Supplementary Material (ESI) for Chemical Communications

A Facile Direct *anti*-Selective Catalytic Asymmetric Mannich Reaction of Aldehydes with Preformed *N*-Boc and *N*-Cbz Imines

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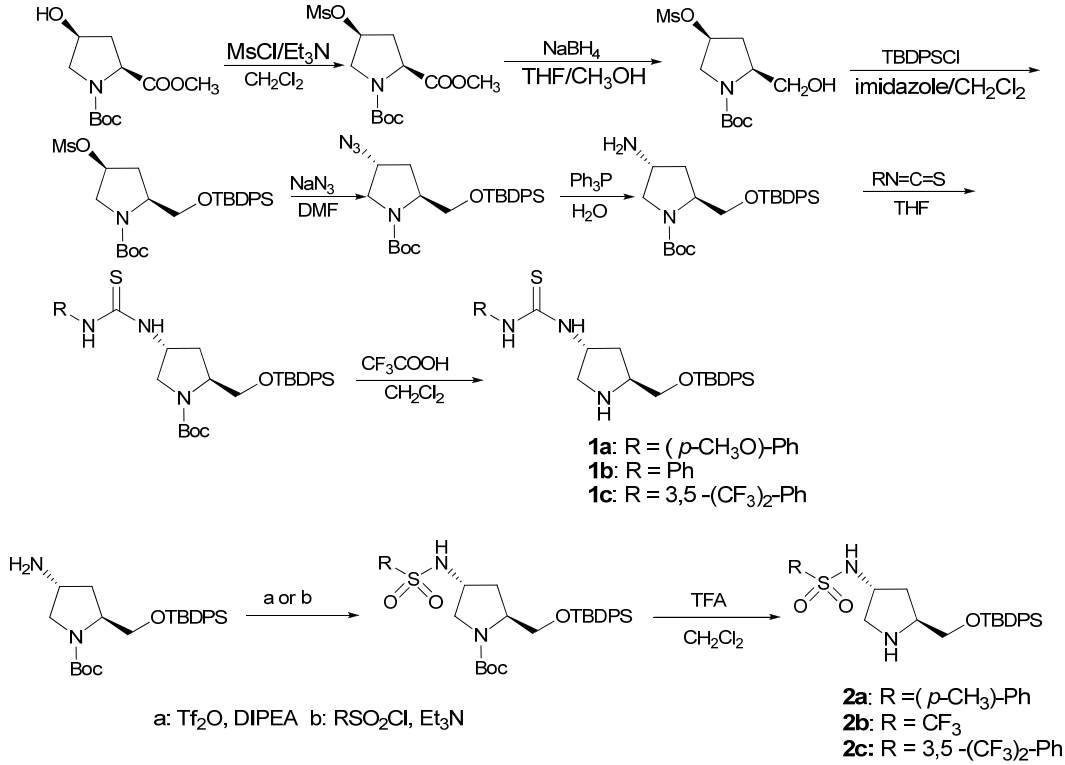
Electronic Supplementary Information

1. General methods

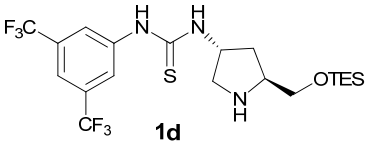
All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial source were used without further purification. Petroleum ether and ethyl acetate for flash column chromatography were distilled before use. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was performed on silica gel H (10-40 μ). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. Chemical shifts are reported in ppm from tetramethyl silane (TMS) with the solvent resonance as the internal standard. Proton signal multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of them. *J*-values are in Hz. Melting points were determined on an X-6 digital melting-point apparatus and were uncorrected. Optical rotations were measured on a Perkin Elmer 341 Polarimeter at λ = 589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column, Chiralpak columns purchased from Daicel Chemical Industries, LTD. ESI HRMS was recorded on a Bruker Apex-2 mass spectrometer in TOF mode.

2. Synthesis of chiral catalysts

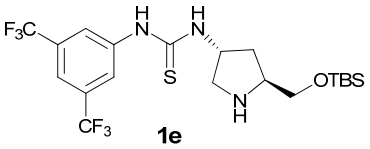
Catalysts 1a, 1b, 1c, 2a, 2b have been reported from (L)-4-hydroxyproline, the details of the synthesis method see the reference.[1] Synthetic routine as follows:



The preparations of catalysts 1d-1f were similar to catalyst 1a.

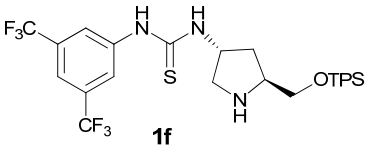


1-(3,5-bis(trifluoromethyl)phenyl)-3-((*3R,5S*)-5-((triethylsilyloxy)methyl)pyrrolidin-3-yl)thiourea (1d): yellowish foam. $[\alpha]_D^{20}$ = + 17.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 0.58 - 0.66 (m, 6H), 0.63 - 0.97 (m, 9H), 2.16 - 2.24 (m, 2H), 3.37 - 3.42 (m, 1H), 3.54 - 3.68 (m, 2H), 3.86 - 3.90 (m, 1H), 3.97 - 3.98 (m, 1H), 5.08 (s, 1H), 6.77 (br, 2H), 7.59 (s, 1H), 8.16 (s, 2H), 8.50 (s, 1H) ppm, ^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = - 0.06, 6.6, 29.7, 32.9, 51.6, 54.2, 59.3, 61.2, 117.8 , 122.6, 131.7, 140.6, 181.3 ppm; HRMS(TOF-ESI) calcd for $C_{20}H_{29}F_6N_3OSSi$ $[M+H]^+$ 502.1783, found 502.1781.



1e

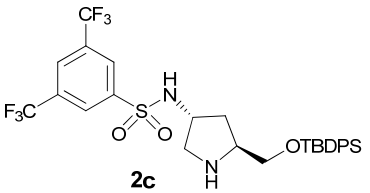
1-(3,5-bis(trifluoromethyl)phenyl)-3-((*3R,5S*)-5-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidin-3-yl)thiourea (1e): yellowish foam. $[\alpha]_D^{20}$ = - 1.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 0.095 - 0.099 (s, 6H), 0.93 (s, 9H), 2.25 - 2.30 (m, 2H), 3.42 - 3.48 (m, 1H), 3.92 - 3.97 (d, 1H, J = 15 Hz), 4.06 - 4.09 (m, 1H), 5.13 (s, 1H), 5.55 (br, 3H), 7.59 (s, 1H), 8.14 (s, 2H), 8.52 - 8.54(m, 1H) ppm, ^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = - 5.5, 18.2, 25.8, 29.7, 32.8, 51.9, 54.0, 59.5, 61.3, 117.9, 121.3, 122.8, 124.9, 131.7, 140.5, 181.3 ppm; HRMS(ESI-TOF) calcd for $C_{20}H_{29}F_6N_3OSSi$ $[M+H]^+$ 502.1783, found 502.1786.



1f

1-(3,5-bis(trifluoromethyl)phenyl)-3-((*3R,5S*)-5-((triphenylsilyloxy)methyl)pyrrolidin-3-yl)thiourea (1f): yellowish foam. $[\alpha]_D^{20}$ = +13.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.81 - 1.93 (m, 1H), 2.01 - 2.08 (m, 1H), 2.92 - 2.98 (m, 1H), 3.11 - 3.15 (m, 1H), 3.58 - 3.69 (m, 2H), 4.77 - 4.87 (m, 1H), 5.34 (br, 2H), 7.30 - 7.59 (m, 17H), 7.94 - 8.01 (m, 2H) ppm, ^{13}C NMR (75.5 MHz, $CDCl_3$) : δ = 33.2, 50.8, 54.4, 59.4, 62.0, 118.1, 121.2, 123.1, 124.8, 127.9, 128.5, 130.8, 131.9, 132.4, 135.1, 140.3, 180.8 ppm; HRMS(ESI-TOF) calcd for $C_{32}H_{29}F_6N_3OSSi$ $[M+H]^+$ 646.1783, found 646.1781.

The preparations of catalysts 2c were similar to catalyst 2a



2c

***N*-((*3R,5S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidin-3-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide (2c):** brown solid, mp: 106 - 108 °C. $[\alpha]_D^{20}$ = -5.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.03 (s, 9H), 1.68 - 1.69 (m, 1H), 1.80 - 1.82 (m, 1H), 2.65 - 2.69 (m, 1H), 3.06 - 3.11 (m, 1H), 3.37 - 3.40 (m, 1H), 3.40 - 3.50 (m, 1H), 3.57 - 3.60 (m, 1H), 3.87 (s, 1H), 4.60 (br, 2H), 7.35 - 7.45 (d, 6H, J = 30 Hz), 7.60 - 7.62 (d, 4H, J = 6 Hz), 8.07(s, 1H), 8.31 (s, 2H) ppm, ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.1, 26.8, 35.1, 52.3, 54.2, 57.8, 65.1, 120.6, 124.3, 125.9, 127.8, 127.2, 129.9, 132.3, 135.5, 144.1 ppm; HRMS(ESI-TOF) calcd for $C_{29}H_{32}F_6N_2O_3SSi$ $[M+H]^+$ 631.1885, found 631.1887.

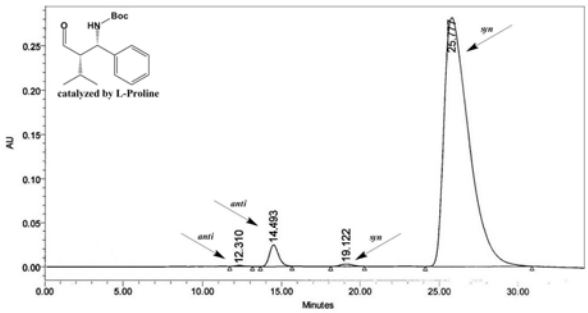
All the *N*-Boc protected α-amido sulfones and *N*-Boc protected imines were prepared by the method reported by Jacobsen.[2] All the *N*-Cbz protected α-amido sulfones and *N*-Cbz protected imines were prepared by the method reported by Dixon.[3]

3. Determination of diastereomeric ratios and enantiomeric purity:

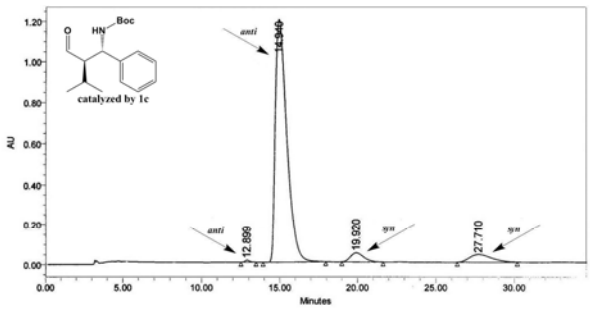
Chiral HPLC analysis was performed on an WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column, Chiralpak columns purchased from Daicel Chemical Industries, Daicel Chiralpak AS-H column with *i*-PrOH/hexane or ethanol/hexane as the eluent was used (all HPLC performed at 25 °C). HPLC traces were compared to the retention time of the racemic samples prepared by carrying out the reactions with (DL) proline or pyrolidine add HAc as the catalyst.

4. Determination of the absolute configuration of the major diastereomer:

The absolute configuration of the obtained *anti*-Mannich products have been confirmed by Maruoka group.[4] The absolute configuration of the *anti*-isomer obtained in the reaction between isovaleraldehyde and *N*-Boc-imine was determined to be (*1S, 2R*) by comparison of the HPLC retention times with the literature data.[4] HPLC analysis: Daicel Chiralpak AS-H, hexane/*i*-PrOH = 100/1, flow rate = 1 mL/min, λ = 205 nm, major product: t_{major} = 14.9 min, t_{minor} = 12.9 min, *anti*: *ee* >99%, *dr* 90/10. (Reference: Daicel Chiralpak AS-H, hexane/i-PrOH = 100/1, flow rate = 1 mL/min, λ = 205 nm, retention time; 10.4 min (*minor*) and 12.2 min (*major*)).

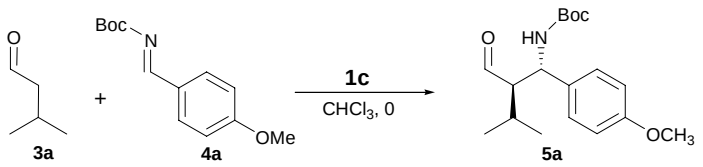


	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.310	47479	0.15	1114	0.36
2	14.493	971505	3.05	24080	7.76
3	19.122	145329	0.46	2621	0.84
4	25.777	30640399	96.34	282401	91.03



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.899	222270	0.32	11134	0.86
2	14.940	61973318	90.07	1202033	92.60
3	19.920	2736358	3.98	45718	3.52
4	27.710	3877457	5.64	39210	3.02

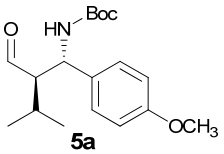
5. General procedure for the *anti*-selective Mannich reaction



anisaldehyde *N*-Boc imine **4a** (0.2 mmol, 1 equiv.) and catalyst **1c** (0.01 mmol, 0.05 equiv.) were dissolved in anhydrous $CHCl_3$ (1 mL), subsequently, isovaleraldehyde **3a** (1.0 mmol, 5 equiv.) was added at 0 °C. The mixture was stirred and monitored by TLC until the imine was completely disappearance. The mixture was worked up by addition of aqueous saturated ammonium chloride solution and extracted with AcOEt (three times). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in *vacuo* and the residue was purified by flash column chromatography (5-10% AcOEt/PE) to afford the corresponding Mannich product. The *ee* and *dr* were determined by a chiral phase Chiralpak AS-H column (96/4 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 20.9 min, t_{minor} = 18.6 min, *anti*: *ee* >99%, *dr* = 95/5)

6. Characterization of the Mannich reaction products:

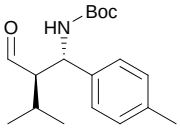
***tert*-butyl (*1S, 2R*)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate**[5]



5a

The title compound was isolated as colorless oil in 94% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 96/4 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 20.9 min, t_{minor} = 18.6 min, *anti*: *ee* >99%, *dr* = 95/5; $[\alpha]_D^{20}$ = - 7.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 - 1.11 (m, 6H), 1.40 (s, 9H), 1.80 - 1.87(m, 1H), 2.54 - 2.60 (m, 1H), 3.79 (s, 3H), 5.08 (br, 1H), 5.32 (d, 1H, *J* = 9 Hz), 6.83(d, 2H, *J* = 8.4 Hz), 7.14 (d, 2H, *J* = 8.7 Hz), 9.76 (d, 1H, *J* = 3.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 21.3, 28.1, 52.5, 55.1, 63.0, 79.7, 114.1, 127.7, 132.8, 155.0, 158.9, 206.1 ppm.

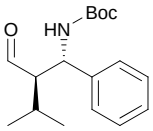
***tert*-butyl (*1S, 2R*)-2-formyl-3-methyl-1-*p*-tolylbutylcarbamate**[5]



5b

The title compound was isolated as colorless oil in 93% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 19.8 min, t_{minor} = 16.3 min, *anti*: *ee* >99%, *dr* = 90/10; $[\alpha]_D^{20}$ = - 4.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 - 1.00 (d, 3H, *J* = 6 Hz), 1.05 - 1.07 (d, 3H, *J* = 6 Hz), 1.43 (s, 9H), 1.80 - 1.87 (m, 1H), 2.33 (s, 3H), 2.56 - 2.58 (m, 1H), 5.08 - 5.13 (m, 1H), 5.33 - 5.35 (d, 1H, *J* = 6 Hz), 7.10 - 7.27 (m, 4H), 9.75 - 9.77 (d, 1H, *J* = 6 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.0, 21.0, 21.3, 28.1, 52.8, 63.0, 79.7, 129.1, 129.4, 137.2, 137.7, 155.1, 206.2 ppm.

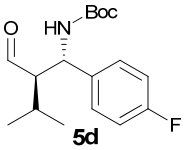
***tert*-butyl (*1S, 2R*)-2-formyl-3-methyl-1-phenylbutylcarbamate**[4,5]



5c

The title compound was isolated as colorless oil in 91% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 100/1 hexane/*i*PrOH, flow rate 1 mL/min, λ = 205 nm, t_{major} = 14.9 min, t_{minor} = 12.9 min, *anti*: *ee* >99%, *dr* = 90/10; $[\alpha]_D^{20}$ = + 6.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.0 - 1.08 (m, 6H), 1.38 (s, 9H), 1.84 - 1.90 (m, 1H), 2.60 - 2.65 (m, 1H), 5.13 (m, 1H), 5.41 - 5.44 (d, 1H, *J* = 9 Hz), 7.26 - 7.36 (m, 5H), 9.75 - 9.76 (d, 1H, *J* = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 21.3, 28.1, 28.2, 53.0, 62.9, 79.8, 126.5, 127.5, 128.7, 140.8, 155.0, 206.2 ppm.

***tert*-butyl (*1S, 2R*)-1-(4-fluorophenyl)-2-formyl-3-methylbutylcarbamate**

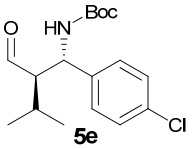


5d

The title compound was isolated as colorless oil in 92% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/ethanol, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 22.3min, t_{minor} = 24.9 min, *anti*: *ee* 98%, *dr* = 90/10; $[\alpha]_D^{20}$ = + 14.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 - 1.03 (d, 3H, *J* =

6 Hz), 1.06 - 1.08 (d, 3H, J = 6 Hz), 1.39 (s, 9H), 1.85 - 1.90 (m, 1H), 2.60 - 2.61 (m, 1H), 5.1 (m, 1H), 5.46 - 5.49 (d, 1H, J = 9 Hz), 6.99 - 7.28 (m, 4H), 9.75 - 9.76 (d, 1H, J = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 21.3, 28.2, 52.4, 62.8, 79.9, 115.4, 115.7, 128.1, 128.2, 136.7, 155.0, 160.3, 163.6, 206.0 ppm; HRMS(ESI-TOF) calcd for $C_{17}H_{24}FNO_3$ $[M+Na]^+$ 332.1638, found 332.1245.

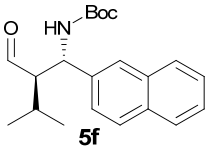
***tert*-butyl (*1S, 2R*)-1-(4-chlorophenyl)-2-formyl-3-methylbutylcarbamate**[5]



5e

The title compound was isolated as colorless oil in 84% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 16.1 min, t_{minor} = 15.6 min, *anti*: *ee* = 98%, *dr* = 95/5; $[\alpha]_D^{20}$ = + 4.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 - 1.08 (m, 6H), 1.39 (s, 9H), 1.87 - 1.93 (m, 1H), 2.60 (s, 1H), 5.08 (m, 1H), 5.50 - 5.53 (d, 1H, J = 9 Hz), 7.19 - 7.22 (d, 2H, J = 9 Hz), 7.29 - 7.32 (d, 2H, J = 9 Hz), 9.73 - 9.74 (d, 1H, J = 3Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 21.2, 28.2, 52.5, 62.6, 79.9, 127.9, 128.8, 133.2, 139.6, 155.0, 205.8 ppm.

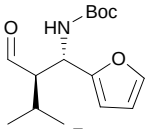
***tert*-butyl (*1S, 2R*)-2-formyl-3-methyl-1-(naphthalen-2-yl)butylcarbamate**



5f

The title compound was isolated as colorless oil in 81% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 23.6 min, t_{minor} = 27.0 min, *anti*: *ee* >99%, *dr* = 92/8; $[\alpha]_D^{20}$ = - 1.6 (c = 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 - 1.04(d, 3H, J = 6 Hz), 1.08 - 1.10 (d, 3H, J = 6 Hz), 1.39 (s, 9H), 1.84 - 1.93 (m, 1H), 2.71 - 2.76 (m, 1H), 5.3 (m, 1H), 5.50 – 5.53 (d, 1H, J = 9 Hz), 7.35 - 7.84 (m, 7H), 9.78 - 9.79 (d, 1H, J = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 18.9, 21.0, 21.3, 28.2, 53.2, 60.3, 62.7, 79.9, 124.3, 125.6, 126.0, 126.3, 127.6, 127.9, 128.7, 132.7, 133.3, 138.1, 155.1, 171.1, 206.0 ppm; HRMS(ESI-TOF) calcd for $C_{21}H_{27}NO_3$ $[M+Na]^+$ 364.1889, found 364.1885.

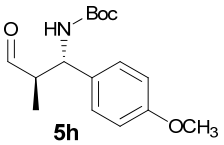
***tert*-butyl (*1S, 2R*)-2-formyl-1-(furan-2-yl)-3-methylbutylcarbamate**



5g

The title compound was isolated as colorless oil in 89% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 98/2 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 16.0 min, t_{minor} = 15.5 min, *anti*: *ee* >99%, *dr* = 91/9; $[\alpha]_D^{20}$ = - 18.6 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 - 1.07(t, 6H, J = 6 Hz), 1.42 (s, 9H), 1.91 - 1.93 (m, 1H), 2.73 - 2.78(m, 1H), 5.23 - 5.31 (m, 2H), 6.20 - 6.22 (d, 1H, J = 6 Hz), 6.30 - 6.31 (m, 1H), 7.33 (s, 1H), 9.80 - 9.82 (d, 1H, J = 6 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 21.1, 27.9, 28.3, 47.3, 60.3, 80.0, 106.7, 110.4, 141.9, 153.3, 155.1, 205.1 ppm; HRMS(ESI-TOF) calcd for $C_{15}H_{23}NO_4$ $[M+Na]^+$ 304.1525, found 304.1527.

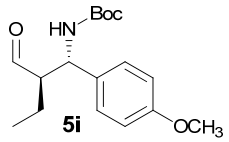
***tert*-butyl (*1S, 2R*)-1-(4-methoxyphenyl)-2-methyl-3-oxopropylcarbamate**



5h

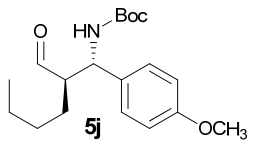
The title compound was isolated as a white solid in 88% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 90/10 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 24.1 min, t_{minor} = 17.9 min, *anti*: *ee* >99%, *dr* = 91/9; mp: 102.3 °C - 105.5 °C, $[\alpha]_D^{20}$ = - 33.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 - 1.02 (d, 3H, *J* = 6 Hz), 1.39 (s, 9H), 2.76 - 2.80 (m, 1H), 3.80 (s, 3H), 4.81 (s, 1H), 5.11 - 5.14 (d, 1H, *J* = 9 Hz), 6.86 - 6.89 (d, 2H, *J* = 9 Hz), 7.16 - 7.19 (d, 2H, *J* = 9 Hz), 9.65 - 9.66 (d, 1H, *J* = 3Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 28.3, 52.3, 55.3, 79.9, 114.1, 127.9, 131.9, 155.1, 159.1, 203.5 ppm; HRMS(ESI-TOF) calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$ 316.1525, found 316.1526.

***tert*-butyl (*1S, 2R*)-2-formyl-1-(4-methoxyphenyl)butylcarbamate**



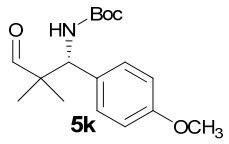
The title compound was isolated as a white solid in 94% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 24.3min, t_{minor} = 18.7, *anti*: *ee* >99%, *dr* = 90/10; mp: 105.2 °C - 106.9 °C, $[\alpha]_D^{20}$ = - 18.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 - 0.92 (t, 3H, *J* = 15 Hz), 1.39 (s, 9H), 1.57 - 1.64 (m, 1H), 2.54 - 2.58 (m, 1H), 3.80 (s, 3H), 4.84 - 4.87 (m, 1H), 5.15 - 5.17 (d, 1H, *J* = 6 Hz), 6.86 - 6.89 (d, 2H, *J* = 9 Hz), 7.17 - 7.20 (d, 2H, *J* = 9 Hz), 9.61 - 9.62 (d, 1H, *J* = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 20.4, 28.3, 53.8, 55.2, 59.6, 79.8, 114.1, 127.9, 132.4, 155.0, 159.0, 204.1 ppm; HRMS(ESI-TOF) calcd for $C_{17}H_{25}NO_4$ $[M+Na]^+$ 330.1681, found 330.1684.

***tert*-butyl (*1S, 2R*)-2-formyl-1-(4-methoxyphenyl)hexylcarbamate**[4]



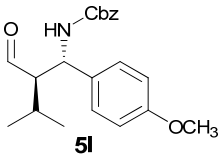
The title compound was isolated as a white solid in 84% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 96/4 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 24.4 min, t_{minor} = not find, *anti*: ee >99%, *dr* = 89/11; mp: 74.2 °C - 76.5 °C; $[\alpha]_D^{20}$ = +2.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 - 0.91 (m,5H), 1.26 - 1.30 (m, 3H), 1.45 (s, 9H), 2.63 - 2.66 (m, 2H), 3.80 (s, 3H), 4.85 (s, 1H), 5.18 - 5.21 (d, 1H, *J* = 9 Hz), 6.86 - 6.89 (d, 2H, *J* = 9 Hz), 7.16 - 7.19 (d, 2H, *J* = 9 Hz), 9.60 - 9.61 (d, 1H, *J* = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.0, 22.4, 22.5, 22.8, 25.2, 26.7, 28.3, 29.2, 55.2, 57.9, 79.8, 114.1, 127.9, 132.4, 155.0, 158.9, 204.0 ppm.

(*R*)-*tert*-butyl 1-(4-methoxyphenyl)-2,2-dimethyl-3-oxopropylcarbamate



The title compound was isolated as a white solid in 70% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 90/10 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 15.0 min, t_{minor} = 12.3 min. *ee* = 92%; mp: 102.5°C - 105 °C; $[\alpha]_D^{20}$ = +1.3 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 6H), 1.38 (s, 9H), 3.79 (s, 3H), 4.79 - 4.82 (d, 1H, *J* = 9 Hz), 5.36 - 5.39 (d,, 1H, *J* = 9 Hz), 6.84 - 6.87 (d, 2H, *J* = 9 Hz), 7.11 - 7.14 (d, 2H, *J* = 9 Hz), 9.56 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 20.7, 28.2, 50.4, 55.2, 58.7, 79.8, 113.6, 128.8, 130.5, 155.1, 158.9, 205.3 ppm; HRMS(ESI-TOF) calcd for $C_{17}H_{25}NO_4$ $[M+Na]^+$ 330.1681, found 330.1684.

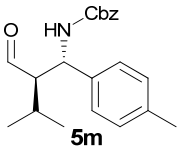
Benzyl (1*S*, 2*R*)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate[5]



5l

The title compound was isolated as colorless oil in 86% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 90/10 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 30.2 min, t_{minor} = 36.8 min, *anti*: *ee* >99%, *dr* = 95/5; $[\alpha]_D^{20}$ = + 5.4 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 - 1.06 (m, 6H), 1.82 - 1.87 (m, 1H), 2.62 - 2.63(m, 1H), 3.87 (s, 3H), 5.04 - 5.05 (m, 2H), 5.09 - 5.14 (m, 1H), 5.66 - 5.69 (d, 1H, *J* = 9 Hz), 6.84 - 6.87 (d, 2H, *J* = 9 Hz), 7.17 - 7.20 (d, 2H, *J* = 9 Hz), 7.31 (s, 5H), 9.76 - 9.77 (d, 1H, *J* = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.4, 28.2, 55.2, 62.6, 66.9, 114.1, 127.7, 127.9, 128.1, 128.4, 132.4, 136.2, 155.6, 158.9, 206.1ppm.

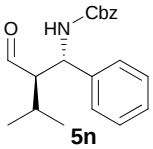
Benzyl (*1S, 2R*)-2-formyl-3-methyl-1-p-tolylbutylcarbamate[5]



5m

The title compound was isolated as colorless oil in 84% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 92/8 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 21.2 min, t_{minor} = not found, *anti*: *ee* >99%, *dr* = 93/7; $[\alpha]_D^{20}$ = + 13.8 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 - 1.09 (m, 6H), 1.80 - 1.89 (m, 1H), 2.32 (s, 3H), 2.61 - 2.64 (m, 1H), 4.99 - 5.12 (m, 2H), 5.16 - 5.18 (m, 1H), 5.72 - 5.75 (d, 1H, *J* = 9 Hz), 7.14 - 7.30 (m, 9H), 9.75 - 9.76 (d, 1H, *J* = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.0, 21.3, 28.2, 53.3, 62.5, 66.9, 126.4, 127.9, 128.0, 128.4, 129.4, 136.2, 137.3, 137.4, 155.6, 206.2 ppm.

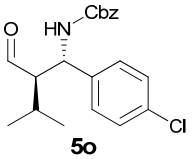
Benzyl (*1S, 2R*)-2-formyl-3-methyl-1-phenylbutylcarbamate



5n

The title compound was isolated as colorless oil in 88% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 90/10 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 21.2 min, t_{minor} = not found, *anti*: *ee* >99%, *dr* 92/8; $[\alpha]_D^{20}$ = + 23.2 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 - 1.08 (m, 6H), 1.84 - 1.96 (m, 1H), 2.67 - 2.68 (m, 1H), 5.01 - 5.10 (m, 2H), 5.16 - 5.21 (m, 1H), 5.76 - 5.79 (d, 1H, *J* = 9 Hz), 7.25 - 7.27 (m, 10H), 9.75 - 9.76 (d, 1H, *J* = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 21.3, 28.3, 53.6, 62.6, 66.9, 126.5, 127.6, 128.0, 128.5, 128.8, 136.2, 136.2, 140.5, 155.7, 206.0 ppm; HRMS(ESI-TOF) calcd for $C_{20}H_{23}NO_3$ $[M+Na]^+$ 348.1576, found 348.1574.

Benzyl (*1S, 2R*)-1-(4-chlorophenyl)-2-formyl-3-methylbutylcarbamate

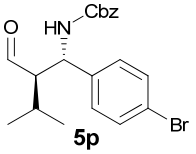


5o

The title compound was isolated as colorless oil in 90% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 31.2 min, t_{minor} = 34.2 min, *anti*: *ee* >99%, *dr* = 94/6; $[\alpha]_D^{20}$ = + 21.6 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 - 1.08 (m, 6H),

1.88 - 1.95 (m, 1H), 2.65(s, 1H), 5.01 - 5.16 (m, 3H), 5.88 - 5.91 (d, 1H, J = 9 Hz), 7.18 - 7.32 (m, 9H), 9.73 - 9.74 (d, 1H, J = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 21.3, 28.4, 52.9, 62.3, 67.0, 127.9, 128.0, 128.1, 128.2, 128.5, 128.9, 133.3, 136.1, 139.2, 155.6, 205.9 ppm; HRMS(ESI-TOF) calcd for $C_{20}H_{22}ClNO_3$ $[M+Na]^+$ 383.1264, found 383.1340.

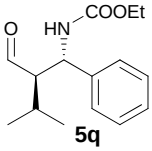
Benzyl (*1S, 2R*)-1-(4-bromophenyl)-2-formyl-3-methylbutylcarbamate



5p

The title compound was isolated as colorless oil in 82% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm: t_{major} = 31.2 min, t_{minor} = 34.2 min, *anti*: *ee* >99%, dr = 94/6; $[\alpha]_D^{20}$ = + 21.6 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 - 1.10 (m, 6H), 1.86 - 1.97 (m, 1H), 2.65(s, 1H), 5.01 - 5.14 (m, 3H), 5.89 - 5.92 (d, 1H, J = 9 Hz), 7.13 - 7.15 (d, 1H, J = 9 Hz), 7.32 (s, 5H), 7.43 - 7.45 (d, 2H, J = 6 Hz), 9.72 - 9.73 (d, 1H, J = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 21.3, 28.4, 53.0, 62.2, 67.0, 121.5, 128.0, 128.1, 128.3, 128.5, 131.8, 136.1, 139.8, 155.6, 205.8 ppm; HRMS(ESI-TOF) calcd for $C_{20}H_{22}BrNO_3$ $[M+Na]^+$ 427.0759, found 427.0716.

Ethyl (*1S, 2R*)-2-formyl-3-methyl-1-phenylbutylcarbamate



5q

The title compound was isolated as white solid in 95% yield. HPLC analysis on a Daicel Chiralpak AS-H column: 94/6 hexane/*i*PrOH, flow rate 0.5 mL/min, λ = 220 nm, t_{major} = 13.6 min, t_{minor} = 18.2 min, *anti*: *ee* >99%, *dr* = 95/5; mp: 88.4°C – 89.5°C, $[\alpha]_D^{20}$ = + 4.0 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 - 1.10 (m, 6H), 1.17 - 1.22 (m, 3H), 1.86 - 1.92 (m, 1H), 2.64 - 2.7 (m, 1H), 4.03 - 4.10 (m, 2H), 5.15 - 5.20 (m, 1H), 5.67 - 5.70 (d, 1H, J = 9 Hz), 7.23 - 7.36 (m, 5H), 9.76 - 9.77 (d, 1H, J = 3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 18.9, 21.3, 28.2, 53.4, 61.0, 62.6, 126.5, 127.6, 128.7, 140.6, 155.9, 206.2 ppm; HRMS(ESI-TOF) calcd for $C_{15}H_{21}NO_3$ $[M+Na]^+$ 286.1619, found 286.1416

7. Reference:

1 (a) C. Wang, C. Yu, C. L. Liu, Y. G. Peng, *Tetrahedron Lett.*, 2009, **50**, 2363; (b) H. Zhang, Y. M. Chuan, Z. Y. Li, Y. G. Peng, *Adv. Synth. Catal.*, 2009, **351**, 2288.

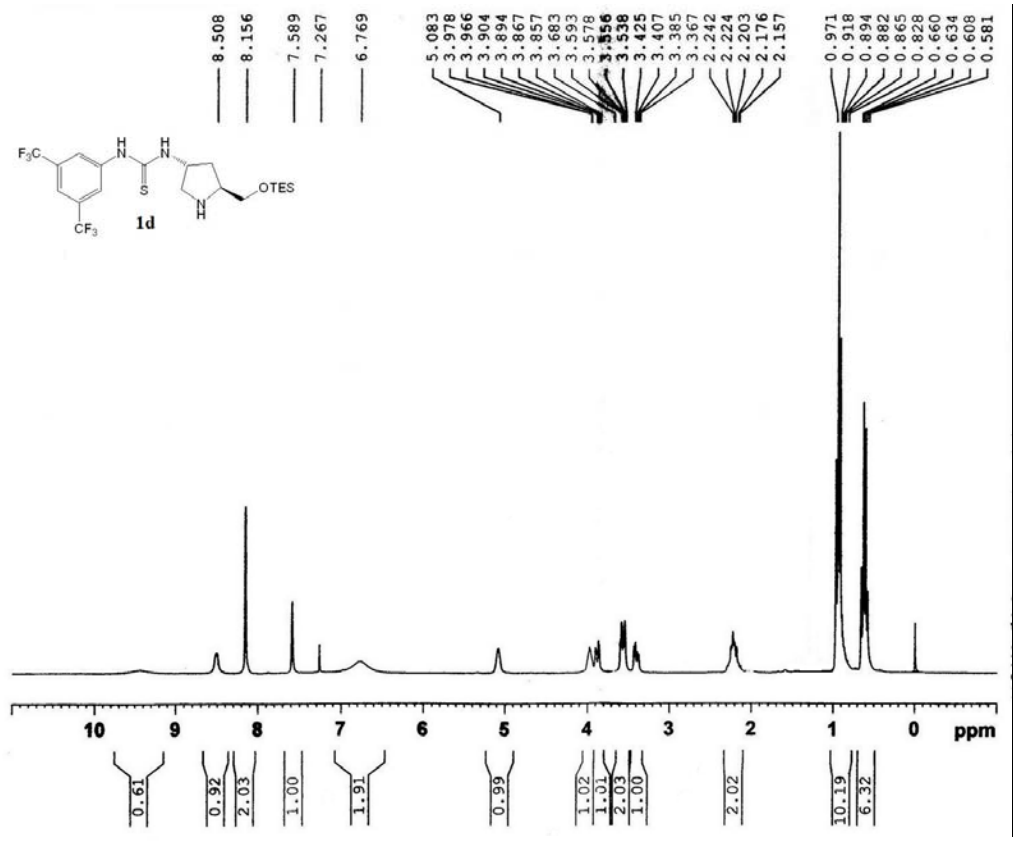
2 A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964.

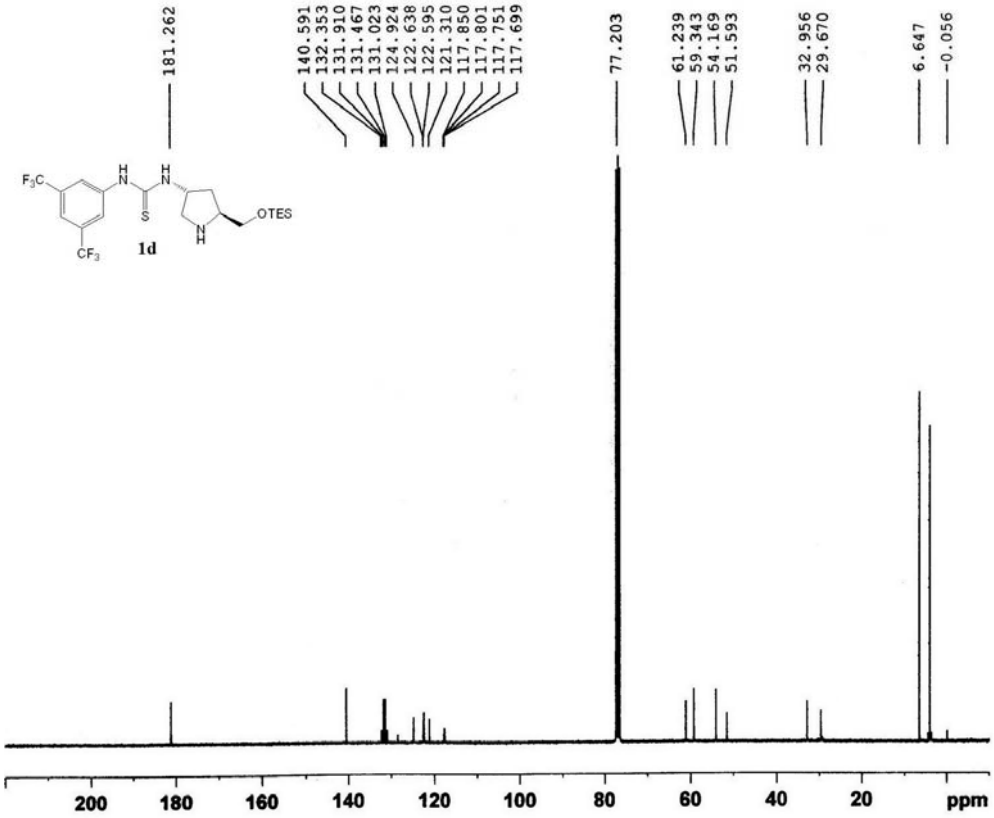
3 A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.*, 2006, 1191.

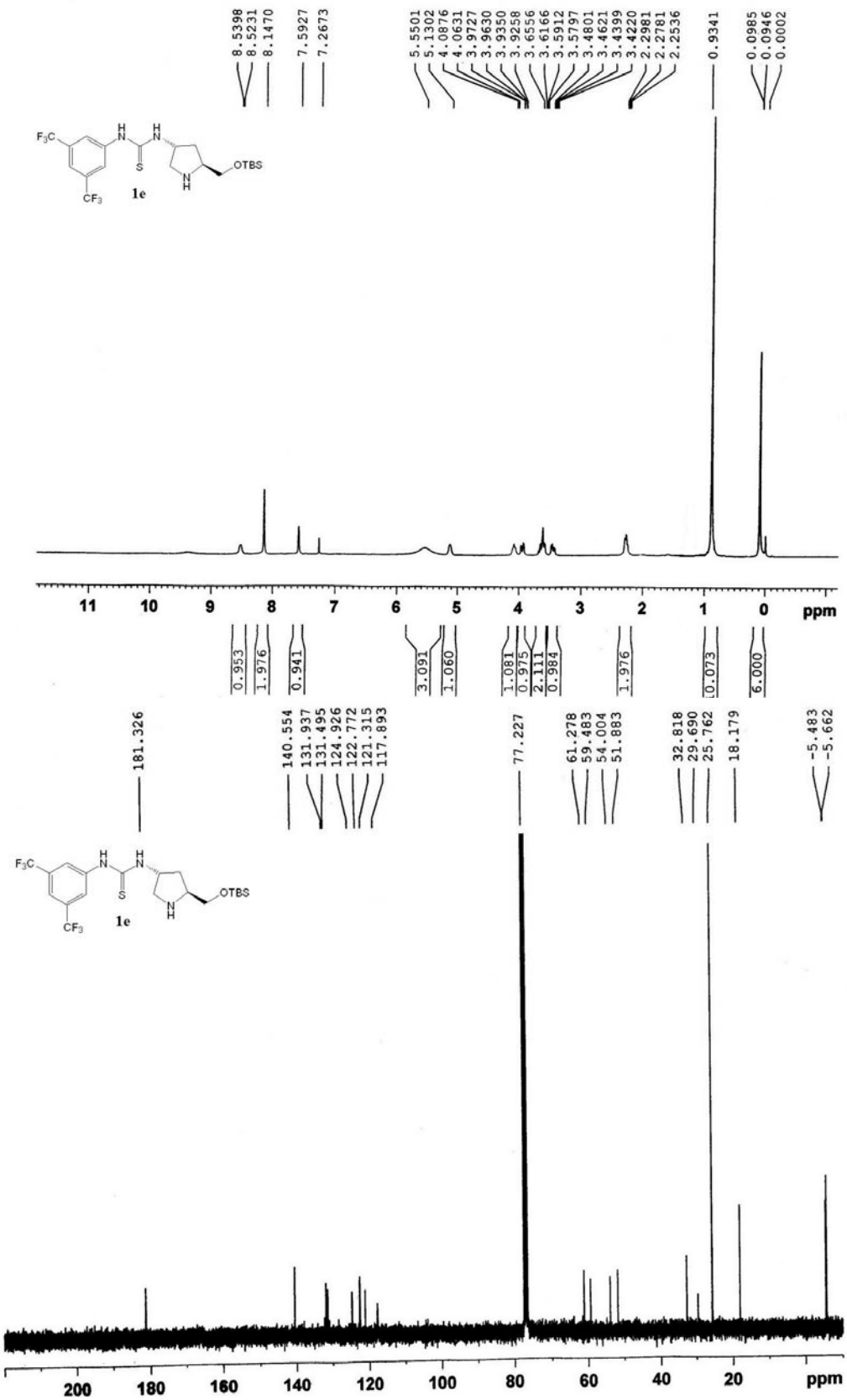
4 (a) T. Kano, Y. Yamaguchi, K. Maruoka, *Angew. Chem. Int. Ed.*, 2009, **48**, 1838; (b) T. Kano, Y. Yamaguchi, K. Maruoka, *Chem. Eur. J.*, 2009, **15**, 6678.

5 P. Galzerano, D. Agostino, G. Bencivenni, L. Sambri, G. Bartoli and P. Melchiorre, *Chem. Eur. J.*, 2010, **16**, 6069.

8. NMR spectra and HPLC for catalysts and part of the Mannich products



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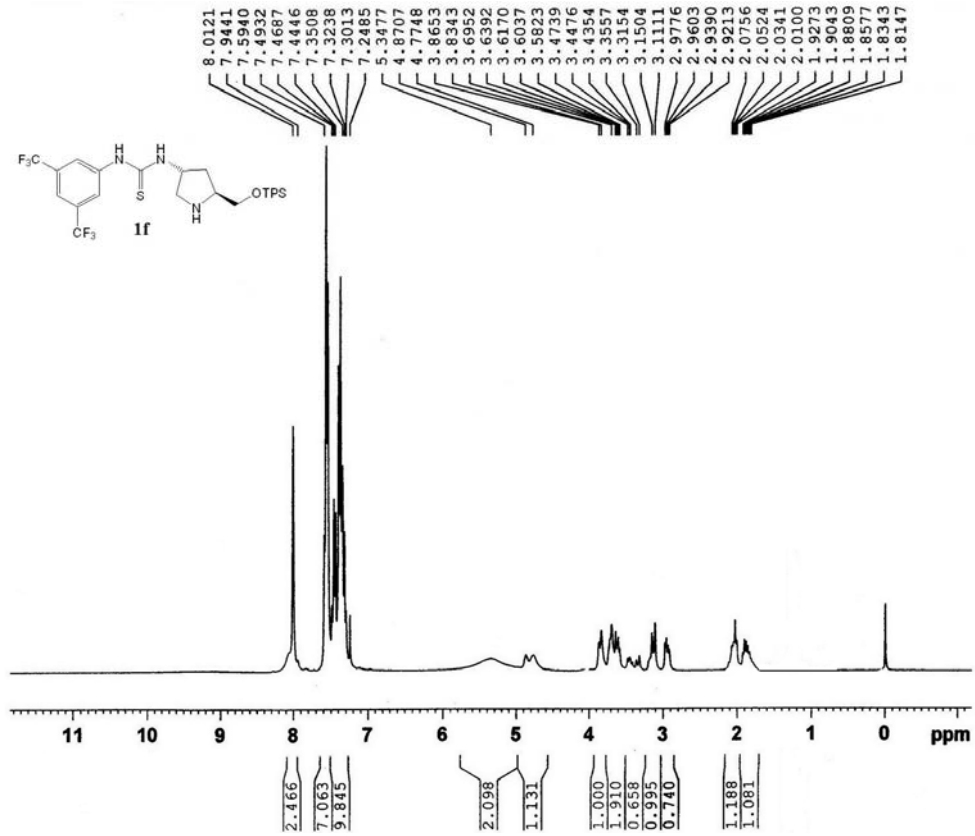
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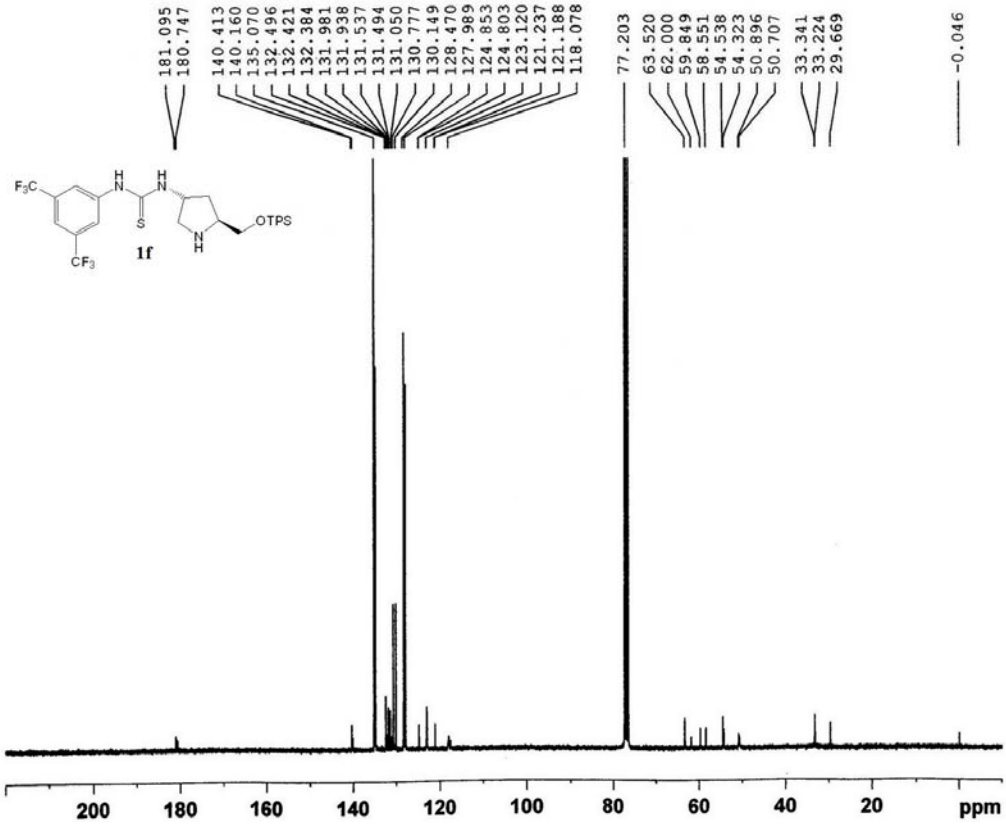
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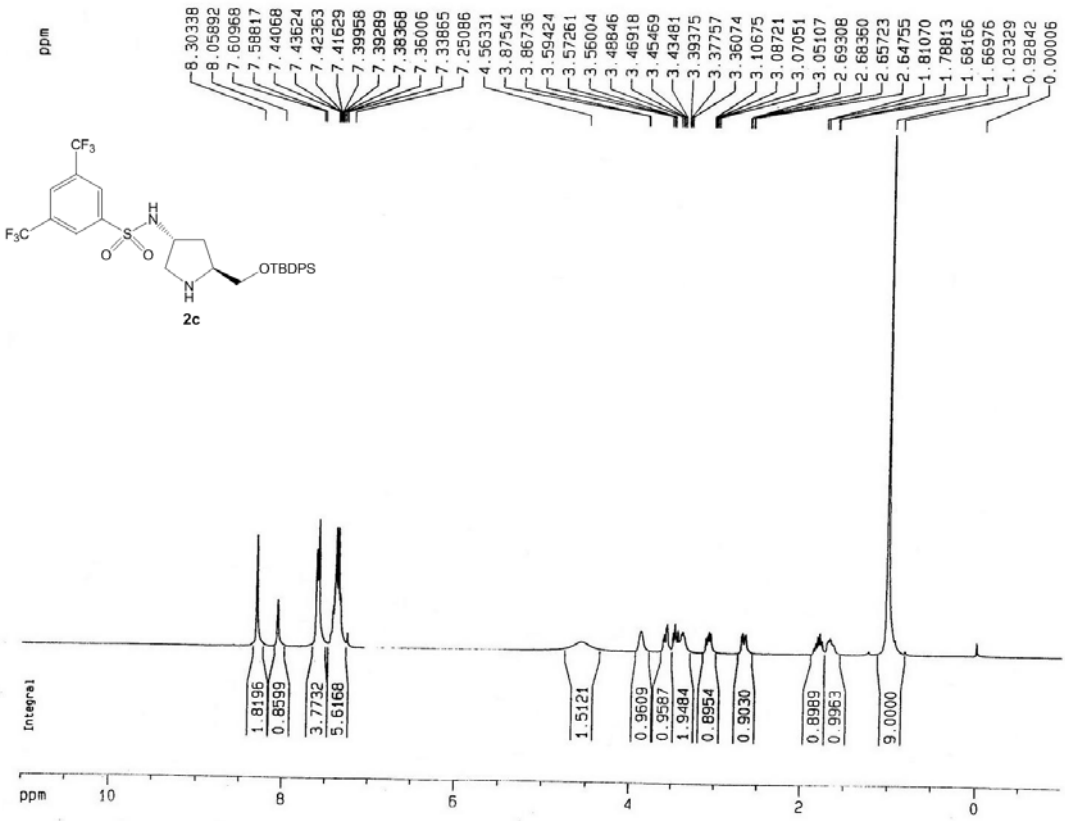
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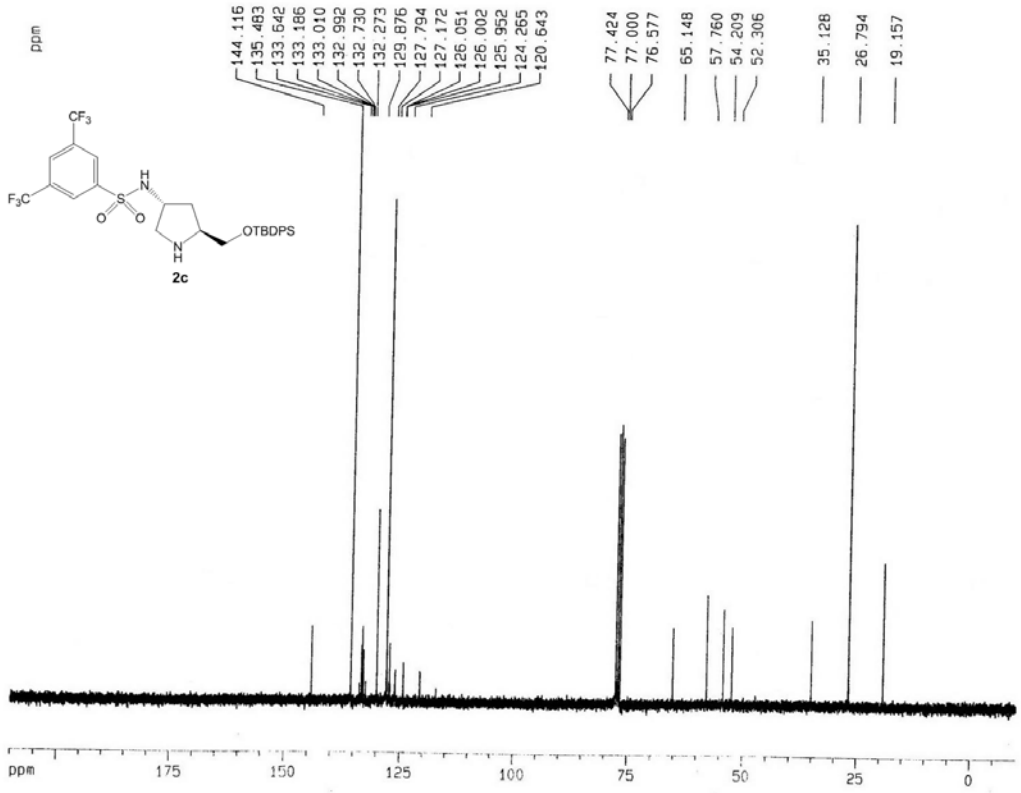
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150
125
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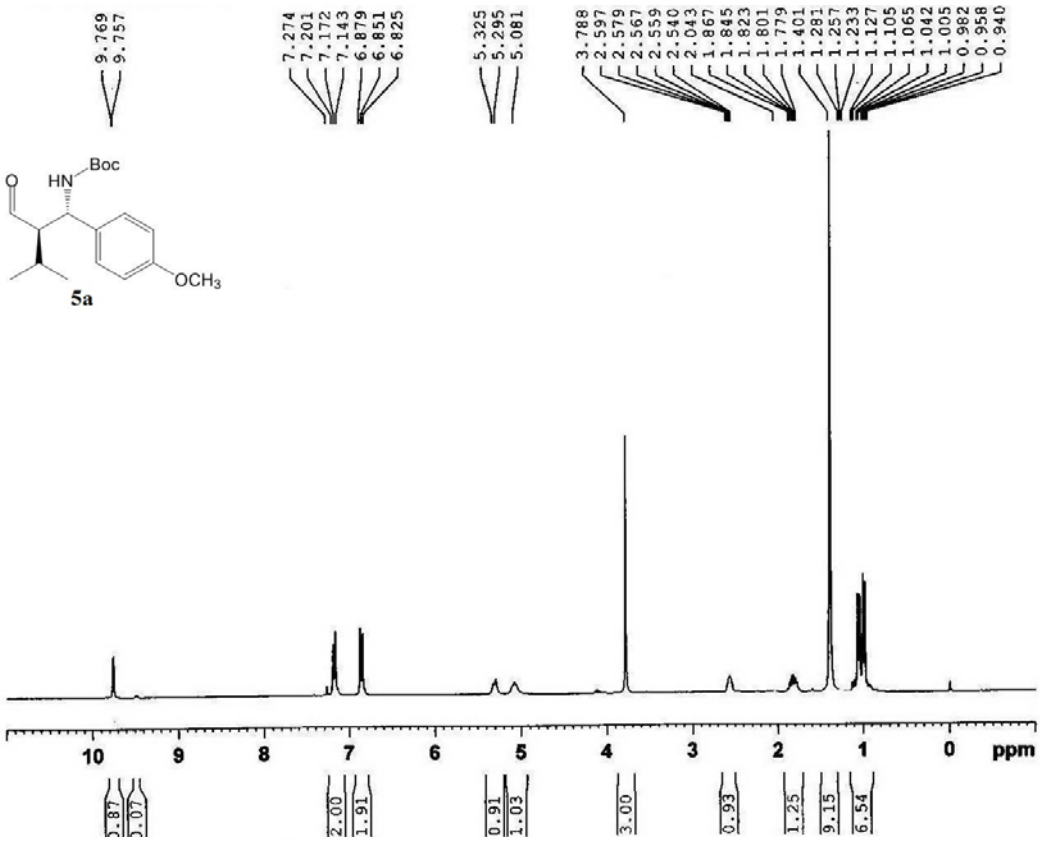
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Boc
HN
O
OCH3
5a
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8
7
6
5
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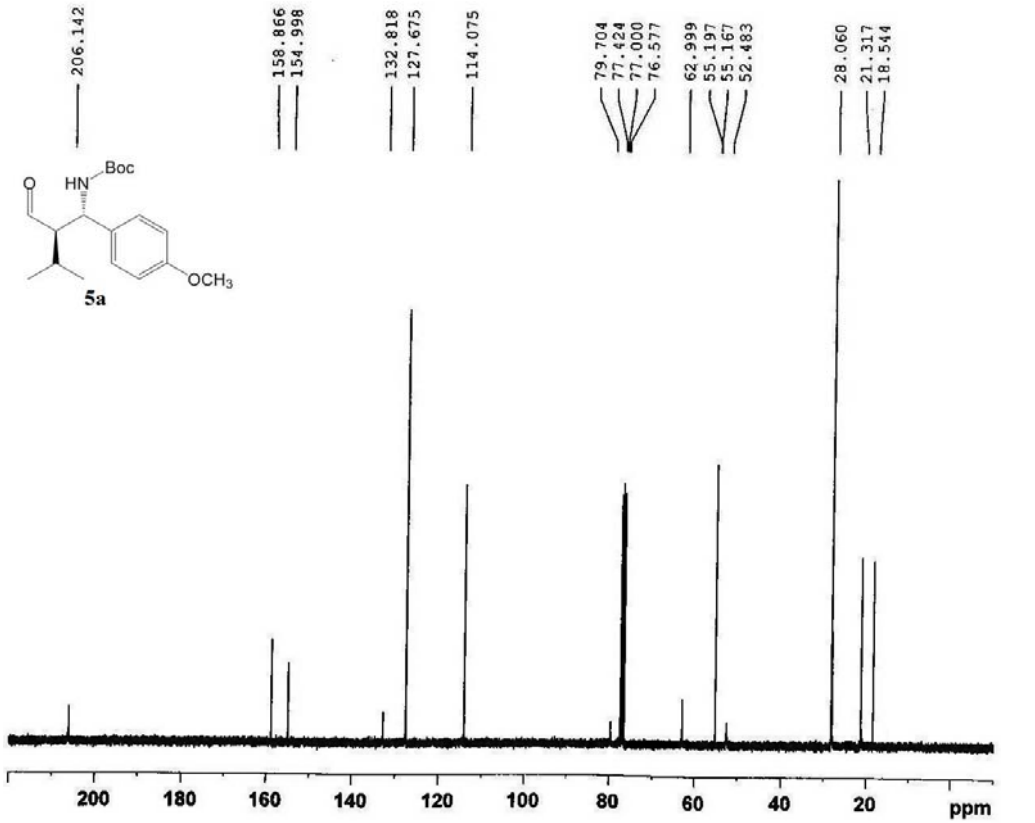
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O
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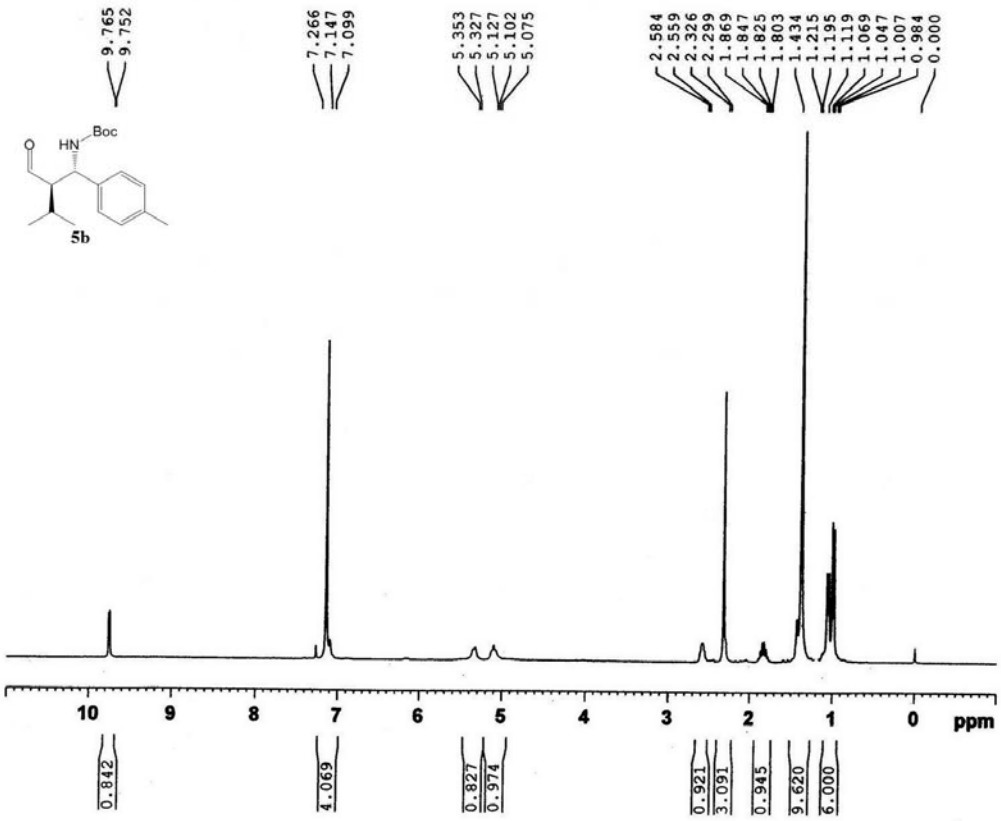
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HN
Boc
O
5b
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9
8
7
6
5
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3
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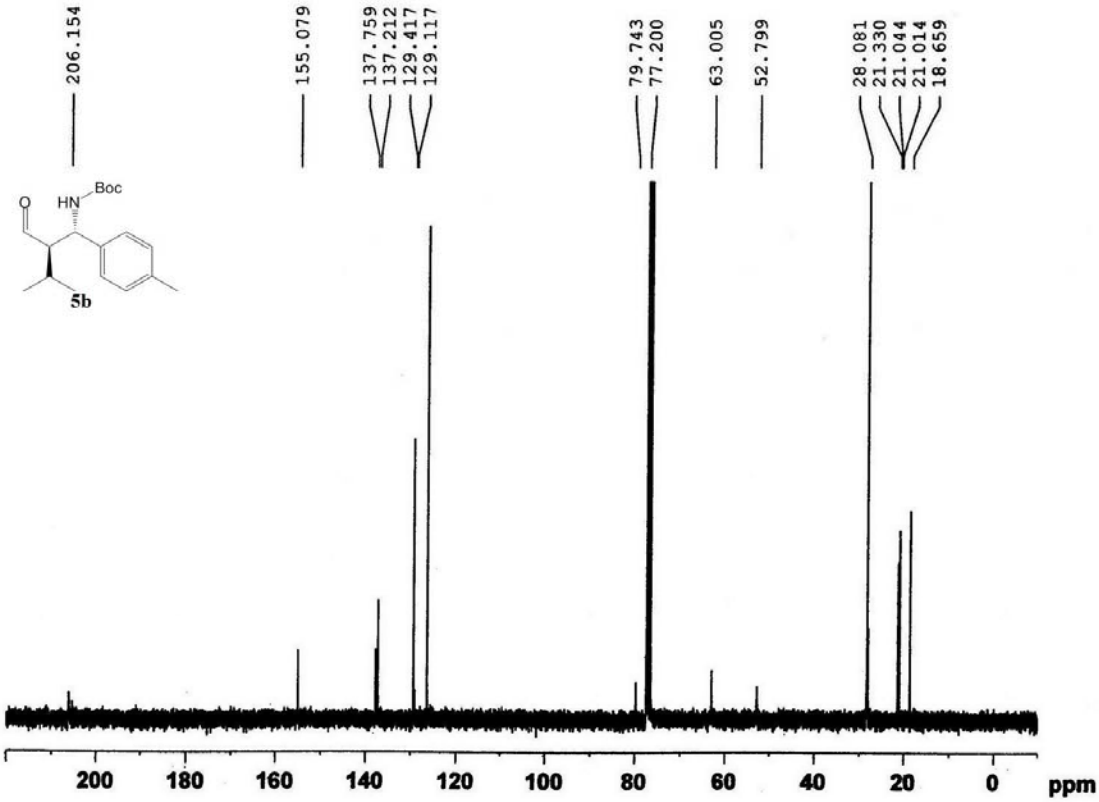
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Boc
O
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120
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40
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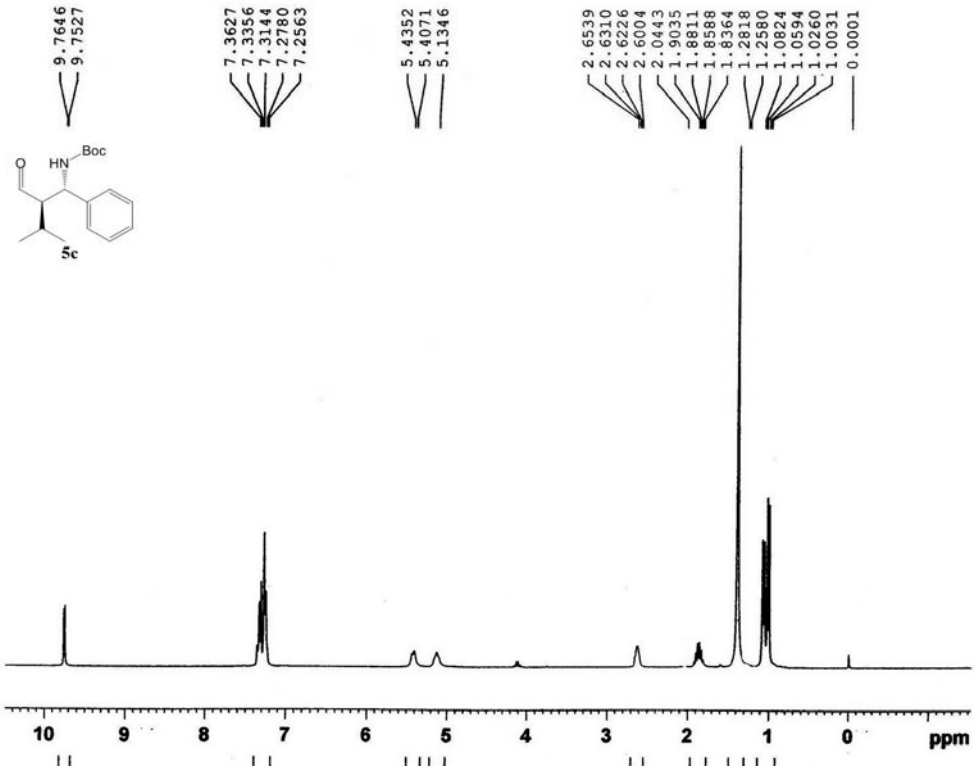
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2.6226
2.6004
2.0443
1.9035
1.8811
1.8588
1.8364
1.2818
1.2580
1.0824
1.0594
1.0260
1.0031
0.0001
Boc
HN
O
5c
10
9
8
7
6
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ppm
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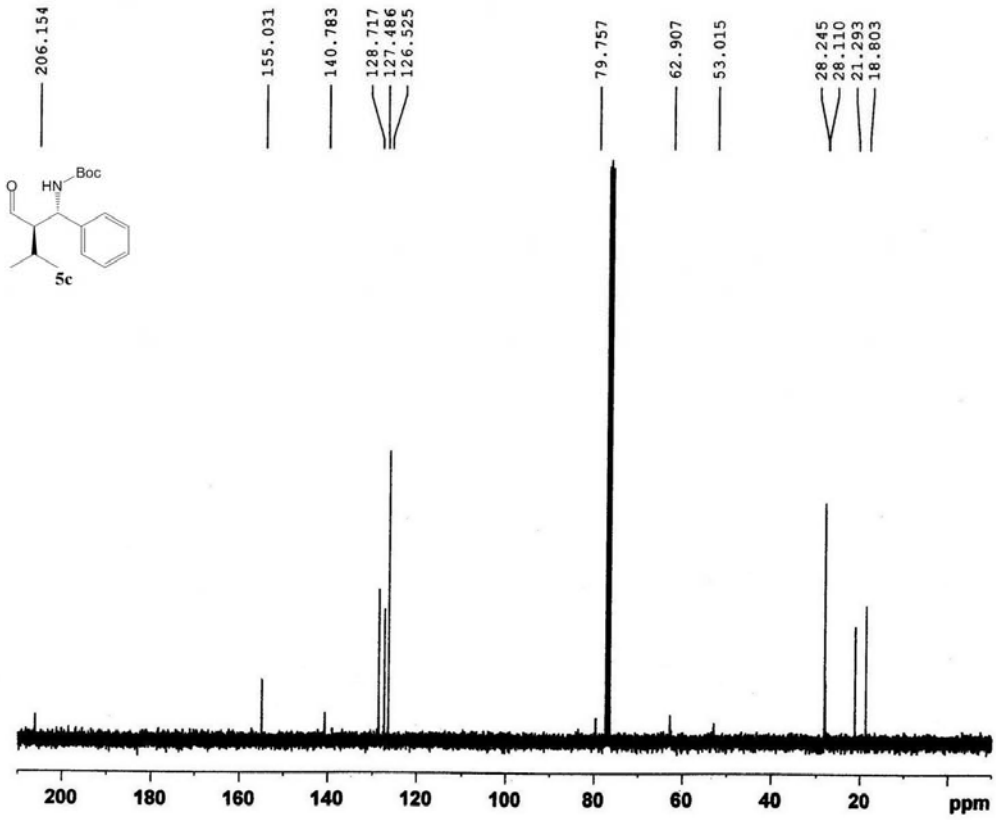
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HN
O
5c
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140
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80
60
40
20
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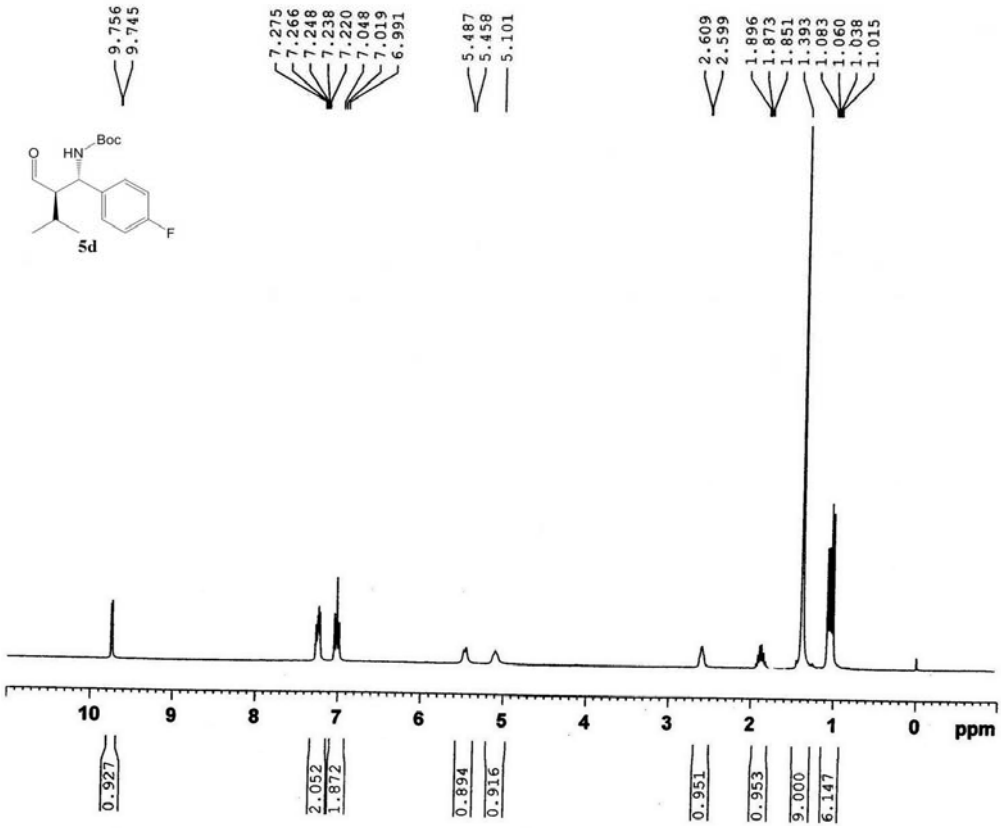
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7.048
7.019
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5.458
5.101
2.609
2.599
1.896
1.873
1.851
1.393
1.083
1.060
1.038
1.015
Boc
HN
O
F
5d
10
9
8
7
6
5
4
3
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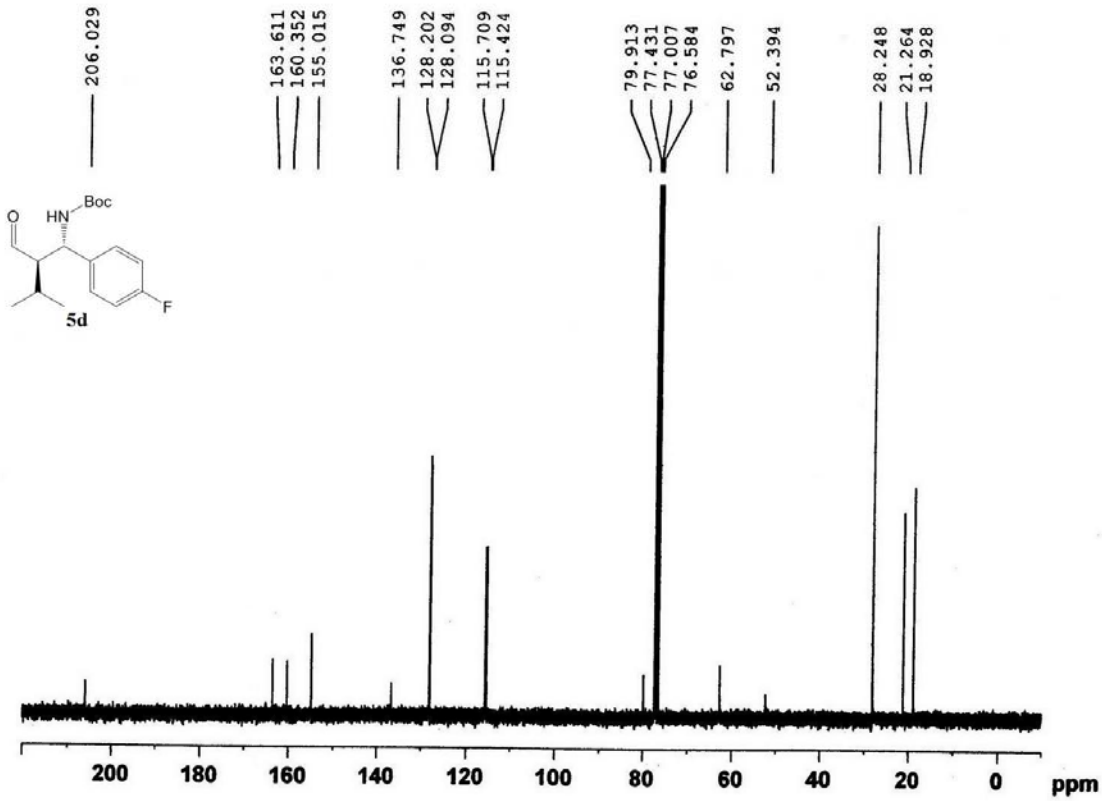
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28.248
21.264
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O
F
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120
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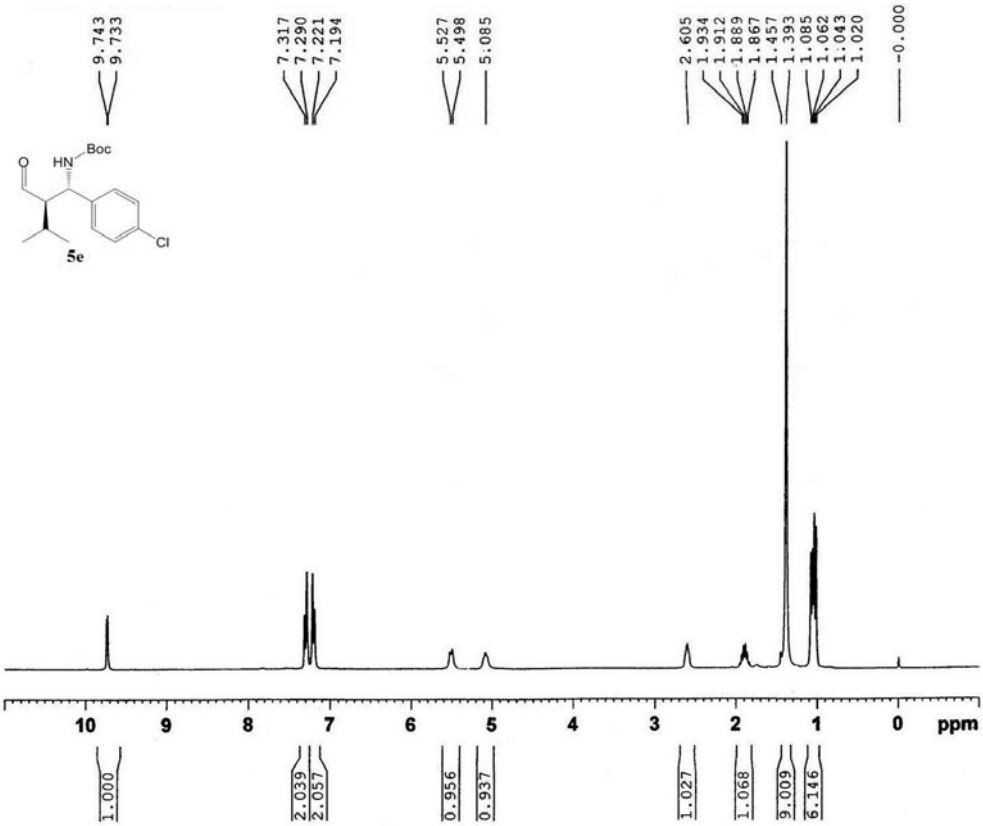
60
40
20
0
ppm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5.498
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2.605
1.934
1.912
1.889
1.867
1.457
1.393
1.085
1.062
1.043
1.020
-0.000
Boc
HN
O
Cl
5e
10
9
8
7
6
5
4
3
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ppm
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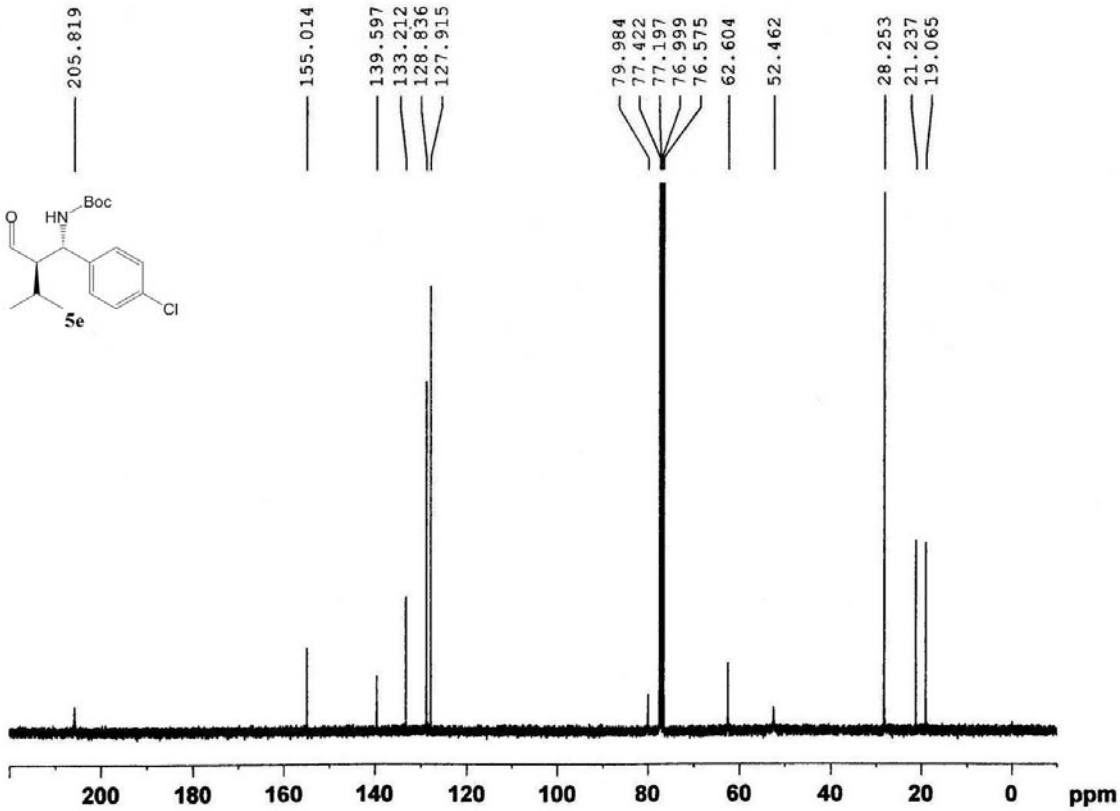
6.146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28.253
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HN
O
Cl
5e
200
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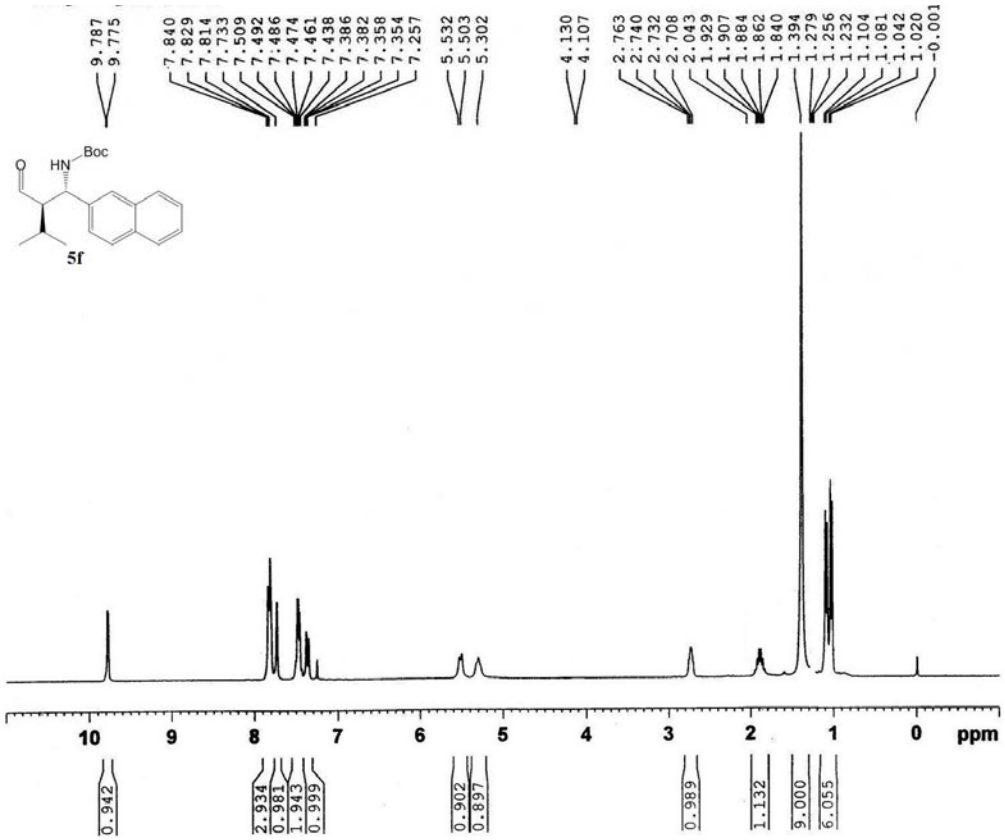
160
140
120
100
80
60
40
20
0
ppm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7.382
7.358
7.354
7.257
5.532
5.503
5.302
4.130
4.107
2.763
2.740
2.732
2.708
2.043
1.929
1.907
1.884
1.862
1.840
1.394
1.279
1.256
1.232
1.104
1.081
1.042
1.020
-0.001
Boc
HN
O
5f
10
9
8
7
6
5
4
3
2
1
0
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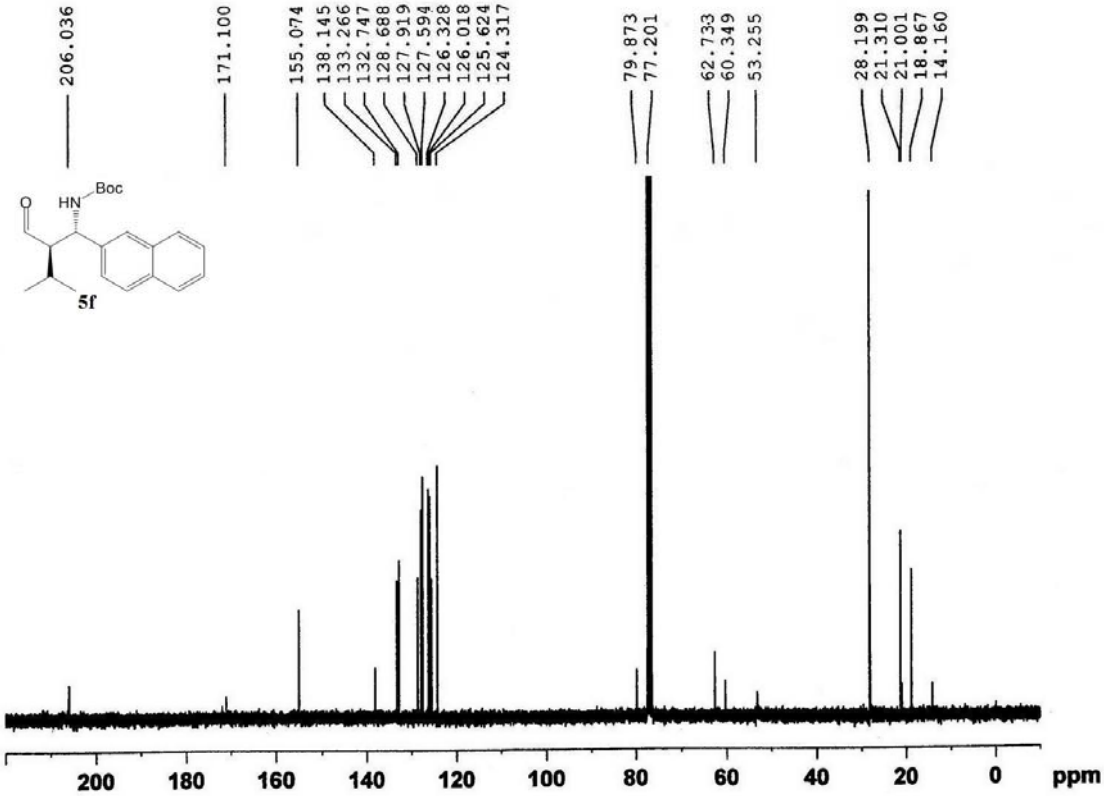
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125.624
124.317
79.873
77.201
62.733
60.349
53.255
28.199
21.310
21.001
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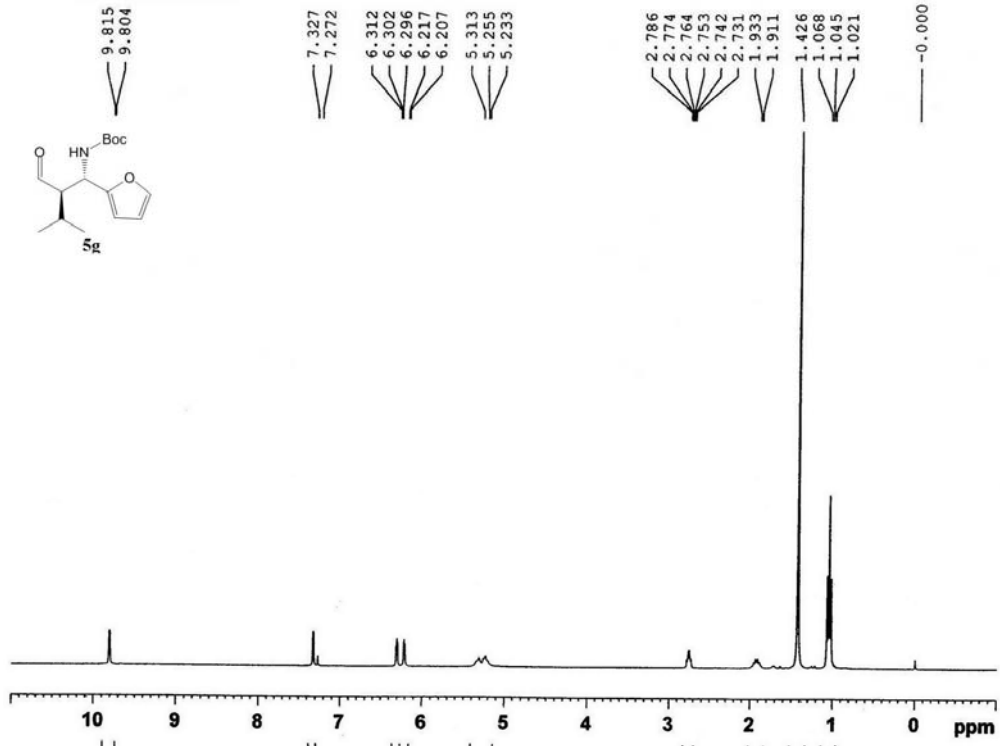
HN
O
5f
200
180
160
140
120
100
80
60
40
20
0
ppm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6.217
6.207
5.313
5.255
5.233
2.786
2.774
2.764
2.753
2.742
2.731
1.933
1.911
1.426
1.068
1.045
1.021
-0.000
Boc
HN
O
5g
10
9
8
7
6
5
4
3
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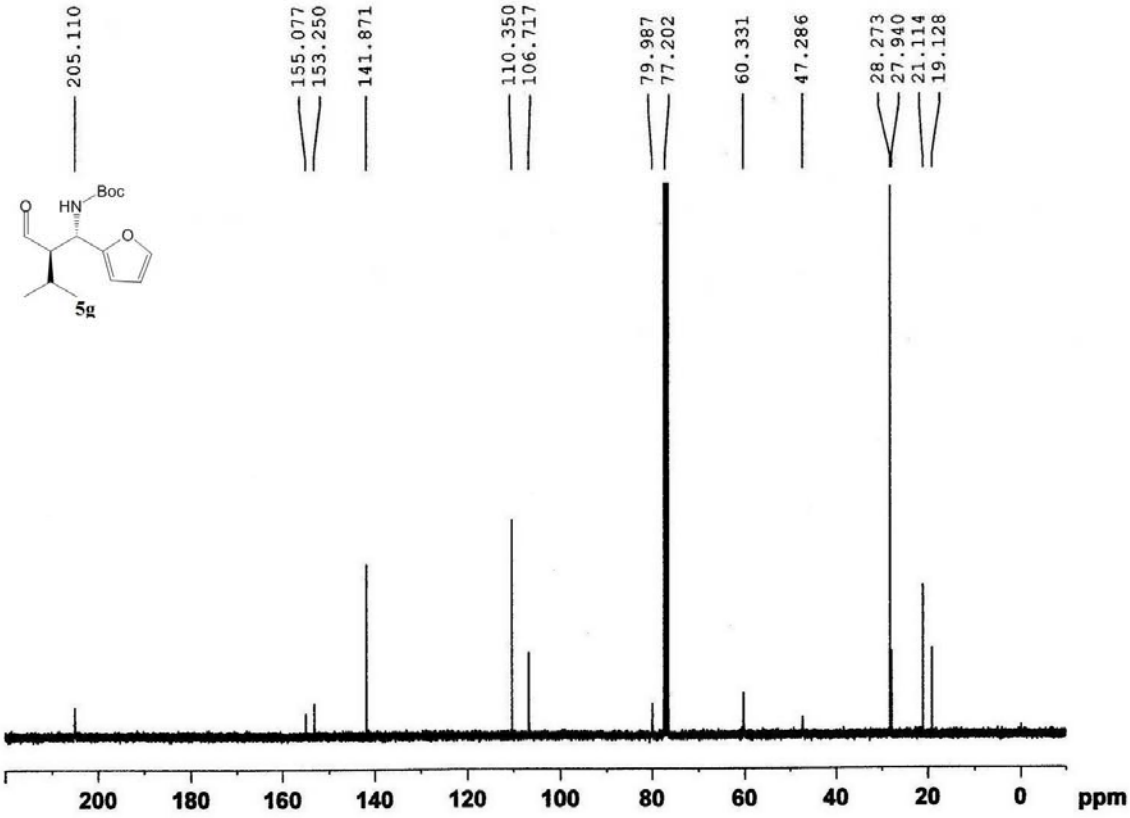
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28.273
27.940
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Boc
HN
O
5g
200
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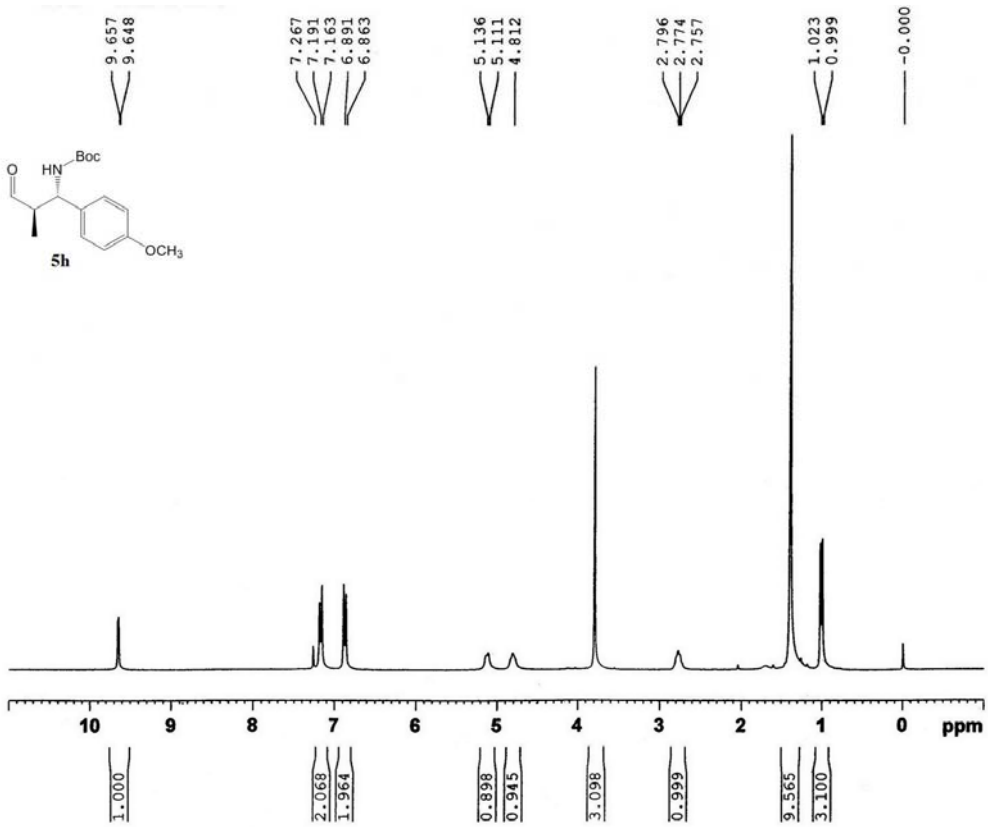
160
140
120
100
80
60
40
20
0
ppm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2.796
2.774
2.757
1.023
0.999
-0.000
Boc
HN
O
OCH3
5h
10
9
8
7
6
5
4
3
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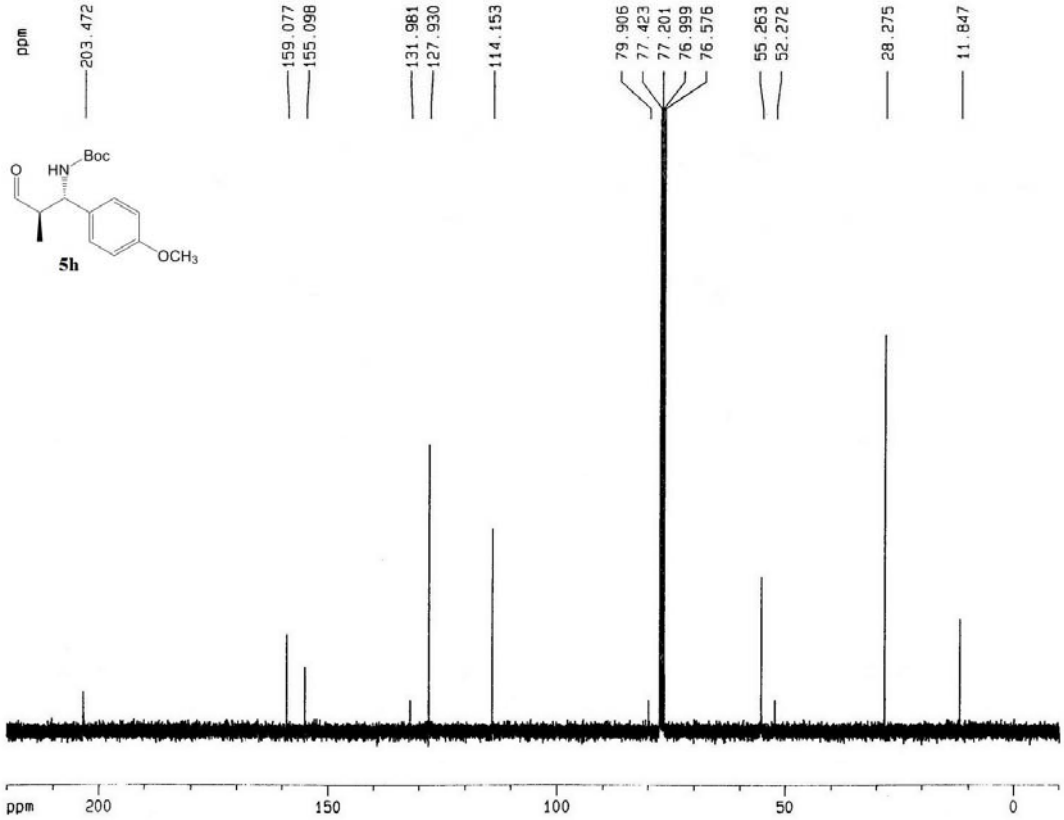
3.100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76.999
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Boc
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O
OCH3
5h
ppm
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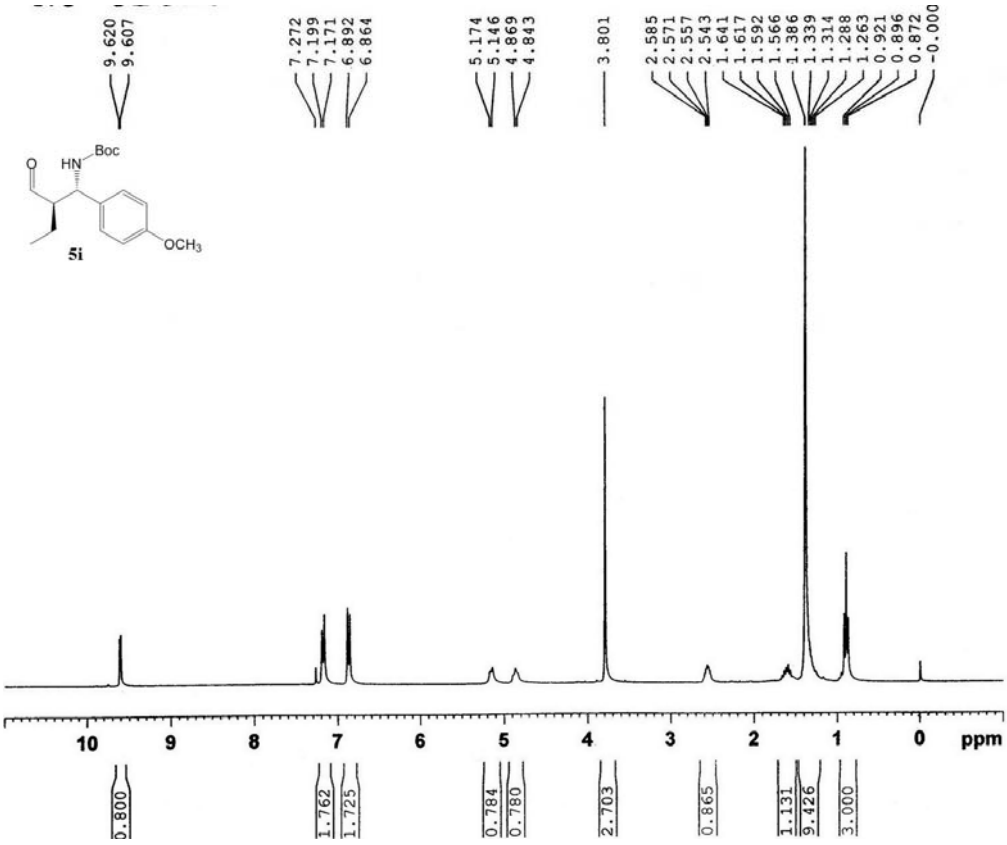
100
50
0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4.843
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2.571
2.557
2.543
1.641
1.617
1.592
1.566
1.386
1.339
1.314
1.288
1.263
0.921
0.896
0.872
-0.000
Boc
HN
O
OCH3
5i
10
9
8
7
6
5
4
3
2
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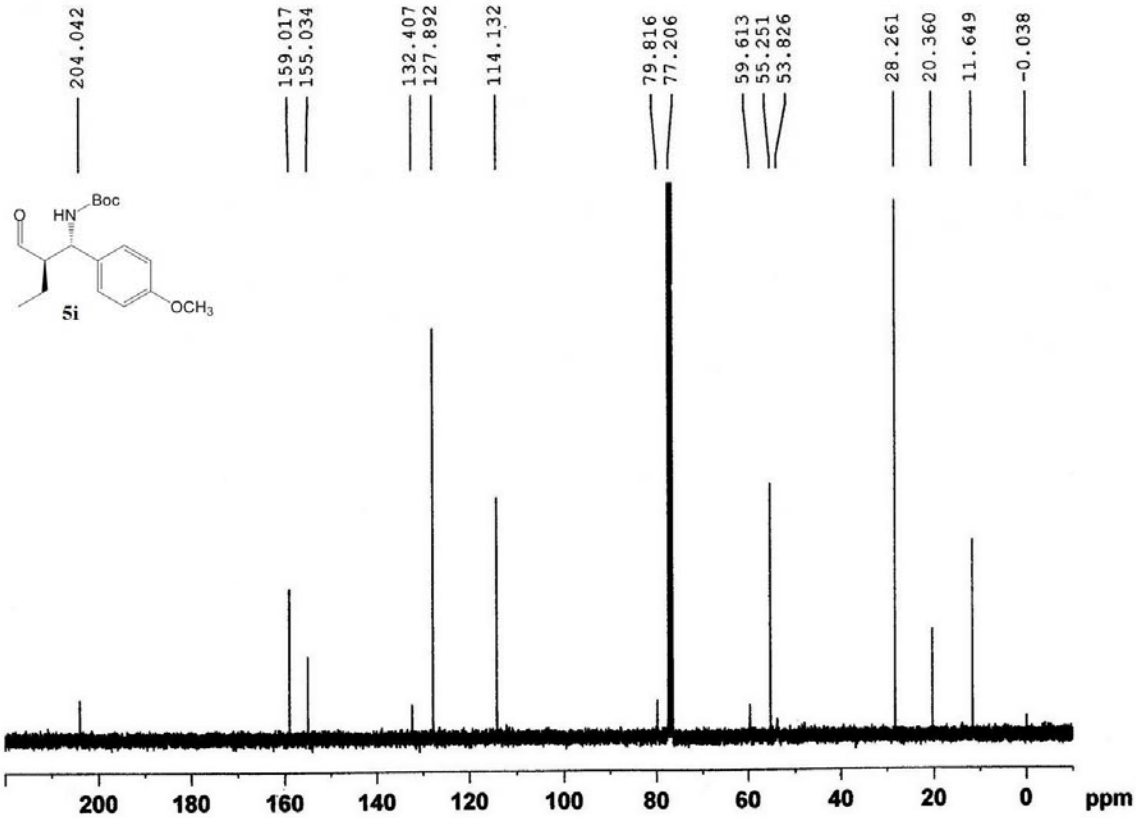
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20.360
11.649
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O
OCH3
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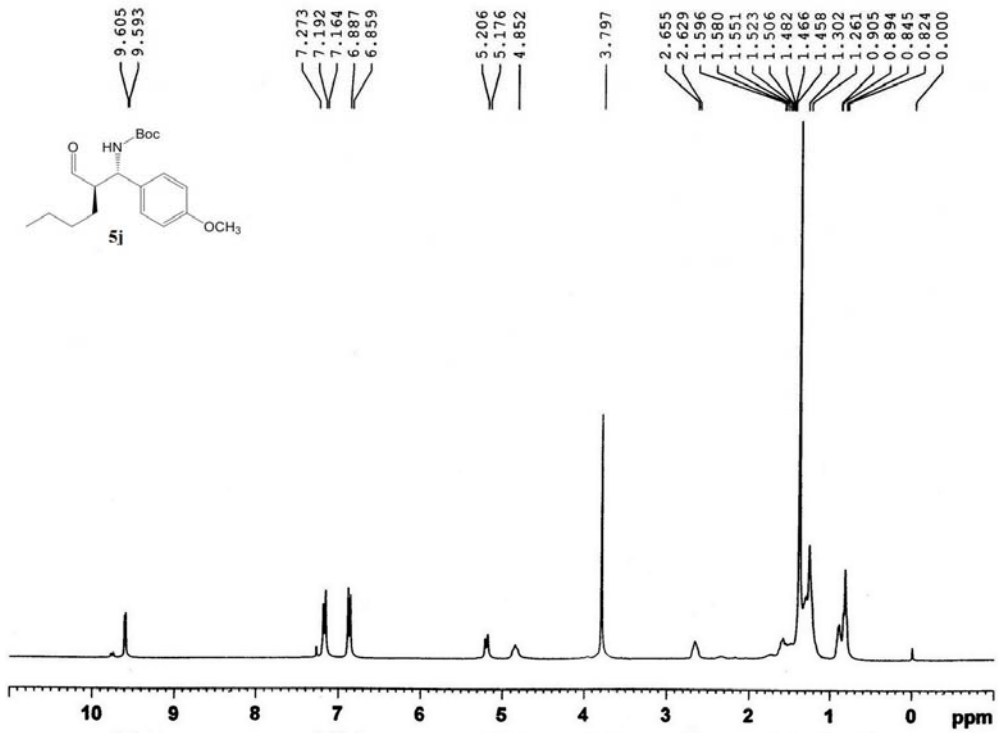
120
100
80
60
40
20
0
ppm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4.852
3.797
2.655
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1.596
1.580
1.551
1.523
1.506
1.482
1.466
1.458
1.302
1.261
0.905
0.894
0.845
0.824
0.000
Boc
HN
O
OCH3
5j
10
9
8
7
6
5
4
3
2
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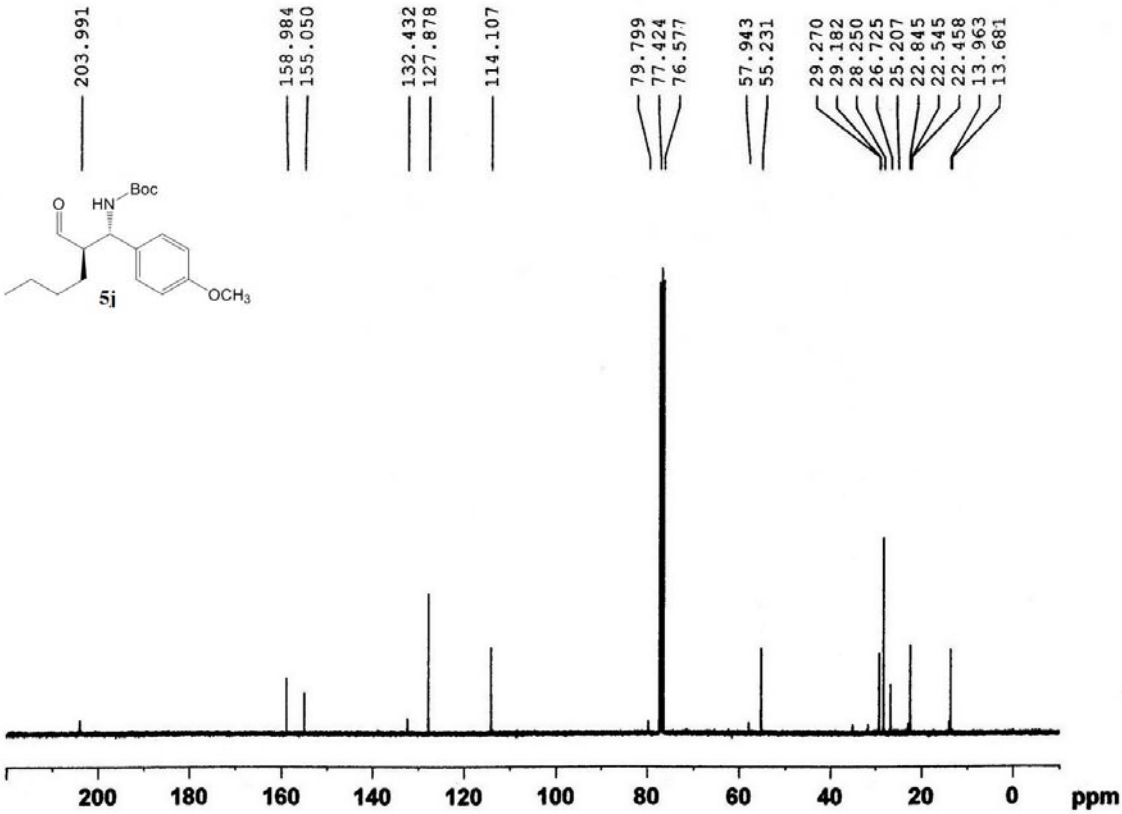
4.810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29.182
28.250
26.725
25.207
22.845
22.545
22.458
13.963
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Boc
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O
OCH3
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200
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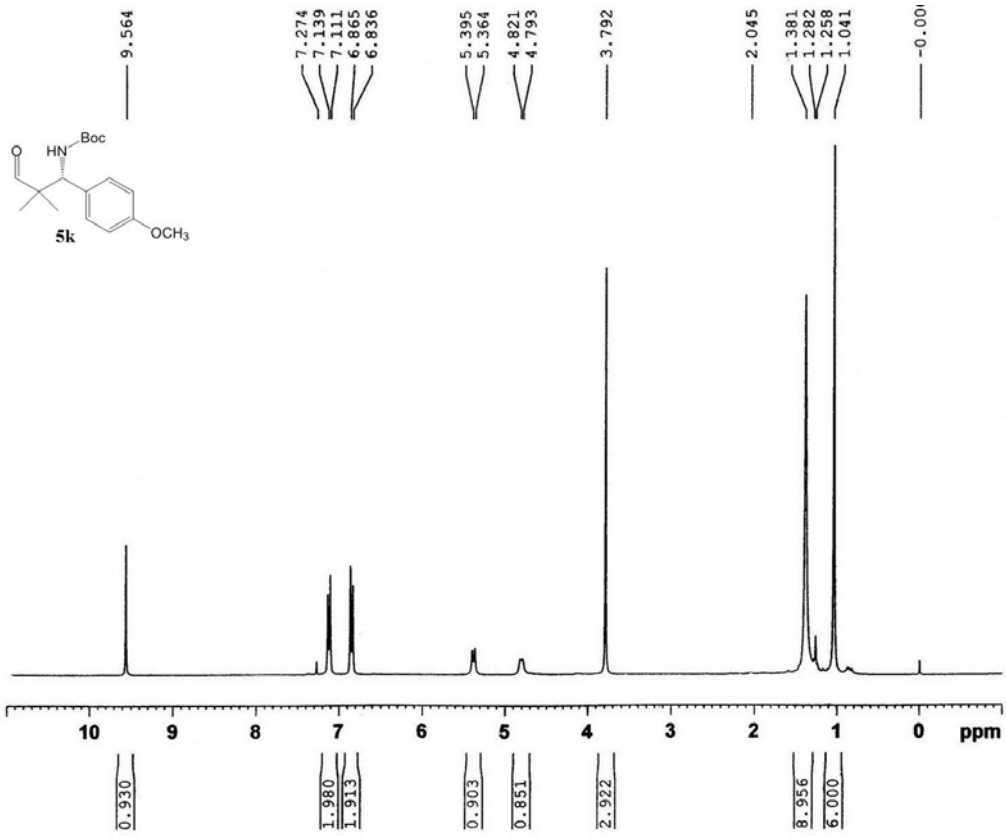
120
100
80
60
40
20
0
ppm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1.381
1.282
1.258
1.041
-0.001
HN
Boc
O
OCH3
5k
10
9
8
7
6
5
4
3
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0
ppm
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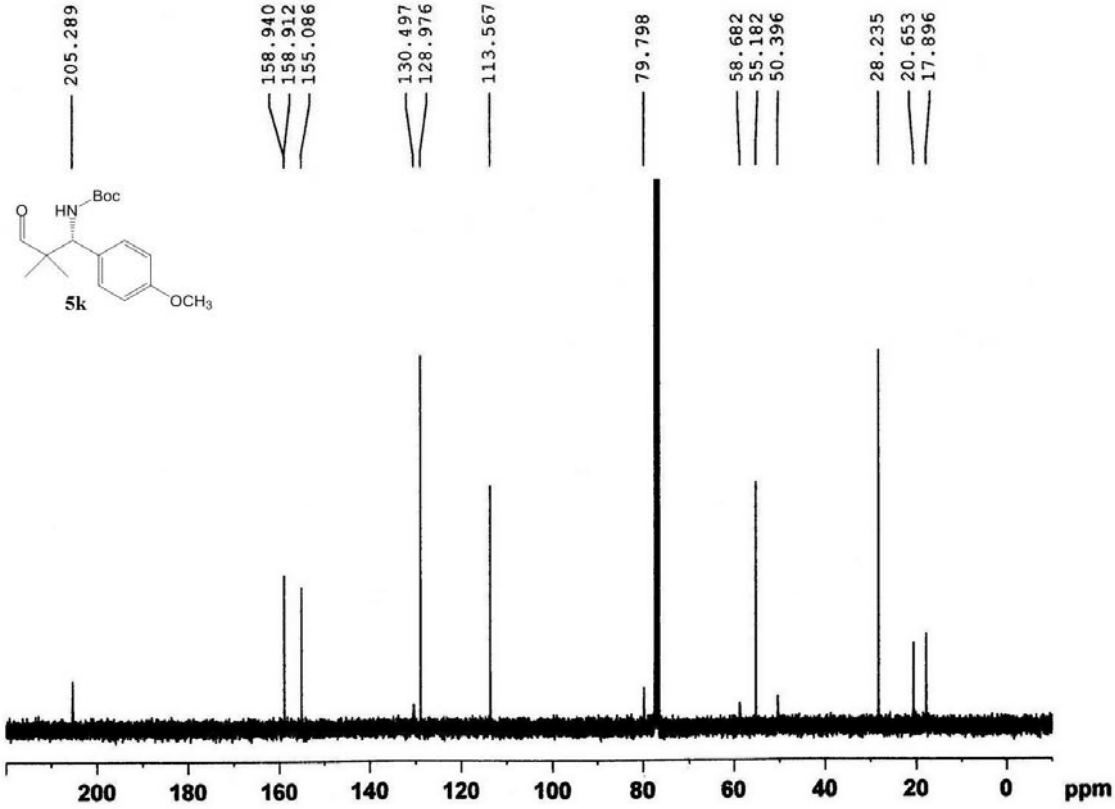
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20.653
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Boc
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OCH3
5k
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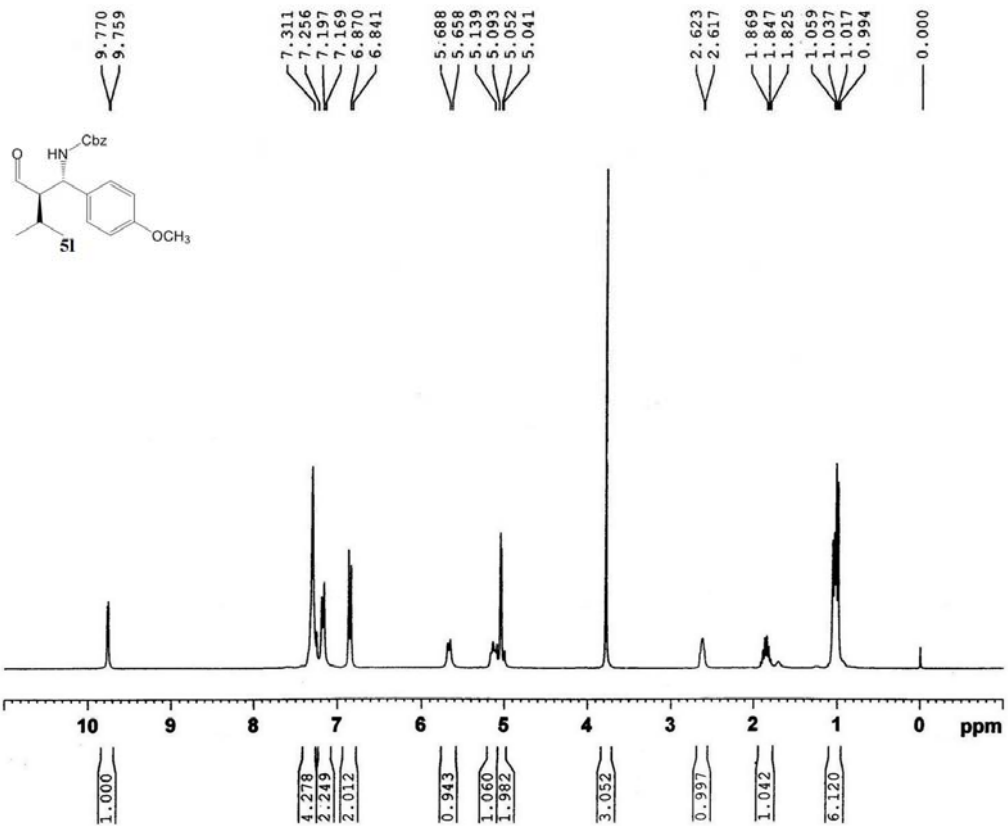
120
100
80
60
40
20
0
ppm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7.169
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6.841
5.688
5.658
5.139
5.093
5.052
5.041
2.623
2.617
1.869
1.847
1.825
1.059
1.037
1.017
0.994
0.000
HN
Cbz
OCH3
51
10 9 8 7 6 5 4 3 2 1 0 ppm
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1.060
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3.052
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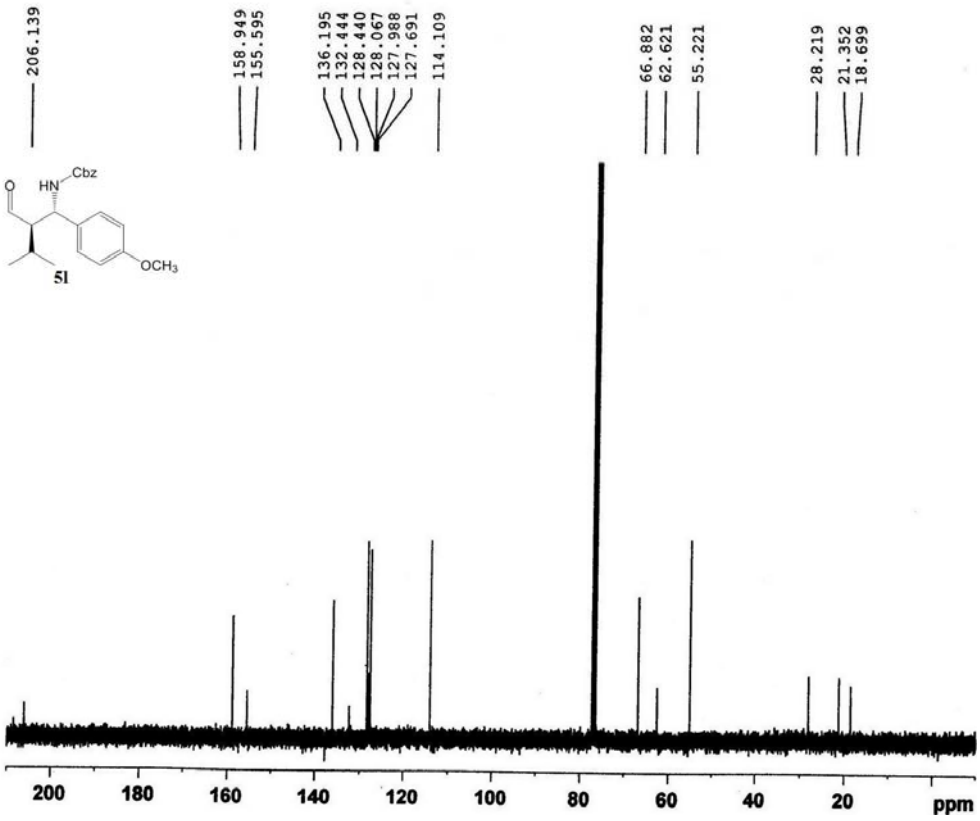
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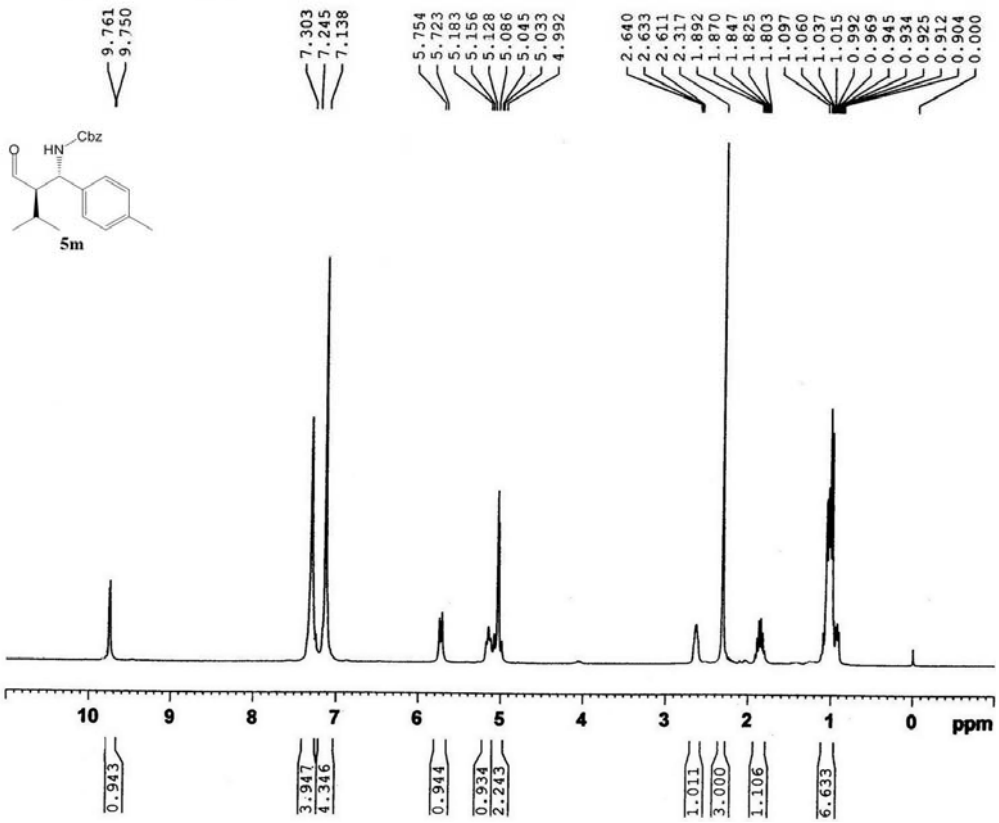
Cbz
OCH3
51
200 180 160 140 120 100 80 60 40 20 ppm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5.128
5.086
5.045
5.033
4.992
2.640
2.633
2.611
2.317
1.892
1.870
1.847
1.825
1.803
1.097
1.060
1.037
1.015
0.992
0.969
0.945
0.934
0.925
0.912
0.904
0.000
HN
Cbz
O
5m
10
9
8
7
6
5
4
3
2
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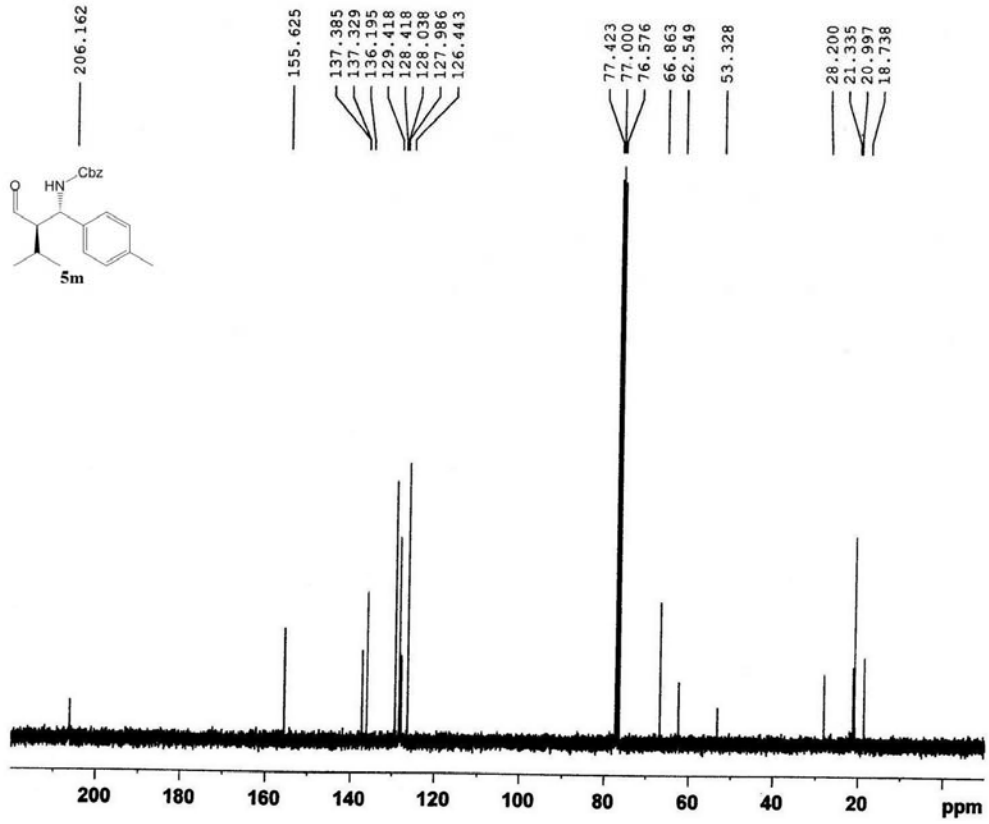
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128.038
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77.423
77.000
76.576
66.863
62.549
53.328
28.200
21.335
20.997
18.738
HN
Cbz
O
5m
200
180
160
140
120
100
80
60
40
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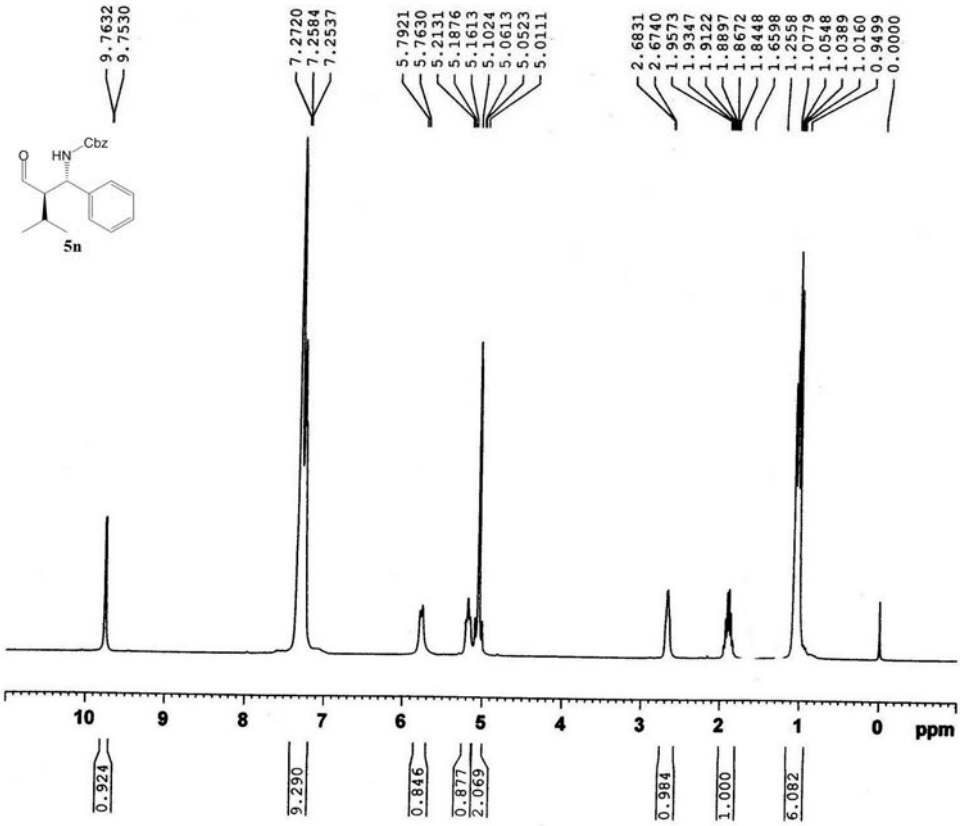
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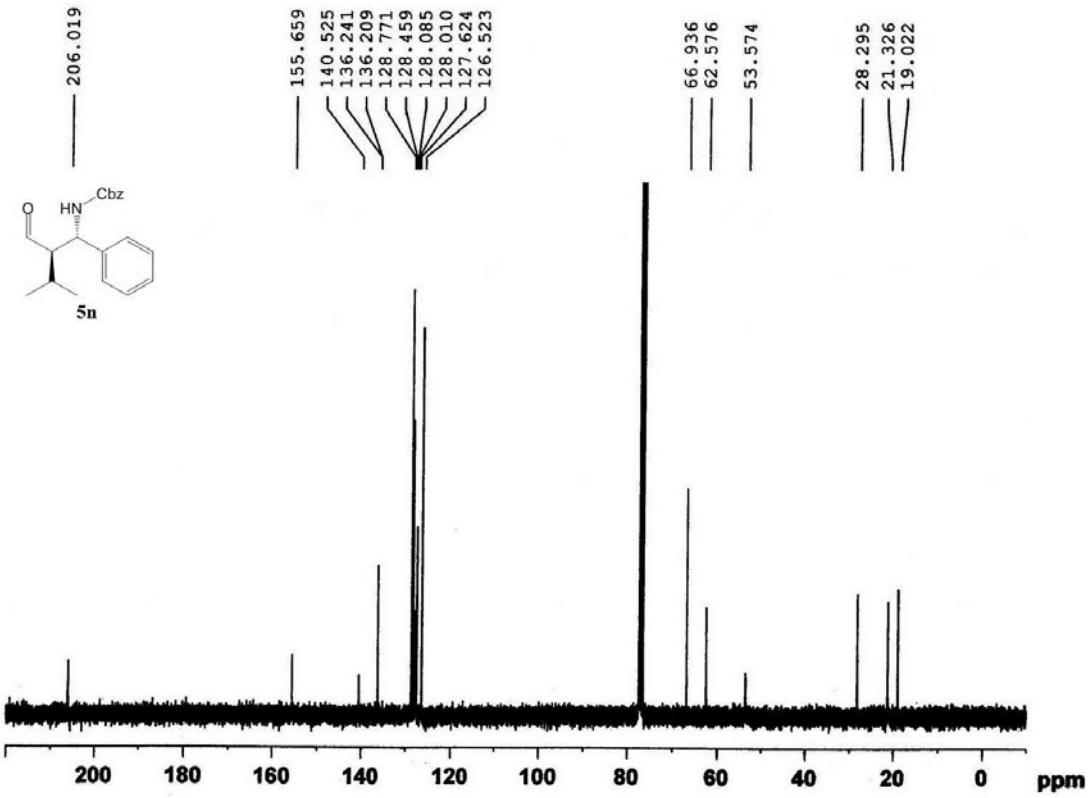
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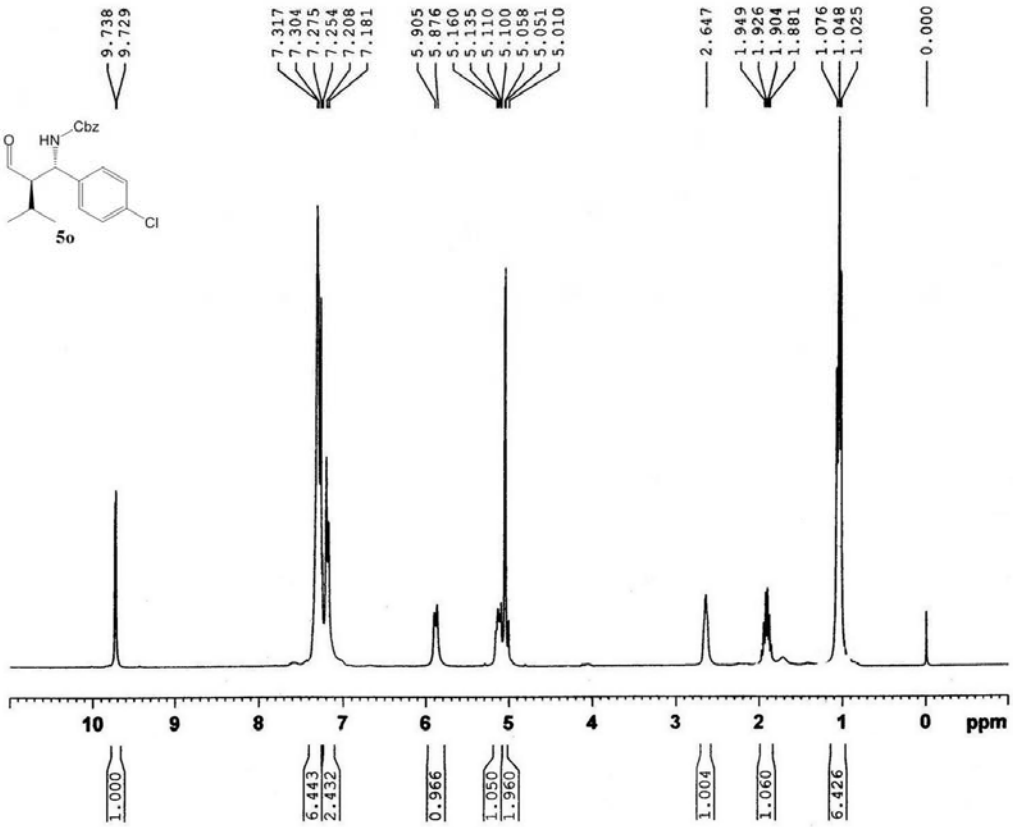
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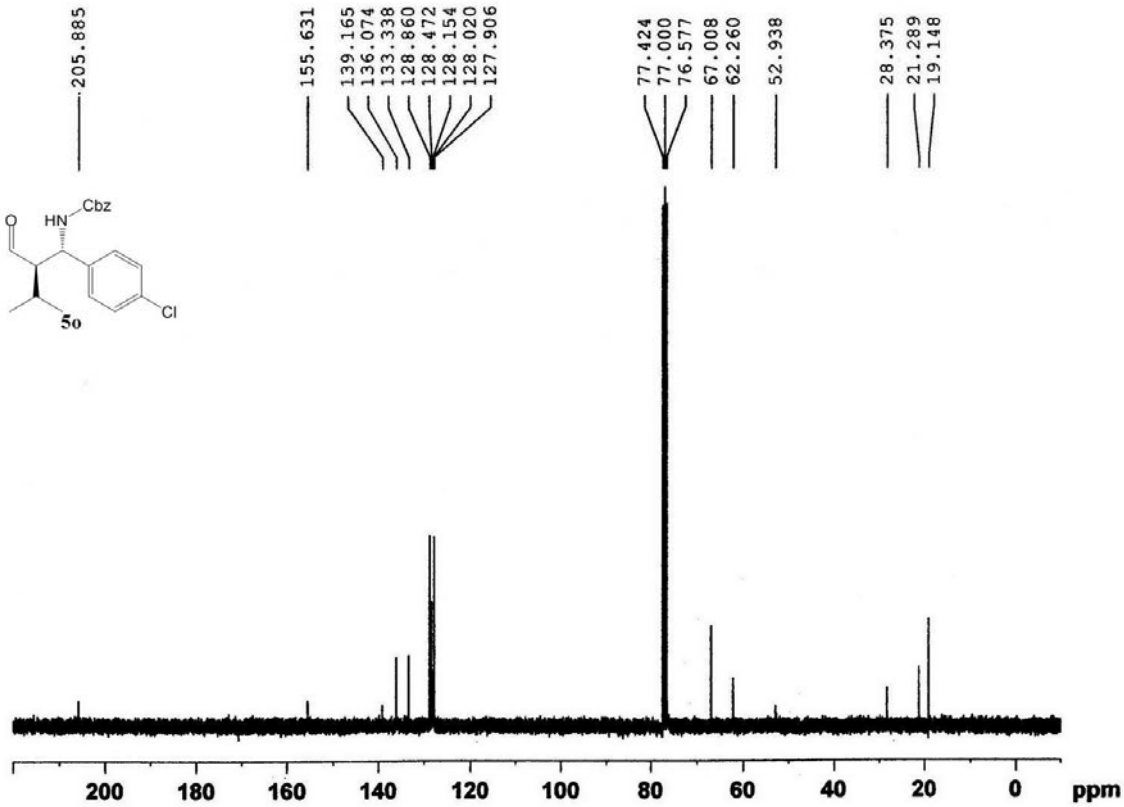
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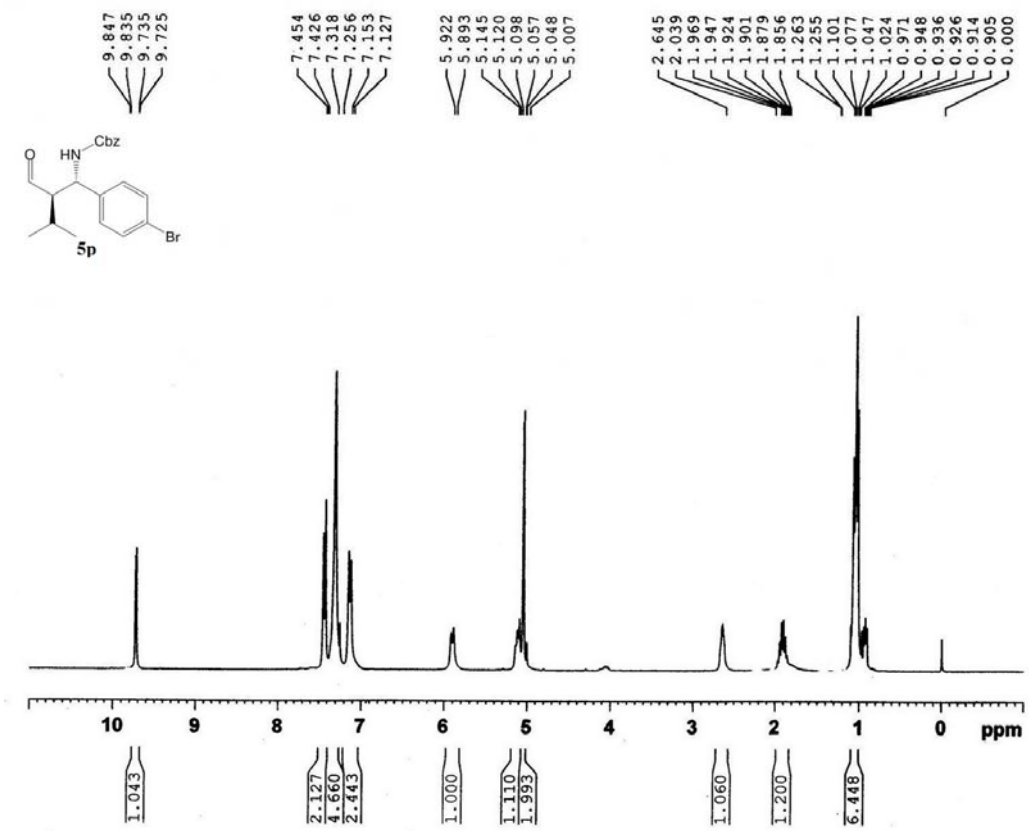
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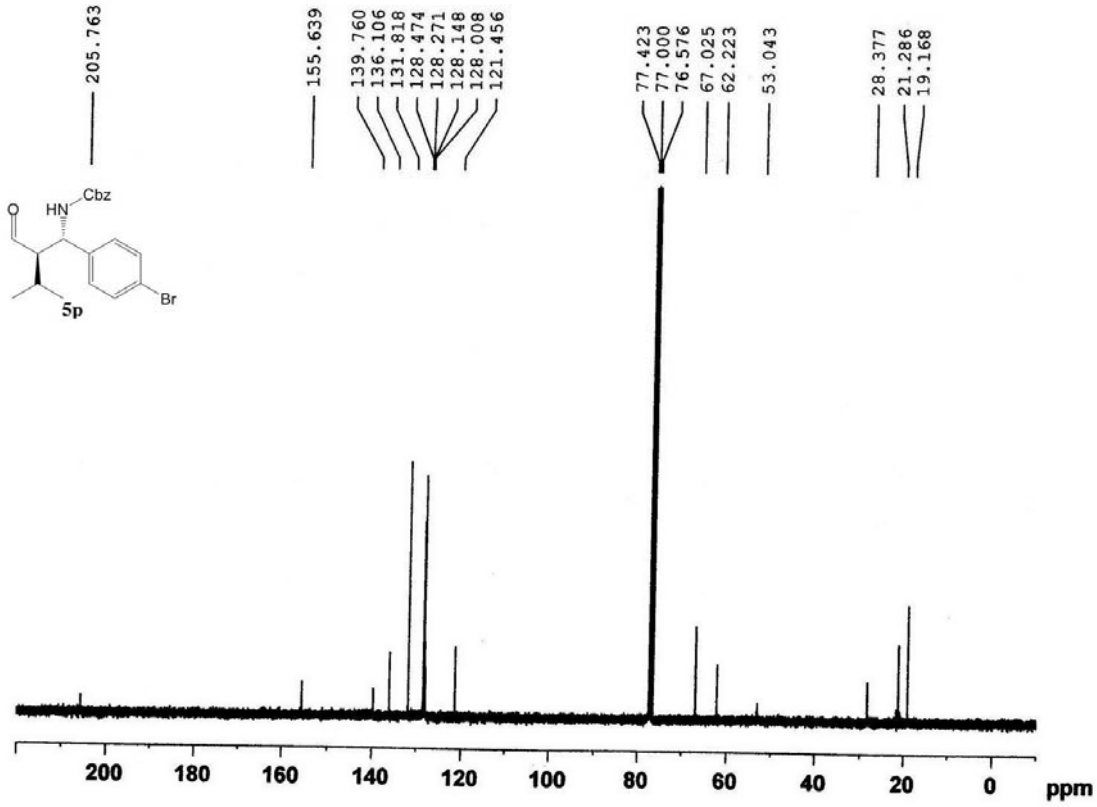
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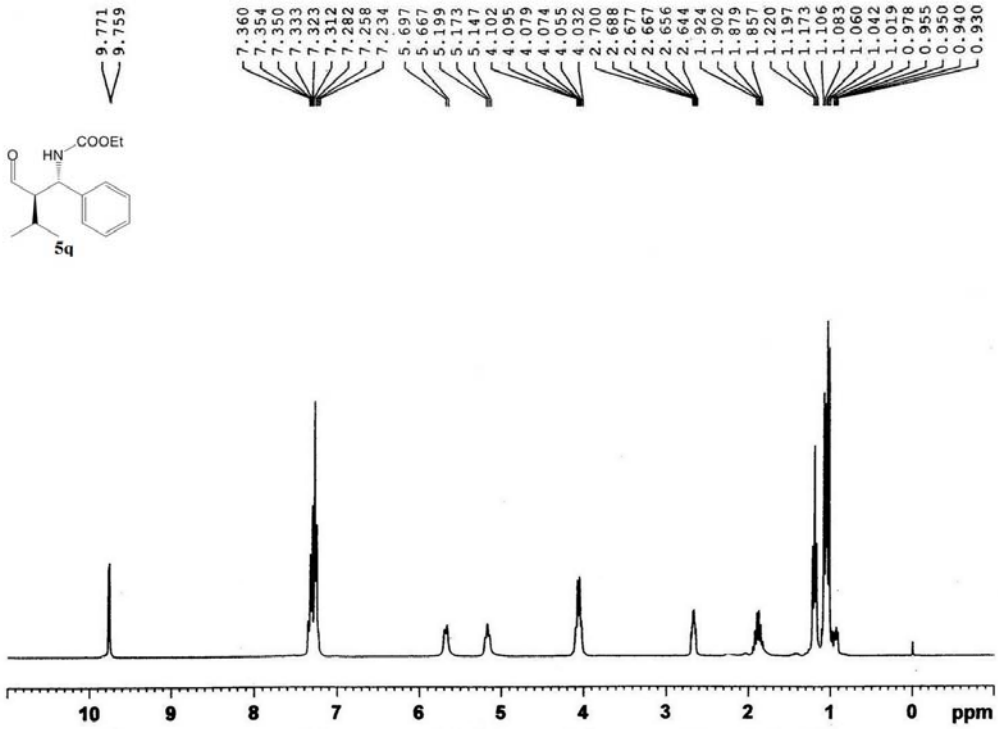
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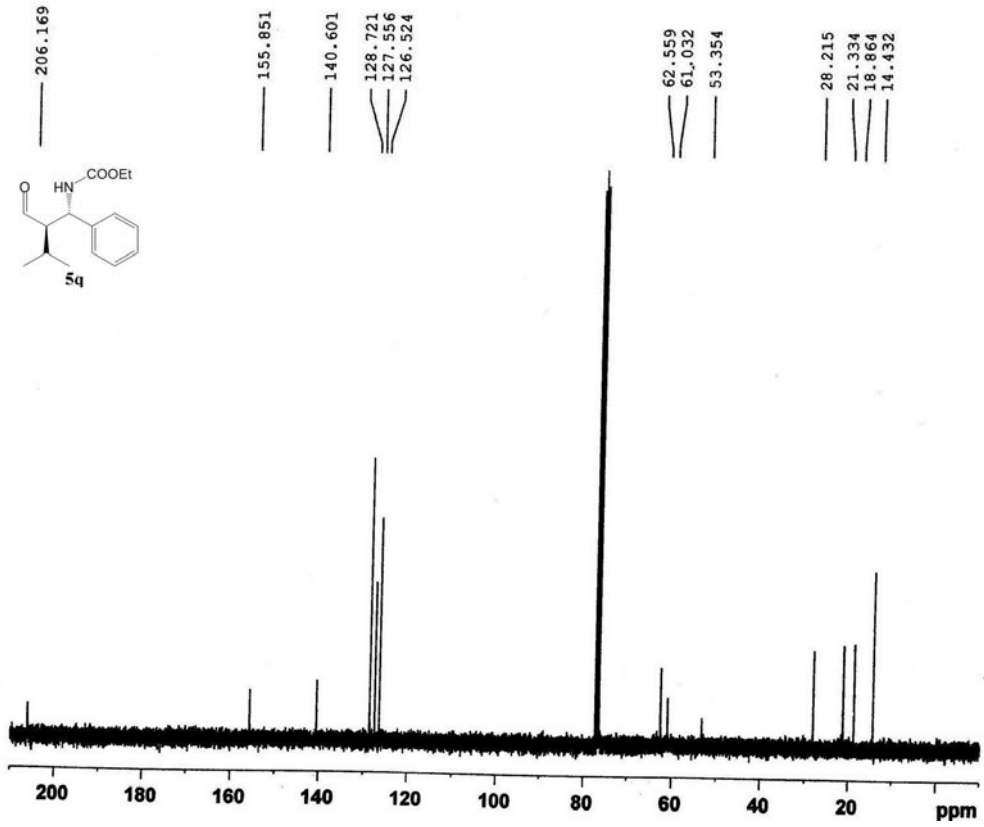
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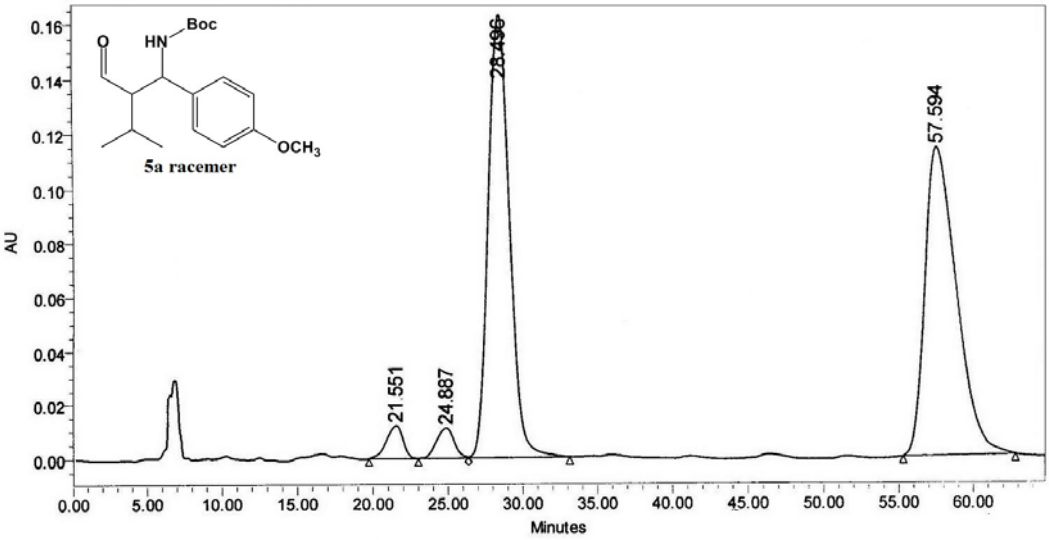
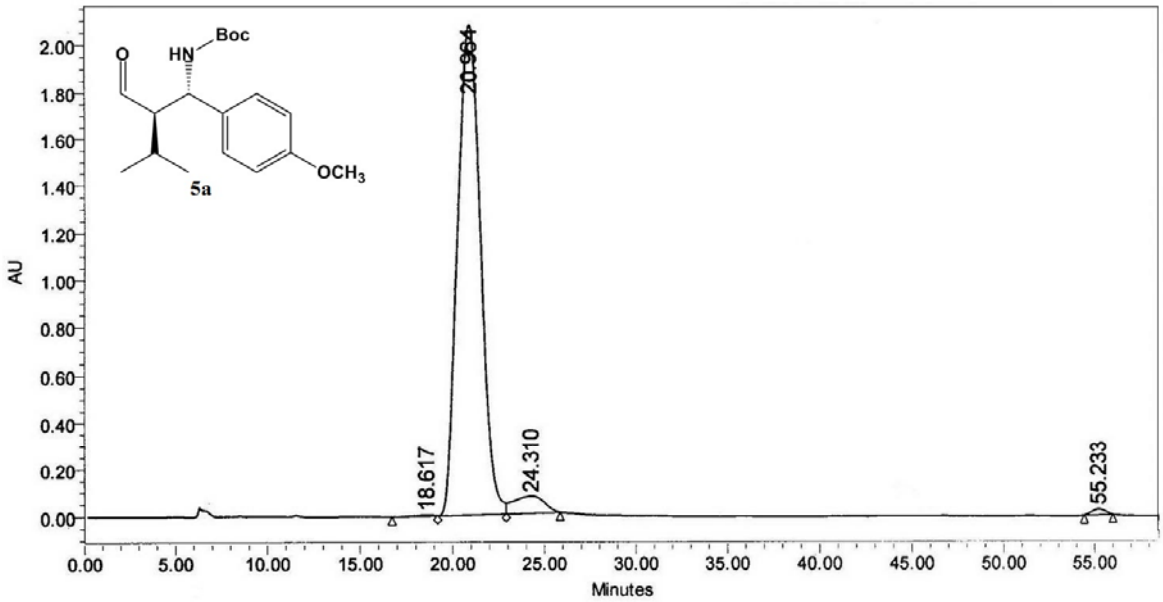
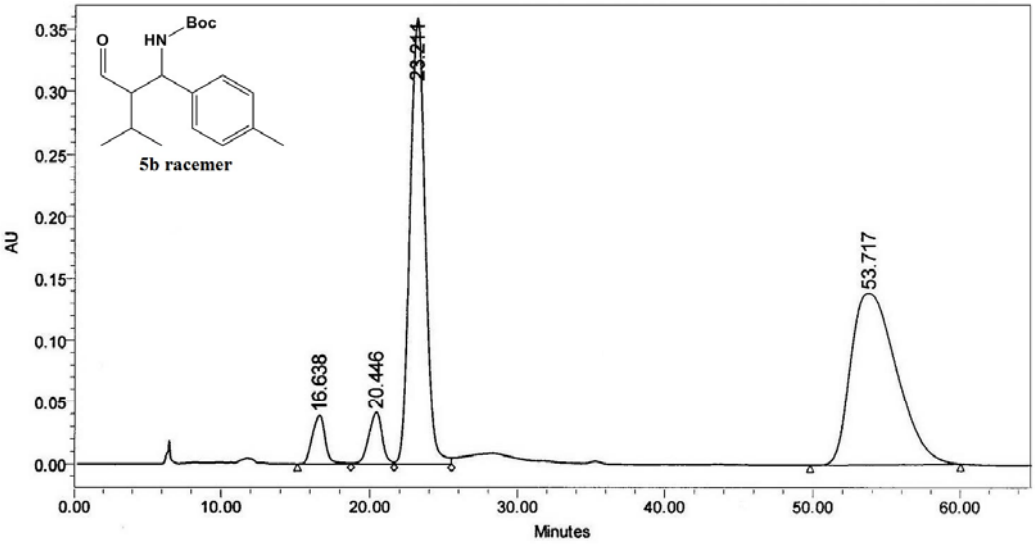


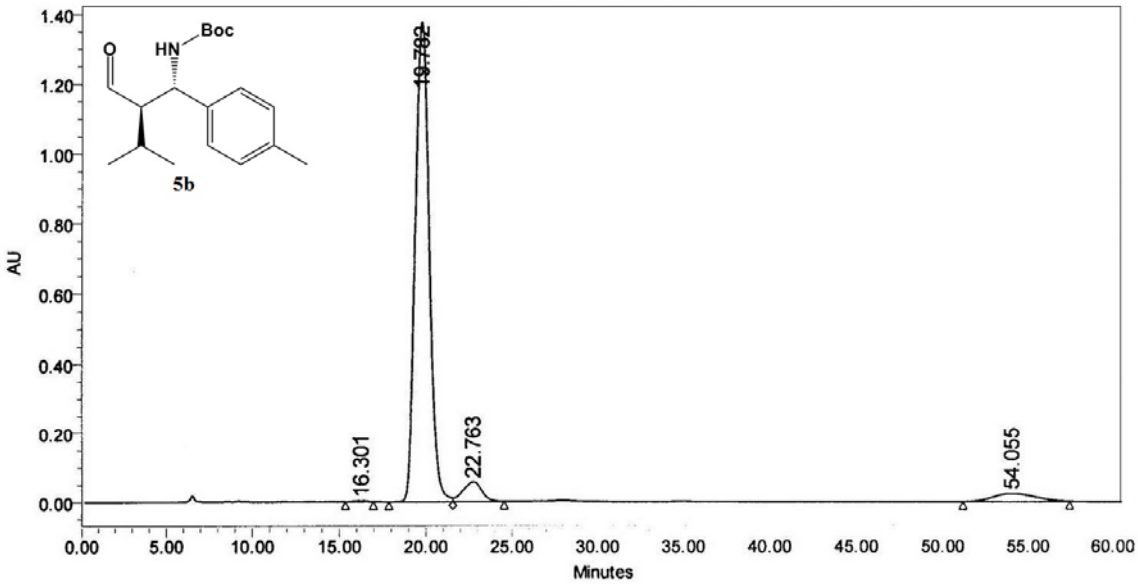
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	21.551	907379	2.61	11969	3.99
2	24.887	888362	2.56	10911	3.64
3	28.496	16158375	46.54	162958	54.34
4	57.594	16766430	48.29	114075	38.04



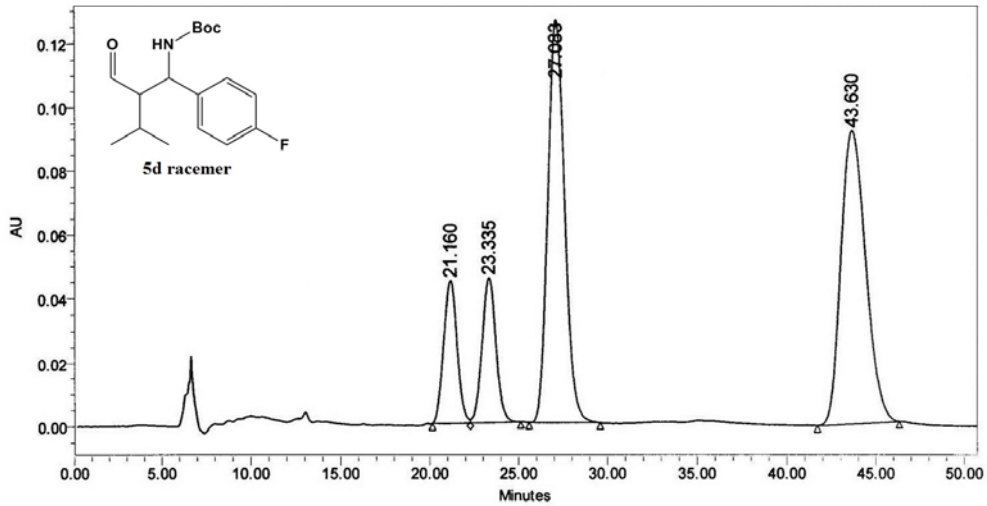
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.617	217154	0.11	3335	0.15
2	20.964	180080289	94.92	2076845	95.52
3	24.310	8215323	4.33	70532	3.24
4	55.233	1214065	0.64	23537	1.08



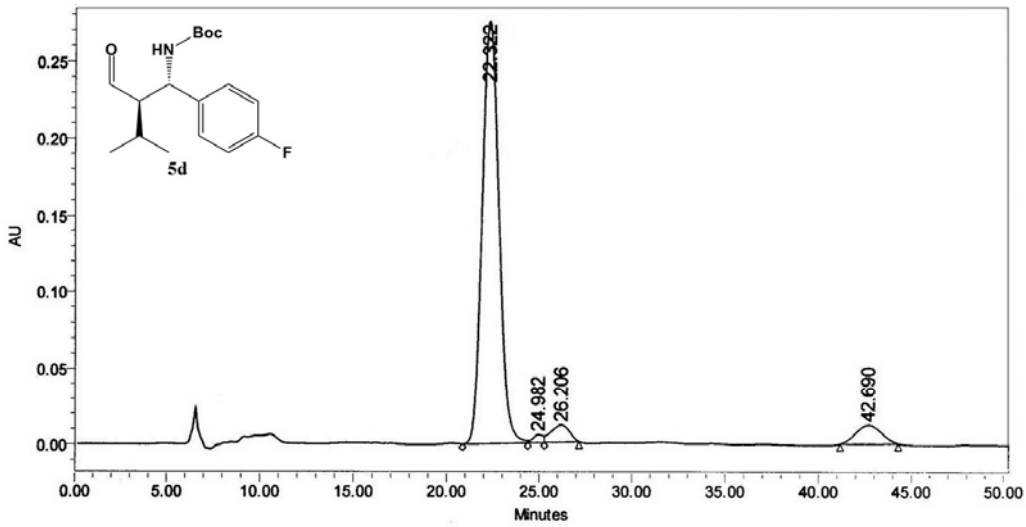
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.638	2322318	3.84	38604	6.68
2	20.446	2577012	4.26	41303	7.14
3	23.211	25718147	42.50	359430	62.15
4	53.717	29902155	49.41	138993	24.03



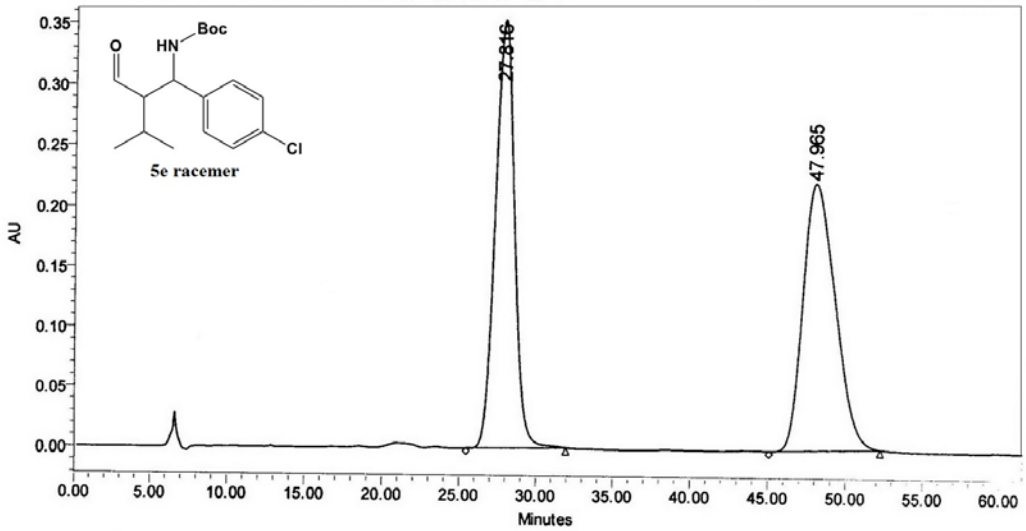
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.301	162095	0.19	3302	0.23
2	19.782	77551631	90.11	1379713	94.24
3	22.763	4295836	4.99	57191	3.91
4	54.055	4054572	4.71	23892	1.63



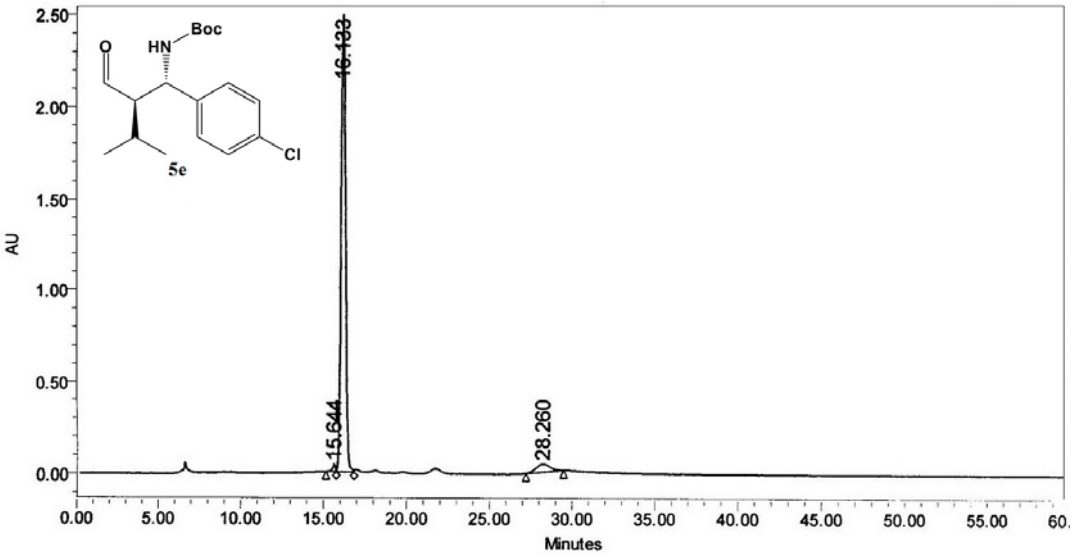
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	21.160	2359661	10.67	44568	14.46
2	23.335	2466314	11.16	45185	14.66
3	27.083	8320676	37.64	126286	40.98
4	43.630	8958901	40.53	92120	29.89



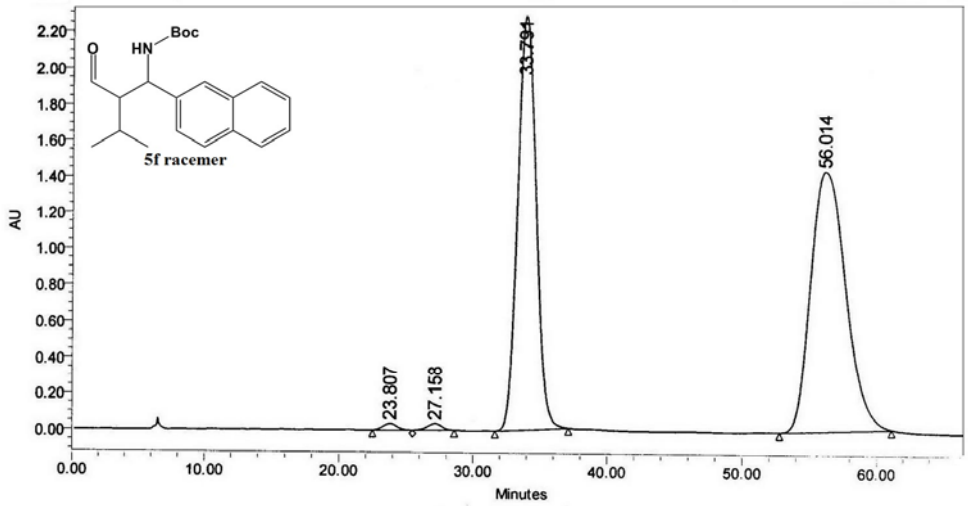
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	22.322	17420806	89.13	275763	90.60
2	24.982	189254	0.97	5123	1.68
3	26.206	769781	3.94	11167	3.67
4	42.690	1165423	5.96	12324	4.05



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	27.816	30774068	48.87	354867	61.40
2	47.965	32202115	51.13	223132	38.60



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.644	449246	0.91	38878	1.51
2	16.133	46729024	94.22	2493213	96.87
3	28.260	2416514	4.87	41705	1.62



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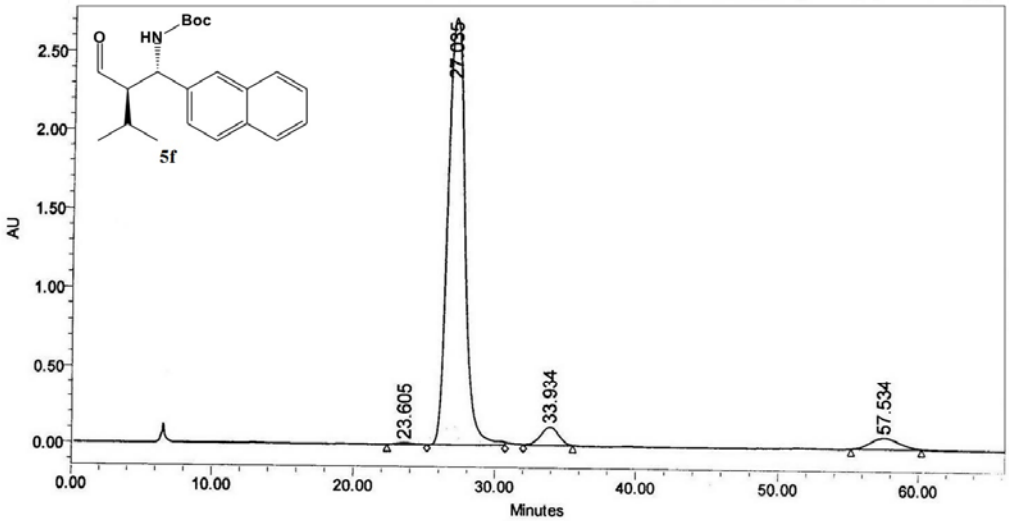
1	23.807	2508519	0.51	35465	0.93
2	27.158	2608548	0.53	35817	0.94
3	33.791	220935047	45.25	2293422	60.19
4	56.014	262241788	53.71	1445448	37.94



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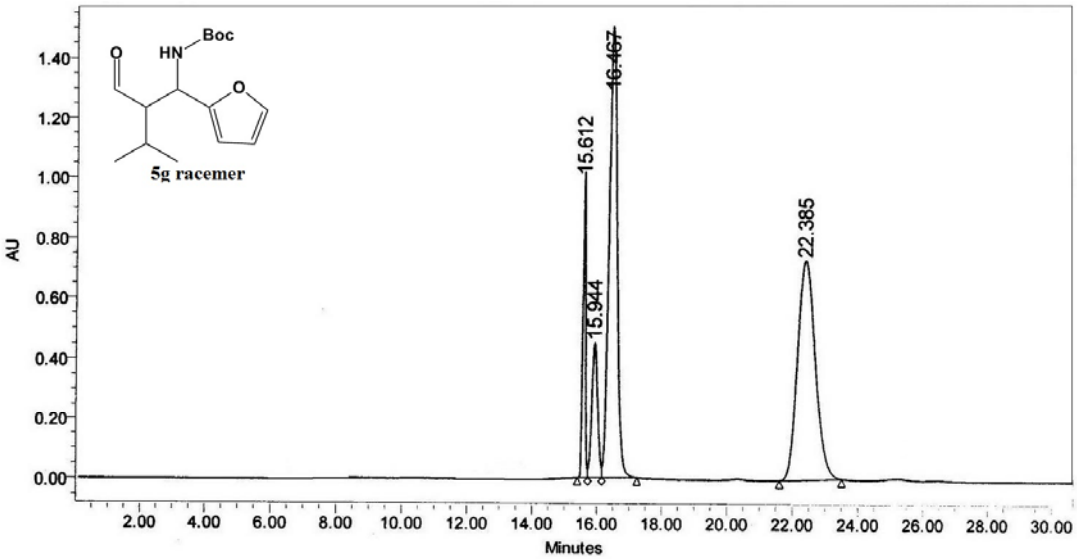
1	23.605	701214	0.28	10787	0.37
2	27.035	230198050	91.74	2729481	93.33
3	33.934	10232793	4.08	115577	3.95
4	57.534	9794474	3.90	68596	2.35



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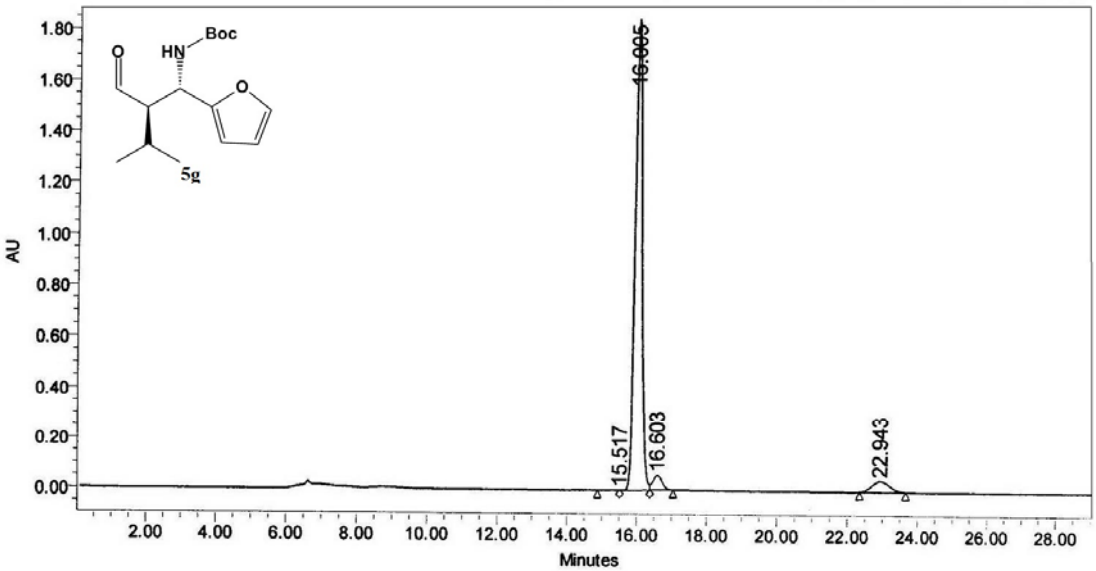
1	15.612	5684460	8.76	1008463	27.27
2	15.944	5620238	8.66	450364	12.18
3	16.467	25960338	40.01	1507577	40.76
4	22.385	27625305	42.57	732064	19.79



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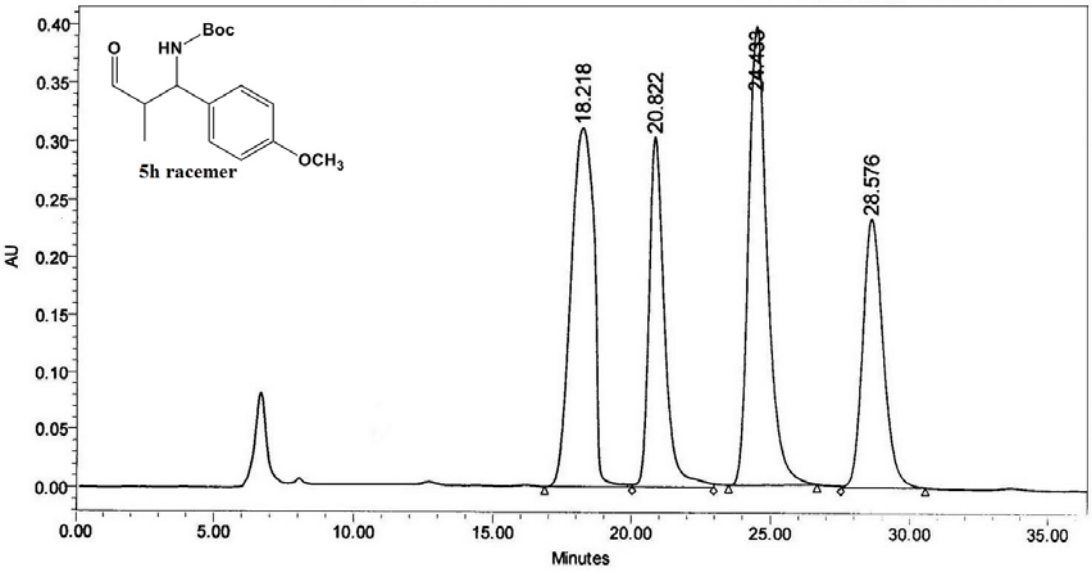
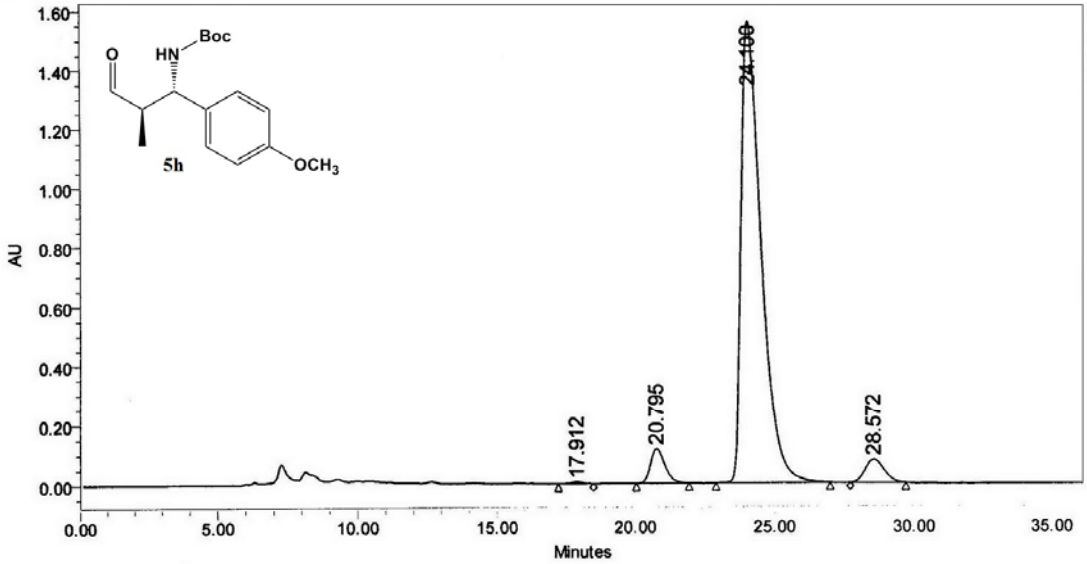
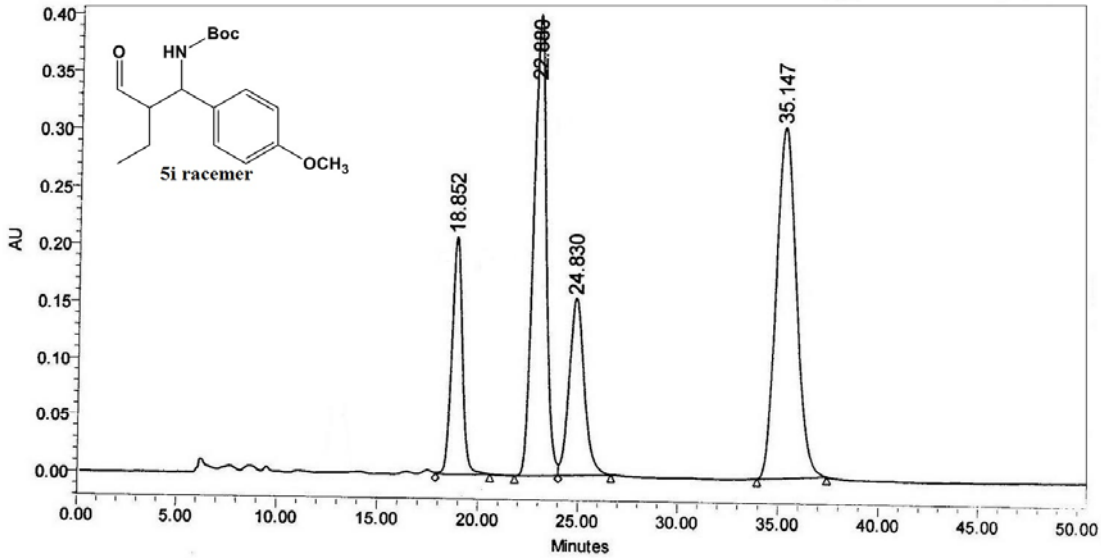
1	15.517	8916	0.03	-665	0.03
2	16.005	25940759	91.16	1855372	94.89
3	16.603	1035463	3.64	57293	2.93
4	22.943	1471967	5.17	41917	2.14



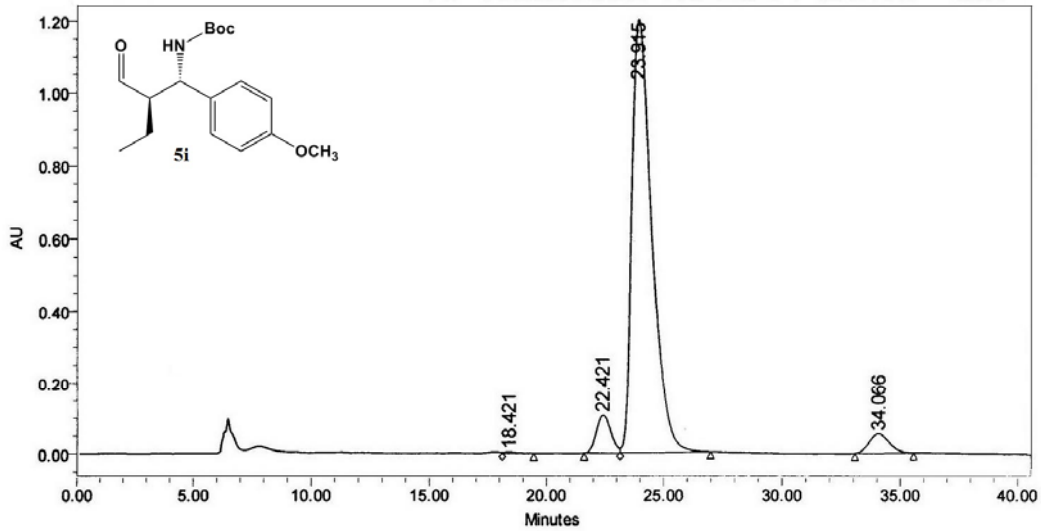
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.218	17997299	29.88	311539	24.94
2	20.822	11766965	19.54	304577	24.39
3	24.433	18565534	30.82	398049	31.87
4	28.576	11903314	19.76	234868	18.80



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.912	194986	0.23	6739	0.38
2	20.795	4134229	4.85	115907	6.59
3	24.100	77123202	90.52	1558367	88.55
4	28.572	3745084	4.40	78901	4.48



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.852	7547761	13.72	208987	19.38
2	22.880	17886168	32.51	404290	37.49
3	24.830	8200124	14.90	156321	14.50
4	35.147	21385559	38.87	308702	28.63



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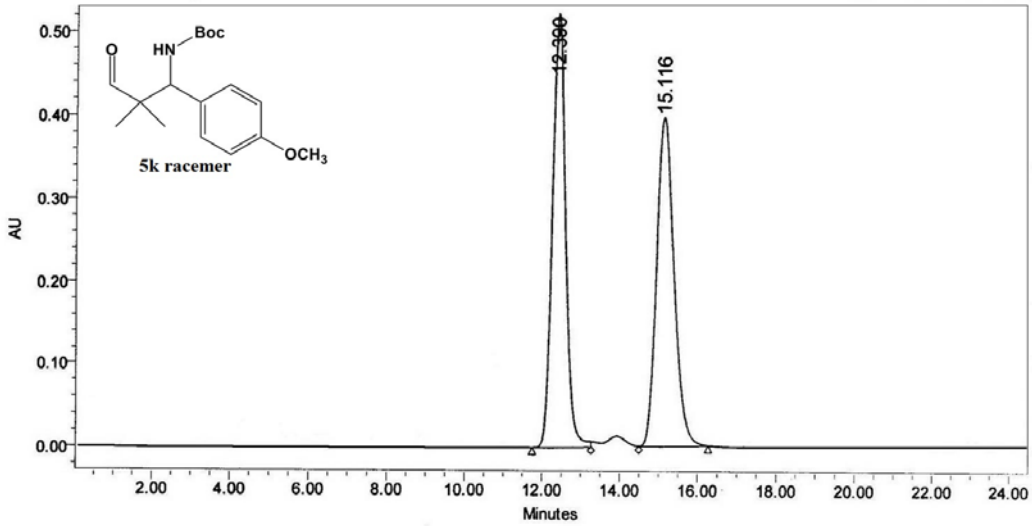
1	18.421	132774	0.17	3666	0.27
2	22.421	4562261	5.78	107537	7.83
3	23.915	71024486	89.95	1205949	87.86
4	34.066	3238883	4.10	55381	4.03



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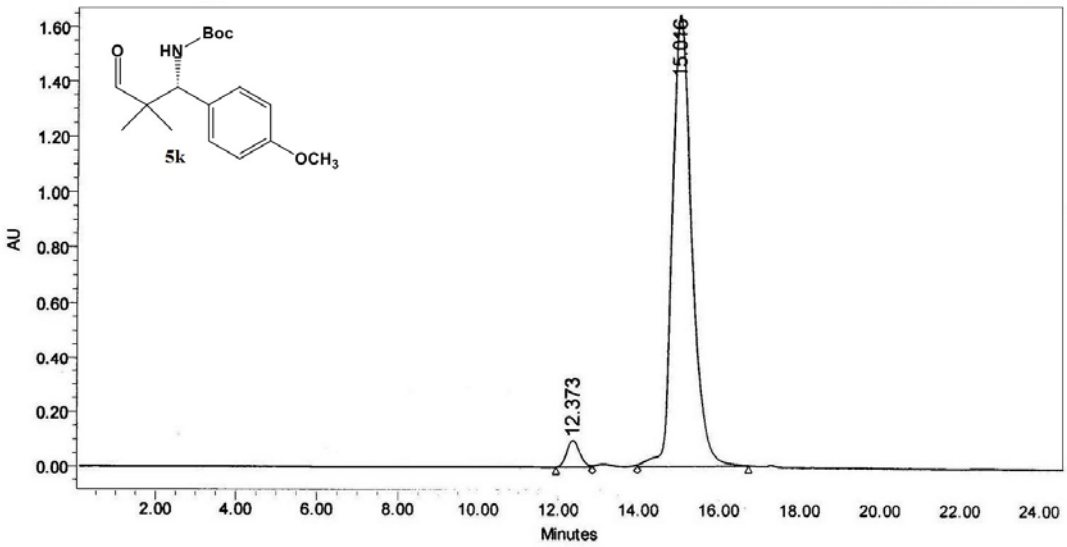
1	12.390	12316732	49.96	525450	56.84
2	15.116	12335466	50.04	398908	43.16



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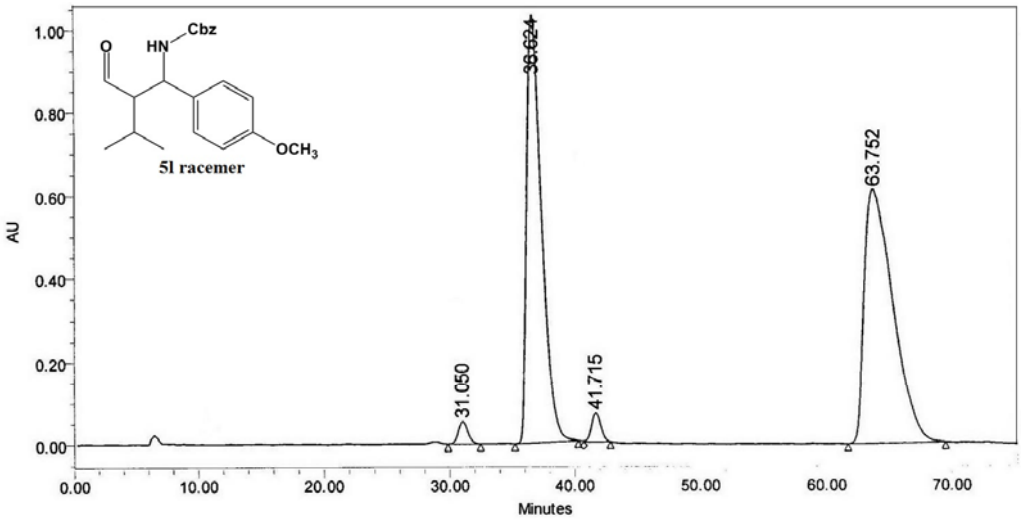
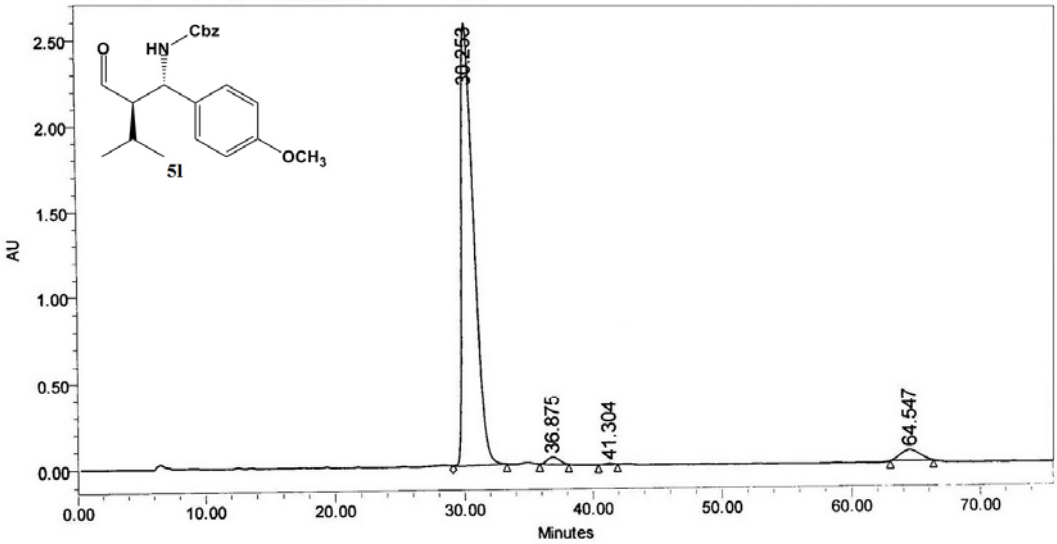
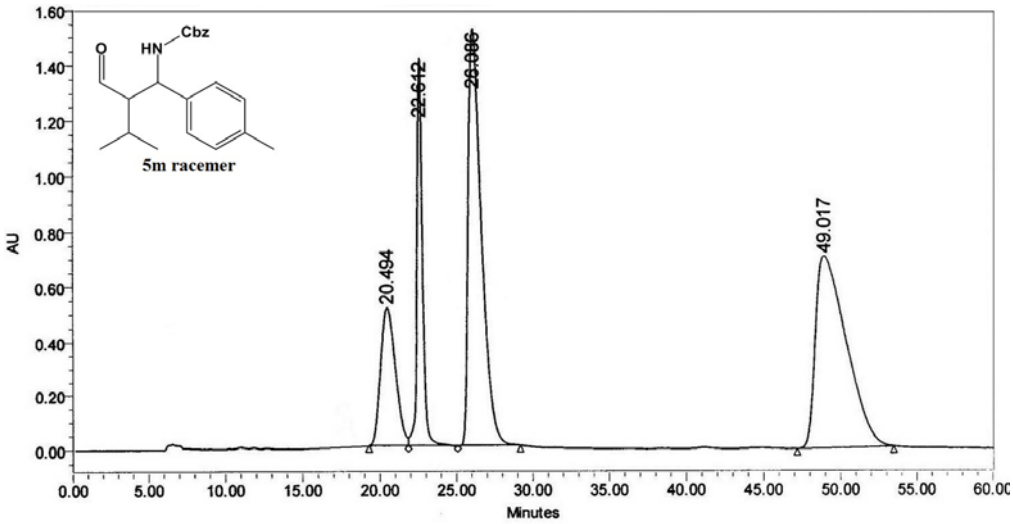
1	12.373	2199605	3.81	98206	5.62
2	15.016	55555415	96.19	1648636	94.38



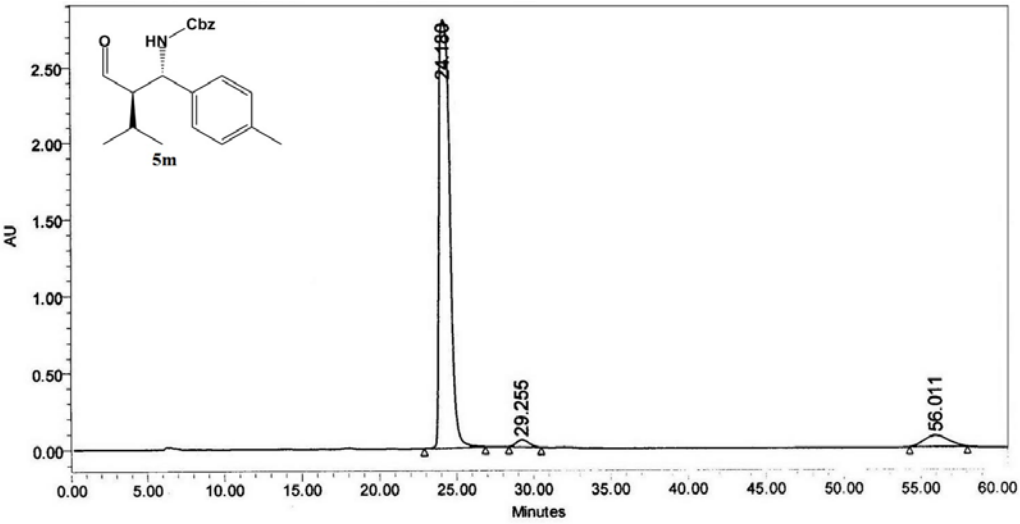
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	31.050	2827172	1.48	53400	3.02
2	36.624	85789300	45.00	1033409	58.36
3	41.715	3630532	1.90	69792	3.94
4	63.752	98403051	51.61	614191	34.68



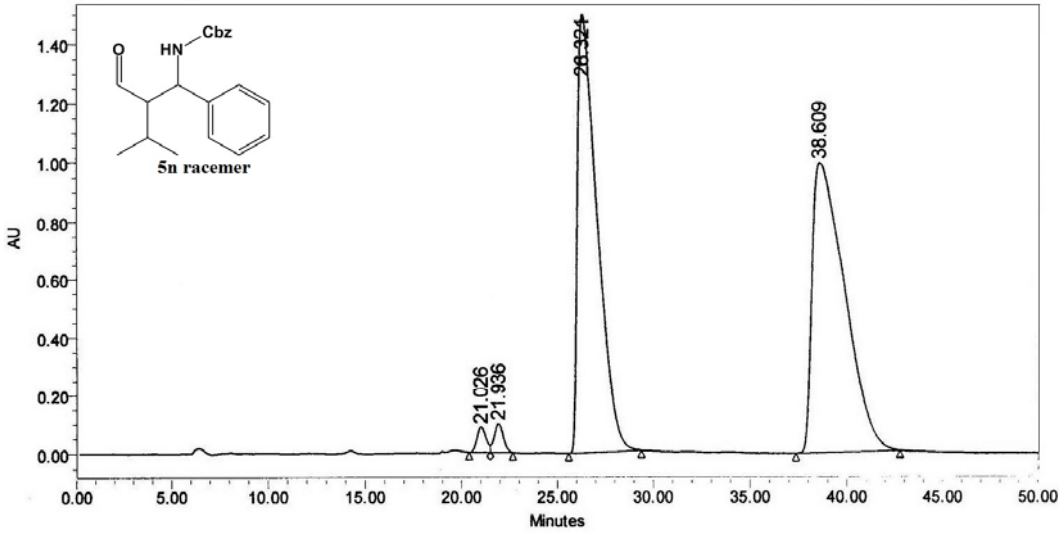
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	30.253	169810766	94.82	2570959	95.94
2	36.875	2574860	1.44	39667	1.48
3	41.304	283214	0.16	6885	0.26
4	64.547	6410229	3.58	62234	2.32



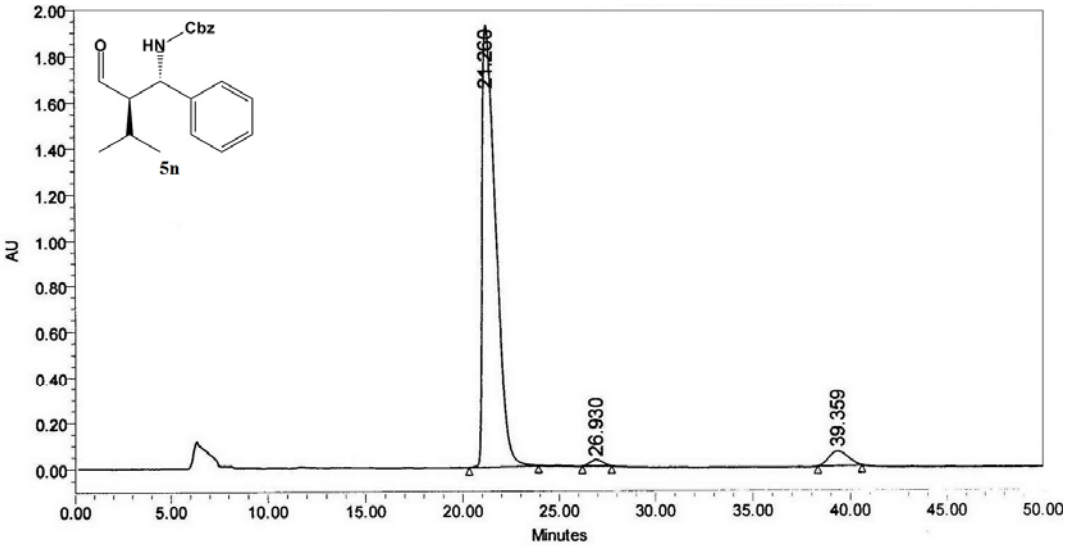
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	20.494	34090791	13.12	508336	12.27
2	22.612	35391320	13.62	1411879	34.09
3	26.086	91553475	35.22	1515694	36.59
4	49.017	98900654	38.05	706008	17.05



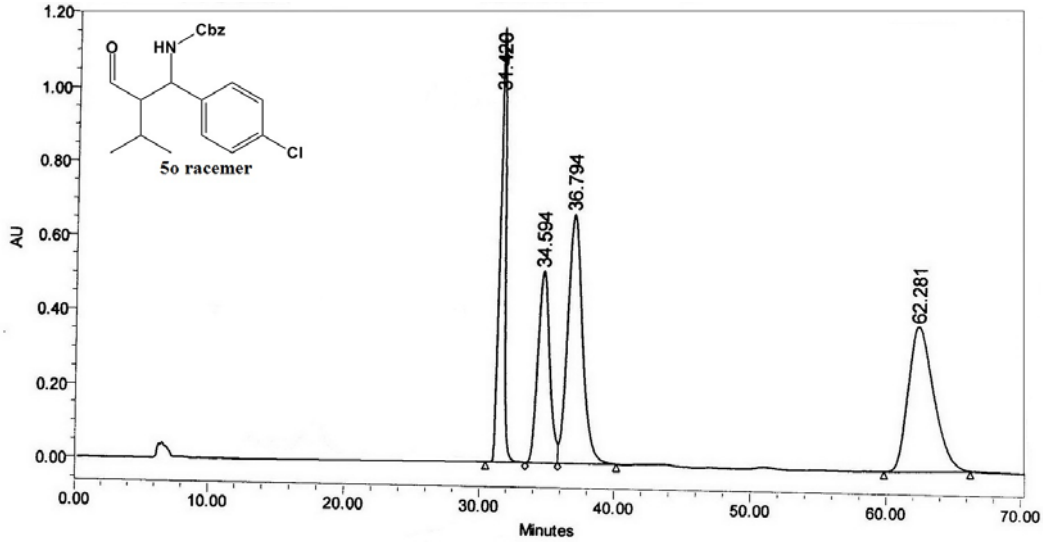
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	24.180	135058787	92.84	2799223	96.00
2	29.255	2504119	1.72	44741	1.53
3	56.011	7913547	5.44	71823	2.46



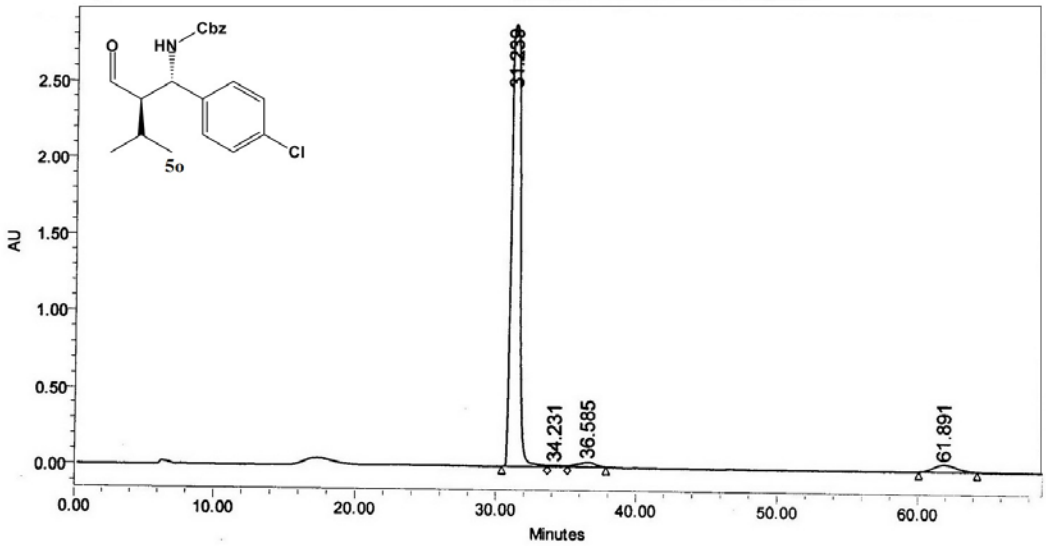
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	21.026	2789316	1.21	85930	3.20
2	21.936	3201070	1.39	97461	3.63
3	26.321	107182197	46.63	1501194	55.96
4	38.609	116703641	50.77	997854	37.20



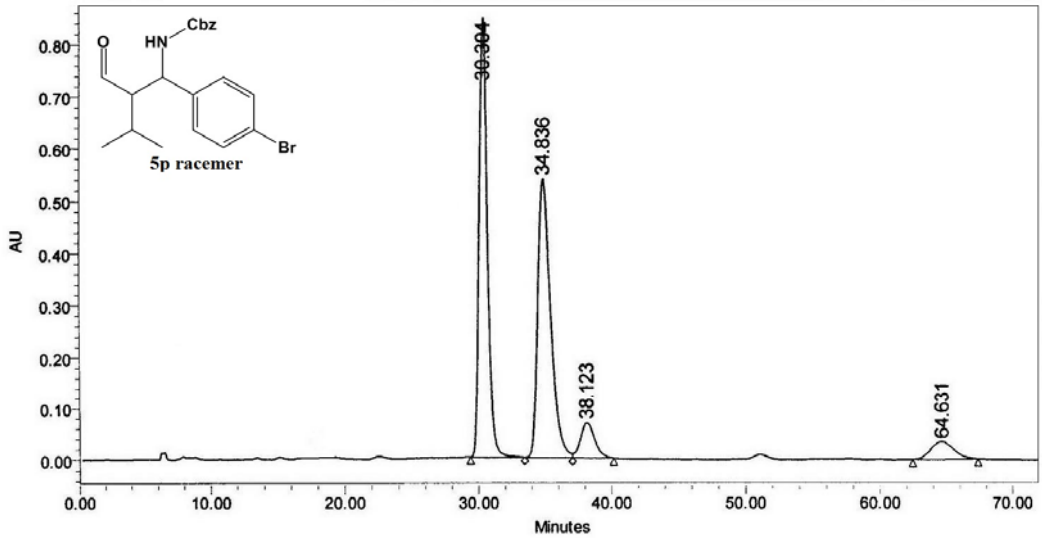
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	21.260	93021699	94.59	1924107	95.67
2	26.930	1190874	1.21	26087	1.30
3	39.359	4129951	4.20	60977	3.03



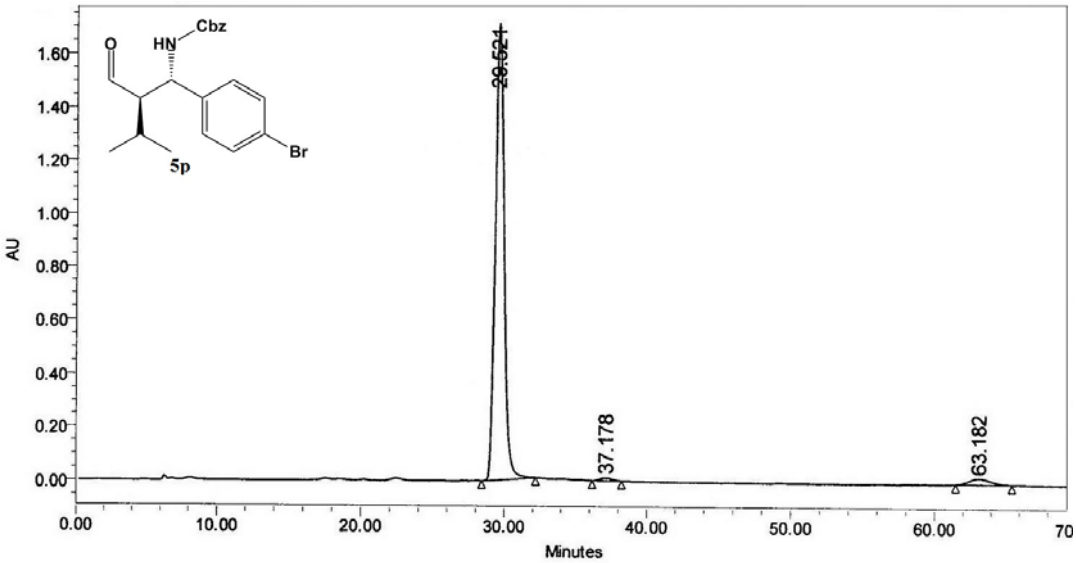
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	31.420	32763066	19.61	1174450	42.61
2	34.594	31536636	18.88	517936	18.79
3	36.794	51177039	30.63	673736	24.44
4	62.281	51581572	30.88	390307	14.16



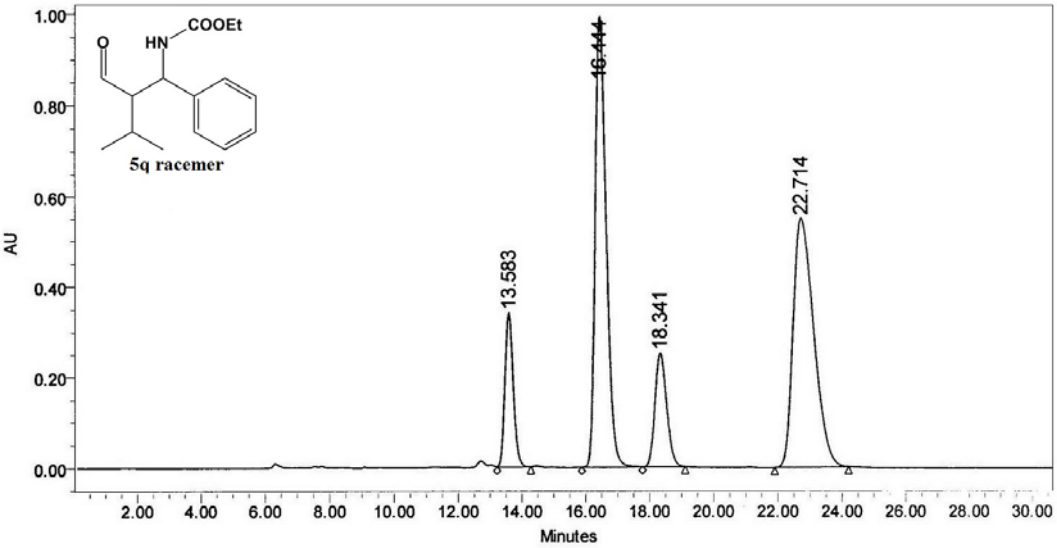
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	31.239	127997586	93.80	2883783	97.22
2	34.231	608979	0.45	8249	0.28
3	36.585	2673224	1.96	29966	1.01
4	61.891	5173490	3.79	44157	1.49



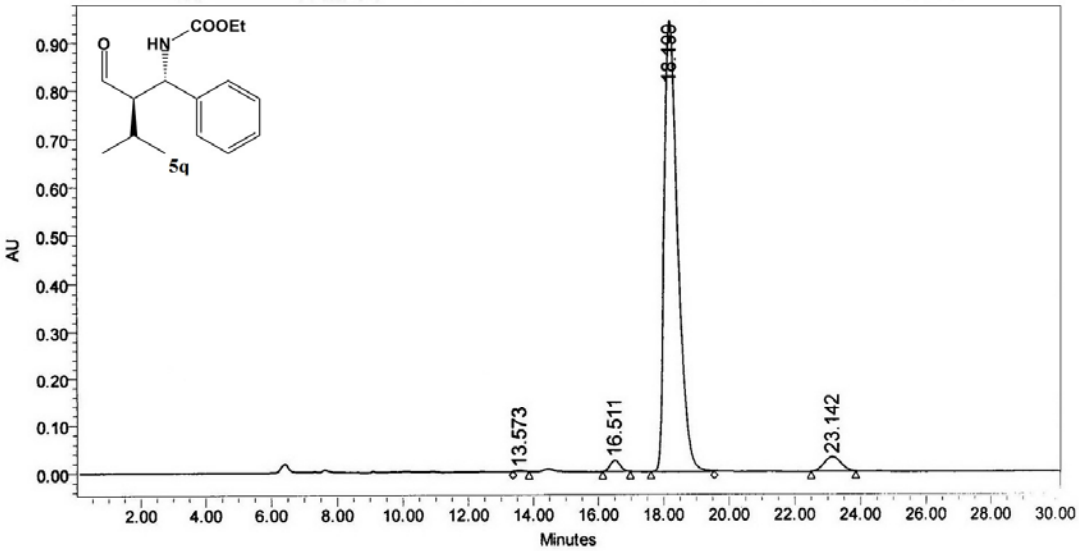
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	30.304	36764759	44.68	846253	56.86
2	34.836	36311464	44.12	538690	36.20
3	38.123	5056531	6.14	68804	4.62
4	64.631	4160937	5.06	34458	2.32



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	29.521	73989751	96.08	1714974	98.13
2	37.178	614157	0.80	10494	0.60
3	63.182	2401158	3.12	22240	1.27



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.583	6177634	10.17	339840	15.91
2	16.444	23797831	39.18	995192	46.60
3	18.341	6314163	10.40	250398	11.72
4	22.714	24449922	40.25	550395	25.77



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.573	39305	0.14	2475	0.25
2	16.511	487962	1.70	23175	2.32
3	18.199	27134355	94.48	944709	94.40
4	23.142	1059560	3.69	30396	3.04