Electronic Supplementary Information for

Stereodivergent and Enantioselective Total Syntheses of Isochaetominines A–C and Eight Diastereomers: A Six-Step Approach
Zhong-Yi Mao, Hui Geng, Tian-Tian Zhang, Yuan-Ping Ruan, Jian-Liang Ye, and Pei-Qiang Huang*a,b

a Department of Chemistry and Fujian Provincial Key Laboratory of Chemical Biology, Collaborative Innovation Centre of Chemistry for Energy Materials, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, PR China
b State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China
E-mail: pqhuang@xmu.edu.cn

Table of Contents

General Procedures and data for step 2 and step 3…………………………...S2-S9

1H NMR and 13C NMR spectra of the synthetic products .......................S10-S39

Chiral HPLC diagrams of compounds 3, 6, 7, 8, ent-3, ent-6, ent-7 and ent-8…………………………………………………………………………………………... ... S40-S44

X-ray structures and crystal data for the proposed structure of
(−)-aniquinazolineD (3) and (+)-14-epi-isochaetominine C (7)-2H2O……… S45
General Procedure for the Step 2 (General Procedure 2)

To a stirring solution of 14 (5.09 mmol) in THF (20 mL) at −20 °C were added successively N-methylmorpholine (0.84 mL, 7.63 mmol) and tBuOCOC1 (0.74 mL, 5.60 mmol). After being stirred at −20 °C under N₂ for 15 min, the resulting suspension was added slowly to a solution of an amino acid benzyl ester p-toluenesulfonic acid salt (10.18 mmol) and N-methylmorpholine (1.68 mL, 15.28 mmol) in THF (36 mL) at −78 °C. The mixture was stirred for 12 h at −20 °C before quenching with a saturated aqueous solution of NH₄Cl (20 mL). The mixture was diluted with water (100 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 3:2) to give the dipeptide derivative.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)propanoate (15a).

Following the general procedure 2, the coupling of (R)-14 (1.80 g, 5.09 mmol) with L-alanine benzyl ester p-toluenesulfonic acid salt (3.57 g, 10.18 mmol) gave compound 15a (2.38 g, yield: 91%) as a yellow solid. Mp 129–131 °C; [α]D²⁰−36.9 (c 1.1, CHCl₃); IR (film) v max: 3415, 1738, 1646, 1529, 1455, 1349, 1198, 1140 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 8.00–7.96 (m, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.56–7.46 (m, 2H), 7.36–7.26 (m, 6H), 7.20–7.13 (m, 2H), 7.12–7.04 (m, 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 5.00 (dd, J = 14.8, 7.2 Hz, 1H), 4.52 (dq, J = 7.2, 7.3 Hz, 1H), 3.49 (dd, J = 14.8, 6.0 Hz, 1H), 3.30 (dd, J = 14.8, 7.2 Hz, 1H), 1.23 (d, J = 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 172.4, 170.3, 166.3, 146.3, 136.1, 135.4, 133.7, 132.4, 130.6, 128.6 (2C), 128.5, 128.3, 128.1 (2C), 127.7, 124.6, 123.3, 122.3, 119.8, 118.6, 111.3, 110.3, 67.0, 54.3, 48.4, 27.2, 17.5; MS (ESI) m/z 537 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C₂₈H₂₆NaO₆Na [M+Na⁺]: 537.1745, found: 537.1750.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)butanoate (15b).
Following the general procedure 2, the coupling of (R)-14 (1.80 g, 5.09 mmol) with L-2-aminobutyric benzyl ester p-toluenesulfonic acid salt (3.72 g, 10.18 mmol) gave compound 15b (2.45 g, yield: 91%) as a yellow solid. Mp 142–144 °C (EtOAc); [α]D20 35.9 (c 0.5, CHCl3); IR (film) νmax: 3421, 1734, 1642, 1530, 1457, 1349, 1196, 1139 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.02–7.97 (m, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.56–7.47 (m, 2H), 7.37–7.26 (m, 6H), 7.20–7.14 (m, 2H), 7.13–7.06 (m, 2H), 6.57 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 7.7 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 5.07–5.01 (m, 1H), 4.55–4.45 (m, 1H), 3.50 (dd, J = 14.8, 6.0 Hz, 1H), 3.32 (dd, J = 14.8, 7.2 Hz, 1H), 1.77–1.56 (m, 2H), 0.73 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.8, 170.5, 166.3, 146.4, 136.2, 135.5, 133.7, 132.4, 130.6, 128.6, 128.6 (2C), 128.4, 128.2 (2C), 127.6, 124.6, 123.2, 122.4, 119.9, 118.6, 111.3, 110.3, 67.0, 54.3, 53.8, 27.3, 25.2, 9.5; MS (ESI) m/z 551 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C₂₉H₂₈N₄O₆Na [M+Na⁺]: 551.1900, found: 551.1908.

Benzyl (S)-2-(((R)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methylbutanoate (15c).

Following the general procedure 2, the coupling of (R)-14 (1.80 g, 5.09 mmol) with benzyl L-valinate p-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound 15c (2.57 g, yield: 93%) as a yellow solid. Mp 148–150 °C (EtOAc); [α]D20 25.6 (c 1.0, CHCl3); IR (film) νmax: 3420, 1733, 1643, 1530, 1459,1349, 1195, 1143 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.97–7.91 (m, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.50–7.42 (m, 2H), 7.34–7.24 (m, 6H), 7.18–7.10 (m, 2H), 7.10–7.02 (m, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.14–5.02 (m, 3H), 4.44 (dd, J = 8.4, 5.3 Hz, 1H), 3.44 (dd, J = 14.9, 6.4 Hz, 1H), 3.26 (dd, J = 14.9, 6.4 Hz, 1H), 2.07–1.95 (m, 1H), 0.74 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 170.8, 166.5, 146.2, 136.2, 135.3, 133.7, 132.2, 130.5, 128.6, 128.5 (2C), 128.3, 128.3 (2C), 127.5, 124.4, 123.2, 122.2, 119.7, 118.6, 111.3, 110.2, 66.9, 57.8, 54.2, 30.8, 27.5, 18.6, 17.7; MS (ESI) m/z 565 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C₃₀H₂₈N₄O₆Na [M+Na⁺]: 565.2058, found: 565.2063.

Benzyl (S)-2-(((S)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methylbutanoate (15c).
butanoate (18).
Following the general procedure 2, the coupling of compound (S)-14 (1.80 g, 5.09 mmol) with benzyl l-valinate p-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound 18 (2.51 g, yield: 91%) as a yellow solid. Mp 83–85 °C (EtOAc); [α]D20 +11.4 (c 1.0, CHCl3); IR (film) νmax: 3420, 1736, 1652, 1527, 1351, 1191, 1140, 1079 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 8.21 (s, 1H), 7.97 (dd, J = 7.6, 1.3 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.56–7.45 (m, 2H), 7.39–7.26 (m, 7H), 7.15 (ddd, J = 7.2, 7.2, 1.0 Hz, 1H), 7.10–7.02 (m, 2H), 6.93 (d, J = 7.7 Hz, 1H), 6.40 (d, J = 7.7 Hz, 1H), 5.08 (d, J = 12.2 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 4.98 (m, 1H), 4.40 (dd, J = 8.3, 5.3 Hz, 1H), 3.46 (dd, J = 14.9, 5.8 Hz, 1H), 3.23 (dd, J = 14.9, 8.1 Hz, 1H), 2.10–2.00 (m, 1H), 0.80 (d, J = 6.9 Hz, 3H), 0.74 (d, J = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl3) δ 170.9, 170.9, 166.2, 146.2, 136.2, 135.4, 133.6, 132.3, 130.5, 128.7, 128.6 (2C), 128.4, 128.3 (2C), 127.4, 124.4, 123.5, 122.1, 119.7, 118.8, 111.2, 110.2, 66.9, 57.7, 54.4, 31.0, 28.0, 18.7, 17.7; MS (ESI) m/z 565 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C₃₀H₃₀N₄O₆Na [M+Na]⁺: 565.2058, found: 565.2059.

Benzyl (R)-2-((S)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methyl–butanoate (21).
Following the general procedure 2, the coupling of compound (S)-14 (1.80 g, 5.09 mmol) with D-valinate p-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound 21 (2.57 g, yield: 93%) as a yellow solid. Mp 148–150 °C (EtOAc); [α]D20 +25.6 (c 1.0, CHCl3); IR (film) νmax: 3414, 1736, 1640, 1534, 1454, 1354, 1194, 1143 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 8.33 (s, 1H), 7.97–7.91 (m, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.50–7.42 (m, 2H), 7.34–7.24 (m, 6H), 7.18–7.10 (m, 2H), 7.10–7.02 (m, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.14–5.02 (m, 3H), 4.44 (dd, J = 8.4, 5.3 Hz, 1H), 3.44 (dd, J = 14.9, 6.4 Hz, 1H), 3.26 (dd, J = 14.9, 6.4 Hz, 1H), 2.07–1.95 (m, 1H), 0.74 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 170.8, 166.5, 146.2, 136.2, 135.3, 133.7, 132.2, 130.5, 128.6, 128.5 (2C), 128.3, 128.3 (2C), 127.5, 124.4, 123.2, 122.2, 119.7, 118.6, 111.3, 110.2, 66.9, 57.8, 54.2, 30.8, 27.5, 18.6, 17.7; MS (ESI) m/z 565 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C₃₀H₃₀N₄O₆Na [M+Na]⁺: 565.2058, found: 565.2056.
Benzyl (R)-2-((R)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methyl–butanoate (24).

Following the general procedure for the step 2, the coupling of compound (R)-14 (1.80 g, 5.09 mmol) with d-valinate p-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound 24 (2.51 g, yield: 91%) as a yellow solid. Mp 83–85 °C (EtOAc); [α]D20 = –11.4 (c 1.0, CHCl3); IR (film) νmax: 3420, 1736, 1652, 1527, 1351, 1191, 1140, 1079 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 8.21 (s, 1H), 7.97 (dd, J = 7.6, 1.3 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.56–7.45 (m, 2H), 7.39–7.26 (m, 7H), 7.15 (ddd, J = 7.2, 7.2, 1.0 Hz, 1H), 7.10–7.02 (m, 2H), 6.93 (d, J = 7.7 Hz, 1H), 6.40 (d, J = 7.7 Hz, 1H), 5.08 (d, J = 12.2 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 4.98 (m, 1H), 4.40 (dd, J = 8.3, 5.3 Hz, 1H), 3.46 (ddd, J = 14.9, 5.8 Hz, 1H), 3.23 (dd, J = 14.9, 8.1 Hz, 1H), 2.10–2.00 (m, 1H), 0.80 (d, J = 6.9 Hz, 3H), 0.74 (d, J = 6.9 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 170.9, 166.2, 166.2, 164.2, 135.4, 135.4, 133.6, 133.6, 133.6, 132.3, 132.3, 128.7, 128.6 (2C), 128.4, 128.3 (2C), 127.4, 124.4, 123.5, 122.1, 119.7, 118.8, 111.2, 110.2, 66.9, 57.7, 54.4, 31.0, 28.0, 18.7, 17.7; MS (ESI) m/z 565 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C30H30N4O6Na [M+Na]+: 565.2058, found: 565.2062.

General Procedure for the Step 3 (General Procedure 3)

To a mixture of zinc powder (776 mg, 11.94 mmol) and THF (50 mL) was added TiCl4 (0.66 mL, 5.98 mmol). The resulting mixture were stirred for 1 h at 50 °C. After cooling to 0 °C, a THF (10 mL) solution of a tryptophan-derived dipeptide (1.50 mmol) and trimethylorthoformate (0.66 mL, 5.98 mmol) were added. The resulting mixture was stirred for 24 h at 0 °C. To the reaction mixture was added brine (10 mL) and the resulting mixture was stirred for 2 h. After separating the phases, the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:3 to DCM: MeOH = 40:1) to give the corresponding quinazolino-dipeptide derivative.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-propanoate (12a).

Following the general procedure 3, the reaction of compound 15a (771 mg, 1.50
mmol) gave compound 12a (704 mg, yield: 95%) as a white solid. Mp 161–163 °C (EtOAc); [α]D20^20 +58.6 (c 1.0, CHCl3); IR (film) νmax: 3318, 2928, 1741, 1662, 1607, 1455, 1327, 1196, 1153 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 8.36 (s, 1H), 8.22–8.16 (m, 2H), 7.42 (dd, J = 8.1, 6.8, 1.4 Hz, 1H), 7.31–7.24 (m, 4H), 7.22–7.18 (m, 2H), 7.15 (dd, J = 8.0, 7.2, 1.1 Hz, 1H), 7.07 (dd, J = 8.0, 7.9, 1.1 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 5.83 (dd, J = 8.5, 7.2 Hz, 1H), 5.05 (d, J = 12.3 Hz, 1H), 5.01 (d, J = 12.3 Hz, 1H), 4.51 (dq, J = 7.3, 7.2 Hz, 1H), 3.72 (dd, J = 14.5, 8.7 Hz, 1H), 3.41 (d, J = 14.5, 7.1 Hz, 1H), 1.20 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl3) δ 171.9, 168.4, 147.5, 144.2, 136.2, 135.2, 134.4, 128.5 (2C), 128.3, 128.0 (2C), 127.5, 127.2, 126.9, 126.9, 123.2, 122.4, 121.4, 119.9, 118.4, 111.3, 109.7, 67.1, 56.5, 48.5, 27.2, 17.6; MS (ESI) m/z 517 (M+Na⁺, 100%), HRMS (ESI, m/z) calcd for C29H26N4O4Na [M+Na]⁺: 517.1846, found: 517.1850.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-butaneate (12b).

Following the general procedure 3, the reaction of compound 15b (792 mg, 1.50 mmol) gave compound 12b (724 mg, yield: 95%) as a white solid. Mp 185–187 °C (EtOAc); [α]D20^20 +47.6 (c 1.0, CHCl3); IR (film) νmax: 3422, 2968, 1738, 1659, 1610, 1477, 1328, 1195, 1140 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 8.40 (s, 1H), 8.24 (br. s, 1H), 8.20 (dd, J = 8.2, 0.9 Hz, 1H), 7.72–7.61 (m, 3H), 7.41 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 7.30–7.26 (m, 4H), 7.21–7.17 (m, 2H), 7.14 (ddd, J = 7.9, 6.8, 0.9 Hz, 1H), 7.06 (ddd, J = 7.9, 7.8, 0.8 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 5.88 (dd, J = 8.5, 7.2 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 4.99 (d, J = 12.2 Hz, 1H), 4.51–4.44 (m, 1H), 3.73 (dd, J = 14.5, 8.7 Hz, 1H), 3.41 (dd, J = 14.5, 7.1 Hz, 1H), 1.76–1.63 (m, 1H), 1.61–1.49 (m, 1H), 0.61 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl3) δ 171.3, 168.7, 161.2, 147.5, 144.3, 136.2, 135.2, 134.4, 128.5 (2C), 128.3, 128.1 (2C), 127.5, 127.2, 126.9, 126.9, 123.2, 122.4, 121.5, 119.8, 118.4, 111.3, 109.6, 67.0, 56.6, 53.8, 27.3, 25.0, 9.2; MS (ESI) m/z 531 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C30H28N4O4Na [M+Na]⁺: 531.2003, found: 531.2000.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-3
-methylbutanoate (12c).

Following the general procedure 3, the reaction of compound 15c (813 mg, 1.50 mmol) gave compound 12c (744 mg, yield: 95%) as a white solid. Mp 165–167 °C (EtOAc); [α]D20 +55.6 (c 1.0, CHCl3); IR (film) νmax: 3417, 2965, 1738, 1659, 1610, 1477, 1328, 1195, 1143 cm−1; 1H NMR (400 MHz, CDCl3) δ 8.41 (s, 1H), 8.30 (s, 1H), 8.22 (dd, J = 8.1, 1.0 Hz, 1H), 7.72–7.62 (m, 3H), 7.41 (ddd, J = 8.1, 6.8, 1.5 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.26–7.17 (m, 5H), 7.14 (ddd, J = 7.9, 6.8, 0.9 Hz, 1H), 7.07 (ddd, J = 7.9, 7.9, 0.9 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.94 (dd, J = 7.6, 7.6 Hz, 1H), 5.03 (d, J = 12.2 Hz, 1H), 4.98 (d, J = 12.2 Hz, 1H), 4.46 (dd, J = 8.5, 5.0 Hz, 1H), 3.74 (dd, J = 14.5, 8.7 Hz, 1H), 0.68 (d, J = 6.8 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 170.8, 168.8, 161.2, 147.5, 144.3, 136.2, 135.1, 134.4, 128.4 (2C), 128.3, 128.2 (2C), 127.4, 127.1, 126.9, 126.8, 123.2, 122.3, 121.4, 119.8, 118.4, 111.3, 109.4, 66.9, 57.7, 56.6, 30.8, 27.4, 18.6, 17.5; MS (ESI) m/z 545 (M+Na+, 100%); HRMS (ESI, m/z) calcd for C31H30N4O4Na [M+Na]+: 545.2159, found: 545.2161.

Benzyl ((S)-2-((S)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-3-methylbutanoate (19).

Following the general procedure 3, the reaction of compound 18 (813 mg, 1.50 mmol) gave compound 19 (752 mg, yield: 96%) as a white solid. Mp 81–83 °C (EtOAc); [α]D20 −31.5 (c 1.0, CHCl3); IR (film) νmax: 3440, 2965, 1729, 1656, 1607, 1556, 1194, 1137 cm−1; 1H NMR (500 MHz, CDCl3) δ 8.44 (s, 1H), 8.21 (dd, J = 8.0, 1.2 Hz, 1H), 8.12 (s, 1H), 7.75–7.66 (m, 2H), 7.50 (d, J = 8.1 Hz, 1H), 7.43 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.38–7.30 (m, 5H), 7.21 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 8.1, 6.8, 0.9 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 5.96 (dd, J = 7.9, 7.9 Hz, 1H), 5.13 (d, J = 12.2 Hz, 1H), 5.07 (d, J = 12.2 Hz, 1H), 4.52 (dd, J = 8.6, 5.1 Hz, 1H), 3.67 (dd, J = 14.9, 8.0 Hz, 1H), 3.40 (dd, J = 14.9, 7.9 Hz, 1H), 2.12–2.04 (m, 1H), 0.75 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 171.1, 169.3, 161.3, 147.4, 144.5, 136.1, 135.3, 134.5, 128.6 (2C), 128.4, 128.3 (2C), 127.4, 127.2, 127.0, 126.7, 123.2, 122.2, 121.3, 119.6, 118.2, 111.3, 109.3, 67.0,
Benzyl (R)-2-((S)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-3-methylbutanoate (22).

Following the general procedure 3, the reaction of compound 21 (813 mg, 1.50 mmol) gave compound 22 (744 mg, yield: 95%) as a white solid. Mp 165–167 °C (EtOAc); \([\alpha]_D^{20} -55.6 (c 1.0, \text{CHCl}_3); \text{IR (film)} v_{\text{max}}: 3417, 2965, 1738, 1659, 1610, 1477, 1328, 1195, 1143 \text{ cm}^{-1}; ^1\text{H NMR (400 MHz, CDCl}_3) \delta 8.41 (s, 1H), 8.30 (s, 1H), 8.22 (dd, \(J = 8.1, 1.0 \text{ Hz, 1H}), 7.72–7.62 (m, 3H), 7.41 (ddd, \(J = 8.1 \text{ Hz, 1H}), 7.26–7.17 (m, 5H), 7.22 (d, \(J = 8.1 \text{ Hz, 1H}), 6.94 (d, \(J = 8.1 \text{ Hz, 1H}), 5.94 (dd, \(J = 7.6, 6.7 \text{ Hz, 1H}), 5.59 (d, \(J = 5.0 \text{ Hz, 1H}), 5.39 (dd, \(J = 14.5, 8.7 \text{ Hz, 1H}), 3.74 (dd, \(J = 14.5, 7.1 \text{ Hz, 1H}), 2.04–1.96 (m, 1H), 0.68 (d, \(J = 6.8 \text{ Hz, 3H}), 0.64 (d, \(J = 6.8 \text{ Hz, 3H}); ^{13}\text{C NMR (100 MHz, CDCl}_3) \delta 170.8, 168.8, 161.2, 147.5, 144.3, 136.2, 135.1, 134.1, 128.4 (2C), 128.1, 128.2 (2C), 127.4, 127.1, 126.9, 126.8, 123.2, 122.3, 121.4, 119.8, 118.4, 111.3, 109.4, 66.9, 57.7, 56.6, 30.8, 27.4, 18.6, 17.5; \text{MS (ESI) } m/z 545 (M+Na^+, 100%); \text{HRMS (ESI, } m/z \text{) calcd for C}_{31}\text{H}_{30}\text{N}_4\text{O}_4\text{Na [M+Na]^+: 545.2159, found: 545.2161.}

Benzyl (R)-2-((R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-3-methylbutanoate (25).

Following the general procedure 3, the reaction of compound 24 (813 mg, 1.50 mmol) gave compound 25 (752 mg, yield: 96%) as a white solid. Mp 81–83 °C (EtOAc); \([\alpha]_D^{20} +31.5 (c 1.0, \text{CHCl}_3); \text{IR (film)} v_{\text{max}}: 3440, 2965, 1729, 1656, 1607, 1556, 1457, 1194, 1137 \text{ cm}^{-1}; ^1\text{H NMR (500 MHz, CDCl}_3) \delta 8.44 (s, 1H), 8.21 (dd, \(J = 8.0, 1.2 \text{ Hz, 1H}), 8.08 (s, 1H), 7.75–7.66 (m, 2H), 7.50 (d, \(J = 8.1 \text{ Hz, 1H}), 7.43 (ddd, \(J = 8.2, 6.8, 1.3 \text{ Hz, 1H}), 7.38–7.30 (m, 5H), 7.21 (d, \(J = 7.2 \text{ Hz, 1H}), 7.13 (d, \(J = 8.6 \text{ Hz, 1H}), 6.93 (ddd, \(J = 8.1, 6.8, 0.9 \text{ Hz, 1H}), 6.90 (d, \(J = 2.3 \text{ Hz, 1H}), 5.96 (dd, \(J = 7.9, 7.9 \text{ Hz, 1H}), 5.13 (d, \(J = 12.2 \text{ Hz, 1H}), 5.07 (d, \(J = 12.2 \text{ Hz, 1H}), 4.52 (dd, \(J = 8.6, 5.1 \text{ Hz, 1H}), 3.67 (dd, \(J = 14.9, 8.0 \text{ Hz, 1H}), 3.40 (dd, \(J = 14.9, 7.9 \text{ Hz, 1H}), 2.12–2.04 (m, 1H), 0.75 (d, \(J = 6.9 \text{ Hz, 3H}), 0.71 (d, \(J = 6.9 \text{ Hz, 3H}); ^{13}\text{C NMR (125 MHz, CDCl}_3)
δ 171.1, 169.3, 161.3, 147.4, 144.5, 136.1, 135.3, 134.5, 128.6 (2C), 128.4, 128.3 (2C), 127.4, 127.2, 127.0, 126.7, 123.2, 122.2, 121.3, 119.6, 118.2, 111.3, 109.3, 67.0, 57.6, 56.5, 31.0, 27.2, 18.8, 17.6; MS (ESI) m/z 545 (M+Na⁺, 100%); HRMS (ESI, m/z) calcd for C₃₁H₃₀N₄O₄Na [M+Na]⁺: 545.2159, found: 545.2156.
$^{1}$H NMR and $^{13}$C NMR spectra of new products

$^{1}$H NMR spectrum of 15a (CDCl$_3$)

$^{13}$C NMR spectrum of 15a (CDCl$_3$)
$^1$H NMR spectrum of 15b (CDCl$_3$)

$^{13}$C NMR spectrum of 15b (CDCl$_3$)
$^1$H NMR spectrum of 15c (CDCl$_3$)

$^{13}$C NMR spectrum of 15c (CDCl$_3$)
$^1\text{H}$ NMR spectrum of 18 (CDCl$_3$)

$^{13}\text{C}$ NMR spectrum of 18 (CDCl$_3$)
$^1$H NMR spectrum of 21 (CDCl$_3$)

$^{13}$C NMR spectrum of 21 (CDCl$_3$)
\(^1\)H NMR spectrum of \textbf{24} (CDCl\textsubscript{3})

\(^{13}\)C NMR spectrum of \textbf{24} (CDCl\textsubscript{3})
$^1$H NMR spectrum of 12a (CDCl$_3$)

$^{13}$C NMR spectrum of 12a (CDCl$_3$)
$^1$H NMR spectrum of **12b** (CDCl$_3$)

$^{13}$C NMR spectrum of **12b** (CDCl$_3$)
$^1$H NMR spectrum of 12c (CDCl$_3$)

$^{13}$C NMR spectrum of 12c (CDCl$_3$)
$^1$H NMR spectrum of 19 (CDCl₃)

$^{13}$C NMR spectrum of 19 (CDCl₃)
$^1$H NMR spectrum of 22 (CDCl$_3$)

$^{13}$C NMR spectrum of 22 (CDCl$_3$)
$^1$H NMR spectrum of 25 (CDCl₃)

$^{13}$C NMR spectrum of 25 (CDCl₃)
$^1$H NMR spectrum of 11a (CDCl$_3$)

$^{13}$C NMR spectrum of 11a (CDCl$_3$)
$^1$H NMR spectrum of 11b (CDCl$_3$)

$^{13}$C NMR spectrum of 11b (CDCl$_3$)
$^1$H NMR spectrum of 1 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 1 (DMSO-$d_6$)
$^1$H NMR spectrum of 17 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 17 (DMSO-$d_6$)
$^1$H NMR spectrum of 11c (CDCl$_3$)

$^{13}$C NMR spectrum of 11c (CDCl$_3$)
$^1$H NMR spectrum of 3 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 3 (DMSO-$d_6$)
$^1$H NMR spectrum of 7 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 7 (DMSO-$d_6$)
$^{1}H$ NMR spectrum of 20 (CDCl$_3$)

$^{13}C$ NMR spectrum of 20 (CDCl$_3$)
$^1$H NMR spectrum of ent-3 (DMSO-$d_6$)

$^{13}$C NMR spectrum of ent-3 (DMSO-$d_6$)
$^1$H NMR spectrum of 23 (CDCl$_3$)

$^{13}$C NMR spectrum of 23 (CDCl$_3$)
$^1$H NMR spectrum of ent-7 (DMSO-$d_6$)

$^{13}$C NMR spectrum of ent-7 (DMSO-$d_6$)
$^{1}H$ NMR spectrum of 26 (CDCl$_3$)

$^{13}C$ NMR spectrum of 26 (CDCl$_3$)
$^1$H NMR spectrum of 4 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 4 (DMSO-$d_6$)
$^1$H NMR spectrum of 5 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 5 (DMSO-$d_6$)
$^1$H NMR spectrum of 6 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 6 (DMSO-$d_6$)
$^1$H NMR spectrum of \textit{ent-8} (CDCl$_3$)

\[ \text{Spectrum Image} \]

$^{13}$C NMR spectrum of \textit{ent-8} (CDCl$_3$)

\[ \text{Spectrum Image} \]
$^1$H NMR spectrum of *ent-6* (DMSO-d6)

$^{13}$C NMR spectrum of *ent-6* (DMSO-d6)
$^{1}H$ NMR spectrum of $8$ (CDCl$_3$)

$^{13}C$ NMR spectrum of $8$ (CDCl$_3$)
HPLC analysis of compound 3 and ent-3

Shimadzu CLASS-VP V6.13 SP2
Column: Chirpak AD-H
Mobile Phase: Hex:EtOH=30:70(v/v)
Flow Rate: 0.8mL/min
CT: 40°C
Sample Name: 3

Detector A-230 nm

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.867</td>
<td>13276112</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Totals 13276112 100.00

Shimadzu CLASS-VP V6.13 SP2
Column: Chirpak AD-H
Mobile Phase: Hex:EtOH=30:70(v/v)
Flow Rate: 0.8mL/min
CT: 40°C
Sample Name: ent-3

Detector A-230 nm

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.840</td>
<td>24538507</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Totals 24538507 100.00

HPLC analysis of the mixture of compound 3 and ent-3

Shimadzu CLASS-VP V6.13 SP2
Column: Chirpak AD-H
Mobile Phase: Hex:EtOH=30:70(v/v)
Flow Rate: 0.8mL/min
CT: 40°C
Sample Name: 3 + ent-3

Detector A-230 nm

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.867</td>
<td>11446715</td>
<td>35.02</td>
</tr>
<tr>
<td>2</td>
<td>11.787</td>
<td>21239230</td>
<td>64.98</td>
</tr>
</tbody>
</table>

Totals 32687945 100.00
HPLC analysis of compound 6 and ent-6

Shimadzu CLASS VP V6.13 SP2
Column: Chiropak AD-H
Mobile Phase: Hex/IPA=70/30(v/v)
Flow Rate: 0.8mL/min
CT: 30°C Sample Name: 6

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21487</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>215857527</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Totals

215857527

100.00

HPLC analysis of the mixture of compound 6 and ent-6

Shimadzu CLASS VP V6.13 SP2
Column: Chiropak AD-H
Mobile Phase: Hex/IPA=70/30(v/v)
Flow Rate: 0.8mL/min
CT: 30°C Sample Name: 6+ ent-6

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.268</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>44695640</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Totals

44695640

100.00
HPLC analysis of compound 7 and ent-7

**Shimadzu CLASS-VP V6.13 SP2**
Column: Chiralpak AD-H
Mobile Phase: Hex/EtOH 30/70(v/v)
Flow Rate: 0.8mL/min
CT: 40°C
Sample Name: \(\pm\)-14-epi-isoconavamine C (7)

**Shimadzu CLASS-VP V6.13 SP2**
Column: Chiralpak AD-H
Mobile Phase: Hex/EtOH 30/70(v/v)
Flow Rate: 0.8mL/min
CT: 40°C
Sample Name: \(\pm\)-14-epi-isoconavamine C (ent-7)

**HPLC analysis of the mixture of compound 7 and ent-7**

**Shimadzu CLASS-VP V6.13 SP2**
Column: Chiralpak AD-H
Mobile Phase: Hex/EtOH 30/70(v/v)
Flow Rate: 0.8mL/min
CT: 40°C
Sample Name: 7 + ent-7

---

**Detector A-250 nm**

<table>
<thead>
<tr>
<th>Pl #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.981</td>
<td>35841093</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>35841093</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Detector A-250 nm**

<table>
<thead>
<tr>
<th>Pl #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28.736</td>
<td>57425127</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>57425127</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Detector A-250 nm**

<table>
<thead>
<tr>
<th>Pl #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.624</td>
<td>19419077</td>
<td>48.09</td>
</tr>
<tr>
<td>2</td>
<td>29.408</td>
<td>20959092</td>
<td>51.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>40475079</td>
<td>100.00</td>
</tr>
</tbody>
</table>
HPLC analysis of compound 8 and ent-8

**Area % Report**

<table>
<thead>
<tr>
<th>Shimadzu CLASS VP V6.13 SP2</th>
<th>Column: Chirapak AD-H</th>
<th>Mobile Phase: Hex/EtOH=50/70(v/v)</th>
<th>Flow Rate: 0.8mL/min</th>
<th>CT: 40°C</th>
<th>Sample Name: 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detector A-250 nm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl #</td>
<td>Retention Time</td>
<td>Area</td>
<td>Area Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>46.965</td>
<td>19095447</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>19095447</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Area % Report**

<table>
<thead>
<tr>
<th>Shimadzu CLASS VP V6.13 SP2</th>
<th>Column: Chirapak AD-H</th>
<th>Mobile Phase: Hex/EtOH=50/70(v/v)</th>
<th>Flow Rate: 0.8mL/min</th>
<th>CT: 40°C</th>
<th>Sample Name: ent-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detector A-230 nm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl #</td>
<td>Retention Time</td>
<td>Area</td>
<td>Area Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28.704</td>
<td>32190413</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>32190413</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HPLC analysis of the mixture of compound 8 and ent-8

**Area % Report**

<table>
<thead>
<tr>
<th>Shimadzu CLASS VP V6.13 SP2</th>
<th>Column: Chirapak AD-H</th>
<th>Mobile Phase: Hex/EtOH=50/70(v/v)</th>
<th>Flow Rate: 0.8mL/min</th>
<th>CT: 40°C</th>
<th>Sample Name: 8-ent-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detector A-230 nm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl #</td>
<td>Retention Time</td>
<td>Area</td>
<td>Area Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28.152</td>
<td>9705454</td>
<td>33.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>47.232</td>
<td>18869477</td>
<td>66.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>28574991</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
X-ray structure and crystal data for the proposed structure of (−)-aniquinazoline D (3)

Crystal Data [for (−)-3]. C_{24}N_{4}O_{4}H_{22} (M = 430.46 g/mol): orthorhombic, space group P2_{1}2_{1}2_{1} (no. 19), a = 7.6889(2) Å, b = 15.5382(5) Å, c = 16.4272(6) Å, V = 1962.58(11) Å^{3}, Z = 4, T = 99.8(5) K, μ(Cu Kα) = 0.832 mm\(^{-1}\), D_{calc} = 1.457 g/cm\(^{3}\), 4748 reflections measured (7.84° ≤ 2θ ≤ 137.68°), 3186 unique (R_{int} = 0.0469, R_{sigma} = 0.0597) which were used in all calculations. The final R_{1} was 0.0413 (>2sigma(I)) and wR_{2} was 0.1026 (all data).

X-ray structure and crystal data of (+)-14-epi-isochaetominine C (7)-2H\(_{2}\)O

Crystal Data [for (+)-14-epi-isochaetominine C (7)-2H\(_{2}\)O]. C_{24}N_{4}O_{6}H_{26} (M = 466.50 g/mol): triclinic, space group P-1 (no. 2), a = 9.3200(6) Å, b = 10.5489(6) Å, c = 12.1772(7) Å, α = 95.818(5)°, β = 90.490(5)°, γ = 111.805(6)°, V = 1104.43(12) Å\(^{3}\), Z = 2, T = 173.00(14) K, μ(Cu Kα) = 0.849 mm\(^{-1}\), D_{calc} = 1.4027 g/cm\(^{3}\), 5671 reflections measured (7.3° ≤ 2θ ≤ 120.36°), 3246 unique (R_{int} = 0.0442, R_{sigma} = 0.0662) which were used in all calculations. The final R_{1} was 0.0380 (>2sigma(I)) and wR_{2} was 0.0947 (all data).