Investigation on the anti-cancer activity of symmetric and unsymmetric cyclic sulfamides

Jaden Jungho Jun,[1,2] Divya Duscharla,[3] Ramesh Ummanni,[3]
Paul R. Hanson,[2,*] Sanjay V. Malhotra[4,5,6*]

1) Department of Pharmaceutical Sciences and Computational Chemical Genomics Screening Center, NIH National Center of Excellence for Computational Drug Abuse Research, Drug Discovery Institute, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania 15261, United States.
2) Department of Chemistry, University of Kansas, 1567 Irving Hill Road, Lawrence, Kansas 66045-7582, United States.
3) Centre for Chemical Biology, Indian Institute of Chemical Technology, Hyderabad 500607, India
4) Department of Cell, Development and Cancer Biology, Oregon Health & Science University, Portland, Oregon 97201
5) Center for Experimental Therapeutics, Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon 97201
6) Lead author

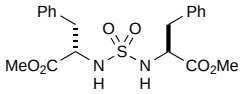
1.	Chemistry	2-22
2.	Biology	23-27
3.	^{1}H and ^{13}C NMR Spectrum	28-54
4.	References	55

1. Chemistry

General methods

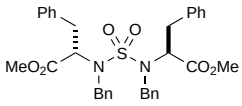
All reactions were carried out in flame-dried glassware under argon. Toluene, THF, Et_2O, and CH_2Cl_2 were purified by passage through a purification system (Solv-Tek) employing activated Al_2O_3. Flash column chromatography was performed with Sorbent Technologies, Inc. silica gel (10930-25, 230-450 mesh). Thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5715-7, Merck). All amino acid precursors were purchased from Advanced Chem Tech. ^1H and ^{13}C spectra were recorded in $CDCl_3$ on either a Bruker DRX-400 or a Bruker AM-500 spectrometer operating at 400/100 MHz and 500/125 MHz, respectively. High-resolution mass spectrometry (HRMS) was obtained on a VG Instrument ZAB double-focusing mass spectrometer. Stretching frequencies were obtained on a Nicolet 320 Fourier Transform Infrared Spectrophotometers. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were determined on a Rudolph Automatic Polarimeter (AUTOPOL IV).

N,N'-Sulfonyl bis-*L*-phenylalanine dimethyl ester (3)



This compound was prepared according to literature procedure.[1] To a solution of *L*-phenylalanine methyl ester hydrochloride (4.01 g, 18.62 mmol) in CH_2Cl_2 (80 mL) was added Et_3N (5.7 mL, 40.90 mmol) for 10 min at 0 °C. Then sulfuryl chloride (0.68 mL, 8.46 mmol) was added over 30 min. The resulting white solid was purified by flash chromatography (2:1 hexanes/EtOAc) to afford the desired diester compound **3** (3.05 g, 86%).

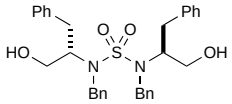
N, N'-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-phenylethyl)-2-methoxycarbonyl]-sulfamide (5)



To a solution of **3** (1.05 g, 2.49 mmol) in CH_3CN (20 mL) was added benzyl bromide (0.7 mL, 6.08 mmol) and K_2CO_3 (1.06 g, 7.67 mmol) and then brought to reflux at 85 °C. The resulting oil was purified by flash chromatography (2:1 hexanes/EtOAc) to afford the desired diester compound **5** as clear oil (1.55 g, 99%). TLC R_f = 0.63 (2:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -24.4 (*c* =1.1, $CHCl_3$); ^1H NMR

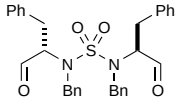
($CDCl_3$, 400 MHz) δ 7.31 (m, 5H), 7.17 (m, 5H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.42 (dd, *J* = 7.9, 6.3 Hz, 1H), 4.27 (d, *J* = 15.4 Hz, 1H), 3.53 (s, 3H), 3.36 (dd, *J* = 14.0, 8.1 Hz, 1H), 3.11 (dd, *J* = 14.0, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 137.9, 136.2, 129.6, 129.1, 128.7, 128.6, 128.1, 126.9, 61.6, 52.3, 50.5, 36.3; FTIR (neat) 3062, 3030, 2951, 1741, 1454, 1437, 1337, 1220, 1147, 1027, 744, 698 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{34}H_{37}N_2O_6S$ $(M+H)^+$ required 601.2372, found 601.2343.

_N, N'_-Bis-benzyl-_N_-_N'_-bis-[(1_S_)-2-hydroxy-1-(2-phenylethyl)ethyl]-sulfamide (9)



To a solution of **5** (1.52 g, 2.53 mmol) in THF (40 mL) was added LAH (526 mg, 13.87 mmol) at 0 °C. The resulting oil was purified by flash chromatography (2:1 hexanes/EtOAc) to afford the desired diester compound **9** as a white solid (1.31 g, 95%). Mp = 163 °C; TLC R_f = 0.35 (2:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -43.6 (*c* = 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 6.9 Hz, 2H), 7.40–7.34 (m, 3H), 7.24–7.19 (m, 3H), 7.01 (d, *J* = 6.1 Hz, 2H), 4.60 (s, 2H), 3.95–3.89 (m, 1H), 3.63 (dd, *J* = 12.1, 0 Hz, 1H), 3.56 (dd, *J* = 12.1, 4.6 Hz, 1H), 3.17 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.45 (s, 1H), 2.35 (dd, *J* = 13.4, 10.9Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 138.7, 129.2, 129.0, 128.8, 128.8, 128.0, 126.7, 61.9, .61.4, 49.1, 37.8; FTIR (neat) 3319, 3028, 2939, 2918, 1494, 1454, 1329, 1321, 1130, 1034, 972, 784, 730 698 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{32}H_{37}N_2O_4S$ $(M+H)^+$ required 545.2474, found 545.2484.

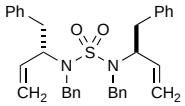
_L_-Phenylalanine-derived C_2-symmetric sulfamide aldehyde (12)



To a solution of oxalyl chloride (0.48 mL, 5.50 mmol) in CH_2Cl_2 (1.5 mL) at -78 ºC under an argon gas atmosphere was added dimethyl sulfoxide (0.48 mL, 6.76 mmol) in CH_2Cl_2 (1.5 mL) for 20 min. After 40 min a solution of **9** (1.21 g, 2.22 mmol) in CH_2Cl_2 (15 mL) was added for 20 min. After 4 h, Et_3N (2.3 mL, 16.50 mmol) was added and the reaction temperature maintained at -78 °C for 30 min and at 0 °C for 2h. The reaction mixture was cooled to -78 °C and aqueous THF (10 mL, THF:H_2O = 1:1) was added. 10 min later, the reaction mixture was warmed up to 0 °C. The reaction mixture was extracted with CH_2Cl_2 (50 mL), washed with 2M HCl, dried ($MgSO_4$), filtered, and concentrated

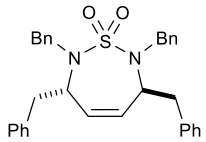
under reduced pressure. The resulting white solid was purified by flash chromatography (2:1 hexanes/EtOAc) to afford the desired dialdehyde sulfamide compound **12** as a white solid (1.19 g, 99%). Mp = 57 °C; TLC R_f = 0.58 (1:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -65.7 (*c* = 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H), 7.32–7.17 (m,10H), 4.33 (d, *J* = 14.9 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 4.04 (dd, *J* = 7.9, 6.2 Hz, 1H), 3.42 (dd, *J* = 14.5, 6.2 Hz, 1H), 3.08 (dd, *J* = 14.5, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.1, 137.6, 135.1, 129.5, 129.2, 129.1, 129.0, 128.8, 127.2, 67.4, 51.0, 34.1; FTIR (neat) 3063, 3030, 2931, 2826, 2729, 1956, 1736, 1602, 1497, 1454, 1328, 1146, 1083, 1053, 1030, 883, 848, 746, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{32}H_{33}N_2O_4S$ $(M+H)^+$ required 541.2161, found 541.2166.

***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-phenylethyl)-2-propenyl]-sulfamide (15)**



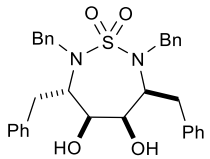
To a solution of methyl triphenyl phosphonium bromide in THF (25 mL) was added *n*-butyllithium (1.6 M in hexane) at 0 °C and the reaction was stirred for 3 h. After cooling down the reaction mixture to -78 °C, the solution of dialdehyde **12** in THF (25 mL) was cooled to -78 °C and added to the Wittig solution and then stirred 16 h. The reaction mixture was extracted with EtOAc (30 mL x 3) and dried ($MgSO_4$). The reaction mixture was filtered and evaporated under reduced pressure to obtain a crude solid. Flash chromatography (10:1 Hexanes/EtOAc) gave 519 mg (50%) of the **15** as a white solid. Mp = 99 °C; TLC R_f = 0.43 (10:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -54.6 (*c* = 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.30 (m, 5H), 7.17–7.12 (m, 3H), 6.94 (d, *J* = 6.2 Hz, 2H), 5.90 (ddd, *J* = 17.8, 10.3, 7.8 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 17.2 Hz, 1H), 4.36 (d, *J* = 15.6, 1H), 4.20 (d, *J* = 15.5 Hz, 1H), 4.21–4.17 (m, 1H), 3.08 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 137.9, 135.6, 129.5, 128.9, 128.7, 128.4, 127.9, 126.4, 119.5, 63.4, 49.8, 40.1; FTIR (neat) 3063, 3028, 2930, 1497, 1454, 1331, 1147, 1045, 1027, 926, 737, 698 cm^{-1}; HRMS calcd for $C_{34}H_{37}N_2O_2S$ $(M+H)^+$ required 537.2576, found 537.2563.

(3*S*,6*S*)-2,3,6,7-Tetrabenzyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (18)



A stirring solution of the diene sulfamide **15** (485 mg, 0.904 mmol) in benzene (30 mL) was degassed with argon for 30 min. The flask was quickly fitted with a condenser containing an argon balloon, and the solution was heated to reflux. The Grubbs' metathesis catalyst **II** (25 mg, 3 mol%) was added to the refluxing solution and maintained at reflux for 18 h. The solution was cooled to room temperature and silica gel was added with DMSO (0.5 mL) and the solution was stirred for 24 h. The solution was filtered, and the solvent was removed under reduced pressure to obtain a crude solid. Flash chromatography (5:1 Hexanes/EtOAc) gave 457 mg (99%) of the **18** as a white solid. Mp = 148 °C; TLC R_f = 0.43 (5:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -47.8 (*c* = 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.06 (m, 10H), 5.56 (s, 1H), 4.83 (d, *J* = 16.2 Hz, 1H), 4.48 (dd, *J* = 9.8, 5.2 Hz, 1H), 4.39 (d, *J* = 16.2 Hz, 1H), 3.01 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.73 (dd, *J* = 13.5, 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 137.7, 130.6, 129.4, 128.8, 128.7, 127.6, 127.5, 126.9, 57.2, 51.9, 40.3; FTIR (neat) 3061, 3028, 2928, 1495, 1454, 1344, 1153, 929, 763, 725, 698 cm^{-1}; HRMS calcd for $C_{32}H_{33}N_2O_2S$ $(M+H)^+$ required 509.2263, found 509.2279.

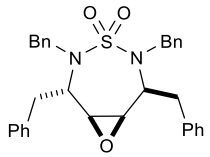
(3*S*,4*R*,5*S*,6*S*)-2,3,67-Tetrabenzyl-2,3,6,7-tetra-hydro-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (21)



To a stirring solution of the sulfamide **18** (72 mg, 0.143 mmol) in distilled water (0.28 mL, 15.54 mmol) and acetone (0.9 mL, 12.26 mmol) was added NMO (25 mg, 0.185 mmol) and OsO_4 (27 mg, 0.143 mmol) in distilled water (0.28 mL, 15.54 mmol) and acetone (0.9 mL, 12.26 mmol) was added NMO (25 mg, 0.s washed with saturated $Na_2S_2O_3$ aqueous solution. The organic layer was washed with brine and dried over $MgSO_4$, filtered, concentrated on a rotary evaporator. Flash chromatography (2:1 Hexanes/EtOAc) gave 67 mg (87%) of the **21** as a white solid. Mp = 102 °C; TLC R_f = 0.29 (2:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = 14.4 (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–6.99 (m, 20H), 4.96 (d, *J* = 17.0 Hz, 1H), 4.73 (d, *J* = 15.8 Hz, 1H), 4.69 (d, *J* = 14.4 Hz, 1H), 4.48 (d, *J* = 14.7 Hz, 1H), 4.00 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.79 (dd, *J* = 7.9, 2.2 Hz, 1H), 3.76 (s, 1H),

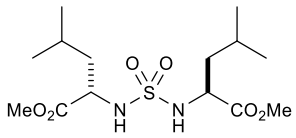
3.72 (dd, *J* = 14.5, 7.8 Hz, 1H), 3.14 (dd, *J* = 14.3, 8.2 Hz, 1H), 3.02 (dd, *J* = 18.4, 13.4 Hz, 1H), 3.00 (s, 1H), 2.86 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.58 (s, 1H), 1.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.5, 138.4, 138.2, 137.3, 129.5, 129.2, 1219.0, 129.0, 128.9, 128.9, 128.8, 128.2, 127.3, 127.3, 127.0, 74.6, 61.1, 60.3, 53.6, 51.7, 39.5, 36.5; FTIR (neat) 3483, 3063, 3028, 2930, 1497, 1454, 1313, 1145, 1063, 1022, 870, 781, 735, 698 cm^{-1}; HRMS calcd for $C_{32}H_{34}N_2O_4S$ $(M+H)^+$ required 543.2318, found 543.2292.

(1*S*,2*R*,6*S*,7*S*)-2,3,5,6-Tetrabenzyl-8-oxa-4-thia-3,5-diaza-bicyclo[5.1.0]octane 4,4-dioxide (23)



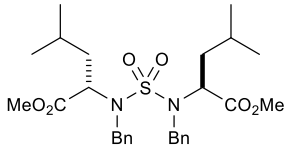
To a stirring solution of the sulfamide **18** (105 mg, 0.206 mmol) in CH_2Cl_2 (3 mL) was added *m*-CPBA (81 mg, 0.469 mmol) at room temperature and the solution was stirred for 24h. The organic layer was extracted with CH_2Cl_2 (20 mL x 3) and ether (30 mL), and the organic layer was washed with saturated $NaHCO_3$ aqueous solution and the organic layer was dried ($MgSO_4$), filtered, concentrated under reduced pressure. Flash chromatography (5:1 Hexanes/EtOAc) gave 57 mg (53%) of the **23** as clear oil. TLC R_f = 0.34 (5:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -18.8 (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.35–7.02 (m, 16H), 7.00 (d, *J* = 5.6 Hz, 2H), 4.93 (d, *J* = 17.3 Hz, 1H), 4.76 (d, *J* = 15.2 Hz, 1H), 4.60 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.57 (d, *J* = 18.2 Hz, 1H), 4.53 (d, *J* = 15.4 Hz, 1H), 4.00–3.95 (m, 1H), 3.24 (dd, *J* = 14.2, 6.3 Hz, 1H), 3.1–2.89 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 129.6, 129.2, 129.0, 128.8, 128.4, 128.0, 127.3, 127.1, 126.9, 59.6, 55.7, 53.6, 38.6; FTIR (neat) 3085, 3028, 2980, 1735, 1602, 1494, 1454, 1367, 1344, 1153, 1095, 1062, 1027, 852, 736, 700 cm^{-1}; HRMS calcd for $C_{32}H_{33}N_2O_3S$ $(M+H)^+$ required 525.2212, found 525.2187.

***N,N'*-Sulfonyl bis-*L*-leucine dimethyl ester (4)**



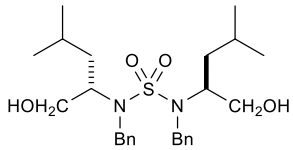
N,N'-Sulfonyl bis-*L*-leucine dimethyl ester **4** were prepared according to literature procedure.[1]

***N, N'* -Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (6)**



To a stirring solution of the leucine-derived sulfamide **4** (500 mg, 1.43 mmol) in CH_3CN (20 mL) at room temperature under an argon atmosphere was added K_2CO_3 (430 mg, 3.13 mmol) and benzyl bromide (0.37 mL, 3.11 mmol). The reaction mixture was heated to reflux for 24 h, filtered, and concentrated under reduced pressure. The filtrate was extracted with EtOAc (50 mL x 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by column chromatography (10:1 hexanes/EtOAc) to afford 750 mg (99%) of the desired dibenzyl sulfamide **6** as clear oil. TLC R_f = 0.28 (10:1 hexanes/EtOAc); $[\alpha]^{D}_{25}$ = 35.9 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.30–7.23 (m, 3H), 4.71 (d, *J* = 15.8 Hz, 1H), 4.44 (d, *J* = 15.8 Hz, 1H), 4.26 (t, *J* = 6.5 Hz, 1H), 3.64 (s, 3H), 1.82–1.77 (m, 1H), 1.58–1.49 (m, 2H), 0.85 (d, *J* = 6.2 Hz, 3H), 0.59 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 137.1, 128.5, 128.4, 127.6, 58.1, 52.1, 50.3, 39.0 24.9, 22.2, 22.0; FTIR (neat) 3031, 2956, 1747, 1497, 1455, 1338, 1147, 755, 698 cm^{-1}; HRMS calcd for $C_{28}H_{41}N_2O_6S$ $(M+H)^+$ required 533.2685, found 533.2672.

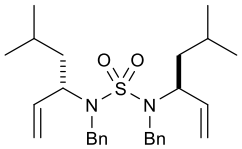
***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-2-hydroxy-1-(2-methylpropyl)ethyl]-sulfamide (10)**



To a stirring solution of **6** (110 mg, 0.22 mmol) in THF (30 mL) at 0 º (under an argon atmosphere was added LAH (160 mg, 4.29 mmol). After 1 h, a 15% NaOH aqueous solution was added to quench the reaction, and the reaction mixture was filtered under reduced pressure. The filtrate was concentrated under reduced pressure and extracted with EtOAc (50 mL x 2). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified by column chromatography (1:1 hexanes/EtOAc) to afford 100 mg (100%) of the desired sulfamide diol **10** as clear oil. TLC R_f = 0.51 (1:1 hexanes/EtOAc); $[\alpha]^{25}_{D}$ = +15.6° (c = 1.00, $CHCl_3$); ^{1}H NMR δ 7.41 (d, *J* = 7.1 Hz, 4H), 7.26–7.16 (m, 6H), 4.49 (d, *J* = 15.8 Hz, 2H), 4.45 (d, *J* = 15.8 Hz, 2H), 3.83–3.75 (m, 2H), 3.63–3.56 (m, 4H), 2.60 (bs, 2H), 1.54–1.44 (m, 2H), 1.44–1.37 (m, 2H), 1.19–1.12 (m, 2H), 0.79 (d, *J* = 6.5 Hz, 6H), 0.73 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5,

128.5, 127.5, 62.5, 58.8, 49.2, 39.5, 25.1, 23.1, 21.7; FTIR (neat) 3386, 3029, 2956, 1604, 1496, 1455, 1323, 1143, 758, 698 cm^{-1}; HRMS calcd for $C_{26}H_{41}N_2O_4S$ $(M+H)^+$ required 477.2787, found 477.2808.

***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-propenyl]-sulfamide (16)**

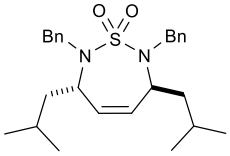


To a stirring solution of oxalyl chloride (0.30 mL, 3.44 mmol) in CH_2Cl_2 (1 mL) at -78 ºC under an argon atmosphere was added DMSO (0.30 mL, 4.23 mmol) in CH_2Cl_2 (1 mL) over 20 min. After 40 min, the sulfamide diol **10** (477 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added over 30 min with an addition funnel, and the funnel was rinsed with CH_2Cl_2 (10 mL). The mixture was stirred at -78 ºC for 5 h and monitored by TLC. Et_3N (1.5 mL, 10.76 mmol) was added over 15 min and stirred at -78 °C for 2 h. THF (4 mL, 1:1 H_2O/THF) was added at -78 °C for 5 min, and the mixture stirred at 0 ºC for h. The reaction mixture was extracted with CH_2Cl_2 (50 mL), washed with 2M HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 507 mg (99%) of the desired dialdehyde sulfamide as a white solid **13** that was carried on immediately without further purification. TLC R_f = 0.91 (1:1 hexanes/EtOAc).

To a stirring solution of CH_3PPh_3Br (2.69 g, 7.53 mmol) in THF (25 mL) at 0 ºC under an argon atmosphere was slowly added a solution of BuLi (3.75 mL, 6.0 mmol, 1.6 M in hexanes) over 3 min. After 3 h, the yellow ylide solution was cooled to -78 ºC and a solution of dial sulfamide (474 mg, 1.00 mmol) in THF (25 mL) at -78 ºC was added via cannula. After 24 h, acetone (30 mL) was added to quench the reaction. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc (50 mL x 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (10:1 hexanes/EtOAc) gave 418 mg (89%) of the desired sulfamide diene **16** as white solid. Mp = 86 °C; TLC R_f = 0.66 (10:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -18.5 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.34–7.22 (m, 3H), 5.86 (ddd, *J* = 17.5, 10.3, 7.8 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 4.34 (d, *J* = 15.6 Hz, 1H), 4.22 (d, *J* = 15.6 Hz, 1H), 4.02 (dd, *J* = 13.6, 7.8 Hz, 1H), 1.52–1.34 (m, 3H), 0.79 (d, *J* = 6.1 Hz, 3H), 0.64 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz)

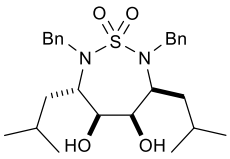
δ 138.1, 136.8, 128.6, 128.4, 127.4, 118.2, 59.8, 49.3, 41.5, 24.6, 23.1, 21.5; FTIR (neat) 3033, 2956, 2930, 1496, 1455, 1332, 1147, 700, 744 cm^{-1}; HRMS calcd for $C_{28}H_{41}N_2O_2S$ $(M+H)^+$ required 469.2889, found 469.2875.

(3*S*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (19)



To a degassed solution of **16** (320 mg, 0.68 mmol) in benzene (25 mL) was added $(ImesH_2)(PCy_3)(Cl)_2Ru$=CHPh (20 mg, 0.030 mmol) at room temperature. After 24 h, DMSO (1.0 mL) and silica gel were added to remove the catalyst. After 24 h, the reaction mixture was filtered, and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 210 mg (69%) of the desired cyclic sulfamide **19** as white solid. Mp = 108 °C; TLC R_f = 0.79 (5:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -55.1 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, *J* = 10.3 Hz, 2H), 7.33–7.22 (m, 3H), 5.52 (s, 1H), 4.86 (d, *J* = 16.0 Hz, 1H), 4.23 (dd, *J* = 9.1, 5.2 Hz, 1H), 4.20 (d, *J* = 16.0 Hz, 1H), 1.61–1.53 (m, 1H), 1.39–1.33 (m, 1H), 1.18–1.11 (m, 1H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.48 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 132.1, 128.3, 127.7, 127.2, 53.4, 50.9, 42.6, 24.2, 22.3, 21.4; FTIR (neat) 3064, 3028, 2957, 1606, 1496, 1338, 1147 cm^{-1}; HRMS calcd for $C_{26}H_{37}N_2O_2S$ $(M+H)^+$ required 441.2576, found 441.2584.

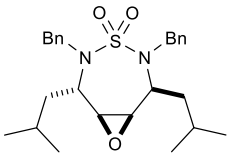
(3*S*,4*R*,5*S*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetra-hydro-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (22)



To a stirring solution of cyclic sulfamide **19** (40 mg, 0.10 mmol) in acetone (630 mL) and water (200 mL) was added NMO (15 mg, 0.12 mmol) and OsO_4 (18 mL, 2.8 mmol, 4 wt% solution in water). After 3 days, the reaction mixture was washed with saturated Na_2SO_3, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 50 mg (99%) of the desired sulfamide diol **22** as a white solid. Mp = 174 °C; TLC R_f = 0.28 (5:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -65.1 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.45 (m, 4H),

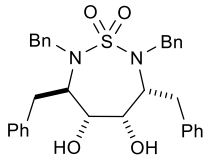
7.35–7.26 (m, 6H), 4.92 (d, *J* = 16.8 Hz, 1H), 4.62 (d, *J* = 16.8 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.46 (d *J* = 16.0 Hz, 1H), 3.81 (ddd, *J* = 9.6, 9.6, 4.4 Hz, 1H), 3.75 (dd, *J* = 4.0, 4.0 Hz, 1H), 3.67 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.48 (ddd, *J* = 10, 5, 5 Hz, 1H), 2.27 (d, *J* = 5.0 Hz, 1H), 2.12 (d, *J* = 7.2 Hz, 1H), 1.79 (ddd, *J* = 13.7, 8.3, 5.4 Hz, 1H), 1.67–1.47 (m, 3H), 1.46–1.36 (m, 1H), 1.31–1.17 (m, 1H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.3, 138.3, 128.6, 128.5, 128.4, 127.6, 127.5, 127.2, 73.9, 71.3, 55.4, 54.4, 51.5, 49.0, 39.8, 36.9, 24.8, 24.1, 23.1, 22.3, 22.1, 21.3; FTIR (neat) 3483, 2956, 1454, 1309, 1144 cm^{-1}; HRMS calcd for $C_{26}H_{39}N_2O_4S$ $(M+H)^+$ required 475.2631, found 475.2609.

(1*S*,2*R*,6*S*,7*S*)-3,5-Dibenzyl-2,6-diisobutyl-8-oxa-4-thia-3,5-diaza-bicyclo[5.1.0]-octane 4,4-dioxide (24)



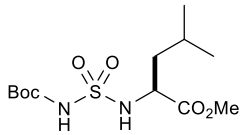
To a stirring solution of **19** (250 mg, 0.56 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added *m*-CPBA (390 mg, 2.27 mmol). After 48 h, the reaction mixture was filtered, and the filtrate was extracted with CH_2Cl_2 (50 mL x 2), and washed with $NaHCO_3$ (saturated aq). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 140 mg (52%) of the desired epoxy sulfamide **24** as clear oil. $[\alpha]^{25}_D$ = -33.9 (c = 1.00, $CHCl_3$); TLC R_f = 0.41 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.05 (m, 10H), 4.83 (d, *J* = 17.1 Hz, 1H), 4.63 (d, *J* = 15.5 Hz, 1H), 4.53 (d, *J* = 15.5 Hz, 1H), 4.42 (d, *J* = 17.1 Hz, 1H), 4.05 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.71 (ddd, *J* = 10, 4.5, 4.5 Hz, 1H), 2.92 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.84 (d, *J* = 4.2 Hz, 1H), 1.85 (ddd, *J* = 14.1, 9.4, 4.9 Hz, 1H), 1.73–1.65 (m, 1H), 1.65–1.55 (m, 1H) 1.45 (ddd, *J* = 14.2, 8.4, 6.2 Hz, 1H), 1.34–1.25 (m, 2H), 0.82 (d, *J* = 5.8 Hz, 3H), 0.76 (d, *J* = 5.8 Hz, 3H), 0.75 (d, *J* = 6.0 Hz, 3H), 0.51 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.4, 138.0, 128.5, 128.4, 128.3, 127.7, 127.1, 126.9, 59.8, 58.4, 54.0, 52.0, 51.8, 51.4, 41.3, 41.1, 24.7, 24.4, 22.5, 22.0, 21.8, 21.5; FTIR (neat) 3031, 2958, 1605, 1496, 1338, 1150 cm^{-1}; HRMS calcd for $C_{26}H_{37}N_2O_3S$ $(M+H)^+$ required 457.2525, found 457.2534.

(3*R*,4*R*,5*S*,6*R*)-2,7-Dibenzyl-3,6-diphenylethyl-2,3,6,7-tetra-hydro-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (25)



Under argon gas atmosphere, Zn powder (35 mg, 0.53 mmol), was added to a solution of $VCl_3(THF)_3$ (348 mg, 0.93 mmol) in CH_2Cl_2 (1 mL) at room temperature, causing a color change from red to green (after stirring for 30 min). A solution of dialdehyde **13** (212 mg, 0.393 mmol) in CH_2Cl_2 (5 mL) was added causing a color change from green to brown. After being stirred for 3h, the reaction solution was opened to air and poured into 1M HCl (10 mL). The two phases were stirred together for 12h giving a colorless CH_2Cl_2 layer and a blue aqueous layer. The organic layer and aqueous layer were separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL x 2). The combined organic layer was washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL) and then dried ($MgSO_4$). The reaction mixture was filtered and evaporated to give white solid. The resulting solid was purified by flash chromatography (3:1 hexanes/EtOAc) to afford the desired diol compound **25** (110 mg, 51%). Mp = 66 °C TLC R_f = 0.29 (2:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -26.3 (*c* = 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–6.97 (m, 20H), 4.92 (d, *J* = 16.9 Hz, 1H), 4.68 (d, *J* = 17.1 Hz, 1H), 4.67 (d, *J* = 14.6 Hz, 1H), 4.46 (d, *J* = 14.7 Hz, 1H), 3.97 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.78 (dd, *J* = 7.7, 0 Hz, 1H), 3.73 (dd, 5.0, 0 Hz, 1H), 3.65 (dd, *J* = 14.6, 8.2 Hz, 1H), 3.10 (dd, *J* = 14.2, 8.6 Hz, 1H), 2.97 (m, 2H), 2.82 (dd, *J* = 14.1, 6.1 Hz, 1H), 2.43 (s, 1H), 1.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.5, 138.4, 138.2, 137.3, 129.5, 129.3, 129.1, 129.0, 128.9, 128.9, 128.8, 128.3, 127.4, 127.3, 127.0, 127.0, 77.4, 77.1, 61.4, 60.4, 53.8, 51.7, 39.7, 36.5; FTIR (neat) 3481, 3062, 2926, 1811, 1496, 1321, 1147, 1062,, 736, 698 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{32}H_{35}N_2O_4S$ $(M+H)^+$ required 543.2318, found 543.2328.

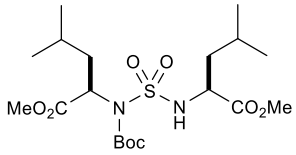
(*S*)-Methyl-2-(*N*-(tert-butoxycarbonyl)sulfamoylamino)-4-methylpentanoate (26)



The solution of chlorosulfonyl isocynate (1.23 mL, 14.13 mmol) in CH_2Cl_2 (40 mL) was added at 0 °C. The 1 M solution of *tert*-butyl alcohol (1.35 mL, 14.6 mmol) in CH_2Cl_2 (14 mL) was added slowly. This solution was cannulated to a solution of H-Val-OMe hydrochloride (2.38 g, 13.12 mmol) and Et_3N (4 mL, 28.7 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was extracted with

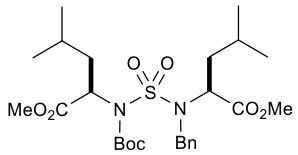
CH_2Cl_2 (40 mL x 3) and the organic layer dried ($MgSO_4$). The reaction mixture was filtered and evaporated under reduced pressure to obtain a crude solid. Flash chromatography (2:1 Hexanes/EtOAc) produced **26** (3.34 g, 78%) as a white solid. Mp = 101 °C; TLC R_f = 0.49 (2:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = 67.3 (*c* = 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (s, 1H), 5.82 (d, *J* = 9.2 Hz, 1H), 4.21 (dd, *J* = 15.1, 8.5 Hz, 1H), 3.75 (s, 3H), 1.83 (qqt, *J* = 20.3, 13.5, 6.7 Hz, 1H), 1.59 (dd, *J* = 7.1, 0 Hz, 1H), 1.57 (dd, *J* = 6.4, 1.6 Hz, 1H), 1.49 (s, 9H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 150.2, 83.9, 55.5, 52.7, 42.2, 28.1, 24.5, 23.0, 21.7; FTIR (neat) 2959, 2937, 1736, 1437, 1369, ,1246, 1146, 972, 827, 731 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{12}H_{24}N_2NaO_6S$ $(M+H)^+$ required 347.1253, found 347.1232.

_N_-[(1,1-Dimethylethoxy)carbonyl]-[_N_-(1_R_)-1-(2-methylpropyl)-2-methoxycarbonyl-_N'_-[(1_S_)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (27)



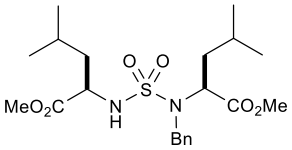
26 (1.75 g, 5.41 mmol) and DIAD (1.07 mL, 5.43 mmol) were dissolved in THF (10 mL) at room temperature and then the mixed solution of methyl (*S*)-2-hydroxy-4-methylpentanoate (0.79 g, 5.40 mmol) and triphenylphosphine (1.42 g, 5.41 mmol) in THF (10 mL) was added at room temperature. The reaction mixture was evaporated under reduced pressure to obtain a crude solid. Flash chromatography (5:1 Hexanes/EtOAc) gave 1.76 g (72%) of the **27** as a white solid. Mp = 74 °C; TLC R_f = 0.47 (5:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -85.7 (*c* = 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.20 (d, *J* = 7.1 Hz, 1H), 4.88 (ddd, *J* = 8.2, 6.5, 0 Hz, 1H), 4.30 (ddd, *J* = 13.3, 7.6, 0 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 1.93 (dd, *J* = 5.6, 1.9 Hz, 1H), 1.91 (dd, *J* = 6.1, 1.4 Hz, 1H), 1.90 (qqt, *J* = 20.4, 13.0, 6.4 Hz, 1H), 1.74 (qqt, *J* = 19.8, 13.0, 6.5 Hz, 1H), 1.64–1.58 (m, 2H), 1.49 (s, 9H), 0.97 (d, *J* = 1.7 Hz, 3H), 0.96 (d, *J* = 1.5 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 171.2, 150.7, 85.0, 59.2, 55.4, 52.7, 52.6, 43.5, 39.6, 28.1, 24.9, 24.4, 23.6, 22.9, 22.1, 21.8; FTIR (neat) 2957, 2872, 1747, 1731, 1433, 1369, 1299, 1284, 1272, 1236, 1151, 1030, 987, 843, 773, 721 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{19}H_{36}N_2NaO_8S$ $(M+H)^+$ required 475.2090, found 475.2080.

***N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-(2-methylpropyl)-2-methoxycarbonyl]-*N'*-benzyl-*N'*-[(1*S*)-1-(2-methylpropyl)-2-ethoxycarbonyl]-sulfamide (28)**



To a solution of **27** (1.62, 3.59 mmol) in CH_3CN (50 mL) with K_2CO_3 (0.70 g, 5.06 mmol) was added benzyl bromide (0.58 mL, 5.04mmol) and heated to 75 °C. After 2 h, the reaction mixture was extracted with EtOAc (50 mL x 2), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (2:1 hexanes/EtOAc) gave 1.37 g (77%) of the desired sulfamide **28** as a white solid. Mp = 98 °C; TLC R_f = 0.24 (10:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = 49.3 (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, *J* = 7.2 Hz, 2H), 7.34–7.24 (m, 3H), 5.05 (d, *J* = 16.8 Hz, 1H), 4.96 (dd, *J* = 8.1, 5.5 Hz, 1H), 4.76 (dd, *J* = 8.3, 5.8 Hz, 1H), 4.68 (d, *J* = 16.8 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.07–1.97 (m, 1H), 1.85 (dd, *J* = 9.6, 4.8 Hz, 1H), 1.87–1.77 (m, 1H), 1.52 (s, 9H), 1.52–1.46 (m, 3H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 5.8 Hz, 3H), 0.52 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 171.2, 150.7, 138.3, 128.5, 128.5, 127.6, 84.5, 59.8, 59.1, 52.5, 52.1, 51.2, 40.1, 39.6, 28.3, 25.1, 24.7, 23.4, 22.2, 22.2, 22.0; FTIR (neat) 3030, 2957, 1743, 1454, 1436, 1369, 1280, 1267, 1251, 1150, 1047, 1029, 731, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{26}H_{43}N_2O_8S$ $(M+H)^+$ required 543.2740, found 543.2750.

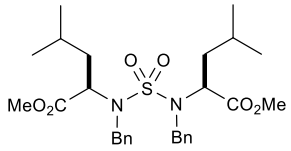
***N*-[(1*R*)-1-(2-Methylpropyl)-2-methoxycarbonyl]-*N'*-benzyl-*N'*-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (29)**



To a solution of **28** (1.28 g, 2.58 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL, 64.90 mmol) at room temperature, and then the reaction solution was stirred for 48 h. The reaction mixture was extracted with EtOAc (50 mL x 2), washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (3:1 hexanes/EtOAc) gave 1.00 g (97%) of the desired sulfamide **29** as clear oil. TLC R_f = 0.68 (3:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = 28.9 (*c* =0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, *J* = 7.1 Hz, 2H), 7.11–7.03 (m, 3H), 5.15 (d, *J* = 9.4 Hz, 1H), 4.40 (d, *J* = 16.0 Hz, 1H), 4.24 (dd, *J* = 7.4, 0 Hz,

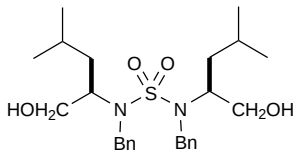
1H), 4.05 (d, *J* = 16.0 Hz, 1H), 3.89 (ddd, *J* = 12.7, 8.4, 6.4 Hz, 1H), 3.58 (s, 3H), 3.52 (s, 3H), 1.59–1.52 (m, 1H), 1.41–1.32 (m, 4H), 1.32–1.21 (m, 1H), 0.73 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H), 0.55 (d, *J* = 6.4 Hz, 3H), 0.33 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 173.2, 137.3, 128.8, 128.6, 128.0, 60.0, 54.5, 52.7, 52.6, 50.9, 42.8, 39.0, 24.8, 24.6, 22.7, 22.6, 22.3, 21.5; FTIR (neat) 3030, 2957, 2870, 1744, 1454, 1437, 1340, 1271, 1201, 1145, 1027, 929, 899, 729, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{35}N_2O_6S$ $(M+H)^+$ required 443.2216, found 443.2202.

***N, N'*-Bis-benzyl-*N*-*N'*- (1*S*),(1*R*)- bis- [1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (30)**



To a solution of **29** (758 mg, 1.90 mmol) in CH_3CN (20 mL) was added K_2CO_3 (602 mg, 4.36 mmol) and benzyl bromide (0.33 mL, 2.87mmol) at room temperature and then the reaction mixture was refluxed for 16h. The reaction mixture was extracted with EtOAc (30 mL x 2), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (10:1 hexanes/EtOAc) gave 923 mg (91%) of the desired sulfamide **30** as clear oil. TLC R_f = 0.36 (10:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45–7.26 (m, 5H), 4.75 (d, *J* = 15.9 Hz, 1H), 4.46 (d, *J* = 15.9 Hz, 1H), 4.30 (dd, *J* = 7.2, 0 Hz, 1H), 3.67 (s, 3H), 1.75 (ddd, *J* = 13.4, 6.7, 6.7 Hz, 1H), 1.59 – 1.53 (m, 1H), 1.49 (ddd, *J* = 13.4, 6.7, 6.7 Hz, 1H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.67 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 137.7, 128.8, 128.6, 127.8, 58.5, 52.2, 50.3, 39.5, 25.0, 22.6, 22.1; FTIR (neat) 3030, 2957, 1743, 1454, 1437, 1344, 1201, 1146, 1027, 865, 698 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{28}H_{41}N_2O_6S$ $(M+H)^+$ required 533.2685, found 533.2672.

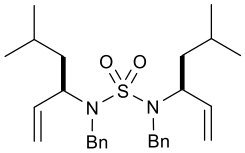
***N,N'*-Bis-benzyl-*N*-[(1*S*)-2-hydroxy-1-(2-methylpropyl)ethyl]-*N'*-[(1*R*)-2-hydroxy-1-(2-methylpropyl)ethyl]-sulfamide (31)**



To a solution of **30** (829 mg, 1.56 mmol) in THF 100 mL was added LAH (739 mg, 19.46 mmol) at 0 °C. After 1h, 15 % of NaOH aqueous solution was added to the reaction solution until the color of solution was changed from colorless to white. The reaction mixture was filtered to remove

white solid and concentrated under reduced pressure. Flash chromatography (1:1 hexanes/EtOAc) gave 750 mg (99%) of the desired sulfamide **31** as white solid. Mp = 104 °C; TLC R_f = 0.55 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, *J* = 7.1 Hz, 2H), 7.35–7.27 (m, 3H), 4.51 (d, *J* = 15.8 Hz, 1H), 4.33 (d, *J* = 15.8 Hz, 1H), 4.00–3.93 (m, 1H), 3.69–3.59 (m, 2H), 2.83 (s, 1H), 1.63–1.53 (m, 1H), 1.27 (ddd, *J* = 13.6, 6.9, 6.9 Hz, 1H), 1.09 (ddd, *J* = 14.2, 7.3, 7.3 Hz, 1H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 128.8, 128.8, 127.9, 63.0, 59.7, 49.0, 39.9, 25.1, 23.2, 22.2; FTIR (neat) 3421, 2957, 2870, 1456, 1325, 1136, 1091, 1053, 871 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{26}H_{41}N_2O_4S$ $(M+H)^+$ required 477.2787, found 477.2791.

***N,N'*-Bis-benzyl-*N*-[(1*S*)-1-(2-methylpropyl)-2-propenyl]-*N'*-[(1*R*)-1-(2-methylpropyl)-2-propenyl]-sulfamide (33)**

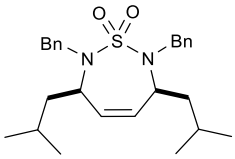


To a stirring solution of oxalyl chloride (0.30 mL, 3.44 mmol) in CH_2Cl_2 (1 mL) at -78 °C under an argon atmosphere was added DMSO (0.30 mL, 4.23 mmol) in CH_2Cl_2 (1 mL) over 20 min. After 30 min, the sulfamide diol **31** (681 mg, 1.43 mmol) in CH_2Cl_2 (10 mL) was added over 30 min with an addition funnel, and the funnel was rinsed with CH_2Cl_2 (10 mL). The mixture was stirred at -78 °C for 5 h and monitored by TLC. Et_3N (1.5 mL, 10.76 mmol) was added over 15 min and stirred at -78 °C for 2 h. THF (4 mL, 1:1 H_2O/THF) was added at -78 °C for 5 min, and the mixture stirred at 0 °C for 6 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL), washed with 2M HCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 671 mg (99%) of the desired dialdehyde sulfamide **32** as a white solid that was carried on immediately without further purification. TLC R_f = 0.87 (1:1 hexanes/EtOAc).

To a stirring solution of CH_3PPh_3Br (3.11 g, 8.72 mmol) in THF (25 mL) at 0 °C under an argon atmosphere was slowly added a solution of BuLi (3.20 mL, 7.04 mmol, 1.6 M in hexanes) over 3 min. After 3 h, the yellow ylide solution was cooled to -78 °C and a solution of dial sulfamide (647 mg, 1.37 mmol) in THF (25 mL) at -78 °C was added via cannulation. After 24 h, 30 mL acetone was added to quench the reaction. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc (50 mL x 2). The combined organic extracts were dried ($MgSO_4$), filtered, and

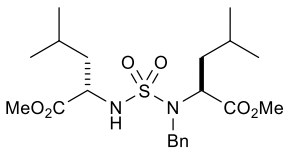
concentrated under reduced pressure. Flash chromatography (10:1 hexanes/EtOAc) gave 555 mg (87%) of the desired sulfamide diene **33** as clear oil. TLC R_f = 0.72 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 6.9 Hz, 2H), 7.35–7.26 (m, 3H), 5.88 (ddd, *J* = 17.5, 10.4, 7.8 Hz, 1H), 5.21 (d, *J* = 10.3 Hz, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.24 (d, *J* = 15.7 Hz, 1H), 4.07 (ddd, *J* = 13.8, 8.2, 0 Hz, 1H), 1.54–1.37 (m, 3H), 0.83 (d, *J* = 6.2 Hz, 3H), 0.69 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 137.1, 128.8, 128.6, 127.7, 118.4, 60.1, 49.6, 41.8, 24.8, 23.3, 21.8; FTIR (neat) 3064, 3029, 2957, 1456, 1332, 1145, 1026, 921, 860, 700 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{28}H_{41}N_2O_2S$ $(M+H)^+$ required 469.2889, found 469.2885.

(3*R*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (34)



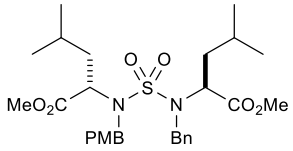
To a degassed solution of **33** (495 mg, 1.06 mmol) in benzene (10 mL) was added $(ImesH_2)(PCy_3)(Cl)_2Ru$=CHPh (63 mg, 0.14 mmol) at room temperature. After 24 h, DMSO (1.0 mL) and silica gel were added to remove the catalyst. After 24 h, the reaction mixture was filtered, and concentrated under reduced pressure. Flash chromatography (5:1 hexanes/EtOAc) afforded 407 mg (85%) of the desired cyclic sulfamide **34** as white solid. Mp = 142 °C; TLC R_f = 0.55 (5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.33–7.23 (m, 3H), 5.90 (d, *J* = 3.3 Hz, 1H), 4.75 (d, *J* = 15.7 Hz, 1H), 4.50 (ddd, *J* = 9.3, 6.1, 3.3 Hz, 1H), 4.02 (d, *J* = 15.7 Hz, 1H), 1.54 (ddd, *J* = 14.0, 9.4, 5.1 Hz, 1H), 1.46–1.36 (m, 1H), 1.19 (ddd, *J* = 14.2, 8.4, 6.3 Hz, 1H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.50 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2, 136.4, 128.5, 128.0, 127.4, 54.9, 50.2, 42.6, 24.4, 22.4, 22.1; FTIR (neat) 3028, 2955, 2866, 1495, 1456, 1360, 1346, 1161, 1148, 1089, 916, 841, 766, 706 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{26}H_{37}N_2O_2S$ $(M+H)^+$ required 440.2497, found 441.2581.

***N*-Benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (7)**



To a stirred solution of **4** (3.82 g, 10.83 mmol) in CH_3CN (20mL) at room temperature under an argon atmosphere was added K_2CO_3 (1.50 g, 10.83 mmol) and benzyl bromide (1.25 mL, 10.86 mmol). After the addition, the reaction mixture was refluxed at 80 °C for 24 hours. The reaction mixture was filtered under reduced aspirator vacuum and extracted with EtOAc (50 mL x 2). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated on a rotary evaporator. The resulting white solid was purified by flash chromatography (silica gel, 6:1 hexanes/EtOAc) to afford the desired monobenzyl sulfamide **7** (2.87 g, 67%). Mp = 64 °C; TLC TLC R_f = 0.35 (6:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -65.7 (*c* = 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 5H) 5.26 (d, *J* = 9.1 Hz, 1H), 4.55 (d, *J* = 15.9, 1H) 4.34 (t, *J* = 7.3 Hz, 1H), 4.28 (d, *J* = 15.9 Hz, 1H) 4.15 (ddd, *J* = 8.4, 8.9, 6.19 Hz, 1H) 3.79 (s, 3H), 3.72 (s, 3H), 1.76 (m, 1H), 1.60 (dd, *J* = 7.4, 7.3 Hz, 2H), 1.56 (dd, *J* = 6.6, 8.3 Hz, 2H) 1.48 (m, 1H), 0.93 (dd, *J* = 7.1, 6.9 Hz, 6H), 0.76 (d, *J* = 6.5 Hz, 3H), 0.55 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 173.1, 137.2, 128.7, 128.6, 127.9, 59.9, 54.6, 52.7, 51.0, 42.9, 39.2, 24.7, 24.6, 22.8, 22.5, 22.2, 21.7; FTIR (neat) 3030, 2957, 1744, 1456, 1437, 1340, 1272, 1203, 1145, 1028, 901, 729, 700 cm^{-1}; HRMS calcd for $C_{21}H_{34}N_2O_6S$ $(M+H)^+$ required 443.2216, found 443.2194.

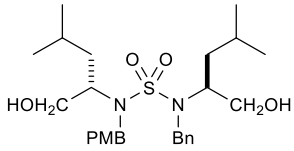
_N_-Benzyl-_N'_-(4-methoxy)-benzyl-_N,N'_-bis-[(1_S_)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (8)



To a stirred solution of **7** (0.30 g, 0.75 mmol) in CH_3CN (20 mL) at room temperature under an argon atmosphere was added K_2CO_3 (0.16 g, 1.18 mmol) and *p*-methoxybenzyl chloride (0.13 mL, 0.96 mmol). After the addition, the reaction mixture was refluxed at 80 °C for 48 h. The reaction mixture was extracted with EtOAc (50 mL x 2). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated on a rotary evaporator. The resulting oil was purified by flash chromatography (silica gel, 6:1 hexanes/EtOAc) to afford the desired compound **8** (0.26 g, 67%). TLC R_f = 0.32 (6:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = 16.9 (*c* = 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.32 (m, 5H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.75 (d, *J* = 15.8 Hz, 1H), 4.65 (d, *J* = 15.5 Hz, 1H), 4.48 (d, *J* = 15.9 Hz, 1H), 4.41 (d, *J* = 15.5 Hz, 1H) 4.30 (t, *J* = 7.0, 6.5 Hz, 1H), 4.28 (t, *J* = 6.9, 6.6 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 1.82 (m, 2H), 1.78 (m, 4H), 0.87 (dd, *J* = 6.2, 1.4 Hz,

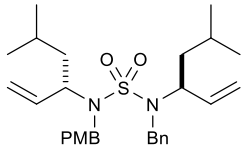
6H), 0.63 (dd, *J* = 6.2, 20.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 172.3, 159.2, 137.3, 130.1, 128.9, 128.6, 128.5, 127.7, 113.8, 58.2, 58.0, 55.3, 52.2, 50.4, 49.8, 49.7, 39.0, 38.9, 24.9, 24.8, 22.4, 22.3, 22.2, 22.1; FTIR (neat) 3081, 2957, 2870, 1744, 1612, 1514, 1456, 1438, 1340, 1247, 1203, 1148, 1036, 869, 833, 750, 700 cm^{-1}; HRMS calcd for $C_{29}H_{43}N_2O_7S$ $(M+H)^+$ required 563.2791, found 563.2794.

_N_-Benzyl-_N'_-(4-methoxy)-benzyl-_N-N'_-bis-[(1_S_)-2-hydroxy-1-(2-methylpropyl)-ethyl]-sulfamide (11)



Following the same procedure as for **9**; Ester **8** (0.48 g, 0.92 mmol) was reduced with LAH (0.71 g, 18.61 mmol) in THF (100 mL). The resulting oil was purified by flash chromatography (1:1 hexanes/EtOAc) to afford the desired diol compound **11** (0.35 g, 77%). Mp = 54 °C; TLC R_f = 0.5 (1:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -73.8 (*c* = 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 7H) 6.86 (d, *J* = 8.5 Hz, 2H), 4.47 (d, *J* = 10.8 Hz, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.77 (m, 2H), 3.61 (d, *J* = 7.4 Hz, 4H), 3.18 (s, 2H), 1.42 (m, 4H), 1.1 (m, 2H), 0.79 (t, *J* = 5.2, 5.2 Hz, 6H), 0.71 (t, *J* = 5.9, 6.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 138.8, 130.6, 130.1, 128.8, 128.7, 127.8, 114.1, 62.9, 62.8, 58.9, 58.9, 55.5, 49.4, 48.8, 39.7, 39.7, 25.4, 25.4, 23.4, 23.4, 22.0, 22.0; FTIR (neat) 3384, 2957, 2341, 1612, 1514, 1465, 1323, 1247, 1141, 1035, 887, 736 cm^{-1}; HRMS calcd for $C_{27}H_{43}N_2O_5S$ $(M+H)^+$ required 507.2893, found 507.2884.

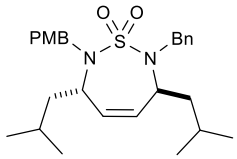
_N_-Benzyl-_N'_-(4-methoxy)-benzyl-_N,N'_-bis-[(1_S_)-1-(2-methylpropyl)-2-propenyl]-sulfamide (17)



Following the same procedure as for **14**; Diol **11** (0.81 g, 1.65 mmol) was oxidized with Dess-Martin periodinane (1.4 g, 3.30 mmol) in CH_2Cl_2 (10 mL). The resulting oil was purified by flash chromatography (1:1 hexanes/EtOAc) to afford the desired aldehyde **14**. (0.73 g, 91%). TLC R_f = 0.8 (1:1 hexanes/EtOAc);

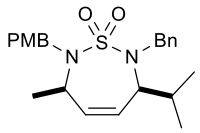
Following the same procedure as for **15**; aldehyde **14** (0.73 g, 1.50 mmol) was transferred to terminal olefin sulfamide with using methyltriphenylphosphonium bromide (3.96 g, 11.07 mmol) in THF (10 mL), potassium bis (trimethylsilyl) amide (20 mL, 10.0 mmol). The resulting solid was purified by flash chromatography (3:1 hexanes/EtOAc) to afford the desired terminal olefin sulfamide **17** as a white solid (0.33 g, 46%). Mp = 95 °C; TLC R_f = 0.85 (3:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = -51.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (m, 7H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.82 (ddd, *J* = 19.7, 12.0, 7.8 Hz, 1H), 5.81 (ddd, *J* = 19.7, 12.0 ,7.8 Hz, 1H), 5.16 (dd, *J* = 10.3, 6.8 Hz, 2H), 5.08 (dd, *J* = 17.2, 3.0 Hz, 2H), 4.33–4.17 (m, 4H), 4.00 (m, 2H), 3.77 (s, 3H), 1.40 (m, 6H), 0.77 (d, *J* = 5.7 Hz, 6H), 0.63 (dd, *J* = 8.4, 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 138.4, 137.4, 134.0, 133.8, 130.3, 130.2, 128.9, 127.6, 118.4, 118.3, 113.9, 60.0, 55.5, 49.5, 49.0, 41.8, 24.8, 23.3, 21.8; FTIR (neat) 3069, 2955, 2931, 1514, 1466, 1456, 1437, 1330, 1248, 1145, 1038, 924, 862, 744, 698 cm^{-1}; HRMS calcd for $C_{29}H_{43}N_2O_3S$ $(M+H)^+$ required 499.2994, found 499.2985.

(3*S*,6*S*)-2-Benzyl-7-(4-methoxy)-benzyl-3,6-diisobutyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (20)



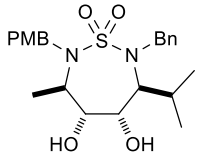
Following the same procedure as for **18**; terminal olefin sulfamide **17** (0.28 g, 0.57 mmol) in benzene (20 mL) was metathesized with using 2nd Grubb's catalyst (0.05g, 0.06 mmol). The resulting oil was purified by flash chromatography (5:1 hexanes/EtOAc) to afford the desired seven membered sulfamide ring **20** (0.04 g, 16%). TLC R_f = 0.51 (5:1 hexanes/EtOAc); $[\alpha]^{25}_D$ = 44.8 (*c* =1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 7.4 Hz, 2H), 7.34–7.23 (m, 5H), 6.86 (d, *J* = 8.6 Hz, 2H), 55.3 (s, 2H), 4.86 (d, *J* = 16.0 Hz, 1H), 4.79 (d, *J* = 15.8 Hz, 1H), 4.24 (ddd, *J* = 0, 5.3, 10.6 Hz, 2H), 4.21 (d, *J* = 9.3 Hz, 1H), 4.18 (d, *J* = 9.1 Hz, 1H), 3.81 (s, 3H), 1.62 (ddd, *J* = 14.3, 10.3, 4.4 Hz, 1H), 1.57(ddd, *J* = 14.3, 10.3, 4.4 Hz, 1H), 1.44–1.33 (m, 2H), 1.17 (m, 2H), 0.83 (d, *J* = 1.6 Hz, 3H), 0.82 (d, *J* = 1.5 Hz, 3H), 0.56 (d, *J* = 6.7 Hz, 3H), 0.47 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 139.2, 132.4, 131.3, 129.3, 128.5, 127.9, 127.3, 113.9, 55.5, 53.7, 53.6, 51.1, 50.5, 42.8, 24.4, 22.6, 21.7; FTIR (neat) 3028, 2957, 1612, 1514, 1467, 1340, 1245, 1170, 1149, 1111, 1035, 860, 829, 766, 745, 725, 698 cm^{-1}; HRMS calcd for $C_{27}H_{39}N_2O_3S$ $(M+H)^+$ required 471.2681, found 471.2671.

2-(3*S*,6*R*)-Benzyl-3-isopropyl-7-(4-methoxybenzyl)-6-methyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine 1,1-dioxide (35)



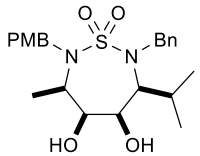
The product was obtained according to the literature procedure.[1]

2-(3*S*,4*S*,5*R*,6*R*)-Benzyl-4,5-dihydroxy-3-isopropyl-7-(4-methoxybenzyl)-6-methyl-1,2,7-thiadiazepane 1,1-dioxide (36)



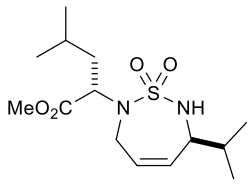
The product was obtained according to the literature procedure.[1]

(3*S*,4*R*,5*S*,6*R*)-2-Benzyl-4,5-dihydroxy-3-isopropyl-7-(4-methoxybenzyl)-6-methyl-1,2,7-thiadiazepane 1,1-dioxide (37)



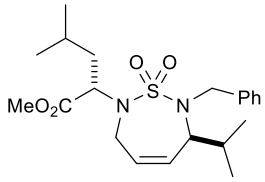
The product was obtained according to the literature procedure.[1]

Methyl (*S*)-2-((*S*)-6-isopropyl-1,1-dioxido-6,7-dihydro-1,2,7-thiadiazepin-2(3H)-yl)-4-Methylpentanoate (38)



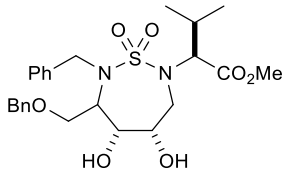
The product was obtained according to the literature procedure.[2]

Methyl (*S*)-2-((*S*)-7-benzyl-6-isopropyl-1,1-dioxido-6,7-dihydro-1,2,7-thiadiazepin-2(3H)-yl)-4-methylpentanoate (39)



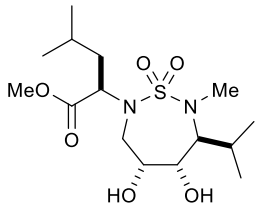
The product was obtained according to the literature procedure.[2]

Methyl (2*S*)-2-((4*S*,5*R*)-7-benzyl-6-((benzyloxy)methyl)-4,5-dihydroxy-1,1-dioxido-1,2,7-thiadiazepan-2-yl)-3-methylbutanoate (40)



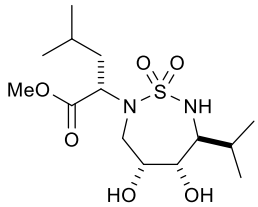
The product was obtained according to the literature procedure.[1]

Methyl (*R*)-2-((4*R*,5*S*,6*S*)-4,5-dihydroxy-6-isopropyl-7-methyl-1,1-dioxido-1,2,7-thiadiazepan-2-yl)-4-methylpentanoate (41)



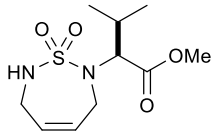
The product was obtained according to the literature procedure.[1]

Methyl (*S*)-2-((4*R*,5*S*,6*S*)-4,5-dihydroxy-6-isopropyl-1,1-dioxido-1,2,7-thiadiazepan-2-yl)-4-methylpentanoate (42)



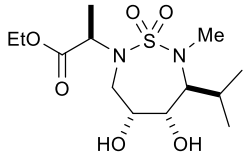
The product was obtained according to the literature procedure.[2]

Methyl (*S*)-2-(1,1-dioxido-6,7-dihydro-1,2,7-thiadiazepin-2(3H)-yl)-3-methylbutanoate (43)



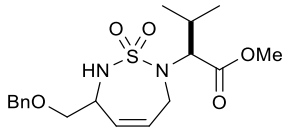
The product was obtained according to the literature procedure.[3]

Ethyl (*R*)-2-((4*R*,5*S*,6*S*)-4,5-dihydroxy-6-isopropyl-7-methyl-1,1-dioxido-1,2,7-thiadiazepan-2-yl)propanoate (44)



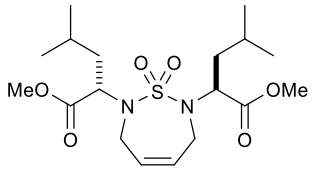
The product was obtained according to the literature procedure.[1]

Methyl (2*S*)-2-(6-((benzyloxy)methyl)-1,1-dioxido-6,7-dihydro-1,2,7-thiadiazepin-2(3H)-yl)-3-methylbutanoate (45)



The product was obtained according to the literature procedure.[1]

Dimethyl 3,3'-(1,1-dioxido-3,6-dihydro-1,2,7-thiadiazepine-2,7-diyl)(3*S*,3'*S*)-bis(5-methyl-2-oxohexanoate) (46)



The product was obtained according to the literature procedure.[4]

2. Biology

Table s1. Antiproliferative (GI_{50}/μM)[a] and cytoxicity (LC_{50}/μM)[b] values for the selected data of compounds against NCI60-cell panel.

Panel/cell line	**18 (NSC 764190)**		**21 (NSC 751486)**		**23 (NSC 751478)**		**25 (NSC 764189)**	
	GI_{50}	LC_{50}	GI_{50}	LC_{50}	GI_{50}	LC_{50}	GI_{50}	LC_{50}
				Leukemia				
CCRF-CEM	3.85	>100	5.96	>20	>7.5	>7.5	>5.0	>5.0
HL-60(TB)	3.43	>100	2.97	>20	4.75	>7.5	>5.0	>5.0
K-562	2.00	>100	3.05	>20	3.34	>7.5	>5.0	>5.0
MOLT-4	2.15	>100	2.86	>20	4.12	>7.5	>5.0	>5.0
RPMI-8226	0.859	>100	4.49	>20	4.92	>7.5	>5.0	>5.0
SR	1.66	>100	nd	nd	nd	nd	nd	nd
				Non-small cell lung cancer				
A549/ATCC	7.67	>100	2.99	19.4	3.78	>7.5	>5.0	>5.0
EKVX	nd	>100	3.43	>20	6.55	>7.5	>5.0	>5.0
HOP-62	>100	>100	3.71	14.5	>7.5	>7.5	>5.0	>5.0
HOP-92	4.40	>100	3.15	14.1	>7.5	>7.5	>5.0	>5.0
NCI-H226	4.35	>100	3.04	12.5	>7.5	>7.5	>5.0	>5.0
NCI-H23	1.66	>100	3.11	14.5	3.47	>7.5	>5.0	>5.0
NCI-H322M	>100	>100	4.48	>20	>7.5	>7.5	>5.0	>5.0
NCI-H460	2.75	>100	3.41	18.3	2.53	>7.5	>5.0	>5.0
NCI-H522	5.46	>100	0.847	14.5	1.83	>7.5	>5.0	>5.0
				Colon cancer				
COLO 205	>100	>100	4.26	>20	>7.5	>7.5	>5.0	>5.0
HCC-2998	>100	>100	3.41	11.3	>7.5	>7.5	>5.0	>5.0
HCT-116	0.535	>100	2.43	10.5	0.844	>7.5	>5.0	>5.0
HCT-15	3.51	>100	4.37	>20	3.92	>7.5	>5.0	>5.0
HT29	42.6	>100	2.63	12.1	>7.5	>7.5	>5.0	>5.0
KM12	9.92	>100	2.94	11.6	7.19	>7.5	>5.0	>5.0
SW-620	nd	>100	3.18	15.9	>7.5	>7.5	>5.0	>5.0
				CNS cancer				
SF-268	7.85	>100	3.44	18.8	6.08	>7.5	>5.0	>5.0
SF-295	0.667	>100	2.62	12.3	1.80	>7.5	>5.0	>5.0
SF-539	>100	>100	3.37	13.6	>7.5	>7.5	>5.0	>5.0
SNB-19	>100	>100	4.69	>20	>7.5	>7.5	>5.0	>5.0
SNB-75	>100	>100	2.31	>20	>7.5	>7.5	>5.0	>5.0
U251	1.11	>100	3.07	13.6	1.84	>7.5	>5.0	>5.0
				Melanoma				
LOX IMVI	1.40	>100	3.28	15.3	5.38	>7.5	>5.0	>5.0
MALME-3M	>100	>100	2.75	14.7	>7.5	>7.5	>5.0	>5.0
M14	nd	>100	3.04	12.1	>7.5	>7.5	>5.0	>5.0

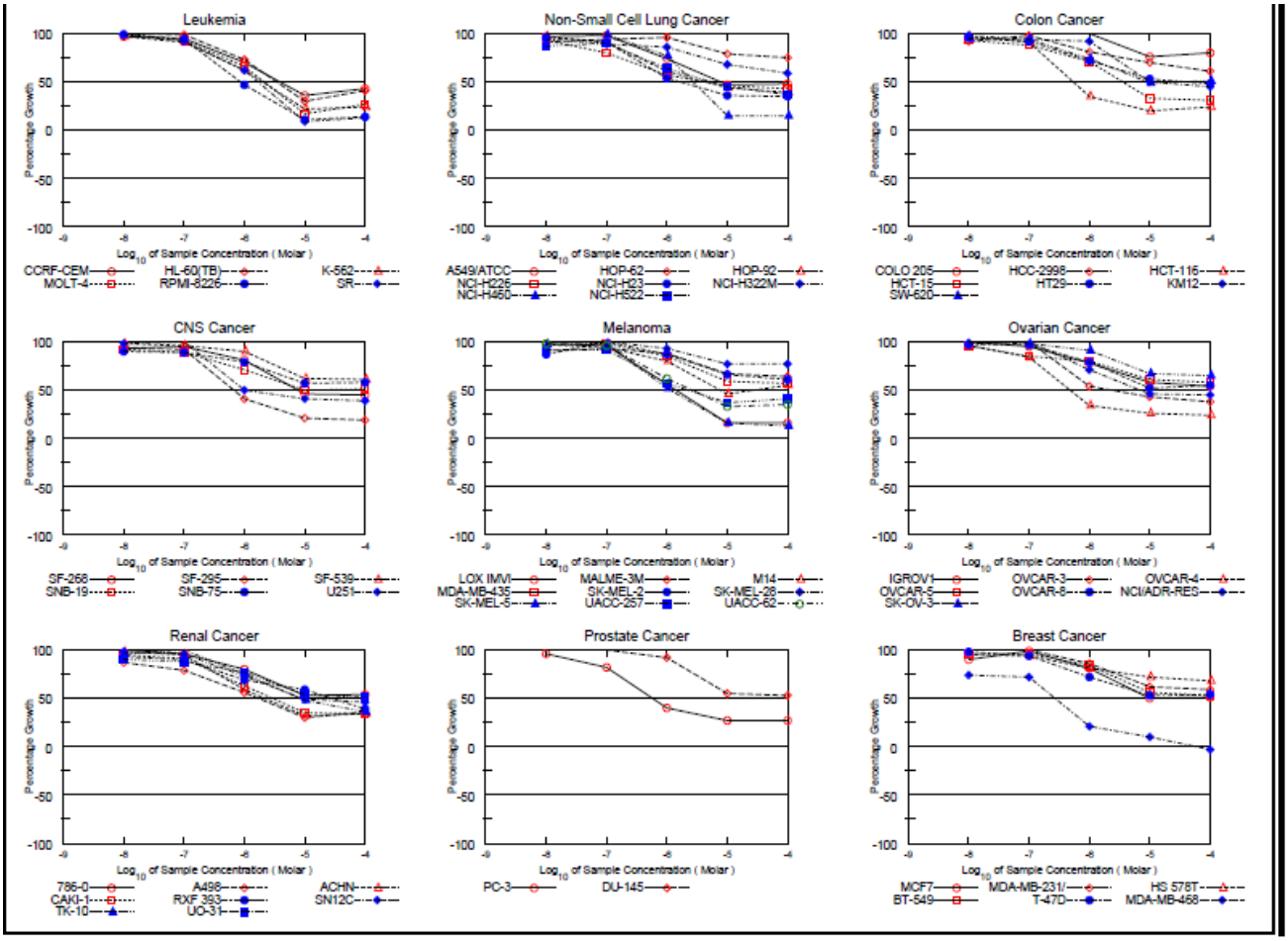
MDA-MB-435	>100	>100	3.33	15.1	>7.5	>7.5	>5.0	>5.0
SK-MEL-2	>100	>100	2.80	11.8	>7.5	>7.5	>5.0	>5.0
SK-MEL-28	>100	>100	3.35	14.2	1.79	>7.5	>5.0	>5.0
SK-MEL-5	1.14	>100	3.05	11.1	2.89	>7.5	>5.0	>5.0
UACC-257	2.23	>100	2.89	12.2	6.75	>7.5	>5.0	>5.0
UACC-62	2.66	>100	2.86	14.3	nd	nd	>5.0	>5.0
Ovarian cancer								
IGROV1	>100	>100	3.57	14.7	5.06	>7.5	>5.0	>5.0
OVCAR-3	2.34	>100	2.90	12.7	4.03	>7.5	>5.0	>5.0
OVCAR-4	0.483	>100	2.72	19.4	>7.5	>7.5	>5.0	>5.0
OVCAR-5	>100	>100	3.57	>20	>7.5	>7.5	>5.0	>5.0
OVCAR-8	>100	>100	4.20	>20	>7.5	>7.5	>5.0	>5.0
NCI/ADR-RES	7.03	>100	3.40	>20	5.23	>7.5	>5.0	>5.0
SK-OV-3	>100	>100	4.15	>20	>7.5	>7.5	>5.0	>5.0
Renal cancer								
786-0	>100	>100	3.24	14.5	5.12	>7.5	>5.0	>5.0
A498	1.77	>100	2.45	10.9	>7.5	>7.5	>5.0	>5.0
ACHN	2.10	>100	6.01	>20	5.88	>7.5	>5.0	>5.0
CAKI-1	2.83	>100	3.65	14.7	0.949	>7.5	>5.0	>5.0
RXF 393	28.0	>100	2.60	10.5	>7.5	>7.5	>5.0	>5.0
SN12C	9.42	>100	3.26	18.1	>7.5	>7.5	>5.0	>5.0
TK-10	8.26	>100	3.77	18.6	3.90	>7.5	>5.0	>5.0
UO-31	>100	>100	2.73	13.1	>7.5	>7.5	>5.0	>5.0
Prostate cancer								
PC-3	0.580	>100	3.48	>20	3.06	>7.5	>5.0	>5.0
DU-145	>100	>100	3.21	17.8	>7.5	>7.5	>5.0	>5.0
Breast cancer								
MCF7	>100	>100	4.77	>20	4.27	>7.5	>5.0	>5.0
MDA-MB-231/ATCC	>100	>100	2.82	14.5	>7.5	>7.5	>5.0	>5.0
HS 578T	>100	>100	3.27	>20	>7.5	>7.5	>5.0	>5.0
BT-549	>100	>100	2.65	11.6	4.09	>7.5	>5.0	>5.0
T-47D	>100	>100	3.95	>20	6.81	>7.5	>5.0	>5.0
MDA-MB-468	0.267	>100	2.98	17.3	0.74	>7.5	>5.0	>5.0

nd: not determined.

[a] GI_{50}: 50% growth inhibition, the concentration of drug resulting in a 50% reduction in net protein increase compared with control cells.

[b] LC_{50}: lethal concentration, the concentration of drug lethal to 50% of cells.

Figure s1. Dose-response curves of **18** for individual sub-panel for all 60 cell lines



Cell culture

The A549 cell lines used in present study were obtained from ATCC (Manassas, USA) and cultivated in DMEM (Sigma) supplemented with 10% fetal bovine serum, 100 units/mL penicillin and streptomycin. To avoid contamination of cells with mycoplasma, cells were regularly tested with the MycoAlert Kit (Cambrex Bio Science, Rockland, ME, USA).

Cytotoxicity evaluation against A549 cells

Cell viability was determined by MTT-micro cultured tetrazolium assay using the reported protocol with minor modifications (ref). Briefly, A549 cells were seeded to flat bottom 96 well plate (5,000 cells/100 µL) and cultured for 18-24 h in the culture medium containing with constant supply of 5% CO_2 in humid incubator. Different concentration of test compound and doxorubicin (as standard control anticancer drug) prepared in DMSO was added to achieve final concentration of 0 to 100 µM

of compound to cells and cells were further continued to grow for 48 h with constant supply of 5% CO_2 in humid incubator. The time course (0 to 72 h) experiment was carried out simultaneously. Filter sterilized MTT dissolved in PBS at 5 mg/mL was added for assay at indicated time intervals. Cells were further incubated in the CO_2 chamber for 2 h. On termination of assay, the medium was removed and 100 µL of DMSO was added to cells. The purple color obtained was measured at 562 nm in a multimode microplate reader (Tecan GENios), its absorbance is directly proportional to cell growth. From the observed percentage age of growth with and without test compound, IC_{50} values were calculated. The results presented are from three independent experiments each in triplicates.

Colony formation assay

For observing long term effects of compound **18** on anchorage-independent growth of A549 cells soft agar assays were performed as reported previously[7]. To perform soft agar assay, bottom agar was prepared by mixing 1% of agarose (Bacto Agar: Becton, Dickinson, Sparks, MD) with 2 × culture medium poured in 6-well plates at 37 ^{0}C to achieve final concentration of 0.5% of agar in 1 × growth medium. Once bottom agar was solidified, 2.5 × 10^4 cells were mixed with cultivation medium containing different concentrations of compound and equal volume of agar solution achieving final concentration of 0.35% agar. The mixture was spread on the surface of base agar plates immediately and incubated under cultivation conditions. To avoid depletion of nutrients, culture medium was replenished every 3 days with fresh medium along with compound. After 14 days of incubation, the colonies observed in plates were stained with 0.005% crystal violet solution. After removing excess staining solution, colonies were observed and counted under a light microscope. Each experiment was performed in triplicates and repeated 3 times. The results analyzed are from three independent experiments each in triplicates.

Wound healing/cell migration assay

Cell migration assays were performed, as reported previously, with minor modifications. Briefly, after harvesting sub confluent A549 cells by trypsinization pellet was resuspended in culture medium by gentle pipetting to obtain single cells. For assays, $5X10^4$ cells/well seeded into 24 well plates and allowed to grow for 18–24 h under standard culture conditions to create a confluent monolayer of cells. To determine the effect of compound on migration of cells, scraping the cells monolayer with p200 pipette tip creates “scratches”. After smoothening the edge of the scratch by

removing debris by washing with 0.5 ml of growth medium and then the medium was replaced with 250 µL of medium containing defined concentration of compound or DMSO as vehicle control. Further cells were incubated to grow for 24 h allowing migration of cells closing the scratches created in the dishes. The images acquired for each sample under a phase-contrast microscope were analyzed to observe influence of compound on migration of cells compared to DMSO treated control.

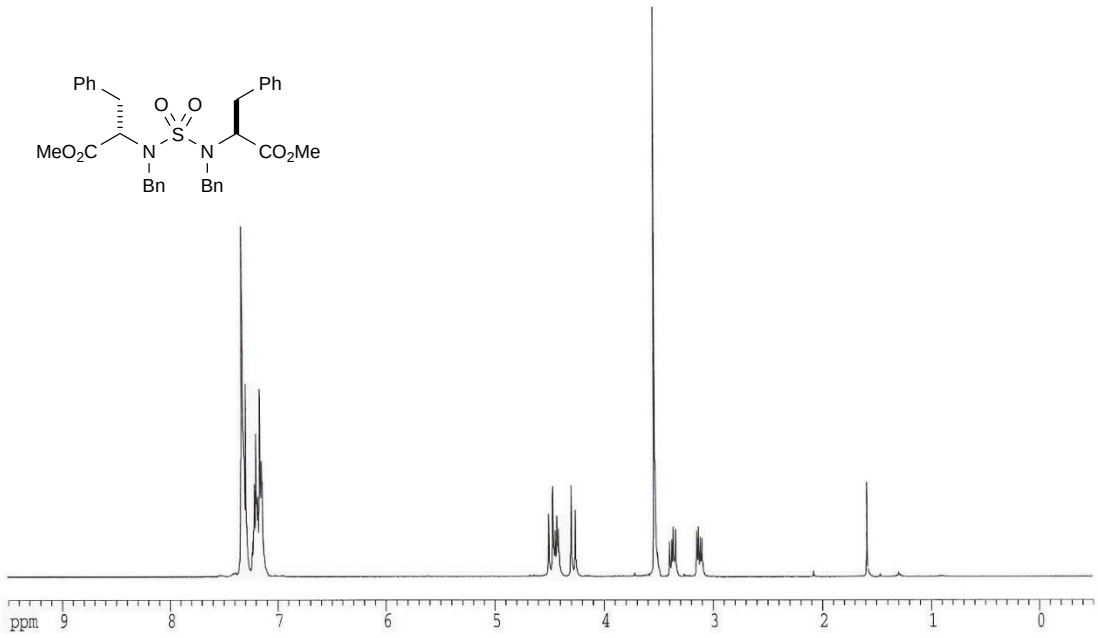
Senescence associated β-gal staining:

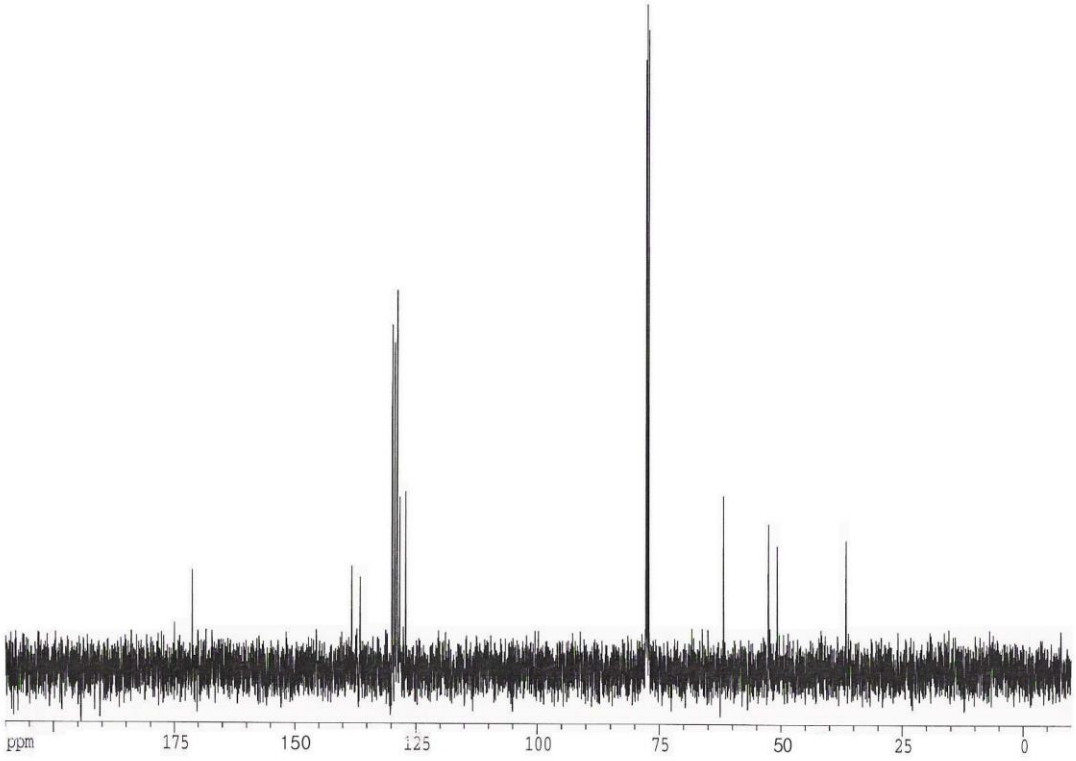
Detection for SA-ß-galactosidase was performed as described previously [ref]. Briefly, A549 cells treated with different concentration of compound or DMSO were harvested at sub confluent density and fixed in phosphate buffered saline containing 2% PFA, 0.25% glutaraldehyde along with 1 mM $MgCl_2$ (pH 6.0). Then the fixed cells were incubated in a staining solution containing potassium cyanide/X-gal in PBS/$MgCl_2$ (pH 6.0) at 37 °C overnight. Slides were analyzed using a Xi72 microscope (10 Å~ magnifications) (Olympus, Japan). The positive cells for β-gal staining upon exposure to compound are marked on images.

PI uptake for cell death

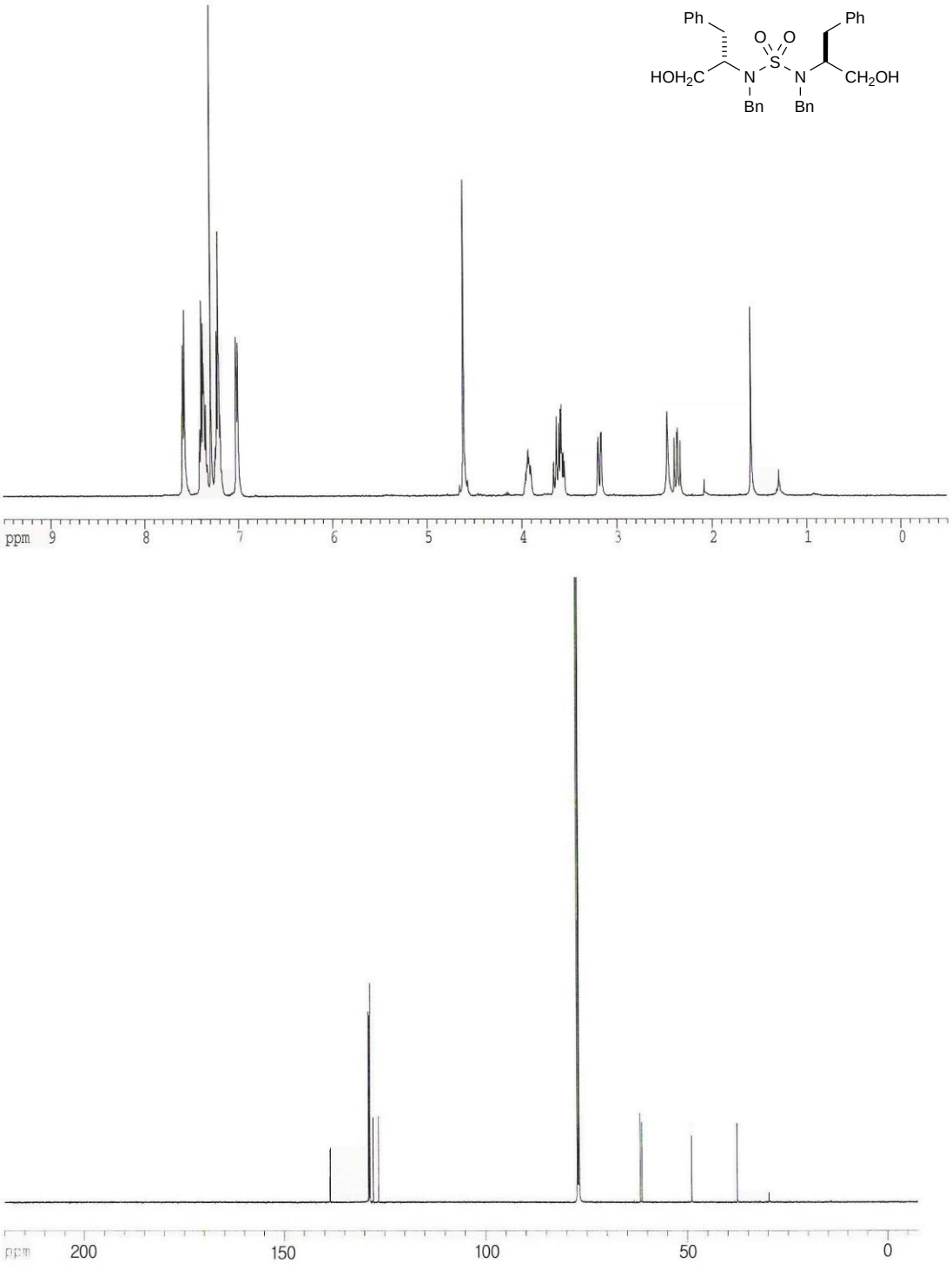
Cell death was analyzed with PI uptake as reported previously with minor modification.[6] Cells were harvested, washed with PBS and fixed in 70% ethanol at -20 °C for overnight. After centrifugation, cells were resuspended in PI solution containing RNase (0.1 mg/mL), Triton X-100 (0.05%), PI (50 µg/mL) and incubated for 1 h in dark at room temperature. After washing with PBS buffer, PI uptake in cells was analyzed by fluorescence activated cell sorting (FACS Calibur System; BD Bio- science, Erembodegem, Belgium) on an FL-2 fluorescence detector (10000 events were recorded for each condition). Flow cytometry data were analyzed using FCS express 4 software (De Novo Software, Los Angeles, CA).

***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-phenylethyl)-2-methoxycarbonyl]-sulfamide (5)**

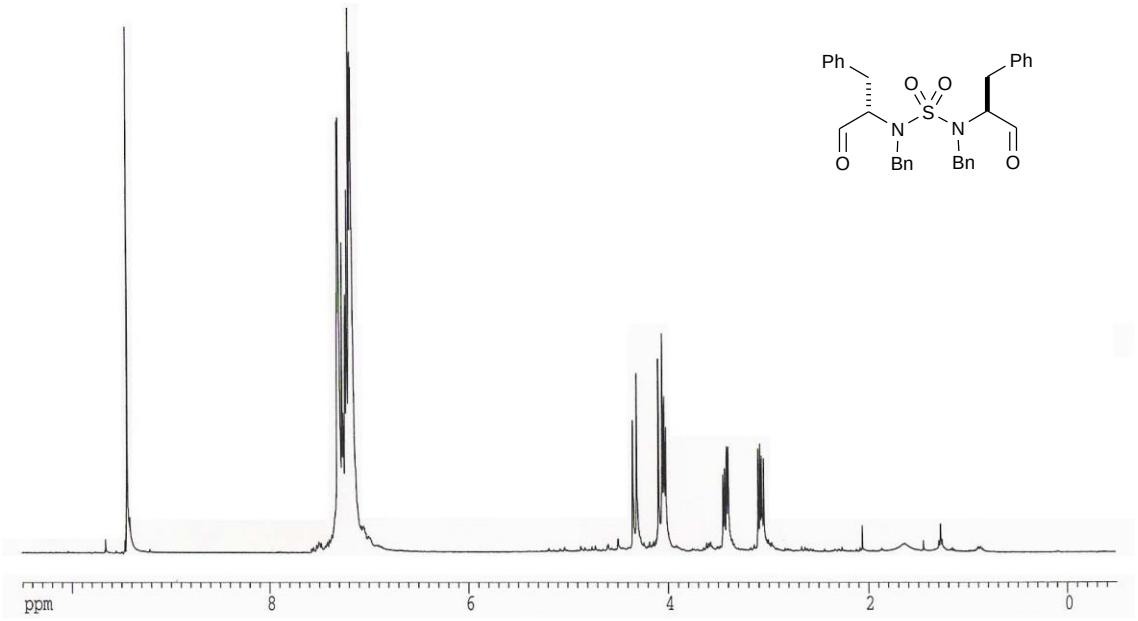


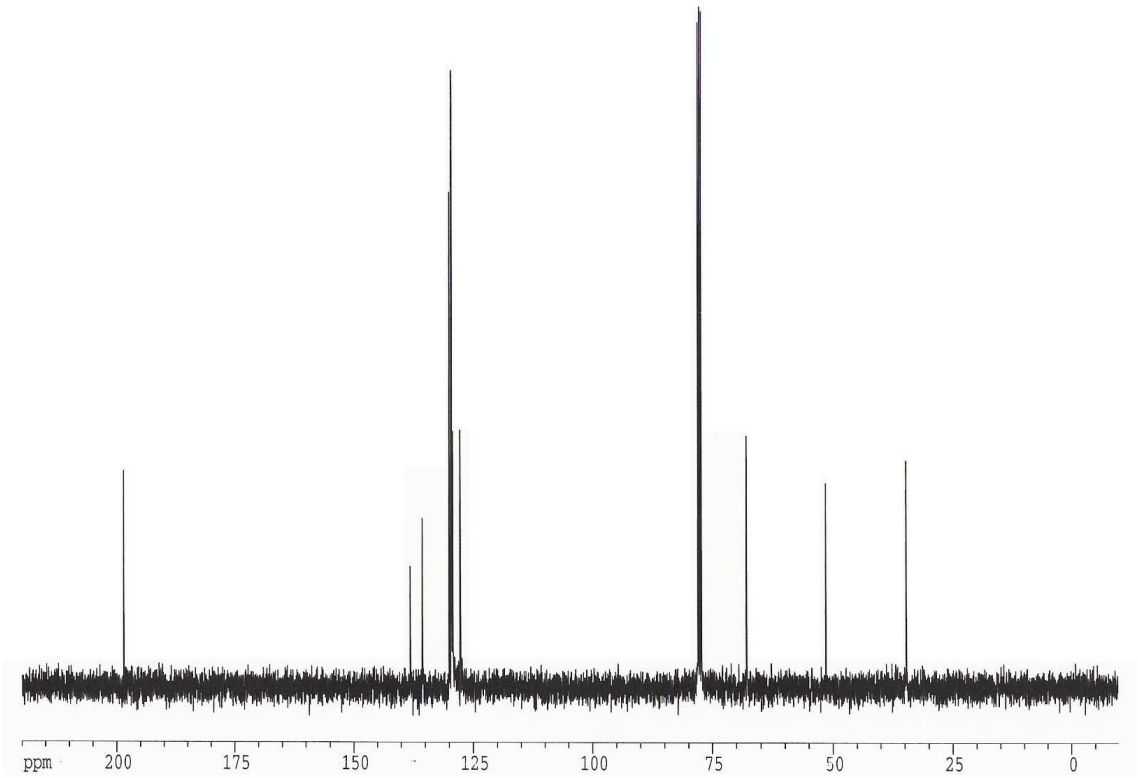


***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-2-hydroxy-1-(2-phenylethyl)ethyl]-sulfamide (9)**

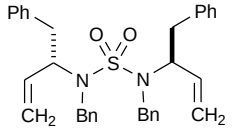


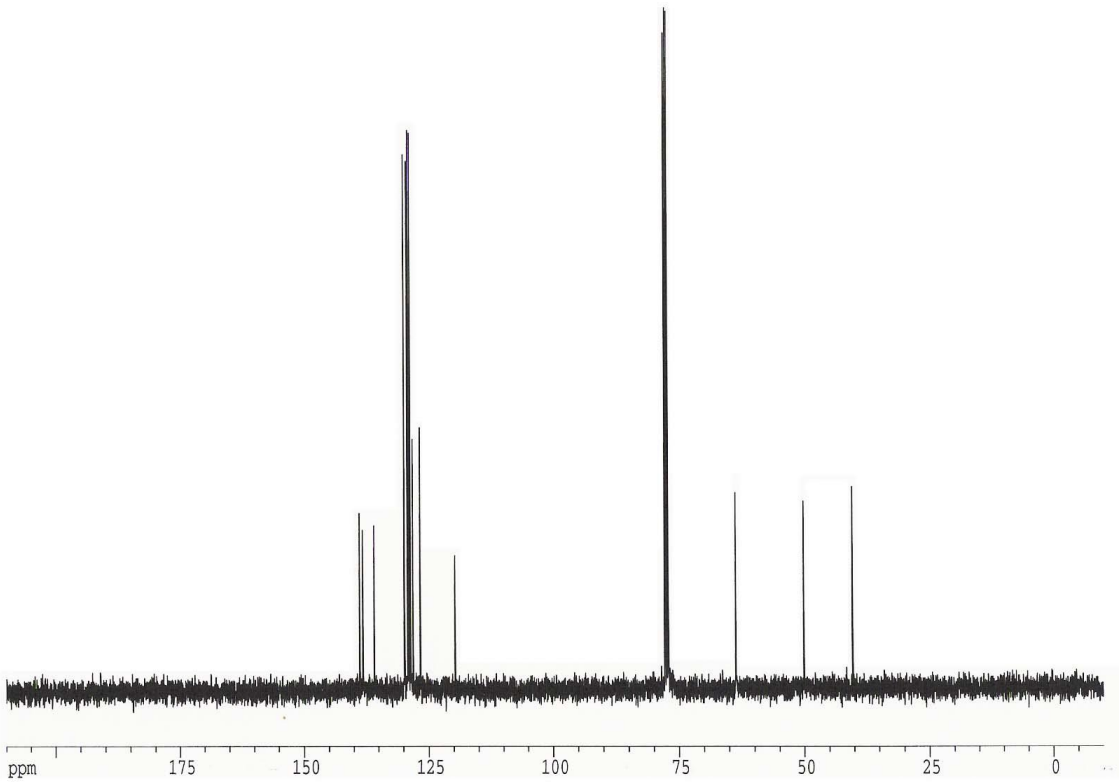
_L_-Phenylalanine-derived C_2-symmetric sulfamide aldehyde (12)



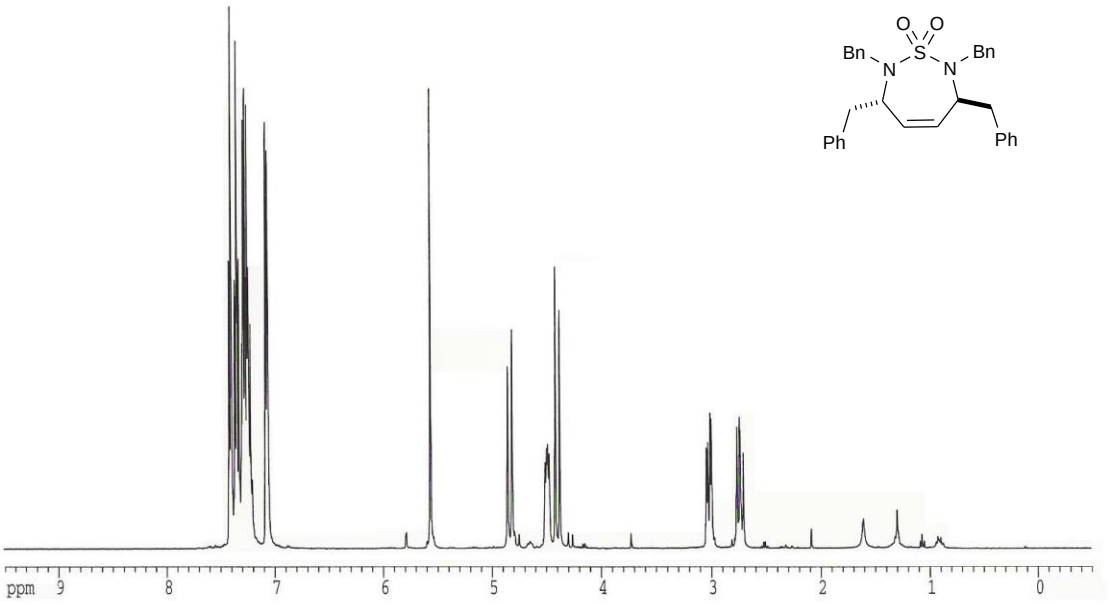


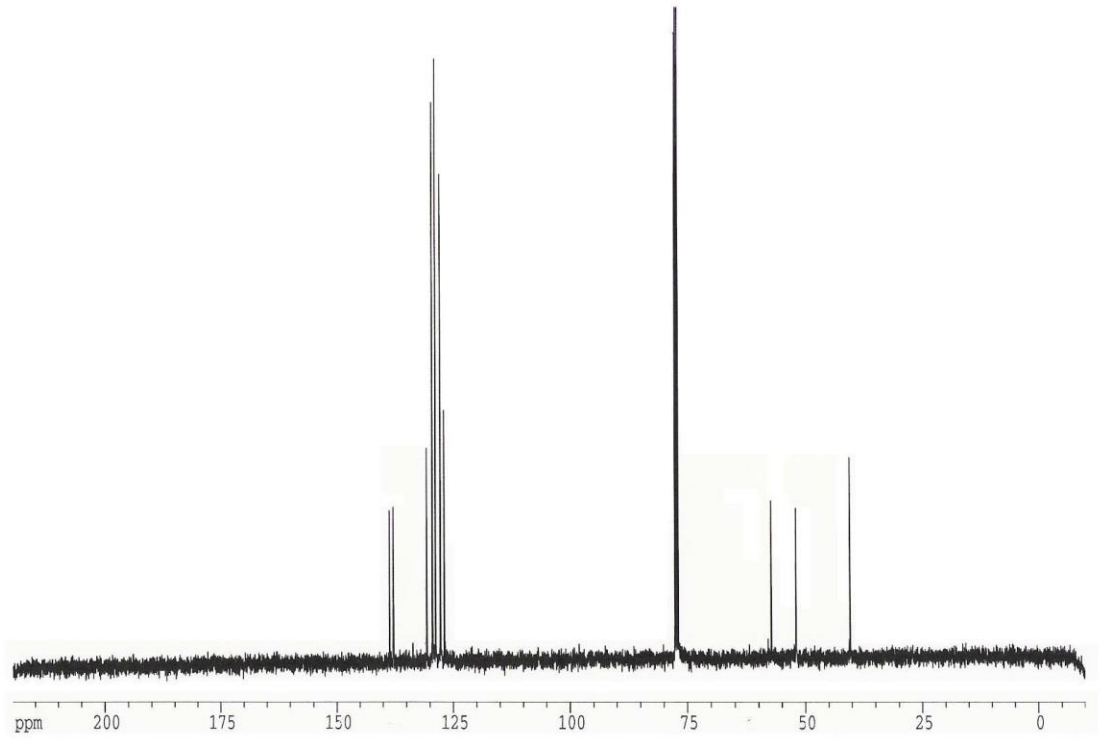
***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-phenylethyl)-2-propenyl]-sulfamide (15)**



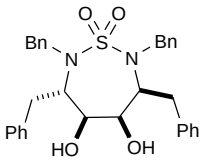


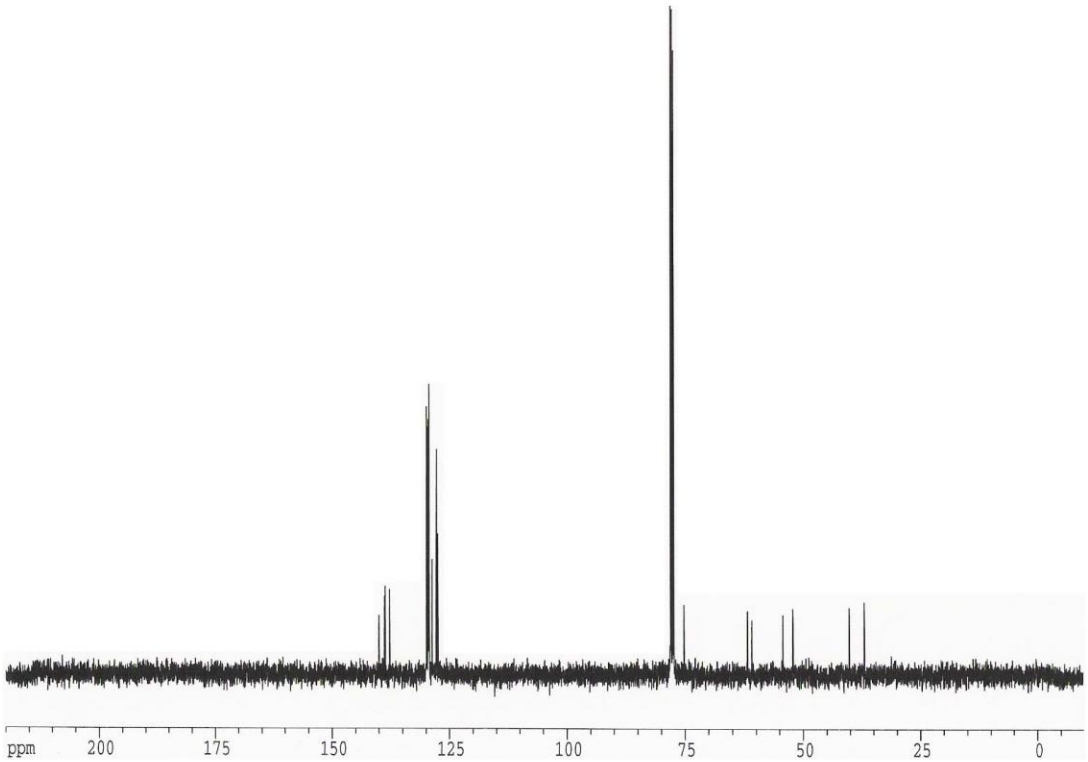
(3*S*,6*S*)-2,3,6,7-Tetrabenzyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (18)



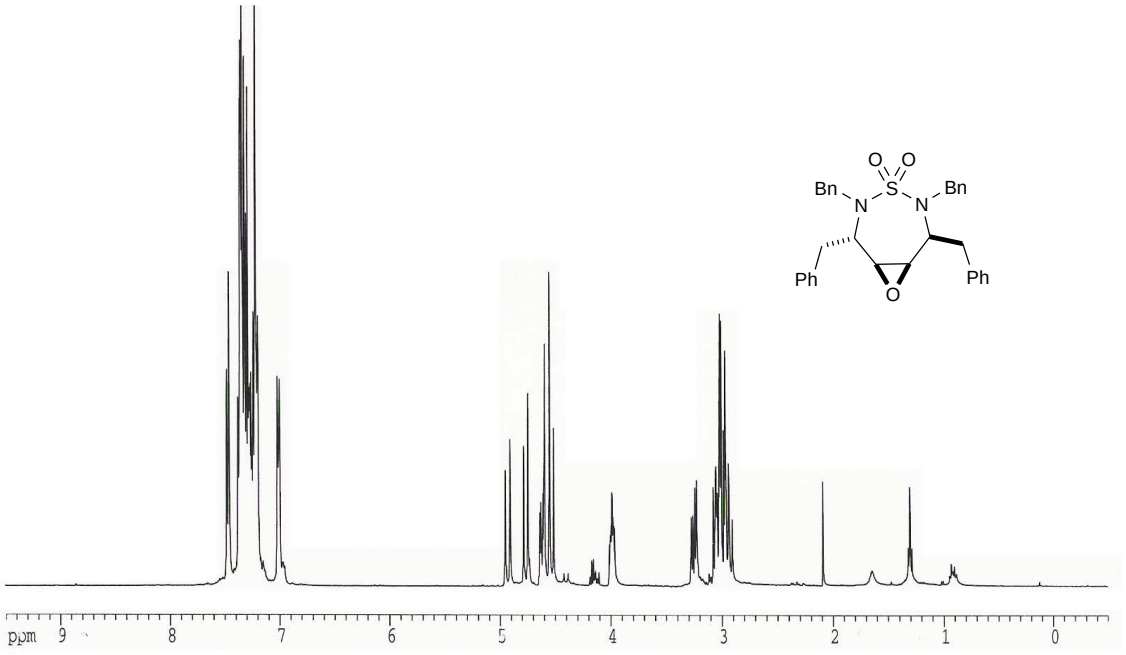


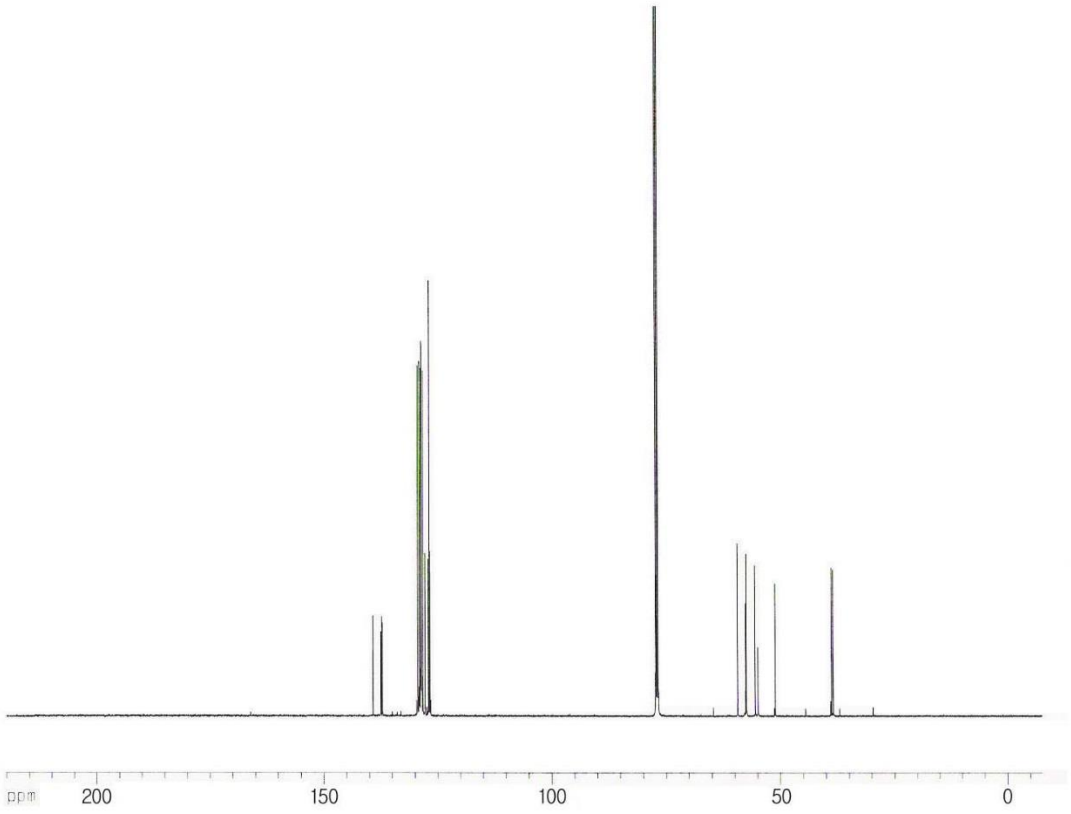
(3*S*,4*R*,5*S*,6*S*)-2,3,67-Tetrabenzyl-2,3,6,7-tetra-hydro-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (21)



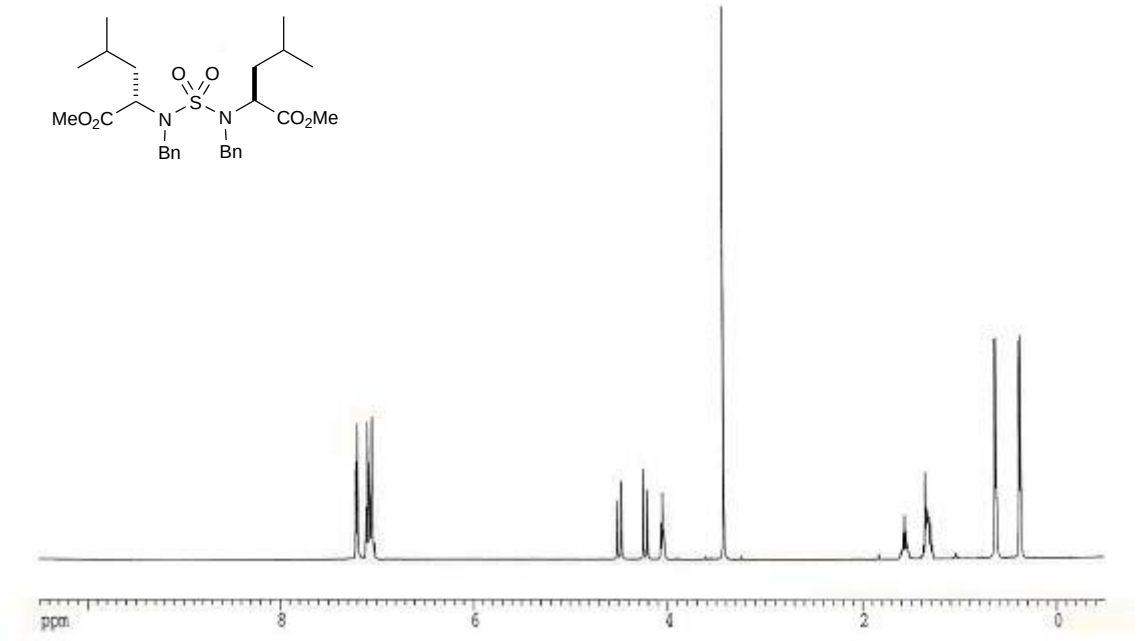


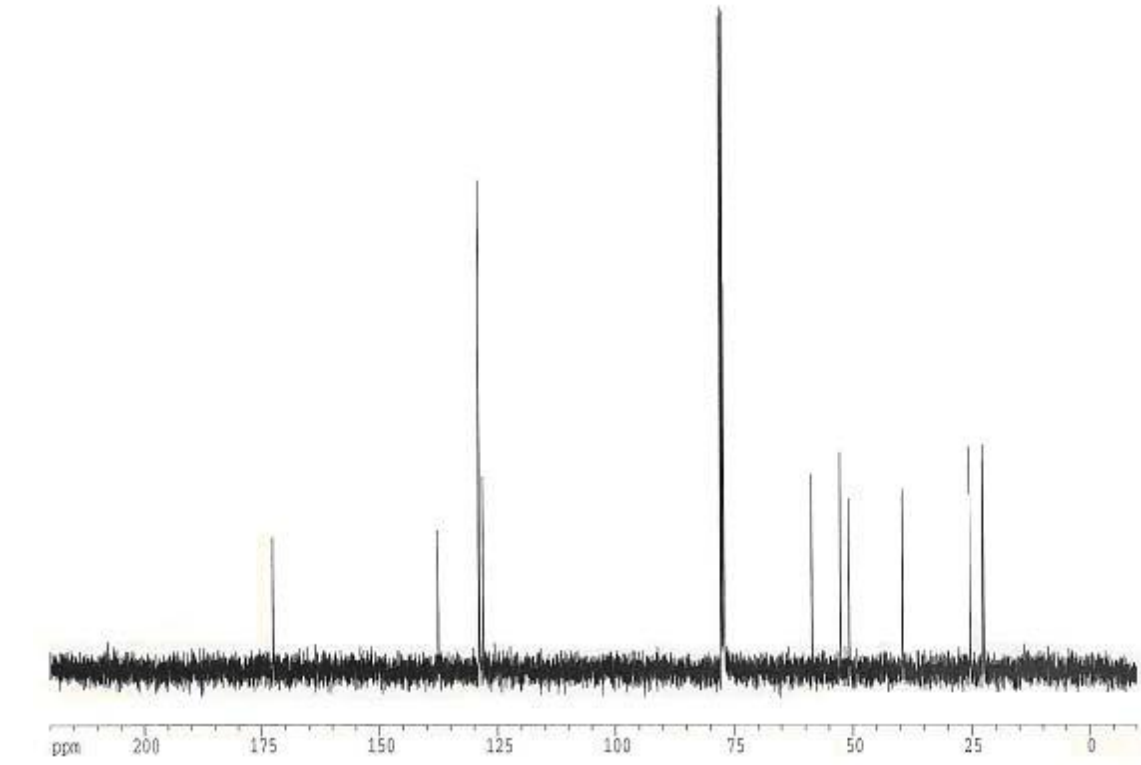
(1*S*,2*R*,6*S*,7*S*)-2,3,5,6-Tetrabenzyl-8-oxa-4-thia-3,5-diaza-bicyclo[5.1.0]octane 4,4-dioxide (23)



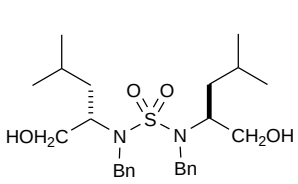


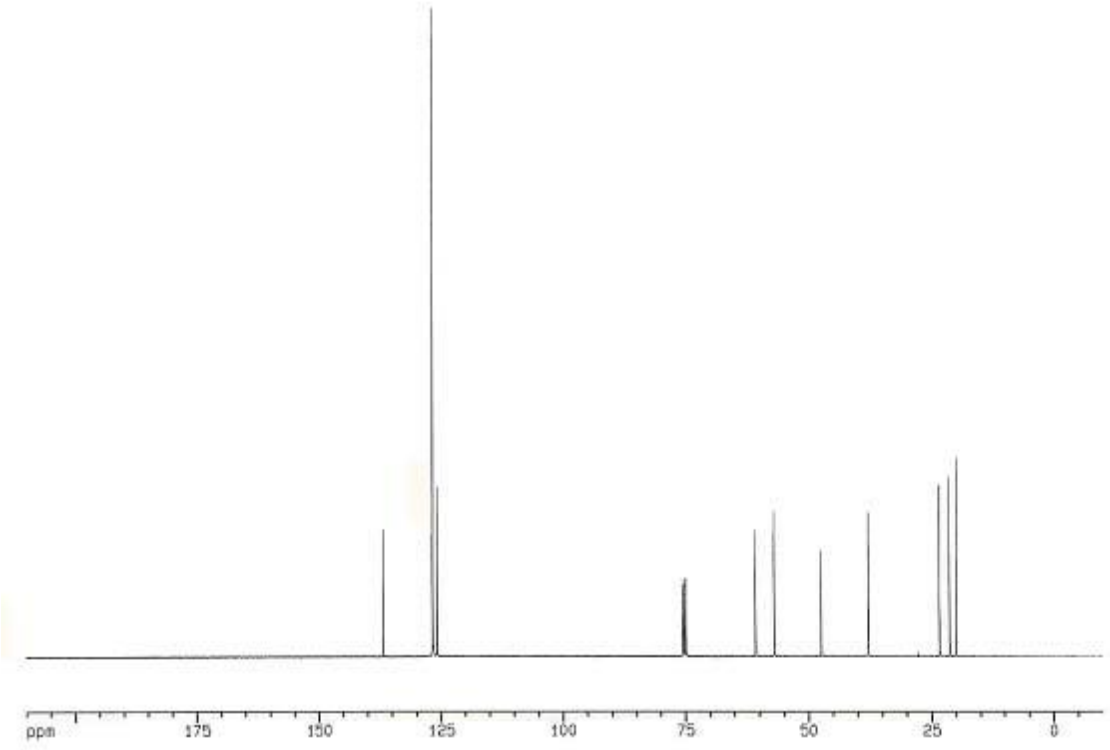
***N, N'* -Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (6)**



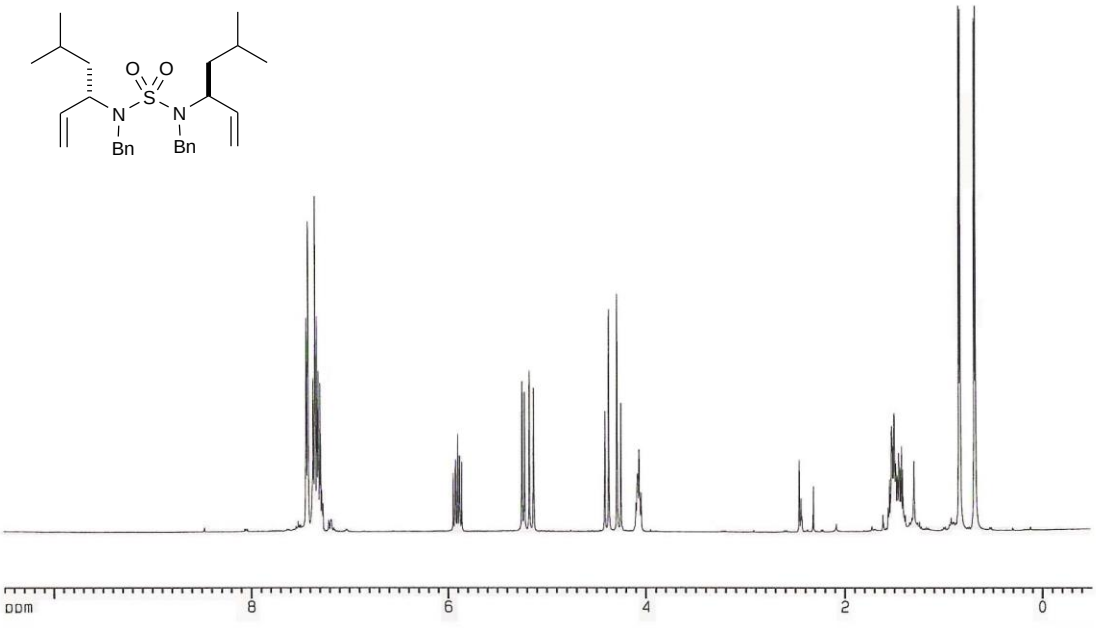


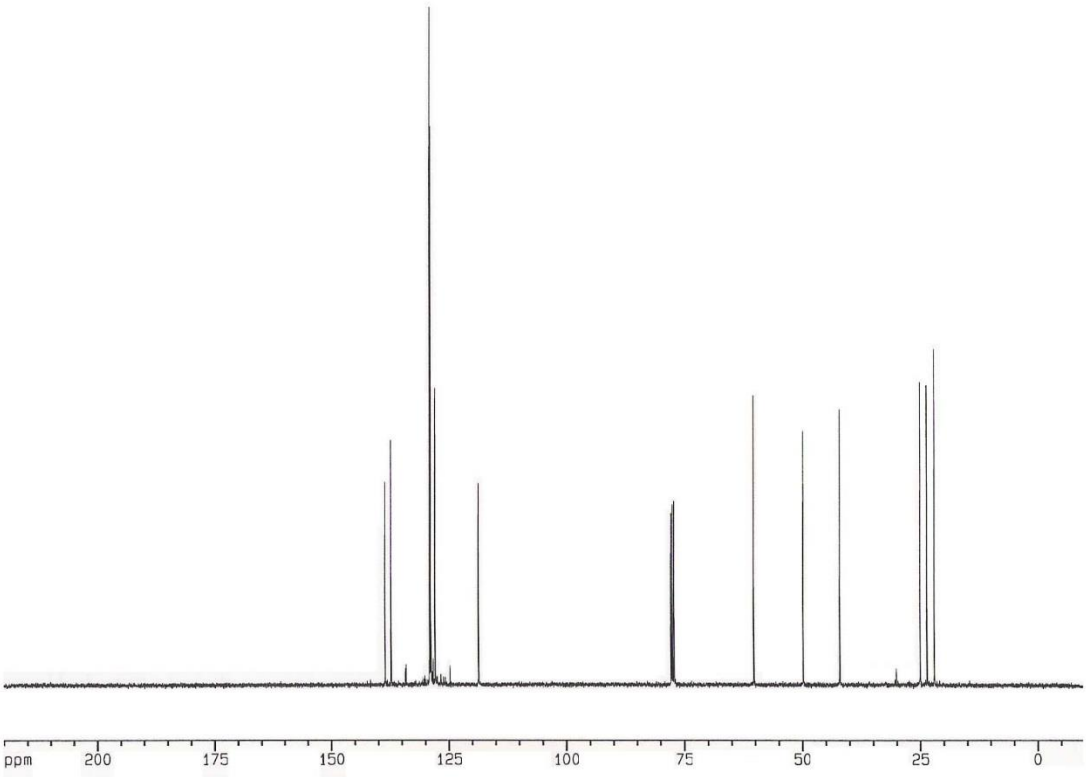
***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-2-hydroxy-1-(2-methylpropyl)ethyl]-sulfamide (10)**



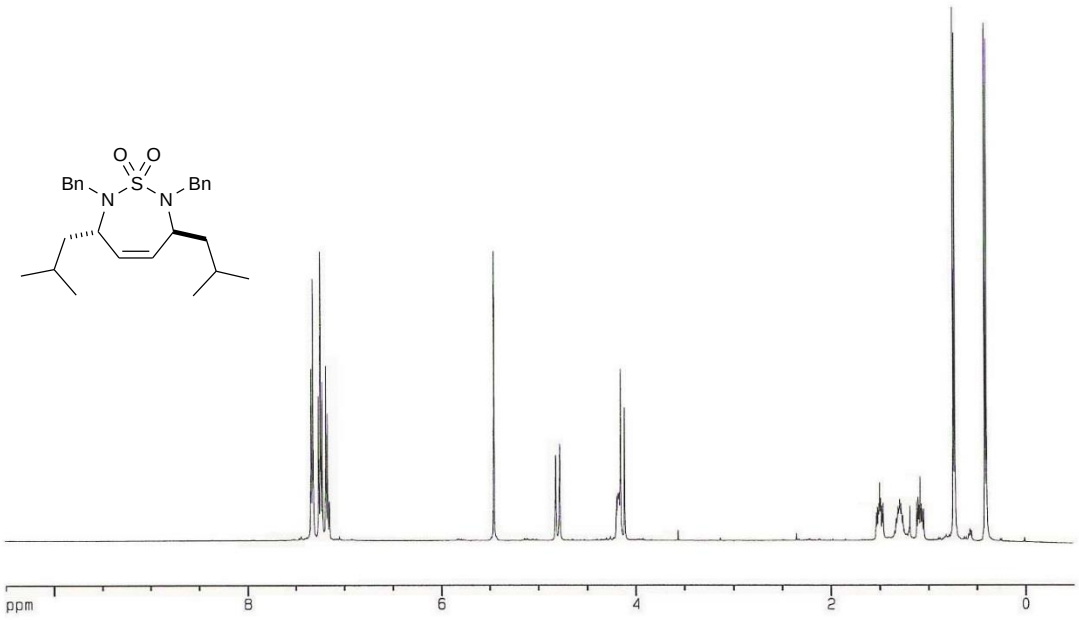


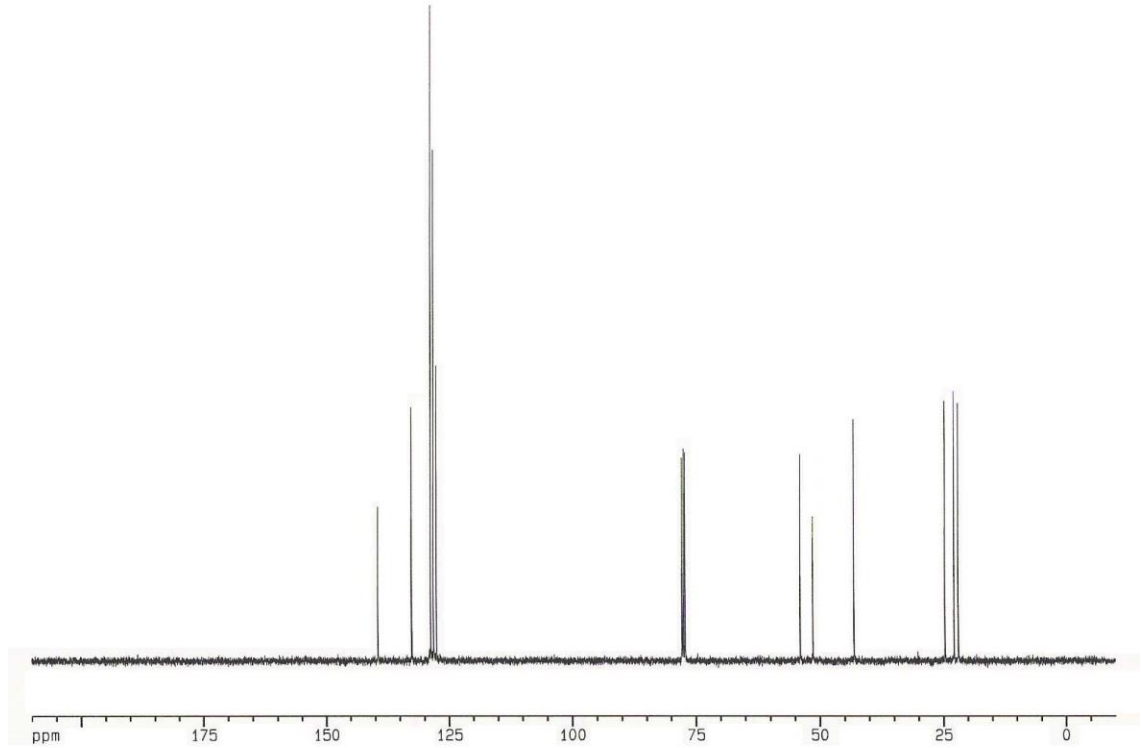
***N, N'*-Bis-benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-propenyl]-sulfamide (16)**



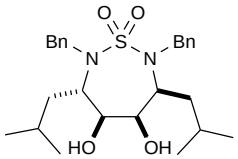


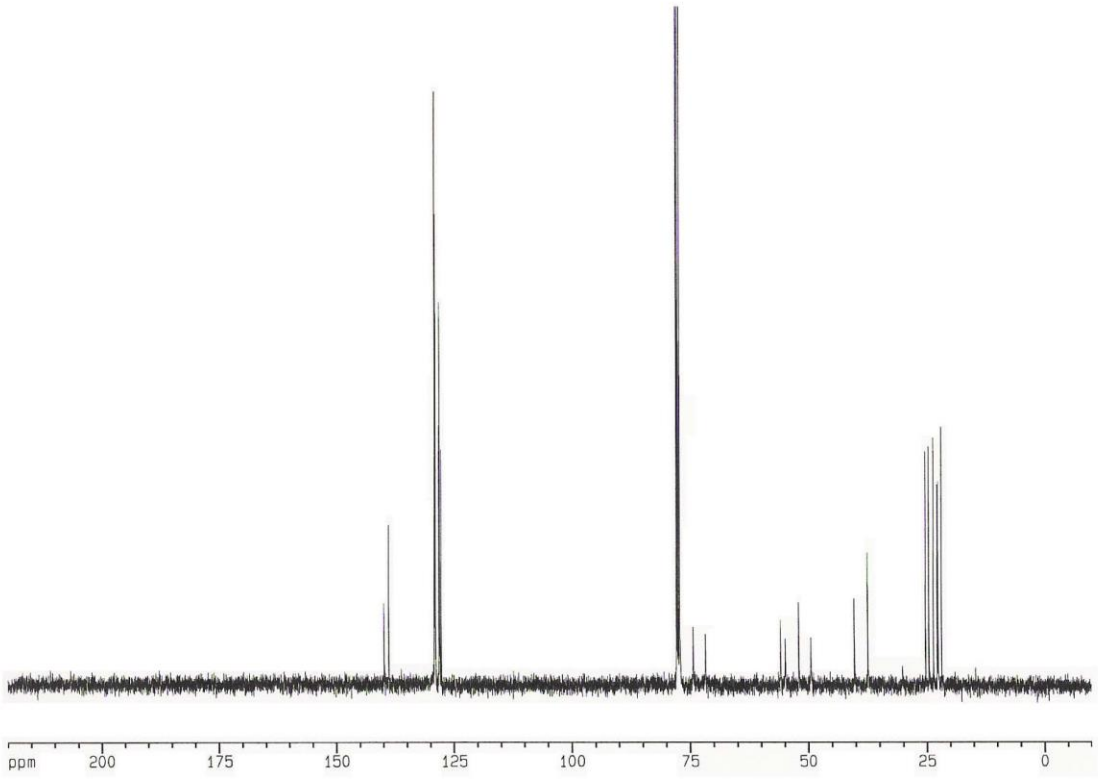
(3*S*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (19)



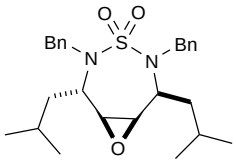


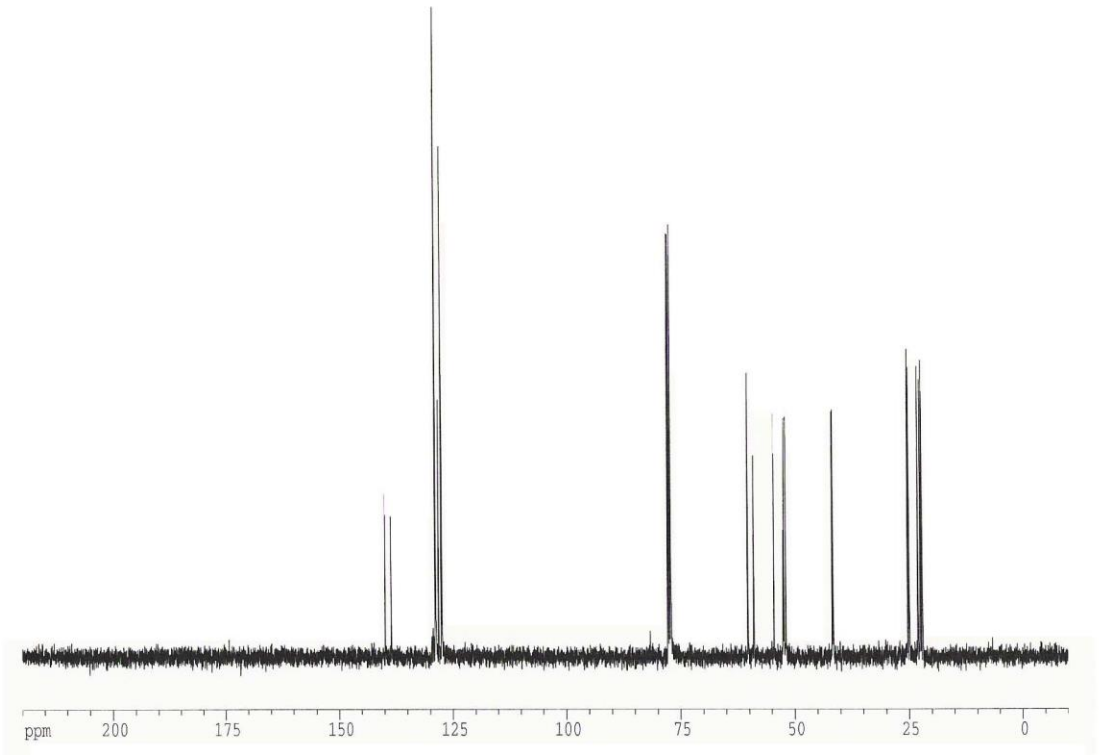
(3*S*,4*R*,5*S*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetra-hydro-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (22)



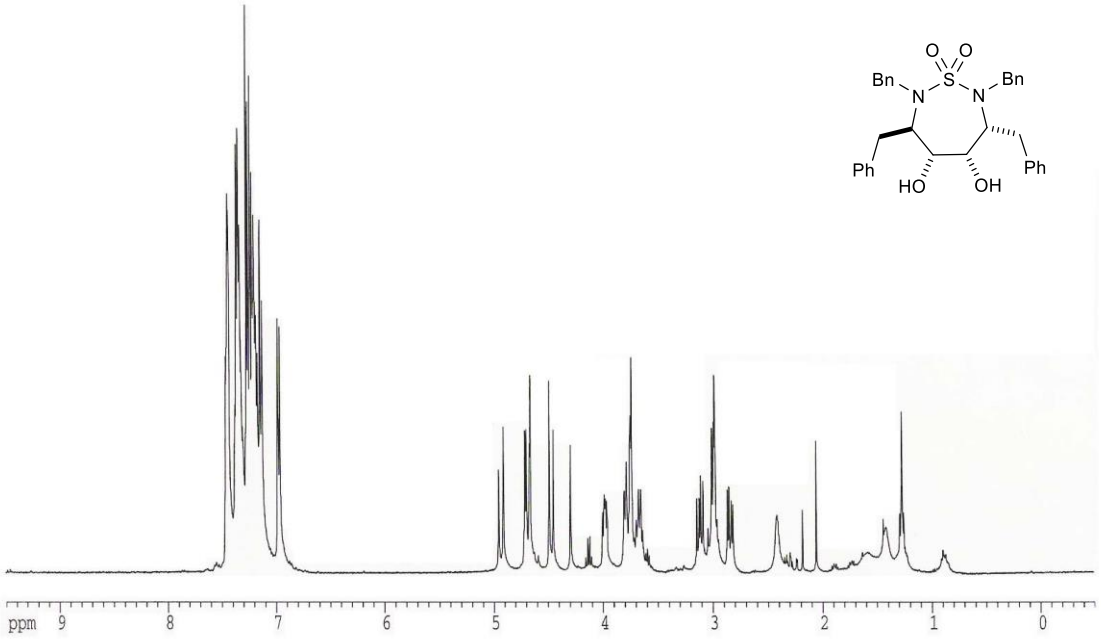


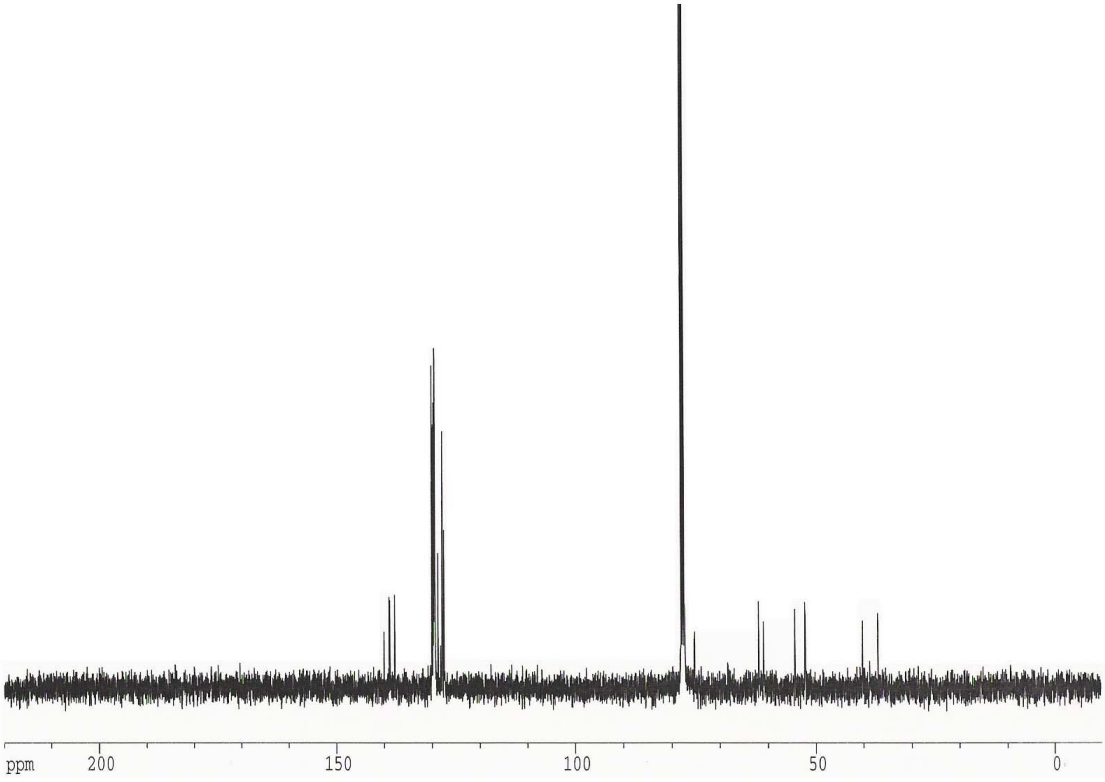
(1*S*,2*R*,6*S*,7*S*)-3,5-Dibenzyl-2,6-diisobutyl-8-oxa-4-thia-3,5-diaza-bicyclo[5.1.0]-octane 4,4-dioxide (24)



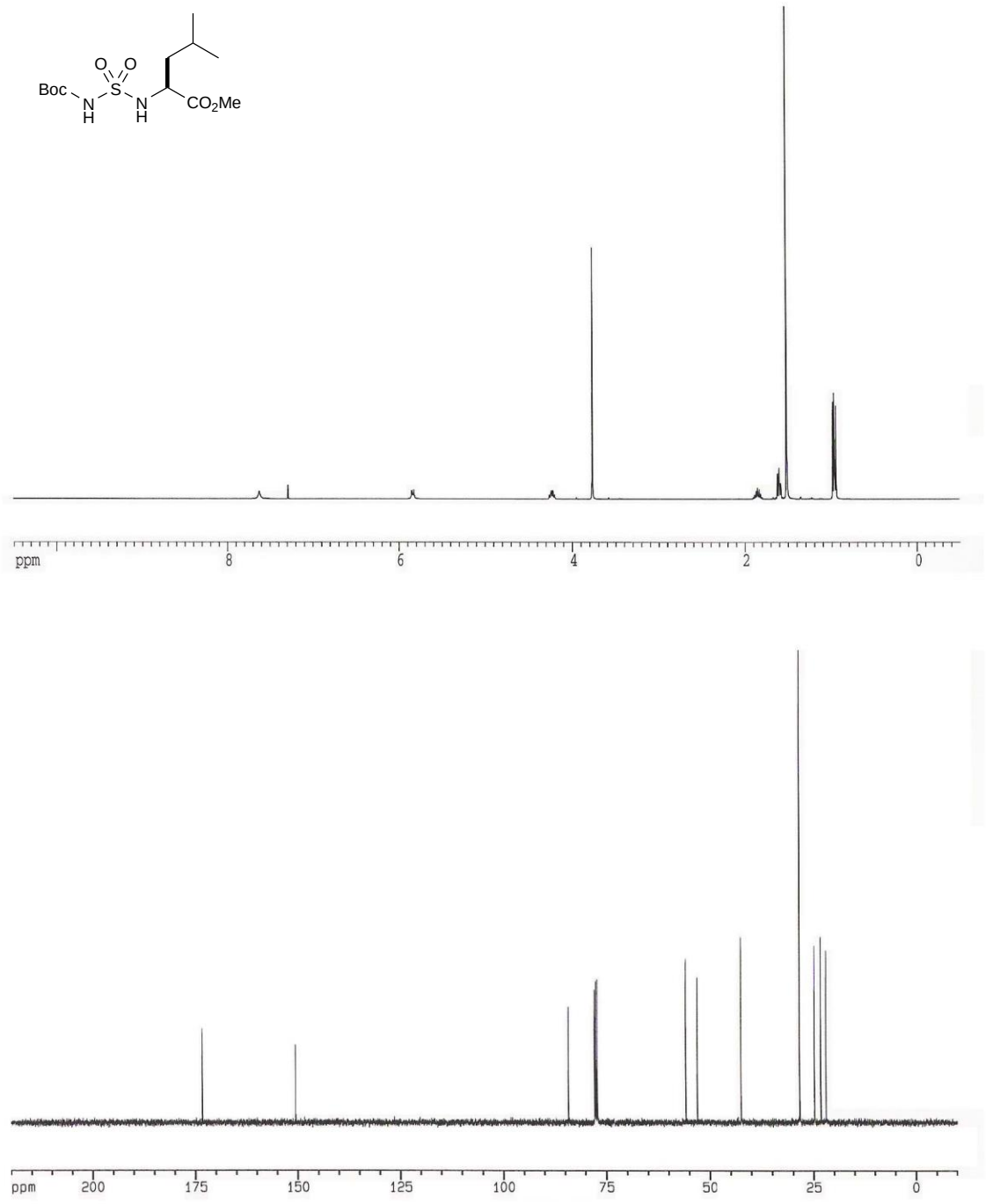


(3*R*,4*R*,5*S*,6*R*)-2,7-Dibenzyl-3,6-diphenylethyl-2,3,6,7-tetra-hydro-4,5-dihydroxy-1,2,7-thiadiazepine-1,1-dioxide (25)

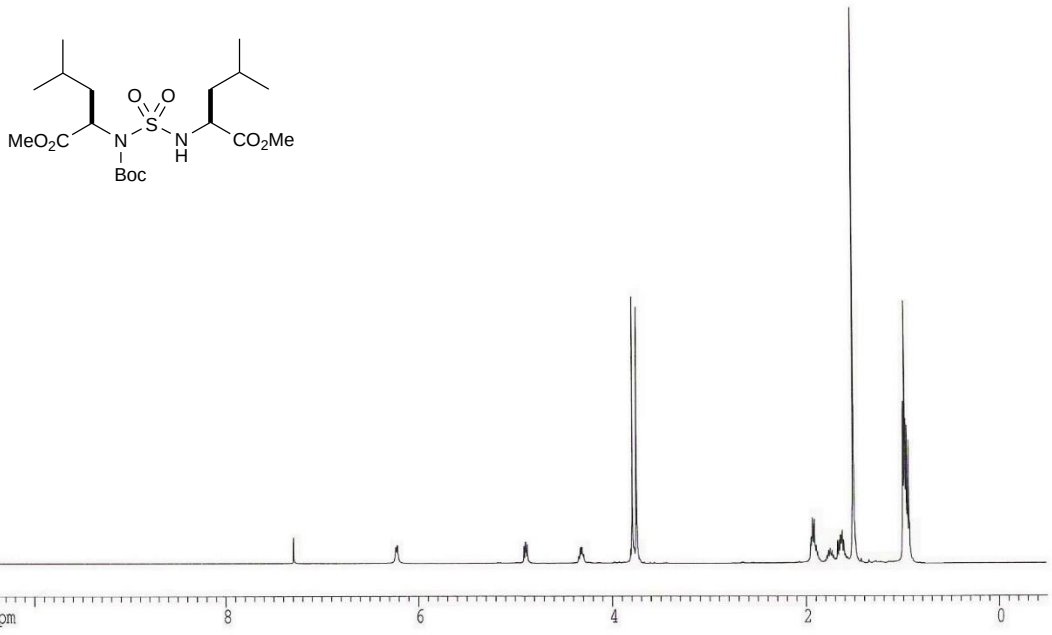


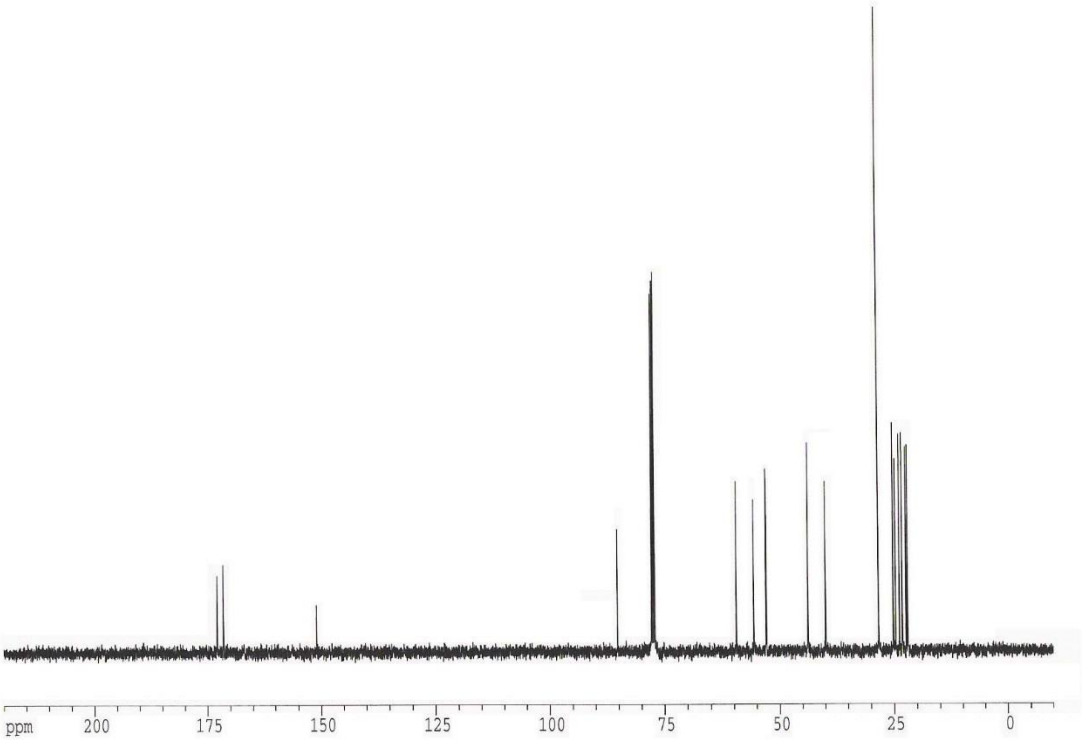


(*S*)-Methyl-2-(*N*-(tert-butoxycarbonyl)sulfamoylamino)-4-methylpentanoate (26)

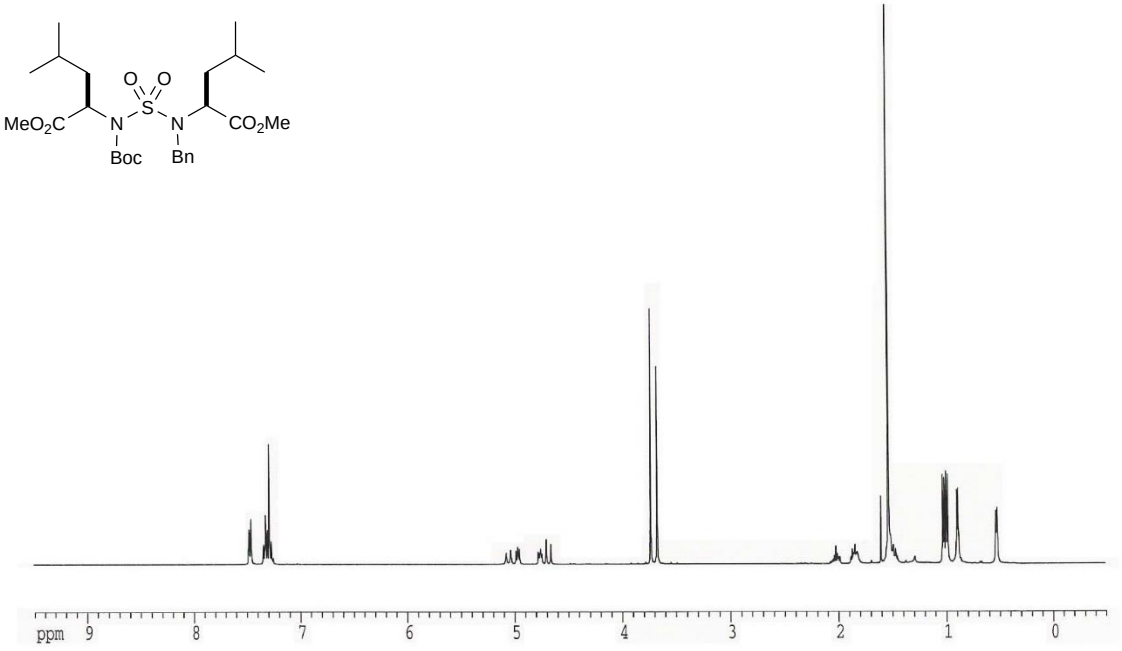


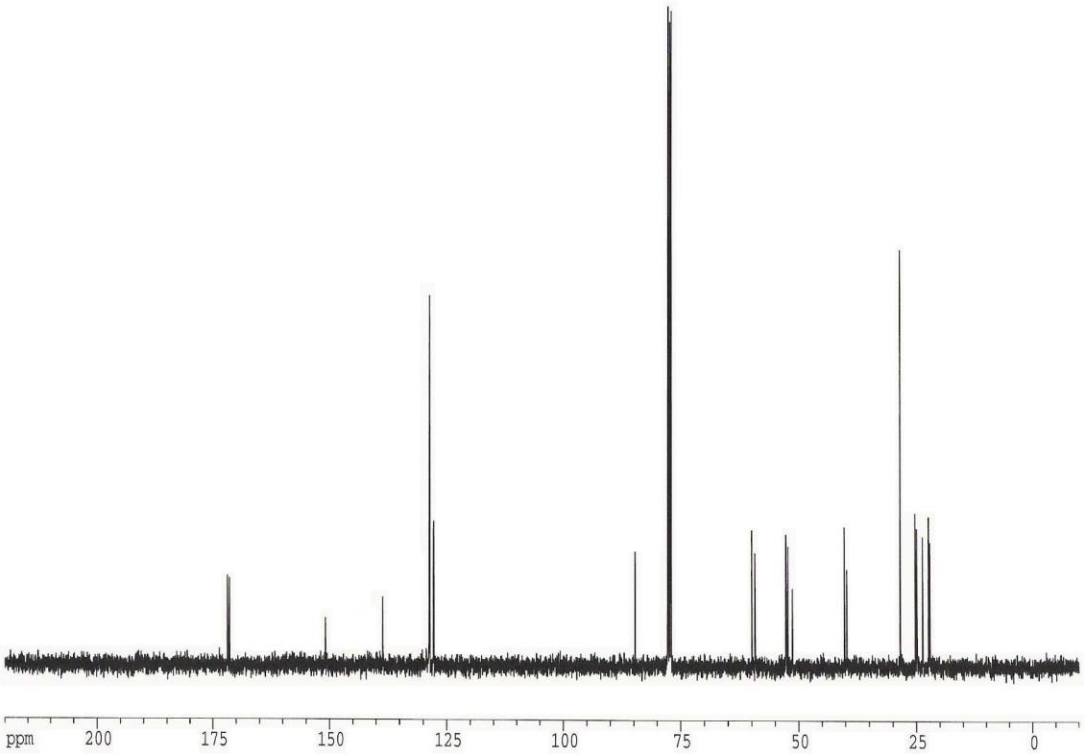
***N*-[(1,1-Dimethylethoxy)carbonyl]-[*N*-(1*R*)-1-(2-methylpropyl)-2-methoxycarbonyl-*N'*-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (27)**



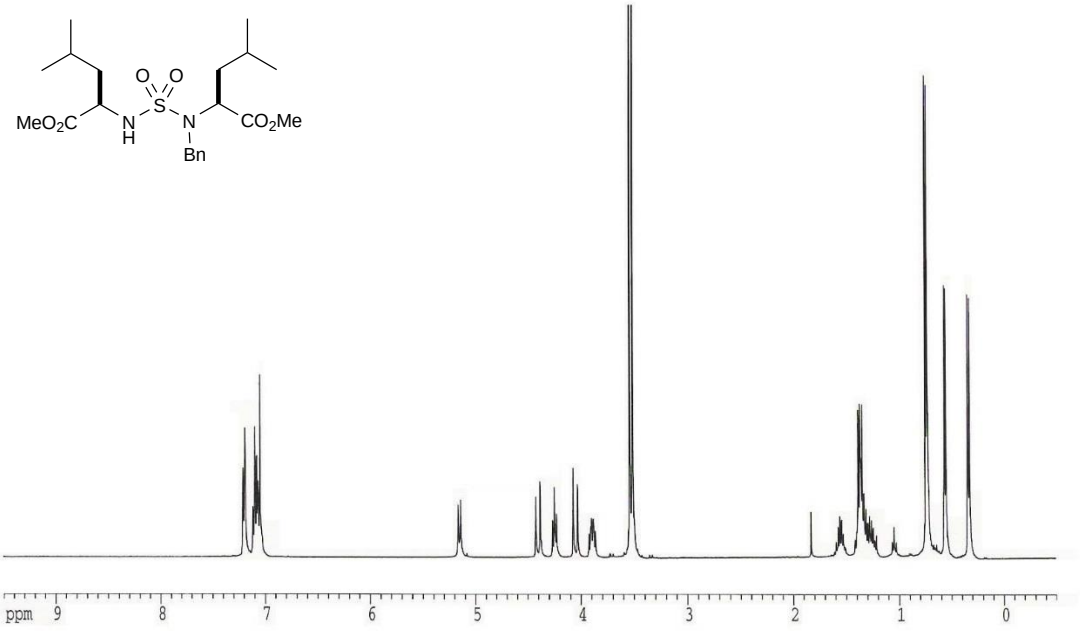


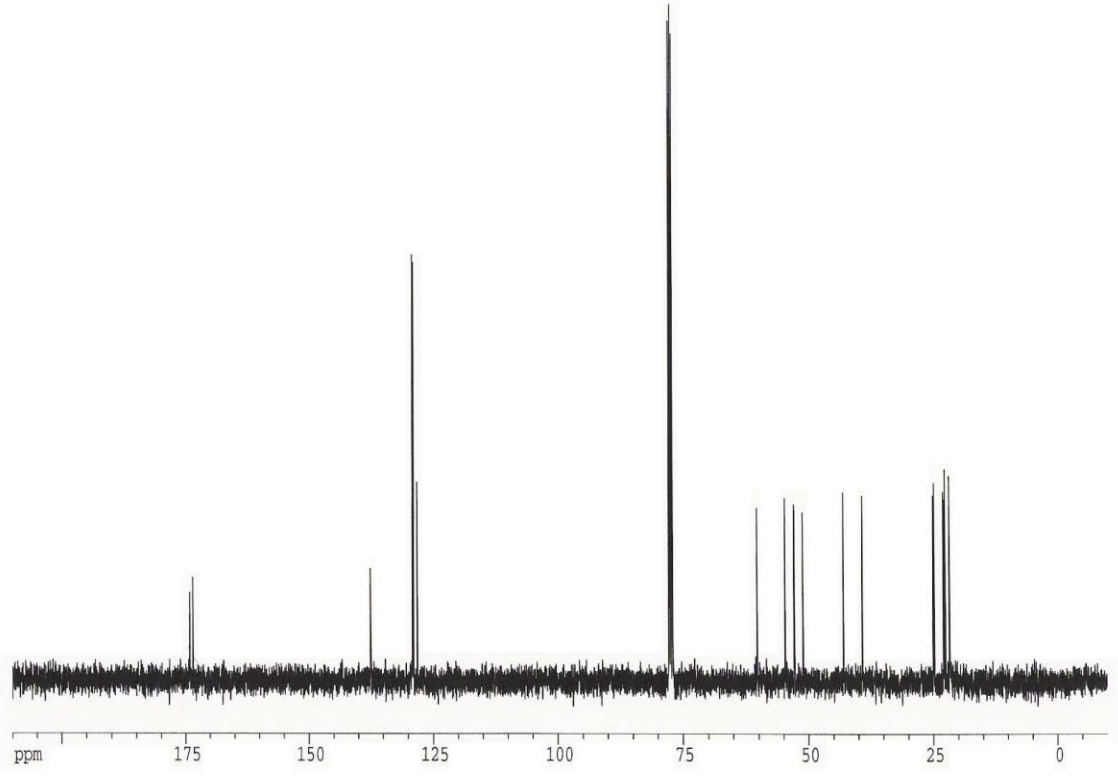
***N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(1*R*)-1-(2-methylpropyl)-2-methoxycarbonyl]-*N'*-benzyl-*N'*-[(1*S*)-1-(2-methylpropyl)-2-ethoxycarbonyl]-sulfamide (28)**



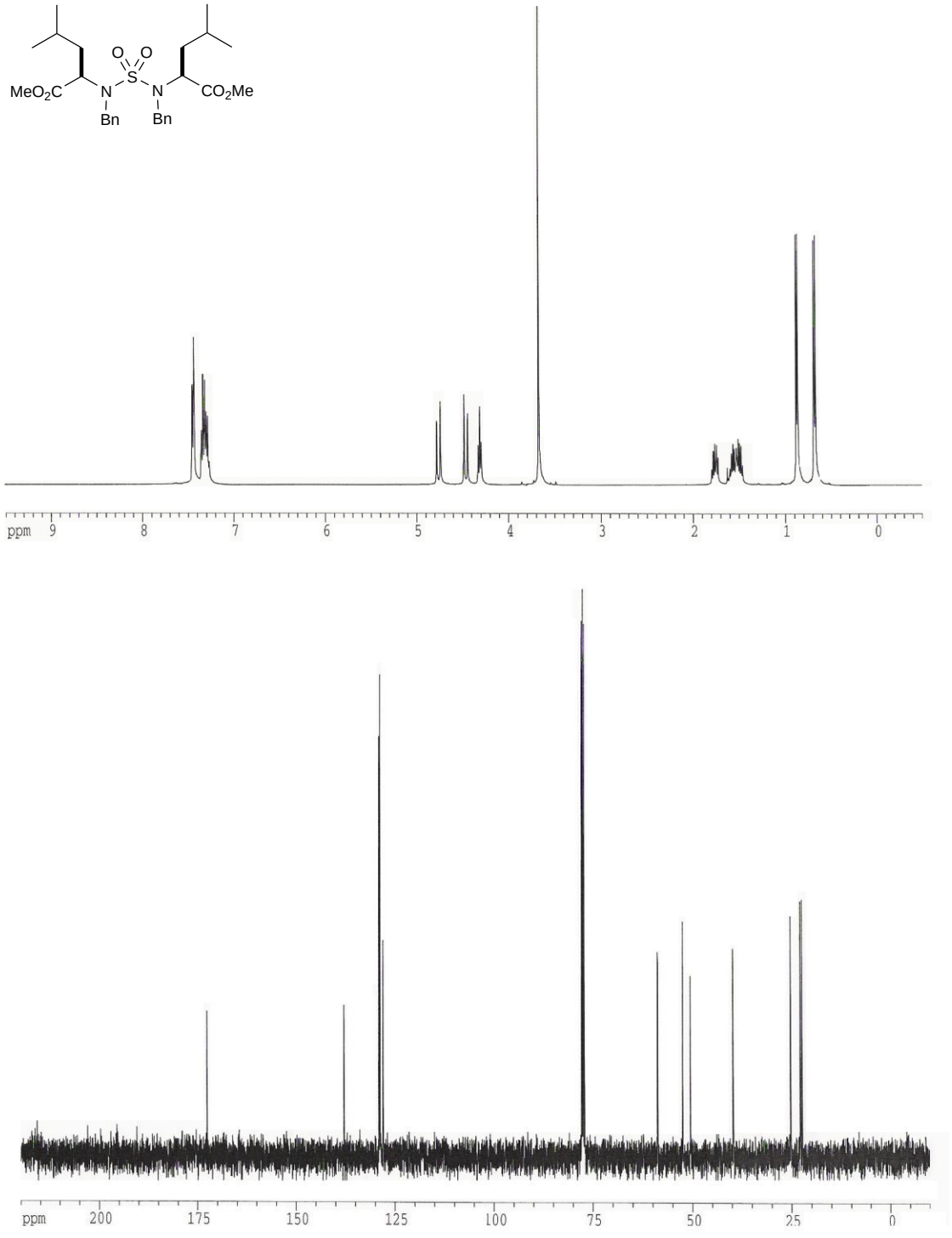


***N*-[(1*R*)-1-(2-Methylpropyl)-2-methoxycarbonyl]-*N'*-benzyl-*N'*-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (29)**

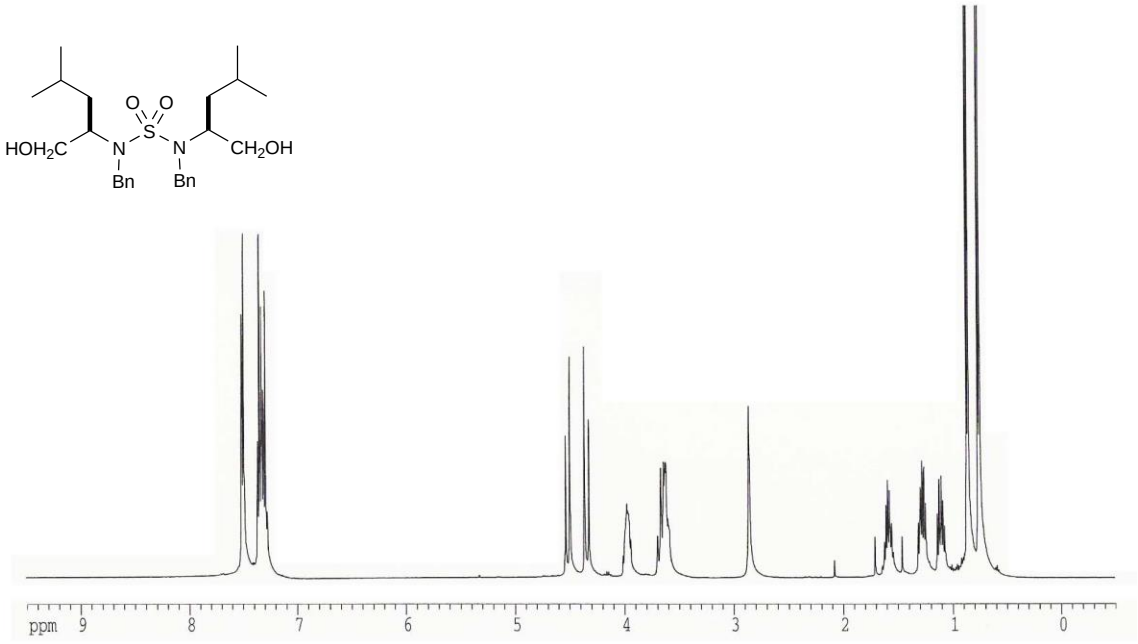


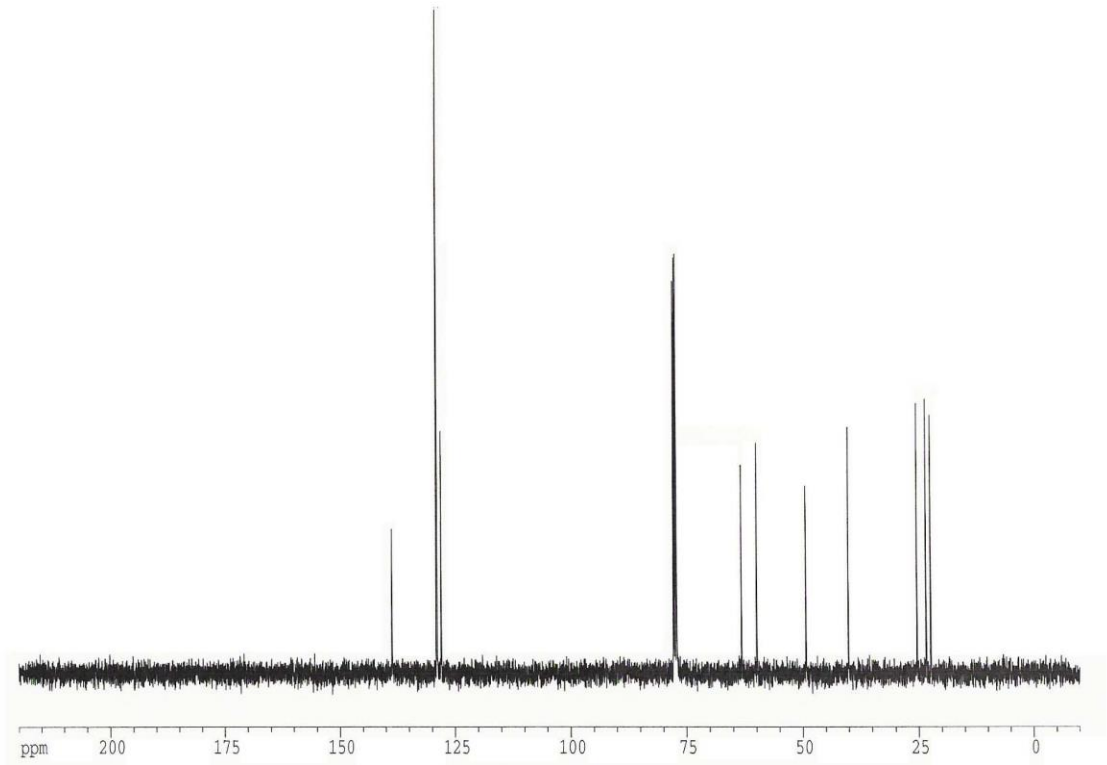


***N, N'*-Bis-benzyl-*N*-*N'*- (1*S*),(1*R*)- bis- [1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (30)**

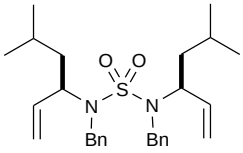


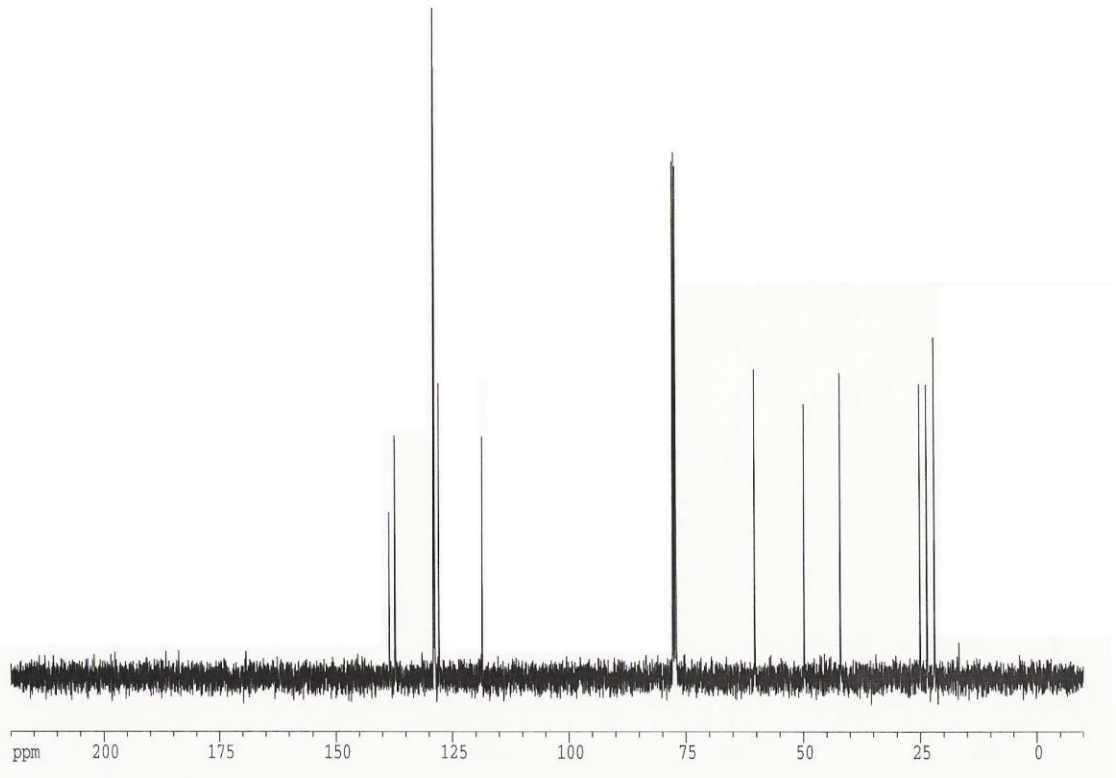
***N,N'*-Bis-benzyl-*N*-[(1*S*)-2-hydroxy-1-(2-methylpropyl)ethyl]-*N'*-[(1*R*)-2-hydroxy-1-(2-methylpropyl)ethyl]-sulfamide (31)**



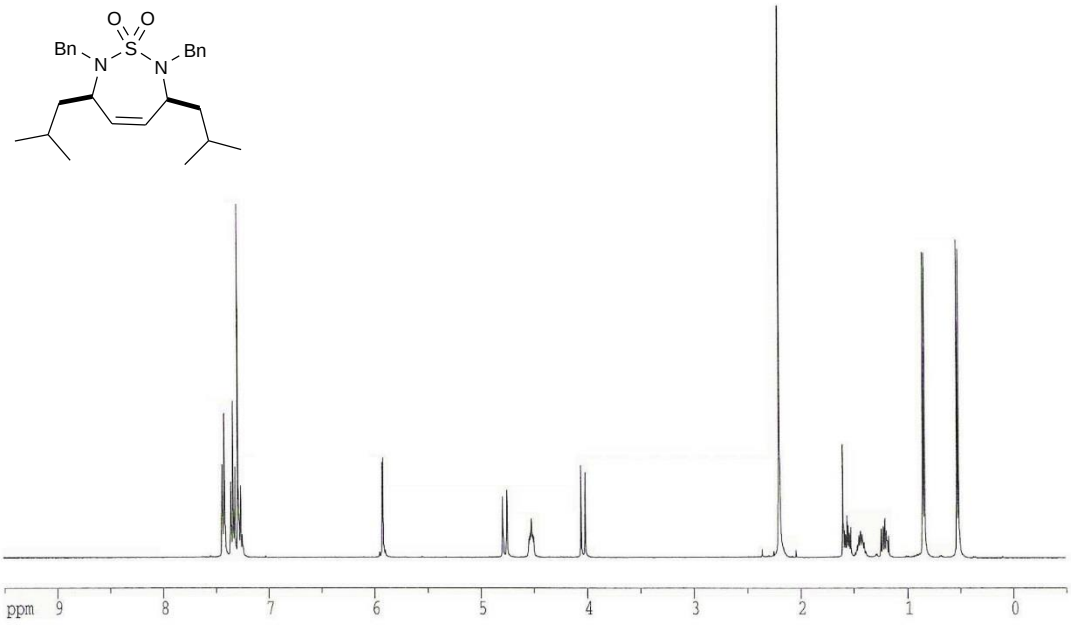


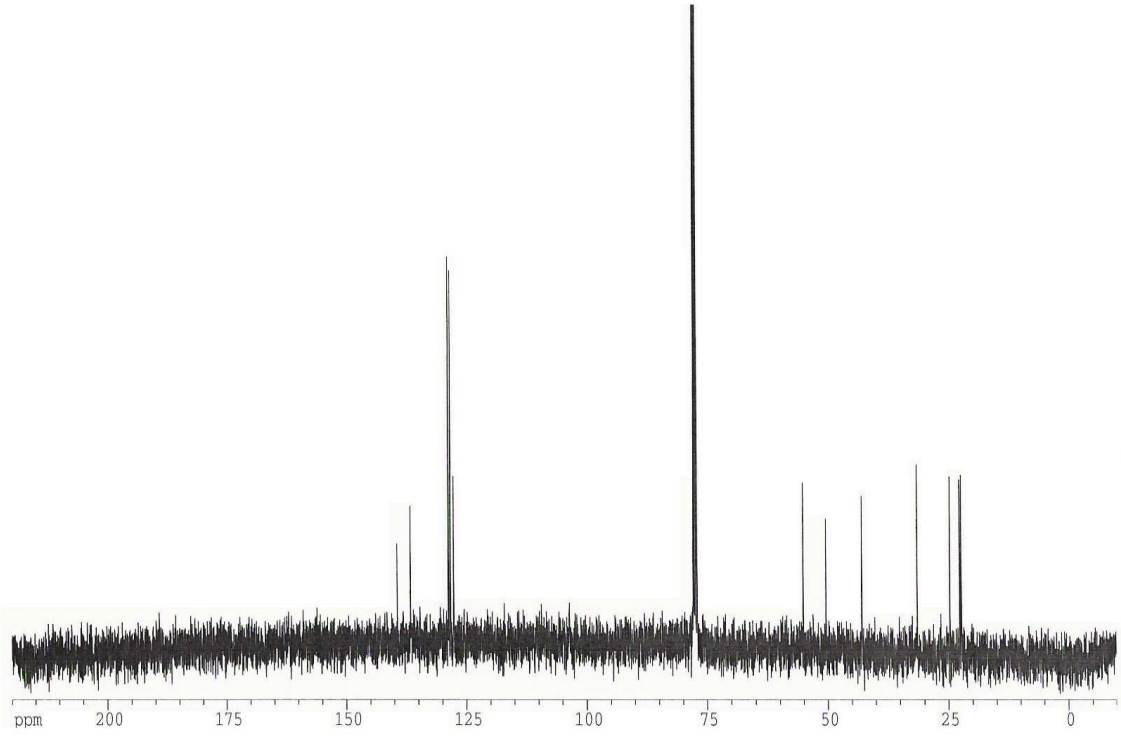
***N,N'*-Bis-benzyl-*N*-[(1*S*)-1-(2-methylpropyl)-2-propenyl]-*N'*-[(1*R*)-1-(2-methylpropyl)-2-propenyl]-sulfamide (32)**



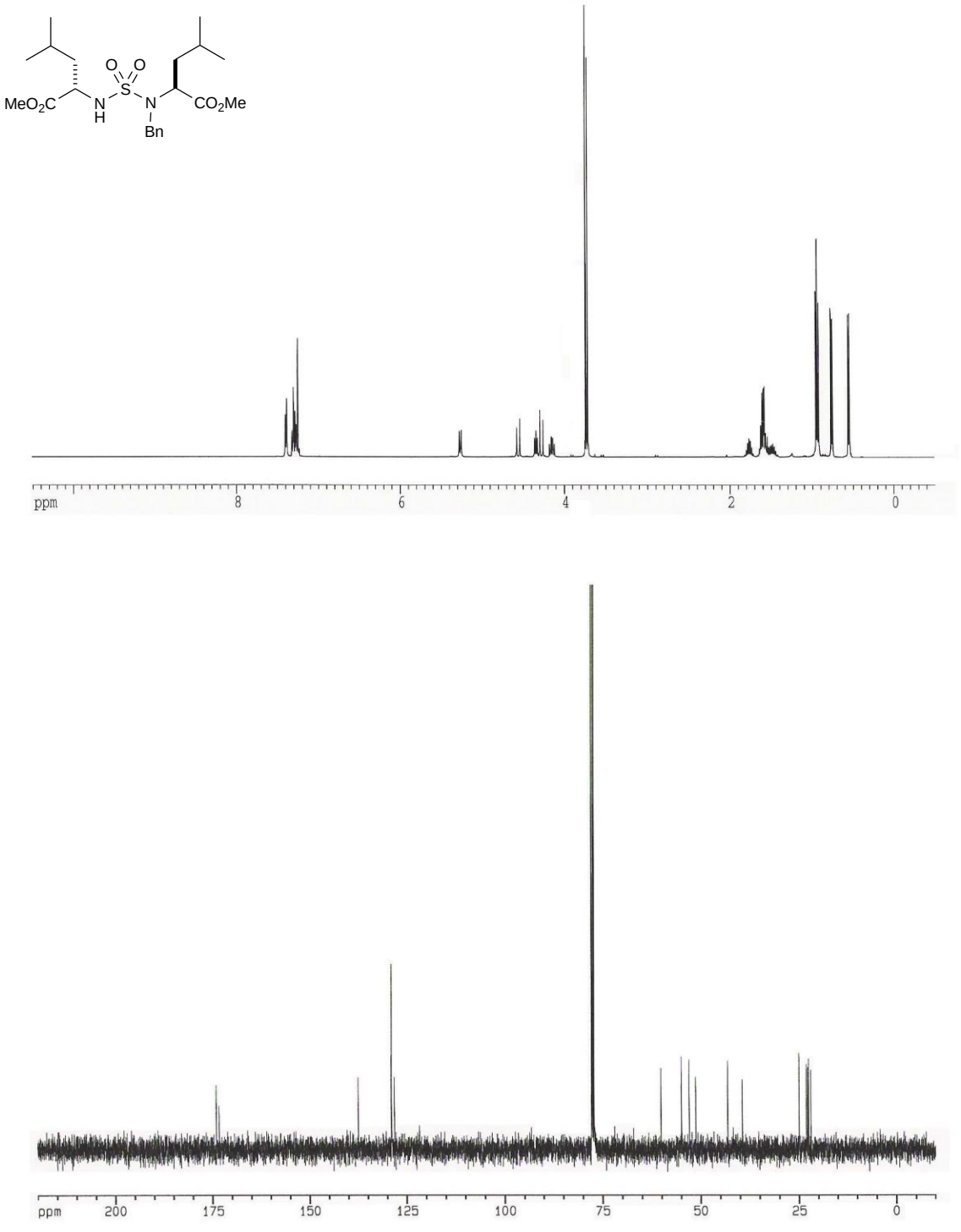


(3*R*,6*S*)-2,7-Dibenzyl-3,6-diisobutyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (33)

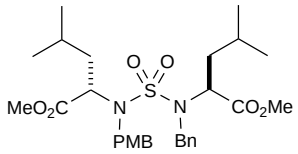


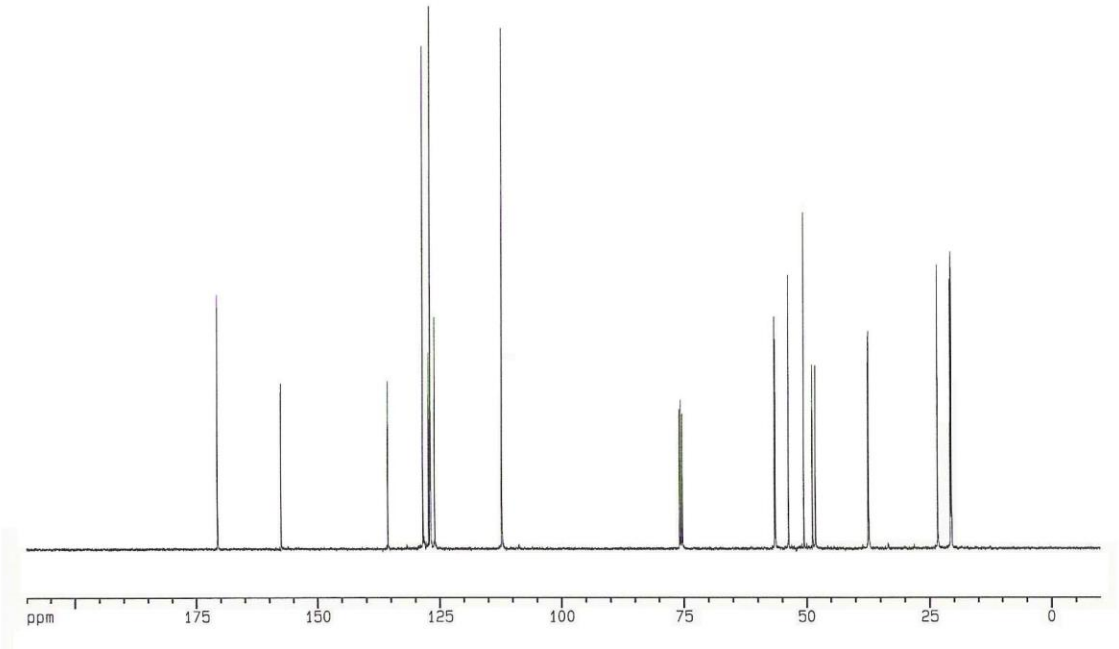


***N*-Benzyl-*N*-*N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (7)**

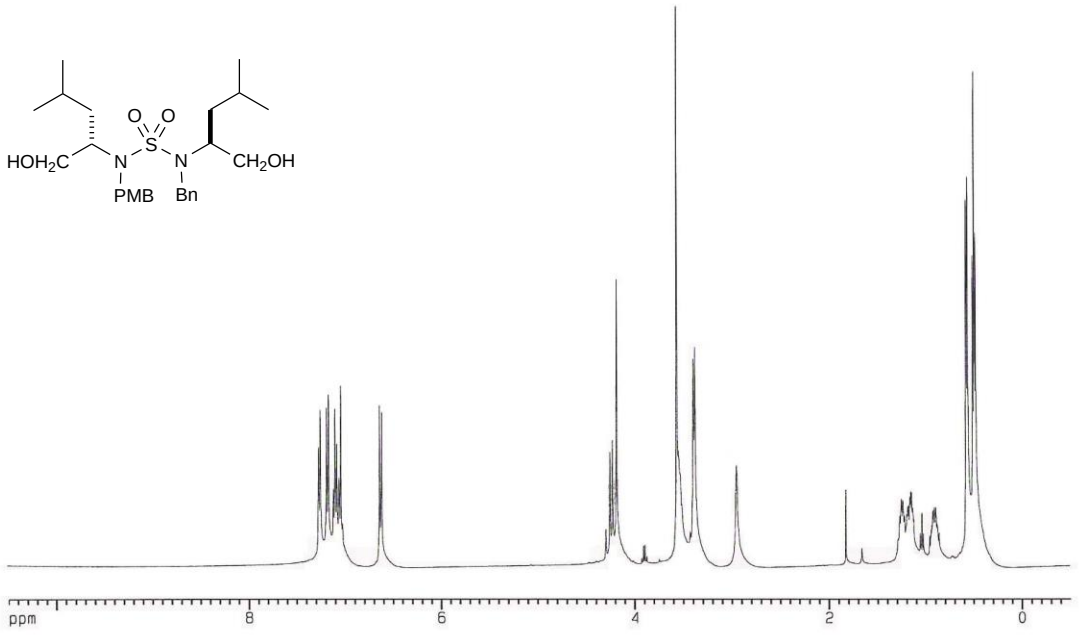


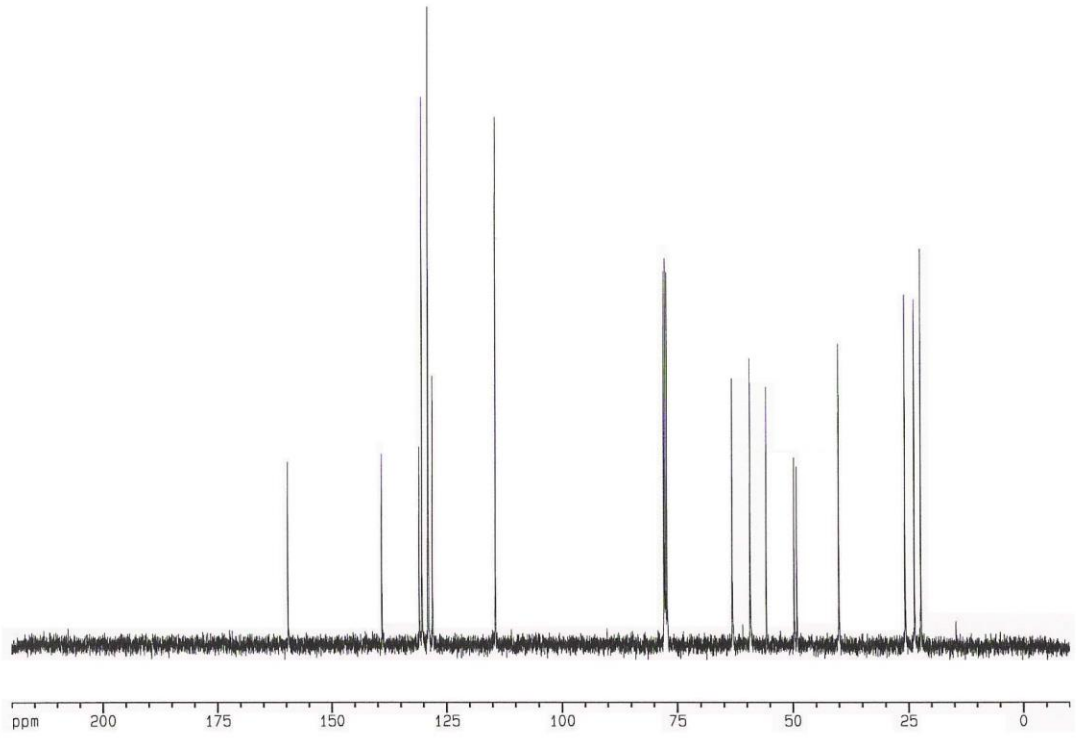
***N*-Benzyl-*N'*-(4-methoxy)-benzyl-*N,N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-methoxycarbonyl]-sulfamide (8)**



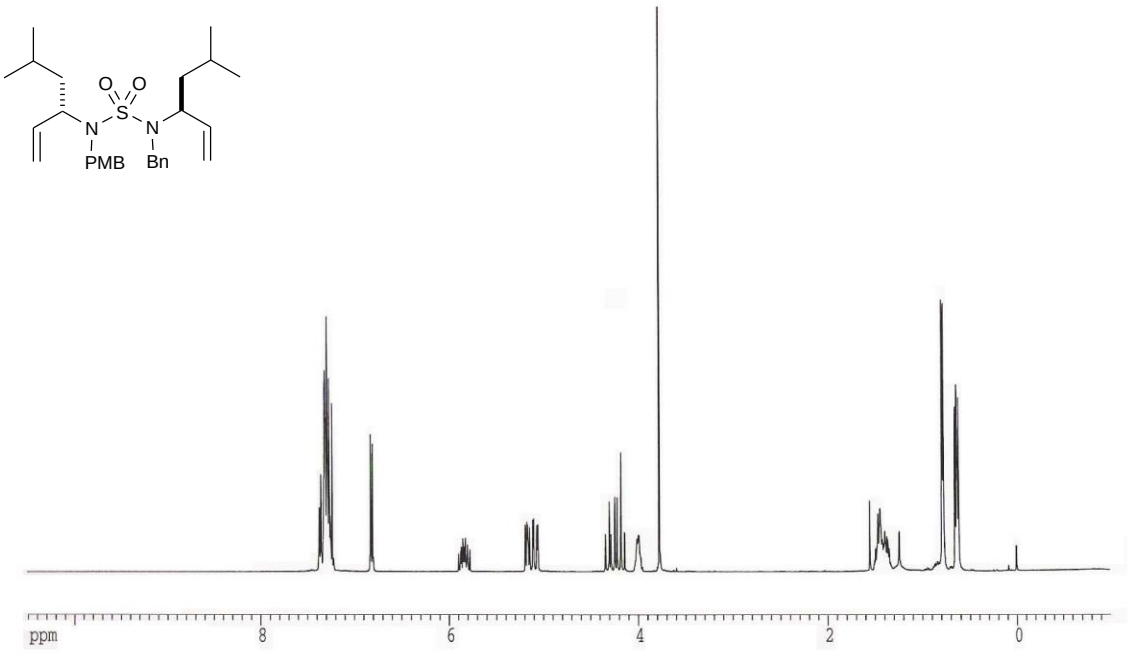


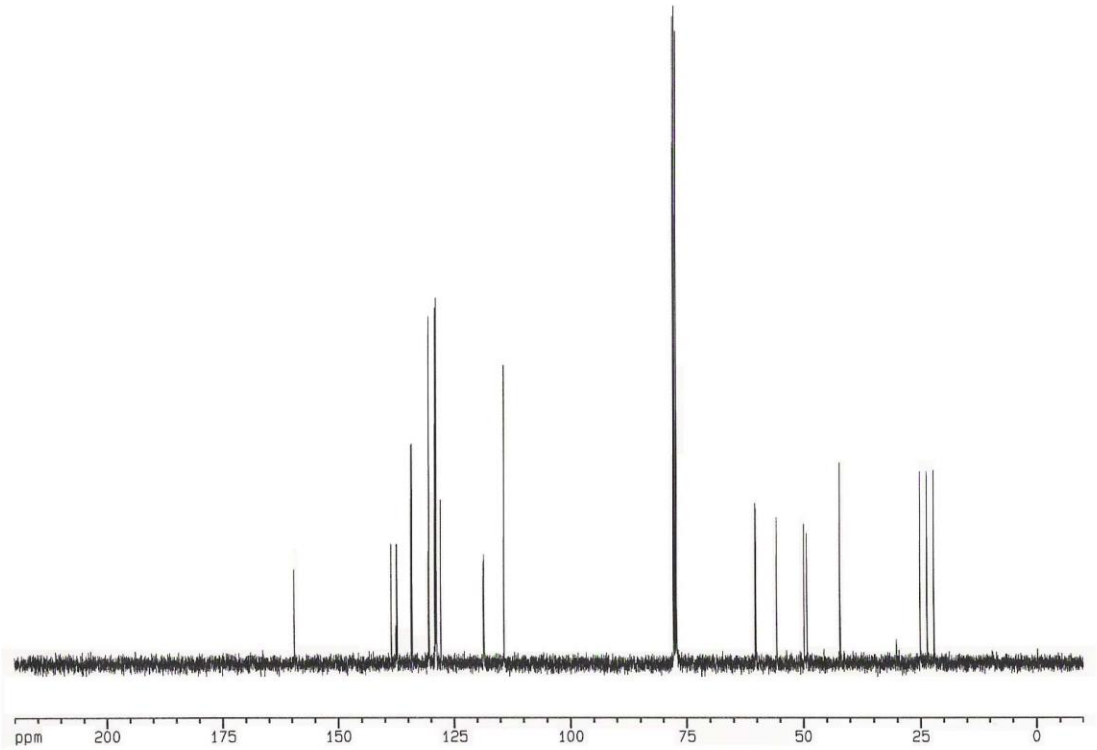
***N*-Benzyl-*N'*-(4-methoxy)-benzyl-*N*-*N'*-bis-[(1*S*)-2-hydroxy-1-(2-methylpropyl)-ethyl]-sulfamide (11)**



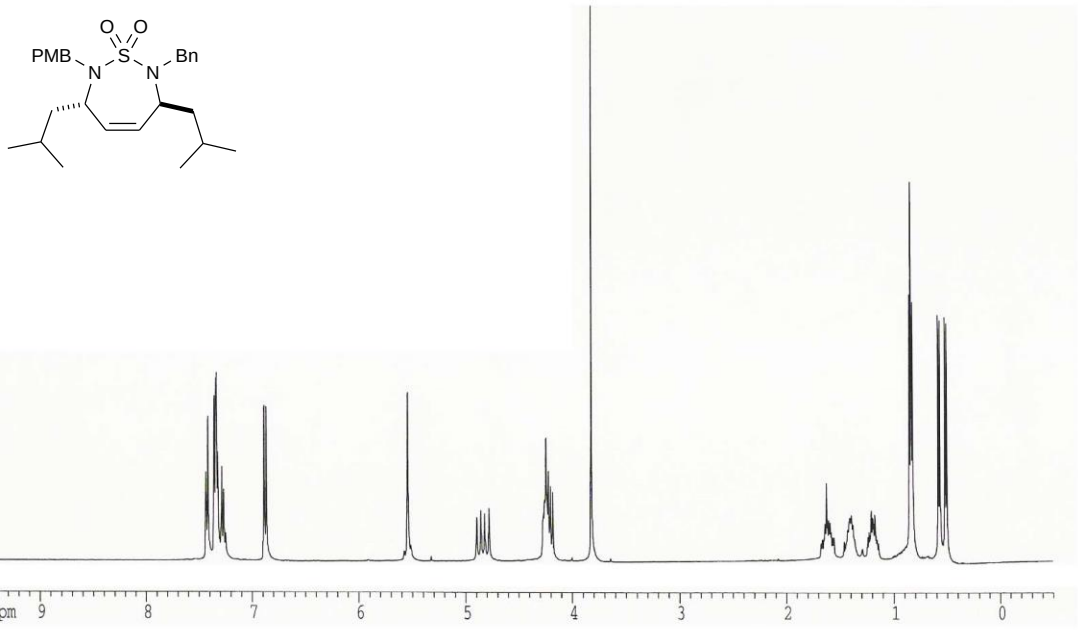


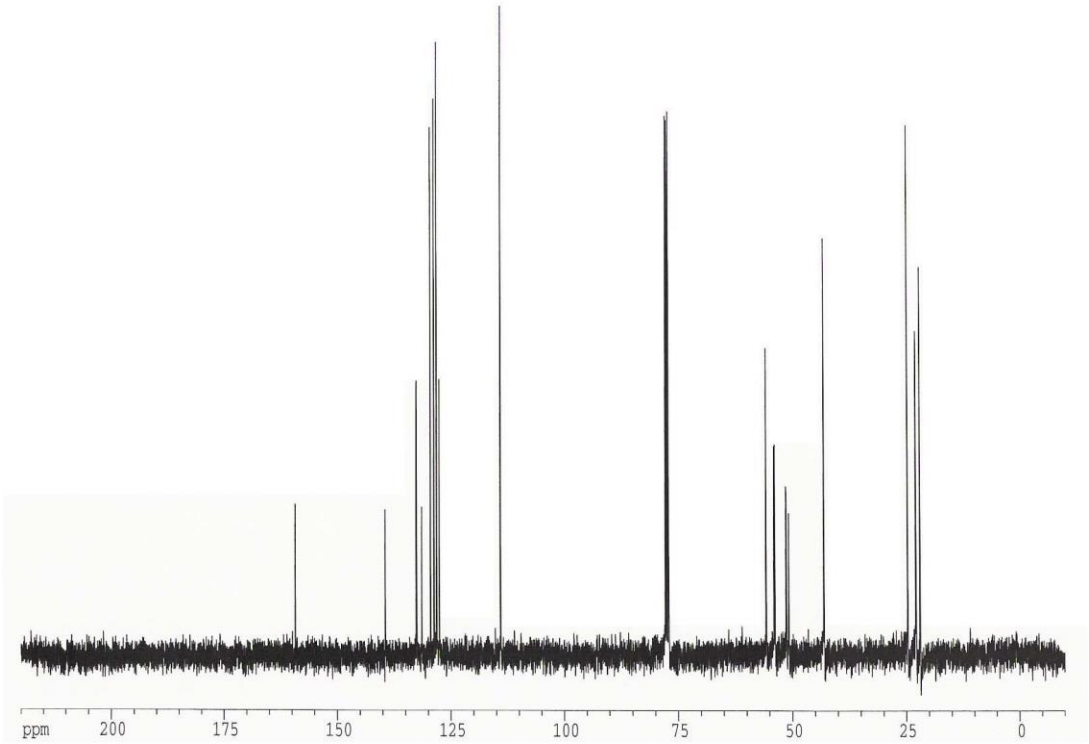
***N*-Benzyl-*N'*-(4-methoxy)-benzyl-*N,N'*-bis-[(1*S*)-1-(2-methylpropyl)-2-propenyl]-sulfamide (17)**





(3*S*,6*S*)-2-Benzyl-7-(4-methoxy)-benzyl-3,6-diisobutyl-2,3,6,7-tetrahydro-1,2,7-thiadiazepine-1,1-dioxide (20)





References

1. Jun, J. H.; Dougherty, J. M.; Jimenez, M. S.; Hanson, P. R. New Strategies to Symmetric and Unsymmetric Cyclic Sulfamide Analogs of DMP 323: A "Sulfur Linchpin"/RCM Approach. *Tetrahedron* **2003**, *59*, 8901–8912.
2. McReynolds, M. D.; Sprott, K. T.; Hanson, P. R., A Concise Route to Structurally Diverse DMP 323 Analogues via Highly Functionalized 1,4-Diamines, *Org. Lett*. **2002**, *4*, 4673–4676.
3. Harned, A. M.; Mukherjee, S.; Flynn, D. L.; Hanson, P. R. Ring-Opening Metathesis Phase-Trafficking (ROMpt) Synthesis: Multistep Synthesis on Soluble ROM Supports. *Org. Lett.* **2003**, *5*, 15–18.
4. Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R., Ring-Closing Metathesis Strategies to Cyclic Sulfamide Peptidomimetics, *Tetrahedron*, **2000**, *56*, 9781–9790.