

# Catalytic Michael Reactions of Ketoesters with a Camphor Derived Acrylate Equivalent: Stereoselective Access to All-Carbon Quaternary Centers

Claudio Palomo,\* Mikel Oiarbide, Jesús M. García, Patricia Bañuelos, José M. Odriozola, Jesús Razkin, Anthony Linden  
[claudio.palomo@ehu.es](mailto:claudio.palomo@ehu.es)

## SUPPORTING INFORMATION

### TABLE OF CONTENTS

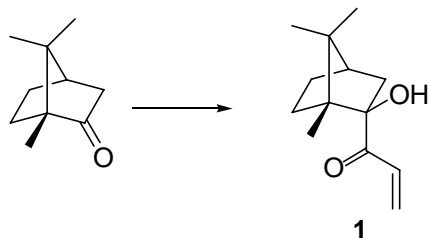
1. General.....	Page 2
2. Preparation of hydroxy enone <b>1</b> from (+)-camphor.....	2
3. Preparation of $\beta$ -keto esters.....	3
4. General procedure for the Michael reaction of <b>1</b> with $\beta$ -keto esters.....	6
5. Data of Michael adducts.....	7
6. Oxidative scission of adducts: synthesis of carboxylic acids.....	14
7. General Procedure for the enantioselective Michael reaction with <b>27</b> .....	17
8. Oxidative scission of adducts <b>29</b> , <b>30</b> , and <b>31</b> .....	19
9. Selected NMR spectra.....	21
10. ORTEP diagram of compound <b>14a</b> .....	58
11. ORTEP diagram of compound <b>23a</b> .....	59

## 1. General

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Acetonitrile (CH<sub>3</sub>CN) was distilled from calcium hydride. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) was distilled from P<sub>2</sub>O<sub>5</sub>. Cu(OTf)<sub>2</sub>, Yb(OTf)<sub>3</sub>, ReCl<sub>5</sub>, La(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, AuCl, Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O, RuCl<sub>3</sub>·nH<sub>2</sub>O, FeCl<sub>3</sub>·6H<sub>2</sub>O, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, Zn(OTf)<sub>2</sub>, Mg(OTf)<sub>2</sub>, ethyl 2-methylacetoacetate, ethyl 2-oxocyclohexanecarboxylate, ethyl and methyl 2-oxocyclopentanecarboxylate were purchased from Aldrich Chemical Co and were used without further purification. Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and p-anisaldehyde solution followed by heating. Melting points were measured with a Mettler FP 80 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Varian Gemini-200 spectrometer and are reported in ppm from internal CHCl<sub>3</sub>. Optical rotations were measured at 25 ±0.2°C on a Jasco Polarimeter DIP-370 in methylene chloride unless otherwise stated. Analytical high performance liquid chromatography (HPLC) was performed on a Waters chromatograph equipped with a diode array UV detector. Combustion analyses were performed on a Carlo Erba CHNS-O EA1108 elemental analyzer.

## 2. Preparation of hydroxy enone **1** from (+)-camphor

### (1*R*)-2-*endo*-propenoyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**1**)<sup>1</sup>



Methoxyallene<sup>2</sup> (2.94 g, 42 mmol) was added to a solution of nBuLi (2.5 M in hexanes, 16 mL, 40 mmol) in THF (20 mL) cooled to -30°C under a nitrogen atmosphere. After

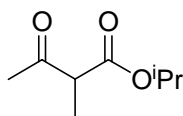
<sup>1</sup> Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288.

<sup>2</sup> (a) Pulz, R.; *Synlett* **2000**, 1697. (b) Brandsma, L.; Verkruijse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*, Elsevier: New York, **1981**. (c) Tius, M.A. *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed.; Wiley: New York, **1995**, Vol. 5, 3316-3320. (d) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas.* **1968**, *87*, 1179. (e) Zimmer, R. *Synthesis* **1993**, 165.

stirring for 30 minutes at the same temperature, TMDA (6.1 mL, 40 mmol) and a solution of (1*R*)-(+)-camphor (3.04 g, 20 mmol) in THF (2.6 mL) were added dropwise. The resulting mixture was allowed to stir for 2 hours at -30 °C and then was quenched with a saturated aqueous solution of NH<sub>4</sub>Cl (20 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL) and washed twice with 1N HCl (15 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure to give the vinyl ketone **1** that was purified by flash silica gel column chromatography using a 1:30 ethyl acetate/hexane mixture as the eluant. Yield: 3.12 g (75%), white solid; m.p. 72-73 °C; [ $\alpha$ ]<sub>D</sub> = - 34.5 (*c* = 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat, cm<sup>-1</sup>) 3488 (OH), 1685 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.88 (dd, 1H, HC=C, *J* = 10.6 Hz, *J'* = 17.2 Hz), 6.34 (dd, 1H, HCH=C, *J* = 2.2 Hz, *J'* = 16.9 Hz), 5.67 (dd, 1H, HCH=C, *J* = 2.2 Hz, *J'* = 10.3 Hz), 2.88 (s, 1H, OH), 2.34-2.25 (m, 1H, HCH), 1.88-1.64 (m, 2H, HCH), 1.44-0.80 (m, 4H, HCH), 1.10 (s, 3H, CH<sub>3</sub>), 0.89 (s, 3H, CH<sub>3</sub>), 0.82 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  201.6, 131.8, 128.7, 86.9, 52.6, 50.6, 45.2, 41.3, 30.2, 26.5, 20.9, 20.4, 10.6; Anal. Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub> (208.33): C, 74.94; H, 9.70. Found: C, 74.85; H, 10.01.

### 3. Preparation of $\beta$ -keto esters

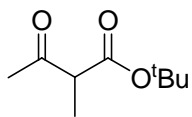
#### Isopropyl 2-methylacetoacetate (**4**)<sup>3</sup>



Titanium tetraisopropoxide (6.4 mL, 21.6 mmol) was added to a solution of ethyl 2-methylacetoacetate (7.4 mL, 50 mmol) in isopropanol (185 mL). The resulting mixture was heated under reflux for 14 h and then concentrated in *vacuo*. The residue was dissolved in hexane (150 mL), and washed with 1 N HCl (2 x 100 mL). The organic layer was dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The residue was distilled in a Kugelrohr apparatus (100° C, 0.18 mmHg) to give the title compound: 6.32 g (80%); colorless liquid; IR (neat, cm<sup>-1</sup>) 1735 (C=O), 1712 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  5.03 (m, 1H, CH), 3.43 (m, 1H, CH), 2.21 (s, 3H, CH<sub>3</sub>), 1.30 (d, 3H, *J* = 6.6 Hz, CH<sub>3</sub>), 1.22 (d, 6H, *J* = 6.6 Hz, 2CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  203.2, 169.6, 68.5, 53.5, 28.1, 21.4, 21.3, 12.4.

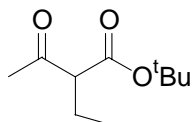
<sup>3</sup> (a) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthes* **1982**, 138. (b) Otera, J.; *Esterification. Methods, Reactions and Applications*, Wiley-VCH, **2003**.

#### ***tert*-Butyl 2-methylacetoacetate (6)<sup>4</sup>**



A solution of diisopropylamine (5.1 mL, 36 mmol) in diethyl ether (60 mL) was cooled to  $-78^{\circ}\text{C}$  under  $\text{N}_2$ , and *n*-butyllithium (14.4 mL, 36 mmol) was added. The resulting mixture was stirred for 15 min. and then a solution of *tert*-butyl propionate (5.4 mL, 36 mmol) in diethyl ether (3 mL) was added dropwise. After stirring for 1 h, a solution of the *N*-methoxy-*N*-methylacetamide (3.2 mL, 30 mmol) in 3 mL of diethyl ether was slowly added. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 3 h, warmed to near room temperature, and poured into 1 N HCl. The mixture was extracted twice with ether, and the combined organic layers were dried over  $\text{MgSO}_4$  and evaporated to dryness. The residue was distilled in a Kugelrohr apparatus ( $70^{\circ}\text{C}$ , 0.18 mmHg) to give the title compound: 3.4 g (66%); colorless liquid; IR (neat,  $\text{cm}^{-1}$ ) 1736 (C=O), 1712 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.35 (m, 1H, CH), 2.17 (s, 3H,  $\text{CH}_3$ ), 1.40 (s, 9H,  $3\text{CH}_3$ ), 1.22 (d, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  203.8, 169.5, 81.6, 54.5, 28.3, 27.8, 12.5.

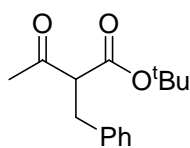
#### ***tert*-Butyl 2-ethylacetoacetate (7)<sup>4</sup>**



A solution of *tert*-butyl butyrate (3.30 g, 22.88 mmol) in diethyl ether (3 mL) was added slowly to a solution of LDA (22.88 mmol, prepared in the usual fashion in 40 mL of ether) at  $-78^{\circ}\text{C}$ . After 30 min., a solution of *N*-methoxy-*N*-methylacetamide (2.7 mL, 25.17 mmol) in diethyl ether (3 mL) was slowly added, and the reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 8 h. The solution was warmed at room temperature and the mixture was then treated as above to give a residue which was purified by distillation ( $95^{\circ}\text{C}$ , 0.18 mmHg): 3.07 g (72%); colorless liquid; IR (neat,  $\text{cm}^{-1}$ ) 1735 (C=O), 1711 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.17 (t, 1H,  $J = 7.3$  Hz, CH), 2.15 (s, 3H,  $\text{CH}_3$ ), 1.77 (m, 2H,  $\text{CH}_2$ ), 1.40 (s, 9H,  $3\text{CH}_3$ ), 0.86 (t, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  203.5, 168.8, 81.6, 62.4, 28.6, 27.9, 21.5, 11.8.

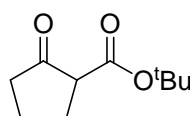
<sup>4</sup> Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229.

### ***tert*-Butyl 2-benzylacetoacetate (8)<sup>5</sup>**



A solution of benzyl bromide (6.0 mL, 50 mmol) in benzene (50 mL) was added to a stirred solution of *tert*-butyl acetoacetate (8.3 mL, 50 mmol) and DBU (7.5 mL, 50 mmol) in benzene (250 mL). The reaction mixture was stirred at room temperature for 48 h, then washed with water and the organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the resulting crude product was purified by distillation (120°C, 0.11 mmHg) to afford the title compound: 4.63 g (37%); colorless liquid; IR (neat, cm<sup>-1</sup>) 1732 (C=O), 1713 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.24-7.14 (m, 5H, arom.), 3.67 (t, 1H, J= 7.3 Hz, CH), 3.09 (d, 2H, J= 7.7 Hz, CH<sub>2</sub>), 2.16 (s, 3H, CH<sub>3</sub>), 1.36 (s, 9H, 3CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 202.7, 168.1, 138.2, 128.7, 128.4, 126.4, 82.0, 62.3, 33.9, 29.5, 27.8.

### ***tert*-Butyl 2-oxocyclopentanecarboxylate (11)<sup>6</sup>**

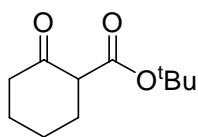


Sodium hydride (60% in oil, 1.51 g, 37.3 mmol) was washed with several portions of dry hexane under nitrogen in the normal way to remove the oil. Dry benzene (15 mL) was added and the suspension was stirred under nitrogen and di-*tert*-butyl adipate (0.19 g, 0.75 mmol) and *tert*-butanol (0.07 mL) were added in one portion. The mixture is then boiled under reflux with vigorous stirring for 30 min. A second portion of di-*tert*-butyl adipate (4.43 g, 17.4 mmol) in dry benzene (7.5 mL) was then added drop-wise to the boiling mixture over 45 min. and the mixture was boiled under reflux with vigorous stirring for a further 4.5 h. The resulting thick suspension was then cooled to 0°C and sufficient 10% aqueous acetic acid was added to obtain a neutral (litmus) solution. The mixture was then poured into water (30 mL), extracted with diethyl ether (2 x 20 mL), the combined extracts washed with saturated aqueous sodium hydrogen carbonate solution (15 mL) and water (15 mL), dried with MgSO<sub>4</sub>, and the solvent removed in vacuo. Distillation under reduced pressure (93°C, 0.11 mmHg) gave the title compound: 2.43 g (73%); colorless liquid; IR (neat, cm<sup>-1</sup>) 1750 (C=O), 1716 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.02 (t, 1H, J= 8.8Hz, CH), 2.30-2.17 (m 4H, 2CH<sub>2</sub>), 2.08 (m, 1H, HCH), 1.83 (m, 1H, HCH), 1.44 (s, 9H, 3CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 212.8, 168.6, 81.7, 55.8, 38.1, 28.0, 27.5, 21.0.

<sup>5</sup> Ono, N.; Yoshimura, T.; Saito, T.; Tamura, R.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jap.* **1979**, 52, 1716.

<sup>6</sup> Henderson, D.; Richardson, K. A.; Taylor, R. J. K. *Synthesis* **1983**, 996.

### ***tert*-Butyl 2-oxocyclohexanecarboxylate (13)<sup>7</sup>**



Sodium hydride (60% in oil, 2.51 g, 62.8 mmol) was washed with several portions of dry hexane under nitrogen in the normal way to remove the oil. Dry benzene (25 mL) was added and the suspension was stirred under nitrogen and di-*tert*-butyl pimelate (0.34 g, 1.30 mmol) and *tert*-butanol (0.13 mL) were added in one portion. The mixture was then boiled under reflux with vigorous stirring for 30 min. A second portion of di-*tert*-butyl pimelate (7.94 g, 29.16 mmol) in dry benzene (12.6 mL) was then added drop-wise to the boiling mixture over 45 min. and the mixture was boiled under reflux with vigorous stirring for a further 4.5 h. The resulting thick suspension was then cooled to 0°C and sufficient 10% aqueous acetic acid was added to obtain a neutral (litmus) solution. The mixture was then poured into water (40 mL), extracted with diethyl ether (2 x 30 mL), the combined extracts washed with saturated aqueous sodium hydrogen carbonate solution (20 mL) and water (20 mL), dried with MgSO<sub>4</sub>, and the solvent removed in vacuo. Distillation under reduced pressure (101°C, 0.21 mmHg) gave the title compound like a tautomers mixture: 4.04 g (67%); colorless liquid; IR (neat, cm<sup>-1</sup>) 1737 (C=O), 1715 (C=O); *Major tautomer* <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 12.38 (s, 1H, OH), 2.25-2.11 (m 4H, 2CH<sub>2</sub>), 1.68-1.53 (m 4H, 2CH<sub>2</sub>), 1.47 (s, 9H, 3CH<sub>3</sub>); *Both tautomers* <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 206.5, 172.4, 171.0, 169.0, 98.7, 81.3, 80.5, 57.7, 41.4, 29.9, 29.0, 28.2, 27.9, 27.1, 23.0, 22.7, 22.4.

## **4. General procedure for the copper catalyzed Michael addition of β-keto esters to vinyl ketone 1**

### **Method A:**

A solution of vinyl ketone **1** (0.1042 g, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) was added drop-wise to a mixture of copper (II) triflate (0.0181 g, 0.05 mmol) and the β-keto ester (1 mL) in 0.4 mL of CH<sub>2</sub>Cl<sub>2</sub> at -20°C. The reaction mixture was stirred at the same temperature overnight. Then, CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added, and the resulting solution was washed twice with 5 mL of water. The organic layer was dried over MgSO<sub>4</sub> and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant EtOAc/hexane 1:10). The diastereomeric ratio was

<sup>7</sup> Van der Baan, J. L.; Bickelhaupt, F. *Tetrahedron* **1974**, 30, 2447.

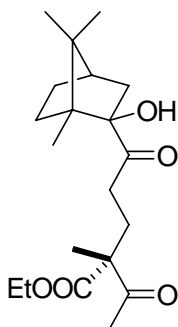
determined in each case by  $^{13}\text{C}$  NMR analyses and in some cases by HPLC analyses. Purification to obtain the major diastereomer was effected by flash column chromatography, using a 1:20 EtOAc-hexane mixture as the eluant.

## Method B

Vinyl ketone **1** (0.1042 g, 0.5 mmol) was added to a mixture of copper (II) triflate (0.0181 g, 0.05 mmol), molecular sieves 4 Å powder (100 mg) and the  $\beta$ -keto ester (1 mL) at  $-20^\circ\text{C}$ . The reaction mixture was stirred at the same temperature overnight. The same work-up and purification procedure of Method A was followed.

## 5. Data of Michael adducts

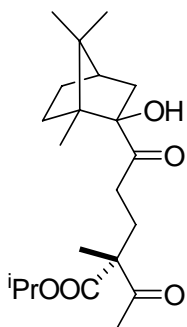
### (R)-Ethyl 2-acetyl-5-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-2-methyl-5-oxopentanoate (**3a**)



The title compound was prepared according to the general procedure **B** from ethyl 2-methylacetoacetate. The mixture was stirred for 18h. The diastereomeric ratio (90:10) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.161 g (91%). Data for **3a**: colorless oil;  $[\alpha]_{\text{D}} = -20.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3514 (OH), 1708 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR

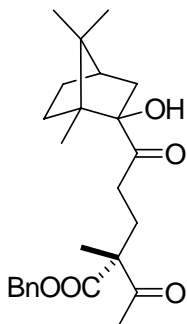
( $\text{CDCl}_3$ )  $\delta$  4.15 (q, 2H,  $J = 7.3$  Hz,  $\text{CH}_2$ ), 2.75 (m, 1H,  $\text{HCH}$ ), 2.71 (s, 1H, OH), 2.39-1.93 (m, 5H,  $2\text{CH}_2$ ,  $\text{HCH}$ ), 2.12 (s, 3H,  $\text{CH}_3$ ), 1.82-1.59 (m, 3H,  $\text{CH}_2$ , CH), 1.34 (m, 2H,  $\text{CH}_2$ ), 1.31 (s, 3H,  $\text{CH}_3$ ), 1.23 (t, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.07 (s, 3H,  $\text{CH}_3$ ), 0.90 (s, 3H,  $\text{CH}_3$ ), 0.80 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.8, 205.6, 172.7, 87.7, 61.5, 58.8, 52.2, 50.5, 45.0, 41.0, 34.4, 30.2, 29.5, 26.4, 26.3, 20.8, 20.5, 19.3, 14.1, 10.6.

**(R)-Isopropyl 2-acetyl-5-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-2-methyl-5-oxopentanoate (14a)**



The title compound was prepared according to the general procedure **A** from isopropyl 2-methylacetoacetate. The mixture was stirred at for 48h. The diastereomeric ratio (91:9) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.133 g (73%). Data for **14a**: m.p. 61-63°C (hexane);  $[\alpha]_{\text{D}} = -15.5$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3514 (OH), 1708 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.00 (m, 1H, CH), 2.74 (s, 1H, OH), 2.76 (m, 1H, HCH), 2.37-1.93 (m, 5H, HCH,  $2\text{CH}_2$ ), 2.09 (s, 3H,  $\text{CH}_3$ ) 1.83-1.57 (m, 4H,  $\text{CH}_2$ , HCH, CH), 1.36 (m, 1H, HCH), 1.27 (s, 3H,  $\text{CH}_3$ ), 1.19 (d, 6H,  $J = 5.8$  Hz,  $2\text{CH}_3$ ), 1.05 (s, 3H,  $\text{CH}_3$ ), 0.89 (s, 3H,  $\text{CH}_3$ ), 0.78 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  212.7, 205.6, 172.2, 87.7, 69.1, 58.8, 52.2, 50.5, 45.0, 41.0, 34.3, 30.2, 29.3, 26.4, 26.2, 21.6, 21.5, 20.8, 20.4, 19.2, 10.7; Anal. Calcd for  $\text{C}_{21}\text{H}_{34}\text{O}_5$  (366.55): C, 68.81; H, 9.37. Found: C, 68.91; H, 9.34.

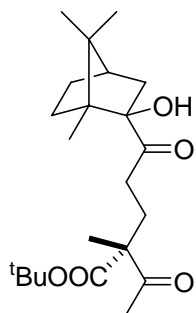
**(R)-Benzyl 2-acetyl-5-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-2-methyl-5-oxopentanoate (15a)**



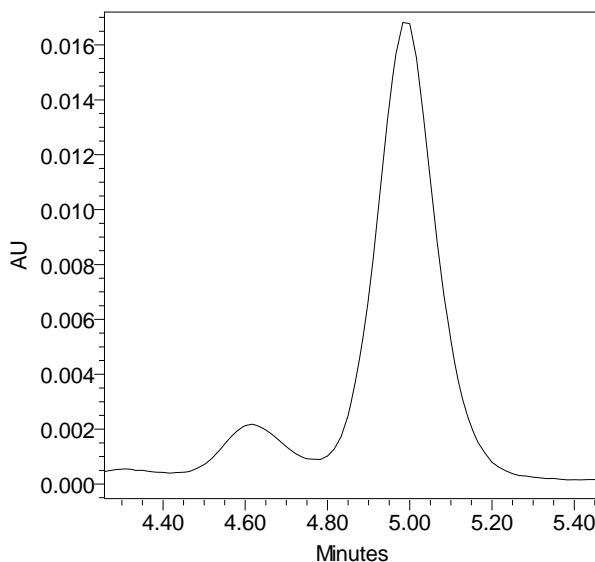
The title compound was prepared according the general procedure **B** from benzyl 2-methylacetoacetate. The mixture was stirred for 40 h. The diastereomeric ratio (85:15) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.139 g (67%). Data for **15a**: IR (neat,  $\text{cm}^{-1}$ ) 3519 (OH), 1711 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.27 (s, 5H,  $\text{C}_6\text{H}_5$ ) 5.09 (s, 2H,  $\text{CH}_2$ ), 2.69 (m, 12H, HCH), 2.64 (s, 1H, OH), 2.31-1.93 (m, 54H, HCH,  $2\text{CH}_2$ ), 2.00 (s, 3H,  $\text{CH}_3$ ) 1.83-1.57 (m, 4H,  $\text{CH}_2$ , HCH, CH), 1.31 (m, 1H, HCH), 1.29 (s, 3H,  $\text{CH}_3$ ), 1.03 (s, 3H,  $\text{CH}_3$ ), 0.83 (s, 3H,  $\text{CH}_3$ ), 0.75 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  212.6, 205.3, 172.5, 135.0, 128.5, 128.4, 128.3, 87.6, 67.2, 58.8, 52.2, 50.5, 45.0, 41.0, 34.3, 30.2, 29.4, 26.4, 26.2, 20.8, 20.4, 19.3, 10.6;



**(R)-*tert*-Butyl 2-acetyl-5-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-2-methyl-5-oxopentanoate (16a)**

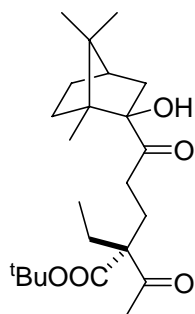


The title compound was prepared according the general procedure **A** from *tert*-butyl 2-methylacetoacetate. The mixture was stirred for 7h. The diastereomeric ratio (93:7) was determined by  $^{13}\text{C}$  NMR analysis and by HPLC analysis (Purospher Si column; Hexane/ $i$ PrOH 99/1; 1 mL/min) after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.171 g (90%). Data for **16a**: colorless oil;  $[\alpha]_{\text{D}} = -12.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3514 (OH), 1737 (C=O), 1708 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.74 (m, 1H, *HCH*), 2.71 (s, 1H, OH), 2.38-1.89 (m, 4H,  $\text{CH}_2$ , *HCH*, *HCH*), 2.11 (s, 3H,  $\text{CH}_3$ ) 1.81-1.59 (m, 4H,  $\text{CH}_2$ , *HCH*, CH), 1.42 (s, 9H, 3 $\text{CH}_3$ ), 1.37 (m, 2H, 2*HCH*), 1.26 (s, 3H,  $\text{CH}_3$ ), 1.07 (s, 3H,  $\text{CH}_3$ ), 0.90 (s, 3H,  $\text{CH}_3$ ), 0.80 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  212.8, 205.8, 171.8, 87.7, 82.1, 59.4, 52.2, 50.5, 45.0, 41.0, 34.4, 30.2, 29.4, 27.9, 26.5, 26.3, 20.8, 20.5, 19.2, 10.7.



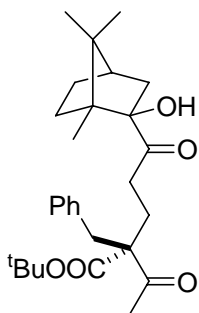
	Retention Time	% Area
1	4.616	7.23
2	4.991	92.77

**(R)-*tert*-Butyl 2-acetyl-2-ethyl-5-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-5-oxopentanoate (17a)**



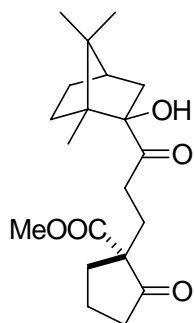
The title compound was prepared according the general procedure **B** from *tert*-butyl 2-ethylacetoacetate. The mixture was stirred for 24h. The diastereomeric ratio (95:5) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.111 g (57%). Data for **17a**: colorless oil;  $[\alpha]_{\text{D}} = -26.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3510 (OH), 1735 (C=O), 1707 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.73 (s, 1H, OH), 2.65 (m, 1H, *H*CH), 2.30-2.00 (m, 4H,  $\text{CH}_2$ , *H*CH, *H*CH), 2.09 (s, 3H,  $\text{CH}_3$ ), 1.81 (q, 2H,  $J = 7.3$  Hz,  $\text{CH}_2$ ), 1.87-1.59 (m, 4H,  $\text{CH}_2$ , CH, *H*CH), 1.41 (s, 9H, 3 $\text{CH}_3$ ), 1.24 (m, 2H,  $\text{CH}_2$ ), 1.07 (s, 3H,  $\text{CH}_3$ ), 0.89 (s, 3H,  $\text{CH}_3$ ), 0.79 (s, 3H,  $\text{CH}_3$ ), 0.74 (t, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  212.7, 205.9, 171.3, 87.7, 82.0, 63.5, 52.1, 50.5, 45.0, 41.0, 33.8, 30.3, 27.9, 26.8, 26.4, 25.3, 24.6, 20.8, 20.4, 10.7, 8.2.

**(S)-*tert*-Butyl 2-acetyl-2-benzyl-5-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-5-oxopentanoate (18a)**



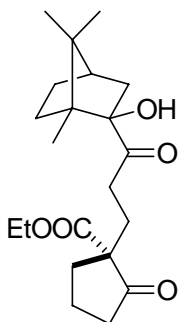
The title compound was prepared according to the general procedure **B** from *tert*-butyl 2-benzylacetoacetate. The mixture was stirred for 19h. The diastereomeric ratio (88:12) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.115 g (50%). Data for **18a**: colorless oil;  $[\alpha]_{\text{D}} = -25.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3512 (OH), 1707 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.24-7.06 (m, 5H, arom.), 3.13 (s, 2H,  $\text{CH}_2$ ), 2.81 (m, 1H, *H*CH), 2.61 (s, 1H, OH), 2.32-2.03 (m, 4H,  $\text{CH}_2$ , *H*CH, *H*CH), 2.15 (s, 3H,  $\text{CH}_3$ ), 1.88-1.66 (m, 4H,  $\text{CH}_2$ , CH, *H*CH), 1.45 (s, 9H, 3 $\text{CH}_3$ ), 1.29 (m, 2H,  $\text{CH}_2$ ), 1.14 (s, 3H,  $\text{CH}_3$ ), 0.97 (s, 3H,  $\text{CH}_3$ ), 0.85 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  212.3, 205.9, 170.8, 136.0, 129.9, 128.2, 126.8, 87.7, 82.5, 64.5, 52.1, 50.6, 45.0, 41.1, 37.7, 33.9, 30.3, 27.9, 27.6, 26.4, 20.8, 20.5, 10.8.

**(R)-Methyl 1-[3-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-3-oxopropyl]-2-oxocyclopentanecarboxylate (19a)**



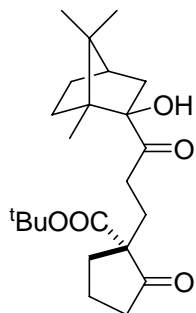
The title compound was prepared according to the general procedure **B** from methyl 2-oxocyclopentanecarboxylate. The mixture was stirred for 30 h. The diastereomeric ratio (76:24) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.133 g (77%). Data for **19a**: colorless oil, IR (neat,  $\text{cm}^{-1}$ ) 3501 (OH), 1752 (C=O), 1722 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.66 (s, 3H,  $\text{CH}_3$ ), 2.80 (s, 1H, OH), 2.82-1.60 (m, 15H,  $7\text{CH}_2$ , CH), 1.32 (m, 2H,  $\text{CH}_2$ ), 1.06 (s, 3H,  $\text{CH}_3$ ), 0.90 (s, 3H,  $\text{CH}_3$ ), 0.80 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  214.4, 213.1, 171.6, 87.5, 59.1, 52.5, 52.3, 50.4, 45.0, 41.0, 37.9, 34.9, 34.0, 30.1, 28.1, 26.4, 20.7, 20.4, 19.6, 10.5.

**(R)-Ethyl 1-[3-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-3-oxopropyl]-2-oxocyclopentanecarboxylate (20a)**

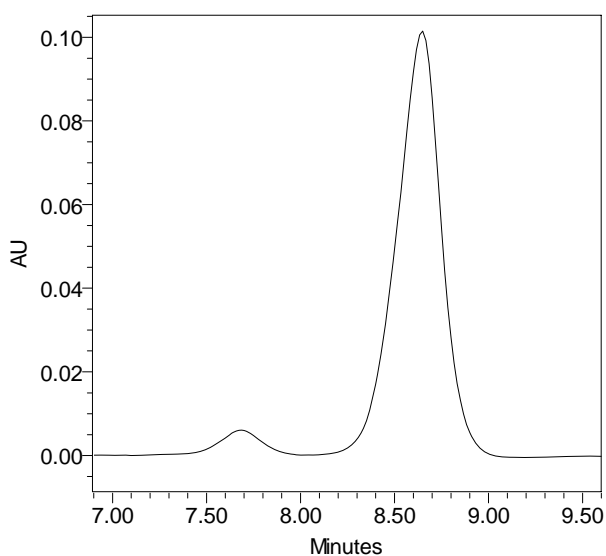


The title compound was prepared according to the general procedure **B** from ethyl 2-oxocyclopentanecarboxylate. The mixture was stirred for 15h. The diastereomeric ratio (80:20) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.179 g (98%). Data for **20a**: colorless oil;  $[\alpha]_{\text{D}} = -28.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3504 (OH), 1748 (C=O), 1720 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.12 (q, 2H,  $J = 7.3$  Hz,  $\text{CH}_2$ ), 2.86-1.60 (m, 15H,  $7\text{CH}_2$ , CH), 2.73 (s, 1H, OH), 1.32 (m, 2H,  $\text{CH}_2$ ), 1.21 (t, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.06 (s, 3H,  $\text{CH}_3$ ), 0.90 (s, 3H,  $\text{CH}_3$ ), 0.80 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  214.5, 213.2, 171.2, 87.5, 61.5, 59.1, 52.4, 50.4, 45.0, 41.0, 37.9, 35.0, 34.1, 30.1, 28.1, 26.5, 20.8, 20.4, 19.6, 14.1, 10.5.

**(R)-*tert*-Butyl 1-[3-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-3-oxopropyl]-2-oxocyclopentanecarboxylate (21a)**

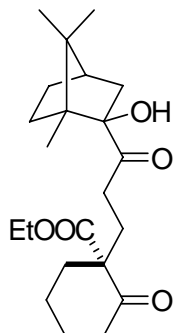


The title compound was prepared according to the general procedure **A** from *tert*-butyl 2-oxocyclopentanecarboxylate. The mixture was stirred for 15h. The diastereomeric ratio (95:5) was determined by  $^{13}\text{C}$  NMR analysis and by HPLC analysis (Purospher Si column; Hexane/ $i$ PrOH 99/1; 1 mL/min) after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.192 g (98%). Data for **21a**: m.p. 94-96°C (hexane);  $[\alpha]_{\text{D}} = -28.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3509 (OH), 1745 (C=O), 1708 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.78 (s, 1H, OH), 2.71 (m, 1H, *HCH*), 2.45-1.57 (m, 14H, 6 $\text{CH}_2$ , CH, *HCH*), 1.20 (m, 2H,  $\text{CH}_2$ ), 1.40 (s, 9H, 3 $\text{CH}_3$ ), 1.07 (s, 3H,  $\text{CH}_3$ ), 0.90 (s, 3H,  $\text{CH}_3$ ), 0.80 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  214.9, 213.5, 170.5, 87.5, 82.0, 59.6, 52.4, 50.3, 45.0, 40.9, 37.9, 35.1, 34.4, 30.2, 28.1, 27.9, 26.5, 20.8, 20.4, 19.6, 10.5; Anal. Calcd for  $\text{C}_{23}\text{H}_{36}\text{O}_5$  (392.59): C, 73.64; H, 8.85. Found: C, 73.66; H, 8.79.



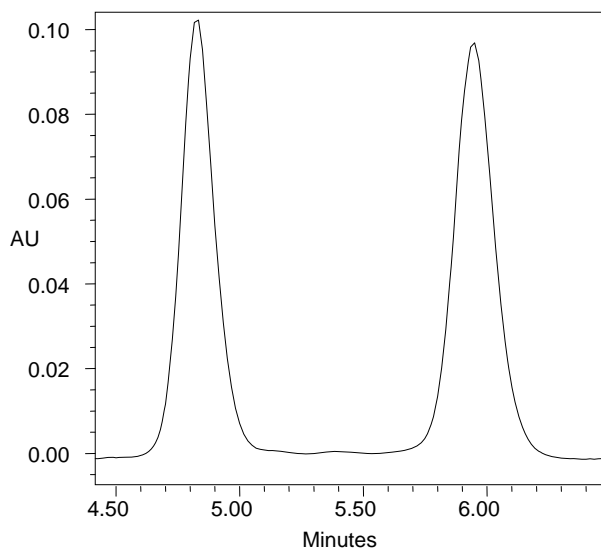
	Retention Time	% Area
1	7.684	5.01
2	8.646	94.99

**(R)-Ethyl 1-[3-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)]-3-oxopropyl]-2-oxocyclohexanecarboxylate (**22a**)**

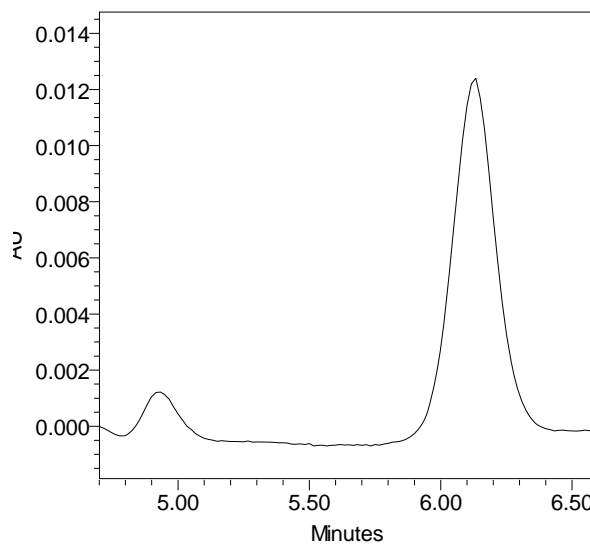


The title compound was prepared according to the general procedure **B** from ethyl 2-oxocyclohexanecarboxylate. The mixture was stirred for 4h. The diastereomeric ratio (91:9) was determined by  $^{13}\text{C}$  NMR analysis and by HPLC analysis (Purospher Si column; Hexane/ $i$ PrOH 99/1; 1 mL/min) after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.176 g (93%). Data for **22a**:

colorless oil;  $[\alpha]_{\text{D}} = -22.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3510 (OH), 1706 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.16 (q, 2H,  $J = 7.3$  Hz,  $\text{CH}_2$ ), 2.75 (s, 1H, OH), 2.72-2.40 (m, 5H,  $2\text{CH}_2$ ,  $\text{HCH}$ ), 2.22 (d, 1H,  $J = 12.4$  Hz, CH), 2.13-1.10 (m, 13H,  $6\text{CH}_2$ ,  $\text{HCH}$ ), 1.24 (t, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.06 (s, 3H,  $\text{CH}_3$ ), 0.89 (s, 3H,  $\text{CH}_3$ ), 0.79 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  213.4, 208.0, 172.1, 87.5, 61.5, 60.1, 52.4, 50.3, 45.0, 41.0, 40.8, 36.9, 34.9, 30.2, 29.4, 27.6, 26.5, 22.6, 20.8, 20.4, 14.2, 10.5.

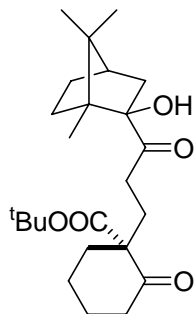


Diastereomeric mixture



	Retention Time	% Area
1	4.929	8.82
2	6.128	91.18

**(R)-*tert*-Butyl 1-[3-[(2R)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]-3-oxo-propyl]-2-oxocyclohexanecarboxylate (23a)**



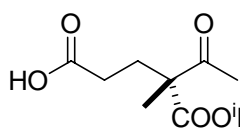
The title compound was prepared according to the general procedure **B** from *tert*-butyl 2-oxocyclohexanecarboxylate. The mixture was stirred for 20h. The diastereomeric ratio (95:5) was determined by  $^{13}\text{C}$ -NMR after removal of the remaining  $\beta$ -keto ester (vacuum evaporation followed by short flash chromatography). Yield: 0.112 g (55%). Data for **23a**: m.p. 96-98°C (hexane);  $[\alpha]_{\text{D}} = -25.0$  ( $c = 1$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat,  $\text{cm}^{-1}$ ) 3513 (OH), 1707 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.73 (s, 1H, OH), 2.61 (m, 2H,  $\text{CH}_2$ ), 2.52-2.22 (m, 3H,  $\text{CH}_2$ , HCH), 2.26 (d, 1H,  $J = 13.2$  Hz, CH), 2.11-1.11 (m, 13H, 6 $\text{CH}_2$ , HCH), 1.43 (s, 9H, 3 $\text{CH}_3$ ), 1.06 (s, 3H,  $\text{CH}_3$ ), 0.90 (s, 3H,  $\text{CH}_3$ ), 0.80 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  213.3, 208.2, 171.1, 87.5, 82.3, 60.6, 52.4, 50.3, 45.0, 41.1, 40.8, 37.0, 34.9, 30.2, 29.6, 28.0, 27.6, 26.5, 22.7, 20.8, 20.4, 10.5; Anal. Calcd for  $\text{C}_{24}\text{H}_{38}\text{O}_5$  (406.62): C, 70.89; H, 9.43. Found: C, 70.86; H, 9.45.

**6. General procedure for the oxidation of Michael adducts to the corresponding carboxylic acids**

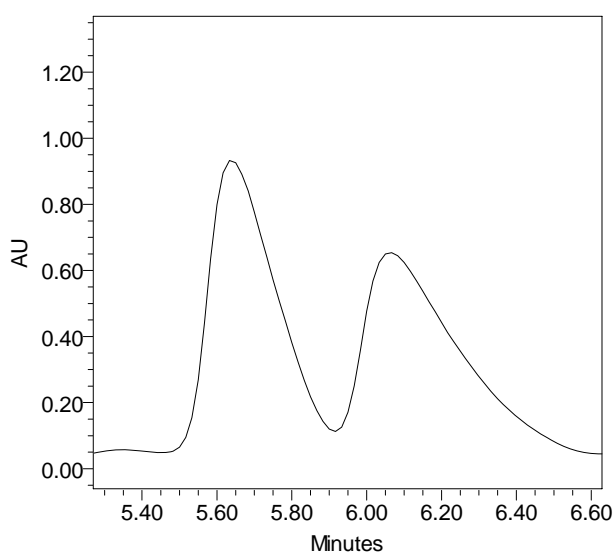
To a solution of the corresponding  $\alpha$ -hydroxy ketone (1 mmol) in acetonitrile (12 mL) at 0 °C was added dropwise a solution of cerium ammonium nitrate (CAN) (1.64 g, 3 mmol) in water (6 mL) and the mixture was stirred at 0 °C for 20 minutes. Then, water (3 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 20 mL). The combined organic extracts were washed with a saturated aqueous solution of  $\text{NaHCO}_3$  (2 x 10 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent evaporated to afford the starting (R)-(+)-camphor in 90% yield.

The basic aqueous layer was acidified by adding concentrate HCl and then extracted with  $\text{CH}_2\text{Cl}_2$  (2x 20 mL). The combined extracts were dried over  $\text{MgSO}_4$ , filtered and the solvent removed under reduced pressure to afford the corresponding carboxylic acid. The enantiomeric ratio was determined by HPLC analysis of the corresponding methyl ester derivatives obtained by treatment of the acids with trimethylsilyl diazomethane in MeOH/benzene.

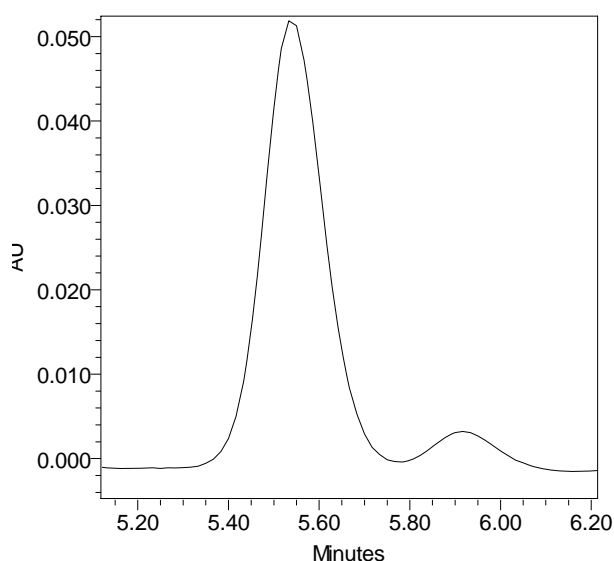
**(R)-4-(isopropoxycarbonyl)-4-methyl-5-oxohexanoic acid (24)**



The title compound was prepared according to general procedure from the mixture **14a/14b** (91:9) (0.366 g, 1 mmol). Yield: 0.195 g (85%). Colorless oil, IR (neat,  $\text{cm}^{-1}$ ) 1709 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.08 (m, 1H, CH), 2.40-2.04 (m, 4H,  $2\text{HCH}$ ,  $2\text{HCH}$ ), 2.17 (s, 3H,  $\text{CH}_3$ ), 1.35 (s, 3H,  $\text{CH}_3$ ), 1.26 (d, 6H,  $J = 6.6$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  204.9, 178.7, 171.7, 69.2, 58.7, 29.3, 26.1, 21.5, 18.9. The enantiomeric ratio (91:9) was determined by HPLC analysis (Chiralpack AS column; Hexane/ $^i\text{PrOH}$  95/5; 0.5 mL/min).

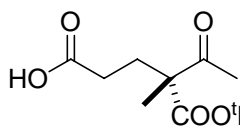


Racemic



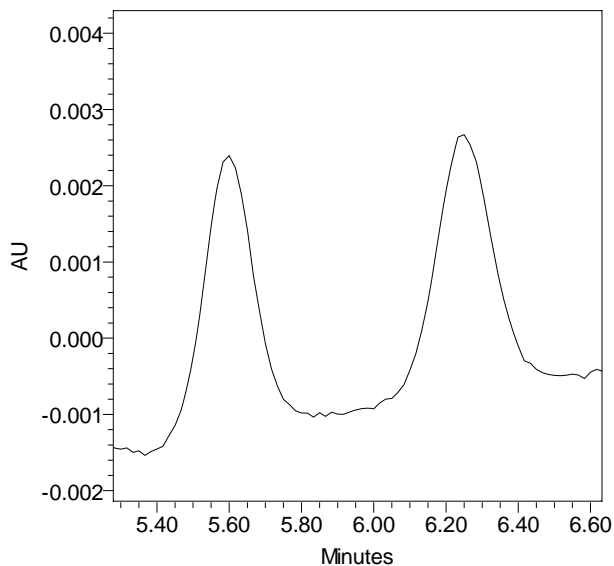
	Retention Time	% Area
1	5.540	90.64
2	5.775	9.36

**(R)-4-(*tert*-butoxycarbonyl)-4-methyl-5-oxohexanoic acid (25)**

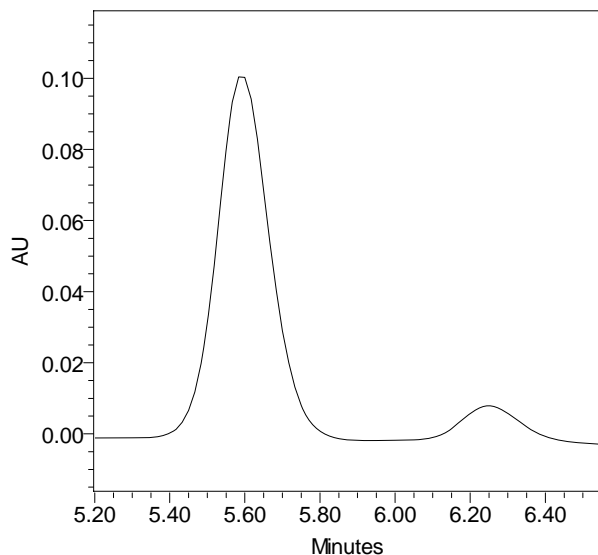


The title compound was prepared according to general procedure from the mixture **16a/16b** (93:7). Yield: (0.380 g, 1 mmol): 0.220 g (90%). Colorless oil, IR (neat,  $\text{cm}^{-1}$ ) 1706 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.39-1.98 (m, 4H,  $2\text{HCH}$ ,  $2\text{HCH}$ ), 2.17 (s, 3H,  $\text{CH}_3$ ), 1.47 (s, 9H,  $3\text{CH}_3$ ), 1.31 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  205.1, 178.9, 171.3, 82.2, 59.3, 29.3,

27.8, 26.1, 18.9. The enantiomeric ratio (93:7) was determined by HPLC analysis (Chiralpack AS column; Hexane/*i*PrOH 92/8; 1 mL/min).

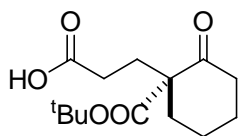


Racemic



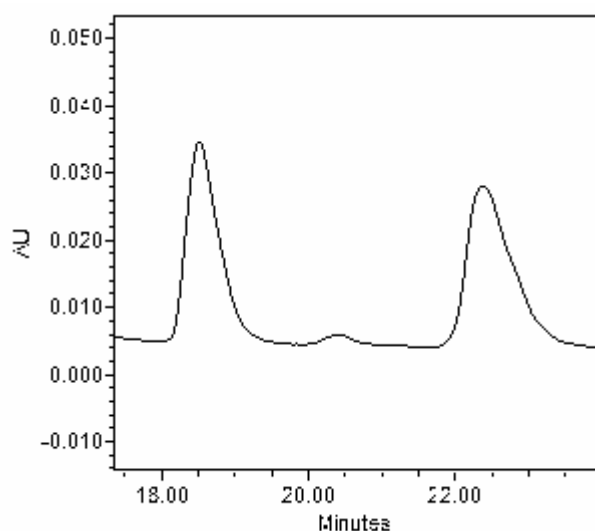
	Retention Time	% Area
1	5.592	92.83
2	6.249	7.17

### 3-((R)-1-(*tert*-Butoxycarbonyl)-2-oxocyclohexyl)propanoic acid (**26**)

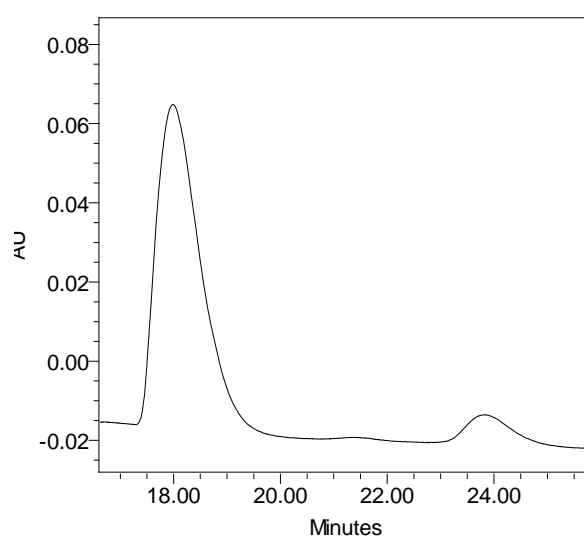


The title compound was prepared according to general procedure from the mixture **23a/23b** (95:5). Yield: (0.406 g, 1 mmol): 0.248 g (92 %), colorless oil, IR (neat,  $\text{cm}^{-1}$ ) 1711 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.57-1.22 (m, 12H, 6CH<sub>2</sub>), 1.44 (s, 9H, 3CH<sub>3</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  207.8, 178.9, 170.6, 82.5, 60.5, 41.1, 36.6, 29.6, 29.3, 27.9, 27.6, 22.6. The enantiomeric ratio (95:5) was determined by HPLC analysis (Chiralcel OD-H column; Hexane/*i*PrOH 98/2; 1 mL/min).





Racemic

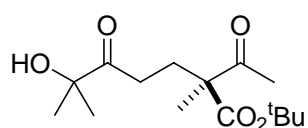


	Retention Time	% Area
1	17.984	94.71
2	23.849	5.29

## 7. General procedure for the enantioselective Michael addition of $\beta$ -keto esters to $\alpha'$ -hydroxy enone **27**

Copper (II) triflate (0.0362 g, 0.1 mmol) and the diamine ligand **28** (0.0498 g, 0.11 mmol) were combined under a nitrogen atmosphere and anhydrous toluene (6 mL) was added. The solution was stirred for 1.5 hours at room temperature. Then, the solution was cooled to 0°C, and a solution of 2-hydroxy-2-methylpent-4-en-3-one (**27**, 0.114 g, 1 mmol) in toluene (2 mL) was added dropwise to the catalyst solution. After stirring at 0°C during 0.5 hours a solution of the corresponding  $\beta$ -keto ester (1 mmol) in toluene (2 mL) was added. The resulting mixture was stirred at 0°C until completion of reaction. Then 1N HCl (10 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 15 mL). The organic layer was dried over  $\text{MgSO}_4$  and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluant EtOAc/hexane 1:5).

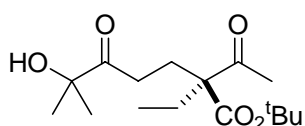
### (S)- *tert*-butyl 2-acetyl-6-hydroxy-2,6-dimethyl-5-oxoheptanoate (**29**)



The title compound was prepared according to the general procedure from *tert*-butyl 2-methylacetoacetate (0.172 g, 1 mmol). The mixture was stirred at 0°C for 16h. The title compound was obtained as a enantiomeric mixture (92:8). Yield: 0.200 g (70%).

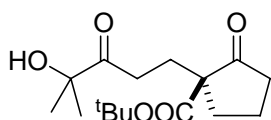
Colorless oil; IR (neat,  $\text{cm}^{-1}$ ) 3503 (OH), 1710 (C=O),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.70 (s, 1H, OH), 2.54 (m, 2H, 2HCH), 2.16 (s, 3H,  $\text{CH}_3$ ) 2.09 (m, 2H, 2HCH), 1.46 (s, 9H, 3 $\text{CH}_3$ ), 1.37 (s, 6H, 2 $\text{CH}_3$ ), 1.30 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  213.4, 205.3, 171.5, 82.1, 59.2, 30.7, 28.7, 27.8, 26.6, 26.5, 26.2, 19.3.

**(S)- *tert*-butyl 2-acetyl-2-ethyl-6-hydroxy-6-methyl-5-oxoheptanoate (30)**



The title compound was prepared according to the general procedure from *tert*-butyl 2-ethylacetoacetate (0.186 g, 1 mmol). The mixture was stirred at  $0^\circ\text{C}$  for 40h. The title compound was obtained as a enantiomeric mixture (88:12). Yield: 0.212 g (70%). Colorless oil; IR (neat,  $\text{cm}^{-1}$ ) 3497 (OH), 1707 (C=O),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.70 (s, 1H, OH), 2.41 (m, 2H, 2HCH), 2.14 (s, 3H,  $\text{CH}_3$ ) 2.09 (m, 2H, 2HCH), 1.86 (q, 2H,  $\text{CH}_2$ ,  $J=7.7$  Hz), 1.46 (s, 9H, 3 $\text{CH}_3$ ), 1.35 (s, 6H, 2 $\text{CH}_3$ ), 1.30 (t, 3H,  $\text{CH}_3$ ,  $J=7.7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  213.4, 205.2, 171.1, 82.1, 63.4, 30.3, 27.8, 26.7, 26.5, 26.4, 24.9, 24.8, 8.2.

**(S)-*tert*-butyl 1-(4-hydroxy-4-methyl-3-oxopentyl)-2-oxocyclopentanecarboxylate (31)**

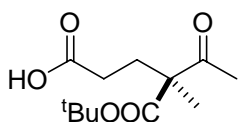


The title compound was prepared according to the general procedure from *tert*-butyl 2-oxocyclopentanecarboxylate (0.184 g, 1 mmol). The mixture was stirred at  $0^\circ\text{C}$  for 16h. The title compound was obtained as a enantiomeric mixture (84:16). Yield: 0.205 g (70%). Colorless oil; IR (neat,  $\text{cm}^{-1}$ ) 3490 (OH), 1745 (C=O), 1715 (C=O).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.89 (m, 2H,  $\text{CH}_2$ ) 2.64-1.78 (m, 8H, 4 $\text{CH}_2$ ), 1.42 (s, 9H, 3 $\text{CH}_3$ ), 1.36 (s, 6H, 2 $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  215.1, 213.8, 170.4, 82.1, 76.3, 59.4, 38.0, 34.7, 30.9, 29.7, 27.9, 27.3, 26.5, 19.6.

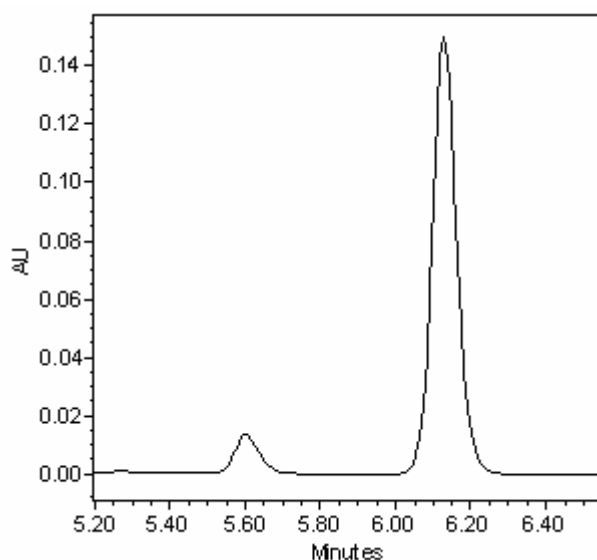
## 8. General procedure for the oxidation of Michael adducts (**29**, **30** and **31**) to the corresponding carboxylic acids

To a solution of the corresponding  $\alpha$ -hydroxy ketone (1 mmol) in acetonitrile (12 mL) at 0 °C was added drop-wise a solution of cerium ammonium nitrate (CAN) (1.64 g, 3 mmol) in water (6 mL) and the mixture was stirred at 0 °C for 20 minutes. Then, water (3 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL). The combined organic extracts were washed with a saturated aqueous solution of NaHCO<sub>3</sub> (2 x 10 mL). The basic aqueous layer was acidified by adding concentrate HCl and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 20 mL). The combined extracts were dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure to afford the corresponding carboxylic acid. The enantiomeric ratio was determined by HPLC analysis of the methyl ester of the corresponding acid.

### (S)-4-(*tert*-butoxycarbonyl)-4-methyl-5-oxohexanoic acid

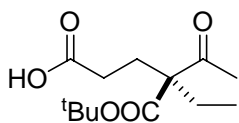


The title compound was prepared according to general procedure from (S)-*tert*-butyl 2-acetyl-6-hydroxy-2,6-dimethyl-5-oxoheptanoate **29** (0.286 g, 1 mmol). Yield: 0.182 g, (75%). Data as **25**. The enantiomeric ratio (92:8) was determined by HPLC analysis (Chiralpack AS column; Hexane/*i*PrOH 92/8; 1 mL/min).



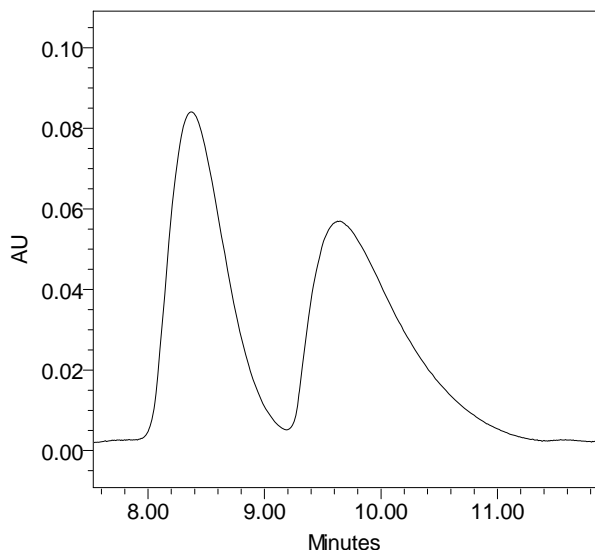
	Retention Time	% Area
1	5.612	8.27
2	6.124	91.73

### (S)-4-(*tert*-butoxycarbonyl)-4-ethyl-5-oxohexanoic acid

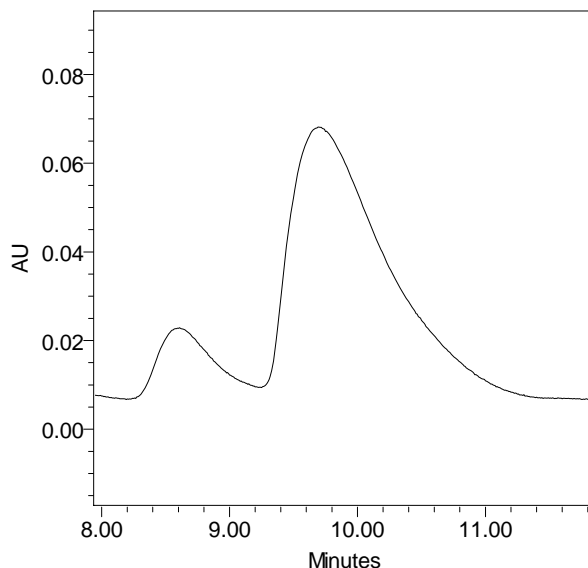


The title compound was prepared according to general procedure from (S)-*tert*-butyl 2-acetyl-2-ethyl-6-hydroxy-6-methyl-5-oxoheptanoate **30** (0.300 g, 1 mmol). Yield: 0.173 g (67%). Colorless oil, IR (neat,  $\text{cm}^{-1}$ ) 1707 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.22 ( $\text{s}_\text{b}$ , 2H, 2HCH), 2.16 (s, 3H,  $\text{CH}_3$ ), 2.16 ( $\text{s}_\text{b}$ , 2H, 2HCH), 1.87 (q, 2H,  $\text{CH}_2$ ,  $J=7.7$  Hz) 1.47 (s, 9H, 3 $\text{CH}_3$ ), 0.8 (t, 3H,  $\text{CH}_3$ ,  $J=7.7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  205.0, 178.4, 171.0, 82.2, 63.4, 29.7, 27.8, 26.6, 25.4, 24.4, 8.1.

The enantiomeric ratio (88:12) was determined by HPLC analysis (Chiralpack AS column; Hexane/ $i$ PrOH 99.5/0.5; 1 mL/min).

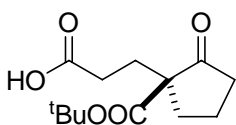


Racemic



	Retention Time	% Area
1	8.604	11.61
2	9.699	88.39

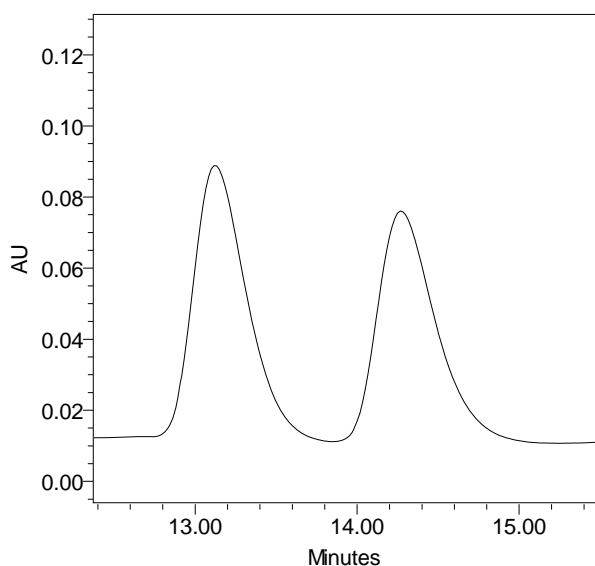
### 3-((S)-1-(*tert*-Butoxycarbonyl)-2-oxocyclopentyl)propanoic acid



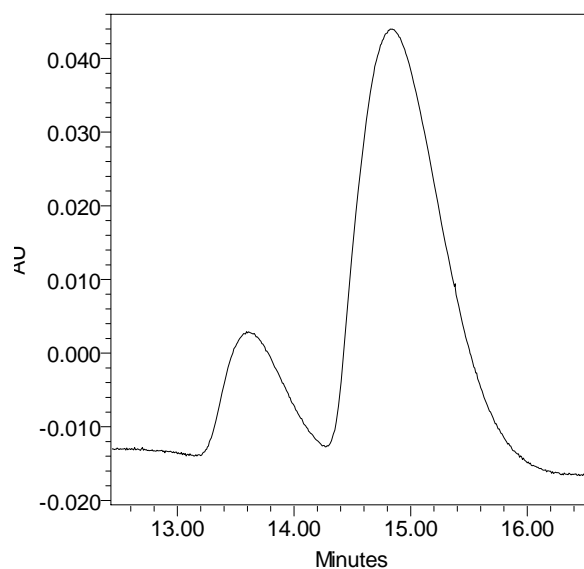
The title compound was prepared according to general procedure from (S)-*tert*-butyl 1-(4-hydroxy-4-methyl-3-oxopentyl)-2-oxocyclopentanecarboxylate **31** (0.298 g, 1

mmol). Yield: 0.215 g (84 %). Colorless oil, IR (neat,  $\text{cm}^{-1}$ ) 1744 (C=O), 1719 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.63-1.82 (m, 11H, 1 OH, 5 $\text{CH}_2$ ), 1.44 (s, 9H, 3 $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  214.7, 178.9, 170.1, 82.2, 59.6, 37.9, 34.0, 29.5, 28.0, 27.9, 19.6.

The enantiomeric ratio (84:16) was determined by HPLC analysis (Chiralcel OD-H column; Hexane/ $i$ PrOH 95/5; 0.5 mL/min).

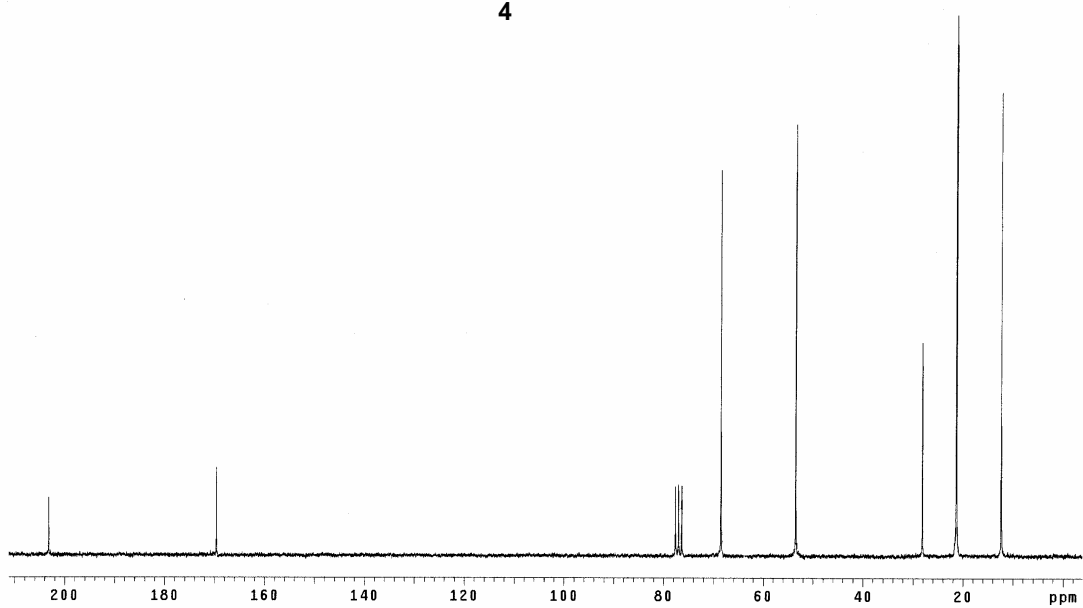
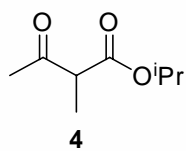
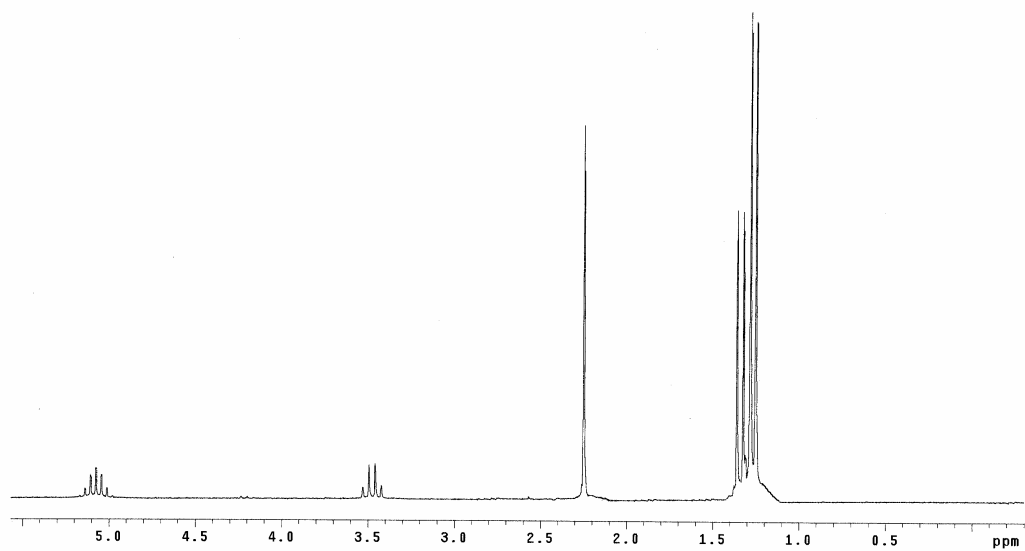
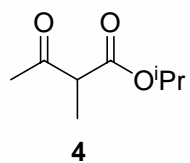


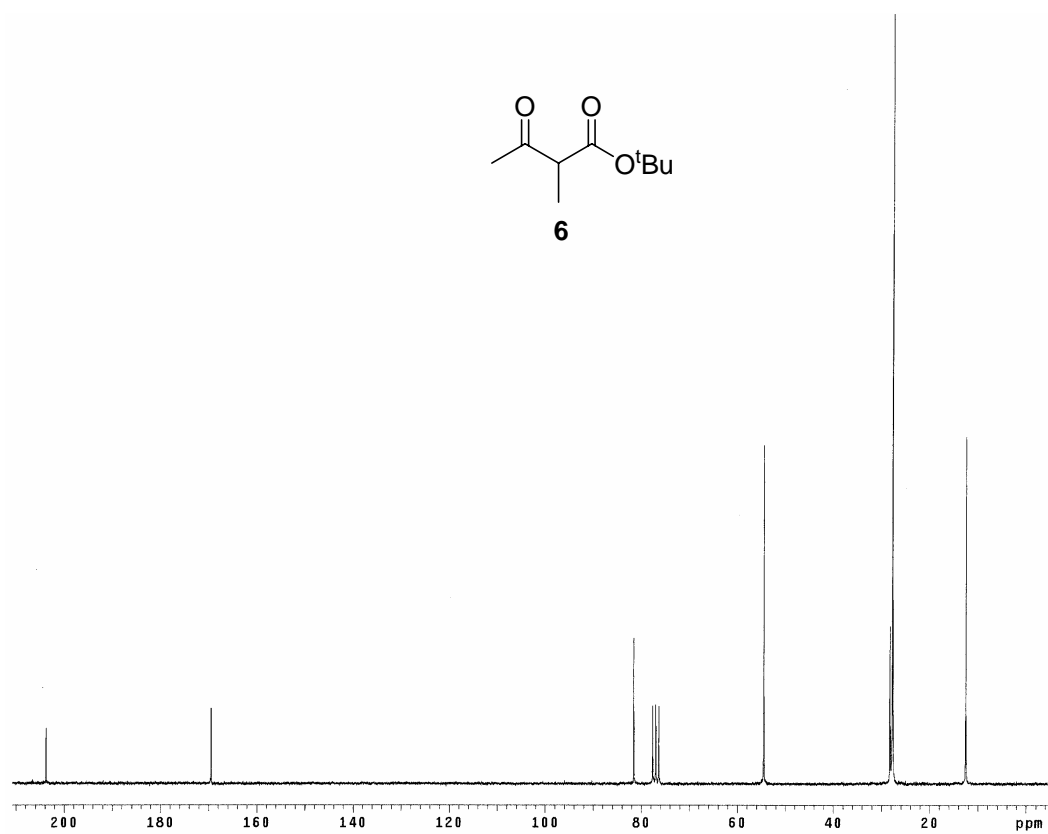
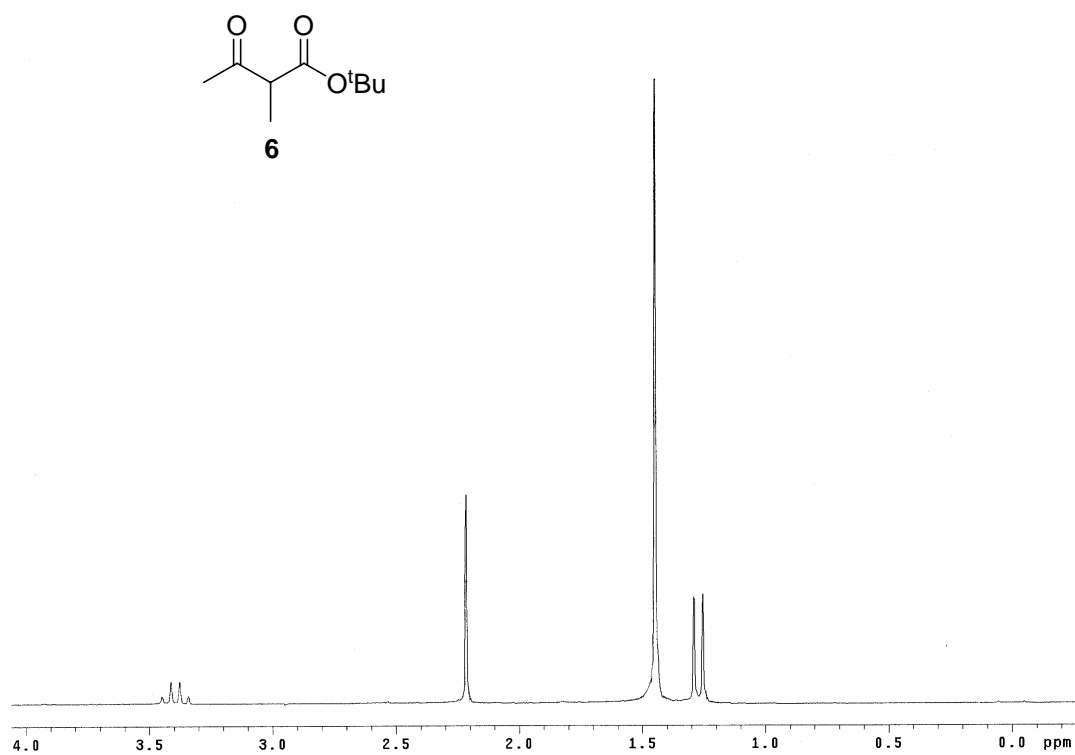
Racemic

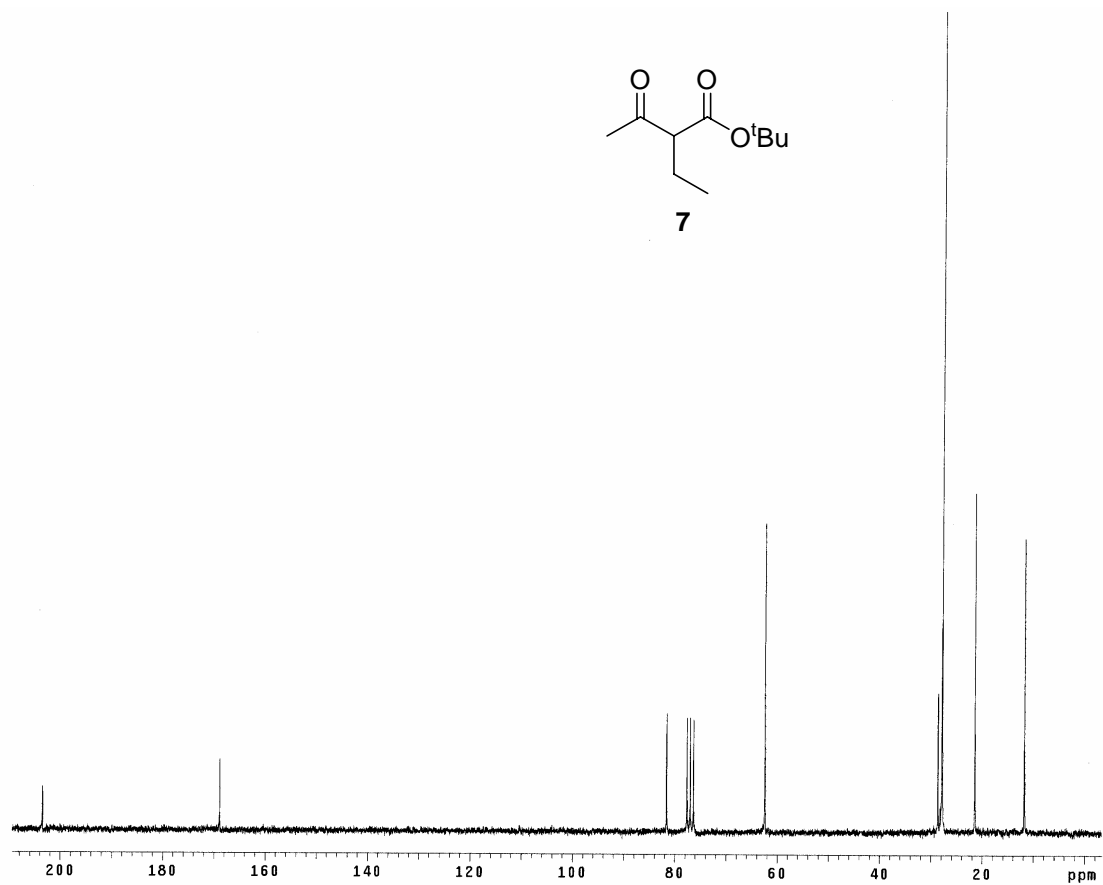
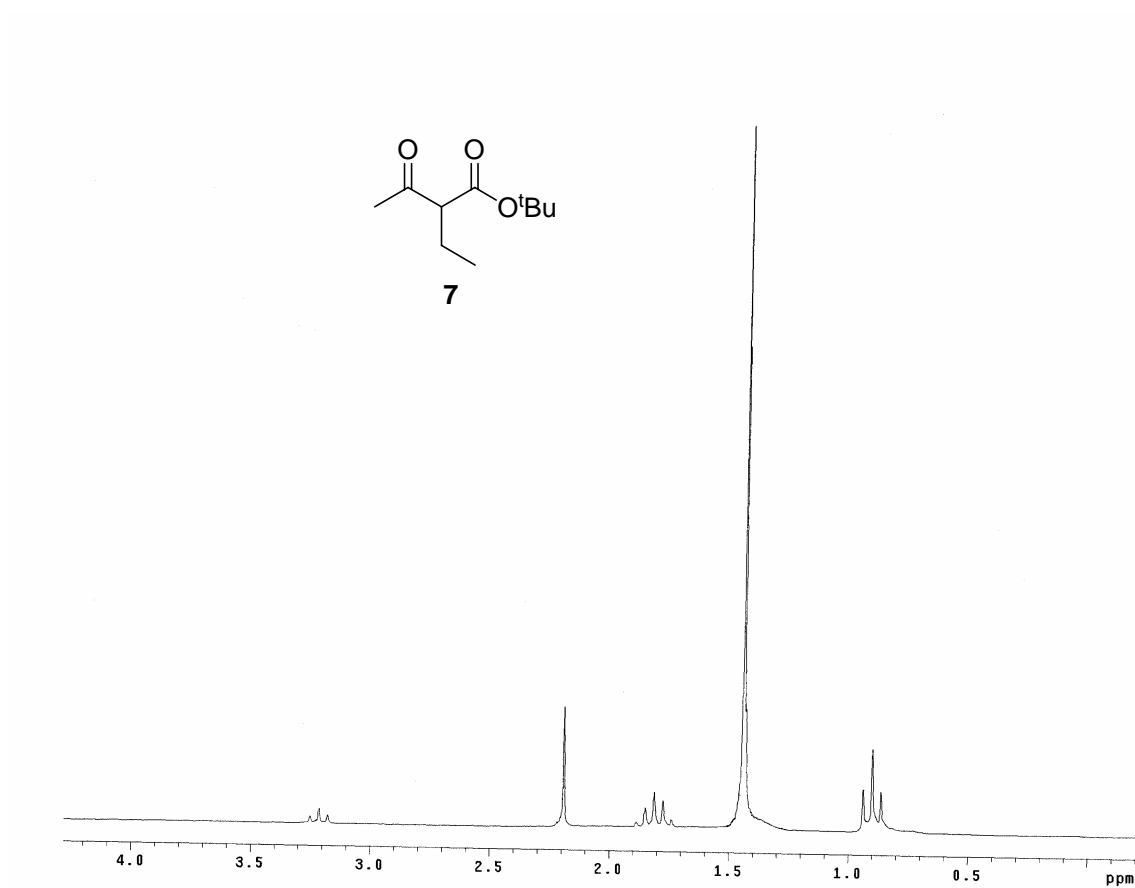


	Retention Time	% Area
1	13.592	15.61
2	14.842	84.39

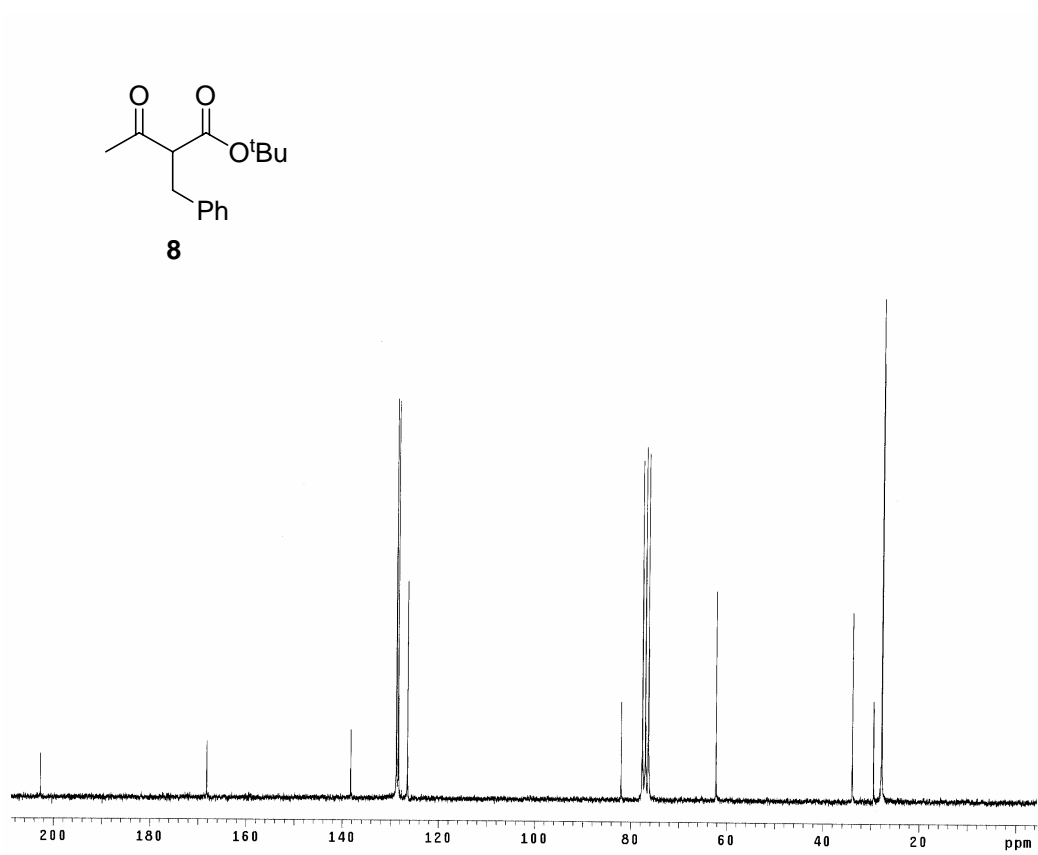
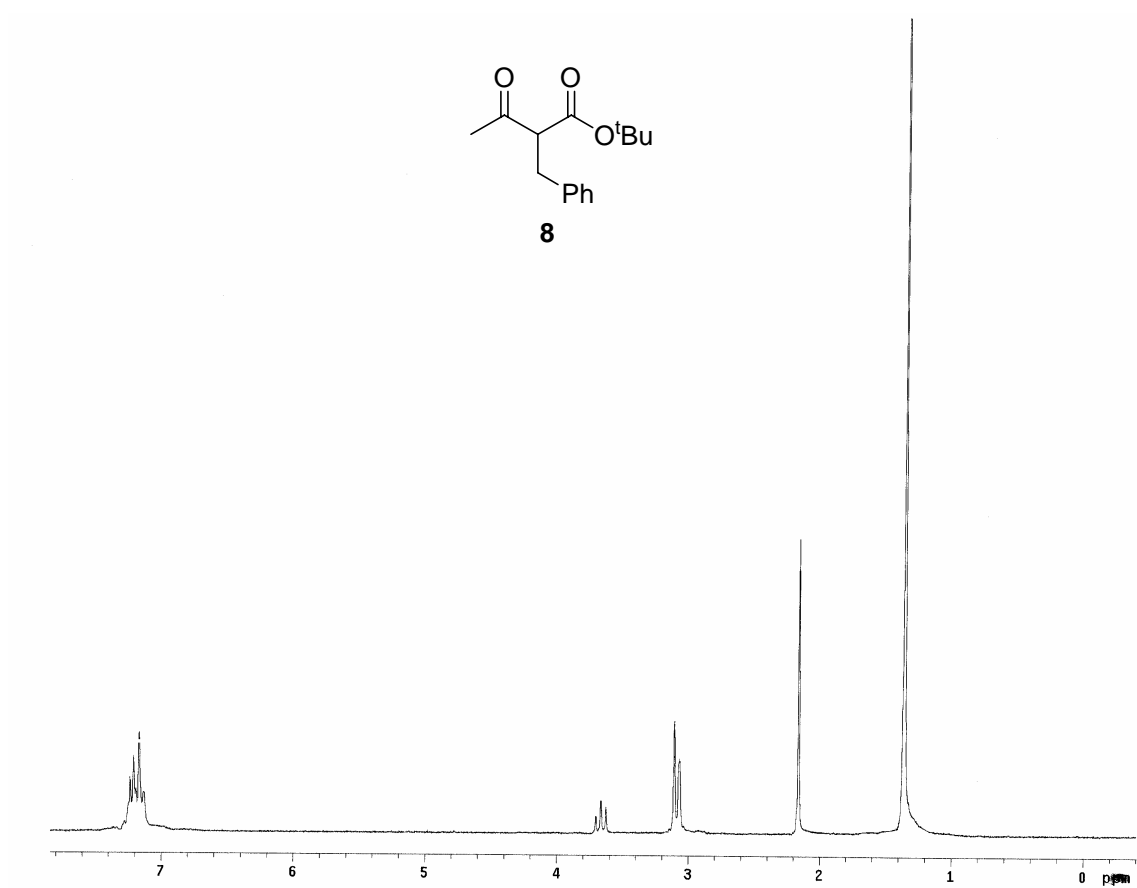
## 9. Selected NMR spectra of Michael adducts and scission products

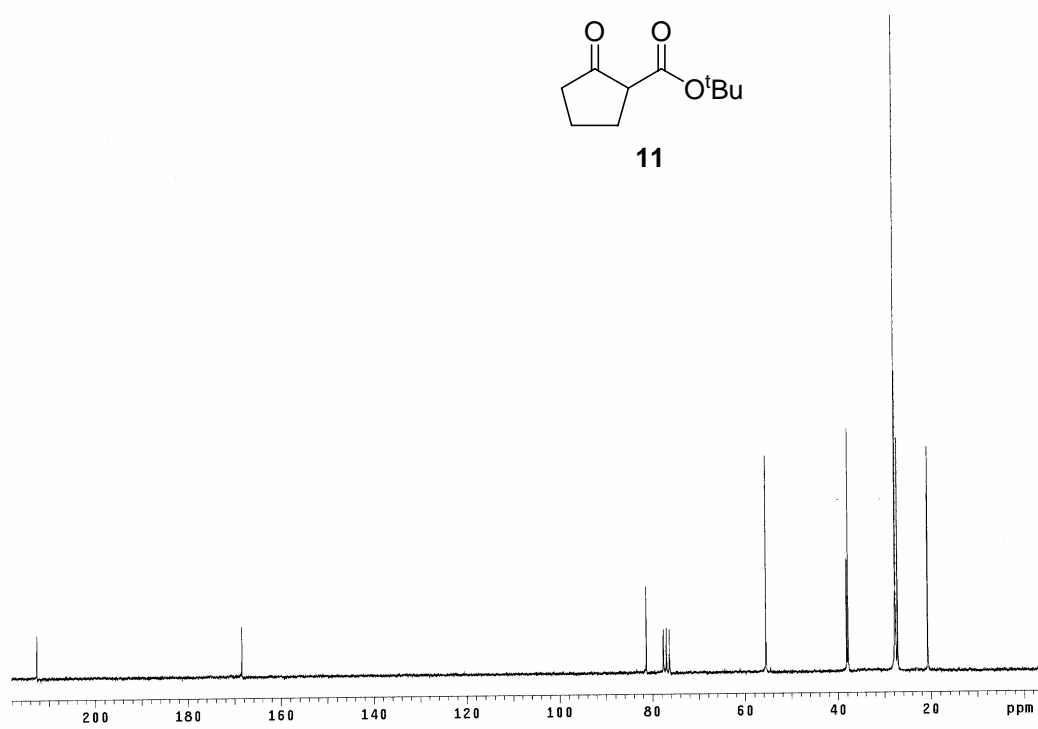
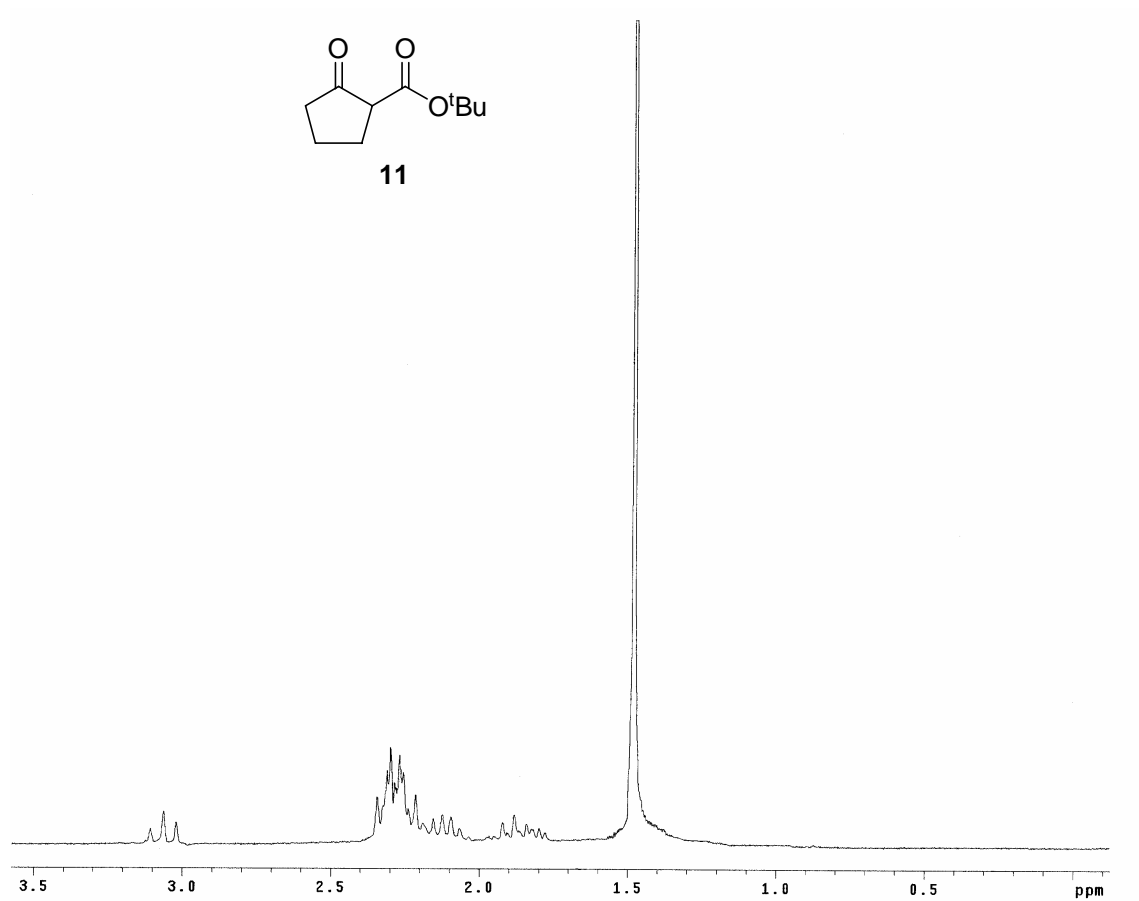


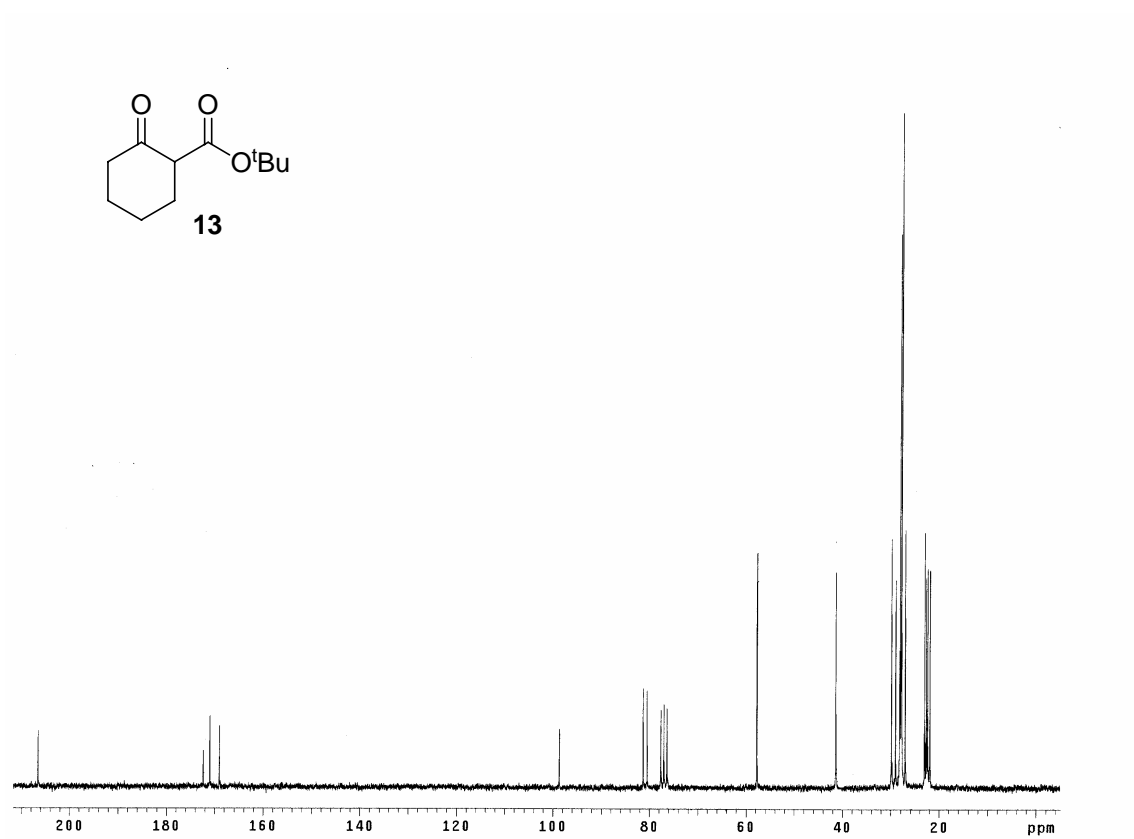
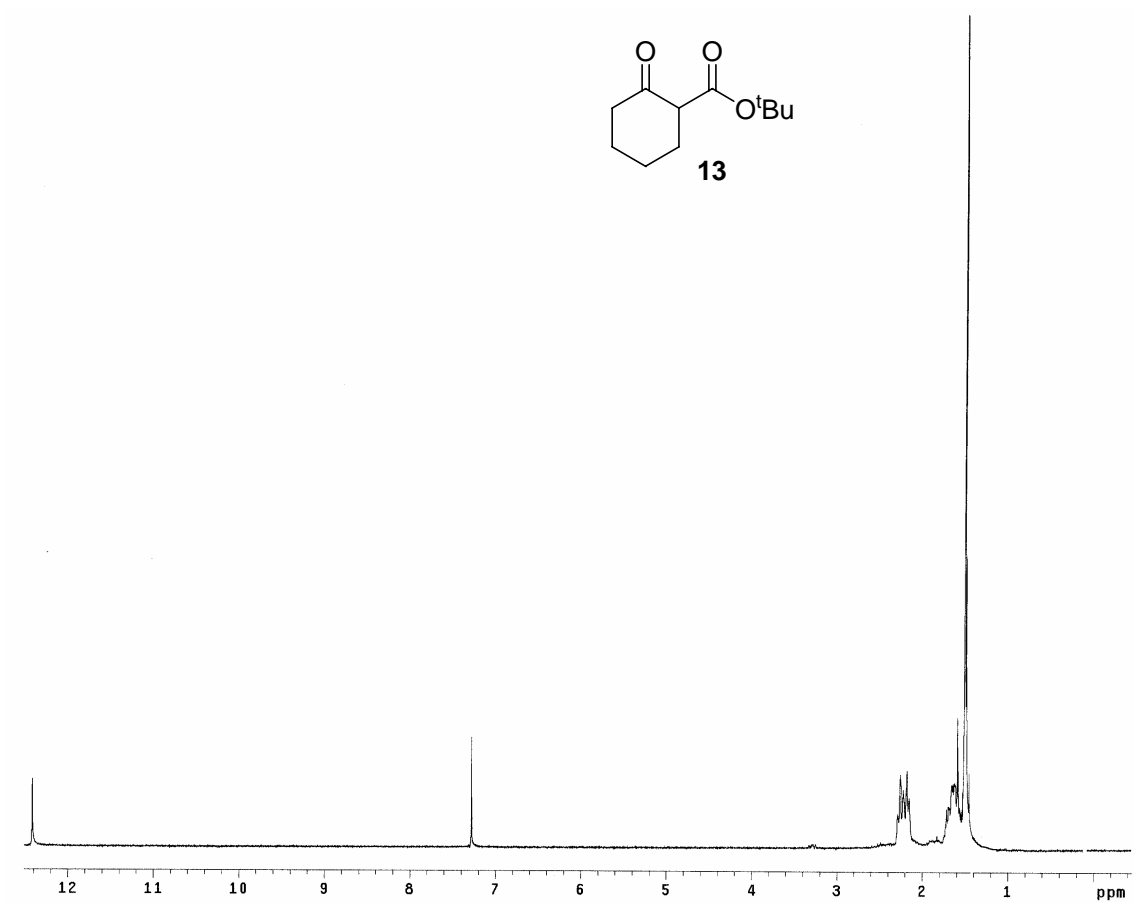


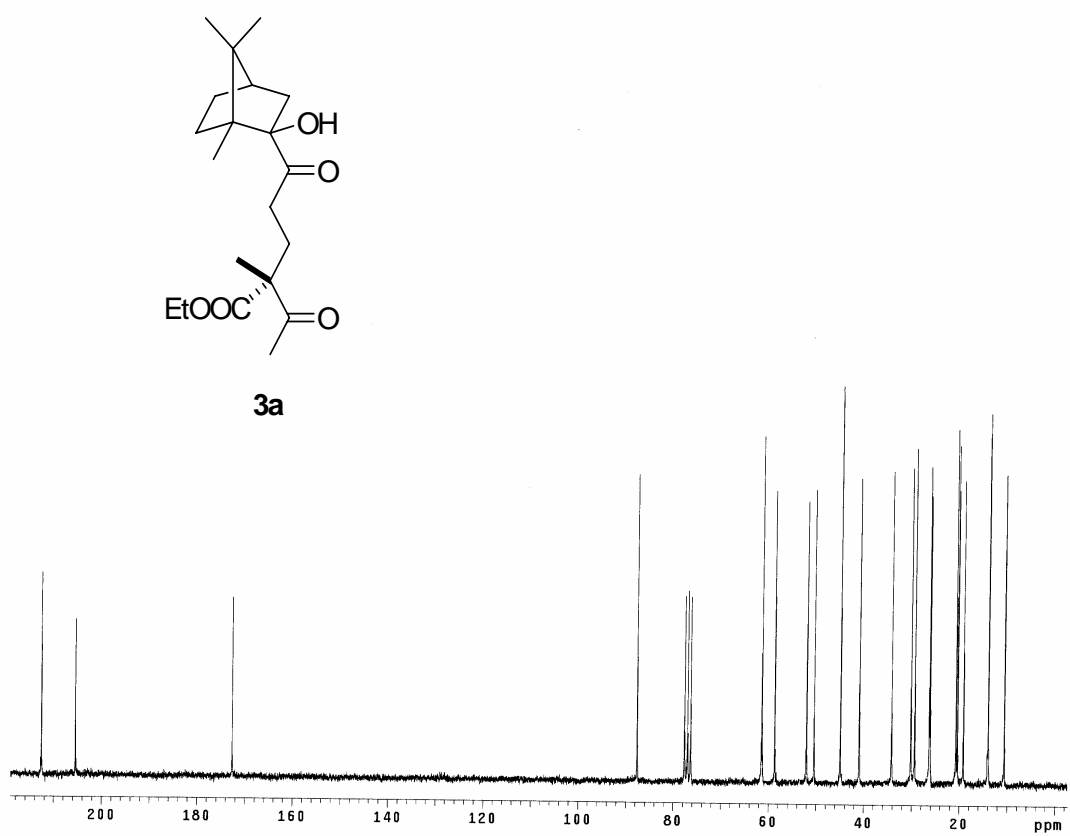
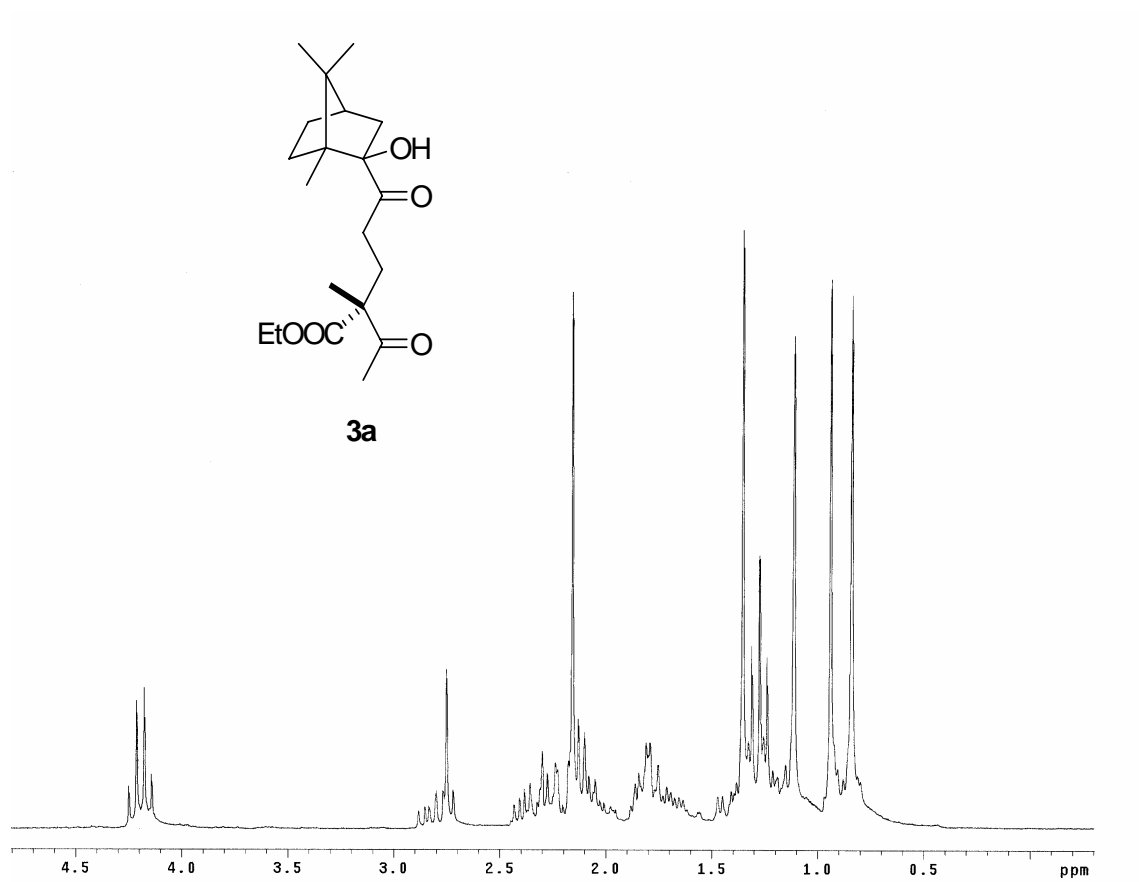


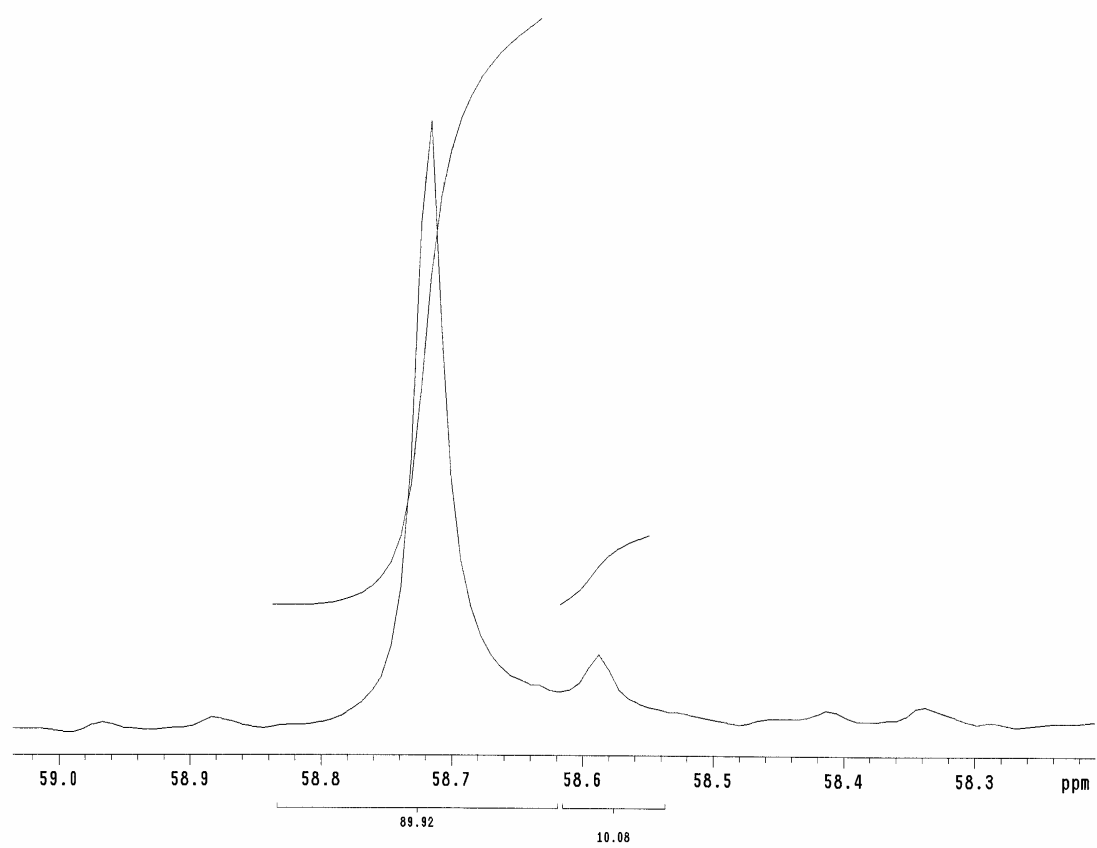
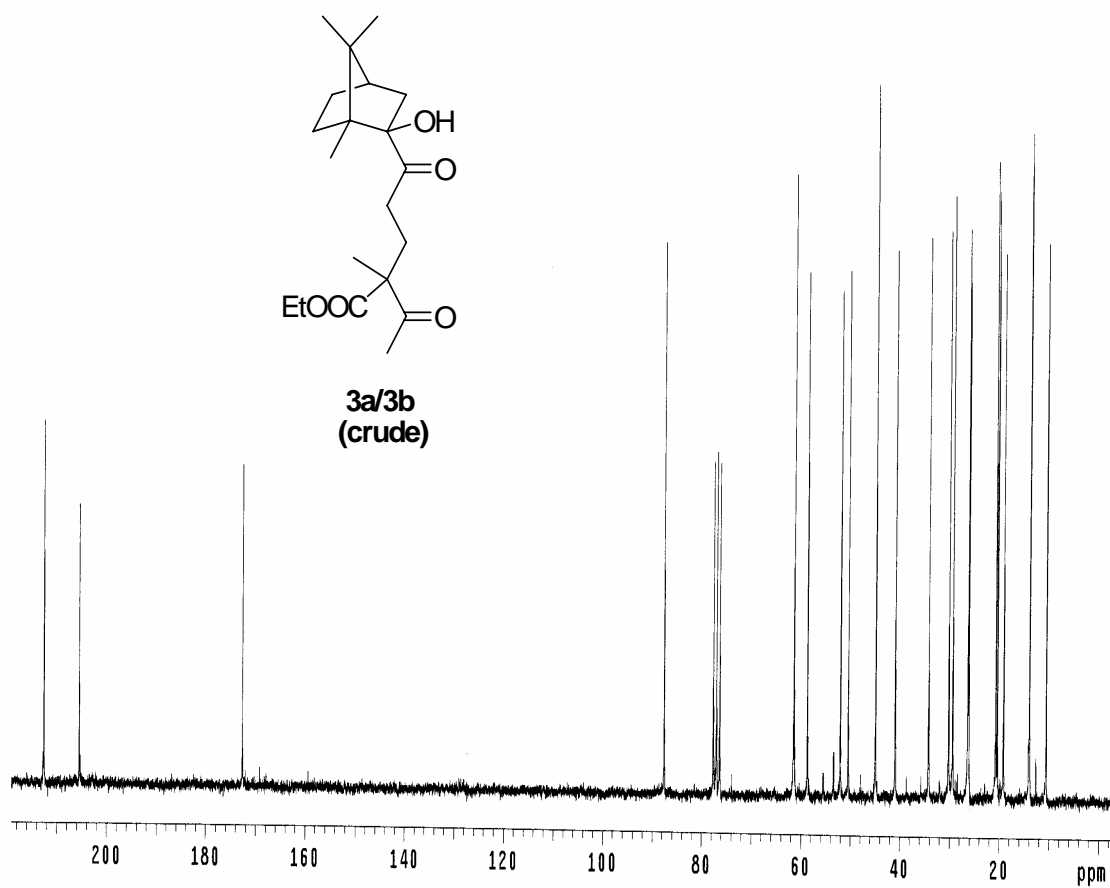


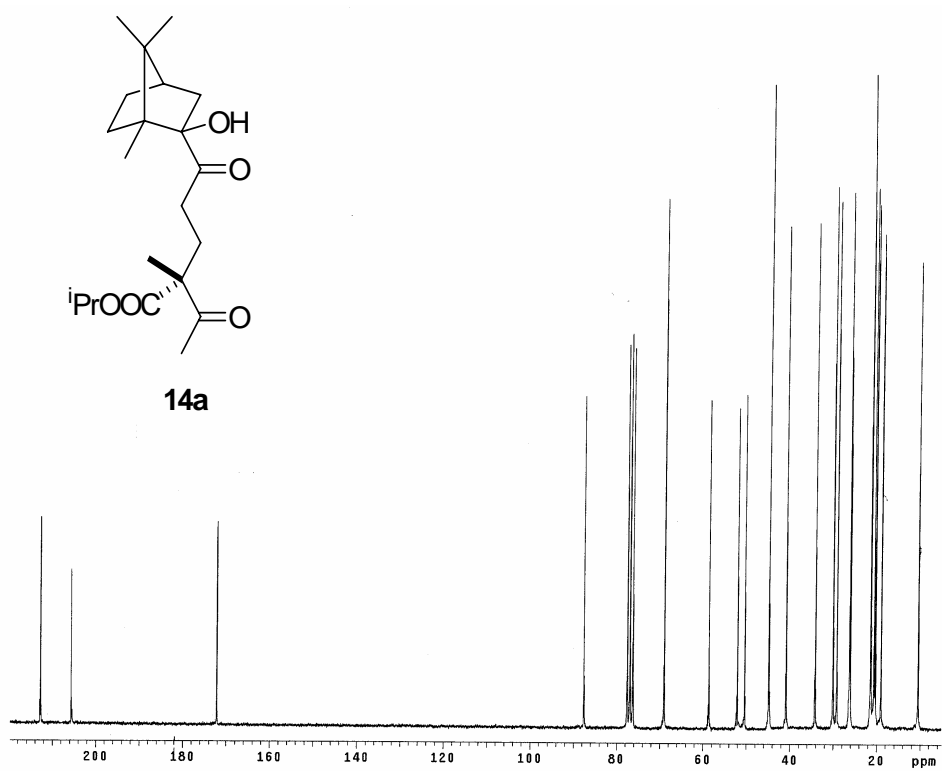
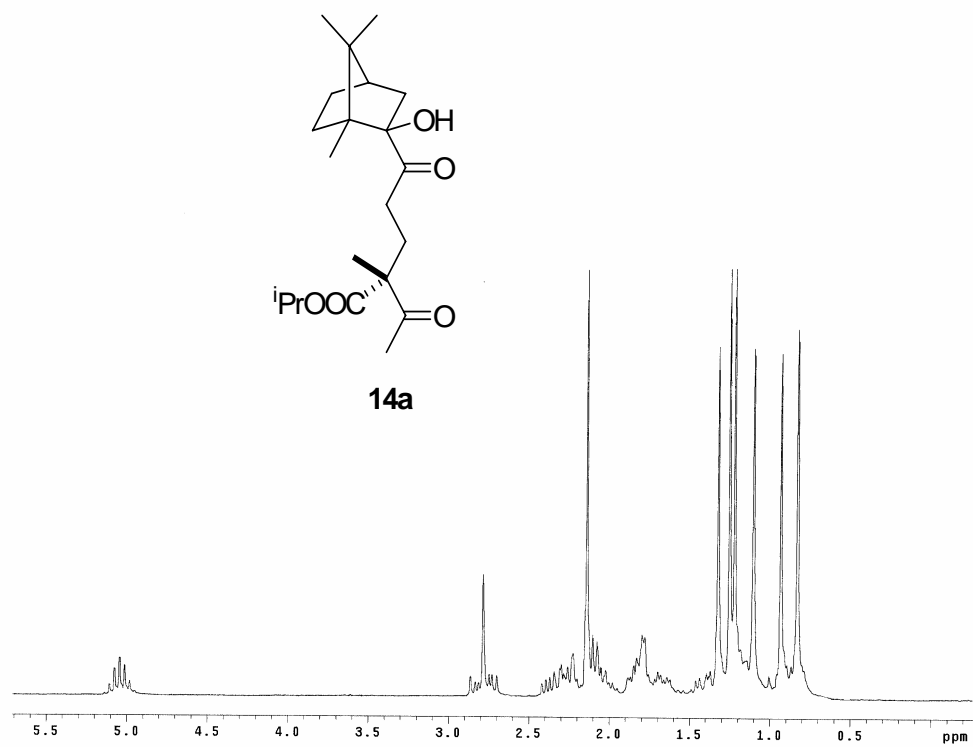


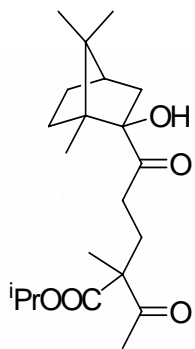




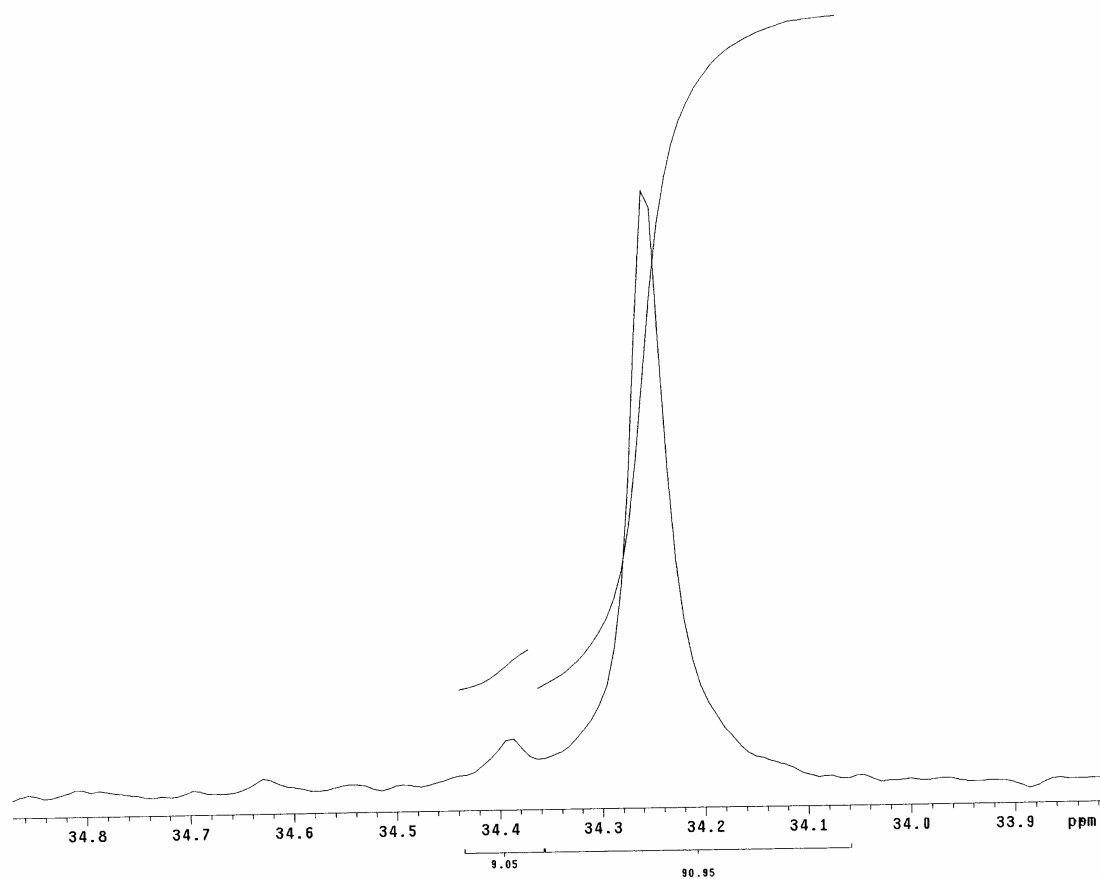
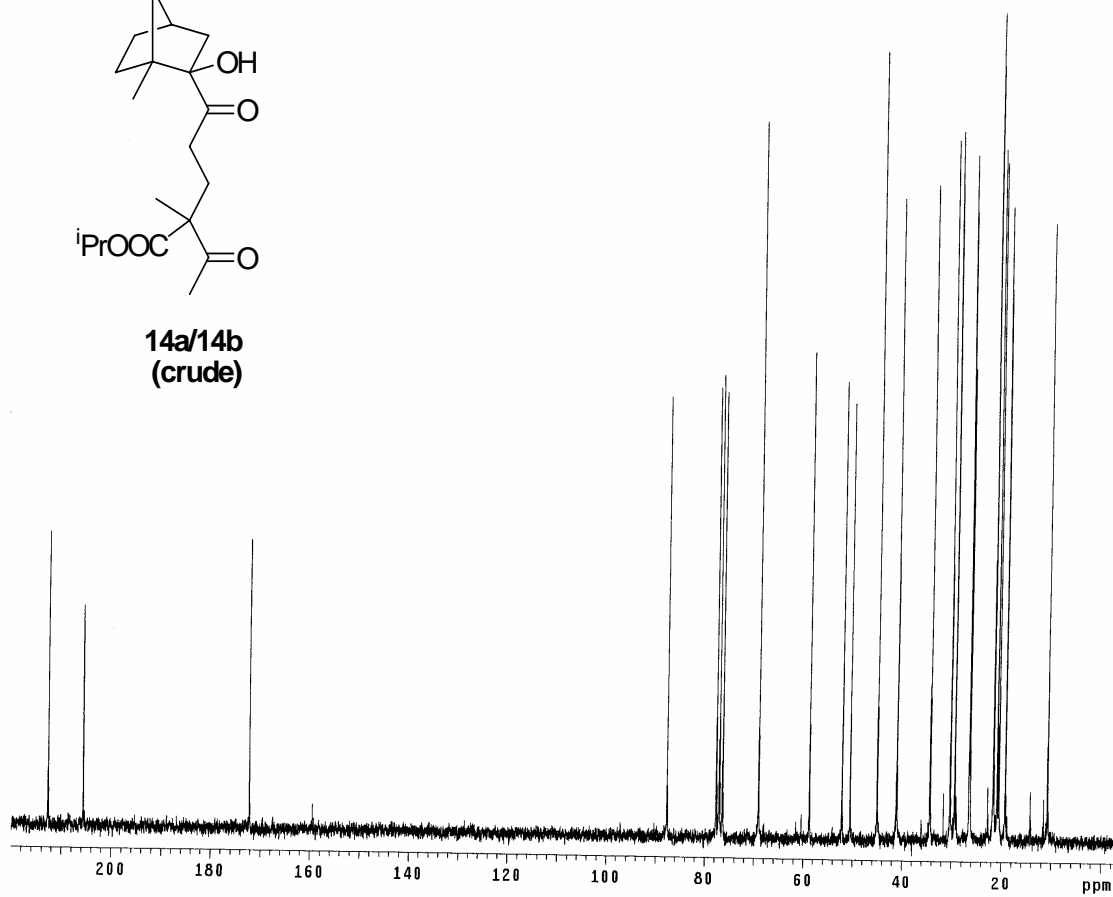


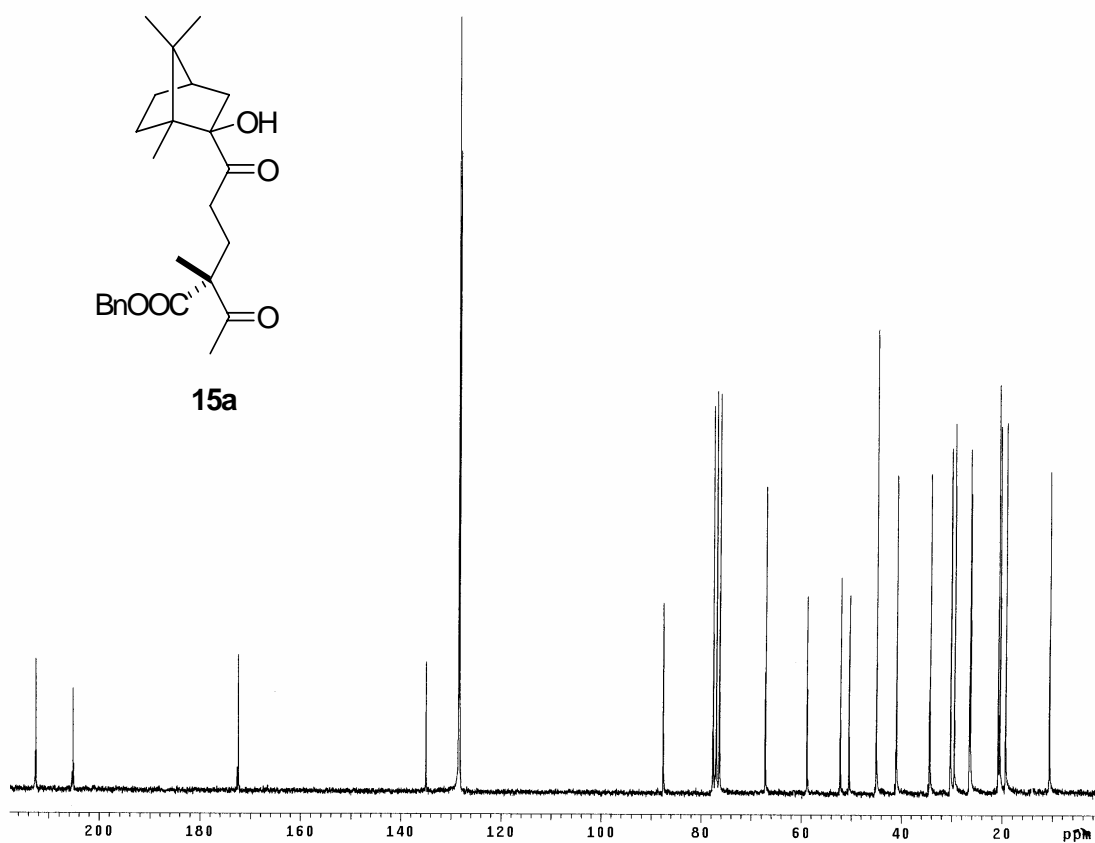
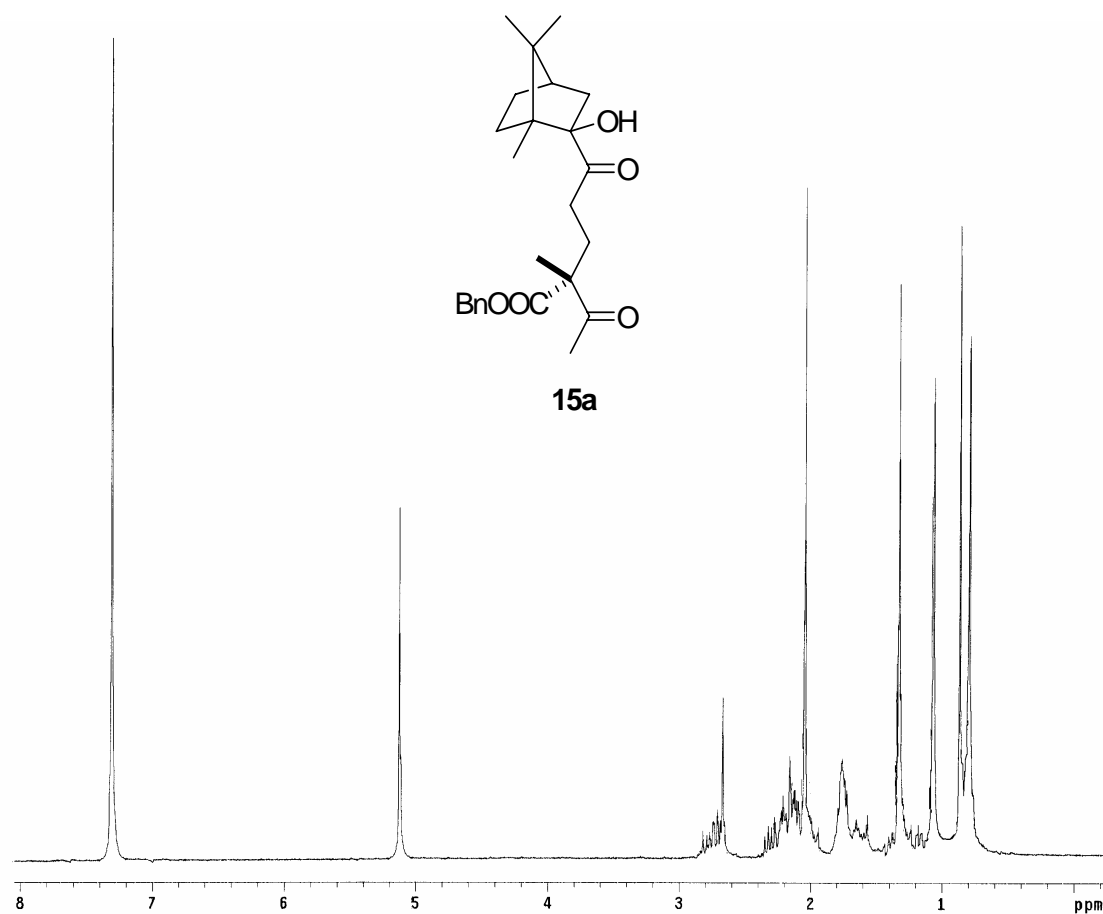




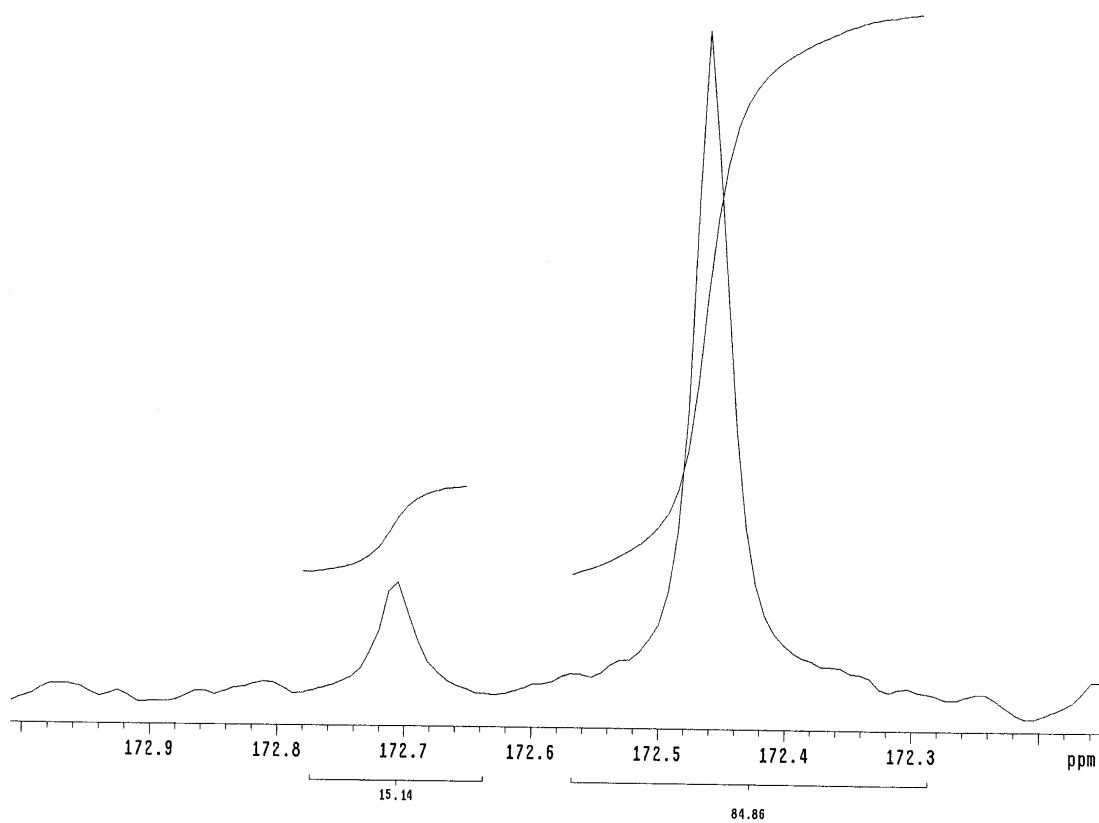
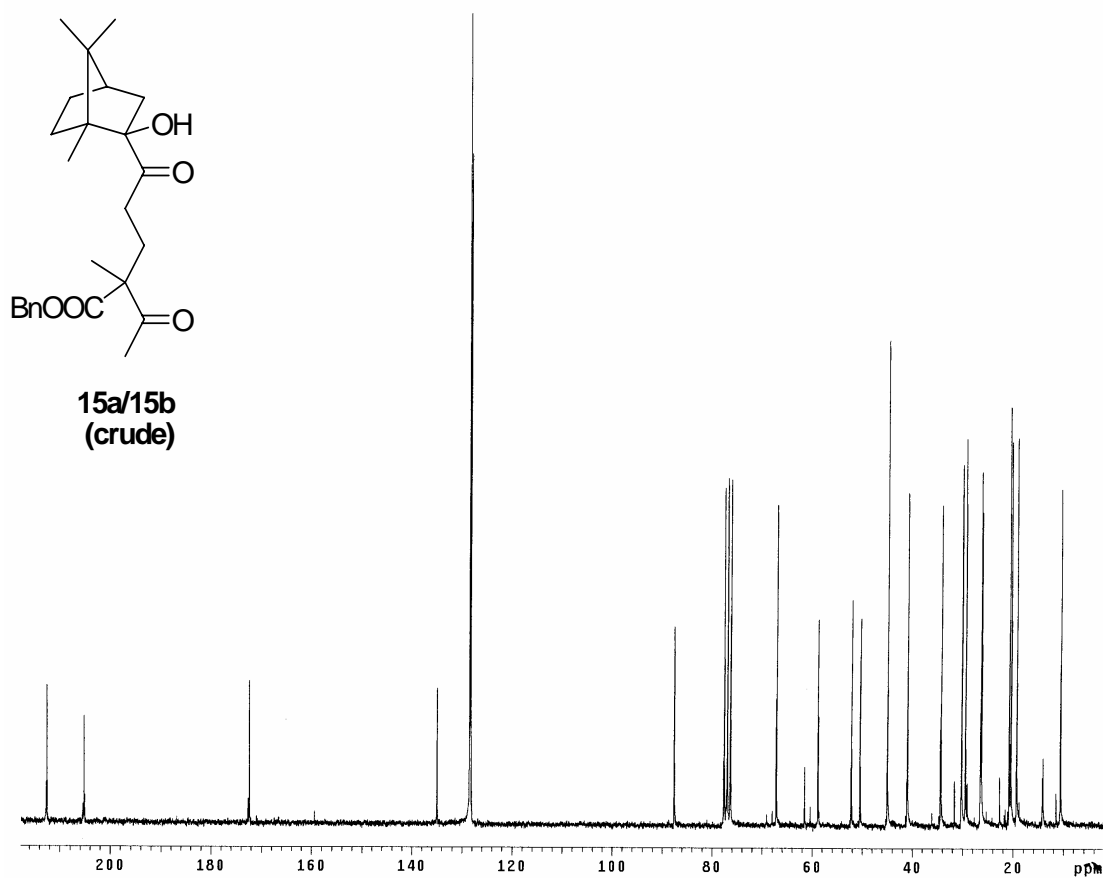


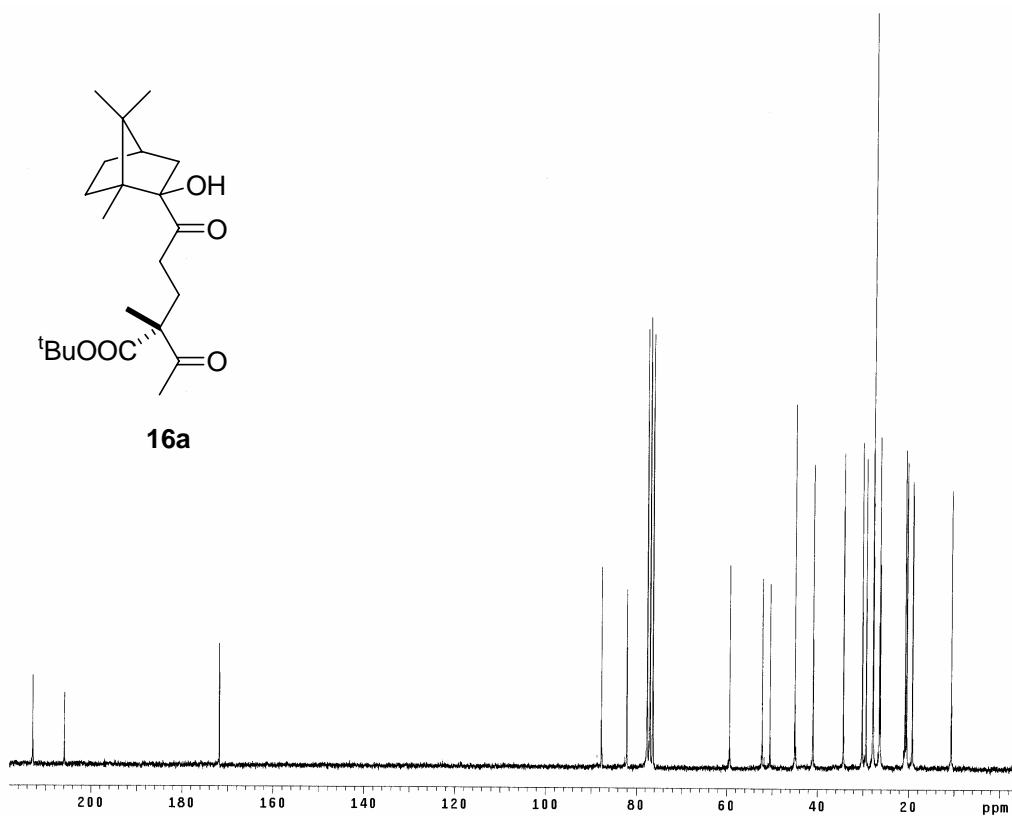
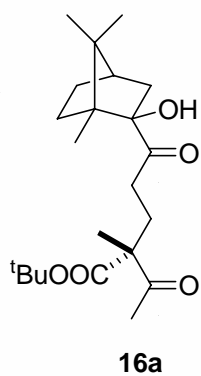
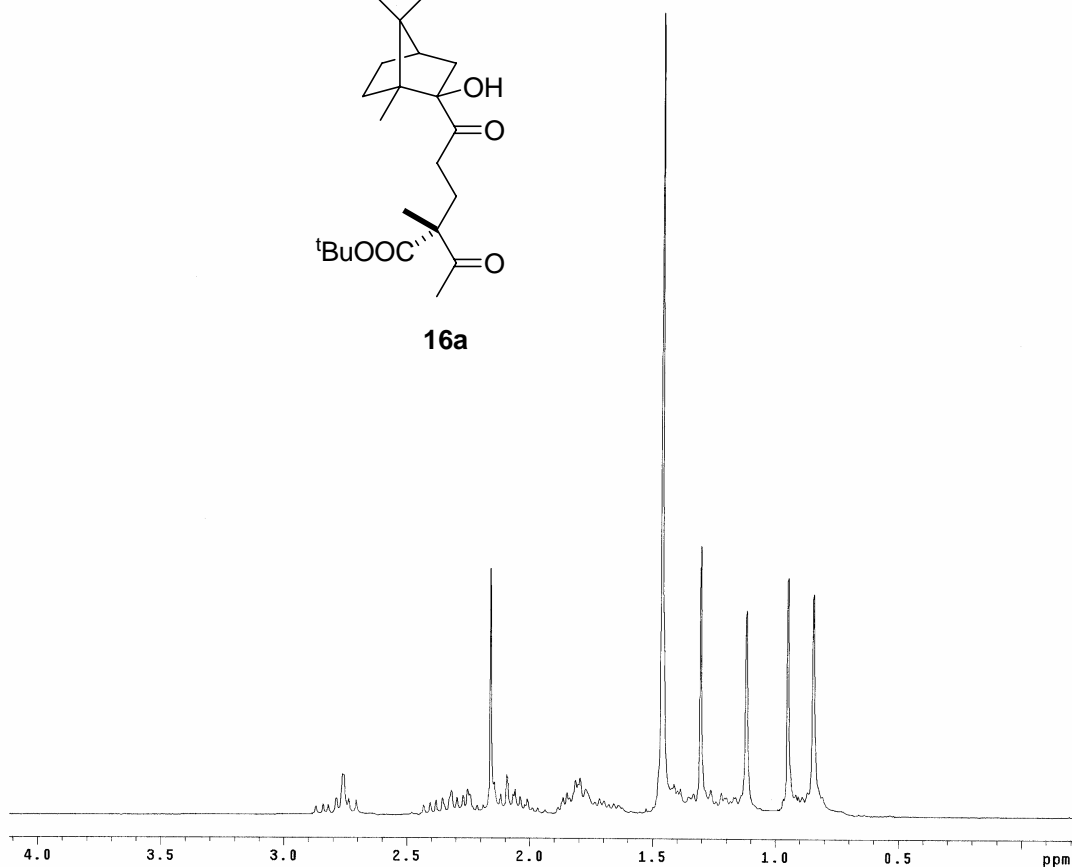
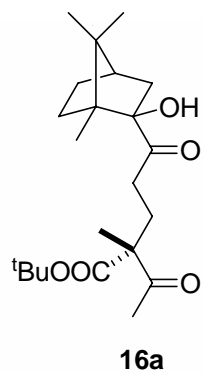
**14a/14b  
(crude)**

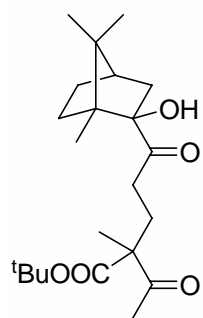




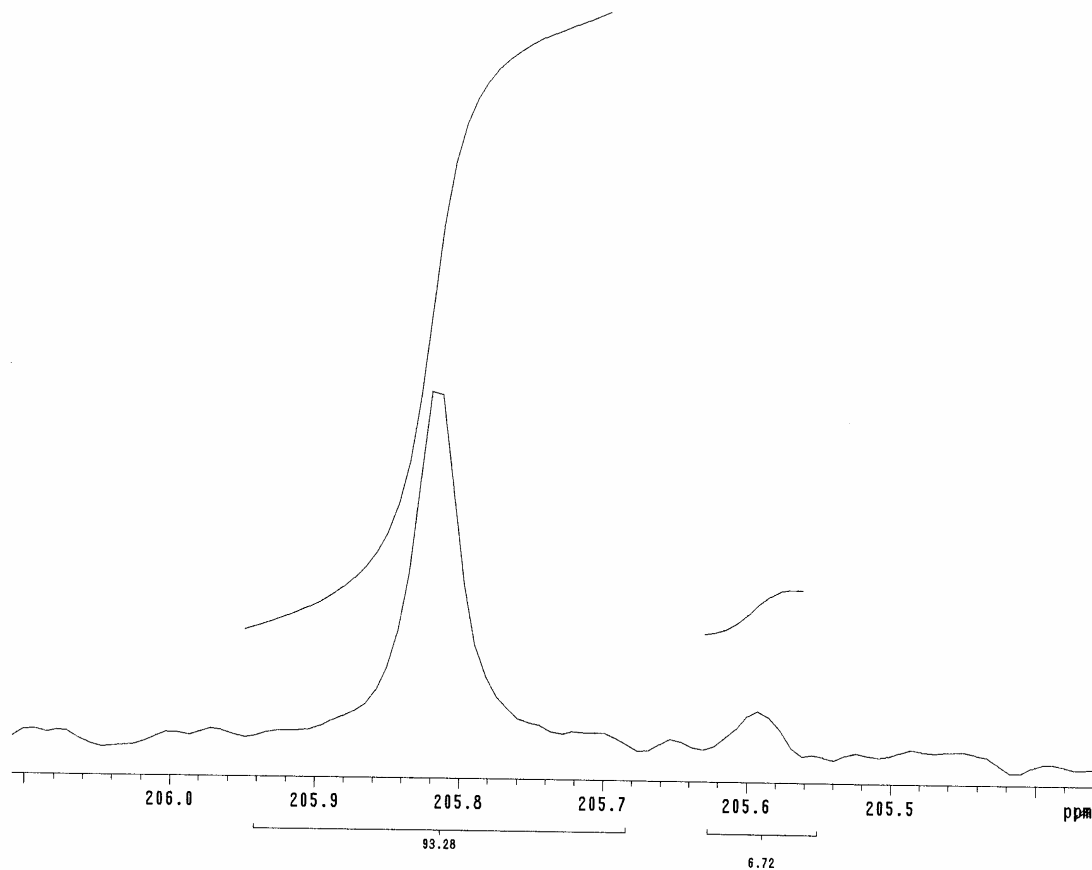
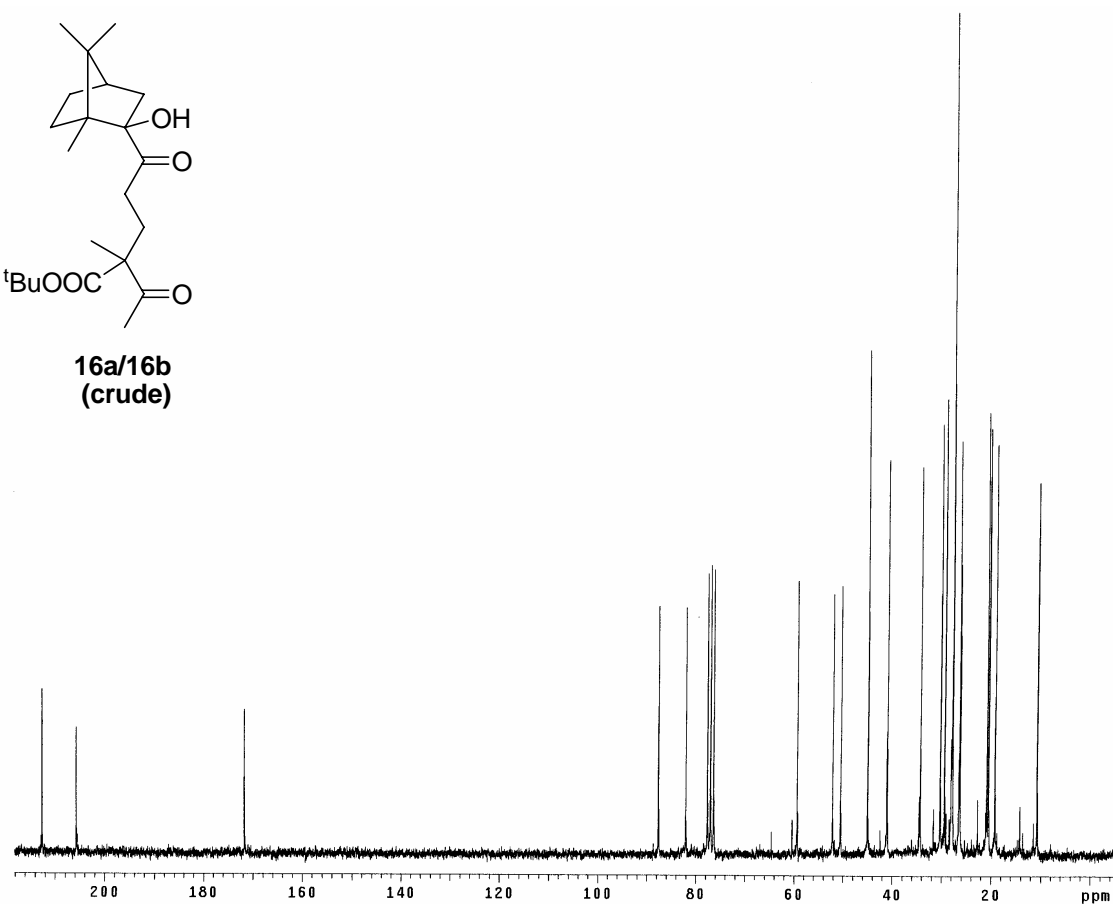


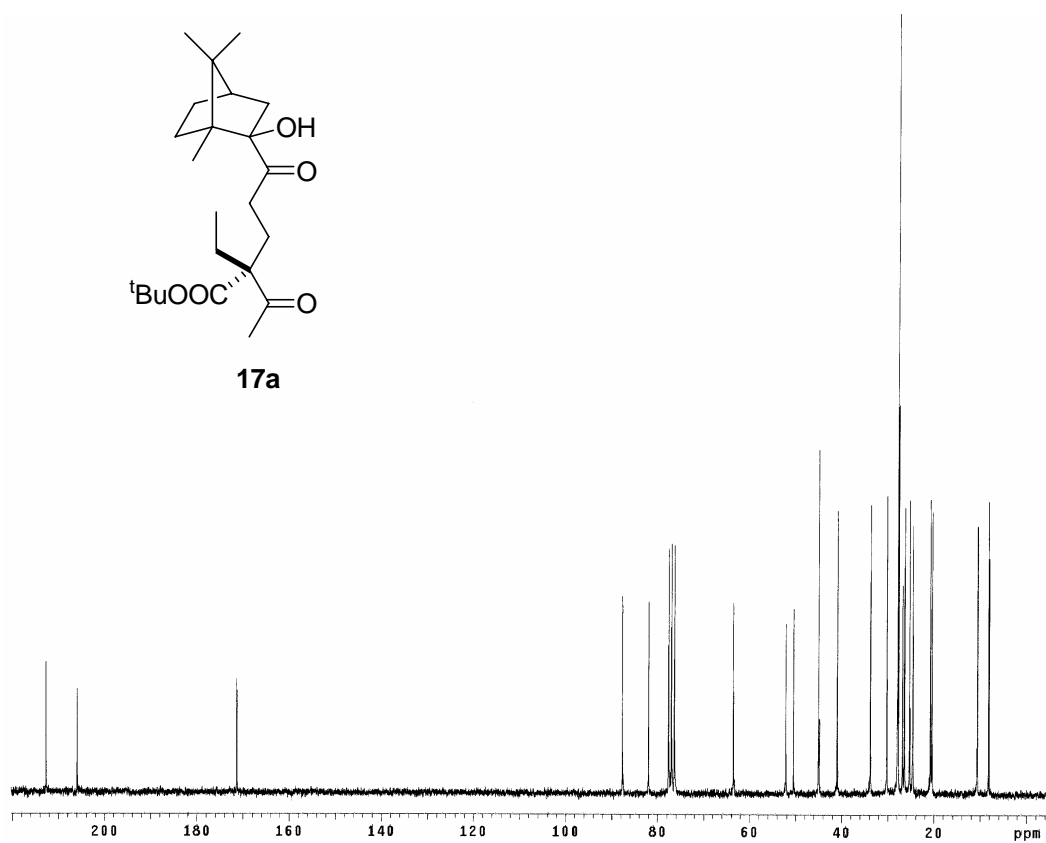
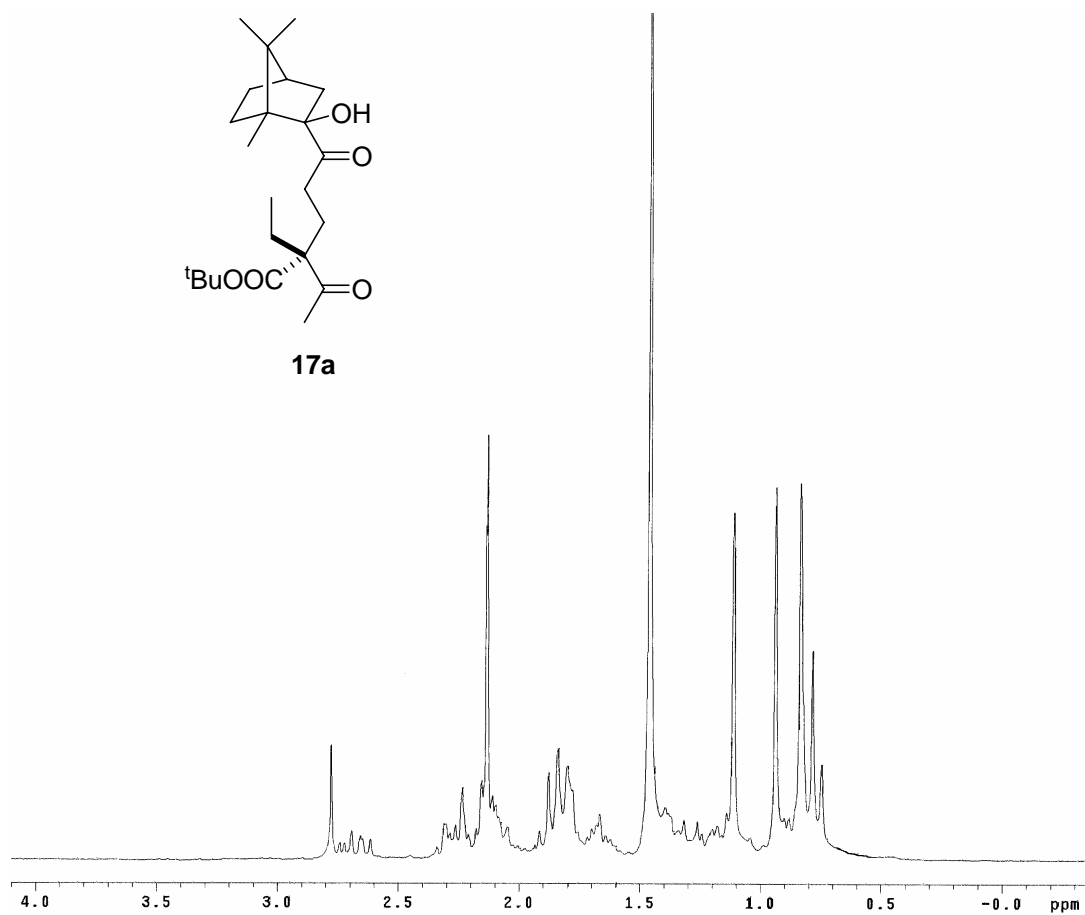


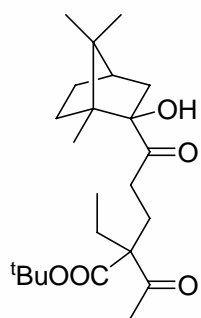




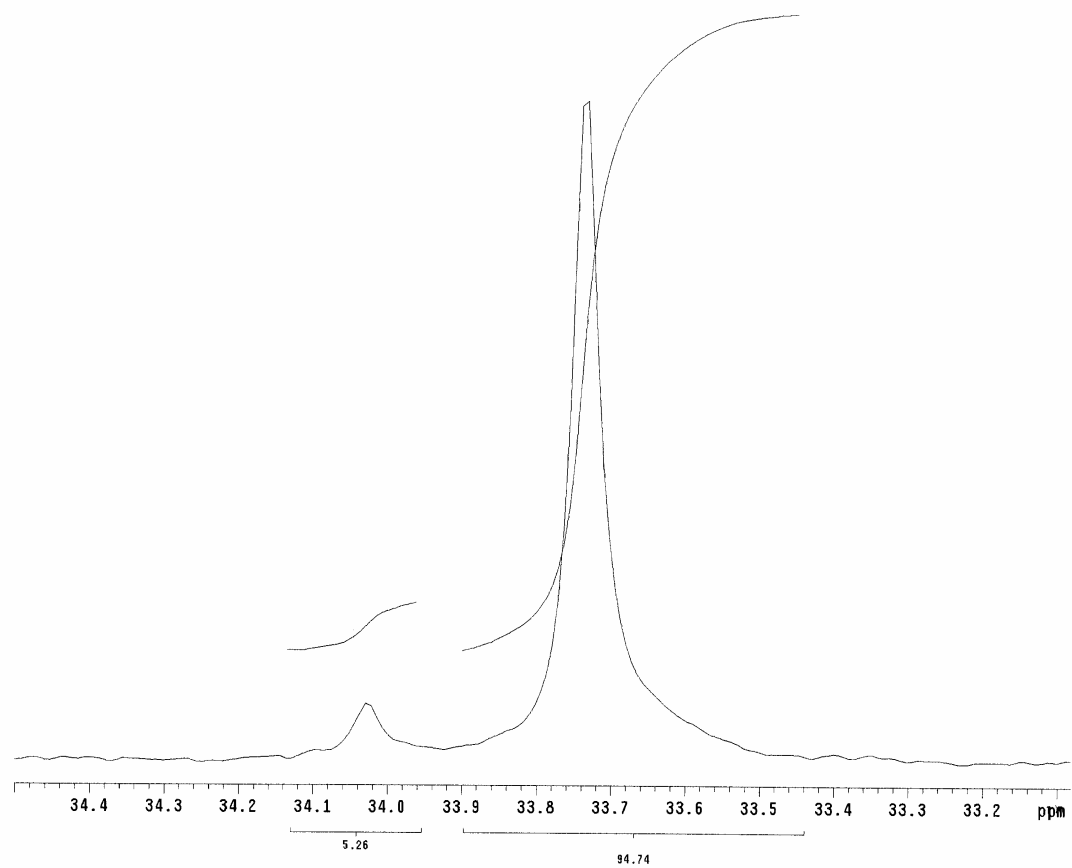
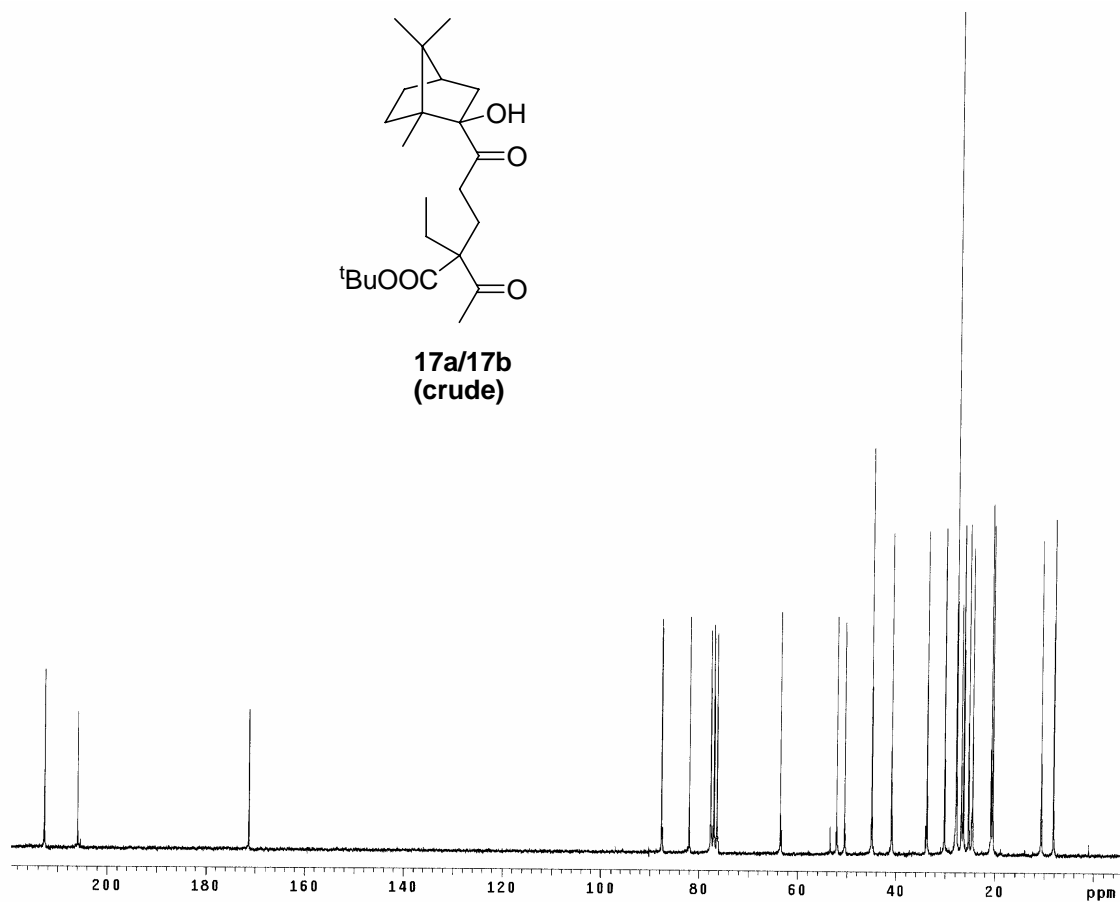
**16a/16b  
(crude)**

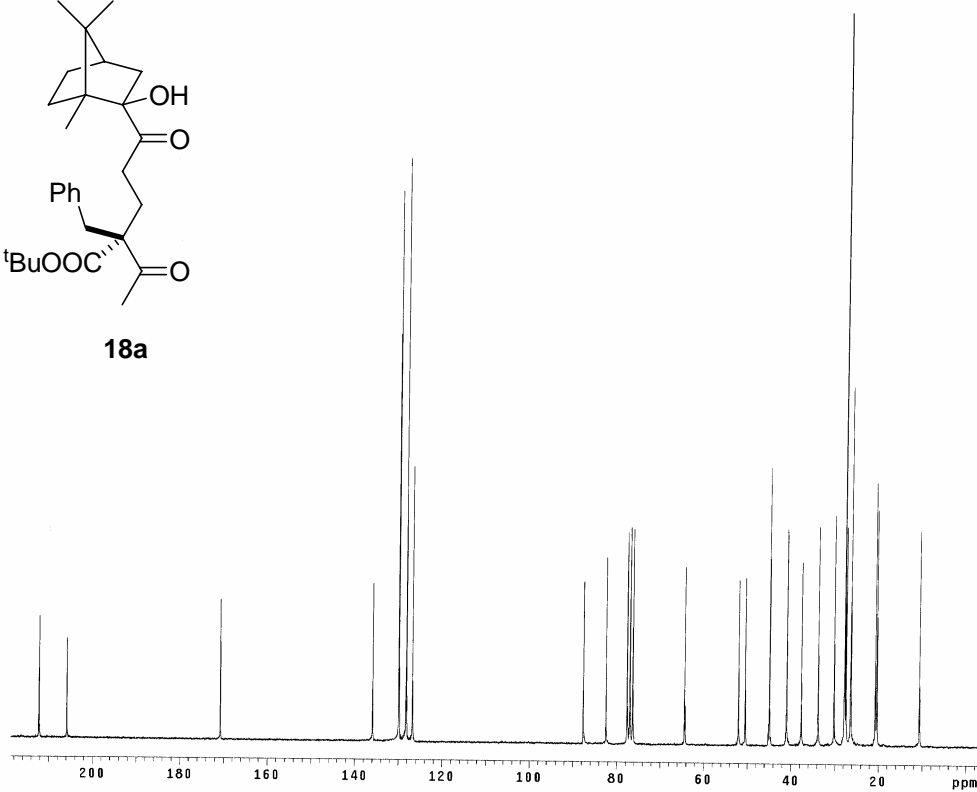
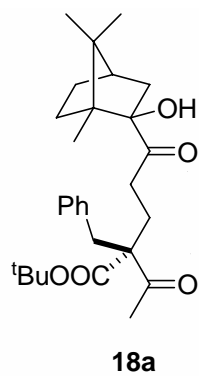
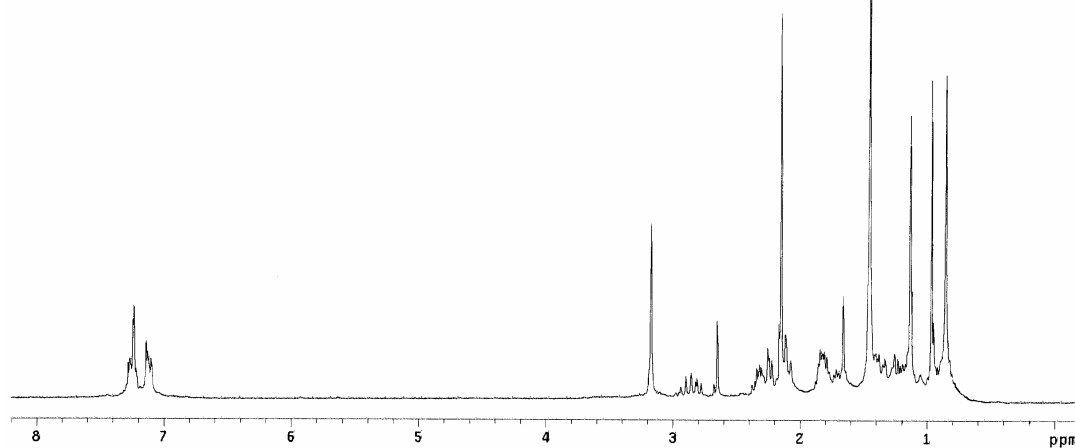
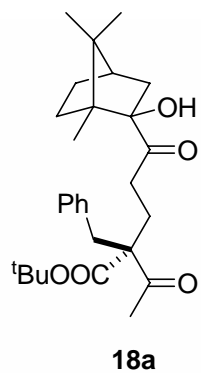


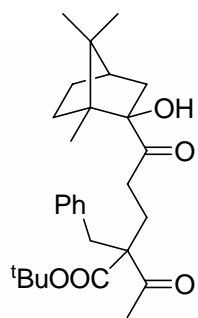




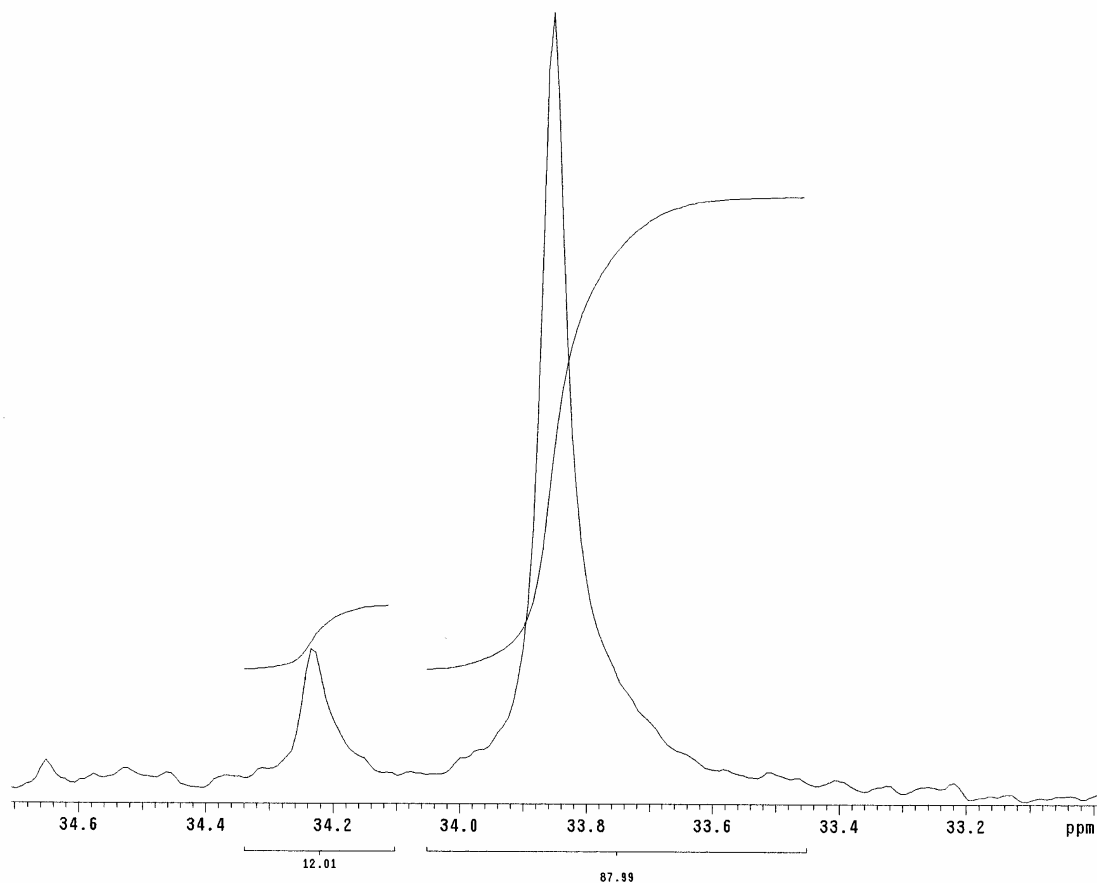
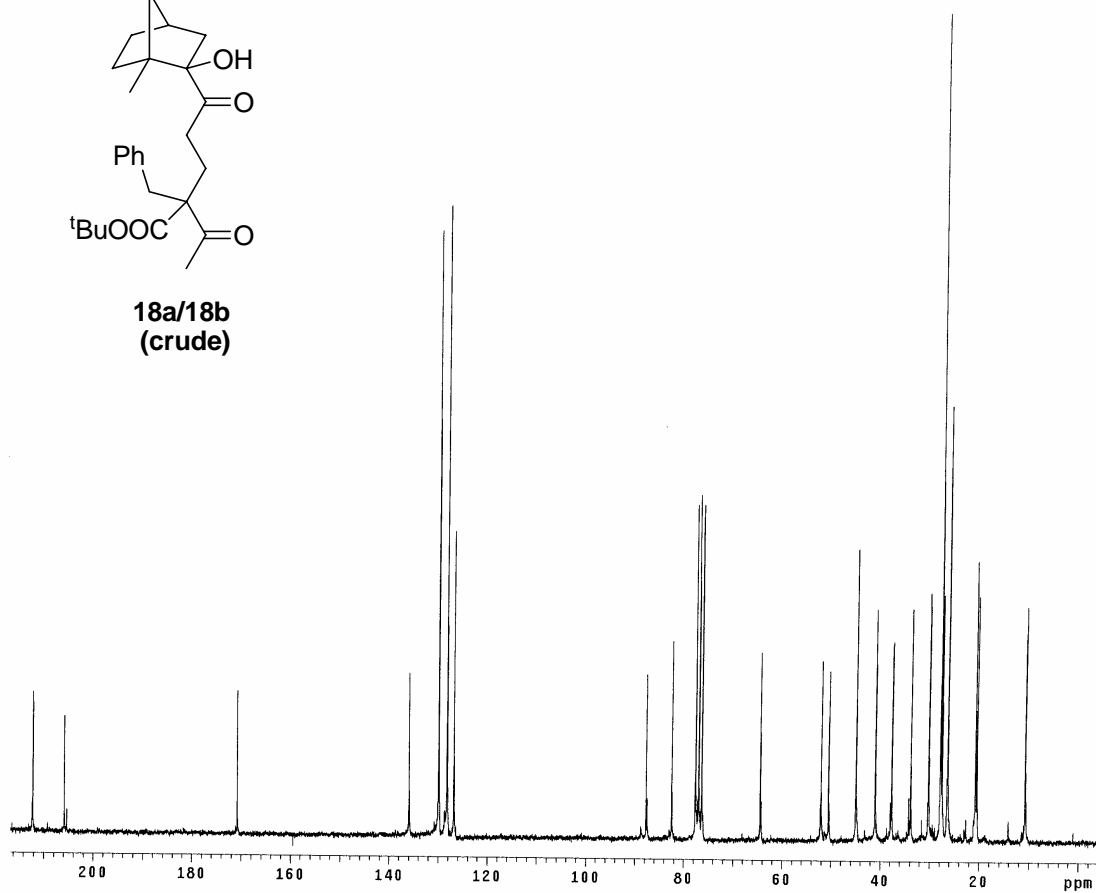
**17a/17b  
(crude)**

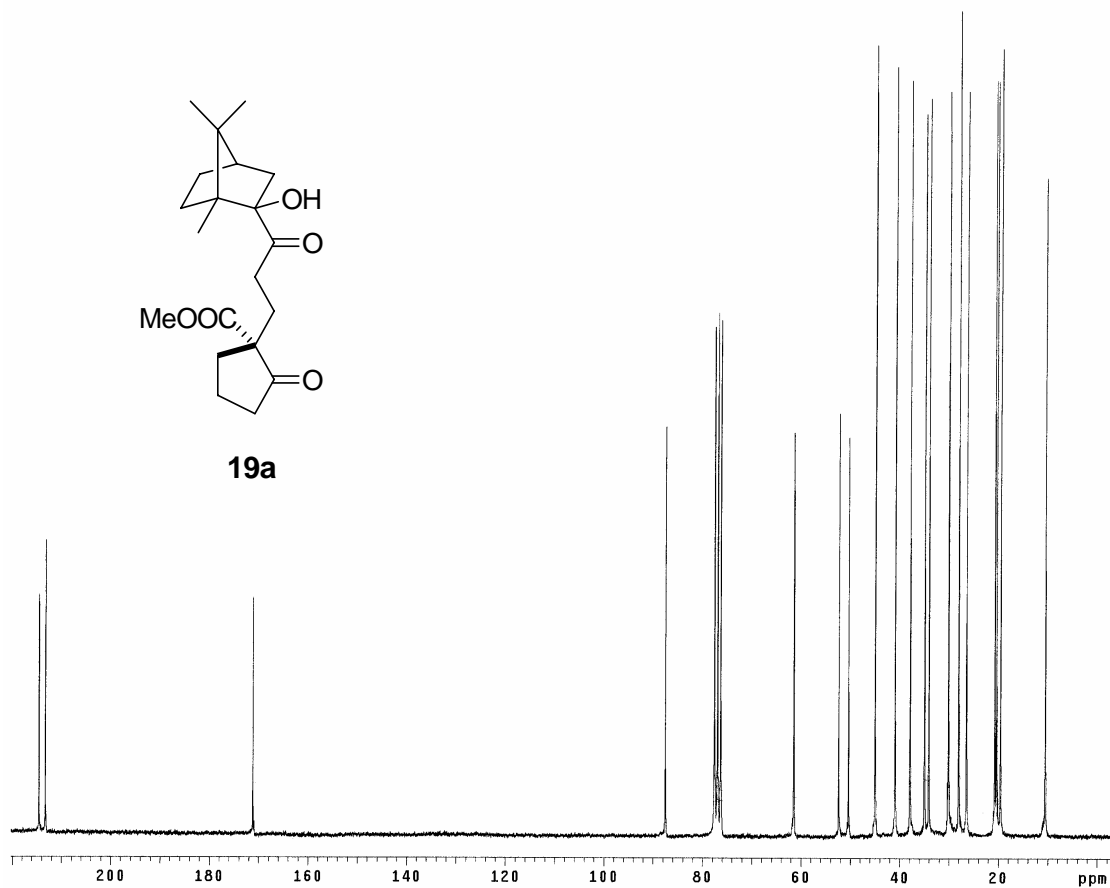
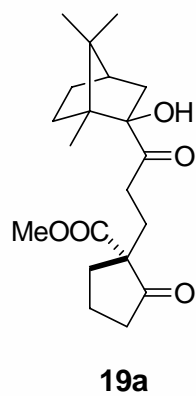
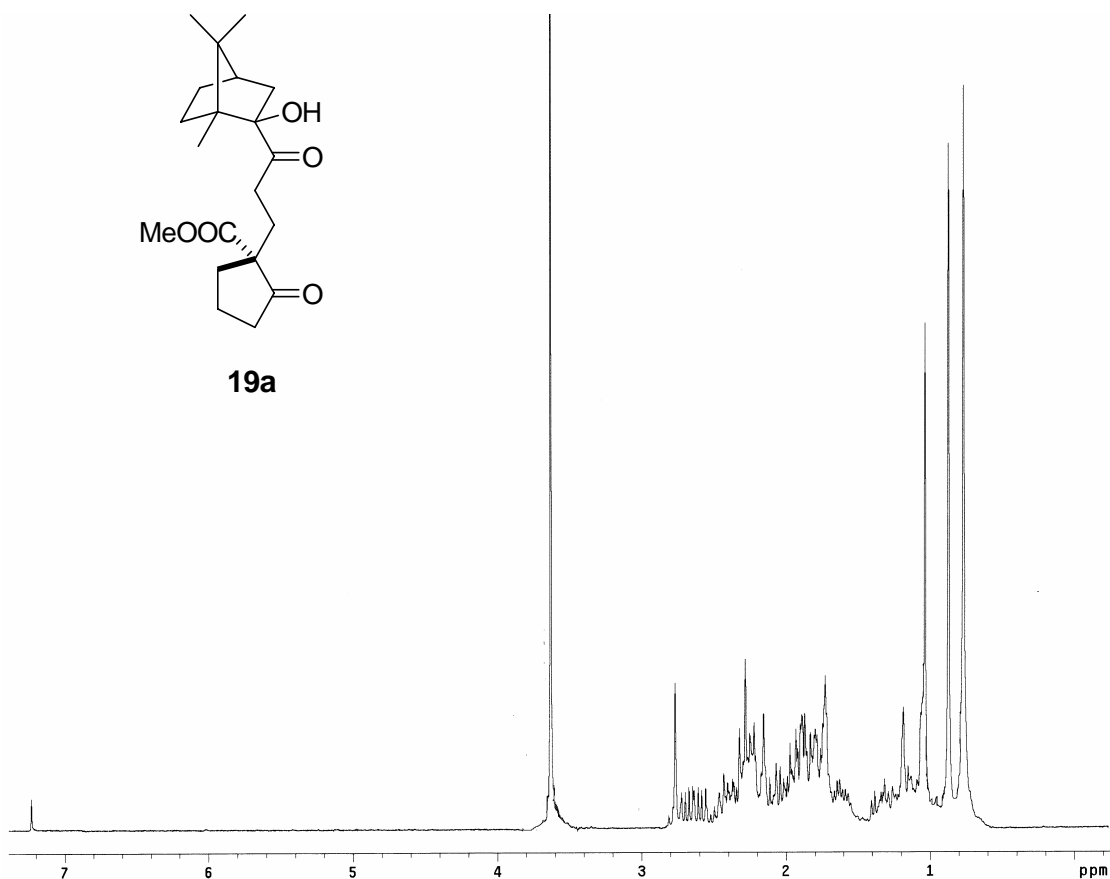
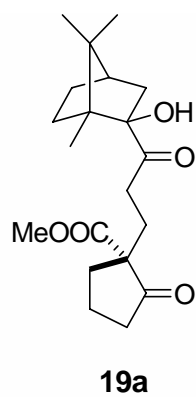




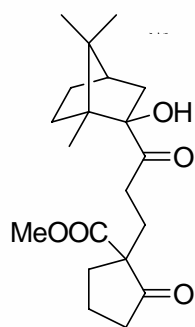


**18a/18b  
(crude)**

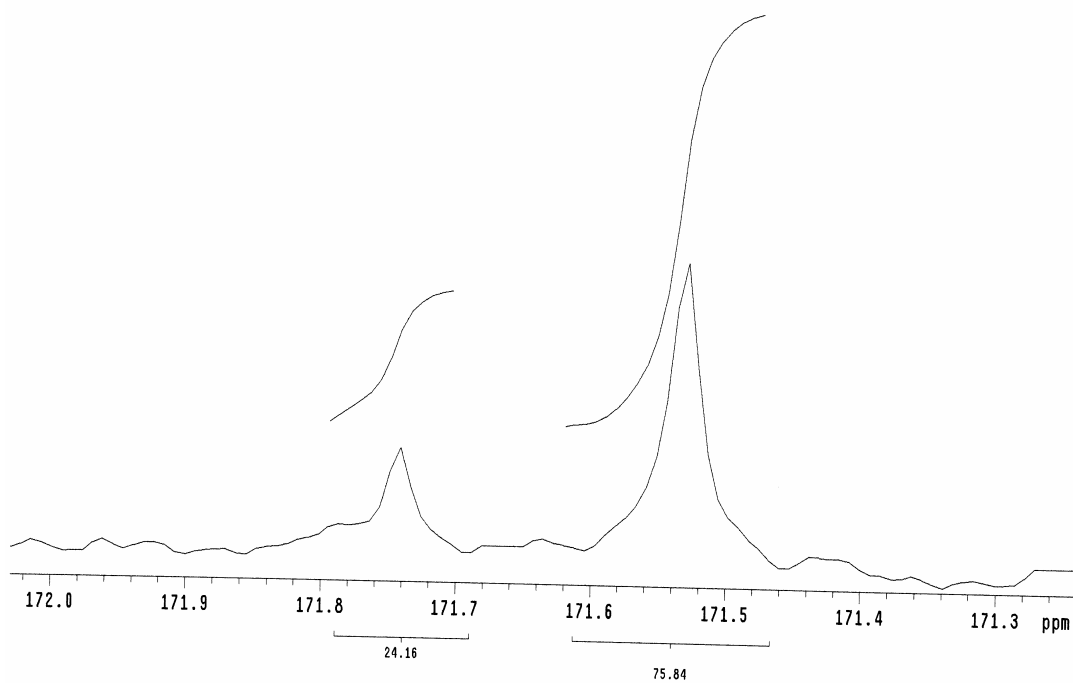
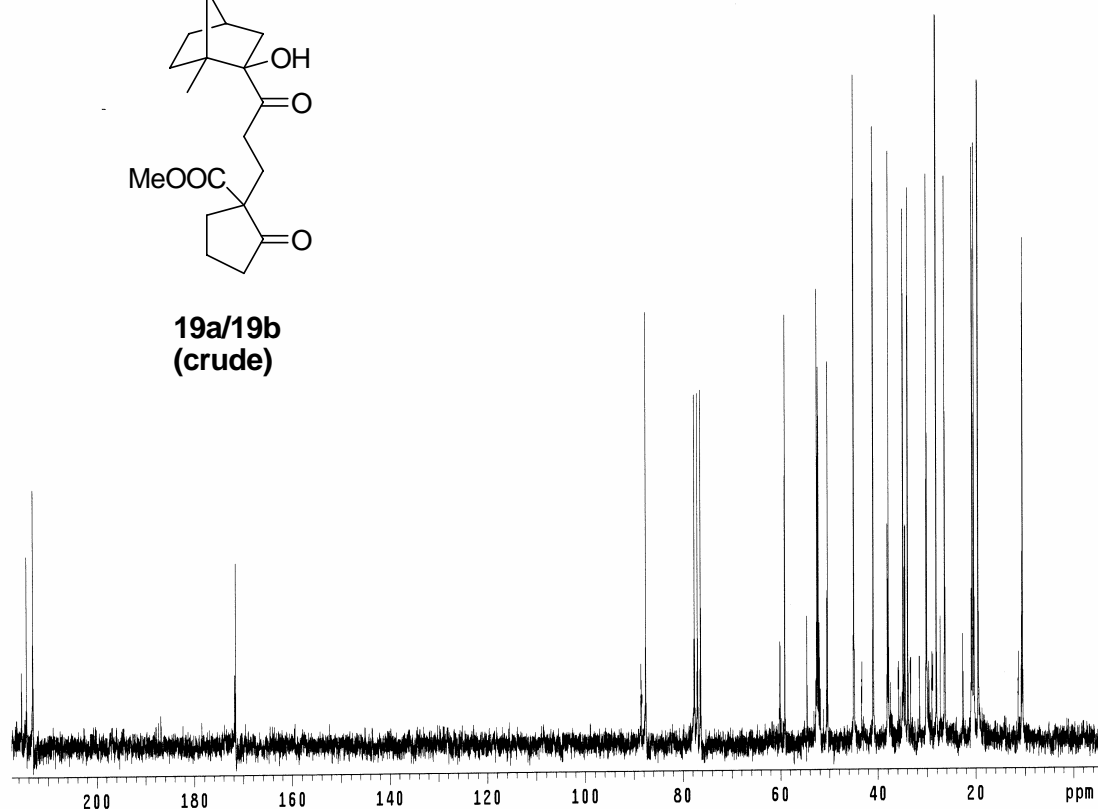


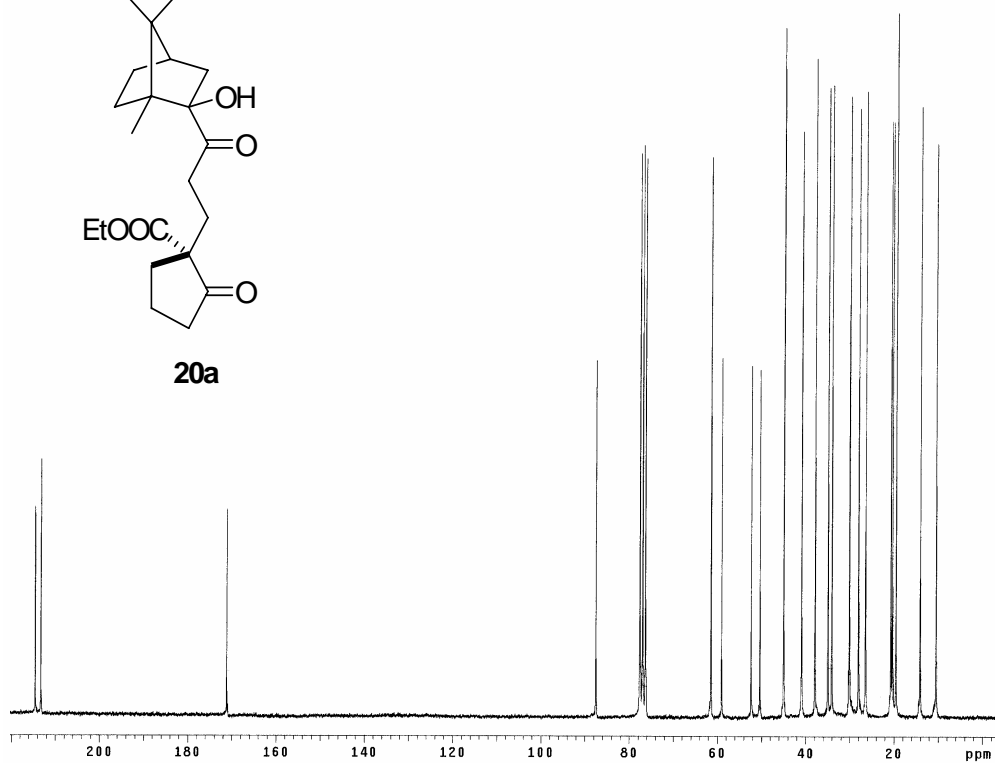
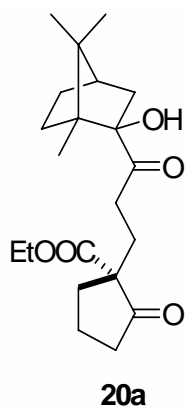
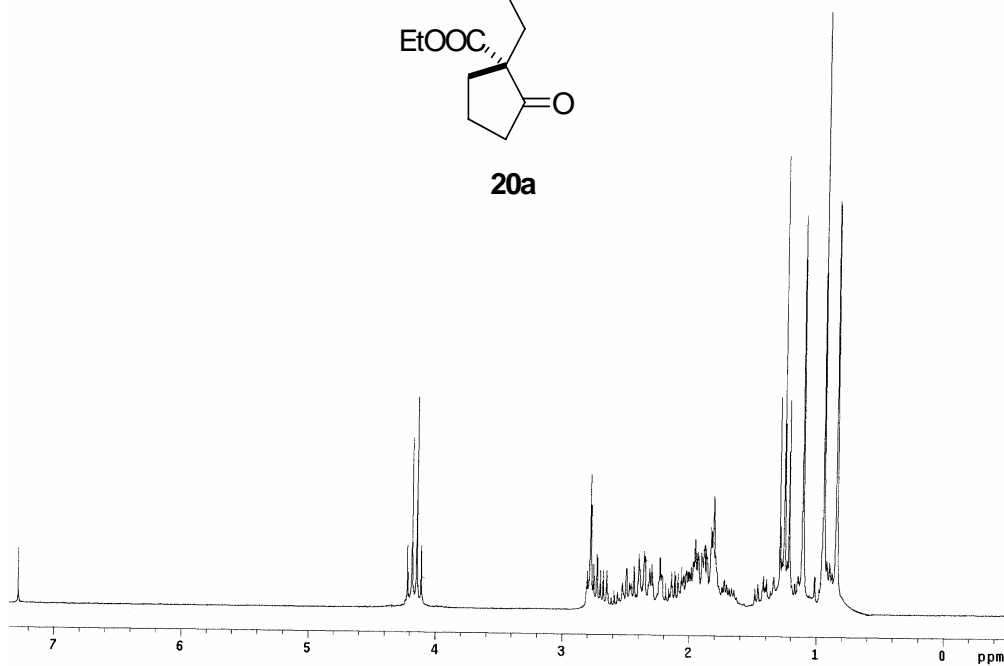
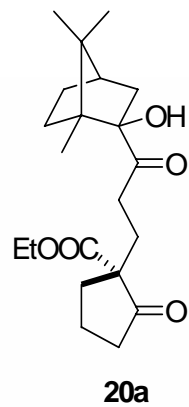


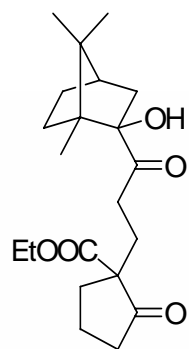




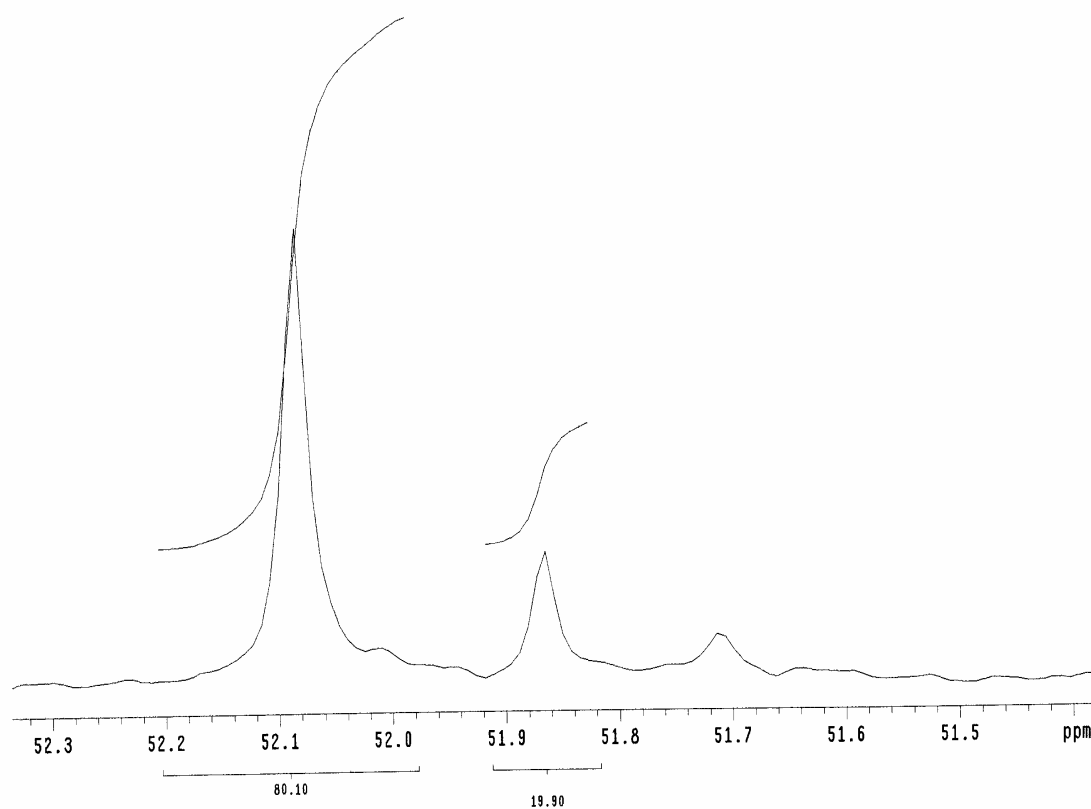
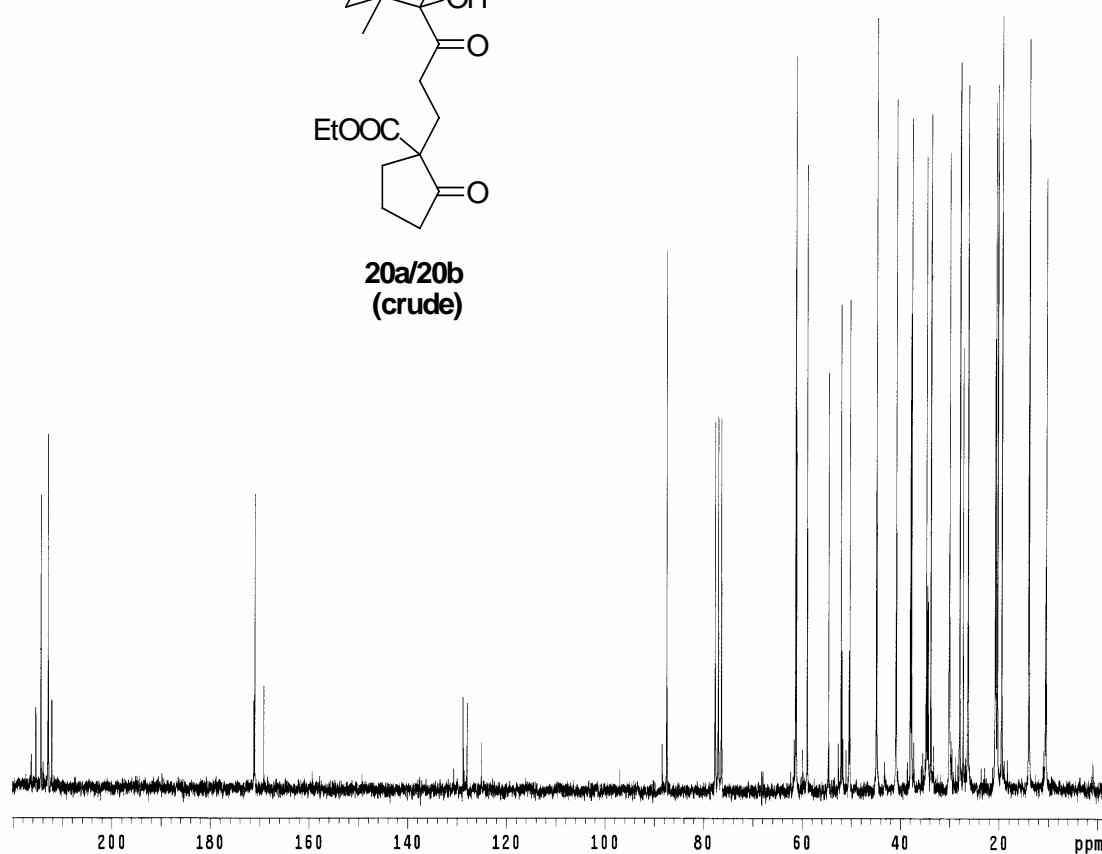
**19a/19b  
(crude)**

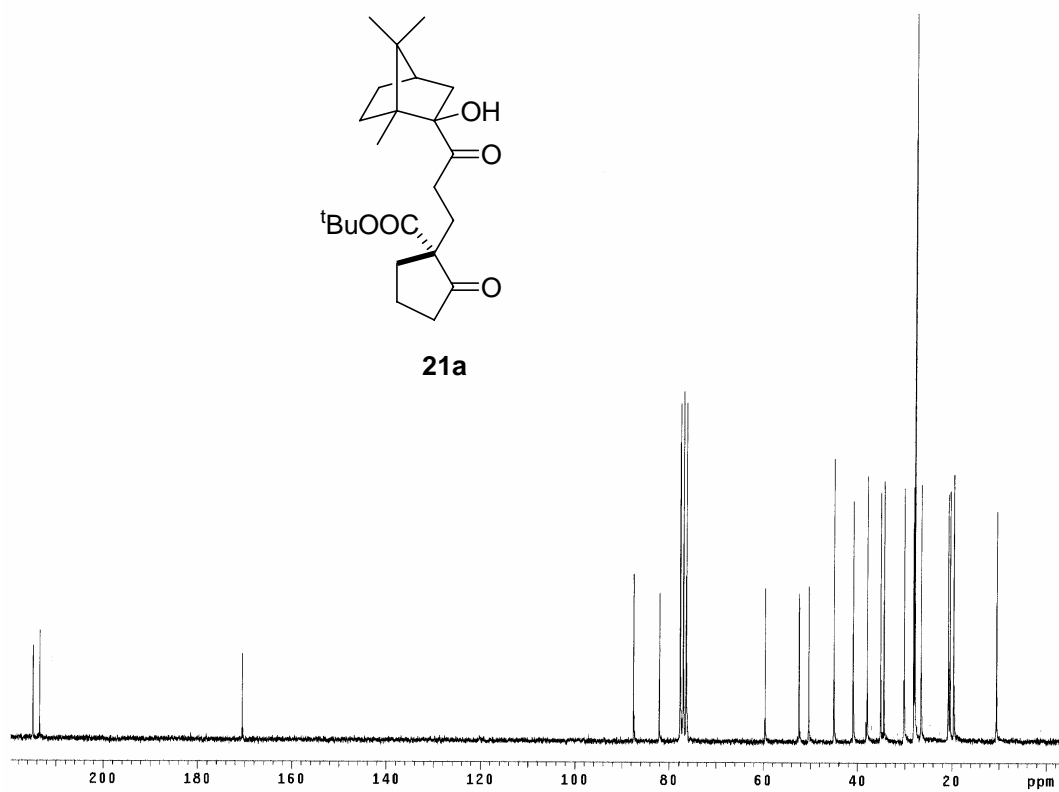
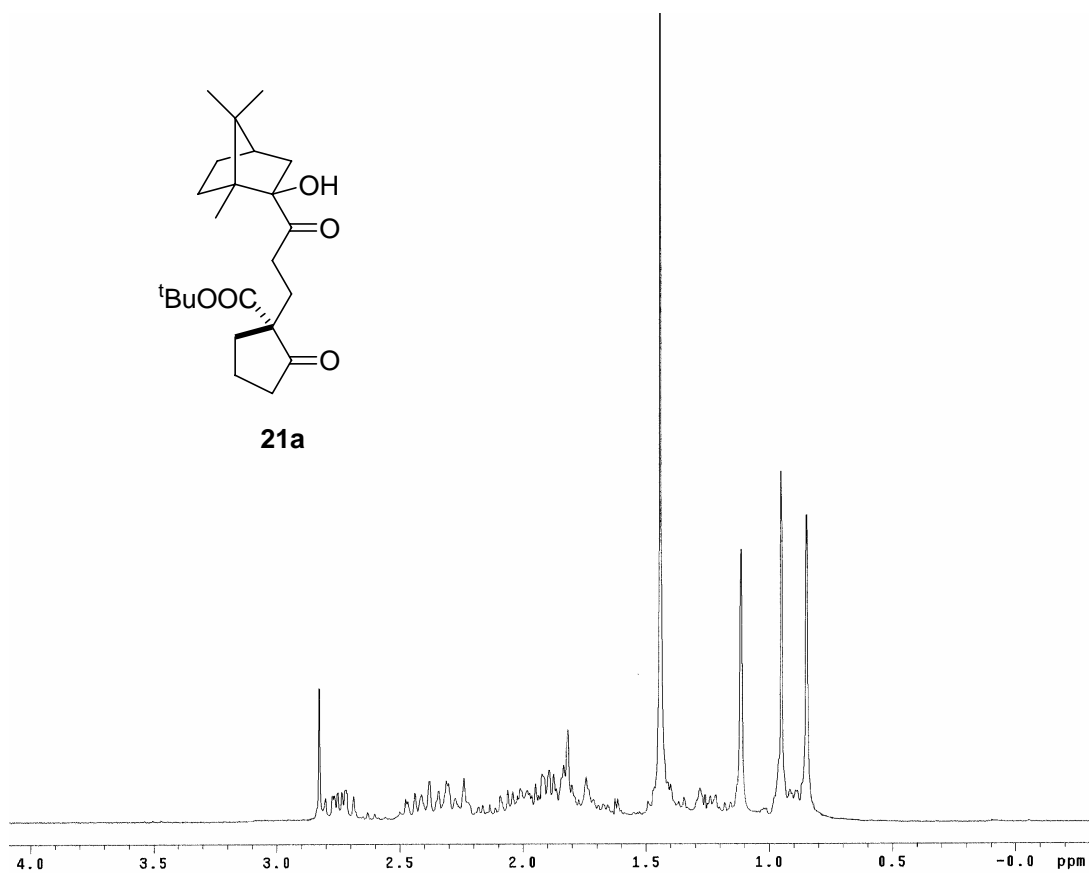


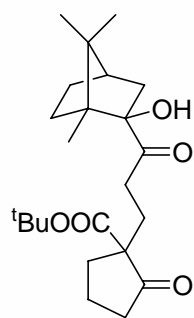




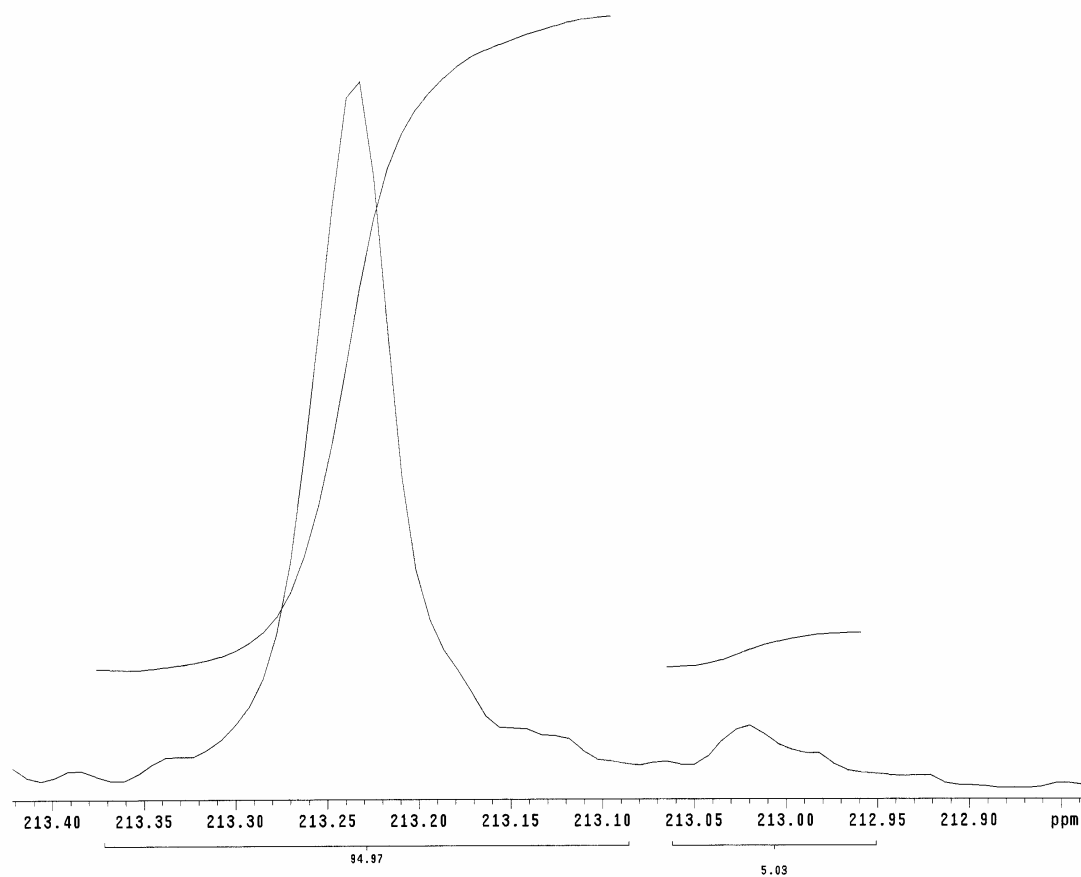
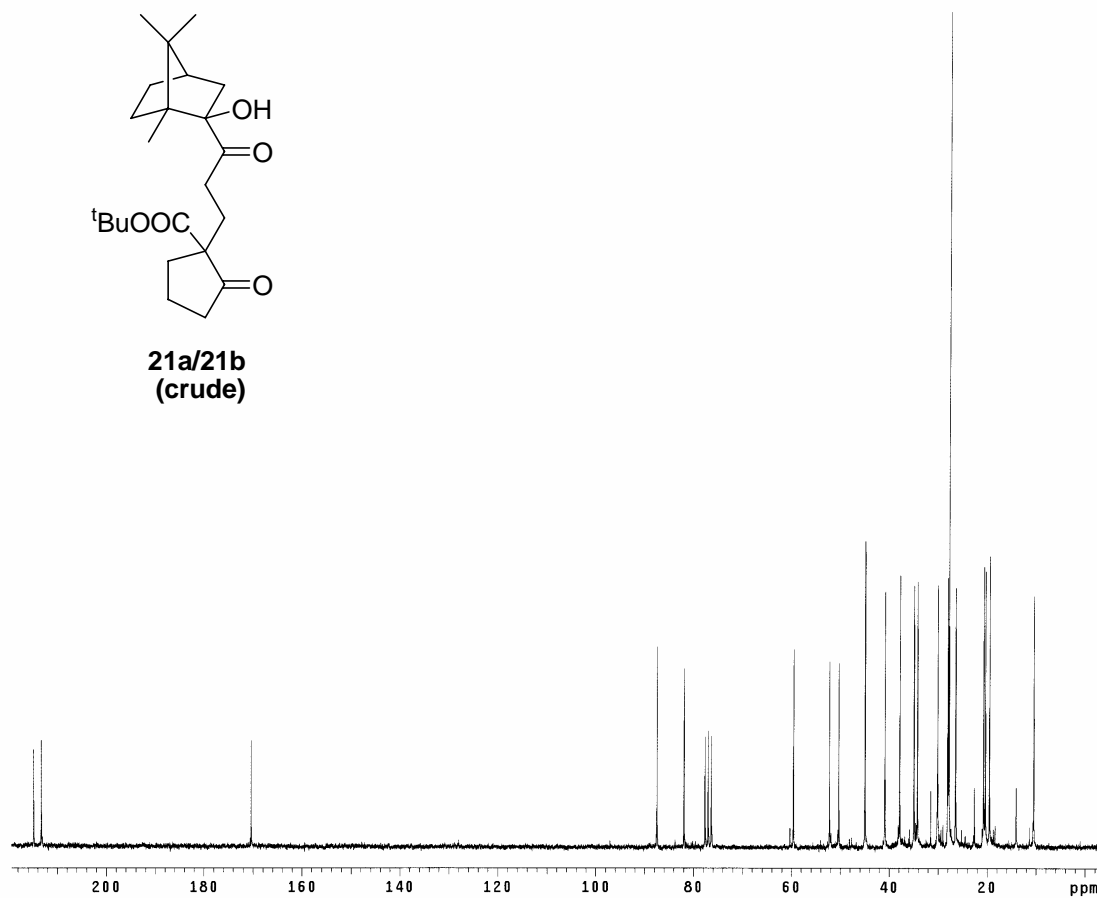
**20a/20b  
(crude)**

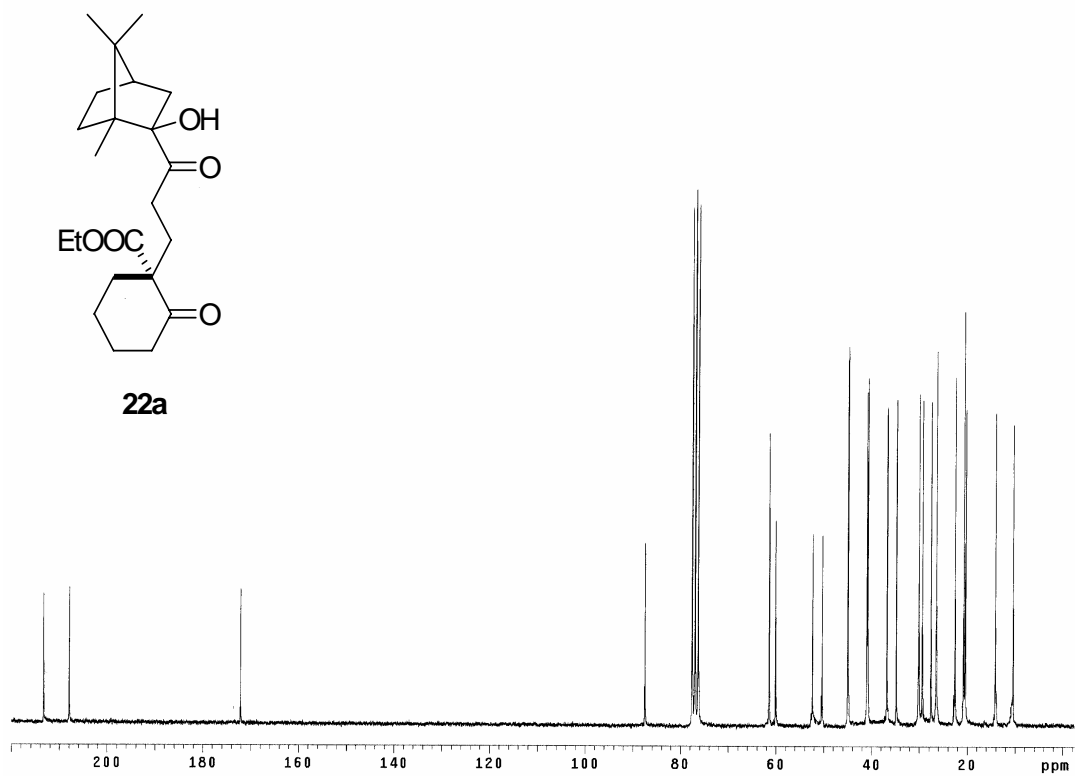
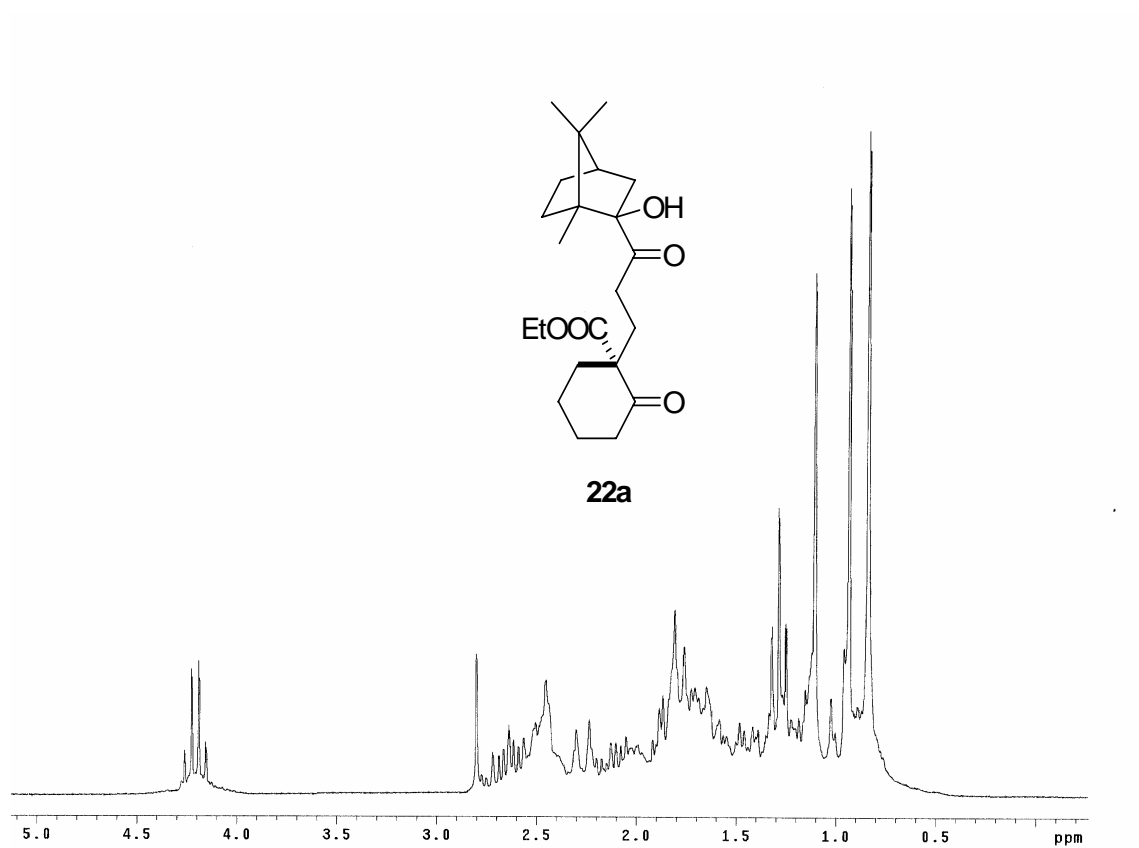


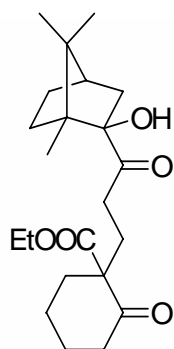




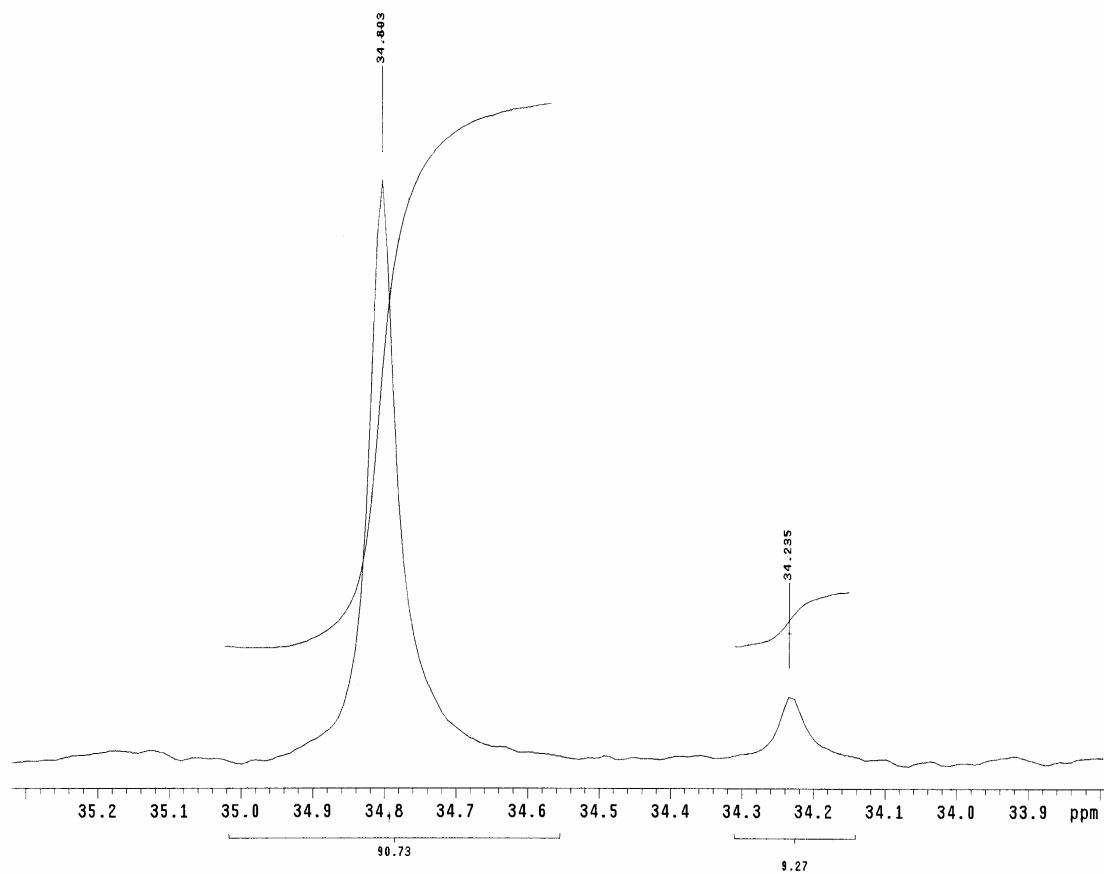
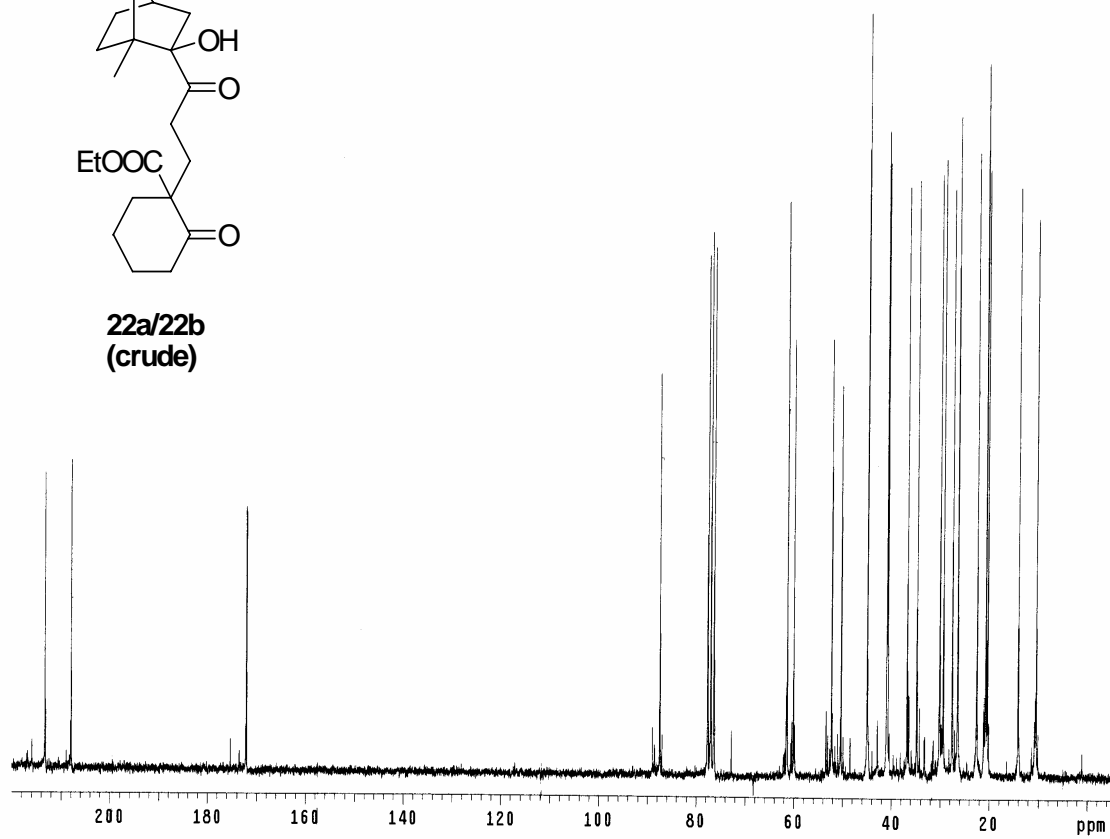
**21a/21b**  
**(crude)**

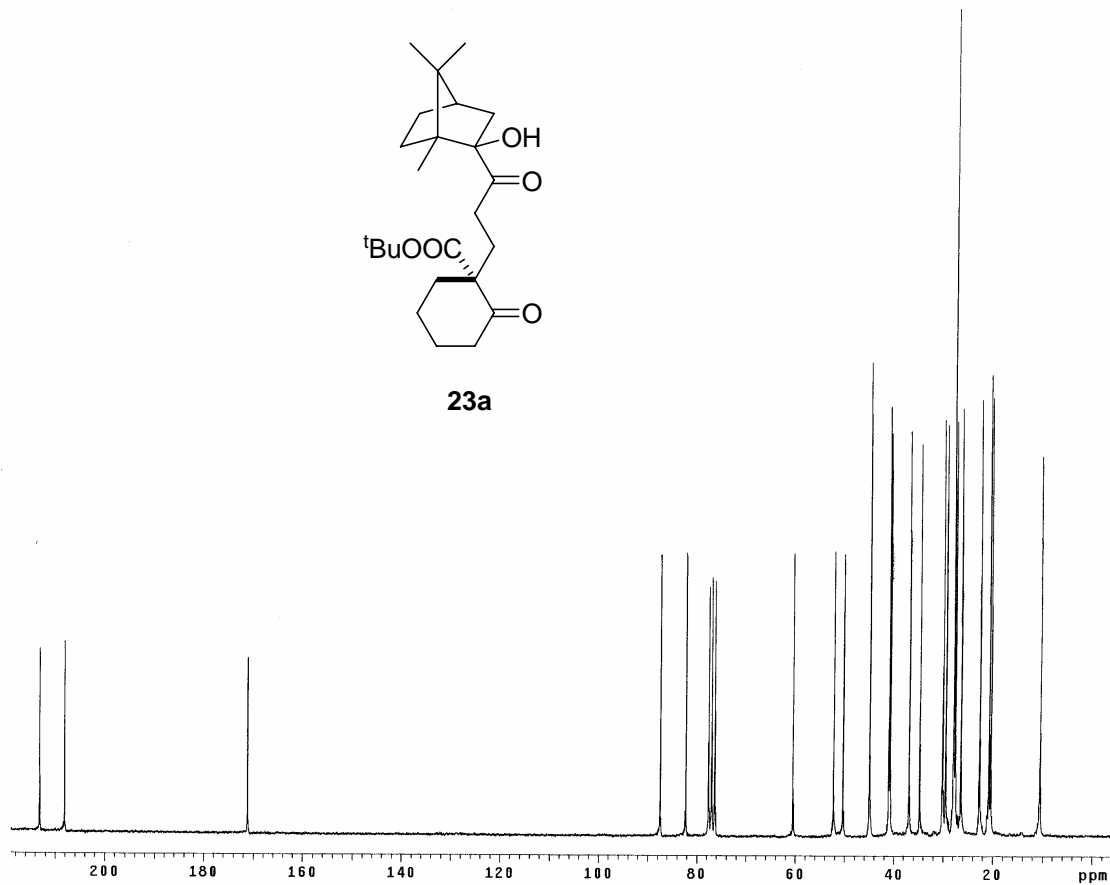
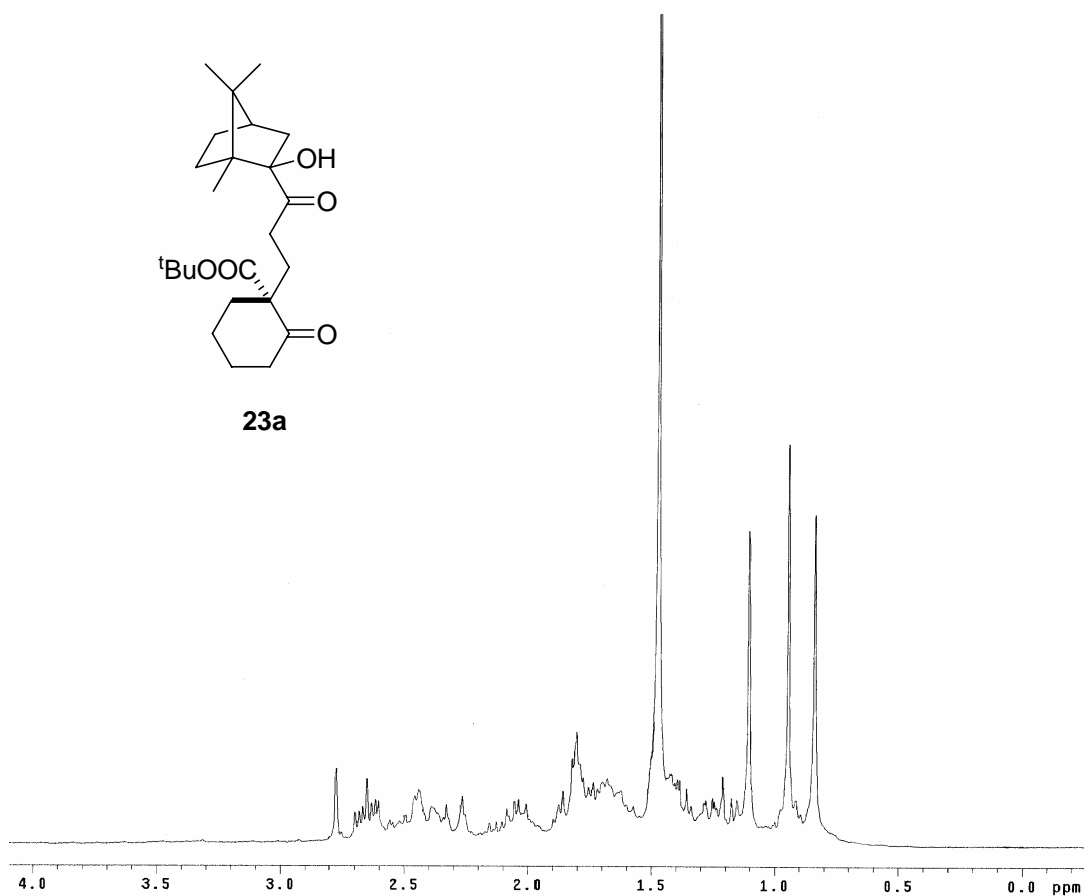




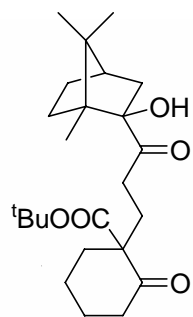


**22a/22b**  
(crude)

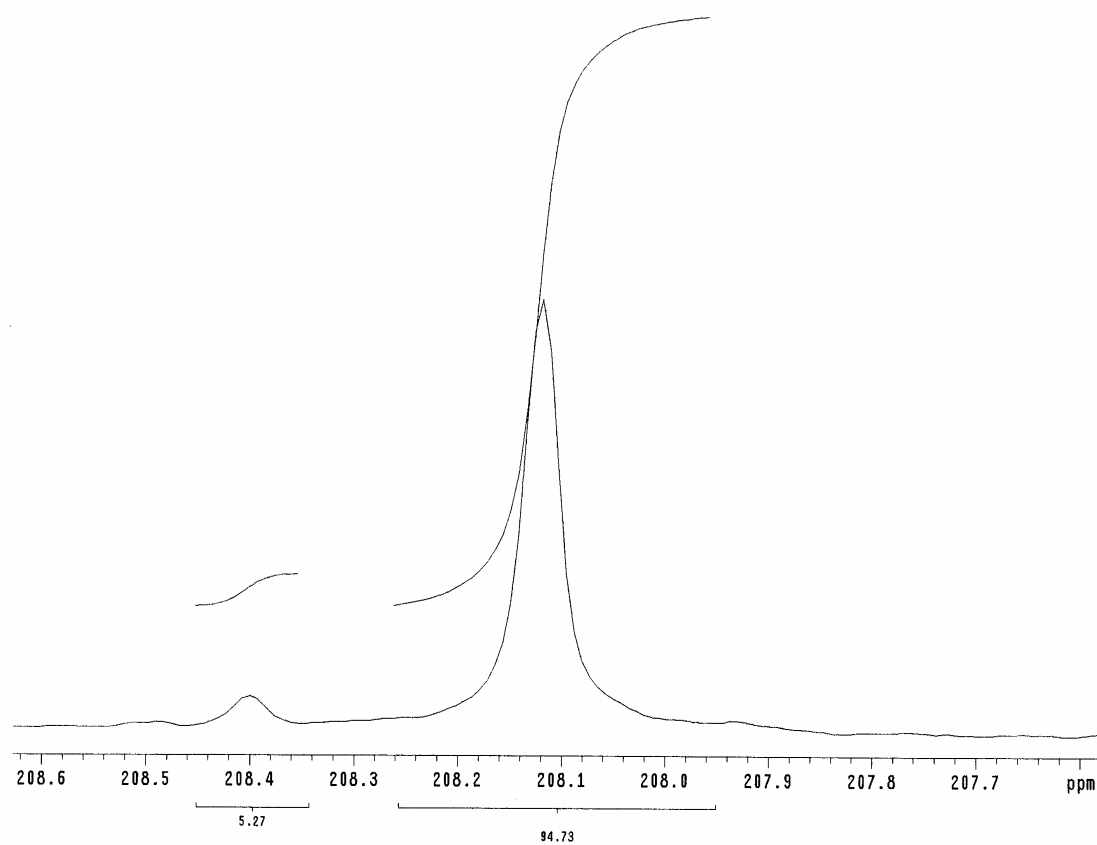
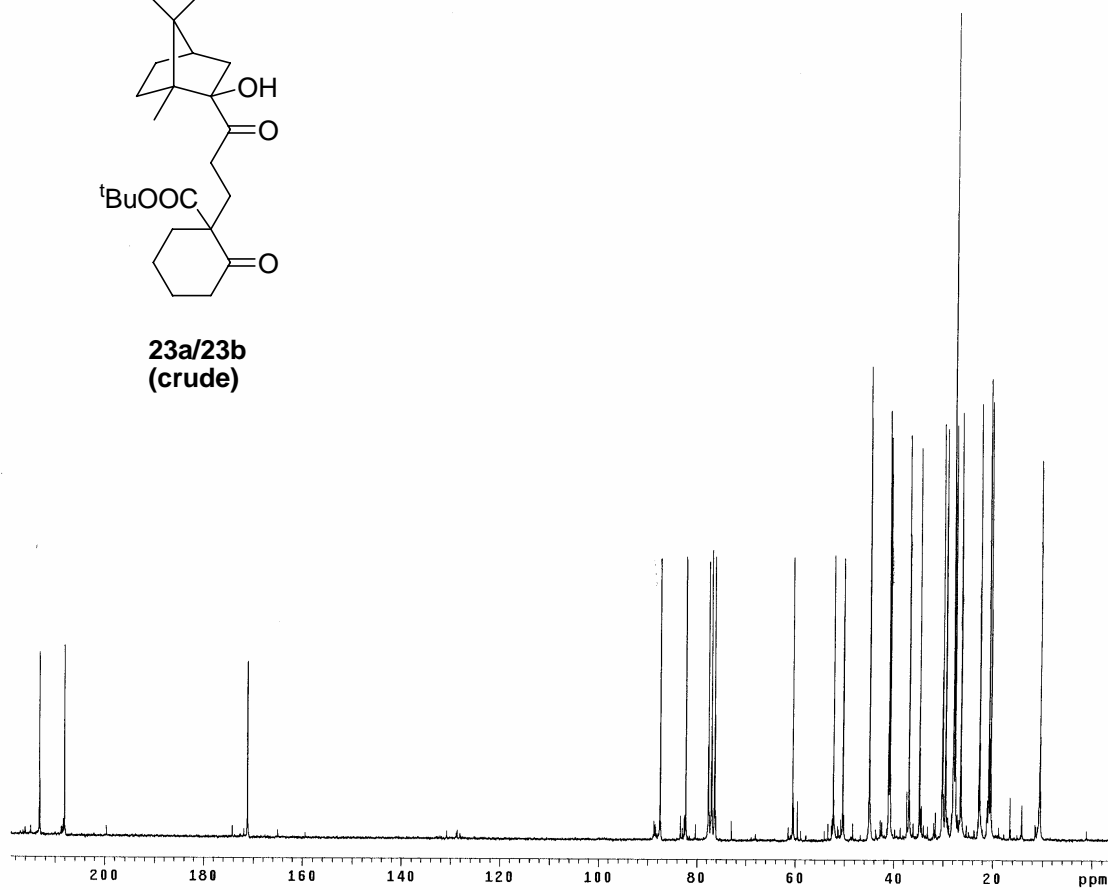


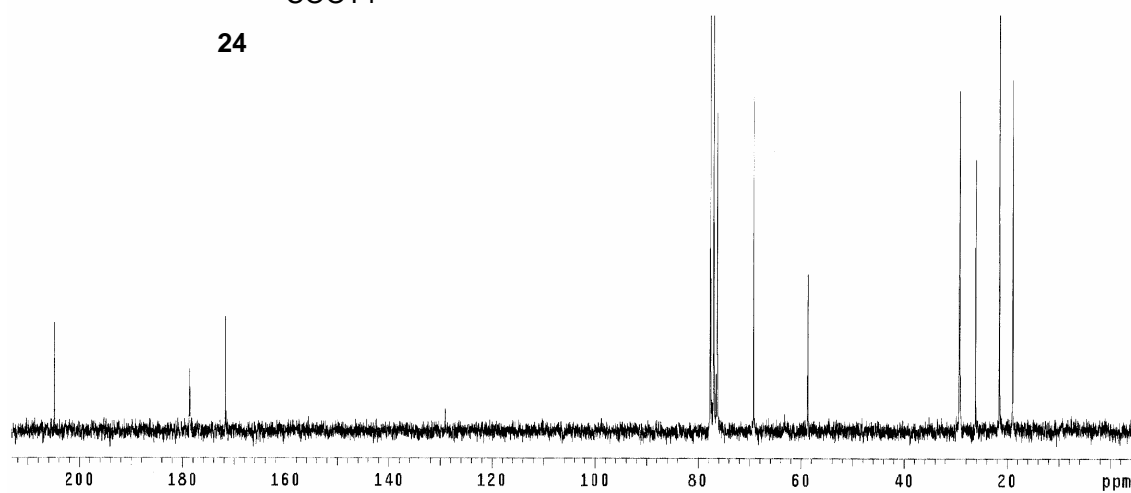
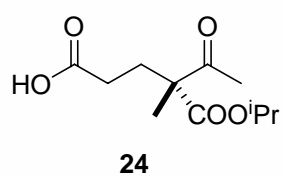
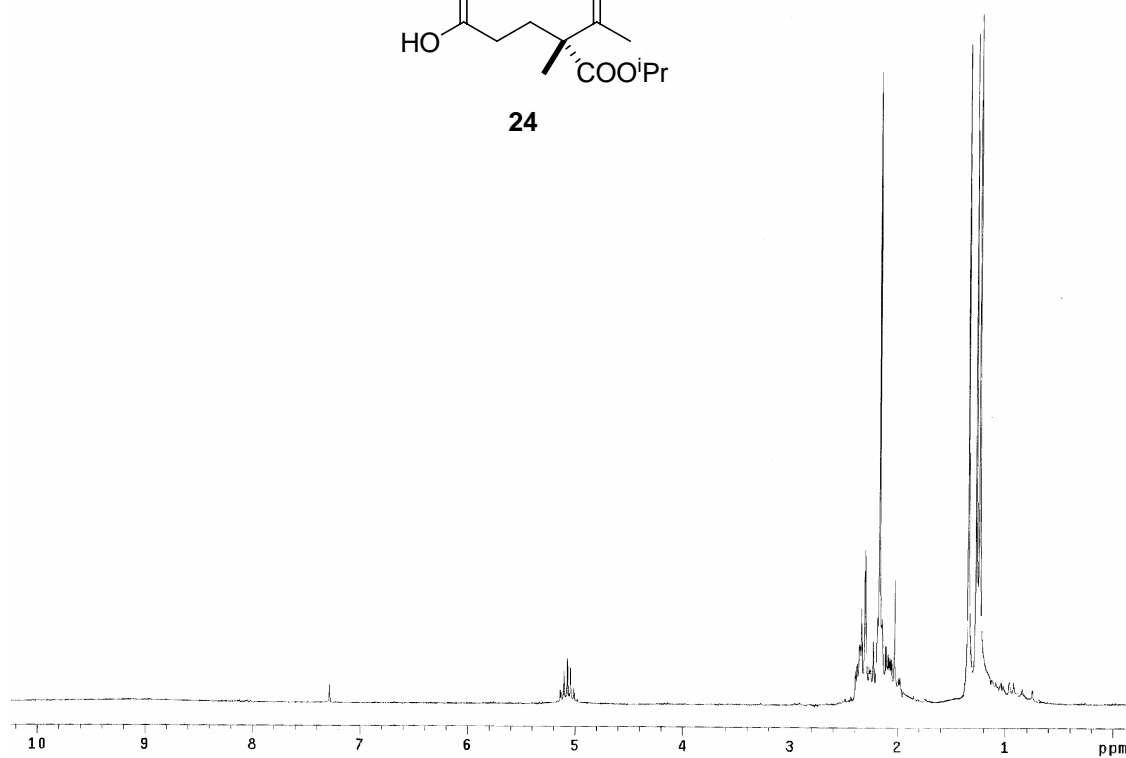
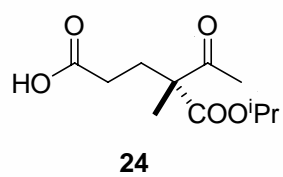


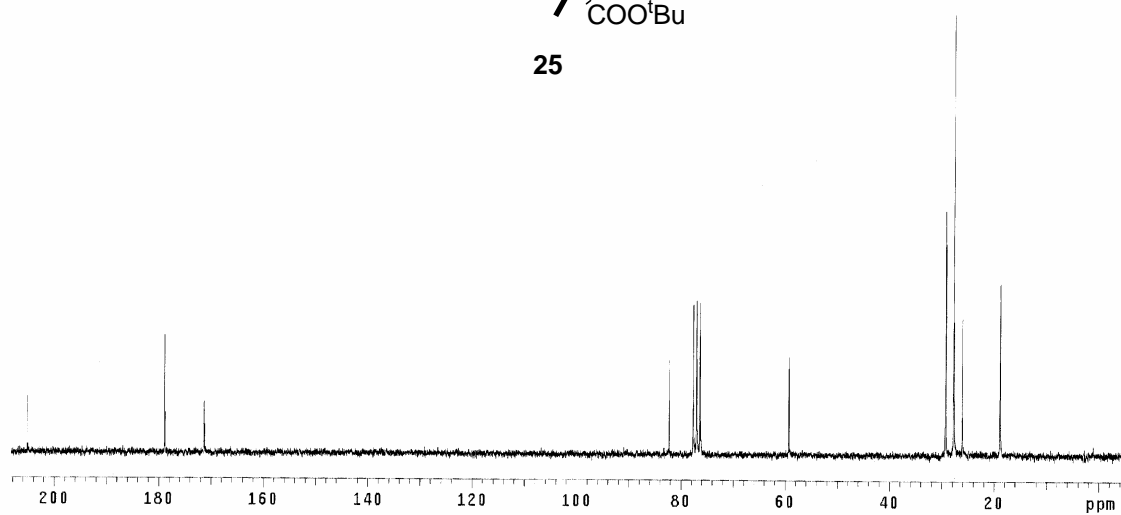
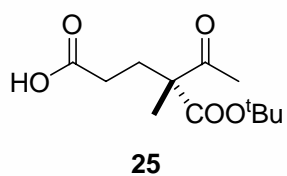
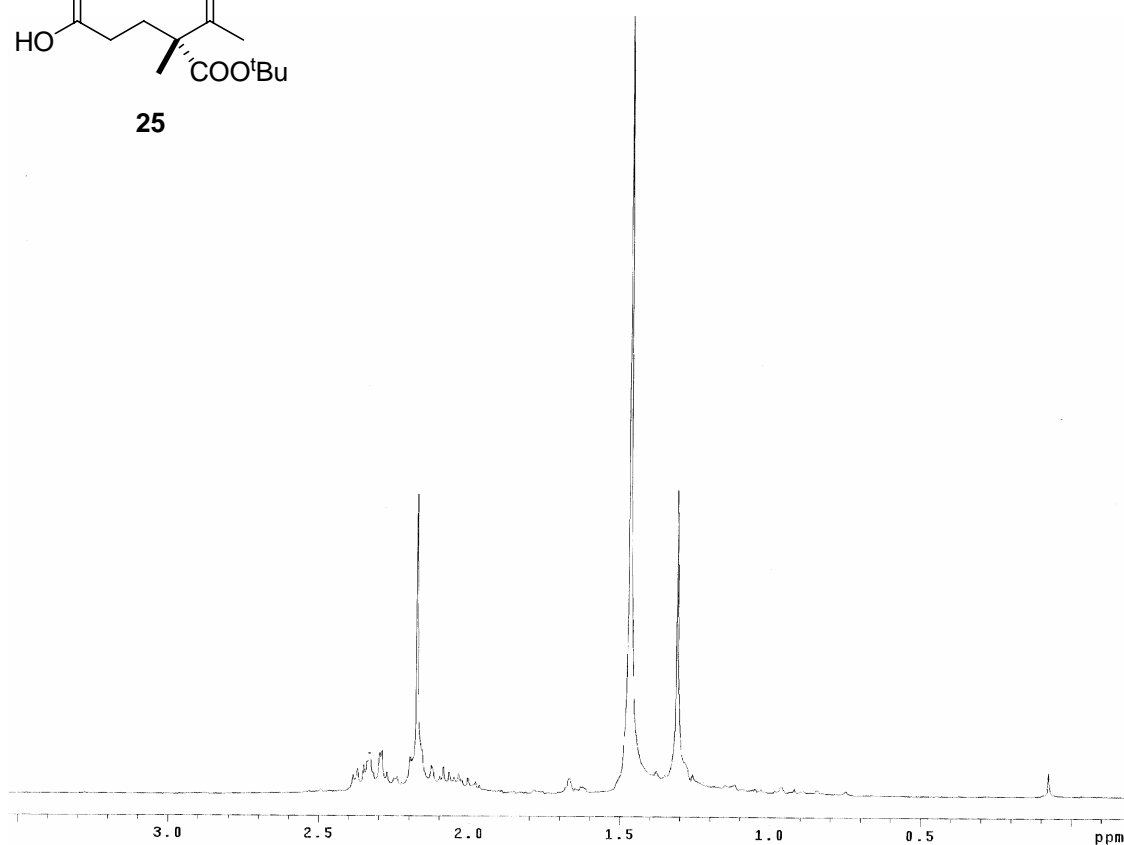
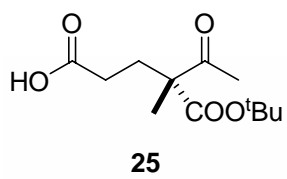


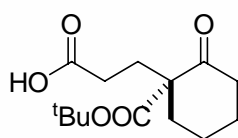


**23a/23b  
(crude)**

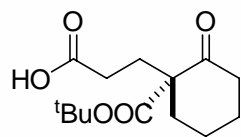
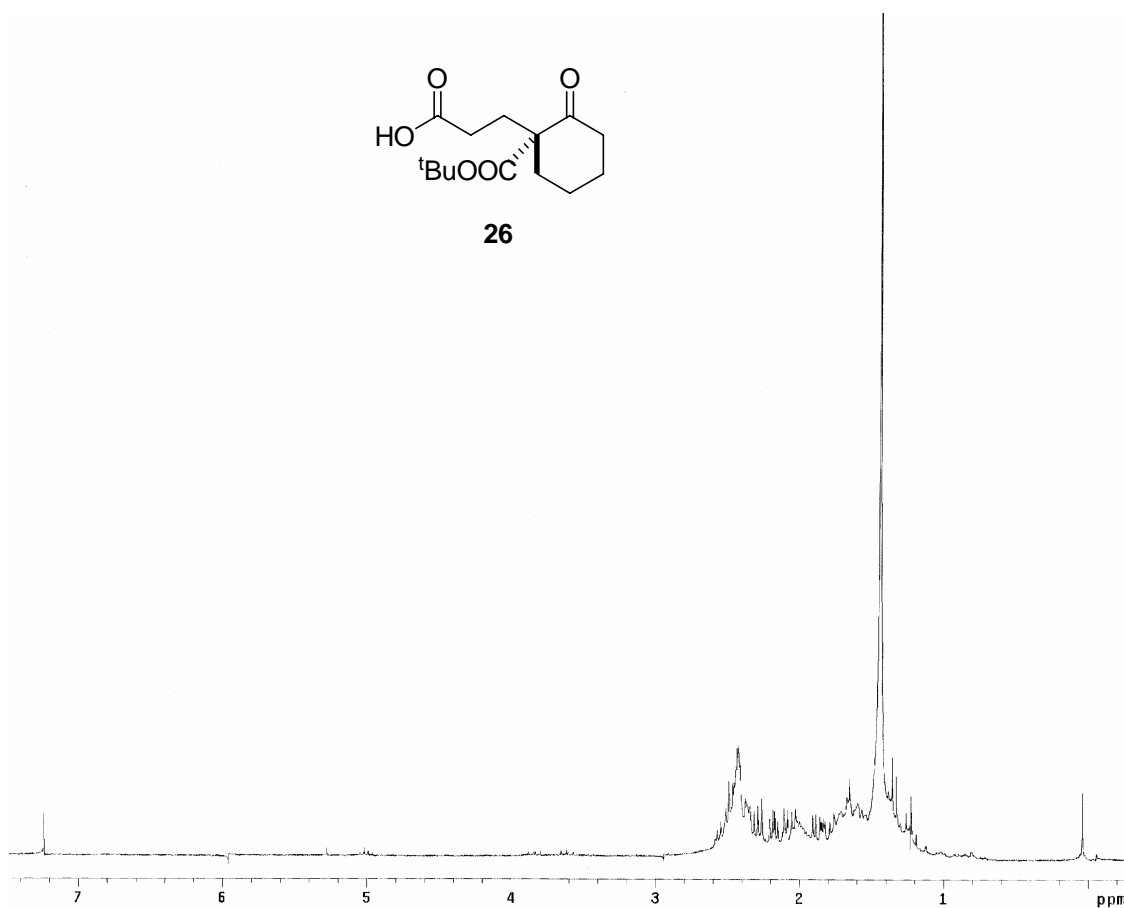




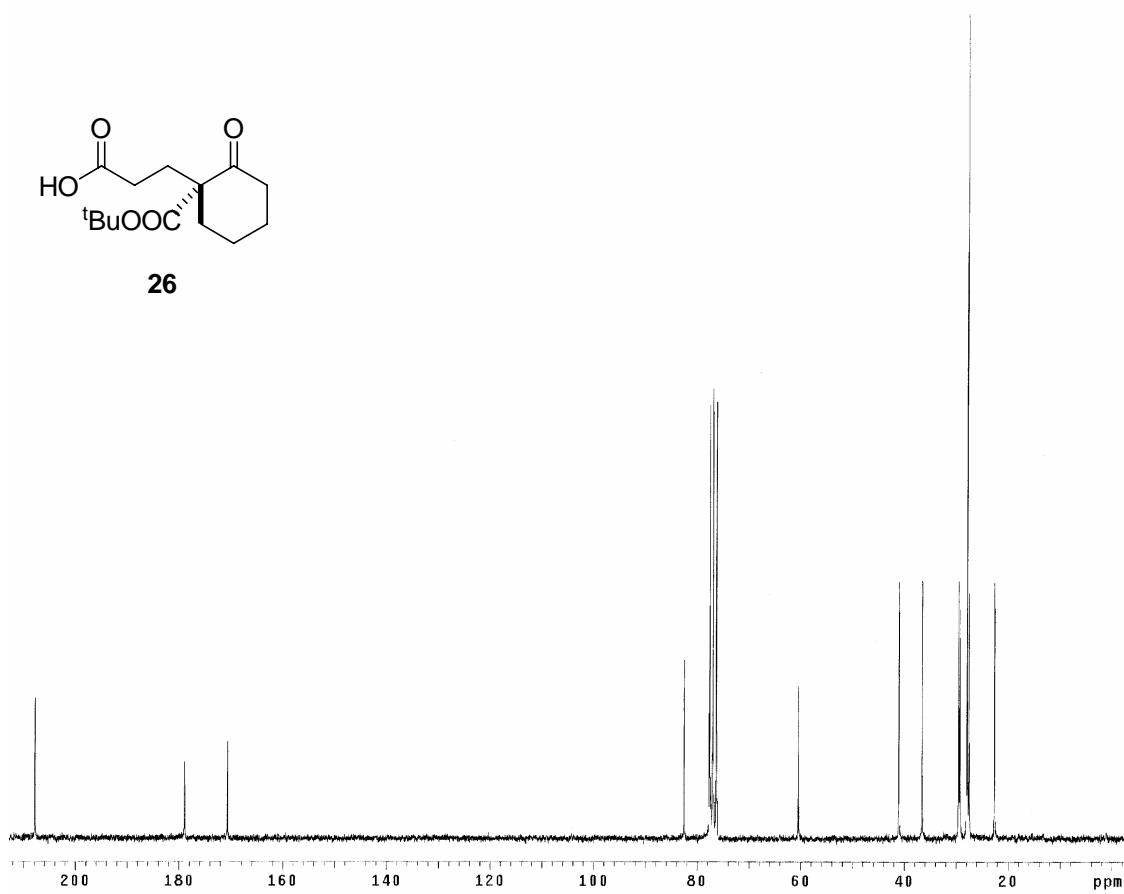


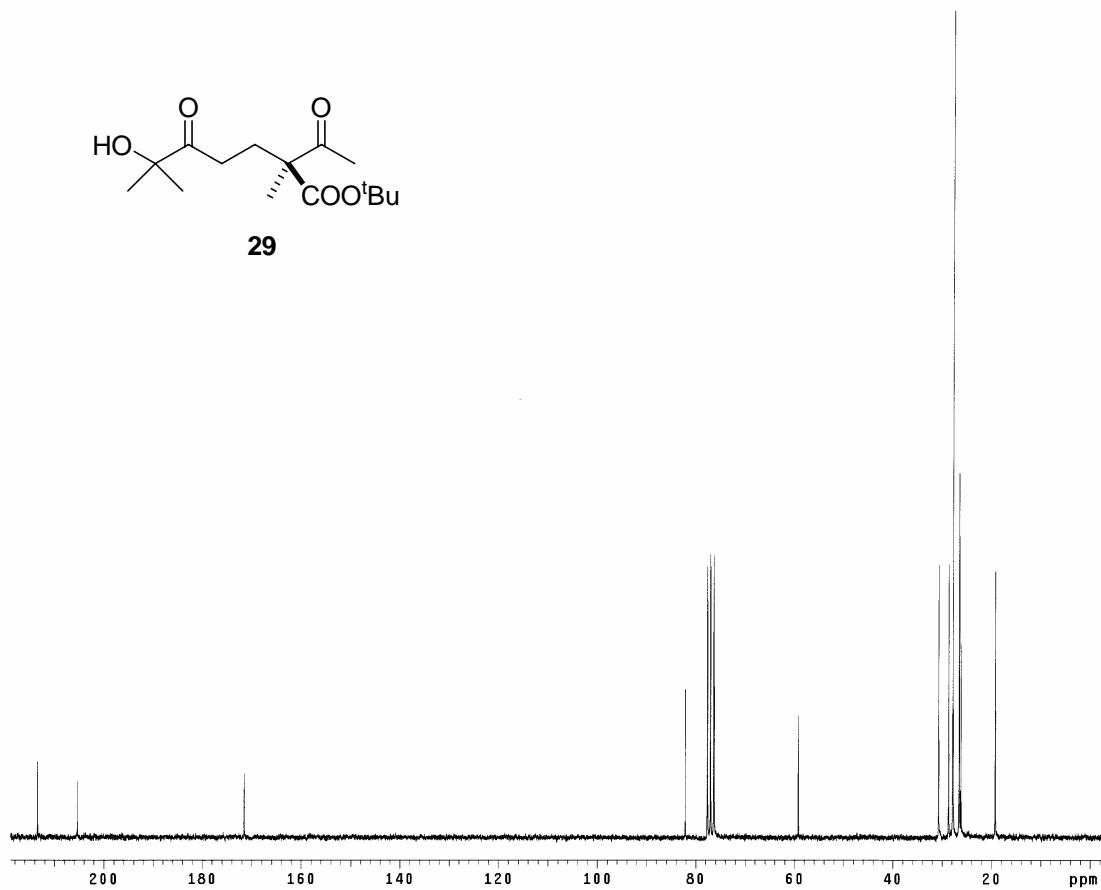
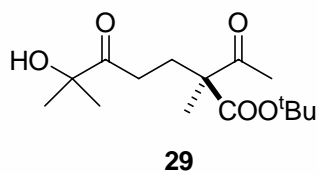
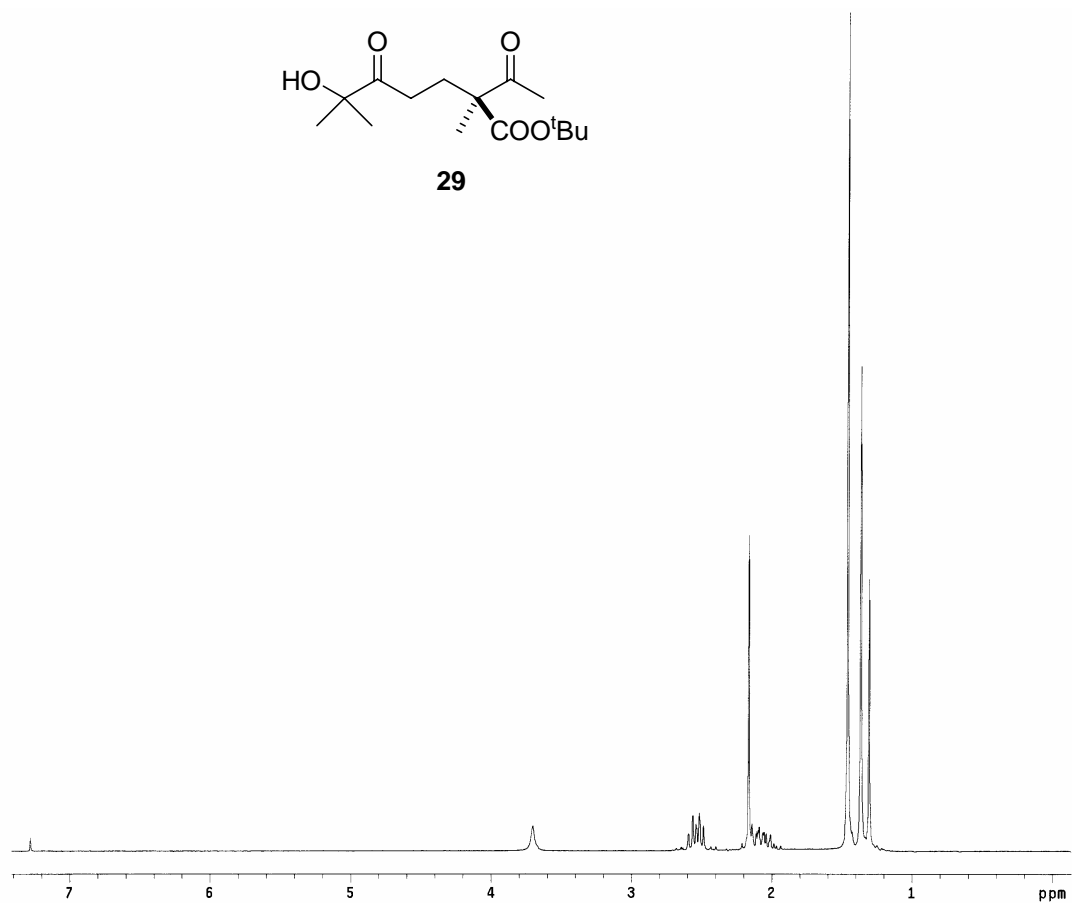
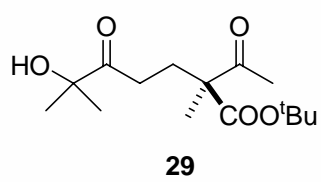


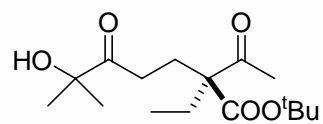
26



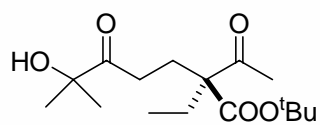
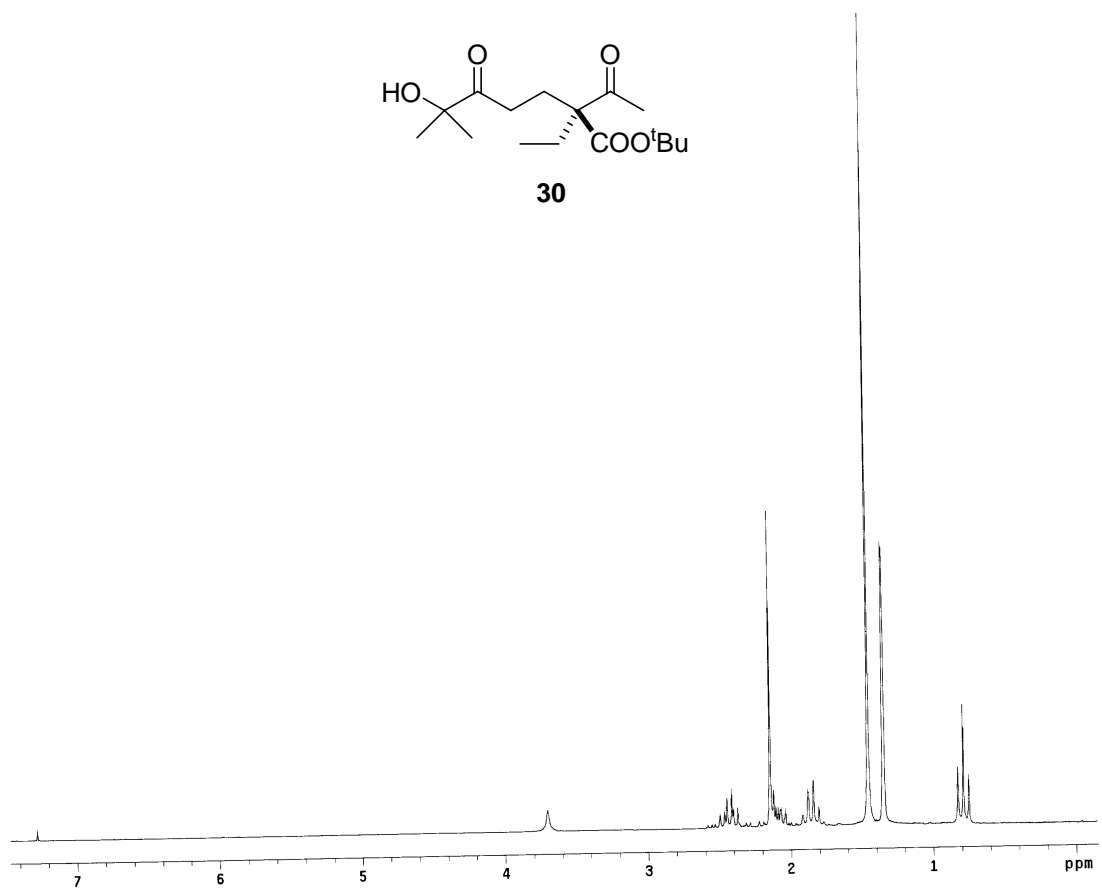
26



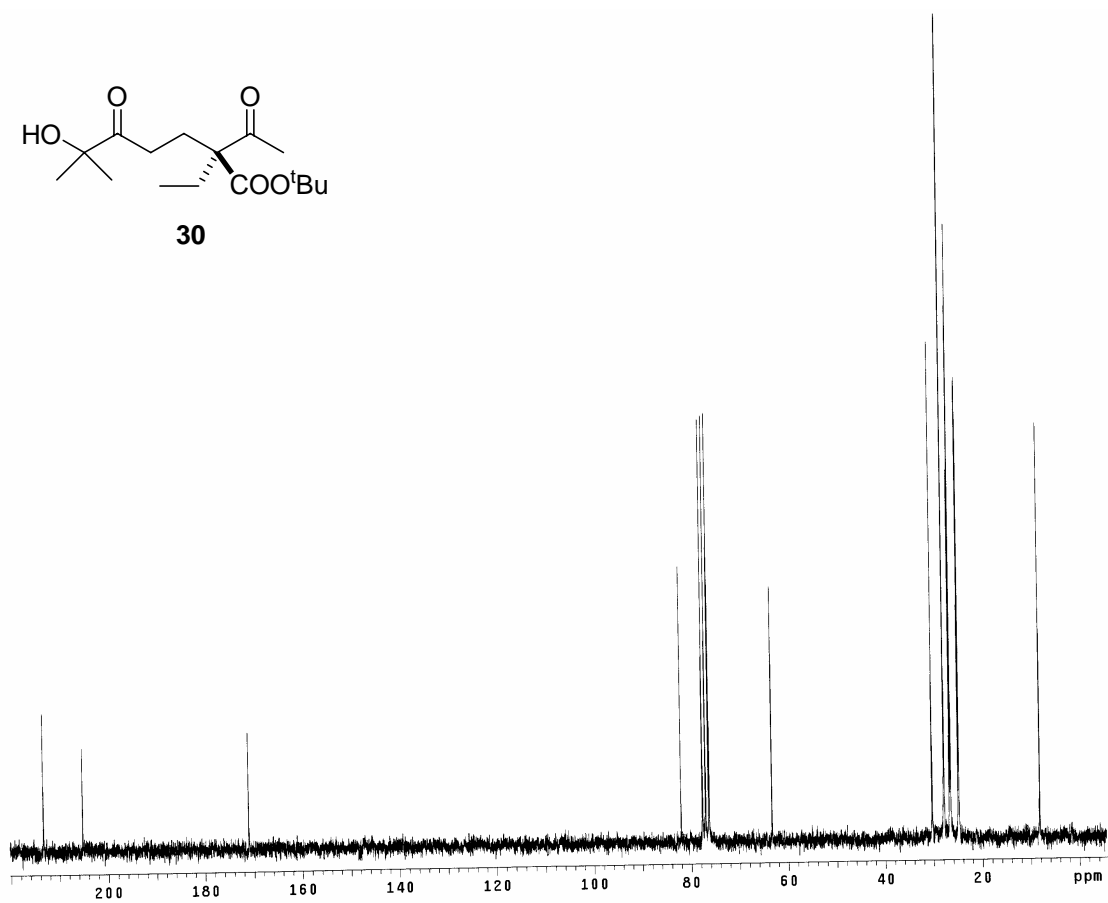


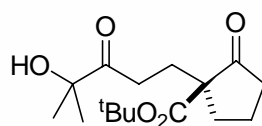


**30**

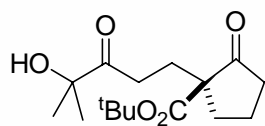
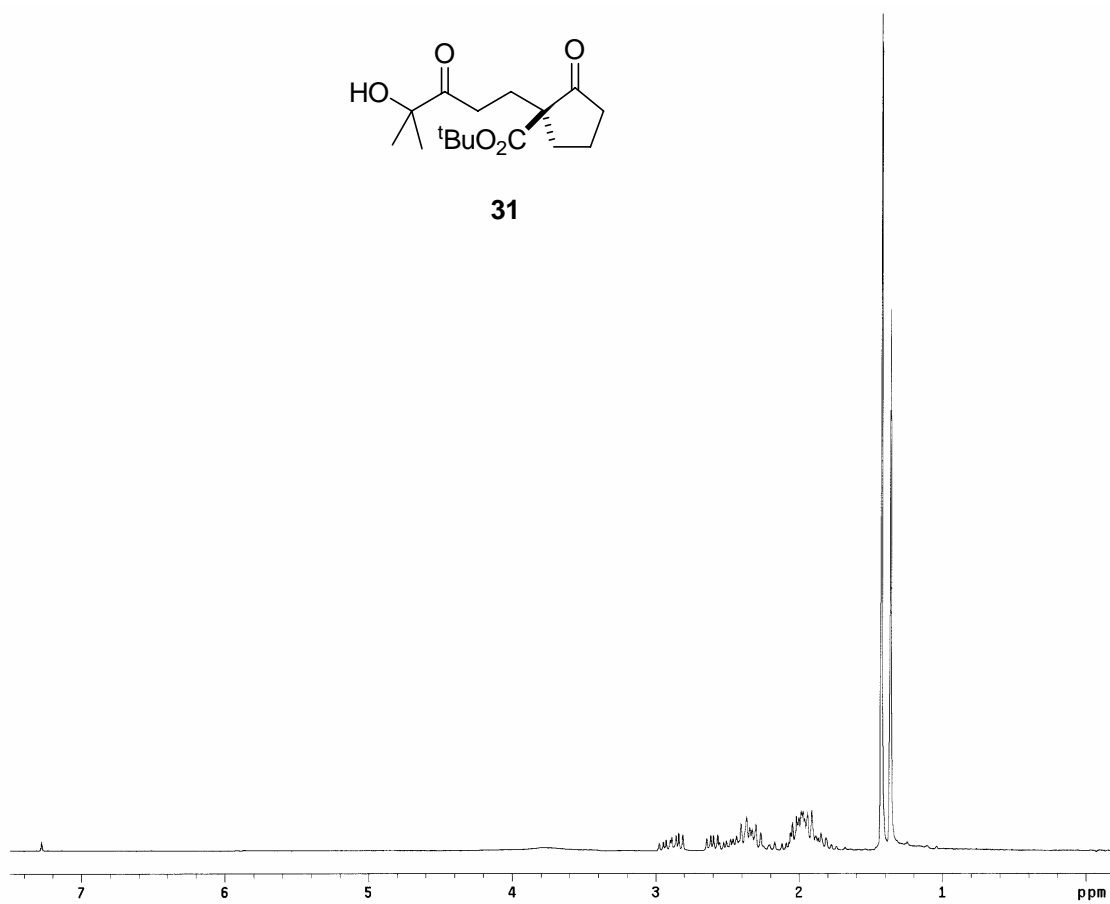


**30**

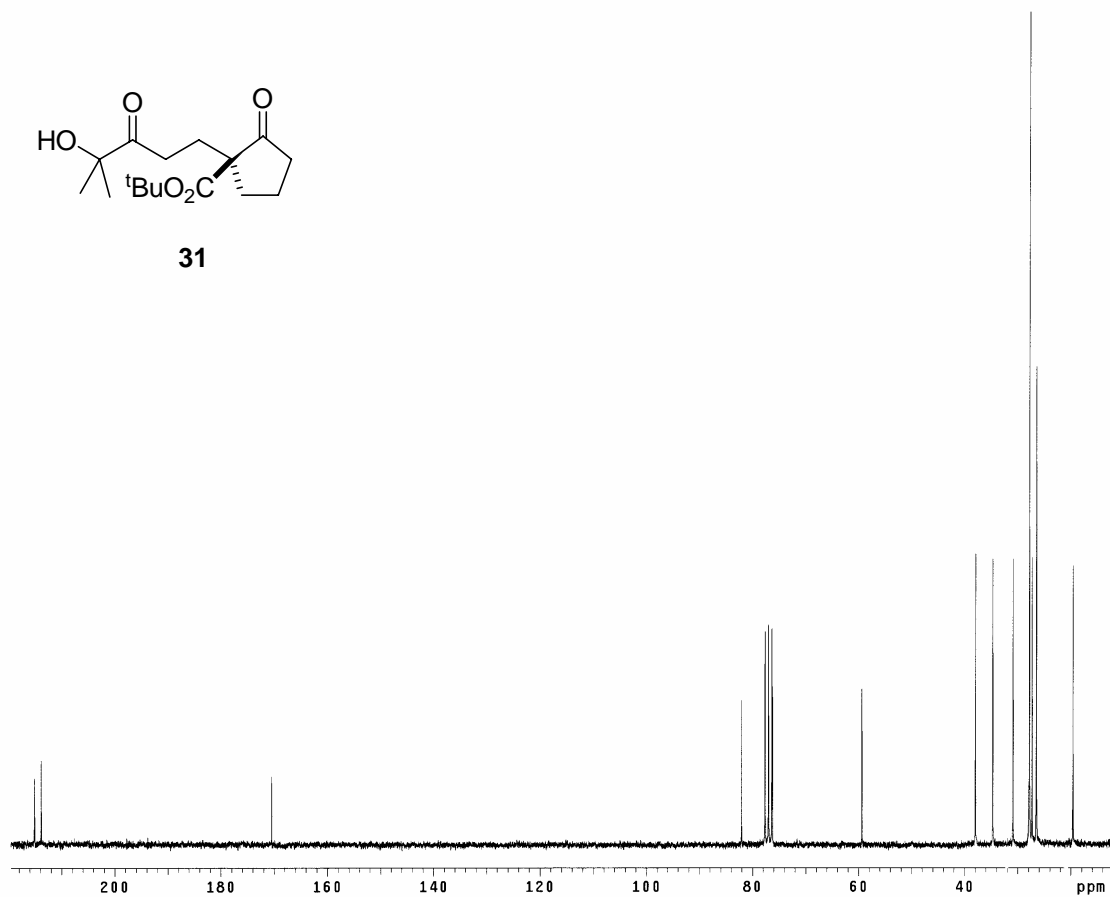


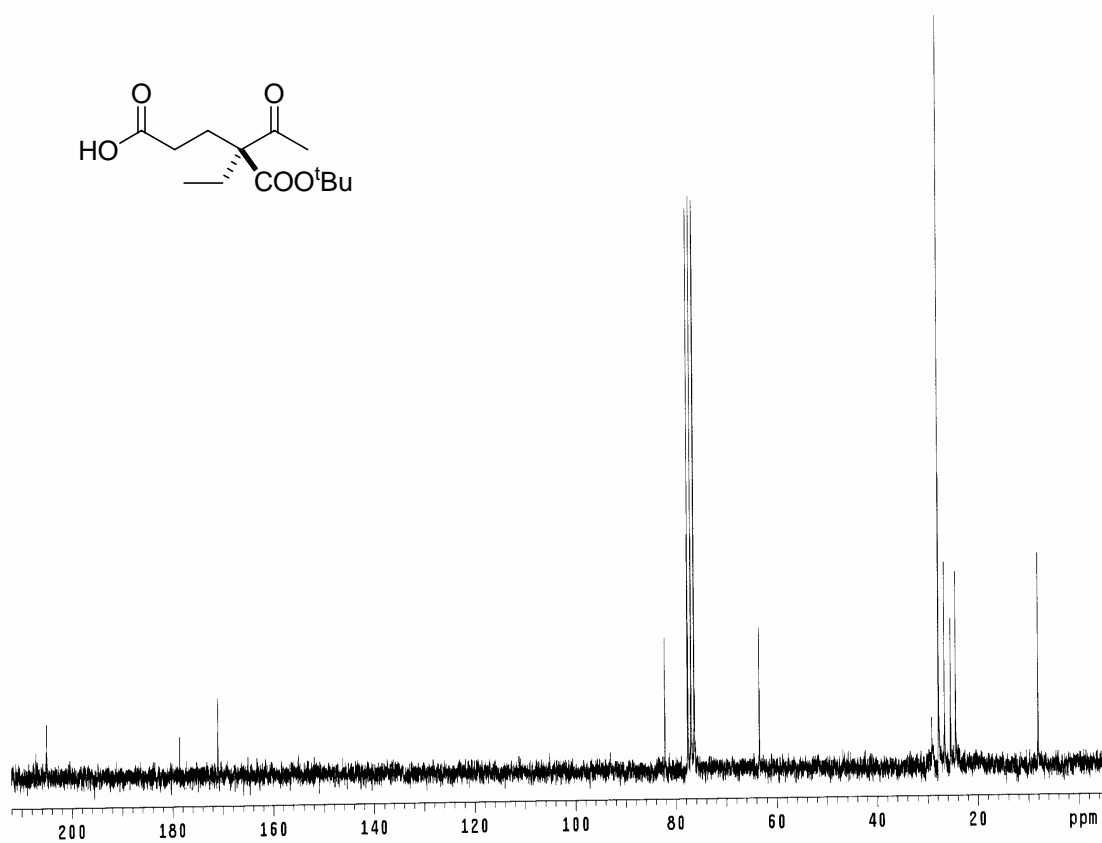
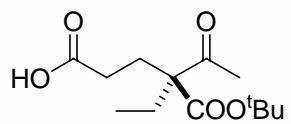
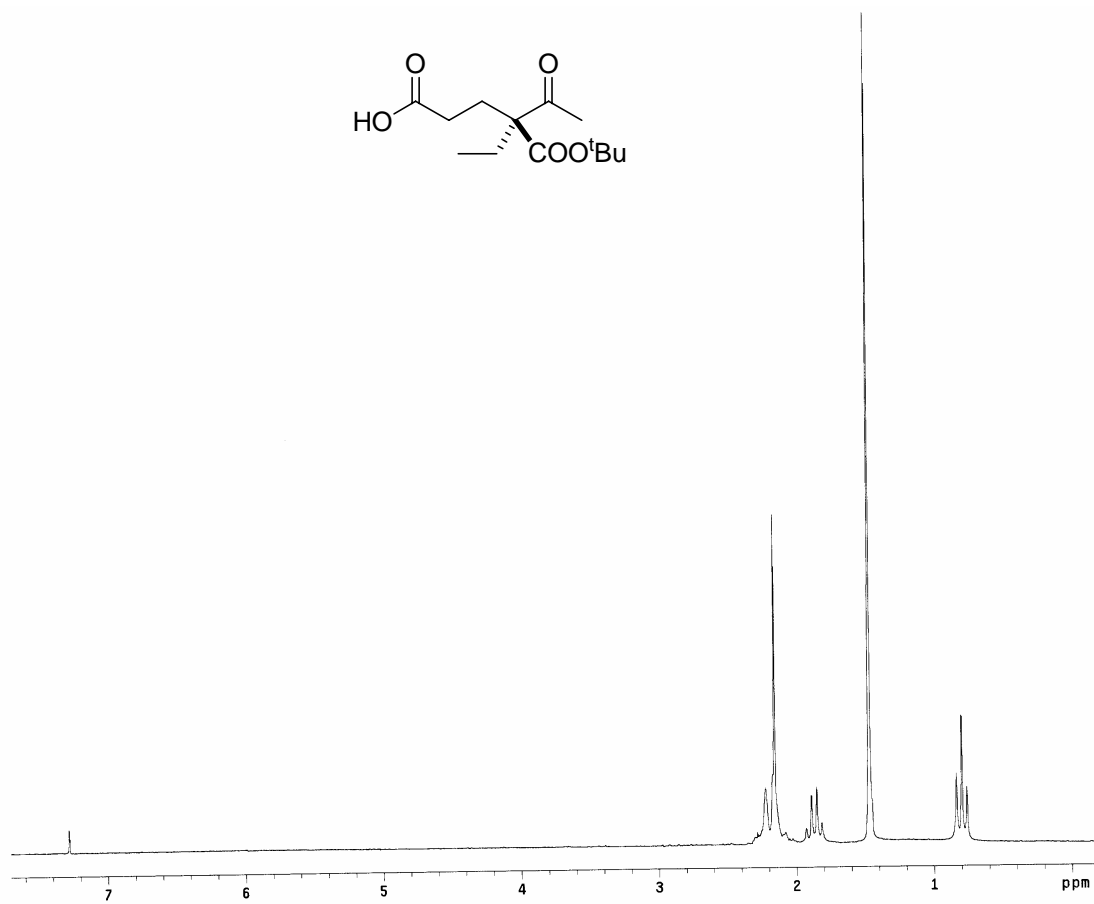
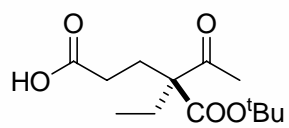


31

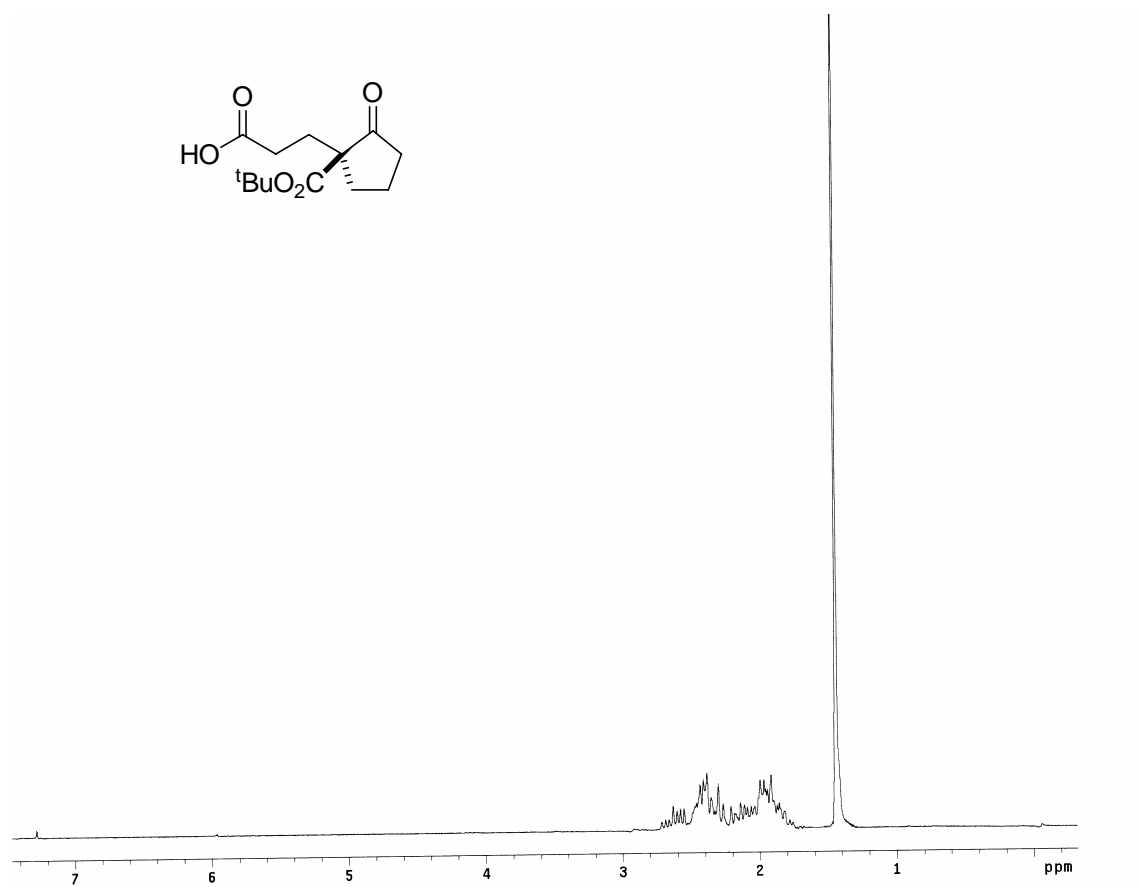


31

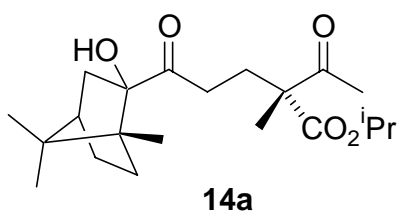
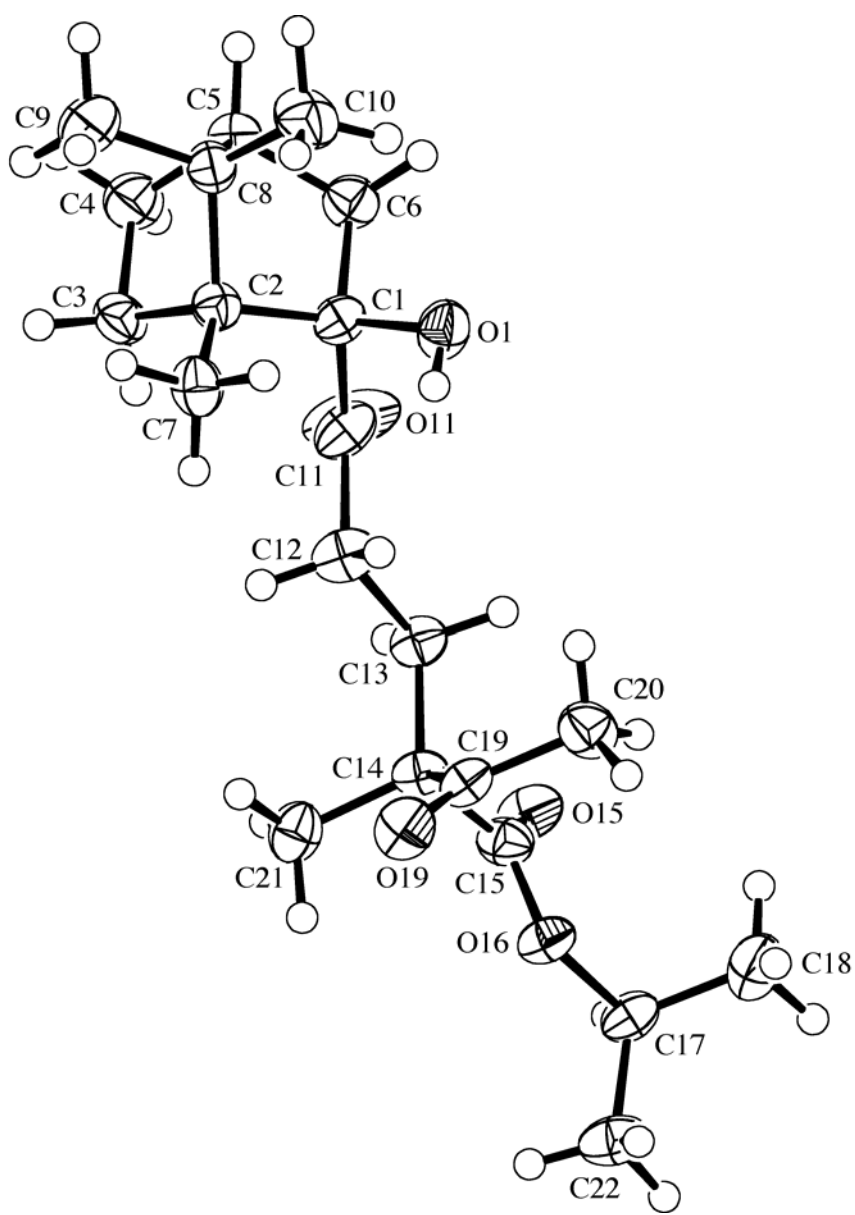




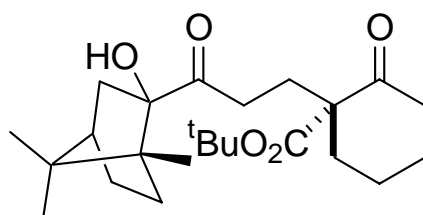
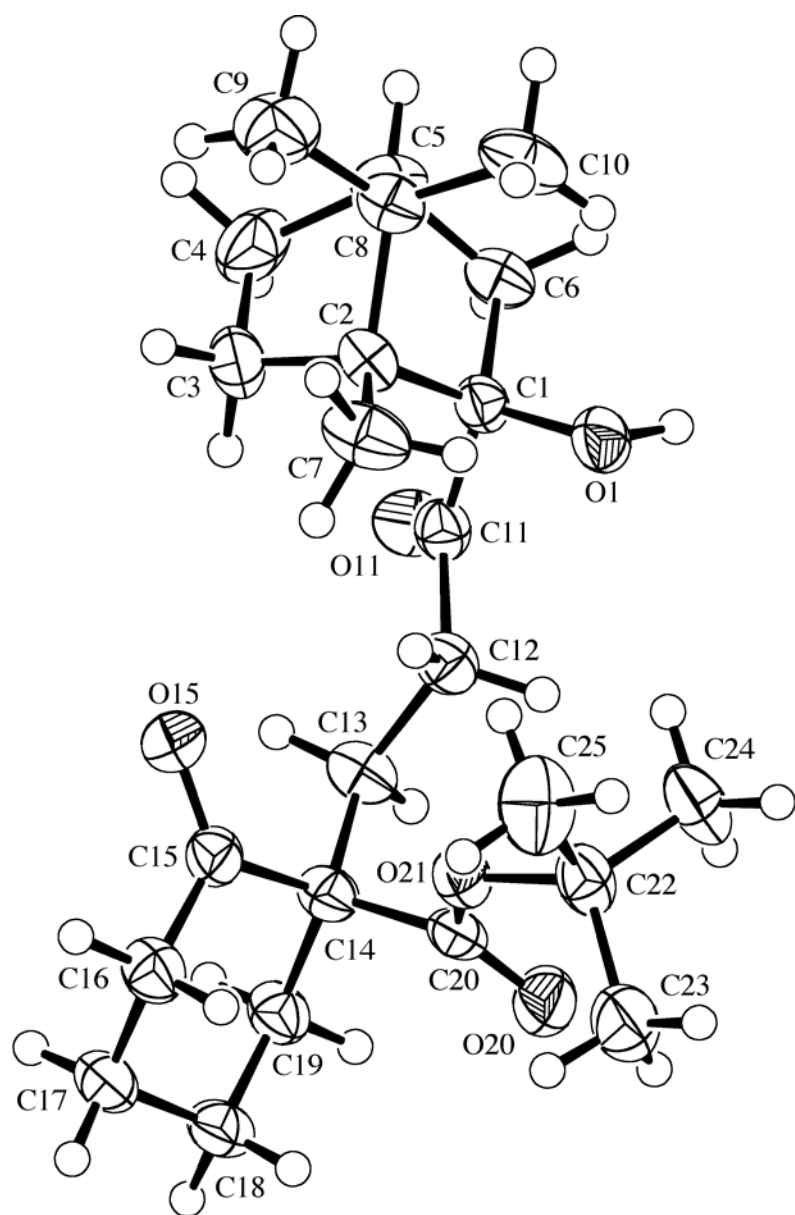




10. ORTEP diagram of compound 14a



11. ORTEP diagram of compound 23a



**23a**