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Supplementary Information

Synthesis of Cyclic 1,3-Diols as Scaffolds for Spatially Directed Libraries

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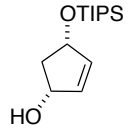
Supporting Information

1. **General Methods**.

Reactions were performed under an inert atmosphere (argon, Ar or nitrogen, N_2) either in flame-dried or oven-dried glassware, or glass sample vial with rubber-lined cap. The stainless steel needles used for handling anhydrous solvents and reagents were oven dried and flushed with N_2 prior to use. Plastic syringes were flushed with N_2 before use. All chemicals were used as received from commercial source, without further purification. Dichloromethane (DCM) and tetrahydrofuran (THF) were dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. Thin-layer chromatography (TLC) was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Visualization was accomplished with UV light or potassium permanganate stain. Flash chromatography was carried out on a semi-automated purification system using normal phase silica flash columns. Infrared (IR) spectra were acquired as thin films or solids. All nuclear magnetic resonance (NMR) spectra (^{1}H and ^{13}C) were recorded on a 400 MHz dual carbon/proton cryoprobe instrument. NMRs were recorded in deuterated chloroform. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of the solvent at δ 7.26 ppm. Coupling constants are given in Hertz (Hz). HRMS data were collected with a LCT Premier time-of-flight mass spectrometer and an electrospray ion source (ESI). Observed optical rotations at 589 nm, were measured using automatic polarimeter. The *er* values of the compounds (1*R*,3*R*)-**9**, (1*S*,3*S*)-**9**, (*R*,*R*)-**14**, and (*S*,*S*)-**14** were determined by gas

chromatography using a 5975CVL MSD triple-axis detector. The *er* value of the compounds (*R*,*R*)-**13**, and (*S*,*S*)-**13** were determined by chiral HPLC on an IC column with a 996 UV detector. Preparative reverse-phase HPLC was performed on a Waters 2767 preparative system [UV (214 nm, 2996 PAD) and mass detection (Micromass ZQ)], using a Waters X-Bridge C18 column (19 × 150, 19 × 10 mm guard column), and water/acetonitrile as eluent with 20% increase in gradient over 4 min at a flow rate of 20 mL/min.

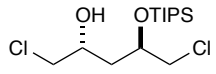
Known compounds: The compounds (*R,R*)-**1**, (*R,R*)-**2**, (*S,S*)-**1**, (*S,S*)-**2**, (1*R,4R*)-**3,** (1*S,4S*)-**3** and **19** were prepared according to the previously reported procedures.[1, 2]



(1*R*,4*S*)-**3**

(1*R*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (3). To a solution of (1*S*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (3.41 g, 13.2 mmol) in THF (100 mL), triphenyl phosphine (13.8 g, 52.8 mmol) and 4-nitrophenyl benzoic acid (8.8 g, 52.8 mmol) were added. Then diethylazodicarboxylate (8.3 mL, 52.8 mmol) was added dropwise and the reaction mixture was stirred at room temperature for overnight. The reaction was quenched with ammonium chloride and was extracted with diethyl ether. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in THF (50 mL) and aq sodium hydroxide (528 mg in 2 mL water, 26.4 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was extracted with diethyl ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The product was obtained by

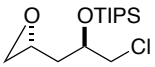
column chromatography in 72% yield (2.4 g) as colorless oil. R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 3282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.98–5.88 (m, 2H), 4.73 (ddt, *J* = 6.9, 4.4, 1.3 Hz, 1H), 4.57 (ddt, *J* = 7.2, 4.6, 1.4 Hz, 1H), 2.70 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.15 (s, 1H), 1.56 (dt, *J* = 13.7, 4.5 Hz, 1H), 1.24–0.87 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 135.7, 75.3, 75.2, 45.1, 18.1, 18.09, 12.2; *m/z* (ESI+) found $[M+H]^+$ 257.1934, $C_{14}H_{29}O_2Si$ requires 257.1937; $[\alpha]_D^{25.3}$ –20.3 (*c* 2.00, MeOH); lit.[3] $[\alpha]_D$ –19.4 (*c* 0.50, MeOH). (1*S*,4*R*)-**3** (2.43 g) was prepared starting from (1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (3.5 g, 13.2 mmol); $[\alpha]_D^{25.3}$ +20.0 (*c* 2.30, MeOH).



(2*R*,4*R*)-**4**

(2*R*,4*R*)-1,5-Dichloro-4-((triisopropylsilyl)oxy)pentan-2-ol (4). To a solution of dichloro diol (*R*,*R*)-**1** (1.00 g, 5.76 mmol) in THF (60 mL) at –78 ºC, *n*-BuLi (2.5 mL, 5.76 mmol, 2.5 M in hexanes) was added dropwise. The reaction mixture was stirred at –78 ºC for 30 min. Triisopropylsilyl chloride (1.11 g, 5.76 mmol) was added via syringe and the reaction mixture was brought to –40 ºC over 2 h. The reaction was allowed to stir at –40 ºC for 4 h and the progress of the reaction was monitored by TLC. The reaction was quenched with saturated aq NH_4Cl and was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 92% yield (1.74 g). R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.34–4.28 (m, 1H), 4.16–4.05 (m, 1H), 3.59 (dd, *J* = 10.9,

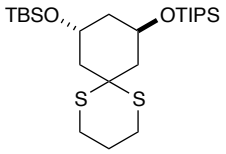
4.3 Hz, 1H), 3.57–3.51 (m, 2H), 3.49 (dd, J = 11.1, 6.2 Hz, 1H), 3.11 (s, 1H), 1.89–1.85 (m, 2H), 1.14–1.02 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.7, 68.1, 50.2, 47.2, 38.0, 18.1, 18.07, 12.6; *m/z* (ESI+) found $[M+H]^+$ 329.1470, $C_{14}H_{31}Cl_2O_2Si$ requires 329.1470; $[\alpha]_D^{24.2}$ +27.1 (*c* .86, DCM). (2*S*,4*S*)-**4** $[\alpha]_D^{23.9}$ –26.6 (*c* 1.0, DCM).



(1*R*,3*R*)-**5**

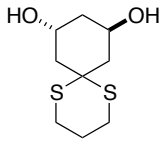
(((*R*)-1-Chloro-3-((*R*)-oxiran-2-yl)propan-2-yl)oxy)triisopropylsilane (5). To a solution of (2*R*,4*R*)-**4** (1.0 g, 3.0 mmol) in anhydrous Et_2O (25 mL) dry KOH powder (0.56 g, 9.9 mmol) was added at 0 ºC and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a bed of anhydrous $MgSO_4$, and the $MgSO_4$ was washed with diethyl ether. The filtrate was concentrated and was subjected to column chromatography to obtain the product as colorless oil in 97% yield (860 mg). R_f = 0.35 (30% EtOAc/hexanes); IR (neat) 2945, 2867, 2358, cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 4.24 (tt, J = 6.4, 4.6 Hz, 1H), 3.57 (dd, J = 4.5, 11.0 Hz, 1H), 3.53 (dd, J = 6.5, 11.0 Hz, 1H), 3.09 (dddd, J = 6.6, 5.1, 3.9, 2.7 Hz, 1H), 2.82 (dd, J = 5.1, 4.0 Hz, 1H), 2.55 (dd, J = 5.1, 2.7 Hz, 1H), 1.89 (ddd, J = 14.0, 6.2, 4.9 Hz, 1H), 1.86–1.79 (m, 1H), 1.12–1.03 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.8, 49.1, 48.4, 47.6, 38.2, 18.22, 18.20, 12.7; *m/z* (ESI+) found 293.1700 $[M+H]^+$, $C_{14}H_{30}ClO_2Si$ requires 293.1704; $[\alpha]_D^{25.3}$ +29.6 (*c* 2.3 , DCM).

By following above procedure, (2*S*,4*S*)-**4** (600 mg, 1.82 mmol) in anhydrous Et_2O (20 mL) on treatment with dry KOH powder (306 mg, 5.5 mmol) provided epoxide (1*S*,3*S*)-**5** as a colorless oil in 95% yield (506 mg). $[\alpha]_D^{24.4}$ –30.6 (*c* 1.1, DCM).



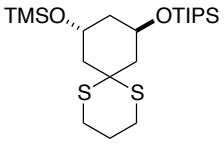
(8*R*,10*R*)-**6**

***tert*-Butyldimethyl(((8*R*,10*R*)-10-((triisopropylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane (6).** To a solution of *tert*-butyl(1,3-dithian-2-yl)dimethylsilane (46 mg, 0.19 mmol) in THF (0.9 mL), *n*-BuLi (0.086 mL, 2.5 M in hexanes), was added dropwise at room temperature. The resulting yellow solution was stirred for 15 min and was transferred dropwise via syringe to a solution of epoxide (1*R*,3*R*)-**5** (56 mg, 0.19 mmol) in THF/HMPA (0.9 mL/0.1 mL) precooled to –40 ºC. The reaction mixture was stirred at –40 ºC for 30 min and then was allowed to rise to room temperature for 16 h. The reaction was diluted with water and was extracted with Et_2O. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography to obtain the product as colorless oil in 88% yield (82 mg). R_f = 0.40 (5% EtOAc/hexanes); IR (neat) 2358, 2329 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (tt, *J* = 7.6, 3.6 Hz, 1H), 4.25 (tt, *J* = 6.2, 3.4 Hz, 1H), 2.91 (ddd, *J* = 14.4, 8.4, 3.5 Hz, 1H), 2.79 (ddd, *J* = 6.0, 3.8, 1.6 Hz, 2H), 2.74 (dt, *J* = 10.9, 3.6 Hz, 1H), 2.44 (d, *J* = 13.4 Hz, 1H), 2.13 (dd, *J* = 13.9, 3.5 Hz, 1H), 2.01–1.74 (m, 5H), 1.67 (ddd, *J* = 13.0, 7.9, 3.4 Hz, 1H), 1.07 (s, 21H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.0, 66.2, 48.6, 46.0, 45.6, 43.8, 26.8, 26.0, 25.6, 18.3, 18.2, 12.5, -4.7, -4.8; *m/z* (ESI+) found $[M+Na]^+$ 513.2685, $C_{24}H_{50}O_2S_2SiNa$ requires 513.2688; $[\alpha]_D^{25.3}$ –6.0 (*c* 1, DCM).



(8*R*,10*R*)-**7**

(8*R*,10*R*)-1,5-Dithiaspiro[5.5]undecane-8,10-diol (7). To a solution of (8*R*,10*R*)-**6** in THF (50 mg, 0.10 mmol), tetrabutylammonium fluoride (0.15 ml, 0.15 mmol, 1M solution in THF) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 94% yield (20 mg). R_f = 0.30 (30% EtOAc/hexanes); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29–4.22 (m, 2H), 3.00–2.85 (m, 6H), 2.27 (dd, *J* = 14.0, 6.8 Hz, 2H), 2.18 (dd, *J* = 14.0, 4.1 Hz, 2H), 2.02 (p, *J* = 5.7 Hz, 2H), 1.87 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.4, 48.3, 43.9, 42.3, 26.5, 25.3; *m/z* (ESI+) found $[M+H]^+$ 221.0672, $C_9H_{17}O_2S_2$ requires 221.0670; $[\alpha]_D^{25.3}$ +39.5 (*c* .85, DCM).

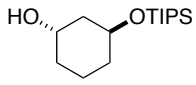


(8*R,10R*)-**8**

Triisopropyl(((8*R*,10*R*)-10-((trimethylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane (8). To a solution of (1,3-dithian-2-yl)trimethylsilane (36 mg, 0.18 mmol) in THF (0.5 mL), *n*-BuLi (0.092 mL, 0.21 mmoL) was added dropwise at room temperature. The resulting yellow solution was stirred for 15 min and was transferred

dropwise via syringe to a solution of epoxide (1*R*,3*R*)-**5** (50 mg, 0.17 mmol) in THF/HMPA (1.7 mL/0.8 mL) precooled to –40 ºC. The resulting light yellow solution was stirred at –40 ºC for 1 h and was then brought to room temperature for 16 h. The reaction mixture was diluted with water and was extracted with diethyl ether. The combined organic layer was washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography to obtain the product as colorless oil in 69% yield (55 mg). R_f = 0.35 (5% EtOAc/hexanes); IR (neat) 2358, 2329 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (td, *J* = 5.7, 2.9 Hz, 1H), 4.30 (dt, *J* = 8.0, 4.2 Hz, 1H), 2.93 (ddd, *J* = 14.4, 8.5, 3.6 Hz, 1H), 2.87–2.77 (m, 2H), 2.77–2.71 (m, 1H), 2.47–2.38 (m, 1H), 2.15 (dd, *J* = 14.1, 3.6 Hz, 1H), 2.05–1.87 (m, 3H), 1.81 (dt, *J* = 13.4, 8.4 Hz, 2H), 1.67 (ddd, *J* = 12.5, 8.2, 3.4 Hz, 1H), 1.08 (s, 21H), 0.13 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.2, 65.9, 48.7, 46.0, 45.7, 43.8, 26.8, 26.7, 25.6, 18.33, 18.29, 12.5, 0.2; *m/z* (ESI+) found $[M+Na]^+$ 471.2219, $C_{21}H_{44}O_2S_2Si_2Na$ requires 471.2219; $[\alpha]_D^{25.2}$ +103.5 (*c* 2.1, DCM).

By following above procedure, 500 mg (1.71 mmol) of the (1*S*,3*S*)-**5** was converted to (8*S*,10*S*)-**8** (1.1 g, 2.4 mmol). $[\alpha]_D^{25.3}$ –104.7 (*c* 2.3, DCM).

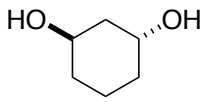


(1*S,3S*)-**9**

(1*S*,3*S*)-3-((Triisopropylsilyl)oxy)cyclohexanol (9). To a solution of (8*R*,10*R*)-**8** (50 mg, 0.11 mmol) in ethanol (1 mL), Raney Nickel (0.3 mL suspension in water) was added in one portion and the reaction mixture was heated to reflux for 4 h. Reaction did not go to completion in 4h [Note: In some cases, an additional 5 mL suspension of Raney

Nickel (washed with ethanol) was added and the reaction was refluxed for further 16 h.] The grey suspension was filtered through a plug of silica and the filtrate was concentrated. The crude reaction mixture was purified by column chromatography to obtain the product in 67% yield (20 mg, 0.085 mmol) as colorless oil. R_f = 0.32 (10% EtOAc/hexanes); IR (neat) 3378 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 4.22 (tt, *J* = 5.8, 3.1 Hz, 1H), 4.07 (td, *J* = 8.9, 4.3 Hz, 1H), 2.00–1.66 (m, 3H), 1.66– 1.42 (m, 7H), 1.41–1.19 (m, 2H), 1.13–0.92 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 68.2, 67.6, 43.5, 35.3, 34.3, 19.4, 18.6, 12.8; $[\alpha]_D^{25.3}$ +3.95 (*c* 2.1, EtOAc); *m/z* (ESI+) found $[M+Na]^+$ 295.2066, $C_{15}H_{32}NaO_2Si$ requires 295.2069. Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30 m × 0.25 mm × 0.12 mm, temperature 145 ºC, $t_{S,S}$ = 10.76 min, $t_{R,R}$ = 11.40 min, *er* > 99:1.

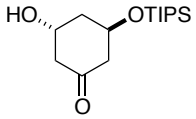
Similarly, 1.02 g (2.28 mmol) of the triisopropyl (((8*S*,10*S*)-10-((trimethylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane in ethanol (20 mL) was treated with Raney-Nickel (5 mL of 50% aq suspension washed with ethanol) to provide (1*R*,3*R*)-**9** as colorless oil (430 mg, 1.35 mmol). $[\alpha]_D^{25.3}$ –4.25 (*c* 2.3, EtOAc); *er* >99:1.



(1*R,3R*)-**20**

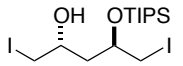
(1*R*,3*R*)-Cyclohexane-1,3-diol (20). To a solution of (1*R*,3*R*)-**9** (410 mg, 1.50 mmol) in THF (15 mL), tetrabutylammonium fluoride (2.3 ml, 2.3 mmol, 1M solution in THF) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and

concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 91% yield (20 mg). R_f = 0.2 (100% EtOAc); IR (neat) 3378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15–4.06 (m, 2H), 1.83–1.55 (m, 8H), 1.52–1.35 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ67.1, 42.2, 33.9, 18.9; $[\alpha]_D^{25.3}$ –3.5 (*c* 2.0, DCM); *m/z* (ESI+) found $[M+Na]^+$ 139.0734, $C_6H_{12}NaO_2$ requires 139.0735.



(3*R*,5*R*)-**10**

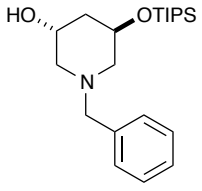
(3*S*,5*S*)-3-Hydroxy-5-((triisopropylsilyl)oxy)cyclohexanone (10). To a solution of (8*R*, 10*R*)-**8** (50 mg, 0.11 mmol) in acetonitrile (0.5 mL), $HgCl_2$ (59 mg, 0.22 mmol) was added in one portion and the reaction mixture was stirred vigorously at room temperature for 16 h. The white suspension was filtered through a plug of silica and the filtrate was concentrated. The crude reaction mixture was purified by column chromatography to obtain the product in 77% yield (24 mg, 0.085 mmol) as colorless oil. R_f = 0.33 (50% EtOAc/hexanes); IR (neat) 3380, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (tt, *J* = 6.3, 3.4 Hz, 1H), 4.43 (t, *J* = 4.0 Hz, 1H), 2.72 (ddt, *J* = 14.2, 4.6, 1.6 Hz, 1H), 2.56 (ddt, *J* = 14.3, 4.0, 1.2 Hz, 1H), 2.47 (ddt, *J* = 14.2, 5.6, 1.5 Hz, 1H), 2.38 (ddd, *J* = 14.2, 8.2, 1.2 Hz, 1H), 2.18 (dddt, *J* = 13.1, 6.5, 3.8, 1.4 Hz, 1H), 2.00–1.92 (m, 1H), 1.64 (s, 1H), 1.13–0.96 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 67.1, 66.5, 50.4, 50.0, 41.7, 18.1, 12.3; *m/z* (ESI+) found $[M+Na]^+$ 309.1859, $C_{15}H_{30}O_2SiNa$ requires 309.1862; $[\alpha]_D^{25.3}$ +42.5 (*c* 1.1, DCM).



(2*R*,4*R*)-**11**

(2*R*,4*R*)-1,5-Diiodo-4-((triisopropylsilyl)oxy)pentan-2-ol (11). A mixture of dichorodiol (2*R*,4*R*)-**4** (300 mg, 0.91 mmol) and NaI in acetone was allowed to reflux for 24 h. The reaction mixture was concentrated and was subjected to column chromatography to obtain the diiodo product as colorless oil in 92% yield (428 mg). R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (ddt, *J* = 8.0, 5.7, 4.1 Hz, 1H), 3.93–3.83 (m, 1H), 3.60 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.54 (dd, *J* = 11.0, 8.1 Hz, 1H), 3.31 (dd, *J* = 10.1, 4.5 Hz, 1H), 3.22 (dd, *J* = 10.1, 6.1 Hz, 1H), 3.20–3.16 (m, 1H), 1.99 (ddd, *J* = 14.4, 5.7, 2.4 Hz, 1H), 1.85 (ddd, *J* = 14.1, 10.2, 3.5 Hz, 1H), 1.10–1.05 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.0, 67.6, 46.8, 40.0, 18.2, 18.1, 15.2, 12.5; *m/z* (ESI+) found $[M+H]^+$ 513.0180, $C_{14}H_{31}I_2O_2Si$ requires 513.0183; $[\alpha]_D^{25.3}$ +16.7 (*c* 1.2 , DCM).

By following above procedure, (2*S*,4*S*)-**4** was obtained in 90% yield using (2*S*,4*S*)-**2.14.1** (1.5 g, 4.5 mmol). $[\alpha]_D^{25.3}$ –16.5 (*c* 0.53, DCM).



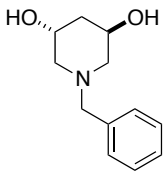
(3*R*,5*R*)-**12**

(3*R*,5*R*)-1-Benzyl-5-((triisopropylsilyl)oxy)piperidin-3-ol (12).

To a solution of diiodo diol (2*R*,4*R*)-**4** (50 mg, 0.097) in ethanol, benzylamine (0.013 mL, 0.12 mmol) was added and the resulting mixture was refluxed for 16 h at 100 ºC. The reaction mixture was diluted with water and was extracted with ethyl acetate. The

combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 88% yield (31 mg, 0.69 mmol). R_f = 0.35 (30% EtOAc/hexanes); IR (neat) 3310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 4.09 (tt, *J* = 9.7, 4.7 Hz, 1H), 3.95 (s, 1H), 3.56 (d, *J* = 3.0 Hz, 2H), 2.95 (ddt, *J* = 10.8, 3.8, 1.8 Hz, 1H), 2.76 (ddt, *J* = 11.4, 3.8, 1.8 Hz, 1H), 2.50 (d, *J* = 10.3 Hz, 1H), 2.19 (dd, *J* = 11.5, 1.9 Hz, 1H), 2.14 (td, *J* = 5.3, 4.4, 3.2 Hz, 1H), 1.93 (dd, *J* = 10.7, 9.4 Hz, 1H), 1.38 (ddd, *J* = 13.2, 10.4, 2.9 Hz, 1H), 1.08–0.91 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 129.1, 128.4, 127.3, 66.3, 65.4, 62.4, 61.4, 59.0, 41.3, 18.2, 12.4; *m/z* (ESI+) found $[M+H]^+$ 364.2676, $C_{21}H_{38}NO_2Si$ requires 364.2672. $[\alpha]_D^{25.3}$ +19.3 (*c* 2.1, EtOH).

Similarly, a mixture of (2*S*,4*S*)-**4** (710 mg, 1.38 mmol) on treatment with benzyl amine (1.66 mmol, 0.18 mL) in ethanol (40 mL) provided (3*S*,5*S*)-1-benzyl-5-((triisopropylsilyl)oxy)piperidin-3-ol as colorless oil in 80% yield (402 mg, 1.11 mmol); $[\alpha]_D^{24.2}$ –20.2 (*c* 1.0, EtOH).

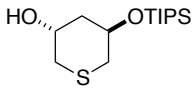


(3*R,5R*)-**13**

(3*R*,5*R*)-1-Benzylpiperidine-3,5-diol (13). To a solution of (3*R*,5*R*)-**12** (300 mg, 0.83 mmol) in THF 1M tetrabutylammonium fluoride (1.2 mL, 1.2 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture

was purified by column chromatography to obtain the product as light brown oil in 94% yield (161 mg, 0.78 mmol). R_f = 0.2 (5% MeOH/DCM); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 4.06–3.98 (m, 2H), 3.64–3.54 (m, 2H), 2.80–2.48 (m, 2H), 2.45–2.27 (m, 2H), 2.13 (s, 2H), 1.82–1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 129.3, 128.6, 127.6, 65.3, 62.4, 59.8, 40.4; *m/z* (ESI+) found $[M+H]^+$ 208.1337, $C_{12}H_{18}NO_2$ requires 208.1338; $[\alpha]_D^{25.3}$ +16.7 (*c* 2.0, EtOH). HPLC (Chiralpak IC column *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, $t_{R,R}$ = 23.06 min, *er* >99:1).

Similarily, a solution of (3*S*,5*S*)-**12** (395 mg, 1.08 mmol) in THF, on treatment with tetrabutylammonium fluoride (1.8 mL, 1M in THF) provided (3*S*,5*S*)-**13** as colorless oil in 92% yield (220 mg, 1.0 mmol); $[\alpha]_D^{23.2}$ –16.7 (*c* 1.1, EtOH); $t_{S,S}$ = 24.93, *er* >99:1.

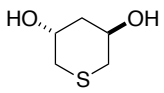


(3*R,5R*)-**14**

(3*R*,5*R*)-5-((Triisopropylsilyl)oxy)thian-3-ol (14). To a solution of diiodo diol (2*R*,4*R*)-**11** (50 mg, 0.15 mmol) in ethanol (1 mL), aqueous sodium sulfide (120 mg, 1.5 mmol) was added and the resulting mixture was refluxed for 16 h at 100 ºC. The solvent was evaporated and the reaction mixture was extracted with ethyl acetate. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as light yellow oil in 88% yield (38 mg, 0.13 mmol). R_f = 0.35 (20% EtOAc/hexanes); IR (neat) 3421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (m, 1H), 4.03 (m, 1H), 3.82–3.67 (m, 2H), 2.90–2.77 (m, 1H), 2.77–2.63 (m, 1H), 2.26 (ddd, *J* = 13.4, 7.4, 6.3 Hz, 1H),

1.82 (ddd, J = 13.0, 5.7, 3.6 Hz, 1H), 1.25 (s, 1H), 1.08–1.01 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 78.8, 76.0, 73.0, 41.1, 37.9, 18.2, 12.2; *m/z* (ESI+) found $[M+H]^+$ 291.1814, $C_{14}H_{31}O_2SSi$ requires 291.1814; $[\alpha]_D^{25.3}$ +26.6 (*c* 0.85, DCM). Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30m × 0.25 mm × 0.12 mm, temperature 160 ºC, $t_{R,R}$ = 13.67 min, $t_{S,S}$ = 14.53 min, $er_{R,R}$ 97:3.

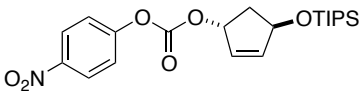
In an identical manner as described above, a solution of (2*S*,4*S*)-**11** (1.23 g, 2.41 mmol) in ethanol (40 mL), aqueous sodium sulfide (1.88 g, 24.1 mmol) on refluxing for 20 h at 100 ºC, followed by column chromatography provided (3*S*,5*S*)-**14** as light yellow oil in 87% yield (618 mg, 2.12 mmol). $[\alpha]_D^{24.2}$ –26.5 (*c* 1.0, DCM); $er_{S,S}$ 97:3.



(*R,R*)-**15**

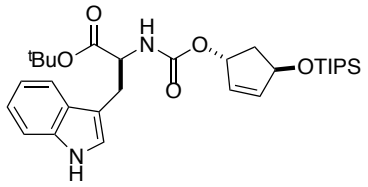
(3*R*,5*R*)-Thiane-3,5-diol (15). To a solution of (3*R*,5*R*)-**14** (312 mg, 1.21 mmol) in THF, tetrabutylammonium fluoride (1.8 mL, 1M in THF) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless viscous mass in 92% yield (149 mg, 1.1 mmol). R_f = 0.25 (100% EtOAc); IR (neat) 3306 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21–4.02 (m, 2H), 2.65 (ddd, J = 13.3, 3.1, 1.0 Hz, 2H), 2.44 (ddd, J = 13.3, 7.4, 1.1 Hz, 2H), 2.23 (s, 2H), 1.73 (t, J = 5.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.6, 41.6, 35.3; *m/z* (ESI+) found $[M+Na]^+$ 157.0297, $C_5H_{10}NaO_2S$ requires 157.0299; $[\alpha]_D^{23.8}$ +22.3 (*c* 2.1, EtOH).

Similarly, a solution of (3*S*,5*S*)-**14** (618 mg, 1.21 mmol) in THF, on treatment with tetrabutylammonium fluoride (1.8 mL, 1M in THF) provided (3*S*,5*S*)-**15** as colorless viscous mass in 92% yield (149 mg, 1.1 mmol); $[\alpha]_D^{23.2}$ –22.9 (*c* 1.1, EtOH).



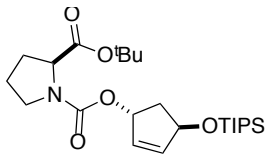
(1*R,4R*)-**16**

4-Nitrophenyl ((1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) carbonate (16). To a solution of (1*R,*4*R*)-**3** (3.5 g, 13.6 mmol) in THF (136 mL), at -78 ºC, *n*-BuLi (5.4 mL, 2.5 M in hexanes) was added dropwise. The solution was stirred for 30 minutes at –78 ºC and a solution of 4-nitrophenyl chloroformate (5.48 g, 27.2 mmol, in 20 mL THF) was added to it quickly. The reaction mixture was stirred at –78 ºC for 1 h and was quenched with saturated ammonium chloride while reaction still at –78 ºC. The reaction was extracted with diethyl ether. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 77% yield (4.4 g). R_f = 0.45 (10% EtOAc/hexanes); IR (neat) 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 9.2 Hz, 2H), 6.14 (dt, *J* = 5.6, 1.6 Hz, 1H), 5.99 (ddd, *J* = 5.6, 1.9, 1.3 Hz, 1H), 5.51 (ddt, *J* = 7.3, 5.0, 1.0 Hz, 1H), 4.84 (ddt, *J* = 6.9, 4.8, 1.0 Hz, 1H), 2.94 (dt, *J* = 14.0, 7.3 Hz, 1H), 1.85 (dt, *J* = 13.9, 4.9 Hz, 1H), 1.31 – 0.71 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 152.3, 145.5, 143.4, 129.7, 125.4, 121.9, 84.6, 76.2, 41.6, 18.1, 12.2; *m/z* (ESI+) found $[M+H]^+$ 422.1999, $C_{21}H_{32}NO_6Si$ requires 422.1999; $[\alpha]_D^{25.3}$ +23.5 (*c* 0.95, DCM).



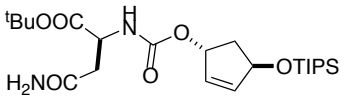
17a

(1*R*,4*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-ene-1-yl-(*tert*-butyl-L-tryptophanate)carbamate (**17a**). To a solution of the carbonate (1*R*,4*R*)-**16** (758 mg, 1.80 mmol) in THF (20 mL), *N*,*N*'-dimethyl aminopyridine (22 mg, 0.18 mmol), Hunig's base (0.63 mL, 3.6 mmol) and *tert*-butyl-L-tryptophanate hydrochloride (641 mg, 2.16 mmol) were added and the reaction mixture was heated at 80 ºC for 18 h. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, ethyl acetate/hexane as eluent) to obtain the product **17a** in 84% yield (819 mg, 1.51 mmol). R_f = 0.2 (30% EtOAc/hexanes); IR (neat) 1747, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.40–7.29 (m, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.04 (dd, *J* = 5.8, 1.8 Hz, 1H), 5.93 (dt, *J* = 5.9, 1.7 Hz, 1H), 5.74 (dt, *J* = 7.2, 2.3 Hz, 1H), 5.18 (d, *J* = 8.1 Hz, 1H), 5.13–5.06 (m, 1H), 4.59 (dt, *J* = 8.2, 5.8 Hz, 1H), 3.27 (qd, *J* = 14.8, 5.8 Hz, 2H), 2.16 (ddd, *J* = 14.5, 5.4, 2.6 Hz, 1H), 2.11–2.02 (m, 1H), 1.38 (s, 9H), 1.06 (d, *J* = 4.3 Hz, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 155.9, 140.9, 136.2, 131.8, 128.0, 122.8, 122.2, 119.6, 119.1, 111.2, 110.5, 82.1, 79.7, 76.4, 55.1, 41.7, 28.1, 18.1, 12.2; *m/z* (ESI+) found $[M+H]^+$ 543.3255, $C_{30}H_{47}N_2O_5Si$ requires 543.3254; $[\alpha]_D^{23.6}$ +232 (*c* 1.0, DCM).



17b

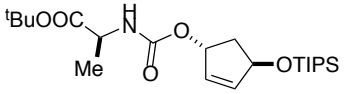
(1*R*,4*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-ene-1-yl-(*tert*-butyl-L-prolinate)carbamate (**17b**). Following similar procedure as mentioned for **17a**, the carbonate (1*R*,4*R*)-**16** (800 mg, 1.90 mmol) on treatment with *tert*-butyl-L-prolinate hydrochloride (474 mg, 2.28 mmol) provided carbamate **17b** in 82% yield (1.56 mmol, 706 mg) as colorless oil. R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1749, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06–5.91 (m, 4H), 5.83 (d, *J* = 8.4 Hz, 1H), 5.69 (m, 1H), 5.10 (ddd, *J* = 6.7, 4.1, 2.0 Hz, 1H), 4.39 (dt, *J* = 9.0, 4.7 Hz, 1H), 2.85 (dd, *J* = 16.0, 5.1 Hz, 1H), 2.70 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.18 (ddd, *J* = 14.4, 6.7, 2.3 Hz, 1H), 2.05 (ddd, *J* = 14.4, 7.0, 4.0 Hz, 1H), 1.42 (s, 10H), 1.08–0.99 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 170.2, 156.4, 141.0, 131.7, 126.2, 115.8, 82.5, 79.9, 76.4, 51.3, 41.6, 37.6, 28.0, 18.0, 12.2; *m/z* (ESI+) found $[M+H]^+$ 454.2985, $C_{24}H_{44}NO_5Si$ requires 454.2989; $[\alpha]_D^{23.6}$ +179 (*c* 1.0, DCM).



17c

(1*R*,4*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-ene-1-yl-(*tert*-butyl-L-asparaginate)carbamate (**17c**). Following similar procedure as mentioned for **17a**, the carbonate (1*R*,4*R*)-**16** (807 mg, 1.92 mmol) on treatment with *tert*-butyl-L-asparaginate hydrochloride (453 mg mg, 2.30 mmol) provided carbamate **17c** in 79% yield (1.52 mmol, 713 mg) as colorless oil. R_f = 0.32 (70% EtOAc/hexanes); IR (neat) 1745, 1715

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (ddd, *J* = 5.8, 1.8, 0.8 Hz, 1H), 5.99 (m, 2H), 5.95–5.87 (m, 1H), 5.83 (d, *J* = 8.4 Hz, 1H), 5.74–5.65 (m, 1H), 5.08 (m, 1H), 4.40 (m, 1H), 2.85 (dd, *J* = 15.9, 5.1 Hz, 1H), 2.69 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.18 (ddd, *J* = 16.6, 8.9, 2.3 Hz, 1H), 2.04 (ddd, *J* = 14.4, 7.0, 4.0 Hz, 1H), 1.42 (s, 9H), 1.06–0.95 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 170.3, 156.4, 141.1, 140.2, 82.5, 79.9, 76.3, 51.3, 41.6, 29.9, 28.0, 18.1, 12.1; *m/z* (ESI+) found $[M+H]^+$ 471.2990, $C_{23}H_{43}N_2O_6Si$ requires 471.2989; $[\alpha]_D^{23.6}$ +89 (*c* 1.1, MeOH).



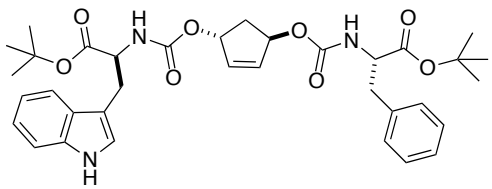
17d

(1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-ene-1-yl-((*tert*-butyl-L-alaninate)carbamate (**17d**). Following similar procedure as mentioned for **17a**, the carbonate (1*R*,4*R*)-**16** (803 mg, 1.91 mmol) on treatment with *tert*-butyl-L-alaninate hydrochloride (415 mg, 2.29 mmol) provided carbamate **17d** in 83% (677 mg, 1.58 mmol) yield as colorless oil. R_f = 0.40 (20% EtOAc/hexanes); IR (neat) 1747, 1711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (ddd, *J* = 5.6, 2.0, 0.6 Hz, 1H), 5.92 (ddd, *J* = 5.6, 2.3, 1.3 Hz, 1H), 5.75–5.65 (m, 1H), 5.22 (m, 1H), 5.09 (qd, *J* = 3.8, 1.7 Hz, 1H), 4.18–4.01 (m, 1H), 2.17 (ddd, *J* = 14.4, 6.7, 2.3 Hz, 1H), 2.05 (ddd, *J* = 14.5, 7.0, 4.0 Hz, 1H), 1.42 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.12–0.93 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 155.7, 140.8, 131.8, 81.8, 79.6, 76.4, 50.1, 41.7, 28.0, 19.0, 18.0, 12.2; *m/z* (ESI+) found $[M+H]^+$ 428.2832, $C_{22}H_{42}NO_5Si$ requires 428.2832; $[\alpha]_D^{23.6}$ –69.7 (*c* 1.2, DCM).

Library Synthesis

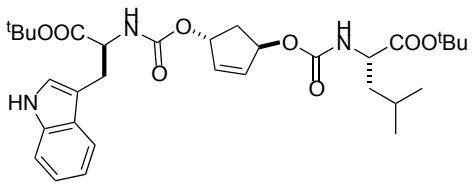
Step I. The TIPS-protected alcohols **17a–17d** (1.5 mmol) were treated with tetrabutylammonium fluoride (3 mL, 3.0 mmol, 1M in THF)) for 2h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered and concentrated to obtain the corresponding unprotected alcohols, which were used as starting for the next step without purification.

Step II. In a 24-well heat transfer block, 2 dram glass vials were placed. Each vial was charged with the appropriate alcohol (50 mg) obtained in step I, the appropriate amino acid isocyanate (3 eq) and *N,N'*-DMAP (0.1 equiv) were added. The vials were flushed with nitrogen gas and closed with the teflon coated caps. The block was heated to 100 ºC for 2 h. The reactions were cooled to room temperature and 2 mL of dichloromethane was added to each vial. Each of the reaction mixture was transferred to reaction tubes charged with tris-(2-aminoethyl)-amine polymer-bound resin (500 mg of loading to each reaction tube) on a 24-well (4 × 6) reaction array. The contents were filtered through the resin, which was then washed with dichloromethane (2 mL). The reaction contents were collected in collection tubes and the solvent was evaporated by purging with nitrogen gas. The crude reaction mixtures on subjecting to mass-directed purification produced 18 compounds in >90% purity and amounts in the range of 5-71 mg.



18a

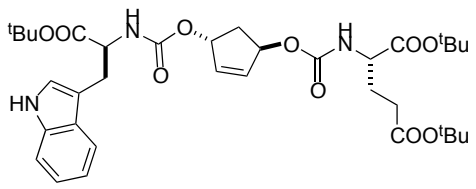
(1*R*,4*R*)-1-((*tert*-butyl-L-tryptophanate-)-4-((*tert*-butyl-L-phenylalaninate)cyclopent-2-ene-1,4-diyl biscarbamate (18a). Yield 29%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1749, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.34–7.24 (m, 3H), 7.24–7.10 (m, 4H), 7.02 (m, 1H), 6.06 (s, 2H), 5.73 (d, *J* = 5.9 Hz, 2H), 5.22 (dd, *J* = 20.4, 8.3 Hz, 2H), 4.77–4.49 (m, 2H), 3.37–3.18(m, 2H), 3.14–3.00 (m, 2H), 2.14 (t, *J* = 5.1 Hz, 2H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 171.1, 170.7, 155.7, 136.2, 135.6, 129.6, 128.5, 127.9, 127.1, 122.8, 122.2, 119.6, 118.9, 111.3, 110.4, 82.4, 82.1, 79.1, 78.9, 60.5, 55.3, 53.5, 38.6, 37.9, 28.1, 21.1, 14.3; *m/z* (ESI+) found $[M+H]^+$ 634.3130, $C_{35}H_{44}N_3O_8$ requires 634.3128; $[\alpha]_D^{22.9}$ +112 (*c* 1.0, DCM).



18c

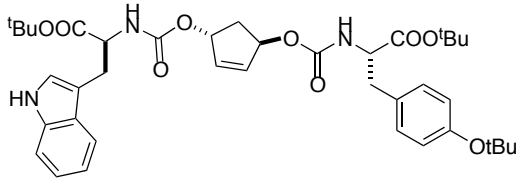
(1*R*,4*R*)-1-((*tert*-butyl-L-tryptophanate-)-4-((*tert*-butyl-L- leucinate)cyclopent-2-ene-1,4-diyl biscarbamate (18c). Yield 44%; R_f = 0.2 (30% EtOAc/hexanes); IR (neat) 1749, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (m, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.21 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.22–5.92 (m, 2H), 5.84–5.51 (m, 2H), 5.15 (m, 2H), 4.72–4.20 (m, 1H), 3.39–3.16 (m, 2H), 2.17 (m, 2H), 1.78–1.55 (m, 1H), 1.48 (s, 9H), 1.41 (s, 9H), 1.04–0.88 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 171.2, 155.7, 136.2, 135.8, 135.6, 127.9, 122.8, 122.3, 119.7, 119.0, 111.3, 110.5, 100.1, 82.1, 82.0, 79.0, 55.1, 42.2, 38.0, 29.8, 28.1, 28.07, 25.0, 23.0, 22.1, 21.2; *m/z* (ESI+) found $[M+H]^+$ 600.3285,

$C_{32}H_{46}N_3O_8$ requires 600.3285; $[\alpha]_D^{23.0}$ –143.9 (*c* 1.0, DCM).



18e

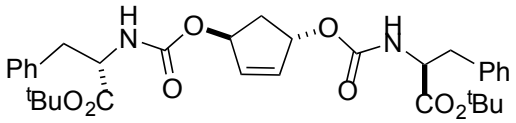
(1*R*,4*R*)-1-(*tert*-butyl-L-tryptophanate)-4-((di-*tert*-butyl-L-glutamate)cyclopent-2-ene-1,4-diyl biscarbamate (18e). Yield 62%; R_f = 0.4 (30% EtOAc/hexanes); IR (neat) 1748, 1714, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.07 (s, 2H), 5.87–5.48 (m, 2H), 5.43–5.17 (m, 2H), 4.74–4.20 (m, 2H), 3.37–3.16 (m, 2H), 2.50–2.12 (m, 5H), 1.99–1.81 (m, 1H), 1.48 (s, 9H), 1.47 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.2, 155.9, 155.7, 136.2, 135.7, 135.6, 127.9, 122.9, 122.2, 119.6, 118.9, 111.3, 110.7, 110.3, 82.4, 82.1, 80.8, 79.1, 78.9, 55.1, 54.0, 37.8, 31.6, 28.2, 28.1, 28.0, 21.1, 14.3; *m/z* (ESI+) found $[M+H]^+$ 672.3490, $C_{35}H_{50}N_3O_{10}$ requires 672.3496; $[\alpha]_D^{23.6}$ +249 (*c* 1.0, DCM).



18f

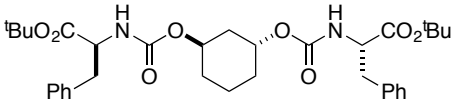
(1*R*,4*R*)-1-(*tert*-butyl-L-tryptophanate)-4-(di-*tert*-butyl-L-tyrosinate)cycopent-2-ene-1,4-diyl-biscarbamate (18f). Yield 67%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1748,

1728, 1715, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (m, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.09–6.98 (m, 3H), 6.91 (d, *J* = 8.1 Hz, 2H), 6.05 (s, 2H), 5.87–5.47 (m, 2H), 5.25–4.87 (m, 2H), 4.72–4.21 (m, 2H), 3.34–3.14 (m, 2H), 3.02 (d, *J* = 6.1 Hz, 2H), 2.23–2.07 (m, 2H), 1.38 (s, 9H), 1.38 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.7, 155.7, 155.6, 154.5, 136.2, 135.7, 131.1, 130.1, 127.9, 124.2, 122.8, 122.3, 121.7, 119.7, 119.0, 111.3, 110.5, 82.4, 82.2, 79.1, 78.9, 78.6, 55.3, 55.1, 38.1, 37.9, 29.0, 28.1, 21.2, 14.2; *m/z* (ESI+) found $[M+H]^+$ 706.3703, $C_{39}H_{52}N_3O_9$ requires 706.3704; $[\alpha]_D^{23.6}$ –219 (*c* 1.6, MeOH).



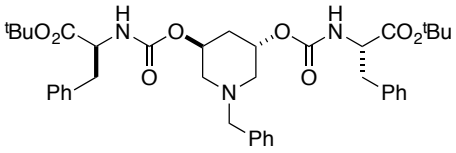
21

(1*R*,3*R*)-Cyclopent-4-ene-1,3-diyl-bis(*tert*-butyl-L-phenylalaninate)carbamate (21). In a 2 dram vial 30 mg of diol, 0.1 mL THF, *tert*-butyl (*S*)-2-isocyanato-3-phenylpropanoate and *N*,*N*-dimethylaminopyridine were added. The mixture was heated at 100 ºC for 2 h. The reaction was cooled to room temperature and the crude reaction mixture was purified by silica-gel chromatography. Yield 66%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat), 1744, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.37–7.20 (m, 6H), 7.17 (d, *J* = 8.0 Hz, 4H) 6.07–5.97 (m, 2H), 5.79–5.64 (m, 2H), 5.18 (m, 2H), 4.51–4.21 (m, 2H), 3.16–2.86 (m, 4H), 2.17 (t, *J* = 5.1 Hz, 2H), 1.41 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ170.6, 155.5, 136.2, 135.6, 129.5, 128.5, 127.1, 82.3, 79.0, 55.2, 38.6, 37.8, 28.0; (*m/z* (ESI+) found $[M+H]^+$ 595.3018, $C_{33}H_{43}N_2O_8$ requires 595.3019; $[\alpha]_D^{24.2}$ +139 (*c* 1.0, DCM).



22

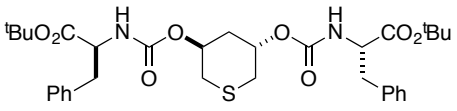
(1*R*,3*R*)-Cyclohexane-1,3-diyl-bis(*tert*-butyl-L-phenylalaninate)carbamate (22). Following similar procedure as mentioned for **21**, the diol (1*R*,3*R*)-**20** on treatment with *tert*-butyl (*S*)-2-isocyanato-3-phenylpropanoate provided carbamat**e 22** in 62% yield as colorless oil in 62% yield. R_f = 0.3 (25% EtOAc/hexanes); IR (neat) 1746, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.62–7.19 (m, 6H), 7.19–7.10 (m, 4H), 5.12 (d, *J* = 7.2 Hz, 2H), 4.73–4.23 (m, 4H), 3.25–2.80 (m, 4H), 2.36–2.13 (m, 2H), 2.05–1.84 (m, *J* = 5.9, 1H), 1.39 (s, 18H), 1.62–0.95 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.0, 136.2, 129.5, 128.4, 126.9, 82.2, 71.2, 55.0, 38.4, 31.1, 27.9, 20.0; *m/z* (ESI+) found $[M+H]^+$ 611.3330, $C_{34}H_{47}N_2O_8$ requires 611.3332; $[\alpha]_D^{23.6}$ +275 (*c* 1.0, DCM).



23

(3*R*,5*R*)-1-Benzylpiperidine-3,5-diyl-bis(*tert*-butyl-L-phenylalaninate)carbamate (23). Following similar procedure as mentioned for biscarbamate **21**, the diol (S,*S*)-**20** on treatment with *tert*-butyl (*S*)-2-isocyanato-3-phenylpropanoate provided carbamat**e 23** in 51% yield as colorless oil. R_f = 0.3 (50% EtOAc/hexanes); IR (neat) 1744, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.36–7.12 (m, 9H), 7.12–7.03 (m, 6H) 5.11(d, *J* = 7.4 Hz,

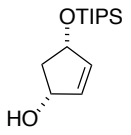
2H), 4.89 (m, 2H), 4.54–4.20 (m, 2H), 3.62–3.37 (m, 2H), 2.97 (d, J = 6.1 Hz, 4H), 2.62–2.46 (m, 2H), 2.42–2.24 (m, 2H), 1.84–1.52 (m, 2H), 1.31 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 155.1, 137.4, 136.3, 129.6, 129.1, 128.5, 128.4, 127.3, 127.0, 82.3, 68.5, 62.3, 56.1, 55.3, 38.7, 34.5, 28.0; *m/z* (ESI+) found $[M+H]^+$ 702.3749, $C_{40}H_{52}N_3O_8$ requires 702.3754; $[\alpha]_D^{23.6}$ +109.7 (*c* 1.0, DCM).



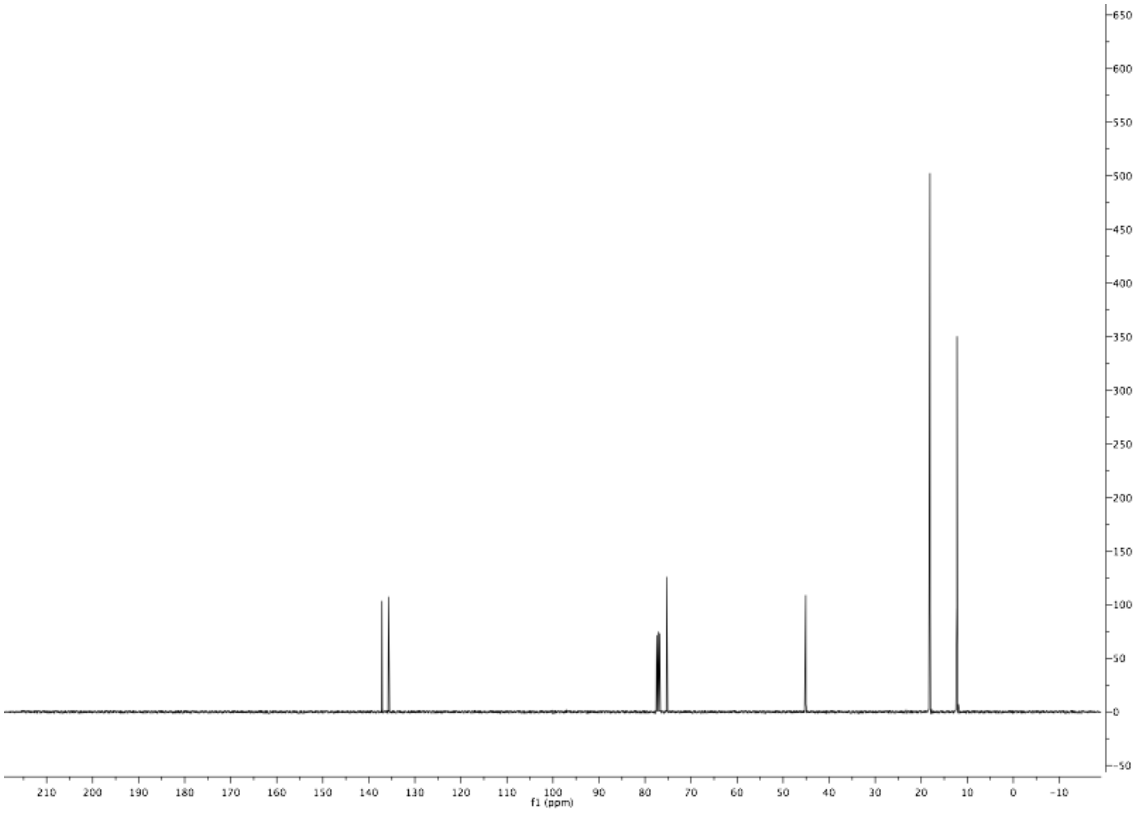
24

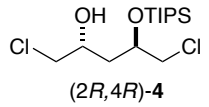
(3*S*,5*S*)-Thiane-3,5-diyl-bis(*tert*-butyl-L-phenylalaninate)carbamate (24).

Following similar procedure as mentioned for biscarbamate **21**, the diol (S,*S*)-**20** on treatment with *tert*-butyl (*S*)-2-isocyanato-3-phenylpropanoate provided carbamate **24** in 57% yield as colorless oil. Yield 57%; R_f = 0.4 (50% EtOAc/hexanes); IR (neat) 1747, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.32–7.19 (m, 6H), 7.19–7.12 (m, 4H), 5.30–4.93 (m, 4H), 4.55–4.33 (m, 2H), 3.16–2.91 (m, 4H), 2.78–2.65 (m, 2H), 2.59–2.48 (m, 2H), 1.87–1.68 (m, 2H), 1.40 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ170.5, 154.7, 136.2, 129.6, 128.5, 127.1, 82.4, 69.1, 55.3, 38.7, 36.0. 31.6, 28.1; (*m/z* (ESI+) found $[M+H]^+$ 629.2899, $C_{33}H_{45}N_2O_8S$ requires 629.2897; $[\alpha]_D^{23.7}$ –129 (*c* 1.7, DCM).

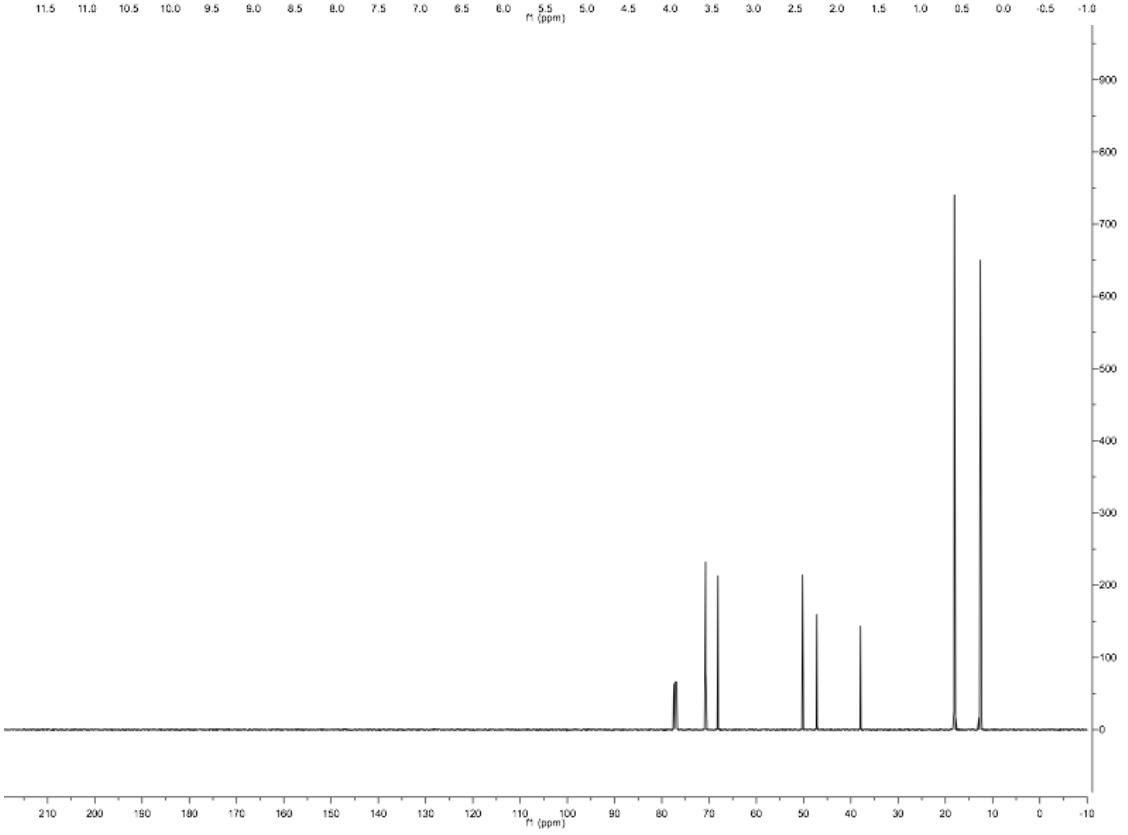


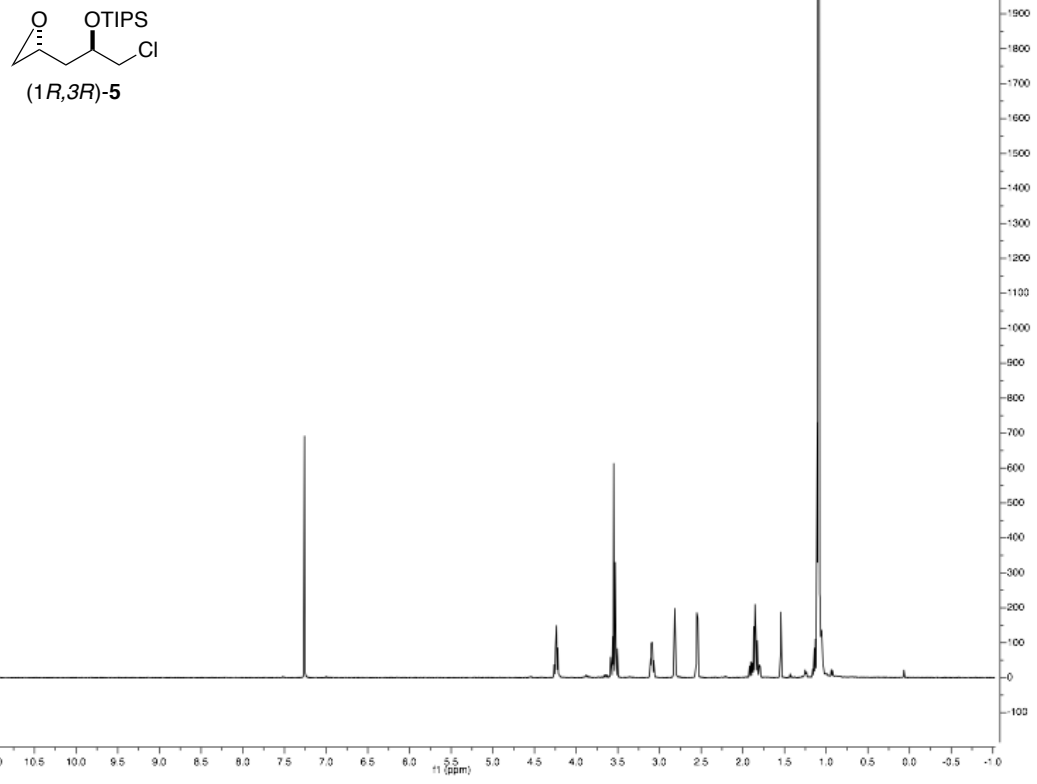
(1*R*,4*S*)-**3**



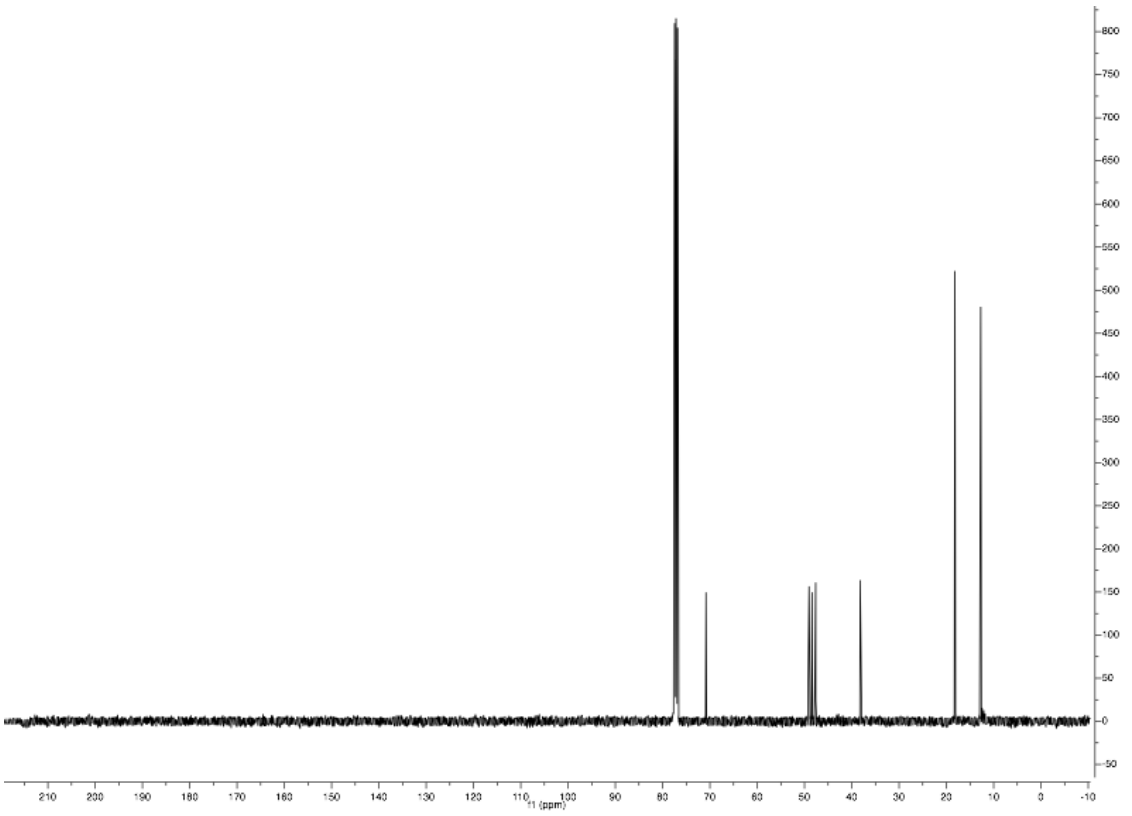


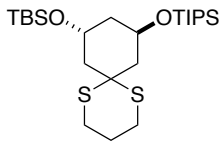
(2*R*,4*R*)-**4**



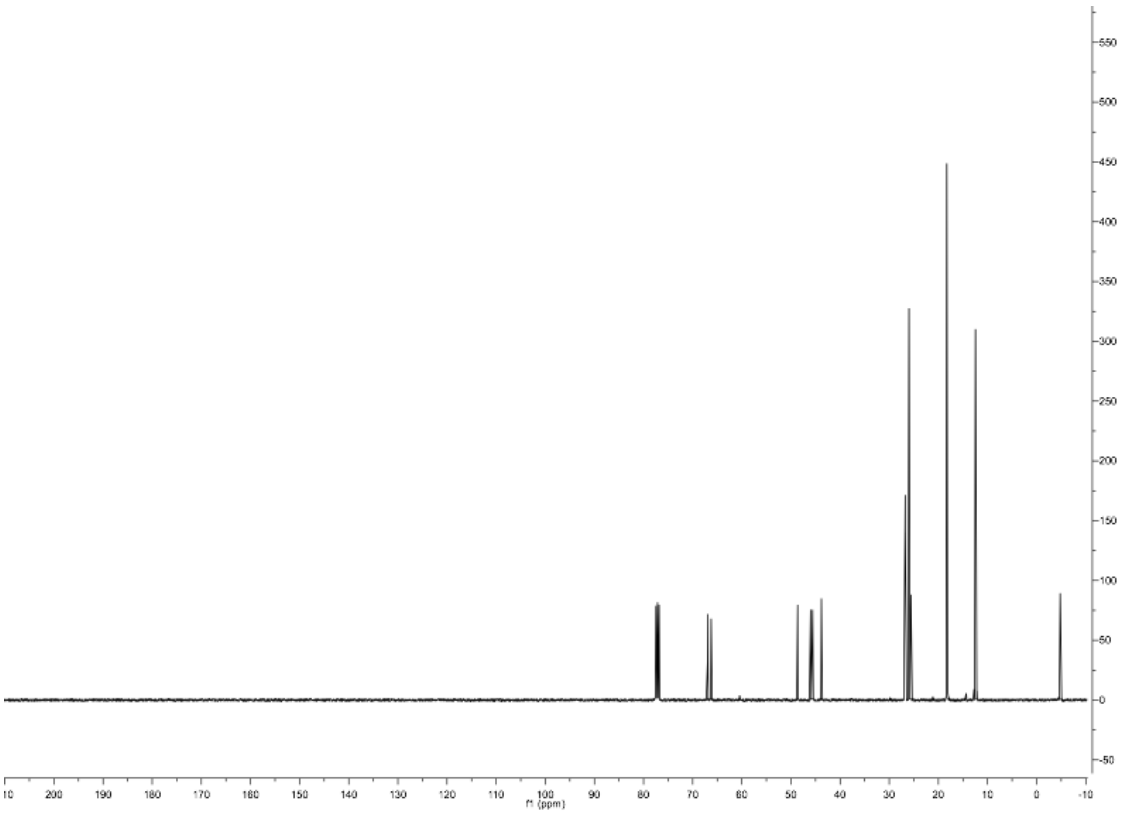


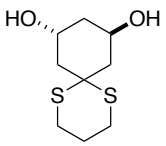
(1*R*,3*R*)-**5**



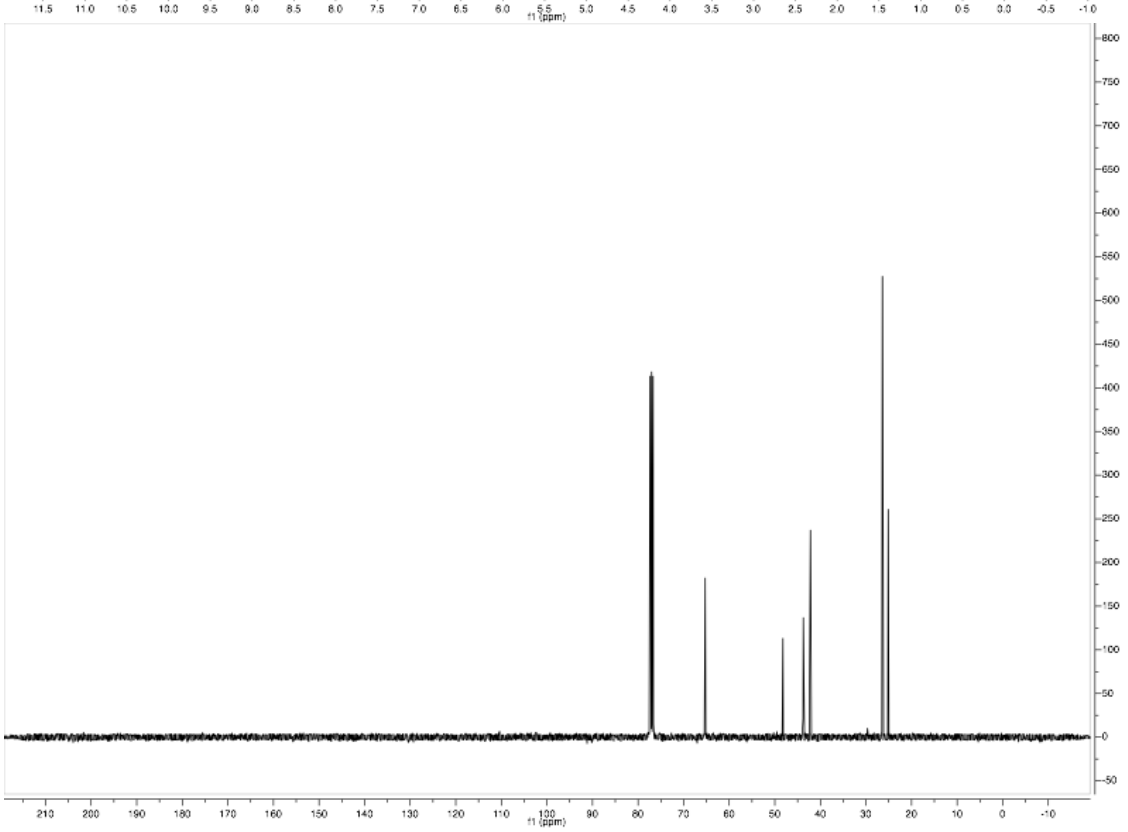


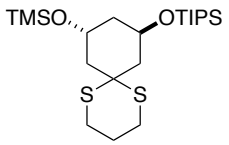
(8*R*,10*R*)-**6**



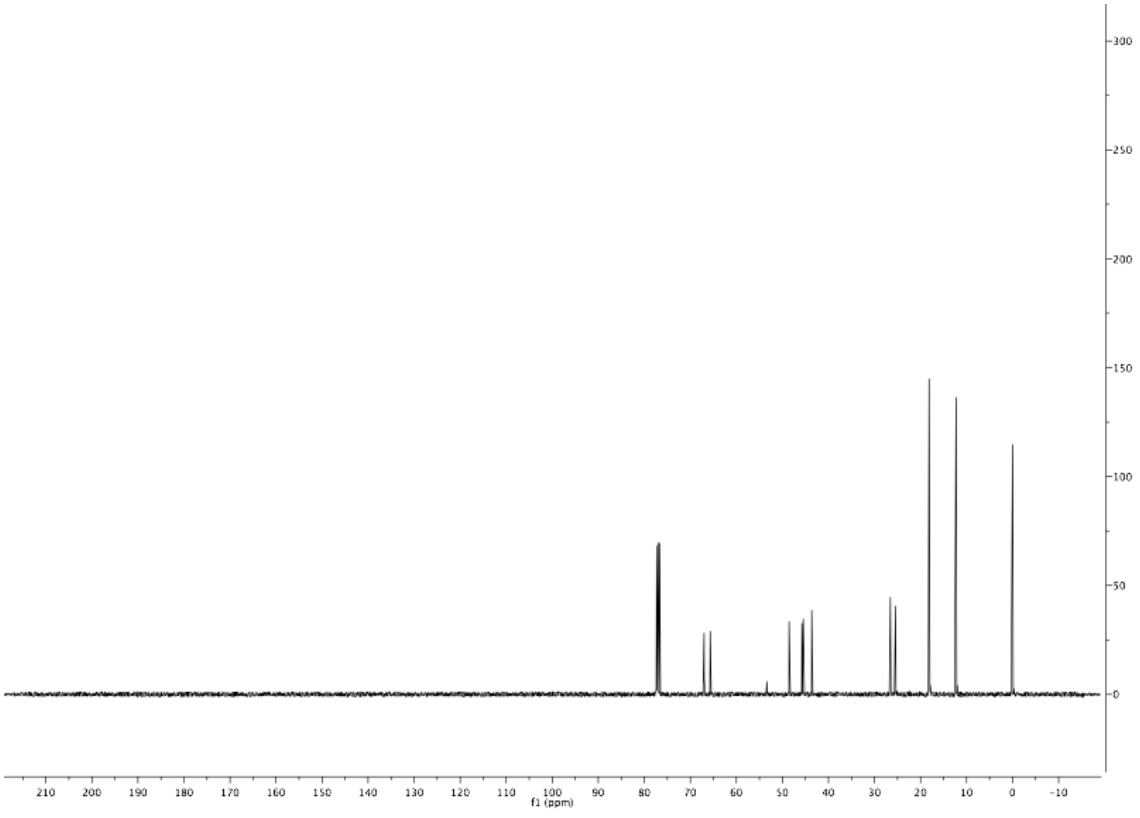


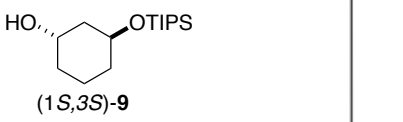
(8*R*,10*R*)-**7**



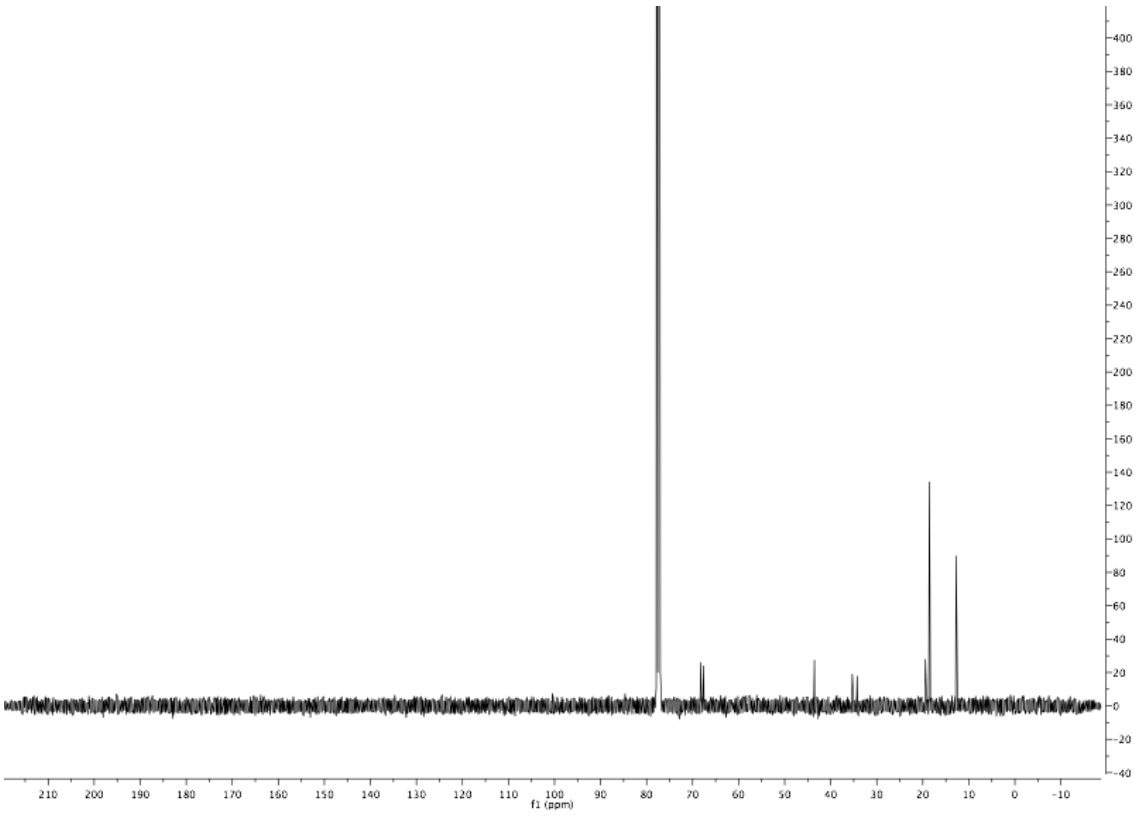


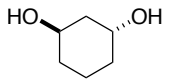
(8*R*,10*R*)-**8**



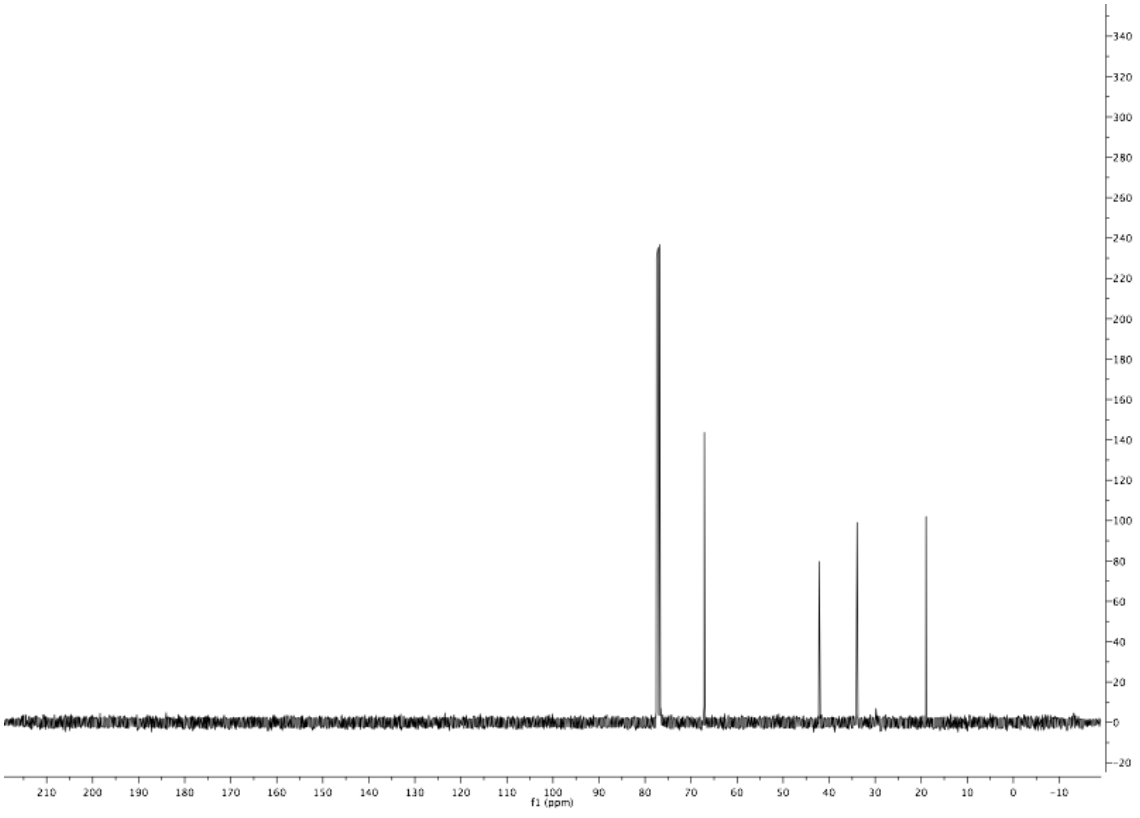


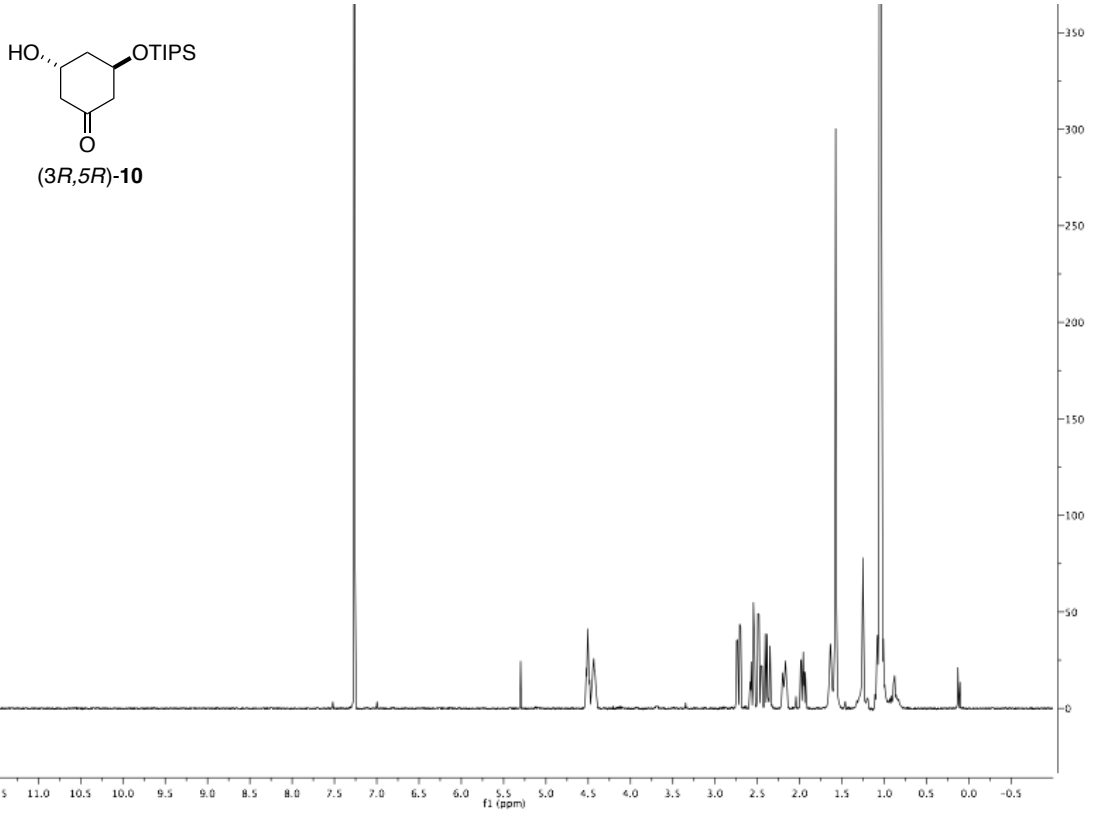
(1*S*,*3S*)-**9**

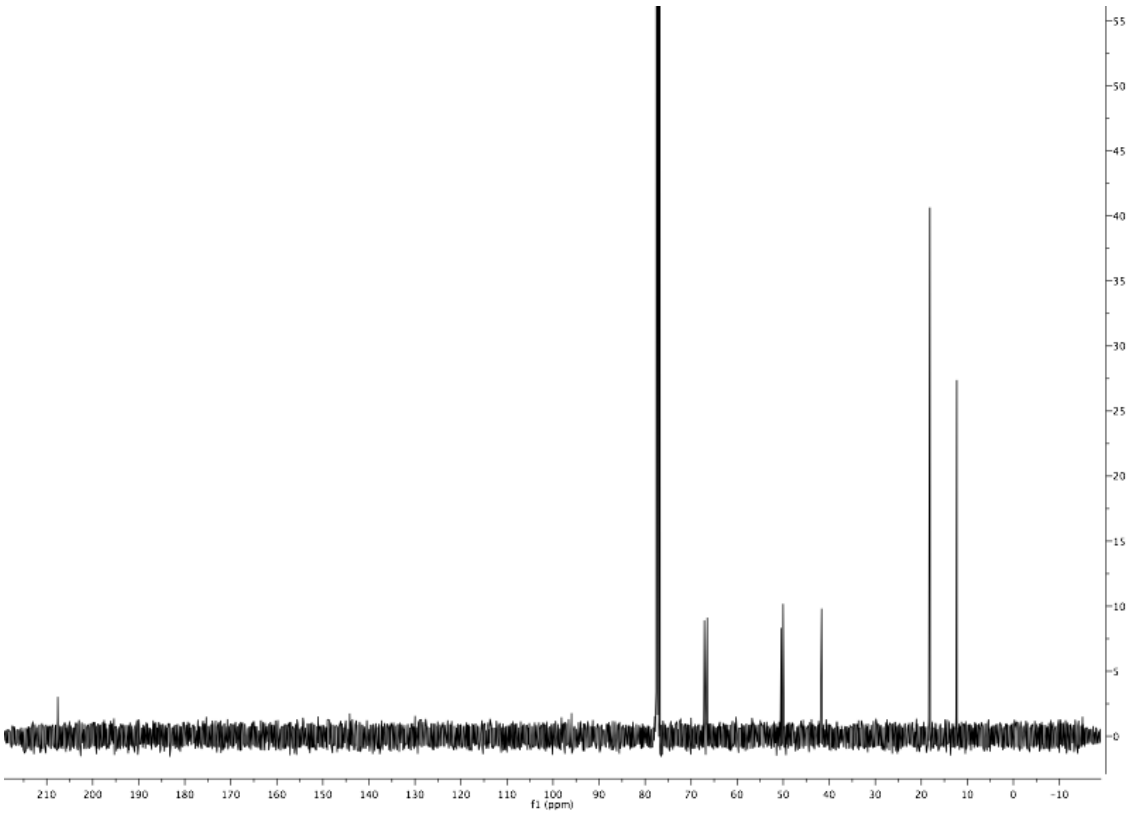


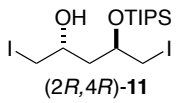


(1*R*,3*R*)-**20**

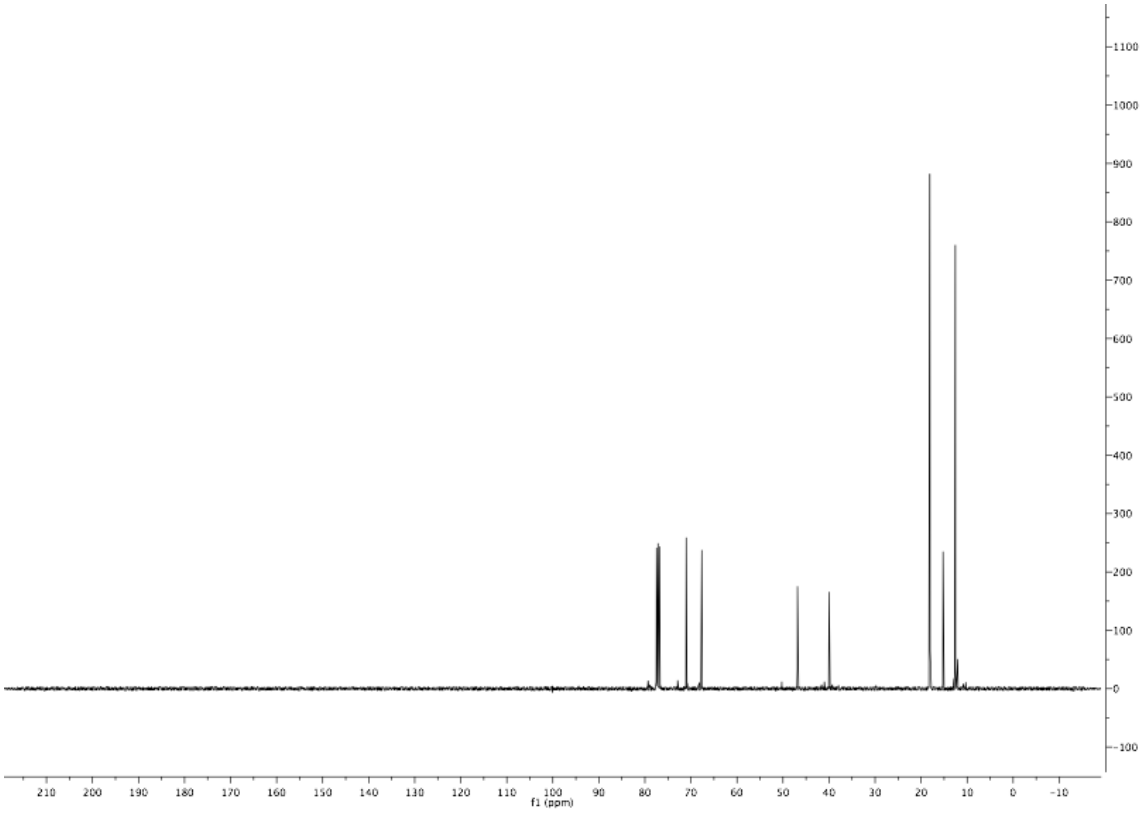


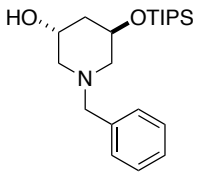

HO
OTIPS
O
(3R,5R)-10
f1 (ppm)


f1 (ppm)

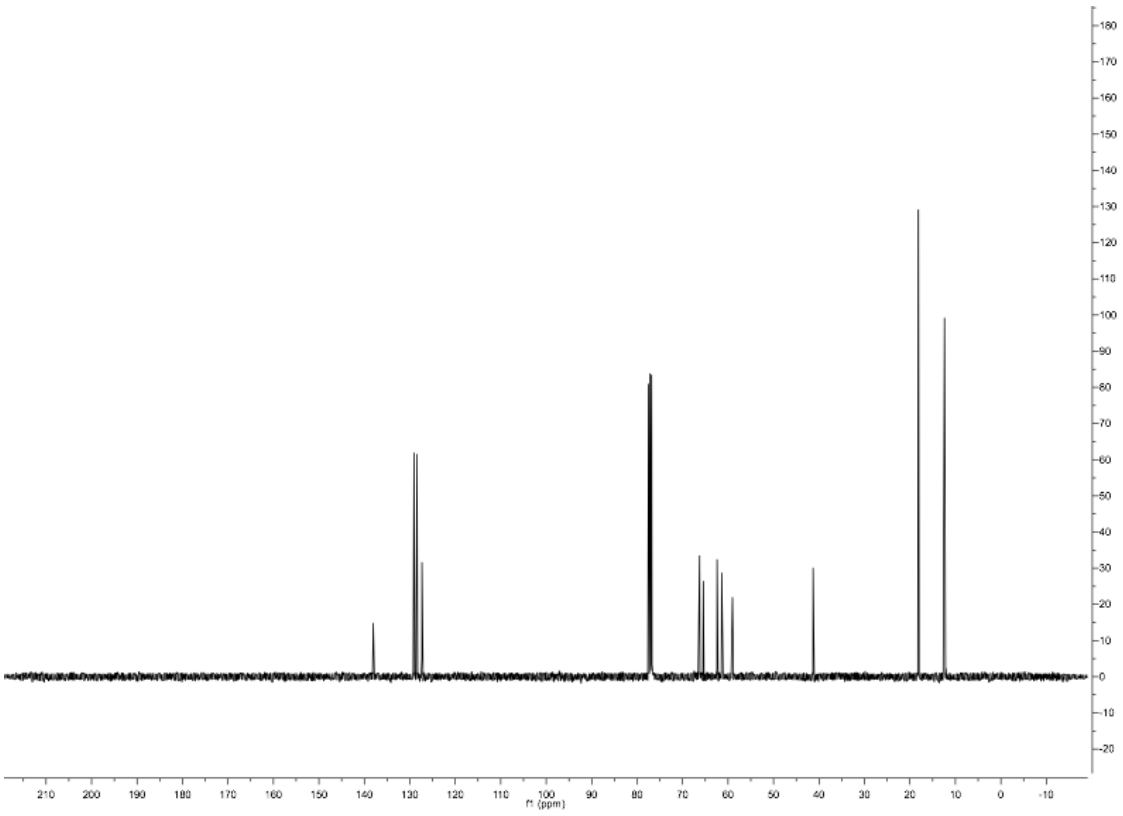


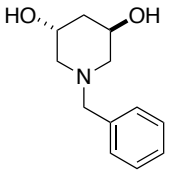
(2*R*,4*R*)-**11**



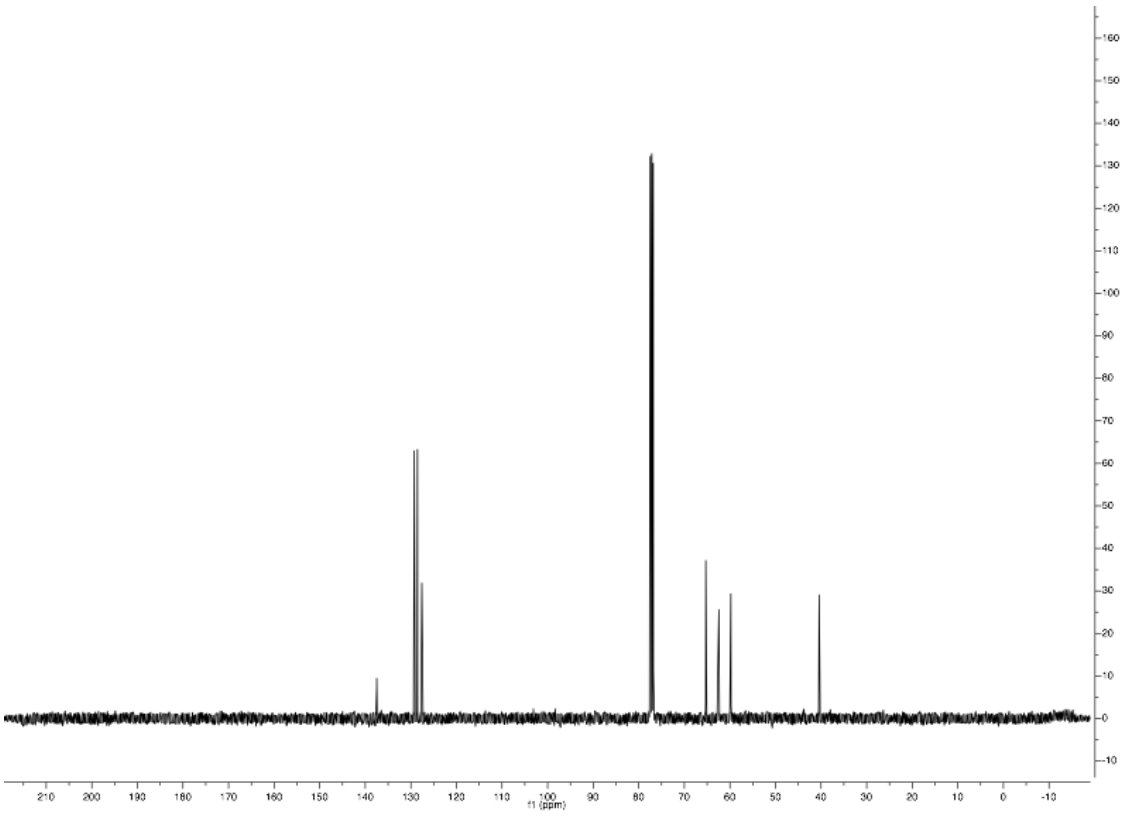


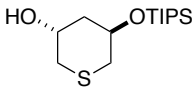
(3*R*,5*R*)-**12**



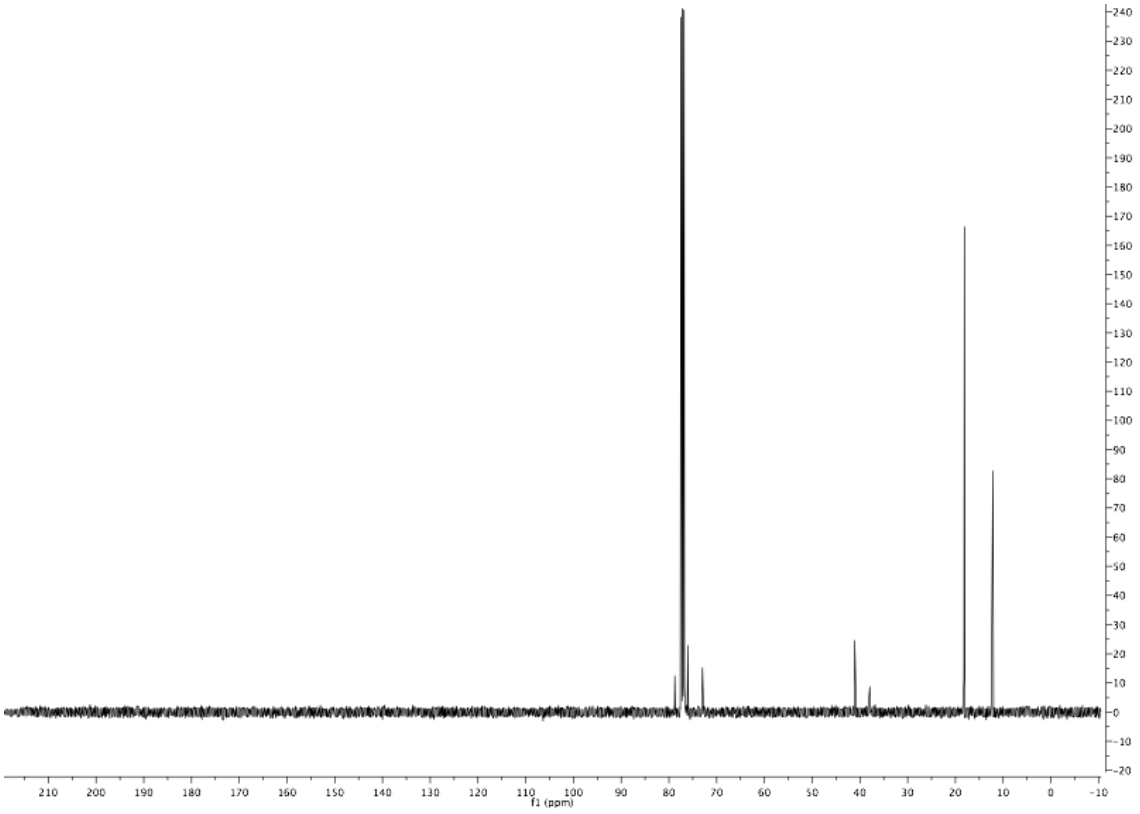


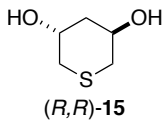
(3*R*,5*R*)-**13**



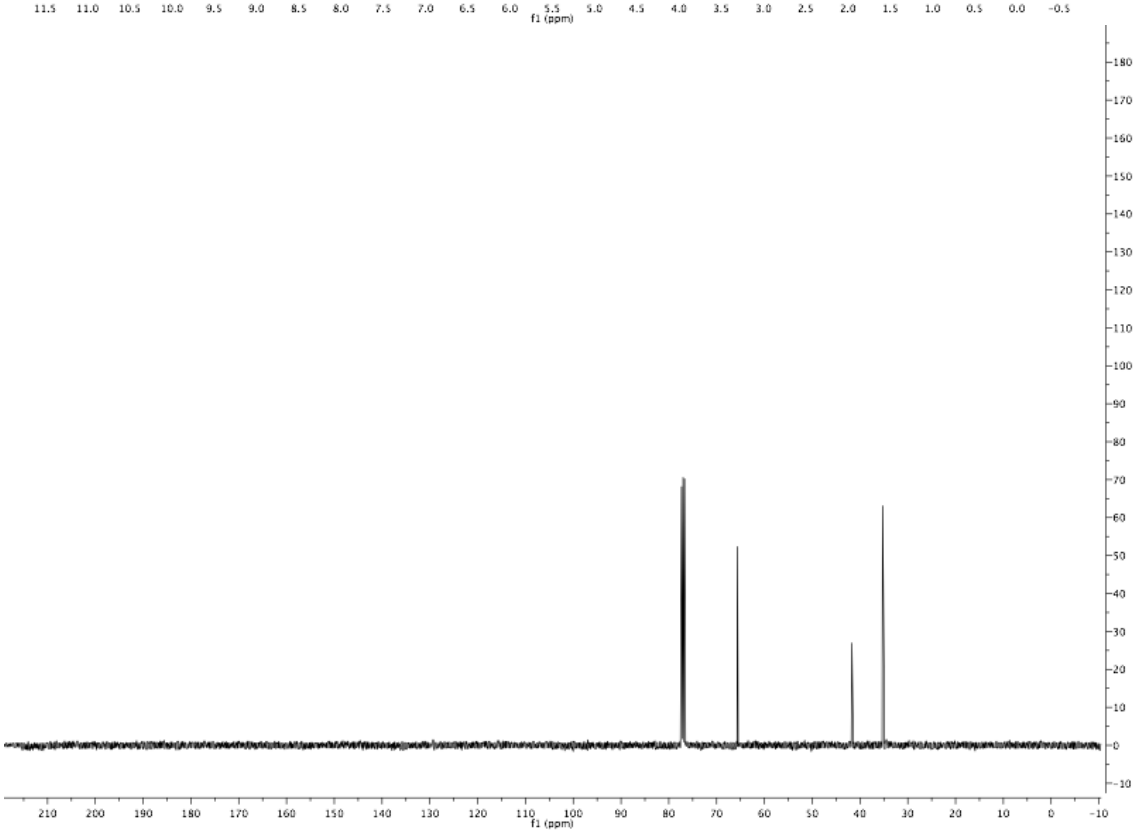


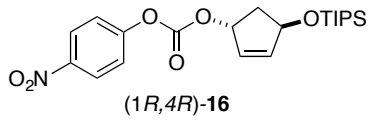
(3*R*,5*R*)-**14**



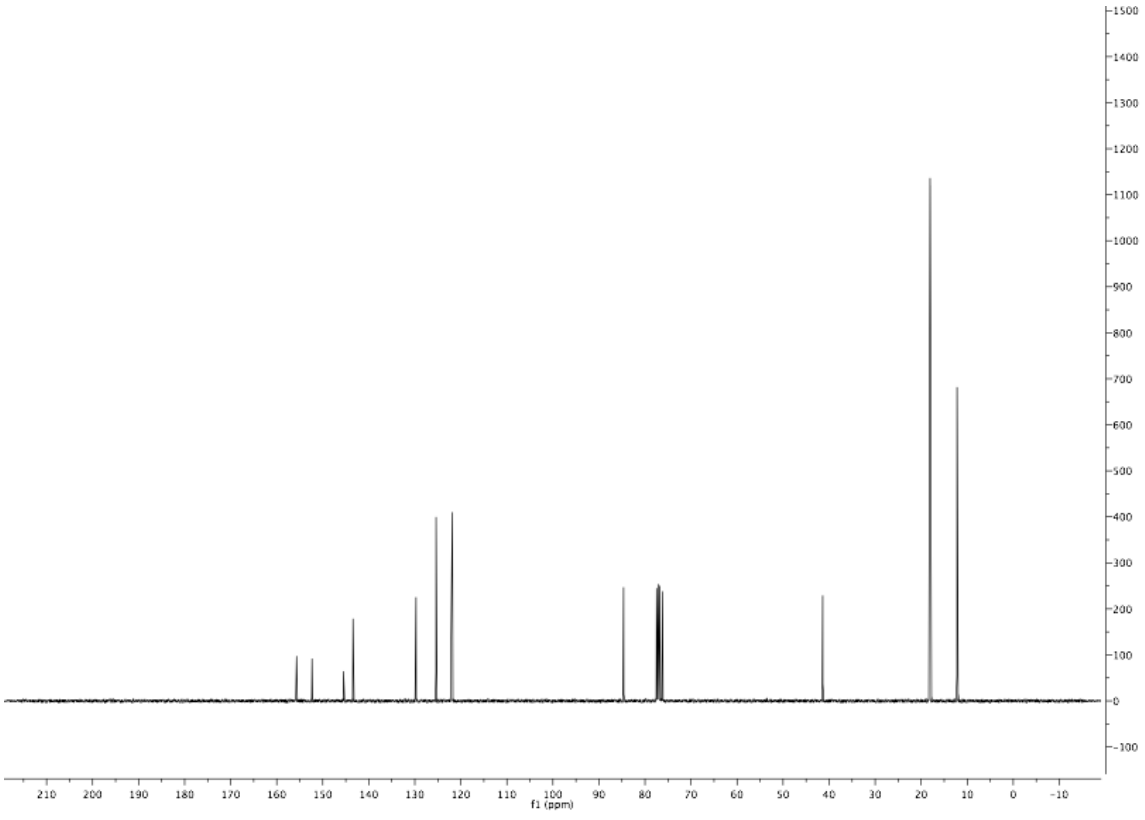


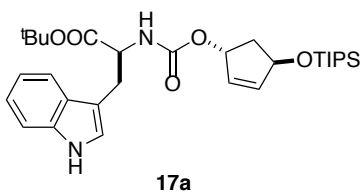
(*R*,*R*)-**15**





(1*R*,4*R*)-**16**





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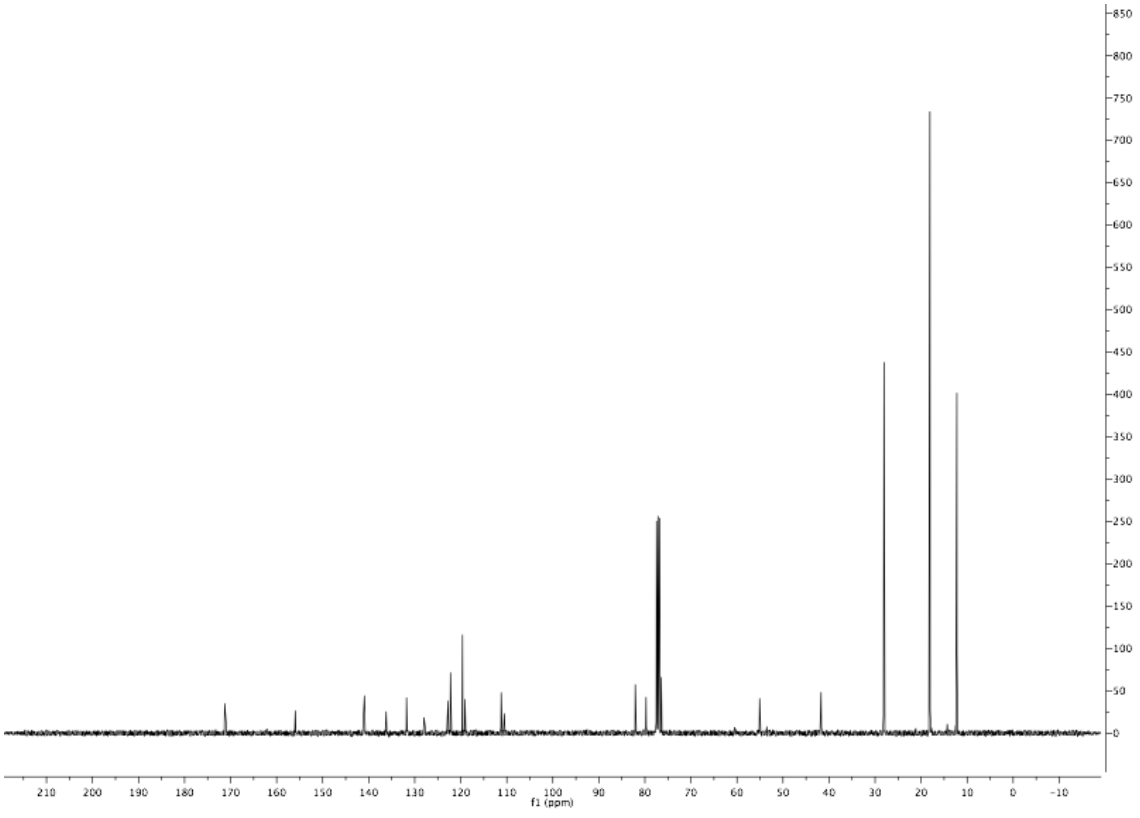

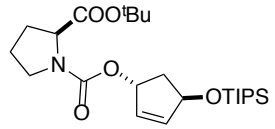

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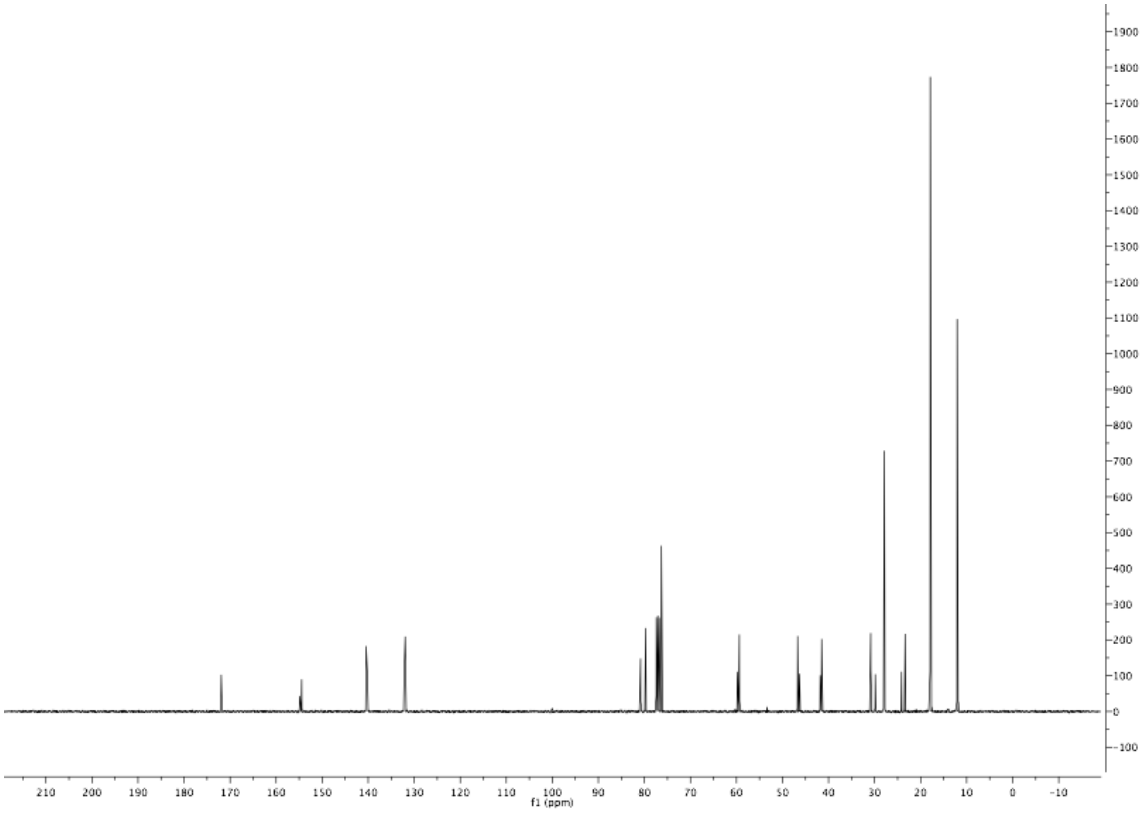

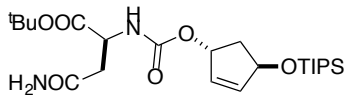

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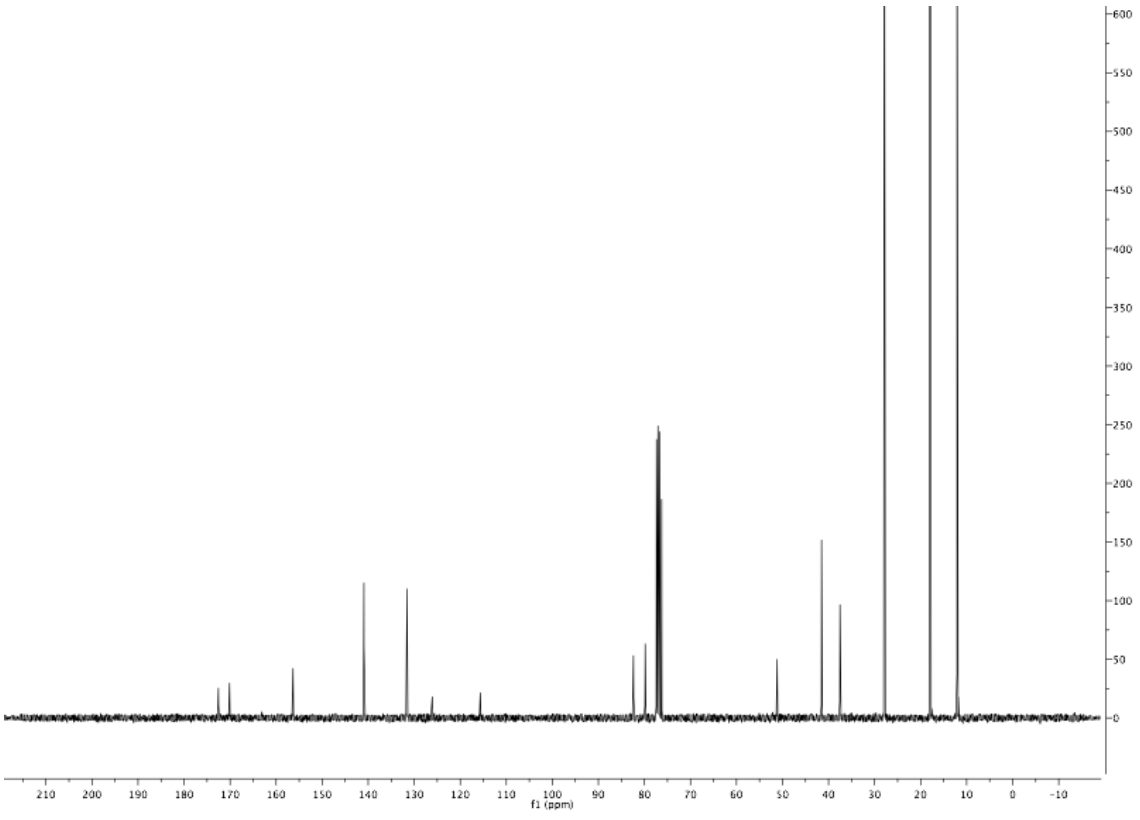

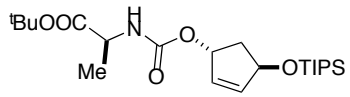

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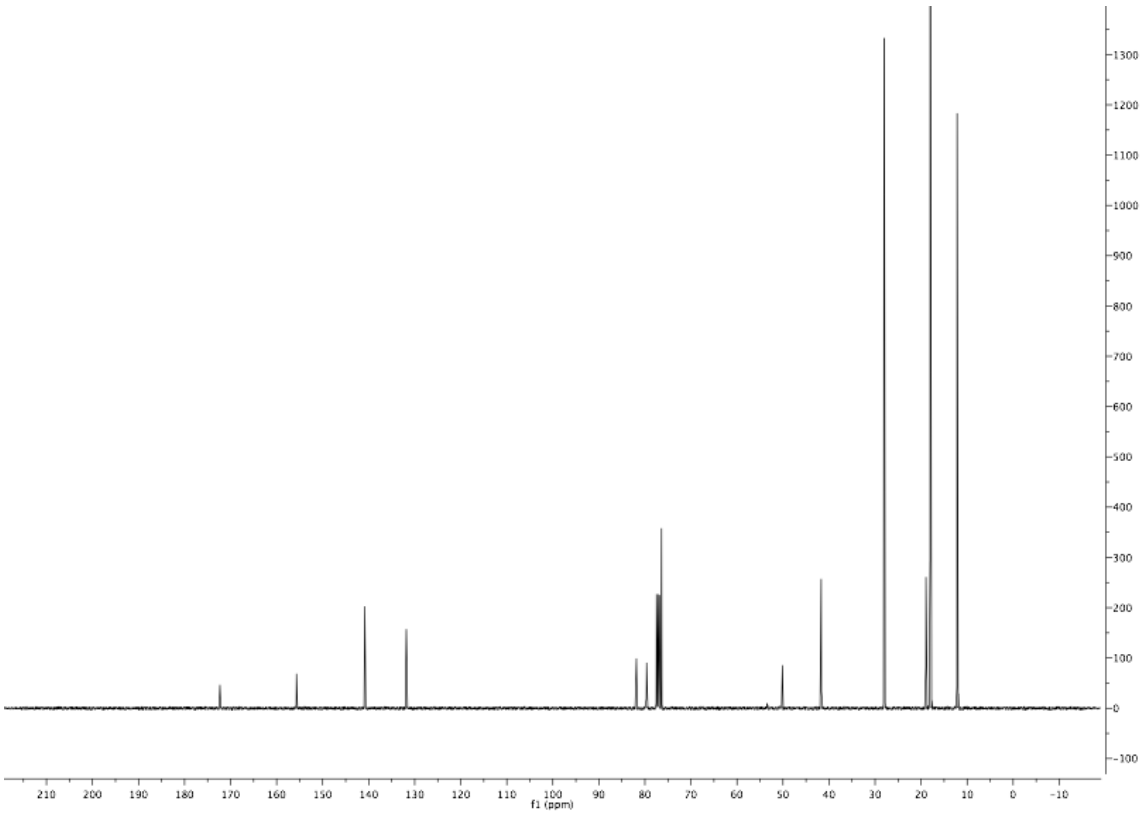

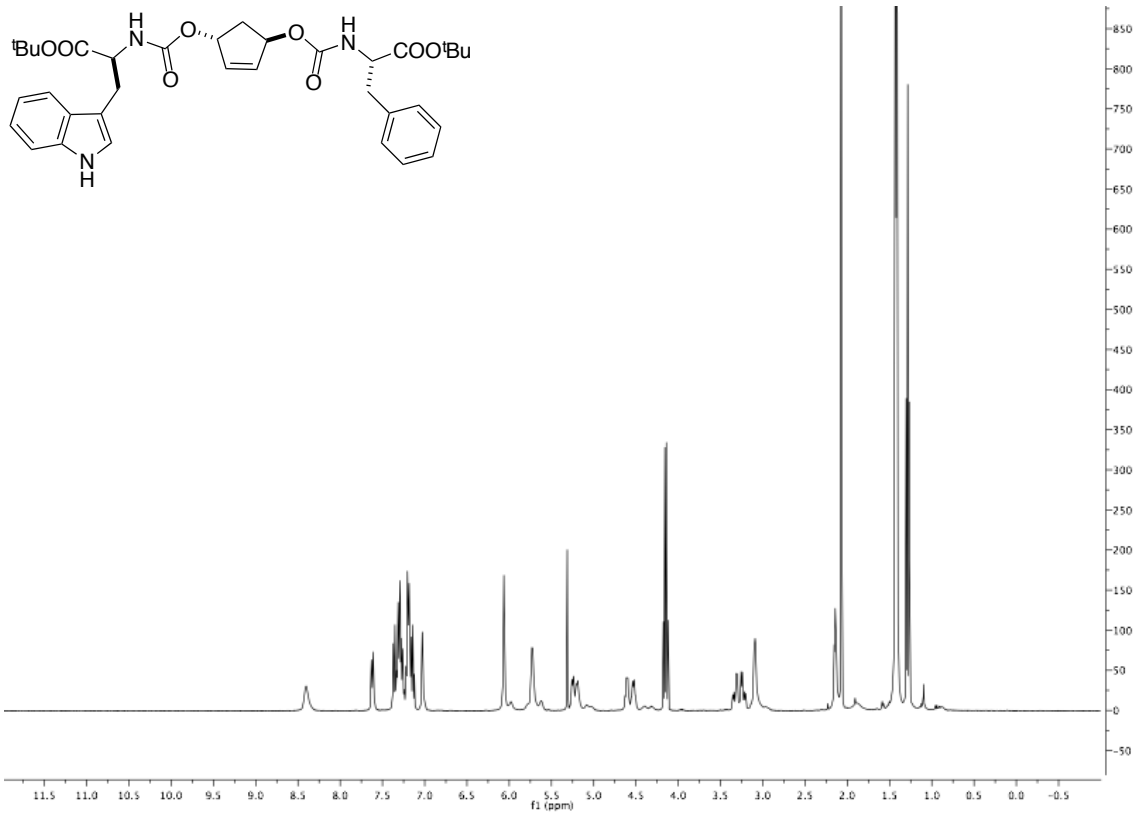
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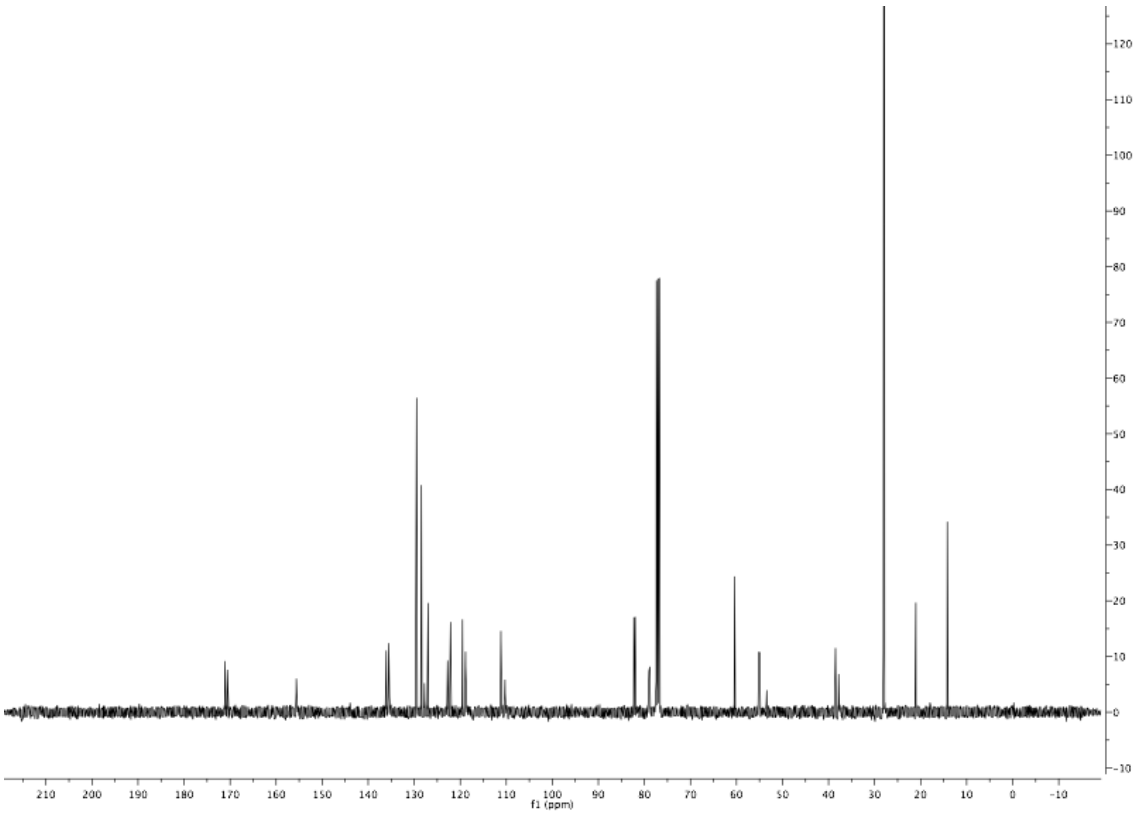
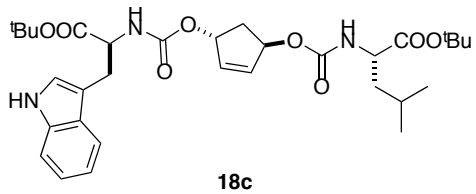
COOtBu
f1 (ppm)


f1 (ppm)



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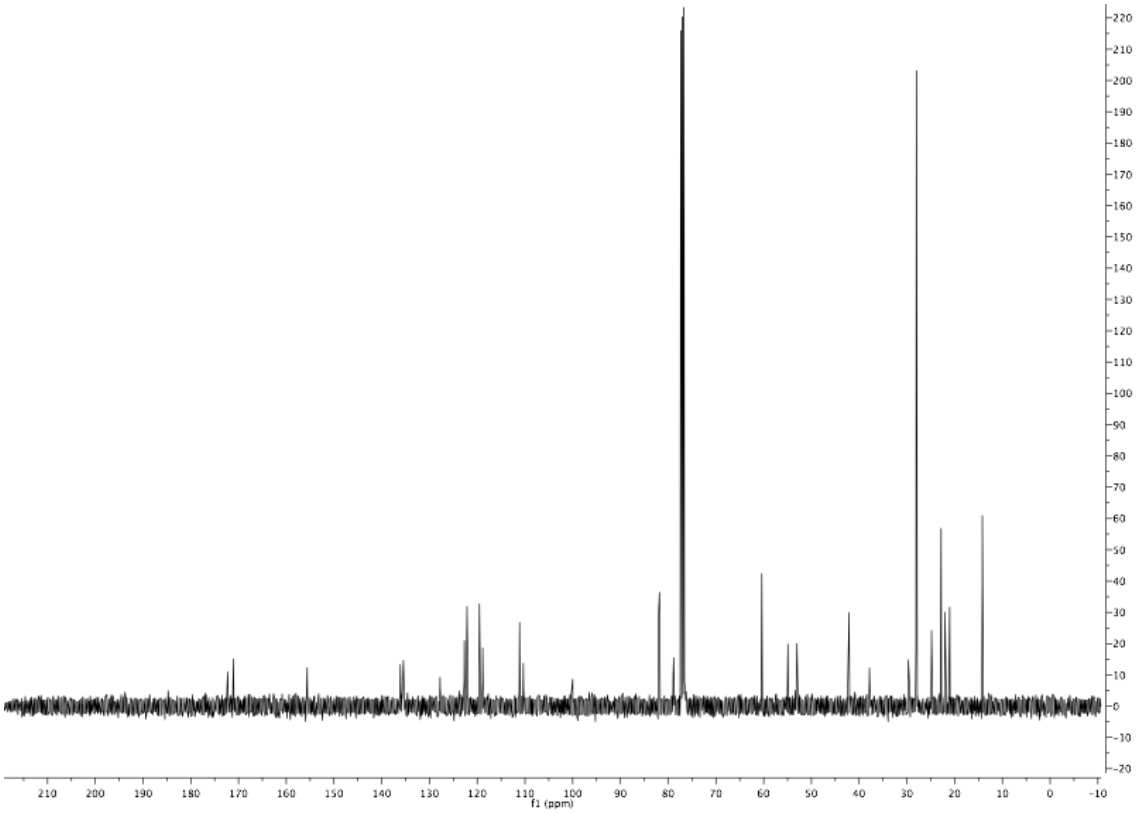

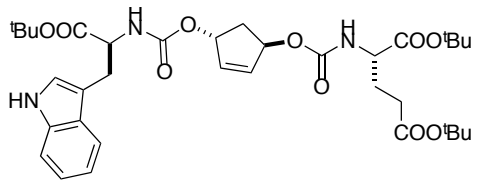

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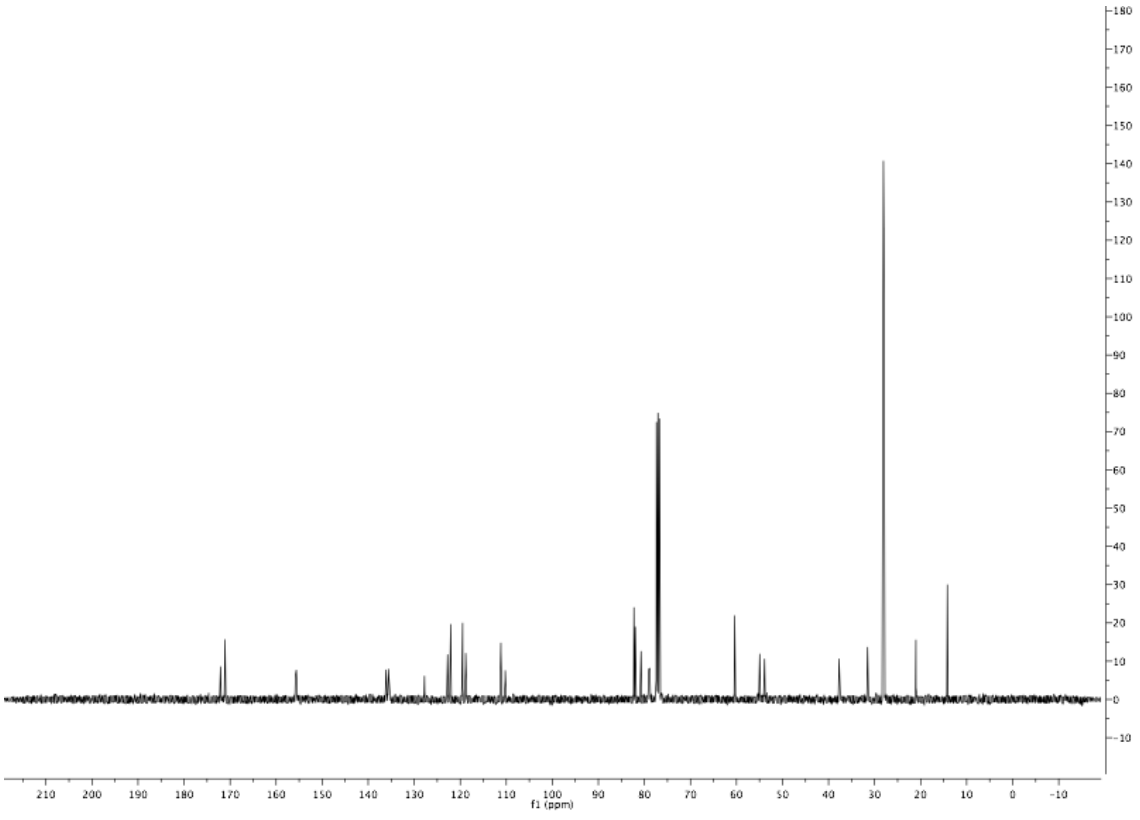

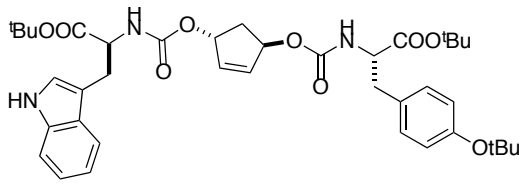

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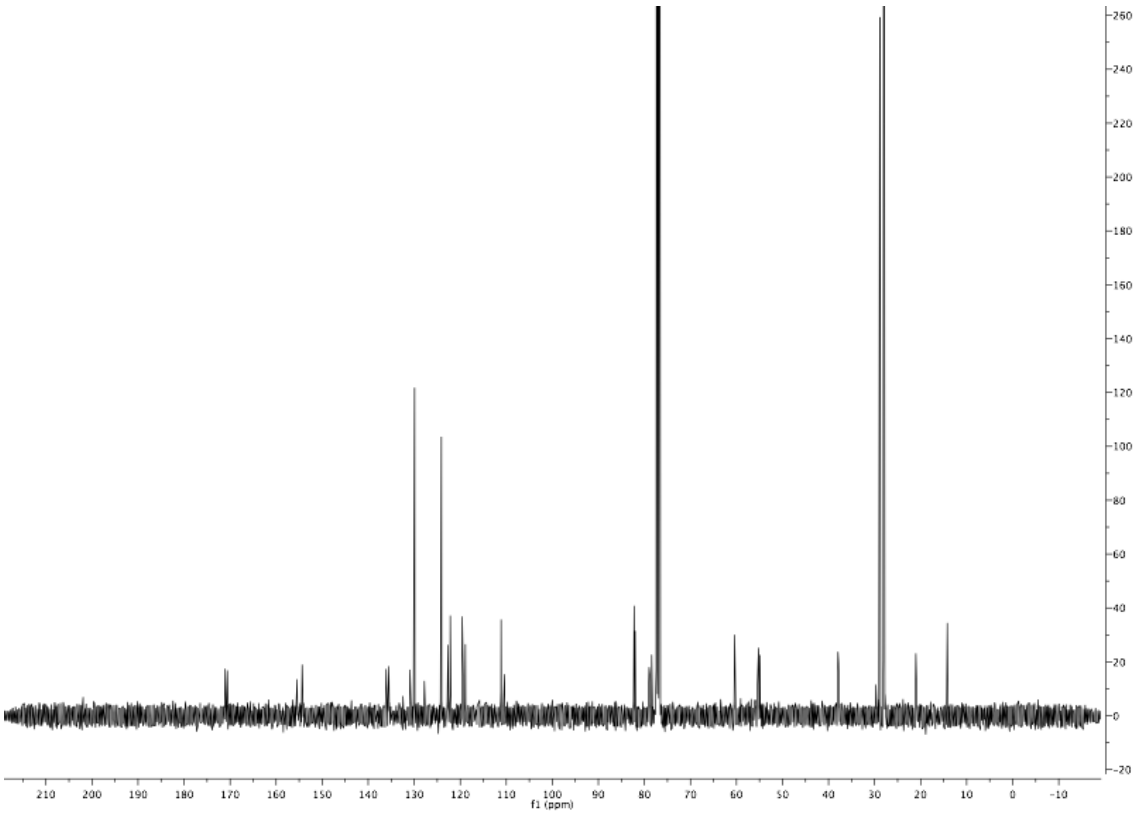

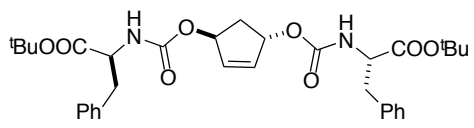
tBuOOC
H
N
O
O
O
O
H
N
COOtBu
Ph
Ph

21

9000
8000
7000
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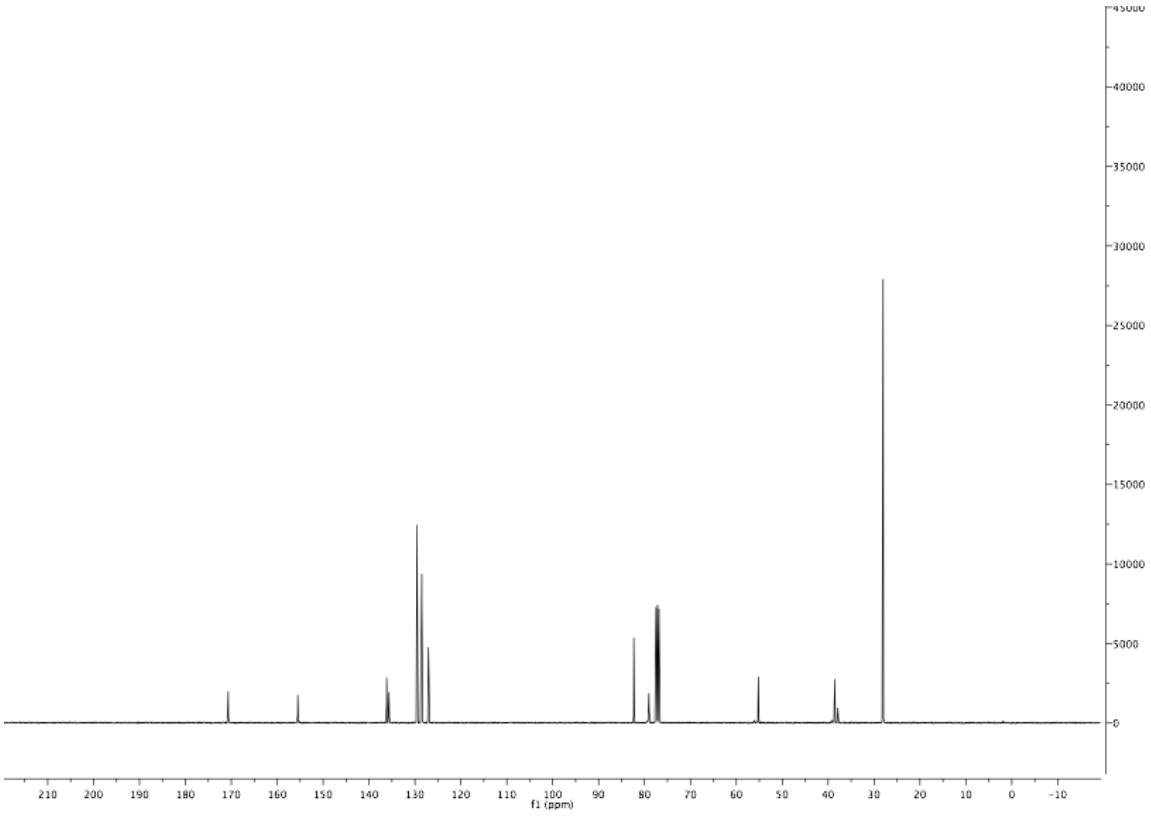
5000
4000
3000
2000
1000
0
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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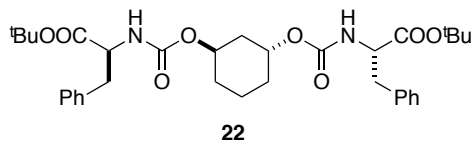
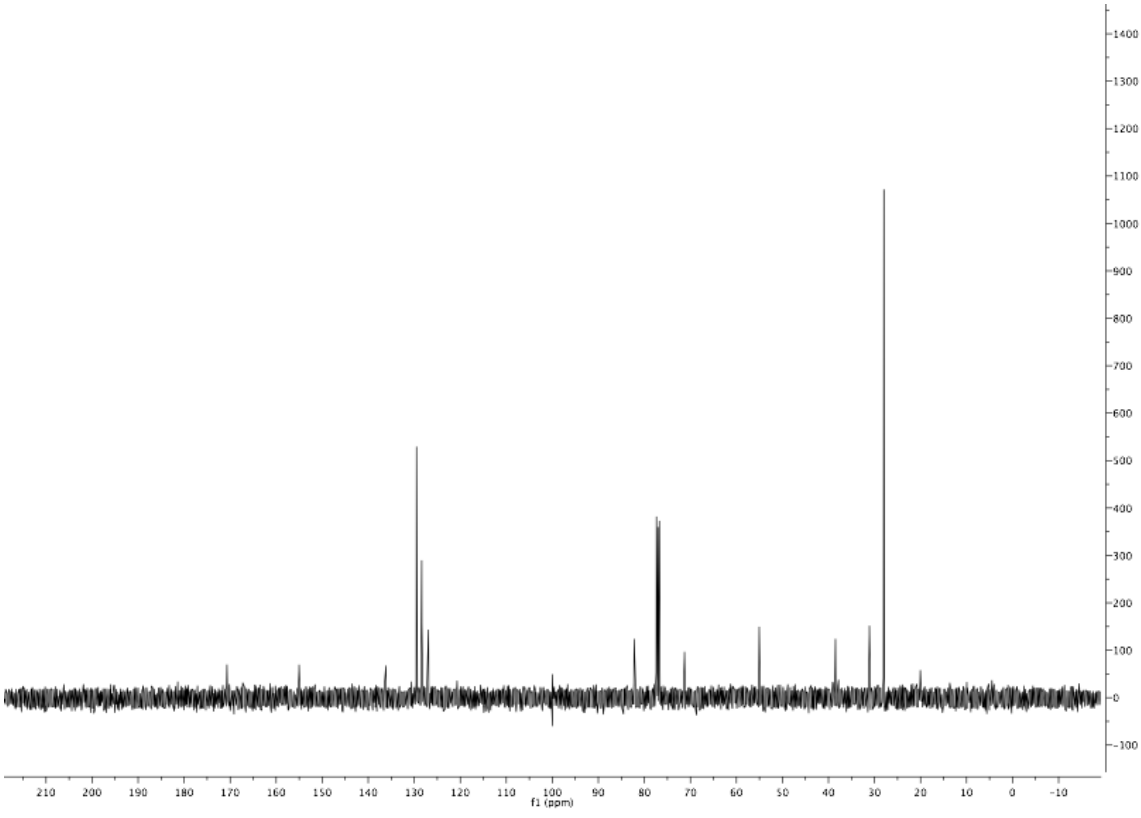
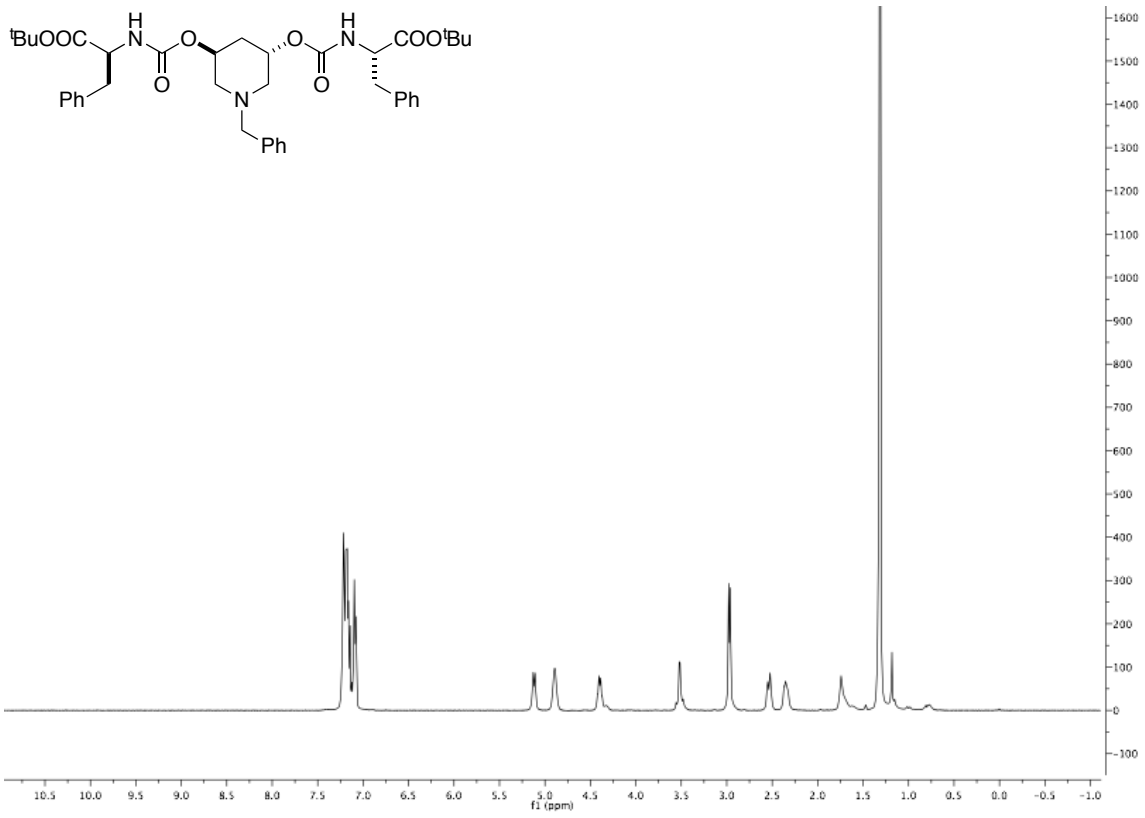
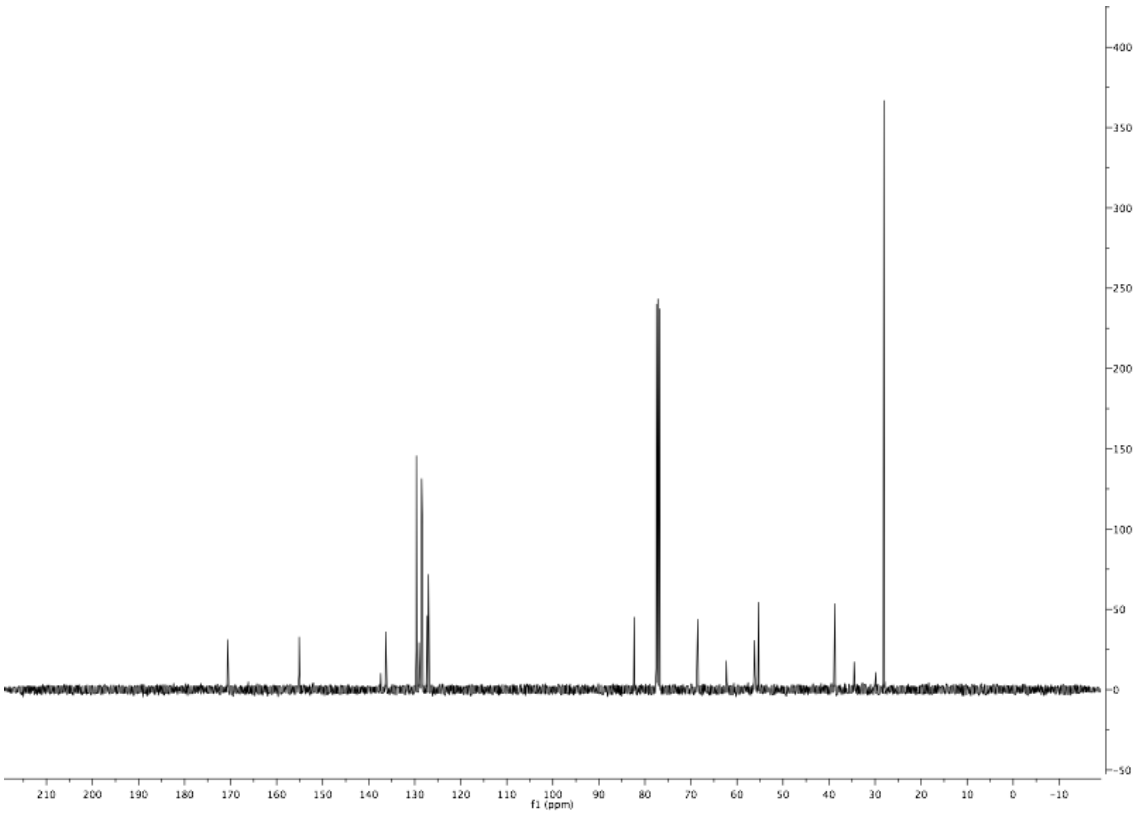
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

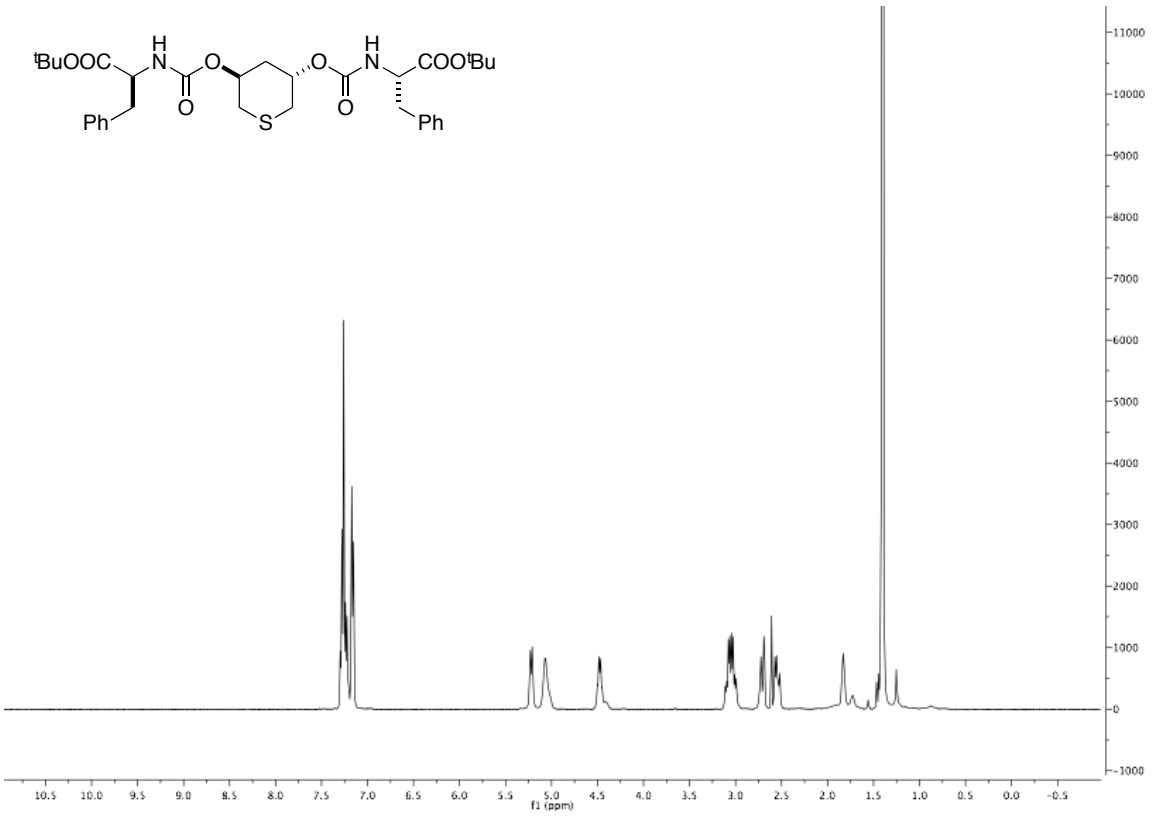


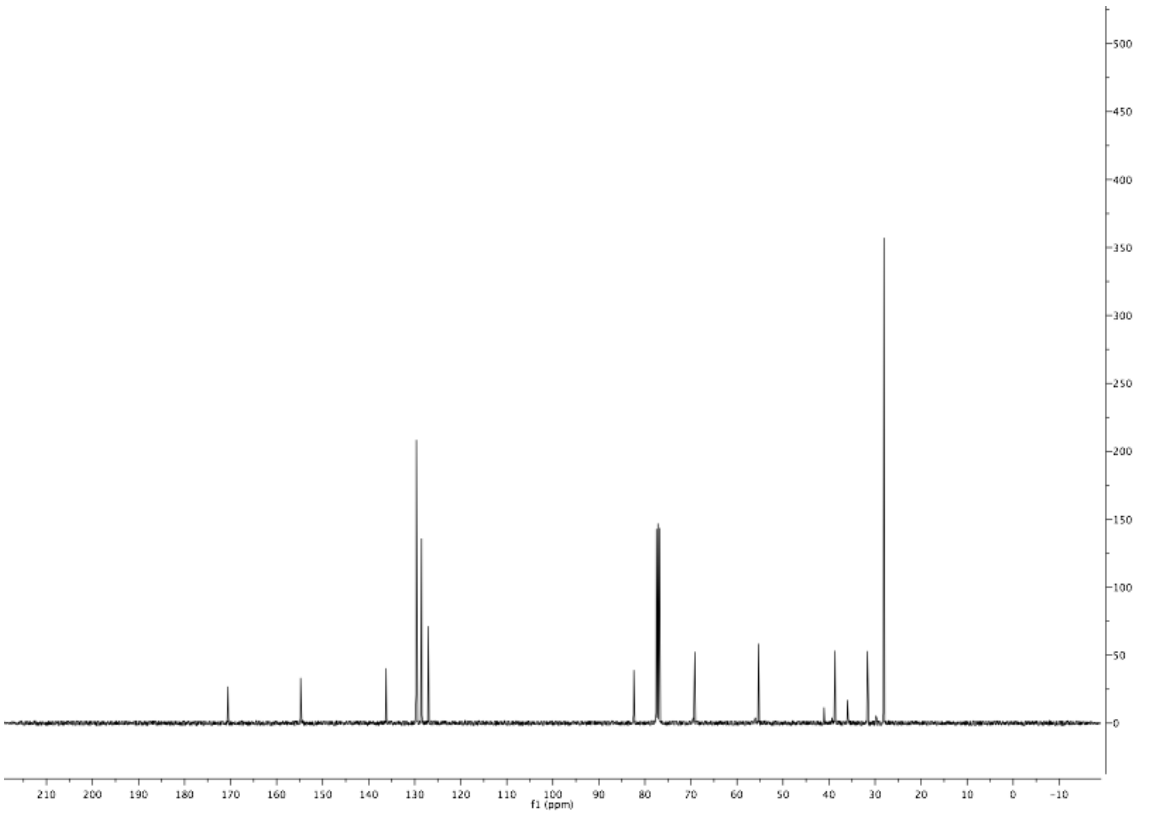
22



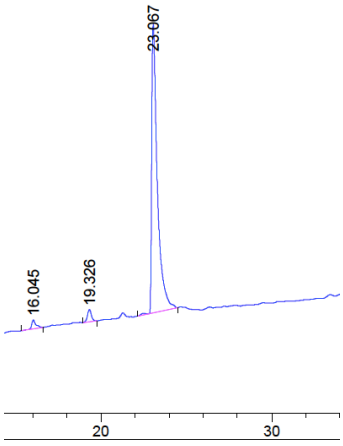

tBuOOC
H
N
O
O
O
O
H
N
COOtBu
Ph
Ph
N
Ph
f1 (ppm)

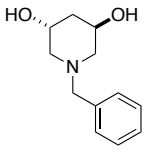

f1 (ppm)


tBuOOC
H
N
O
O
Ph
O
S
O
H
N
COOtBu
Ph
f1 (ppm)


f1 (ppm)

HPLC Chromatogram of (3*R*,5*R*)-**13**

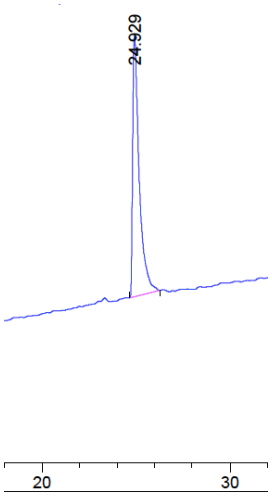


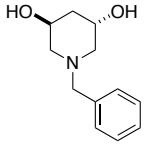


(3*R*,5*R*)-**13**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.146	BB	0.0952	14.64608	2.19900	0.7899
2	3.517	BB	0.1733	67.83061	5.03170	3.6584
3	9.497	BB	0.1923	238.22630	18.70262	12.8484
4	16.045	BB	0.2559	35.44135	1.98901	1.9115
5	19.326	BB	0.2425	43.47663	2.70975	2.3449
6	23.067	BB	0.3281	1454.50818	63.56471	78.4470

HPLC Chromatogram of (*S*,*S*)-**13**

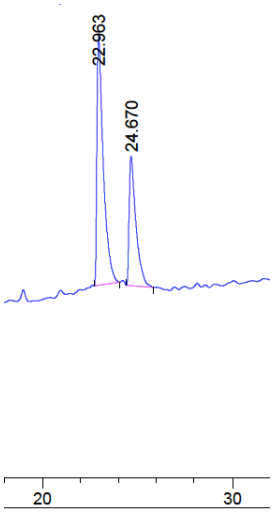




(3*S*,5*S*)-**13**

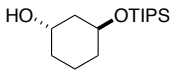
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.151	BB	0.0943	13.62585	2.06866	1.5028
2	3.522	BB	0.2354	96.45295	5.12981	10.6378
3	24.929	BB	0.3505	796.62103	32.94642	87.8594

HPLC Chromatogram of (±)-**13**



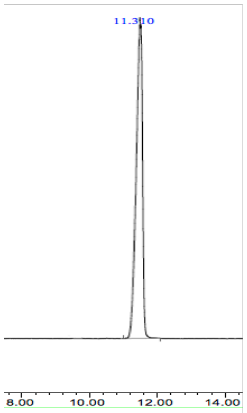
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.132	BB	0.0807	11.15532	2.05689	0.8484
2	3.616	BB	0.2628	107.72001	5.12220	8.1928
3	9.462	BB	0.1885	132.99872	10.39729	10.1154
4	22.963	BB	0.3374	686.02350	29.27623	52.1762
5	24.670	BB	0.3601	376.92209	15.15425	28.6672

GC Chromatogram of (1*S*,3*S*)-**9**



(1*S*,3*S*)-**9**

GC Chromatogram of (1*R*,3*R*)-**9**

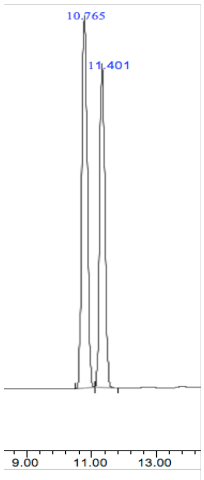


peak #	R.T. first min	max scan	last scan	PK scan	TY	peak height	corr. area	% max.	corr. % of total
1	10.577	1310	1345	1426	BB	339928	41094767	100.00%	100.00%

(1*R*,3*R*)-**9**

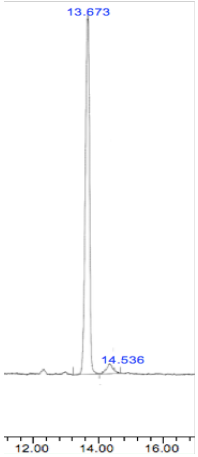
peak #	R.T. first min	max scan	last scan	PK scan	TY	peak height	corr. area	% max.	corr. % of total
1	11.310	1430	1477	1524	BB	382546	17230723	100.00%	100.00%

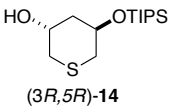
GC Chromatogram of (±)-**9**



peak #	R.T. first min	max scan	last scan	PK scan	TY	peak height	corr. area	% max.	corr. % of total
1	10.765	1320	1367	1420	BB	339928	41094767	100.000%	56.864%
2	11.401	1420	1457	1501	BB	265233	31173342	75.857%	43.135%

GC Chromatogram of (3*R*,5*R*)-**14**

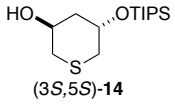




(3*R*,5*R*)-**14**

peak #	R.T. first min	max scan	last scan	PK scan	TY	peak height	corr. area	% max.	corr. % of total
1	13.673	1682	1736	1776	BV	339928	61284767	100.00%	96.824%
2	14.536	1778	1846	1872	BB	69787	2010140	3.28%	3.175%

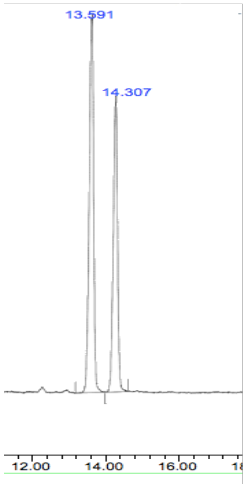
GC Chromatogram of (3*S*,5*S*)-**14**



(3*S*,5*S*)-**14**

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	13.606	1676	1728	1830	BB	69676	1568302	3.07%	2.978%
2	14.413	1830	1894	1947	BV	329928	51084767	100.00%	97.022%

GC Chromatogram of (±)-**14**



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	13.591	1686	1726	1778	BB	399928	41094767	100.00%	56.071%
2	14.307	1778	1827	1854	PB	329233	31173342	75.86%	42.534%

1. Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J., Optically pure 1,3-diols from (2R,4R)- and (2S,4S)-1,2:4,5-diepoxypentane. *J. Org. Chem.* **1991,** *56* (17), 5161-5169.
2. Singh, G.; Meyer, A.; Aube, J., Stereodivergent Synthesis of Enantioenriched 4-Hydroxy-2-cyclopentenones. *J. Org. Chem.* **2014,** *79* (1), 452-458.
3. Gracias, V.; Zeng, Y.; Desai, P.; Aube, J., Ring Expansive Routes to Quinolizidine Alkaloids: Formal Synthesis of (-)-Lasubine II. *Org. Lett.* **2003,** *5* (26), 4999-5001.