**Synthetic Studies on the MARDi Cascade: Stereoselective Synthesis of Heterocyclic Seven-Membered Rings**

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**Supporting Information**

**Experimental section**

General experimental:

MeOH was dried by refluxing with magnesium and then distilled under argon. $K_2CO_3$ was dried by prolonged storage at 140 °C in an oven. The reactions were monitored by TLC, which were performed on Merck 60F254 plates and visualized with an ethanolic solution of *p*-anisaldehyde and sulfuric acid or an ethanolic solution of molybdophosphoric acid. Flash chromatography was performed with Merck 230-400 mesh silica gel. NMR data were recorded on a Brücker Avance 200, Avance 300 or Avance 400 spectrometer in $CDCl_3$ or $C_6D_6$, and chemical shifts ($\delta$) are given in ppm relative to the residual $CHCl_3$ signal for $^1$H NMR (7.25 ppm) and relative to the deutered solvent signal for $^{13}$C NMR (77.0 ppm); coupling constants (*J*) are in Hertz, and the classical abbreviations are used to describe the signal multiplicity; peak assignment and relative configurations have been established from standard COSY and NOESY NMR data. Mass spectra were recorded on a API *III* Plus Sciex spectrometer.

General procedure for the preparation of diesters **3a-d**:

An oven dried, two-necked, round-bottomed flask under an argon atmosphere equipped with a

magnetic Teflon-coated stirring bar is charged at room temperature, in that order, with 1.0 mmol of β-ketoester **1** and 25 mL of MeOH. At 0 °C, the required amount of $K_2CO_3$ (see Table 1) is added and the mixture is stirred for 10 minutes, and 100 μL (1.5 mmol) of acrolein **2a** are then added. The reaction mixture is slowly warmed to room temperature and stirred at that temperature for 16 hours (entries 1-4 and 8) or 30 hours (entries 5-7). Water (20 mL) is then added to the reaction mixture and methanol is removed under reduced pressure; the resulting aqueous layer is extracted three times with ethyl acetate and the combined organic layers are washed with brine, dried with anhydrous sodium sulfate, filtrated and concentrated to give the crude product. The crude product is purified by flash chromatography on silica gel eluted with increasing amount of ether or ethyl acetate in petrol ether. The acid **3c** (R = H) is obtained by acidification of the previously extracted aqueous layer, which is then extracted three times with ethyl acetate and the combined organic layers are dried with anhydrous sodium sulfate, filtrated and concentrated to give the clean crude product.

General procedure for the preparation of diesters **3e-j**:

An oven dried, two-necked, round-bottomed flask under an argon atmosphere equipped with a magnetic Teflon-coated stirring bar is charged at room temperature, in that order, with 1.0 mmol of β-ketoester **1** and 25 mL of MeOH. At 0 °C, 150 μL (1.0 mmol) of DBU are added and the mixture is stirred for 10 minutes, and 1.5 mmol of aldehyde **2b** or **2c** are then added. The reaction mixture is slowly warmed to room temperature and stirred at that temperature for 20 hours. Water (20 mL) is then added to the reaction mixture and methanol is removed under reduced pressure; the resulting aqueous layer is extracted three times with ethyl acetate and the combined organic layers are washed with brine, dried with anhydrous sodium sulfate, filtrated and concentrated to

give the crude product. The crude product is purified by flash chromatography on silica gel eluted with increasing amount of ether or ethyl acetate in petrol ether.

General procedure for the preparation of acids **4**:

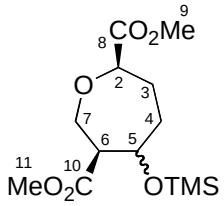
An oven dried, two-necked, round-bottomed flask under an argon atmosphere equipped with a magnetic Teflon-coated stirring bar is charged at room temperature, in that order, with 1.0 mmol of β-ketoester **1** and 25 mL of MeOH. At 0 °C, 75 μL (0.5 mmol) of DBU are added and the mixture is stirred for 10 minutes, and 1.5 mmol of aldehyde **2d** or **2e** is then added. The reaction mixture is slowly warmed to room temperature and stirred at that temperature for 20 hours. Water (20 mL) is then added to the reaction mixture and methanol is removed under reduced pressure; the resulting aqueous layer is washed twice with ethyl acetate and acidified with conc. HCl. The acidic aqueous layer is then extracted three times with ethyl acetate, and the combined organic layers are dried with anhydrous sodium sulfate, filtrated and concentrated to give the crude product. For thiepines **4c,d** the crude product was very clean. For oxepine **4a** and azepine **4b**, the crude product is purified by flash chromatography on silica gel eluted with increasing amount of ethyl acetate and acetic acid in petrol ether. Acetic acid could hardly be removed from the pure acids **4a,b**, and thus analytical samples were obtained as their methyl esters **5a,b**.

Preparation of diesters **5a,b**:

An oven dried round-bottomed flask under an argon atmosphere equipped with a magnetic Teflon-coated stirring bar is charged at room temperature with the acid **4a,b** and MeOH (0.05M). At 0 °C, 2 equiv of boron trifluoride-diethyl ether complex are added and the mixture is slowly warmed to room temperature and stirred at that temperature for 13 hours. Water is then added and methanol is removed under reduced pressure; the resulting aqueous layer is extracted three times

with ethyl acetate, and the combined organic layers are washed with brine, dried with anhydrous sodium sulfate, filtrated and concentrated to give the crude product which is purified by flash chromatography on silica gel eluted with ether in petrol ether.

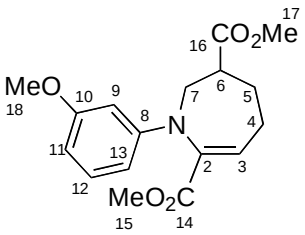
**Characterization data:**




**3a** (R = TMS)

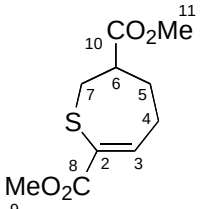
Oxepane **3a** (R = TMS, major isomer α-OTMS): $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.23 (dd, *J* = 9.7, 6.1 Hz, 1H, H2), 4.01-4.11 (m, 1H, H5), 3.92 (dd, *J* = 13.1, 8.2 Hz, 1H, H7), 3.79 (dd, *J* = 13.1, 3.1 Hz, 1H, H7), 3.69 (s, 3H, H9 or H11), 3.66 (s, 3H, H9 or H11), 2.69 (ddd, *J* = 8.2, 8.2, 3.1 Hz, 1H, H6), 2.10-2.21 (m, 1H, H3), 1.73-1.98 (m, 3H, H3 and H4), 0.06 (s, 9H, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.8 (C), 172.5 (C), 76.9 (CH), 73.2 (CH), 63.5 ($CH_2$), 56.0 (CH), 52.1 ($CH_3$), 51.9 ($CH_3$), 32.5 ($CH_2$), 25.5 ($CH_2$), 0.1 ($CH_3$); MS (ESI+) *m/z* 322 ($[M+NH_4]^+$, 100%), 305 ($[M+H]^+$, 75%).

Minor isomer β-OTMS: $^{1}$H NMR (300 MHz, $CDCl_3$, selected resonances) $\delta$ 3.71 (s, H9 or H11), 3.68 (s, H9 or H11), 0.06 (s, TMS); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.6 (C), 172.3 (C), 76.5 (CH), 68.2 (CH), 62.2 ($CH_2$), 54.4 (CH), 52.0 ($CH_3$), 51.8 ($CH_3$), 30.6 ($CH_2$), 23.2 ($CH_2$), 0.0 ($CH_3$)



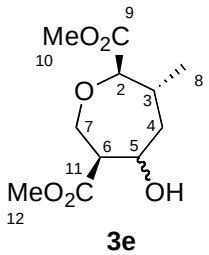

**3c** (R = Me)

Azepine **3c** (R = Me): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 7.9 Hz, 1H, H12), 6.63 (t, *J* = 5.6 Hz, 1H, H3), 6.33 (m, 3H, H9-H11-H13), 4.30 (dd, *J* = 15.1, 5.1 Hz, 1H, H4), 3.75 (s, 3H, H15 or H17 or H18), 3.65 (s, 3H, H15 or H17 or H18), 3.63 (s, 3H, H15 or H17 or H18), 3.63 (dd, *J* = 15.1, 10.3 Hz, 1H, H4), 3.00 (m, 1H, H6), 2.45-2.60 (m, 1H, H7), 2.21-2.34 (m, 1H, H7), 1.74-1.95 (m, 2H, H5); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.2 (C), 166.0 (C), 160.7 (C), 146.9 (C), 138.5 (C), 133.4 (CH), 130.0 (CH), 108.0 (CH), 104.3 (CH), 101.6 (CH), 55.1 ($CH_3$), 52.2 ($CH_3$), 51.8 ($CH_3$), 51.3 ($CH_2$), 42.1 (CH), 25.3 ($CH_2$), 25.2 ($CH_2$); MS (ESI+) *m/z* 320 ($[M+H]^+$, 100%).



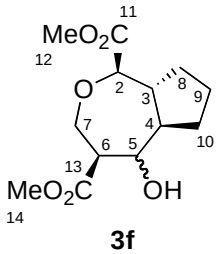

**3d**

Thiepine **3d**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 6.7, 6.6 Hz, 1H, H3), 3.75 (s, H9 or H11), 3.69 (s, H9 or H11), 3.00-3.11 (m, 2H, H7), 2.86-2.98 (m, 1H, H6), 2.59-2.72 (m, 1H, H4), 2.36-2.50 (m, 1H, H4), 2.19 (dddd, *J* = 14.3, 9.2, 4.9, 1.5 Hz, 1H, H5), 1.92 (dddd, *J* = 14.3, 9.7, 7.9, 1.5 Hz, 1H, H5); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 165.7 (C), 143.5 (CH), 132.5 (C), 52.5 ($CH_3$), 51.9 ($CH_3$), 46.1 (CH), 34.6 ($CH_2$), 26.6 ($CH_2$), 25.5 ($CH_2$); MS (FAB+) *m/z* 231 ($[M+H]^+$, 23%), 136 (50%), 73 (100%), 39 (79%).




**3e**

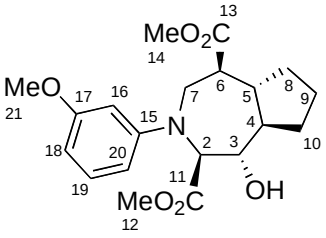
Oxepane **3e** (major isomer α-OH): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 3.84-4.06 (m, 3H, H5 and H7), 3.68-3.74 (m, 1H, H2), 3.72 (s, 3H, H10 or H12), 3.71 (s, 3H, H10 or H12), 2.87-2.98 (m, 1H, OH), 2.66 (ddd, *J* = 9.6, 9.6, 4.6 Hz, 1H, H6), 2.05-2.24 (m, 1H, H3), 1.79-1.88 (m, 2H, H4), 0.99 (d, *J* = 6.7 Hz, 3H, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.2 (C), 172.6 (C), 83.3 (CH), 72.3 (CH), 63.3 ($CH_2$), 54.5 (CH), 52.2 ($CH_3$), 51.9 ($CH_3$), 41.4 ($CH_2$), 31.6 (CH), 19.2 ($CH_3$); MS (FAB+) *m/z* 247 ($[M+H]^+$, 15%), 229 (15%), 169 (19%), 154 (44%), 136 (51%), 77 (58%), 59 (100%), 39 (82%).



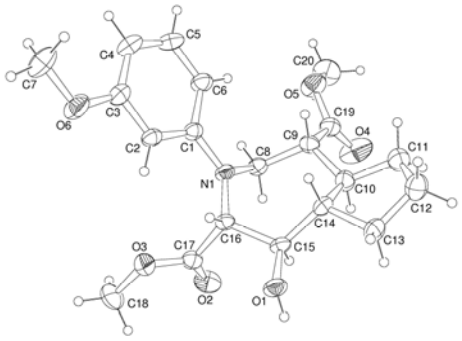

**3f**

Oxepane **3f** (major isomer α-OH): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 3.87-3.96 (m, 3H, H5 and H7), 3.63-3.72 (m, 1H, H2), 3.70 (s, 3H, H12 or H14), 3.69 (s, 3H, H12 or H14), 2.72 (ddd, *J* = 9.7, 8.2, 5.9 Hz, 1H, H6), 1.95-2.20 (m, 3H, H3-4 and H8), 1.41-1.94 (m, 5H, H8-10); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.2 (C), 173.1 (C), 80.8 (CH), 76.9 (CH), 62.6 ($CH_2$), 55.1 (CH), 52.1 ($CH_3$), 51.9 ($CH_3$), 49.3 (CH), 41.7 (CH), 31.3 ($CH_2$), 30.5 ($CH_2$), 24.1 ($CH_2$); MS (ESI+) *m/z* 290 ($[M+NH_4]^+$, 100%), 273 ($[M+H]^+$, 48%).

Minor isomer β-OH: $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.6 (C), 172.2 (C), 80.5 (CH), 72.5 (CH), 68.0 ($CH_2$), 52.2 ($CH_3$), 51.8 ($CH_3$), 48.2 (CH), 45.0 (CH), 43.7 (CH), 30.9 ($CH_2$), 27.7 ($CH_2$), 25.9 ($CH_2$).

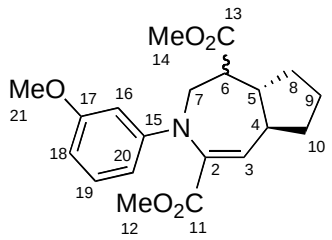



**3g**




Azepane **3g**: needles from $Et_2O$:pentane at -35 ˚C; mp 163 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.7, 8.7 Hz, 1H, H19), 6.32-6.40 (m, 3H, H16-H18-H20), 4.19 (dd, J = 8.2, 1.0 Hz, 1H, H2), 4.04 (ddd, *J* = 8.2, 8.2, 3.3 Hz, 1H, H3), 3.79 (s, 3H, H12 or H13 or H21), 3.75 (s, 3H, H12 or H13 or H21), 3.73 (s, 3H, H12 or H13 or H21), 3.70 (dd, *J* = 15.6, 3.7 Hz, 1H, H7), 3.28 (dd, *J* = 15.6, 10.8 Hz, 1H, H7), 2.79 (d, *J* = 3.3 Hz, 1H, OH), 2.51-2.60 (m, 1H, H6), 1.77-2.07 (m, 4H, H4-H5-H8-H10), 1.47-1.75 (m, 2H, H8-H10), 1.17-1.32 (m, 2H, H9); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.2 (C), 173.9 (C), 160.9 (C), 149.0 (C), 130.2 (CH), 104.5 (CH), 102.5 (CH), 98.2 (CH), 79.3 (CH), 66.4 (CH), 54.8 ($CH_3$), 52.2 ($CH_3$), 51.6 ($CH_3$), 49.2 ($CH_2$), 48.5 (CH), 48.5 (CH) 48.3 (CH), 31.6 ($CH_2$), 29.4 ($CH_2$), 21.6 ($CH_2$); MS (ESI+) *m/z* 378 ($[M+H]^+$, 100%).

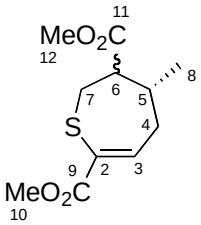
The ORTEP view of **3g** shows the non-depicted enantiomer (ellipsoids are at 30% probability). The CIF for **3g** is available free of charge via the Internet at http://pubs.acs.org.




**3h**

Azepine **3h** (major isomer β-$CO_2$Me): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 8.1, 8.1 Hz, 1H, H19), 6.53 (d, *J* = 2.3 Hz, 1H, H3), 6.17-6.42 (m, 3H, H16-H18-H20), 4.20-4.34 (broad dd, *J* undetermined, 1H, H7), 3.69-3.82 (masked dd, *J* undetermined, 1H, H7), 3.75 (s, 3H, H12 or H13 or H21), 3.64 (s, 3H, H12 or H13 or H21), 3.63 (s, 3H, H12 or H13 or H21), 3.22-3.35 (m, 1H, H6), 3.06-3.19 (m, 1H, H4), 1.35-2.12 (m, 7H, H5 and H8-10); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.5 (C), 166.2 (C), 160.6 (C), 147.1 (C), 136.7 (C), 135.4 (broad CH), 129.9 (CH), 108.6 (CH), 104.6 (CH), 102.3 (CH), 55.1 ($CH_3$), 52.2 ($CH_2$), 52.2 ($CH_3$), 51.3 ($CH_3$), 43.6 (CH), 42.0 (CH), 40.6 (CH), 32.0 ($CH_2$), 29.2 ($CH_2$), 22.8 ($CH_2$); MS (ESI+) *m/z* 360 ($[M+H]^+$, 100%).

Minor isomer α-$CO_2$Me: $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 165.7 (C), 160.8 (C), 146.4 (C), 138.1 (C), 135.8 (broad CH), 130.1 (CH), 106.6 (CH), 103.4 (CH), 100.3 (CH), 55.1 ($CH_3$), 52.1 ($CH_3$), 51.7 ($CH_3$), 50.2 ($CH_2$), 49.9 (CH), 44.1 (CH), 43.6 (CH), 32.3 ($CH_2$), 31.6 ($CH_2$), 22.6 ($CH_2$).

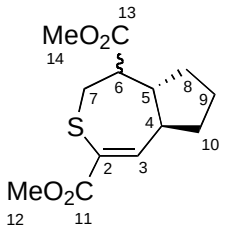



**3i**

Thiepine **3i** (major isomer β-$CO_2$Me): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 7.4, 6.3 Hz,

1H, H3), 3.73 (s, 3H, H10 or H12), 3.67 (s, 3H, H10 or H12), 3.02 (dd, *J* = 14.6, 3.6 Hz, 1H, H7), 2.83 (dd, *J* = 14.6, 7.0 Hz, 1H, H7), 2.55 (ddd, *J* = 9.1, 7.0, 3.5 Hz, 1H, H6), 2.41-2.48 (m, 2H, H4), 2.19-2.32 (m, 1H, H5), 0.97 (d, *J* = 6.7 Hz, 3H, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.0 (C), 165.6 (C), 143.4 (CH), 133.0 (C), 53.6 (CH), 52.5 ($CH_3$), 51.8 ($CH_3$), 35.3 ($CH_2$), 34.2 ($CH_2$), 30.8 (CH), 21.2 ($CH_3$); MS (FAB+) *m/z* 245 ($[M+H]^+$, 8%), 207 (11%), 185 (12%), 147 (26%), 73 (100%).

Minor isomer α-$CO_2$Me: $^1$H NMR (300 MHz, $CDCl_3$, selected resonances) δ 3.73 (s, 3H, H10 or H12), 3.64 (s, 3H, H10 or H12), 0.84 (d, *J* = 7.1 Hz, 3H, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.7 (C), 165.7 (C), 142.7 (CH), 132.0 (C), masked (CH), 51.6 ($CH_3$), 51.0 ($CH_3$), 33.7 ($CH_2$), 31.0 ($CH_2$), 30.3 (CH), 16.7 ($CH_3$).



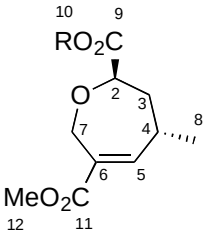

**3j**

Thiepine **3j** (major isomer β-$CO_2$Me): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 3.2 Hz, 1H, H3), 3.73 (s, 3H, H12 or H14), 3.66 (s, 3H, H12 or H14), 3.28-3.39 (m, 1H, H4), 3.32 (dd, *J* = 14.3, 10.2 Hz, 1H, H7), 3.10-3.19 (m, 1H, H6), 2.85 (dd, *J* = 14.2, 4.5 Hz, 1H, H7), 2.45-2.64 (m, 1H, H5), 1.99-2.13 (m, 1H, H10), 1.31-1.93 (m, 5H, H8-10); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.5 (C), 165.8 (C), 147.2 (CH), 129.8 (C), 52.5 ($CH_3$), 51.5 ($CH_3$), 47.3 (CH), 42.3 (CH), 40.1 (CH), 35.5 ($CH_2$), 33.9 ($CH_2$), 30.2 ($CH_2$), 24.3 ($CH_2$); MS (ESI+) *m/z* 271 ($[M+H]^+$, 100%).

Minor isomer α-$CO_2$Me: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.0 Hz, 1H, H3), 3.74 (s,

3H, H12 or H14), 3.65 (s, 3H, H12 or H14), 2.89-3.01 (m, 1H, H7), 2.65-2.79 (m, 1H, H4), 2.56-2.63 (m, 1H, H7), 2.01-2.16 (m, 1H, H10), 1.50-2.00 (m, 6H, H5-6 and H8-10), 1.25-1.41 (m, 1H, H9); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.1 (C), 165.9 (C), 151.9 (CH), 131.5 (C), 53.9 (CH), 52.5 ($CH_3$), 51.8 ($CH_3$), 45.6 (CH), 43.1 (CH), 35.0 ($CH_2$), 33.7 ($CH_2$), 32.4 ($CH_2$), 23.5 ($CH_2$); MS (ESI+) *m/z* 271 ($[M+H]^+$, 100%).

A very minor unknown product could not be removed from both diastereomers of **3j** (see spectra).

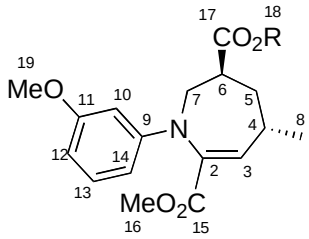



**4a**: R = H
**5a**: R = Me

Oxepines **4a**: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.37 (broad s, 1H, H10), 6.84 (d, *J* = 4.2 Hz, 1H, H5), 4.73 (d, *J* = 16.6 Hz, 1H, H7), 4.44 (d, *J* = 16.6 Hz, 1H, H7), 4.41 (dd, *J* = 6.3, 6.3 Hz, 1H, H2), 3.67 (s, 3H, H12), 2.69-2.86 (m, 1H, H4), 2.13-2.21 (m, 2H, H3), 1.14 (d, *J* = 7.2 Hz, 3H, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 175.3 (C), 166.4 (C), 148.8 (CH), 130.7 (C), 75.1 (CH), 65.0 ($CH_2$), 51.8 ($CH_3$), 36.2 ($CH_2$), 30.0 (CH), 20.1 ($CH_3$).

Oxepine **5a**: $^1$H NMR (300 MHz, $CDCl_3$) δ 6.88 (ddd, *J* = 4.4, 2.2, 1.8 Hz, 1H, H5), 4.75 (ddd, *J* = 16.6, 1.8, 1.8 Hz, 1H, H7), 4.44 (ddd, *J* = 16.6, 2.3, 1.5 Hz, 1H, H7), 4.41 (dd, *J* = 6.7, 6.7 Hz, 1H, H2), 3.75 (s, 3H, H10 or H12), 3.70 (s, 3H, H10 or H12), 2.75-2.92 (m, 1H, H4), 2.18 (ddd, *J* = 14.6, 6.9, 3.3 Hz, 1H, H3), 2.10 (ddd, *J* = 14.6, 8.2, 6.4 Hz, 1H, H3), 1.17 (d, *J* = 7.4 Hz, 3H, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 166.2 (C), 148.4 (CH), 131.0 (C), 75.1 (CH), 64.9

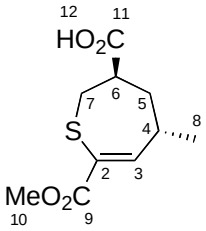
($CH_2$), 52.0 ($CH_3$), 51.6 ($CH_3$), 36.2 ($CH_2$), 30.0 (CH), 19.7 ($CH_3$); MS (ESI+) *m/z* 246 ($[M+NH_4]^+$, 100%), 229 ($[M+H]^+$, 60%).




**4b**: R = H
**5b**: R = Me

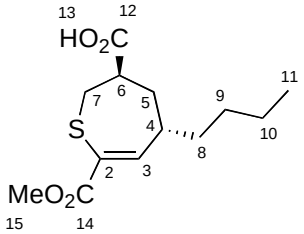
Azepine **4b**: $^1$H NMR (300 MHz, $CDCl_3$) δ 10.87 (broad s, 1H, H18), 7.15 (dd, *J* = 8.2, 8.2 Hz, 1H, H13), 6.30-6.46 (m, 4H, H3-H10-H12-H14), 4.33 (dd, *J* = 14.9, 5.9 Hz, 1H, H7), 3.78 (dd, *J* = 14.9, 3.6 Hz, 1H, H7), 3.78 (s, 3H, H16 or H19), 3.66 (s, 3H, H16 or H19), 3.10-3.21 (m, 1H, H6), 2.74-2.91 (m, 1H, H4), 1.86 (broad d, *J* = 14.6 Hz, H5), 1.72 (ddd, *J* = 14.6, 10.8, 6.1 Hz, H5), 1.15 (d, *J* = 7.2 Hz, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 180.1 (C), 166.3 (C), 160.6 (C), 147.0 (C), 137.6 (CH), 136.6 (C), 130.0 (CH), 108.5 (CH), 104.7 (CH), 102.0 (CH), 55.1 ($CH_3$), 52.2 ($CH_3$), 51.0 ($CH_2$), 40.3 (CH), 32.5 ($CH_2$), 30.5 (CH), 22.2 ($CH_3$).

Azepine **5b**: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 8.2, 8.2 Hz, 1H, H13), 6.26-6.41 (m, 4H, H3-H10-H12-H14), 4.23 (dd, *J* = 15.1, 5.9 Hz, 1H, H7), 3.75 (dd, *J* = 15.1, 7.2 Hz, 1H, H7), 3.74 (s, 3H, H16 or H18 or H19), 3.65 (s, 3H, H16 or H18 or H19), 3.62 (s, 3H, H16 or H18 or H19), 3.02-3.14 (m, 1H, H6), 2.71-2.86 (m, 1H, H4), 1.86 (ddd, *J* = 14.3, 3.4, 3.2 Hz, H5), 1.72 (ddd, *J* = 14.3, 10.8, 6.1 Hz, H5), 1.11 (d, *J* = 7.2 Hz, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.3 (C), 166.1 (C), 160.6 (C), 147.1 (C), 137.7 (CH), 136.6 (C), 129.9 (CH), 108.4 (CH), 104.5 (CH), 102.0 (CH), 55.1 ($CH_3$), 52.1 ($CH_3$), 51.7 ($CH_3$), 51.1 ($CH_2$), 40.3 (CH), 32.8 ($CH_2$), 30.4 (CH), 22.1 ($CH_3$); MS (ESI+) *m/z* 334 ($[M+H]^+$, 100%).




**4c**

Thiepine **4c**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.35 (broad s, 1H, H12), 6.96 (d, *J* = 4.9 Hz, 1H, H3), 3.76 (s, 3H, H10), 3.28 (dd, *J* = 14.1, 7.7 Hz, 1H, H7), 3.03-3.13 (m, 1H, H6), 2.89-3.01 (m, 1H, H4), 2.89 (dd, *J* = 14.1, 4.1 Hz, 1H, H7), 2.07 (ddd, *J* = 14.3, 4.8, 1.8 Hz, 1H, H5), 1.99 (ddd, *J* = 14.3, 9.7, 5.1 Hz, 1H, H5), 1.18 (d, *J* = 7.2 Hz, 3H, H8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 179.1 (C), 165.9 (C), 149.3 (CH), 130.1 (C), 52.5 ($CH_3$), 43.0 (CH), 33.5 ($CH_2$), 32.5 ($CH_2$), 31.3 (CH), 22.1 ($CH_3$); MS (ESI+) *m/z* 231 ($[M+H]^+$, 100%).



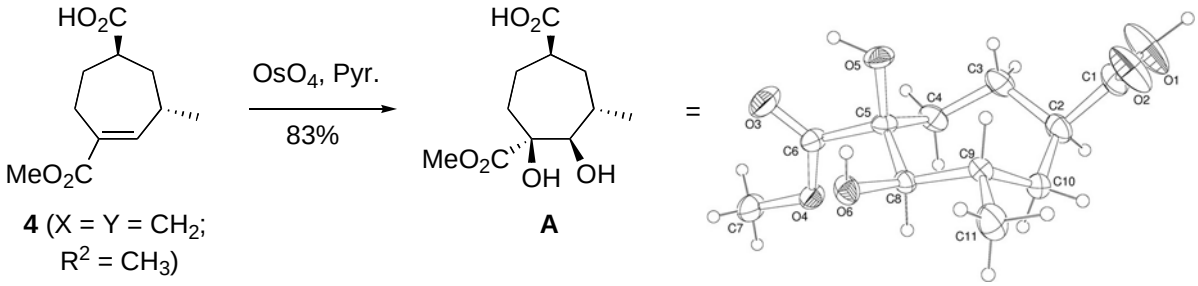

**4d**

Thiepine **4d**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 11.1 (broad s, 1H, H13), 7.00 (d, *J* = 5.1 Hz, 1H, H3), 3.73 (s, 3H, H15), 3.22 (dd, *J* = 13.9, 7.4 Hz, 1H, H7), 2.99-3.10 (m, 1H, H6), 2.84 (dd, *J* = 13.9, 3.8 Hz, 1H, H7), 2.69-2.83 (m, 1H, H4), 2.06 (ddd, *J* = 14.2, 5.1, 1.8 Hz, 1H, H5), 1.89 (ddd, *J* = 14.2, 10.5, 5.4 Hz, 1H, H5), 1.29-1.62 (m, 2H, H8), 1.19-1.36 (m, 4H, H9-H10), 0.80-0.91 (m, 3H, H11); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 179.5 (C), 165.9 (C), 149.0 (CH), 130.4 (C), 52.5 ($CH_3$), 43.0 (CH), 36.4 (CH), 35.9 ($CH_2$), 33.3 ($CH_2$), 30.8 ($CH_2$), 28.9 ($CH_2$), 22.6 ($CH_2$),

13.8 ($CH_3$); MS (ESI+) *m/z* 273 ($[M+H]^+$, 100%).

Structure revision of the cycloheptenic acid **4** (X = Y = $CH_2$; $R^2$ = $CH_3$):

The initially reported[18b] incorrect *cis* stereochemistry of the carbocyclic analog **4** (X = Y = $CH_2$; $R^2$ = $CH_3$) has been revisited and confirmed to be *trans* by X-ray diffraction analysis of the diol **A** obtained by dihydroxylation of the cycloheptenic acid **4** (X = Y = $CH_2$; $R^2$ = $CH_3$).

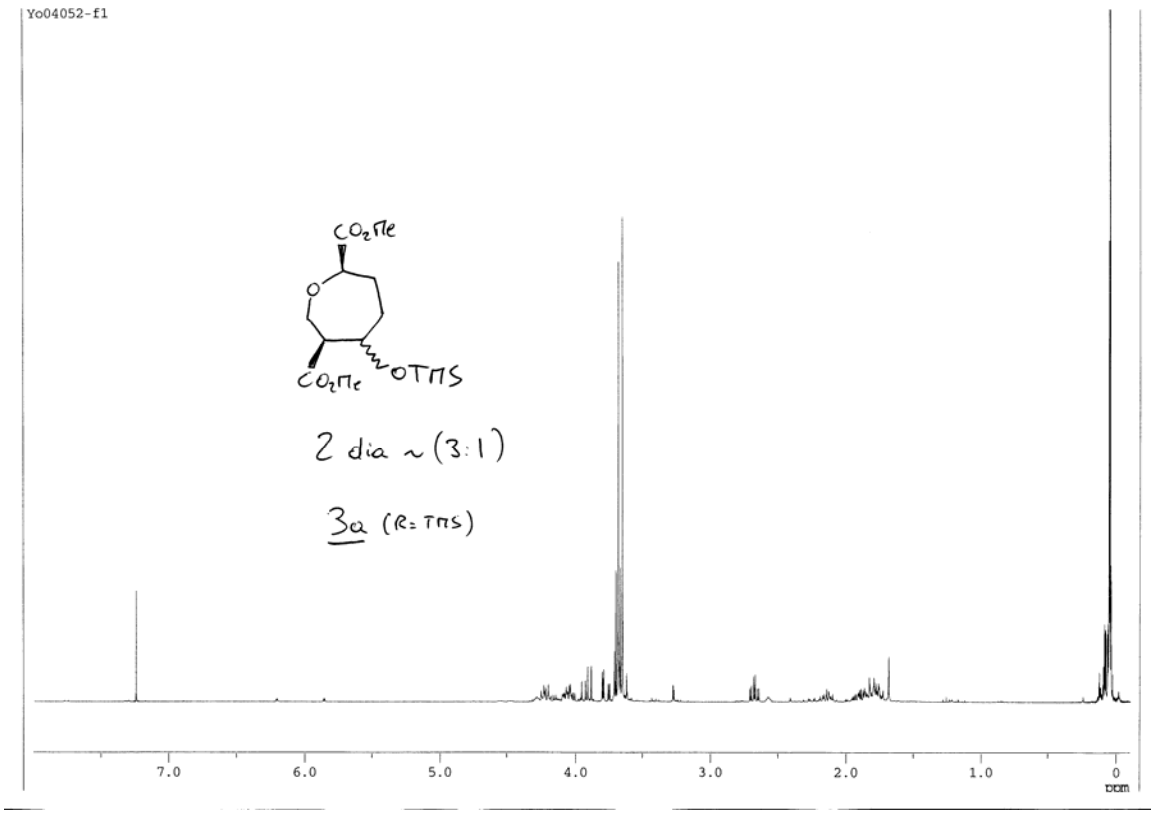


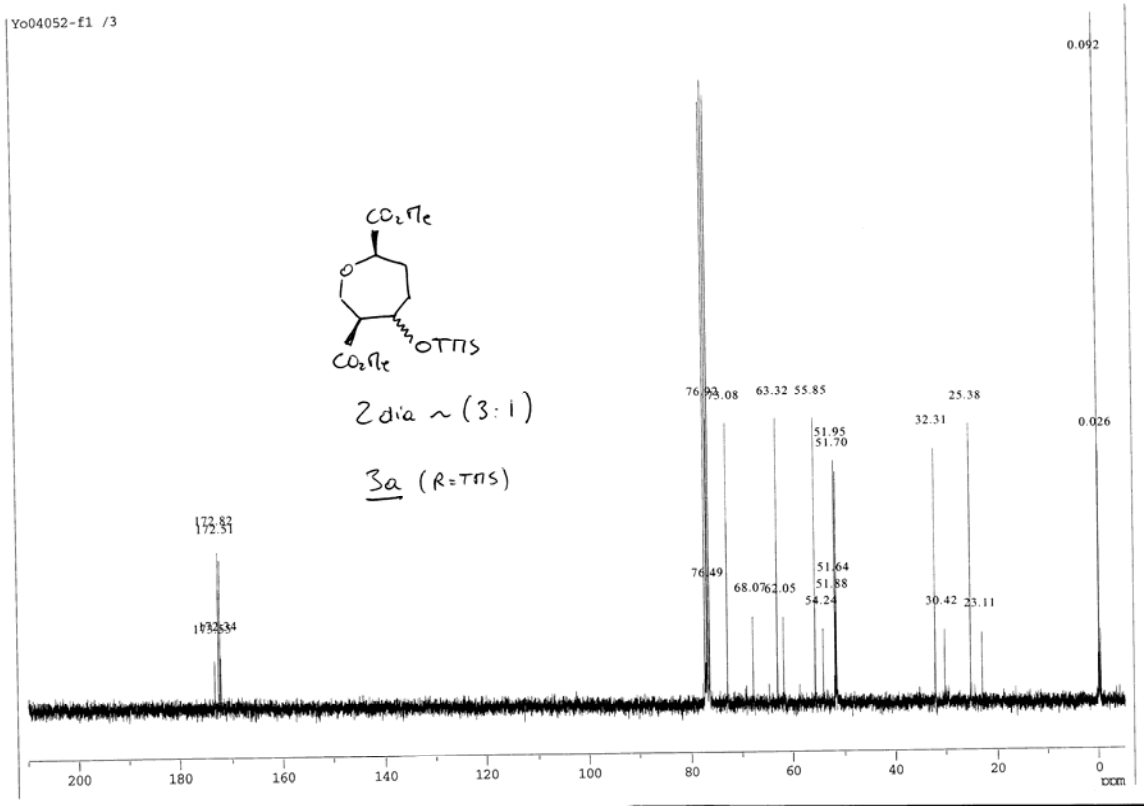

**4** (X = Y = $CH_2$; $R^2$ = $CH_3$)

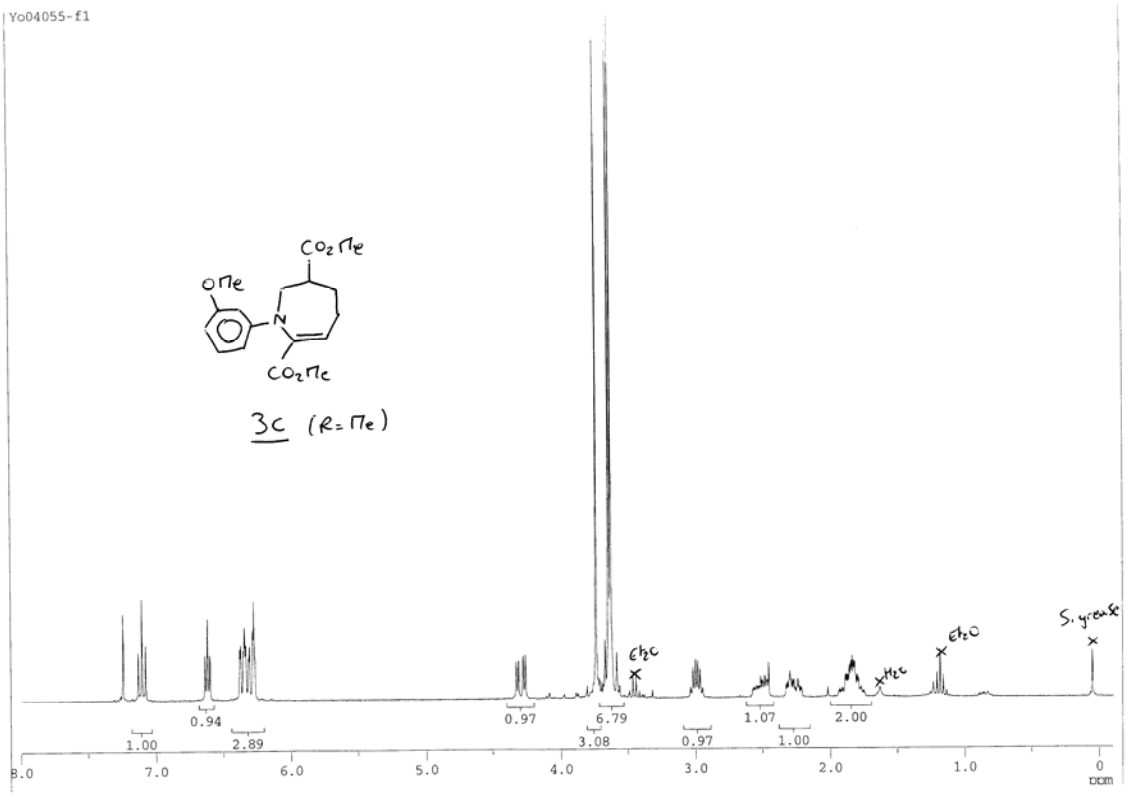
**A**

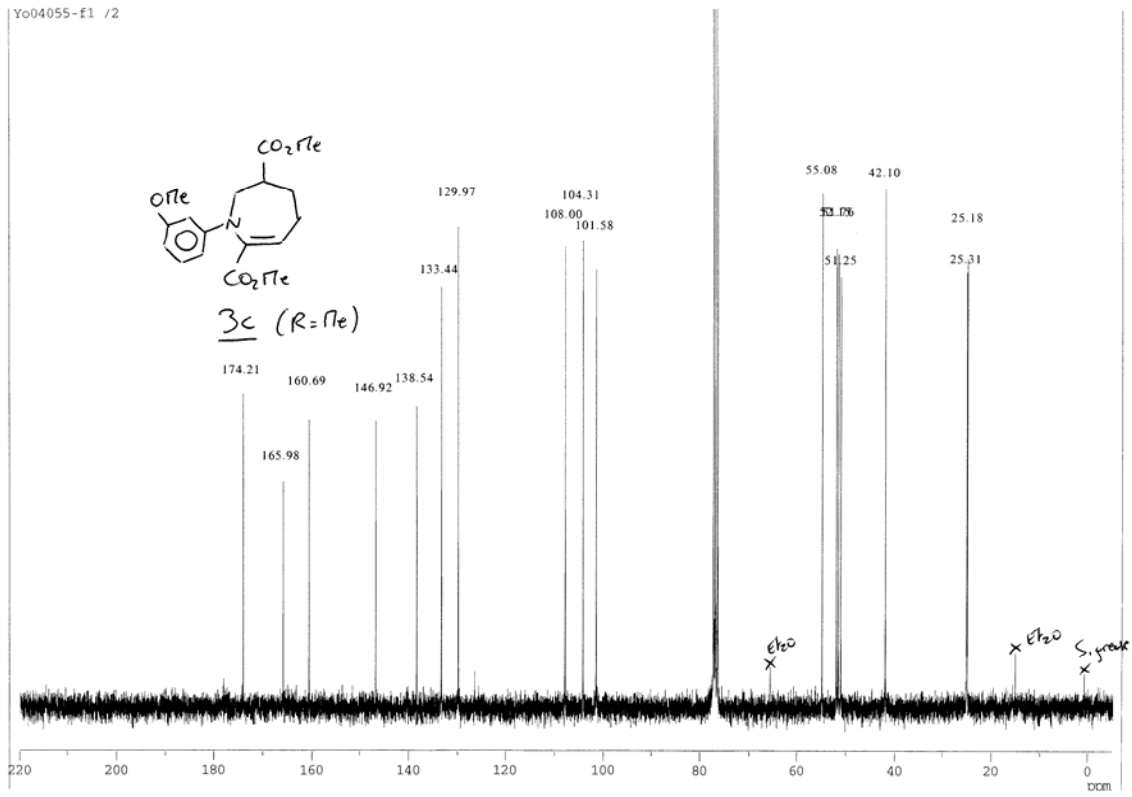
Diol **A**: needles from AcOEt:hexane by slow evaporation at room temperature; mp 137 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.49 (broad s, 1H), 3.44 (d, *J* = 9.9 Hz, 1H), 2.67 (dddd, *J* = 10.5, 6.7, 6.7, 3.1 Hz, 1H), 2.20 (dddd, *J* = 14.3, 10.9, 10.8, 2.7 Hz, 1H), 1.70-2.05 (m, 6H), 1.59 (ddd, *J* = 15.6, 9.1, 6.8 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), $CO_2H$ masked; $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) δ 20.5 ($CH_3$), 22.9 ($CH_2$), 32.7 (CH), 33.2 ($CH_2$), 35.1 ($CH_2$), 41.4 (CH), 52.6 ($CH_3$), 79.9 (C), 81.2 (CH), 177.3 (C), 177.5 (C); MS (ESI-) *m/z* 245 ($[M-H]^-$, 100%).

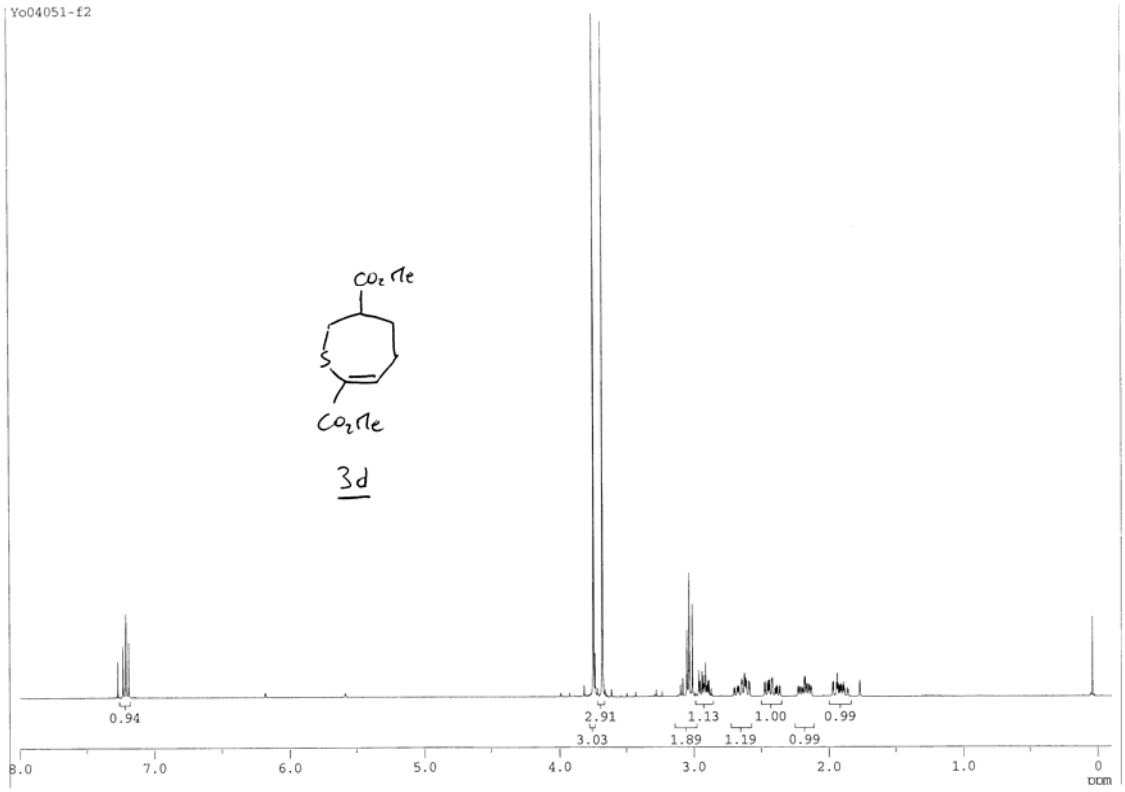
The ellipsoids in the ORTEP view of **A** are at 30% probability. The CIF for **A** is available free of charge via the Internet at http://pubs.acs.org or http://www.ccdc.cam.ac.uk under the CCDC number 615710.

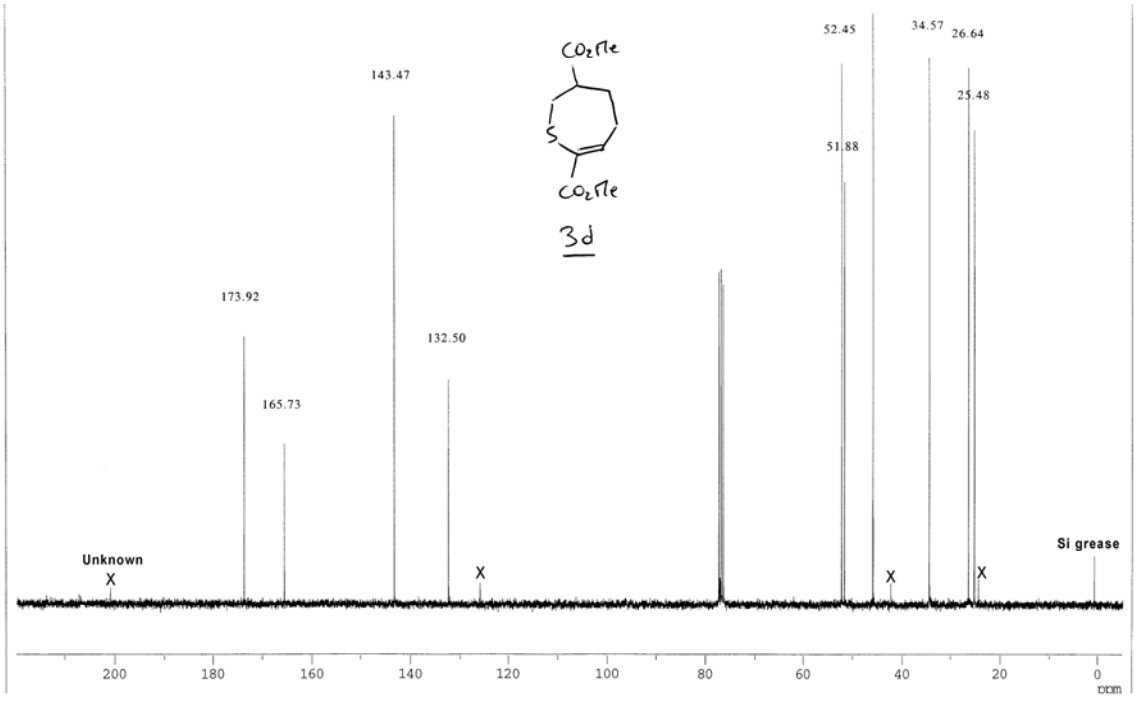

Yo04052-f1
CO2Me
O
CO2Me
OTMS
2 dia ~ (3:1)
3a (R=TMS)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

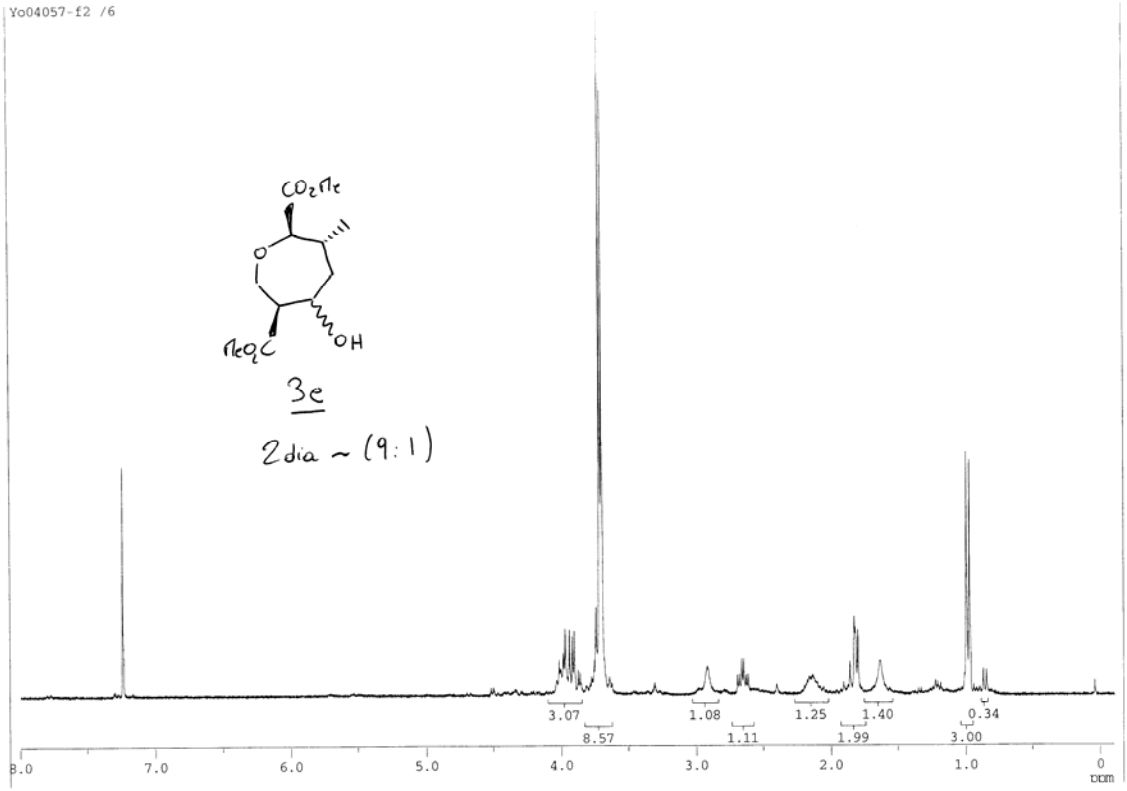

Yo04052-f1 /3
CO2Me
O
CO2Me
OTMS
2 dia ~ (3:1)
3a (R=TMS)
0.092
0.026
76.93
73.08
63.32
55.85
51.95
51.70
25.38
32.31
76.49
68.07
62.05
51.64
51.88
54.24
30.42
23.11
172.82
172.31
200
180
160
140
120
100
80
60
40
20
0
ppm

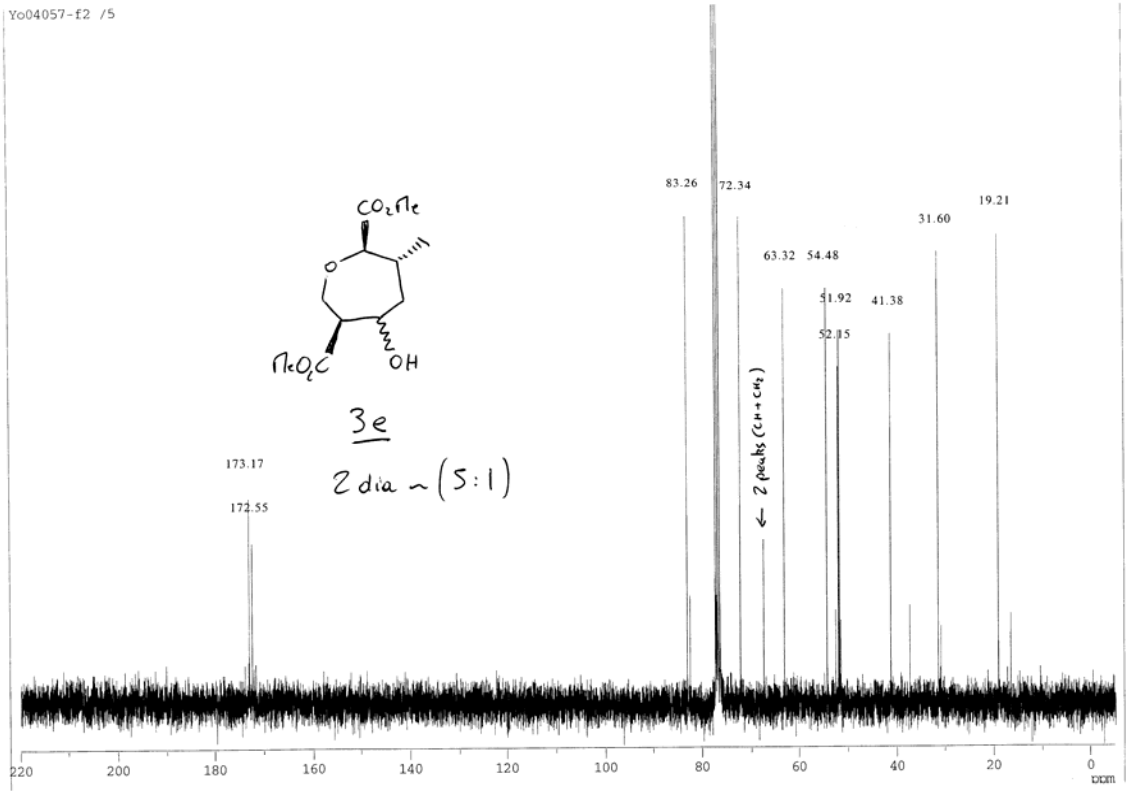

Yo04055-f1
OMe
CO2Me
CO2Me
3c (R=Me)
1.00
0.94
2.89
0.97
6.79
3.08
0.97
1.07
1.00
2.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

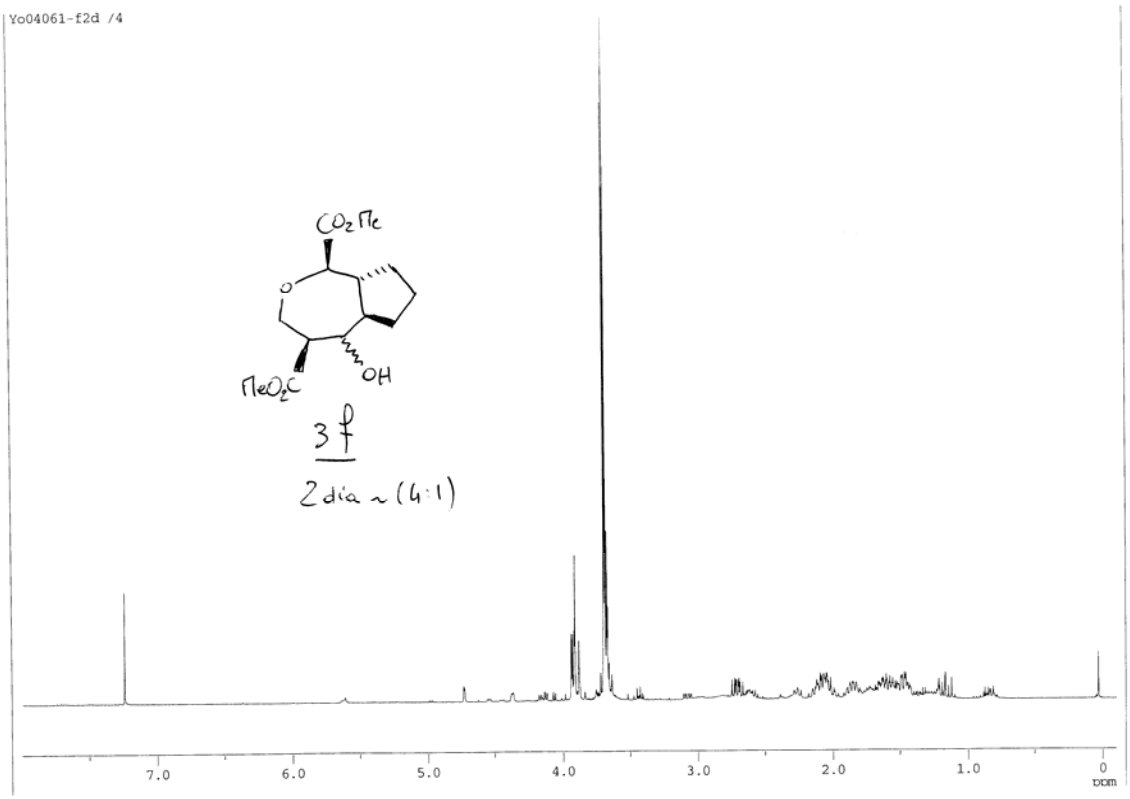

Yo04055-f1 /2
OMe
CO2Me
CO2Me
3c (R=Me)
174.21
165.98
160.69
146.92
138.54
133.44
129.97
104.31
108.00
101.58
55.08
51.25
42.10
25.18
25.31
220
200
180
160
140
120
100
80
60
40
20
0
ppm

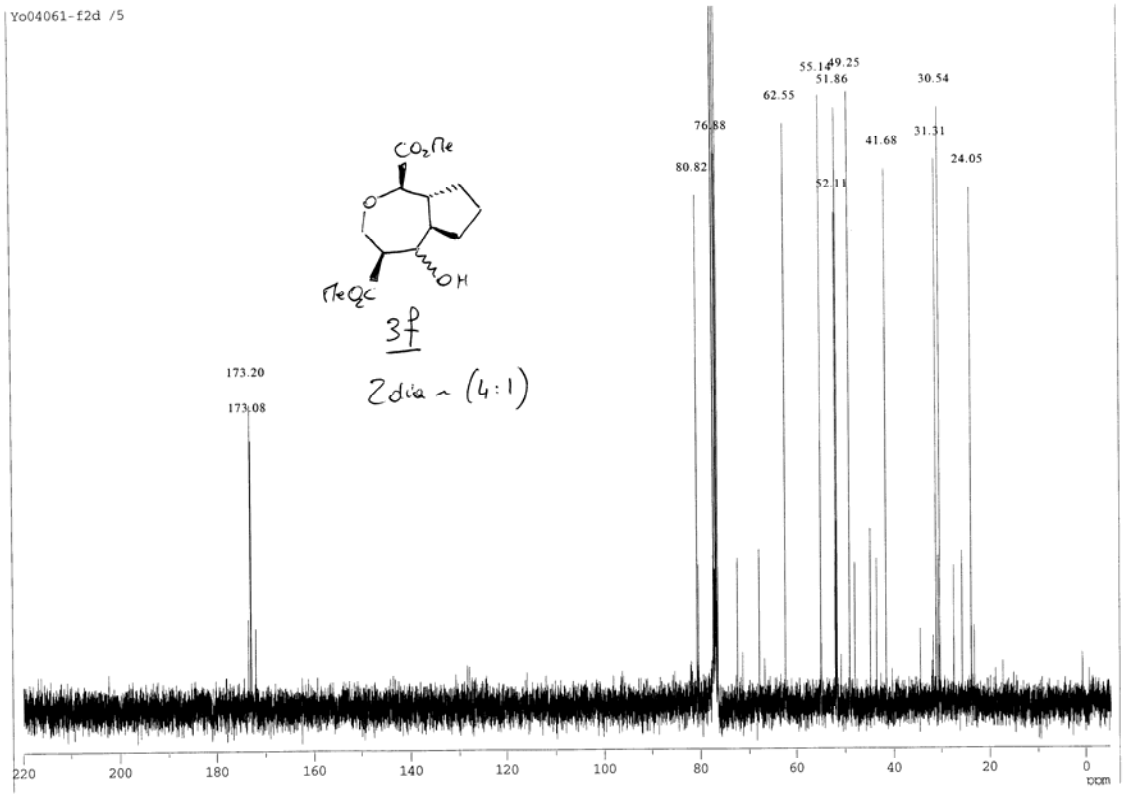

Yo04051-f2
CO2Me
CO2Me
3d
0.94
2.91
3.03
1.13
1.89
1.00
1.19
0.99
0.99
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

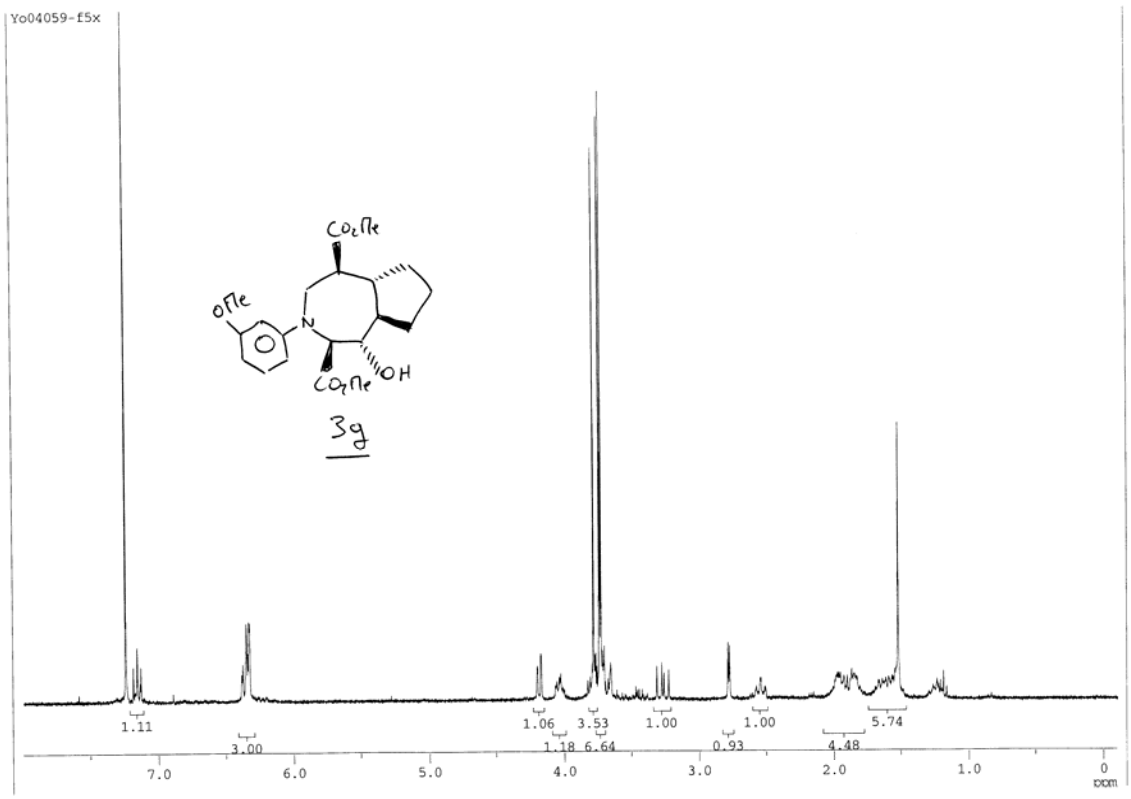

CO2Me
CO2Me
3d
143.47
173.92
165.73
132.50
52.45
51.88
34.57
26.64
25.48
Unknown
X
X
X
X
Si grease
200
180
160
140
120
100
80
60
40
20
0
ppm

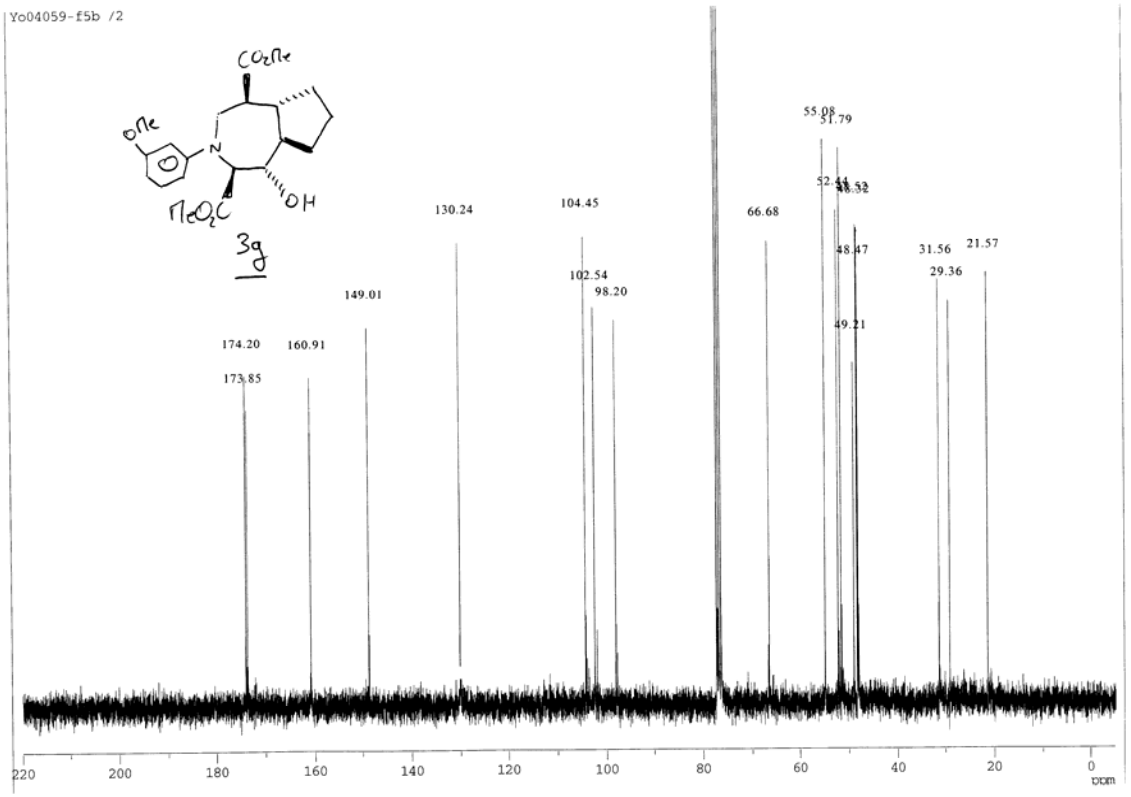

Yo04057-f2 /6
CO2Me
MeO2C
OH
3e
2 dia ~ (9:1)
3.07
8.57
1.08
1.11
1.25
1.99
1.40
0.34
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

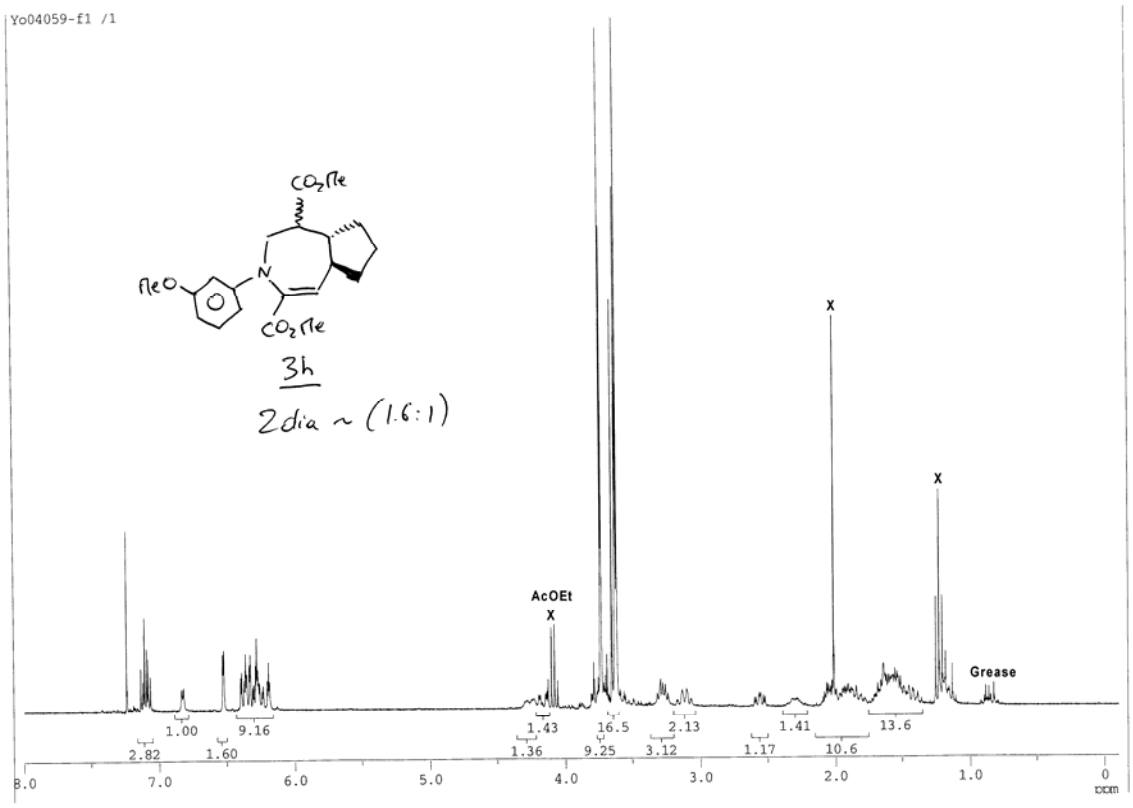

Yo04057-f2 /5
CO2Me
MeO2C
OH
3e
2 dia ~ (5:1)
173.17
172.55
83.26
72.34
63.32
54.48
51.92
52.15
41.38
31.60
19.21
← 2 peaks (CH + CH2)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

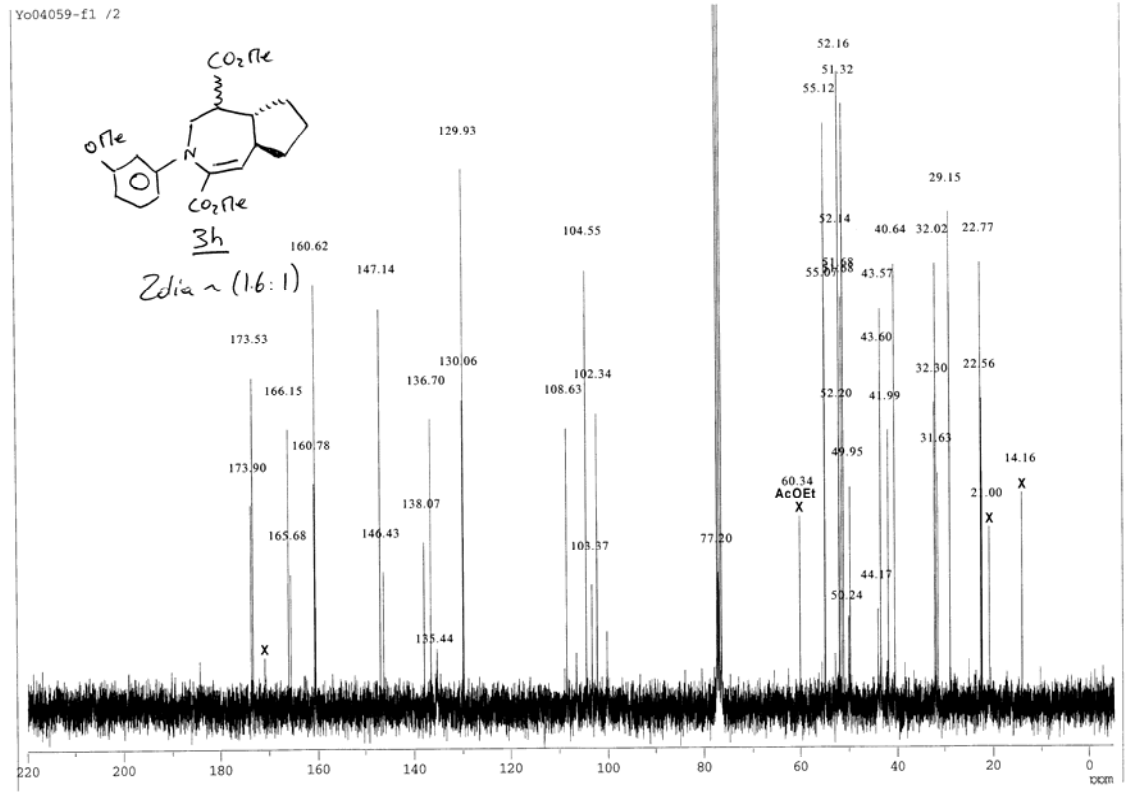

Yo04061-f2d /4
3f
2 dia ~ (4:1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

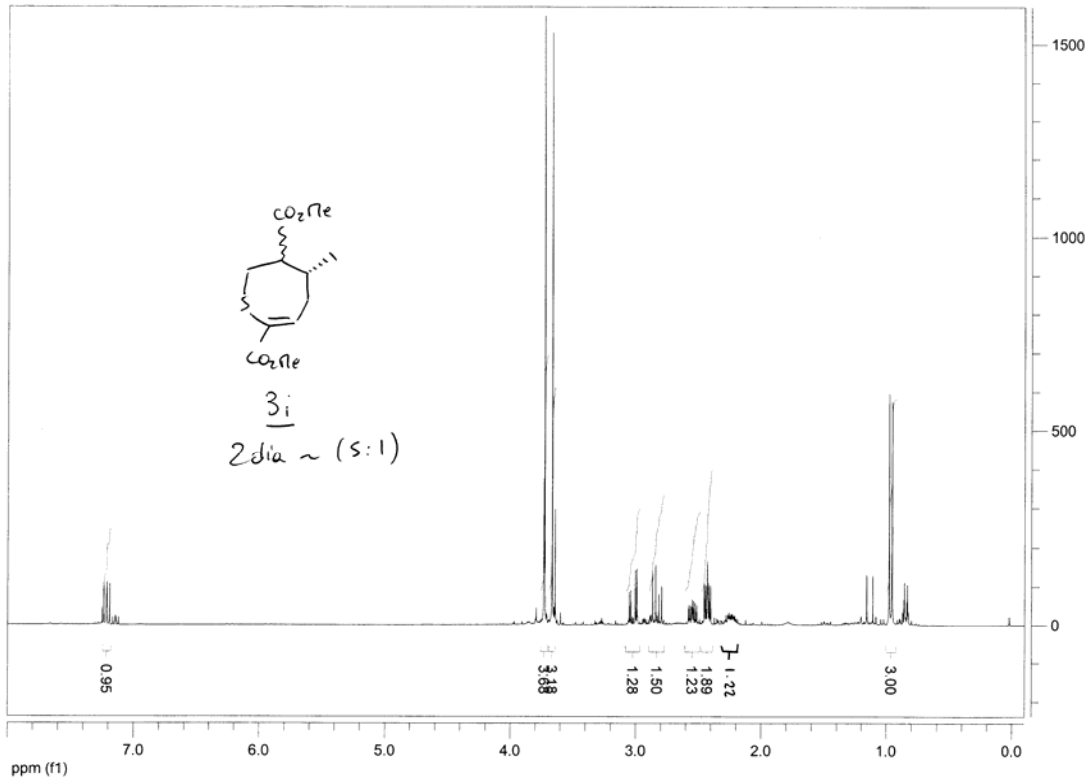

Yo04061-f2d /5
3f
2 dia ~ (4:1)
173.20
173.08
80.82
76.88
62.55
55.14
51.86
49.25
52.11
41.68
31.31
30.54
24.05
220
200
180
160
140
120
100
80
60
40
20
0
ppm

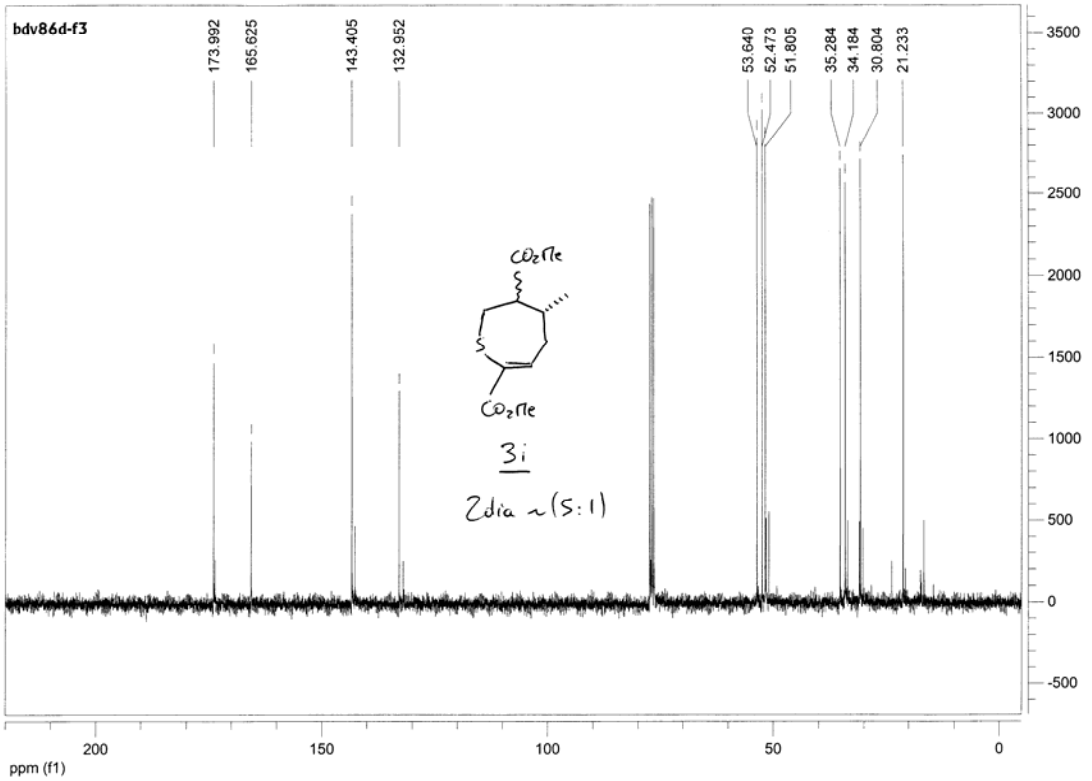

Yo04059-f5x
3g
1.11
3.00
1.06
1.18
3.53
6.64
1.00
0.93
1.00
4.48
5.74
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

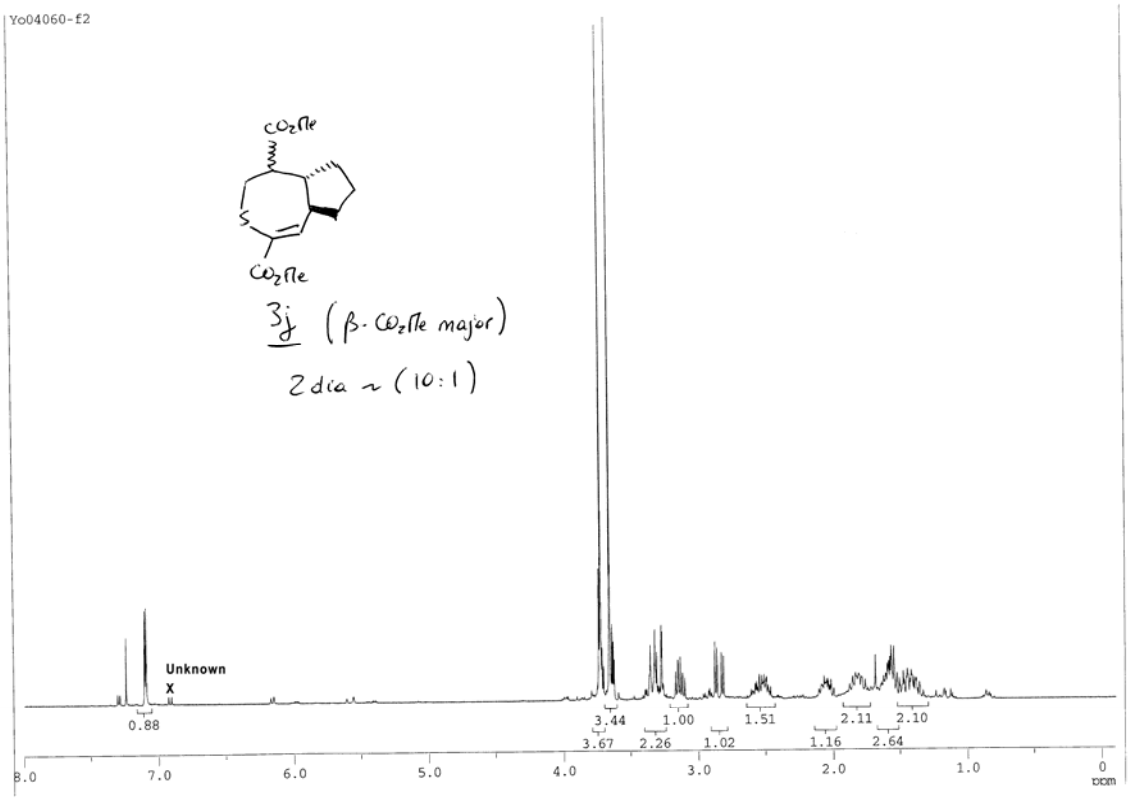

Yo04059-f5b /2
3g
174.20
173.85
160.91
149.01
130.24
104.45
102.54
98.20
66.68
55.08
51.79
52.44
48.47
49.21
31.56
29.36
21.57
220
200
180
160
140
120
100
80
60
40
20
0
ppm

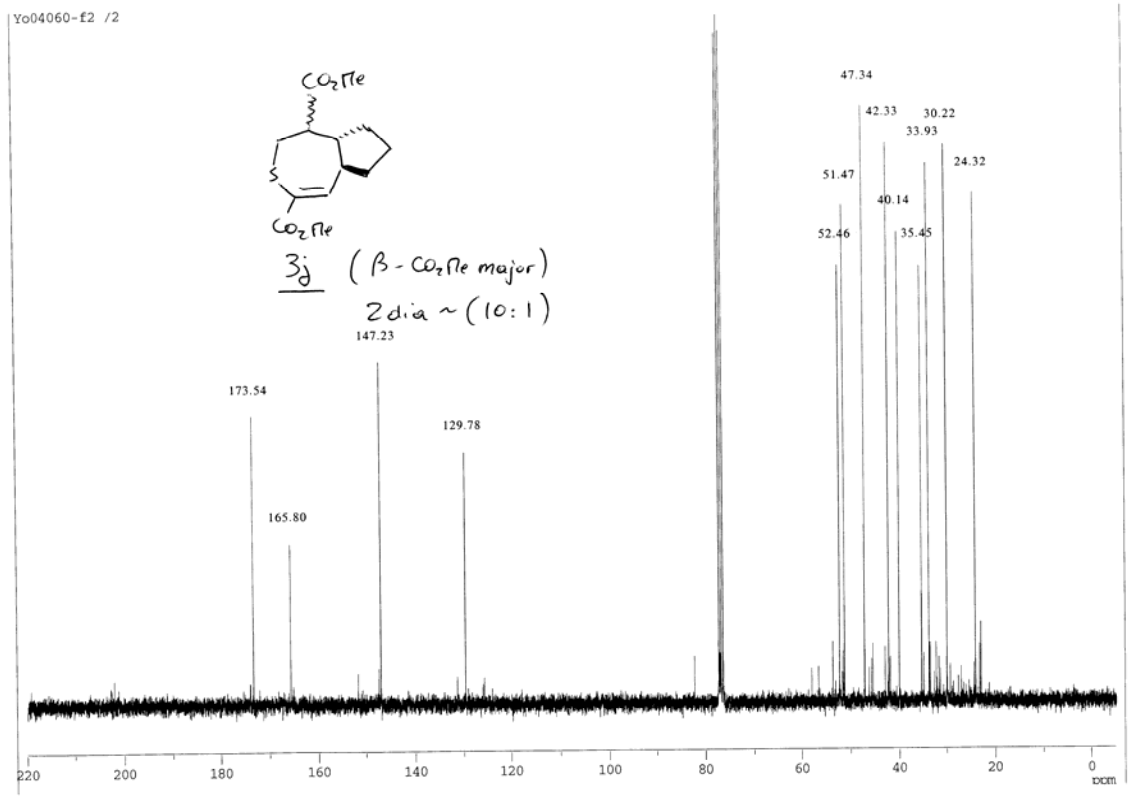

Yo04059-f1 /1
3h
2dia ~ (1.6:1)
AcOEt
X
X
X
Grease
1.00
9.16
2.82
1.60
1.43
16.5
2.13
1.41
13.6
1.36
9.25
3.12
1.17
10.6
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

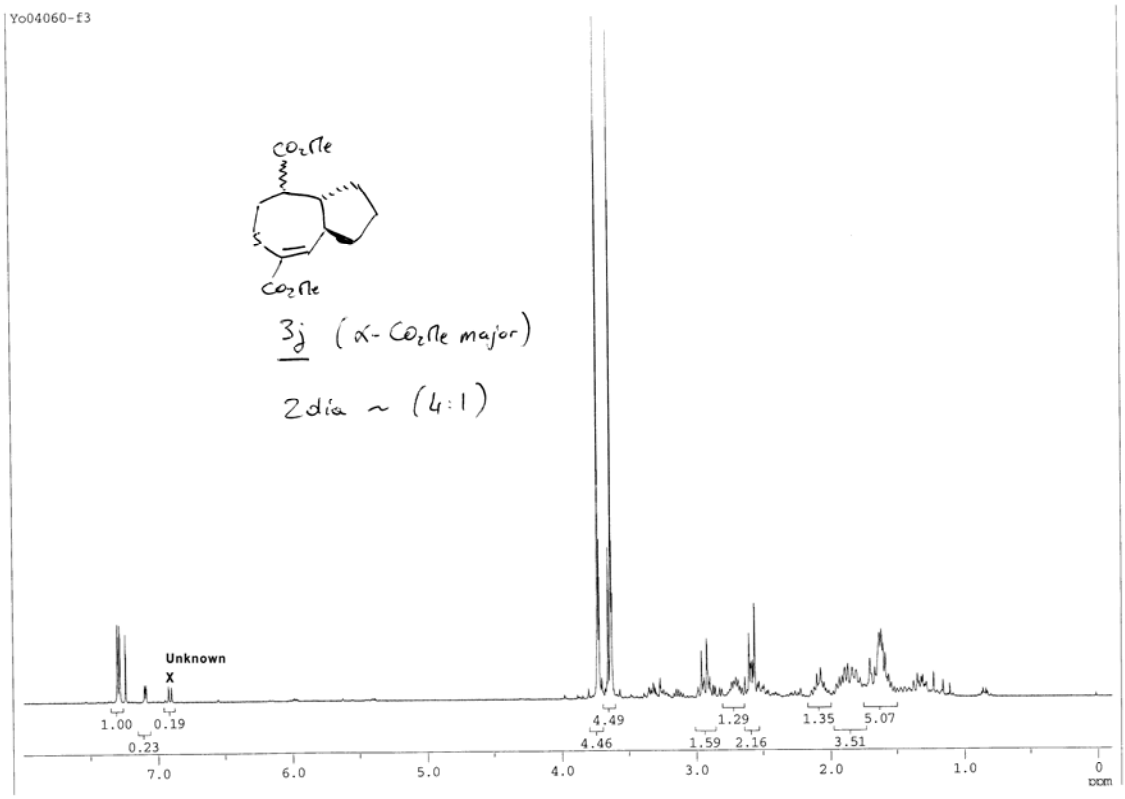

Yo04059-f1 /2
3h
2dia ~ (1.6:1)
52.16
51.32
55.12
129.93
29.15
52.14
40.64
32.02
22.77
104.55
160.62
147.14
43.57
173.53
43.60
130.06
136.70
102.34
108.63
32.30
22.56
166.15
52.20
41.99
160.78
31.63
49.95
14.16
173.90
60.34
AcOEt
X
2.00
X
X
138.07
165.68
146.43
103.37
77.20
44.17
52.24
135.44
X
220
200
180
160
140
120
100
80
60
40
20
0
ppm

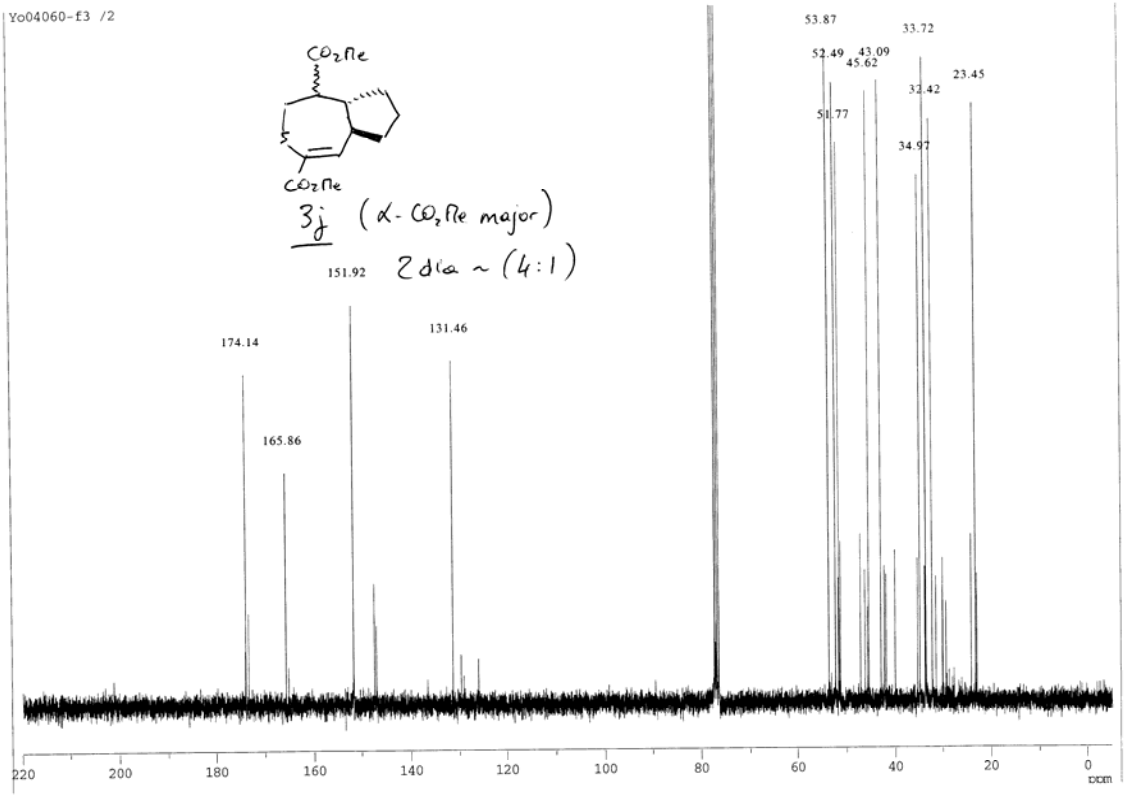

CO2Me
CO2Me
3i
2dia ~ (5:1)
0.95
3.18
3.08
1.28
1.50
1.89
1.23
1.22
3.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)
1500
1000
500
0

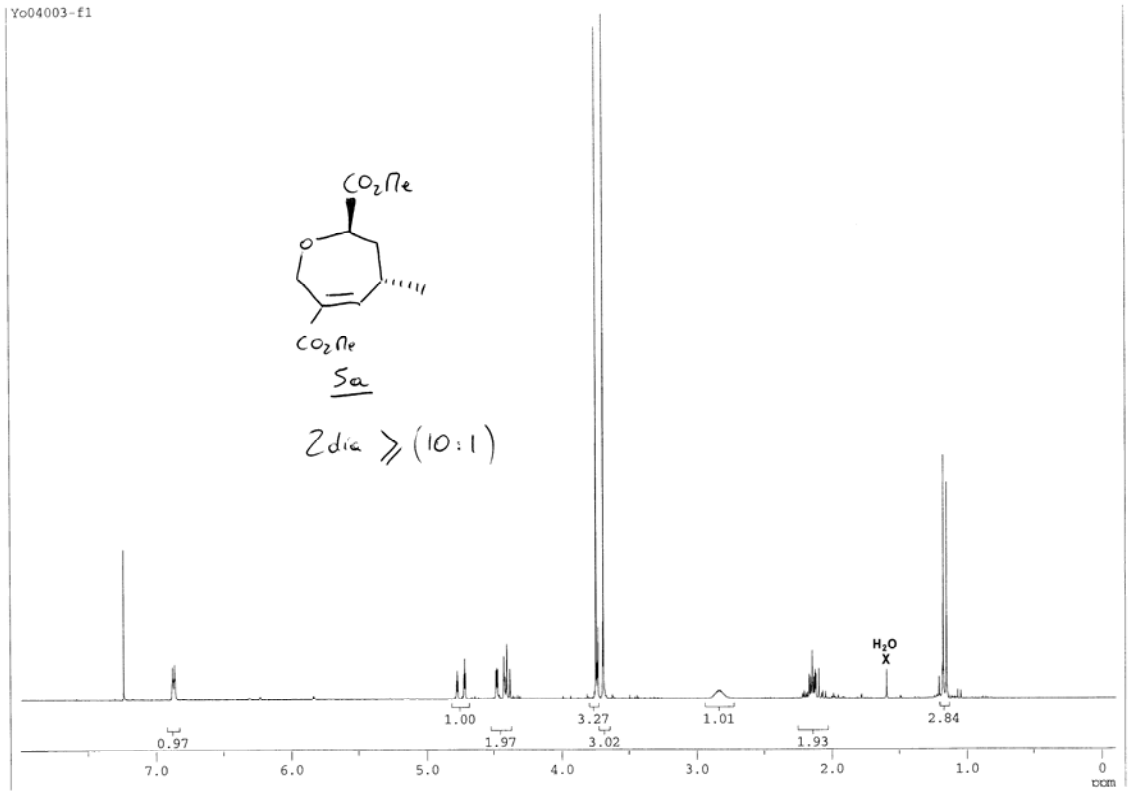

bdv86d-f3
173.992
165.625
143.405
132.952
53.640
52.473
51.805
35.284
34.184
30.804
21.233
CO2Me
CO2Me
3i
2dia ~(5:1)
200
150
100
50
0
ppm (f1)
3500
3000
2500
2000
1500
1000
500
0
-500

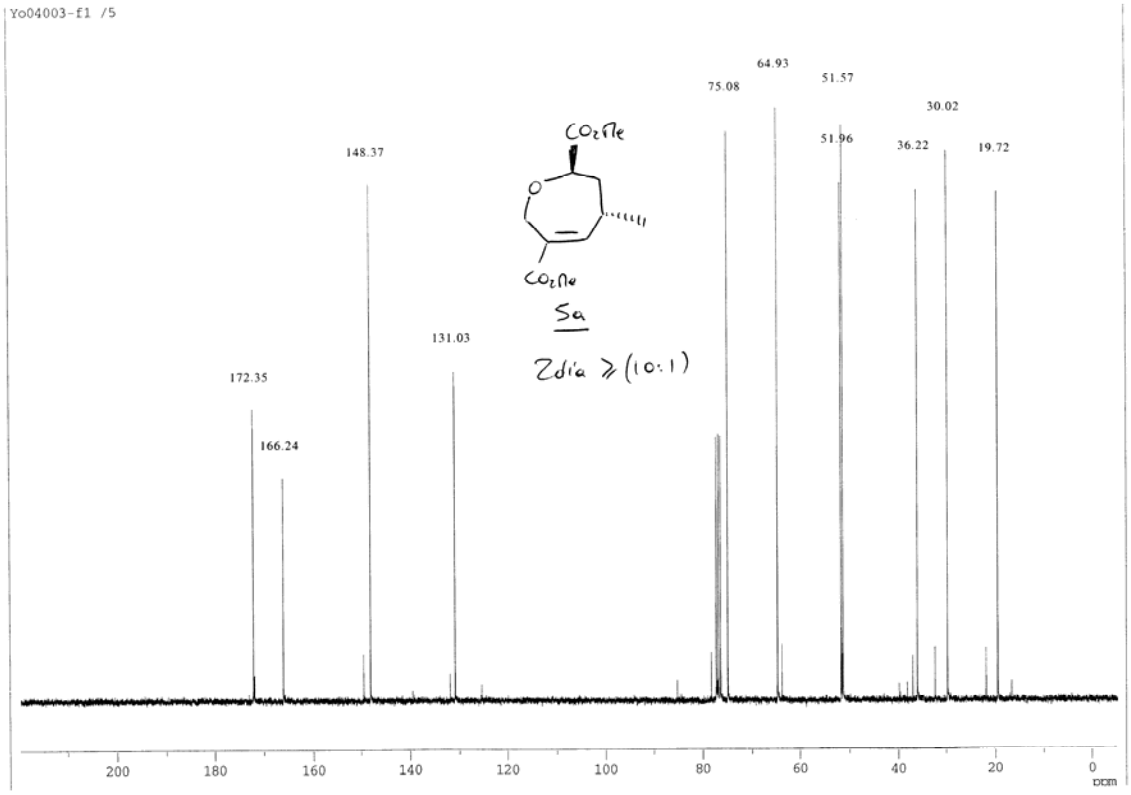

Yo04060-f2
CO2Me
CO2Me
3j (β-CO2Me major)
2 dia ~ (10:1)
Unknown
X
0.88
3.44
3.67
1.00
2.26
1.51
1.02
2.11
1.16
2.10
2.64
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

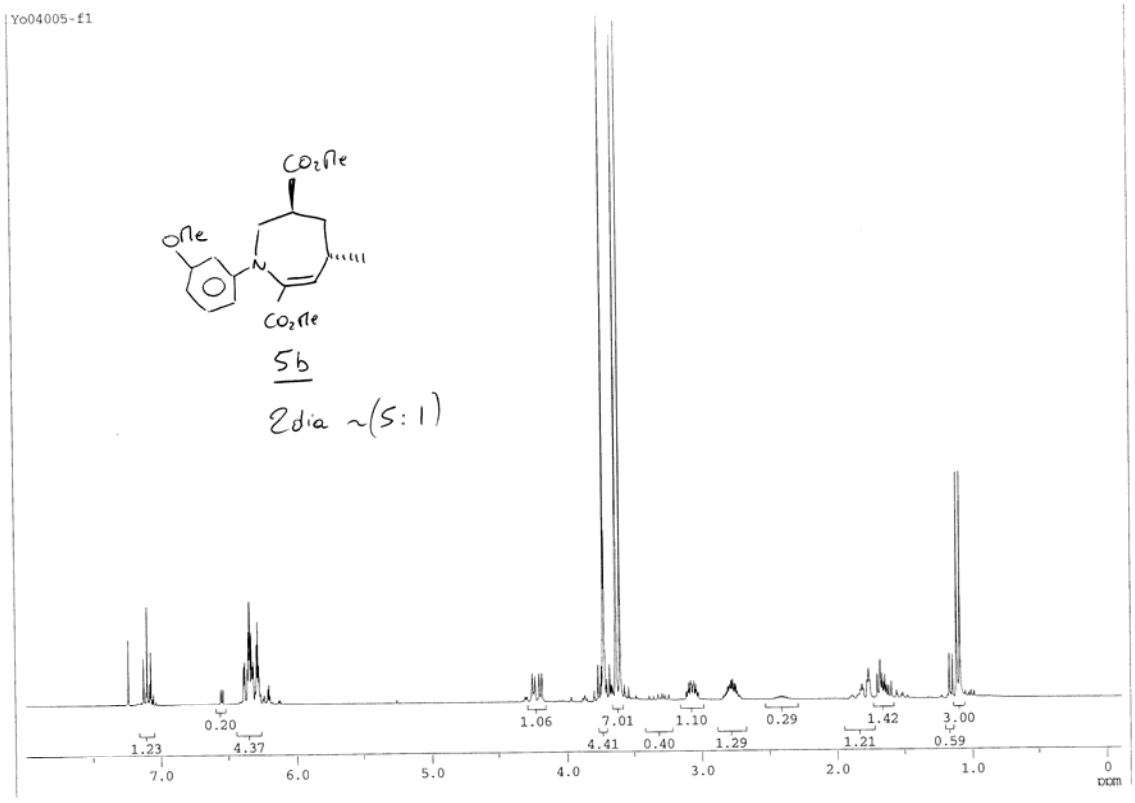

Yo04060-f2 /2
CO2Me
CO2Me
3j (β-CO2Me major)
2 dia ~ (10:1)
147.23
173.54
165.80
129.78
47.34
42.33
30.22
33.93
24.32
51.47
40.14
52.46
35.45
220
200
180
160
140
120
100
80
60
40
20
0
ppm

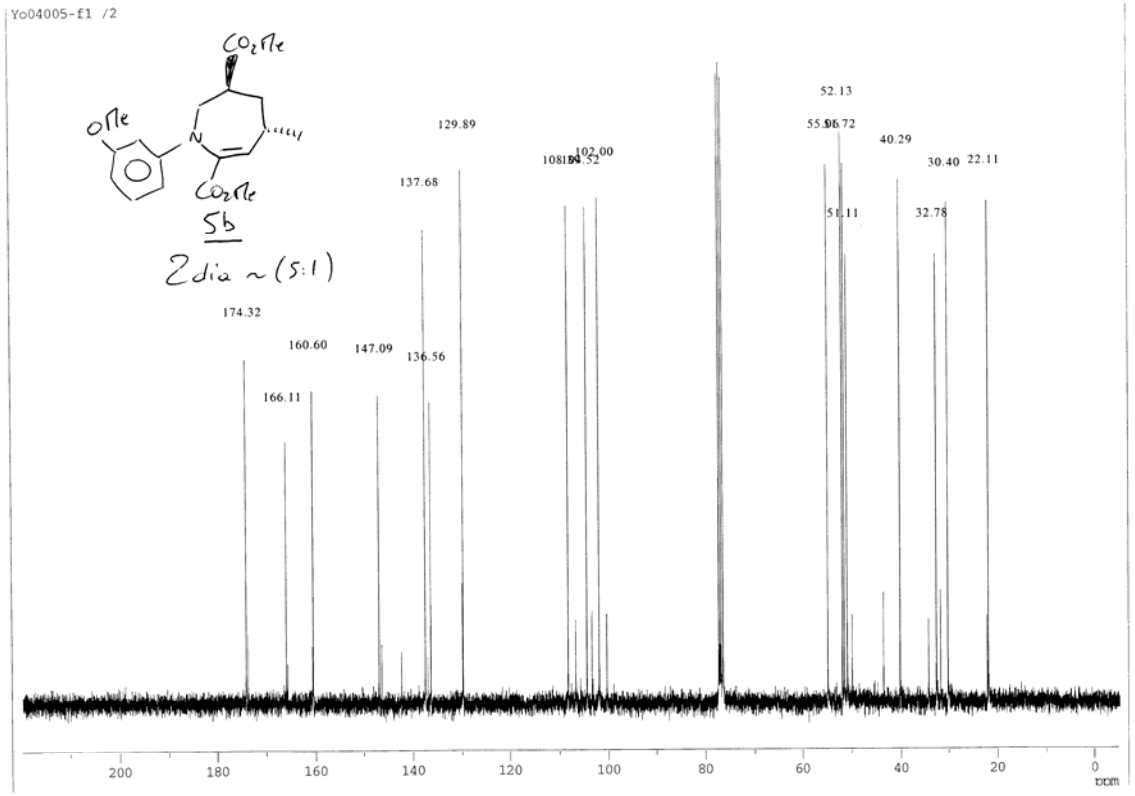

Yo04060-f3
CO2Me
CO2Me
3j (α-CO2Me major)
2 dia ~ (4:1)
Unknown
X
1.00
0.19
0.23
4.49
4.46
1.29
1.59
2.16
1.35
5.07
3.51
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

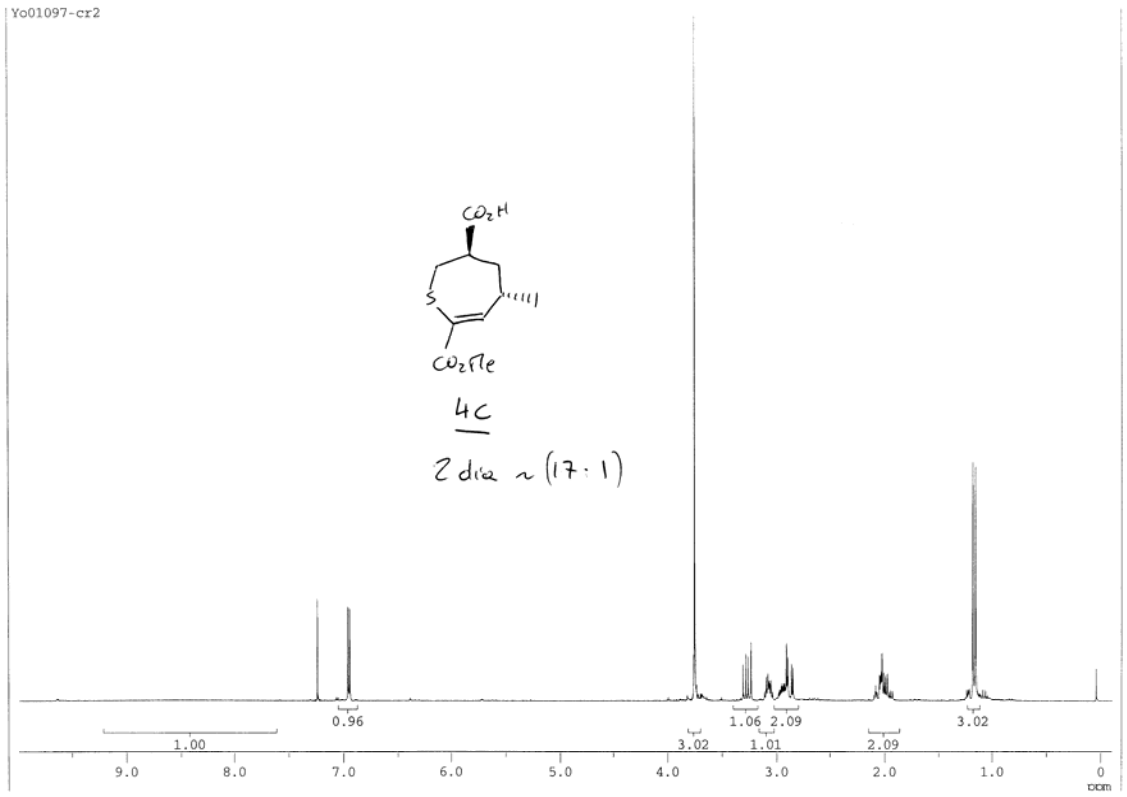

Yo04060-f3 /2
CO2Me
CO2Me
3j (α-CO2Me major)
2 dia ~ (4:1)
151.92
174.14
165.86
131.46
53.87
52.49
43.09
45.62
33.72
23.45
32.42
51.77
34.97
220
200
180
160
140
120
100
80
60
40
20
0
ppm

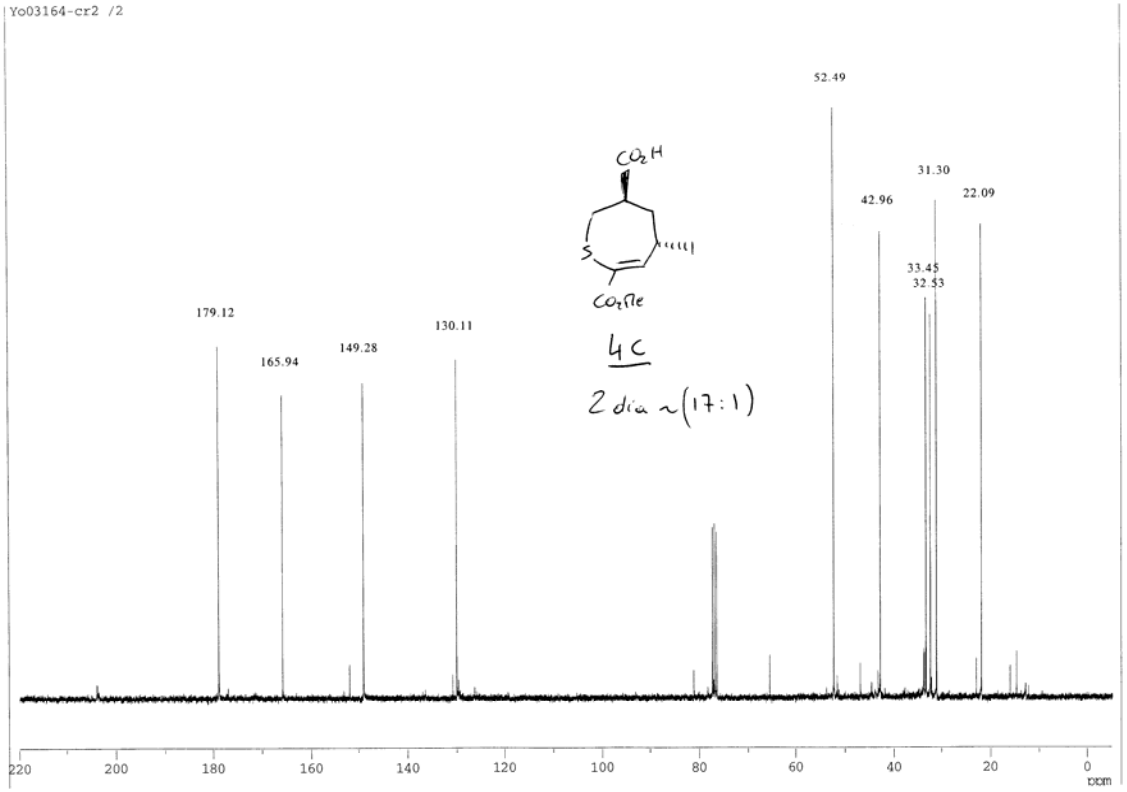

Yo04003-f1
CO2Me
O
CO2Me
5a
2dia ≫ (10:1)
H2O
X
0.97
1.00
1.97
3.27
3.02
1.01
1.93
2.84
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

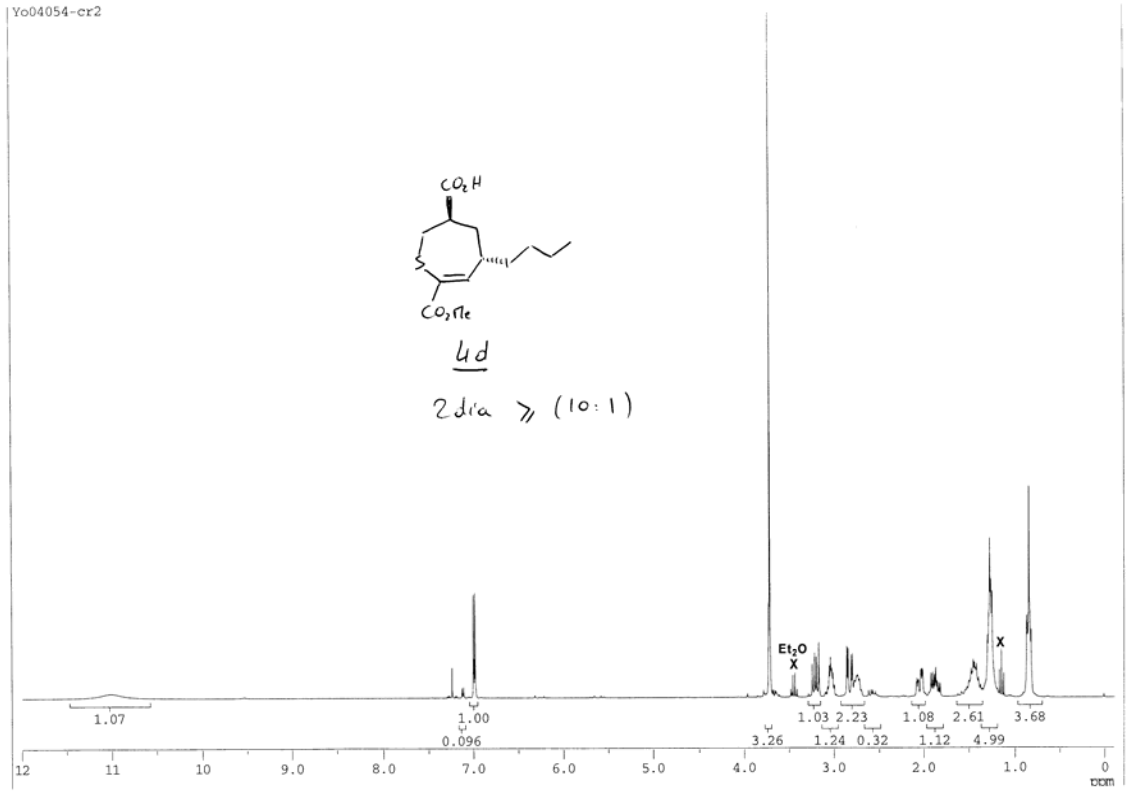

Yo04003-f1 /5
CO2Me
O
CO2Me
5a
2dia ≫ (10:1)
172.35
166.24
148.37
131.03
75.08
64.93
51.57
51.96
36.22
30.02
19.72
200
180
160
140
120
100
80
60
40
20
0
ppm

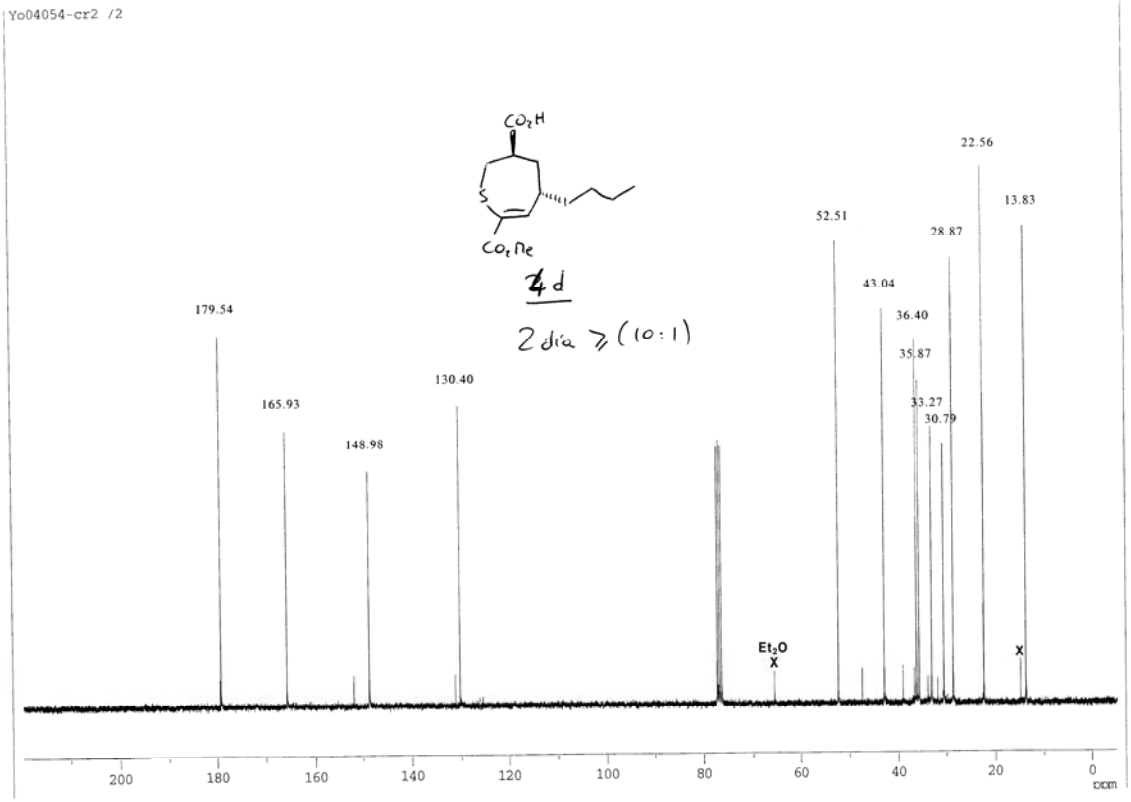

Yo04005-f1
5b
2dia ~(5:1)
0.20
1.23
4.37
1.06
7.01
4.41
1.10
0.40
1.29
0.29
1.42
1.21
3.00
0.59
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

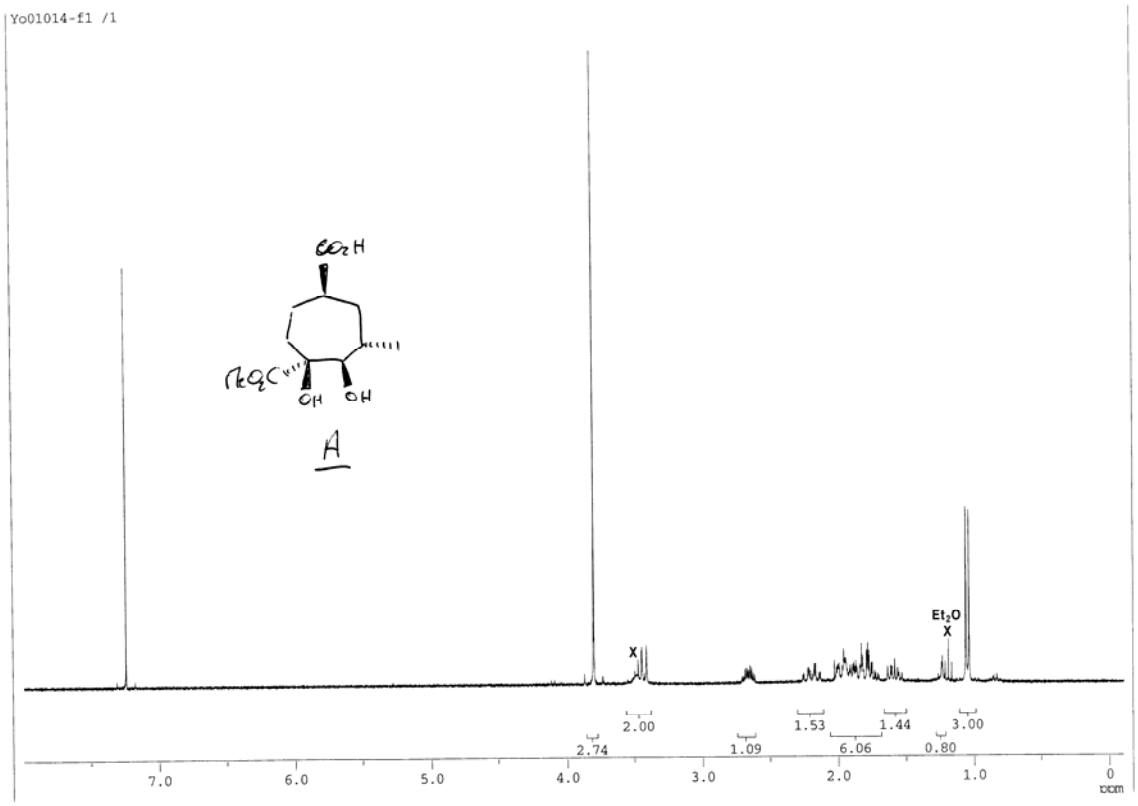

Yo04005-f1 /2
5b
2dia ~(5:1)
174.32
166.11
160.60
147.09
137.68
136.56
129.89
108.52
102.00
52.13
51.11
40.29
32.78
30.40
22.11
200
180
160
140
120
100
80
60
40
20
0
ppm

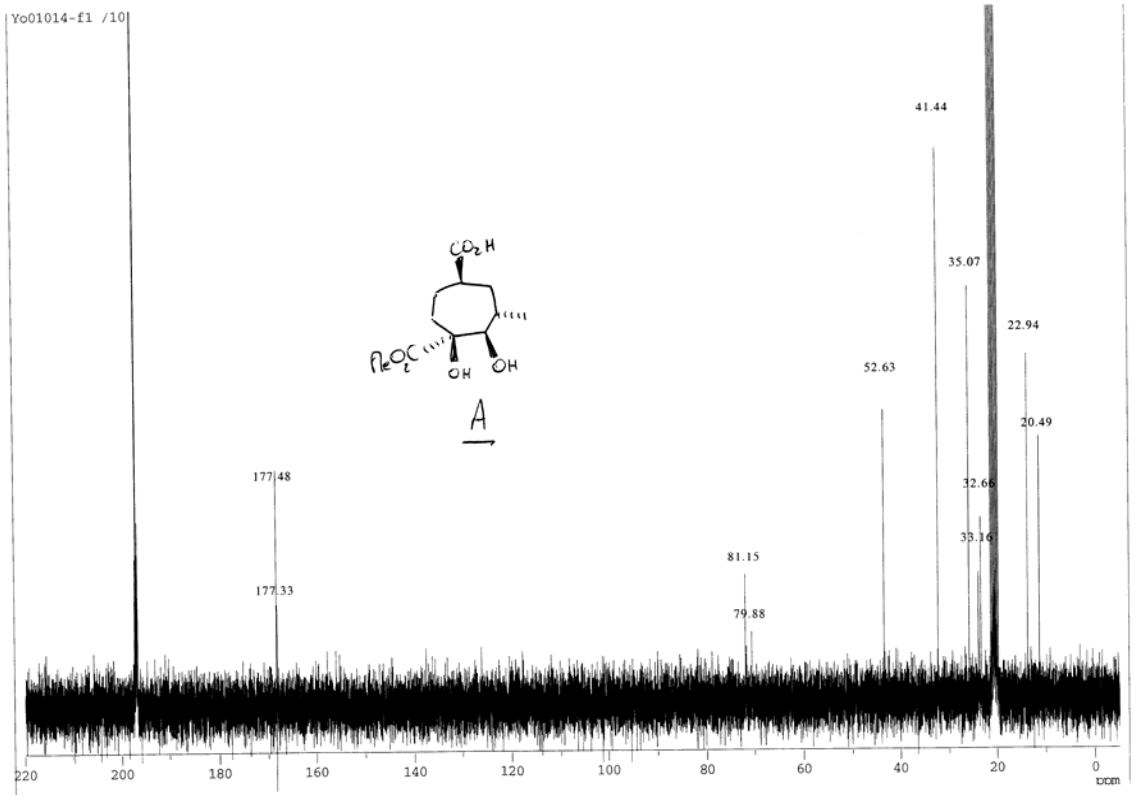

Yo01097-cr2
CO2H
S
CO2Me
4c
2 dia ~ (17:1)
0.96
1.06
2.09
3.02
1.00
3.02
1.01
2.09
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

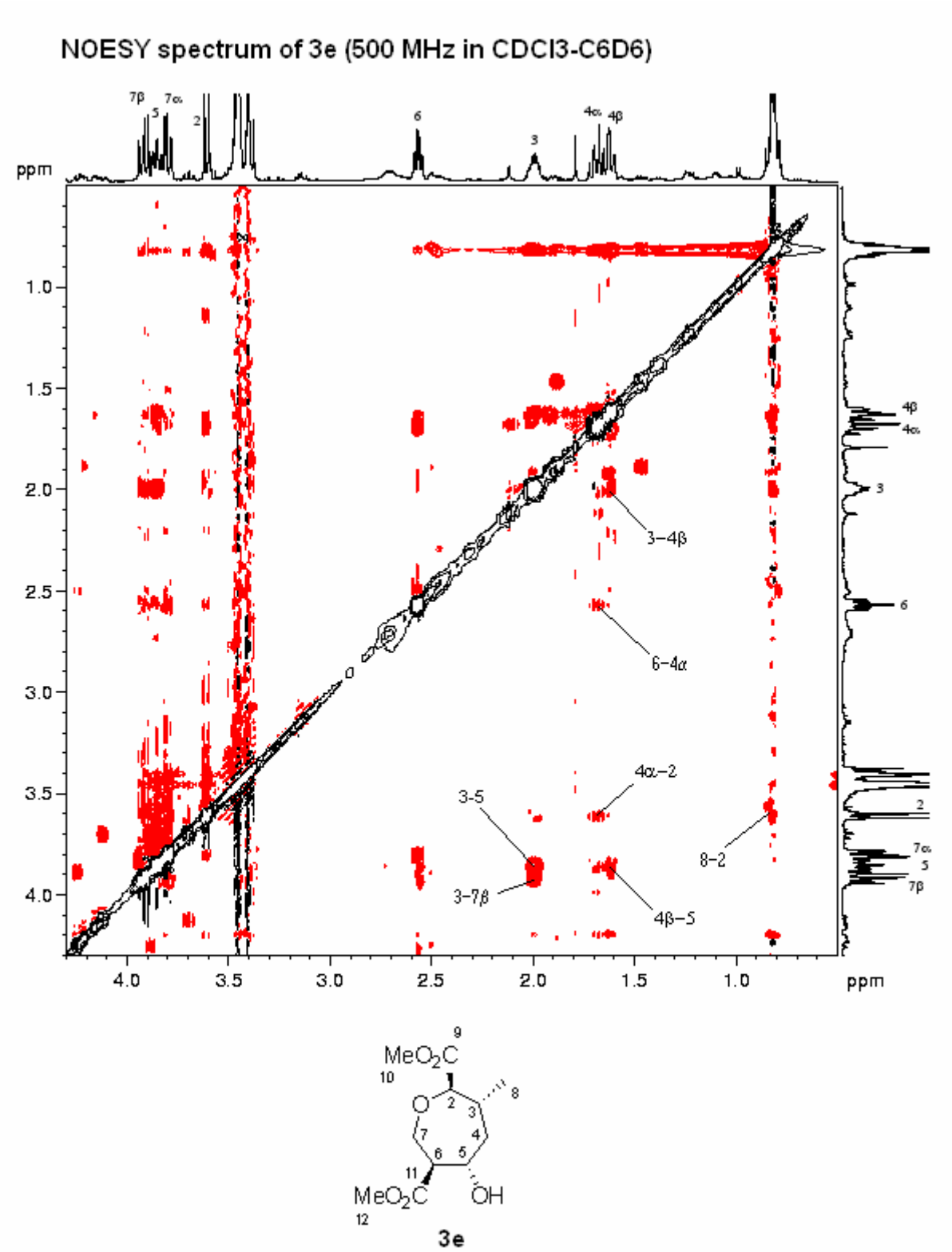

Yo03164-cr2 /2
52.49
31.30
42.96
22.09
33.45
32.53
179.12
165.94
149.28
130.11
CO2H
S
CO2Me
4c
2 dia ~ (17:1)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Yo04054-cr2
CO2H
CO2Me
4d
2 dia ≥ (10:1)
Et2O
X
X
1.07
1.00
0.096
1.03
2.23
1.08
2.61
3.68
3.26
1.24
0.32
1.12
4.99
12
11
10
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm


Yo04054-cr2 /2
CO2H
CO2Me
4d
2 dia ≥ (10:1)
179.54
165.93
148.98
130.40
52.51
43.04
36.40
35.87
33.27
30.79
28.87
22.56
13.83
Et2O
X
X
200
180
160
140
120
100
80
60
40
20
0
ppm


Yo01014-f1 /1
CO2H
OH OH
A
X
Et2O
X
2.00
1.53
1.44
3.00
2.74
1.09
6.06
0.80
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

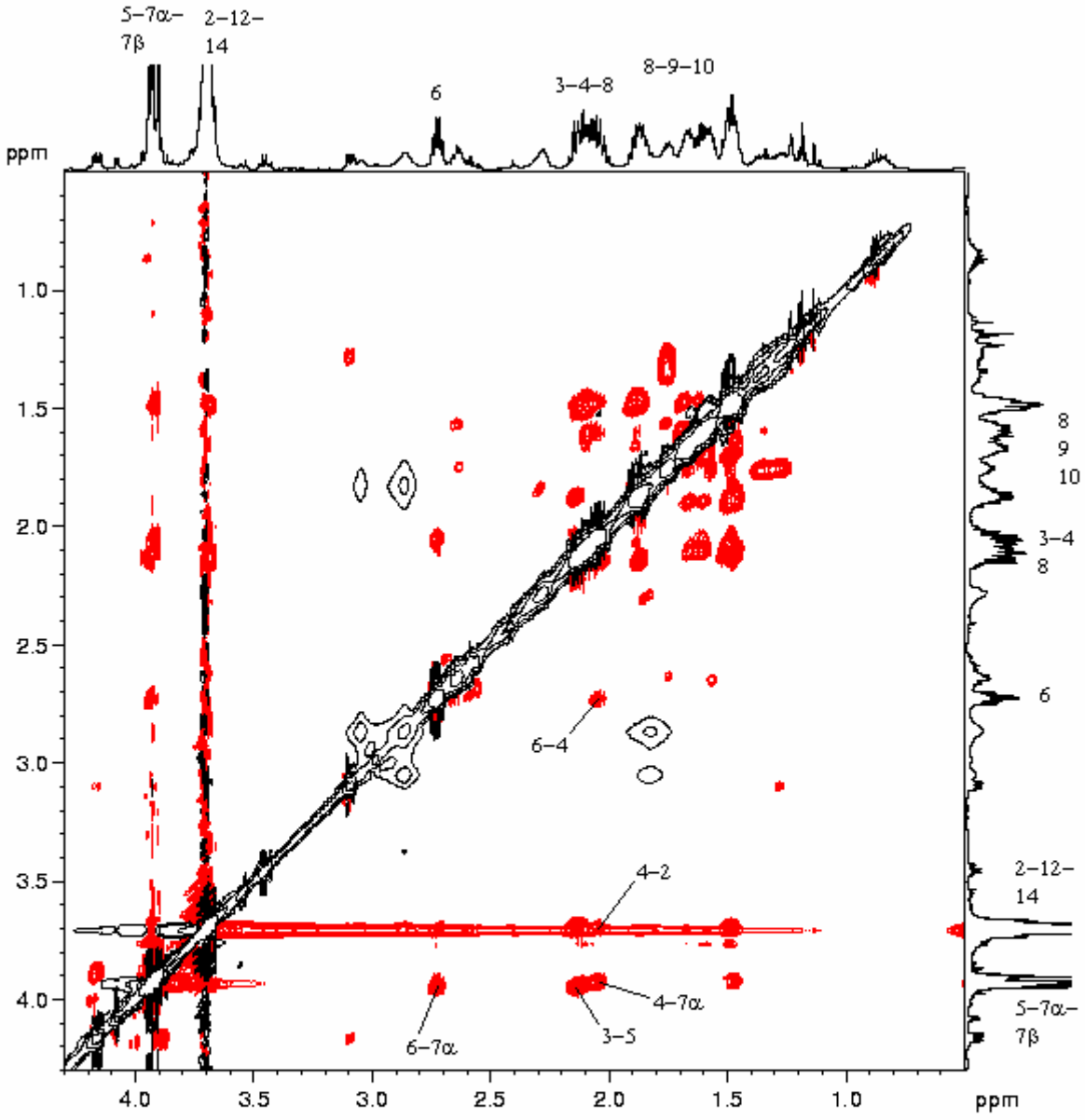

Yo01014-f1 /10
CO2H
OH OH
A
41.44
35.07
22.94
52.63
20.49
177.48
32.66
33.16
81.15
177.33
79.88
220
200
180
160
140
120
100
80
60
40
20
0
ppm

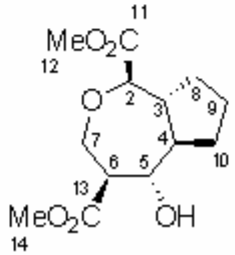

NOESY spectrum of 3e (500 MHz in CDCl3-C6D6)
ppm
7β
7α
5
2
6
3
4α
4β
1.0
1.5
2.0
2.5
3.0
3.5
4.0
3–4β
6–4α
4α–2
3-5
3–7β
4β–5
8–2
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


MeO2C
9
10
O
2
3
8
7
4
6
5
11
MeO2C
OH
12

**3e**

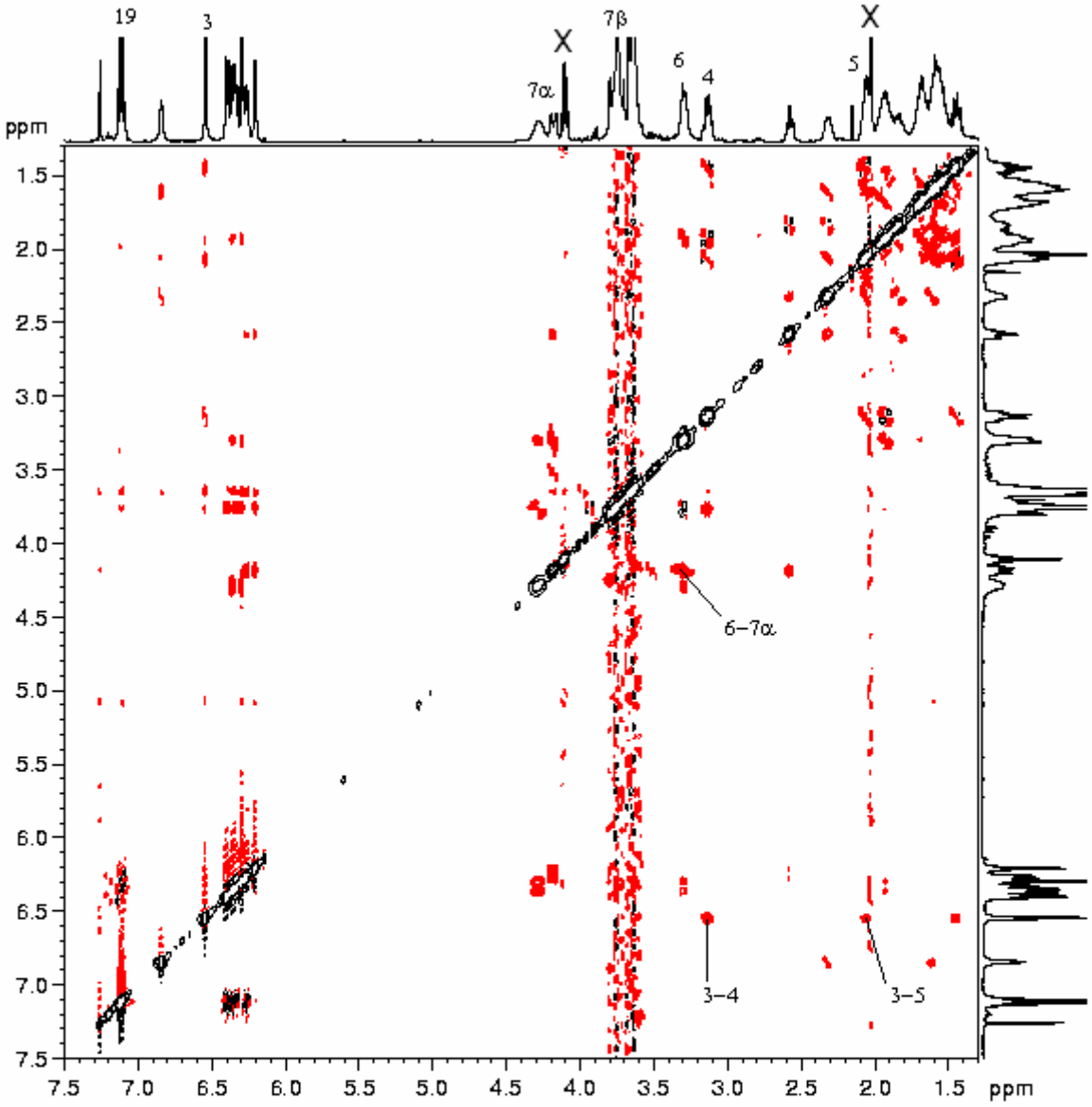
NOESY spectrum of 3f (500 MHz in CDCl3)

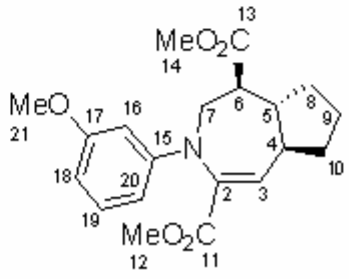


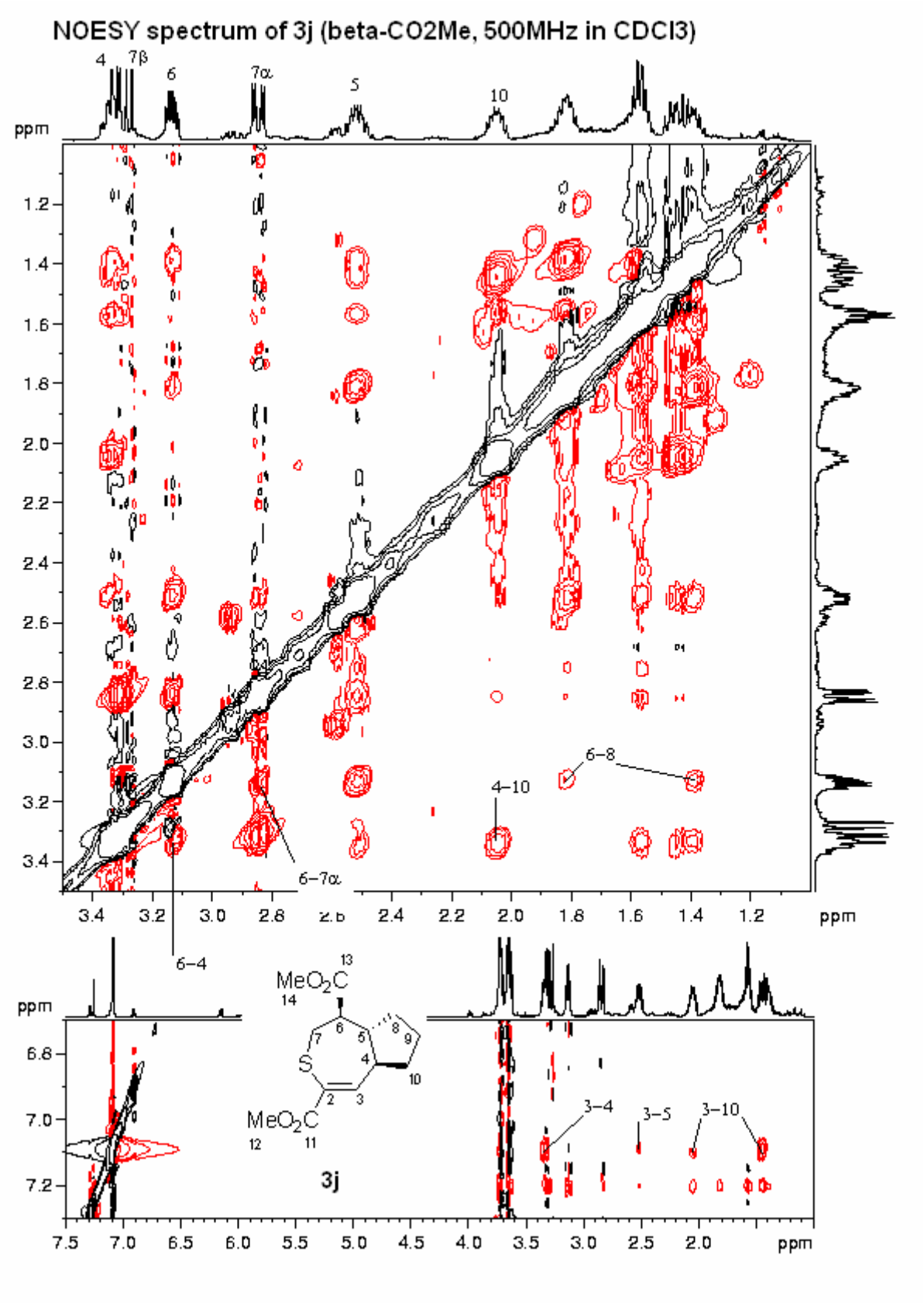

**3f**

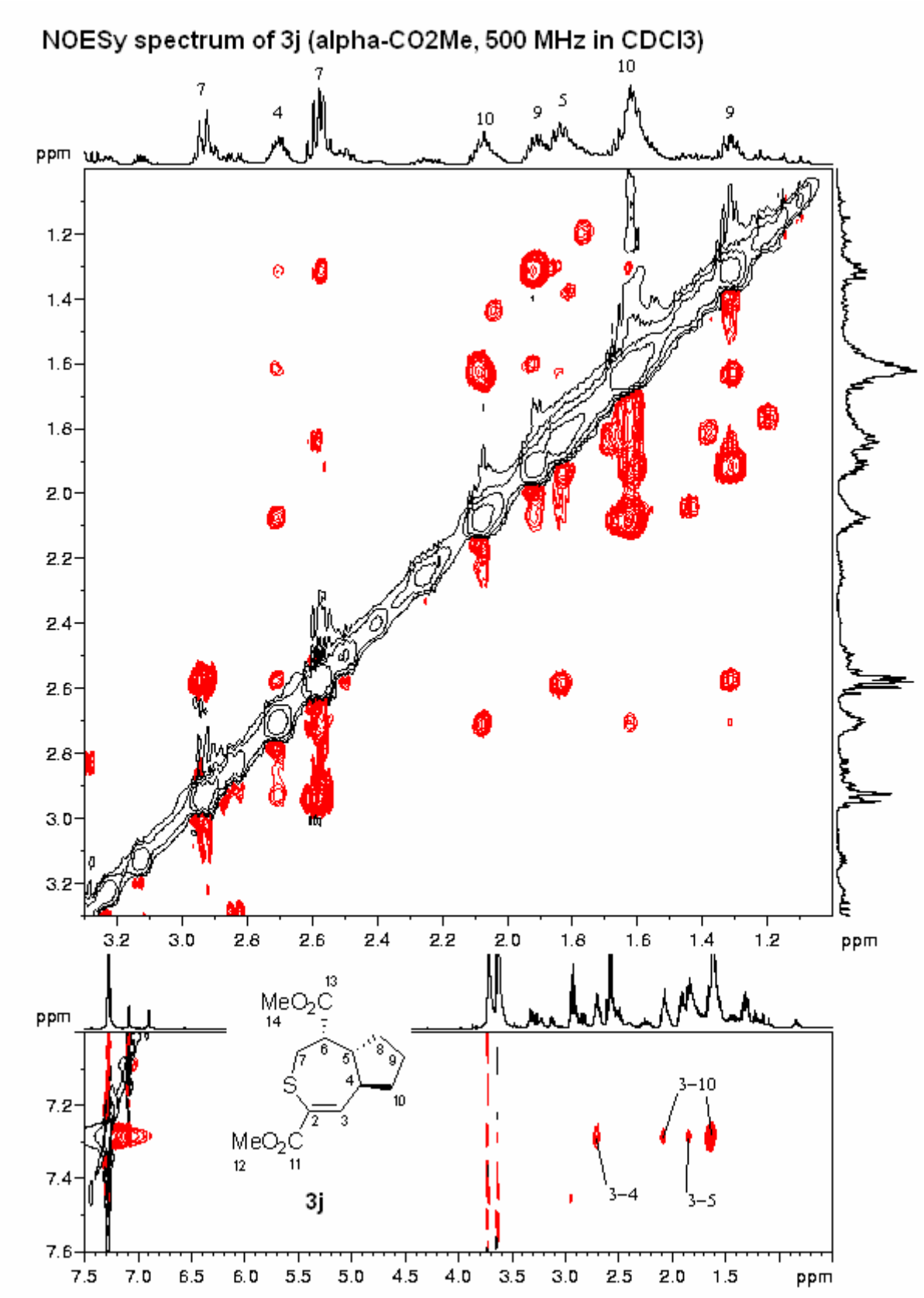
NOESY spectrum of 3h (500 MHz in CDCl3)



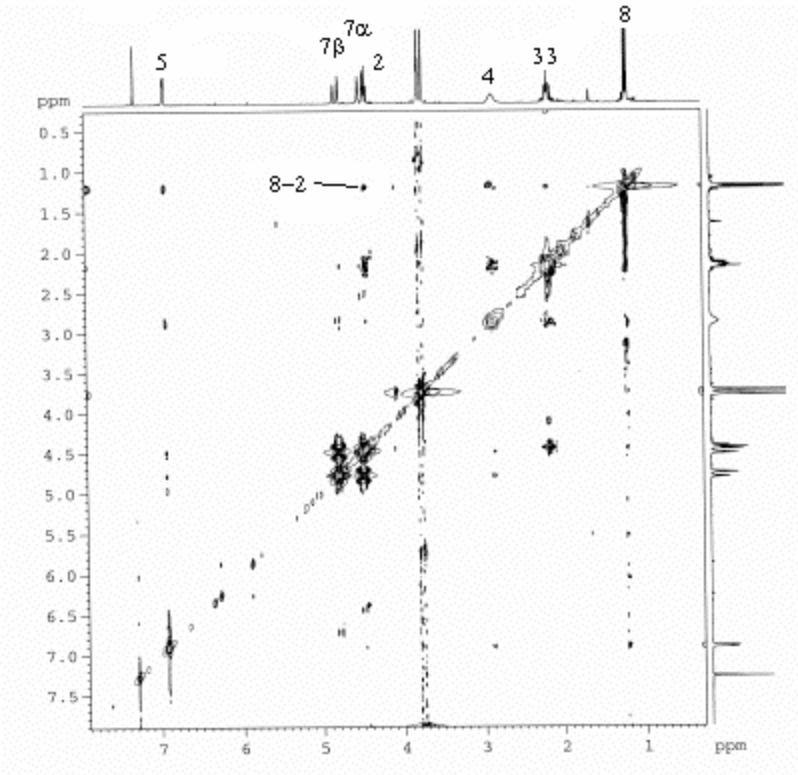



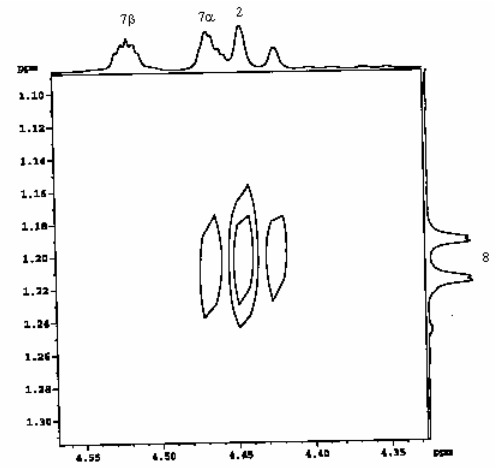

**3h**

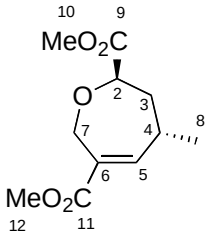

NOESY spectrum of 3j (beta-CO2Me, 500MHz in CDCl3)
4
7β
6
7α
5
10
ppm
6–4
6–7α
4–10
6–8
3–4
3–5
3–10
MeO2C
MeO2C
3j


NOESy spectrum of 3j (alpha-CO2Me, 500 MHz in CDCl3)
ppm
7
4
7
10
9
5
10
9
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 ppm
MeO2C
13
14
MeO2C
12
11
S
1
2
3
4
5
6
7
8
9
10
3j
3–10
3–4
3–5
7.2
7.4
7.6
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm

**NOESY spectrum of 5a (300 MHz, CDCl3)**

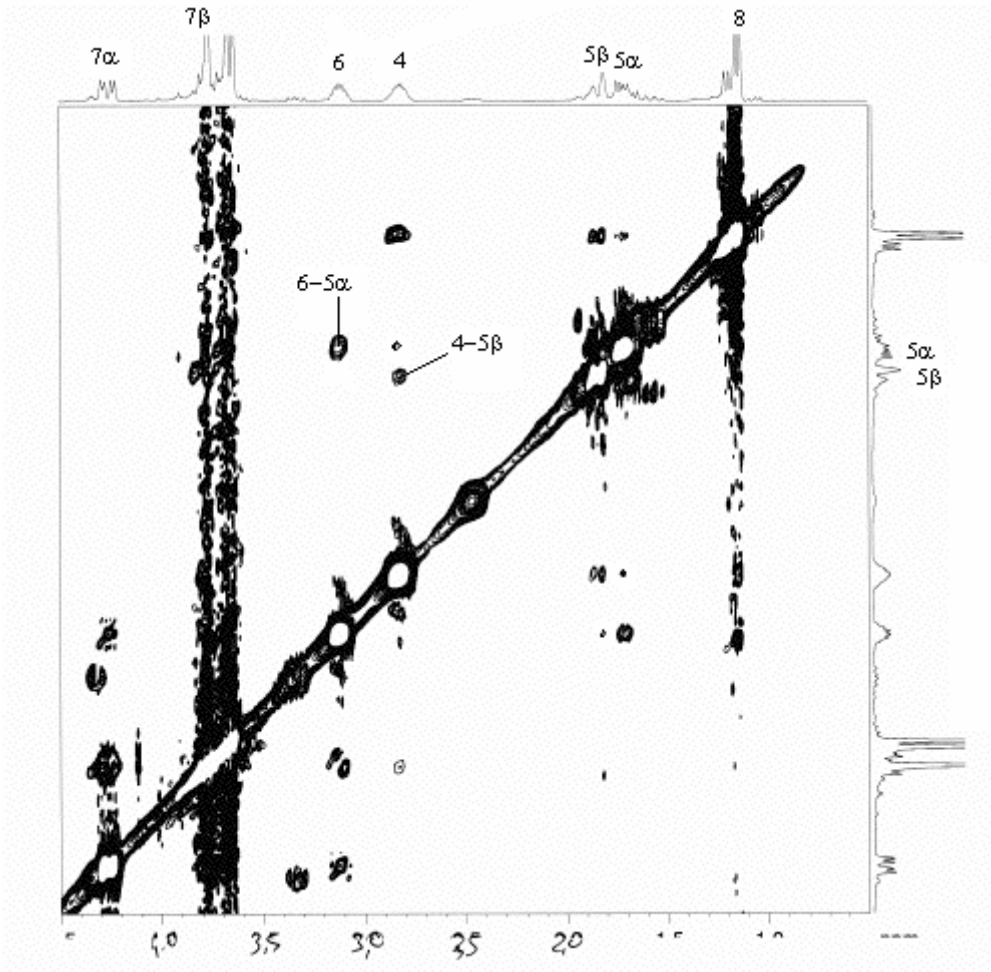


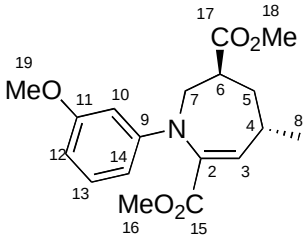




**5a**

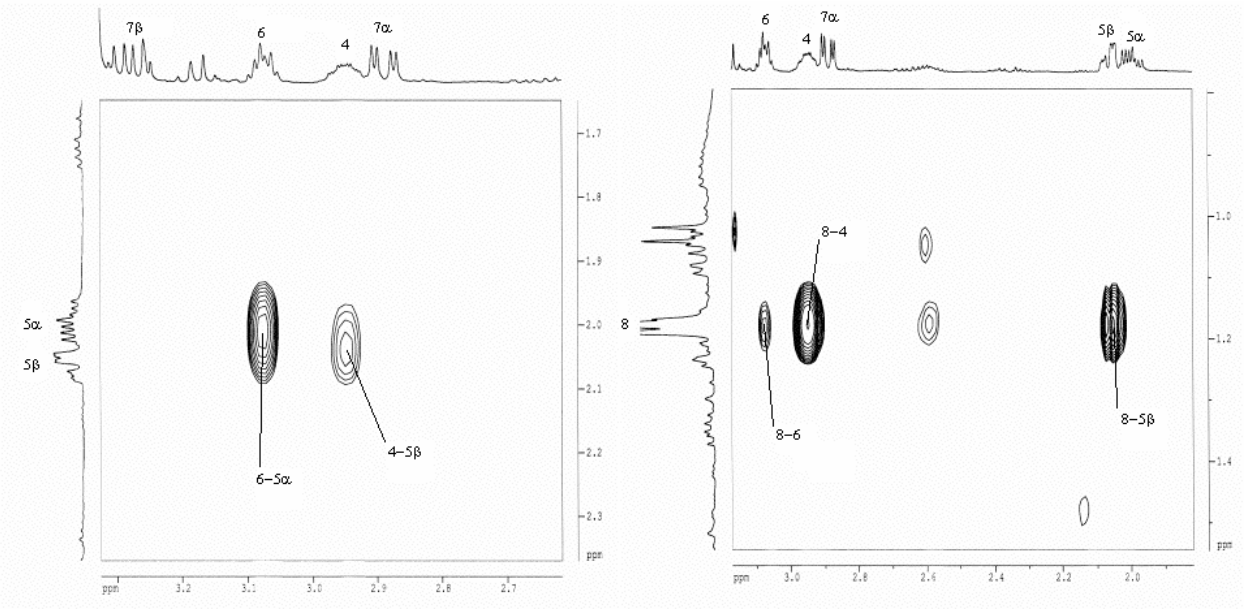
**NOESY spectrum of 5b (300 MHz, CDCl3)**

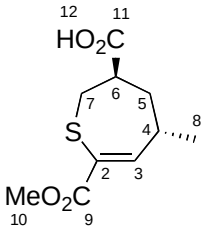



**5b**

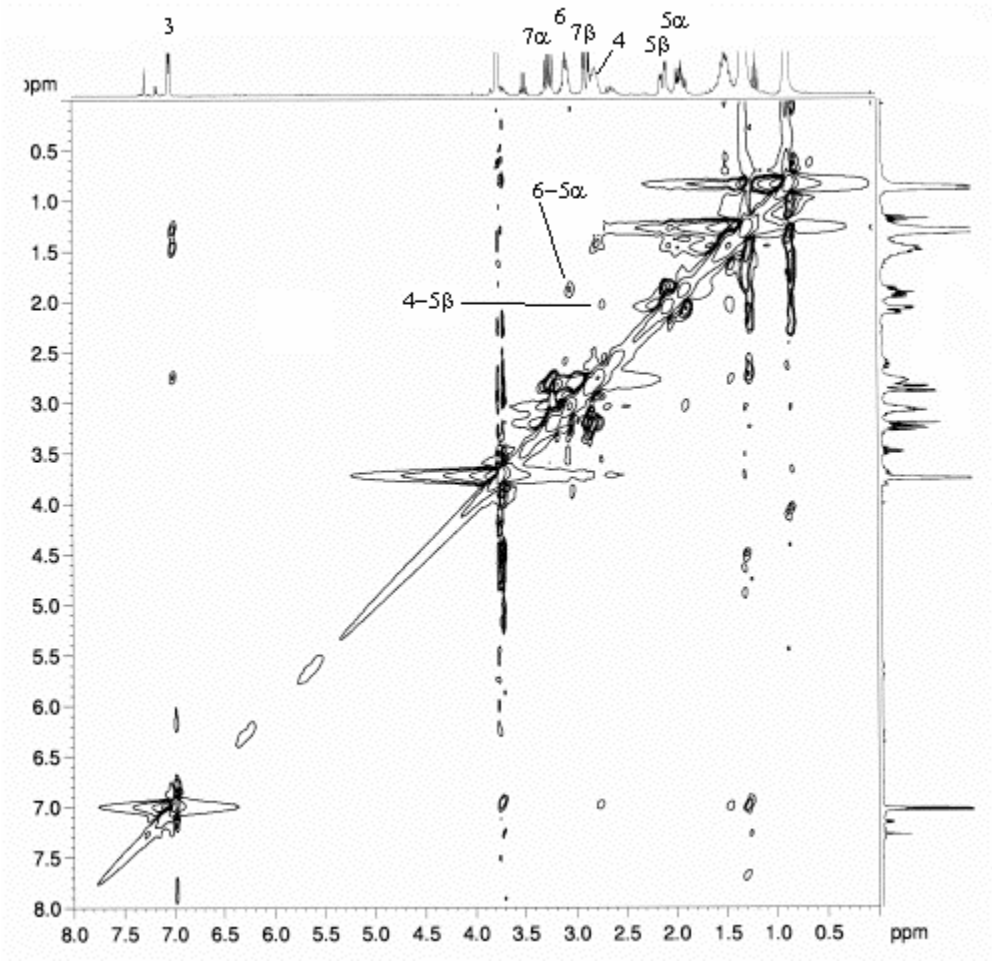
## NOESY spectrum of 4c (500 MHz, CDCl3)

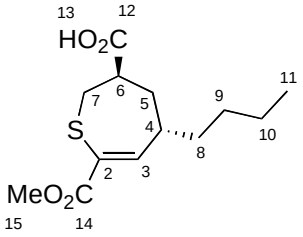



**4c**

**NOESY spectrum of 4d (300 MHz, CDCl3)**




**4d**