Supporting Information for

Asymmetric syntheses of enantiopure C(5)-substituted transpentacins via diastereoselective Ireland-Claisen rearrangements

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1. Experimental

1.1. General Experimental

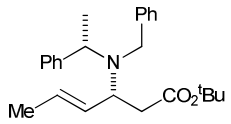
All reactions involving organometallic or other moisture sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] Water was purified by an Elix® UV–10 system. BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Optical rotations were recorded in a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. $^1H–^1H$ COSY, $^1H–^{13}C$ HMQC, and $^1H–^{13}C$ HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K Rosen and F. J Timmers, *Organometallics*, 1996, **15**, 1518.

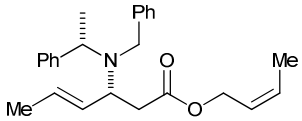
1.2. Experimental Data

tert-Butyl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 10



BuLi (2.0 M in hexanes, 23.0 mL, 46.1 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (10.1 g, 47.6 mmol) in THF (165 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **9**[2] (5.0 g, 29.7 mmol, >99:1 dr) in THF (65 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **10** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **10** as a colourless oil (10.1 g, 89%, >99:1 dr); $[\alpha]_D^{20}$ +23.6 (*c* 1.0 in $CHCl_3$); {lit.[3] for enantiomer $[\alpha]_D^{23}$ −23.3 (*c* 2.04 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.68–1.71 (3H, m, C(6)*H*$_3$), 2.23 (1H, dd, *J* 14.1, 9.4, C(2)*H*$_A$), 2.35 (1H, dd, *J* 14.1, 5.6, C(2)*H*$_B$), 3.67 (2H, app s, NC*H*$_2$Ph), 3.72–3.79 (1H, m, C(3)*H*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 5.48–5.59 (2H, m, C(4)*H*, C(5)*H*), 7.17–7.23 (2H, m, *Ph*), 7.26–7.34 (6H, m, *Ph*), 7.38–7.41 (2H, m, *Ph*).

(*Z*)-But-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 11



Step 1: TFA (10 mL) was added to a stirred solution of **10** (2.50 g, 6.59 mmol, >99:1 dr) in CH_2Cl_2 (20 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the resultant mixture was washed with satd aq $NaHCO_3$ (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (2.20 g); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, d, *J* 6.9, C(α)*Me*), 1.71–1.73 (3H, m, C(6)*H*$_3$), 2.21 (1H, dd, *J* 17.2, 4.4, C(2)*H*$_A$), 2.39 (1H, dd, *J* 17.2, 11.5, C(2)*H*$_B$), 3.67 (1H, d, *J* 13.6, NC*H*$_A$H$_B$Ph), 3.80 (1H, ddd, *J* 11.5, 7.9, 4.4, C(3)*H*), 3.92 (1H, d, *J* 13.6, NCH$_A$*H*$_B$Ph), 4.09 (1H, q, *J* 6.9, C(α)*H*), 5.47–5.54 (1H, m, C(4)*H*), 5.61–5.70 (1H, m, C(5)*H*), 7.17–7.29 (10H, m, *Ph*).

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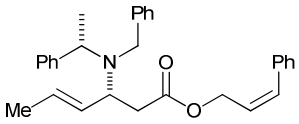
[2] S. K. Bagal, S. G. Davies, A. M. Fletcher, J. A. Lee, P. M. Roberts, P. M. Scott and J. E. Thomson, *Tetrahedron Lett.*, 2011, **52**, 2216.
[3] S. G. Davies and G. D. Smyth, *J. Chem. Soc., Perkin Trans. 1* 1996, 2467.

Step 2: A stirred solution of the residue (2.20 g) in CH_2Cl_2 (25 mL) was cooled to 0 °C and treated sequentially with $(COCl)_2$ (0.6 mL, 6.92 mmol) and DMF (20 μL, 0.26 μmol). The reaction mixture was then allowed to warm to rt over 1 h and concentrated *in vacuo*. The residue was dissolved in in CH_2Cl_2 (25 mL), the resultant solution was cooled to 0 °C, and a solution of **23** (670 mg, 9.23 mmol, >99:1 dr) was then added. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **11** as a colourless oil (1.42 g, 57% from **10**, >99:1 dr); $[\alpha]_D^{20}$ +15.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 1734 (C=O), 1494 (C=C), 1171, 699; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (3H, dt, *J* 6.9, 0.9, C(4')H_3), 1.61 (3H, d, *J* 5.4, C(6)H_3), 2.24 (1H, dd, *J* 14.3, 8.2, C(2)H_A), 2.38 (1H, dd, *J* 14.3, 6.5, C(2)H_B), 3.57 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 3.62 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 3.90–3.95 (1H, m, C(3)*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.35–4.40 (1H, m, C(1')H_A), 4.45–4.50 (1H, m, C(1')H_B), 5.31–5.39 (1H, m, C(2')*H*), 5.41–5.52 (2H, m, C(4)*H*, C(5)*H*), 5.55–5.64 (1H, m, C(3')*H*), 7.09–7.14 (2H, m, *Ph*), 7.17–7.21 (4H, m, *Ph*), 7.24–7.29 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.1 (*C*(4')), 16.8 (C(α)*Me*), 18.0 (*C*(6)), 38.6 (*C*(2)), 50.3 (N*C*H$_2$Ph), 56.8 (*C*(3)), 56.8 (*C*(α)), 59.8 (*C*(1')), 124.4 (*C*(2')), 126.5, 126.6 (*o*,*m*,*p*-*Ph*), 127.1 (*C*(5)), 127.8, 127.9, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 129.1 (*C*(3')), 131.1 (*C*(4)), 141.3, 144.3 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 378 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{32}NO_2^+$ ([M+H]$^+$) requires 378.2428; found 378.2434.

(*Z*)-3'-Phenylprop-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 12

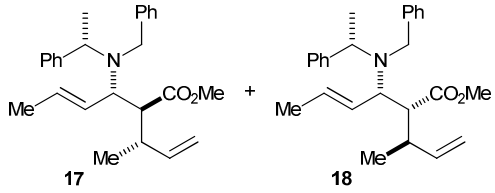


Step 1: TFA (10 mL) was added to a stirred solution of **10** (2.55 g, 6.70 mmol, >99:1 dr) in CH_2Cl_2 (20 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the resultant mixture was washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (2.50 g).

Step 2: A stirred solution of the residue (2.50 g) in CH_2Cl_2 (25 mL) was cooled to 0 °C and treated sequentially with $(COCl)_2$ (0.6 mL, 7.06 mmol) and DMF (20 μL, 0.26 μmol). The reaction mixture was then allowed to warm to rt over 1 h and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL), the resultant solution was cooled to 0 °C, and a solution of **24** (1.26 g, 9.41 mmol, >99:1 dr) was then added. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the

resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **12** as a colourless oil (1.86 g, 63% from **10**, >99:1 dr); $[\alpha]_D^{20}$ +5.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 1735 (C=O), 1494 (C=C), 1167, 699; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.71 (3H, d, *J* 5.3, C(6)H_3), 2.36 (1H, dd, *J* 14.2, 8.1, C(2)H_A), 2.51 (1H, dd, *J* 14.2, 6.8, C(2)H_B), 3.68 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 3.74 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 3.80–3.85 (1H, m, C(3)*H*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.64–4.69 (1H, m, C(1')H_A), 4.75–4.80 (1H, m, C(1')H_B), 5.51–5.60 (2H, m, C(4)*H*, C(5)*H*), 5.63–5.72 (1H, m, C(2')*H*), 6.64 (1H, d, *J* 11.6, C(3')*H*), 7.16–7.23 (6H, m, *Ph*), 7.25–7.32 (5H, m, *Ph*), 7.35–7.40 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 18.0 (*C*(6)), 38.6 (*C*(2)), 50.3 (N*C*H$_2$Ph), 56.8 (*C*(α)), 56.7 (*C*(3)), 61.3 (*C*(1')), 126.1 (*C*(2')), 126.6, 126.6 (*o*,*m*,*p*-*Ph*), 127.2 (*C*(5)), 127.4, 127.8, 127.9, 128.1, 128.3, 128.4, 128.7 (*o*,*m*,*p*-*Ph*), 131.1 (*C*(4)), 132.4 (*C*(3')), 136.1, 141.3, 144.3 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI^+) 440 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{34}NO_2^+$ ($[M+H]^+$) requires 440.2584; found 440.2566.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 17 and methyl (2*R*,3*S*,2'*R*,α*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 18



Step 1: TMSCl (3.01 mL, 23.8 mmol) was added dropwise to a stirred solution of **11** (3.00 g, 7.90 mmol, >99:1 dr) in PhMe (30 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 23.8 mL, 23.8 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed brine (150 mL), then dried and concentrated *in vacuo* to give an 80:20 mixture of **13** and **14**. Purification *via* flash column chromatography (gradient elution, 0% → 8% acetone in 30–40 °C petrol) gave **14** as a yellow oil (574 mg, >99:1 dr); $[\alpha]_D^{20}$ +12.9 (*c* 0.7 in $CHCl_3$); ν_{max} (ATR) 2965 (C–H), 1703 (C=O), 1494 (C=C), 699; δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, *J* 6.9, C(1')H_3), 1.34 (3H, d, *J* 6.9, C(α)*Me*), 1.60–1.62 (3H, m, C(6)H_3), 2.24 (1H, app t, *J* 6.9, C(2)*H*), 2.42–2.50 (1H, m, C(2')*H*), 3.45–3.49 (1H, m, C(3)*H*), 3.52 (1H, d, *J* 14.1, NCH_AH$_B$Ph), 3.75 (1H, d, *J* 14.1, NCH$_A$$H_B$Ph), 4.09 (1H, q, *J* 6.9, C(α)*H*), 4.64–4.74 (2H, m, C(4')H_2), 5.43–5.59 (3H, m, C(4)*H*), C(5)*H*, C(3')*H*), 7.08–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(α)*Me*), 17.5 (*C*(1')), 18.0 (*C*(6)), 35.2 (*C*(2')), 51.9 (N*C*H$_2$Ph), 53.1 (*C*(2)), 57.2 (*C*(α)), 61.7 (*C*(3)), 113.6 (*C*(4')), 127.0 (*o*,*m*,*p*-*Ph*),

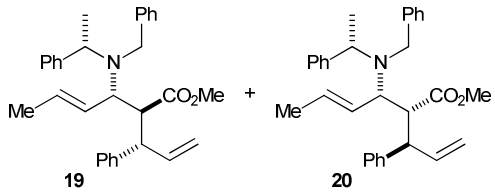
127.2 (*C*(4)), 127.3, 128.3, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 130.8 (*C*(5), 139.6 (*i*-*Ph*), 141.1 (*C*(3')), 142.5 (*i*-*Ph*), 177.0 (*C*(1)); *m*/*z* (ESI^+) 378 ($[M+H]^+$, 100%), 400 ($[M+Na]^+$, 4%); HRMS (ESI^+) $C_{25}H_{31}NNaO_2^+$ ($[M+Na]^+$) requires 400.2247; found 400.2239. Further elution (eluent 30–40 °C petrol/acetone, 92:8) gave **13** as a yellow oil (1.79 g, >99:1 dr); $[\alpha]_D^{20}$ +15.2 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1704 (C=O), 1495 (C=C), 698; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, d, *J* 7.1, C(1')H_3), 1.45 (3H, d, *J* 7.0, C(α)*Me*), 1.77–1.79 (3H, m, C(6)H_3), 2.16–2.19 (1H, m, C(2)*H*), 2.37–2.44 (1H, m, C(2')*H*), 3.62 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.68 (1H, app t, *J* 10.4, C(3)*H*), 3.87 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 3.99 (1H, q, *J* 7.0, C(α)*H*), 4.64–4.75 (2H, m, C(4')H_2), 5.37 (1H, ddd, *J* 15.4, 9.8, 1.7, C(4)*H*), 5.54–5.61 (1H, m, C(3')*H*), 5.61–5.68 (1H, m, C(5)*H*), 7.13–7.23 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 18.1 (*C*(6)), 19.2 (*C*(1')), 37.6 (*C*(2')), 49.2 (*C*(2)), 50.8 (N*C*H_2Ph), 59.4 (*C*(3)), 60.5 (*C*(α)), 114.7 (*C*(4')), 126.2 (*C*(4)), 127.8, 127.9, 128.3, 128.5, 128.5, 129.4 (*o*,*m*,*p*-*Ph*), 133.5 (*C*(5)), 135.4, 140.0 (*i*-*Ph*), 140.3 (*C*(3')), 174.4 (*C*(1)); *m*/*z* (ESI^+) 378 ($[M+H]^+$, 100%), 400 ($[M+Na]^+$, 5%); HRMS (ESI^+) $C_{25}H_{31}NNaO_2^+$ ($[M+Na]^+$) requires 400.2247; found 400.2241.

Step 2 (*for* ***17***): A solution of **13** (1.79 g) in MeCN (8 mL) was treated sequentially with DBU (1.42 ml, 9.48 mmol) and MeI (0.65 mL, 10.4 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and 2.0 M aq HCl (80 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **17** as a colourless oil (1.39 g, 45% from **11**, >99:1 dr); $[\alpha]_D^{20}$ −10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3026, 2966 (C–H), 1734 (C=O), 1495 (C=C), 1150, 699; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 7.1, C(1')H_3), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.68 (3H, ddd, *J* 6.1, 1.0, 0.8, C(6)H_3), 2.15–2.23 (1H, m, C(2')*H*), 2.59–2.63 (1H, m, C(2)*H*), 3.34 (3H, s, O*Me*), 3.42–3.48 (1H, m, C(3)*H*), 3.47 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.71 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.65–4.76 (2H, m, C(4')H_2), 5.24–5.31 (1H, m, C(5)*H*), 5.36–5.44 (1H, m, C(4)*H*), 5.59–5.68 (1H, m, C(3')*H*), 7.04–7.22 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 18.0 (*C*(6)), 19.6 (*C*(1')), 37.4 (*C*(2')), 50.3 (N*C*H_2Ph), 50.6 (O*Me*), 54.0 (*C*(2)), 56.1 (*C*(α)), 60.5 (*C*(3)), 114.6 (*C*(4')), 126.2, 126.4, 127.6, 127.8, 127.9 (*o*,*m*,*p*-*Ph*), 128.2 (*C*(5)), 128.9 (*o*,*m*,*p*-*Ph*), 130.0 (*C*(4)), 139.2 (*C*(3')), 140.2, 144.6 (*i*-*Ph*), 173.0 (*C*(1)); *m*/*z* (ESI^+) 392 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{33}NNaO_2^+$ ($[M+Na]^+$) requires 414.2404; found 414.2405.

Step 2 (*for* ***18***): A solution of **14** (573 mg, >99:1 dr) in MeCN (5.7 mL) was treated sequentially with DBU (454 µl, 3.04 mmol) and MeI (208 µL, 3.34 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*.

Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **18** as a colourless oil (438 mg, 14% from **11**, >99:1 dr); $[\alpha]_D^{20}$ −8.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2968 (C–H), 1732 (C=O), 1494 (C=C), 1153, 700; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.8, C(1')H_3), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.75–1.77 (3H, m, C(6)H_3), 2.48 (1H, dd, *J* 8.2, 6.4, C(2)*H*), 2.56–2.65 (1H, m, C(2')*H*), 3.49–3.54 (1H, m, C(3)*H*), 3.56 (3H, s, O*Me*), 3.70 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.78 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.75–4.83 (2H, m, C(4')H_2), 5.45–5.61 (2H, m, C(3')*H*, C(5)*H*), 5.69–5.75 (1H, m, C(4)*H*), 7.22–7.27 (2H, m, *Ph*), 7.30–7.36 (6H, m, *Ph*), 7.41–7.43 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 17.7 (*C*(1')), 18.0 (*C*(6)), 35.9 (*C*(2')), 50.7 (O*Me*), 50.9 (N*C*H_2Ph), 55.4 (*C*(2)), 57.1 (*C*(α)), 59.3 (*C*(3)), 113.6 (*C*(4')), 126.6, 126.6, 127.9, 128.0, 128.0 (*o*,*m*,*p*-*Ph*), 128.2 (*C*(4)), 128.8 (*o*,*m*,*p*-*Ph*), 129.2 (*C*(5)), 140.4 (*C*(3')), 141.1, 144.3 (*i*-*Ph*), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 392 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{33}NNaO_2^+$ ([M+Na]$^+$) requires 414.2404; found 414.2408.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hex-4-enoate 19 and methyl (2*R*,3*S*,1'*R*,α*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 20

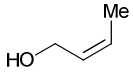


Step 1: TMSCl (2.18 mL, 17.3 mmol) was added dropwise to a stirred solution of **12** (2.53 g, 5.75 mmol, >99:1 dr) in PhMe (25.3 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 17.3 mL, 17.3 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give a 76:24 mixture of **15** and **16** as a brown oil (2.00 g).

Step 2: A solution of the residue in MeCN (25.3 mL) was treated sequentially with DBU (1.72 mL, 11.5 mmol) and MeI (0.79 mL, 12.7 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and 2.0 M aq HCl (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (250 mL) and brine (250 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 2% Et_2O in 30–40 °C petrol) gave **20** as a white solid (413 mg, 16%

from **12**, >99:1 dr); mp 82–83 °C; $[\alpha]_D^{20}$ +26.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 1731 (C=O), 1494 (C=C), 1167, 699; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.8, C(α)*Me*), 1.62–1.64 (3H, m, C(6)H_3), 2.86 (1H, dd, *J* 10.8, 5.4, C(2)*H*), 2.96 (1H, dd, *J* 9.9, 5.4, C(3)*H*), 3.21–3.26 (1H, m, C(1')*H*), 3.51 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.53 (3H, s, O*Me*), 3.63 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.81 (1H, q, *J* 6.8, C(α)*H*), 4.72–4.76 (2H, m, C(3')H_2), 4.92 (1H, dq, *J* 15.4, 6.5, C(5)*H*), 5.57–5.66 (1H, m, C(2')*H*), 5.79 (1H, ddd, *J* 15.4, 9.9, 1.7, C(4)*H*), 6.47–6.49 (2H, m, *Ph*), 6.95–7.03 (3H, m, *Ph*), 7.12–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 18.0 (C(6)), 50.2 (*C*(1')), 51.1 (O*Me*), 51.5 (N*C*H_2Ph), 54.6 (*C*(2)), 56.0 (*C*(α)), 59.8 (*C*(3)), 115.0 (*C*(3')), 126.0, 126.4, 126.6 (*o*,*m*,*p*-*Ph*), 126.9 (*C*(4)), 127.8, 127.9, 128.1, 128.1, 128.3, 128.7 (*o*,*m*,*p*-*Ph*), 130.6 (*C*(5)), 139.6 (*C*(2')), 140.3, 141.2, 144.0 (*i*-*Ph*), 174.6 (*C*(1)); *m*/*z* (ESI$^+$) 454 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{35}NNaO_2^+$ ($[M+Na]^+$) requires 476.2560; found 476.2550. Further elution gave **19** as a colourless oil which solidified upon standing (1.81 g, 69% from **12**; >99:1 dr); mp 63–64 °C; $[\alpha]_D^{20}$ −65.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 1737 (C=O), 1494 (C=C), 1166, 699; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.52–1.54 (3H, m, C(6)H_3), 3.03 (1H, dd, *J* 10.8, 6.6, C(2)*H*), 3.21 (3H, s, O*Me*), 3.22–3.27 (1H, m, C(3)*H*), 3.44 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.54 (1H, t, *J* 10.8, C(1')*H*), 3.70 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.73–4.85 (2H, m, C(3')H_2), 4.99–5.06 (1H, m, C(4)*H*), 5.35 (1H, dq, *J* 15.3, 6.4, C(5)*H*), 5.94–6.04 (1H, m, C(2')*H*), 6.94–7.20 (2H, m, *Ph*), 7.01–7.23 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 18.0 (C(6)), 50.3 (N*C*H_2Ph), 50.4 (*C*(3)), 50.7 (O*Me*), 54.7 (*C*(2)), 55.8 (*C*(α)), 61.6 (*C*(1')), 116.2 (*C*(3')), 126.1, 126.2, 126.5, 127.6, 127.8, 127.8, 127.9, 128.2 (*o*,*m*,*p*-*Ph*), 128.5 (*C*(4)), 129.0 (*o*,*m*,*p*-*Ph*), 129.9 (*C*(5)), 137.5 (*C*(2')), 140.0, 142.9, 144.6 (*i*-*Ph*), 172.9 (*C*(1)); *m*/*z* (ESI$^+$) 454 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{35}NNaO_2^+$ ($[M+Na]^+$) requires 476.2560; found 476.2553.

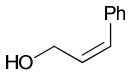
(*Z*)-2-Buten-1-ol 23



$NaBH_4$ (2.02 g, 53.5 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (13.3 g, 53.5 mmol) in MeOH (263 mL) at 0 °C and the resultant black mixture was allowed to warm to rt over 15 min. $(CH_2NH_2)_2$ (8.87 mL, 133 mmol) and a solution of **21** (15.0 g, 214 mmol) in MeOH (113 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of hydrogenation was closely monitored by TLC analysis [R_f (**21**) = 0.50, R_f (**23**) = 0.40 using eluent 30–40 °C petrol/Et_2O, 50:50]. Once complete (~6 h) the reaction mixture was filtered through Celite® (eluent Et_2O) and the solvent was removed by distillation. Et_2O (200 mL) was then added to the residue and the resultant pink suspension was filtered through Celite® (eluent Et_2O) and the solvent was again removed by distillation to give

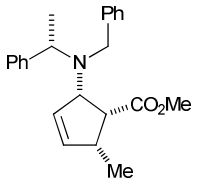
23 as an orange oil (10.2 g, 66%, >99:1 dr);[4] δ_H (400 MHz, $CDCl_3$) 1.62–1.68 (3H, m, C(4)H_3), 1.90 (1H, br s, O*H*), 4.15–4.21 (2H, m, C(1)H_2), 5.54–5.63 (2H, m, C(2)*H*, C(3)*H*).

(*Z*)-3-Phenylprop-2-en-1-ol 24



$NaBH_4$ (355 mg, 9.39 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (2.35 g, 9.44 mmol) in MeOH (88 mL) at 0 °C and the resultant black mixture was stirred and allowed to warm to rt over 15 min. $(CH_2NH_2)_2$ (1.56 mL, 23.3 mmol) and a solution of **22** (5.00 g, 37.8 mmol) in MeOH (38 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of hydrogenation was closely monitored by TLC analysis [R_f (**22**) = 0.50, R_f (**24**) = 0.39 using eluent 30–40 °C petrol/Et_2O, 50:50]. Once complete (~3.5 h) the reaction mixture was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. EtOAc (200 mL) was then added to the residue and the resultant pink suspension was filtered through Celite® (eluent EtOAc) and the filtrate concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 80:20) gave **24** as a pale yellow oil (4.70 g, 93%, >99:1 dr);[5,6] δ_H (400 MHz, $CDCl_3$) 1.90 (1H, br s, O*H*), 4.45 (2H, dd, *J* 6.6, 1.8, C(1)H_2), 5.88 (1H, ddd, *J* 11.8, 6.6, 6.4, C(2)*H*), 6.56–6.60 (1H, m, C(3)*H*), 7.20–7.23 (2H, m, *Ph*), 7.26–7.30 (1H, m, *Ph*), 7.34–7.38 (2H, m, *Ph*).

Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 25

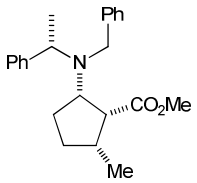


Grubbs I catalyst (72 mg, 0.09 mmol) was added to a degassed solution of **18** (85 mg, 0.22 mmol, >99:1 dr) in CH_2Cl_2 (8.6 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and $P(CH_2OH)_3$ (539 mg, 4.34 mmol), Et_3N (0.06 mL, 0.43 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 30 min, then filtered and concentrated *in vacuo* to give **25** as an orange oil (58 mg, 77%, >99:1 dr);[7] $[\alpha]_D^{20}$ −22.5 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1737 (C=O), 1494 (C=C), 1161, 699; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 7.3, C(5)*Me*), 1.28 (3H, d, *J* 6.6, C(α)*Me*), 2.55–2.65 (1H, m,

[4] J. Rehbein, S. Leick and M. Hiersemann, *J. Org. Chem.*, 2009, **74**, 1531.
[5] D. J. Vyas and M. Oestreich, *Chem. Commun.*, 2010, **46**, 568.
[6] J. N. Denis, A. E. Greene, A. A. Serra and M. J. Luche, *J. Org. Chem.*, 1986, **51**, 46.
[7] Attempted chromatographic purification of compound **25** resulted in decomposition.

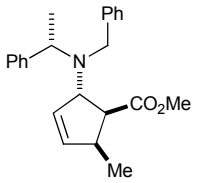
C(5)*H*), 2.88 (1H, app t, *J* 8.2, C(1)*H*), 3.54 (3H, s, O*Me*), 3.76 (1H, d, *J* 14.4, NCH_AH_BPh), 3.86 (1H, q, *J* 6.6, C(α)*H*), 4.01–4.05 (1H, m, C(2)*H*), 4.06 (1H, d, *J* 14.4, NCH_AH_BPh), 5.56 (1H, dt, *J* 5.7, 2.4, C(4)*H*), 5.79 (1H, ddd, *J* 5.7, 2.4, 2.3, C(3)*H*), 7.10–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (C(α)*Me*), 15.7 (C(5)*Me*), 40.0 (*C*(5)), 50.7 (O*Me*), 52.6 (N*C*H_2Ph), 54.1 (*C*(1)), 56.0 (*C*(α)), 66.7 (*C*(2)), 126.4, 126.5, 127.8, 127.9, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 130.4 (*C*(3)), 135.8 (*C*(4)), 141.4, 144.2 (*i*-*Ph*), 172.5 (*C*O_2Me); *m*/*z* (ESI^+) 350 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{27}NNaO_2^+$ ($[M+Na]^+$) requires 372.1934; found 372.1925.

Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopentane-1-carboxylate 26



Pd/C (29 mg, 50% w/w by substrate) was added to a degassed solution of **25** (58 mg, 0.17 mmol, >99:1 dr) in MeOH (4.2 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 20 min. The reaction mixture was then degassed, filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **26** as a colourless oil (5 mg, 9%, >99:1 dr); $[\alpha]_D^{20}$ –26.1 (*c* 0.3 in $CHCl_3$); ν_{max} (ATR) 2959 (C–H), 1730 (C=O), 699; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 7.1, C(5)*Me*), 1.33 (3H, d, *J* 6.9, C(α)*Me*), 1.53–1.63 (1H, m, C(4)H_A), 1.67–1.78 (2H, m, C(3)H_A, C(4)H_B), 2.00–2.08 (1H, m, C(5)*H*), 2.10–2.18 (1H, m, C(3)H_B), 2.85 (1H, t, *J* 6.2, C(1)*H*), 3.24–3.31 (1H, m, C(2)*H*), 3.62 (3H, s, O*Me*), 3.64 (1H, d, *J* 15.2, NCH_AH_BPh), 3.80 (1H, d, *J* 15.2, NCH_AH_BPh), 4.16 (1H, q, *J* 6.9, C(α)*H*), 7.15–7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 16.1 (C(5)*Me*), 27.7 (*C*(3)), 29.9 (*C*(4)), 34.9 (*C*(5)), 50.8 (O*Me*), 51.6 (N*C*H_2Ph), 53.8 (*C*(1)), 57.8 (*C*(α)), 65.5 (*C*(2)), 126.2, 126.6, 127.8, 127.9, 128.0, 128.0 (*o*,*m*,*p*-*Ph*), 142.8, 143.1 (*i*-*Ph*), 173.8 (*C*O_2Me); *m*/*z* (ESI^+) 352 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{30}NO_2^+$ ($[M+H]^+$) requires 352.2271; found 352.2258.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 27



Method A (*from **17***): Grubbs I catalyst (589 mg, 0.72 mmol) was added to a degassed solution of **17** (530 mg, 1.79 mmol, >99:1 dr) in CH_2Cl_2 (71 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **27** as a colourless oil (530 mg, 85%, >99:1 dr); $[\alpha]_D^{20}$ +190.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2969 (C–H), 1734 (C=O), 1493 (C=C), 1170, 699; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 7.1, C(5)*Me*), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.83 (1H, dd, *J* 9.2, 5.6, C(1)*H*), 2.29–2.98 (1H, m, C(5)*H*), 3.38 (3H, s, O*Me*), 3.57 (1H, d, *J* 15.0, NCH_AH_BPh), 3.62 (1H, d, *J* 15.0, NCH_AH_BPh), 3.77 (1H, q, *J* 6.9, C(α)*H*), 4.41–4.44 (1H, m, C(2)*H*), 5.53–5.55 (1H, m, C(4)*H*), 5.58–5.60 (1H, m, C(3)*H*), 7.08–7.24 (8H, m, *Ph*), 7.30–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(5)*Me*), 16.4 (C(α)*Me*), 41.1 (*C*(5)), 50.1 (N*C*H_2Ph), 50.5 (*C*(1)), 51.0 (O*Me*), 57.7 (*C*(α)), 67.3 (*C*(2)), 126.5, 126.5, 127.7, 127.8, 128.1 (*o*,*m*,*p*-*Ph*), 131.7 (*C*(3)), 136.9 (*C*(4)), 141.7, 143.9 (*i*-*Ph*), 173.9 (*C*O_2Me); *m*/*z* (ESI$^+$) 350 ([M+H]$^+$, 100%), 372 ([M+Na]$^+$, 10%); HRMS (ESI$^+$) $C_{23}H_{28}NO_2^+$ ([M+H]$^+$) requires 350.2115; found 350.2118.

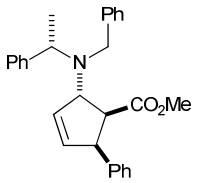
Method B (*from **11***) – *Step 1:* TMSCl (0.20 mL, 1.59 mmol) was added dropwise to a stirred solution of **11** (200 mg, 0.53 mmol) in PhMe (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 1.59 mL, 1.59 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (20 mL) and 1.0 M aq HCl (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give to give an 80:20 mixture of **13** and **14** as an orange oil (223 mg).

Method B (*from **11***) – *Step 2*: A solution of the residue of **13** and **14** (223 mg) in MeCN (2 mL) was treated sequentially with DBU (0.16 mL, 1.06 mmol) and MeI (0.07 mL, 1.17 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 2.0 M aq HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give an 80:20 mixture of **17** and **18** as an orange oil (165 mg).

Method B (*from **11***) – *Step 3*: Grubbs I catalyst (139 mg, 0.17 mmol) was added to a degassed solution of the residue of **17** and **18** (165 mg) in CH_2Cl_2 (16.5 mL) at rt and the resultant mixture was heated at 40 °C for 24

h. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. Resubjection of the crude reaction mixture to these reaction conditions twice more gave **27**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **27** as a colourless oil (107 mg, 63% from **11**, >99:1 dr); $[\alpha]_D^{20}$ +191.3 (*c* 1.0 in $CHCl_3$).

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-phenylcyclopent-3-ene-1-carboxylate 28



Method A (*from **19***): Grubbs I catalyst (121 mg, 0.15 mmol) was added to a degassed solution of **19** (167 mg, 0.37 mmol, >99:1 dr) in CH_2Cl_2 (120 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **28** as a colourless oil which solidified upon standing (122 mg, 80%, >99:1 dr); mp 72–73 °C; $[\alpha]_D^{20}$ +208.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 1728 (C=O), 1493 (C=C), 699; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.9, (C(α)*Me*), 2.78 (3H, s, O*Me*), 3.10 (1H, dd, *J* 10.3, 5.4, C(1)*H*), 3.64 (1H, d, *J* 14.8, NCH_AH_BPh), 3.72 (1H, d, *J* 14.8, NCH_AH_BPh), 3.81 (1H, q, *J* 6.9, C(α)*H*), 4.13–4.17 (1H, m, C(5)*H*), 4.62–4.64 (1H, m, C(2)*H*), 5.69 (1H, app dt, *J* 5.7, 2.2, C(4)*H*), 5.89 (1H, ddd, *J* 5.7, 2.2, 2.1, C(3)*H*), 6.91–6.93 (2H, m, *Ph*), 7.02–7.26 (11H, m, *Ph*), 7.34–7.36 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 50.1 (NCH_2Ph), 50.7 (O*Me*), 52.2 (*C*(1)), 53.4 (*C*(5)), 58.0 (*C*(α)), 67.3 (*C*(2)), 126.6, 126.6, 126.7, 127.7, 127.7, 127.9, 128.1, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 133.7 (*C*(4)), 134.7 (*C*(3)), 140.0, 141.6, 143.6 (*i*-*Ph*), 172.7 (CO_2Me); *m*/*z* (ESI^+) 412 ($[M+H]^+$, 100%), 434 ($[M+Na]^+$, 10%); HRMS (ESI^+) $C_{28}H_{29}NNaO_2^+$ ($[M+Na]^+$) requires 434.2091; found 434.2073.

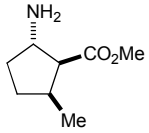
Method B (*from **12***) – *Step 1:* TMSCl (0.17 mL, 1.37 mmol) was added dropwise to a stirred solution of **12** (200 mg, 0.45 mmol) in PhMe (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 1.37 mL, 1.37 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (20 mL) and 1.0 M aq HCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give to give a 76:24 mixture of **15** and **16** as an orange oil (199 mg).

Method B (*from **12***) – *Step 2*: A solution of the residue of **15** and **16** (199 mg) in MeCN (2 mL) was treated sequentially with DBU (0.14 mL, 0.91 mmol) and MeI (0.06 mL, 1.00 mmol) at rt. The reaction mixture was

stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 2.0 M aq HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give a 76:24 mixture of **19** and **20** as an orange oil (237 mg).

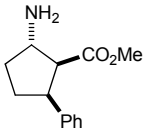
Method B (*from* ***12***) – *Step 3*: Grubbs I catalyst (82 mg, 0.10 mmol) was added to a degassed solution of the residue of **19** and **20** (237 mg) in CH_2Cl_2 (20 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The resultant mixture was allowed to cool to rt and concentrated *in vacuo*. Resubjection of the crude reaction mixture to these reaction conditions twice more gave **28**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **28** as a colourless oil (96 mg, 51% from **12**, >99:1 dr).

Methyl (*S*,*S*,*S*)-2-amino-5-methylcyclopentane-1-carboxylate 29



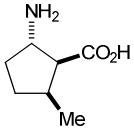
$Pd(OH)_2/C$ (250 mg, 50% w/w by substrate) was added to a degassed solution of **27** (500 mg, 1.43 mmol, >99:1 dr) in MeOH (36 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 98:2) gave **29** as a white solid (188 mg, 83%, >99:1 dr); mp 65–67 °C; $[\alpha]_D^{20}$ +52.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2962 (C–H), 1732 (C=O), 1484; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 7.2, C(5)*Me*), 1.22–1.33 (2H, m, C(4)H_2), 1.53 (2H, br s, NH_2), 1.84–1.96 (1H, m, C(3)H_A), 1.99–2.09 (1H, m, C(3)H_B), 2.38–2.49 (2H, m, C(1)*H*, C(5)*H*), 3.56–3.65 (1H, m, C(2)*H*), 3.63 (3H, s, O*Me*); δ_C (125 MHz, $CDCl_3$) 17.5 (C(5)*Me*), 32.0 (*C*(4)), 34.1 (*C*(3)), 35.4 (*C*(5)), 51.3 (O*Me*), 54.2 (*C*(2)), 58.0 (*C*(1)), 174.4 (*C*O_2Me); *m*/*z* (ESI^+) 158 ($[M+H]^+$, 100%), 180 ($[M+Na]^+$, 5%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1175.

Methyl (*S*,*S*,*S*)-2-amino-5-phenylcyclopentane-1-carboxylate 30



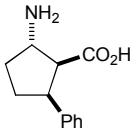
$Pd(OH)_2/C$ (300 mg, 50% w/w by substrate) was added to a degassed solution of **28** (600 mg, 1.47 mmol, >99:1 dr) in MeOH (42 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **30** as a white solid (277 mg, 87%, >99:1 dr); mp 56–60 °C; $[\alpha]_D^{20}$ −15.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2950 (C–H), 1728 (C=O), 1206; δ_H (400 MHz, $CDCl_3$) 1.46–1.56 (3H, m, C(3)H_A, NH_2), 1.98–2.08 (1H, m, C(4)H_A), 2.16–2.22 (1H, m, C(4)H_B), 2.23–2.33 (1H, m, C(3)H_B), 2.85 (1H, dd, *J* 10.0, 7.5, C(1)*H*), 3.24 (3H, s, O*Me*), 3.63–3.69 (1H, m, C(5)*H*), 3.83–3.89 (1H, m, C(2)*H*), 7.14–7.19 (3H, m, *Ph*), 7.24–7.27 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.7 (*C*(3)), 34.9 (*C*(4)), 47.1 (*C*(5)), 51.0 (O*Me*), 55.0 (*C*(2)), 59.5 (*C*(1)), 126.4, 127.9, 128.0 (*o*,*m*,*p*-*Ph*), 142.1 (*i*-*Ph*), 173.6 (*C*O_2Me); *m*/*z* (ESI$^+$) 220 ($[M+H]^+$, 100%), 242 ($[M+Na]^+$, 5%); HRMS (ESI$^+$) $C_{13}H_{17}NNaO_2^+$ ($[M+Na]^+$) requires 242.1151; found 242.1154.

(*S*,*S*,*S*)-2-Amino-5-methylcyclopentane-1-carboxylic acid 31



A stirred solution of **29** (50 mg, 0.32 mmol, >99:1 dr) in 6.0 M aq HCl (7 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **31** as a white solid (48 mg, 84%, >99:1 dr); mp 214–219 °C (dec.); $[\alpha]_D^{20}$ +67.0 (*c* 1.0 in H_2O); ν_{max} (ATR) 3428 (N–H), 2970 (C–H), 1739 (C=O), 1576; δ_H (400 MHz, D_2O) 0.76 (3H, d, *J* 7.3, C(5)*Me*), 1.26–1.35 (1H, m, C(4)H_A), 1.44–1.53 (1H, m, C(3)H_A), 1.84–1.92 (1H, m, C(4)H_B), 2.08–2.17 (1H, m, C(3)H_B), 2.32–2.42 (1H, m, C(5)*H*), 2.61 (1H, app t, *J* 8.2, C(1)*H*), 3.73 (1H, app q, *J* 8.1, C(2)*H*); δ_C (100 MHz, D_2O) 16.3 (C(5)*Me*), 29.1 (*C*(4)), 31.6 (*C*(3)), 35.6 (*C*(5)), 53.8 (*C*(2)), 56.2 (*C*(1)), 179.7 (*C*O_2H); *m*/*z* (ESI$^+$) 144 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_7H_{14}NO_2^+$ ($[M+H]^+$) requires 144.1019; found 144.1023.

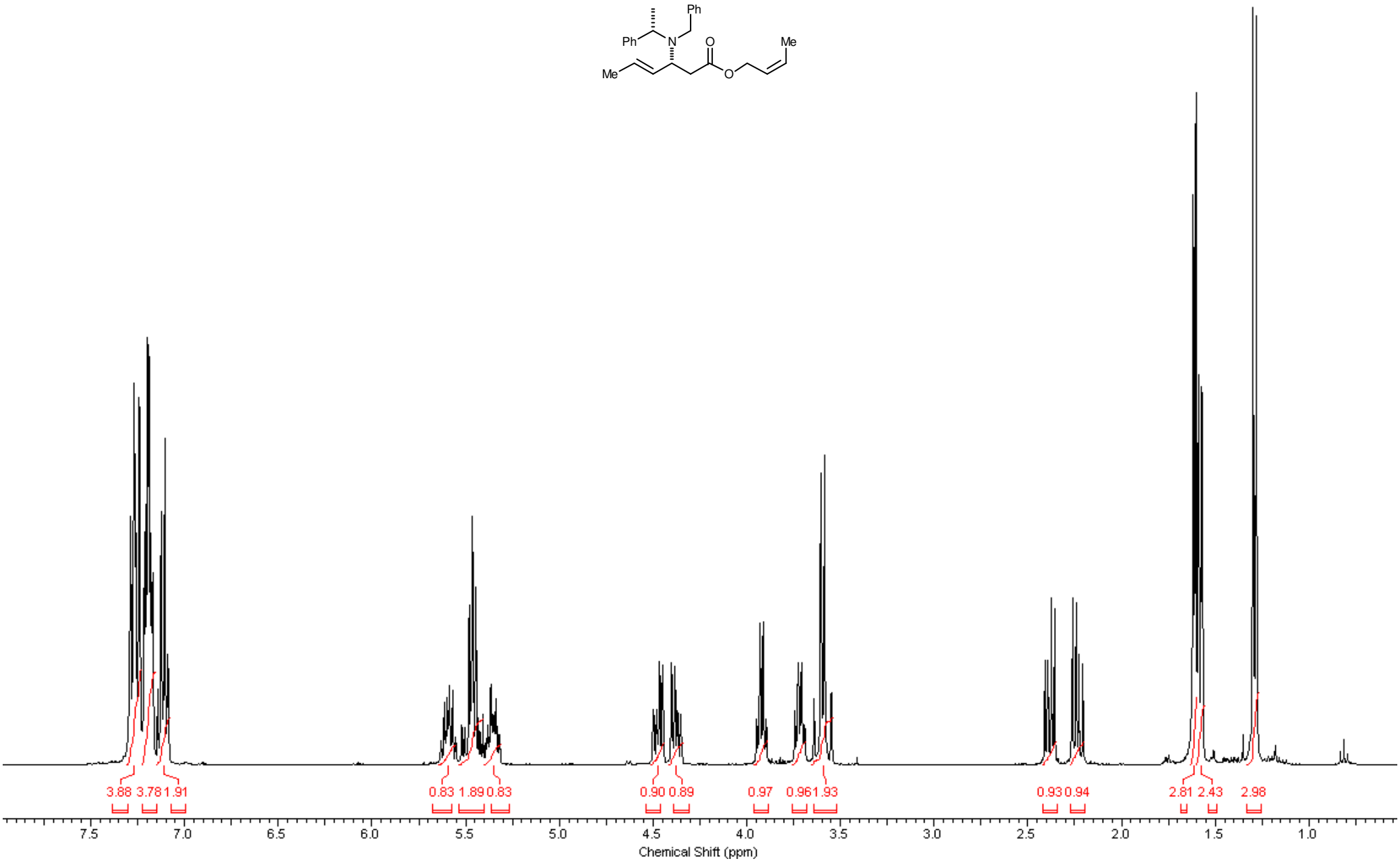
(*S*,*S*,*S*)-2-Amino-5-phenylcyclopentane-1-carboxylic acid 32



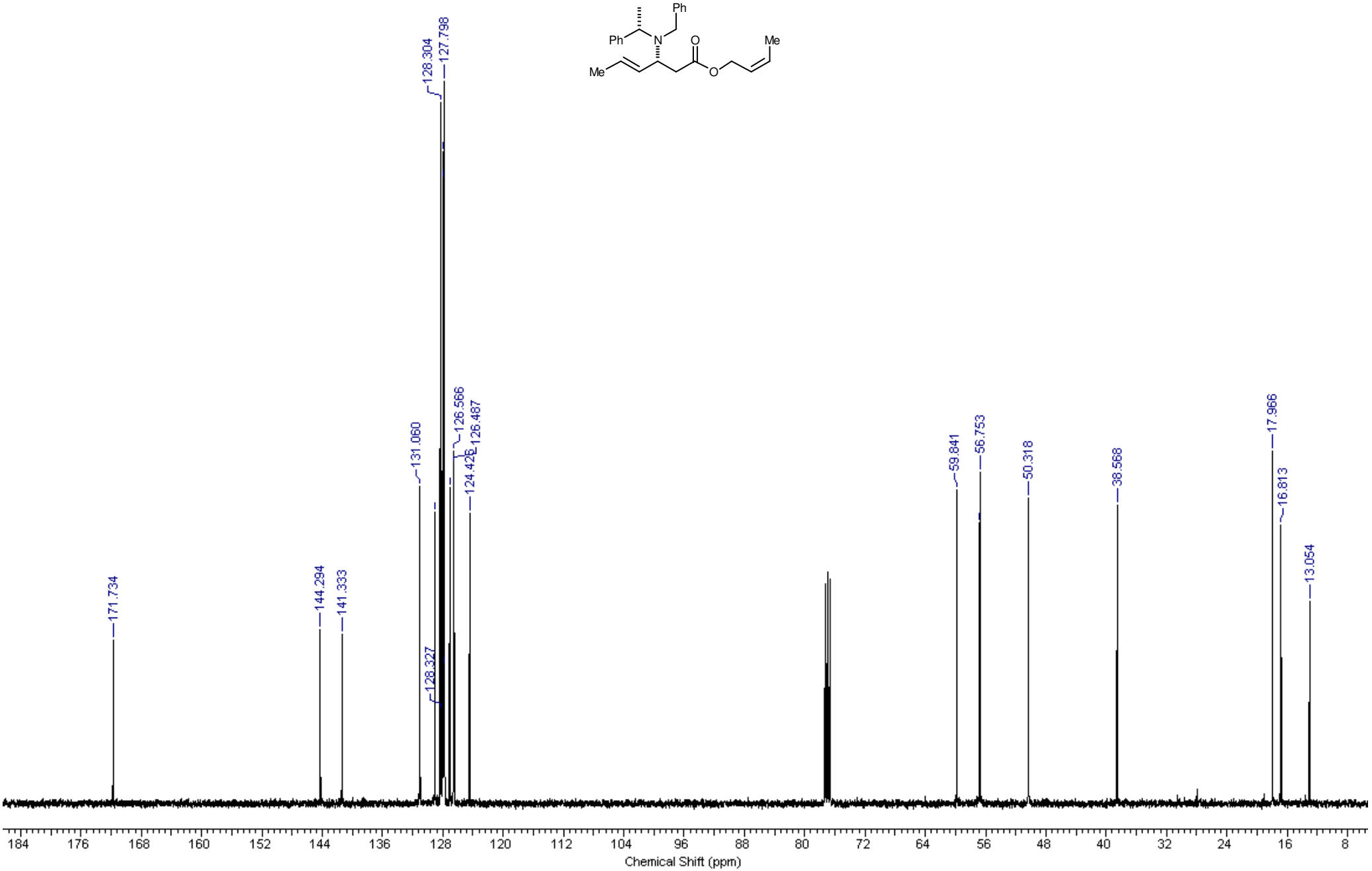
A stirred solution of **30** (161 mg, 0.74 mmol, >99:1 dr) in 6.0 M aq HCl (23 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (3 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **32** as a white solid (134 mg, 89%, >99:1 dr); mp 215–218 °C (dec.); $[\alpha]_D^{20}$ +17.5 (*c* 0.5 in H_2O); ν_{max} (ATR) 3469, 3030 (N–H), 2944 (C–H), 1567, 700; δ_H (400 MHz, D_2O) 1.61–1.71 (1H, m, C(3)H_A), 1.89–1.98 (1H, m, C(4)H_A), 2.11–2.20 (1H, m, C(4)H_B), 2.29–2.37 (1H, m, C(3)H_B), 2.94–2.98 (1H, m, C(1)*H*), 3.53–3.59 (1H, m, C(5)*H*), 3.90 (1H, app q, *J* 8.3, C(2)*H*), 7.11–7.27 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 29.4 (*C*(3)), 30.1 (*C*(4)), 46.4 (*C*(5)), 53.9 (*C*(2)), 56.7 (*C*(1)), 126.7, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 141.8 (*i*-*Ph*), 177.9 (*C*O_2H); *m*/*z* (ESI$^+$) 206 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{15}NNaO_2^+$ ([M+Na]$^+$) requires 228.0995; found 228.0994.

2. Copies of ^{1}H and ^{13}C NMR spectra

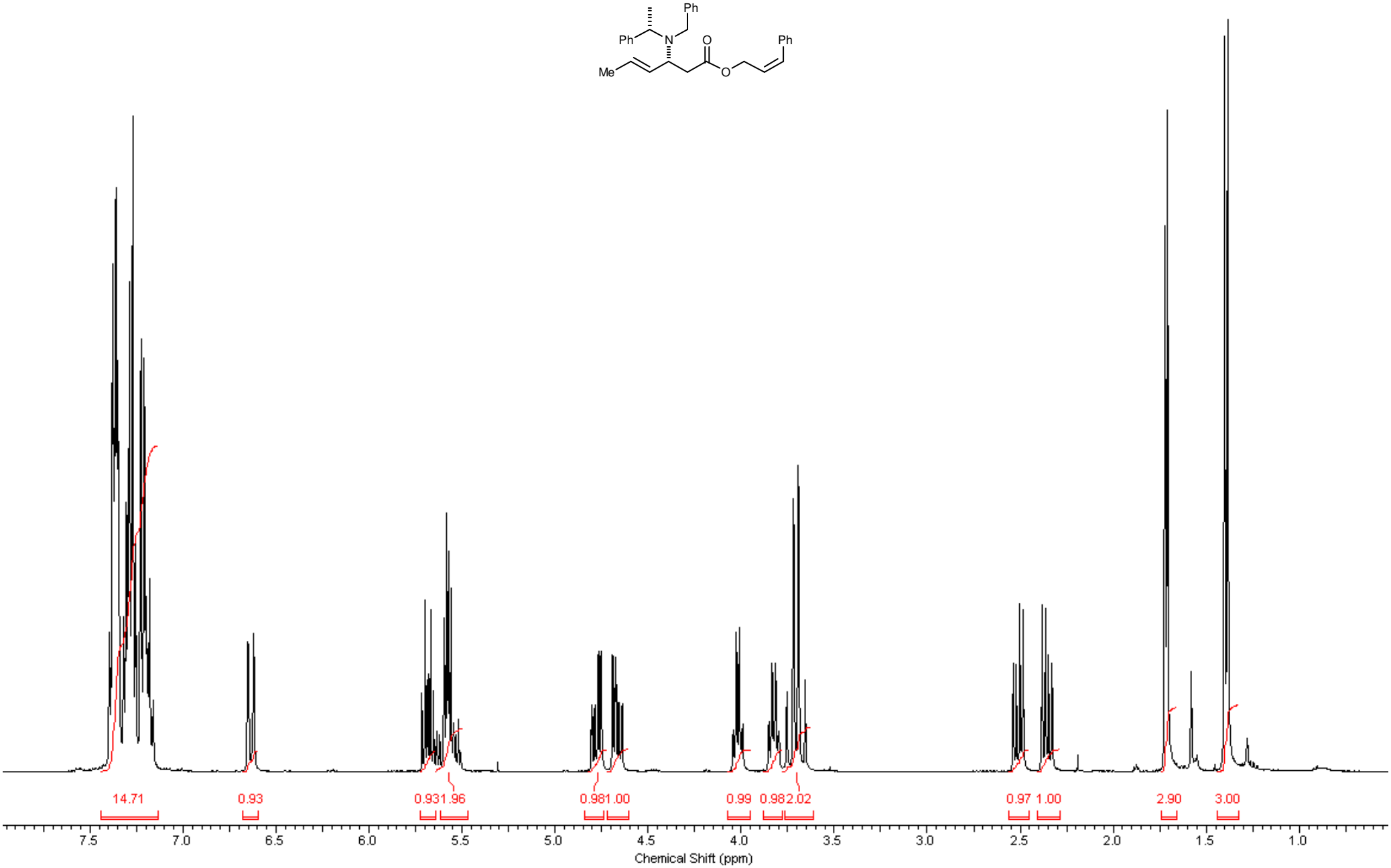
(*Z*)-But-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 11 (400 MHz ^{1}H, $CDCl_3$)



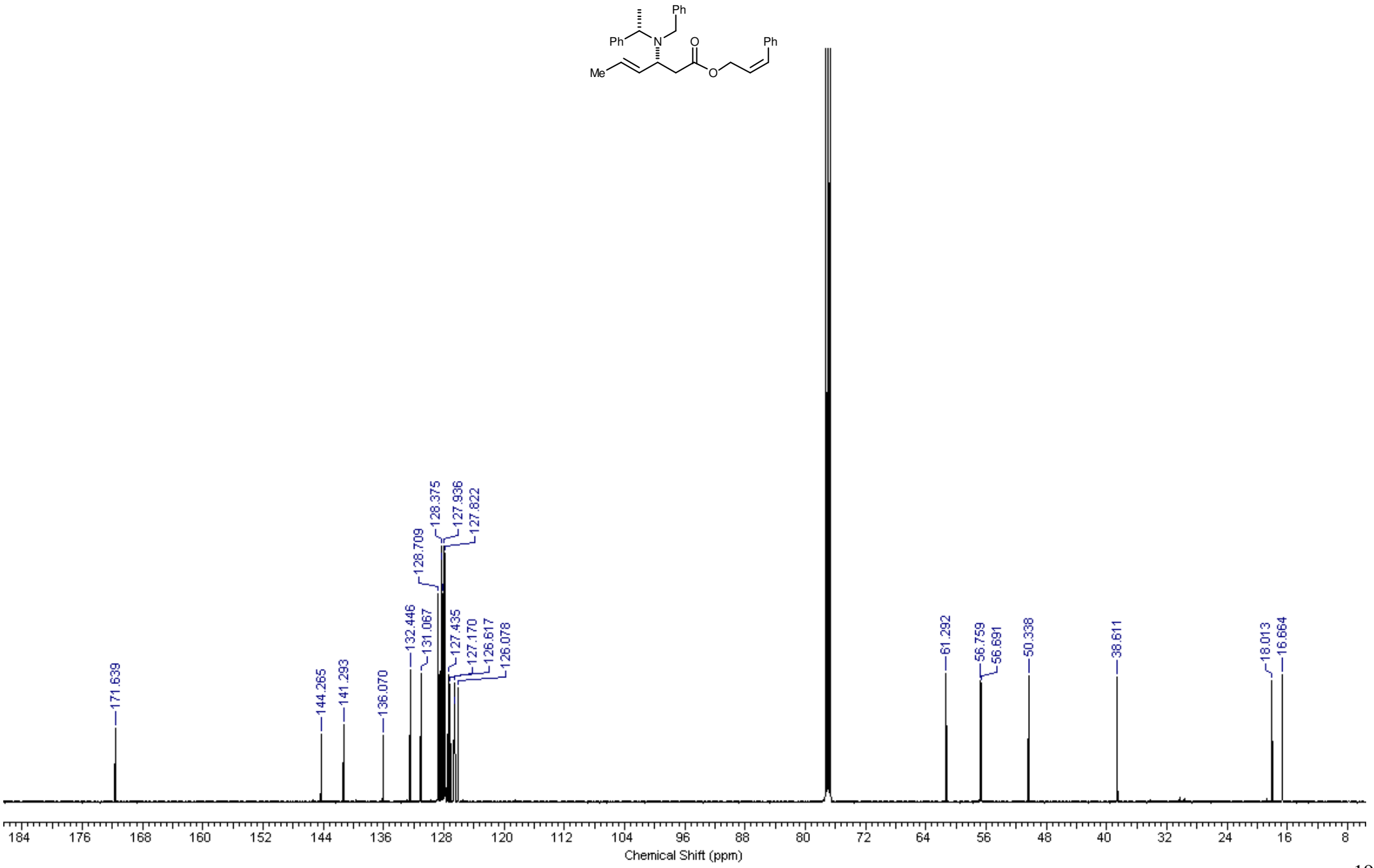
(*Z*)-But-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 11 (100 MHz ^{13}C, $CDCl_3$)



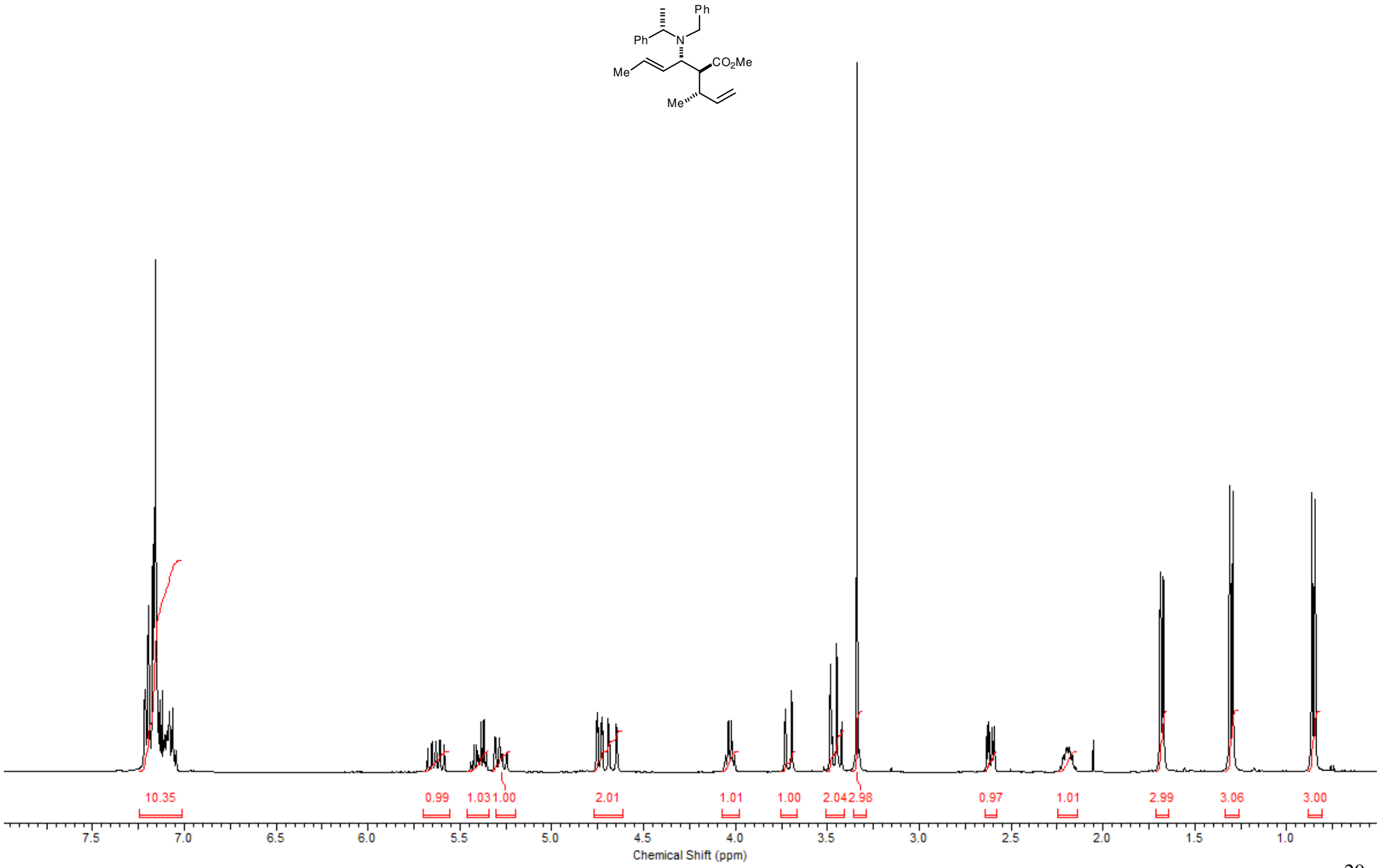
(*Z*)-3'-Phenylprop-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 12 (400 MHz ^{1}H, $CDCl_3$)



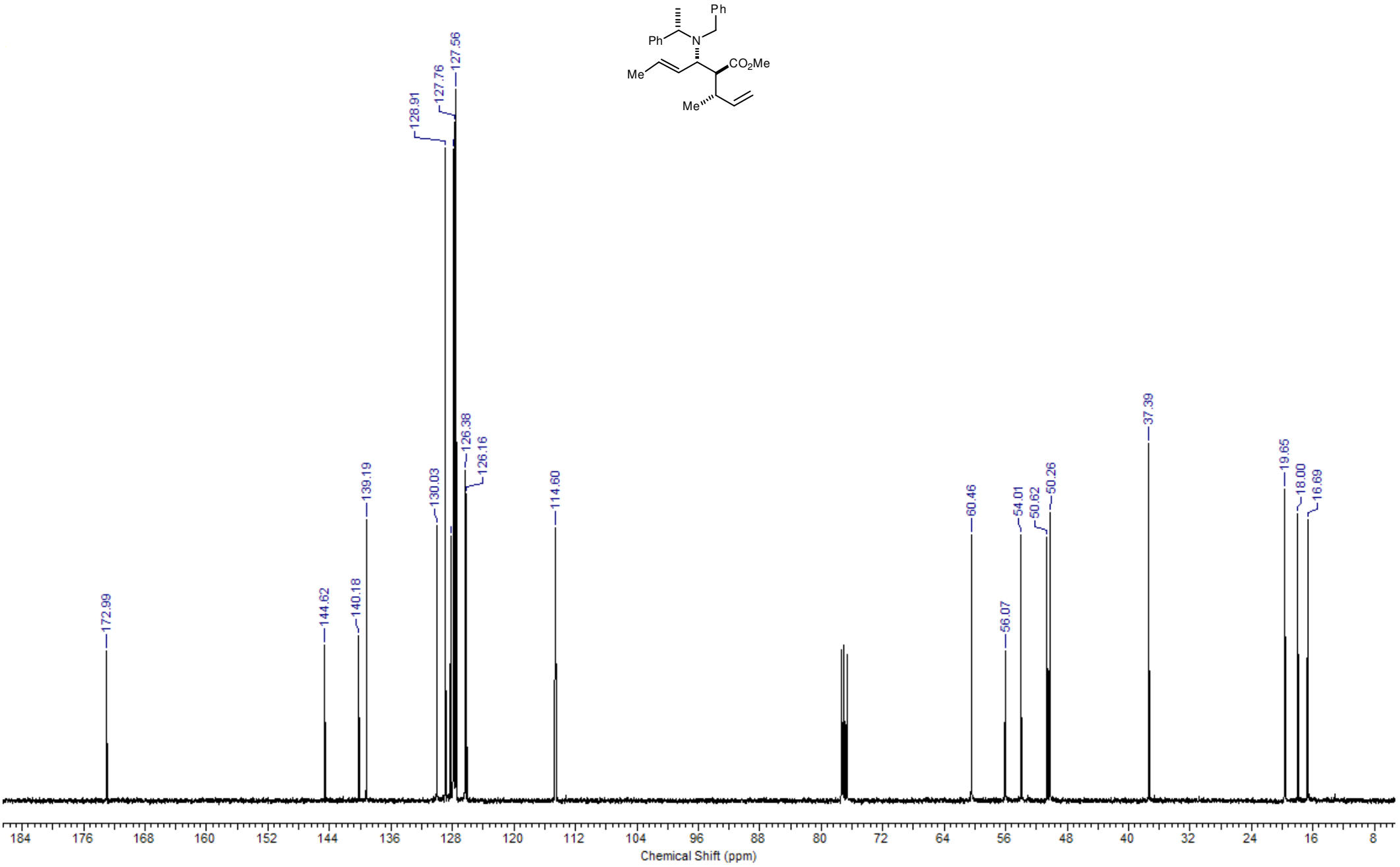
(*Z*)-3'-Phenylprop-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 12 (125 MHz ^{13}C, $CDCl_3$)



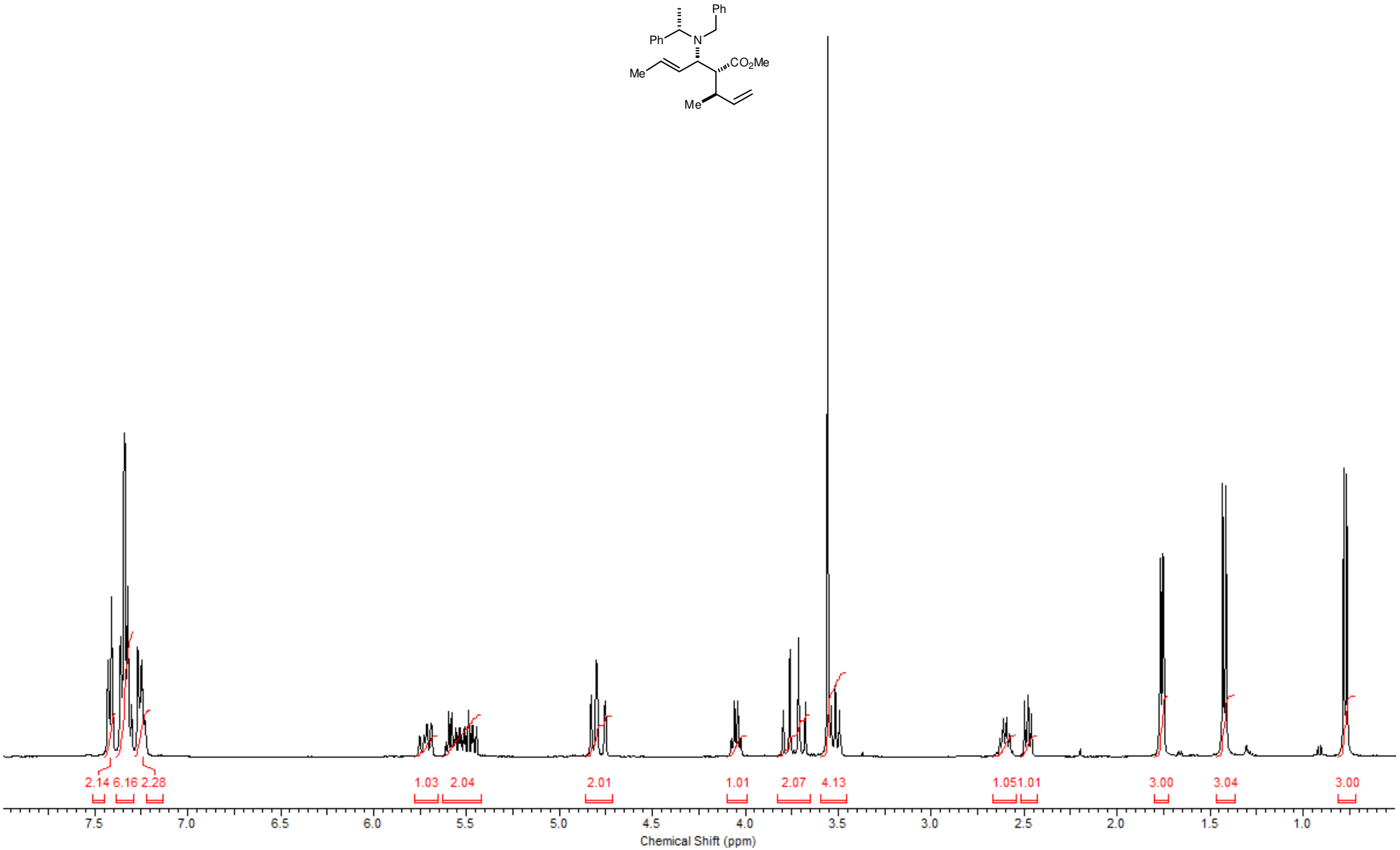
Methyl (*S*,*S*,*S*,*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 17 (400 MHz ^{1}H, $CDCl_3$)



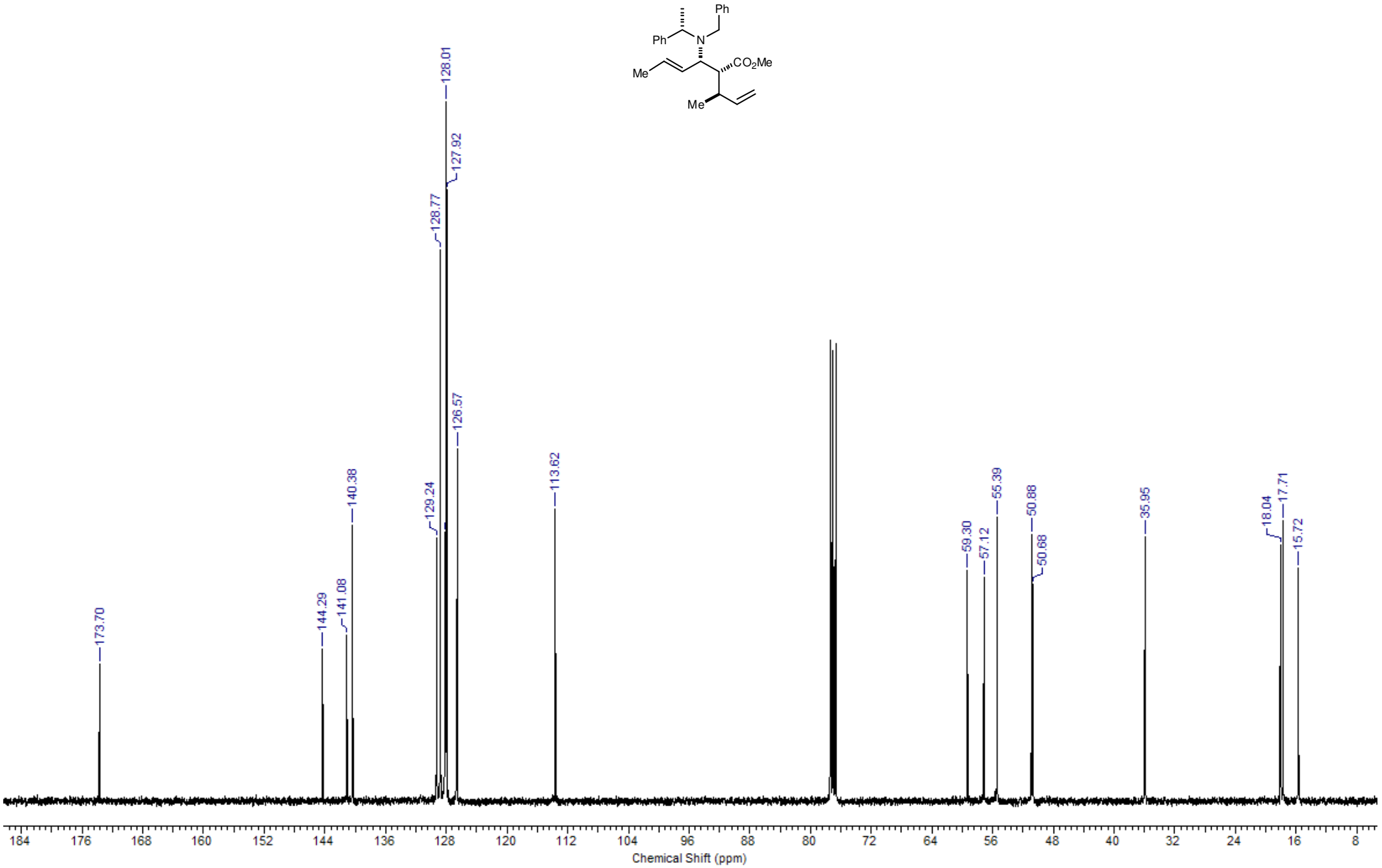
Methyl (*S*,*S*,*S*,*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 17 (100 MHz ^{13}C, $CDCl_3$)



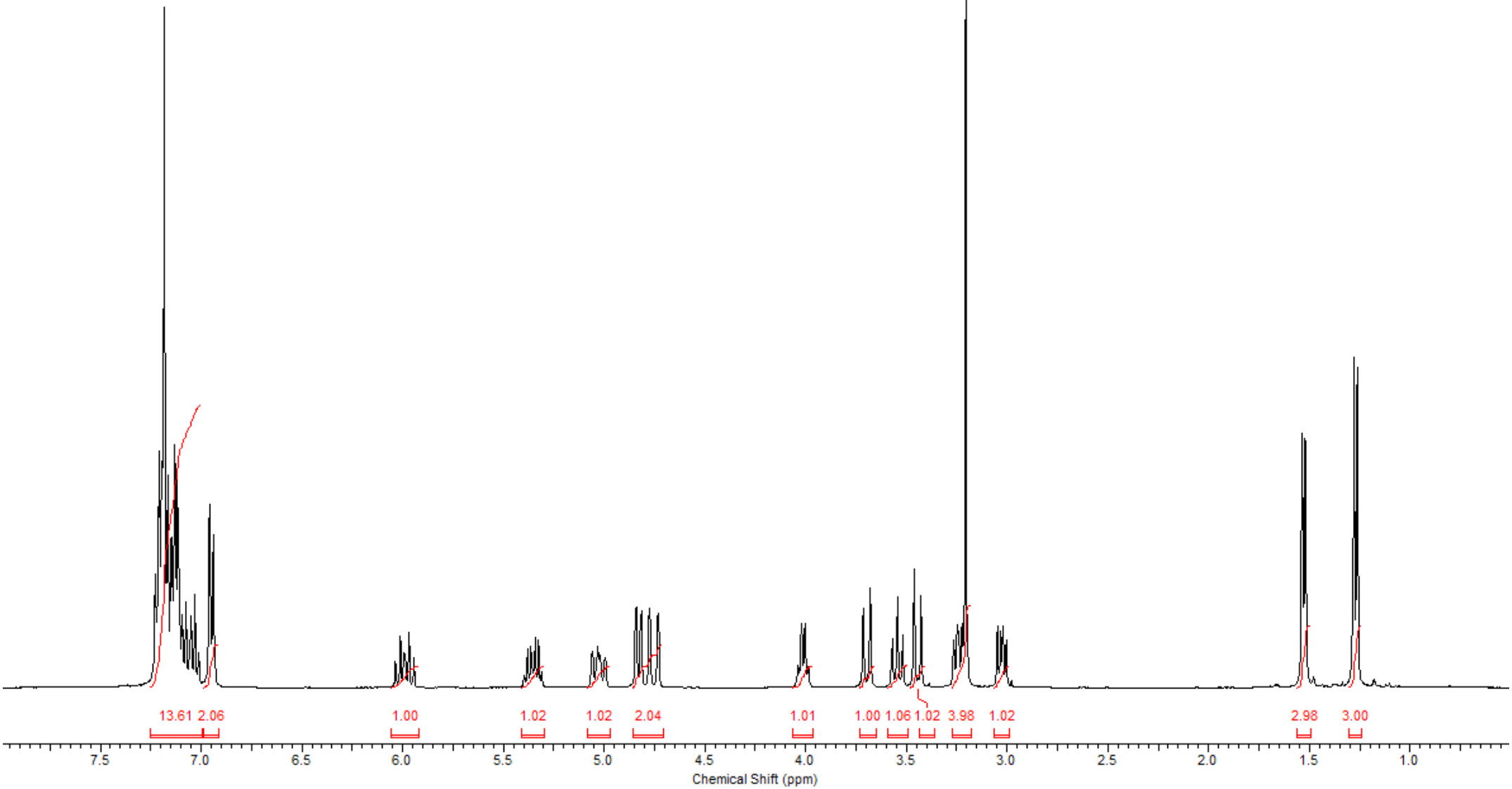
Methyl (2*R*,3*S*,1'*R*,α*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 18 (400 MHz ^{1}H, $CDCl_3$)



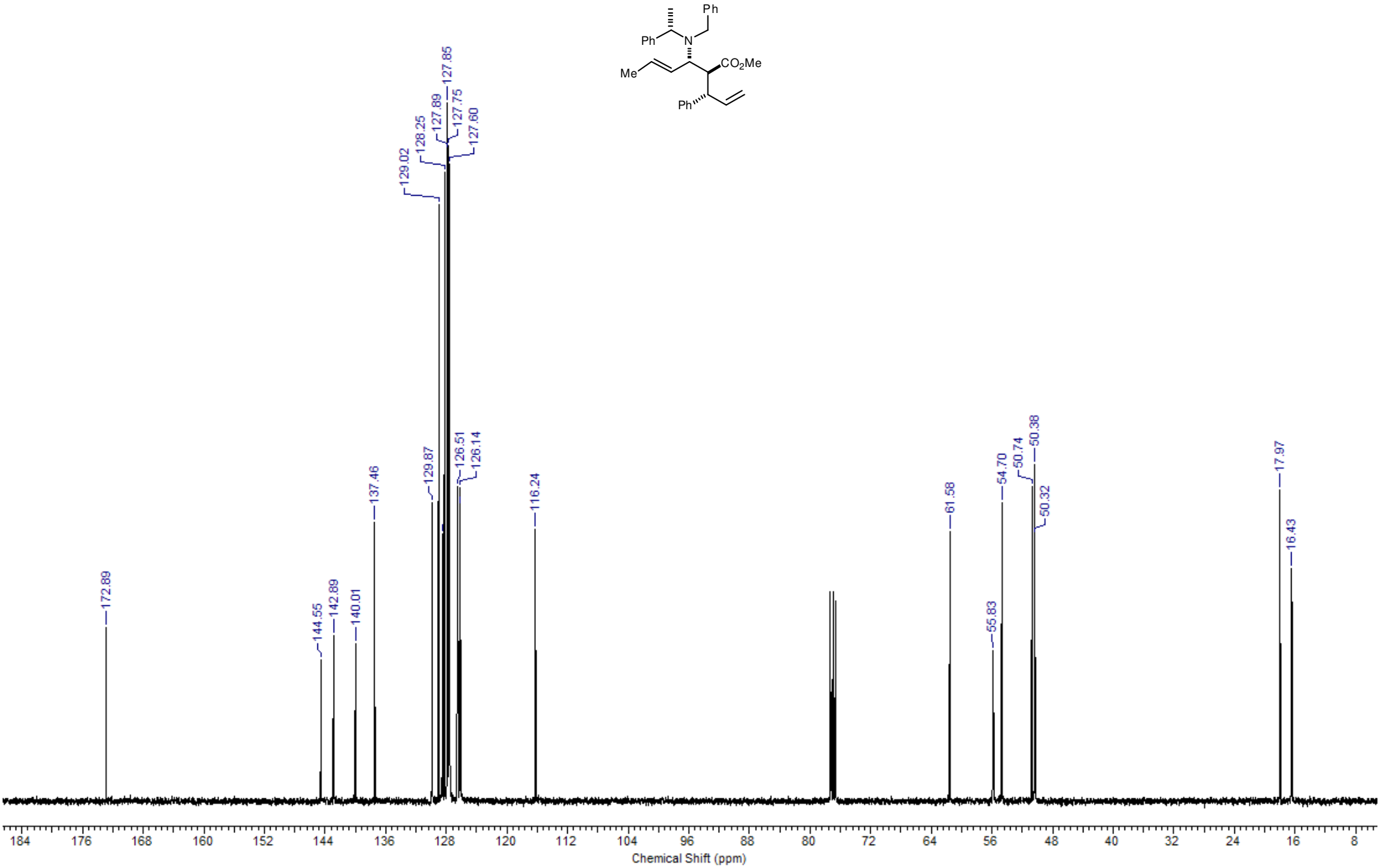
Methyl (2*R*,3*S*,1'*R*,α*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 18 (100 MHz ^{13}C, $CDCl_3$)



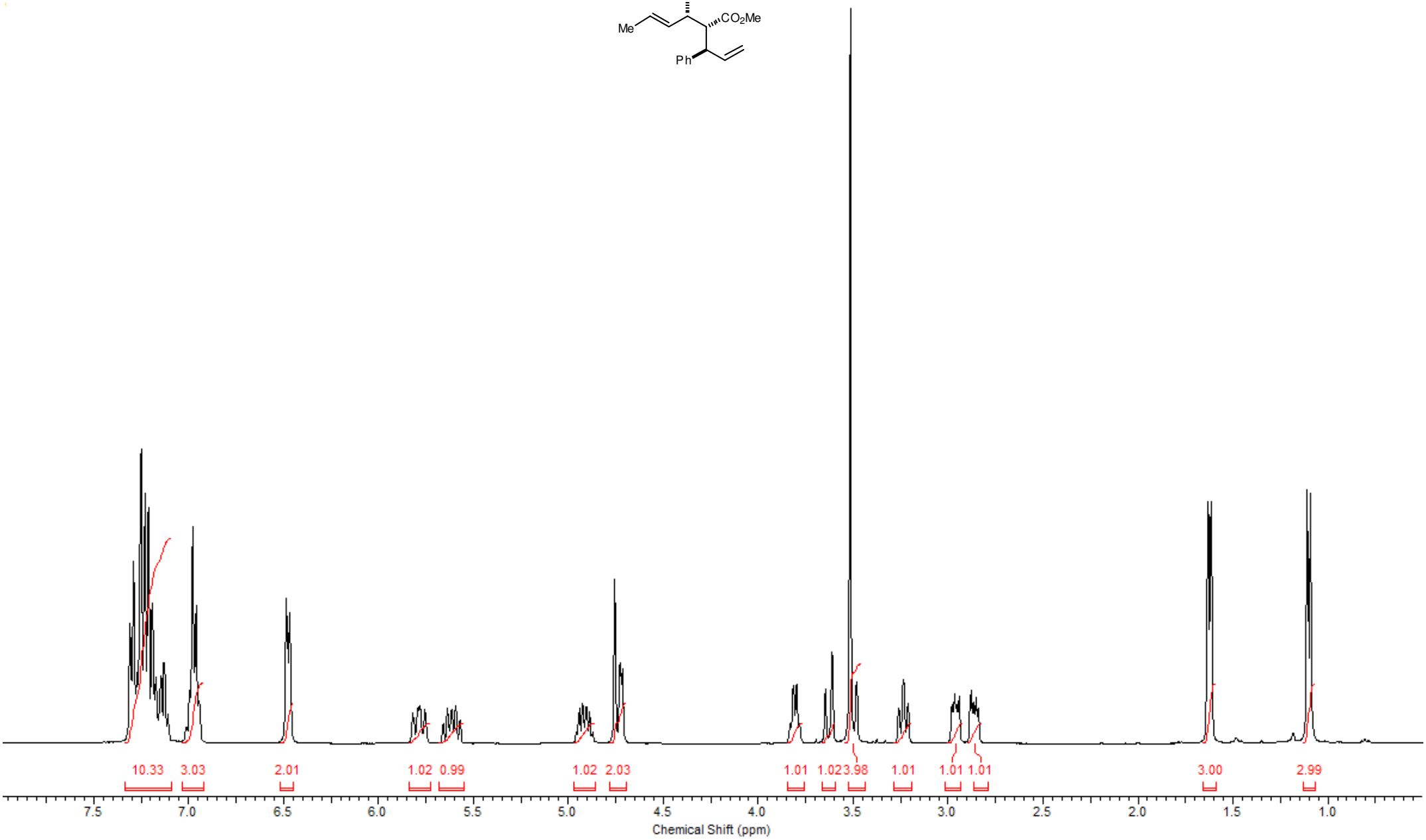
Methyl (*S*,*S*,*S*,*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 19 (400 MHz ^{1}H, $CDCl_3$)



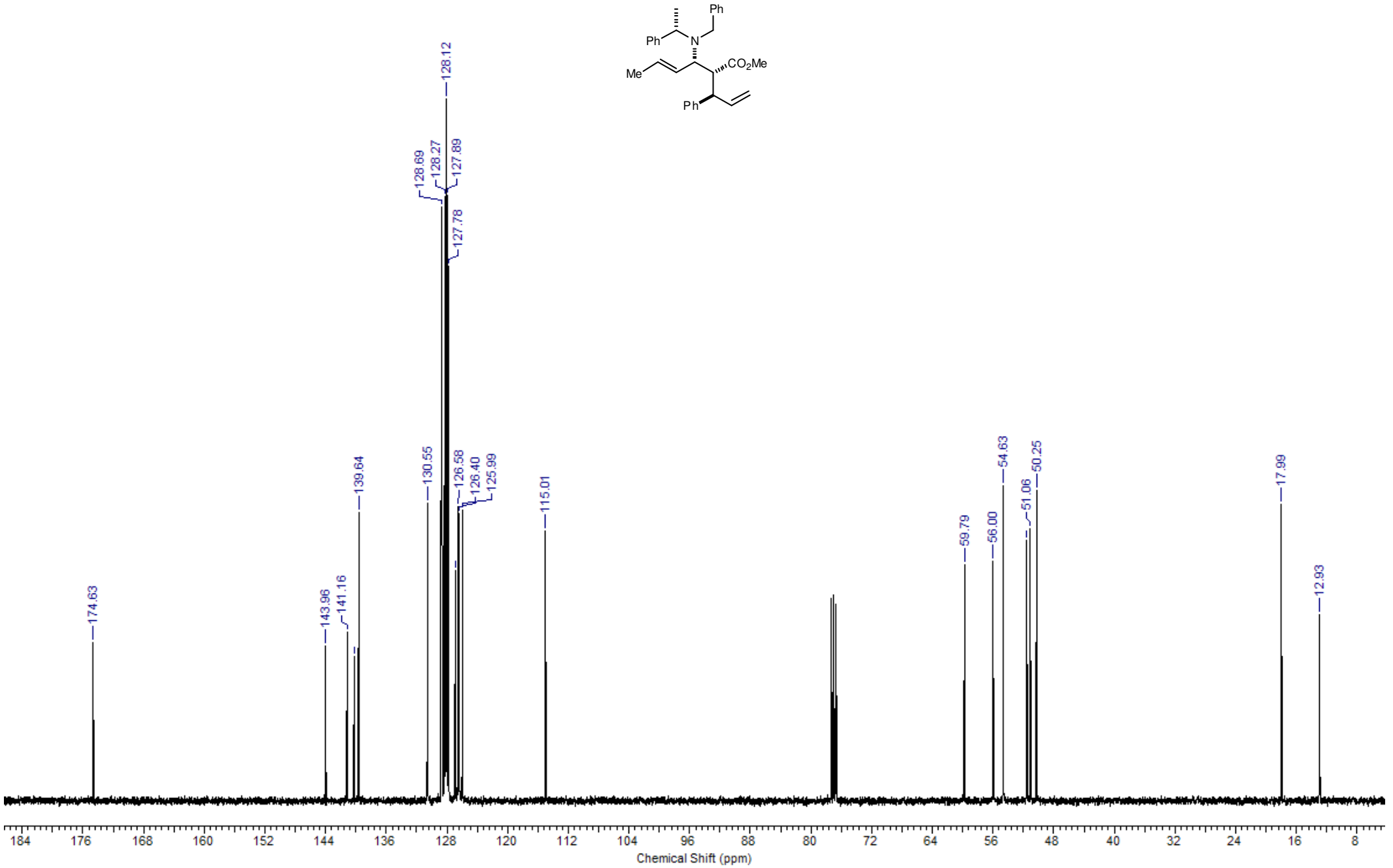
Methyl (*S*,*S*,*S*,*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 19 (100 MHz ^{13}C, $CDCl_3$)



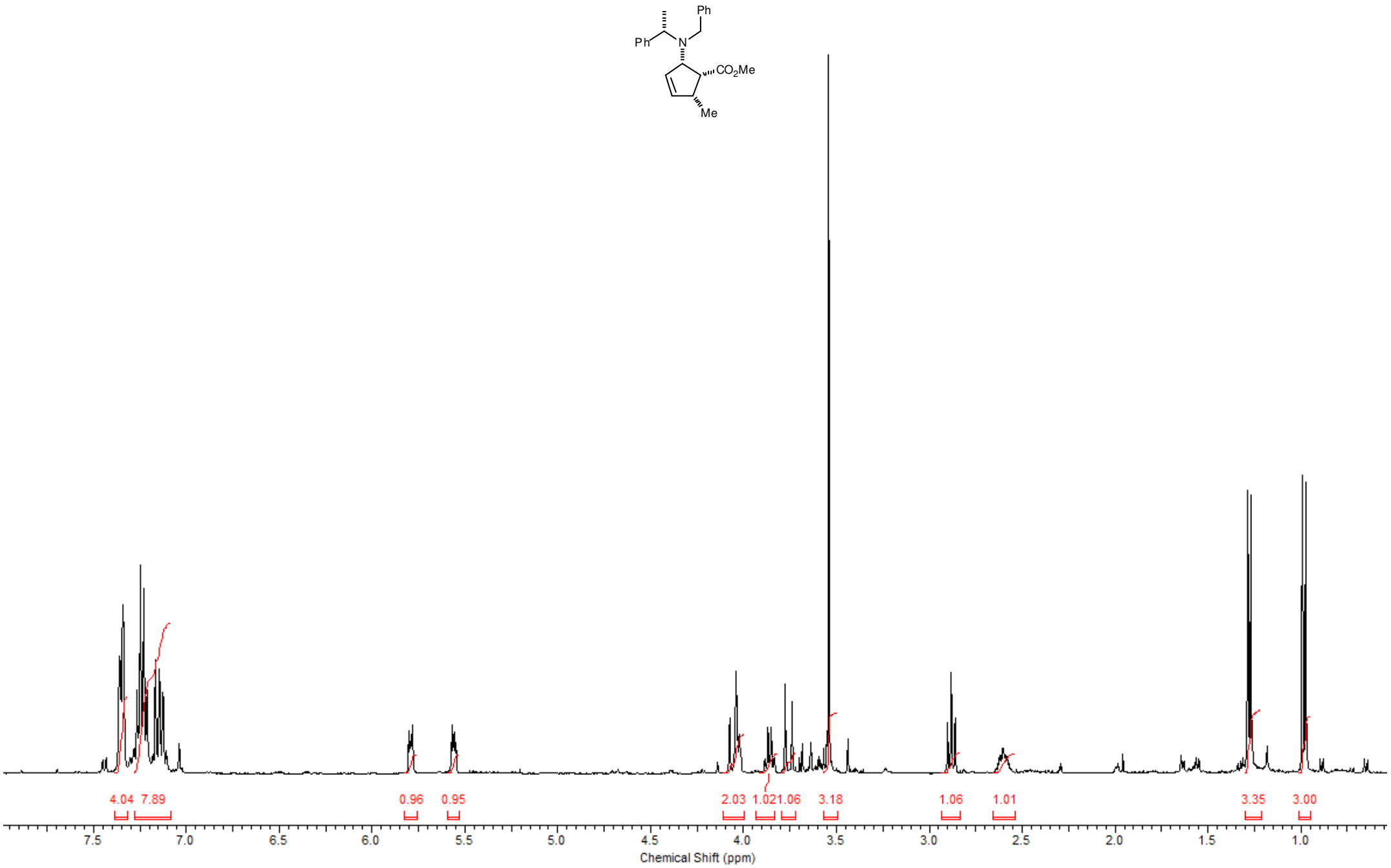
Methyl (2*R*,3*S*,1'*R*,α*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 20 (400 MHz ^{1}H, $CDCl_3$)



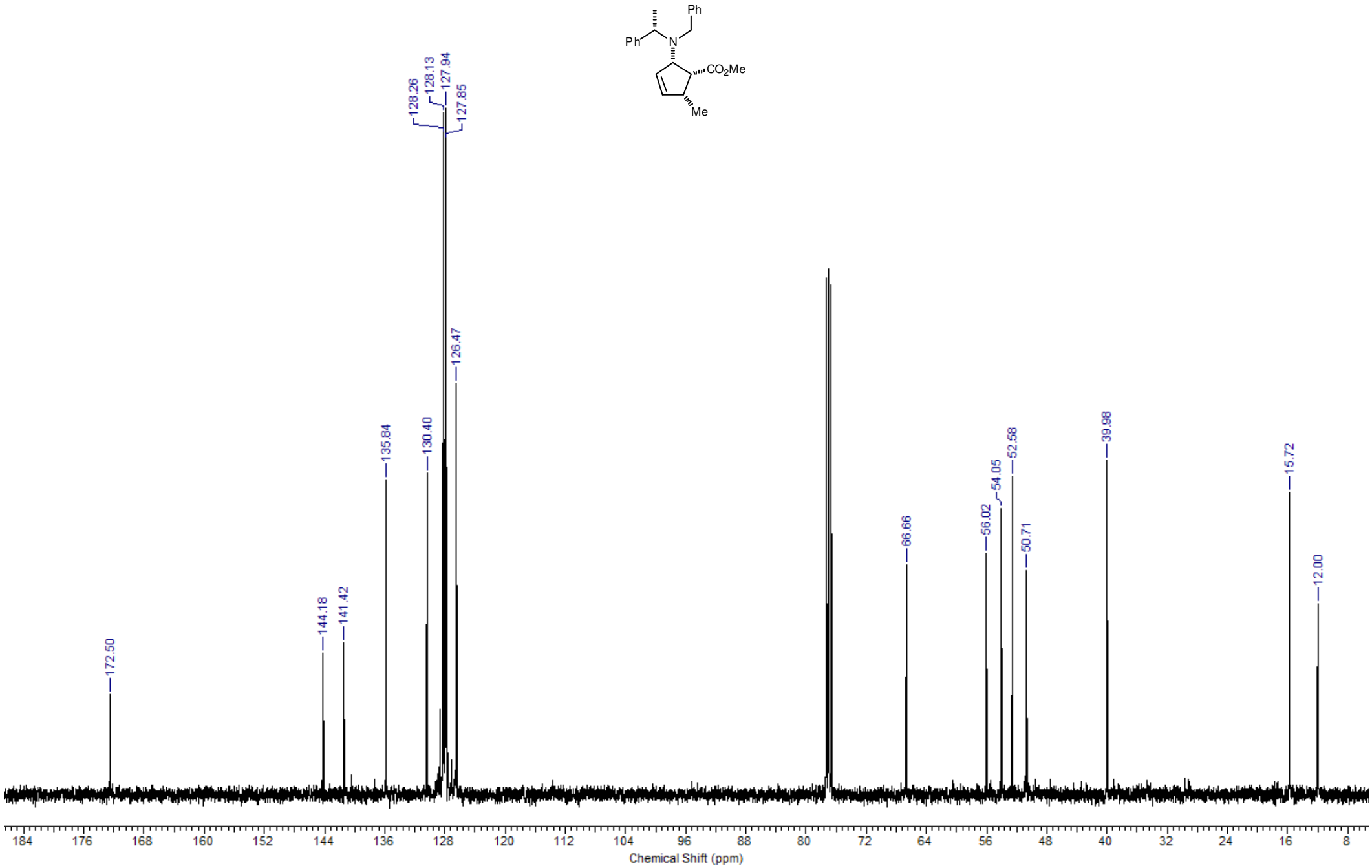
Methyl (2*R*,3*S*,1'*R*,α*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 20 (100 MHz ^{13}C, $CDCl_3$)



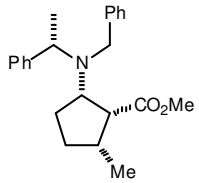
Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 25 (400 MHz ^{1}H, $CDCl_3$)

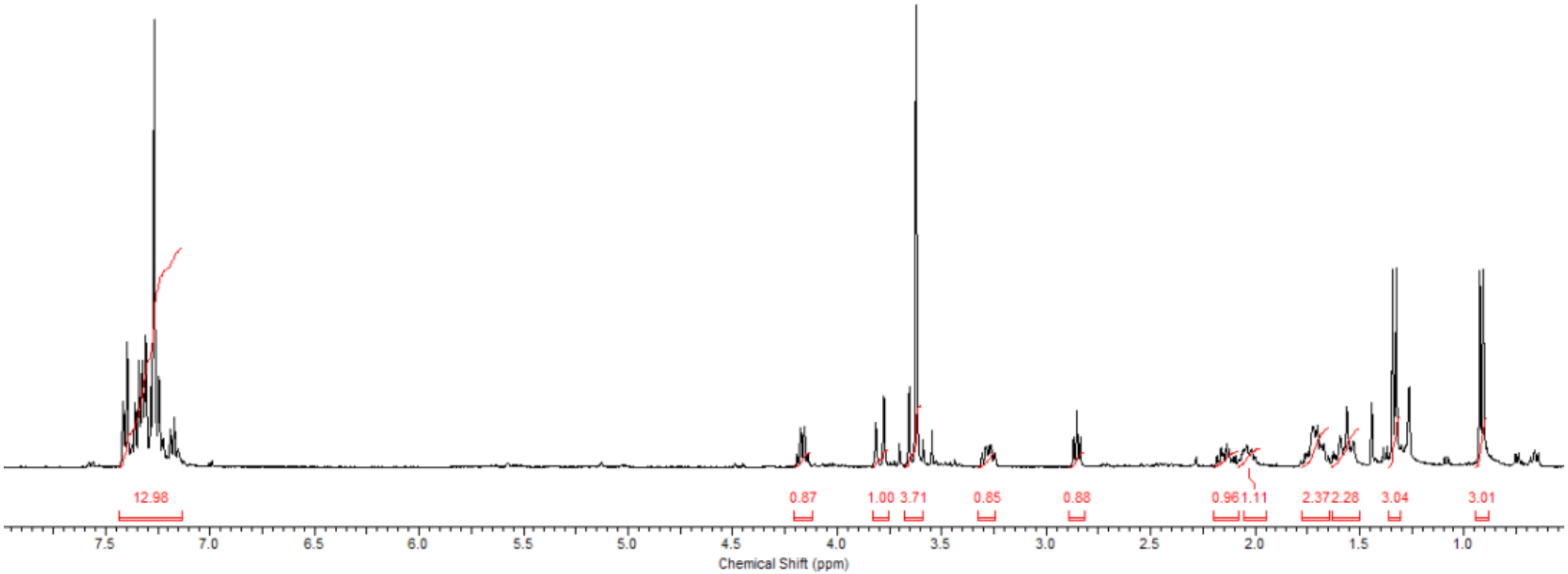


Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 25 (100 MHz ^{13}C, $CDCl_3$)

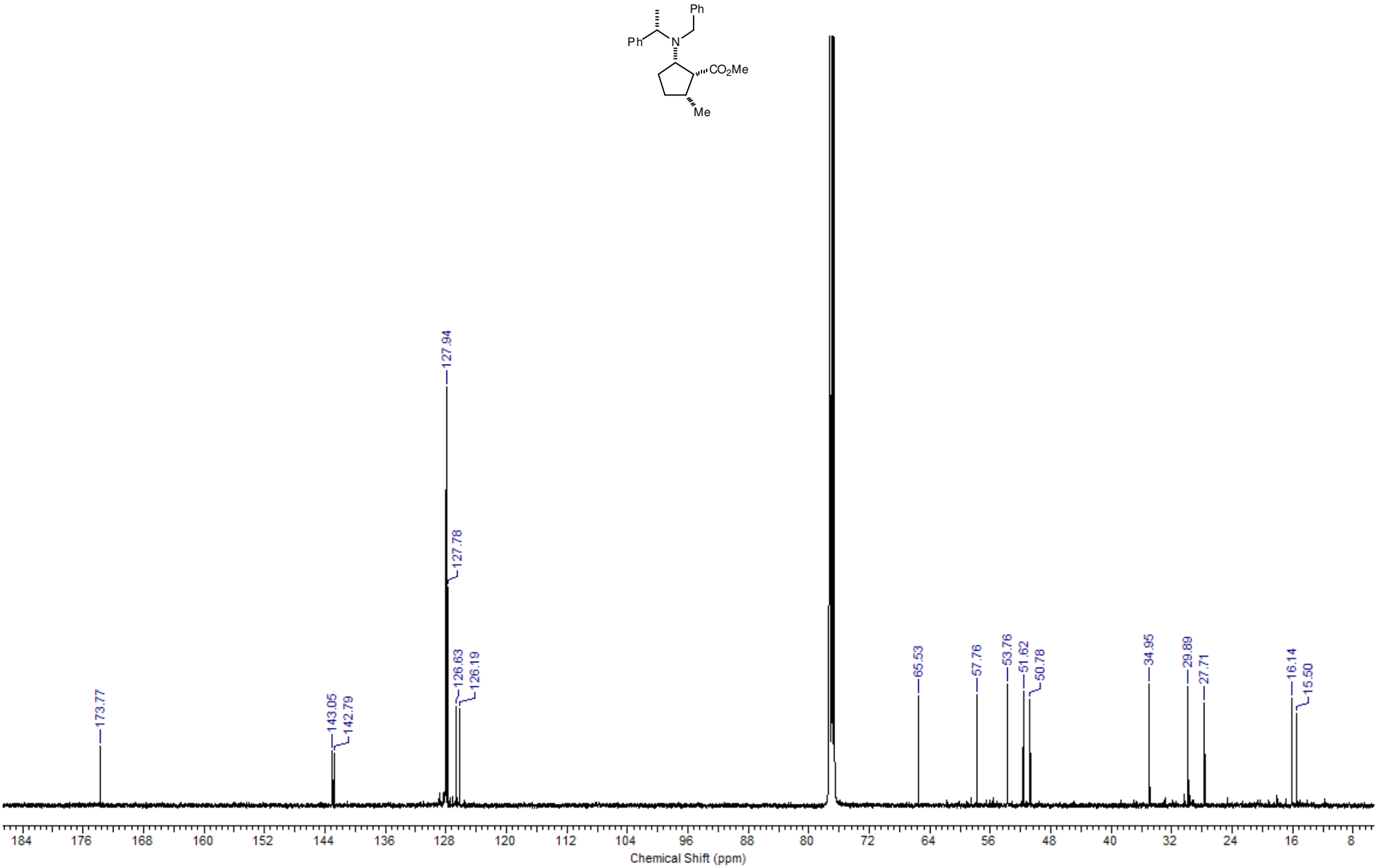


Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopentane-1-carboxylate 26 (400 MHz ^{1}H, $CDCl_3$)

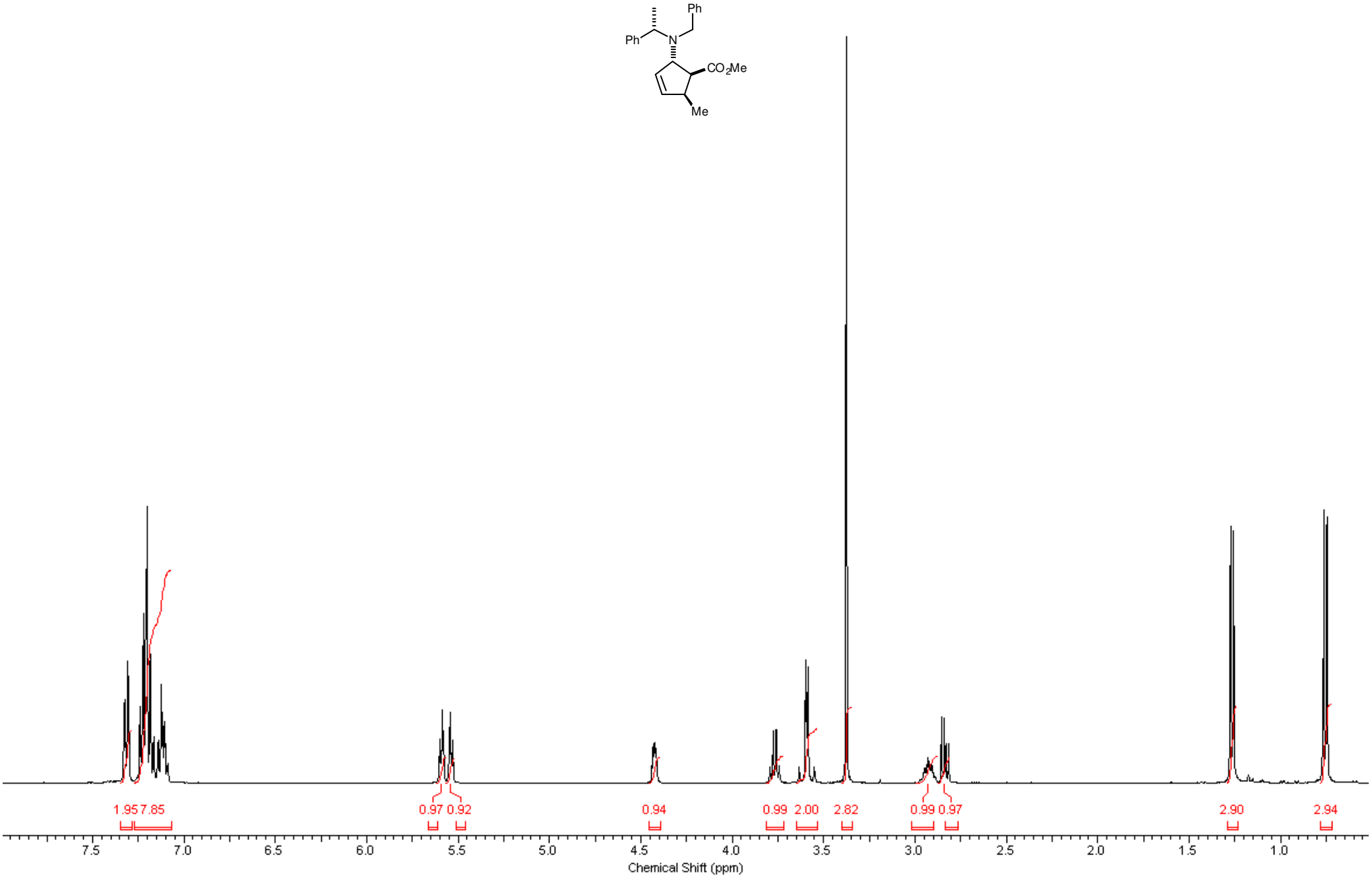




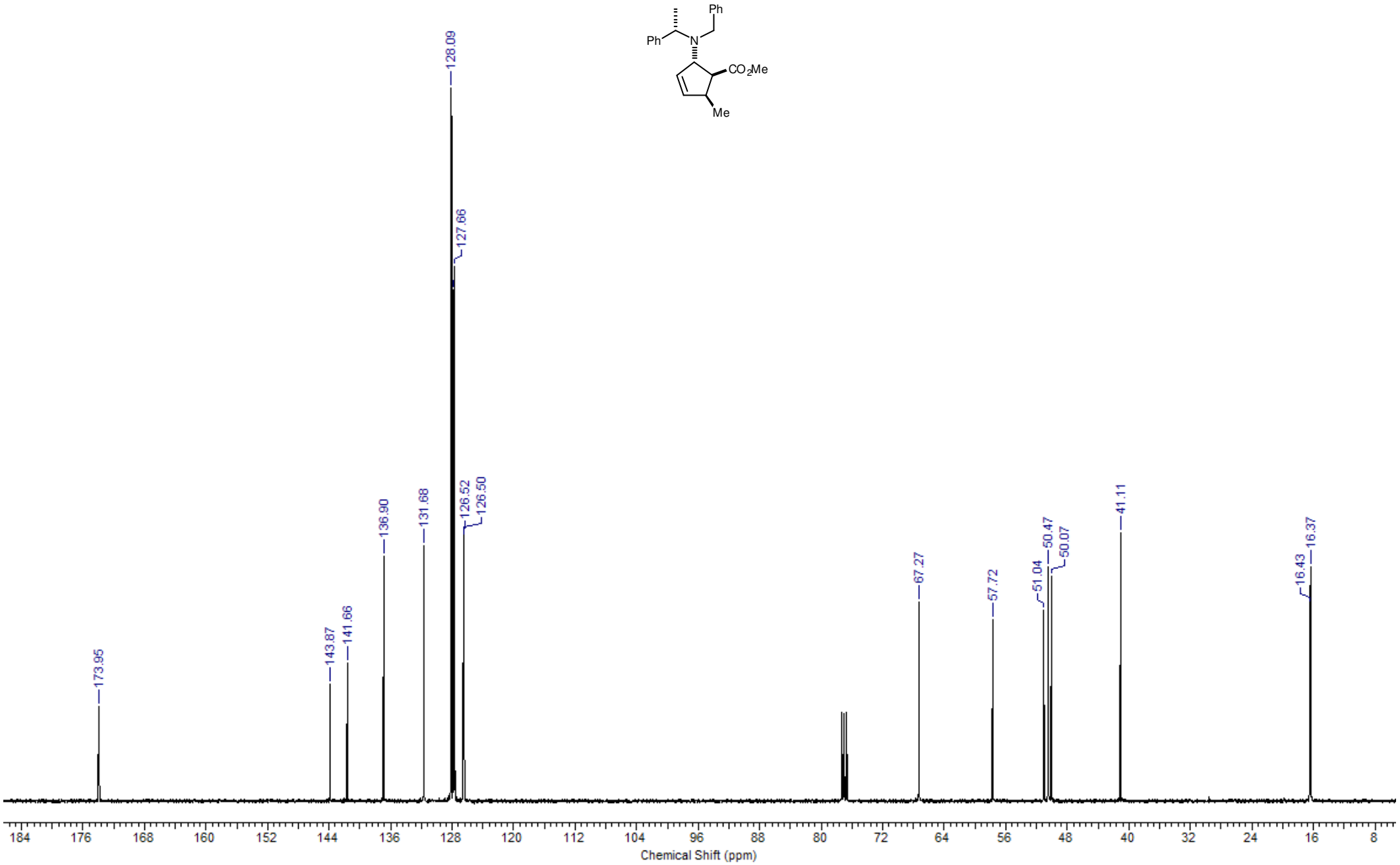
Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopentane-1-carboxylate 26 (125 MHz ^{13}C, $CDCl_3$)



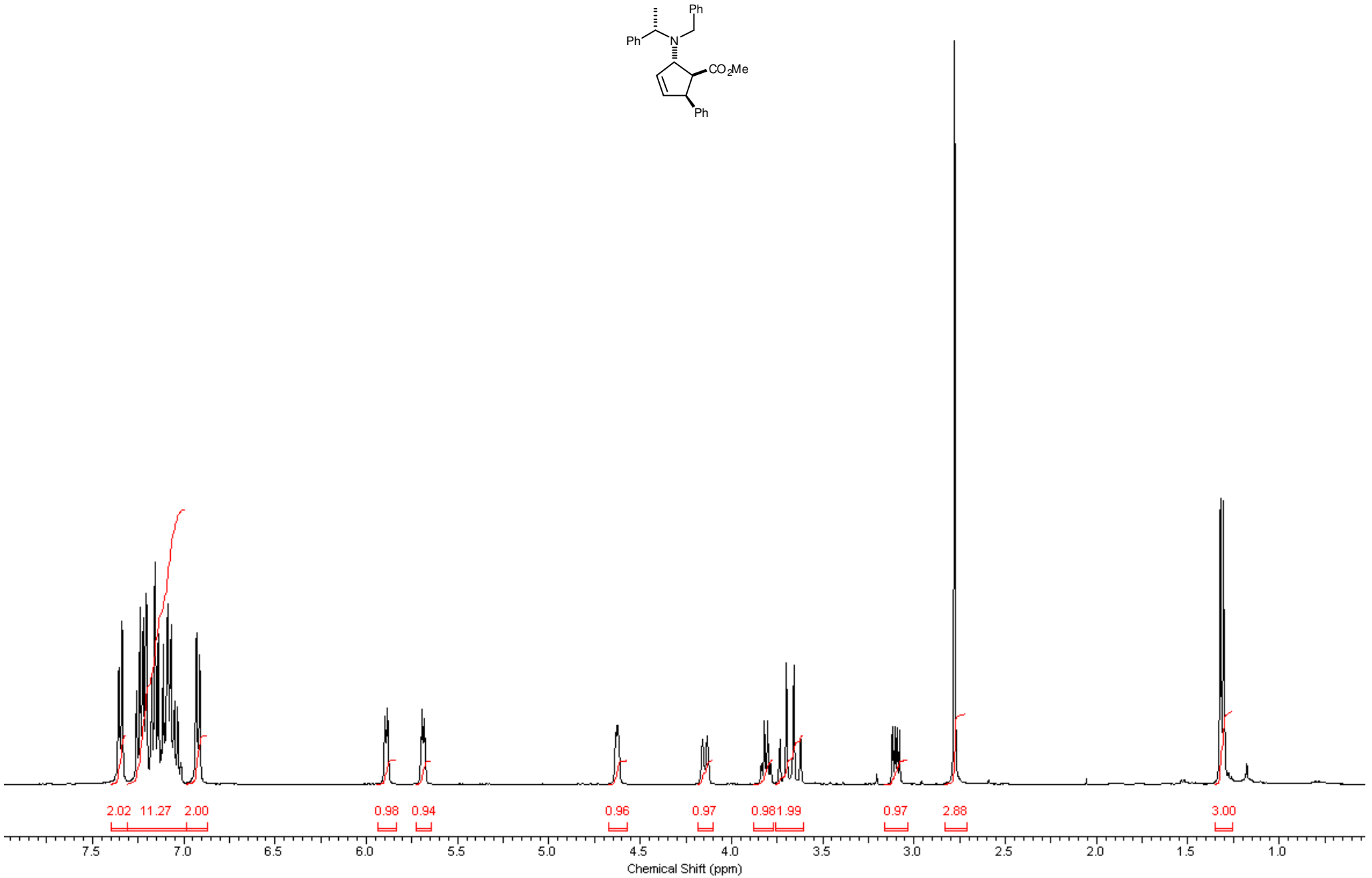
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 27 (400 MHz ^{1}H, $CDCl_3$)



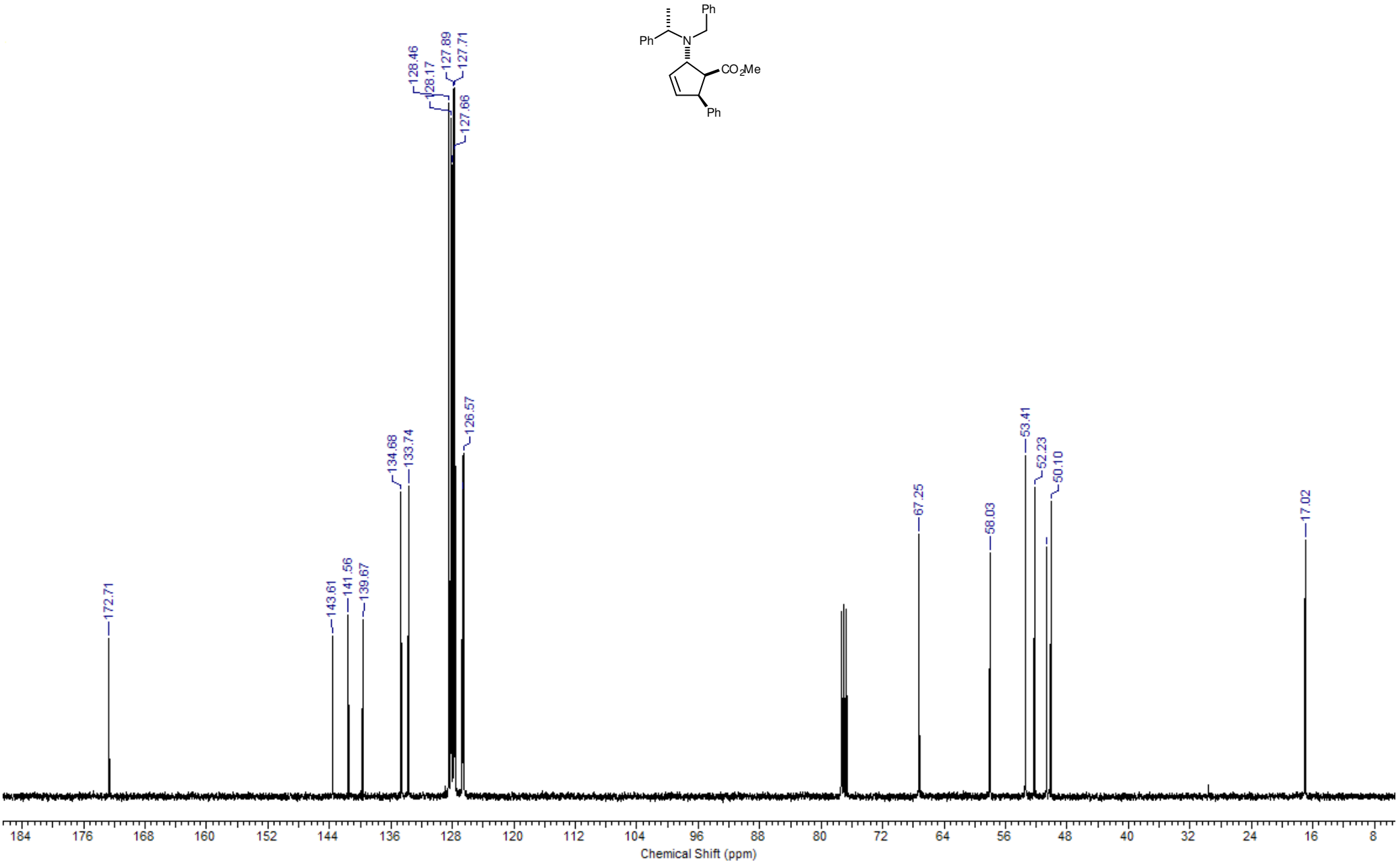
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 27 (100 MHz ^{13}C, $CDCl_3$)



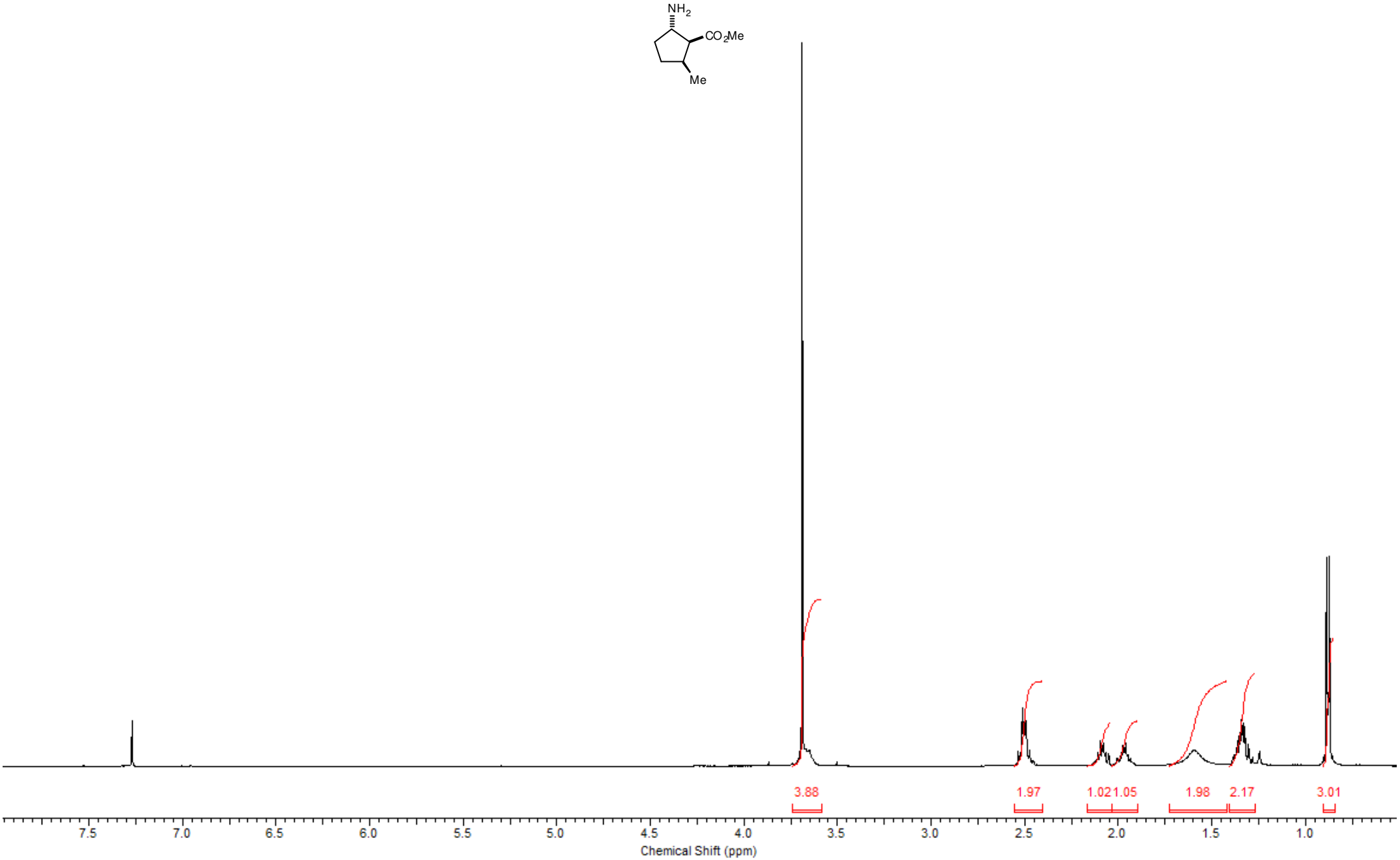
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-phenylcyclopent-3-ene-1-carboxylate 28 (400 MHz ^{1}H, $CDCl_3$)



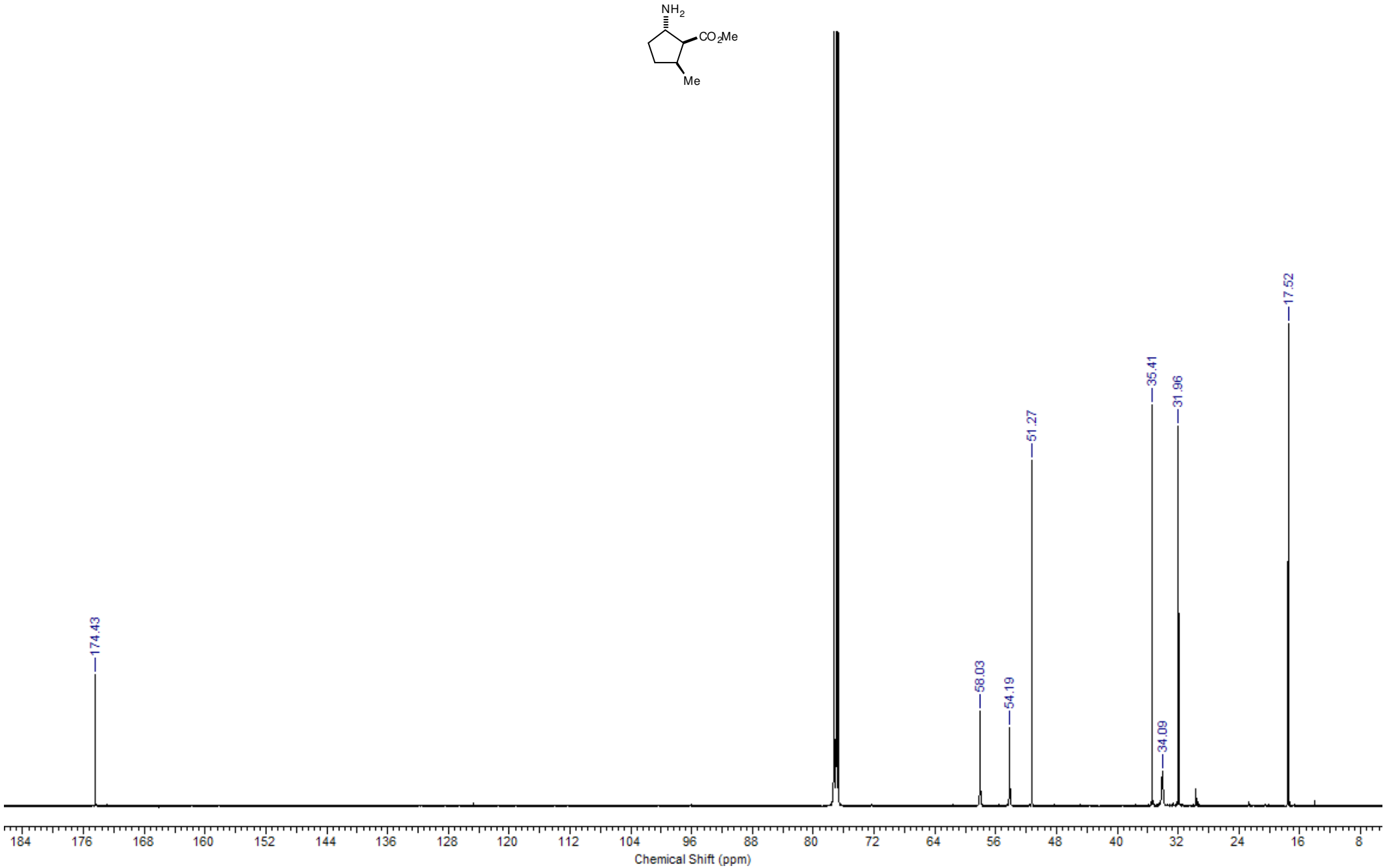
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-phenylcyclopent-3-ene-1-carboxylate 28 (100 MHz ^{13}C, $CDCl_3$)



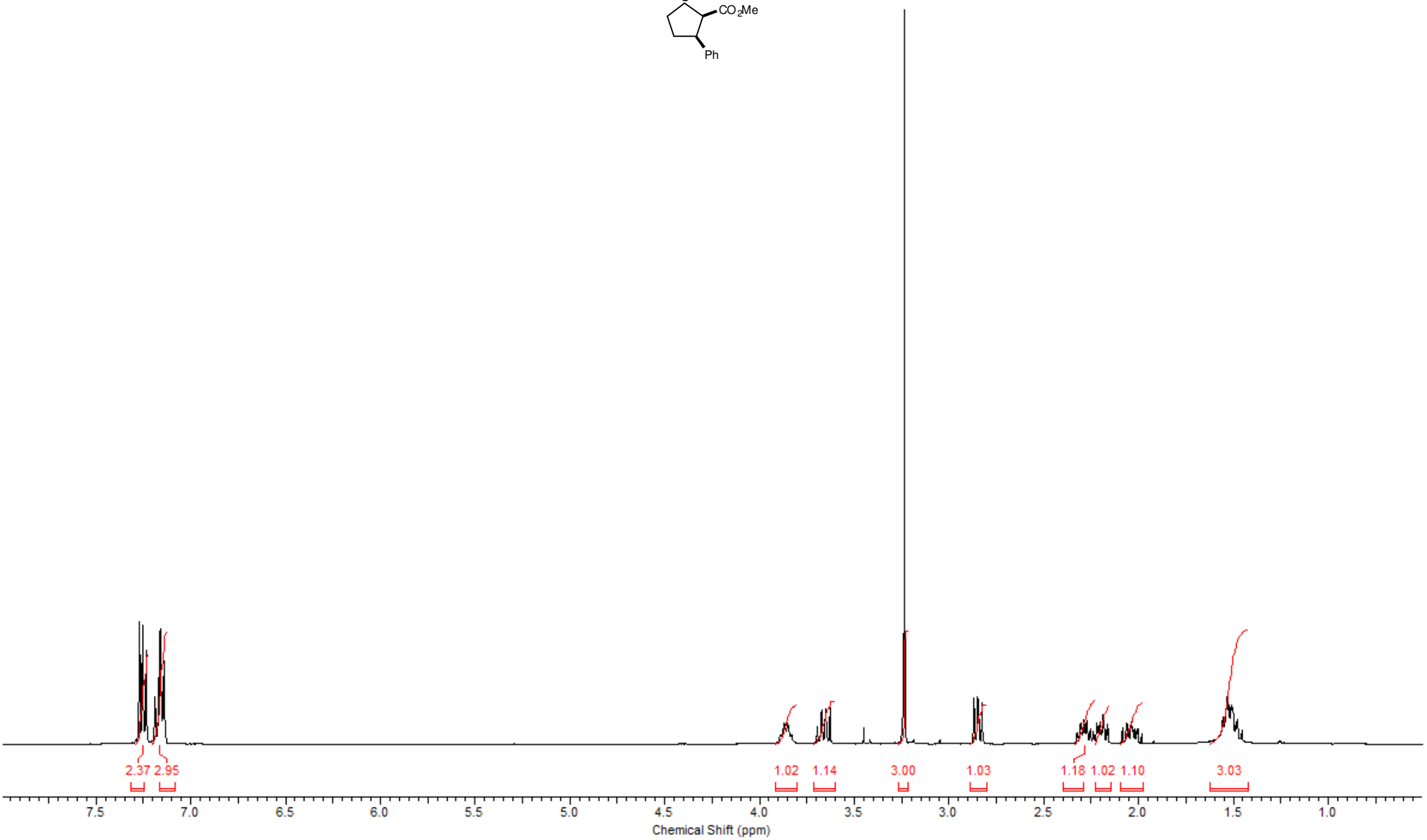
Methyl (*S*,*S*,*S*)-2-amino-5-methylcyclopentane-1-carboxylate 29 (400 MHz ^{1}H, $CDCl_3$)



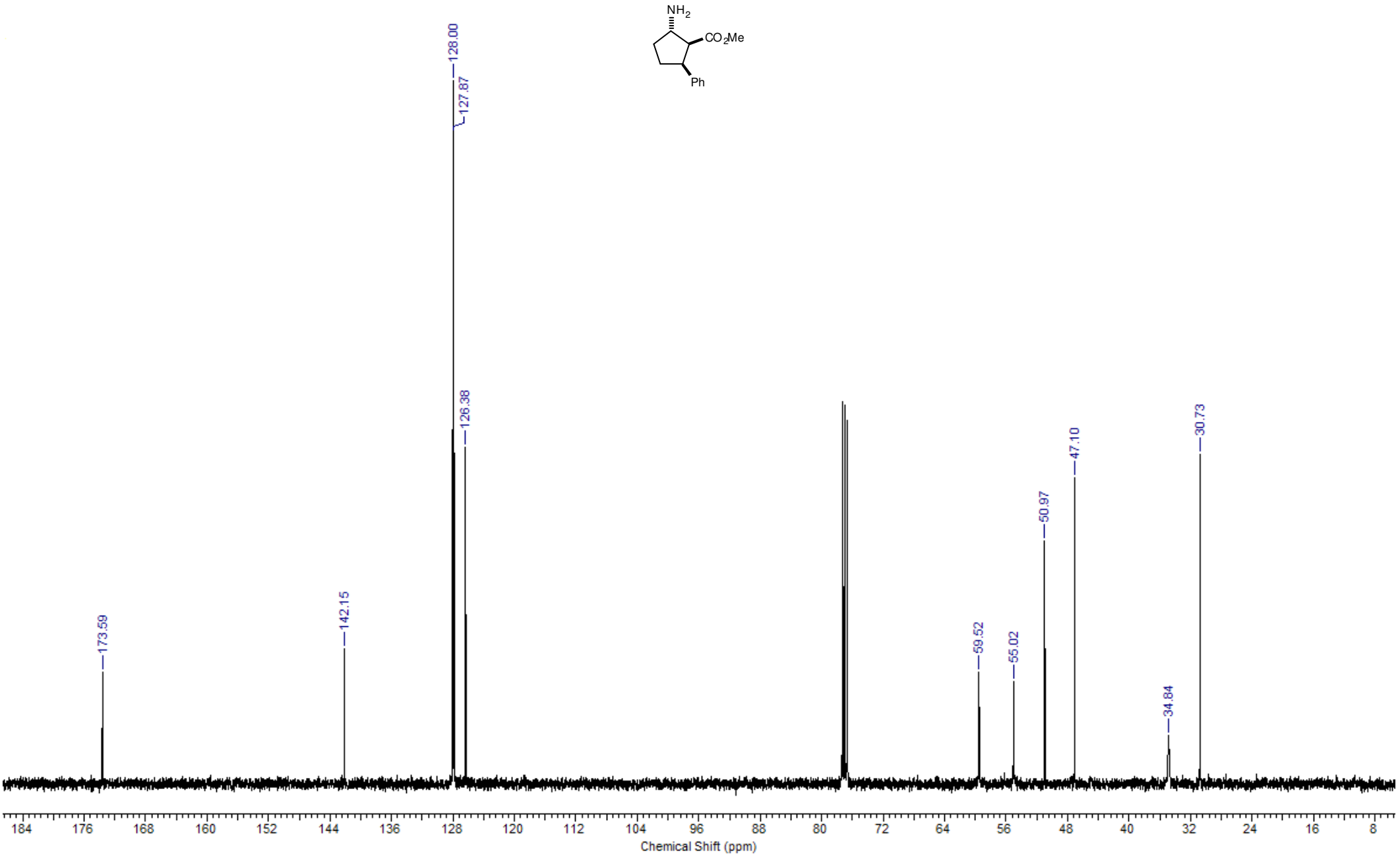
Methyl (*S*,*S*,*S*)-2-amino-5-methylcyclopentane-1-carboxylate 29 (125 MHz ^{13}C, $CDCl_3$)



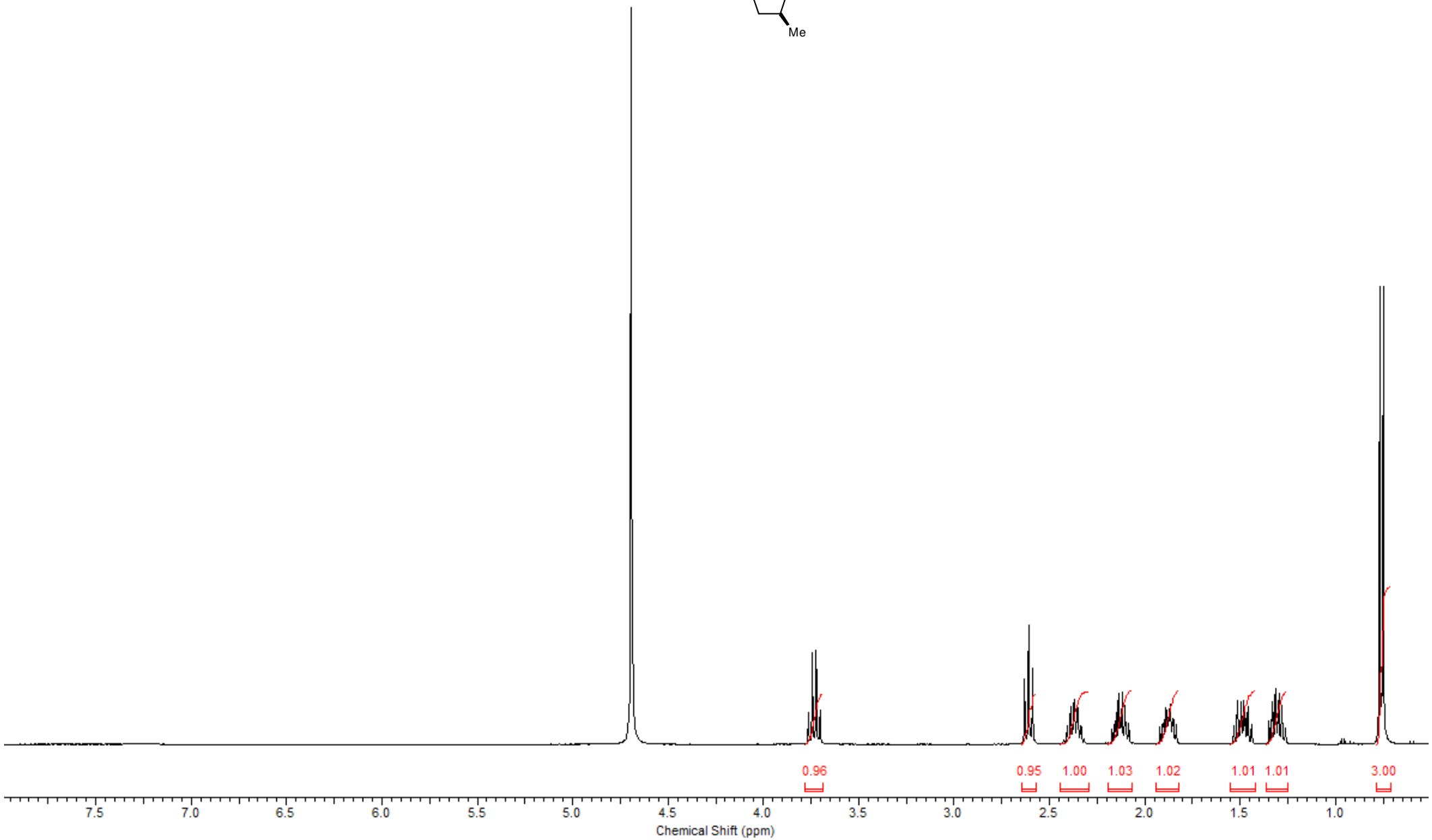
Methyl (*S*,*S*,*S*)-2-amino-5-phenylcyclopentane-1-carboxylate 30 (400 MHz ^{1}H, $CDCl_3$)



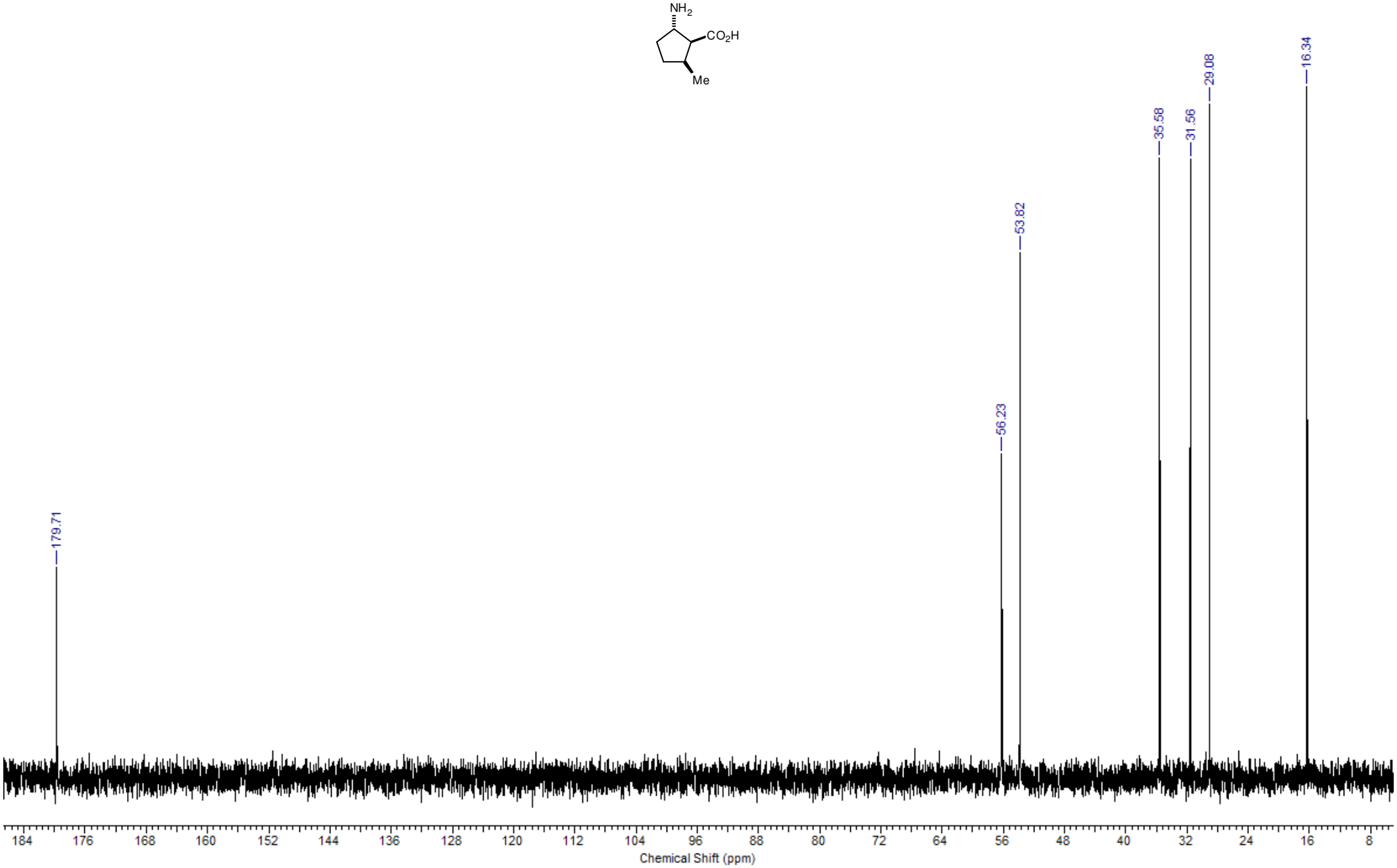
Methyl (*S*,*S*,*S*)-2-amino-5-phenylcyclopentane-1-carboxylate 30 (100 MHz ^{13}C, $CDCl_3$)



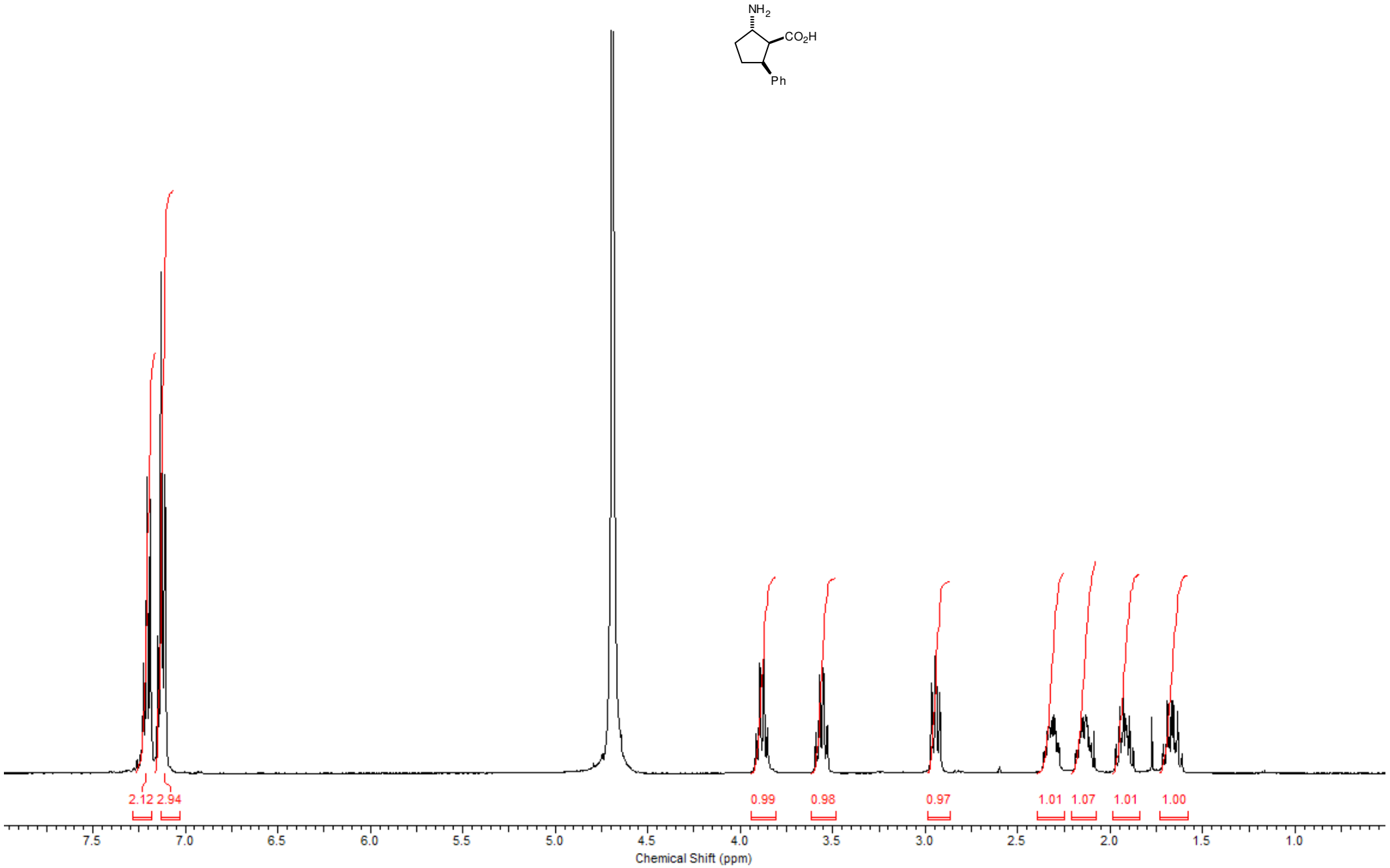
(*S*,*S*,*S*)-2-Amino-5-methylcyclopentane-1-carboxylic acid 31 (400 MHz ^{1}H, D_2O)



(*S*,*S*,*S*)-2-Amino-5-methylcyclopentane-1-carboxylic acid 31 (100 MHz ^{13}C, D_2O)



(*S*,*S*,*S*)-2-Amino-5-phenylcyclopentane-1-carboxylic acid 32 (400 MHz ^{1}H, D_2O)



(*S*,*S*,*S*)-2-Amino-5-phenylcyclopentane-1-carboxylic acid 32 (125 MHz ^{13}C, D_2O)