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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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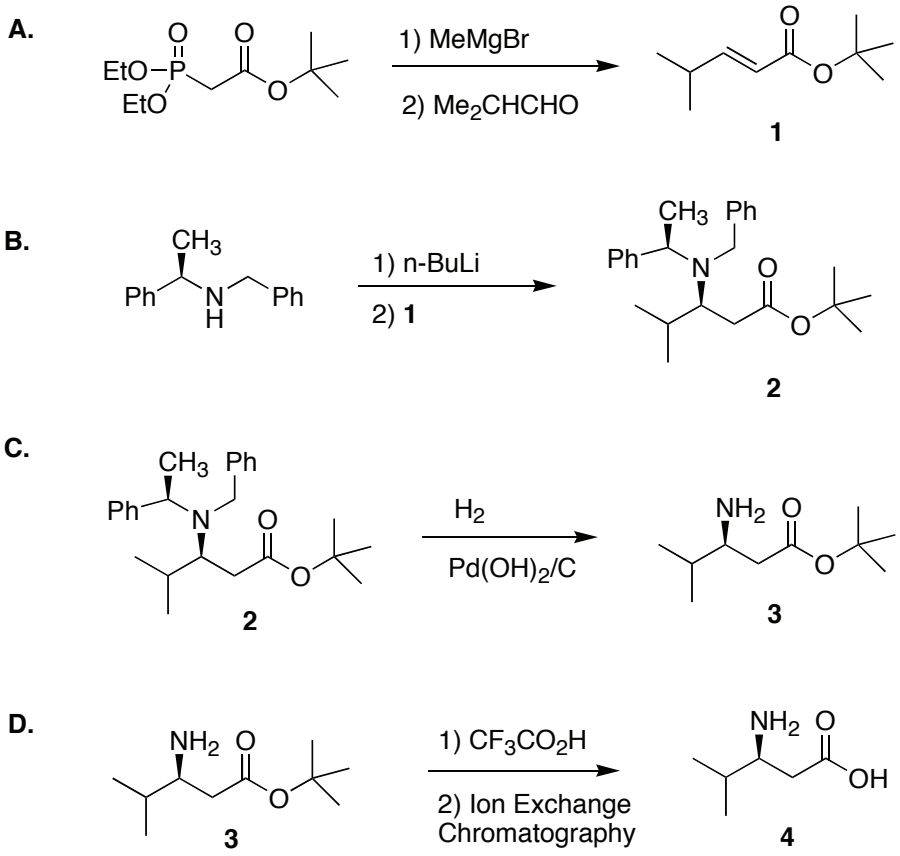
LITHIUM AMIDES AS HOMOCHIRAL AMMONIA EQUIVALENTS FOR CONJUGATE ADDITIONS TO α,β-UNSATURATED ESTERS: ASYMMETRIC SYNTHESIS OF (*S*)-β-LEUCINE



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1. Procedure

A. t-Butyl (E)-4-methylpent-2-enoate (**1**). An oven-dried 1-L, three-necked, round-bottomed flask equipped with a 3-cm oval Teflon-coated stir bar is fitted with two septa on the outer necks and a reflux condenser on the center neck. The reflux condenser is fitted with a nitrogen gas inlet adapter connected to a nitrogen line and a gas bubbler. A thermocouple thermometer probe is inserted through one of the septa. The flask is allowed to cool under a flow of nitrogen. It is charged with *t*-butyl diethylphosphonoacetate (17.8

g, 70.4 mmol, uncorrected for purity, 1.0 equiv) (Note 1) followed by anhydrous tetrahydrofuran (150 mL) (Note 2) and cooled to 2 °C using an ice bath. A 2.93 M solution of methylmagnesium bromide in diethyl ether (25.3 g, 24.5 mL, 71.7 mmol, 1.02 equiv) (Note 3) is added via syringe to the stirred solution over a period of 15 min, resulting in an exotherm to 8 °C and the evolution of gas (gentle bubbling of the reaction mixture). After the addition is complete, stirring is continued at 0–5 °C for 30 min. Isobutyraldehyde (5.73 g, 79.5 mmol, 1.1 equiv) is added dropwise to the reaction mixture via syringe over 5 min, resulting in a slight exotherm from 2 °C to 6 °C. The ice-bath is replaced with a heating mantle and the mixture is heated to reflux (62 °C) for 2 h. The heating mantle is removed and the reaction flask is allowed to cool to 23 °C over 30 min (Note 4). The reflux condenser is replaced with a 250-mL pressure-equalizing dropping funnel, which is charged with saturated aqueous ammonium chloride solution (200 mL). The reaction mixture is quenched by the dropwise addition of the saturated aqueous ammonium chloride solution over a period of 10 min, with vigorous stirring being continued throughout (Note 5). After the addition is complete, diethyl ether (100 mL) is added and the mixture is transferred to a 1-L separatory funnel. The layers are separated and the aqueous layer is extracted with diethyl ether (2 x 100 mL). The combined organic layers are washed with saturated aqueous sodium chloride (100 mL), filtered through a bed of anhydrous sodium sulfate (50 g, rinsed with 2 x 75 mL diethyl ether) and concentrated by rotary evaporation (20 °C water bath, 100 mmHg, decreased to 20 mmHg) (Note 6) to give the crude reaction product **1** (20 g) as a colorless oil. The crude product is purified by chromatography on silica gel (Note 7) to afford *t*-butyl (*E*)-4-methylpent-2-enoate **1** (11.4 g, 95% yield) as a colorless oil having an *E*/*Z* ratio of 142:1 (Notes 8 and 9).

B. t-Butyl (3S,αR)-3-[N-benzyl-N-(α-methylbenzyl)amino]-4-methylpentanoate (**2**). An oven-dried 500-mL, three-necked, round-bottomed flask with a 3-cm oval Teflon-coated magnetic stir bar is fitted with a nitrogen gas inlet adapter connected to a nitrogen line and gas bubbler and is allowed to cool under a stream of nitrogen. The remaining two necks are fitted with septa. A thermocouple thermometer probe is inserted through one of the septa. The flask is charged with (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (20.1 g, 95 mmol, 1.6 equiv) (Note 10) and anhydrous tetrahydrofuran (200 mL) (Note 11) and cooled to −72 °C (internal temperature) using a dry-ice/acetone bath in a dish-shaped Dewar flask. A

2.37 M solution of *n*-butyllithium in hexanes (27.1 g, 39.1 mL, 93 mmol, 1.55 equiv) (Note 12) is added dropwise via syringe (Note 13) over 10 min. The temperature increases to –64 °C at the end of the addition (Note 14). After the addition is complete, stirring is continued at –75 to –70 °C for 30 min. *t*-Butyl (*E*)-4-methylpent-2-enoate **1** (10.1 g, 59.4 mmol, 1.0 equiv) is added dropwise by syringe (Note 13) over 15 min, keeping the internal temperature between –76 to –74 °C (Note 15). When the addition is complete, stirring is continued at –76 to –74 °C for 3 h (Note 16). The dry-ice bath is removed and the reaction mixture is allowed to warm to –50 °C over 20 min. The nitrogen gas adapter is replaced with a 100-mL pressure-equalizing dropping funnel and the gas adapter is moved to the top of the dropping funnel. The dropping funnel is charged with saturated aqueous ammonium chloride solution (60 mL). The reaction mixture is quenched by the dropwise addition of the saturated aqueous ammonium chloride solution over a period of 10 min, with vigorous stirring being continued throughout. The mixture warms to –25 °C during the quench (Note 17). The dark orange solution turns pale yellow and a white precipitate is formed. After the addition is complete, a water bath is used to warm the mixture to room temperature over 15 min. The mixture is diluted with saturated aqueous sodium chloride (60 mL) and stirred for 15 min. The white precipitate dissolves. The mixture is transferred to a 1-L separatory funnel. The layers are separated and the aqueous layer is extracted with diethyl ether (2 x 100 mL). The combined organic layers are concentrated by rotary evaporation (40 °C water bath, 150 mmHg, decreased to 20 mmHg) to provide 34 g of crude product (Note 18). The resultant pale yellow oil is dissolved in dichloromethane (300 mL) and washed sequentially with 0.5 M aqueous citric acid solution (2 x 200 mL) (Note 19), saturated aqueous sodium bicarbonate (200 mL), and saturated aqueous sodium chloride (200 mL). The organic layer is filtered through a bed of sodium sulfate (50 g, rinsed with 2 x 75 mL of dichloromethane) and the filtrate is concentrated by rotary evaporation (40 °C water bath, 150 mmHg, decreased to 20 mmHg) to give the crude reaction product **2** (22.2 g) as a viscous, pale yellow oil. The crude product is purified by chromatography on silica gel (Note 20) to afford *t*-butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methylpentanoate **2** (20.6 g, containing 2 wt% hexane by ^{1}H NMR analysis, 89% corrected yield) as a viscous, colorless oil (Note 21).

C. t-Butyl (S)-3-amino-4-methylpentanoate (**3**). *t*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methylpentanoate **2** (19.1 g, 50.0 mmol) and methanol (200 mL) (Note 22) are added to a 500-mL round-bottomed flask and the contents are swirled to completely dissolve the oil. The solution is transferred to a 500-mL borosilicate Parr bottle and 20% wet palladium hydroxide on carbon (5.0 g) is added. The bottle is connected to a Parr shaker hydrogenation apparatus and flushed by 3 vacuum purge/hydrogen fill cycles. The hydrogenation reaction is then carried out under 40 psi hydrogen pressure with shaking at 21–24 °C for 6 h (Note 23). The vessel is vented and 3 nitrogen fill/vacuum purge cycles are carried out to remove hydrogen from the solution. The solution is vacuum filtered through a bed of Solka-Floc (50 g) in a 350-mL medium porosity sintered glass funnel and washed with methanol (3 x 100 mL). The catalyst cake is kept wet with methanol throughout the filtration to minimize the potential for the palladium to ignite (Note 24). The hazy filtrate is transferred to a 1-L round bottomed flask and is concentrated by rotary evaporation (40 °C water bath, 20 mmHg) to give the crude reaction product **3** (9.6 g) as a pale yellow oil. The crude product is purified by chromatography on silica gel (Note 25) to afford *t*-butyl (*S*)-3-amino-4-methylpentanoate **3** (7.8 g, 83% yield) as pale yellow oil (Note 26).

D. (S)-3-Amino-4-methylpentanoic acid [(S)-β-leucine] (**4**). *t*-Butyl (*S*)-3-amino-4-methylpentanoate **3** (6.60 g, 35.2 mmol) and dichloromethane (15 mL) (Note 27) are added to a 250-mL round-bottomed flask equipped with a 2-cm Teflon-coated magnetic stir bar. The flask is fitted with a septum, through which a thermocouple temperature probe and an 18-gauge needle connected to a nitrogen line and gas bubbler are inserted. The solution is cooled to 5 °C (internal temperature) using an ice bath. Trifluoroacetic acid (15 mL) is added dropwise via syringe over a period of 10 min, resulting in a temperature rise to 9 °C. The cooling bath is removed and the reaction mixture is stirred at 21–23 °C for 13 h. The solution is concentrated by rotary evaporation (40 °C water bath, 20 mmHg) to give a pale orange residue. Toluene (50 mL) is added to the residue and the mixture is concentrated by rotary evaporation (60 °C water bath, 20 mmHg). A further 50 mL of toluene is added and the evaporation process is repeated to afford crude product as a gum (12 g) (Note 28). Diethyl ether (30 mL) and a 2-cm oval Teflon-coated magnetic stir bar are added to the flask. The flask is fitted with a septum through which a thermocouple temperature probe and an 18-gauge needle with an outlet to a nitrogen line and gas bubbler are

inserted. A 2 M solution of hydrogen chloride in diethyl ether (30 mL) is added dropwise via syringe to the stirred solution over a 5 min period. The temperature rises to 35 °C and the mixture becomes a thick white slurry, which is stirred for 1 h at ambient temperature (35 °C initial, cooling in air to 23 °C). The stir bar is removed and the mixture is concentrated by rotary evaporation (40 °C water bath, 100 mmHg, decreased to 20 mmHg) to afford the crude hydrochloride salt of **4** (10.7 g) as a white solid (Note 29). The crude product is purified by ion-exchange resin chromatography (Note 30) to afford (*S*)-3-amino-4-methylpentanoic acid [(*S*)-β-leucine] **4** (4.06–4.30 g, 88–93% yield) as a tan crystalline solid (Notes 31-34).

2. Notes

1. *t*-Butyl diethylphosphonoacetate (95%) was obtained from Alfa Aesar. The submitters prepared it by heating *t*-butyl bromoacetate (Sigma-Aldrich, 98%) and triethylphosphite (Sigma-Aldrich, 98%) for 2 h without solvent, followed by distillation under vacuum.[3]

2. The following materials used in step A were obtained from Sigma-Aldrich: tetrahydrofuran (anhydrous, >99.9%, inhibitor-free), methylmagnesium bromide (3.0 M in diethyl ether), isobutyraldehyde (≥99%), pentane (Chromasolv, >99%), diethyl ether (ACS reagent, anhydrous, BHT-inhibited), and silica gel (230-400 mesh, 60 Å). De-ionized tap water was used throughout.

3. Methylmagnesium bromide was titrated before use as follows: *n*-Butanol (350 mg, 4.72 mmol) and 1,10-phenanthroline (2 mg) are dissolved in tetrahydrofuran (7 mL) in a 25-mL round-bottomed flask equipped with a 0.5-cm oval Teflon-coated magnetic stir bar and a septum pierced with an 18-gauge nitrogen-inlet needle connected to a nitrogen line and gas bubbler. The stirred solution is cooled in an ice-bath, then 3 M methylmagnesium bromide in diethyl ether is added dropwise via a weighed syringe to a persistent pink endpoint. The syringe is weighed before and after addition (difference 1.67 g, 1.61 mL, corresponding to a solution molarity of 2.93). The submitters titrated against salicylaldehyde phenylhydrazone following the procedure described by Love and Jones.[4]

4. The reaction is >98% complete as determined by ^{1}H NMR analysis as follows: A 0.1 mL aliquot of the reaction mixture is added to 1 mL of $CDCl_3$ and 0.5 mL of saturated aqueous ammonium chloride, shaken, then the bottom organic phase is filtered through a cotton plug into an NMR tube

for analysis. The doublet of the CH_2 group at 2.9 ppm and the quartet of the CH_2 group of the ethyl group at 4.2 ppm of the starting material compared to the olefinic resonances of the product at 5.7 and 6.8 ppm are diagnostic for reaction completion.

5. When ammonium chloride solution is first added to the reaction mixture a white precipitate is formed; this subsequently dissolves when addition of all the ammonium chloride solution is complete, giving a clear solution. The mixture warms to 30 °C during the quench with no external cooling.

6. The product **1** is volatile and the temperature of the water bath should not be increased above 20 °C while the solution is being concentrated on the rotary evaporator.

7. A 3-cm glass column is wet-packed (pentane) with 80 g of silica gel topped with 0.5 cm of sand. The crude reaction product **1** is loaded neat on the column and eluted with 500 mL of a 5:1 mixture of pentane:diethyl ether, taking 50 mL fractions. The chromatography is monitored by TLC (R_f = 0.3 in pentane:diethyl ether, 50:1). The product elutes in fractions 3-5. The eluent is concentrated by rotary evaporation (20 °C water bath, 150 mm Hg, decreased to 20 mm Hg) (Note 6) to constant weight. The pure product **1** contains 0.7 wt% residual tetrahydrofuran by ^{1}H NMR analysis.

8. The geometric isomer purity of **1** is assessed by peak integration of the ^{13}C-^{1}H satellite peaks corresponding to C(2)*H* of the (*E*)-isomer (δ_H 5.68 ppm) against the ^{12}C-^{1}H peaks corresponding to C(2)*H* and C(3)*H* of the (*Z*)-isomer [δ_H 5.56 ppm (dd, *J* 11.5, 1.0 Hz) and 5.90 ppm (dd, *J* 11.5, 9.9 Hz), respectively] in the quantitative ^{1}H NMR spectra of the crude reaction mixture and the pure product.[5]

9. *t*-Butyl (*E*)-4-methylpent-2-enoate **1** has the following physical and spectroscopic data: ν_{max} (thin film) 2968, 2873, 1715, 1652, 1460, 1367, 1301, 1155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.04 (6 H, d, *J* = 6.8 Hz, C(4)*Me*$_2$), 1.48 (9 H, s, C*Me*$_3$), 2.40–2.45 (1 H, m, C(4)*H*), 5.68 (1 H, dd, *J* = 15.7, 1.5 Hz, C(2)*H*), 6.83 (1 H, dd, *J* = 15.7, 6.6 Hz, C(3)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5 (C(4)*Me*$_2$), 28.4 (C*Me*$_3$), 31.0 (*C*(4)), 80.1 (*C*Me$_3$), 120.5 (*C*(2)), 154.3 (C(3)), 166.6 (*C*(1)); MS (ESI$^+$) *m/z* 193 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) *m/z* calcd. for $C_{10}H_{18}NaO_2^+$ ([M+Na]$^+$) 193.1199; found 193.1205.

10. (*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine was obtained from Sigma-Aldrich and used without purification. The enantiomeric excess

quoted by the vendor was 97.1%. The submitters prepared it from reductive alkylation of (*R*)-α-methylbenzylamine (Acros Organics, >99%, 99% ee).

11. The following materials used in step B were obtained from Sigma-Aldrich: tetrahydrofuran (anhydrous, >99.9%, inhibitor-free), 2.5 M butyllithium in hexanes, citric acid (ACS reagent grade, >99.5%), dichloromethane (ACS reagent grade, >99.5%), ethyl acetate (ACS reagent grade, >99.5%), and hexanes (ACS reagent grade, >98.5%). Ammonium chloride, sodium bicarbonate, and sodium sulfate were sourced from Fisher.

12. *n*-Butyllithium was titrated against diphenylacetic acid before use as follows: Diphenylacetic acid (0.766 g, 3.61 mmol) is dissolved in tetrahydrofuran (10 mL) in a 25-mL round-bottomed flask equipped with a 0.5 cm oval Teflon-coated magnetic stir bar and a septum pierced with an 18-gauge nitrogen-inlet needle connected to a nitrogen line and gas bubbler. The stirred solution is cooled in an ice-bath. *n*-Butyllithium is added dropwise via a weighed syringe until a yellow color persists. The syringe is weighed before and after addition (difference 1.05 g, 1.52 mL, corresponding to a solution molarity of 2.37).

13. The syringe is weighed before and after addition to determine the amount of *n*-butyllithium and *t*-butyl (*E*)-4-methylpent-2-enoate **1** added.

14. With the addition of the first few drops of *n*-butyllithium the reaction mixture turns from clear and colorless to clear and light pink, and darkens as further *n*-butyllithium solution is added.

15. With the addition of the first few drops of *t*-butyl (*E*)-4-methylpent-2-enoate **1** solution, the reaction mixture turns from dark pink to bright orange, which persists as further *t*-butyl (*E*)-4-methylpent-2-enoate **1** solution is added. The solution remains orange for the rest of the reaction.

16. The reaction is followed by ^{1}H NMR as follows. A 0.1 mL reaction aliquot is quenched into a mixture of 1 mL of $CDCl_3$ and 1 mL of saturated aqueous ammonium chloride. The organic layer is separated and filtered through a plug of sodium sulfate and cotton into an NMR tube. The olefin peaks at 5.7 and 6.8 ppm of the starting material are compared to the product peak at 3.2 ppm to assess reaction completion. After a 1.5 h reaction time, 13% starting material remained.

17. The submitters quenched the reaction at −78 °C after 2 h. In cases where the intermediate lithium β-amino enolate is unstable with respect to retro-conjugate addition at elevated temperatures, the quench should be performed at −78 °C.

18. ^{1}H NMR analysis of the crude product indicated about 1% unreacted starting material.

19. The citric acid wash removes >95% of the unreacted (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine.

20. A 3-cm glass column is wet-packed (hexanes) with silica gel (100 g) topped with 0.5 cm sand. The crude reaction product **2** is dissolved in dichloromethane (10 mL), loaded on the column, and eluted with 1 L of a 97:3 mixture of hexanes:ethyl acetate, taking 75 mL fractions. The chromatography is monitored by TLC (R_f = 0.5 in ethyl acetate:hexanes, 5:95). The product elutes in fractions 3-10. The eluent is concentrated by rotary evaporation (40 °C water bath, 20 mmHg) to constant weight.

21. *t*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methyl-pentanoate **2** has the following physical and spectroscopic data: $[\alpha]^{22}_{D}$ −1.7 (*c* 2.0, chloroform); IR (thin film) ν_{max} 3102, 3080, 2973, 1947, 1875, 1807, 1731, 1601, 1454, 1369, 950 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3 H, d, *J* = 6.8 Hz, C(4)*Me*$_A$), 1.12 (3 H, d, *J* = 6.8 Hz, C(4)*Me*$_B$), 1.41 (3 H, d, *J* = 7.1 Hz, C(α)*Me*), 1.42 (9 H, s, C*Me*$_3$), 1.67–1.73 (1 H, m, C(4)*H*), 1.81 (1 H, dd, *J* = 16.1, 2.0 Hz, C(2)*H*$_A$), 1.97 (1 H, dd *J* = 16.1, 9.5 Hz, C(2)*H*$_B$), 3.24–3.28 (1 H, m, C(3)*H*), 3.49 (1 H, d, *J* = 15.0 Hz, NC*H*$_A$), 3.77 (1 H, d, *J* = 15.0 Hz, NC*H*$_B$), 3.74–3.81 (1 H, m, C(α)*H*), 7.22–7.48 (10 H, m, *Ph*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.8 (C(4)*Me*$_A$), 20.4 (C(α)*Me*), 21.3 (C(4)*Me*$_B$), 28.2 (C*Me*$_3$), 33.0 (*C*(4)), 36.5 (*C*(2)), 51.4 (N*C*H$_2$), 58.0 (*C*(3)), 58.2 (*C*(α)), 80.1 (*C*Me$_3$), 126.8, 127.1 (*p-Ph*), 128.2, 128.4, 128.5 (2 degenerate peaks) (*o*-, *m-Ph*), 141.8, 142.1 (*i-Ph*), 172.6 (*C*(1)); MS (ESI$^+$) *m/z* 382 ([M+H]$^+$, 100%); HRMS (ESI$^+$) calcd. for $C_{25}H_{36}NO_2^+$ ([M+H]$^+$) 382.2741; found 382.2742. An analytically pure sample was prepared by dissolving 200 mg of the product oil in 5 mL of 50:50 pentane:diethyl ether, filtering through a 0.45 micron PTFE syringe filter, concentrating under vacuum, and vacuum drying at 50 °C for 20 h: Anal. calcd. for $C_{25}H_{35}NO_2$: C, 78.70; H, 9.25; N, 3.67; found: C, 78.34; H, 9.15; N, 3.70.

22. The following materials used in step C were obtained from Sigma-Aldrich: methanol (ACS reagent grade, 99.8%), triethylamine (>99.5%, SureSeal bottle), ethyl acetate (ACS reagent grade, >99.5%), and hexanes (ACS reagent grade, >98.5%). 20% Palladium hydroxide (wet) on carbon was sourced from BASF.

23. The reaction was monitored by hydrogen pressure drop. Hydrogen uptake was complete in 1 h, but the hydrogenation was continued for 6 h to ensure complete conversion.

24. Once the cake is thoroughly rinsed with methanol to wash off all product, it is wetted with water and transferred as a water slurry to a PTFE bottle to hold the palladium waste for recycling.

25. A 3-cm glass column is wet-packed (1.5% triethylamine in hexanes) with silica gel (150 g) topped with 0.5 cm sea sand. The crude product is loaded neat to the column and the flask rinsed with dichloromethane (2 x 5 mL) to ensure complete transfer. The column is eluted as follows: (1) 400 mL of 1:3 ethyl acetate:hexanes containing 1.5% triethylamine, (2) 400 mL of 1:1 ethyl acetate:hexanes containing 1.5% triethylamine, (3) 400 mL ethyl acetate containing 2 % triethylamine, taking 50 mL fractions. The product **3** (R_f = 0.25 in 1:2 ethyl acetate:hexanes containing 1.5% triethylamine, visualized using both potassium permanganate (yellow spot on purple background) and iodine) is obtained in fractions 9-20, which are concentrated by rotary evaporation (40 °C water bath, 20 mmHg) in a 500 mL round-bottomed flask to constant weight (7.82 g, 83% yield). ^{1}H NMR analysis indicated <1 % ethyl acetate in the product. Fractions 8 and 21-25 were combined and concentrated to constant weight (0.55 g). The purity of these fractions was assessed by ^{1}H NMR as approx. 80% (0.44 g corrected for purity, 5% yield).

26. *t*-Butyl (*S*)-3-amino-4-methylpentanoate **3** has the following physical and spectroscopic data: $[\alpha]^{22}_D$ −24 (*c* 2.0, chloroform); IR (thin film) ν_{max} 3387, 3321, 2964, 2933, 2874, 1727, 1597, 1466, 1392, 1367, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3 H, d, *J* = 6.7 Hz, C(4)*Me*$_A$), 0.91 (3 H, d, *J* = 6.7 Hz, C(4)*Me*$_B$), 1.30 (2 H, br s, N*H*$_2$), 1.45 (9 H, s, C*Me*$_3$), 1.58-1.63 (1 H, m, C(4)*H*), 2.14 (1 H, dd, *J* = 15.3, 10.0 Hz, C(2)*H*$_A$), 2.37 (1 H, dd *J* = 15.3, 3.5 Hz, C(2)*H*$_B$), 2.98 (1 H, ddd, *J* = 10.0, 15.3, 3.5 Hz, C(3)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 19.0 (C(4)*Me*$_2$), 28.3 (C*Me*$_3$), 33.5 (*C*(4)), 41.2 (*C*(2)), 53.8 (*C*(3)), 80.6 (*C*Me$_3$), 172.6 (*C*(1)); MS (ESI$^+$) *m/z* 210 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) *m/z* calcd. for $C_{10}H_{21}NNaO_2^+$ ([M+Na]$^+$) 210.1465; found 210.1469. An analytical sample is prepared by re-chromatographing a portion of the rich cut of the original chromatography, as follows: silica gel (15 g) is wet-packed (3:1 hexanes:ethyl acetate containing 1.5% triethylamine) in a 1-cm column topped with 0.5 cm sand. Compound **3** (0.53 g) is added neat to the column and is eluted sequentially with 30 mL 3:1 hexanes: ethyl acetate containing 1.5% triethylamine, 60 mL 1:1 hexanes: ethyl acetate containing 1.5% triethylamine, and 90 mL 1:2 hexanes: ethyl acetate, taking 10 mL fractions. Fractions 6 and 7 are combined, filtered through a 0.45 micron syringe filter

and concentrated by rotary evaporation to constant weight (290 mg). Anal. calcd. for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48; found: C, 63.87; H, 11.20; N, 7.48.

27. The following materials used in step D were sourced from Sigma-Aldrich and used as received: trifluoroacetic acid (ReagentPlus, >99%), dichloromethane (ACS reagent grade, >99.5%), 2 M hydrogen chloride in diethyl ether, Dowex resin 50WX4-200, and racemic β-leucine. Ammonium hydroxide was sourced from Fisher.

28. ^{1}H NMR analysis (CD_3OD) indicated approx 8% unreacted starting material.

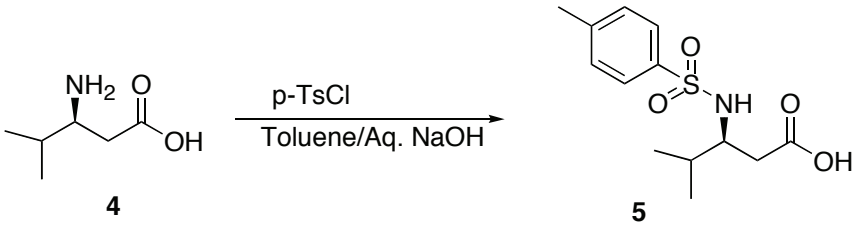
29. ^{1}H NMR analysis (CD_3OD) indicated approx 4% unreacted starting material and an equimolar quantity of diethyl ether.

30. A glass column (3 cm internal diameter) is wet-packed (water) with Dowex® 50WX4-200 ion-exchange resin (100 g). The column is equilibrated by sequential elution with water (200 mL), methanol (200 mL), water (200 mL), 1 M aqueous hydrogen chloride solution (200 mL) and water (500 mL). The crude reaction product **4** is diluted with distilled water (20 mL) and the resultant solution is loaded on to the column. The column is eluted with 100 mL of distilled water followed by 800 mL of 1 M aqueous ammonium hydroxide solution, taking 150 mL fractions. The fractions containing product are identified by spotting on a silica TLC plate and staining with potassium permanganate solution (yellow spot on purple background upon heating). Fractions 3-5 are concentrated by rotary evaporation (60 °C water bath, 20 mmHg) to constant weight in a 500-mL round-bottomed flask to afford 4.19–4.30 g (88-93% yield) of product **4**. This material contained 0.5 wt% water by Karl Fisher titration. Fractions 2, 6, and 7 are combined and concentrated to afford 4.75 g of a white solid that contained no product by ^{1}H NMR (peak at –75.5 ppm by ^{19}F analysis indicates the presence of a trifluoromethyl group).

31. Due to lack of a chromophore and lack of volatility, the purity of **4** could not be assessed by HPLC or GC. Therefore, the weight percent purity of **4** recovered from the ion-exchange chromatography was determined by ^{1}H NMR using both ethylene glycol and 1,2-dimethoxyethane as internal standards, as follows. β-Leucine (41.1 mg, 31.3 μmol) and 1,2-dimethoxyethane (67.1 mg, 74.5 μmol) are accurately weighed in a 5-mm NMR tube, then D_2O (0.7 mL) is added. The ^{1}H NMR analysis is carried out with a 5 second delay to ensure complete relaxation (10 second delay gave the same results, while a 0.1 second delay gave a 6% lower response for 1,2-

dimethoxyethane). The dimethyl resonances (apparent triplet) of the product at 0.9 ppm are integrated vs. the 4 CH_2 protons at 3.6 ppm for 1,2-dimethoxyethane. The average of several integrations gave a molar ratio of product:standard of 0.414 vs. the 0.420 ratio of the weighed samples, indicating a wt % of 98.6%. An additional weighing was carried out with 1,2-dimethoxyethane and 2 weighings and NMR analyses were carried out using ethylene glycol as standard, providing an average wt% assay of 98.4 ± 0.7% for material isolated directly from the ion-exchange chromatography.

32. A chiral HPLC assay was developed on the β-leucine *N*-*p*-toluenesulfonamide derivative **5.** The derivatization procedure is as follows:



4 **5**

β-Leucine (108 mg, 0.82 mmol), *p*-toluenesulfonyl chloride (1.48 g, 7.8 mmol, 10 equiv), 2 N sodium hydroxide (7 mL, 14 mmol), toluene (7 mL), and a 1-cm oval Teflon-coated magnetic stir bar are added to a 50-mL round-bottomed flask sealed with a septum through which is inserted a thermocouple thermometer probe and an 18-gauge syringe needle connected to a nitrogen line and gas bubbler. The mixture is warmed to 55–60 °C using a heating mantle and vigorously stirred for 22 h at this temperature. The mixture is cooled, and transferred to a 50-mL separatory funnel along with water (5 mL) and toluene (5 mL). The layers are separated. 6 M aqueous hydrogen chloride (3 mL) is added to the aqueous layer. The mixture is transferred to a 50-mL separatory funnel and extracted with diethyl ether (2 x 15 mL). The organic layer is washed with water (10 mL), then filtered through a bed of magnesium sulfate and concentrated by rotary evaporation (40 °C water bath, 20 mmHg) to constant weight to afford (*S*)-3-[*N*-(*p*-toluenesulfonyl)amino]-4-methylpentanoic acid **5** (132 mg, 56% yield). This non-purified material is used to determine the optical purity of β-leucine using the chiral SFC method described below. A portion of **5** is recrystallized (90 mg dissolved in 3 mL toluene at 80 °C, cooled to ambient temperature, held for 15 h, filtered to afford 70 mg) to provide **5** with the following physical and spectroscopic data: mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (6 H, app t, J = 6.7 Hz, C(4)Me_2), 1.88 (1 H, app octet, J = 6.8 Hz, C(4)*H*), 2.45 (1 H, dd, J = 16.2, 5.7 Hz, C(2)H_A), 2.46 (3 H, s,

CH_3), 2.54 (1 H, dd, J = 16.2, 5.0 Hz, C(2)H_B), 3.32–3.41 (1 H, m, C(3)*H*), 5.17 (1 H, d, J = 9.2 Hz, N*H*), 7.30–7.34 (2 H, m, *Ar)*, 7.78–7.81 (2 H, m, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.6, 19.0 (C(4)*Me*$_2$), 21.6 (Ar*Me*), 31.6 (*C*(4)), 36.1 (*C*(2)), 56.0 (*C*(3)), 127.2, 129.7, 137.8, 143.5 (*Ar*), 175.8 (*C*(1)). The racemic derivative was similarly prepared and recrystallized from toluene, providing racemic **5** with mp 117–119 °C. A chiral supercritical fluid chromatography (SFC) method was developed for chiral analysis of the 4-toluenesulfonamide derivative (**5**): AD-H (250 x 4.6 mm, 5 μm) column, gradient method using methanol with 25mM *i*-butylamine, 4% methanol /CO_2 for 4 min then ramp at 6%/min to 40% methanol /CO_2, hold at 40% for 5 minutes, 3.0 mL/min, 200 bar, 35 °C, 230 nm, 15 minutes run time; minor enantiomer elutes at 7.3 min, major at 8.0 min. The enantiomeric excess of the derivatized, non-recrystallized **5** derived from β-leucine isolated directly from the resin column was 96% ee. Since the enantiomeric excess of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine used in the conjugate addition was 97%, the reaction diastereoselectivity of this step was 99%.

33. An analytically pure sample is prepared by recrystallization. β-Leucine **4** (1.04 g) is added to methanol (20 mL) in a 100-mL round bottomed flask with a 1-cm oval Teflon-coated stir bar and warmed in a 50 °C oil bath with stirring to dissolve the solids. The solution is quickly poured into a 50-mL syringe and hot filtered through a 0.45 micron PTFE syringe filter into a 100-mL round-bottomed flask. The solution is concentrated by rotary evaporation (40 °C water bath, 20 mmHg) to 5 mL. Partial crystallization occurs during this concentration step. After concentration, a 1-cm oval Teflon-coated stir bar is added to the flask, then *t*-butyl methyl ether (15 mL) is added at 22 °C over 20 min to the stirred mixture, resulting in further crystallization. After the addition is complete, the mixture is stirred for 1 h at 21–22 °C, then vacuum filtered through a 30-mL medium porosity sintered glass funnel, washed with *t*-butyl methyl ether (5 mL) and dried in a vacuum oven for 3 h at 60 °C to afford (*S*)-3-amino-4-methylpentanoic acid **4** (0.82 g, 79% yield) as a white crystalline powder. The ee of the recrystallized β-leucine is only marginally improved over the crude material (97 vs 96%).

34. (*S*)-3-Amino-4-methylpentanoic acid **4** purified by recrystallization has the following physical and spectroscopic data: ee 97%; mp 197–198 °C, lit.[6a] 182 °C, lit.[6b] 201-202.5 °C, lit.[6c] 202–210 °C, lit.[6d] 206 °C, lit.[6e] 212 °C; $[\alpha]_D^{20}$ –53 (*c* 2.0, water), –52 (c 0.5, water), –40 (c 0.5, 1.N hydrochloric

acid), lit.[6a] +40.3 [(*R*)-isomer, *c* 1, water], lit.[6b] +55.2 [(*R*)-isomer, *c* 1, water], lit.[6c] –39.2 [(*S*)-isomer, c 0.5, water], lit.[6d] +47 [(*R*)-isomer, *c* 1, water], lit.[6e] +52.3 [reported as (*S*)-isomer, but drawn as (*R*)-isomer, c 0.6 water], lit.[6f] +51.5 [reported as (*S*)-isomer, c 0.6, water]; IR (KBr) ν_{max} 3397, 2965, 2936, 1649, 1621, 1467, 1326, 1262 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 0.92 (6 H, app t, *J* = 7.0 Hz, C(4)*Me*$_2$), 1.88 (1 H, app octet, *J* = 6.8 Hz, C(4)*H*), 2.33 (1 H, dd, *J* = 16.7, 9.3 Hz, C(2)H_A), 2.50 (1 H, dd *J* = 16.7, 4.2 Hz, C(2)H_B), 3.24–3.28 (1 H, m, C(3)*H*); ^{13}C NMR (100 MHz, D_2O) δ: 17.3, 17.4 (C(4)*Me*$_2$), 30.0 (*C*(4)), 36.0 (*C*(2)), 54.9 (*C*(3)), 178.5 (*C*(1)); *m/z* (ESI^+) 154 ($[M+Na]^+$, 100%); HRMS (ESI^+) *m/z* calcd. for $C_6H_{13}NNaO_2^+$ ($[M+Na]^+$) 154.0838; found 154.0841; Anal. calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68; found: C, 54.84; H, 9.95; N, 10.64.

Safety and Waste Disposal Information

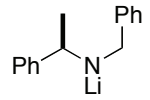
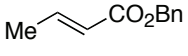
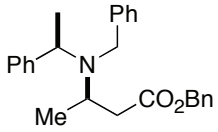
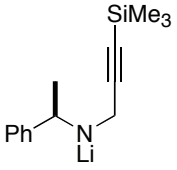
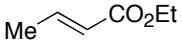
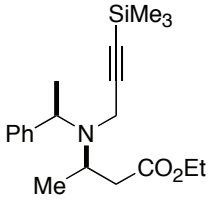
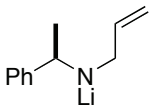
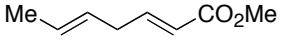
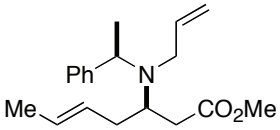
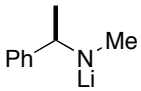
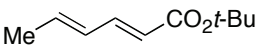
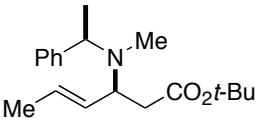
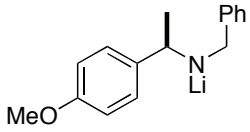
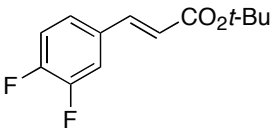
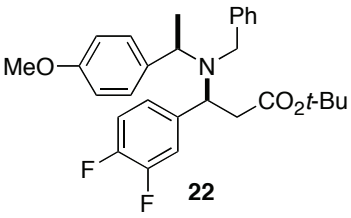
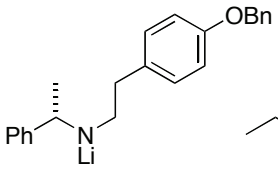
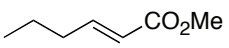
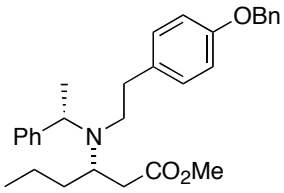
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC; 1995.

3. Discussion

The conjugate addition reaction was first reported by Komnenos in 1883, who demonstrated the 1,4-addition of diethyl sodiomalonate to diethyl ethylidenemalonate.[7] A range of carbon and heteroatom based nucleophiles have since been shown to participate in this reaction manifold. In 1991, Davies and Ichihara described the highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **6** to benzyl crotonate **12**, which gave β-amino ester (3*R*,α*R*)-**18** in 95% de. Global hydrogenolytic *N*-deprotection of β-amino ester mediated by Pearlman's catalyst [$Pd(OH)_2$/C] proceeded under 5 atm of hydrogen to give the corresponding free β-amino acid, (*R*)-3-aminobutanoic acid, in quantitative yield and >95% ee.[8] This methodology has since been developed into a generally applicable synthesis of either enantiomer of homochiral β-amino acids, via conjugate addition of homochiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated *t*-butyl ester,[9] followed by hydrogenolytic *N*-debenzylation and ester hydrolysis.[10] A range of homochiral lithium amides that are readily derived from commercially available, homochiral α-methylbenzylamine derivatives has been developed,

which allow for either differential *N*-deprotection or further elaboration in synthesis. All members of this family of lithium amides undergo highly diastereoselective conjugate addition to a wide range of α,β-unsaturated esters and amides to give the corresponding diastereo- and enantiomerically pure, homochiral β-amino ester or amide product (Table 1). This lithium amide conjugate addition methodology has been expanded to allow the stereoselective, in situ elaboration of the intermediate lithium (*Z*)-β-amino enolate to give access to homochiral α-substituted-β-amino esters; it has been employed for the synthesis of hundreds of β-amino esters, amides and acids in enantiomerically pure form, and has found utility in a plethora of synthetic applications, including total syntheses, initiation of tandem asymmetric processes, and molecular recognition phenomena. Its scope and utility was comprehensively reviewed in 2005.[11]

Table 1 Representative members of the lithium amide family **6-11** and α,β-unsaturated esters **12-17** for conjugate addition.

Lithium amide	α,β-Unsaturated carbonyl	Conjugate addition product	Yield (de)	Reference
 (*R*)-**6**	 **12**	 **18**	88 (95)	8
 (*R*)-**7**	 **13**	 **19**	72 (90)	12
 (*R*)-**8**	 **14**	 **20**	73(>96)	13
 (*R*)-**9**	 **15**	 **21**	71 (91)	14
 (*R*)-**10**	 **16**	 **22**	86 (90)	15
 (*S*)-**11**	 **17**	 **23**	82 (>97)	16

1. Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: steve.davies@chem.ox.ac.uk.

2. The checker would like to thank Zainab Pirzada for development of the chiral HPLC assay, Scott Hoerrner and Anthony Houck for assistance with the hydrogenation experiments, and Mirlinda Biba for determination of the specific rotations.

3. For a representative experimental procedure see: Harwood, L. M.; Moody, C. J.; Percy, J. M. *Experimental Organic Chemistry – Standard and Microscale*, **1999**, 2nd ed, Blackwell Publishing, p. 569-570.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

t-Butyl diethylphosphonoacetate (27784-76-5)
Methylmagnesium bromide (75-16-1)
Isobutyraldehyde; 2-methylpropionaldehyde; 2-methylpropanal (78-84-2)
t-Butyl (*E*)-4-methylbut-2-enoate (87776-18-9)
(*R*)-α-Methylbenzylamine; (*R*)-α-phenylethylamine; (*R*)-1-phenylethylamine (3886-69-9)
(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine; (*R*)-*N*-benzyl-α-phenylethylamine; (*R*)-*N*-benzyl-1-phenylethylamine (38235-77-7)
Butyllithium; lithium-1-butanide (109-72-8)
t-Butyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amine]-4-methylpentanoate (38235-77-7)
Palladium hydroxide on carbon; Pearlman's catalyst (12135-22-7)
t-Butyl 3-amino-4-methylpentanoate (202072-47-7)
Trifluoroacetic acid (76-05-1)
(*S*)-3-Amino-4-methylpentanoic acid; (*S*)-β-homovaline; (*S*)-β-leucine (40469-85-0)
(*S*)-3-[*N*-(*p*-toluenesulfonyl)amino]-4-methylpentanoic acid (936012-07-6)

Steve Davies obtained a B.A. in Chemistry (1973) and D.Phil. in Organic Synthesis (1975) at the University of Oxford, following which he undertook postdoctoral fellowship positions with Professor M. L. H. Green at Oxford and with Professor Sir Derek Barton in France. He began his independent research career first as a member of the C.N.R.S. (1978-80) in France, followed by appointment as a Lecturer in Organic Chemistry (1980-96), Professor of Chemistry (1996-2006), and Chairman of Chemistry and Waynflete Professor of Chemistry (2006 to date) at Oxford. The development of novel and efficient methods for the production of enantiomerically pure compounds has formed the main focus of his research; highlights include stereoselective organometallic chemistry, the development of chiral relay networks, and homochiral ammonia equivalents.

Paul Roberts graduated with an M.Chem. from Jesus College, Oxford, in 2000, which was followed by a D.Phil. with Professor Steve Davies in the area of the asymmetric synthesis of piperidine alkaloids employing a ring closing metathesis approach. In 2005, he took up a post-doctoral position with Professor Davies at Oxford, where his research interests centre upon natural product synthesis and the development of new stereoselective methodologies, for example to effect the chemo- and stereoselective functionalisation of allylic amines with a range of electrophilic reagents.

After graduating from Keio University, Japan, in 2000, Ai (Matsuno) Fletcher studied for a Ph.D. at Imperial College London under supervision of Dr Chris Braddock with an O.R.S. award. During her Ph.D. she developed two novel methodologies: “one-pot” cascade catalysis of allylic isomerisation and olefin metathesis, and the cyclopropyl methyl silane terminated Prins reaction. Since completing her Ph.D. in 2004, she explored a range of chemistry, such as enantioselective synthesis of DNA analogues and palladium catalysis as a post-doctoral researcher at the University of Regensburg, and at the University of Bath. In 2007 she joined the group of Professor Steve Davies in Oxford, where she has been involved with the development of asymmetric synthetic methodology and novel ammonia-based energy technology.

2009-067
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nmr400b c-13

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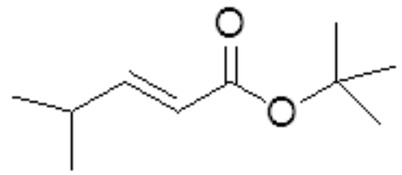

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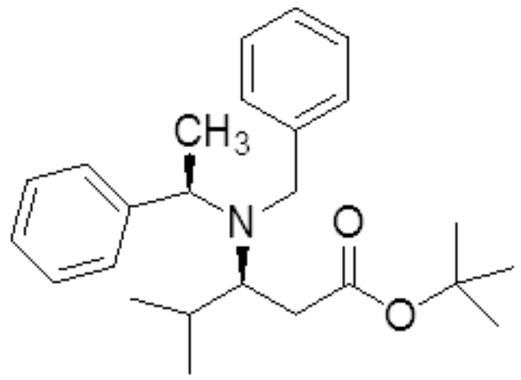
======== CHANNEL f1 ========
NUC1                13C
P1                 3.30 usec
PL1                6.00 dB
SFO1        100.5584512 MHz

======== 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          100.5473716 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



172.65
142.14
141.80
128.51
128.45
128.16
127.11
126.78
80.07
77.54
77.43
77.22
76.91
58.19
57.97
51.42
36.48
33.05
28.23
21.28
20.38
19.83

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

2009-070
t-Bu ester amine
nmr400b c-13

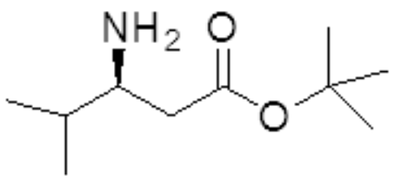
```
Current Data Parameters
NAME           2009-070
EXPNO                 7
PROCNO                1

F2 - Acquisition Parameters
Date_          20090808
Time              13.27
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG           zgdc
TD               65536
SOLVENT          CDCl3
NS                3213
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          100.5473741 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



172.64

80.57
77.52
77.21
76.89

53.82

41.25

33.55

28.32

19.02
17.95

2009-095B
Derivatized beta-leucine
nmr400b c-13

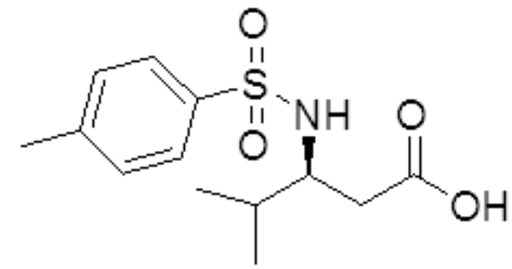
```
Current Data Parameters
NAME           2009-095
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20091101
Time              14.57
INSTRUM           spect
PROBHD   5 mm QNP  1H/1
PULPROG           zgdc
TD               65536
SOLVENT          CDCl3
NS                4331
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                4.00 usec
PL1               0.00 dB
SFO1        100.5584512 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2           100.00 usec
PL2             120.00 dB
PL12             24.50 dB
SFO2        399.8719994 MHz

F2 - Processing parameters
SI                32768
SF          100.5473910 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC               1.00
```



2009-092
beta-leucine
nmr400b c-13

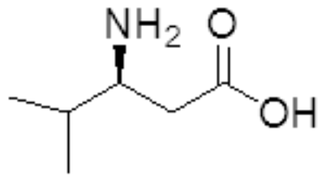
```
Current Data Parameters
NAME           2009-092
EXPNO                11
PROCNO                1

F2 - Acquisition Parameters
Date_           20091031
Time               12.40
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zgdc
TD                 65536
SOLVENT            CDCl3
NS                  1357
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                  4.00 usec
PL1                 0.00 dB
SFO1         100.5584512 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2               120.00 dB
PL12               24.50 dB
SFO2         399.8719994 MHz

F2 - Processing parameters
SI                 32768
SF           100.5473910 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



2009-067
fr 3-5
nmr400b h-1

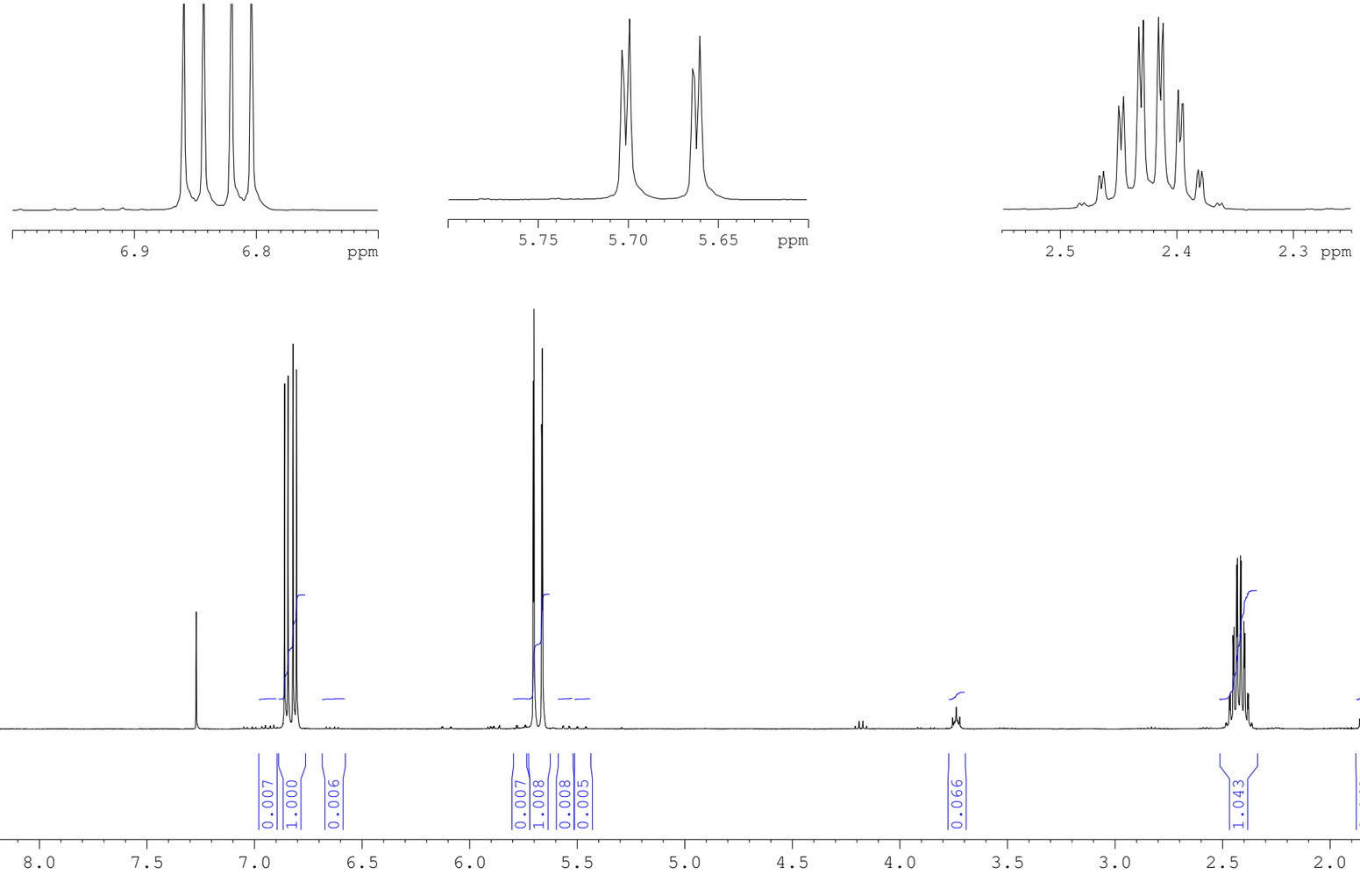
```
Current Data Parameters
NAME            2009-067
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090801
Time               10.43
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                  80.6
DW                 76.000 usec
DE                  7.00 usec
TE                 300.1 K
D1            0.10000000 sec
TD0                    1

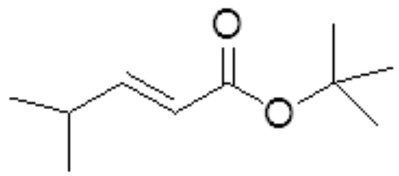
======== CHANNEL f1 ========
NUC1                  1H
P1                 11.50 usec
PL1                 6.00 dB
SFO1         399.8724694 MHz

F2 - Processing parameters
SI                 16384
SF           399.8700087 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	7.2705	2907.2549	1.07
2	6.8599	2743.0683	3.21
3	6.8436	2736.5504	3.22
4	6.8207	2727.3934	3.56
5	6.8044	2720.8755	3.27
6	5.7036	2280.6986	3.20
7	5.6999	2279.2191	3.83
8	5.6643	2264.9837	2.88
9	5.6607	2263.5442	3.46
10	2.4500	979.6815	0.86
11	2.4463	978.2020	0.93
12	2.4331	972.9237	1.49
13	2.4294	971.4442	1.57
14	2.4162	966.1659	1.58
15	2.4124	964.6464	1.57
16	2.3992	959.3681	0.98
17	2.3955	957.8886	0.92
18	1.4780	591.0079	100.00
19	1.0678	426.9812	0.64
20	1.0553	421.9828	36.36
21	1.0383	415.1850	38.12
22	1.0328	412.9857	2.65



2009-076
fr 2-4
nmr500d h-1



```
Current Data Parameters
NAME           2009-076
EXPNO                 4
PROCNO                1

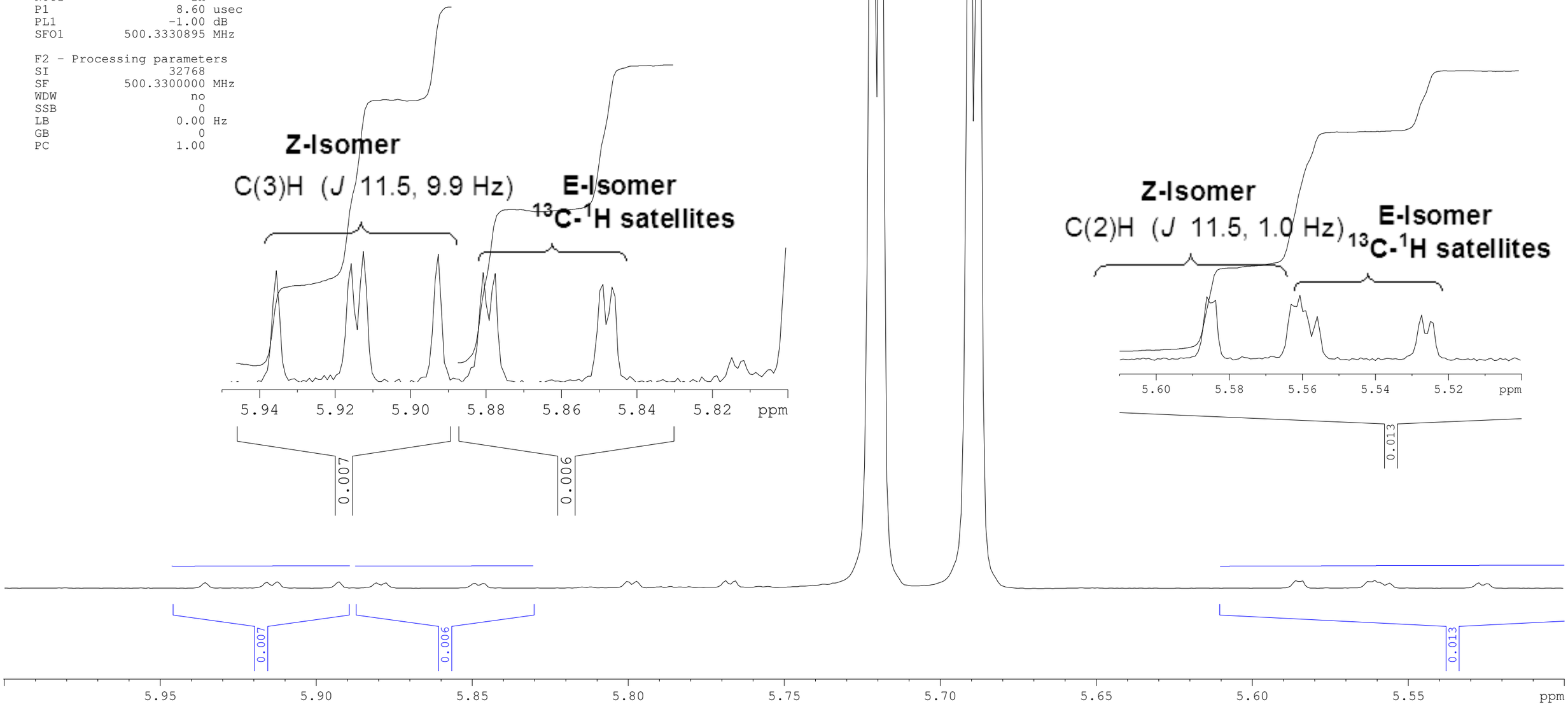
F2 - Acquisition Parameters
Date_          20090822
Time              14.07
INSTRUM           spect
PROBHD   5 mm PABBI 1H-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    4
SWH           13020.833 Hz
FIDRES         0.198682 Hz
AQ             2.5166323 sec
RG                   64
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          500.3300000 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	5.9360	2969.9589	0.12
2	5.9162	2960.0523	0.13
3	5.9129	2958.4013	0.14
4	5.8932	2948.5448	0.14
5	5.8811	2942.4908	0.11
6	5.8782	2941.0398	0.12
7	5.8497	2926.7804	0.10
8	5.8468	2925.3294	0.10

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	5.5863	2794.9935	0.17
2	5.5611	2782.3852	0.17
3	5.5564	2780.0336	0.11
4	5.5278	2765.7242	0.11
5	5.5250	2764.3232	0.09



2009-079
conjugate addition product
chromatographed
Fr 3-8
nmr400b h-1

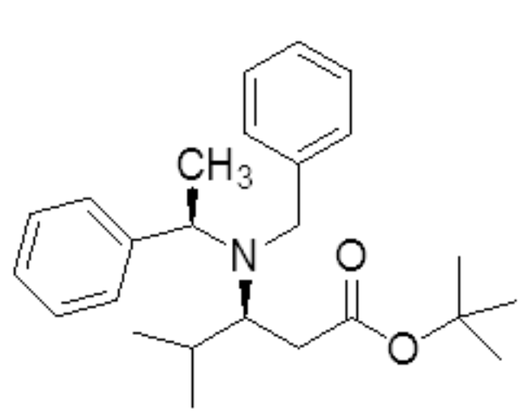
Current Data Parameters
NAME 2009-079
EXPNO 1
PROCNO 1

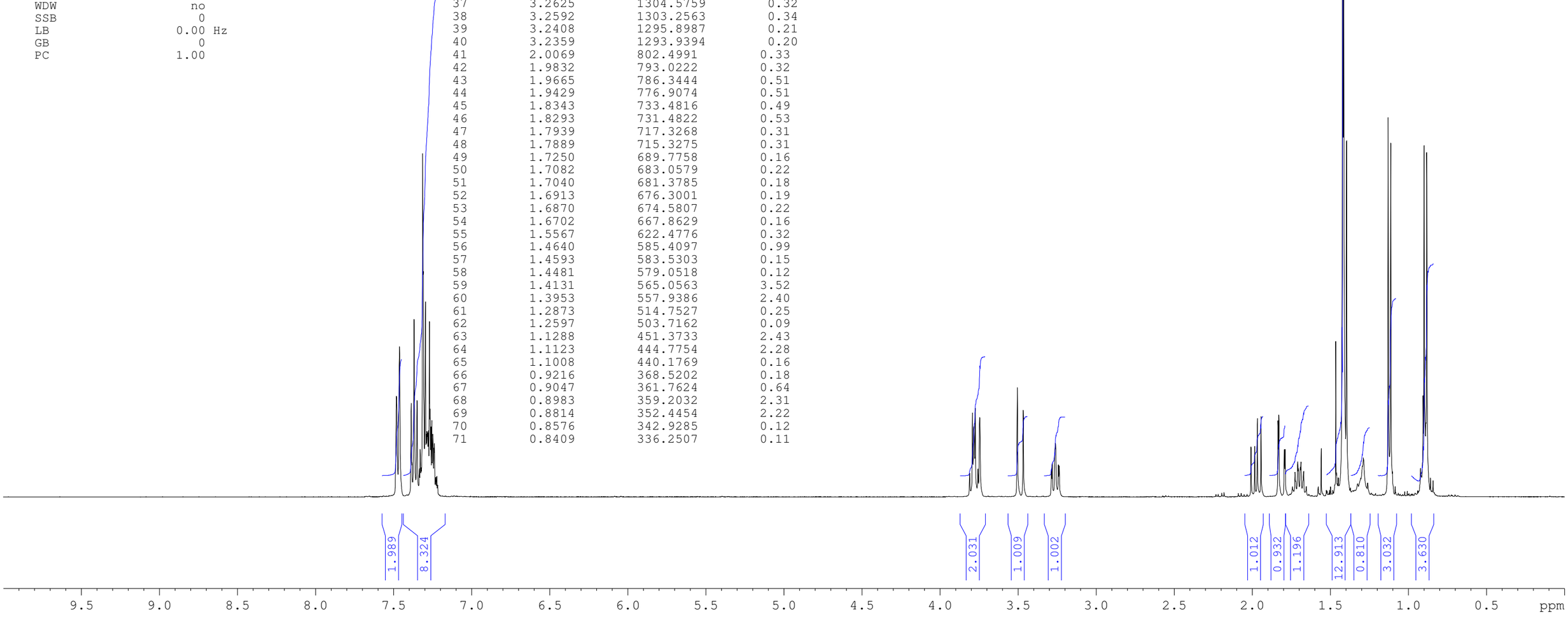
F2 - Acquisition Parameters
Date_ 20090830
Time 14.33
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 64
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 128
DW 76.000 usec
DE 7.00 usec
TE 300.0 K
D1 0.10000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 11.20 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]	Intensity
1	7.4810	2991.4275	0.64
2	7.4622	2983.9100	0.96
3	7.3870	2953.8398	0.60
4	7.3828	2952.1603	0.22
5	7.3688	2946.5621	1.13
6	7.3495	2938.8446	0.61
7	7.3349	2933.0065	0.18
8	7.3295	2930.8472	0.30
9	7.3233	2928.3680	0.18
10	7.3133	2924.3693	2.20
11	7.3098	2922.9698	1.45
12	7.2956	2917.2916	1.26
13	7.2899	2915.0124	0.41
14	7.2851	2913.0930	0.42
15	7.2814	2911.6135	0.41
16	7.2765	2909.6541	0.42
17	7.2704	2907.2149	1.12
18	7.2669	2905.8154	0.57
19	7.2605	2903.2562	0.45
20	7.2551	2901.0969	0.49
21	7.2484	2898.4178	0.40
22	7.2410	2895.4587	0.31
23	7.2387	2894.5390	0.34
24	7.2305	2891.2601	0.12
25	7.2279	2890.2204	0.11
26	7.2230	2888.2611	0.13
27	3.8095	1523.3048	0.15
28	3.7917	1516.1871	0.53
29	3.7826	1512.5483	0.45
30	3.7741	1509.1494	0.58
31	3.7563	1502.0317	0.18
32	3.7451	1497.5532	0.51
33	3.5039	1401.1045	0.71
34	3.4663	1386.0694	0.55
35	3.2859	1313.9329	0.18
36	3.2809	1311.9335	0.21
37	3.2625	1304.5759	0.32
38	3.2592	1303.2563	0.34
39	3.2408	1295.8987	0.21
40	3.2359	1293.9394	0.20
41	2.0069	802.4991	0.33
42	1.9832	793.0222	0.32
43	1.9665	786.3444	0.51
44	1.9429	776.9074	0.51
45	1.8343	733.4816	0.49
46	1.8293	731.4822	0.53
47	1.7939	717.3268	0.31
48	1.7889	715.3275	0.31
49	1.7250	689.7758	0.16
50	1.7082	683.0579	0.22
51	1.7040	681.3785	0.18
52	1.6913	676.3001	0.19
53	1.6870	674.5807	0.22
54	1.6702	667.8629	0.16
55	1.5567	622.4776	0.32
56	1.4640	585.4097	0.99
57	1.4593	583.5303	0.15
58	1.4481	579.0518	0.12
59	1.4131	565.0563	3.52
60	1.3953	557.9386	2.40
61	1.2873	514.7527	0.25
62	1.2597	503.7162	0.09
63	1.1288	451.3733	2.43
64	1.1123	444.7754	2.28
65	1.1008	440.1769	0.16
66	0.9216	368.5202	0.18
67	0.9047	361.7624	0.64
68	0.8983	359.2032	2.31
69	0.8814	352.4454	2.22
70	0.8576	342.9285	0.12
71	0.8409	336.2507	0.11





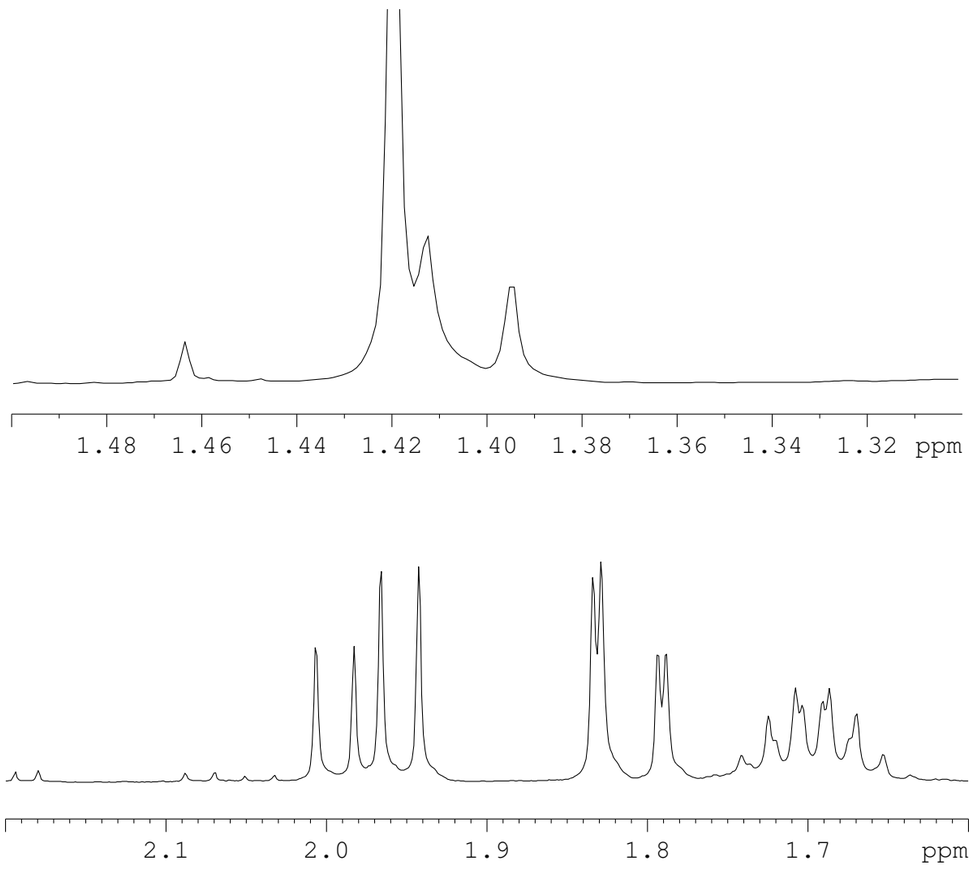
2009-079
conjugate addition product
chromatographed
Fr 3-8
nmr400b h-1

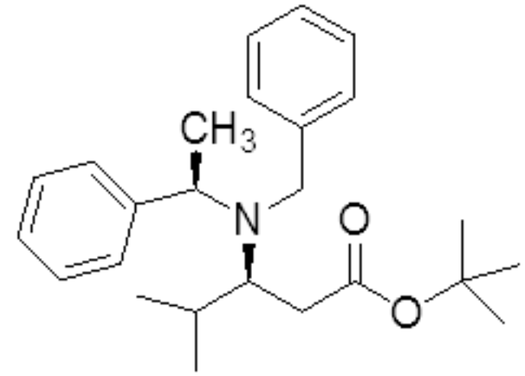
```
Current Data Parameters
NAME           2009-079
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20090830
Time              14.33
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                 128
DW                76.000 usec
DE                 7.00 usec
TE                300.0 K
D1           0.10000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                1H
P1                 11.20 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
```





2009-070
t-Bu ester amine
nmr400b h-1

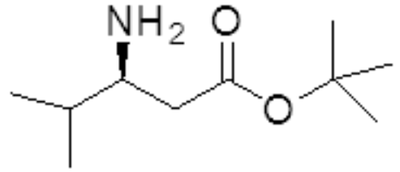
```
Current Data Parameters
NAME           2009-070
EXPNO                 6
PROCNO                1

F2 - Acquisition Parameters
Date_          20090808
Time              13.19
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                  128
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          399.8700090 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity
1	2.9897	1195.4914	0.22
2	2.9808	1191.9325	0.24
3	2.9768	1190.3330	0.24
4	2.9675	1186.6143	0.26
5	2.9657	1185.8945	0.28
6	2.9566	1182.2557	0.25
7	2.9526	1180.6562	0.26
8	2.9438	1177.1373	0.24
9	2.3910	956.0892	0.49
10	2.3822	952.5703	0.47
11	2.3525	940.6942	0.62
12	2.3437	937.1753	0.63
13	2.1654	865.8785	0.65
14	2.1412	856.2017	0.62
15	2.1270	850.5235	0.49
16	2.1028	840.8467	0.46
17	1.6243	649.5089	0.19
18	1.6113	644.3105	0.20
19	1.6071	642.6311	0.31
20	1.5943	637.5128	0.26
21	1.5902	635.8733	0.22
22	1.5774	630.7550	0.20
23	1.4488	579.3317	20.00
24	1.4434	577.1724	1.22
25	1.4035	561.2176	0.20
26	1.3189	527.3886	0.18
27	1.2887	515.3125	0.14
28	0.9129	365.0413	3.05
29	0.9030	361.0826	3.16
30	0.8959	358.2435	3.09
31	0.8860	354.2848	2.98
32	0.8811	352.3255	0.25

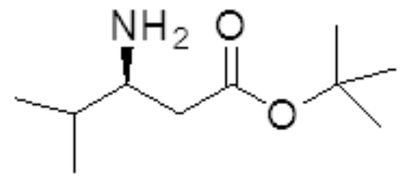


```
Current Data Parameters
NAME            2009-070
EXPNO                  6
PROCNO                 1

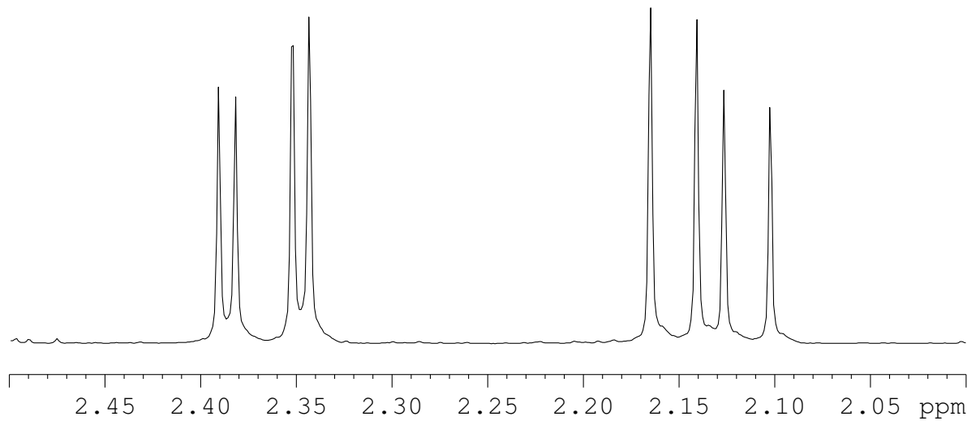
F2 - Acquisition Parameters
Date_           20090808
Time               13.19
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    64
DS                     2
SWH             6578.947 Hz
FIDRES          0.200774 Hz
AQ              2.4904180 sec
RG                   128
DW                76.000 usec
DE                 7.00 usec
TE                300.1 K
D1            0.10000000 sec
TD0                    1

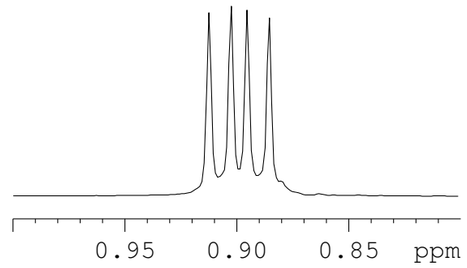
======== CHANNEL f1 ========
NUC1                  1H
P1                 11.50 usec
PL1                 6.00 dB
SFO1         399.8724694 MHz

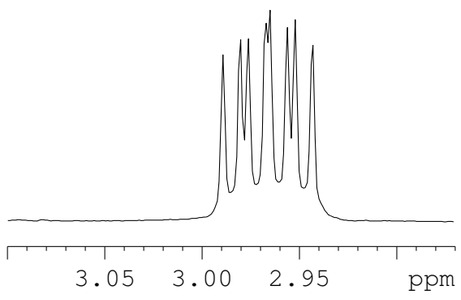
F2 - Processing parameters
SI                 16384
SF           399.8700090 MHz
WDW                   no
SSB                    0
LB                 0.00 Hz
GB                     0
PC                  1.00
```

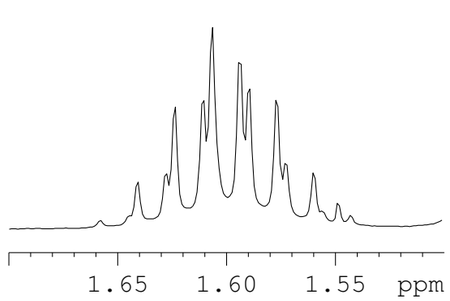


2009-070
t-Bu ester amine
nmr400b h-1

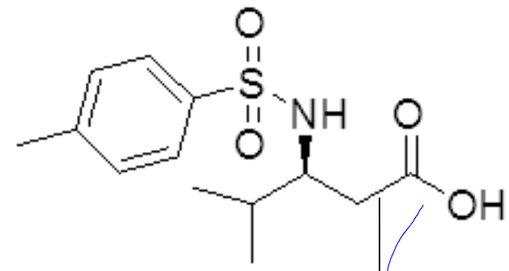








2009-095B
After pH swing
nmr400b h-1



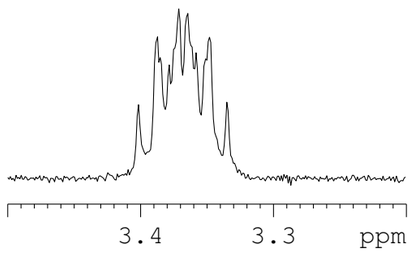

```
Current Data Parameters
NAME            2009-095
EXPNO                  3
PROCNO                 1

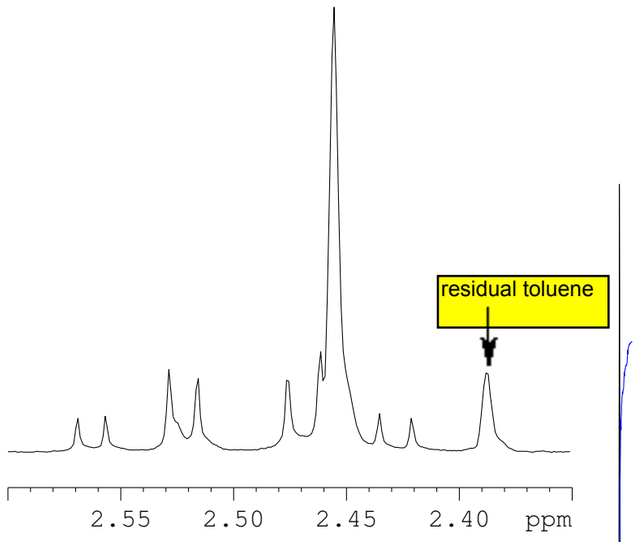
F2 - Acquisition Parameters
Date_           20091101
Time               14.47
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    32
DS                     2
SWH             6578.947 Hz
FIDRES          0.200774 Hz
AQ              2.4904180 sec
RG                 912.3
DW                76.000 usec
DE                 7.00 usec
TE                300.0 K
D1             0.10000000 sec
TD0                    1

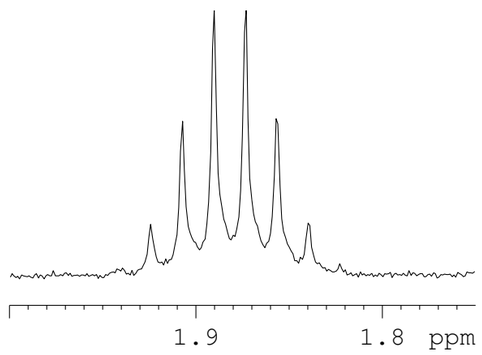
======== CHANNEL f1 ========
NUC1                  1H
P1                 11.20 usec
PL1                 6.00 dB
SFO1         399.8724694 MHz

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]	Intensity
1	7.8073	3121.9051	0.66
2	7.8023	3119.9057	4.98
3	7.7980	3118.1863	2.10
4	7.7860	3113.3878	1.67
5	7.7815	3111.5884	5.47
6	7.7771	3109.8290	1.31
7	7.3399	2935.0058	3.60
8	7.3383	2934.3660	4.13
9	7.3176	2926.0887	3.68
10	7.3054	2921.2103	0.61
11	7.3011	2919.4909	0.46
12	7.2928	2916.1719	15.42
13	7.2893	2914.7724	2.10
14	7.2737	2908.5344	0.30
15	7.2686	2906.4951	0.71
16	7.2154	2885.2220	0.83
17	7.2086	2882.5029	0.47
18	7.1982	2878.3442	0.52
19	7.1958	2877.3845	0.57
20	7.1937	2876.5448	0.48
21	7.1886	2874.5055	0.40
22	5.1806	2071.5665	1.30
23	5.1575	2062.3295	1.35
24	3.4020	1360.3577	0.38
25	3.3881	1354.7995	0.72
26	3.3788	1351.0808	0.58
27	3.3717	1348.2417	0.85
28	3.3651	1345.6025	0.84
29	3.3586	1343.0034	0.64
30	3.3486	1339.0047	0.71
31	3.3353	1333.6864	0.40
32	2.5695	1027.4660	1.22
33	2.5572	1022.5476	1.29
34	2.5290	1011.2712	2.93
35	2.5164	1006.2329	2.65
36	2.4765	990.2781	2.68
37	2.4619	984.4400	3.51
38	2.4560	982.0807	15.46
39	2.4358	974.0033	1.37
40	2.4216	968.3252	1.22
41	2.3882	954.9695	2.82
42	1.9247	769.6298	0.31
43	1.9077	762.8320	0.90
44	1.8907	756.0342	1.55
45	1.8738	749.2764	1.57
46	1.8570	742.5586	0.94
47	1.8399	735.7208	0.33
48	1.2940	517.4318	1.74
49	0.9145	365.6811	0.95
50	0.9042	361.5625	0.63
51	0.8904	356.0442	11.06
52	0.8735	349.2864	20.00
53	0.8568	342.6086	9.91







2009-092
beta-leucine
nmr400b h-1

```
Current Data Parameters
NAME            2009-092
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091031
Time               12.30
INSTRUM            spect
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    22
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                300.0 K
D1           0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 11.20 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
```