An Ugi-type Condensation of α-Isocyanoacetamide and Chiral Cyclic Imine under a New Catalytic System

Sheng Li, Ruijiao Chen, Xiubing Liu, Li Pan, Liang Xia, Xiaochuan Chen*

Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China, and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China.

E-mail: chenxc@scu.edu.cn

SUPPORTING INFORMATION

A. General Information S_2
B. General procedure and the spectral characterization data of the products S_3
C. Copies of the NMR spectra S_{11}
D. NOESY Spectra of compounds 6c and 6f S_{28}
A. General Information

IR spectra were recorded on a commercial spectrophotometer. Optical rotations were reported as follows: \([\alpha]_{D}^{T}\) (c: g/100 mL, in solvent). \(^1\)H-NMR spectra were recorded on commercial instruments (400 or 600 MHz) with TMS as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz), integration. \(^{13}\)C-NMR data were collected on commercial instruments (100 or 150 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. HR-ESIMS spectra were recorded using a commercial apparatus and methanol or Dichloromethane was used to dissolve the sample.

Solvents for reaction were distilled prior to use: Toluene from CaH\(_2\), Methanol was distilled from magnesium turnings. Trifluoroethanol (TFE) and other reagents were obtained from commercial suppliers unless otherwise stated. 4 Å Molecular sieves was powdered <50 µm, which was activated at 120°C for 5 h and stored under nitrogen.
B. General procedure and the spectral characterization data of the products

1. General Procedure for the Ugi-type Condensation of Ketoimine 5 and Isocyanides 1.

To a 0.4M solution of the imine 5 (1 equiv) in TFE were added successively isocyanides 1 (1 equiv) and phenyl phosphilic acid (0.1 equiv for 1a-d or 0.25 equiv for 1e, 1f and 1g or 0.5 equiv for 1h). After being stirred at r.t. for 20 minutes, then additional 1 (0.8 equiv for 1a or 0.4 equiv for other isocyanides) was added. The resulting mixture was stirred until imine consumed (TLC control), and quenched with 0.1% aqueous NaHCO₃, and extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated. The crude material was purified by flash column chromatography (silica gel) to afforded the desired product 6.

6a: Stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (5:1 to 3:2) as eluent. Yield: 86%; Yellow gel; [α]D²⁰ -51 (c = 0.9, in CH₂Cl₂); IR (neat): 3311, 2968, 2856, 1744, 1609, 1452, 1240, 1117, 898, 752, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.12-7.36 (m, 5H), 5.97 (s, 1H), 4.31 (dd, J = 3.2, 10.5 Hz, 1H), 4.18 (t, J = 10.3 Hz, 1H), 3.72-3.85 (m, 4H), 3.48-3.58 (m, 1H), 2.93-3.02 (m, 4H), 2.75 (dd, J = 6.8, 13.5 Hz, 1H), 2.51 (br s, 1H), 1.73 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.3, 157.5, 155.5, 136.3, 129.0, 128.8, 127.0, 102.8, 74.3, 66.0, 60.6, 49.5, 48.1, 37.8, 26.1; HRMS (ESI⁺): m/z calculated for C₁₉H₂₃N₃O₄Na [M+Na]⁺: 380.1586, found: 380.1589.
6b: Stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (5:1 to 3:1) as eluent. Yield: 93%; Colorless gel; $\left[\alpha\right]_D^{20}$ -12 (c = 1.5, in CH$_2$Cl$_2$); IR (neat): 3314, 2960, 2915, 2854, 1744, 1453, 1233, 1116, 755, 700 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.05-7.34 (m, 10H), 4.30 (dd, $J = 3.4$, 10.5 Hz, 1H), 4.18 (t, $J = 10.4$ Hz, 1H), 3.80 (d, $J = 15.4$ Hz, 1H), 3.75 (d, $J = 15.7$ Hz, 1H), 3.64-3.70 (m, 4H), 3.52-3.61 (m, 1H), 2.81-2.89 (m, 4H), 2.73 (dd, $J = 5.2$, 13.7 Hz, 1H), 2.55 (dd, $J = 8.7$, 13.7 Hz, 1H), 2.27 (br s, 1H), 1.73 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 167.8, 157.5, 152.3, 139.5, 136.3, 128.9, 128.8, 128.5, 128.4, 127.0, 126.3, 124.8, 74.4, 66.8, 60.9, 50.8, 49.5, 37.6, 31.8, 26.1; HRMS (ESI$^+$): m/z calculated for C$_{26}$H$_{30}$N$_3$O$_4$ [M+H]$^+$: 448.2236, found: 448.2229.

6c: Stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (4:1 to 2:1) as eluent. Yield: 93%; Yellow gel; $\left[\alpha\right]_D^{20}$ -22 (c = 2, in CH$_2$Cl$_2$); IR (neat): 3314, 2964, 2855, 1747, 1656, 1452, 1200, 1115, 918, 701 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.15-7.36 (m, 5H), 4.30-4.36 (m, 1H), 4.23 (t, $J = 10.7$ Hz, 1H), 3.71-3.77 (m, 4H), 3.62-3.71 (m, 1H), 2.88-2.94 (m, 4H), 2.75-2.87 (m, 2H), 2.51-2.61 (m, 1H), 2.34 (br s, 1H), 1.78 (s, 3H), 1.17 (t, $J = 7.4$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 168.0, 157.6, 150.4, 136.3, 132.3, 128.9, 128.8, 127.0, 74.4, 66.9, 60.8, 51.3, 49.3, 37.6, 26.3, 25.3, 21.9, 21.8; HRMS (ESI$^+$): m/z calculated for C$_{22}$H$_{29}$N$_3$O$_4$Na [M+Na]$^+$: 422.2056, found: 422.2057.

6d: Stirred for 1 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (2:1 to 1:2) as eluent. Yield: 92%; Colorless gel; $\left[\alpha\right]_D^{20}$ -31 (c = 0.7, in CH$_2$Cl$_2$); IR (neat): 3312, 2922, 2854, 1744, 1213, 1116, 753,
701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.22-7.33 (m, 5H), 4.33 (dd, J = 3.5, 10.5 Hz, 1H), 4.19 (t, J = 10.4 Hz, 1H), 3.72-3.78 (m, 4H), 3.46-3.55 (m, 1H), 2.88-2.93 (m, 4H), 2.76 (dd, J = 5.1, 13.7 Hz, 1H), 2.59 (dd, J = 8.7, 13.7 Hz, 1H), 2.06 (s, 3H), 1.73 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.8, 157.1, 151.7, 136.3, 128.9, 128.8, 127.0, 121.3, 74.3, 66.8, 60.8, 50.7, 49.6, 37.7, 25.9, 11.2; HRMS (ESI⁺): m/z calculated for C₂₀H₂₅N₃O₄Na [M+Na]⁺: 394.1743, found: 394.1749.

6e: Stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (3:1 to 2:3) as eluent. Yield: 87%; Yellow gel; [α]D²⁰ -23 (c = 4.1, in CH₂Cl₂); IR (neat): 3314, 2960, 2854, 1744, 1233, 1116, 755, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.16-7.31 (m, 5H), 4.34 (dd, J = 3.4, 10.4 Hz, 1H), 4.18 (t, J = 10.4 Hz, 1H), 3.81 (s, 2H), 3.65-3.74 (m, 4H), 2.94-3.01 (m, 4H), 2.34 (br s, 1H), 1.76 (s, 3H), 1.57-1.67 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 168.1, 158.1, 152.3, 139.4, 128.5, 128.4, 126.2, 124.9, 73.4, 66.8, 60.8, 54.2, 50.9, 31.8, 29.8, 26.4, 18.7, 18.6; HRMS (ESI⁺): m/z calculated for C₂₂H₂₉N₃O₄Na [M+Na]⁺: 422.2056, found: 422.2062.

6f: Stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether / acetone (12:1 to 8:1) as eluent. Yield: 84%; Yellow gel; [α]D²⁰ -45 (c = 0.1, in CH₂Cl₂); IR (neat): 3353, 2935, 2854, 1741, 1631, 1448, 1198, 754, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.31-7.45 (m, 5H), 4.54 (dd, J = 6.0, 8.4 Hz, 1H), 4.38 (s, 1H), 4.35-4.39 (m, 2H), 3.74-3.82 (m, 4H), 2.98-3.06 (m, 4H), 2.82-2.93 (m, 1H), 1.85 (s, 3H), 1.22 (d, J = 5.4 Hz, 3H), 1.20 (d, J = 5.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.7, 157.7, 150.5, 137.7, 132.5, 128.9, 128.7, 127.4, 75.2, 66.9, 61.1, 53.7, 51.4, 26.5, 25.5, 21.9; HRMS (ESI⁺): m/z calculated for C₂₁H₂₉N₃O₄ [M+H]⁺: 386.2080, found: 386.2072.

6g: Stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether / acetone (20:1 to 10:1) as eluent. Yield: 88%; Colorless gel; [α]D²⁰
-9 (c = 0.5, in CH₂Cl₂); IR (neat): 3334, 2964, 1747, 1656, 1459, 1201, 1117 cm⁻¹; 
¹H NMR (400 MHz, CDCl₃): δ (ppm) 4.30 (dd, J = 3.0, 10.2 Hz, 1H), 4.17 (t, J = 10.4 Hz, 1H), 3.73-3.81 (m, 4H), 2.98-3.05 (m, 5H), 2.80-2.92 (m, 1H), 2.40 (br s, 1H), 2.16-2.30 (m, 1H), 1.97 (dq, J = 7.6, 21.4 Hz, 1H), 1.69 (dq, J = 7.0, 20.6 Hz, 1H), 1.19 (d, J = 1.2 Hz, 3H), 1.18 (d, J = 1.2 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H), 0.93-1.00 (m, 6H); 
¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.8, 157.6, 150.7, 132.1, 73.3, 66.9, 64.9, 54.3, 51.4, 33.2, 29.7, 25.3, 22.0, 21.9, 18.7, 18.6, 8.2; HRMS (ESI⁺): m/z calculated for C₁₉H₃₁N₃O₄Na [M+Na]⁺: 388.2212, found: 388.2219.

6h: Stirred for 1.25 h, the product was isolated by flash column chromatography using petroleum ether / ethyl ether (2:1 to 1:1) as eluent. Yield: 98%; Colorless gel; [α]D²⁰ -21 (c = 1.6, in CH₂Cl₂); IR (neat): 3316, 2965, 2854, 1745, 1654, 1456, 1199, 1116, 977, 702 cm⁻¹; 
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.13-7.54 (m, 5H), 4.28 (dd, J = 3.2, 10.3 Hz, 1H), 4.16 (t, J = 10.3 Hz, 1H), 3.67-3.83 (m, 5H), 2.89-2.95 (m, 4H), 2.76-2.87 (m, 2H), 2.61 (dd, J = 8.9, 13.8 Hz, 1H), 2.30 (br s, 1H), 2.24 (dq, J = 7.4, 21.3 Hz, 1H), 1.92 (dq, J = 7.4, 21.3 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); 
¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.6, 157.3, 150.6, 136.5, 132.1, 129.0, 128.8, 126.9, 74.3, 66.9, 64.9, 51.3, 49.4, 37.7, 32.8, 25.3, 21.9, 21.8, 8.2; HRMS (ESI⁺): m/z calculated for C₂₃H₃₂N₃O₄ [M+H]⁺: 414.2393, found: 414.2387.

6i: Stirred for 1h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (2:3 to 1:3) as eluent. Yield: 64%; Colorless gel; [α]D²⁰ -1 (c = 0.7, in CH₂Cl₂); IR (neat): 3299, 2964, 2856, 1656, 1499, 1452, 1200, 1115, 754, 702 cm⁻¹; 
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.71-7.78 (m, 4H), 7.12-7.32 (m, 5H), 3.55-3.64 (m, 1H), 3.28 (t, J = 11.1 Hz, 1H), 3.15 (dd, J = 3.7, 11.3 Hz, 1H), 3.00 (s, 3H), 2.86-2.91 (m, 4H), 2.77-2.86 (m, 2H), 2.63 (dd, J = 8.8, 13.7 Hz, 1H), 2.20 (br s, 1H), 1.66 (s, 3H), 1.14-1.22 (m, 6H); 
¹³C NMR (100 MHz, CDCl₃): δ (ppm) 167.6, 159.4, 149.8, 137.1, 132.1, 128.9, 128.7, 126.8, 66.9, 60.7, 55.5, 51.4,
6j: Stirred for 1h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (2:1 to 1:1) as eluent. Yield: 81%; Yellow gel; $[\alpha]_D^{20} +2$ (c = 3.3, in CH$_2$Cl$_2$); IR (neat): 3300, 2962, 2859, 1656, 1452, 1115, 735, 701 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.12-7.30 (m, 5H), 3.73-3.75 (m, 4H), 7.44-7.55 (m, 2H), 3.32-3.39 (m, 1H), 3.26 (dd, $J = 11.1$, 21.9 Hz, 1H), 3.16 (dd, $J = 3.8$, 11.2 Hz, 1H), 2.87-2.89 (m, 4H), 2.78-2.85 (m, 2H), 2.61 (dd, $J = 9.0$, 13.8 Hz, 1H), 2.16 (br s, 1H), 1.66 (s, 3H), 1.54-1.60 (m, 2H), 1.35-1.40 (m, 2H), 1.17 (d, $J = 2.1$ Hz, 3H), 1.15 (d, $J = 2.1$ Hz, 3H), 0.94 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 167.3, 156.0, 150.0, 137.1, 132.2, 128.8, 128.7, 126.8, 67.0, 60.7, 53.2, 51.5, 49.4, 47.1, 39.6, 29.0, 25.7, 25.4, 22.0, 21.9, 20.0, 13.9; HRMS (ESI$^+$): m/z calculated for C$_{26}$H$_{39}$N$_4$O$_3$ [M+H]$^+$: 455.3022, found: 455.3024.

6k (major isomer): Stirred for 4 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (4:1 to 3:1) as eluent. Yield: 84%; Colorless gel; $[\alpha]_D^{20} -12$ (c = 0.6, in CH$_2$Cl$_2$); IR (neat): 3315, 2938, 2851, 1744, 1629, 1448, 1235, 1197, 702 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.80-7.86 (m, 2H), 7.20-7.42 (m, 8H), 4.35 (dd, $J = 3.5$, 10.4 Hz, 1H), 4.22 (t, $J = 10.4$ Hz, 1H), 3.67-3.78 (m, 1H), 2.92-3.00 (m, 4H), 2.81 (dd, $J = 4.6$, 13.7 Hz, 1H), 2.58 (dd, $J = 9.2$, 13.7 Hz, 1H), 2.51 (br s, 1H), 1.75 (s, 3H), 1.54-1.72 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 167.8, 156.8, 153.1, 136.4, 132.0, 129.1, 128.9, 128.3, 127.0, 126.7, 125.8, 122.6, 74.5, 60.9, 51.2, 49.6, 37.7, 26.6, 25.8, 23.8; HRMS (ESI$^+$): m/z calculated for C$_{26}$H$_{39}$N$_4$O$_3$ [M+H]$^+$: 432.2287, found: 432.2290.

6k' (minor isomer): Stirred for 4 h, the product was isolated by flash column chromatography using
dichloromethane as eluent. Yield: 6.5%; Colorless gel; $[\alpha]_D^{20}$ -73 (c = 0.4, in CH$_2$Cl$_2$); IR (neat): 3305, 2938, 2852, 1743, 1631, 1448, 1221, 755, 702 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.77-8.00 (m, 2H), 7.19-7.42 (m, 8H), 4.28-4.34 (m, 2H), 3.51-3.67 (m, 1H), 3.00-3.13 (m, 4H), 2.88 (dd, $J$ = 6.9, 13.6 Hz, 1H), 2.88 (dd, $J$ = 6.7, 13.6 Hz, 1H), 2.42 (br s, 1H), 1.82 (s, 3H), 1.55-1.75 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 169.1, 156.6, 153.2, 136.7, 132.0, 129.1, 128.9, 128.3, 127.0, 126.7, 125.9, 122.6, 73.4, 59.7, 51.2, 50.5, 38.5, 25.9, 25.0, 23.9; HRMS (ESI$^+$): m/z calculated for C$_{26}$H$_{30}$N$_3$O$_3$ [M+H]$^+$: 432.2287, found: 432.2279.

6l: Stirred for 4h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (6:1 to 3:2) as eluent. Yield: 73%; Colorless gel; $[\alpha]_D^{20}$ -7 (c = 0.6, in CH$_2$Cl$_2$); IR (neat): 3313, 2937, 2852, 1746, 1451, 1232, 1159, 728, 699 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.05-7.35 (m, 10H), 4.28 (dd, $J$ = 3.5, 10.4 Hz, 1H), 4.17 (t, $J$ = 10.4 Hz, 1H), 3.79 (d, $J$ = 15.6 Hz, 1H), 3.73 (d, $J$ = 15.6 Hz, 1H), 3.52-3.61 (m, 1H), 2.80-2.88 (m, 4H), 2.73 (dd, $J$ = 5.4, 13.7 Hz, 1H), 2.56 (dd, $J$ = 8.6, 13.7 Hz, 1H), 2.29 (br s, 1H), 1.72 (s, 3H), 1.46-1.61 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 168.0, 156.9, 153.8, 139.8, 136.3, 128.9, 128.8, 128.5, 128.3, 126.9, 126.1, 123.6, 74.3, 60.8, 51.9, 49.4, 37.7, 31.8, 26.1, 25.8, 23.8; HRMS (ESI$^+$): m/z calculated for C$_{27}$H$_{31}$N$_3$O$_3$Na[M+Na]$^+$: 468.2263, found: 468.2268.

6m: Stirred for 1.5 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (3:1 to 3:2) as eluent. Yield: 85%; Yellow gel; $[\alpha]_D^{20}$ -3 (c = 0.7, in CH$_2$Cl$_2$); IR (neat): 3312, 2973, 2873, 1743, 1621, 1449, 1234, 1156, 751, 701 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.58-7.63 (m, 2H), 7.18-7.40 (m, 8H), 4.34 (dd, $J$ = 3.5, 10.5 Hz, 1H), 4.22 (t, $J$ = 10.4 Hz, 1H), 3.75-3.82 (m, 1H), 3.13-3.26 (m, 4H), 2.80 (dd, $J$ = 4.9, 13.7 Hz, 1H), 2.61 (dd, $J$ = 8.9, 13.7 Hz, 1H), 1.88-1.97 (m, 4H), 1.75 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 167.9, 154.7, 151.0, 136.4, 132.5, 129.1, 128.8, 128.1, 127.0, 126.5, 126.1, 119.2, 74.4, 60.8, 50.2, 49.5, 37.8, 26.8, 25.4; HRMS (ESI$^+$): m/z calculated for C$_{25}$H$_{26}$N$_3$O$_3$ [M+H]$^+$: 418.2131, found: 418.2137.
6n: Stirred for 2h, the product was isolated by flash column chromatography using dichloromethane / ethyl ether (100:1 to 40:1) as eluent. Yield: 78%; White gel; [α]_D^{20} -13 (c = 0.4, in CH₂Cl₂); IR (neat): 3297, 2975, 2932, 2850, 1734, 1449, 1230, 729, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.04-7.32 (m, 10H), 4.30 (dd, J = 3.1, 10.4 Hz, 1H), 4.18 (t, J = 10.4 Hz, 1H), 3.68-3.80 (m, 2H), 3.53-3.63 (m, 1H), 2.88 (q, J = 7.2 Hz, 4H), 2.74 (dd, J = 5.2, 13.7 Hz, 2H), 2.55 (dd, J = 8.7, 13.5 Hz, 1H), 2.24 (br s, 1H), 1.73 (s, 3H), 0.90 (t, J = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 168.1, 158.5, 151.3, 139.7, 136.3, 129.0, 128.9, 128.8, 128.7, 128.3, 127.1, 126.1, 74.4, 60.9, 49.5, 48.0, 38.0, 31.6, 26.1, 13.4; HRMS (ESI⁺): m/z calculated for C_{26}H_{32}N_{3}O_{3} [M+H]^+: 434.2444, found: 434.2449.


To a 0.04M solution of 6 (1 equiv) in toluene was added maleic anhydride (1.2 equiv). The resulting mixture was heated to reflux. After completed consumption of 6 (TLC control), the mixture was filtrated and solvents were removed under vacuum. The crude compound was purified by chromatography (flash chromatography, SiO₂).

15a: Heated for 6 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (3:1 to 2:3) as eluent. Yield: 43%; Colorless gel; [α]_D^{20} +105 (c = 0.6, in CH₂Cl₂); IR (neat): 2923, 2853, 1760, 1700, 1452, 1369, 1111 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.66 (s, 1H), 7.21-7.36 (m, 5H), 4.61-4.70 (m, 1H), 4.43-4.56 (m, 2H), 3.86-3.91 (m, 4H), 3.30(dd, J = 3.6, 13.8 Hz, 1H), 3.22 (dd, J = 8.1, 13.8 Hz, 1H), 2.88-3.04 (m, 4H), 2.71 (s, 3H), 1.56 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 168.4, 167.1, 160.6, 156.9, 148.5, 135.6, 129.8, 128.8, 127.3, 122.0, 120.7, 67.7, 67.0, 64.1, 52.0, 50.7, 37.5, 23.5, 22.2; HRMS (ESI⁺): m/z calculated for C_{23}H_{25}N_{3}O_{4}Na [M+Na]^+: 430.1743, found: 430.1749.
15b: Heated for 6 h, the product was isolated by flash column chromatography using petroleum ether / ethyl acetate (3:1 to 3:2) as eluent. Yield: 40%; white crystal; mp 198-200 °C; $[\alpha]_D^{20} +50$ (c = 1.2, in CH$_2$Cl$_2$); IR (KBr): 2962, 2893, 2851, 1755, 1707, 1444, 1346, 1226, 1109, 894, 702 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.78 (s, 1H), 7.13-7.39 (m, 5H), 4.62 (dd, $J = 6.8$, 12.3 Hz, 1H), 4.35-4.57 (m, 3H), 4.21-4.30 (m, 1H), 3.76-3.88 (m, 4H), 2.81-2.90 (m, 2H), 2.71-2.80 (m, 2H), 2.20-2.32 (m, 1H), 2.00 (s, 3H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 168.3, 167.0, 163.2, 157.5, 148.8, 139.1, 128.9, 128.3, 126.3, 123.6, 122.5, 67.3, 67.1, 64.7, 54.6, 52.9, 40.5, 31.0, 23.7, 19.6, 18.3; HRMS (ESI$^+$): m/z calculated for C$_{25}$H$_{30}$N$_3$O$_4$ [M+H]$^+$: 436.2236, found: 436.2240.
C. Copies of the NMR spectra
18
$6k$ major isomer

$6k$ major isomer
6k* minor isomer
D. NOESY Spectra of compounds 6c and 6f