/EtOAc) to give a mixture of **12** and its *syn*-isomer (419 mg, 71%) as a white solid in a ratio of more than 20:1. Data for **12** (*anti*-isomer): R_f = 0.38 (2:1 hexane/EtOAc); mp 106–107 °C; ^{1}H NMR (50 °C) δ 1.39 (s, 9H), 2.85 (dd, 1H, *J* = 14.1, and 7.6), 2.96 (dd, 1H, *J* = 14.1, and 5.2), 3.16 (dd, 1H, *J* = 6.5, and 1.5), 3.49 (d, 1H, *J* = 1.5), 3.73–3.81 (m, 1H), 3.77 (s, 3H), 4.41 (br d, 1H, *J* = 7.8), 7.20–7.36 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 28.1, 36.7, 50.1, 51.5, 52.2, 58.9, 78.0, 126.2, 128.1, 129.1, 137.9, 155.2, 168.9; IR (KBr) 3371, 2980, 1754, 1677, 1212 cm^{-1}; Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.54; H, 7.39; N, 4.16; HRMS calcd for $C_{17}H_{24}NO_5$ (M^++H) 322.1654, found 322.1654.

4.3.3. Methyl (3*R*,4*S*)-*N*-*tert*-buthoxycarbonyl-4-amino-3-hydroxy-5-phenylpentanoate 13

To a solution of **12** and its *syn*-isomer (173 mg, 0.54 mmol) in ethyl acetate (12 mL) was added 5% palladium on carbon (229 mg, 0.11 mmol). The solution was stirred under 10 atm of H_2 gas for 3 d at room temperature. The palladium catalyst was then filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified with SiO_2 chromatography (hexane/EtOAc = 8:1) to give **13** (103 mg, 59%) as a white solid (72% yield based on recovered starting materials). The unreacted starting material (29 mg, 17%) was recovered and reused. R_f = 0.16 (2:1 hexane/EtOAc); mp 118–120 °C; $[\alpha]_D^{20} = -19.9$ (*c* 0.2, CH_3OH); ^{1}H NMR δ 1.35 (s, 9H), 2.51 (dd, 1H, *J* = 16.5, and 8.7), 2.53–2.62 (m, 1H), 2.84 (dd, 1H, *J* = 13.9, and 8.3), 2.97 (dd, 1H, *J* = 13.9, and 4.3), 3.59–3.69 (m, 1H), 3.72 (s, 3H), 3.77–3.82 (m, 1H), 3.94–4.05 (m, 1H), 4.52 (br d, 1H, *J* = 7.3), 7.17–7.33 (m, 5H); ^{13}C NMR δ 28.2, 35.8, 38.0, 51.9, 55.1, 70.0, 79.7, 126.5, 128.5, 129.5, 137.5, 155.8, 173.4; IR (KBr) 3359, 2981, 1741, 1686, 1255; HRMS calcd for $C_{17}H_{26}NO_5$ (M^++H) 324.1811, found 324.1810.

4.3.4. (3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-4-amino-3-hydroxy-5-phenylpentanoic acid 4

To a solution of **13** (141 mg, 0.44 mmol) in THF (2 mL) and H_2O (2 mL) was added NaOH (52 mg, 1.31 mmol). The mixture was stirred for 1 h at room temperature. Then, a cold aq solution of 1 M HCl (3 mL) was added to the resulting mixture and the mixture was partitioned between H_2O (2 × 20 mL) and EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The solid residue was purified with SiO_2 column chromatography (95:5:1 CH_2Cl_2/MeOH/AcOH) to give **4** (103 mg, 76%) as a white solid. R_f = 0.19 (95:5:1 CH_2Cl_2/MeOH/AcOH); mp 181–183 °C {lit.[6b] mp 183–185 °C}; $[\alpha]_D^{20} = -17.9$ (*c* 0.024, CH_3OH) {lit.[6b] $[\alpha]_D^{20} = -17.2$ (*c* 1.4, CH_3OH)}; ^{1}H NMR (CD_3OD) δ 1.29 (s, 9H), 2.38 (dd, 1H, *J* = 15.5, and 9.2), 2.51–2.63 (m, 2H), 3.10 (dd, 1H, *J* = 13.7, and 3.7), 3.64–3.71 (m, 1H), 3.91–3.97 (m, 1H), 7.14–7.26 (m, 5H); ^{13}C NMR (CD_3OD) δ 28.7, 37.7, 40.4, 58.0, 72.1, 79.9, 127.0, 129.1, 130.4, 140.2, 158.0, 176.3; IR (KBr) 3356, 2980, 1725, 1687.; HRMS(CI) calcd for $C_{16}H_{24}NO_5$ (M^++H) 310.1654, found 310.1654.

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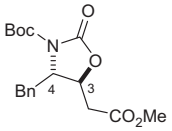

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