

Enantioselective Synthesis of 4-Substituted Tetrahydroisoquinolines *via*
Palladium-Catalyzed Intramolecular Friedel-Crafts Type Allylic
Alkylation of Phenols

Zheng-Le Zhao^{a,b}, Qing Gu^b, Xin-Yan Wu^{a*} and Shu-Li You^{a,b*}

^a Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, China

^b State Key Laboratory of Organometallic Chemistry Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences 345 Lingling Lu, Shanghai 200032, China
Fax (+86) 21-54925087; E-mail: xinyanwu@ecust.edu.cn, or slyou@sioc.ac.cn

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General Methods. Unless stated otherwise, all reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purified and dried according to standard methods prior to use.

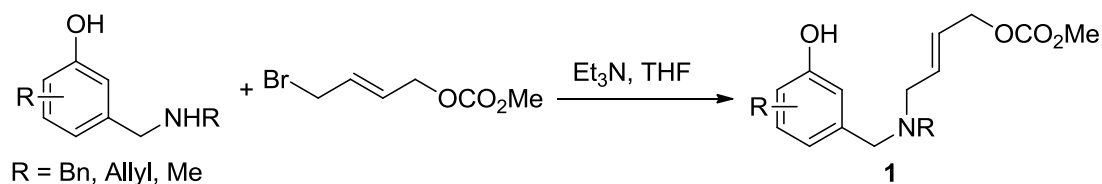
^1H and ^{13}C NMR spectra were recorded on a Varian instrument (300, 400 MHz and 75, 100 MHz, respectively) and internally referenced to tetramethylsilane signal or residualprotio solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ , ppm).

The Trost ligands¹, the substituted phenol amines and (*E*)-4-bromo-but-2-enyl methyl ester² were prepared according to the reported procedures.

(1) (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (b) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228.

(2) Trost, B. M.; Sacchi, K. L.; Schroeder, G. M.; Asakawa, N. *Org. Lett.* **2002**, *4*, 3427.

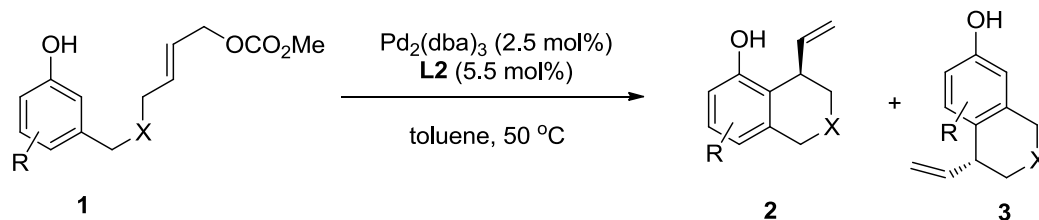
General Procedure for Synthesis of the Substituted Allylic Carbonates



Substrates **1a-j**, **1o** were prepared according to the previously reported methods (refer to: *Org. Lett.* **2012**, *14*, 2579.).

To a solution of the substituted phenol amine (2.0 mmol, 1.0 equiv) and Et₃N (0.33 mL, 2.4 mmol, 1.2 equiv) in dry THF (25 mL), carbonic acid (*E*)-4-bromo-but-2-enyl methyl ester (836 mg, 4.0 mmol, 2.0 equiv) was added at 0 °C. The ice bath was then removed and the reaction mixture was stirred at room temperature for 6-12 h. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated through a pad of celite and washed with EtOAc. The solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (PE/EA = 6/1) to afford the desired product **1**.

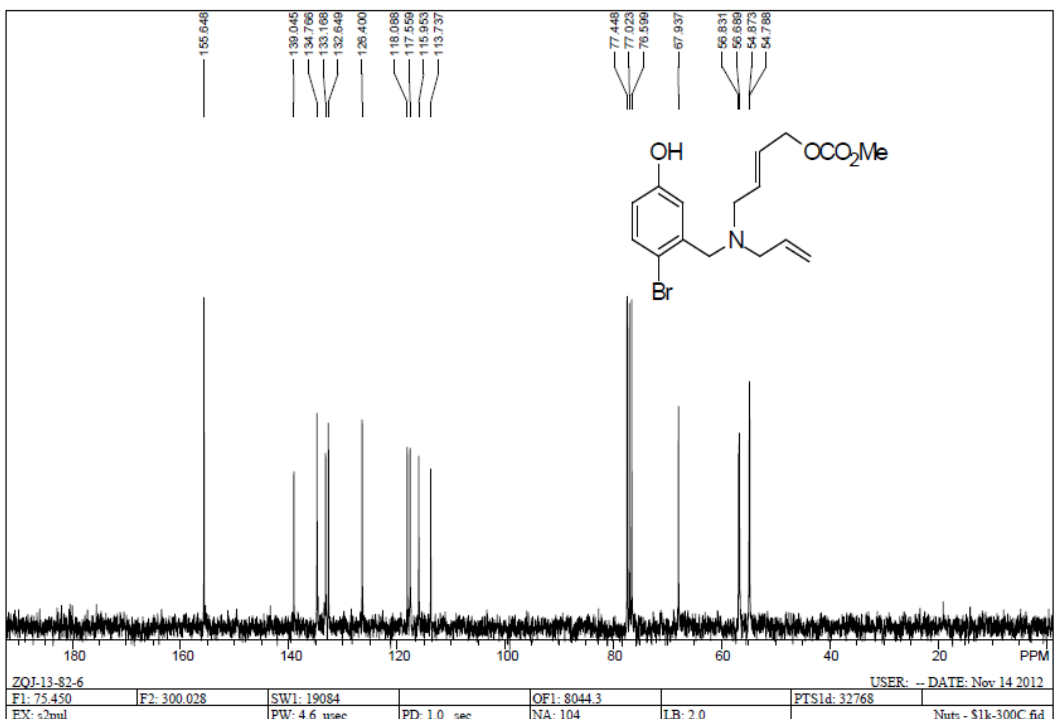
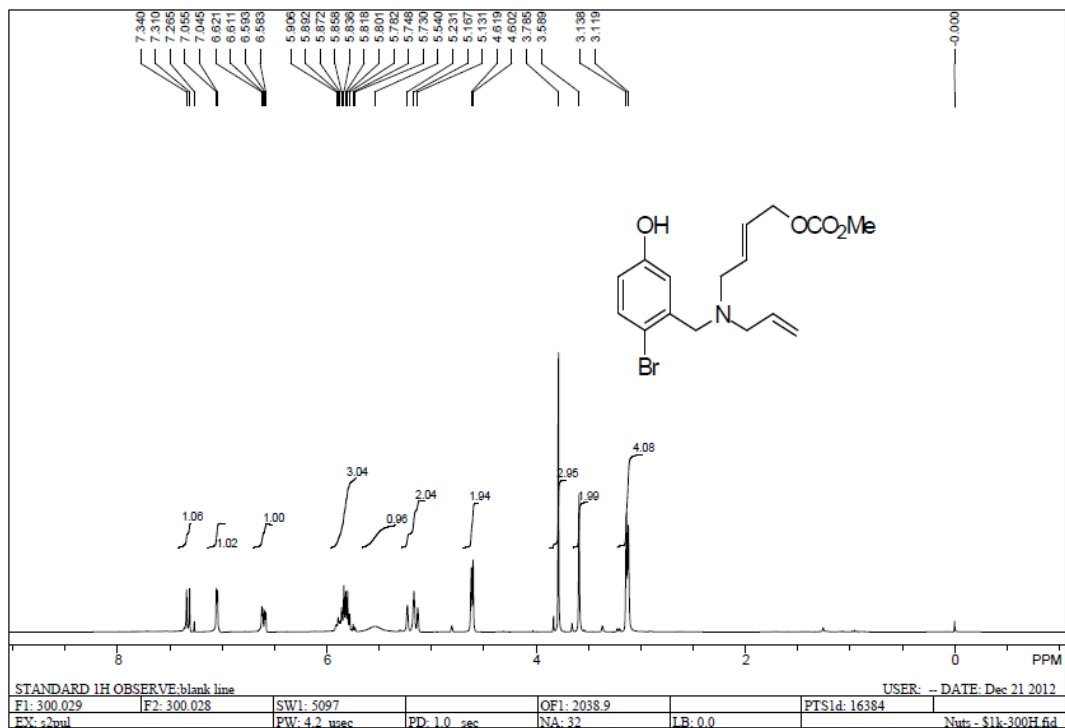
General Procedure for Palladium-Catalyzed Intramolecular Enantioselective Allylic Alkylation Reaction



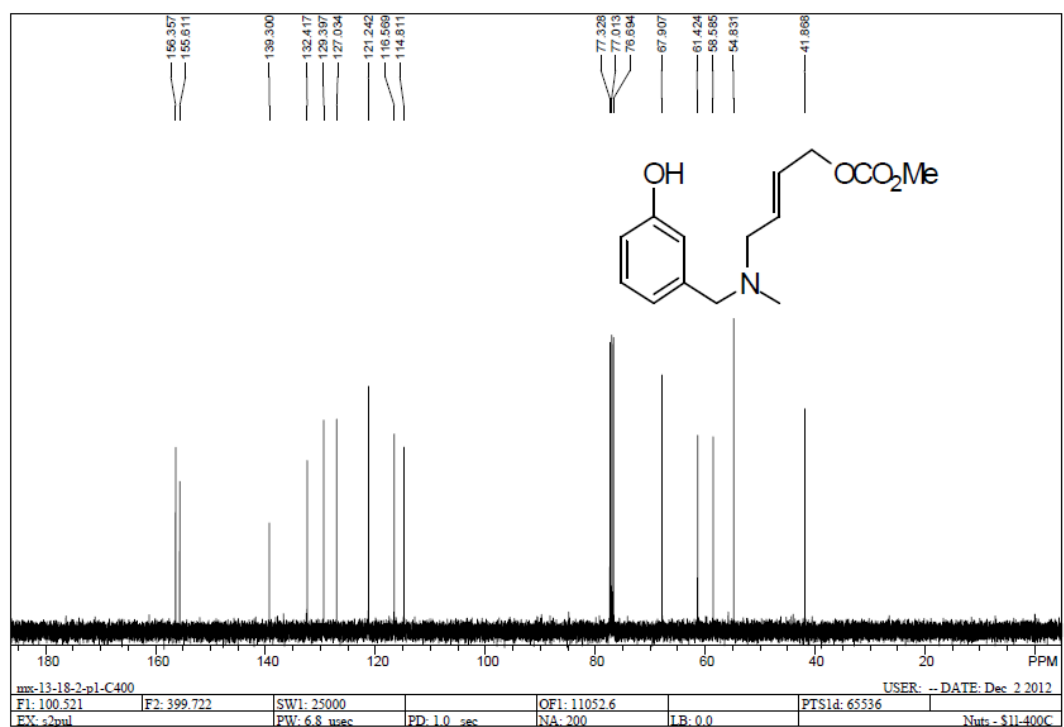
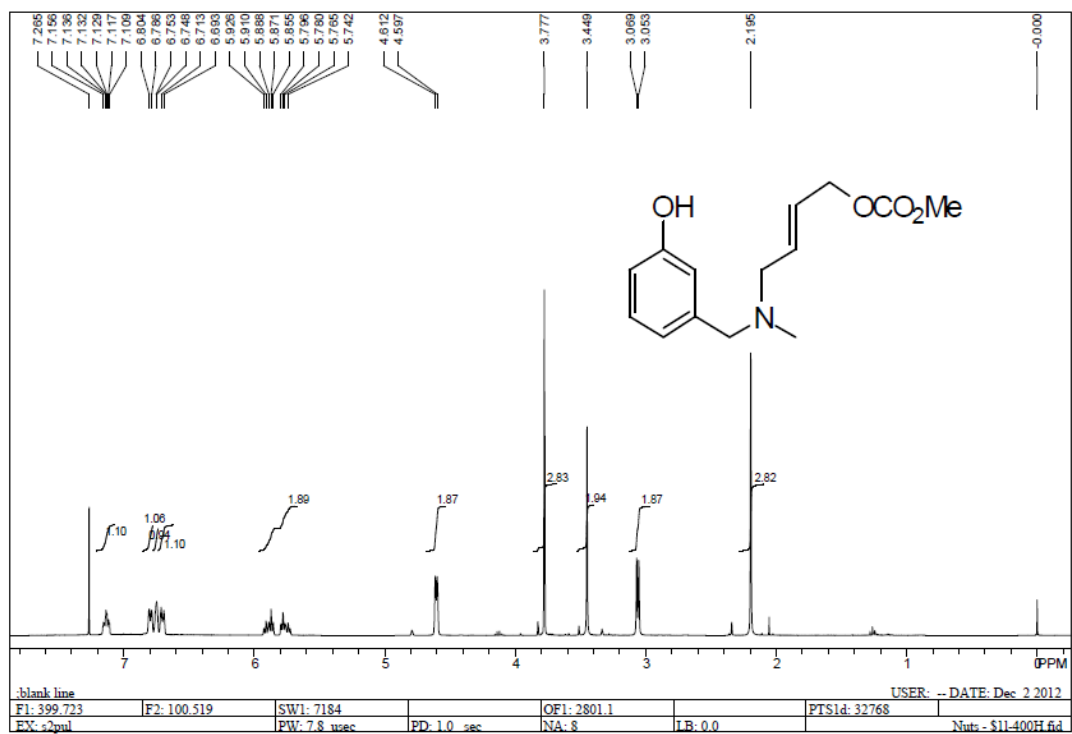
To a flame-dried Schlenk tube under argon, Pd₂(dba)₃ (6.9 mg, 0.0075 mmol, 2.5 mol %), (1*R*, 2*R*)-DACH-phenyl Trost ligand (**L2**) (12 mg, 0.018 mmol, 5.5 mol%), toluene (1 mL) was added. The reaction mixture was heated at 50 °C for 30 min, after that allyl carbonate **1** (0.30 mmol, dissolved in 1.0 mL toluene) was added. The reaction mixture was stirred at 50 °C. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated through a pad of celite and washed with EtOAc. Then the solvent were removed under reduced pressure. The **2/3** ratio was determined by ¹H NMR of the crude reaction mixture. Then the residue was purified by silica gel column chromatography (PE/EA = 8/1) to afford the desired products **2** and **3**.

Copies of NMR Spectra and HPLC

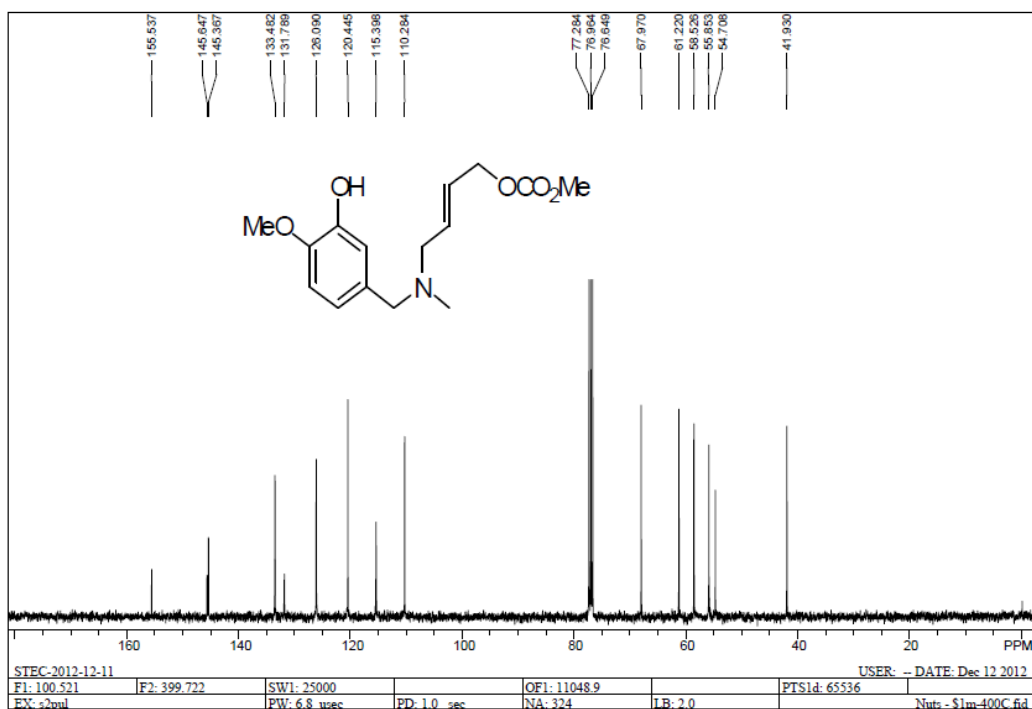
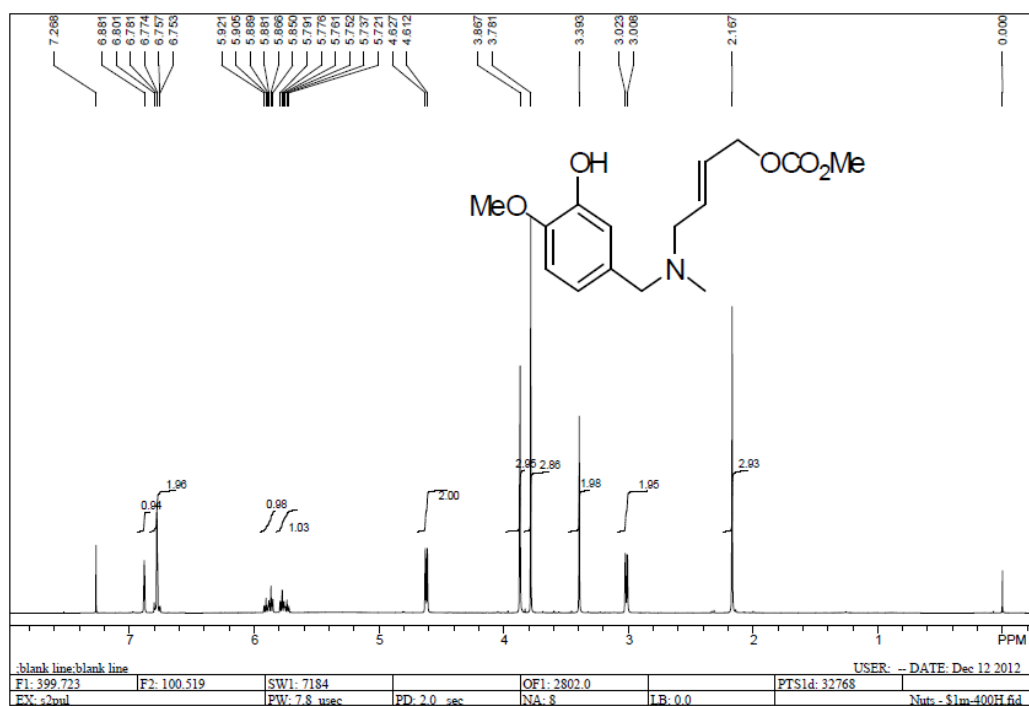
1k



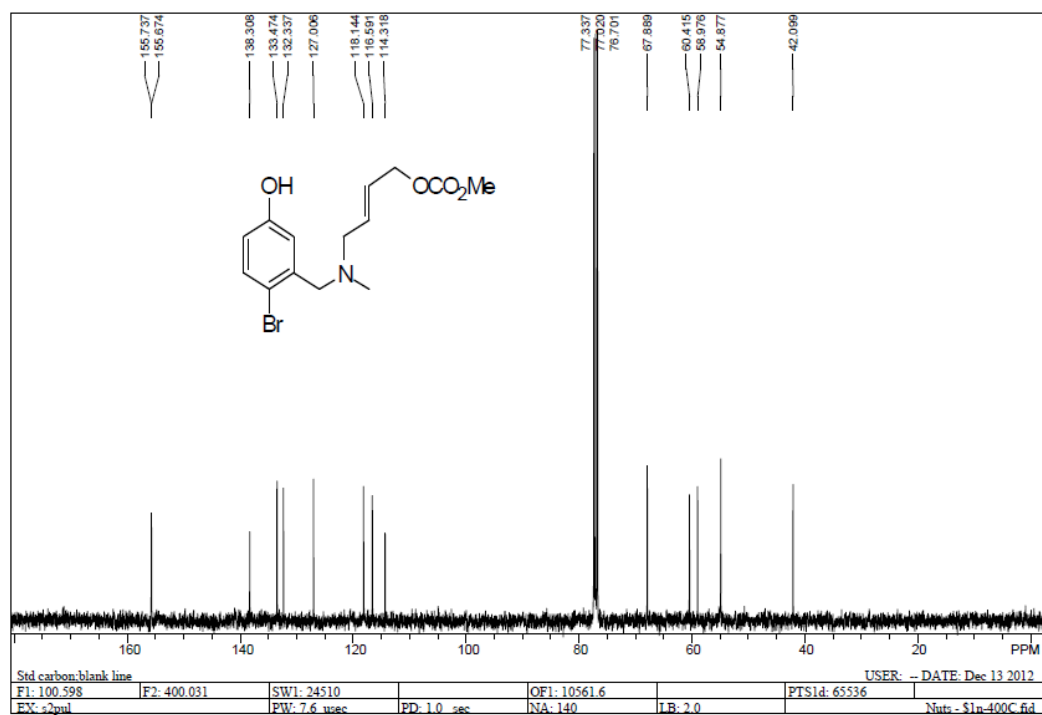
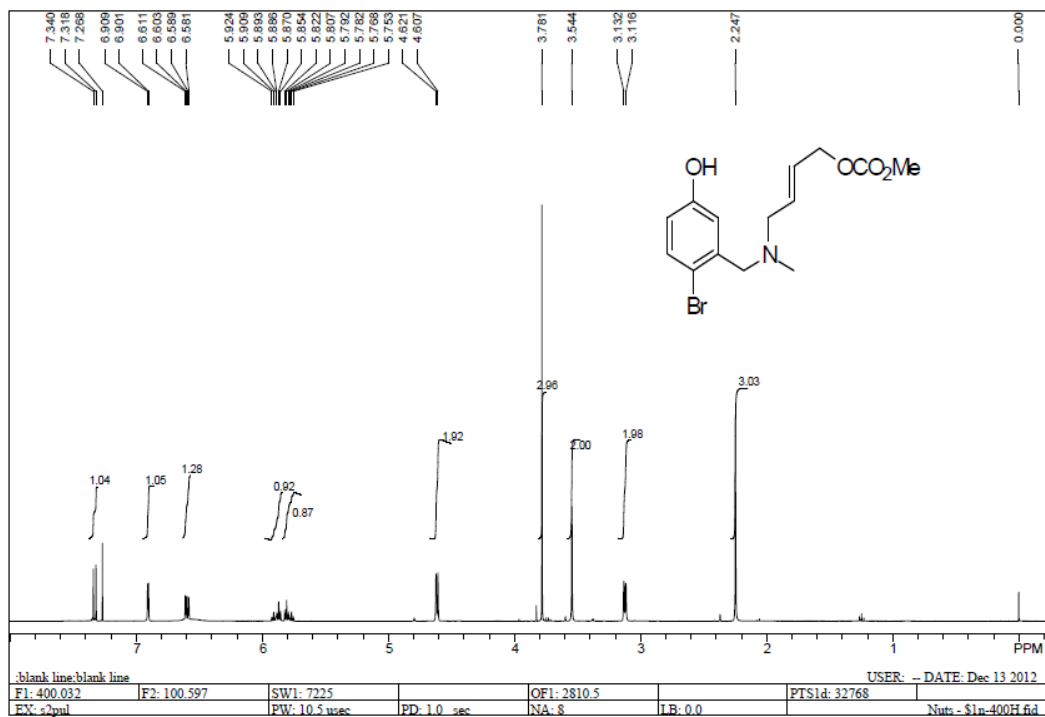
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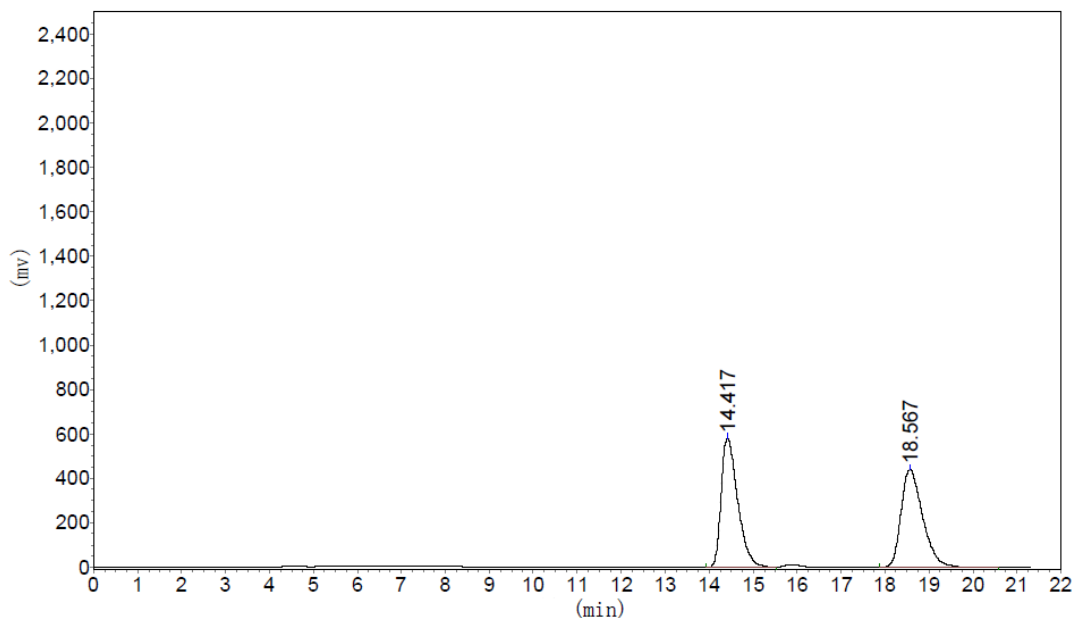
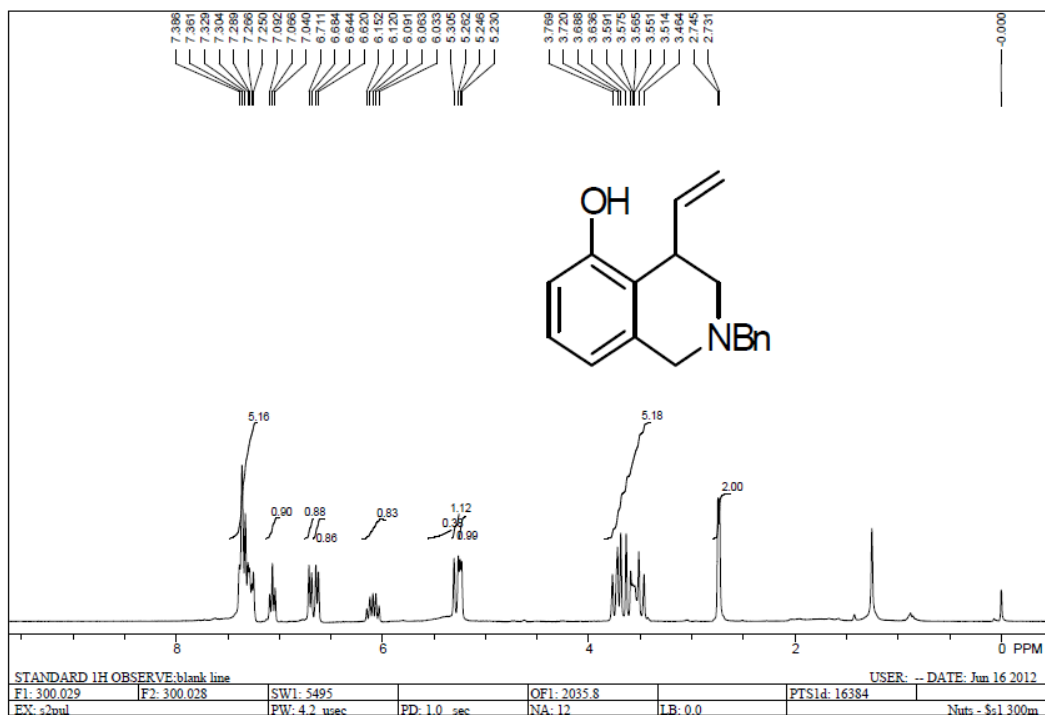
1m



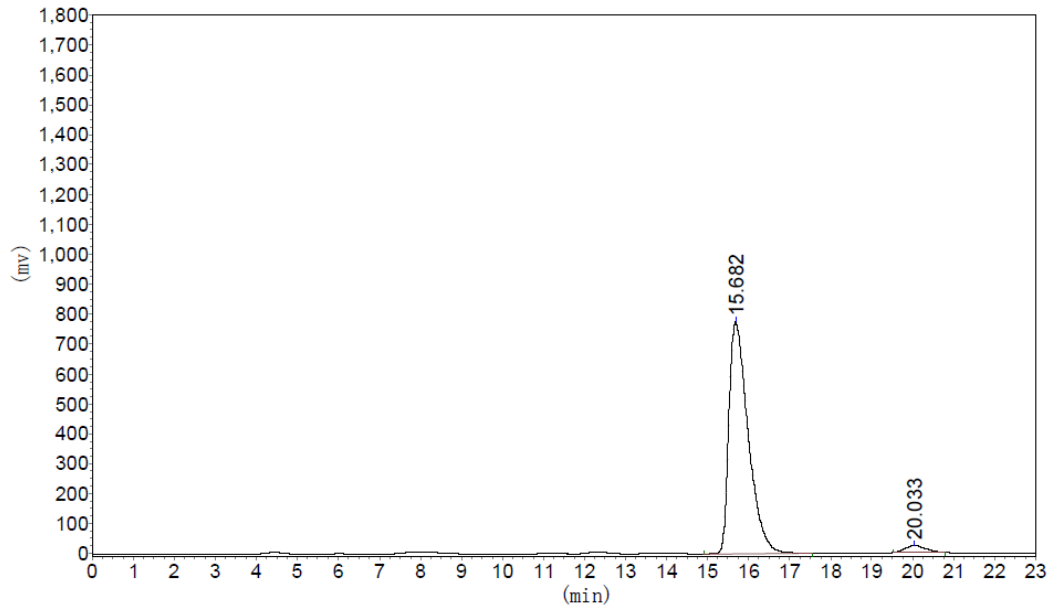
1n



2a

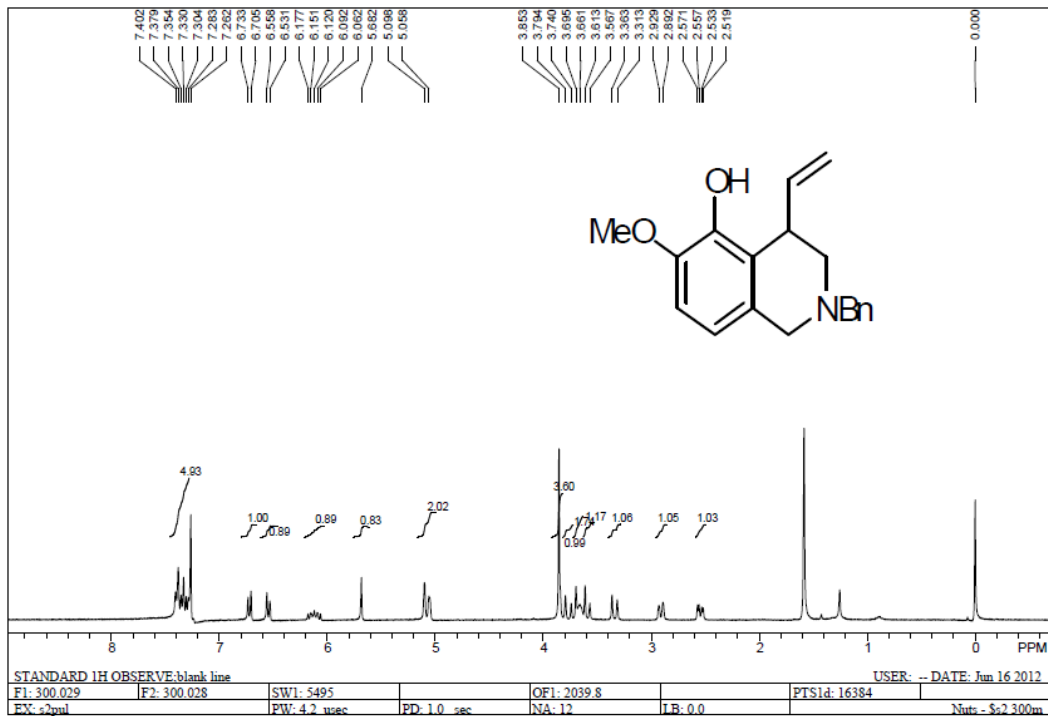


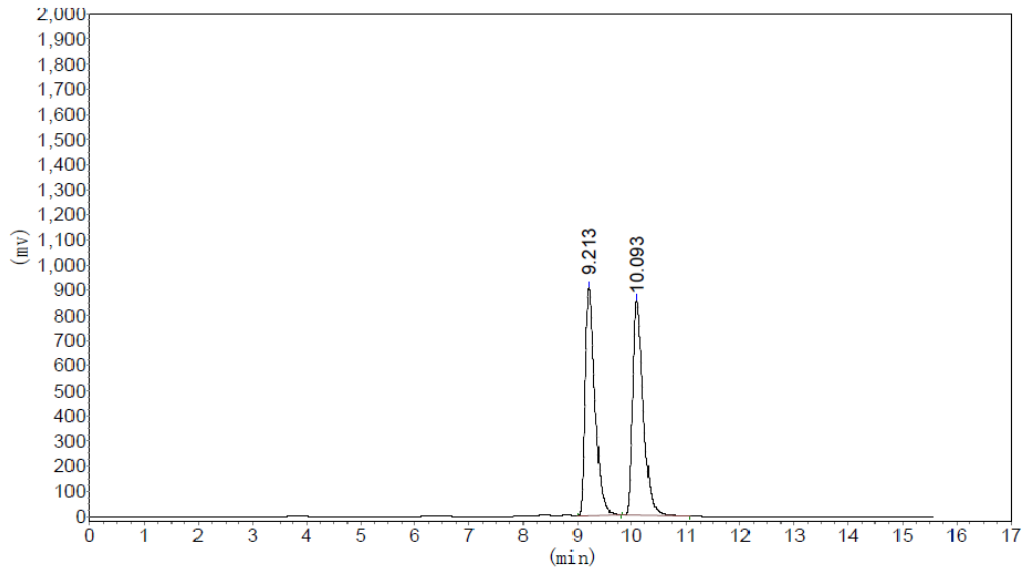
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.417	579699.125	15021199.000	50.2033
2	18.567	438363.188	14899569.000	49.7967
Total		1018062.313	29920768.000	100.0000



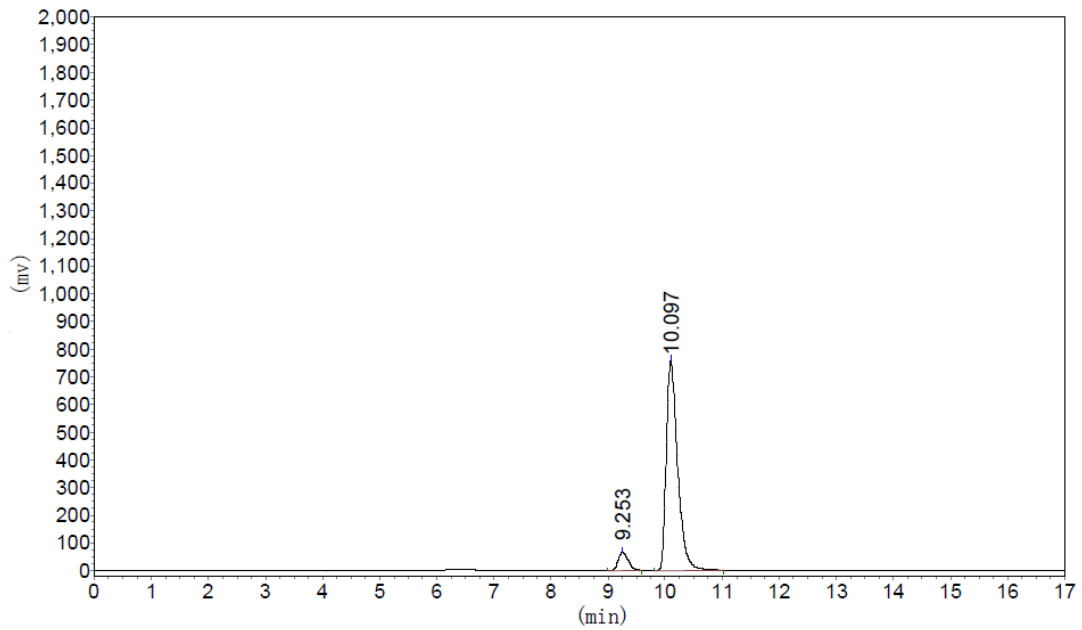
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	15.682	774587.188	25364782.000	96.5331
2	20.033	24677.736	910958.563	3.4669
Total		799264.924	26275740.563	100.0000

2b



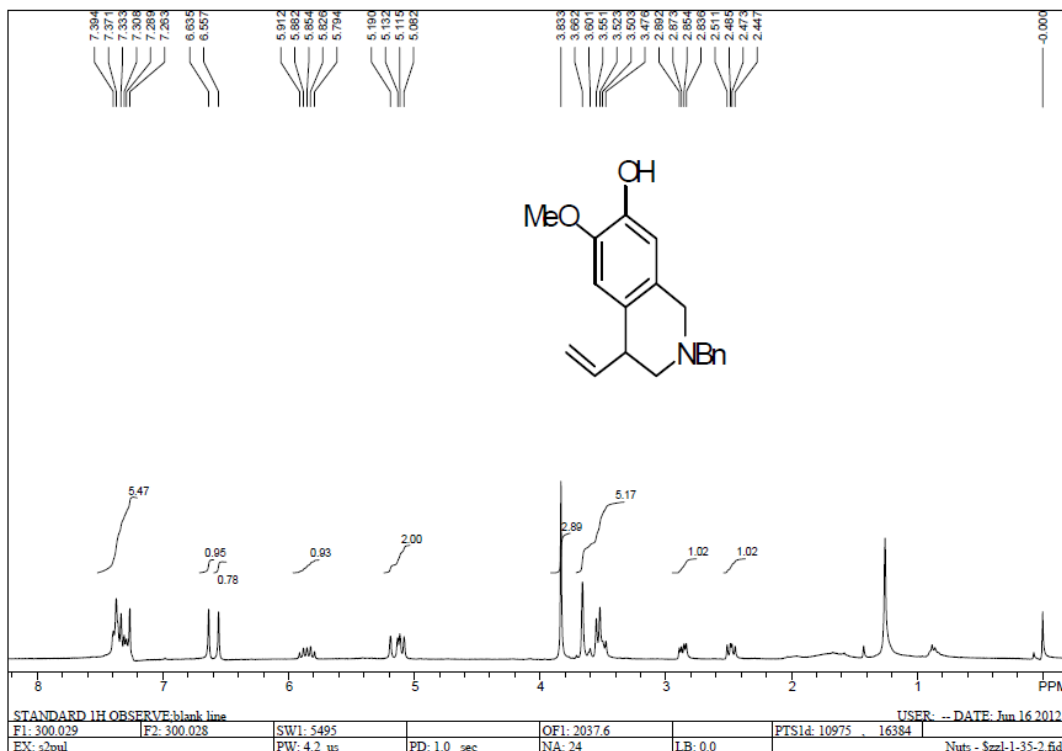


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	9.213	911170.625	11573544.000	49.6305
2	10.093	857304.063	11745871.000	50.3695
Total		1768474.688	23319415.000	100.0000

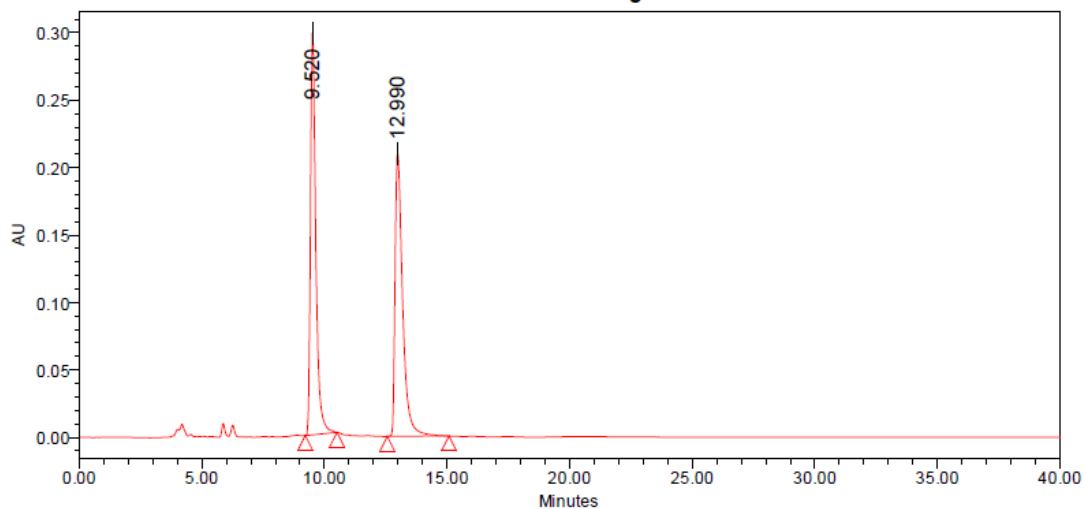


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	9.253	65357.195	819019.250	7.2738
2	10.097	758672.438	10440836.000	92.7262
Total		824029.633	11259855.250	100.0000

3b



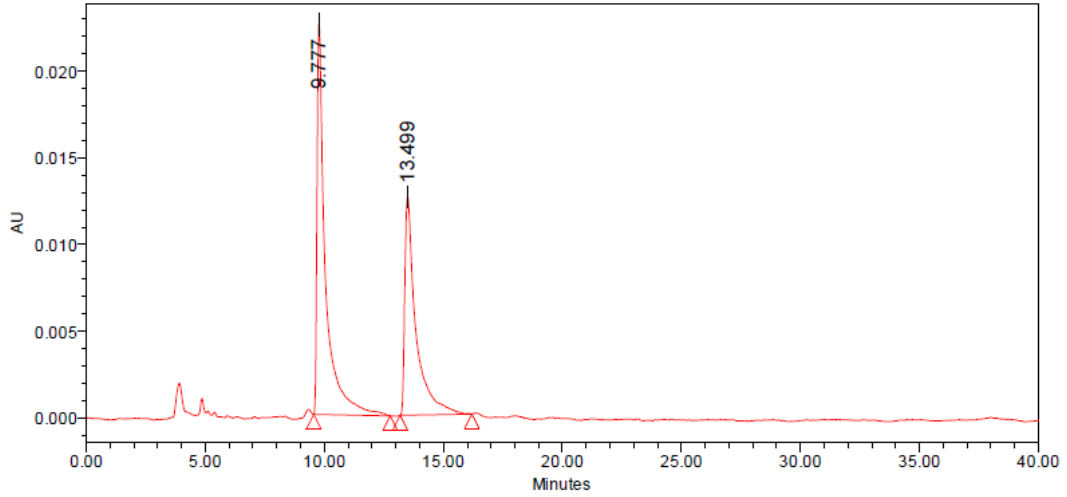
Auto-Scaled Chromatogram



Peak Results

Retention Time (min)	Area ($\mu\text{V}^2\text{sec}$)	% Area
9.520	4524110	50.11
12.990	4505040	49.89

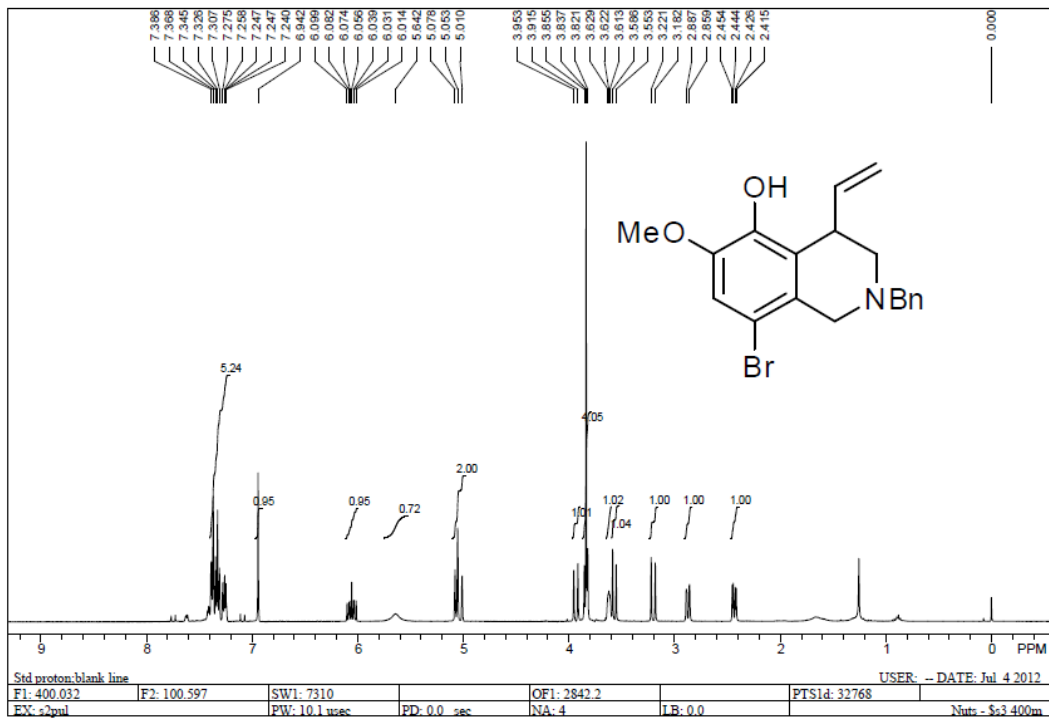
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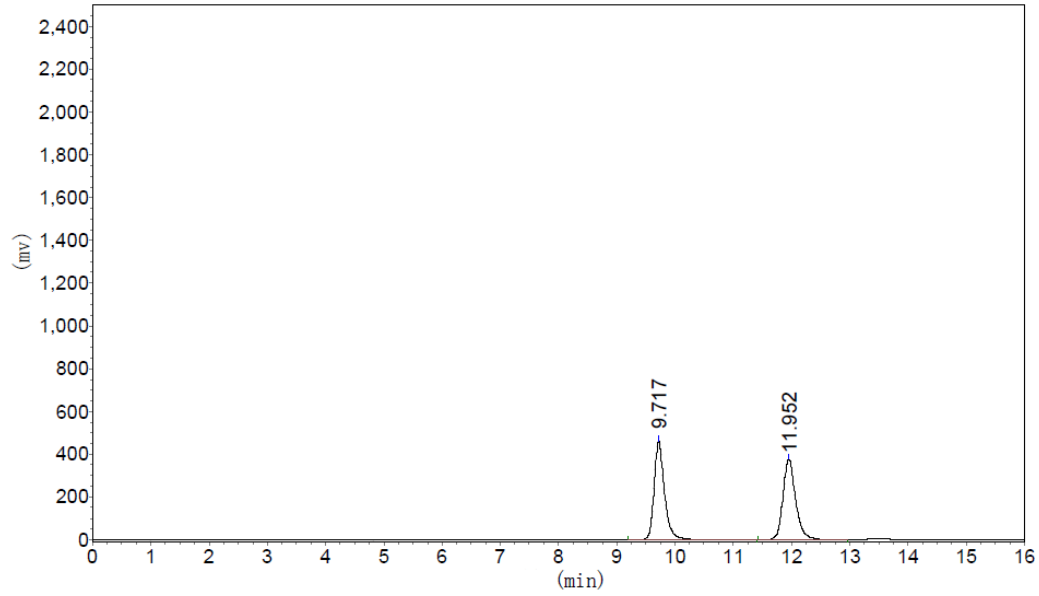


Peak Results

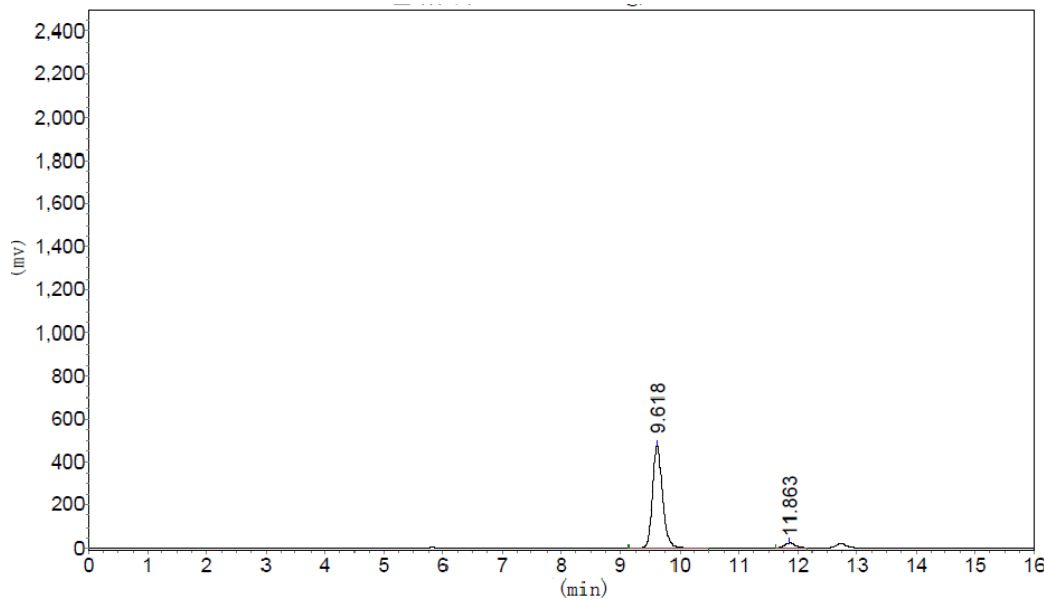
Retention Time (min)	Area (μV*sec)	% Area	
1	9.777	556125	57.63
2	13.499	408831	42.37

2c



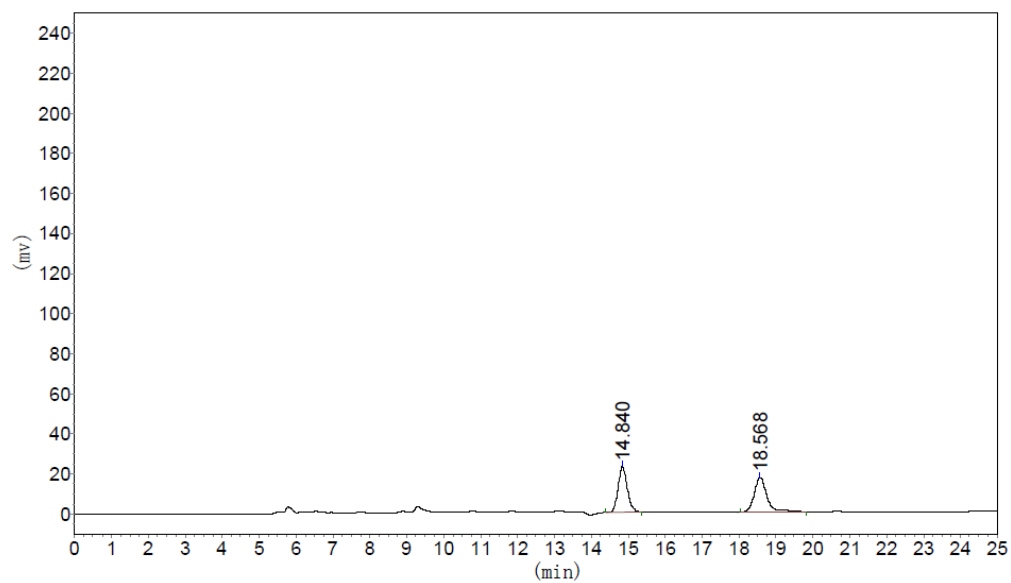
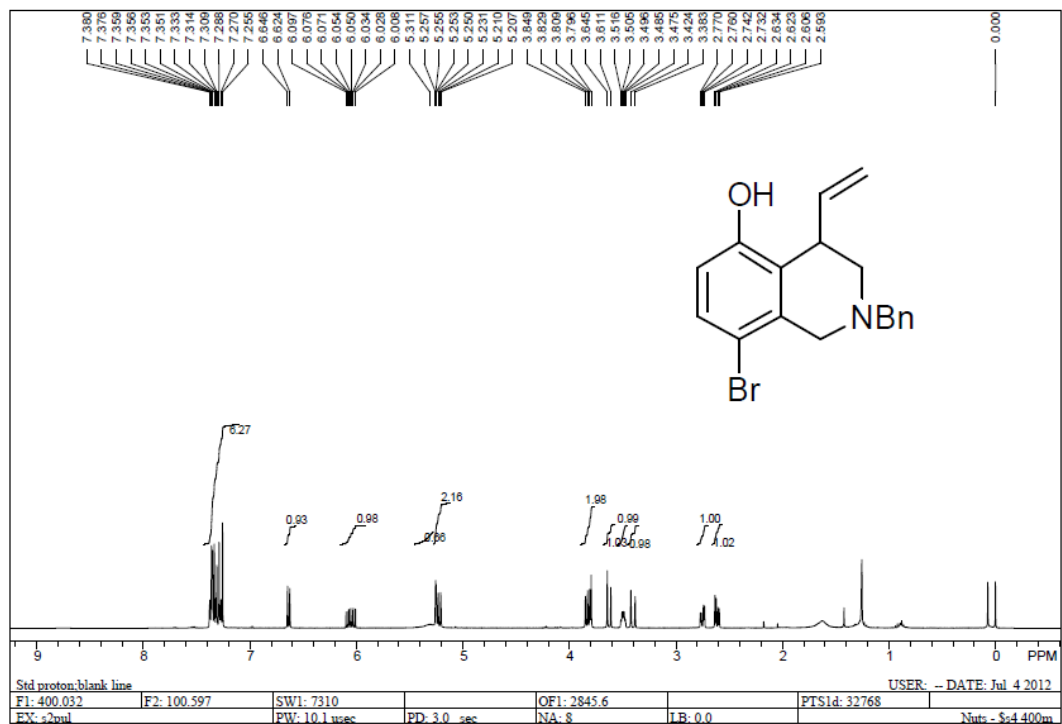


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	9.717	462778.875	5720537.000	50.3435
2	11.952	376938.219	5642463.500	49.6565
Total		839717.094	11363000.500	100.0000

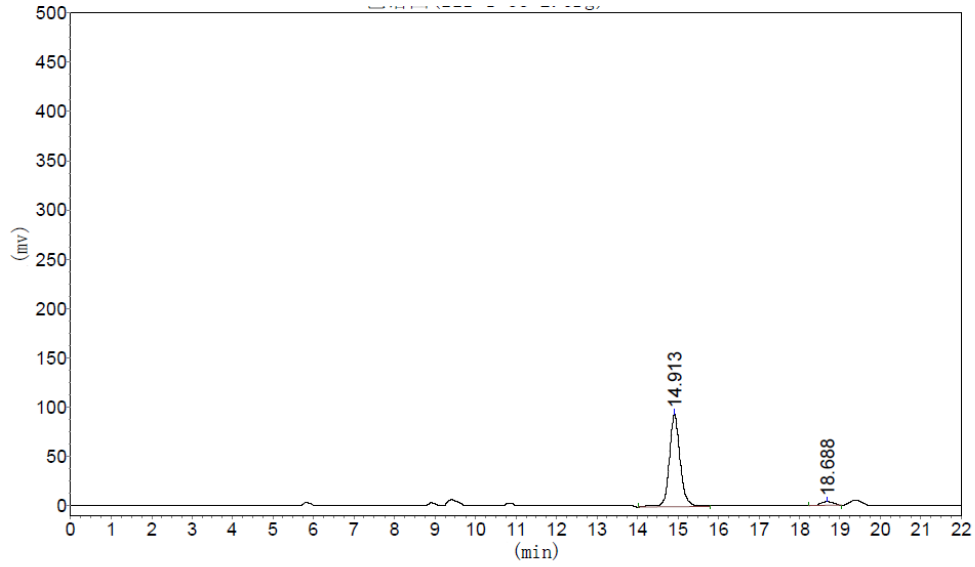


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	9.618	475712.188	5719961.000	94.8290
2	11.863	22777.473	311905.875	5.1710
Total		498489.660	6031866.875	100.0000

2d

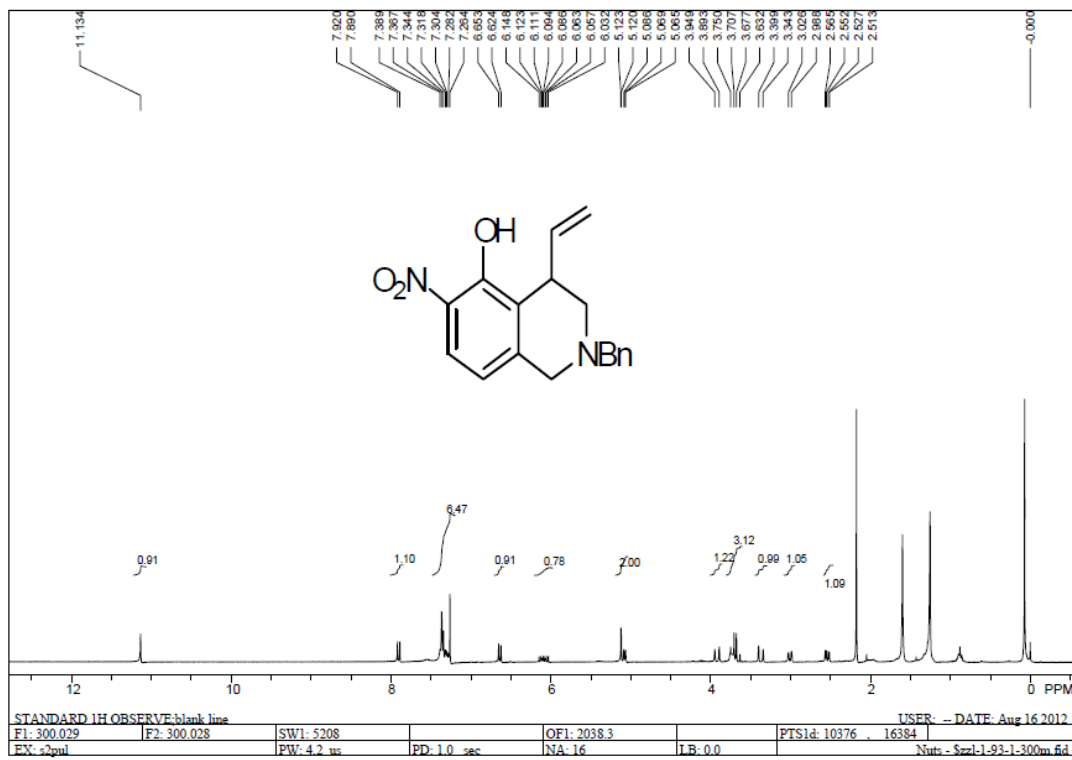


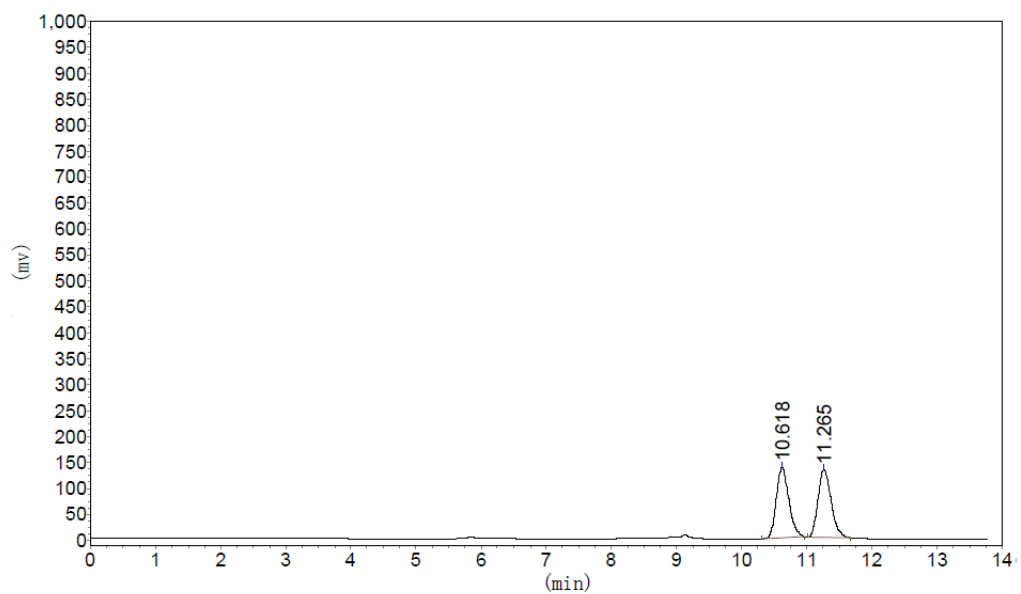
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.840	22891.139	395427.813	49.2940
2	18.568	17213.246	406754.781	50.7060
Total		40104.385	802182.594	100.0000



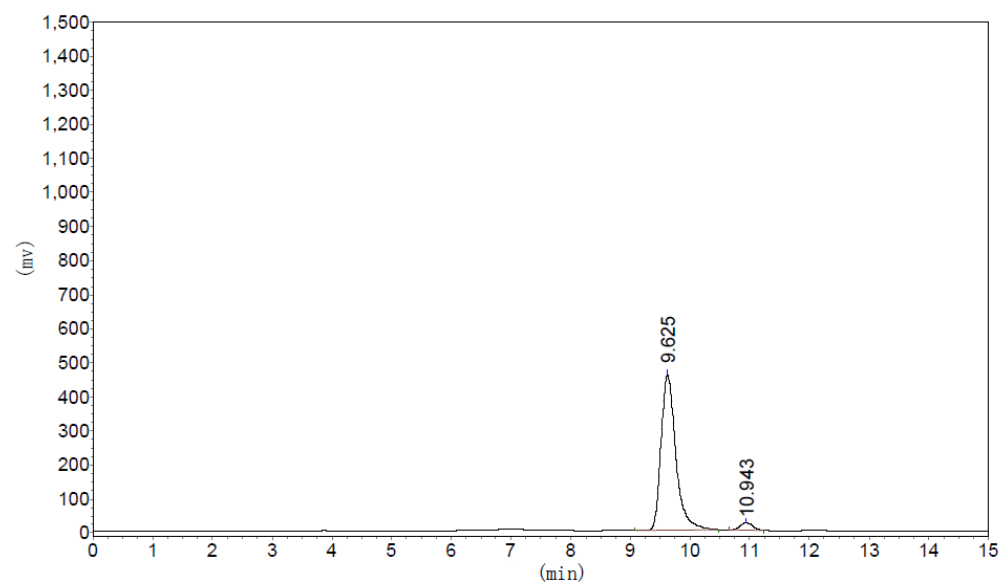
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.913	93991.555	1724479.375	95.6549
2	18.688	3947.226	78333.203	4.3451
Total		97938.781	1802812.578	100.0000

2e



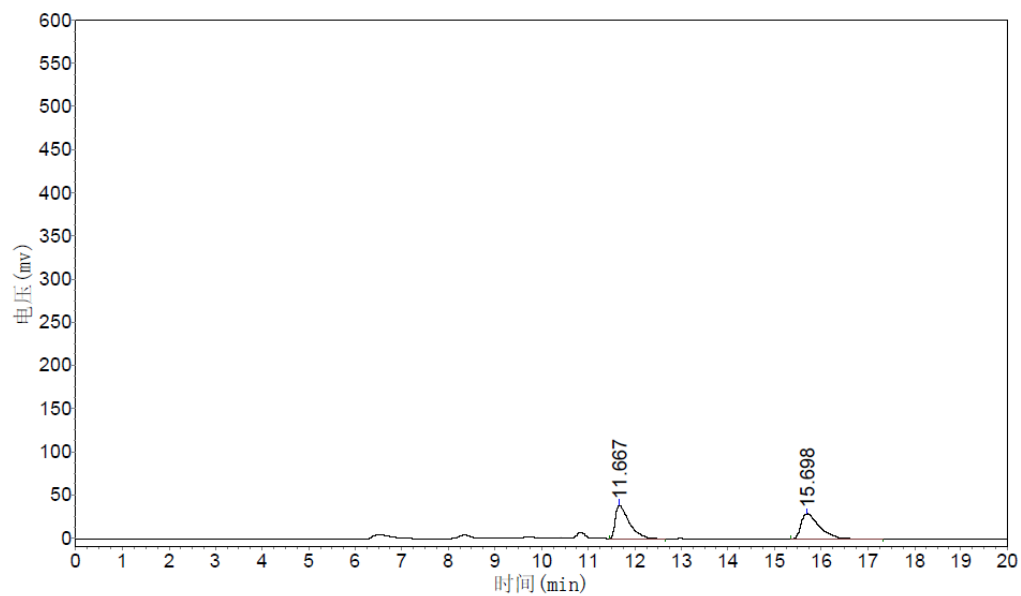
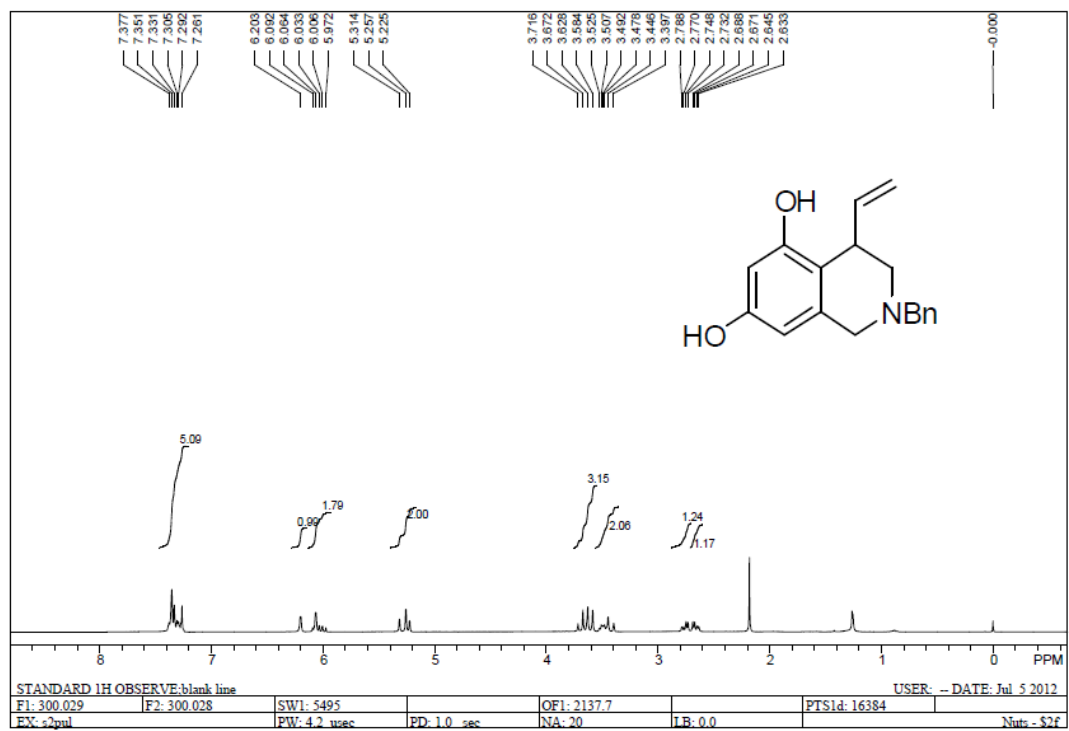


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	10.618	135844.109	1804174.125	49.9046
2	11.265	130447.852	1811074.000	50.0954
Total		266291.961	3615248.125	100.0000

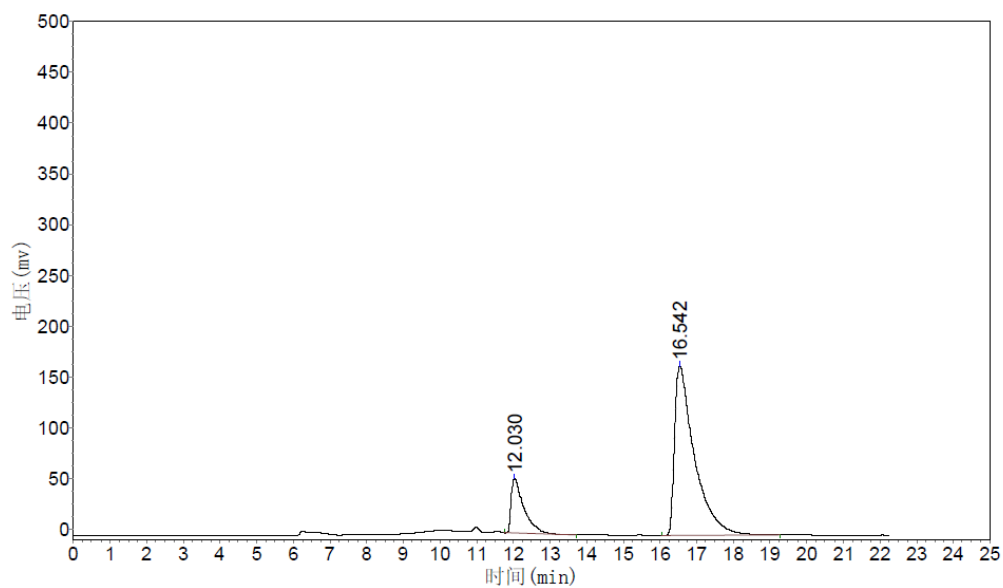


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	9.625	456211.594	7916918.500	96.1708
2	10.943	20820.307	315224.063	3.8292
Total		477031.900	8232142.563	100.0000

2f

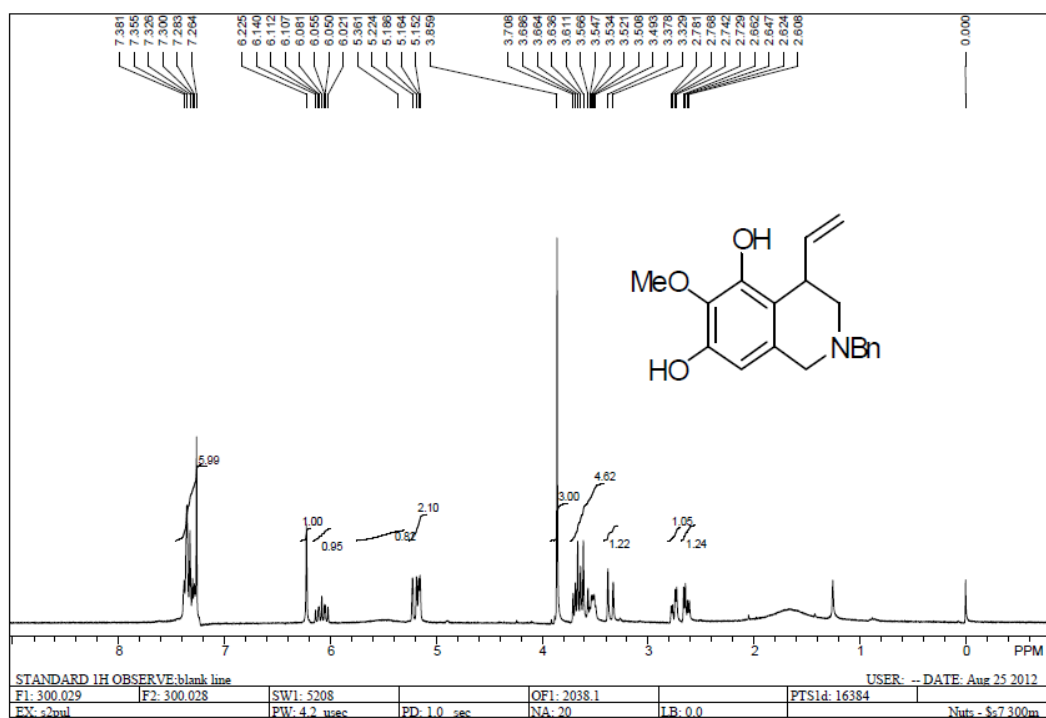


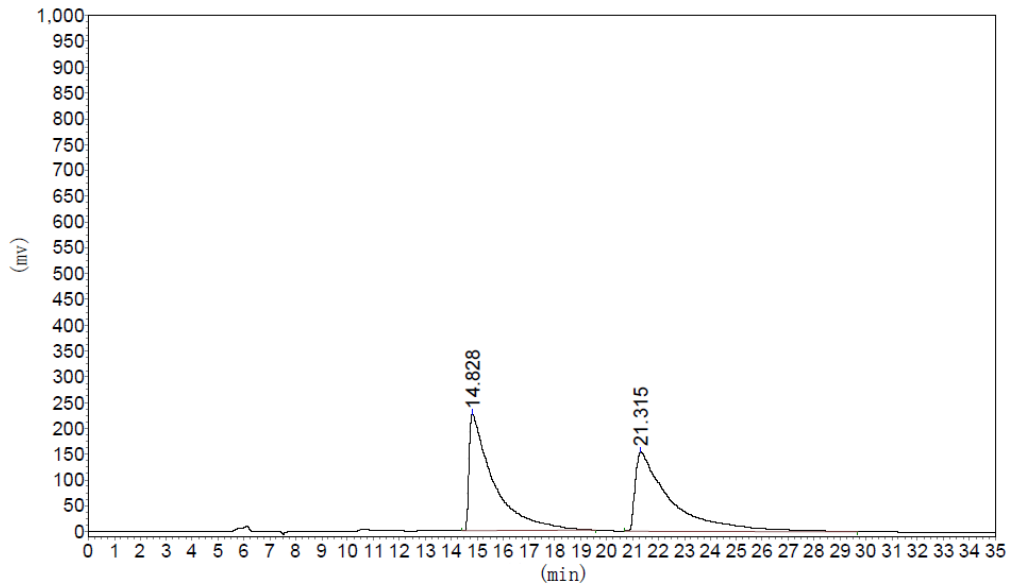
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	11.667	39163.109	811369.125	50.2230
2	15.698	29372.490	804162.688	49.7770
Total		68535.600	1615531.813	100.0000



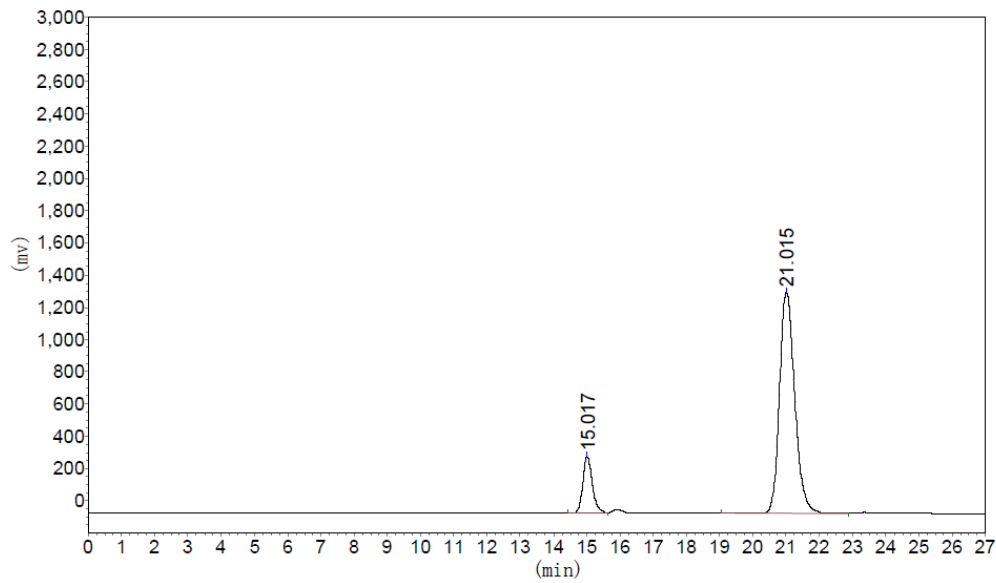
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	12.030	53682.711	1291634.250	17.0831
2	16.542	166665.719	6269235.500	82.9169
Total		220348.430	7560869.750	100.0000

2g



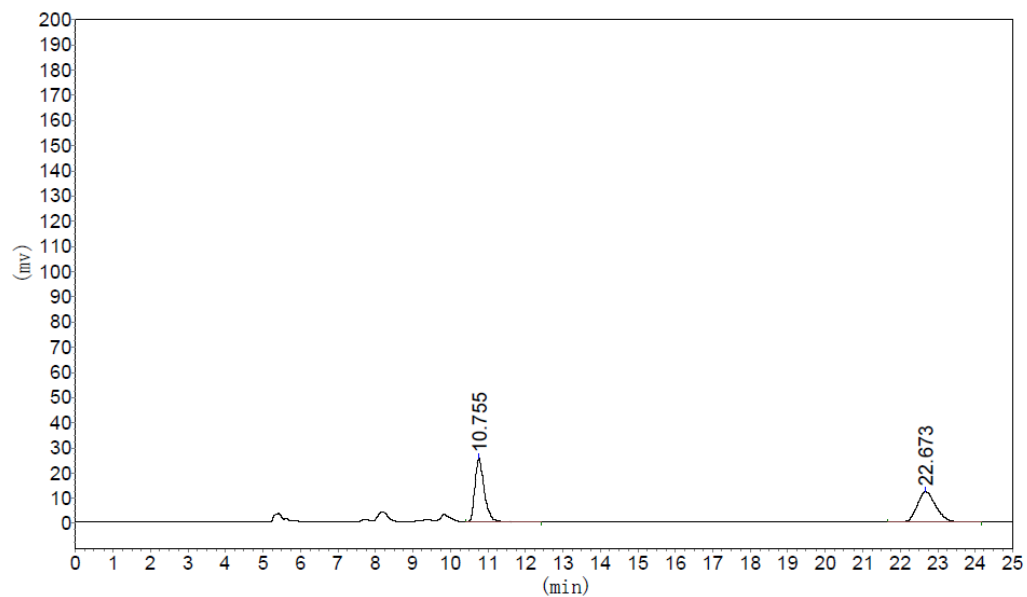
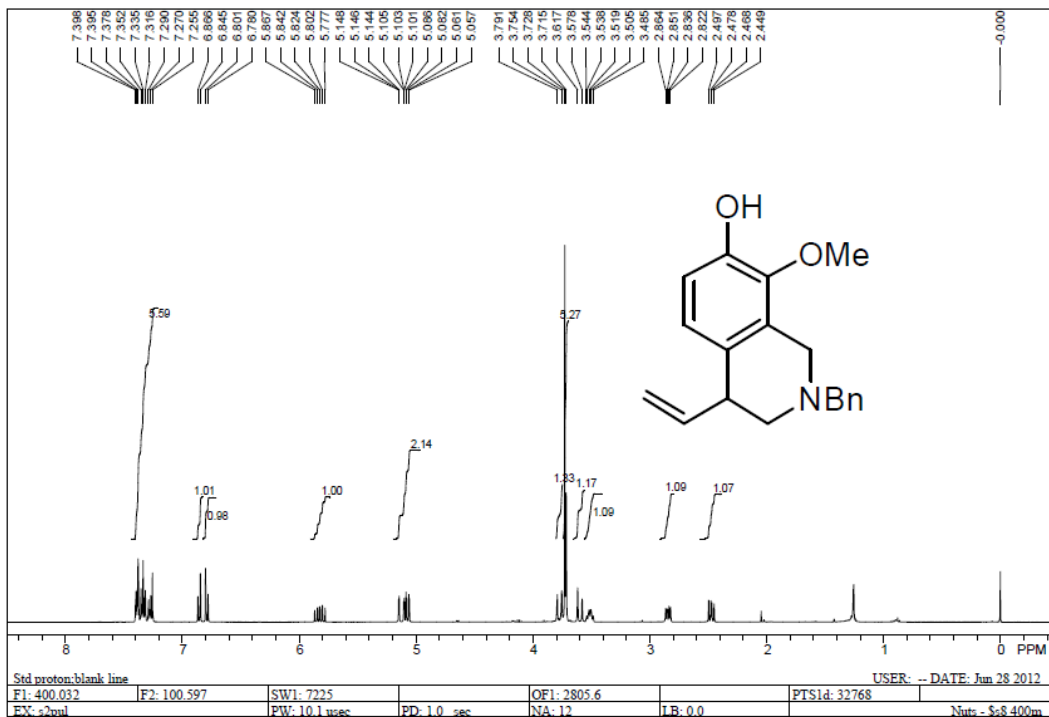


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.828	225774.078	14778660.000	50.6736
2	21.315	152538.938	14385764.000	49.3264
Total		378313.016	29164424.000	100.0000

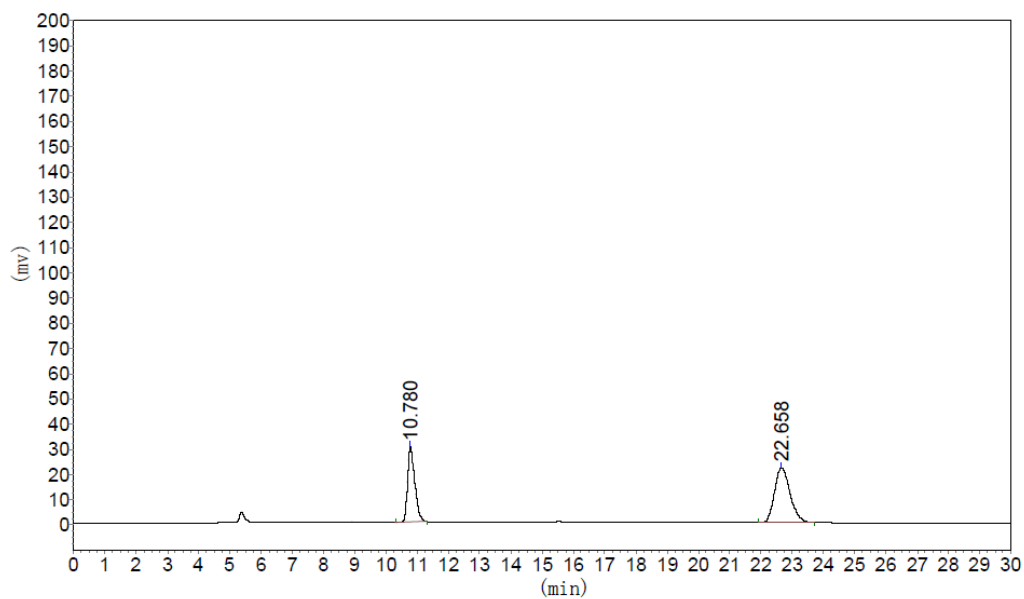


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	15.017	350631.406	7072797.000	13.8754
2	21.015	1371830.875	43900764.000	86.1246
Total		1722462.281	50973561.000	100.0000

3h

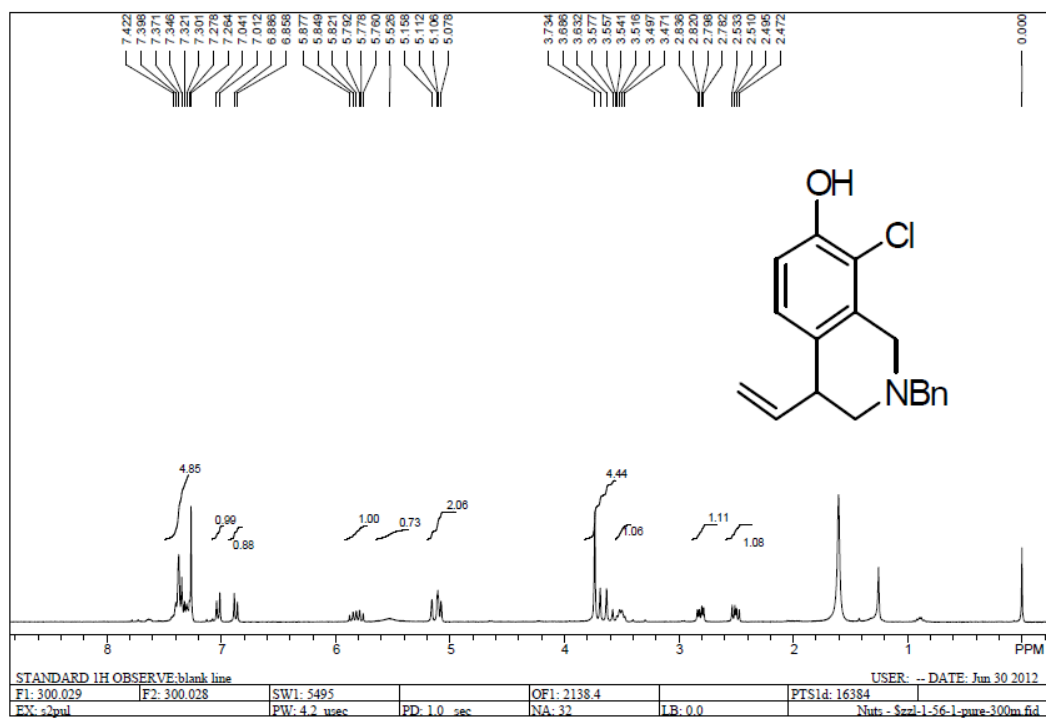


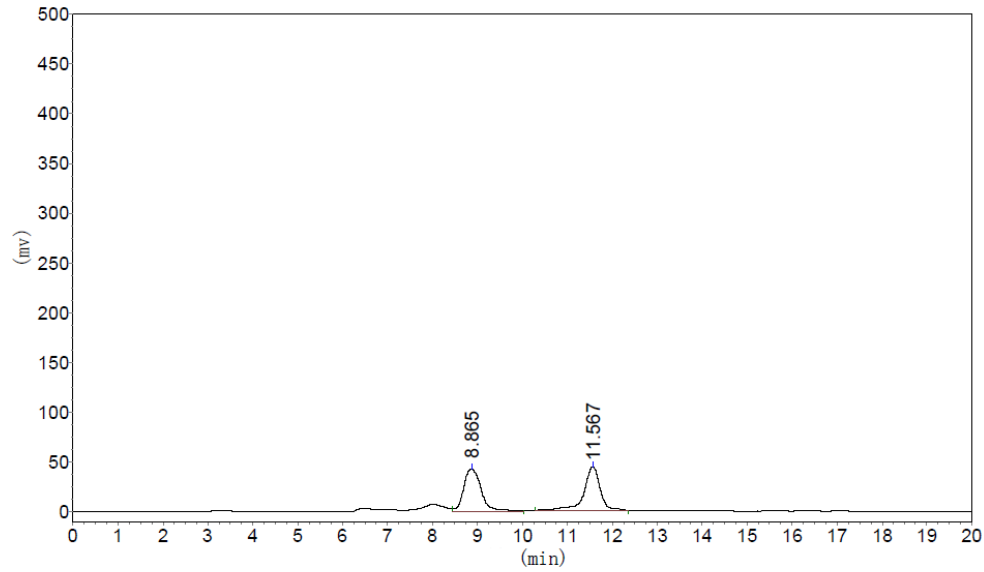
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	10.755	25401.350	444447.875	50.9432
2	22.673	12112.518	427990.094	49.0568
Total		37513.867	872437.969	100.0000



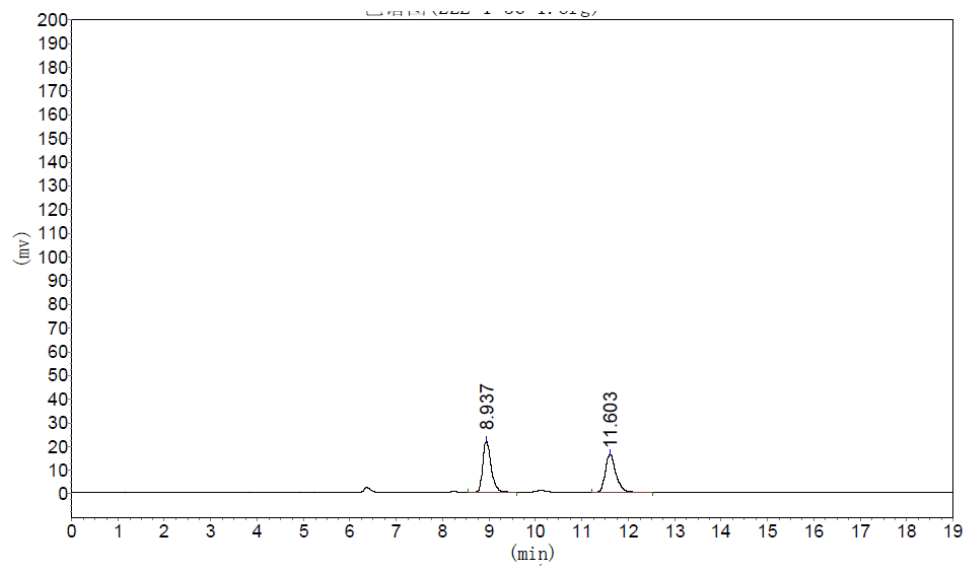
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	10.780	30051.648	483567.219	39.2321
2	22.658	21757.299	749013.188	60.7679
Total		51808.947	1232580.406	100.0000

3i



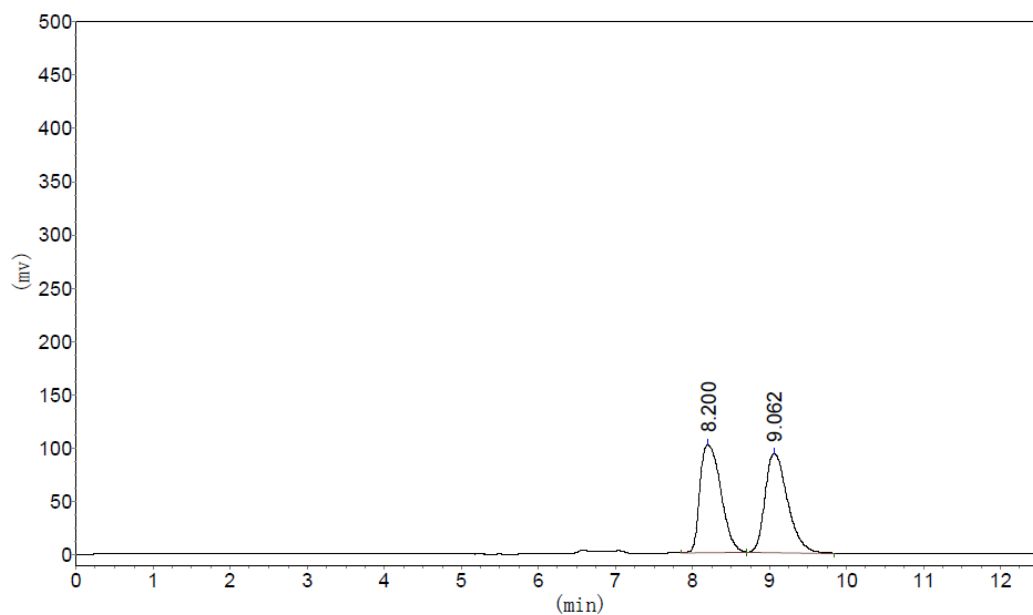
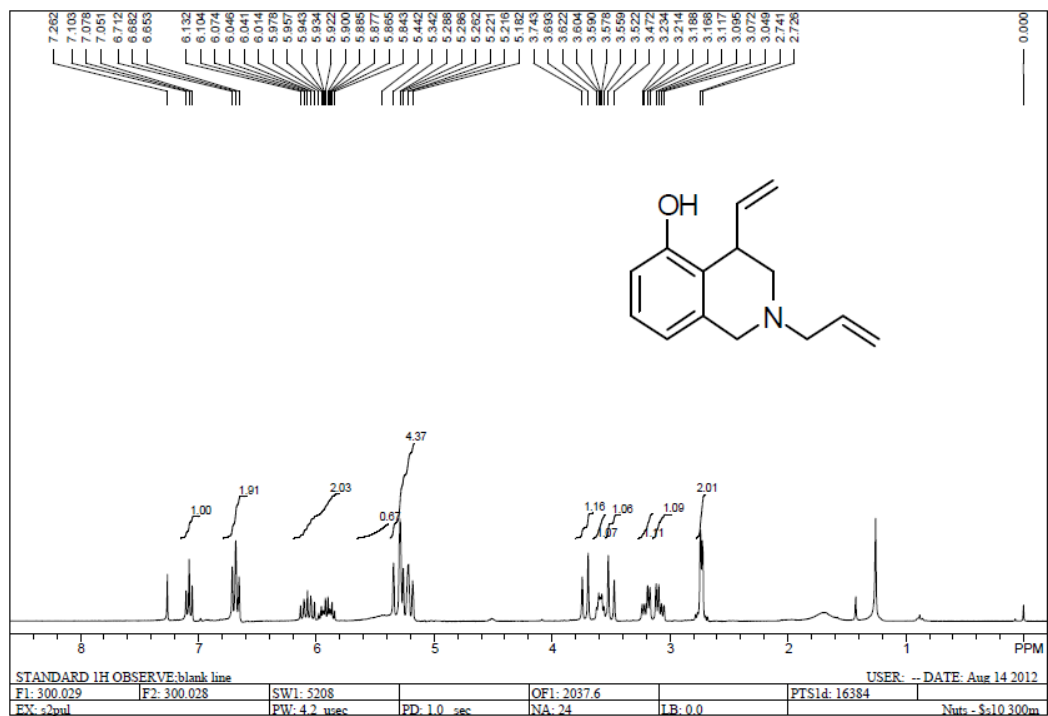


Peak No.	R. Time	Peak Height	Peak Area	Percent
1	8.865	42290.895	1126388.000	50.0740
2	11.567	44074.895	1123060.625	49.9260
Total		86365.789	2249448.625	100.0000

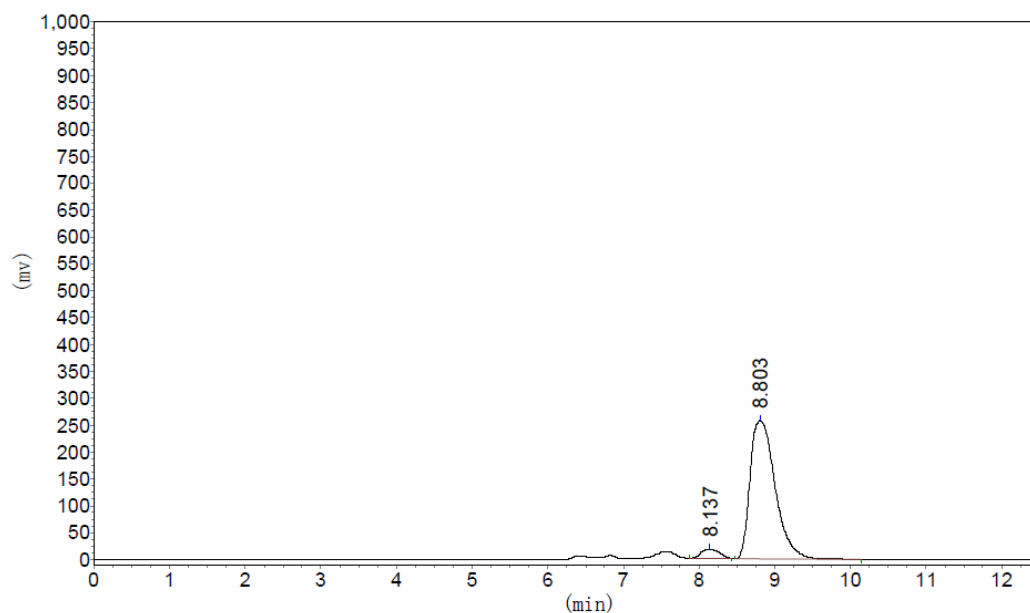


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1	8.937	21595.457	269102.281	51.6510
2	11.603	16003.080	251898.359	48.3490
Total		37598.537	521000.641	100.0000

2j

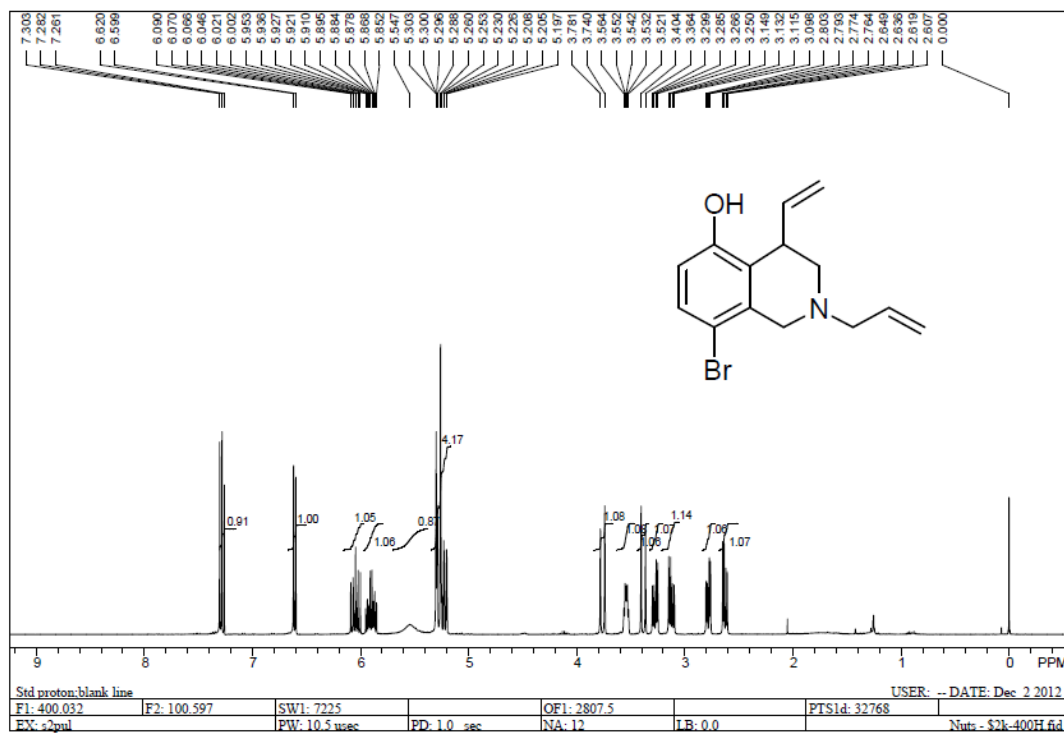


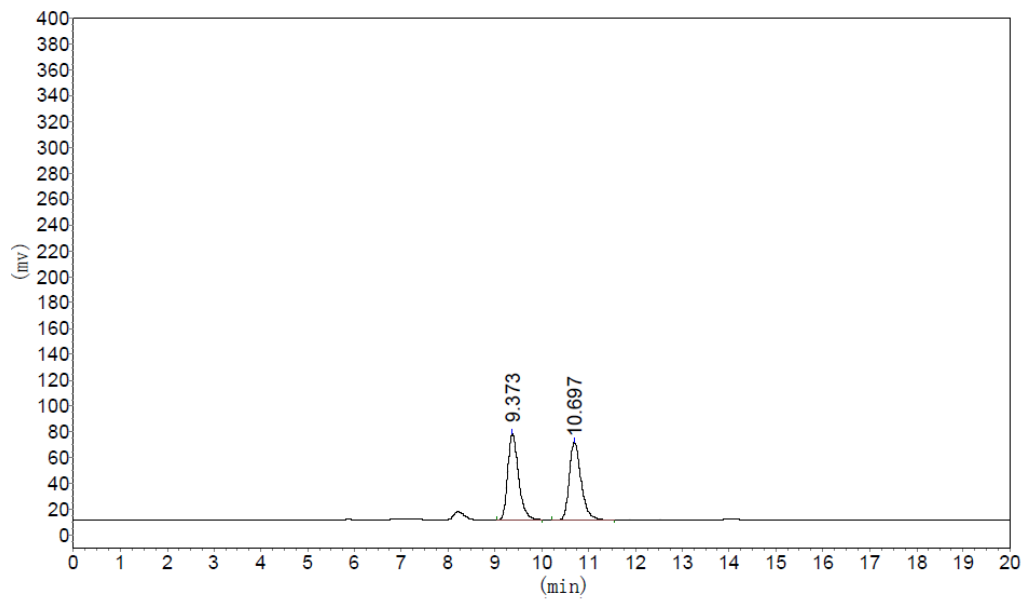
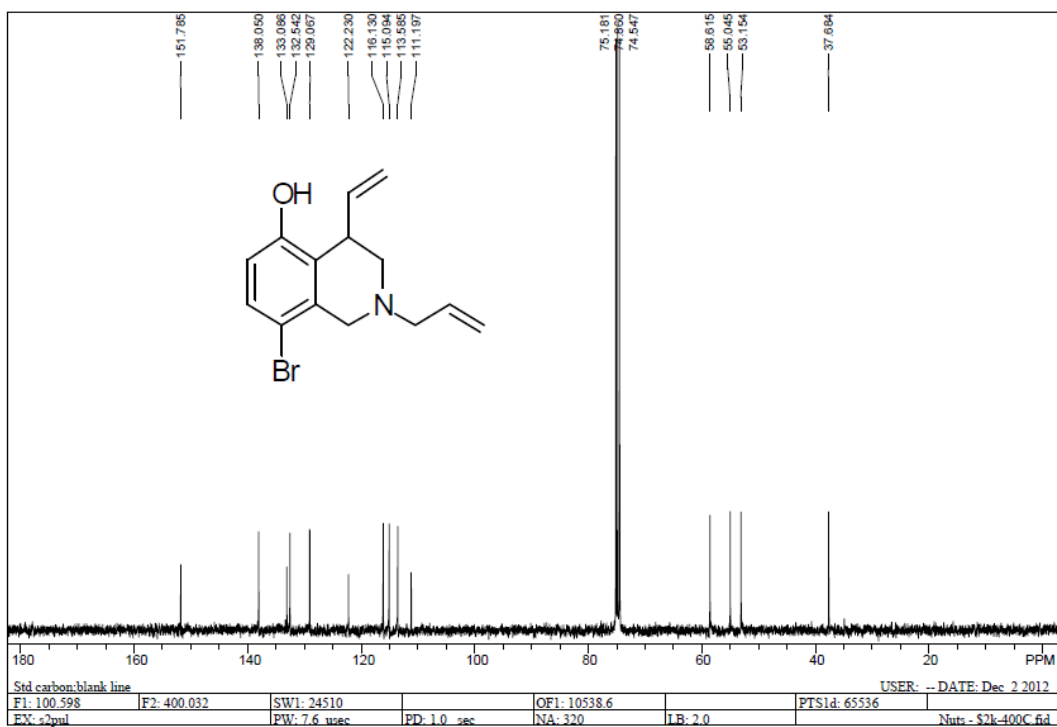
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	8.200	101251.406	1897255.625	50.1748
2	9.062	92674.672	1884033.625	49.8252
Total		193926.078	3781289.250	100.0000



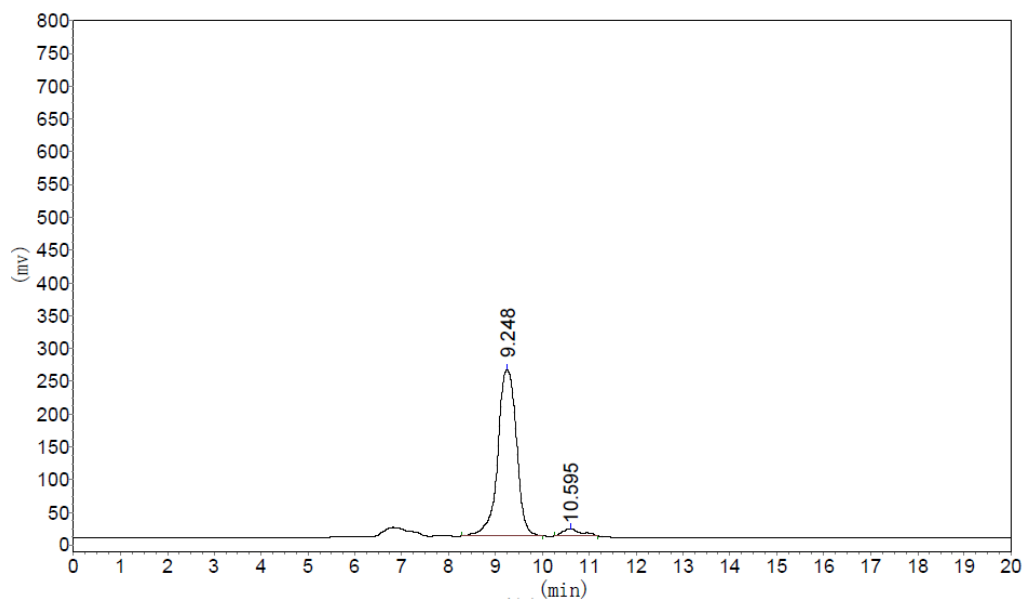
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	8.137	16194.304	277860.406	4.4988
2	8.803	256949.531	5898503.000	95.5012
Total		273143.835	6176363.406	100.0000

2k



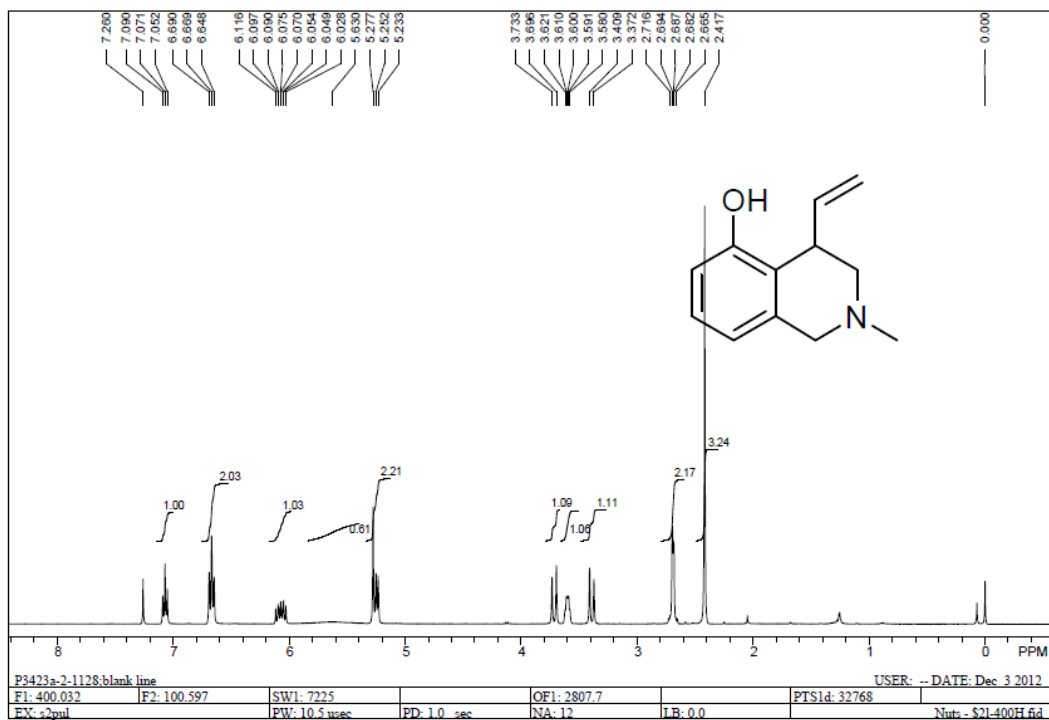


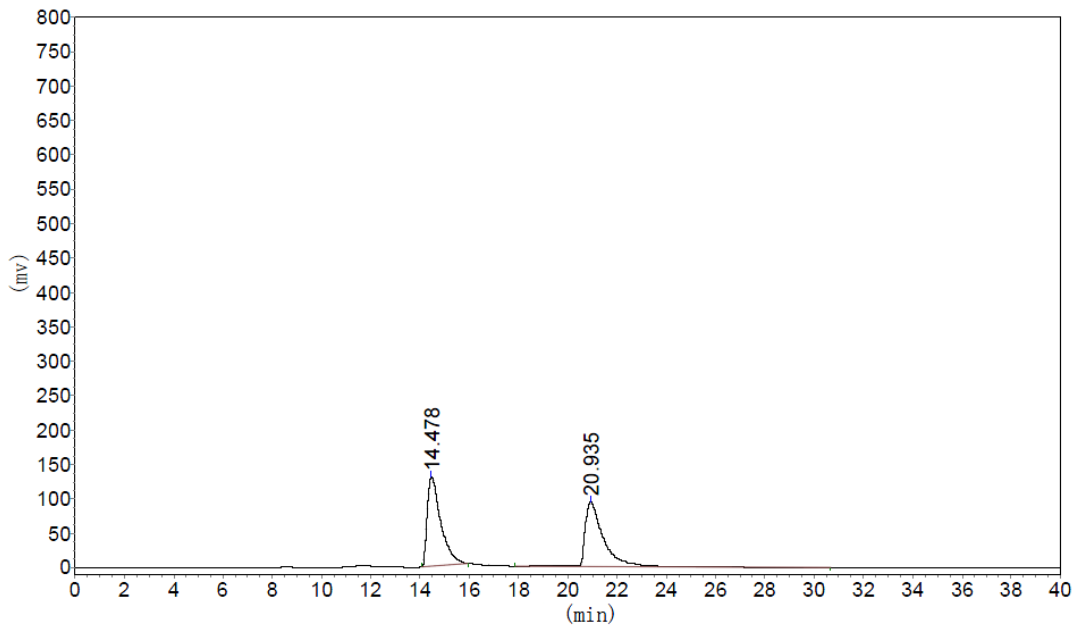
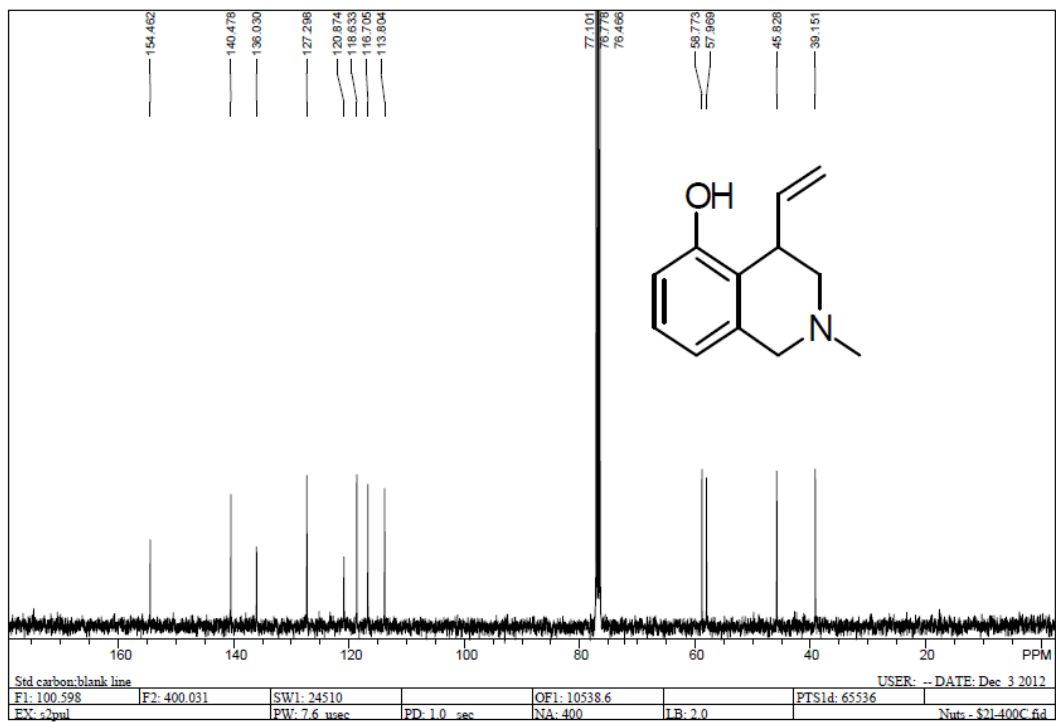
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	9.373	66231.359	1055711.375	50.0400
2	10.697	59720.484	1054022.750	49.9600
Total		125951.844	2109734.125	100.0000



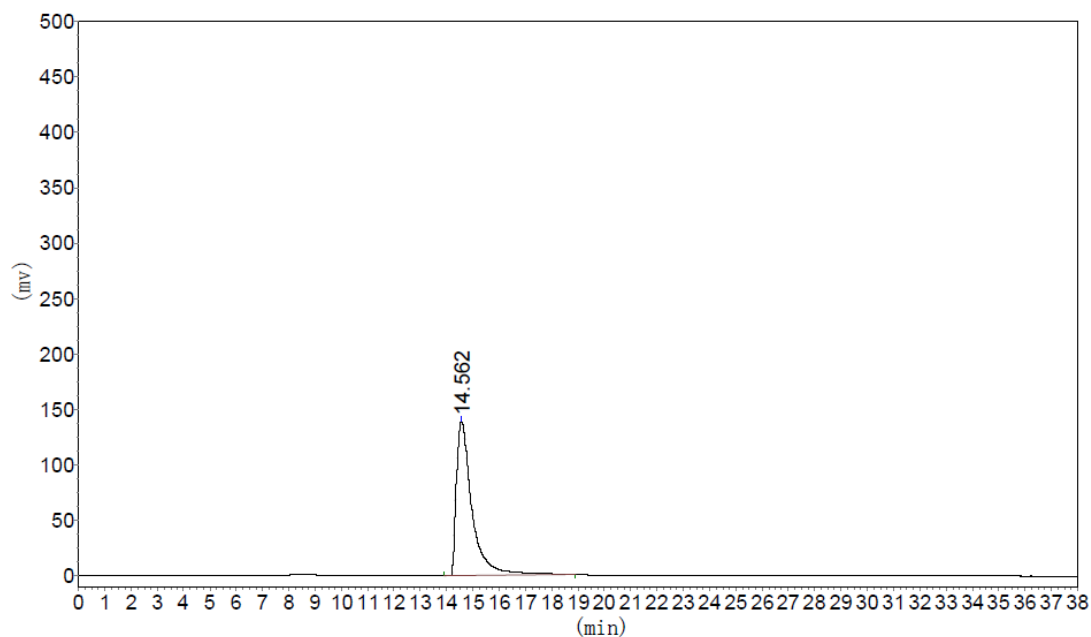
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	9.248	253410.250	6957067.500	96.1478
2	10.595	10199.615	278739.594	3.8522
Total		263609.865	7235807.094	100.0000

21



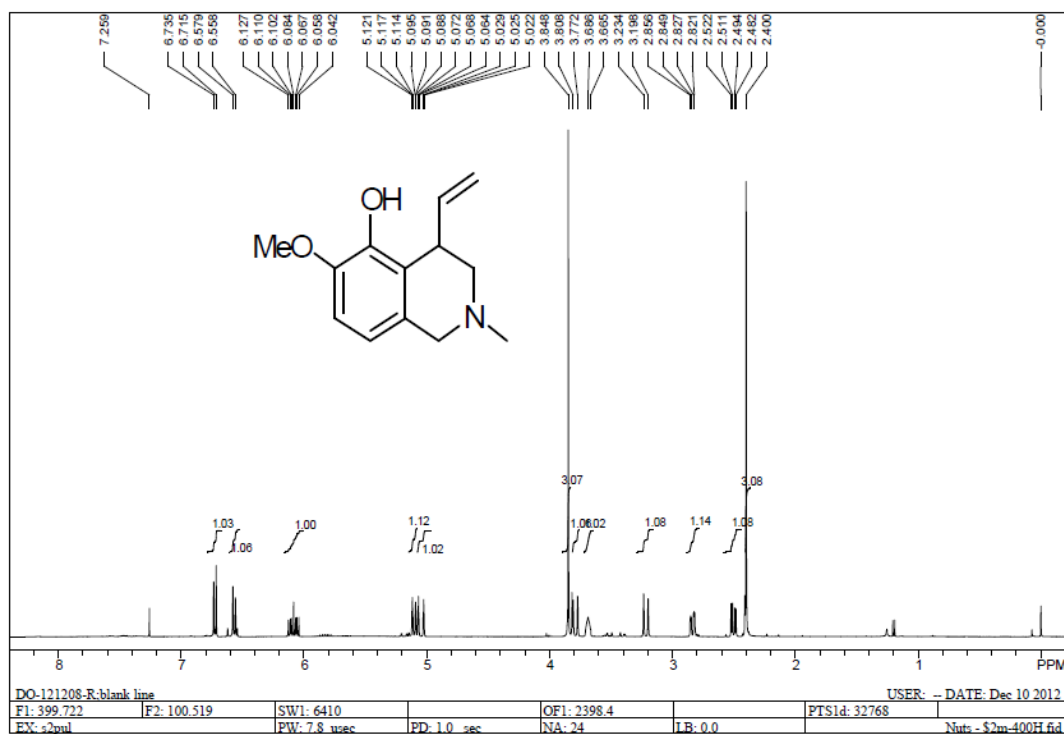


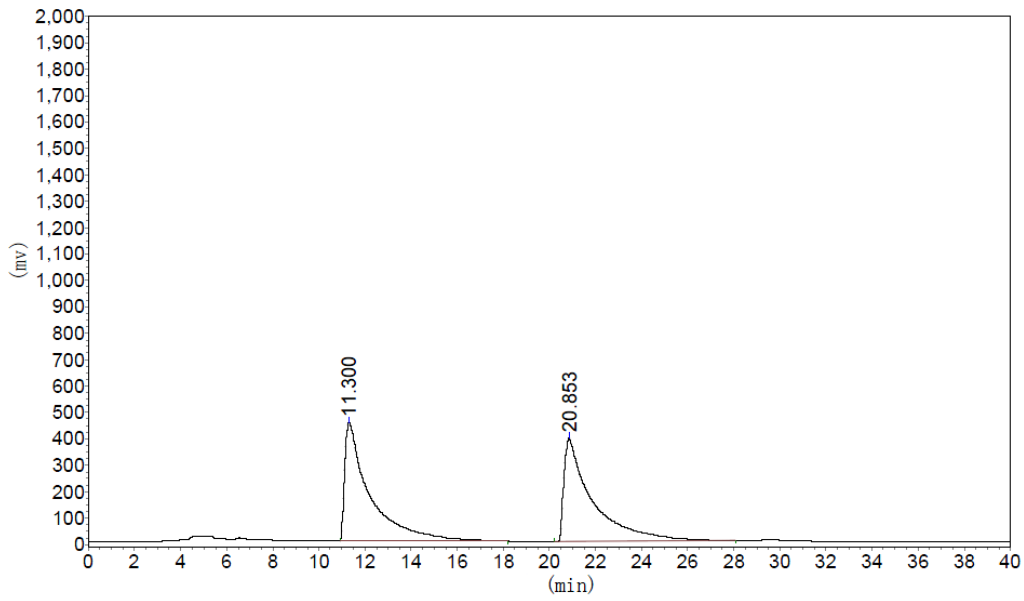
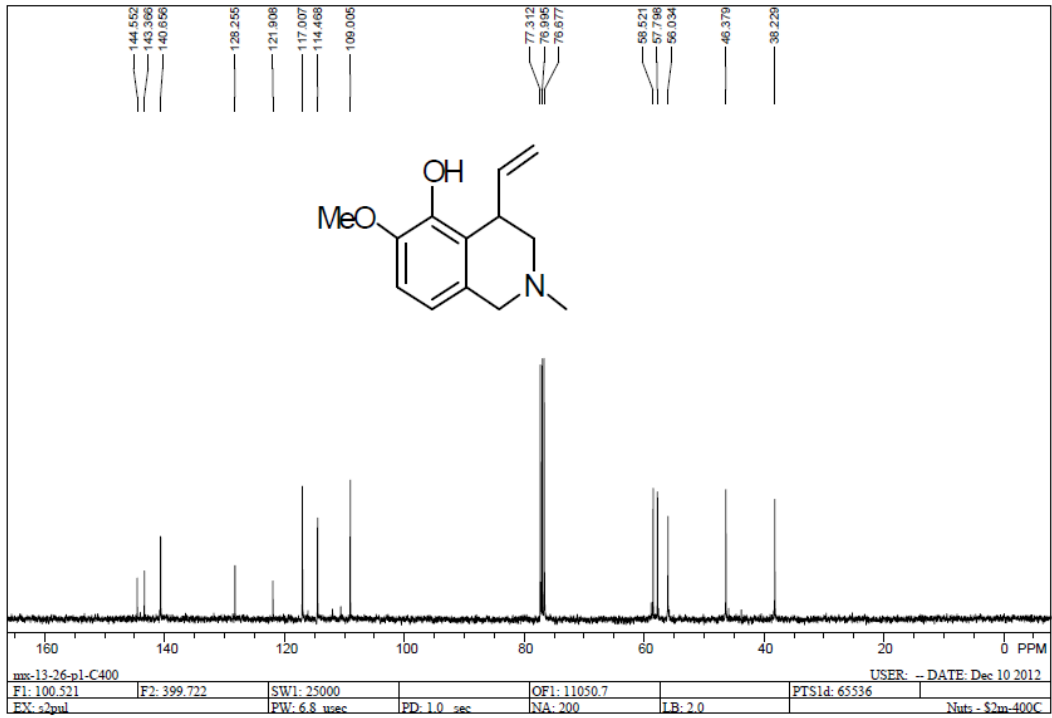
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.478	129253.047	4962077.500	50.8697
2	20.935	93473.320	4792417.000	49.1303
Total		222726.367	9754494.500	100.0000



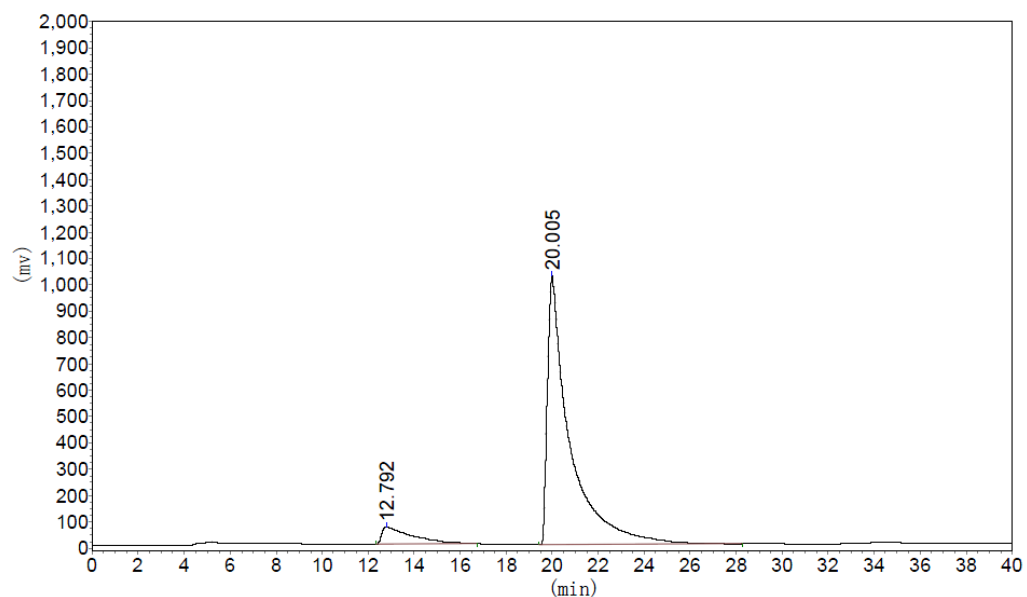
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.562	139288.547	5790752.000	100.0000
Total		139288.547	5790752.000	100.0000

2m



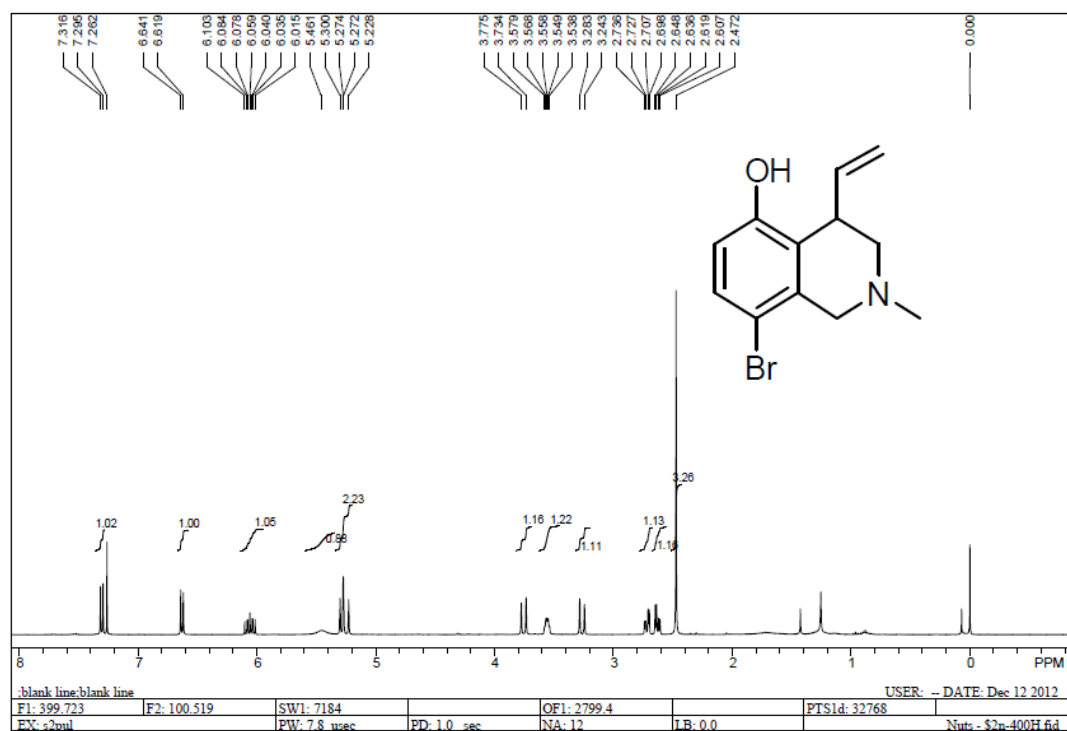


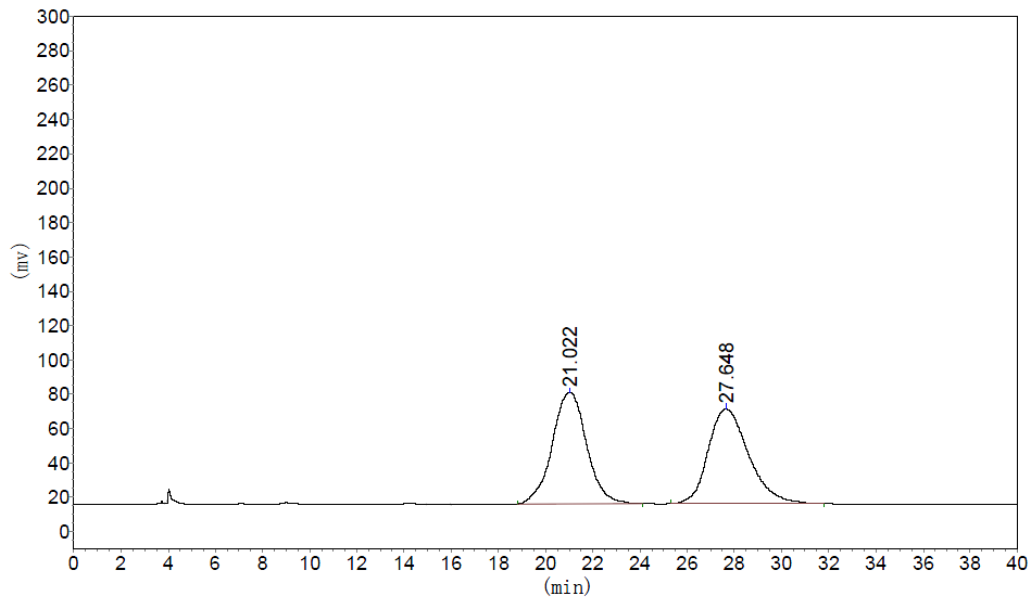
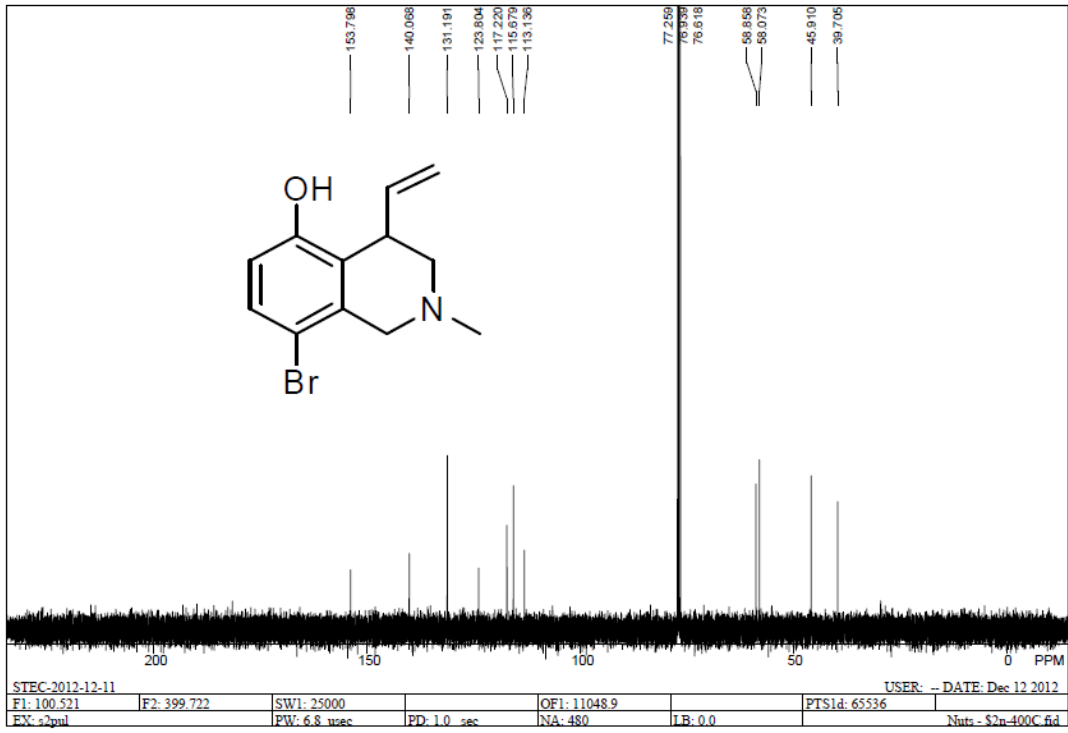
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	11.300	448902.844	33978716.000	50.3657
2	20.853	392255.313	33485298.000	49.6343
Total		841158.156	67464014.000	100.0000



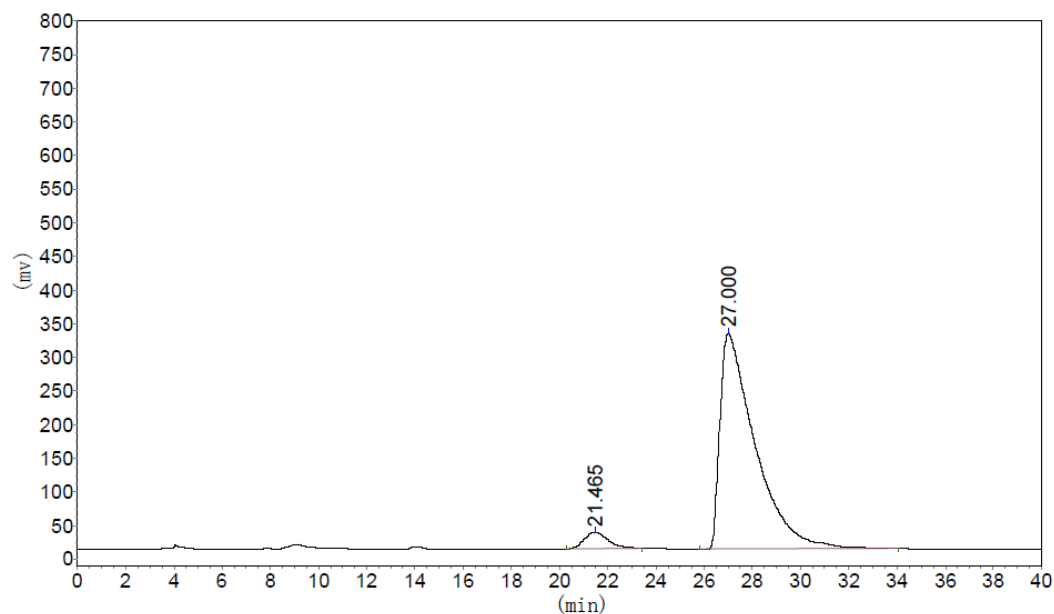
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	12.792	64345.637	5984864.000	8.0115
2	20.005	1019144.938	68718920.000	91.9885
Total		1083490.574	74703784.000	100.0000

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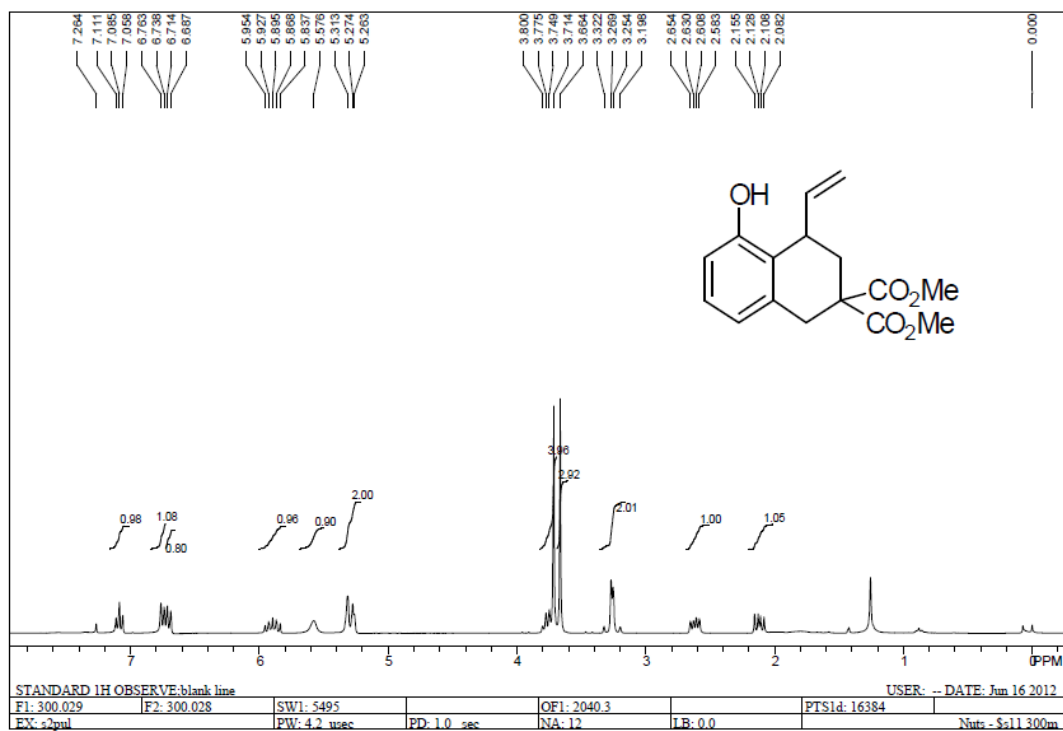


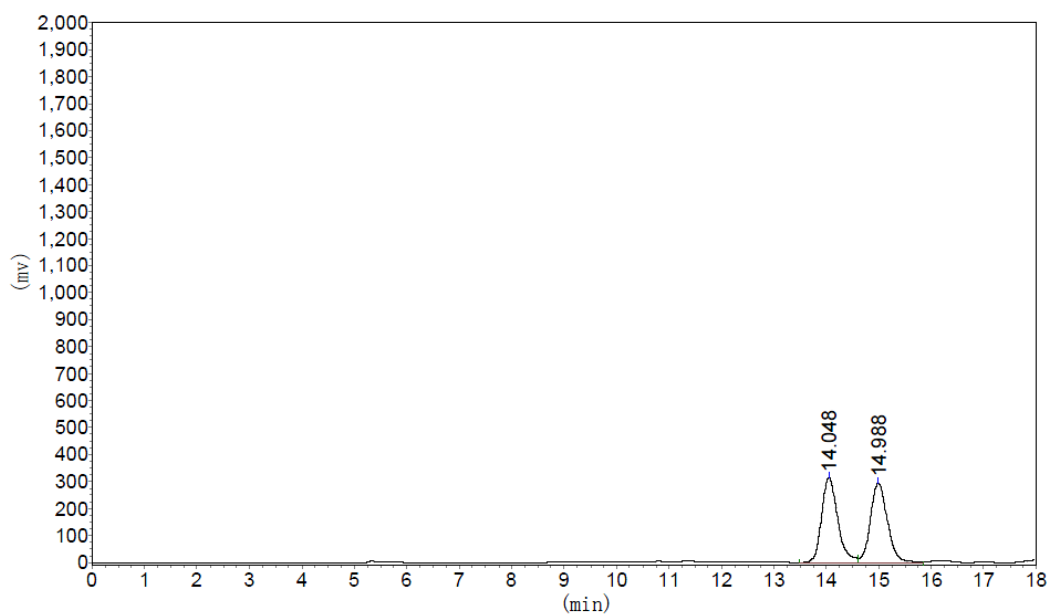
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	21.022	64812.734	6559499.500	50.0824
2	27.648	55035.203	6537922.000	49.9176
Total		119847.938	13097421.500	100.0000



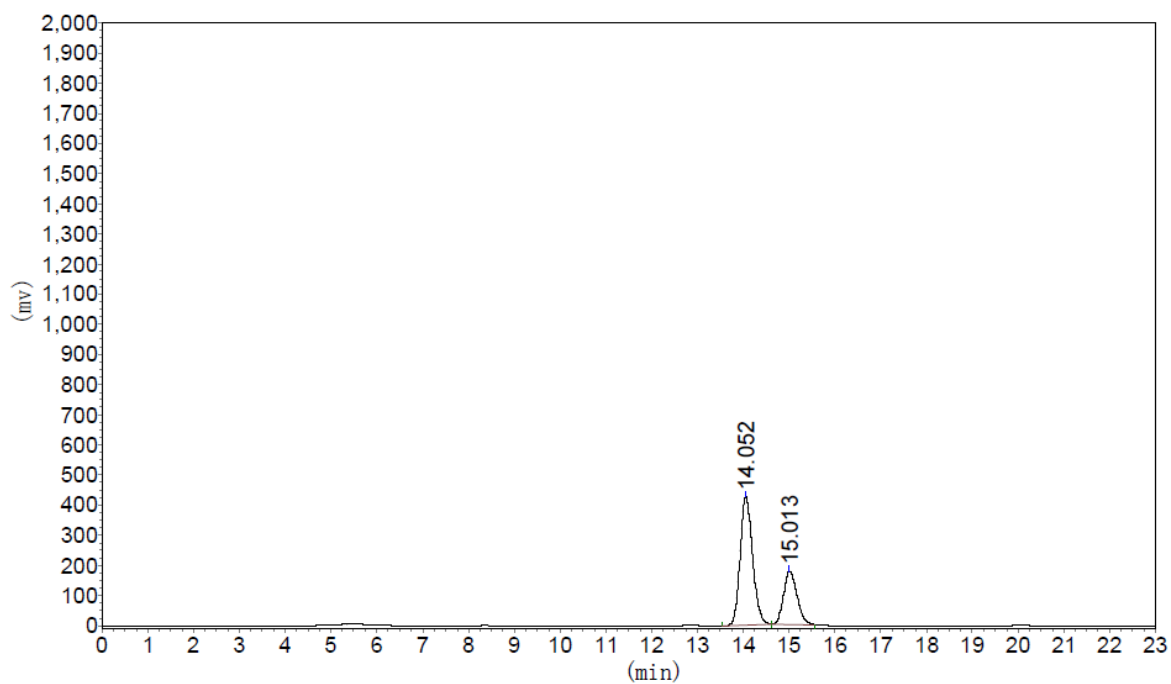
Peak No.	R. Time	Peak Height	Peak Area	Percent
1	21.465	24167.959	1636739.000	4.8379
2	27.000	319349.500	32194760.000	95.1621
Total		343517.459	33831499.000	100.0000

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Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.048	314464.906	6720794.000	50.4646
2	14.988	294460.781	6597050.500	49.5354
Total		608925.688	13317844.500	100.0000



Peak No.	R. Time	Peak Height	Peak Area	Percent
1	14.052	424222.844	8023370.000	69.1368
2	15.013	177128.672	3581699.500	30.8632
Total		601351.516	11605069.500	100.0000