This version of the ESI published 08th March 2024 replaces the original version published 08th October 2019. This version contains new NMR spectra.

Highly Stereoselective Gram Scale Synthesis of All the Four Diastereoisomers of Boc-protected 4-Methylproline Carboxylates

Kehuan Sun †,[a,c] Cheng Tao†,[b,c,d] Bohua Long,*[c,d] Xiaobin Zeng,*[e]

Zhengzhi Wu,*[c,d] Ronghua Zhang*[a]

a. College of traditional Chinese Medicine, Jinan University, Guangzhou 510632, China.

b. Integrated Chinese and Western Medicine Postdoctoral Research Station, Jinan University.

c. The First Affiliated Hospital of Shenzhen University, Shenzhen 518035, China.

d. Shenzhen Institute of Geriatric Medicine, Shenzhen, 518035, China.

e. Central Laboratory of Longhua Branch, Second Clinical Medical College (Shenzhen People's Hospital) of Jinan University, Shenzhen 518109, China.

† These authors contributed equally to this work.

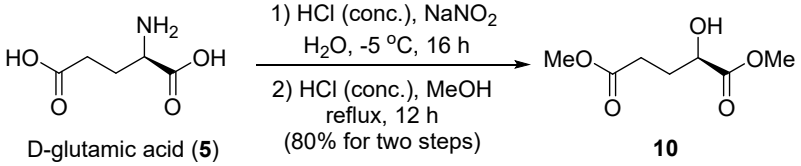
Content

General Experimental

Commercially available reagents were used without further purification unless otherwise stated. All solvents were distilled prior to use: toluene, benzene, diethyl ether and tetrahydrofuran were distilled from Na/benzophenone; while dichloromethane, dimethylformamide, acetonitrile, triethylamine and diisopropylethylamine were distilled from CaH_2. Methanol was distilled under a N_2 atmosphere from Mg/I_2. All reactions were conducted in oven-dried (120 °C) or flame-dried glasswares under a N_2 atmosphere, and at ambient temperature (20 to 25 °C) unless otherwise stated. All non-aqueous reactions were performed by standard syringe in septa techniques. Evaporation and concentration under reduced pressure was performed at 50-500 mbar. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) on a Bruker Avance AV600 or 400 at 600 MHz (150 MHz) or 400 MHz (100 MHz), respectively. Chemical shifts are reported as δ values (ppm) referenced to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent residual. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. Some peptide intermediates exist as rotational conformers, the chemical shift for the minor isomers were indicated using parentheses next to the peak for their major isomers. Mass spectra were measured on ABI Q-star Elite. Optical rotations were measured on a Perkin-Elmer 351 polarimeter at 589 nm with a 100 mm path length cell at 20 °C (reported as follows: concentration (c in g/100 mL), solvent). The reaction progresses were checked on pre-coated thin layer chromatography (TLC) plates. TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm) which, after development, were visualized under UV light at 254nm. Flash column chromatography was performed using the indicated solvents on E. Qingdao silica gel 60 (230-400 mesh ASTM). Yields refer to chromatographically purified compounds, unless otherwise stated.

Experimental procedures

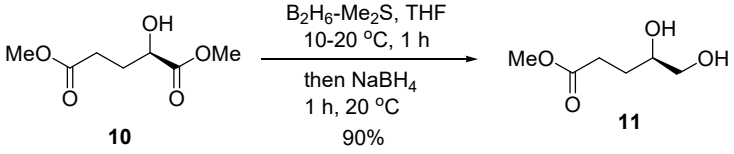
dimethyl (R)-2-hydroxypentanedioate (10)



L-glutamic acid **5** (20.0 g, 0.14 mol) was dissolved in concd HCl (40 mL) and H_2O (20 mL), then a solution of $NaNO_2$ (14.0 g, 0.20 mol) in H_2O (40 mL) was added slowly at -5 °C. The reaction mixture was stirred for 20 h at room temperature and evaporated in vacuo to give a residue, which was dispersed with EtOAc. The precipitate was filtered off and washed with EtOAc. The filtrate was dried over anhydrous Na_2SO_4, concentrated to give a crude product. The crude product was dissolved in MeOH (100 mL), added with 0.1 mL concd HCl. The mixture was then stirred under reflux for 12 h, and cooled to room temperature, excess solid $NaHCO_3$ was added. The reaction mixture was stirred for a further 0.5 h, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified via silica gel column with PE/EA (4:1) to give the dimethyl (R)-2-hydroxypentanedioate (**10**) as colorless oil (19.2 g, 80%). The spectral data for synthetic **10** was identical with those published by Kulkarni et al.[1]

[1] Ananda Rao Podilapu, Suvarn S. Kulkarni. *Org. Lett.*, **2014**, 16, 4336-4339.

(R)-methyl 4,5-dihydroxypentanoate (11)

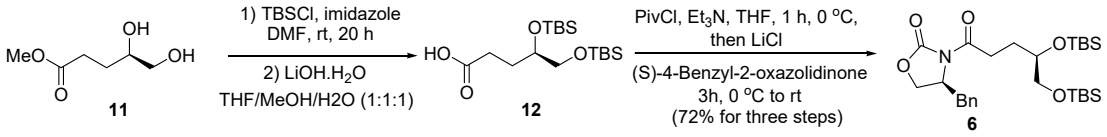


(R)-dimethyl 2-hydroxypentanedioate **10** (80 g, 0.45 mol) was dissolved in dry tetrahydrofuran (600 mL) under nitrogen. Borane dimethyl sulfide complex (10 M, 46 mL) was added over 20 min (maintaining the temperature at 10-20 °C using a cold water bath). The solution was stirred for 1 h. Sodium borohydride (1.0 g, 0.026 mol) was added in five portions over 25 min (using cooling to keep the temperature below 20 °C). The mixture was stirred for 1 h, after which TLC showed no starting material. Dry methanol (200 mL) was added and the solution was stirred for 1h. The solvent

was evaporated and the residue was dissolved in methanol (200 mL). The solvent was evaporated again and the residue was azeotroped with toluene (2×200 mL)，and the crude was purified on silica gel using EtOAc as the eluent to afford the diol **11** as viscous colorless oil (60.5 g, 90%). The spectral data for synthetic **11** was identical with that published by Winkler et al.[2]

[2] J. W. Winkler, J. Uddin, C. N. Serhan, N. A. Petasis, *Org. Lett.* **2013**, *15*, 1424.

(S)-3-((R)-4,5-bis(tert-butyldimethylsilyloxy)pentanoyl)-4-benzyloxazolidin-2-one (6)



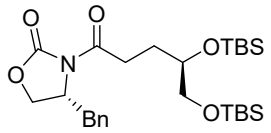
To a solution of above diol **11** (35.0 g, 0.24 mol) in DMF (150 mL) at 0 °C was added imidazole (54.5 g, 0.8 mol), and TBSCl (83.0 g, 0.55 mmol). After 30 min the mixture was warmed to ambient temperature and was stirred for an additional 20 h, then evaporated in vacuo to remove DMF. The residue was diluted with H_2O (400 mL). The aqueous phase was extracted with dichloromethane (3×300 mL). The combined organic phase was washed with 3M $KHSO_4$ solution (300 mL), H_2O (250 mL), brine (250 mL), then dried over sodium sulfate (anhydrous) and concentrated in vacuo, which was used for next step directly.

$LiOH{\cdot}H_2O$ (44 g, 1.06 mol) was added to a solution of the crude TBS ether above in THF/MeOH/H_2O (1:1:1, 600 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, then allowed to warm to room temperature within 5 h. The solution was concentrated in *vacuo*, then diluted with water (300 mL) and adjusted to pH 2 by dropwise addition of aq. HCl (1.0 M). The aqueous phase was extracted with ethyl acetate (3×400 mL). The combined organic phase was washed by brine (200 mL), dried over sodium sulfate (anhydrous) and concentrated in vacuo to give the acid **12** as an oil which was used for next step directly.

To the above acid **12** in dry THF (500 mL) at 0 °C was added Et_3N (88.4 mL, 636 mmol) and PivCl (26 mL, 212 mmol) under N_2 atmosphere. After 1 h, LiCl (36.0 g, 848 mmol) and (S)-4-Benzyl-2-oxazolidinone (37.6 g, 212 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 h, which allowed to warm to room temperature within 3 h. The solution was concentrated in vacuo, then diluted with water (300 mL), The aqueous phase was extracted with ethyl acetate (3×300 mL). The combined organic phase was washed by brine (300 mL), dried over sodium sulfate

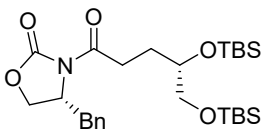
(anhydrous) and concentrated in vacuo. The residue was purified by silica gel column chromatography (EA/PE, 1:10) to afford **6** (88.6 g, 72% over three steps) as an oil. $[\alpha]_D^{25}$ + 82.2 (c 1.37, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 5H), 4.69 (ddt, *J* = 10.2, 6.8, 3.3 Hz, 1H), 4.26 – 4.10 (m, 2H), 3.79 (p, *J* = 7.0 Hz, 1H), 3.60 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.47 (dd, *J* = 10.0, 6.7 Hz, 1H), 3.32 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.15 – 2.92 (m, 2H), 2.79 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.03 (ddt, *J* = 14.0, 10.0, 5.7 Hz, 1H), 1.88 – 1.72 (m, 1H), 0.92 (d, *J* = 2.5 Hz, 18H), 0.09 (dd, *J* = 6.6, 3.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.39, 153.05, 135.36, 129.40, 128.93, 127.30, 71.98, 67.21, 66.11, 55.13, 37.91, 31.53, 28.51, 25.97, 25.86, 18.36, 18.08, -4.35, -4.85, -5.34, -5.38. HRMS (ESI) m/z: calculated for $C_{27}H_{47}NNaO_5Si_2$ $[M+Na]^+$: 544.2890, found 544.2870. Using the same procedure as described for the synthesis of **6**, compound **6'**, **ent-6**, **ent-6'** were prepared.

(R)-3-((R)-4,5-bis(tert-butyldimethylsilyloxy)pentanoyl)-4-benzyloxazolidin-2-one (6')



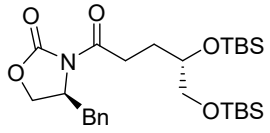
6', colorless liquid; yield 78%; $[\alpha]_D^{25}$ -47.8 (c 0.92, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.22 (m, 5H), 4.68 (ddt, *J* = 10.2, 6.8, 3.2 Hz, 1H), 4.19 (p, *J* = 6.3, 5.8 Hz, 2H), 3.85 – 3.74 (m, 1H), 3.61 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.48 (dd, *J* = 9.9, 6.8 Hz, 1H), 3.33 (d, *J* = 13.3 Hz, 1H), 3.15 – 2.95 (m, 2H), 2.77 (dd, *J* = 13.2, 9.7 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.76 (dd, *J* = 14.6, 6.9 Hz, 1H), 0.92 (d, *J* = 2.4 Hz, 18H), 0.15 – 0.00 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.32, 153.36, 135.37, 129.39, 128.91, 127.28, 72.03, 67.30, 66.08, 55.14, 37.91, 31.62, 28.56, 25.96, 25.86, 18.35, 18.06, -4.33, -4.80, -5.35, -5.38. HRMS (ESI) m/z: calculated for $C_{27}H_{47}NNaO_5Si_2$ $[M+Na]^+$: 544.2890, found 544.2859.

(R)-3-((R)-4,5-bis(tert-butyldimethylsilyloxy)pentanoyl)-4-benzyloxazolidin-2-one (ent-6)



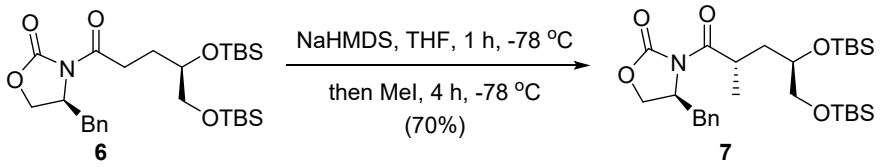
ent-6, colorless liquid; yield 80%; $[\alpha]_D^{25}$ - 66.0 (c 0.80, MeOH); The spectral data for **ent-6** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **6**.

(S)-3-((S)-4,5-bis(tert-butyldimethylsilyloxy)pentanoyl)-4-benzyloxazolidin-2-one (ent-6')



ent-6', colorless liquid; yield 78%; $[\alpha]_D^{25}$ +10.0 (c 0.50, MeOH); The spectral data for **ent-6'** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **6'**.

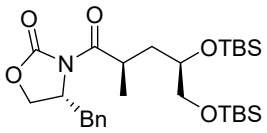
(S)-3-((2S,4R)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentanoyl)-4-benzyloxazolidin-2-one (7)



To a solution of the above **6** (55 g, 105.4 mmol) in dry THF (400 mL) was added NaHMDS (2.0 M in THF, 64 mL) at -78 °C under N_2. After 1h, MeI (14 mL, 212 mmol) was added. The reaction mixture was stirred at -78 °C for 4 h. The reaction was quenched with saturated aqueous solution of NH_4Cl (300 mL). The solution was concentrated in vacuo and the aqueous phase was extracted with ethyl acetate (3×300 mL). The combined organic phase was washed by brine (200 mL), dried over sodium sulfate (anhydrous) and concentrated in vacuo. The residue was purified by silica gel column chromatography (EA/PE, 1:10) to afford **7** (39.6 g, 70%) as an oil. $[\alpha]_D^{25}$ +80.0 (c 0.85, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 5H), 4.77 – 4.59 (m, 1H), 4.16 (d, *J* = 5.7 Hz, 2H), 3.89 (s, 1H), 3.82 – 3.73 (m, 1H), 3.51 (dq, *J* = 16.6, 9.9, 7.2 Hz, 2H), 3.26 (d, *J* = 13.0 Hz, 1H), 2.77 (dd, *J* = 12.9, 9.9 Hz, 1H), 2.21 (ddd, *J* = 13.5, 9.3, 4.1 Hz, 1H), 1.55 (dt, *J* = 12.9, 5.0 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 19.7 Hz, 18H), 0.09 – 0.01 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.87, 152.80, 135.38, 129.45, 128.90, 127.28, 71.32, 66.97, 65.88, 55.26, 37.90, 37.24, 33.47, 25.98, 25.82, 19.15, 18.07, -4.34, -5.02, -5.35, -5.39. HRMS (ESI) m/z: calculated for $C_{28}H_{49}NNaO_5Si_2$ $[M+Na]^+$: 558.3047, found 558.3019.

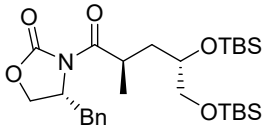
Using the same procedure as described for the synthesis of **7**, compound **7'**, **ent-7**, **ent-7'** were prepared.

(S) -3-((2R,4R)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentanoyl)-4-benzyloxazolidin-2-one (7')



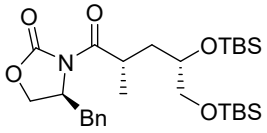
7', colorless liquid; yield 66%; $[\alpha]_D^{25}$ -53.6 (c 1.03, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 6.89 (m, 5H), 4.61 (ddt, *J* = 9.8, 6.8, 3.6 Hz, 1H), 4.11 (q, *J* = 5.4, 4.3 Hz, 2H), 3.86 – 3.75 (m, 1H), 3.67 (dq, *J* = 10.9, 5.3 Hz, 1H), 3.51 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.37 (dd, *J* = 10.0, 6.3 Hz, 1H), 3.20 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.71 (dd, *J* = 13.3, 9.6 Hz, 1H), 1.82 (ddd, *J* = 13.9, 8.2, 5.7 Hz, 1H), 1.68 (ddd, *J* = 13.7, 8.0, 4.3 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 4.2 Hz, 18H), 0.06 – -0.01 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.19, 152.72, 135.34, 129.44, 128.87, 127.27, 70.86, 67.77, 65.89, 55.22, 37.84, 37.34, 34.11, 25.96, 25.82, 18.36, 18.02, 17.84, -4.22, -4.81, -5.36, -5.38. HRMS (ESI) m/z: calculated for $C_{28}H_{49}NNaO_5Si_2$ $[M+Na]^+$: 558.3047, found 558.3027.

(R)-3-((2R,4S)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentanoyl)-4-benzyloxazolidin-2-one (ent-7)



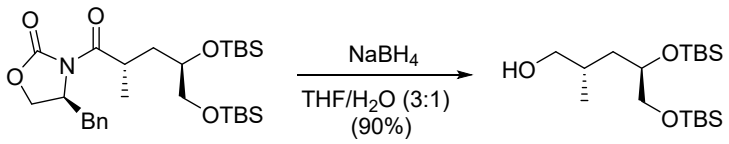
ent-7, colorless liquid; yield 73%; $[\alpha]_D^{25}$ -80.0 (c 0.66, MeOH); The spectral data for **ent-7** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **7**.

(S) -3-((2S,4S)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentanoyl)-4-benzyloxazolidin-2-one (ent-7')



ent-7', colorless liquid; yield 73%; $[\alpha]_D^{25}$ +35.0 (c 0.30, MeOH); The spectral data for **ent-7** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **7'**.

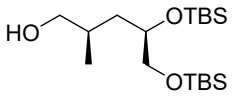
(2S,4R)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentan-1-ol (13)



7 **13**

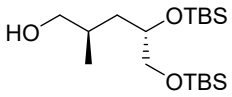
To a solution of the above **7** (39.6 g, 73.8 mmol) in THF/H_2O (3:1) (800 mL) was added $NaBH_4$ (17.0 g, 448 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then allowed to slowly warm to room temperature within 18 h. The reaction was quenched with saturated aqueous solution of NH_4Cl (300 mL). The solution was concentrated in vacuo. The aqueous phase was extracted with ethyl acetate (3×300 mL). The combined organic phase was washed by brine (300 mL), dried over sodium sulfate (anhydrous) and concentrated in vacuo. The residue was purified by silica gel column chromatography (EA/PE, 1:10) to afford **13** (24.1 g, 90%). $[\alpha]_D^{25}$ + 4.3 (0.47, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (p, *J* = 5.6 Hz, 1H), 3.61 – 3.50 (m, 2H), 3.50 – 3.41 (m, 1H), 3.41 – 3.31 (m, 1H), 3.22 (s, 1H), 1.93 – 1.81 (m, 1H), 1.61 (s, 1H), 1.51 – 1.43 (m, 1H), 0.89 (d, *J* = 4.1 Hz, 18H), 0.88 (s, 3H), 0.07 (dd, *J* = 19.3, 2.8 Hz, 12H).^{13}C NMR (100 MHz, $CDCl_3$) δ 72.14, 68.61, 66.20, 39.85, 31.85, 25.94, 25.82, 18.66, -4.47, -4.89, -5.35, -5.43. HRMS (ESI) m/z: calculated for $C_{18}H_{42}NaO_3Si_2$ $[M+Na]^+$: 385.2570, found 385.2560.

Using the same procedure as described for the synthesis of **13**, compound **13'**, **ent-13**, **ent-13'** were prepared.



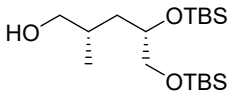
13', colorless liquid; yield 92%; $[\alpha]_D^{25}$ +22.3 (c 0.27, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (dtd, *J* = 6.8, 3.3, 1.5 Hz, 1H), 3.59 – 3.54 (m, 1H), 3.45 (d, *J* = 6.2 Hz, 2H), 3.38 (dd, *J* = 10.0, 6.7 Hz, 1H), 1.96 – 1.77 (m, 2H), 1.45 (dd, *J* = 8.5, 4.7 Hz, 1H), 1.39 (dd, *J* = 8.5, 3.7 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 3.5 Hz, 18H), 0.08 – 0.02 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.34, 69.01, 67.83, 38.30, 31.98, 25.95, 25.90, 18.35, 18.12, 16.93, -4.09, -4.72, -5.32, -5.36. HRMS (ESI) m/z: calculated for $C_{18}H_{42}NaO_3Si_2$ $[M+Na]^+$: 385.2570, found 385.2566.

(2R,4S)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentan-1-ol (ent-13)



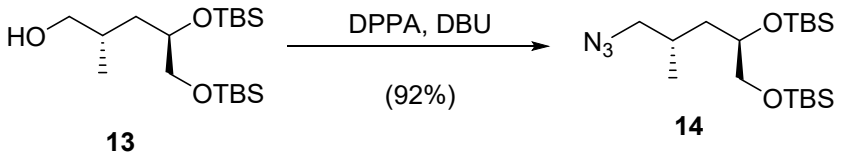
ent-13, colorless liquid; yield 90%; $[\alpha]_D^{25}$ -6.0 (1.0, MeOH); The spectral data for **ent-13** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **13**.

(2S,4S)-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentan-1-ol (ent-13')



ent-13', colorless liquid; yield 94%; $[\alpha]_D^{25}$ -23.5 (c 0.33, MeOH); The spectral data for **ent-13** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **13'**.

(2S,4R)-1-azido-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentane (14)

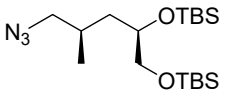


13 **14**

To a solution of the above **13** (24.1 g, 66.4 mmol) in xylene or toluene (500 mL) was added DPPA (26 mL, 121 mmol) and DBU (18 mL, 121 mmol). The reaction mixture was heated at 110 ^{o}C for 10-30 h. After concentrated in *vacuo,* the residue was purified by silica gel column chromatography (EA/PE, 1:20) to afford **14** (23.7 g, 92%) as an oil. $[\alpha]_D^{25}$ +17.5 (0.55, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (q, *J* = 5.4 Hz, 1H), 3.53 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.32 (dd, *J* = 11.9, 4.7 Hz, 1H), 3.06 (dd, *J* = 11.8, 7.7 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.65 – 1.57 (m, 1H), 1.34 – 1.29 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 4.0 Hz, 18H), 0.06 (d, *J* = 8.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.31, 67.49, 57.63, 39.15, 29.87, 25.94, 25.88, 19.02, -4.14, -4.73, -5.35, -5.39. HRMS (ESI) m/z: calculated for $C_{18}H_{41}N_3NaO_2Si_2$ $[M+Na]^+$: 410.2635, found 410.2631.

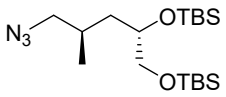
Using the same procedure as described for the synthesis of **14**, compound **14'**, **ent-14**, **ent-14'** were prepared.

(2R,4R)-1-azido-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentane (14')



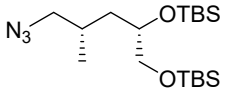
14', colorless liquid; yield 95%; $[\alpha]_D^{25}$ +34.4 (c 0.90, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (dddd, *J* = 8.7, 6.6, 4.1, 2.6 Hz, 1H), 3.55 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.36 (dd, *J* = 9.9, 6.7 Hz, 1H), 3.22 (dd, *J* = 11.9, 5.9 Hz, 1H), 3.12 (dd, *J* = 11.9, 7.0 Hz, 1H), 2.05 – 1.85 (m, 1H), 1.48 – 1.35 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 4.7 Hz, 18H), 0.06 (dd, *J* = 8.3, 1.0 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.94, 67.82, 58.64, 39.04, 29.70, 25.95, 25.86, 18.34, 18.10, 17.46, -4.03, -4.81, -5.33, -5.36. HRMS (ESI) m/z: calculated for $C_{18}H_{41}N_3NaO_2Si_2$ $[M+Na]^+$: 410.2635, found 410.2632.

(2R,4S)-1-azido-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentane (ent-14)



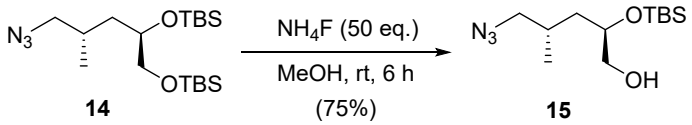
ent-14, colorless liquid; yield 93%; $[\alpha]_D^{25}$ -14.0 (0.50, MeOH); The spectral data for **ent-12** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **14**.

(2S,4S)-1-azido-4,5-bis(tert-butyldimethylsilyloxy)-2-methylpentane (ent-14')



ent-14', colorless liquid; yield 95%; $[\alpha]_D^{25}$ -10.5 (c 0.30, MeOH); The spectral data for **ent-14'** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **14'**.

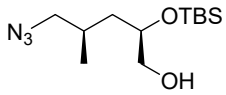
(2R,4S)-5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentan-1-ol (15)



To a solution of above **14** (23.7 g, 61.0 mmol) in MeOH (500 mL) at room temperature was added NH_4F (113 g, 3.06 mol). After 6h, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (400 mL). The solution was concentrated in *vacuo.* The aqueous phase was extracted with dichloromethane (3×300 mL). The combined organic phase was washed with H_2O (200 mL), brine (200 mL). The organic phase was then dried over sodium sulfate (anhydrous) and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (EA/PE, 1:5) to afford **15** (12.5 g, 75%) as an oil. $[\alpha]_D^{25}$ +29.4 (c 0.38, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (dtd, *J* = 6.5, 5.0, 3.8 Hz, 1H), 3.58 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.44 (dd, *J* = 11.1, 4.9 Hz, 1H), 3.26 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.12 (dd, *J* = 12.0, 6.9 Hz, 1H), 1.88 (s, 1H), 1.81 – 1.74 (m, 1H), 1.59 (ddd, *J* = 13.1, 7.1, 5.9 Hz, 1H), 1.42 – 1.35 (m, 1H), 1.00 (s, 3H), 0.90 (s, 9H), 0.13 – 0.07 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.80, 66.05, 57.78, 38.29, 30.10, 25.79, 18.28, 18.03, -4.48, -4.52. HRMS (ESI) m/z: calculated for $C_{12}H_{27}N_3NaO_2Si$ $[M+Na]^+$: 296.1770, found 296.1766.

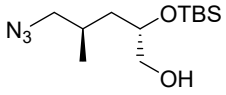
Using the same procedure as described for the synthesis of **15**, compound **15'**, **ent-15**, **ent-15'** were prepared.

(2R,4R)-5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentan-1-ol (15')



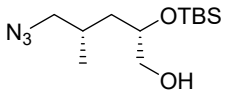
15', colorless liquid; yield 70%; $[\alpha]_D^{25}$ +48.9 (c 0.065, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (dq, *J* = 8.6, 4.4 Hz, 1H), 3.59 (dd, *J* = 11.1, 4.0 Hz, 1H), 3.45 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.23 (dd, *J* = 12.0, 5.9 Hz, 1H), 3.15 (dd, *J* = 12.0, 6.7 Hz, 1H), 1.93 – 1.80 (m, 1H), 1.77 (s, 1H), 1.69 – 1.62 (m, 1H), 1.30 – 1.23 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.10 (d, *J* = 1.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.54, 66.85, 58.20, 38.40, 29.84, 25.81, 17.79, -4.34, -4.61. HRMS (ESI) m/z: calculated for $C_{12}H_{27}N_3NaO_2Si$ $[M+Na]^+$: 296.1770, found 296.1771.

(2S,4R)-5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentan-1-ol (ent-15)



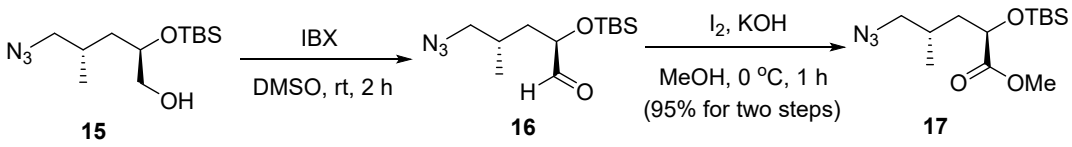
ent-15, colorless liquid; yield 72%; $[\alpha]_D^{25}$ -16.0 (c 1.0, MeOH); The spectral data for **ent-15** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **15**.

(2S,4S)-5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentan-1-ol (ent-15')



ent-15', colorless liquid; yield 66%; $[\alpha]_D^{25}$ -50.5 (c 0.35, MeOH); The spectral data for **ent-15'** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **15'**.

(2R,4S)-methyl 5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentanoate (17)



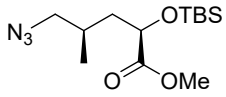
To a solution of the above **15** (12.5 g, 45.7 mmol) in DMSO (100 mL) was added IBX (28 g, 100 mmol) at room temperature. After 3h, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (600 mL). The aqueous phase was extracted with EtOAc (3×300 mL). The combined organic phase was washed with H_2O (300 mL), brine (300 mL). The organic phase was then dried over sodium sulfate (anhydrous) and concentrated in vacuo to afford **16** as an oil which was used for next step directly.

To a solution of the above **16** in MeOH (300 mL) was added KOH (15.5 g, 274 mmol) and I_2

(34.8 g, 137.1 mmol) at 0 °C. After 2h, the reaction was quenched with saturated aqueous solution of $NaHSO_3$ (400 mL) and 1M aq. HCl (300 mL). The aqueous phase was extracted with CH_2Cl_2 (3×300 mL). The combined organic phase was washed with H_2O (200 mL), brine (200 mL). The organic phase was then dried over sodium sulfate (anhydrous) and concentrated in vacuo. The residue was purified by silica gel column chromatography (EA/PE, 1:50) to afford **17** (13.0 g, 95%) as an oil; $[\alpha]_D^{25}$ + 46.5 (c 0.18, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (dd, *J* = 7.4, 5.0 Hz, 1H), 3.72 (s, 3H), 3.32 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.16 (dd, *J* = 12.0, 6.8 Hz, 1H), 1.92 (dq, *J* = 13.0, 6.7 Hz, 1H), 1.78 (ddd, *J* = 14.0, 7.2, 5.0 Hz, 1H), 1.66 – 1.60 (m, 1H), 1.00 (s, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 8.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.99, 70.57, 57.10, 51.80, 39.25, 29.94, 25.68, 18.49, 18.21, -4.97, -5.37. HRMS (ESI) m/z: calculated for $C_{13}H_{27}N_3NaO_3Si$ $[M+Na]^+$: 324.1719, found 324.1722.

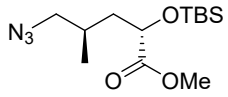
Using the same procedure as described for the synthesis of **17**, compound **17'**, **ent-17**, **ent-17'** were prepared.

(2R,4R)-methyl 5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentanoate (17')



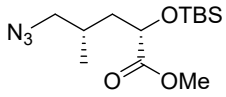
17', colorless liquid; yield 90%; $[\alpha]_D^{25}$ +33.1 (c 0.63, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 9.4, 3.6 Hz, 1H), 3.72 (s, 3H), 3.27 – 3.11 (m, 2H), 1.96 (td, *J* = 6.1, 3.2 Hz, 1H), 1.81 (ddd, *J* = 13.6, 9.4, 4.1 Hz, 1H), 1.51 (ddd, *J* = 13.4, 9.5, 3.6 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 10.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.32, 70.18, 58.00, 51.86, 39.30, 29.79, 25.69, 18.23, 17.01, -4.90, -5.41. HRMS (ESI) m/z: calculated for $C_{13}H_{27}N_3NaO_3Si$ $[M+Na]^+$: 324.1719, found 324.1726.

(2S,4R)-methyl 5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentanoate (ent-17)



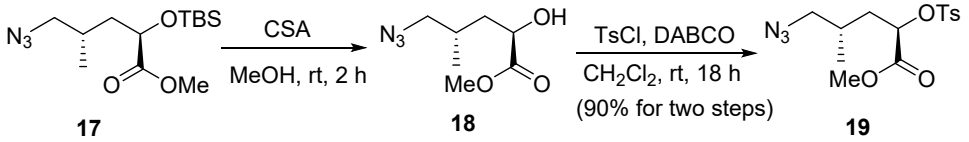
ent-17, colorless liquid; yield 92%; $[\alpha]_D^{25}$ -28.5 (c 1.0, MeOH); The spectral data for **ent-17** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **17**.

(2S,4S)-methyl 5-azido-2-(tert-butyldimethylsilyloxy)-4-methylpentanoate(ent-17')



ent-17', colorless liquid; yield 85%; $[\alpha]_D^{25}$ -12.0 (c 0.55, MeOH); The spectral data for **ent-17'** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **17'**.

(2R,4S)-methyl 5-azido-4-methyl-2-(tosyloxy)pentanoate (19)



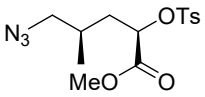
17 **18** **19**

To a solution of the above **17** (13.0 g, 43.1 mmol) in MeOH (200 mL) was added camphorsulfonic acid (23.2 g, 100 mmol) at room temperature. After 2 h, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (200 mL). The aqueous phase was extracted with CH_2Cl_2 (3×300 mL). The combined organic phase was washed with H_2O (200 mL), brine (200 mL). The organic phase was then dried over sodium sulfate (anhydrous) and concentrated in vacuo to afford **18** as an oil which was used for next step directly.

To a solution of the above **18** in CH_2Cl_2 (400 mL) was added DABCO (14.5 g, 129.3 mmol) and TsCl (16.4 g, 86.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for an additional 18 h. After concentrated in vacuo, the residue was purified by silica gel column chromatography (EA/PE, 1:10) to afford **19** (13.2 g, 90% over two steps) as an oil. $[\alpha]_D^{25}$ +52.0 (c 0.26, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.90 (dd, *J* = 8.8, 4.2 Hz, 1H), 3.65 (s, 3H), 3.17 (dd, *J* = 5.1, 2.4 Hz, 2H), 2.45 (s, 3H), 1.92 – 1.82 (m, 2H), 1.80 – 1.71 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.11, 145.34, 133.00, 129.82, 128.10, 75.68, 56.05, 52.58, 36.05, 29.63, 21.67, 18.09. HRMS (ESI) m/z: calculated for $C_{14}H_{19}N_3NaO_5S$ $[M+Na]^+$: 364.0943, found 364.0953.

Using the same procedure as described for the synthesis of **19**, compound **19'**, **ent-19**, **ent-19'** were prepared.

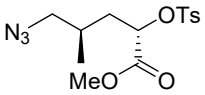
(2R,4R)-methyl 5-azido-4-methyl-2-(tosyloxy)pentanoate (19')



19', colorless liquid; yield 80%; $[\alpha]_D^{25}$ +57.0 (c 0.20, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.72 (m, 2H), 7.40 – 7.29 (m, 2H), 4.88 (dd, *J* = 10.2, 3.4 Hz, 1H), 3.63 (s, 3H), 3.16 (dd, *J* = 6.1, 1.8 Hz, 2H), 2.44 (s, 3H), 1.94 (ddd, *J* = 14.2, 10.2, 3.9 Hz, 1H), 1.82 (ddd, *J* = 10.1, 6.6, 3.7 Hz, 1H), 1.59 (ddd, *J* = 14.2, 9.7, 3.4 Hz, 1H), 0.87 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

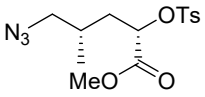
169.23, 145.26, 132.88, 129.74, 128.02, 75.33, 57.24, 52.54, 36.15, 29.54, 21.59, 16.31. HRMS (ESI) m/z: calculated for $C_{14}H_{19}N_3NaO_5S$ $[M+Na]^+$: 364.0943, found 364.0953.

(2S,4R)-methyl 5-azido-4-methyl-2-(tosyloxy)pentanoate (ent-19)



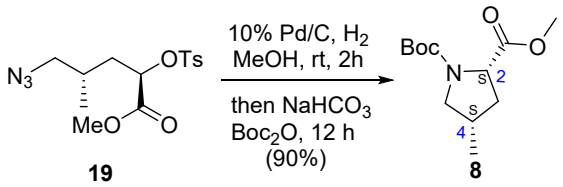
ent-19, colorless liquid; yield 85%; $[\alpha]_D^{25}$ -55.0 (c 0.65, MeOH); The spectral data for **ent-19** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **19**.

(2S,4S)-methyl 5-azido-4-methyl-2-(tosyloxy)pentanoate (ent-19')



ent-19', colorless liquid; yield 76%; $[\alpha]_D^{25}$ -59.5 (c 0.40, MeOH); The spectral data for **ent-19'** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **19'**.

(2S,4S)-1-tert-butyl 2-methyl 4-methylpyrrolidine-1,2-dicarboxylate (8)

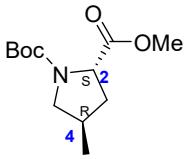


Palladium-carbon (2.0 g, 10%) was added to a solution of compound **19** (13.2 g, 38.7 mmol) in MeOH (200 mL) under a nitrogen atmosphere. The reaction vessel was sealed and the resulting solution was stirred at room temperature for 2 h under a hydrogen atmosphere. Then $NaHCO_3$ (10.0 g, 120 mmol) and Boc_2O (9.2 mL, 40 mmol) were added to this solution under N_2. The reaction mixture was stirred at room temperature for an additional 12 h. The catalyst was removed by filtration through a pad of celite and washed with MeOH (300 mL). After concentrated in *vacuo,* the residue was purified by silica gel column chromatography (EA/PE, 1:6) to afford the corresponding **8** as an oil (8.5 g, 90%). $[\alpha]_D^{25}$ -84.7 (c 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) (*exists as rotamers*) δ 4.18 (ddd, *J* = 38.9, 9.1, 7.6 Hz, 1H), 3.71 – 3.60 (m, 1H), 3.68 (d, *J* = 7.3 Hz, 3 H), 2.93 (td, *J* = 10.1, 1.7 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.18 (d, *J* = 6.6 Hz, 1H), 1.55 – 1.44 (m, 1H), 1.41 (s, 3H), 1.36 (s, 6H), 1.01 (dd, *J* = 9.1, 6.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) (*exists as rotamers*) δ 173.71, 173.48, 154.12, 153.41, 79.76, 79.70, 59.60, 59.15, 53.66, 53.17, 51.96,

51.78, 38.83, 37.95, 33.16, 32.49, 28.31, 28.16, 16.92, 16.80. HRMS (ESI) m/z: calculated for $C_{12}H_{21}NNaO_4$ $[M+Na]^+$: 266.1368, found 266.1371.

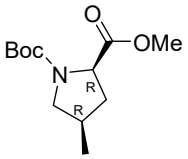
Using the same procedure as described for the synthesis of **8**, compound **8'**, **ent-8**, **ent-8'** were prepared.

(2S,4R)-1-tert-butyl 2-methyl 4-methylpyrrolidine-1,2-dicarboxylate (8')



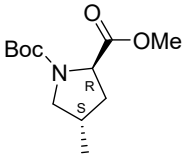
8', colorless liquid; yield 80%; $[\alpha]_D^{25}$ -5.3 (c 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) (*exists as rotamers*) δ 4.30 (ddd, *J* = 59.2, 9.0, 2.6 Hz, 1H), 3.73 – 3.64 (m, 1H), 3.71 (d, *J* = 3.4 Hz, 3H), 3.01 – 2.82 (m, 1H), 2.38 (ddd, *J* = 15.8, 10.4, 5.8 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.89 – 1.73 (m, 1H), 1.45 (s, 3H), 1.39 (d, *J* = 1.7 Hz, 6H), 1.02 (dd, *J* = 7.0, 3.8 Hz, 3H).^{13}C NMR (150 MHz, $CDCl_3$) (*exists as rotamers*) δ 173.71, 173.45, 154.40, 153.72, 79.78, 59.18, 58.90, 53.50, 53.04, 52.07, 51.90, 38.39, 37.59, 32.01, 31.16, 28.41, 28.28, 17.41, 17.32. HRMS (ESI) m/z: calculated for $C_{12}H_{21}NNaO_4$ $[M+Na]^+$: 266.1368, found 266.1371.

(2R,4R)-1-tert-butyl 2-methyl 4-methylpyrrolidine-1,2-dicarboxylate (ent-8)



ent-8, colorless liquid; yield 85%; $[\alpha]_D^{25}$ +78.5 (c 0.50, MeOH); The spectral data for **ent-8** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **8**.

(2R,4S)-1-tert-butyl 2-methyl 4-methylpyrrolidine-1,2-dicarboxylate (ent-8')



ent-8', colorless liquid; yield 76%; $[\alpha]_D^{25}$ +11.5 (c 0.25, MeOH); The spectral data for **ent-8'** (^{1}H, ^{13}C NMR and HMRS) was identical with those for **8'**.

NMR Spectra

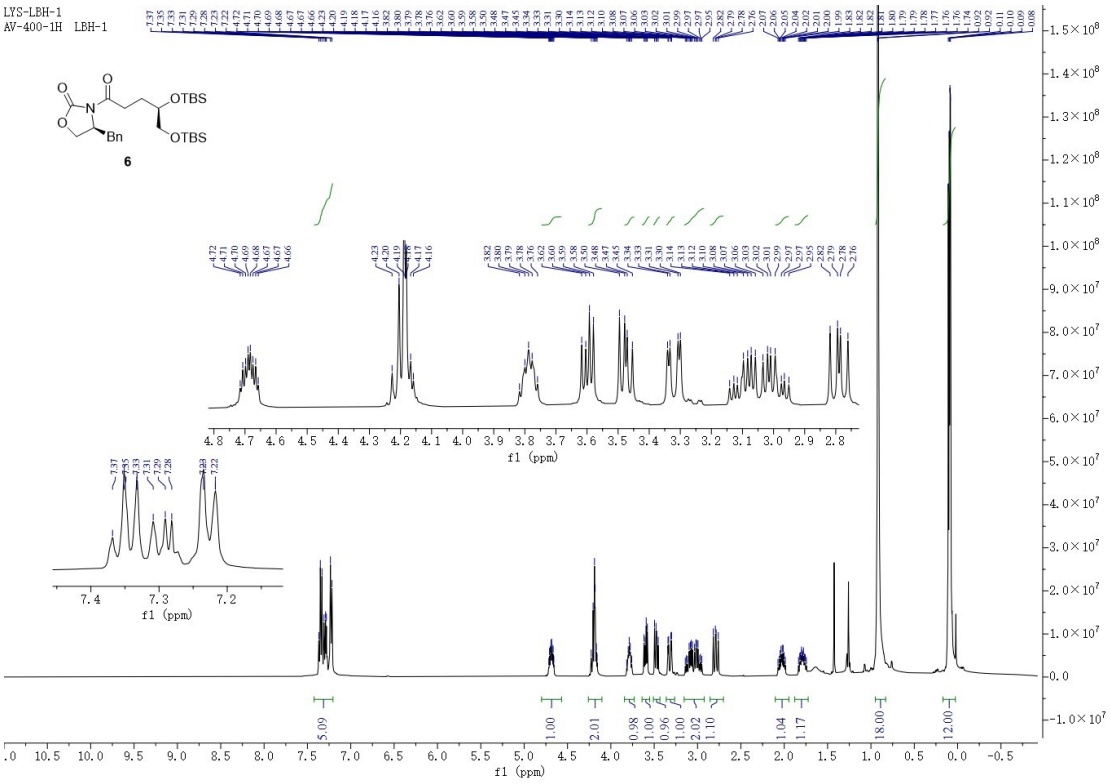


Figure S1. ^{1}H NMR of **6** ($CDCl_3$, 400 MHz)

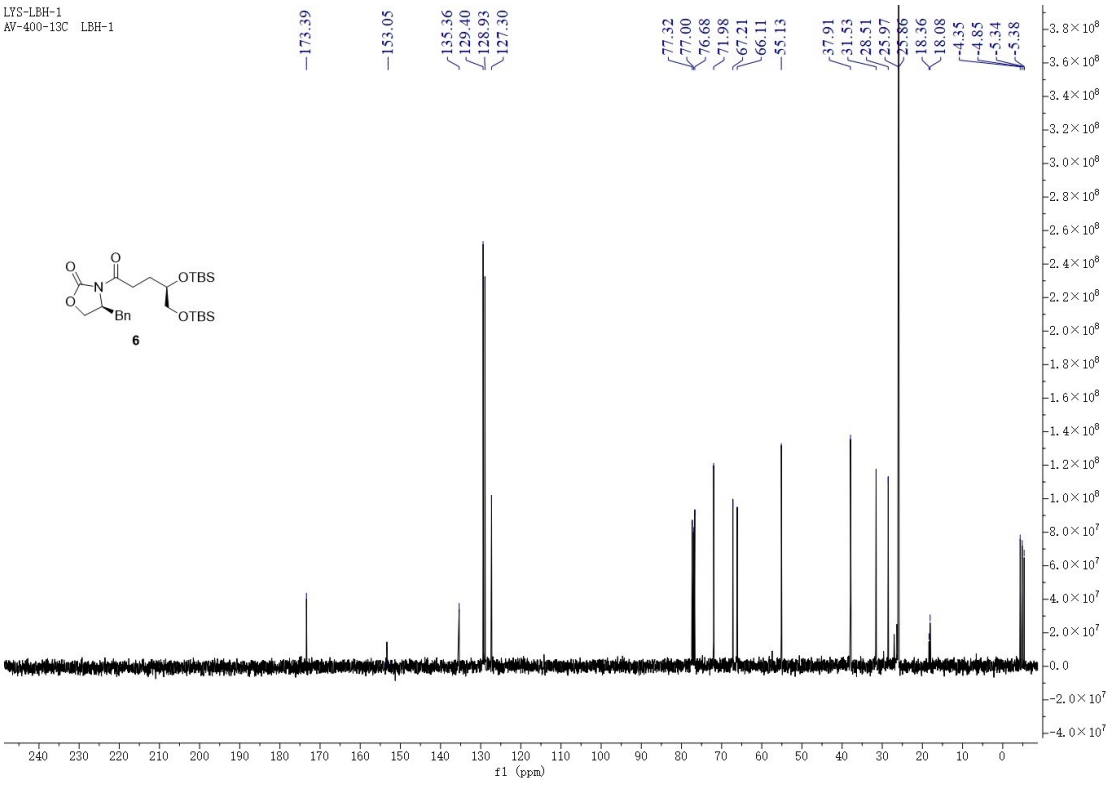


Figure S2. ^{13}C NMR of **6** ($CDCl_3$, 100 MHz)

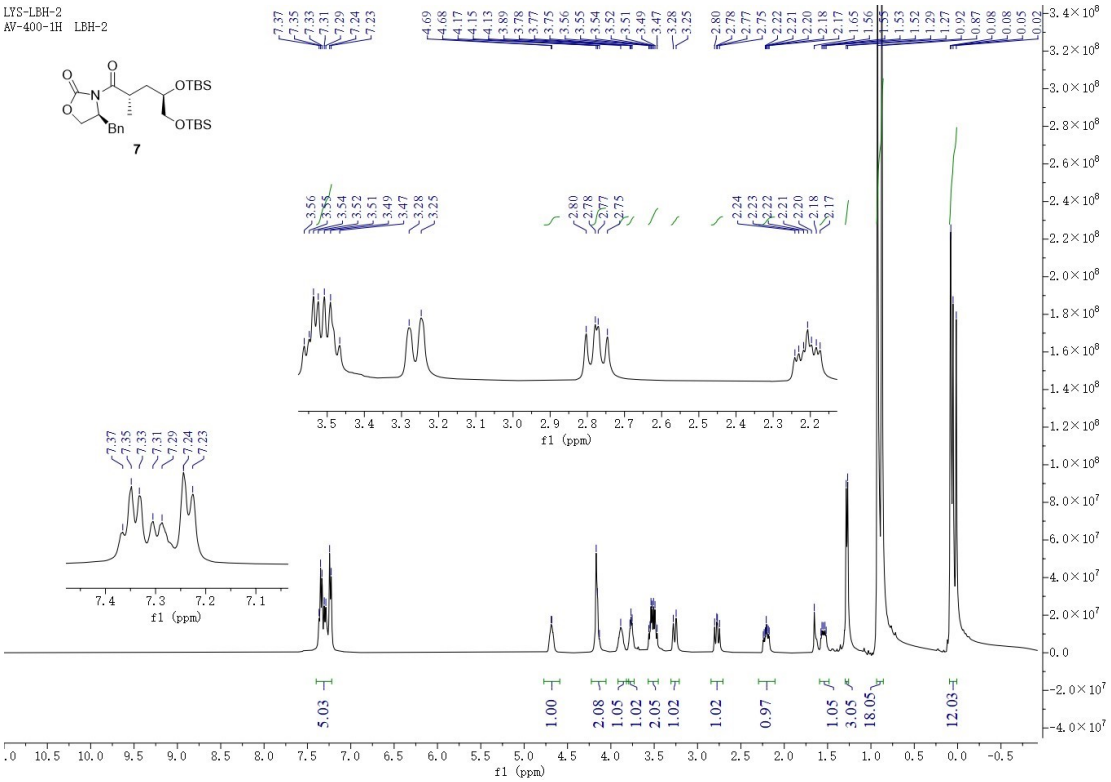


Figure S3. ^{1}H NMR of **7** ($CDCl_3$, 400 MHz)

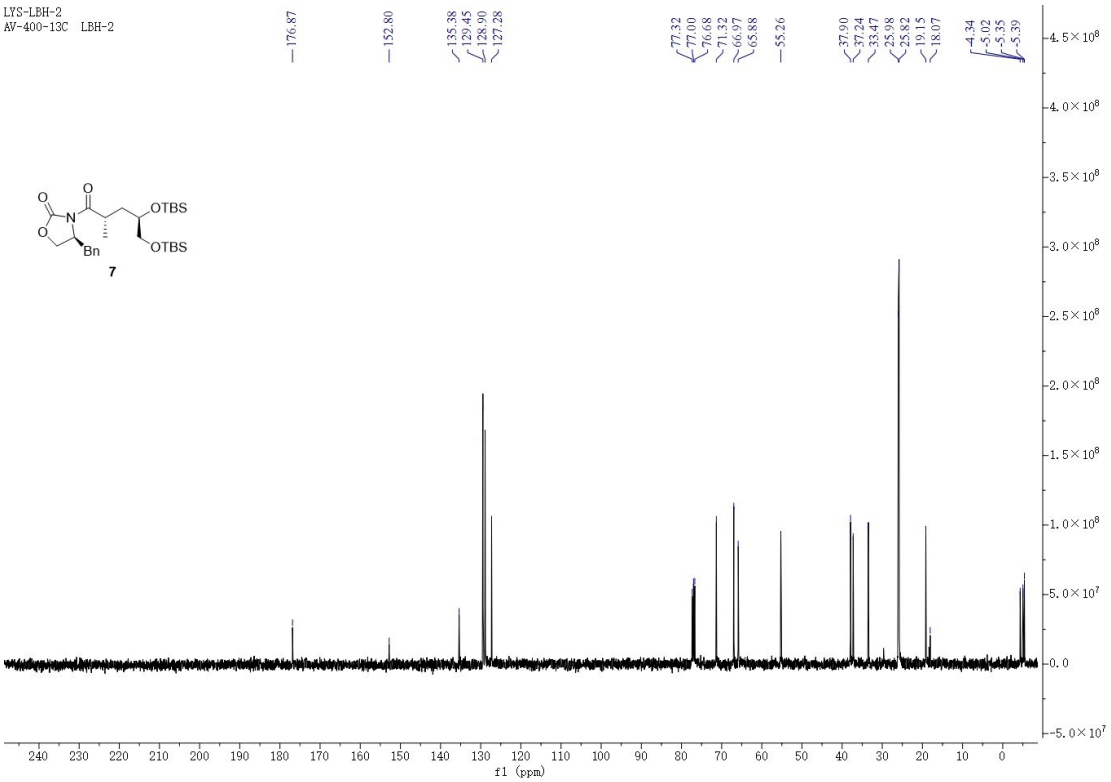


Figure S4. ^{13}C NMR of **7** ($CDCl_3$, 100 MHz)

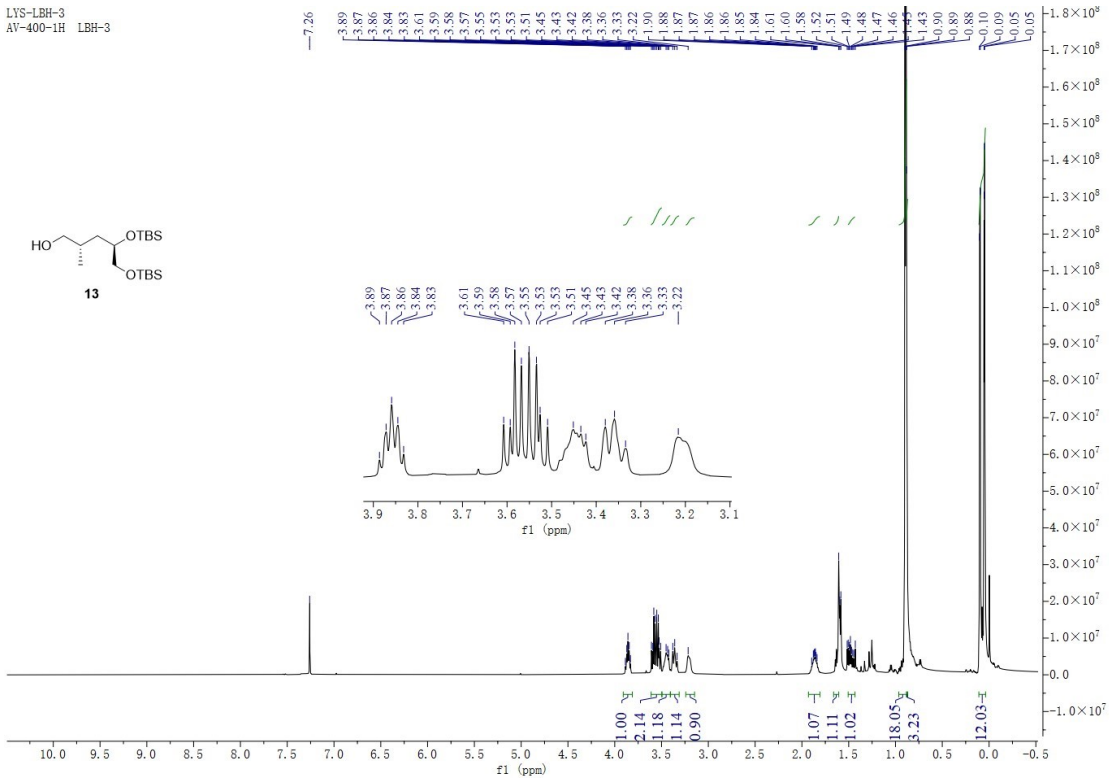


Figure S5. ^{1}H NMR of **13** ($CDCl_3$, 400 MHz)

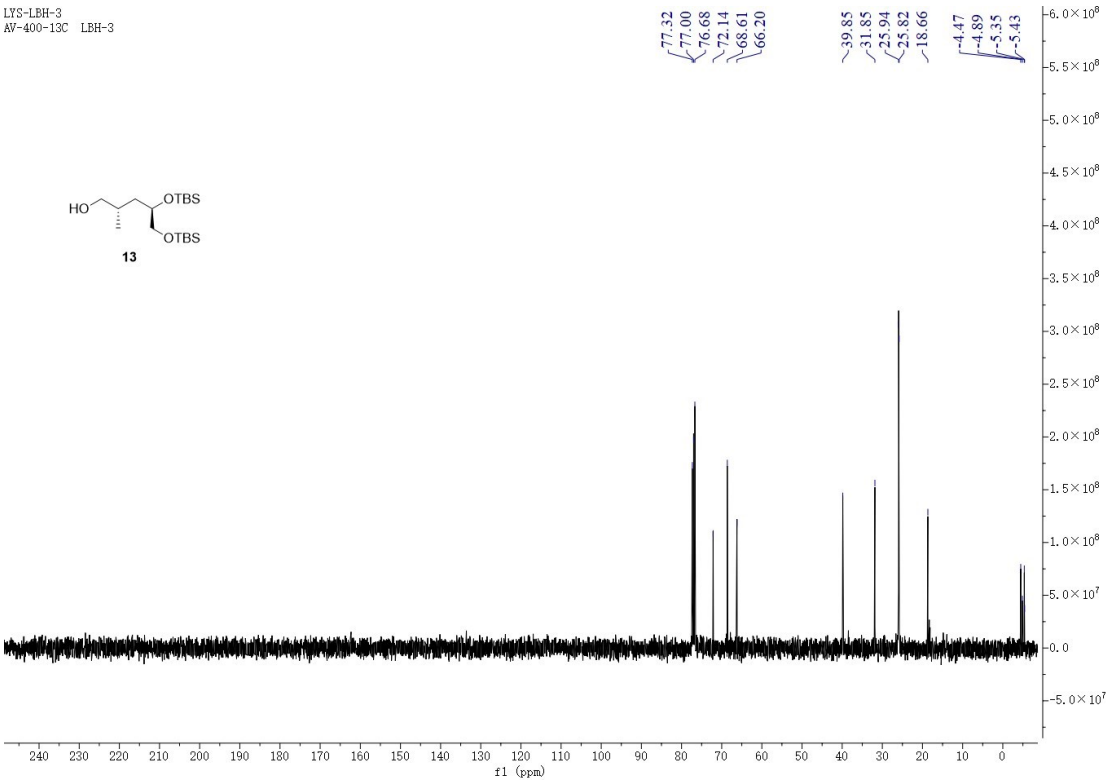


Figure S6. ^{13}C NMR of **13** ($CDCl_3$, 100 MHz)

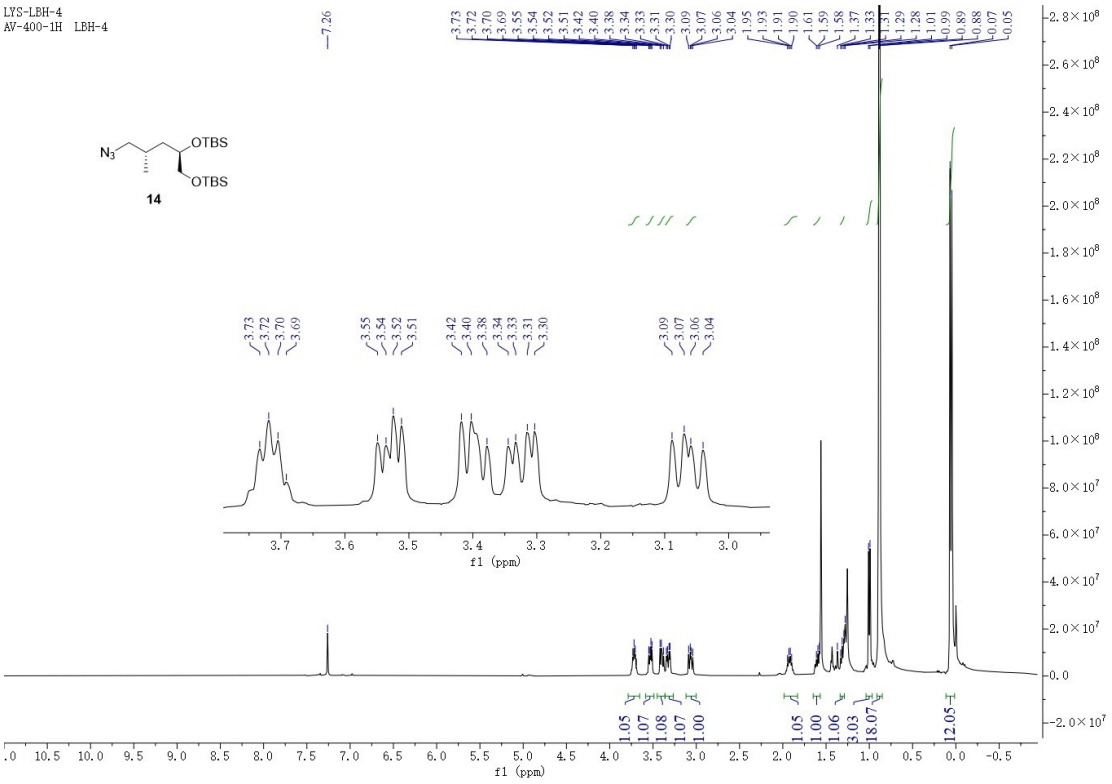


Figure S7. ^{1}H NMR of **14** ($CDCl_3$, 400 MHz)

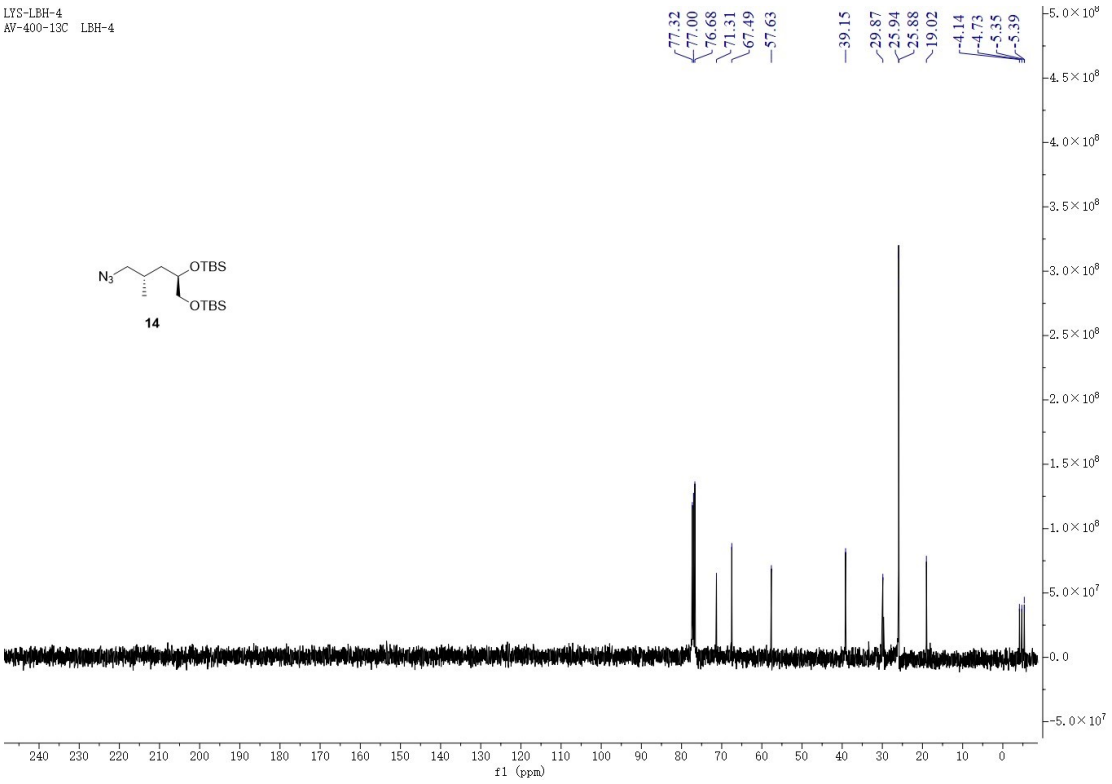


Figure S8. ^{13}C NMR of **14** ($CDCl_3$, 100 MHz)

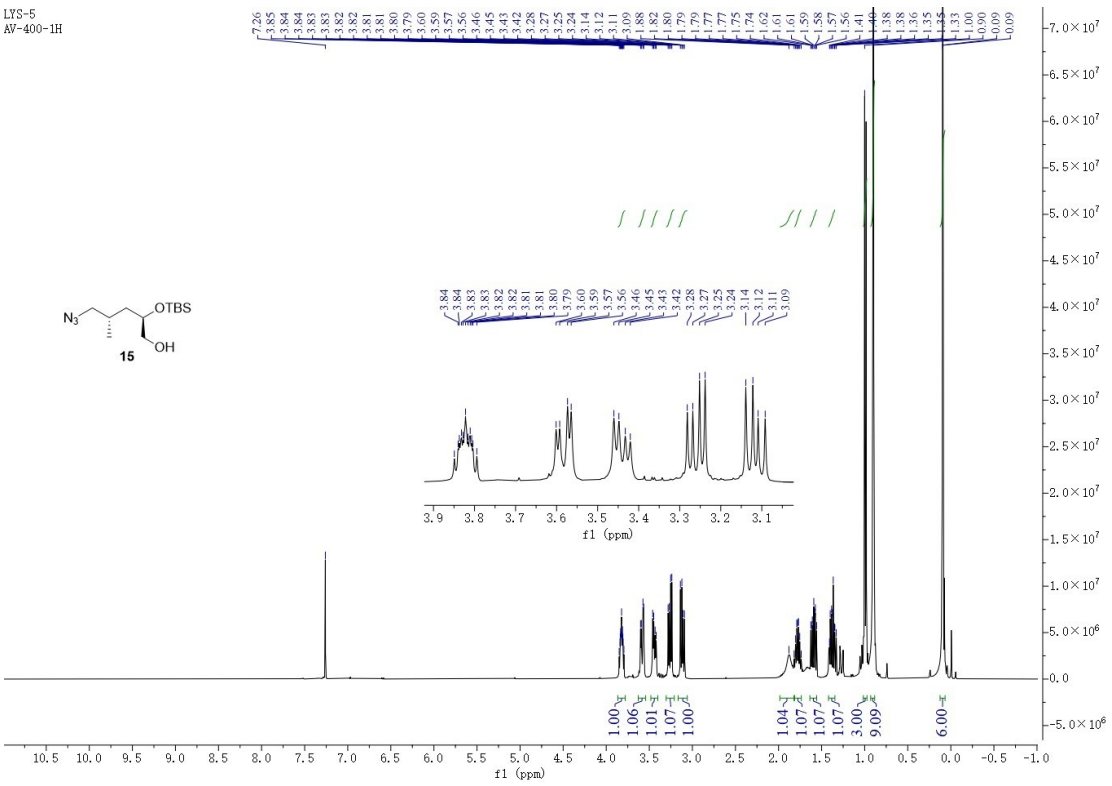


Figure S9. ^{1}H NMR of **15** ($CDCl_3$, 400 MHz)

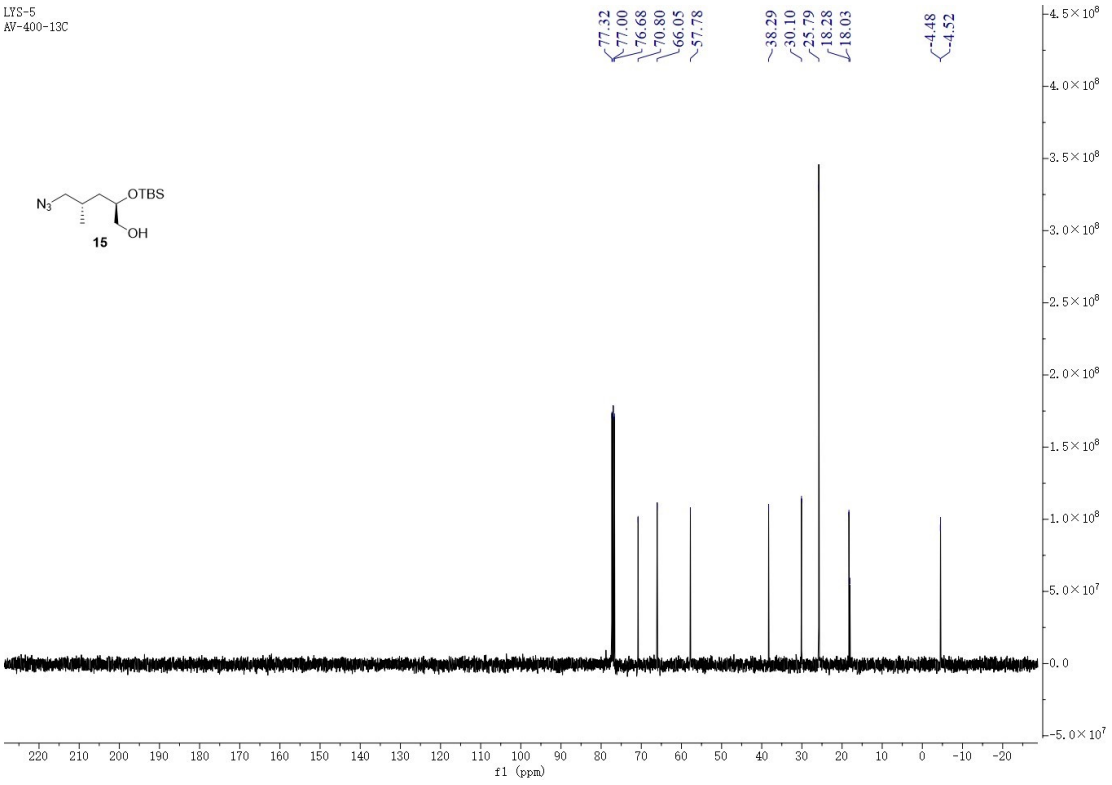


Figure S10. ^{13}C NMR of **15** ($CDCl_3$, 100 MHz)

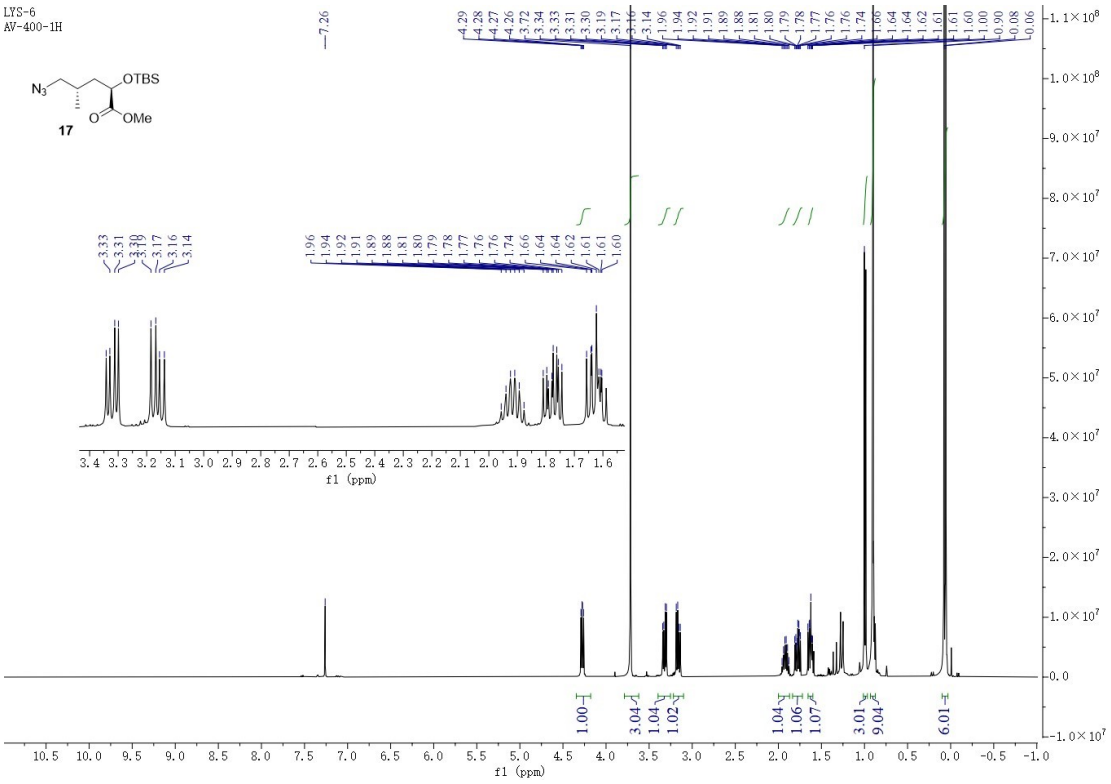


Figure S11. ^{1}H NMR of **17** ($CDCl_3$, 400 MHz)

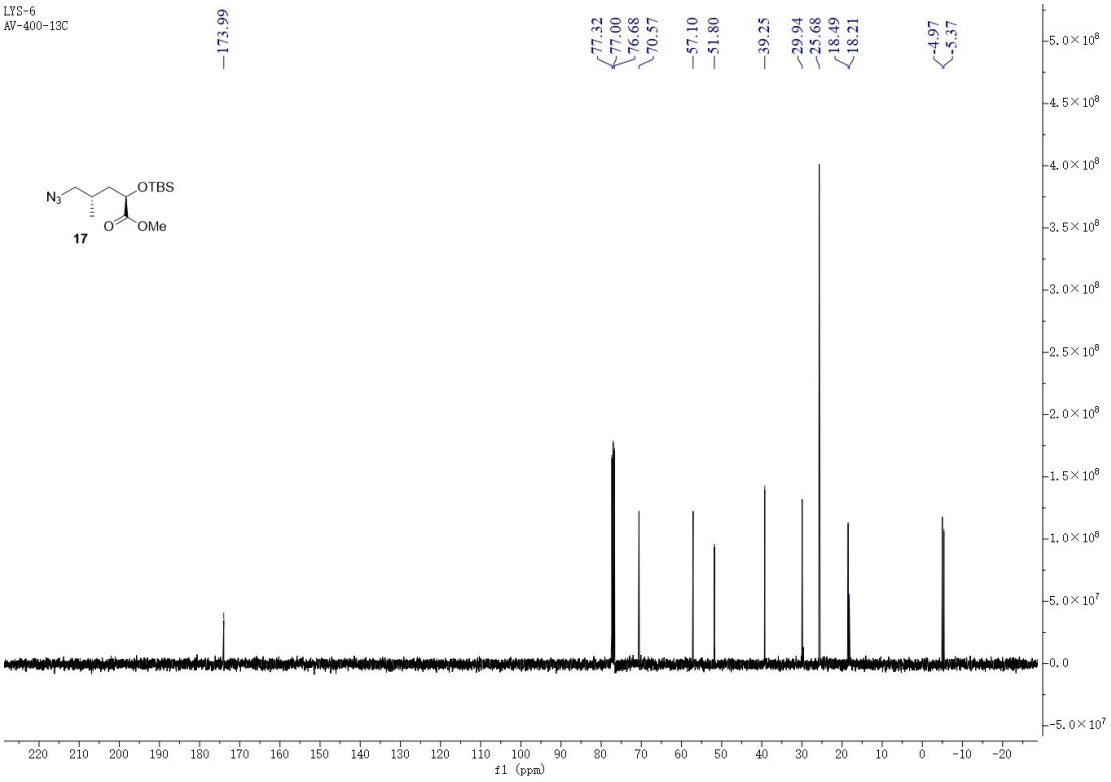


Figure S12. ^{13}C NMR of **17** ($CDCl_3$, 100 MHz)

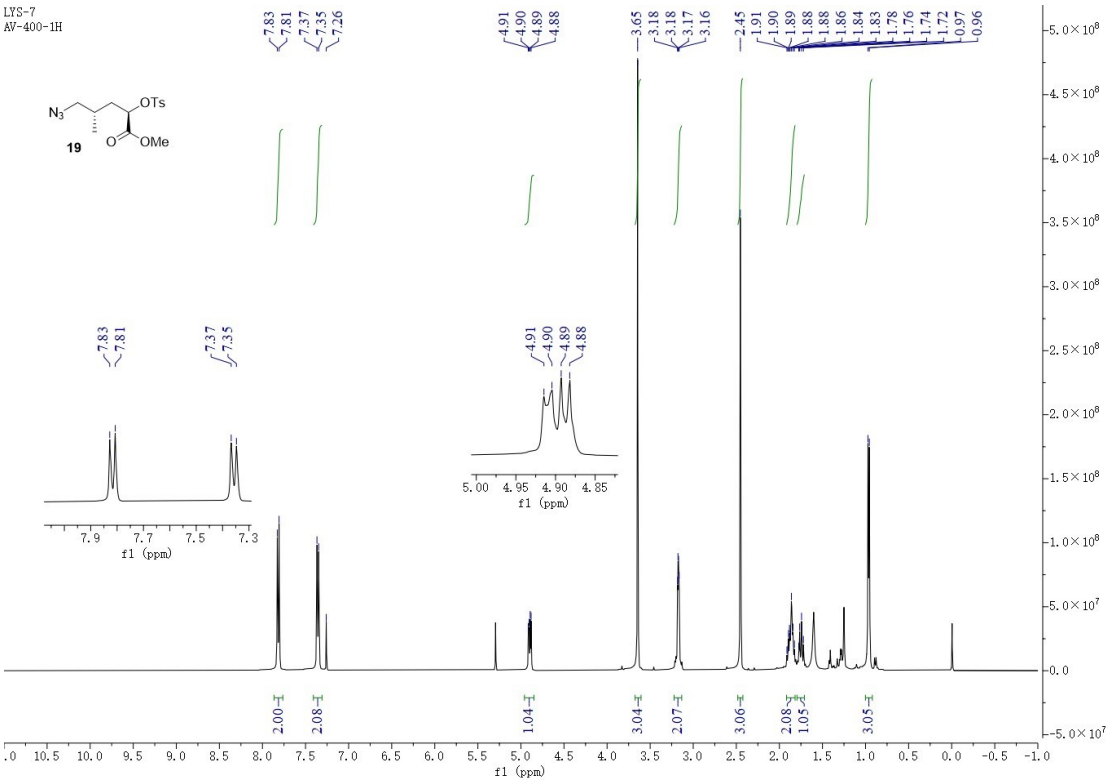


Figure S13. ^{1}H NMR of **19** ($CDCl_3$, 400 MHz)

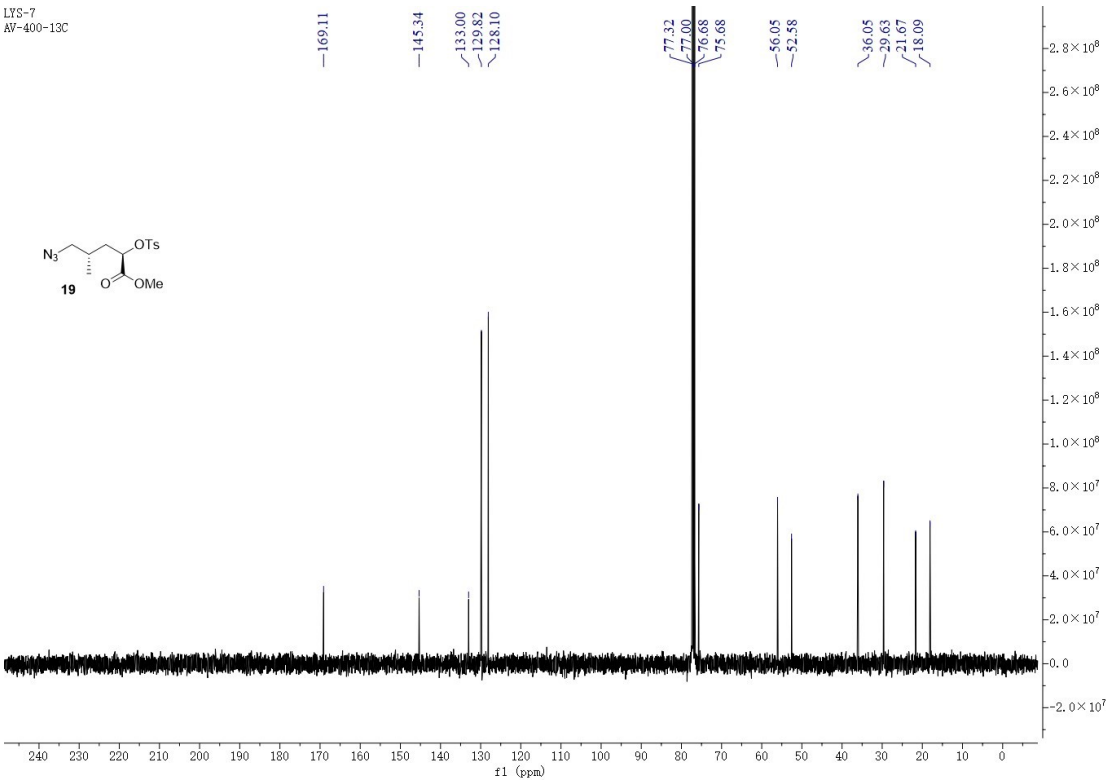


Figure S14. ^{13}C NMR of **19** ($CDCl_3$, 100 MHz)

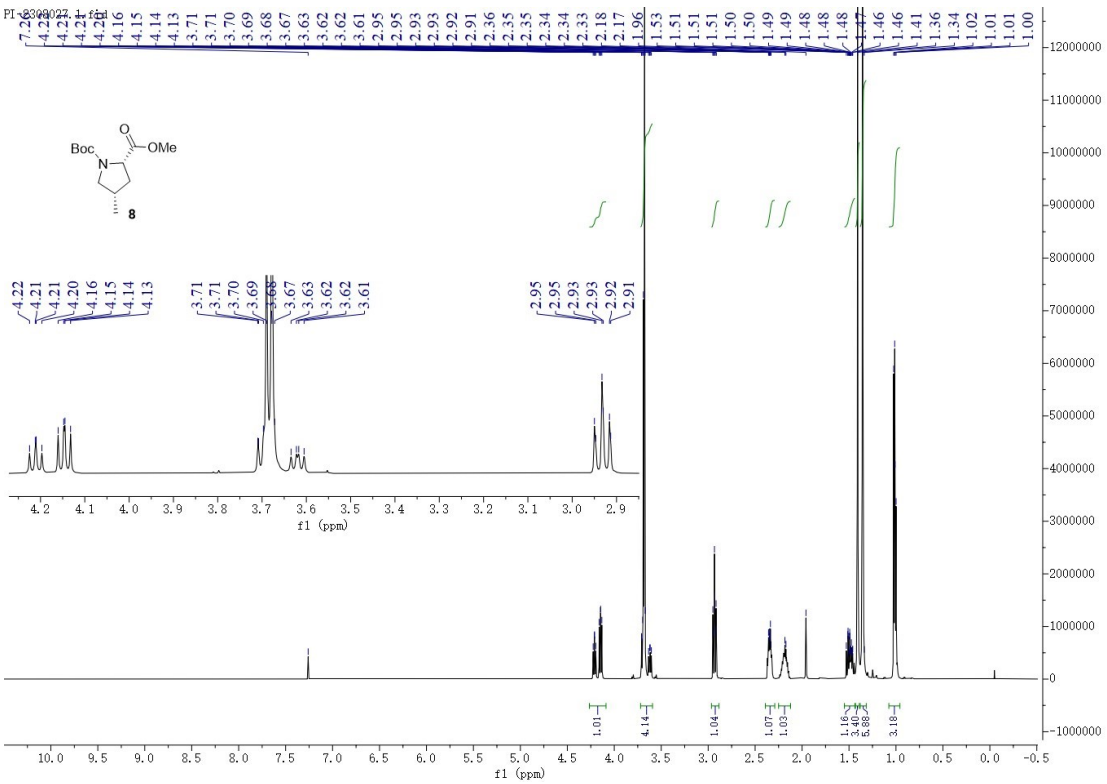


Figure S15. ^{1}H NMR of **8** ($CDCl_3$, 600 MHz)

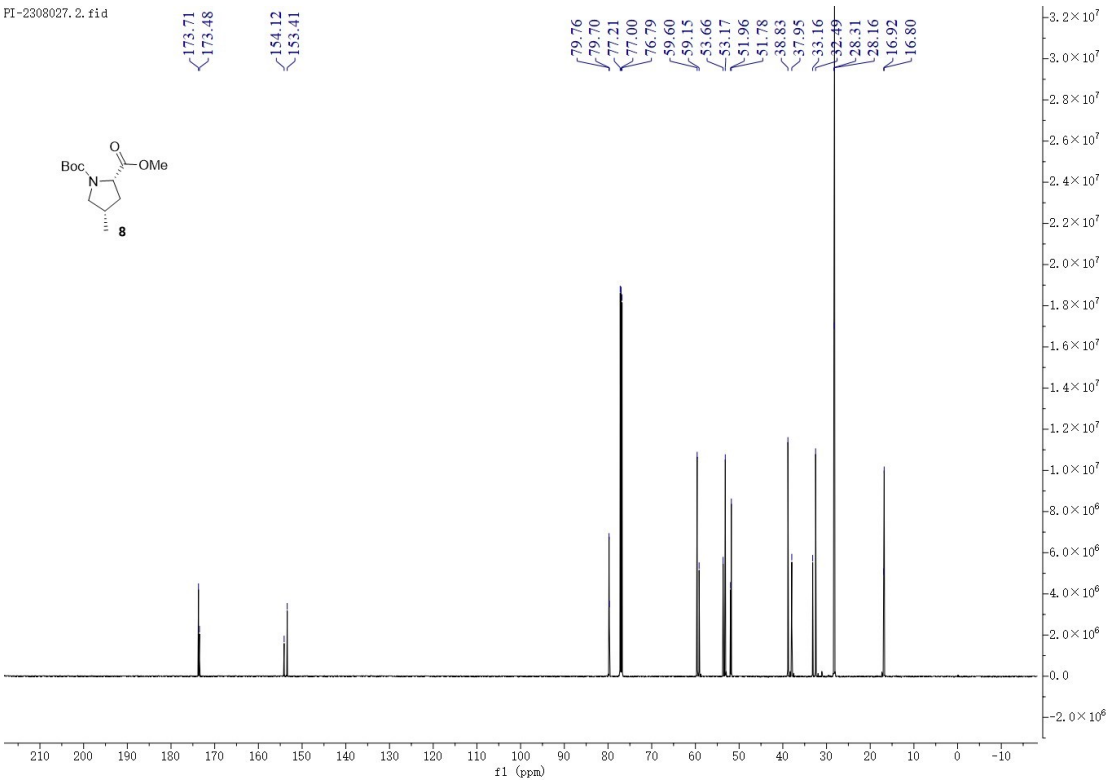


Figure S16. ^{13}C NMR of **8** ($CDCl_3$, 150 MHz)

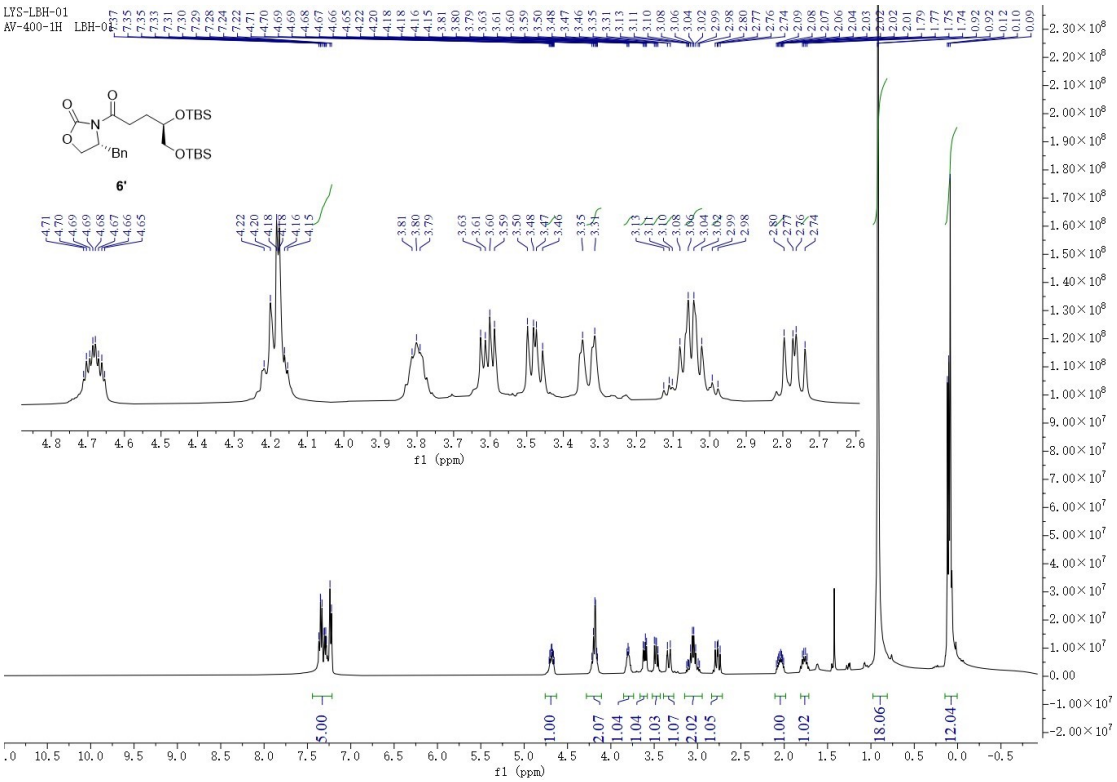


Figure S17. ^{1}H NMR of **6'** ($CDCl_3$, 400 MHz)

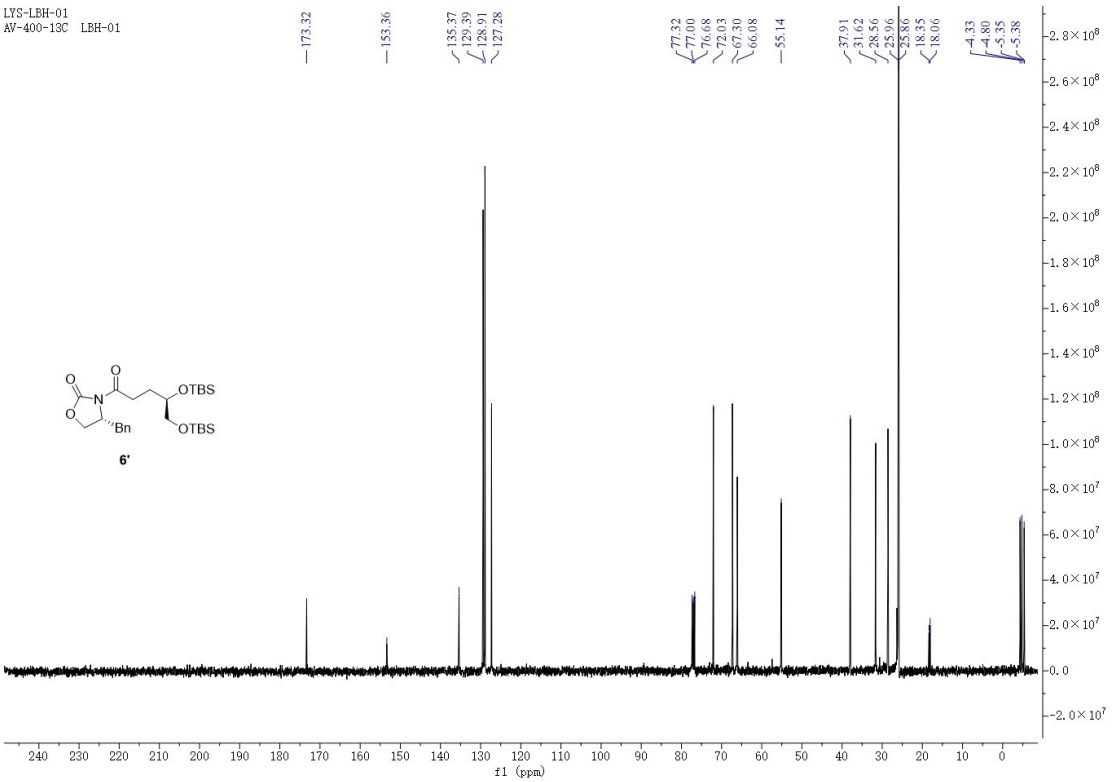


Figure S18. ^{13}C NMR of **6'** ($CDCl_3$, 100 MHz)

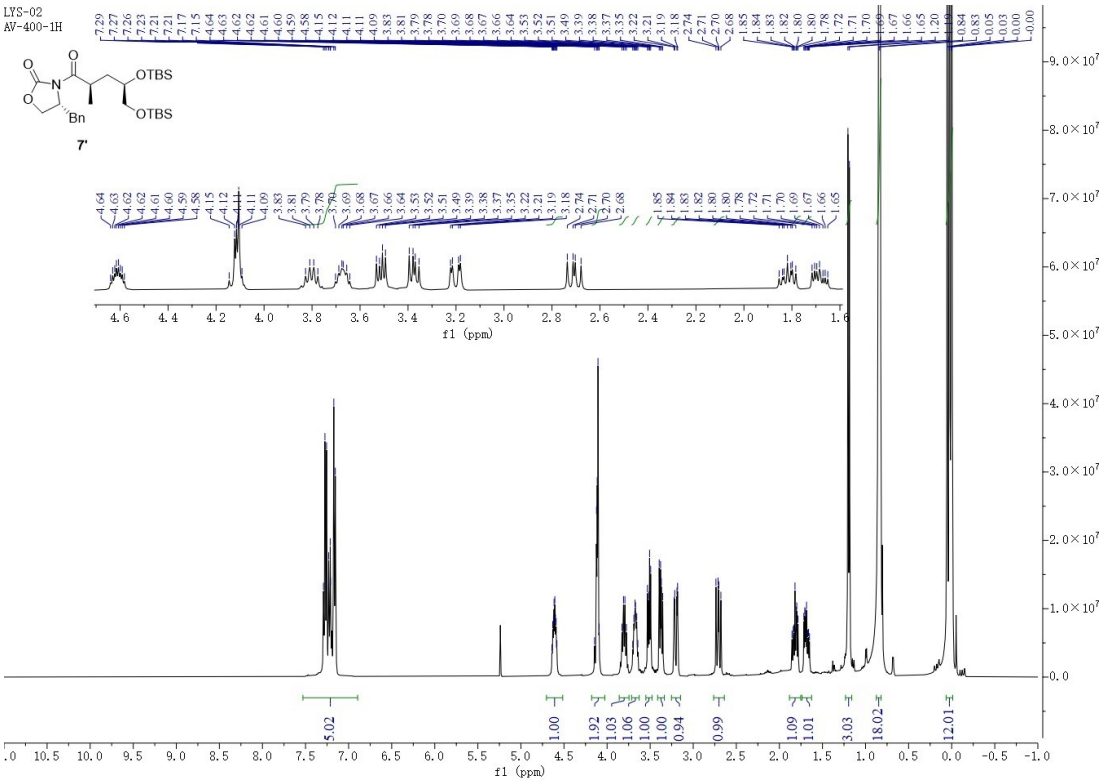


Figure S19. ^{1}H NMR of **7'** ($CDCl_3$, 400 MHz)

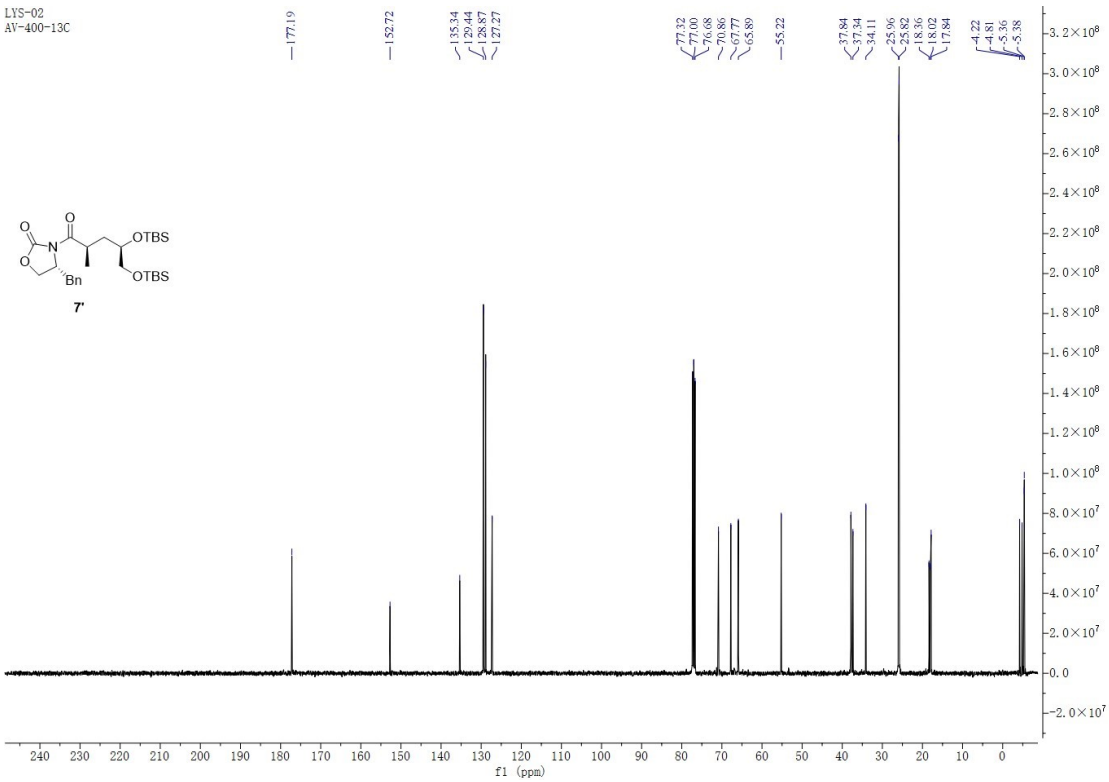


Figure S20. ^{13}C NMR of **7'** ($CDCl_3$, 100 MHz)

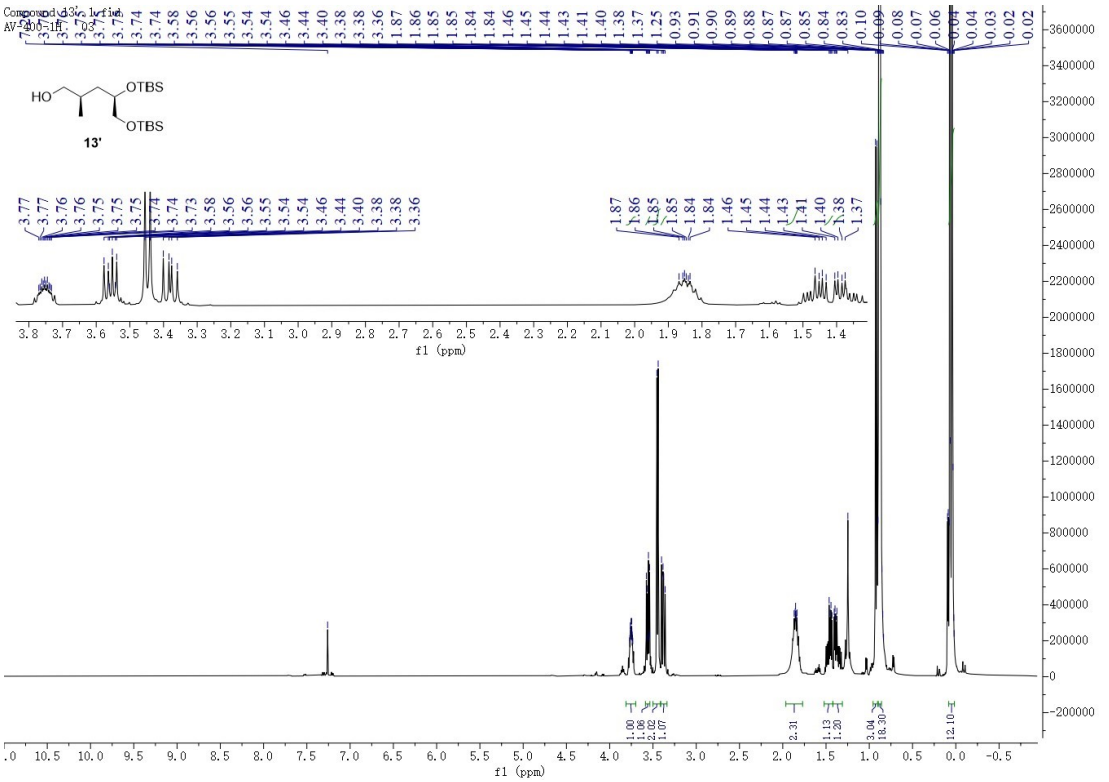


Figure S21. ^{1}H NMR of **13'** ($CDCl_3$, 400 MHz)

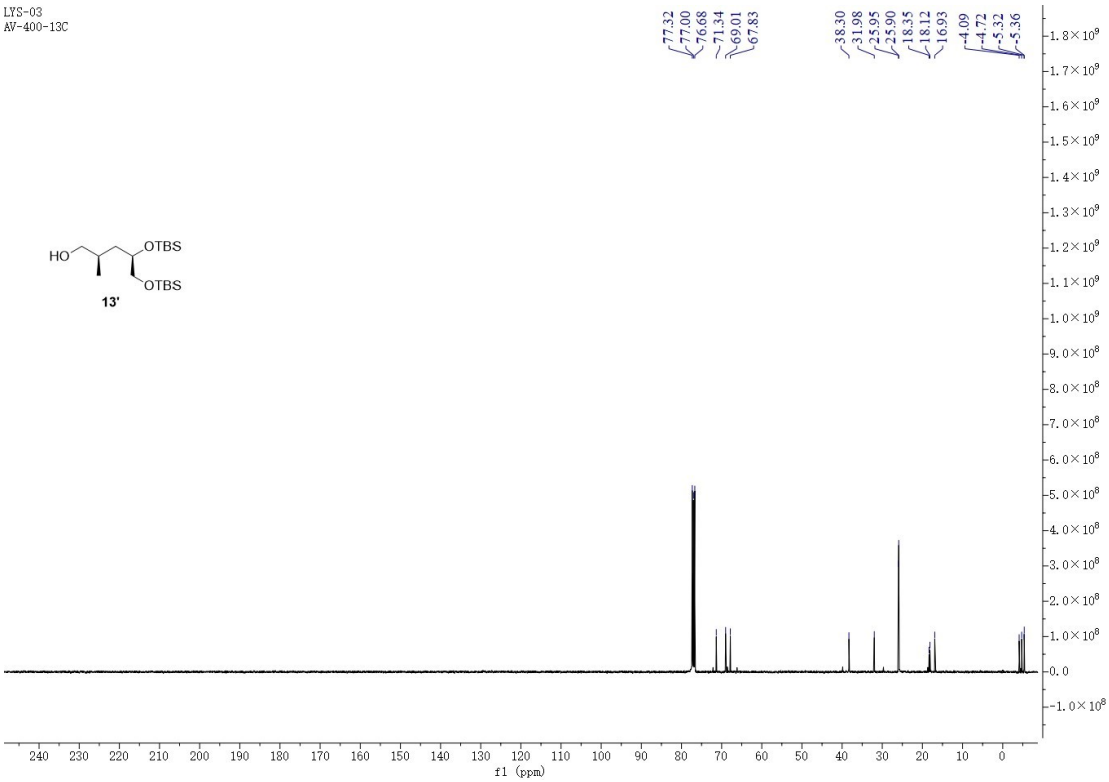


Figure S22. ^{13}C NMR of **13'** ($CDCl_3$, 100 MHz)

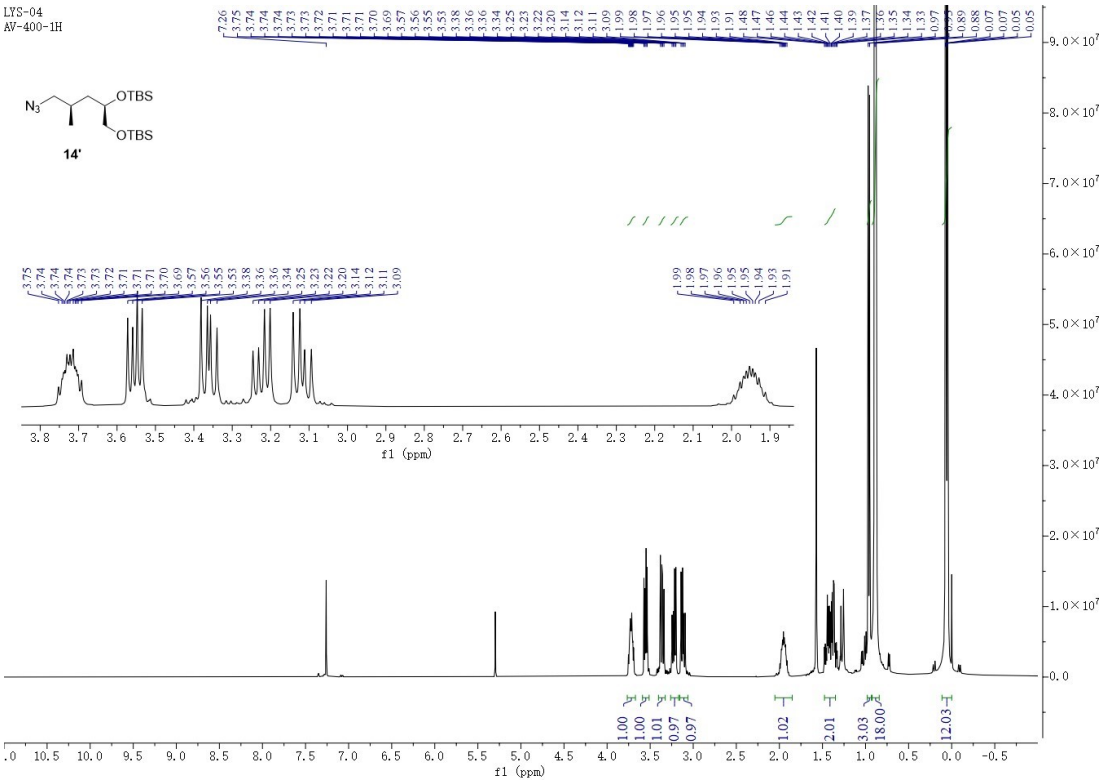


Figure S23. ^{1}H NMR of **14'** ($CDCl_3$, 400 MHz)

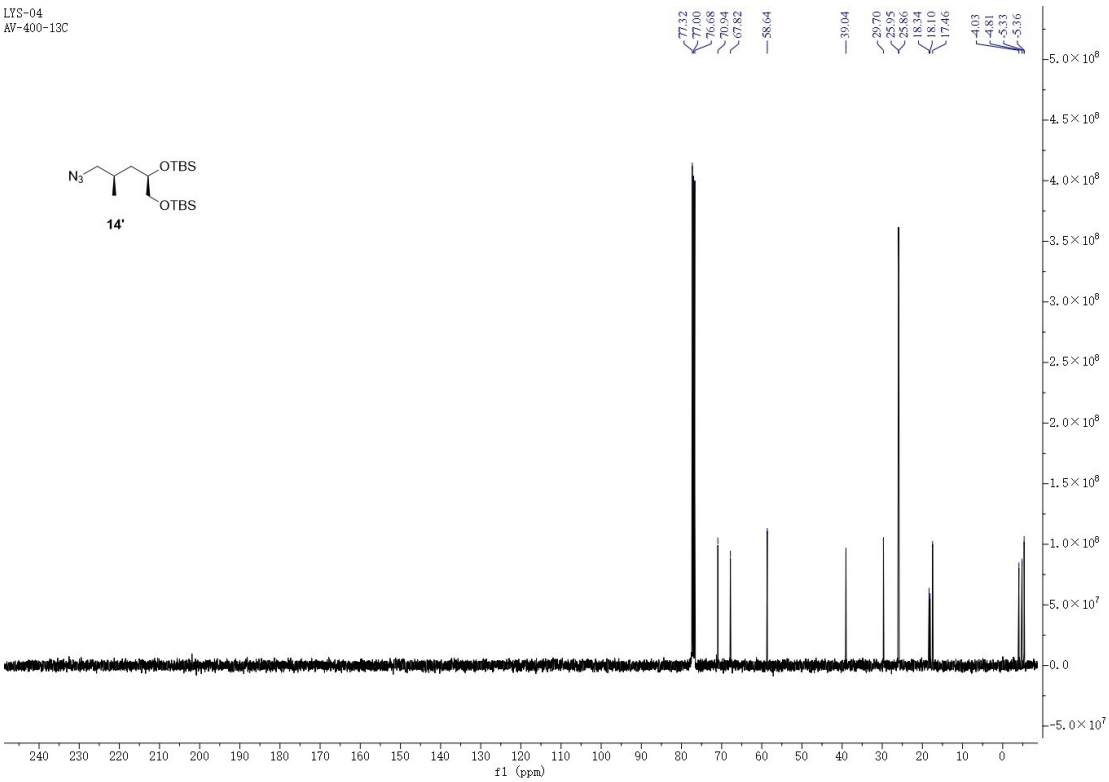


Figure S24. ^{13}C NMR of **14'** ($CDCl_3$, 100 MHz)

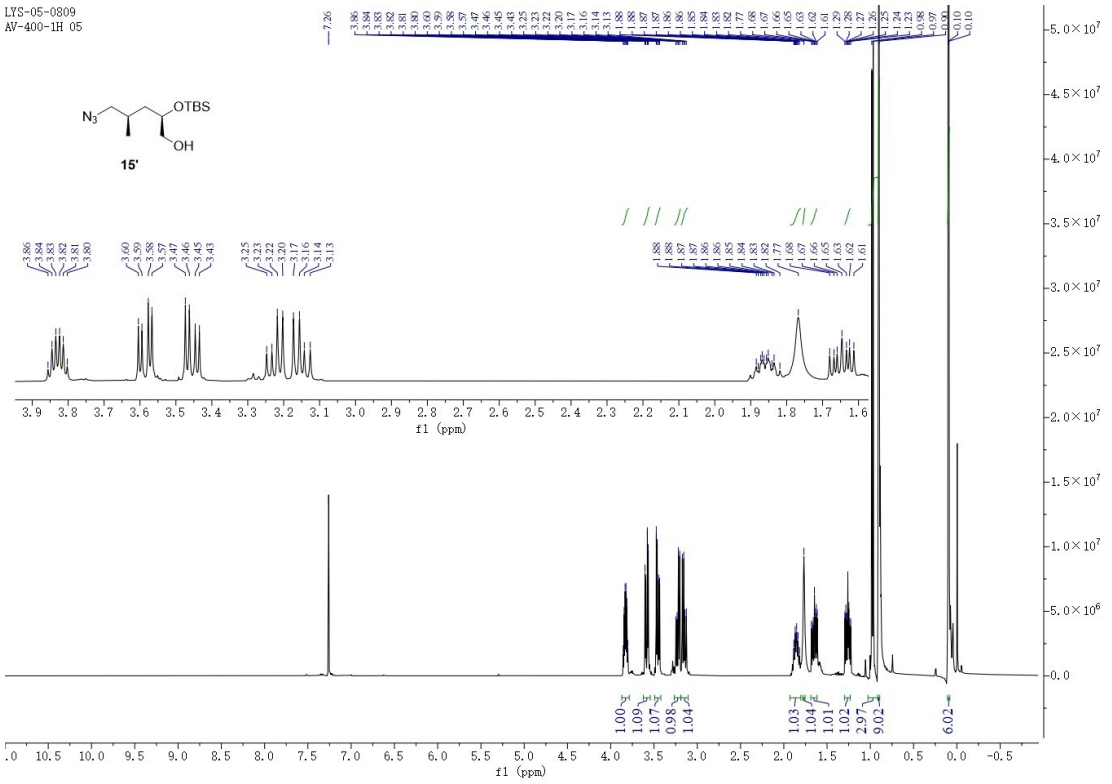


Figure S25. ^{1}H NMR of **15'** ($CDCl_3$, 400 MHz)

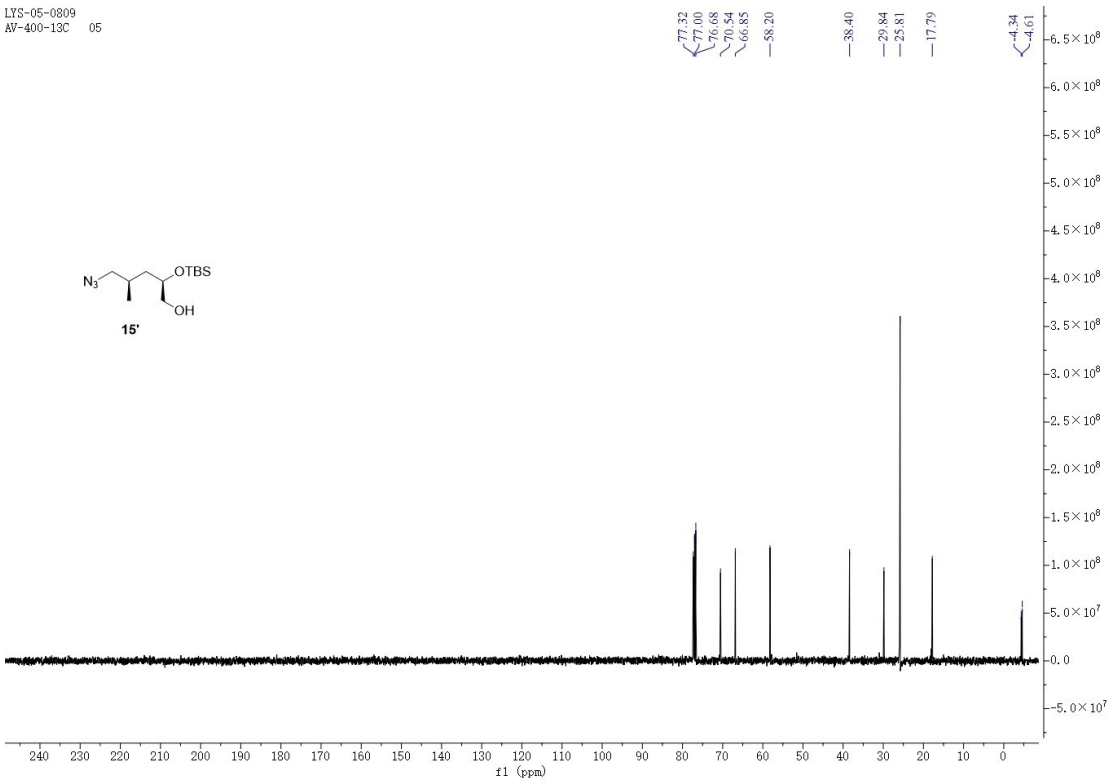


Figure S26. ^{13}C NMR of **15'** ($CDCl_3$, 100 MHz)

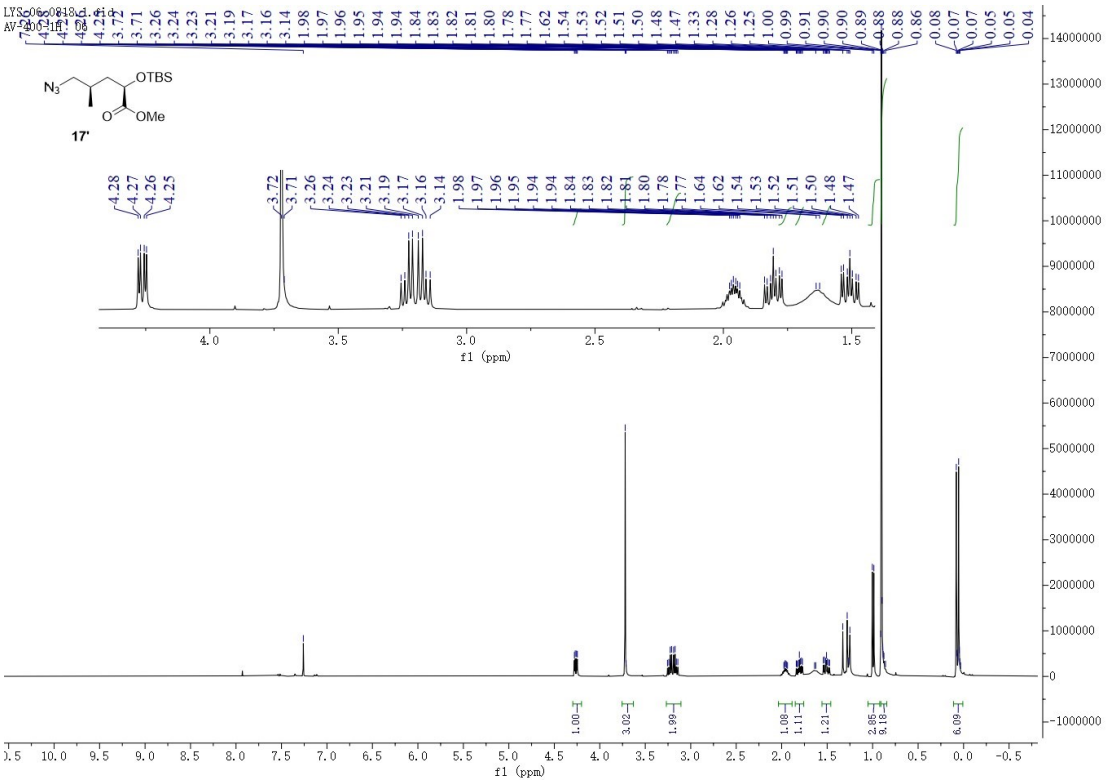


Figure S27. ^{1}H NMR of **17'** ($CDCl_3$, 400 MHz)

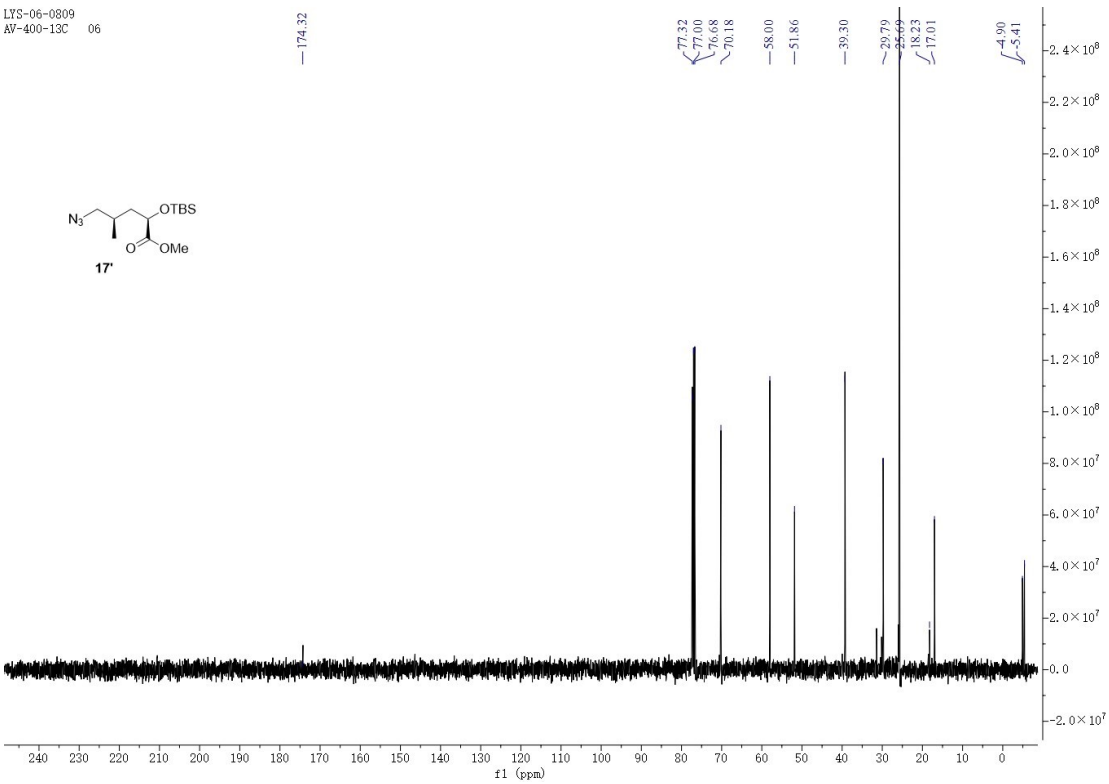


Figure S28. ^{13}C NMR of **17'** ($CDCl_3$, 100 MHz)

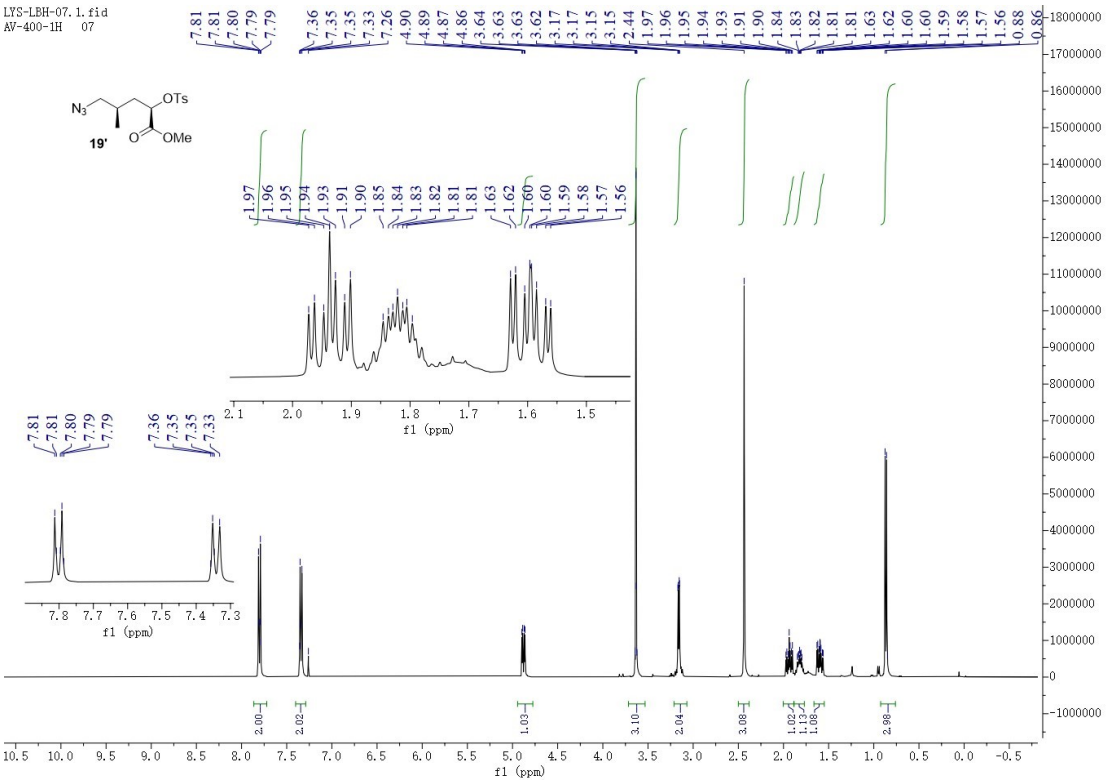


Figure S29. ^{1}H NMR of **19'** ($CDCl_3$, 400 MHz)

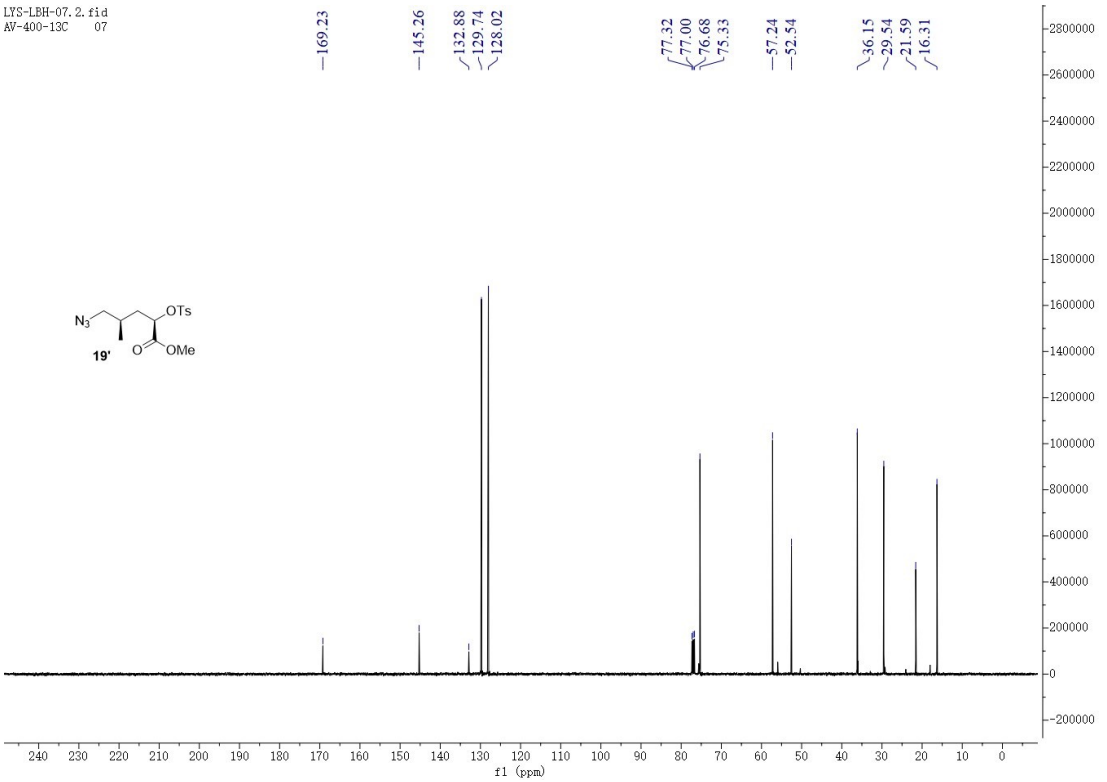


Figure S30. ^{13}C NMR of **19'** ($CDCl_3$, 100 MHz)

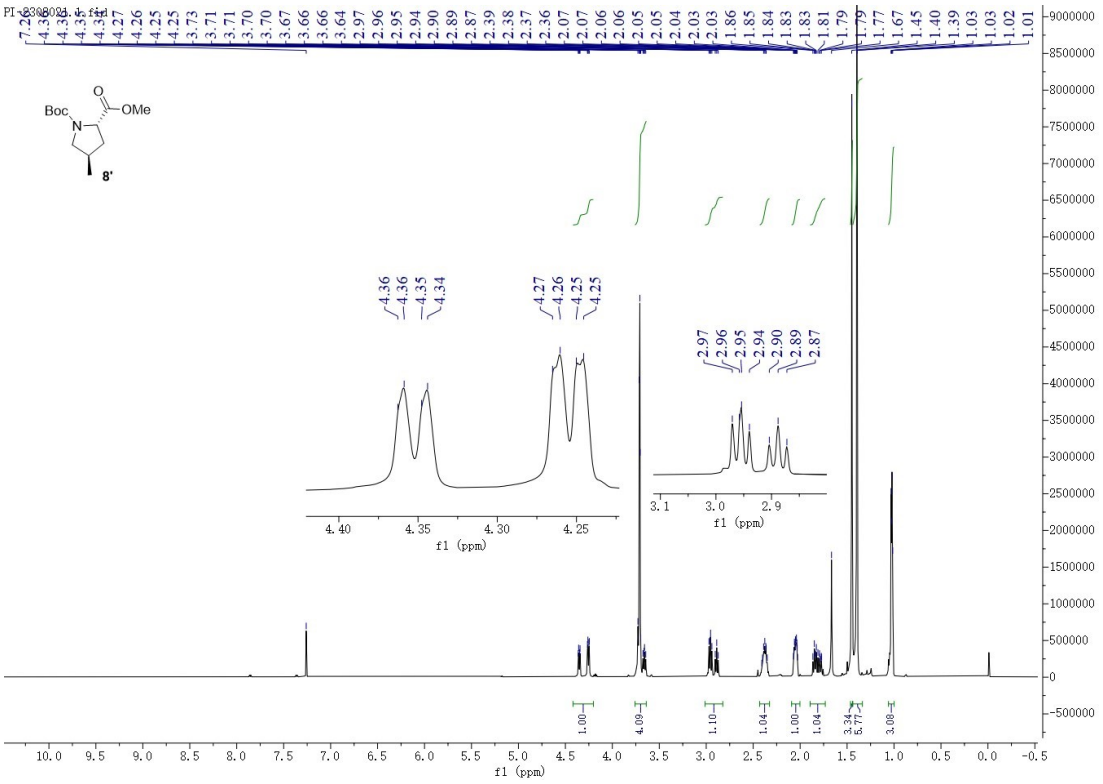


Figure S31. ^{1}H NMR of **8'** ($CDCl_3$, 600 MHz)

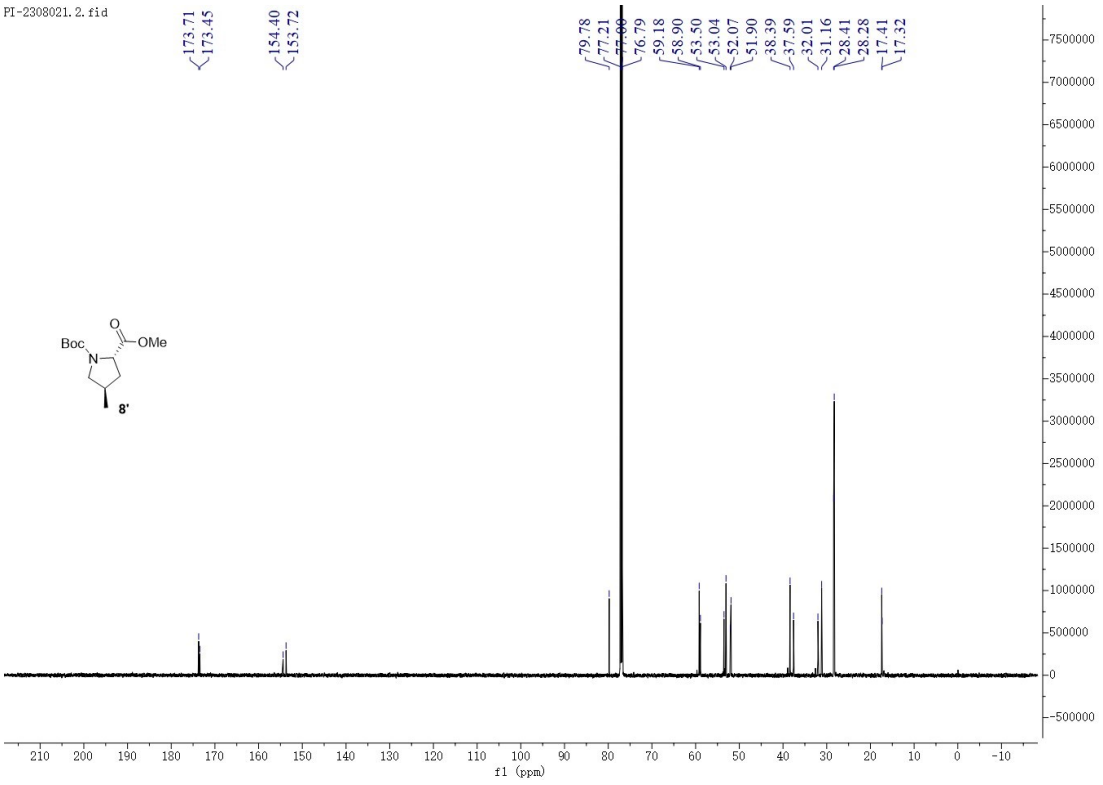


Figure S32. ^{13}C NMR of **8'** ($CDCl_3$, 150 MHz)