Two methods for the preparation of sitagliptin phosphate via chemical resolution and asymmetric hydrogenation

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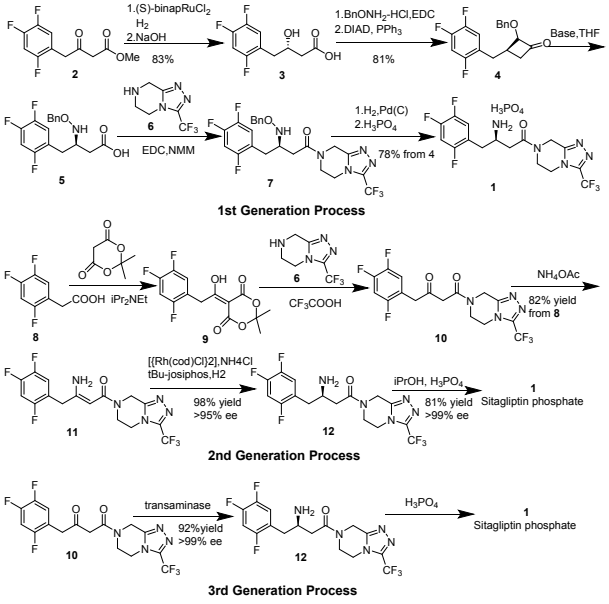
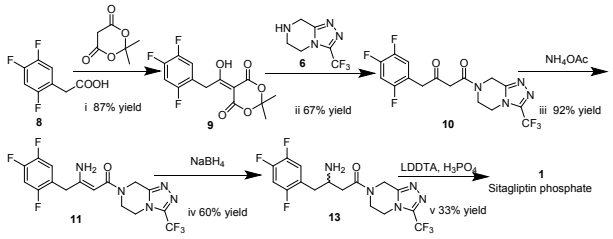
Abstract

Two effective processes have been developed for the preparation of sitagliptin phosphate. The approach of chemical resolution obtained R-sitagliptin in five steps from commercially available starting materials using the inexpensive $NaBH_4$ to reduce the enamine and then using (-)-Di-p-toluoyl-L-tartaric acid to resolute racemates in 11% yield overall. The route successfully avoids the use of expensive noble metal as catalysts compared with traditional synthesis methods, resulting in greatly reduced costs and simplified synthetic routes. Other alternative asymmetric hydrogenation of β-ketomide route of the synthesis of sitagliptin was found, two of the intermediates were firstly synthesized.

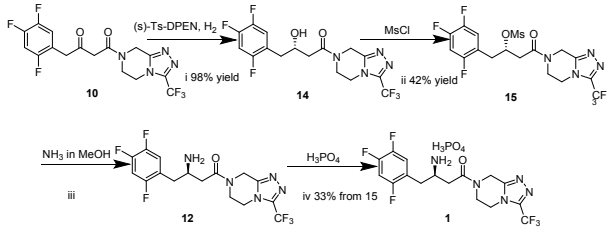
Keywords: Type 2 diabetes; Sitagliptin phosphate; Chemical resolution; Asymmetric hydrogenation; Synthesis



Scheme 1 Merck's three generations synthesis processes

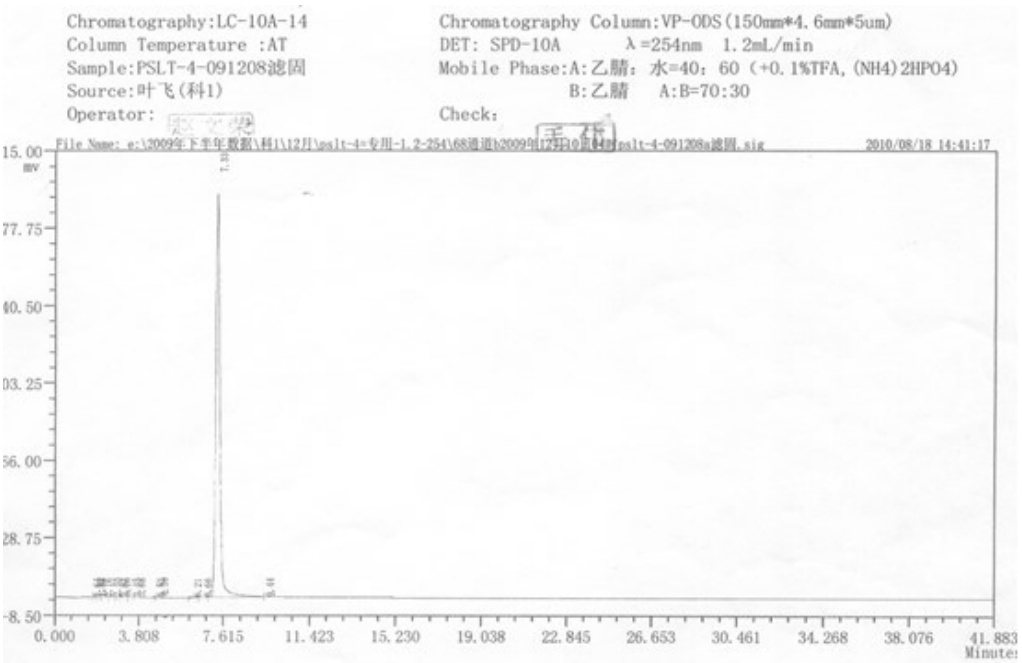


Scheme 2 The process for the preparation of sitagliptin phosphate via chemical resolution



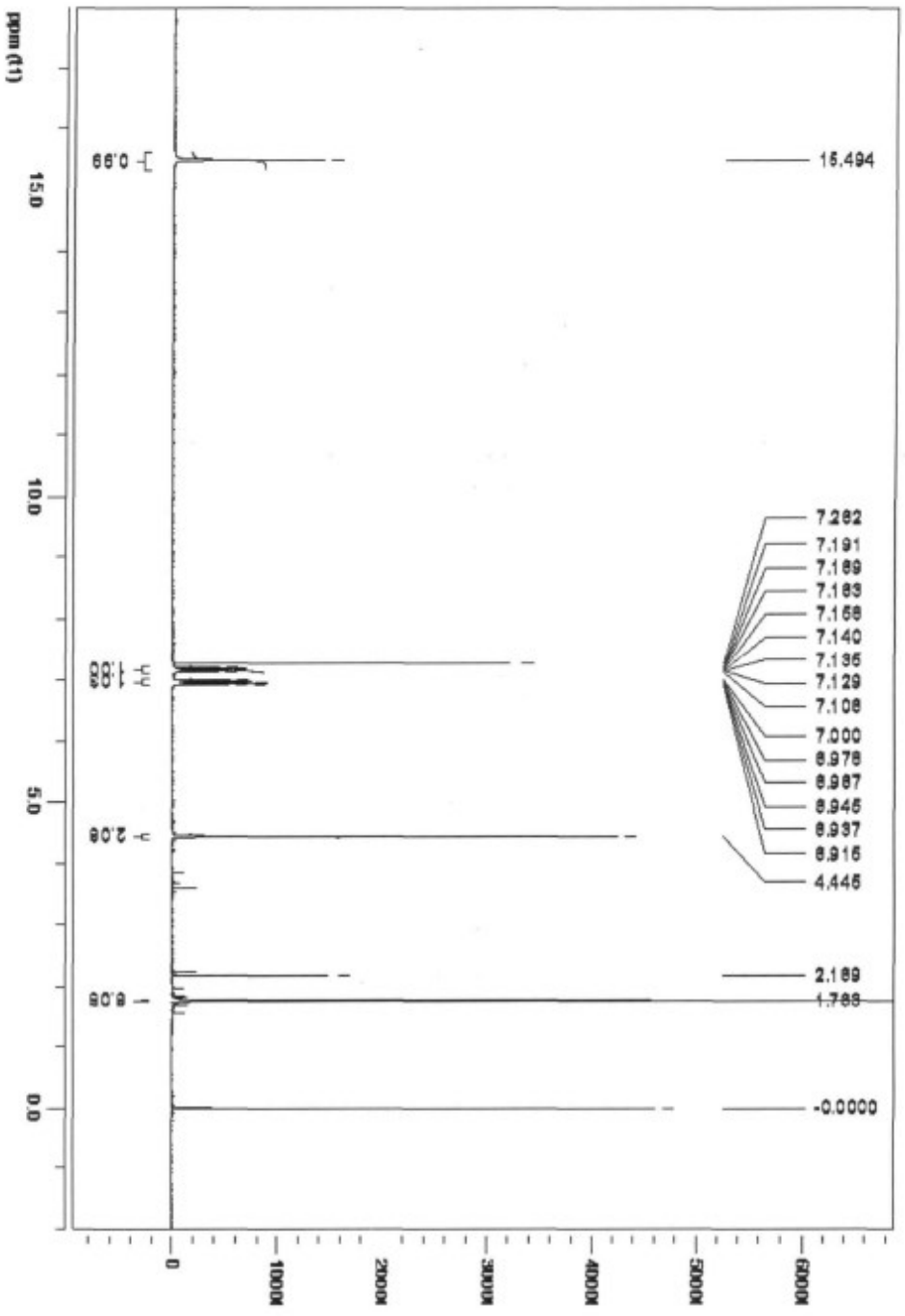
Scheme 3 The process for the preparation of sitagliptin phosphate via asymmetric hydrogenation

HPLC chromatograms and 1H and 13C NMR spectra copies of the product and key intermediates are provided as follows:

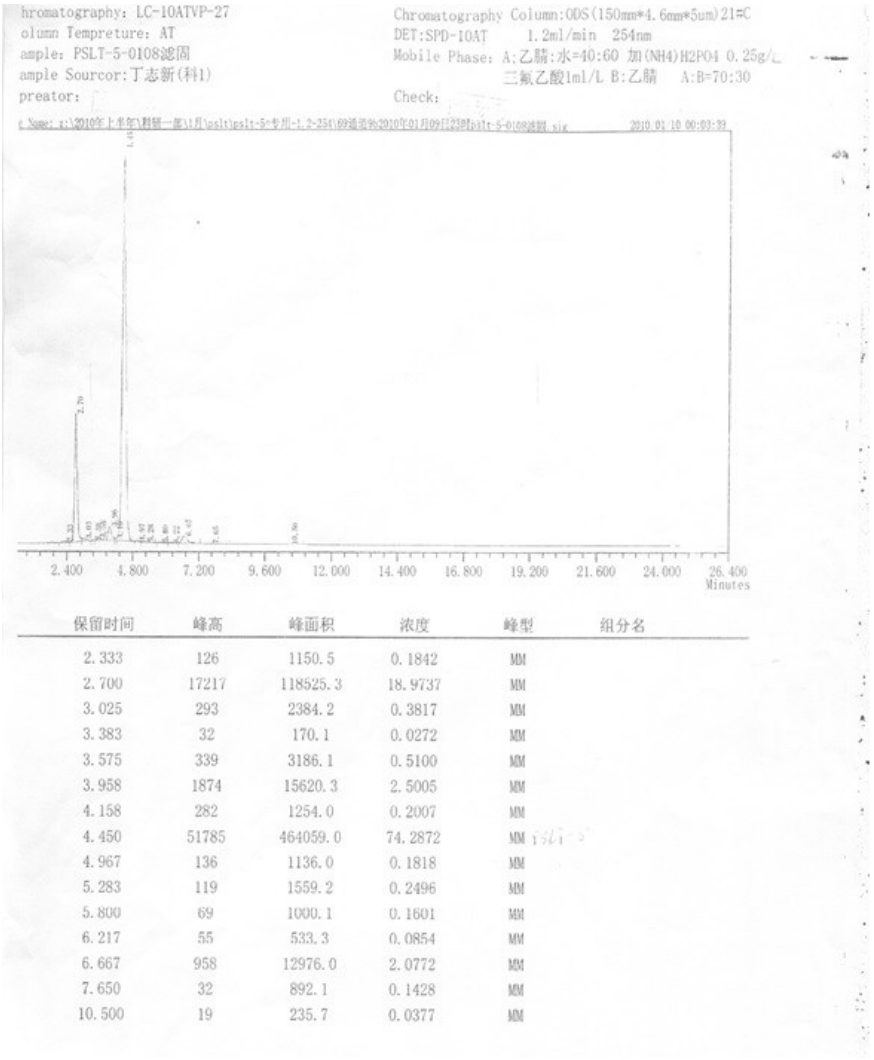


ID	保留时间	峰高	峰面积	浓度	峰型	组分名
0	1.642	50	331.4	0.0135	MM	
1	1.817	330	2005.6	0.0815	MM	
2	1.883	150	1127.3	0.0458	MM	
3	2.158	197	1544.0	0.0628	MM	
4	2.550	283	1915.3	0.0778	MM	
5	2.867	80	483.4	0.0196	MM	
6	3.000	408	2872.0	0.1167	MM	
7	3.450	22	171.0	0.0070	MM	
8	3.675	66	513.3	0.0209	MM	
9	4.517	26	144.5	0.0059	MM	
10	4.700	586	4649.8	0.1890	MM	
11	6.208	121	1551.6	0.0631	MM	
12	6.658	146	1464.1	0.0595	MM	
13	7.333	194306	2439608.9	99.1529	MM	
14	9.442	152	2068.8	0.0841	MM	

HPLC spectra of 5-[1-Hydroxy-2-(2,4,5-trifluorophenyl) ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione **9**

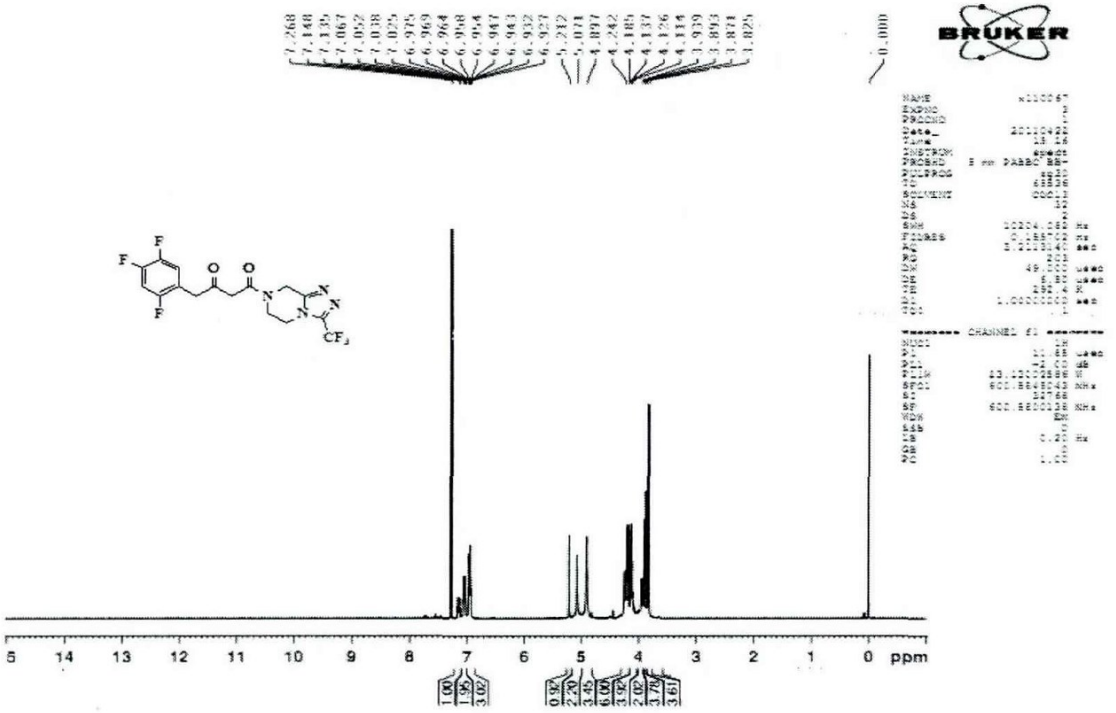


1H NMR spectra of 5-[1-Hydroxy-2-(2,4,5-trifluorophenyl) ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione **9**

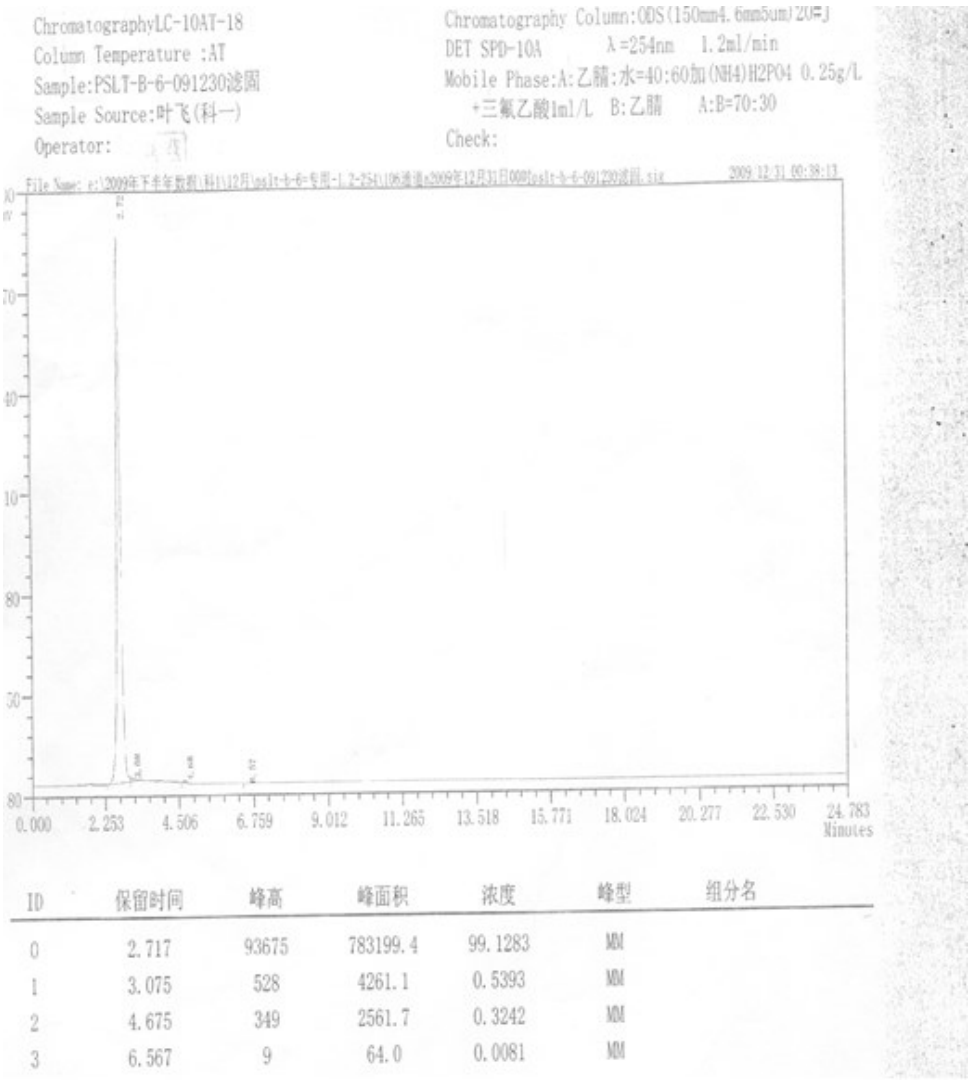


保留时间	峰高	峰面积	浓度	峰型	组分名
2.333	126	1150.5	0.1842	MM	
2.700	17217	118525.3	18.9737	MM	
3.025	293	2384.2	0.3817	MM	
3.383	32	170.1	0.0272	MM	
3.575	339	3186.1	0.5100	MM	
3.958	1874	15620.3	2.5005	MM	
4.158	282	1254.0	0.2007	MM	
4.450	51785	464059.0	74.2872	MM	
4.967	136	1136.0	0.1818	MM	
5.283	119	1559.2	0.2496	MM	
5.800	69	1000.1	0.1601	MM	
6.217	55	533.3	0.0854	MM	
6.667	958	12976.0	2.0772	MM	
7.650	32	892.1	0.1428	MM	
10.500	19	235.7	0.0377	MM	

HPLC spectra of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)bytan-2-one **10**

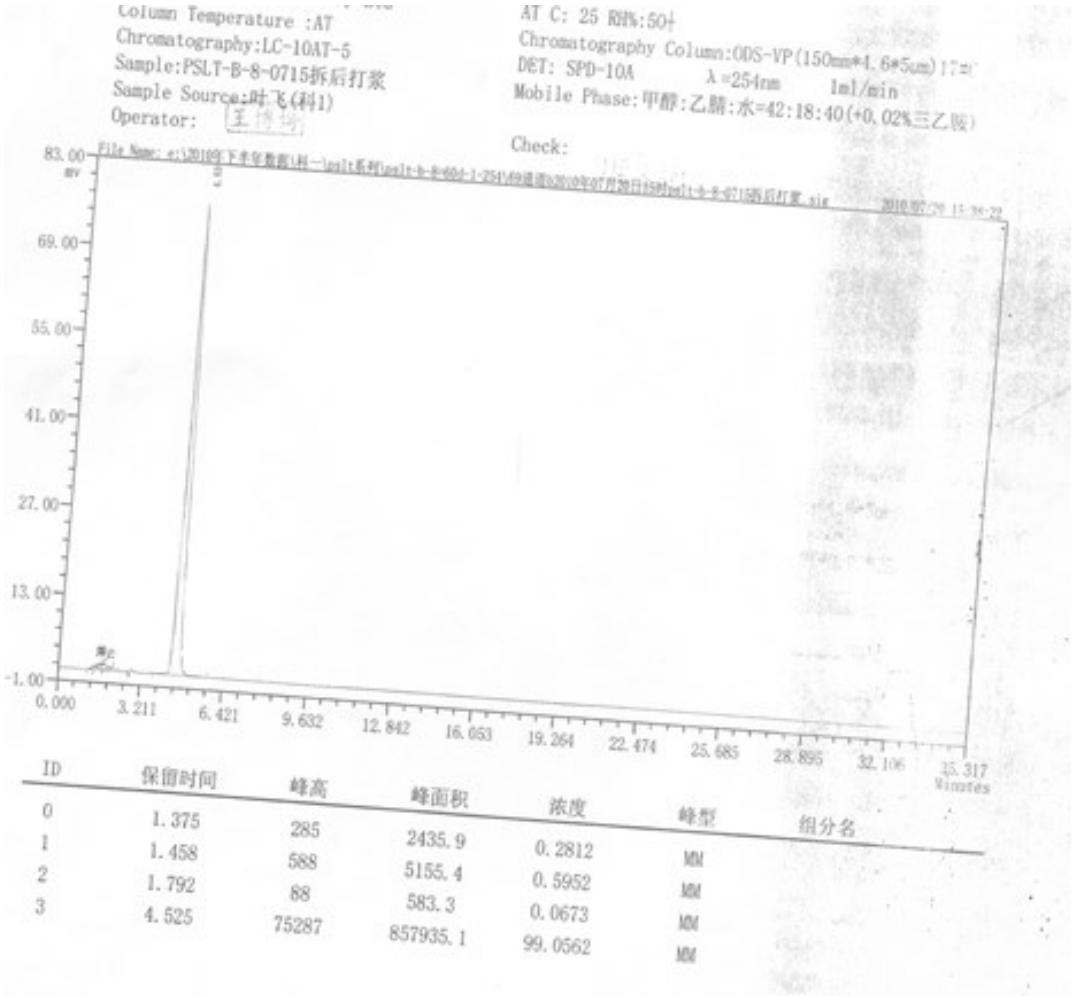


1H NMR spectra of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)bytan-2-one **10**



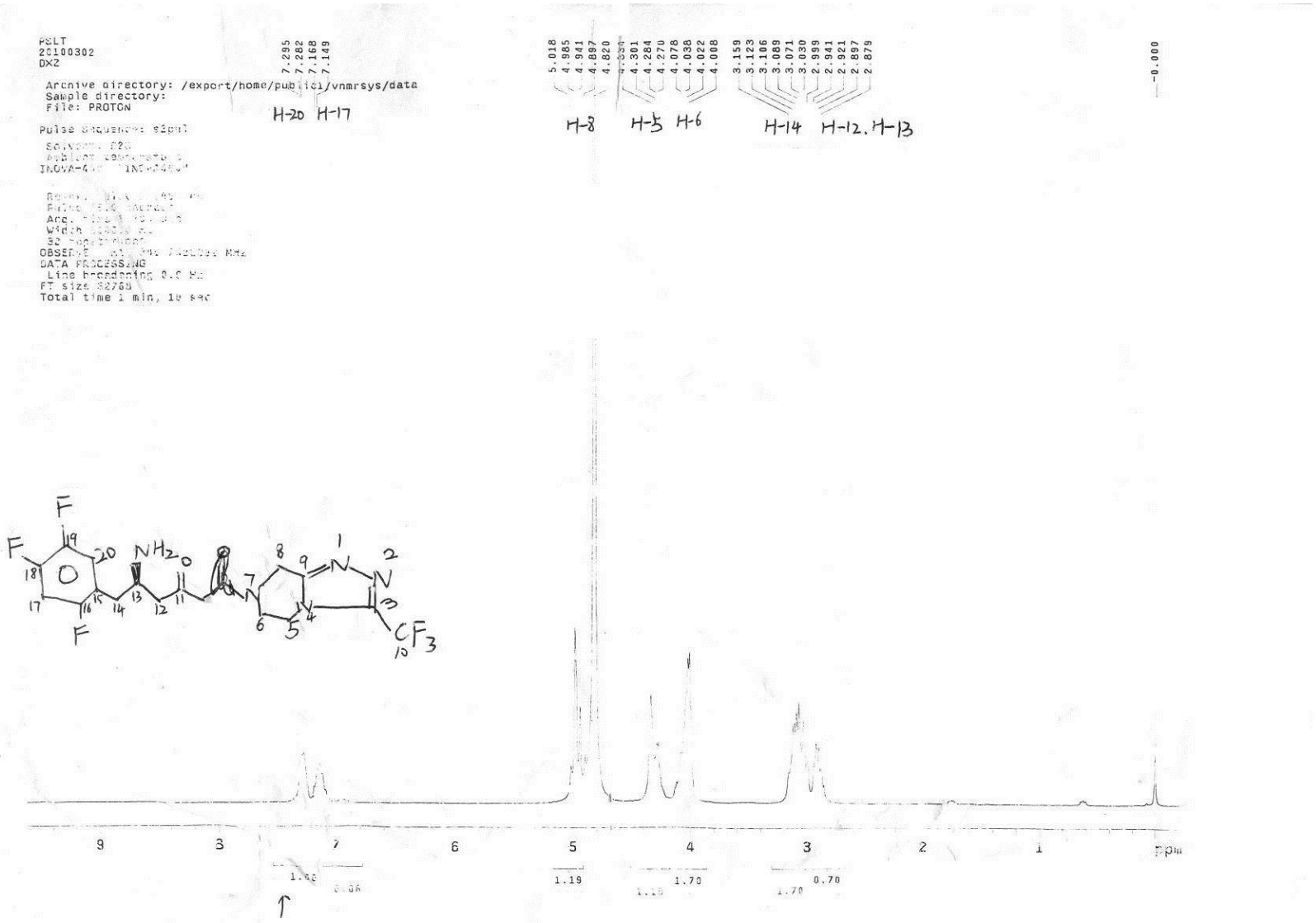
ID	保留时间	峰高	峰面积	浓度	峰型	组分名
0	2.717	93675	783199.4	99.1283	MM	
1	3.075	528	4261.1	0.5393	MM	
2	4.675	349	2561.7	0.3242	MM	
3	6.567	9	64.0	0.0081	MM	

HPLC spectra of (Z)-3-Amino-1-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazo-lo[4,3-a]pyrazin-7-yl)-4-(2,4,5-trifluoro-phenyl)-but-2-en-1-one **11**

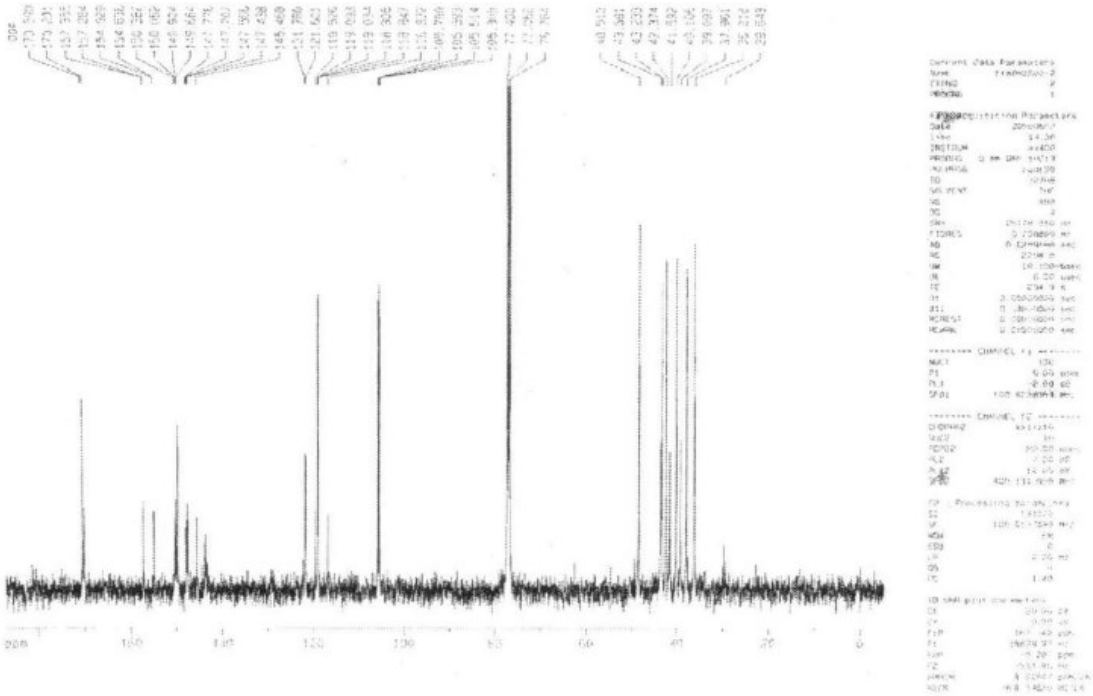


ID	保留时间	峰高	峰面积	浓度	峰型	组分名
0	1.375	285	2435.9	0.2812	MM	
1	1.458	588	5155.4	0.5952	MM	
2	1.792	88	583.3	0.0673	MM	
3	4.525	75287	857935.1	99.0562	MM	

HPLC pectra of Sitagliptin **1**



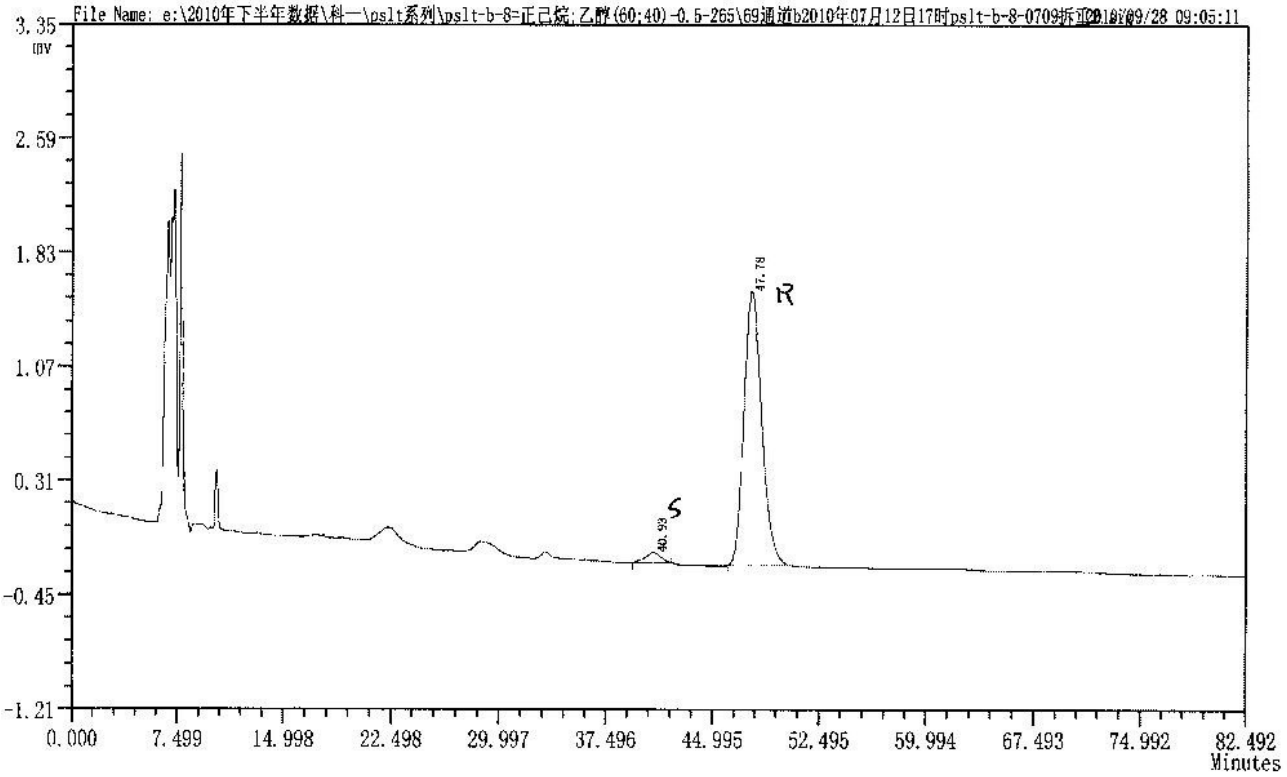
1H NMR spectra of Sitagliptin **1** in Scheme 2



13C NMR spectra of Sitagliptin **1** in Scheme 2

Chromatography:LC-28
Column Temperature :AT
Sample:PSLT-B-8-0709拆重2
Source:叶飞(科一)
Operator:

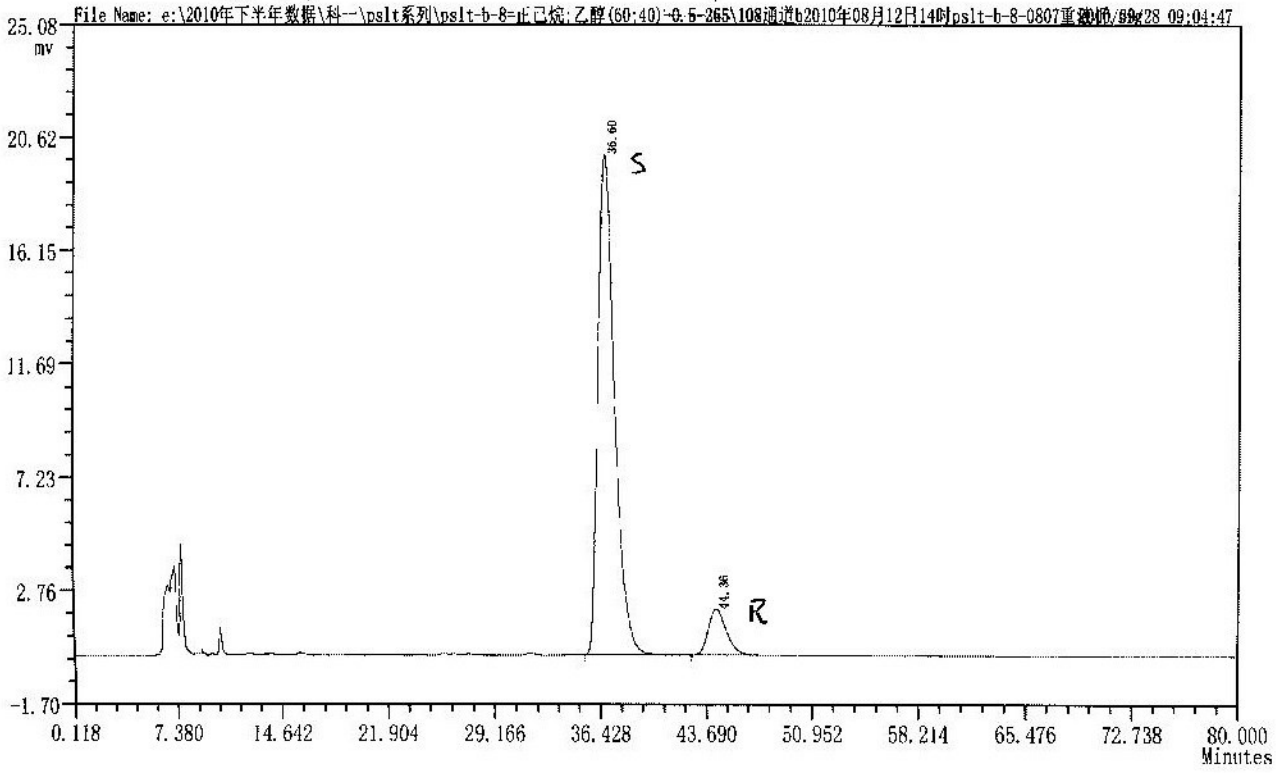
Chromatography Column:VP-ODS(150mm*4.6mm 5um)23#C
DET: SPD-10A λ=265nm 0.5mL/min
Mobile Phase:正己烷:乙醇=60:40-0.5-265
Check:



ID	保留时间	峰高	峰面积	浓度	峰型	组分名
0	40.933	69	5135.0	1.8245	MM S	
1	47.783	1830	159210.5	98.1755	MM R	

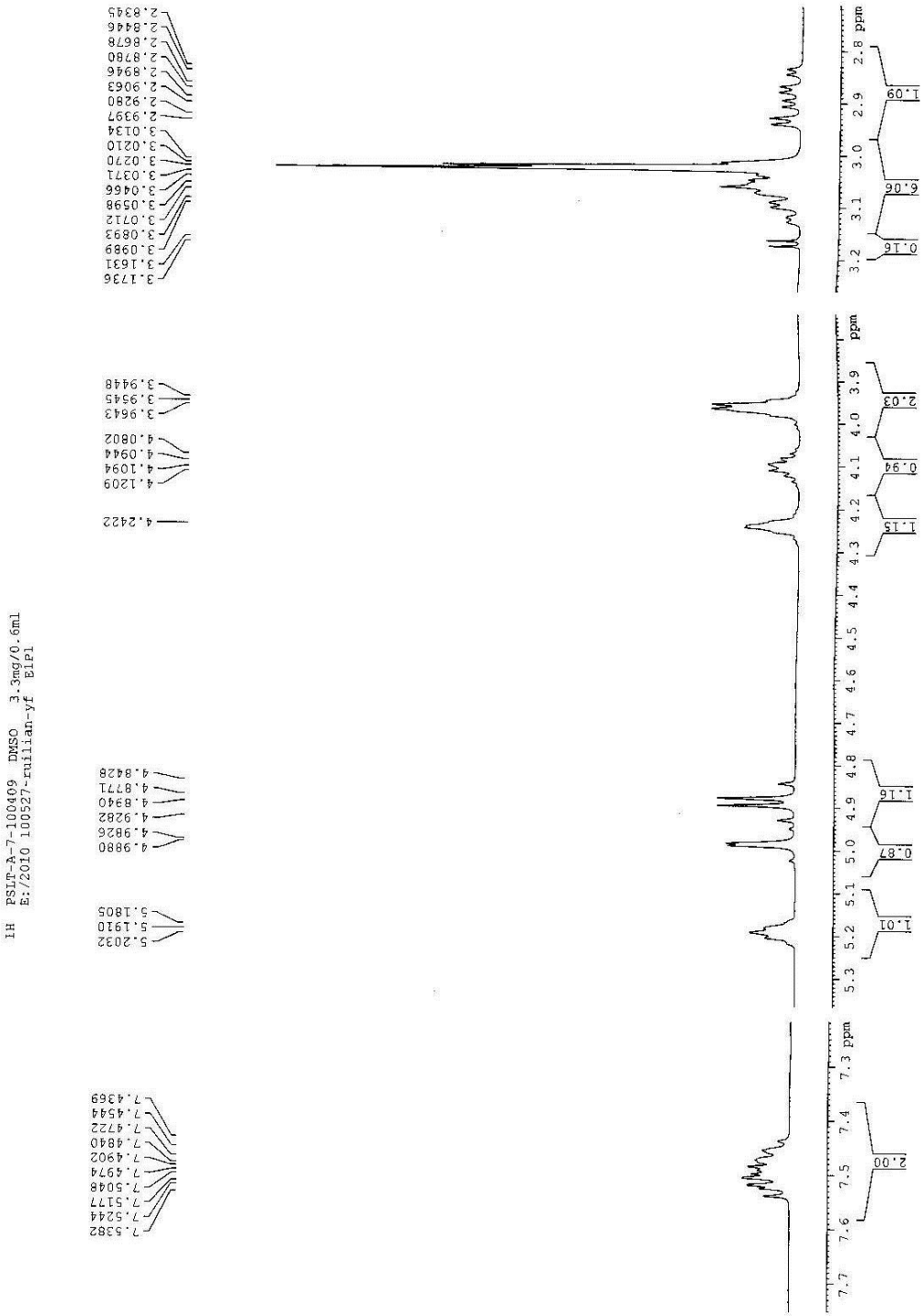
Chiral HPLC chromatograms of R-Sitagliptin **1**

Chromatography:LC-28 Chromatography Column:VP-ODS(150mm*4.6mm 5um)23#C
Column Temperature :AT DET: SPD-10A λ=265nm 0.5mL/min
Sample:PSLT-B-8-0807重液析 Mobile Phase:正己烷:乙醇=60:40-0.5-265
Source:叶飞(科一)
Operator: Check:

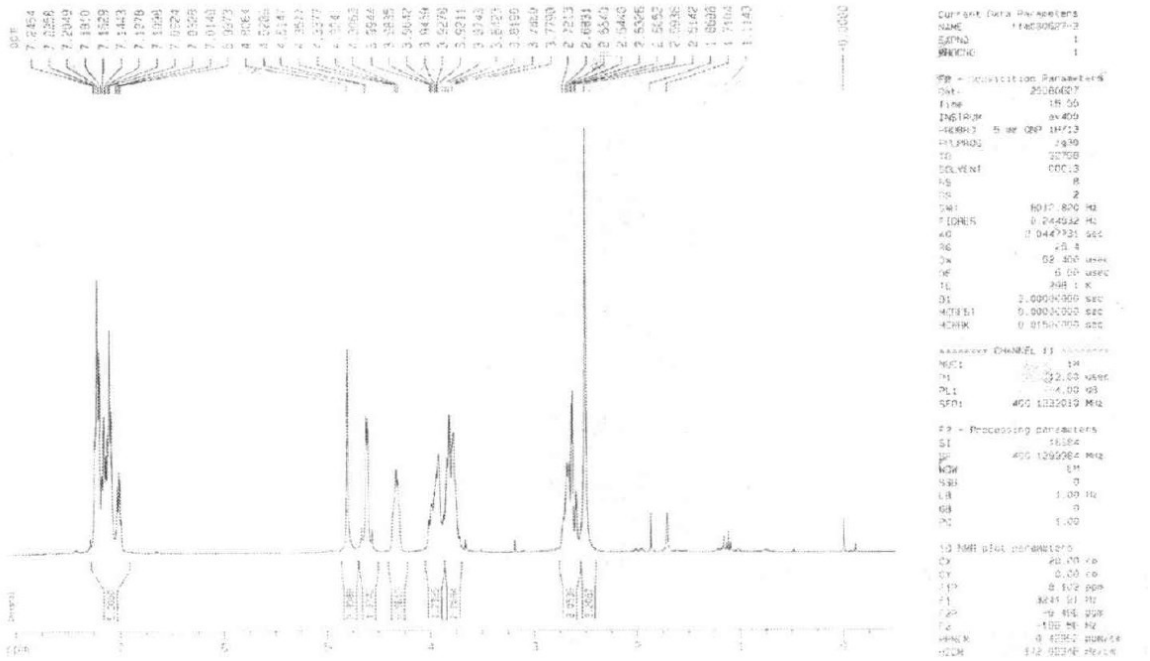


ID	保留时间	峰高	峰面积	浓度	峰型	组分名
0	36.600	19681	1543880.1	90.7566	MM	S
1	44.358	1817	157241.0	9.2434	MM	R

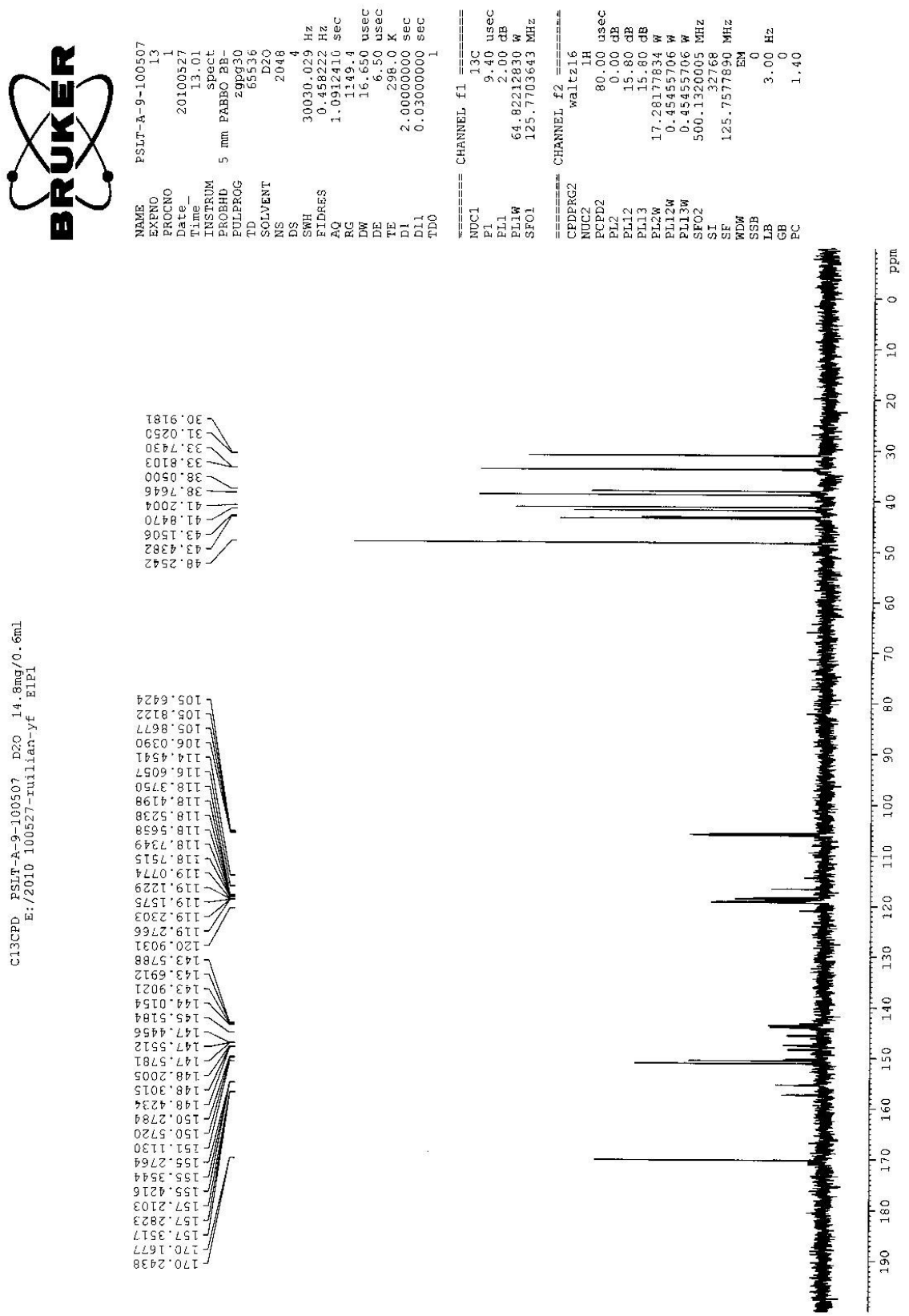
Chiral HPLC chromatograms of S-Sitagliptin



1H NMR spectra of methanesulfonate **15**



1H NMR spectra of Sitagliptin **1** in Scheme 3



13C NMR spectra of Sitagliptin **1** in Scheme 3