Stereoselective Asymmetric Hydrogenation of 2-Benzamidomethyl-3-oxobutanoate catalyzed by Pregosin's hydrido complexes of type Ru(H)(*p*-cymene)(bis-phosphine)(SbF_6)

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Supporting information

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Experimental Section

General Remarks

All catalysts purchased from Sigma Aldrich and were used as received. Solvents used were analytical grade and were used as received from Merck India Pvt. Ltd. Racemic 2-Benzamidomethyl-3-oxobutanoate was supplied by Unimark Remedies India private Ltd. The Thin Layer Chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates using ethyl acetate and hexanes as eluting agents. All products were characterized by ^{1}H-NMR spectroscopy. The ^{1}H spectra of samples were recorded on a Innova 500 MHz, and/or a Bruker-Avance-300 MHz Spectrometer using TMS as an internal standard in $CDCl_3$. High performance liquid chromatography (HPLC) was performed using an Shimazdu series liquid chromatography equipped with a dual pump and UV detector (fixed at 240 nm) using a CHIRALPAK IA column and/or CHIRALPAK AD column. For AD column type we have used isopropanol/hexanes 10:90 as eluting agent with a flow rate of 0.6mL/min and UV detection at 254nm. For CHIRALPAK IA column we have used n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v) as eluting agent with flow rate of 1mL/min and UV detection using PDA detector.

Preparation of Pregosin's hydrido complexes of type Ru(H)(*p*-cymene)(bis-phosphine)(SbF_6):

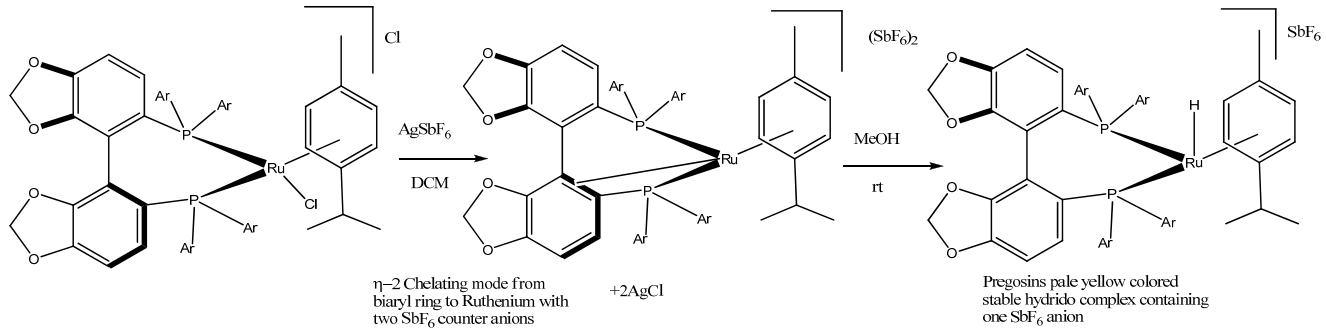
The pregosin's catalyst was synthesized by reacting 25 mg of Ruthenium di halo arene with two equiv of $AgSbF_6$ in 3mL methanol at 65˚C for 30 minutes under nitrogen atmosphere. Upon the reaction, a dark brown solution of the catalyst of Ruthenium di halo arene turned pale yellow followed by the precipitation of AgCl salts.

Asymetric hydrogenation of 2-Benzamidomethyl-3-oxobutanoate:

The above mother liquor (3 mL) containing Pregosin's catalyst was pippetted out using a syringe and transferred to an autoclave containing 1.0

mmol of **2-Benzamidomethyl-3-oxobutanoate** dissolved in 12 mL methanol. (total volume 15 mL). Then the reduction reaction was conducted at 808 psi of hydrogen gas at 70˚C for six hours in a Parr autoclave with substrate to catalyst ratio (S/C) of 60. After the quantitative completion of the reaction, which was determined by TLC, the crude reaction mixture after removing all solvents under reduced pressure was subjected to HPLC analysis to determine both diastereoselectivity and enantioselectivity of the products.

SCHEME 1



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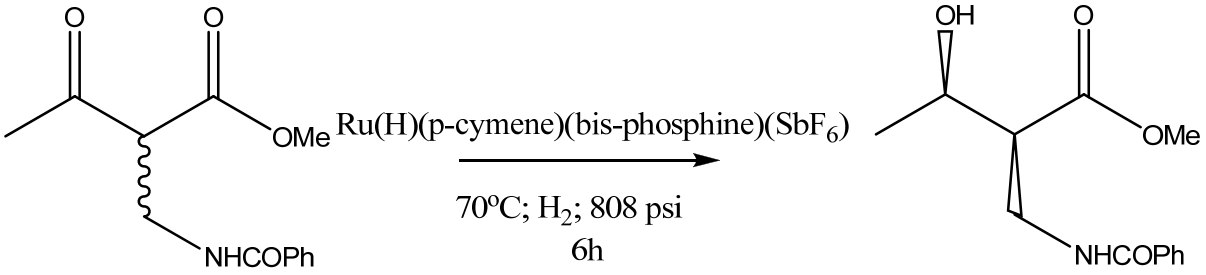
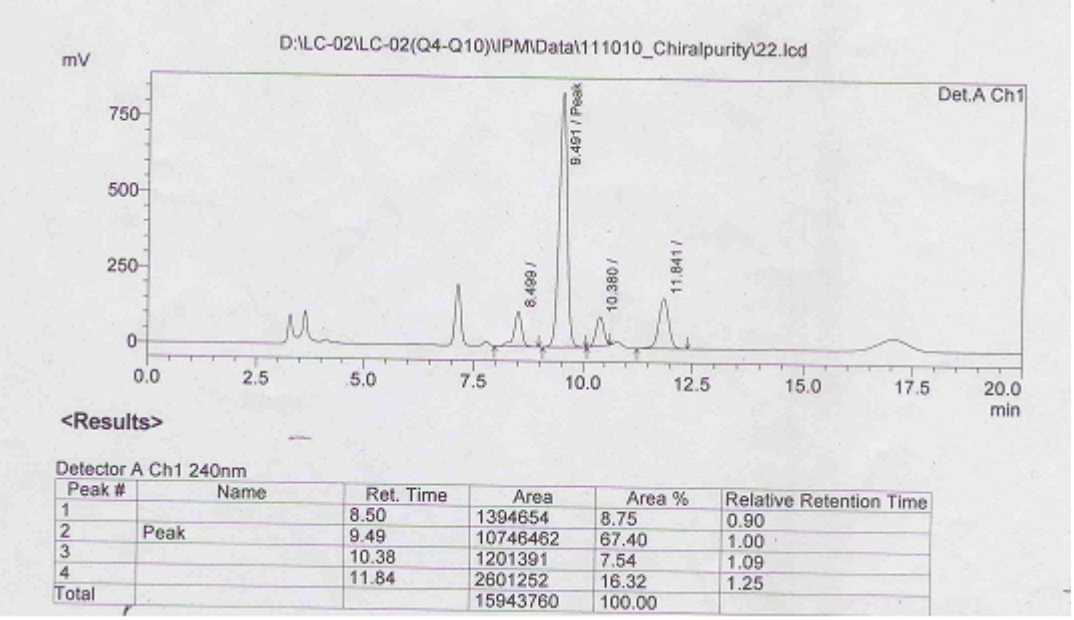


2-benzamidomethyl-3-oxobutanoate (**1**)

syn-(2S,3R)-**2**

HPLC data of*(2S,3R)-methyl-2-(benzamido-methyl)3-hydroxybutanoate:*

Table 1(Entry 1)Ru(H)(*p*-cymene)((S)-DTBM Segphos)-(SbF_6) in MeOH :
Data: 69% ee, 52 % de Column : Chiralpak IA (4.6X 250mm),Eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v);

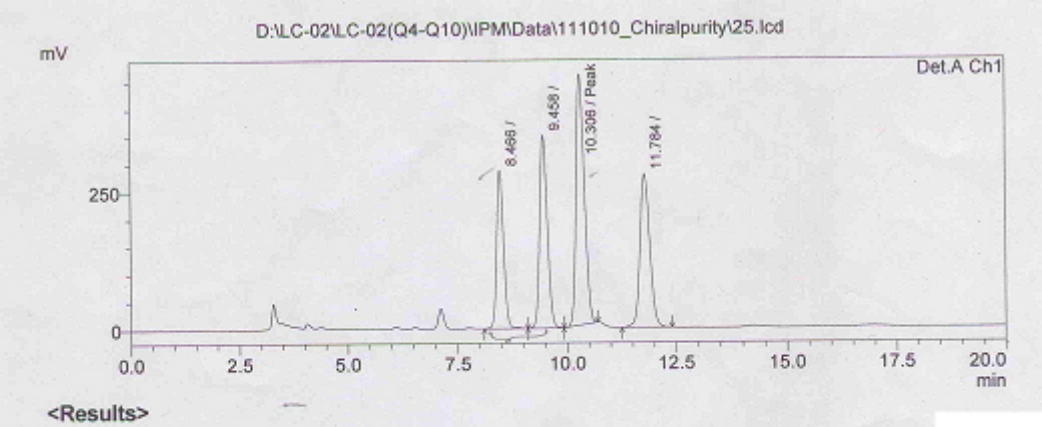


<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %	Relative Retention Time
1		8.50	1394654	8.75	0.90
2	Peak	9.49	10746462	67.40	1.00
3		10.38	1201391	7.54	1.09
4		11.84	2601252	16.32	1.25
Total			15943760	100.00	

Table1 (Entry 2) Ru(H)(*p*-cymene)((S)-DTBM Segphos)-Cl in MeOH:
Data: 25% ee, 16 % de Column: Chiralpak IA (4.6X 250mm) Eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v);



<Results>

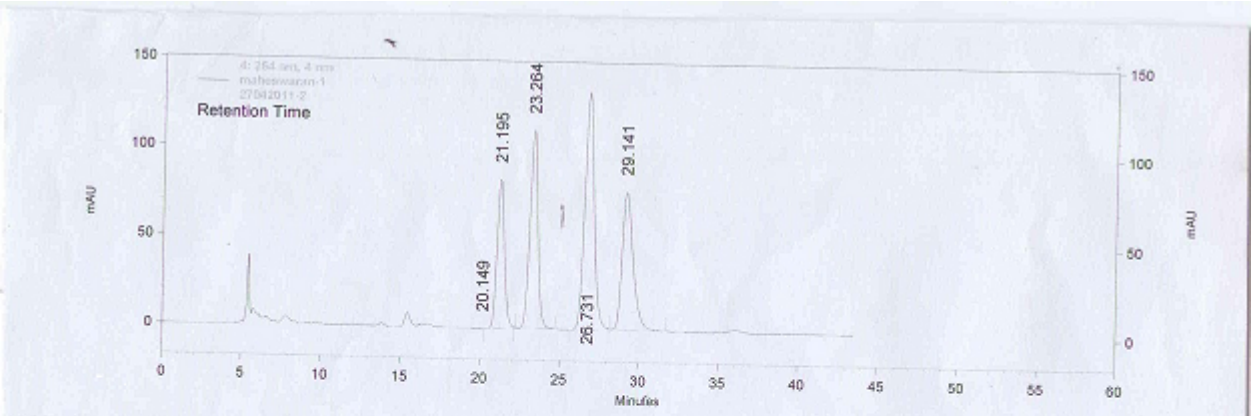
Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %	Relative Retention Time
1		8.47	3141565	17.65	0.82
2		9.46	4259604	23.93	0.92
3	Peak	10.31	6040758	33.94	1.00
4		11.78	4355581	24.47	1.14
Total			17797508	100.00	

Chiralpak-IA column: Peak 1 at 8.47 ret. time corresponds to syn-(2S,3R) isomer; peak 2 at 9.46 ret. time corresponds to *syn*-(2R,3S) isomer; peak 3 at 10.31 corresponds to *anti*-(2R,3R) isomer; and finally peak at 11.78 corresponds to *anti*-(2S,3S) isomer.

HPLC Conditions: Isocratic; Chiralpak-IA column (250x4.6mm), 5µ using n-Hexane/Ethanol/Diethylamide in the ratio of 85:15:0.2(v/v/v); UV Detection (240nm); diode array flow rate = 1.0mL/min at 25˚C.

Table1 (Entry 2) Ru(H)(*p*-cymene)((S)-DTBM Segphos)-Cl in MeOH:
Data: 18% ee, 16 % de Column: Chiralpak AD (4.6X 250mm) Eluting agent: hexanes: isopropanol (9:1)



4: 254 nm, 4 nm

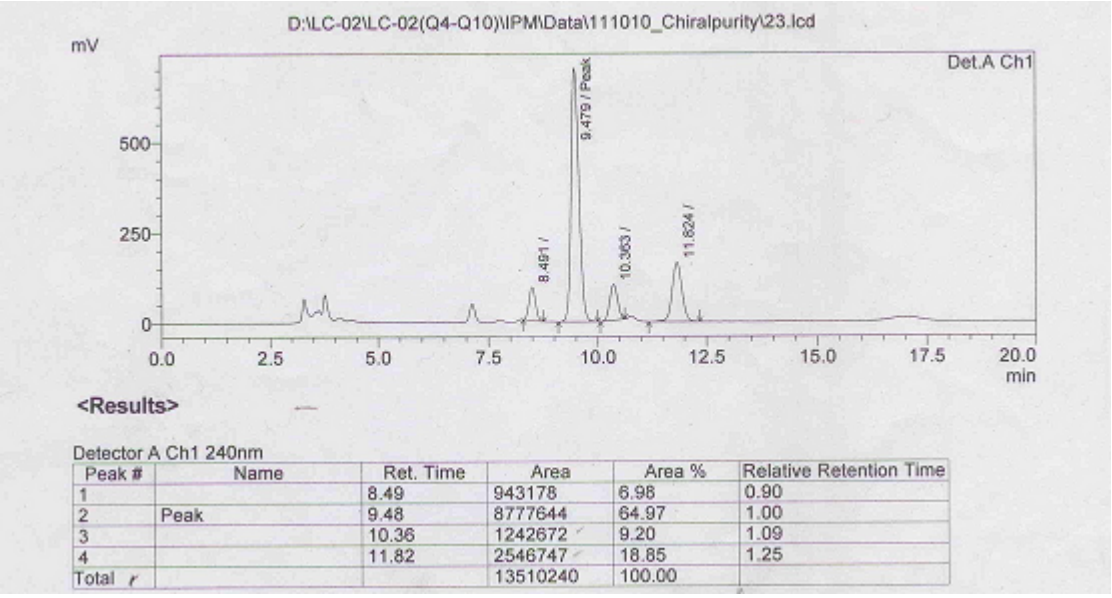
Pk #	Retention Time	Area	Area Percent	Lambda Max
1	20.149	0	0.00	198
2	21.195	2645877	17.05	224
3	23.264	3805715	24.53	224
4	26.731	5433557	35.02	224
5	29.141	3632326	23.41	224
Totals		15517475	100.00	

In Chiralpak-AD column: : Peak 1 at 21.195 ret. time corresponds to syn-(2S,3R) isomer; peak 2 at 23.264 ret. time corresponds to *syn*-(2R,3S) isomer; peak 3 at 26.731 corresponds to *anti*-(2R,3R) isomer; and finally peak at 29.141 corresponds to *anti*-(2S,3S) isomer.

HPLC Conditions: hexane:isopropanol = 90:10, flow: 0.6mL/min, UV detectior: diode array; UV detection.

Table1(Entry 3)Ru(H)(*p*-cymene)((S)-DTBM Segphos)-(PF_6) in MeOH:

Data: 81% ee, 44 % de; Column: Chiralpak IA (4.6X 250mm) Eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v).



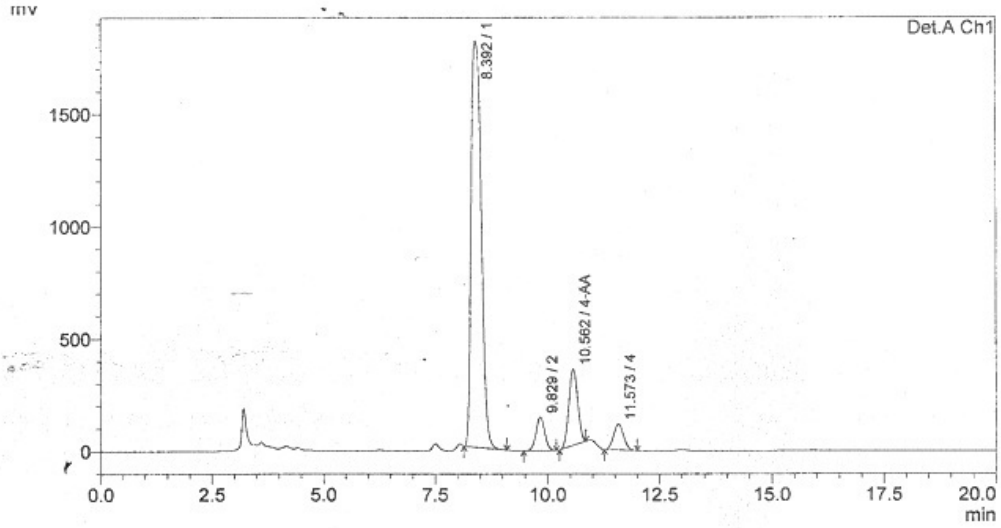
<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %	Relative Retention Time
1		8.49	943178	6.98	0.90
2	Peak	9.48	8777644	64.97	1.00
3		10.36	1242672	9.20	1.09
4		11.82	2546747	18.85	1.25
Total			13510240	100.00	

Table1(Entry 4)Ru(H)(*p*-cymene)((R)-DTBM Segphos)-(PF_6) in EtOH

Data: 87% ee, 63 % de; Column: Chiralpak IA (4.6X 250mm) Eluting agent: n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v).



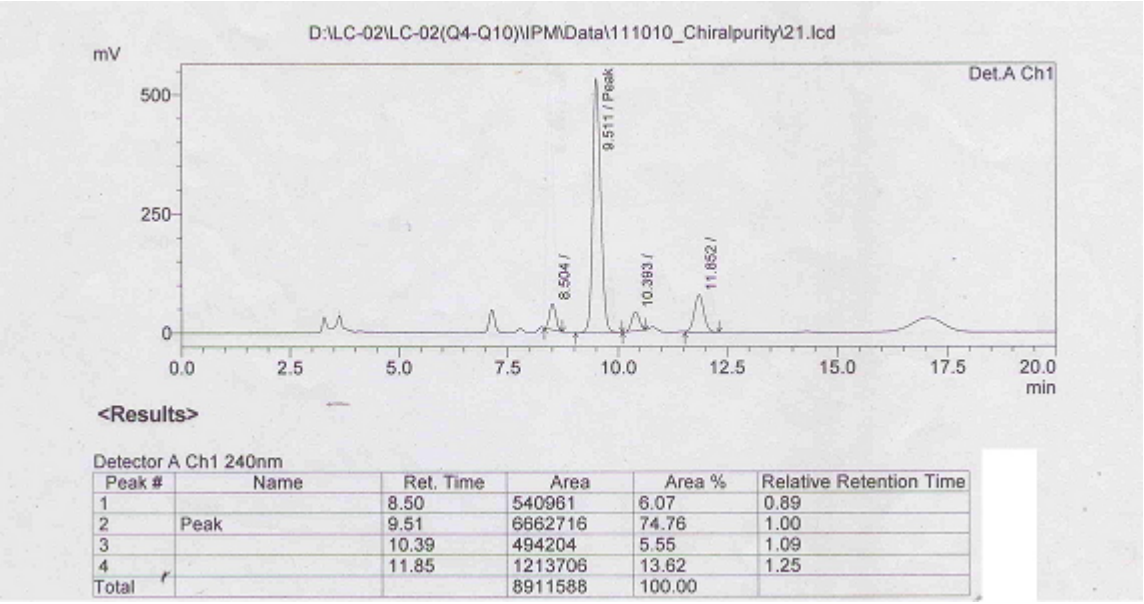
<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %
1	1	8.392	28440487	76.98
2	2	9.829	2004111	5.42
3	4-AA	10.562	4699050	12.72
4	4	11.573	1803788	4.88
Total			36947437	100.00

Table1 (Entry 5) Ru(H)(*p*-cymene)((S)-DTBM Segphos)-(PF_6 +SbF_6) in MeOH:

Data: 84% ee, 61 % de; Column: Chiralpak IA (4.6X 250mm), Eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v).



<Results>

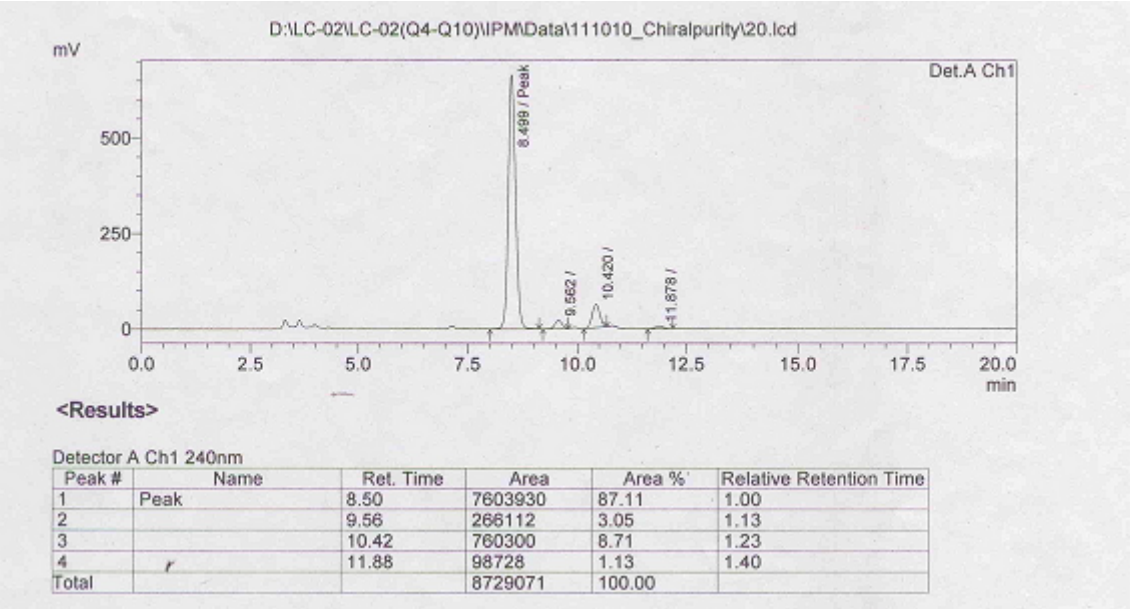
Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %	Relative Retention Time
1		8.50	540961	6.07	0.89
2	Peak	9.51	6662716	74.76	1.00
3		10.39	494204	5.55	1.09
4		11.85	1213706	13.62	1.25
Total			8911588	100.00	

Table1 (Entry 6) Ru(H)(*p*-cymene)((S)-DTBM Segphos)-(PF_6 +SbF_6) in EtOH

Data: 94% ee, 90 % de; Column: Chiralpak IA (4.6X 250mm), Eluting agent:

using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v).



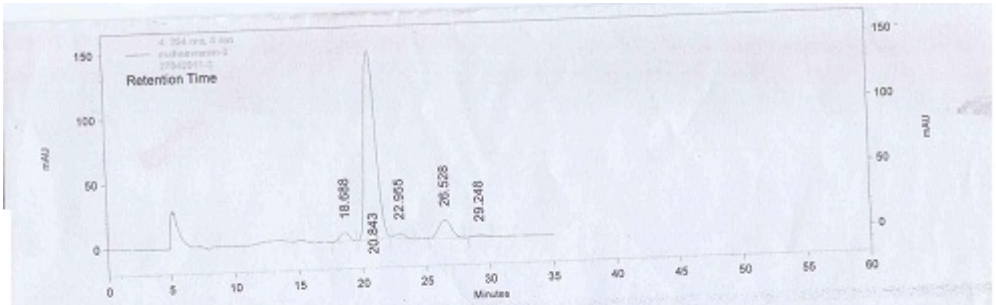
<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %	Relative Retention Time
1	Peak	8.50	7603930	87.11	1.00
2		9.56	266112	3.05	1.13
3		10.42	760300	8.71	1.23
4		11.88	98728	1.13	1.40
Total			8729071	100.00	

Table1 (Entry 7) Ru(H)(*p*-cymene)((R)-DTBM Segphos)-(SbF_6) in EtOH

Data: 98% ee, 85 % de; Column :Chiralpak-AD (4.6X 250mm) eluting agent: hexanes: isopropanol (9:1)



4: 254 nm, 4 nm

Pk #	Retention Time	Area	Area Percent	Lambda Max
1	18.688	340575	3.24	225
2	20.843	8976553	85.51	224
3	22.955	178162	1.70	225
4	26.528	941302	8.97	225
5	29.248	60627	0.58	225
Totals		10497219	100.00	

In Chiralpak-AD column: : Peak 1 at 20.843 ret. time corresponds to syn-(2S,3R) isomer peak 2 at 22.955 corresponds *syn*-(2R,3S) isomer of methyl ester; peak 3 at 26.528 corresponds to *anti*-(2R,3R) isomer; and finally peak at 29.248 corresponds to *anti*-(2S,3S) isomer. A lone peak at 18.688min corresponds to ethyl ester of the product.

HPLC trace of Racemic 3-hydroxyBenzamidomethylbutanoate

(Reaction repeated once again using conditions mentioned in Table 1; entry 2)Column type CHIRALPAK-IA using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v).

ANALYTICAL DEVELOPMENT LAB
UNIMARK REMEDIES LTD, AHMEDABAD

Sample ID	: Imipenem
Sample Name	: Racemic Mixture
Experiment	: Chiral Purity
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Date Processed	: 25-Jul-2012
Time Processed	: 2:38:00 PM
Column Name	: CHIRALPAK IA
Column Dimension	: (250X4.6)mm, 5µm
Column Number	: CIH-L51-199
LNB Ref	:DJS(ADL-385)030
Vail#	: 2
Injection Volum	: 10 uL
Analyst	:

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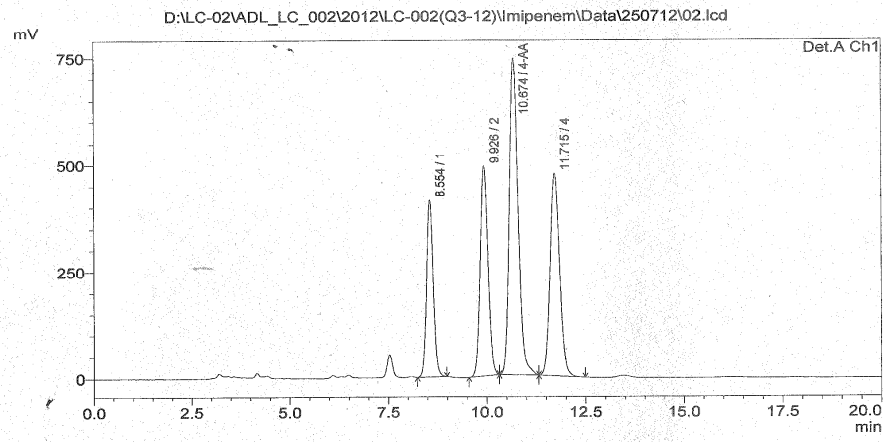

<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %	Theoretical Plate#	Tailing Factor	Resolution
1	1	8.554	4844552	15.60	12010	1.1	0.0
2	2	9.926	6734164	21.69	11829	1.1	4.1
3	4-AA	10.674	11539635	37.17	11012	1.2	1.9
4	4	11.715	7928663	25.54	11230	1.1	2.5
Total			31047013	100.00			

Table1 (Entry 8) Ru(H)(*p*-cymene)((R)-DM BINAP)-(SbF_6) in EtOH

Data: 73% ee, 02 % de; Column :Chiralpak IA (4.6X 250mm) eluting agent:

using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v).

ANALYTICAL DEVELOPMENT LAB
UNIMARK REMEDIES LTD, AHMEDABAD

Sample ID	: Imipenem
Sample Name	: DM-BINAP
Experiment	: Chiral Purity
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Date Processed	: 25-Jul-2012
Time Processed	: 4:51:48 PM
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Column Dimension	: (250X4.6)mm, 5µm
Column Number	: CIH-L51-199
LNB Ref	:DJS(ADL-385)030
Vail#	: 3
Injection Volum	: 10 uL
Analyst	:

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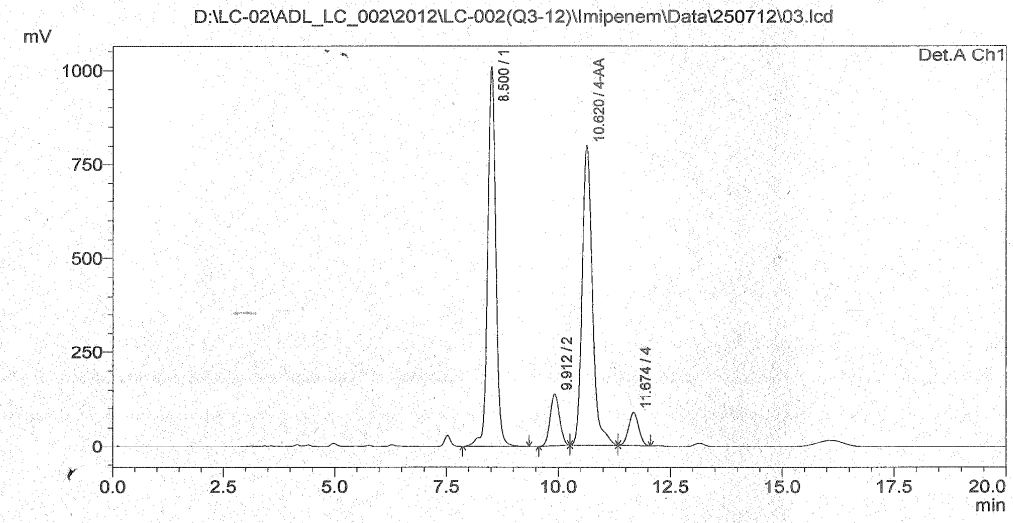

<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %
1	1	8.500	12656796	44.15
2	2	9.912	1981915	6.91
3	4-AA	10.620	12689868	44.27
4	4	11.674	1338957	4.67
Total			28667537	100.00

Table1 (Entry 9) Ru(H)(*p*-cymene)((R)-DM Segphos)-(SbF_6) in EtOH

Data: 87% ee, 03% de; Column :Chiralpak IA (4.6X 250mm) eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v);

ANALYTICAL DEVELOPMENT LAB
UNIMARK REMEDIES LTD, AHMEDABAD

Sample ID	: Imipenem
Sample Name	: DM-SEGPHOS
Experiment	: Chiral Purity
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Time Processed	: 4:53:50 PM
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Column Dimension	: (250X4.6)mm, 5µm
Column Number	: CIH-L51-199
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Injection Volum	: 10 uL
Analyst	:

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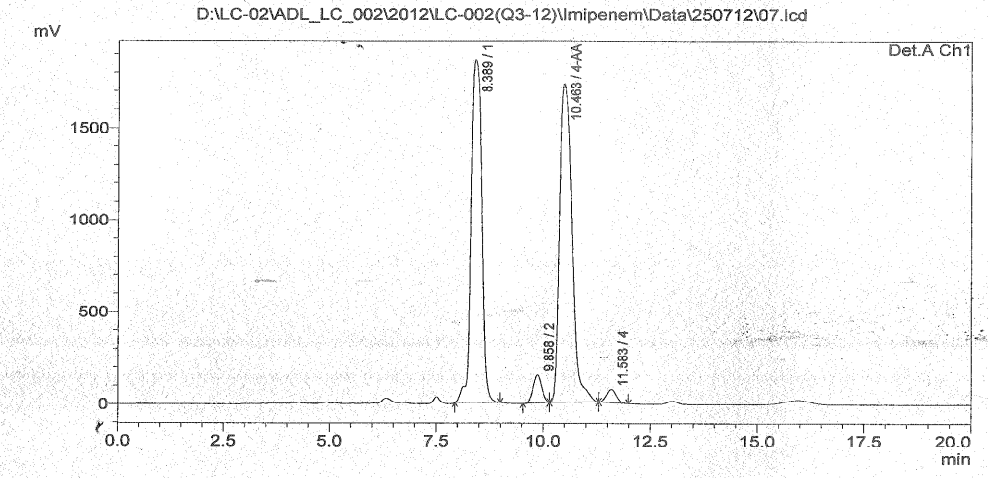

<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %
1	1	8.389	32032171	45.72
2	2	9.858	2164312	3.09
3	4-AA	10.463	34731822	49.57
4	4	11.583	1130962	1.61
Total			70059266	100.00

Table1 (Entry 10) Ru(H)(*p*-cymene)((R)-Tolyl-BINAP)-(SbF_6) in EtOH

Data: 74% ee, 02 % de; Column :Chiralpak IA (4.6X 250mm) eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v);

ANALYTICAL DEVELOPMENT LAB
UNIMARK REMEDIES LTD, AHMEDABAD

Sample ID	: Imipenem
Sample Name	: T-BINAP
Experiment	: Chiral Purity
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Batch Filename	: D:\LC-02\ADL_LC_002\2012\LC-002(Q3-12)\Imipenem\Sequence\250712\250712_4-AA_Chiral Purity.lcl
Date Acquired	: 25-Jul-2012 3:04:53 PM
Date Processed	: 25-Jul-2012
Time Processed	: 4:52:06 PM
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Column Dimension	: (250X4.6)mm, 5µm
Column Number	: CIH-L51-199
LNB Ref	:DJS(ADL-385)030
Vail#	: 4
Injection Volum	: 10 uL
Analyst	:

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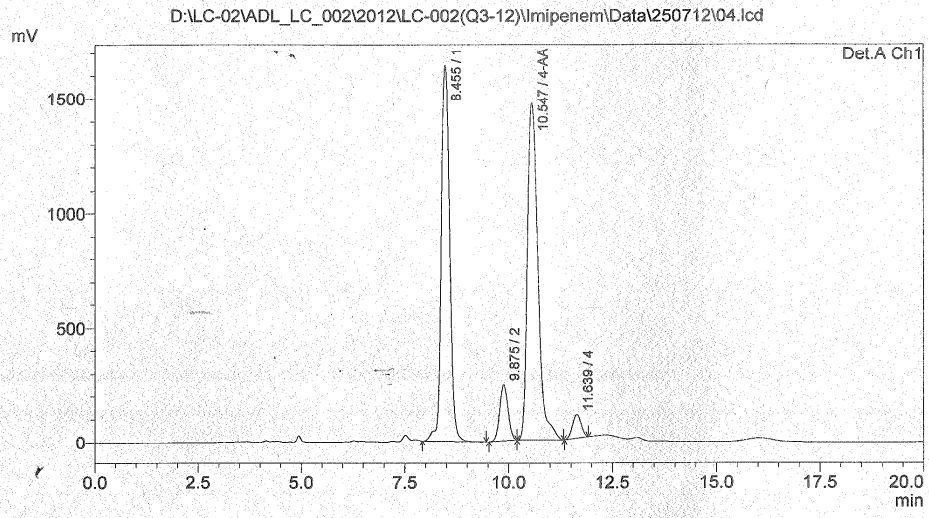

<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %
1	1	8.455	23114129	42.72
2	2	9.875	3461049	6.40
3	4-AA	10.547	26040428	48.12
4	4	11.639	1495583	2.76
Total			54111189	100.00

Table1 (Entry 11) Ru(H)(*p*-cymene)((R)-BINAP)-(SbF_6) in EtOH

Data: 78% ee, 06 % de; Column :Chiralpak IA (4.6X 250mm) eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v);

ANALYTICAL DEVELOPMENT LAB
UNIMARK REMEDIES LTD, AHMEDABAD

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Sample Name	: BINAP
Experiment	: Chiral Purity
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LNB Ref	:DJS(ADL-385)030
Vail#	: 5
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Analyst	: DJS 25 July 12

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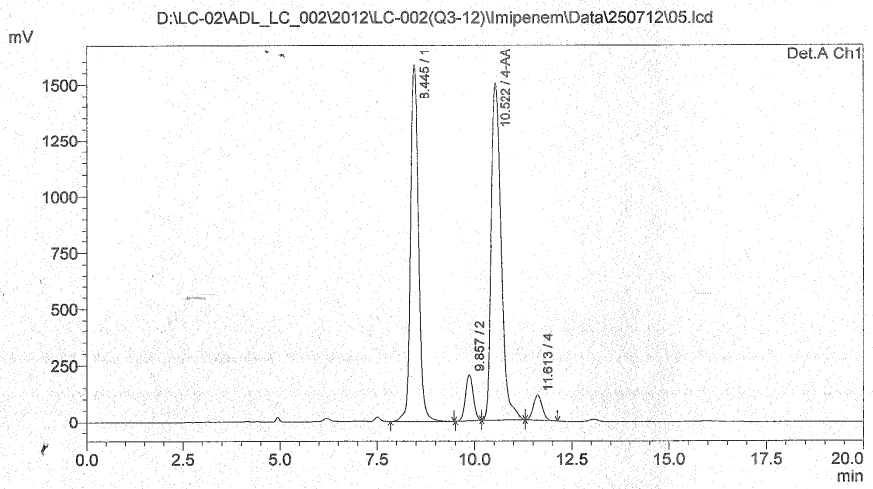

<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %
1	1	8.445	22461529	42.01
2	2	9.857	2777208	5.19
3	4-AA	10.522	26525486	49.61
4	4	11.613	1706357	3.19
Total			53470580	100.00

Table1 (Entry 12) Ru(H)(*p*-cymene)((R)-SEGPHOS)-(SbF_6) in EtOH

Data: 74% ee, 18 % de; Column :Chiralpak IA (4.6X 250mm) eluting agent: using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v);

ANALYTICAL DEVELOPMENT LAB
UNIMARK REMEDIES LTD, AHMEDABAD

Sample ID	: Imipenem
Sample Name	: SEGPHOS
Experiment	: Chiral Purity
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Batch Filename	: D:\LC-02\ADL_LC_002\2012\LC-002(Q3-12)\Imipenem\Sequence\250712\250712_4-AA_Chiral Purity.lcl
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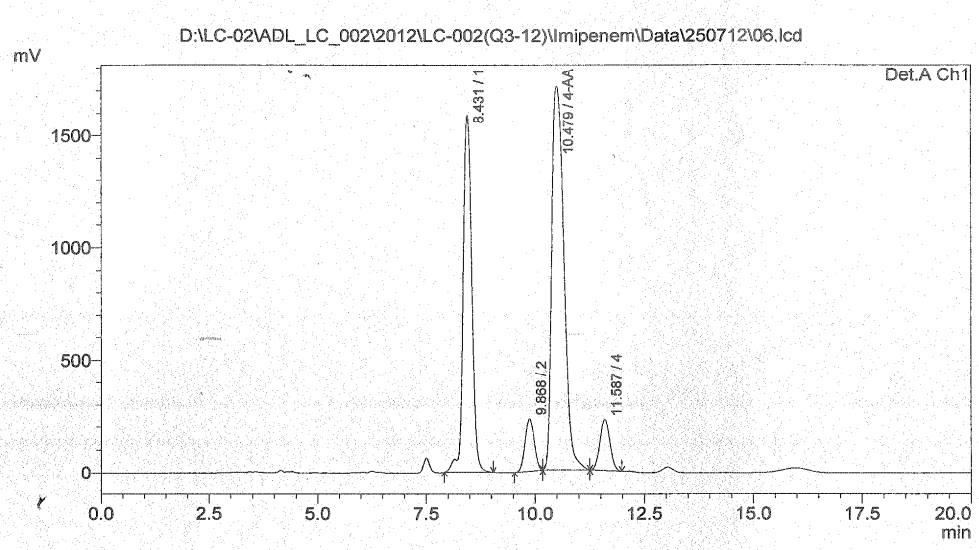
Date Processed	: 25-Jul-2012
Time Processed	: 4:53:22 PM
Column Name	: CHIRALPAK IA
Column Dimension	: (250X4.6)mm, 5µm
Column Number	: CIH-L51-199
LNB Ref	:DJS(ADL-385)030
Vail#	: 6
Injection Volum	: 10 uL
Analyst	:

<Chromatogram>



<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %
1	1	8.431	21953791	35.52
2	2	9.868	3338489	5.40
3	4-AA	10.479	32944917	53.31
4	4	11.587	3561998	5.76
Total			61799193	100.00

HPLC trace of Racemic starting material 2-Benzamidomethyl-3-oxobutanoate

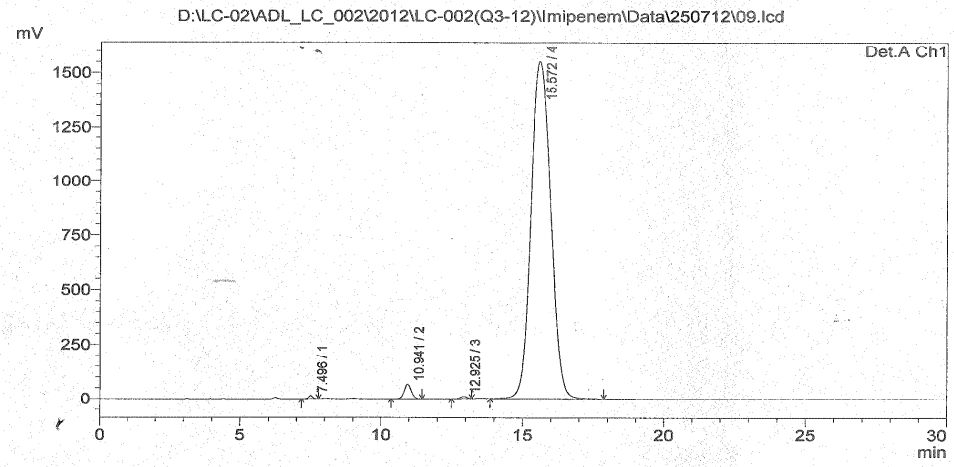
(Column :Chiralpak IA (4.6X 250mm) eluting agent:
using n-Hexane/Ethanol/Diethylamine in the ratio of 85:15:0.2(v/v/v))

ANALYTICAL DEVELOPMENT LAB
UNIMARK REMEDIES LTD, AHMEDABAD

Sample ID	: Imipenem
Sample Name	: Standard Matrial
Experiment	: Chiral Purity
Data Filename	: D:\LC-02\ADL_LC_002\2012\LC-002(Q3-12)\Imipenem\Data\250712\09.lcd
Method Filename	: D:\LC-02\ADL_LC_002\2012\LC-002(Q3-12)\Imipenem\Method\Chiral Purity 4-AA\Purity_4AA.lcm
Batch Filename	: D:\LC-02\ADL_LC_002\2012\LC-002(Q3-12)\Imipenem\Sequence\250712\250712_4-AA_Chiral Purity.lcl
Date Acquired	: 25-Jul-2012 4:49:12 PM
Date Processed	: 25-Jul-2012
Time Processed	: 5:22:24 PM
Column Name	: CHIRALPAK IA
Column Dimension	: (250X4.6)mm, 5µm
Column Number	: CIH-L51-199
LNB Ref	:DJS(ADL-385)030
Vail#	: 9
Injection Volum	: 10 uL
Analyst	:

<Chromatogram>

D:\LC-02\ADL_LC_002\2012\LC-002(Q3-12)\Imipenem\Data\250712\09.lcd



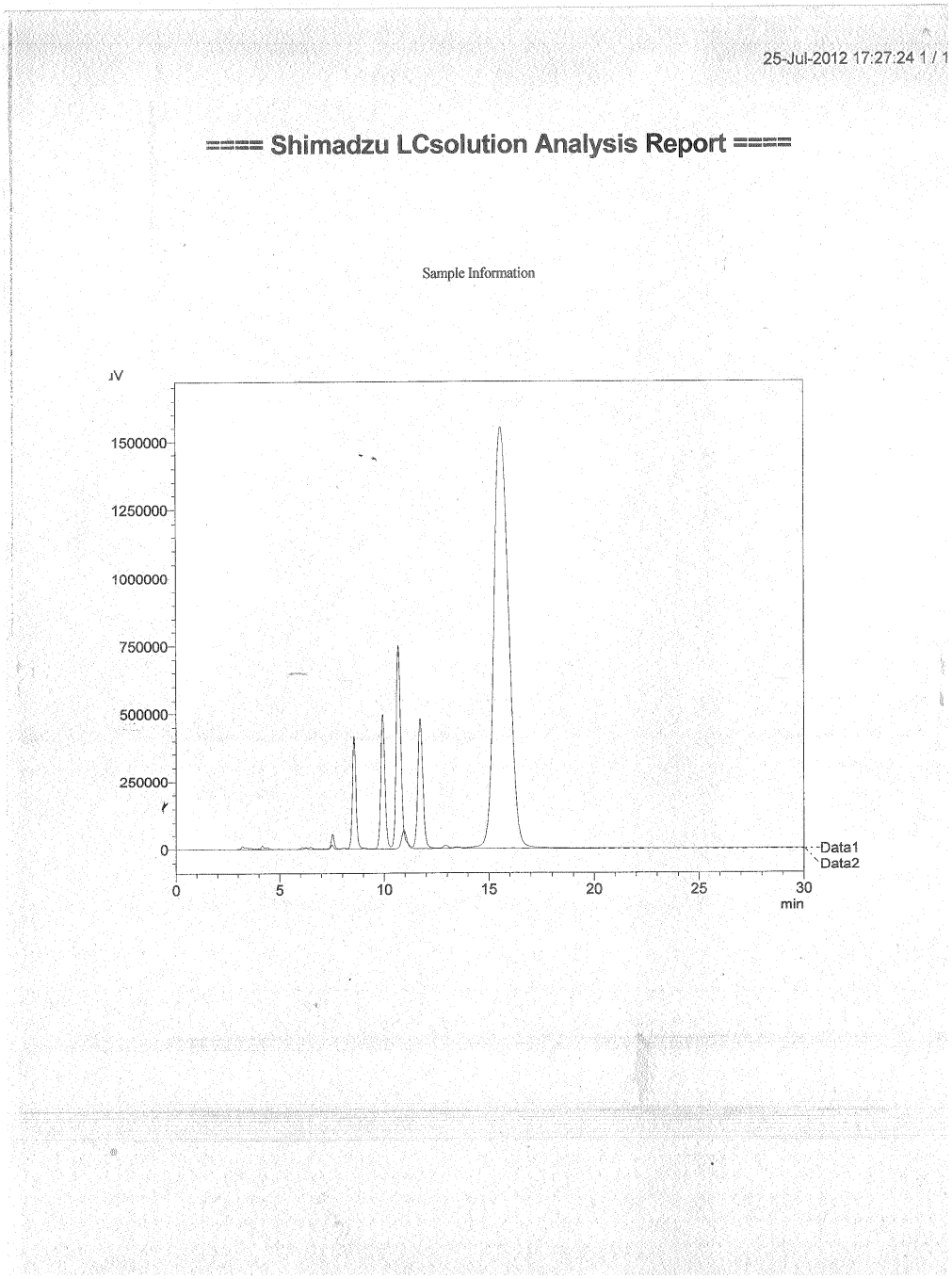
<Results>

Detector A Ch1 240nm

Peak #	Name	Ret. Time	Area	Area %
1	1	7.496	140663	0.18
2	2	10.941	1165957	1.53
3	3	12.925	172340	0.23
4	4	15.572	74945128	98.06
Total			76424088	100.00

Comments: Racemic starting material didn't resolve and appear farther from reduction products under our column type (Chiralpak-I) and under our elutent conditions but certainly it is not present in the HPLC traces of Table1; entries 1-12.

Overlay HPLC trace of starting material (2-benzamidomethyl-3-oxobutanoate) and Racemic 2-benzamidomethyl-3-hydroxybutanoate



Comments: An overlay HPLC trace is presented above which demonstrates that the chiral reduced isomers of 2-benzamidomethyl-3-hydroxybutanoate is distinct from 2-benzamidomethyl-3-oxobutanoate. Hence, there is no presence of this ketone starting material for Table1; entries 1-12 as the asymmetric reduction is complete and quantitative with Pregosin's hydrido complexes.