Determination of the Absolute Configurations of Microtermolides A and B

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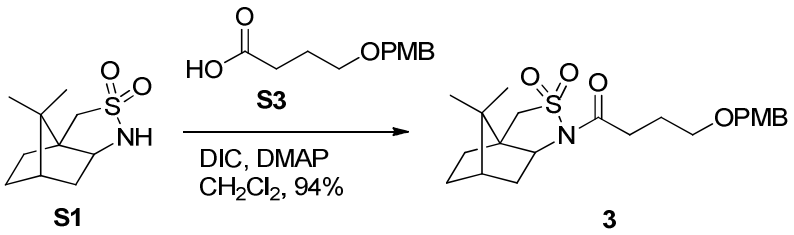
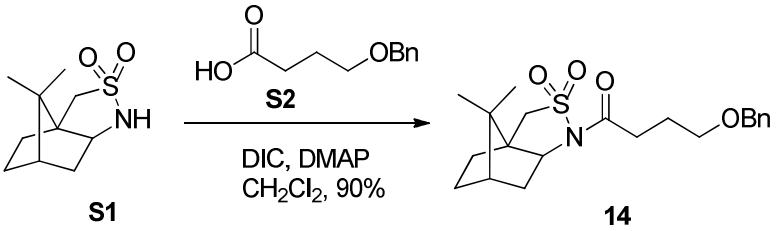
1. Experimental section



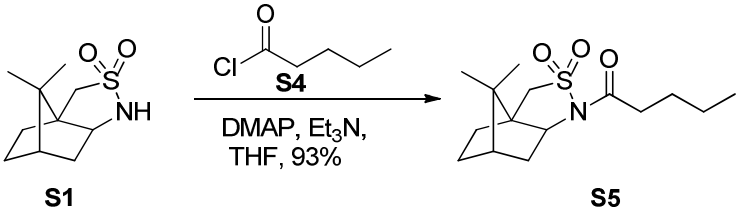
1-((3a*R*,6*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[c]isothiazol-1-yl)-4-((4-methoxybenzyl)oxy)butan-1-one (3).

Compound **3** was synthesized based on literature.[1]



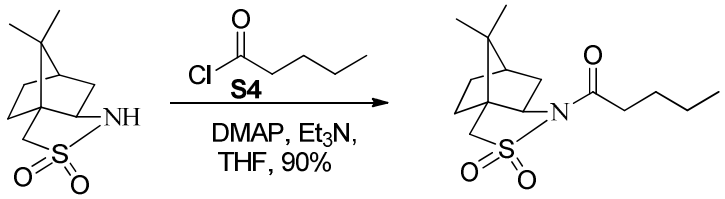
4-(benzyloxy)-1-((3a*R*,6*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[c]isothiazol-1-yl)butan-1-one (14).

Compound **14** was synthesized based on literature.[1]



1-((3a*R*,6*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[c]isothiazol-1-yl)pentan-1-one (S5).

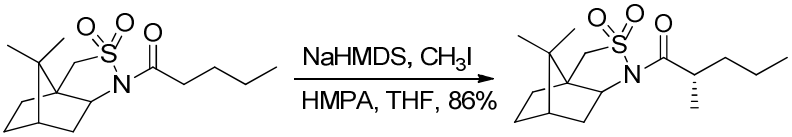
To a stirred solution of **S1** (1.6 g, 7.5 mmol), Et_3N (1.6ml, 11.2 mmol) and DMAP (92.0 mg, 0.8 mmol) in THF (10 ml) was added n-Pentanoyl chloride **S4** (1.0 g, 8.3 mmol) at 0 ºC. After stirred for half an hour, the reaction was quenched by aqueous HCl. The aqueous phase was extracted with ethyl acetate (3 × 30 mL) and washed successively by aqueous NaOH. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Petroleum ether : ethyl acetate = 8:1) to obtain **S5** (2.1 g; 93%).



S6 **S7**

1-((6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[c]isothiazol-1-yl)pentan-1-one (S7).

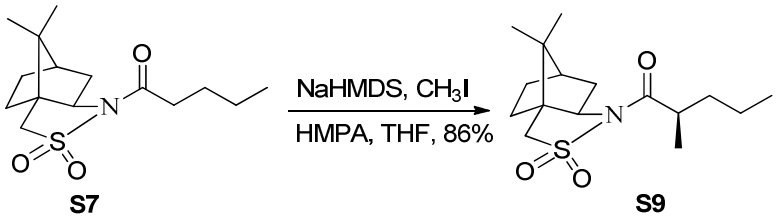
Compound S7 was synthesized according to protocol in previous reporting.[2]



S5 **S8**

(2*S*)-1-((3a*R*,6*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[c]isothiazol-1-yl)-2-methylpentan-1-one (S8).

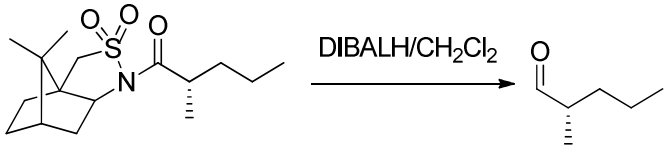
Under argon atmosphere, to a stirred solution of **S5** (3.8 g, 12.8 mmol) in THF (90ml) was added NaHMDS (8.3 ml, 16.6 mmol) at -78 ºC. After 1 hour, HMPA (7.0 ml, 38.3 mmol) was added to this temperature followed by MeI (2.4 ml, 38.3 mmol). The reaction was warmed to room temperature and stirred overnight before saturated aqueous NH_4Cl (20 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Petroleum ether: ethyl acetate = 20:1) to obtain **S8** (3.4 g; 86 %). $[\alpha]^{26}_{D}$ = +105.0 (*c* 1.0, $CHCl_3$)^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, *J* = 6.3 Hz, 1H), 3.49 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 3.11–3.00 (m, 1H), 2.04 (d, *J* = 6.2 Hz, 2H), 1.94–1.81 (m, 3H), 1.80–1.70 (m, 1H), 1.43–1.25 (m, 5H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.14 (s, 3H), 0.95 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 65.2, 53.3, 48.3, 47.8, 44.7, 40.2, 38.7, 34.9, 32.9, 26.5, 20.9, 20.6, 20.0, 19.1, 14.2; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{27}NO_3SNa^+$, 336.1609; found: 336.1608.



S7 S9

(2*R*)-1-((6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[c]isothiazol-1-yl)-2-methylpentan-1-one (S9).

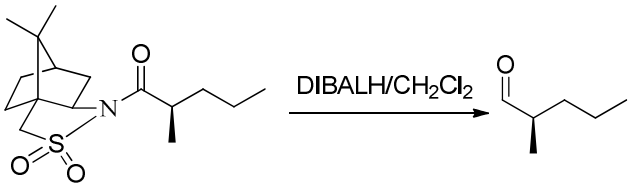
The procedure was the same as the procedure above. $[\alpha]^{26}{}_{D}$ = -104.6 (*c* 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (t, *J* = 6.3 Hz, 1H), 3.49 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 3.10–3.01 (m, 1H), 2.04 (d, *J* = 6.2 Hz, 2H), 1.94–1.82 (m, 3H), 1.79–1.71 (m, 1H), 1.43–1.27 (m, 5H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.14 (s, 3H), 0.96 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 65.2, 53.3, 48.3, 47.8, 44.7, 40.2, 38.6, 34.9, 32.9, 26.6, 20.9, 20.6, 20.0, 19.1, 14.2; HRMS–MALDI (m/z) :[M+Na]+ calcd for $C_{16}H_{27}NO_3SNa^+$, 336.1609; found: 336.1610.



S8 18a

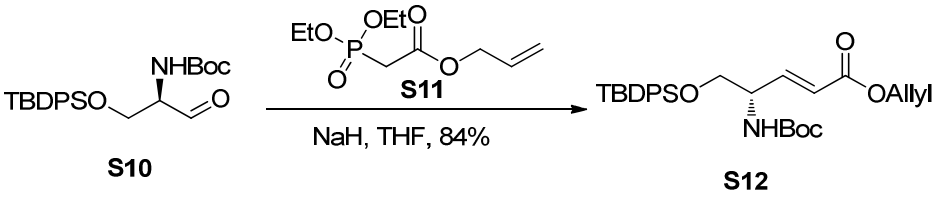
(*S*)-2-methylpentanal (18a).

Under argon atmosphere, to a solution of compound **S8 (**5.0 g, 16.0 mmol) in CH_2Cl_2 (50 mL) was added DIBAL-H (1.5 M in toluene, 16.0 mL, 24.0 mmol) at -78 ºC. After stirred for 1.5h at – 78 ºC, the reaction was quenched by addition of $NaHSO_4$ (5.0 g) in water (50 mL). The resulting mixture was diluted with hexane (60 mL), and the aqueous layer was extracted with hexane (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes: CH_2Cl_2 = 2:1). The eluents were concentrated carefully. The solution of product was dried (1.00 g of 4 Å molecular sieves), and store in – 20 ºC overnight. The upper clear solution was used for the next step directly.



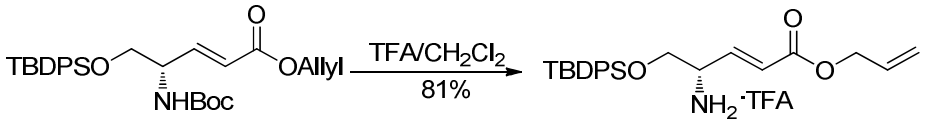
(*R*)-2-methylpentanal (18b).

The procedure was the same as the procedure above.



(*S*,*E*)-allyl-4-((tert-butoxycarbonyl)amino)-5-((*tert*-butyldiphenylsilyl)oxy)pent-2-enoate (S12).

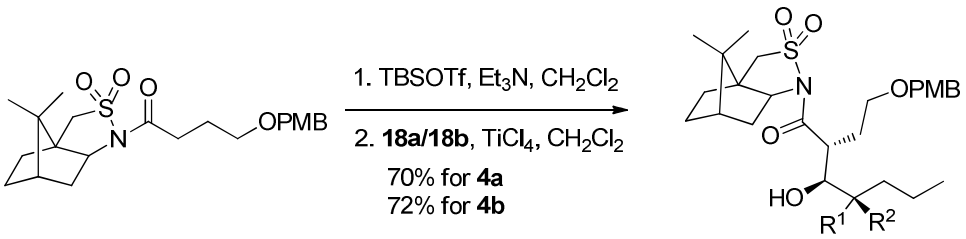
To a stirred suspension of NaH (1.0 g, 25.4 mmol) in THF (68 mL) was added triethyl phosphonoacetate **S11** (7.2 g, 30.5 mmol), and the mixture was stirred at 0 °C for 30 min. **S10** (5.4 g, 12.7 mmol) in THF (15 mL) was added, and the mixture was stirred at 25 °C for 10 min. H_2O (30 mL) was added to quench the reaction, and the aqueous layer was extracted with ethyl acetate (3 × 60 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate = 20:1) to obtain **S12** (13.0 g, 84%). $[\alpha]^{26}_{D}$ = -2.7 (*c* 10.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.55 (m, 4H), 7.49–7.34 (m, 6H), 6.96 (dd, *J* = 15.7, 5.0 Hz, 1H), 6.02 (dd, *J* = 15.7, 1.7 Hz, 1H), 5.99–5.90 (m, 1H), 5.34 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.94 (d, *J* = 7.1 Hz, 1H), 4.66 (d, *J* = 5.5 Hz, 2H), 4.47–4.40 (m, 1H), 3.79 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.71 (dd, *J* = 10.0, 4.0 Hz, 1H), 1.46 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 155.3, 146.9, 135.7, 135.6, 133.0, 132.8, 132.3, 130.1, 130.0, 127.9, 121.8, 118.3, 80.0, 65.5, 65.2, 53.2, 28.5, 26.93, 19.4; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{29}H_{39}NO_5SiNa^+$, 532.2495; found: 532.2493.



S12 **11**

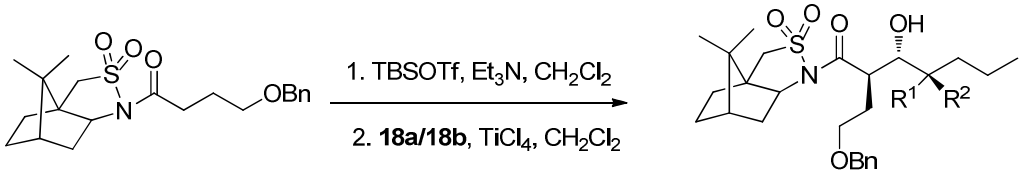
(*R*,*E*)-5-(allyloxy)-1-((*tert*-butyldiphenylsilyl)oxy)-5-oxopent-3-en-2-aminium 2,2,2-trifluoroacetate (11).

To a solution of **S12** (1.0 g, 1.9 mmol) in CH_2Cl_2 (45 mL) was added trifluoroacetic acid (15.0 mL, 34.0 mmol). The mixture was stirred for 4 h before all volatiles were removed under reduced pressure. Then the mixture was directly purified through column chromatography (petroleum ether:ethyl acetate = 10:1 to 2:1) to give the title product **11** (0.8 g, 81%).



3

4a R^1=H, R^2=Me
4b R^1=Me, R^2=H



14

15a R^1=H, R^2=Me
15b R^1=Me, R^2=H

General preparation of 4a, 4b, 15a and 15b.

To a solution of the chiral amide **3/14** (1 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added triethylamine (1.3 mmol, 1.3 equiv) and TBSOTf (1.2 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature overnight; the resulting solution was directly used for the next step.

To a solution of the chiral aldehyde **18a/18b** (1.5 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 1.5 mL, 1.5 mmol) dropwise at – 78 ºC. After 5 min, the solutionabove was added to the reaction mixture. The reaction was stirred at – 78 ^oC for 3 h before saturated aqueous NH_4Cl (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to obtain **4a** or **4b** or **15a** or **15b**.

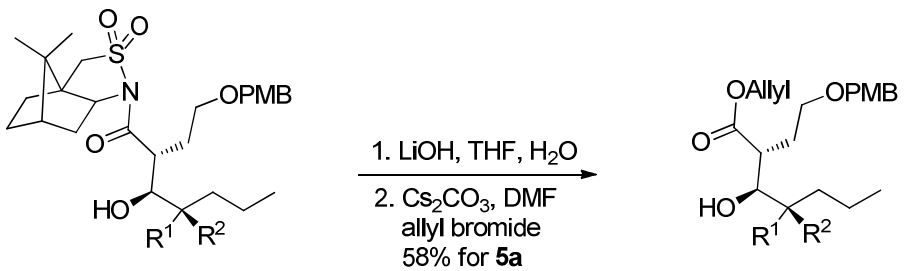
(2*R*,3*R*,4*R*)-1-((3a*R*,6*S*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,6-methanobenzo[c]isothiazol-1-yl)-3-hydroxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methylheptan-1-one (**4a**). $[\alpha]^{27}{}_D$ = +42.7 (*c* 4.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3534, 2955, 2872, 1688, 1513, 1245, 1128, 820, 769; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 3.79 (s, 3H), 3.76–3.72 (m, 1H), 3.55–3.48 (m, 4H), 3.42–3.36 (m, 2H), 2.63 (br s, 1H), 2.22–2.12 (m, 2H), 2.06–2.00 (m, 1H), 1.87–1.81 (m, 4H), 1.58–1.48 (m, 2H), 1.46–1.38 (m, 1H), 1.30 (d, *J* = 7.9 Hz, 3H), 1.16 (s, 3H), 1.10–1.05 (m, 1H), 0.96-0.95 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 159.1, 130.9, 129.4, 113.7, 78.5, 72.4, 67.9, 65.6, 55.3, 53.3, 48.3, 47.8, 45.8, 44.7, 38.6, 36.0, 33.0, 32.0, 29.0, 26.5, 20.7, 20.2, 20.0, 16.7, 14.4; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{28}H_{43}NO_6SNa^+$, 544.2709; found: 544.2708

4b:$[\alpha]^{29}{}_D$ = +34.8 (*c* 2.3, $CHCl_3$); ^1H NMR (400 MHz, CDCl3) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.34 (d, *J* = 11.0 Hz, 1H), 3.79 (s, 3H), 3.73–3.68 (m, 1H), 3.62 (t, *J* = 8.3 Hz, 1H), 3.51 (t, *J* = 5.1 Hz, 2H), 3.49 (d, *J* = 14.1 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H), 3.34–3.28 (m, 1H), 2.29–2.24 (m, 2H), 2.15 (dt, *J* = 15.5, 6.9 Hz, 1H), 2.02 (dd, *J* = 13.8, 7.9 Hz, 1H), 1.88–1.81 (m, 3H), 1.76–1.69 (m, 1H), 1.40 (dd, *J* = 11.3, 5.7 Hz, 1H), 1.35–1.23 (m, 6H),

1.16 (s, 3H), 0.94 (s, 3H), 0.88–0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 159.2, 131.0, 129.5, 113.8, 72.6, 68.2, 65.8, 55.4, 53.4, 48.3, 47.8, 47.0, 44.8, 38.5, 36.3, 35.2, 33.0, 29.1, 26.5, 20.8, 20.4, 20.0, 14.3, 12.4; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{28}H_{43}NO_6SNa^+$, 544.2709; found: 544.2705.

15a: $[\alpha]^{29}_D$ = +42.9 (*c* 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.17 (m, 5H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 3.70–3.67 (m, 1H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.47–3.43 (m, 1H), 3.43 (d, *J* = 13.9 Hz, 1H), 3.37–3.33 (m, 1H), 3.33 (d, *J* = 13.8 Hz, 1H), 2.51 (brs, 1H), 2.18–2.09 (m, 2H), 1.99–1.95 (m, 1H), 1.84–1.78 (m, 4H), 1.53–1.43 (m, 2H), 1.41–1.34 (m, 1H), 1.24–1.20 (m, 3H), 1.10 (s, 3H), 1.05–1.01 (m, 1H), 0.91–0.88 (m, 6H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 138.8, 128.3, 127.8, 127.4, 78.5, 72.7, 68.1, 65.6, 53.3, 48.2, 47.8, 45.8, 44.7, 38.5, 36.0, 32.9, 32.0, 29.0, 26.5, 20.7, 20.2, 20.0, 16.7, 14.3; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{41}NO_5SNa^+$, 514.2603; found: 514.2600.

15b: $[\alpha]^{11}_D$ = +34.7 (*c* 5.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.17 (m, 5H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 3.66–3.61 (m, 1H), 3.57 (t, *J* = 9.5 Hz, 1H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.43 (d, *J* = 13.9 Hz, 1H), 3.32 (d, *J* = 13.9 Hz, 1H), 3.28–3.24 (m, 1H), 2.23–2.17 (m, 2H), 2.14–2.06 (m, 1H), 1.98–1.93 (m, 1H), 1.80–1.74 (m, 3H), 1.71–1.64 (m, 1H), 1.39–1.31 (m, 1H), 1.29–1.14 (m, 5H), 1.10 (s, 3H), 0.87 (s, 3H), 0.83–0.78 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 138.8, 128.3, 127.9, 127.5, 72.9, 68.5, 65.7, 53.3, 48.3, 47.8, 47.0, 44.7, 38.5, 36.5, 35.2, 32.9, 29.8, 29.1, 26.5, 20.8, 20.4, 20.0, 14.3, 12.4; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{41}NO_5SNa^+$, 514.2603; found: 514.2600.



4a R^1=H, R^2=Me
4b R^1=Me, R^2=H

5a R^1=H, R^2=Me
5b R^1=Me, R^2=H

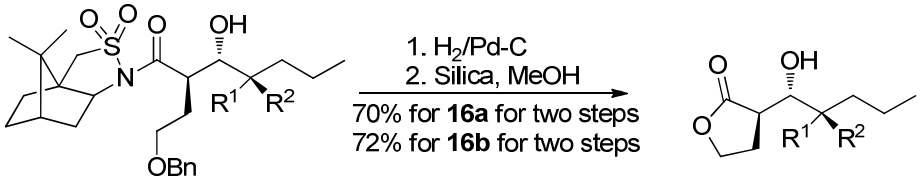
(2*R*,3*R*,4*R*)-allyl-3-hydroxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methylheptanoate (**5a**). To a solution of **4a** (2.2 g 4.2 mmol) in THF, CH_3OH and H_2O (24 mL, 6 mL, 6 mL) was added $LiOH·H_2O$ (885 mg 21.1 mmol) at room temperature. After being stirred for 4 h at this temperature, the reaction mixture was acidified to pH = 2.0 with aqueous 10% $NaHSO_4$ solution, and was extracted with EtOAc. The solvent were evaporated, and the resulting mixture was directly used for the next step without further purification.

The crude acid was dissolved in methanol (10 mL), and was added a solution of Cs_2CO_3 (688 mg, 2.1 mmol) in H_2O (10 mL) slowly at 0 ℃. The mixture was allowed

H_2O (20 mL) was added, and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified with column chromatography on silica gel (petroleum ether: ethyl acetate= 20 : 1) to afford the desired compound **5a** (890 mg, 58% for two steps) as a colorless oil.$[\alpha]^{27}{}_D$ = +15.5 (*c* 1.2, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3520, 2866, 1726, 1611, 1513, 1459, 1173, 1096, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.93–5.83 (m, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.59 (dd, *J* = 13.1, 5.6 Hz, 2H), 4.52 (dd, *J* = 13.1, 5.7 Hz, 2H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.54–3.49 (m, 1H), 3.47–3.42 (m, 1H), 3.37–3.31 (m, 1H), 2.89–2.85 (m,

1H), 2.67 (br s, 1H), 2.15–2.06 (m, 1H), 1.96–1.88 (m, 1H), 1.63–1.56 (m, 1H), 1.48–1.38 (m, 2H), 1.23–1.12 (m, 2H), 0.92–0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 159.3, 132.0, 130.5, 129.4, 118.8, 113.9, 76.9, 72.8, 67.6, 65.3, 55.4, 44.7, 37.5, 34.3, 30.6, 20.1, 16.2, 14.5; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{32}O_5Na^+$, 387.2147; found: 387.2148.

5b:$[\alpha]^{29}_D$ = +2.3(*c* 3.0, $CHCl_3$);IR (KBr, cm^{-1}) ν_{max}: 3521, 3079, 2956, 2865, 1727, 1612, 1513, 1173, 933; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.93–5.83 (m, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.59 (dd, *J* = 13.2, 5.8 Hz, 1H), 4.53 (dd, *J* = 13.2, 5.8 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.52–3.42 (m, 3H), 2.84–2.79 (m, 1H), 2.45 (br s, 1H), 2.05–1.96 (m, 1H), 1.92–1.84 (m, 1H), 1.59–1.49 (m, 1H), 1.43–1.32 (m, 2H), 1.29–1.22 (m, 1H), 1.19–1.10 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 159.3, 132.1, 130.5, 129.4, 118.7, 113.9, 75.7, 72.8, 67.6, 65.4, 55.4, 45.8, 36.2, 35.9, 30.1, 20.1, 14.3, 14.0; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{32}O_5Na^+$, 387.2147; found: 387.2145.



15a R^1 = H, R^2 = Me
15b R^1 = Me, R^2 = H

16a R^1 = H, R^2 = Me
16b R^1 = Me, R^2 = H

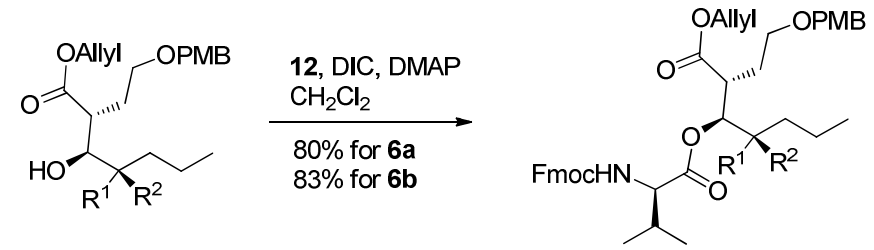
(*R*)-3-((1*R*,2*R*)-1-hydroxy-2-methylpentyl)dihydrofuran-2(3*H*)-one (**16a**).

Pd-C (400 mg) was added in one portion to a stirred solution of the benzyl ether **15a** (1.3 g, 2.65 mmol) in CH_3OH (150 ml) at room temperature, and the apparatus was then evacuated prior to the introduction of hydrogen gas. The mixture was stirred at room temperature for 24h under one atmosphere of hydrogen, then filtered through

celite. The filter cake was washed with EtOAc and the combined organic washings were then concentrated in vacuum to give the primary alcohol and directly used for the next step.

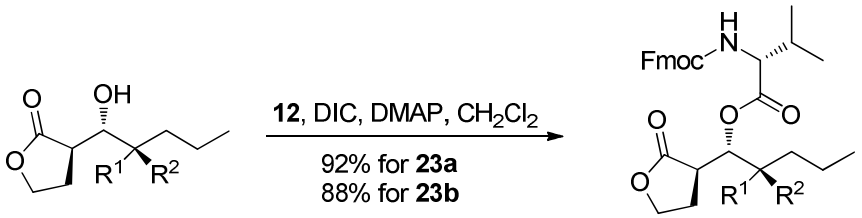
To a solution of the primary alcohol in MeOH (50 ml) was added silica (2 g) at room temperature, after 24 h, filtered and evaporated under reduced pressure. The residue was further purified through column chromatography (petroleum ether : ethyl acetate = 20:1) to the title product **16a** (345 mg, 70% for two steps) as an oil.$[\alpha]^{29}_{D}$ = 1.6(*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3463, 2925, 2867, 1757, 1459, 1214, 1091, 1025, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (td, *J* = 8.9, 1.7 Hz, 1H), 4.21 (ddd, *J* = 10.5, 9.1, 6.4 Hz, 1H), 3.76 (br s, 1H), 3.63 (dd, *J* = 8.5, 3.3 Hz, 1H), 2.73 (dt, *J* = 11.6, 8.7 Hz, 1H), 2.33–2.23 (m, 1H), 2.08–1.97 (m, 1H), 1.52–1.44 (m, 1H), 1.40–1.34 (m, 1H), 1.30–1.22 (m, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 76.4, 67.0, 42.3, 35.9, 32.0, 26.2, 20.6, 16.7, 14.5; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{10}H_{18}NO_3Na^+$, 209.1154; found: 209.1154.

16b: $[\alpha]^{29}_{D}$ = -19.8 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3517, 2929, 2872, 1753, 1459, 1329, 1136, 1023, 936; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (td, *J* = 8.9, 1.4 Hz, 1H), 4.15 (ddd, *J* = 10.7, 9.1, 6.4 Hz, 1H), 3.87 (br s, 1H), 3.64 (d, *J* = 9.2 Hz, 1H), 2.62 (dt, *J* = 11.7, 9.1 Hz, 1H), 2.26–2.18 (m, 1H), 1.95–1.84 (m, 1H), 1.47–1.38 (m, 2H), 1.34–1.24 (m, 3H), 0.87–0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 74.0, 66.9, 42.2, 35.9, 35.2, 25.7, 20.3, 14.2, 12.2; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{10}H_{18}NO_3Na^+$, 209.1154; found: 209.1150.



5a R^1=H, R^2=Me
5b R^1=Me, R^2=H

6a R^1=H, R^2=Me
6b R^1=Me, R^2=H



16a R^1=H, R^2=Me
16b R^1=Me, R^2=H

23a R^1=H, R^2=Me
23b R^1=Me, R^2=H

General preparation of 6a, 6b, 23a and 23b.

To a solution of acid 12 (1.2 mmol, 1.2 equiv) and the alcohol ester 5a/5b/16a/16b (1 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) was added DMAP (0.6 mmol, 0.6 equiv)) and DIC (2 mmol, 2 equiv) under argon atmosphere at 0°C. The reaction mixture was stirred for 4 h at 20°C, and diluted with CH_2Cl_2 (10 mL), and then quenched with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to obtain **6a** or **6b** or **23a** or **23b**.

(2*R*,3*R*,4*R*)-allyl-3-(((*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanoyl)oxy)-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methylheptanoate (**6a**): $[\alpha]^{27}{}_D$ = +26.0 (*c* 0.9, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}:3362, 2961, 2869, 1733, 1514, 1456, 1261, 1096, 1025,804; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.64–7.61 (m, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.30 (td, *J* = 7.4, 2.9 Hz, 2H), 7.22 (d, *J* =

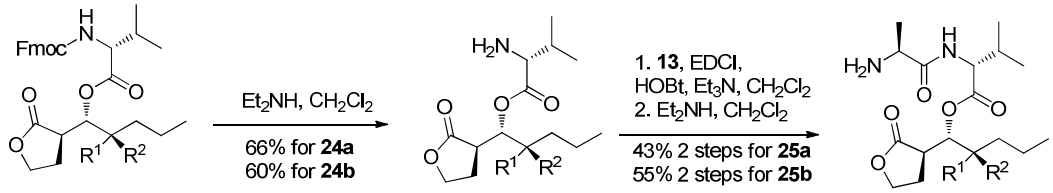
8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.92–5.83 (m, 1H), 5.43 (d, J = 9.2 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.22 (d, J = 10.4 Hz, 1H), 5.08 (t, J = 6.0 Hz, 1H), 4.54 (d, J = 5.6 Hz, 2H), 4.41–4.39 (m, 2H), 4.39 (s, 2H), 4.31 (dd, J = 9.0, 4.5 Hz, 1H), 4.24 (t, J = 7.0 Hz, 1H), 3.79 (s, 3H), 3.51–3.44 (m, 1H), 3.43–3.37 (m, 1H), 3.06–3.04 (m, 1H), 2.21–2.17 (m, 1H), 2.01–1.92 (m, 1H), 1.86–1.73 (m, 2H), 1.44–1.30 (m, 2H), 1.20–1.07 (m, 2H), 1.00 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 171.5, 159.3, 156.4, 144.1, 144.0, 141.4, 132.1, 130.4, 129.4, 127.8, 127.2, 125.3, 120.1, 118.7, 113.9, 79.0, 72.8, 67.3, 67.2, 65.4, 59.5, 55.4, 47.4, 44.4, 34.9, 33.6, 31.1, 29.6, 19.9, 19.5, 17.3, 16.1, 14.3; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{41}H_{51}NO_8Na^+$, 708.3512; found: 708.3509.

6b: $[\alpha]^{29}_D$ =+6.7 (c 1.8, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 354, 3062, 2960, 2872, 1733, 1611, 1456, 1175, 988; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.65–7.61 (m, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.31 (t, J = 6.1 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 5.91–5.83 (m, 1H), 5.41 (d, J = 9.2 Hz, 1H), 5.31 (d, J = 17.0 Hz, 1H), 5.23 (d, J = 10.6 Hz, 1H), 5.20–5.17 (m, 1H), 4.53 (d, J = 5.3 Hz, 2H), 4.41–4.40 (m, 2H), 4.40 (s, 2H), 4.32 (dd, J = 9.1, 4.4 Hz, 1H), 4.25 (t, J = 7.0 Hz, 1H), 3.79 (s, 3H), 3.48 (dd, J = 9.8, 4.7 Hz, 1H), 3.44–3.38 (m, 1H), 3.06–3.01 (m, 1H), 2.21–2.17 (m, 1H), 1.99–1.92 (m, 1H), 1.85–1.77 (m, 2H), 1.41–1.29 (m, 3H), 1.17–1.11 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H), 0.92–0.87 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.4, 159.3, 156.3, 144.1, 143.9, 141.4, 132.0, 130.4, 129.4, 127.8, 127.1, 125.2, 120.0, 118.7, 113.8, 78.1, 72.8, 67.3, 67.1, 65.5, 59.4, 55.3, 47.3, 44.9, 35.6, 34.5, 31.0, 29.5, 20.1, 19.5, 17.3, 14.2, 14.1; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{41}H_{51}NO_8Na^+$, 708.3512; found: 708.3505.

23a: $[\alpha]^{29}_D$ = +7.2(c 2.5, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3345, 3042, 2925, 2872,

1771, 1726, 1518, 1227, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.76 (d, J = 7.5 Hz, 2H), 7.64–7.61 (m, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 5.32 (d, J = 9.2 Hz, 1H), 5.10–5.02 (m, 1H), 4.40 (d, J = 7.2 Hz, 2H), 4.34–4.28 (m, 2H), 4.25 (t, J = 7.0 Hz, 1H), 4.16 (dd, J = 16.4, 8.7 Hz, 1H), 2.95 (td, J = 9.7, 5.0 Hz, 1H), 2.37–2.22 (m, 2H), 2.18–2.04 (m, 2H), 1.47–1.32 (m, 2H), 1.24–1.18 (m, 1H), 1.15–1.11 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.1 Hz, 6H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 171.9, 156.5, 144.2, 143.9, 141.4, 127.8, 127.2, 125.3, 120.1, 77.4, 67.2, 66.1, 59.6, 47.3, 40.3, 34.4, 33.8, 30.8, 26.0, 19.8, 19.6, 17.4, 16.0, 14.3;HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{30}H_{37}NO_6Na^+$, 530.2519; found: 530.2517.

23b: IR (KBr, cm^{-1}) ν_{max}: 3350, 2960, 2871, 1755, 1710, 1533, 1263, 1070, 963; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.76 (d, J = 7.5 Hz, 2H), 7.64–7.61 (m, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 5.35 (d, J = 9.2 Hz, 1H), 5.12 (t, J = 5.9 Hz, 1H), 4.40 (d, J = 7.2 Hz, 2H), 4.36–4.29 (m, 2H), 4.25 (t, J = 7.1 Hz, 1H), 4.18–4.14 (m, 1H), 2.96–2.89 (m, 1H), 2.36–2.26 (m, 2H), 2.11–1.98 (m, 2H), 1.37–1.32 (m, 3H), 1.21–1.13 (m, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 171.8, 156.5, 144.1, 143.9, 141.4, 127.8, 127.2, 125.3, 120.0, 76.2, 67.2, 66.0, 59.5, 47.3, 40.4, 35.4, 34.7, 30.7, 26.2, 20.0, 19.6, 17.3, 14.4, 14.2; HRMS–MALDI (m/z): $[M+Na]^+$ calcdfor $C_{30}H_{37}NO_6Na^+$, 530.2519; found: 530.2518.



23a R^1=H, R^2=Me
23b R^1=Me, R^2=H

24a R^1=H, R^2=Me
24b R^1=Me, R^2=H

25a R^1=H, R^2=Me
25b R^1=Me, R^2=H

General preparation of 24a, 24b, 25a, 25b.

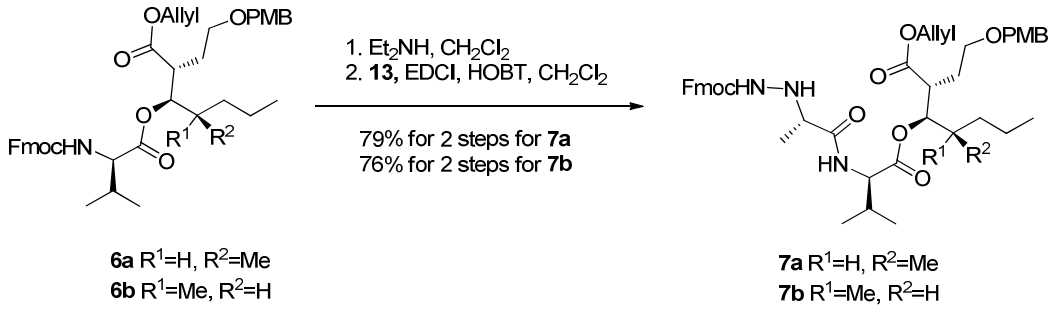
To a solution of Fmoc-protected amino acid 23a/23b (1 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added Et_2NH(10 mL) at room temperature. After 2 hour, the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain **24a** or **24b or 25a or 25b**.

(*R*)-(1*R*,2*R*)-2-methyl-1-((*R*)-2-oxotetrahydrofuran-3-yl)pentyl-2-amino-3-methylbutanoate (24a): $[\alpha]^{29}{}_D$ = +34.0 (*c* 0.2, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3336, 2929, 2874, 1772, 1525, 1460, 1256, 1105, 1028; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dd, *J*= 7.1, 5.1 Hz, 1H), 4.29 (td, *J* = 8.8, 3.7 Hz, 1H), 4.15 (dd, *J* = 16.5, 8.6 Hz, 1H), 3.29 (d, *J* = 4.8 Hz, 1H), 2.92 (ddd, *J* = 17.3, 11.1, 6.4 Hz, 1H), 2.33 (ddd, *J* = 16.6, 12.7, 3.6 Hz, 1H), 2.11–1.97 (m, 3H), 1.61 (br s, 2H), 1.41–1.29 (m, 2H), 1.21–1.13 (m, 1H), 1.09–1.01 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 2H), 0.88 (d, *J* = 6.4 Hz, 2H), 0.87–0.83 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 175.2, 76.7, 66.1, 60.5, 40.2, 34.4, 33.9, 31.5, 26.0, 19.8, 19.7, 16.9, 16.1, 14.3; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{27}NO_4Na^+$, 308.1838; found: 308.1838.

24b: $[\alpha]^{29}{}_D$ = +11.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (t, *J* = 6.0 Hz, 1H), 4.33 (td, *J* = 8.8, 3.6 Hz, 1H), 4.19 (dt, *J* = 16.2, 8.2 Hz, 1H), 3.33 (d, *J* = 5.0 Hz, 1H), 2.91 (td, *J* = 9.4, 6.5 Hz, 1H), 2.40–2.31 (m, 1H), 2.10–1.96 (m, 2H), 1.60 (br s, 2H), 1.41–1.30 (m, 3H), 1.20–1.12 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.91–0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 175.1, 75.5, 66.1, 60.7, 40.3, 35.7, 34.8, 31.6, 26.4, 20.1, 19.8, 17.1, 14.4, 14.3. HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{27}NO_4Na^+$, 308.1838; found: 308.1836.

25a: $[\alpha]^{29}_{D}$ = +11.6(*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 1H), 5.01 (dd, *J* = 7.7, 4.0 Hz, 1H), 4.50 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.28 (td, *J* = 8.7, 3.6 Hz, 1H), 4.16 (dd, *J* = 16.5, 8.4 Hz, 1H), 3.66–3.55 (m, 1H), 2.95 (td, *J* = 9.4, 4.0 Hz, 1H), 2.36–2.24 (m, 2H), 2.22–2.03 (m, 4H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.28–1.18 (m, 3H), 1.15–1.06 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 175.5, 171.6, 77.4, 66.3, 57.6, 50.8, 40.3, 34.3, 34.2, 30.8, 26.1, 21.4, 19.7, 19.7, 17.8, 16.1, 14.4. HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{32}N_2O_5Na^+$, 379.2209; found: 379.2209.

25b: $[\alpha]^{29}_{D}$ = +19.3(*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.69 (d, *J* = 8.9 Hz, 1H), 5.06 (t, *J* = 5.9 Hz, 1H), 4.50 (dd, *J* = 9.2, 5.1 Hz, 1H), 4.30 (td, *J* = 8.8, 3.5 Hz, 1H), 4.17 (dd, *J* = 16.2, 8.8 Hz, 1H), 3.57 (d, *J* = 6.8 Hz, 1H), 2.93 (td, *J* = 9.5, 5.6 Hz, 1H), 2.37–2.19 (m, 2H), 2.14–2.01 (m, 5H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.31–1.24 (m, 2H), 1.19–1.11 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.90–0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.8, 175.6, 171.5, 76.5, 66.2, 57.5, 50.8, 40.4, 35.5, 34.6, 30.7, 26.4, 21.5, 20.0, 19.7, 17.7, 14.7, 14.3; HRMS–MALDI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{32}N_2O_5Na^+$, 379.2209; found: 379.2208.



6a R^1=H, R^2=Me
6b R^1=Me, R^2=H

7a R^1=H, R^2=Me
7b R^1=Me, R^2=H

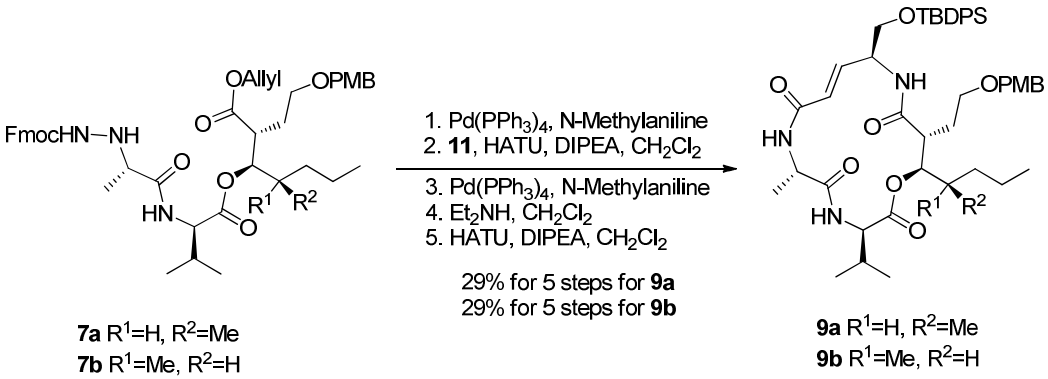
(2*R*,3*R*,4*R*)-allyl-3-(((*R*)-2-((S)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amin

o)propanamido)-3-methylbutanoyl)oxy)-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methylheptanoate (**7a**). To a solution of Fmoc-protected amino acid **6a** (450 mg, 0.62 mml) in CH_2Cl_2 (8 mL) was added $HNEt_2$ (4 mL) at room temperature. After 2 hour, the solvent was removed under reduced pressure. The residue was purified by column chromatography (petroleum ether : ethyl acetate =10 : 1- 4 : 1) to give the amine (290 mg, 95%).

The obtained amine (220 mg, 0.475 mml) and L-Fmoc-alanine **13** (177 mg, 0.57 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL), and HOBt (87 mg, 0.57 mmol), EDCI (109 mg, 0.57 mmol), Et_3N (57 mg, 0.57 mmol) was added successively. The reaction mixture was stirred overnight and the solvent was removed. The residue was dissolved in EtOAc (30 mL) and washed successively with 1% HCl, sat.$NaHCO_3$, brine, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 4:1) to give the title compound **7a** (300 mg, 83%) as a white solid. $[\alpha]^{27}_{D}$ = +19.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3365, 2934, 2872, 1734, 1680, 1514, 1456, 1247, 1177, 1093, 745. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H)，7.20 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 1H), 5.91–5.81 (m, 2H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.03–5.00 (m, 1H), 4.55–4.51 (m, 3H), 4.43–4.38 (m, 3H), 4.36 (s, 2H), 4.22 (t, *J* = 7.1 Hz, 1H), 3.77 (s, 3H), 3.48–3.43 (m, 1H), 3.40–3.34 (m , 1H), 3.04 (dt, *J* = 9.4, 4.6 Hz, 1H), 2.17–2.12 (m , 1H), 1.94–1.88 (m, 1H), 1.82–1.77 (m, 1H), 1.74–1.63 (m, 1H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.40–1.29 (m, 2H), 1.21–1.07 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 172.3, 170.5, 159.2, 156.1, 143.9, 143.9，141.3, 131.8, 130.3, 129.3, 127.8, 127.1, 125.1,

120.0, 118.7, 113.8, 78.7, 72.7, 67.1, 65.5, 57.9, 55.3, 50.7, 47.2, 44.3, 34.9, 33.8, 31.2, 29.6, 19.7, 19.4, 18.9, 17.7, 15.9, 14.2; $[M+Na]^+$ calcd for $C_{44}H_{56}NO_8Na^+$, 779.3884; found: 779.3882.

7b: $[\alpha]^{29}_D$ = +3.7 (*c* 1.2, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3315, 2961, 2872, 1734, 1515, 1244, 1178, 1086, 983; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 1H), 5.88–5.79 (m, 2H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.3 Hz, 1H), 5.10 (t, *J* = 5.7 Hz, 1H), 4.53–4.48 (m, 3H), 4.42–4.38 (m, 3H), 4.36 (s, 2H), 4.22 (t, *J* = 7.0 Hz, 1H), 3.78 (s, 3H), 3.48–3.42 (m, 1H), 3.40–3.34 (m, 1H), 3.02 (dt, *J* = 10.0, 5.1 Hz, 1H), 2.15–2.10 (m, 1H), 1.95–1.86 (m, 1H), 1.81–1.68 (m, 2H), 1.43 (d, *J* = 6.5 Hz, 3H), 1.40–1.29 (m, 3H), 1.15–1.07 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.90–0.85 (m, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.2, 170.5, 159.3, 156.2, 144.0, 143.9, 141.4, 131.9, 130.3, 129.4, 127.8, 127.2, 125.2, 120.1, 118.9, 113.9, 78.1, 72.8, 67.2, 65.7, 57.9, 55.4, 50.7, 47.3, 45.0, 35.6, 34.7, 31.2, 29.8, 29.6, 20.0, 19.5, 18.8, 17.8, 14.4, 14.2;HRMS–MALDI (m/z): $[M+Na]^+$ calcdfor$C_{44}H_{56}N_2O_9Na^+$,779.3884; found: 779.3880.



7a R^1=H, R^2=Me
7b R^1=Me, R^2=H

9a R^1=H, R^2=Me
9b R^1=Me, R^2=H

(3*R*,6*S*,11*S*,14*R*,15*R*,*E*)-11-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropyl-

14-(2-((4-methoxybenzyl)oxy)ethyl)-6-methyl-15-((*R*)-pentan-2-yl)-1-oxa-4,7,12-triazacyclopentadec-9-ene-2,5,8,13-tetraone (**9a**).To a solution of **7a** (210 mg, 0.278 mmol) in anhydrous THF (5 mL), $Pd(PPh_3)_4$ (64 mg, 0.055 mmol) and N-methylaniline (59 mg, 0.55 mmol). The reaction mixture was stirred for 30 min at room temperature, concentrated and purified through column chromatography (Petroleum ether : ethyl acetate = 20 : 1 to 1 : 1) to afford an acid, which was used directly in the next step.

The obtained acid above and amine **11** (233 mg, 0.46 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL), and DIPEA (119 mg, 0.92 mmol), HATU (380 mg, 0.92 mmol). The reaction mixture was stirred for 2h, and the solvent was removed. The residue was dissolved in EtOAc (20 mL), and was washed successively with 1 % HCl, sat.$NaHCO_3$, brine, dried over Na_2SO_4 and filtrated; the mother liquid was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 4 : 1) to give the amide(200 mg, 65% for two steps) as a colorless oil.

The amide above (130 mg, 0.117 mmol) and $Pd(PPh_3)_4$ (27 mg, 0.023 mmol) was dissolved in anhydrous THF (3 mL). And N-methylaniline (25 mg, 0.23 mmol) was added. After 30min, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether : ethyl acetate = 4 : 1 to 1 : 1) to afford an acid.

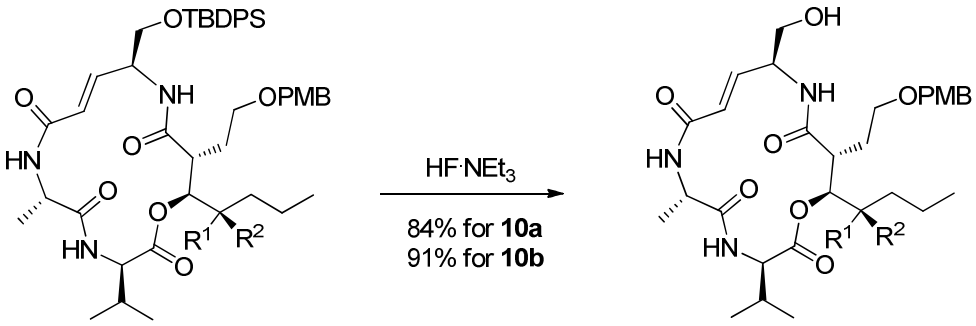
The carboxylic acid was dissolved in CH_2Cl_2 (1.6 mL) and diethylamine (0.8 mL), the reaction mixture was stirred at room temperature for 1 h, and then the solvent was removed under reduced pressure to give a crude amino acid.

The residue above was dissolved in CH_2Cl_2 (120 mL), and DIPEA (132 mg, 1.02

mmol) and HATU (309 mg, 0.814 mmol) was added successively at 0°C. After addition was completed, the reaction mixture was allowed to warm to room temperature and stirred for 24 h. The solvent was removed under reduced pressure; the residue was dissolved in EtOAc (50 mL) and washed successively with 1% HCl, sat. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 1: 5) to give the cyclic product **9a** (44 mg, 29% for five steps) as a power.$[\alpha]^{29}_{D}$ = +32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 7.68 (d, *J* = 6.9 Hz, 4H), 7.44–7.38 (m, 6H), 7.10 (dd, *J* = 15.2, 2.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.11 (d, *J* = 15.3 Hz, 1H), 5.46 (d, *J* = 10.7 Hz, 1H), 4.47 (d, *J* = 6.7 Hz, 1H), 4.39–4.33 (m, 1H), 4.16 (d, *J* = 11.6 Hz, 1H), 4.12 (d, *J* = 11.6 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.63–3.59 (m, 1H), 3.34 (t, *J* = 6.1 Hz, 2H), 2.95 (td, *J* = 10.2, 3.9 Hz, 1H), 2.15–2.03 (m, 1H), 1.91–1.81 (m, 2H), 1.75–1.66 (m, 1H), 1.53–1.48 (m, 1H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.35–1.23 (m, 3H), 1.05 (s, 9H), 0.98–0.92 (m, 12H); ^{13}C NMR (100 MHz, MeOD) δ 174.9, 174.3, 170.6, 168.8, 160.6, 145.5, 136.5, 133.9, 133.8, 131.1, 130.9, 130.3, 128.9, 128.9, 119.5, 114.5, 79.9, 73.4, 67.9, 66.8, 59.0, 55.5, 53.0, 52.5, 46.2, 35.0, 33.5, 33.0, 30.6, 27.2, 21.4, 19.9, 19.8, 18.7, 18.5, 16.9, 14.4; $[M+Na]^+$ calcd for $C_{47}H_{65}N_3O_8SiNa^+$, 850.4439; found: 850.4436.

9b. $[\alpha]^{27}_{D}$ = +17.8 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3311, 2956, 2864, 1727, 1517, 1248, 1106, 1036, 841; ^{1}H NMR (400 MHz, MeOD) δ 7.69 (d, *J* = 6.4 Hz, 4H), 7.46–7.38 (m, 6H), 7.10 (dd, *J* = 15.1, 2.7 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.11 (dd, *J* = 15.1, 2.2 Hz, 1H), 5.53 (d, *J* = 10.6 Hz, 1H), 4.47–4.73 (m, 1H), 4.37–4.31 (m, 1H), 4.16 (d, *J* = 11.3 Hz, 1H), 4.12 (d, *J* = 11.3 Hz, 1H), 3.74 (s, 3H), 3.67 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.60 (dd, *J* = 9.9, 7.0 Hz, 1H), 3.37–3.33 (m, 1H), 2.89 (td, *J* = 10.1, 4.0 Hz, 1H), 2.09–2.02 (m, 1H), 1.86–1.80 (m, 1H), 1.75–1.67

(m, 1H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.35–1.29 (m, 4H), 1.05 (s, 9H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ 174.8, 174.3, 170.3, 168.8, 160.6, 145.6, 136.6, 133.9, 133.8, 131.1, 131.0, 130.9, 130.4, 128.9, 128.8, 119.4, 114.5, 77.8, 73.5, 67.8, 66.8, 59.2, 55.5, 53.0, 52.6, 46.6, 37.4, 34.7, 33.5, 30.5, 27.2, 21.3, 20.0, 19.8, 18.7, 18.7, 14.3, 13.3; $[M+Na]^+$ calcd for $C_{47}H_{65}N_3O_8SiNa^+$, 850.4439; found: 850.4436.



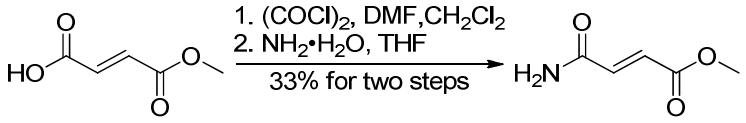
9a R^1=H, R^2=Me
9b R^1=Me, R^2=H

10a R^1=H, R^2=Me
10b R^1=Me, R^2=H

(3*R*,6*S*,11*S*,14*R*,15*R*,*E*)-11-(hydroxymethyl)-3-isopropyl-14-(2-((4-methoxybenzyl)oxy)ethyl)-6-methyl-15-((*R*)-pentan-2-yl)-1-oxa-4,7,12-triazacyclopentadec-9-ene-2,5,8,13-tetraone (**10a**). To a solution of **9a** (40 mg, 0.048 mmol) in dry THF (4 mL) was added Et_3N (98 mg, 0.97 mmol) and followed by 3HF·NEt_3 (110 μL, 1.93 m mol). The mixture was stirred under argon at room temperature for 4 h. The mixture w as directly purified through column chromatography (ethyl acetate : CH_3OH = 10 : 1) to afford **10a** (24 mg, 84%) as a solid. $[\alpha]^{24}{}_D$ = +44.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 8.32 (d, *J* = 9.9 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.96 (dd, *J* = 15.1, 2.8 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.11 (dd, *J* = 15.1, 2.2 Hz, 1H), 5.45 (d, *J* = 10.0Hz 1H), 4.74–4.69 (m, 1H), 4.51–4.36 (m, 4H), 3.78 (s, 3 H), 3.63–3.51 (m, 4H), 3.01 (td, *J* = 10.4, 4.0 Hz, 1H), 2.13–2.03 (m, 1H), 1.95–1.84 (m, 2H), 1.78–1.69 (m, 1H), 1.60–1.49 (m, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.34–1.28

(m, 3H), 0.98–0.92 (m, 12H); ^{13}C NMR (100 MHz, MeOD) δ 175.0, 174.5, 170.6, 16 9.0, 160.7, 146.0, 131.3, 130.5, 119.6, 114.6, 80.0, 73.4, 67.8, 64.5, 59.1, 55.5, 53.5, 5 2.5, 46.3, 35.0, 33.5, 33.1, 30.5, 21.4, 19.9, 18.7, 18.4, 16.9, 14.3; $[M+Na]^+$ calcd for $C_{31}H_{47}N_3O_8Na^+$, 612.3258; found: 612.3258.

10b. $[\alpha]^{29}_D$ = +40.8 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max}: 3275, 2958, 2870, 1729, 1679, 1517, 1247, 1177, 844; ^{1}H NMR (400 MHz, MeOD) δ 7.75 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 15.1, 2.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.10 (d, *J* = 15.2 Hz, 1H), 5.53 (d, *J* = 10.6 Hz, 1H), 4.74–4.69 (m, 1H), 4.49–4.34 (m, 4H), 3.78 (s, 3H), 3.61–3.52 (m, 4H), 2.95 (td, *J* = 10.3, 3.9 Hz, 1H), 2.08–2.02 (m, 1H), 1.89–1.84 (m, 2H), 1.77–1.70 (m, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.37–1.30 (m, 3H), 1.17–1.08 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.6 Hz, 3H), 0.95 (d, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}CNMR (100 MHz, MeOD) δ 174.8, 174.4, 170.3, 168.9, 160.7, 146.0, 131.3, 130.6, 119.6, 114.6, 77.9, 73.5, 67.7, 64.5, 59.2, 55.5, 53.4, 52.5, 46.6, 37.4, 34.8, 33.5, 30.7, 21.4, 20.0, 18.7, 18.6, 14.3, 13.4; $[M+Na]^+$ calcd for $C_{31}H_{47}N_3O_8Na^+$, 612.3258; found: 612.3258.

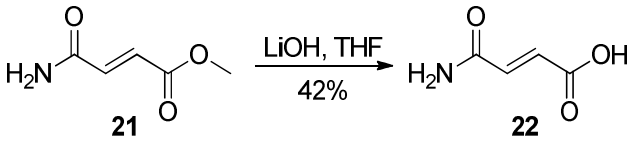


20 **21**

(*E*)-methyl 4-amino-4-oxobut-2-enoate (**21**).

To a solution of **20** (2 g, 15 mmol) in CH_2Cl_2 was added oxalyl chloride (2.93 g, 23 mmol), and then 0.1 ml DMF was added. The reaction mixture was stirred for 30 min. The mixture was concentrated to get a solid which can be used without further purification. The solid was dissolved in anhydrous THF (10 mL). And the solution was added to a mixture of $NH_3{\cdot}H_2O$ (5 mL) in THF (10 mL) at 0°C. After 30 min, the

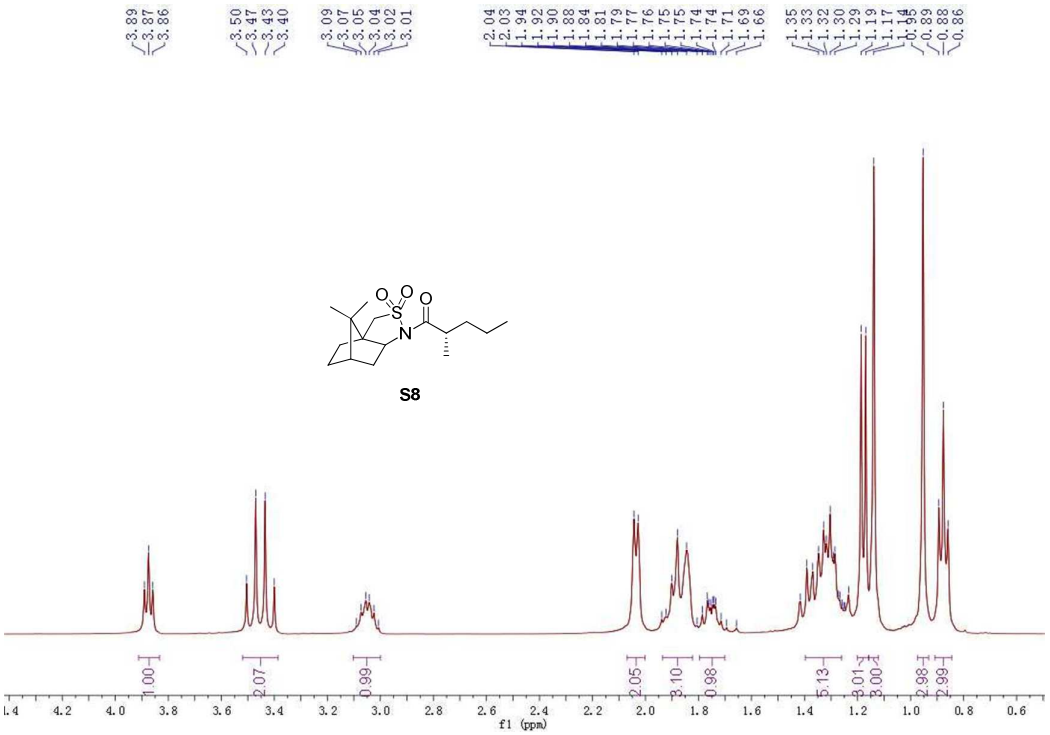
reaction mixture was quenched by H_2O, and extracted with CH_2Cl_2. The mother solution was evaporated under reduced pressure and the residue was further purified through column chromatography (petroleum ether : ethyl acetate = 10:1 to 1:1) to give the title product **21** (660 mg, 33% for two steps) as a white solid.^{1}H NMR (400 MHz, MeOD) δ 7.03 (d, J = 15.6 Hz, 1H), 6.73 (d, J = 15.6 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 168.0, 167.1, 137.4, 130.9, 52.4.



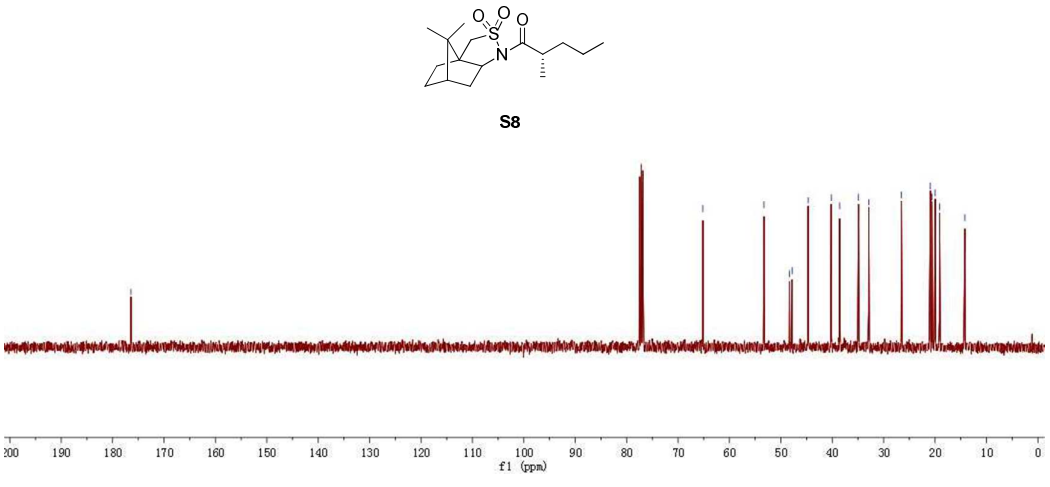
(*E*)-4-amino-4-oxobut-2-enoic acid (**22**).

To a solution of **21** (600 mg, 4.65 mml) in H_2O/THF (9 mL/9 mL) was added $LiOH{\cdot}H_2O$ (322 mg, 7.67 mml), after half an hour, the solvents were evaporated in vacuum and directly purified through chromatography (CH_2Cl_2:CH_3OH = 5%) to give the title product **22** (227 mg, 42%) as a white solid.IR (KBr, cm^{-1}) ν_{max}: 3399, 3165, 2923, 2848, 1690, 1428, 1306, 1191, 947; ^{1}H NMR (400 MHz, MeOD) δ 7.00 (d, J = 15.6 Hz, 1H), 6.69 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, MeOD) δ 168.3, 168.2, 137.2, 131.9; HRMS–ESI (m/z): $[M-H]^+$ calcd for $C_4H_4NO_3^-$, 114.0191; found: 114.0190.

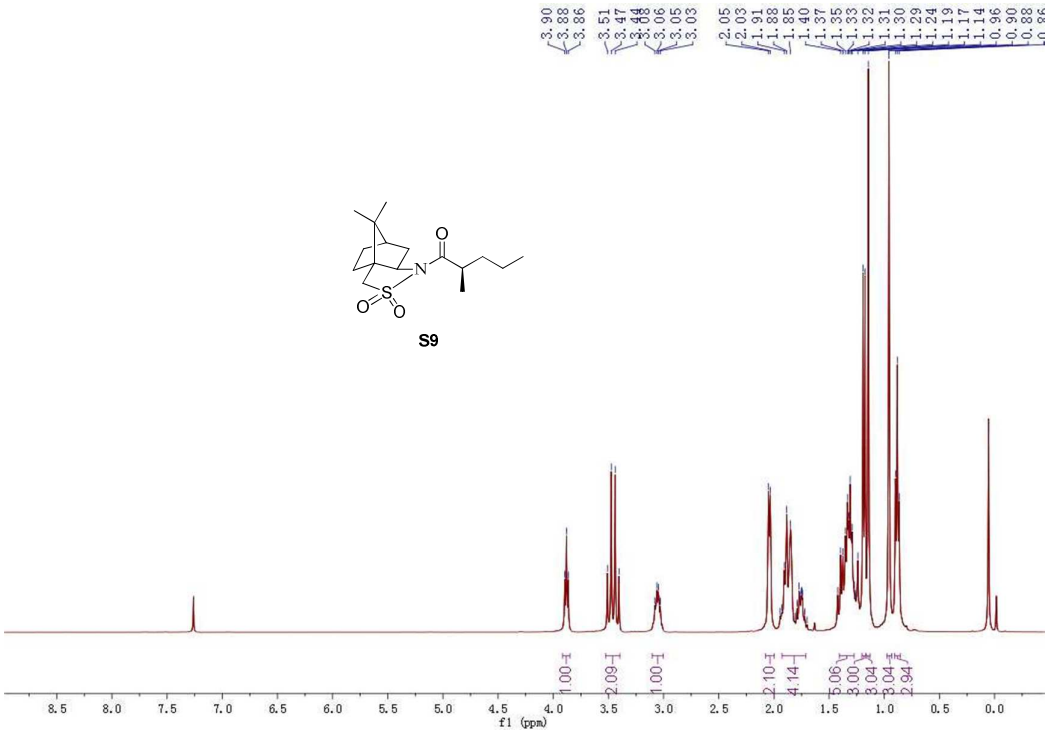
2. Copies of NMR Spectra



S8



S8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0.88
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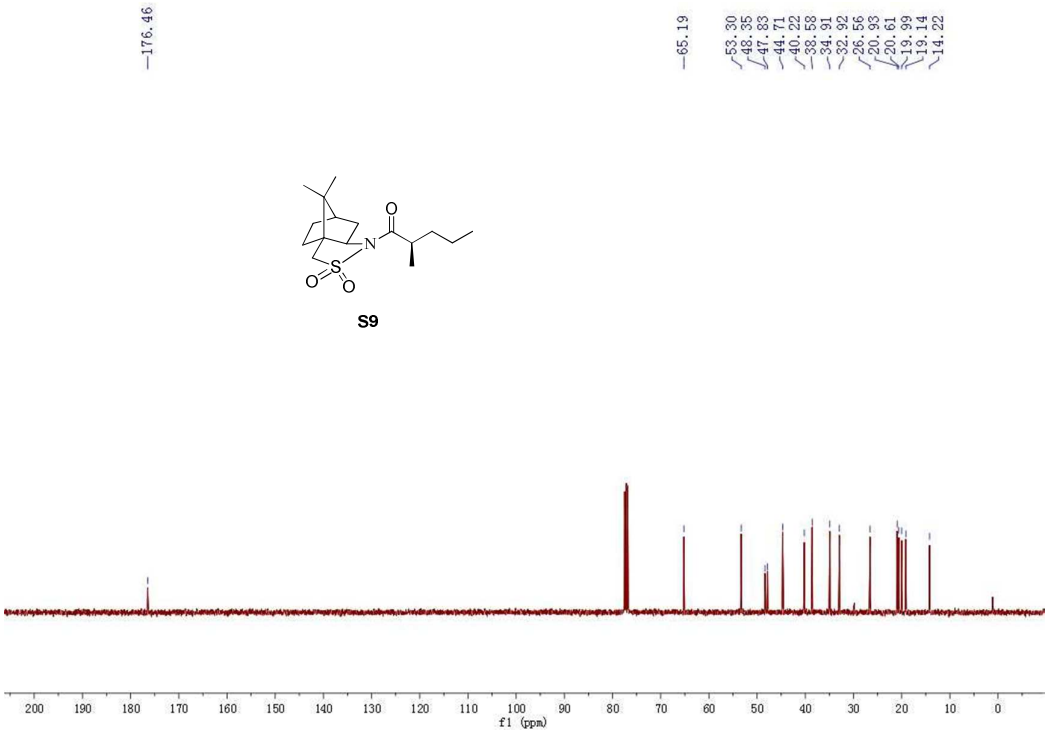
2.09
1.00
2.10
4.14
5.06
3.00
3.04
3.04
2.94
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

S9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32.92
26.56
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19.99
19.14
14.22
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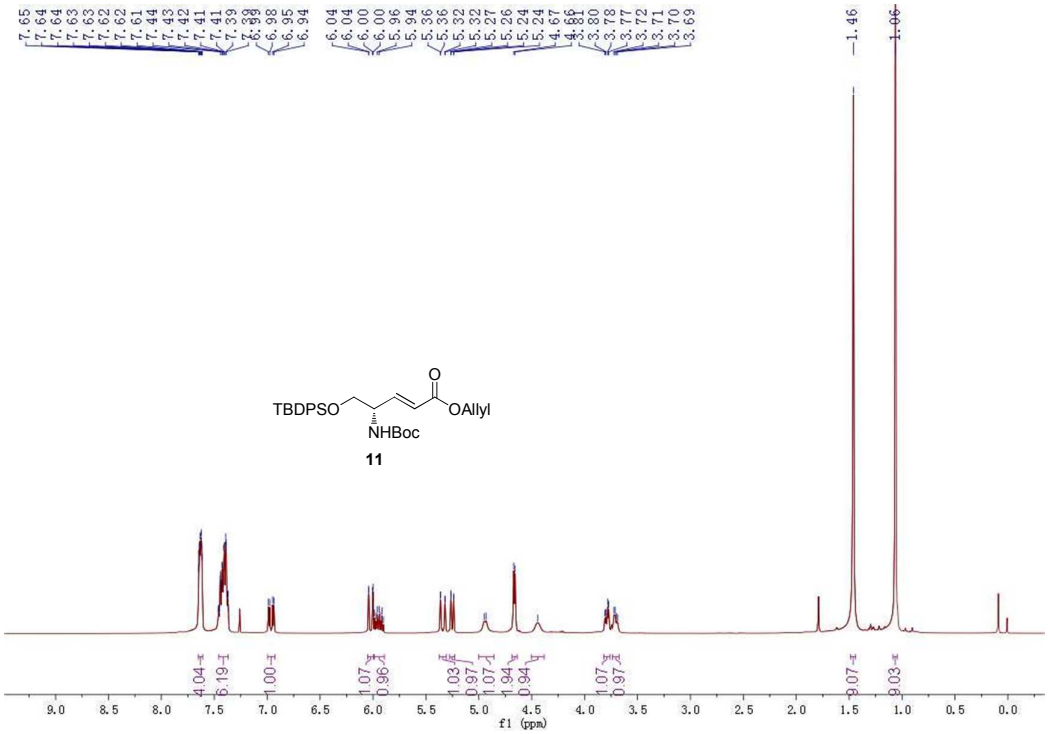
f1 (ppm)

S9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11
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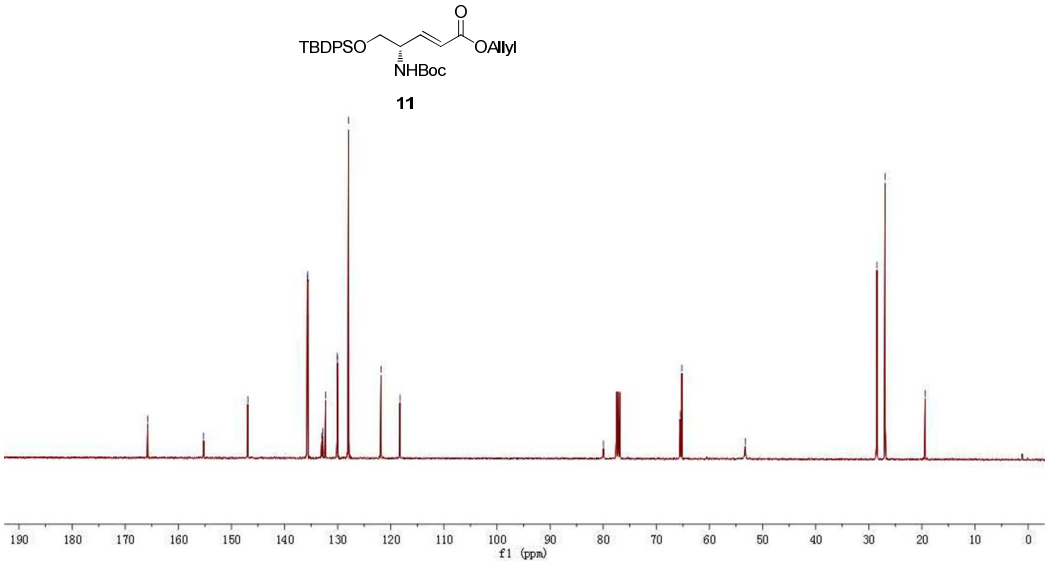
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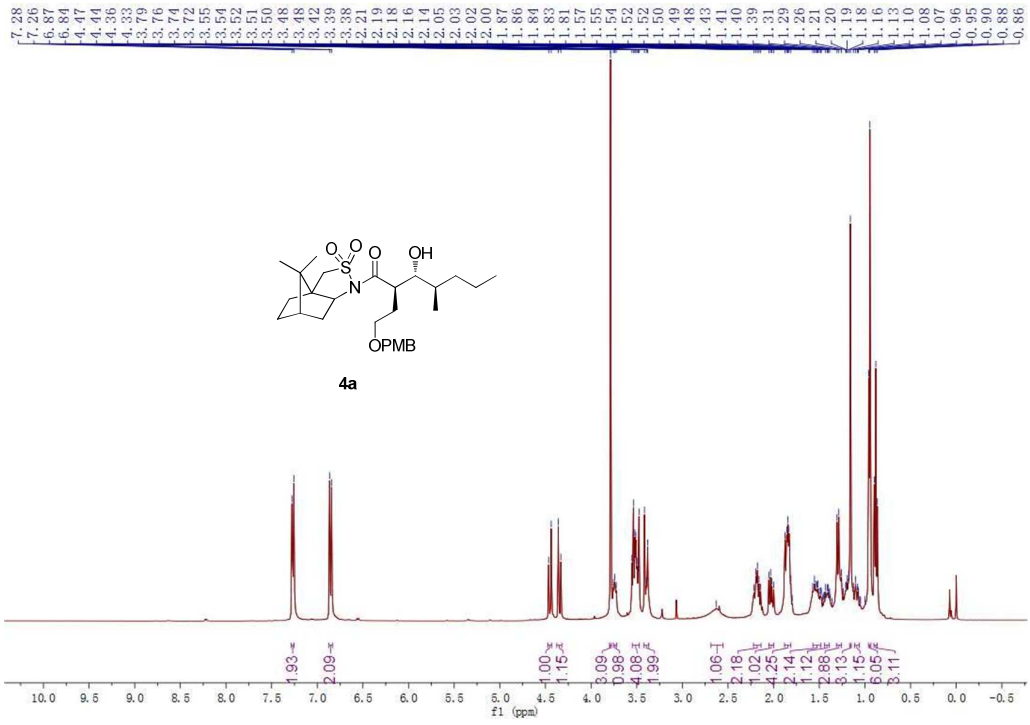
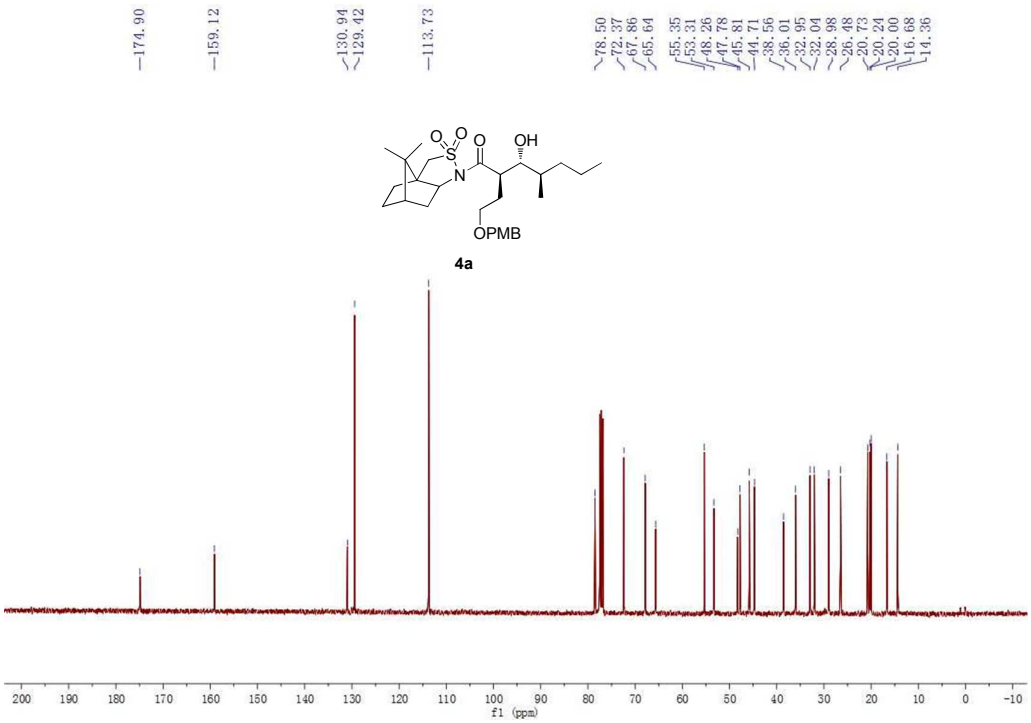
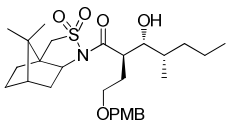
11
f1 (ppm)



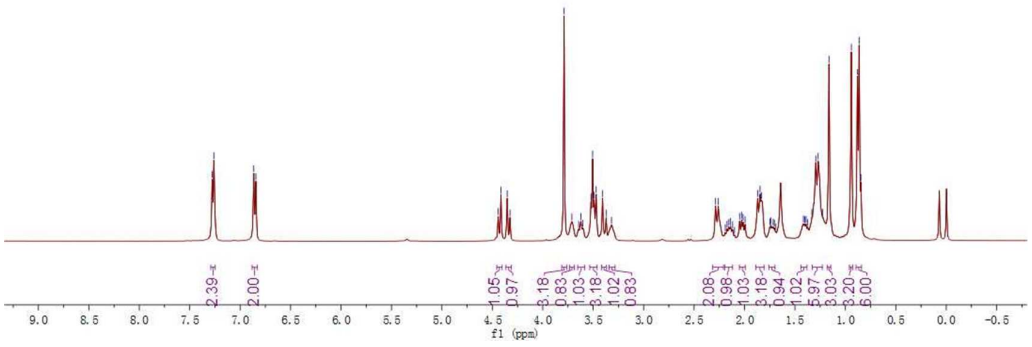
4a

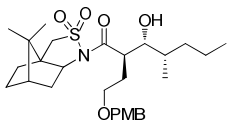


4a

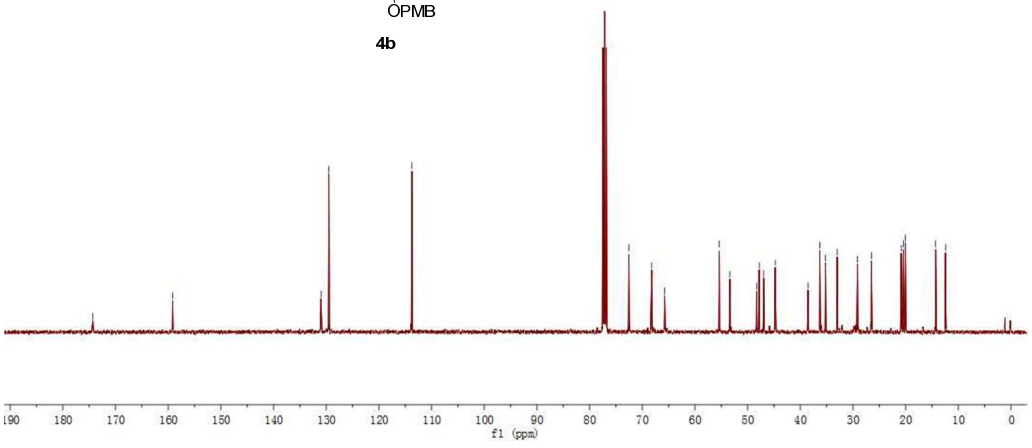

O
O
S
N
O
OH
OPMB

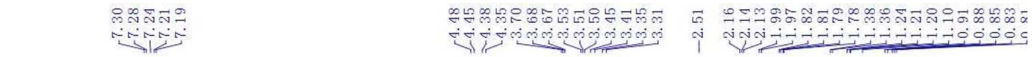
4b

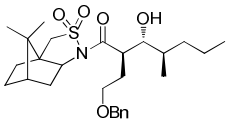

2.39
2.00
1.05
0.97
3.18
0.83
1.03
3.18
1.02
0.83
2.08
0.98
1.03
3.18
0.94
1.02
5.97
3.03
3.20
6.00
f1 (ppm)


O
O
S
N
O
OH
OPMB

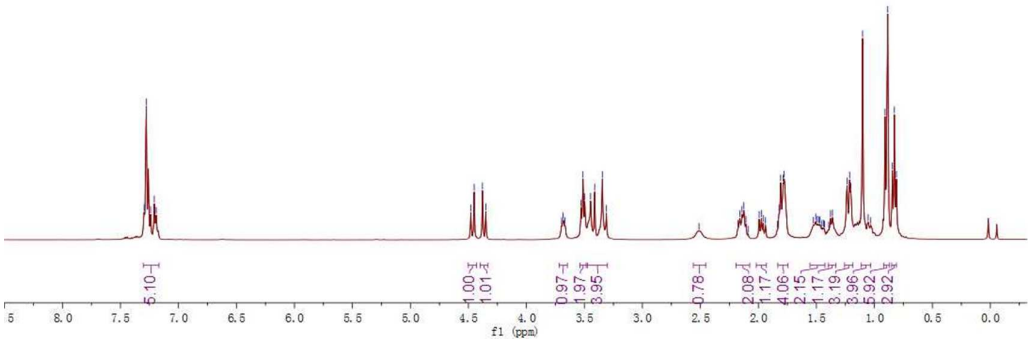
4b


f1 (ppm)

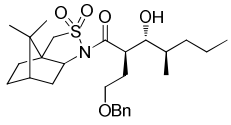

7.30
7.28
7.24
7.21
7.19
4.48
4.45
4.38
4.35
3.70
3.68
3.67
3.53
3.51
3.50
3.45
3.41
3.35
3.31
2.51
2.16
2.14
2.13
1.99
1.97
1.82
1.81
1.79
1.78
1.38
1.36
1.24
1.21
1.20
1.10
0.91
0.88
0.85
0.83
0.81


O
O
S
N
O
OH
OBn

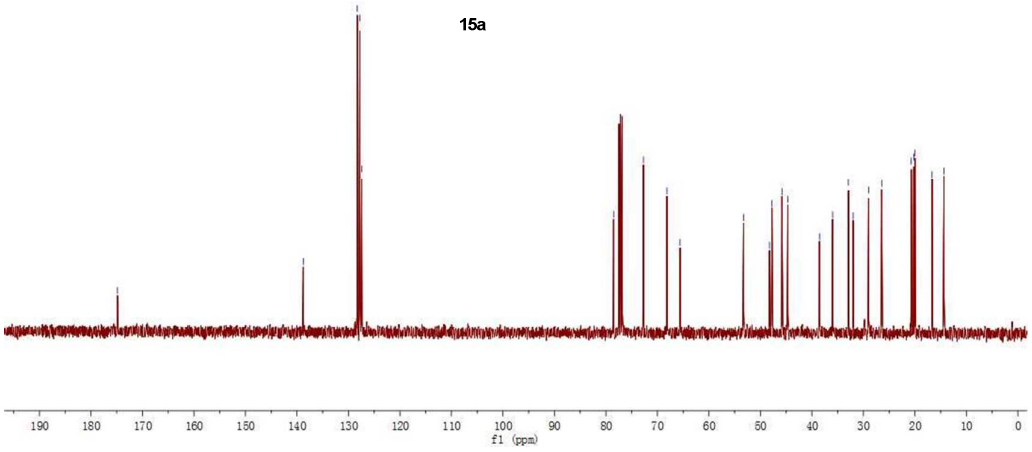
15a

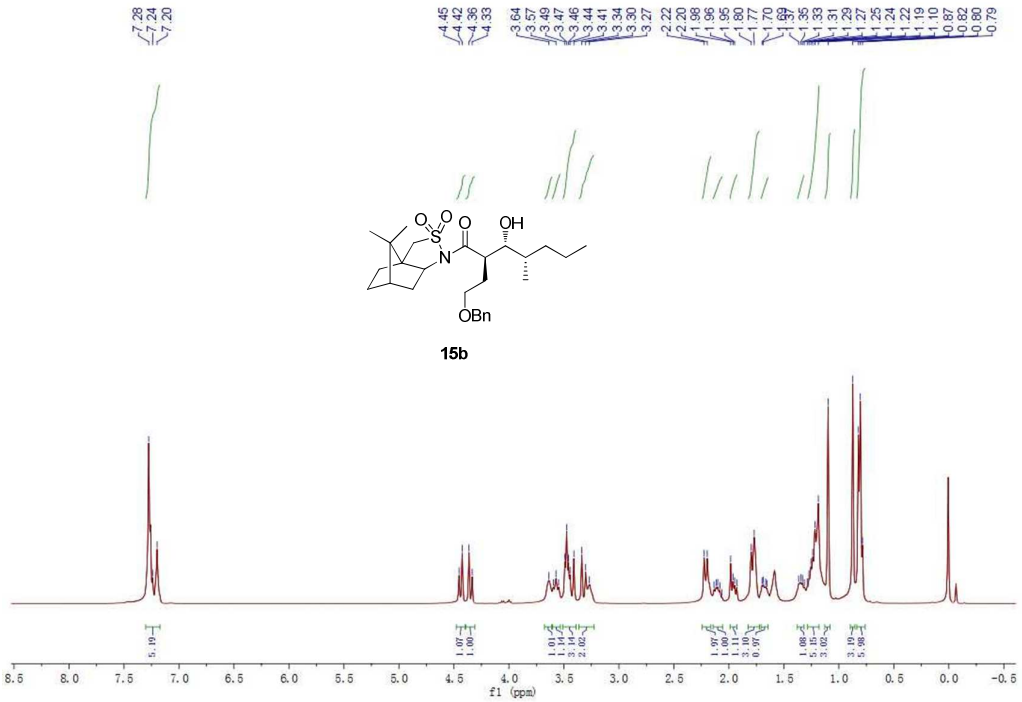

5.10
1.00
1.01
0.97
1.97
3.95
0.78
2.08
1.17
4.06
2.15
1.17
3.19
3.96
5.92
2.92
f1 (ppm)


174.86
138.78
128.28
127.79
127.43
78.51
72.71
68.15
65.61
53.27
48.23
47.76
45.82
44.68
38.53
35.98
32.92
31.99
28.99
26.45
20.71
20.23
19.98
16.67
14.35

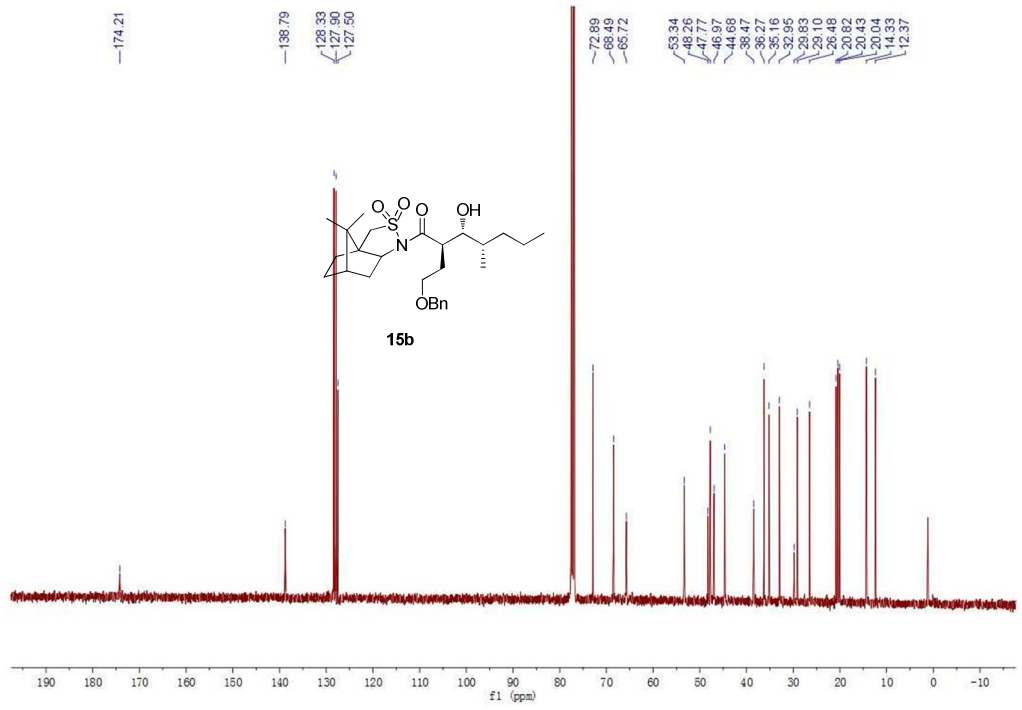

O
O
S
N
O
OH
OBn

15a

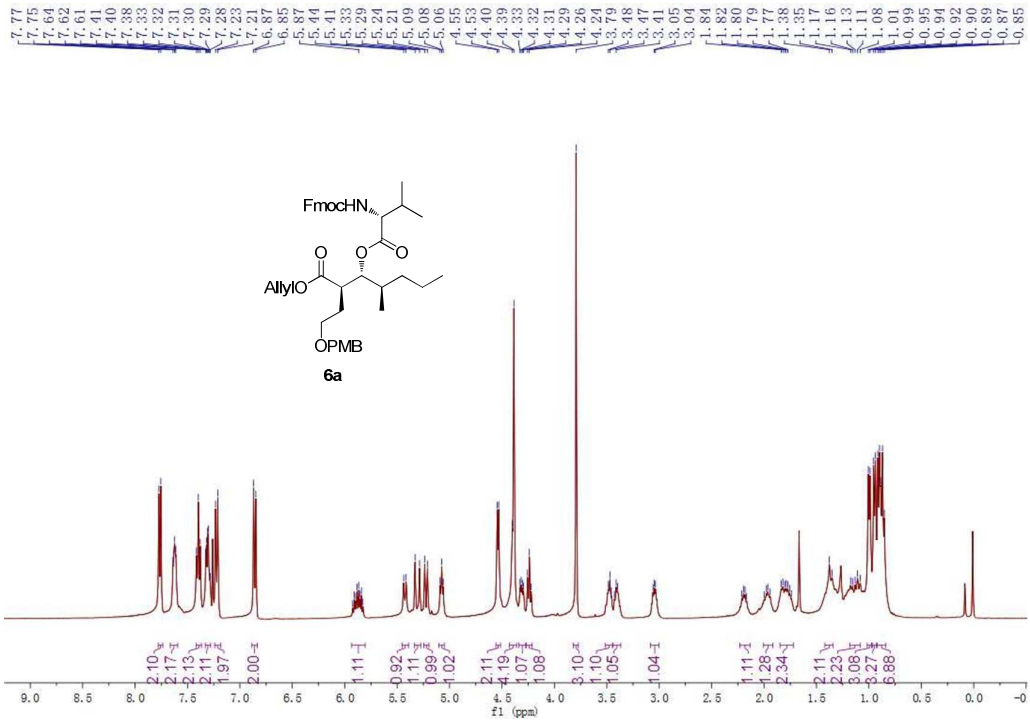

f1 (ppm)

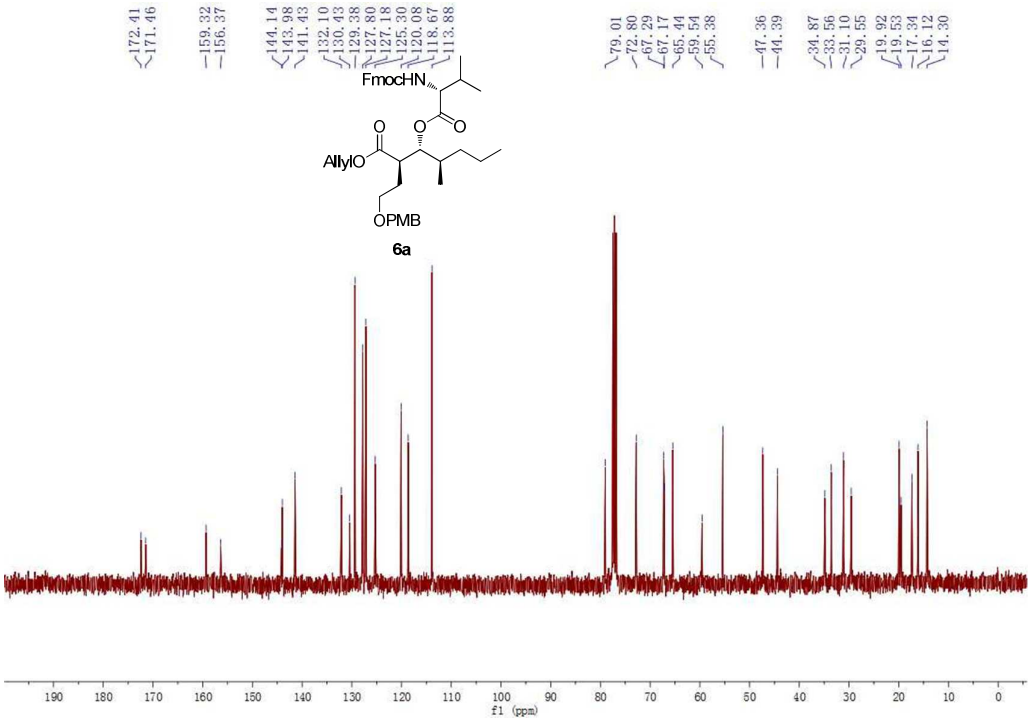

7.28
7.24
7.20
4.45
4.42
4.36
4.33
3.64
3.57
3.49
3.47
3.46
3.44
3.41
3.34
3.30
3.27
2.22
2.20
1.98
1.96
1.95
1.80
1.77
1.70
1.69
1.37
1.35
1.33
1.31
1.29
1.27
1.25
1.24
1.22
1.19
1.10
0.87
0.82
0.80
0.79
O
O
S
N
O
OH
OBn
5.19
1.07
1.00
1.01
1.14
3.14
2.02
1.97
1.00
1.11
3.10
0.95
1.08
5.15
3.02
3.19
5.98
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)

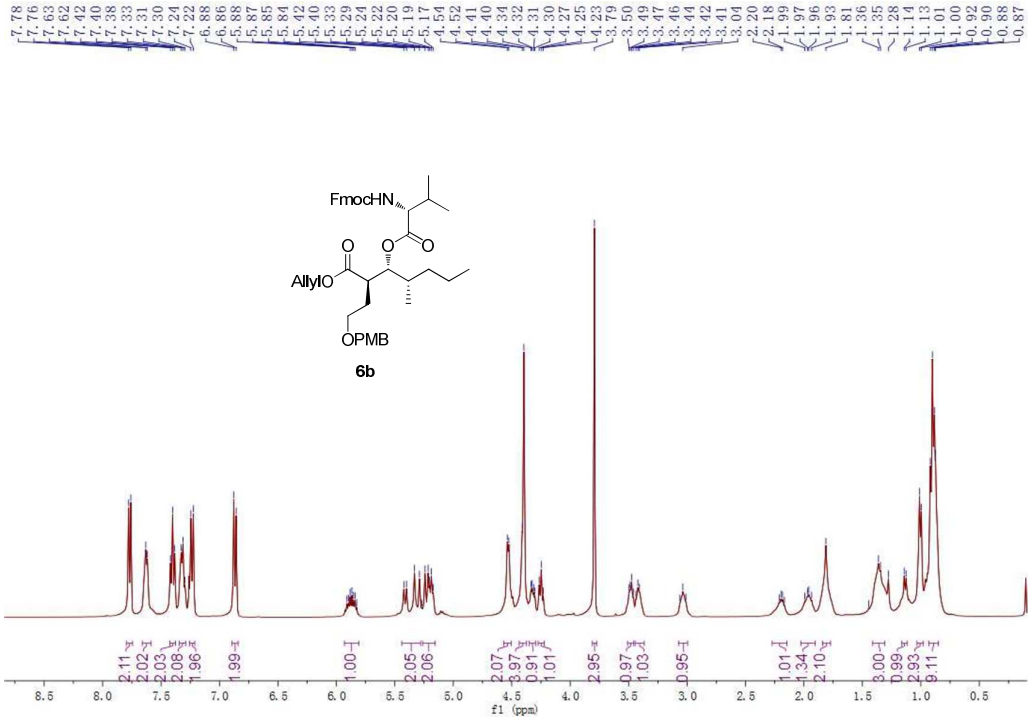
15b

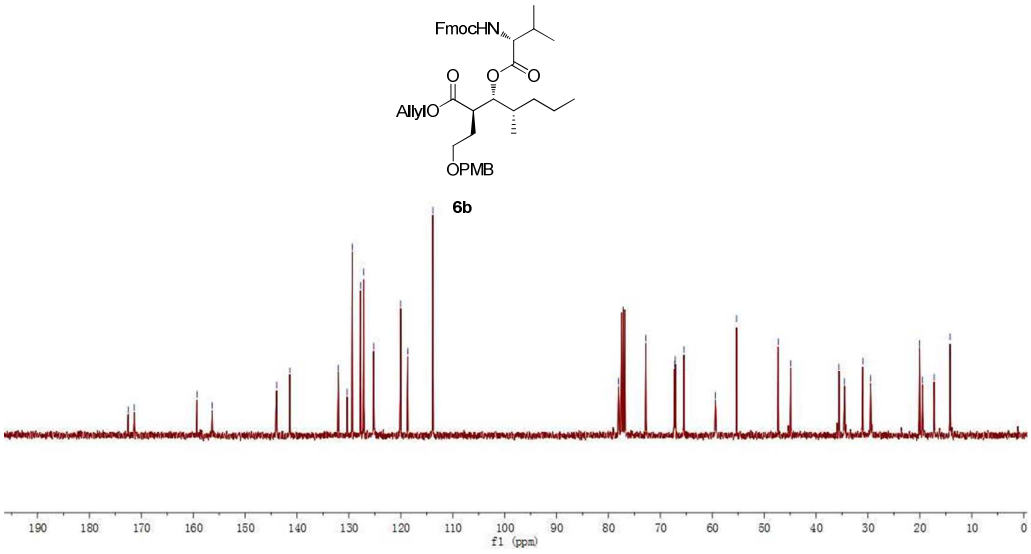

174.21
138.79
128.33
127.90
127.50
72.89
68.49
65.72
53.34
49.26
47.77
46.97
44.68
38.47
36.27
35.16
32.95
29.83
29.10
26.48
20.82
20.43
20.04
14.33
12.37
O
O
S
N
O
OH
OBn
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

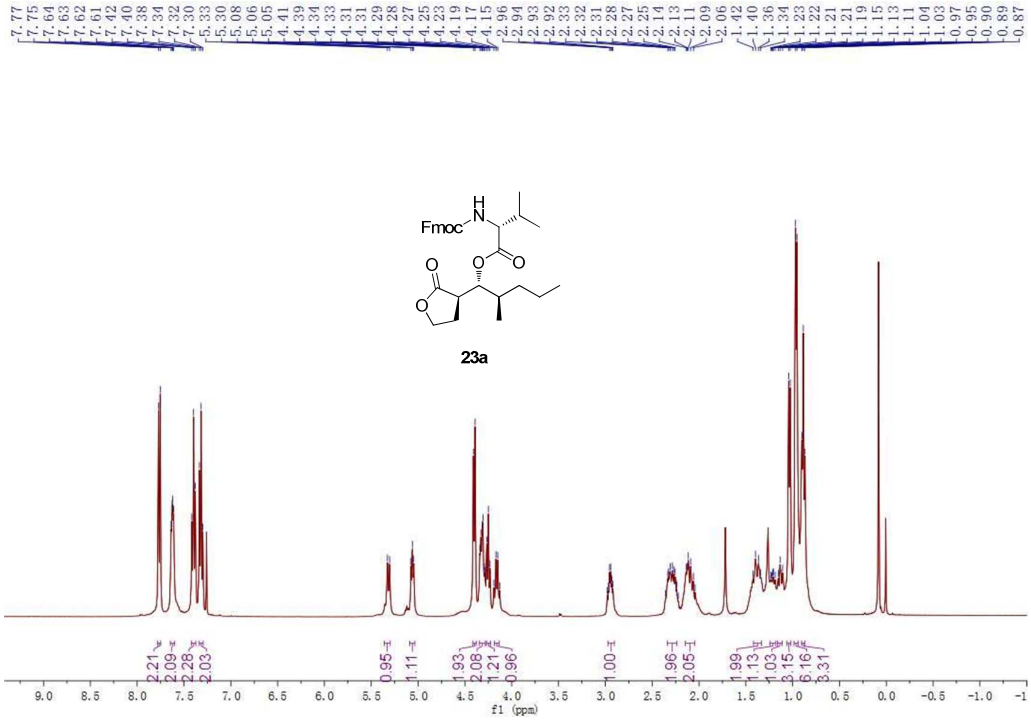
15b

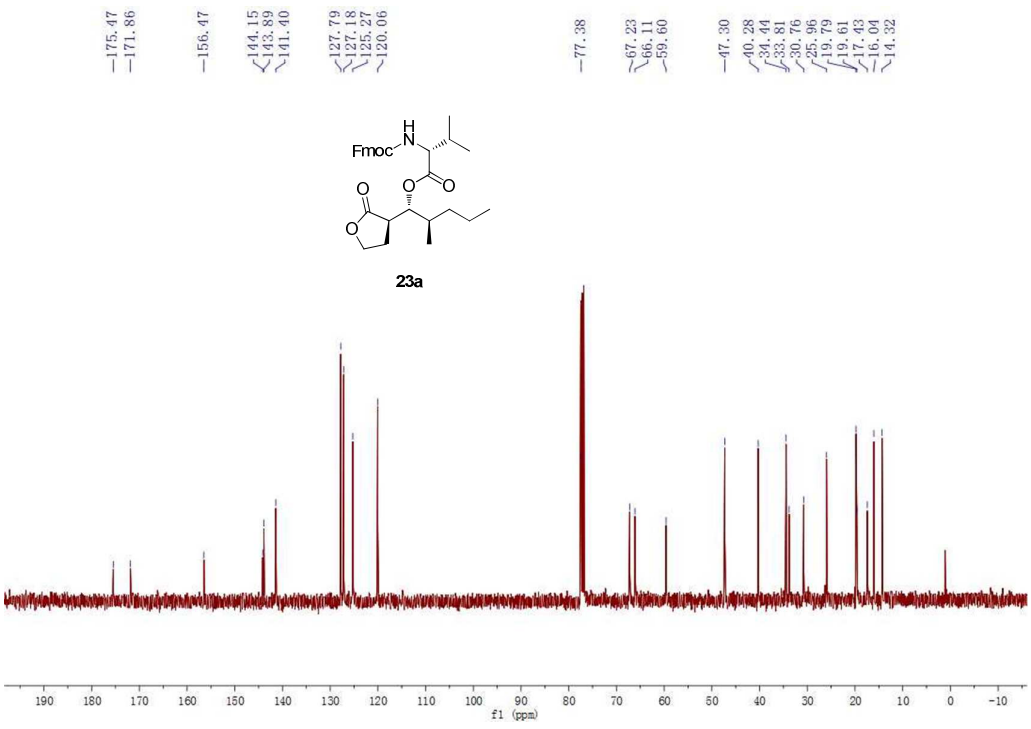

FmocHN
O
O
O
AllylO
OPMB
6a
f1 (ppm)

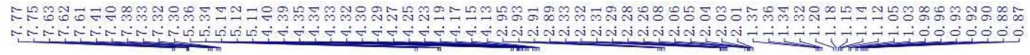

FmocHN
O
O
O
AllylO
OPMB
6a
f1 (ppm)

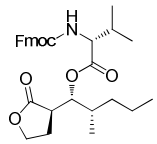

FmocHN
O
O
O
AllylO
OPMB
6b
f1 (ppm)


FmocHN
O
O
O
AllylO
OPMB
6b
f1 (ppm)

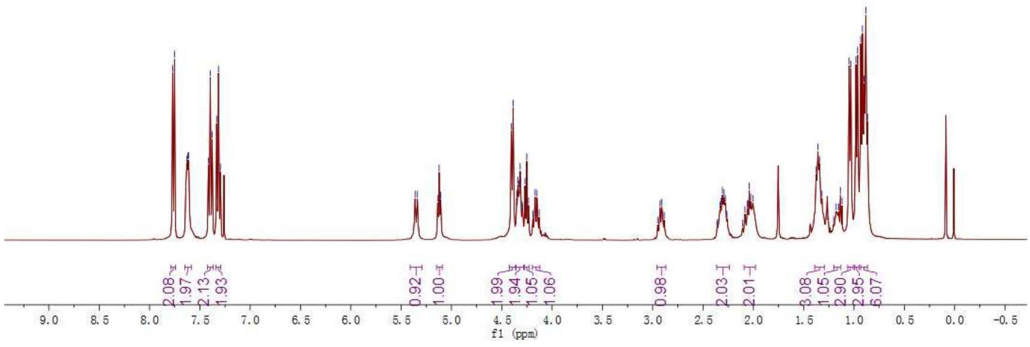

7.77 7.75 7.64 7.63 7.62 7.61 7.42 7.40 7.38 7.34 7.32 7.30 5.33 5.30 5.08 5.06 5.05 4.41 4.39 4.34 4.33 4.31 4.31 4.29 4.28 4.27 4.25 4.23 4.19 4.17 4.15 2.96 2.94 2.93 2.92 2.33 2.32 2.31 2.28 2.27 2.25 2.14 2.13 2.11 2.09 2.06 1.42 1.40 1.36 1.34 1.23 1.22 1.21 1.21 1.19 1.15 1.13 1.11 1.04 1.03 0.97 0.95 0.90 0.89 0.87
Fmoc
H
N
O
O
O
O
23a
2.21 2.09 2.28 2.03 0.95 1.11 1.93 2.08 1.21 0.96 1.00 1.96 2.05 1.99 1.13 1.03 3.15 6.16 3.31
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 -1.0 -1
f1 (ppm)


175.47 171.86 156.47 144.15 143.89 141.40 127.79 127.18 125.27 120.06 77.38 67.23 66.11 59.60 47.30 40.28 34.44 33.81 30.76 25.96 19.79 19.61 17.43 16.04 14.32
Fmoc
H
N
O
O
O
O
23a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

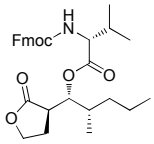



Fmoc
H
N
O
O
O
O

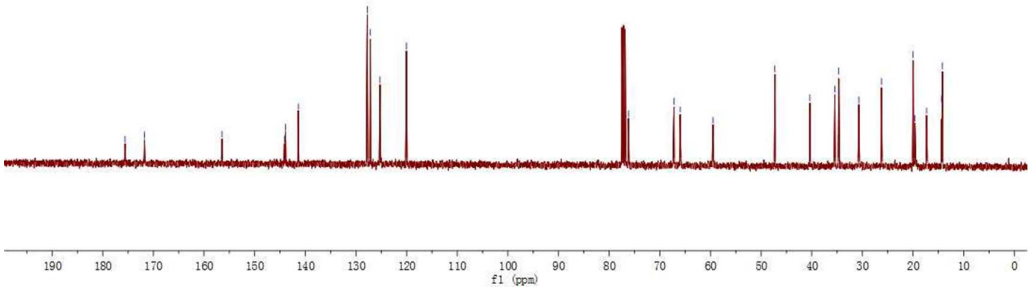
23b

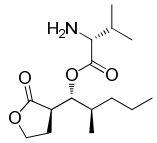

2.08
1.97
2.13
1.93
0.92
1.00
1.99
1.94
1.05
1.06
0.98
2.03
2.01
3.08
1.05
2.90
2.95
6.07
f1 (ppm)


175.60
171.76
156.45
144.13
143.90
141.38
127.76
127.16
125.26
120.04
76.19
67.20
65.98
59.50
47.28
40.37
35.44
34.66
30.70
26.23
19.99
19.63
17.33
14.36
14.20

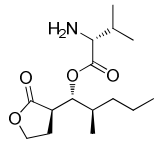

Fmoc
H
N
O
O
O
O

23b

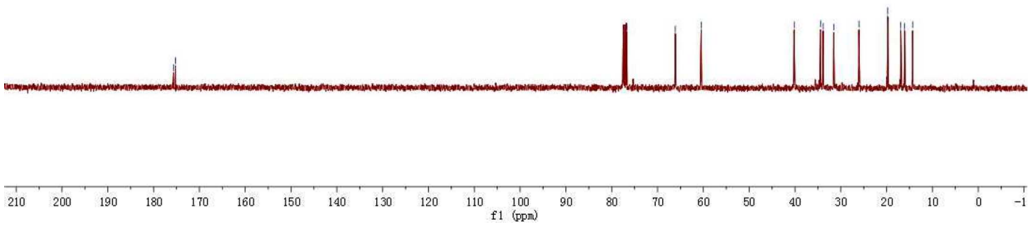

f1 (ppm)

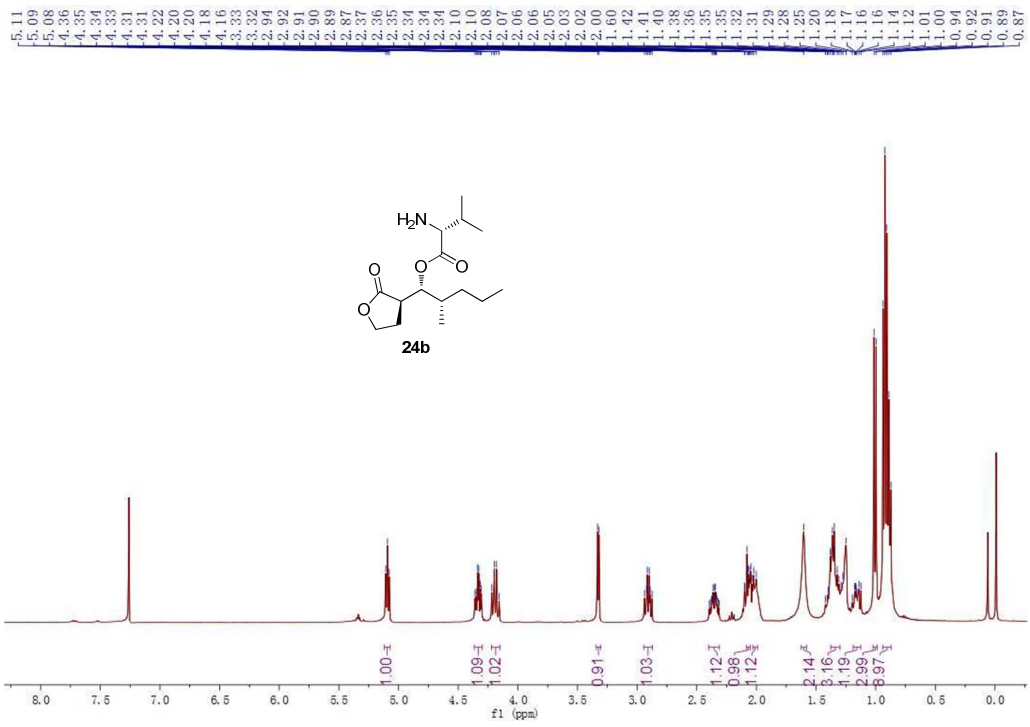


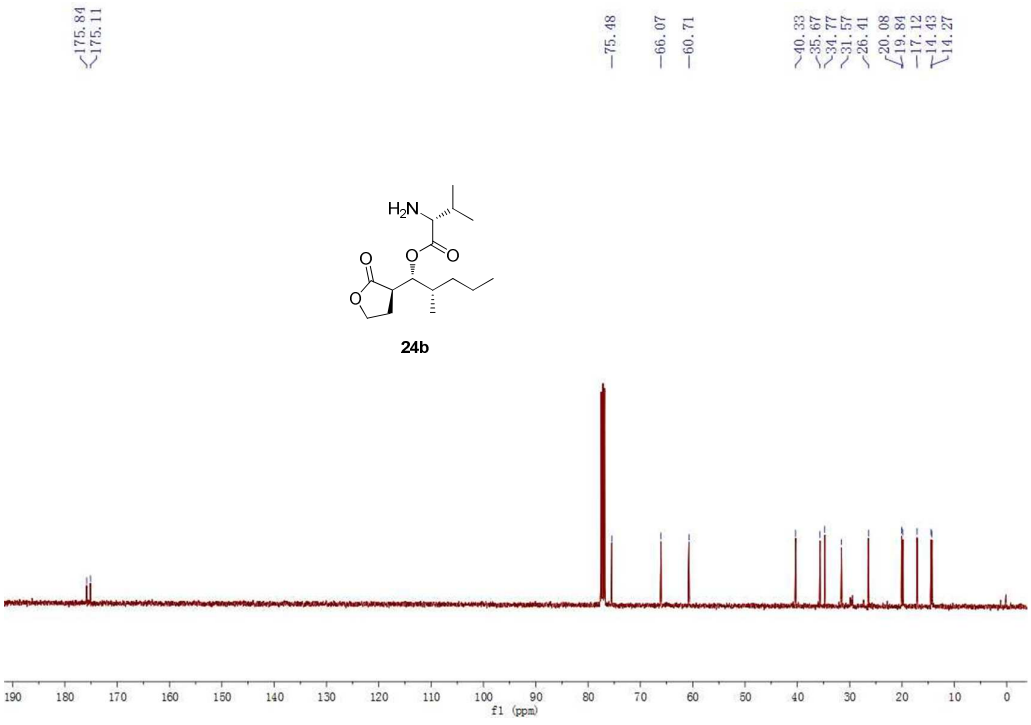
24a

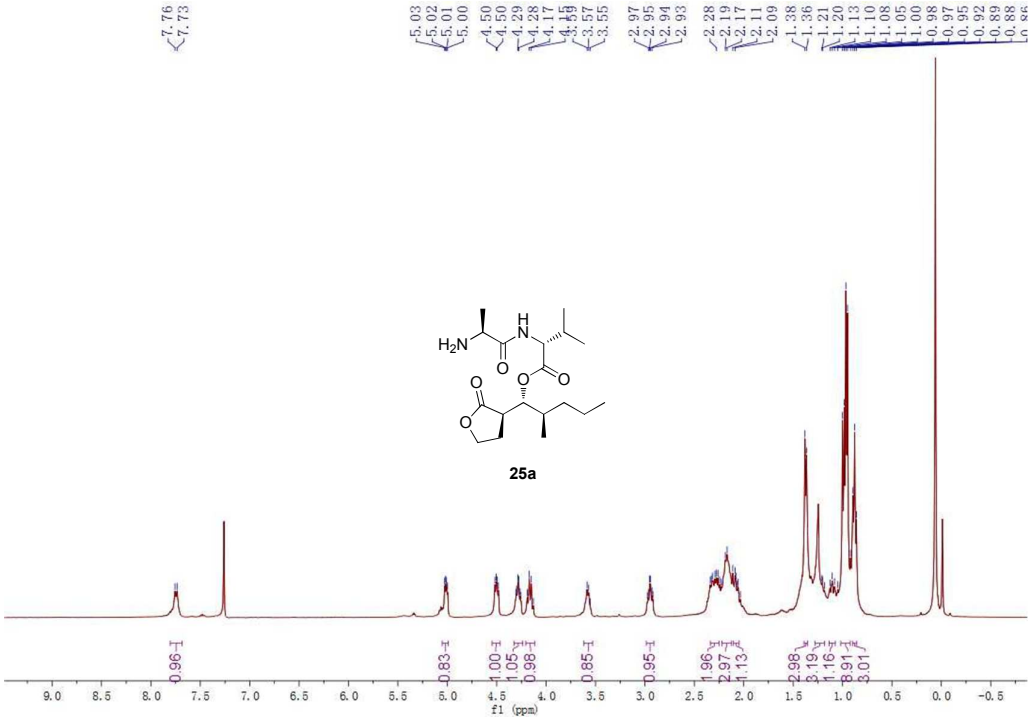


24a

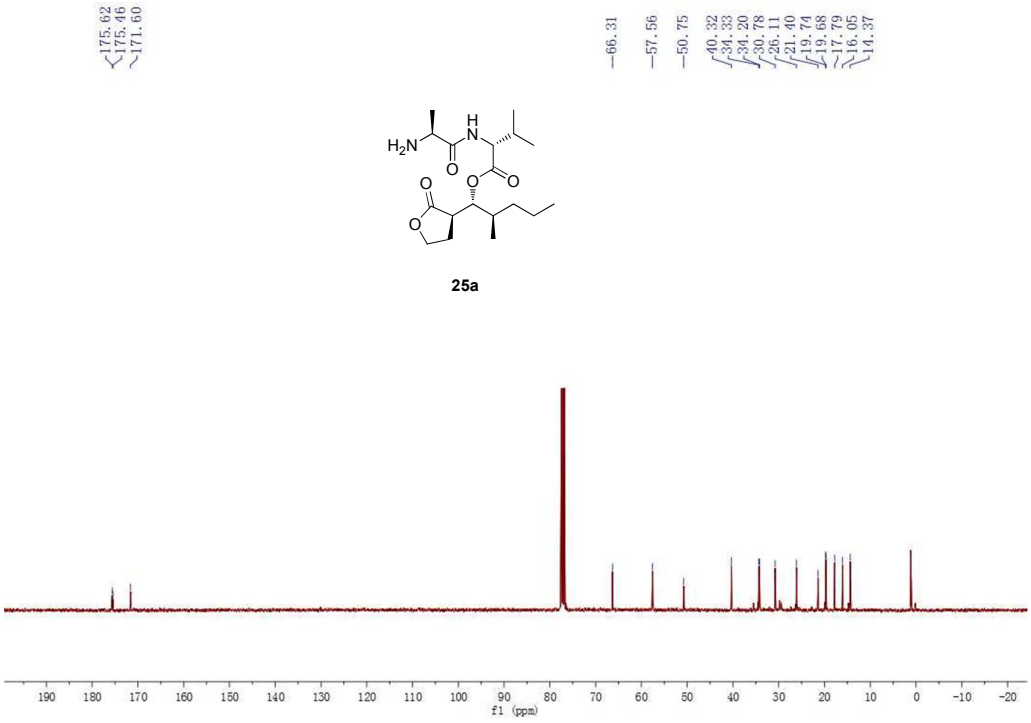



5.11 5.09 5.08 4.36 4.35 4.34 4.33 4.31 4.31 4.22 4.20 4.20 4.18 4.16 3.33 3.32 2.94 2.92 2.91 2.90 2.89 2.87 2.37 2.36 2.35 2.34 2.34 2.34 2.10 2.08 2.07 2.06 2.06 2.05 2.03 2.02 2.00 1.60 1.42 1.41 1.40 1.38 1.36 1.35 1.35 1.32 1.31 1.29 1.28 1.25 1.20 1.18 1.17 1.16 1.16 1.14 1.12 1.01 1.00 0.94 0.92 0.91 0.89 0.87
H2N
O
O
O
O
24b
1.00 1.09 1.02 0.91 1.03 1.12 0.98 1.12 2.14 3.16 1.19 2.99 8.97
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
f1 (ppm)

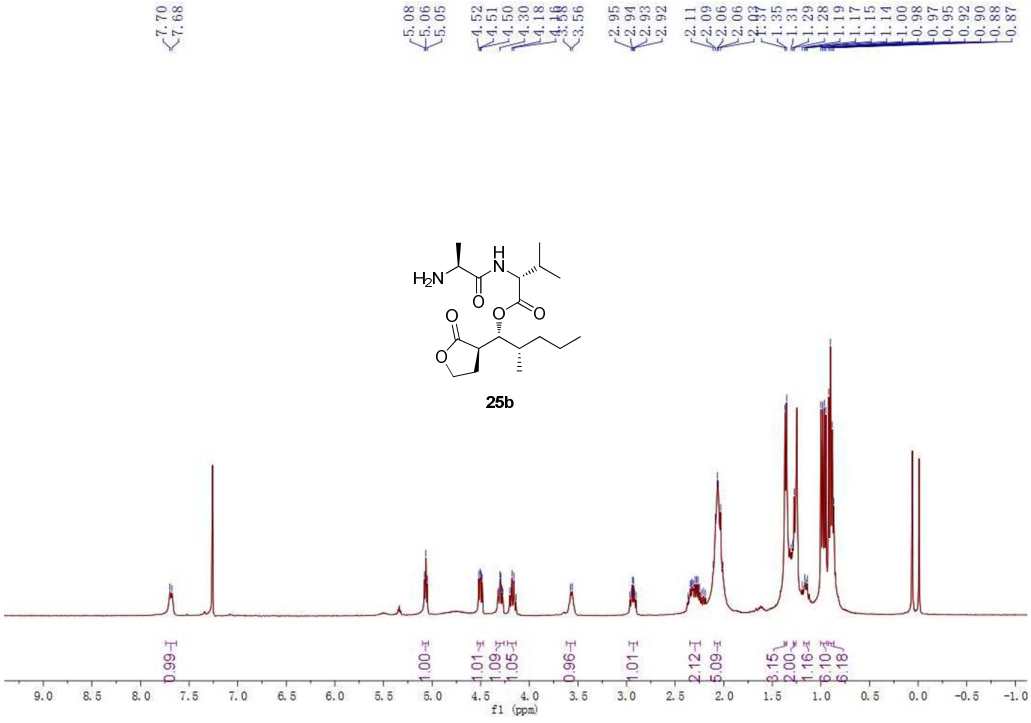

175.84 175.11 75.48 66.07 60.71 40.33 35.67 34.77 31.57 26.41 20.08 19.84 17.12 14.43 14.27
H2N
O
O
O
O
24b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

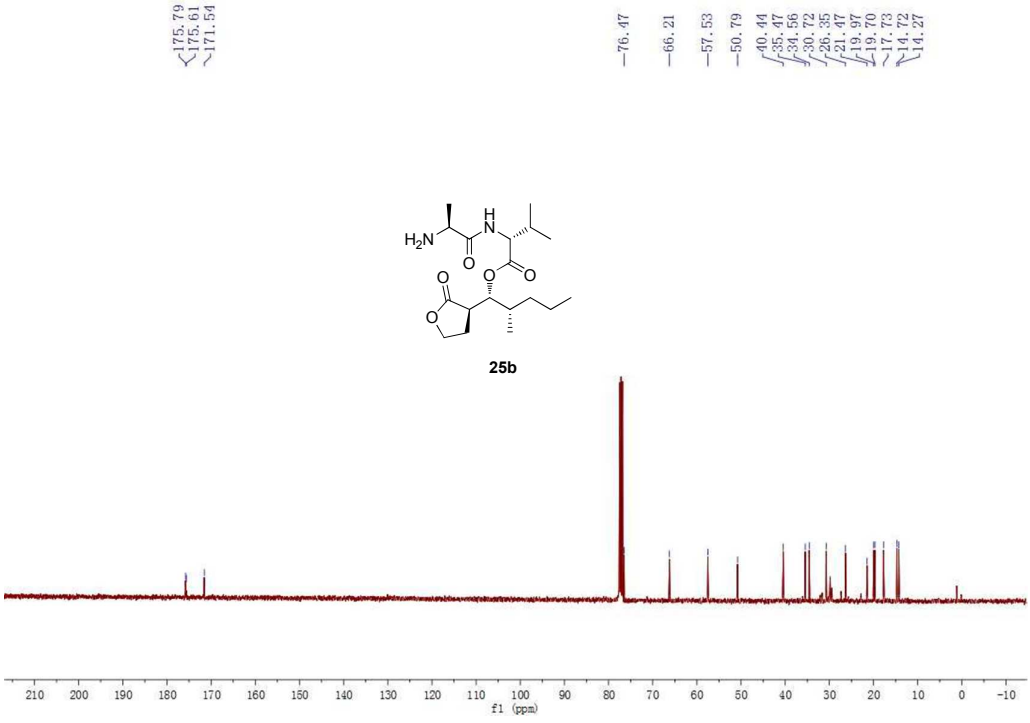

7.76
7.73
5.03
5.02
5.01
5.00
4.50
4.50
4.29
4.28
4.17
4.15
3.57
3.55
2.97
2.95
2.94
2.93
2.28
2.19
2.17
2.11
2.09
1.38
1.36
1.21
1.20
1.13
1.10
1.08
1.05
1.00
0.98
0.97
0.95
0.92
0.89
0.88
0.96
0.83
1.00
1.05
0.98
0.85
0.95
1.96
2.97
1.13
2.98
3.19
1.16
8.91
3.01
f1 (ppm)

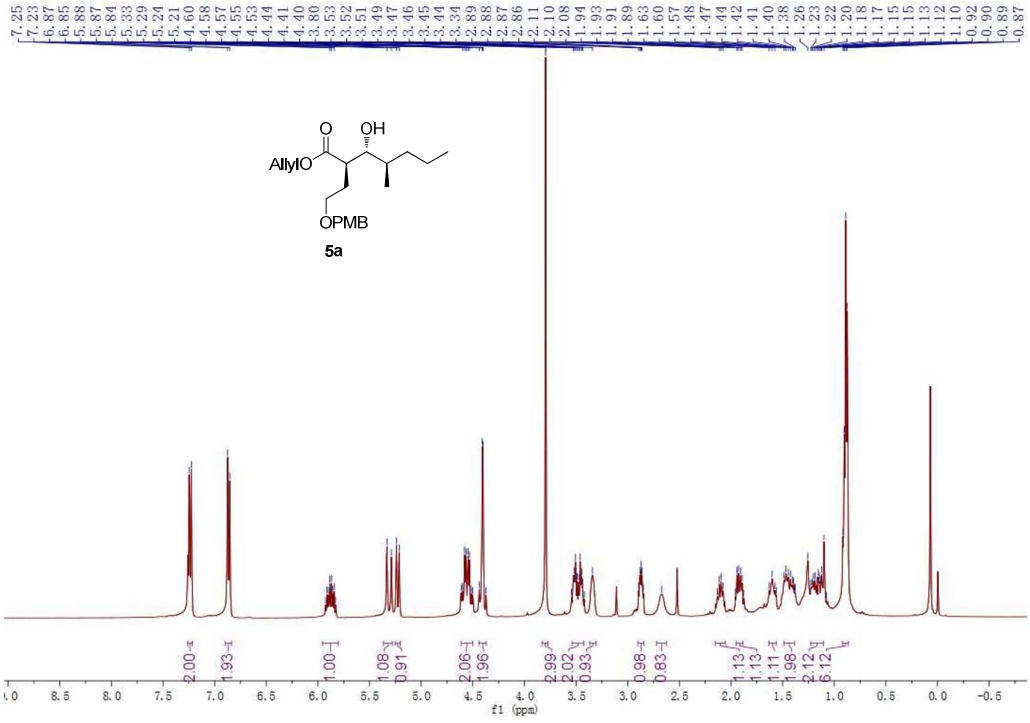
25a


175.62
175.46
171.60
66.31
57.56
50.75
40.32
34.33
34.20
30.78
26.11
21.40
19.74
19.68
17.79
16.05
14.37
f1 (ppm)

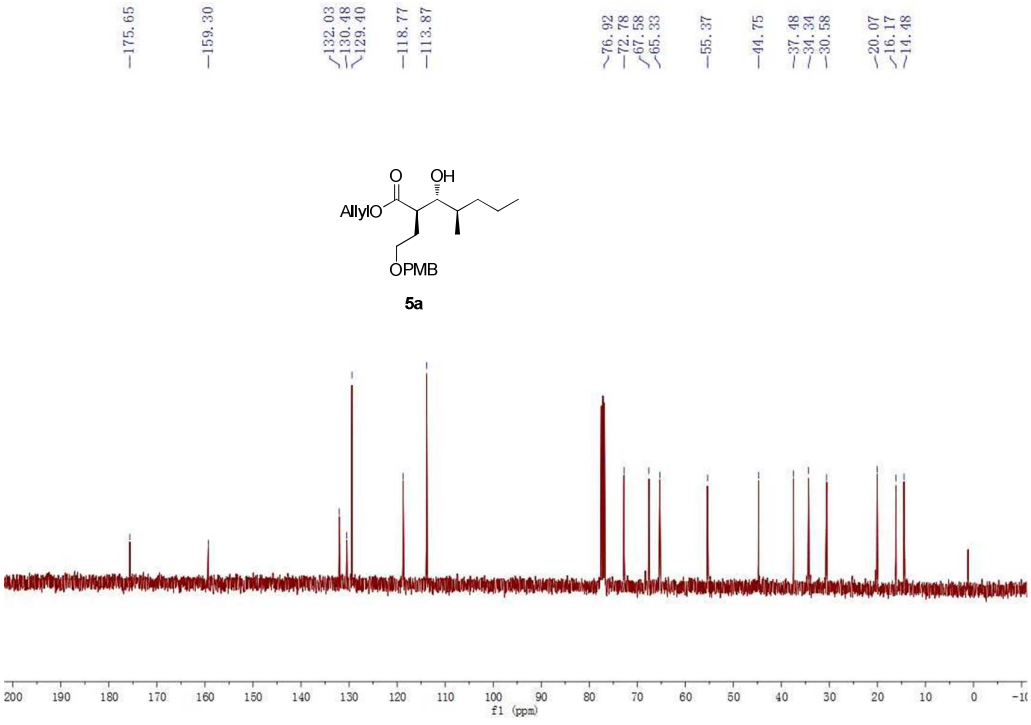
25a


7.70
7.68
5.08
5.06
5.05
4.52
4.51
4.50
4.30
4.18
3.56
2.95
2.94
2.93
2.92
2.11
2.09
2.06
2.06
1.37
1.35
1.31
1.29
1.28
1.19
1.17
1.15
1.14
1.00
0.98
0.97
0.95
0.92
0.90
0.88
0.87
H2N
H
N
O
O
O
O
O
O
25b
0.99
1.00
1.01
1.09
1.05
0.96
1.01
2.12
5.09
3.15
2.00
1.16
6.10
6.18
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 -1.0
f1 (ppm)

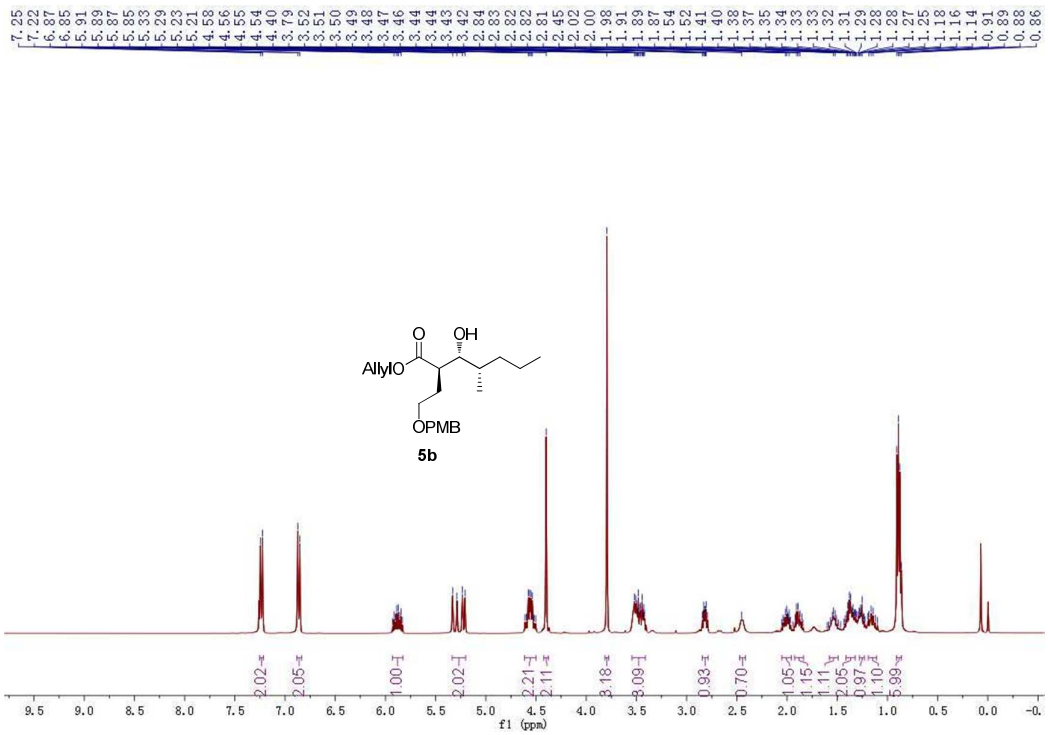

175.79
175.61
171.54
76.47
66.21
57.53
50.79
40.44
35.47
34.56
30.72
26.35
21.47
19.97
19.70
17.73
14.72
14.27
H2N
H
N
O
O
O
O
O
O
25b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

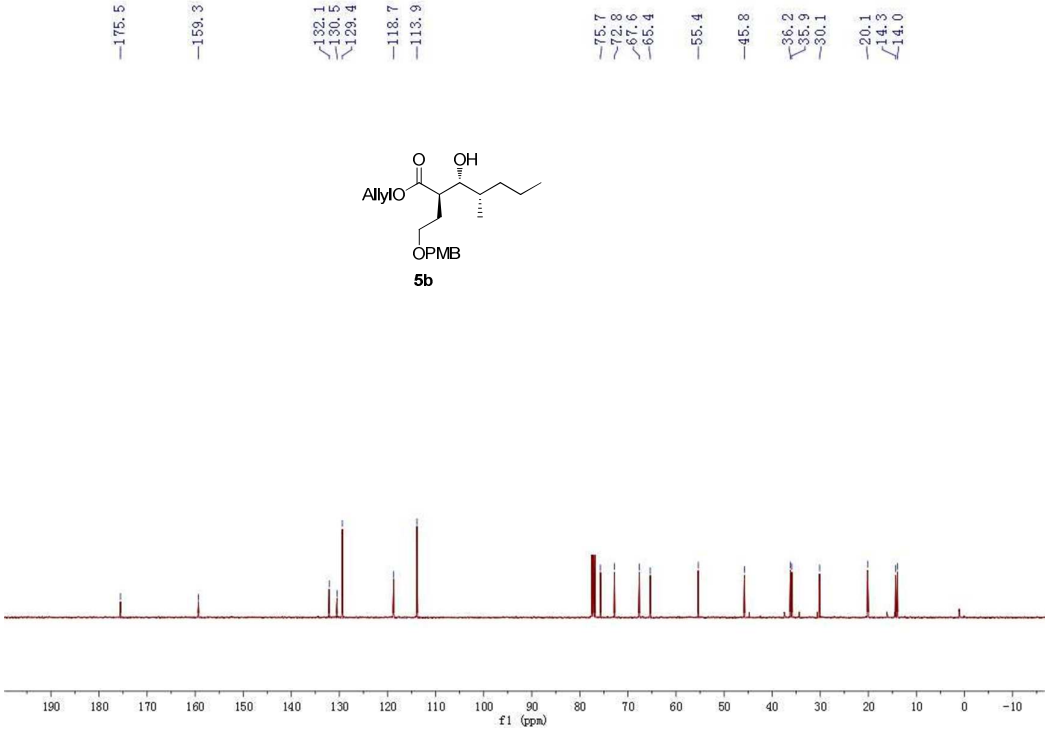


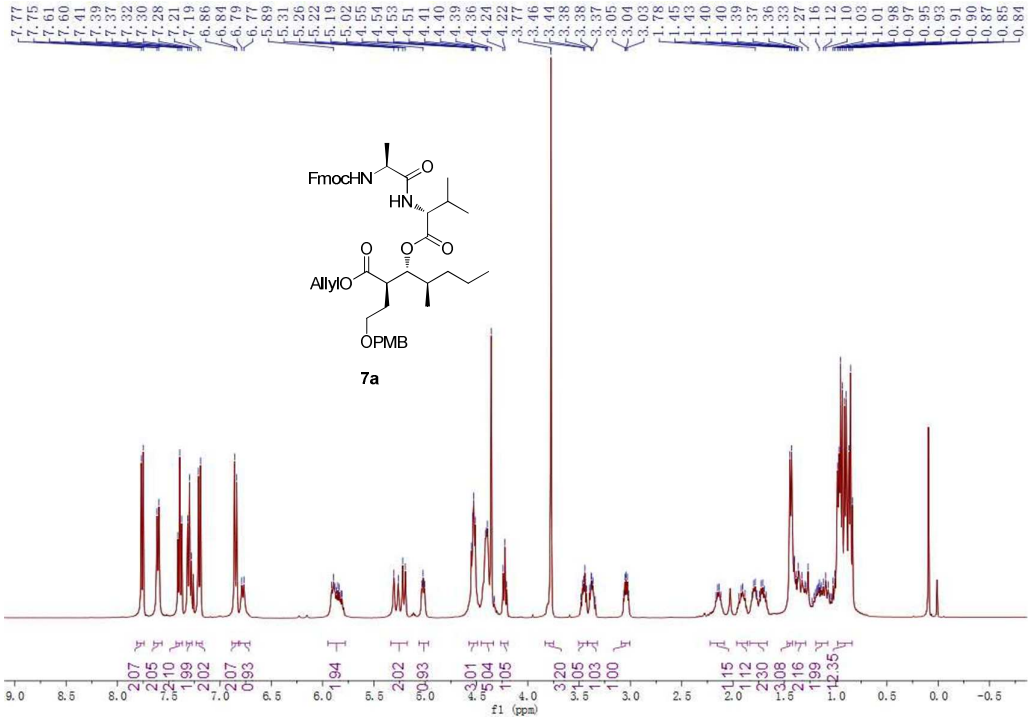
5a

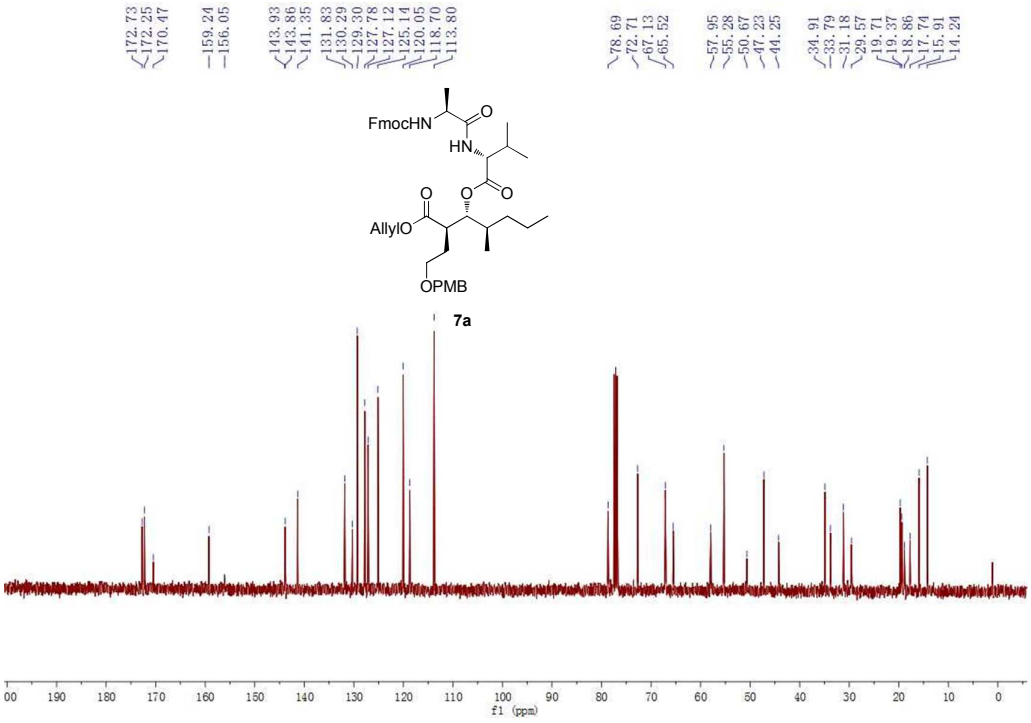


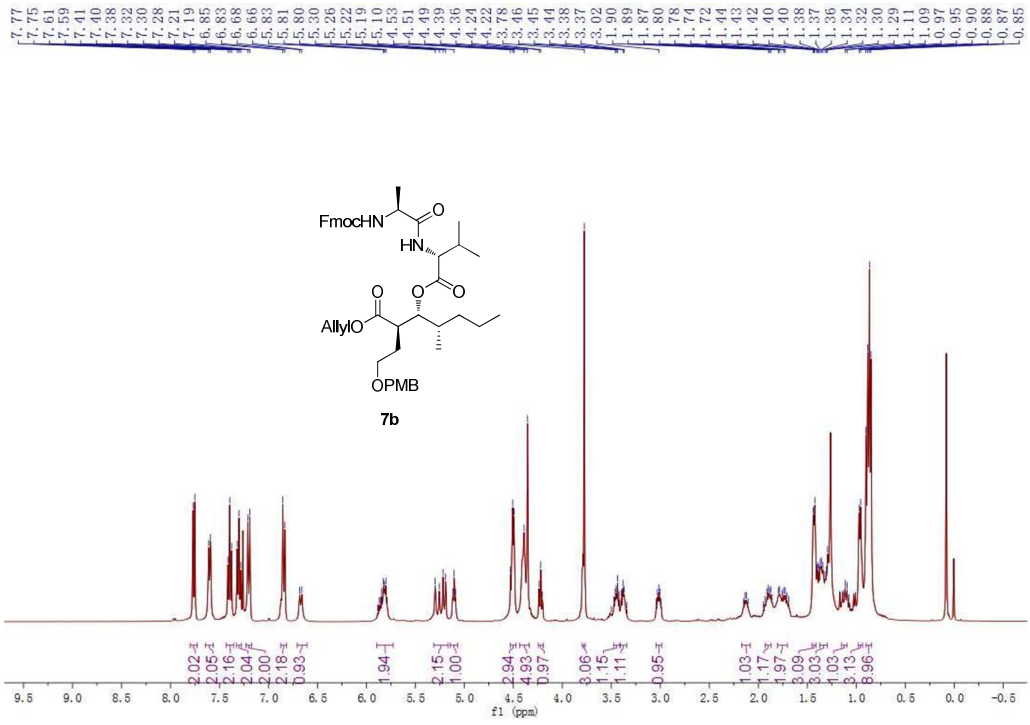
5a

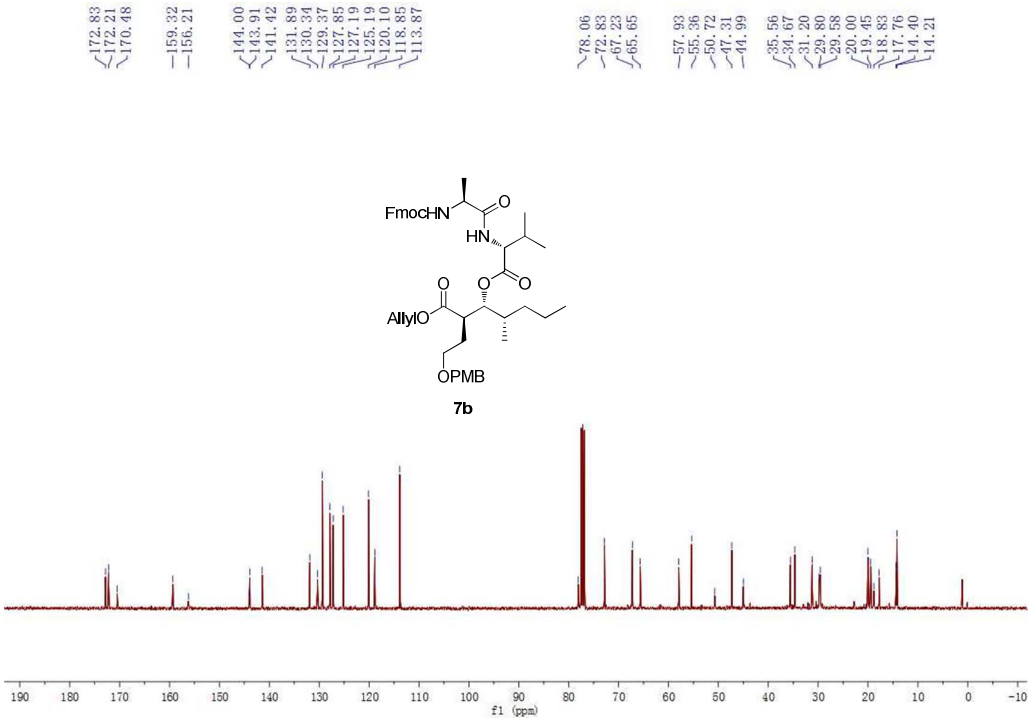

AllylO
O
OH
OPMB
5b
f1 (ppm)

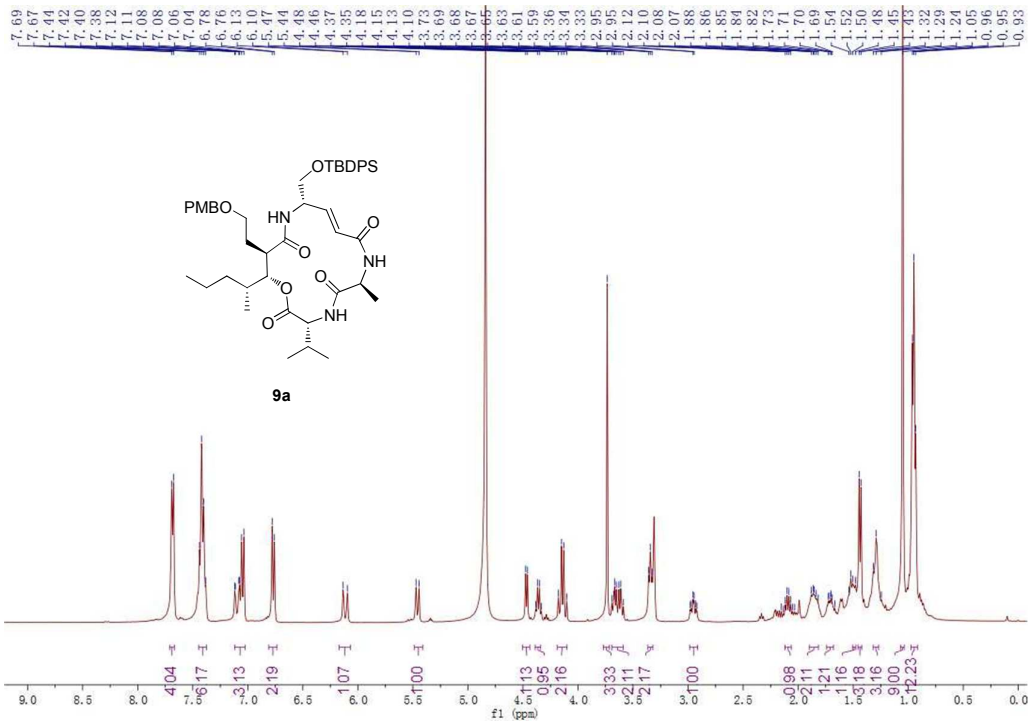

AllylO
O
OH
OPMB
5b
f1 (ppm)

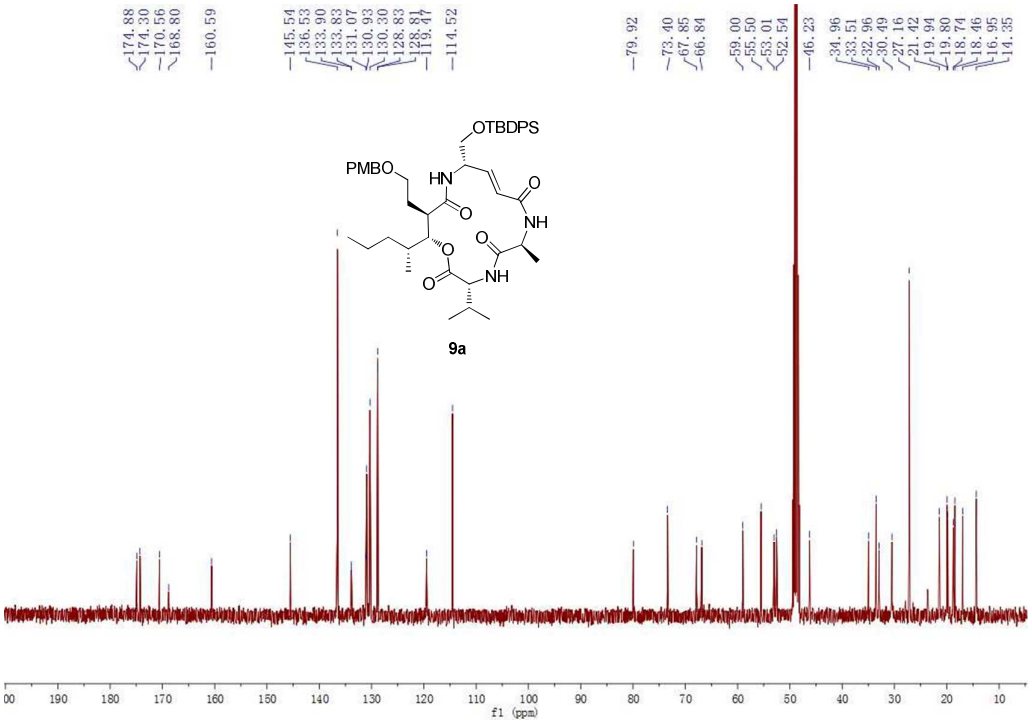

FmocHN
HN
O
O
O
O
AllylO
OPMB
7a
f1 (ppm)

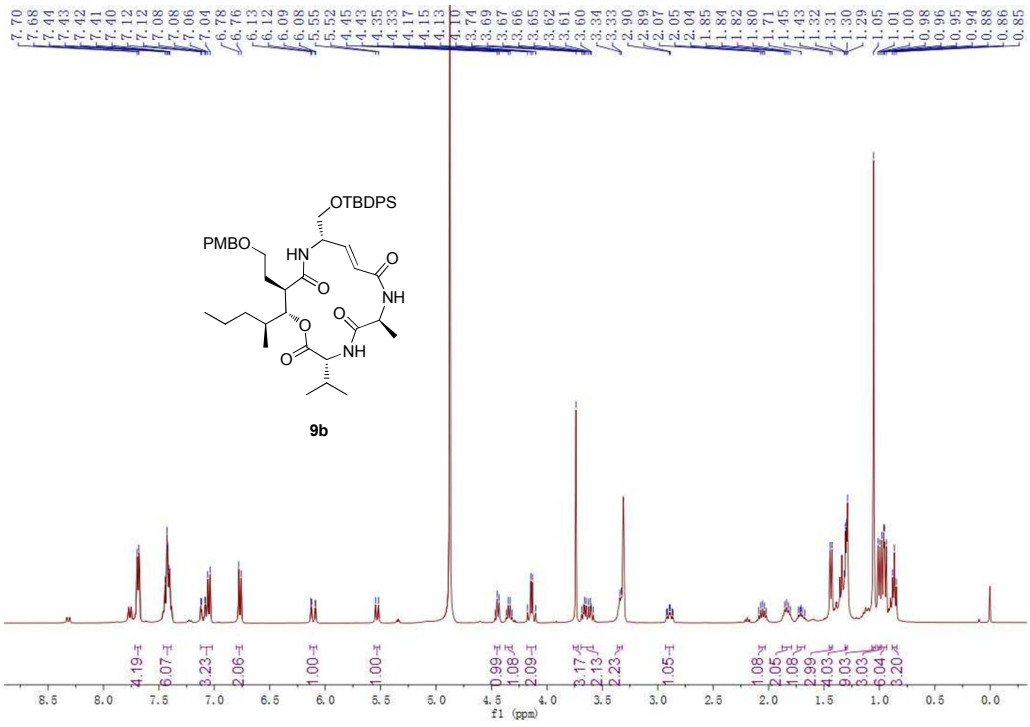

FmocHN
HN
O
O
O
O
AllylO
OPMB
7a
f1 (ppm)

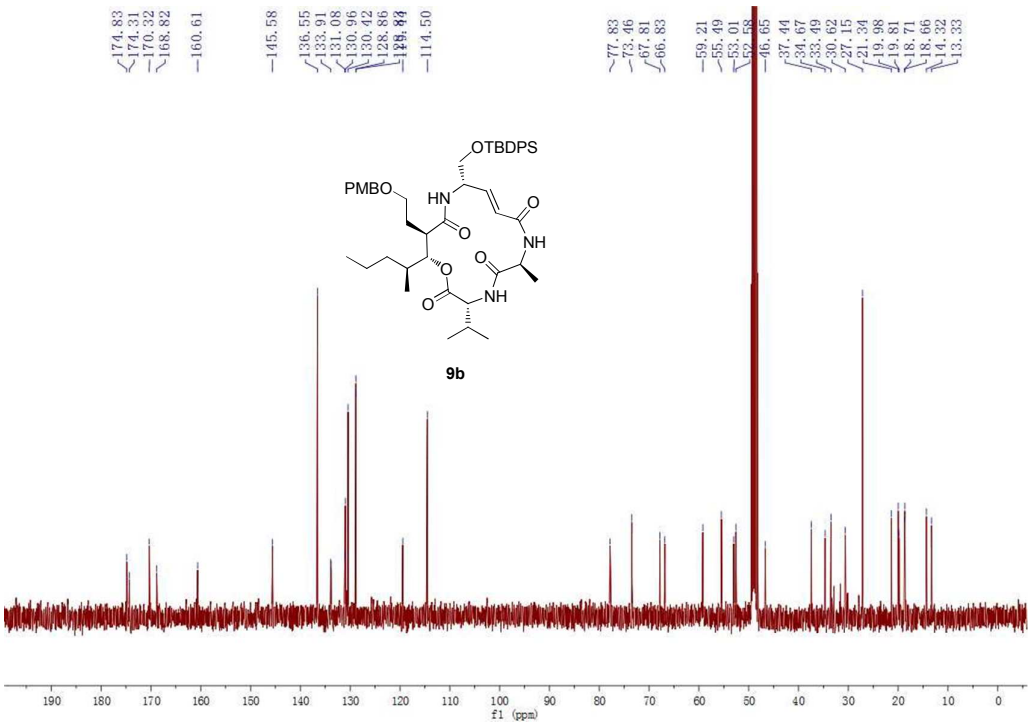

FmocHN
HN
O
O
O
O
AllylO
OPMB
7b
f1 (ppm)

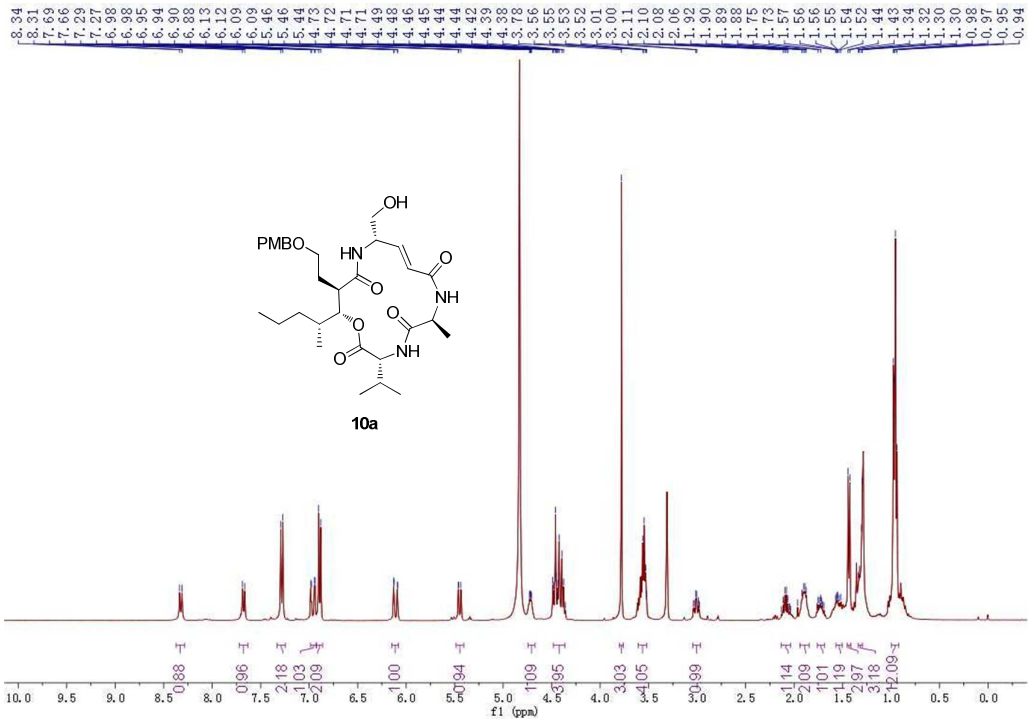

FmocHN
HN
O
O
O
O
AllylO
OPMB
7b
f1 (ppm)


OTBDPS
PMBO
HN
O
NH
O
O
NH
O
O
9a
f1 (ppm)

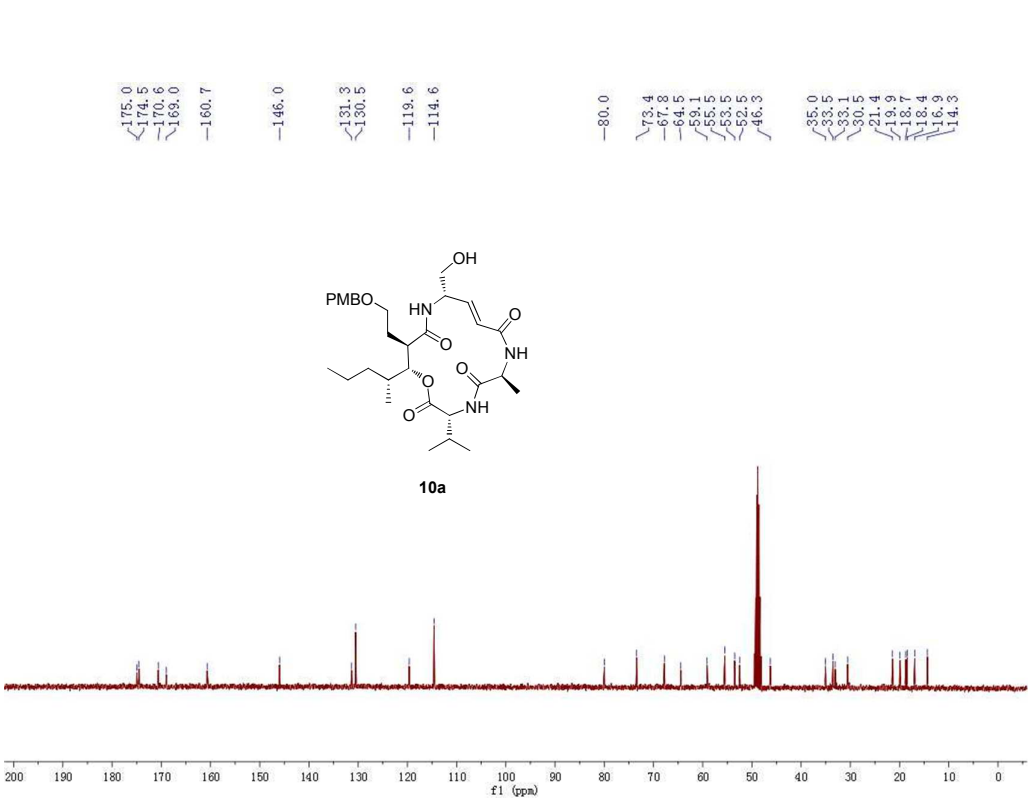

OTBDPS
PMBO
HN
O
NH
O
O
NH
O
O
9a
f1 (ppm)


OTBDPS
PMBO
HN
O
NH
O
O
NH
O
9b
f1 (ppm)

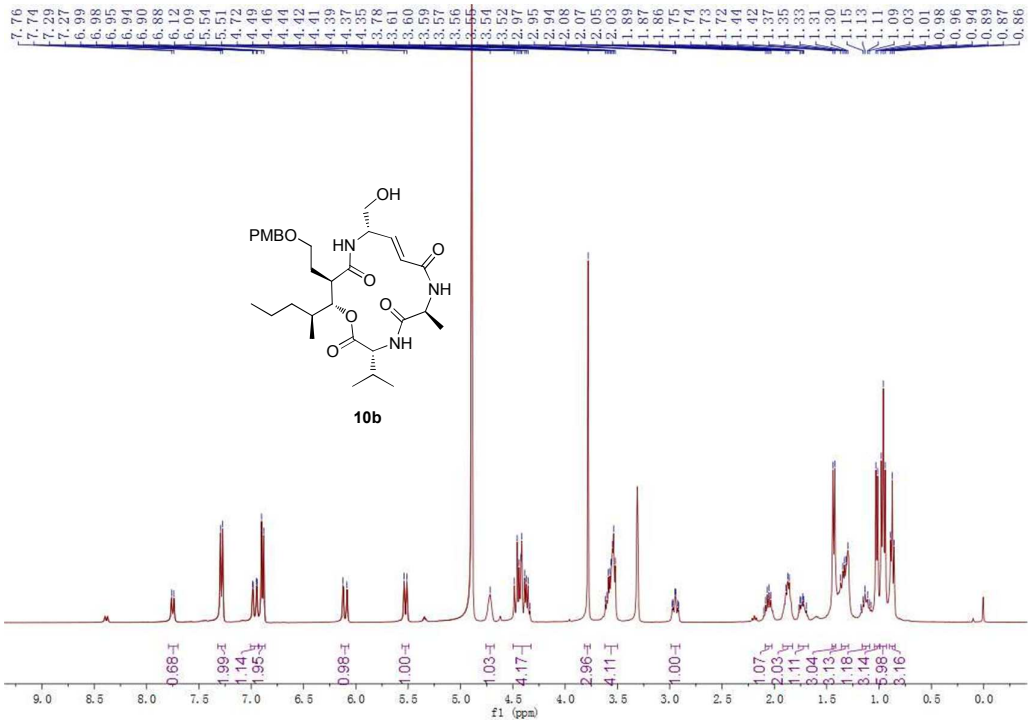

OTBDPS
PMBO
HN
O
NH
O
O
NH
O
9b
f1 (ppm)

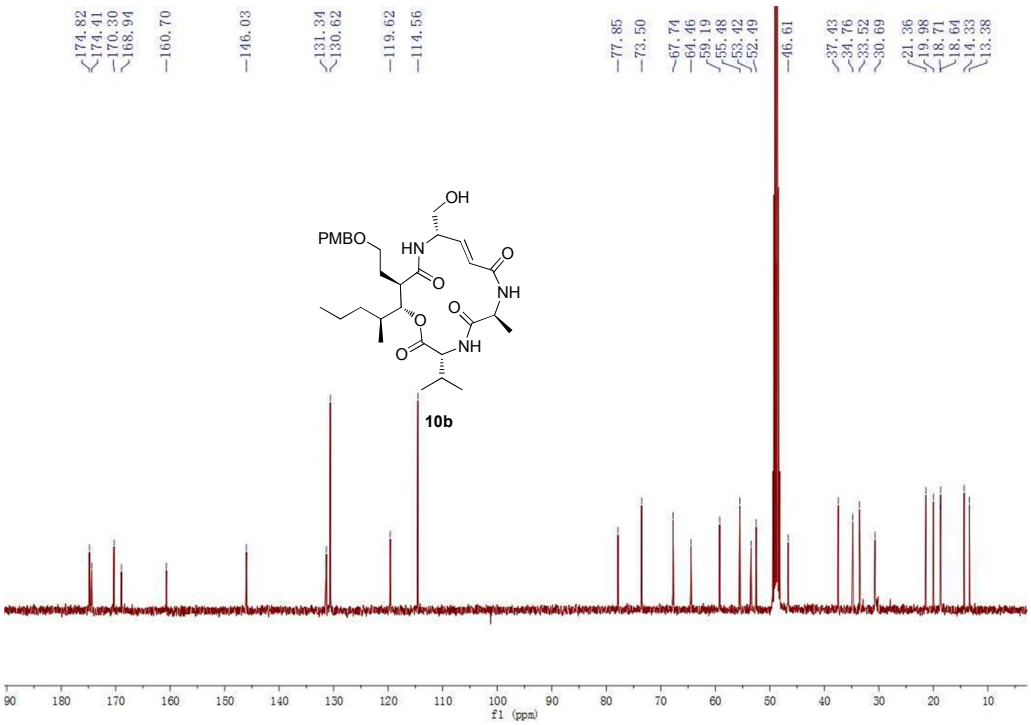


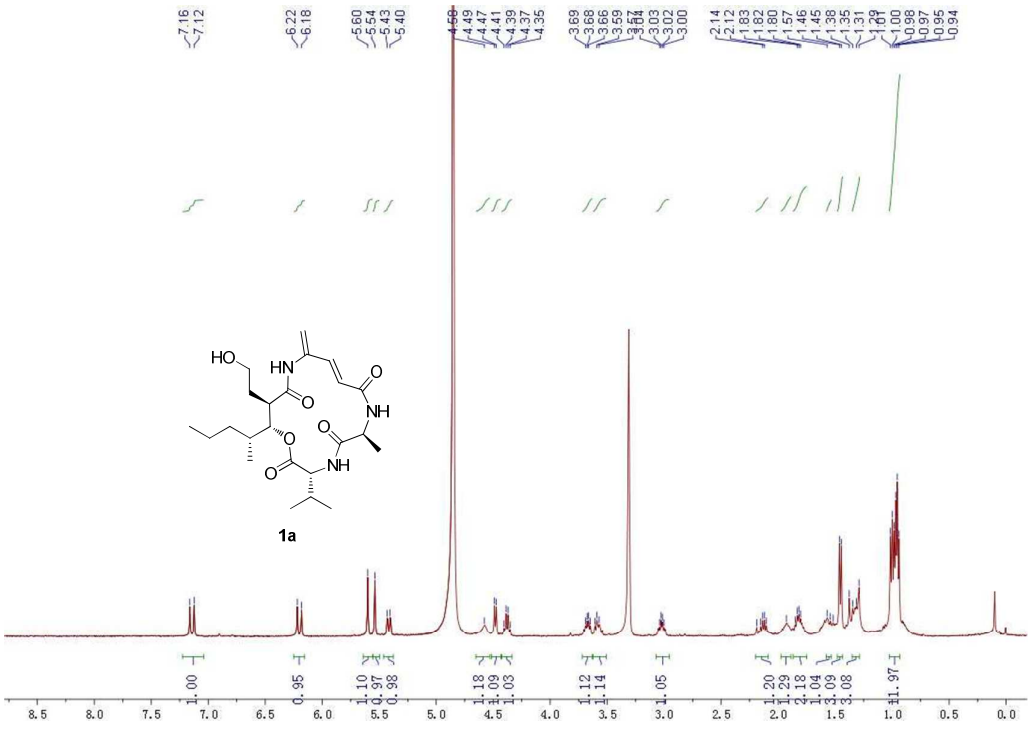
10a

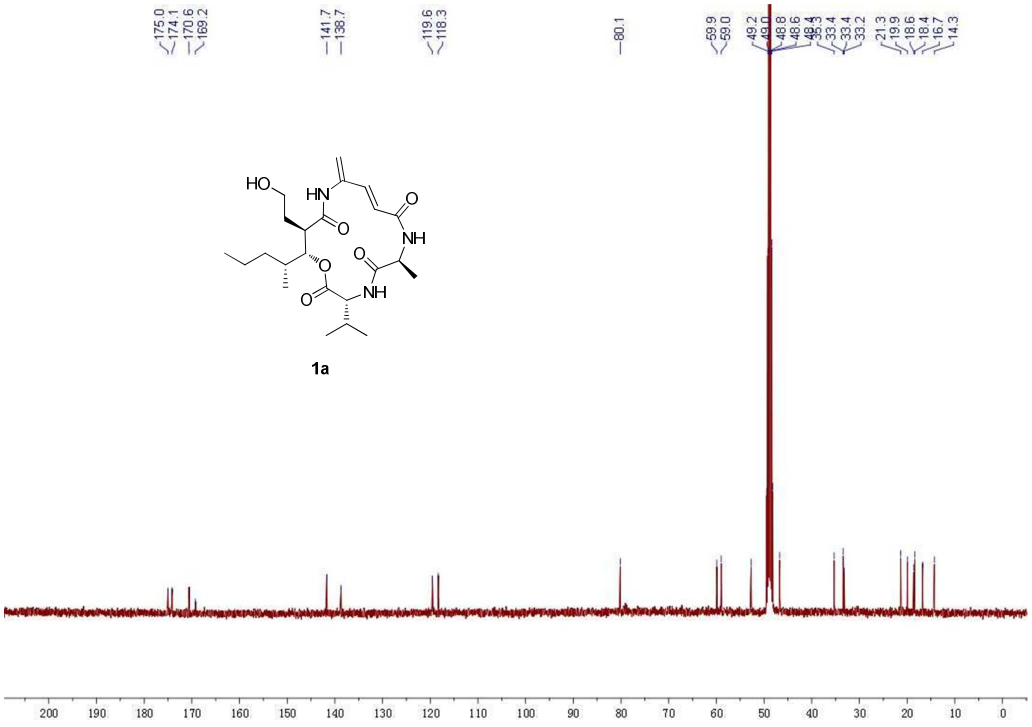


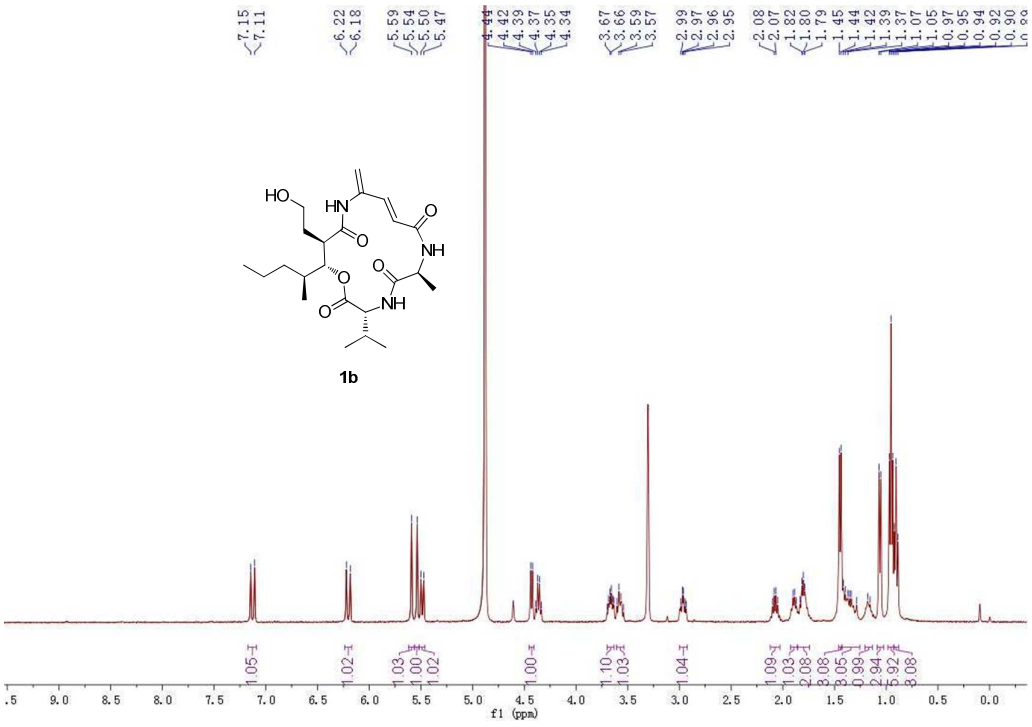
10a

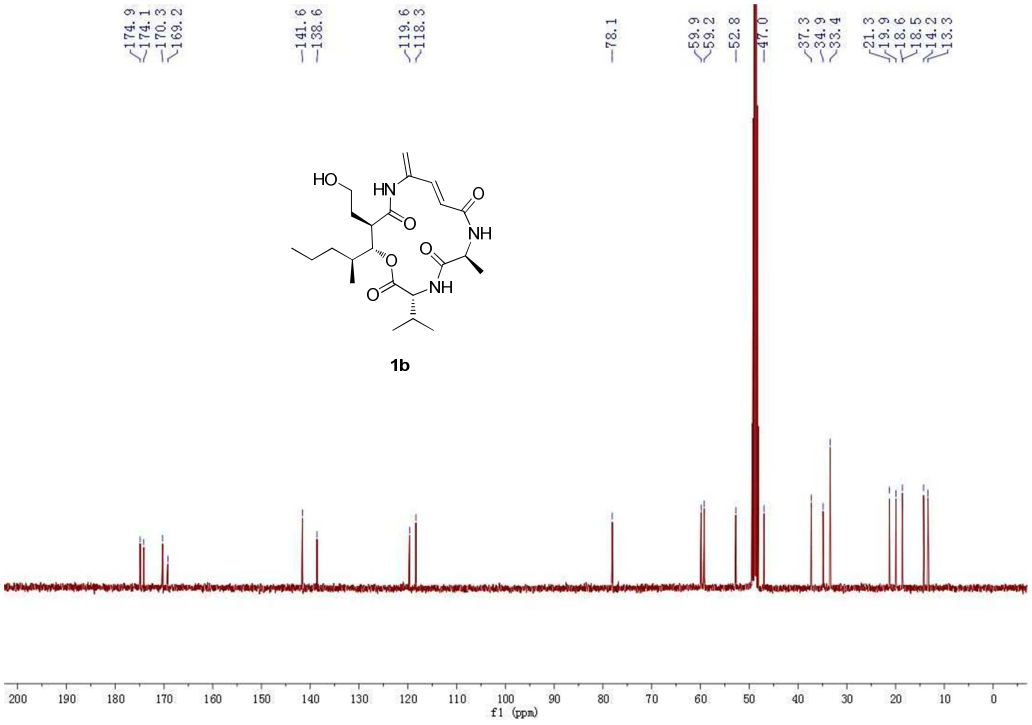

OH
PMBO
HN
O
NH
O
O
NH
O
10b
f1 (ppm)

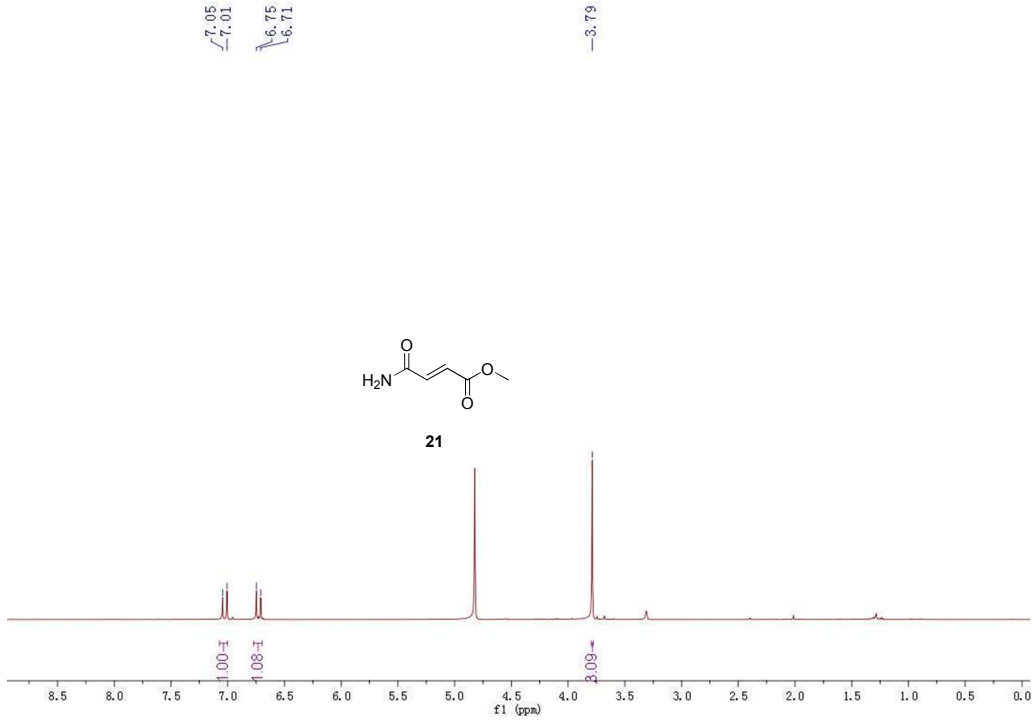

OH
PMBO
HN
O
NH
O
O
NH
O
10b
f1 (ppm)


HO
HN
O
O
NH
O
O
NH
1a

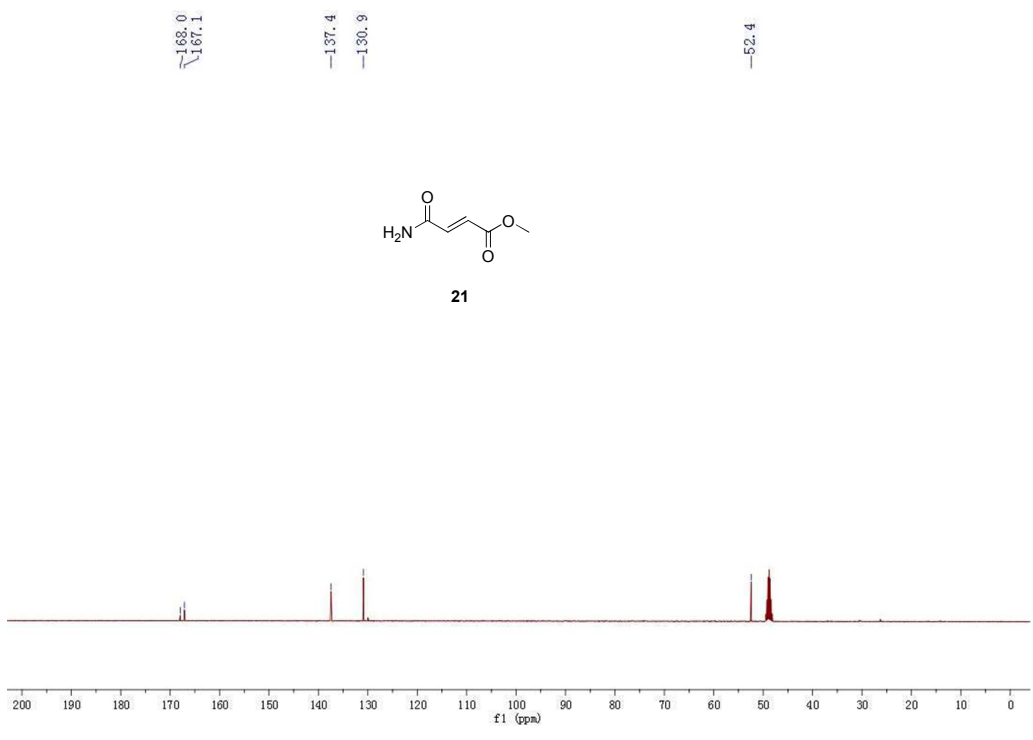

HO
HN
O
O
NH
O
O
NH
1a


HO
HN
O
O
NH
O
O
O
NH
1b
f1 (ppm)

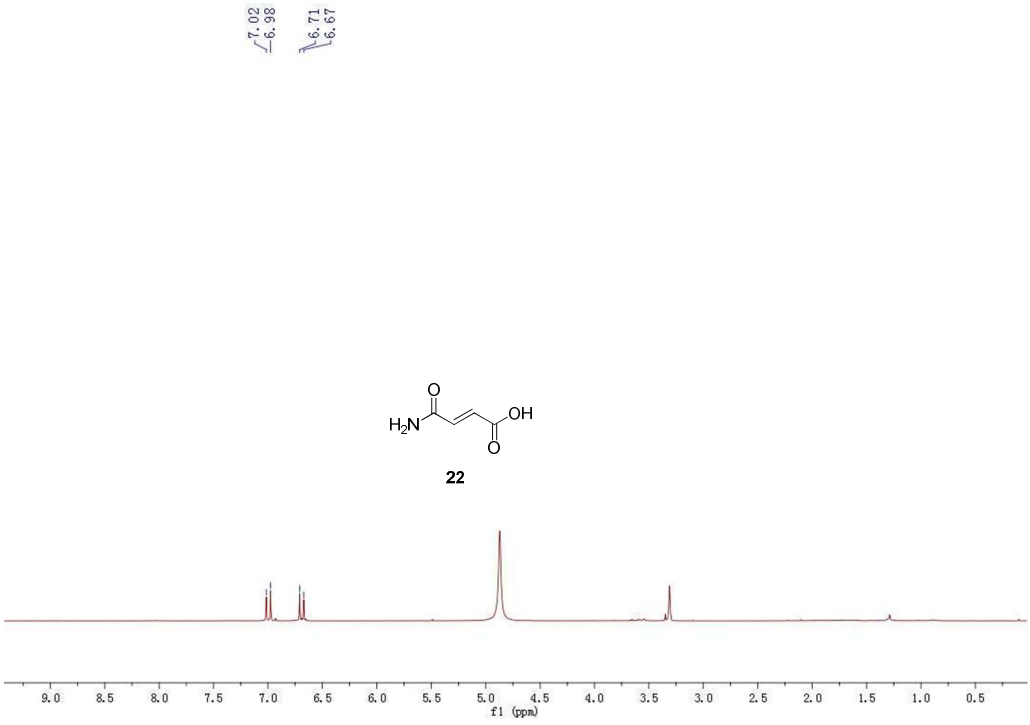

HO
HN
O
O
NH
O
O
O
NH
1b
f1 (ppm)

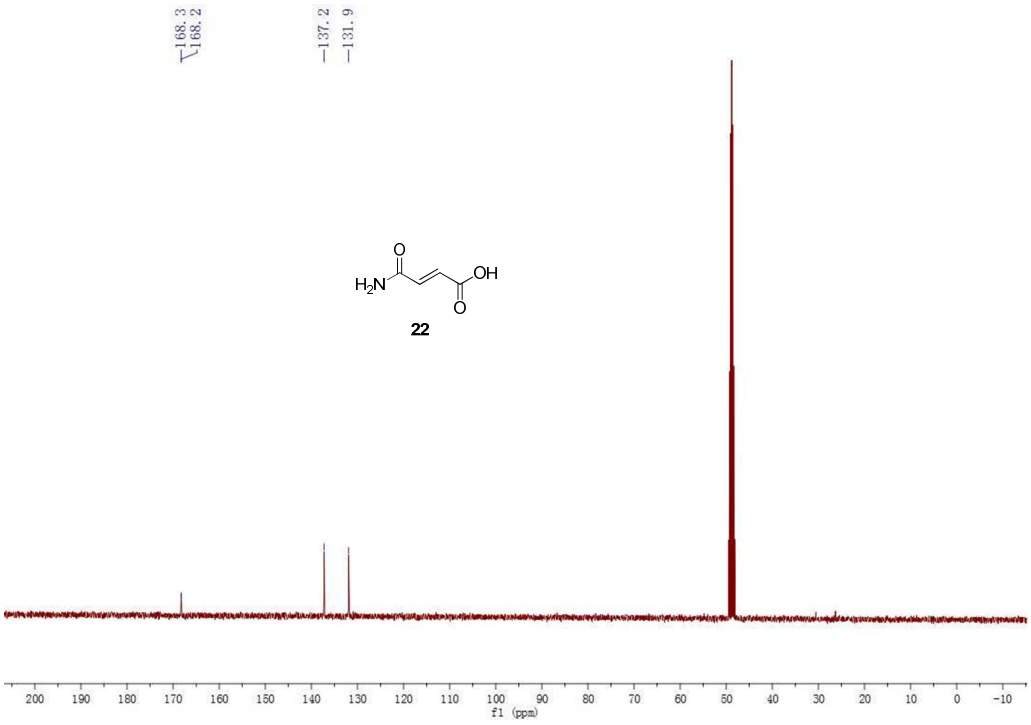

7.05
7.01
6.75
6.71
3.79
1.00
1.08
3.09
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

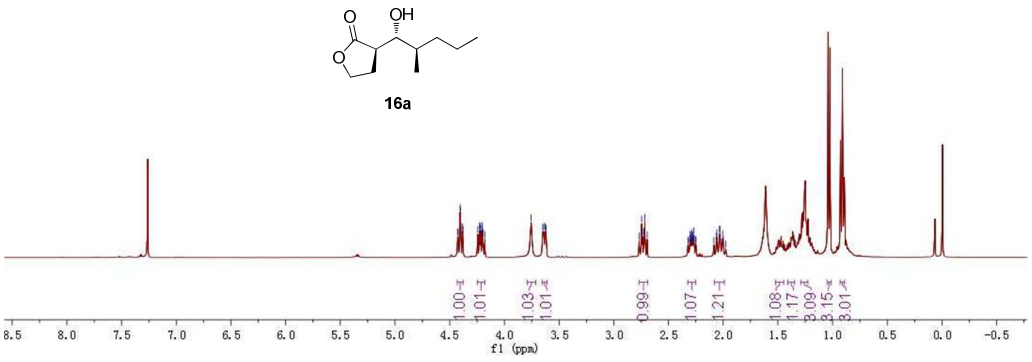
21

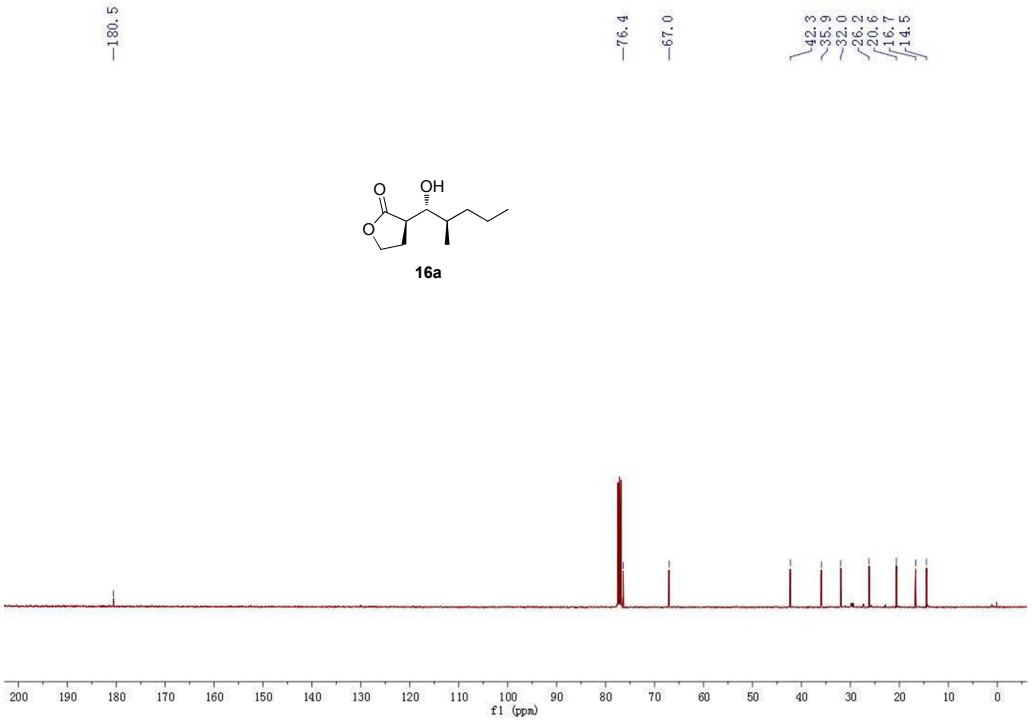

168.0
167.1
137.4
130.9
52.4
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

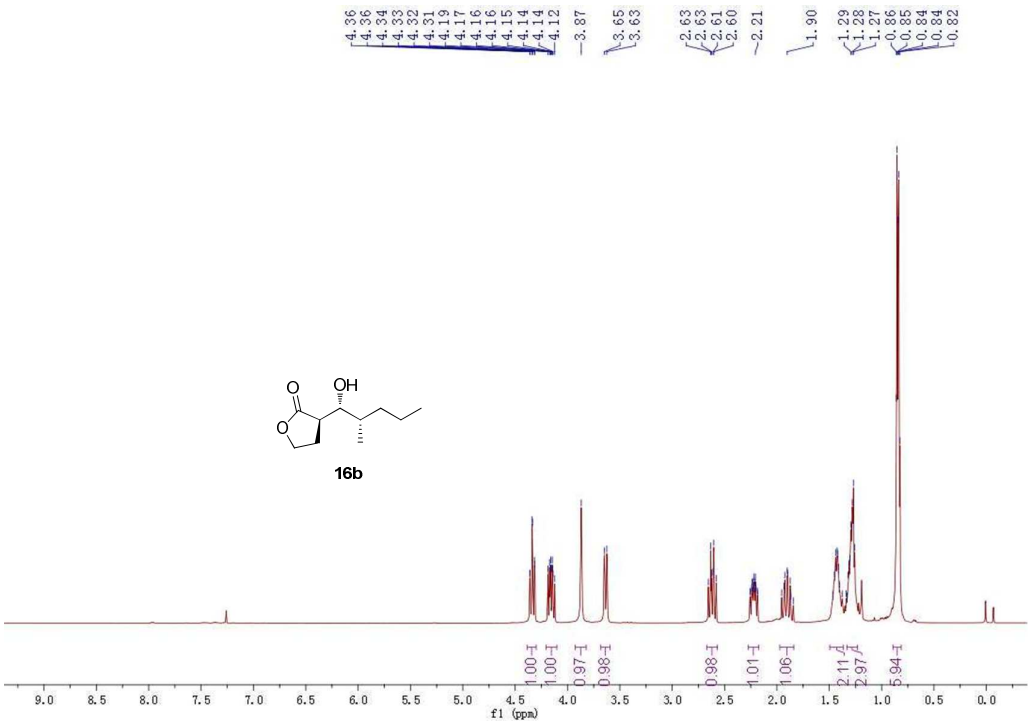
21

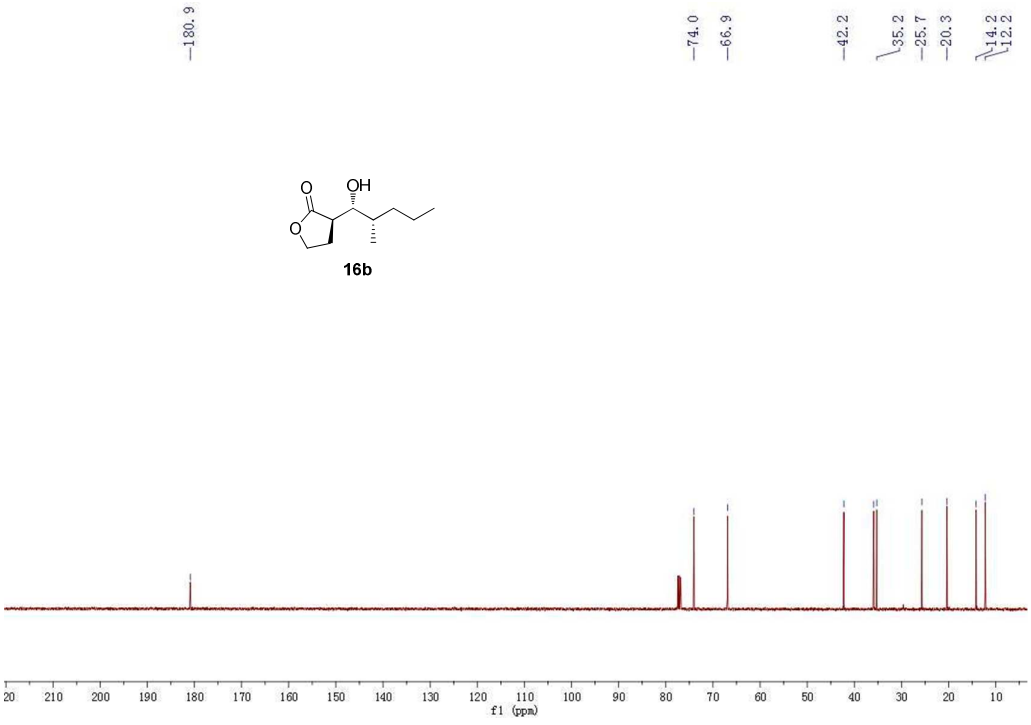

7.02
6.98
6.71
6.67
O
H2N
OH
O
22
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

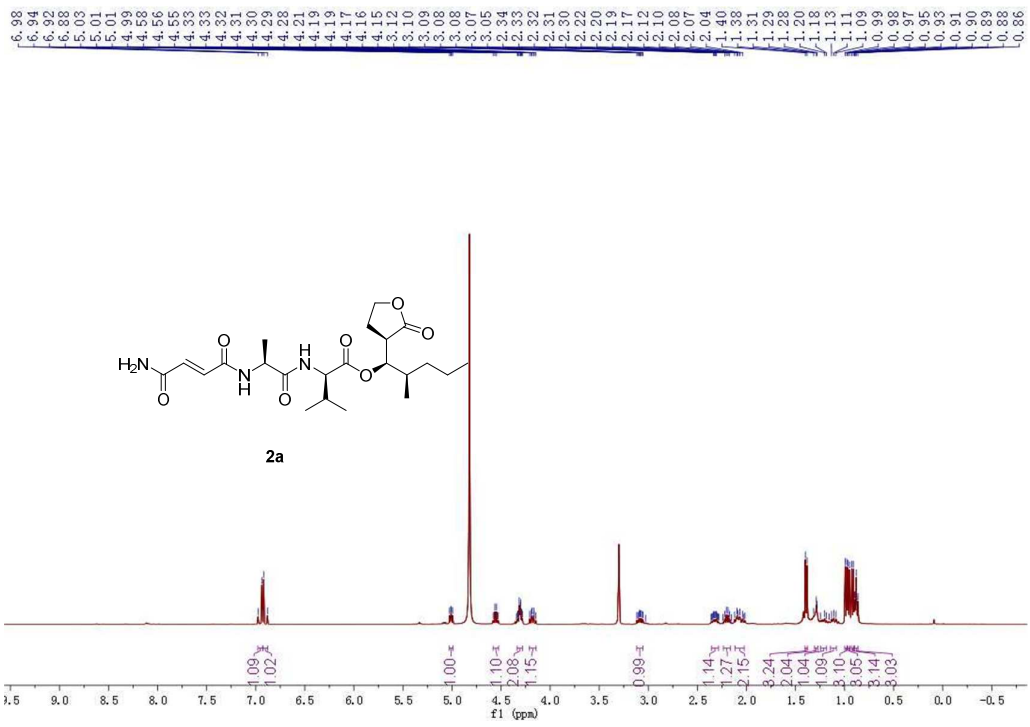

168.3
168.2
137.2
131.9
O
H2N
OH
O
22
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

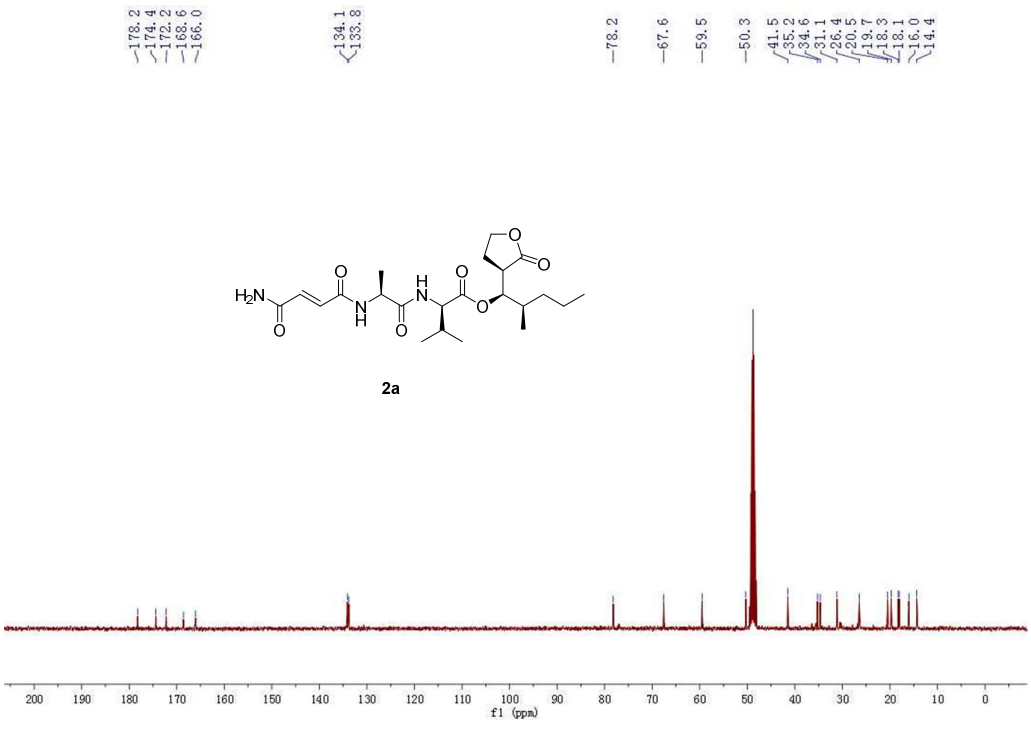

16a
1.00
1.01
1.03
1.01
0.99
1.07
1.21
1.08
1.17
3.09
3.15
3.01
f1 (ppm)

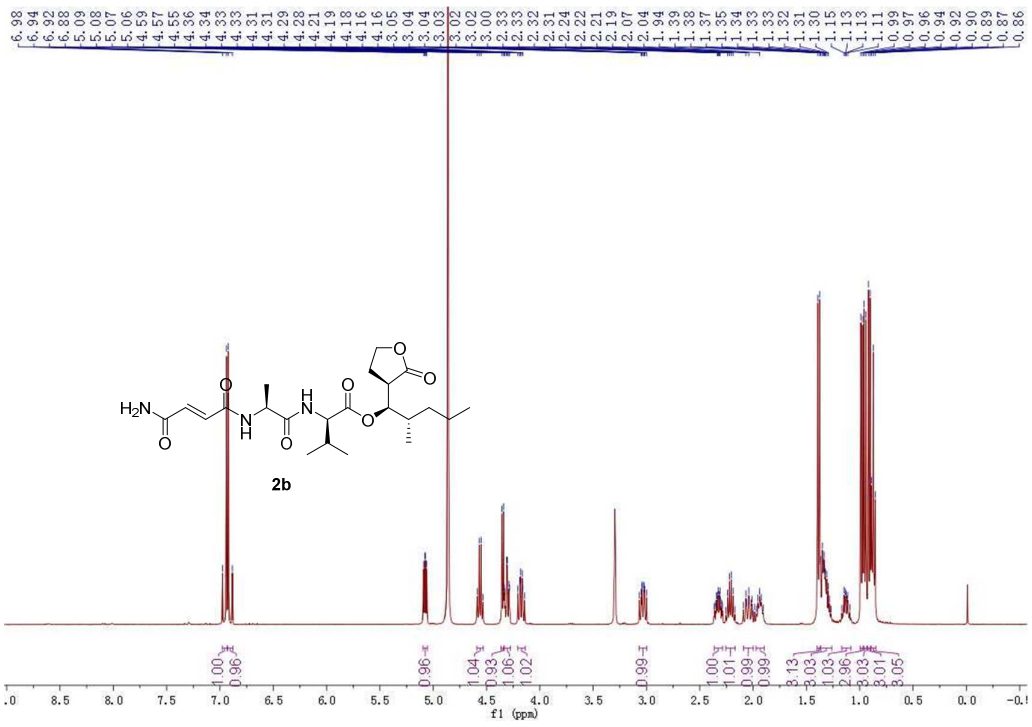

180.5
76.4
67.0
42.3
35.9
32.0
26.2
20.6
16.7
14.5
16a
f1 (ppm)

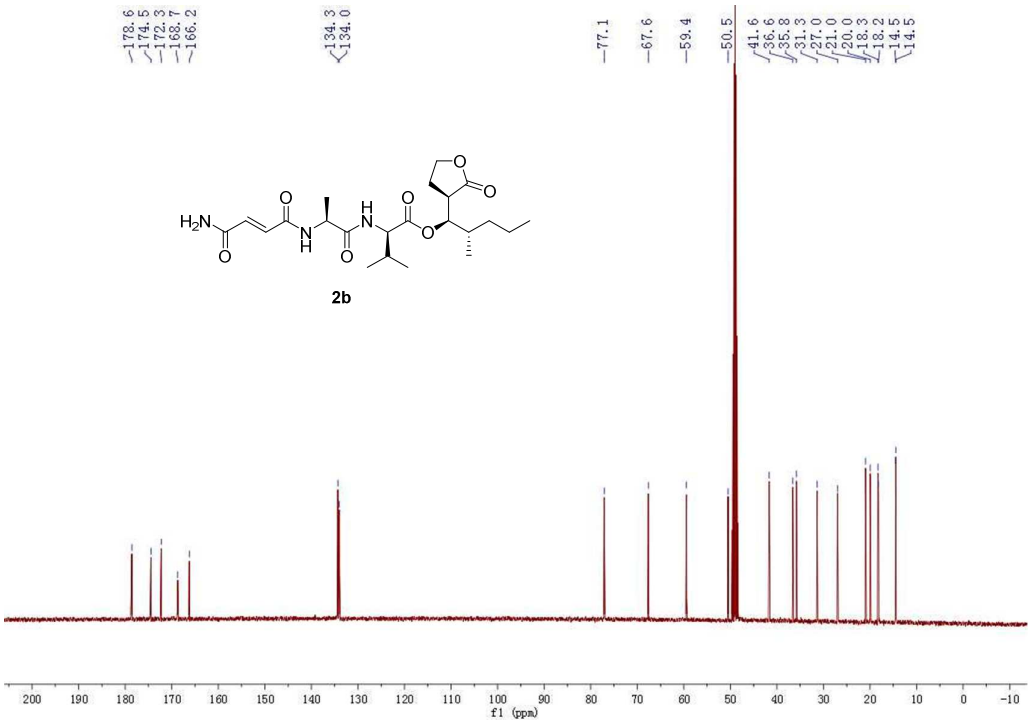

4.36
4.36
4.34
4.33
4.32
4.31
4.19
4.17
4.16
4.16
4.15
4.14
4.14
4.12
3.87
3.65
3.63
2.63
2.63
2.61
2.60
2.21
1.90
1.29
1.28
1.27
0.86
0.85
0.84
0.84
0.82
O
OH
O
16b
1.00
1.00
0.97
0.98
0.98
1.01
1.06
2.11
2.97
5.94
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


180.9
74.0
66.9
42.2
35.2
25.7
20.3
14.2
12.2
O
OH
O
16b
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


2a
f1 (ppm)


2a
f1 (ppm)


2b
f1 (ppm)


2b
f1 (ppm)

3. References

1.Yang, Z. T.; Yang, G.; Ma, M. Y.; Li, J. N.; Liu, J. W.; Wang, J. H.; Jiang, S. D.; Zhang, Q.; Chen, Y. *Org. Lett.* **2015**, *17*, 5725-5727.

2.Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Kiran, M. U. *J. Org. Chem.* **2006**, *71*, 337-340.