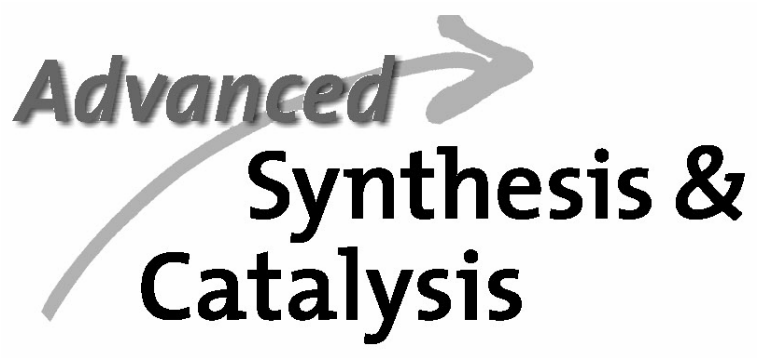

Supporting Information

Supporting information for

4, 4´-Disubstituted-$_L$-proline Catalyzes the Direct Asymmetric Michael Addition of Aldehydes to Nitrostyrenes

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General

Unless otherwise indicated, all reagents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA). Flash column chromatography was performed on silica gel H (10-40 μ). NMR spectra were recorded on 300 or 500 MHz instruments. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra were recorded on a spectrometer. Mass spectra (MS) were measured with a spectrometer. Elemental analyses were performed. Melting point were measured on a digital melting- point apparatus. Optical rotations were measured on a JASCO P-1010 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.

General procedure for the synthesis of catalysts 1 see the paper of "Highly Enantioselective Catalysts of 4,4′-Disubstituted L-Proline for Direct Aldol Reactions"(*Adv. Synth. Catal.* **2006,** *348*, 2223**.).**

4,4′-Di(naphthalene-1-ylmethyl)-$_L$-pyroline

white solid, $[\alpha]_D^{24.3}$ –41.9 (*c* 0.66, MeOH); m.p. 251-253 °C; IR (KBr) ν = 3141, 1630, 1401, 781 cm^{-1}; ^1H NMR (d_6-DMSO, 300MHz) δ = 8.05 (d, *J* = 9.3 Hz,1H), 7.90 (m, 5H), 7.50-7.30 (m, 8H), 3.75 (t, *J* = 8.1 Hz, 1H), 3.20 (s, 4H), 3.00 (s, 2H), 2.00 (dd, *J* = 15.5 Hz, 5.1 Hz, 1H), 1.80 (dd, *J* = 15.5 Hz, 8.1 Hz, 1H).

Typical procedure for the Michael reaction using the catalyst 1 in *i*-PrOH

The following procedure for the reaction of isovaleraldehyde (**2a**) with nitrostyrene (**3a**) in *i*-PrOH using catalyst **1** is representative. To a mixture of catalyst **1** (20 mg, 0.05 mmol), DMAP (12 mg, 0.05 mmol) and isovaleraldehyde **2a** (0.28 mL, 2.5 mmol) in *i*-PrOH (1.0 mL) nitrostyrene **3a** (37 mg, 0.25 mmol) was added at 0 °C under 1 atm argon. The reaction mixture was stirred for 3 d, then quenched with 5mL saturated NH_4Cl, extracted with ethyl acetate (5 mL×3), and dried with over Na_2SO_4. Purification by flash chromatography (hexane/EtOAc 18/1) afforded product. The relative and absolute configurations of the Michael adducts were determined by comparison with ^1H NMR spectroscopic analysis and optical rotation. The enantiomeric excess was determined by HPLC with Daicel Chiralpak AS, AD or OD-H.

Compounds of **4a**, **4c**-**4i** are known.[1-6] Compounds of **4b, 4j** and **4k** are new.

(2*R*,3*S*)-2-isopropyl-4-nitro-3-phenylbutanal 4a

Colorless oil. Yield: 87%; $[\alpha]_D^{24.3}$ 37.4 (*c* 2.55, $CHCl_3$); IR (neat) ν = 2964, 1717, 1553, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.84 (s, 1H), 7.26 (m, 3H), 7.10 (m, 2H), 4.73-4.46 (m, 2H), 3.93-3.79 (m, 1H), 2.70 (d, *J* = 10.2 Hz, 1H), 1.62 (dd, *J* = 13.5 Hz, 6.6 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H). enantiomeric excess: 90%, determined by HPLC(Daicel Chiralpak AD, *i*-PrOH/Hexane 10/90), UV 254nm, flow rate 1.0 mL/ min, t_{major} 12.1 min and t_{minor} 13.8 min.

(2*R*,3*S*)-3-(4-bromophenyl)-2-isopropyl-4-nitrobutanal 4b

White solid. Yield: 75%;$[\alpha]_D^{22.2}$ 25.3 (*c* 2.85, $CHCl_3$); m.p. 105-106 °C； IR (KBr) ν = 2964, 1718, 1553, 1379, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.90 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.4 Hz, 1.5 Hz, 2H), 7.07 (dd, *J* = 8.4 Hz, 1.5Hz, 2H) 4.71-4.65 (m, 1H), 4.58-4.50 (m, 1H), 3.88 (m, 1H), 2.77-2.73 (m, 1H), 1.70 (m, 1H), 1.10 (dd, *J* = 7.2 Hz, 1.2 Hz, 3H), 0.86 (dd, *J* = 7.2 Hz, 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ = 203.8, 136.2, 132.3, 129.7, 122.1, 78.6, 58.5, 41.4, 27.9, 21.6, 16.9; MS (EI); *m/z*(%): 313(0.56), 43(100); Analysis: Calcd. for $C_{13}H_{16}BrNO_3$: C, 49.70; H, 5.13; N, 4.46; Found: C, 49.89; H, 5.04; N, 4.24. enantiomeric excess: 91%, determined by HPLC(Daicel Chiralpak AD, *i*-PrOH/Hexane 10/90), UV 254nm, flow rate 1.0 mL/min, t_{major} 14.6 min and t_{minor} 22.4 min.

(2*R*,3*S*)-2-isopropyl-3-(naphthalen-1-yl)-4-nitrobutanal 4c

Colorless oil. Yield: 89%; $[\alpha]_D^{22.5}$ 59.6 (*c* 2.95, $CHCl_3$); IR (neat) ν = 2963, 1718, 1551, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.94 (s, 1H), 8.17 (brs, 1H), 7.85 (dd, *J* = 23.7 Hz, 7.5 Hz,, 2H), 7.60-7.32 (m, 4H), 4.82 (m, 3H), 3.06 (brs, 1H), 1.76 (s, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.83 (d, *J* = 6.3 Hz, 3H). enantiomeric excess: 87%, determined by HPLC(Daicel Chiralpak OD-H, ^{i}PrOH/Hexane 20/80), UV 254nm, flow rate 0.5 mL/ min, t_{minor} 35.3 min and t_{major} 38.7 min.

(2*R*,3*S*)-2-methyl-4-nitro-3-phenylbutanal 4d

Colorless oil. Yield: 77%; $[\alpha]_D^{22.3}$ 24.7 (*c* 1.60, $CHCl_3$); IR (neat) ν = 2971, 1724, 1553 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.71 (d, *J* = 1.5 Hz, 1H), 7.36-7.15 (m, 5H), 4.83-4.64 (m, 2H), 3.87-3.77 (m, 1H), 2.83-2.72 (m, 1H), 1.00 (d, *J* = 6.9 Hz,

3H). enantiomeric excess: 94%, determined by HPLC(Daicel Chiralpak OD-H, *i*-PrOH/Hexane 7/93), UV 237nm, flow rate 1.0 mL/ min, t_{minor} 34.3 min and t_{major} 49.9 min.

(2*R*,3*S*)-2-ethyl-4-nitro-3-phenylbutanal 4e

Colorless oil. Yield: 76%; $[\alpha]_D^{23.7}$ 40.5 (*c* 0.45, $CHCl_3$); IR (neat) ν = 2968, 1719, 1553, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.72 (d, *J* = 2.7 Hz, 1H), 7.26 (m, 5H), 4.84-4.59 (m, 2H), 3.85-3.75 (m, 1H), 2.68 (m, 1H), 1.53 (m, 1H), 0.83 (t, *J* = 7.5 Hz, 3H). enantiomeric excess: 95%, determined by HPLC(Daicel Chiralpak AD, *i*-PrOH/Hexane 10/90), UV 254nm, flow rate 1.0 mL/ min, t_{major} 12.3 min and t_{minor} 13.6 min.

(*R*)-2-((S)-2-nitro-1-phenylethyl)pentanal 4f

Colorless oil. Yield: 66%; $[\alpha]_D^{23.8}$ 59.2 (*c* 0.5, $CHCl_3$); IR (neat) ν = 2960, 1722, 1553, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.70 (d, *J* = 1.2 Hz, 1H), 7.34-7.16 (m, 5H), 4.64 (m, 2H), 3.82-3.74 (dd, *J* = 15.3 Hz, 9.0 Hz, 1H), 2.71 (t, *J* = 8.7 Hz, 1H), 1.49-1.19 (m, 4H), 0.80 (d, *J* = 6.9 Hz, 3H). enantiomeric excess: 90%, determined by HPLC(Daicel Chiralpak OD-H, *i*-PrOH/Hexane 10/90), UV 254nm, flow rate 1.0 mL/ min, t_{minor} 22.6 min and t_{major} 28.1 min.

(*R*)-2-((*S*)-2-nitro-1-phenylethyl)hexanal 4g

Colorless oil. Yield: 74%; $[\alpha]_D^{24.6}$ 36.3 (*c* 1.25, $CHCl_3$); IR (neat) ν = 3419, 2930, 2860, 1722, 1556, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.70 (d, *J* = 2.4 Hz, 1H), 7.34 (m, 3H), 7.18 (m, 2H), 4.74-4.60 (m, 2H), 3.81-3.73 (ddd, *J* = 15.0 Hz, 9.9 Hz, 5.4 Hz, 1H), 2.73-2.66 (m, 1H), 1.51-1.10 (m, 6H), 0.78 (t, *J* = 6.3 Hz, 3H).

enantiomeric excess: 86%, determined by HPLC(Daicel Chiralpak OD-H, *i*-PrOH/Hexane 10/90), UV 254nm, flow rate 1.0 mL/ min, t_{minor} 24.4 min and t_{major} 27.6 min.

(*R*)-2-((*S*)-2-nitro-1-phenylethyl)heptanal 4h

Colorless oil. Yield: 79%; $[\alpha]_D^{24.0}$ 56.9 (*c* 1.25, $CHCl_3$); IR (neat) ν = 2929, 1722, 1554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.62 (s, 1H), 7.24-7.09 (m, 5H), 4.71-4.52 (m, 2H), 3.71 (m, 1H), 2.62 (m, 1H), 1.34-1.09 (m, 8H), 0.73 (s, 3H). enantiomeric excess: 94%, determined by HPLC(Daicel Chiralpak OD-H, *i*-PrOH/Hexane 10/90), UV 254nm, flow rate 1.0 mL/ min, t_{minor} 19.6 min and t_{major} 23.6 min.

(*R*)-2,2-dimethyl-4-nitro-3-phenylbutanal 4i

Colorless oil. Yield: 73%; $[\alpha]_D^{21.5}$ 3.5 (*c* 1.50, $CHCl_3$); IR (neat) ν = 2973, 1725, 1554, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.53 (s, 1H), 7.30-7.19 (m, 5H), 4.86 (t, *J* = 12.9 Hz, 1H), 4.70 (d, *J* = 12.9 Hz, 1H), 3.80 (d, *J* = 11.7 Hz, 1H), 1.13 (s, 3H), 1.00 (s, 3H). enantiomeric excess: 67%, determined by HPLC(Daicel Chiralpak AS, *i*-PrOH/Hexane 10/90), UV 254nm, flow rate 0.5 mL/ min, t_{minor} 20.3 min and t_{major} 23.3 min.

(*R*)-3-(4-bromophenyl)-2,2-dimethyl-4-nitrobutanal 4j

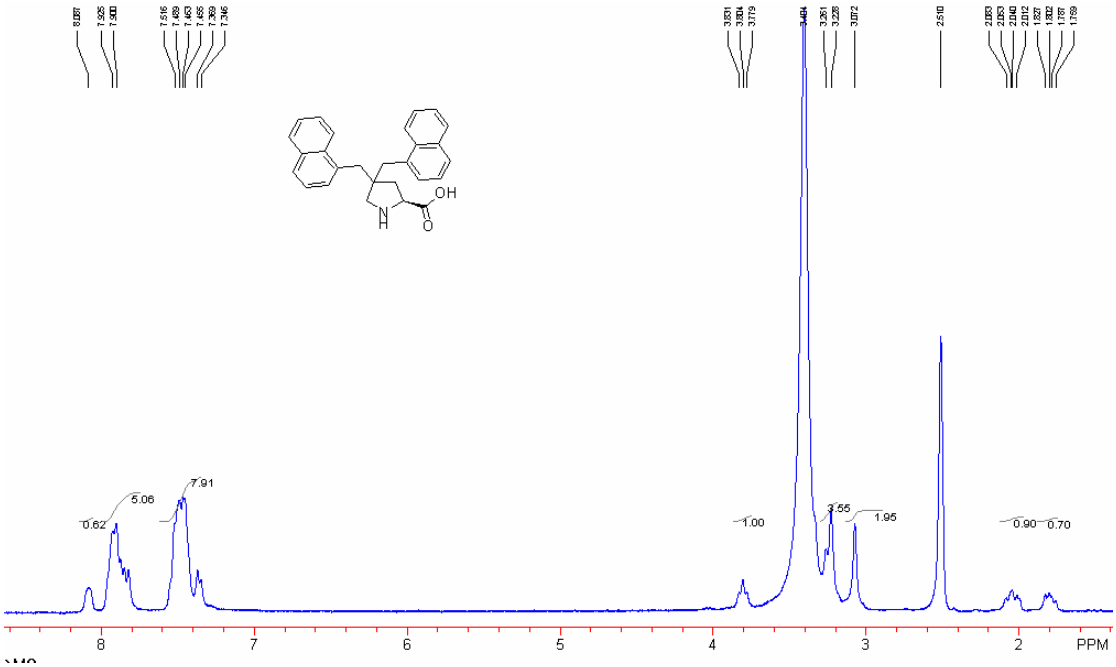
White solid. Yield: 80%; $[\alpha]_D^{24.1}$ 4.4 (*c* 0.20, $CHCl_3$); m.p. 105-106 °C； IR (KBr) ν = 2973, 1724, 1553, 1378, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.49 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 4.78 (m, 2H), 3.75 (d, *J* = 11.1 Hz, 1H), 1.12 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ = 203.7, 134.6, 131.9,

130.7, 122.2, 76.1, 48.1, 48.0, 21.7,18.9; MS (EI); *m/z*(%): 299 (3.55), 182 (100); Analysis: Calcd. for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; N, 4.67; Found: C, 48.00; H, 4.62; N, 4.42. enantiomeric excess: 70%, determined by HPLC(Daicel Chiralpak AD, ^{i}PrOH/Hexane 10/90), UV 254nm, flow rate 0.5 mL/min, t_{major} 21.8 min and t_{minor} 27.2 min.

(2*R*,3*R*)-3-(3-(benzyloxy)-4-methoxyphenyl)-2-methyl-4-nitrobutanal 4k

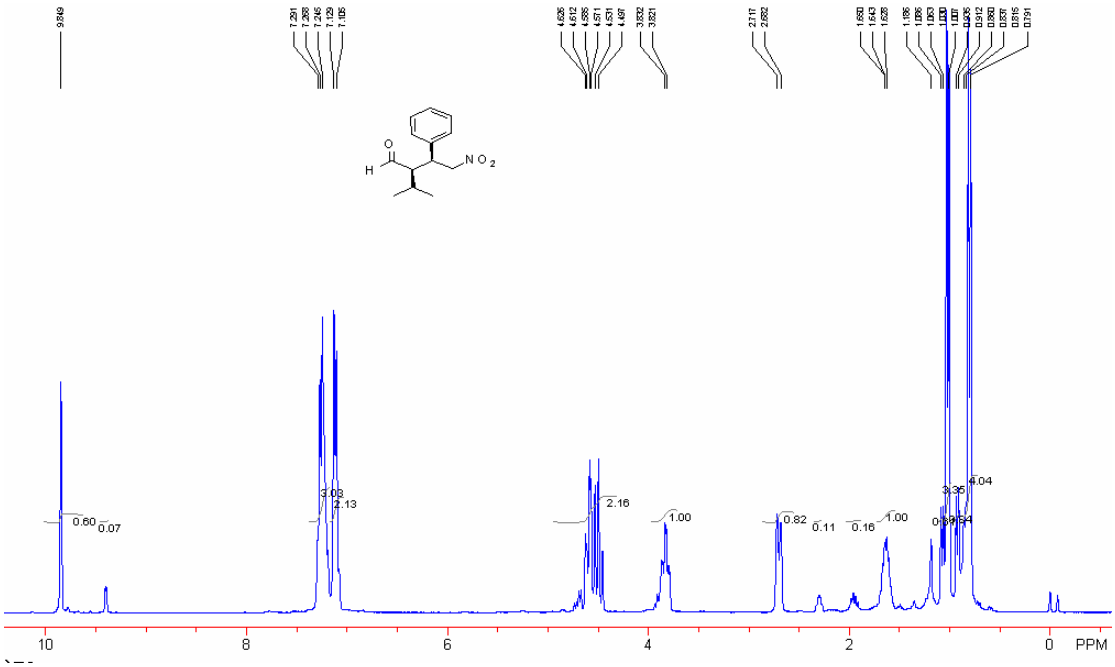
Colorless oil. Yield: 78%; $[\alpha]_D^{24.1}$ 0.39 (*c* 1.26, $CHCl_3$); IR (neat) ν = 3504, 2966, 1720, 1551 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.60 (s, 0.34H, *syn*), 9.41 (s, 0.20H, *anti*), 7.40-7.33 (m, 5H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.73 (t, *J* = 9.0 Hz, 1H), 6.63 (s, 1H), 5.14 (s, 2H), 4.75-4.65 (m, 1H), 4.59-4.52 (dd, *J* = 11.4 Hz, 9.6 Hz, 1H), 3.84 (s, 3H), 3.71-3.62 (m, 1H), 2.73-2.56 (m, 1H), 1.11 (d, *J* = 8.4 Hz, 1.1H, *anti*), 0.88 (d, *J* = 8.4 Hz, 2.8H, *syn*); ^{13}C NMR (100 MHz, $CHCl_3$) δ = 202.3, 149.6, 148.1, 136.8, 128.7, 128.5, 127.9, 127.4, 121.1, 121.0, 114.6, 112.0, 78.1, 55.9, 48.5, 48.4, 43.4, 11.8; MS (EI); *m/z* (%): 65 (4.75), 92 (8.08), 343 (13.76), 91(100); HR MS $C_{19}H_{21}NO_5$: Calc.343.1420; Found: 343.1416. enantiomeric excess: 73% (*syn*), 58% (*anti*), determined by HPLC(Daicel Chiralpak OD-H, *i*-PrOH/Hexane 5/95), UV 220nm, flow rate 1 mL/min, *syn*-product: t_{major} 63.2 min and t_{minor} 52.1 min; *anti*-product: t_{major} 70.4 min and t_{minor} 57.0 min.

^{1}H NMR spectra for catalysts **1**

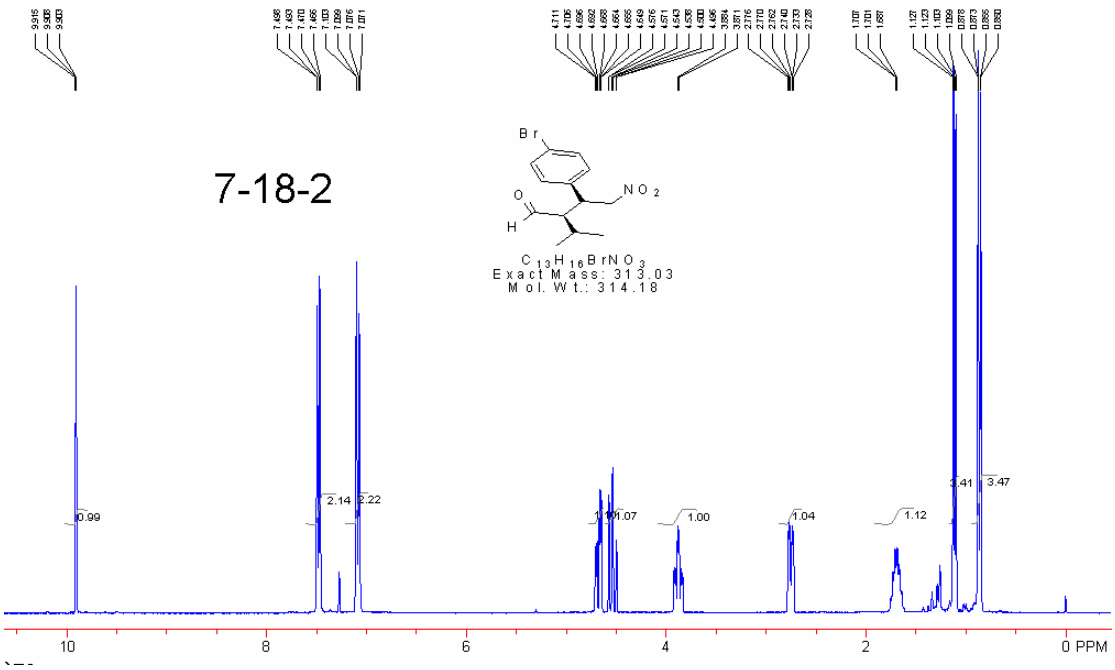


NMR spectra for compounds 4a-j

^{1}H NMR spectra for compounds **4a**



^{1}H NMR spectra for compounds **4b**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6
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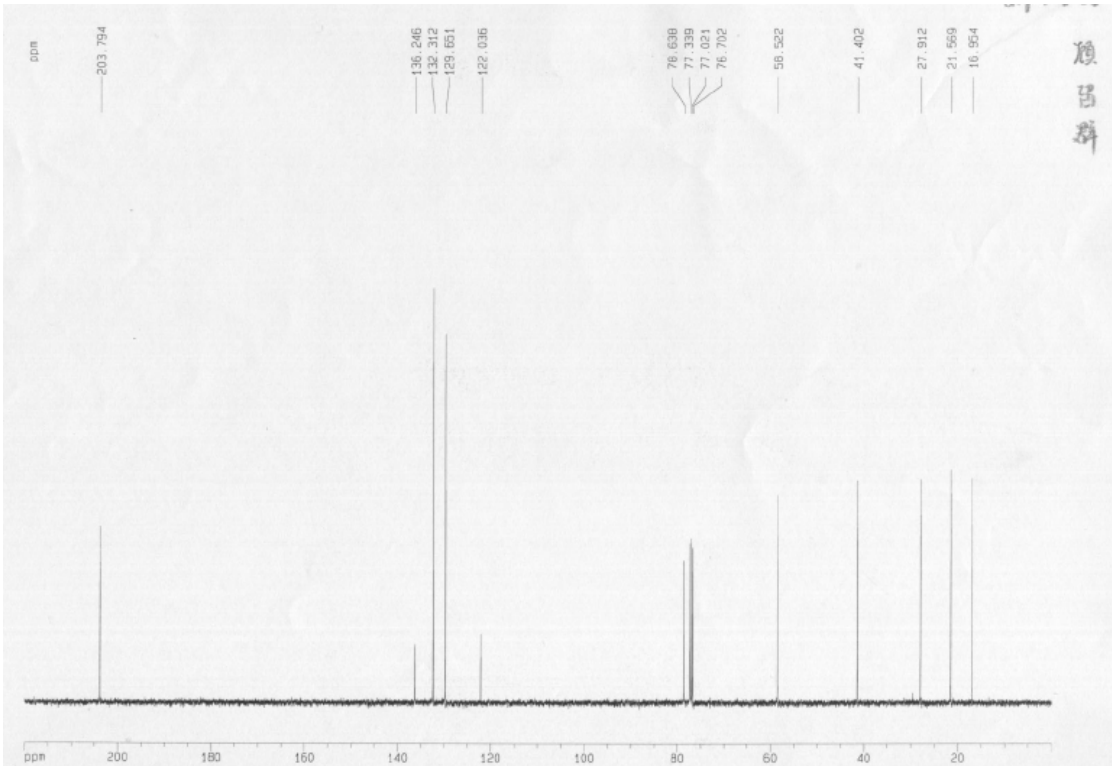
^{13}C NMR spectra for compounds **4b**



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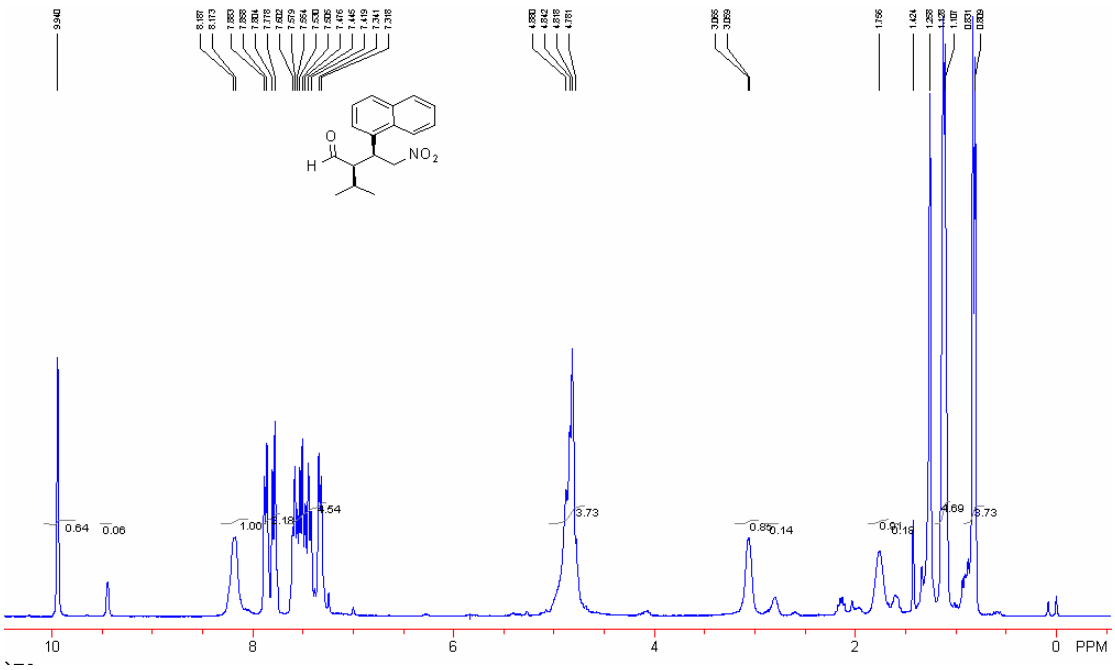
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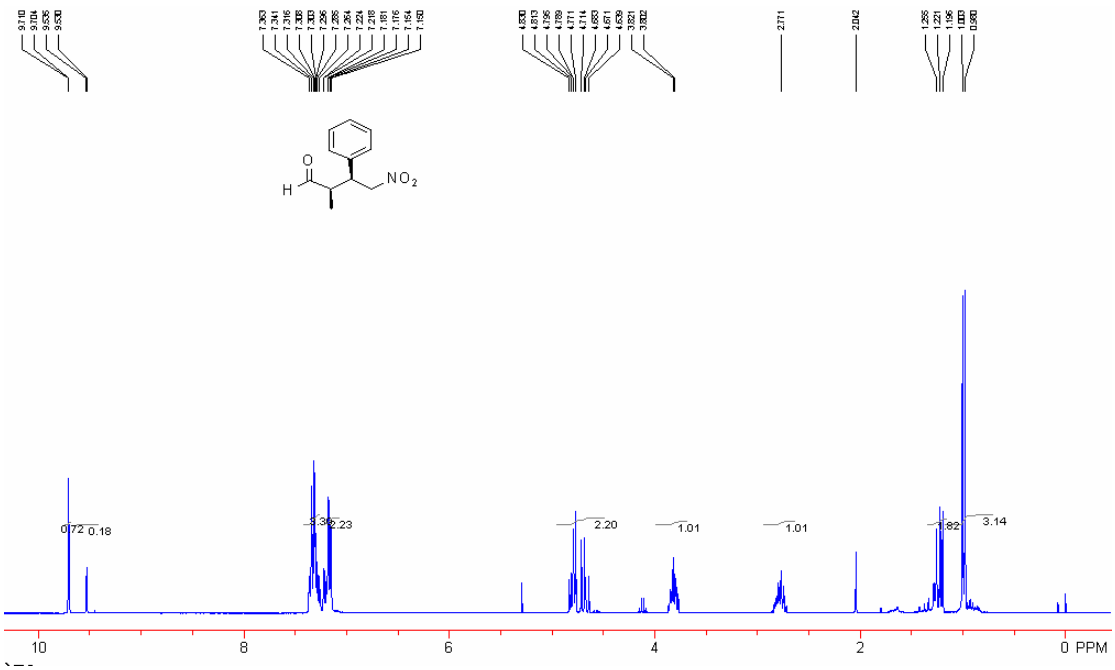
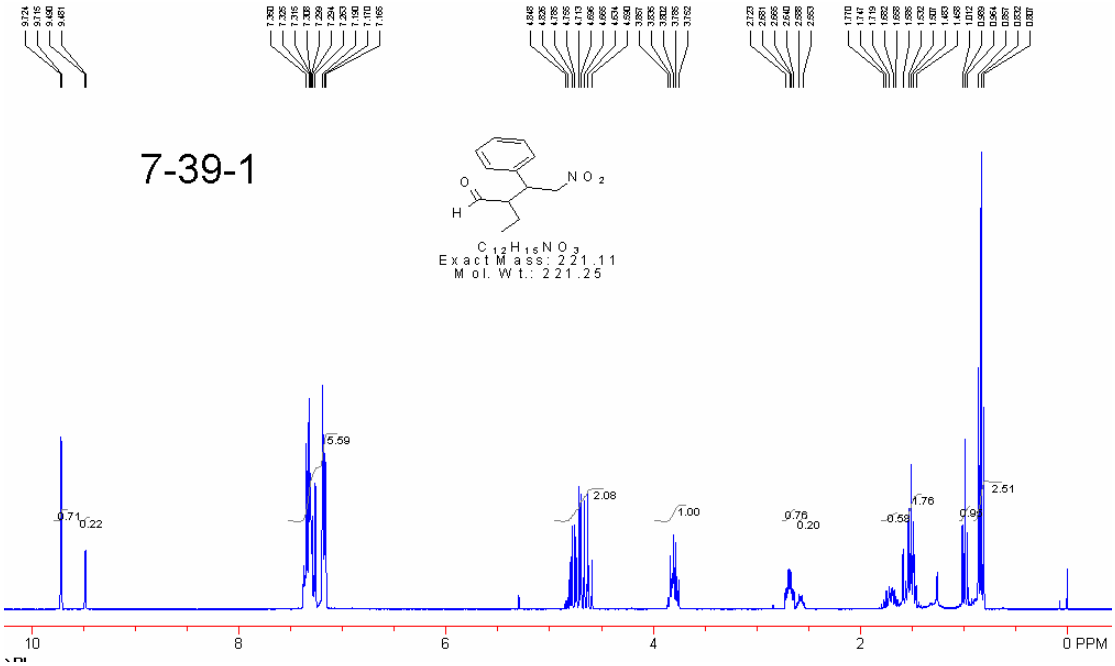


^{1}H NMR spectra for compounds **4e**



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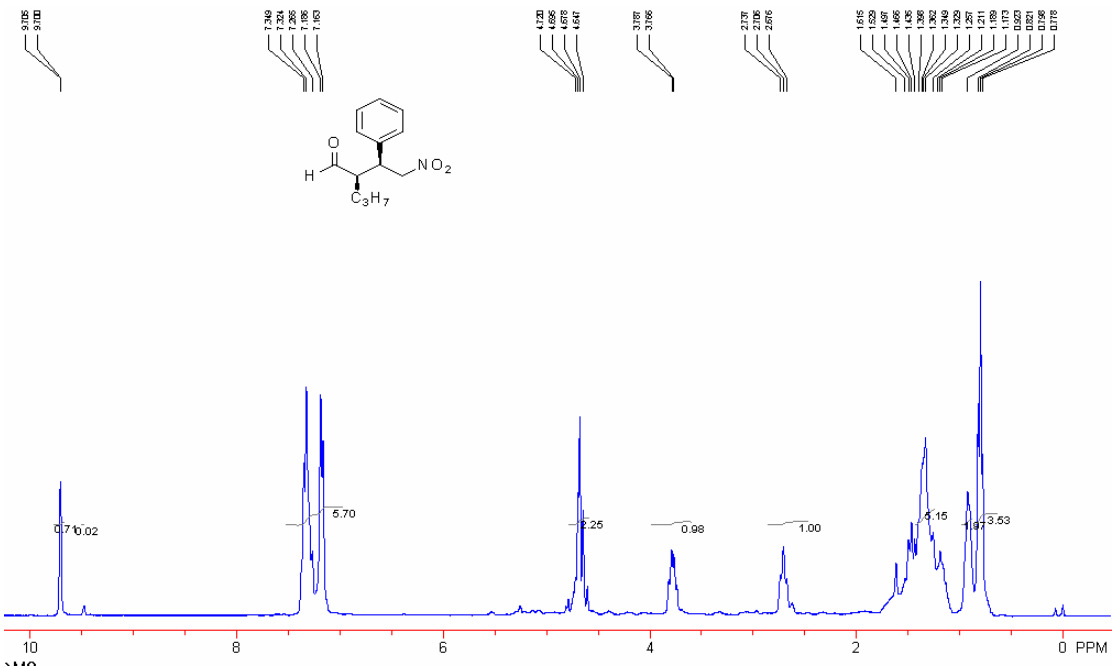

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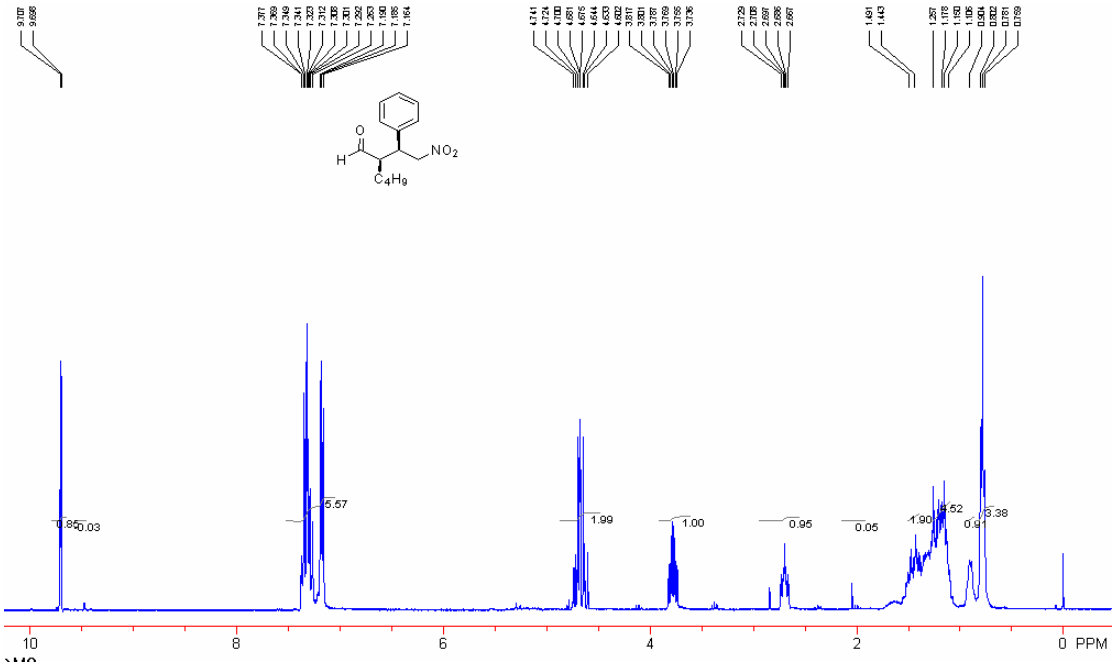

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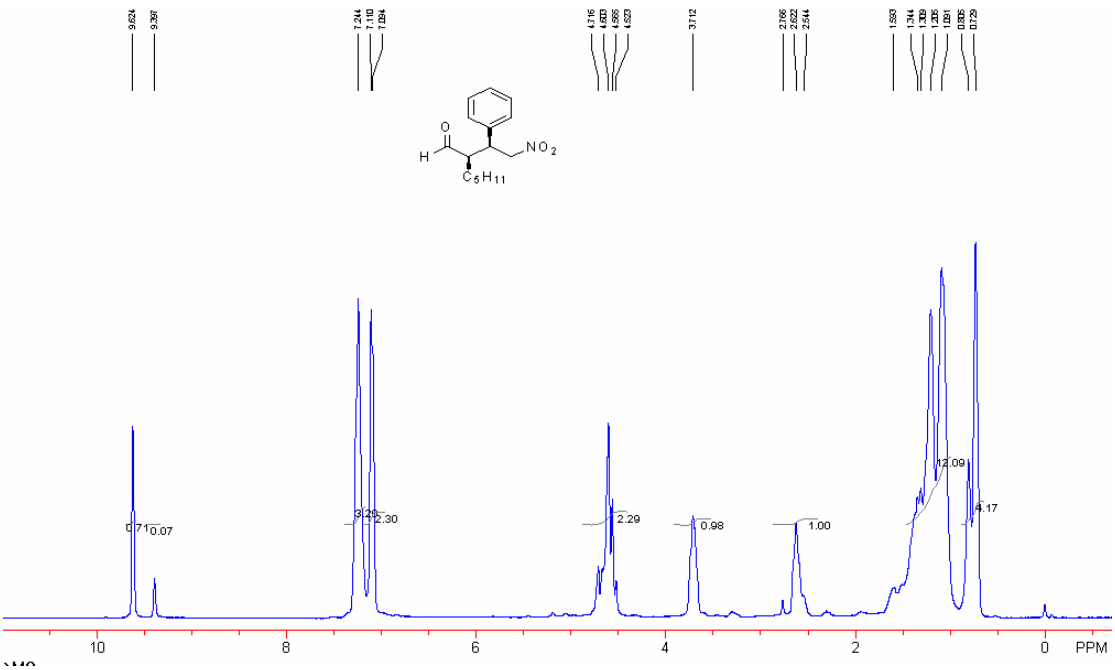

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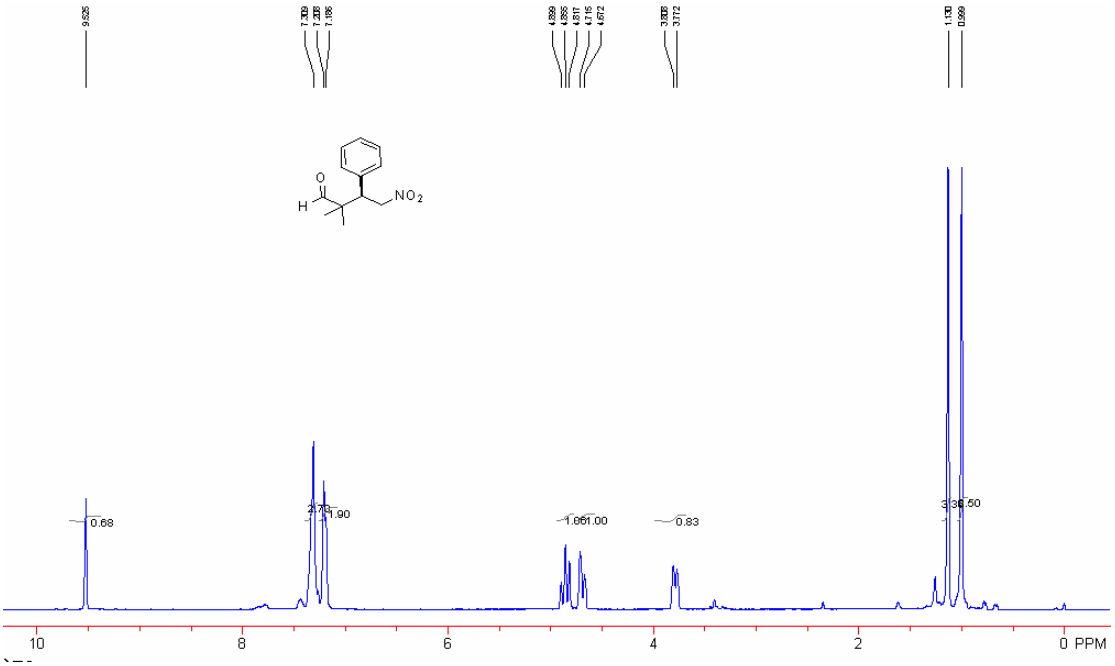
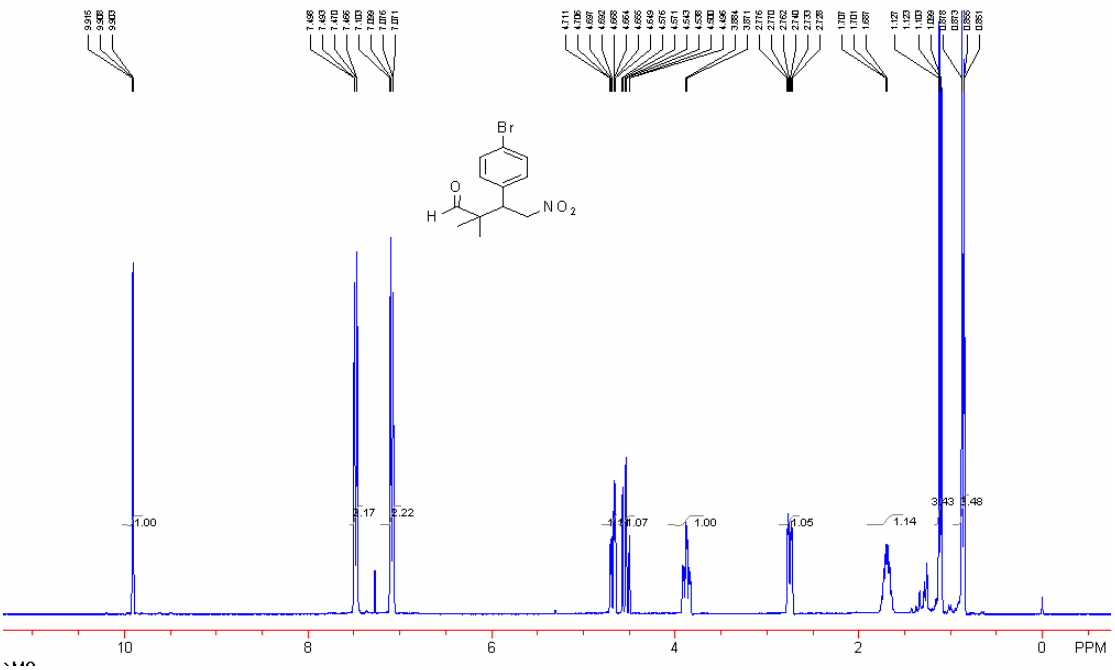
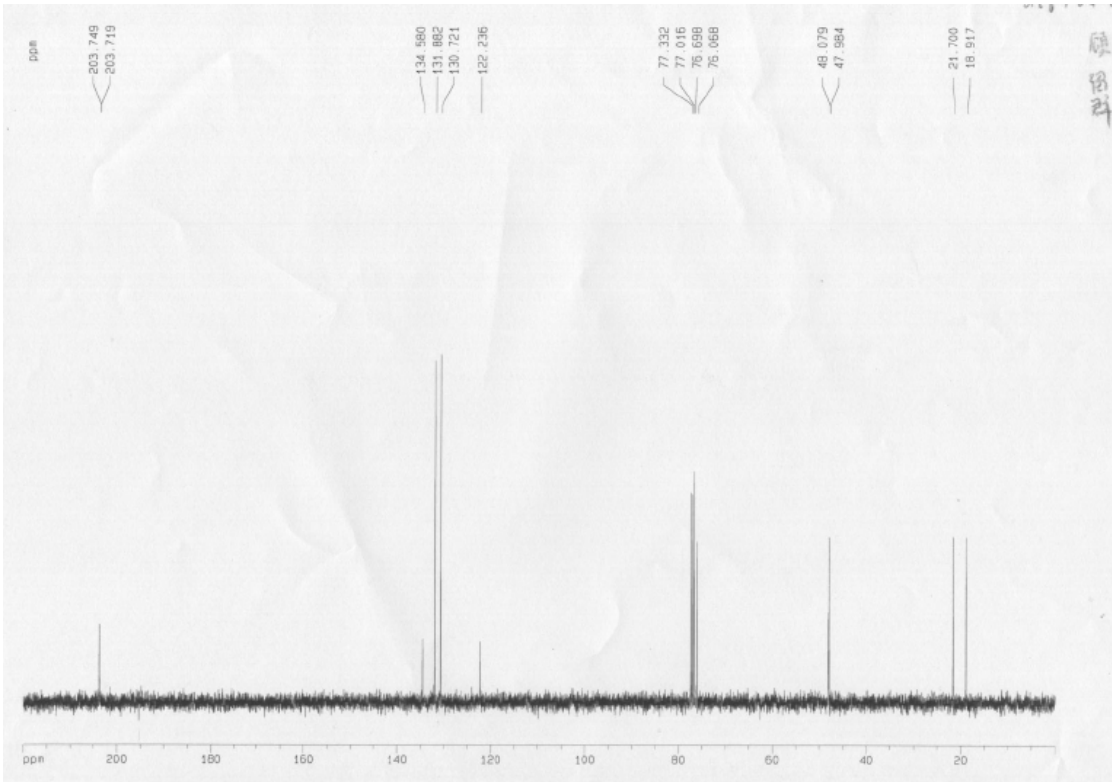


^{1}H NMR spectra for compounds **4j**



^{13}C NMR spectra for compounds **4j**



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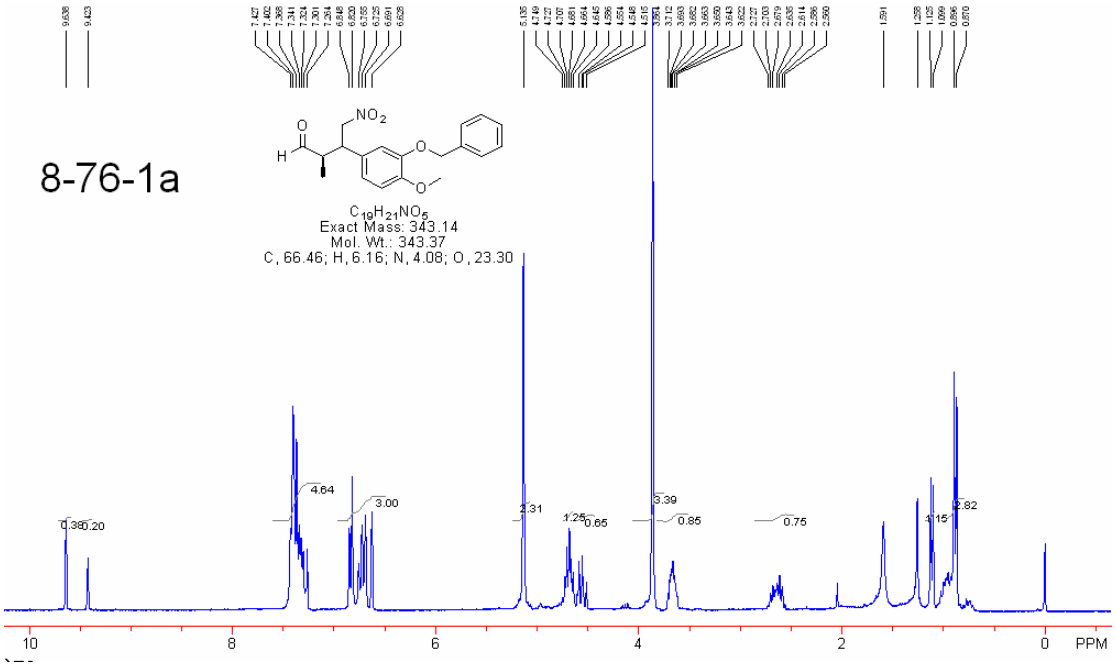
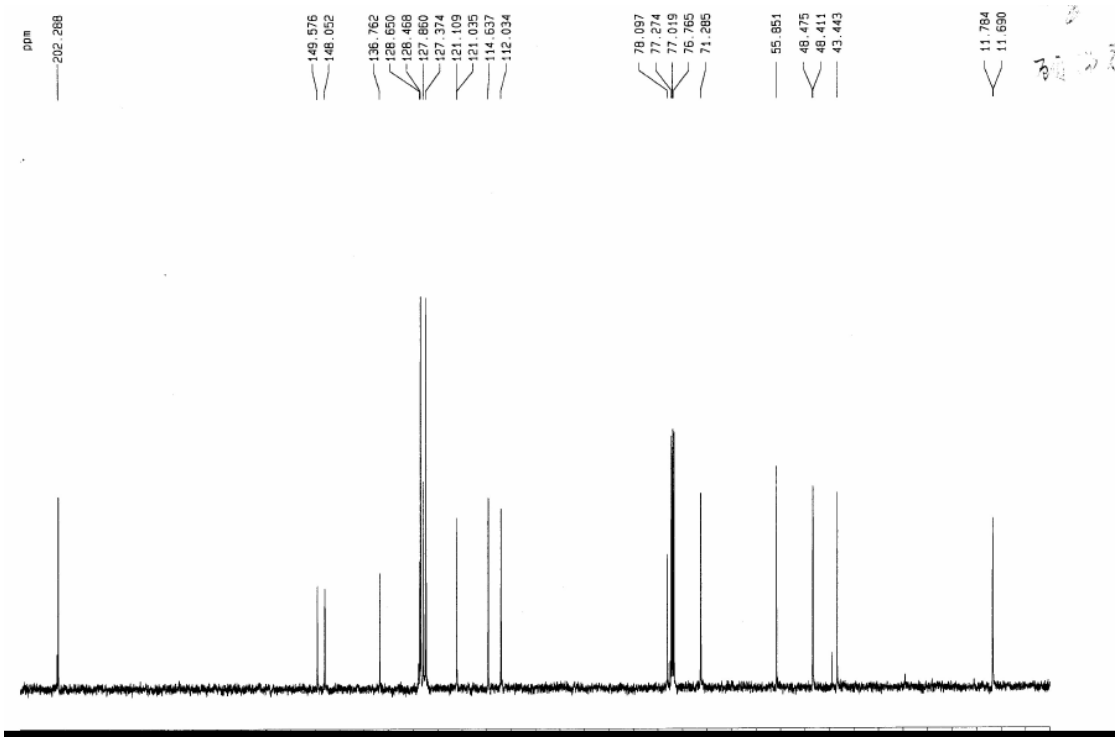
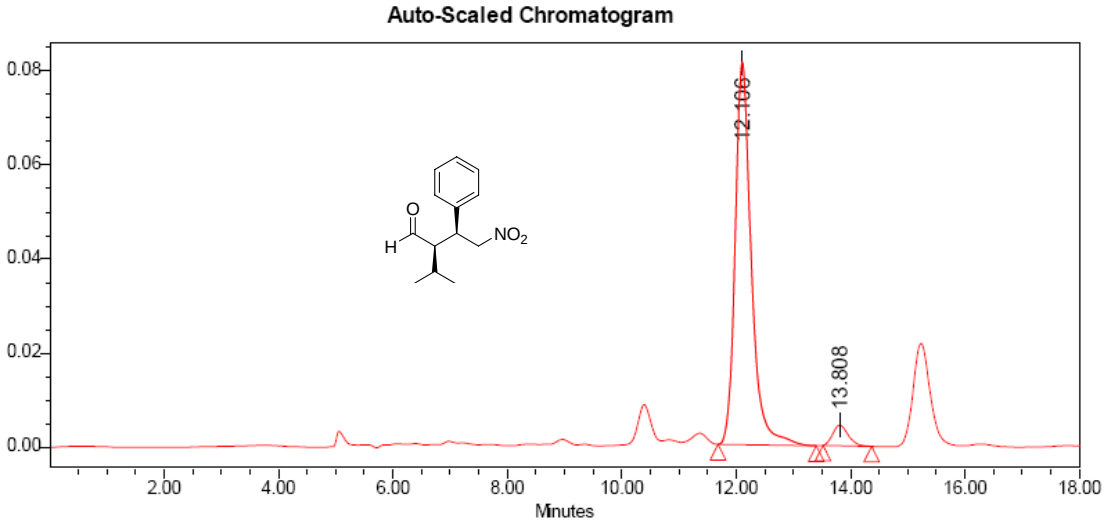


^{13}C NMR spectra for compounds **4k**



HPLC spectra for compounds 4a-k

HPLC spectra for compounds **4a**



Peak Results

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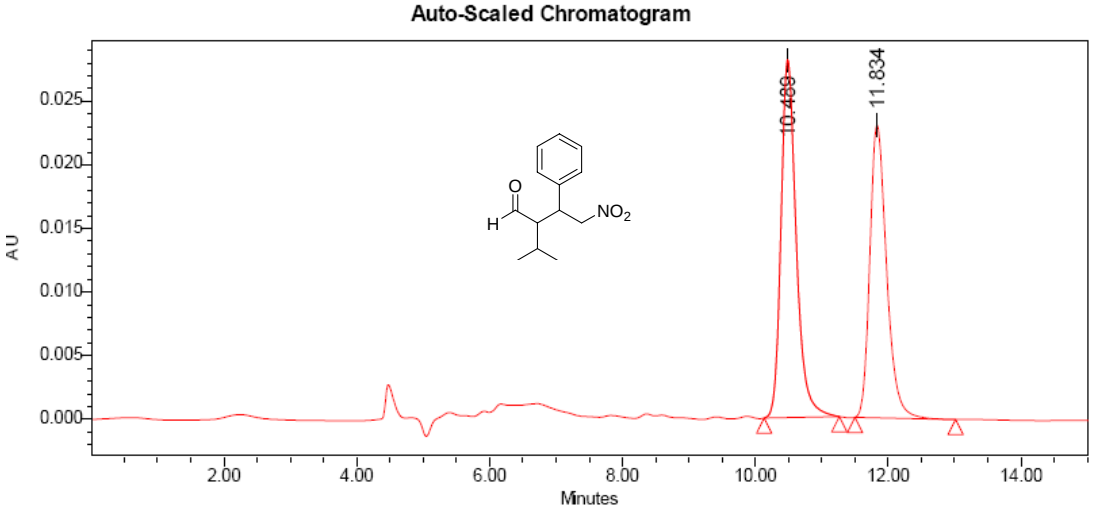

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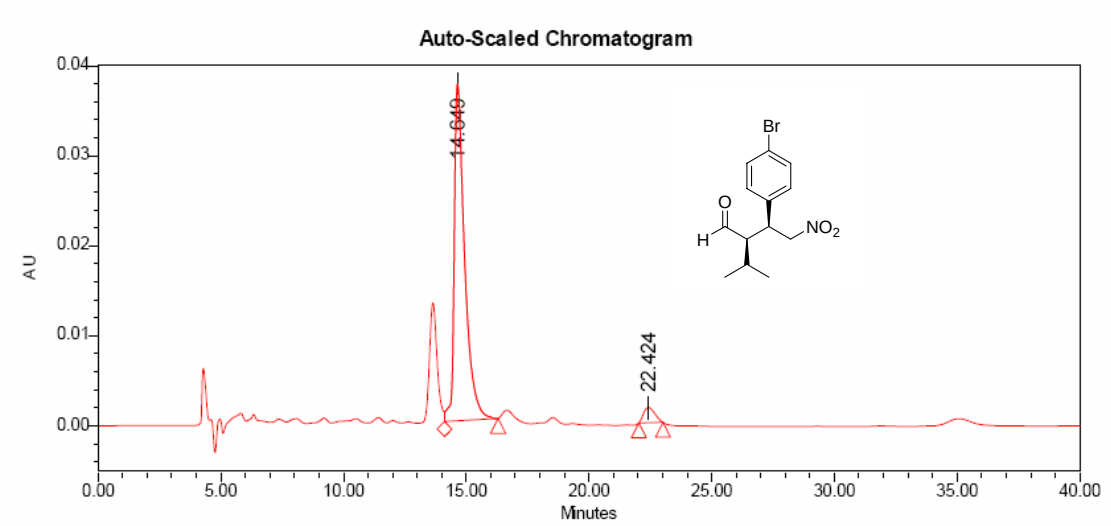

Peak Results

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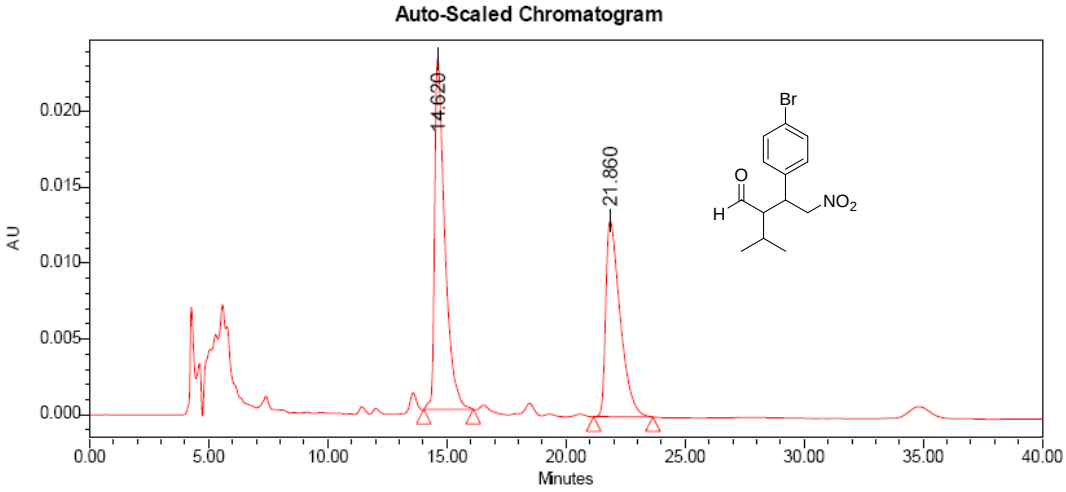
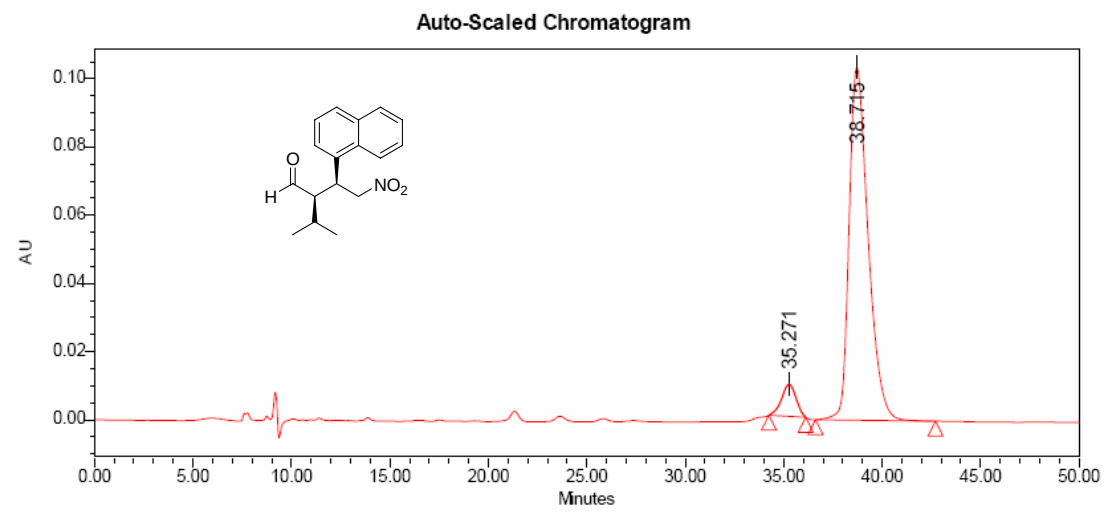
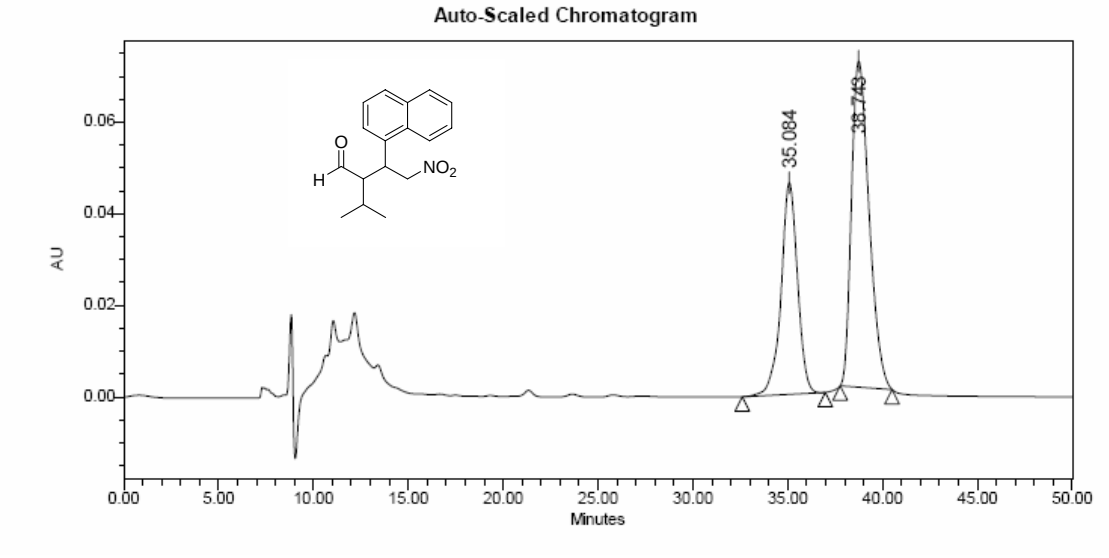


HPLC spectra for compounds **4c**

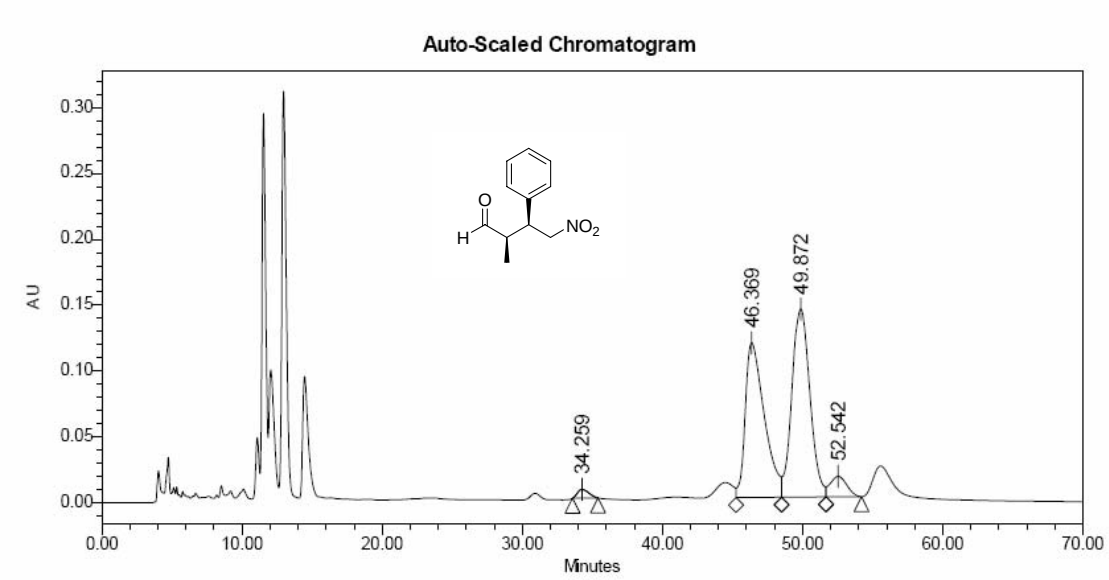


Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		35.271	480920	6.48		9380	8.32	
2		38.715	6942189	93.52		103412	91.68	

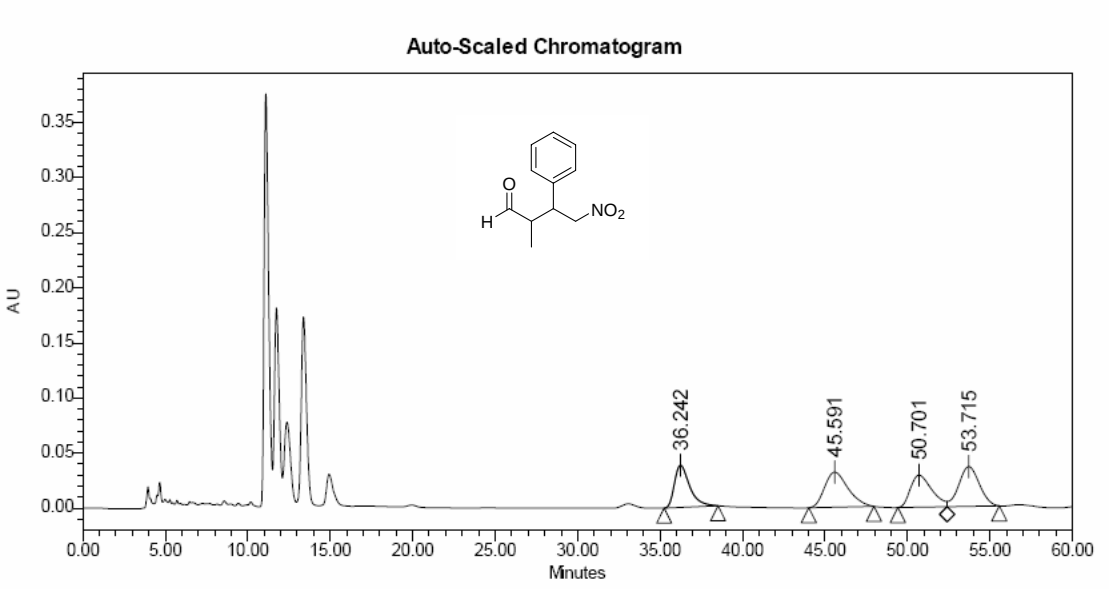


HPLC spectra for compounds **4d**

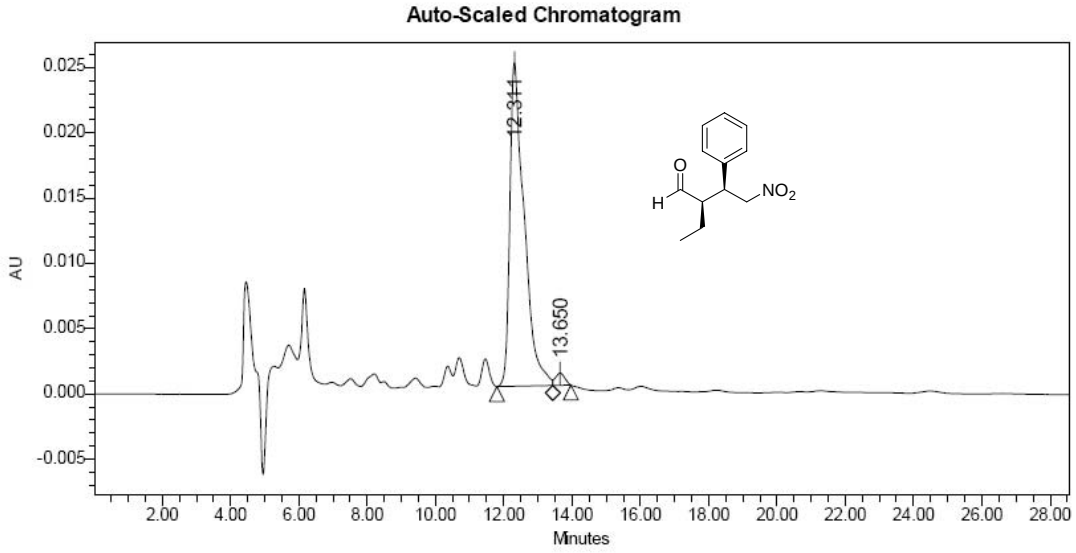


Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		34.259	372577	1.45		6670	2.36	
2		46.369	11098563	43.31		117562	41.56	
3		49.872	12866596	50.20		143012	50.56	
4		52.542	1290528	5.04		15599	5.52	

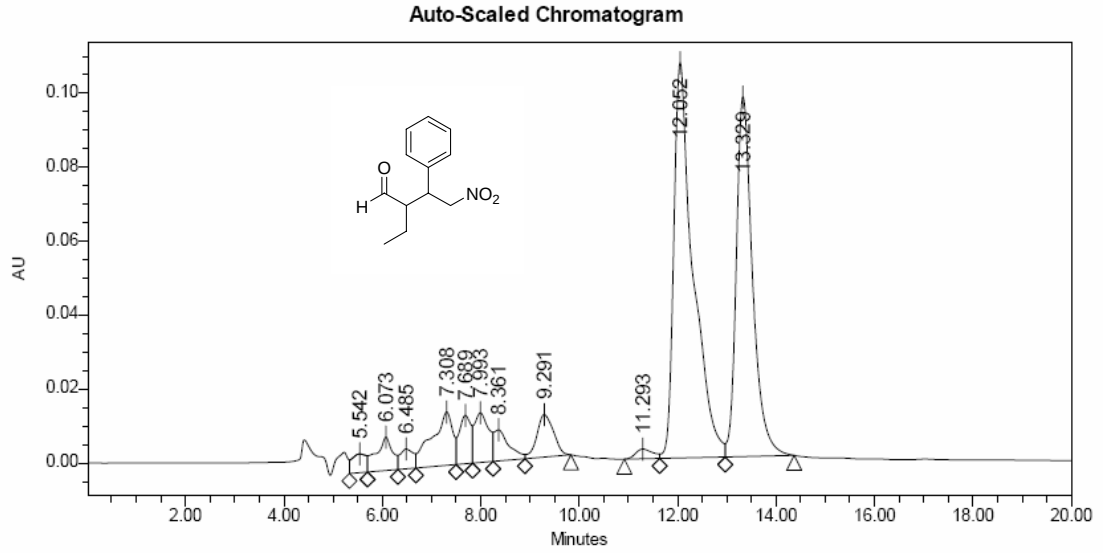


HPLC spectra for compounds **4e**

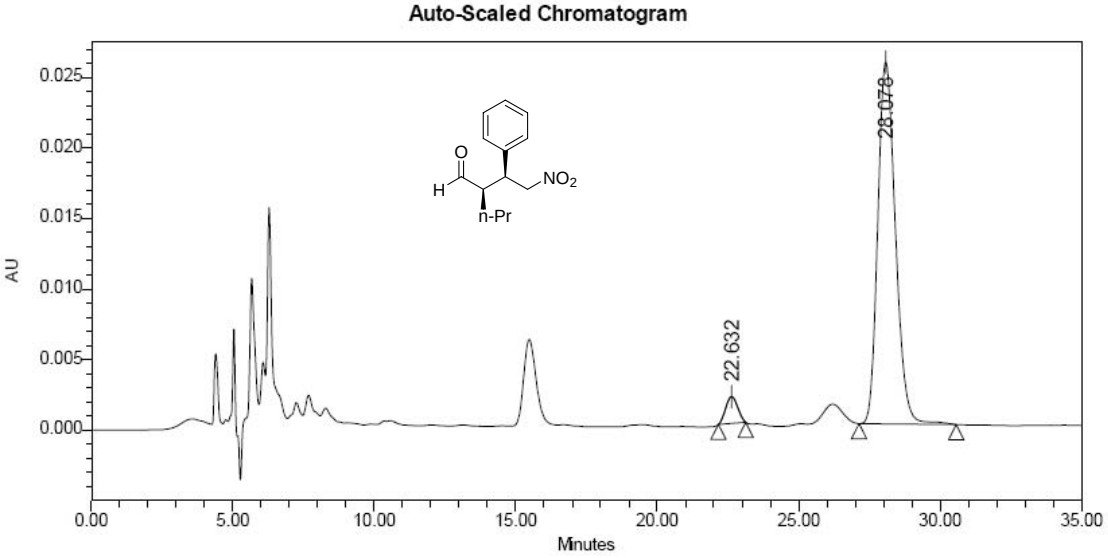


Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		12.311	724203	97.57		24802	96.38	
2		13.650	18015	2.43		932	3.62	

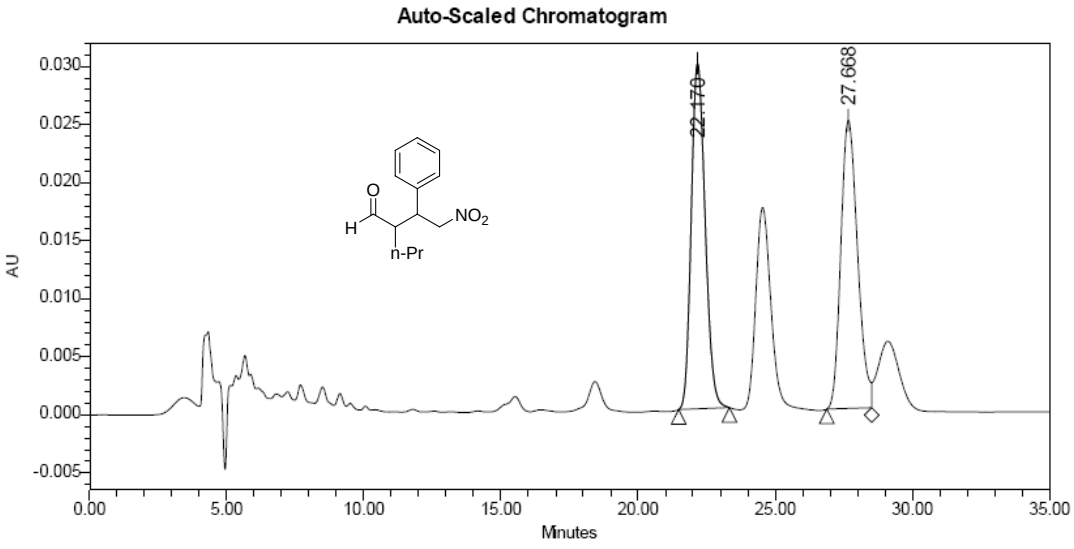


HPLC spectra for compounds **4f**

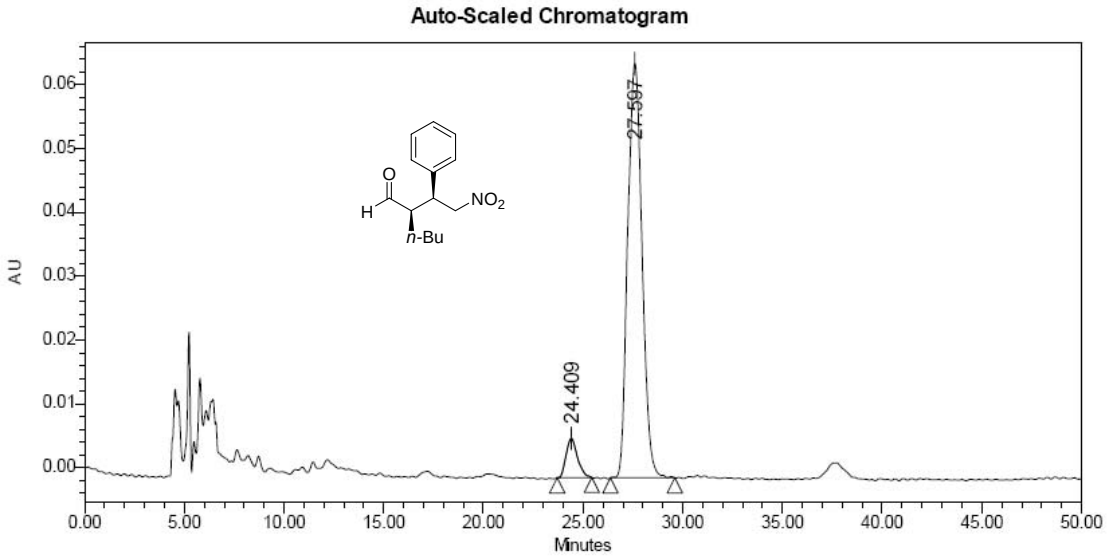


Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		22.632	55683	4.77		1893	6.88	
2		28.078	1111906	95.23		25627	93.12	

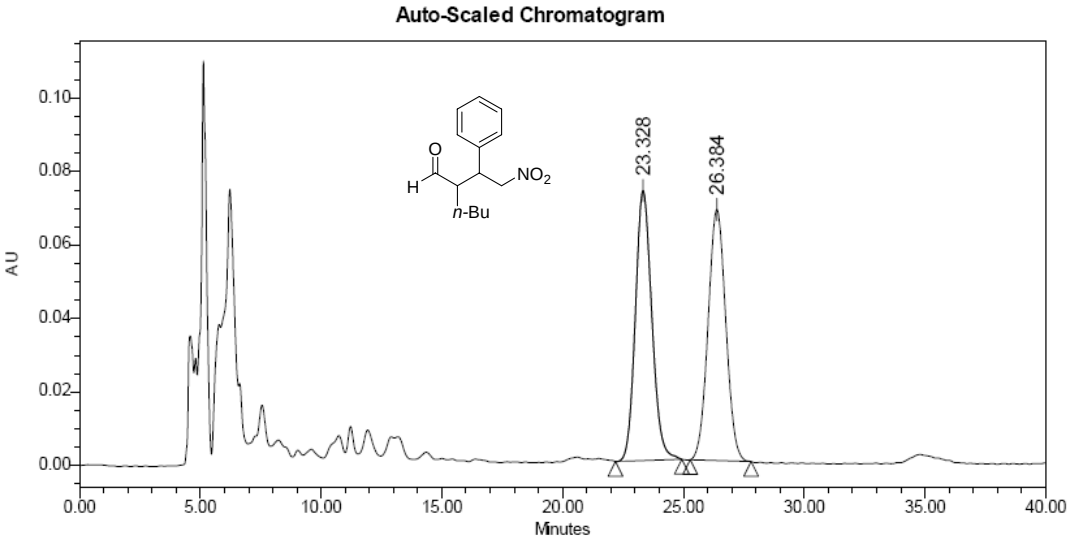


HPLC spectra for compounds **4g**

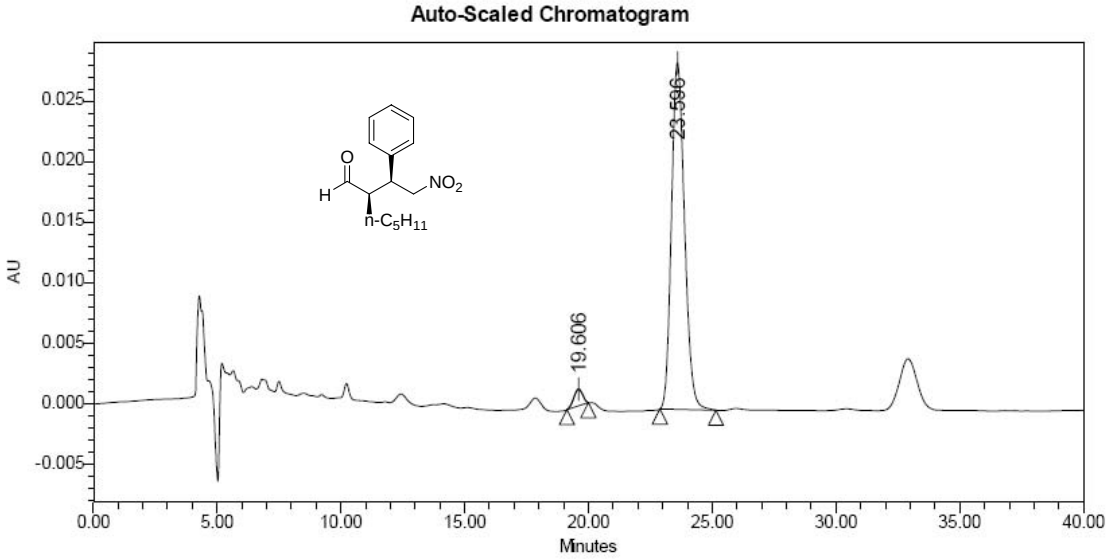


Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		24.409	243431	6.99		6141	8.65	
2		27.597	3239419	93.01		64867	91.35	

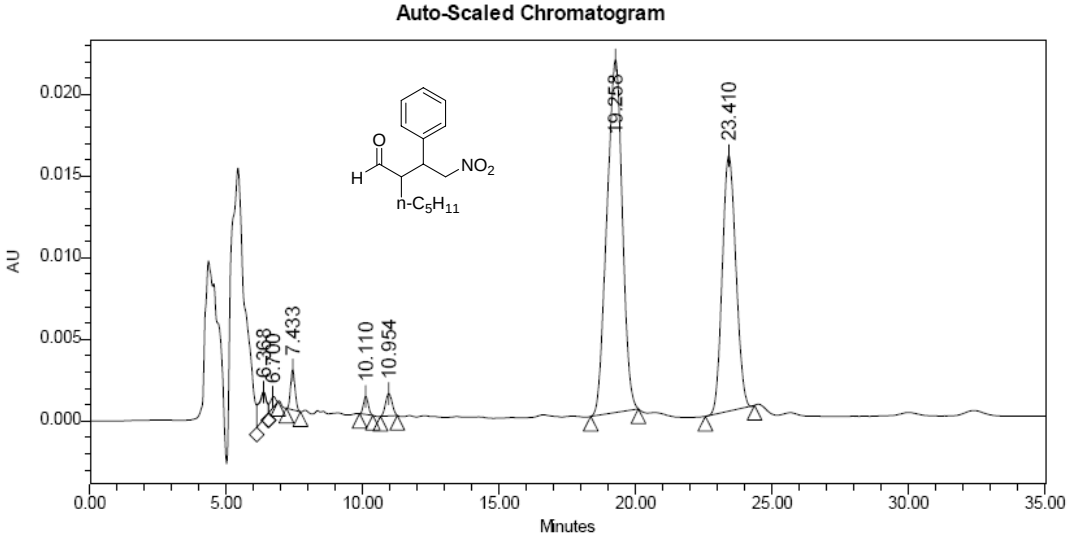


HPLC spectra for compounds **4h**

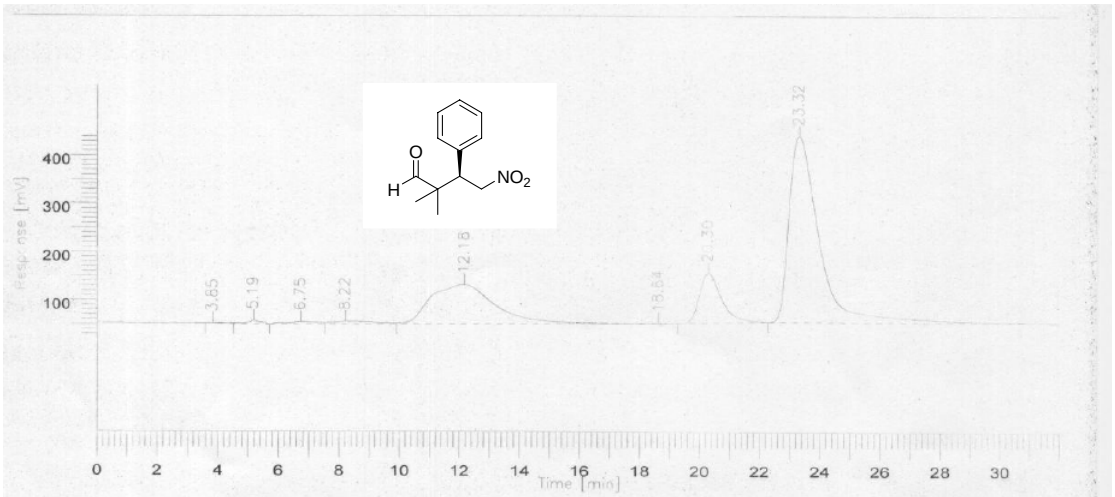


Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		19.606	34157	3.15		1374	4.58	
2		23.596	1050177	96.85		28596	95.42	

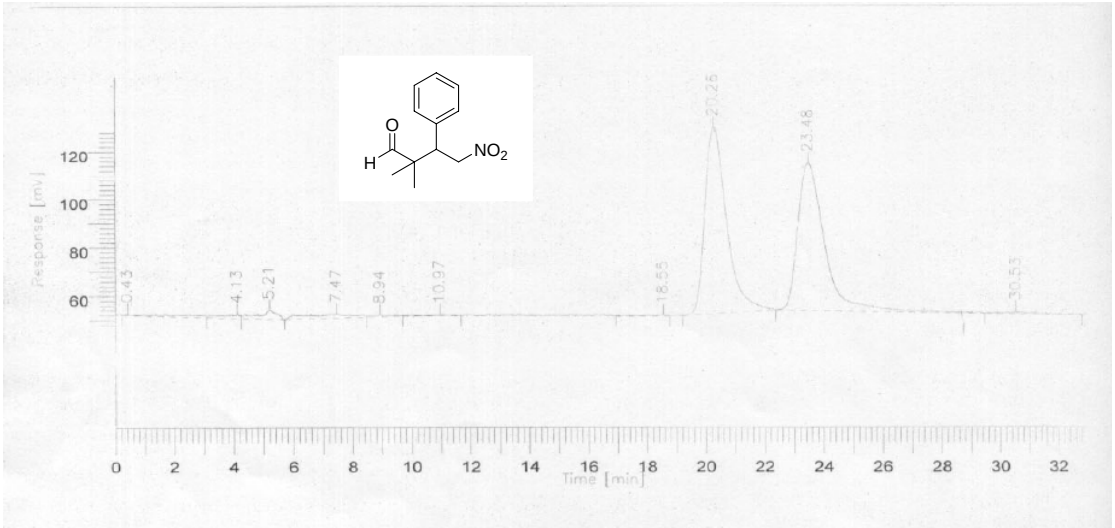


HPLC spectra for compounds **4i**

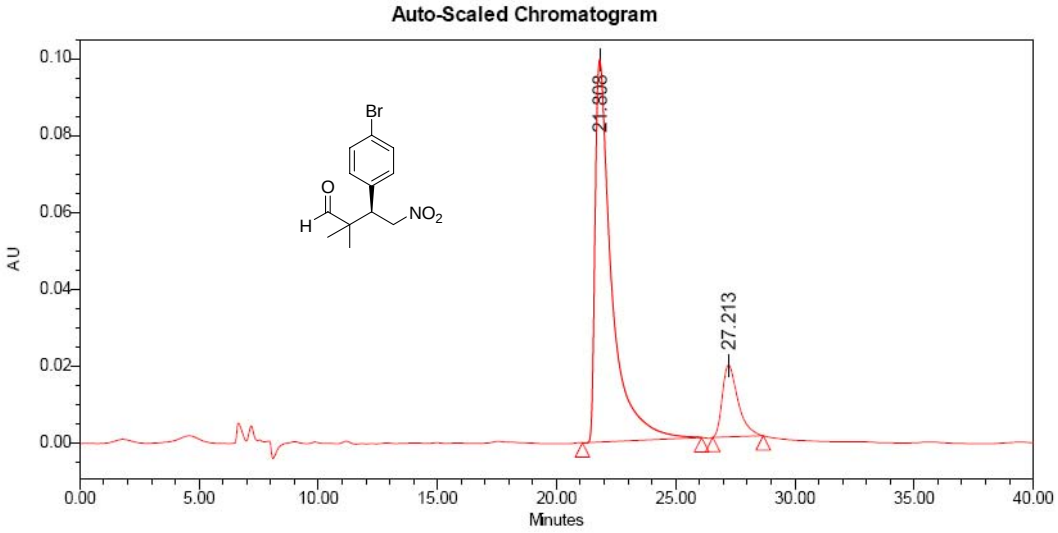


DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]	Height [uv]	Area [%]	BL
1	3.849	39993.56	803.51	0.09	BV
2	5.190	237316.44	8009.14	0.52	VB
3	6.745	440278.77	5786.94	0.96	BV
4	8.224	624302.59	6363.85	1.36	VV
5	12.179	12099235.25	81722.89	26.36	VE
6	18.637	124922.00	1172.27	0.27	EB
7	20.301	5259493.50	103662.23	11.46	BB
8	23.317	27070997.00	386215.70	58.98	BB
		45896539.12	593736.53	100.00	

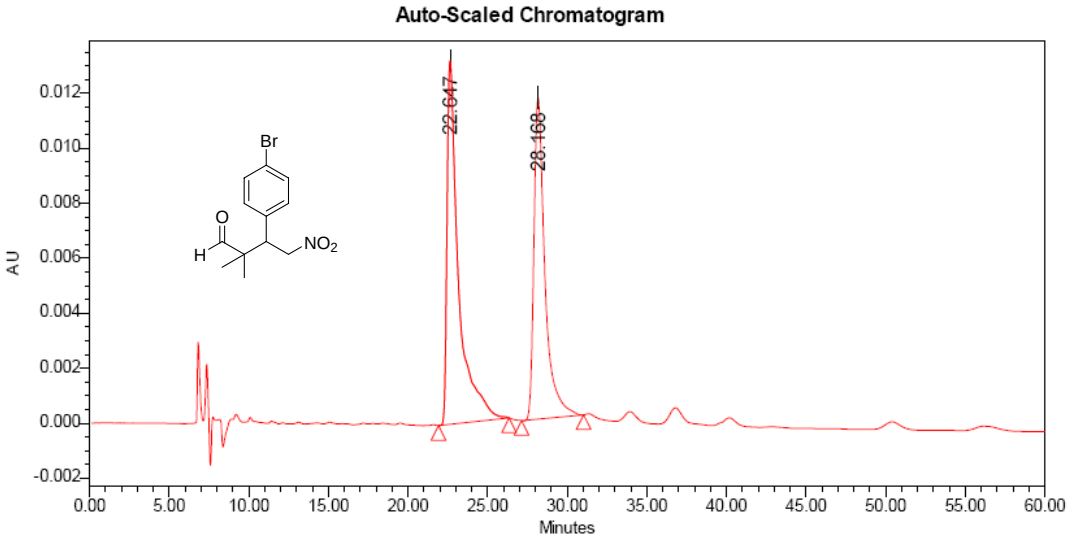


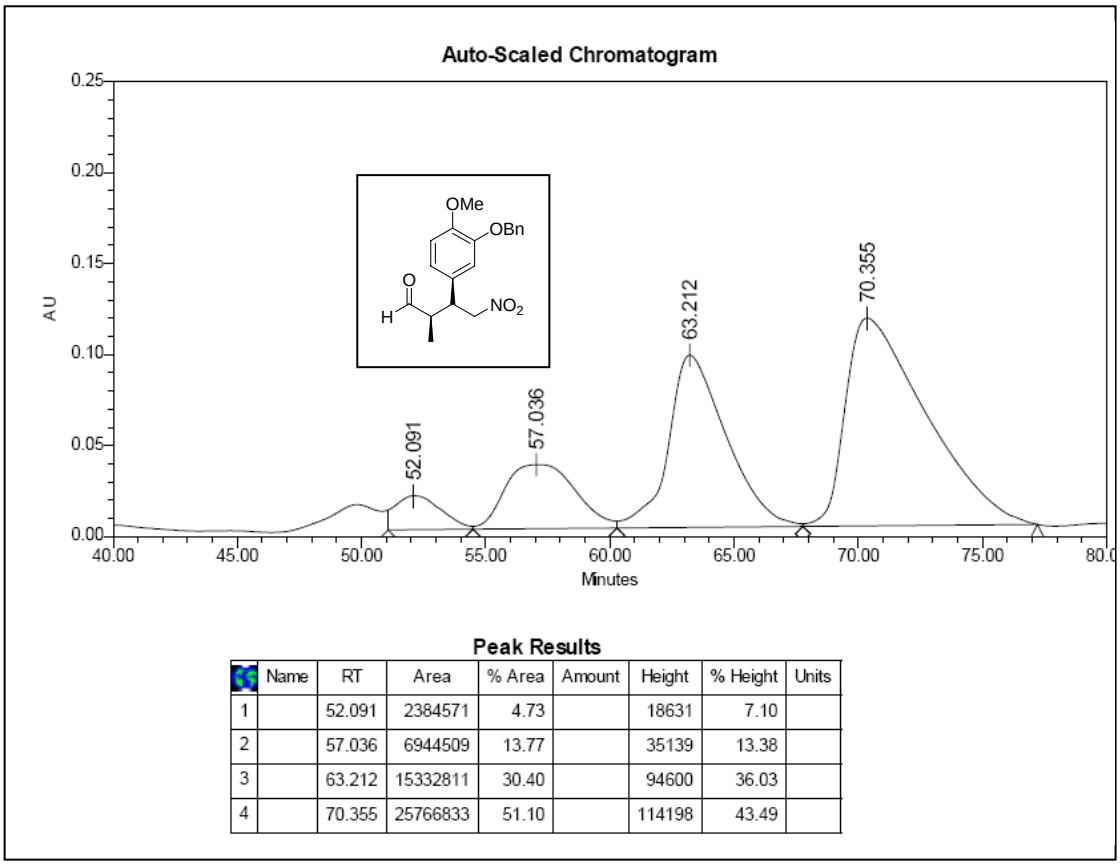
HPLC spectra for compounds **4j**



Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		21.808	4805927	84.87		99534	84.20	
2		27.213	857019	15.13		18677	15.80	

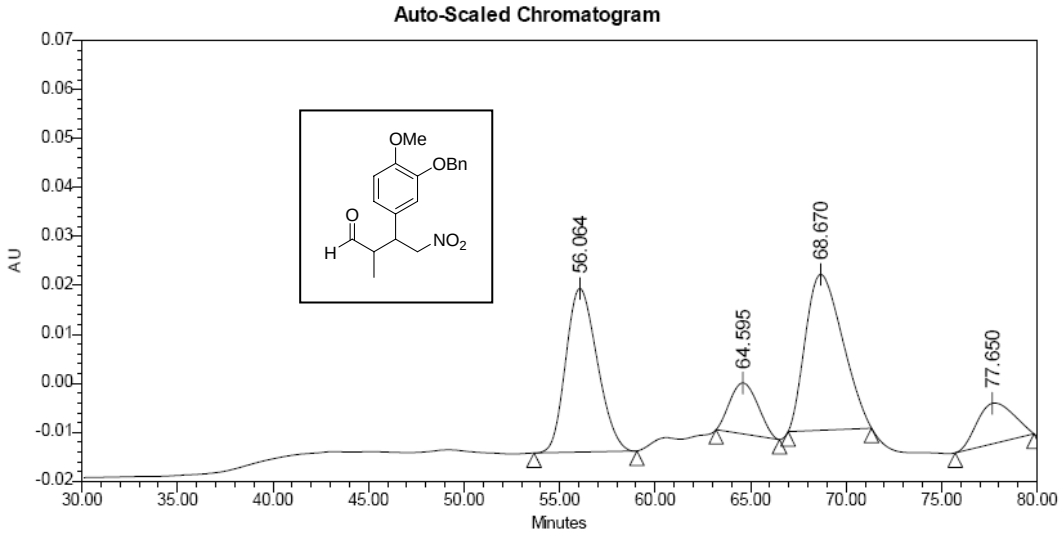




Peak Results

	Name	RT	Area	% Area	Amount	Height	% Height	Units
1		52.091	2384571	4.73		18631	7.10	
2		57.036	6944509	13.77		35139	13.38	
3		63.212	15332811	30.40		94600	36.03	
4		70.355	25766833	51.10		114198	43.49	

HPLC spectra for compounds **4k**



Reference

(1) Betancort, J. M.; Barbas III, C. F. *Org. Lett.* **2001**, *3*, 3737.

(2) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.

(3) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Sylett*., **2005**, 611.

(4) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4* 3611.

(5) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *117*, 1369

(6) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.