

**Facile Synthesis of Highly Functionalized *N*-Methyl Amino Acids Without Side Chain Protection**

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**Supporting Information**

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## General Methods:

Infrared spectra were recorded as thin films on salt plates with  $\nu_{\max}$  in inverse centimeters. Proton ( $^1\text{H}$  NMR) and carbon ( $^{13}\text{C}$  NMR) magnetic resonance spectra were recorded at 500 MHz and 125 MHz, respectively, except where noted. NMR shifts are reported as delta ( $\delta$ ) units in parts per million (ppm) and coupling constants ( $J$ ) are reported in Hertz (Hz). The following abbreviations were utilized to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. High-resolution mass measurements were obtained on an ESITOF mass spectrometer. Melting points are uncorrected. MeOH was used from the bottle without distillation and all reactions were performed without attention to moisture or air exposure. Flash chromatography was performed on silica gel 60, 40-63 mesh using ethyl acetate: hexanes mixtures as solvent unless otherwise indicated. The hydrochloride salts of amino esters are commercially available.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compounds **14**, **16**, **17**, **23**, **25** and **26** are provided.

## General procedure for the formation of selected *N*-benzyl-*N*-methyl amino esters

### (A):

The hydrochloride salt of the free amine methyl or *tert*-butyl ester was dissolved in a minimum amount of methanol and neutralized with 10 mequiv (mmols exchange per mL resin) of Amberlite IRA-410 (OH form) using the batch technique. After gentle stirring for 5 minutes the liquid phase was separated and concentrated to yield the neutral amine. The neutral amine was dissolved in MeOH to make a 0.1 M solution. To this solution, 1.05 equiv of benzaldehyde was added in one portion. After 1 h of stirring at room temperature 1.05 equiv of  $\text{NaBH}_3\text{CN}$  was added. After stirring for 18 h, 1.0 equiv of solid powder paraformaldehyde<sup>a</sup> was added and allowed to dissolve<sup>b</sup>. Following full dissolution an additional 1.05 equiv of  $\text{NaBH}_3\text{CN}$  was added and the reaction was allowed to stir at room temperature for 18 h. For work-up conditions please see specific amino esters.

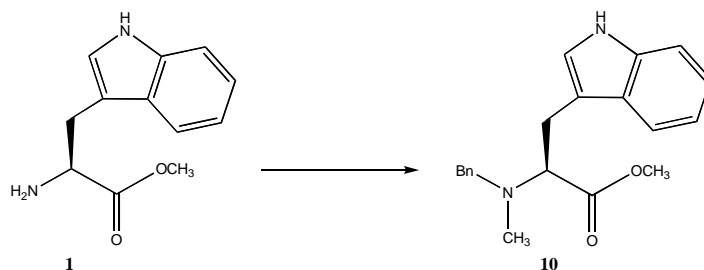
<sup>a</sup> It was essential to use either the powder form of solid paraformaldehyde or finely ground granular paraformaldehyde.

<sup>b</sup> Dissolution of paraformaldehyde is amino ester dependent. For approximate times of dissolution, please refer to specific amino esters.

### General procedure for the formation of *N*-methyl amino esters (B):

The *N*-benzyl-*N*-methyl amino ester was dissolved in methanol to create a 0.1M solution. After degassing, 0.5 weight equiv of Pd(OH)<sub>2</sub> (20% Pd) was added and the solution was placed on a Parr hydrogenator and treated with 55 psi of H<sub>2</sub> for 18 h. Filtration through celite and concentration *in vacuo* afforded the *N*-methyl amino ester.

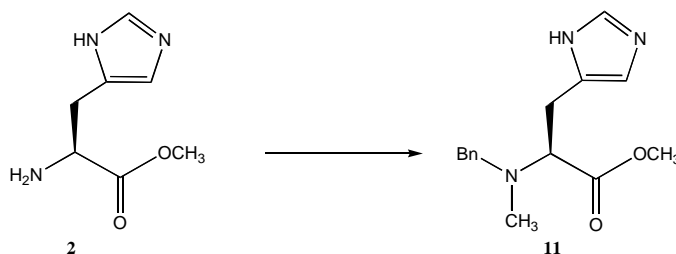
### *N*-benzyl-*N*-methyl-*L*-tryptophan methyl ester (**10**)



H-Trp-OMe·2HCl (500 mg, 1.96 mmol), MeOH (19.6 mL), PhCHO (209  $\mu$ L, 2.06 mmol), NaBH<sub>3</sub>CN (129 mg, 2.06 mmol), (CH<sub>2</sub>O)<sub>n</sub> (184 mg, 1.96 mmol (for MW = 90.1)), NaBH<sub>3</sub>CN (129 mg, 2.06 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 3 h.

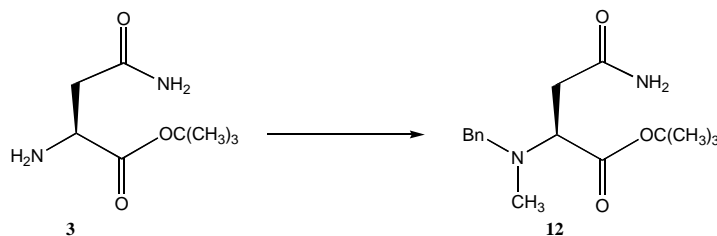
Workup: The reaction mixture was concentrated *in vacuo*. Ethyl acetate was added and the resulting slurry was filtered through celite and concentrated *in vacuo*. Flash column chromatography, eluting with ethyl acetate: hexanes (1:3) on neutralized silica gel (NEt<sub>3</sub>) afforded **10** (563 mg, 89%) as a clear oil. IR (thin film) 3419.2, 3059.9, 2923.6, 1741.8, 1601.1, 1492.9, 1452.1 cm<sup>-1</sup>; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.02 (s, 1H), 7.46 (d, 1H, *J* = 8.0Hz), 7.28-7.20 (m, 6H), 7.14 (dd, 1H, *J* = 6.2Hz, *J* = 13.4Hz), 7.06 (t, 1H, *J* = 7.4Hz), 6.92 (d, 1H, *J* = 2.0Hz), 3.84 (d, 1H, *J* = 13.5 Hz), 3.73 (dd, 1H, *J* = 5.8Hz, *J* = 9.0Hz), 3.62 (d, 1H, *J* = 12.5 Hz), 3.61 (s, 3H), 3.33 (dd, 1H, *J* = 9.1 Hz, *J* = 14.4 Hz), 3.09 (dd, 1H, 5.8 Hz, *J* = 14.4 Hz), 2.36 (s, 3H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  172.8, 139.4, 136.2, 128.9, 128.4, 127.6, 127.1, 122.8, 121.9, 119.3, 118.8, 112.200, 111.2, 66.4, 58.9, 51.1, 38.3, 25.8; [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -21.4 (*c* = 0.025 in MeOH); HRMS calc'd for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M+H], 323.17541, found 323.17436.

### ***N*-benzyl-*N*-methyl-*L*-histidine methyl ester (**11**)**



H-His-OMe·2HCl (500 mg, 2.06 mmol), MeOH (20.6 mL), PhCHO (220  $\mu$ L, 2.17 mmol), NaBH<sub>3</sub>CN (143 mg, 2.17 mmol), (CH<sub>2</sub>O)<sub>n</sub> (194 mg, 2.06 mmol (for MW = 90.1)), NaBH<sub>3</sub>CN (143 mg, 2.17 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 5 h. Workup: The reaction mixture was concentrated *in vacuo*, taken up in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed twice with 5 mL of de-ionized water. Drying with anhydrous MgSO<sub>4</sub> and concentration *in vacuo* yielded **11** (554 mg, 99%) as clear oil. IR (thin film) 3059.9, 2923.6, 1601.1, 1492.9, 1452.1 cm<sup>-1</sup>; <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.54 (d, 1H, *J* = 0.7 Hz), 7.33-7.24 (m, 5H), 6.81 (s, 1H), 3.79 (d, 1H, *J* = 11.0 Hz), 3.76 (s, 3H), 3.64 (d, 1H, *J* = 13.3 Hz), 3.62 (dd, 1H, *J* = 6.9 Hz, *J* = 7.9 Hz), 3.11 (dd, 1H, *J* = 6.8 Hz, *J* = 15.3 Hz), 2.99 (dd, 1H, *J* = 7.8 Hz, *J* = 15.5 Hz), 2.33 (s, 3H); <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  172.5, 138.8, 134.6, 129.1, 128.6, 127.5, 65.9, 59.3, 51.7, 48.3, 37.9, 25.8; [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -50.8 (*c* = 0.012 in MeOH); HRMS calc'd for C<sub>15</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub> [M+H], 274.15500, found 274.15396.

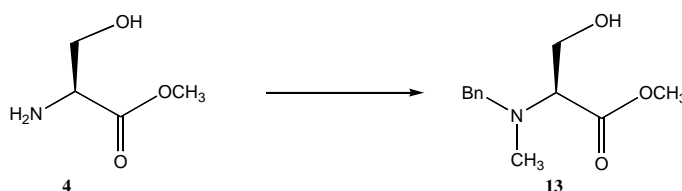
### ***N*-benzyl-*N*-methyl-*L*-asparagine *tert*-butyl ester (**12**)**



H-Asn-OBu<sup>t</sup>·2HCl (250mg, 1.11 mmol), MeOH (11.1 mL), PhCHO (119  $\mu$ L, 1.17 mmol), NaBH<sub>3</sub>CN (77 mg, 1.17 mmol), (CH<sub>2</sub>O)<sub>n</sub> (106 mg, 1.11 mmol (for MW = 90.1)), NaBH<sub>3</sub>CN (77 mg, 1.17 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 3 h. Workup: The reaction mixture was concentrated, taken up in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed twice with 5 mL of de-ionized water. Drying with anhydrous MgSO<sub>4</sub> and

concentration *in vacuo* yielded **12** (270 mg, 83%) as clear oil.  $^1\text{H-NMR}$  (500 MHz, (125 MHz,  $\text{CDCl}_3$ ))  $\delta$  7.31 (m, 5H), 3.82 (d, 1H,  $J = 13.3$  Hz), 3.69 (d, 1H,  $J = 13.0$  Hz), 3.68 (dd, 1H,  $J = 2.7$  Hz,  $J = 6.4$  Hz), 2.61 (dd, 2H,  $J = 7.6$  Hz,  $J = 16.3$  Hz), 2.32 (s, 3H), 1.51 (s, 9H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.2, 170.1, 138.3, 129.1, 128.6, 127.6, 82.2, 62.9, 59.0, 37.4, 35.1, 28.4; IR (thin film)  $\text{cm}^{-1}$ ;  $[\alpha]_{\text{D}}^{23} = -47.9$  ( $c = 0.047$  in MeOH); HRMS calc'd for  $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]$ , 293.18597, found 293.18371.

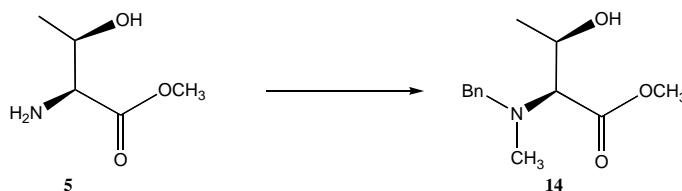
### *N*-benzyl-*N*-methyl-*L*-serine methyl ester (**13**)



H-Ser-OMe·HCl (500 mg, 3.21 mmol), MeOH (32.1 mL), PhCHO (343  $\mu\text{L}$ , 3.37 mmol),  $\text{NaBH}_3\text{CN}$  (212 mg, 3.37 mmol),  $(\text{CH}_2\text{O})_n$  (302 mg, 3.21 mmol (for MW = 90.1)),  $\text{NaBH}_3\text{CN}$  (212 mg, 3.37 mmol). Approximate time for dissolution of  $(\text{CH}_2\text{O})_n$ : 5 h.

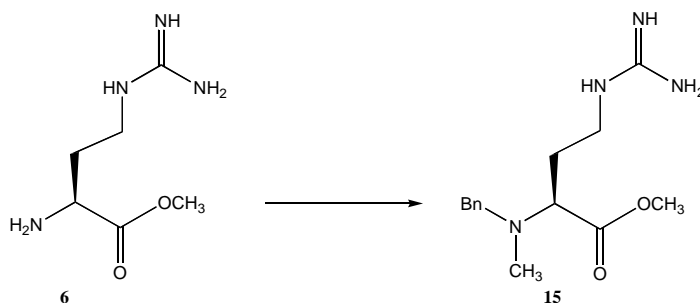
Workup: The reaction mixture was concentrated *in vacuo*. Ethyl acetate was added and the resulting slurry was filtered through celite and concentrated *in vacuo*. Flash column chromatography, eluting with ethyl acetate: hexanes (1:2) on neutralized silica gel ( $\text{NEt}_3$ ) afforded **13** (643 mg, 90%) as a clear oil. IR (thin film) 3441.0, 3025.8, 2923.7, 1730.7, 1601.1, 1493.0, 1452.1  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34–7.25 (m, 5H), 3.85 (d, 1H,  $J = 13.2$  Hz), 3.80 (dd, 1H,  $J = 3.9$  Hz,  $J = 10.0$  Hz), 3.75 (s, 3H), 3.75 (dd, 1H,  $J = 5.1$  Hz,  $J = 14.4$  Hz), 3.73 (d, 1H,  $J = 13.3$  Hz), 3.54 (dd, 1H,  $J = 6.2$  Hz,  $J = 9.3$  Hz), 2.33 (s, 3H);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 138.5, 129.1, 128.6, 127.6, 65.9, 59.3, 59.0, 51.6, 37.6;  $[\alpha]_{\text{D}}^{23} = -37.8$  ( $c = 0.015$  in MeOH); HRMS calc'd for  $\text{C}_{12}\text{H}_{18}\text{NO}_3$   $[\text{M}+\text{H}]$ , 224.12812, found 224.12819.

### *N*-benzyl-*N*-methyl-*L*-threonine methyl ester (**14**)



H-Thr-OMe·HCl (500 mg, 2.94 mmol), MeOH (29.4 mL), PhCHO (315  $\mu$ L, 3.10 mmol), NaBH<sub>3</sub>CN (205 mg, 3.10 mmol), (CH<sub>2</sub>O)<sub>n</sub> (276 mg, 2.94 mmol (for MW = 90.1)), NaBH<sub>3</sub>CN (205 mg, 3.10 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 4 h. Workup: The reaction mixture was concentrated *in vacuo*. Ethyl acetate was added and the resulting slurry was filtered through celite and concentrated *in vacuo*. Flash column chromatography, eluting with ethyl acetate on neutralized silica gel (NEt<sub>3</sub>) afforded **14** (661 mg, 99%) as a clear oil. IR (thin film) 3442.7, 3025.8, 2923.7, 1601.1, 1492.9, 1452.9 cm<sup>-1</sup>; (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.30 (m, 5H), 3.97 (dq, 1H, *J* = 6.0 Hz, *J* = 12.1 Hz), 3.81 (d, 1H, 13.1 Hz), 3.760 (s, 3H), 3.56 (d, 1H, *J* = 13.1 Hz), 3.07 (d, 1H, *J* = 9.8 Hz), 2.27 (s, 3H), 1.16 (d, 3H, *J* = 5.9 Hz); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.4, 138.1, 129.1, 128.6, 127.6, 63.1, 59.6, 51.3, 37.9, 19.3; [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -68.2 (*c* = 0.033 in MeOH) [lit<sup>1</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -111.7 (*c* = 1.0 MeOH)]; HRMS calc'd for C<sub>13</sub>H<sub>20</sub>NO<sub>3</sub> [M+H], 238.14377, found 238.14592.

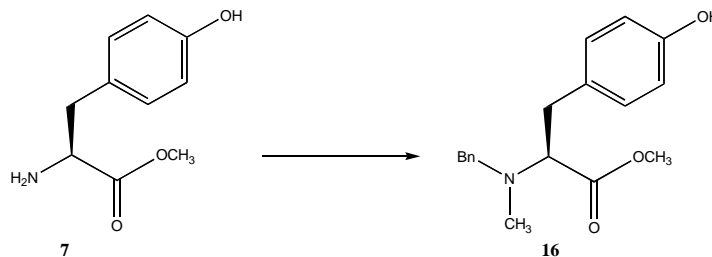
#### ***N*-benzyl-*N*-methyl-*L*-arginine methyl ester (**15**)**



H-Arg-OMe·2HCl (500mg, 1.91 mmol), methanol (19.1 mL), PhCHO (204  $\mu$ L, 2.01mmol), NaBH<sub>3</sub>CN (126 mg, 2.01 mmol), (CH<sub>2</sub>O)<sub>n</sub> (179 mg, 1.91 mmol (for MW=90.1)), NaBH<sub>3</sub>CN (126 mg, 2.01 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 2 h. Workup: The reaction mixture was concentrated, taken up in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed twice with 5 mL of de-ionized water. Drying with anhydrous MgSO<sub>4</sub> was followed by concentration *in vacuo*. Flash column chromatography, eluting with methanol: dichloromethane 1:9 on neutralized silica gel (NEt<sub>3</sub>) afforded **15** (370 mg, 66%) as a pale yellow oil. IR (thin film) 3357.2, 3025.8, 1601.2, 1452.0 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.32-7.22 (m, 5H), 6.87 (brs, 1H), 6.26 (brs, 3H), 3.73 (d, 2H, *J* = 13.2 Hz), 3.72 (s, 3H), 3.61 (d, 2H, *J* = 13.3 Hz), 3.31 (dd, 1H, *J* = 5.4 Hz, *J* = 12.3 Hz),

3.28 (t, 2H,  $J = 5.4$  Hz), 2.24 (s, 3H), 1.78-1.56 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  ;  $[\alpha]_{\text{D}}^{23} = -39.6$  ( $c = 0.015$  in MeOH); HRMS cal'd for  $\text{C}_{15}\text{H}_{25}\text{N}_4\text{O}_2$   $[\text{M}+\text{H}]$ , 293.19720, found 293.19575.

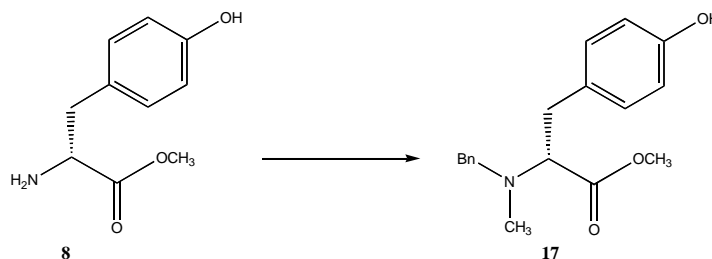
### *N*-benzyl-*N*-methyl-*L*-tyrosine methyl ester (**16**)



H-Tyr-OMe·HCl (500 mg, 2.16 mmol), MeOH (21.6 mL), PhCHO (230  $\mu\text{L}$ , 2.27 mmol),  $\text{NaBH}_3\text{CN}$  (142 mg, 2.27 mmol),  $(\text{CH}_2\text{O})_n$  (202 mg, 2.16 mmol (for MW = 90.1)),  $\text{NaBH}_3\text{CN}$  (142 mg, 2.27 mmol). Approximate time for dissolution of  $(\text{CH}_2\text{O})_n$ : 3 h.

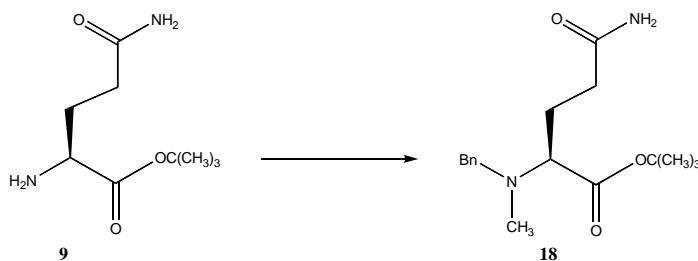
Workup: The reaction mixture was concentrated *in vacuo*. Ethyl acetate was added and the resulting slurry was filtered through celite and concentrated *in vacuo*. Flash column chromatography, eluting with ethyl acetate on neutralized silica gel ( $\text{NEt}_3$ ) afforded **16** (609 mg, 94%) as a clear oil. IR (thin film) 3025.9, 2923.7, 1601.1, 1492.9, 1452.1  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27-7.17 (m, 5H), 6.93 (d, 2H,  $J = 8.4$  Hz), 6.67 (d, 2H,  $J = 8.5$  Hz), 3.73 (d, 1H,  $J = 13.5$  Hz), 3.58 (s, 3H), 3.54 (d, 1H,  $J = 13.5$  Hz), 3.51 (dd, 1H,  $J = 6.6$  Hz,  $J = 8.7$  Hz), 2.97 (dd, 1H,  $J = 8.7$  Hz,  $J = 13.7$  Hz), 2.86 (dd, 1H,  $J = 6.6$  Hz,  $J = 13.7$  Hz), 2.30 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.0, 154.7, 138.8, 130.3, 129.6, 128.9, 128.6, 128.3, 127.7, 127.2, 65.2, 58.9, 51.3, 38.1, 35.0;  $[\alpha]_{\text{D}}^{23} = -39.2$  ( $c = 0.011$  in MeOH); HRMS calc'd for  $\text{C}_{18}\text{H}_{22}\text{NO}_3$   $[\text{M}+\text{H}]$ , 300.15942, found 300.15782.

### *N*-benzyl-*N*-methyl-*D*-tyrosine methyl ester (**17**)



H-D-Tyr-OMe·HCl (500 mg, 2.16 mmol), MeOH (21.6 mL), PhCHO (230  $\mu$ L, 2.27 mmol), NaBH<sub>3</sub>CN (142 mg, 2.27 mmol), (CH<sub>2</sub>O)<sub>n</sub> (202 mg, 2.16 mmol (for MW = 90.1)), NaBH<sub>3</sub>CN (142 mg, 2.27 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 3 h. Workup: The reaction mixture was concentrated *in vacuo*. Ethyl acetate was added and the resulting slurry was filtered through celite and concentrated *in vacuo*. Flash column chromatography, eluting with ethyl acetate on neutralized silica gel (NEt<sub>3</sub>) afforded **17** (611 mg, 95%) as a clear oil. IR (thin film) 3025.8, 2923.7, 1601.1, 1492.9, 1452.0 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.27 (m, 5H), 7.01 (d, 2H, *J* = 7.9 Hz), 6.73 (d, 2H, *J* = 7.6 Hz), 3.78 (d, 1H, *J* = 13.5), 3.66 (s, 3H), 3.59 (d, 1H, *J* = 13.5 Hz), 3.55 (t, 1H, *J* = 7.5 Hz), 3.03 (dd, 1H, *J* = 8.6 Hz, *J* = 13.7 Hz), 2.92 (dd, 1H, *J* = 6.7 Hz, *J* = 13.7 Hz), 2.31 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  173.0, 154.6, 139.0, 130.5, 130.1, 129.0, 128.8, 128.4, 127.9, 127.2, 66.7, 59.0, 51.3, 38.2, 35.1; [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 37.4 (*c* = 0.010 in MeOH); HRMS calc'd for C<sub>18</sub>H<sub>22</sub>NO<sub>3</sub> [M+H], 300.15942, found 300.15953.

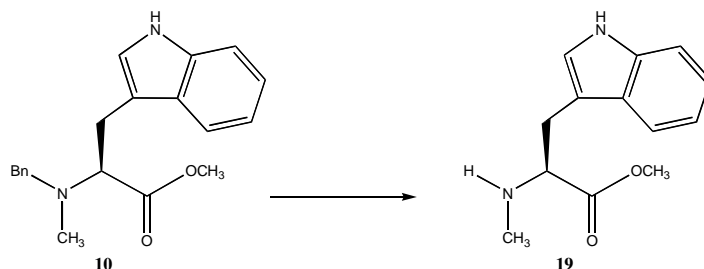
#### ***N*-benzyl-*N*-methyl-*L*-glutamine *tert*-butyl ester (**18**)**



H-Gln-OBu<sup>t</sup>·2HCl (250mg, 1.05 mmol), MeOH (10.4 mL), PhCHO (112  $\mu$ L, 1.10 mmol), NaBH<sub>3</sub>CN (73 mg, 1.10 mmol), (CH<sub>2</sub>O)<sub>n</sub> (94 mg, 1.05 mmol (for MW = 90.1)), NaBH<sub>3</sub>CN (94 mg, 1.10 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 2 h. Workup: The reaction mixture was concentrated *in vacuo*, taken up in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed twice with 5 mL of de-ionized water. Drying with anhydrous MgSO<sub>4</sub> and concentration *in vacuo* yielded **18** (275 mg, 99%) as clear oil. IR (thin film) 3059.9, 2923.6, 1601.1, 1492.9, 1452.1, 756.7 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.30 (m, 5H), 3.81 (d, 1H, *J* = 13.4 Hz), 3.67 (d, 1H, *J* = 13.4 Hz), 2.31 (m, 2H), 2.29 (s, 3H), 1.98 (dd, 1H, *J* = 7.7 Hz, *J* = 15.3 Hz), 1.54 (s, 9H), 1.52 (m, 2H); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD)  $\delta$  178.6, 173.1, 140.7, 130.1, 129.4, 128.2, 66.6, 60.2, 37.8, 33.1, 28.8, 26.5; [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -43.7

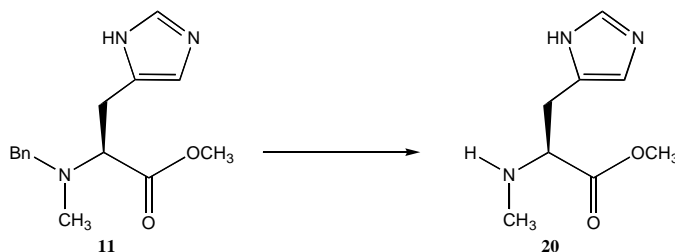
( $c = 0.010$  in MeOH); HRMS calc'd for  $C_{17}H_{22}N_2O_3$  [M+H], 307.20162, found 307.19969.

### *N*-methyl-*L*-tryptophan methyl ester (**19**)



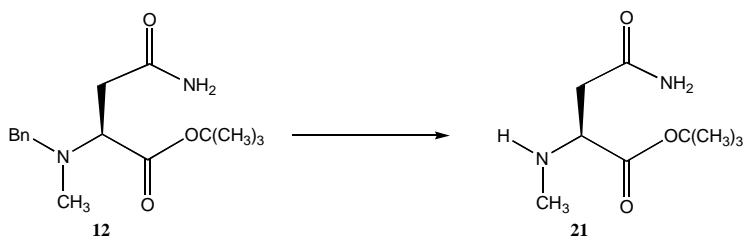
Bn,Me-Trp-OMe (633mg, 1.96 mmol), Pd(OH)<sub>2</sub> (317 mg), MeOH (19.6 mL) afforded **19** (449 mg, 99%). IR (thin film) 1732.5, 1447.0, 1353.8, 1032.6 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.79 (s, 1H), 7.29 (d, 1H,  $J = 8.1$  Hz), 7.19 (t, 1H,  $J = 7.5$  Hz), 7.09 (t, 1H,  $J = 7.5$  Hz), 6.96 (s, 1H), 3.64 (s, 3H), 3.57 (t, 1H,  $J = 6.5$  Hz), 3.20 (dd, 1H,  $J = 5.9$  Hz,  $J = 14.5$  Hz), 3.12 (dd, 1H,  $J = 7.1$  Hz,  $J = 14.4$  Hz), 2.35 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 174.9, 136.4, 127.4, 123.3, 122.0, 119.4, 118.6, 111.4, 110.5, 63.7, 51.9, 34.7, 29.0;  $[\alpha]_D^{23} = 34.3$  ( $c = 0.036$  in MeOH) [lit<sup>2</sup> (as HCl salt)  $[\alpha]_D = 47.8$  ( $c = 0.48$  in MeOH)]; HRMS calc'd for  $C_{13}H_{17}N_2O_2$  [M+H], 233.12845, found 233.12665.

### *N*-methyl-*L*-histidine methyl ester (**20**)



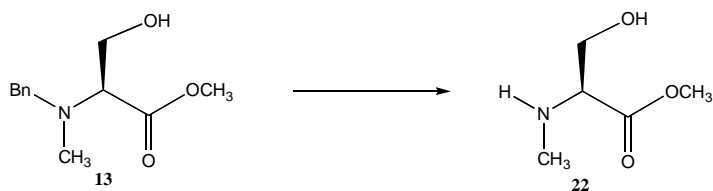
Bn,Me-His-OMe (558 mg, 2.04 mmol), Pd(OH)<sub>2</sub> (279 mg), MeOH (20.0 mL) afforded **20** (371mg, 99%). IR (thin film) 2952.5, 1732.0, 1435.5, 1176.1, 824.5 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.49 (s, 1H), 6.77 (s, 1H), 3.68 (s, 3H), 3.45 (dd, 1H,  $J = 5.0$  Hz,  $J = 7.6$  Hz), 2.99 (dd, 1H,  $J = 5.1$  Hz,  $J = 14.9$  Hz), 2.86 (dd, 1H,  $J = 7.7$  Hz,  $J = 14.9$  Hz), 2.36 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 174.7, 135.1, 132.5, 63.2, 52.1, 34.7, 29.9;  $[\alpha]_D^{23} = 10.0$  ( $c = 0.007$  in MeOH); HRMS calc'd for  $C_8H_{14}N_3O_2$ , [M+H], 184.10805, found 184.10921.

***N*-methyl-*L*-asparagine *tert*-butyl ester (**21**)**



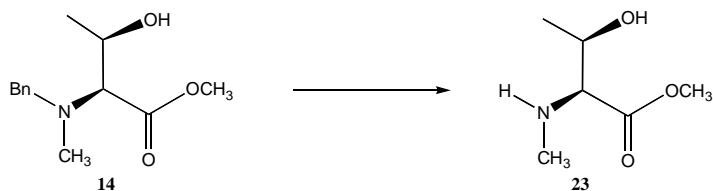
Bn,Me-Asn-OBu<sup>t</sup> (172 mg, 0.59 mmol), Pd(OH)<sub>2</sub> (86 mg), MeOH (5.9 mL) afforded **21** (119 mg, 99%). IR (thin film) 3206.1, 2979.0, 1726.9, 1673.8, 1156.6 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 3.42 (t, 1H, *J* = 6.5 Hz), 2.56 (dd, 1H, *J* = 6.5 Hz, *J* = 15.5 Hz), 2.50 (dd, 1H, *J* = 7.0 Hz, *J* = 15.5 Hz), 2.36 (s, 3H), 1.48 (s, 9H); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 175.5, 173.8, 82.9, 42.1, 38.8, 34.4, 28.6; [α]<sub>D</sub><sup>23</sup> = -10.3 (*c* = 0.033 in MeOH); HRMS calc'd for C<sub>9</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>, [M+H], 203.13902, found 203.13909.

***N*-methyl-*L*-serine methyl ester (**22**)**



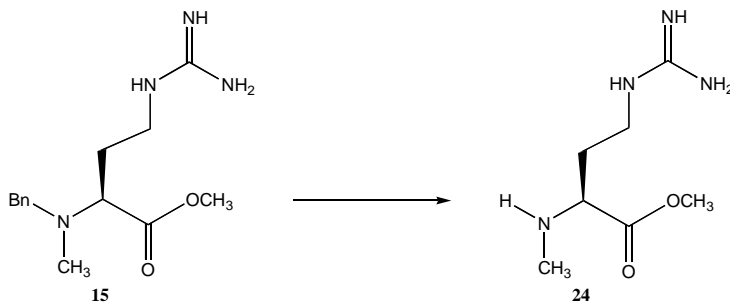
Bn,Me-Ser-OMe (307 mg, 1.37 mmol), Pd(OH)<sub>2</sub> (154 mg), MeOH (13.7 mL) afforded **22** (144 mg, 79%). IR (thin film) 3325.4, 2954.7, 1733.3, 1214.1, 1064.8 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 3.79 (dd, 1H, *J* = 4.0 Hz, *J* = 5.0 Hz), 3.78 (m, 1H), 3.78 (s, 3H), 3.33 (t, 1H, *J* = 5.0 Hz), 2.41 (s, 3H); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 174.4, 65.8, 63.3, 52.5, 34.5; [α]<sub>D</sub><sup>23</sup> = -3.6° (*c* = 0.016 in MeOH) [lit<sup>3</sup> (as TFA salt) [α]<sub>D</sub><sup>28</sup> = -7.4 (in acetone)]; HRMS calc'd for C<sub>5</sub>H<sub>12</sub>NO<sub>3</sub>, [M+H], 134.08117, found 134.08216.

### *N*-methyl-*L*-threonine methyl ester (**23**)



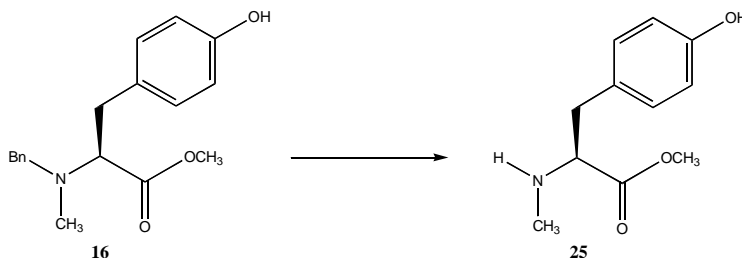
Bn,Me-Thr-OMe (522 mg, 2.20 mmol), Pd(OH)<sub>2</sub> (261 mg), MeOH (22.0 mL) afforded **23** (215 mg, 67%). IR (thin film) 3444.7, 2957.7, 1731.3, 1673.8, 1055.8 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 3.88-3.83 (m, 1H), 3.75 (s, 3H), 3.19 (d, 1H, 5.9 Hz), 2.34 (s, 3H), 1.19 (d, 3H, *J* = 6.4 Hz); <sup>13</sup>C-NMR (125 MHz, CD<sub>3</sub>OD) δ 175.0, 70.7, 69.0, 52.4, 35.2, 20.1; [α]<sub>D</sub><sup>23</sup> = -10.9 (*c* = 0.028 in MeOH) [lit<sup>1</sup> [α]<sub>D</sub><sup>25</sup> = -18.7 (*c* = 1.0 in MeOH)]; HRMS calc'd for C<sub>6</sub>H<sub>14</sub>NO<sub>3</sub> [M+H], 148.09682, found 148.09806.

### *N*-methyl-*L*-arginine methyl ester (**24**)



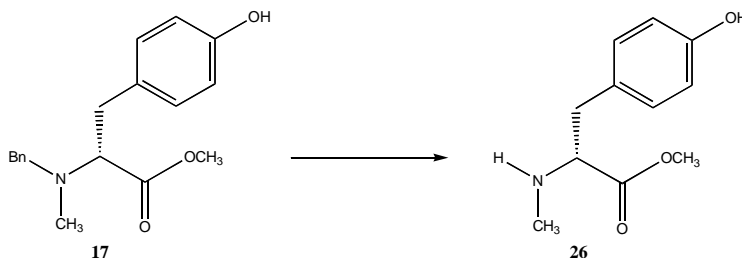
Bn,Me-Arg-OMe (188mg, 0.643 mmol), Pd(OH)<sub>2</sub> (94 mg), MeOH (6.4 mL) afforded **24** as a pale yellow oil (111 mg, 85%). IR (thin film) 2959.3, 1746.6, 1469.9, 1235.0, 1055.8 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 3.84 (s, 3H), 3.24 (t, 2H, *J* = 7.0 Hz), 3.17 (m, 1H), 2.63 (s, 3H); <sup>13</sup>C-NMR (125 MHz, CD<sub>3</sub>OD) δ 172.0, 158.8, 62.2, 53.6, 41.9, 33.2, 28.4, 25.8; [α]<sub>D</sub><sup>23</sup> = 7.6 (*c* = 0.017 in MeOH); HRMS calc'd for C<sub>8</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub> [M+H], 203.15025, found 203.15029.

### *N*-methyl-*L*-tyrosine methyl ester (**25**)



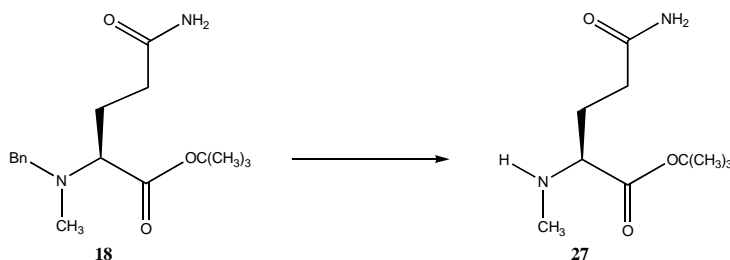
Bn,Me-Tyr-OMe (518mg, 1.73 mmol), Pd(OH)<sub>2</sub> (260 mg), MeOH (17.3 mL). Re-crystallization from CH<sub>2</sub>Cl<sub>2</sub> afforded **25** as a white crystalline solid (350 mg, 97%). mp 108-109 °C [lit<sup>4</sup> 109-111 °C]; IR (thin film) 3309.0, 2953.3, 1734.8, 1516.7, 1248.9 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ= 6.97 (d, 2H, *J* = 8.4 Hz), 6.65 (d, 2H, *J* = 8.5 Hz), 4.58 (brs, 1H), 3.69 (s, 3H), 3.45 (t, 1H, *J* = 6.6 Hz), 2.93 (dd, 1H, *J* = 6.4 Hz, *J* = 13.8 Hz), 2.89 (dd, 1H, *J* = 6.7 Hz, *J* = 13.8 Hz), 2.38 (s, 3H); <sup>13</sup>C-NMR (500 MHz, CDCl<sub>3</sub>) δ 174.8, 155.6, 130.4, 127.9, 115.9, 64.7, 52.0, 38.5, 34.7; [α]<sub>D</sub><sup>23</sup> = 23.9° (*c* = 0.060 in MeOH) [lit<sup>4</sup> [α]<sub>D</sub><sup>28</sup> = 39.3 (*c* = 1.9 in EtOH)]; HRMS calc'd for C<sub>11</sub>H<sub>16</sub>NO<sub>3</sub> [M+H], 210.11247, found 210.11096.

### *N*-methyl-*D*-tyrosine methyl ester (**26**)



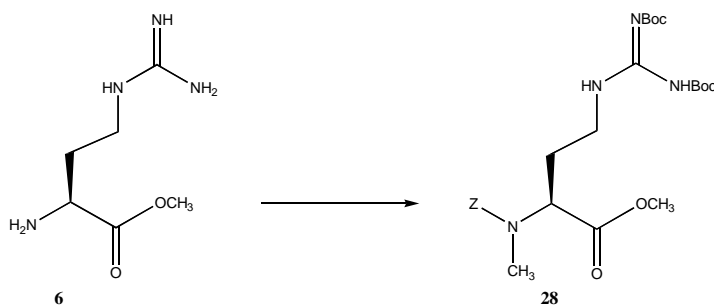
Bn,Me-*D*-Tyr-OMe (456 mg, 1.52 mmol), Pd(OH)<sub>2</sub> (228 mg), MeOH (15.2 mL). Re-crystallization from CH<sub>2</sub>Cl<sub>2</sub> afforded **26** as a white crystalline solid (251 mg, 79%). Mp 107-109 °C; IR (thin film) 3307.6, 2953.9 1733.1, 1516.5, 1248.2 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 6.96 (d, 2H, *J* = 8.5 Hz), 6.70 (d, 2H *J* = 8.0 Hz), 5.42 (brs, 1H), 3.66 (s, 3H), 3.44 (t, 1H, *J* = 6.9 Hz), 2.90 (dd, 1H, *J* = 6.3 Hz, *J* = 14.4 Hz), 2.87 (dd, 1H, *J* = 6.8 Hz, *J* = 14.8 Hz), 2.35 (s, 3H); <sup>13</sup>C-NMR (500 MHz, CDCl<sub>3</sub>) δ 174.9, 155.7, 130.4, 127.9, 115.9, 64.8, 52.1, 38.6, 34.7; [α]<sub>D</sub><sup>23</sup> = -21.4 (*c* = 0.034 in MeOH); HRMS calc'd for C<sub>11</sub>H<sub>16</sub>NO<sub>3</sub> [M+H], 210.11247, found 210.11087.

### *N*-methyl-*L*-glutamine *tert*-butyl ester (**27**)



Bn,Me-Gln-OBu<sup>t</sup> (254 mg, 0.96 mmol), Pd(OH)<sub>2</sub> (127 mg), MeOH (9.6 mL) afforded **27** (177 mg, 82%). IR (thin film) 2978.8, 1682.6, 1369.4, 1152.2, 840.7 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 3.21 (t, 1H, *J* = 6.5 Hz), 2.34 (s, 3H), 2.27 (m, 2H), 1.94 (m, 2H), 1.49 (s, 9H); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 178.5, 174.8, 83.1, 64.4, 34.5, 32.7, 29.6, 29.4; [α]<sub>D</sub><sup>23</sup> = -11.0 (*c* = 0.006 in MeOH); HRMS calc'd for C<sub>10</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub> [M+H], 217.15467, found 217.15522.

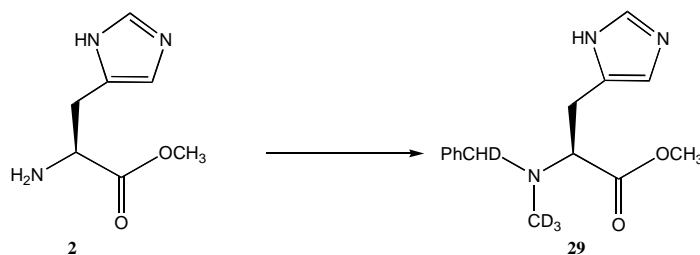
### *N*-carbonylbenzyloxy-*N*-methyl-*L*-arginine (bis *tert*-butoxy carbonyl) methyl ester (**28**)



H-Arg-OMe·2HCl (500 mg, 1.91 mmol), MeOH (19.1 mL), PhCHO (.204 mL, 2.01 mmol), NaBH<sub>3</sub>CN (126 mg, 2.01 mmol), (CH<sub>2</sub>O)<sub>n</sub> (179 mg, 1.91 mmol (for MW = 90.1)), NaBH<sub>3</sub>CN (126 mg, 2.01 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 2h. Workup: The reaction mixture was concentrated, taken up in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed twice with 3 mL of de-ionized water. The organic layer was dried with anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to afford Bn,Me-Arg-OMe (370 mg, 66%). Bn,Me-Arg-OMe (1.43 mmol, 419 mg) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. Diisopropylethylamine (749 μL, 4.3 mmol) and Boc<sub>2</sub>O (938 mg, 4.3 mmol) were added in that order and the reaction was allowed to proceed at rt for 48 h in an inert atmosphere. The reaction mixture was washed twice with water, dried over MgSO<sub>4</sub> and concentrated *in vacuo*.

Flash column chromatography, eluting with EtOAc: Hex (3:2) afforded Bn,Me-Arg(*bis*-Boc)-OMe (651 mg, 92%). Bn,Me-Arg(*bis*-Boc)-OMe (1.32 mmol, 651 mg) was dissolved in EtOH (13 mL) and degassed. Pd/C (10% Pd) was added to the mixture carefully and the vessel was treated with 20 psi H<sub>2</sub> for 4.5 h. The solution was filtered through celite and concentrated *in vacuo* to give Me-Arg(*bis*-Boc)-OMe (382 mg, 72%). Me-Arg(*bis*-Boc)-OMe (0.95 mmol, 382 mg) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9.5 mL), diisopropylethylamine (182 μL, 1.04 mmol) and *Z*-succinate (1.04 mmol, 260 mg) were added in that order, and the reaction was allowed to proceed for 18 h at rt under an inert atmosphere. The reaction mixture was washed twice with water, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Flash column chromatography, eluting with EtOAc: Hex (1:4) afforded Me,*Z*-Arg(*bis*-Boc)-OMe **28** (51 mg, 10%). IR (thin film) 3385.0, 2977.6, 1712.8, 1609.9, 1148.8 cm<sup>-1</sup>; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>, rotamers) δ 7.38-7.28 (m, 5H), 5.25 (d, 1H, *J* = 20.5 Hz), 5.14 (d, 1H, *J* = 14.9 Hz), 4.80 and 4.69 (2 dd, 1H, *J* = 4.8 Hz, *J* = 10.8 Hz), 3.74-3.70 (m, 3H), 3.63-3.59 (m, 2H), 2.91 (s, 3H), 1.99-1.37 (m, 22H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>, rotamers), δ 172.2, 172.1, 163.7, 160.6, 157.1, 156.5, 155.0, 136.7, 136.6, 128.8, 128.6, 128.1, 127.8, 83.9, 78.7, 67.5, 58.8, 58.7, 52.3, 52.1, 44.3, 43.9, 28.4, 28.1, 26.2, 25.4, 24.9; [α]<sup>23</sup><sub>D</sub> = -14.2 (*c* = 0.010 in CHCl<sub>3</sub>) [lit<sup>5</sup> [α]<sup>19</sup><sub>D</sub> = -13.0 (*c* = 0.5 in CHCl<sub>3</sub>)]; HRMS calc'd for C<sub>22</sub>H<sub>41</sub>N<sub>4</sub>O<sub>8</sub> [M+H], 489.29189, found 489.29460.

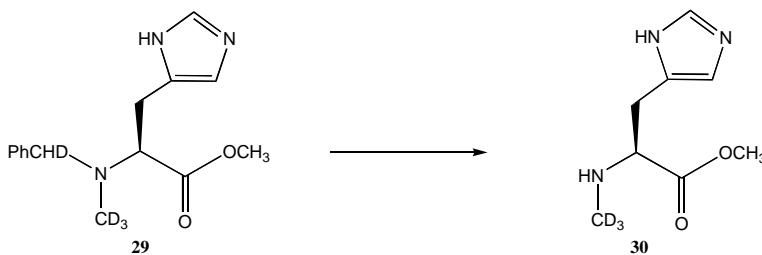
***N*-(1-deutero benzyl)-*N*-trideuteromethyl-*L*-histidine methyl ester (**29**)**



H-His-OMe·2HCl (500 mg, 2.06 mmol), MeOH (20.6 mL), PhCHO (220 μL, 2.17 mmol), NaBD<sub>3</sub>CN (143 mg, 2.17 mmol), (CD<sub>2</sub>O)<sub>n</sub> (198 mg, 2.06 mmol (for MW=96.1)), NaBH<sub>3</sub>CN (143 mg, 2.17 mmol). Approximate time for dissolution of (CH<sub>2</sub>O)<sub>n</sub>: 5h. Workup: The reaction mixture was concentrated, taken up in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed twice with 5 mL of de-ionized water. Drying with anhydrous MgSO<sub>4</sub> and

concentrated *in vacuo* yielded **29** (550 mg, 96%) as clear oil. IR (thin film) 3025.8, 2923.7, 1734.7 1492.9, 1452.0, 1028.4, 756.7  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.516 (s, 1H), 7.36-7.23 (m, 5H), 3.75 (s, 3H), 3.70 (s, 1H), 3.10 (dd, 1H,  $J = 6.8$ ,  $J = 15.3$ ), 2.99 (ddd, 1H,  $J = 0.8$  Hz,  $J = 8.1$ Hz,  $J = 15.3$  Hz); (150 MHz,  $\text{CDCl}_3$ )  $\delta$  172.5, 138.8, 134.6, 129.1, 128.7, 127.6, 65.9, 59.3, 51.7, 48.3, 37.9, 25.9;  $[\alpha]_{\text{D}}^{23} = -55.1^\circ$  ( $c = 0.012$  in MeOH); HRMS calc'd for  $\text{C}_{15}\text{H}_{16}\text{D}_4\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]$ , 278.18066, found 278.17990.

### ***N*-deuteromethyl-*L*-histidine methyl ester (**30**)**



PhCHD,CD<sub>3</sub>-His-OMe (200 mg, 0.73 mmol), Pd(OH)<sub>2</sub> (100 mg), MeOH (7.3 mL) afforded **30** (120 mg, 88%). IR (thin film) 2952.0, 1736.5, 1437.0, 1210.9, 1031.5  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (s, 1H), 6.76 (s, 1H), 3.67 (s, 3H), 3.45 (dd, 1H,  $J = 5.2$  Hz,  $J = 7.5$  Hz), 2.98 (dd, 1H,  $J = 5.1$  Hz,  $J = 14.8$  Hz), 2.85 (dd, 1H,  $J = 7.6$  Hz,  $J = 14.8$  Hz);  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.6, 135.1, 132.5, 128.5, 127.1, 63.1, 52.1, 50.2, 29.9;  $[\alpha]_{\text{D}}^{23} = 11.8$  ( $c = 0.017$  in MeOH); HRMS calc'd for  $\text{C}_8\text{H}_{11}\text{D}_3\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]$ , 187.12713, found 187.12868.

<sup>1</sup> Boger, D.L.; Teramoto, S.; Cai, H. *Bioorg. and Med. Chem.*, **1997**, *5*, 1577-1589.

<sup>2</sup> Ghosal, S.; Chauhan, R.B.P.S.; Mehta, R. *Phytochemistry*, **1975**, *14*, 830-2. For *N*-methyl-*D*-tryptophan methyl ester:  $[\alpha]_{\text{D}}^{23} = -51.8^\circ$  ( $c = 1.1$  in  $\text{CHCl}_3$ ) Chu, K.S.; Negrete, G.R., Konopelski, J.P. *J.Org. Chem.*, **1991**, *56*, 5196-5202.

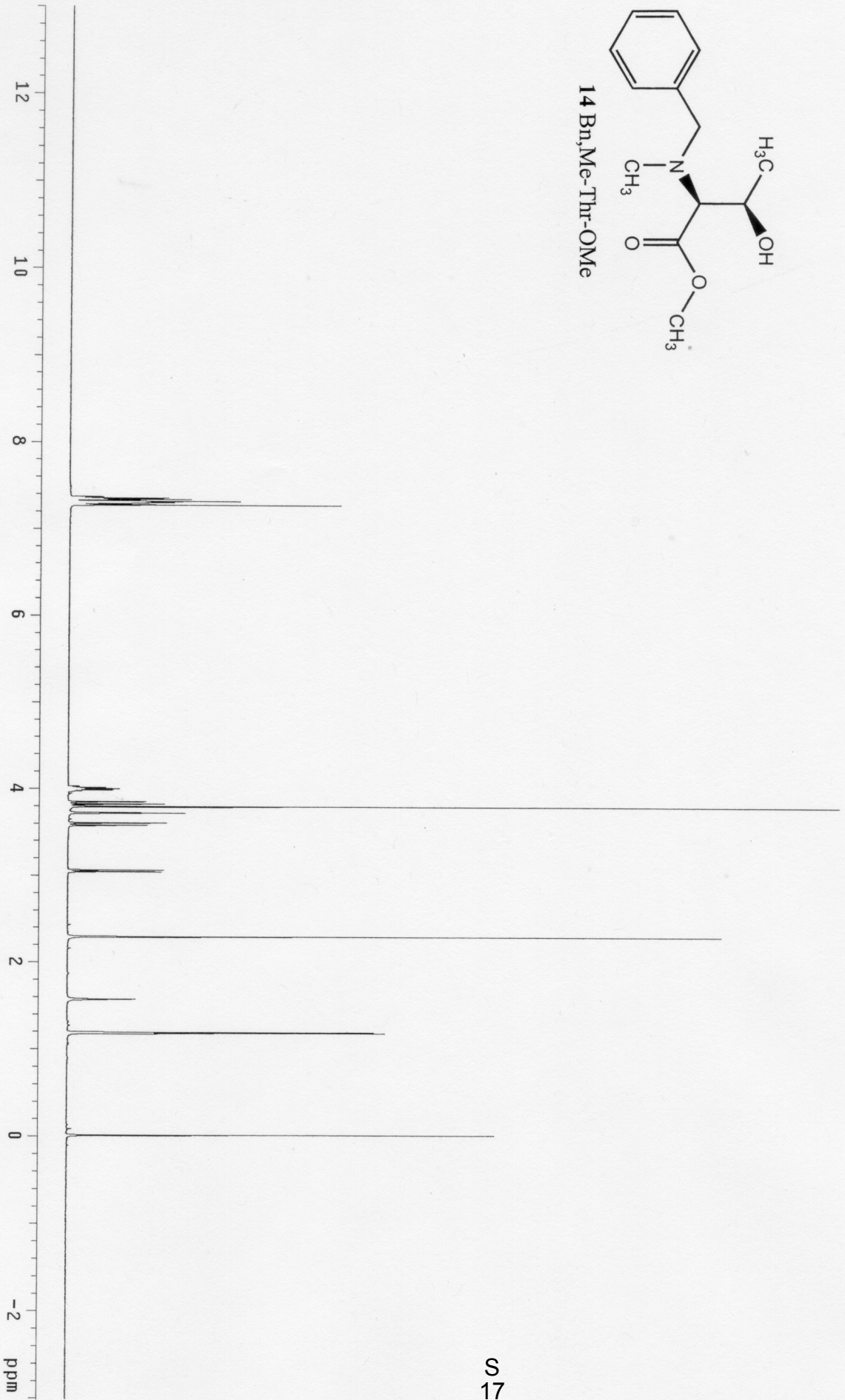
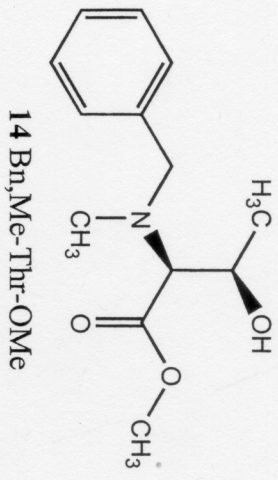
<sup>3</sup> Grieco, P.A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746-5749.

<sup>4</sup> Huguenin, R.L; Boissonnas, R.A. *Helv. Chim. Acta*, **1961**, *44*, 213-231.

<sup>5</sup> Hughes, A.B. *Org. Lett.* **2002**, *4*, 3767-3769.

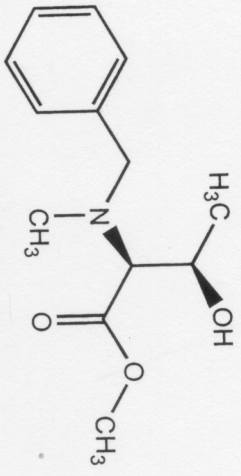
KMIII-168

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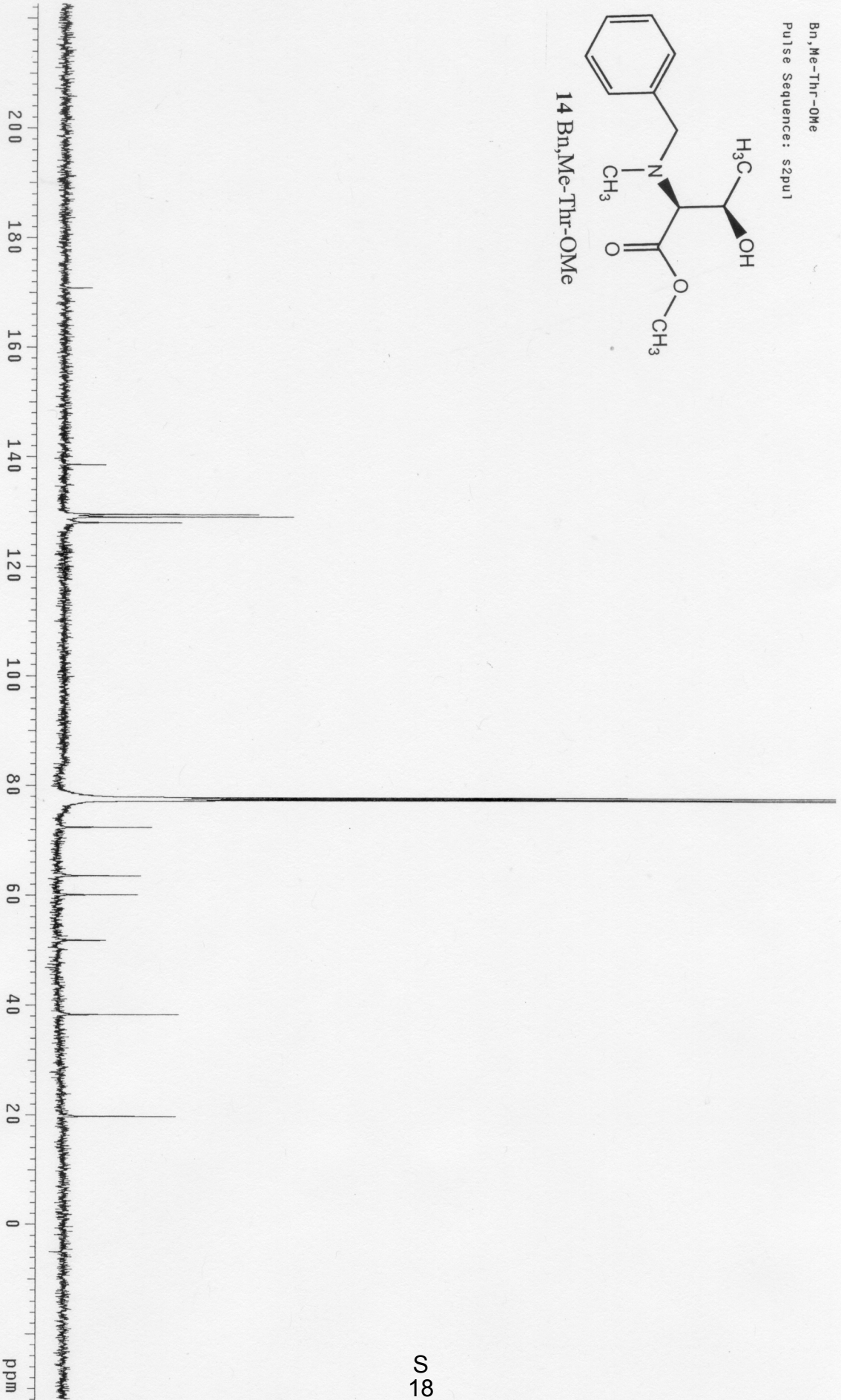


Bn, Me-Thr-OMe

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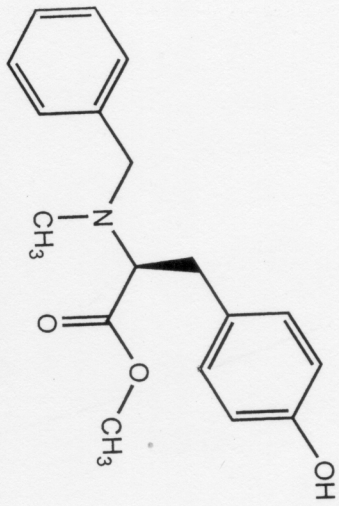


14 Bn, Me-Thr-OMe

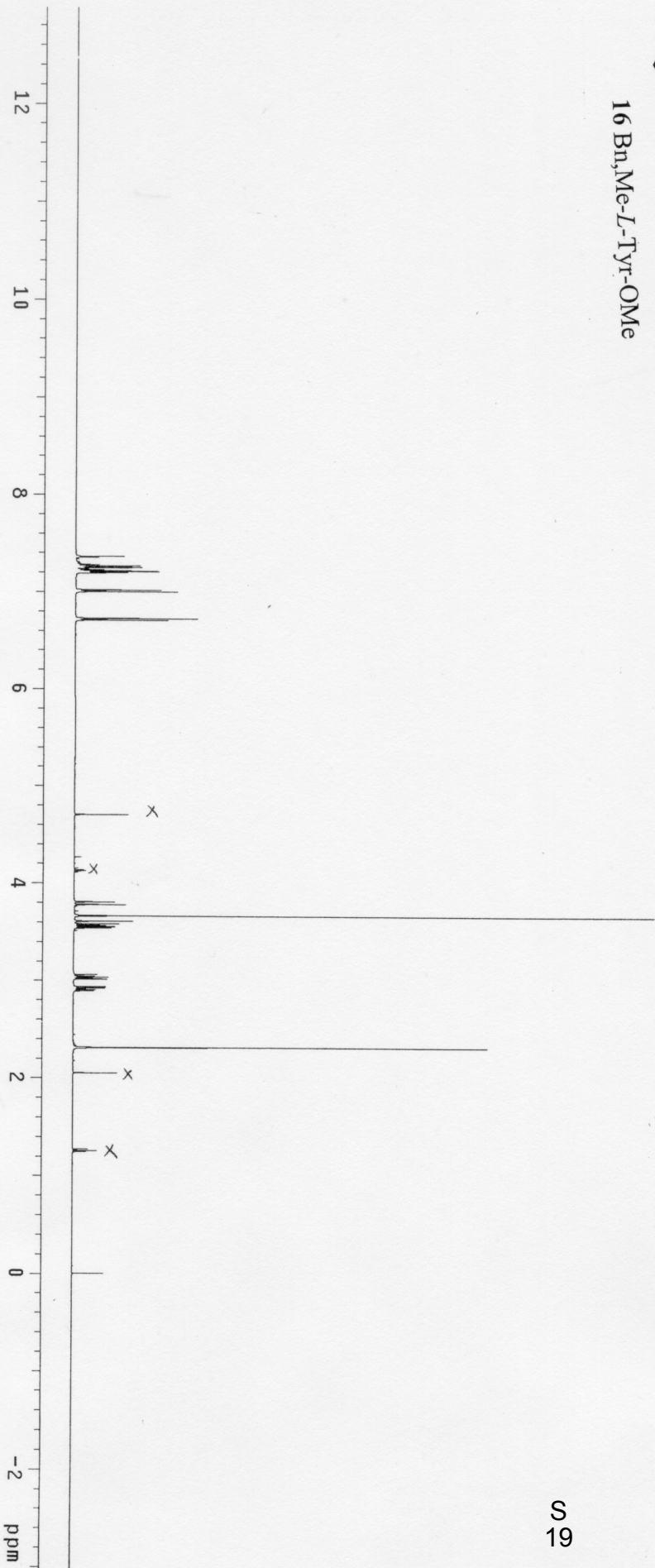


KW111-115

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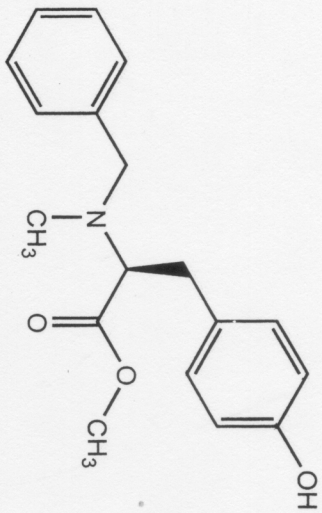


16 Bn, Me-L-Tyr-OMe

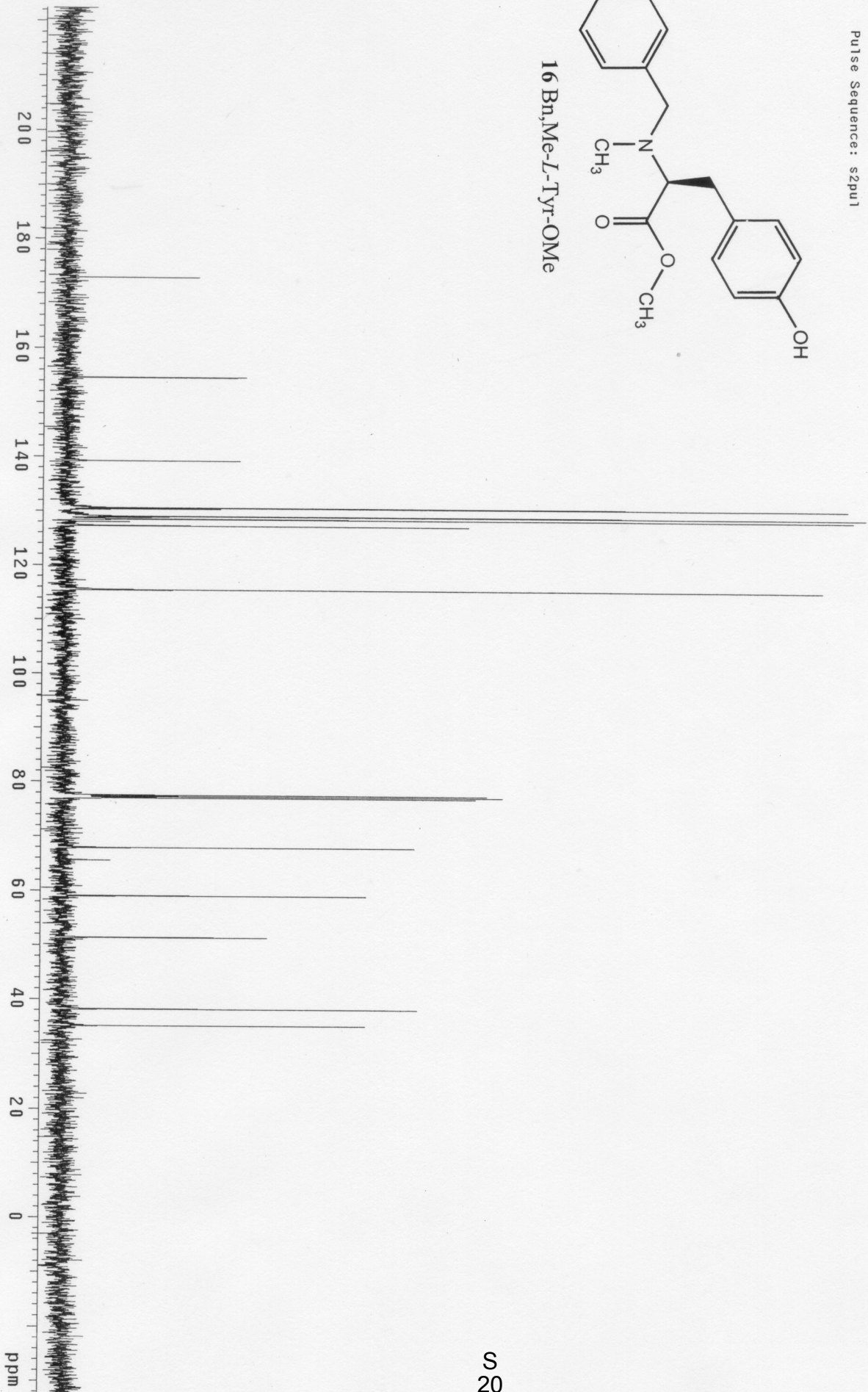


KNW111-115

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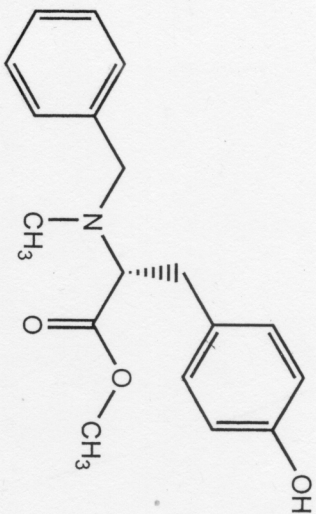


16 Bn, Me-L-Tyr-OMe



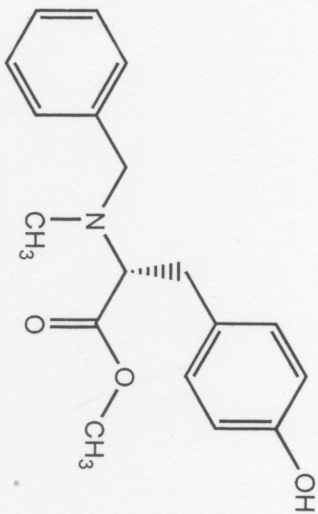
KMIII-123

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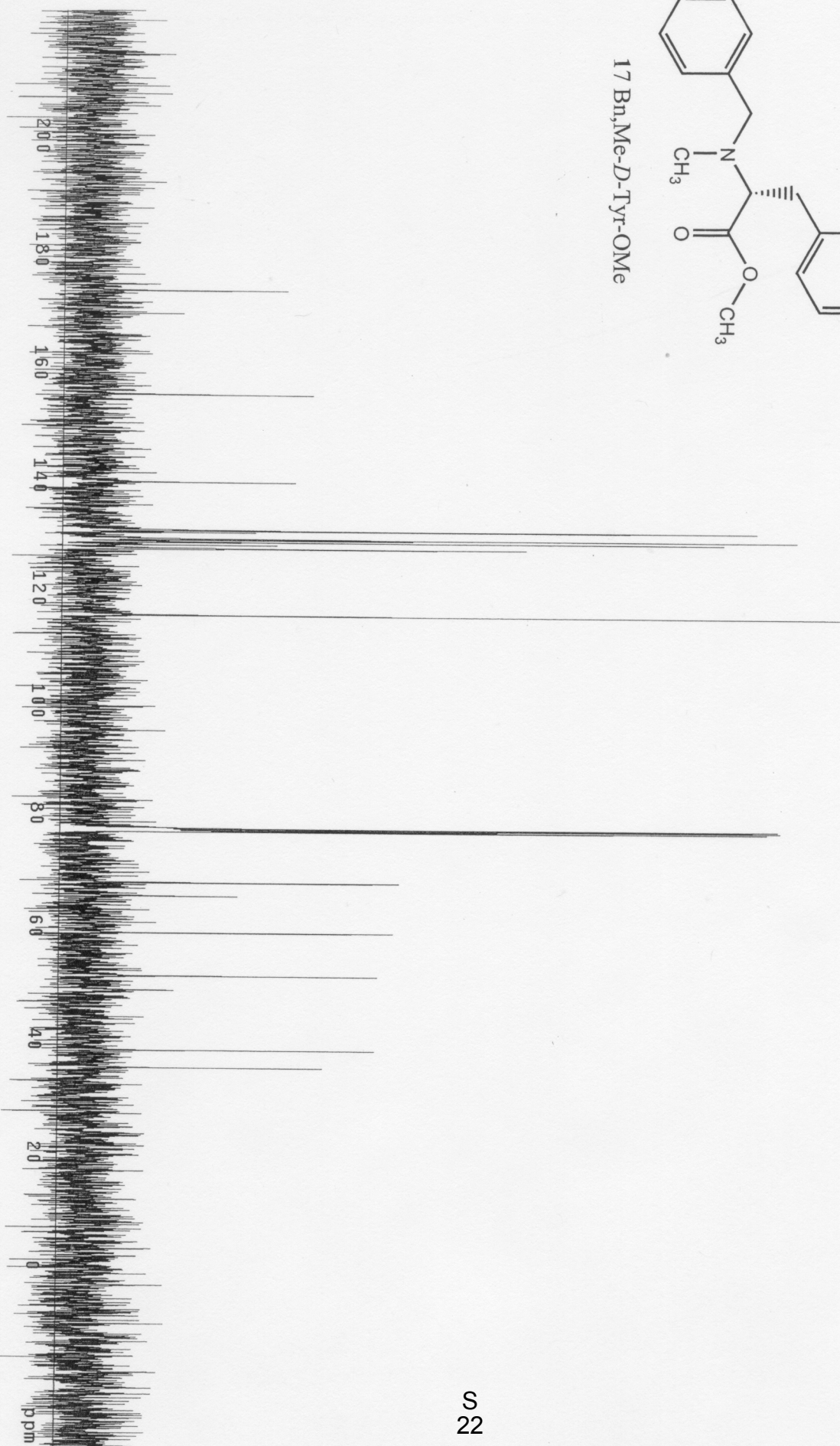


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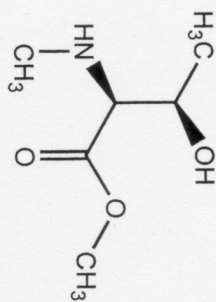


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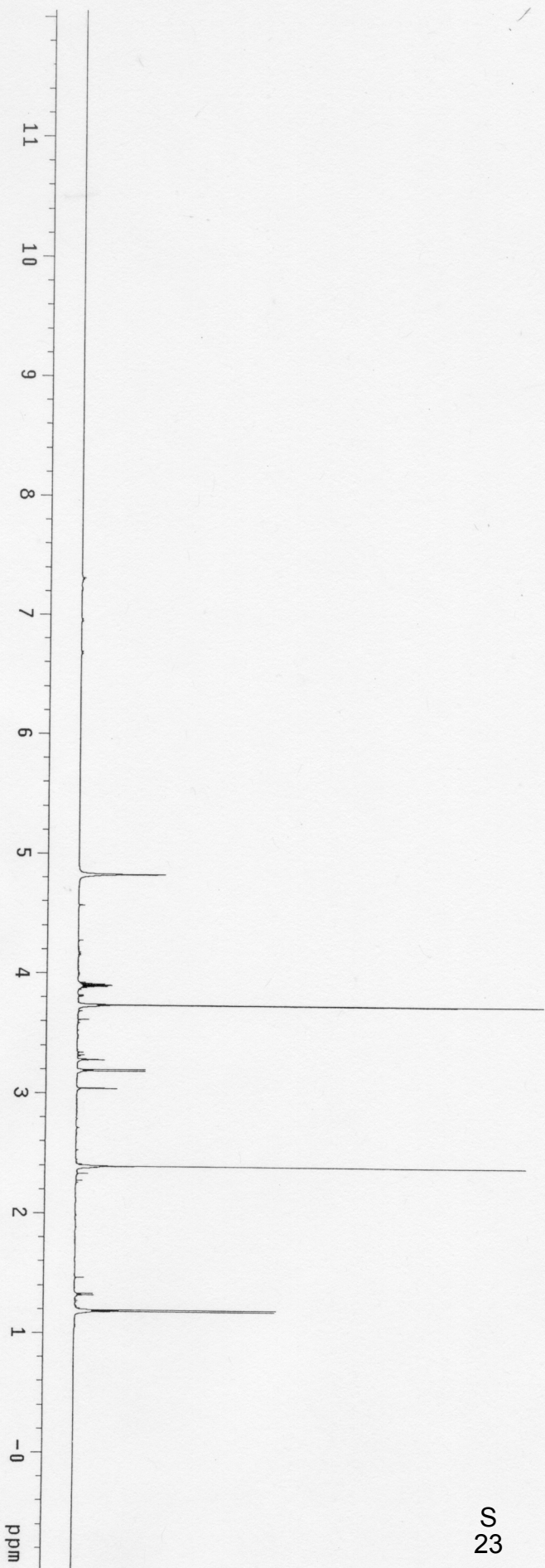


Me-Thr-OMe

Pulse Sequence: szpu1

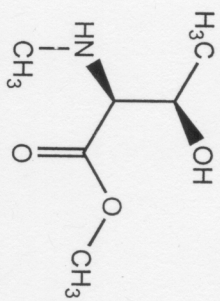


23 Me-Thr-OMe

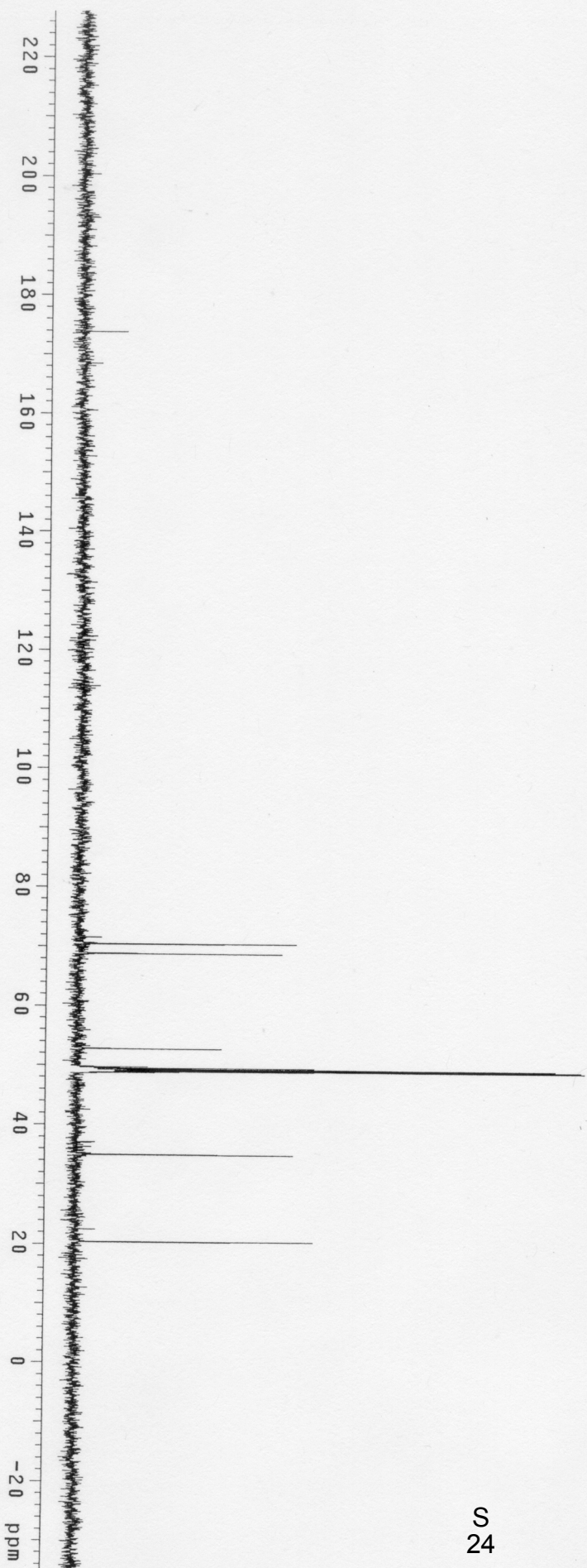


Me-Thr-OMe

Pulse Sequence: s2pu1

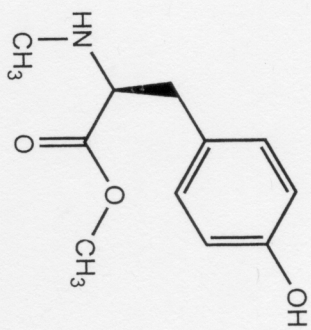


23 Me-Thr-OMe

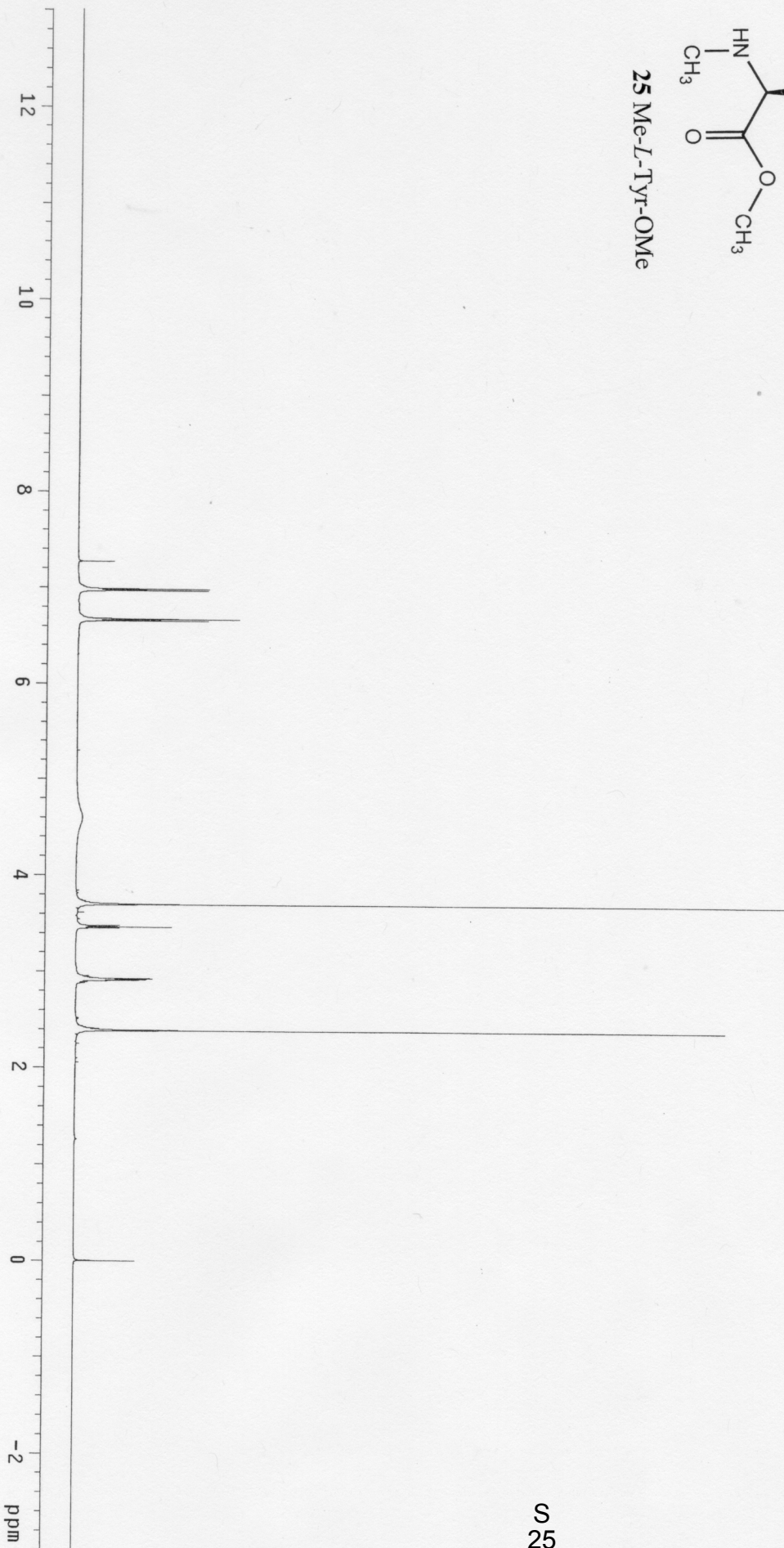


Me-Tyr-OMe

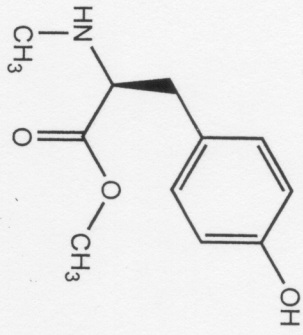
Pulse Sequence: s2pu1



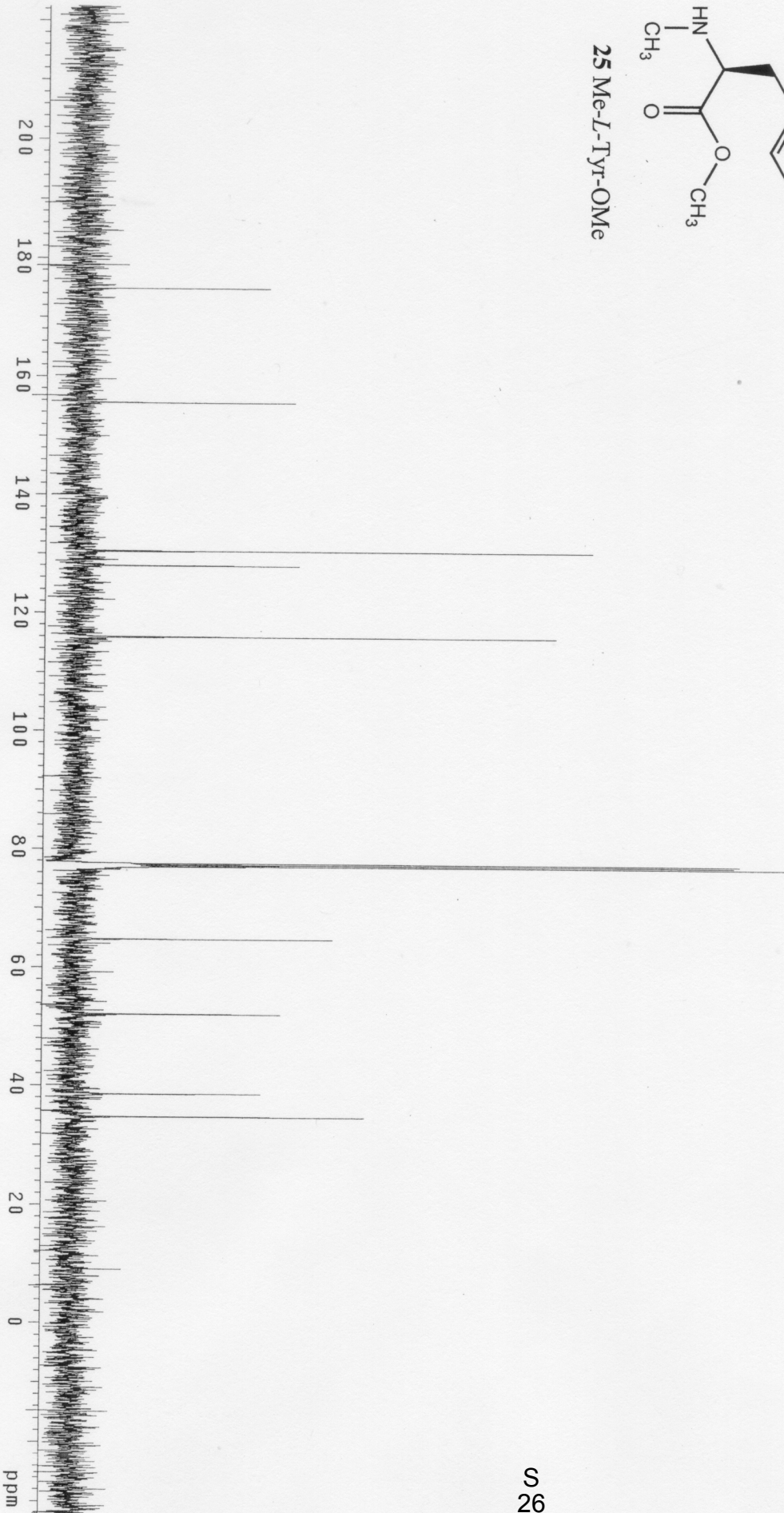
**25** Me-L-Tyr-OMe



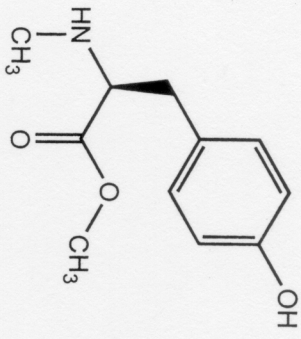
STANDARD CARBON PARAMETERS  
Pulse Sequence: s2pu1



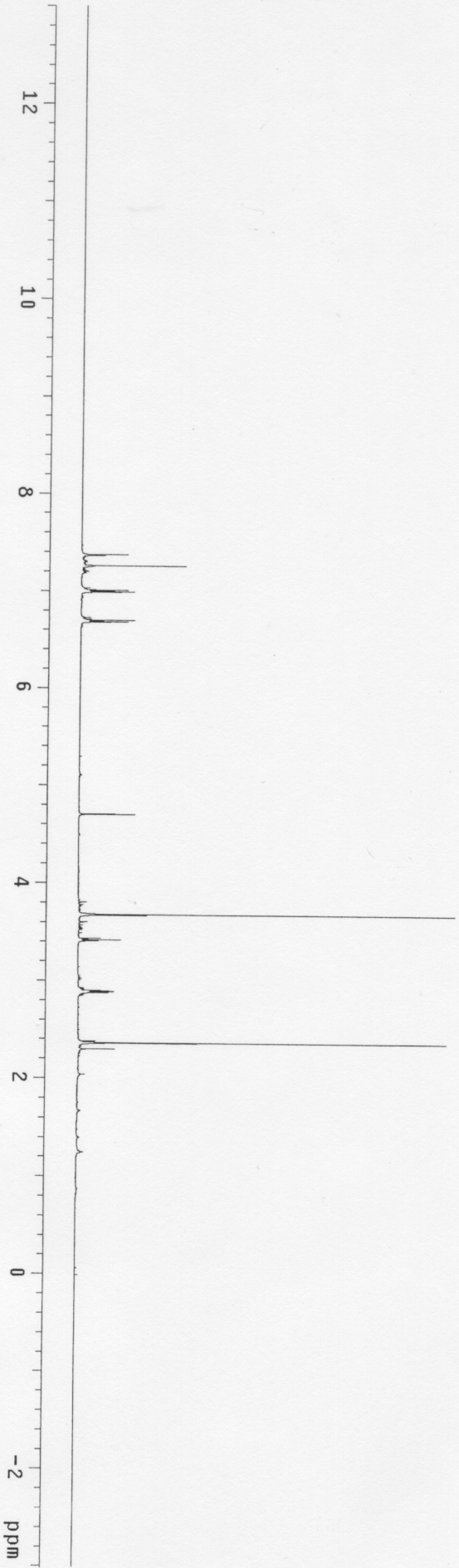
25 Me-L-Tyr-OMe



KMIII- Me-D-Tyr-OMe  
Pulse Sequence: s2pu1

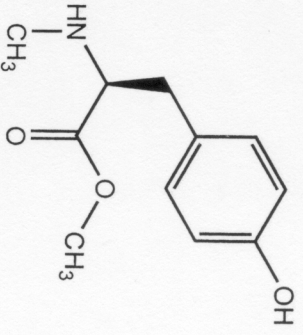


26 Me-D-Tyr-OMe



Me-D-Tyr-OMe

Pulse Sequence: s2pu1



26 Me-D-Tyr-OMe

