Supplementary Material (ESI) for Chemical Communications

Supplementary Information for

Reactivity of 2-acylaminoacrylates with ketene diethyl acetal; [2+2] cycloadditions vs. tandem condensations

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General Procedures. Melting points are uncorrected. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Kieselgel 60 (230–400 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, concentrated under reduced pressure using a rotary evaporator. NMR spectra were recorded at 300 MHz (^1H) and at 75 MHz (^{13}C) and signals are reported in ppm downfield from TMS. Microanalyses were carried out on a CE Instruments EA-1110 analyser and were in good agreement with the calculated values.

1-Benzamido-2,2-diethoxycyclobutane-1-carboxylic acid methyl ester (6). 2-Benzamidoacrylate **3** (307 mg, 1.5 mmol) was dissolved in ^{t}BuOH (17 mL) under an inert atmosphere and ketene diethyl acetal **5** (0.4 mL, 3 mmol) was added. The mixture was warmed at 83 °C and then another solution of ketene diethyl acetal **5** (1.6 mL, 12 mmol) in ^{t}BuOH (6 mL) was added by a syringe pump (20 min). After 48 h stirring at this temperature, the solvent was evaporated and the crude was purified by silica gel column chromatography, eluting with hexane/EtOAc (7:3), to yield 246 mg (51%) of **6**

as a yellow solid (mp = 64-66 ºC). ^{1}H NMR ($CDCl_3$): δ 1.06 (t, 3H, J = 6.0 Hz), 1.24 (t, 3H, J = 6.0 Hz), 1.70-1.77 (m, 1H), 2.18-2.24 (m, 2H), 2.77-2.84 (m, 1H), 3.45 (q, 2H, J = 6.0 Hz), 3.56 (q, 2H, J = 6.0 Hz), 3.70 (s, 3H), 7.34-7.44 (m, 4H), 7.70-7.74 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.0, 15.1, 24.7, 28.3, 52.4, 57.8, 58.4, 66.9, 101.6, 127.0, 128.5, 131.6, 133.6, 165.9, 169.9. Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.46. Found: C, 63.45; H, 7.19; N, 4.42.

1-Acetamido-2,2-diethoxycyclobutane-1-carboxylic acid methyl ester (7). 2-Acetamidoacrylate **4** (1.43 g, 10 mmol) was dissolved in ^{t}BuOH (50 mL) under an inert atmosphere and ketene diethyl acetal **5** (2.6 mL, 20 mmol) was added. The mixture was warmed at 83 °C and then another solution of ketene diethyl acetal **5** (10.4 mL, 80 mmol) in ^{t}BuOH (30 mL) was added by a syringe pump (90 min). After 48 h stirring at this temperature, the solvent was evaporated and the crude was purified by silica gel column chromatography, eluting with hexane/EtOAc (3:7), to yield 1.66 g (64%) of **7** as a white solid (mp = 58-60 ºC). ^{1}H NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 6.0 Hz), 1.28 (t, 3H, J = 6.0 Hz), 1.64-1.74 (m, 1H), 2.02 (s, 3H), 2.23 ('t', 2H, J = 9.0 Hz), 2.74-2.83 (m, 1H), 3.46 (q, 2H, J = 6.0 Hz), 3.58 (q, 2H, J = 6.0 Hz), 3.76 (s, 3H), 6.73 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 15.0, 15.1, 22.9, 24.7, 28.3, 52.4, 57.7, 58.3, 66.8, 101.4, 169.1, 170.1. Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.46; H, 8.07; N, 5.53.

1-Acetamido-2,2,4,4-tetraethoxycyclohexane-1-carboxylic acid methyl ester (10). First method (from **4**): 2,6-di-*tert*-butyl-4-bromophenol (2.28 g, 8 mmol) was dissolved in CH_2Cl_2 (10 mL) under an inert atmosphere and $AlMe_3$ (2 mL, 2M solution in hexane) was slowly added. The solution was stirred for 1 h, then 2-acetamidoacrylate **4** (286 mg,

2 mmol) and ketene diethyl acetal **5** (1.32 mL, 10 mmol) were added and the reaction was stirred for 1 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue that was purified by silica gel column chromatography, eluting with hexane/EtOAc (4:6), to yield 603 mg (80%) of **10** as a colourless oil.

Second method (from **7**): 2,6-di-*tert*-butyl-4-bromophenol (570 mg, 2 mmol) was dissolved in CH_2Cl_2 (10 mL) under an inert atmosphere and $AlMe_3$ (0.5 mL, 2M solution in hexane) was slowly added. The solution was stirred for 1 h, then compound **7** (130 mg, 0.5 mmol) and ketene diethyl acetal **5** (0.33 mL, 2.5 mmol) were added and the reaction was stirred for 10 min. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue that was purified by silica gel column chromatography, eluting with hexane/EtOAc (4:6), to yield 115 mg (61%) of **10** as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.06-1.15 (m, 12H), 1.44-1.52 (m, 1H), 1.72 (d, 1H, J = 15.0 Hz), 1.91-2.00 (m, 4H), 2.23 (d, 1H, J = 15.0 Hz), 2.32-2.36 (m, 2H), 3.34-3.58 (m, 7H), 3.66-3.75 (m, 4H), 6.26 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.6, 15.1, 15.3, 15.4, 23.7, 25.6, 27.4, 38.7, 52.0, 55.0, 55.1, 56.9, 57.7, 65.6, 99.3, 101.3, 170.2, 171.5. Anal. Calcd. for $C_{18}H_{33}NO_7$: C, 57.58; H, 8.86; N, 3.73. Found: C, 57.69; H, 8.78; N, 3.70.

***N*-(1-Hydroxymethyl-2-oxocyclobutyl)acetamide (11)**. To a solution of $LiBH_4$ (1.93 mL, 2M solution in THF) in dry Et_2O (35 mL), a solution of **7** (500 mg, 1.93 mmol) in dry Et_2O (15 mL) was added under an inert atmosphere, at 0 ºC. The reaction was warmed up to rt and stirred at this temperature for 7 h. The reaction was filtered and washed with Et_2O and EtOH. The organic solution was evaporated, disssolved in

$CHCl_3/^iPrOH$ (4:1) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue, which was purified by silica gel column chromatography, eluting with hexane/EtOAc (2:8). This compound was dissolved in THF (40 mL) and 1N HCl (10 mL) was added. The mixture was stirred for 5 h at rt and the solvent evaporated. The crude was purified by silica gel column chromatography, eluting with MeOH/EtOAc (1:9) to give 182 mg (60% yield for two steps) of **11** as a white solid (mp = 110-112 ºC). ^{1}H NMR (CD_3OD): δ 1.86 (s, 3H), 2.08 (td, 1H, J = 6.0 Hz, J = 12.0 Hz), 2.27-2.36 (m, 1H), 2.66-2.78 (m, 1H), 2.87-2.97 (m, 1H), 3.53 (d, 1H, J = 9.0 Hz), 3.64 (d, 1H, J = 9.0 Hz). ^{13}C NMR (CD_3OD): δ 21.8, 22.8, 42.1, 63.5, 77.5, 173.0, 209.9. Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.39; H, 7.17; N, 8.83.

***N*-[1-(*tert*-Butyldiphenylsilanyloxymethyl)-*t*-2-hydroxycyclobutyl]-*r*-acetamide (12)**. Alcohol **11** (306 mg, 1.95 mmol) was dissolved in DMF (25 mL). Then, imidazole (397 mg, 5.85 mmol) and TBDPSCl (1.47 mL, 6.06 mmol) were added and the mixture was stirred at rt for 20 h. Subsequently, the reaction was evaporated to low pressure and an aqueous solution of 5% $NaHCO_3$ and EtOAc (15 mL) were added. The organic layer was separated and the aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1). This residue, corresponding to the protected ketone (520 mg, 1.32 mmol), was dissolved in THF (20 mL) and the resulting solution was added to a suspension of $NaBH_4$ (55 mg, 1.45 mmol) at 0 °C in EtOH (30 mL). The suspension was stirred at rt for 3 h and HCl 2N (2 mL) was added dropwise. The mixture was diluted with $CHCl_3/^iPrOH$ (4:1) (40 mL) and washed with brine (30 mL). The organic layer was dried, filtered and evaporated. The crude was

purified by silica gel column chromatography, eluting with hexane/EtOAc (4:6) to give 399 mg of the pure alcohol **12** (52%) as a white solid (mp = 117-119 ºC). ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H), 1.43-1.48 (m, 1H), 1.73-1.86 (m, 4H), 2.08-2.23 (m, 2H), 3.96-4.04 (m, 2H), 4.27 (t, 1H, J = 9.0 Hz), 5.89 (br s, 1H), 7.36-7.43 (m, 6H), 7.60-7.65 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 19.4, 21.2, 23.2, 24.2, 26.7, 26.9, 29.7, 62.6, 63.1, 71.8, 127.7, 127.8, 129.7, 129.8, 133.3, 133.5, 135.5, 135.5, 170.2. Anal. Calcd. for $C_{23}H_{31}NO_3Si$: C, 69.48; H, 7.86; N, 3.52. Found: C, 69.61; H, 7.72; N, 3.47.

***N*-[*t*-2-Benzyloxy-1-(*tert*-butyldiphenylsilanyloxymethyl)cyclobutyl]-*r*-acetamide (13)**. To a stirred solution of alcohol **12** (120 mg, 0.30 mmol) in dry Et_2O under an inert atmosphere, benzyl-2,2,2-trichloroacetimidate (67 μL, 0.36 mmol) was added. The solution was cooled to 0 °C and triflic acid (5 μL, 0.06 mmol) was added dropwise, whereupon a white solid precipitated, which redissolved on warming to rt over 5 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL), extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (7:3) to give 59 mg (40% yield) of **13** as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.52-1.65 (m, 1H), 1.77-1.86 (m, 4H), 2.10-2.29 (m, 2H), 3.90-3.98 (m, 2H), 4.46, (s, 2H), 4.83 (t, 1H, J = 9.0 Hz), 5.73 (br s, 1H), 7.21-7.24 (m, 5H), 7.36-7.45 (m, 6H), 7.63-7.67 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 19.3, 20.8, 23.4, 24.3, 26.9, 63.1, 64.2, 71.9, 76.7, 127.5, 127.8, 127.8, 128.2, 129.8, 129.9, 133.0, 133.2, 135.6, 135.6, 138.5, 170.1. Anal. Calcd. for $C_{30}H_{37}NO_3Si$: C, 73.88; H, 7.65; N, 2.87. Found: C, 73.72; H, 7.61; N, 2.92.

***N*-[*t*-2-Acetoxy-1-(*tert*-butyldiphenylsilanyloxymethyl)cyclobutyl]-*r*-acetamide (14)**. To a stirred solution of alcohol **12** (173 mg, 0.44 mmol) in pyridine (4 mL) under an inert atmosphere, Ac_2O (1.25 mL, 13 mmol) and DMAP (53 mg, 0.44 mmol) were

added. After stirring for 5 h at rt, Et_2O (15 mL) was added and the organic layer was washed with aqueous 0.5% HCl, aqueous saturated $NaHCO_3$ and brine, dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/EtOAc (3:7) to give 166 mg (87%) of **14** as a white solid (mp = 108-110 ºC). ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H), 1.90, (s, 3H), 1.91, (s, 3H), 1.97-2.10, (m, 3H), 2.20-2.26 (m, 1H), 3.86 (d, 1H, J = 12.0 Hz), 3.98 (d, 1H, J = 12.0 Hz), 4.98-5.10 (m, 1H), 6.49 (br s, 1H), 7.37-7.44 (m, 6H), 7.62-7.67 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 19.1, 20.6, 22.7, 23.0, 23.4, 26.6, 61.9, 62.8, 72.6, 127.5, 127.6, 129.5, 129.6, 132.6, 133.3, 135.3, 135.4, 168.9, 171.5. Anal. Calcd. for $C_{25}H_{33}NO_4Si$: C, 68.30; H, 7.57; N, 3.19. Found: C, 68.42; H, 7.68; N, 3.07.

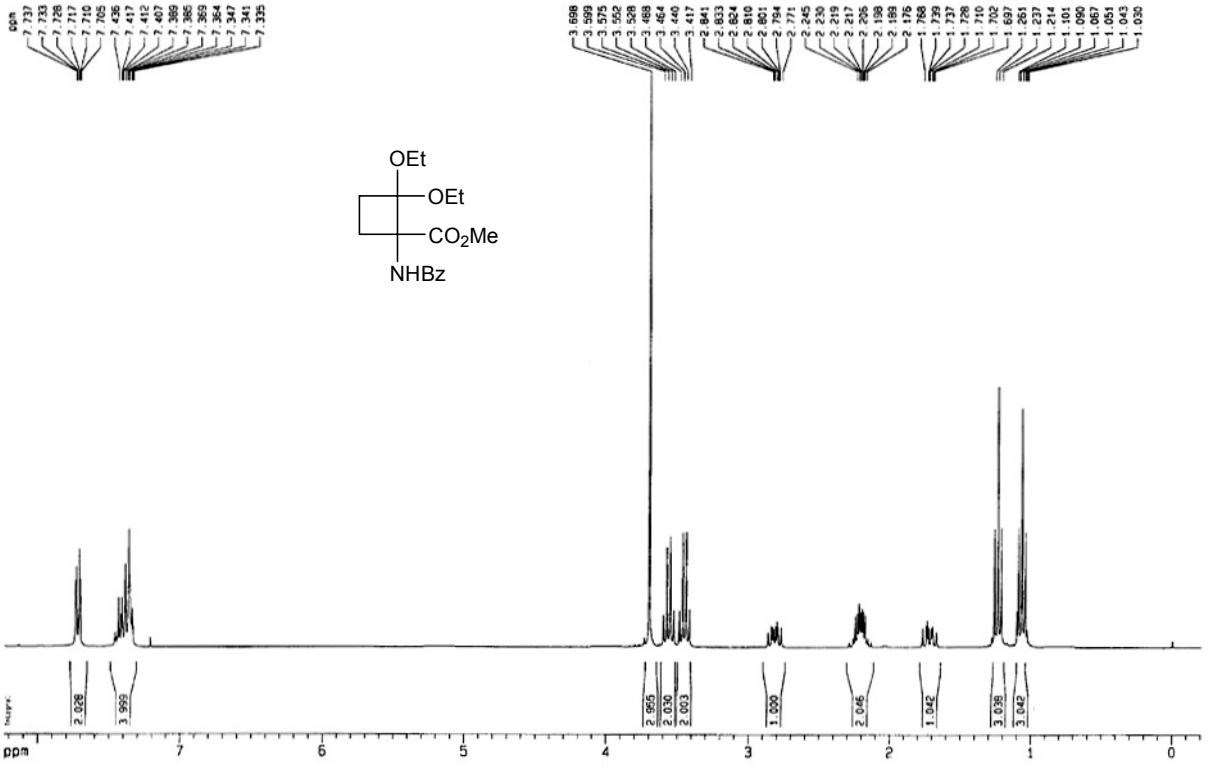
1-Acetamido-*c*-2-benzyloxycyclobutane-*r*-1-carboxylic acid methyl ester (15). To a solution of compound **13** (58 mg, 0.12 mmol) in dry THF (5 mL), tetrabutylammonium fluoride (147 μL, 1M solution in THF) was added. The mixture was stirred for 4 h at rt, quenched by addition of aqueous saturated NH_4Cl and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1) to give the corresponding alcohol. A 1.5-fold excess of Jones reagent was dropwise added to a solution of this alcohol in acetone (5 mL) at 0 ºC over 5 min. The mixture was stirred at 0 ºC for 2 h. The excess of Jones reagent was destroyed with 2-propanol. The mixture was then diluted with water (10 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were dried and concentrated. In order to purified it, we transformed the carboxylic acid in its methyl ester by addition of diazomethane to a solution of the carboxylic acid in Et_2O. The mixture was stirred for 10 min, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1) to give 17 mg

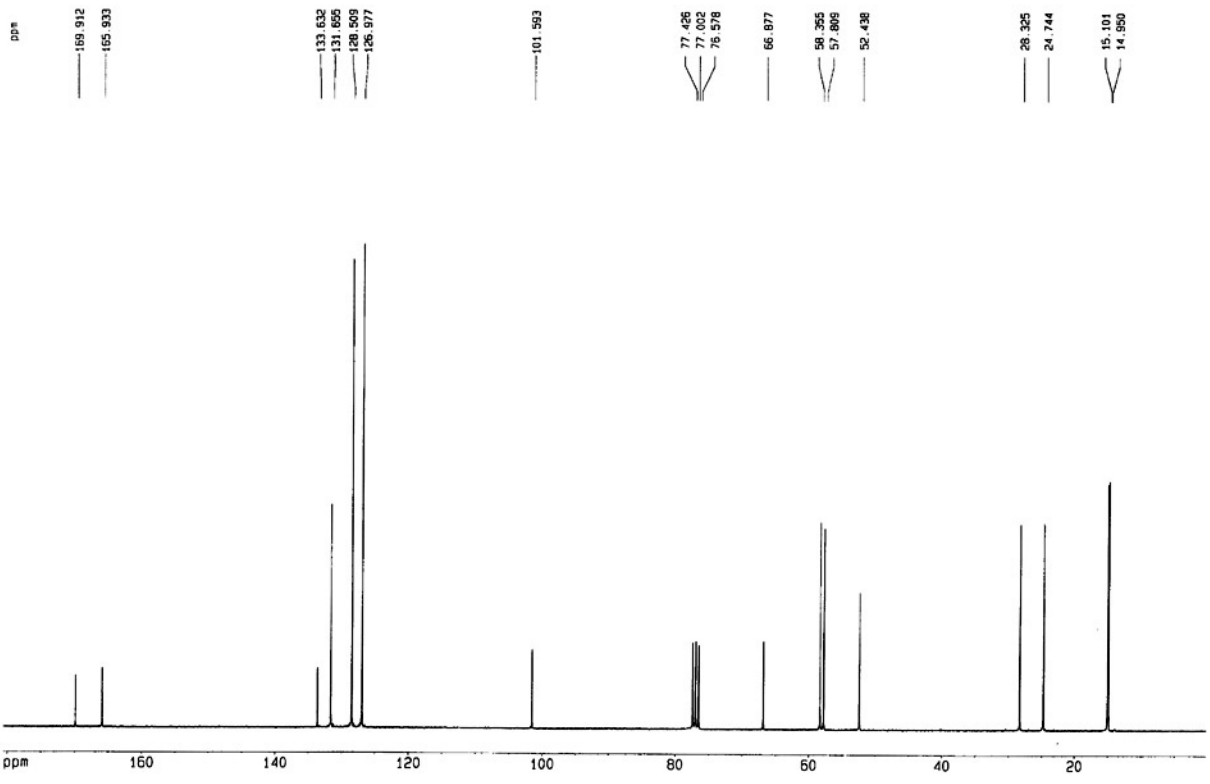
(50%) of **15** as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.92 (s, 3H), 2.18-2.31 (m, 3H), 2.44-2.52 (m, 1H), 3.82 (s, 3H), 4.46-4.49 (m, 2H), 4.52-4.62 (m, 1H), 6.14 (br s, 1H), 7.24-7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 22.7, 23.6, 24.4, 52.7, 66.4, 71.6, 76.9, 127.9, 127.9, 128.4, 137.6, 169.8, 171.6. Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.83; H, 7.02; N, 5.12.

1-Acetamido-*c*-2-acetoxycyclobutane-*r*-1-carboxylic acid methyl ester (16). To a solution of compound **14** (166 mg, 0.37 mmol) in dry THF (15 mL), tetrabutylammonium fluoride (370 μL, 1M solution in THF) was added. The mixture was stirred for 30 min at rt, quenched by addition of aqueous saturated NH_4Cl and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with a gradient of MeOH/EtOAc (0:10→1:9) to give the corresponding alcohol. A 1.5-fold excess of Jones reagent was dropwise added to a solution of this alcohol in acetone (10 mL) at 0 ºC over 5 min. The mixture was stirred at 0 ºC for 1 h. The excess of Jones reagent was destroyed with 2-propanol. The mixture was then diluted with water (10 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were dried and concentrated. In order to purified it, we transformed the carboxylic acid in its methyl ester by addition of diazomethane to a solution of the carboxylic acid in Et_2O. The mixture was stirred for 10 min, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (3:7) to give 33 mg (38%) of **16** as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.82-1.92 (m, 1H), 1.99 (s, 3H), 2.04 (s, 3H), 2.27-2.40 (m, 2H), 2.86-2.94 (m, 1H), 3.76 (s, 3H), 5.05 (t, 1H, J = 9.0 Hz), 6.82 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.4, 22.9, 23.3, 24.8, 52.6, 65.2, 71.4, 170.1, 170.2, 171.7. Anal. Calcd. for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.28; H, 6.73; N, 6.13.

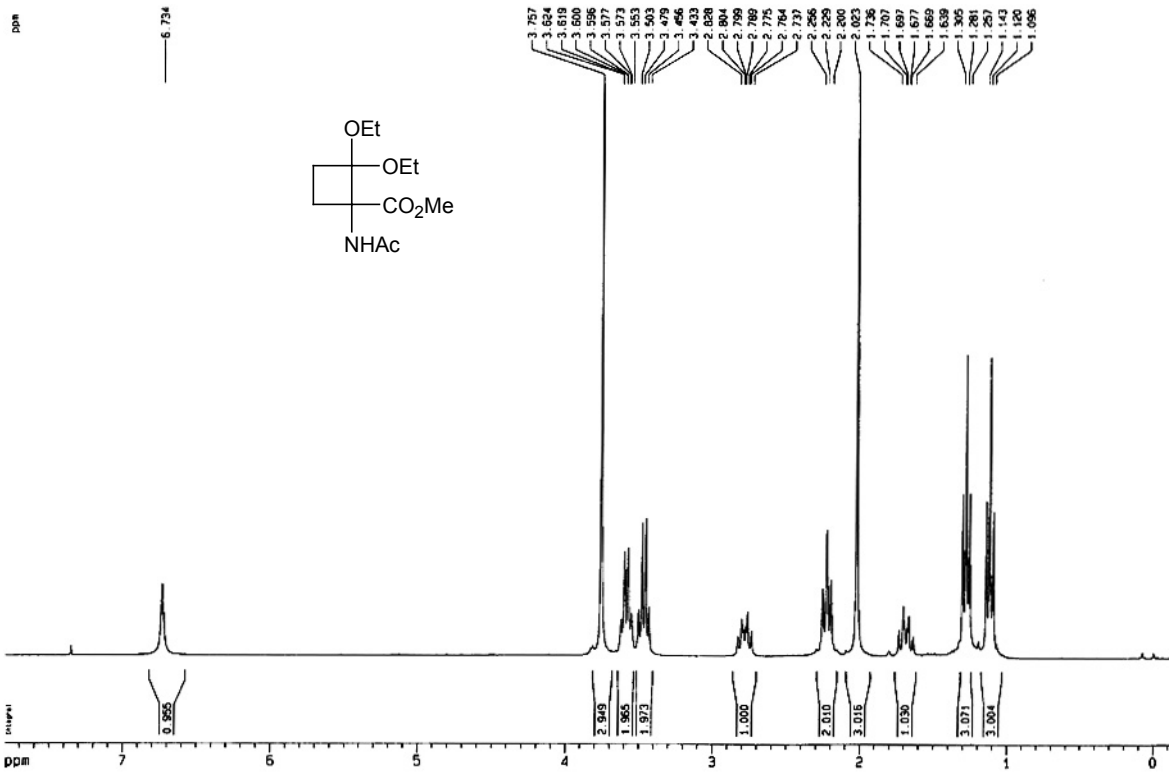
1-Acetamido-2-ethoxy-4-oxocyclohex-2-ene-1-carboxylic acid ethyl ester (17). To a solution of compound **10** (603 mg, 1.61 mmol) in THF (40 mL), an aqueous 1 N HCl solution (10 mL) was added. The solution was stirred at rt for 12 h and then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried, filtered and concentrated. The crude was dissolved in EtOH (50 mL) and DBU (2.0 mL, 13 mmol) was added. The reaction was stirred for 1 h and 1 N HCl (4 mL) was added and the excess of solvent was removed. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with MeOH/EtOAc (5:95) to give 336 mg (78%) of compound **17** as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.22-1.30 (m, 6H), 2.00 (s, 3H), 2.21-2.27 (m, 1H), 2.41-2.50 (m, 1H), 2.54-2.64 (m, 1H), 2.82-2.90 (m, 1H), 3.84-3.92 (m, 2H), 4.22-4.29 (m, 2H), 5.50 (s, 1H), 6.66 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 23.5, 29.9, 33.6, 61.1, 63.0, 65.1, 105.5, 169.1, 169.9, 170.5, 197.7. Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.10; H, 7.01; N, 5.12.

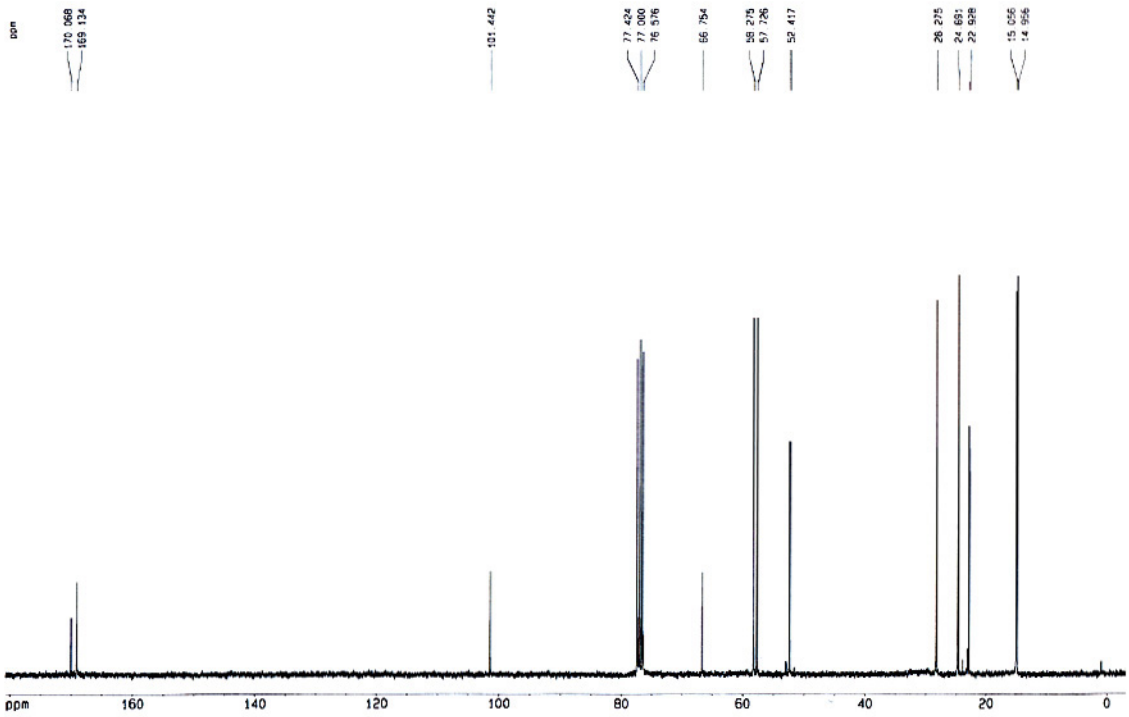
1-Benzamido-2,2-diethoxycyclobutane-1-carboxylic acid methyl ester (6).

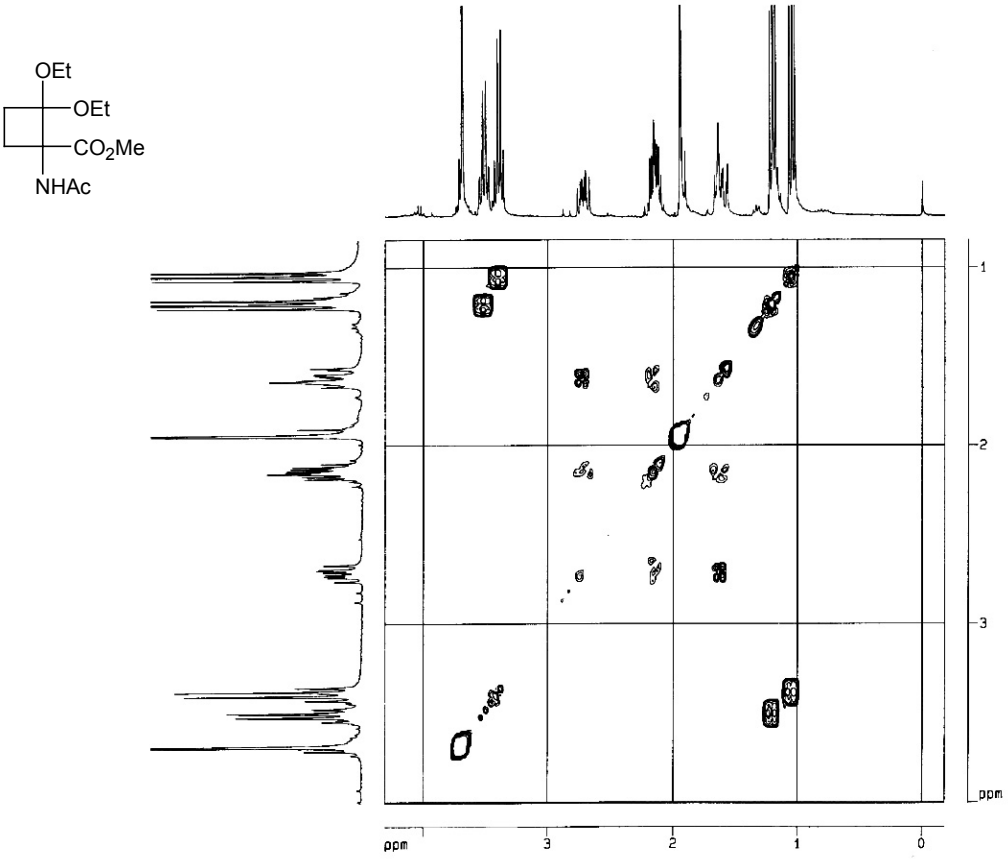


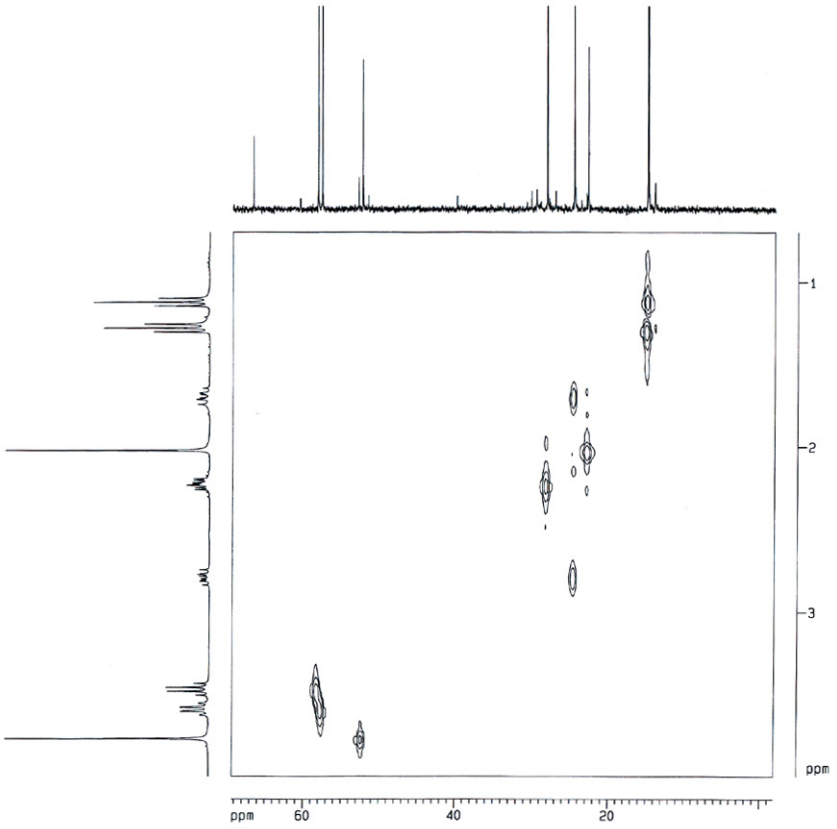


1-Acetamido-2,2-diethoxycyclobutane-1-carboxylic acid methyl ester (7).

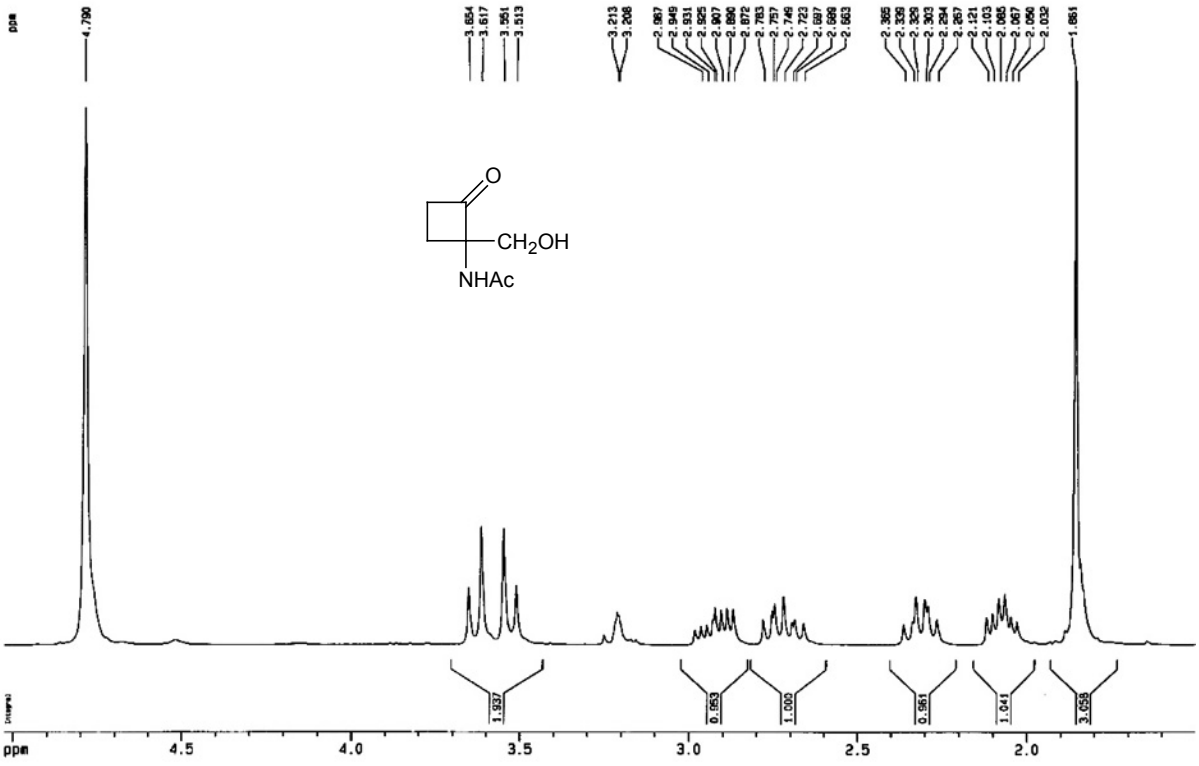


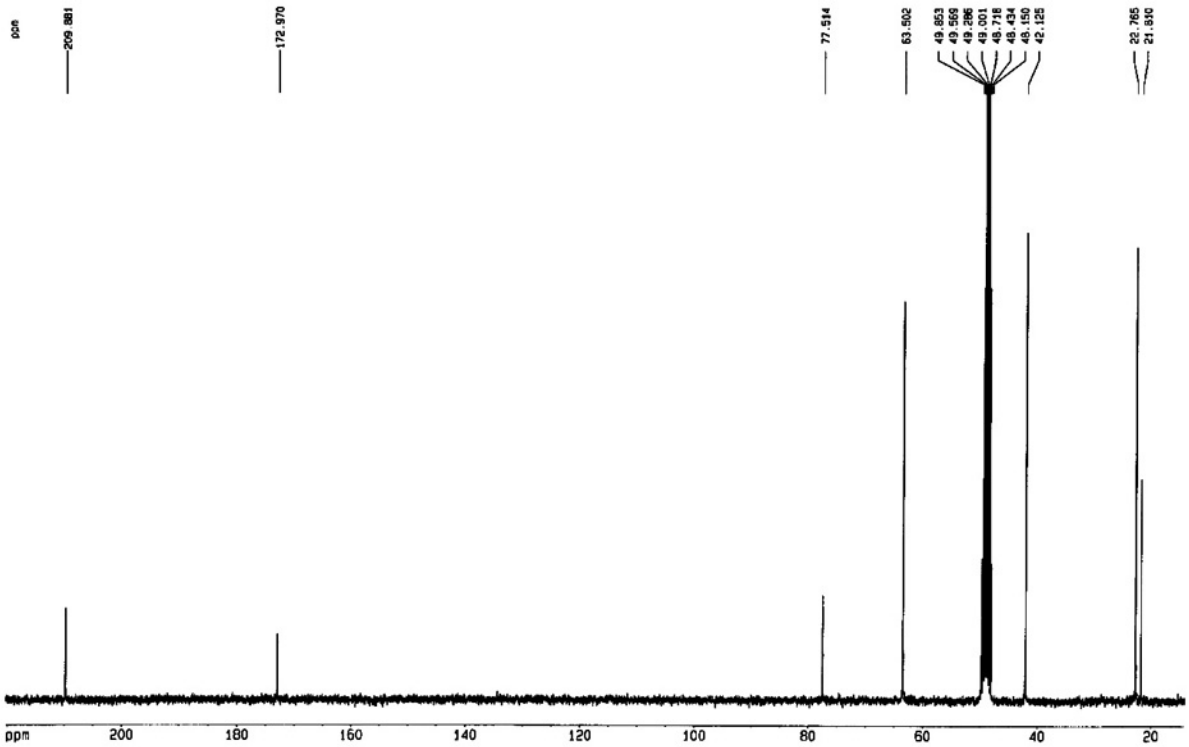


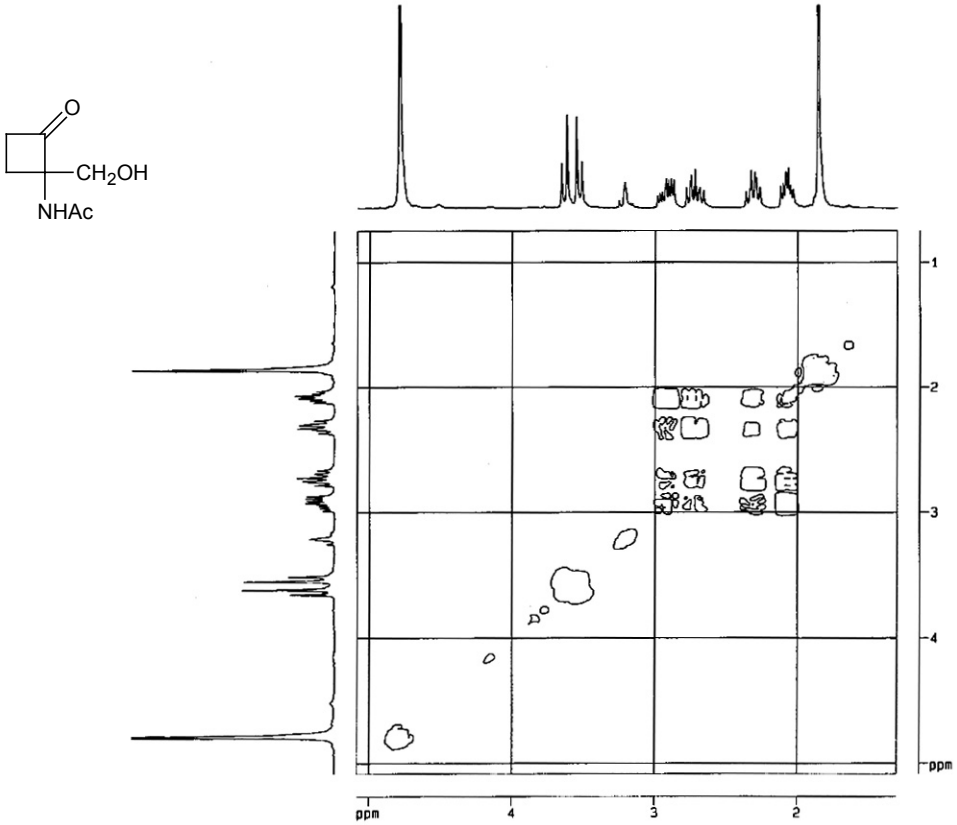


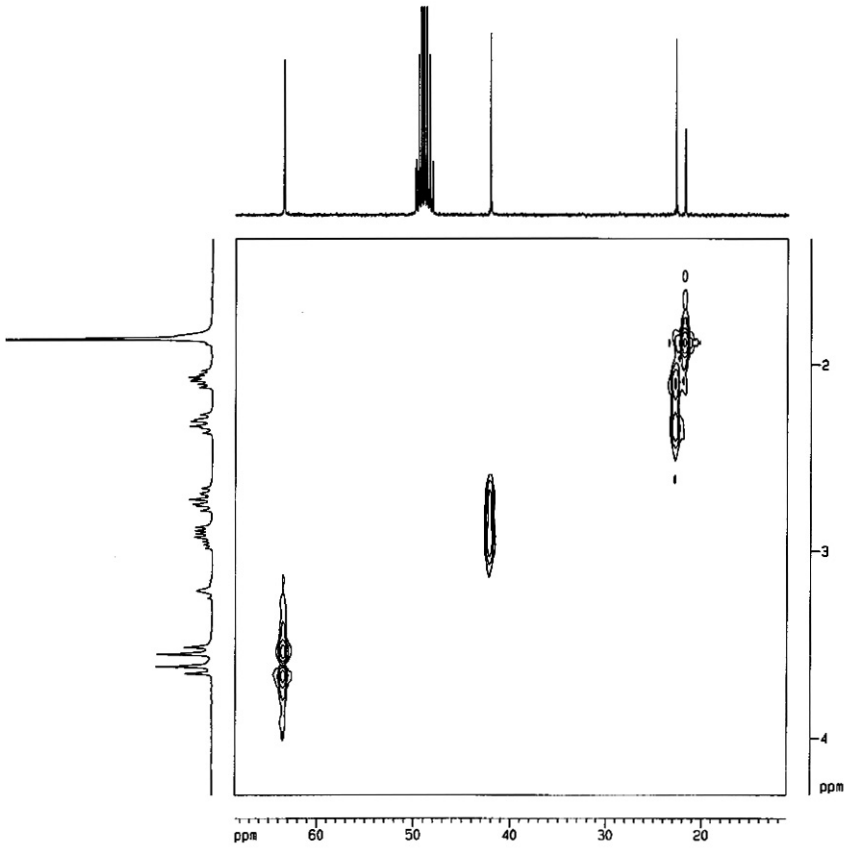


***N*-(1-Hydroxymethyl-2-oxocyclobutyl)acetamide (11)**

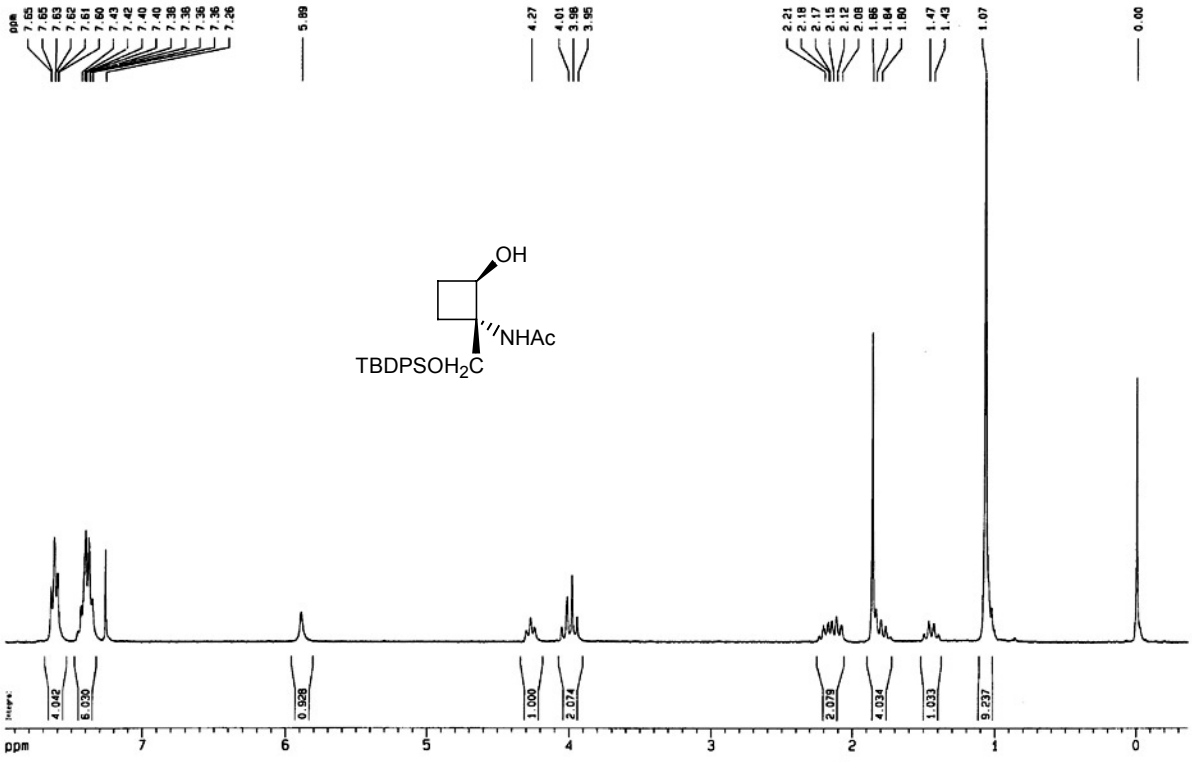


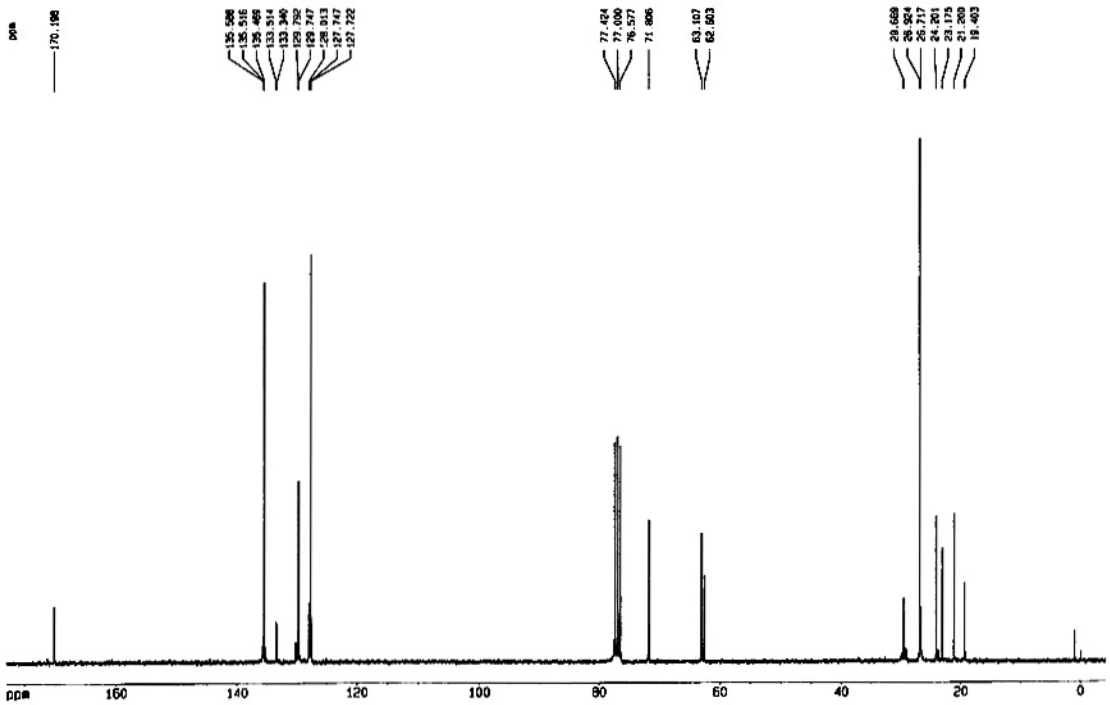


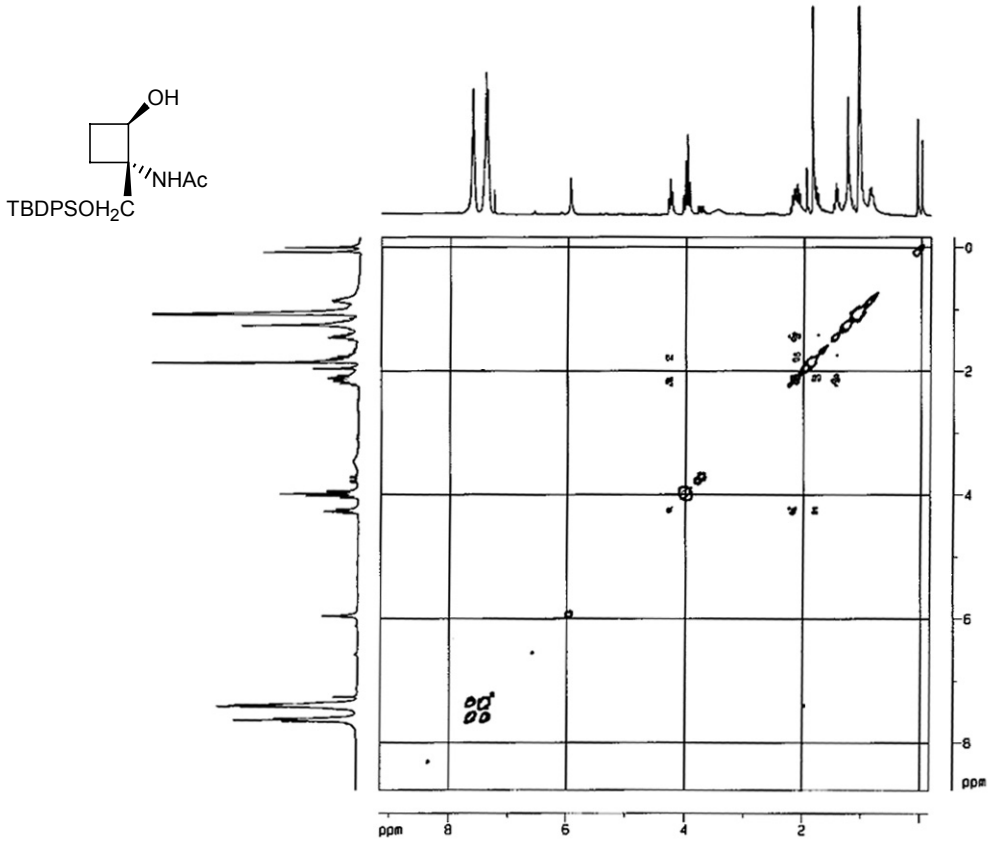


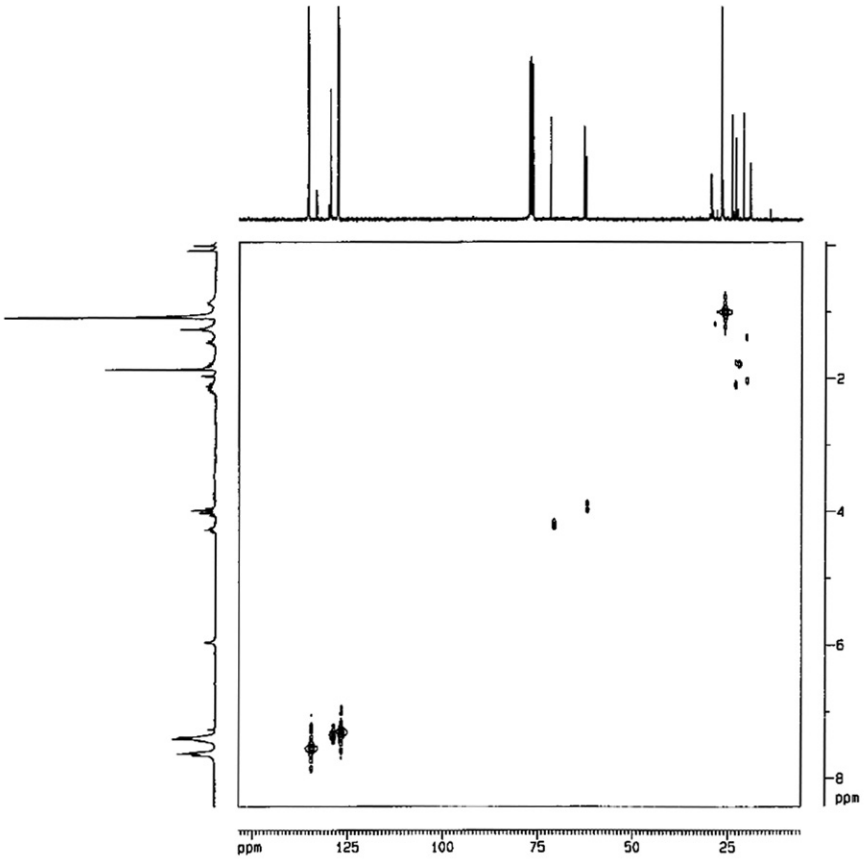


***N*-[1-(*tert*-Butyldiphenylsilanyloxymethyl)-*t*-2-hydroxycyclobutyl]-*r*-acetamide (12)**

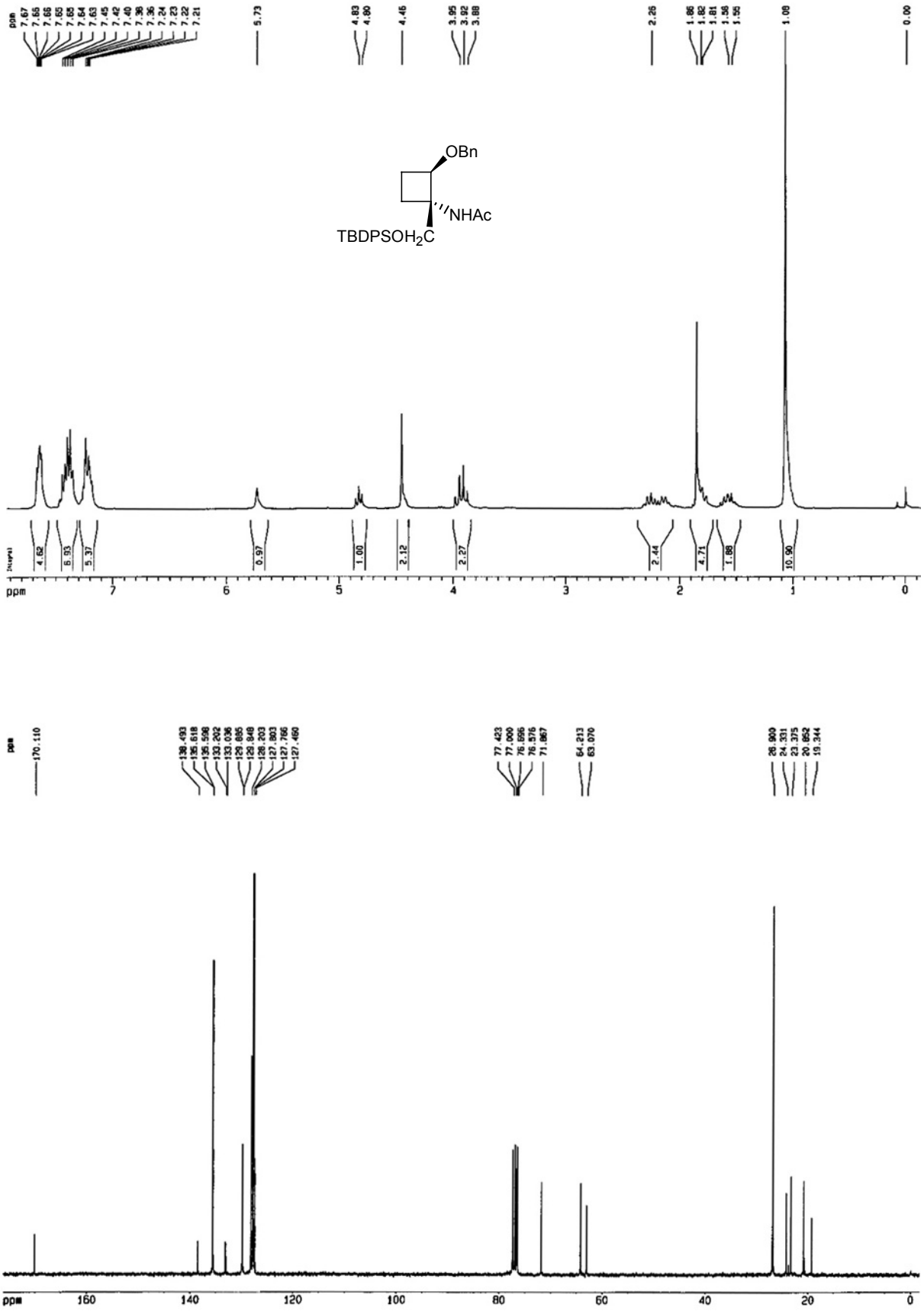


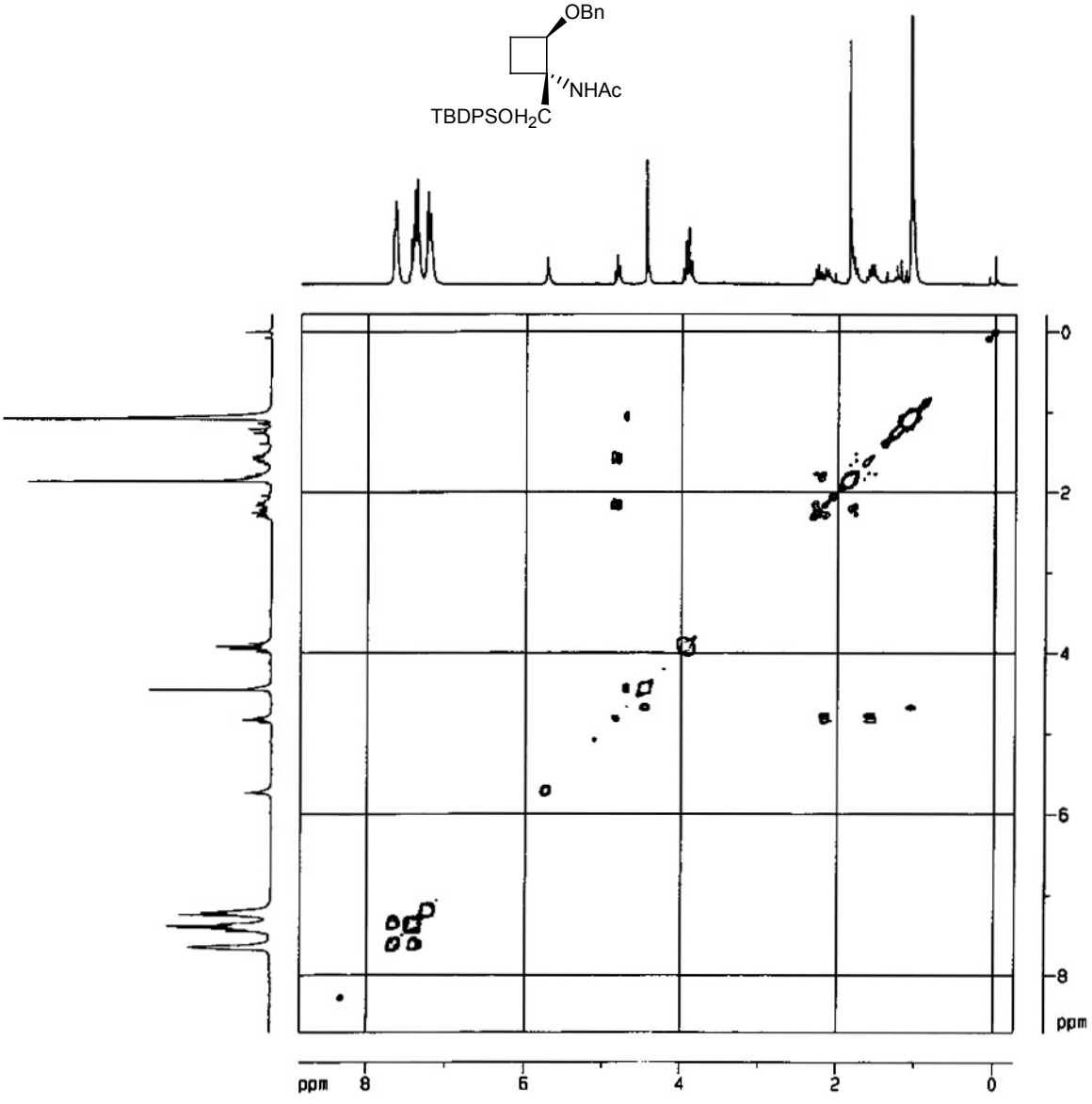




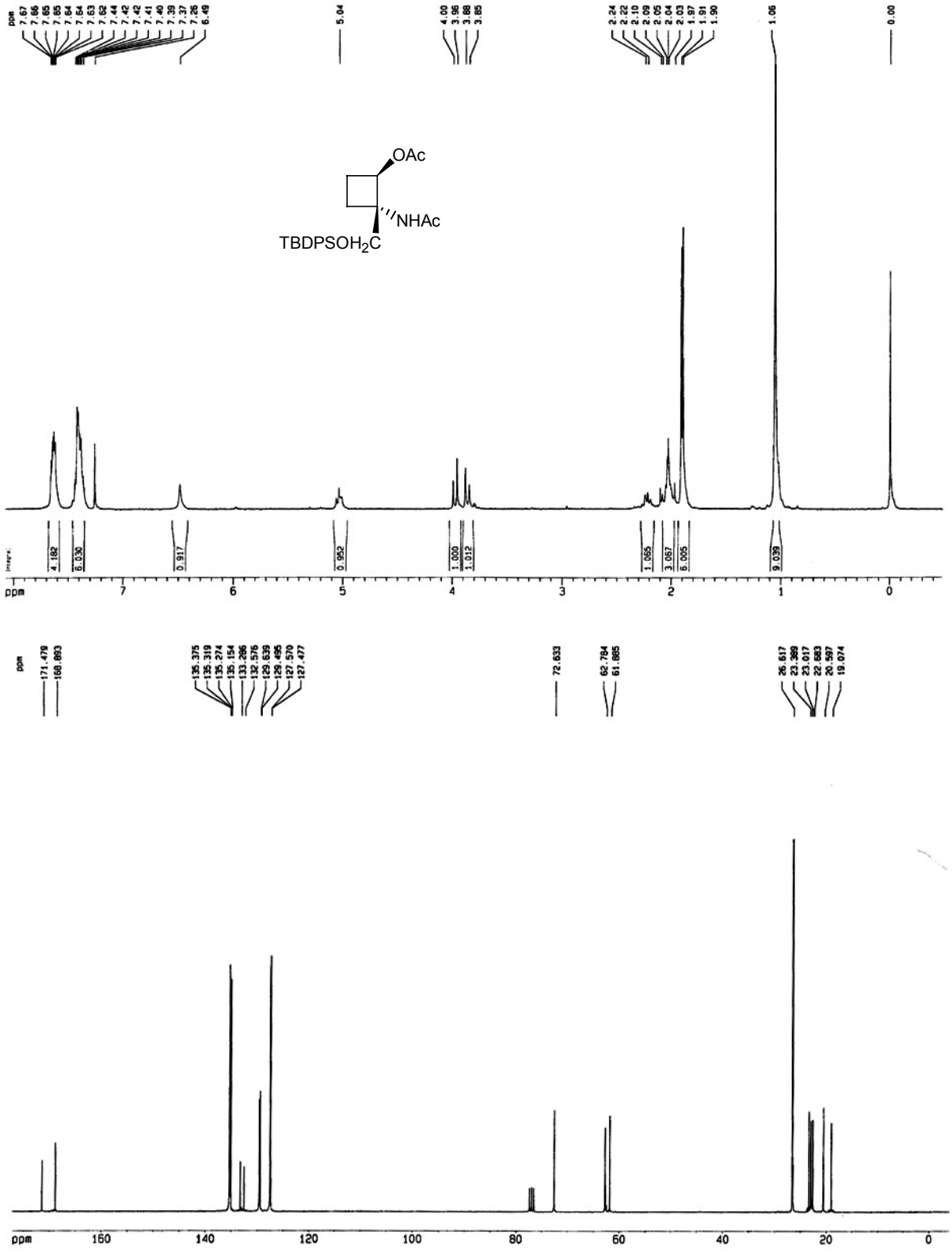


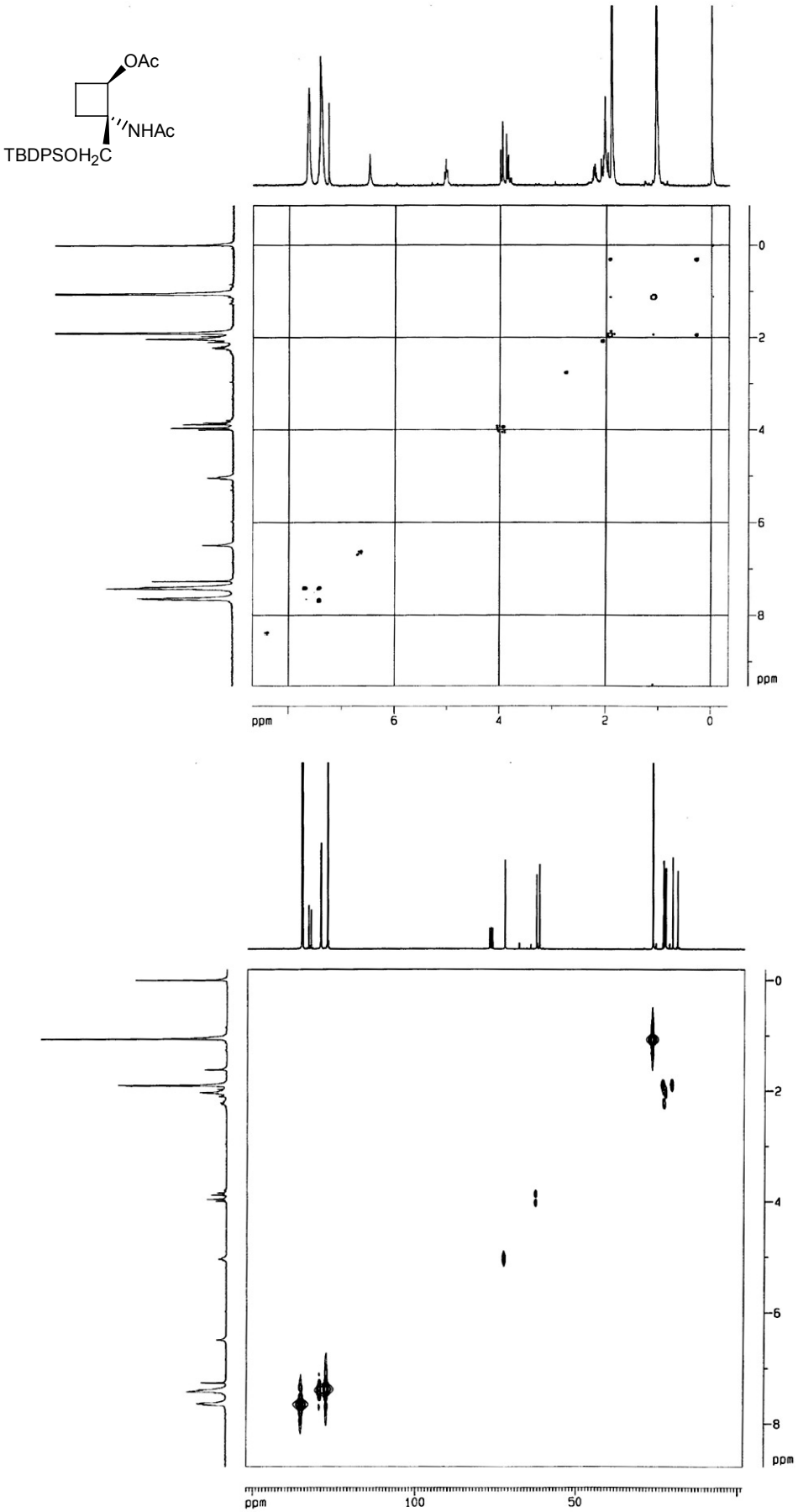
***N*-[*t*-2-Benzyloxy-1-(*tert*-butyldiphenylsilanyloxymethyl)cyclobutyl]-*r*-acetamide (13)**



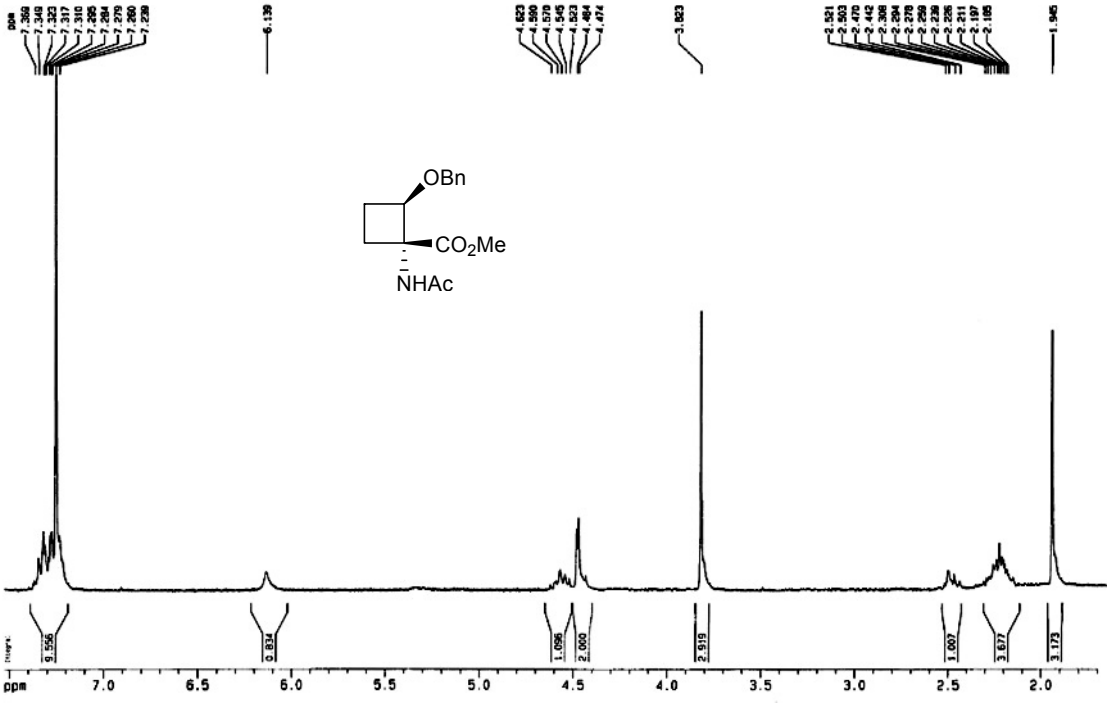


_N_-[_t_-2-Acetoxy-1-(_tert_-butyldiphenylsilanyloxymethyl)cyclobutyl]-_r_-acetamide (14)

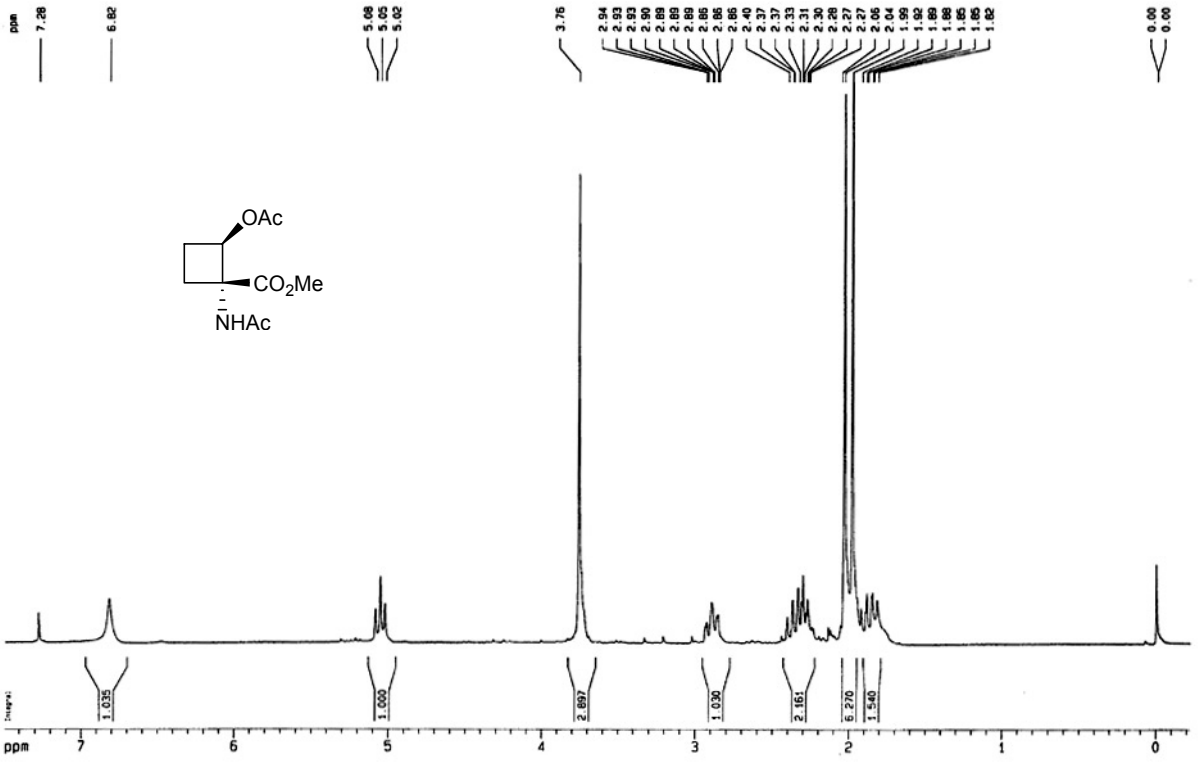


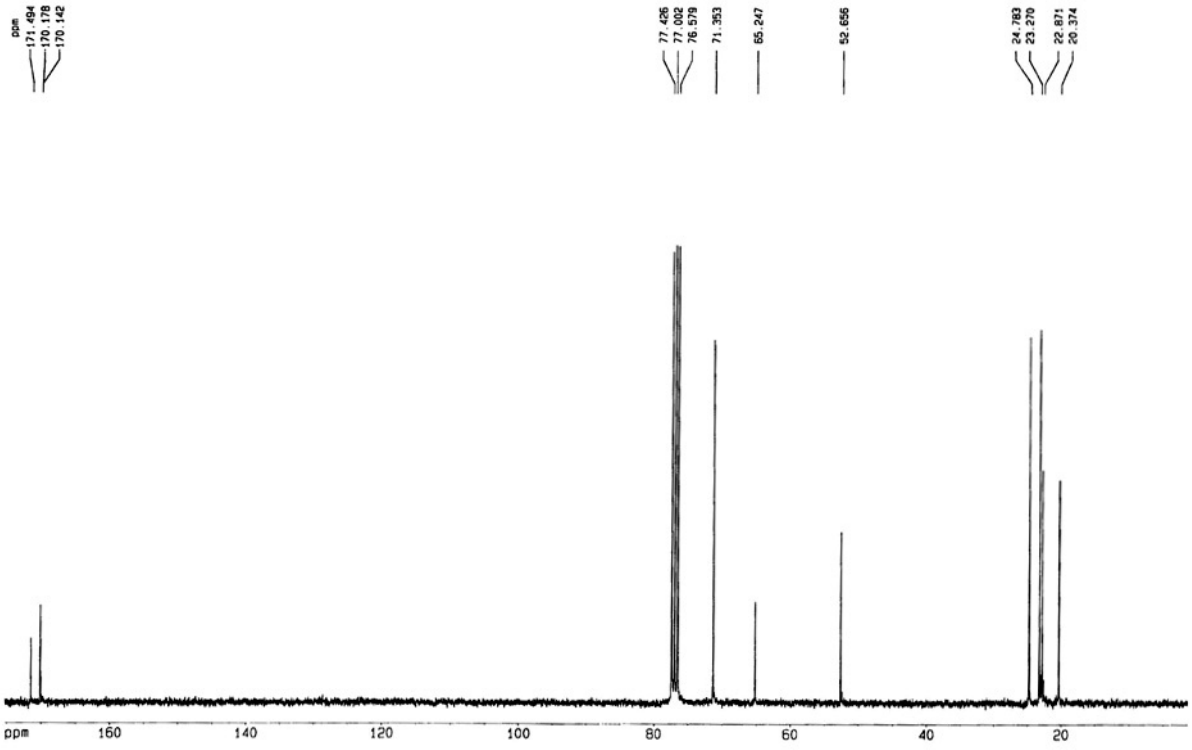


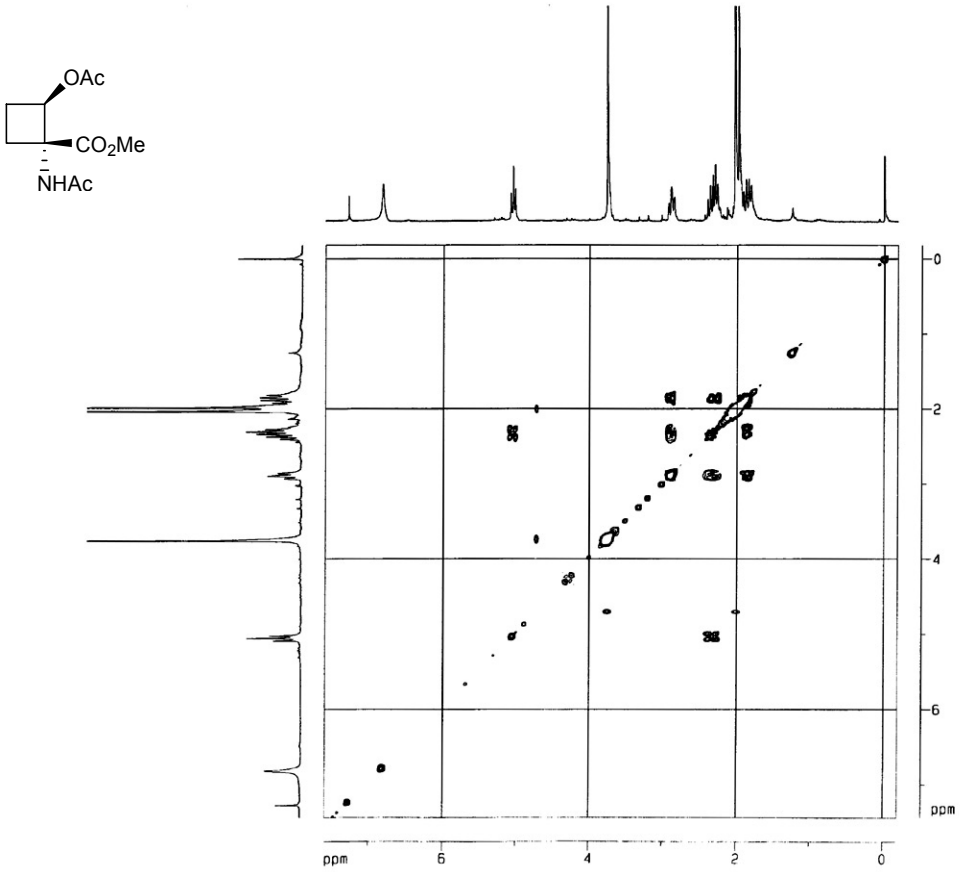
1-Acetamido-*c*-2-benzyloxycyclobutane-*r*-1-carboxylic acid methyl ester (15)

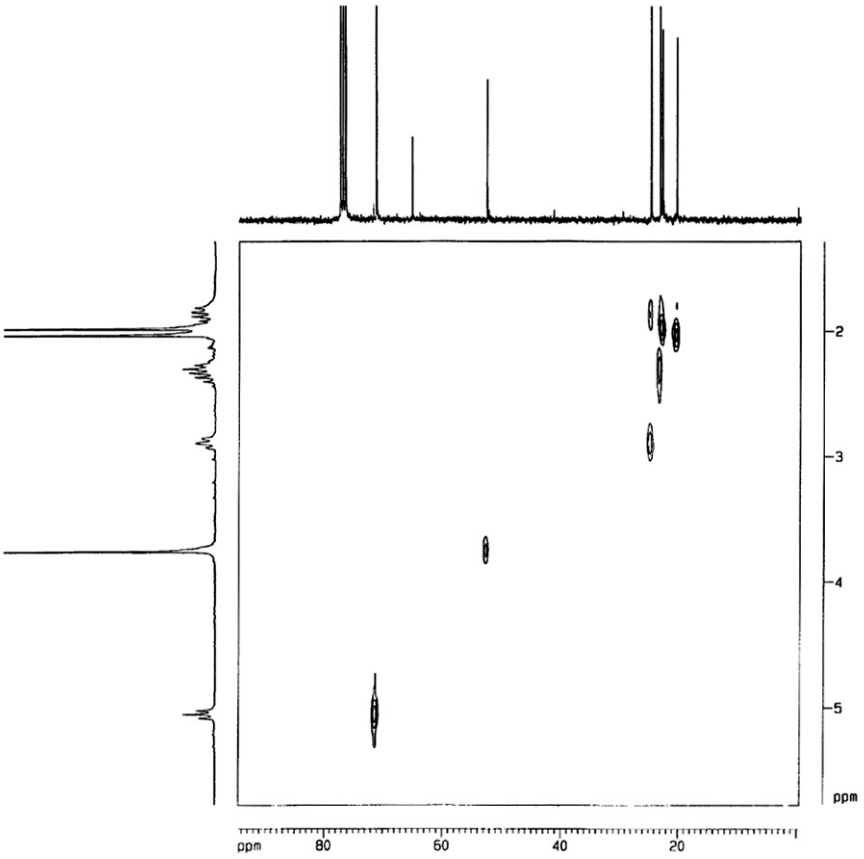


1-Acetamido-*c*-2-acetoxycyclobutane-*r*-1-carboxylic acid methyl ester (16)

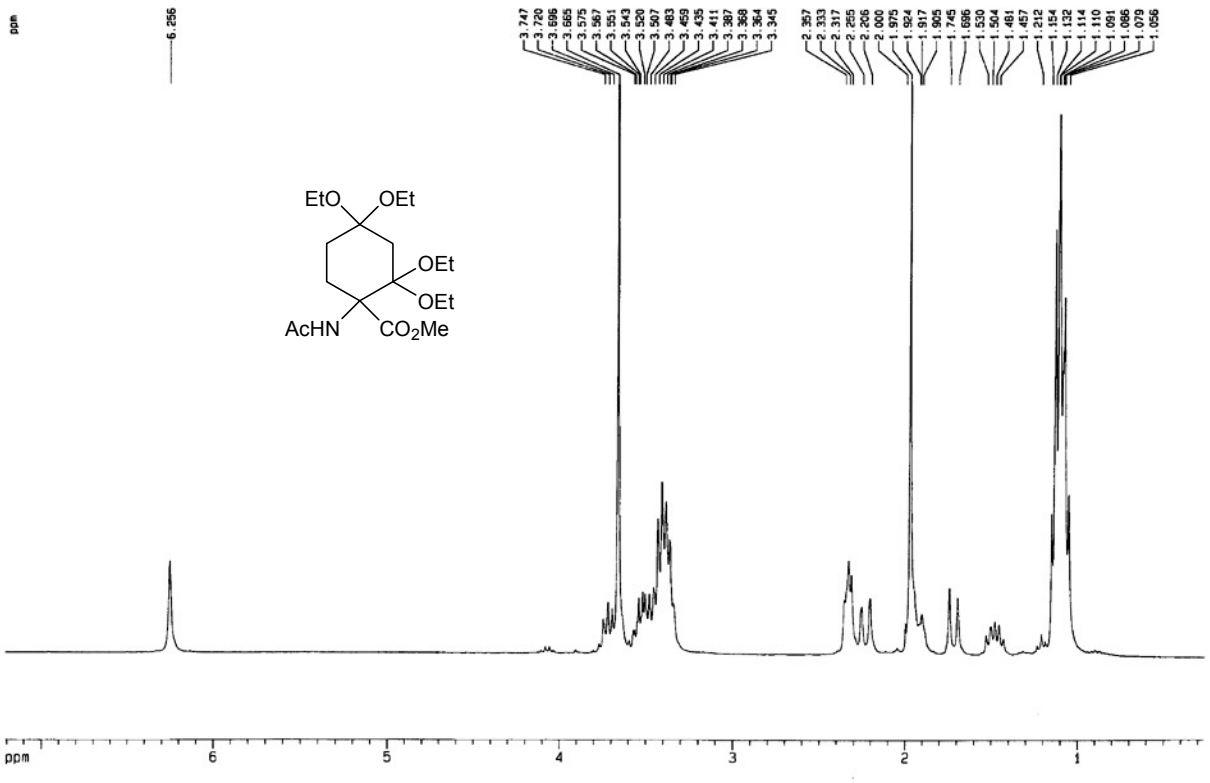


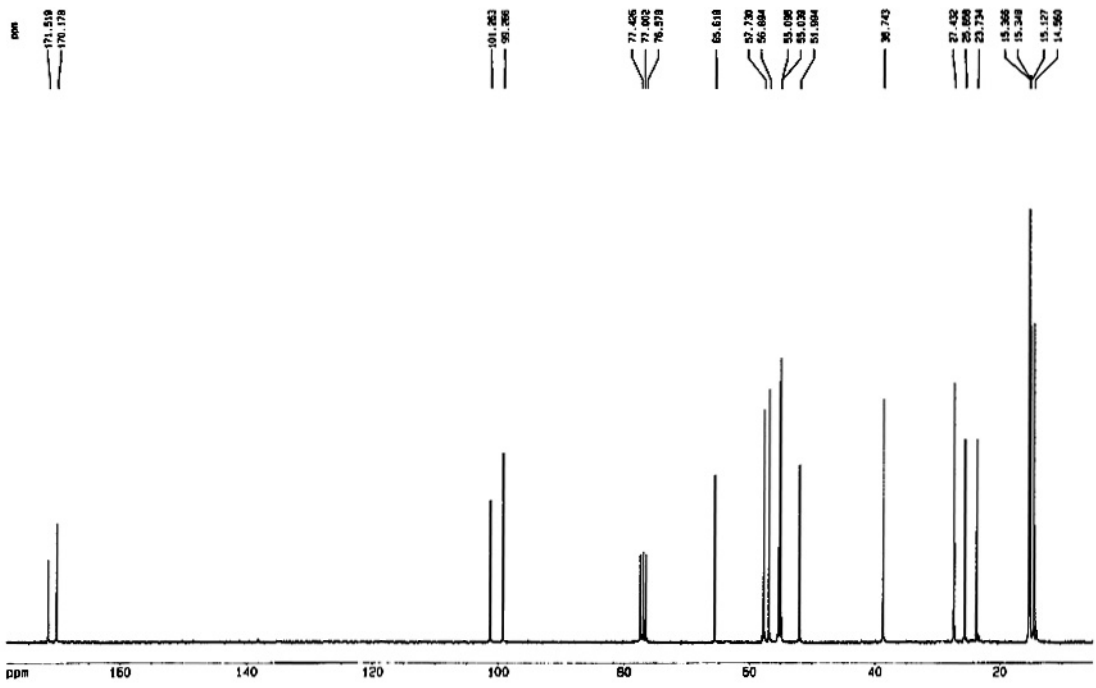


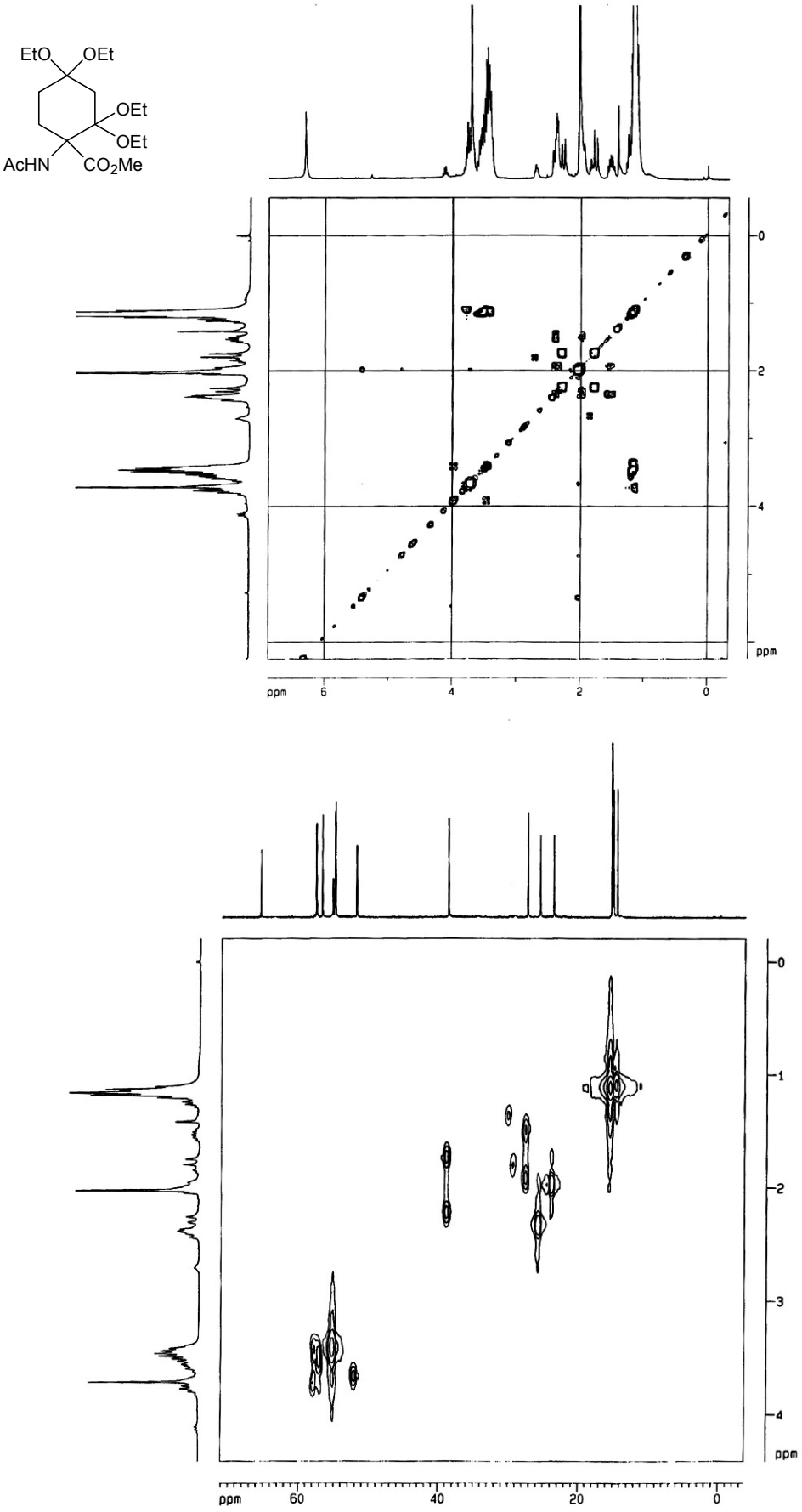

OAc
CO2Me
NHAc
ppm
6
4
2
0
ppm


ppm
80
60
40
20
ppm

1-Acetamido-2,2,4,4-tetraethoxycyclohexane-1-carboxylic acid methyl ester (10)







1-Acetamido-2-ethoxy-4-oxocyclohex-2-ene-1-carboxylic acid ethyl ester (17)