SUPPORTING INFORMATION

First Asymmetric Synthesis of Cytotoxic Marine Natural Product Palau'imide and Assignment of its C-20 Stereochemistry

Hong-Qiao Lan,[a] Yuan-Ping Ruan,[a] and Pei-Qiang Huang [a, b]*

[a]*Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China*;
[b] *State Key Laboratory of Bioorganic and Natural Products Chemistry, 354 Fenglin Lu, Shanghai 200032, P. R. China*
Fax: 86-592-2186400; pqhuang@xmu.edu.cn

Contents

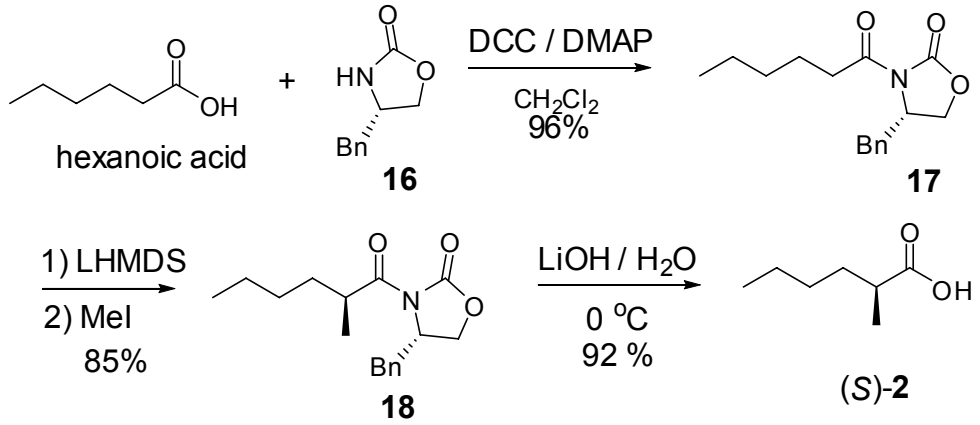
[#] CCDC-756363 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Methods

Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 341 automatic polarimeter. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian unity +500 NMR spectrometer or a Bruker AV 400 NMR spectrometer. Unless otherwise noted, ^{1}H NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus and Finnigan Mat-LCQ (ESI direct injection). HRMS spectra were recorded on a Shimadzu LCMS-IT-TOF apparatus. Elemental analyses were performed using a Vario RL analyzer. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Methylene dichloride was distilled from phosphorus pentoxide. Silica gel (zhifu, 300-400 mesh) from Yantai silica gel factory (China) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate / petroleum ether (PE) (60-90 °C) mixture.

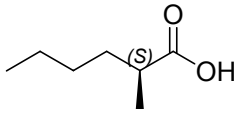
Experimental Procedures

Synthesis of (*S*)-2-methylhexanoic acid (2) (Scheme 1)



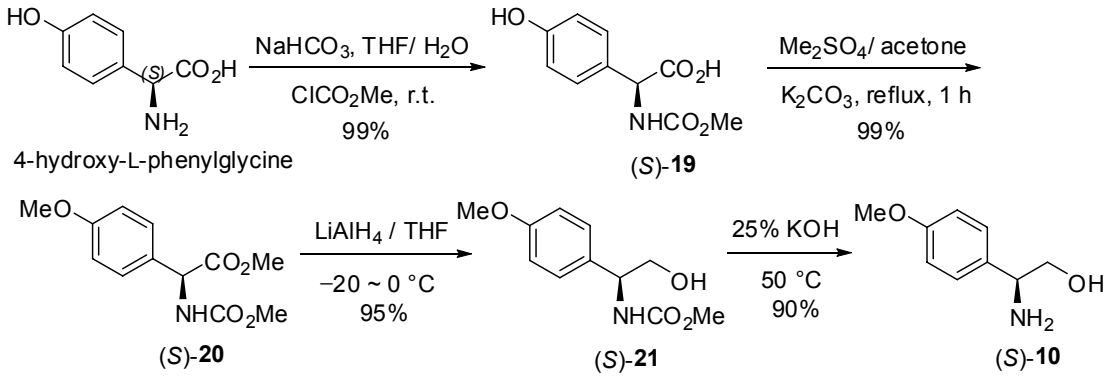
Scheme 1

(*S*)-2-Methylhexanoic acid (2)



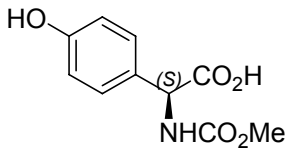
To a cooled (0 °C) solution of the known imide (2*S*)-**18**[1] (1.109 g, 3.83 mmol), prepared starting from hexanoic acid and (4*S*)-4-(phenylmethyl)-2-oxazolidione (**16**), in a mixed solvent system THF (32 mL)/H_2O (8 mL) were added successively a solution of 30% H_2O_2 (4.0 mL, 38.3 mmol) and 4.0 M aqueous LiOH (5 mL, 20 mmol) at 0 °C. After stirring for 2 h, the mixture was concentrated at reduced pressure, and the residue was diluted with H_2O. The resulting mixture was acidified with 1 N HCl until pH 2 and then extracted with EtOAc (4 ×20 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/ PE = 1/ 5) to give the known (*S*)-2-methylhexanoic acid (*S*)-**2** (458 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ +22.6 (*c* 5.1, Et_2O) {lit.[2] $[\alpha]_D^{20}$ +21.2 (*c* 5.5, Et_2O), 88% *e.e.*}; IR (KBr) ν_{max}: 2963, 2930, 2874, 1700, 1462, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (t, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.27-1.35 (m, 4H), 1.40-1.47 (m, 1H), 1.64-1.72 (m, 1H), 2.46 (hex, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 16.7, 22.5, 29.2, 33.1, 39.3, 183.6; MS (ESI, *m/z*): 153 ($M+Na^+$, 100).

Synthesis of the chiral auxiliary (*S*-10) (Scheme 2)



Scheme 2

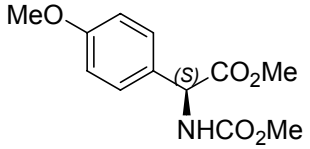
(*S*)-2-(4-Hydorxyphenyl)-2-[(methoxycarbonyl)amino] acetic acid (19)



Methyl chloroformate (8.5 mL, 110.0 mmol) was added to a solution of 4-hydroxy-L-phenylglycine (16.7 g, 100.0 mmol) and $NaHCO_3$ (25.0 g, 300 mmol) in a mixture of H_2O/ THF (500 mL/ 500 mL). After stirring at room temperature overnight

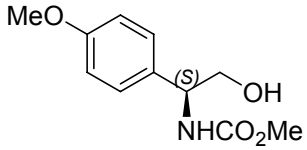
the mixture was diluted with H_2O and washed with Et_2O. The aqueous layer was acidified and extracted with EtOAc (3 ×100 mL). The combined organic phases were washed (H_2O), dried ($MgSO_4$) and concentrated to afford compound (*S*)-**19** (22.3 g, 99%) as a white solid, which without further purification, was used for the next step. Mp 132-133 °C (EtOAc/ Et_2O); $[\alpha]_D^{20}$ +197.3 (*c* 1.15, EtOH); IR (KBr) ν_{max}: 3383, 3226, 3033, 2957, 1735, 1659, 1531, 1448, 1389, 1178, 1052 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 3.54 (s, 3H), 4.99 (d, *J* = 7.8 Hz, 1H), 6.70-6.73 (m, 2H), 7.16-7.19 (m, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 9.45 (br s, 1H), 12.66 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 51.5, 57.5, 115.1, 115.1, 127.2, 128.9, 128.9, 156.3, 157.1, 172.5; MS (ESI, *m/z*): 248 ($M + Na^+$, 100). HRMS Calcd. for $[C_{10}H_{11}NO_5+H]^+$: 226.0715; found 226.0706.

Methyl (*S*)-2-[(methoxycarbonyl)amino]-2-(4-methoxyphenyl) acetate (20)



To a mixture of acid (*S*)-**19** (16.9 g, 75.0 mmol) and K_2CO_3 (25.9 g, 187.5 mmol) in dry acetone (150 mL) was added dropwise (over 30 minutes) dimethyl sulfate (15.6 mL, 165 mmol). The mixture was heated at reflux for 1.5 h, then cooled to rt, diluted with H_2O and extrated with EtOAc (3 ×100 mL). The combined organic phases were washed successefully with H_2O, sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered and concentrated. Filtration of the residue through silica gel (EtOAc/ PE = 1 / 1) afforded (*S*)-**20** (18.8 g, 99%) as a white solid. Mp 86-87 °C (EtOAc/ PE); $[\alpha]_D^{20}$ +157.4 (*c* 1.0, EtOH); IR (KBr) $\nu_{max:}$ 3347, 3008, 2955, 2836, 1743, 1724, 1611, 1513, 1440, 1342, 1249, 1178, 1056, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.67 (s, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 5.30 (d, *J* = 7.2 Hz, 1H), 5.69 (br s, 1H), 6.86-6.90 (m, 2H), 7.26-7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.4, 52.7, 55.3, 57.3, 114.3, 114.3, 128.4, 128.4, 128.7, 156.0, 159.7, 171.6; MS (ESI, *m/z*): 276 ($M + Na^+$, 100). Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.53; N, 5.97. Found: C, 56.93; H, 5.91; N, 5.59.

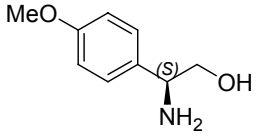
(*S*)-2-[(Methoxycarbonyl)amino]-2-(4-methoxyphenyl)-1-ethanol (21)



To a suspension of $LiAlH_4$ (7.3 g, 192.1 mmol) in THF (240 mL) was added dropwise a solution of ester (*S*)-**20** (24.2 g, 96.0 mmol) in THF (240 mL) at –20 °C under N_2 for 2 h. The mixture was allowed to warm up to 0 °C over 2 h. The resultant mixture was acidified with a 4N HCl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 ×100 mL). The organic phases were washed (H_2O; brine), dried ($MgSO_4$) and concentrated. Filtration of the residue through silica gel (EtOAc/ PE = 2/ 1) afforded alcohol (*S*)-**21** (20.5 g, 95%) as a white solid. Mp 123-124 °C (EtOAc/ PE); $[\alpha]_D^{20}$ +84.2 (*c* 1.0, EtOH); IR (KBr) ν_{max}: 3331, 3074, 2996, 2957, 2840, 1699, 1612, 1514, 1462, 1247, 1179, 1058, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.37 (br s, 1H), 3.67 (s, 3H), 3.79 (s, 3H), 3.79-3.82 (m, 2H), 4.77 (br s, 1H), 5.43 (br s, 1H), 6.87-6.89 (m, 2H), 7.21-7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.3, 55.3, 56.6, 66.5 114.2, 114.2, 127.7, 127.7, 131.2, 157.1, 159.2; MS (ESI, *m/z*): 248 ($M + Na^+$, 100). Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.95; H, 6.75; N, 6.09.

Chiral HPLC analysis using a CHIRALPAK AD-H column (hex./ EtOH = 6/ 4, t_R = 6.24 min for *S*-enantiomer; t_R = 6.84 min for *R*-enantiomer) showed that the *ee*% of (*S*)-**21** was 99.5%.

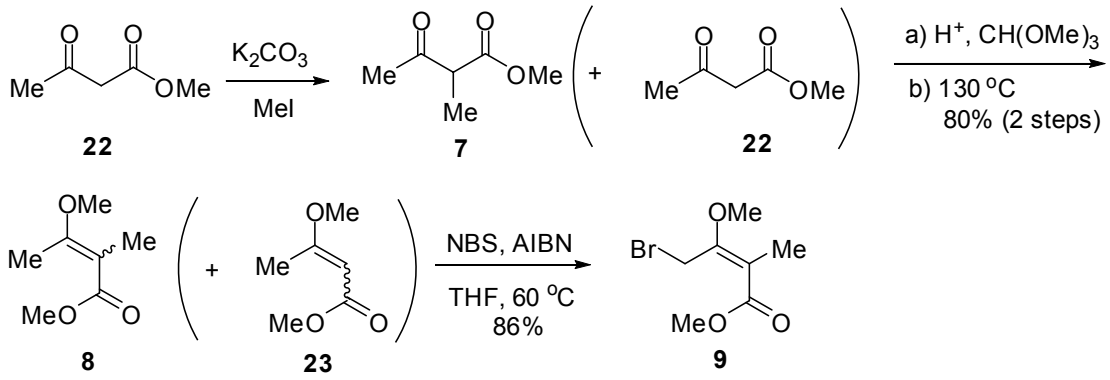
(*S*)-2-Amino-2-(4-methoxyphenyl)-1-ethanol (10)



A solution of alcohol (*S*)-**21** (13.5 g, 60.0 mmol) in 25% KOH (aq.) was stirred at 50 °C overnight. The mixture was extracted with EtOAc (3 ×100 mL). The combined organic phases were washed (H_2O), dried ($MgSO_4$) and concentrated. The residue was recrystallized (EtOAc/ Et_2O) to yield amino alcohol (*S*)-**10** (9.0 g, 90%) as a white solid. Mp 93-94 °C (EtOAc/ Et_2O) {lit.[3] Mp 92-93 °C (toluene)}; $[\alpha]_D^{20}$ +27.0 (*c* 1.0, EtOH) {lit.[4] $[\alpha]_D$ +22.6 (*c* 1.0, EtOH), 98% *e.e.*}; IR (KBr) ν_{max}: 3423, 3348, 3287, 2930, 2894, 2838, 1614, 1586, 1518, 1464, 1330, 1251, 1179, 1062, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.52 (dd, *J* = 8.2, 10.7 Hz, 1H), 3.69 (dd, *J* = 4.4, 10.7 Hz, 1H), 3.80 (s, 3H), 3.99 (dd, *J* = 4.4, 8.2 Hz, 1H), 6.87-6.91 (m, 2H),

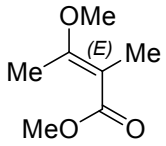
7.23-7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.3, 56.7, 68.1, 114.0, 114.0, 127.5, 127.5, 134.9, 159.0; MS (ESI, *m/z*): 168 ($M + H^+$, 100).

Synthesis of (*E*)-4-bromo-3-methoxy- 2-methyl-2-butenoate (9) (Scheme 3)



Scheme 3

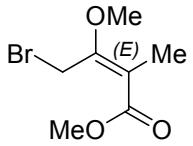
Methyl 3-Methoxy-2-methylbut-2-enoate (8)



To a mixture of methyl 2-methyl-3-oxobutanoate **7** (18.33 g, 141 mmol) and trimethyl orthoformate (18.5 mL, 169 mmol) was added concentrated sulfuric acid (3 drops). After stirring at rt for 24 h, a slight excess of quinoline (6 drops) was added to neutralize the sulfuric acid. Distillation of the dark mixture under reduced pressure afforded a crude product. $MeSO_3H$ was added to this crude product and the mixture was heated at 130 °C at 100 mmHg for 2 h, then distillated under reduced pressure to afford methyl 3-methoxy-2-methylbut-2-enoate (**8**) (16.24 g, yield: *ca.* 80%) as a colorless liquid.

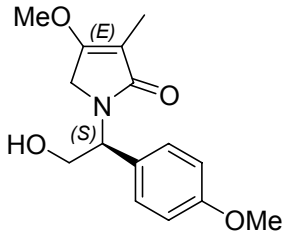
Because methyl 2-methylacetoacetate (**7**) was contaminated with a small amount of the starting methyl acetoacetate (**22**) due to a too small difference in b.p.s and volatility of the product. For the same reason, compound **8** was contaminated with a small amount of compound **23**. This product could be used directly for the subsequent bromination, and the purification was performed at the stage of compound **9**.

Methyl (*E*)-4-Bromo-3-methoxy-2-methylbut-2-enoate (9)



To a solution of methyl 3-methoxy-2-methylbut-2-enoate (**8**) (2.658 g, 18.5 mmol) in THF (180 mL) were added NBS (3.296 g, 18.5 mmol) and AIBN (cat.). The mixture was stirred at 60 °C for 1 h. After removing the solvent under reduced pressure, the residue was dissolved in H_2O (100 mL) and extracted with ether (3 ×30 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (EtOAc/ PE = 1/ 30) to give labile compound **9** (3.540 g, 86%) as a labile colorless oil, which was used immediately in the subsequent step. IR (KBr) ν_{max}: 3015, 2984, 2941, 2832, 1716, 1462, 1439, 1369, 1096, 1141 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.86 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 4.73 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.5, 35.6, 52.3, 62.7, 113.5, 160.7, 167.7; MS (ESI, *m/z*): 223 ($M+H^+$, 100), 225 ($M+H^+$, 93).

1-[(*S*)-2-Hydroxy-1-(4-methoxyphenyl)ethyl]-4-methoxy-3-methyl-1*H*-pyrrol-2(5*H*)-one (6)

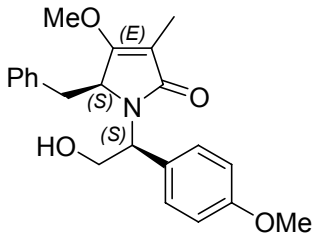


To a solution of amino alcohol (*S*)-**10** (1.105 g, 6.61 mmol) in MeCN (30 mL) was added dropwise a solution of compound **9** (1.475 g, 6.61 mmol) in MeCN (6 mL) over 1 h. The mixture was refluxed for 15 min. After starting the addition of compound **9**, a solution of Et_3N (0.9 mL, 6.61 mmol) in MeCN (3.0 mL) was added in parallel over 1 h. After completion of additions, the reflux was maintained for 6 h. MeCN was distilled off, and the residue was dissolved in H_2O (30 mL). The resultant mixture was extracted with EtOAc (3 ×15 mL). The combined organic extracts were washed (H_2O, and brine), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc) to give tetramate derivative **6** (1.428 g, 78%) as a white solid. Mp. 99-100 °C (EtOAc/ PE); $[\alpha]_D^{20}$ +45.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3374, 2955, 2925, 2863,

2834, 1651, 1613, 1314, 1453, 1346, 1250, 1179, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.81 (s, 3H), 3.60 (d, *J* = 17.4 Hz, 1H), 3.78 (partially overlapped, d, *J* = 17.4 Hz, 1H), 3.79 (partially overlapped, s, 3H), 3.80 (partially overlapped, s, 3H), 3.96-4.06 (m, 2H), 4.10-4.18 (m, 1H), 4.96 (dd, *J* = 3.6, 9.1 Hz, 1H), 6.85-6.90 (m, 2H), 7.15-7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.0, 47.5, 55.3, 57.2, 60.0, 64.3, 104.7, 114.2, 114.2, 128.5, 128.5, 129.9, 159.2, 165.5, 174.6; MS (ESI, *m/z*): 278 ($M+H^+$, 76), 300 ($M+Na^+$, 100); Anal Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.99; H, 7.13; N, 5.05. Chiral HPLC analysis using a Chiralpak AD-H column (hex./ EtOH = 7:3, t_R = 9.17 min. for *R*-enantiomer; t_R = 9.82 min. for *S*-enantiomer) showed that the *e.e.* of (*S*)-**6** was >99%.

(*S*)-5-Benzyl-1-((*S*)-2-hydroxy-1-(4-methoxyphenyl)ethyl)-4-methoxy-3-methyl-1*H*-pyrrol-2(5*H*)-one (11)

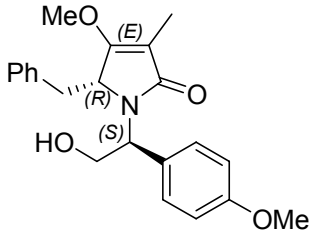
To a solution of tetramate derivative (*S*)-**6** (520 mg, 1.87 mmol) in THF (38 mL) and HMPA (1.62 mL, 9.35 mmol) was added dropwise *t*-BuLi (1.5 M in hexane, 2.5 mL, 3.74 mmol) at −78 ºC. After stirring for 1 h, benzyl bromide (0.66 mL, 5.62 mmol) was added. The mixture was stirred at the same temperature for 7 h. The reaction was quenched with 10 mL of saturated aqueous ammonium chloride. The resulting mixture was extracted with EtOAc (3 ×15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/ PE= 1/ 2) to give compounds **11** (441 mg, 62 %), **12** (72 mg, 10%), and **13** (125 mg, 18%).



Compound **11**: white solid. Mp: 162-163 °C (EtOAc/ PE); $[\alpha]_D^{20}$ +40.3 (*c* 0.62, $CHCl_3$); IR (KBr) ν_{max}: 3357, 3059, 3025, 2947, 2926, 2855, 2830, 1651, 1607, 1513, 1449, 1379, 1325, 1249, 1171, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.82 (s, 3H), 2.87 (dd, *J* = 4.8, 14.3 Hz, 1H), 3.09 (dd, *J* = 4.1, 14.3 Hz, 1H), 3.78 (partially overlapped, s, 3H), 3.77-3.82 (partially overlapped, m, 1H), 3.93 (dd, *J* = 3.2, 12.4 Hz,

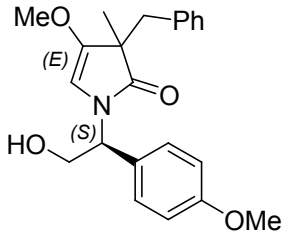
1H), 3.96 (s, 3H), 4.17 (dd, *J* = 7.6, 12.4 Hz, 1H), 4.45 (dd, *J* = 3.2, 7.6 Hz, 1H), 6.82-6.86 (m, 2H), 6.98-7.03 (m, 2H), 7.10-7.12 (m, 2H), 7.20-7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.1, 35.0, 55.3, 58.3, 60.0, 62.3, 65.0, 103.5, 114.1, 114.1, 126.9, 128.2, 128.2, 128.3, 128.3, 129.4, 129.4, 130.4, 135.1, 159.1, 166.8, 174.7; MS (ESI, *m/z*): 368 ($M+H^+$, 96), 390 ($M+Na^+$, 100). Anal calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.55; H, 6.85; N, 3.73.

(*R*)-5-Benzyl-1-((*S*)-2-hydroxy-1-(4-methoxyphenyl)ethyl)-4-methoxy-3-methyl-1*H*-pyrrol-2(5*H*)-one (12)



Compound **12**: white solid. Mp 160-161.5 °C (EtOAc/ PE); $[\alpha]_D^{20}$ −30.6 (*c* 0.7, $CHCl_3$); IR (KBr) ν_{max}: 3382, 3062, 3029, 3001, 2949, 2933, 2837, 1713, 1655, 1612, 1514, 1453, 1387, 1331, 1251, 1179, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.89 (s, 3H), 2.84 (dd, *J* = 5.3, 14.5 Hz, 1H), 2.92 (dd, *J* = 4.8, 14.5 Hz, 1H), 3.56-3.63 (m, 1H), 3.81 (s, 3H), 3.91 (s, 3H), 3.99-4.04 (m, 2H), 4.22-4.32 (m, 1H), 4.65 (dd, *J* = 4.0, 8.2 Hz, 1H), 6.80-6.87 (m, 4H), 7.09-7.14 (m, 3H), 7.19 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.2, 36.8, 55.3, 58.3, 61.4, 62.7, 64.9, 103.5, 113.9, 113.9, 126.5, 128.0, 128.0, 129.2, 129.2, 129.2, 129.2, 130.1, 136.0, 159.0, 167.3, 175.2; MS (ESI, *m/z*): 368 (M + H^+, 89), 390 (M + Na^+, 100). HRMS Calcd. for $[C_{12}H_{25}NO_4+H]^+$: 368.1862; found: 368.1861.

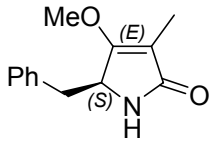
3-Benzyl-1-((*S*)-2-hydroxy-1-(4-methoxyphenyl)ethyl)-4-methoxy-3-methyl-1*H*-pyrrol-2(3*H*)-one (13)



Compound **13**: white solid. Mp: 162-163 °C (EtOAc / PE); $[\alpha]_D^{20}$ +9.8 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3382, 3062, 3029, 3001, 2949, 2933, 2837, 1713, 1655, 1612,

1514, 1453, 1387, 1331, 1251, 1179, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 3H), 2.91 (d, *J* = 12.9 Hz, 1H), 3.00 (d, *J* = 12.9 Hz, 1H), 3.54 (s, 3H), 3.76 (s, 3H), 3.89-3.97 (m, 2H), 4.79 (dd, *J* = 4.5, 6.8 Hz, 1H), 5.04 (s, 1H), 6.60-6.65 (m, 2H), 6.68-6.73 (m, 2H), 7.10-7.13 (m, 2H), 7.18-7.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 41.4, 52.6, 55.2, 56.3, 57.8, 63.6, 100.8, 113.9, 113.9, 126.5, 128.0, 128.0, 128.1, 128.1, 128.5, 129.6, 129.6, 136.7, 149.8, 158.8, 177.0; MS (ESI, *m/z*): 368 ($M+H^+$, 100), 390 ($M+Na^+$, 40). HRMS Calcd. for $[C_{12}H_{25}NO_4+H]^+$: 368.1862; found 368.1859.

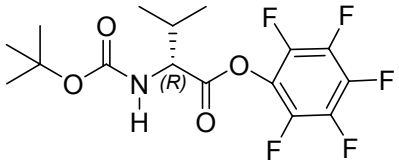
(*S*)-5-Benzyl-4-methoxy-3-methyl-1*H*-pyrrol-2(*5H*)-one (5)



To a solution of compound **11** (356 mg, 0.97 mmol) in a mixed solvent system CH_3CN (72 mL)/ H_2O (24 mL) was added ceric ammonium nitrate (2.658 g, 4.85 mmol) in one portion. After stirring at rt for 30 min, H_2O (5 mL) was added and the mixture extracted with EtOAc (3 ×20 mL). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 2/ 1) to give compound **5** (168 mg, 80 %) as a white solid. Mp: 116-117 °C (EtOAc/PE); $[\alpha]_D^{20}$ –43.3 (*c* 0.61, $CHCl_3$); IR (KBr) ν_{max}: 3273, 3059, 3029, 2951, 2926, 2851, 1682, 1662, 1453, 1386, 1330, 1230, 1106, 1012 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.94 (s, 3H), 2.50 (dd, *J* = 9.4, 13.5 Hz, 1H), 3.18 (dd, *J* = 3.4, 13.5 Hz, 1H), 4.00-4.06 (m, 1H), 4.08 (s, 3H), 5.43 (br s, 1H), 7.10-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.0, 39.1, 57.4, 58.5, 102.7, 127.0, 128.7, 128.7, 129.1, 129.1, 137.1, 168.7, 174.8; MS (ESI, *m/z*): 240 ($M+Na^+$, 100). Anal calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.67; H, 7.00; N, 6.38.

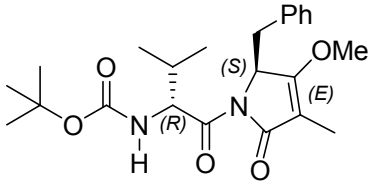
Chiral HPLC analysis using a Chiralpak AD-H column (hex./EtOH = 8:2, t_R = 13.1 min. for *S*-enantiomer; t_R = 16.0 min. for *R*-enantiomer) showed that the *e.e.* for (*S*)-**5** was >99%.

***t*-Butoxycarbonyl-D-valine Pentafluorophenyl Ester (4)**



N-Boc-D-Valine (1.523 g, 7.0 mmol), C_6F_5OH (1.419 g, 7.71 mmol) and DCC (1.593 g, 7.73 mmol) were added to EtOAc (30 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 3 h. After filtration, the solvent was removed and the residue was purified by column chromatography on silica gel (EtOAc/PE = 1:30) to give activated ester **4** (2.466 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ +18.5 (*c* 1.15, $CHCl_3$); {lit.[5] $[\alpha]_D^{20}$ −18.1 (*c* 1.0, $CHCl_3$) for (*S*)-**4**}. IR (KBr) ν_{max}: 3336, 2975, 2926, 2872, 1788, 1713, 1521, 1368, 1171, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two rotamers, M/ m = 4.6: 1) δ: 1.03 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.47 (s, 9H), 2.30-2.38 (m, 1H), 4.34 (br m, 1H, rotamer m), 4.57 (dd, *J* = 4.8, 8.7 Hz, 1H, rotamer M), 4.69 (br m, 1H, rotamer m), 5.01 (d, *J* = 8.6 Hz, 1H, rotamer M); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4, 18.9, 28.2, 28.2, 28.2, 31.1, 58.7, 80.5, 124.7, 136.6, 138.4, 139.2, 139.7, 140.9, 142.4, 155.4, 168.7; MS (ESI, *m/z*): 406 ($M+Na^+$, 100).

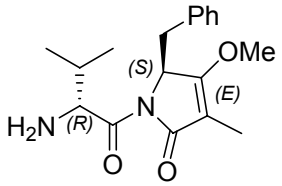
_N_-Boc-D-Val-(_S_)-5-Benzyl-4-methoxy-3-methyl-1_H_-pyrrol-2(5_H_)-one (15)



To a stirring solution of tetramate derivative **5** (81 mg, 0.37 mmol) in anhydrous THF (4 mL) was added *n*-BuLi (1.6 M in hexane, 0.23 mL, 0.37 mmol) at –78 °C over 10 min. Active ester **4** (156 mg, 0.41 mmol) in THF (2 mL) was then added, and the mixture was stirred for 30 min at the same. The reaction was quenched with AcOH (0.1 mL) in THF (2 mL) and extracted with EtOAc (3 ×15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure. After purification by flash column chromatography on silica gel (EtOAc/ PE = 1/ 5) compound **15** (130 mg, 85%) was obtained as a white solid. Mp. 116-117 °C (EtOAc/ PE); $[\alpha]_D^{20}$ +145.7 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3438, 3374, 2966, 2930, 2868, 1723, 1661, 1496, 1455, 1390, 1366, 1322, 1234, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (d, *J* = 6.9 Hz, 3H), 1.07

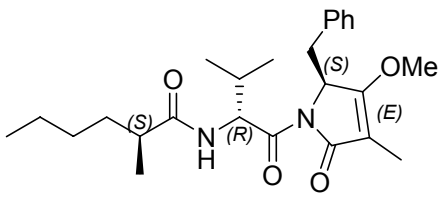
(d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 1.74 (s, 3H), 2.01-2.18 (m, 1H), 3.13 (dd, *J* = 2.8, 14.0 Hz, 1H), 3.37 (dd, *J* = 5.2, 14.0 Hz, 1H), 4.07 (s, 3H), 4.72 (br s, 1H), 5.22 (d, *J* = 7.8 Hz, 1H), 5.17-5.26 (m, 1H), 6.91-6.99 (m, 2H), 7.13-7.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.6, 15.7, 20.3, 28.3, 28.3, 28.3, 30.1, 35.0, 58.0, 58.4, 58.6, 79.4, 104.0, 127.0, 128.0, 128.0, 129.4, 129.4, 134.4, 156.0, 170.0, 170.9, 172.1; MS (ESI, *m/z*): 417 ($M+H^+$, 100), 439 ($M+Na^+$, 40). Anal calcd for $C_{23}H_{32}N_2O_5$: C, 66.32; H, 7.74; N, 6.73. Found: C, 66.53; H, 7.92; N, 6.79.

D-Val-(*S*)-5-Benzyl-4-methoxy-3-methyl-1*H*-pyrrol-2(5*H*)-one (3)



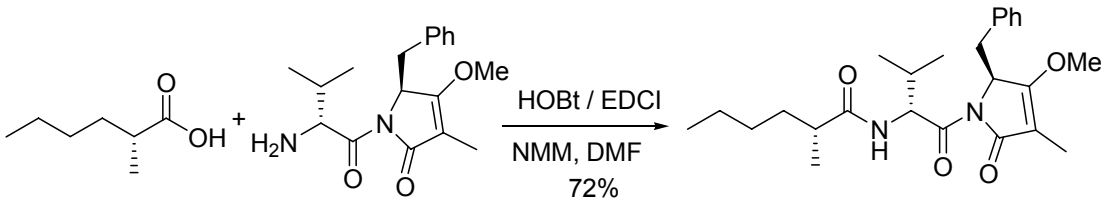
To a stirring solution of compound **15** (67 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (4 mL) was added TFA (0.2 mL) at 0 °C. The mixture was stirred for 3h. After removal of TFA in *vacuum*, the residue was dissolved in EtOAc, and successively washed with 10 %Na_2CO_3 and brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc) to give compound **3** (47 mg, 93%) as a colorless oil. $[\alpha]_D^{20}$ +44.0 (*c* 0.9, $CHCl_3$); IR (KBr) ν_{max}: 3376, 3082, 3058, 3023, 2953, 2925, 2853, 1723, 1659, 1454, 1386, 1322, 1236, 1107, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.75 (d, *J* = 1.1 Hz, 3H), 1.99-2.07 (m, 1H), 3.15 (dd, *J* = 3.0, 14.0 Hz, 1H), 3.39 (dd, *J* = 5.1, 14.0 Hz, 1H), 4.07 (s, 3H), 4.41 (d, *J* = 1.8 Hz, 1H), 4.74-4.77 (m, 1H), 6.96-6.99 (m, 2H), 7.17-7.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.7, 15.2, 20.7, 29.7, 30.7, 35.1, 58.2, 58.6, 59.3, 103.9, 127.0, 128.0, 130.0, 134.5, 170.1, 171.2, 175.5; MS (ESI, *m/z*): 317 ($M+H^+$, 100). HRMS calcd. for $[C_{18}H_{24}N_2O_3+H]^+$: 317.1860; found: 317.1867.

(+)-Palau'imide (1)



To a solution of compound **2** (10 mg, 0.076 mmol) in DMF (2 mL) were added HOBt (20 mg, 0.15 mmol) and EDCI (16 mg, 0.079 mmol) at –15 °C. After stirring for 30 min, the mixture was allowed warming to room temperature. To the resultant mixture was added NMM (0.024 mL, 0.22 mmol) and compound **3** (23 mg, 0.072 mmol) in DMF (1 mL). After stirring at rt overnight, the mixture was diluted with EtOAc (50 mL) and washed successively with 10 % HCl, 10 % Na_2CO_3, and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/ PE = 1/ 5) to give palau'imide (**1**) (22 mg, 72 %) as a white amorphous solid. $[\alpha]_D^{20}$ +51 (*c* 0.32, MeOH) {lit.[6] $[\alpha]_D^{25}$ +50 (*c* 0.33, MeOH)}; IR (KBr) ν_{max}: 3385, 2960, 2928, 1725, 1659, 1587, 1455, 1322, 1245, 1196, 1095, 1018 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.26-1.33 (m, 4H), 1.36-1.43 (m, 1H), 1.61-1.70 (m, 1H), 1.76 (d, *J* = 0.8 Hz, 3H), 2.11-2.18 (m, 1H), 2.28 (hex, *J* = 6.9 Hz, 1H), 3.15 (dd, *J* = 2.9, 14.0 Hz, 1H), 3.38 (dd, *J* = 5.1, 14.0 Hz, 1H), 4.08 (s, 3H), 4.69-4.72 (m, 1H), 5.64 (br d, *J* = 8.4 Hz, 1H), 6.94-6.97 (m, 2H), 7.18-7.19 (m, 1H), 7.19-7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.7, 14.0, 16.1, 18.2, 20.5, 22.7, 29.6, 29.7, 30.5, 33.9, 35.0, 41.8, 58.2, 58.6, 104.0, 127.1, 128.0, 128.0, 129.5, 129.5, 134.4, 170.0, 170.9, 171.7, 176.7; MS (ESI, *m/z*): 429 ($M+H^+$, 100), 451 ($M+Na^+$, 63). HRMS calcd. for $[C_{25}H_{36}N_2O_4 + H]^+$: 429.2747; found: 429.2744.

(*R,R,S*)-Palau'imide (16)



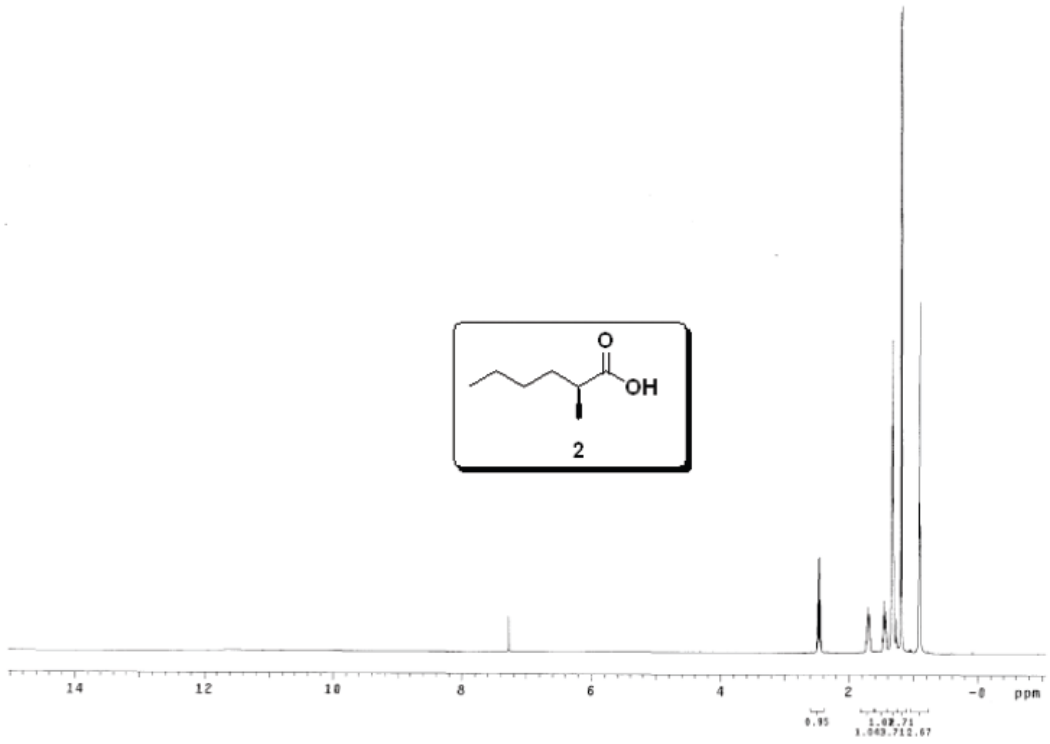
(*R*)-**2** **3** (*R,R,S*)-palau'imide (**16**)

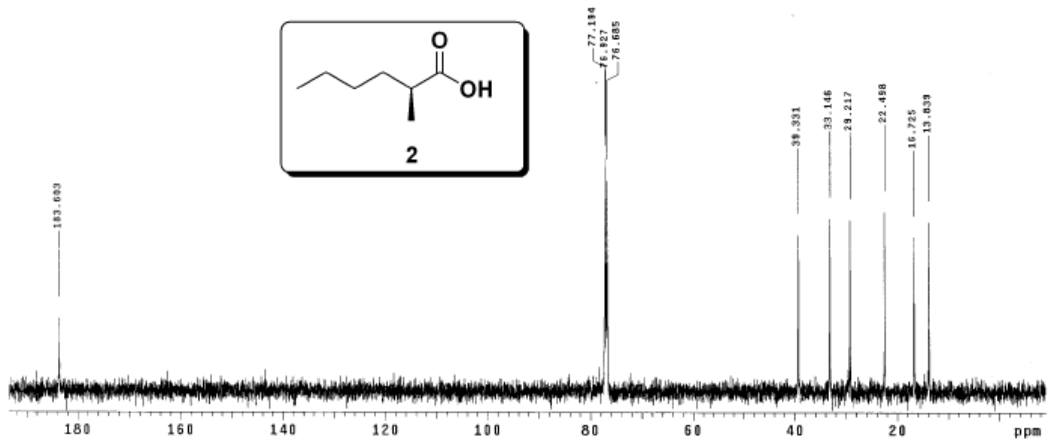
To a solution of compound (*R*)-**2** (10 mg, 0.076 mmol) in DMF (1 mL) were added HOBt (20 mg, 0.15 mmol) in DMF (0.8 mL) and EDCI (16 mg, 0.079 mmol) in DMF (1 mL) at 0 °C. After stirring for 30 min, the mixture was allowed warming to room temperature. To the resultant mixture was added NMM (0.012 mL, 0.11 mmol) and compound **3** (12 mg, 0.038 mmol) in DMF (1 mL). After stirring at rt 16h, the mixture was diluted with H_2O (50 mL) and extracted with Et_2O (5× 10 mL). The

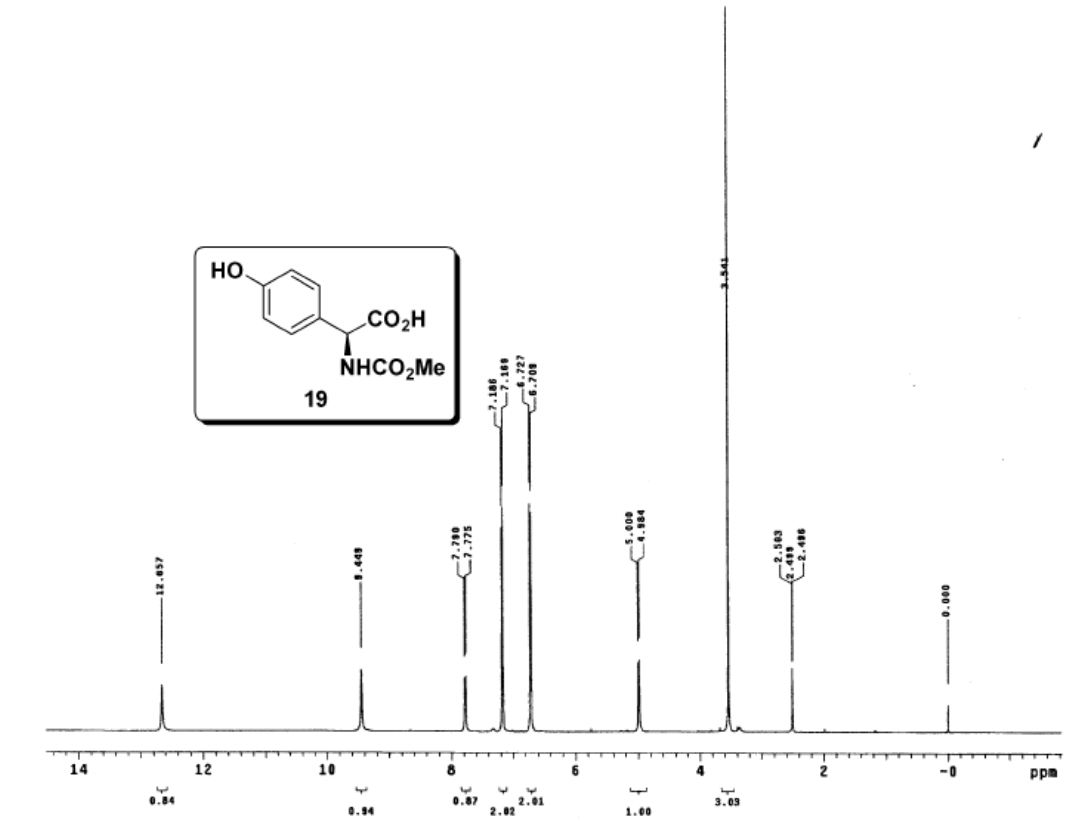
combined organic phases were washed successively with 10 % HCl, 10 % Na_2CO_3, H_2O and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/ PE = 1/ 5) to give (*R,R,S*)-palau'imide (**16**) (12 mg, 74 %) as a wax solid. $[\alpha]_D^{20}$ +149 (*c* 1.0, MeOH); IR (KBr) ν_{max}: 3025, 2959, 2930, 2868, 1723, 1653, 1603, 1515, 1449, 1321, 1230, 1196, 1142, 977 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.26-1.35 (m, 4H), 1.36-1.46 (m, 1H), 1.61-1.71 (m, 1H), 1.76 (d, *J* = 0.8 Hz, 3H), 2.10-2.18 (m, 1H), 2.27 (hex, *J* = 6.9 Hz, 1H), 3.15 (dd, *J* = 3.0, 14.0 Hz, 1H), 3.38 (dd, *J* = 5.2, 14.0 Hz, 1H), 4.08 (s, 3H), 4.69-4.71 (m, 1H), 5.63 (br d, *J* = 8.6 Hz, 1H), 6.95-6.97 (m, 2H), 7.17-7.19 (m, 2H), 7.20-7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.7, 14.0, 16.1, 17.8, 20.5, 22.6, 29.7, 30.5, 34.1, 35.0, 41.7, 56.5, 58.2, 58.6, 104.0, 127.1, 128.0, 128.0, 129.5, 129.5, 134.4, 170.1, 170.9, 171.8, 176.6; MS (ESI, *m/z*): 429 ($M+H^+$, 100), 451 ($M+Na^+$, 63). HRMS calcd for $[C_{25}H_{36}N_2O_4 + H]^+$: 429.2747; found: 429.2744.

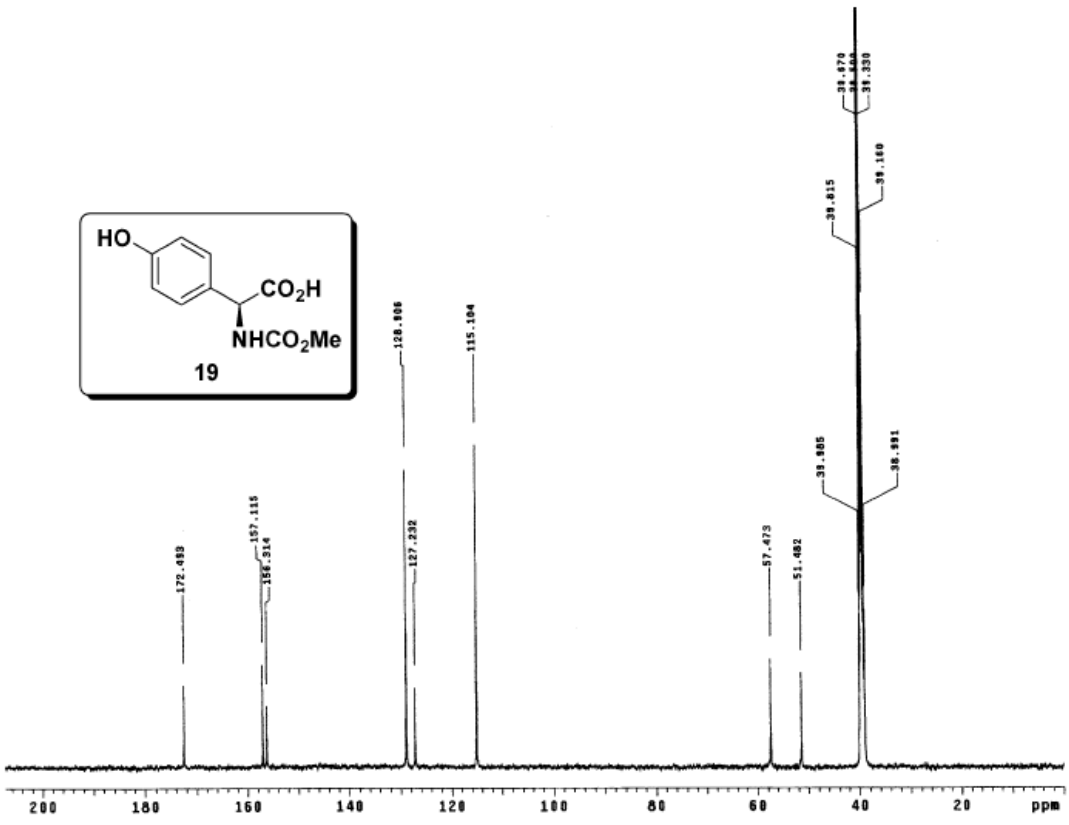
Reference

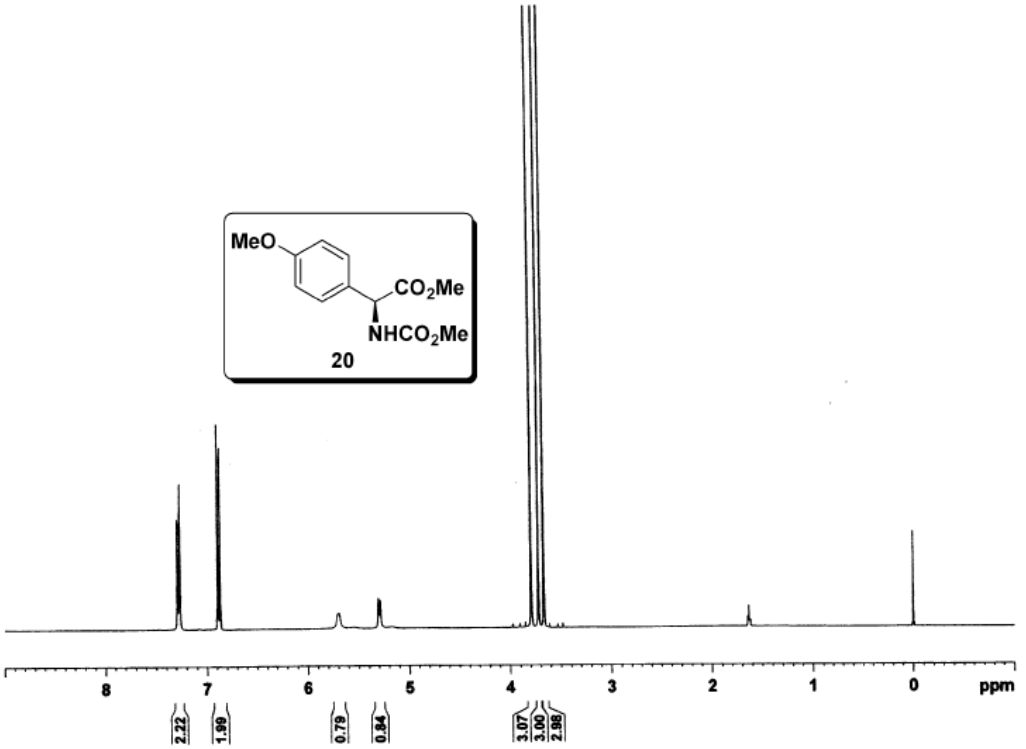
1. Decicco, C. P.; Grover, P. *J. Org. Chem.* **1996**, *61*, 3534.
2. Harlan, L. G.; Chung, C. T. *J. Org. Chem.* **1983**, *48*, 3986.
3. Kawasaki, K.; Katsuki, T. *Tetrahedron*, **1997**, *53*, 6337.
4. O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519.
5. Ward, D. E.; Vázquez, A.; Pedras, M. S. C. *J. Org. Chem.* **1999**, *64*, 1657.
6. Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *Tetrahedron* **2002**, *58,* 7959.

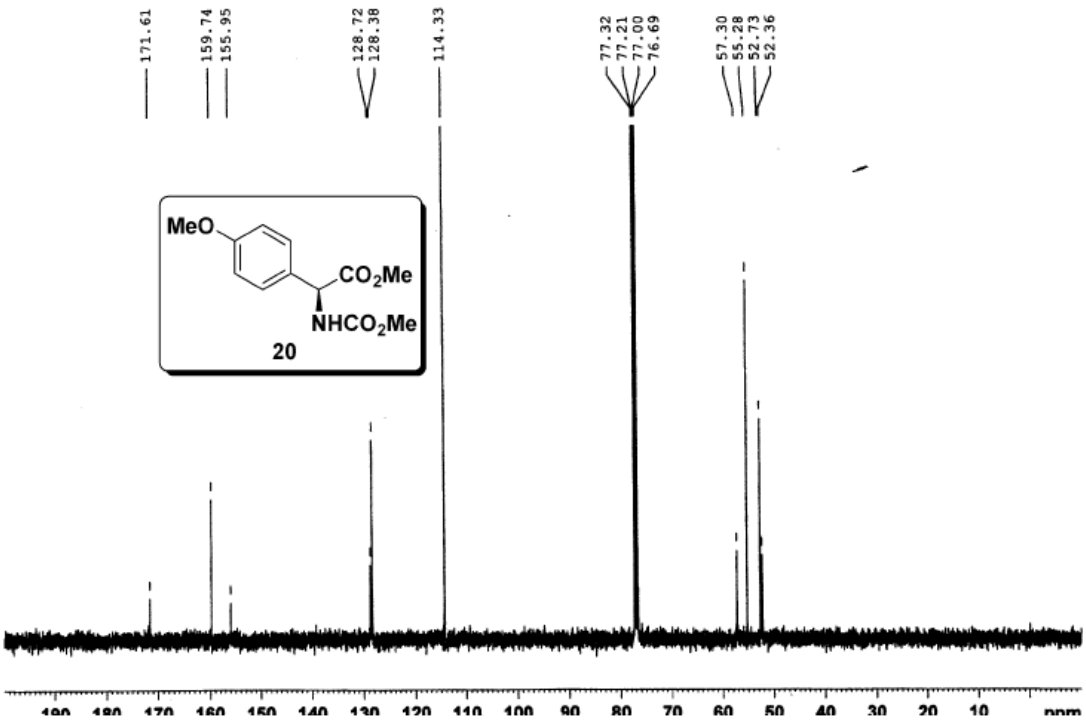

O
OH
2
14
12
10
8
6
4
2
0
ppm

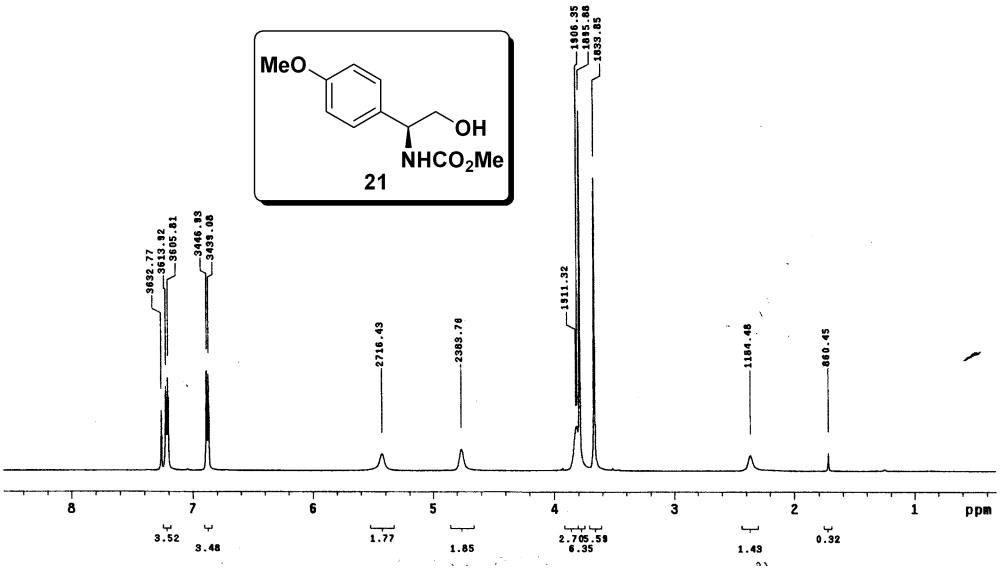

O
OH
2
183.683
77.194
76.827
76.685
39.331
33.146
29.217
22.498
16.725
13.839
180
160
140
120
100
80
60
40
20
ppm

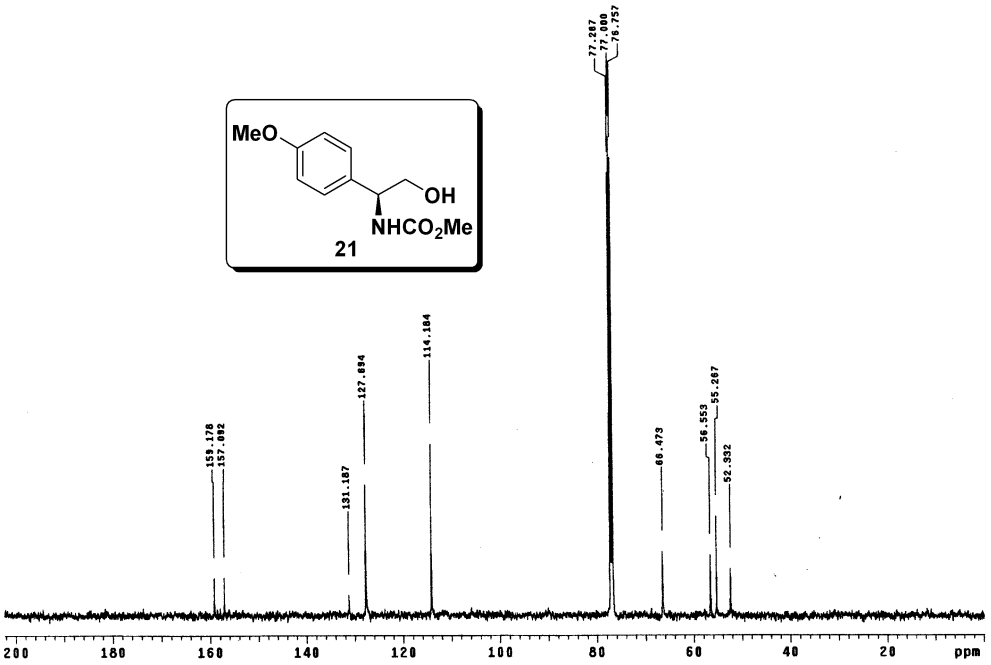

HO
CO2H
NHCO2Me
19
12.657
8.449
7.790
7.775
7.188
7.168
6.727
6.708
5.000
4.984
3.541
2.563
2.489
2.486
0.000
14
12
10
8
6
4
2
-0
ppm
0.84
0.94
0.87
2.02
2.01
1.00
3.03

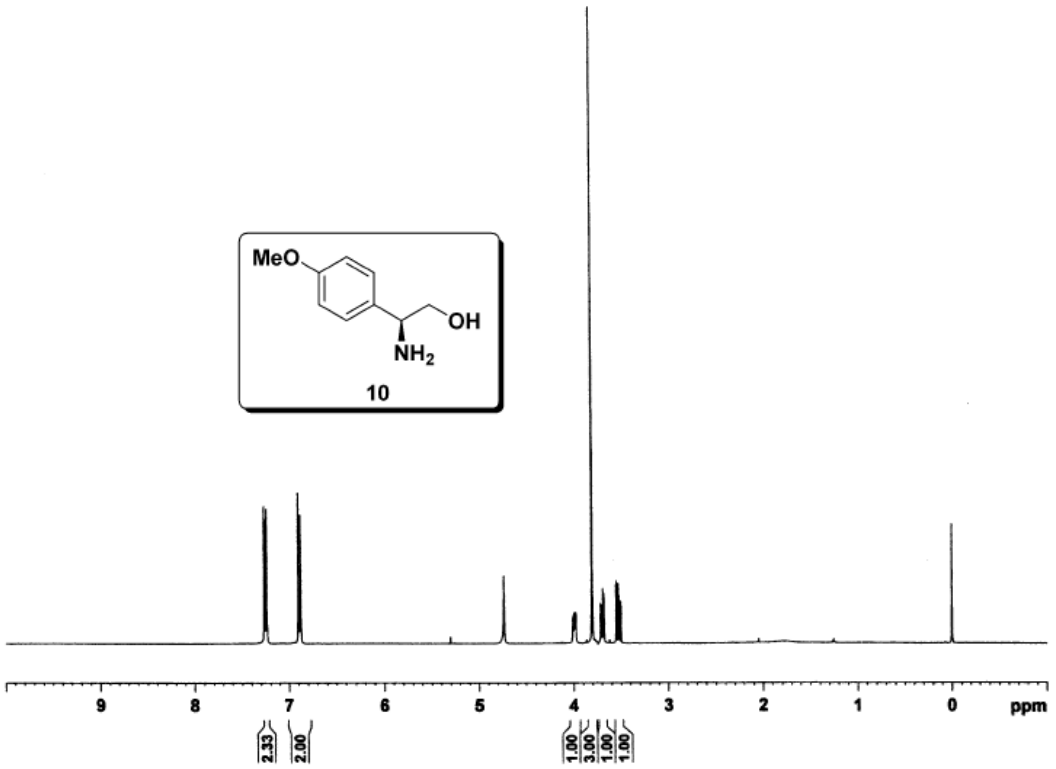

HO
CO2H
NHCO2Me
19
172.493
157.115
156.314
128.806
127.232
115.104
57.473
51.482
39.670
39.466
39.330
39.160
39.015
38.865
38.991
200
180
160
140
120
100
80
60
40
20
ppm

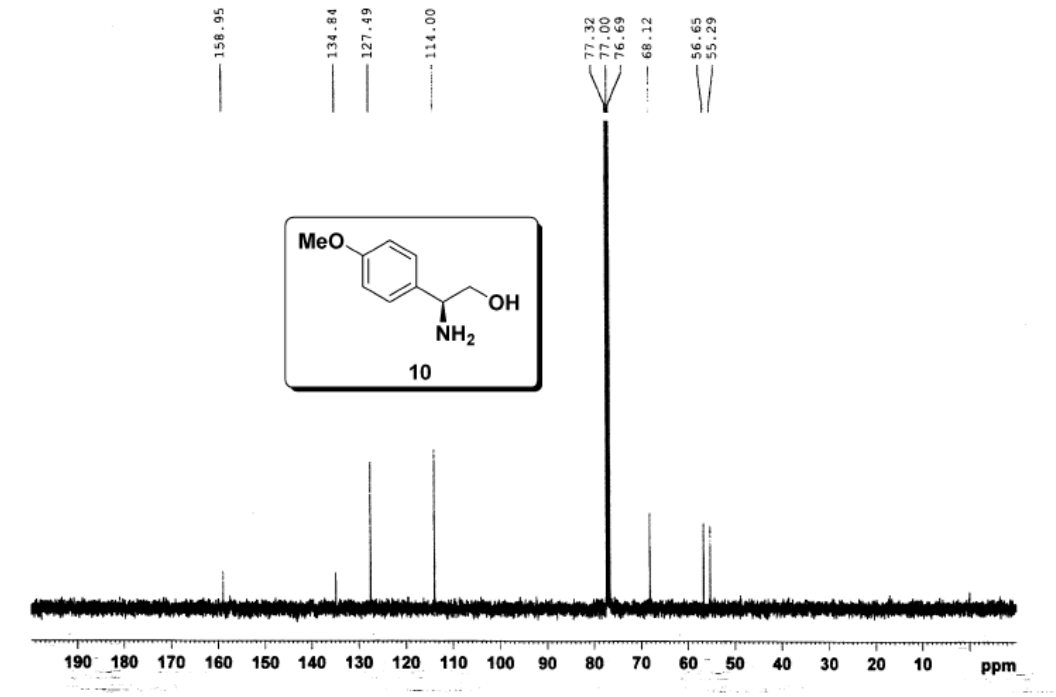

MeO
CO2Me
NHCO2Me
20
8
7
6
5
4
3
2
1
0
ppm
2.22
1.99
0.79
0.84
3.07
3.00
2.98

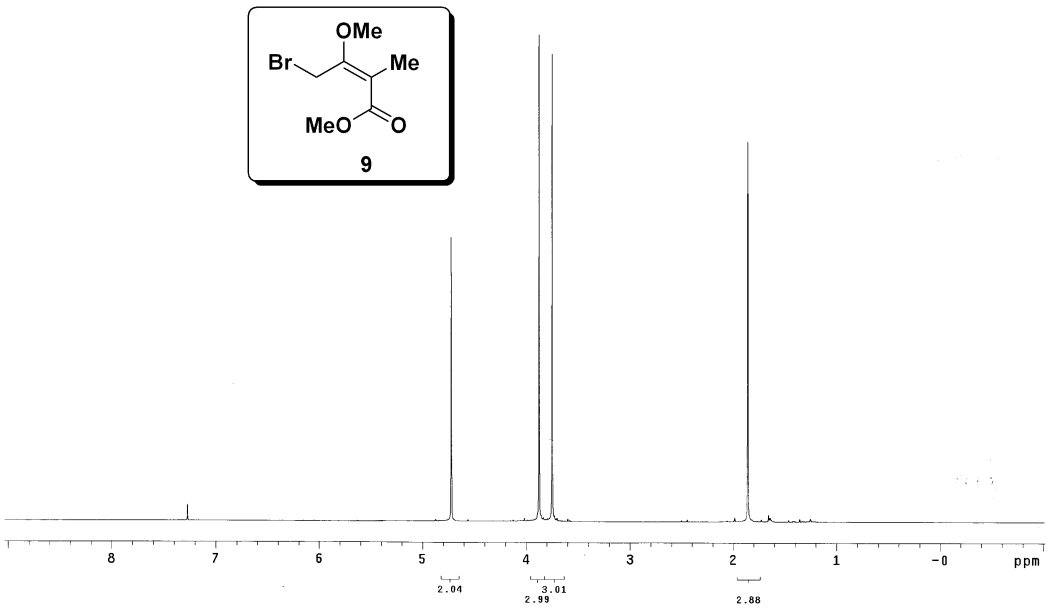

171.61
159.74
155.95
128.72
128.38
114.33
77.32
77.21
77.00
76.69
57.30
55.28
52.73
52.36
MeO
CO2Me
NHCO2Me
20
ppm

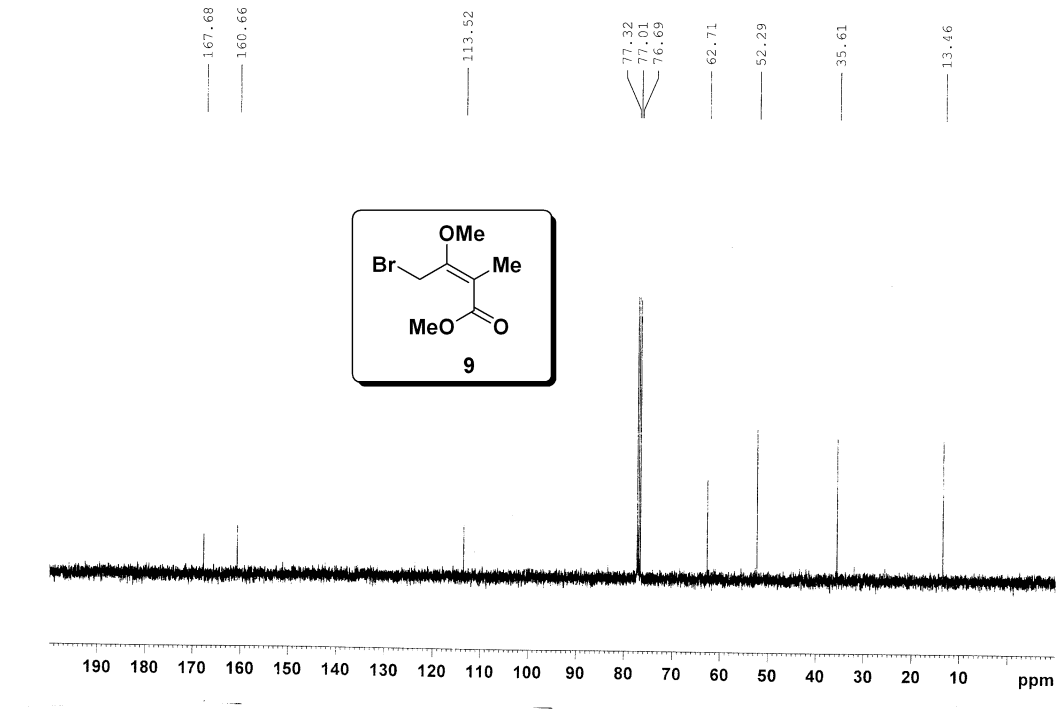

MeO
OH
NHCO2Me
21
3632.77
3613.82
3605.61
3446.53
3439.06
2716.43
2389.76
1911.32
1906.35
1895.88
1893.85
1184.48
880.45
8
7
6
5
4
3
2
1
ppm
3.52
3.48
1.77
1.85
2.705.58
6.35
1.43
0.32

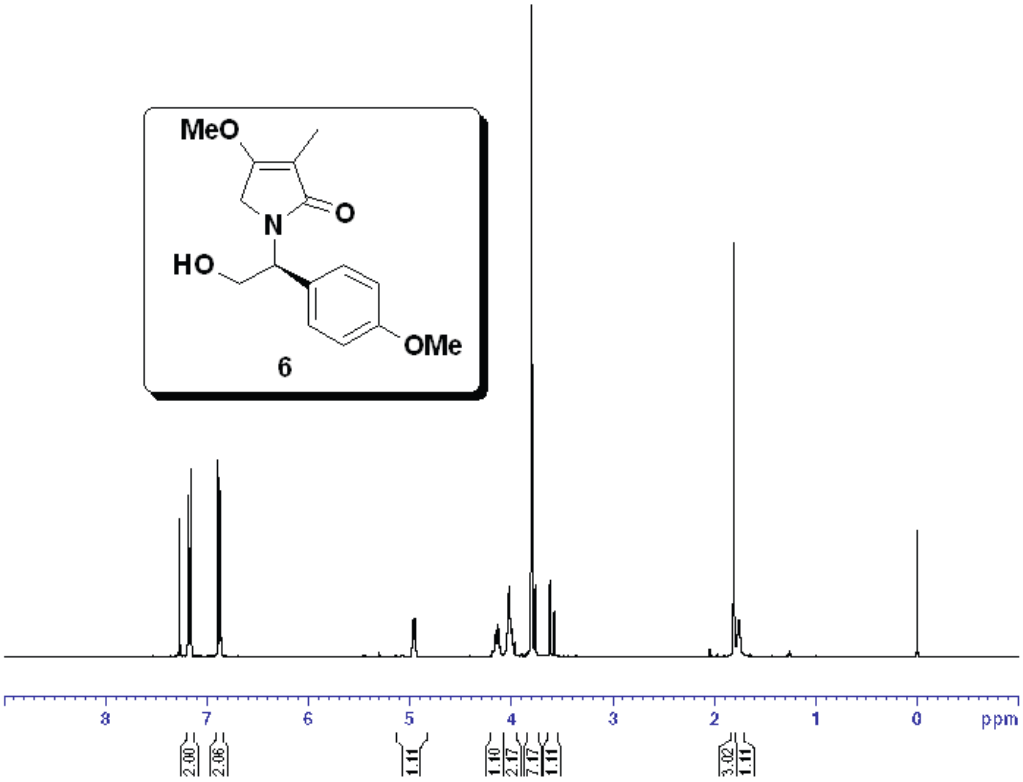

MeO
OH
NHCO2Me
21
159.178
157.092
131.187
127.894
114.184
77.287
77.000
76.757
66.473
56.553
55.287
52.332
200
180
160
140
120
100
80
60
40
20
ppm

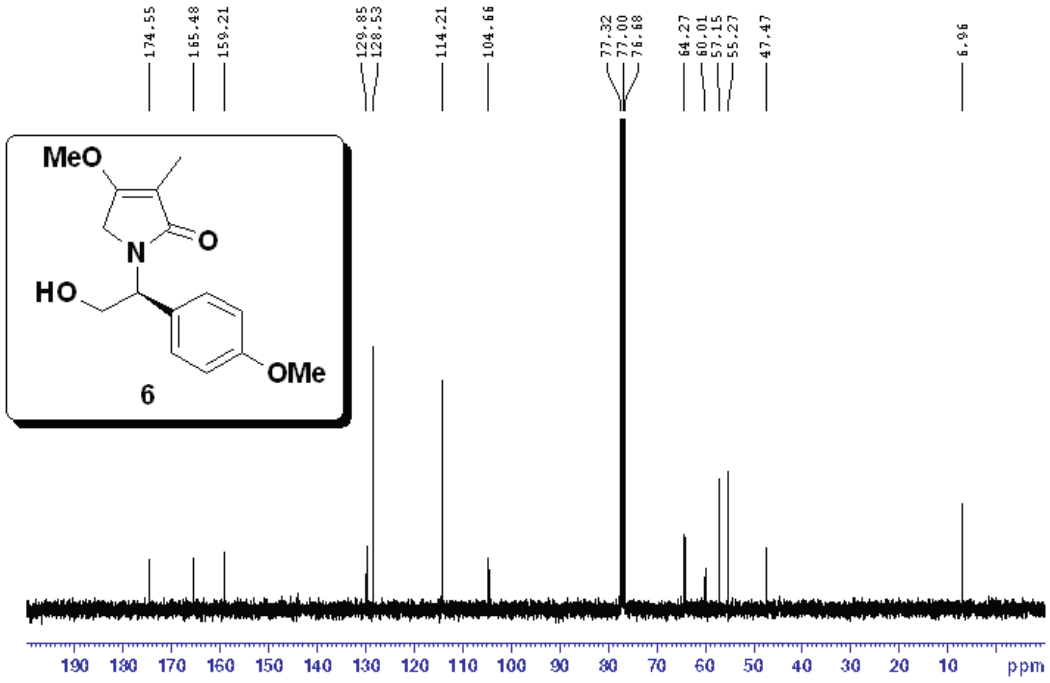

MeO
OH
NH2
10
9
8
7
6
5
4
3
2
1
0
ppm
2.33
2.00
1.00
3.00
1.00
1.00

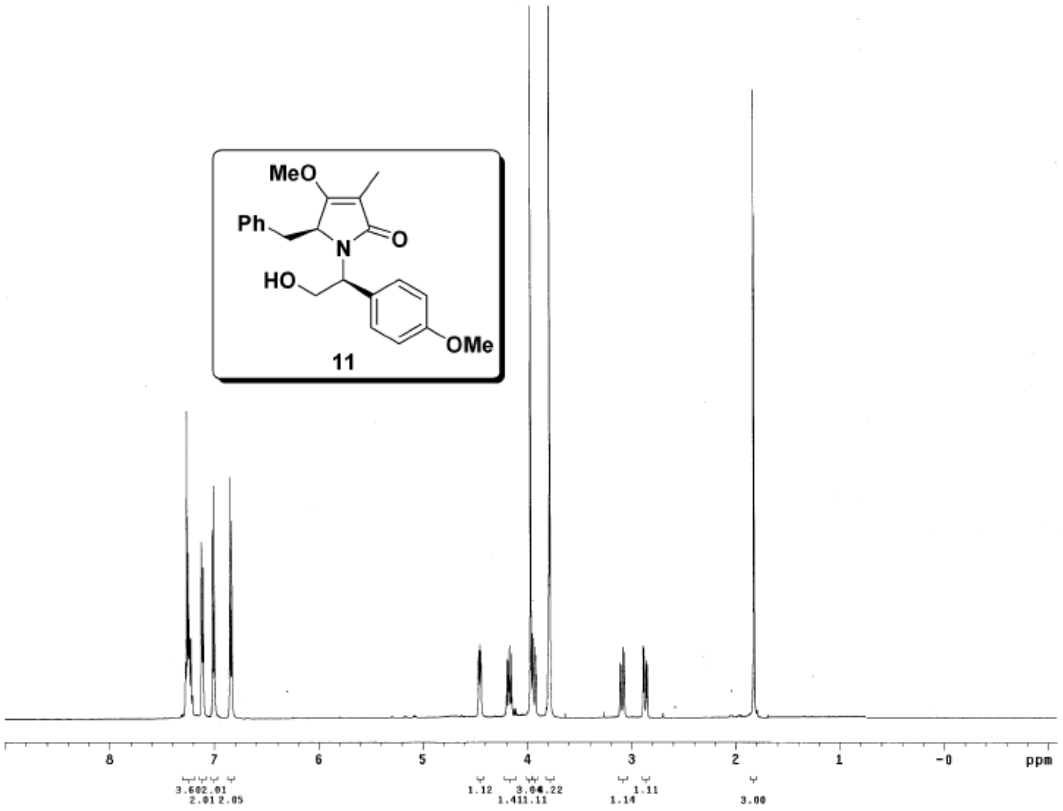

158.95
134.84
127.49
114.00
77.32
77.00
76.69
68.12
56.65
55.29
MeO
OH
NH2
10
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

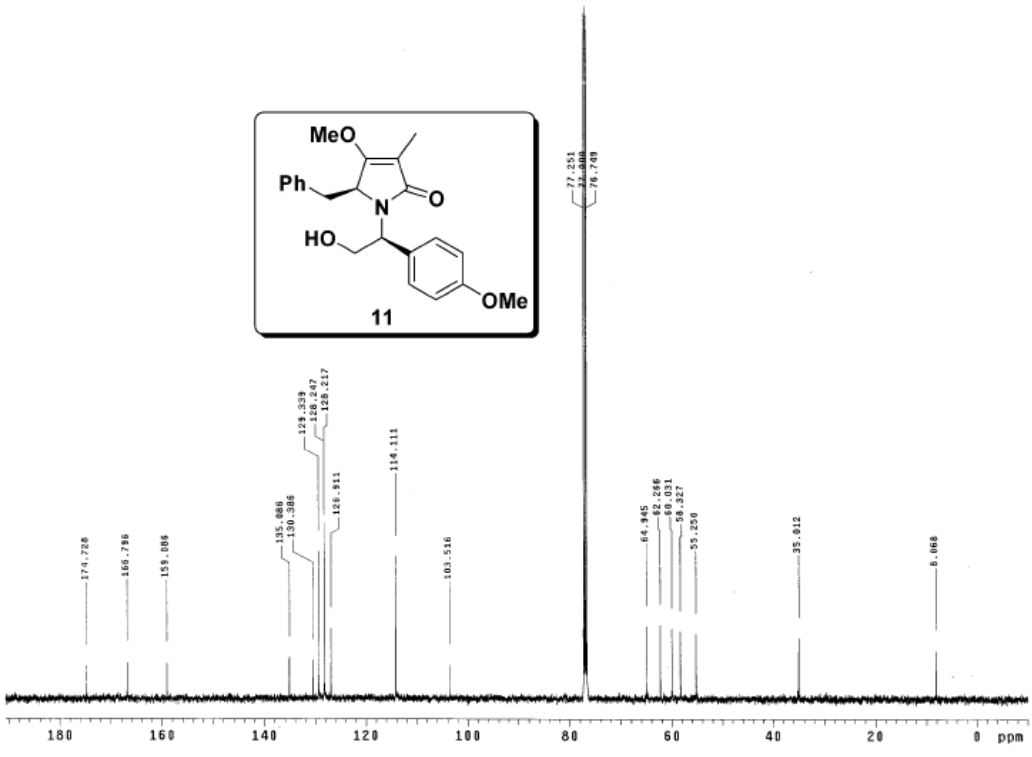

OMe
Br
Me
MeO
O
9
8
7
6
5
4
3
2
1
-0
ppm
2.04
3.01
2.99
2.88


167.68
160.66
113.52
77.32
77.01
76.69
62.71
52.29
35.61
13.46
OMe
Br
Me
MeO
O
9
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
O
N
HO
OMe
6
3
7
6
5
4
3
2
1
0
ppm
2.00
2.06
1.11
1.10
2.17
2.12
1.11
3.02
1.11


174.55
165.48
159.21
129.85
128.53
114.21
104.66
77.32
77.00
76.68
64.27
60.01
57.15
55.27
47.47
6.96
MeO
O
N
HO
OMe
6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
Ph
N
O
HO
OMe
11
8
7
6
5
4
3
2
1
-0
ppm


MeO
Ph
N
O
HO
OMe
11
77.251
76.748
174.728
166.796
159.086
135.688
130.386
129.039
128.247
128.217
126.911
114.111
103.516
64.945
62.266
60.031
56.327
55.250
35.012
8.068
180
160
140
120
100
80
60
40
20
0
ppm

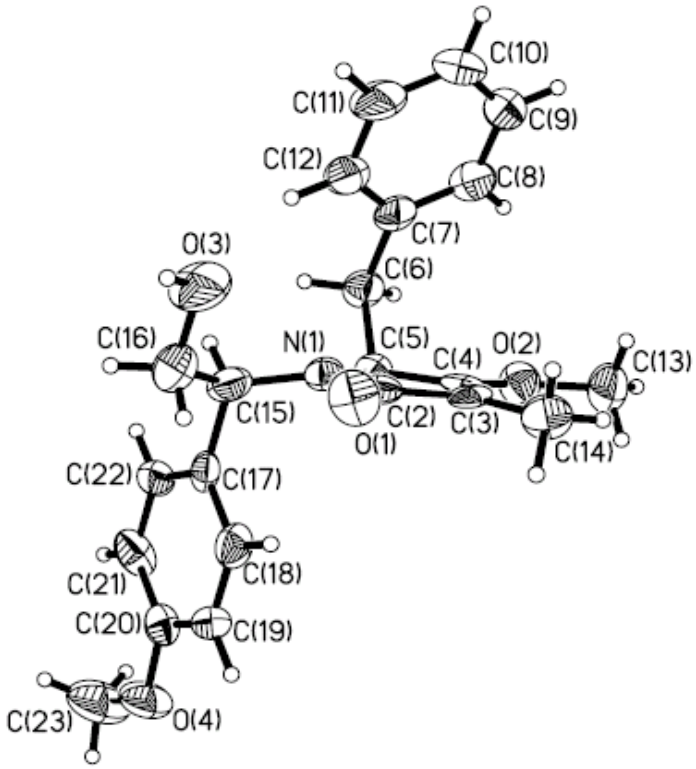
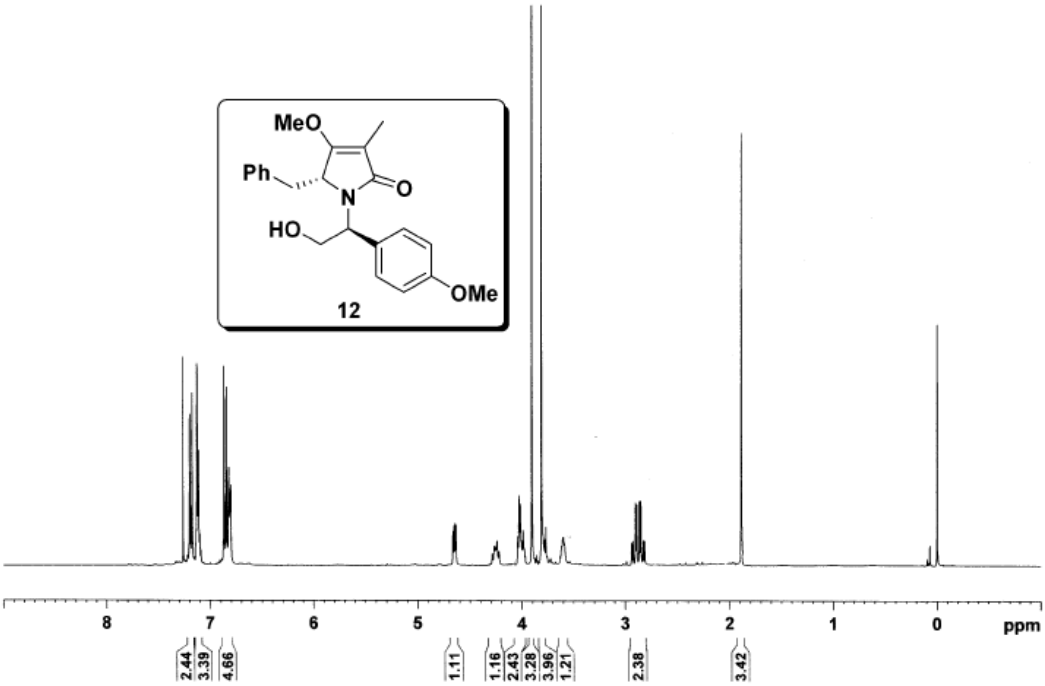
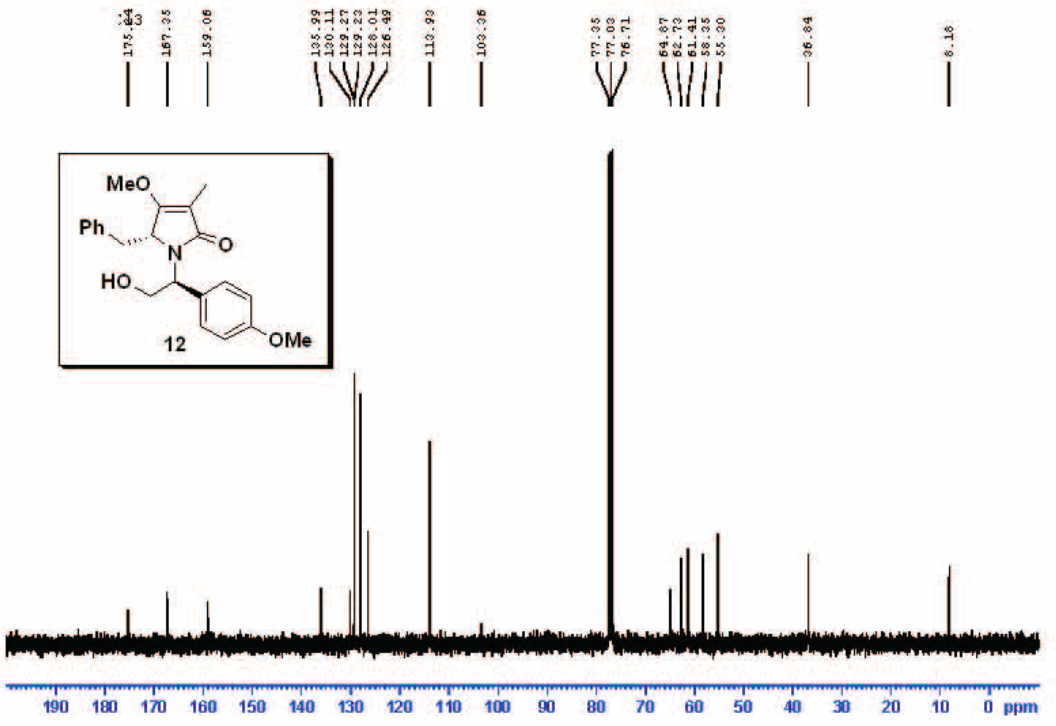
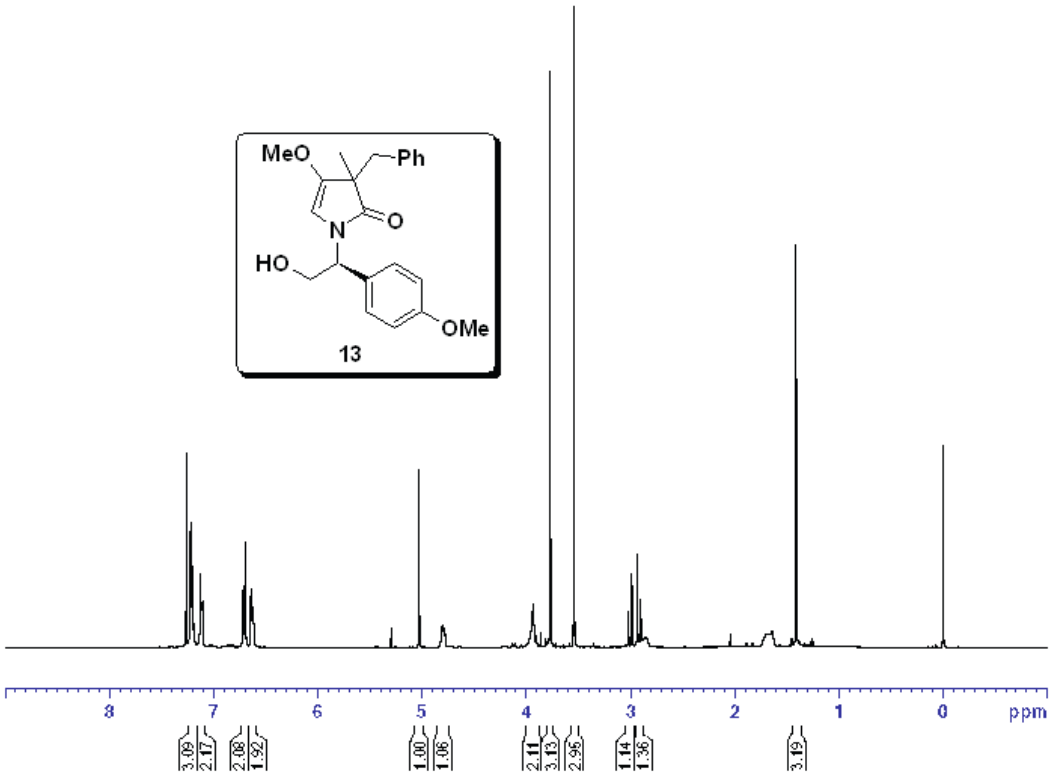
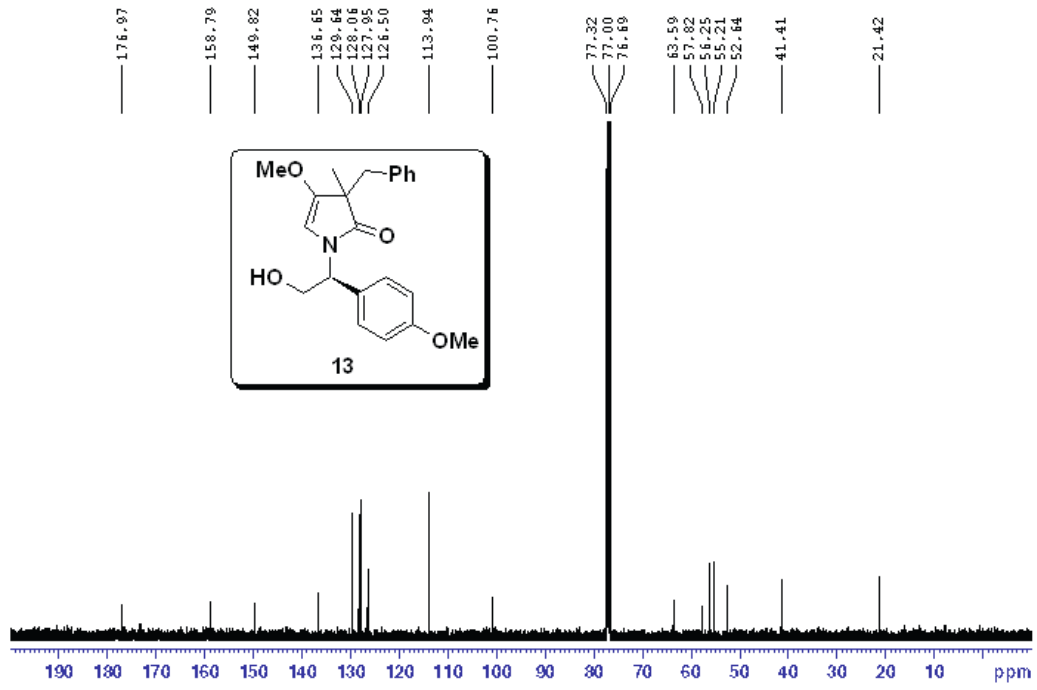


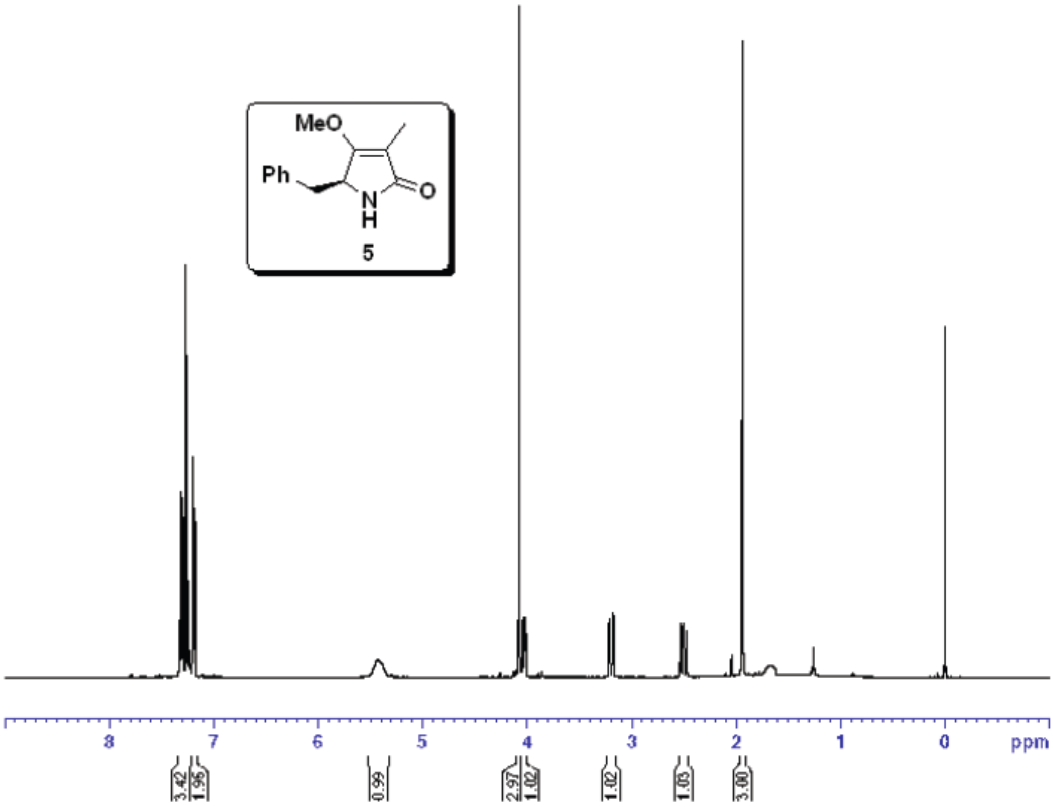
Figure 1. The X-ray structure of methyl tetramate derivative **11**.

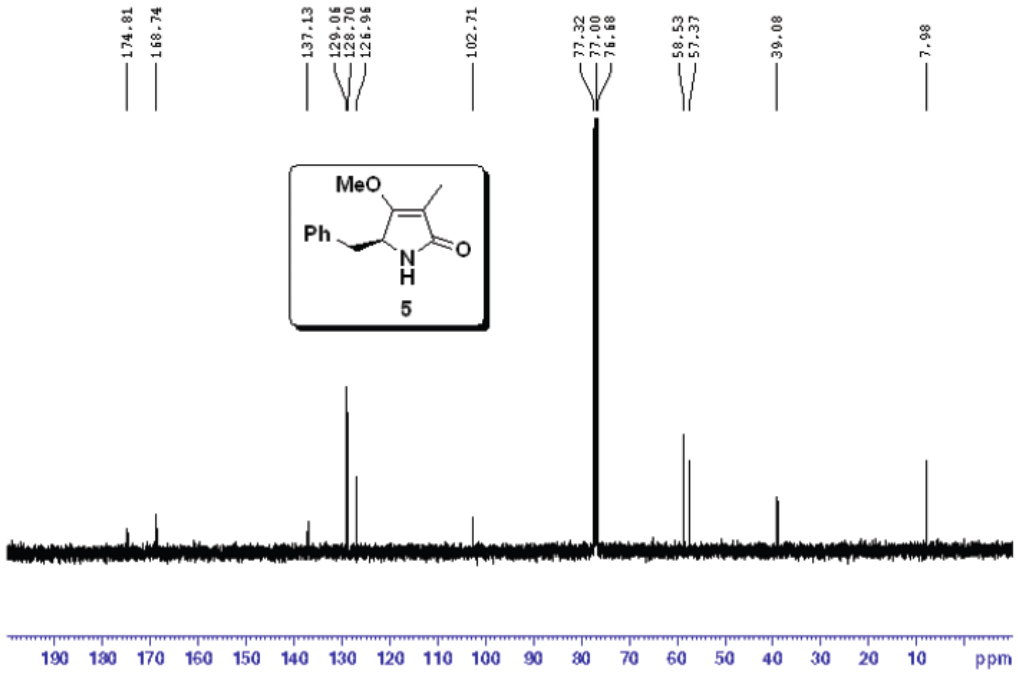

MeO
Ph
N
O
HO
OMe
12
8
7
6
5
4
3
2
1
0
ppm
2.44
3.39
4.66
1.11
1.16
2.43
3.28
3.96
1.21
2.38
3.42

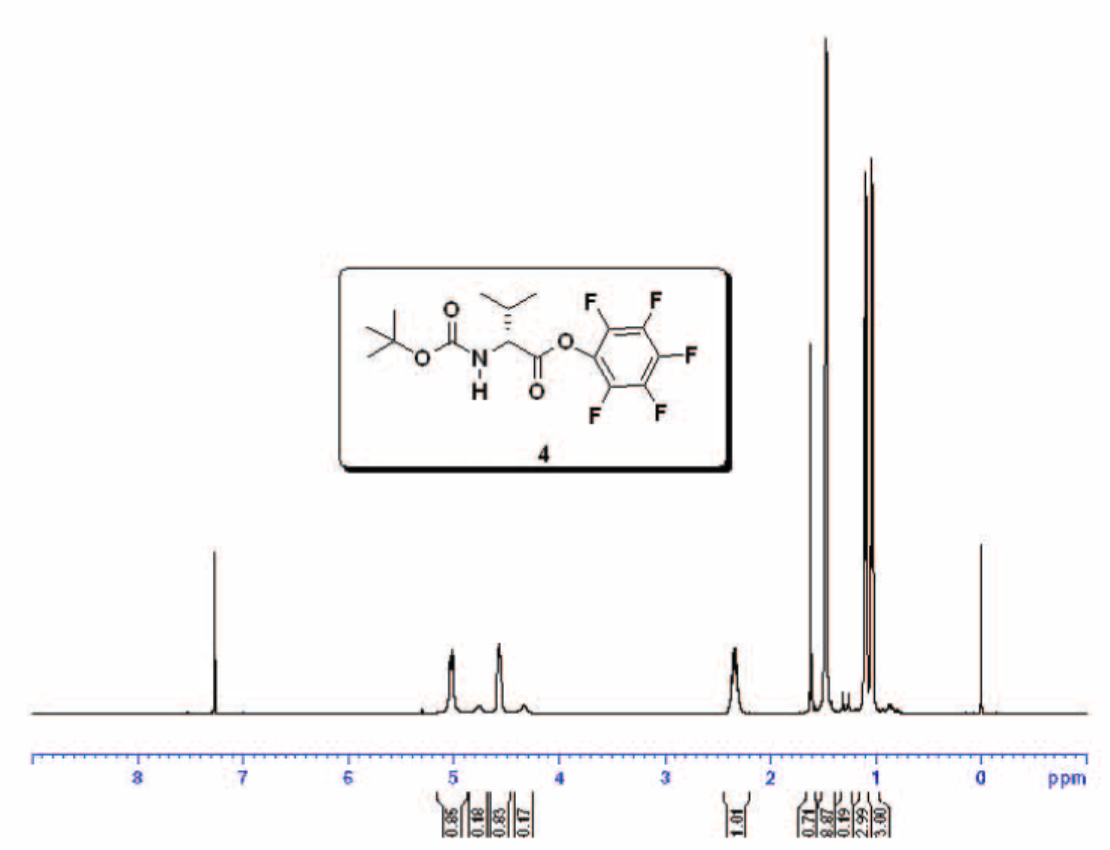

175.24
167.35
159.06
135.99
130.11
129.27
129.23
128.01
126.49
113.93
100.36
77.35
77.08
76.71
64.87
62.73
61.41
58.35
55.30
36.84
6.16
MeO
Ph
N
O
HO
OMe
12
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

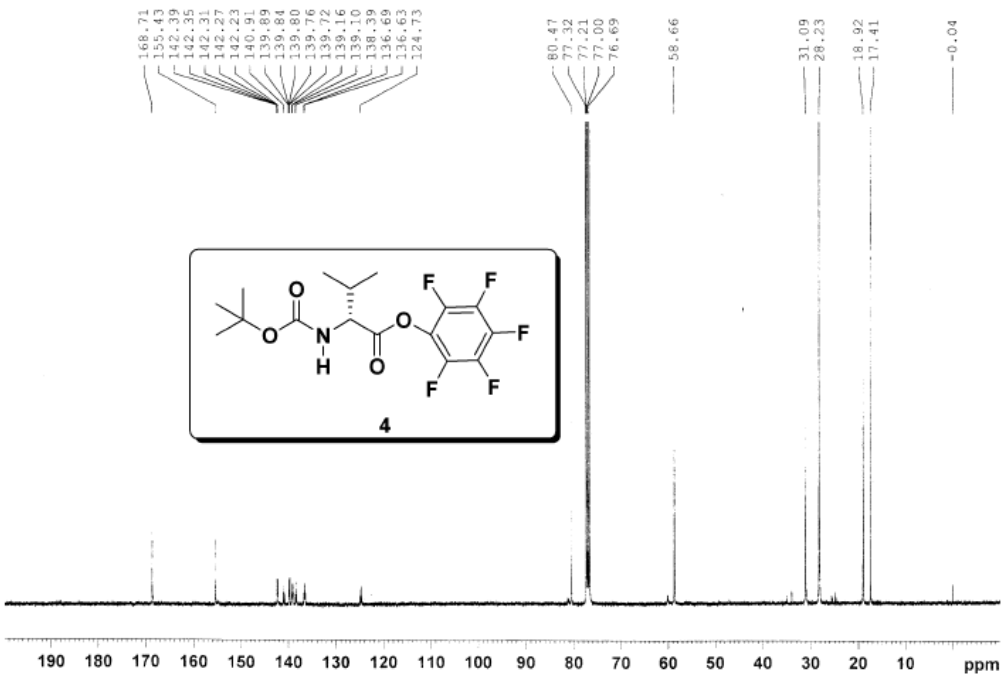

MeO
Ph
O
N
HO
OMe
13
8
7
6
5
4
3
2
1
0
ppm
3.09
2.17
2.08
1.92
1.00
1.06
2.11
3.13
2.96
1.14
1.36
3.19

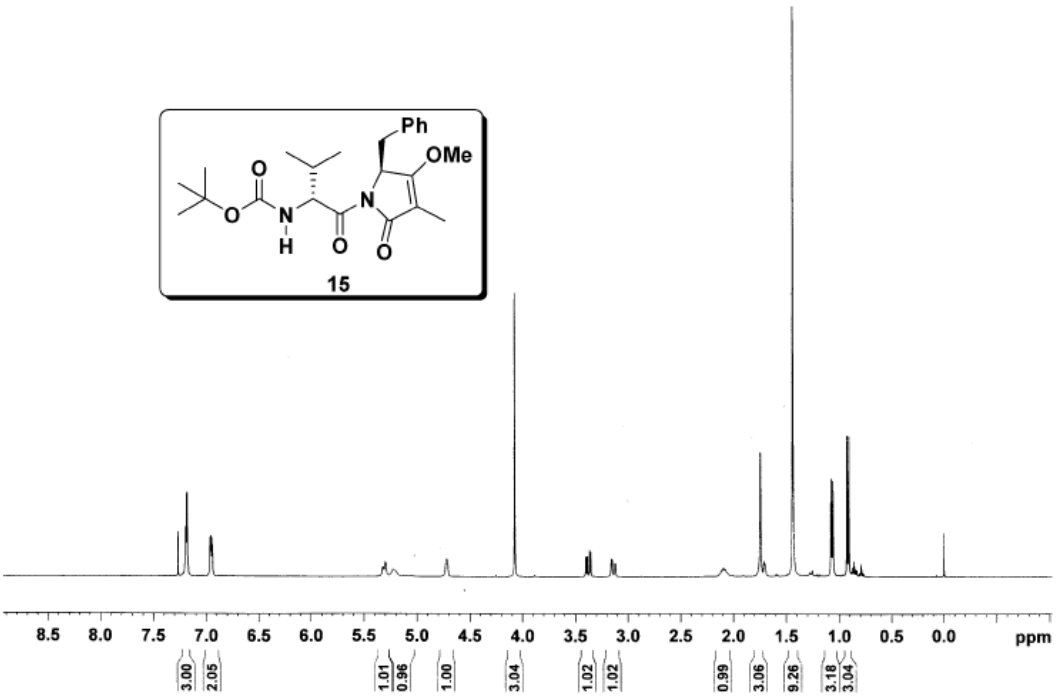

176.97
158.79
149.82
136.65
129.64
128.06
127.95
126.50
113.94
100.76
77.32
77.00
76.69
63.59
57.82
56.25
55.21
52.64
41.41
21.42
MeO
Ph
O
N
HO
OMe
13
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

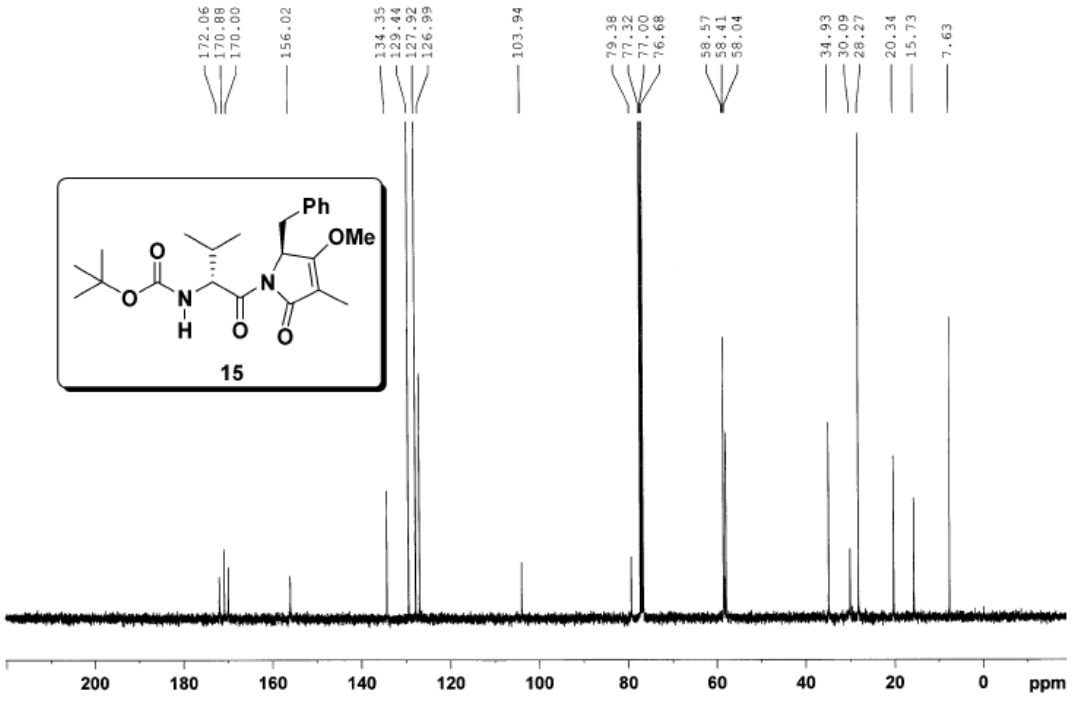

MeO
Ph
N
H
O
5
8
7
6
5
4
3
2
1
0
ppm
3.42
1.95
0.99
2.97
1.02
1.02
1.03
3.00

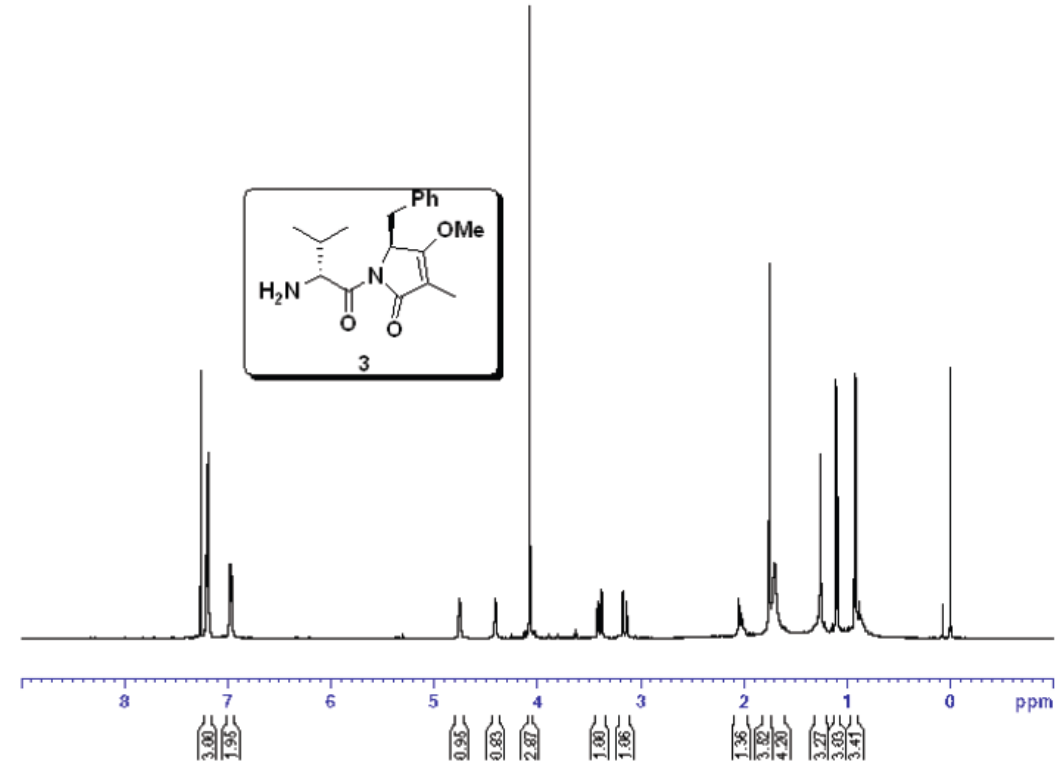

174.81
168.74
137.13
129.06
128.70
126.96
102.71
77.32
77.00
76.68
58.53
57.37
39.08
7.98
MeO
Ph
N
H
O
5
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

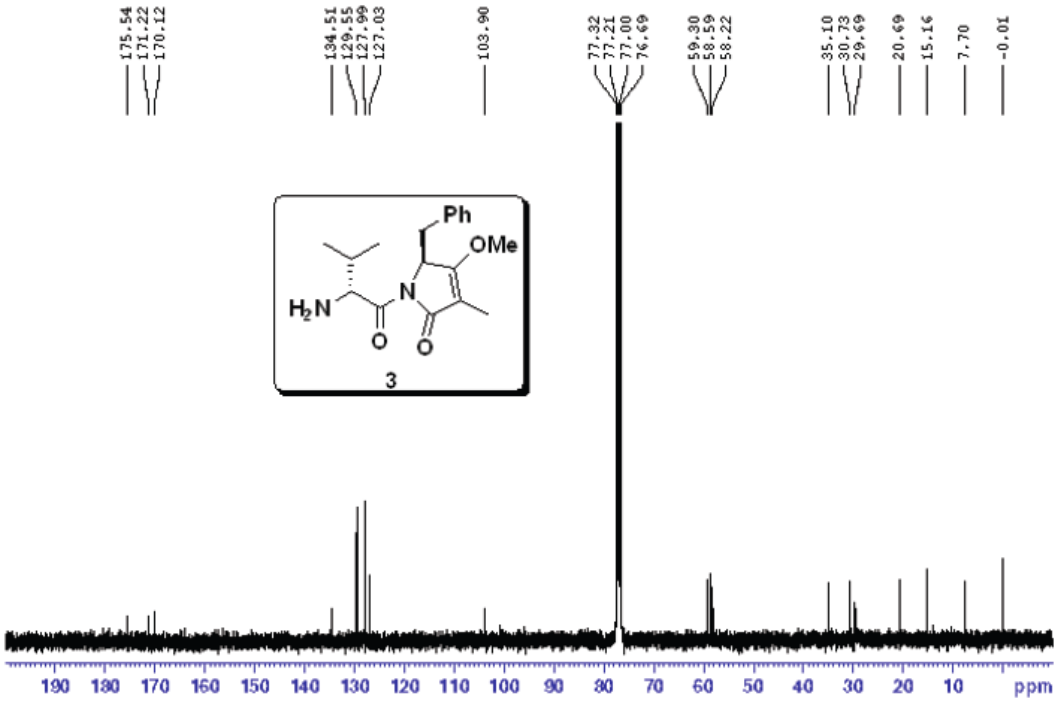

4
3
7
6
5
4
3
2
1
0
ppm
0.85
0.16
0.83
0.17
1.01
0.71
8.87
0.19
2.99
3.00

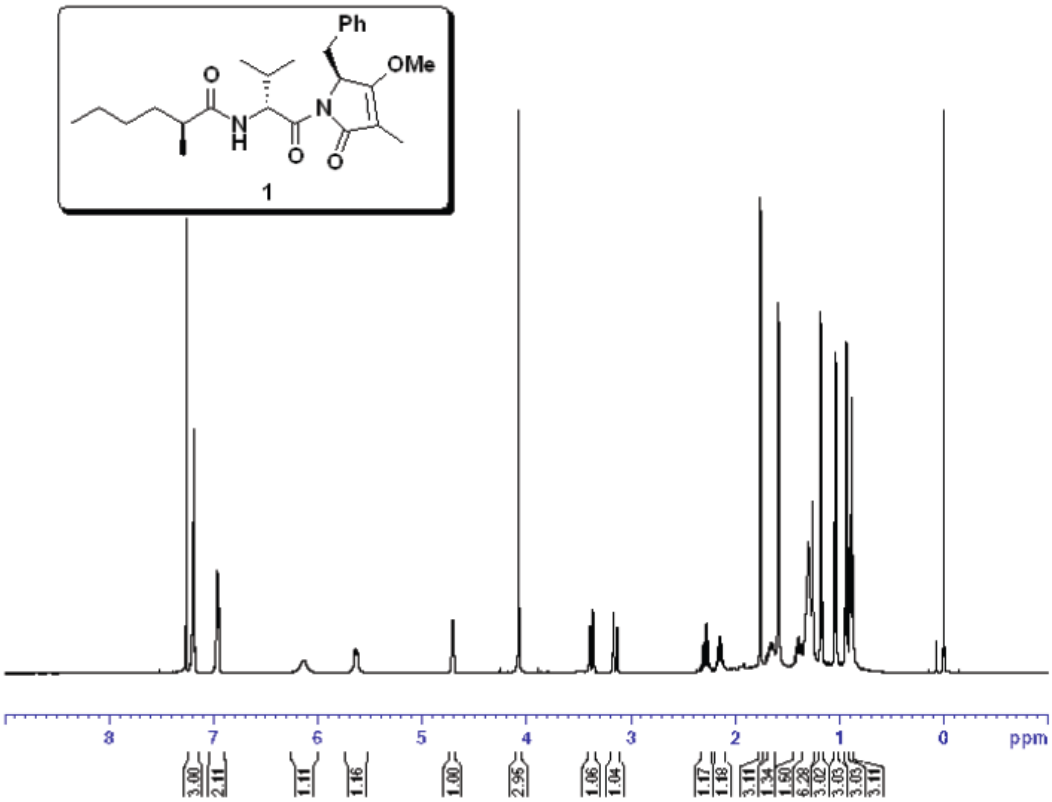

168.71
155.43
142.39
142.35
142.31
142.27
142.23
140.91
139.89
139.84
139.80
139.76
139.72
139.16
139.10
138.39
136.69
136.63
124.73
80.47
77.32
77.21
77.00
76.69
58.66
31.09
28.23
18.92
17.41
-0.04
4
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

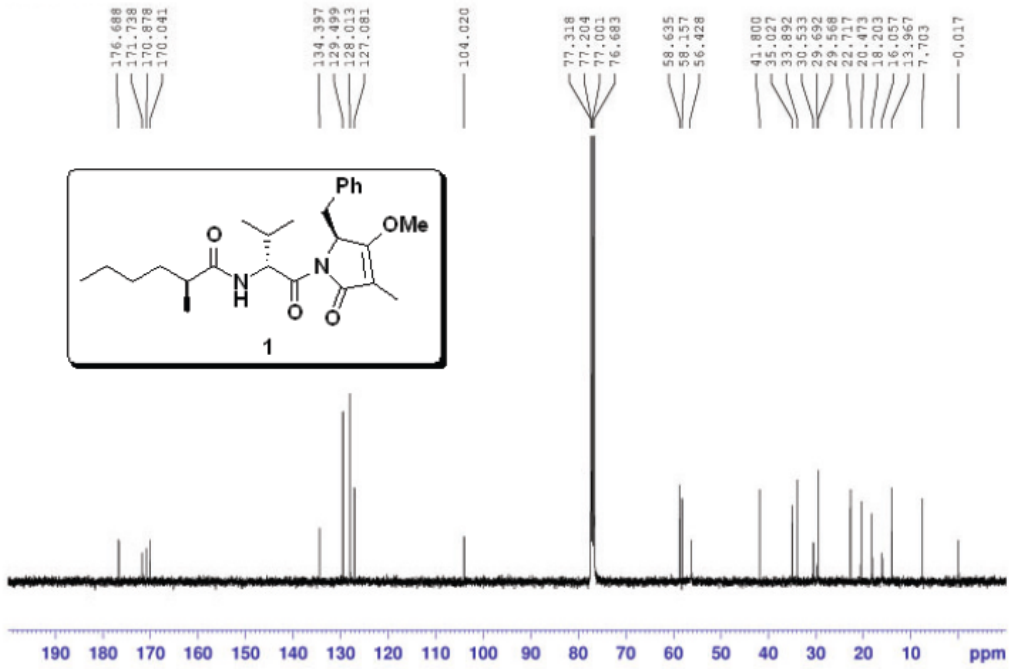

Ph
OMe
O
N
H
O
O
O
N
15
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
3.00 2.05 1.01 0.96 1.00 3.04 1.02 1.02 0.99 3.06 9.26 3.18 3.04

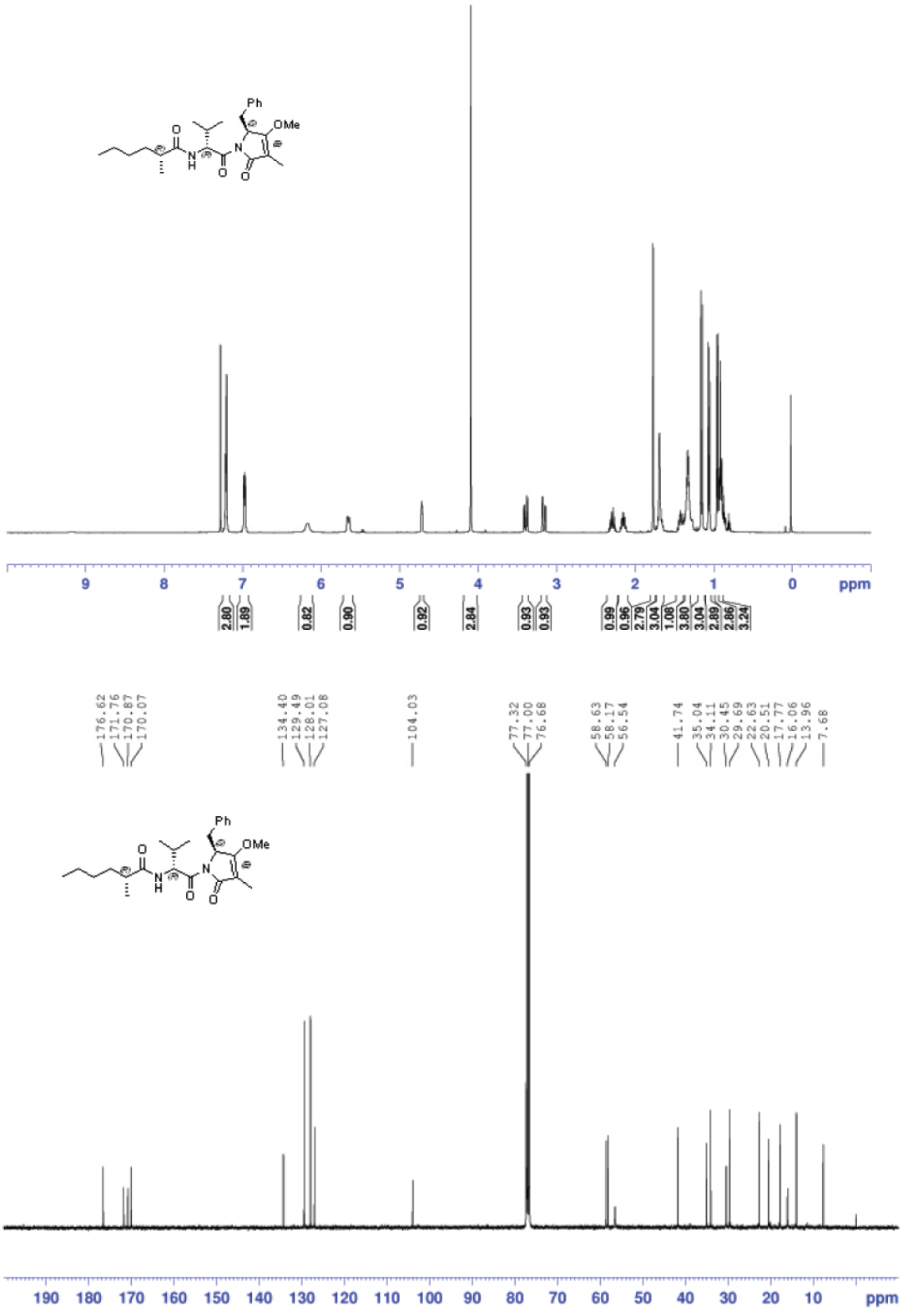

172.06
170.88
170.00
156.02
134.35
129.44
127.92
126.99
103.94
79.38
77.32
77.00
76.68
58.57
58.41
58.04
34.93
30.09
28.27
20.34
15.73
7.63
Ph
OMe
O
N
H
O
O
O
N
15
200 180 160 140 120 100 80 60 40 20 0 ppm


Ph
OMe
H_2N
N
O
O
3
8
7
6
5
4
3
2
1
0
ppm
3.00
1.95
0.95
0.83
2.87
1.00
1.06
1.36
3.82
4.20
3.27
3.03
3.41


175.54
171.22
170.12
134.51
129.55
127.99
127.03
103.90
77.32
77.21
77.00
76.69
59.30
58.59
58.22
35.10
30.73
29.69
20.69
15.16
7.70
-0.01
Ph
OMe
H_2N
N
O
O
3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Ph
OMe
O
N
H
O
N
O
O
1
8
7
6
5
4
3
2
1
0
ppm
3.00
2.11
1.11
1.16
1.00
2.95
1.06
1.04
1.17
1.18
3.11
1.34
1.50
6.28
3.02
3.05
3.05
3.11


176.688
171.738
170.878
170.041
134.397
129.499
128.013
127.081
104.020
77.318
77.204
77.001
76.683
58.635
58.157
56.428
41.800
35.027
33.892
30.533
29.692
29.568
22.717
20.473
18.203
16.057
13.967
7.703
-0.017
Ph
OMe
O
N
H
O
N
O
O
1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Ph
OMe
9 8 7 6 5 4 3 2 1 0 ppm
2.80 1.89 0.82 0.90 0.92 2.84 0.93 0.93 0.99 0.96 2.79 3.04 1.08 3.80 3.04 2.89 2.86 3.24
176.62 171.76 170.87 170.07 134.40 129.49 128.01 127.08 104.03 77.32 77.00 76.68 58.63 58.17 56.54 41.74 35.04 34.11 30.45 29.69 22.63 20.51 17.77 16.06 13.96 7.68
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm