Practical synthesis of potential endothelin receptor antagonists of 1,4-benzodiazepine-2,5-dione derivatives bearing substituents at the C_3-, N_1- and N_4-positions

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Supplementary information: supporting synthetic procedures and compound characterization

The synthetic procedures and characterization for compounds **7** and **8** (Scheme 1, A) have been described.[16]

(+)-(*S*)-7-Chloro-2,5-dioxo-1-(3-methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-3-acetic acid methyl ester (10b). Treatment of **9** (1.07 g, 3.8 mmol) with 3-methoxybenzyl bromide (0.53 mL, 3.8 mmol), according to the representative procedure I, gave **10b** (1.26 g, 83%). Solid, mp 55–57 ^{o}C; R_f = 0.40 (hexane/EtOAc, 1:1); $[\alpha]^{28}_{D}$ = +62.3 (c = 0.75, $CDCl_3$); IR ($CDCl_3$, cm^{-1}) 3270, 2959, 1734, 1670; δ_H (400 MHz, $CDCl_3$) 2.81 (1 H, dd, J = 16.8, 4.8 Hz), 3.19 (1 H, dd, J = 16.8, 9.2 Hz), 3.71 (3 H, s), 3.77 (3 H, s), 4.36 (1 H, ddd, J = 9.2, 5.2, 4.8 Hz), 4.90 (1 H, d, J = 16.0 Hz), 5.18 (1 H, d, J = 16 Hz), 6.67 (1 H, d, J = 2.0 Hz), 6.71–6.77 (2 H, m), 7.15–7.22 (2 H, m), 7.39 (1 H, dd, J = 8.8, 2.8 Hz), 7.81 (1 H, dd, J = 4.4, 2.8 Hz), 8.10 (1 H, d, J = 5.2 Hz); δ_C (100 MHz, $CDCl_3$) 170.7, 169.2, 167.8, 160.0, 138.6, 137.8, 132.7, 131.9, 130.0, 129.9, 129.6, 123.6, 118.7, 113.3, 111.8, 55.1, 53.4, 52.2, 52.0, 49.5, 33.1; MS (FAB) 403 (63%, M^+ + H), 154 (100), 121 (94); Anal. $C_{20}H_{19}N_2O_5Cl$ requires: C, 59.63; H, 4.75; N, 6.95. Found: C, 59.16; H, 4.81; N, 6.35.

(+)-(*S*)-4-Benzyl-7-chloro-2,5-dioxo-1-(3-methoxybenzyl)-2,3,4,5-tetra-hydro-1*H*-1,4-benzodiazepine-3-acetic acid methyl ester (11b). Alkylation of **10b** (68 mg, 0.17 mmol) with benzyl bromide (0.1 mL, 0.84 mmol), according to the representative procedure II, gave **11b** (57 mg, 68%). Oil, R_f = 0.40 (hexane/EtOAc, 7:3); $[\alpha]^{28}_{D}$ = +21.1 (c = 0.5, $CDCl_3$) ; ν_{max} (film, cm^{-1})

2952, 1752, 1646; δ_H (400 MHz, $CDCl_3$) 2.63 (1 H, dd, *J* = 16.8, 2.2 Hz), 3.28 (1 H, dd, *J* = 16.8, 6.6 Hz), 3.55 (3 H, s), 3.73 (3 H, s), 4.37 (1 H, d, *J* = 16 Hz), 4.78 (1 H, dd, *J* = 6.6, 2.2 Hz), 4.80 (1 H, d, *J* = 16.0 Hz), 5.15 (1 H, d, *J* = 16.0 Hz), 5.21 (1 H, d, *J* = 16.0 Hz), 6.67–6.78 (3 H, m), 7.13–7.38 (8 H, m), 7.91 (1 H, d, *J* = 2.4 Hz); δ_H (100 MHz, $CDCl_3$) 170.3, 168.3, 167.5, 160.0, 138.5, 137.9, 137.2, 132.4, 131.7, 130.6, 130.5, 129.9 (2 ×), 128.8 (2 ×), 127.5, 127.0, 122.8, 118.6, 113.4, 111.6, 55.2, 53.0, 52.1, 51.4, 47.3, 31.8; MS (FAB) 493 (58%, M^++1), 121 (92), 91 (100). Anal. $C_{27}H_{25}N_2O_5Cl$ requires: C, 65.79; H, 5.11; N, 5.68. Found: C, 65.41; H, 5.17; N, 5.95.

(–)-(*S*)-*N*-[4-(Methoxycarbonyl)benzyl] aspartic acid dimethyl ester (14a). The reductive amination of methyl 4-formylbenzoate (1.39 mL, 11.05 mmol) with dimethyl L-aspartate hydrochloride (2.70 g, 13.26 mmol), according to the representative procedure III, gave **14a** (2.83 g, 91%). Oil; R_f = 0.50 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = –32.6 (CH_2Cl_2, *c* = 0.42); ν_{max} (film, cm^{-1}) 3344, 2958, 2850, 1738, 1614, 1440, 1283, 1173, 1112, 1021; δ_H ($CDCl_3$, 400 MHz) 7.96 (2H, d, *J* = 8.0 Hz), 7.37 (2H, d, *J* = 8.0 Hz), 3.94 (1H, d, *J* = 10.4 Hz), 3.92 (3H, s), 3.76 (1H, d, *J* = 10.4 Hz), 3.70 (3H, s), 3.66 (3H, s), 3.62 (1H, dd, *J* = 5.6, 7.0 Hz), 2.73 (1H, dd, *J* = 5.6, 15.6 Hz), 2.66 (1H, dd, *J* = 7.0, 15.6 Hz); δ_H ($CDCl_3$, 100 MHz) 173.8, 171.0, 166.8, 144.8, 129.5 (2 ×), 128.9, 127.9 (2 ×), 56.8, 52.0, 51.9, 51.7, 51.5, 37.8; HRMS $C_{15}H_{20}NO_6$ ($M + H^+$) requires 310.1291, found 310.1289.

(–)-(*S*)-*N*-(3-Methoxybenzyl) aspartic acid dimethyl ester (14c). The reductive amination of *m*-anisaldehyde (0.69 mL, 5.53 mmol) with dimethyl L-aspartate hydrochloride (1.35 g, 6.63 mmol), according to the representative procedure III, gave **14c** (1.45 g, 93%). Oil, R_f = 0.50 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = –53.8 (CH_2Cl_2, *c* = 0.56); ν_{max} (film, cm^{-1}) 3342, 2957, 2842, 1738, 1604, 1440, 1266, 1169, 1047; δ_H ($CDCl_3$, 400 MHz) 7.15 (1H, dd, *J* = 8.0, 8.0 Hz), 6.83 (1H, s), 6.83 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 8.0 Hz), 3.83 (1H, d, *J* = 12.4 Hz), 3.77 (3H, s), 3.70 (3H, s), 3.65 (1H, d, *J* = 12.4 Hz), 3.61 (3H, s), 3.62–3.58 (1H, m), 2.68 (1H, dd, *J* = 6.0, 15.6 Hz), 2.61 (1H, dd, *J* = 6.8, 15.6 Hz); δ_C ($CDCl_3$, 100 MHz) 173.7, 170.9, 159.5, 141.0, 129.0, 120.1, 113.3, 112.4, 56.6, 54.8, 51.8, 51.6, 51.5, 37.6; HRMS $C_{14}H_{20}NO_5$ ($M + H^+$) requires 282.1341, found 282.1335.

(–)-(*S*)-*N*-[3-(Methoxycarbonyl)methoxybenzyl] aspartic acid dimethyl ester (14d). The reductive amination of methyl (3-formylphenoxy)acetate (3.00 g, 15.45 mmol) with dimethyl L-aspartate hydrochloride (3.78 g, 18.55 mmol), according to the representative procedure III, gave

14d (5.09 g, 97%). Oil; R_f = 0.35 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = –21.1 (CH_2Cl_2, *c* = 0.19); ν_{max} (film, cm^{-1}) 3337, 2923, 2854, 1734, 1589, 1437, 1262, 1164, 1083; δ_H ($CDCl_3$, 400 MHz) 7.20 (1H, dd, *J* = 7.5 Hz, 8.2 Hz), 6.91 (1H, d, *J* = 7.5 Hz), 6.88 (1H, s), 6.76 (1H, d, *J* = 8.2 Hz), 4.61 (2H, s), 3.84 (1H, d, *J* = 13.5 Hz), 3.77 (3H, s), 3.75 (1H, d, *J* = 13.5 Hz), 3.71 (3H, s), 3.65 (3H, s), 3.61 (1H, dd, *J* = 5.9 Hz, 6.4 Hz), 2.72 (1H, dd, *J* = 5.9 Hz, 15.9 Hz), 2.65 (1H, dd, *J* = 6.4 Hz, 15.9 Hz); δ_C ($CDCl_3$, 100 MHz) 173.9, 171.2, 169.4, 157.9, 141.2, 129.5, 121.6, 114.3, 113.3, 65.2, 56.7, 52.2, 52.1, 51.8, 51.6, 37.8; HRMS $C_{16}H_{22}NO_7$ ($M + H^+$) requires 340.1396, found 340.1393.

(–)-(*S*)-*N*-[4-(Methoxycarbonyl)benzyl]-*N*-(2-nitrobenzoyl) aspartic acid dimethyl ester (15a). Amidation of *N*-[4-(methoxycarbonyl)benzyl] aspartic acid dimethyl ester **14a** (2.00g, 6.47 mmol) with 2-nitrobenzoyl chloride (1.08 mL, 7.76 mmol), according to the representative procedure IV, gave **15a** (2.67g, 90%). Solid; mp = 128–130 °C; R_f = 0.38 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = –145.9 (CH_2Cl_2, *c* = 0.99); ν_{max} (KBr, cm^{-1}) 2958, 1734, 1654, 1534, 1438, 1351, 1284, 1182, 1110; δ_H ($CDCl_3$, 400 MHz) 8.19 (1H, d, *J* = 8.4 Hz), 7.98 (2H, d, J = 6.4 Hz), 7.68–7.64 (1H, m), 7.57–7.53 (1H, m), 7.46–7.40 (3H, m), 4.53 (1H, d, *J* = 15.8 Hz), 4.43 (1H, d, *J* = 15.8 Hz), 3.89 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 3.55–3.52 (2H, m), 3.15 (1H, br); δ_C ($CDCl_3$, 100 MHz) 171.0, 169.4, 167.9, 165.9, 144.7, 141.3, 135.1, 131.1, 130.8, 129.2 (2 ×), 128.9, 128.2 (2 ×), 127.7, 125.0, 55.5, 52.6, 52.3, 52.1, 51.7, 32.7; HRMS $C_{22}H_{23}N_2O_9$ ($M + H^+$) requires 459.1404, found 459.1411.

(–)-(*S*)-*N*-(4-Chloro-2-nitrobenzoyl)-*N*-(3-methoxybenzyl) aspartic acid dimethyl ester (15c). Amidation of *N*-(3-methoxybenzyl) aspartic acid dimethyl ester **14c** (2.81 g, 10.01 mmol) with 4-chloro-2-nitrobenzoyl chloride (2.50 g, 12.01 mmol), according to the representative procedure IV, gave **15c** (4.00 g, 86%). Gel; R_f = 0.42 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = –98.5 (CH_2Cl_2, *c* = 0.53); ν_{max} (film, cm^{-1}) 2958, 1741, 1654, 1605, 1540, 1438, 1352, 1268, 1157, 1050; δ_H ($CDCl_3$, 400 MHz) 8.16 (1H, s), 7.63 (1H, d, *J* = 8.2 Hz), 7.42 (1H, d, *J* = 8.2 Hz), 7.23–7.19 (1H, m), 6.91 (1H, s), 6.84–6.80 (2H, m), 4.43 (1H, d, *J* = 15.6 Hz), 4.36 (1H, d, *J* = 15.6 Hz), 3.79 (3H, s), 3.75 (3H, s), 3.71 (3H, s), 3.59–3.44 (2H, m), 3.06–3.02 (1H, br); δ_C ($CDCl_3$, 100 MHz) 172.0, 169.5, 167.1, 159.9, 145.6, 136.2, 136.1, 134.5, 129.8, 129.5, 129.3, 124.9, 120.2, 113.9, 113.4, 55.9, 55.2, 54.0, 52.7, 52.0, 33.4; HRMS $C_{21}H_{22}ClN_2O_8$ ($M + H^+$) requires 465.1065, found 465.1058.

(−)-(*S*)-*N*-(2,4-Dinitrobenzoyl)-*N*-(3-methoxybenzyl) aspartic acid dimethyl ester (15d). Amidation of *N*-(3-methoxybenzyl) aspartic acid dimethyl ester **14c** (3.60 g, 12.79 mmol) with 2,4-dinitrobenzoyl chloride (3.29 g, 15.35 mmol), according to the representative procedure IV, gave **15d** (5.53 g, 91%). Solid; mp = 48–50 °C; R_f = 0.50 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = −121.3 (CH_2Cl_2, *c* = 0.93); ν_{max} (KBr, cm^{-1}) 3118, 2959, 1739, 1653, 1604, 1539, 1492, 1438, 1349, 1268, 1162; δ_H ($CDCl_3$, 400 MHz) 8.98 (1H, d, *J* = 2.0 Hz), 8.46 (1H, d, *J* = 8.4 Hz), 7.66 (1H, d, *J* = 8.4 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 6.98–6.79 (3H, m), 4.50–4.29 (4H, m), 3.77 (3H, s), 3.73 (3H, s), 3.60–3.40 (3H, m), 3.12 (1H, br); δ_C ($CDCl_3$, 100 MHz) 171.9, 169.0, 165.9, 159.8, 147.9, 145.0, 137.1, 135.7, 129.8, 129.7, 128.6, 120.2, 120.0, 113.7, 113.4, 56.2, 55.3, 54.1, 52.9, 52.2, 33.5; HRMS $C_{21}H_{22}N_3O_{10}$ ($M + H^+$) requires 476.1305, found 476.1308.

(−)-(*S*)-*N*-(3-Methoxybenzyl)-*N*-(2-nitrobenzoyl) aspartic acid dimethyl ester (15e). Amidation of *N*-(3-methoxybenzyl) aspartic acid dimethyl ester **14c** (1.56 g, 5.53 mmol) with 2-nitrobenzoyl chloride (0.93 mL, 6.64 mmol), according to the representative procedure IV, gave **15e** (2.12 g, 89%). Gel; R_f = 0.40 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = −128.0 (CH_2Cl_2, *c* = 0.97); ν_{max} (film, cm^{-1}) 2958, 1739, 1652, 1533, 1493, 1439, 1350, 1267, 1168, 1042; δ_H ($CDCl_3$, 400 MHz) 8.20 (1H, d, *J* = 8.4 Hz), 7.71–7.49 (3H, m), 7.22 (1H, t, *J* = 7.6 Hz), 6.95–6.80 (3H, m), 4.41 (2H, m), 3.80 (3H, s), 3.77 (3H, s), 3.73 (3H, s), 3.60–3.50 (2H, m), 3.07 (1H, br); δ_C ($CDCl_3$, 100 MHz) 172.1, 169.7, 168.0, 159.9, 145.1, 136.5, 134.5, 132.1, 130.1, 129.8, 128.2, 124.8, 120.4, 113.9, 113.4, 55.8, 55.2, 53.9, 52.7, 52.0, 33.4; HRMS $C_{21}H_{23}N_2O_8$ ($M + H^+$) requires 431.1454, found 431.1451.

(−)-(*S*)-*N*-[3-(Methoxycarbonyl)methoxybenzyl]-*N*-(2-nitrobenzoyl) aspartic acid dimethyl ester (15f). Amidation of amine **14d** (3.00 g, 11.94 mmol) with 2-nitrobenzoyl chloride (2.92 g, 14.33 mmol), according to the representative procedure IV, gave **15f** (4.88 g, 94%). Gel; R_f = 0.28 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = −111.6 (CH_2Cl_2, *c* = 0.23); ν_{max} (film, cm^{-1}) 3026, 2959, 1741, 1653, 1608, 1534, 1493, 1440, 1351, 1244, 1169, 1086; δ_H ($CDCl_3$, 400 MHz) 8.18 (1H, d, *J* = 8.0 Hz), 7.69 (1H, dd, *J* = 7.4, 7.7 Hz), 7.55 (1H, dd, *J* = 7.7, 8.0 Hz), 7.47 (1H, d, *J* = 7.4 Hz), 7.21 (1H, d, *J* = 7.6 Hz), 6.99–6.81 (3H, m), 4.65 (2H, s), 4.45–4.35 (2H, m), 3.80 (3H, s), 3.76 (3H, s), 3.72 (3H, s), 3.62–3.45 (2H, m), 3.05 (1H, br); δ_C ($CDCl_3$, 100 MHz) 172.1, 169.6, 169.4, 168.2, 158.1, 145.0, 136.6, 134.6, 131.7, 130.3, 129.9, 128.1, 124.7, 121.4, 114.7,

113.8, 65.1, 55.8, 53.7, 52.7, 52.2, 52.0, 33.2; HRMS $C_{23}H_{25}N_2O_{10}$ (M + H^+) requires 489.1509, found 489.1510.

(+)-(*S*)-4-[4-(Methoxycarbonyl)benzyl]-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (16a). Reduction and in situ cyclization of **15a** (2.00 g, 4.09 mmol), according to the representative procedure V, gave **16a** (1.53 g, 88%). Solid; mp = 93–94 °C; R_f = 0.25 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = +17.0 (CH_2Cl_2, *c* = 0.78); ν_{max} (KBr, cm^{-1}) 3235, 2958, 1700, 1642, 1482, 1439, 1410, 1284, 1197,1112; δ_H (DMSO-d_6, 400 MHz) 10.63 (1H, s), 7.89 (2H, d, *J* = 8.0 Hz), 7.83 (1H, d, *J* = 7.6 Hz), 7.59–7.55 (1H, m), 7.40 (2H, d, *J* = 8.0 Hz), 7.31–7.28 (1H, m), 7.14–7.12 (1H, d, *J* = 7.6 Hz), 4.90 (1H, d, *J* = 16.4 Hz), 4.67 (1H, d, *J* = 16.4 Hz), 4.52 (1H, dd, *J* = 5.2, 9.6 Hz), 3.83 (3H, s), 3.45 (3H, s), 3.04 (1H, dd, *J* = 10.0, 16.0 Hz), 2.78 (1H, dd, *J* = 5.2, 16.0 Hz); δ_C (DMSO-d_6, 100 MHz) 170.2, 169.6, 168.1, 166.0, 143.4, 136.7, 132.5, 131.0, 129.3 (2 ×), 128.4, 127.3 (2 ×), 126.4, 124.3, 120.7, 52.2, 52.1, 51.6, 46.0, 30.9; HRMS $C_{21}H_{20}N_2O_6$ (M + H^+) requires 397.1400, found 397.1393. Anal. $C_{21}H_{20}N_2O_6$ (+ 0.25 H_2O) requires: C, 62.92; H, 5.15; N, 6.99. Found: C, 62.86; H, 5.46; N, 7.05.

(+)-(*S*)-8-Chloro-4-(3-methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (16c). The reduction and in situ cyclization of nitro compound **15c** (1.72 g, 4 mmol) was realized by heated with zinc powder (2.61 g, 40 mmol) and NH_4Cl (1.07 g, 20 mmol) in refluxing MeOH (40 mL) for 1.5 h to give benzodiazepine **16c** (1.35g, 85%). Solid; mp = 77–78 °C; R_f = 0.48 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = +20.8 (CH_2Cl_2, *c* = 1.01); ν_{max} (KBr, cm^{-1}) 3232, 2959, 1746, 1700, 1640, 1603, 1423, 1368, 1262, 1162, 1052; δ_H (DMSO–d_6, 400 MHz) 10.73 (1H, s), 7.38 (1H, d, *J* = 8.4 Hz), 7.34 (1H, d, *J* = 8.4 Hz), 7.21–7.17 (2H, m), 6.81–6.77 (3H, m), 4.81 (1H, d, *J* = 16.0 Hz), 4.53–4.49 (2H, m), 3.69 (3H, s), 3.47 (3H, s), 3.02 (1H, dd, *J* = 9.2, 16.6 Hz), 2.81 (1H, dd, *J* = 5.2, 16.6 Hz); δ_C (DMSO–d_6, 100 MHz) 170.2, 169.7, 167.2, 159.3, 139.1, 138.0, 136.6, 133.1, 129.5, 125.4, 124.3, 120.0, 119.0, 112.4 (2 ×), 54.9, 52.3, 51.7, 46.1, 30.8; HRMS $C_{20}H_{20}ClN_2O_5$ (M + H^+) requires 403.1061, found 403.1052. Anal. $C_{20}H_{19}ClN_2O_5$ (+ 0.25 H_2O) requires: C, 58.97; H, 4.83; N, 6.88. Found: C, 59.05; H, 4.65; N, 6.72.

(+)-(*S*)-8-Amino-4-(3-methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (16d). Reduction and in situ cyclization of **15d** (1.00 g, 2.10 mmol), according to the representative procedure V, gave **16d** (0.81 g, 78%). Solid; mp = 188–190 °C; $[\alpha]^{23}_D$ = +7.9 (DMF, *c* = 0.68); ν_{max} (KBr, cm^{-1}) 3459, 3357, 3222, 2957, 1739, 1689, 1633, 1600, 1442, 1406,

1331, 1279, 1205, 1043; δ_H (DMSO-d_6, 400 MHz) 7.47 (1H, d, J = 8.4 Hz), 7.18 (1H, d, J = 7.6 Hz), 6.78–6.74 (2H, m), 6.45 (1H, d, J = 8.4 Hz), 6.20 (1H, s), 5.94 (1H, s), 4.76 (1H, d, J = 16.4 Hz), 4.49 (1H, dd, J = 4.8, 10.0 Hz), 4.44 (1H, d, J = 16.4 Hz), 3.73 (3H, s), 3.50 (3H, s), 2.98 (1H, dd, J = 10.0, 16.8 Hz), 2.74 (1H, dd, J = 4.8, 16.8 Hz); δ_C (DMSO-d_6, 100 MHz) 170.2, 169.5, 168.2, 159.0, 152.4, 139.7, 138.1, 132.2, 129.2, 118.8, 113.6, 112.2, 112.0, 110.5, 103.0, 54.9, 52.5, 51.6, 45.9, 31.2; HRMS $C_{20}H_{22}N_3O_5$ (M + H^+) requires 384.1559, found 384.1558.

(+)-(*S*)-4-(3-Methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (16e). Reduction and in situ cyclization of **15e** (2.38 g, 5.53 mmol), according to the representative procedure V, gave **16e** (1.63 g, 80%). Solid; mp = 77–79 °C; R_f = 0.29 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = +11.7 (CH_2Cl_2, c = 1.61); ν_{max} (KBr, cm^{-1}) 3230, 2958, 1740, 1696, 1641, 1484, 1440, 1412, 1303, 1262, 1163, 1051; δ_H (DMSO-d_6, 400 MHz) 10.62 (1H, s), 7.81 (1H, d, J = 6.8 Hz), 7.55 (1H, t, J = 8.4 Hz), 7.29–7.18 (2H, m), 7.12 (1H, d, J = 8.0 Hz), 6.82–6.77 (3H, m), 4.82 (1H, d, J = 16.4 Hz), 4.55–4.48 (2H, m), 3.70 (3H, s), 3.47 (3H, s), 3.03 (1H, dd, J = 10.0, 16.4 Hz), 2.80 (1H, dd, J = 5.2, 16.6 Hz); δ_C (DMSO-d_6, 100 MHz) 170.3, 169.8, 168.0, 159.3, 139.3, 136.7, 132.4, 131.0, 129.4, 126.6, 124.3, 120.7, 119.0, 112.4 (2 ×), 54.9, 52.3, 51.6, 46.0, 30.9; HRMS $C_{20}H_{21}N_2O_5$ (M + H^+) requires 369.1450, found 369.1449.

(+)-(*S*)-4-[3-(Methoxycarbonyl)methoxybenzyl]-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (16f). Reduction and in situ cyclization of **15f** (2.00 g, 4.36 mmol), according to the representative procedure V, gave **16f** (1.56 g, 90%). Solid; mp = 64–66 °C; R_f = 0.20 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = +15.0 (CH_2Cl_2, c = 0.19); ν_{max} (KBr, cm^{-1}) 3240, 2966, 1741, 1697, 1637, 1484, 1440, 1401, 1303, 1219, 1163, 1089; δ_H (DMSO-d_6, 400 MHz) 10.63 (1H, s), 7.82 (1H, d, J = 7.6 Hz), 7.58–7.54 (1H, m), 7.30–7.27 (1H, m), 7.22–7.18 (1H, m), 7.12 (1H, d, J = 8.4 Hz), 6.85 (1H, d, J = 7.2 Hz), 6.79 (1H, s), 6.79–6.76 (1H, m), 4.73 (2H, s), 4.72 (1H, d, J = 16.0 Hz), 4.58 (1H, d, J = 16.0 Hz), 4.51 (1H, dd, J = 4.4, 9.8 Hz), 3.65 (3H, s), 3.46 (3H, s), 3.04 (1H, dd, J = 9.8, 17.0 Hz), 2.75 (1H, dd, J = 4.4, 17.0 Hz); δ_C (DMSO-d_6, 100 MHz) 170.3, 169.7, 169.2, 168.0, 157.6, 139.5, 136.7, 132.4, 131.0, 129.5, 126.6, 124.3, 120.7, 119.7, 113.1, 112.8, 64.5, 52.3, 51.8, 51.6, 46.0, 30.9; HRMS $C_{22}H_{23}N_2O_7$ (M + H^+) requires 427.1505, found 427.1505. Anal. $C_{22}H_{22}N_2O_7$ (+ 0.5 H_2O) requires: C, 60.68; H, 5.32; N, 6.43. Found: C, 60.80; H, 4.97; N, 6.20

(+)-(*S*)-1-Benzyl-4-[4-(methoxycarbonyl)benzyl]-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (17a). Alkylation of **16a** (1.40 g, 3.53 mmol) with benzyl bromide (0.43 mL, 3.53 mmol), according to the representative procedure I, gave **17a** (1.39 g, 81%). Solid; mp = 72–74 °C; R_f = 0.35 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = +96.0 (CH_2Cl_2, *c* = 1.05); ν_{max} (KBr, cm^{-1}) 2957, 1724, 1684, 1648, 1604, 1463, 1400, 1283, 1194, 1111, 1022; δ_H ($CDCl_3$, 400 MHz) 7.97 (2H, d, *J* = 6.8 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.45 (1H, t, *J* = 8.0 Hz), 7.34–7.20 (7H, m), 7.12 (2H, d, *J* = 6.8 Hz), 5.20 (1H, d, *J* = 16.0 Hz), 5.12 (1H, d, *J* = 16.0 Hz), 4.92 (1H, d, *J* = 16.0 Hz), 4.82 (1H, dd, *J* = 4.4 Hz, 10.4 Hz), 4.47 (1H, d, *J* = 16.0 Hz), 3.89 (3H, s), 3.55 (3H, s), 3.23 (1H, dd, *J* = 10.4 Hz, 16.4 Hz), 2.58 (1H, dd, *J* = 4.4 Hz, 16.4 Hz); δ_C ($CDCl_3$, 100 MHz) 170.3, 168.9, 168.4, 166.7, 142.7, 140.1, 136.5, 132.6, 130.9, 130.1 (2 ×), 129.4, 129.2, 128.8 (2 ×), 127.4, 127.1 (2 ×), 126.6 (2 ×), 126.3, 121.6, 53.0, 52.1 (2 ×), 51.8, 47.0, 32.0; HRMS $C_{28}H_{27}N_2O_6$ ($M + H^+$) requires 487.1869, found 487.1871; Anal. $C_{28}H_{26}N_2O_6$ requires: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.79; H, 5.19; N, 5.66.

(+)-(*S*)-1-Benzyl-8-chloro-4-(3-methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (17c). Alkylation of **16c** (1.60 g, 3.97 mmol) with benzyl bromide (0.48 mL, 3.97 mmol), according to the representative procedure I, gave **17c** (1.80 g, 92%). Solid; mp = 62–64 °C; R_f = 0.53 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = +68.6 (CH_2Cl_2, *c* = 0.55); ν_{max} (KBr, cm^{-1}) 2957, 1740, 1689, 1649, 1596, 1492, 1433, 1374, 1299, 1052; δ_H ($CDCl_3$, 400 MHz) 7.86 (1H, d, *J* = 8.4 Hz), 7.30–7.19 (6H, m), 7.11 (2H, d, *J* = 7.2 Hz), 6.84–6.77 (3H, m), 5.14 (1H, d, *J* = 16.0 Hz), 5.08 (1H, d, *J* = 16.0 Hz), 4.95 (1H, d, *J* = 16.0 Hz), 4.76 (1H, dd, *J* = 4.0 Hz, 10.4 Hz), 4.33 (1H, d, *J* = 16.0 Hz), 3.76 (3H, s), 3.57 (3H, s), 6.55 (1H, dd, *J* = 10.4, 16.6 Hz), 2.67 (1H, dd, *J* = 4.0, 16.6 Hz); δ_C ($CDCl_3$, 100 MHz) 170.4, 168.3, 168.0, 160.0, 141.0, 139.0, 138.4, 136.0, 132.2, 129.8, 129.0 (2 ×), 127.9, 127.6, 126.6 (2 ×), 126.5, 121.6, 119.4, 112.9, 112.8, 55.2, 53.1, 52.1, 51.6, 47.2, 31.9; HRMS $C_{27}H_{26}ClN_2O_5$ ($M + H^+$) requires 493.1530, found 493.1524; Anal. $C_{27}H_{25}ClN_2O_5$ requires: C, 65.79; H, 5.11; N, 5.68. Found: C, 65.58; H, 4.81; N, 5.51.

(+)-(*S*)-8-Amino-1-benzyl-4-(3-methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (17d). Solid; mp = 89–91 °C; R_f = 0.30 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = +2.4 (CH_2Cl_2, *c* = 0.19); ν_{max} (KBr, cm^{-1}) 3475, 3362, 3238, 2959, 1735, 1677, 1607, 1458, 1397, 1298, 1196, 1051; δ_H ($CDCl_3$, 400 MHz) 7.72 (1H, d, *J* = 8.4 Hz), 7.31–7.15 (6H, m), 6.85–6.80

(2H, m), 6.76 (1H, d, J = 8.0 Hz), 6.55 (1H, d, J = 8.4 Hz), 6.36 (1H, d, J = 2.4 Hz), 5.25 (1H, d, J = 16.0 Hz), 5.11 (1H, d, J = 16.0 Hz), 4.86 (1H, dd, J = 4.0, 10.0 Hz), 4.75 (1H, d, J = 16.0 Hz), 4.26 (1H, d, J = 16.0 Hz), 3.95 (2H, br), 3.77 (3H, s), 3.56 (3H, s), 3.26 (1H, dd, J = 10.0, 16.6 Hz), 2.61 (1H, dd, J = 4.0, 16.6 Hz); δ_C ($CDCl_3$, 100 MHz) 170.7, 169.1, 168.6, 159.7, 150.3, 142.1, 139.7, 136.9, 132.6, 129.7, 128.8 (2 ×), 127.2, 126.3 (2 ×), 119.3, 119.1, 112.7, 112.6 (2 ×), 105.9, 55.2, 53.1, 52.1, 52.0, 47.1, 32.0; HRMS $C_{27}H_{28}N_3O_5$ ($M + H^+$) requires 474.2029, found 474.2032. Anal. $C_{27}H_{27}N_3O_5$ (+ 0.25 H_2O) requires: C, 67.84; H, 5.80; N, 8.79. Found: C, 67.90; H, 5.82; N, 8.49.

(–)-(*S*)-1-Benzyl-8-benzylamino-4-(3-methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (17e). Solid, mp = 82–84 °C; R_f = 0.35 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = –11.8 (CH_2Cl_2, c = 0.24); ν_{max} (KBr, cm^{-1}) 3369, 2959, 1740, 1681, 1610, 1495, 1438, 1298, 1196; δ_H ($CDCl_3$, 400 MHz) 7.73 (1H, d, J = 8.4 Hz), 7.33–7.17 (9 H, m), 7.06 (2H, d, J = 6.8 Hz), 6.86–6.76 (3H, m), 6.53 (1H, d, J = 8.8 Hz), 6.28 (1H, s), 5.19 (1H, d, J = 15.8 Hz), 5.11 (1H, d, J = 16.2 Hz), 4.88 (1H, dd, J = 4.2, 10.8 Hz), 4.65 (1H, d, J = 15.8 Hz), 4.49 (1H, br), 4.28 (1H, d, J = 16.2 Hz), 4.22–4.18 (2H, m), 3.79 (3H, s), 3.58 (3H, s), 3.27 (1H, dd, J = 10.8, 16.4 Hz), 2.63 (1H, dd, J = 4.2, 16.4 Hz); δ_C ($CDCl_3$, 100 MHz) 170.7, 169.2, 168.6, 159.8, 151.1, 142.0, 139.8, 137.9, 136.9, 132.2, 129.6, 128.7 (2 ×), 128.6 (2 ×), 127.4, 127.1 (3 ×), 126.4 (2 ×), 119.2, 117.9, 112.6, 112.5, 111.0, 103.5, 55.1, 53.1, 51,9, 51.9, 47.3, 47.1, 32.0; HRMS $C_{34}H_{34}N_3O_5$ ($M + H^+$) requires 564.2498, found 564.2485. Anal. $C_{34}H_{33}N_3O_5$ requires: C, 72.45; H, 5.90; N, 7.46. Found: C, 72.06; H, 6.01; N, 7.25.

(+)-(*S*)-1-benzyl-8-dibenzylamino-4-(3-methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (17f). Solid, mp = 76–78 °C; R_f = 0.50 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = +7.4 (CH_2Cl_2, c = 0.15); ν_{max} (KBr, cm^{-1}) 2959, 1740, 1684, 1640, 1604, 1456, 1408, 1361, 1300, 1196; δ_H ($CDCl_3$, 400 MHz) 7.71 (1H, d, J = 8.8 Hz), 7.35–7.11 (14H, m), 6.86–6.80 (4H, m), 6.75 (1H, d, J = 8.4 Hz), 6.63 (1H, d, J = 8.8 Hz), 6.34 (1H, s), 5.09 (1H, d, J = 16.4 Hz), 5.07 (1H, d, J = 15.6 Hz), 4.90 (1H, dd, J = 4.0, 10.8 Hz), 4.58 (2H, d, J = 18.0 Hz), 4.47 (2H, d, J = 18.0 Hz), 4.43 (1H, d, J = 16.4 Hz), 4.28 (1H, d, J = 15.6 Hz), 3.76 (3H, s), 3.56 (3H, s), 3.26 (1H, dd, J = 10.8, 16.8 Hz), 2.62 (1H, dd, J = 4.0, 16.8 Hz); δ_C ($CDCl_3$, 100 MHz) 170.8, 169.2, 168.7, 159.8, 151.7, 141.8, 139.8, 136.9, 136.8 (2 ×), 132.2, 129.7, 128.8 (4 ×), 128.5 (2 ×), 127.6, 127.2 (2 ×), 126.9 (2 ×), 126.3 (4 ×), 119.3, 117.2, 112.6 (2 ×), 110.1, 103.9, 55.2, 53.1,

52.0, 51.8, 47.1 (3 ×), 32.1; HRMS $C_{41}H_{40}N_3O_5$ ($M + H^+$) requires 654.2968, found 654.2975. Anal. $C_{41}H_{39}N_3O_5$ requires: C, 75.32; H, 6.01; N, 6.43. Found: C, 75.04; H, 6.19; N, 6.16.

(+)-(*S*)-1-[3-(5-Hexenyloxy)benzyl]-4-(3-methoxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (17g). Alkylation of **16e** (358 mg, 0.97 mmol) with 3-(5-hexenoxy)benzyl bromide (261 mg, 0.97 mmol), according to the representative procedure I, gave **17g** (459 mg, 85%). Solid; mp = 40–42 °C; R_f = 0.50 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = +52.3 (CH_2Cl_2, *c* = 1.10); ν_{max} (KBr, cm^{-1}) 2943, 1740, 1684, 1650, 1604, 1461, 1399, 1261, 1159, 1049; δ_H ($CDCl_3$, 400 MHz) 7.93 (1H, d, *J* = 7.6 Hz), 7.44–7.17 (5H, m), 6.85–6.69 (6H, m), 5.81–5.74 (1H, m), 5.28 (1H, d, *J* = 16.0 Hz), 5.18 (1H, d, *J* = 16.0 Hz), 5.00–4.91 (2H, m), 4.82 (1H, dd, *J* = 4.0, 10.8 Hz), 4.77 (1H, d, *J* = 16.0 Hz), 4.21 (1H, d, *J* = 16.0 Hz), 3.92–3.87 (2H, m), 3.78 (3H, s), 3.55 (3H, s), 3.29 (1H, dd, *J* = 10.8, 16.8 Hz), 2.64 (1H, dd, *J* = 4.0, 16.8 Hz), 2.08 (2H, q, *J* = 6.8 Hz), 1.77–1.69 (2H, m), 1.54–1.48 (2H, m); δ_C ($CDCl_3$, 100 MHz) 170.5 (C), 168.8 (C), 168.6 (C), 159.9 (C), 159.6 (C), 140.2 (C), 139.3 (C), 138.5 (CH), 138.3 (C), 132.5 (CH), 130.9 (CH), 129.8 (2 × CH), 129.2 (C), 126.1 (CH), 121.3 (CH), 119.2 (CH), 118.4 (CH). 114.7 (CH_2), 113.7 (CH), 112.7 (2 × CH), 112.2 (CH), 67.6 (CH_2), 55.2 (CH_3), 53.0 (CH), 52.0 (CH_3), 51.7 (CH_2), 47.2 (CH_2), 33.4 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 25.3 (CH_2); HRMS $C_{33}H_{37}N_2O_6$ ($M + H^+$) requires 557.2652, found 557.2654.

(–)-(*S*)-1-{3-{2-[2-(2-Azido-ethoxy)-ethoxy]-ethoxy}benzyl}-7-chloro-3-isopropyl-4-(3-methoxybenzyl)-1,4-benzodiazepine-2,5-dione (17h). Alkylation of **16b** (131 mg, 0.35 mmol) with 3-(8-azido-3,6-dioxa-octoxy)benzyl bromide (121 mg, 0.35 mmol), according to the representative procedure I, gave **17h** (185 mg, 83%). Oil; R_f = 0.55 (EtOAc/hexane, 3:2); $[\alpha]^{23}_D$ = –159.7 (CH_2Cl_2, *c* = 0.55); ν_{max} (KBr, cm^{-1}) 2936, 2108, 1673, 1645, 1601, 1472, 1266, 1127, 1050; δ_H ($CDCl_3$, 400 MHz) 7.79 (1H, s), 7.30 (1H, d, *J* = 8.8 Hz), 7.24–7.05 (3H, m), 6.93–6.90 (2H, m), 6.80 (1H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J* = 8.4 Hz), 6.62–6.61 (2H, m), 4.98–4.94 (3H, m), 4.55 (1H, d, *J* = 14.4 Hz), 3.99–3.92 (2H, m), 3.80–3.62 (12H, m), 3.33 (2H, t, *J* = 4.4 Hz), 1.43–1.38 (1H, m), 0.80 (3H, d, *J* = 6.0 Hz), 0.58 (3H, d, *J* = 6.8 Hz); δ_C ($CDCl_3$, 100 MHz) 169.1, 164.7, 159.5, 158.8, 137.9, 137.3, 137.1, 131.9, 131.2, 131.1, 130.1, 129.6, 129.4, 122.6, 121.1, 119.2, 114.1, 113.7, 113.6, 112.9, 72.6, 70.7, 70.6, 70.0, 69.6, 67.2, 55.2, 55.2, 51.7, 50.6, 28.1, 19.8, 19.6; HRMS $C_{33}H_{39}ClN_5O_6$ ($M + H^+$) requires 636.2589, found 636.2594.

(+)-(*S*)-1-Benzyl-3-(methoxycarbonyl)methyl-4-[3-(methoxycarbonyl)methoxybenzyl]-1,4-benzodiazepine-2,5-dione (17i). Alkylation of **16f** (1.30 g, 3.05 mmol) with benzyl bromide (0.37 mL, 3.05 mmol), according to the representative procedure I, gave **17i** (1.35 g, 86%). Solid, mp = 52.0–54.0 °C; $[\alpha]^{22}_{D}$ = +61.8 ($CHCl_3$, *c* = 0.59); ν_{max} (KBr, cm^{-1}) 2958, 1740, 1648; δ_H ($CDCl_3$, 400 MHz) 7.92 (1H, d, *J* = 7.6 Hz), 7.45–7.41 (1H, m), 7.32–7.19 (6H, m), 7.13 (2H, d, *J* = 7.2 Hz), 6.90 (1H, d, *J* = 7.2 Hz), 6.86 (1H, s), 6.77 (1H, d, *J* = 8.0 Hz), 5.22 (1H, d, *J* = 16.0 Hz), 5.13 (1H, d, *J* = 16.0 Hz), 4.91 (1H, d, *J* = 16.0 Hz), 4.80 (1H, dd, *J* = 10.4, 4.4 Hz), 4.60 (2H, s), 4.31 (1H, d, *J* = 16.0 Hz), 3.78 (3H, s), 3.56 (3H, s), 3.26 (1H, dd, *J* = 16.8, 10.4 Hz), 2.64 (1H, dd, *J* = 16.8, 4.4 Hz); δ_C ($CDCl_3$, 100 MHz) 170.5, 169.3, 168.8, 168.6, 158.2, 140.1, 139.5, 136.6, 132.5, 130.9, 129.9, 129.3, 128.8 (2 ×), 127.3, 126.5 (2 ×), 126.2, 121.4, 120.5, 113.7, 113.3, 65.3, 53.0, 52.3, 52.1, 51.7, 47.0, 31.9; HRMS $C_{29}H_{29}N_2O_7$ ($M + H^+$) requires 517.1975, found 517.1978. Anal. $C_{29}H_{28}N_2O_7$ requires: C, 67.43; H, 5.46; N, 5.42. Found: C, 67.19; H, 5.70; N, 5.56.

(+)-(*S*)-1-Benzyl-4-(4-carboxybenzyl)-3-carboxymethyl-1,4-benzodiazepine-2,5-dione (17j). To a solution of ester **17a** (0.50 g, 1.03 mmol) in THF (0.75 mL) was added a solution of LiOH monohydrate (100 mg, 2 mmol) in water (5 mL) at 0 °C. The mixture was stirred at 25 °C for 9 h, and partitioned between EtOH (50 mL) and brine (50 mL of 2 M solution). The aqueous phase was separated, acidified with HCl (1 M) to pH < 1, and extracted with CH_2Cl_2 (50 mL × 3). The organic phase was combined, dried (Na_2SO_4), and concentrated under reduced pressure to give acid **17j** (0.41 g, 87%). Solid; mp = 145–147 °C; R_f = 0.40 (MeOH/CH_2Cl_2, 1:4); $[\alpha]^{23}_{D}$ = +180.1 (CH_2Cl_2, *c* = 0.63); ν_{max} (KBr, cm^{-1}) 3066, 2933, 1684, 1653, 1613, 1465, 1400, 1255, 1175, 1110; δ_H (DMSO–d_6, 400 MHz) 7.85 (2H, d, *J* = 8.4 Hz), 7.75 (1H, d, *J* = 7.6 Hz), 7.57–7.53 (1H, m), 7.42 (1H, d, *J* = 8.4 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 7.33 (1H, t, *J* = 8.4 Hz), 7.24–7.18 (3H, m), 7.04 (2H, d, *J* = 7.2 Hz), 5.14 (1H, d, *J* = 16.0 Hz), 5.05 (1H, d, *J* = 16.0 Hz), 4.82 (1H, d, *J* = 16.4 Hz), 4.72 (1H, d, *J* = 16.4 Hz), 4.66 (1H, dd, *J* = 4.0, 10.8 Hz), 3.08 (1H, dd, *J* = 10.8, 16.4 Hz), 2.70 (1H, dd, *J* = 4.0, 16.8 Hz); δ_C (DMSO-d_6, 100 MHz) 171.3, 168.7, 167.9, 167.2, 142.8, 139.3, 137.1, 132.4, 130.4, 129.6, 129.4 (2 ×), 129.3, 128.5 (2 ×), 127.3 (2 ×), 127.1, 126.7 (2 ×), 125.8, 121.6, 52.6, 49.4, 46.0, 31.8; HRMS $C_{26}H_{23}N_2O_6$ ($M + H^+$) requires 459.1556, found 459.1552. Anal. $C_{26}H_{22}N_2O_6$ (+ 0.5 H_2O) requires: C, 66.80; H, 4.96; N, 5.99. Found: C, 66.86; H, 4.78; N, 6.01.

(+)-(*S*)-1-Benzyl-4-[3-(carboxymethoxy)benzyl]-3-carboxymethyl-1,4-benzodiazepine-2,5-dione (17k). Saponification of **17i** (1.30 g, 2.52 mmol), by a procedure similar to that for **17j**, gave **17k** (1.02 g, 83%). Solid; mp = 118–120 °C; R_f = 0.20 (MeOH/CH_2Cl_2, 1:9); $[\alpha]^{23}_D$ = +99.8 (DMF, *c* = 1.25); ν_{max} (KBr, cm^{-1}) 3442, 2981, 1735, 1685, 1605, 1465, 1401, 1255, 1158, 1085; δ_H (DMSO-d_6, 400 MHz) 7.75 (1H, d, *J* = 7.6 Hz), 7.55 (1H, m), 7.42 (1H, d, *J* = 8.0 Hz), 7.33 (1H, m), 7.25–7.18 (4H, m), 7.07 (2H, d, *J* = 6.8 Hz), 6.87 (2H, m), 6.78 (1H, d, *J* = 8.0 Hz), 5.16 (1H, d, *J* = 16.0 Hz), 5.08 (1H, d, *J* = 16.0), 4.73 (1H, d, *J* = 16.0 Hz), 4.68–4.59 (4H, m), 3.12 (1H, dd, *J* = 10.4, 16.8 Hz), 2.67 (1H, dd, *J* = 4.0, 16.8 Hz); δ_C (DMSO-d_6, 100 MHz) 171.3, 170.1, 168.7, 167.8, 157.8, 139.4, 139.1, 137.1, 132.3, 130.4, 129.4, 129.4, 128.5 (2 ×), 127.0, 126.7 (2 ×), 125.7, 121.5, 119.6, 113.3, 112.8, 64.5, 52.5, 49.3, 46.0, 31.7; HRMS $C_{27}H_{25}N_2O_7$ ($M + H^+$) requires 489.1662, found 489.1661.

(+)-(*S*)-1-Benzyl-8-chloro-4-(3-hydroxybenzyl)-3-(methoxycarbonyl)methyl-1,4-benzodiazepine-2,5-dione (17l) and (+)-(*S*)-1-benzyl-3-carboxymethyl-8-chloro-4-(3-hydroxybenzyl)-1,4-benzodiazepine-2,5-dione (17m). To a solution of anisole **17c** (493 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was added BBr_3 (4 mL of 1 M solution in CH_2Cl_2) dropwise at −78 °C. The mixture was stirred at −78 °C for 30 min, and at 0 °C for another 15 min. The reaction was quenched by pouring the mixture into ice water (30 mL), and extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine (30 mL), dried (Na_2SO_4), concentrated, and chromatographed on a silica gel column by elution with hexane/EtOAc (7:3) to afford **17l** (225 mg, 47%) and **17m** (140 mg, 30%).

Compound **17l**: Solid, mp = 94–96 °C; R_f = 0.35 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = +52.5 (CH_2Cl_2, *c* = 1.09); ν_{max} (KBr, cm^{-1}) 3359, 2959, 1740, 1685, 1647, 1596, 1438, 1297, 1242, 1000; δ_H (DMSO-d_6, 400 MHz) 9.34 (1H, s), 7.72 (1H, d, *J* = 8.4 Hz), 7.60 (1H, s), 7.38 (1H, d, *J* = 8.4 Hz), 7.25–7.15 (3H, m), 7.08–7.00 (3H, m), 6.70 (1H, s), 6.67 (1H, d, *J* = 8.0 Hz), 6.61 (1H, d, *J* = 8.4 Hz), 5.26 (1H, d, *J* = 16.0 Hz), 5.00 (1H, d, *J* = 16.0 Hz), 4.67 (1H, dd, *J* = 5.0, 10.0 Hz), 4.60 (2H, s), 3.48 (3H, s), 3.15 (1H, dd, *J* = 10.0, 16.6 Hz), 2.81 (1H, dd, *J* = 5.0, 16.6 Hz); δ_C (DMSO-d_6, 100 MHz) 170.2, 168.3, 166.9, 157.4, 140.0, 138.9, 136.6 (2 ×), 132.0, 129.3, 128.6 (2 ×), 128.4, 127.2, 127.1 (2 ×), 125.9, 121.7, 117.8, 114.2, 114.1, 52.5, 51.7, 48.7, 45.9, 31.4; HRMS $C_{26}H_{24}ClN_2O_5$ ($M + H^+$) requires 479.1374, found 479.1360. Anal. $C_{26}H_{23}ClN_2O_5$ (+ 0.5 H_2O) requires: C, 64.00; H, 4.96; N, 5.74. Found: C, 63.72; H, 4.83; N, 5.87.

Compound **17m**: Solid, mp = 145–147 °C; R_f = 0.21 (MeOH/CH_2Cl_2, 1:9); $[\alpha]^{23}_D$ = +95.9 (DMF, *c* = 0.15); ν_{max} (KBr, cm^{-1}) 3388, 2919, 1680, 1633, 1595, 1437, 1288, 1235; δ_H (DMSO–d_6, 400 MHz) 7.72 (1H, d, *J* = 8.4 Hz), 7.54 (1H, s), 7.37 (1H, d, *J* = 8.4 Hz), 7.26–7.18 (3H, m), 7.09–7.04 (3H, m), 6.71 (1H, s), 6.67 (1H, d, *J* = 7.6 Hz), 6.63 (1H, d, *J* = 8.0 Hz), 5.22 (1H, d, *J* = 16.2 Hz), 5.03 (1H, d, *J* = 16.2 Hz), 4.62 (1H, d, *J* = 4.4 Hz), 4.59 (1H, d, *J* = 4.4 Hz), 4.61–4.60 (1H, m), 3.08 (1H, dd, *J* = 10.4, 16.0 Hz), 2.61 (1H, dd, *J* = 4.0, 16.0 Hz); δ_C (DMSO-d_6, 100 MHz) 168.9, 166.9, 157.4 (2 ×), 140.2, 139.1, 136.8, 136.5, 132.0, 129.3, 128.6 (2 ×), 128.5, 127.2, 126.9 (2 ×), 125.7, 121.5, 117.7, 114.1 (2 ×), 52.9, 48.7, 46.0, 32.0; HRMS $C_{25}H_{22}ClN_2O_5$ ($M + H^+$) requires 465.1217, found 465.1209. Anal. $C_{25}H_{21}ClN_2O_5$ (+ 1.5 H_2O) requires: C, 61.04; H, 4.92; N, 5.69. Found: C, 61.40; H, 4.65; N, 5.63.

(+)-(3*S*)-1-Benzyl-8-(2-bromoacetylamino)-4-(3-methoxybenzyl)-3-(methoxycarbonyl) methyl-1,4-benzodiazepine-2,5-dione (17o). To a mixture of compound **17d** (142.1 mg, 0.3 mmol) and K_2CO_3 (414.6 mg, 3 mmol) in CH_3CN (10 mL) was added bromoacetyl bromide (0.134 mL, 1.5 mmol) at 0 °C. The mixture was stirred at reflux temperature for 3 h and quenched with saturated NH_4OH solution (10 mL). Then CH_3CN was removed under reduced pressure and the mixture was extracted with CH_2Cl_2 (10 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford pure **17o** (136.7 mg, 0.23 mmol) in 77% yield. solid; mp = 103–105 °C; R_f = 0.16 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ = +77.1 (CH_2Cl_2, *c* = 0.15); ν_{max} (KBr, cm^{-1}) 3271, 2959, 1739, 1685, 1608, 1540, 1437, 1310, 1202, 1043; δ_H ($CDCl_3$, 400 MHz) 8.20 (1H, br), 7.88 (1H, d, *J* = 8.4 Hz), 7.76 (1H, s), 7.28–7.18 (5H, m), 7.11 (2H, d, *J* = 7.2 Hz), 6.84–6.77 (3H, m), 5.10–5.05 (3H, m), 4.79 (1H, dd, *J* = 4.4, 10.4 Hz), 4.33 (1H, d, *J* = 16.0 Hz), 3.96 (2H, s), 3.78 (3H, s), 3.56 (3H, s), 3.26 (1H, dd, *J* = 10.4, 16.8 Hz), 2.66 (1H, dd, *J* = 4.4, 16.8 Hz); δ_C ($CDCl_3$, 100 MHz) 170.5, 168.4, 168.3, 163.7, 159.9, 140.8, 140.7, 139.1, 136.2, 131.8, 129.8, 128.8 (2 ×), 127.5, 126.8 (2 ×), 125.7, 119.3, 116.9, 112.9, 112.6, 112.1, 55.2, 53.1, 52.1, 51.3, 47.1, 31.9, 29.1; HRMS $C_{29}H_{29}BrN_3O_6$ ($M + H^+$) requires 594.1240, found 594.1234. Anal. $C_{29}H_{28}BrN_3O_6$ (+ 0.25 H_2O) requires: C, 58.15; H, 4.80; N, 7.02. Found: C, 58.04; H, 5.02; N, 6.75.

The synthetic procedures by a liquid-phase combinatorial synthesis and characterization for compounds **20a–o** (Scheme 2, B) have been previously described.[21]