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(54) Titre : PROCEDE SERVANT A FABRIQUER DU DOCETAXEL ANHYDRE CRISTALLIN
(54) Title: PROCESS FOR MAKING CRYSTALLINE ANHYDROUS DOCETAXEL

(57) Abrégé/Abstract:
New anhydrous crystalline form of docetaxel and process of making anhydrous docetaxel and docetaxel trihydrate are provided.

ABSTRACT

New anhydrous crystalline form of docetaxel and process of making anhydrous docetaxel and docetaxel trihydrate are provided.

PROCESS FOR MAKING CRYSTALLINE ANHYDROUS DOCETAXEL

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel crystalline forms of docetaxel and process for the preparation thereof.

2. Description of the Related Art

Docetaxel is a compound found to exhibit anti-tumor activity. It is presently sold under the trademark TAXOTERE®. While there are known techniques for synthesizing docetaxel, there is still a need for improved chemical processes which can produce this anti- cancer compound and in a form where the compound is chemically stable.

SUMMARY OF THE INVENTION

In accordance with the first aspect of the present invention, a novel crystalline anhydrous docetaxel characterized by a powder x-ray diffraction with peaks at about 8.0, 12.4, and 16.8 ± 0.2 degrees two-theta is found.

Preferably, the novel crystalline anhydrous docetaxel is further characterized by a powder x-ray diffraction pattern with peaks at about 11.3, 13.8, 15.4, 20.3, and 23.3 ± 0.2 degrees two-theta. More

preferably, crystalline anhydrous docetaxel is further characterized by a powder x-ray diffraction pattern with peaks at about 4.6, 9.2, 18.1, 18.4, 19.5, 20.8, 22.5, 23.7, 24.1, 28.3, and 30.6 and ± 0.2 degrees two-theta. The novel crystalline anhydrous docetaxel is preferably characterized by a powder x-ray diffraction pattern as substantially depicted in Figure 3 or Figure 4.

It is surprisingly found that the crystalline anhydrous form of docetaxel in accordance with the present invention is more stable than trihydrated form (see Figure 1). The crystalline anhydrous form of docetaxel in accordance with the present invention in a therapeutically effective amount may be formulated with at least one pharmaceutically acceptable excipient to form a pharmaceutical composition. Such a composition may be administered to a mammal, such as human, to treat a proliferative disorder.

In accordance with the second aspect of the present invention, a process of producing a crystalline anhydrous docetaxel is provided. The process comprises (a) combining docetaxel and halohydrocarbon to form a solution; and (b) adding an antisolvent to the solution to precipitate the crystalline. The halohydrocarbon is prefererably chlorohydrocarbon, more preferably, dichloromethane . The antisovlent may be C3-C8 linear or branched alkanes, preferably, n-heptane.

In accordance with the third aspect of the present invention, a process of producing docetaxel trihydrate is provided. The process comprises a) combining anhydrous docetaxel, and acetonitrile; b) heating the mixture of step a) to about 30-60°C; c) adding water to the mixture of the heated mixture of step d); cooling the

mixture of c) to about 10-30°C to obtain a slurry; and e) filtering, washing, and drying the slurry of step d) to obtain docetaxel trihydrate.

The present application also provides a new process of synthesizing docetaxel and new crystalline docetaxel trihydrate as explained in detail below.

The various features of novelty which characterize the invention are pointed out with particularity in the claims annexed to and forming a part of the disclosure. For a better understanding of the invention, its operating advantages, and specific objects attained by its use, reference should be had to the drawing and descriptive matter in which there are illustrated and described preferred embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

Figure 1 illustrates the stability of crystalline anhydrous docetaxel and docetaxel trihydrate.

Figure 2 shows a semisynthetic process of making docetaxel.

Figure 3 shows an X-ray powder diffraction pattern of crystalline anhydrous docetaxel prepared in accordance with the process described in the present application.

Figure 4 lists x-ray diffraction peaks for crystalline anhydrous docetaxel prepared in accordance with the process described in the present application.

Figure 5 also shows a semisynthetic process of making docetaxel.

Figures 6-7 shows an X-ray powder diffraction pattern of crystalline anhydrous docetaxel prepared in

accordance with the process described in the present application.

Figure 8 lists x-ray diffraction peaks for crystalline anhydrous docetaxel prepared in accordance with the process described in the present application.

Figure 9 shows DSC pattern of crystalline anhydrous docetaxel prepared in accordance with the process described in the present application.

Figures 10-13 show IR pattern of crystalline anhydrous docetaxel prepared in accordance with the process described in the present application.

Figures 14-15 shows an X-ray powder diffraction pattern of crystalline docetaxel trihydrate prepared in accordance with the process described in the present application.

Figure 16 lists x-ray diffraction peaks for crystalline docetaxel trihydrate prepared in accordance with the process described in the present application.

Figure 17 shows DSC pattern of crystalline docetaxel trihydate prepared in accordance with the process described in the present application.

Figures 18-21 show IR pattern of crystalline docetaxel trihydrate prepared in accordance with the process described in the present application.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

As an example, the semisynthetic process used to make docetaxel is outlined in the Figure 1. This process comprise the synthesis of a certain oxazolidine (A-5) from (2R,3S)-3-phenylisoserine HCl as the starting material. 10-deacetyl-baccatin III that has 2,2,2-tri-

chloroethoxy-carbonyl protecting groups in both the 7 and 10 positions (SPT1141-M1) is then esterified with the oxazolidine (A-5) in the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine in toluene to produce an ester intermediate (SPT1141-M2). The ester intermediate is converted to docetaxel by a five-step procedure. Hydrochloric acid hydrolysis produces the β-amino ester (SPT1141-M3). T-butoxycarbonyl is attached to produce SPT1141-M4. The 2,2,2-tri-chloroethoxy-carbonyl protecting groups are removed by reacting SPT1141-M4 with zinc and acetic acid to produce SPT1141-M5. Further removal of protecting groups by reaction with ozone in methanol and subsequently by reaction with o-phenylenediamine and acetic acid in tetrahydrofuran produces crude docetaxel.

In the step described as Step 8a, Purification, the crude docetaxel is dissolved in ethyl acetate, filtered, concentrated under vacuum to produce a residue, dichloromethane is added to dissolve the residue and the solution is purified by chromatography with acetone and n-heptane as the eluant. The purified solution is concentrated under vacuum and the docetaxel is obtained by filtering.

In Step 8b, recrystallization - anhydrous, the purified docetaxel is dissolved in dichloromethane, n-heptane is added and the solution is seeded with docetaxel seed. The solution is cooled and the resulting slurry is filtered and the wet cake is dried to provide anhydrous docetaxel. The resulting anhydrous docetaxel can be further converted to the trihydrate form in Step 8c, recrystallization (trihydrate form) by mixing the anhydrous docetaxel with acetonitrile and

glacial acetic acid, adding water at a temperature between 30 to 50 0C, then adding more water and seeding with docetaxel seed. The resulting slurry is then filtered and washed with water and the wet cake is dried under vacuum at 60 0C to provide docetaxel trihydrate.

We surprisingly found that the anhydrous form of docetaxel is more stable (2168-115-16) than trihydrated form (1883-12-11, 1883-12-21, 2016-109-05) in acetonitrile . See Figure 1. Also, the anhydrous form is more stable in acetonitrile than in acetonitrile/water (9/1). These data showed that docetaxel is less stable in co-water solvent. Docetaxel is more stable in non-water solvent than co-water solvent (ACN/water/acetic acid) . Further more, an impurity of docetaxel, 7-epi-docetaxel, is generated more rapidly in co-water solvent than in non-water solvent. The growth of 7-epi-docetaxel can be suppressed by the addition of acetic acid.

More detailed description of each step of the process shown in Figure 2 is provided below.

Step 1 : Protection

10-Deacetyl baccatin 111 (approx. 14 Kg), pyridine (approx. 137 Kg), and 2, 2, 2-trichloroethyl chloroformate (approx. 14 Kg) are charged into a suitable vessel. The resulting mixture is stirred at not more than (NMT) 1O°C. After the reaction is complete, the solution is quenched with water followed by extraction with dichloromethane; the organic layer is separated and washed with water. The organic layer is concentrated at NMT 60°C, and water is added for precipitation. The solids are collected and washed with water. The wet cake

is then suspended in ethyl acetate and heptanes are added. The solids are isolated, washed, and dned under vacuum at NMT 60°C to provide SPT1141 M1 (approx. 22 Kg).

Step 2-1: Hydrolysis

SPT2039 A4 (approx. 2.7 Kg), tetrahydrofuran (approx. 11 Kg), and about 1 N lithium hydroxide solution (approx. 6.6 Kg) are charged into a suitable vessel. The mixture is stirred. After the reaction is complete, toluene and hydrochloric acid are added to adjust the mixture to pH < 3. The organic layer is washed with sodium chloride solution, and magnesium sulfate is added to remove water. The filtrate is concentrated to provide SPT2039 A5 in toluene solution, and the mixture is used directly in the next step.

Step 2-2: Coupling Reaction

SPT1141 M1 (approx. 3.8 Kg), toluene (approx. 11 Kg), 4-dimethyiaminopyridjne (approx. 114 g), and 1,^{3}-dicyclohexylcarbondiimide (approx. 1.3 Kg) are added to the mixture from step 2-1 . The reaction mixture is stirred. After the reaction is complete, the reaction mixture is quenched with hydrochloric acid. The slurry is filtered, and the filtrate is collected and separated. The organic layer is washed with sodium bicarbonate solution followed by water. The organic phase is concentrated to provide SPT11141 M2 in toluene solution, and the mixture is used directly in the next step.

Step 3: Deprotection

Tetrahydrofuran (approx. 21 Kg) is added to the above mixture. The solution is cooled to NMT 10°C, and a

solution of hydrochloric acid in methanol is slowly added. The mixture is stirred at below 40°C until the reaction is complete. Ethyl acetate and sodium bicarbonate solution are then added to the resulting mixture. The organic iayer is collected and washed with sodium chloride solution. After concentration, SPT1141 M3 is dissolved in ethyl acetate, and the solution is used directly in the next step.

Step 4: BOC protection

Dl-tert-butyl dicarbonate (approx. 1 Kg) is charged into a suitable vessel containing a solution of 4-dimethylaminopyridine (approx. 15 g) in SPT1141 M3 solution. After the reaction is complete,~ the solution is quenched with diluted hydrochloric acid, and sodium chloride solution is added. The organic layer is concentrated, and tetrahydrofuran is added to provide SPT1141 M4 solution. The solution is used directly in the next step.

Step 5: Deprotection

Zinc (approx. 2.7 Kg), glacial acetic acid (approx. 10.8 Kg), tetrahydrofuran, and SPT1141 M4 solution are charged into a suitable vessel. After the reaction is complete, the mixture is filtered, and the filtrate is solvent swapped with isopropanol. Water is added to the resulting solution. The solids are filtered and washed to provide crude SPT1141 M5 (approx. 4Kg).

Crude SPT1141 M5 (approx. 4 Kg) and dichloromethane (approx. 54 Kg) are charged into a suitable vessel. The solution is extracted with sodium chloride solution. Glacial acetic acid is added to the organic layer. The mixture is then concentrated and heptanes is added for

crystallization. The solids are filtered, washed and dried to provide SPT1141 M5 (approx. 3.3 Kg).

Step 6: Ozonolysis

Ozone is added at NMT -40°C to a suitable vessel containing a mixture of SPT1141 M5 (approx. 5.5 Kg), methanol (approx. 88 Kg), and glacial acetic acid (approx. 55 g) while maintaining the temperature at NMT -40°C. After the reaction is complete, dimethyl sulfide are added while maintaining the temperature at NMT -40°C, and the mixture is warmed to 20 to 30°C. The mixture is concentrated, and water is added for precipitation. The solids are filtered, washed, and dried to provide SPT1141 M6 (approx. 4.6 Kg).

Step 7: Condensation

Glacial acetic acid (approx. 5 Kg) is charged into a suitable vessel containing a solution of SPT1141 M6 (approx. 4.6 Kg) and 1 ,2-phenylenedjamine (approx. 1.8 Kg) in tetrahydrofuran (approx. 110 Kg). The mixture Is then reacted under air at NMT 60°C, and 1 ,2-phenylenediamine is added. After the reaction is complete,° the reaction mixture is concentrated and solvent swapped with methanol at NMT 60°C. The solid by-products are removed, and the filtrate is mixed with a solution of hydrochloric acid. The solids are isolated, washed, and dried to provide crude docetaxel" (approx. 4 Kg).

Step 8a: Purification

Crude docetaxel (approx. 3 Kg) arid ethyl acetate (approx. 41 Kg) are charged into a suitable vessel. The mixture is stirred at NMT 60°C and is filtered through a filter bed pie-coated with Celite, activated carbon, and activated acidic day. The filter bed is washed with

ethyl acetate, and the filtrate is collected and concentrated under vacuum at NMT 60°C until the volume of residue is approx. 9 L Dichloromethane is then charged to the residue to provide crude docetaxel solution (for column chromatography).

Step 8b: Recrystallization –Anhydrous Form

Docetaxel for crystallization (about 1 Kg) and dichioromethane are charge into a suitable vessel. The mixture is stirred at NMT 45°C until the solid is dissolved, and n-heptane is added for crystallization. The slurry is filtered, washed, and dried to provide approx. 0.8kg of docetaxel anhydrous. The solid" is then used for the trihydrate formation.

Step 8c: Recrystallization (Docetaxel Trihydrate)

Docetaxel anhydrous (about 0.8 Kg), acetonitriie (about 3.8 Kg) and glacial acetic acid (about 7.6 g) are charged into a suitable vessel. The mixture is heated to NMT 45°C, and purified process water (about 9.6 Kg) is added for precipitation. The slurry is filtered, washed and dried under a moist environment to provide docetaxel trihydrate (about 0.7 Kg).

Figure 5 also illustrates a semisynthetic process used to make docetaxel.

The invention is not limited by the embodiments described above which are presented as examples only but can be modified in various ways within the scope of protection defined by the appended patent claims.

Claims:

1. Crystalline N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyl taxol trihydrate characterized by a powder x-ray diffraction pattern with peaks at about 8.8, 13.9, and 17.7 ± 0.2 degrees two-theta.

2. The crystalline N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyl taxol trihydrate of claim 1 further characterized by a powder x-ray diffraction pattern with peaks at about 4.4, 11.0, and 22.2 ± 0.2 degrees two-theta.

3. The crystalline N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyl taxol trihydrate of claim 1 further characterized by an infrared spectrum having bands at about 710, 1268, 1737, 2981, and 3374 (cm^{-1}).

4. A process of producing docetaxel trihydrate comprising:

a) combining docetaxel and acetonitrile;

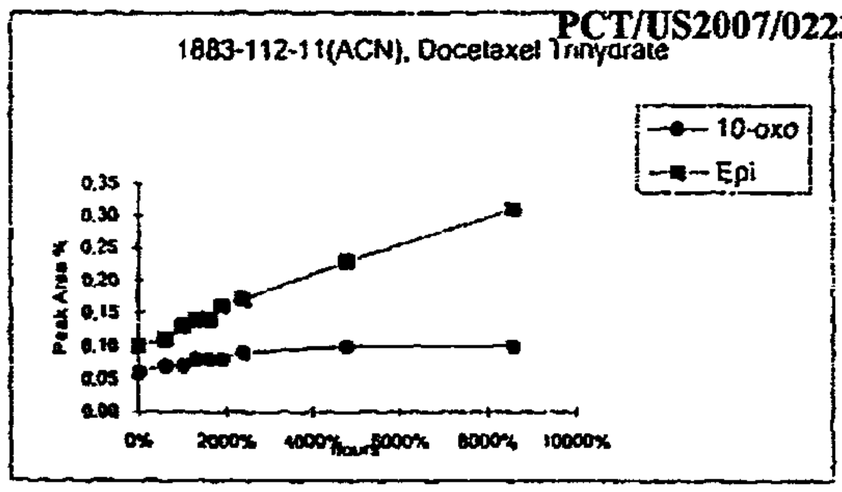
b) heating the mixture of step (a) to about 30-45^{0}C;

c) adding water to the mixture of the heated mixture of step b);

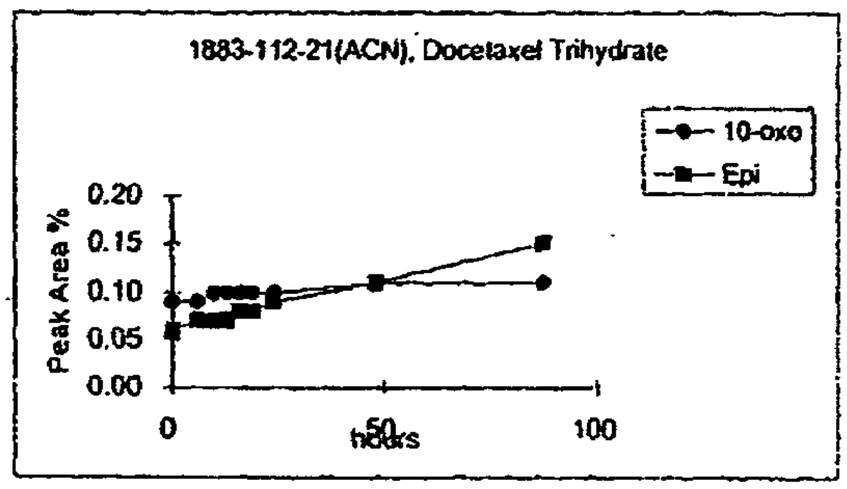
d) cooling the mixture of c) to about 10-30^{0}C to obtain a slurry; and

e) filtering, washing, and drying the slurry of step (d) to obtain docetaxel trihydrate.

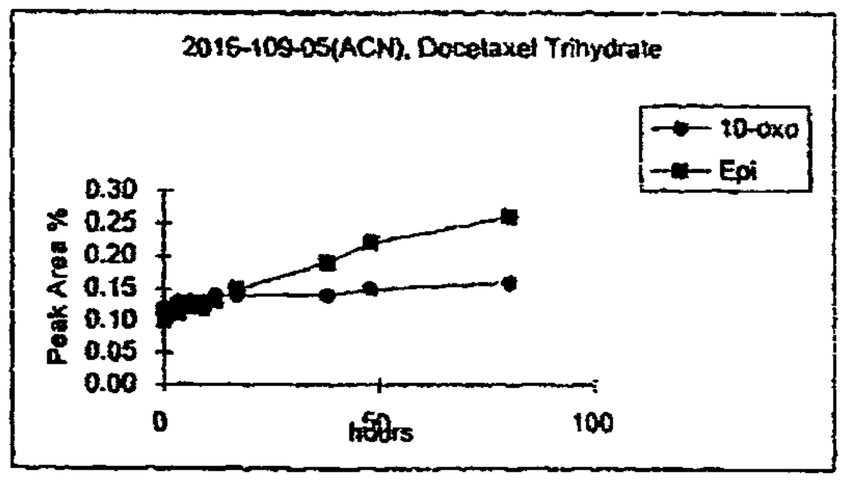
10-oxo(%)	Epi(%)
0	0.06	0.10
6	0.07	0.11
10	0.07	0.13
13	0.08	0.14
16	0.08	0.14
19	0.08	0.16
24	0.09	0.17
48	0.10	0.23
86	0.10	0.31



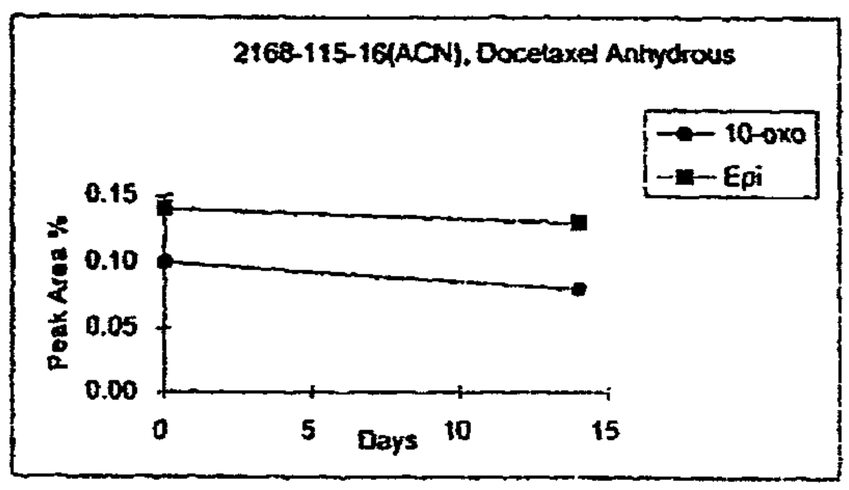
Hours	10-oxo(%)	Epi(%)
0	0.09	0.06
6	0.09	0.07
10	0.10	0.07
13	0.10	0.07
16	0.10	0.08
19	0.10	0.08
24	0.10	0.09
48	0.11	0.11
87	0.11	0.15



Hours	10-oxo(%)	Epi(%)
0	0.12	0.10
3	0.13	0.11
6	0.13	0.12
9	0.13	0.12
12	0.14	0.13
17	0.14	0.15
38	0.14	0.19
48	0.15	0.22
80	0.16	0.26



Days	10-oxo(%)	Epi(%)
0	0.10	0.14
14	0.08	0.13



Hours	10-oxo(%)	Epi(%)
0	0.07	0.10
5	0.08	0.11
12	0.07	0.13
24	0.07	0.14
43	0.07	0.19

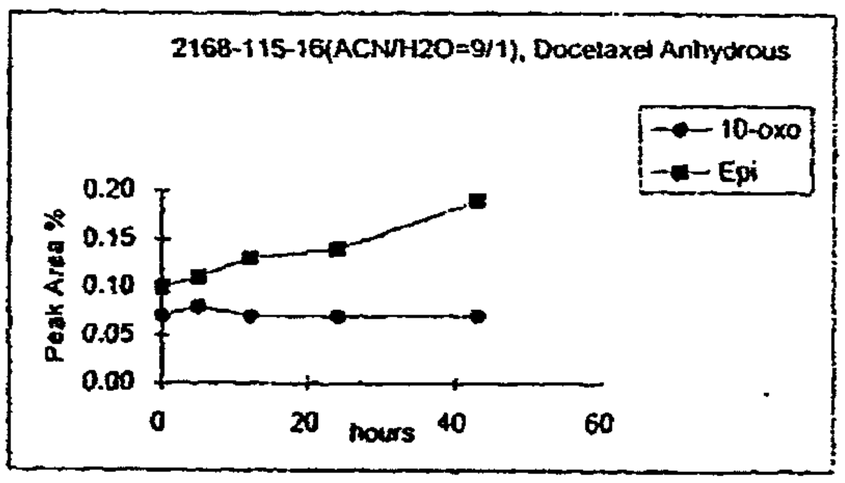


Figure 1

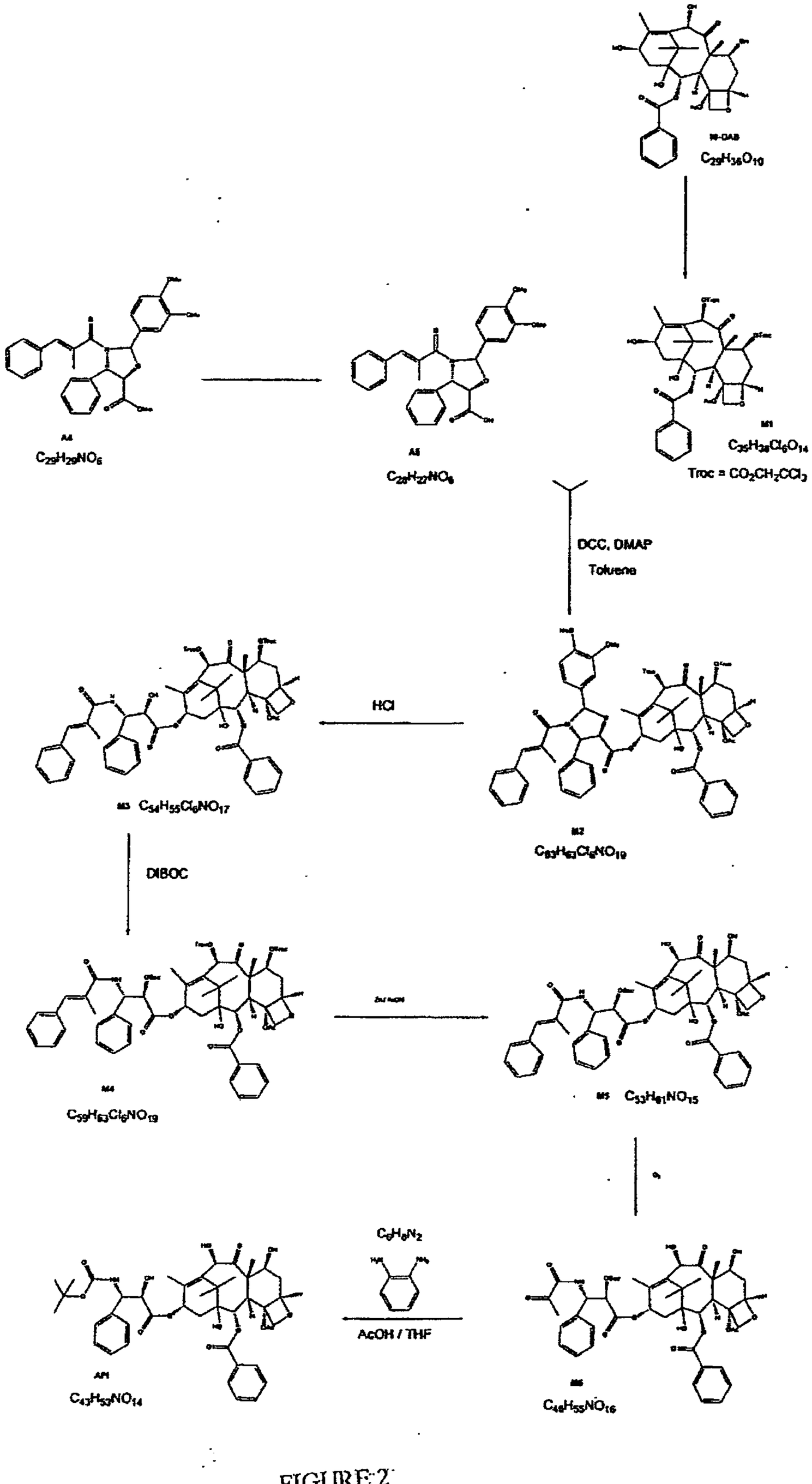

10-DAB
$C_{29}H_{36}O_{10}$
A4
$C_{29}H_{29}NO_6$
A5
$C_{28}H_{27}NO_6$
M1
$C_{35}H_{38}Cl_6O_{14}$
Troc = $CO_2CH_2CCl_3$
DCC, DMAP
Toluene
HCl
M3 $C_{54}H_{55}Cl_6NO_{17}$
M2
$C_{83}H_{63}Cl_6NO_{19}$
DIBOC
M4
$C_{59}H_{63}Cl_6NO_{19}$
M5 $C_{53}H_{61}NO_{15}$
$C_6H_6N_2$
AcOH / THF
A11
$C_{43}H_{53}NO_{14}$
M6
$C_{48}H_{55}NO_{16}$

FIGURE 2

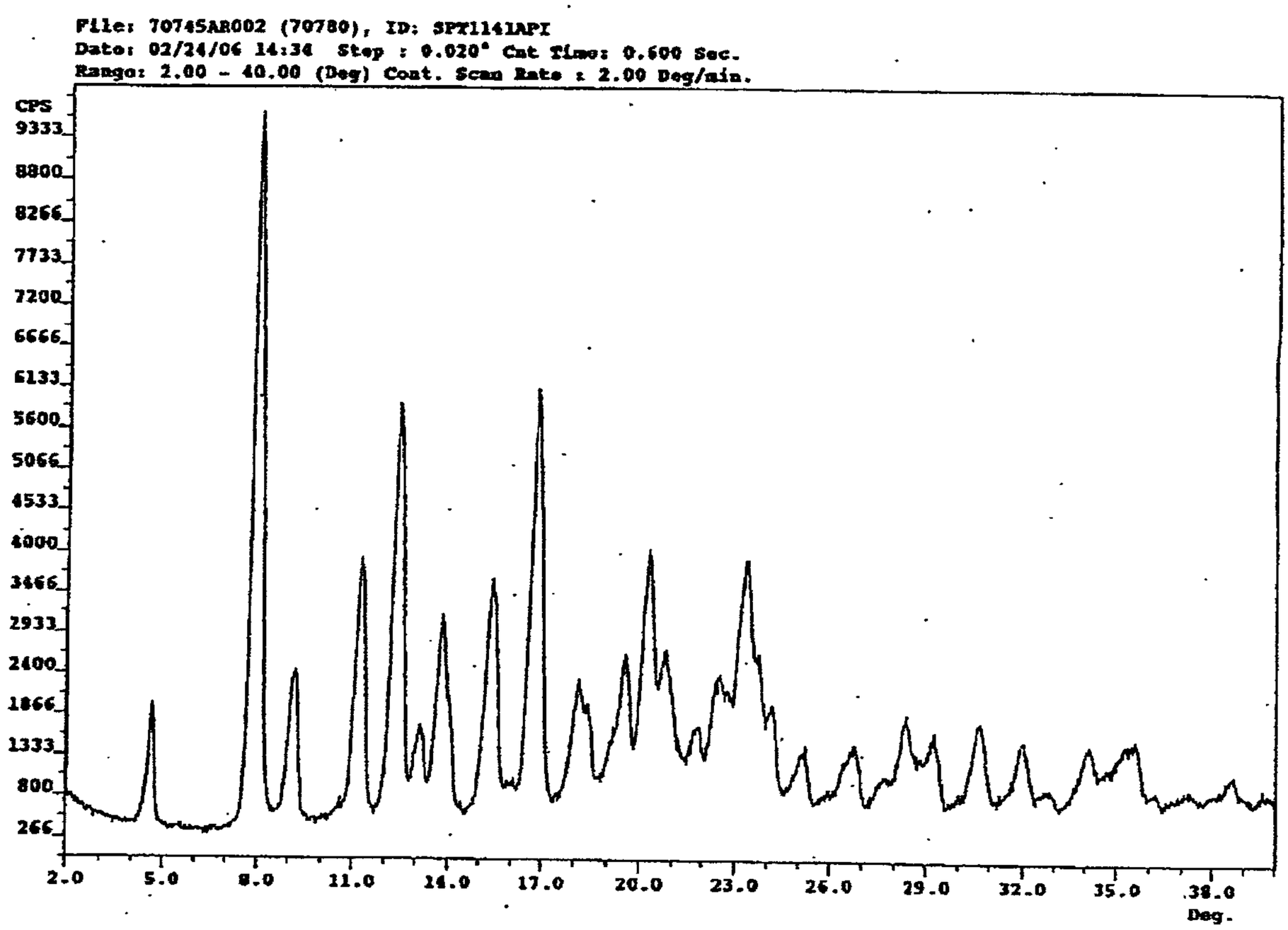

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FIGURE 3

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Detector:
Type: Fixed Slits
XZ Configuration: No
Tube:
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XZ Configuration: No

Peaks:

Position (Deg.)	Position (Deg.)	FWHM (Deg.)	Corr.Fact	Intensity (cps)	Rel. Int. (%)	FWHM (L)	FWHM (Deg.)	Atom	Source	Curve	Strain	CSize	CSize Source
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7.9988	11.0442	0.0000	0.0000	6120.42	100.00	0.1600	0.0000	979.3	PFind	None	0.00	0.00	None
9.1761	9.6294	0.0000	0.0000	1221.58	19.96	0.1600	0.0000	195.5	PFind	None	0.00	0.00	None
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35.2350	2.5450	0.0000	0.0000	420.27	6.87	0.1600	0.0000	67.2	PFind	None	0.00	0.00	None
35.4331	2.5313	0.0000	0.0000	427.08	6.98	0.1600	0.0000	68.3	PFind	None	0.00	0.00	None
35.9708	2.5212	0.0000	0.0000	453.28	7.41	0.1600	0.0000	69.5	PFind	None	0.00	0.00	None

Page: 1

Figure 4

CA 02756603 2011-10-26

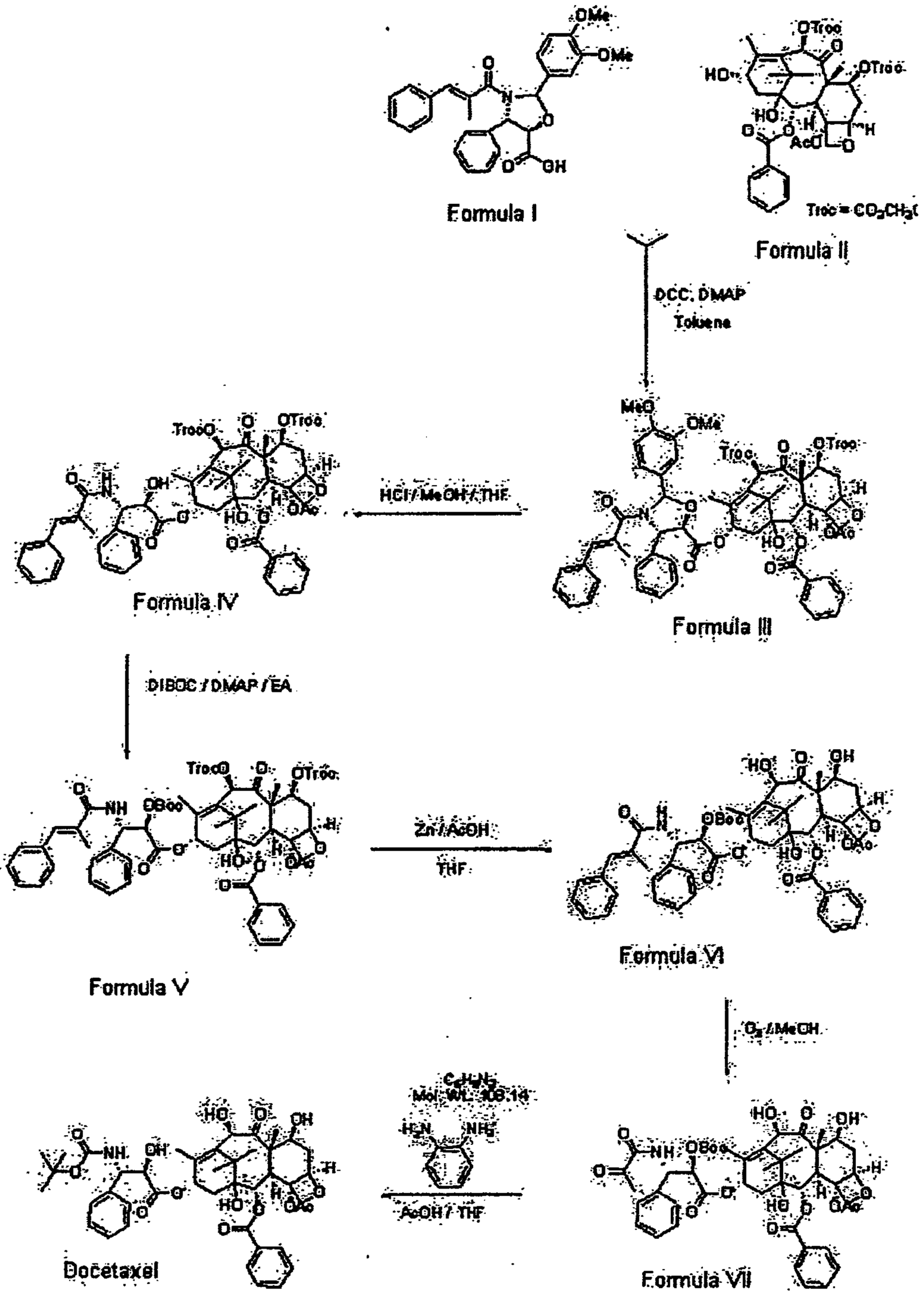
Formula I
Formula II
DCC, DMAP
Toluene
Formula IV
HCl / MeOH / THF
Formula III
DIBOC / DMAP / EA
Zn / AcOH
THF
Formula V
Formula VI
O3 / MeOH
Docetaxel
AcOH / THF
Formula VII

Figure 5

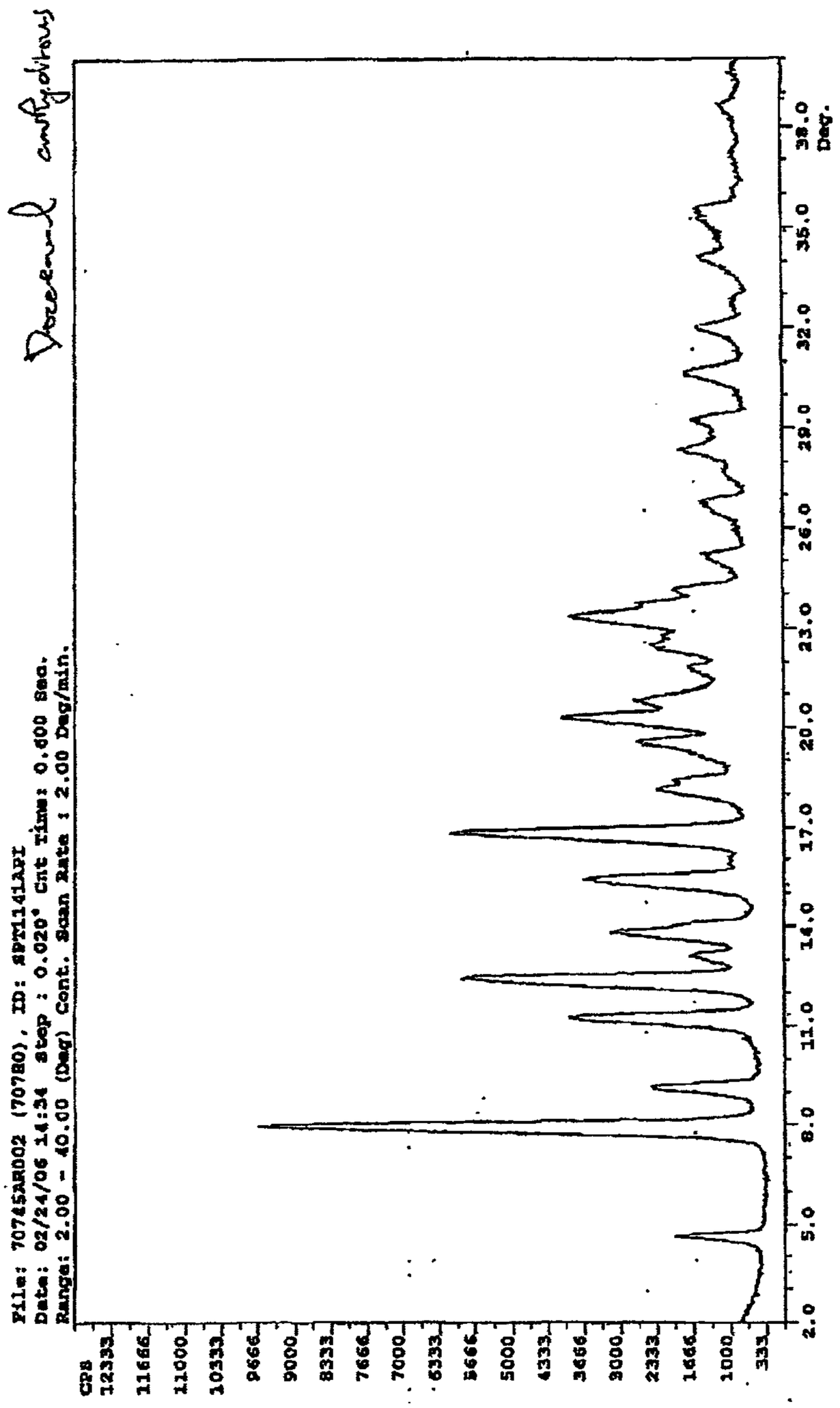
File: 70745AR002 (70780), ID: SPT114LAPI
Data: 02/24/06 14:34 Step : 0.020° Cnt Time: 0.600 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 2.00 Deg/min.
CPS
12333
11666
11000
10333
9666
9000
8333
7666
7000
6333
5666
5000
4333
3666
3000
2333
1666
1000
333
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0 Deg.

Figure 6

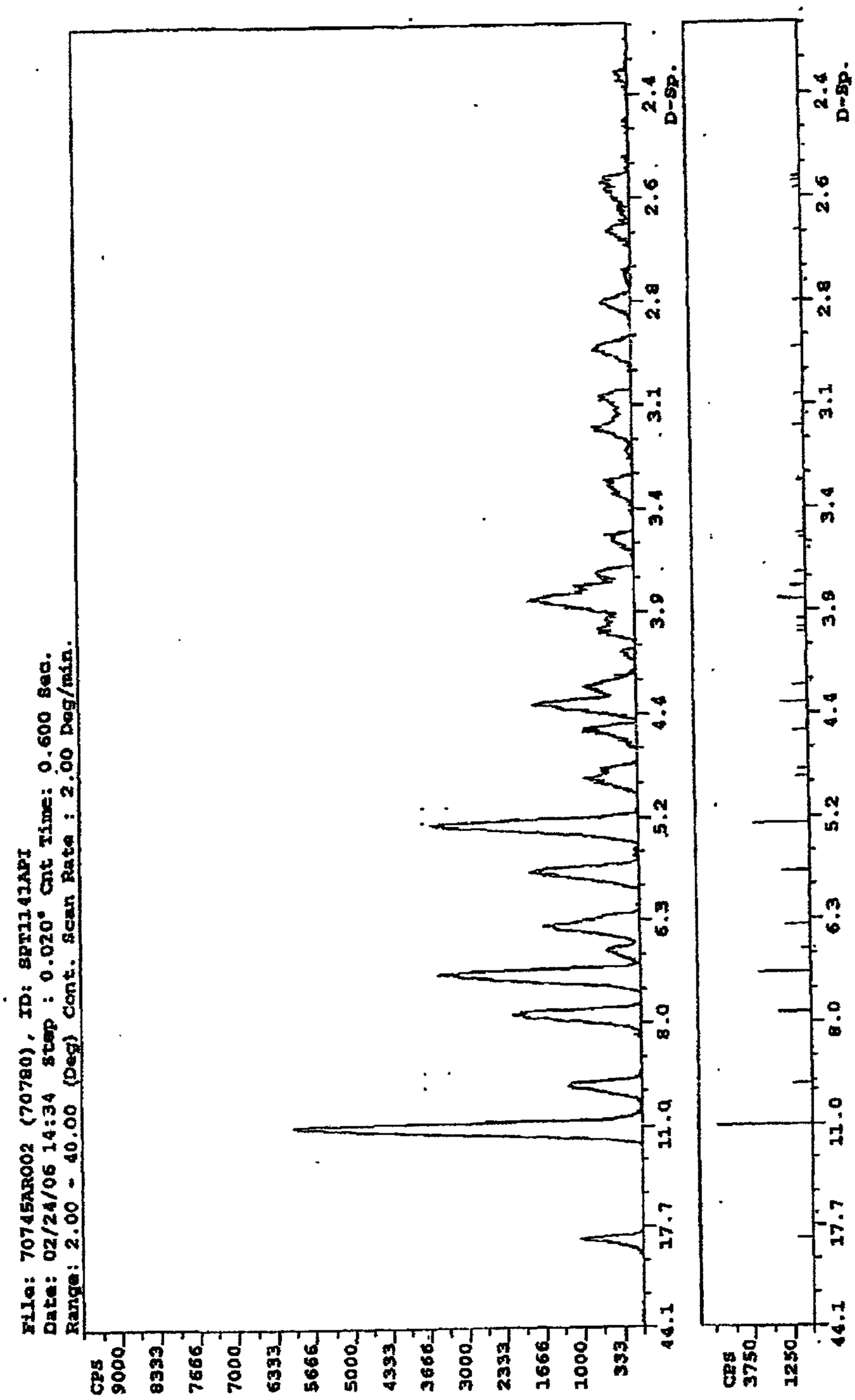
File: 70745AR002 (70780), ID: SPT141API
Date: 02/24/06 14:34 Step : 0.020° Cnt Time: 0.600 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 2.00 Deg/min.
CPS
9000
8333
7666
7000
6333
5666
5000
4333
3666
3000
2333
1666
1000
333
44.1
17.7
11.0
8.0
6.3
5.2
4.4
3.9
3.4
3.1
2.8
2.6
2.4
D-Sp.
CPS
3750
1250

Figure 7

File: Untitled2

ID: SPT11%1API
Comment: S870748AR002

Scan Type: Normal
Start Angle: 2 deg.
Stop Angle: 40 deg.
Num Points: 1901
Step Size: 0.02 deg.
Datafile Res: 1600
Scan Rate: 2.000000
Scan Mode: Continuous
Wavelength: 1.540562

Diffractometer Optics:
Detector:
Type: Fixed Slits
X2 Configuration: No
Tube:
Type: Fixed Slits
X2 Configuration: No

Peaks:

Position (Deg.)	Position (DSp.)	ESD (Deg.)	Corr.Fact	Intensity (cps)	Rel. Int. (%)	FWHM (L)	ESD (Deg.)	Area	Source	Curve	Strain	CSize	CSize Source
4.6319	19.0618	0.0000	0.0000	1007.97	16.47	0.1600	0.0000	161.3	PFind	None	0.00	0.00	None
7.9988	11.0442	0.0000	0.0000	6120.42	100.00	0.1600	0.0000	979.3	PFind	None	0.00	0.00	None
9.1763	9.6294	0.0000	0.0000	1221.58	19.96	0.1600	0.0000	195.5	PFind	None	0.00	0.00	None
11.2681	7.8460	0.0000	0.0000	2096.80	34.26	0.1600	0.0000	335.5	PFind	None	0.00	0.00	None
12.4388	7.1101	0.0000	0.0000	3297.00	53.87	0.1600	0.0000	527.5	PFind	None	0.00	0.00	None
13.1044	6.7504	0.0000	0.0000	536.93	8.77	0.0800	0.0000	85.9	PFind	None	0.00	0.00	None
13.8138	6.4053	0.0000	0.0000	1560.50	25.50	0.1600	0.0000	249.7	PFind	None	0.00	0.00	None
15.3800	5.7584	0.0000	0.0000	1756.73	28.70	0.1600	0.0000	281.1	PFind	None	0.00	0.00	None
16.8244	5.2653	0.0000	0.0000	3510.17	57.35	0.1600	0.0000	561.6	PFind	None	0.00	0.00	None
18.1375	4.8870	0.0000	0.0000	830.97	13.58	0.1600	0.0000	133.0	PFind	None	0.00	0.00	None
18.3600	4.8282	0.0000	0.0000	648.52	10.60	0.1600	0.0000	103.8	PFind	None	0.00	0.00	None
19.4800	4.5531	0.0000	0.0000	920.00	15.03	0.1200	0.0000	110.4	PFind	None	0.00	0.00	None
20.3008	4.3709	0.0000	0.0000	1734.52	28.34	0.1600	0.0000	277.5	PFind	None	0.00	0.00	None
20.8137	4.2642	0.0000	0.0000	820.57	13.41	0.1600	0.0000	131.3	PFind	None	0.00	0.00	None
22.4000	3.9657	0.0000	0.0000	557.53	9.11	0.1600	0.0000	89.2	PFind	None	0.00	0.00	None
22.5138	3.9459	0.0000	0.0000	609.77	9.96	0.1600	0.0000	97.6	PFind	None	0.00	0.00	None
22.7400	3.9072	0.0000	0.0000	516.67	8.44	0.1600	0.0000	82.7	PFind	None	0.00	0.00	None
23.3481	3.8068	0.0000	0.0000	1733.32	28.32	0.1600	0.0000	277.3	PFind	None	0.00	0.00	None
23.7044	3.7504	0.0000	0.0000	960.75	15.70	0.1600	0.0000	153.7	PFind	None	0.00	0.00	None
24.1187	3.6869	0.0000	0.0000	658.47	10.76	0.1600	0.0000	105.4	PFind	None	0.00	0.00	None
25.1138	3.5430	0.0000	0.0000	361.68	5.91	0.1600	0.0000	57.9	PFind	None	0.00	0.00	None
25.2200	3.5283	0.0000	0.0000	503.33	8.22	0.1400	0.0000	60.3	PFind	None	0.00	0.00	None
26.7200	3.3336	0.0000	0.0000	453.33	7.41	0.1600	0.0000	72.5	PFind	None	0.00	0.00	None
26.7725	3.3271	0.0000	0.0000	432.43	7.07	0.1600	0.0000	60.5	PFind	None	0.00	0.00	None
28.3444	3.1481	0.0000	0.0000	634.00	10.36	0.1600	0.0000	101.4	PFind	None	0.00	0.00	None
29.2325	3.0525	0.0000	0.0000	538.18	8.79	0.1600	0.0000	86.1	PFind	None	0.00	0.00	None
30.6200	2.9173	0.0000	0.0000	640.17	10.46	0.1600	0.0000	102.4	PFind	None	0.00	0.00	None
31.9031	2.7960	0.0000	0.0000	498.47	8.14	0.1600	0.0000	79.8	PFind	None	0.00	0.00	None
34.0412	2.6319	0.0000	0.0000	355.78	5.81	0.1400	0.0000	56.9	PFind	None	0.00	0.00	None
35.2350	2.5450	0.0000	0.0000	420.27	6.87	0.1600	0.0000	67.2	PFind	None	0.00	0.00	None
35.4331	2.5313	0.0000	0.0000	427.08	6.98	0.1600	0.0000	68.3	PFind	None	0.00	0.00	None
35.5788	2.5212	0.0000	0.0000	453.28	7.41	0.1600	0.0000	63.5	PFind	None	0.00	0.00	None

Figure 8

WO 2008/051465 PCT/US2007/022309 2011-10-26 CA 02756603

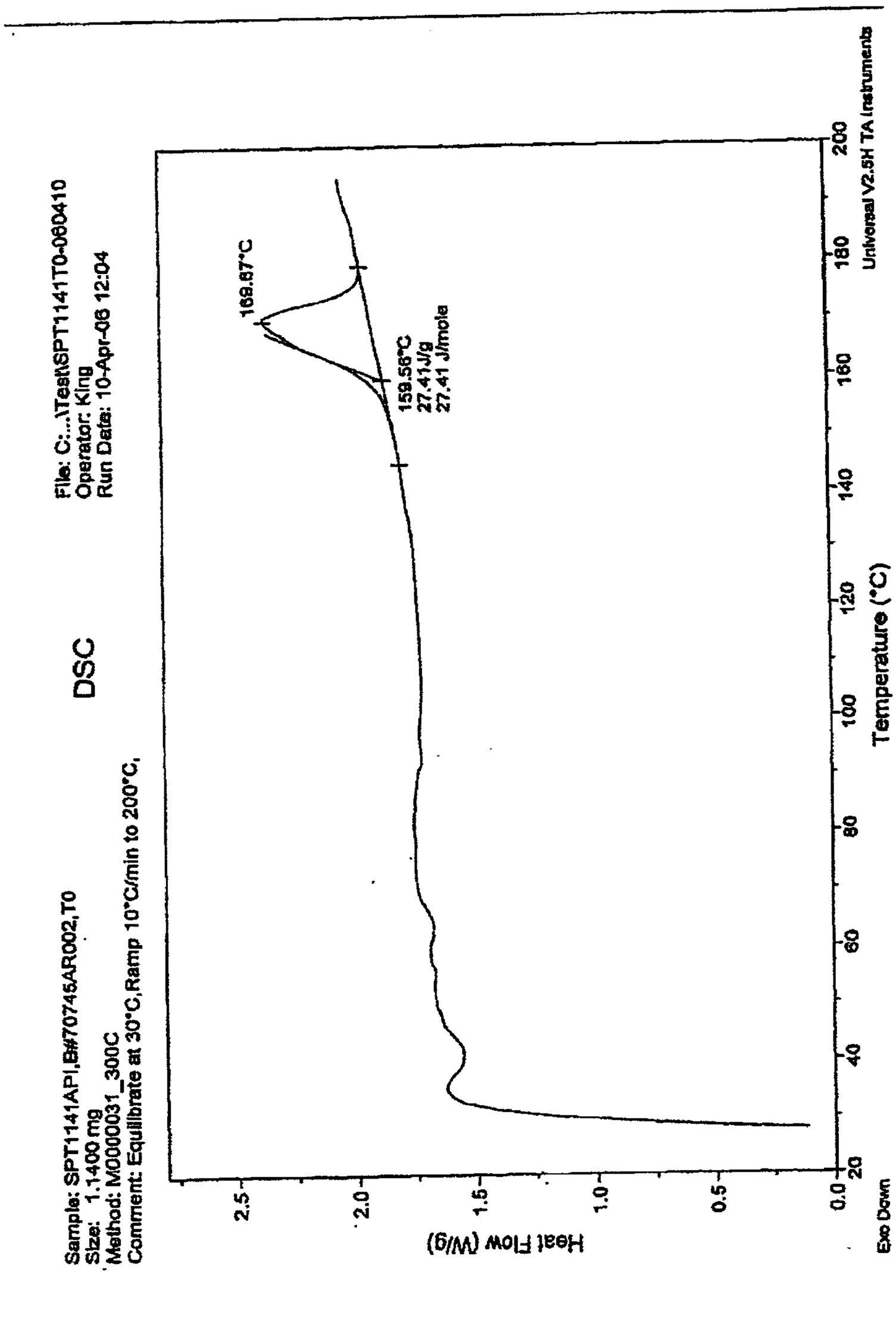
DSC
File: C:...\Test\SPT1141T0-060410
Operator: King
Run Data: 10-Apr-06 12:04
Sample: SPT1141API,B#70745AR002,T0
Size: 1.1400 mg
Method: M0000031_300C
Comment: Equilibrate at 30°C,Ramp 10°C/min to 200°C,
168.87°C
159.56°C
27.41J/g
27.41 J/mole
Heat Flow (W/g)
Exo Down
Temperature (°C)
Universal V2.5H TA Instruments

Figure 9

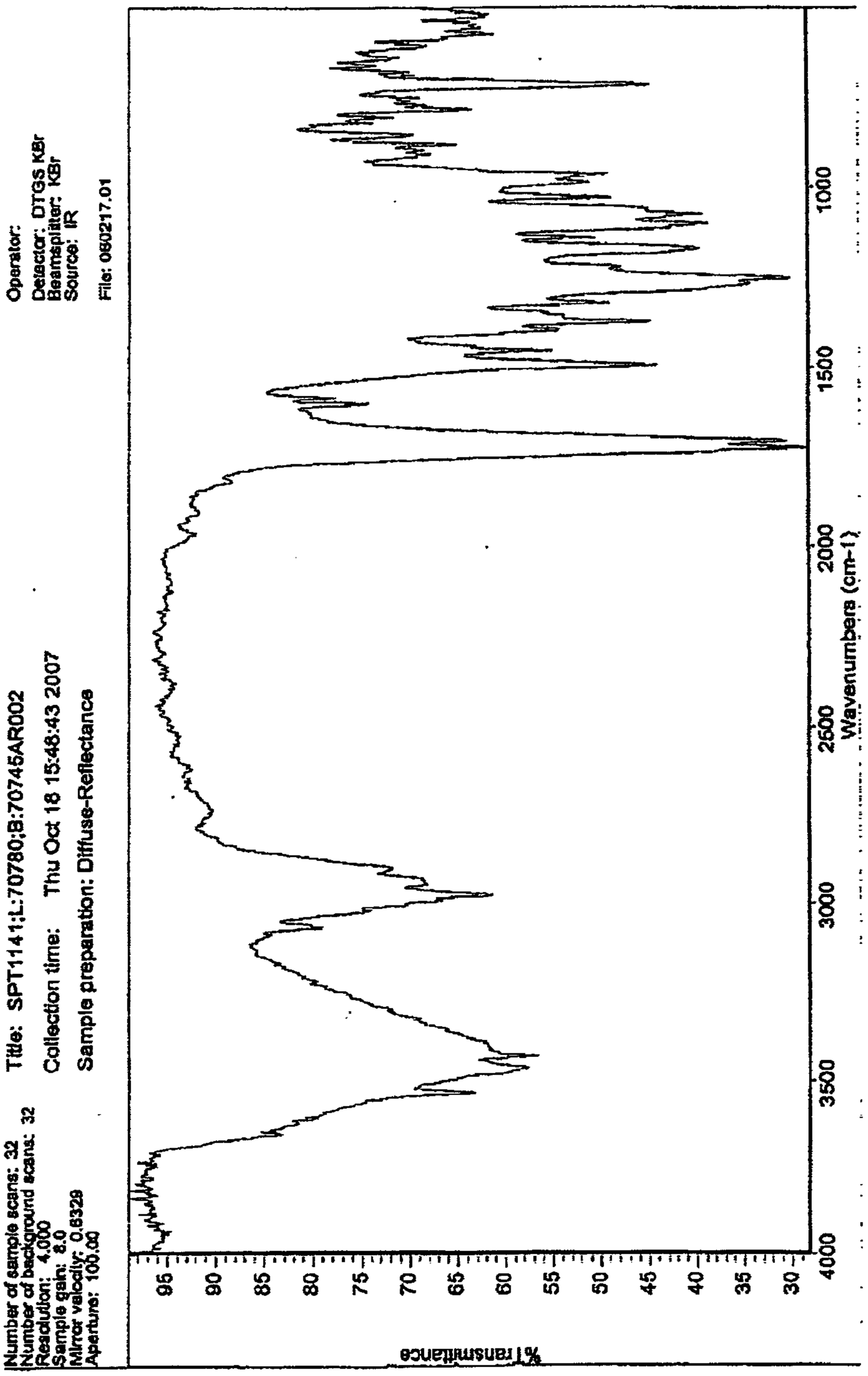
Operator:
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
File: 080217.01
Number of sample scans: 32
Number of background scans: 32
Resolution: 4.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00
Title: SPT1141;L:70780;B:70745AR002
Collection time: Thu Oct 18 15:48:43 2007
Sample preparation: Diffuse-Reflectance
%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2600
2000
1500
1000
95
90
85
80
75
70
65
60
55
50
45
40
35
30

Figure 10

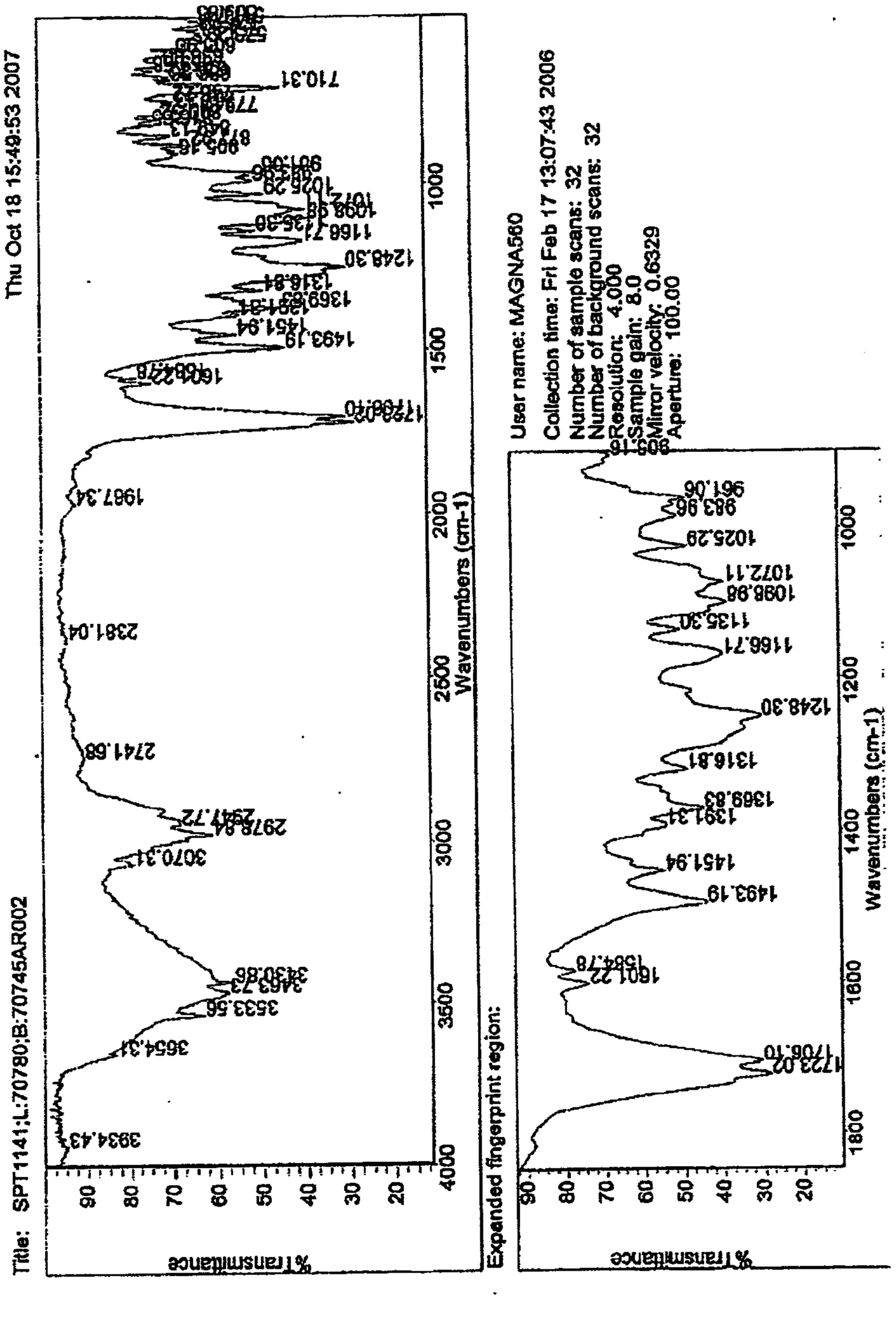
Title: SPT1141;L:70780;B:70745AR002
Thu Oct 18 15:49:53 2007
%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
3934.43
3654.31
3533.56
3463.73
3430.86
3070.31
2978.84
2947.72
2741.68
1987.34
2381.04
1723.02
1706.10
1601.22
1584.78
1493.19
1451.94
1391.31
1369.83
1316.81
1248.30
1166.71
1135.30
1098.98
1072.11
1025.29
983.96
961.06
Expanded fingerprint region:
User name: MAGNA560
Collection time: Fri Feb 17 13:07:43 2006
Number of sample scans: 32
Number of background scans: 32
Resolution: 4.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00
1800
1600
1400
1200
1000
800

Figure 11

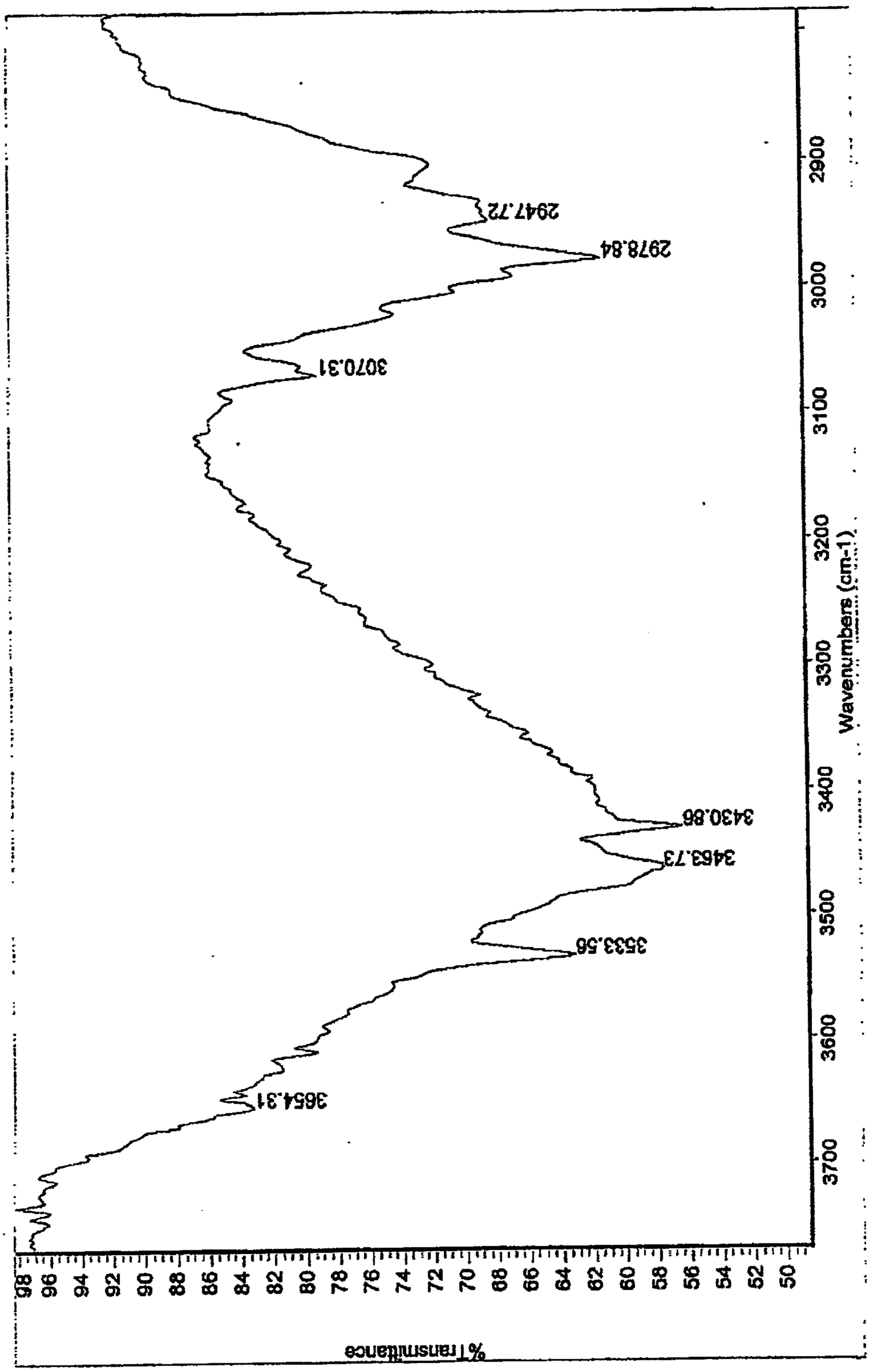
2947.72
2978.84
3070.31
3454.31
3533.56
3463.73
3430.86
2900
3000
3100
3200
3300
3400
3500
3600
3700
Wavenumbers (cm-1)
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
%Transmittance

Figure 12

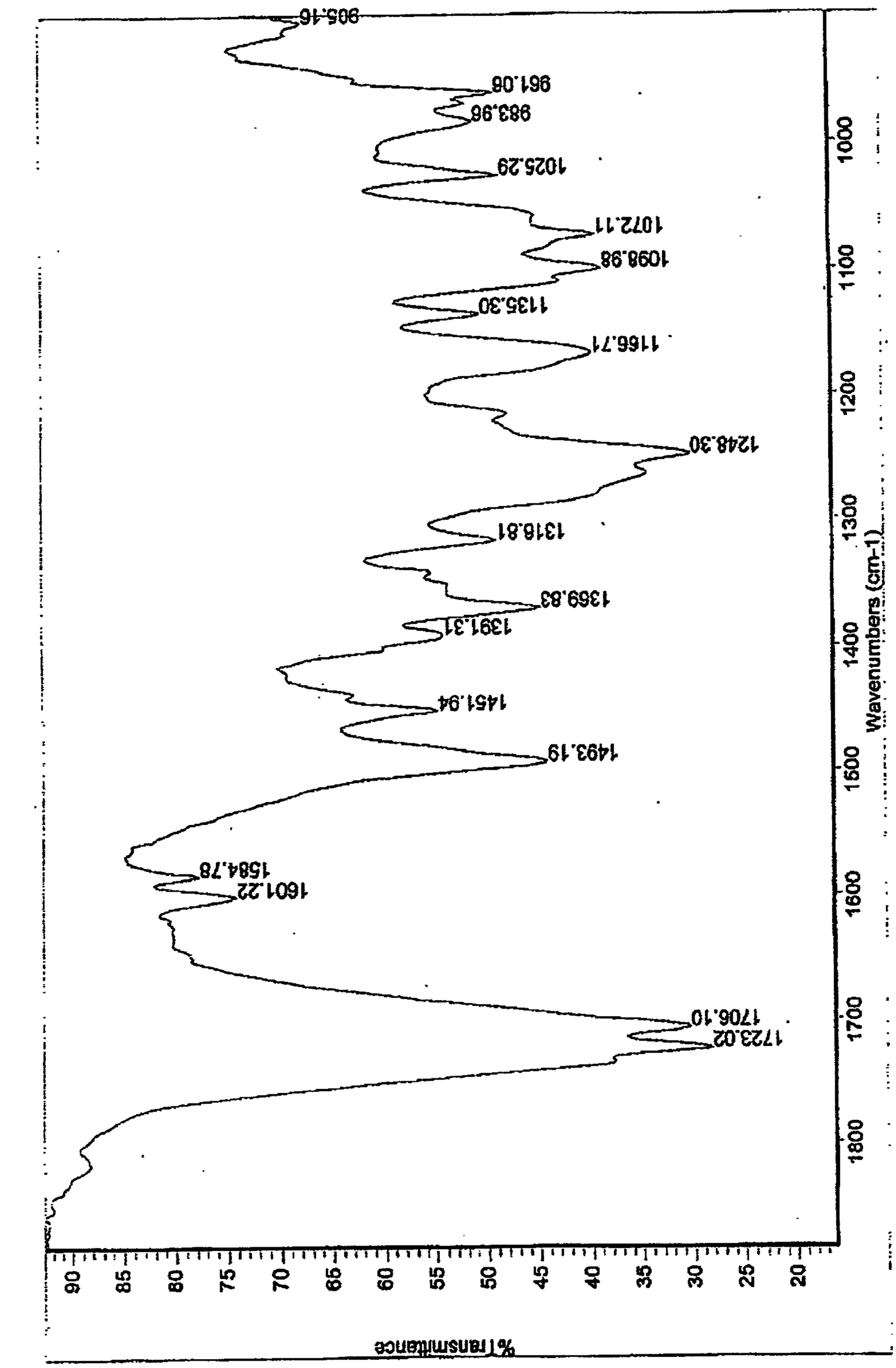
905.16
961.08
983.96
1025.29
1072.11
1098.98
1135.30
1166.71
1248.30
1318.81
1359.83
1391.31
1451.94
1493.19
1584.78
1601.22
1706.10
1723.02
%Transmittance
Wavenumbers (cm-1)

Figure 13

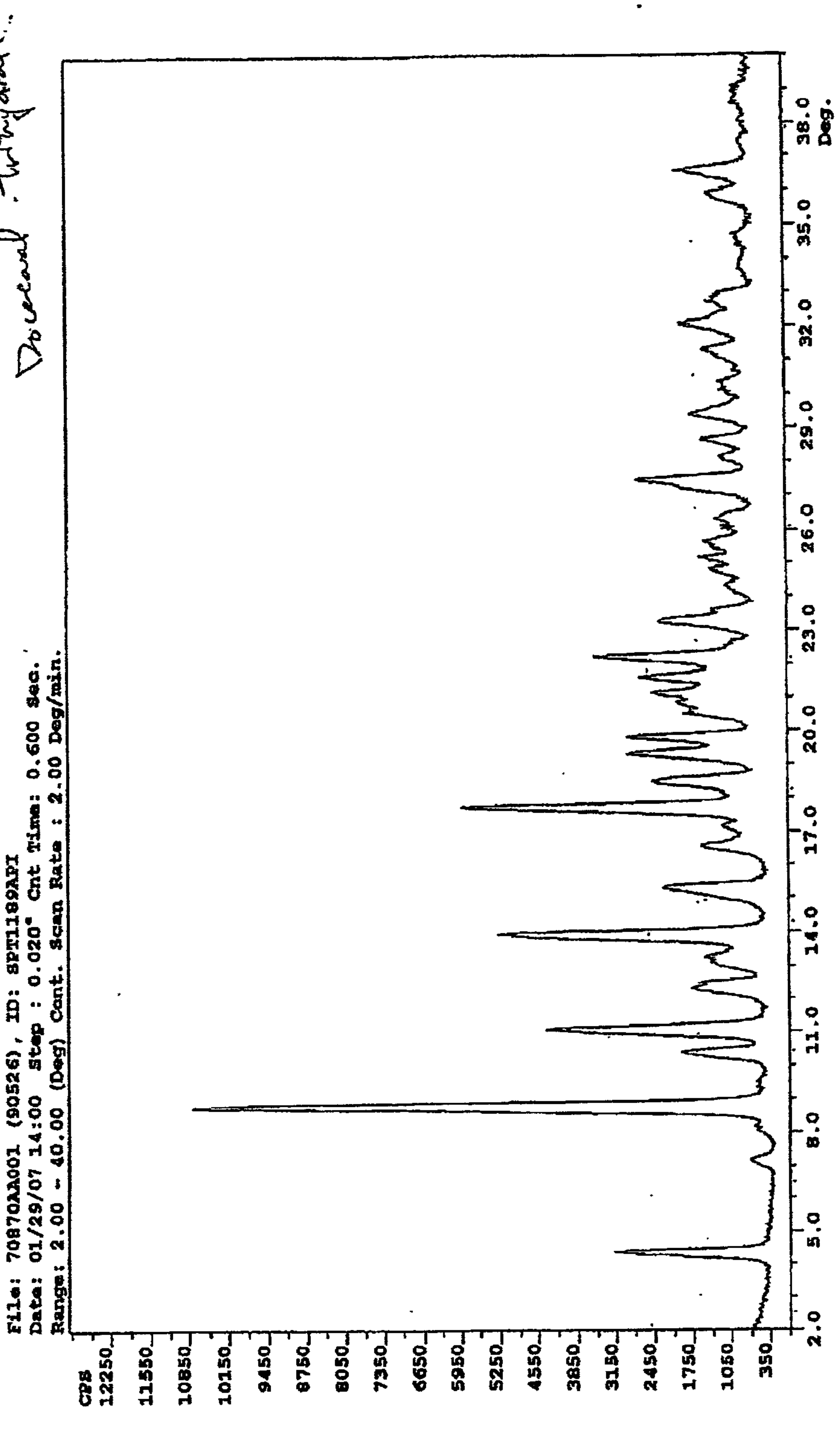
File: 70870AA001 (90526), ID: SPT1189API
Date: 01/29/07 14:00 Step : 0.020° Cnt Time: 0.600 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 2.00 Deg/min.
CPS
12250
11550
10850
10150
9450
8750
8050
7350
6650
5950
5250
4550
3850
3150
2450
1750
1050
350
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Figure 14

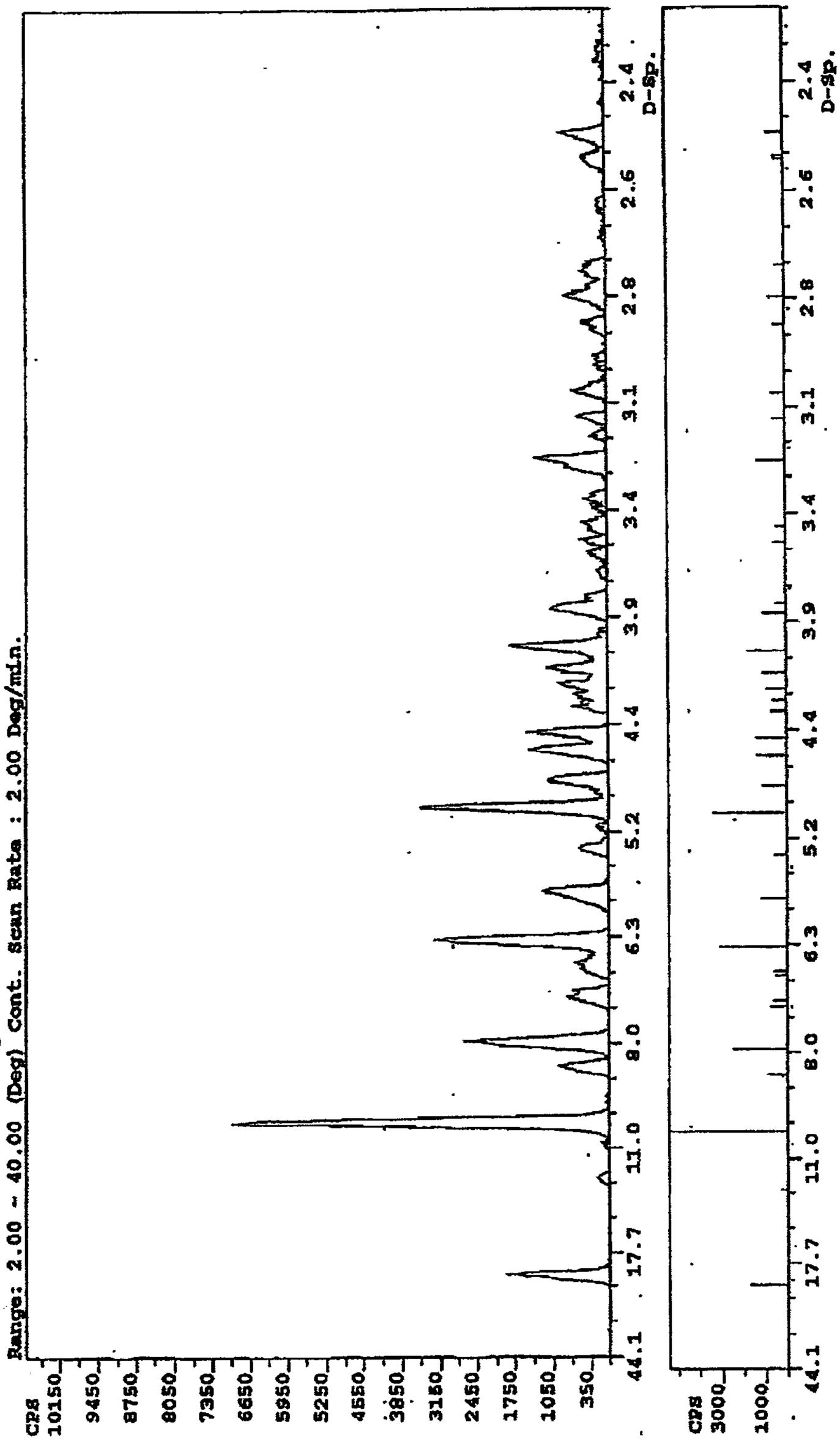
File: 70870AA001 (905261, ID: SPT189API
Data: 01/29/07 14:00 Step : 0.020° Cnt Time: 0.600 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 2.00 Deg/min.
CPS
10150
9450
8750
8050
7350
6650
5950
5250
4550
3850
3150
2450
1750
1050
350
2.4
2.6
2.8
3.1
3.4
3.9
4.4
5.2
6.3
8.0
11.0
17.7
44.1
D-Sp.

Figure 15

File: Untitled1

ID: SPT1189API
Comment: B#70870AA001

Scan Type: Normal
Start Angle: 2 deg.
Stop Angle: 40 deg.
Num Points: 1901
Step Size: 0.02 deg.
Datafile Res: 1600
Scan Rate: 2.000000
Scan Mode: Continuous
Wavelength: 1.540562

Diffractometer Optics:
Detector:
Type: Fixed Slits
X2 Configuration: No
Tube:
Type: Fixed Slits
X2 Configuration: No

Peaks:

Position (Deg.)	Position (DSp.)	ESD (Deg.)	Corr.Fact	Intensity (cps)	Rel. Int. (%)	FWHM (L)	ESD (Deg.)	Area	Source	Curve	Strain	CSize	CSize Source
4.3719	20.1948	0.0000	0.0000	1780.00	25.60	0.1600	0.0000	284.8	PFind	None	0.00	0.00	None
7.1075	12.4269	0.0000	0.0000	265.14	3.81	0.0000	0.0000	0.0	Manual	None	0.00	0.00	None
8.7675	10.0774	0.0000	0.0000	6952.43	100.00	0.1600	0.0000	1112.4	PFind	None	0.00	0.00	None
10.3594	8.5322	0.0000	0.0000	911.70	13.11	0.1600	0.0000	145.9	PFind	None	0.00	0.00	None
11.0700	7.9860	0.0000	0.0000	2525.17	36.32	0.1600	0.0000	404.0	PFind	None	0.00	0.00	None
12.2819	7.2006	0.0000	0.0000	725.77	10.44	0.1200	0.0000	116.1	PFind	None	0.00	0.00	None
12.4456	7.1062	0.0000	0.0000	603.23	8.68	0.1600	0.0000	72.4	PFind	None	0.00	0.00	None
13.1150	6.7450	0.0000	0.0000	497.47	7.16	0.1600	0.0000	79.6	PFind	None	0.00	0.00	None
13.2463	6.6785	0.0000	0.0000	565.42	8.13	0.1000	0.0000	90.5	PFind	None	0.00	0.00	None
13.9275	6.3533	0.0000	0.0000	3111.03	44.75	0.1600	0.0000	497.8	PFind	None	0.00	0.00	None
15.2775	5.7948	0.0000	0.0000	1165.85	16.77	0.1600	0.0000	186.5	PFind	None	0.00	0.00	None
16.5294	5.3586	0.0000	0.0000	518.88	7.46	0.1200	0.0000	83.0	PFind	None	0.00	0.00	None
17.6975	5.0075	0.0000	0.0000	3406.78	49.00	0.1600	0.0000	545.1	PFind	None	0.00	0.00	None
18.4606	4.8021	0.0000	0.0000	1104.02	15.88	0.1600	0.0000	176.6	PFind	None	0.00	0.00	None
19.3144	4.5918	0.0000	0.0000	1370.93	19.72	0.1600	0.0000	219.3	PFind	None	0.00	0.00	None
19.7819	4.4843	0.0000	0.0000	1413.98	20.34	0.1600	0.0000	226.2	PFind	None	0.00	0.00	None
20.5200	4.3246	0.0000	0.0000	673.33	9.68	0.1600	0.0000	80.8	PFind	None	0.00	0.00	None
20.8463	4.2577	0.0000	0.0000	584.72	8.41	0.1600	0.0000	93.6	PFind	None	0.00	0.00	None
21.1300	4.2011	0.0000	0.0000	872.03	12.54	0.1600	0.0000	104.6	PFind	None	0.00	0.00	None
21.5963	4.1115	0.0000	0.0000	1069.35	15.38	0.1600	0.0000	171.1	PFind	None	0.00	0.00	None
22.1894	4.0029	0.0000	0.0000	1760.90	25.33	0.1200	0.0000	281.7	PFind	None	0.00	0.00	None
23.2488	3.8228	0.0000	0.0000	1043.55	15.01	0.1600	0.0000	167.0	PFind	None	0.00	0.00	None
23.5000	3.7825	0.0000	0.0000	430.00	6.18	0.1600	0.0000	68.8	PFind	None	0.00	0.00	None
25.2075	3.5300	0.0000	0.0000	515.00	7.41	0.1400	0.0000	51.5	PFind	None	0.00	0.00	None
25.6388	3.4716	0.0000	0.0000	450.63	6.48	0.1600	0.0000	56.1	PFind	None	0.00	0.00	None
27.4406	3.2476	0.0000	0.0000	1330.93	19.14	0.1600	0.0000	186.3	PFind	None	0.00	0.00	None
28.6437	3.1139	0.0000	0.0000	508.95	7.32	0.1600	0.0000	81.4	PFind	None	0.00	0.00	None
29.3736	3.0381	0.0000	0.0000	582.17	8.37	0.1600	0.0000	93.1	PFind	None	0.00	0.00	None
31.2800	2.8572	0.0000	0.0000	468.33	6.74	0.0800	0.0000	37.5	PFind	None	0.00	0.00	None
32.0211	2.7926	0.0000	0.0000	732.08	10.53	0.1600	0.0000	117.1	PFind	None	0.00	0.00	None
32.9000	2.7201	0.0000	0.0000	411.67	5.92	0.1600	0.0000	65.9	PFind	None	0.00	0.00	None
35.8600	2.5021	0.0000	0.0000	429.17	6.17	0.1600	0.0000	68.7	PFind	None	0.00	0.00	None
35.9400	2.4967	0.0000	0.0000	423.57	6.09	0.1200	0.0000	50.8	PFind	None	0.00	0.00	None
36.5744	2.4548	0.0000	0.0000	782.05	11.25	0.1200	0.0000	125.1	PFind	None	0.00	0.00	None

Figure 16

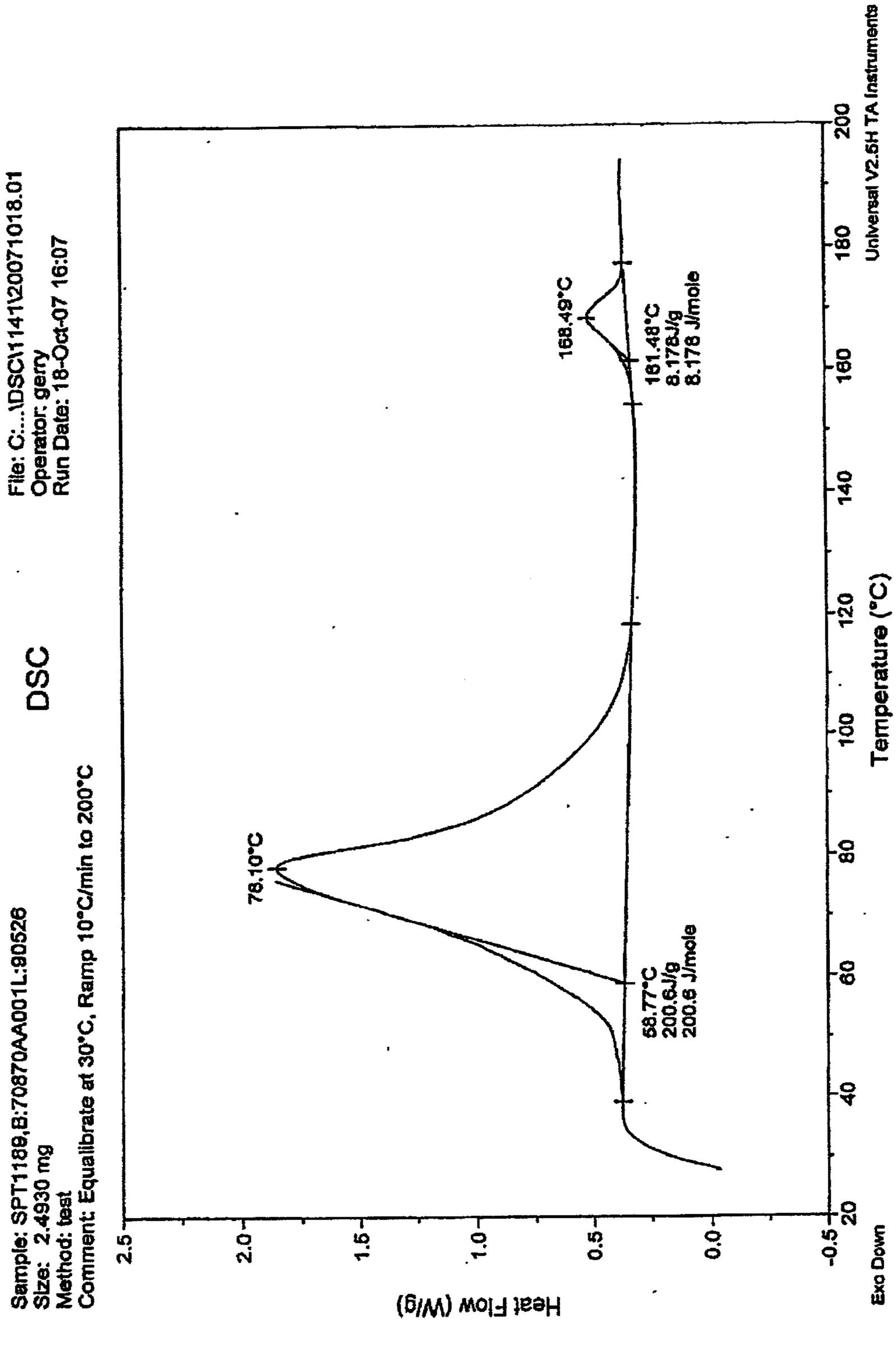
DSC
File: C:...\DSC\1141\20071018.01
Operator: gerry
Run Date: 18-Oct-07 16:07
Sample: SPT1189,B:70870AA001L:90526
Size: 2.4930 mg
Method: test
Comment: Equalibrate at 30°C, Ramp 10°C/min to 200°C
168.49°C
161.48°C
8.178J/g
8.178 J/mole
78.10°C
58.77°C
200.6J/g
200.6 J/mole
Heat Flow (W/g)
Exo Down
Temperature (°C)
Universal V2.5H TA Instruments

Figure 17

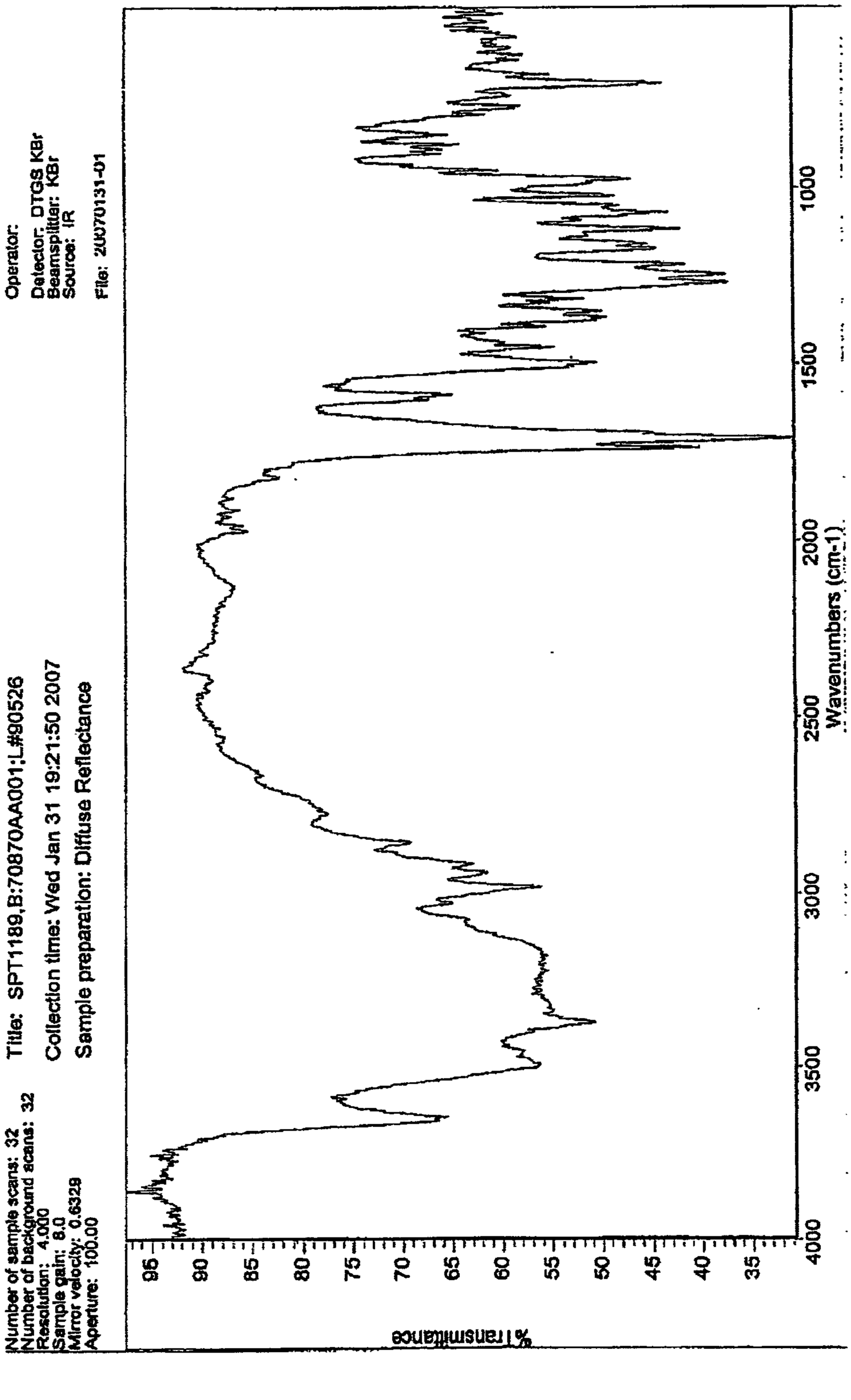
Operator:
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
File: 2007013101-01
Number of sample scans: 32
Number of background scans: 32
Resolution: 4.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00
Title: SPT1189,B:70870AA001;L#90526
Collection time: Wed Jan 31 19:21:50 2007
Sample preparation: Diffuse Reflectance
%Transmittance
Wavenumbers (cm-1)
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000

Figure 18

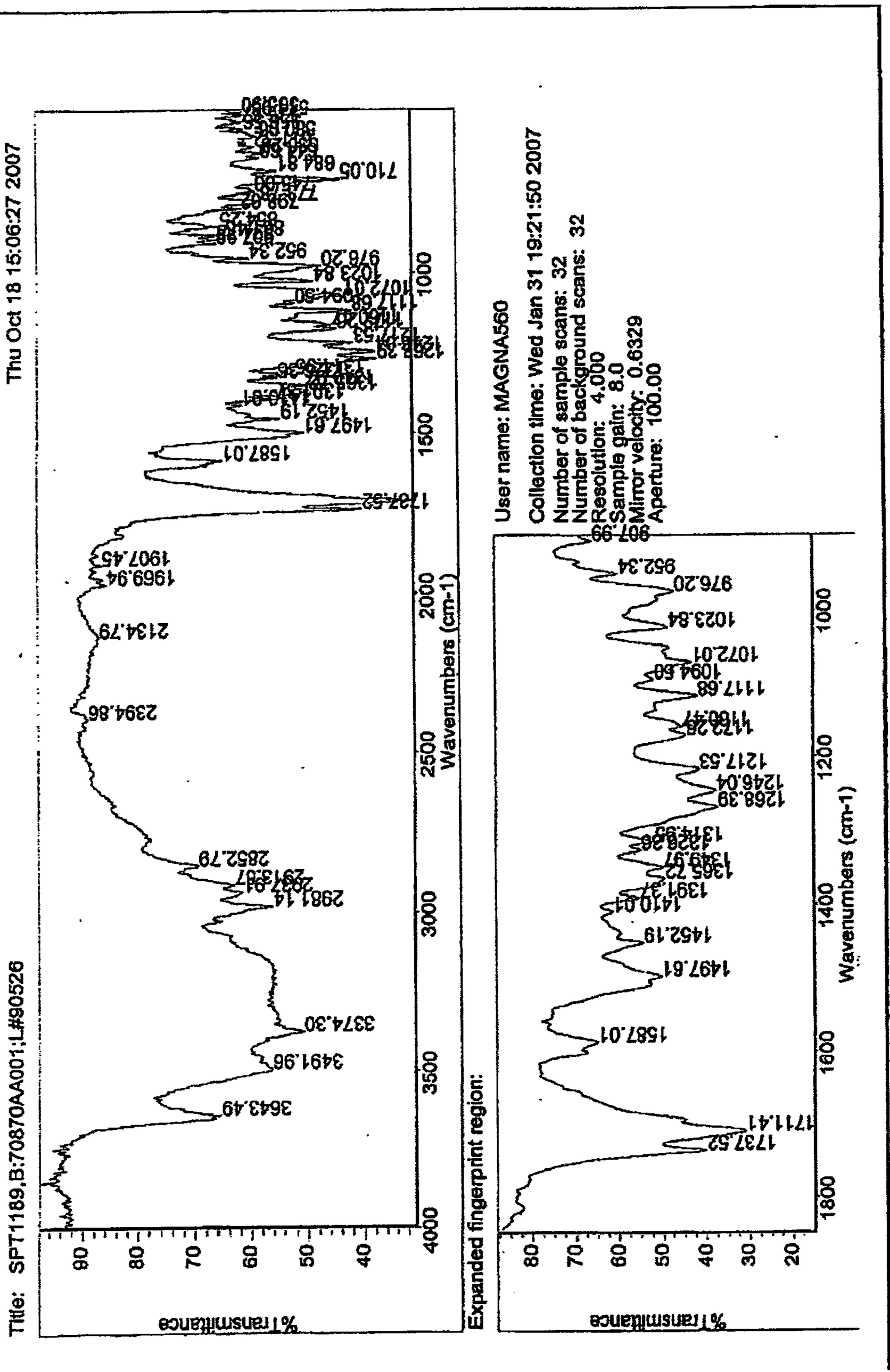
Title: SPT1189,B:70870AA001;L#90526
%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
3643.49
3491.96
3374.30
2981.14
2937.94
2913.87
2852.79
2394.86
2134.79
1969.94
1907.45
1737.52
1587.01
1497.61
1452.19
1410.01
1391.37
1365.22
1349.57
1328.26
1314.95
1268.39
1246.04
1217.53
1172.28
1160.47
1117.68
1094.50
1072.01
1023.84
976.20
952.34
907.99
884.91
710.05
Expanded fingerprint region:
%Transmittance
Wavenumbers (cm-1)
1800
1600
1400
1200
1000
User name: MAGNA560
Collection time: Wed Jan 31 19:21:50 2007
Number of sample scans: 32
Number of background scans: 32
Resolution: 4.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00
Thu Oct 18 15:06:27 2007

Figure 19

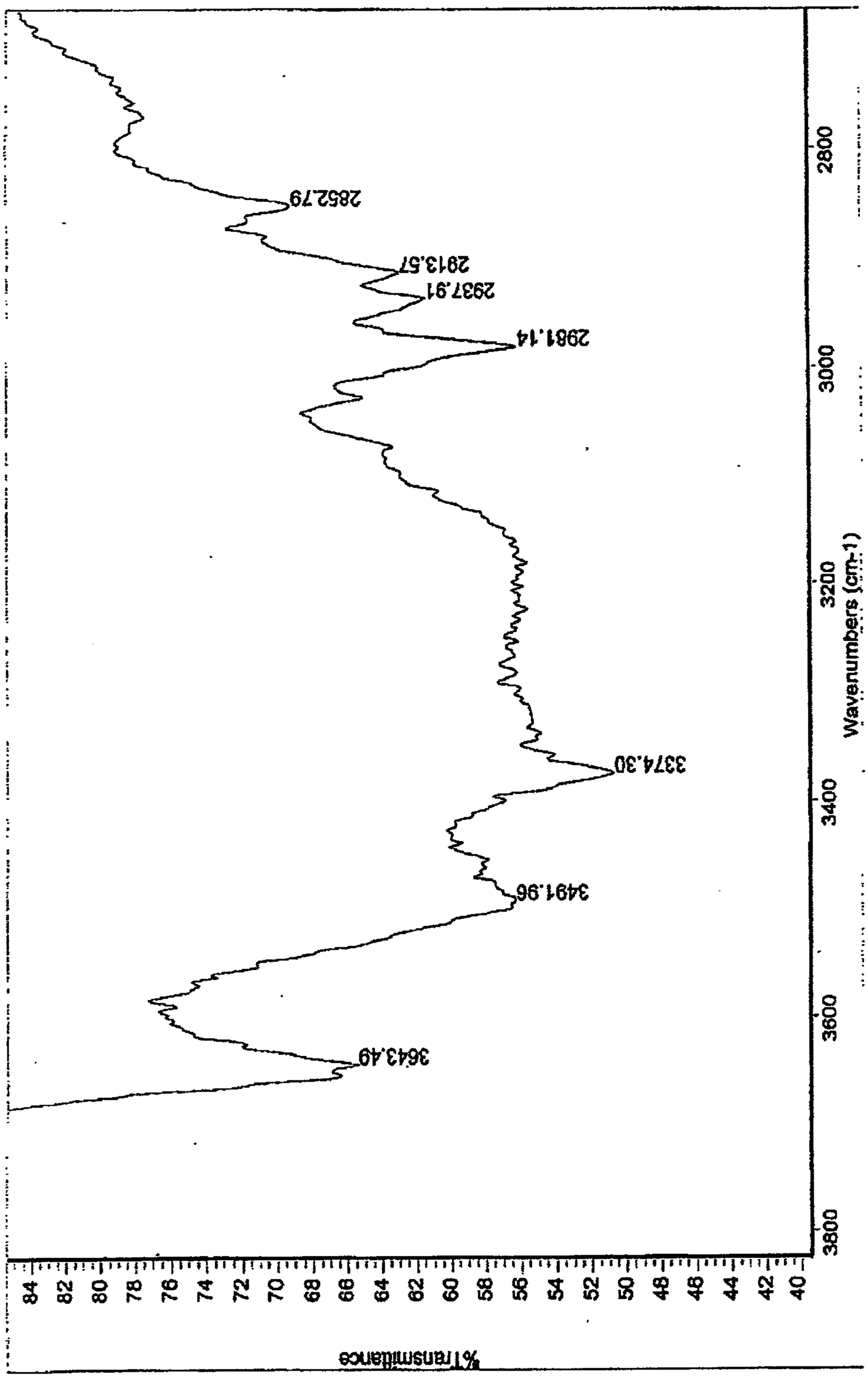
2852.79
2913.57
2937.91
2981.14
3374.30
3491.96
3643.49
%Transmittance
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40
3800
3600
3400
3200
3000
2800
Wavenumbers (cm-1)

Figure 20

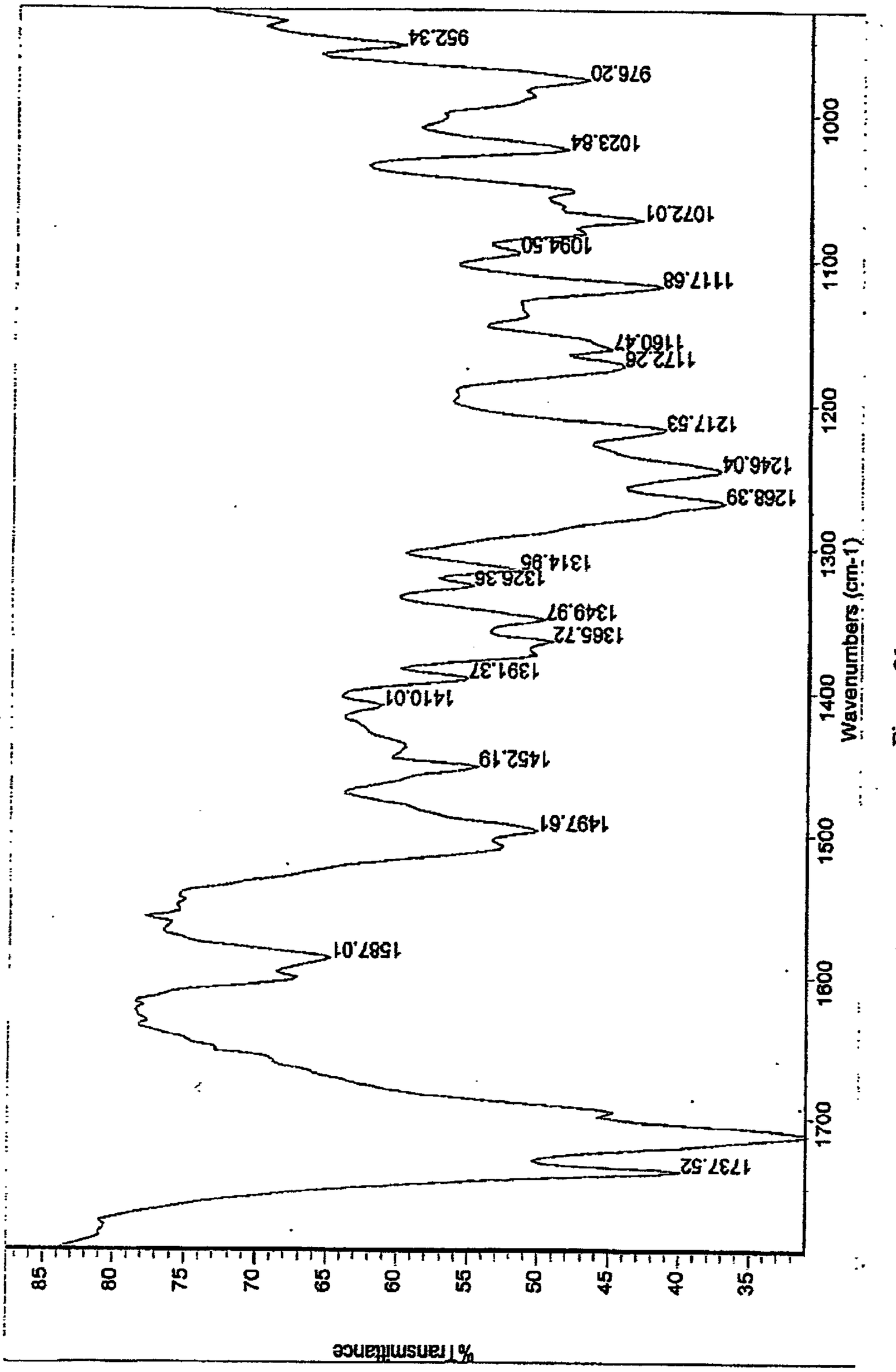
952.34
976.20
1023.84
1072.01
1094.50
1117.68
1160.47
1172.28
1217.53
1246.04
1268.39
1314.85
1326.36
1349.97
1365.72
1391.37
1410.01
1452.19
1497.61
1587.01
1737.52
% Transmittance
Wavenumbers (cm-1)

Figure 21