Supporting Information

Bifunctional Organocatalyst for Methanolytic Desymmetrization of Cyclic Anhydrides: Increasing Enantioselectivity by Catalyst Dilution

Ho Sik Rho, Sang Ho Oh, Ji Woong Lee, Jin Young Lee, Jik Chin and Choong Eui Song**

Department of Chemistry, Sungkyunkwan University, Suwon, 440-746 (Korea)
R&D center, AmorePacific Corporation, Yongin, 446-729 (Korea)
Department of Chemistry, University of Toronto, 80 St. George st. Toronto, ON (Canada)

General. Anhydrides (**1a**, **1b**, **1d**, **1e**) were purchased from Aldrich and used without further purification. Anhydride **1c** was obtained from **1d** by hydrogenation of the double bond. Quinine a[1]nd hydroquinine were purchased from Aldrich and used without further purification. Thiourea and urea catalysts (**I-II**) were synthesized by the literature procedure.[1]
Chromatographic purification of products was carried out by flash chromatography using Merck silica gel 60 (230–400 mesh). Thin-layer chromatography was carried out on Merck silica gel 60F plates. HPLC analyses were performed on a Jasco 1100 Series instrument equipped with an isostatic pump using Hypersil Column (200 × 4.6 mm). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on Varian 300 spectrometers using TMS as an internal standard.

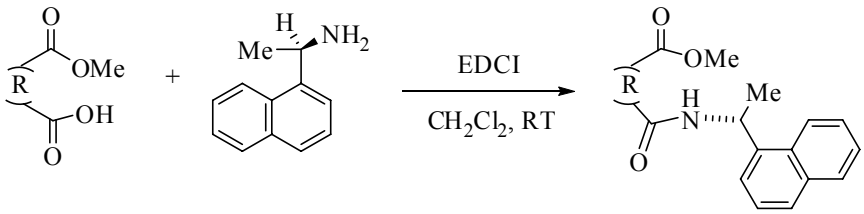
General procedure for methanolysis of prochiral cyclic anhydrides
Methanol (202 μL, 5 mmol) was added dropwise to a stirred solution of anhydrides (0.5 mmol) and catalysts (**I–IV**) (5–10%) in appropriate solvents (2.5–80 mL) at the temperature

[1] B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett*. **2005**, *7*, 1967-1969.

indicated in table 2. The reaction mixture was stirred at that temperature until the starting material was consumed, as indicated by TLC analysis (1–30h). The reaction was quenched by adding HCl (1N, 3 mL) in one portion. The aqueous phase was extracted with EtOAc (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the crude product. Purification by column chromatography (EtOAc/Hexanes) gave hemiester products (**2a**–**2e**)

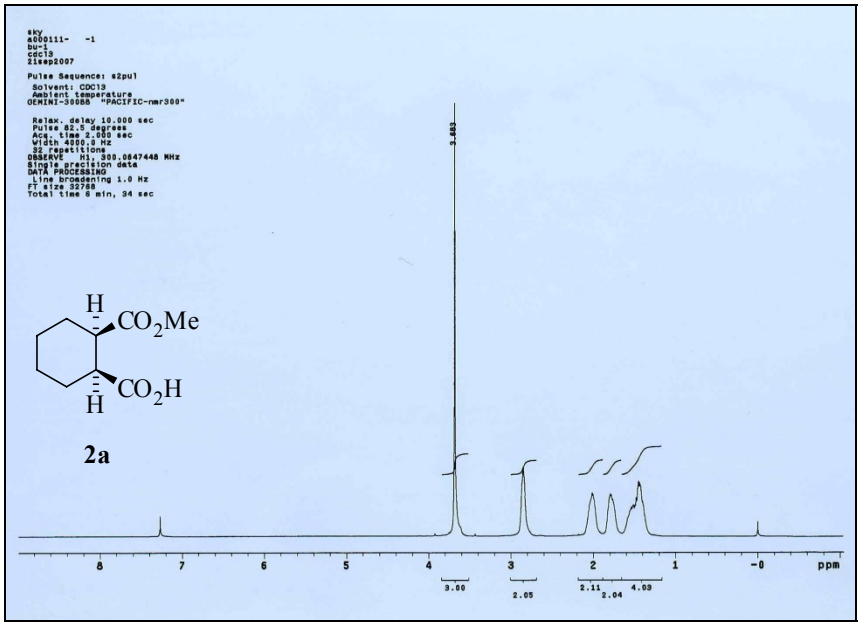
The enantiomeric excess (*ee*) of each product was determined by HPLC analysis of a diastereomeric mixture of the corresponding amide-ester prepared from hemiester accordimg to literature procedure[2] (Scheme 1).

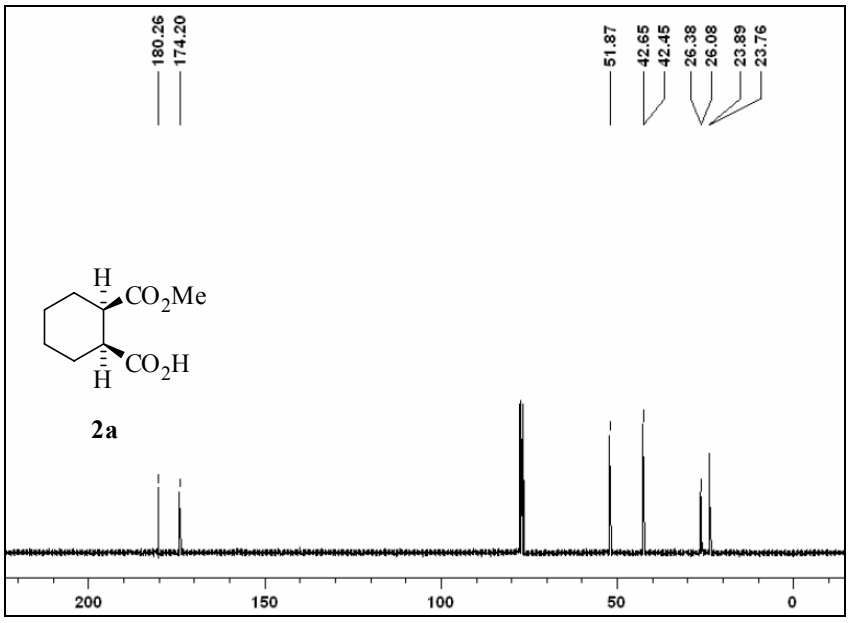
Scheme 1



[2] Y, M, Song, J. S. Choi, J. W. Yang, H. Han, *Tetrahedron Lett*. **2004**, *45*, 3301-3304.

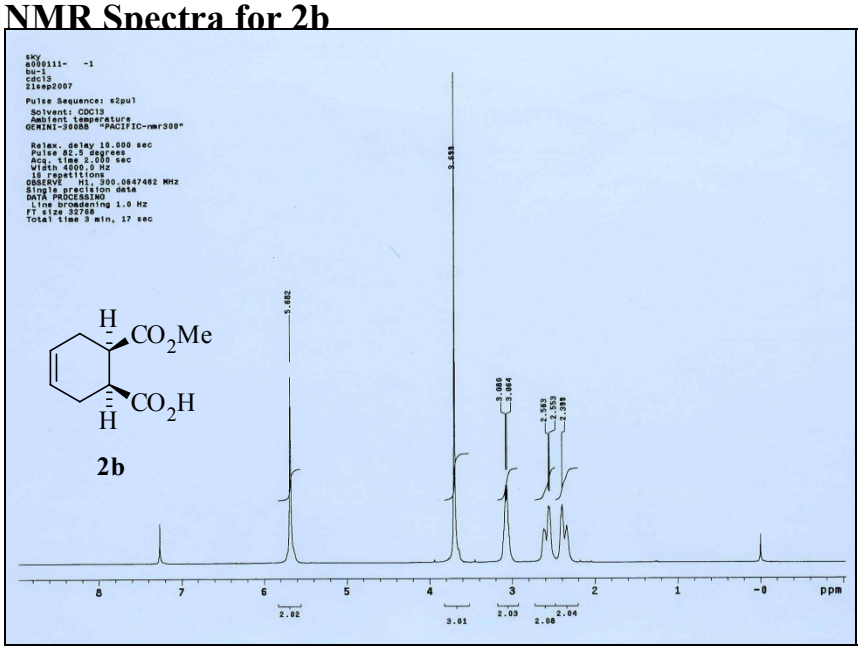
NMR Spectra for 2a

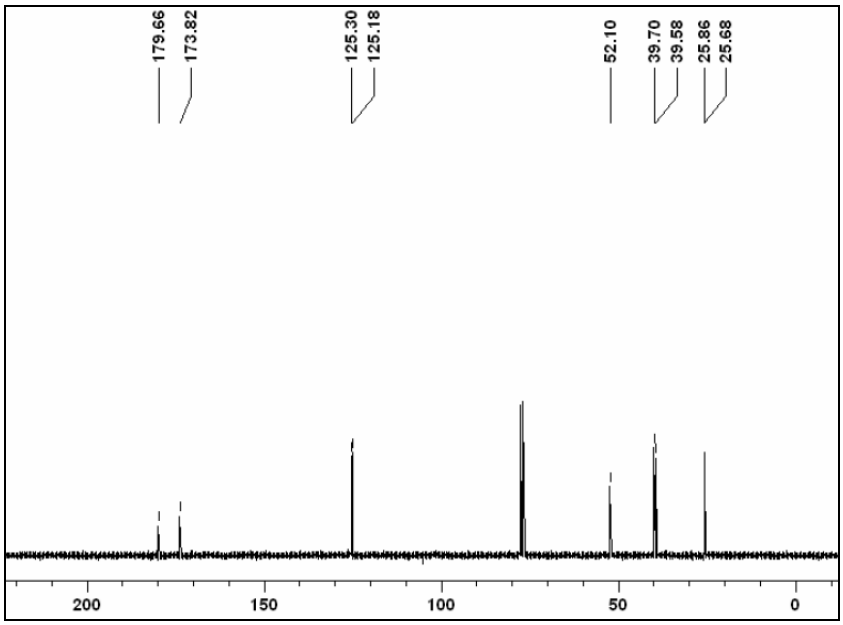




^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36-1.62 (m, 4H), 1.72-1.84 (m, 2H), 1.96-2.10 (m, 2H), 2.80-2.92 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.76, 23.89, 26.08, 26.38, 42.45, 42.65, 51.87, 174.20, 180.26; The ee value was determined by HPLC analysis (Hypersil, 40 : 1, Hexanes : IPA, 1 mL/min, t(minor) = 8.50 min, t(major) = 11.79 min) of the diastereomeric mixture of the corresponding amide-ester prepared as described previously.

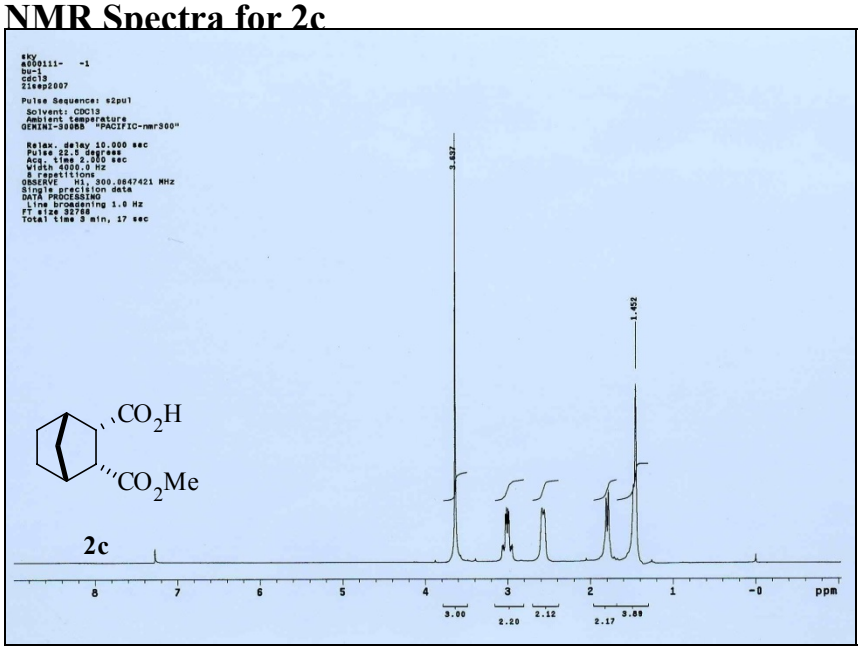
NMR Spectra for 2b

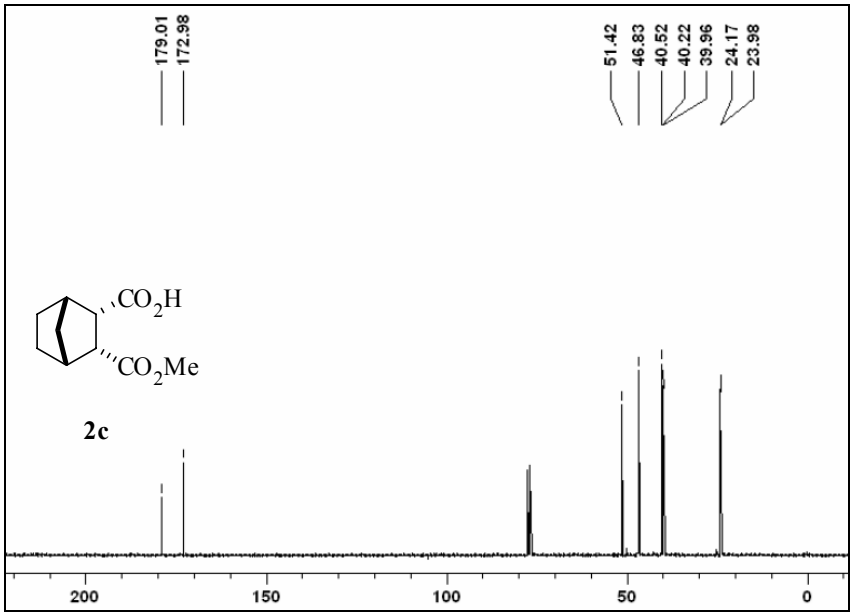




^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32-2.65 (m, 4H), 3.02-3.12 (m, 2H), 3.69 (s, 3H), 5.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.68, 25.86, 39.58, 39.70, 52.10, 125.18, 125.30, 173.82, 179.66; The ee value was determined by HPLC analysis (Hypersil, 40 : 1, Hexanes : IPA, 1 mL/min, t(minor) = 11.02 min, t(major) = 14.68 min) of the diastereomeric mixture of the corresponding amide-ester prepared as described previously.

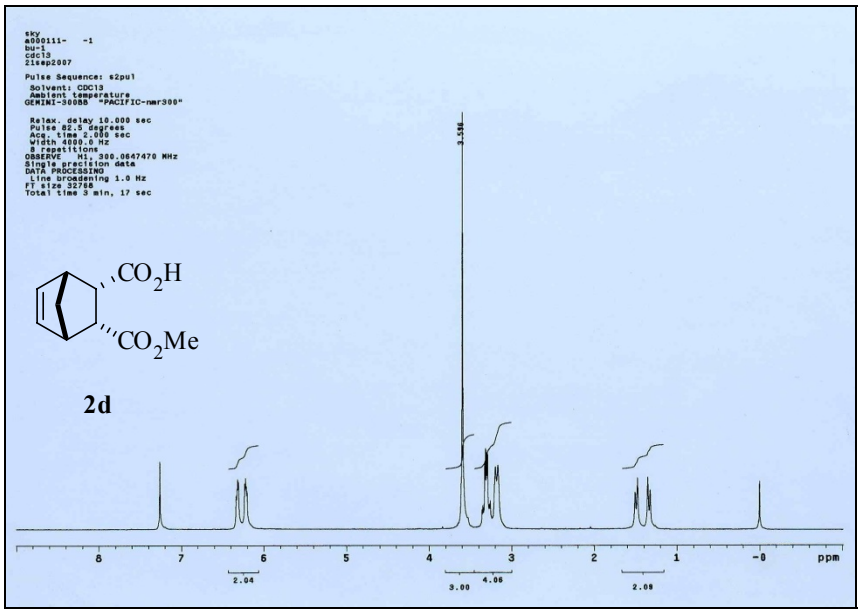
NMR Spectra for 2c

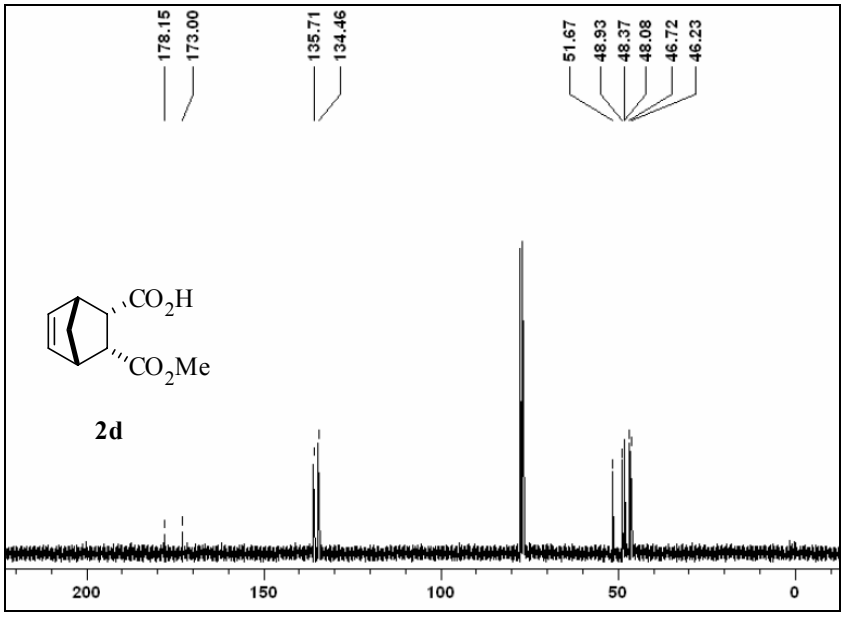




^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.58 (m, 4H), 1.75-1.83 (m, 2H), 2.57-2.62 (m, 2H), 2.82-3.04 (m, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.98, 24.17, 39.96, 40.22, 40.52, 46.83, 51.42, 172.98, 179.01; The ee value was determined by HPLC analysis (Hypersil, 40 : 1, Hexanes : IPA, 1 mL/min, t(minor) = 12.04 min, t(major) = 17.99 min) of the diastereomeric mixture of the corresponding amide-ester prepared as described previously.

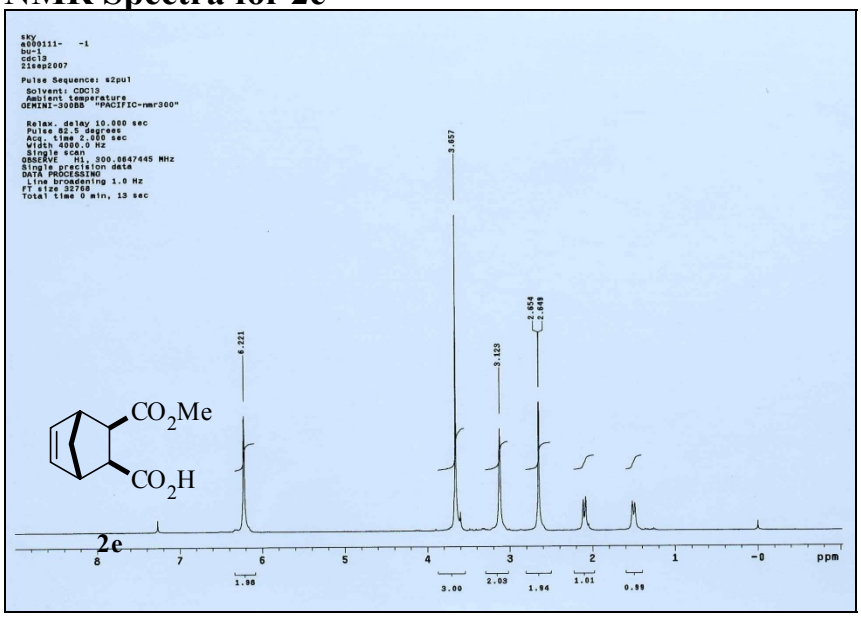
NMR Spectra for 2d

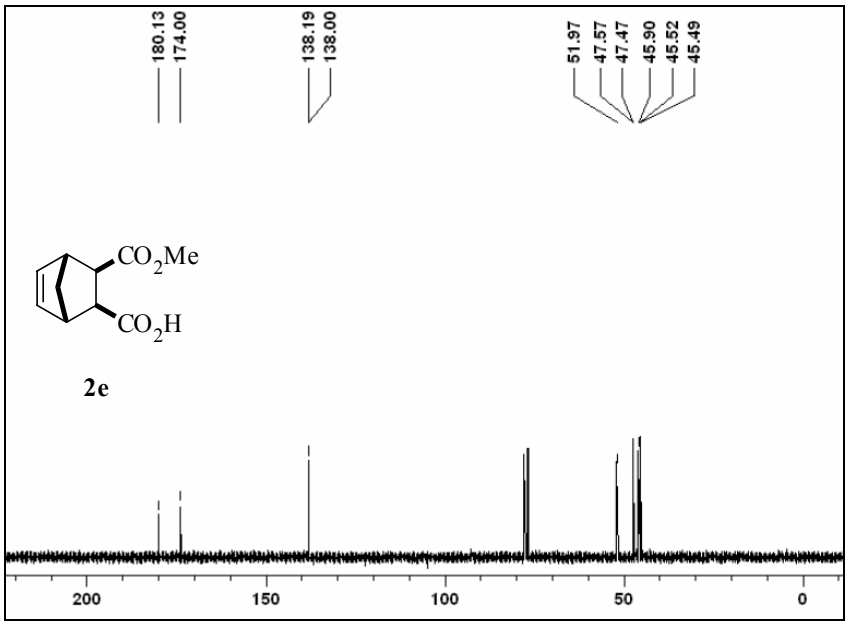




^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (bd, *J* = 9.0 Hz, 1H), 1.50 (dt, *J* = 9.0 Hz and 1.8 Hz, 1H), 3.01-3.41 (m, 4H), 3.59 (s, 3H), 6.21 (dd, *J* = 5.0 and 3.0 Hz, 1H), 6.33 (dd, *J* = 5.0 and 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.23, 46.72, 48.08, 48.37, 48.93, 51.67, 134.46, 135.71, 173.00, 178.15; The ee value was determined by HPLC analysis (Hypersil, 40 : 1, Hexanes : IPA, 1 mL/min, t(minor) = 16.56 min, t(major) = 23.25 min) of the diastereomeric mixture of the corresponding amide-ester prepared as described previously.

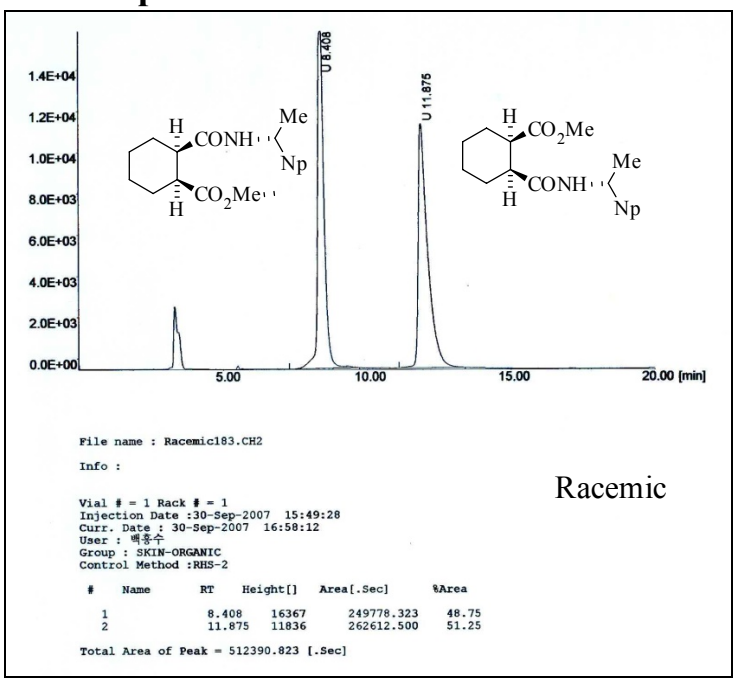
NMR Spectra for 2e





^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (bd, J = 9.0 Hz, 1H), 2.13 (bd, J = 9.0 Hz, 1H), 2.62 (m, 2H), 3.09 (m, 2H), 3.65 (s, 3H), 6.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.49, 45.52, 45.90, 47.47, 47.57, 51.97, 138.00, 138.19, 174.00, 180.13; The ee value was determined by HPLC analysis (Hypersil, 40 : 1, Hexanes : IPA, 1 mL/min, t(minor) = 15.23 min, t(major) = 16.20 min) of the diastereomeric mixture of the corresponding amide-ester prepared as described previously.

HPLC Spectra for Table 1



Tabel 1. Entry 1 (Catalyst **I** – 10 mol%)

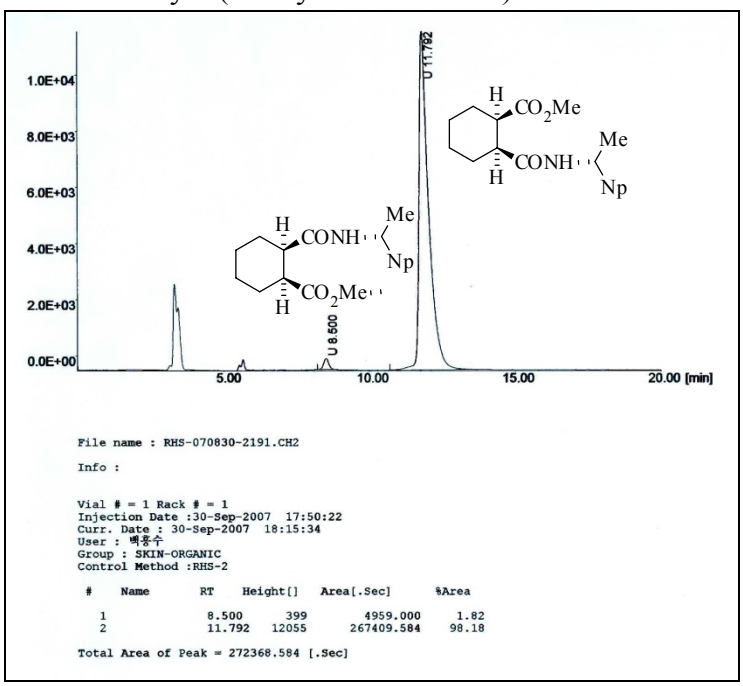
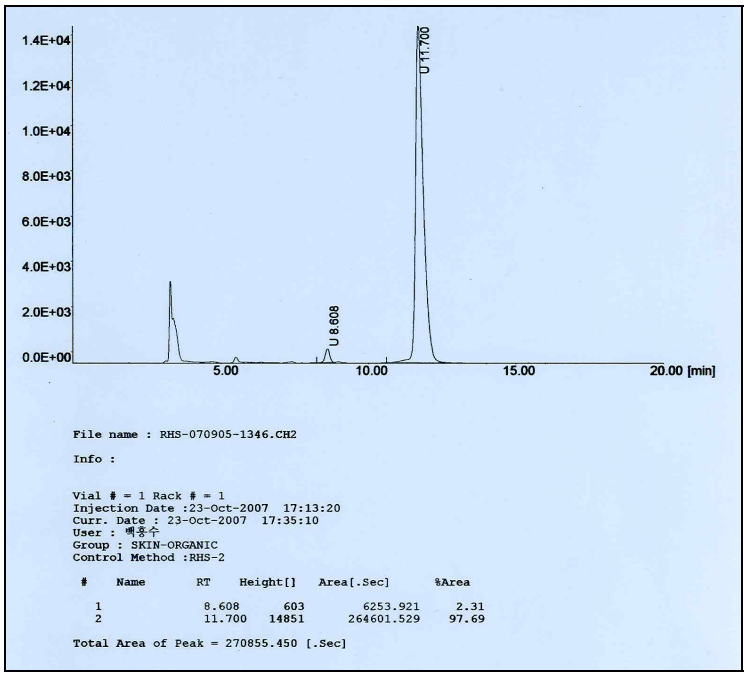


Table 1. Entry 2 (Catalyst **I** – 5 mol%)



File name : RHS-070905-1346.CH2

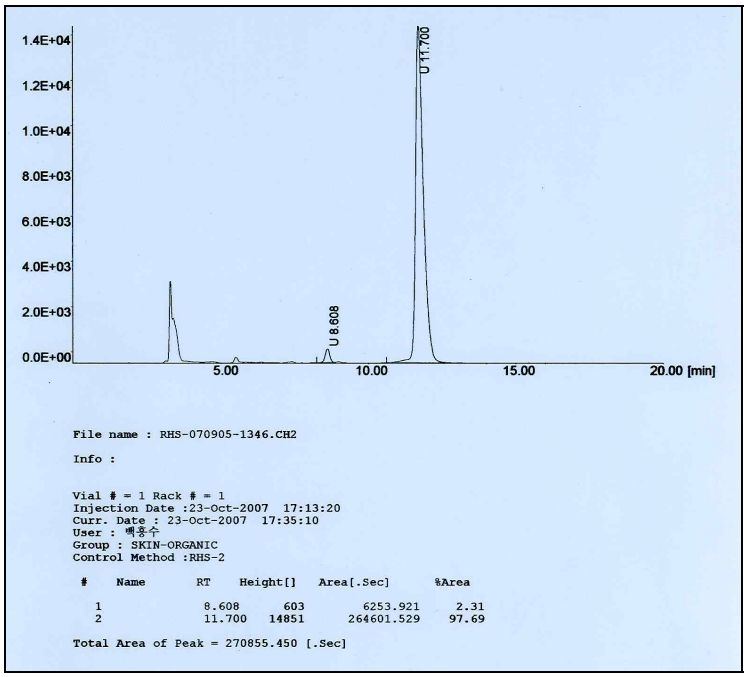
Info :

Vial # = 1 Rack # = 1
Injection Date :23-Oct-2007 17:13:20
Curr. Date : 23-Oct-2007 17:35:10
User : 백용수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.608	603	6253.921	2.31
2		11.700	14851	264601.529	97.69

Total Area of Peak = 270855.450 [.Sec]

Table 1. Entry 3 (Catalyst **II** – 10 mol%)



File name : RHS-070905-1346.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date :23-Oct-2007 17:13:20
Curr. Date : 23-Oct-2007 17:35:10
User : 백용수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.608	603	6253.921	2.31
2		11.700	14851	264601.529	97.69

Total Area of Peak = 270855.450 [.Sec]

Table 1. Entry 4 (Catalyst **III** – 10 mol%)

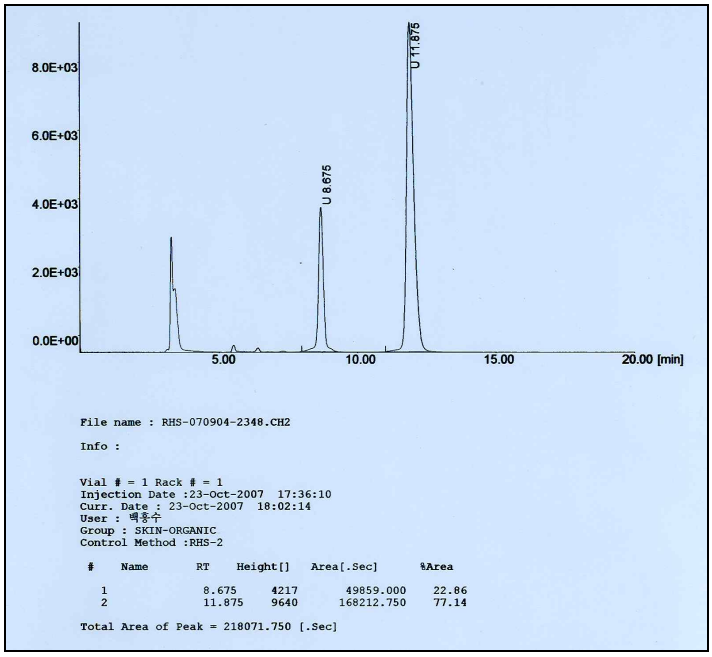


Table 1. Entry 5 (Catalysy **IV** – 10 mol%)

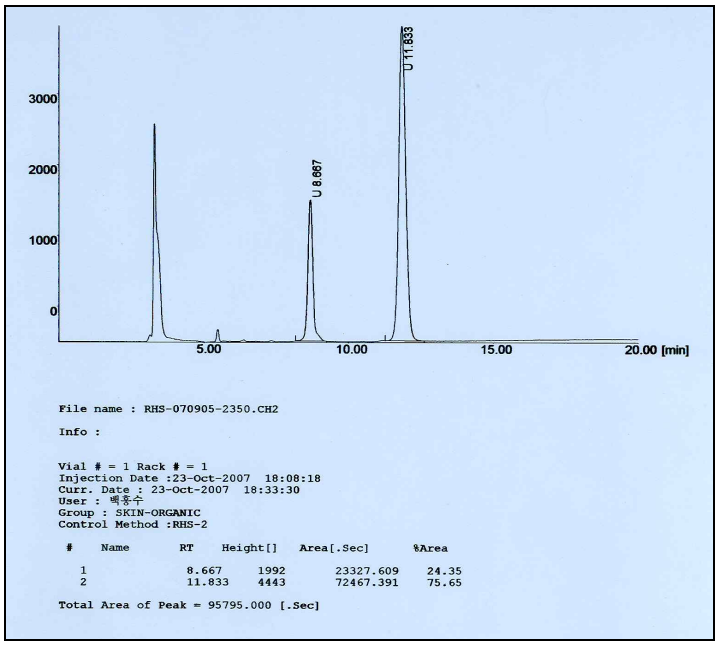


Table S1. Supporting Data for Figure 2: Solvent Effect on Enantioselectivity [a]

Entry	Solvent	Temperature	Time (h)	Yield (%)[b]	% *ee*[c]
1	Dioxane (40 mL)	RT	10	85	97
2	THF (40 mL)	RT	10	84	95
3	Et_2O (40 mL)	RT	10	80	94
4	CH_2Cl_2 (40 mL)	RT	10	80	75
5	Toluene (40 mL)	RT	10	75	74
6	Methyl cyclohexane (40 mL)	RT	10	79	43
7	MeOH (40 mL)[d]	RT	3	82	31

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.5 mmol), 10 equiv of MeOH (5 mmol) and catalysts **I** (10 mol%) in solvent (40 mL) at RT. [b] Isolated yields after chromatographic purification. [c] Determined by HPLC (see below HPLC profiles). [d] MeOH was used as solvent and reagent.

Table S2. Supporting Data for Figure 2: Concentration Effect on Enantioselectivity [a]

Entry	Solvent	Temperature	Time (h)	Yield (%)[b]	% *ee*[c]
8	THF (2.5 mL)	RT	0.6	82	82
9	THF (5 mL)	RT	1	84	87
10	THF (20 mL)	RT	7	83	93
11	THF (80 mL)	RT	15	81	96

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.5 mmol), 10 equiv of MeOH (5 mmol) and catalysts **I** (10 mol%) in solvent (THF) at RT. [b] Isolated yields after chromatographic purification. [c] Determined by HPLC (see below HPLC profiles).

Table S3. Temperature Effect on Enantioselectivity [a]

Entry	Solvent	Temperature	Time (h)	Yield (%)[b]	% *ee*[c]
1	THF (2.5 mL)	0 °C	5.5	81	81
2	THF (2.5 mL)	-20 °C	11	80	77
3	THF (40 mL)	0 °C	18	82	95
4	THF (40 mL)	-20 °C	30	78	95

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.5 mmol), 10 equiv of MeOH (5 mmol) and catalysts **I** (10 mol%) in solvent (THF). [b] Isolated yields after chromatographic purification. [c] Determined by HPLC (see below HPLC profiles).

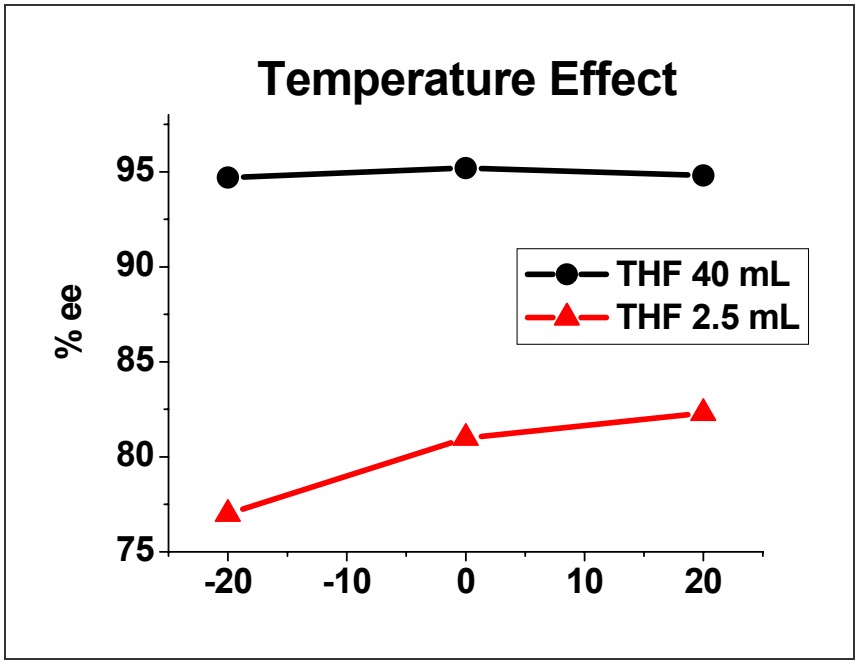


Table S1. Entry 1 (Dioxane 40 mL, RT)

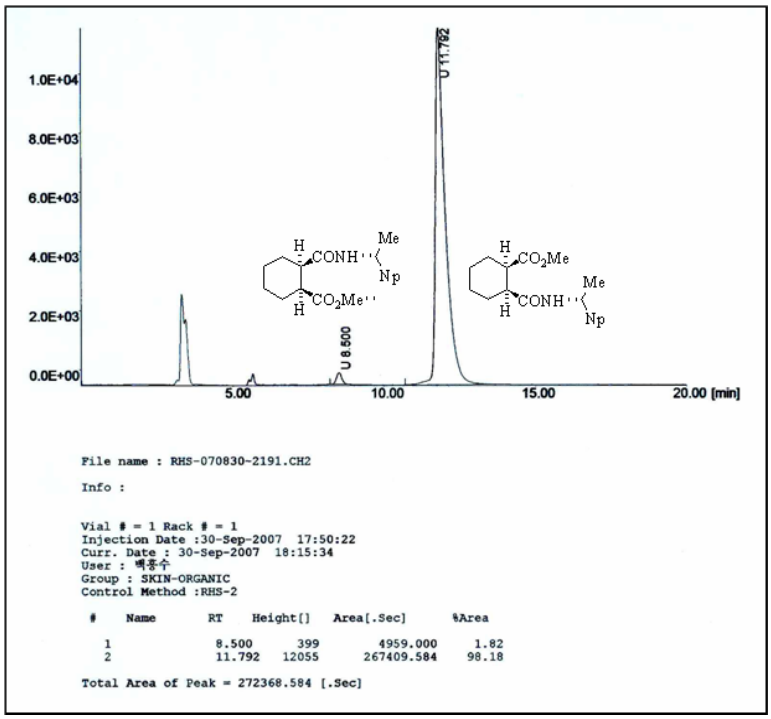


Table S1. Entry 2 (THF 40 mL, RT)

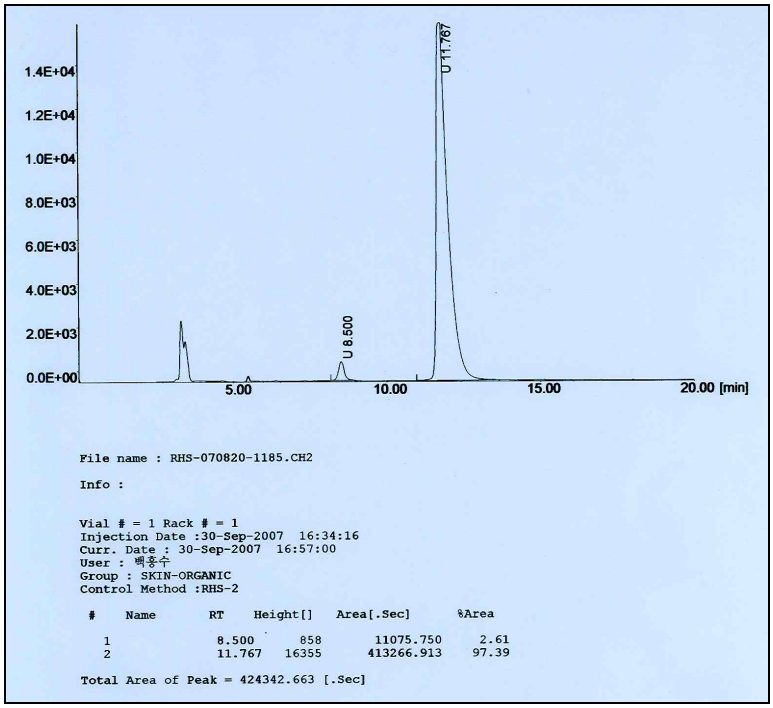
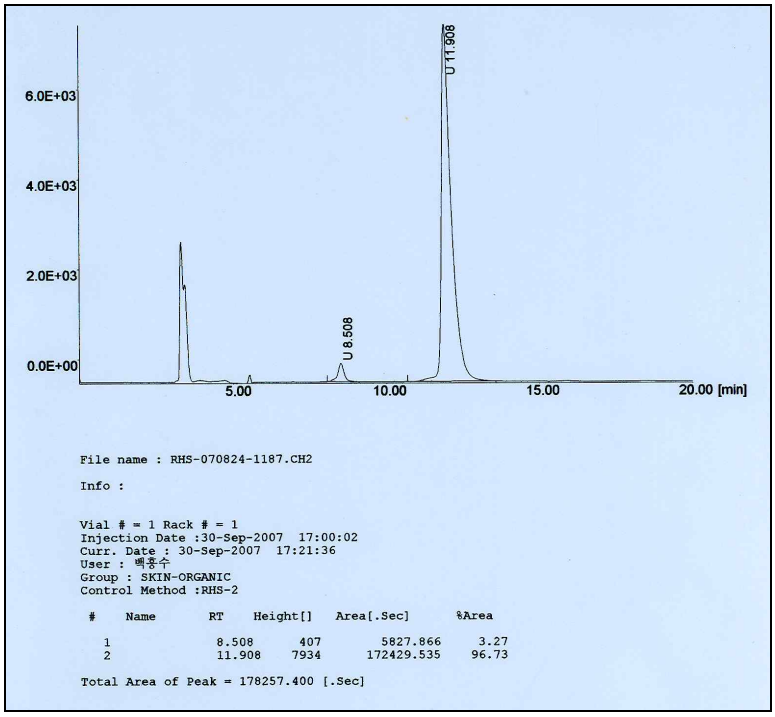


Table S1. Entry 3 (Diethyl Ether 40 mL, RT)



File name : RHS-070824-1187.CH2

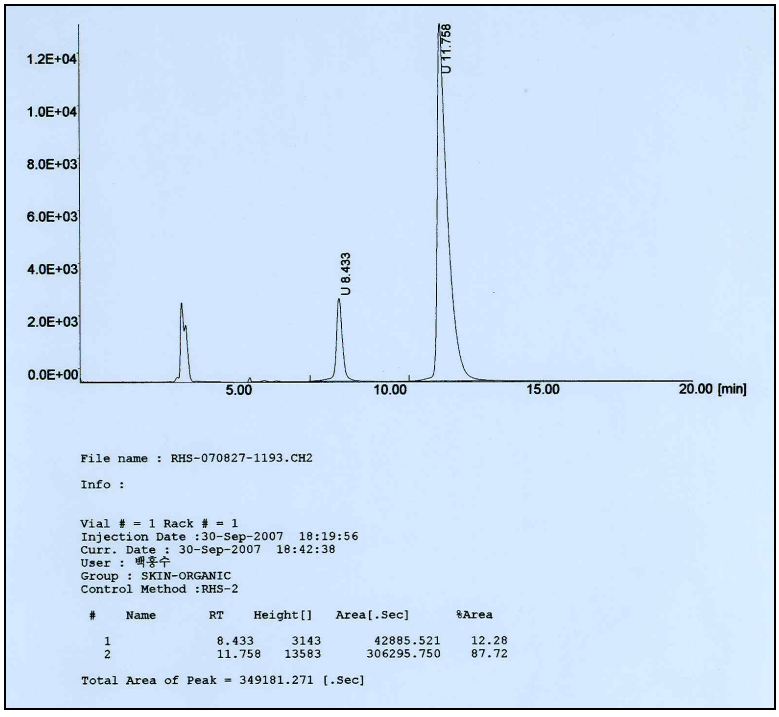
Info :

Vial # = 1 Rack # = 1
Injection Date :30-Sep-2007 17:00:02
Curr. Date : 30-Sep-2007 17:21:36
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.508	407	5827.866	3.27
2		11.908	7934	172429.535	96.73

Total Area of Peak = 178257.400 [.Sec]

Table S1. Entry 4 (Dichloromethane 40 mL, RT)



File name : RHS-070827-1193.CH2

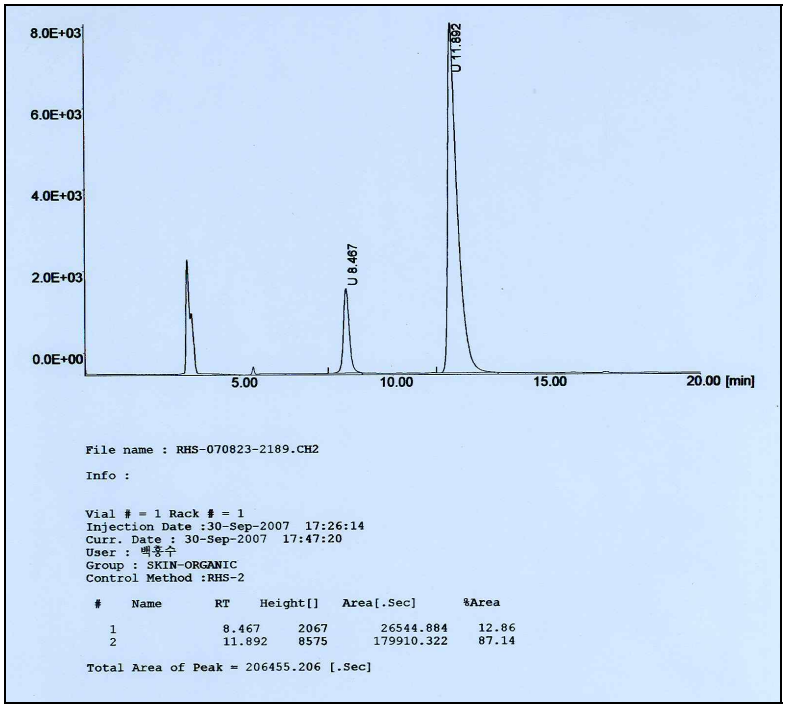
Info :

Vial # = 1 Rack # = 1
Injection Date :30-Sep-2007 18:19:56
Curr. Date : 30-Sep-2007 18:42:38
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.433	3143	42885.521	12.28
2		11.758	13583	306295.750	87.72

Total Area of Peak = 349181.271 [.Sec]

Table S1. Entry 5 (Tolene 40 mL, RT)



File name : RHS-070823-2189.CH2

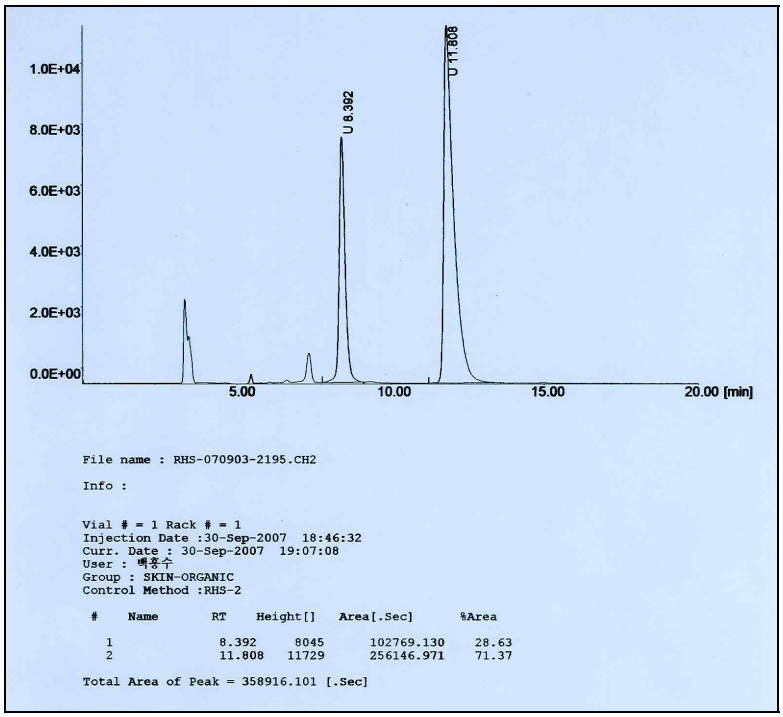
Info :

Vial # = 1 Rack # = 1
Injection Date :30-Sep-2007 17:26:14
Curr. Date : 30-Sep-2007 17:47:20
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.467	2067	26544.884	12.86
2		11.892	8575	179910.322	87.14

Total Area of Peak = 206455.206 [.Sec]

Table S1. Entry 6 (Methylcyclohexane 40 mL, RT)



File name : RHS-070903-2195.CH2

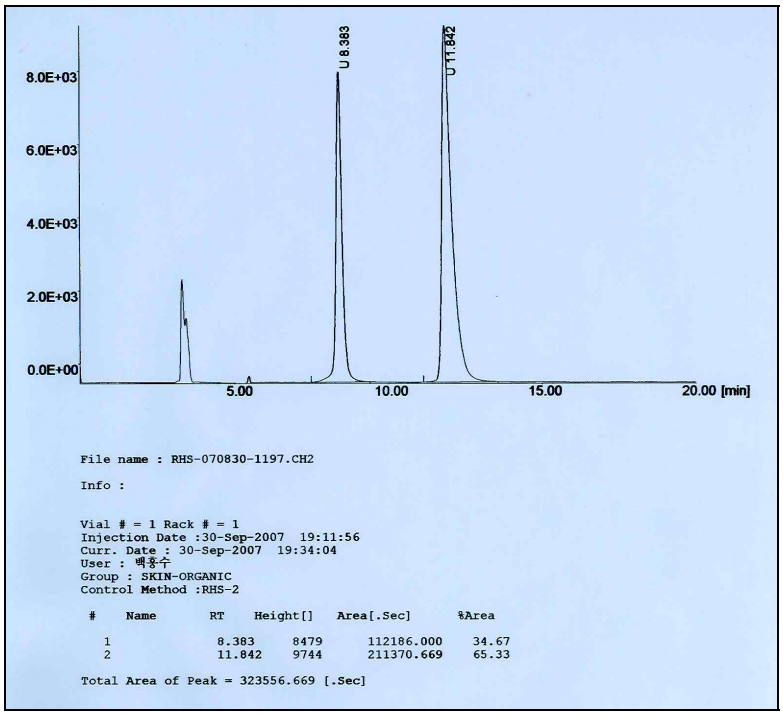
Info :

Vial # = 1 Rack # = 1
Injection Date :30-Sep-2007 18:46:32
Curr. Date : 30-Sep-2007 19:07:08
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.392	8045	102769.130	28.63
2		11.808	11729	256146.971	71.37

Total Area of Peak = 358916.101 [.Sec]

Table S1. Entry 7 (Methanol 40 mL, RT)



File name : RHS-070830-1197.CH2

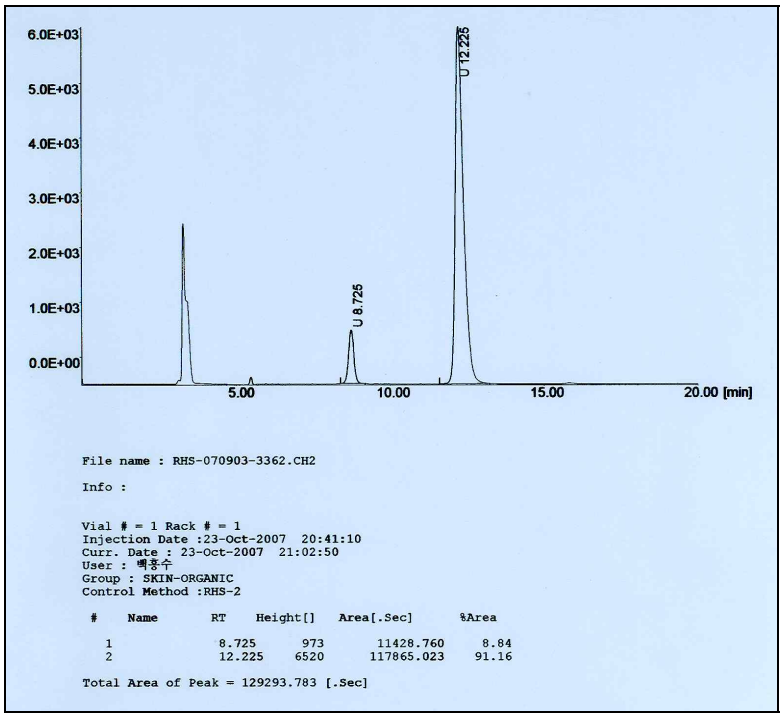
Info :

Vial # = 1 Rack # = 1
Injection Date :30-Sep-2007 19:11:56
Curr. Date : 30-Sep-2007 19:34:04
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.383	8479	112186.000	34.67
2		11.842	9744	211370.669	65.33

Total Area of Peak = 323556.669 [.Sec]

Table S2. Entry 1 (THF 2.5 mL, RT)



File name : RHS-070903-3362.CH2

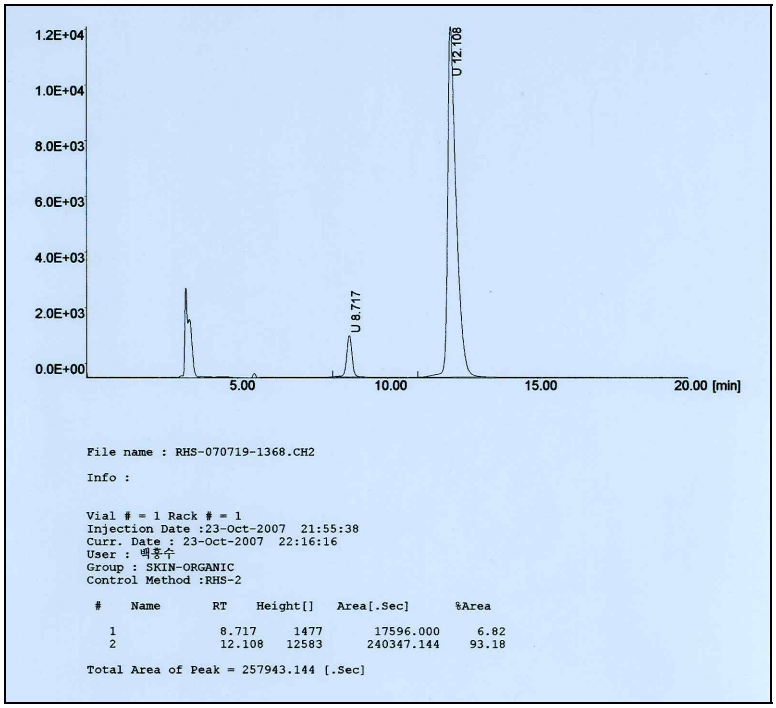
Info :

Vial # = 1 Rack # = 1
Injection Date :23-Oct-2007 20:41:10
Curr. Date : 23-Oct-2007 21:02:50
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.725	973	11428.760	8.84
2		12.225	6520	117865.023	91.16

Total Area of Peak = 129293.783 [.Sec]

Table S2. Entry 2 (THF 5 mL, RT)



File name : RHS-070719-1368.CH2

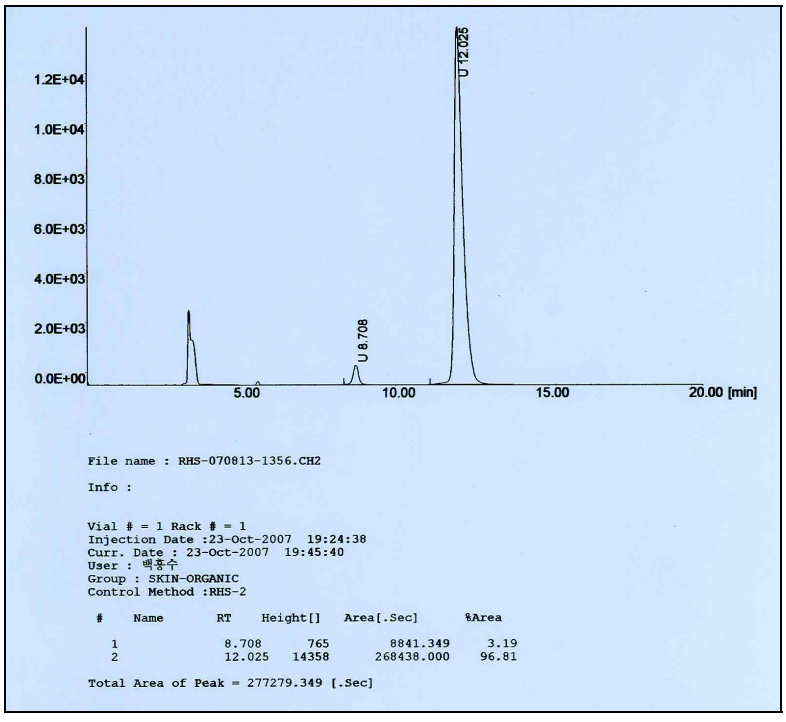
Info :

Vial # = 1 Rack # = 1
Injection Date :23-Oct-2007 21:55:38
Curr. Date : 23-Oct-2007 22:16:16
User : 배홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.717	1477	17596.000	6.82
2		12.108	12583	240347.144	93.18

Total Area of Peak = 257943.144 [.Sec]

Table S2. Entry 3 (THF 20 mL, RT)



File name : RHS-070813-1356.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date :23-Oct-2007 19:24:38
Curr. Date : 23-Oct-2007 19:45:40
User : 배홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.708	765	8841.349	3.19
2		12.025	14358	268438.000	96.81

Total Area of Peak = 277279.349 [.Sec]

Table S2. Entry 4 (THF 80 mL, RT)

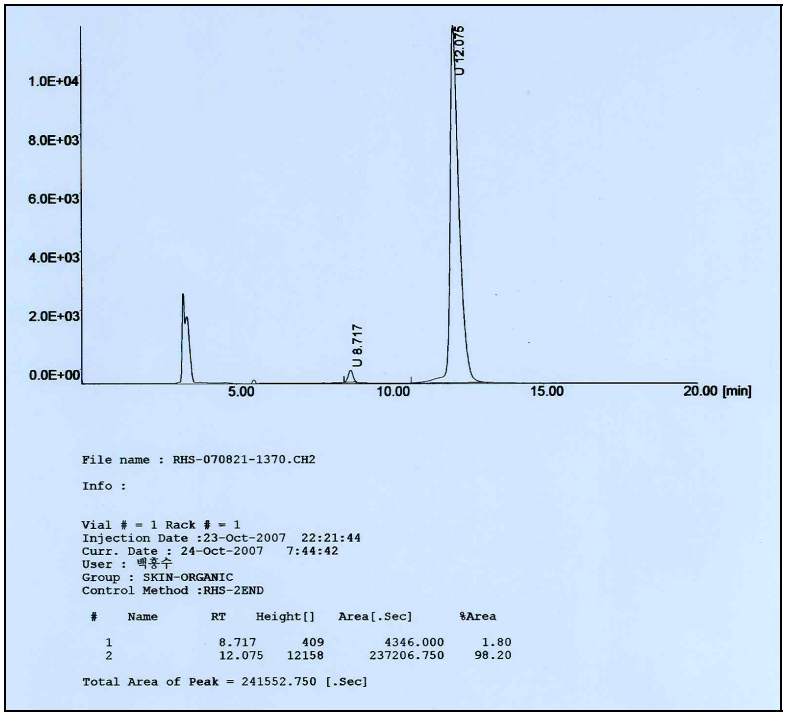


Table S3. Entry 1 (THF 2.5 mL, 0 ^{o}C)

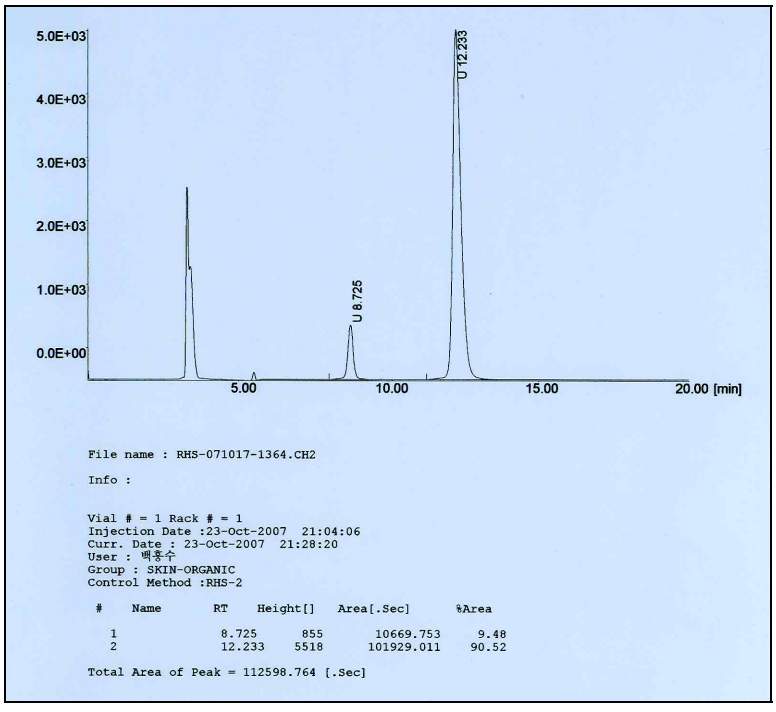


Table S3. Entry 2 (THF 2.5 mL, -20 ^{o}C)

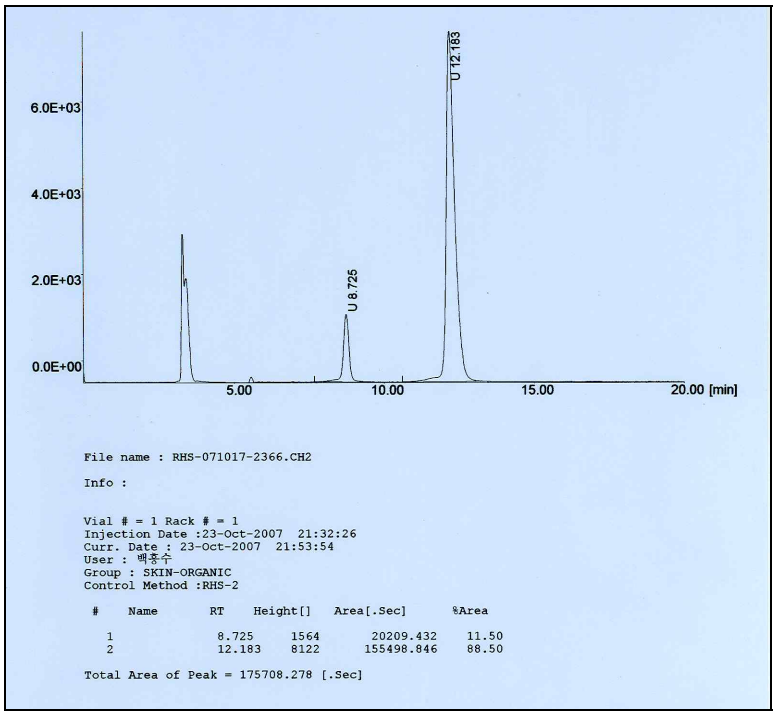


Table S3. Entry 3 (THF 40 mL, 0 ^{o}C)

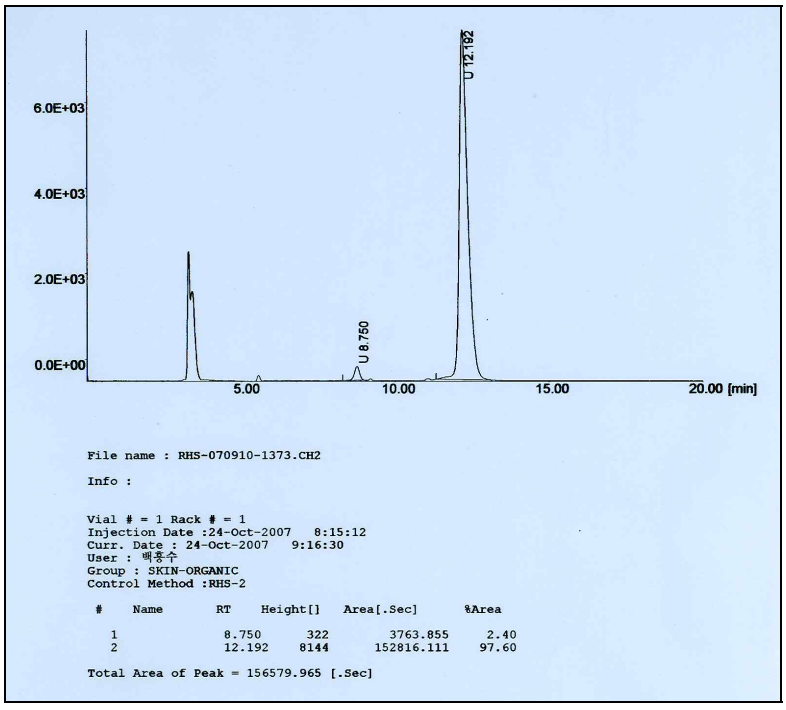
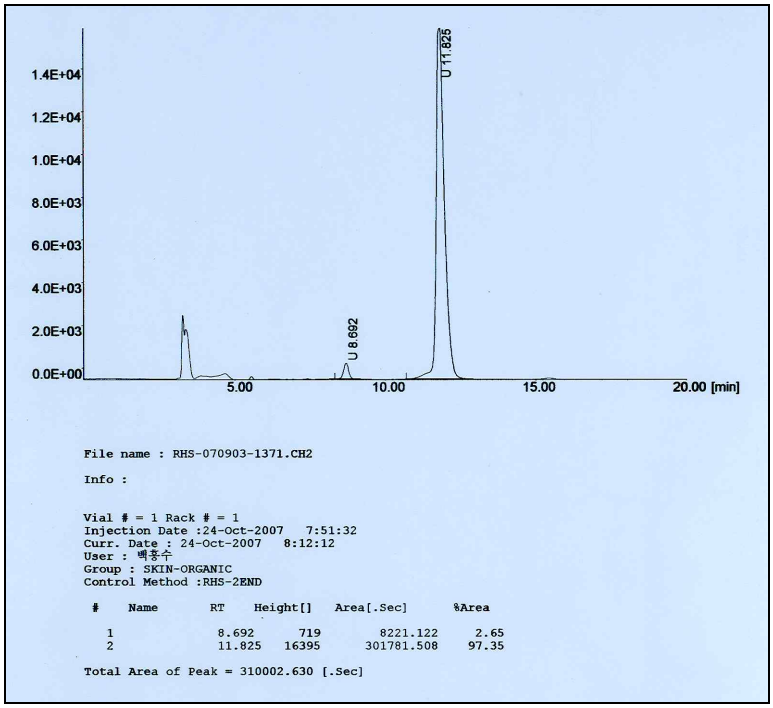


Table S3. Entry 4 (THF 40 mL, -20 ^{o}C)



File name : RHS-070903-1371.CH2

Info :

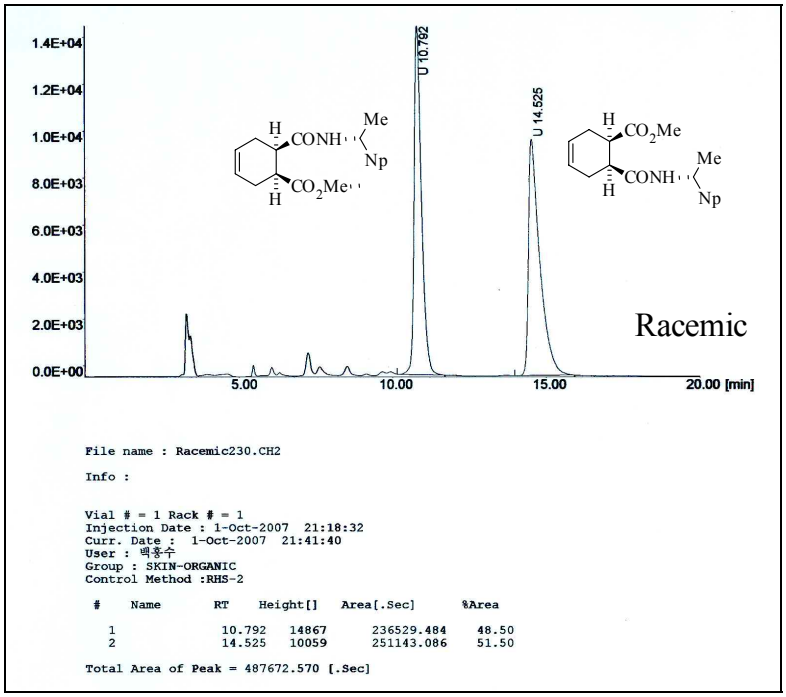
Vial # = 1 Rack # = 1
Injection Date :24-Oct-2007 7:51:32
Curr. Date : 24-Oct-2007 8:12:12
User : 백종수
Group : SKIN-ORGANIC
Control Method :RHS-2END

#	Name	RT	Height[]	Area[.Sec]	%Area
1		8.692	719	8221.122	2.65
2		11.825	16395	301781.508	97.35

Total Area of Peak = 310002.630 [.Sec]

HPLC Spectra for Table 2

Table 2. Entry 1



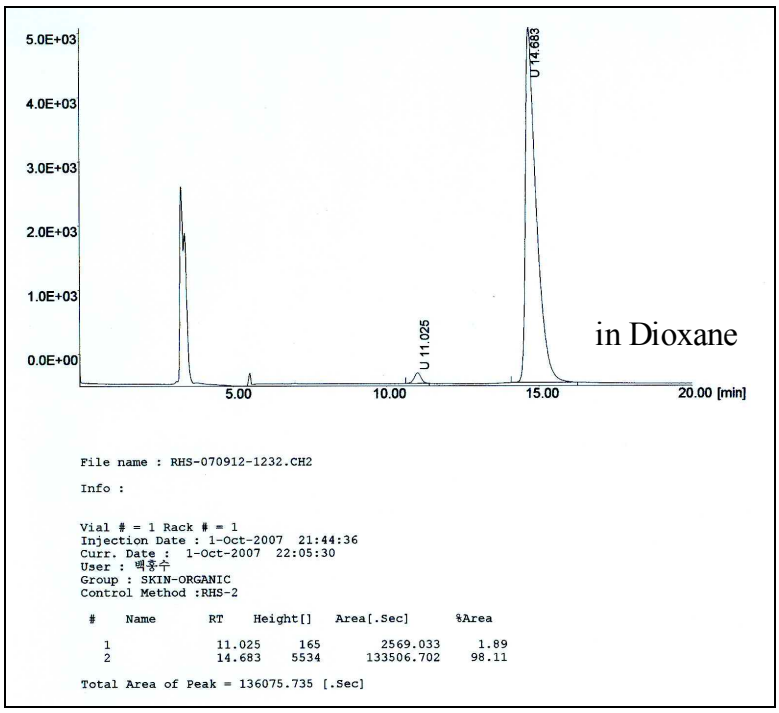
File name : Racemic230.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date : 1-Oct-2007 21:18:32
Curr. Date : 1-Oct-2007 21:41:40
User : 백용수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		10.792	14867	236529.484	48.50
2		14.525	10059	251143.086	51.50

Total Area of Peak = 487672.570 [.Sec]



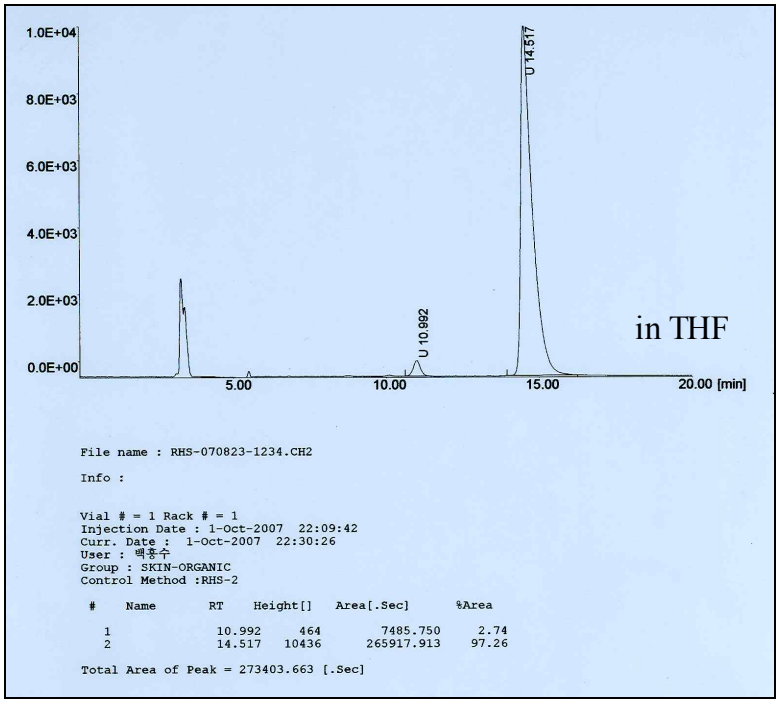
File name : RHS-070912-1232.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date : 1-Oct-2007 21:44:36
Curr. Date : 1-Oct-2007 22:05:30
User : 백용수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		11.025	165	2569.033	1.89
2		14.683	5534	133506.702	98.11

Total Area of Peak = 136075.735 [.Sec]



File name : RHS-070823-1234.CH2

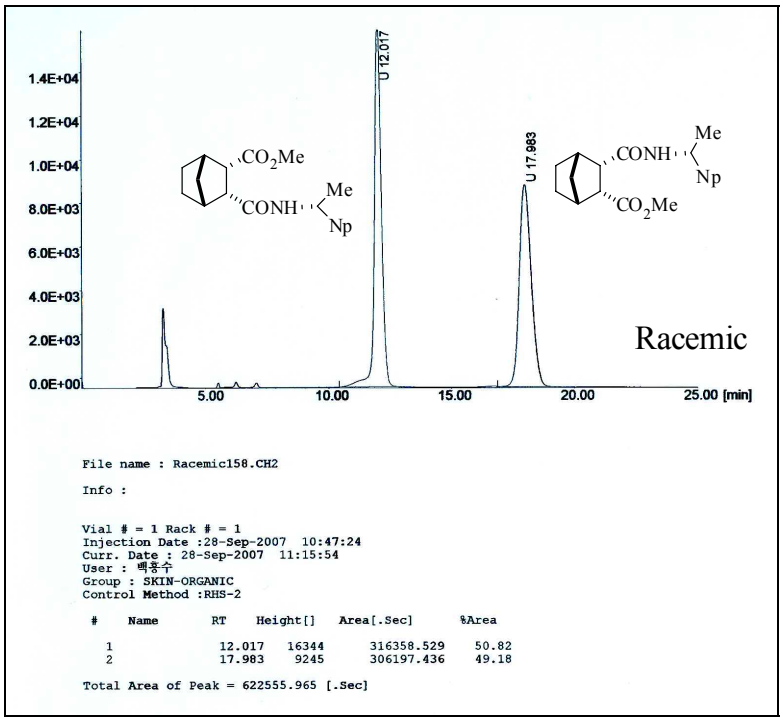
Info :

Vial # = 1 Rack # = 1
Injection Date : 1-Oct-2007 22:09:42
Curr. Date : 1-Oct-2007 22:30:26
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		10.992	464	7485.750	2.74
2		14.517	10436	265917.913	97.26

Total Area of Peak = 273403.663 [.Sec]

Table 2. Entry 2



File name : Racemic158.CH2

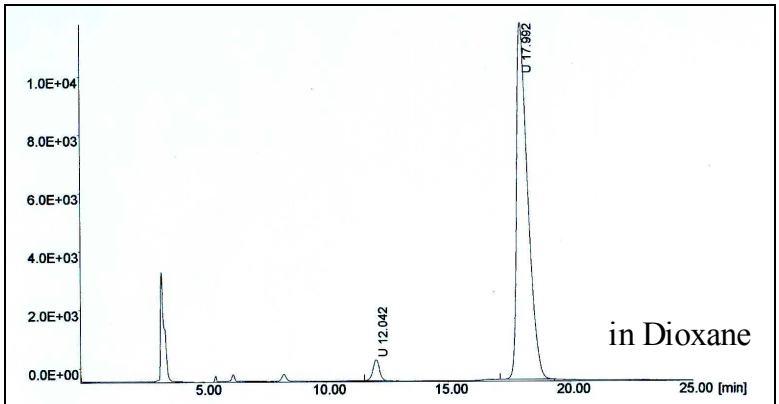
Info :

Vial # = 1 Rack # = 1
Injection Date :28-Sep-2007 10:47:24
Curr. Date : 28-Sep-2007 11:15:54
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		12.017	16344	316358.529	50.82
2		17.983	9245	306197.436	49.18

Total Area of Peak = 622555.965 [.Sec]

.



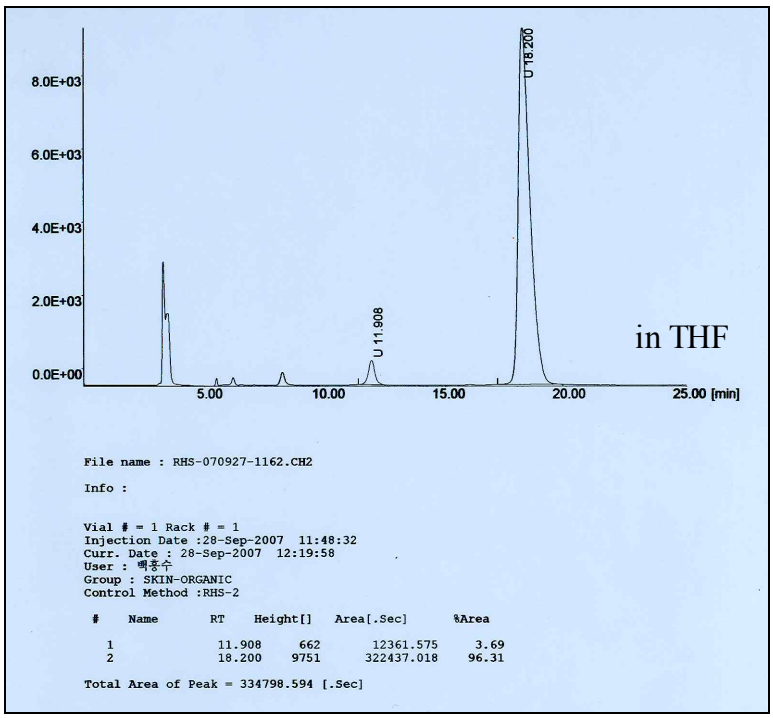
File name : RHS-070928-1156.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date :28-Sep-2007 10:17:16
Curr. Date : 28-Sep-2007 10:44:18
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		12.042	718	13153.459	3.36
2		17.992	12236	378637.500	96.64

Total Area of Peak = 391790.959 [.Sec]



File name : RHS-070927-1162.CH2

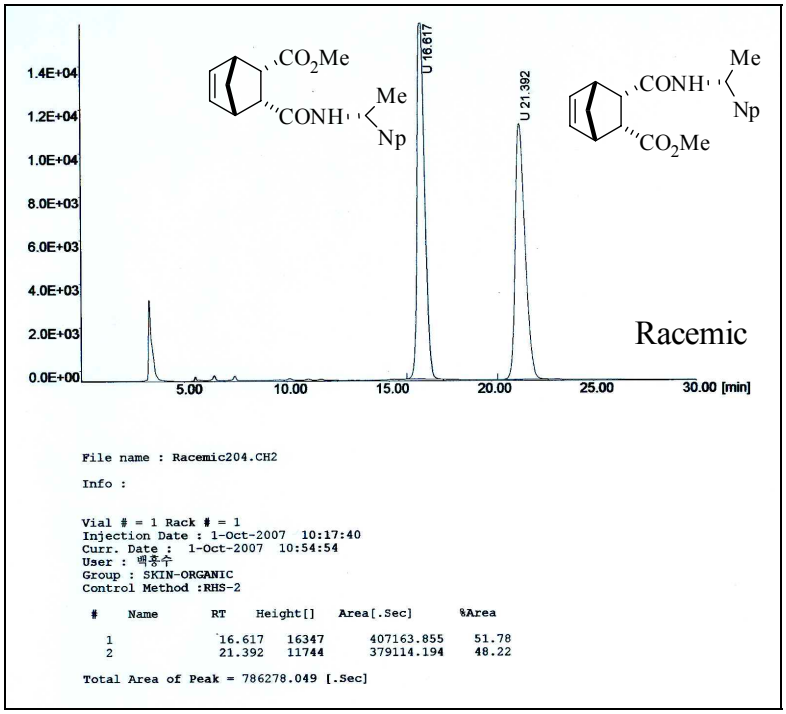
Info :

Vial # = 1 Rack # = 1
Injection Date :28-Sep-2007 11:48:32
Curr. Date : 28-Sep-2007 12:19:58
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		11.908	662	12361.575	3.69
2		18.200	9751	322437.018	96.31

Total Area of Peak = 334798.594 [.Sec]

Table 2. Entry 3



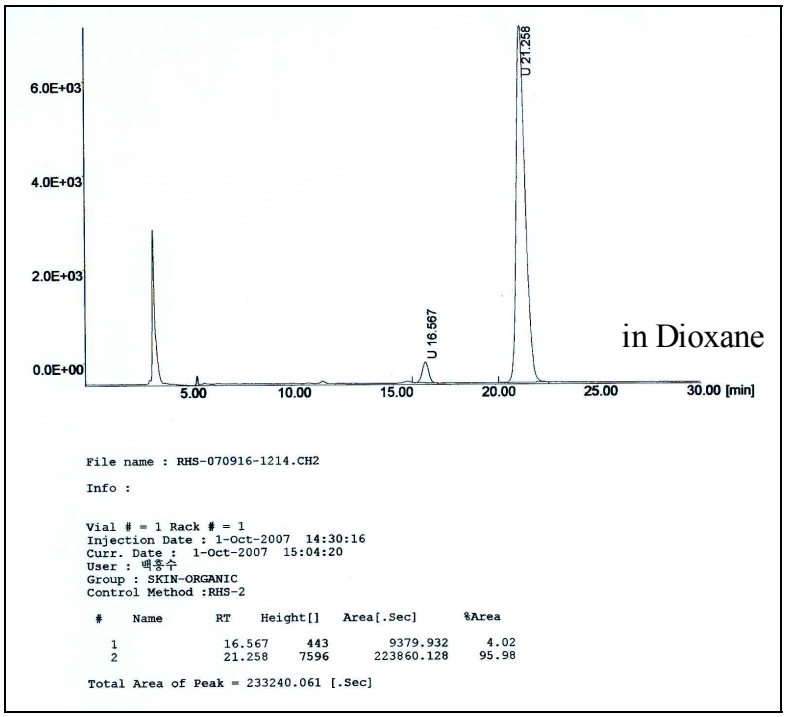
File name : Racemic204.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date : 1-Oct-2007 10:17:40
Curr. Date : 1-Oct-2007 10:54:54
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		16.617	16347	407163.855	51.78
2		21.392	11744	379114.194	48.22

Total Area of Peak = 786278.049 [.Sec]



File name : RHS-070916-1214.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date : 1-Oct-2007 14:30:16
Curr. Date : 1-Oct-2007 15:04:20
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		16.567	443	9379.932	4.02
2		21.258	7596	223860.128	95.98

Total Area of Peak = 233240.061 [.Sec]

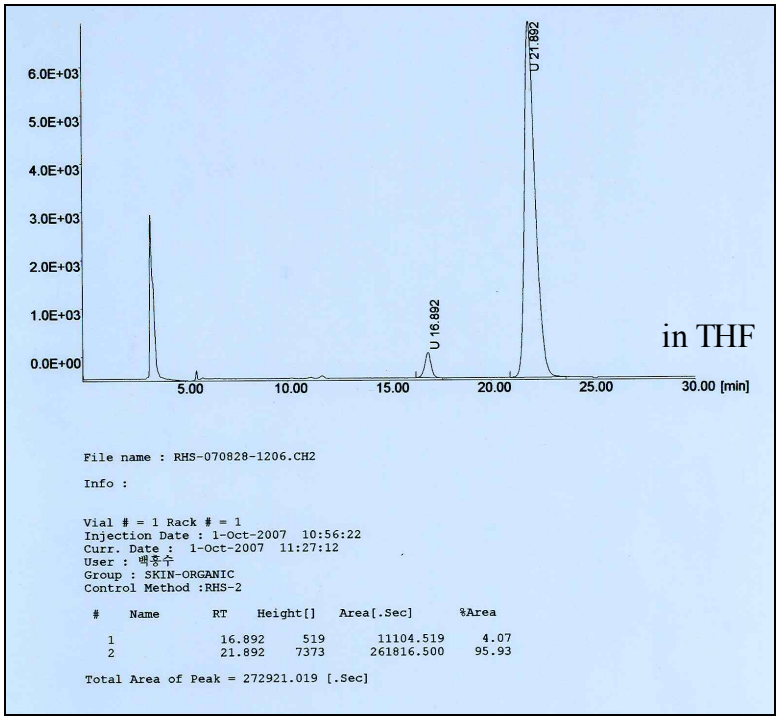
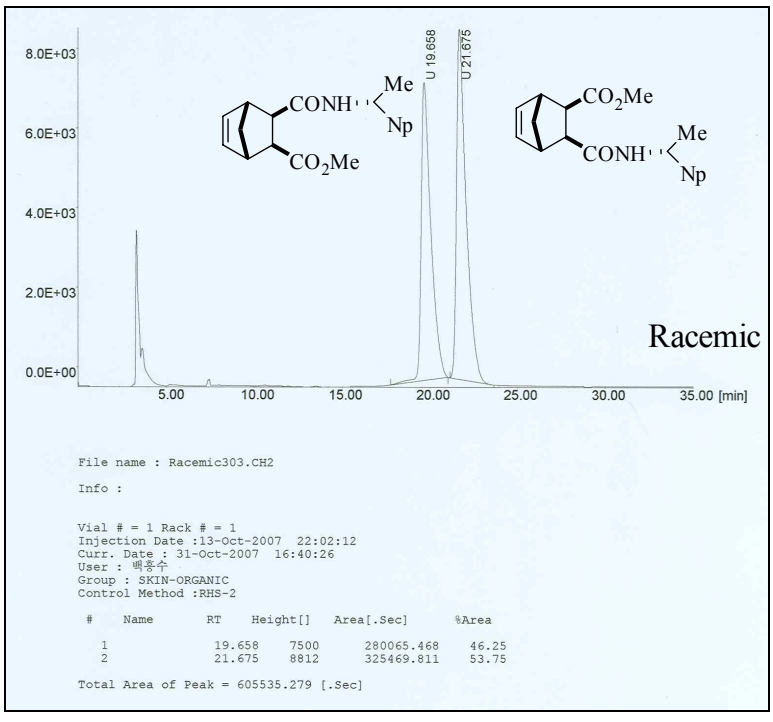
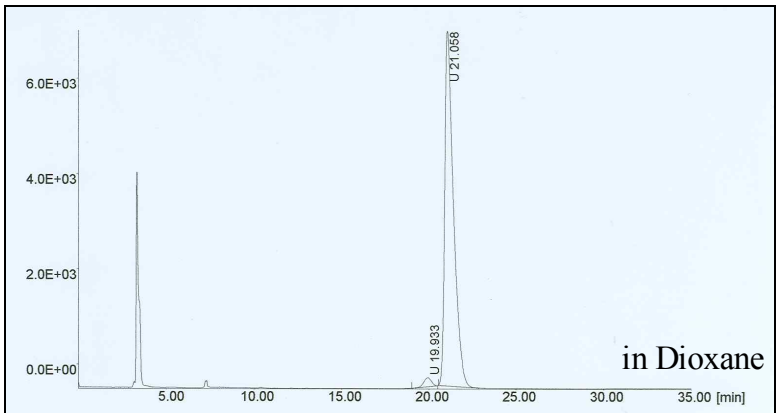


Table 2. Entry 4





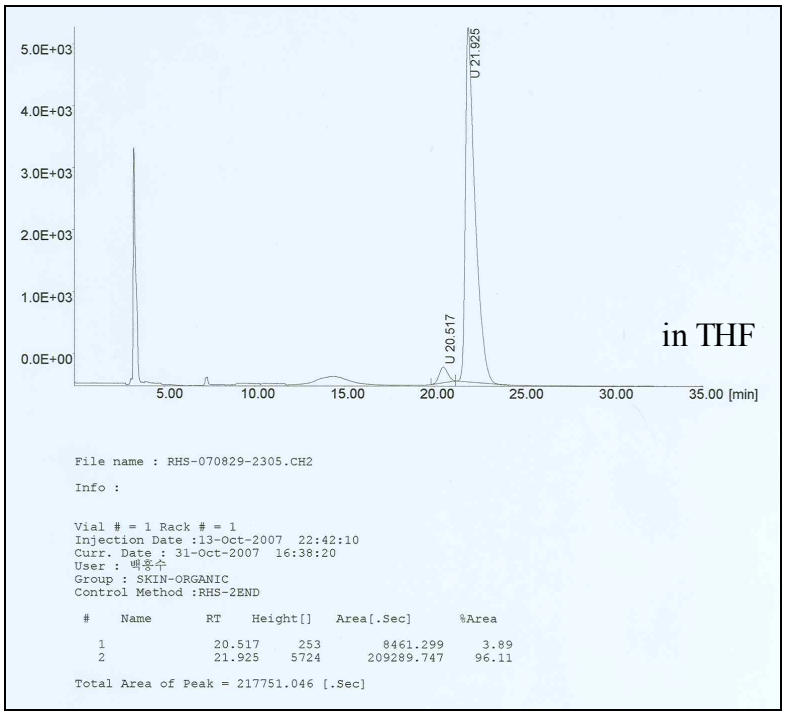
File name : RHS-070829-2306.CH2

Info :

Vial # = 1 Rack # = 1
Injection Date :15-Oct-2007 13:22:52
Curr. Date : 31-Oct-2007 16:37:06
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2

#	Name	RT	Height[]	Area[.Sec]	%Area
1		19.933	193	5808.271	2.26
2		21.058	7453	250851.207	97.74

Total Area of Peak = 256659.478 [.Sec]



File name : RHS-070829-2305.CH2

Info :

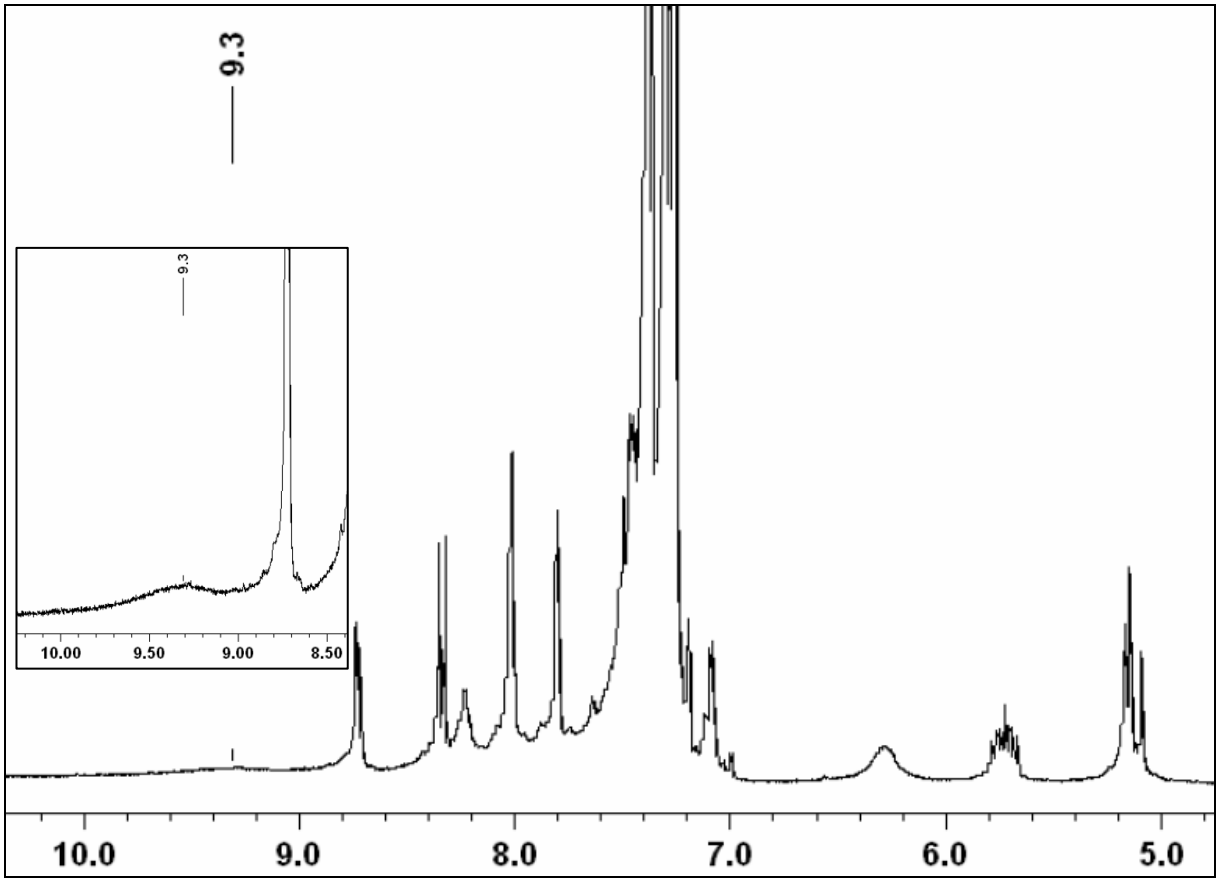
Vial # = 1 Rack # = 1
Injection Date :13-Oct-2007 22:42:10
Curr. Date : 31-Oct-2007 16:38:20
User : 백홍수
Group : SKIN-ORGANIC
Control Method :RHS-2END

#	Name	RT	Height[]	Area[.Sec]	%Area
1		20.517	253	8461.299	3.89
2		21.925	5724	209289.747	96.11

Total Area of Peak = 217751.046 [.Sec]

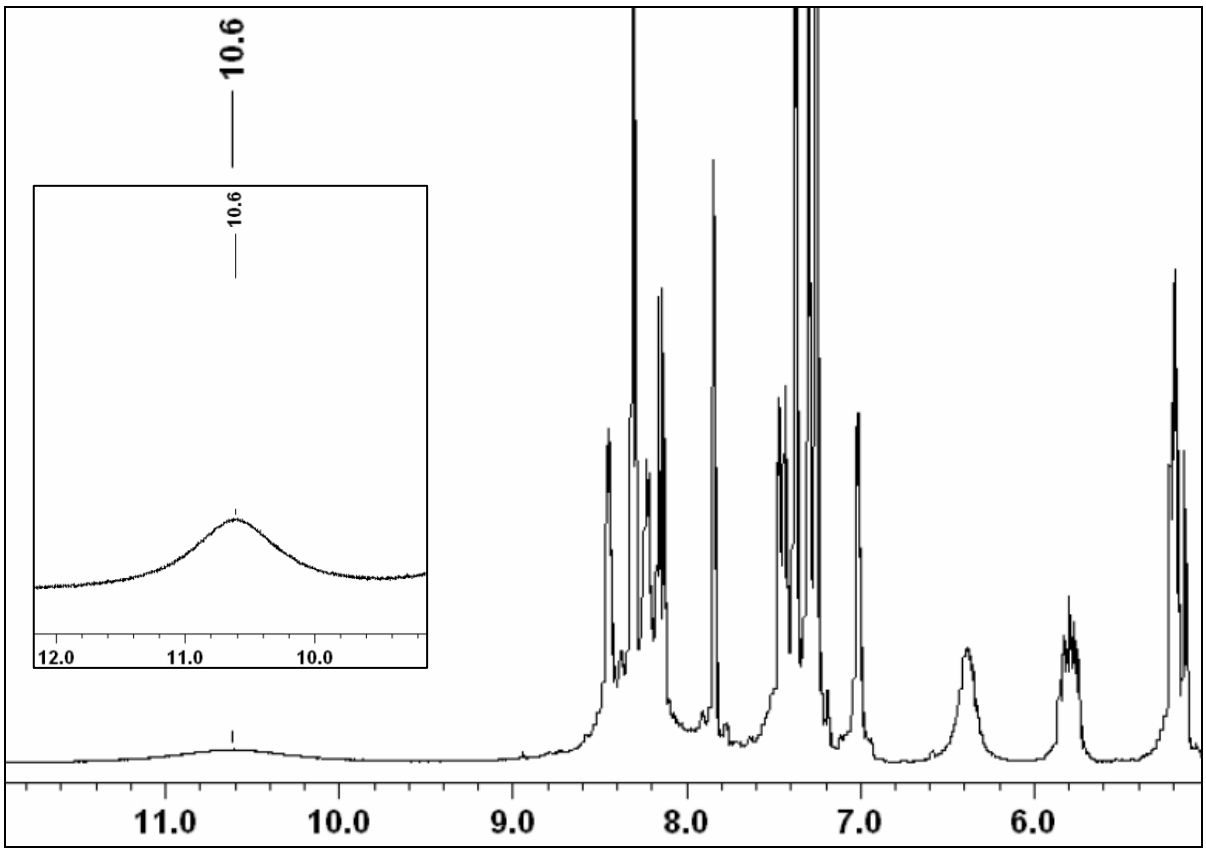
^{1}H NMR Spectroscopic Data for Self-Association of Catalyst I

Catalyst **I** (10 mM in d_8-Toluene, RT)



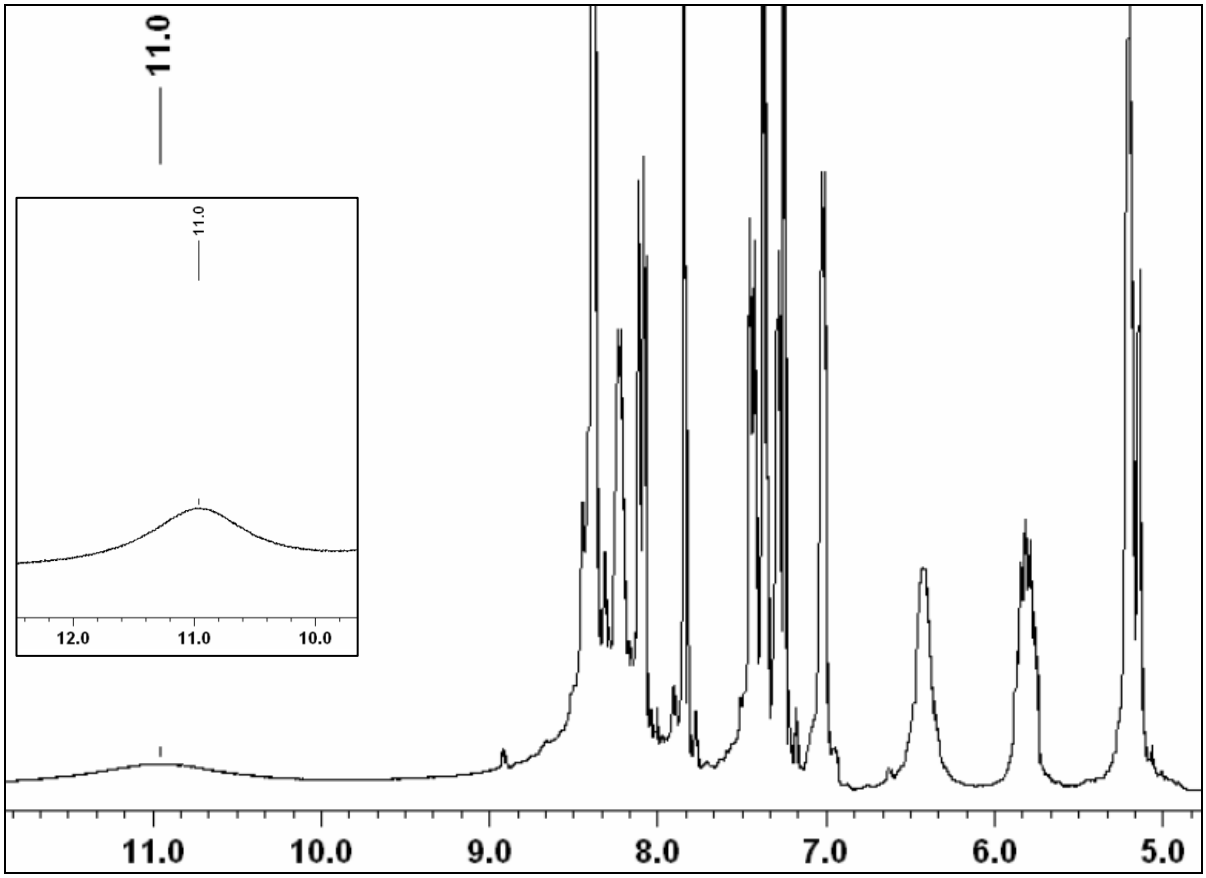
N-H Chemical shift : 9.3 ppm

Catalyst **I (** 67.5 mM in d_8-Toluene, RT)



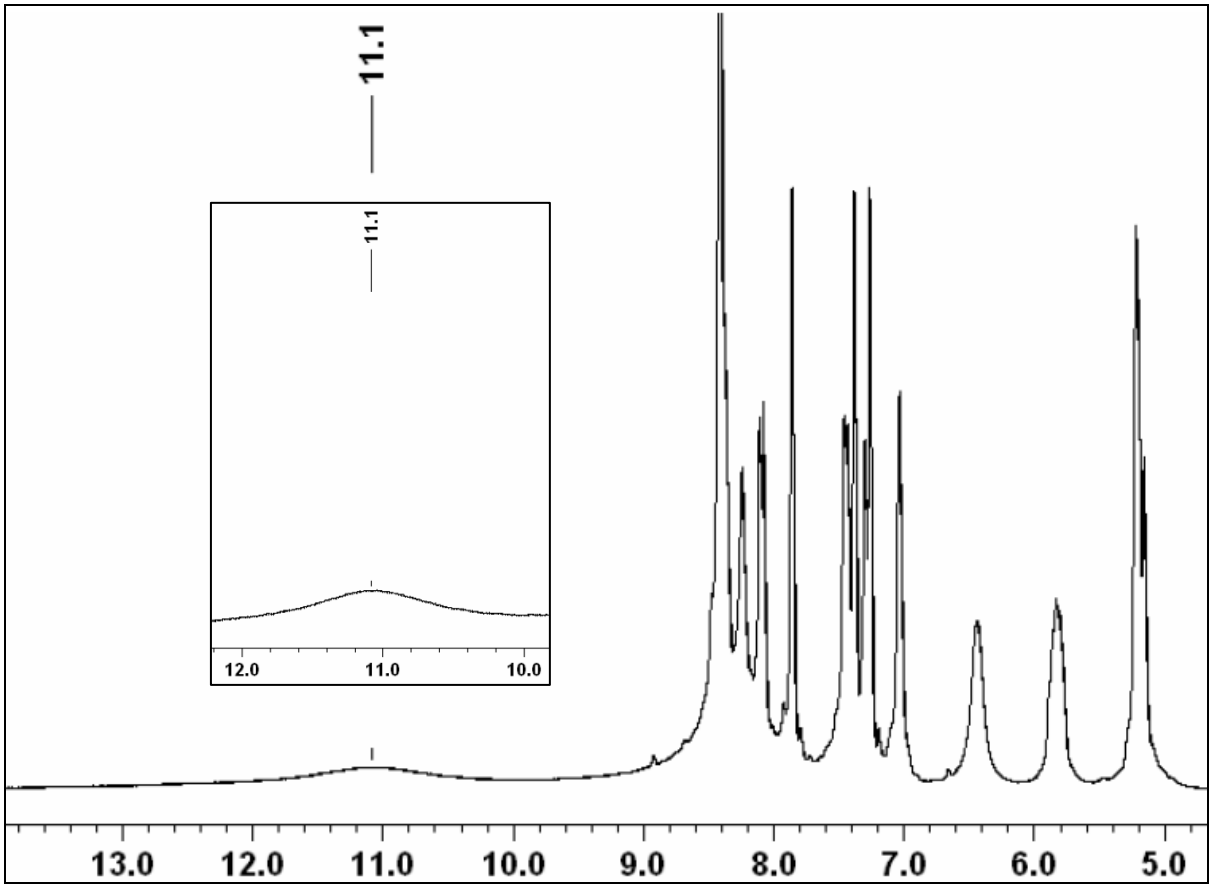
N-H Chemical shift : 10.6 ppm

Catalyst **I** (139 mM in d_8-Toluene, RT)



N-H Chemical shift : 11.0 ppm

Catalyst **I** (212 mM in d_8-Toluene, RT)



N-H Chemical shift : 11.1 ppm

Figure S-1. Computed Structures of **I-3d** and **I-ent-3d**

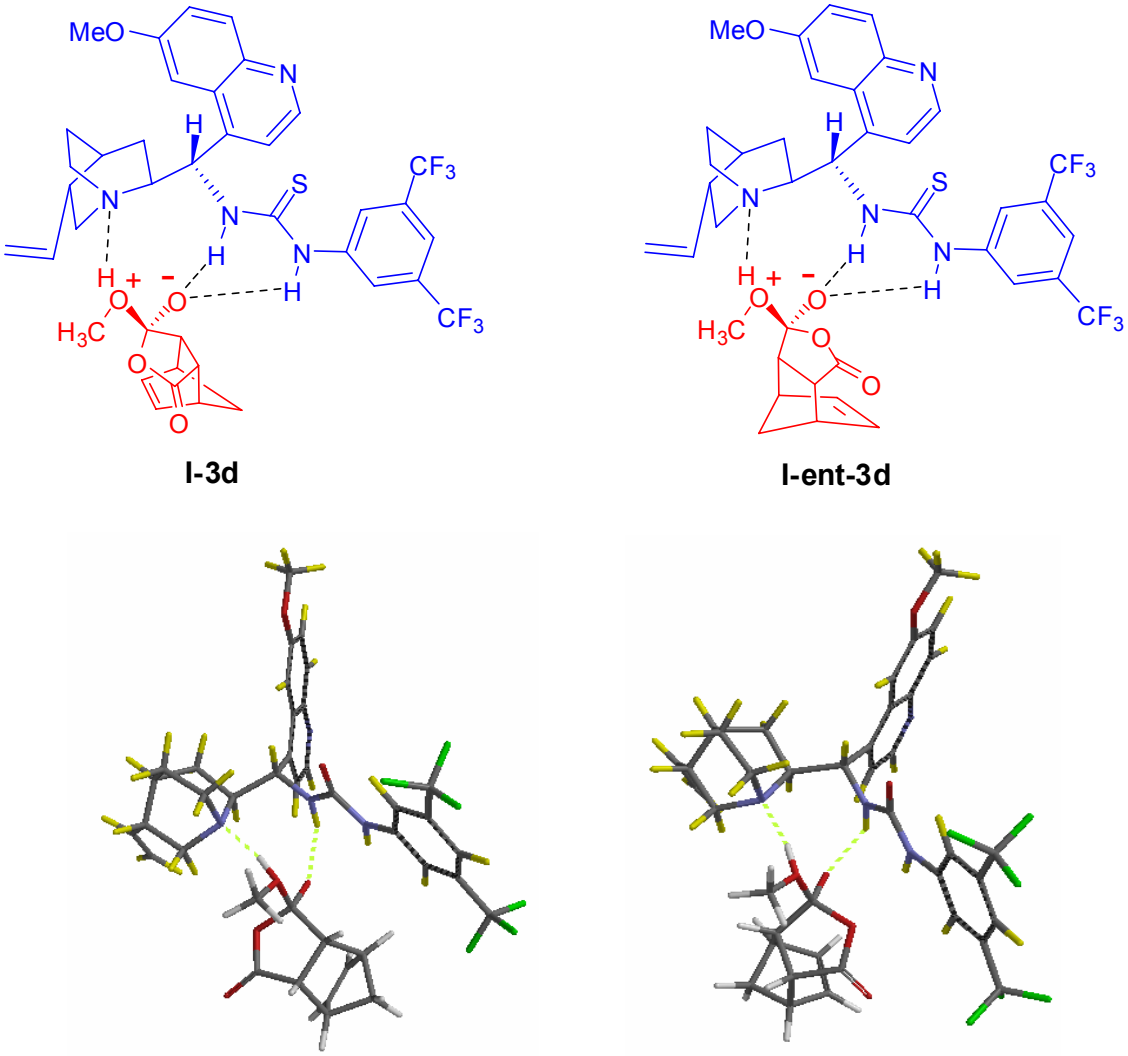


Table S-4. Transition state energy for **I-3** and **I-ent-3**

Substrate	E for **I-3** (in hartree)	E for **I-ent3** (in hartree)	ΔE (in hartrre)	ΔE (kcal)
1a	-2704.595525	-2704.593124	0.002401	1.505615
1b	-2703.361477	-2703.357996	0.003481	2.182462
1c	-2742.676366	-2742.673837	0.002528	1.585244
1d	-2741.43547	-2741.43385	0.001621	1.016242
1e	-2741.439809	-2741.437039	0.002769	1.736288