Unprecedented, Fully Recyclable, Solid-Supported Reagent for the Kinetic Resolution of Racemic Amines through Enantioselective *N*-Acetylation

Stellios Arseniyadis, Pithani V. Subhash, Alain Wagner* and Charles Mioskowski*

Université Louis Pasteur de Strasbourg, UMR 7514 associée au CNRS, Laboratoire de Synthèse Bioorganique Faculté de Pharmacie, 74, Route du Rhin, 67401 Illkirch-Graffenstaden.

Alain Valleix

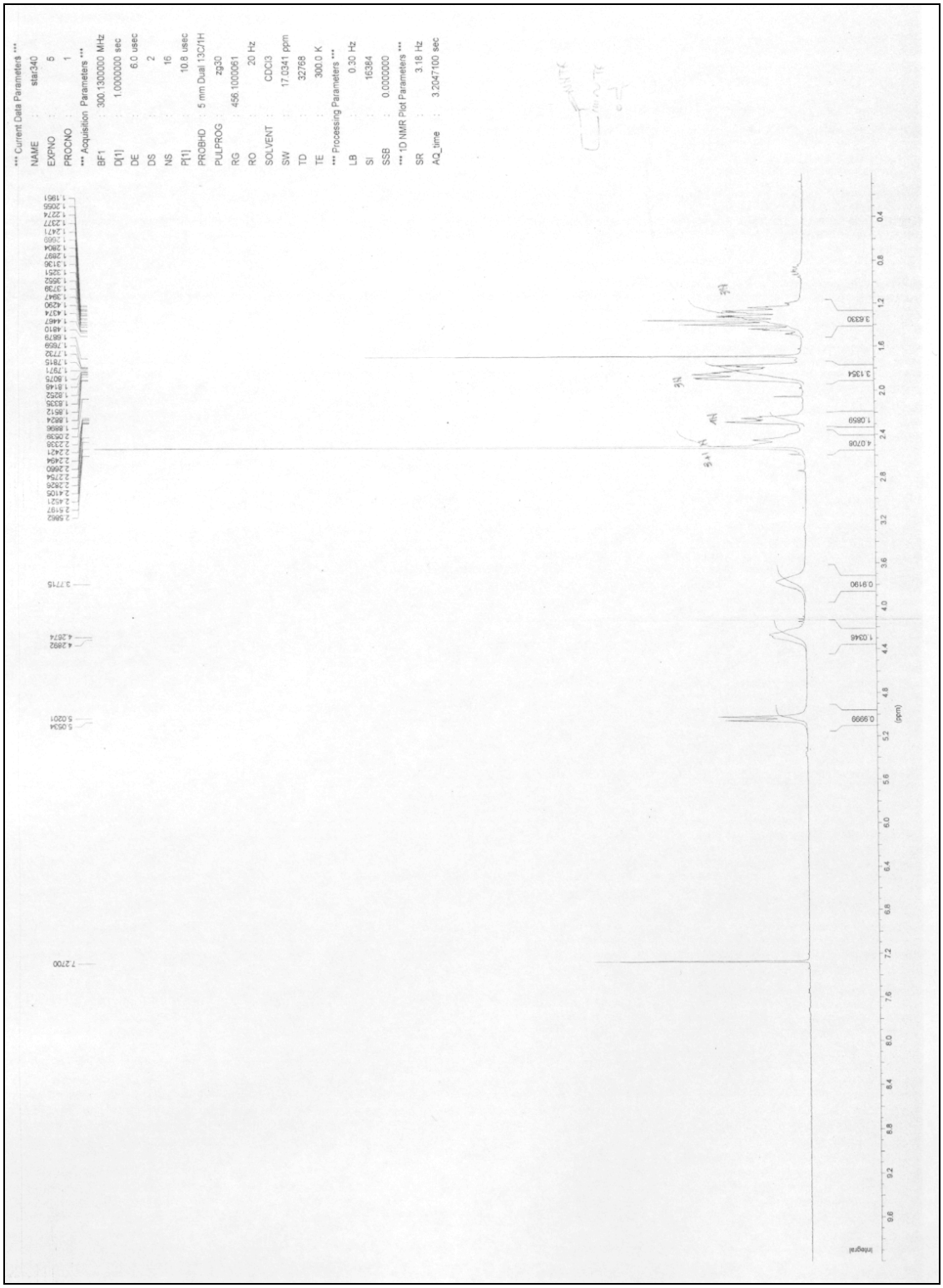
CEA-Saclay, Service des Molécules Marquées, Bât. 547 Département de Biologie Cellulaire et Moléculaire, F-91191, Gif-sur-Yvette.

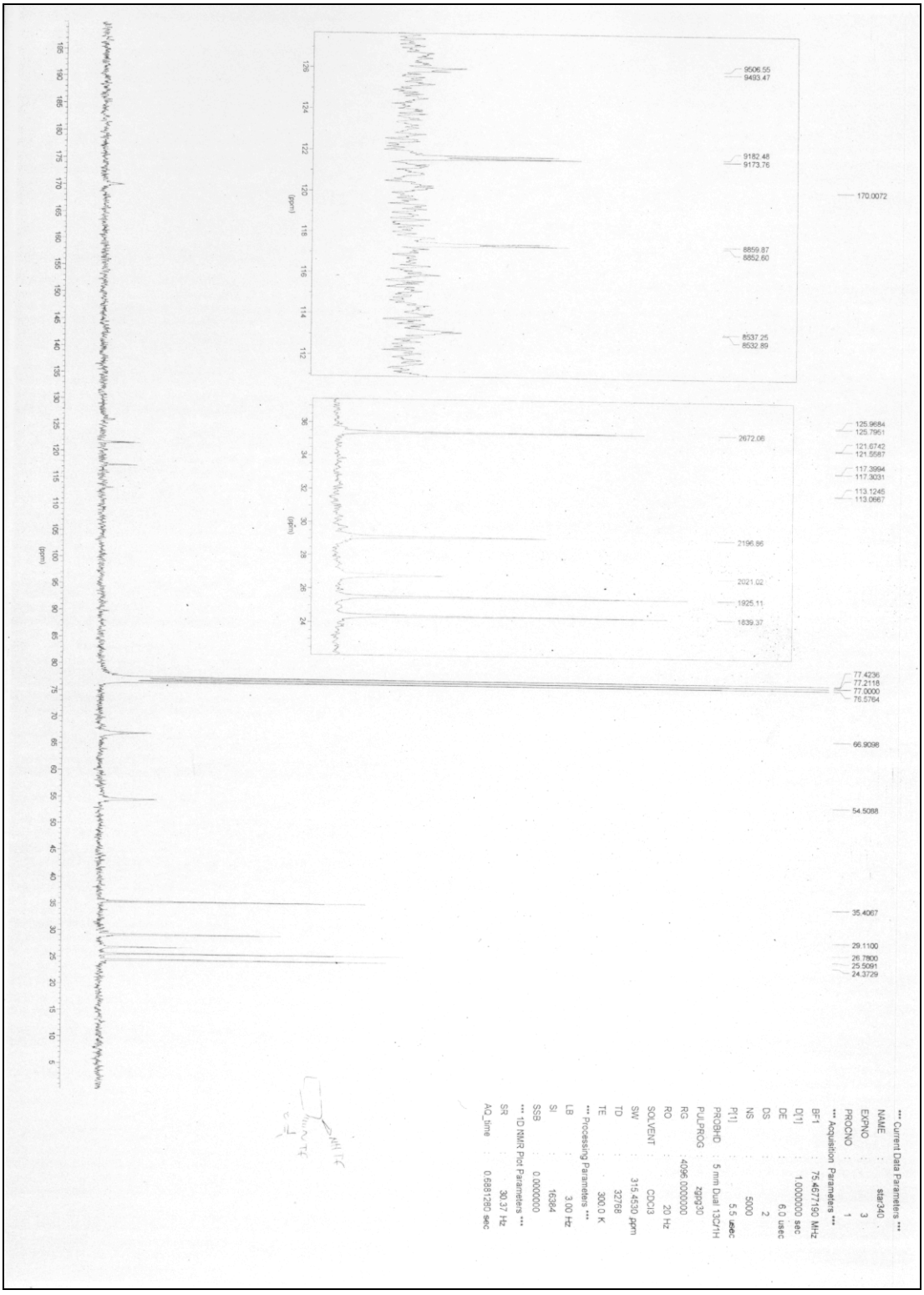
Supporting Information

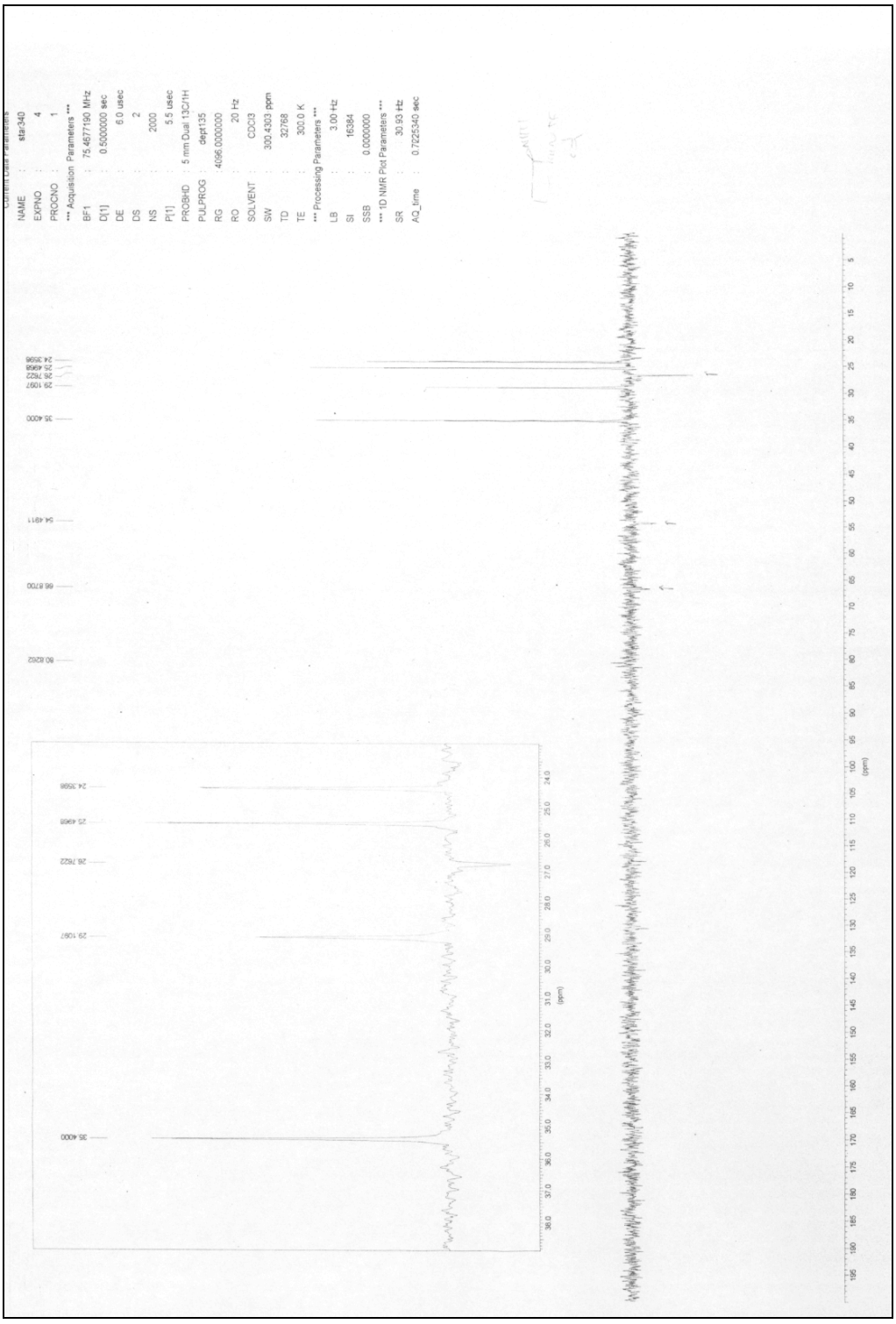
General Considerations. Glassware was oven-dried before use and cooled to room temperature under N_2. All solvents were commercially available and used without further purification unless noted otherwise. Yields and ee's in the tables refer to isolated yields (average of at least two runs) of compounds which are ≥95% pure as determined by ^{1}H NMR. All products were characterized by ^{1}H NMR, ^{13}C NMR, and infrared (IR) spectroscopy. Analytical thin-layer chromatography (TLC) were performed using 2.5 cm x 5 cm plates coated with a 0.25 mm thickness of silica gel 60F-254 Merck, and visualization was accomplished with ultraviolet light or with ethanolic bromocresol green. Flash chromatography were performed using silica gel 60 Merck (40-60 mm). IR spectra were taken on a Perkin Elmer 1600 FT-IR spectrophotometer with samples prepared as KBr pellets (2-8 mg of product was pulverized with 100 mg of KBr and pressed into a pellet in standard fashion). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP-200 SY or on a Bruker DPX 300 spectrometer at ambient temperature. All ^{1}H NMR spectra (200 or 300 MHz) are reported as follows: chemical shift in parts per million, ppm, downfield from tetramethylsilane as an internal standard (scale), multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet, integration, and coupling constant (Hz). All ^{13}C NMR spectra (50 or 75 MHz) are determined with complete proton decoupling and reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77 ppm. Analytical chiral HPLC were performed on Daicel Chiralcel OD column (250 mm x 4.6 mm). Mass spectra were

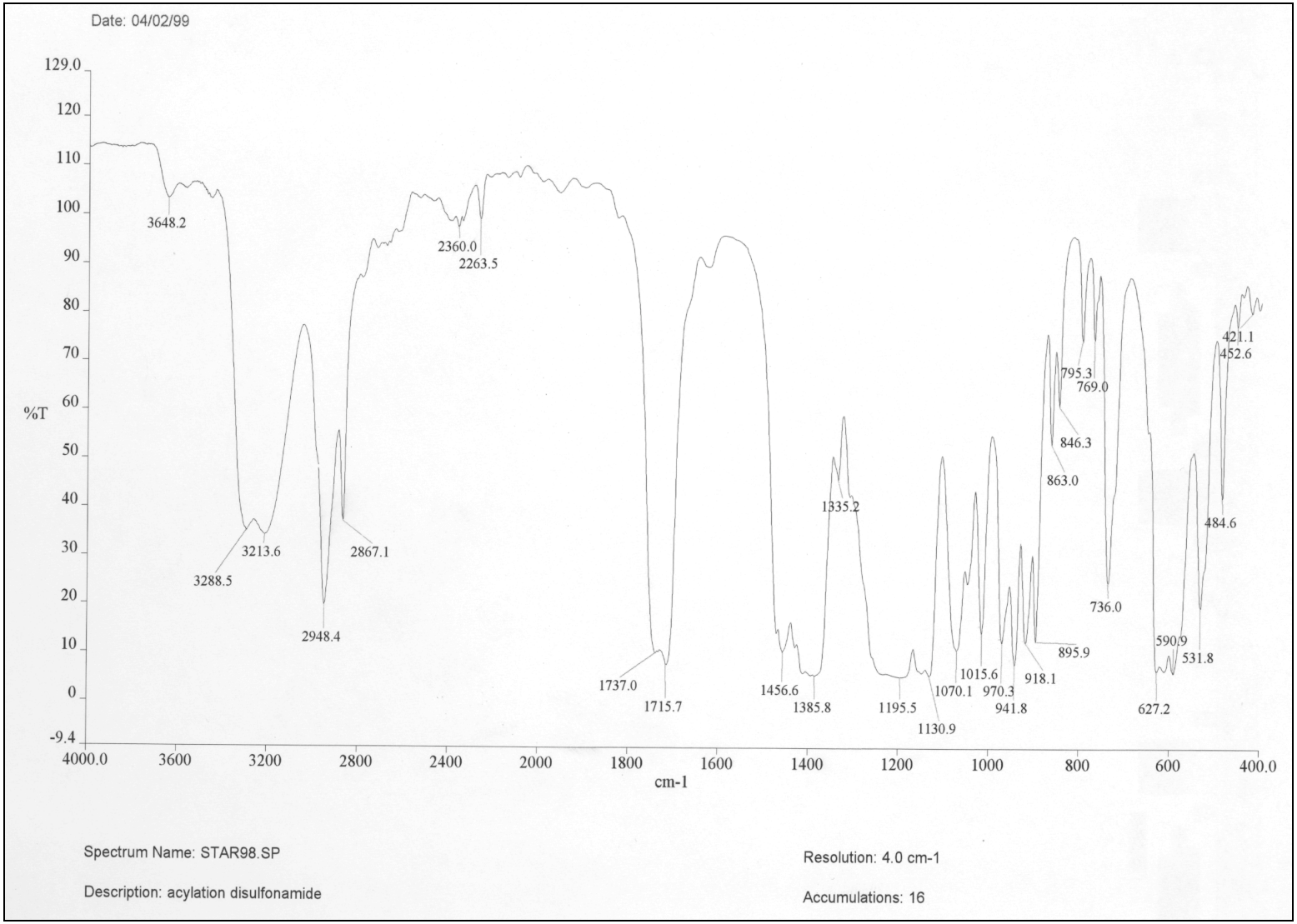
recorded on a Finnigan-Mat 4600 spectrometer. Melting points were obtained using a Reichert-Jung melting point apparatus.

(1*S*,2*S*)-*N*-Acetyl-1,2-*bis*-trifluoromethanesulfonamidocyclohexane (1). Freshly distilled acetyl chloride (1.88 mL, 2.64 mmol) was added dropwise by syringe to a stirred solution of 1,2-*bis*-(trifluoromethanesulfonamido)-cyclohexane (Aldrich; 1.00 g, 2.64 mmol) and triethylamine (5.50 mL, 3.96 mmol) in Et_2O (20 mL) at -20 °C. The mixture was stirred 3h at 0 °C, time after which the solvent was removed under reduced pressure. The resulting residue was subjected to flash chromatography on silica gel (EtOAc/*n*-Hexane: 1/9) to afford the desired product as a white solid in 85% yield. mp = 111 °C; $[\alpha]^{20}_D$ = +17.46° (c = 1.5; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 to 1.60 (m, 3H), 1.70 to 2.00 (m, 3H), 2.05 to 2.35 (m, 1H), 2.35 to 2.60 (m, 1H), 2.52 (s, 3H), 3.60 to 4.05 (m, 1H), 4.10 to 4.60 (m, 1H), 5.04 (d, *J*=10 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.5, 26.8, 29.1, 35.4, 54.5, 66.9, 119.4, 119.5, 170.0; FTIR (CsI) ν 3296, 3221, 2947, 2868, 1737, 1716, 1456, 1385, 1233, 1200, 1131, 1071, 1016, 971, 942, 918, 896, 737, 611, 532. MS (IC/NH_3, m/z) = 438 $[M+NH4]^+$.

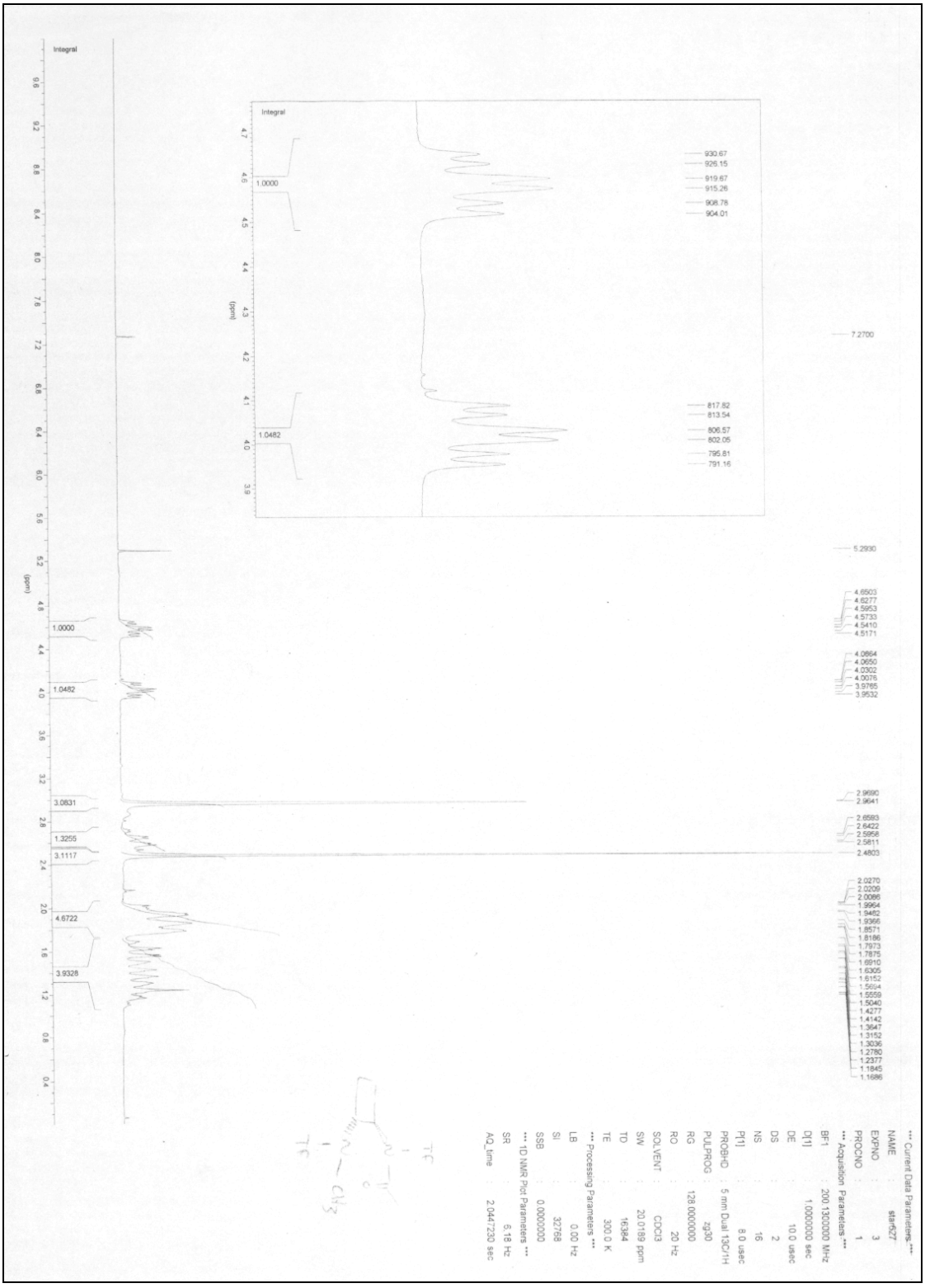

*** Current Data Parameters ***
NAME star340
EXPNO 5
PROCNO 1
*** Acquisition Parameters ***
BF1 300.1300000 MHz
D[1] 1.0000000 sec
DE 6.0 usec
DS 2
NS 16
P[1] 10.8 usec
PROBHD 5 mm Dual 13C/1H
PULPROG zg30
RG 456.1000061
RO 20 Hz
SOLVENT CDCl3
SW 17.0341 ppm
TD 32768
TE 300.0 K
*** Processing Parameters ***
LB 0.30 Hz
SI 16384
SSB 0.0000000
*** 1D NMR Plot Parameters ***
SR 3.18 Hz
AQ_time 3.2047100 sec
7.2700
5.0534
5.0201
4.2892
4.2574
3.7715
2.5862
2.5197
2.4521
2.4105
2.3826
2.3754
2.3660
2.2464
2.2338
2.2421
2.0539
1.8896
1.8624
1.8512
1.8335
1.8252
1.8148
1.8075
1.7971
1.7915
1.7732
1.7659
1.6879
1.4910
1.4667
1.4374
1.4290
1.3947
1.3739
1.3652
1.3351
1.3136
1.2897
1.2804
1.2660
1.2471
1.2377
1.2274
1.2055
1.1861
0.9999
1.0346
0.9190
1.0659
4.0708
3.1354
3.6330
Integral
(ppm)

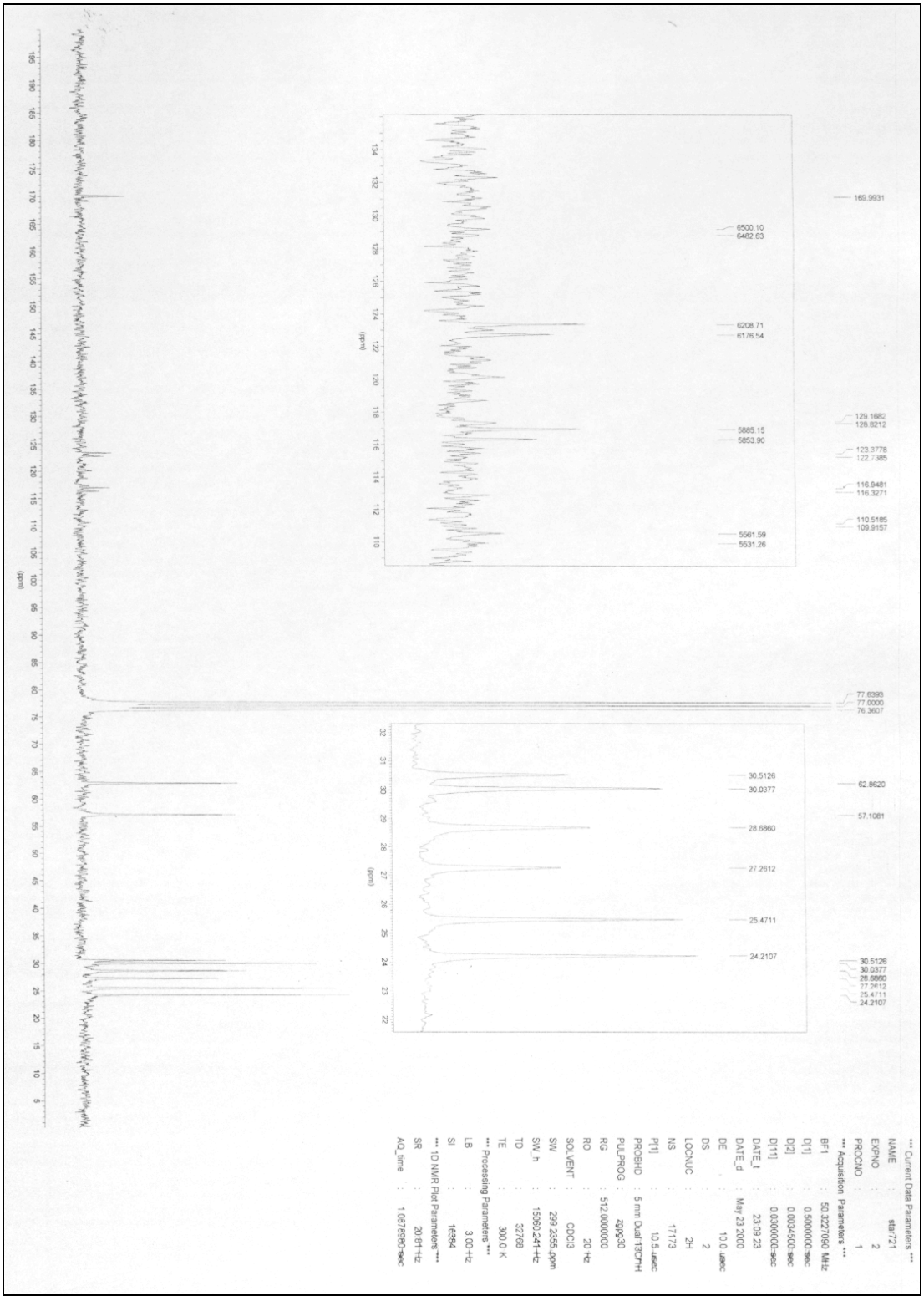

*** Current Data Parameters ***
NAME star340
EXPNO 3
PROCNO 1
*** Acquisition Parameters ***
BF1 75.4677190 MHz
D[1] 1.0000000 sec
DE 6.0 usec
DS 2
NS 5000
P[1] 5.5 usec
PROBHD 5 mm Dual 13C/1H
PULPROG zgpg30
RG 4096.0000000
RO 20 Hz
SOLVENT CDCl3
SW 315.4530 ppm
TD 32768
TE 300.0 K
*** Processing Parameters ***
LB 3.00 Hz
SI 16384
SSB 0.0000000
*** 1D NMR Plot Parameters ***
SR 30.37 Hz
AQ_time 0.6581280 sec
9506.55
9493.47
9182.48
9173.76
8859.87
8852.60
8537.25
8532.89
170.0072
125.9684
125.7961
121.6742
121.5587
117.3994
117.3031
113.1245
113.0667
2672.06
2196.86
2021.02
1925.11
1839.37
77.4236
77.2118
77.0000
76.5764
66.9098
54.5088
35.4067
29.1100
26.7800
25.5091
24.3729
(ppm)

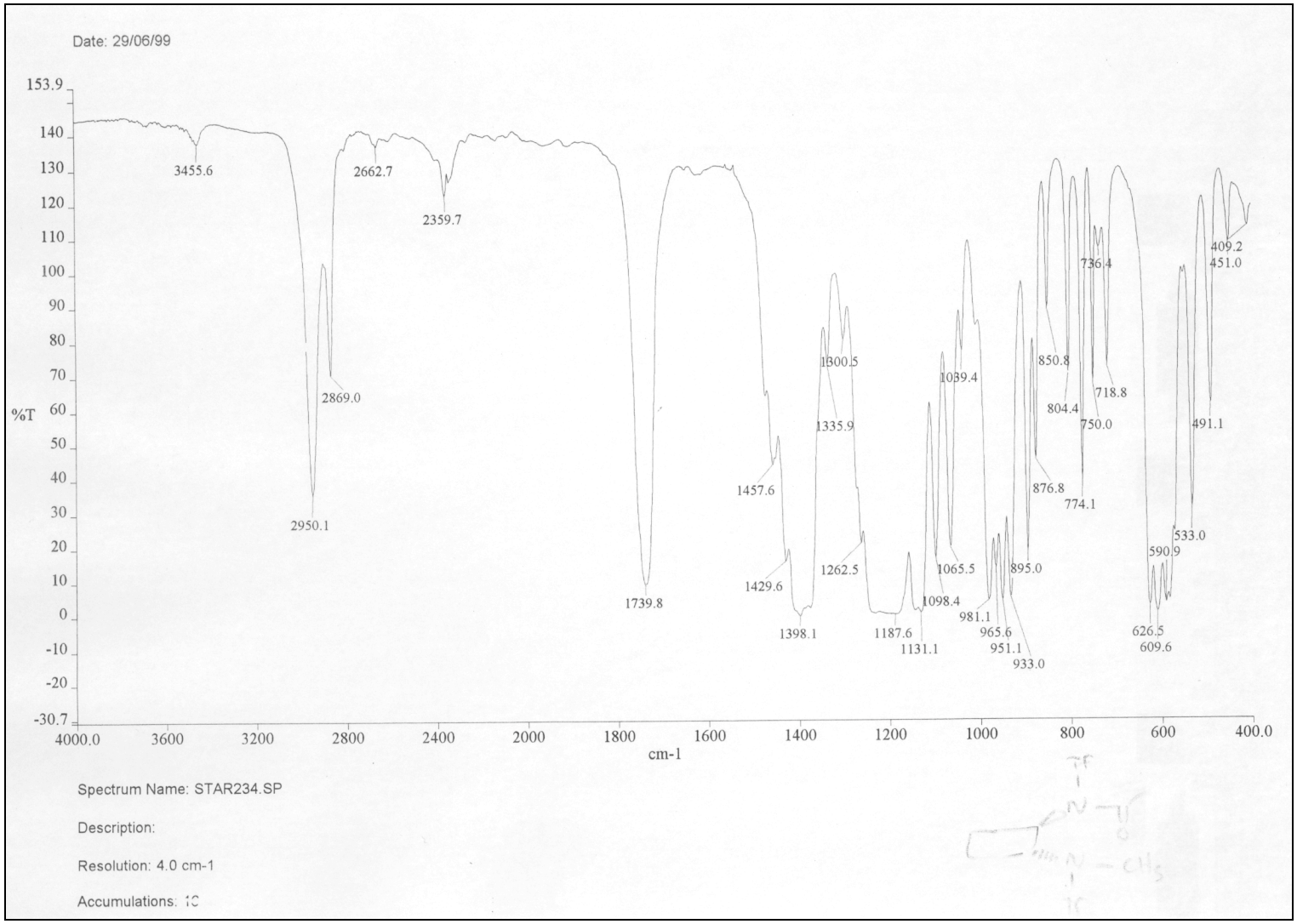

Current Data Parameters
NAME sta/340
EXPNO 4
PROCNO 1
*** Acquisition Parameters ***
BF1 75.4577190 MHz
D[1] 0.6000000 sec
DE 6.0 usec
DS 2
NS 2000
P[1] 5.5 usec
PROBHD 5 mm Dual 13C/1H
PULPROG dept135
RG 4096.0000000
RO 20 Hz
SOLVENT CDCl3
SW 300.4303 ppm
TD 32768
TE 300.0 K
*** Processing Parameters ***
LB 3.00 Hz
SI 16384
SSB 0.0000000
*** 1D NMR Plot Parameters ***
SR 30.93 Hz
AQ_time 0.7225340 sec
35.4000
29.1057
26.7522
25.4968
24.3598
54.4811
66.8700
80.8262
(ppm)


Date: 04/02/99
129.0
120
110
100
90
80
70
60
50
40
30
20
10
0
-9.4
%T
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1
3648.2
3288.5
3213.6
2948.4
2867.1
2360.0
2263.5
1737.0
1715.7
1456.6
1385.8
1335.2
1195.5
1130.9
1070.1
1015.6
970.3
941.8
918.1
895.9
863.0
846.3
795.3
769.0
736.0
627.2
590.9
531.8
484.6
452.6
421.1
Spectrum Name: STAR98.SP
Description: acylation disulfonamide
Resolution: 4.0 cm-1
Accumulations: 16

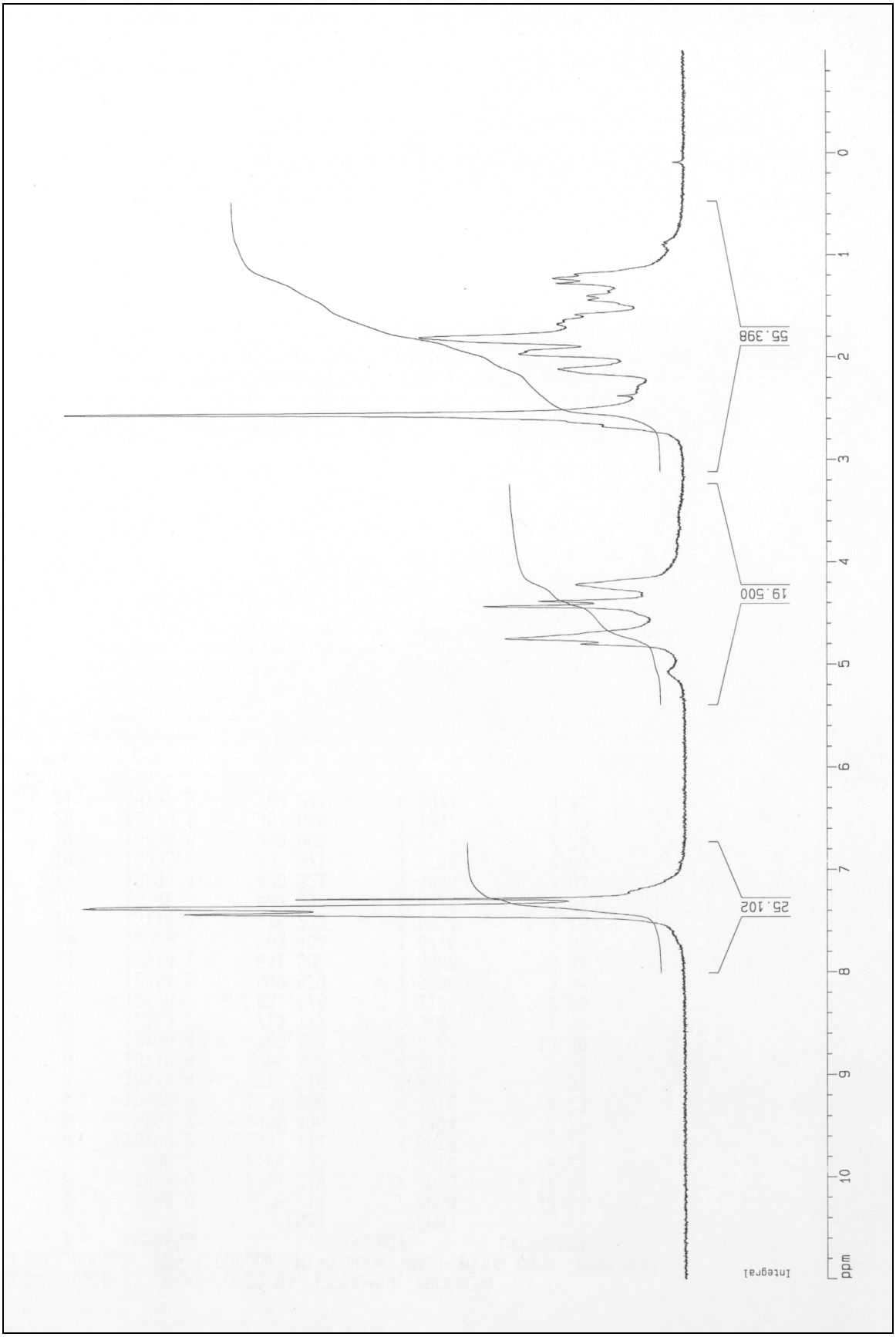
(1*S*,2*S*)-*N*-Acetyl-*N'*-methyl-1,2-*bis*-trifluoromethanesulfonamidocyclohexane (2). A solution of diazomethane (25 mmol) in Et_2O (20 mL) prepared from 1-methyl-3-nitro-1-nitrosoguanidine was added cautiously dropwise to a stired solution of (1*S*,2*S*)-*N*-acetyl-1,2-*bis*-(trifluoromethanesulfonamido)-cyclohexane **(1*S*,2*S*)-1** (1.00 g, 2.38 mmol) in Et_2O (20 mL) at 0 °C. The resulting mixture was maintained under an inert atmosphere (N_2) and stirred at room temperature overnight. TLC analysis (EtOAc/*n*-Hexane: 2/8) showed complete conversion of the precursor. Evaporation of the solvent under reduced pressure, followed by flash chromatography on silica gel (EtOAc/*n*-Hexane: 5/95), afforded the desired *N*-methyl derivative as a colourless oil in quantitative yield. mp 38-40 °C; $[\alpha]^{20}_D$ = +6.22° (c = 4.1; $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 1.00 to 1.65 (m, 3H), 1.68 to 2.05 (m, 4H), 2.48 (s, 3H), 2.40 to 2.75 (m, 1H), 2.96 (s, 3H), 4.02 (td, *J*=11.37 Hz and *J*=4.28 Hz, 1H), 5.58 (td, 1H, *J*=10.95 Hz et *J*=4.52 Hz, 1H); ^{13}C RMN (50 MHz, $CDCl_3$) = 24.2, 25.5, 27.3, 28.7, 30.0, 30.5, 57.1, 62.8, 119.5, 120.2, 169.9 ppm. FTIR (CsI) = 3455, 2950, 2869, 1740, 1398, 1190, 1131, 1098, 1065, 981, 951, 933, 895, 774, 609, 533, 491; MS (IC/NH_3, m/z)= 452 $[M+NH4]^+$.


Integral
1.0000
1.0482
3.0831
1.3255
3.1117
4.6722
3.9328
(ppm)
Integral
1.0000
1.0482
(ppm)
930.67
926.15
919.67
915.26
908.78
904.01
817.82
813.54
806.57
802.05
795.81
791.16
7.2700
5.2930
4.6503
4.6277
4.5953
4.5733
4.5410
4.5171
4.0864
4.0650
4.0302
4.0076
3.9765
3.9532
2.9690
2.9641
2.6583
2.6422
2.5958
2.5811
2.4803
2.0270
2.0209
2.0086
1.9964
1.9482
1.9366
1.8571
1.8186
1.7973
1.7875
1.6910
1.6305
1.6152
1.5954
1.5559
1.5040
1.4277
1.4142
1.3947
1.3152
1.3036
1.2780
1.2377
1.1945
1.1686
*** Current Data Parameters ***
NAME stahr527
EXPNO 3
PROCNO 1
*** Acquisition Parameters ***
BF1 200.1300000 MHz
D[1] 1.0000000 sec
DE 10.0 usec
DS 2
NS 16
P[1] 8.0 usec
PROBHD 5 mm Dual 13C/1H
PULPROG zg30
RG 128.0000000
RO 20 Hz
SOLVENT CDCl3
SW 20.0189 ppm
TD 16384
TE 300.0 K
*** Processing Parameters ***
LB 0.00 Hz
SI 32768
SSB 0.0000000
*** 1D NMR Plot Parameters ***
SR 6.18 Hz
AQ_time 2.0447230 sec

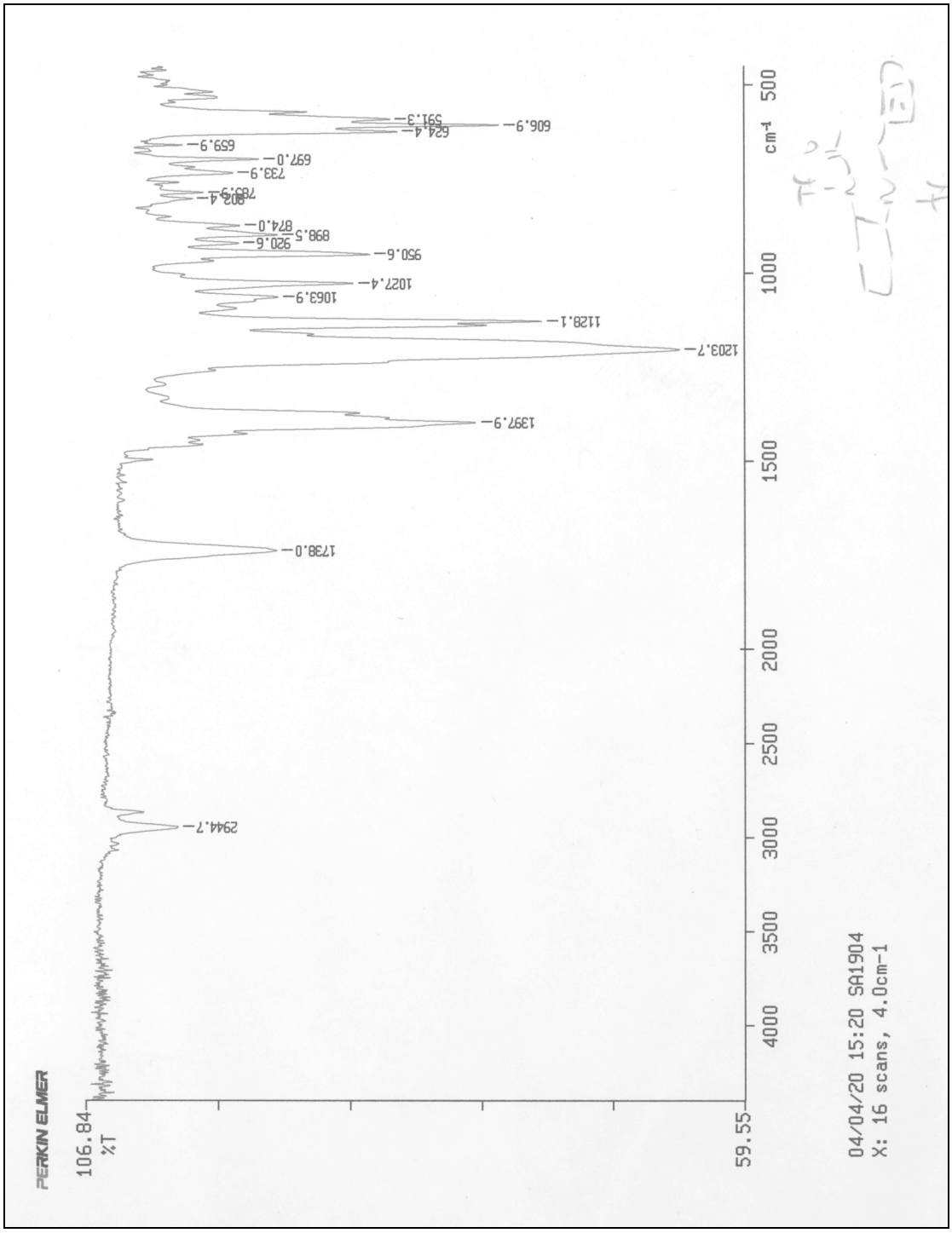

169.9931
6500.10
6482.63
6208.71
6176.54
5885.15
5853.90
5561.59
5531.26
129.1682
128.8212
123.3778
122.7385
116.9481
116.3271
110.5185
109.9157
77.6393
77.0000
76.3607
62.8620
57.1081
30.5126
30.0377
28.6860
27.2612
25.4711
24.2107
(ppm)
*** Current Data Parameters ***
NAME stai721
EXPNO 2
PROCNO 1
*** Acquisition Parameters ***
BF1 50.3227080 MHz
D[1] 0.5000000 sec
D[2] 0.0034500 sec
D[11] 0.0300000 sec
DATE_t 23:09:23
DATE_d May 23 2000
DE 10.0 usec
DS 2
LOCNUC 2H
NS 17173
P[1] 10.5 usec
PROBHD 5 mm Dual 13C/1H
PULPROG zgpg30
RG 512.0000000
RO 20 Hz
SOLVENT CDCl3
SW 299.2355 ppm
SW_h 15060.241 Hz
TD 32768
TE 300.0 K
*** Processing Parameters ***
LB 3.00 Hz
SI 16384
*** 1D NMR Plot Parameters ***
SR 20.61 Hz
AQ_time 1.087690 sec


Date: 29/06/99
153.9
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30.7
%T
3455.6
2662.7
2359.7
2869.0
2950.1
1739.8
1457.6
1429.6
1398.1
1300.5
1335.9
1262.5
1187.6
1131.1
1098.4
1039.4
1065.5
981.1
965.6
951.1
933.0
895.0
850.8
876.8
804.4
774.1
736.4
750.0
718.8
626.5
609.6
590.9
533.0
491.1
409.2
451.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1
Spectrum Name: STAR234.SP
Description:
Resolution: 4.0 cm-1
Accumulations: 10

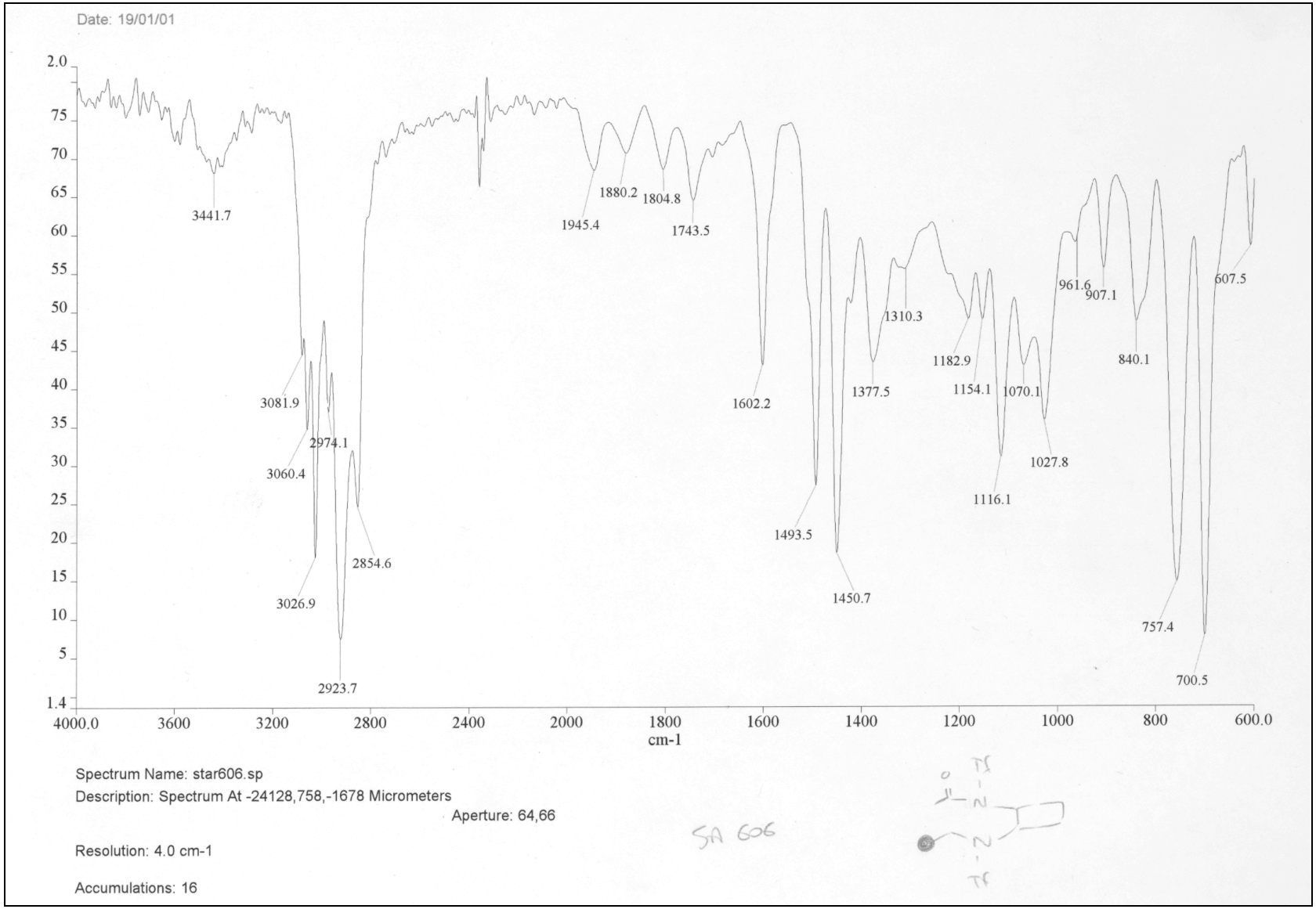
(1*S*,2*S*)-*N*-Acetyl-*N'*-benzyl-1,2-*bis*-trifluoromethanesulfonamidocyclohexane (3). A solution of **(1*S*,2*S*)-1** (650 mg, 1.55 mmol) in dry dichloromethane (10 mL) is added to a solution of benzyldiazonium (4.64 mmol) prepared according to the procedure developed by Reese,[1] in 5 mL of dichloromethane at room temperature. When the nitrogen evolution ceased, evaporation of the solvent under reduced pressure, followed by flash chromatography on silica gel (EtOAc/*n*-Hexane: 1/9), afforded the desired *N*-benzyl derivative as a colourless oil in 86 % yield. $[\alpha]^{20}_{D}$ = +10.43 (c = 0.23; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 to 2.30 (6m, 7H), 2.55 (s, 3H), 2.40 to 2.79 (m, 1H), 4.05 to 4.28 (m, 1H), 4.38 and 4.75 (2d, 2H, *J*=15 Hz), 4.55 to 4.75 (m, 1H), 7.18 to 7.60 (m, 5H); ^{13}C RMN (75 MHz, $CDCl_3$) δ 23.6, 25.4, 27.5, 28.9, 33.7, 48.8, 58.9, 64.4, 119.6, 119.5, 128.6, 129.6, 135.1, 170.1. FTIR (CsI) ν 2945, 1738, 1398, 1204, 1128, 1027, 951, 898, 734, 607. MS (IC/NH_3, m/z) = 528 $[M+NH4]^+$.


55.398
19.500
25.102
Integral
ppm
10
9
8
7
6
5
4
3
2
1
0

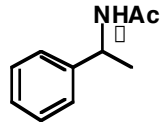
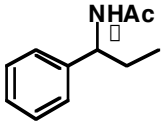
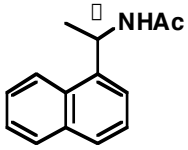
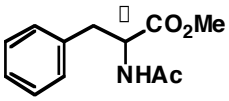
ppm
212.090
209.612
201.395
171.004
170.299
170.095
163.089
151.075
148.650
146.616
135.880
135.145
134.506
130.894
130.405
130.118
129.652
128.843
128.588
128.476
126.034
125.885
121.755
121.603
117.462
117.312
113.024
106.780
77.446
77.227
77.022
76.599
66.589
64.371
63.570
62.736
61.979
58.910
58.311
49.384
48.807
48.459
33.721
31.609
31.311
30.576
29.716
28.872
27.522
26.641
25.400
24.656
23.773
22.807
8.698
1.786
-13.701
-14.265
-14.976
ppm
200
180
160
140
120
100
80
60
40
20
0


PERKIN ELMER
106.84
%T
59.55
4000
3500
3000
2500
2000
1500
1000
500
cm-1
2944.7
1738.0
1397.9
1203.7
1128.1
1063.9
1027.4
950.6
920.6
898.5
874.0
802.4
769.9
733.9
697.0
659.9
624.4
591.3
606.9
04/04/20 15:20 SA1904
X: 16 scans, 4.0cm-1

(1*S*,2*S*)-*N*-Acetyl-*N'*-polymer-supported-1,2-*bis*-trifluoromethanesulfonamidocyclohexane (4). Polymer-supported reagent **4** was prepared in four steps starting Merrifield resin; each step being monitored using IR spectroscopy (recorded using a Perkin-Elmer 2000 FT-IR directly on the resin beads). The solid-phase synthesis was initiated by treating commercially available Merrifield resin (chloromethylated polystyrene, 1% cross-linked divinylbenzene, 1.58 mmol.g^{-1}) with 4-hydroxy-benzaldehyde and sodium hydroxyde in DMSO (90°C),[2] to afford the benzaldehyde resin **5** ($n_{C=O}$=1695 cm^{-1}) in excellent yield (>95% determined by elementary analysis; loading=1.39 mmol.g^{-1}). Resin **5** was then treated with 1,3,5-triisopropylbenzene-sulfonyl hydrazine at room temperature leading to the supported hydrazone **6** which was subsequently treated with potassium hydroxyde in a MeOH/THF mixture (90°C).[3] The resulting supported benzyl diazonium salt **7** reacted at room temperature with (1*S*,2*S*)-*N*-acetyl-1,2-*bis*-trifluoromethanesulfonamidocyclohexane **(1*S*,2*S*)-1** in DMF leading to the desired supported chiral reagent **4** ($n_{C=O}$=1743 cm^{-1}). The loading of resin **4** was determined as 0.58 mmol.g^{-1} by treating it with an excess of (±)-1-phenylethylamine and quantifying the recovered acetylated product. This value was also confirmed by fluorine elemental analysis. Polymer-supported reagent **4** was prepared in a 65% overall yield from readily available Merrifield resin.


Date: 19/01/01
2.0
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
1.4
3441.7
3081.9
3060.4
2974.1
3026.9
2923.7
2854.6
1945.4
1880.2
1804.8
1743.5
1602.2
1493.5
1450.7
1377.5
1310.3
1182.9
1154.1
1116.1
1070.1
1027.8
961.6
907.1
840.1
757.4
700.5
607.5
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1
Spectrum Name: star606.sp
Description: Spectrum At -24128,758,-1678 Micrometers
Aperture: 64,66
Resolution: 4.0 cm-1
Accumulations: 16
SA 606

General procedure for enantioselective acetylation of secondary alkylamines. Racemic amine (0.5 mmol) was added by syringe to an agitated solution of supported chiral acetylating agent (0.10 mmol) in the chosen solvent system at room temperature, and the mixture was agitated for 3 hr. The resin was then filtered, washed with dichloromethane, and the solvents were removed under reduced pressure. The resulting residue was then purified by flash chromatography on silica gel (EtOAc/*n*-Hexane: 1/1) and analyzed by HPLC using a chiral stationary phase.

Product	ee assay	Conditions	Retention Time of first isomer (min)	Retention Time of second isomer (min)
	Chiralcel OD	35°C 0.8 ml / min Pentane / EtOH 98/2	38.57 (*R*)	42.75 (*S*)
	Chiralcel OD	35°C 1 ml / min Hexane / EtOH 97/3	13.98	16.85
	Chiralcel OD	30°C 1.2 mL / min Hexane / EtOH 85/15	4.00	5.75
	Chiralcel OD	35°C 0.8 mL / min Hexane / EtOH 97/3	20.18	23.57

[1] Reese, C. B.; Dudman, C. C. *Synthesis* **1982**, *5*, 419.
[2] Beebe, X.; Chiappari, C. L.; Olmstead, M. M.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.*, **1995**, *60*, 4204.
[3] Bhalay, G.; Dunstan, A. R. *Tetrahedron Lett.*, **1998**, *39*, 7803.