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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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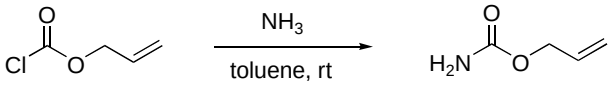
ENANTIOSELECTIVE PREPARATION OF DIHYDROPYRIMIDONES

[(*S*)-1-Benzyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic methyl ester]

A.



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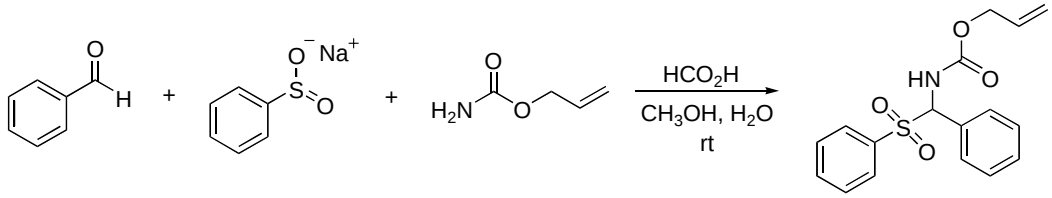
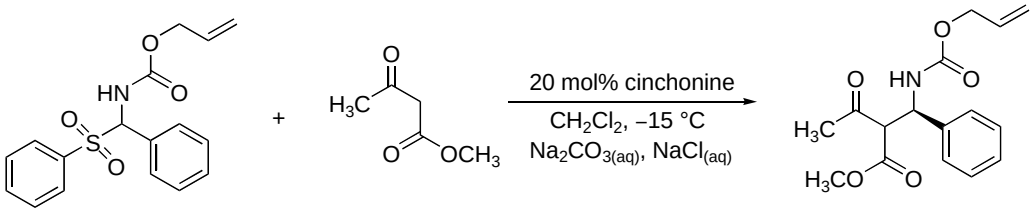
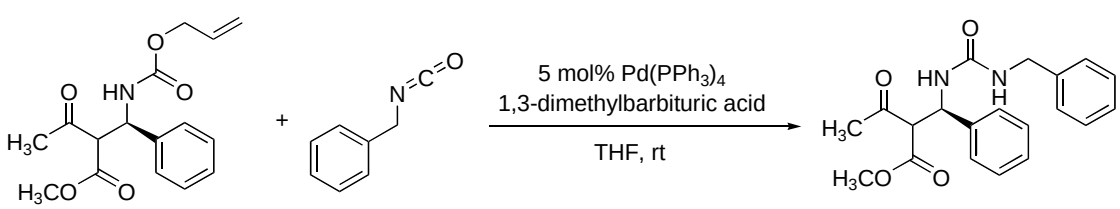


C.



D.



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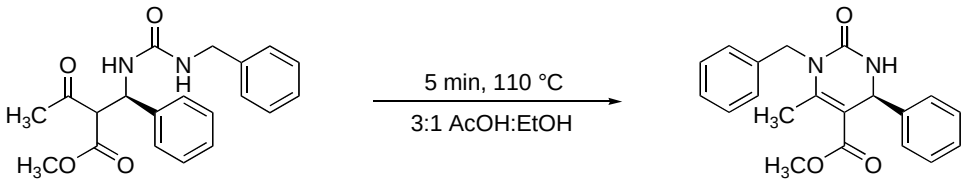

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1. Procedure

A. Allyl carbamate. An empty 3-necked, 1-L round-bottom flask is fitted with a stopper on the middle neck and septa on each of the outer necks. Through one septum of the empty flask is inserted a 6-mm glass tube which is connected to an ammonia gas cylinder via vacuum tubing. Through the other septum is inserted a 6-mm glass tube which is connected to the reaction flask via vacuum tubing. This empty flask serves as a trap to prevent backflow of the flask contents into the lecture bottle.

A trap to neutralize discharged ammonia gas is also constructed as follows. To a 3-necked, 1-L flask is added 400 mL of 10% HCl, which is gently stirred using a magnetic stir bar (3 cm). The middle neck of the flask is stoppered, one neck is left open to the atmosphere, and the third neck is fitted with a septum through which is inserted a 6 mm ID x 5 cm glass tube. The glass tube is situated well above the contents of the acid solution to prevent any back flow. The glass tube is connected via vacuum tubing to an empty 1-L 3-necked flask equipped with a stopper on the middle neck and septa on each of the outer necks, with each septa pieced with a 6 mm ID x 5 cm glass tube. The tube in one outer neck is connected via vacuum tubing to the HCl quench flask, while the tube in the other outer neck is connected via vacuum tubing to the reaction flask. The empty flask between the reaction flask and the flask containing aq. HCl ensures no back flow of the aq. solution or water vapor into the reaction flask.

An oven-dried, 1-L, three-necked round-bottom flask is equipped with an overhead mechanical stirrer. One neck of the flask is fitted with a septum through which has been inserted a 6-mm ID x 20 cm length glass tube that will extend into the contents of the flask (Note 1). A thermocouple probe is also inserted through this septum to monitor temperature. The outlet of this tube is connected to the empty 3-necked 1-liter flask and ammonia cylinder via vacuum tubing. The third neck of the reaction flask is similarly fitted with a septum pierced with a short 6 mm ID x 5 cm length glass tube, situated well above the contents of the flask, which is connected via the empty flask to the flask containing 10% aq. HCl.

To the reactor flask is charged by weight allyl chloroformate (84.0 g, 1.00 equiv, 697 mmol) and toluene (400 mL) (Notes 2, 3). The flask is immersed in a room temperature water bath. The solution is mechanically stirred at 300 rpm while bubbling ammonia gas through the solution at a rate to maintain the internal temperature below 45 °C. Ammonia addition is

continued for 5.5 hours. Ammonium chloride (white solid) precipitates throughout the course of the reaction and the reaction mixture becomes quite thick. When complete consumption of the starting material is verified by NMR assay (Note 4), the reaction mixture is vacuum filtered through a 150-mL sintered glass funnel. The solids are washed with 3 x 70 mL portions of toluene and the resulting clear solution is concentrated under reduced pressure by rotary evaporation (30 mmHg, 35 °C water bath) to 75.4 g (Note 5). The remaining crude oil is distilled under vacuum at 65–67 °C (1–2 mmHg) to provide 63.2 g (89.7%) of allyl carbamate as a clear oil (Notes 6, 7).

B. (Benzenesulfonyl-phenyl-methyl)-carbamic acid allyl ester. An oven-dried, 1-L round-bottomed flask, equipped with a rubber septum and an oval 3-cm stir bar, is charged with benzenesulfinic acid sodium salt (25.6 g, 1.43 equiv, 154 mmol), allyl carbamate (15.5 g, 1.43 equiv, 154 mmol), methanol (100 mL) and water (200 mL). The reaction mixture is stirred at ambient temperature until homogeneous (about 5 min). Benzaldehyde (11.1 g, 1.00 equiv, 107 mmol) is added by syringe, weighing the syringe before and after addition, followed by addition of formic acid (39.5 g of 91 wt% solution, 7.3 equiv, 781 mmol). The reaction mixture is stirred for 4 days at room temperature (21–22 °C), during which time the formation of a heavy white precipitate occurs (Note 8). The mixture is vacuum filtered via a 150-mL medium porosity sintered glass funnel. The white solid is washed with two 40 mL portions of 3:1 water:methanol. The solid is air-dried to provide 21.8 g of (benzenesulfonyl-phenylmethyl)-carbamic acid allyl ester. The supernatant from the filtration is placed back in the 1-L flask and is stirred for an additional 4 days at ambient temperature. The mixture is then vacuum filtered via a 60-mL medium porosity sintered glass funnel, washed twice with 20 mL of 3:1 water:methanol, and air dried to afford 4.9 g as a second crop having comparable purity by NMR to the first crop. The total yield of the reaction is 26.7 g (75%) (Notes 9, 10).

C. 2-[(R)-Allyloxycarbonylamino-phenyl-methyl)-3-oxo-butyric acid methyl ester. A 1-L, three-necked, round-bottom flask is equipped with an internal thermometer, an overhead mechanical stirrer and a 500-mL pressure-equalizing addition funnel. The three-necked flask is charged with (+)-cinchonine (1.77 g, 0.20 equiv, 6.0 mmol) and (benzenesulfonyl-phenyl-methyl)-carbamic acid allyl ester (9.97 g, 1.00 equiv, 30.1 mmol). Anhydrous dichloromethane (300 mL) is added, and the solution is stirred for about 5 min, during which time the majority of solids are dissolved. The

flask is submerged in an isopropyl alcohol bath cooled to –25 °C (Note 11) and the solution is mechanically stirred at 500 rpm. Once the reaction mixture has cooled to –15 °C (monitored by the internal thermometer), methyl acetoacetate (10.7 g, 3.0 equiv, 92.3 mmol) is added *via* syringe over 2 minutes. After 10 min, 300 mL of an aqueous Na_2CO_3/NaCl solution (15.0 g of sodium carbonate is dissolved in 300 mL of water, and then saturated with 150 g of sodium chloride) is added to the 500-mL pressure-equalizing addition funnel. The aqueous solution is added dropwise to the reaction mixture over 1 h, while maintaining an internal temperature of –15 °C (Note 12). The heterogeneous solution is mechanically stirred at 500 rpm for 27 h while maintaining an internal temperature of –15 °C. At the end of the reaction, the cold solution is transferred to a 1-L separatory funnel and the bottom organic layer is separated (Note 13). The aqueous layer is washed with two 250 mL portions of dichloromethane. The organic layers are combined, dried over sodium sulfate, filtered and concentrated by rotary evaporation (30 mmHg, 30 °C bath temperature). The remaining residue (17.8 g) is purified by column chromatography over silica gel (Note 14) to provide 8.69–9.00 g (95–98 %) of 2-[(*R*)-allyloxycarbonylamino-phenyl-methyl)-3-oxo-butyric acid methyl ester as a white solid (Notes 15, 16).

D. 2-[(R)-(3-Benzyl-ureido)-phenyl-methyl]-3-oxo-butyric acid methyl ester. An oven-dried, 500-mL round-bottom flask, equipped with a 3-cm oval magnetic stir bar, is charged with anhydrous BHT-free tetrahydrofuran (160 mL) and benzyl isocyanate (4.74 g, 1.46 equiv, 35.6 mmol). The flask is fitted with a vacuum adapter and is degassed via three vacuum/nitrogen purge cycles. Tetrakis(triphenylphosphine)palladium(0) (1.24 g, 0.045 equiv, 1.07 mmol) is then added and dissolved by stirring the mixture. The vacuum adapter is replaced with a rubber septum pierced with a needle connected to a nitrogen inlet. A second oven-dried, 250-mL round-bottom flask equipped with a 2-cm oval magnetic stir bar is charged with 1,3-dimethylbarbituric acid (2.09 g, 0.53 equiv, 12.9 mmol) and 2-[(*R*)-allyloxycarbonylamino-phenyl-methyl)-3-oxo-butyric acid methyl ester (7.44 g, 1.00 equiv, 24.40 mmol) (Note 17). Anhydrous BHT-free tetrahydrofuran (80 mL) is added, yielding a homogeneous solution upon stirring. The flask is fitted with a vacuum adapter and degassed with three vacuum/nitrogen purge cycles. The vacuum adapter is then removed and replaced with a septum. The solution in the second flask is transferred dropwise *via* cannula to the stirring solution of tetrakis(triphenylphosphine)palladium(0), benzyl isocyanate and anhydrous

tetrahydrofuran over 5 min followed by a 5 mL tetrahydrofuran rinse of the flask. An exotherm of about 5 °C occurs over 10 min. The reaction is stirred for 5 h at 21–22 °C, during which time the solution changes from yellow to a pale orange (Note 18). The solution is concentrated by rotary evaporation (30 mmHg, 30 °C bath), and the resulting residue is purified by column chromatography over silica gel (Note 19) to afford 6.07 g (70%) of 2-[(*S*)-(3-benzyl-ureido)-phenyl-methyl]-3-oxo-butyric acid methyl ester (Note 20) as a pale yellow oil.

E. (S)-1-Benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic methyl ester. An oven-dried, 250-mL round-bottom flask, equipped with 2-cm oval magnetic stir bar and a water condenser, is charged with 2-[(*R*)-(3-benzyl-ureido)-phenyl-methyl]-3-oxo-butyric acid methyl ester (6.62 g having 85% purity (Note 20), 5.63 g corrected for purity, 1.00 equiv, 15.9 mmol), anhydrous 200-proof ethanol (15 mL) and anhydrous acetic acid (45 mL). The reaction solution is stirred at room temperature until homogeneous. The 250-mL round-bottomed flask is submerged in an oil bath and the solution is heated to reflux (107 °C) for 5 min. The solution is cooled to room temperature and transferred to a 250-mL separatory funnel. Dichloromethane (100 mL) and 5% aqueous brine (50 mL) are added, the two phases are mixed well by shaking, then the lower organic phase is separated. The organic layer is extracted with 2 x 50 mL portions of 5% aqueous brine (Note 21). The remaining organic layer is dried over sodium sulfate, filtered and concentrated via rotary evaporation (30 mmHg, 30 °C bath temperature) to an oil (7.2 g). The resulting residue is purified by column chromatography over silica gel (Note 22) to afford 4.13 g (77%) of (*S*)-1-benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic methyl ester as a white solid (Notes 23–25).

2. Notes

1. The inlet tube has to be sufficiently wide to prevent plugging as ammonium chloride buildup results in a thick mixture during the reaction. The tube is positioned to supply ammonia gas subsurface but not interfere with the stir blade.

2. The submitters used benzene in their procedure.

3. Allyl chloroformate (97%), formic acid (88%), cinchonine (85%), methyl acetoacetate (99%), sodium carbonate (>99.5%), 1,3-

dimethylbarbituric acid (99%), benzyl isocyanate (99%), benzaldehyde (99+% redistilled), toluene (99%), methanol (99%), ethanol (99.5%), ethyl acetate (99.5%), hexanes (99.5%) and glacial acetic acid (99+%) were obtained from Aldrich Chemical Co., Inc. and were used as received. Sodium chloride (99%) was obtained from VWR and used as received. Tetrakis(triphenylphosphine)palladium(0) (99%) was obtained from Strem Chemicals Inc. and used as received. Benzenesulfonic acid sodium salt (97%) was obtained from Acros. Ammonia gas was obtained from Linde Gas LLC and was used as received. The submitters obtained all anhydrous solvents from Thermo Fisher Scientific Inc. and purified through use of a dry solvent system (pressure filtration under argon through activated alumina). The checkers used anhydrous solvents as received from Aldrich Chemical Co.

4. The reaction was followed by ^{1}H NMR by diluting a sample into $CDCl_3$ and integrating the methylene protons of the allyl group of the starting material and product. The reaction progressed as follows: 50% conversion at 1.5 h, 85% conversion at 3 h, and >99% conversion at 5 h.

5. NMR analysis indicated the mixture contained 89 % allyl carbamate by weight, along with 11 wt% toluene. The distillate from the concentration was analyzed by NMR and contained no product.

6. Two fractions were collected, a small forecut at 65–66 °C (3.87 g) and the main cut, 66–67 °C, (59.36 g). The fractions were combined after NMR analysis indicated similar purity. Approximately 3 mL remained as pot residue, and about 10 mL of toluene was collected in the dry-ice vacuum trap.

7. Allyl carbamate has the following physical properties: clear oil; bp 207-208 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.55 (dd, J = 5.6, 1.5 Hz, 2 H), 5.2 (br, 2 H, NH_2), 5.21 (dd, J = 10.5, 1.4 Hz, 1 H), 5.31 (dd, J = 17.1, 1.4 Hz, 1 H), 5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 65.8, 117.9, 132.8, 157.2; IR (thin film, cm^{-1}): 2400, 1728, 1216; HRMS *m/z* 124.0368 [($M + Na^+$) calcd for $C_4H_7NO_2Na^+$: 124.0374]. The purity (>99%) was determined by GC with a Agilent J&W HP-5 column (0.32 mm × 30 m)(oven temperature: 110 °C; head pressure: 60 kPa; retention time: 3.8 min).

8. The reaction is monitored by ^{1}H NMR by taking an aliquot of the reaction, diluting in DMSO-d_6, and integrating the benzaldehyde resonance at 10 ppm relative to the total aromatic protons. The reaction is about 80% complete in 4 days.

9. The submitters dried the material by addition of 100 mL toluene and concentrating to a solid by rotary evaporation.

10. (Benzenesulfonyl-phenyl-methyl)-carbamic acid allyl ester has the following physical properties: white solid; mp 148–150 °C. (Submitters report mp 162-165 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.42 (d, J = 5.2 Hz, 2 H), 5.22 (m, 2 H), 5.76 (m, 1 H), 6.01 (dd, J = 10.8, 10.5 Hz, 2 H), 7.39–7.46 (m, 5 H), 7.53 (m, 2 H), 7.66 (m, 1 H), 7.86 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.0 MHz) δ: 66.7, 74.7, 118.7, 129.0 (degenerate), 129.0, 129.4, 129.7, 130.1, 132.1, 134.3, 136.8, 154.7; IR (thin film, cm^{-1}): 3334, 3063, 1730, 1527, 1496, 1448, 1308, 1235, 1141, 1081, 691; HRMS *m/z* 354.0796 [(M + Na^+) calcd for $C_{17}H_{17}NO_4NaS^+$: 354.0776]. The purity (>95%) was determined by ^{1}H NMR.

11. Chilling system Thermo NESLAB CB-60 with cryotrol probe was used by the submitters; a Julabo FT 901 chiller was used by the checkers The isopropyl alcohol bath temperature is monitored using a thermometer.

12. Maintaining the temperature near –15 °C during the addition of base is critical. In one run by the checkers, the temperature rose to –6 °C during the addition, which resulted in a decrease in the ee (85% vs 91%).

13. The initial extraction is carried out at 0 °C to prevent racemization of the product. The 2-phase mixture contains solids (which were determined to be cinchonine and related by-products by NMR). The solids are kept with the upper aqueous phase in all the separations.

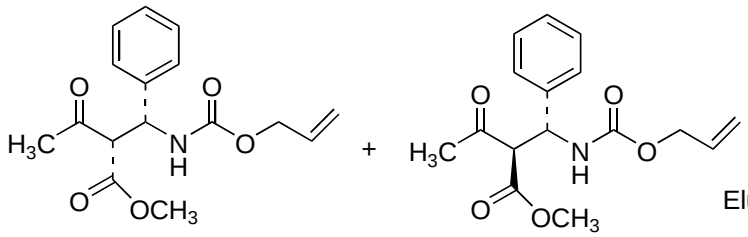
14. The residue is dissolved in 40 mL of anhydrous dichloromethane and is loaded onto a 3-in.×12-in. column, wet-packed (10% ethyl acetate in hexanes) with 300 g of silica gel (submitters used Sorbent Technologies, 60 Å; checkers used EM Sciences, EM60, 230-400 mesh), and eluted with a gradient of ethyl acetate in hexanes (1 L of 20%, 2.5 L of 30%). The desired product is collected in fractions of 100-mL volume. TLC analysis is performed on silica gel with 30% ethyl acetate in hexanes as eluent, visualization with ultraviolet light and by staining with ceric ammonium molybdate. R_f = 0.3. Methyl acetoacetate elutes just before the product. If less silica gel is used, methyl acetoacetate is not fully separated from the product. ^{1}H NMR analysis of the combined fractions indicates the product is a ~1:1 mixture of diastereomers.

15. A single diastereomer can be isolated by crystallization of the diastereomeric mixture, as follows. 400 mg of the diastereomeric mixture is added to 20 mL hexanes and heated to reflux. Ethyl acetate (1.5 mL) is added to fully dissolve all solids, then the solution is allowed to cool to

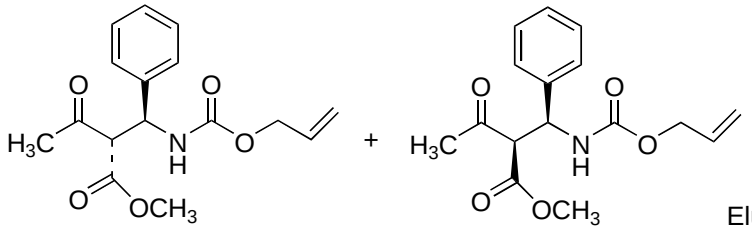
ambient temperature with stirring. After stirring overnight (15 hours) the mixture is filtered and washed with 5 mL hexanes to provide 320 mg of white needles after drying in ambient air. ^{1}H NMR analysis indicated an 88:12 mixture of diastereomers. The high recovery (80%) and the fact that the supernatant contained a 1:1 mixture of diastereomers suggested a racemization/crystallization process was occurring, funneling the mixture to the less soluble diastereomer. One additional recrystallization under the same procedure provided one diastereomer (97.5:2.5 diastereomeric ratio and >99% ee by the chiral HPLC method outlined below). 2-[(*R*)-Allyloxycarbonylamino-phenyl-methyl)-3-oxo-butyric acid methyl ester has the following physical properties: white solid, single diastereomer; mp 96–98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) less soluble diastereomer δ: 2.15 (s, 3 H), 3.70 (s, 3 H), 4.07 (d, *J* = 5.5 Hz, 1 H), 4.55 (dd, *J* = 4.3, 1.0 Hz, 2 H), 5.20 (d, *J* = 10.3 Hz, 1 H), 5.27 (d, *J* = 17.0 Hz, 1 H), 5.48 (dd, *J* = 6.2, 9.1 Hz, 1 H), 5.88 (m, 1 H), 6.12 (br d, *J* = 9 Hz, 1 H), 7.24–7.35 (m, 5 H). More soluble diastereomer δ: 2.33 (s, 3 H), 3.65 (s, 3 H), 4.02 (br s, 1 H), 4.55 (m, 2 H), 5.20 (d, *J* = 10.0 Hz, 1 H), 5.29 (d, *J* = 16.5 Hz, 1 H), 5.58 (m, 1 H), 5.90 (m, 1 H), 6.40 (s, 1 H), 7.22–7.37 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) less soluble diastereomer, δ: 31.0, 53.0, 54.6, 63.2, 66.0, 117.9, 126.3, 126.6, 128.0, 128.7, 128.9, 132.9, 139.6, 155.7, 167.9, 203.3; more soluble diastereomer, δ: 29.1, 52.6, 53.5, 64.3, 66.0, 118.3, 126.3, 126.6, 128.0, 128.5, 128.9, 132.8, 139.4, 155.9, 169.2, 201.0; IR (thin film, cm^{-1}), both diastereomers reported: 3374, 2955, 1718, 1527, 1434, 1360, 1248, 1048, 993, 904, 730. HRMS *m/z* 328.1167 [(M + Na^+) calcd for $C_{16}H_{19}NO_5Na^+$: 328.1161]. The purity (>98%) was determined by HPLC-ELSD (210 nm).

16. The four diastereomers were separated by a normal phase HPLC method using a Chiralpak AD-H column (250 x 4.6 mm, 5 micron) with isocratic elution consisting of 15% (1:1 MeOH:EtOH) and 85% heptane, a flow rate of 1.0 mL/min and detection at 210 nm. Elution times: major enantiomeric pair (13.5 and 16 min), minor enantiomeric pair (10.5 and 11.5 min). The enantiomeric ratio was determined to be 95:5 on the diastereomeric mixture isolated from the silica gel chromatography. The material that was recrystallized twice showed none of the minor enantiomer (detection limit 0.5%). This diastereomer reverts back to a 1:1 mixture in a solution of methanol over a 24 hour period. The opposite enantiomeric pair was prepared by carrying out the reaction using cinchonidine instead of

cinchonine. The reaction with cinchonidine carried out at 0–5 °C provided an 89:11 enantiomeric ratio.



Elution times: 13.5 and 16 min



Elution times: 10.5 and 11.5 min

17. The weight is corrected for 4% residual ethyl acetate present from the previous step.

18. The reaction was followed by TLC on silica gel with 1:1 ethyl acetate/hexanes as eluent (R_f = 0.3). The reaction was >90% complete by TLC analysis in 2 hours.

19. The residue is combined with 6 mL of dichloromethane to make the oil mobile and is loaded onto a 3-in.×12-in. column, wet-packed (10% ethyl acetate in hexanes) with 380 g of silica gel (submitters used Sorbent Technologies, 60 Å; checkers used EM Sciences EM60, 230-400 mesh), and eluted with a gradient of ethyl acetate in hexanes (2 L of 25%, 1 L of 33%, 2 L of 40%, 1.5 L of 50%). The desired product is collected in fractions of 100-mL volume. TLC analysis is performed on silica gel with 50% ethyl acetate in hexanes as eluent, visualization with ultraviolet light and by staining with ceric ammonium molybdate. R_f = 0.30.

20. The weight of the isolated oil is 7.14 g. The yield of 6.07g is corrected based on a purity of 85%, which includes 10% ethyl acetate by weight and an estimated 5% impurity. 2-[(*R*)-(3-Benzyl-ureido)-phenyl-methyl]-3-oxo-butyric acid methyl ester has the following physical properties: white solid; mp 100-102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, both diastereomers reported) δ: 2.22 (s, 3 H), 2.30 (s, 3 H), 3.53 (s, 3 H), 3.60 (s, 3 H), 4.01 (d, *J* = 8.4 Hz, 1 H), 4.06 (d, *J* = 4.5 Hz, 1 H), 4.28 (m, 4 H), 5.38 (t, *J* = 5.8 Hz, 1 H), 5.47 (t, *J* = 5.8 Hz, 1 H), 5.62 (dd, *J* = 9.4, 7.7 Hz, 1 H), 5.79 (dd, *J* = 9.7, 4.8 Hz, 1 H), 6.13 (d, *J* = 9.4 Hz, 1 H), 6.40 (d, *J* = 9.8 Hz,

1 H), 7.17–7.30 (m, 20 H). ^{13}C NMR ($CDCl_3$, 100 MHz, both diastereomers reported) δ: 29.1, 30.1, 44.5, 44.6, 52.3, 52.4, 52.7, 53.8, 64.2, 64.6, 126.3, 126.7, 127.5, 127.6, 128.7, 128.8, 139.3, 139.4, 140.1, 140.3, 157.5, 157.6, 168.1, 169.8, 202.2, 204.0. IR (thin film, cm^{-1}): 3408, 3019, 1740, 1709, 1687, 1527, 1453, 1364, 1216, 929, 909, 700. HRMS *m/z* 355.1690 [(M + H^+) calcd for $C_{20}H_{22}N_2O_4^+$: 355.1613]. The purity (>90%) was determined by HPLC-ELSD (210 nm).

21. When just water is employed for the extractions, the separation is very slow and incomplete.

22. The residue is loaded onto a 3-in.×12-in. column, wet-packed (10% ethyl acetate in hexanes) with 220 g of silica gel (submitters used Sorbent Technologies, 60 Å; checkers used EM Sciences EM60, 230-400 mesh), and eluted with a gradient of ethyl acetate in hexanes (1 L of 20%, 1L of 30%, 500 mL of 40%, 1 L 50%). The desired product is collected in fractions of 100-mL volume. TLC analysis on silica gel with 50% ethyl acetate in hexanes as eluent and visualization with ultraviolet light and stained with ceric ammonium molybdate. R_f = 0.6.

23. (*S*)-1-Benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic methyl ester has the following physical properties: white solid; mp 136–137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.45 (s, 3 H), 3.64 (s, 3 H) 4.88 (d, *J* = 16.4 Hz, 1 H), 5.21 (d, *J* = 16.1 Hz, 1 H), 5.45 (s, 1 H), 5.99 (s, 1 H), 7.11 (d, *J* = 7.7 Hz, 2 H), 7.22–7.29 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.7, 46.2, 51.6, 54.0, 104.9, 126.5, 126.6, 127.4, 128.0, 128.90, 128.93, 138.1, 143.2, 149.5, 154.2, 166.7. IR (thin film, cm^{-1}): 3234, 2948, 1685, 1623, 1456, 1387, 1257, 1203, 1164, 1106, 696. HRMS *m/z* 359.1375 [(M + Na^+) calcd for $C_{20}H_{20}N_2O_3^+$: 359.1372]. $[\alpha]^{23}_D$ – 29.8 (*c* 1.00, $CHCl_3$). The purity (>95%) was determined by HPLC-ELSD (210 nm).

24. The enantiomeric ratio of the product was determined to be 95:5 using the following reverse phase HPLC method: Chiralcel OD-RH, (150 x 4.6 mm), 5 micron, isocratic elution, A: 0.1% H_3PO_4, B: MeCN, A: 45: B: 55; flow of 1.0 mL/min., ambient temp., detection at 210 nm. Major enantiomer elutes at 6.5 min, minor at 8 min. A normal phase HPLC method can also be employed: Chiralcel OD, (250 x 4.6 mm), 10 micron, isocratic elution, A: 2-propanol, B: heptane, A: 5: B: 95, flow of 1.0 mL/min., ambient temp., detection at 210 nm; Major enantiomer elutes at 31 min, minor at 39 min.

25. The checkers used the following recrystallization procedure to upgrade the final product to optical purity: In a 100-mL round-bottomed flask equipped with a 1.5 cm oval magnetic stir bar is added (*S*)-1-benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic methyl ester (2.00 g, 95:5 er) and ethyl acetate (20 mL). The mixture is warmed to 50 °C in a water bath with stirring to dissolve the solids. While warm, *n*-heptane (20 mL) is added dropwise with stirring over 5 min, resulting in crystallization of a white solid. The mixture is cooled over 20 min to ambient temperature and is stirred for 1 h to afford a thick slurry. The mixture is vacuum filtered through a 30 mL sintered glass funnel and washed with 10 mL of 1:1 heptane/EtOAc to provide 1.59 g (80%) of white needles after air drying. The ee was determined to be >99.5% based on the limit of detection of the reverse phase HPLC method in Note 24.

The submitters used the following recrystallization procedure to upgrade the final product to optical purity: In a 150-mL Erlenmeyer flask, (*S*)-1-benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic methyl ester (3.5 g, 95:5 er) is added to boiling diethyl ether (60 mL). The solution is boiled until most of the solid has dissolved. The solution is cooled in an ice-water bath until complete crystallization is observed (approximately 20 minutes). The pure dihydropyrimidone crystals are vacuum filtered, and are rinsed with two 20 mL portions of cold diethyl ether. The remaining mother liquor is concentrated under reduced pressure, and the resulting solid is transferred to a 150-mL Erlenmeyer flask containing boiling diethyl ether (30 mL). The solution is boiled until most solid has dissolved, and subsequently cooled in an ice-water bath until complete crystallization is observed (approximately 20 minutes). The crystals are filtered, and rinsed with 2 x 10 mL portions of cold diethyl ether. The solids are combined and dried under reduced pressure to yield 2.70 g (77 %) of (*S*)-1-benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetra-hydropyrimidine-5-carboxylic methyl ester. The enantiomeric ratio of the product was determined to be >99:1 using the normal phase HPLC method in Note 24.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press: Washington, DC, 1995.

3. Discussion

Chiral dihydropyrimidones are an important class of heterocycles that range in biological and pharmacological behavior.[2] While racemic dihydropyrimidones are easily prepared through use of the Biginelli reaction,[3] few methods provide dihydropyrimidinones in enantioenriched form.[4] The Mannich addition of β-ketoesters to acyl imines catalyzed by the cinchona alkaloids provides a chiral amine precursor to the enantioenriched dihydropyrimidinone core.[5]

The Mannich reaction proceeds well for aryl imines, however, in the case of aliphatic imines, tautomerization to the enamine restricts reactivity for nucleophilic addition. Recent methodology overcomes this challenge through the development of a biphasic cinchona alkaloid-catalyzed Mannich reaction utilizing α-amido sulfones.[6] The bench-stable and easily prepared *α*-amido sulfones serve as precursors to acyl imines; the acyl imine is formed *in situ* in the presence of sodium carbonate and the cinchona alkaloid catalyst.[7] Utilization of the *α*-amido sulfones in the cinchona alkaloid-catalyzed asymmetric Mannich reaction provides good control of enantioselectivity and scalability.

Conversion of the chiral amine precursor to the asymmetric dihydropyrimidone proceeds through two high yielding synthetic steps. Formation of the chiral primary amine and addition of benzyl isocyanate provides the benzyl ureido intermediate in high yield. The heterocycle is formed using reflux or microwave conditions in the presence of acetic acid and ethanol. Both methods provide the dihydropyrimidone in high yield with retention of stereochemistry.

With this methodology, a library of dihydropyrimidones was synthesized with three points of diversity (Table 1). The *α*-amido sulfone, *β*-ketoester and isocyanate were each altered to provide a diverse set of heterocycles in high yields and enantioselectivities. The stereochemical configuration of the dihydropyrimidone is dictated by the choice of cinchona alkaloid catalyst used in the Mannich reaction.

Table 1. Diverse Library of Asymmetric Dihydropyrimidones

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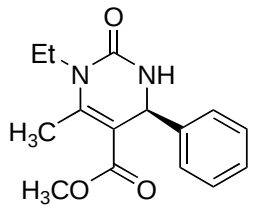
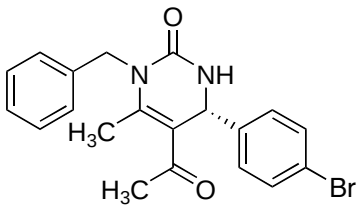
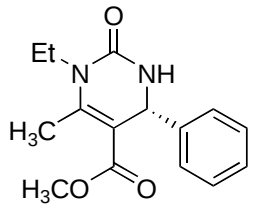
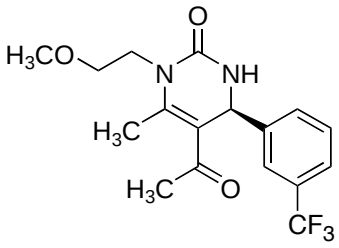
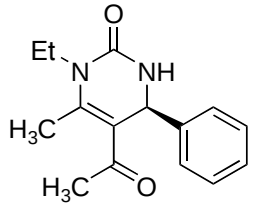
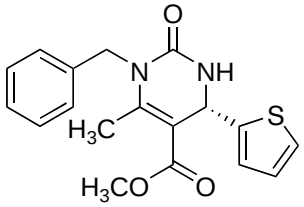
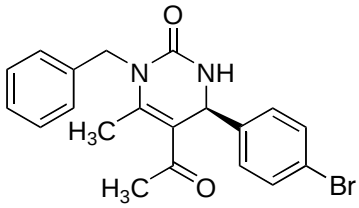
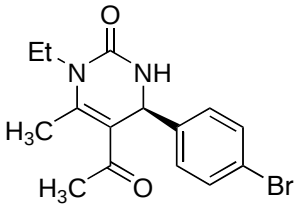
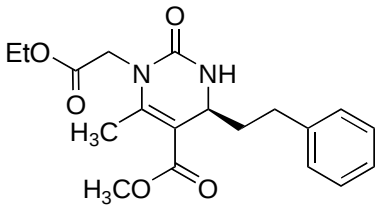
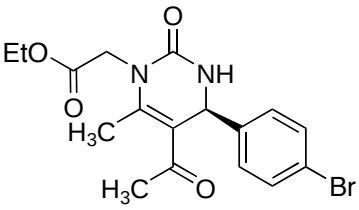
	71 95.5: 4.5		68 95.5 ; 4.5*
	72 96 : 4*		67 95.5 ; 4.5
	71 95.5 : 4.5		68 96 : 4*
	67 95 : 5		66 95 : 5
	70 95 : 5		63 95 : 5

*cinchonidine was used in place of cinchonine

1. Department of Chemistry, Boston University, Boston, MA 02215.
2. For reviews on dihydropyrimidones, see: (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879-888. (b) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043-1058.
3. (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360-416. (b) Kappe, C. O. Tetrahedron **1993**, *49*, 6937-6963.
4. (a) Chen, X.; Yu, X.; Liu, H.; Chun, L.; Gong, L. *J. Am. Chem. Soc.* **2006**, *128*, 14802-14803. (b) Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386-16387. (c) Schnell, B.; Strauss, U.T.; Verdino, P.; Faber, K.; Kappe, C. O.; *Tetrahedron: Asymmetry* **2000**, *11*, 1449-1453. (d) Kleidernigg, O.P.; Kappe, C.O. *Tetrahedron: Asymmetry* **1997**, *8*, 2057-2067. (e) Lewandowske, K.; Murer, P.; Svec, F.; Frechet, J.M. J. *J. Comb. Chem.* **1999**, *1*, 105-112. (d) Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W. *Tetrahedron* **1992**, *48*, 5473-5480. (e) Kontrec, D.; Vinkovic, V.; Sunjic, V.; Schuiki, B.; Fabian, W. M.; Kappe, C. O. *Chirality* **2003**, *15*, 550. (f) Muñoz-Muñiz, O.; Juaristi, E. *ARKIVOC* **2003**, *11*, 16-26. (g) Guillena, G.; Ramon, D.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693-700.
5. (a) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc*. **2005**, *127*, 11256-11257. (b) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett*. **2006**, *8*, 2003-2006. (c) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *ASAP*, DOI: 10.1021/jo701777g.
6. Review: Petrini, M. *Chem. Rev.* **2005**, *105*, 3949-3977.
7. (a) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75. (b) Kanazawa, S. M.; Denis, J. N.; Greene, S. E. *J. Org. Chem.* **1994**, *59*, 1238-1240. (c) Zawadzki, S.; Zwierzak, A. *Tetrahedron Lett.* **2004**, *45*, 8505-8506. (d) Morton, J.; Rahim, A.; Walker, E. R. H. *Tetrahedron Lett.* **1982**, *23*, 4123-4126.

Chemical Abstracts Nomenclature (Registry Number)

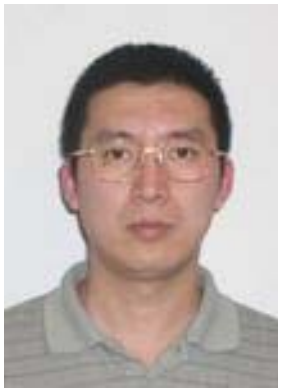
Carbamic acid, 2-propen-1-yl ester; (2114-11-6)
Carbamic acid, *N*-[phenyl(phenylsulfonyl)methyl]-, 2-propen-1-yl ester; (921767-12-6)
(*β R*)-Benzenepropanoic acid, *α*-acetyl-*β*-[[(2-propen-1-yloxy)carbonyl]amino]-, methyl ester; (921766-57-6)

(*β R*)-Benzenepropanoic acid, *α*-acetyl-*β*-[[[(phenylmethyl)amino]carbonyl]amino]-, methyl ester; (865086-76-6)

(4*S*)-5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl-1-(phenylmethyl)-, methyl ester; (865086-56-2)

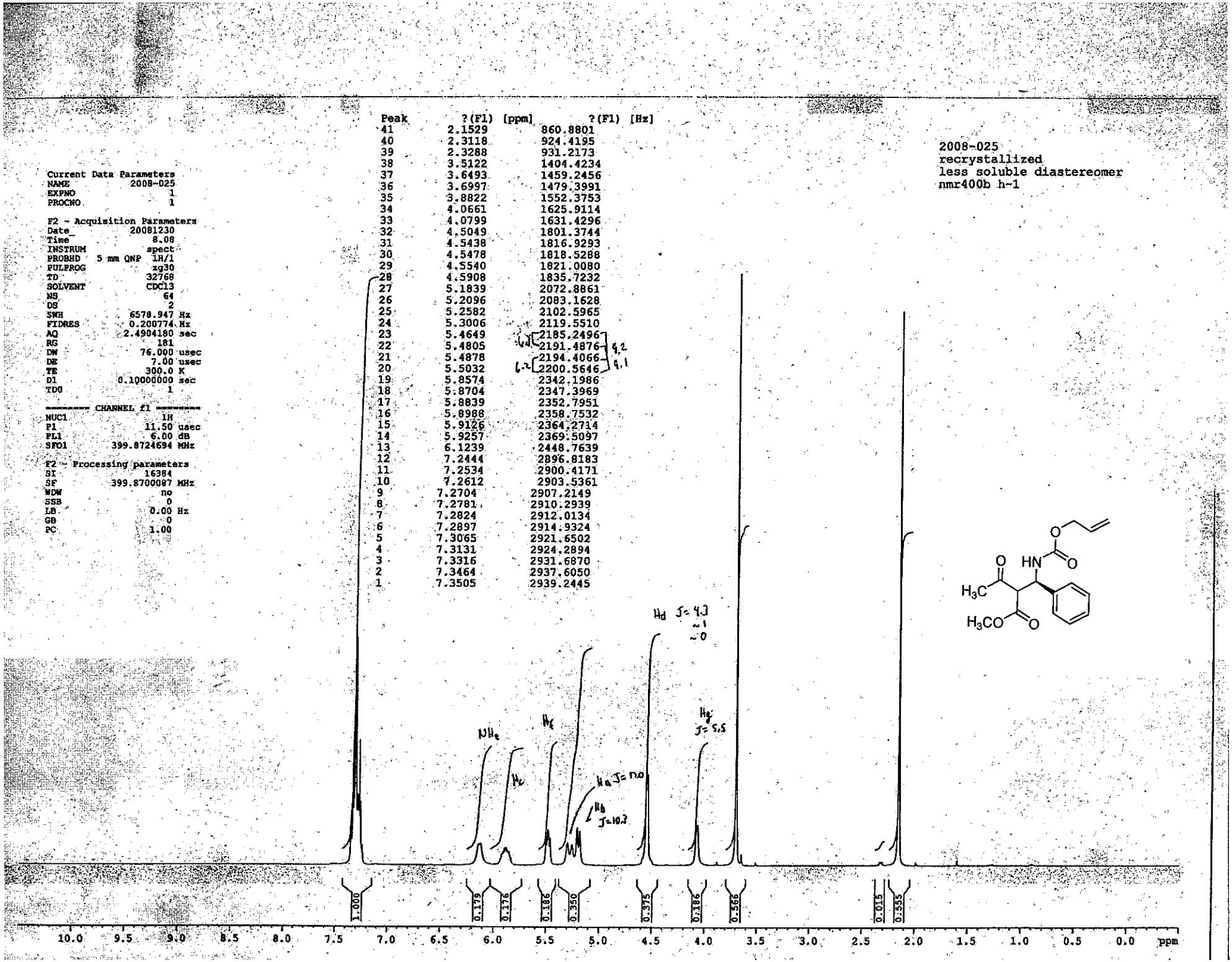
Scott E. Schaus studied chemistry at Boston University, where he completed his undergraduate degree in 1995. He received his Ph.D. in organic chemistry from Harvard University in 1999 under the direction of Professor Eric N. Jacobsen. His graduate work focused on the development of chiral salen transition metal catalysts and reactions for use in synthesis. He carried out his postdoctoral research as an NIH Postdoctoral Fellow in Professor Andrew G. Myers's laboratories studying the use of genomic technologies to facilitate drug target identification. In 2001 he joined the Department of Chemistry at Boston University as an Assistant Professor and, in 2002, he became one of the co-principal investigators of the Center for Chemical Methodology and Library Development at Boston University. His research interests include the development of asymmetric catalytic reactions for synthesis, new methodologies for library synthesis, and drug target identification and validation.

Jennifer Goss was born in Houston, Texas, in 1983. She received a B.S. in Chemistry in at Texas A&M University in College Station, Texas, where she performed undergraduate research in polymer chemistry with Professor Steven Miller. She began pursuing a doctorate degree in Organic chemistry in 2005 in the lab of Professor Scott E. Schaus. Her research focuses on catalytic asymmetric syntheses of dihydropyrimidones.



Peng Dai obtained his B. S. degree from the University of Science and Technology of China in 1997. He completed his Ph. D. studies in December 2004 under the guidance of Prof. Patrick H. Dussault at the University of Nebraska-Lincoln, where he studied asymmetric synthesis of peroxide natural products. He joined the CMLD-BU in November 2005 and works on the synthesis of dihydropyrimidones and related chemical libraries.

Sha Lou was born in He Bei, China, in 1979. He received a B.S. in Chemistry at Beijing University of Chemical Technology in 2002, where he conducted undergraduate research in fullerene functionalizations with Professor Shen-yi, Yu. He is currently pursuing a Ph.D. degree under the direction of Professor Scott E. Schaus. His research has focused on transition metal- and organic molecule-catalyzed asymmetric carbon-carbon bond forming reactions and synthesis.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17 5.8839 2352.7951
16 5.8988 2358.7532
15 5.9126 2364.2714
14 5.9257 2369.5097
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10 7.2612 2903.5361
9 7.2704 2907.2149
8 7.2781 2910.2939
7 7.2824 2912.0134
6 7.2897 2914.9324
5 7.3065 2921.6502
4 7.3131 2924.2894
3 7.3316 2931.6870
2 7.3464 2937.6050
1 7.3505 2939.2445
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nmr400b h-1
Hd J= 9.3
Hc
Hf
Hg J= 5.5
Ha J= 17.0
Hb J=10.3
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0.179
0.176
0.186
0.350
0.375
0.186
0.566
0.015
0.535
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
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ppm

2008-002
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65.78

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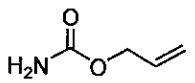

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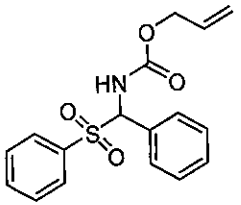

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11	77.5521	7797.6599
10	118.6519	11930.1369
9	128.9851	12969.1130
8	129.2494	12995.6877
7	129.6982	13040.8133
6	130.0810	13079.3029
5	130.1262	13083.8476
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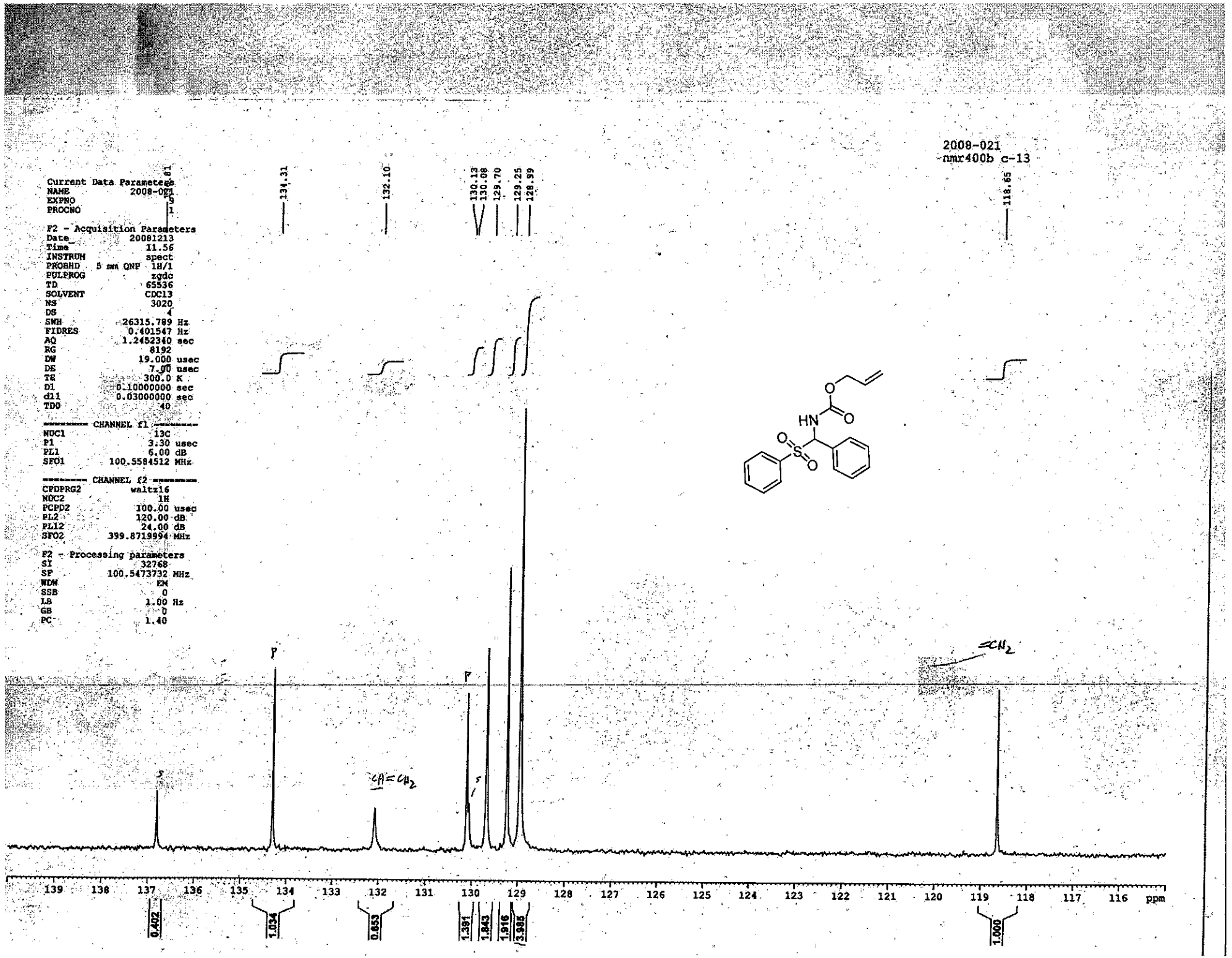
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FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
DW 19.000 usec
DE 7.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec
TD0 40
CHANNEL f1
NUC1 13C
P1 3.30 usec
PL1 6.00 dB
SFO1 100.5584512 MHz
CHANNEL f2
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NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 24.00 dB
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134.31
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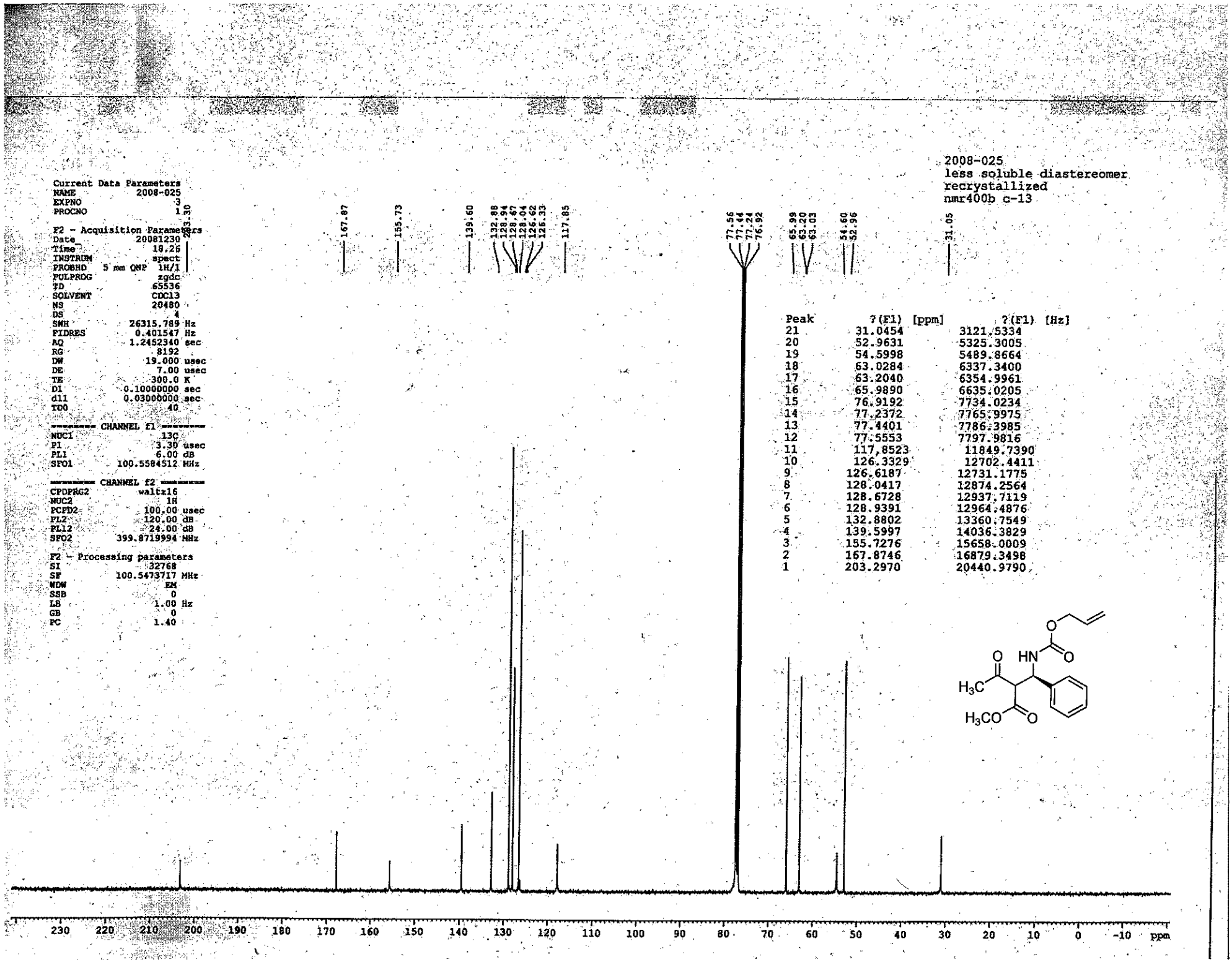
118.65
HN
O
O
S
O
O
=CH2
CH=CH2
139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122 121 120 119 118 117 116 ppm
0.402
1.034
0.853
1.381
1.843
1.916
3.986
1.000


2008-025
less soluble diastereomer
recrystallized
nmr400b c-13
Current Data Parameters
NAME 2008-025
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20081230
Time 18.26
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 20480
DS 4
SWH 26315.789 Hz
FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
DW 19.000 usec
DE 7.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec
TD0 40
======== CHANNEL f1 ========
NUC1 13C
P1 3.30 usec
PL1 6.00 dB
SFO1 100.5584512 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 24.00 dB
SFO2 399.8719994 MHz
F2 - Processing parameters
SI 32768
SF 100.5473717 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
203.30
167.87
155.73
139.60
132.88
128.94
128.67
128.04
126.62
126.33
117.85
77.56
77.44
77.24
76.92
65.99
63.20
63.03
54.60
52.96
31.05
Peak ?(F1) [ppm] ?(F1) [Hz]
21 31.0454 3121.5334
20 52.9631 5325.3005
19 54.5998 5489.8664
18 63.0284 6337.3400
17 63.2040 6354.9961
16 65.9890 6635.0205
15 76.9192 7734.0234
14 77.2372 7765.9975
13 77.4401 7786.3985
12 77.5553 7797.9816
11 117.8523 11849.7390
10 126.3329 12702.4411
9 126.6187 12731.1775
8 128.0417 12874.2564
7 128.6728 12937.7119
6 128.9391 12964.4876
5 132.8802 13360.7549
4 139.5997 14036.3829
3 155.7276 15658.0009
2 167.8746 16879.3498
1 203.2970 20440.9790
O
HN
O
O
H3C
H3CO
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

2009-029
fr 26-34
nmr400b c-13

Current Data Parameters
NAME 2009-029
EXPNO 2
PROCNO 1

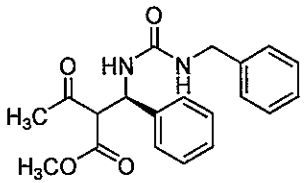
F2 - Acquisition Parameters
Date_ 20090208
Time 15.35
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 1229
DS 4
SWH 26315.789 Hz
FIDRES 0.401547 Hz
AQ 1.2452340 sec
RG 8192
DW 19.000 usec
DE 7.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec
TD0 40

CHANNEL f1
NUC1 13C
P1 3.30 usec
PL1 6.00 dB
SFO1 100.5584512 MHz

CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 24.00 dB
SFO2 399.8719994 MHz

F2 - Processing parameters
SI 32768
SF 100.5473751 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Peak	?(F1) [ppm]	?(F1) [Hz]
1	204.0331	20514.9926
2	202.1950	20330.1765
3	171.3794	17231.7488
4	169.7593	17068.8520
5	168.0883	16900.8374
6	158.6058	15947.3969
7	157.6099	15847.2617
8	157.5268	15838.9062
9	140.3364	14110.4567
10	140.1186	14088.5574
11	139.6247	14038.8971
12	139.4464	14020.9695
13	139.2812	14004.3591
14	128.8008	12950.5824
15	128.7750	12947.9882
16	128.7151	12941.9654
17	128.6587	12936.2946
18	127.7382	12843.7407
19	127.6510	12834.9730
20	127.5502	12824.8378
21	127.3592	12805.6333
22	127.3133	12801.0181
23	127.2736	12797.0264
24	126.7385	12743.2235
25	126.2886	12697.9872
26	77.5505	7797.4992
27	77.4350	7785.8860
28	77.2328	7765.5553
29	76.9145	7733.5511
30	64.5927	6494.6264
31	64.2275	6457.9065
32	60.5790	6091.0594
33	53.7853	5407.9707
34	52.7409	5302.9591
35	52.3869	5267.3653
36	52.3561	5264.2684
37	44.6002	4484.4330
38	44.5685	4481.2457
39	44.4891	4473.2622
40	30.1485	3031.3525
41	29.0614	2922.0475
42	21.1969	2131.2927
43	14.3608	1443.9407



230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

2009-030
Recrystallized
nmr500c c-13

Current Data Parameters
NAME 2009-030
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090207
Time 12.24
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgdc
TD 131072
SOLVENT CDCl3
NS 1812
DS 4
SWH 40322.582 Hz
FIDRES 0.307637 Hz
AQ 1.6253552 sec
RG 8192
DW 12.400 usec
DE 6.50 usec
TE 299.8 K
D1 0.10000000 sec
d11 0.03000000 sec
TD0 40

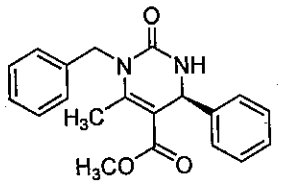
======== CHANNEL f1 ========
NUC1 13C
P1 2.50 usec
PL1 0.00 dB
SFO1 125.7703648 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL12 11.50 dB
PL2 120.00 dB
SFO2 500.1325007 MHz

F2 - Processing parameters
SI 65536
SF 125.7577641 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

166.73 154.15 149.54 143.25 138.10 128.93 128.90 128.05 127.40 126.65 126.50 104.89 77.48 77.23 76.97 54.07 51.56 46.20 16.74

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity	Annotation
1	166.7340	20968.0950	2.09	
2	154.1461	19385.0689	2.08	
3	149.5367	18805.4010	2.15	
4	143.2501	18014.8123	1.95	
5	138.1028	17367.4993	2.46	
6	128.9324	16214.2503	9.37	
7	128.9015	16210.3644	9.74	
8	128.0526	16103.6087	4.66	
9	127.4040	16022.0422	4.66	
10	126.6535	15927.6610	7.78	
11	126.4974	15908.0302	9.80	
12	104.8939	13191.2223	1.41	
13	77.4814	9743.8876	14.70	
14	77.2273	9711.9326	15.00	
15	76.9734	9680.0027	14.71	
16	54.0689	6799.5840	3.77	
17	51.5628	6484.4224	4.45	
18	46.2019	5810.2476	3.36	
19	16.7432	2105.5874	4.70	



230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

2008-002
allyl carbamate

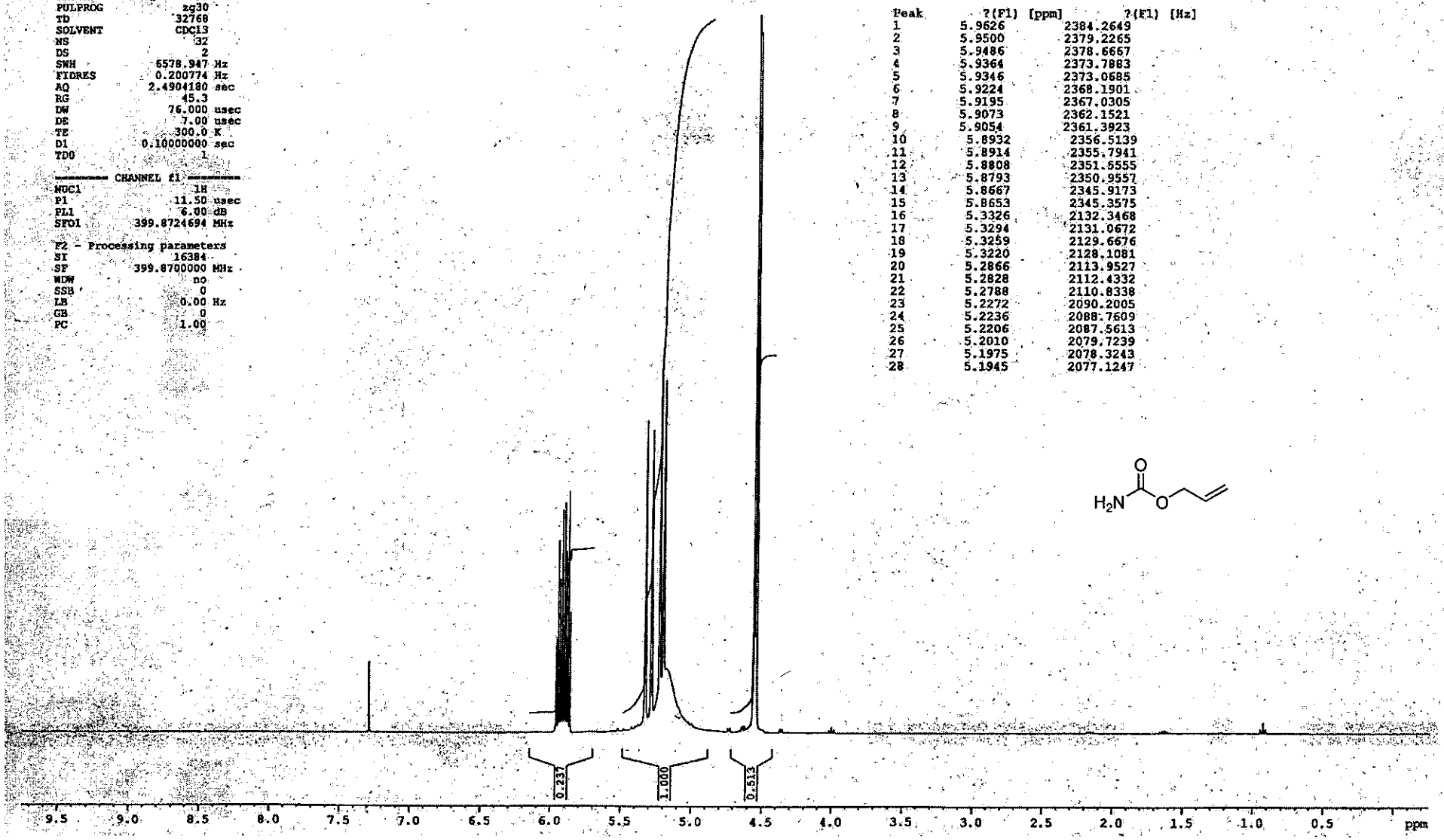
Current Data Parameters
NAME 2008-002
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090228
Time 12.19
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 45.3
DW 76.000 usec
DE 7.00 usec
TE 300.0 K
D1 0.10000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 11.50 usec
PL1 6.00 dB
SFO1 399.8724694 MHz

F2 - Processing parameters
SI 16384
SF 399.8700000 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Peak	?(F1) [ppm]	?(F1) [Hz]
1	5.9626	2384.2649
2	5.9500	2379.2265
3	5.9486	2378.6667
4	5.9364	2373.7883
5	5.9346	2373.0685
6	5.9224	2368.1901
7	5.9195	2367.0305
8	5.9073	2362.1521
9	5.9054	2361.3923
10	5.8932	2356.5139
11	5.8914	2355.7941
12	5.8808	2351.5555
13	5.8793	2350.9557
14	5.8667	2345.9173
15	5.8653	2345.3575
16	5.3326	2132.3468
17	5.3294	2131.0672
18	5.3259	2129.6676
19	5.3220	2128.1081
20	5.2866	2113.9527
21	5.2828	2112.4332
22	5.2788	2110.8338
23	5.2272	2090.2005
24	5.2236	2088.7609
25	5.2206	2087.5613
26	5.2010	2079.7239
27	5.1975	2078.3243
28	5.1945	2077.1247



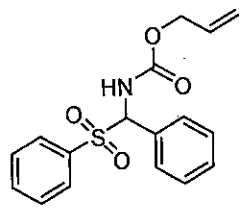
2008-021
2nd crop after toluene flush
nmr400b h-1

Current Data Parameters
NAME 2008-021
EXPNO 8
PROCNO 1

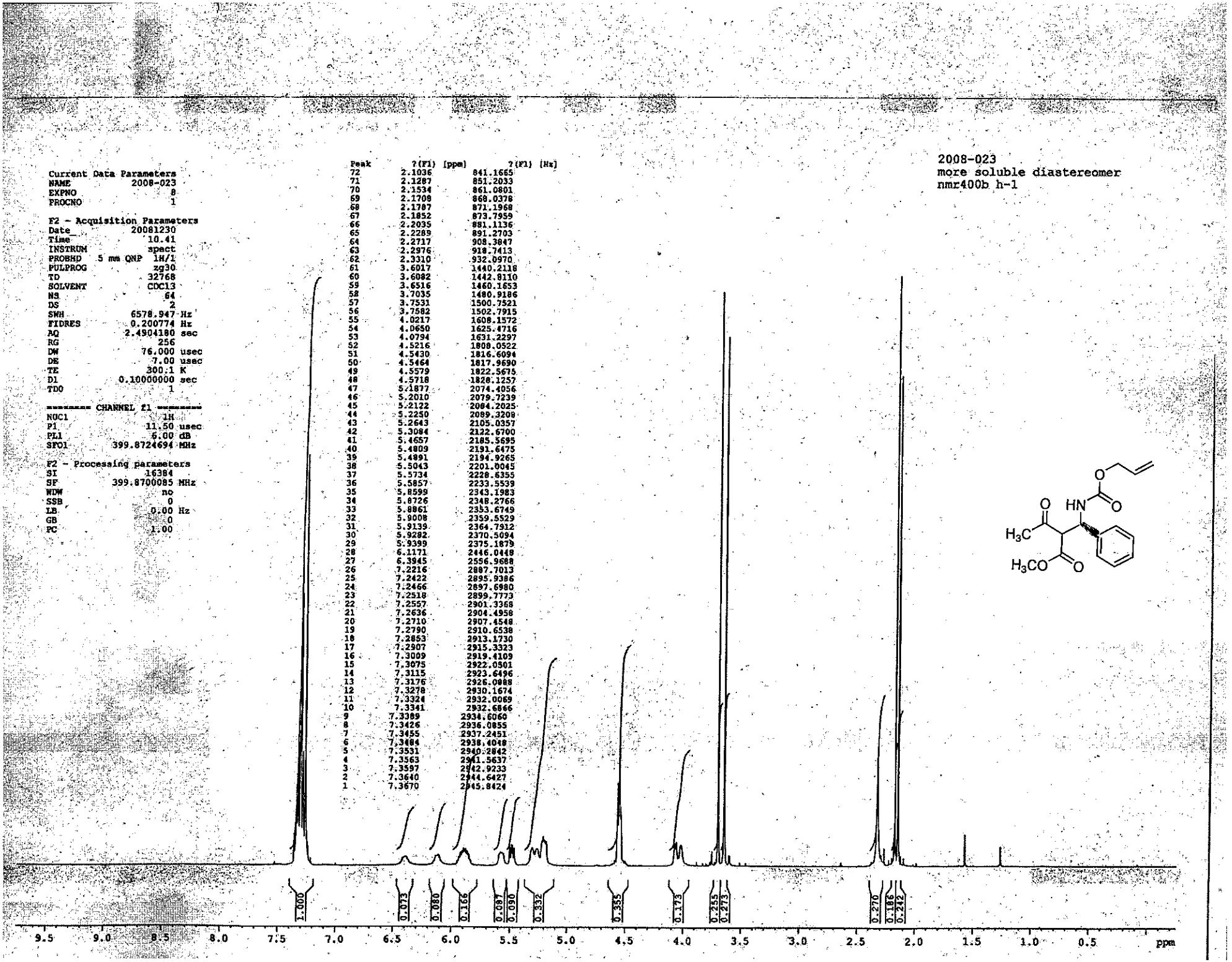
F2 - Acquisition Parameters
Date_ 20081213
Time 11.50
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 143.7
DW 76.000 usec
DE 7.00 usec
TE 299.9 K
D1 0.10000000 sec
TD0 1

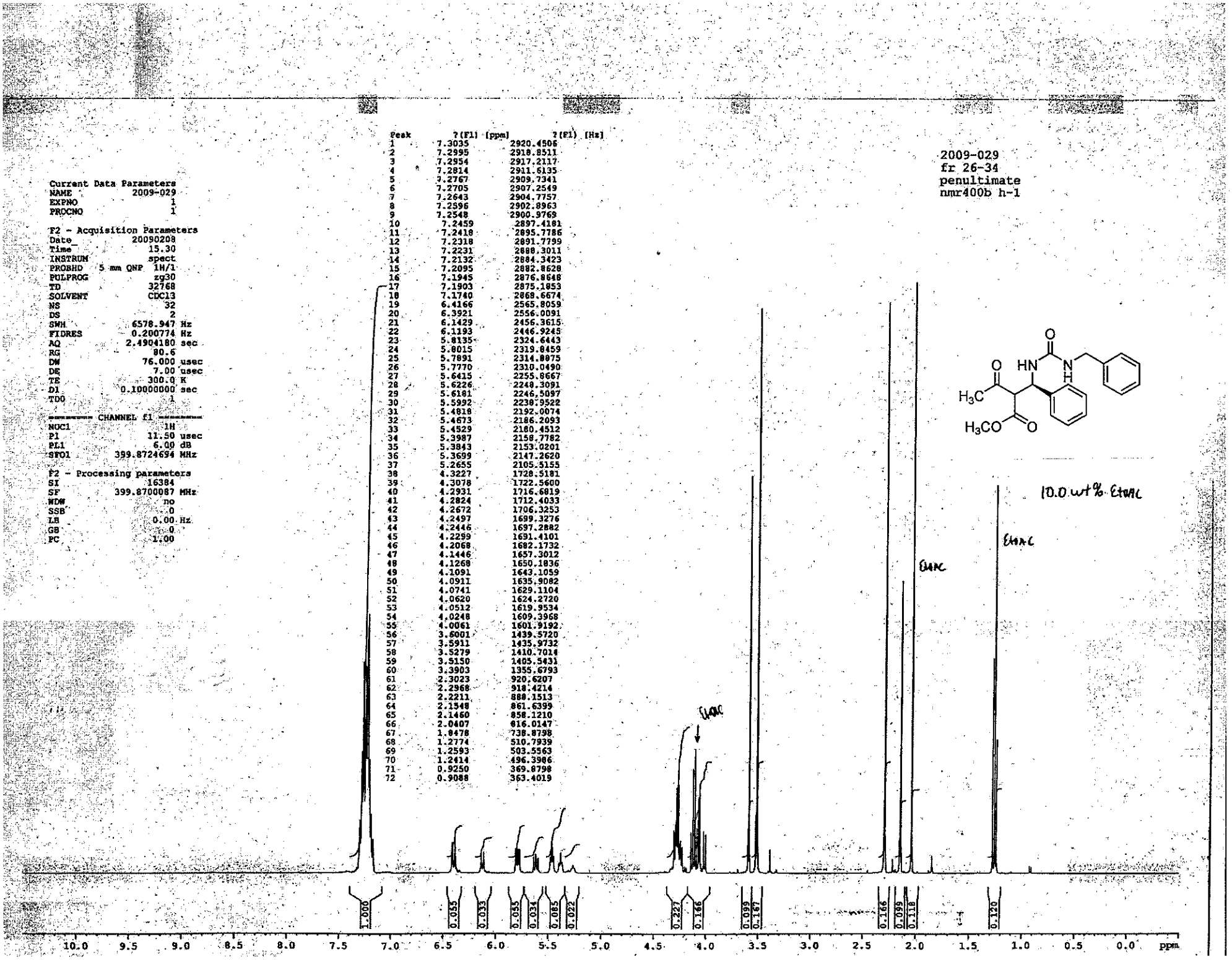
======== CHANNEL f1 ========
NUC1 1H
P1 11.50 usec
PL1 6.00 dB
SFO1 399.6724694 MHz

F2 - Processing parameters
SI 16384
SF 399.8700091 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00



Peak	?(F1) [ppm]	?(F1) [Hz]
33	4.4124	1764.3864
32	4.4252	1769.5048
31	5.1751	2069.3673
30	5.2017	2080.0038
29	5.2483	2098.6378
28	5.7390	2294.8540
27	5.7644	2305.0107
26	5.7791	2310.8888
25	5.9565	2381.8257
24	5.9829	2392.3823
23	6.0464	2417.7740
22	6.0724	2428.1706
21	7.2697	2906.9350
20	7.3582	2942.3235
19	7.3698	2946.9620
18	7.3737	2948.5215
17	7.3786	2950.4808
16	7.3895	2954.8394
15	7.3940	2956.6388
14	7.3974	2957.9984
13	7.4242	2968.7149
12	7.4344	2972.7936
11	7.4408	2975.3528
10	7.4477	2978.1119
9	7.4550	2981.0309
8	7.5001	2999.0651
7	7.5391	3014.6600
6	7.6356	3053.2474
5	7.6383	3054.3271
4	7.6541	3060.6450
3	7.6703	3067.1229
2	7.6728	3068.1226
1	7.8799	3150.9357


2008-023
more soluble diastereomer
nmr400b h-1
Current Data Parameters
NAME 2008-023
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date 20081230
Time 10.41
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 256
DW 76.000 usec
DE 7.00 usec
TE 300.1 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 11.50 usec
PL1 6.00 dB
SFO1 399.8724694 MHz
F2 - Processing parameters
SI 16384
SF 399.8700085 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
Peak ?(F1) [ppm] ?(F1) [Hz]
72 2.1036 841.1665
71 2.1287 851.2033
70 2.1534 861.0801
69 2.1708 868.0378
68 2.1787 871.1968
67 2.1852 873.7959
66 2.2035 881.1136
65 2.2289 891.2703
64 2.2717 908.3847
63 2.2976 918.7413
62 2.3310 932.0970
61 3.6017 1440.2118
60 3.6082 1442.8110
59 3.6516 1460.1653
58 3.7035 1480.9186
57 3.7531 1500.7521
56 3.7582 1502.7915
55 4.0217 1608.1572
54 4.0650 1625.4716
53 4.0794 1631.2297
52 4.5216 1808.0522
51 4.5430 1816.6094
50 4.5464 1817.9690
49 4.5579 1822.5675
48 4.5718 1828.1257
47 5.1877 2074.4056
46 5.2010 2079.7239
45 5.2122 2084.2025
44 5.2250 2089.3208
43 5.2643 2105.0357
42 5.3084 2122.6700
41 5.4657 2185.5695
40 5.4809 2191.6475
39 5.4891 2194.9265
38 5.5043 2201.0045
37 5.5734 2228.6355
36 5.5857 2233.5539
35 5.8599 2343.1983
34 5.8726 2348.2766
33 5.8861 2353.6749
32 5.9008 2359.5529
31 5.9139 2364.7912
30 5.9282 2370.5094
29 5.9399 2375.1879
28 6.1171 2446.0448
27 6.3945 2556.9688
26 7.2216 2887.7013
25 7.2422 2895.9386
24 7.2466 2897.6980
23 7.2518 2899.7773
22 7.2557 2901.3368
21 7.2636 2904.4958
20 7.2710 2907.4548
19 7.2790 2910.6538
18 7.2853 2913.1730
17 7.2907 2915.3323
16 7.3009 2919.4109
15 7.3075 2922.0501
14 7.3115 2923.6496
13 7.3176 2926.0888
12 7.3278 2930.1674
11 7.3324 2932.0069
10 7.3341 2932.6866
9 7.3389 2934.6060
8 7.3426 2936.0855
7 7.3455 2937.2451
6 7.3484 2938.4048
5 7.3531 2940.2842
4 7.3563 2941.5637
3 7.3597 2942.9233
2 7.3640 2944.6427
1 7.3670 2945.8424
1.000
0.073
0.080
0.166
0.087
0.090
0.332
0.355
0.173
0.255
0.273
0.270
0.186
0.242
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
O
HN
O
H3C
H3CO
O
O


Current Data Parameters
NAME 2009-029
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date 20090208
Time 15.30
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 80.6
DW 76.000 usec
DE 7.00 usec
TE 300.0 K
D1 0.10000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.50 usec
PL1 6.00 dB
SFO1 399.8724694 MHz
F2 - Processing parameters
SI 16384
SF 399.8700087 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
Peak ?(F1) [ppm] ?(F1) [Hz]
1 7.3035 2920.4506
2 7.2995 2918.8511
3 7.2954 2917.2117
4 7.2814 2911.6135
5 7.2767 2909.7341
6 7.2705 2907.2549
7 7.2643 2904.7757
8 7.2596 2902.8963
9 7.2548 2900.9769
10 7.2459 2897.4181
11 7.2418 2895.7786
12 7.2318 2891.7799
13 7.2231 2888.3011
14 7.2132 2884.3423
15 7.2095 2882.8628
16 7.1945 2876.8648
17 7.1903 2875.1853
18 7.1740 2868.6674
19 6.4166 2565.8059
20 6.3921 2556.0091
21 6.1429 2456.3615
22 6.1193 2446.9245
23 5.8135 2324.6443
24 5.8015 2319.8459
25 5.7891 2314.8975
26 5.7770 2310.0490
27 5.6415 2255.8667
28 5.6226 2248.3091
29 5.6181 2246.5097
30 5.5992 2238.9522
31 5.4818 2192.0074
32 5.4673 2186.2093
33 5.4529 2180.4512
34 5.3987 2158.7782
35 5.3843 2153.0201
36 5.3699 2147.2620
37 5.2655 2105.5155
38 4.3227 1728.5181
39 4.3078 1722.5600
40 4.2931 1716.6819
41 4.2824 1712.4033
42 4.2672 1706.3253
43 4.2497 1699.3276
44 4.2446 1697.2882
45 4.2299 1691.4101
46 4.2068 1682.1732
47 4.1446 1657.3012
48 4.1268 1650.1836
49 4.1091 1643.1059
50 4.0911 1635.9082
51 4.0741 1629.1104
52 4.0620 1624.2720
53 4.0512 1619.9534
54 4.0248 1609.3968
55 4.0061 1601.9192
56 3.6001 1439.5720
57 3.5911 1435.9732
58 3.5279 1410.7014
59 3.5150 1405.5431
60 3.3903 1355.6793
61 2.3023 920.6207
62 2.2968 918.4214
63 2.2211 888.1513
64 2.1548 861.6399
65 2.1460 858.1210
66 2.0407 816.0147
67 1.8478 738.8798
68 1.2774 510.7939
69 1.2593 503.5563
70 1.2414 496.3986
71 0.9250 369.8798
72 0.9088 363.4019
2009-029
fr 26-34
penultimate
nmr400b h-1
EtOAc
EtOAc
10.0 wt% EtOAc
1.000
0.055
0.033
0.055
0.034
0.085
0.022
0.227
0.166
0.099
0.187
0.166
0.099
0.118
0.120
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

2009-030
recrystallized product
nmr500d h-1

Current Data Parameters
NAME 2009-030
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20090207
Time 11.13
INSTRUM spect
PROBHD 5 mm PATXI 1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 30
DS 4
SWH 13020.833 Hz
FIDRES 0.198682 Hz
AQ 2.5166707 sec
RG 128
DW 38.400 usec
DE 6.50 usec
TE 295.0 K
D1 0.10000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 8.60 usec
PL1 -1.00 dB
SFO1 500.3330895 MHz

F2 - Processing parameters
SI 32768
SF 500.3300094 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity	Annotation
1	7.2909	3647.8561	3.34	
2	7.2831	3643.9535	5.80	
3	7.2777	3641.2517	8.40	
4	7.2738	3639.3004	9.64	
5	7.2694	3637.0990	8.66	
6	7.2631	3633.9469	8.74	
7	7.2573	3631.0450	2.39	
8	7.2484	3626.5920	6.51	
9	7.2410	3622.8896	3.78	
10	7.2343	3619.5374	3.35	
11	7.2286	3616.6855	1.69	
12	7.2226	3613.6835	0.64	
13	7.1186	3561.6492	4.10	
14	7.1032	3553.9441	3.19	
15	5.9868	2995.3757	1.91	
16	5.4465	2725.0474	2.79	
17	5.4407	2722.1455	2.33	
18	5.2300	2616.7259	0.66	
19	5.1978	2600.6153	0.75	
20	4.8931	2448.1648	0.90	
21	4.8603	2431.7539	0.74	
22	3.6497	1826.0544	1.64	
23	3.6370	1819.7002	10.70	
24	3.6337	1818.0492	20.00	
25	2.4625	1232.0626	1.59	
26	2.4477	1224.6578	16.89