Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

**Supporting Information**

for

*Angew. Chem. Int. Ed.* Z50655

© Wiley-VCH 2003

69451 Weinheim, Germany

# Catalytic highly enantioselctive direct amination of β-keto esters

***Mauro Marigo, Karsten Juhl, and Karl Anker Jørgensen****

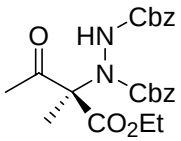
Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

**General Methods.** The $^{1}H$ and $^{13}C$ NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to $CHCl_3$ ($\delta$ = 7.26) for $^{1}H$ NMR and relative to the central $CDCl_3$ resonance ($\delta$ = 77.0) for $^{13}C$ NMR. The NMR spectra were run at 60 $^{o}C$ due to line broadning. Coupling constants in $^{1}H$ NMR are in Hz. Solvents were dried according to standard procedures. Flash chromatography (FC) was carried out using FlashMaster II from Jones Chromatography using Merck silica gel 60 (230-400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $CH_2Cl_2$ was used as solvent. The enantiomeric excess (ee) of the products was determined by HPLC using Chiralcel OD or Daicel Chiralpack AD or AS columns with *i*-PrOH/hexane as eluent.

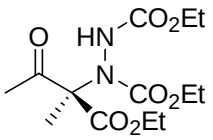
**Materials.** (*S*)-(-)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline, $Cu(OTf)_2$, ethyl 2-oxocyclo-pentane-carboxylate (**1h**), ethyl 2-oxocyclohexanecarboxylate (**1i**), n-butyllithium, *tert*-butylpropionate, *N*,*O*-dimethylhydroxylamine hydrochloride, ethyl azodicarboxylate were purchased from Aldrich and used as received, ethyl 2-methylacetoacetate (**1a**) and benzyl diazocarboxylate were purchased from Aldrich and used after purification, trimethylsilyl diazomethane were purchased from Lancaster and used as received. β-Keto ester **1b** was prepared by reaction of methylketene dimer with the appropriate alcohol following a literature procedure.[1] β-Keto esters **1d**,**e**,**f**,**g** were prepared by acylation of *tert*-butylpropionate and *tert*-butyl-4-pentenoate

by *N*-methoxy-*N*-methylamides following a literature procedure.[2] β-Keto esters **1c**,**j** were prepared by C-alkoxycarbonylation of appropriate ketone following a literature procedure.[3]

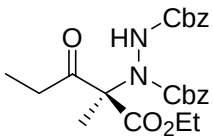
**General Procedure for Catalytic Asymmetric Direct Amination of β-Keto Esters.** In an oven dried Schlenk tube equipped with a magnetic stirrer bar, $Cu(OTf)_2$ (9 mg, 0.025mmol) and (*S*)-(-)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) (9.2 mg, 0.026 mmol) were added. The mixture was stirred under vacuum for 2 h and filled with $N_2$. Dry $CH_2Cl_2$ (10 mL) was added and the solution was stirred for 1 h. 1 mL of the solution was transferred in another oven dried Schlenk and 1 mL dry $CH_2Cl_2$ was added. 0.50 mmol of the β-keto ester was added followed by the addition of dibenzyl azodicarboxylate (180 mg, 0.60 mmol). After 16 h at room temperature the product was isolated by FC.




***N´,N*-Bis(benziloxycarbonyl)-2-hydrazino-2-methyl-3-oxo-butyric acid ethyl ester (3a)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*-PrOH (80/20): flow rate 1.0 mL/min: $\tau_{maior}$ = 23.4; $\tau_{minor}$ = 9.4 min; HRMS $C_{25}H_{30}N_2O_7$ $[M+Na]^+$ calculated: 465.1638; found: 465.1661; $[\alpha]_D$= -11.7 (c = 20 mg/mL, 98% ee).

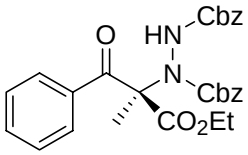



***N´,N*-Bis(ethoxycarbonyl)-2-hydrazino-2-methyl-3-oxo-butyric acid ethyl ester (3ab)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*-PrOH (92/8): flow rate 1.0 mL/min: $\tau_{maior}$ = 32.6 min; $\tau_{minor}$ = 19.2 min; HRMS $C_{13}H_{22}N_2O_7$ $[M+Na]^+$ calculated: 341.1325, found: 341.1354; $[\alpha]_D$ = -13.8 (c = 7 mg/mL, >95% ee).

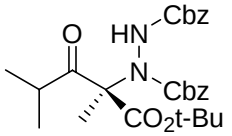



***N´,N*-Bis(benzyloxycarbonyl)-2-hydrazino-2-methyl-3-oxo-penta-noic acid ethyl ester (3b)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*-PrOH (92/8): flow rate 1.0 mL/min: $\tau_{maior}$ = 45.0 min;

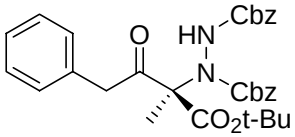
$\tau_{minor}$ = 20.6 min; HRMS $C_{24}H_{28}N_2O_7$ $[M+Na]^+$ calculated: 479.1794; found: 479.1770; $[\alpha]_D$ = -7.2 (c = 23 mg/mL, 98% ee).



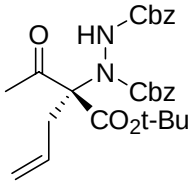

***N´,N*-Bis(benzyloxycarbonyl)-2-hydrazino-2-methyl-3-oxo-3-phe-nyl-butyric acid ethyl ester (3c)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*-PrOH (92/8): flow rate 1.0 mL/min: $\tau_{maior}$ = 30.2 min; $\tau_{minor}$ = 15.1 min; HRMS $C_{28}H_{28}N_2O_7$ $[M+Na]^+$ calculated: 527.1794, found: 527.1817; $[\alpha]_D$ = -82.7 (c = 20 mg/mL, 98% ee).



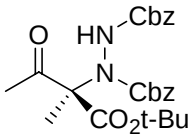

***N´,N*-Bis(benzyloxycarbonyl)-2-hydrazino-2,4-dimethyl-3-oxo-pen-tanoic acid *tert*-butyl ester (3d)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OD column (hexane/*i*-PrOH (98/2): flow rate 1.0 mL/min: $\tau_{maior}$ = 23.6 min; $\tau_{minor}$ = 21.4 min; HRMS $C_{27}H_{34}N_2O_7$ $[M+Na]^+$ calculated: 521.2264; found: 521.2296; $[\alpha]_D$ = -1.0 (c = 11 mg/mL, 98% ee).



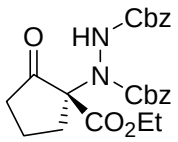

***N´,N*-Bis(benzyloxycarbonyl)-2-hydrazino-2-methyl-3-oxo-penta-noic acid *tert*-butyl ester (3e)** The ee was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*-PrOH (80/20): flow rate 1.0 mL/min: $\tau_{maior}$ = 23.8 min; $\tau_{minor}$ = 9.4 min; HRMS $C_{27}H_{34}N_2O_7$ $[M+Na]^+$ calculated: 569.264; found: 569.2301; $[\alpha]_D$ = -22.0 (c =16 mg/mL, 98% ee).



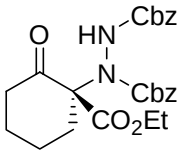

***N´,N*-Bis(benzyloxycarbonyl)-2-hydrazino-2-acethyl-pent-4-enoic acid *tert*-butyl ester (3f)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OD column (hexane/*i*-PrOH (92/8): flow rate 1.0 mL/min: $\tau_{maior}$ = 15.0 min; $\tau_{minor}$ = 11.6 min; HRMS $C_{27}H_{32}N_2O_7$ $[M+Na]^+$ calculated: 519.2107; found: 519.2116; $[\alpha]_D$ = -5.5 (c = 17 mg/mL, 98% ee).



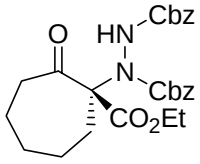

***N´,N*-Bis(benzyloxycarbonyl)-2-hydrazino-2-methyl-3-oxo-butyric acid *tert*-butyl ester (3g)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*-PrOH (92/8): flow rate 1.0 mL/min: $\tau_{maior}$ = 46.2 min; $\tau_{minor}$ = 9.5 min; HRMS $C_{24}H_{28}N_2O_7$ $[M+Na]^+$ calculated:493.1951; found: 493.1958; $[\alpha]_D$ = -18.2 (c = 9 mg/mL, 98% ee).



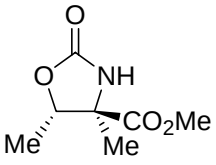

***N´,N*-Bis(benzyloxycarbonyl)-1-hydrazino-2-oxo-cyclohexanecar-boxylic acid ethyl ester (3h)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*-PrOH (88/12): flow rate 1.0 mL/min: $\tau_{maior}$ = 9.8 min; $\tau_{minor}$ = 14.9 min; HRMS $C_{25}H_{28}N_2O_7$ $[M+Na]^+$ calculated: 477.1638, found: 477.1636; $[\alpha]_D$= +3.7 (c = 11 mg/mL, 99% ee).




***N´,N*-Bis(benzyloxycarbonyl)-1-hydrazino-2-oxo-cyclohexanecar-boxylic acid ethyl ester (3i)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OD column (hexane/*i*-PrOH (96/4): flow rate 1.0 mL/min: $\tau_{maior}$ = 14.3 min; $\tau_{minor}$ = 20.1 min; HRMS $C_{25}H_{28}N_2O_7$ $[M+Na]^+$ calculated: 491.1794; found: 491.1803; $[\alpha]_D$ = -1.8 (c = 13 mg/mL, 99% ee).

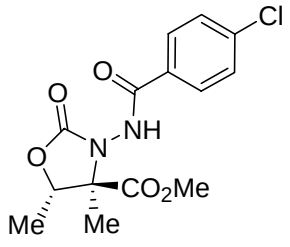



***N´,N*-Bis(benzyloxycarbonyl)-1-hydrazino-2-oxo-cycloheptanecar-boxylic acid ethyl ester (3j)** The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OD column (hexane/i-PrOH (92/8): flow rate 1.0 mL/min: $\tau_{maior}$ = 16.7 min; $\tau_{minor}$ =15.1 min; HRMS $C_{26}H_{30}N_2O_7$ $[M+Na]^+$ calculated: 505.1951, found: 505.1945; $[\alpha]_D$ = +1.8 (c = 17 mg/mL, 99% ee).




**(4*R*,5*S*) 4,5-Dimetyl-4-methoxycarbonyl-2-oxazolidinone (7)** in an oven dried Schlenk tube equipped with a magnetic stirrer bar, $Cu(OTf)_2$ (7.2 mg, 0.020mmol) and (*S*)-(-)-2,2'-isopropylidene-

bis(4-phenyl-2-oxazoline) (7.4 mg, 0.021mmol) were added. The mixture was stirred under vacuum for 2 h and filled with $N_2$. Dry $CH_2Cl_2$ (8 mL) was added and the solution was stirred for 1 h. 2.00 mmol of **1a** were added followed by the addition of dibenzyl azodicarboxylate **2a** (720 mg, 2.40 mmol). After 16 h at room temperature reaction mixture was filtered through a plug of silica to remove the catalyst. The crude product was concentrated *in-vacuo* and solved in 10 mL of THF. The solution was cooled to –78 ºC and 3.6 mL of a 1M L-selectride solution in THF was added. After 90 min the solution was allowed to warm near room temperature and 10 mL 0.5M NaOH was added. After stirring 16 h the mixture was poured into a separation funnel together with 5 mL of brine and 50 mL of $Et_2O$. The ether fraction was back extracted with 6 mL of 0.5N NaOH and brine. The aqueous phase was acidificated with 1 N $KHSO_4$ and extracted with EtOAc (3x30 mL). The organic phase was dried with $Na_2SO_4$ and concentrated *in-vacuo*. The residue was dissolved in 4mL of MeOH and 10 mL of toluene and 1.4 mL of a 2M trimethylsilyl diazomethane solution in hexane was added drop wise. After 15 min excess of trimethylsilyl diazomethane was decomposed by adding a few drops of acetic acid. After evaporation the crude product was placed in a flask equipped with a magnetic stirrer bar and 75 mg 10% Pd/C and 5 mL of MeOH. The flask was filled with $H_2$ and stirred for 6 h at room temperature. The reaction mixture was filtered through celite with a mixture of MeOH/$CH_2Cl_2$ (50/50) and the solvent was evaporated. 4mL of acetic acid was added together with 600 mg of Zn and 0.4 mL of acetone. The mixture was stirred at 60 ºC for 72 h adding 600 mg of Zn every 24 h. The suspension was filtered and most of acetic acid was removed *in-vacuo*. The residue was suspended in EtOAc and extracted with $NaHCO_3$. The organic phase was dried on $Na_2SO_4$ and concentrated. The crude product was purified by FC to give **7** (25% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.58 ( bs, 1H, N**H**), 4.84 ( q, *J*=6.6, 1H, C**H**), 3.79 (s, 3H, OC**H$_3$**), 1.44 (m, 6H, CHC**H$_3$** and CC**H$_3$**); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.7, 157.5, 81.3, 77.6, 63.3, 53.1, 23.3, 19.5, 15.2; HRMS $C_7H_{11}NO_4$ $[M+Na]^+$ calculated: 196.0586; found: 196.0450; $[\alpha]_D$ = -12.0 (c =12 mg/mL, 98% ee).




**(4*R*,5*S*) 3-(4-Chloro-benzoylamino)-4,5-dimethyl-4-methoxycarbo-nyl-2-oxazolidinone (8)** 1 mmol of **3a** was solved in 5 mL of THF. The solution was cooled to –78 ºC and 1.8 mL of a 1M L-selectride solution in THF was added. After 90 min the solution was allowed to warm near room temperature and 5 mL 0.5M NaOH was added. After stirring 16 h the mixture was poured

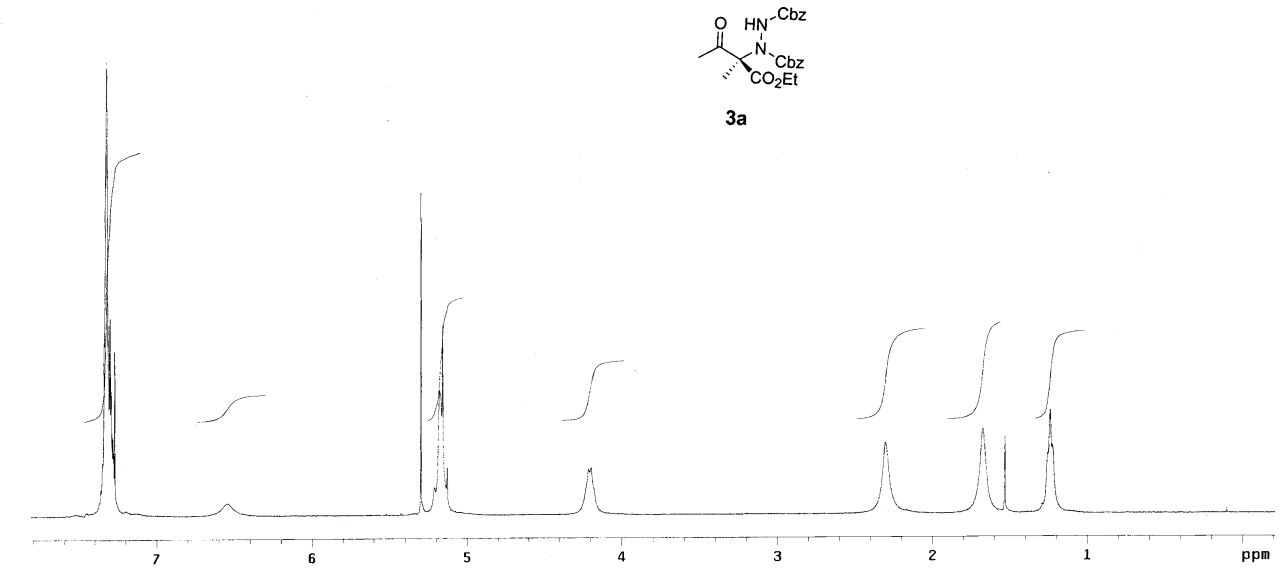
into a separation funnel together with 5 mL of brine and 25 mL of $Et_2O$. The ether fraction was back extracted with 6 mL of 0.5N NaOH and brine. The aqueous phase was acidificated with 1 N $KHSO_4$ and extracted with EtOAc (3x30 mL). The organic phase was dried with $Na_2SO_4$ and concentrated *in-vacuo*. The residue was dissolved in 2mL of MeOH and 5 mL of toluene and 1.0 mL of a 2M trimethylsilyl diazomethane solution in hexane was added drop wise. After 15 min excess of trimethylsilyl diazomethane was decomposed by adding a few drops of acetic acid. After evaporation the crude product was placed in a flask equipped with a magnetic stirrer bar and 40 mg 10% Pd/C and 5 mL of MeOH. The flask was filled with $H_2$ and stirred for 6 h at room temperature. The reaction mixture was filtered through celite with a mixture of MeOH/$CH_2Cl_2$ (50/50). After evaporation the crude product was placed in a flask together with a magnetic stirrer bar and 5 ml of $CH_2Cl_2$. 4-Chloro benzoyl chloride was added (0.55 mmol) followed by addition of pyridine (0.55 mmol) drop wise. The mixture was poured into a separation funnel together with 10 ml of 1 N HCl and brine and 25 mL of EtOA , the organic phase was dried with $Na_2SO_4$ and concentrated *in-vacuo* and the product was purified by FC. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.74 ( bs, 1H, N**H**), 7.71 (d, *J*=8.4, 2H, Ar**H**), 7.35 (d, *J*=8.4, 2H, Ar**H**), 4.85 q, *J*=6.6, 1H, C**H**), 3.84 (s, 3H, OC**H$_3$**), 1.56 (d, *J*=6.6, 3H, C**H$_3$**), 1.49 (s, 3H, C**H$_3$**); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.7, 165.7, 155.2, 138.9, 129.2, 128.9, 67.8, 53.4, 15.9, 15.3, 1.0; HRMS $C_{14}H_{15}ClN_2O_5$ $[M+Na]^+$ calculated: 349.0567, found: 349.0571 $[\alpha]_D$ = +39.5 (c = 8 mg/mL, 98% ee).


(1) L. Hitermann; A. Togni *Helv. Chim. Acta*, **2000**, *83*, 2425-2435.

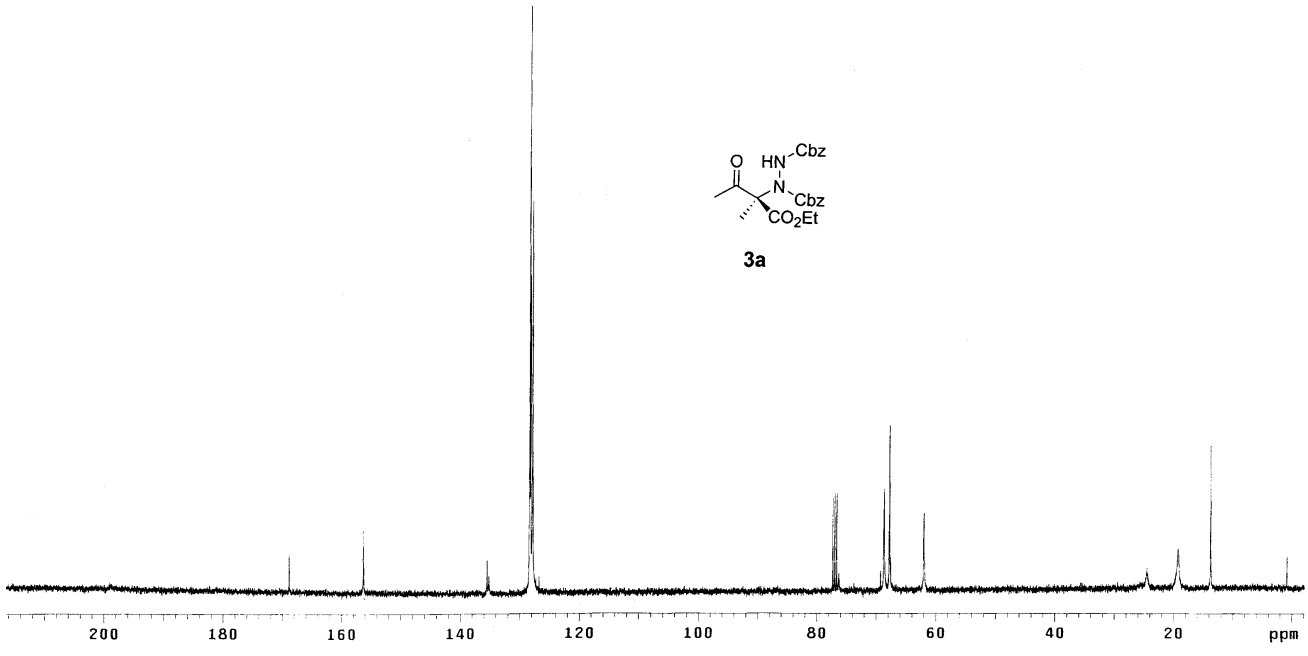
(2) A. J. Turner; Jacks W.S. *J. Org. Chem.*, **1989**, *54*, 4229-4231.

**(3)** J. Helleou; K. J. Kingston; G. A. Fallis *Synthesis* **1984**, 1014-1017.

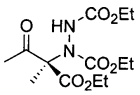
# NMR spectra



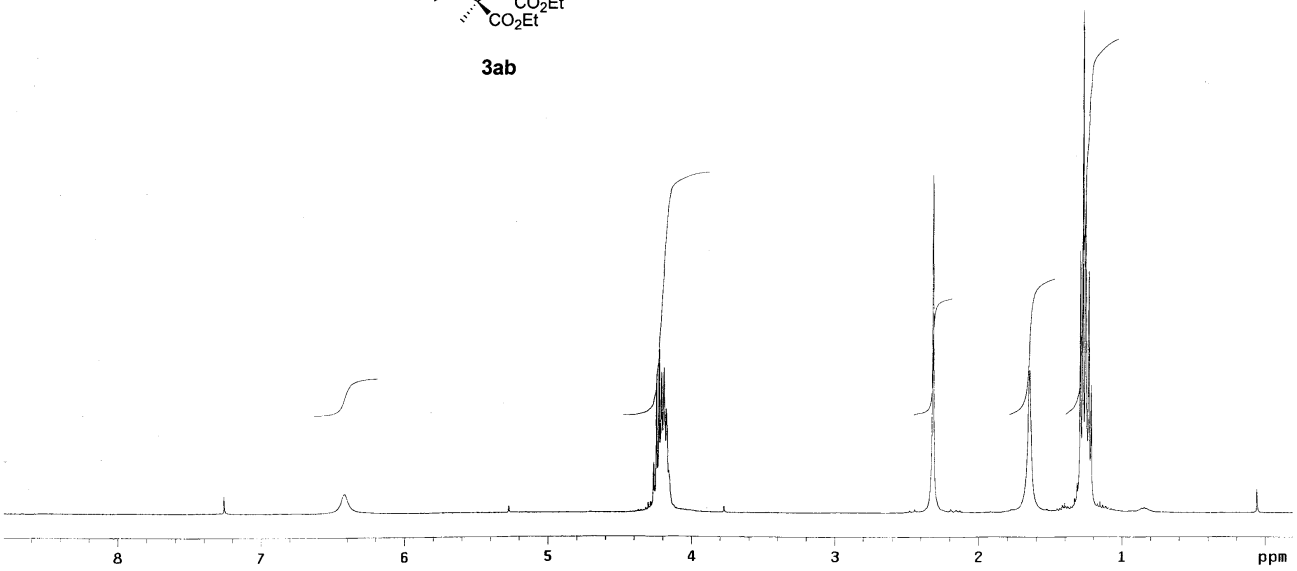

**3a**

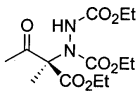



**3a**

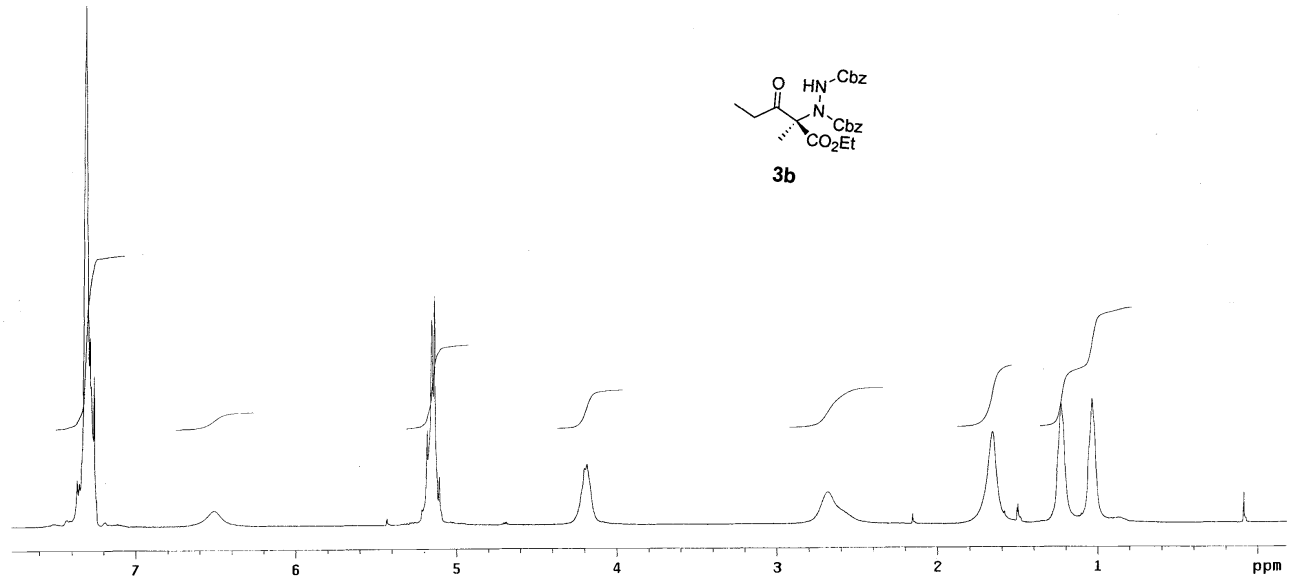


**3ab**

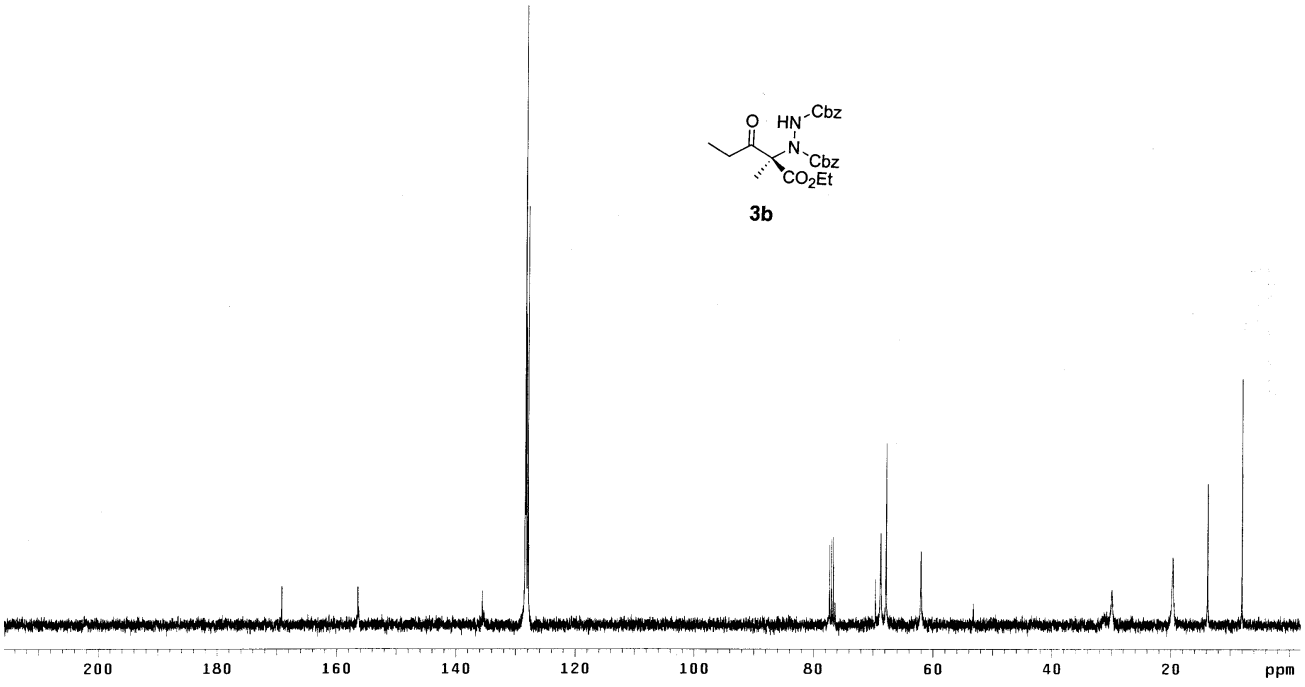


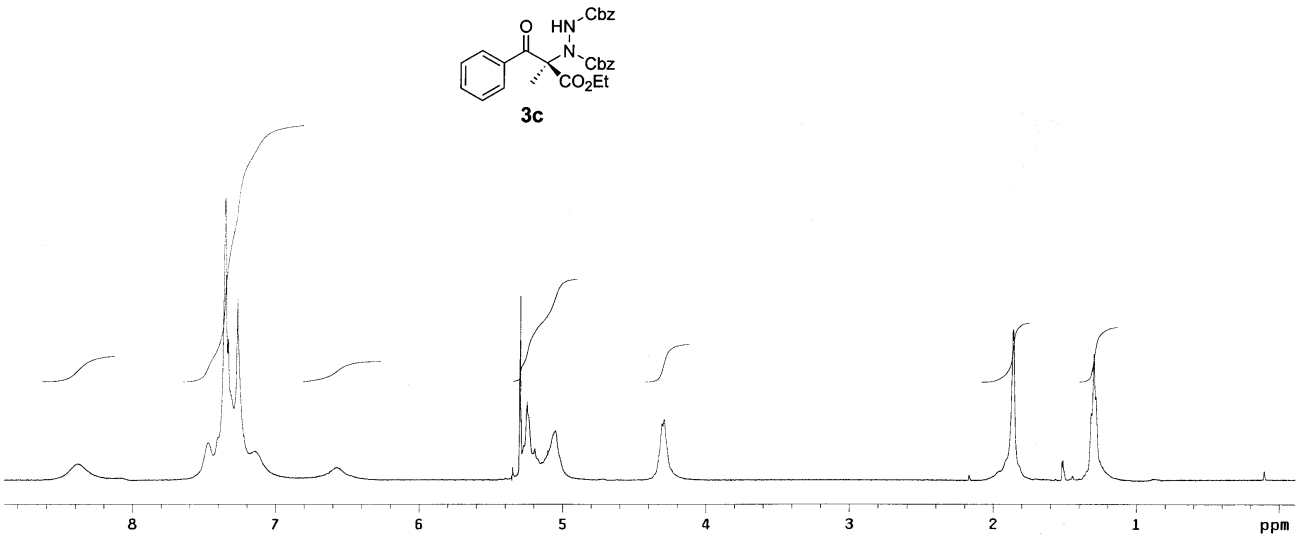
**3ab**

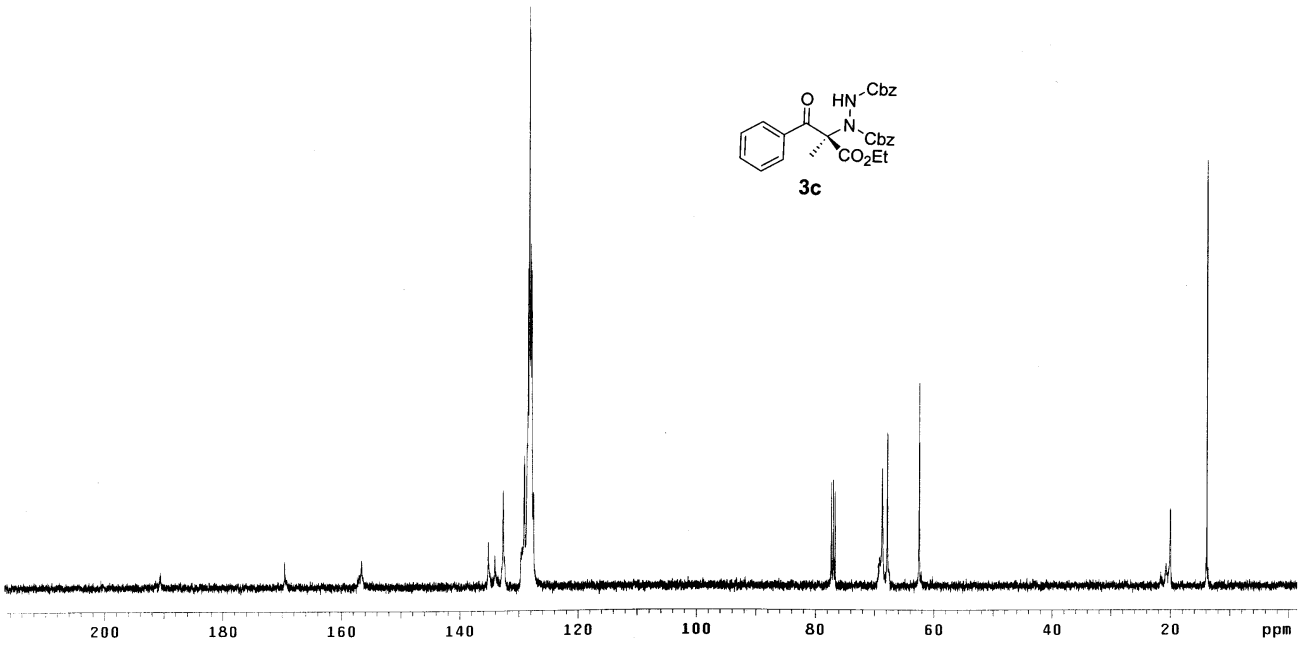

O
HN
Cbz
N
Cbz
CO2Et
7
6
5
4
3
2
1
ppm

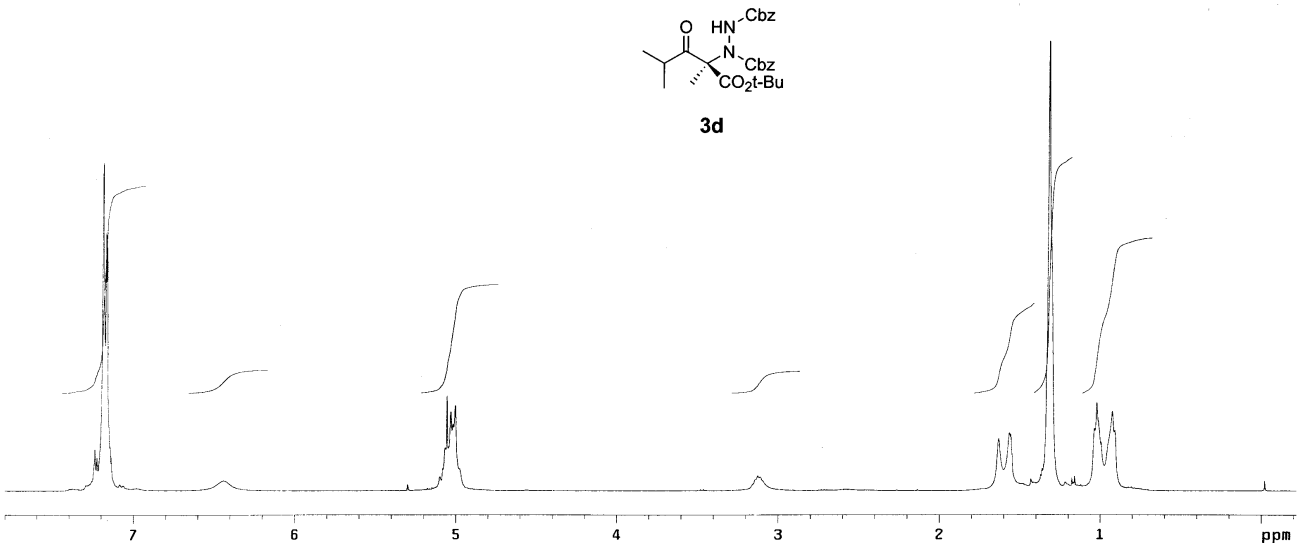
**3b**


O
HN
Cbz
N
Cbz
CO2Et
200
180
160
140
120
100
80
60
40
20
ppm

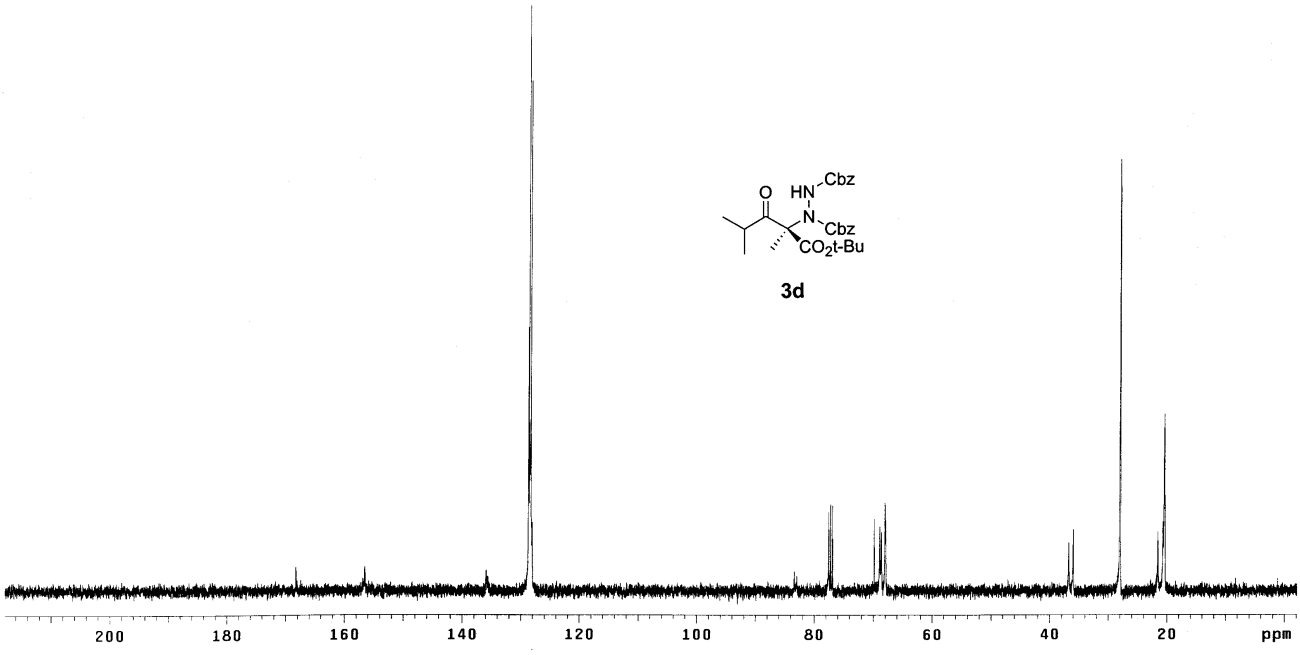
**3b**


O
HN
Cbz
N
Cbz
CO2Et
3c
8
7
6
5
4
3
2
1
ppm

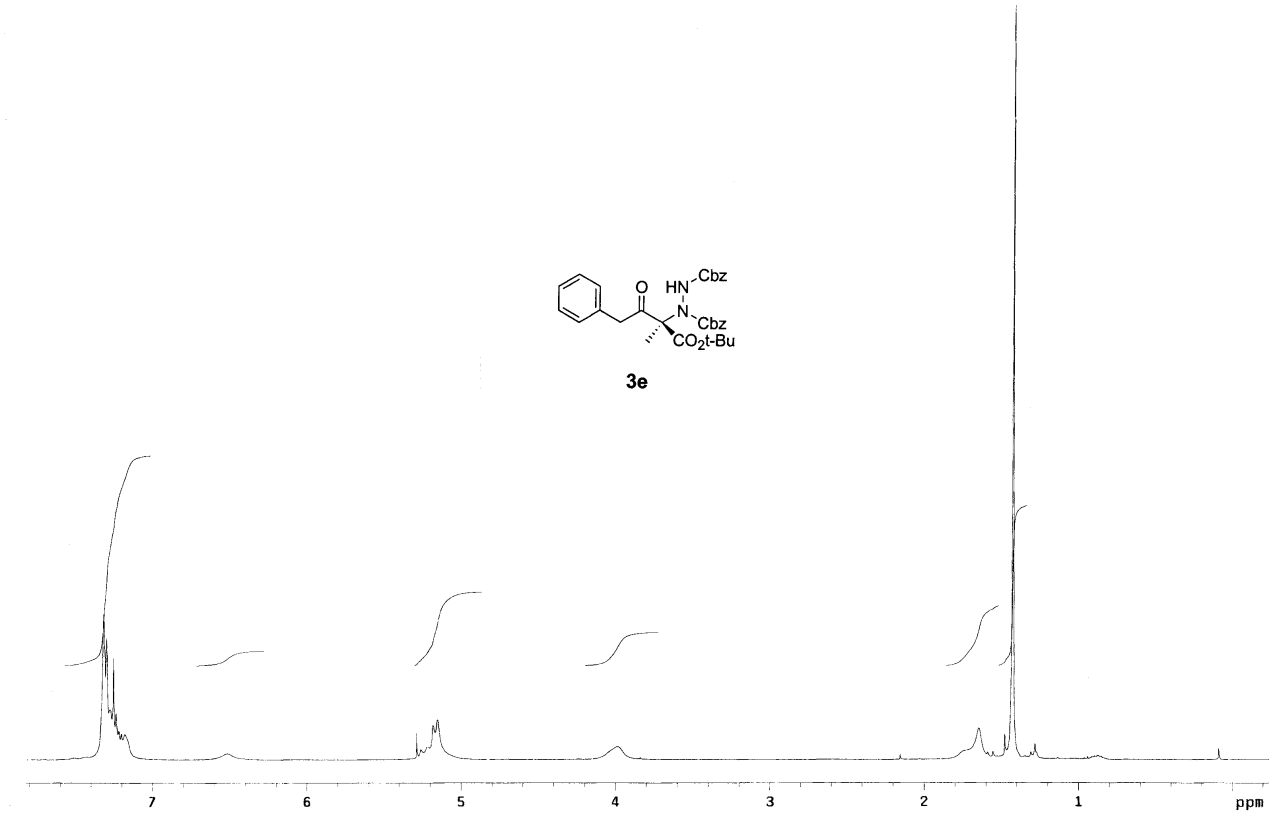

O
HN
Cbz
N
Cbz
CO2Et
3c
200
180
160
140
120
100
80
60
40
20
ppm


O
HN
Cbz
N
Cbz
CO2t-Bu
7
6
5
4
3
2
1
ppm

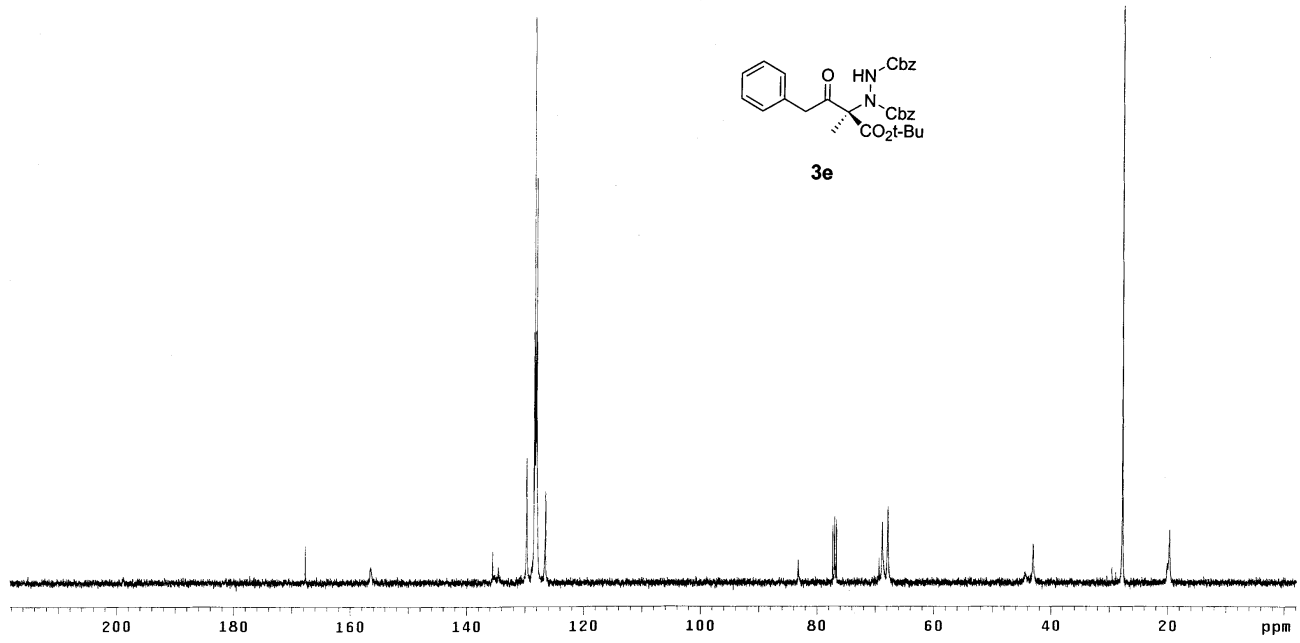
**3d**


O
HN
Cbz
N
Cbz
CO2t-Bu
200
180
160
140
120
100
80
60
40
20
ppm

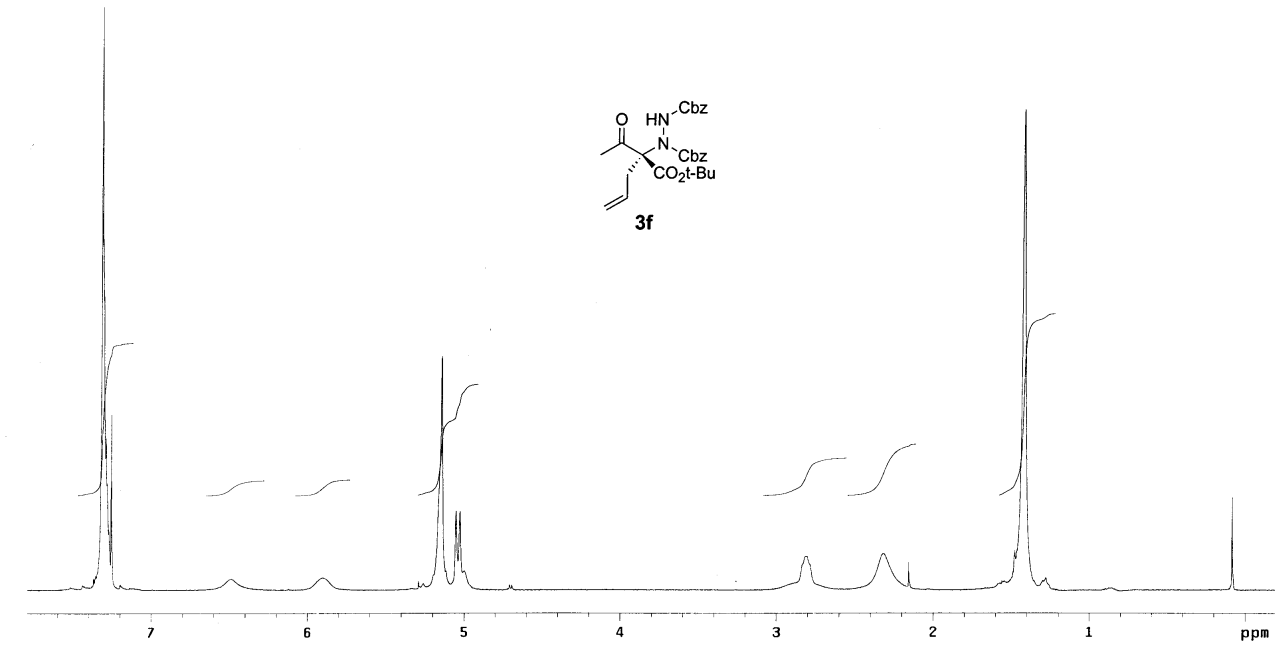
**3d**


HN
Cbz
O
N
Cbz
CO2t-Bu
7
6
5
4
3
2
1
ppm

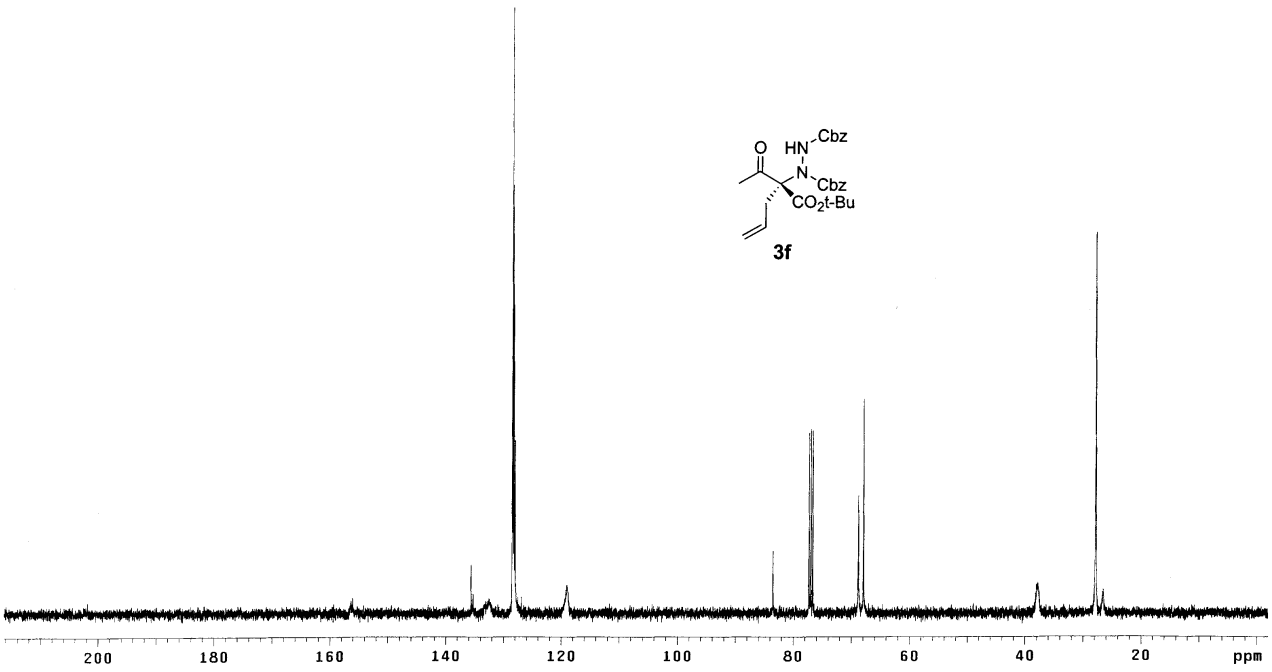
**3e**


HN
Cbz
O
N
Cbz
CO2t-Bu
200
180
160
140
120
100
80
60
40
20
ppm

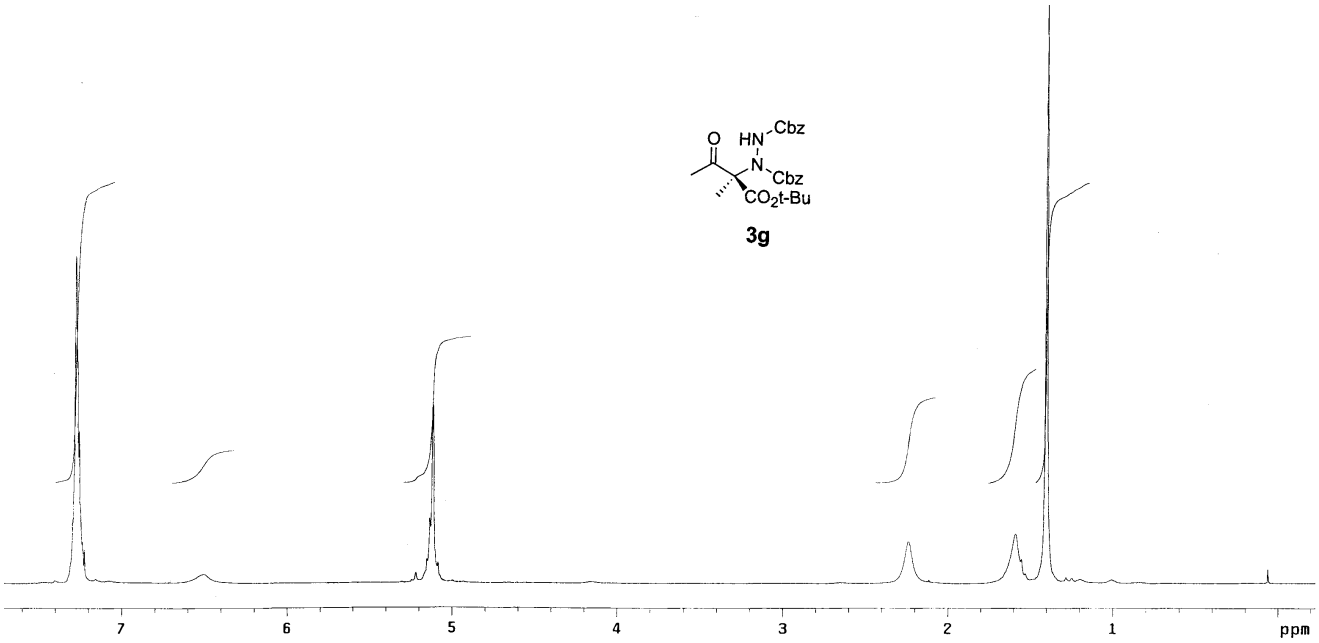
**3e**

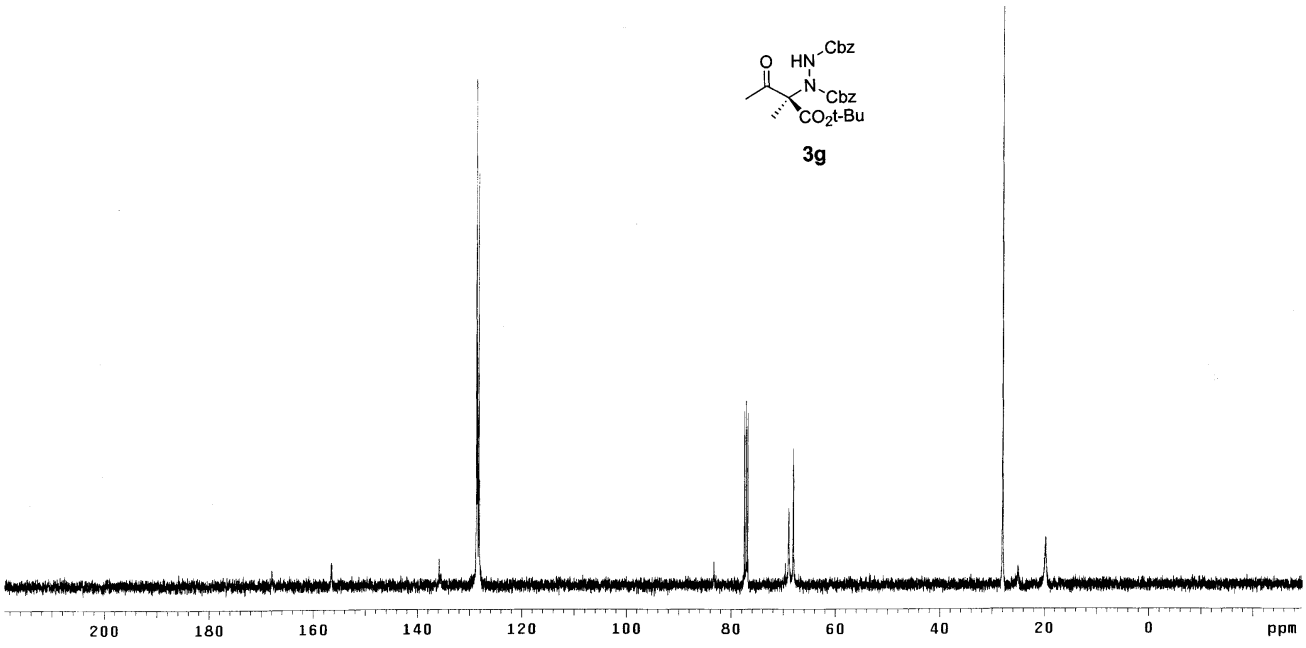

O
HN
Cbz
N
Cbz
CO2t-Bu
7
6
5
4
3
2
1
ppm

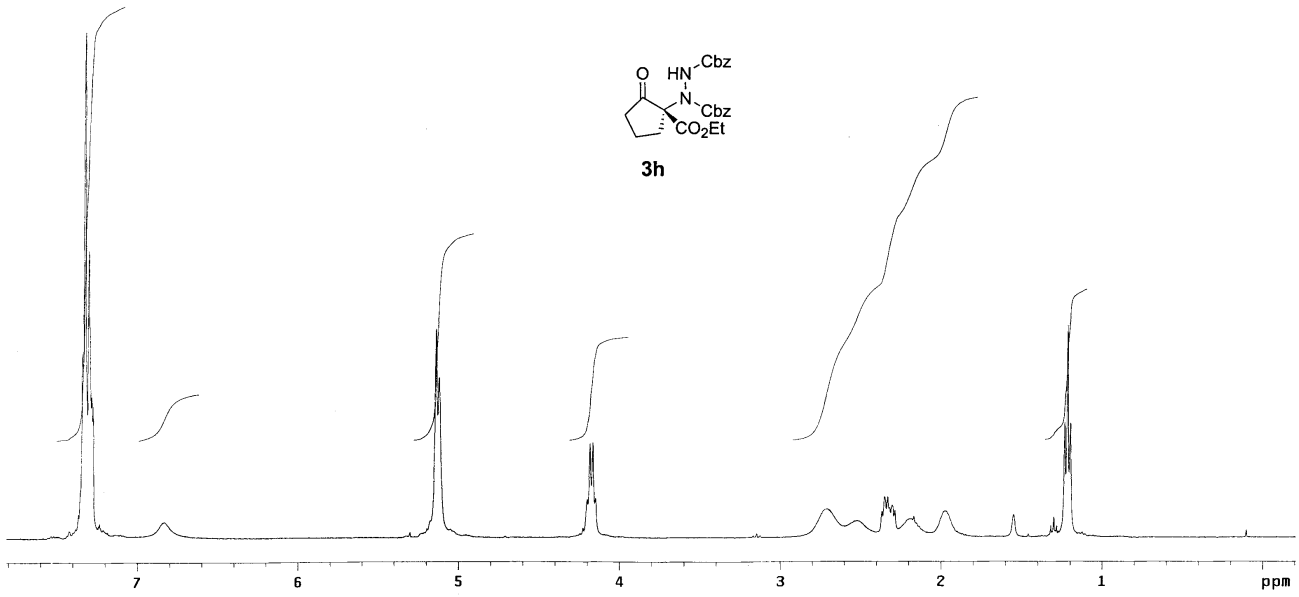
**3f**

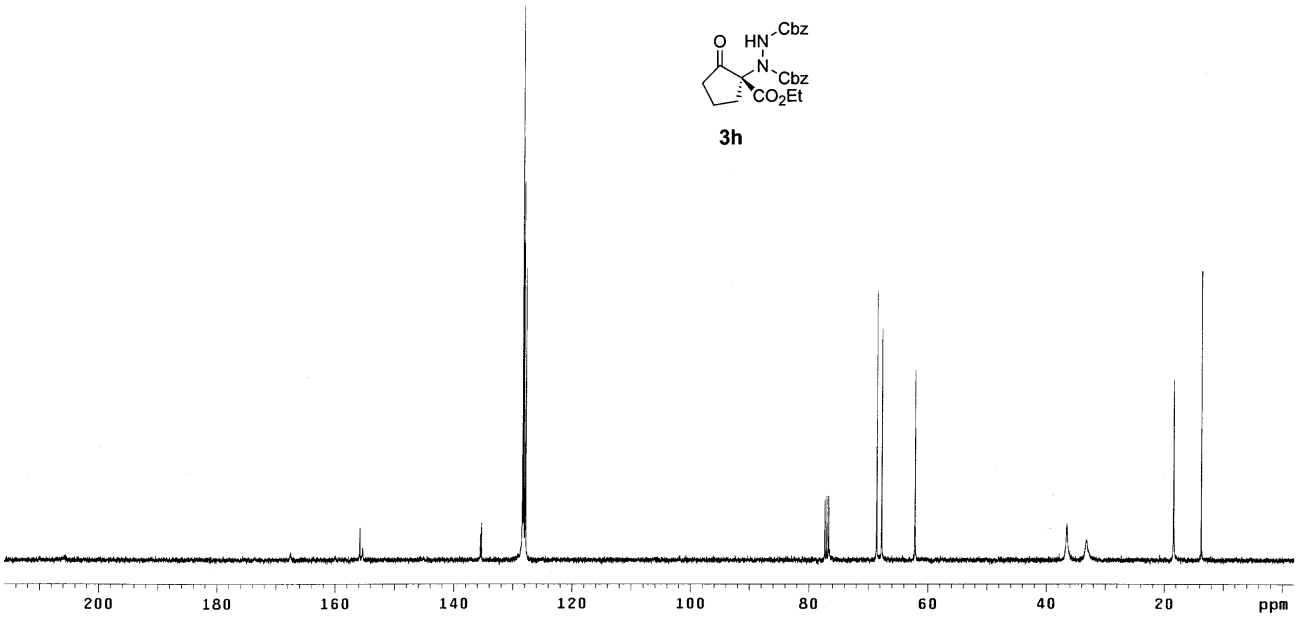

O
HN
Cbz
N
Cbz
CO2t-Bu
200
180
160
140
120
100
80
60
40
20
ppm

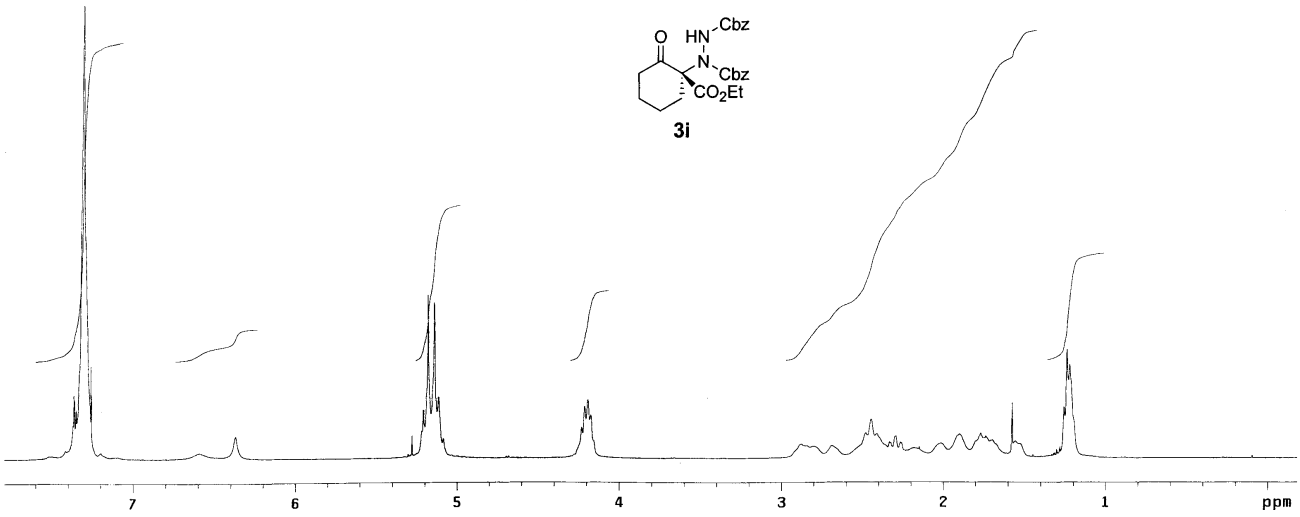
**3f**

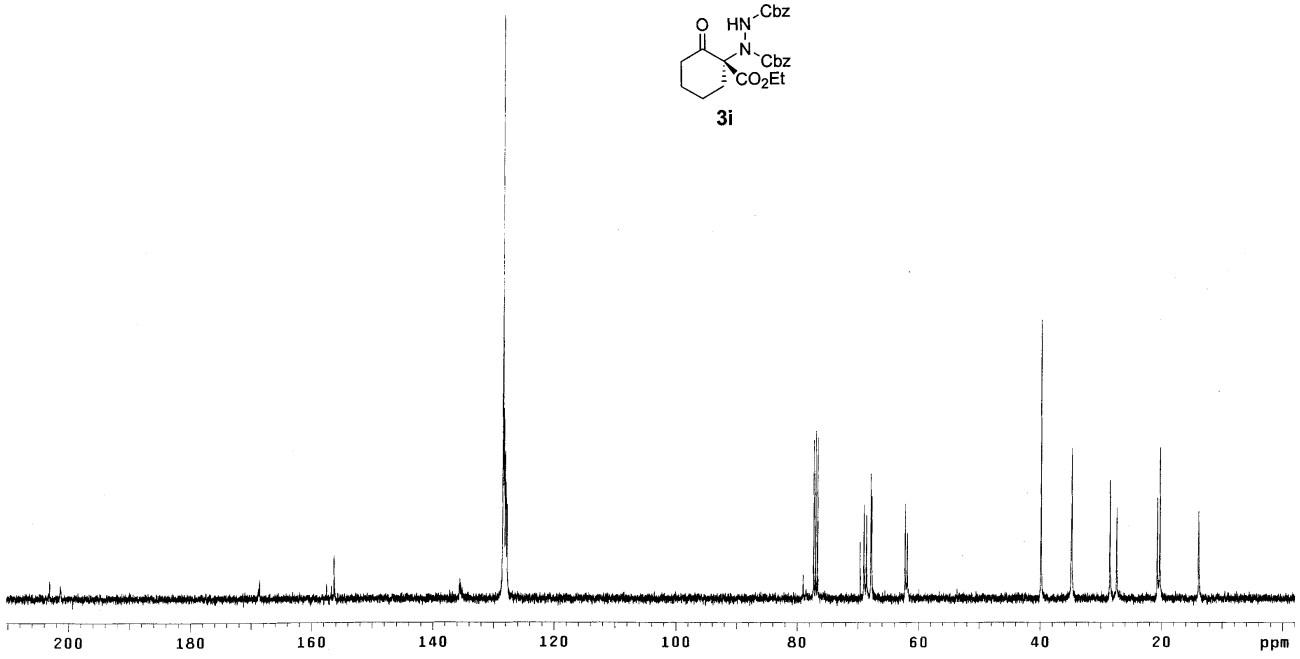

O
HN
Cbz
N
Cbz
CO2t-Bu
3g
7
6
5
4
3
2
1
ppm

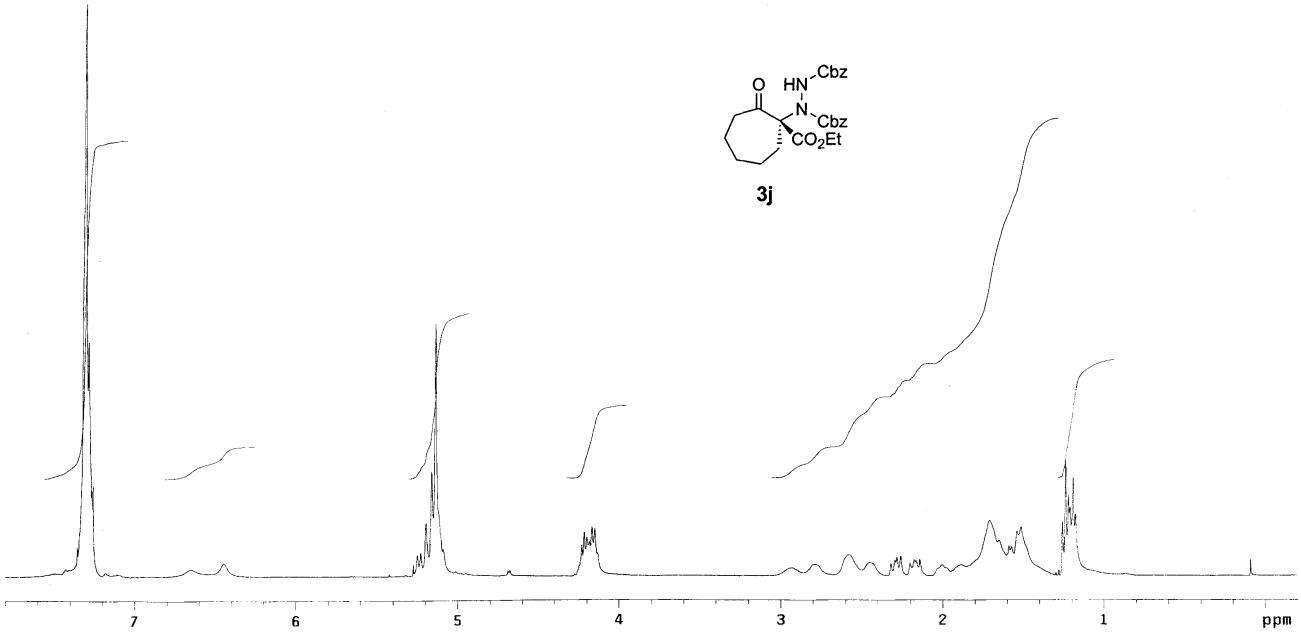

O
HN
Cbz
N
Cbz
CO2t-Bu
3g
200
180
160
140
120
100
80
60
40
20
0
ppm


O
HN
Cbz
N
Cbz
CO2Et
3h
7
6
5
4
3
2
1
ppm

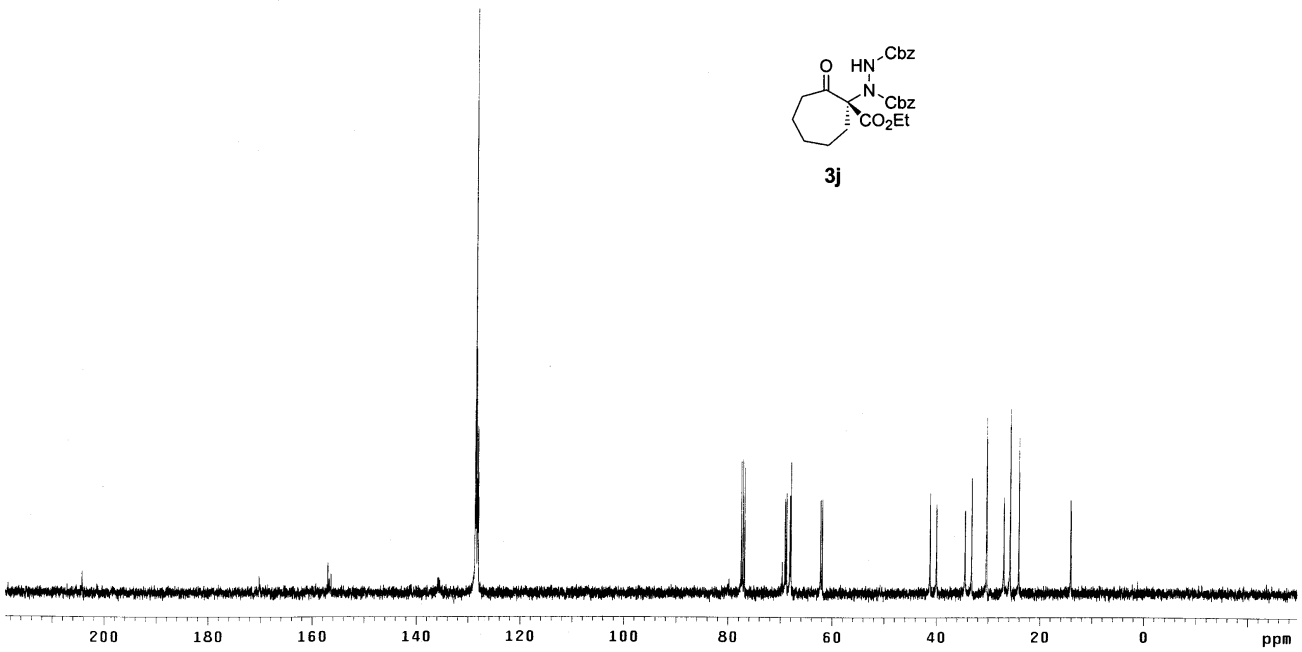

O
HN
Cbz
N
Cbz
CO2Et
3h
200
180
160
140
120
100
80
60
40
20
ppm


O
HN
Cbz
N
Cbz
CO2Et
3i
7
6
5
4
3
2
1
ppm


O
HN
Cbz
N
Cbz
CO2Et
3i
200
180
160
140
120
100
80
60
40
20
ppm


O
HN
Cbz
N
Cbz
CO2Et
7
6
5
4
3
2
1
ppm

**3j**


O
HN
Cbz
N
Cbz
CO2Et
200
180
160
140
120
100
80
60
40
20
0
ppm

**3j**