8 Experimental section

8.1 Instrumentation / procedure

Routine nuclear magnetic resonance (NMR) spectra were recorded on a VARIAN GEMINI-200 VXR-200 (^{1}H : 200 MHz and ^{13}C : 50 MHz), a BRUCKER AC-250 (^{1}H : 250 MHz and ^{13}C : 62.5 MHz) and a VARIAN GEMINI-2000 (^{1}H : 300 MHz and ^{13}C : 75 MHz). High field spectra were recorded on a BRUCKER AM-500 (^{1}H : 500 MHz and ^{13}C : 125 MHz). ^{1}H chemical shifts (δH) are reported in ppm downfield from internal tetramethylsilane or calibrated from $CHCl_3$ in the case of silyl containing compounds. ^{13}C NMR spectra were recorded using $CDCl_3$ as the internal standard.

Low resolution mass spectra were recorded using VARIAN MATT-44 and FINNIGAN MAT-TSQ 70 spectrometers.

Infra-red spectra (IR) were recorded, as KBr discs or thin films, on a PERKIN ELMER 681 spectrometer and recorded in cm^{-1}.

Elemental analyses were carried out at the university of Stuttgart, Germany.

Thin layer chromatographies (tlc) were performed on TLC plastic sheets, Silica gel 60 F_{254} (MERCK). The plates were visualised using ultra-violet light (256 nm) and developed using $KMnO_4$ and/or vanillin stain and/or I_2/SiO_2 which were prepared according to the following procedures :

Potassium Permanganate: This stain was prepared by dissolving 3 g of $KMnO_4$ and 20 g of K_2CO_3 in 5 mL of 5% NaOH and 300 mL of water.

Vanillin: This stain was prepared by dissolving 2 g of vanillin in 100 mL of EtOH containing 1 mL of conc. H_2SO_4. The plate was developed by heating.

I_2: A jar of fine grade silica gel impregnated with iodine was used. The plate was immersed in the silica gel for a few seconds.

Column chromatographies were performed using MERCK silica gel 60 (230-400 mesh) under pressure with the stated solvents.

All solvents were routinely distilled prior to use. Dry solvents were obtained by standard procedures according to D. D. Perrin and D. R. Perrin, *Purification of Laboratory Chemicals*. All compounds (Acros, Aldrich, Fluka and Lancaster) were used as received unless otherwise stated. All reactions were carried out under an atmosphere of argon in flame-dried apparatus with magnetic stirring, unless otherwise indicated.

Microwave irradiation was carried out in PROLABO 402 Synthewave oven (power 300W, frequency 2450 MHz).

UV irradiation was carried out using a High-pressure mercuric-arc lamp (150 W). A typical spectrum is presented in Figure 8-1.

Visible irradiation was carried out using a tungsten lamp (500 W).

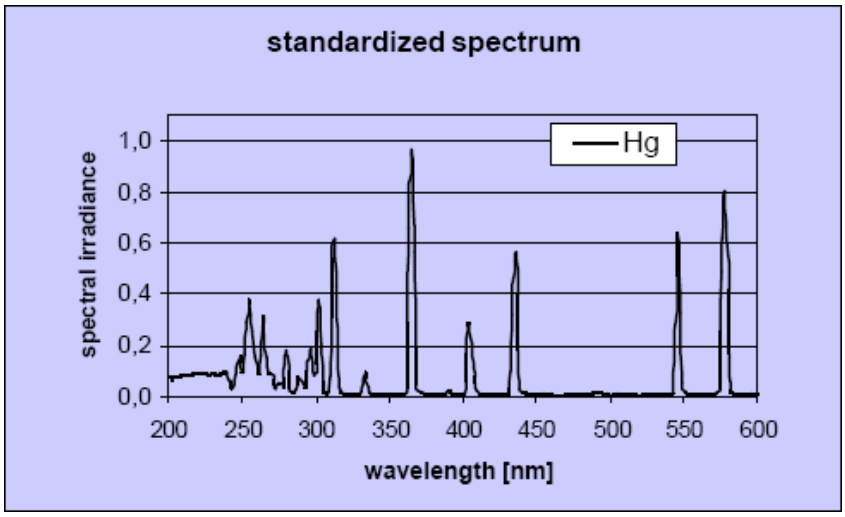
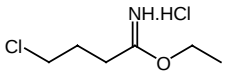
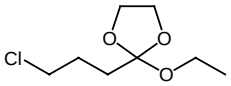


Figure 8-1

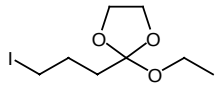
8.2 List of compounds



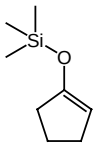
ethyl 4-chlorobutanimidate hydrochloride p. 261



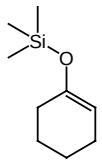
2-(3-chloropropyl)-2-ethoxy-1,3-dioxolane p. 263



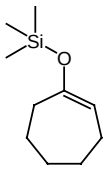
2-ethoxy-2-(3-iodopropyl)-1,3-dioxolane p. 264



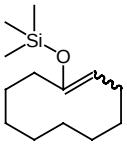
cyclopentenyloxytrimethylsilane p. 266



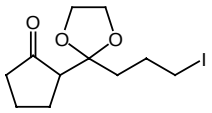
cyclohexenyloxytrimethylsilane p. 267



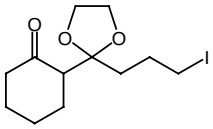
(*E*)-cycloheptenyloxytrimethylsilane p. 268



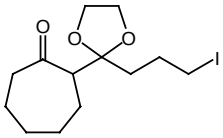
cyclodecenyloxytrimethylsilane p. 270



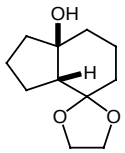
2-(2-(3-iodopropyl)-1,3-dioxolan-2-yl) cyclopentanone p. 271



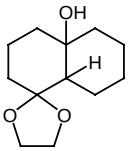
2-(2-(3-iodopropyl)-1,3-dioxolan-2-yl) cyclohexanone p. 273



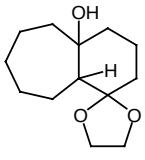
2-(2-(3-iodopropyl)-1,3-dioxolan-2-yl) cycloheptanone p. 274



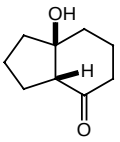
(3a*S**,7a*R**)-7a-hydroxyperhydro-4-indenone-ethyleneacetal p. 276



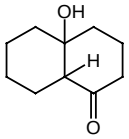
4a-hydroxyperhydro-1-naphthalenone-ethyleneacetal p. 278



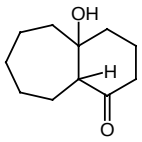
4a-hydroxyperhydrobenzo[a] cyclohepten-1-one-ethyleneacetals p. 281



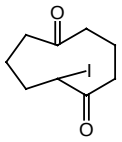
(3a*R**,7a*S**)-7a-hydroxy-octahydroinden-4-one p. 284



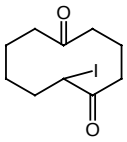
4a-hydroxy-octahydronaphthalen-1(2*H*)-one p. 285



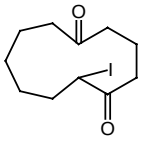
4a-hydroxy-decahydrobenzo[7] annulen-1-one p. 288



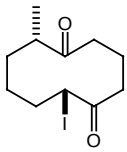
6-iodocyclononane-1,5-dione p. 290



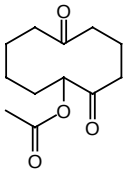
6-iodocyclodecane-1,5-dione p. 292



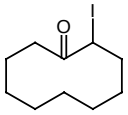
6-iodocycloundecane-1,5-dione p. 294



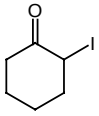
(6*R**,10*S**)-6-iodo-10-methylcyclodecane-1,5-dione p. 295



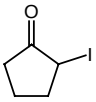
2,6-dioxocyclodecyl acetate p. 297



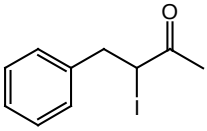
2-iodocyclodecanone p. 298



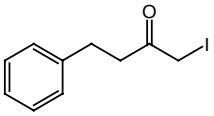
2-iodocyclohexanone p. 301



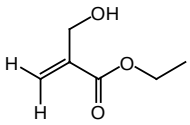
2-iodocyclopentanone p. 302



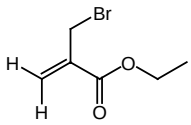
3-iodo-4-phenylbutan-2-one p. 303



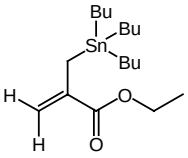
1-iodo-4-phenylbutan-2-one p. 303



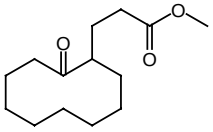
ethyl 2-(hydroxymethyl)acrylate p. 306



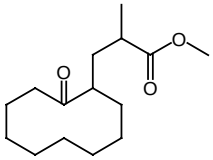
ethyl 2-(bromomethyl)acrylate p. 307



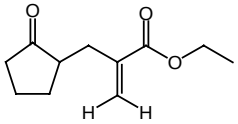
ethyl 2-((tributylstannyl)methyl)acrylate p. 309



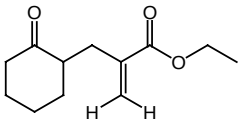
methyl 3-(2-oxocyclodecyl)propanoate p. 310



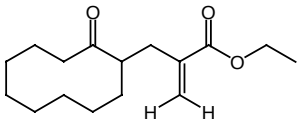
methyl 2-methyl-3-(2-oxocyclodecyl)propanoate p. 312



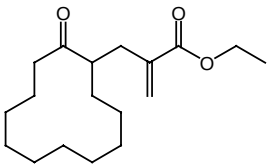
ethyl 2-((2-oxocyclopentyl)methyl)acrylate p. 313



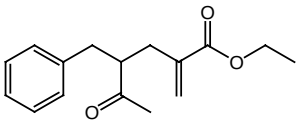
ethyl 2-((2-oxocyclohexyl)methyl)acrylate p. 314



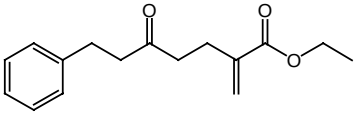
ethyl 2-((2-oxocyclodecyl)methyl)acrylate p. 316



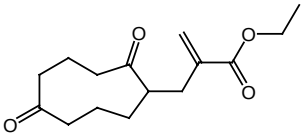
ethyl 2-((2-oxocyclododecyl)methyl)acrylate p. 317



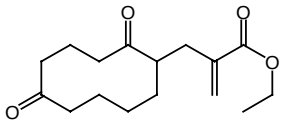
ethyl 4-benzyl-2-methylene-5-oxohexanoate p. 318



ethyl 2-methylene-5-oxo-7-phenylheptanoate p. 320

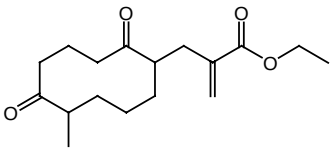


ethyl 2-((2,6-dioxocyclononyl)methyl)acrylate p. 321



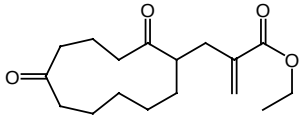
ethyl 2-((2,6-dioxocyclodecyl) methyl)acrylate

p. 323



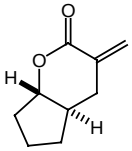
ethyl 2-((7-methyl-2,6-dioxocyclodecyl) methyl)acrylate

p.324



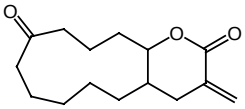
ethyl 2-((2,6-dioxocycloundecyl) methyl)acrylate

p. 326



(4a*R*,7a*S*)-3-methylene-hexahydro cyclopenta[*b*]pyran-2(3*H*)-one

p. 328



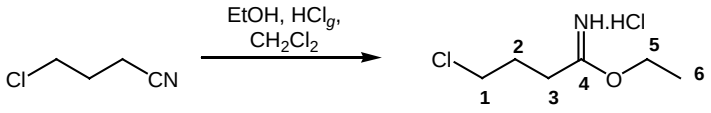
3-methylene-dodecahydro-[1]cycloundeca[*b*]pyran-2,10-dione

p. 329

*8.3 Synthesis of orthoester **259** and silyl enol ethers **258***

8.3.1 Ethyl 4-chlorobutanimidate hydrochloride

Reaction :



294 **295**

Figure 8-2

Procedure :

A solution of 4-chlorobutyronitrile **294** (48.3 g, 0.46 mol, 1 eq) and ethanol (32.2 g, 40 mL, 0.70 mol, 1.5 eq) in CH_2Cl_2 (500 mL) was cooled to –15°C and HCl_g was bubbled through it for 1.5 h. The reaction mixture was stirred at 8 °C for 6 days.

The solvent was removed under reduced pressure and the residue was washed with cold ether (2 x 200 mL). After drying under high vacuum (24h), the desired compound was obtained as a white solid (82 g, *96%*).

Analysis :

IR: 2906 cm^{-1} (stretching CH), 1651 cm^{-1} (C=N), 1092 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.51 (t, 3H, *J* = 7.0 Hz, H-6), 2.18-2.34 (m, 2H, H-2), 2.96 (t, 2H, *J* = 7.5 Hz, H-3), 3.65 (t, 2H, *J* = 6.2 Hz, H-1), 4.67 (q, 2H, *J* = 7.1 Hz, H-5).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 13.5 (C-6), 28.33 (C-2), 30.8 (C-3), 43.2 (C-1), 71.0 (C-5), 178.2 (C-4).

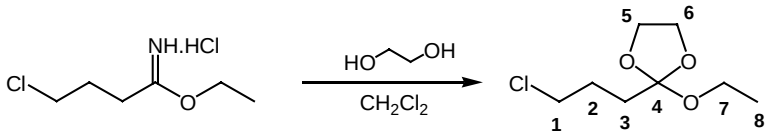
MS (FAB-MNBA) m/z (relative intensity): (M+1) 186 (5%); [(M+1)-HCl] 150 (4%).

CAS : 89224-42-0

Johnson, R. E.; Schlegel, D. C. Eur. Pat. Appl., 1992, p 139

8.3.2 2-(3-chloropropyl)-2-ethoxy-1,3-dioxolane

Reaction :



295 **296**

Figure 8-3

Procedure :

A solution of ethyl 4-chlorobutanimidate hydrochloride **295** (82 g, 0.44 mol, 1 eq) and 1,2-ethanediol (21.5 g, 30 mL, 0.47 mol, 1 eq) in CH_2Cl_2 (1.8 L) was stirred at rt under inert atmosphere for 7 days.

The solvent was removed under reduced pressure and the residue was dispersed in Et_2O (200 mL). After filtration, ether was removed under reduced pressure and CH_2Cl_2 (200 mL) was added to the resulting oil. This solution was stirred in the presence of aqueous KOH (2N, 250 mL) for 16h.

After separation, the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the orthoester **296** as a yellow oil (56.7 g, 66%).

Analysis :

IR: 2974 and 2897 cm^{-1} (stretching CH), 1218, 1093, 1070, 1058, 952 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.2 (t, 3H, *J* = 7.1 Hz, H-8), 1.9-2.0 (m, 4H, H-2 and 3), 3.5-3.7 (m, 4H, H-1 and 7), 3.9-4.1 (m, 4H, H-5 and 6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 14.7 (C-8), 26.9 (C-2), 32.4 (C-3), 44.4 (C-1), 56.7 (C-7), 64.5 (C-5 and 6), 121.8 (C-4).

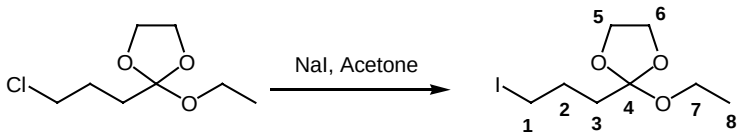
MS (EI, 70 eV): (M+1) 195 (10%); ($M^{\cdot+}$) 194 (3%); ($M^{\cdot+}$-Cl) 159 (8%); 151 (43%); 149 (100%); 117 (30%).

CAS : 335645-38-0

(a) Pastor, I. M.; Yus, M. *Tetrahedron Lett.* **2001**, *42*, 1029. (b) Markó, I. E.; Vanherck, J.-C.; Ates, A.; Tinant, B.; Declercq, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3333. (c) Maulide, N.; Vanherck, J.-C.; Markó, I. E. *Eur. J. Org. Chem.* **2004**, 3962.

8.3.3 2-Ethoxy-2-(3-iodopropyl)-1,3-dioxolane

Reaction :



296 **259**

Figure 8-4

Procedure :

A solution of ethyl 2-(3-chloropropyl)-2-ethoxy-1,3-dioxolane **296** (10 g, 0.056 mol, 1 eq) and sodium iodide (16.7 g, 40 mL, 0.11 mol, 2 eq) in acetone (110 mL) was stirred at reflux under an inert atmosphere for 15h.

The solvent was removed under reduced pressure and the residue was dispersed in Et_2O (200 mL). After filtration, the organic layer was washed with saturated aqueous $Na_2S_2O_3$ (2 x 100 mL), dried over $MgSO_4$ and evaporated to give 12.4 g of **259** (77%) as a yellow oil.

Analysis :

IR: 2895 and 2972 cm^{-1} (stretching CH), 1383, 1225, 1175 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.2 (t, 3H, *J* = 7.1 Hz, H-8), 1.8-2.0 (m, 4H, H-2 and 3), 3.2 (t, 4H, *J*= 6.7 Hz, H-1), 3.5 (q, 2H, *J*= 7.1 Hz, H-7), 3.9-4.1 (m, 4H, H-5 and 6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 6.7 (C-1), 15.3 (C-8), 28.2 (C-2), 36.3 (C-3), 57.4 (C-7), 64.9 (C-5 and 6), 121.9 (C-4).

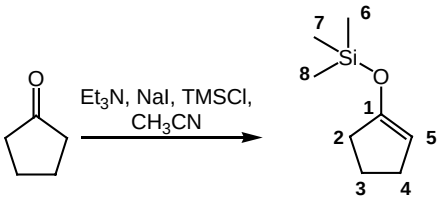
MS (EI, 70 eV): (M+1) 287 (10%); ($M^{\bullet+}$-CH_3CH_2O) 241 (100%); (M^{+}-I) 159 (3%)

CAS : 198895-90-8

Markó, I. E.; Ates, A. *Synlett* **1999**, 1033.

8.3.4 1-cyclopentenyl (1,1,1-trimethylsilyl) ether

Reaction :



293a **258a**

Figure 8-5

Procedure :

A solution of sodium iodide (9.4 g, 0.06 mol, 1.25 eq) in CH_3CN (80 mL) was added to neat cyclopentanone (4.2 g, 0.05 mol, 1eq), TMSCl (6.8 g, 0.06 mol, 1.25eq) and Et_3N (6.4 g, 0.06mol, 1.25eq). The reaction mixture was stirred at rt for 17h.

The organic layer was extracted with pentane (3 x 40 mL). The pentane layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the desired product **258a** as a colorless liquid (5 g, 64%).

Analysis :

IR: 2958, 2901 and 2851 cm^{-1} (stretching CH), 1647, 1343, 1252, 923, 894, 865 and 844 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 0.2 (s, 9H, H-6, 7 and 8), 1.7-1.9 (m, 2H, H- 3), 2.1-2.3 (m, 4H, H-2 and 4), 4.6 (m, 1H, H-5).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 0.1 (C-6, 7 and 8), 21.3 (C-3), 28.6 (C-4), 33.5 (C-2), 102.1 (C-5), 154.9 (C-1).

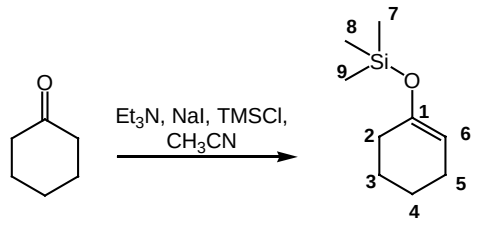
CAS : 19980-43-9

Procedure : *see* Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron Lett.* **1987**, *43*, 2075.

Ref. product : Birkofer, L.; Dickopp, H. *Chem. Ber.* **1969**, *102*, 14.

8.3.5 1-cyclohexenyl (1,1,1-trimethylsilyl) ether

Reaction :



293b **258b**

Figure 8-6

Procedure :

A solution of sodium iodide (9.4 g, 0.06 mol, 1.25 eq) in CH_3CN (80 mL) was added to neat cyclohexanone (5.0 g, 0.05 mol, 1eq), TMSCl (6.8 g, 0.06 mol, 1.25eq) and Et_3N (6.4 g, 0.06mol, 1.25eq). The reaction mixture was stirred at rt for 17h.

The organic layer was extracted with pentane (3 x 40 mL). The pentane layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the desired product as a colorless liquid (6,6 g, 85%).

Analysis :

IR: 2931, 2959 and 2841 cm^{-1} (stretching CH), 1669, 1267, 1251, 1192,1171, 896, 845, 753 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 0.2 (s, 9H, H-7, 8 and 9), 1.4-1.6 (m, 2H, H-3 or 4), 1.6-1.8 (m, 2H, H-3 or 4), 1.95-2.05 (m, 4H, H-5 and 2), 4.85-4.95 (m, 1H, H-6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 0.3 (C-7, 8 and 9), 22.4, 23.2 and 23.8 (C-3, 4 and 5), 29.9 (C-2), 104.2 (C-6), 150.3 (C-1).

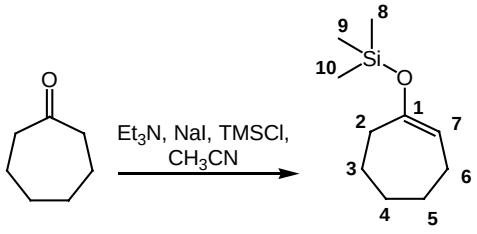
CAS : 6651-36-1

Procedure : *see* Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron Lett.* **1987**, *43*, 2075.

Ref. product : Krueger, C. R.; Rochow, E. G. *J. Organometallic. Chem.* **1964**, *1*, 476.

8.3.6 1-cycloheptenyl (1,1,1-trimethylsilyl) ether

Reaction :



293c **258c**

Figure 8-7

Procedure :

A solution of sodium iodide (9.4 g, 0.06 mol, 1.25 eq) in CH_3CN (80 mL) was added to neat cycloheptanone (5.6 g, 0.05 mol, 1eq), TMSCl (6.8 g, 0.06 mol, 1.25eq) and Et_3N (6.4 g, 0.06 mol, 1.25eq). The reaction mixture was stirred at rt for 17h.

The organic layer was extracted with pentane (3 x 40 mL). The pentane layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the desired product as a colorless liquid (6.5 g, 70%).

Analysis :

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 0.16 (s, 9H, H-8, 9 and 10), 1.44-1.74 (m, 6H, H-3, 4 and 5), 1.9-2.0 (m, 2H, H-6), 2.16-2.25 (m, 2H, H-2), 5.0 (t, 1H, *J*= 6.6 Hz, H-7).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 0.2 (C-8, 9 and 10), 25.2, 25.3, 27.8 (C-3, 4 and 5), 31.5 (C-6), 35.5 (C-2), 108.7 (C-7), 156.0 (C-1).

CAS : 22081-48-7

Procedure : *see* Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron Lett.* **1987**, *43*, 2075.

Ref. product : Birkofer, L.; Dickopp, H. *Chem. Ber.* **1969**, *102*, 14.

8.3.7 1-cyclodecenyl (1,1,1-trimethylsilyl) ether

Reaction :

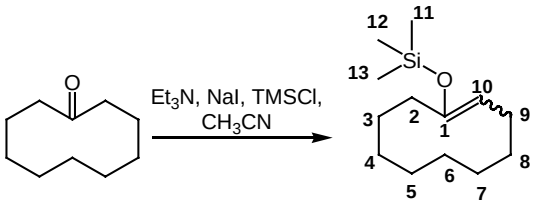


Figure 8-8

Procedure :

A solution of sodium iodide (3.6 g, 0.024 mol, 1.25 eq) in acetonitrile (30 mL) was added to neat cyclodecanone (3.0 g, 0.020 mol, 1eq), chloro(trimethyl)silane (2.6 g, 0.024 mol, 1.25eq) and triethylamine (2.5 g, 0.024 mol, 1.25eq). The reaction mixture was stirred at rt under inert atmosphere for 17h.

The organic layer was extracted with pentane (3x20 mL). The pentane layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the desired product as colorless liquid (4.25 g, *Z*: *E* 2:1 , 99%).

Analysis :

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 0.10 and 0.13 (2 s, 9H, H-11, 12 and 13), 1.2-1.4 (m, 12H, H-4 to 8), 1.93 (t, 2H, *J*= 6 Hz, H-2), 2.03-2.11 and 2.11-2.19 (2 m, 2H, H-9), 4.49 (t, *J*= 8.4 Hz, H-10 *E*) and 4.57 (t, *J*= 7.6 Hz, H-10 *Z*) (1H).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 0.5 (C-11, 12 and 13), 21.0 (C-3), 21.05 (C-4), 24.9 (C-5), 25.6 (C-6), 26.4 (C-7), 26.7 (C-8), 27.4 (C-9 *Z*), 28.2 (C-9 *E*), 29.0 (C-2 *E*), 37.6 (C-2 *Z*), 107.1 (C-10 *E*), 110.8 (C-10 *Z*), 149.7 (C-1 *Z*), 151.16 (C-1 *E*).

CAS : 74173-16-3 (product *Z*) 74173-15-2 (product *E*)

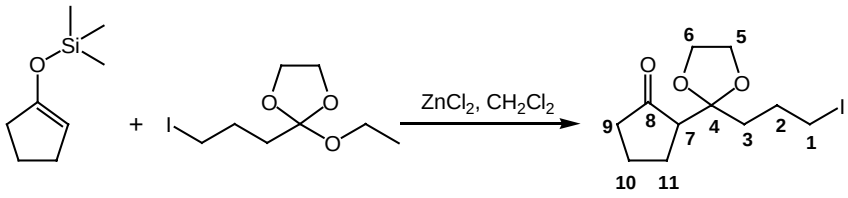
Procedure : *see* Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron Lett.* **1987**, *43*, 2075.

Ref. product : Friedrich, E.; Kalinowski, H. O.; Lutz, W. *Tetrahedron* **1980**, *36*, 1051.

*8.4 Synthesis of bicyclic products **255***

8.4.1 2-[2-(3-iodopropyl)-1,3-dioxolan-2-yl]-1-cyclopentanone

Reaction :



258a **259** **260a**

Figure 8-9

Procedure :

$ZnCl_2$ (2.4g, 17 mmoL, 0.7 eq) was added to a solution of 1-cyclopentenyl (1,1,1-trimethylsilyl) ether **258a** (3.9g, 25 mmol, 1 eq) and 2-

ethoxy-2-(3-iodopropyl)-1,3-dioxolane **259** (8.6g, 30 mmol, 1.2 eq) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at rt for 4h.

A saturated aqueous solution of $NaHCO_3$ (60mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The pooled organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. After purification by flash chromatography (PE:EA, 1:3, Rf=0.37), the desired product was obtained as a yellow oil (5.0 g, 62%).

Analysis :

IR: 2884 and 2964 cm^{-1} (stretching C-H), 1734 cm^{-1} (stretching C=O), 1372, 1242, 1149, 1100, 1045 and 950 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.60-2.30 (m, 10H, H-2, 3 and 9-11), 2.51 (t, 1H, *J* =8.8 Hz, H-7), 2.12-3.33 (m, 2H, H-1), 3.95-4.10 (m, 4H, H-5-6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 6.5 (C-1), 20.1, 25.5, 28.0, 36.8, 39.7 (C-2, 3 and 9-11), 53.6 (C-7), 65.3, 65.5 (C-5 and 6), 111.0 (C-4), 216.7 (C-8).

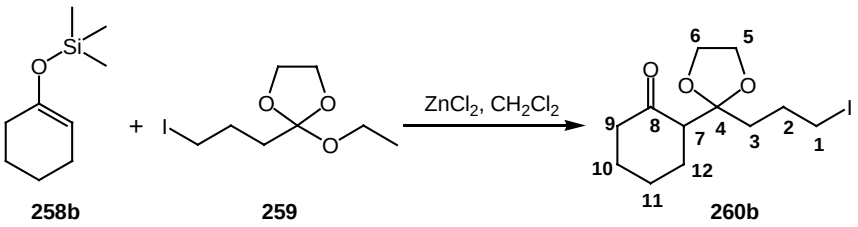
MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 324 (0.5 %); 285 (10%); 253.7 (37 %); 171.8 (100 %); 126.8 (30 %); 44.9 (87 %).

CAS : 240420-64-8

Markó, I. E.; Ates, A. *Synlett* **1999**, 1033.

8.4.2 2-[2-(3-iodopropyl)-1,3-dioxolan-2-yl]-1-cyclohexanone

Reaction :



258b **259** **260b**

Figure 8-10

Procedure :

$ZnCl_2$ (0.78 g, 5 mmoL, 0.6 eq) was added to a solution of 1-cyclohexenyl (1,1,1-trimethylsilyl) ether **258b** (2.16 g, 13 mmol, 1.4 eq) and 2-ethoxy-2-(3-iodopropyl)-1,3-dioxolane **259** (2.65 g, 9 mmol, 1 eq) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at rt under inert atmosphere for 15h.

A saturated aqueous solution of $NaHCO_3$ (60 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The pooled organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. After purification by flash chromatography (PE:EA, 4:1, Rf = 0.35), the desired product was obtained as a yellow oil (1.3 g, 43%).

Analysis :

IR: 2942, 2894 and 2858 cm^{-1} (stretching C-H), 1702 cm^{-1} (stretching C=O), 1443, 1369, 1285, 1226, 1130, 906, 790 and 712 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.50-2.40 (m, 12H, H-2, 3 and 9-12), 2.55-2.65 (m, 1H, H-7), 3.00-3.20 (m, 2H, H-1), 3.80-3.90 (m, 4H, H-5-6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 6.6 (C-1), 24.4, 27.6, 27.7, 28.6, 36.3, 42.9 (C-2, 3 and 9-12), 56.6 (C-7), 65.2 (C-5 and 6), 110.2 (C-4), 210.1 (C-8).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) absent; ($M^{\cdot+}$-C_6H_9O) 241 (100 %); ($I(CH_2)_3CO^+$) 197 (4 %); ($I(CH_2)_3^+$) 169 (65 %).

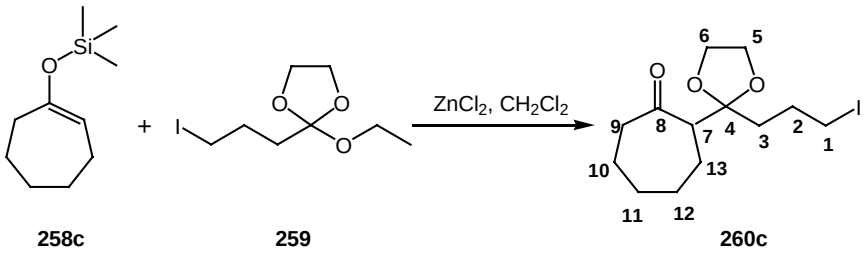
EA: ($C_{12}H_{19}O_3I$) *calculated* : C, 42.62%; H, 5,66%; *found*: C, 43.02%; H, 5.82%.

CAS : 240420-65-9

Markó, I. E.; Ates, A. *Synlett* **1999**, 1033.

8.4.3 2-[2-(3-iodopropyl)-1,3-dioxolan-2-yl]-1-cycloheptanone

Reaction :



258c **259** **260c**

Figure 8-11

Procedure :

$ZnCl_2$ (1.4 g, 10 mmoL, 0.65 eq) was added to a solution of 1-cycloheptenyl (1,1,1-trimethylsilyl) ether **258c** (3.0 g, 16 mmol, 1 eq) and 2-ethoxy-2-(3-iodopropyl)-1,3-dioxolane **259** (5.03 g, 17 mmol, 1.1 eq) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at rt under inert atmosphere for 5h.

A saturated aqueous solution of $NaHCO_3$ (60 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The pooled organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. After purification by flash chromatography (PE:EA, 3:1, Rf = 0.5), the desired product was obtained as a yellow oil (3.34 g, 83%).

Analysis :

IR: 2927 and 2854 cm^{-1} (stretching C-H), 1700 cm^{-1} (stretching C=O), 1458, 1443, 1237, 1090 and 950 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.00-2.10 (m, 12H, H-2, 3 and 10-13), 2.33-2.45 (m, 1H, H-7), 2.60-2.80 (m, 2H, H-9), 3.10-3.20 (m, 2H, H-1), 3.95 (m, 4H, H- 5 and 6).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 6.7 (C-1), 25.3, 26.0, 27.3, 27.8, 29.9, 36.7, 43.0 (C-2, 3 and 9-13), 56.5 (C-7), 65.1, 65.4 (C-5 and 6), 110.9 (C-4), 213.7 (C-8).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) absent; ($M^{\cdot+}$-$C_7H_{11}O$) 241 (100 %); ($I(CH_2)_3CO^+$) 197 (25 %); ($M^{\cdot+}$ - $I(CH_2)_3^+$) 183 (50 %); 154.9 (30 %); 149 (35 %); 113.1 (20 %).

CAS : 240420-66-0

Markó, I. E.; Ates, A. *Synlett* **1999**, 1033.

8.4.4 (3a*S**,7a*R**)-7a-hydroxyperhydro-4-indenone-ethyleneketal

Reaction :

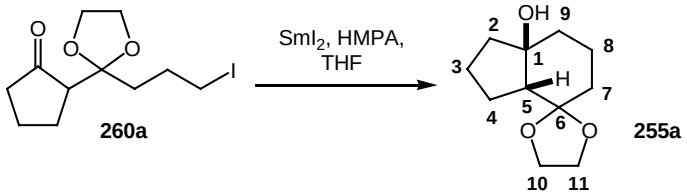


Figure 8-12

Procedure :

A solution of diiodoethane (6.76 g, 24 mmol, 4 eq) in THF[255] (120 mL) was added by cannula over Sm metal (40-mesh, 3.78 g, 25 mmol, 4.2 eq) covered by THF (3 mL). The resulting solution was heated with a heat gun and became dark blue. After 1h at rt, under inert atmosphere, HMPA[256] (10.5 mL, 10.74 g, 60 mmol, 10 eq) was added and the colour of the solution changed to purple. After an additional 1h at rt, a solution of 2-[2-(3-iodopropyl)-1,3-dioxolan-2-yl]-1-cyclopentanone **260a** (2 g, 6 mmol, 1 eq) in THF (30 mL) was transfered by cannula to the reaction mixture. No change of colour was observed.

[255] THF distilled and degassed was used.
[256] Freshly distilled (over CaH_2) HMPA was used.

After 1h, a saturated aqueous solution of $NaHCO_3$ (100 mL) was added and the aqueous layer was extracted with Et_2O (3 x 70 mL). The organic solvents were evaporated under reduced pressure and the residue was dissolved in pentane (100 mL), washed with a saturated aqueous solution of NH_4Cl (3x50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (PE:EA, 3:1, Rf = 0.48) affording the desired product as a colorless oil[257] (574 mg, 50%).

Analysis :

IR: 3441 cm^{-1} (stretching O-H), 2946 and 2878 cm^{-1} (stretching C-H), 1456, 1337, 1226, 1150, 1069, 942 and 899 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.35-2.00 (m, 13H, H-2-3 and 7-9), 3.05 (s, 1H, OH), 3.85-4.15 (m, 4H, H-10 and 11).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 19.5, 19.6 (C-3 and 8), 24.9 (C-4), 29.6 (C-7), 32.6 (C-9), 38.8 (C-2), 52.1 (C-5), 64.2, 64.3 (C-10 and 11), 80.4 (C-1), 111.0 (C-6).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 198 (5 %); ($M^{\cdot+}$-OH) 181 (9 %); ($M^{\cdot+}$-H_2O) 180 (40 %); ($M^{\cdot+}$ -C_2H_4O) 136 (50 %); 99 (100 %); 86 (52 %); 55 (35 %); 41 (14 %).

EA : ($C_{11}H_{18}O_3$) *calculated*: C, 66.65%; H, 9.15%; *found*: C, 66.56%; H, 9.18%.

CAS : 222616-60-6

Markó, I. E.; Ates, A. *Synlett* **1999**, 1033.

[257] *Cis* stereochemistry based upon C-1 chemical deplacement.

8.4.5 4a-hydroxyperhydro-1-naphthalenone-ethyleneketals

Reaction :

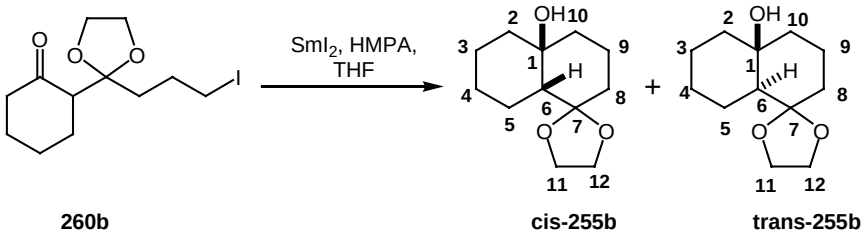


Figure 8-13

Procedure :

A solution of diiodomethane (4.5 mL, 14.99 g, 56 mmol, 4 eq) in THF[258] (250 mL) was added by cannula over Sm metal (40-mesh, 10.32 g, 68 mmol, 4.8 eq). The resulting solution was heated with a heat gun and became dark blue. After 1h at rt, under inert atmosphere, HMPA[259] (24.5 mL, 25.09 g, 140 mmol, 10 eq) was added and the colour of the solution changed to purple. After an additional 1h at rt, a solution of 2-[2-(3-iodopropyl)-1,3-dioxolan-2-yl]-1-cyclohexanone **260b** (4.83 g, 14 mmol, 1 eq) in THF (100 mL) was transfered by cannula to the reaction mixture. No change of colour was observed.

After 1h, a saturated aqueous solution of $NaHCO_3$ (200mL) was added and the aqueous layer was extracted with Et_2O (3x200 mL). The organic solvents were evaporated under reduced pressure and the residue was dissolved in pentane (300 mL), washed with a saturated aqueous

[258] Distilled and degassed THF was used.
[259] Freshly distilled (over CaH_2) HMPA was used.

solution of NH_4Cl (3x100 mL), dried over $MgSO_4$ and evaporated under reduced pressure. After purification by flash chromatography (PE:EA, 3:1), the desired product was obtained with 95 % yield (*trans* (4aR*, 8aR*)-4a-hydroxyoctahydro-1(2H)-naphtone-ethyleneketal (594 mg, 20 %, colorless oil, Rf = 0.53) and *cis* (4aR*, 8aS*) 4a-hydroxyoctahydro-1(2H)-naphtone-ethyleneketal (2.23 g, 75 %, white solid, Rf= 0.37)).

Analysis :

a) (4aR, 8aR*)-4a-hydroxyperhydro-1-naphthalenone-ethyleneketal*[260]

IR: 3534 and 3506 cm^{-1} (stretching O-H), 2927 and 2880 cm^{-1} (stretching C-H), 1450, 1398, 1174, 1080, 1029, 936, 833 and 698 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.10-1.90 (m, 15H, H-2 to 10), 3.56 (s, 1H, OH), 3.85-4.00 (m, 4H, H-11 and 12).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 18.7 (C-3), 19.3 (C-4), 21.2 (C-9), 25.8 (C-5), 35.5 (C-10), 38.9 (C-8),39.3 (C-2), 50.0 (C-6), 64.5, 65.5 (C-11 and 12), 71.4 (C-1), 110.4 (C-7).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 212 (30 %); ($M^{\cdot+}$-H_2O) 194 (100 %); ($M^{\cdot+}$-$CHOCH_2^{\cdot}$) 169 (70 %); ($194^{\cdot+}$-C_2H_4O) 150 (80 %); 99 (67 %); 86 (35 %); 55 (8 %).

EA: ($C_{12}H_{20}O_3$) *calculated*: C, 67,89%; H, 9,50%; *found*: C, 68,01%; H, 9,35%.

[260] Stereochemistry based upon X-Ray diffraction of corresponding hydroxyketone (A. Ates)

b) (4aR, 8aS*)-4a-hydroxyperhydro-1-naphthalenone -ethyleneketal*

IR: 3518 cm^{-1} (stretching O-H), 2932 and 2876 cm^{-1} (stretching C-H), 1456, 1395, 1340, 1267, 1177, 1153, 1074, 921 and 755 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.15-1.91 (m, 15H, H-2 to 10), 3.90-4.06 (m, 4H, H-11 and 12), 4.62 (s, 1H, OH).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 18.6 (C-9), 23.5 (C-3), 25.7 (C-4), 25.8 (C-5), 29.6 (C-10), 30.3 (C-8),39.5 (C-2), 49.3 (C-6), 63.8, 64.1 (C-11 and 12), 72.6 (C-1), 111.8 (C-7).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 212 (10 %); ($M^{\cdot+}$-H_2O) 194 (37 %); ($M^{\cdot+}$-$CHOCH_2^{\cdot}$) 169 (15 %); ($194^{\cdot+}$-C_2H_4O) 150 (60 %); 99 (100 %); 86 (60 %); 55 (38 %).

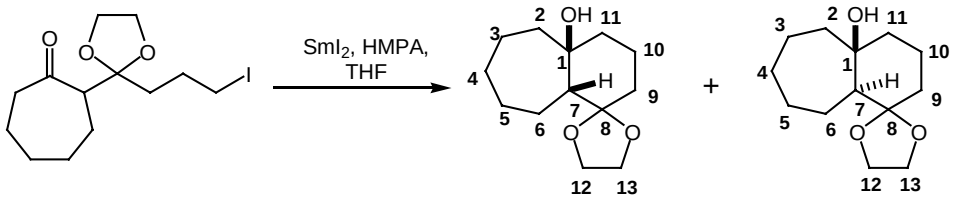
EA: ($C_{12}H_{20}O_3$) *calculated*: C, 67.89%; H, 9.50%; *found*: C, 67.71%; H, 9.56%.

CAS : 222616-55-9

Markó, I. E.; Ates, A. *Synlett* **1999**, 1033.

8.4.6 4a-hydroxyperhydrobenzo[*a*]cyclohepten-1-one-ethyleneketals

Reaction :



260c ***cis*-255c** ***trans*-255c**

Figure 8-14

Procedure :

A solution of diiodomethane (4.9 mL, 16.2 g, 60.5 mmol, 4 eq) in THF[261] (250 mL) was added by cannula over Sm metal (40-mesh, 10.0 g, 66.5 mmol, 4.4 eq). The resulting solution was heated with a heatgun and became dark blue. After 1h at rt, under inert atmosphere, HMPA[262] (26.5 mL, 27.1 g, 150 mmol, 10 eq) was added and the coulor of the solution changed to purple. After an additional 1h at rt, a solution of 2-[2-(3-iodopropyl)-1,3-dioxolan-2-yl]-1-cycloheptanone **260c** (5.32 g, 15 mmol, 1 eq) in THF (100 mL) was transfered by cannula to the reaction mixture. No change of colour was observed.

After 1h, a saturated aqueous solution of $NaHCO_3$ (200 mL) was added and the aqueous layer was extracted with Et_2O (3 x 200 mL). The

[261] Distilled and degassed THF was used.
[262] Freshly distilled (over CaH_2) HMPA was used.

organic solvents were evaporated under reduced pressure and the residue was dissolved in pentane (300 mL), washed with a saturated aqueous solution of NH_4Cl (3x100 mL), dried over $MgSO_4$ and evaporated under reduced pressure. After purification by flash chromatography (PE:EA, 3:1), the desired product was obtained in 71 % yield. We recovered three fractions after the column: **(1)** *trans* (4aR*, 9aR*)-4a-hydroxydecahydro-1H-benzo [a] cyclohepten-1-one ethyleneketal (110 mg, 3.2 %, colorless oil, Rf = 0.54) **(2)** *cis-trans* mixture (1.37 g, 40 %) and **(3)** *cis* (4aR*, 9aS*) 4a-hydroxydecahydro-1H-benzo [a] cyclohepten-1-one ethyleneketal (1.06 g, 31 %, colorless oil, Rf= 0.48).

Analysis :

a) (4aR, 9aR*)-4a-hydroxyperhydrobenzo[a]cyclohepten-1-one-ethyleneketal*[263]

IR (film): 3541 cm^{-1} (stretching O-H), 2933 cm^{-1} (stretching C-H), 1459, 1444, 1345, 1141, 1022 and 904 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.20-1.90 (m, 17H, H-2 to 11), 3.59 (s, 1H, OH), 3.85-4.05 (m, 4H, H-12 and 13).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 18.8 (C-10),19.5 (C-3) 20.6 (C-6), 26.7 (C-5), 27.5 (C-4), 34.3 (C-9), 40.4 (C-11),43.0 (C-2), 52.7 (C-7), 64.0, 65.1 (C-12 and 13), 73.9 (C-1), 111.6 (C-8).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 226 (43 %); ($M^{\cdot+}$-OH) 209 (40 %); ($M^{\cdot+}$-H_2O) 208 (100 %); ($M^{\cdot+}$-$CHOCH_2^{\cdot}$) 183 (98 %); ($208^{\cdot+}$-

[263] Stereochemistry based on C-1 chemical deplacement (A. Ates)

C_2H_4O) 164 (90 %); ($164^{\cdot+}$-C_2H_4) 136 (38 %); 122 (60 %); 99 (100 %); 86 (88 %); 55 (57 %).

EA: ($C_{13}H_{22}O_3$) *calculated*: C, 68.99%; H, 9.80%; *found*: C, 69.00%; H, 9.84%.

CAS : 639090-45-2

b) (4aR, 8aS*)-4a-hydroxyperhydrobenzo[a]cyclohepten-1-one-ethyleneketal*

IR: 3521 cm^{-1} (stretching O-H), 2934 cm^{-1} (stretching C-H), 1458, 1401, 1341, 1098, 916 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.01-1.83 (m, 17H, H-2 to 11), 3.88-4.02 (m, 4H, H-12 and 13), 4.33 (s, 1H, OH).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 18.7 (C-10), 21.1 (C-3), 25.9 (C-6), 30.6 (C-5), 30.8 (C-9), 31.0 (C-4), 35.2 (C-11), 42.8 (C-2), 51.8 (C-7), 63.7, 64.0 (C-12 and 13), 75.4 (C-1), 112.0 (C-8).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 226 (32 %); ($M^{\cdot+}$-OH) 209 (33 %); ($M^{\cdot+}$-H_2O) 208 (100 %); ($M^{\cdot+}$-$CHOCH_2^{\cdot}$) 183 (78 %); ($208^{\cdot+}$-C_2H_4O) 164 (82 %); ($164^{\cdot+}$-C_2H_4) 136 (25 %); 122 (45 %); 99 (95 %); 86 (78 %); 55 (39 %).

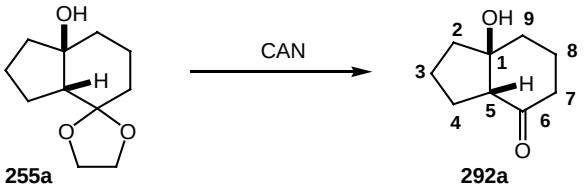
EA: ($C_{13}H_{22}O_3$) *calculated*: C, 68.99%; H, 9.80%; *found*: C, 68.61%; H, 9.76%.

CAS : 240420-69-3

8.5 Deprotection of acetals with CAN

8.5.1 (3a*S**,7a*R**)-7a-hydroxyperhydro-4-indenone

Reaction :



255a **292a**

Figure 8-15

Procedure :

A solution of (3aS*,7aR*)-7a-hydroxyoctahydro-4H-indene-4-one-ethyleneketal **255a** (200 mg, 1 mmol, 1 eq) in 6 mL of a 1:1 mixture of CH_3CN : borate buffer (pH=8) was heated to 70°C. After addition of CAN (17 mg, 0.03 mmol, 0.03 eq), the reaction mixture was stirred at 70°C for 1.5 h.

After cooling at rt, the reaction mixture was diluted with H_2O (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The desired product was obtained as a colorless oil (144 mg, 93%).

Analysis :

IR: 3423 cm^{-1} (stretching O-H), 2959 and 2875 cm^{-1} (stretching C-H), 1699 (C=O), 1458, 1345, 1311, 1157, 1079 and987 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.52-2.28 (m, 10H), 2.29-2.49 (m, 2H), 2.51-2.74 (m, 2H, OH, H-7b or H-5).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 21.1, 21.3, 24.6, 34.7, 38.1, 39.3 (C-2-4 and 7-9), 60.9 (C-5), 84.3 (C-1), 211.6 (C-6).

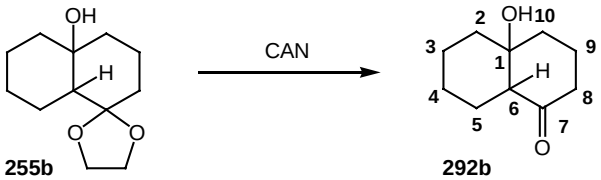
MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 154 (100 %); ($M^{\cdot+}$-OH) 137 (81 %); ($M^{\cdot+}$-H_2O) 136 (93 %); ($M^{\cdot+}$ -CO) 126 (82 %); ($136^{\cdot+}$-C_2H_4) 108 (95%); 139 (78%); 125 (61%); 113 (63%); 111 (90%); 108 (95%); 97 (64%); 84 (82%); 70 (63%); 55 (96%); 42 (83%).

CAS : 222616-63-9

Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799.

8.5.2 4a-hydroxyperhydro-1-naphthalenone

Reaction :



255b **292b**

Figure 8-16

Procedure :

A solution of 4a-hydroxyoctahydro-1(2H)-naphtone-ethyleneketals **255b** (200 mg, 0.94 mmol, 1 eq) in 6 mL of a 1:1 mixture of CH_3CN : borate buffer (pH=8) was heated to 70°C. After addition of CAN (16 mg, 0.03 mmol, 0.03 eq), the reaction mixture was stirred at 70°C for 50 min.

After cooling at rt, the reaction mixture was diluted with H_2O (10 mL). The aqueous layer was extracted with DCM (3 x10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The desired product was obtained as a colorless oil (153 mg, 97%).

Analysis :

a) (4aS,8aS*)-4a-hydroxyperhydro-1-naphthalenone*[264]

IR (film): 3409 cm^{-1} (stretching O-H), 2958, 2936 and 2858 cm^{-1} (stretching C-H), 1695 (C=O), 1460, 1147, 1129, 948 and 843 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.10-1.30 (m, 1H), 1.42 –2.01 (m, 10H), 2.02-2.22 (m, 1H), 2.27-2.48 (m, 3H), H-2-10.

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 20.3, 20.8, 21.7, 24.7, 38.6, 39.4, 41.2 (C-2-5, 8-10), 56.3 (C-6), 75.4 (C-1), 211.2 (C-7).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 168 (100 %); ($M^{\cdot+}$-H_2O) 150 (40%) (100 %); ($M^{\cdot+}$-CO) 140 (8 %); ($140^{\cdot+}$-CH_3) 125 (20 %); 139 (17%); 108 (10%).

[264] Stereochemistry proved by X-Ray diffraction (A. Ates)

EA: ($C_{10}H_{16}O_2$) *calculated*: C, 71,39%; H, 9,59%; *found*: C, 71,33%; H, 9,60%.

CAS : 3468-73-3

b) (4aS,8aR*)-4a-hydroxyperhydro-1-naphthalenone*

IR: 3437 cm^{-1} (stretching O-H), 2934 and 2864 cm^{-1} (stretching C-H), 1707 (C=O)1450, 1353, 1141 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.14-1.92 (m, 9H) and 1.93-2.52 (m, 6H), (H-2-10).

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 20.6, 22.7, 23.7, 25.7, 33.7, 28.2, 38.3 (C-2-5, 8-10), 59.1 (C-6), 74.6 (C-1), 212.7 (C-7).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 168 (100 %); ($M^{\cdot+}$-H_2O) 150 (50 %); ($M^{\cdot+}$-CO) 140 (10 %); ($140^{\cdot+}$-CH_3) 125 (26 %); 139 (20%); 125 (26%); 113 (30%); 55 (12%).

EA: ($C_{10}H_{16}O_3$) *calculated*: C, 71.39%; H, 9.59%; *found*: C, 70.93%; H, 9.70%.

CAS : 77951-54-3

Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I. E. *Tetrahedron Lett.* **2003**, *59*, 8989.

8.5.3 4a-hydroxyperhydrobenzo[*a*]cyclohepten-1-one

Reaction :

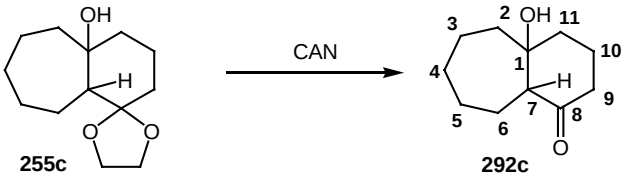


Figure 8-17

Procedure :

A solution of 4a-hydroxydecahydro-1H-benzo [a] cyclohepten-1-one ethyleneketals **255c** (200 mg, 0.88 mmol, 1 eq) in 6 mL of a 1:1 mixture of CH_3CN : borate buffer (pH=8) was heated to 70°C. After addition of CAN (16 mg, 0.03 mmol, 0.03 eq), the reaction mixture was stirred at 70°C for 50 min.

After cooling at room temperature, the reaction mixture was diluted with H_2O (10 mL). The aqueous layer was extracted with DCM (3 x 10mL). Combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The desired product was obtained as a colorless oil (154 mg, 96%).

Analysis :

a) (4a*S**,9a*R**)-4a-hydroxyperhydrobenzo[*a*]cyclohepten-1-one

IR (film): 3441 cm^{-1} (stretching O-H), 2928 and 2856 cm^{-1} (stretching C-H), 1699 (C=O), 1456, 1314, 1233, 1201, 989 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.20-2.14 (m, 15H), 2.24-2.35 (m, 2H) (H-2-6 and 9-12), 2.40 (d, *J* = 7.7 Hz, 1H, H-7)

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 20.8, 20.8, 28.5, 29.5, 30.15, 34.9, 38.5, 43.9 (C-2-6, 9-11), 62.5 (c-6), 78 (C-1), 214.6 (C-8).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 182 (82 %); ($M^{\cdot+}$-OH) 165 (25%); ($M^{\cdot+}$-H_2O) 164 (100%); ($M^{\cdot+}$-CO) 154 (41 %); ($154^{\cdot+}$-CH_3) 139 (65 %); ($164^{\cdot+}$-C_2H_4) 136 (55 %); 149 (57%); 113 (63%); 55 (65%).

EA: ($C_{11}H_{18}O_2$) calculated : C, 72.49% ; H, 9.95% ; found : C, 72.69%; H, 10.03%

CAS : 639090-47-4

b) (4a*S**,9a*S**)-4a-hydroxyperhydrobenzo[*a*]cyclohepten-1-one

IR (film): 3460 cm^{-1} (stretching O-H), 2918 and 2853 cm^{-1} (stretching C-H), 1696 (C=O), 1450, 1390, 1296, 1177, 1003, 945 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.11-2.44 (m, 17H)

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 20.2, 21.5, 21.7, 26.9, 28.5, 39.2, 40.5, 43.8 (C-2-6, 9-11), 60.6 (c-6), 78.5 (C-1), 211.4 (C-8).

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 182 (100 %); ($M^{\cdot+}$-H_2O) 164 (22%); ($M^{\cdot+}$-CO) 154 (45 %); ($154^{\cdot+}$-CH_3) 139 (66 %); ($164^{\cdot+}$-C_2H_4) 136 (43 %); 122 (43%); 111 (41%); 55 (47%).

EA: ($C_{11}H_{18}O_2$) calculated : C, 72.49% ; H, 9.95% ; found : C, 71.97%; H, 9.83%

Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I. E. *Tetrahedron Lett.* **2003**, *59*, 8989.

8.6 Fragmentation

8.6.1 6-Iodocyclononane-1,5-dione

Reaction :

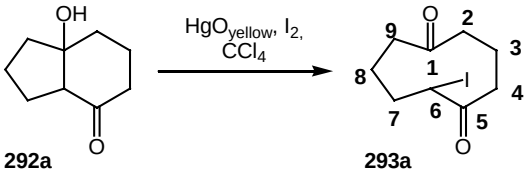


Figure 8-18

Procedure :

HgO_{yellow} (210 mg, 0.97 mmol, 3 eq) and iodine (240 mg, 0.95 mmol, 2.9 eq) were added to a solution of (3a*S**,7a*R**)-7a-hydroxyperhydro-4-indenone **292a** (50 mg, 0.32 mmol, 1 eq) in CCl_4 (5 mL). The reaction mixture was stirred at rt under irradiation (visible light) for 3 hours.

The solution was filtrated over Celite® and the filter cake was washed with CH_2Cl_2 (3 x 3 mL). The resulting solution was treated with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 10 mL) and water (2 x 10 mL). The organic layer was separated, dried over $MgSO_4$ and the solvents were removed under reduced pressure. 6-Iodocyclononane-1,5-dione (85 mg, 93 %) was obtained as a yellow solid (mp = 65-70°C)

Analysis :

IR (film): 2954 cm^{-1} (stretching C-H), 1700 (C=O), 1462, 1442, 1359, 1316, 1100, 732 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 1.72-1.85 (m, 1H, H-8a), 1.89-2.00 (m, 1H, H-8b), 2.09-2.28 (m, 3H, H-3 et H-7a), 2.29-2.42 (m, 4H, H-4a, H-9, H-7b), 2.49 (ddd, *J* = 10.8 Hz, *J* = 6.0 Hz, *J* = 3.6Hz, 1H, H-4b), 2.60-2.72 (m, 2H, H-2), 4.37 (dd, *J* = 12.3 Hz, *J* = 3.7 Hz, 1H, H-6)

^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 21.36, 24.46, 29.86 (C-6), 33.95, 34.20, 38.78, 41.60, 207.39 (C-5), 213.85 (C-1)

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 280 (12 %); ($M^{\cdot+}$-I) 153 (77%); (153^{+}-H2O) 135 (92 %); ($164^{\cdot+}$-C_2H_4) 125 (43 %); 107 (90%); 97 (61%); 84 (42%); 55 (100%).

8.6.2 6-Iodocyclodecane-1,5-dione

Reaction :

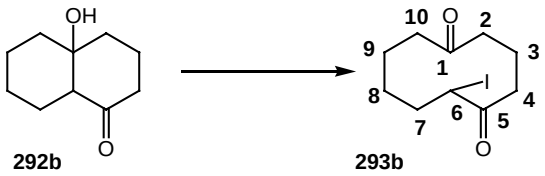


Figure 8-19

Procedure (a) :

HgO_{yellow} (960 mg, 4.46 mmol, 3 eq) and iodine (1020 mg, 4.02 mmol, 2.9 eq) were added to a solution of 4a-hydroxyperhydro-1-naphthalenone **292b** (250 mg, 1.49 mmol, 1 eq) in CCl_4 (20 mL). The reaction mixture was stirred at rt under irradiation (visible light) for 5 hours.

The solution was filtrated over Celite® and the filter cake was washed with CH_2Cl_2 (3 x 10 mL). The resulting solution was treated with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 30 mL) and water (2 x 30 mL). The organic layer was separated, dried over $MgSO_4$ and the solvents were removed under reduced pressure. 6-Iodocyclodecane-1,5-dione (399 mg, 93%) was obtained as a yellow solid (mp = 81-82°C)

Procedure (b):

$PhI(OAc)_2$ (707 mg, 3.3 mmol, 2 eq) and iodine (558 mg, 3.3 mmol, 2 eq) were added to a solution of 4a-hydroxyperhydro-1-naphthalenone

292b (200 mg, 1.64 mmol, 1 eq) in CH_2Cl_2 (100 mL). The resulting mixture was stirred at rt for 2 hours.

The organic layer was washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting oil was purified by flash column chrommatography (50:50 PE :Ether; Rf = 0.5). 6-Iodocyclodecane-1,5-dione (338 mg, 67 %) was obtained as yellow solid.

Analysis :

IR (film): 2930 and 2880 cm^{-1} (stretching C-H), 1699 (C=O), 1437, 1372, 1318, 1316, 1120 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 1.31-1.43 (m, 1H, H-8a), 1.60-1.76 (m, 3H, H-8b and H-9), 1.75-2.06 (m, 1H, H-3a), 2.07-2.16 (m, 2H, H-3b and H-7), 2.24 (dddd, *J* = 15.4 Hz, *J* = 11.5 Hz, *J* = 6.7 Hz, *J* = 4.7 Hz, 1H, H-10a), 2.44 (ddd, *J* = 16.4 Hz, *J* = 6.8 Hz, *J* = 4.2 Hz, 1H, H-4a), 2.44 (ddd, J^1= 14.4, J^2= 7.0 Hz, J^3 = 7.0 Hz, 1H, H-10b), 2.58 (ddd, *J* = 16.4 Hz, *J* = 9.7 Hz, *J* = 4.4 Hz, 1H, H-4b), 2.75-2.86 (m, 2H, H-2), 4.43 (dd, *J* =11.5 Hz, *J* =3.3 Hz, 1H, H-6)

^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 19.70 (C-3), 22.30 (C-9), 27.22 (C-8), 31.81 (C-6), 34.69 (C-2), 34.98 (C-7), 40.32 (C-4), 43.78 (C-10), 206.64 (C-5), 213.23 (C-1)

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 294 (4 %); ($M^{\cdot+}$-I) 167 (100 %); (167^+-H_2O) 149 (58 %); (167^+-C_2H_4) 139 (26 %); 107 (37%); 121 (44%); 97 (60%); 55 (57%).

8.6.3 6-Iodocycloundecane-1,5-dione

Reaction :

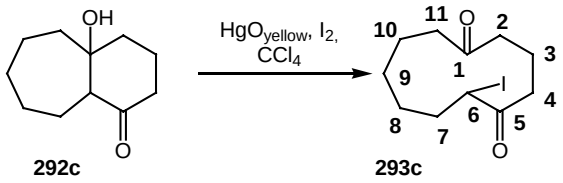


Figure 8-20

Procedure :

HgO_{yellow} (75 mg, 0.34 mmol, 3 eq) and iodine (85 mg, 0.33 mmol, 2.9 eq) were added to a solution of 4a-hydroxyperhydrobenzo[*a*]cyclohepten-1-one **292c** (21 mg, 0.11 mmol, 1 eq) in CCl_4 (1.5 mL). The reaction mixture was stirred at rt under irradiation (visible light) for five hours.

The solution was filtrated over Celite® and the filter cake was washed with CH_2Cl_2 (3 x 4 mL). The resulting solution was treated with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 10mL) and water (2 x 10mL). The organic layer was separated, dried over $MgSO_4$ and the solvents were removed under reduced pressure. 6-iodocycloundecane-1,5-dione (31 mg, 90%) were obtained as a yellow solid (mp = 79-80°C)

Analysis :

IR (film): 2938, 2875 and 2848 cm^{-1} (stretching C-H), 1703 (C=O), 1460, 1436, 1367, 1189, 1087 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm): 1.08-1.52 (m, 4H), 1.70-2.42 (m, 8H), 2.55-2.69 (m, 2H), 2.77 (ddd, *J* = 17.3, *J* = 6.6 Hz, *J* = 4.9 Hz, 1H, H-2a), 2.95 (ddd, *J* = 17.4 Hz, *J* = 8.2 Hz, *J* = 5.1 Hz, 1H, H-2b), 4.28 (dd, *J* =11.5 Hz, *J* =3.3 Hz, 1H, H-6)

^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm): 18.30, 22.97, 26.18, 26.88, 30.61 (C-6), 33.84, 34.30, 40.17, 41.63, 207.19 (C-5), 213.46 (C-1)

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 308 (6 %); ($M^{\cdot+}$-$H^{\cdot}$) 307 (6 %); ($M^{\cdot+}$-H_2) 306 (20 %); ($M^{\cdot+}$-I) 181 (100 %); (181^{+}-H_2O) 163 (40 %); 97 (35%); 55 (80%).

8.6.4 6-Iodo-10-méthylcyclodecane-1,5-dione

Reaction :

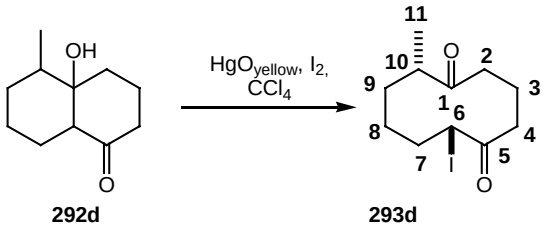


Figure 8-21

Procedure :

HgO_{yellow} (268 mg, 1.23 mmol, 3 eq) and iodine (304 mg, 1.19 mmol, 2.9 eq) were added to a solution of 4a-hydroxy-5-methyloctahydro-1(*2H*)-naphtone **292d** (75 mg, 0.41 mmol, 1 eq) in CCl_4 (1.5 mL). The reaction mixture was stirred at rt under irradiation (visible light) for 5 hours.

The solution was filtrated over celite® and the filter cake was washed with CH_2Cl_2 (3 x 5 mL). The resulting solution was treated with a saturated

aqueous solution of $Na_2S_2O_3$ (2 x 10 mL) and water (2 x 10 mL). The organic layer was separated, dried over $MgSO_4$ and the solvents were removed under reduced pressure. *cis*-6-iodo-10-methylcyclodecane-1,5-dione (119 mg, 94%) were obtained as a yellow solid (mp = 83-84°C)

Analysis :

IR (film): 3008, 2969, 2940 and 2887 cm^{-1} (stretching C-H), 1702 (C=O), 1466, 1375, 1194, 1083, 905, 740 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 1.00 (d, *J*= 6.7 Hz, 3H, 11), 1.10-1.21 (m, 1H, H-8a), 1.40-1.54 (m, 1H, H-9a), 1.63-1.81 (m, 2H, H-8b and H-9b), 1.87-2.01 (m, 1H, H-3a), 2.04-2.22 (m, 3H, H-3b and H-7), 2.39 (ddd, *J* = 17.6, *J* = 5.6 Hz, *J* = 4.0 Hz, 1H, H-4a), 2.55-2.70 (m, 3H, H-2a, H-4b and H-10), 2.98 (ddd, *J* = 15.0 Hz, *J* = 10.2 Hz, *J* = 4.0 Hz, 1H, H-2b), 4.31 (dd, *J* =11.7 Hz, *J* =4.0 Hz, 1H, H-6)

^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 16.27 (C-11), 19.26 (C-3), 24.99 (C-8), 31.42 (C-9), 31.64 (C-6), 33.68 (C-2), 35.47 (C-7), 39.79 (C-4), 46.85 (C-10), 207.09 (C-5), 215.39 (C-1)

MS (EI, 70 eV) m/z (relative intensity): ($M^{\cdot+}$) 308 (46 %)

($M^{\cdot+}$-I) 181 (93 %)

139 (45%), 111 (50%), 97 (52%), 55 (95%), 42 (100%)

8.6.5 2,6-dioxocyclodecyl acetate

Reaction :

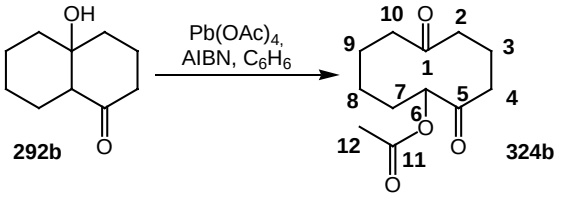


Figure 8-22

Procedure :

$Pb(OAc)_4$[265] (536 mg, 1.20 mmol, 2 eq) and AIBN (10 mg, 0.06 mmol, 0.1 eq) were added to a solution of 4a-hydroxyperhydro-1-naphthalenone (100 mg, 0.6 mmol, 1 eq) in refluxing benzene (2 mL) and the reaction mixture was refluxed for 24h.

This solution was cooled at rt and Et_2O (5 mL) was added. The organic layer was washed with an aqueous, saturated solution of NaCl (3 x 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting oil was purified by preparative TLC (PE/Ether; 80/20; Rf = 0.2) to give 2,6-dioxocyclodecyl acetate (57 mg, 45%) as a white solid.

Analysis :

IR (film): 2931 and 2863 cm^{-1} (stretching C-H), 1744 (COOEt), 1680 (C=O), 1634, 1388, 1373, 1236, 1214, 1070, 1053, 1006 cm^{-1}

[265] $Pb(OAc)_4$ was first crystallised in AcOH and then dried over P_2O_5/KOH for 24h.

^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm): 1.45-1.60 (m, 2H, 8), 1.60-1.75 (m, 2H, H-3), 2.00-2.15 (m, 3H, H-7 and H-9a), 2.15-2.25 (m, 1H, H-9b), 2.18 (s, 3H, H-12), 2.3-2.4 (m, 3H) and 2.45-2.55 (m, 3H) (H-2, H-4 and H-10), 5.30 (dd, J = 13.5 Hz, J = 5.5 Hz, 1H, H-6)

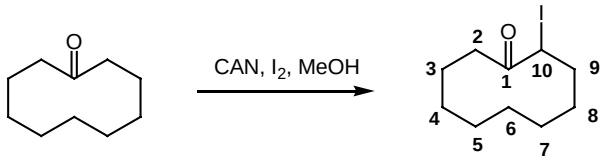
^{13}C-NMR (125 MHz, $CDCl_3$) δ(ppm): 21.0 (C-12), 21.8, 21.9, 22.1, 22.2 (C-3, C-7-9), 73.7 (C-6), 156.4 (C-5), 170.5 (C-11), 193.6 (C-1)

MS (EI, 70 eV) m/z (relative intensity): No M^+; (M^+-CO_2CH_3) 167 (65 %); 149 (19%), 122 (13%), 86 (4%), 84 (6%)

8.7 Synthesis of α-iodoketone

8.7.1 2-iodo-1-cyclodecanone

Reaction I :



336 **337**

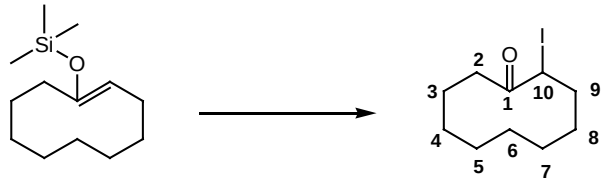
Figure 8-23

Procedure :

CAN (900 mg, 1.5 mmol, 0.5 eq) was added to a solution of iodine (820 mg, 3 mmol, 1 eq) and cyclodecanone (500 mg, 3 mmol, 1 eq) in MeOH (40 mL). The reaction mixture was stirred at rt for 15h.

H_2O (100 mL) was added and the layers were separated. The aqueous layer was extracted with ether (2 x 150 mL). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (3 x 100 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. After purification by flash column chromatography (PE : AE, 98:2, Rf = 0.3), the desired product was obtained with 63 % yield (530 mg).

Reaction II :



Procedure(a) :

A solution of iodine (1.5 g, 6 mmol, 1 eq) and AgOAc (1 g, 6 mmol, 1 eq) in CH_2Cl_2 (45 mL) was stirred at rt for 15 min, then, 1-cyclodecenyl (1,1,1-trimethylsilyl) ether (1.4 g, 6 mmol, 1 eq) was added and the reaction mixture was stirred for an additionnal 15 min.

The reaction mixture was filtered and the filter cake (AgI) was washed with CH_2Cl_2 (15 mL). The collected filtrates were stirred with Bu_4NF (12 mL, 1.0 M sol. In THF) for an additional 30 min.

The organic layer was washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 50 mL) and water (1 x 50 mL), dried over $MgSO_4$ and the solvet was removed under reduced pressure. After purification by flash column chromatography (PE : EA, 98:2, Rf = 0.3), the desired product was obtained in 33 % yield (550 mg).

Procedure (b) :

A solution of 1-cyclodecenyl (1,1,1-trimethylsilyl) (4.2 g, 18 mmol, 1 eq) in CH_2Cl_2 (70 mL) was cooled to 0°C and N-iodosuccinimide (4.1 g, 18 mmol, 1 eq) was added. The reaction mixture was kept at this temperature for 30 min.

The reaction mixture was dilluted with CH_2Cl_2 (50 mL) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (2x50 mL) and water (1 x 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (PE : EA, 98:2, Rf=0.3), the desired product was obtained in 89 % yield (4.5 g).

Analysis :

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.20-2.20 (m, 13H, H-3b to 9), 2.50-2.70 (m, 2H, H-2a and 3a), 2.90-3.00 (m, 1H, H-2b), 4.90 (dd, *J*= 3.9Hz, *J*= 12Hz, 1H, H-10).

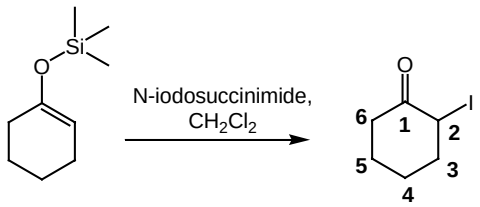
^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 23.6, 24.0, 24.6, 25.3, 25.4, 25.5, 29.2, 35.7, 37.0 (C-2-10), 207.4 (C-1).

CAS : 649767-27-1

Horiuchi, C. A.; Takeda, A.; Chai, W.; Ohwada, K.; Ji, S.-J.; Takahashi, T. T. *Tetrahedron Lett.* **2003**, *44*, 9307.

8.7.2 2-iodo-1-cyclohexanone

reaction :



258b **449b**

Figure 8-24

Procedure :

A solution of 1-cyclohexenyl (1,1,1-trimethylsilyl) (5.0 g, 29 mmol, 1 eq) in CH_2Cl_2 (70 mL) was cooled to 0°C and N-iodosuccinimide (6.6 g, 29 mmol, 1 eq) was added. The reaction mixture was kept at this temperature for 30 min.

The reaction mixture was dilluted with CH_2Cl_2 (50 mL) and was washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 50 mL) and water (1x50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash chromatography (PE : EA, 90:10, Rf=0.2), the desired product was obtained in 66 % yield (4.25 g).

Analysis :

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.7-2.5 (m, 8H, H-3 to H-6), 4.93 (dd, *J* = 3.8 Hz, *J* = 12.1 Hz, 1H, H-2)

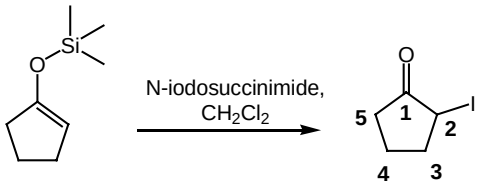
^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 20.2, 21.4 (C-4 and C-5), 27.0 (C-2), 36.7, 35.1 (C-3 and C-6), 212.7 (C-1)

CAS : 35365-19-6

Cantacuzene, J.; Jantzen, R.; Ricard, D. *Tetrahedron Lett.* **1972**, *28*, 717.

8.7.3 2-iodo-1-cyclopentanone

reaction :



258a **449a**

Figure 8-25

Procedure :

A solution of 1-cyclopentenyl (1,1,1-trimethylsilyl) (5.0 g, 32 mmol, 1 eq) in CH_2Cl_2 (70 mL) was cooled to 0°C and N-iodosuccinimide (7.2 g, 32 mmol, 1 eq) was added. The reaction mixture was kept at this temperature for 2 h.

The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 50 mL) and water (1 x 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (PE : EA, 95:5, Rf = 0.15), the desired product was obtained in 85 % yield (5.69 g).

Analysis :

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.85-2.4 (m, 6H, H-3 to H-5), 4.50 (dd, *J* = 3.7 Hz, *J* = 12.0 Hz, 1H, H-2)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 21.3 (C-4), 26.4 (C-2), 34.9, 35.3 (C-3 and C-5), 212.9 (C-1)

CAS : 69381-32-4

Rubottom, G. M.; Mott, R. C. *J. Org. Chem.* **1979**, *44*, 1731.

8.7.4 3-iodo-4-phenylbutan-2-one and 1-iodo-4-phenylbutan-2-one

Reaction :

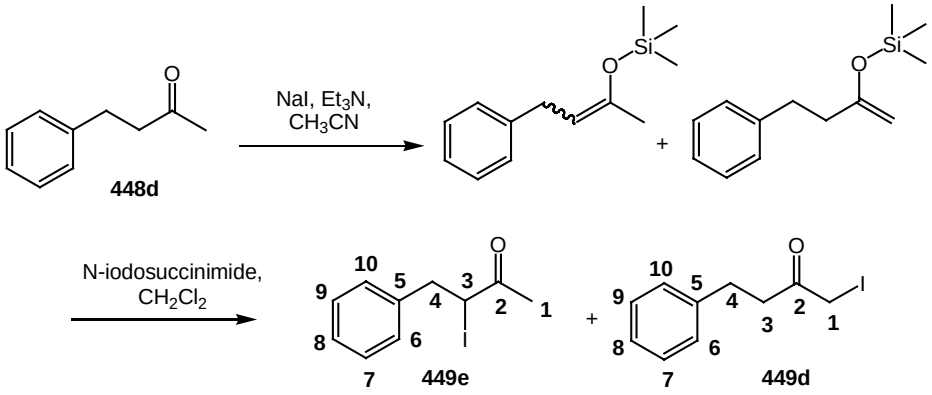


Figure 8-26

Porcedure (step 1):

A solution of sodium iodide (7.04 g, 47 mmol, 1.25 eq) in CH_3CN (60 mL) was added to neat 4-phenyl-2-butanone (5.0 g, 34 mmol, 1 eq), TMSCl (5.1 g, 5.97 mL, 47 mmol, 1.25 eq) and triethylamine (4.7 g, 6.55 mL, 47 mmol, 1.25 eq). The reaction mixture was stirred at rt for 17h.

The resulting mixture was extracted with pentane (3 x 20 mL). The pentane layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the desired product. The crude material was engaged immediately in the next step.

Procedure (step 2) :

A solution of [1-methyl-3-phenyl-1-propenyl (1,1,1-trimethylsilyl) ether and 1-phenethylvinyl (1,1,1-trimethylsilyl) ether] (34 mmol, 1 eq) in CH_2Cl_2 (70 mL) was cooled to 0°C and N-iodosuccinimide (8.3 g, 37 mmol, 1.1 eq) was added. The reaction mixture was maintened at this temperature for 2 h.

The resulting mixture was dilluted with CH_2Cl_2 (50 mL) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 50 mL) and water (1 x 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After purification by flash column chromatography (PE : EA, 90:10), two different products were obtained: F_1 (Rf = 0.2) 1-iodo-4-phenyl-2-butanone as a white solid (3.21 g, 35%) and F_2 (Rf = 0.15) 3-iodo-4-phenyl-2-butanone as a yellow oil (2.31 g, 25%).

Analysis :

a) 1-iodo-4-phenyl-2-butanone

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 2.90-3.10 (m, 4H, H-3 et H-4), 3.77 (s, 2H, H-1), 7.15-7.35 (m, 5H, H-6 to 10)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 6.3 (C-1), 30.1 (C-4), 40.7 (C-3), 126.2 (C-8), 128.2 and 128.4 (C-6, C-7, C-9 and C-10), 140.2 (C-5), 201.9 (C-2)

CAS : 352276-27-8

Mukaiyama, T.; Takuwa, T.; Yamane, K.; Imachi, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 813.

b) 3-iodo-4-phenyl-2-butanone

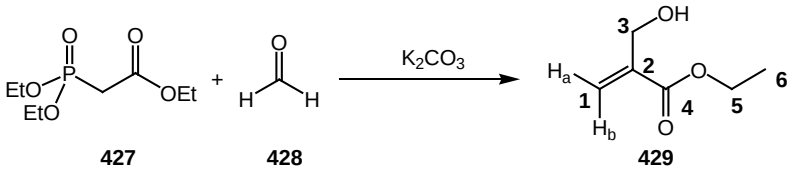
^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 2.37 (s, 3H, H-1), 3.20 (dd, *J*=5.75 Hz, *J*=12 Hz, 1H, H-4a), 3.43 (dd, *J*=6.75 Hz, *J*=11.4 Hz, 1H, H-4b), 4.71 (t, *J* = 6.5, 1H, H-3), 7.05-7.20 (m, 5H, H-6 to 10)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 26.6 (C-1), 32.2 (C-4), 40.7 (C-3), 126.9 (C-8), 128.5 and 128.8 (C-6, C-7, C-9 and C-10), 138.6 (C-5), 201.9 (C-2)

8.8 Synthesis of acrylates

8.8.1 Ethyl α-(hydroxymethyl)acrylate

Reaction :



427 **428** **429**

Figure 8-27

Procedure :

Paraformaldehyde (15.6 g, 0.52 mol, 4 eq) and H_3PO_4 (0.4 mL, 1.0 M aq. sol.) in water (40 mL) were heated at 90°C for 5 h to form a clear solution.

The reaction mixture was cooled to rt and triethylphosphonoacetate (28.6 g, 0.13 mol, 1 eq) was added in one portion. A solution of K_2CO_3 (19.8 g, 0.14 mol, 1.1 eq) in water (20 mL) was then added slowly over 1.5 h. The temperature of the reaction mixture was kept between 35°C and 45°. After addition, the reaction mixture was cooled rapidly to –5°C and Et_2O (50 mL), followed by brine (50 mL) were added.

The aqueous phase was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting oil was distilled (18 mmHg, 93-97°C) to afford ethyl α-(hydroxymethyl)acrylate (9.83g, 58%).

Analysis :

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.44 (t, *J* = 6.9 Hz, 3H, H-6), 3.03 (large s, 1H, OH), 4.36 (q, *J* = 7.2 Hz, 2H, H-5), 4.45 (s, 2H, H-3), 5.97 (s, 1H, H-1a), 6.38 (s, 1H, H-1b)

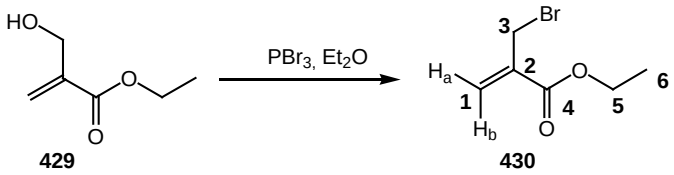
^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 14.1 (C-6), 60.8 (C-5), 62.1 (C-3), 125.2 (C-1), 139.4 (C-2), 166.1 (C-4)

CAS : 10029-04-6

Rosenthal, R. W.; Schwartzman, L. H.; Greco, N. P.; Proper, R. *J. Org. Chem.* **1963**, *28*, 2835.

8.8.2 Ethyl α-(bromomethyl)acrylate

Reaction :



429 **430**

Figure 8-28

Procedure :

A solution of ethyl α-(hydroxymethyl)acrylate (9.83 g, 0,076 mol, 1 eq) in ether (80 mL) was cooled to –9°C. PBr_3 (9.94 g, 3.45 mL, 0,036 mol, 0.47 eq) was added slowly over 30 min. The reaction mixture was allowed to warm to rt and it was stirred for an additional 3 h.

The solution was cooled to –10°C and water (20 mL) was added. The resulting solution was stirred at –10°C for 1.5h. After separation, the aqueous layer was extracted with pentane (3 x 30 mL) and the combined organic layers were washed with a saturated aqueous solution of NH_4Cl (2 x 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting oil was purified by distillation (18 mmHg, 85-87°C) to give 11.3 g of ethyl α-(bromomethyl)acrylate (77%).

Analysis :

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.30 (t, *J* = 7.2 Hz, 3H, H-6), 4.15 (s, 2H, H-3), 4.24 (q, *J* = 7.2 Hz, 2H, H-5), 5.92 (s, 1H, H-1a), 6.29 (s, 1H, H-1b)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 14.1 (C-6), 29.4 (C-3), 61.2 (C-5), 128.7 (C-1), 137.4 (C-2), 164.6 (C-4)

CAS : 17435-72-2

Ferris, A. F. *J. Org. Chem.* **1955**, *20*, 780.

8.8.3 ethyl 2-[(1,1,1-tributylstannyl)methyl]acrylate

Reaction :

Figure 8-29

Procedure :

Ethyl α-(bromomethyl) acrylate (7.97 g, 6.9 mL, 0.024 mol, 1 eq) was added to a suspension of magnesium powder (0.66 g, 0,027 mol, 1.1 eq), $PbBr_2$ (0.51 g, 1.35 mmol, 0.05 eq) and Bu_3SnCl (5.2 g, 0.027 mol, 1.1 eq) in THF (25 mL). The reaction mixture was stirred at rt for 4 h.

The suspension was diluted with pentane (20 mL) and filtreted over Celite®. The filtrate was evaporated under reduced pressure. The residue was dissolved in ether (30 mL) and stirred in the presence of Et_3N (0.91 g, 1.25 mL, 9 mmol) for 10 min. The solution was filtreted over a plug of silice and evaporated under reduced pressure. The resulting oil was purified by distillation (0.37 mmHg, 105°C) to give 4.6 g of ethyl α-(tributylstannylmethyl)acrylate (42%).

Analysis :

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 0.75-0.95 and 1.25-1.56 (m, 21H), 1.95 (d, *J* = 0.9 Hz, 2H, H-3), 4.2 (q, *J* = 7.2 Hz, 2H, H-5), 5.26 (d, *J* = 1.8 Hz, 1H, H-1a), 5.79 (d, *J* = 2.1 Hz, 1H, H-1b)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 9.7 (CH_2x3), 13.6 (C-6), 13.7 (CH_3x3), 14.9 (C-3), 27.4 (CH_2x3), 29.0 (CH_2x3), 60.6 (C-5), 118.3 (C-1), 141.2 (C-2), 168.3 (C-4)

CAS : 108286-71-1

Baldwin, J. E.; Adlington, R. M.; Sweeney, J. B. *Tetrahedron Lett.* **1986**, *27*, 5423.

8.9 Radical reactions of α-iodoketones

8.9.1 methyl 3-(2-oxocyclodecyl)propanoate

Reaction :

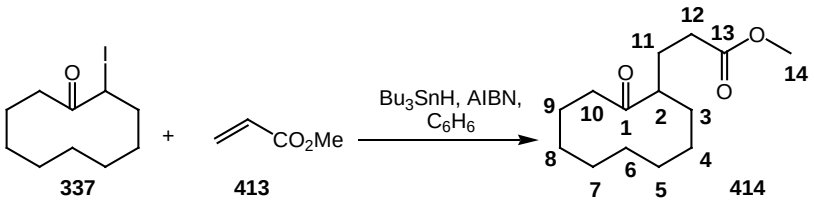


Figure 8-30

Procedure :

A solution of Bu_3SnH (104 mg, 0.1 mL, 0.36 mmol, 1 eq) and AIBN (6 mg, 0.036 mmol, 0.1 eq) in benzene (0.5 mL) was added over 2h to a

solution of 2-iodocyclodecanone (100 mg, 0.36 mmol, 1 eq) and methyl acrylate (153 mg, 0.16 mL, 1.78 mmol, 5 eq) in refluxing benzene (1 mL).

The reaction mixture was dilluted with CH_3CN (3 mL) and the resulting solution was washed with pentane (3 x 5 mL). The CH_3CN layer was evaporated under reduced pressure and the crude product was purified by flash column chromatography (PE : Et_2O, 85:15, Rf = 0.38) to give 36 mg of methyl 3-(2-oxocyclodecyl)propanoate (42 %).

Analysis :

IR: 2927 cm^{-1} (stretching C-H), 1739 and 1702 cm^{-1} (C=O), 1473, 1438, 1375, 1254, 1172 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.2-2.0 (m, 16H), 2.28 (dt, *J* = 7.5 Hz, *J* = 1.2 Hz, 2H, H-12), 2.42 (ddd, *J* = 16.5 Hz, *J* = 8.1 Hz, *J*= 3.6 Hz, 1H, H-10a), 2.69 (ddd, *J* = 16.5 Hz, *J* = 9.0 Hz, *J*= 3.6 Hz, 1H, H-10b), 2.7 (m, 1H, H-2), 3.67 (s, 3H, H-14)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 23.4, 24.0, 24.7, 24.9, 25.1, 25.6 (C-4 to C-9), 28.4 (C-11), 30.8 (C-3), 31.9 (C-12), 41.3 (C-10), 51.6 (C-2), 51.9 (C-14), 173.8 (C-13), 216.7 (C-1)

MS (CI, CH_4-NO_2) m/z (relative intensity): (M^+) 240 (31 %); (M^+-OCH_3) 209 (100 %)

HRMS (EI+) : calculated mass (240.1725) found mass (240.1717)

8.9.2 methyl 2-methyl-3-(2-oxocyclodecyl)propanoate

Reaction :

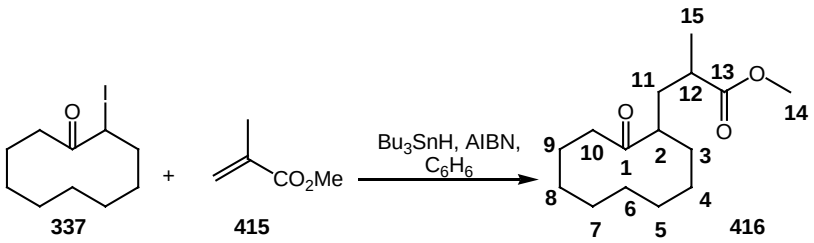


Figure 8-31

Procedure :

A solution of Bu_3SnH (209 mg, 0.2 mL, 0.72 mmol, 1 eq) and AIBN (12 mg, 0.072 mmol, 0.1 eq) in benzene (1 mL) was slowly added over 30 min to a solution of 2-iodocyclodecanone (200 mg, 0.72 mmol, 1 eq) and methyl methacrylate (356 mg, 0.24 mL, 3.56 mmol, 5 eq) in refluxing benzene (2 mL).

The reaction mixture was dilluted with CH_3CN (6 mL) and the resulting solution was washed with pentane (3 x 10 mL). The CH_3CN layer was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Ether, 90:10, Rf = 0.35) to give 153 mg of methyl 2-methyl-3-(2-oxocyclodecyl)propanoate (84 %).

Analysis :

IR: 2929 and 2850 cm^{-1} (stretching C-H), 1737 and 1696 cm^{-1} (C=O), 1462, 1377, 1262, 1196, 1166, 1050, 827, 736 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.15 (d, *J* = 7.2 Hz, 3H, H-15), 1.2-2.0 (m, 16H), 2.4-2.5 (m, 2H, H-12 and H-10a), 2.6-2.8 (m, 2H, H-10b and H-2), 3.67 (s, 3H, H-14)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 17.8 (C-15), 23.4, 24.1, 24.8, 25.2, 25.3, 25.7 (C-4 to C-9), 30.7, 37.3 (C-3 and C-11), 37.6 (C-12), 40.8 (C-10), 50.2 (C-2), 51.8 (C-14), 176.8 (C-13), 216.3 (C-1)

MS (APCI) m/z (relative intensity): (M^++1) 255 (5 %); (M+) 254 (38 %); 224 (15 %); 223 (100 %); 205 (9 %); 195 (22 %); 187 (8 %).

HRMS (CI+) : calculated mass (254.1882) found mass (254.1879)

8.9.3 ethyl 2-((2-oxocyclopentyl)methyl)acrylate

Reaction :

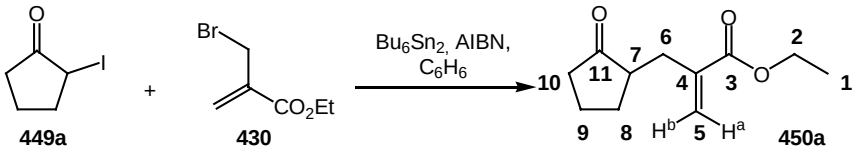


Figure 8-32

Procedure :

A solution of 2-iodocyclopentanone (107 mg, 0.51 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (196 mg, 0.13 mL, 1.02 mmol, 2 eq), Bu_6Sn_2 (295 mg, 0.26 mL, 0.51 mmol, 1 eq) and AIBN (17 mg, 0.10 mmol, 0.2 eq) in benzene (1 mL) was degassed and then refluxed for 2.5 h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Et_2O, 90:10

→ 80:20 , Rf = 0.25) to give 95 mg of ethyl 2-((2-oxocyclopentyl)methyl)acrylate (95 %).

Analysis :

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.3 (t, J = 7.1 Hz, 3H, H-1), 1.3-2.4 (m, 8H), 2.8 (dd, J^1 = 14.0 Hz, J^2 = 4.2 Hz, 1H, H-6a), 4.18 (q, J = 7.1 Hz, 2H, H-2), 5.6 (s, 1H, H-5b), 6.2 (s, 1H, H-5a)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 14.1 (C-1), 20.4, 29.3, 32.0 (C-6, C-8 and C-9), 37.8 (C-10), 48.3 (C-7), 60.7 (C-2), 126.1 (C-5), 138.8 (C-4), 166.8 (C-3), 219.7 (C-11)

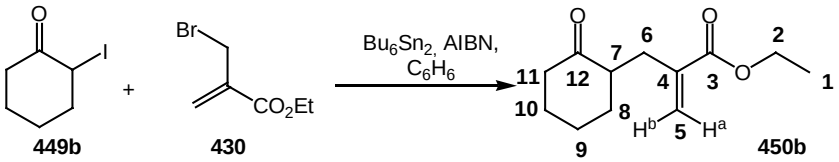
MS (CI, CH_4-NO_2) m/z (relative intensity): (M^++1) 197 (57 %); 151 (100%); 133 (12%); 123 (37%); 105 (24%); 95 (56%); 93 (9%); 79 (34%); 67 (36%); 55 (9%); 43 (9 %).

CAS : 54312-35-5

Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, *55*, 5977.

8.9.4 ethyl 2-((2-oxocyclohexyl)methyl)acrylate

Reaction :



449b **430** **450b**

Figure 8-33

Procedure :

A solution of 2-iodocyclohexanone (107 mg, 0.48 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (185 mg, 0.13 mL, 0.96 mmol, 2 eq), Bu_6Sn_2 (278 mg, 0.24 mL, 0.51 mmol, 1 eq) and AIBN (16 mg, 0.10 mmol, 0.2 eq) in benzene (1 mL) was degassed and then refluxed for 2.5h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Et_2O, 90:10 $\rightarrow$ 80:20 , Rf = 0.20) to give 85 mg of ethyl 2-((2-oxocyclohexyl)methyl)acrylate (85 %).

Analysis :

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.25 (t, *J* = 7.1 Hz, 3H, H-1), 1.25-1.34 (m, 1H), 1.55-1.66 (m, 2H), 1.78-1.86 (m, 1H), 1.97-2.12 (m, 3H), 2.22-2.42 (m, 2H), 2.47-2.60 (m, 1H), 2.87 (dd, *J* = 13.8 Hz, *J* = 4.8 Hz, 1H, H-6a), 4.15 (q, J = 7.2 Hz, 2H, H-2), 5.52 (d, *J* = 1.5 Hz, 1H, H-5b), 6.15 (d, *J* = 1.5 Hz, 1H, H-5a)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 14.2 (C-1), 25.1, 28.1, 32.0, 33.7 (C-6 and C-8 to C-10), 42.1 (C-11), 49.2 (C-7), 60.6 (C-2), 126.5 (C-5), 138.4 (C-4), 166.8 (C-3), 211.8 (C-11)

MS (CI, CH_4-NO_2) m/z (relative intensity): (M^++1) 211 (52 %); (M^+) 210 (8%); 193 (6 %); 182 (8 %); 166 (10 %); 165 (100 %); 164 (9 %); 136 (9 %).

CAS : 54312-36-6

Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, *55*, 5977.

8.9.5 ethyl 2-((2-oxocyclodecyl)methyl)acrylate

Reaction :

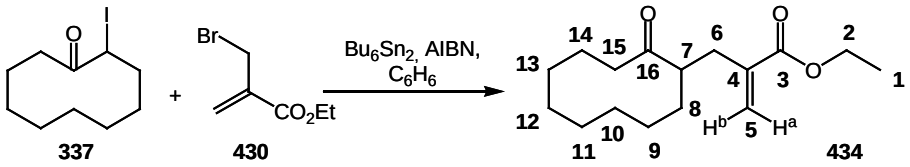


Figure 8-34

Procedure :

A solution of 2-iodocyclodecanone (2.0 g, 7.1 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (1.38 g, 0.93 mL, 7.1 mmol, 1 eq), Bu_6Sn_2 (4.94 g, 4.3 mL, 8.5 mmol, 1 eq) and AIBN (230 mg, 0.2 mmol, 0.2 eq) in benzene (20 mL) was degassed and refluxed for 2.5 h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Et_2O, 1:0 $\rightarrow$ 95:05 $\rightarrow$ 90:10 , Rf = 0.20) to give 1.21 g of ethyl 2-((2-oxocyclodecyl) methyl)acrylate (64 %).

Analysis :

IR: 2927 and 2871 cm^{-1} (stretching C-H), 1713 cm^{-1} (C=O), 1629 cm^{-1} (C=C-C=O), 1472, 1445, 1369, 1326, 1179, 1137, 1026, 950, 819, 737 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.28 (t, *J* = 7.2 Hz, 3H, H-1), 1.2-1.9 (m, 16H), 2.20-2.31 (m, 2H), 2.61 (ddd, *J* = 16.2 Hz, *J* = 9.0 Hz, *J* =

3.3 Hz, 1H), 2.99-3.10 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H, H-2), 5.48 (s, 1H, H-5b), 6.12 (d, *J* = 1.5 Hz, 1H, H-5a)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 14.1 (C-1), 23.0, 23.3, 23.5, 24.1. 24.7, 24.8, 25.1, 25.2 (C-6 and C-8 to C-14), 42.3 (C-15), 50.3 (C-7), 60.7 (C-2), 126.9 (C-5), 138.0 (C-4), 166.7 (C-3), 214.7 (C-16)

MS (CI, CH_4-NO_2) m/z (relative intensity): (M^++1) 267 (100 %)
249 (23 %), 181 (17 %), 174 (13 %), 162 (8 %)

HRMS (CI+) : calculated mass (267.1960) found mass (267.1947)

8.9.6 ethyl 2-((2-oxocyclododecyl)methyl)acrylate

Reaction :

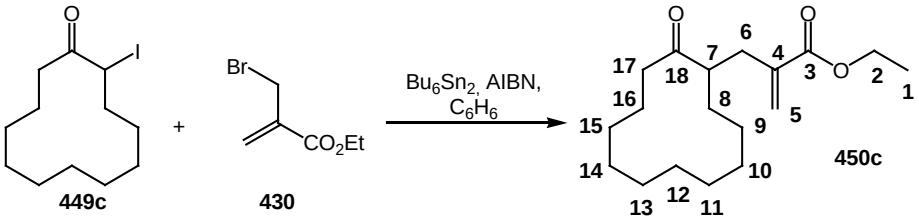


Figure 8-35

Procedure :

A solution of 2-iodocyclododecanone (2.5 g, 8.11 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (3.1 g, 2.12 mL, 16.22 mmol, 2 eq), Bu_6Sn_2 (4.7 g, 4.10 mL, 8.11 mmol, 1 eq) and AIBN (0.26 g, 1.62 mmol, 0.2 eq) in benzene (20 mL) was degassed and refluxed for 2.5h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Et_2O, 1:0 →

95:05 Rf = 0.15) to give 1.7 g of ethyl 2-((2-oxocyclododecyl)methyl)acrylate (71 %).

Analysis :

IR: 2932 and 2864 cm^{-1} (stretching C-H), 1718 cm^{-1} (C=O), 1628 cm^{-1} (C=C-C=O), 1469, 1411, 1368, 1326, 1188, 1140, 1025, 946 cm^{-1}

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.05-1.38 (m, 17H), 1.47-1.83 (m, 4H), 2.19-2.40 (m, 2H), 2.53-2.73 (m, 2H), 2.82-2.97 (m, 1H), 4.18 (q, *J* = 7.5 Hz, 2H, H-2), 5.52 (d, *J* = 1.2 Hz, 1H, H-5b), 6.15 (d, *J* = 1.6 Hz, 1H, H-5a)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 14.1 (C-1), 21.9, 22.2, 23.7, 23.9, 24.0, 25.6, 25.9, 29.1, 33.4, 38.2 (C-6 and C-8 to C-17), 49.6 (C-7), 60.7 (C-2), 126.6 (C-5), 138.3 (C-4), 166.8 (C-3), 213.7 (C-18)

MS (APCI) m/z (relative intensity): (M^{+}+1) 295 (100 %); 250 (16 %); 249 (95 %)

HRMS (EI+) : calculated mass (294.2195) found mass (294.2193)

8.9.7 <u>ethyl 4-benzyl-2-methylene-5-oxohexanoate</u>

Reaction :

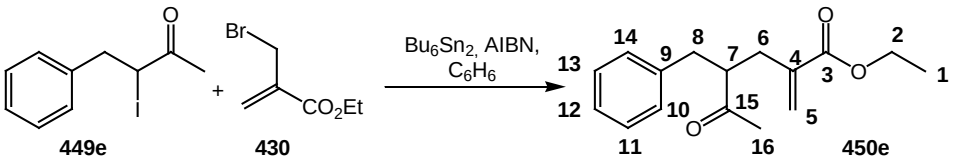


Figure 8-36

Procedure :

A solution of 3-iodo-4-phenylbutan-2-one (105 mg, 0.38 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (147 mg, 0.1 mL, 0.76 mmol, 2 eq), Bu_6Sn_2 (220 mg, 0.19 mL, 0.38 mmol, 1 eq) and AIBN (13 mg, 0.07 mmol, 0.2 eq) in benzene (1 mL) was degassed and refluxed for 2.5 h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Et_2O, 90:10 $\rightarrow$ 85:15, Rf = 0.25) to give 75 mg of ethyl 4-benzyl-2-methylene-5-oxohexanoate (76 %).

Analysis :

IR: 3027, 2981 and 2928 cm^{-1} (stretching C-H), 1716 cm^{-1} (C=O), 1630 cm^{-1} (C=C-C=O), 1496, 1369, 1303, 1183, 1138, 1028, 951, 737, 701 cm^{-1}

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.28 (t, *J* = 7.1 Hz, 3H, H-1), 1.92 (s, 3H, H-16), 2.41 (dd, *J* = 14.3, *J* = 6.0, 1H), 2.55-2.75 (m, 2H), 2.80-2.93 (m, 1H), 3.09-3.22 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H, H-2), 5.54 (d, *J* = 1.2 Hz, 1H, H-5b), 6.18 (d, *J* = 1.2 Hz, 1H, H-5a), 7.09-7.32 (m, 5H, H-10 to H-14)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 14.1 (C-1), 31.0 (C-16), 34.4, 37.9 (C-6 and C-8), 52.9 (C-7), 60.8 (C-2), 126.4 (C-12), 127.3 (C-5), 128.5, 128.8 (C-10, C-11, C-13 and C-14), 137.9, 139.1 (C-4 and C-9), 166.7 (C-3), 211.6 (C-15)

MS (CI, CH_4-NO_2) m/z (relative intensity): (M^++1) 261 (19 %)
215 (17 %), 210 (12 %), 182 (100 %), 155 (11 %), 149 (20 %), 135 (46 %)

HRMS (EI) : calculated mass (260.1412) found mass (260.1400)

8.9.8 ethyl 2-methylene-5-oxo-7-phenylheptanoate

Reaction :

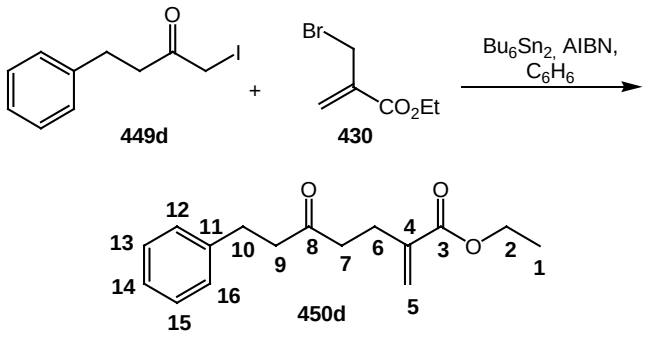


Figure 8-37

Procedure :

A solution of 1-iodo-4-phenylbutan-2-one (105 mg, 0.38 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (147 mg, 0.1 mL, 0.76 mmol, 2 eq), Bu_6Sn_2 (220 mg, 0.19 mL, 0.38 mmol, 1 eq) and AIBN (13 mg, 0.07 mmol, 0.2 eq) in benzene (1 mL) was degassed and refluxed for 2h30.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Ether, 90:10 $\rightarrow$ 85:15, Rf = 0.25) to give 75 mg of ethyl 2-methylene-5-oxo-7-phenylheptanoate (76 %).

Analysis :

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.46 (t, *J* = 7.2 Hz, 3H, H-1), 2.69-2.79 (m, 4-H, H-6 and H-10), 2.90 (t, *J* = 7.8 Hz, 2H) and 3.06 (t, *J* = 7.5 Hz, 2H) (H-7 and H-9), 4.36 (q, *J* = 7.2 Hz, 2H, H-2), 5.70 (d, *J* = 0.9 Hz, 1H, H-5b), 6.31 (d, *J* = 1.5 Hz, 1H, H-5a), 7.27-7.48 (m, 5H, H-12 to H-16)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 14.2 (C-1), 26.2, 29.7 (C-6 and C-10), 41.7, 44.2 (C-7 and C-9), 60.6 (C-2), 125.4 (C-14), 126.0 (C-5), 128.2, 128.3 (C-12, C-13, C-15 and C-16), 139.3, 140.8 (C-4 and C-11), 166.7 (C-3), 208.4 (C-8)

MS (CI, CH_4-NO_2) m/z (relative intensity): (M^++1) 261 (5 %); 215 (6 %); 210 (11 %); 182 (100 %); 155 (6 %); 149 (14 %); 136 (39 %).

HRMS (EI) : calculated mass (260.1412) found mass (260.1408)

8.9.9 ethyl 2-((2,6-dioxocyclononyl)methyl)acrylate

Reaction :

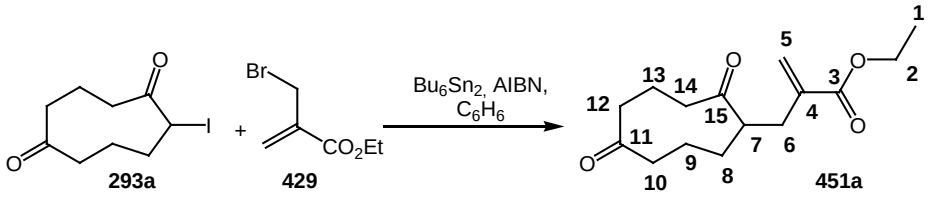


Figure 8-38

Procedure :

A solution of 6-iodocyclononane-1,5-dione (180 mg, 0.64 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (248 mg, 0.17 mL, 1.29 mmol, 2 eq), Bu_6Sn_2 (371 mg, 0.32 mL, 0.64 mmol, 1 eq) and AIBN (10 mg, 0.06 mmol, 0.1 eq) in benzene (2 mL) was degassed and refluxed for 2.5h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Ether, 90:10 $\rightarrow$ 75:25, Rf = 0.25) to give 120 mg of ethyl 2-((2,6-dioxocyclononyl)methyl)acrylate (70 %).

Analysis :

IR: 2929 cm^{-1} (stretching C-H), 1707 cm^{-1} (C=O), 1630 cm^{-1} (C=C-C=O), 1444, 1370, 1189, 1146, 1108, 1024, 908, 734, 649 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.31 (t, *J* = 7.2 Hz, 3H, H-1), 1.62-1.86 (m, 5H), 2.04-2.14 (m, 2H), 2.22-2.55 (m, 7H), 2.75-2.85 (m, 1H, H-7), 4.20 (q, *J* = 6.9 Hz, 2H, H-2), 5.49 (d, *J* = 1.2 Hz, 1H, H-5b), 6.16 (d, *J* = 1.5 Hz, 1H, H-5a)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 14.2 (C-1), 20.9, 21.2 (C-9 and C-13), 29.4, 34.4 (C-6 and C-8), 38.8, 43.4 (C-10, C-12 and-14), 51.2 (C-7), 60.9 (C-2), 127.0 (C-5), 137.9 (C-4), 166.6 (C-3), 214.8 (C-11), 216.3 (C-15)

MS (ESI) m/z (relative intensity): (M^+) 266 (100 %); 249 (23 %), 244 (8 %), 115 (29 %), 83 (9 %)

HRMS (EI+) : calculated mass (266.1518) found mass (266.1506)

8.9.10 ethyl 2-((2,6-dioxocyclodecyl)methyl)acrylate

Reaction :

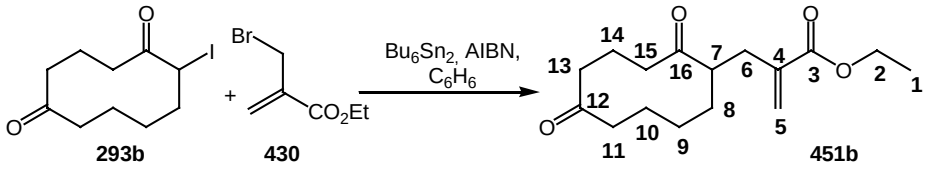


Figure 8-39

Procedure :

A solution of 6-iodocyclodecane-1,5-dione (200 mg, 0.68 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (157 mg, 0.11 mL, 0.82 mmol, 1.2 eq), Bu_6Sn_2 (475 mg, 0.42 mL, 0.82 mmol, 1.2 eq) and AIBN (23 mg, 0.14 mmol, 0.2 eq) in benzene (4 mL) was degassed and refluxed for 2.5 h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Ether, 90:10 → 75:25 , Rf = 0.27) to give 100 mg of ethyl 2-((2,6-dioxocyclodecyl)methyl)acrylate (55 %).

Analysis :

IR: 2933 and 2868 cm^{-1} (stretching C-H), 1710 cm^{-1} (C=O), 1629 cm^{-1} (C=C-C=O), 1466, 1369, 1325, 1179, 1152, 1027, 948, 818 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 1.26 (t, *J* = 7.2 Hz, 3H, H-1), 1.16-2.78 (m, 17H), 4.16 (q, *J* = 7.2 Hz, 2H, H-2), 5.48 (s, 1H, H-5b), 6.10 (d, *J* = 0.9 Hz, 1H, H-5a)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 14.2 (C-1), 18.3, 23.6, 29.8, 33.4, 38.7, 39.3, 44.2 (C-6, C-8 to C-11 and C-13 to C-15), 51.8 (C-7), 60.7 (C-2), 126.8 (C-5), 137.8 (C-4), 166.5 (C-3), 214.3, 214.8 (C-12 and C-16)

MS (APCI, +c) m/z (relative intensity): (M^++1) 281 (37%); (M^+) 280 (93 %); 262 (100 %); 253 (1 %); 235 (69 %); 217 (40 %); 134 (33 %).

HRMS (EI+) : calculated mass (280.1674) found mass (280.1679)

8.9.11 ethyl 2-((7-methyl-2,6-dioxocyclodecyl)methyl)acrylate

Reaction :

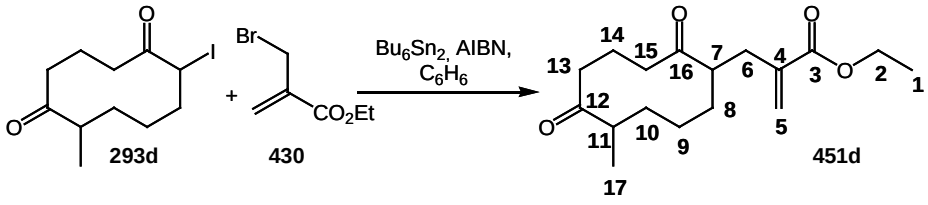


Figure 8-40

Procedure :

A solution of 6-iodo-10-methylcyclodecane-1,5-dione (105 mg, 0.34 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (131 mg, 0.09 mL, 0.68 mmol, 2 eq), Bu_6Sn_2 (197 mg, 0.17 mL, 0.34 mmol, 1 eq) and AIBN (6 mg, 0.03 mmol, 0.2 eq) in benzene (1 mL) was degassed and refluxed for 2.5h.

The resulting solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (PE : Ether, 90:10

→ 75:25) to give 20 mg of ethyl 2-[(1R,7S)-7-methyl-2,6-dioxocyclodecyl]methylacrylate (20 %, Rf = 0.30) and 40 mg of ethyl 2-[(1R,7R)-7-methyl-2,6-dioxocyclodecyl]methylacrylate.

Analysis :

a) ethyl 2-[(1R,7S)-7-methyl-2,6-dioxocyclodecyl]methylacrylate

IR: 2958, 2931 and 2872 cm^{-1} (stretching C-H), 1714 and 1695 cm^{-1} (C=O), 1629 cm^{-1} (C=C-C=O), 1465, 1370, 1272, 1202, 1095, 1026, 953, 861, 818, 736, 703 cm^{-1}

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 0.92 (d, *J* = 6.7 Hz, 3H, H-17), 1.26 (t, *J* = 7.1 Hz, 3H, H-1), 1.17-1.47 (m, 6H, H-8, H-9 and H-10), 1.83-2.00 (m, 2H, H-14), 2.07-2.29 (m, 3H, H-6a, H-13a and H-15a), 2.45-2.62 (m, 2H, H-6b and H-11), 2.67-2.94 (m, 3H, H-7, H-13b and H-15b), 4.16 (q, *J* = 7.1 Hz, 2H, H-2), 5.47 (s, 1H, H-5b), 6.10 (d, *J* = 1.6 Hz, 1H, H-5a)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 14.1 (C-1), 14.7 (C-17), 17.8 (C-14), 20.7 (C-9), 30.2 (C-8), 31.9 (C-10), 33.0 (C-6), 37.9 (C-13), 40.2 (C-15), 47.0 (C-11), 51.5 (C-7), 60.7 (C-2), 126.8 (C-5), 138.1 (C-4), 166.7 (C-3), 215.3 (C-16), 216.3 (C-12)

MS (APCI, +c) m/z (relative intensity): (M^+) 294 (7 %)
277 (15%), 259 (46%), 249 (100%), 231 (95%), 213 (58%), 203 (30%), 195 (16%), 185 (38%)

HRMS (EI+) : calculated mass (294.1831) found mass (294.1828)

b) ethyl 2-[(1R,7R)-7-methyl-2,6-dioxocyclodecyl]methylacrylate

IR: 2960, 2934 and 2874 cm^{-1} (stretching C-H), 1710 cm^{-1} (C=O), 1629 cm^{-1} (C=C-C=O), 1446, 1370, 1328, 1305, 1179, 1148, 1054, 915, 733 cm^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 0.80 (d, *J* = 7.2 Hz, 3H, H-17), 0.77-1.06 (m, 3H), 1.27 (t, *J* = 7.0 Hz, 3H, H-1), 1.13-1.39 (m, 3H), 1.70-1.79 (m, 2H), 1.81-1.96 (m, 1H), 1.96-2.13 (m, 1H), 2.47-2.60 (m, 2H), 2.62-2.75 (m, 2H), 4.14 (q, *J* = 7.0 Hz, 2H, H-2), 5.47 (s, 1H, H-5b), 6.10 (d, *J* = 0.9 Hz, 1H, H-5a)

^{13}C-NMR (75 MHz, $CDCl_3$) δ(ppm): 14.0, 14.1 (C-1 and C-17), 16.9, 22.4, 24.7, 32.2, 35.5, 38.0, 39.4 (C-6, C-8 to C-10 and C-13 to C-15), 39.4 (C-11), 61.0 (C-7), 67.7 (C-2), 128.3 (C-5), 136.0 (C-4), 166.8 (C-3), 210.0 (C-12 and C-16)

MS (APCI, +c) m/z (relative intensity): (M^+) 294 (12 %); 277 (67 %); 259 (18 %); 249 (39 %); 231 (100 %); 213 (55 %); 203 (18 %); 195 (8 %); 185 (21 %).

HRMS (EI+) : calculated mass (294.1831) found mass (294.1841)

8.9.12 ethyl 2-((2,6-dioxocycloundecyl)methyl)acrylate

Reaction :

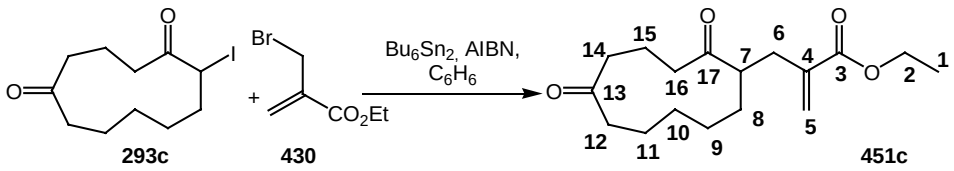


Figure 8-41

Procedure :

A solution of 6-iodocycloundecane-1,5-dione (700 mg, 2.27 mmol, 1 eq), ethyl 2-(bromomethyl)acrylate (876 mg, 0.59 mL, 4.54 mmol, 2 eq), Bu_6Sn_2 (1.32 g, 1.15 mL, 2.27 mmol, 1 eq) and AIBN (74 mg, 0.45 mmol, 0.2 eq) in benzene (8 mL) was degassed and refluxed for 2.5 h.

The resulting solution was evaporated under reduced pressure and the crude product was purified by flash column chromatography (PE : Ether, 90:10 $\rightarrow$ 75:25) to give 447 mg of ethyl 2-((2,6-dioxocycloundecyl)methyl)acrylate (67 %).

Analysis :

IR: 2935 cm^{-1} (stretching C-H), 1708 cm^{-1} (C=O), 1629 cm^{-1} (C=C-C=O), 1463, 1369, 1255, 1182, 1025, 949, 872, 819, 727 cm^{-1}

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.26 (t, *J* = 7.1 Hz, 3H, H-1), 1.18-1.32 (m, 3H), 1.44-1.56 (m, 2H), 1.62-1.75 (m, 2H), 1.80-1.94 (m, 2H), 2.06-2.88 (m, 10H), 4.16 (q, *J* = 7.1 Hz, 2H, H-2), 5.45 (d, *J* = 1.2 Hz, 1H, H-5b), 6.10 (s, 1H, H-5a)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 14.1 (C-1), 17.3, 23.0, 24.3, 26.9, 29.3, 34.2, 38.6, 39.3, 42.2 (C-6, C-8 to C-12 and C-14 to C-16), 51.1 (C-7), 60.7 (C-2), 126.6 (C-5), 138.1 (C-4), 166.6 (C-3), 214.0, 215.2 (C-13 and C-17)

MS (APCI, +c) m/z (relative intensity): (M^+) 294 (11 %); 277 (100 %); 259 (11 %); 249 (17 %); 248 (20 %); 239 (40 %); 225 (21 %).

HRMS (CI+) : calculated mass (294.1831) found mass (294.1829)

8.10 Synthesis of α-methylene δ-valerolactones

8.10.1 (4aR*,7aS*)-3-methylene-hexahydrocyclopenta[b]pyran-2(3H)-one

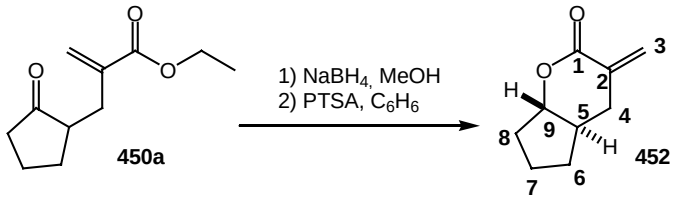


Figure 8-42

Procedure

To a cold (-78 °C) and stirred solution of ethyl 2-((2-oxocyclopentyl)methyl)acrylate (210 mg, 1 mmol, 1 eq) in methanol (10 mL), under anhydrous conditions, $NaBH_4$ (38 mg, 1 mmol, 1 eq) in methanol (5 mL) was added in 1 portion. After 4 h at –78°C, the solution was warmed to 0 °C and treated with 1M HC1 (30 mL). After stirring for an additional 2 h at rt, aqueous $NaHCO_3$ (20 mL) was added. The aqueous layer was extracted with CH_2C1_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and the solvents were evaporated under reduced pressure.

The residue was dissolved in benzene (25 mL) and refluxed in the presence of p-toluenesulfonic acid (17 mg, 0.1 mmol, 0.1 eq), using a Dean-Stark trap. After 1.5 h, the mixture was cooled to rt, diluted with ether (20 mL), washed with a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL), dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The residual oil was purified by flash column chrommatography (PE : Et_2O,

80:20) to give 138 mg of the desired product (81%) as a white solid (mp 44 °C).

Analysis :

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.38-1.14 (m, 1 H), 2.03-1.52 (m, 5 H), 2.21-2.04 (m, 1 H), 2.34 (dd, *J* = 13 Hz, *J* = 16 Hz, 1 H), 2.87 (dd, *J* = 4 Hz, *J* = 16 Hz, 1 H), 4.07 (td, *J* = 8, *J* = 10 Hz, 1 H, H-9), 5.61 (s, 1 H, H-3b), 6.49 (s, 1 H, H-3a).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 19.5, 26.2, 28.8, 32.6 (C-4 and C-6 to C-8), 40.4 (C-5), 83.8 (C-9), 127.3 (C-3), 133.3 (C-2), 166.3 (C-1).

CAS : 54312-52-6
Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, *55*, 5977.

8.10.2 3-methylene-dodecahydro-[1]cycloundeca[b]pyran-2,10-dione

Reaction

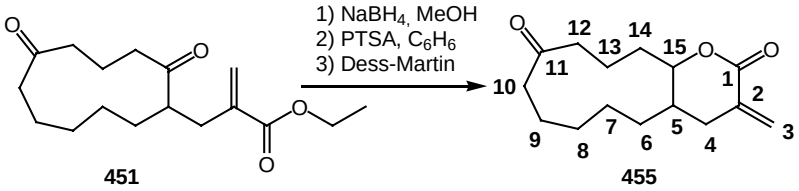


Figure 8-43

Procedure

To a cold (-78 °C) and stirred solution of ethyl 2-((2,6-dioxocycloundecyl)methyl)acrylate (100 mg, 0.3 mmol, 1 eq) in methanol (4

mL), under anhydrous conditions, $NaBH_4$ (26 mg, 0.6 mmol, 2 eq) in methanol (4 mL) was added in 1 portion. After 3 h at –78°C, the solution was warmed to 0 °C and treated with 1M HC1 (10 mL). After stirring for an additional 2 h at rt, aqueous $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with CH_2C1_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and the solvents were evaporated under reduced pressure.

The residue was dissolved in benzene (15 mL) and refluxed in the presence of p-toluenesulfonic acid (6 mg, 0.03 mmol, 0.1 eq), using a Dean-Stark trap. After 1.5 h, the mixture was cooled, diluted with ether (10 mL), washed with a saturated aqueous solution of $NaHCO_3$ (2 x 20 mL), dried over $MgSO_4$ and the solvents were evaporated under reduce pressure.

The residual oil was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Dess-Martin reagent (382 mg, 0.9 mmol, 3 eq) was added and the reaction mixture was kept at this temperature for 4 h. After addition of 1M NaOH (5 mL), the resulting solution was allowed to warm to rt and the stirring was continued for an additionnal 4h. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residual oil was purified by preparative TLC (Et_2O, Rf = 0.45) to give 37 mg (50 %) of the desired product as a 1:1 mixture of two diastereoisomers.

Analysis :

^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.1-2.9 (m, 38H), 4.2-4.3 (m, 1H, H-15 (1 dia)), 4.4-4.5 (m, 1H, H-15 (1 dia)), 5.50 and 5.51 (two singlet

partially overlaped, 2H, H-3b (2 dias)), 6.32-6.37 (m, 1H, H-3a (1 dia)), 6.37-6.44 (m, IH, H-3a (1 dia)).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ(ppm): 18.0, 18.8, 22.5, 22.8, 23.9, 26.1, 26.7, 26.8, 28.8, 31.2, 31.6, 34.1, 34.5, 35.0, 41.3, 42.1, 42.5, 42.5; 80.9 and 83.7 (C-15, 2 dias), 127.4 and 128.7 (C-3, 2 dias), 133.1 and 133.9 (C-2, 2 dias), 165.6 (C-1, 2 dias), 213.3 and 213.4 (C-11, 2 dias)

MS (APCI, +c) m/z (relative intensity): (M^++1) 251 (30 %); 233 (100 %); 215 (25 %), 187 (30 %)