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# Asymmetric Synthesis of 3,4-Disubstituted Proline Derivatives: Application in Synthesis of Hepatitis C Virus Protease Inhibitor Telaprevir

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**Keywords:** Synthetic methods / Asymmetric synthesis / Medicinal chemistry / Antivirus agents / Amino acids

A practical asymmetric synthesis of 3,4-disubstituted proline derivatives has been realized with high stereoselectivity and moderate yield. The key steps involved are desymmetric ring-opening reaction of commercially available anhydrides, intramolecular Strecker reaction and thermodynamically controlled cyanide hydrolysis. Based on this methodology, the synthesis of HCV protease inhibitor Telaprevir was achieved.

## Introduction

Conformationally constrained cyclic proline derivatives are used widely as modified amino acid building blocks in peptide synthesis because their exclusive amide bond conformation has a dramatic impact on the three-dimensional structures of peptides and proteins.[1] These proline structural units have been used in many marketed drugs, such as Trandolapril, Saxagliptin, Telaprevir and Boceprevir (Figure 1). In particular, Hepatitis C virus (HCV) protease inhibitors, Telaprevir and Boceprevir, both contain 3,4-disubstituted bicyclic proline units to successfully treat HCV infections.[2]

To date, several methods have been reported to synthesize optically pure 3,4-disubstituted proline derivatives: (i) resolution of racemic proline derivatives;[3] (ii) asymmetric Michael addition reactions with a chiral auxiliary, chiral phase-transfer catalyst, and chiral Ni complexes;[4] (iii) catalyzed cycloaddition reactions;[5] (iv) palladium-catalyzed intramolecular coupling reactions;[6] (v) intramolecular Pauson–Khand reactions and ring-closing-metathesis reactions,[7] and (vi) desymmetrization of pyrrolidines through enzymatic catalysis. A chemical method was also efficient at synthesizing these compounds.[8] Although the described methods were effective at synthesizing specific structures, more general and practical methods are needed to construct optically pure 3,4-disubstituted proline derivatives.

We realized that the chiral substituted proline moiety of Telaprevir could be synthesized from the corresponding anhydride through a stereoselective anhydride opening reaction.[9] Although one patent claimed to use this methodology to synthesize a Boceprevir intermediate,[10] we found the methodology was not suitable for the Telaprevir intermediate. In this work, we have developed a practical approach to construct optically pure 3,4-disubstituted proline derivatives.

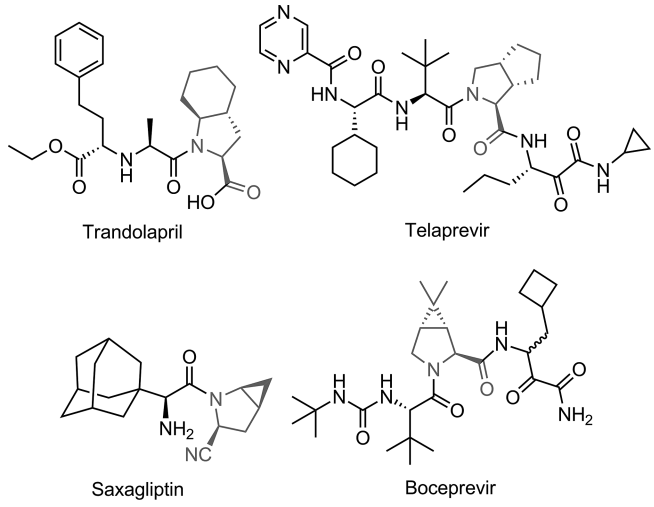


Figure 1. Marketed drugs that contain substituted proline moieties.

## Results and Discussion

To develop our strategy, we initially synthesized proline unit **8a** in Telaprevir as a model template (Scheme 1). Asymmetric ring opening of anhydride **1a** with methanol in the presence of quinidine afforded acid **2a** with 98% *ee*.[9d] Amidation of **2a** with diphenylamine gave amide **3a** in 69% yield from **1a**. Reduction of **3a** with borane dimethylsulfide ($BH_3$·DMS) afforded amino alcohol **4a** in 94% yield. Hydrogenation of **4a** in the presence of di-*tert*-butyl dicarbonate ($Boc_2O$) in methanol at room temperature afforded

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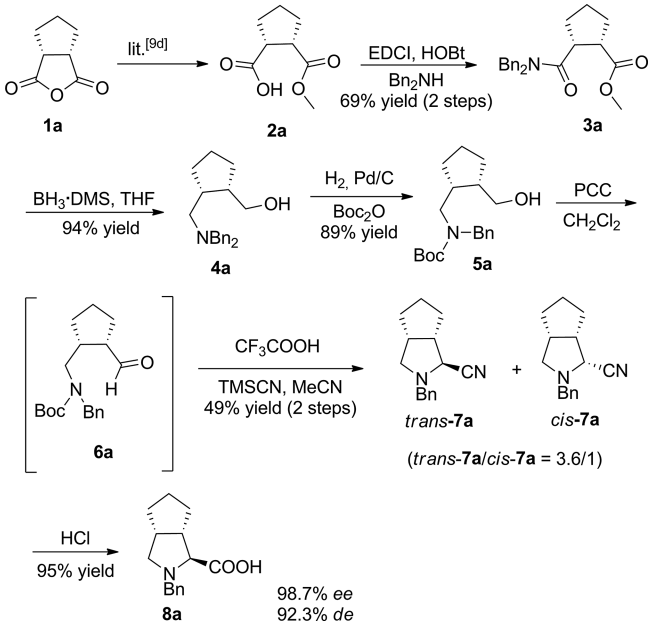
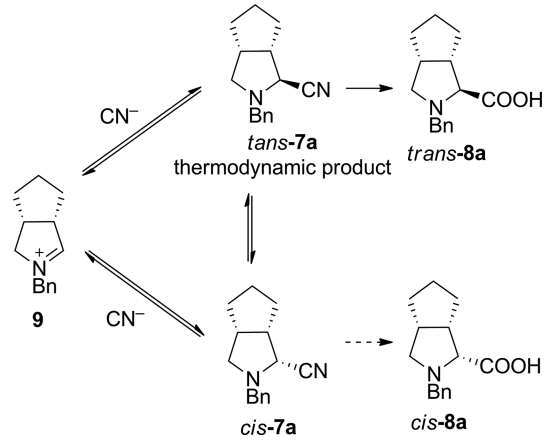
alcohol **5a** in 89% yield together with trace amounts of the double debenzylation product. Oxidation of **5a** with pyridinium chlorochromate (PCC) gave aldehyde **6a**. Boc-deprotection of **6a** with trifluoroacetic acid, followed by intramolecular Strecker reaction with trimethylsilyl cyanide (TMSCN) in MeCN provided amino cyanides *trans*-**7a** and *cis*-**7a** (3.6:1) in 49% yield. We tried to separate *trans*-**7a** and *cis*-**7a** by column chromatography, however, they isomerized during purification and storage. Thus, the mixture of *trans*-**7a** and *cis*-**7a** was used directly in the next step. Surprisingly, hydrolysis of this mixture in HCl solution at reflux temperatures afforded near optically pure amino acid **8a** in 95% yield. We speculate that unstable *cis*-**7a** is quickly converted into more stable *trans*-**7a** through iminium cation **9**,[11] which leads to dominant formation of *trans*-**8a** (Scheme 2). The absolute configuration of **8a** was confirmed by debenzylation reaction to give a compound with known configuration.[8a]




Scheme 1. Synthesis of **8a**.




Scheme 2. Proposed pathway for stereoselective enrichment of *trans*-**8a**.

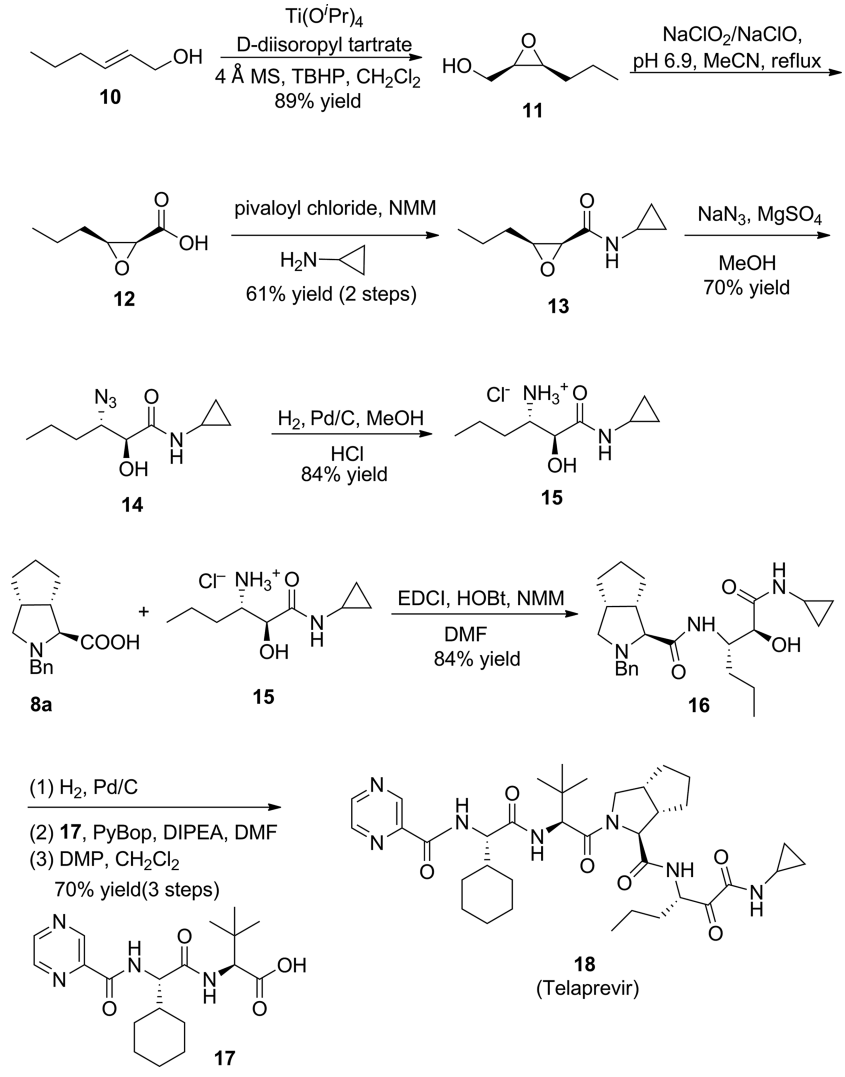
Based on the above method, we used other anhydrides to construct the corresponding chiral proline derivatives. As shown in Table 1, asymmetric ring-opening reaction of anhydrides **1** with methanol in the presence of quinidine (Table 1, Entries 1–6,) or quinine (Table 1, Entries 7 and 8,) afforded chiral acids **2** in high enantioselectivity (89–99% *ee*). The configuration of **8d** (Table 1, Entry 4) was further confirmed by NOESY spectroscopy (see the Supporting Information).

Table 1. Asymmetric synthesis of 3,4-disubstituted proline derivatives.

| Entry | Anhydride | Product | *ee*[a] | *dr*[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| 1[d] | **1a** | **8a** | 99 | >20/1 | 27 |
| 2[d] | **1b** | **8b** | 98 | 10/1 | 25 |
| 3[d] | **1c** | **8c** | 96 | >20/1 | 6 |
| 4[d] | **1d** | **8d** | >99 | >20/1 | 22 |
| 5[d] | **1e** | **8e** | >99 | >20/1 | 22 |
| 6[d] | **1f** | **8f** | >99 | 2/1 | 38 |
| 7[e] | **1a** | **8g** | 94 | 20/1 | 21 |
| 8[e] | **1c** | **8h** | 89 | >20/1 | 10 |

[a] The *ee* was determined by chiral HPLC. [b] The *dr* was determined by $^1$H NMR spectroscopy. [c] Isolated yield over 7 steps. [d] Ring-opening reaction with quinidine. [e] Ring-opening reaction with quinine.




Scheme 3. Synthesis of HCV protease inhibitor Telaprevir.

When quinine was used as the chiral catalyst, we obtained proline derivatives **8g** and **8h** with D-configuration. The total yields were 6–38% for 7 steps.

With **8a** in hand, we continued to synthesize HCV protease inhibitor Telaprevir (Scheme 3). To begin with we developed a new synthesis of amino alcohol **15** as another key intermediate of Telaprevir. Sharpless epoxidation of *trans*-2-hexenol **10** afforded epoxide **11** in 89% yield and 91% *ee*. Oxidation of **11** with $NaClO_2$, NaClO, and (2,2,6,6-tetramethyl-1-piperidinyl)oxidanyl (TEMPO) in buffer (pH = 6.9) gave acid **12**, which was treated with cyclopropylamine to afford amide **13** in 61% yield. Regioselective ring opening of **13** with $NaN_3$ provided azide **14** in 70% yield. Hydrogenation of **14**, followed by acidification with con. HCl, gave a crude product, which was recrystallized from 2-propanol to afford **15** in 84% yield and 99% *ee*. Next, condensation of **8a** with **15** furnished dipeptide derivative **16** in 84% yield. Debenzylation of **16**, followed by condensation with acid **17** and Dess–Martin oxidation,[8c] gave **18** (Telaprevir) in 70% yield. The spectroscopic data of **18** was identical to that reported in the literature.[12]

## Conclusions

In conclusion, we have developed a facile asymmetric synthesis of 3,4-disubstituted proline derivatives that is highlighted by asymmetric ring opening of substituted anhydrides, intramolecular Strecker reaction, and thermodynamically-controlled cyanide hydrolysis. High stereoselectivity and moderate yield were achieved for construction of these challenging molecules with several chiral centers. Moreover, a practical synthesis of HCV protease inhibitor Telaprevir was achieved in 16% yield over 11 linear steps based on the above methodology and new synthesis of amino alcohol **15**. Further studies are underway to explore the utility of these chiral proline building blocks in drug design and synthesis.

## Experimental Section

**General Information:** $^1$H and $^{13}$C NMR spectra were recorded with an ACF* 300Q Bruker or ACF* 500Q Bruker spectrometer. Low- and high-resolution mass spectra were recorded in electron impact mode. The mass analyzer type used for HRMS measurements was TOF. Reactions were monitored with TLC on silica gel 60 F254 plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out with silica gel (200–300 mesh, Qingdao Ocean Chemical Company, China). Compounds **2a**–**2h** were prepared according to the procedure reported.[9d] The crude acid was used in the next step without further purification.

**General Procedure for the Preparation of 3:** To a solution of crude acid **2** (10.75 mmol, 1.0 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI; 3.06 g, 16.13 mmol), hydroxybenzotriazole (HOBt; 2.3 g, 17.2 mmol) in $CH_2Cl_2$ (44 mL) at 0 °C. 4-Methylmorpholine (NMM; 2.5 mL) was added at 0 °C for 30 min. Then dibenzylamine (3.2 mL) was added to the mixture. The reaction mixture was then stirred overnight at room temperature. The solvent was evaporated and the residue was diluted with EtOAc, washed with HCl (1 N), saturated $NaHCO_3$ solution, and brine. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give the product.

**3a:** Eluent petroleum ether/ethyl acetate (5:1). Colorless oil (2.8 g, 69% yield, 98.7% *ee*). [Chiralpak IC column (0.46 cm × 25 cm); *n*-hexane/*i*PrOH = 80:20; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 34.52 min (major), $t_R$ = 37.82 min (minor)]. $[\alpha]_D^{25}$ = +39.9 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.41–7.22 (m, 10 H), 4.72–4.40 (m, 4 H), 3.67 (s, 3 H), 3.49–3.42 (m, 1 H), 2.86 (dd, *J* = 17.4, 8.0 Hz, 1 H), 2.39–2.31 (m, 1 H), 2.00–1.94 (m, 4 H), 1.65–1.58 (m, 1 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 174.9, 174.2, 137.6, 136.6, 128.9, 128.5, 128.4, 128.3, 128.2, 127.6, 127.3, 127.0, 126.5, 53.1, 51.5, 49.9, 48.1, 48.0, 43.7, 30.9, 28.2, 24.4 ppm. MS (ESI): *m*/*z* = 352.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{22}H_{26}NO_3$ [M + H]$^+$ 352.1913; found 352.1915.

**3b:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (2.68 g, 68% yield, 98% *ee*). [Chiralpak IC column (0.46 cm × 25 cm); *n*-hexane/*i*PrOH = 80:20; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 29.70 min(major), $t_R$ = 32.00 min (minor)]. $[\alpha]_D^{25}$ = +42.0 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.41–7.16 (m, 10 H), 4.85 (d, *J* = 15.0 Hz, 1 H), 4.60 (d, *J* = 18.0 Hz, 1 H), 4.35 (d, *J* = 18.0 Hz, 1 H), 4.24 (d, *J* = 15.0 Hz, 1 H), 3.72 (s, 3 H), 3.39–3.34 (m, 1 H), 2.57–2.53 (m, 1 H), 2.40–2.32 (m, 1 H), 2.08–2.04 (m, 1 H), 1.94–1.89 (m, 2 H), 1.69–1.41 (m, 3 H), 1.41–1.20 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 177.6, 174.2, 140.7, 140.0, 128.8, 128.5, 128.1, 127.6, 127.0, 126.8, 51.5, 49.9, 47.2, 43.2, 38.7, 27.6, 25.1, 24.3, 22.2 ppm. MS (ESI): *m*/*z* = 366.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{23}H_{28}NO_3$ [M + H]$^+$ 366.2069; found 366.2073.

**3c:** Eluent petroleum ether/ethyl acetate (5:1). Colorless oil (2.31 g, 57% yield, 96% *ee*). [Chiralpak IC column (0.46 cm × 25 cm); *n*-hexane/*i*PrOH = 80:20; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 33.95 min (major), $t_R$ = 36.26 min (minor)]. $[\alpha]_D^{25}$ = +48.1 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.42–7.18 (m, 10 H), 6.45–6.42 (m, 1 H), 6.13–6.10 (m, 1 H), 4.97 (d, *J* = 15.0 Hz, 1 H), 4.84 (d, *J* = 18.0 Hz, 1 H), 4.48 (d, *J* = 18.0 Hz, 1 H), 4.19 (d, *J* = 15.0 Hz, 1 H), 3.68 (s, 3 H), 3.66–3.63 (m, 1 H), 3.23–3.10 (m, 3 H), 1.62–1.48 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 173.8, 173.5, 138.4, 138.3, 137.4, 136.6, 128.9, 128.8, 128.4, 127.6, 127.4, 126.4, 51.5, 50.1, 48.7, 47.4, 47.2, 45.9, 44.9, 44.6 ppm. MS (ESI): *m*/*z* = 376.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{26}NO_3$ [M + H]$^+$ 376.1913; found 376.1918.

**3d:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (2.56 g, 63% yield, 99% *ee*). [Chiralpak IC column (0.46 cm × 25 cm); *n*-hexane/*i*PrOH = 80:20; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 30.74 min (minor), $t_R$ = 32.70 min (major)]. $[\alpha]_D^{25}$ = +49.7 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.18 (m, 10 H), 6.18–6.10 (m, 2 H), 4.99 (d, *J* = 15.0 Hz, 1 H), 4.70 (d, *J* = 18.0 Hz, 1 H), 4.43 (d, *J* = 18.0 Hz, 1 H), 4.24 (d, *J* = 15.0 Hz, 1 H), 3.70 (t, *J* = 4.1 Hz, 1 H), 3.57 (s, 3 H), 3.29 (s, 1 H), 3.00–2.86 (m, 2 H), 2.06–2.03 (m, 1 H), 1.46 (dd, *J* = 8.6, 1.4 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 174.6, 174.1, 137.4, 136.6, 135.9, 128.7, 128.0, 127.5, 126.8, 51.6, 49.9, 48.6, 48.4, 48.3, 46.7, 45.4, 45.1 ppm. MS (ESI): *m*/*z* = 376.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{26}NO_3$ [M + H]$^+$ 376.1913; found 376.1918.

**3e:** Eluent petroleum ether/ethyl acetate (10:1). Colorless oil (4.02 g, 96% yield, 99% *ee*). [Chiralpak IC column (0.46 cm × 25 cm); *n*-hexane/*i*PrOH = 80:20; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 43.15 min (minor), $t_R$ = 49.10 min (major)]. $[\alpha]_D^{25}$ = +37.2 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.44–7.19 (m, 10 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 4.64 (d, *J* = 18.0 Hz, 1 H), 4.31 (d, *J* = 15.0 Hz, 1 H), 4.04 (d, *J* = 15.0 Hz, 1 H), 3.70 (s, 3 H), 3.48–3.44 (m, 1 H), 2.64 (d, *J* = 10.6 Hz, 1 H), 2.40–2.28 (m, 1 H), 2.17 (s, 1 H), 1.82–1.76 (m, 2 H), 1.73–1.38 (m, 6 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 175.1, 173.7, 138.8, 136.8, 128.8, 128.5, 128.2, 127.6, 127.2, 126.5, 50.9, 49.9, 47.7, 43.4, 43.2, 28.1, 26.1, 24.9, 21.6, 21.3 ppm. MS (ESI): *m*/*z* = 392.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{26}NO_3$ [M + H]$^+$ 392.2226; found 392.2232.

**3f:** Eluent petroleum ether/ethyl acetate (5:1). Colorless oil (3.13 g, 86% yield, 99% *ee*). [Chiralpak IC column (0.46 mm × 25 cm); *n*-hexane/*i*PrOH = 95:5; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 32.34 min (minor), $t_R$ = 33.98 min (major)]. $[\alpha]_D^{25}$ = +43.0 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.38–7.14 (m, 10 H), 4.57 (s, 2 H), 4.42 (s, 2 H), 3.73 (s, 3 H), 2.71 (s, 2 H), 1.29 (s, 6 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 176.2, 175.2, 137.4, 136.5, 128.9, 128.6, 128.2, 127.6, 127.4, 126.4, 51.6, 49.8, 48.3, 43.6, 39.2, 17.1, 16.5 ppm. MS (ESI): *m*/*z* = 378.1 [M + K]$^+$. HRMS (ESI): calcd. for $C_{21}H_{25}NO_3K$ [M + K]$^+$ 378.1472; found 378.1477.

**3g:** Eluent petroleum ether/ethyl acetate (5:1). Colorless oil (2.68 g, 66% yield, 94% *ee*). [Chiralpak IC column (0.46 cm × 25 cm); *n*-hexane/*i*PrOH = 80:20; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 32.51 min (minor), $t_R$ = 34.74 min (major)]. $[\alpha]_D^{25}$ = –50.9 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.43–7.22 (m, 10 H), 4.72–4.40 (m, 4 H), 3.67 (s, 3 H), 3.47–3.39 (m, 1 H), 2.89 (dd, *J* = 17.0, 8.4 Hz, 1 H), 2.42–2.29 (m, 1 H), 2.03–1.92 (m, 4 H), 1.69–1.59 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 174.9, 174.2, 137.5, 136.5, 128.8, 128.5, 128.3, 127.6, 127.3, 126.5, 51.5, 49.9, 47.9, 43.6, 30.8, 28.2, 24.4 ppm. MS (ESI): *m*/*z* = 352.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{22}H_{26}NO_3$ [M + H]$^+$ 352.1913; found 352.1915.

**3h:** Eluent petroleum ether/ethyl acetate (5:1). Colorless oil (2.62 g, 65% yield, 89% *ee*). [Chiralpak IC column (0.46 cm × 25 cm); *n*-hexane/*i*PrOH = 80:20; flow rate: 0.5 mL/min; detection wavelength: 254 nm; $t_R$ = 28.34 min (minor), $t_R$ = 29.61 min (major)]. $[\alpha]_D^{25}$ = –56.8 (*c* = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40–7.14 (m, 10 H), 6.39 (dd, *J* = 5.5, 3.2 Hz, 1 H), 6.07 (dd, *J* = 5.5, 2.8 Hz, 1 H), 4.92 (d, *J* = 18.0 Hz, 1 H), 4.80 (d, *J* = 18.0 Hz, 1 H), 4.44 (d, *J* = 18.0 Hz, 1 H), 4.14 (d, *J* = 18.0 Hz, 1 H), 3.64 (s, 3 H), 3.61–3.59 (m, 1 H), 3.19 (s, 1 H), 3.09–3.06 (m, 2 H), 1.64–

1.43 (m, 3 H), 1.45 (dd, $J$ = 8.7, 1.5 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 174.6, 174.1, 137.4, 136.6, 135.9, 128.7, 128.0, 127.5, 126.7, 51.6, 49.9, 48.6, 48.4, 48.3, 46.7, 45.4, 45.0 ppm. MS (ESI): $m/z$ = 376.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{24}H_{26}NO_3$ $[M + H]^+$ 376.1913; found 376.1918.

**General Procedure for the Preparation of 4:** To a solution of **3** (8.06 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (THF; 54 mL) at 0 °C under nitrogen was added a solution of $BH_3$·DMS solution (20.1 mL, 2.0 mol/L, 5.0 equiv.) dropwise. The mixture was then heated to reflux for 1 h, then quenched with HCl/methanol solution at 0 °C. The solvent was removed, the residue was diluted with EtOAc, and washed with saturated $NaHCO_3$ solution and brine. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give the product.

**4a:** Eluent petroleum ether/ethyl acetate (10:1). Colorless oil (2.32 g, 94% yield). $[\alpha]_D^{25}$ = +27.9 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.29 (m, 10 H), 3.91 (d, $J$ = 12.0 Hz, 2 H), 3.36–3.11 (m, 1 H), 3.23 (d, $J$ = 15.0 Hz, 2 H), 3.19–3.12 (m, 1 H), 2.78 (t, $J$ = 12.2 Hz, 1 H), 2.58–2.43 (m, 1 H), 2.31–2.25 (m, 1 H), 2.17 (dd, $J$ = 12.7, 3.2 Hz, 1 H), 1.87–0.89 (m, 6 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 136.9, 129.7, 128.3, 127.3, 63.1, 58.2, 55.9, 53.1, 44.1, 38.1, 31.8, 28.7, 24.0 ppm. MS (ESI): $m/z$ 310.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{28}NO$ $[M + H]^+$ 310.2171; found 310.2174.

**4b:** Eluent petroleum ether/ethyl acetate (15:1). Colorless oil (2.18 g, 84% yield). $[\alpha]_D^{25}$ = +37.5 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.24 (m, 10 H), 4.99 (s, 1 H), 3.86 (d, $J$ = 12.0 Hz, 2 H), 3.34 (dd, $J$ = 11.6, 5.1 Hz, 1 H), 3.22 (d, $J$ = 12.0 Hz, 2 H), 2.94–2.84 (m, 2 H), 2.21–2.17 (m, 1 H), 2.02 (dd, $J$ = 12.9, 2.6 Hz, 1 H), 1.86–1.81 (m, 1 H), 1.58–0.96 (m,8 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.7, 129.9, 128.6, 127.4, 64.2,58.7, 54.6, 40.6, 33.3, 31.3, 25.6, 24.8, 22.8 ppm. MS (ESI): $m/z$ = 324.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{22}H_{30}NO$ $[M + H]^+$ 324.2327; found 324.2330.

**4c:** Eluent petroleum ether/ethyl acetate (15:1). Colorless oil (2.09 g, 79% yield). $[\alpha]_D^{25}$ = +35.6 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.25 (m, 10 H), 6.19–6.17 (m, 2 H), 3.99 (d, $J$ = 13.0 Hz, 2 H), 3.48 (d, $J$ = 9.0 Hz, 1 H), 3.15–3.08 (m, 3 H), 2.80 (t, $J$ = 12.0 Hz, 1 H), 2.40 (d, $J$ = 6.0 Hz, 2 H), 2.33 (dd, $J$ = 12.9, 3.3 Hz, 1 H), 2.07–1.99 (m, 1 H), 1.86–1.81 (m, 1 H), 1.16 (s, 2 H), 0.88–0.85 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 138.2, 136.9, 129.8, 128.4, 127.5, 77.5, 77.0, 76.6, 64.2, 58.6, 57.3, 47.7, 46.1, 44.3, 43.8, 37.5 ppm. MS (ESI): $m/z$ = 334.21 $[M + H]^+$. HRMS (ESI): calcd. for $C_{23}H_{28}NO$ $[M + H]^+$ 334.2171; found 334.2176.

**4d:** Eluent petroleum ether/ethyl acetate (15:1). Colorless oil (2.25 g, 85% yield). $[\alpha]_D^{25}$ = +56.1 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.25 (m, 10 H), 6.18 (d, $J$ = 6.3 Hz, 1 H), 5.92 (d, $J$ = 6.3 Hz, 1 H), 3.89 (d, $J$ = 15.0 Hz, 2 H), 3.81 (s, 1 H), 3.57–3.52 (m, 1 H), 3.31 (d, $J$ = 15.0 Hz, 2 H), 2.96 (t, $J$ = 9.0 Hz, 1 H), 2.62 (s, 1 H), 2.49 (s, 1 H), 2.41 (d, $J$ = 6.0 Hz, 2 H), 1.43–1.34 (m, 1 H), 1.33–1.26 (m, 2 H), 1.10 (d, $J$ = 9.0 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.9, 137.8, 133.3, 129.7, 128.3, 127.2, 66.1, 59.5, 59.3, 49.5, 46.9, 45.9, 44.7, 42.5 ppm. MS (ESI): $m/z$ = 334.21 $[M + H]^+$. HRMS (ESI): calcd. for $C_{23}H_{28}NO$ $[M + H]^+$ 334.2171; found 334.2176.

**4e:** Eluent petroleum ether/ethyl acetate (15:1). Colorless oil (2.32 g, 83% yield). $[\alpha]_D^{25}$ = +13.0 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.27 (m, 10 H), 3.97 (d, $J$ = 9.0 Hz, 2 H), 3.40 (t, $J$ = 12.0 Hz, 1 H), 3.22–3.17 (m, 3 H), 2.33 (t, $J$ = 12.0 Hz, 1 H), 2.08–2.03 (m, 2 H), 1.55–1.24 (m, 11 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 139.4, 132.5, 131.2, 130.8, 130.1, 65.9, 61.1, 58.7, 44.7, 37.2, 32.7, 30.8, 29.6, 29.3, 23.7, 23.3 ppm. MS (ESI): $m/z$ = 372.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{24}H_{31}NONa$ $[M + Na]^+$ 372.2303; found 372.2313.

**4f:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (1.77 g, 74% yield). $[\alpha]_D^{25}$ = +27.9 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz,$CDCl_3$): $\delta$ = 7.34–7.25 (m, 10 H), 5.06 (s, 1 H), 3.82 (d, $J$ = 12.0 Hz, 2 H), 3.51 (dd, $J$ = 11.3, 3.7 Hz, 1 H), 3.38–3.28 (m, 3 H), 2.11–2.02 (m, 1 H), 1.96 (dd, $J$ = 12.0, 3.0 Hz, 1 H), 1.76–1.70 (m, 1 H), 0.87 (d, $J$ = 9.0 Hz, 3 H), 0.62 (d, $J$ = 9.0 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.4, 129.7, 129.3, 128.2, 127.1, 66.6, 58.8, 55.8, 39.2, 33.8, 18.2, 10.6 ppm. MS (ESI): $m/z$ = 298.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{28}NO$ $[M + H]^+$ 298.2171; found 298.2175.

**4g:** Eluent petroleum ether/ethyl acetate (10:1). Colorless oil (2.01 g, 82% yield). $[\alpha]_D^{25}$ = –33.1 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.29 (m, 10 H), 3.91 (d, $J$ = 12.0 Hz, 2 H), 3.36–3.31 (m, 2 H), 3.24 (d, $J$ = 12.0 Hz, 2 H), 3.16 (t, $J$ = 12.0 Hz, 1 H), 2.78 (t, $J$ = 12.0 Hz, 2 H), 2.52–2.45 (m, 1 H), 2.35–2.25 (m, 1 H), 2.22–2.15 (m, 2 H), 1.89–0.89 (m, 6 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 136.8, 127.6, 129.9, 127.4, 62.9, 58.3, 55.9, 53.1, 44.1, 38.1, 31.8, 28.7, 22.1 ppm. MS (ESI): $m/z$ = 310.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{28}NO$ $[M + H]^+$ 310.2171; found 310.2174.

**4h:** Eluent petroleum ether/ethyl acetate (16:1). Colorless oil (1.85 g, 70% yield). $[\alpha]_D^{25}$ = –37.1 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.35–7.26 (m, 10 H), 6.02–5.99 (m, 1 H), 5.77–5.74 (m, 1 H), 3.84 (d, $J$ = 12.0 Hz, 2 H), 3.70–3.67 (m, 1 H), 3.42–3.34 (m, 3 H), 2.76 (s, 1 H), 2.44 (s, 1 H), 2.31 (dd, $J$ = 15.0, 6.0 Hz, 1 H), 2.07–1.99 (m, 1 H), 1.96–1.89 (m, 1 H), 1.45–1.36 (m, 2 H), 0.85–0.78 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.9, 137.8, 133.3, 129.7, 128.3, 127.2, 66.1, 59.5, 59.2, 49.5, 46.9, 45.9, 44.7, 42.5 ppm. MS (ESI): $m/z$ = 334.21 $[M + H]^+$. HRMS (ESI): calcd. for $C_{23}H_{28}NO$ $[M + H]^+$ 334.2171; found 334.2176.

**General Procedure for the Preparation of 5:** A solution of **4** (7.43 mmol, 1.0 equiv.), $Boc_2O$ (5.13 g, 11.43 mmol), Pd/C (464 mg, 20% by weight) in methanol (47 mL) was charged with hydrogen (1 atm). The mixture was stirred at room temperature for 45 min, then filtered and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give the product.

**5a:** Eluent petroleum ether/ethyl acetate (5:1). Colorless oil (2.14 g, 89% yield). $[\alpha]_D^{25}$ = +19.3 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.33–7.21 (m, 5 H), 4.45 (s, 2 H), 3.63–3.59 (m, 1 H), 3.51–3.47 (m, 1 H), 3.34 (s, 1 H), 3.12–3.08 (m, 1 H), 2.32–2.25 (m, 1 H), 2.15–2.10 (m, 1 H), 1.98 (s, 1 H), 1.59–1.51 (m, 1 H), 1.49–1.45 (m, 10 H), 1.40–1.32 (m, 1 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 156.2, 138.5, 128.4, 127.3, 127.1, 79.9, 63.1, 45.9, 44.5, 40.2, 29.6, 28.4, 27.7, 22.5 ppm. MS (ESI): $m/z$ = 320.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{19}H_{30}NO_3$ $[M + H]^+$ 320.2226; found 320.2229.

**5b:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (1.98 g, 80% yield). $[\alpha]_D^{25}$ = +31.4 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.72 (s, 1 H), 7.33–7.20 (m, 5 H), 4.59 (s, 1 H), 4.30 (s, 1 H), 3.61 (s, 1 H), 3.50–3.46 (m, 2 H), 2.98 (s, 1 H), 2.09 (s, 1 H), 1.77 (s, 1 H), 1.55–1.52 (m, 3 H), 1.44 (s, 10 H), 1.40–1.20 (m, 4 H), 0.88 (s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 206.7, 137.6, 127.9, 126.6, 79.5, 51.4, 50.2, 47.3, 35.5, 27.8, 27.6, 25.8, 24.5, 23.3, 23.2 ppm. MS (ESI): $m/z$ = 356.2 $[M + Na]^+$. HRMS

(ESI): calcd. for $C_{20}H_{31}NO_3Na$ $[M + Na]^+$ 356.2202; found 356.2206.

**5c:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (1.88 g, 73% yield). $[\alpha]_D^{25}$ = +13.9 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.32–7.20 (m, 5 H), 4.58 (d, *J* = 15.0 Hz, 1 H), 4.28 (d, *J* = 15.0 Hz, 1 H),3.44–3.31 (m, 3 H), 3.08–3.01 (m, 1 H), 2.12–2.04 (m, 2 H), 1.76–1.68 (m, 3 H), 1.60–1.31 (m, 13 H), 1.23–1.04 (m, 3 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 160.7, 141.5, 128.4, 127.3, 127.1, 79.8, 67.7, 62.5, 52.3, 46.4, 39.6, 38.8, 37.2, 29.1, 28.4, 22.4 ppm. MS (ESI): *m*/*z* = 368.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{31}NO_3Na$ $[M + Na]^+$ 368.2202; found 368.2208.

**5d:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (1.99 g, 77% yield). $[\alpha]_D^{25}$ = +24.0 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.21 (m, 5 H), 4.54–4.46 (m, 2 H), 3.35 (d, *J* = 6.0 Hz, 1 H), 3.18–3.10 (m, 1 H), 2.91 (s, 1 H), 2.27 (s, 1 H), 2.06 (s, 1 H), 1.80 (s, 1 H), 1.56–1.34 (m, 15 H), 1.30–1.22 (m, 2 H), 1.03 (s, 1 H), 0.90–0.89 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 156.2, 140.7, 128.4, 127.3, 127.1, 79.8, 64.4, 51.5, 48.3, 46.1, 41.5, 38.2, 36.8, 29.6, 28.4, 22.2 ppm. MS (ESI): *m*/*z* = 368.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{31}NO_3Na$ $[M + Na]^+$ 368.2202; found 368.2208.

**5e:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (1.68 g, 62% yield). $[\alpha]_D^{25}$ = +13.0 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.34–7.20 (m, 5 H), 4.40 (s, 2 H), 3.77–3.71 (m, 1 H), 3.59–3.53 (m, 1 H), 3.42–3.38 (m, 2 H), 2.16–2.08 (m, 1 H), 2.00–1.93 (m, 1 H), 1.78–1.66 (m, 2 H), 1.59–1.55 (m, 4 H), 1.47 (s, 2 H), 1.44 (s, 9 H), 1.36–1.26 (m, 3 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 157.3, 139.6, 128.4, 127.2, 126.9, 79.7, 62.5, 49.9, 44.4, 41.2, 36.4, 28.3, 26.5, 26.3, 26.0, 20.7 ppm. MS (ESI): *m*/*z* = 382.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{22}H_{33}NO_3Na$ $[M + Na]^+$ 382.2358; found 382.2368.

**5f:** Eluent petroleum ether/ethyl acetate (8:1). Colorless oil (1.94 g, 85% yield). $[\alpha]_D^{25}$ = +23.1 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.32–7.22 (m, 5 H), 4.57–4.52 (m, 1 H), 4.36–4.29 (m, 1 H), 3.59–3.49 (m, 2 H), 3.32 (s, 1 H), 2.74 (s, 1 H), 1.93–1.89 (m, 1 H), 1.75 (s, 2 H), 1.45 (s,9 H), 0.91 (d, *J* = 6.0 Hz, 3 H), 0.80 (s, 3 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 156.7, 138.4, 128.4, 127.1, 80.8, 65.4, 51.2, 50.0, 34.0, 28.3,14.5, 13.8 ppm. MS (ESI): *m*/*z* = 330.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{29}NO_3Na$ $[M + Na]^+$ 330.2045; found 330.2050.

**5g**: Eluent petroleum ether/ethyl acetate (5:1). Colorless oil (2.09 g, 87% yield). $[\alpha]_D^{25}$ = –27.5 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.43–7.37 (m, 5 H), 4.56 (s, 2 H), 3.73–3.69 (m, 1 H), 3.61–3.58 (m, 1 H), 3.45 (s, 1 H), 3.23–3.18 (m, 1 H), 2.41–2.38 (m, 1 H), 2.25–2.21 (m, 1 H), 2.09 (s, 1 H), 1.81–1.73 (m, 3 H), 1.71–1.64 (m, 1 H), 1.64–1.55 (m, 10 H), 1.50–1.45 (m, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 156.2, 138.5, 128.5, 127.3, 127.1, 79.9, 63.1, 45.9, 44.5, 40.2, 29.6, 28.4, 27.7, 22.5 ppm. MS (ESI): *m*/*z* = 320.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{19}H_{30}NO_3$ $[M + H]^+$ 320.2226; found 320.2229.

**5h:** Eluent petroleum ether/ethyl acetate (6:1). Colorless oil (2.03 g, 79% yield). $[\alpha]_D^{25}$ = –24.1 (*c* = 0.1, $CH_3OH$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.22 (m, 5 H), 4.60 (d, *J* = 15.0 Hz, 1 H), 4.31 (d, *J* = 15.0 Hz, 1 H), 3.43 (s, 1 H), 3.39–3.33 (m, 1 H), 3.11–3.03 (m, 1 H), 2.14 (s, 1 H), 2.07–2.06 (m, 1 H), 1.91 (s, 1 H), 1.80–1.66 (m, 1 H), 1.56–1.53 (m, 2 H), 1.48 (s, 9 H), 1.42–1.39 (m, 2 H), 1.30–1.21 (m, 2 H), 1.17–1.09 (m, 2 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 160.6, 141.5, 128.4, 127.3, 127.1, 79.8, 67.7, 62.5, 52.3, 46.4, 39.6, 38.9, 37.2, 29.1, 28.4, 22.4 ppm. MS (ESI): *m*/*z* = 368.2 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{31}NO_3Na$ $[M + Na]^+$ 368.2202; found 368.2208.

**General Procedure for the Preparation of 6:** To a solution of **5** (6.7 mmol, 1.0 equiv.) in $CH_2Cl_2$ (74 mL) at room temperature was added PCC (2.89 g, 13.4 mmol), then the mixture was stirred for 1 h, filtered through Celite and concentrated in vacuo to give the crude aldehyde, which was used in the next step without further purification.

**General Procedure for the Preparation of 7:** To a solution of crude aldehyde **6** (5.86 mmol, 1.0 equiv.) in $CH_2Cl_2$ (37 mL) was added $CF_3COOH$ (6.7 mL) dropwise. After 1 h, the excess $CF_3COOH$ and solvent was removed. The residue was diluted with $CH_3CN$ (37 mL), then TMSCN (2.2 mL) was added. The mixture was stirred for 3 h. The solvent was removed and the residue was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to give the product as the mixture of *endo* and *exo*.

**7a:** Eluent petroleum ether/ethyl acetate (30:1). Colorless oil (904.9 mg, 49% yield from **5a**, 3.6:1 *dr*). $[\alpha]_D^{25}$ = +20.2 (*c* = 0.1, $CH_3OH$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.35–7.25 (m, 5 H), 4.00 (d, *J* = 10.0 Hz, 0.25 H), 3.85 (d, *J* = 10.0 Hz, 0.75 H), 3.66 (d, *J* = 10.0 Hz, 0.25 H), 3.62 (d, *J* = 15.0 Hz, 0.75 H), 3.53 (d, *J* = 15.0 Hz, 0.25 H), 3.42 (s, 0.75 H), 2.81–2.77 (m, 1 H), 2.75–2.71 (m, 1 H), 2.67–2.61 (m, 1.7 H), 2.36–2.33 (m, 0.25 H), 1.89–1.81 (m, 1.75 H), 1.79–1.77 (m, 1 H), 1.75–1.55 (m, 1 H), 1.47–1.37 (m, 3 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 137.9, 128.9, 128.5, 127.4, 117.6, 59.7, 58.6, 56.7, 55.9, 48.5, 45.5, 42.4, 41.3, 34.4, 33.6, 30.5, 27.3, 26.8 ppm. MS (ESI): *m*/*z* = 227.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{19}N_2$ $[M + H]^+$ 227.1548; found 227.1550.

**7b:** Eluent petroleum ether/ethyl acetate (40:1). Colorless oil (980.5 mg, 61% yield from **5b**, 5.7:1 *dr*). $[\alpha]_D^{25}$ = +29.0 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.53–7.18 (m, 5 H), 4.06 (d, *J* = 13.0 Hz, 0.14 H), 3.96 (d, *J* = 10.0 Hz, 0.86 H), 3.90 (s, 0.14 H), 3.82 (d, *J* = 10.0 Hz, 0.86 H), 3.66 (d, *J* = 13.0 Hz, 0.14 H), 3.50 (d, *J* = 5.0 Hz, 0.86 H), 2.90 (t, *J* = 5.0 Hz,0.14 H), 2.83 (t, *J* = 10.0 Hz, 0.86 H), 2.80–2.74 (m, 1 H), 2.70–2.66 (m, 0.14 H), 2.61–2.52 (m, 0.86 H), 2.41–2.37 (m, 0.86 H), 2.29–2.12 (m, 0.14 H), 1.94–1.87 (m, 1 H), 1.78–1.67 (m, 1 H), 1.64–1.51 (m, 4 H), 1.49–1.36 (m, 2 H), 1.35–1.26 (m, 1 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 138.2, 128.7, 128.5, 127.3, 118.9, 58.4, 57.2, 54.9, 43.3, 35.5, 26.5, 26.2, 23.2, 20.9 ppm. MS (ESI): *m*/*z* = 241.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{21}N_2$ $[M + H]^+$ 241.1705; found 241.1707.

**7c:** Eluent petroleum ether/ethyl acetate (40:1). Colorless oil (347.9 mg, 21% yield from **5c**, 4.9:1 *dr*). $[\alpha]_D^{25}$ = +38.7 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.35–7.28 (m, 5 H), 4.01 (d, *J* = 12.0 Hz, 0.17 H), 3.89 (d, *J* = 15.0 Hz, 0.83 H), 3.75 (d, *J* = 9.0 Hz, 0.19 H), 3.54 (d, *J* = 15.0 Hz, 1 H), 3.47 (d, *J* = 12.0 Hz, 0.2 H), 3.38 (d, *J* = 3.0 Hz, 0.8 H), 2.85–2.79 (m, 0.8 H), 2.76–2.70 (m, 0.2 H), 2.53–2.45 (m, 1 H), 2.40–2.37 (m,1 H), 2.36–2.19 (m, 2 H), 2.09–2.01 (m, 1 H), 1.92 (d, *J* = 9.0 Hz, 1 H), 1.58 (s, 2 H), 1.52–1.48 (m,2 H), 1.27 (s, 2 H), 1.26–1.06 (m, 3 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 139.0, 128.8, 128.4, 127.4, 118.7, 58.7, 57.5, 56.6, 52.7, 45.9, 41.3, 40.7, 34.3, 28.5, 28.2 ppm. MS (ESI): *m*/*z* = 226.2 $[M - CN]^+$. HRMS (ESI): calcd. for $C_{16}H_{20}N$ $[M - CN]^+$ 226.1596; found 226.1599.

**7d:** Eluent petroleum ether/ethyl acetate (45:1). Colorless oil (543.2 mg, 53% yield from **5d**, 3.0:1 *dr*). $[\alpha]_D^{25}$ = +18.8 (*c* = 0.1, $CH_3OH$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.30 (m, 5 H), 4.01 (d, *J* = 12.0 Hz, 0.25 H), 3.89 (d, *J* = 15.0 Hz, 0.75 H), 3.75 (d, *J* = 6.0 Hz, 0.25 H), 3.54 (d, *J* = 12.0 Hz, 0.75 H), 3.47 (d, *J* = 12.0 Hz, 0.25 H), 3.38 (d, *J* = 3.0 Hz, 0.75 H), 2.86–2.79 (m, 0.78

H), 2.76–2.70 (m, 0.29 H), 2.53–2.47 (m, 1 H), 2.40–2.37 (m, 1 H), 2.29–2.02 (m, 3 H), 1.94–1.91 (m, 1 H), 1.59–1.54 (m, 1 H), 1.49–1.42 (m, 2 H), 1.28 (s, 1 H), 1.19–1.12 (m, 2 H), 1.08 (d, $J$ = 12.0 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 140.2, 128.7, 128.4, 127.3, 114.8, 58.6, 57.5, 56.5, 52.6, 45.8, 41.3, 40.7, 34.3, 28.5, 28.1 ppm. MS (ESI): $m/z$ = 226.2 [M – CN]$^+$. HRMS (ESI): calcd. for $C_{16}H_{20}N$ [M – CN]$^+$ 226.1596; found 226.1599.

**7e:** Eluent petroleum ether/ethyl acetate (50:1). Colorless oil (860.3 mg, 48% yield from **5e**, 20:1 *dr*). $[\alpha]_D^{25}$ = +37.0 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.25 (m, 5 H), 3.88 (d, $J$ = 12.9 Hz, 1 H), 3.65 (d, $J$ = 12.9 Hz, 1 H), 3.59 (s, 1 H), 2.85 (d, $J$ = 9.6 Hz, 1 H), 2.77–2.71 (m, 1 H), 2.51 (d, $J$ = 10.3 Hz, 1 H), 2.33–2.27 (m, 1 H), 1.90–1.84 (m, 1 H), 1.74–1.64 (m, 1 H), 1.56–1.50 (m, 6 H), 1.37–1.26 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.9, 128.7, 128.4, 127.4, 117.9, 57.8, 56.4, 45.9, 38.2, 28.1, 28.0, 25.8,21.1, 20.7 ppm. MS (ESI): $m/z$ = 240.1 [M – CN]$^+$. HRMS (ESI): calcd. for $C_{17}H_{22}N$ [M – CN]$^+$ 240.1749; found 240.1745.

**7f:** Eluent petroleum ether/ethyl acetate (20:1). Colorless oil (1.06 g, 73% yield from **5f**, 1.3:1 *dr*). $[\alpha]_D^{25}$ = +3.25 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.28 (m, 5 H), 3.98–3.83 (m, 1 H), 3.74 (d, $J$ = 6.0 Hz, 0.5 H), 3.72–3.61 (m, 1 H), 3.28 (d, $J$ = 6.0 Hz, 0.5 H), 3.02–2.84 (m, 1 H), 2.63–2.37 (m, 1 H), 2.12–1.78 (m, 2 H), 1.20–1.13 (m, 3 H), 1.08–1.00 (m, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.6, 128.8, 128.6, 128.4, 127.3, 127.2, 118.6, 116.3, 60.4, 60.0, 59.7, 58.9, 56.8, 56.7, 46.8, 43.6, 39.9, 38.5, 18.9, 18.4,18.2, 14.6 ppm. MS (ESI): $m/z$ = 188.1 [M – CN]$^+$. HRMS (ESI): calcd. for $C_{13}H_{18}N$ [M – CN]$^+$ 188.1439; found 188.1442.

**7g:** Eluent petroleum ether/ethyl acetate (30:1). Colorless oil (859.2 mg, 47% yield from 5 g, 3.1:1 *dr*). $[\alpha]_D^{25}$ = –23.6 ($c$ = 0.1, $CH_3OH$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.28 (m, 5 H), 4.02 (d, $J$ = 13.0 Hz, 0.25 H), 3.87 (d, $J$ = 13.2 Hz, 0.75 H), 3.68 (d, $J$ = 7.9 Hz, 0.25 H), 3.63 (d, $J$ = 13.2 Hz, 0.75 H), 3.54 (d, $J$ = 13.0 Hz, 0.25 H), 3.44 (s, 0.75 H), 2.75–2.62 (m, 3.8 H), 2.38–2.34 (m, 0.3 H), 1.90–1.86 (m,2 H),1.76–1.60 (m, 1 H), 1.45–1.42 (m, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.9, 128.9, 128.5, 127.4, 117.6, 59.7, 58.6, 56.6, 55.9, 48.5, 45.5, 42.4, 41.3, 34.4, 33.6, 30.5, 27.3, 26.8 ppm. MS (ESI): $m/z$ = 227.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{19}N_2$ [M + H]$^+$ 227.1548; found 227.1550.

**7h:** Eluent petroleum ether/ethyl acetate (40:1). Colorless oil (608.2 mg, 36% yield from **5h**, 2.8:1 *dr*). $[\alpha]_D^{25}$ = –20.1 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36–7.26 (m, 5 H), 3.89–3.81 (m, 1 H), 3.66 (d, $J$ = 15.0 Hz, 0.72 H), 3.58–3.50 (m, 1 H), 3.36 (s, 0.31 H), 2.88–2.80 (m, 1 H), 2.66–2.64 (m, 1 H), 2.50–2.36 (m, 2 H), 2.35–2.26 (m, 2 H), 2.07–1.90 (m, 1 H), 1.70–1.53 (m, 2 H), 1.47–1.37 (m, 2 H), 1.32–1.26 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 140.2, 128.7, 128.4, 127.3, 114.8, 58.6, 57.5, 56.5, 52.6, 45.8, 41.3, 40.7, 34.2, 28.5, 28.1 ppm. MS (ESI): $m/z$ = 226.2 [M – CN]$^+$. HRMS (ESI): calcd. for $C_{16}H_{20}N$ [M – CN]$^+$ 226.1596; found 226.1599.

**General Procedure for the Preparation of 8:** A solution of **7**, as a mixture of *endo* and *exo* (2.16 mmol, 1.0 equiv.) in con. HCl (21 mL) was heated to reflux for 20 h. The solvent was then removed to give the desired product in excellent optical purity.

**8a:** White solid (500 mg, 95% yield), m.p. 275–277 °C. $[\alpha]_D^{25}$ = +28.0 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 7.38 (s, 5 H), 4.45 (d, $J$ = 12.0 Hz, 1 H), 4.11 (d, $J$ = 12.0 Hz, 1 H), 3.67–3.64 (m, 1 H), 3.57–3.51 (m, 1 H), 2.78–2.69 (m, 3 H), 1.71–1.47 (m, 6 H) ppm. $^{13}$C NMR (125 MHz, $D_2O$): $\delta$ = 173.5, 132.9, 132.3, 131.8, 131.5, 74.0, 60.5, 59.8, 49.6, 42.2, 33.3, 32.5, 25.9 ppm. MS (ESI): $m/z$ = 246.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{20}NO_2$ [M + H]$^+$ 246.1494; found 246.1496.

**8b:** White solid (503 mg, 89%yield), m.p. 269–271 °C. $[\alpha]_D^{25}$ = +37.1 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (500 MHz, $D_2O$): $\delta$ = 7.53–7.49 (m, 5 H), 4.55 (d, $J$ = 10.0 Hz, 1 H), 4.41 (d, $J$ = 15.0 Hz, 1 H), 4.06–3.99 (m, 2 H), 3.75–3.72 (m, 1 H), 3.35 (t, $J$ = 10.0 Hz, 1 H), 2.48–2.41 (m, 2 H), 1.84–1.81 (m, 1 H), 1.72–1.65 (m, 1 H), 1.60–1.49 (m, 4 H), 1.39–1.37 (m, 1 H) ppm. $^{13}$C NMR (125 MHz, $D_2O$): $\delta$ = 173.7, 133.1, 132.5, 131.5, 72.6, 62.2, 59.9, 44.3, 38.1, 28.1, 27.1, 26.1, 23.8 ppm. MS (ESI): $m/z$ = 260.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{16}H_{22}NO_2$ [M + H]$^+$ 260.1651; found 260.1653.

**8c:** White solid (515.8 mg, 88% yield), m.p. 276–277 °C. $[\alpha]_D^{25}$ = +56.1 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 7.38 (s, 5 H), 4.46 (d, $J$ = 12.8 Hz, 1 H), 4.09 (d, $J$ = 12.8 Hz, 1 H), 3.64–3.59 (m, 1 H), 3.53–3.46 (m, 1 H), 2.32 (s, 1 H), 2.24–2.12 (m, 2 H), 2.07 (s, 1 H), 1.47–1.38 (m, 3 H), 1.15 (d, $J$ = 9.0 Hz, 1 H), 1.06–1.01 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 174.0, 133.3, 132.7, 132.3, 131.8, 73.3, 59.9, 59.7, 53.8, 46.6, 42.0, 41.5, 33.9, 29.5 ppm. MS (ESI): $m/z$ = 272.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{17}H_{22}NO_2$ [M + H]$^+$ 272.1651; found 272.1658.

**8d:** White solid (580.3 mg, 99% yield), m.p. 255–256 °C. $[\alpha]_D^{25}$ = +24.9 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 7.43 (s, 5 H), 4.50 (d, $J$ = 12.0 Hz, 1 H), 4.12 (d, $J$ = 12.0 Hz, 1 H), 3.61–3.50 (m, 2 H), 2.76–2.69 (m, 1 H), 2.35 (s, 1 H), 2.26–2.15 (m, 2 H), 2.10 (s, 1 H), 1.57–1.51 (m, 3 H), 1.21–0.99 (m, 3 H) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 173.8, 154.8, 130.6, 130.0, 129.2,71.2, 57.2, 56.9, 52.1, 44.5, 39.4, 38.8, 31.2, 26.8 ppm. MS (ESI): $m/z$ = 272.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{17}H_{22}NO_2$ [M + H]$^+$ 272.1651; found 272.1658.

**8e:** White solid (576.5 mg, 94% yield), m.p. 285–287 °C. $[\alpha]_D^{25}$ = +54.5 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 7.36 (s, 5 H), 4.50 (d, $J$ = 12.8 Hz, 1 H), 4.14 (d, $J$ = 12.6 Hz, 1 H), 3.87 (d, $J$ = 8.8 Hz, 1 H), 3.15 (s, 1 H), 3.11–2.98 (m, 1 H), 2.79–2.38 (m, 1 H), 1.63–1.31 (m, 9 H) ppm. $^{13}$C NMR (75 MHz, $D_2O$, [D4]-MeOH): $\delta$ = 171.0, 144.6, 132.2, 131.6, 130.6, 69.5, 58.6, 56.3, 45.7, 38.4, 26.5, 26.2, 26.1, 26.0, 20.1, 19.9 ppm. MS (ESI): $m/z$ = 308.2 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{18}H_{23}NO_2Na$ [M + Na]$^+$ 308.1626; found 308.1634.

**8f:** White solid (483.4 mg, 96% yield), m.p. 251–252 °C. $[\alpha]_D^{25}$ = +10.0 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 7.42–7.00 (m, 5 H), 4.43–4.30 (m, 2 H), 3.74 (d, $J$ = 12.0 Hz, 1 H), 3.60–3.53 (m, 1 H), 3.24–3.17 (m, 1 H), 2.18–2.13 (m, 1 H), 1.91–1.84 (m, 1 H), 1.11 (d, $J$ = 6.0 Hz, 3 H), 0.98 (d, $J$ = 6.0 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 157.5, 134.8, 130.8, 130.2, 129.2, 73.7, 59.6, 46.1, 38.6, 18.5, 14.3, 14.1 ppm. MS (ESI): $m/z$ = 334.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{20}NO_2$ [M + H]$^+$ 188.1442; found 234.1497.

**8g:** White solid (505 mg, 96% yield), m.p. 270–272 °C. $[\alpha]_D^{25}$ = –30.0 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 7.50–7.49 (m, 5 H), 4.56 (d, $J$ = 10.0 Hz, 1 H), 4.23 (d, $J$ = 10.0 Hz, 1 H), 3.85 (d, $J$ = 5.0 Hz, 1 H), 3.68–3.66 (m, 1 H), 2.89–2.82 (m, 3 H), 1.86–1.83 (m, 1 H), 1.80–1.74 (m, 2 H), 1.72–1.61 (m, 2 H), 1.60–1.54 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 173.5, 132.9, 132.4, 131.8, 131.5, 74.0, 60.5, 59.8, 49.6, 42.2, 33.3, 32.5, 25.9 ppm. MS (ESI): $m/z$ = 246.1 [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{20}NO_2$ [M + H]$^+$ 246.1494; found 246.1496.

**8h:** White solid (515.8 mg, 86% yield), m.p. 275–276 °C. $[\alpha]_D^{25}$ = –36.2 ($c$ = 0.1, $CH_3OH$). $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 7.43 (s, 5 H), 4.50 (d, $J$ = 13.0 Hz, 1 H), 4.12 (d, $J$ = 12.8 Hz, 1 H), 3.62–3.46 (m, 2 H), 2.85–2.67 (m, 1 H), 2.35 (s, 1 H), 2.19 (dd, $J$ = 14.8, 8.8 Hz, 2 H), 2.10 (s, 1 H), 1.69–1.37 (m, 3 H), 1.32–0.90 (m, 3

H) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 173.8, 154.8, 130.7, 130.1, 129.2, 71.2, 57.2, 56.9, 52.1, 44.5, 39.4, 38.8, 31.2, 26.8 ppm. MS (ESI): *m*/*z* = 272.2 $[M + H]^+$. HRMS (ESI): calcd. for $C_{17}H_{22}NO_2$ $[M + H]^+$ 272.1651; found 272.1658.

**Procedure for the Preparation of 11:** To a solution of dry $CH_2Cl_2$ (10 mL) at –23 °C under a $N_2$ atmosphere titanium(IV) isopropoxide (0.29 mL) was added. After being stirred for 30 min, D-diisopropyltartrate (0.286 mL) and (*E*)-2-hexene-1-ol (100 mg, 0.99 mmol) in $CH_2Cl_2$ (0.33 mL) was added. After being stirred for 30 min, *tert*-butyl hydroperoxide (TBHP; 0.37 mL, 5.36 M in $CH_2Cl_2$) was added. The reaction mixture was stirred at –23 °C for 1 h, before water (5.8 mL) was added, and the reaction warmed to room temperature for 1 h. Next, a saturated solution of sodium hydroxide (30%) with sodium chloride (0.5 mL) was added and stirred for 30 min, filtered through Celite to give a clear, colorless solution and extracted with $CH_2Cl_2$. The organic layer was dried with $Na_2SO_4$ and concentrated, and the residue was purified by chromatography (petroleum ether/ethyl acetate) to give the desired product (103 mg, 89% yield). Colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.90 (d, *J* = 12.4 Hz, 1 H), 3.16 (t, *J* = 6.4 Hz, 1 H), 2.92 (m, 2 H), 1.83 (s, 1 H), 1.56–1.43 (m, 4 H), 0.96 (t, *J* = 7.3 Hz, 3 H) ppm. MS (ESI): *m*/*z* = 116.1 $[M + H]^+$.

**Procedure for the Preparation of 12:** TEMPO (18.69 mg, 0.12 mmol) was added to a mixture of **11** (100 mg, 0.86 mmol) in acetonitrile (5.16 mL) and sodium phosphate buffer (4.3 mL) at room temperature. The mixture was heated at 35 °C, then sodium chlorite (0.311 g) in water (2.4 mL. 3.44 mmol), and bleach (61.92 μL) in water (1.37 mL) were added into the reaction mixture simultaneously. The resulting mixture was heated to 100 °C for 2 h. The mixture was made basic by the addition of NaOH solution (1*N*; pH = 8–9), extracted with EtOAc. The organic layer was discarded, and sodium thiosulfate was added to the aqueous layer, acidified with HCl solution (1*N*; pH = 2), extracted with EtOAc. The combined organic layer was dried with $Na_2SO_4$, concentrated under reduced pressure to obtain the crude acid , which was used in the next step without further purification. $^1$H NMR (500 MHz, $[D_6]$DMSO): $\delta$ = 12.88 (br. s, 1 H), 3.12 (d, *J* = 1.8 Hz, 1 H), 3.05–3.02 (m, 1 H), 1.57–1.24 (m, 4 H), 0.95 (t, *J* = 7.3 Hz, 3 H) ppm. MS (ESI): *m*/*z* = 131.2 $[M + H]^+$.

**Procedure for the Preparation of 13:** To a mixture of **12** (42 mg, 0.32 mmol), NMM (38.8 μL) in anhydrous THF (1 mL) at –5 °C and pivaloylchloride (43.35 μL) was added. The mixture was stirred for 15 min at this temperature and cyclopropylamine (24.4 μL, 0.352 mmol) was added before the reaction mixture was warmed to room temperature for 3 h. The reaction was quenched by water, extracted with EtOAc, and the combined organic layers were washed with HCl (1*N*), dried with $Na_2SO_4$, and concentrated under reduced pressure to obtain the crude product, which was purified by chromatography (petroleum ether/ethyl acetate = 5:1) to get the product (29.1 mg, 60.6% yield) as a solid with a low melting point. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 6.17 (s, 1 H), 3.18 (s, 1 H), 2.88–2.75 (m, 1 H), 2.68–2.70 (m, 1 H), 1.63–1.45 (m, 4 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 0.77–0.75 (m, 2 H), 0.49–0.45 (m, 2 H) ppm. MS (ESI): *m*/*z* = 192.1 $[M + Na]^+$.

**Procedure for the Preparation of 14:** A mixture of **13** (95.87 mg, 0.56 mmol), sodium azide (145.6 mg, 2.24 mmol), and anhydrous magnesium sulfate (269.6 mg) in methanol (1.5 mL) was heated to 70 °C for 5 h. The mixture was diluted with methanol and filtered through a pad of Celite. The solvent was removed under reduced pressure, the residue was diluted with EtOAc and water, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried with $Na_2SO_4$. The solvent was removed to give the crude product, which was purified by chromatography (petroleum ether/ethyl acetate = 5:1) to give the product as a white powder (83 mg, 69.7% yield). $^1$H NMR (500 MHz, $[D_6]$DMSO): $\delta$ = 7.88 (s, 1 H), 5.97 (d, *J* = 5.0 Hz, 1 H), 4.03–4.01 (m, 1 H), 3.44 (d, *J* = 10.0 Hz, 1 H), 2.68–2.65 (m, 1 H), 1.58–1.29 (m, 4 H), 0.88 (t, *J* = 5.0 Hz, 3 H), 0.61 (d, *J* = 5.0 Hz, 2 H), 0.49 (d, *J* = 5.0 Hz, 2 H) ppm. MS (ESI): *m*/*z* = 235.1 $[M + Na]^+$.

**Procedure for the Preparation of 15:** A vessel that contained Pd/C (10%, 70 mg) and **14** (693 mg, 3.2 mmol) in methanol (32 mL) was charged with hydrogen (1 bar) at room temperature for 2.5 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to give the crude product. To a solution of product in methanol, hydrochloric acid (1.0 equiv.) was added. The solution was concentrated under reduced pressure to get a crude product, which was recrystallization from 2-propanol to give a white powder (516 mg, 84% yield). $^1$H NMR (500 MHz, $[D_6]$-DMSO): $\delta$ = 8.14 (s, 3 H), 8.05 (s, 1 H), 6.27 (s, 1 H), 4.22 (s, 1 H), 3.38 (s, 1 H), 2.67 (s, 1 H), 1.48–1.23 (m, 4 H), 0.83 (t, *J* = 10.0 Hz, 3 H), 0.61 (d, *J* = 5.0 Hz, 2 H), 0.52 (d, *J* = 5.0 Hz, 2 H) ppm. MS (ESI): *m*/*z* = 223.0 $[M + H]^+$.

**Procedure for the Preparation of 16:** To a solution of **8** (166.2 mg, 0.68 mmol, 1.0 equiv.), **15** (151.4 mg, 0.68 mmol), EDCI (194 mg, 1.02 mmol), and HOBt (145 mg, 1.09 mmol) in dimethylformamide (DMF; 5 mL) at 0 °C was added NMM (0.3 mL) dropwise. The reaction mixture was kept at 0 °C for 30 min. Then the resulting mixture was stirred overnight at room temperature. The solvent was removed and the residue was diluted with EtOAc, and washed with HCl (1*N*), saturated $NaHCO_3$ solution, and brine. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 1:1) to give the product as white powder. (198.6 mg, 80.4% yield). $[\alpha]_D^{25}$ = +74.5 (*c* = 0.1, $CH_3OH$). $^1$H NMR (500 MHz, $[D_6]$DMSO): $\delta$ = 7.83 (s, 1 H), 7.43 (d, *J* = 10.0 Hz, 1 H), 7.35–7.29 (m, 5 H), 5.69 (s, 1 H), 4.18–4.06 (m, 1 H), 3.92 (s, 1 H), 3.89–3.87 (d, *J* = 10.0 Hz, 1 H), 3.09–3.06 (d, *J* = 15.0 Hz, 1 H), 2.93–2.91 (t, *J* = 5.0 Hz, 1 H), 2.67–2.64 (m, 1 H), 2.44–2.41 (m, 3 H), 1.74–1.72 (t, *J* = 5.0 Hz, 1 H), 1.52–1.16 (m, 10 H), 0.87–0.78 (m, 3 H), 0.59–0.47 (m, 4 H) ppm. $^{13}$C NMR (125 MHz, $[D_6]$DMSO): $\delta$ = 172.8, 172.1, 138.2, 129.0, 127.9, 126.9, 74.9, 73.4, 59.1, 58.1, 49.9, 49.5, 40.6, 31.4, 30.8, 23.9, 22.1, 18.8, 13.8, 5.4, 5.3 ppm. MS (ESI): *m*/*z* = 414.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{24}H_{36}N_3O_3$ $[M + H]^+$ 414.2757; found 414.2760.

**Procedure for the Preparation of 18:** A vessel that contained Pd/C (10%, 12 mg) and **16** (55.7 mg, 0.13 mmol) in methanol (1 mL) was charged with hydrogen (1 bar) at room temperature overnight. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to give a crude product, to which was added **17** (40.41 mg, 0.107 mmol) and DIPEA (27.7 μL). The mixture was dissolved in DMF (1 mL), cooled to 0 °C, and PyBop (72.39 mg, 0.139 mmol) was added, before the reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed and the residue was diluted with EtOAc, and washed with HCl (1*N*), saturated $NaHCO_3$ solution, and brine. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in $CH_2Cl_2$ (3 mL), and Dess–Martin reagent (162.08 mg, 0.382 mmol) was added before the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography ($CH_2Cl_2$/

MeOH = 70:1) to give the product as a white powder (61.1 mg, 70% yield). $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$ = 9.20 (s, 1 H), 8.91 (d, $J$ = 2.2 Hz, 1 H), 8.76 (s, 1 H), 8.67 (d, $J$ = 4.9 Hz, 1 H), 8.49 (d, $J$ = 9.1 Hz, 1 H), 8.20 (dd, $J$ = 12.7, 8.0 Hz, 2 H), 4.96 (s, 1 H), 4.68 (dd, $J$ = 20.1, 11.5 Hz, 1 H), 4.54 (d, $J$ = 9.0 Hz, 1 H), 4.28 (d, $J$ = 3.0 Hz, 1 H), 3.74 (d, $J$ = 7.9 Hz, 1 H), 3.68–3.61 (m, 1 H), 2.75 (d, $J$ = 4.4 Hz, 1 H), 2.64 (s, 1 H), 1.88–1.30 (m, 19 H), 1.27–0.78 (m, 21 H),0.66 (d, $J$ = 5.3 Hz, 2 H), 0.60 (dd, $J$ = 19.8, 3.9 Hz, 2 H) ppm. MS (ESI): $m/z$ = 680.4 [M + H]$^+$.

**Supporting Information** (see footnote on the first page of this article): Copies of all spectra and chromatographic data.

## Acknowledgments

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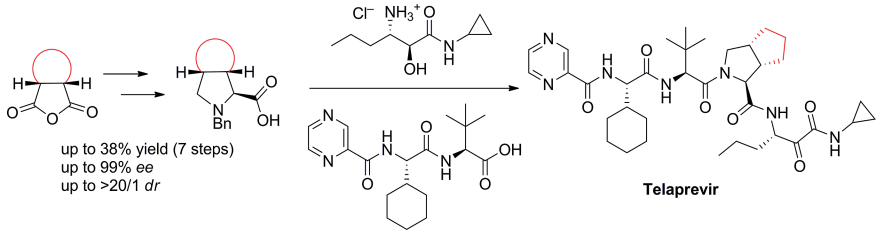
**Asymmetric Synthesis**




Asymmetric synthesis of 3,4-disubstituted proline derivatives was developed through asymmetric ring opening of substituted anhydrides, intramolecular Strecker reaction, and thermodynamically controlled cyanide hydrolysis with high stereoselectivity and moderate yield. HCV protease inhibitor Telaprevir was synthesized by using the above methodology.



**Keywords:** Synthetic methods / Asymmetric synthesis / Medicinal chemistry / Antivirus agents / Amino acids