Supporting Information

A New Process for the Preparation of Methyl Carbonates

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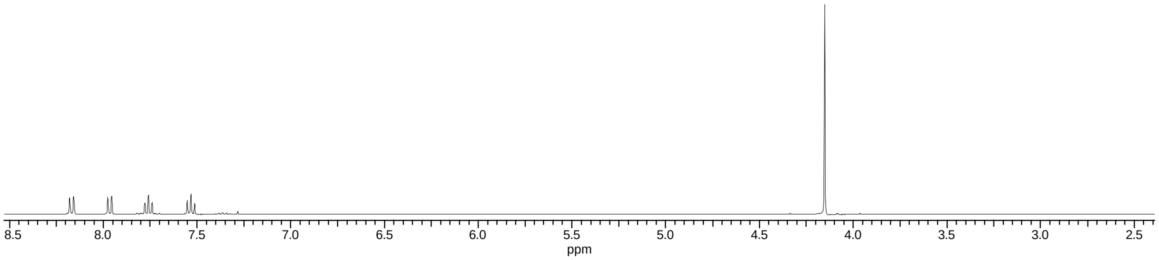
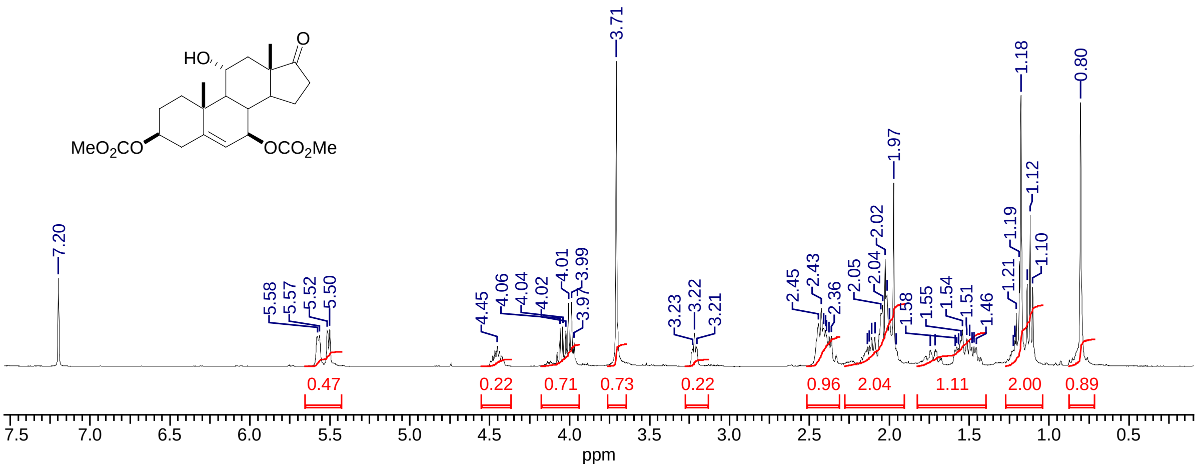
Preparation of 1H-Benzotriazole-1-carboxylic acid, methyl ester, 3-oxide ***6a***

Commercial hydrated HOBt was dried azeotropicly with anhydrous THF (3x) on a rotary evaporator. HOBT (150 g, 1110 mmol) was slurried in CH_2Cl_2 (1500 ml) and cooled to 0-5 C. TEA (186 ml, 1332 mmol) was slowly added while keeping the temperature below 5 C. When the addition was complete all the solids dissolved. With temperature kept below 5 C, methylchloroformate (91 ml, 1221 mmol) was slowly added with stirring. Stirring at 0-5 C was continued for 1 hour after the addition was complete and then mixture was warmed to room temperature. CH_2Cl_2 (500 ml) and H_2O (500 ml) were added and the layers separated. The organic layer was washed with H_2O (600 ml), dried over $MgSO_4$, filtered and concentrated. The solids were slurried in a minimum of EtOAc, filtered and dried on a nitrogen press to afford 193.3 g (90% yield) of **6a**.



Preparation of dicarbonate ***2b*** *and* ***2c*** *using pyridine and methyl chloroformate*

A solution of the triol **1** (2.0 g, 6.24 mmol) in 5 mL of pyridine was cooled to 0 C and treated with a solution of methyl chloroformate (3.4 mL, 43.7 mmol) in 5 mL of CH_2Cl_2. The mixture was slowly warmed to rt and then 50 mL of a water and CH_2Cl_2 were added. The aqueous was extracted with 3x 20 mL of CH_2Cl_2. The combined organic layers were washed with 20 mL of water and concentrated. Silica gel chromatography with 50% EtOAc/Hex afforded 1.3g (48% yield) of the dicarbonate **2b** and 0.51g (17% yield) of the tricarbonate **2c,** MS Calc for: $C_{28}H_{40}O_{10}$ m/z 559.2519 $(M+Na)^+$, found: 559.2531



O
HO
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OCO$_2$Me
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5.58
5.57
5.52
5.50
4.45
4.06
4.04
4.02
4.01
3.99
3.97
3.71
3.23
3.22
3.21
2.45
2.43
2.36
2.05
2.04
2.02
1.97
1.58
1.55
1.54
1.51
1.46
1.21
1.19
1.18
1.12
1.10
0.80
0.47
0.22
0.71
0.73
0.22
0.96
2.04
1.11
2.00
0.89
7.5
7.0
6.5
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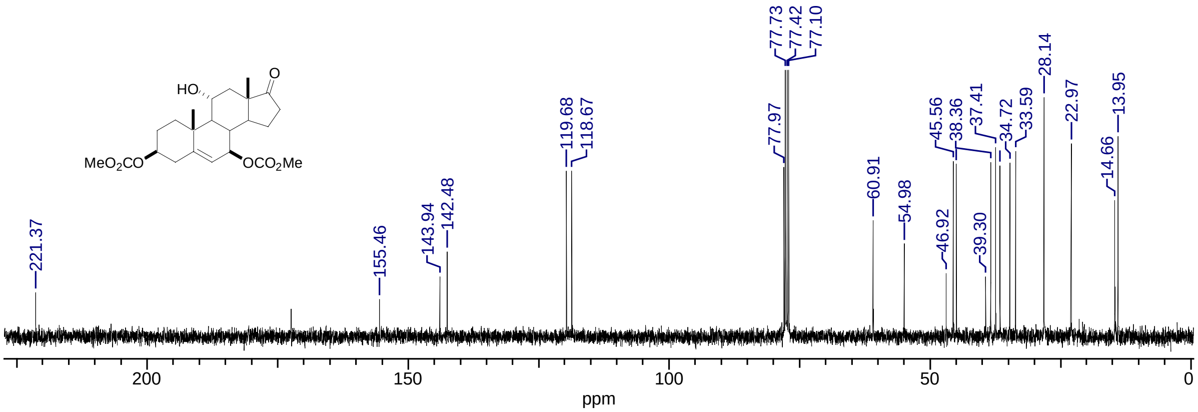

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OCO$_2$Me
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119.68
118.67
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45.56
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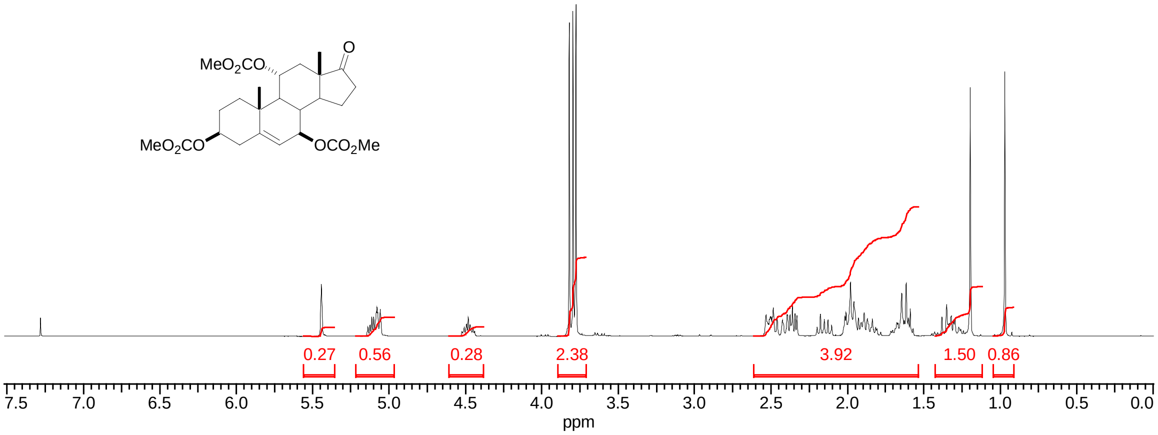

O
MeO$_2$CO
MeO$_2$CO
OCO$_2$Me
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0.56
0.28
2.38
3.92
1.50
0.86
7.5
7.0
6.5
6.0
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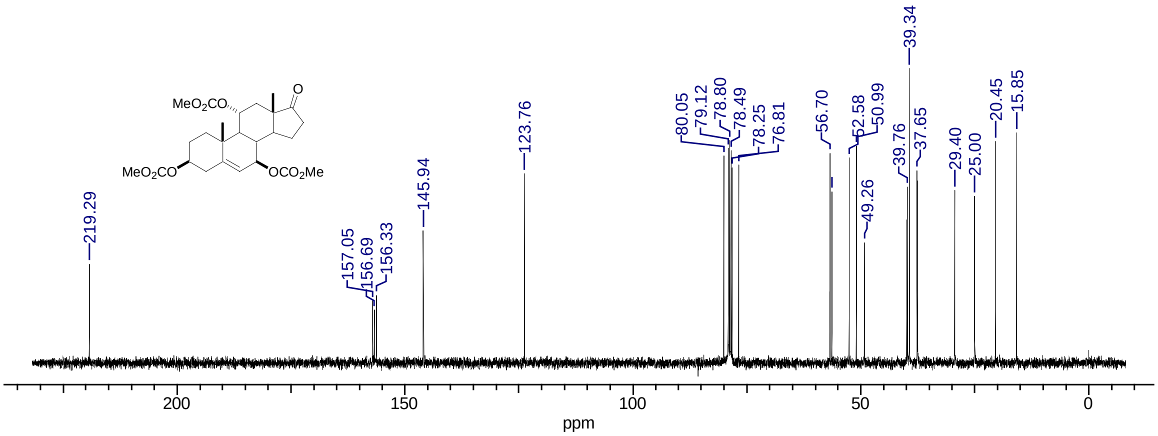


*Preparation of the dicrbonate **2b** using TMEDA/methyl chloroformate*

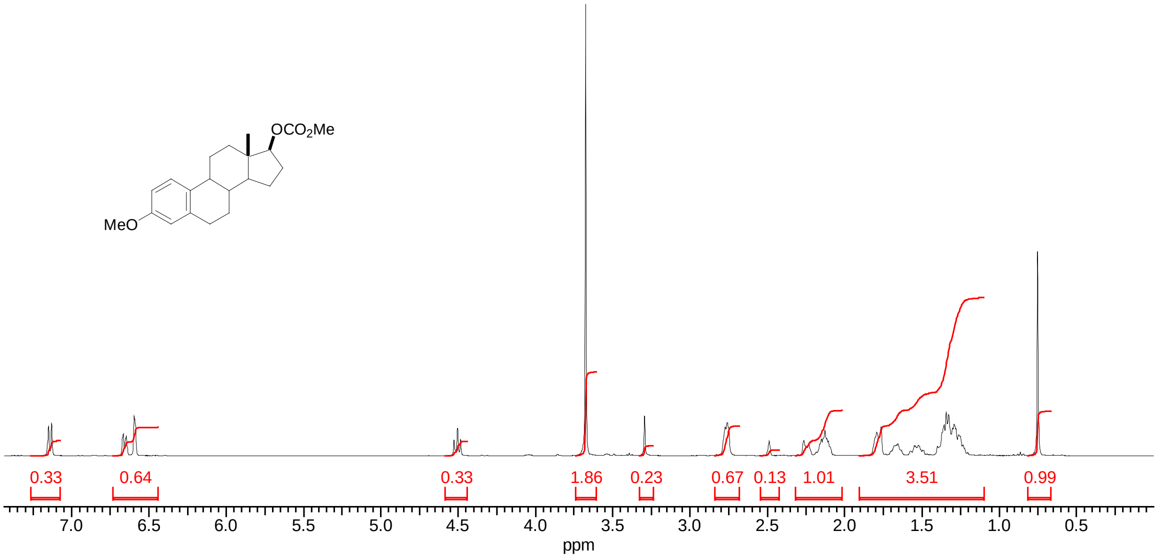
Slurried 7 ,11 -OH DHEA (2.0g, 6.242mmol) in CH_2Cl_2 (40mL) and added TMEDA (1.13mL, 7.49mmol). Cooled the slurry to -15 C and added methyl chloroformate (965 L, 12.48mmol). The reaction was warmed to rt and stirred for 3hrs. TLC analysis indicated that the dicarbonate was the predominant product accompanied by trace amounts of mono and tricarbonate. Added 1eq more TMEDA (942 L, 6.242mmol) and methyl chloroformate (483 L, 6.242mmol). The reaction was complete in a couple hrs by TLC. Added EtOAc and H_2O and separated the layers. The organic was dried over $MgSO_4$ and concentrated to a white solid. The crude product was dissolved in hot EtOAc (25mL) and allowed to cool. After crystallization heptane (50mL) was added and the white crystals were cooled in an ice bath and **2b** was collected by filtration (2.13g, 78% yield).

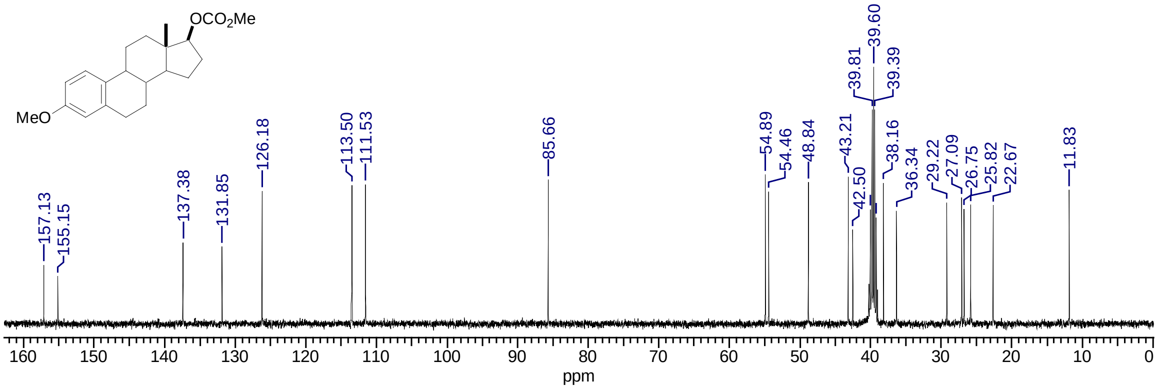
*Preparation of **2c** using BtOCO$_2$Me*

To a 3N 250 ml RBF was charged triol (10.00g, 31 mmol) dissolved in pyridine (100 ml). To this solution was added TEA (31 ml, 218 mmol), MeO_2COBT (24.2 g, 125 mmol), and DMAP (1.2 g, 9.4 mmol). The slurry was stirred for 2 hours at which time everything dissolved. TLC (75/25 EtOAc/Hexane, CAM stain) indicated the reaction was not complete. Additional MeO_2COBT (12 g, 62 mmol) and TEA (10 ml, 73 mmol) were added. Once solids dissolved the reaction was complete by TLC. Water (300 ml) was slowly added to crystallize the product. The slurry was cooled in an ice bath, filtered and washed with 10% HCl (2 x 35 ml) and hexane (3 x 50 ml). The solids were dried in vacuum oven for 24 hours to give 14.2 grams (92 % yield) of tricarbonate **2c**.

*Preparation of carbonate **8***

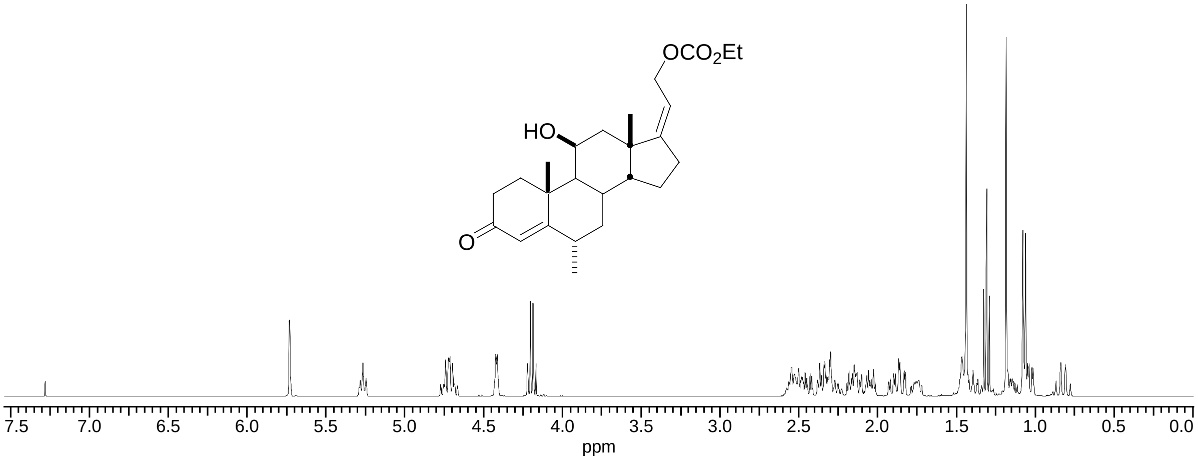
A solution of 2.0 g, 7.0 mmol of the alcohol in 20 mL pyridine and 5 mL TEA was treated with 100 mg of DMAP. The temperature was adjusted to 25 C. $BtOCO_2Me$ (2.25 g, 10.5 mmol) was then added and the solution stirred for 3 h. TLC shows the reaction to be incomplete and thus an additional 1.6 g of $BtOCO_2Me$ was added. The mixture was stirred at 25 C overnight. Water was added to the solution and the product crystallized directly. The solids were filtered, washed with water, and dried in a nitrogen press to afford 2.16 g (90% yield) of the carbonate 8. MS Calc for $C_{21}H_{28}O_4$ *m/z* 345.2066 $(M+H)^+$, found: 345.2058.

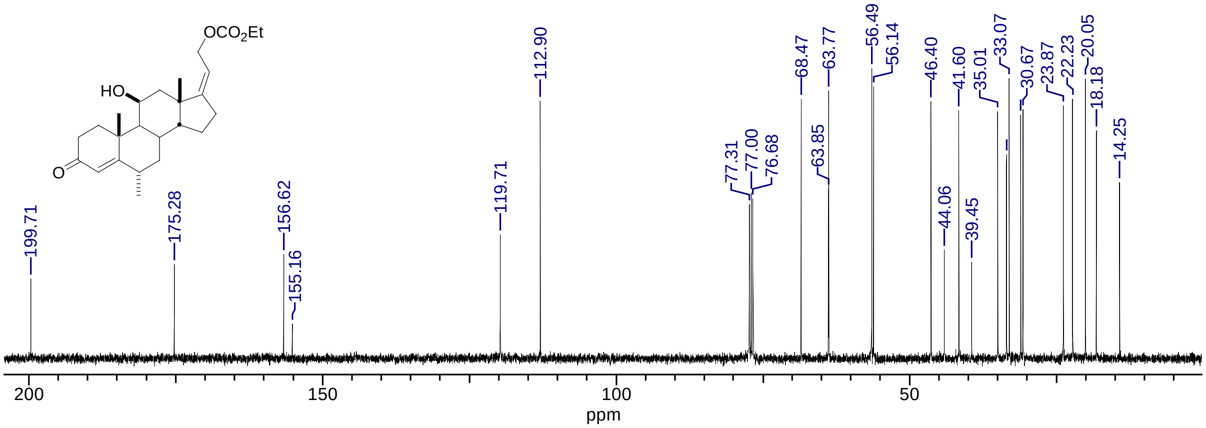




*Preparation of the carbonate **9***

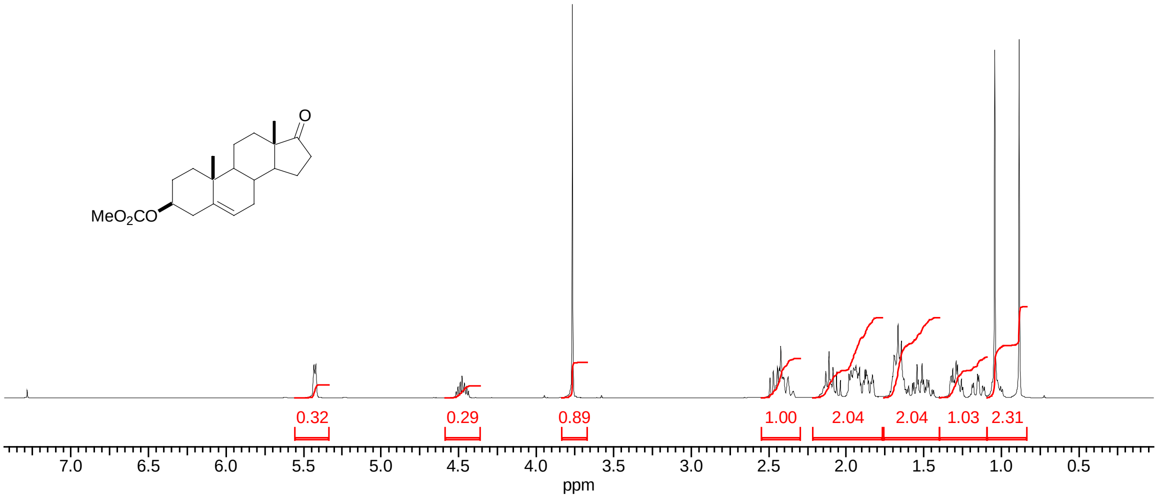
A mixture of the diol (2.0 g, 5.81 mmol) 20 mL of pyridine, 5 mL of TEA and BtOCO$_2$Me (4.8 g, 23.2 mmol) was combined at 25 C and equilibrated in the Multimax. DMAP (100 mg) was then added which resulted in a rapid reaction. The reaction was complete in 30 min based on the T$_r$-T$_j$ value. The solution was poured into water and the carbonate **13** isolated with EtOAc. Chromatography of the crude carbonate on silica with 40% EtOAc/Hex afforded 2.25 g (93% yield) of carbonate **9**.

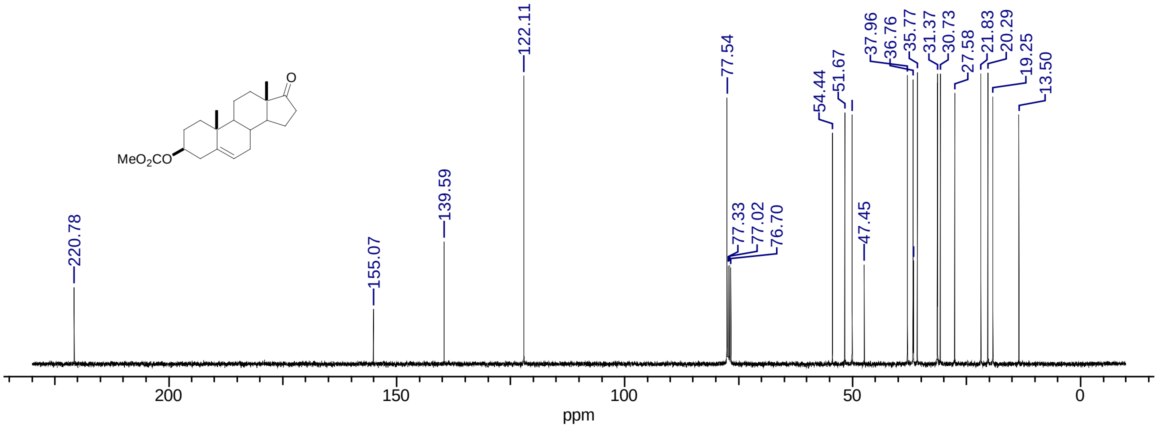




*Preparaion of carbonate **10***

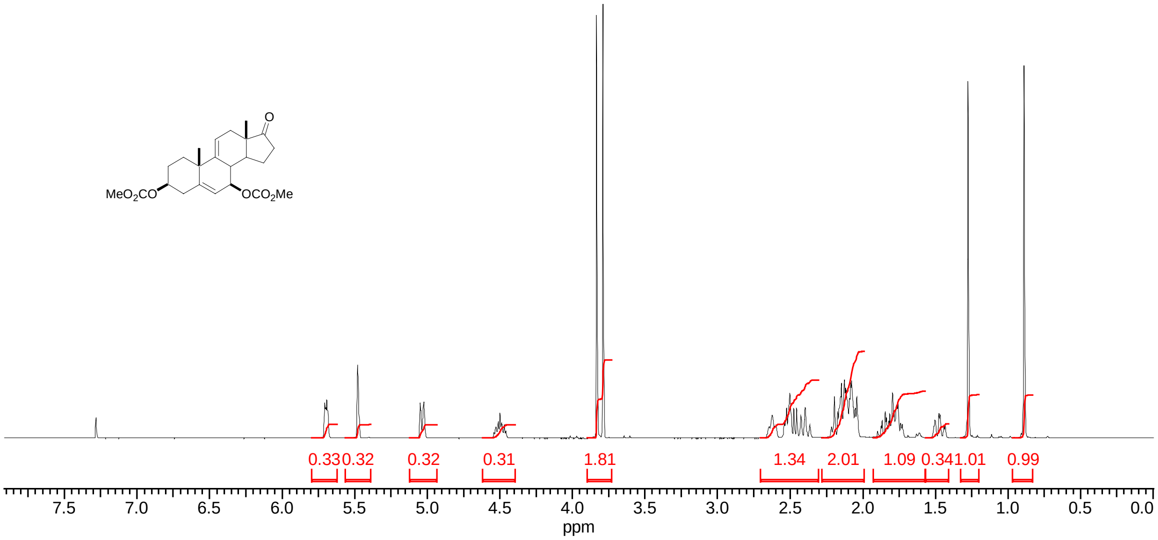
A mixture of the DHEA (2.0 g, 7.05 mmol), 9.5 mL of pyridine, 2.5 mL of TEA and a catalytic amount of DMAP was treated with 2.32 g (12.0 mmol) of BtOCO$_2$Me and stirred at rt overnight. Water was added to the solution to knock out the carbonate. The solids were filtered and dried on a N$_2$ press to afford 2.30 g (94.5% yield) of the carbonate **10**. MS Calc for $C_{21}H_{30}O_4$ *m/z* 346.1244 $(M+H)^+$, found: 346.1238.

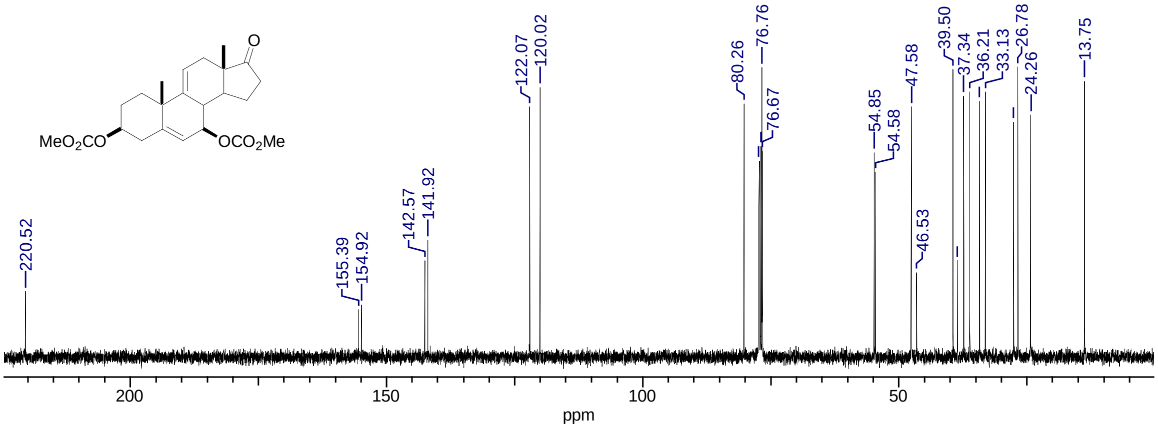




*Preparation of dicarbonate **11** with MeO_2COBt*

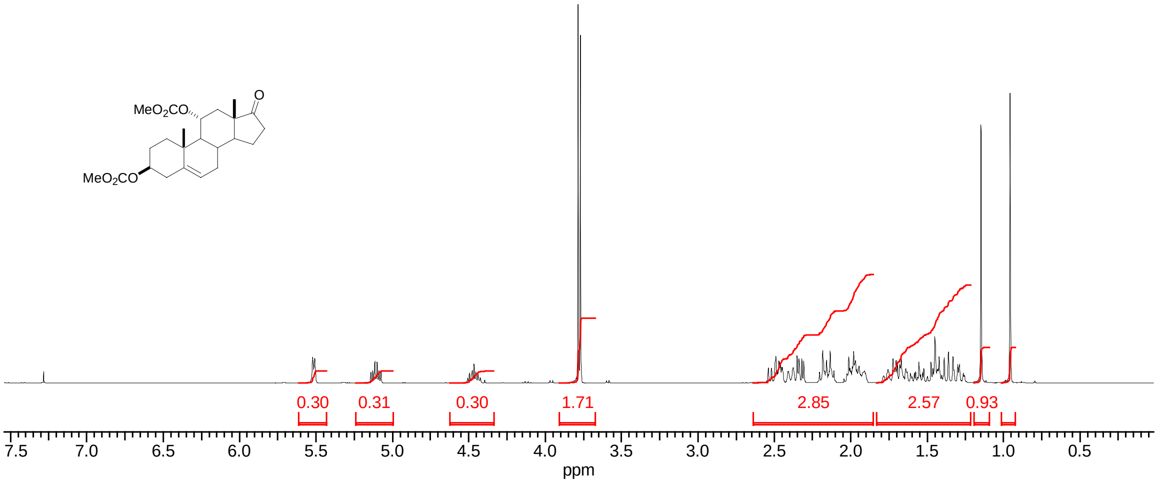
A solution of 2.12 g, 7.00 mmol of the diol in 20 mL of pyridine and 5 mL of TEA was treated with 100 mg of DMAP and the temperature adjusted to 25 C. $BtOCO_2Me$ (4.08 g, 21.0 mmol) was then added after 3 h an additional 1.6 g of $BtOCO_2Me$ was added to drive the reaction to completion. When the reaction was complete water was added and the product isolated with EtOAc. The crude dicarbonate was chromatographed on silica with 25% EtOAc/Hex to afford 2.42 g (89.5% yield) of pure **11.** . MS Calc for $C_{23}H_{32}O_7$ *m/z* 441.1889 $(M+Na)^+$, found: 441.1898.

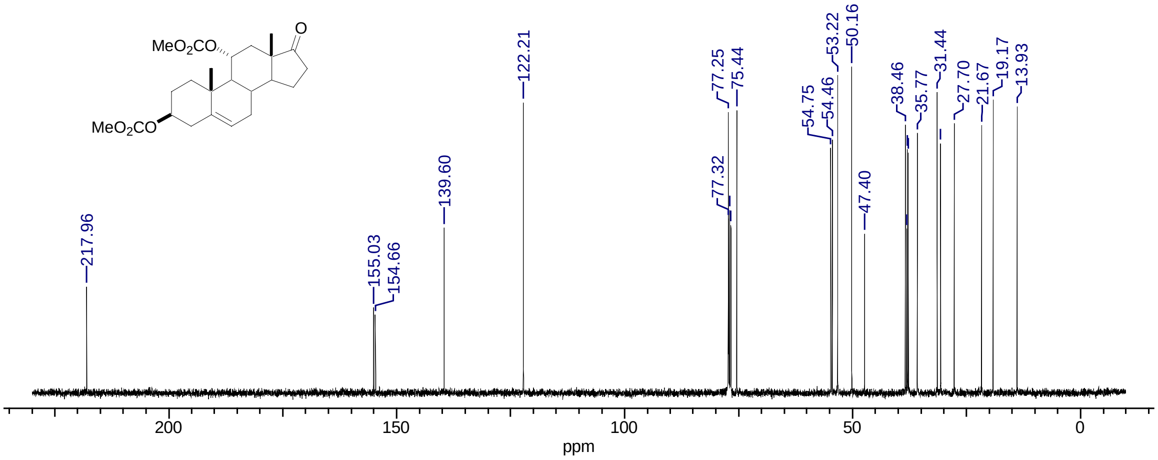




Preparation of carbonate ***12***

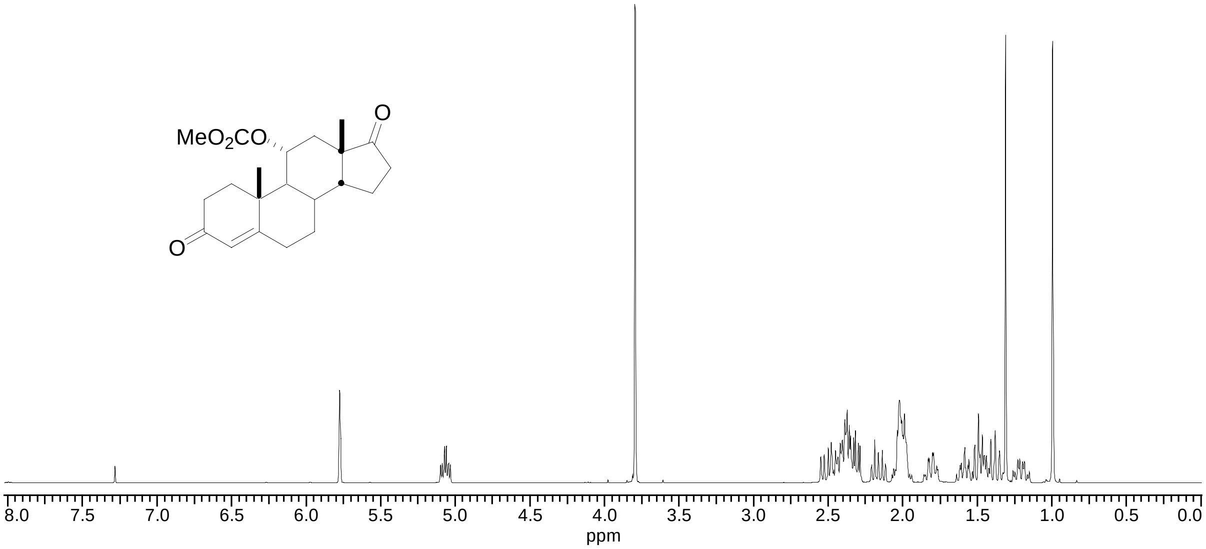
A solution of the diol (1.0 g, 2.76 mmol) was dissolved in 15 mL of pyridine and treated with 0.31 g of TEA, 0.034 of DMAP and 1.07 g (5.52 mmol) of BtOCO$_2$Me. The solution was stirred at rt overnight and the product isolated with EtOAc. Chromatography on silica gel and crystallization from EtOAc/Hex afforded 0.9 g (78% yield) of the dicarbonate **12**.

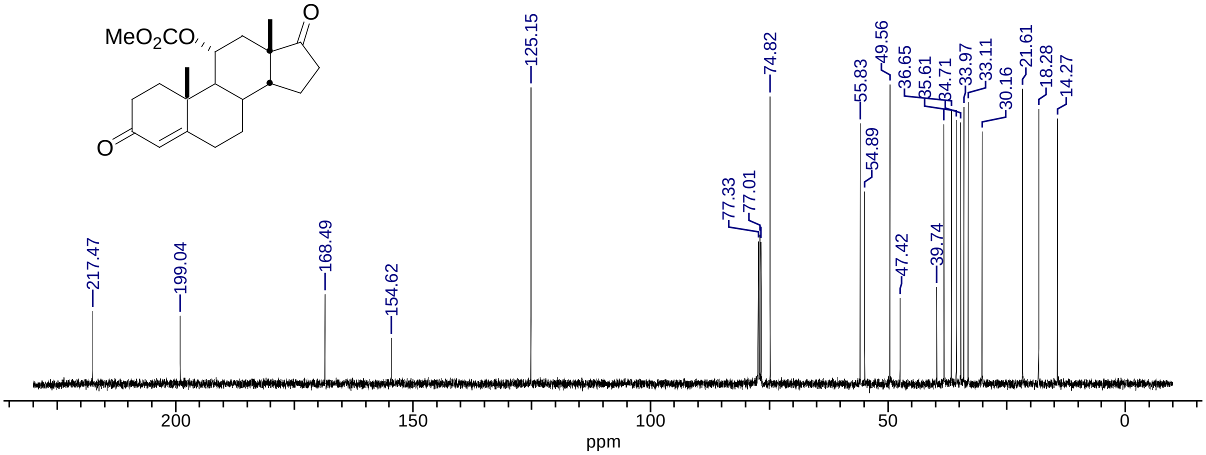




*Preparation of carbonate **13***

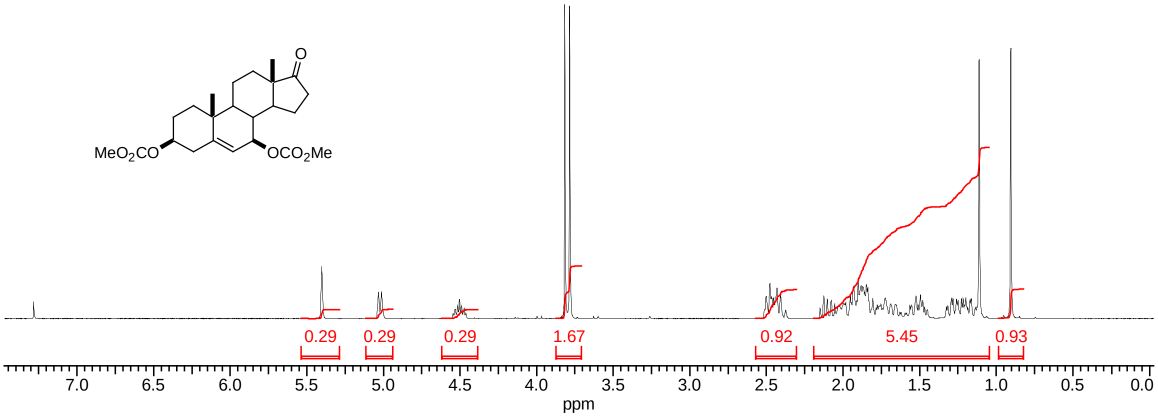
The steroid (530 mg, 1.76 mmol) was dissolved in 5 mL of pyridine and treated with 1 mL of TEA, 50 mg of DMAP and 850 mg of BtOCO$_2$Me. The mixture was stirred at rt until TLC (50:50 EtOAc/Hex) indicated complete reaction. Water was added to knock out the product. Filtration and drying afforded 497 mg (79% yield) of the carbonate **13**. MS Calc for $C_{23}H_{32}O_7$ *m/z* 443.2045 $(M+Na)^+$, found: 443.2055.

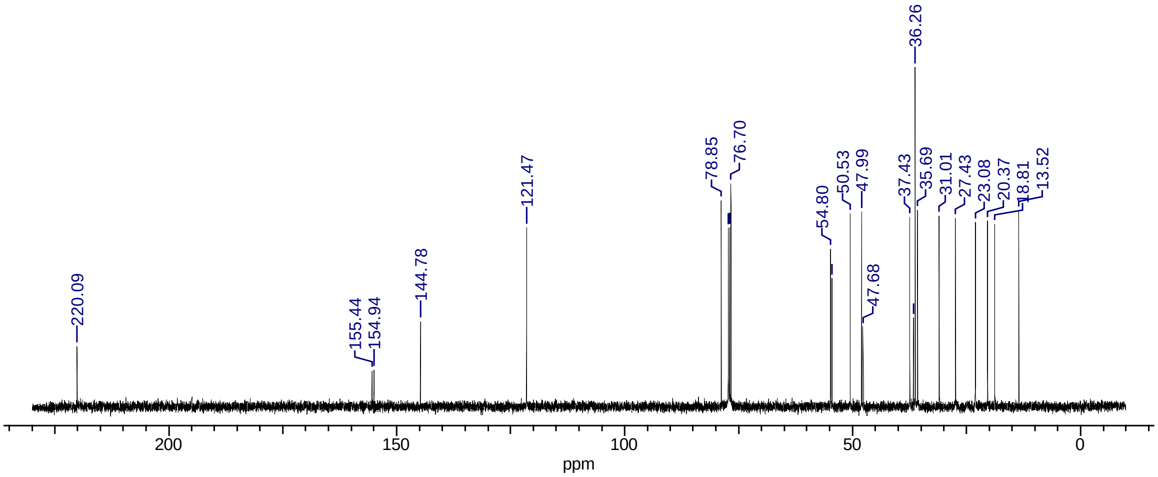




*Preparation of the Dicarbonate **14** with BtOCO$_2$Me*

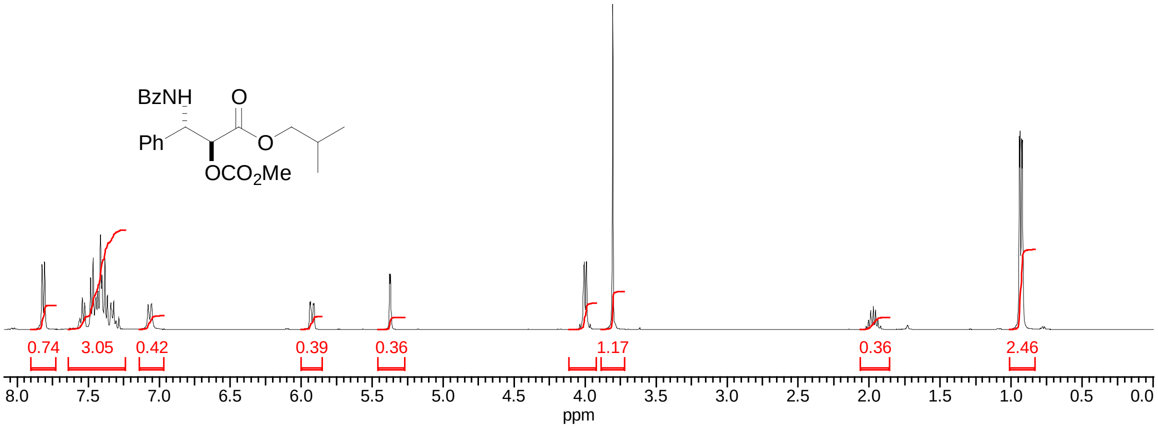
The diol (2.0 g, 6.56 mmol) in 15 mL of pyridine and 5 mL of TEA was treated with 4.8 g of BtOCO$_2$Me and 500 mg of DMAP at rt. The mixture was allowed to stir at rt overnight at which point TLC (50% EtOAc/Hex) indicated the reaction complete. Water was added to knock out the product. The solids were filtered, washed with water and dried on a N$_2$ press to give 2.62 g (95% yield) of the dicarbonate **14.** MS Calc for $C_{23}H_{32}O_7$ *m/z* 443.2045 (M+Na)$^+$, found: 443.2041.

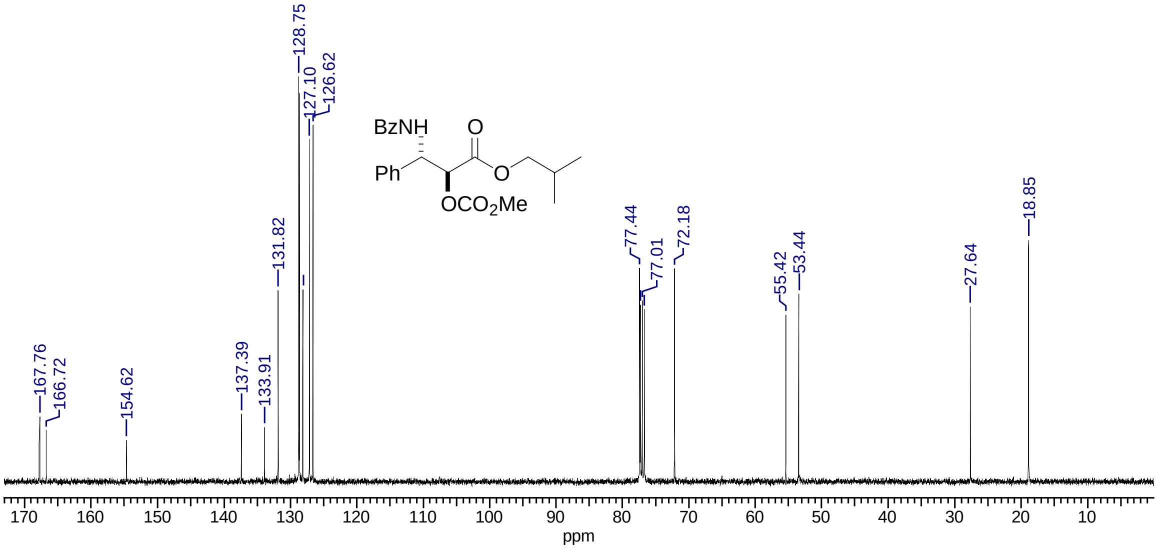




Preparation of Phenyl isoserine carbonate ***15***

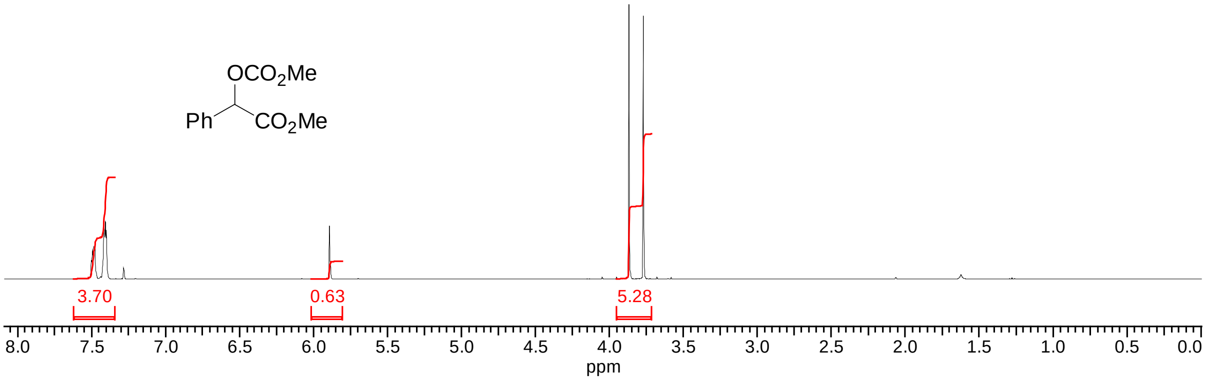
The alcohol (2.08 g, 61.0 mmol) was dissolved in 20 mL pyridine and 5 mL TEA, treated with 135 mg of DMAP and 2.36 g, 122.0 mmol of $BtOCO_2Me$ at 25 C. The reaction was monitored using the ASI Multimax and TLC. Both techniques indicate that the reaction is complete in about 15 min. Water was added to the solution and the product isolated with EtOAc to give a viscous oil (2.54 g). This was chromatographed on silica gel with 20% EtOAc/Hex to afford **15** (2.0 g, 82.5%). MS Calc for $C_{22}H_{25}NO_6$ *m/z* 400.1760 $(M+H)^+$, found: 400.1761.

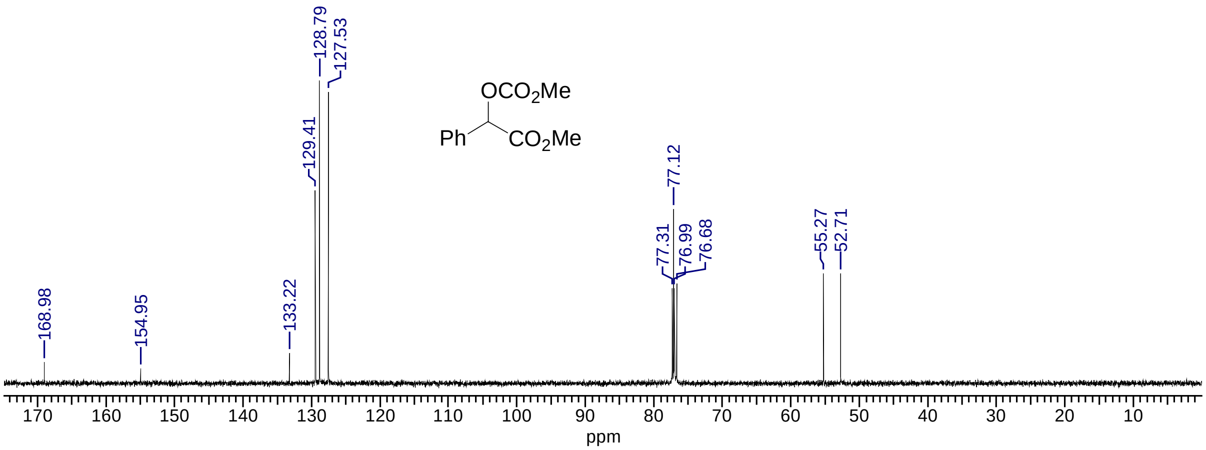




*Preparation of Carbonate **16***

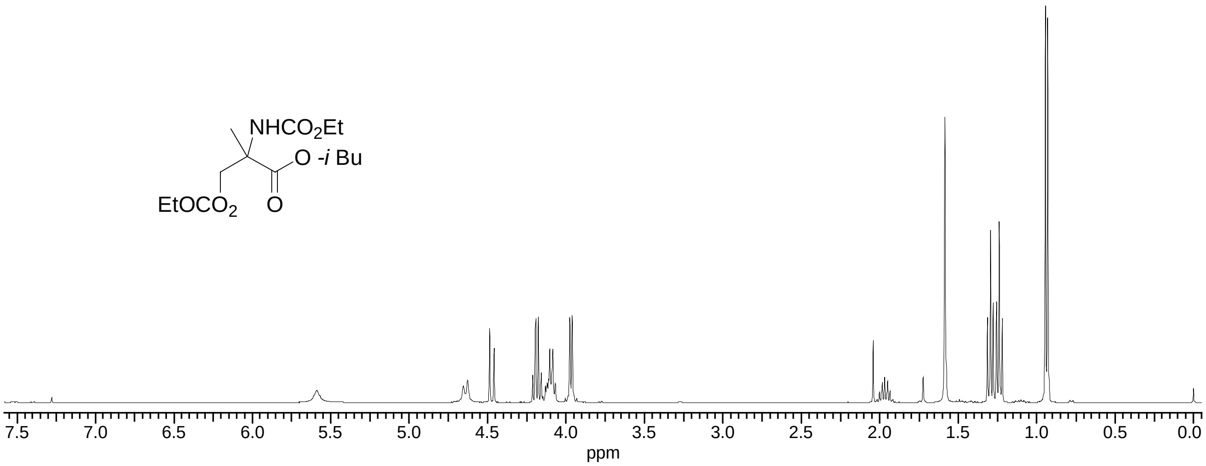
A mixture of 0.5g of methyl mandelate, 3.7 mg of DMAP, 0.46mL of triethylamine and 10mL of pyridine was treated with 1.16 g (6.02 mmol) of $BtOCO_2Me$. After 20 min TLC (1:1 EtOAc/Hex) indicated the reaction was complete. EtOAc and water were added to the solution. The organic and aqueous layer was separated and the aqueous was extracted with EtOAc. The organic layers were combined and washed with 10% HCl to remove pyridine followed by water. The solution was concentrated and product was isolated from the crude mixture by chromatography to afford 470 mg (70% yield) of the carbonate **16**. MS Calc for $C_{12}H_{14}O_5$ *m/z* 239.0920 $(M+H)^+$, found 239.0920.

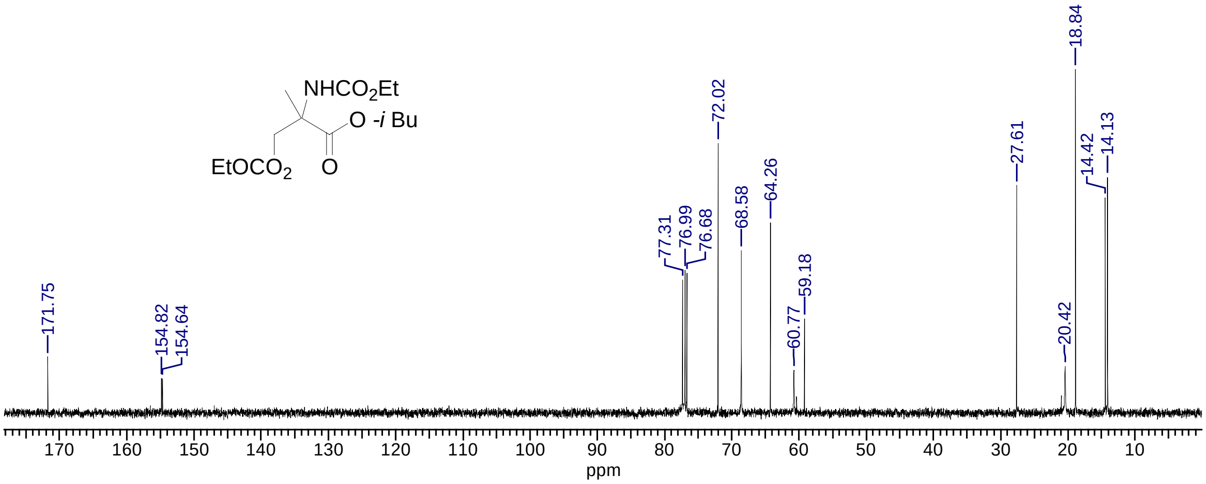




Preparation of Carbonate ***17.***

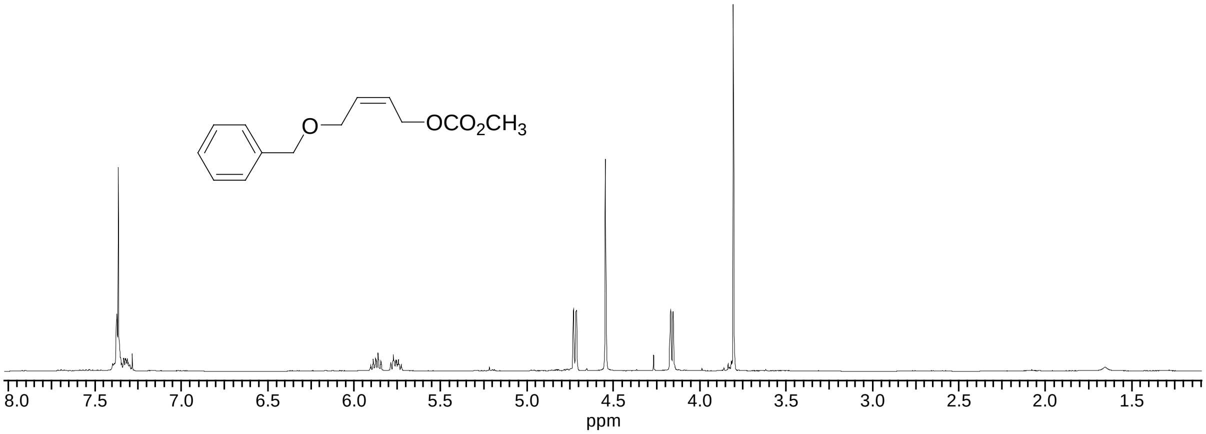
A solution of 1.0 g (6.2 mmol) of the amino alcohol was dissolved in 15 mL of pyr and 1.15 mL of TEA. The solution was treated with 3.11 g (15.02 mmol) of $BtOCO_2Et$ and 7.5 mg of DMAP. The mixture was stirred at rt until TLC (70/30 EtOAc/Hex ninhydrin stain) indicated the reaction to be complete. Isolation with EtOAc after H_2O addition afforded the crude material which was purified by chromatography with EtOAc/Hex to afford 1.4 g (71% yield) of **17.** MS Calc for $C_{14}H_{25}NO_7$ *m/z* 320.1709 $(M+H)^+$, found: 320.1703

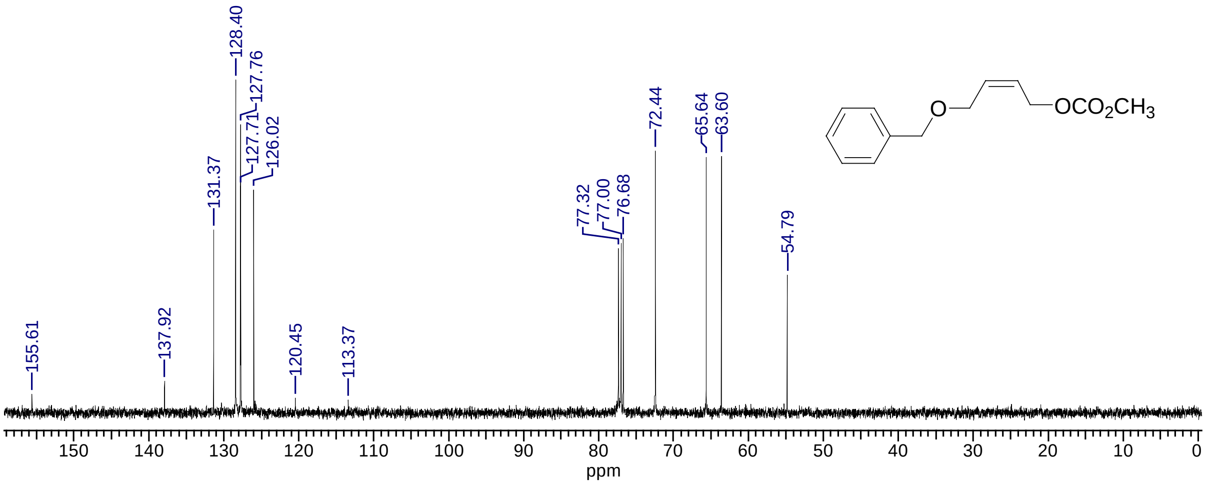




*Preparation of carbonate **18**.*

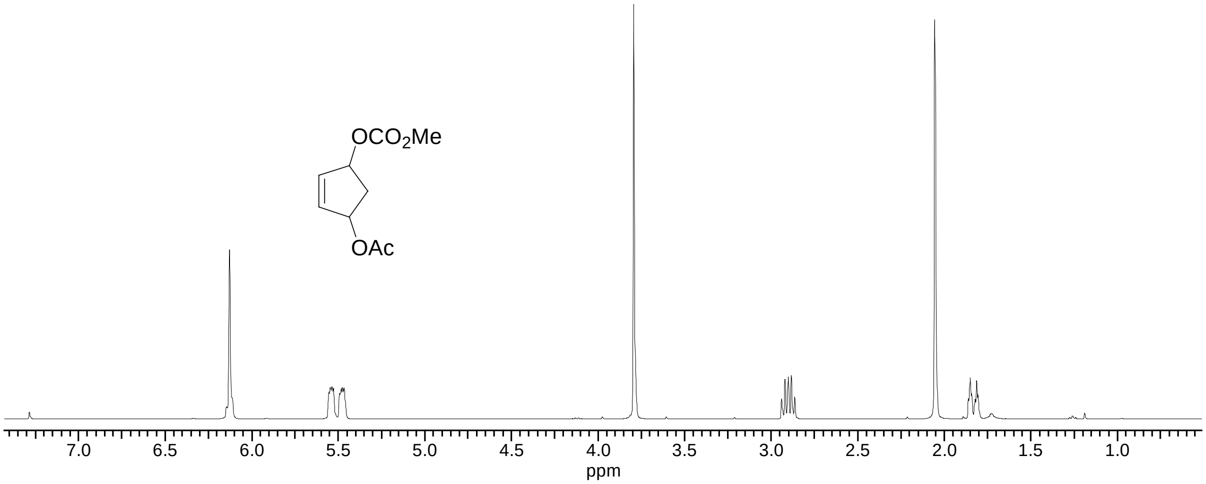
A solution of 0.5g of the alcohol, 4.7mg of DMAP, 0.59mL of triethylamine, and 10mL of DMF was treated with 1.48g of the $BtOCO_2Me$. The reaction went to completion in 20 minutes. EtOAc and water were added to the mixture. The organic and aqueous layer was separated and the aqueous was extracted with EtOAc. The organic layer was washed with 10% HCl and water. The solution was concentrated and the product was isolated by chromatography to afford 0.65 g (98% yield) of the carbonate **18**. MS Calcd for $C_{13}H_{16}O_4$ *m/z* 237.1127 $(M+H)^+$, found: 237.1133.

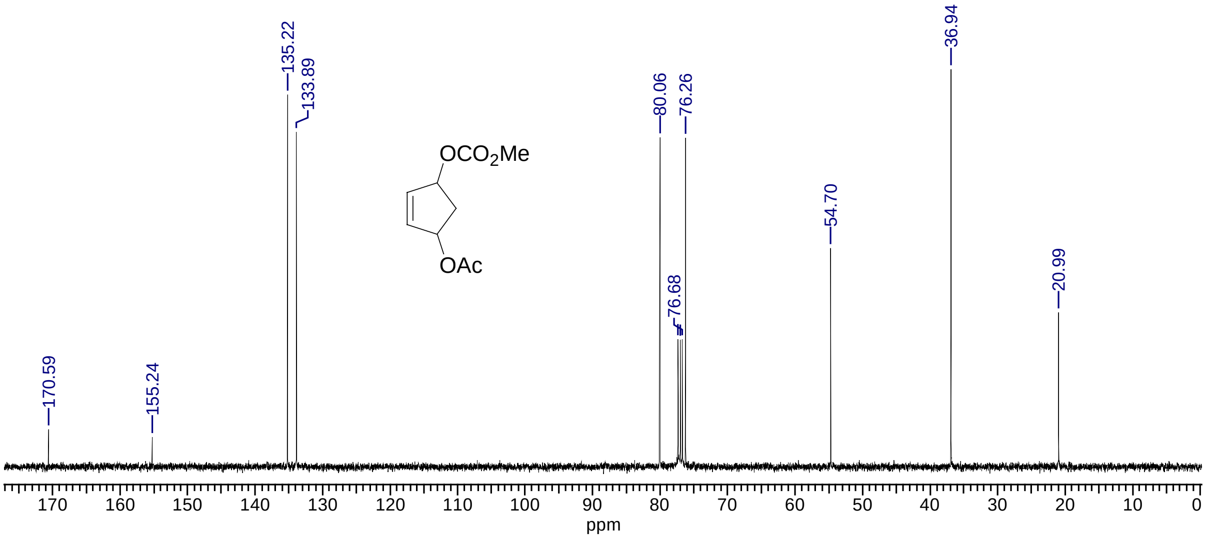




Preparation of carbonate ***19b***

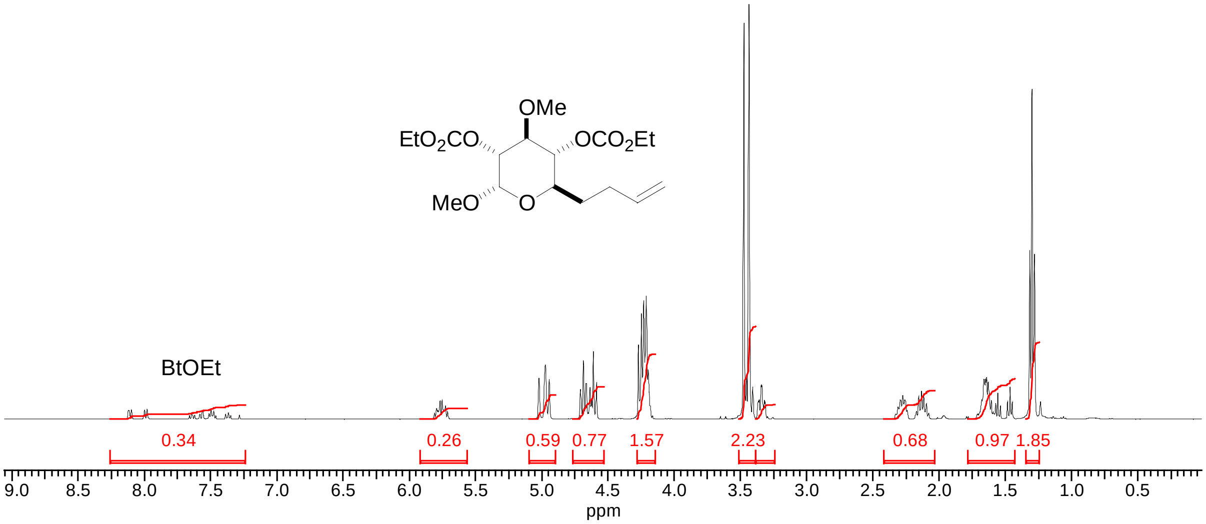
A solution of 2.0 g (14.1 mmol) of the acetate **19a** in 20 mL of pyridine and 5 mL of TEA was treated with 100 mg of DMAP and 5.45 g (28.0 mmol) of $BtOCO_2Me$ was stirred at 25 C. When TLC shows the reaction to be complete, the product was isolated with EtOAc after H_2O addition to give 2.8 g (99% yield) of the carbonate **19b.**

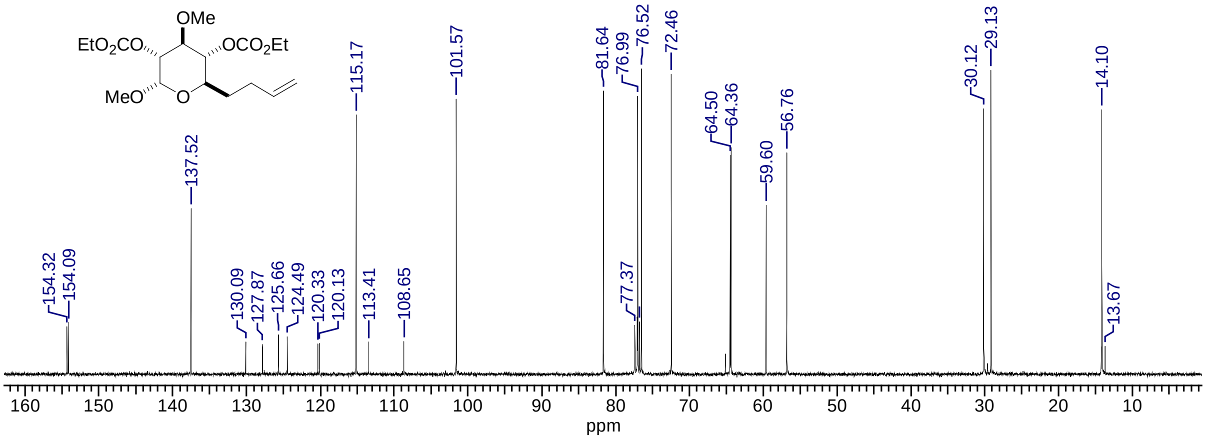




*Preparation of carbonate **20***

To a round bottom flask .5g of the diol, 2.6mg of DMAP, .33mL of triethylamine and 10mL of pyridine was added. 1.78g (4 equivalents) of EtO_2COBt was added to the reaction mixture. When TLC indicated complete reaction EtOAc and water were added to the mixture. The product was extracted with EtOAc and the solution washed with 10% HCl to remove pyridine, followed by a water wash. The solution was concentrated and product was isolated from the crude mixture by chromatography. The BtOEt by-product could not be separated to give a clean sample of the dicarbonate **20**. MS calc for: $C_{17}H_{28}O_9$ *m/z* 377.1811 $(M+H)^+$, found: 377.1797





Preparation of Cinnamyl carbonate ***22***

Cinnamyl alcohol (1.5 g, 11.2 mmol) was dissolved in 20 mL of pyridine and 5 mL of TEA. The temperature was adjusted to 25 C using the Multimax. The $BtOCO_2Me$ (3.3 g, 17.0 mmol) was then added. The multimax shows a temperature rise followed by a slow decay curve. After about 15 min. the reaction was complete. This was confirmed by TLC (at 1 h). Water was added to the mixture and the product isolated with MTBE. Pyridine was removed by a 10% HCl wash followed by a water wash. The organic was dried over $MgSO_4$ and concentrated. Vacuum drying affords 1.95 g (98.5% yield) of the carbonate **22**.