Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Enantioselective Organocatalytic Oxyamination of Unprotected 3-Substituted Oxindoles

Xavier Companyó, Guillem Valero, Oriol Pineda, Teresa Calvet, Mercè Font-Bardía, Albert Moyano, Ramon Rios

Supporting Information: Details on the theoretical calculation of the ECD spectrum of compound (*S*)-**3a**. Copies of the ^{1}H and ^{13}C NMR spectra, and HPLC traces of compounds **3a**-**3i**. (TUC = Takemoto's thiourea catalyst **IX**)

Theoretical determination of the ECD spectrum of compound (*S*)-**3a**.

In the first place, we set out to examine the conformational preferences of this compound. Since the X-ray diffraction structure of enantiopure **3a** had shown the presence, in the solid state, of hydrogen bonding between the hydroxylamine moiety and the oxyndole carbonyl, we modelized and optimized a conformer having an intramolecular hydrogen bond (that will subsequently be referred to as conformer A), using DFT[1] at the B3LYP/6-31G(d)[2] level (Figure SI-1).

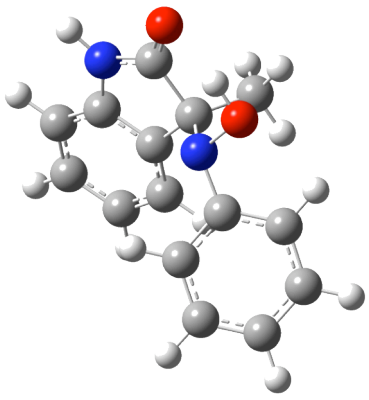


Figure SI-1. Conformer A (with intramolecular hydrogen bonding) of (*S*)-**3a**, calculated at the B3LYP/6-31G(d) level.

We decided next to explore the conformational space of **3a** at the same computational level. A systematic search, starting from conformer A, revealed the existence of two other stable conformers, B and C, without hydrogen bonding between the hydroxylamino and the carboxamide moities (Figures SI-2 and SI-3, respectively).

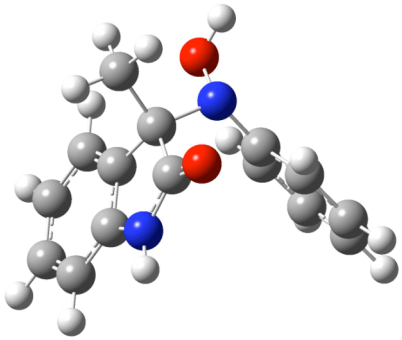


Figure SI-2. Conformer B of (*S*)-**3a**, calculated at the B3LYP/6-31G(d) level.

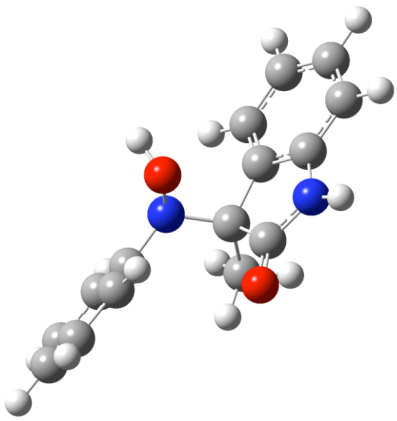


Figure SI-3. Conformer C of (*S*)-**3a**, calculated at the B3LYP/6-31G(d) level.

These three structures were then optimized in methanol solution by using a solvation simulation (Self-Consistent Reaction Field/Polarized Continuum Model, SCRF-PCM)[3] both at the B3LYP/6-31G(d) and at the B3LYP/6-31 + G(d) levels of theory. Since it has been shown that DFT functionals are not suitable for describing weak interactions between groups,[4] and that the use of Truhlar's parametrized M0X functionals or of MP2 methods gives more accurate results,[5] single-point calculations of the energy using these optimized geometries were next performed at the MP2/6-31G(d) and at the MP2/6-31 + G(d)

levels of theory, both in the gas phase and in methanol solution. After correction for ZPE, MP2 relative energies were compared, and conformer populations at 298 K were calculated assuming Maxwell-Boltzmann statistics. The results of these calculations are summarized in Table SI-1.

Table SI-1. Relative energies and populations (at 298 K) of conformers A, B and C of compound **3a**, calculated at different levels of theory.

Entry	Calculation level	Conformation	Rel. Energy (kcal mol^{-1})	Population
1	MP2/6-31G(d)	A	0.60	25.9%
		B	0.00	65.5%
		C	1.30	8.6%
2	MP2/6-31+G(d)	A	1.96	4.4%
		B	0.00	92.6%
		C	2.21	3.0%
3	MP2/6-31G(d)–CH_3OH	A	3.34	0.5%
		B	0.00	85.2%
		C	1.15	14.3%
4	MP2/6-31+G(d)–CH_3OH	A	3.37	0.5%
		B	**0.00**	**96.4%**
		C	2.21	3.1%

In all instances conformation B was the more stable one, and its relative stability increased both with the introduction of diffuse functions (entry 2) and with the solvation simulation (entries 3 and 4). At the highest level of calculation (entry 4), the estimated population of conformer B is higher than 96%; moreover, the calculated geometry of B is very similar to that of enantiopure **3a** in the solid state (compare Figure SI-2 with Figure 3 of the article). This conformation was thus used in a time-dependent DFT calculation, at the B3LYP/6-311++G(d,p) level, to simulate the ECD.

[1] Gaussian 0.9, Revision A 02, M. J. Frisch *et al.*, Gaussian, Inc., Wallingford CT, **2009**.

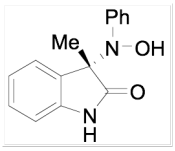
[2] a) A. D. Becke, *J. Chem. Phys.* 1993, **98**, 5648-5652; b) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B* 1988, **37**, 785-790; c) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* 1994, **98**, 11623-11627.

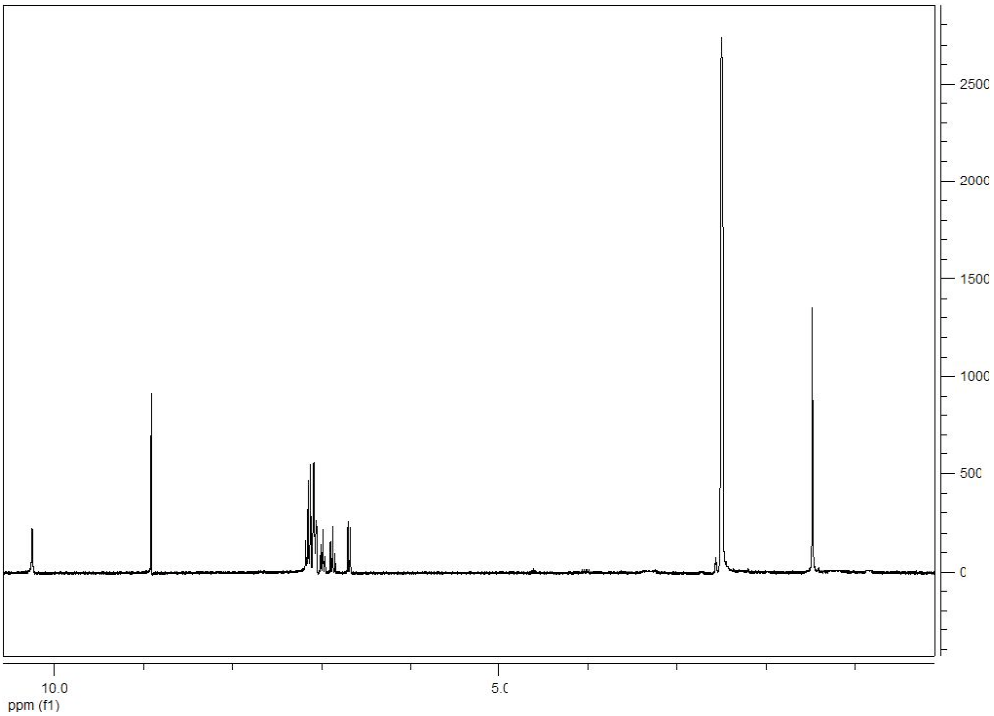
[3] a) S. Miertus and J. Tomasi, *Chem. Phys.* 1982, **65**, 239-245; b) S. Miertus, E. Scrocco and J. Tomasi, *Chem. Phys.* 1981, **55**, 117-129.

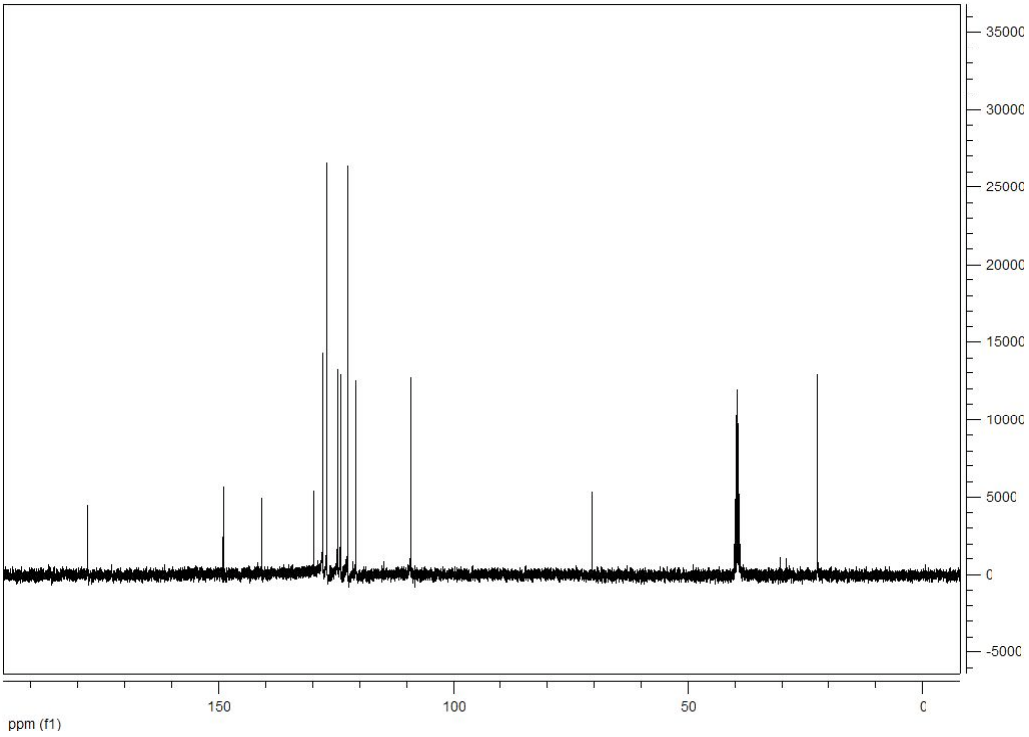
[4] a) Y. Zhao and D. G. Truhlar, *J. Chem. Theory Comput.* 2007, **3**, 289-300. b) Y. Zhao and D. G. Truhlar, *J. Chem. Theory Comput.* 2005, **1**, 415-432. c) Y. Zhao and D. G. Truhlar, *Phys. Chem. Chem. Phys.* 2005, **7**, 2701-2705.

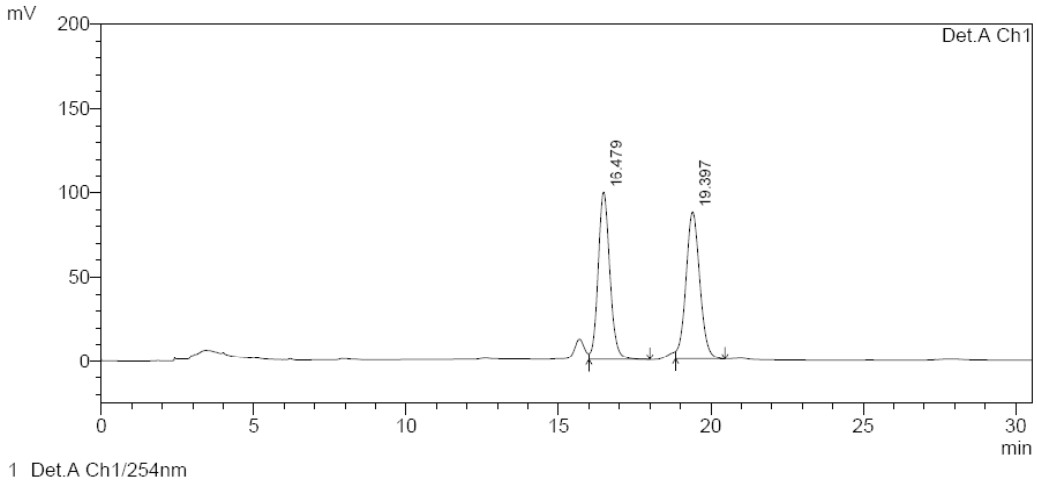
[5] a) J. Zheng, Y. Zhao and D. G. Truhlar, *J. Chem. Theory Comput.* 2007, **3**, 569-582. b) P. H.-Y. Cheong, C. Y. Legault, J. M. Um, N. Çelebi-Ölçüm and K. N. Houk, *Chem. Rev.* 2011, **111**, 5042-5137.

3a







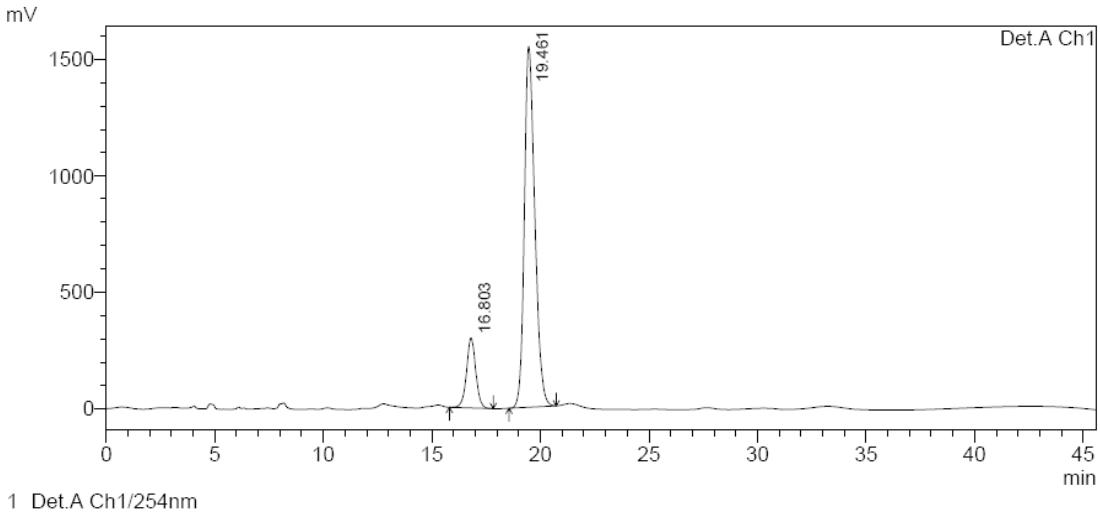


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.479	2661215	99220	49.107	53.270
2	19.397	2758051	87037	50.893	46.730
Total		5419265	186258	100.000	100.000

(*S*,*S*)-TUC

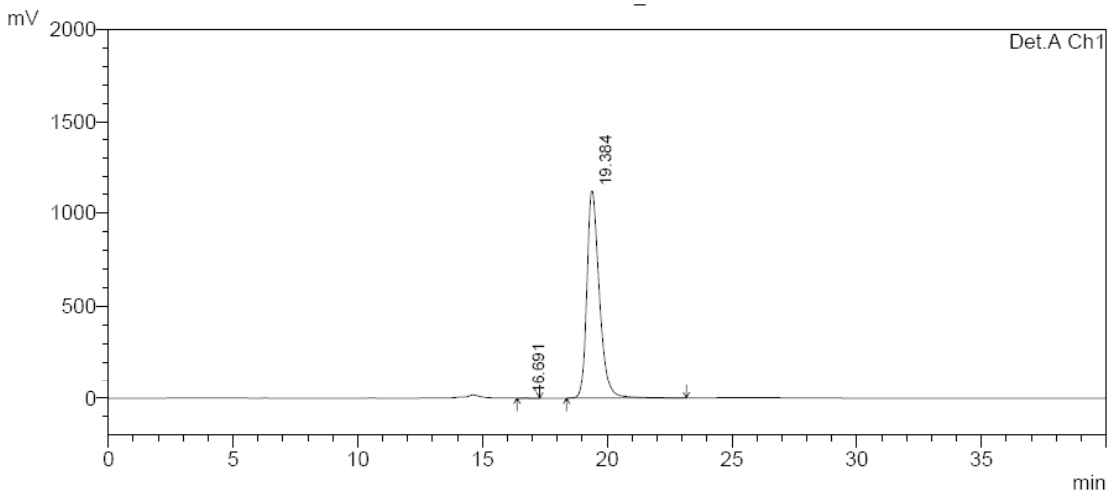


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.803	8945572	303257	14.718	16.379
2	19.461	51836046	1548277	85.282	83.621
Total		60781619	1851534	100.000	100.000

(*S,S*)-TUC (filtration)



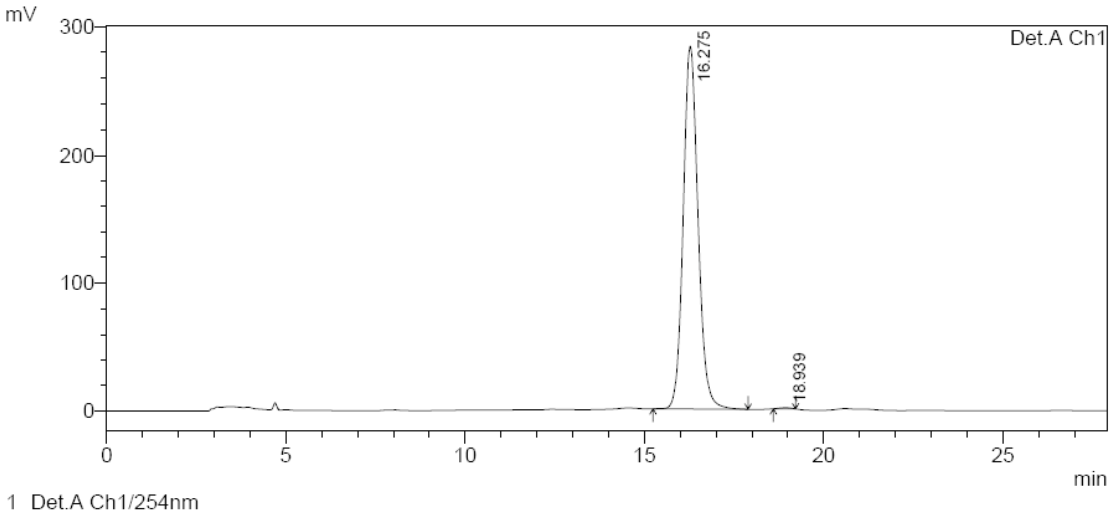
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.691	2693	115	0.007	0.010
2	19.384	38980607	1123195	99.993	99.990
Total		38983300	1123310	100.000	100.000

(*R,R*)-TUC



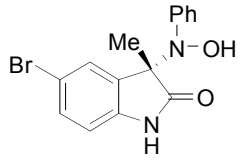
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.275	8153975	283458	99.752	99.670
2	18.939	20312	939	0.248	0.330
Total		8174287	284397	100.000	100.000

3b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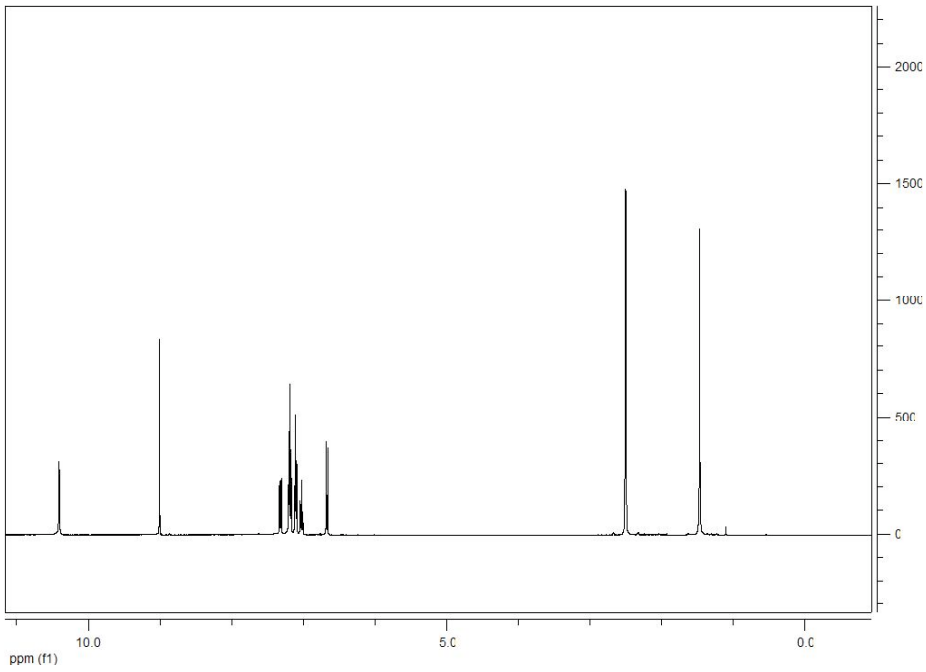
O
N
H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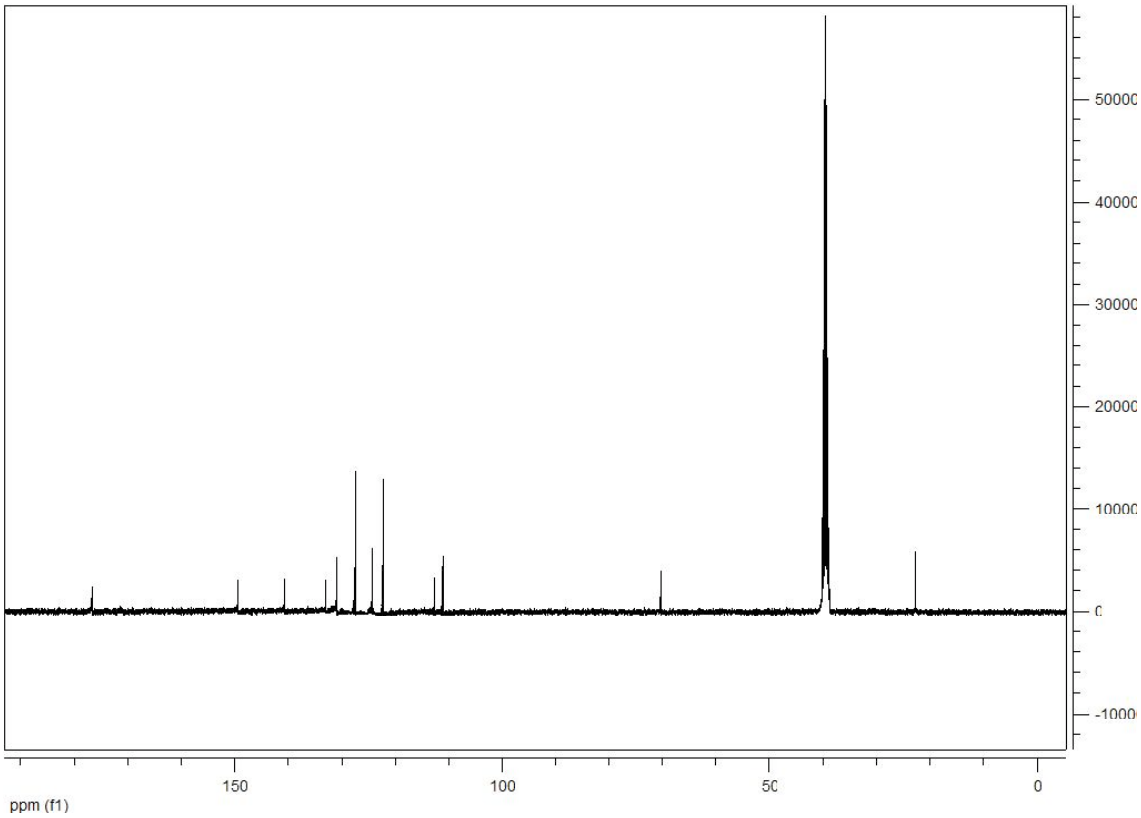
ppm (f1)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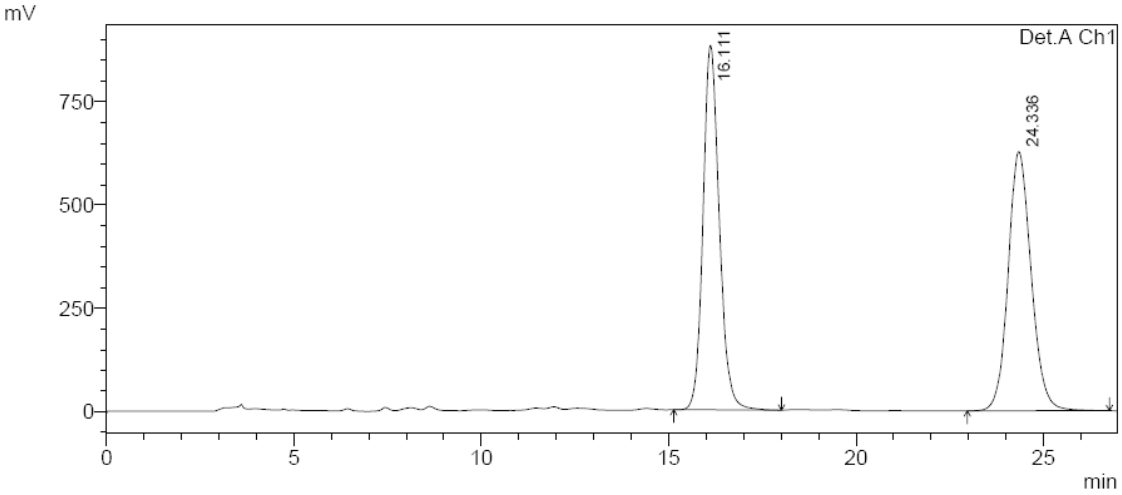


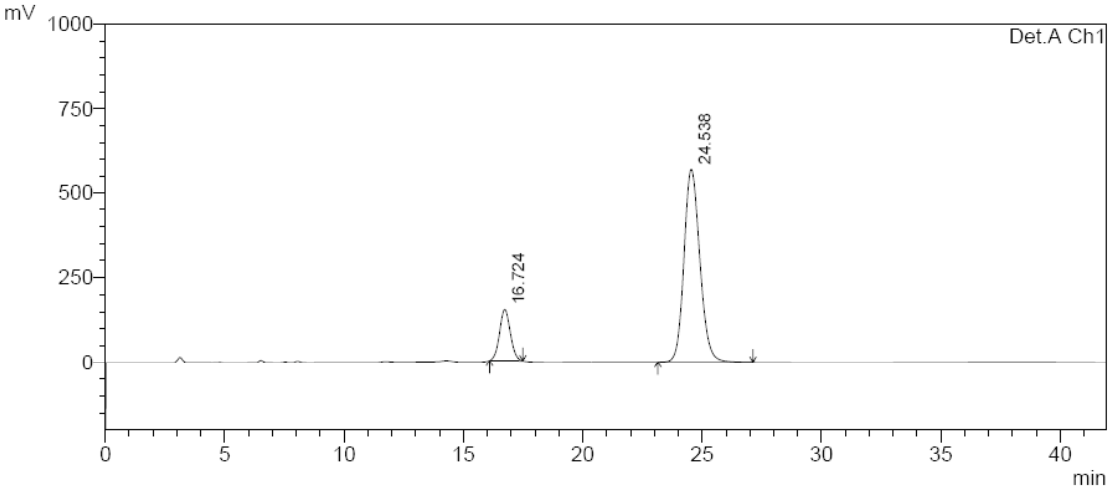
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.111	26655036	881970	49.720	58.361
2	24.336	26955521	629261	50.280	41.639
Total		53610556	1511231	100.000	100.000

(*S*,*S*)-TUC



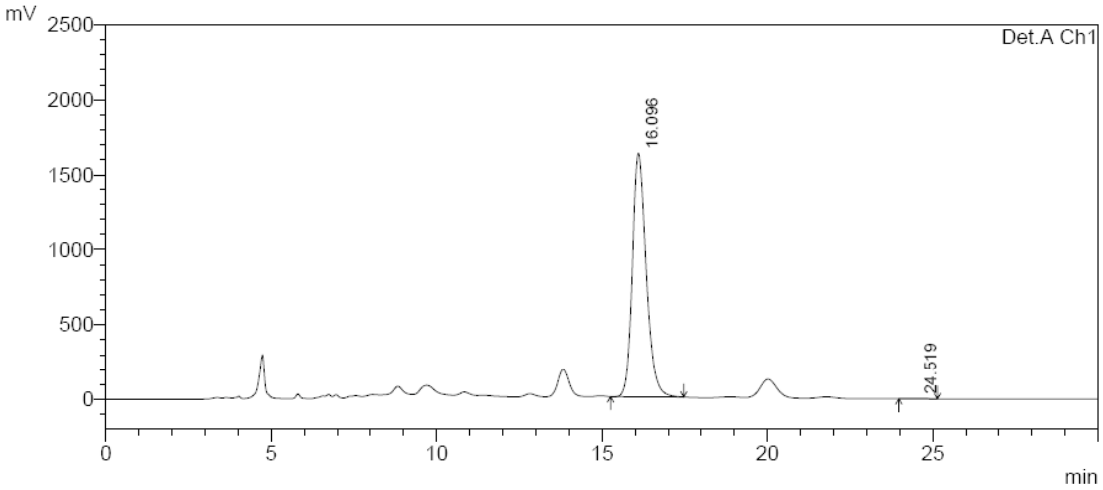
1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.724	4769431	151255	15.329	20.964
2	24.538	26345238	570239	84.671	79.036
Total		31114669	721493	100.000	100.000

(*R*,*R*)-TUC



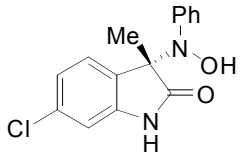
1 Det.A Ch1/254nm

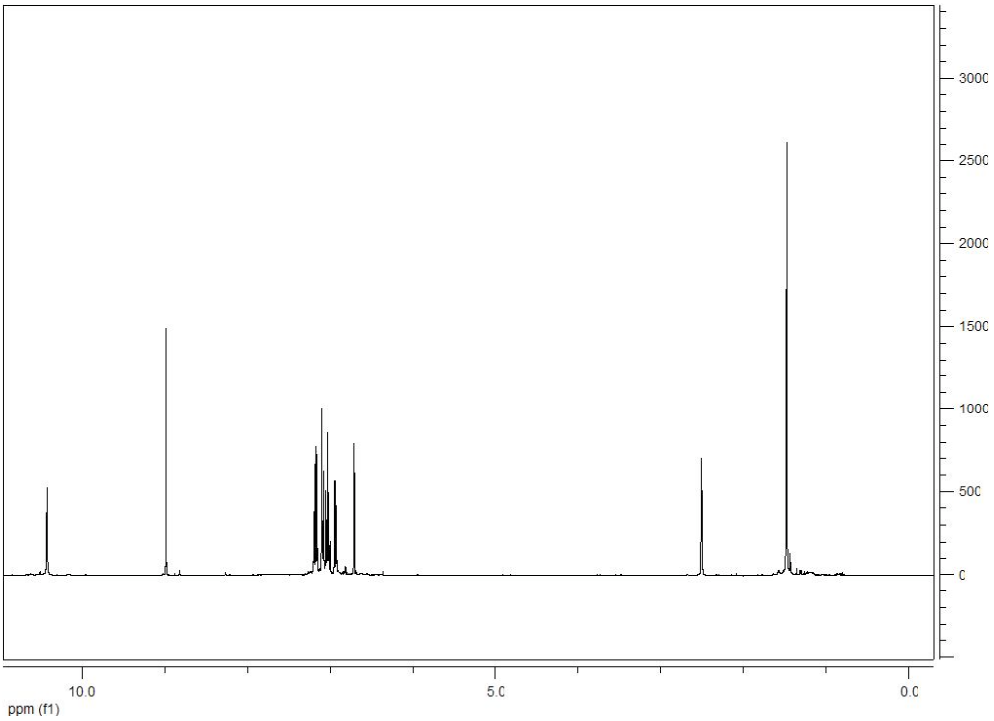
PeakTable

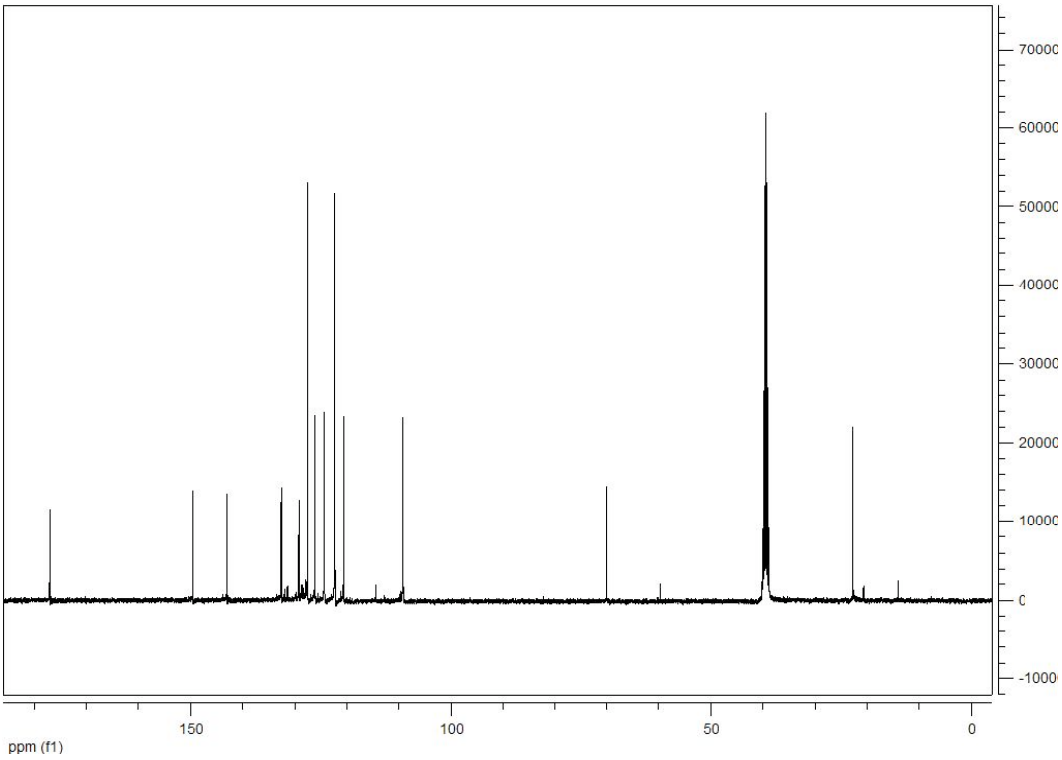
Detector A Ch1 254nm

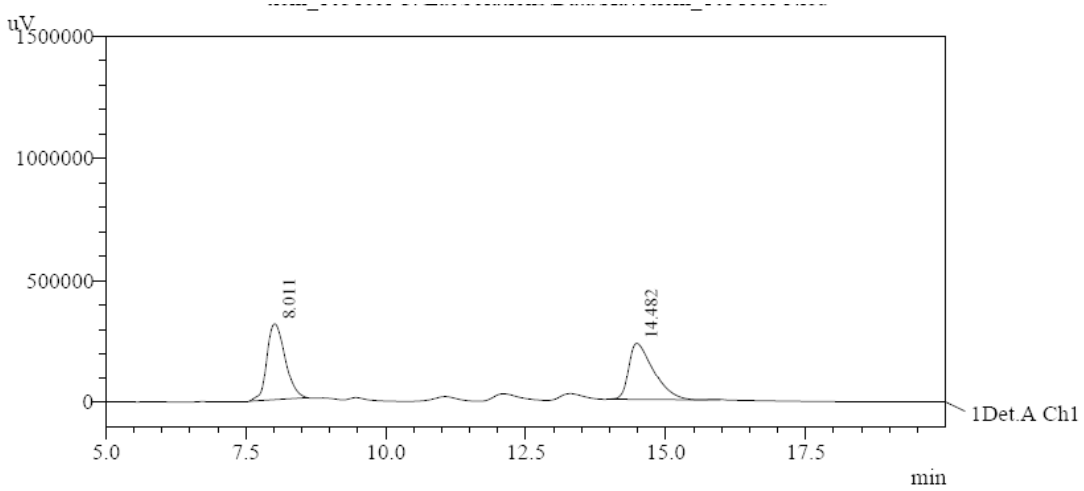
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.096	47563082	1628410	99.931	99.942
2	24.519	32851	953	0.069	0.058
Total		47595934	1629362	100.000	100.000

3c









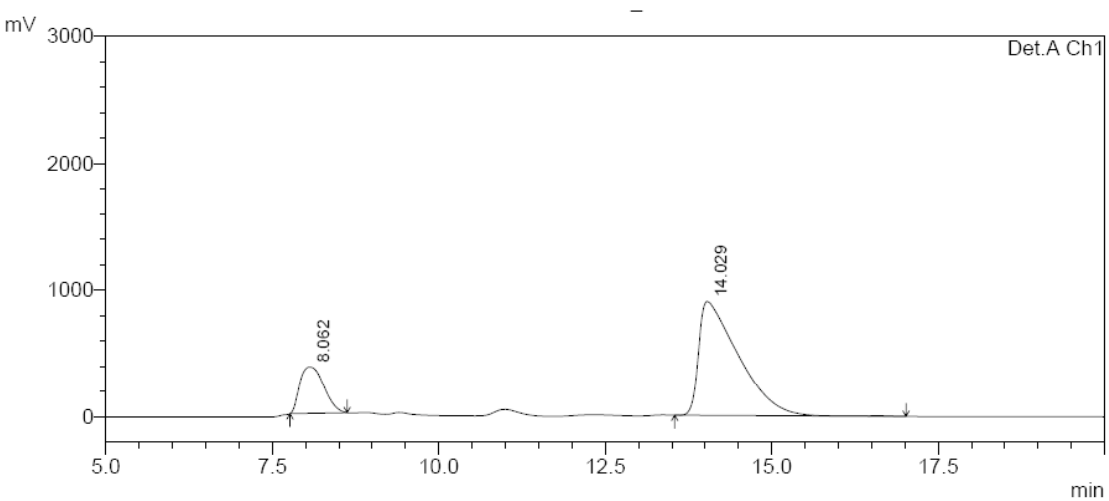
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.011	7133870	314058	49.844	57.388
2	14.482	7178391	233195	50.156	42.612
Total		14312262	547253	100.000	100.000

(*S*,*S*)-TUC



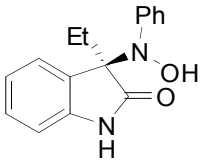
1 Det.A Ch1/254nm

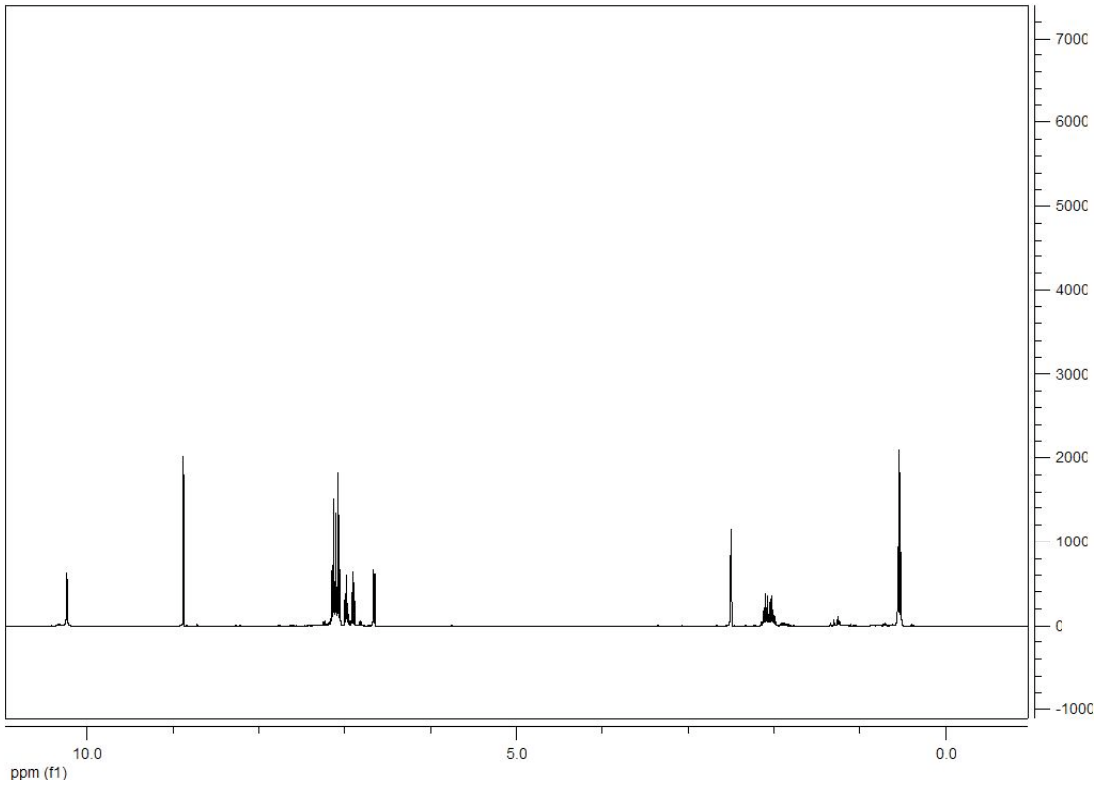
PeakTable

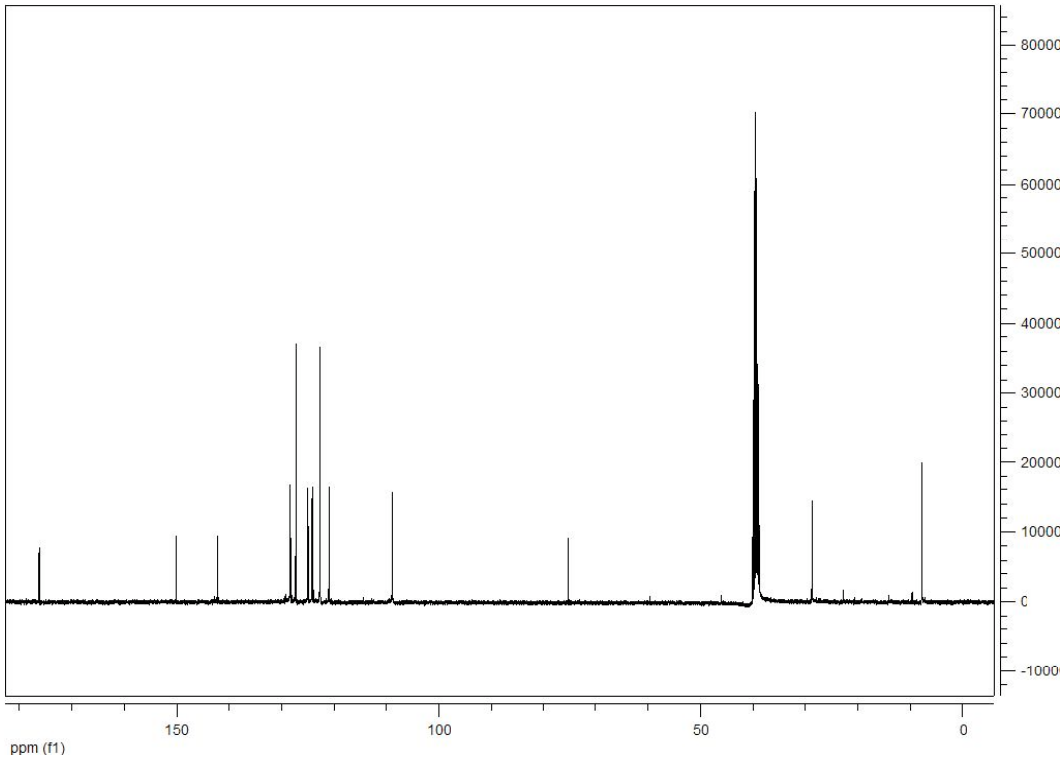
Detector A Ch1 254nm

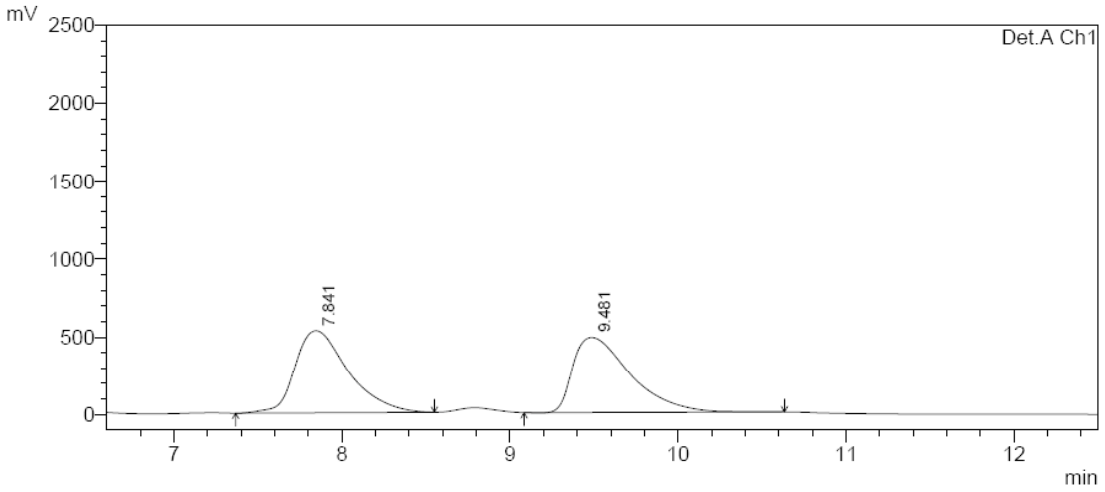
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.062	9313717	369773	19.862	29.102
2	14.029	37577301	900826	80.138	70.898
Total		46891019	1270599	100.000	100.000

3d









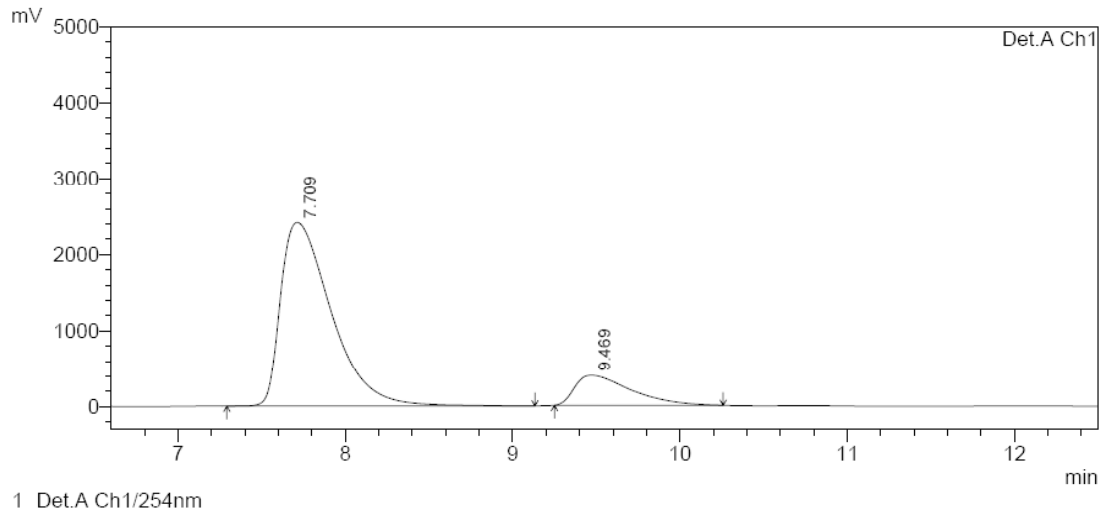
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.841	11730730	531375	50.387	52.247
2	9.481	11550519	485666	49.613	47.753
Total		23281249	1017041	100.000	100.000

(*R*,*R*)-TUC



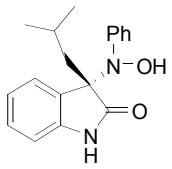
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.709	50892059	2412581	84.700	85.916
2	9.469	9193341	395480	15.300	14.084
Total		60085401	2808061	100.000	100.000

3e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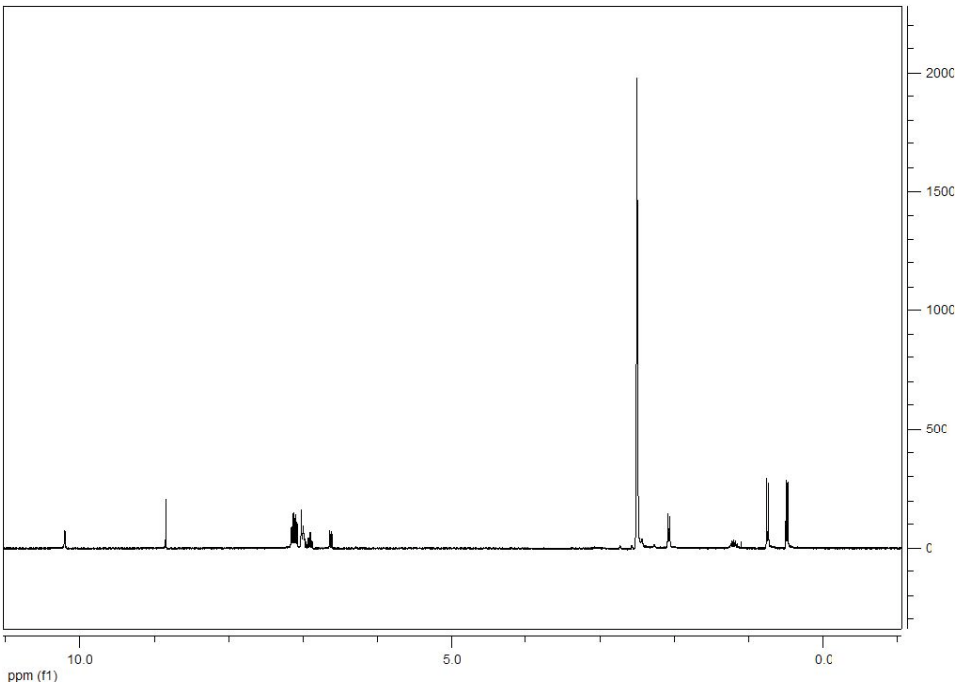
OH
O
N
H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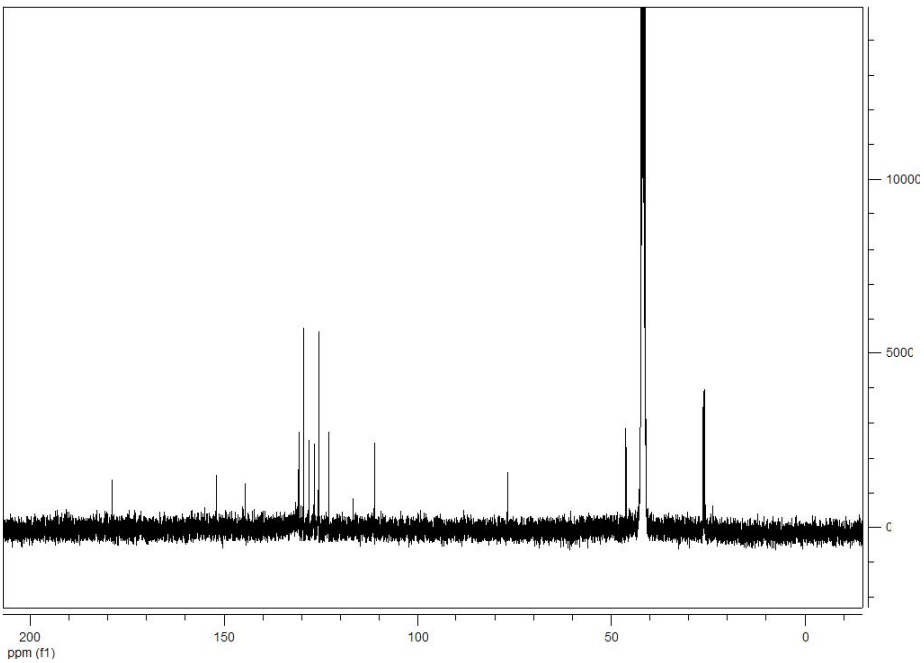
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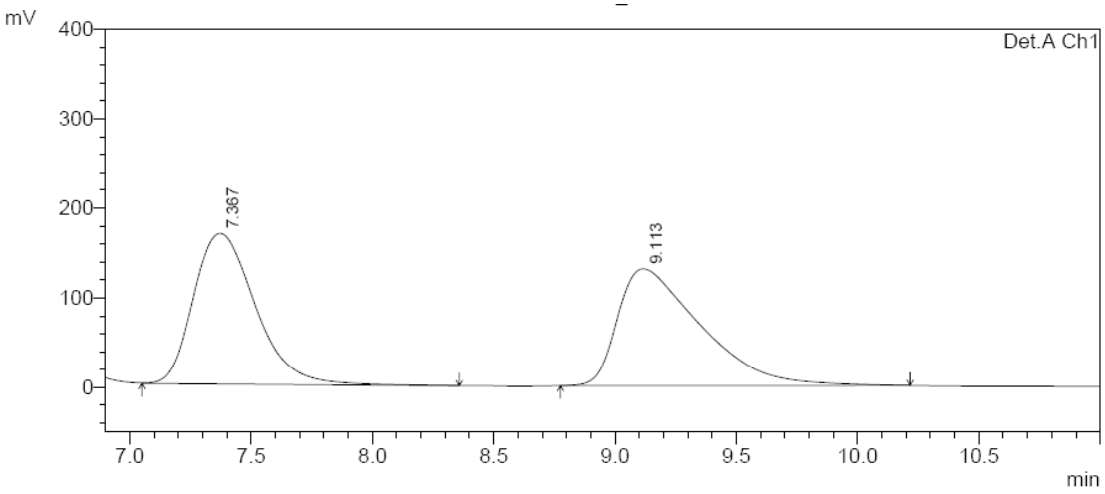


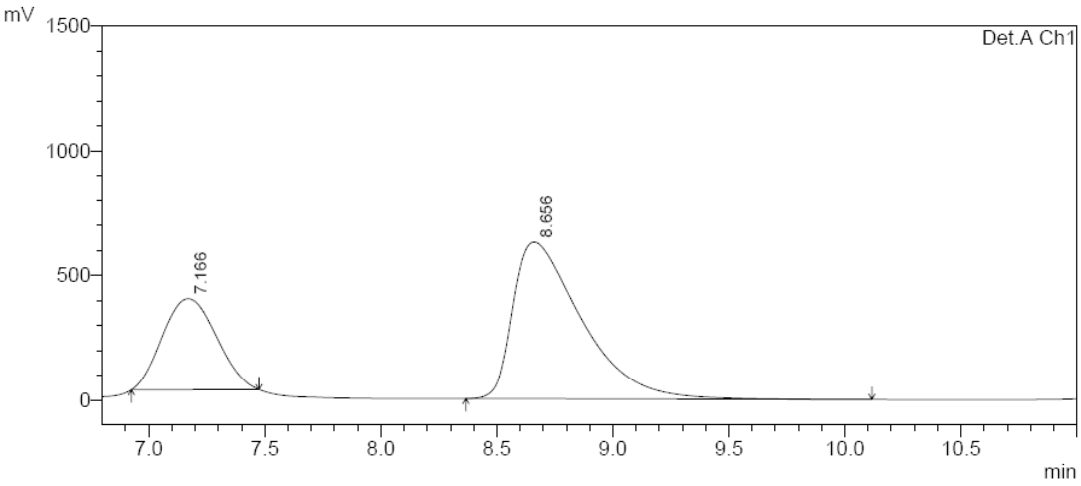
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %
1	7.367	2998187	49.131
2	9.113	3104306	50.869
Total		6102493	100.000

(*S*,*S*)-TUC



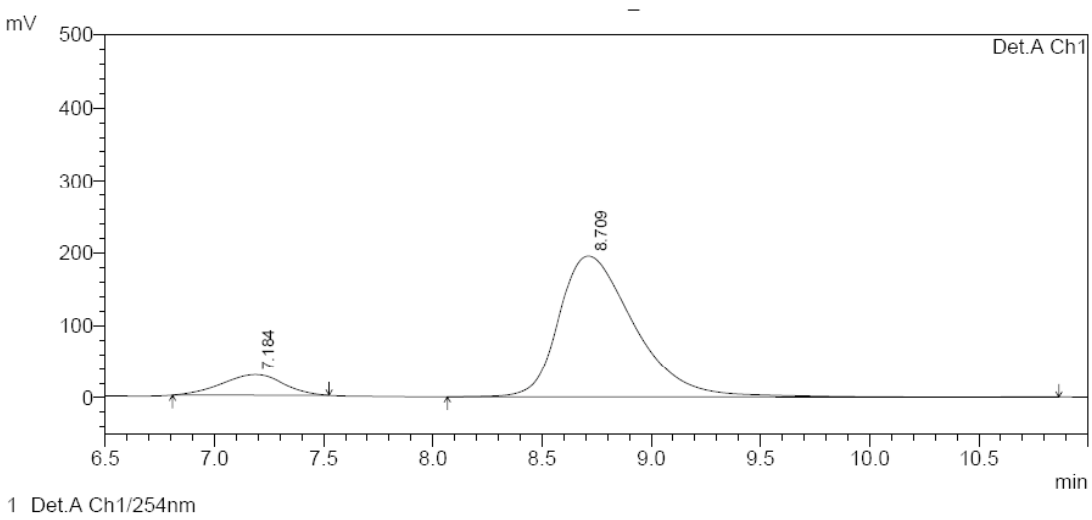
1 Det.A Ch1/220nm

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.166	5925131	364725	31.318	36.774
2	8.656	12994079	627073	68.682	63.226
Total		18919210	991798	100.000	100.000

(*S,S*)-TUC (with filtration)

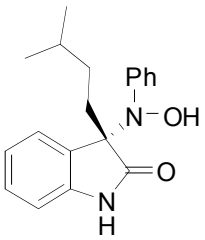


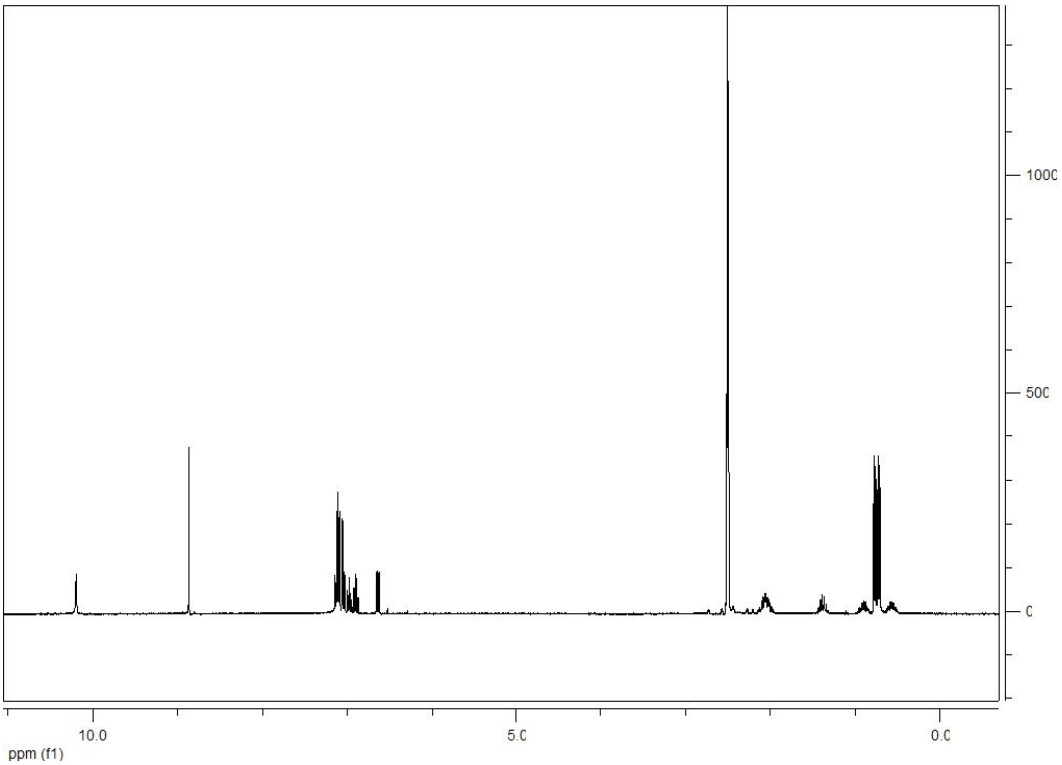
PeakTable

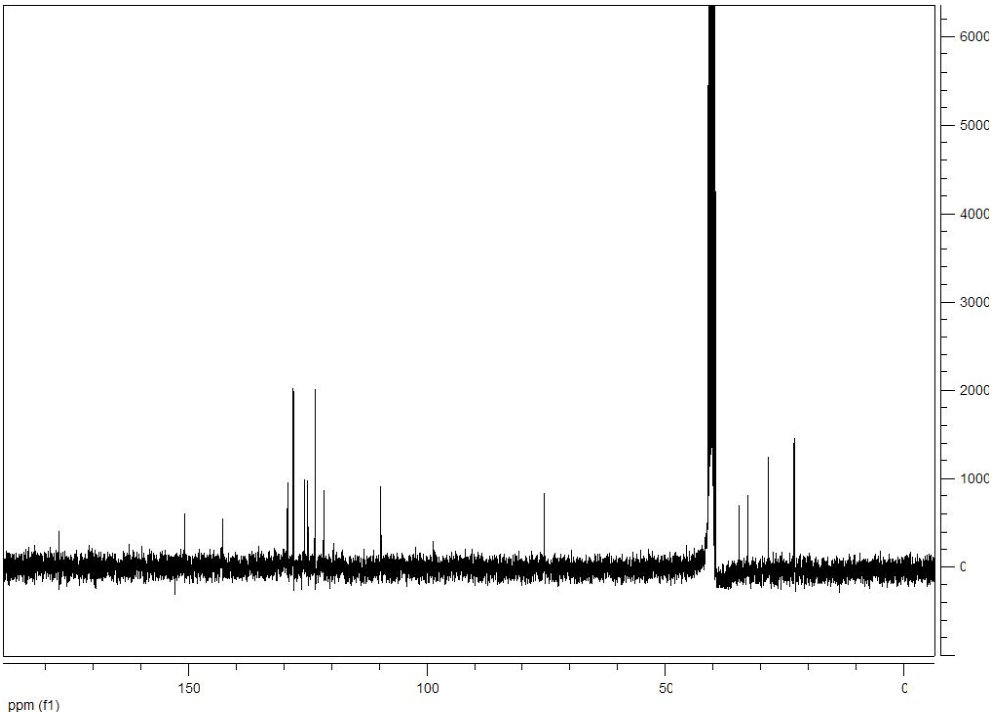
Detector A Ch1 254nm

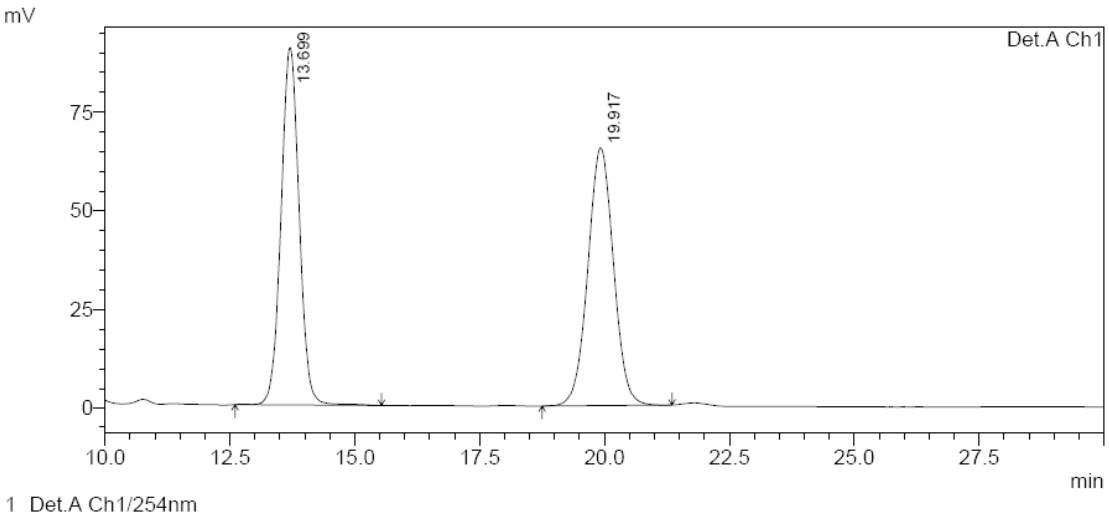
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.184	548448	28240	10.484	12.667
2	8.709	4682807	194693	89.516	87.333
Total		5231255	222932	100.000	100.000

3f







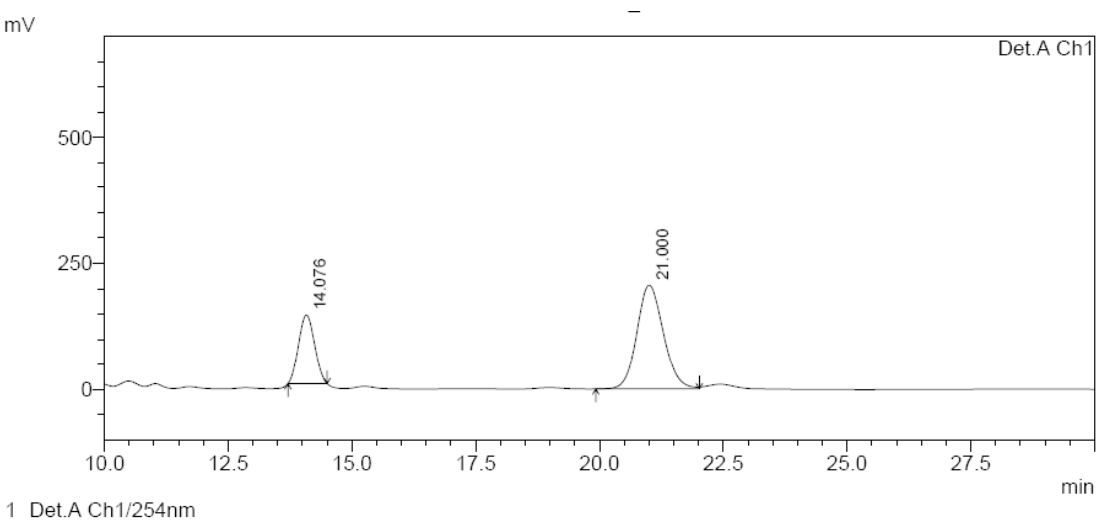


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.699	2304091	90701	49.497	58.036
2	19.917	2350912	65582	50.503	41.964
Total		4655003	156283	100.000	100.000

(*S*,*S*)-TUC

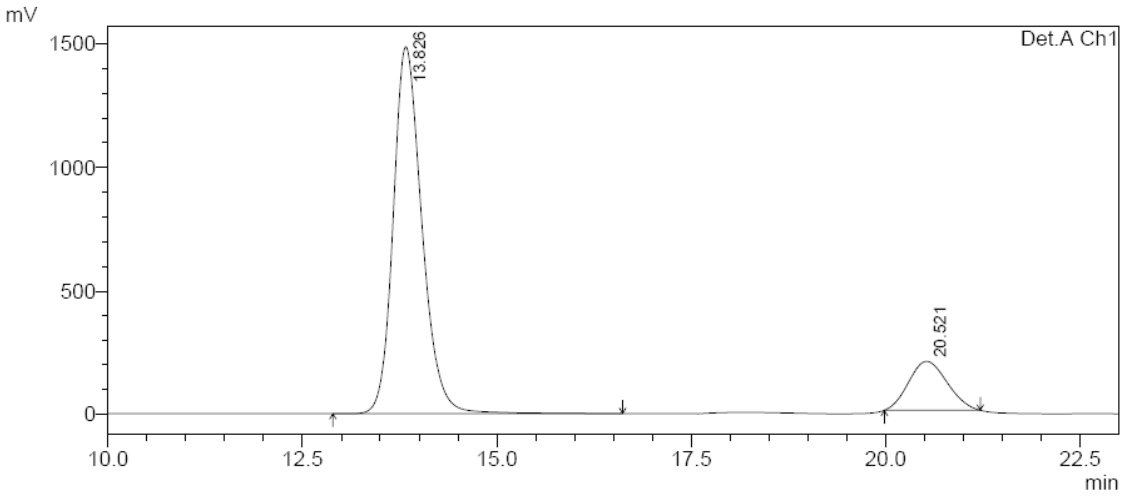


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.076	3093534	137240	28.530	39.941
2	21.000	7749649	206367	71.470	60.059
Total		10843183	343607	100.000	100.000

(*R*,*R*)-TUC



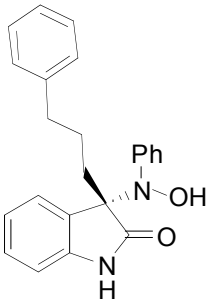
1 Det.A Ch1/254nm

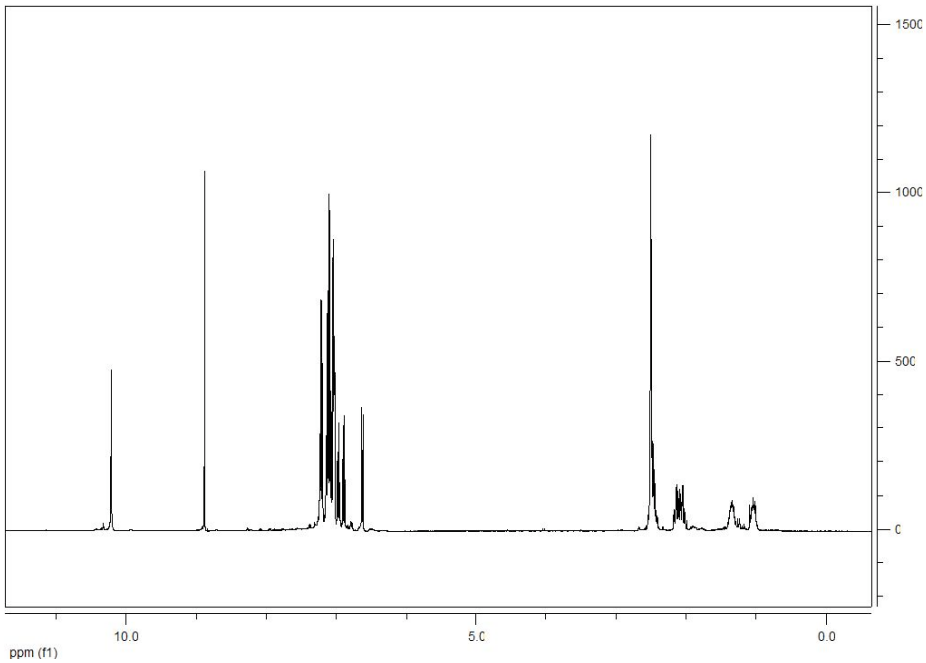
PeakTable

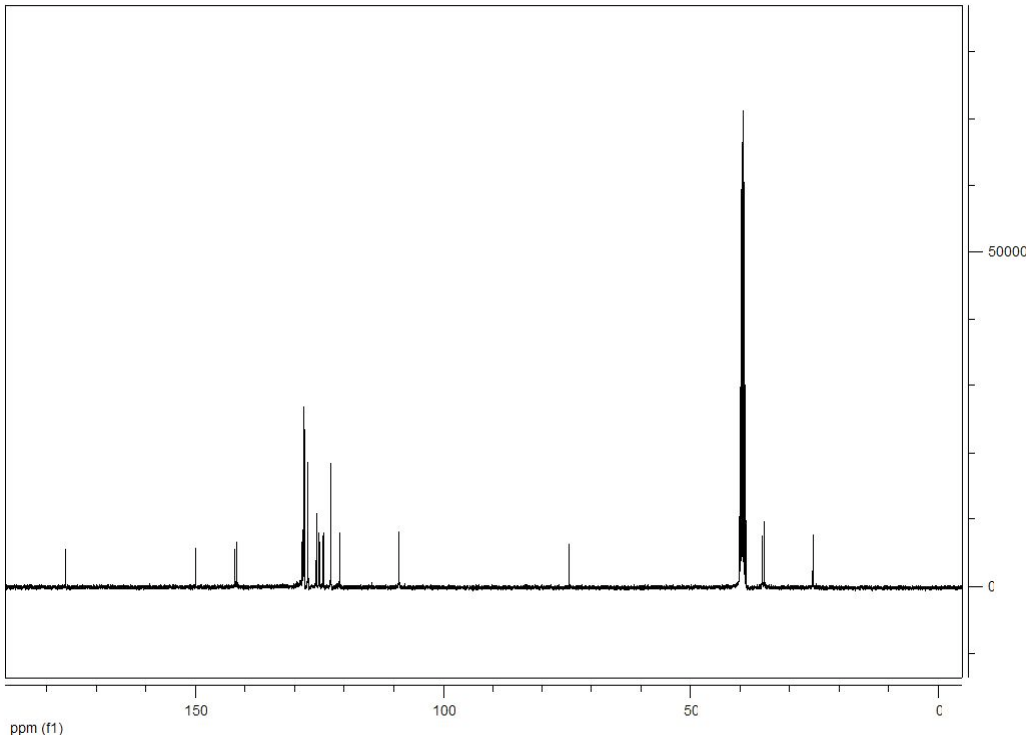
Detector A Ch1 254nm

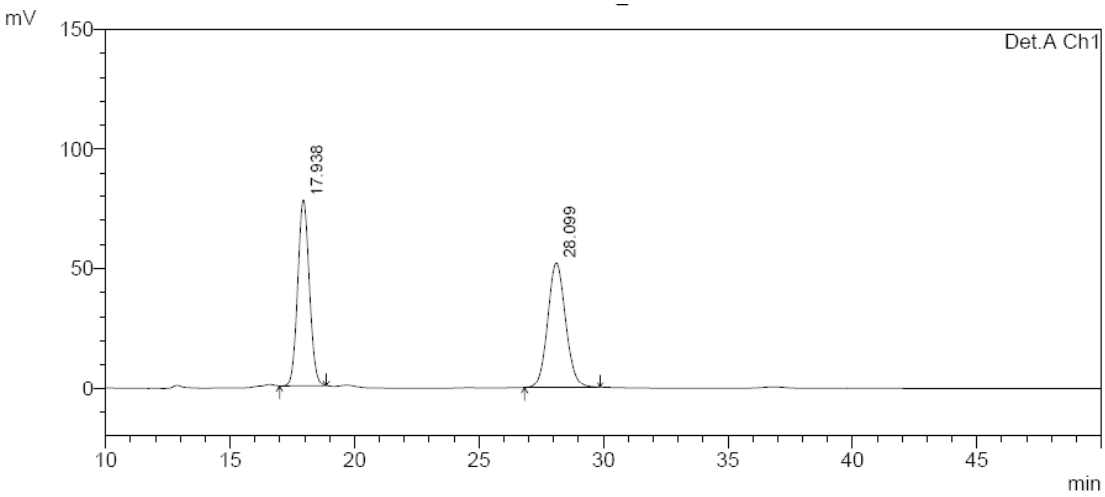
Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.826	38229535	1485979	84.882	88.272
2	20.521	6808735	197434	15.118	11.728
Total		45038270	1683413	100.000	100.000

3g









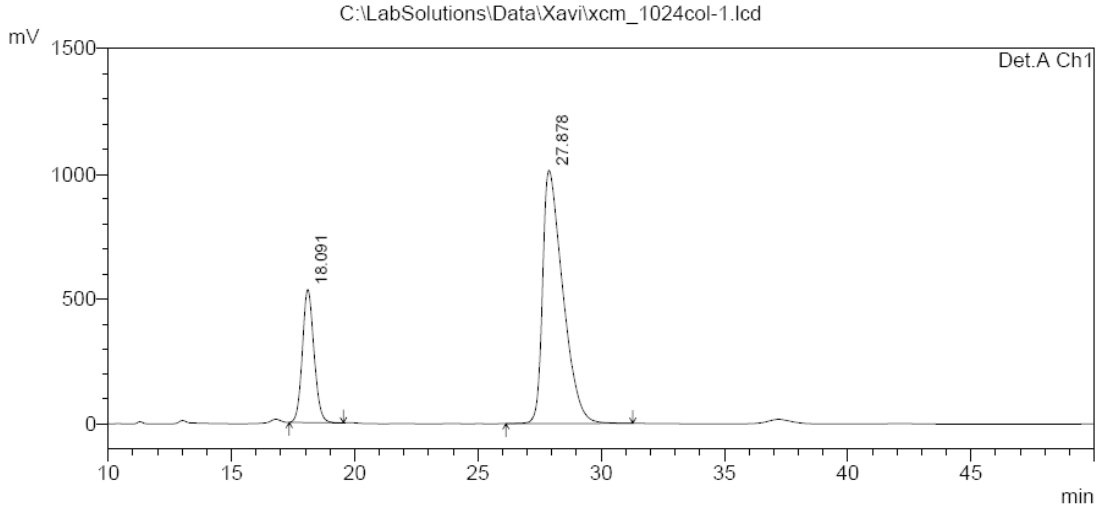
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.938	2532788	77527	49.143	59.837
2	28.099	2621152	52037	50.857	40.163
Total		5153939	129564	100.000	100.000

(*S,S*)-TUC



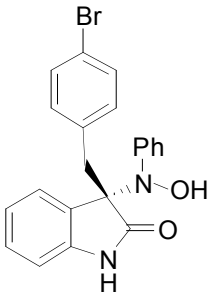
1 Det.A Ch1/230nm

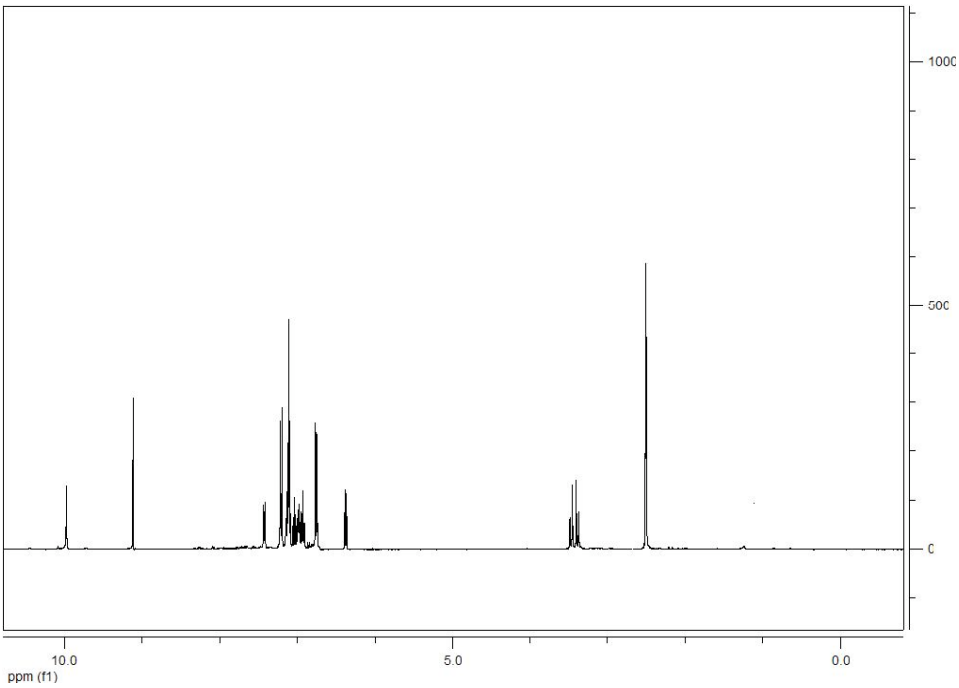
PeakTable

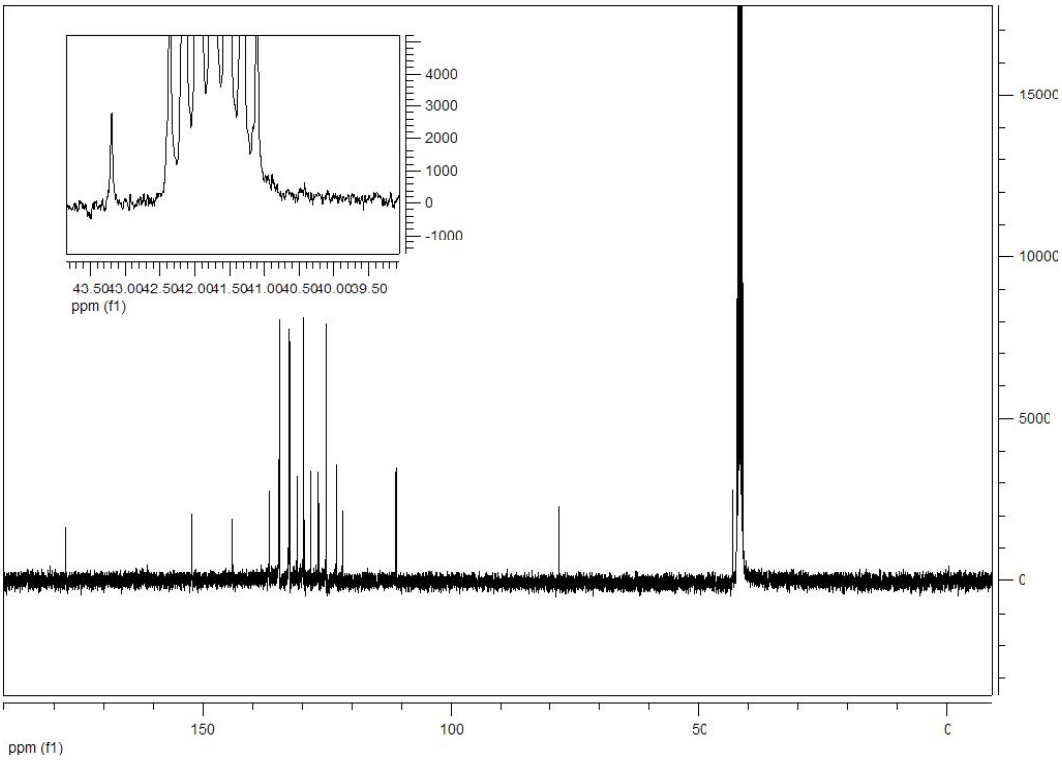
Detector A Ch1 230nm

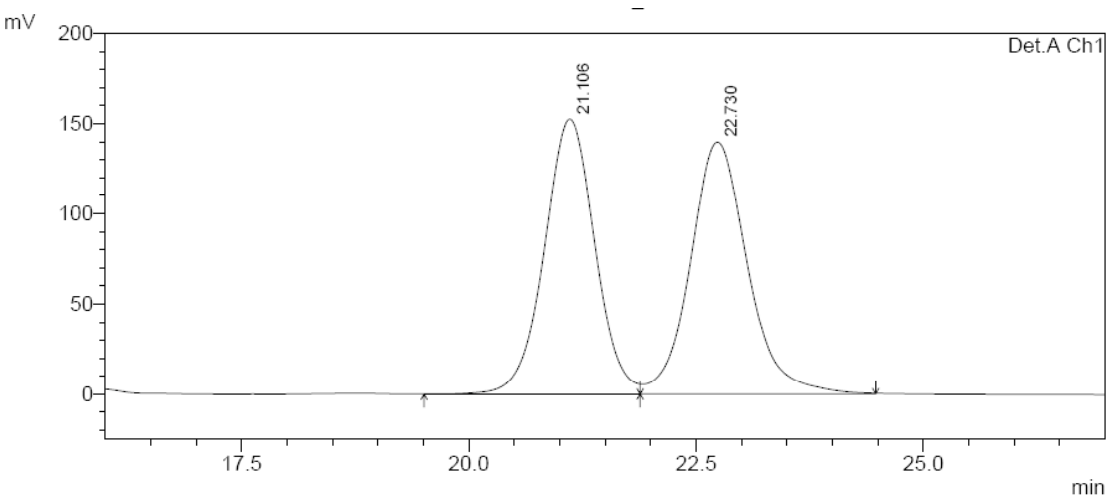
Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.091	17478381	532691	23.220	34.420
2	27.878	57794862	1014937	76.780	65.580
Total		75273242	1547627	100.000	100.000

3h







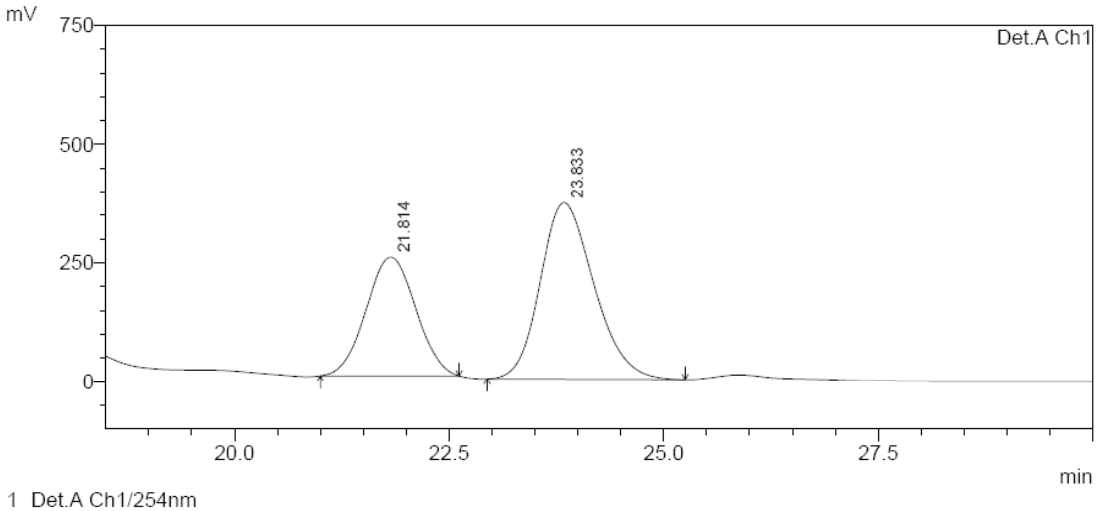


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.106	5892841	152549	49.165	52.196
2	22.730	6092915	139712	50.835	47.804
Total		11985756	292260	100.000	100.000

(*S*,*S*)-TUC

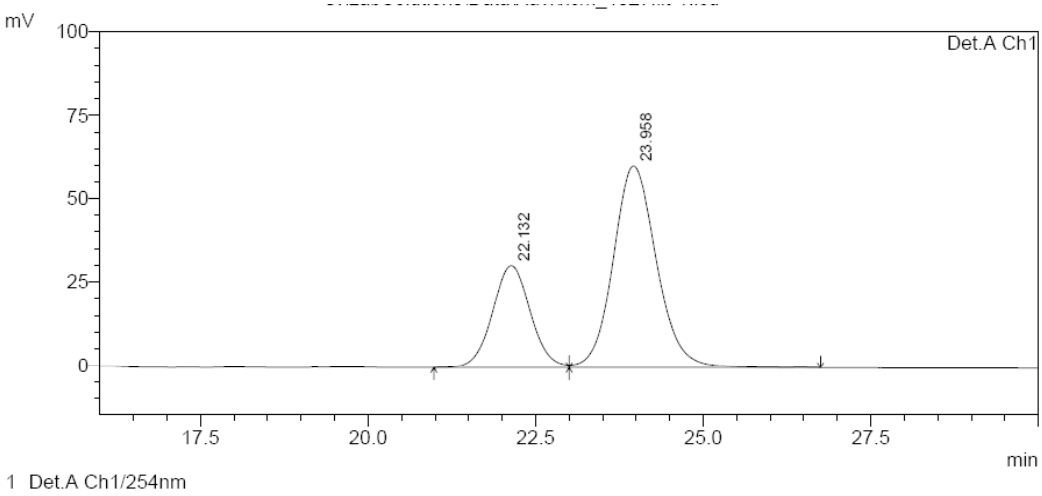


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.814	10043421	249317	38.338	40.222
2	23.833	16153294	370534	61.662	59.778
Total		26196715	619851	100.000	100.000

(*S,S*)-TUC (with product filtration)



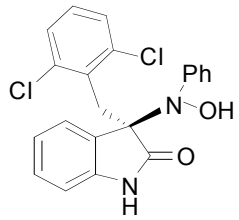
1 Det.A Ch1/254nm

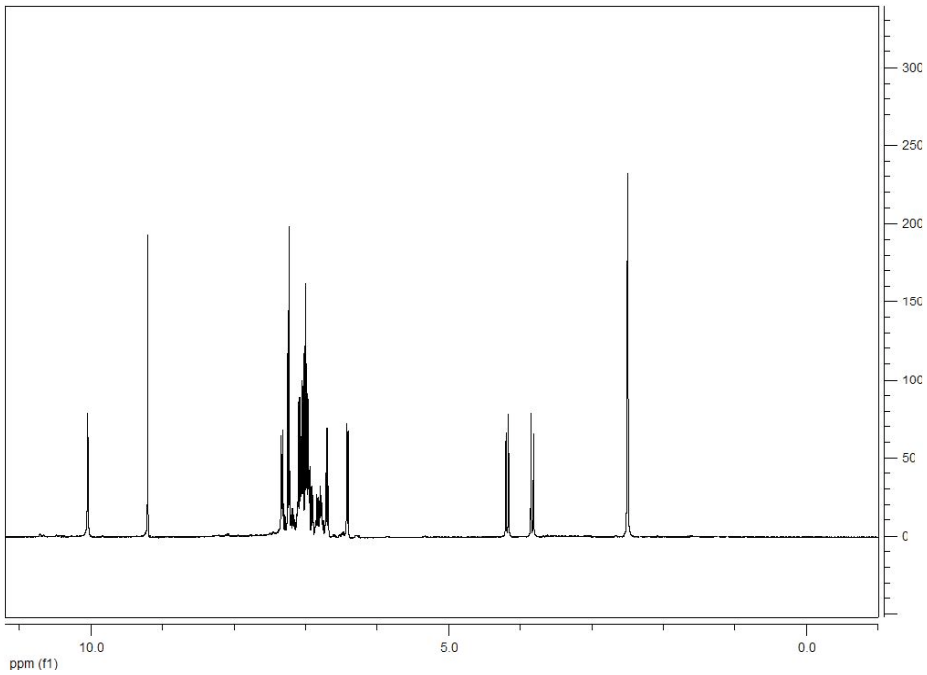
PeakTable

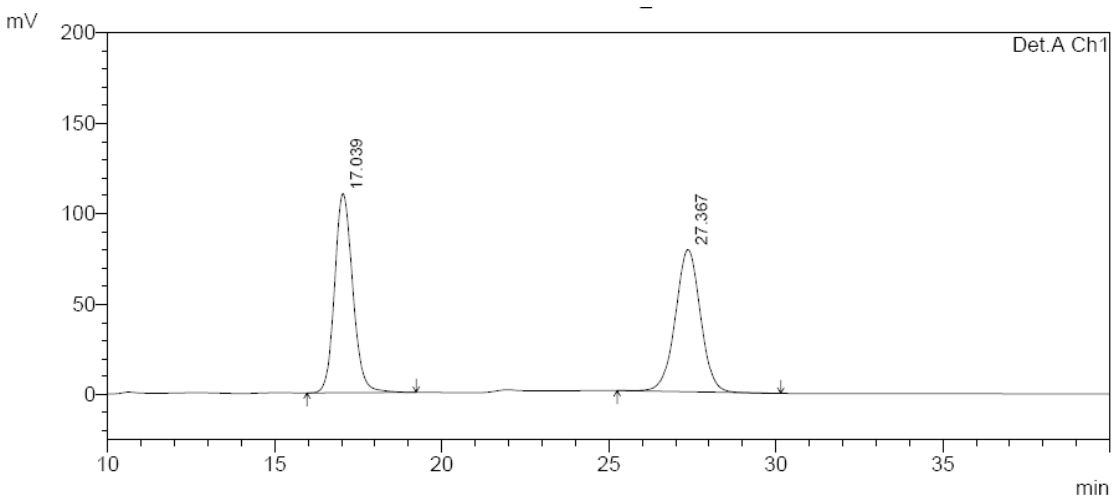
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.132	1210786	30546	30.721	33.502
2	23.958	2730473	60630	69.279	66.498
Total		3941260	91176	100.000	100.000

3i





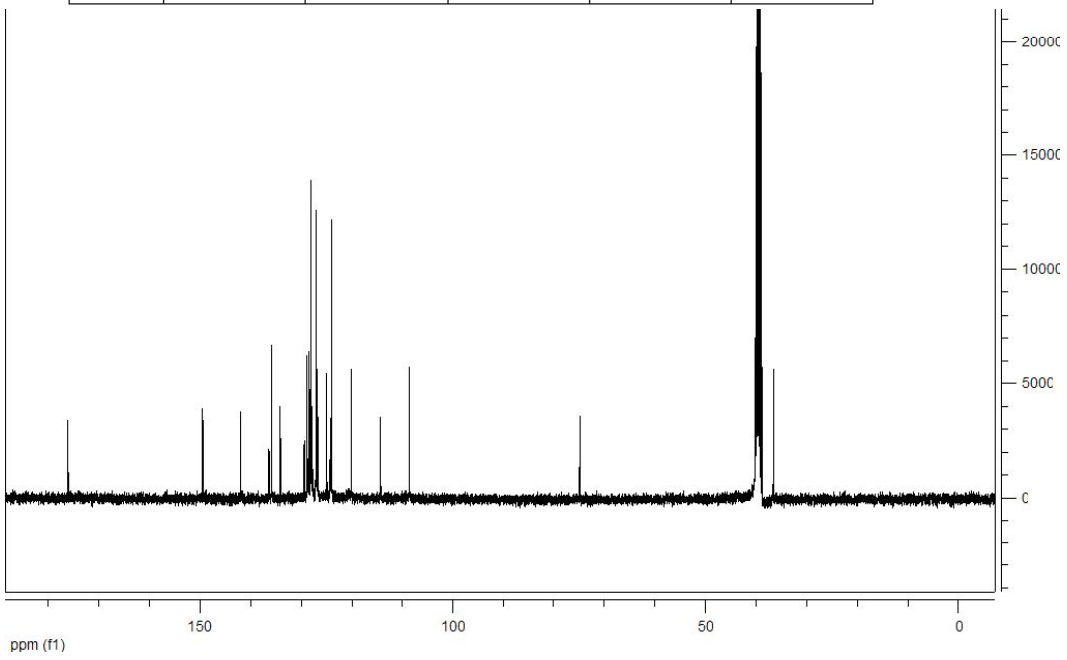


1 Det.A Ch1/254nm

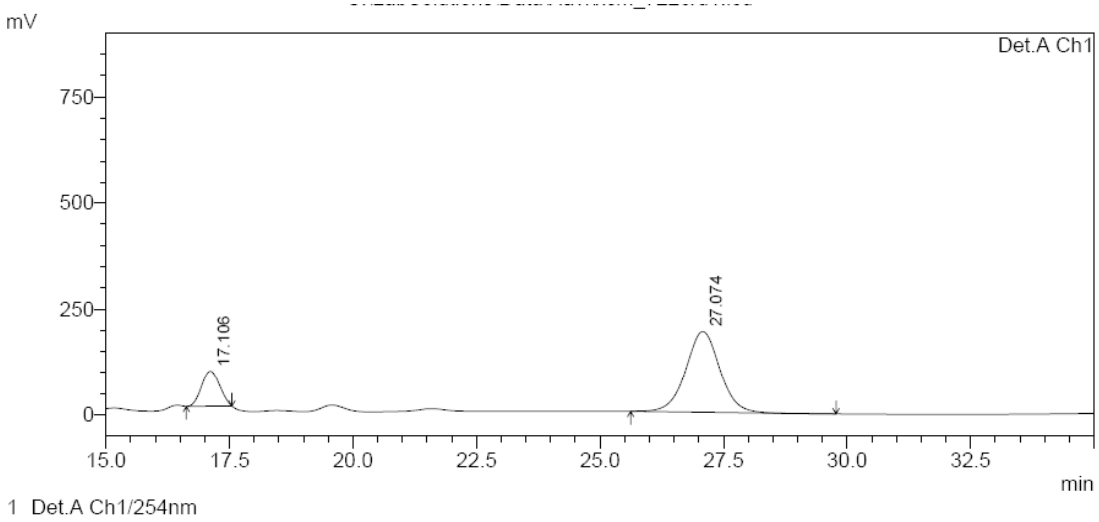
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.039	4176468	110062	50.298	58.301
2	27.367	4127043	78722	49.702	41.699
Total		8303511	188784	100.000	100.000



(*R*,*R*)-TUC

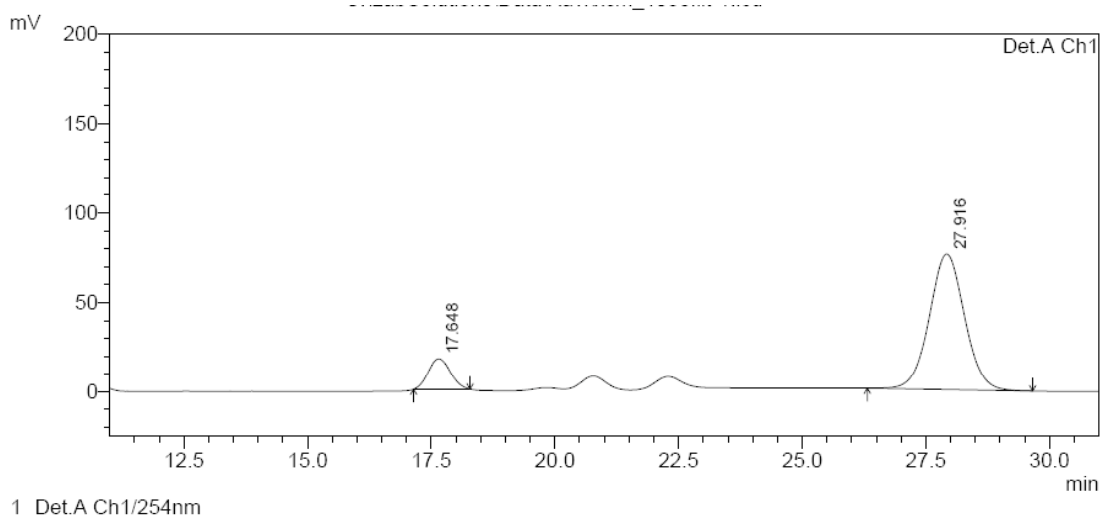


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.106	2131600	83789	18.803	30.425
2	27.074	9204735	191608	81.197	69.575
Total		11336335	275397	100.000	100.000

(*R,R*)-TUC (with product filtration)



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.648	535977	17239	12.426	18.513
2	27.916	3777434	75879	87.574	81.487
Total		4313411	93117	100.000	100.000