Supporting Information

Stereoselective Synthesis and Rearrangement-Fragmentation of Arylidene *N*-Alkoxydiketopiperazines

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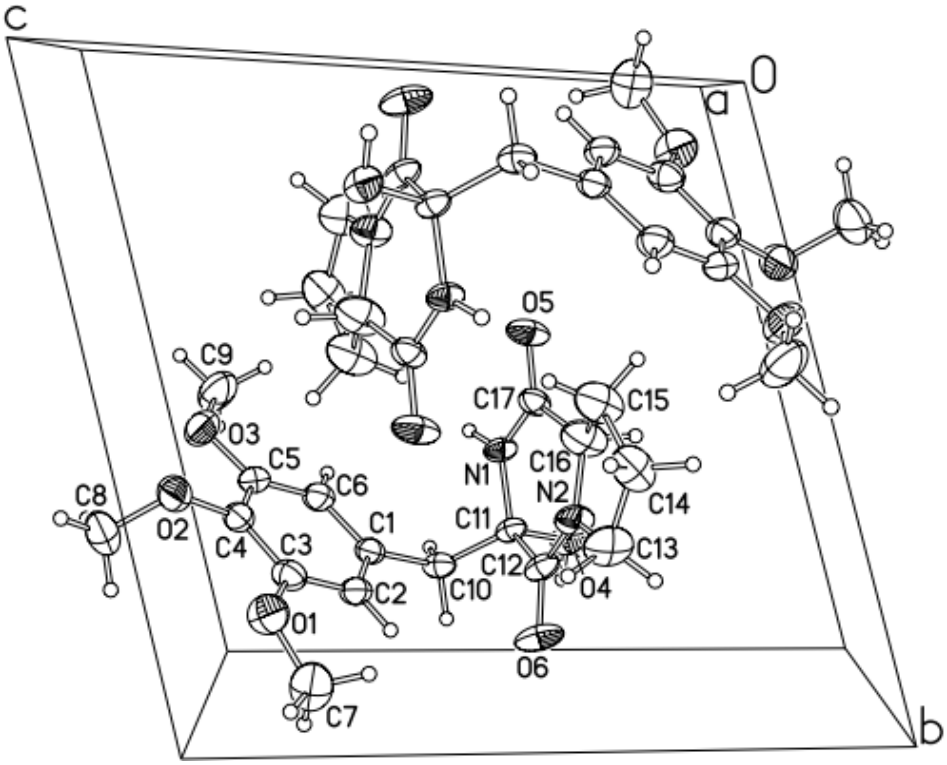
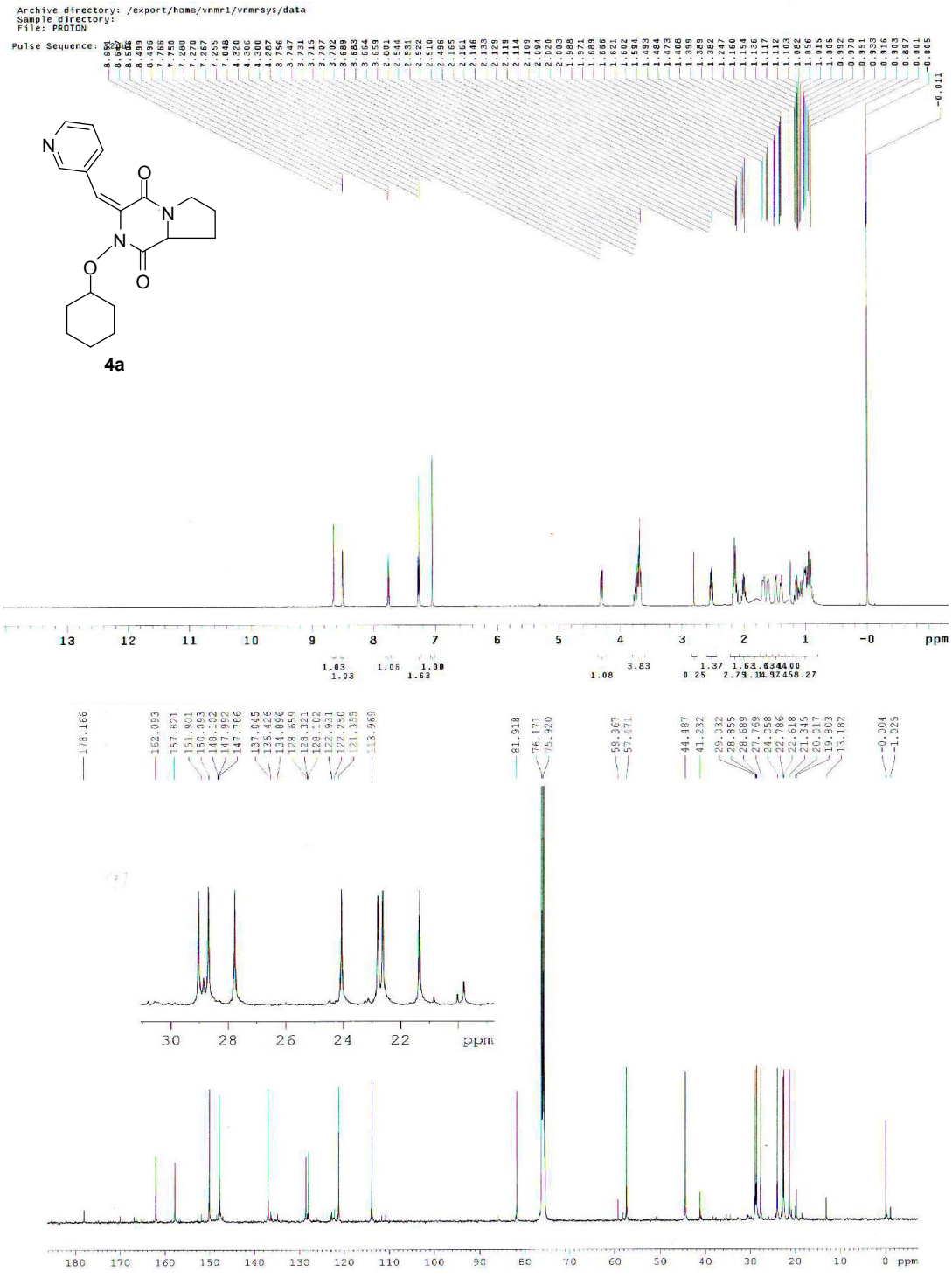


Figure 1. Enantiomers **5a** (top) and **6a** in the racemic crystal structure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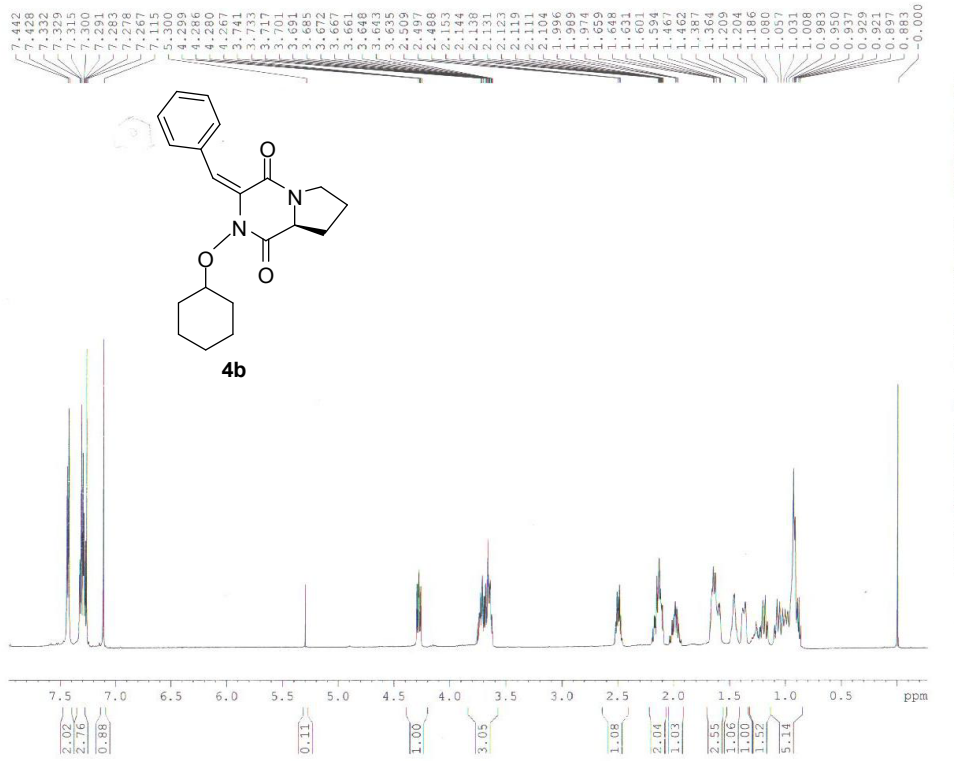
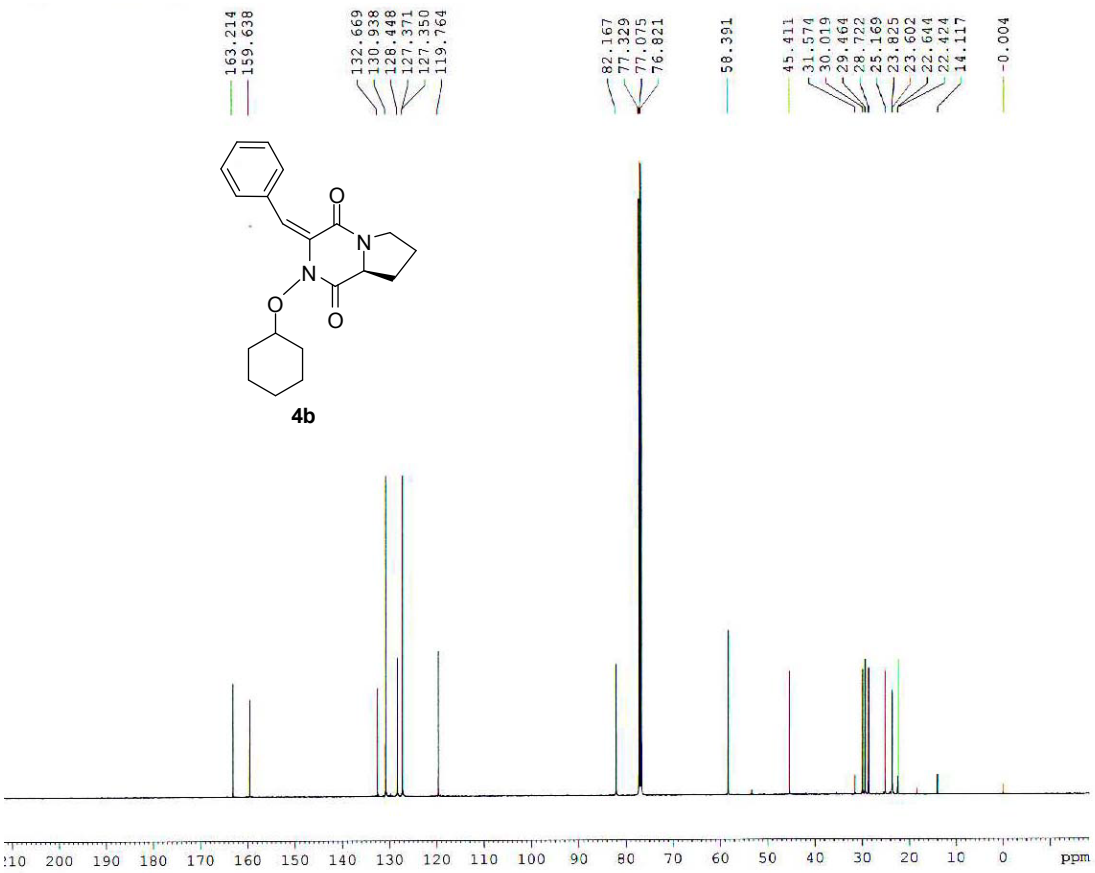
***Cyclo*[*N*-cyclohexyloxy-2-(phenylmethylene)glycyl-prolyl] 4b**

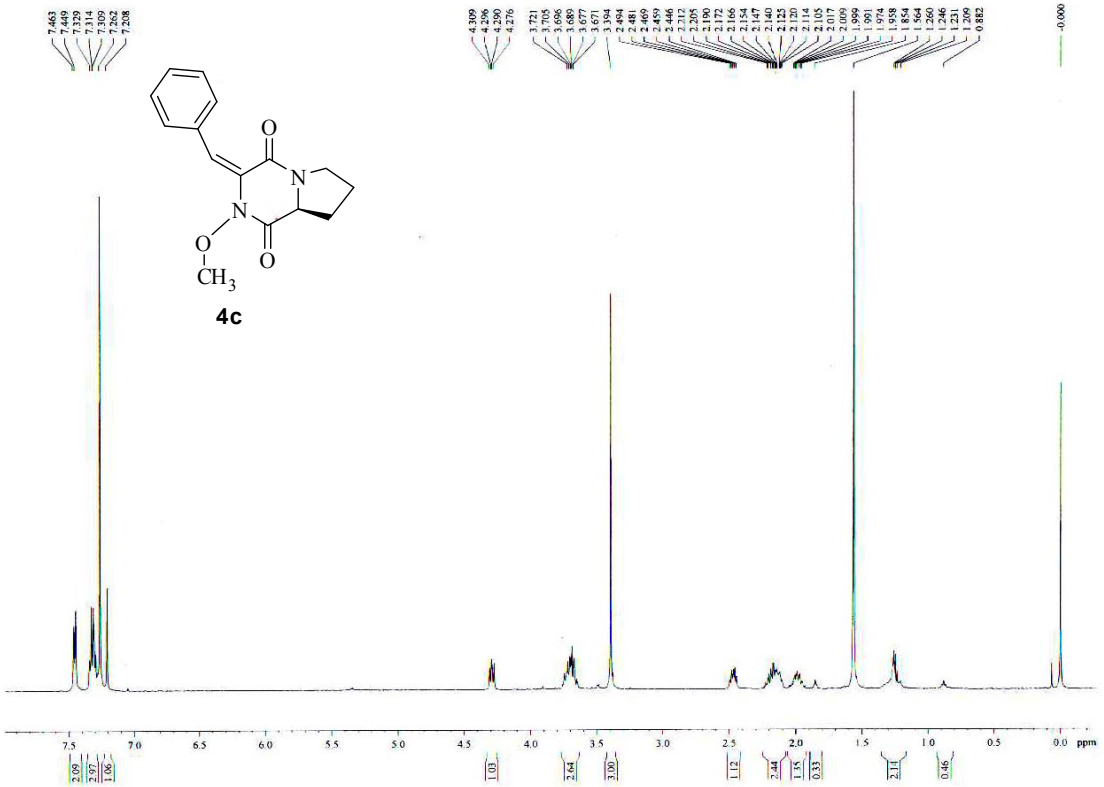
The product **4b** was obtained according to the general procedure in 85% yield after purification by flash chromatography (EtOAc/hexane, 1:2). IR (KBr) ν 1701, 1670, 1624, 1585, 1503 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 0.88-1.08 (m, 5H), 1.18-1.20 (m, 1H), 1.36-1.39 (m, 1H), 1.46-1.47 (m, 1H), 1.63-1.66 (m, 2H), 1.97-2.00 (m, 1H), 2.10-2.15 (m, 2H), 2.59-2.51 (m, 1H), 3.63-3.74 (m, 3H), 4.29 (q, J 6.5 Hz, 1H), 7.12 (s, 1H), 7.28-7.33 (m, 3H), 7.43 (d, J 7.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 163.2, 159.6, 132.7, 130.9(2), 128.4, 127.4(2), 119.8, 82.2, 58.4, 45.4, 30.0, 29.5, 28.7, 25.2, 23.8, 23.6, 22.6, 22.4; Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23; Found: C, 70.59; H, 7.15; N, 8.26.

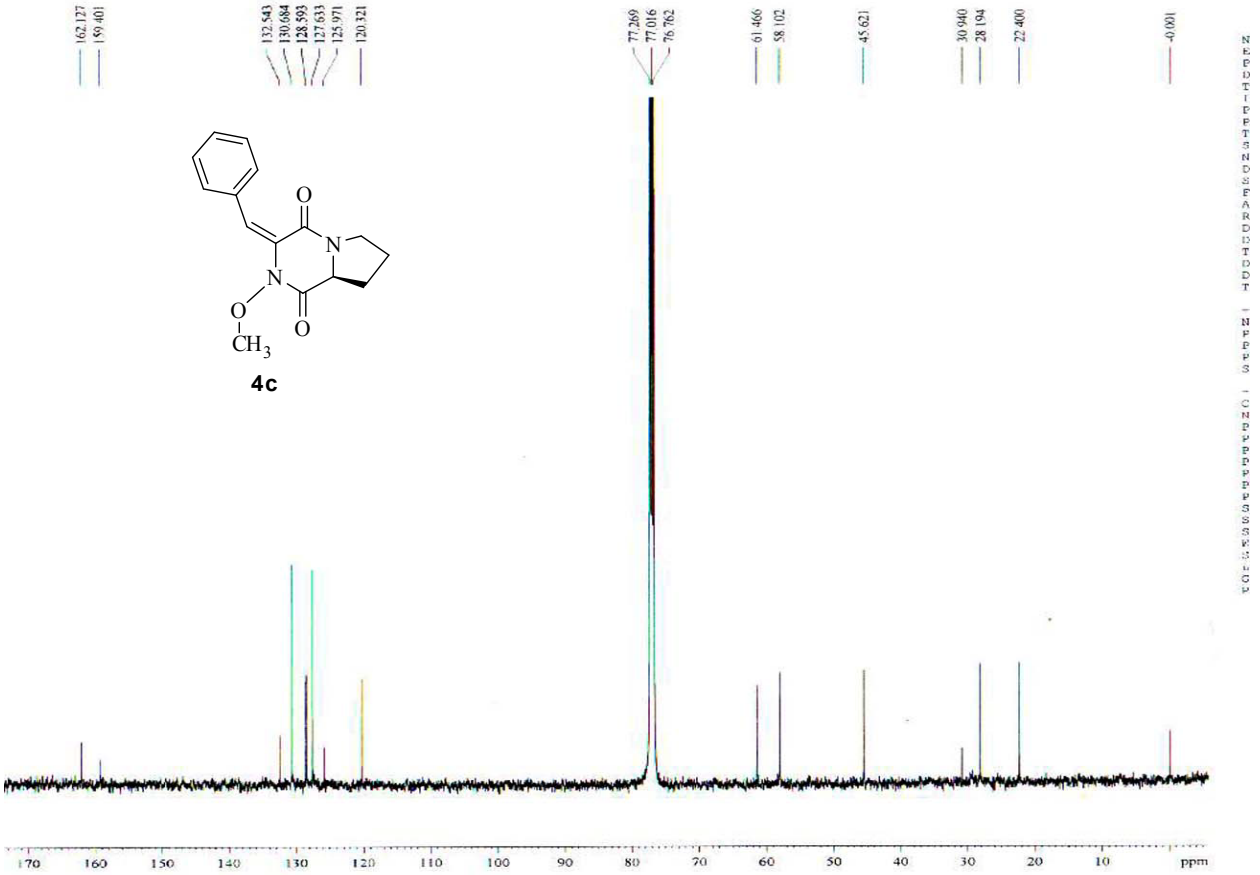




***Cyclo*[*N*-methyloxy-2-(phenylmethylene)glycyl-prolyl] 4c**

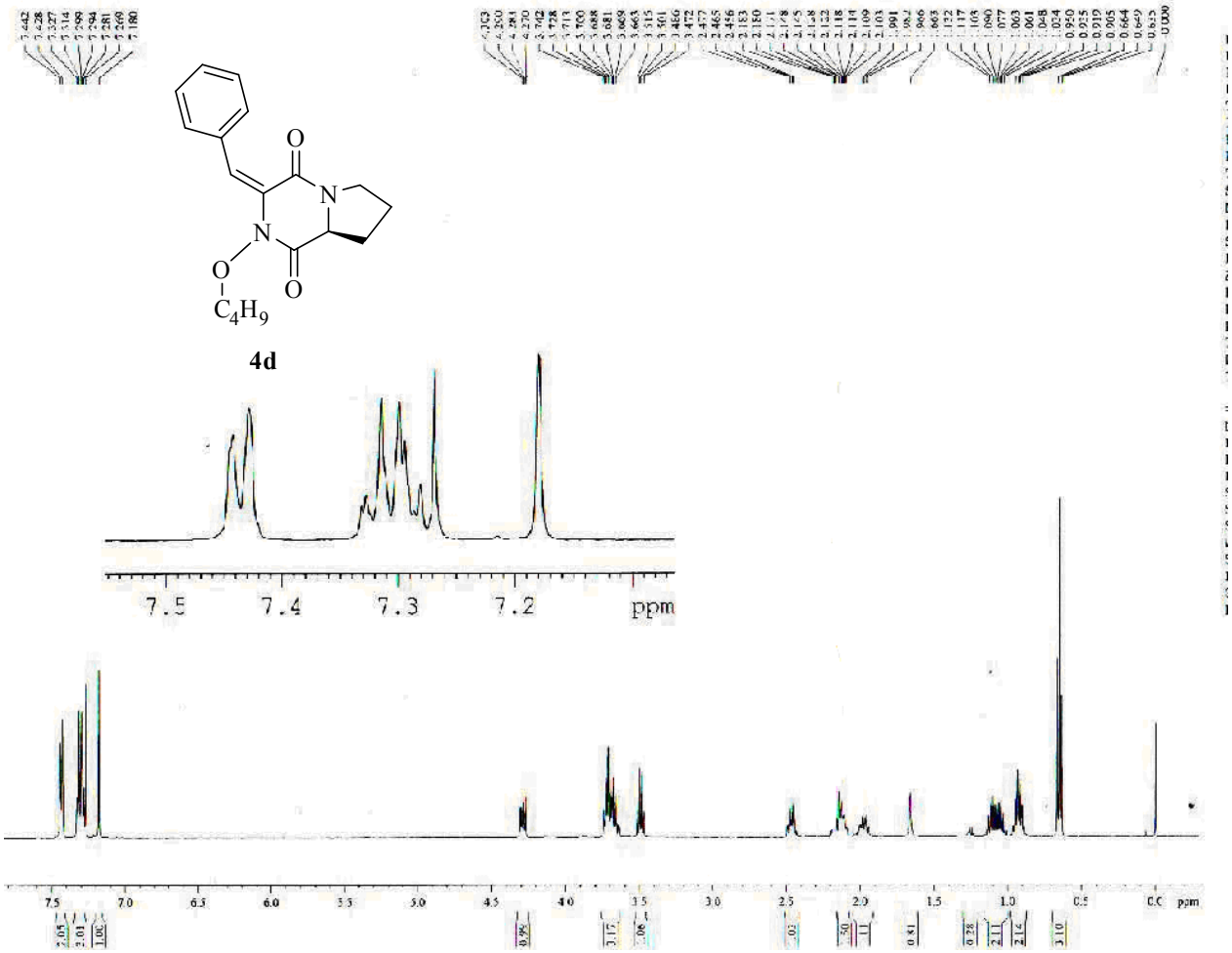
The product **4c** was obtained according to the general procedure in 87% yield after purification by flash chromatography (EtOAc/hexane, 1:2). Chiral HPLC analyses of the product showed a major peak for the (*S*)-enantiomer at R_f 14.5 min (99.3% e.e.) compared to racemic **4c** (synthesized by using racemic **3c**) which showed two equal peaks with R_fs of 14.5 min and 15.5 min for the (*S*)- and (*R*)-enantiomers respectively. IR (KBr) ν 1698, 1674, 1622, 1578, 1506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.85-2.02 (m, 1H), 2.11-2.21 (m, 2H), 2.45-2.49 (m, 1H), 3.39 (s, 3H), 3.67-3.72 (m, 2H), 4.29 (q, J 7.0 Hz, 1H), 7.21 (s, 1H), 7.31-7.33 (m, 3H), 7.45 (d, J 7.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 162.1, 159.4, 132.5, 130.7 (2), 128.6, 127.6 (2), 126.0, 120.3, 61.5, 58.1, 45.6, 28.2, 22.4; Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; Found: C,66.20; H, 5.97; N, 10.33.

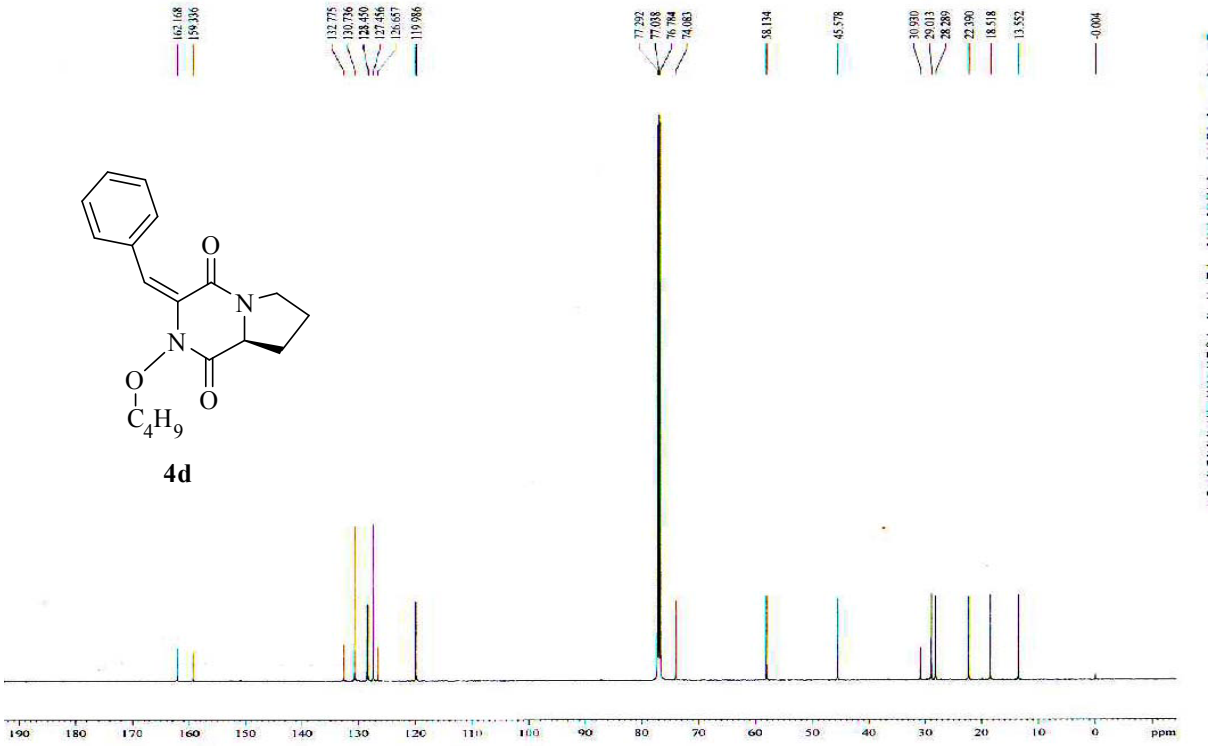




***Cyclo*[*N*-butyloxy-2-(phenylmethylene)glycyl-prolyl] 4d**

The product **4d** was obtained according to the general procedure in 80% yield after purification by flash chromatography (EtOAc/hexane, 1:2). IR (KBr) ν 1705, 1680, 1618, 1577, 1503 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 0.65 (t, J 7.0Hz, 3H), 0.91-0.95 (m, 2H), 1.03-1.13 (m, 2H), 1.96-1.99 (m, 1H), 2.10-2.18 (m, 2H), 2.46-2.48 (m, 1H), 3.49 (q, J 7.0 Hz, 1H), 3.66-3.74 (m, 3H), 4.29 (q, J 6.5 Hz, 1H), 7.18 (s, 1H), 7.28-7.33 (m, 3H), 7.44 (d, J 7.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 162.2, 159.3, 132.8, 130.7(2), 128.5, 127.5(2), 126.6, 120.0, 74.1, 58.1, 45.6, 29.0, 28.3, 22.4, 18.5, 13.6; Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91; Found: C,68.81; H, 7.09; N, 8.94.

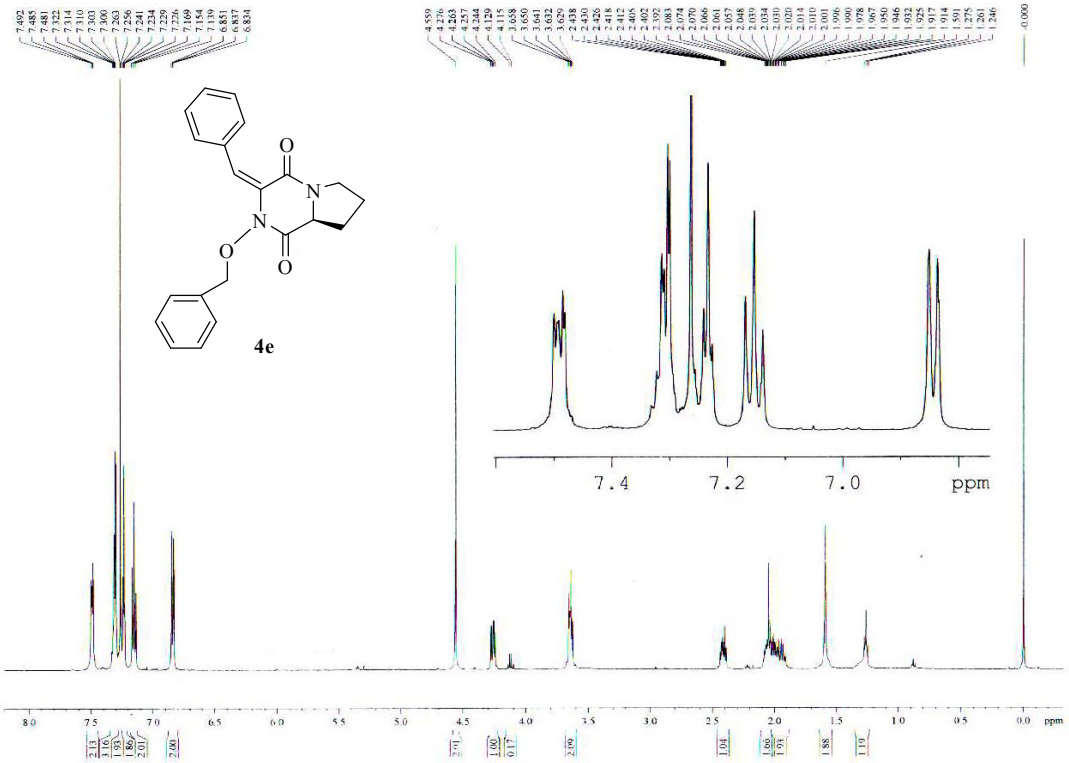


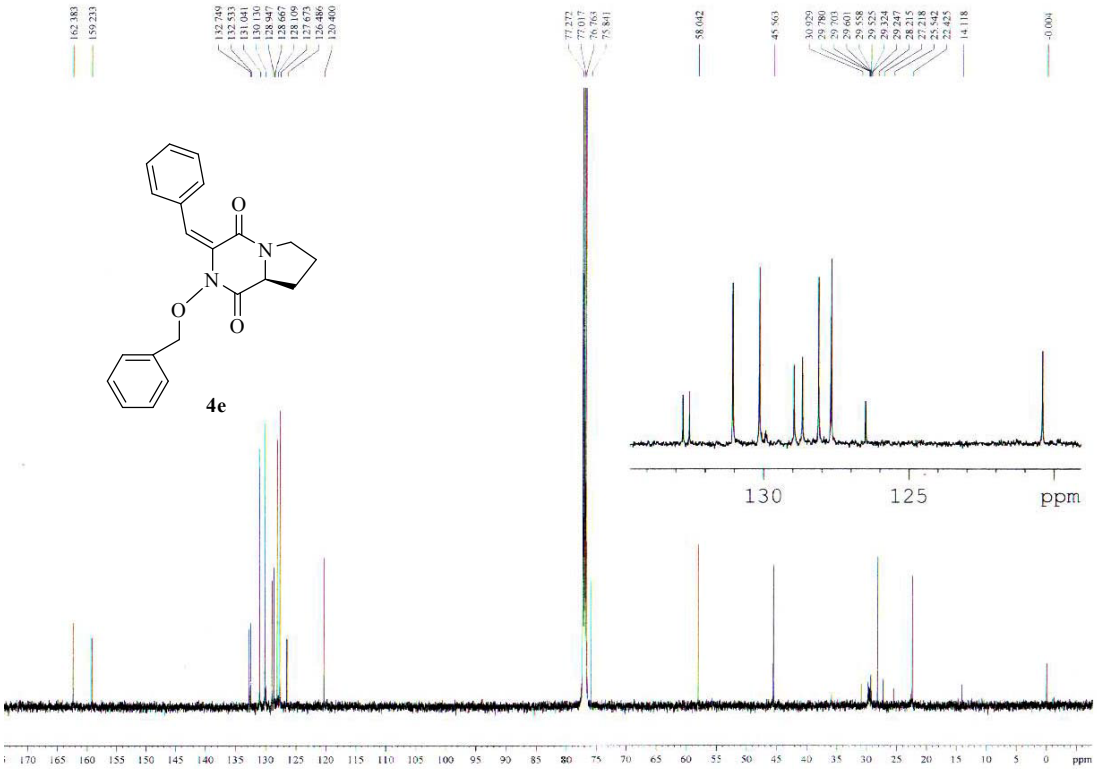


4d

***Cyclo*[*N*-benzyloxy-2-(phenylmethylene)glycyl-prolyl] 4e**

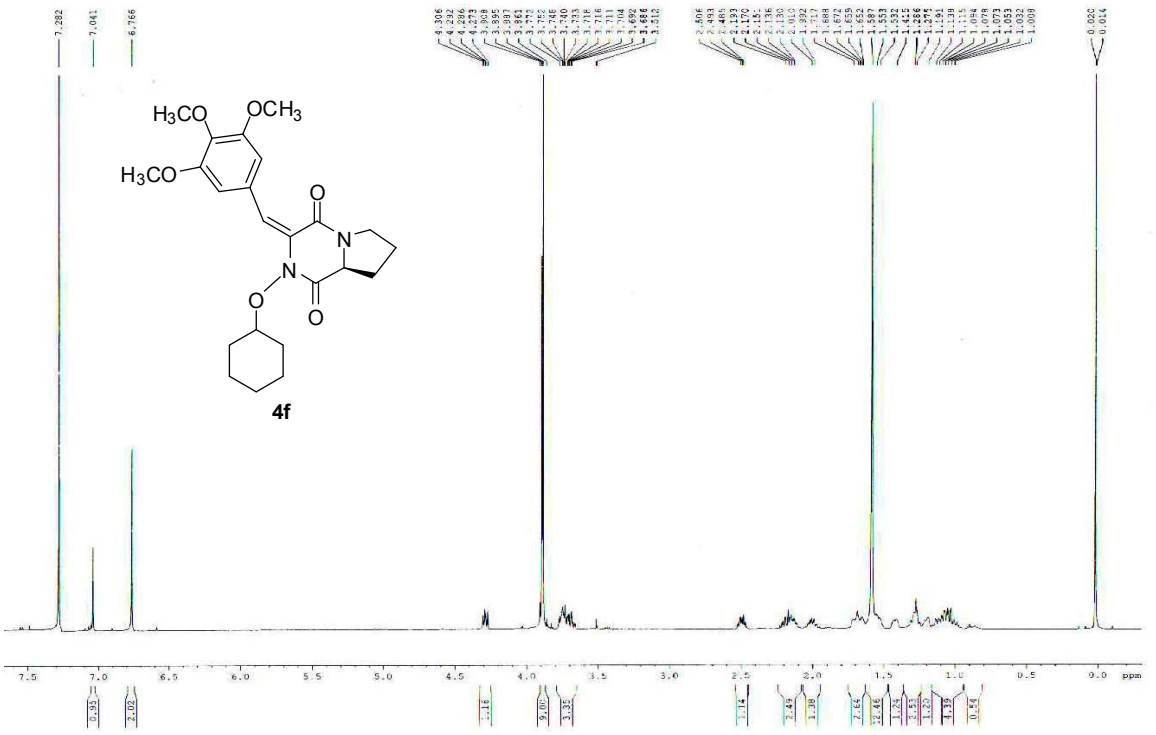
The product **4e** was obtained according to the general procedure in 88% yield after purification by flash chromatography (EtOAc/hexane, 1:2). IR (KBr) ν 1706, 1681, 1618, 1589, 1577, 1511, 1503 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 1.92-2.08 (m, 3H), 2.39-2.44 (m, 1H), 3.63-3.66 (m, 2H), 4.26 (q, J 6.5 Hz, 1H), 4.56 (s, 2H), 6.83-6.85 (m, 2H), 7.14-7.17 (m, 2H), 7.23-7.25 (m, 2H), 7.30-7.32 (m, 3H), 7.48-7.49 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 162.4, 159.2, 132.7, 132.5, 131.0(2), 130.1(2), 128.9, 128.7, 128.1(2), 127.7(2), 126.5, 120.4, 75.8, 58.0, 45.6, 29.5, 22.4; Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04; Found: C,72.44; H, 5.82; N, 8.08.

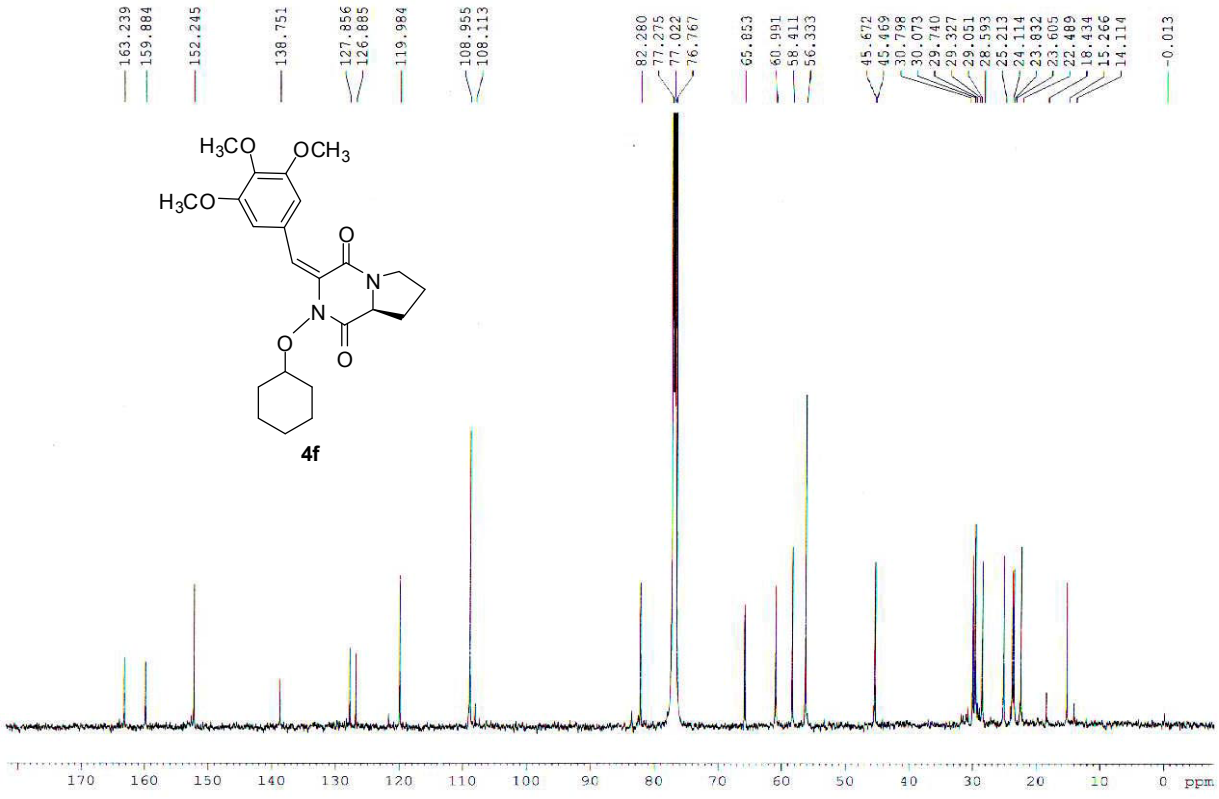




***Cyclo*[*N*-cyclohexyloxy-2-[(3,4,5-trimethyloxy)phenylmethylene]glycyl-prolyl] 4f**

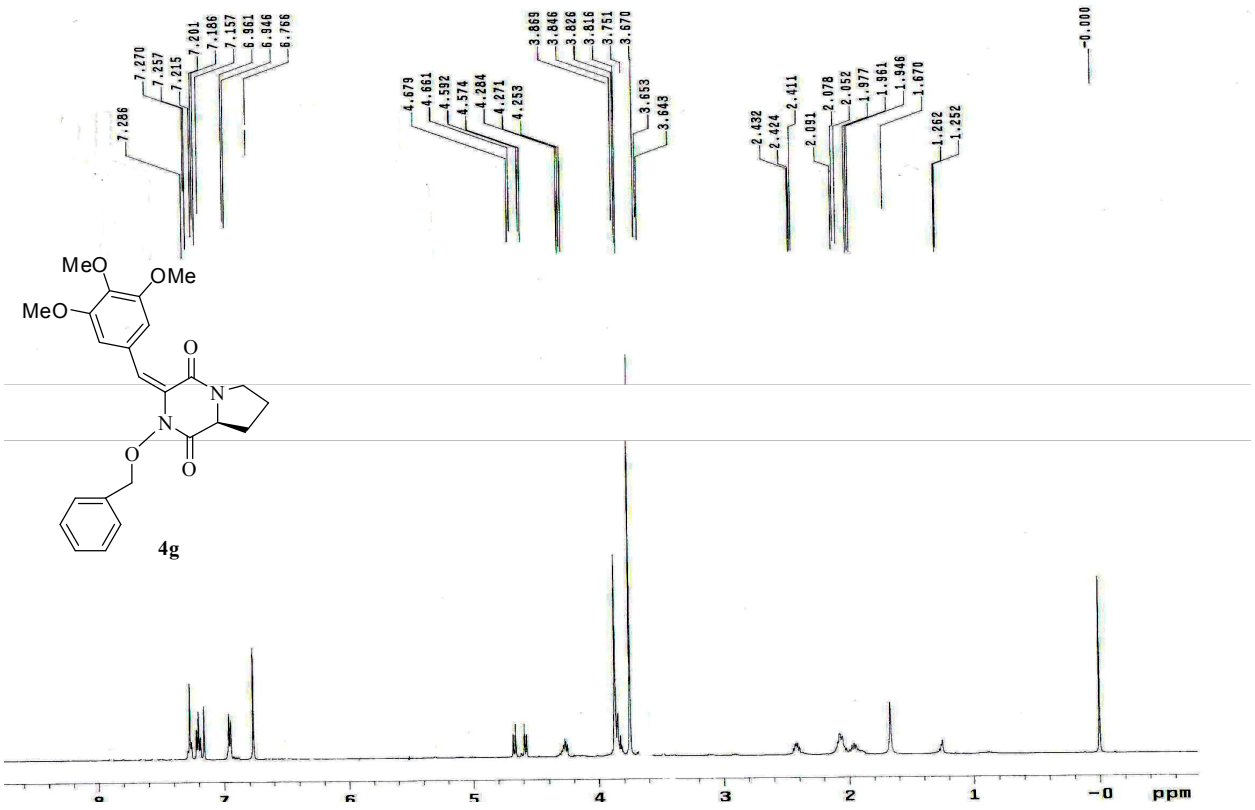
The product **6f** was obtained according to the general procedure in 83% yield after purification by flash chromatography (EtOAc/hexane, 1:2). IR (KBr) ν 1693, 1678, 1621, 1583, 1503,1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 1.01-1.14 (m, 4H), 1.19 (br, 1H), 1.28-1.29 (m, 2H), 1.42 (br, 1H), 1.65-1.72 (m, 2H), 1.99-2.01 (m, 1H), 2.13-2.19 (m, 2H), 2.49-2.51 (m, 1H), 3.69-3.77 (m, 3H), 3.86-3.90 (m, 9H), 4.29 (q, J 7.0 Hz, 1H), 6.77 (s, 2H), 7.04 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 163.2, 159.9, 152.2, 138.8 , 127.9, 126.9, 119.9, 108.5(2), 82.28, 65.9, 61.0, 58.4, 56.3(2), 45.5, 30.8, 30.1, 28.6, 25.2, 23.8, 23.6, 22.5; Anal. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51; Found: C, 64.21; H, 7.07; N, 6.48.





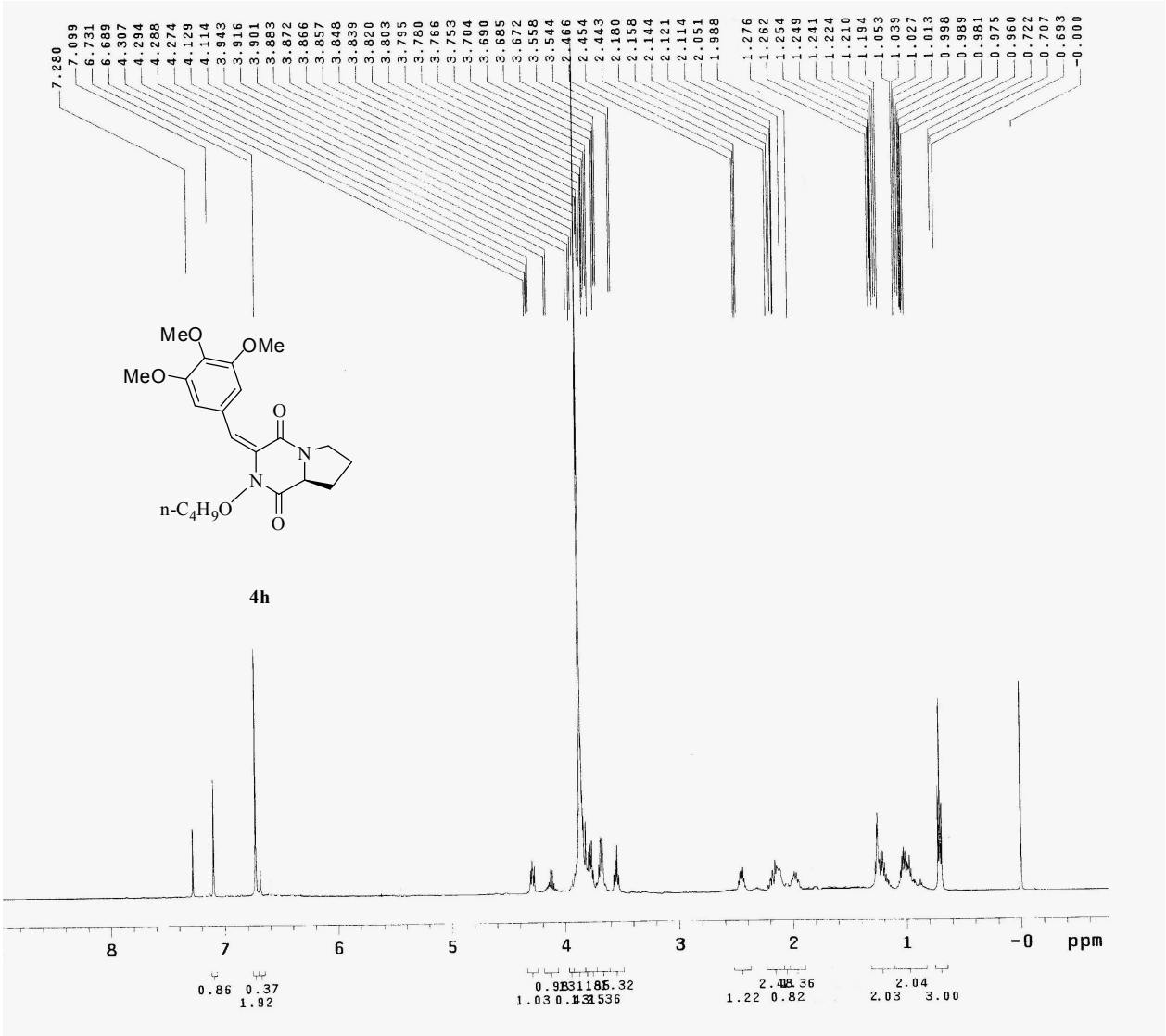
***Cyclo*[*N*-benzyloxy-2-[(3,4,5-trimethyloxy)phenylmethylene]glycyl-prolyl] 4g**

The product **4g** was obtained according to the general procedure in 87% yield after purification by flash chromatography (EtOAc/hexane, 1:2). IR (KBr) ν 1698, 1677, 1621, 1608, 1583, 1503, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.67 (s, 2H), 1.95-1.98 (m, 1H), 2.05-2.09 (m, 2H), 2.41-2.43 (m, 1H), 3.75 (s, 6H), 3.87(s, 3H), 4.25-4.28 (m, 1H), 4.58 (d, J 9.0 Hz, 1H), 4.68 (d, J=9.0 Hz, 1H), 6.77 (s, 2H), 6.95 (d, J=7.5 Hz, 2H), 7.16 (s, 1H), 7.19-7.26 (m, 3H) ppm; Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39; Found: C, 65.75; H, 6.01; N, 6.42.



***Cyclo*[*N*-butyloxy-2-[(3,4,5-trimethyloxy)phenylmethylene]glycyl-prolyl] 4h**

The product **4h** was obtained according to the general procedure in 85% yield after purification by flash chromatography (EtOAc/hexane, 1:2). IR (KBr) ν 1701, 1676, 1608, 1583, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 0.71 (t, J 7.0 Hz, 3H), 0.96-1.05 (m, 2H), 1.19-1.28 (m, 2H), 1.99-2.05 (m, 1H), 2.11-2.18 (m, 2H), 2.44-2.47 (m, 1H), 3.55 (dd, J 7.0 and J 7.5 Hz, 1H), 3.67-3.70 (m, 2H), 3.77-3.80 (m, 1H), 3.85 (s, 9H), 4.27-4.31 (m, 1H), 6.69 (s, 2H), 7.10 (s, 1H) ppm; Anal. Calcd for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93; Found: C, 62.39; H, 7.02; N, 6.98.

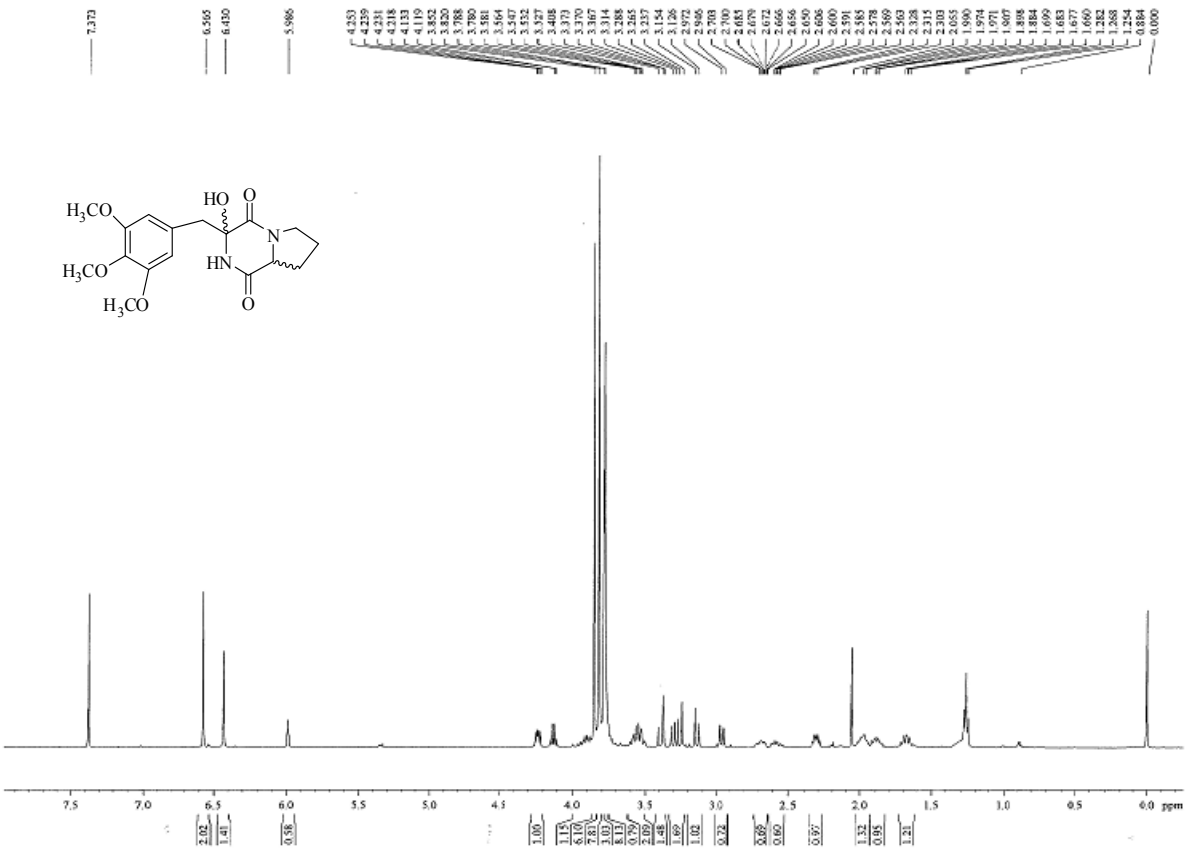


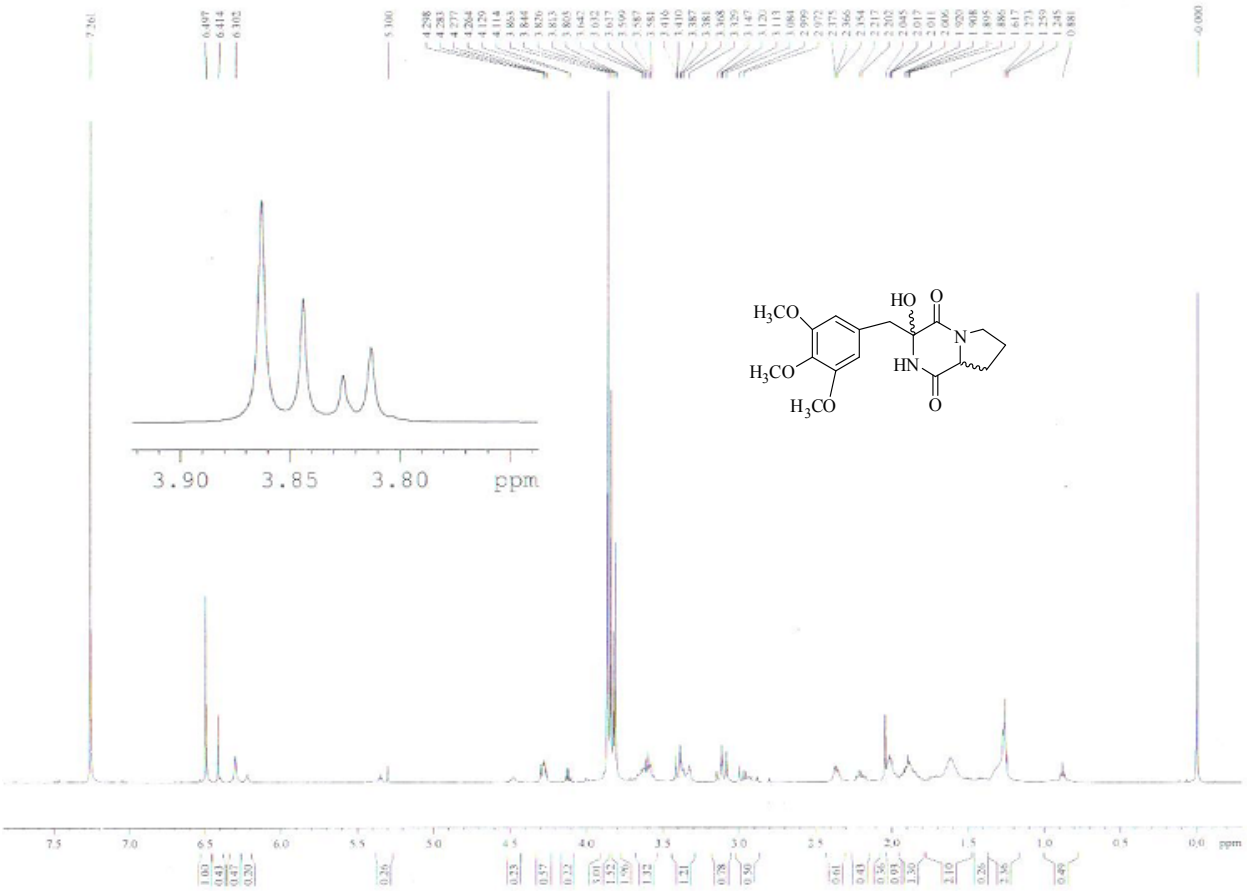
Preparation of *cyclo*[2-hydroxy-2-[(3,4,5-trimethyloxy)phenylmethyl]glycyl-prolyl] 5a and 6a

To the solution of 1.0 mmol **4g** and 20 ml CH_2Cl_2, 2 drops conc. HCl was added to with stirred. The reaction was continued 4 h at RT. The solvent was removed in vacuo, then 30 mL water was added, and extracted with CH_2Cl_2 (30 ml x 3). The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated to give the product (184 mg, 53%) as a colourless solid. The reaction solution was left to stand for 2 days, after which, crystals **5a**/**6a** were obtained suitable for

X-ray crystallographic analysis. IR (KBr) ν3526, 3346, 3151, 1715, 1672, 1608, 1576, 1503, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.66-1.70 (m, 1H), 1.88-1.91 (m, 1H), 1.97-1.99 (m, 1H), 2.30-2.33 (m, 1H), 2.56-2.61 (m, 1H), 2.65-2.70 (m, 1H), 2.95-2.97 (m, 1H), 3.13-3.15 (m, 1H), 3.26-3.31 (m, 2H), 3.37-3.41 (m, 2H), 3.53-3.58 (m, 2H), 3.78 (br, 3H), 3.78(s, 3H), 3.79 (s, 3H), 3.82 (s, 6H), 3.85 (s, 6H), 3.90-3.97 (m, 1H), 4.22-4.25 (m, 1H), 5.99 (s, 1H), 6.43 (s, 2H), 6.57 (s, 2H) ppm; Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00; Found: C, 58.32; H, 6.38; N, 8.06.

Note: Compound **4h**, in place of **4g** (above) as the starting material, underwent the same reaction resulting yield of rearrangement-fragmentation product in 48% yield.





^{1}H NMR of **5** and **6** from crystallization solution in $CDCl_3$