"Asymmetric cyclopentannulation reactions : scope and limitation/"

Schanen, Patrick

ABSTRACT

The first part of this dissertation is devoted to the study of an asymmetric [3+2] cycloaddition sequence developed in our laboratory. The cycloaddition sequence used a sulfonamide-based homoenolate equivalent which was cyclocondensed with a cyclic enone. The stereochemistry of the final product was fixed during the first step, the Michael addition to the enone. Our study focused thus on the Michael addition of sulfonamides to enones. We have synthesized a series of chiral and achiral sulfonamides. We then studied the regiochemistry and the stereochemistry of the addition of the anions derived from these sulfonamides to cyclohexenone. The presence of a heteroatom at the (gamma)-carbon of the sulfonamide was crucial for the regiochemical outcome of the reaction. The substituent on the sulfonamide also influenced the facial selectivity of the reaction with chiral sulfonamides, but had no influence on the diastereoselectivity with achiral sulfonamides. The sequence had been applied to v...

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Experimental part

1 Generalities

1.1 Apparatus

- Infrared spectra were recorded on a Bio-Rad FTS-135 spectrometer.
- $^1$H NMR spectra were recorded at 200 or 300 MHz on a Varian Gemini 200, VXR 200 or Gemini 300BB in a deuterated solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts are given in ppm; coupling constants are given in Hz.
- $^{13}$C NMR spectra were recorded at 50 or 75 MHz on a Varian Gemini 200, VXR 200 or Gemini 300 in a deuterated solvent used as internal standard (CDCl$_3$: 77 ppm; MeOD-d$_4$: 49 ppm; DMSO-d$_6$: 39.5 ppm).
- $^{19}$F NMR spectra were recorded at 288.5 MHz on a Varian Gemini 300 spectrometer with hexafluorobenzene as internal standard (-163 ppm).
- Mass spectra were recorded on a Varian MAT-44 or a FINNIGAN MAT TSQ 70 spectrometer in the laboratory of Professor de Hoffmann and Professor Habib-Jiwan.
- High resolution mass spectra (HRMS) were performed by Professor Flammang at Université de Mons-Hainaut.
- Elemental analyses were realized in the laboratory of Dr Stone at University College, London
- GC analyses were performed on a CE Instruments GC 8000$^{\text{Top}}$ with a Merck-Hitachi D-2500 Chromato Integrator on a Cp-Sil 8 CB WCOT Fused Silica (30 m x 0.25 mm – 0.25 µm) column; chiral GC analyses were done on a CE Instruments HRGC 5300 with a Merck-Hitachi D-2500 Chromato Integrator or a Thermo Finnigan Trace GC with a Thermo Finnigan ChromCard program on a Chirasil Dex (25 m x 0.25 mm – 0.25 µm) column. Temperature programs are given as follows: (initial temperature (°C) / initial time (min) / ramp (°C/min) / final temperature (°C) / final time (min)) or (initial temperature (°C) / initial time (min) / ramp (°C/min) / intermediate temperature (°C) / ramp (°C/min) / final temperature (°C) / final time (min)).
- Optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter. Concentrations are given in g/100 ml.
- Melting points were measured with a Büchi apparatus (oil bath) and are uncorrected.
- Bulb-to-bulb distillations were performed with a Büchi GKR 50 or GKR 51.

1.2 Techniques

- All reactions were realized under argon atmosphere unless otherwise stated.
- Phase-transfer reactions were performed with an Electrothermal Reacto-Station RS1000.
- For reactions at 0°C, flasks were placed in an ice bath; for reactions at -78°C, flasks were placed in a dry-ice / iso-propanol bath; intermediate temperatures were realized by adding the desired quantity of dry-ice to iso-propanol; for longer reaction times flasks were placed in an iso-propanol bath cooled by a Haake EK90 cryostat.
- Evaporation of solvents was performed at ±35°C with a rotary evaporator connected to a water pump (~16 mmHg) unless otherwise stated.
- Flash chromatographies were performed on silica gel "60 Merck 40-63 µm". Solvents used were of technical grade and distilled prior to use. \( R_f \) values were determined on silicagel plates Merck 60 F254 on aluminum support. Spots were visualized using UV light (\( \lambda = 254 \text{ mm} \)) or revealed using an aqueous potassium permanganate solution.
- \( n \)-butyllithium in hexanes was titrated in dry THF using 2,5-dimethoxybenzyllic alcohol or diphenylacetic acid.
- \( \text{CH}_2\text{Cl}_2 \) and benzene were dried over CaH\(_2\) and distilled.
- THF, diethyl ether and toluene were dried over Na / benzophenone and distilled.
- Ethanol was dried over mg with a trace of iodine and distilled.
- DMSO was distilled and stored over activated molecular sieves 4Å.
- Hexamethylphosphoramide was dried over CaH\(_2\) and distilled.
- Triethylamine was dried over CaH\(_2\) and distilled.
- Enones, sulfonyl chlorides were distilled prior to use.
- Copper(II) triflate, zinc(II) chloride, and, when specified, potassium fluoride were dried by heating overnight at 150°C under reduced pressure.
1.3 Abbreviations and symbols

1.3.1 Reagents and solvents

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<th>Chemisorption</th>
<th>Meaning</th>
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<tr>
<td>AcOEt</td>
<td>ethyl acetate</td>
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<tr>
<td>CH$_2$Cl$_2$</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<tr>
<td>Et$_3$N</td>
<td>triethylamine</td>
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<td>Et$_2$O</td>
<td>diethyl ether</td>
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<td>EtOH</td>
<td>ethanol</td>
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<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<tr>
<td>MeOH</td>
<td>methanol</td>
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<td>n-BuLi</td>
<td>n-butyllithium</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TBDMSCl</td>
<td>tert-butyldimethylsilyl chloride</td>
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<tr>
<td>TIPSCl</td>
<td>tri-iso-propylsilyl chloride</td>
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<td>TMS</td>
<td>tetramethylsilane</td>
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<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
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1.3.2 Abbreviations

<table>
<thead>
<tr>
<th>Chemisorption</th>
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<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
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<tr>
<td>CI</td>
<td>chemical ionization</td>
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<tr>
<td>b.p.</td>
<td>boiling point</td>
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<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>Δ</td>
<td>heating at reflux</td>
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<td>EI</td>
<td>electronic impact</td>
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<tr>
<td>eq.</td>
<td>equivalents</td>
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<td>Et</td>
<td>ethyl</td>
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<td>FAB</td>
<td>fast atom bombardment</td>
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<td>GC</td>
<td>capillary gas chromatography</td>
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<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>m</td>
<td>massif</td>
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<td>Me</td>
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<tr>
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<td>mult</td>
<td>multiplet</td>
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<td>M.W.</td>
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<td>Description</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
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<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>ratio of fronts</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
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<tr>
<td>s</td>
<td>singlet</td>
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<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt;</td>
<td>retention time</td>
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2 Synthesis of 27

2.1 Synthesis of 2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylic acid tert-butyl ester 31

M.F.: C_{12}H_{23}NO_3 (M.W. 229.31)          RN: 155728-50-0


In a flame-dried three-necked flask equipped with an addition funnel, a reflux condenser and a mechanical stirrer, 62 g (270.4 mmol; 1 eq.) of 1,1-dimethylethyl (2S)-2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylate 224 were dissolved in 314 ml of dry Et_2O. The mixture was cooled to 0°C and 213 ml (220.7 g; 676 mmol; 2.5 eq.) of methylmagnesium bromide, 3.0M in diethyl ether, were slowly added. After the addition was complete, the mixture was stirred for 3 hours. The reaction was quenched by the addition of a saturated solution of NH_4Cl. The 2 phases were separated and the aqueous phase was extracted 2 times with Et_2O. The organic phase was washed with a saturated solution of NaCl, dried over MgSO_4, filtered and evaporated under reduced pressure.

The product was obtained as a white solid and was pure enough to be used without any further purification.

Yield: 59.36 g (96 %)

\[ \text{H NMR (CDCl}_3, 200 \text{ MHz): 1.07 and 1.16 (2 s, 6 H, 6, 7); 1.48 (s, 9 H, 11); 1.6-2.15 (m, 4 H, 2, 3); 3.16 (m, 1 H, 1); 3.7 (m, 1 H, 4); 3.87 (m, 1 H, 1); 5.92 (broad s, 1 H, 8)} \]

\[ \text{C NMR (CDCl}_3, 50 \text{ MHz): 23.9 and 28.8 (2, 3); 27.4 and 27.9 (6, 7); 28.1 (11); 28.8 (3); 48.0 (1); 67.0 (4); 73.3 (5); 80.0 (10); 152.3 (9)} \]

\[ \text{IR (solid deposit, cm}^{-1}\text{): 1171; 1401; 1666 (C=O); 2975 (C-H); 3370 (O-H)} \]

\[ \text{Mass (Cl +Q1MS): 130 ([M-(COO-t-Bu}]^+, 21%); 156 ([M-(O-t-Bu}]^+, 38%); 174 (100%); 230 ([M+H]^+, 18%)} \]

\[ \text{GC (100/0/10/290/15): } t_R = 10.93 \text{ min} \]
2.2 Synthesis of 2-[(2S)-pyrrolidin-2-yl]propan-2-ol 30

M.F.: C\textsubscript{7}H\textsubscript{15}NO (M.W. 129.2)  
RN: 92053-25-3


In a flask equipped with a reflux condenser, 72.59 g (1.815 mol; 7.01 eq.) of sodium hydroxide were dissolved in 294 ml of MeOH. 59.36 g (258.8 mmol; 1 eq.) of (2S)-2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carboxylic acid tert-butyl ester 31 were slowly added. The mixture was then refluxed for 24 hours. After being cooled to room temperature, the solvent was evaporated. The residue was dissolved in ether and filtered. After evaporation of the solvent, a small quantity of a saturated solution of NH\textsubscript{4}Cl was added. The aqueous phase was extracted with a large quantity of CHCl\textsubscript{3}. The organic phase was dried over MgSO\textsubscript{4}, filtered and evaporated under reduced pressure.

**Yield:** 32.89 g (98 %)

\[
\begin{align*}
\text{NH} \\
\text{1} \\
\text{2} \\
\text{4} \\
\text{5} \\
\text{6} \\
\text{7} \\
\end{align*}
\]

\[\text{1H NMR (CDCl}_3, 200 \text{ MHz):} \ 1.12 \text{ and } 1.16 \text{ (2 s, 6 H, 6, 7); } 1.58-1.77 \text{ (m, 4 H, 2, 3); } 2.81-3.05 \text{ (m, 3 H, 1, 4)}
\]

\[\text{13C NMR (CDCl}_3, 75 \text{ MHz):} \ 25.6 \text{ and } 26(6, 7); 26.1 \text{ and } 26.5 \text{ (2, 3); } 46.8 \text{ (1); } 67.2 \text{ (4); } 70.2 \text{ (5)}
\]

**IR (liquid film, cm\textsuperscript{-1}):** 1157, 1377; 2971 (C-H); 3346 (O-H)

**GC (100/0/10/290/20):** \text{t}\textsubscript{R} = 7.41 min

2.3 Synthesis of 2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carbaldehyde 33

M.F.: C\textsubscript{8}H\textsubscript{15}NO\textsubscript{2} (M.W. 157.21)  
RN: 129149-57-1


In a flame-dried flask 32.89 g (254.5 mmol; 1 eq.) of 2-pyrrolidin-2-yl-propan-2-ol 30 were dissolved in 82.22 ml (75.4 g; 1.017 mol; 3.99 eq.) of ethyl formate. The mixture
was stirred for 2 days. The volatile compounds were evaporated to obtain a viscous oil. The product was purified by bulb-to-bulb distillation under reduced pressure (125°C at 6·10⁻³ mbar).

Yield: 20 g (51 %)

\[\text{1H NMR (CDCl}_3, 300 MHz): 1.09, 1.15, 1.18 \text{ and } 1.23 \text{ (4 s, 6 H, 6, 7); 1.51-2.22 (m, 4 H, 2, 3); 3.29-3.40 (m, 1 H, 1); 3.65-3.81 (m, 2 H, 1, 4); 8.30 \text{ and } 8.40 \text{ (2 s, 1 H, 8)}}\]

\[\text{13C NMR (CDCl}_3, 75 MHz): 22.4, 23.0, 26.4 \text{ and } 26.5 \text{ (6, 7); 22.9, 23.0, 26.8 \text{ and } 28.4 \text{(2, 3); 44.1 \text{ and } 48.8 \text{ (1); 66.1 \text{ and } 67.1 \text{ (4); 72.5 (5); 163.2 \text{ and } 163.5 (8)}}\]

\[\text{IR (liquid film, cm}^{-1}\text{): 1651 (C=O); 2975 (C-H); 3384 (O-H)}\]

b.p.: 125°C at 6·10⁻³ mbar

2.4 Synthesis of (2S)-2-(1-methoxy-1-methylethyl)pyrrolidine-1-carbaldehyde 34

M.F.: C₉H₁₇NO₂ (M.W. 171.23)   RN: 129173-93-9


In a flame-dried three-necked flask equipped with a reflux condenser, an addition funnel and a magnetic stirrer, 6.743 g (168.6 mmol; 1.3 eq.) of sodium hydride were put into suspension in 210 ml of dry THF. 20.39 g (129.6 mmol; 1 eq.) of 2-(1-hydroxy-1-methylethyl)pyrrolidine-1-carbaldehyde 33 in solution in 12 ml of THF were slowly added via the addition funnel. The mixture was stirred for 15 minutes. 18.59 ml (24.78 g; 194.5 mmol; 1.5 eq.) of dimethyl sulfate were then added through the addition funnel. Stirring was maintained for 20 hours. The mixture was then cooled to 0°C and 10 ml of water were slowly added. Solvents were evaporated and water was added to the residue. The aqueous phase was extracted 5 times with CH₂Cl₂. The organic phase was washed with water, dried over MgSO₄, filtered and evaporated under reduced pressure.

Yield: 28.84 g of crude product.
2.5 Synthesis of (2S)-(-)-2-(1-methoxy-1-methylethyl)pyrrolidine 27

M.F.: C₈H₁₇NO (M.W. 143.22)  
RN: 118971-00-9


In a flask equipped with a reflux condenser were put 297 ml of a 10% KOH solution. 22.2 g (129.6 mmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)pyrrolidine-1-carboxaldehyde 34 were then slowly added. The mixture was refluxed for 90 minutes. Once cooled to room temperature, it was extracted 5 times with Et₂O. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by bulb-to-bulb distillation (120°C at 15 mmHg).

Yield: 14.1 g (76 %)

**H NMR** (CDCl₃, 300 MHz): 1.14 and 1.18 (2 s, 6 H, 6, 7); 1.66-1.75 (m, 4 H, 2, 3); 2.81-2.85 (m, 1 H, 1); 2.97-3.05 (m, 2 H, 1, 4); 3.22 (s, 3 H, 8)  
**C NMR** (CDCl₃, 75 MHz): 21.3 and 21.9 (6, 7); 25.8 and 26.4 (2, 3); 47.0 (1); 49.1 (8); 66.9 (4); 76.1 (5)  
**IR** (liquid film, cm⁻¹): 2827 (O-CH₃); 2970 (C-H); 3347 (N-H)  
**Mass** (Cl/CH₄⋅N₂O): 70 ([C₄H₈N]+, 34%); 112 ([M-OMe]+, 100%); 144 ([M+H]+, 20%)  
[α]D²₀ = -24.0° (c=0.876; CHCl₃) [lit.: -24.5° (c=2.36; CH₃OH)]  
**b.p.:** 120°C at 15 mmHg
3 Synthesis of sulfonyl chlorides

3.1 Synthesis of 3-methyl-1-butanesulfonyl chloride 35

M.F.: C₅H₁₁ClO₂S (M.W. 170.65)  
RN: 22795-37-5

In a three-necked flask equipped with a magnetical stirrer, a thermometer, a gas inlet and a gas outlet, 1 g (1.197 ml; 9.595 mmol; 1 eq.) of 3-methylbutane-1-thiol was put into suspension in 30 ml of water. The flask was placed in an ice-bath and chlorine was then bubbled through the mixture. The temperature was kept below 10°C. When the mixture was yellowish green, the reaction was stopped. The aqueous phase was extracted with Et₂O. The organic phase was washed with a saturated solution of NaHSO₃ and a saturated solution of NaHCO₃, dried over MgSO₄, filtered and evaporated under reduced pressure. The product was obtained sufficiently pure to be used without purification.

Yield: 1.534 g (94%)

Aspect: colorless oil

\[ \text{ClO}_2\text{S} \]

\(^1\text{H NMR}\) (CDCl₃, 300 MHz): 0.90 (d, \(^3\jmath_{4,3} = 6.5\), 6 H, 4); 1.90 (mult, 1 H, 3); 1.89-1.98 (m, 2 H, 2); 3.66 (mult, 2 H, 1)

\(^{13}\text{C NMR}\) (CDCl₃, 50 MHz): 21.8 (4); 26.8 (3); 32.6 (2); 64.1 (1)

IR (liquid film, cm⁻¹): 1166 (O=S=O); 1373 (O=S=O); 2962 (C-H)

Mass (EI +Q1MS): 43 ([(CH₃)₂CH]⁺, 100%); 55 ([(CH₃)₂CHCH₂]⁺, 45%); 70 ([M-SO₂Cl]⁺, 87%); 169 ([M-H]⁺, 2%)

3.2 Synthesis of 6-chloro-1-hexanesulfonyl chloride 37

M.F.: C₆H₁₂ClO₂S (M.W. 219.12)  
RN: 1633-80-3

In a three-necked flask equipped with a magnetical stirrer, a thermometer, a gas inlet and a gas outlet, 1 g (7.449 mmol; 1 eq.) of 6-mercapto-1-hexanol was put into suspension in 9.4 ml of water. The flask was placed in an ice-bath and chlorine was then bubbled through the mixture. The temperature was kept below 10°C. When the mixture was yellowish green the reaction was stopped. The aqueous phase was
extracted with Et₂O. The organic phase was washed with a saturated solution of NaHSO₃ and a saturated solution of NaHCO₃, dried over MgSO₄, filtered and evaporated under reduced pressure.

The product was obtained sufficiently pure to be used without purification. It could be purified by bulb-to-bulb distillation (125°C at 6.10⁻² mbar) but it degraded upon heating.

**Yield:** 1.258 g (77%)

**Aspect:** colorless oil

\[
\text{Cl}_2\text{S} \quad \text{Cl}
\]

\(^1\text{H} \text{NMR} \) (CDCl₃, 200 MHz): 1.44-1.65 (m, 4 H, 3, 4); 1.74-1.86 (m, 2 H, 5); 2.01-2.16 (m, 2 H, 2); 3.55 (t, \(^3\text{J}_{2.5} = 6.3, 2 \text{ H, 6); 3.68 \) (mult, 2 H, 1)

\(^13\text{C} \text{NMR} \) (CDCl₃, 50 MHz): 24.2 (2); 26.2 (4); 27.4 (3); 32.1 (5); 44.5 (6); 65.4 (1)

\( \text{IR} \) (liquid film, cm⁻¹): 1165 (O=S=O); 1373 (O=S=O); 2864; 2940 (C-H)

\( \text{Mass} \) (Cl/CH₄-N₂O₂): 83 (100%); 119 ([M-SO₂Cl]⁺ (³⁵Cl), 18%); 121 ([M-SO₂Cl]⁺ (³⁷Cl), 6%); 183 ([M-Cl]⁺ (³⁵Cl), 23%); 185 ([M-Cl]⁺ (³⁷Cl), 9%); 219 ([M+H]⁺ (2 x ³⁵Cl), 31%); 221 ([M+H]⁺ (³⁵Cl + ³⁷Cl), 22%); 223 ([M+H]⁺ (2 x ³⁷Cl), 5%)

**b.p.:** 125°C at 6·10⁻³ mbar

### 4 Synthesis of sulfonamides

#### 4.1 General procedure

In a flame-dried two-necked flask equipped with a magnetical stirrer, 1 eq. of amine and 1 eq. of Et₃N were dissolved in Et₂O or CH₂Cl₂. The solution was stirred and 1 eq. of sulfonyl chloride was slowly added. The stirring was maintained for 4 hours. After that time the reaction mixture was filtered and the solvent evaporated.

The product was purified by flash chromatography.

#### 4.2 Synthesis of sulfonamides containing no other function

##### 4.2.1 Synthesis of 1-methylsulfonylpyrrolidine 11

**M.F.:** C₅H₁₁NO₂S (M.W. 149.2)  
**RN:** 51599-68-9

Following the general procedure described in 4.1 with:
2.8 ml (33.51 mmol, 1 eq.) of pyrrolidine
4.66 ml (33.51 mmol, 1 eq.) of Et₃N
2.59 ml (33.51 mmol, 1 eq.) of methanesulfonyl chloride
34 ml of ether
Flash chromatography: CH₂Cl₂ 100 %

Yield: 2.2 g (44%)

\[
\text{1H NMR (CDCl₃, 300 MHz): 1.95 (m, 4 H, 2); 2.82 (s, 3 H, 3); 3.33 (m, 4 H, 1)}
\]

\[
\text{13C NMR (CDCl₃, 75 MHz): 25.1 (2); 33.5 (3); 47.3 (1)}
\]

IR (liquid film, cm⁻¹): 1147 (NSO₂); 1328 (NSO₂); 2984 (C-H)

Mass (Cl/CH₄-N₂O): 150 ([M+H]⁺, 100%)

m.p.: 69-70°C

4.2.2 Synthesis of (2S)-1-methylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 14

M.F.: C₉H₁₉NO₃S (M.W. 221.31)


Following the general procedure described in 4.1 with:
5.978 g (41.7 mmol, 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)pyrrolidine 27
5.8 ml (41.7 mmol, 1 eq.) of Et₃N
3.23 ml (41.7 mmol, 1 eq.) methanesulfonyl chloride
60 ml of Et₂O
Flash chromatography (ether : petroleum ether 90 : 10).

Yield: 8.159 g (88 %)

Aspect: colorless oil

TLC: Rᵢ = 0.36 (ether : petroleum ether 90 : 10)
**Experimental part**

**1H NMR** (CDCl₃, 200 MHz): 1.16 and 1.19 (2 s, 6 H, 6, 7); 1.71-2.93 (m, 4 H, 2, 3); 2.91 (s, 3 H, 9); 3.09-3.28 (m, 1 H, 1); 3.18 (s, 3 H, 8); 3.67-3.81 (m, 1 H, 1); 3.91-4.01 (m, 1 H, 4)

**13C NMR** (CDCl₃, 50 MHz): 21.5 (6, 7); 25.7 and 26.8 (2, 3); 38.4 (9); 49.2 (8); 49.6 (1); 66.5 (4); 77.7 (5)

**IR** (liquid film, cm⁻¹): 1151 (NSO₂); 1332 (NSO₂); 2831 (O-CH₃); 2979 (C-H)

**Mass** (Cl/CH₄-N₂O): 190 ([M-OMe]+, 100); 222 ([M+H]+, 5%)

[α]D²₀: -32.5° (c=0.553; CHCl₃) [lit.: -31.4° (c=1.65; CHCl₃)]

4.2.3 **Synthesis of 1-ethylsulfonylpyrrolidine 38**

M.F.: C₆H₁₃NO₂S (M.W. 163.23)  
RN: 73343-03-0

Following the general procedure described in 4.1 with:
2 ml (1.704 g; 23.95 mmol; 1 eq.) of pyrrolidine
3.33 ml (2.424 g; 23.95 mmol; 1 eq.) of Et₃N
2.27 ml (3.08 g; 23.95 mmol; 1 eq.) of ethanesulfonyl chloride
34.31 ml of ether

Flash chromatography: ether : petroleum ether 80 : 20

Yield: 3.55 g (91 %)

Aspect: colorless oil

TLC: Rf = 0.6 (ether : petroleum ether 80 : 20)

1H NMR (CDCl₃, 200 MHz): 1.38 (t, 3J₄-3 = 7, 3 H, 4); 1.90-2.00 (m, 4 H, 1); 3.01 (q, 3J₃-4 = 7.3, 2 H, 3); 3.30-3.40 (m, 4 H, 2)

13C NMR (CDCl₃, 50 MHz): 7.4 (4); 25.3 (2); 43.5 (1); 47.2 (3)

IR (liquid film, cm⁻¹): 1148 (NSO₂); 1328 (NSO₂); 2960 (C-H)

Mass (Cl/CH₄-N₂O): 70 ([C₄H₈N]+, 32%); 162 (36%); 164 ([M+H]+, 100%); 166 (60%); 327 ([2M+H]+, 26%)

4.2.4 **Synthesis of (2S)-1-ethylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 43**

M.F.: C₁₀H₂₁NO₃S (M.W. 235.34)
Experimental part

Following the general procedure described in 4.1 with:
2.073 g (14.473 mmol, 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)pyrrolidine 27
2 ml (14.473 mmol, 1 eq.) of Et₃N
1.37 ml (14.473 mmol, 1 eq.) of ethanesulfonyl chloride
21 ml of Et₂O
Flash chromatography: ether : petroleum ether 90 : 10

**Yield:** 3.073 g (90 %)

**Aspect:** yellow oil

\[
\begin{array}{c}
\text{H} \quad \text{N} \quad \text{O} \\
\text{S} \quad \text{O} \\
\text{N} \quad \text{S} \\
\text{O} \\
\text{H} \quad \text{N} \\
\text{O} \\
\end{array}
\]

**¹H NMR** (CDCl₃, 300 MHz): 1.14 and 1.17 (s, 6 H, 6, 7); 1.37 (t, \(^3J_{12-9} = 3.3, 3\) H, 10); 1.70-2.10 (m, 4 H, 2, 3); 3.02-3.19 (m, 1 H, 1); 3.14 (mult, 2 H, 9); 3.21 (s, 3 H, 8); 3.78-3.82 (m, 1 H, 1); 4.08-4.13 (m, 1 H, 4)

**¹³C NMR** (CDCl₃, 75 MHz): 9.2 (10); 21.3 and 21.5 (6, 7); 26.2 and 27.3 (2, 3); 46.5 (9); 49.2 (8); 50.1 (1); 65.9 (4); 77.7 (5)

**IR** (liquid film, cm⁻¹): 1330 (NSO₂); 1460 (NSO₂); 2831 (O-CH₃); 2979 (C-H)

**Mass** (Cl/CH₄-N₂O): 204 ([M-OMe]+, 100%); 236 ([M+H]+, 1.5%)

\[ \alpha \]₂₀°: -39.8° (c=0.176; CHCl₃)

**Elemental analysis:**

calculated (%): C: 51.04; H: 8.99; N: 5.95; S: 13.62
found (%): C: 50.48; H: 8.93; N: 5.80; S: 13.94

4.2.5 **Synthesis of 1-[(3-methylbutyl)sulfonyl]pyrrolidine 39**

**M.F.:** C₉H₁₉NO₂S (M.W. 205.31)

Following the general procedure described in 4.1 with:
0.75 ml (9 mmol, 1 eq.) of pyrrolidine
1.25 ml (9 mmol, 1 eq.) of Et₃N
1.534 ml (9 mmol, 1 eq.) of 3-methyl-1-butanesulfonyl chloride
20 ml of CH₂Cl₂
Purification by recrystallization in ether

**Yield:** 1.447 g (78 %)

**Aspect:** white crystals

**TLC:** $R_f = 0.52$ (petroleum ether : AcOEt 2 : 1)

![N-S-O](image)

$^1$H NMR (CDCl$_3$, 300 MHz): 0.94 ($d, ^3J_{6-5}=6.4, 6$ H, 6); 1.60-1.75 ($m, 3$ H, 4, 5); 1.90-2.00 ($m, 4$ H, 2); 2.90-3.00 ($m, 2$ H, 3); 3.30-3.40 ($m, 4$ H, 1)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 22.0 ($6$); 25.8 ($2$); 27.3 ($5$); 31.8 ($4$); 47.6 ($1$); 48.2 ($3$)

**IR** (liquid film, cm$^{-1}$): 1139 (NSO$_2$); 1328 (NSO$_2$); 2875 (C-H)

**Mass** (EI +Q1MS): 43 ([CH(CH$_3$)$_2$]$^+$, 33%); 55 ([CH$_2$CH(CH$_3$)$_2$]$^+$, 15%); 70 ([N(CH$_2$)$_4$]$^+$, 100%); 71 ([CH$_2$CH$_2$CH(CH$_3$)$_2$]$^+$, 94%); 205 (M$^{++}$, 8%)

**Elemental analysis:**

Calculated (%): C: 52.65; H: 9.32; N: 6.82

Found (%): C: 52.29; H: 9.26; N: 6.66

4.2.6 **Synthesis of (2$S$)-(1-methoxy-1-methylethyl)-1-[(3-methylbutyl)sulfonyl]pyrrolidine 44**

**M.F.:** C$_{13}$H$_{27}$NO$_3$S (M.W. 277.42)

Following the general procedure described in 4.1 with:

- 1 g (6.981 mmol; 1 eq.) of (2$S$)-2-(1-methoxy-1-methylethyl)pyrrolidine 27
- 970 µl (706 mg; 6.981 mmol; 1 eq.) of Et$_3$N
- 1.191 g (6.981 mmol; 1 eq.) of 3-methyl-1-butanesulfonyl chloride
- 10 ml of EtO

Flash chromatography: ether : petroleum ether 80 : 20

**Yield:** 1.719 g (89 %)

**Aspect:** colorless oil

**TLC:** $R_f = 0.67$ (ether : petroleum ether 80 : 20)
\[ ^1H \text{ NMR (CDCl}_3, \text{ 300 MHz): 0.93 and 0.95 (d, } ^3J_{12,13-11} = 4.2, \text{ 6 H, 12, 13); 1.14 and 1.17 (2 s, 6 \text{ H, 6, 7); 1.62-2.15 (m, 7 \text{ H, 2, 3, 10, 11); 3.00-3.20 (m, 3 \text{ H, 1, 9); 3.21 (s, 3 \text{ H, 8)); 3.77-3.91 (m, 1 H, 1); 4.05-4.18 (m, 1 H, 4) } \]

\[ ^13C \text{ NMR (CDCl}_3, \text{ 75 MHz): 20.9, 21.3, 21.9 and 22.0 (6, 7, 12, 13); 27.1 (11); 26.1 and 27.1 (2, 3); 31.7 (10); 49.0 (8); 49.8 (1); 50.4 (9); 65.9 (4); 77.7 (5) } \]

\[ \text{IR (liquid film, cm}^{-1}\text{): 1140 (NSO}_2) \text{; 1327 (NSO}_2\text{); 2958 (C-H) } \]

\[ \text{Mass (EI +Q1MS): 70 ([N(CH}_2)_4]^+ \text{, 30%); 73 ([C(CH}_3)_2OMe]^+, 100%); 204 ([M-C(CH}_3)_2OMe]^+, 66%); 246 ([M-OMe]^+, 4%) } \]

\[ \alpha]_{20}^D : -45.1^\circ \text{ (c=0.244; CHCl}_3) \]

\[ \text{HRMS: calculated for C}_{13}H_{28}NO_3S^+: 278.178991; \text{ found 278.174233; calculated for C}_{12}H_{24}NO_2S^+ ([M-OMe]^+): 246.152776; found: 246.151716 } \]

### 4.3 Synthesis of orthoesters

#### 4.3.1 Synthesis of 1-(ethenylsulfonyl)pyrrolidine 40

\[ \text{M.F.: C}_6\text{H}_{11}\text{NO}_2\text{S (M.W. 161.21) } \text{RN: 87975-58-4} \]

\[ \text{Reference: Huart, C. PhD-Thesis UCL-ORSY, 1995} \]

In a flame-dried three-necked flask equipped with a magnetical stirrer, 5.632 ml (4.799 g; 67.47 mmol; 1.1 eq.) of pyrrolidine and 17.1 ml (12.41 g; 122.6 mmol; 2 eq.) of Et\(_3\)N were dissolved in 60 ml of CH\(_2\)Cl\(_2\). The solution was cooled to 0°C and 6.406 ml (10 g; 61.34 mmol; 1 eq.) of 2-chloro-1-ethanesulfonyl chloride were slowly added. After 45 minutes, the mixture was allowed to come to room temperature. 90 minutes later, 100 ml of water were added. The aqueous phase was extracted 3 times with CH\(_2\)Cl\(_2\). The organic phase was dried over MgSO\(_4\), filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 25 : 75).

\[ \text{Yield: 6.019 g (61%)} \]

\[ \text{Aspect: slightly yellow oil} \]

\[ \text{TLC: R}_f = 0.56 \text{ (AcOEt : petroleum ether 75 : 25)} \]
4.3.2 Synthesis of (2S)-1-ethenylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 45

M.F.: C_{10}H_{19}NO_{3}S (M.W. 233.32)  
RN: 190510-68-0


In a flame-dried three-necked flask equipped with a magnetic stirrer, 7.975 g (55.68 mmol; 1.1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)pyrrolidine 27 and 14.11 ml (10.24 g; 101.2 mmol; 2 eq.) of Et_{3}N were dissolved in 50 ml of CH_{2}Cl_{2}. The mixture was cooled to 0°C and 5.286 ml (8.251 g; 50.61 mmol; 1 eq.) of 2-chloro-1-ethanesulfonyl chloride were slowly added. After stirring for 45 minutes at 0°C, the mixture was allowed to come to room temperature. The stirring was continued for 90 minutes. Then 100 ml of water were added. The aqueous phase was extracted 3 times with CH_{2}Cl_{2}. The organic phase was dried over MgSO_{4}, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 9.43 g (80 %)

Aspect: yellow oil

TLC: R_{f} = 0.61 (petroleum ether : AcOEt 25 : 75)
Experimental part

$^1$H NMR (CDCl$_3$, 300 MHz): 1.18 and 1.22 (2 s, 6 H, 6, 7); 1.70-2.10 (m, 4 H, 2, 3); 3.19 (s, 3 H, 8); 3.20-3.30 (m, 1 H, 1); 3.49-3.59 (m, 1 H, 1); 3.75-3.81 (m, 1 H, 4); 5.94 (d, $^3$$J$$_{10a-9} = 9.9$; 1 H, 10a); 6.24 (d, $^3$$J$$_{10b-9} = 16.5$; 1 H, 10b); 6.46 (dd; $^3$$J$$_{9-10b} = 16.4$; $^3$$J$$_{9-10a} = 9.6$; 1 H, 9)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 21.7 and 22.4 (2, 3); 25.4 and 26.4 (6, 7); 49.3 (1); 49.5 (8); 67.4 (4); 77.6 (5); 126.5 (10); 134.1 (9)

IR (liquid film, cm$^{-1}$): 1151 (NSO$_2$); 1345 (NSO$_2$); 1737; 2978 (C-H)

Mass (Cl +Q1MS): 73 ([C(CH$_3$)$_2$OMe]$^+$, 2%); 202 ([M-OMe]$^+$, 100%); 234 ([M+H]$^+$, 6%)

4.3.3 Synthesis of 3-(pyrrolidinosulfonyl)propionitrile 48

M.F.: C$_7$H$_{12}$N$_2$O$_2$S (M.W. 188.24)


In a three-necked flask equipped with a magnetic stirrer and an addition funnel, 2.179 g (13.51 mmol; 1 eq.) of 1-(ethenylsulfonyl)pyrrolidine 40 were dissolved in 53 ml of DMF. In an Erlenmeyer, 1.76 g (27.03 mmol; 2 eq.) of potassium cyanide and 1.084 g (20.27 mmol; 1.5 eq.) of ammonium chloride were dissolved in 7.8 ml of water. This solution was poured into the addition funnel and added slowly to the solution containing the sulfonamide. The reaction mixture was stirred for 65 hours at room temperature. The solvents were then evaporated under high vacuum in an evaporator with cold-trap condenser to obtain a cream-colored solid.

50 ml of water and 50 ml of CH$_2$Cl$_2$ were added to the solid. The aqueous phase was extracted 3 times with CH$_2$Cl$_2$. The organic phase was washed with a saturated solution of NaCl, dried over MgSO$_4$, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (AcOEt : ether 50 : 50) and recrystallization from AcOEt / hexane.

Yield: 1.795 g (71 %)

Aspect: white crystals (needles)

TLC: $R_f = 0.6$ (AcOEt : ether 50 : 50)
Experimental part

$^1$H NMR (CDCl$_3$, 200 MHz): 1.98 (m, 4 H, 2); 2.88 (t, $^3J_{4,3} = 7.2$, 2 H, 4); 3.26 (t, $^3J_{3,4} = 7$, 2 H, 3); 3.41 (m, 4 H, 1)

$^{13}$C NMR (CDCl$_3$, 50 MHz): 12.8 (4); 25.8 (2); 45.4 (3); 47.8 (1); 116.9 (5)

IR (solid deposit, cm$^{-1}$): 1140 (NSO$_2$); 1333 (NSO$_2$); 2245 (C=N); 2986 (C-H)

Mass (EI +Q1MS): 54 ([CH$_2$CH$_2$CN]$^+$, 12.3%); 70 ([M-SO$_2$CH$_2$CH$_2$CN]$^+$, 100%); 134 ([M-(CH$_2$CH$_2$CN)]$^+$, 21.3%); 187 ([M-H]$^+$, 21.5%); 188 (M$^{+}$, 10.5%)

m.p.: 102.5-103°C (lit.: 104°C)

GC (100/0/10/290/20): t$_R$ = 12.22 min

4.3.4 Synthesis of 3-[(2S)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]propionitrile 49

M.F.: C$_{11}$H$_{20}$N$_2$O$_3$S (M.W. 260.35) RN: 190510-69-1


In a three-necked flask equipped with an addition funnel, 6.77 g (29.01 mmol; 1 eq.) of (2S)-1-ethenylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 45 were dissolved in 115 ml of DMF. In an Erlenmeyer, 3.778 g (58.03 mmol; 2 eq.) of potassium cyanide and 2.328 g (43.52 mmol; 1.5 eq.) of ammonium chloride were dissolved in 16.75 ml of water. This solution was transferred into the addition funnel and added slowly to the flask. The mixture was stirred for 16 hours at room temperature. The solvents were evaporated under high vacuum in an evaporator with cold-trap condenser to obtain a cream-colored solid.

50 ml of CH$_2$Cl$_2$ and 50 ml of water were added to the solid obtained. The aqueous phase was extracted 3 times with CH$_2$Cl$_2$. The organic phase was washed with a saturated solution of NaCl, dried over MgSO$_4$, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 6.27 g (83 %)

Aspect: white solid

TLC: R$_f$ = 0.41 (petroleum ether : AcOEt 60 : 40): 0.59 (petroleum ether : AcOEt 1 : 2)
\textbf{1H NMR} (CDCl$_3$, 200 MHz): 1.12 and 1.15 (2 s, 6 H, 6, 7); 1.65-2.12 (m, 4 H, 2, 3); 2.87 (t, $^3J_{10,9} = 7.6$, 2 H, 10); 3.02-3.18 (m, 1 H, 1); 3.23 (s, 3 H, 8); 3.42 (ddd, $^2J_{9,9'} = 13.8$; $^3J_{9,10} = 7.3$; $^3J_{9,10} = 7.2$, 1 H, 9); 3.61 (ddd, $^2J_{9,9'} = 13.7$; $^3J_{9,10} = 7.8$; $^3J_{9,10} = 7.8$, 1 H, 9); 3.89-4.01 (m, 1 H, 1); 4.11-4.21 (m, 1 H, 4)

\textbf{13C NMR} (CDCl$_3$, 50 MHz): 12.8 (10); 20.0 and 21.6 (6, 7); 26.5 and 28.1 (2, 3); 48.2 (1); 49.15 (8); 50.3 (9); 66.9 (4); 78.2 (5); 117.0 (11)

\textbf{Mass} (EI +Q1MS): 54 ([CH$_2$CH$_2$CN]$^+$, 2%); 70 ([N(CH$_2$)$_4]^+$, 12%); 73 ([C(CH$_3$)$_2$OMe]$^+$, 100%); 142 ([M-(SO$_2$CH$_2$CH$_2$CN)]$^+$, 3%); 187 ([M-(C(CH$_3$)$_2$OMe)]$^+$, 21%); 229 ([M-(OMe)]$^+$, 7%)

$\alpha_{20}^0$: -7.7° (c=0.145; CHC$_3$)

\textbf{m.p.:}  62-62.5°C (lit.: 61°C)
\textbf{GC} (100/0/10/290/20): $t_R = 15.63$ min

4.3.5 Synthesis of 1-(ethyloxy)-3-(pyrrolidin-1-ylsulfonyl)propan-1-iminium chloride 50

\textbf{M.F.:} C$_9$H$_{19}$ClN$_2$O$_3$S (M.W. 270.77)

\textbf{Reference:} Huart, C. \textit{PhD-thesis UCL-ORSY, 1995}

In a flame-dried three-necked flask equipped with a gas inlet, a gas outlet, an internal thermometer and a magnetic stirrer, 2.196 g (11.665 mmol; 1 eq.) of 3-(pyrrolidinosulfonyl)propionitrile 48 were dissolved in 9.7 ml of dry CH$_2$Cl$_2$ and 1.027 ml (806 mg; 17.497 mmol; 1.5 eq.) of dry ethanol. After complete dissolution, the mixture was cooled to -40°C. Freshly synthesized HCl, prepared by the addition of H$_2$SO$_4$ to NH$_4$Cl, was then bubbled through the mixture until saturation. The temperature was raised to 5°C and the mixture was stirred for 20 hours. The solvents were evaporated under reduced pressure in a rotary evaporator connected to a trap containing silica gel.

The foamy residue obtained was triturated with dry ether and the solvent evaporated under reduced pressure. This operation was repeated until a white solid was obtained.

\textbf{Yield:} 3.159 g (quant.)
1H NMR (CDCl₃, 200 MHz): 1.52 (t, 3J₇,₆ = 7.0, 3 H, 7); 1.90-2.03 (m, 4 H, 2); 3.22 (t, 3J₄,₃ = 6.4, 2 H, 4); 3.35-3.48 (m, 4 H, 1); 3.53 (t, 3J₃,₂ = 6.7, 2 H, 3); 4.69 (q, 3J₆,₇ = 7.0, 2 H, 6); 11.75 (broad s, 1 H, NH₂⁺); 12.60 (broad s, 1 H, NH₂⁺)

13C NMR (DMSO, 200 MHz): 13.4 (7); 25.3 (2); 27.3 (4); 43.1 (3); 47.5 (1); 69.7 (6); 176.2 (5)

4.3.6 Synthesis of 1-(ethyloxy)-3-({(2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-yl}sulfonyl)-propan-1-iminium chloride 51

M.F.: C₁₃H₂₇ClN₂O₄S (M.W. 342.88)


In a flame-dried three-necked flask equipped with a gas inlet, a gas outlet, an internal thermometer and a magnetical stirrer, 5.154 g (19.79 mmol; 1 eq.) of 3-[(2S)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]propionitrile 49 were dissolved in 16.5 ml of dry CH₂Cl₂ and 1.742 ml (1.367 g; 29.69 mmol; 1.5 eq.) of dry ethanol. After complete dissolution, the mixture was cooled to -40°C. Freshly synthesized HCl, prepared by the addition of H₂SO₄ to NH₄Cl, was then bubbled through the mixture until saturation. The temperature was raised to 5°C and the mixture was stirred for 20 hours. The solvents were evaporated under reduced pressure in a rotary evaporator connected to a trap containing silica gel.

The foamy residue obtained was triturated with dry ether and the solvent evaporated under reduced pressure. This operation was repeated until a white solid was obtained.

Yield: 6.788 g (quant.)

1H NMR (CDCl₃, 200 MHz): 1.14 (s, 6 H, 6, 7); 1.51 (t, 3J₁₃,₁₂ = 7.5, 3 H, 13); 1.67-2.12 (m, 4 H, 2, 3); 3.09-3.89 (m, 6 H, 1, 9, 10); 3.20 (s, 3 H, 8); 4.07-4.11 (m, 1 H, 4); 4.65-4.73 (m, 2 H, 12); 11.62 (broad s, 1 H, NH₂⁺); 12.51 (broad s, 1 H, NH₂⁺)

13C NMR (CDCl₃, 50 MHz): 13.2 (13); 20.2 and 21.2 (6, 7); 26.0 (10); 27.5 and 27.9 (2, 3); 47.0 (1); 48.9 (8); 50.1 (9); 66.4 (4); 71.0 (12); 77.7 (5); 176.4 (11)
4.3.7 Synthesis of 1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 52

M.F.: C_{13}H_{27}NO_{5}S (M.W. 309.42)


In a flame-dried flask, 3.158 g (11.662 mmol; 1 eq.) of freshly prepared 1-(ethyloxy)-3-[(pyrrolidin-1-yl)sulfonyl]propan-1-iminium chloride 50 were dissolved in 24 ml of dry CH_{2}Cl_{2} and 8.2 ml of dry ethanol. The reaction mixture was stirred for 65 hours at room temperature. The precipitate (NH_{4}Cl) that formed during the reaction was eliminated by filtration. The filtrate was evaporated under reduced pressure. The resulting oil was dissolved in 30 ml of dry Et_{2}O and stirred for 10 minutes. The precipitate that formed (amide) was eliminated by filtration. The filtrate was then stirred in the presence of 30 ml of a 2N solution of KOH (hydrolysis of the ester). The stirring should be slow enough not to mix the 2 phases. It was continued until all the ester had disappeared (followed by IR). The 2 phases were separated and the aqueous phase was extracted 4 times with Et_{2}O. The organic phase was dried over 2 g of drierite 10-20 mesh and then filtered through a pad of dry Na_{2}SO_{4}. The drierite was washed with Et_{2}O and the filtrate was evaporated under reduced pressure.

Yield: 2.55 g (71 %)

Aspect: colorless oil

\[\text{H NMR (CDCl}_{3}\text{, 300 MHz): } 1.21 (t, ^{3}J_{7.6} = 7, 9 \text{ H, 7}); 1.88-1.98 (m, 4 \text{ H, 2}); 2.28 (\text{mult, 2 H, 4}); 3.04 (\text{mult, 2 H, 3}); 3.31-3.42 (m, 4 \text{ H, 1}); 3.53 (t, ^{3}J_{6.7} = 7.1, \text{ 6 H, 6})\]

\[\text{C NMR (CDCl}_{3}\text{, 50 MHz): } 15.0 \text{ (7)}; 25.8 \text{ (2)}; 26.1 \text{ (4)}; 44.2 \text{ (3)}; 47.7 \text{ (1)}; 57.5 \text{ (6)}; 113.9 \text{ (5)}\]

IR (liquid film, cm\(^{-1}\)): 1072 (C-O); 1147 (NSO\(_{2}\)); 1329 (NSO\(_{2}\)); 2977 (C-H)

4.3.8 Synthesis of (2S)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10

M.F.: C_{17}H_{35}NO_{6}S (M.W. 381.52)

RN: 190510-70-4
Reference: Huart, C. *PhD-Thesis UCL-ORSY, 1995*

In a flame-dried flask, 2.265 g (6.605 mmol; 1 eq.) of freshly prepared 1-(ethyloxy)-3-((2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-yl)sulfonyl)propan-1-iminium chloride 51 were dissolved in 14 ml of dry CH$_2$Cl$_2$ and 4.6 ml of dry ethanol. The reaction mixture was stirred for 65 hours at room temperature. The precipitate (NH$_4$Cl) that formed during the reaction was eliminated by filtration. The filtrate was evaporated under reduced pressure. The resulting oil was dissolved in 27 ml of dry Et$_2$O and stirred for 10 minutes. The precipitate that formed (amide) was eliminated by filtration. The filtrate was then stirred in the presence of 21 ml of a 2N solution of KOH (hydrolysis of the ester). The stirring should be slow enough not to mix the 2 phases. It was continued until all the ester had disappeared (followed by IR). The 2 phases were separated and the aqueous phase was extracted 4 times with Et$_2$O. The organic phase was dried over 2 g of drierite 10-20 mesh and then filtered through a pad of dry Na$_2$SO$_4$. The drierite was washed with Et$_2$O and the filtrate was evaporated under reduced pressure.

**Yield:** 1.423 g (56 %)

**Aspect:** colorless oil

![Chemical Structure](image)

**$^1$H NMR** (CDCl$_3$, 300 MHz): 1.14 and 1.18 (2 s, 6 H, 6, 7); 1.21 (t, $^3J_{13-12}$ = 7.5, 9 H, 13); 1.69-2.03 (m, 4 H, 2, 3); 2.28 (mult, 2 H, 10); 3.07-3.16 (m, 3 H, 1, 9); 3.20 (s, 3 H, 8); 3.53 (q, $^3J_{12-13}$ = 7.5, 6 H, 12); 3.74-3.82 (m, 1 H, 1); 4.05-4.11 (m, 1 H, 4)

**$^{13}$C NMR** (CDCl$_3$, 50 MHz): 15.1 (13); 21.4 and 21.6 (6, 7); 26.3, 26.5 and 27.2 (2, 3, 10); 47.3 (9); 49.3 (8); 50.0 (1); 57.4 (12); 66.4 (4); 77.8 (5); 113.9 (11)

**IR** (liquid film, cm$^{-1}$): 1072 (C-O); 1145 (NSO$_2$); 1326 (NSO$_2$); 2874 (OCH$_3$); 2978 (C-H)

[$\alpha$]$^D_{20}$: -60.8° (c=0.296; CHCl$_3$)
4.4 Synthesis of ketals

4.4.1 Synthesis of 1-[(3,3-diethoxypropyl)sulfonyl]pyrrolidine 56

M.F.: C_{11}H_{23}NO_4S (M.W. 265.36)

In a flame-dried two-necked flask, 200 mg (1.34 mmol; 1 eq.) of 1-(methylsulfonyl)pyrrolidine 11 were dissolved in 10 ml of THF and 466 µl (480 mg; 2.68 mmol; 2 eq.) of HMPA. The mixture was cooled to -78°C and 670 µl (456 mg; 1.34 mmol; 1 eq.) of n-BuLi, 2M solution in hexane, were slowly added. After 60 minutes of reaction, 202 µl (264 mg; 1.34 mmol; 1 eq.) of bromoacetaldehyde diethyl acetal were added. The mixture was allowed to come to room temperature and the stirring was continued for 2 hours. The reaction was quenched by the addition of a saturated solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 200 mg (56 %)

Aspect: yellow oil

TLC: R_f = 0.77 (petroleum ether : AcOEt 60 : 40)

1H NMR (CDCl₃, 300 MHz): 1.19 and 1.20 (2 t, 3J_7,6 = 7, 6 H, 7); 1.89-1.98 (m, 4 H, 2); 2.09 (mult, 2 H, 4); 3.05 (mult, 2 H, 3); 3.30-3.40 (m, 4 H, 1); 3.51 and 3.66 (2 mult, 4 H, 6); 4.59 (mult, 1 H, 5)

13C NMR (CDCl₃, 50 MHz): 15.2 (7); 25.7 (2); 27.8 (4); 44.8 (3); 47.6 (1); 62.1 (6); 101.0 (5)

IR (liquid film, cm⁻¹): 1145 (NSO2); 1330 (NSO2); 2976 (C-H)

Mass (Cl - Q1MS): 127 (45%); 264 ([M-H]^+ , 35%)

4.4.2 Synthesis of (2S)-1-[(3,3-diethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 57

M.F.: C_{15}H_{31}NO_5S (M.W. 337.47)
In a flame-dried two-necked flask, 1000 mg (4.518 mmol; 1 eq.) of (2S)-1-methylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 14 were dissolved in 34 ml of THF and 1.572 ml (1.619 g; 9.036 mmol; 2 eq.) of HMPA. The mixture was cooled to -78°C and 2.053 ml (1.396 g; 4.518 mmol; 1 eq.) of n-BuLi, 2.2M solution in hexane, were slowly added. After 60 minutes of reaction, 680 µl (890 mg; 4.518 mmol; 1 eq.) of bromoacetaldehyde diethyl acetal were added. The mixture was allowed to come to room temperature and the stirring was continued for 2 hours. The reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 90 : 10).

**Yield:** 484 mg (32 %)

**Aspect:** colorless oil

**TLC:** R₀ = 0.58 (petroleum ether : AcOEt 60 : 40)

1H NMR (CDCl₃, 300 MHz): 1.14 and 1.17 (2 s, 6 H, 6, 7); 1.21 (t, 3J₁₃-₁₂ = 6.9, 6 H, 13); 1.72-2.04 (m, 6 H, 2, 3); 2.12 (mult, 2 H, 10); 3.05 (mult, 1 H, 1); 3.16 (mult, 1 H, 9); 3.21 (8); 3.51 and 3.67 (2 mult, 4 H, 12); 3.79 (mult, 1 H, 1); 4.07 (mult, 1 H, 4); 4.61 (t, 3J₁₁-₁₀ = 4.6, 1 H, 11)

13C NMR (CDCl₃, 75 MHz): 15.2 (13); 21.2 and 21.5 (6, 7); 26.2 and 27.9 (2, 3); 27.2 (10); 47.5 (9); 49.2 (8); 49.9 (1); 62.0 (12); 66.3 (4); 77.8 (5); 101.0 (11)

IR (liquid film, cm⁻¹): 1145 (NSO₂); 1335 (NSO₂); 2975 (C-H)

Mass (Cl -Q1MS): 109 (18%); 248 (100%); 336 ([M-H]⁻, 60%)

\[ [\alpha]_{D}^{20} = -18.2^\circ \ (c=0.329; \text{CHCl}_3) \]

**4.4.3 Synthesis of (2S)-1-[[2-(1,3-dioxolan-2-yl)ethyl]sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 58**

M.F.: C₁₃H₂₅NO₅S (M.W. 307.4)

In a flame-dried two-necked flask 1000 mg, (4.518 mmol; 1 eq.) of (2S)-1-methylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 14 were dissolved in 34 ml of
THF and 1.572 ml (1.619 g; 9.036 mmol; 2 eq.) of HMPA. The mixture was cooled to -78°C and 2.053 ml (1.396 g; 4.518 mmol; 1 eq.) of n-BuLi, 2.2M solution in hexane, were added. After 60 minutes of reaction, 468 µl (754 mg; 4.518 mmol; 1 eq.) of 2-bromomethyl-1,3-dioxolane were added. The mixture was allowed to come to room temperature and after 2 hours of reaction, a few ml of a saturated solution of NH₄Cl were added. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (mounting: petroleum ether : AcOEt 95 : 5 + 10% Et₃N; elution: petroleum ether : AcOEt 95 : 5).

**Yield:** 686 mg (49 %)

Besides, 337 mg (34 %) of (2S)-1-methylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine 27 were recovered.

**Aspect:** colorless oil

**TLC:** Rₜ = 0.32 (petroleum ether : AcOEt 60 : 40)

![Structure diagram](image)

**¹H NMR** (CDCl₃, 300 MHz): 1.12 and 1.16 (2 s, 6 H, 6, 7); 1.72-2.05 (m, 4 H, 2, 3); 2.19 (mult, 2 H, 10); 3.06-3.17 (m, 1 H, 1); 3.19-3.25 (m, 1 H, 9); 3.16 (s, 3 H, 8); 3.77-3.86 (m, 1 H, 1); 3.92 (mult, 4 H, 12); 4.05-4.11 (m, 1 H, 4); 5.01 (t, ³J₁₁-₁₀ = 3.9, 1 H, 11)

**¹³C NMR** (CDCl₃, 75 MHz): 21.0 and 21.5 (6, 7); 26.2, 27.3 and 27.9 (2, 3, 10); 49.2 (8); 46.7 and 50.0 (1, 9); 65.0 (12); 66.2 (4); 77.9 (5); 102.2 (11)

**IR** (liquid film, cm⁻¹): 1138 (NSO₂); 1331 (NSO₂); 2977 (C-H)

**Mass** (Cl/CH₄-N₂O): 73 ([C(CH₃)₂OMe]⁺, 18%); 190 (53%); 276 ([M-OMe]⁺, 100%); 308 ([M+H]⁺, 7%)

**GC** (100/0/10/290/15): tₕ = 17.46 min

\[\alpha\] = -46.5° (c=0.129; CHCl₃)

**HRMS:** calculated for C₁₃H₂₅NO₅S⁺: 308.153170; found: 308.152277
4.5 Synthesis of ethers and thioethers

4.5.1 Synthesis of 1-[(3-chloropropyl)sulfonyl]pyrrolidine 41

M.F.: C₇H₁₄ClNO₂S (M.W. 211.7)  
RN: 146475-49-2

Following the general procedure described in 4.1 with:
2 ml (1.704 g; 23.95 mmol; 1 eq.) of pyrrolidine
3.33 ml (2.424 g; 23.95 mmol; 1 eq.) of Et₃N
2.913 ml (4.241 g; 23.95 mmol; 1 eq.) of 3-chloropropanesulfonyl chloride
21 ml of CH₂Cl₂
Flash chromatography: AcOEt : CH₂Cl₂ 1 : 1

Yield: 5.23 g (quant.)

Aspect: white solid

TLC: Rᵣ = 0.29 (CH₂Cl₂ 100%)

¹H NMR (CDCl₃, 300 MHz): 1.96 (mult, 4 H, 2); 2.30 (mult, 2 H, 4); 3.14 (t, ³J₃₆₄ = 11.2, 2 H, 3); 3.34-3.41 (m, 4 H, 1); 3.70 (t, ³J₅₆ = 9.0, 2 H, 5)

¹³C NMR (CDCl₃, 75 MHz): 25.8 (2); 26.6 (4); 43.0 (5); 46.6 (3); 47.7 (1)

Mass (Cl/CH₄-N₂O): 70 ([NC₄H₈]⁺, 100%); 77 ([C₆H₅Cl]⁺, 26%); 212 ([M+H⁺]⁺ (³⁵Cl), 48%); 214 ([M+H⁺]⁺ (³⁷Cl), 25%)

4.5.2 Synthesis of 1-[6-chlorohexyl]sulfonyl]pyrrolidine 42

M.F.: C₁₀H₂₀ClNO₂S (M.W. 253.78)

Following the general procedure described in 4.1 with:
200 µl (170 mg; 2.395 mmol; 1 eq.) of pyrrolidine
333 µl (242 mg; 2.395 mmol; 1 eq.) of Et₃N
525 mg (2.395 mmol; 1 eq.) of 6-chlorohexylsulfonyl chloride
3.4 ml of CH₂Cl₂
Flash chromatography: petroleum ether : AcOEt 70 : 30

Yield: 424 mg (70%)
**Aspect**: white solide

**TLC**: Rf = 0.25 (petroleum ether : AcOEt 80 : 20); 0.33 (petroleum ether : AcOEt 70 : 20)

\[
\text{N O} \quad 1 \\
\text{2 3 4 5 6 7 8 Cl}
\]

**1H NMR** (CDCl₃, 200 MHz): 1.42-1.55 (m, 4 H, 5, 6); 1.74-1.90 (m, 4 H, 4, 7); 1.94 (mult, 4 H, 2); 2.96 (mult, 2 H, 3); 3.36 (mult, 4 H, 1); 3.54 (t, \(^3J_{B,2} = 6.5\), 2 H, 8)

**13C NMR** (CDCl₃, 50 MHz): 23.1 (4); 25.8 (2); 26.3 (6); 27.7 (5); 32.1 (7); 41.6 (1); 44.7 (8); 49.4 (3)

**Mass** (Cl/CH₄-N₂O): 218 ([M-Cl]⁺, 16%); 254 ([M+H]⁺ (³⁵Cl), 100%); 256 ([M+H]⁺ (³⁷Cl), 43%)

**m.p.**: 55-56°C

**Elemental analysis:**

calculated (%): C: 47.33; H: 7.94; N: 5.52; S: 12.63

found (%): C: 47.11; H: 7.97; N: 5.11; S: 13.02

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**4.5.3 Synthesis of (2S)-1-[(3-chloropropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 46**

**M.F.**: C\(_{11}\)H\(_{22}\)ClNO\(_3\)S (M.W. 283.81)

Following the general procedure described in 4.1 with:

- 5 g (34.9 mmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)pyrrolidine 27
- 4.852 ml (3.532 g; 34.9 mmol; 1 eq.) of Et₃N
- 4.244 ml (6.18 g; 34.9 mmol; 1 eq.) of 3-chloropropanesulfonyl chloride
- 50 ml of Et₂O

Flash chromatography: petroleum ether : AcOEt 70 : 30

**Yield**: 8.74 g (88 %)

**Aspect**: slightly yellow oil

**TLC**: Rₙ = 0.67 (petroleum ether : AcOEt 60 : 40)
1H NMR (CDCl3, 300 MHz): 1.13 and 1.17 (2 s, 6 H, 6, 7); 1.70-2.07 (m, 4 H, 2, 3); 2.30 (mult, 2 H, 10); 3.04-3.18 (m, 4 H, 2, 3); 3.28 (t, 3J9-10 = 7.4, 2 H, 9); 3.69 (t, 3J14-13 = 6.4, 2 H, 14); 4.04-4.14 (m, 1 H, 4).

13C NMR (CDCl3, 75 MHz): 20.9 and 21.5 (C6, 7); 26.3 (C10); 26.7 and 27.4 (C2, 3); 43.1 (C11); 49.2 (C8); 51.9-49.9 (C1, 9, 12); 66.0 (C4); 77.8 (C5).

IR (liquid film, cm⁻¹): 1146 (NSO2); 1330 (NSO2); 2943 (C-H)

Mass (CI/CH4-N2O): 252 ([M-OMe]+ (35Cl), 100%); 254 ([M-OMe]+ (37Cl), 48%); 284 ([M+H]+ (35Cl), 3%); 286 ([M+H]+ (37Cl), 1.5%)

GC (100/0/10/290/20): tR = 16.06 min

HRMS: calculated for C11H21ClNO3S+: 282.093068; found: 282.092264

4.5.4 Synthesis of (2S)-1-[(6-chlorohexyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 36

M.F.: C14H28ClNO3S (M.W. 325.89)

Following the general procedure described in 4.1 with:
400 mg (2.792 mmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)pyrrolidine 27
388 µl (282 mg; 2.792 mmol; 1 eq.) of Et3N
612 mg (2.792 mmol; 1 eq.) of 6-chlorohexylsulfonyl chloride
4 ml of CH2Cl2
Flash chromatography: petroleum ether : AcOEt 70 : 30

Yield: 462 mg (51%)

Aspect: colorless oil
TLC: Rf = 0.61 (petroleum ether : AcOEt 70: 30)

1H NMR (CDCl3, 200 MHz): 1.13 and 1.16 (2 s, 6 H, 6, 7); 1.40-1.53 (m, 4 H, 11, 12); 1.69-2.04 (m, 8 H, 2, 3, 10, 13); 3.05-3.17 (m, 1 H, 1); 3.07 (t, 3J9,10 = 7.8, 2 H, 9); 3.21 (s, 3 H, 8); 3.54 (t, 3J14,13 = 6.4, 2 H, 14); 3.74-3.86 (m, 1 H, 1); 4.04-4.14 (m, 1 H, 4)

13C NMR (CDCl3, 50 MHz): 21.1 and 21.5 (6, 7); 23.2 (10); 26.3 (12); 27.2-26.2 (2, 3); 27.6 (11); 32.1 (13); 44.7 (14); 49.2 (8); 51.9-49.9 (1, 9); 66.0 (4); 77.8 (5)

IR (Film liquide (FT), cm⁻¹): 1146 (NSO2); 1330 (NSO2); 2943 (C-H)
Experimental part

**Mass** (Cl/CH4-N2O): 83 (100%); 165 (49%); 294 ([M-OMe]+ (35Cl), 55%); 296 ([M-OMe]+ (37Cl), 28%); 326 ([M+H]+ (35Cl), 4%); 328 ([M+H]+ (37Cl), 2%)

4.5.5 Synthesis of 1-[[3-iodopropyl]sulfonyl]pyrrolidine 55

**M.F.:** C7H14INO2S (M.W. 303.15)

A mixture of 5.23 g (24.7 mmol; 1 eq.) of 1-[[3-chloropropyl]sulfonyl]pyrrolidine and of 3.814 g (25.44 mmol; 1.03 eq.) of sodium iodide in 29 ml of acetone was refluxed in a flask equipped with a reflux condenser for 16 hours. The mixture was cooled to room temperature, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (CH2Cl2 : AcOEt 50 : 50).

**Yield:** 6.12 g (82%)

**Aspect:** yellow solid

1H NMR (CDCl3, 300 MHz): 1.92-2.00 (m, 4 H, 2); 2.33 (mult, 2 H, 4); 3.09 (mult, 2 H, 3); 3.32 (t, 3J5-4 = 6.6, 2 H, 5); 3.33-3.42 (m, 4 H, 1)

13C NMR (CDCl3, 75 MHz): 3.7 (5); 25.8 (2); 27.1 (4); 47.7 (1); 49.9 (3)

**IR** (solid deposit, cm⁻¹): 736; 1133 (NSO2); 1327 (NSO2); 2976 (C-H)

**Mass** (Cl/CH4-N2O): 70 ([N(CH2)4]+, 14%); 176 ([M-I]+, 100%); 304 ([M+H]+, 58%)

**m.p.:** 84-85°C

4.5.6 Synthesis of 1-[(6-iodohexyl)sulfonyl]pyrrolidine 60

**M.F.:** C10H20INO2S (M.W. 345.23)

A mixture of 424 mg (1.67 mmol; 1 eq.) of 1-[[6-(chlorohexyl)sulfonyl]pyrrolidine and of 288 mg (1.921 mmol; 1.15 eq.) of sodium iodide in 2ml of acetone was refluxed in a flask equipped with a reflux condenser for 16 hours. The mixture was cooled to room temperature, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 70 : 30).

**Yield:** 404 mg (70%)
**Aspect:** yellow solid

**TLC:** Rf = 0.53 (petroleum ether : AcOEt 70 : 30)

![TLC Image]

**1H NMR** (CDCl₃, 200 MHz): 1.40-1.51 (m, 4 H, 4, 7); 1.74-1.89 (m, 4 H, 5, 6); 1.94 (mult, 4 H, 2); 2.96 (mult, 2 H, 3); 3.20 (t, J₈,₇ = 6.9, 2 H, 8); 3.36 (mult, 4 H, 1)

**13C NMR** (CDCl₃, 50 MHz): 6.7 (8); 23.0 (4); 25.8 (2); 27.3 (5); 29.8 (6); 32.9 (7); 47.6 (1); 49.2 (3)

**Mass** (Cl/CH₄-N₂O): 70 ([C₄H₈N]⁺, 100%); 218 ([M-I]⁺, 57%); 346 ([M+H]⁺, 38%)

**m.p.:** 52-53°C

**Elemental analysis:**

Calculated (%): C: 34.79; H: 5.84; N: 4.06; S: 9.29

Found (%): C: 34.77; H: 6.00; N: 3.92; S: 9.15

### 4.5.7 Synthesis of (2S)-1-(3-iodopropane-1-sulfonyl)-2-(1-methoxy-1-methylethyl)pyrrolidine 61

**M.F.:** C₁₁H₂₂INO₃S (M.W. 375.26)

In a flask equipped with a reflux condenser, 2.94 g (10.35 mmol; 1 eq.) of (2S)-1-(3-chloropropane-1-sulfonyl)-2-(1-methoxy-1-methylethyl)pyrrolidine 46 and 1.599 g (10.66 mmol; 1.03 eq.) of sodium iodide in 12 ml of acetone were refluxed for 16 hours. The mixture cooled down to room temperature was filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 70 : 30).

**Yield:** 3.75 g (96 %)

**Aspect:** yellow oil

**TLC:** Rf = 0.41 (petroleum ether : AcOEt 80 : 20)

![TLC Image]

**1H NMR** (CDCl₃, 300 MHz): 1.13 and 1.17 (2 s, 6 H, 6, 7); 1.73-2.08 (m, 4 H, 2, 3); 2.34 (mult, 2 H, 10); 3.21 (t, J₁₁,₁₀ = 6.3, 2 H, 11); 3.22 (s, 3 H, 8); 3.05-3.16 (m, 1 H, 1); 3.31 (mult, 2 H, 9); 3.78-3.87 (m, 1 H, 1); 4.07-4.13 (m, 1 H, 4)
13C NMR (CDCl₃, 75 MHz): 3.6 (11); 21.0 and 21.5 (6, 7); 26.7 (10); 26.3 and 27.4 (2, 3); 49.3 (8); 50.0 and 52.9 (1, 9); 66.3 (4); 77.9 (5)

Mass (Cl/CH₄-N₂O): 85 (100%); 248 ([M-I]^+, 12%); 344 ([M-OMe]^+, 26%); 376 ([M+H]^+, 1%)

HRMS: calculated for C₁₁H₂₃INO₃S⁺: 376.044343; found: 376.043432

4.5.8 Synthesis of (2S)-1-(6-iodohexane-1-sulfonyl)-2-(1-methoxy-1-methylethyl)pyrrolidine 62

M.F.: C₁₄H₂₈INO₃S (M.W. 417.34)

In a flask equipped with a reflux condenser, 462 mg (1.417 mmol; 1 eq.) of (2S)-1-[(6-chlorohexyl)sulfonyl]-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidine 36 and 244 mg (1.63 mmol; 1.15 eq.) of sodium iodide in 2 ml of acetone were refluxed for 16 hours. The mixture cooled down to room temperature was filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20).

Yield: 466 mg (99%)

Aspect: white solid

TLC: Rf = 0.26 (petroleum ether : AcOEt 80 : 20)

1H NMR (CDCl₃, 200 MHz): 1.49-1.52 (m, 4 H, 11, 12); 1.71-2.01 (m, 8 H, 2, 3, 10, 13); 3.07 (t, 3J₉₋₁₀ = 8.0, 2 H, 9); 3.19 (t, 3J₁₄₋₁₃ = 6.8, 2 H, 14); 3.21 (s, 3 H, 8); 3.74-3.86 (m, 1 H, 1); 4.04-4.12 (m, 1 H, 4)

13C NMR (CDCl₃, 50 MHz): 6.5 (14); 21.3 and 21.6 (6, 7); 23.2 (10); 26.3 and 27.3 (2, 3, 11); 29.9 (12); 33.0 (13); 49.2 (4); 50.0 and 52.1 (1, 9); 66.2 (8); 77.9 (5)

Mass (Cl/CH₄-N₂O): 73 ([C₄H₇N]^+, 33%); 110 (35%); 142 ([N]^+, 27%); 260 ([M-I-OMe]^+, 100%); 294 (31%); 386 ([M-OMe]^+, 5%); 418 ([M+H]^+, 1%)

m.p.: 53-54°C
4.5.9  Synthesis of 1-[(3-ethoxypropyl)sulfonyl]pyrrolidine 59

**M.F.:** C$_9$H$_{19}$NO$_3$S (M.W. 221.31)

In a flame-dried two-necked flask equipped with a reflux condenser, 152 mg (6.597 mmol; 2 eq.) of sodium were reacted with 10 ml of ethanol. When all the sodium had reacted, 1 g (3.298 mmol; 1 eq.) of 1-[(3-iodopropyl)sulfonyl]pyrrolidine 55 dissolved in 29 ml of ethanol and 7 ml of THF was added. The mixture was then refluxed for 4 hours. Once cooled down to room temperature, some water was added. The solvents were evaporated. The residue was dissolved in a mixture of water and CH$_2$Cl$_2$. The aqueous phase was extracted with CH$_2$Cl$_2$. The organic phase was dried over MgSO$_4$, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20).

**Yield:** 359 mg (49 %)

**Aspect:** colorless oil

**TLC:** $R_f$ = 0.23 (petroleum ether : AcOEt 2 : 1)

**$^1$H NMR** (CDCl$_3$, 300 MHz): 1.20 ($t$, $^3J_{7-6}$ = 12.0, 3 H, 7); 1.89-1.98 ($m$, 4 H, 2); 2.00-2.16 ($m$, 2 H, 4); 3.18 ($m ult$, 2 H, 3); 3.32-3.41 ($m$, 4 H, 1); 3.50 ($m ult$, 4 H, 5, 6)

**$^{13}$C NMR** (CDCl$_3$, 75 MHz): 15.3 (7); 23.8 (4); 25.7 (2); 46.5 (3); 47.6 (1); 66.1 and 68.1 (5, 6)

**IR** (liquid film, cm$^{-1}$): 1147 (NSO$_2$); 1329 (NSO$_2$); 2974 (C-H)

**Mass** (Cl/CH$_4$N$_2$O): 151 ([M-NC$_4$H$_8$]$^+$, 1%); 176 ([M-OEt]$^+$, 89%); 222 (M$^+$, 100%)

**GC (100/0/10/290/15):** $t_R$ = 13.22 min

Besides, 350 mg (48 %) of 1-[(2-(ethyloxy)propyl)sulfonyl]pyrrolidine 68 were obtained:

**$^1$H NMR** (CDCl$_3$, 300 MHz): 1.20 ($t$, $^3J_{7-6}$ = 7.0, 3 H, 7); 1.33 ($d$, $^3J_{5-4}$ = 6.7, 3 H, 5); 1.94 ($m ult$, 4 H, 2); 2.95 ($d d$, $^2J_{3.3'}$ = 14.4, $^3J_{3.4}$ = 5.5, 1 H, 3); 3.28 ($d d$, $^2J_{3.3'}$ = 14.4, $^3J_{3.4}$ = 6.7, 1 H, 3); 3.34 ($m ult$, 4 H, 1); 3.49 and 3.60 (2 $m ult$, 2 H, 6); 3.98 ($s e x t$, $^3J_{4.3}$ = $^3J_{4.5}$ = 5.9, 1 H, 4)
4.5.10 Synthesis of (2S)-1-[(3-ethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 65

M.F.: C_{13}H_{27}NO_4S (M.W. 293.42)

In a flame-dried two-necked flask, 182 mg (7.909 mmol; 2 eq.) of sodium were reacted with 12 ml of dry EtOH. The mixture was stirred until complete reaction of the sodium. In a second flask, 1.389 g (3.954 mmol; 1 eq.) of (2S)-1-[(3-iodopropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 61 were dissolved in 35 ml of dry EtOH and 8.4 ml of THF. This solution was added to the first flask and the resulting mixture was refluxed for 4 hours. The mixture was cooled to room temperature and some water was added. The solvents were evaporated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over MgSO_4, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20).

Yield: 580 mg (50 %)

Aspect: colorless oil

TLC: R_f = 0.48 (petroleum ether : AcOEt 60 : 40)

^1H NMR (CDCl_3, 200 MHz): 1.14 and 1.17 (2 s, 6 H, 6, 7); 1.19 (t, J_{13-12} = 7.3, 3 H, 13); 1.72-2.17 (m, 6 H, 2, 3, 10); 3.04-3.23 (m, 3 H, 1, 9); 3.21 (s, 3 H, 8); 3.50 (mult, 4 H, 11, 12); 3.73-3.86 (m, 1 H, 1); 4.04-4.13 (m, 1 H, 4)

^13C NMR (CDCl_3, 75 MHz): 15.0 (13); 21.1 and 21.5 (6, 7); 23.9 (10); 26.1 and 27.1 (2, 3); 49.1 (8); 49.2 and 49.9 (1, 9); 66.2 (4); 66.0 and 68.3 (11, 12); 77.8 (5)

IR (liquid film, cm^{-1}): 1140 (NSO_2); 1327 (NSO_2); 2976 (C-H)

Mass (CI +Q1MS): 69 ([NC_4H_7]^+, 23%); 73 ([C(CH_3)_2OMe]^+, 100%); 85 (94%); 101 (74%); 146 (95%); 161 (31%); 294 ([M+H]^+, 22%)

GC (100/0/10/290/20): t_R = 17.1 min

[a]_D^{20} : -34.1° (c=0.176; CHCl_3)
4.5.11 Synthesis of 1-[[3-(ethylsulfanyl)propyl]sulfonyl]pyrroldine 63

**M.F.:** C₉H₁₉NO₂S₂ (M.W. 237.37)

In a flame-dried two-necked flask, 500 mg (1.649 mmol; 1 eq.) of 1-[(3-iodopropyl)sulfonyl]pyrrolidine 55 and 205 mg (2.437 mmol; 1.47 eq.) of sodium ethanethiolate were dissolved in 25 ml of THF. The mixture was stirred for 18 hours at room temperature. The reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted twice with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 281 mg (72 %)

**Aspect:** colorless oil

\[
\begin{align*}
\text{H NMR (CDCl₃, 200 MHz):} & \quad 1.26 (t, 3J₇-₆ = 7.4, 3 H, 7); 1.94 (\text{mult}, 4 H, 2); 2.11 (\text{mult}, 2 H, 4); 2.55 (q, 3J₆-₇ = 7.4, 2 H, 6); 2.67 (t, 3J₅-₄ = 6.9, 2 H, 5); 3.11 (\text{mult}, 2 H, 3); 3.37 (\text{mult}, 4 H, 1) \\
\text{C NMR (CDCl₃, 50 MHz):} & \quad 14.6 (7); 23.0 (4); 25.6 (6); 25.8 (2); 30.0 (5); 47.6 (1); 47.8 (3) \\
\text{Mass (CI +Q1MS):} & \quad 70 ([N(CH₂)₄]⁺, 4%); 167 ([M-N(CH₂)₄]⁺, 100%); 176 ([M-SEt]⁺, 32%); 212 (54%); 238 ([M+H]⁺, 12%) \\
\text{GC (100/0/290/15):} & \quad t_R = 16.87 \text{ min}
\end{align*}
\]

4.5.12 Synthesis of (2S)-1-[[3-(ethylsulfanyl)propyl]sulfonyl]-2-(1-methoxy-1-methylethyl)-pyrroldine 66

**M.F.:** C₁₃H₂₇NO₅S₂ (M.W. 309.48)

In a flame-dried two-necked flask, 1 g (2.664 mmol; 1 eq.) of (2S)-1-[(3-iodopropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)-pyrroldine 61 and 331 mg (3.937 mmol; 1.47 eq.) of sodium ethanethiolate were dissolved in 40 ml of THF. After 18 hours of stirring the reaction was quenched by the addition of a saturated
solution of NH₄Cl. The aqueous phase was extracted twice with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20).

Yield: 768 mg (93 %)

Aspect: yellow oil

\[ \text{\textbf{1H NMR}} \quad (\text{CDCl}_3, 300 \text{ MHz}): 1.13 \text{ and } 1.17 (2 \text{ s, } 6 \text{ H, } 6, 7); 1.26 (t, \text{ } \text{J}_{13-12} = 7.4, 3 \text{ H, } 13); 1.72-2.06 (m, 4 \text{ H, } 2, 3); 2.11 (\text{mult, } 2 \text{ H, } 10); 2.54 (q, \text{ } \text{J}_{12-13} = 7.4, 2 \text{ H, } 12); 2.66 (t, \text{ } \text{J}_{11-10} = 7.1, 2 \text{ H, } 11); 3.06-3.17 (m, 1 \text{ H, } 1); 3.21 (s, 3 \text{ H, } 8); 3.21 (t, \text{ } \text{J}_{9-10} = 7.7, 2 \text{ H, } 9); 3.76-3.85 (m, 1 \text{ H, } 1); 4.05-4.11 (m, 1 \text{ H, } 4)
\]

\[ \text{\textbf{13C NMR}} \quad (\text{CDCl}_3, 75 \text{ MHz}): 14.6 (13); 21.1 \text{ and } 21.5 (6, 7); 23.2 (10); 25.5 \text{ and } 26.2 (2, 3); 27.3 \text{ and } 30.0 (11, 12); 49.2 (8); 49.9 \text{ and } 50.8 (1, 9); 66.2 (4); 77.8 (5)
\]

\[ \text{IR (liquid film, } \text{cm}^{-1}): 1142 (\text{NSO}_2); 1326 (\text{NSO}_2); 2976 (\text{C-H})
\]

\[ \text{Mass (Cl +Q1MS): 155 (87%); 252 (100%); 278 ([M-OMe]^+, 28%); 310 ([M+H]^+, 9%)
\]

\[ \text{GC (100/0/10/290/20): } t_R = 19.64 \text{ min}
\]

\[ [\alpha]_{20}^D : -41.8 \degree (c=0.263; \text{CHCl}_3)
\]

\[ \text{HRMS: calculated for } \text{C}_{13}\text{H}_{28}\text{NO}_3\text{S}_2^+: 310.151063; \text{found: 310.149812}
\]

\[ \text{4.5.13 Synthesis of 1\text{-}[(6\text{-}(\text{ethylsulfanyl})\text{hexyl})\text{sulfonyl}]\text{pyrrolidine 64}}
\]

\[ \text{M.F.: } \text{C}_{12}\text{H}_{25}\text{NO}_2\text{S}_2 \text{ (M.W. 279.45)}
\]

In a flame-dried two-necked flask, 160 mg (463.4 µmol; 1 eq.) of 1\text{-}[(6\text{-}(\text{iodohexyl})\text{sulfonyl})\text{pyrrolidin} \text{60} \text{ and 58 mg (684.8 µmol; 1.47 eq.) of sodium ethanethiolate were dissolved in 7 ml of THF. The mixture was stirred for 18 hours at room temperature. The reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted twice with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 70 : 30).

Yield: 96 mg (74 %)

Aspect: colorless oil
1H NMR (CDCl₃, 200 MHz): 1.25 (t, 3J₁₀-₉ = 7.3, 3 H, 10); 1.37-1.54 (m, 4 H, 6, 7); 1.55-1.70 (m, 2 H, 5); 1.72-1.89 (m, 2 H, 4); 1.94 (mult, 4 H, 2); 2.53 (q, 3J₉-₁₀ = 7.4, 2 H, 9); 2.53 (t, 3J₈-₇ = 7.3, 2 H, 8); 2.96 (mult, 2 H, 3); 3.36 (mult, 4 H, 1)

13C NMR (CDCl₃, 50 MHz): 14.7 (10); 23.1 (4); 25.8 (2, 6); 28.0 (5); 28.3 (6); 29.1 (7); 31.4 (8); 47.6 (1); 49.3 (3)

IR (liquid film, cm⁻¹): 1140 (NSO₂); 1330 (NSO₂); 2975 (C-H)

Mass (Cl/CH₄-N₂O): 59 (100%); 209 ([M-NC₄H₈]⁺, 15%); 280 ([M+H]⁺, 7%)

HRMS: calculated for C₁₂H₂₆NO₂S₂⁺: 280.140498; found: 280.139857

4.5.14 Synthesis of (2S)-1-[(6-(ethylsulfanyl)hexyl)sulfonyl]-2-(1-methoxy-1-methylethyl)-pyrrolidine 67

M.F.: C₁₆H₃₃NO₂S₂ (M.W. 351.56)

In a flame-dried two-necked flask, 450 mg (1.078 mmol; 1 eq.) of (2S)-1-[(6-iodohexyl)sulfonyl]-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidine 62 and 134 mg (1.593 mmol; 1.47 eq.) of sodium ethanethiolate were dissolved in 16 ml of THF. After 18 hours of stirring, the reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted twice with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20).

Yield: 332 mg (88%)

Aspect: colorless oil

1H NMR (CDCl₃, 200 MHz): 1.14 and 1.17 (2 s, 6 H, 6, 7); 1.26 (t, 3J₁₆-₁₅ = 7.4, 3 H, 16); 1.38-1.52 (m, 4 H, 12, 13); 1.54-1.68 (m, 2 H, 11); 1.71-2.02 (m, 6 H, 2, 3, 10); 2.53 (t, 3J₁₄-₁₃ = 7.2, 2 H, 14); 2.54 (q, 3J₁₅-₁₆ = 7.4, 2 H, 15); 3.07 (t, 3J₉-₁₀ = 7.4, 2 H, 9); 3.12-3.22 (m, 1 H, 1); 3.21 (s, 3 H, 8); 3.72-3.86 (m, 1 H, 1); 4.04-4.12 (m, 1 H, 4)
Experimental part

\[\text{\^{13}C NMR (CDCl}_3, 50 \text{ MHz):} \ 14.7 \ (16); \ 21.2 \text{ and 21.5 (6, 7);} \ 23.2 \ (10); \ 25.8 \ (15); \ 26.2 \ (11); \ 28.0 \ (12); \ 28.3 \ (13); \ 27.2 \text{ and 29.1 (2, 3);} \ 31.4 \ (14); \ 49.2 \ (8); \ 49.9 \text{ and 52.0 (1, 9);} \ 66.0 \ (4); \ 77.9 \ (5)\]

\[\text{IR (liquid film, cm}^{-1}) : \ 1139 \ (\text{NSO}_2); \ 1330 \ (\text{NSO}_2); \ 2974 \ (\text{C-H})\]

\[\text{Mass (Cl/CH}_4\text{-N}_2\text{O):} \ 258 \ ([\text{M-OMe-SCH}_2\text{CH}_3]^+, \ 100); \ 320 \ [\text{M-OMe}]^+, \ 15\%); \ 352 \ ([\text{M+H}]^+, \ 1\%); \ [\alpha]^{20}_2 : -29.3^\circ \ (c=0.273; \text{CHCl}_3)\]

\[\text{HRMS: calculated for C}_{16}\text{H}_{34}\text{NO}_{3}\text{S}_2^+: \ 352.198013; \ \text{found:} \ 352.197477\]

4.5.15 Synthesis of 1-[(2-ethoxyethyl)sulfonyl]pyrrolidine 69

M.F.: C₈H₁₇NO₃S (M.W. 207.28)

In a flame-dried two-necked flask 71 mg (3.101 mmol; 1 eq.) of sodium were reacted with 9.1 ml of EtOH. After complete reaction, 500 mg (3.101 mmol; 1 eq.) of 1-(ethenylsulfonyl)pyrrolidine 40 dissolved in 4.55 ml of EtOH were slowly added. The mixture was stirred for 2 hours at room temperature and then quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 589 mg (92%)

Aspect: yellow oil

TLC: \(R_f = 0.38\) (petroleum ether : AcOEt 60 : 40)

\[1^H \text{ NMR (CDCl}_3, 200 \text{ MHz):} \ 1.21 \ (t, 3J_{5-6} = 7.0, 3 \text{ H, 6}); \ 1.92 \ (\text{mult, 4 H, 2}); \ 3.26 \ (t, 3J_{3-4} = 6.2, 2 \text{ H, 3}); \ 3.37 \ (\text{mult, 4 H, 1}); \ 3.53 \ (\text{q, 3J}_{5-6} = 7, 2 \text{ H, 5}); \ 3.82 \ (t, 3J_{4-3} = 6.0, 2 \text{ H, 4});\]

\[\text{\^{13}C NMR (CDCl}_3, 50 \text{ MHz):} \ 15.0 \ (6); \ 25.8 \ (2); \ 47.6 \ (1); \ 49.8 \ (3); \ 64.3 \ (5); \ 66.7 \ (4)\]

\[\text{IR (liquid film, cm}^{-1}) : \ 1145 \ (\text{NSO}_2); \ 1330 \ (\text{NSO}_2); \ 2976 \ (\text{C-H})\]

\[\text{Mass (Cl{-Q1MS):} \ 208 \ ([\text{M+H}]^+, \ 100\%); \ 415 \ ([2\text{M+H}]^+, \ 15\%)\]

\[\text{GC (100/0/10/290/15):} \ t_R = 12.62 \text{ min}\]

Elemental analysis:

calculated (%): C: 46.35; H: 8.26; N: 6.75; O: 23.15; S: 15.46
4.5.16 Synthesis of (2S)-1-[(2-ethoxyethyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine \textbf{70}

**M.F.:** $C_{12}H_{25}NO_4S$ (M.W. 279.39)

In a flame-dried two-necked flask 76 mg (3.3 mmol; 1 eq.) of sodium were reacted with 9.7 ml of EtOH. After complete reaction, 770 mg (3.3 mmol; 1 eq.) of (2S)-1-ethenylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine \textbf{45} dissolved in 4.8 ml of EtOH were slowly added. The mixture was stirred for 2 hours at room temperature and then quenched by the addition of a saturated solution of $\text{NH}_4\text{Cl}$. The aqueous phase was extracted with $\text{CH}_2\text{Cl}_2$. The organic phase was dried over $\text{MgSO}_4$, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 750 mg (81%)

**Aspect:** colorless oil

**TLC:** $R_f = 0.62$ (petroleum ether : AcOEt 60 : 40)

![Structural formula of the compound](image)

$^1\text{H NMR}$ (CDCl$_3$, 200 MHz): 1.15 and 1.17 (2 s, 6 H, 6, 7); 1.21 ($t$, $^3J_{12-11} = 7.0$, 3 H, 12); 1.72-2.06 (m, 4 H, 2, 3); 3.06-3.20 (m, 1 H, 1); 3.21 (s, 3 H, 8); 3.35 (mult, 2 H, 9); 3.53 (q, $^3J_{11-12} = 7.0$, 2 H, 11); 3.71-3.90 (m, 3 H, 1, 10); 4.02-4.11 (m, 1 H, 4)

$^{13}\text{C NMR}$ (CDCl$_3$, 50 MHz): 14.9 (12); 21.4 and 21.6 (6, 7); 26.0 and 27.2 (2, 3); 49.2 (8); 49.8 (1); 52.1 (9); 64.4 and 66.6 (10, 11); 66.4 (4); 77.9 (5)

**IR** (liquid film, cm$^{-1}$): 1152 (NSO$_2$); 1330 (NSO$_2$); 2977 (C-H)

**Mass** (CI +Q1MS): 248 ([M-OMe]$^+$, 100%); 280 ([M+H]$^+$, 15%)

**GC** (100/0/10/290/15): $t_R = 16.09$ min

$[\alpha]_D^{20} : -110^\circ$ (c=0.291; CHCl$_3$)
5 Synthesis of Michael acceptors

5.1 Synthesis of unsaturated lactams

5.1.1 Synthesis of 1-methyl-3-phenylsulfanylpyrrolidin-2-one 76

M.F.: C_{11}H_{13}NOS (M.W. 207.29)


In a flame-dried three-necked flask, 2.906 ml (2.098 g; 20.73 mmol; 2 eq.) of diisopropylamine were dissolved in 12 ml of THF. The mixture was cooled to 0°C and 8.295 ml (20.73 mmol; 2 eq.) of n-BuLi, 2.5M solution in hexane, were added. The mixture was stirred for 10 minutes and then cooled to -78°C. 1 ml (1.028 g; 10.36 mmol; 1 eq.) of 1-methyl-2-pyrrolidinone dissolved in 6 ml of THF was slowly added. After 35 minutes at -78°C, 2.264 g (10.36 mmol; 1 eq.) of phenyl disulfide dissolved in 5 of THF and 1.804 ml (1.858 g; 10.36 mmol; 1 eq.) of HMPA were added. The stirring was continued for 35 minutes, then the temperature was raised to -20°C over a period of 30 minutes and finally the mixture was allowed to come to room temperature. The mixture was poured into 100 ml of water and the aqueous phase was extracted 3 times with ether. The organic phase was washed with a 10% solution of NaOH, with water, with a 10% solution of HCl and with water. It was dried over MgSO_{4}, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 50 : 50).

Yield: 1.292 g (60 %)

Aspect: yellow oil

$^1$H NMR (CDCl$_3$, 200 MHz): 1.94-2.13 (m, 1 H, 3); 2.35-2.56 (m, 1 H, 3); 2.78 (s, 3 H, 1); 2.94-3.09 (m, 1 H, 2); 3.11-3.25 (m, 1 H, 2); 3.72-3.82 (m, 1 H, 4); 7.20-7.69 (2 m, 5 H, 7, 8, 9)

$^{13}$C NMR (CDCl$_3$, 50 MHz): 26.2 (3); 29.9 (1); 47.0 (2); 47.4 (4); 127.7 (9); 128.6 and 128.8 (7, 8); 132.8 (6); 171.9 (5)

IR (liquid film, cm$^{-1}$): 1682 (C=O); 2879 (C-H); 3056 (C-H arom)

Mass (Cl +Q1MS): 98 ([M-SC$_6$H$_5$]$^+$, 8%); 111 ([SC$_6$H$_5$]$^+$, 7%); 130 ([M-C$_6$H$_5$]$^+$, 18%); 180 (100%); 208 ([M+H]$^+$, 58%)
5.1.2 Synthesis of 1-methyl-3-(phenylsulfanyl)piperidin-2-one

**M.F.:** C_{12}H_{15}NOS (M.W. 221.31)  
**RN: 59953-51-4**


In a flame-dried three-necked flask, 4.954 ml (3.576 g; 35.34 mmol; 2 eq.) of diisopropylamine were dissolved in 21 ml of THF. The mixture was cooled to 0°C and 14.13 ml (35.34 mmol; 2 eq.) of n-BuLi, 2.5M solution in hexane, were added. The mixture was stirred for 10 minutes and then cooled to -78°C. 2 ml (2 g; 17.67 mmol; 1 eq.) of 1-methylpiperidin-2-one dissolved in 11 ml of THF were slowly added. After 35 minutes at -78°C, 3.858 g (17.67 mmol; 1 eq.) of phenyl disulfide dissolved in 8.5 ml of THF and 3.075 ml (3.167 g; 17.67 mmol; 1 eq.) of HMPA were added. The stirring was continued for 35 minutes, then the temperature was raised to -20°C over a period of 30 minutes and finally the mixture was allowed to come to room temperature. The mixture was poured into 100 ml of water and the aqueous phase was extracted 3 times with ether. The organic phase was washed with a 10% solution of NaOH, with water, with a 10% solution of HCl and with water. It was dried over MgSO_{4}, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 50 : 50).

**Yield:** 2.99 g (76 %)

**TLC:** R_{f} = 0.38 (CH\textsubscript{2}Cl\textsubscript{2} : AcOEt 1 : 1)

\[
\begin{align*}
&\text{H NMR} \ (\text{CDCl}_3, 300 \text{ MHz}): & 1.71-2.19 \ (m, 4 \text{ H}, 3, 4); & 2.97 \ (s, 3 \text{ H}, 1); & 3.26-3.32 \ (m, 2 \text{ H}, 2); & 3.88 \ (t, ^3J_{5,4} = 3, \ 1 \text{ H}, 5); & 7.21-7.6 \ (2 \text{ m}, 5 \text{ H}, 8, 9, 10) \\
&\text{C NMR} \ (\text{CDCl}_3, 50 \text{ MHz}): & 20.2 \ (3); & 28.5 \ (4); & 35.1 \ (1); & 48.7 \ (5); & 49.75 \ (2); & 127.2 \ (10); & 128.8 \text{ and } 132.3 \ (8, 9); & 134.7 \ (7); & 168.1 \ (6) \\
&\text{IR} \ (\text{liquid film, cm}^{-1}): & 1645 \ (\text{C}=\text{O}); & 2934 \ (\text{C}-\text{H}); & 3055 \ (\text{C}-\text{H arom}) \\
&\text{Mass} \ (\text{CI} + \text{Q1MS}): & 89 \ (17\%); & 167 \ (100\%); & 195 \ (16\%); & 222 ((\text{M+H})^+, 6\%)
\end{align*}
\]

5.1.3 Synthesis of 1-methyl-3-(phenylselanyl)pyrrolidin-2-one

**M.F.:** C_{11}H_{13}NOSe (M.W. 254.19)  
**RN: 59953-52-5**

In a flame-dried three-necked flask, 2.906 ml (2.098 g; 20.73 mmol; 2 eq.) of diisopropylamine were dissolved in 12 ml of THF. The mixture was cooled to 0°C and 8.295 ml (20.73 mmol; 2 eq.) of n-BuLi, 2.5M solution in hexane, were added. The mixture was stirred for 10 minutes and then cooled to -78°C. 1 ml (1.028 g; 10.36 mmol; 1 eq.) of 1-methyl-2-pyrrolidinone dissolved in 6 ml of THF was slowly added. After 35 minutes at -78°C, 1.986 g (10.36 mmol; 1 eq.) of phenylselenenyl chloride dissolved in 5 of THF et 1.804 ml (1.858 g; 10.36 mmol; 1 eq.) of HMPA were added. The stirring was continued for 35 minutes, then the temperature was raised to -20°C over a period of 30 minutes and finally the mixture was allowed to come to room temperature. The mixture was poured into 100 ml of water and the aqueous phase was extracted 3 times with ether. The organic phase was washed with a 10% solution of NaOH, with water, with a 10% solution of HCl and with water. It was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 50 : 50).

Yield: 1.580 g (60 %)

**1H NMR** (CDCl₃, 300 MHz): 2.15 (mult, 1 H, 3); 2.54 (mult, 1 H, 3); 2.74 (s, 3 H, 1); 2.82 (mult, 1 H, 2); 3.15 (dt, 3J₂,₃ = 9.5, 3J₂₂ = 3.3, 1 H, 2); 3.87 (dd, 3J₄,₃ = 9.3, 3J₄₃ = 3.8, 1 H, 4); 7.20-7.49 (m, 3 H, 8, 9); 7.59-7.72 (m, 2 H, 7)

**13C NMR** (CDCl₃, 75 MHz): 27.1 (3); 30.0 (1); 40.9 (4); 47.7 (2); 127.3 (6); 128.4 (9); 129.1 (8); 135.7 (7); 173.1 (5)

**Mass** (Cl/CH₄-N₂O): 83 ([NCH₂CH₂CHC=O]⁺, 100%); 252 ([M+H]⁺ (76Se), 2%); 254 ([M+H]⁺ (78Se), 5%); 256 ([M+H]⁺ (80Se), 9%)

5.1.4 **Synthesis of 1-methyl-3-phenylselanylpiperidin-2-one 81**

**M.F.:** C₁₂H₁₅NOSe (M.W. 268.21)

mixture was stirred for 10 minutes. It was then cooled to -78°C and 569.6 µl (567 mg; 5.018 mmol; 1 eq.) of 1-methylpiperid-2-one dissolved in 3 ml of THF were slowly added. After 35 minutes of stirring at -78°C, 961 mg (5.018 mmol; 1 eq.) of phenylselenenyl chloride in 2.5 ml of THF and 873 µl (899 mg; 5.018 mmol; 1 eq.) of HMPA were added. The stirring was continued for 35 minutes, then the temperature was raised to -20°C over a period of 30 minutes and finally the mixture was allowed to come to room temperature. The mixture was poured into 100 ml of water and the aqueous phase was extracted 3 times with ether. The organic phase was washed with a 10% solution of NaOH, with water, with a 10% solution of HCl and with water. It was dried over MgSO$_4$, filtered and evaporated under reduced pressure.

Yield: 883 mg (65 %)

Aspect: colorless oil

\[
\begin{align*}
\text{H NMR (CDCl3, 300 MHz):} & \quad 1.98-2.19 (m, 4 H, 3, 4); 2.96 (s, 3 H, 1); 3.29 (t, J_{2-3} = 4.8, 2 H, 2); 4.04 (t, J_{5-4} = 3.6, 1 H, 5); 7.22-7.72 (2 m, 5 H, 8, 9, 10) \\
\text{^13C NMR (CDCl3, 75 MHz):} & \quad 22.7 (3); 27.9 (1); 34.8 (4); 46.1 (2); 49.5 (5); 129.0 (10); 129.1 (8); 129.2 (7); 129.2 (9); 172.1 (6) \\
\text{Mass (Cl-Q1MS):} & \quad 153 ([C_6H_5Se]^-(^{76}\text{Se}), 23\%); 155 ([C_6H_5Se]^-(^{78}\text{Se}), 58\%); 157 ([C_6H_5Se]^-(^{80}\text{Se}), 100\%); 268 ([M-H]^-(^{80}\text{Se}), 4\%)
\end{align*}
\]

5.1.5 Synthesis of 1-methyl-3-(phenylsulfinyl)pyrrolidin-2-one 78

M.F.: C$_{11}$H$_{13}$NO$_2$S (M.W. 223.28)  
RN: 63914-40-9


In a flask, 775 mg (3.738 mmol; 1 eq.) of 1-methyl-3-phenylsulfanylpyrrolidin-2-one 76 were dissolved in 12 ml of MeOH. The mixture was cooled to 0°C and 808 mg (3.738 mmol; 1 eq.) of sodium periodate dissolved in a minimum amount of water were added. The ice bath was removed and the stirring was maintained for 1 hour. The reaction mixture was filtered and the precipitate was washed several times with MeOH. The filtrate was evaporated. The residue was dissolved in Et$_2$O, dried over MgSO$_4$, filtered and evaporated under reduced pressure.
Yield: 912 mg (quant.) as a mixture of 2 diastereomers

Aspect: colorless oil

\[
\begin{array}{c}
\text{H NMR (CDCl}_3, \text{300 MHz): 1.70, 2.08, 2.22 and 2.44-2.64 (3 mult + m, 2 H, 3); 2.56}
\newline\text{and 2.94 (2 s, 3 H, 1); 3.04 and 3.33 (2 mult, 2 H, 2); 3.55 and 4.20 (2 mult, 1 H, 4);}
\newline\text{7.45-7.68 (2 m, 5 H, 7, 8, 9)}
\end{array}
\]

\[
\begin{array}{c}
\text{C NMR (CDCl}_3, \text{75 MHz): 13.8 and 15.3 (3); 29.4 and 30.0 (1); 47.6 and 47.8 (2);}
\newline\text{65.3 and 66.6 (4); 123.9 and 124.8 (7); 128.6 and 129.1 (8); 130.8 and 131.6 (9);}
\newline\text{143.2 (6); 166.4 and 168.0 (5)}
\end{array}
\]

\[
\begin{array}{c}
\text{IR (liquid film, cm}^{-1}\text{: 1048 (S-O); 1684 (C=O); 2928 (C-H)}
\end{array}
\]

\[
\begin{array}{c}
\text{Mass (Cl/CH}_4\text{-N}_2\text{O): 98 ([M-SOC}_6\text{H}_5]^+, 100\%); 208 ([M-Me]^+, 8\%); 224 ([M+H]^+, 4\%)}
\end{array}
\]

5.1.6 Synthesis of 1-methyl-3-(phenylsulfinyl)piperidin-2-one 79

M.F.: C_{12}H_{15}NO_{2}S (M.W. 237.31)


In a flame-dried two-necked flask, 1.161 g (5.245 mmol; 1 eq.) of 1-methyl-3-(phenylsulfinyl)piperidin-2-one 77 were dissolved in 27 ml of CH$_2$Cl$_2$. The mixture was cooled to 0°C and 1.122 g (5.245 mmol; 1 eq.) of sodium periodate dissolved in a minimum amount of water were added. The ice bath was removed and the stirring continued for 1 hour. The mixture was then filtered and the precipitate washed several times with MeOH. The filtrate was evaporated. The residue was dissolved in Et$_2$O, dried over MgSO$_4$, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (CH$_2$Cl$_2$ : AcOEt 50 : 50 + 10% EtOH)

Yield: 850 mg (68 %)

Aspect: colorless oil
Experimental part

5.1.7 Synthesis of 1-methyl-1,5-dihydro-2H-pyrrol-2-one 73

M.F.: C₅H₇NO (M.W. 97.11)  
RN: 13950-21-5


In a flask equipped with a reflux condenser, 910 mg (4.075 mmol; 1 eq.) of 1-methyl-3-(phenylsulfinyl)pyrrolidin-2-one 78 were dissolved in 23 ml of toluene. 411 mg (4.89 mmol; 1.2 eq.) of sodium bicarbonate were added and the mixture was refluxed for 75 minutes. After that time, the mixture was cooled to room temperature and filtered over celite. The celite was washed with CH₂Cl₂ and the filtrate was evaporated under reduced pressure.

The product was purified by flash chromatography (Et₂O : CH₂Cl₂ 50 : 50).

Yield: 213 mg (54 %)

Aspect: colorless oil

\[
\begin{align*}
\text{H NMR} \ (\text{CDCl}_3, \ 300 \text{ MHz}) & : \ 3.05 \ (s, \ 3 \text{ H}, \ 1); \ 3.99 \ (s, \ 2 \text{ H}, \ 2); \ 6.19 \ (m, \ 1 \text{ H}, \ 4); \ 7.05 \ (m, \ 1 \text{ H}, \ 3) \\
\text{C NMR} \ (\text{CDCl}_3, \ 75 \text{ MHz}) & : \ 27.8 \ (1); \ 54.5 \ (2); \ 123.7 \ (4); \ 142.2 \ (3); \ 171.3 \ (5) \\
\text{Mass (Cl +Q1MS)} & \ : \ 98 \ ([\text{M+H}]^+, \ 100\%) 
\end{align*}
\]
5.1.8 Synthesis of 5,6-dihydro-1-methyl-2(1H)-pyridinone 74

M.F.: C₆H₉NO (M.W. 111.14)  
RN: 69003-17-4


From 1-methyl-3-(phenylsulfinyl)piperidin-2-one 79:
In a flask equipped with a reflux condenser, 850 mg (3.581 mmol; 1 eq.) of 1-methyl-3-(phenylsulfinyl)piperidin-2-one 79 were dissolved in 20 ml of toluene. 361 mg (4.298 mmol; 1.2 eq.) of sodium bicarbonate were added and the mixture was heated to reflux for 75 minutes. The mixture was cooled to room temperature and filtered over celite. The celite was washed with CH₂Cl₂ and the filtrate was evaporated. The product was purified by flash chromatography (Et₂O + 10% EtOH).

Yield: 308 mg (77 %)

From 1-methyl-3-phenylselanyl piperidin-2-one 81:
300 mg (1.118 mmol; 1 eq.) of 1-methyl-3-phenylselanyl piperidin-2-one 81 were dissolved in 7 ml of CH₂Cl₂. 98 µl (108 mg; 1.118 mmol; 1 eq.) of hydrogen peroxide were then slowly added. When the oxidation was complete (2 hours), the organic phase was washed 5 times with a saturated solution of NaHCO₃, twice with water and twice with a saturated solution of NaCl, dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (Et₂O + 10% EtOH).

Yield: 105 mg (85 %)

Aspect: colorless oil

\[
\begin{align*}
&1H \text{ NMR (CDCl}_3, 300 \text{ MHz): } 2.41 \ (\text{mult}, 2 \ H, 3); \\
&\quad 2.99 \ (s, 3 \ H, 1); \\
&\quad 3.41 \ (t, \ 3J_{2,3} = 7.2, 2 \ H, 2); \\
&\quad 5.92 \ (td, \ 3J_{5,4} = 6.5, \ 4J_{5,3} = 1.3, 1 \ H, 5); \\
&\quad 6.53 \ (dt, \ 3J_{4,5} = 6.6, \ 3J_{4,3} = 2.7, 1 \ H, 4) \\
&13C \text{ NMR (CDCl}_3, 75 \text{ MHz): } 23.8 \ (3); \\
&\quad 34.2 \ (1); \\
&\quad 47.3 \ (2); \\
&\quad 125.2 \ (5); \\
&\quad 139.0 \ (4); \\
&\quad 165.0 \ (6) \\
&\text{IR (liquid film, cm}^{-1}) \ : \\n&\quad 818; \\
&\quad 1664 \ (C=O); \\
&\quad 2941 \ (C-H) \\
&\text{GC (100/0/10/290/20): } t_R = 10.06 \text{ min}
\end{align*}
\]
5.2 Synthesis of 2,2-dimethylhex-4-en-3-one 75

5.2.1 Synthesis of 5-hydroxy-2,2-dimethylhexan-3-one 83

M.F.: C₈H₁₆O₂ (M.W. 144.21)  
RN: 173343-33-4


In a flame-dried two-necked flask equipped with an addition funnel, 6.164 ml (4.45 g; 43.98 mmol; 1.1 eq.) of diisopropylamine were dissolved in 60 ml of THF. The mixture was cooled to 0°C and 17.59 ml (12.19 g; 43.98 mmol; 1.1 eq.) of n-BuLi, 2.5M solution in hexane, were added. After 15 minutes at 0°C, the mixture was cooled to -78°C. 5 ml (4.005 g; 39.98 mmol; 1 eq.) of pinacolone were added and the stirring was continued for 30 minutes. Then 2.235 ml (1.761 g; 39.98 mmol; 1 eq.) of acetaldehyde in 100 ml of THF were slowly added. After 15 minutes, the dry-ice bath was removed and the reaction was immediately quenched by the addition of 2.5 ml (2.641 g; 43.98 mmol; 1.1 eq.) of acetic acid dissolved in Et₂O. Water was added to dissolve the salts formed. The two phases were separated and the aqueous phase was extracted 2 times with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

The product was obtained sufficiently pure to be used without purification.

Yield: 5.76 g (quant.)

Aspect: yellow oil

TLC: Rf = 0.7 (petroleum ether : AcOEt 60 : 40)

\[ \text{IR (liquid film, cm}^{-1}\text{): 1703 (C=O); 2972 (C-H); 3447 (O-H)} \]

\[ \text{Mass (CI +Q1MS): 85 ([OCC(CH₃)₃]^+, 100%); 127 ([M-OH]^+, 56%); 145 ([M+H]^+, 78%)} \]
5.2.2 Synthesis of (E)-2,2-dimethylhex-4-en-3-one 75

**M.F.:** C₈H₁₄O (M.W. 126.19)  
**RN: 20971-19-1**


In a flask equipped with a Dean-Stark apparatus, 5.17 g (35.85 mmol; 1 eq.) of 5-hydroxy-2,2-dimethylhexan-3-one 83 and 617 mg (3.585 mmol; 0.1 eq.) of para-toluenesulfonic acid were mixed in 127 ml of toluene. The mixture was heated to reflux until the volume of recovered water was constant. The solution was cooled to room temperature and washed with a saturated solution of NaHCO₃. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20) or by distillation (75°C at 18 mmHg).

**Yield:** 2.884 g (64 %)

**Aspect:** yellow oil

\[
\begin{align*}
\text{O} & \\
\text{1} & \\
\text{2} & \\
\text{3} & \\
\text{4} & \\
\text{5} & \\
\text{6} & \\
\end{align*}
\]

\( ^1H \text{ NMR} \) (CDCl₃, 200 MHz): 1.15 (s, 9 H, 1); 1.90 (dd, \( ^3J_{6,5} = 10.2, ^4J_{6,4} = 1.4, 3 \text{ H}, 6 \)); 6.46 (qd, \( ^3J_{4,5} = 20.4, ^4J_{4,6} = 1.4, 1 \text{ H}, 4 \)); 6.88 (qd, \( ^3J_{5,4} = 22.4, ^3J_{5,6} = 10.0, 1 \text{ H}, 5 \))

\( ^13\text{C NMR} \) (CDCl₃, 50 MHz): 18.1 (6); 26.2 (1); 42.7 (2); 125.8 (4); 142.4 (5); 203.9 (3)

**IR** (liquid film, cm⁻¹): 1691 (C=O); 2970 (C-H)

**Mass** (Cl/CH₄-N₂O): 85 ([OCC(CH₃)]⁺, 37); 127 ([M+H]⁺, 100%)

**b.p.:** 75°C (18 mmHg)

**GC** (60/0/10/290/10): t_R = 5.74 min

6 Michael addition of sulfonamides

6.1 General procedure

In a flame-dried three-necked flask, HMPA, THF and a small quantity of \( \alpha \)-phenanthroline were introduced. \( n \)-BuLi was then slowly added until the color changed to red. 1 eq. of the sulfonamide was added and the mixture was cooled down to -78°C. 1.05 eq of 2.5M \( n \)-BuLi were then added. After 1 hour, 1.1 eq. of the Michael
acceptor were added. The reaction mixture was maintained at -78°C for 1 hour, after which 3.5 eq. of Et₃N were added followed by 3.85 eq. of chlorotrimethylsilane. The stirring was continued for 30 minutes and the mixture was allowed to come to room temperature. A few ml of diluted HCl were then added. The solution was concentrated under reduced pressure. Ether was added and the organic phase was washed 5 times with a saturated solution of NaCl to remove HMPA, dried over MgSO₄, filtered and evaporated under reduced pressure. The products were separated and purified by flash chromatography.

6.2 Michael addition of achiral sulfonamides to cyclohexenone

6.2.1 Addition of 1-methylsulfonylpyrrolidine 11

Following the general procedure described in 6.1 with:
28 mg (186 µmol; 1 eq.) of 1-methylsulfonylpyrrolidine 11
132 µl (195.3 µmol; 1.05 eq.) of n-BuLi, 1.48M solution in hexane
20 µl (20 mg; 204.6 µmol; 1.1 eq.) of 2-cyclohexen-1-one
91 µl (66 mg; 655.5 µmol; 3.52 eq.) of Et₃N
91 µl (78 mg; 717.9 µmol; 3.85 eq.) of TMSCl
259 µl (267 mg; 1.488 mmol; 8 eq.) of HMPA
1.8 ml of THF
Flash chromatography: petroleum ether : AcOEt 50 : 50

Only 1,2-addition product was obtained:

*1-[(pyrrolidin-1-ylsulfonyl)methyl]cyclohex-2-en-1-ol* 84

M.F.: C₁₁H₁₉NO₃S (M.W. 245.33)

Reference: Huart, C. *PhD-Thesis UCL-ORSY, 1995*

Yield: 43 ml (95%)
Aspect: viscous oil
$^1$H NMR (CDCl$_3$, 200 MHz): 5.89 (dt, $^3$J$_{6-5}$ = 10.2, $^3$J$_{6-7}$ = 3.5, 6); 5.75 (d, $^3$J$_{5-6}$ = 10.2, 5); 3.75 (s, 1 H, OH); 3.13-3.45 (m, 4 H, 1); 3.17 (s, 2 H, 3); 1.50-2.50 (m, 6 H, 7, 8, 9); 1.90-1.98 (m, 4 H, 2)

$^{13}$C NMR (CDCl$_3$, 50 MHz): 18.7 (8); 24.8 (9); 25.7 (2); 35.4 (7); 47.6 (1); 57.4 (3); 68.2 (4); 130.0 and 130.9 (5, 6)

IR (liquid film, cm$^{-1}$): 1145 (NSO$_2$); 1325 (NSO$_2$); 2935 (C-H); 3470 (O-H)

Mass (Cl/CH$_4$-N$_2$O): 97 ([C$_6$H$_8$O]$^+$, 100%); 180 (44%); 193 (34%); 228 ([M-OH]$^+$, 7%); 246 ([M+H]$^+$, 2%)

6.2.2 Addition of 1-ethylsulfonylpyrrolidine 38

Following the general procedure described in 6.1 with:
500 mg (3.063 mmol; 1 eq.) of 1-(ethylsulfonyl)pyrrolidine 38
1.3 ml (2.665 mmol; 0.87 eq.) of n-BuLi, 2.05 M solution in hexane
326 µl (324 mg; 3.369 mmol; 1.1 eq.) of 2-cyclohexen-1-one
1.5 ml (1.092 g; 10.79 mmol; 3.52 eq.) of Et$_3$N
1.5 ml (1.284 g; 11.81 mmol; 3.85 eq.) of TMSCI
4.263 ml (4.391 g; 24.5 mmol; 8 eq.) of HMPA
29 ml of THF

Flash chromatography: petroleum ether : AcOEt 50 : 50

1,4- and 1,2-addition products were obtained in a 65 : 35 ratio. After purification we obtained:

3-[1-(pyrrolidin-1-ylsulfonyl)ethyl]cyclohexanone 85

M.F.: C$_{12}$H$_{21}$NO$_3$S (M.W. 259.36)

Yield: 500 mg (55%) as a mixture of 2 diastereomers (ratio: 83 : 17)

Aspect: viscous oil

TLC: R$_f$ = 0.37 (petroleum ether : AcOEt 50 : 50)
$^1$H NMR (CDCl$_3$, 200 MHz): 1.36 ($d$, $^3J_{4,3} = 7.1$, 3 H, 4); 1.50-2.20 (m, 4 H, 9, 10); 1.79-2.01 (m, 4 H, 2); 2.20-2.75 (m, 5 H, 5, 6, 8); 2.97 ($dq$, $^3J_{3,4} = 7.2$, $^3J_{5,5} = 3$, 1 H, 3); 3.12 ($dq$, $^3J_{3,4} = 6.6$, $^3J_{5,5} = 2.7$, 1 H, 3); 3.28-3.47 (m, 4 H, 1)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 10.5 (4); 24.9 (9); 26.0 (2); 29.6 (10); 38.7 (5); 40.9 (8); 43.3 (6); 48.1 (1); 59.3 (3); 60.8 (3); 210.0 (7)

IR (liquid film, cm$^{-1}$): 1141 (NSO$_2$); 1320 (NSO$_2$); 1705 (C=O); 2961 (C-H)

Mass (Cl$^+$+Q1MS): 59 (22%); 125 (9%); 154 (25%); 190 (7%); 208 (100%); 257 (19%); 260 ([M+H]$^+$, 51%)

HRMS: calculated for C$_{12}$H$_{22}$NO$_3$S$^+$: 260.132041; found: 260.131466

$^1$H NMR (CDCl$_3$, 200 MHz): 1.36 ($d$, $^3J_{4,3} = 7.1$, 3 H, 4); 1.45-2.45 (m, 6 H, 8, 9, 10); 1.86-2.00 (m, 4 H, 2); 3.01 ($mult$, 1 H, 3); 3.32-3.48 (m, 4 H, 1); 5.90-5.40 (m, 2 H, 6, 7)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 13.8 (4); 17.9 (9); 24.7 (10); 25.9 (2); 34.2 (8); 48.3 (1); 70.8 and 71.5 (3); 71.7 (5); 129.9 (6); 132.1 (7)

IR (liquid film, cm$^{-1}$): 1141 (NSO$_2$); 1311 (NSO$_2$); 1648 (C=C); 2943 (C-H); 3481 (O-H)

Mass (Cl$^+$+Q1MS): 59 (45%); 72 (24%); 89 (27%); 97 (11%); 107 (27%); 136 (100%); 164 (85%); 178 (20%); 204 (30%); 242 ([M-OH]$^+$, 49%); 258 ([M-H]$^+$, 16%)

HRMS: calculated for C$_{12}$H$_{22}$NO$_3$S$^+$: 260.132041; found: 260.131705

1-[1-(pyrrolidinyl-1-sulfonyl)ethyl]cyclohex-2-en-1-ol 86

M.F.: C$_{12}$H$_{21}$NO$_3$S (M.W. 259.36)

Yield: 211 mg (25%)

Aspect: viscous oil

TLC: $R_f$ = 0.48 (petroleum ether : AcOEt 50 : 50)

**minor isomer**
6.2.3 Addition of 1-[(3-methylbutyl)sulfonyl]pyrrolidine 39

Following the general procedure described in 6.1 with:
500 mg (2.435 mmol; 1 eq.) of 1-(3-methyl-1-butanesulfonyl)pyrrolidine 39
1.022 ml (2.557 mmol; 1.05 eq.) of n-BuLi, 2.5M solution in hexane
259 µl (257 mg; 2.678 mmol; 1.1 eq.) of 2-cyclohexen-1-one
1.192 ml (868 mg; 8.579 mmol; 3.52 eq.) of Et₃N
1.192 ml (1.02 g; 9.396 mmol; 3.85 eq.) of TMSCl
3.389 ml (3.491 g; 19.48 mmol; 8 eq.) of HMPA
23 ml of THF
Flash chromatography: ether : AcOEt 80 : 20

1,4- and 1,2-addition products were obtained in a 79 : 21. After purification we obtained:

3-[3-methyl-1-(pyrrolidin-1-ylsulfonyl)butyl]cyclohexanone 95
M.F.: C₁₅H₂₇NO₃S (M.W. 301.44)

Yield: 529 mg (72 %) as a mixture of 2 diastereomers (ratio: 86 : 14)

Aspect: viscous oil
TLC: R_f = 0.35 (ether : AcOEt 80 : 20)

¹H NMR (CDCl₃, 300 MHz): 0.96 (mult, 6 H, 6, 7); 1.50-2.20 (m, 7 H, 4, 5, 12, 13); 1.85-2.00 (m, 4 H, 2); 2.20-2.69 (m, 5 H, 8, 9, 11); 2.96 (dt, ³J₃.₄ = 5.8, ³J₃.₈ = 2.4, 1 H, 3); 3.32-3.48 (m, 4 H, 1)

¹³C NMR (CDCl₃, 50 MHz): 22.1 and 22.4 (6, 7); 25.0 (12); 25.7 (2); 26.1 (5); 28.2 (13); 35.1 (4); 39.0 (8); 40.8 (11); 44.5 (9); 47.8 (1); 63.4 (3); 63.5 (3); 210.0 (10)
IR (liquid film, cm⁻¹): 1129 (NSO₂); 1317 (NSO₂); 1710 (C=O); 2965 (C-H)
Mass (CI+Q1MS): 97 ([C₆H₉O]⁺, 52%); 136 (12%); 149 (9%); 167 (6%); 193 (11%); 204 ([M-C₆H₉O]⁺, 79%); 206 (100%); 302 ([M+H]⁺, 10%)
HRMS: calculated for C₁₅H₂₈NO₃S⁺: 302.178991; found: 302.178435

* minor isomer
Experimental part

1-[3-methyl-1-(pyrrolidine-1-sulfonyl)butyl]cyclohex-2-enol 96

M.F.: C_{15}H_{27}NO_{3}S (M.W. 301.44)

Yield: 99 mg (13 %)

Aspect: viscous oil
TLC: R_f = 0.66 (ether : AcOEt 80 : 20)

\[\begin{array}{c}
\text{H NMR (CDCl}_3, 200 MHz): 0.92 (d, ^3J_{6,7-5} = 6, 6 H, 6, 7); 1.15-2.45 (m, 13 H, 2, 4, 5, 11, 12, 13); 3.05-3.22 (m, 1 H, 3); 3.30-3.55 (m, 4 H, 1); 5.45-6.00 (m, 2 H, 9, 10) \\
\text{C NMR (CDCl}_3, 50 MHz): 17.8 (12); 22.7 and 23.0 (6, 7); 24.6 (13); 25.8 (2); 27.0 (5); 31.6 (4); 36.6 (11); 47.6 (1); 68.5 (3); 72.1 (8); 130.0 (9); 132.0 (10) \\
\text{IR (liquid film, cm}^{-1}): 1137 (\text{NSO}_2); 1313 (\text{NSO}_2); 1634 (\text{C}=\text{C}); 2957 (\text{C-H}); 3481 (\text{O-H}) \\
\text{Mass (Cl +Q1MS): 79 (6%); 84 (10%); 136 (11%); 149 (8%); 179 (28%); 206 ([M-C_6H_9O]^+, 100%); 215 (36%); 284 ([M-OH]^+, 13%); 292 (23%); 302 ([M+H]^+, 5%) \\
\text{HRMS: calculated for C_{15}H_{28}NO_{3}S^+: 302.178991; found: 302.178070} 
\end{array}\]

6.2.4  Addition of 1-[(3-ethoxypropyl)sulfonyl]pyrrolidine 59

Following the general procedure described in 6.1 with:
150 mg (681.6 µmol; 1 eq.) of (3-ethoxypropane)sulfonylpyrrolidine 59
447 µl (715.7 µmol; 1.05 eq.) of n-BuLi, 1.6M solution in hexane
72 µl (72 mg; 749.8 µmol; 1.1 eq.) of 2-cyclohexen-1-one
333 µl (243 mg; 2.401 mmol; 3.52 eq.) of Et_3N
333 µl (286 mg; 2.630 mmol; 3.85 eq.) of TMSCl
949 µl (977 mg; 5.453 mmol; 8 eq.) of HMPA
6.4 ml of THF
Flash chromatography: petroleum ether : AcOEt 60 : 40
1,4- and 1,2 addition products were obtained in a 83 : 17 ratio. After purification we obtained:

3-[3-ethoxy-1-(pyrrolidin-1-ylsulfonyl)propyl]cyclohexanone 97
M.F.: C\textsubscript{15}H\textsubscript{27}NO\textsubscript{4}S (M.W. 317.44)

Yield: 112 mg (52 %) as amixture of 2 diastereomers (ratio: 87 : 13)

Aspect: colorless oil
TLC: R\textsubscript{f} = 0.10 (petroleum ether : AcOEt 60 : 40)

\hspace{1cm}

1\textsuperscript{H} NMR (CDCl\textsubscript{3}, 300 MHz): 1.19 (t, \textsuperscript{3}J\textsubscript{7-6} = 7.2, 3 H, 7); 1.53-1.86 (m, 4 H, 12, 13); 1.90-1.97 (m, 4 H, 2); 2.08-2.46 (m, 7 H, 4, 8, 9, 11); 3.19 (dt, \textsuperscript{3}J\textsubscript{3,4} = 6.1, \textsuperscript{3}J\textsubscript{3,8} = 2.4, 1 H, 3); 3.34-3.41 (m, 4 H, 1); 3.44 (q, \textsuperscript{3}J\textsubscript{6-7} = 7.8, 2 H, 6); 3.43-3.60 (m, 2 H, 5)

\hspace{1cm}

\hspace{1cm}

1\textsuperscript{3}C NMR (CDCl\textsubscript{3}, 75 MHz): 15.1 (7); 25.1 (12); 25.8 (2); 26.7 (4); 28.3 (13); 39.0 (8); 40.9 (11); 44.5 (9); 47.8 (1); 62.0 (3\textsuperscript{*}); 62.1 (3); 66.2 and 67.7 (5, 6); 210.0 (10)

IR (liquid film, cm\textsuperscript{-1}): 1142 (NSO\textsubscript{2}); 1320 (NSO\textsubscript{2}); 1711 (C=O); 2972 (C-H)

Mass (Cl/CH\textsubscript{4}-N\textsubscript{2}O): 193 ([\text{CH}_{2}]\textsubscript{4}NSO\textsubscript{2}(\text{CH}_{2})\textsubscript{3}O]+, 43%); 222 ([M-C\textsubscript{6}H\textsubscript{9}O]\textsuperscript{+}, 100%); 272 ([M-OEt]\textsuperscript{+}, 3%); 318 ([M+H]\textsuperscript{+}, 7%)

GC (100/0/10/250/20): t\textsubscript{R} = 25.70 min (minor); t\textsubscript{R} = 26.26 min (major)

HRMS: calculated for C\textsubscript{15}H\textsubscript{28}NO\textsubscript{4}S\textsuperscript{+}: 318.173905; found: 318.173511

1-[3-ethoxy-1-(pyrrolidin-1-ylsulfonyl)propyl]cyclohex-2-en-1-ol 98
M.F.: C\textsubscript{15}H\textsubscript{27}NO\textsubscript{4}S (M.W. 317.44)

Yield: 22 mg (10 %)

Aspect: colorless oil

\textsuperscript{*} minor isomer
\[ \text{Experimental part} \]

\[ \text{H NMR (CDCl}_3, \text{300 MHz): 1.07 (t, }^3\text{J}_7-6 = 7, \text{ 3 H, 7); 1.45-2.40 (m, 12 H, 2, 4, 11, 12, 13); 3.05-3.51 (m, 9 H, 1, 3, 5, 6); 5.55-5.97 (m, 2 H, 9, 10) } \]

\[ \text{C NMR (CDCl}_3, \text{75 MHz): 15.2 (7); 24.7 (4); 25.6 (12); 25.75 (2); 28 (13); 47.4 (11); 47.6 (1); 65.9 and 66.0 (5, 6); 68.3 (3); 69.5 (8); 130.5 (10); 131.6 (9) } \]

\[ \text{IR (liquid film, cm}^{-1}: 1142 (\text{NSO}_2); 1324 (\text{NSO}_2); 2956 (\text{C-H); 3483 (O-H) } \]

\[ \text{Mass (Cl } + \text{Q1MS): 72 (55%); 165 (68%); 236 (99%); 255 ([M-OH-EtO]^{+}, 17%); 300 ([M-OH]^+, 49%); 318 ([M+H]^+, 7%); 374 (100%) } \]

\[ \text{GC (100/0/10/250/20): } t_R = 22.86 \text{ min (minor); } t_R = 22.96 \text{ min (major) } \]

\[ 6.2.5 \text{ Addition of 1-[(3-(ethylsulfanyl)propyl)sulfonyl]pyrrolidine 63 } \]

Following the general procedure described in 6.1 with:

150 mg (631.9 µmol; 1 eq.) of 1-[(3-ethylsulfanyl)propyl)sulfonyl]pyrrolidine 63

301 µl (663.5 µmol; 1.05 eq.) of n-BuLi, 2.2M solution in hexane

67 µl (67 mg; 695.1 µmol; 1.1 eq.) of 2-cyclohexen-1-one

309 µl (225 mg; 2.226 mmol; 3.52 eq.) of Et\(_3\)N

309 µl (265 mg; 2.438 mmol; 3.85 eq.) of TMSCl

880 µl (906 mg; 5.055 mmol; 8 eq.) of HMPA

5.9 ml of THF

Flash chromatography: petroleum ether : AcOEt 90 : 10

Only 1,4-addition product was obtained:

\[ 3-[(3-(ethylsulfanyl)-1-(pyrrolidin-1-ylsulfonyl)propyl)cyclohexanone 99 \]

\[ \text{M.F.: C}_{15}\text{H}_{27}\text{NO}_3\text{S}_2 \text{ (M.W. 333.5) } \]

\[ \text{Yield: 122 mg (58 %) as a mixture of 2 diastereomers (ratio: 90 : 10) } \]

\[ \text{Aspect: colorless viscous oil } \]

\[ \text{TLC: } R_f = 0.5 \text{ (petroleum ether : AcOEt 80 : 20) } \]
**Experimental part**

\[ 
\begin{array}{c}
1.21 (t, 3 J_{J,6} = 7.1, 3 H, 7); 1.50-2.40 (m, 11 H, 4, 8, 9, 11, 12, 13); 1.81-1.95 (m, 4 H, 2); 2.49 (q, 3 J_{J,7} = 7.1, 2 H, 6); 2.67 (t, 3 J_{J,4} = 7.1, 2 H, 5); 3.18 (dt, 3 J_{J,5} = 5.8, 3 J_{J,8} = 2.3, 1 H, 3); 3.26-3.4 (m, 4 H, 1) \\
\text{C NMR (CDCl}_3, 50 MHz): 14.6 (7); 25.0 (12); 25.8 (2); 25.9 (4); 28.6 (13); 29.8 (5); 29.9 (6); 38.8 (8); 40.8 (11); 44.2 (9); 47.8 (1); 63.5 (3'); 63.7 (3); 210.1 (10) \\
\text{IR (liquid film, cm}^{-1}): 1139 (NSO}_2; 1317 (NSO}_2; 1712 (C=O); 2963 (C-H) \\
\text{Mass (Cl +Q1MS): 176 (100%), 352 ([M+H]^+, 1%)} \\
\text{GC (100/0/10/290/15): t}_R = 22.11 \text{ min (minor)}; t_R = 22.44 \text{ min (major)} \\
\end{array}
\]

### 6.2.6 Addition of 1-[[3,3,3-tris(ethyloxy)propyl]sulfonyl]pyrrolidine 52

Following the general procedure described in 6.1 with:
- 398 mg (1.221 mmol; 1 eq.) of 1-[[3,3,3-tris(ethyloxy)propyl]sulfonyl]pyrrolidine 52
- 661 µl (1.282 mmol; 1.05 eq.) of n-BuLi, 1.94M solution in hexane
- 130 µl (129 mg; 1.343 mmol; 1.1 eq.) of 2-cyclohexen-1-one
- 598 µl (435 mg; 4.303 mmol; 3.52 eq.) of Et$_3$N
- 598 µl (512 mg; 4.713 mmol; 3.85 eq.) of TMSCl
- 1.7 ml (1.751 g; 9.773 mmol; 8 eq.) of HMPA
- 11.5 ml of THF

Only 1,4-addition product was obtained:

\(1-[[3,3,3-tris(ethyloxy)-1-[[3-[[trimethylsilyl]oxy]cyclohex-2-en-1-yl]propyl]sulfonyl]pyrrolidine 100\)

**M.F.:** C$_{22}$H$_{43}$NO$_6$SSi (**M.W.** 477.73)

**Reference:** Huart, C. *PhD-Thesis UCL-ORSY, 1995*

**Yield:** 580 mg (quant.)

*minor isomer*
Aspect: colorless oil

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6.3.2 Addition of (2S)-1-ethylsulfonyl-2-(1-methoxy-1-methylethyl)pyrrolidine

Following the general procedure described in 6.1 with:

500 mg (2.124 mmol; 1 eq.) of (2S)-1-(ethylsulfonyl)-2-(1-methoxy-1-methylethyl)pyrrolidine

892 µl (2.23 mmol; 1.05 eq.) of n-BuLi, 2.5M solution in hexane

226 µl (224 mg; 2.377 mmol; 1.1 eq.) of 2-cyclohexen-1-one

1.04 ml (757 mg; 7.484 mmol; 3.52 eq.) of Et₃N

1.04 ml (890 mg; 8.197 mmol; 3.85 eq.) of TMSCl

2.957 ml (3.045 g; 16.99 mmol; 8 eq.) of HMPA

20 ml of THF

Flash chromatography: ether : petroleum ether 60 : 40

1,4- and 1,2-addition products were obtained in a 50 : 50 ratio. After purification we obtained:

3-{1-[2(S)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]ethyl}cyclohexanone 116

M.F.: C_{16}H_{29}NO₄S (M.W. 331.47)

Yield: 279 mg (40 %)
**Aspect:** viscous oil

**TLC:** $R_f = 0.14$ (ether : petroleum ether 60 : 40)

\[
\begin{align*}
1^H \text{ NMR} \text{ (CDCl}_3, 300 \text{ MHz}): & \quad 1.08 \text{ and } 1.13 \text{ (2 s, 6 H, 6, 7)}; \\
& \quad 1.38 \text{ (mult, 3 H, 10)}; \\
& \quad 1.51-2.60 \text{ (m, 13 H, 2, 3, 11, 12, 14, 15, 16)}; \\
& \quad 2.92-3.07 \text{ (m, 1 H, 1)}; \\
& \quad 3.22 \text{ (s, 3 H, 8)}; \\
& \quad 3.48 \text{ (mult, 1 H, 9)}; \\
& \quad 3.86-4.01 \text{ (m, 1 H, 1)}; \\
& \quad 4.20-4.35 \text{ (m, 1 H, 4)}
\end{align*}
\]

\[
\begin{align*}
13^C \text{ NMR} \text{ (CDCl}_3, 50 \text{ MHz}): & \quad 9.0 \text{ (10)}; \\
& \quad 20.2 \text{ and } 21.4 \text{ (6, 7)}; \\
& \quad 25.0 \text{ and } 26.7 \text{ (15, 16)}; \\
& \quad 28.1 \text{ and } 29.2 \text{ (2, 3)}; \\
& \quad 38.5 \text{ (11)}; \\
& \quad 42.1 \text{ and } 43.6 \text{ (12, 14)}; \\
& \quad 48.9 \text{ (8)}; \\
& \quad 50.6 \text{ (1)}; \\
& \quad 61.0 \text{ (9)}; \\
& \quad 61.3 \text{ (9*)}; \\
& \quad 65.5 \text{ (4)}; \\
& \quad 78.1 \text{ (5)}; \\
& \quad 210.0 \text{ (13)}
\end{align*}
\]

**IR (liquid film, cm$^{-1}$):** 1141 (NSO$_2$); 1320 (NSO$_2$); 1705 (C=O); 2961 (C-H)

**Mass (Cl +Q1MS):** 206 (12%); 248 (100%); 280 (26%); 331 (M$^+$, 1%)

**HRMS:** calculated for C$_{16}$H$_{29}$NO$_4$S$^+$: 332.189556; found: 332.189770

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**M.F.:** C$_{16}$H$_{29}$NO$_4$S (M.W. 331.47)

**Yield:** 256 mg (37 %) as a mixture of 2 diastereomers (ratio: 56 : 44)

**Aspect:** viscous oil

**TLC:** $R_f = 0.37$ (ether : petroleum ether 60 : 40)

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*minor isomer
**Experimental part**

**H NMR** (CDCl$_3$, 300 MHz): 1.14 and 1.17 (2 s, 6 H, 6, 7); 1.38 (mult, 3 H, 10); 1.50-2.60 (m, 10 H, 2, 3, 14, 15, 16); 3.00-3.15 (m, 1 H, 1); 3.19 (s, 3 H, 8); 3.48 (mult, 1 H, 9); 3.75-3.85 (m, 1 H, 1); 4.06-4.12 (m, 1 H, 4); 5.95-5.45 (m, 2 H, 12, 13)

**13C NMR** (CDCl$_3$, 75 MHz): 7.9 (10); 21.2 and 21.5 (6, 7); 26.3 and 27.2 (2, 3); 23.0, 26.9 and 27.4 (14, 15, 16); 49.1 (8); 50.0 (1); 58.0 (9); 66.0 (4); 71.5 (11); 77.8 (5); 130.1 and 131.9 (12, 13)

**IR** (liquid film, cm$^{-1}$): 1150 (NSO$_2$); 1324 (NSO$_2$); 2977 (C-H); 3490 (O-H)

**Mass** (CI +Q1MS): 45 (55%); 73 ([C(CH$_3$)$_2$OMe]$^+$, 3%); 144 (25.5%); 176 (8%); 190 (12%); 204 (30%); 206 (8%); 248 (48%); 258 ([M-C(CH$_3$)$_2$OMe]$^+$, 13%); 260 (25%); 282 ([M-OH-OMe]$^+$, 100%); 300 (17%); 314 ([M-OH]$^+$, 55%); 330 ([M-H]$^+$, 8%)

**HRMS**: calculated for C$_{16}$H$_{30}$NO$_4$S$^+$: 332.189556; found: 332.189587

### 6.3.3 Addition of (2S)-(1-methoxy-1-methylethyl)-1-[(3-methylbutyl)sulfonyl]pyrrolidine 44

Following the general procedure described in 6.1 with:

- 500 mg (1.802 mmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)-1-(3-methylbutyl)sulfonylpyrrolidine 44
- 1.153 ml (1.892 mmol; 1.05 eq.) of n-BuLi, 1.64M solution in hexane
- 192 µl (190 mg; 1.982 mmol; 1.1 eq.) of 2-cyclohexen-1-one
- 882 µl (642 mg; 6.349 mmol; 3.52 eq.) of Et$_3$N
- 882 µl (755 mg; 6.953 mmol; 3.85 eq.) of TMSCl
- 2.508 ml (2.583 g; 14.41 mmol; 8 eq.) of HMPA
- 17 ml of THF

Flash chromatography: ether : petroleum ether 80 : 20

1,4- and 1,2-addition products were obtained in a 68 : 32 ratio. After purification we obtained:

3-{1-[(2S)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]-3-methylbutyl}-cyclohexanone 118

**M.F.:** C$_{19}$H$_{35}$NO$_4$S (M.W. 373.55)

**Yield:** 350 mg (52 %) as a mixture of 2 diastereomers (ratio: 90 : 10)

**Aspect:** brown oil

**TLC:** $R_f = 0.63$ (ether : petroleum ether 80 : 20)
1H NMR (CDCl₃, 200 MHz): 0.95 (mult, 6 H, 12, 13); 1.13 and 1.09 (2 s, 6 H, 6, 7); 1.2-2.6 (m, 15 H, 2, 3, 10, 11, 15, 17, 18, 19); 2.69-2.81 (m, 1 H, 14); 2.95 (mult, 1 H, 9); 3.21 (s, 3 H, 8); 3.45-3.55 (m, 1 H, 1); 3.90-4.04 (m, 1 H, 1); 4.25-4.36 (m, 1 H, 4)

13C NMR (CDCl₃, 50 MHz): 20.2, 21.3, 21.8 and 22.7 (6, 7, 12, 13); 26.1 (11); 25.2 and 26.6 (18, 19); 28.0 and 29.5 (2, 3); 33.9 (10); 38.4 (14); 40.8 (15); 42.7 (17); 48.9 (8); 50.8 (1); 63.9 (9); 64.7 (9'); 65.5 (4); 77.9 (5); 210.0 (16)

IR (liquid film, cm⁻¹): 1140 (NSO₂); 1317 (NSO₂); 1713 (C=O); 2957 (C-H)

Mass (Cl +Q1MS): 84 (100 %); 300 ([M-C(CH₃)₂OMe]⁺, 1%); 342 ([M-OMe]⁺, 5%); 374 ([M+H]⁺, 2%)

HRMS: calculated for C₁₉H₃₆NO₄S⁺: 374.236506; found: 374.235452

1-{1-[(2S)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]-3-methylbutyl}-cyclohex-2-enol 119

M.F.: C₁₉H₃₅NO₄S (M.W. 373.55)

Yield: 142 mg (21 %)

Aspect: brown oil

1H NMR (CDCl₃, 200 MHz): 0.95 (mult, 6 H, 12, 13); 1.15 and 1.18 (2 s, 6 H, 6, 7); 1.23-2.50 (m, 13 H, 2, 3, 10, 11, 17, 18, 19); 3.02 (mult, 1 H, 9); 3.20 (s, 3 H, 8); 3.43-3.52 (m, 1 H, 1); 3.70-3.80 (m, 1 H, 1); 4.20-4.30 (m, 1 H, 4); 5.50-5.95 (m, 2 H, 15, 16)

* minor isomer
**Experimental part**

\[ ^{13}C \text{ NMR (CDCl}_3, \text{ 75 MHz): 18.0 (18); 21.2 \text{ and 21.8 (6, 7); 22.9 (12, 13); 25.0 (19); 26.8 (11); 26.1 \text{ and 27.2 (2, 3); 31.0 (10); 36.5 (17); 49.1 (8); 50.4 (1); 65.4 (4); 68.0 (9); 72.4 (14); 77.7 (5); 130.6 \text{ and 131.4 (15, 16))} \]

**IR (liquid film, \text{ cm}^{-1})**: 1127 (NSO\_2); 1340 (NSO\_2); 2957 (C-H); 3481 (O-H)

**Mass (Cl +Q1MS)**: 73 ([C(CH\_3\_2)OMe]^+, 14%); 144 (100%); 244 (72%); 300 ([M-C(CH\_3\_2)OMe]^+, 28%); 356 ([M-OH]^+, 55%); 374 ([M+H]^+, 22%)

**HRMS**: calculated for C\textsubscript{19}H\textsubscript{36}NO\textsubscript{4}S\textsuperscript{+}: 374.236506; found: 374.235807

### 6.3.4 Addition of (2S)-1-[(3-ethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 65

Following the general procedure described in 6.1 with:

200 mg (681.6 \mu mol; 1 eq.) of (2S)-(1-methoxy-1-methylethyl)-1-(3-ethoxypropyl)sulfonylpyrrolidine 65

391 \mu l (715.6 \mu mol; 1.05 eq.) of n-BuLi, 1.83M solution in hexane

73 \mu l (72 mg; 749.7 \mu mol; 1.1 eq.) of 2-cyclohexen-1-one

334 \mu l (243 mg; 2.401 mmol; 3.52 eq.) of Et\textsubscript{3}N

334 \mu l (286 mg; 2.629 mmol; 3.85 eq.) of TMSCl

949 \mu l (977 mg; 5.452 mmol; 8 eq.) of HMPA

6.4 ml of THF

Flash chromatography: petroleum ether : AcOEt 80 : 20

Only 1,4-addition product was obtained:

3-(3-ethoxy-1-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl)propyl)cyclohexanone 120

**M.F.**: C\textsubscript{19}H\textsubscript{35}NO\textsubscript{5}S (M.W. 389.55)

**Yield**: 260 mg (98 \%) as a mixture of 3 diastereomers (ratio: 83 : 10 : 7)

**Aspect**: yellow oil
**Experimental part**

\( ^1H \) NMR (CDCl\(_3\), 300 MHz): 1.16-1.08 (2 s, 6 H, 6, 7); 1.22 (\( t, ^3J_{13\text{-}12} = 6.9, 3 \) H, 13); 1.47-2.57 (\( m, 15 \) H, 2, 3, 10, 14, 15, 17, 18, 19); 2.92 (\( \text{mult}, 1 \) H, 1); 3.21 (s, 3 H, 8); 3.49 (q, \( ^3J_{12\text{-}13} = 6.9, 2 \) H, 12); 3.52-3.71 (\( m, 5 \) H, 9, 11); 3.92-4.01 (\( m, 1 \) H, 1); 4.25-4.31 (\( m, 1 \) H, 4)

\( ^{13}C \) NMR (CDCl\(_3\), 75 MHz): 15.2 (13); 20.4 and 21.5 (6, 7); 25.4, 25.5 and 26.8 (10, 18, 19); 28.2 and 29.5 (2, 3); 38.5 (14); 41.1 (15); 42.8 (17); 49.1 (8); 51.0 (1); 63.0 (9) 63.5 (9*); 65.6 (4); 66.2 and 68.5 (11, 12); 78.1 (5); 210.7 (16)

IR (liquid film, cm\(^{-1}\)): 1137 (NSO\(_2\)); 1317 (NSO\(_2\)); 1713 (C=O); 2975 (C-H)

Mass (Cl/CH\(_4\)-N\(_2\)O): 73 ([C(CH\(_3\)_2OMe]\(^+\), 2%); 183 ([M-SO\(_2\)N\(^*\)]\(^+\), 29%); 316 ([M-(C(CH\(_3\)_2OMe)]\(^+\), 13%); 344 ([M-OEt]\(^+\), 6%); 358 ([M-OMe]\(^+\), 100%); 390 ([M+H]\(^+\), 66%)

GC (150/0/10/290/20): \( t_R = 18.33 \) min; 18.85 min (major); 19.14 (minor)

6.3.5 Addition of (2S)-1-[(3-ethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 65 (0 eq. of HMPA)

Following the general procedure with:

200 mg (681.6 µmol; 1 eq.) of (2S)-(1-methoxy-1-methylethyl)-1-(3-ethoxypropyl)sulfonylpyrrolidine 65
341 µl (715.6 µmol; 1.05 eq.) of n-BuLi, 2.1M solution in hexane
73 µl (72 µmol; 1.1 eq.) of 2-cyclohexen-1-one
334 µl (243 mg; 2.401 mmol; 3.52 eq.) of Et\(_3\)N
334 µl (286 mg; 2.629 mmol; 3.85 eq.) of TMSCl
0 ml of HMPA
6.4 ml THF
Flash chromatography: petroleum ether : AcOEt 80 : 20

Only 1,2-addition product was obtained:

1-(3-ethoxy-1-\{[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl}propyl)-cyclohex-2-en-1-ol 125
M.F.: C\(_{19}\)H\(_{35}\)NO\(_5\)S (M.W. 389.55)

Yield: 218 mg (82 %)

Aspect: yellow oil

* minor isomer
$^{1}H$ NMR (CDCl$_3$, 200 MHz): 1.11 and 1.13 (2 s, 6 H, 6, 7); 1.18 ($t$, $J_{13-12} = 7.1$, 3 H, 13); 1.60-2.50 (m, 12 H, 2, 3, 10, 17, 18, 19); 2.97-3.11 (m, 1 H, 9); 3.21 (s, 3 H, 8); 3.43-3.90 (m, 6 H, 1, 11, 12); 4.19-4.30 (m, 1 H, 4); 5.89-6.12 (m, 2 H, 15, 16)

$^{13}C$ NMR (CDCl$_3$, 50 MHz): 15.1 (13); 21.7 and 21.8 (6, 7); 22.7 (18); 24.7 (10); 26.0 and 27.2 (2, 3); 28.0 (19); 34.4 (17); 49.0 (8); 50.1 (1); 65.4 (4); 67.5 (9); 68.6 and 69.2 (11, 12); 71.2 (14); 77.7 (5); 128.7 (16); 131.9 (15)

IR (liquid film, cm$^{-1}$): 1125 (NSO$_2$); 1319 (NSO$_2$); 1685 (C=C); 2974 (C-H); 3481 (O-H)

Mass (Cl +Q1MS): 73 ([C(CH$_3$)$_2$OMe]$^+$, 9%); 97 ([C$_6$H$_9$O]$^+$, 95%); 216 (71%); 262 (100%); 372 ([M-OH]$^+$, 10%); 390 ([M+H]$^+$, 5%)

6.3.6 Addition of (2S)-1-[[3-(ethylsulfanyl)propyl]sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 66

Following the general procedure described in 6.1 with:
150 mg (484.6 µmol; 1 eq.) of (2S)-1-[[3-(ethylsulfanyl)propyl]sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 66
231 µl (508.9 µmol; 1.05 eq.) of n-BuLi, 2.2M solution in hexane
52 µl (51 mg; 533.1 µmol; 1.1 eq.) of 2-cyclohexen-1-one
237 µl (173 mg; 1.707 mmol; 3.52 eq.) of Et$_3$N
237 µl (203 mg; 1.87 mmol; 3.85 eq.) of TMSCl
675 µl (695 mg; 3.877 mmol; 8 eq.) of HMPA
4.6 ml of THF
Flash chromatography: petroleum ether : AcOEt 80 : 20

Only 1,4-addition product was obtained:

3-(3-(ethylsulfanyl)-1-[[[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]-
sulfonyl]propyl]cyclohexanone 121

M.F.: C$_{19}$H$_{35}$NO$_4$S$_2$ (M.W. 405.61)
Yield: 152 mg (77 %) as a mixture of 2 diastereomers (ratio: 90 : 10)

Aspect: yellow oil

\begin{align*}
\text{H NMR (CDCl}_3, 300 MHz): & 1.06 \text{ and } 1.13 \ (2 \text{ s, } 6 \text{ H, 6, 7});\ 1.27 \ (t, \ 3J_{13-12} = 8.3, \ 3 \text{ H,} 13); \ 1.56-2.52 \ (m, \ 14 \text{ H,} 2, 3, 10, 15, 17, 18, 19); \ 2.57 \ (q, \ 3J_{12-13} = 8.3, \ 2 \text{ H, } 12); \\
& 2.74-2.83 \text{ and } 2.88-3.00 \ (2 \text{ m, } 4 \text{ H, } 1, 11, 14); \ 3.23 \ (s, \ 3 \text{ H, } 8); \ 3.64-3.7 \ (m, \ 1 \text{ H, } 9); \\
& 3.93-4.02 \ (m, \ 1 \text{ H, } 1); \ 4.24-4.51 \ (m, \ 1 \text{ H, } 4) \\
\text{C NMR (CDCl}_3, 50 MHz): & 14.7 \ (13); \ 20.3 \text{ and } 21.5 \ (6, \ 7); \ 25.2 \text{ and } 25.3 \ (18, \ 19); \\
& 25.8 \ (12); \ 26.8 \ (10); \ 28.2 \text{ and } 29.7 \ (2, \ 3); \ 30.4 \ (11); \ 38.5 \ (14); \ 41.0 \text{ and } 42.8 \ (15, \ 17); \\
& 49.2 \ (8); \ 51.0 \ (1); \ 64.8 \ (9); \ 65.8 \ (4); \ 66.1 \ (9^\prime); \ 78.1 \ (5); \ 209.9 \ (16^\prime); \ 210.4 \ (16) \\
\text{IR (liquid film, cm}^{-1}): & 1134 \ (\text{NSO}_2); \ 1308 \ (\text{NSO}_2); \ 1712 \ (\text{C=O}); \ 2974 \ (\text{C-H})
\end{align*}

Mass (Cl -Q1MS): 246 ([N*SO₂C₃H₅]⁺, 100%); 282 (58%); 344 ([M-SEt]⁺, 3%); 404 ([M-H]⁺, 1%)

GC (150/0/10/290/20): tᵣ = 21.35 min (minor); tᵣ = 22.22 min (major)

6.3.7 Addition of (2S)-1-[(3,3-diethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 57

Following the general procedure described in 6.1 with:

150 mg (416 µmol; 1 eq.) of (2S)-1-[(3,3-diethoxypropyl)sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 57

199 µl (436.8 µmol; 1.05 eq.) of n-BuLi, 2.2M solution in hexane

44 µl (43 mg; 457.6 µmol; 1.1 eq.) of 2-cyclohexen-1-one

204 µl (148 mg; 1.465 mmol; 3.52 eq.) of Et₃N

204 µl (174 mg; 1.605 mmol; 3.85 eq.) of TMSCl

580 µl (596 mg; 3.328 mmol; 8 eq.) of HMPA

3.9 ml of THF

Flash chromatography: petroleum ether : AcOEt 80 : 20

* minor isomer
3-(3,3-diethoxy-1-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl)-propyl)cyclohexanone 122

**M.F.:** C$_{21}$H$_{39}$NO$_6$S (M.W. 433.6)

**Yield:** 137 mg (76 %) as a mixture of 2 diastereomers (ratio: 85 : 15)

**Aspect:** yellow oil

**TLC:** $R_f$ = 0.17 (petroleum ether : AcOEt 80 : 20)

$^1$H NMR (CDCl$_3$, 300 MHz): 1.07 and 1.13 (2 s, 6 H, 6, 7); 1.22 ($t$, $^3$J$_{13-12}$ = 6.0, 6 H, 13); 1.56-2.55 ($m$, 14 H, 2, 3, 10, 14, 15, 17, 18, 19); 2.72-2.81 ($m$, 1 H, 17); 2.95 (mult, 1 H, 1); 3.21 (s, 3 H, 8); 3.61-3.57 (2 mult + m, 5 H, 9, 12); 3.95 (mult, 1 H, 1); 4.24 (mult, 1 H, 4); 4.89 (dd, $^3$J$_{11-10}$ = 8.4, $^3$J$_{11-10'}$ = 3.0, 1 H, 11)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 15.4 (13); 20.1 and 21.5 (6, 7); 25.3, 28.0, 26.8, 29.9, 29.4 (2, 3, 10, 18, 19); 38.5 (14); 41.1 (15); 42.7 (17); 49.0 (8); 50.9 (1); 62.2 (9); 62.2 (12); 66.0 (4); 78.0 (5); 101.6 (11); 210.4 (16)

**IR** (liquid film, cm$^{-1}$): 1135 (NSO$_2$); 1325 (NSO$_2$); 1713 (C=O); 2975 (C-H)

**Mass** (Cl/CH$_4$-N$_2$O): 73 ([C(CH$_3$)$_2$OMe]$^+$, 30%); 112 (46%); 144 (61%); 181 (65%); 278 (87%); 324 (100%); 360 ([M-C(CH$_3$)$_2$OMe]$^+$, 5%); 434 ([M+H]$^+$, 1%)

**GC** (100/0/10/290/20): $t_R$ = 22.97 min (minor); $t_R$ = 23.43 min (major)

6.3.8 Addition of (2S)-1-[[2-(1,3-dioxolan-2-yl)ethyl]sulfonyl]-2-(1-methoxy-1-methylethyl)pyrrolidine 58

Following the general procedure described in 6.1 with:

109 mg (354.5 µmol; 1 eq.) of (2S)-1-[[2-(1,3-dioxolan-2-yl)ethyl]sulfonyl]-2-(1-methoxy-1-methylethyl)-pyrrolidine 58

149 µl (372.3 µmol; 1.05 eq.) of n-BuLi, 2.5M solution in hexane

38 µl (37 mg; 390 µmol; 1.1 eq.) of 2-cyclohexen-1-one

174 µl (126 mg; 1.249 mmol; 3.52 eq.) of Et$_3$N

174 µl (148 mg; 1.368 mmol; 3.85 eq.) of TMSCl
Yield: 109 mg (76 %) as a mixture of 3 diastereomers (ratio: 69 : 29 : 2)

3-[2-(1,3-dioxolan-2-yl)-1-{[(2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-y]sulfonyl}ethyl]cyclohexanone 123

M.F.: C_{19}H_{33}NO_{6}S (M.W. 403.53)

Aspect: colorless oil

TLC: R_f = 0.21 (petroleum ether : AcOEt 60 : 40)

1H NMR (CDCl₃, 300 MHz): 1.12 and 1.15 (2 s, 6 H, 6, 7); 1.65-2.48 (m, 15H, 2, 3, 10, 13, 14, 16, 17, 18); 3.02-3.11 (m, 1 H, 1); 3.18 (s, 3 H, 8); 3.75-3.98 (2 mult + 2 m, 6 H, 1, 9, 12); 4.99 (t, ^3J_{11-10} = 4.0, 1 H, 11)

13C NMR (CDCl₃, 75 MHz): 20.2 and 21.4 (6, 7); 25.2, 26.7, 28.2, 29.2 and 29.8 (2, 3, 10, 17, 18); 38.5 (13); 41.0 and 42.9 (14, 16); 49.0 (8); 51.0 (1); 62.0 (9); 64.7 and 65.0 (12); 65.5 (4); 78.1 (5); 102.7 (11); 210.6 (15)

IR (liquid film, cm⁻¹): 1135 (NSO₂); 1316 (NSO₂); 1713 (C=O); 2941 (C-H)

GC (100/0/10/290/20): 23.55 min (major); 24.18 min; 24.42 min (minor)

6.3.9 Addition of (2S)-2-(1-methoxy-1-methylethyl)-1-[[3,3,3-triethoxypropyl] sulfonyl]pyrrolidine 10

Following the general procedure described in 6.1 with:
200 mg (524.2 µmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)-1-[[3,3,3-triethoxypropyl] sulfonyl]pyrrolidine 10
229 µl (550.4 µmol; 1.05 eq.) of n-BuLi, 2.4M solution in hexane
56 µl (55 mg; 576.6 µmol; 1.1 eq.) of 2-cyclohexen-1-one
257 µl (186 mg; 1.846 mmol; 3.52 eq.) of Et₃N
257 µl (219 mg; 2.022 mmol; 3.85 eq.) of TMSCl
730 µl (751 mg; 4.193 mmol; 8 eq.) of HMPA
4.9 ml of THF

Only 1,4-addition product was obtained:

\[
\text{ethyl } 3-[[2S)-2-(1\text{-methoxy-1-methylethyl})\text{cyclopentyl}][\text{sulfonyl}]-3-(3\text{-oxocyclohexyl})\text{propanoate 124}
\]

\[
\text{M.F.: } \text{C}_{19}\text{H}_{33}\text{NO}_{6}\text{S (M.W. 403.53)}
\]

\[\text{Yield: } 228 \text{ mg (quant.)}\]

\[\text{Aspect: yellow oil}\]

\[\begin{align*}
\text{\HNeur}{(\text{CDCl}_3, 200 \text{ MHz})} & : 1.06 \text{ and } 1.11 (2 \text{s, 6 H, 6, 7}); 1.28 (t, J_{13, 12} = 7.0, 3 \text{ H, 13}); 1.50-3.00 (m, 17 \text{ H, 1, 2, 3, 9, 10, 14, 15, 17, 18, 19}); 3.21 (s, 3 \text{ H, 8}); 3.80-3.91 (m, 1 \text{ H, 1}); 4.04-4.30 (m, 3 \text{ H, 4, 12}) \\
\text{\CNeur}{(\text{CDCl}_3, 75 \text{ MHz})} & : 14.1 (13); 20.3 \text{ and } 21.4 (6, 7); 25.1 \text{ and } 26.6 (2, 3); 27.8 \text{ and } 29.4 (18, 19); 30.3 (10); 38.3 (14); 40.9 \text{ and } 43.0 (15, 17); 49.1 (8); 50.8 (1); 61.1 (12); 62.0 (9); 65.5 (4); 77.9 (5); 171.3 (11); 209.7 (16) \\
\text{IR (liquid film, cm}^{-1}\text{)} & : 1139 (\text{NSO}_2); 1320 (\text{NSO}_2); 1715 (\text{C} = \text{O}_{\text{ketone}}); 1738 (\text{C} = \text{O}_{\text{ester}}); 2977 (\text{C-H}) \\
\text{Mass (Cl/CH}_4\text{-N}_2\text{O)} & : 73 ([\text{C(CH}_3)_2\text{OMe}]^+, 6\%); 97 ([\text{C}_6\text{H}_9\text{O}]^+, 100\%); 180 (66\%); 276 (26\%); 306 ([\text{M-C}_6\text{H}_9\text{O}]^+, 2\%); 404 ([M+H]^+, 1\%) \\
\text{HRMS: calculated for } \text{C}_{19}\text{H}_{34}\text{NO}_{6}\text{S}\text{+: 404.210685; found: 404.209317}\n\end{align*}\]

### 6.4 Michael addition to other acceptors

#### 6.4.1 Addition of 65 to crotonaldehyde

Following the general procedure described in 6.1 with:

- 200 mg (681.6 µmol; 1 eq.) of \((2S)-1-[[3\text{-ethoxypropyl}]\text{sulfonyl}]-2-(1\text{-methoxy-1-methylethyl})\text{pyrrolidine 65}\)
- 375 µl (715.6 µmol; 1.05 eq.) of \(n\)-BuLi, 1.91M solution in hexane
61 µl (52 mg; 749.7 µmol; 1.1 eq.) of crotonaldehyde
334 µl (242 mg; 2.401 mmol; 3.52 eq.) of Et₃N
334 µl (285 mg; 2.629 mmol; 3.85 eq.) of TMSCl
950 µl (977 mg; 5.452 mmol; 8 eq.) of HMPA
5.7 ml of THF
Flash chromatography: petroleum ether : AcOEt 60 : 40

Only 1,2-addition product was obtained:

7-(ethyloxy)-5-([(2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-yl]sulfonyl)hept-2-en-4-ol 128

M.F.: C₁₇H₃₃NO₅S (M.W. 363.51)

Yield: 100 mg (40 %)

Aspect: yellow oil

^{1}H NMR (CDCl₃, 300 MHz): 1.09 and 1.12 (2 s, 6 H, 6, 7); 1.18 (t, 3J₁₃-₁₂ = 7.1, 3 H, 13); 1.58-2.18 (m, 6 H, 2, 3, 10); 1.73 (d, 3J₁₇-₁₆ = 6.5, 3 H, 17); 3.04 (mult, 1 H, 9); 3.14-3.25 (m, 1 H, 1); 3.22 (s, 3 H, 8); 3.48 and 3.61 (2 mult + m, 5 H, 1, 11, 12); 4.01 (mult, 1 H, 4); 4.29 (dd, 3J = 8.8, 3J = 6.2, 14); 4.26 (broad s, 1 H, OH); 5.43 (mult, 1 H, 16); 5.83 (mult, 1 H, 15)

^{13}C NMR (CDCl₃, 75 MHz): 15.1 (13); 17.7 (17); 20.1 and 21.4 (6, 7); 23.4 (10); 26.9 and 28.2 (2, 3); 49.1 (8); 51.4 (1); 64.0 (4); 65.8 (9); 65.8 and 68.2 (11, 12); 69.3 (14); 78.2 (5); 127.5 (15); 129.6 (16)

IR (liquid film, cm⁻¹): 1150 (NSO²); 1325 (NSO²); 2980 (C-H); 3510 (O-H)

Mass (Cl/CH₄-N₂O): 262 ([M-OMe-C₄H₇O]^+, 100%); 346 ([M-OH]^+, 8%); 364 ([M+H]^+, 10%)

GC (60/0/10/290/15): tᵣ = 24.68 min

HRMS: calculated for C₁₇H₃₄NO₅S⁺: 364.215770; found: 364.215853
6.4.2 Addition of 65 to 2,2-dimethylhex-4-en-3-one 75

Following the general procedure with:
200 mg (681.6 µmol; 1 eq.) of (2S)-1-{[3-(ethyloxy)propyl]sulfonyl}-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidine 65
330 µl (715.6 µmol; 1.05 eq.) of n-BuLi, 2.17M solution in hexane
95 mg (749.7 µmol; 1.1 eq.) of (E)-2,2-dimethylhex-4-en-3-one 75
334 µl (242 mg; 2.401 mmol; 3.52 eq.) of Et₃N
334 µl (285 mg; 2.629 mmol; 3.85 eq.) of TMSCl
949 µl (977 mg; 5.452 mmol; 8 eq.) of HMPA
6.4 ml of THF
Flash chromatography: petroleum ether : AcOEt 60 : 40

Only 1,4-addition product was obtained:

8-ethoxy-6-[(2S)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]-2,2,5-trimethyloctan-3-one 126
M.F.: C₂₁H₄₁NO₅S (M.W. 419.62)

Yield: 212 mg (74 %)

TLC: Rᵢ = 0.5 (petroleum ether : AcOEt 80 : 20)

¹H NMR (CDCl₃, 300 MHz): 1.00 (d, 3J₁₉-₁₄ = 6.8, 3 H, 19); 1.10 and 1.14 (2 s, 6 H, 6, 7); 1.12 (s, 9 H, 18); 1.18 (t, 3J₁₃-₁₂ = 7.1, 3 H, 13); 1.62-2.50 (m, 7 H, 2, 3, 10, 14); 2.64 (mult, 1 H, 15); 2.82-2.98 (m, 1 H, 15); 3.01-3.12 (m, 1 H, 1); 3.18 (s, 3 H, 8); 3.40-3.69 (m, 5 H, 9, 11, 12); 3.82-3.95 (m, 1 H, 4); 4.25 (mult, 1 H, 1)

¹³C NMR (CDCl₃, 75 MHz): 14.8 (13); 19.1 (19); 20.7 and 21.5 (6, 7); 25.4 (10); 26.2 (18); 26.6 and 27.7 (2, 3); 36.7 (14); 38.1 (15); 42.2 (17); 49.1 (8); 50.6 (1); 63.1 (9); 65.7 (4); 66.1 and 68.7 (11, 12); 78.1 (5); 207.5 (16)

IR (liquid film, cm⁻¹): 1138 (NSO₂); 1319 (NSO₂); 1705 (C=O); 2974 (C-H)

Mass (Cl +Q1MS): 73 ([C(CH₃)₂OMe]⁺, 16%); 142 ([N⁺]⁺, 19%); 213 ([M-SO₂N⁺]⁺, 100%); 346 ([M-C(CH₃)₂OMe]⁺, 10%); 388 ([M-OMe]⁺, 19%); 420 ([M+H]⁺, 50%)
GC (150/0/10/290/20): t_R = 17.23 min (major); 17.42 min (minor); 17.74 min

**Elemental analysis:**
calculated (%): C: 60.1; H: 9.84; N: 3.33; O: 19.06; S: 7.64
found (%): C: 60.19; H: 10.28; N: 3.31; O: 18.83; S: 7.37

**6.4.3 Addition of (2S)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10 to 2,2-dimethylhex-4-en-3-one 75**

Following the general procedure with:

- 200 mg (524.2 µmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10
- 246 µl (550.4 µmol; 1.05 eq.) of n-BuLi, 2.24M solution in hexane
- 73 mg (576.6 µmol; 1.1 eq.) of (E)-2,2-dimethylhex-4-en-3-one 75
- 257 µl (186 mg; 1.846 mmol; 3.52 eq.) of Et₃N
- 257 µl (219 mg; 2.022 mmol; 3.85 eq.) of TMSCl
- 0 ml of HMPA
- 5 ml of THF

Only 1,4-addition product was obtained:

**3-[(2S)-(1-methoxy-1-methylethyl)pyrrolidine-1-sulfonyl]-4,7,7-trimethyl-6-oxo-octanoic acid ethyl ester 127**

**M.F.:** C₂₁H₃₉NO₆S (M.W. 433.6)

**Yield:** 159 mg (70 %); the crude product was composed of 38% of the desired product and 34% of the corresponding silylated enol ether, which was hydrolyzed to 127.

**1H NMR** (CDCl₃, 200 MHz): 1.12, 1.14 and 1.15 (3 s, 15 H, 6, 7, 18); 1.15 (d, 3 J₁₉-₁₄ = 4.9, 3 H, 19); 1.27 (t, 3 J₁₃-₁₂ = 7.2, 3 H, 13); 1.62-2.23 (m, 7 H, 2, 3, 14, 15); 2.50 (mult, 2 H, 10); 2.83 (mult, 1 H 9); 2.95-3.18 (m, 1 H, 1); 3.21 (s, 3 H, 8); 3.76-3.90 (m, 1 H, 1); 4.02-4.15 (m, 1 H, 4); 4.18 (q, 3 J₁₂-₁₃ = 7.2, 2 H, 12)
$^{13}$C NMR (CDCl$_3$, 50 MHz): 13.9 (13); 18.9 (19); 20.0 and 21.2 (6, 7); 26.0 (18); 26.5 and 27.8 (2, 3); 30.4 (10); 36.6 (14); 39.6 (15); 44.0 (17); 48.9 (8); 60.9 (12); 62.2 (9); 62.4 (9$^*$); 65.8 (4); 77.9 (5); 170.1 (11); 214.1 (16)

IR (liquid film, cm$^{-1}$): 1154 (NSO$_2$); 1325 (NSO$_2$); 1706 (C=O ketone); 1738 (C=O ester); 2977 (C-H)

Mass (Cl/CH$_4$-N$_2$O): 276 ([M-COC(CH$_3$)$_3$-COOEt]$^+$, 100); 434 ([M+H]$^+$, 5%)

GC (150/0/10/290/15): 18.26 min (major); 18.61 (minor)

HRMS: calculated for C$_{21}$H$_{40}$NO$_6$S$: 434.257635; found: 434.255391

6.4.4 Addition of 1-[(3-methylbutyl)sulfonyl]pyrrolidine 39 to N,N-dimethylacrylamide

In a flame-dried two-necked flask, 150 mg (730.5 µmol; 1 eq.) of 1-(3-methyl-1-butanesulfonyl)pyrrolidine 39 were dissolved in 6.9 ml of THF. The solution was cooled to -78°C and 307 µl (767.1 µmol; 1.05 eq.) of n-BuLi, 2.5M solution in hexane, were slowly added. After 60 minutes of reaction, a mixture of 83 µl (79 mg; 803.6 µmol; 1.1 eq.) of N,N-dimethylacrylamide and 216 µl (246 mg; 803.6 µmol; 1.1 eq.) of triisopropylisilyl trifluoromethanesulfonate dissolved in some THF were added. The mixture was stirred for 60 minutes at -78°C then heated to room temperature. A few ml of a saturated solution of NH$_4$Cl were then added. The aqueous phase was extracted with CH$_2$Cl$_2$. The organic phase was dried over MgSO$_4$, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (150 ml of petroleum ether : AcOEt 80 : 20; then 150 ml of petroleum ether : AcOEt 60 : 40).

Yield: 70 mg (31.5 %)

$^{N,N,6}$trimethyl-4-(pyrrolidin-1-ylsulfonyl)heptanamide 114

M.F.: C$_{14}$H$_{28}$N$_2$O$_3$S (M.W. 304.44)

Besides 42 mg (28 %) of 1-(3-methyl-1-butanesulfonyl)pyrrolidine were recovered.
**Experimental part**

**1H NMR** (CDCl₃, 200 MHz): 0.92 and 0.95 (2 d, 3J₆:₅ = 6.0, 3J₅:₆ = 5.9, 6 H, 6); 1.44-2.16 (m, 5 H, 4, 5, 7); 1.88-1.97 (m, 4 H, 2); 2.61 (mult, 2 H, 8); 2.95 and 3.02 (2 s, 6 H, 10); 3.18 (mult, 1 H, 3); 3.34-3.45 (m, 4 H, 1)

**13C NMR** (CDCl₃, 75 MHz): 21.5 and 23.3 (6); 24.3 (7); 25.3 (5); 25.9 (2); 29.6 (8); 35.4 and 37.1 (10); 37.9 (4); 48.1 (1); 59.2 (3); 172.1 (9)

**IR** (liquid film, cm⁻¹): 1142 (NSO₂); 1320 (NSO₂); 1652 (C=O); 2957 (C-H)

**Mass** (Cl +Q1MS): 87 (100%); 174 (10%); 265 (6%); 305 ([M+H]+, 1%)

**GC** (100/0/10/290/15): tᵣ = 19.97 min

### 6.4.5 Addition of pyrrolidine to 5,6-dihydro-2H-pyran-2-one 72

In a flame-dried two-necked flask, 145 µl (123 mg; 1.741 mmol; 1 eq.) of pyrrolidine were added to a solution of 150 µl (170 mg; 1.741 mmol; 1 eq.) of 5,6-dihydro-2H-pyran-2-one 72 in 4.2 ml of CH₂Cl₂. The mixture was stirred for 72 hours at room temperature. The solvent was removed under reduced pressure. The product was purified by flash chromatography (AcOEt : CH₂Cl₂ 50 : 50 + 10% EtOH).

**Yield:** 200 mg (68 %)

**4-pyrrolidin-1-yltetrahydro-2H-pyran-2-one 225**

**M.F.:** C₉H₁₅NO₂ (M.W. 169.22)  
**RN:** 168482-09-5

Besides, 53 mg (31 %) of 5,6-dihydro-2H-pyran-2-one were recovered.

**Aspect:** brown oil

**TLC:** Rᵣ = 0.14 (CH₂Cl₂ : AcOEt 50 : 50 + 10% EtOH)
Experimental part

**1H NMR** (CDCl₃, 200 MHz): 1.69-2.17 (m, 6 H, 2, 7); 2.50-2.80 (m, 5 H, 3, 6); 3.82-3.45 (2 m, 2 H, 4); 4.37 (mult, 2 H, 1)

**13C NMR** (CDCl₃, 50 MHz): 23.1 (7); 28.45 (2); 36.5 (4); 51.2 (6); 56.7 (3); 66.4 (1); 170.3 (5)

**IR** (liquid film, cm⁻¹): 1635; 1732 (C=O); 2968 (C-H)

**Mass** (Cl/CH₄-N₂O): 99 ([C₅H₇O₂]⁺, 47%); 170 ([M+H]⁺, 100%)

**GC** (50/0/10/290/0): tᵣ = 15.31 min

### 6.4.6 Addition of pyrrolidine to furan-2(5H)-one 71

In a flame-dried two-necked flask, 235 µl (200 mg; 2.818 mmol; 1 eq.) of pyrrolidine were added to a solution of 200 µl (237 mg; 2.818 mmol; 1 eq.) of furan-2(5H)-one 71 in 6.8 ml of CH₂Cl₂. The mixture was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure.

The product was purified by flash chromatography (AcOEt : EtOH 90 : 10).

**Yield:** 307 mg (70 %)

Besides, 36 mg (15 %) of furan-2(5H)-one were recovered

**4-pyrrolidin-1-ylidihydrofuran-2(3H)-one 226**

**M.F.:** C₈H₁₃NO₂ (M.W. 155.19)  
**RN:** 168482-08-4

**Aspect:** yellow oil

**TLC:** Rᵢ = 0.16 (AcOEt : EtOH 90 : 10)

![Diagram](image)

**1H NMR** (CDCl₃, 200 MHz): 1.70-1.86 (m, 4 H, 6); 2.45-2.59 (m, 4 H, 5); 2.60 (mult, 2 H, 3); 3.22 (mult, 1 H, 2); 4.29 (mul, 2 H, 1)

**13C NMR** (CDCl₃, 50 MHz): 23.0 (6); 33.8 (3); 51.5 (5); 59.6 (2); 71.6 (1); 175.4 (4)

**IR** (liquid film, cm⁻¹): 1179 (C-O); 1772 (C=O); 2965 (C-H)

**Mass** (Cl/CH₄-N₂O): 156 ([M+H]⁺, 100%); 184 ([M+C₂H₅]⁺, 29%)

**GC** (50/0/10/290/0): tᵣ = 13.1 min
**6.4.7  Addition of pyrrolidine to 1-methyl-5,6-dihydropyridin-2(1H)-one 74**

In a two-necked flask, 150 µl (127 mg; 1.799 mmol; 1 eq.) of pyrrolidine were added to a solution of 200 mg (1.799 mmol; 1 eq.) of 1-methyl-5,6-dihydropyridin-2(1H)-one 74 in 4.4 ml of CH₂Cl₂. The mixture was stirred for 30 hours. After this time no reaction had occurred. A small quantity of K₂CO₃ was added and the stirring continued for 70 hours. The solvent was then removed under reduced pressure. 20 ml of water and 20 ml of CH₂Cl₂ were added to the residue. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (Et₂O : EtOH 90 : 10).

**Yield:** 130 mg (40 %)

Besides, 70 mg (35 %) of 1-methyl-5,6-dihydropyridin-2(1H)-one were recovered.

**1-methyl-4-pyrrolidin-1-ylpiperidin-2-one 227**

**M.F.:** C₁₀H₁₈N₂O (M.W. 182.26)

**Aspect:** yellow oil

**TLC:** Rᵣ = 0.18 (Et₂O : EtOH 90 : 10)

![Structural formula](image)

**¹H NMR** (CDCl₃, 200 MHz): 1.70-1.89 (m, 4 H, 8); 2.02-2.19 (m, 2 H, 3); 2.43 (mult, 2 H, 5); 2.50-2.72 (m, 5 H, 4, 7); 2.94 (s, 3 H, 1); 3.30 (mult, 2 H, 2)

**¹³C NMR** (CDCl₃, 50 MHz): 23.15 (8); 28.6 (3); 34.1 (1); 38.3 (5); 47.25 (2); 51.5 (7); 58.5 (4); 168.6 (6)

**IR** (liquid film, cm⁻¹): 1341 (C-N amide); 1635 (C=O); 2964 (C-H)

**Mass** (Cl/CH₄-N₂O): 183 ([M+H]⁺, 100%); 211 ([M+C₂H₅]⁺, 7%)

**GC** (50/0/10/290/0): tᵣ = 18.44 min
7 Cyclization

7.1 Cyclization of cyclohexenone

7.1.1 Synthesis of (2S)-(1-methoxy-1-methylethyl)-1-[3,3,3-triethoxy-1-(3-trimethylsilanyloxycyclohex-2-enyl)propane-1-sulfonyl]pyrrolidine 130

M.F.: C_{26}H_{51}NO_{7}SSi (M.W. 549.83)

Following the general procedure described in 6.1 with:
200 mg (524.2 µmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10
323 µl (550.4 µmol; 1.05 eq.) of n-BuLi, 2.4M solution in hexane
56 µl (55 mg; 576.6 µmol; 1.1 eq.) of 2-cyclohexen-1-one
257 µl (186 mg; 1.846 mmol; 3.52 eq.) of Et_{3}N
257 µl (219 mg; 2.022 mmol; 3.85 eq.) of TMSCl
730 µl (751 mg; 4.193 mmol; 8 eq.) of HMPA
4.9 ml of THF
quenched with a saturated solution of NH_{4}Cl

Yield: 260 mg (90 %) crude product sufficiently pure to be used for the next step.

Aspect: colorless oil

\[
\text{H NMR (CDCl}_3, 300 MHz): 0.41 \ (20); 1.09 \text{ and } 1.12 \ (2 \ s, \ 6 \ H, \ 6, \ 7); 1.25 \ (t, \ ^3J_{13-12} = 6.8, \ 13); 1.45-2.27 \ (m, \ 10 \ H, \ 2, \ 3, \ 17, \ 18, \ 19); 2.42 \ (dd, \ ^2J_{10-10'} = 18.1, \ ^3J_{10-9} = 4.1, \ 1 H, \ 10); 2.98 \ (dd, \ ^2J_{10-10'} = 18.1, \ ^3J_{10-9} = 6.8, \ 1 H, \ 10); 3.03-3.15 \ (m, \ 1 H, \ 1); 3.20 \ (s, \ 3 H, \ 8); 3.44-3.95 \ (m, \ 9 \ H, \ 1, \ 9, \ 12, \ 14); 4.21-4.31 \ (m, \ 1 H, \ 4); 5.14 \ (s, \ 1 H, \ 15)
\]

\[
\text{C NMR (CDCl}_3, 75 MHz): 0.3 \ (20); 15.1 \ (13); 20.8 \text{ and } 21.5 \ (6, \ 7); 23.0 \ (18); 26.7 \text{ and } 26.9 \ (2, \ 3); 27.6 \ (19); 28.5 \ (10); 29.6 \ (17); 35.8 \ (14); 49.1 \ (8); 50.8 \ (1); 57.4 \ (12); 62.0 \ (9); 66.1 \ (4); 77.9 \ (5); 105.2 \ (15); 113.9 \ (11); 152.1 \ (16)
\]
7.1.2 Synthesis of 3,3-bis(ethyloxy)-1-(((2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-yl)sulfonyl)octahydro-4H-inden-4-one

M.F.: C_{21}H_{37}NO_6S (M.W. 431.588)

RN: 163362-43-4


In a flame-dried two-necked flask equipped with a magnetic stirrer, 260 mg (472.8 µmol; 1 eq.) of (2S)-(1-methoxy-1-methylethyl)-1-[3,3,3-triethoxy-1-(3-trimethylsilanyloxycyclohex-2-enyl)propane-1-sulfonyl]pyrrolidine 130 were dissolved in 2.9 ml of CH_2Cl_2. The mixture was cooled to -78°C and 9 µl (10 mg; 47.28 µmol; 0.1 eq.) of trimethylsilyl trifluoromethanesulfonate were slowly added. The mixture was stirred for 45 minutes. Then a few ml of a saturated solution of NaHCO_3 were added and the temperature was raised to room temperature. The aqueous phase was extracted 3 times with CH_2Cl_2. The organic phase was washed with water and with a saturated solution of NaCl, dried over MgSO_4, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20).

Yield: 97 mg (48 %)

TLC: R_f = 0.72 (petroleum ether : AcOEt 80 : 20)

H NMR (CDCl_3, 200 MHz): 1.12 and 1.15 (2 s, 6 H, 6, 7); 1.14 and 1.20 (2 t, 3J_{19-18} = 7.3, 6 H, 19); 1.58-2.21 (m, 8 H, 2, 3, 14, 15,); 2.36 and 2.56 (2 mult, 4 H, 10, 16); 2.77-3.10 (m, 2 H, 1, 17); 3.17 (d, 3J_{12-17} = 9.0, 1 H, 12); 3.21 (s, 3 H, 8); 3.33-3.92 (m, 6 H, 1, 9, 18); 4.22 (dd, 3J_{4-3} = 8.8, 3J_{4-3} = 5.0, 1 H, 4)

C NMR (CDCl_3, 50MHz): 15.2 and 15.3 (19); 20.9 and 21.5 (6, 7); 23.6 (16); 26.7 (15); 27.5 and 28.7 (2, 3); 35.4 (10); 41.8 (14); 42.4 (17); 49.2 (8); 50.8 (1); 56.7 and 58.4 (18); 59.4 (12); 64.3 (9); 66.2 (4); 78.1 (5); 110.3 (11); 208.5 (13)

IR (liquid film, cm^{-1}): 1137 (NSO_2); 1322 (NSO_2); 1704 (C=O); 2975 (C-H)
7.1.3 Synthesis of 3,3-bis(ethyloxy)-1-\(((2S)-2-[1-methyl-1-\text{(methyloxy)ethyl}]\text{pyrrolidin-1-yl\text{]}sulfonyl)octahydro-1H-inden-4-ol 132

\textbf{M.F.:} C_{21}H_{39}NO_6S (M.W. 433.604)

\textbf{Reference:} Huart, C. PhD-Thesis UCL-ORSY, 1995

In a flame-dried two-necked flask equipped with a magnetical stirrer, 73 mg (169.1 µmol; 1 eq.) of 3,3-bis(ethyloxy)-1-\(((2S)-2-[1-methyl-1-\text{(methyloxy)ethyl}]\text{pyrrolidin-1-yl\text{]}sulfonyl)octahydro-4H-inden-4-one 131 were dissolved in 2.4 ml of CH_2Cl_2. The mixture was cooled to -78°C and 338 µl (292 mg; 338.2 µmol; 2 eq.) of diisobutylaluminum hydride were slowly added. After 20 minutes at that temperature, the reaction was quenched by the addition of a saturated solution of NH_4Cl. The mixture was allowed to come to room temperature and was acidified by the addition of HCl. The aqueous phase was extracted 4 times with CH_2Cl_2. The organic phase was washed once with a 1M solution of HCl, 3 times with a saturated solution of NaCl, dried over MgSO_4, filtered and evaporated under reduced pressure.

\textbf{Yield:} 82 mg (quant.)

\textbf{Aspect:} colorless oil

\textbf{\textsuperscript{1}H NMR} (CDCl_3, 300 MHz): 1.12 and 1.15 (2 s, 6 H, 6, 7); 1.20 and 1.22 (2 t, 3J_{19-18} = 7.2, 6 H, 19); 1.20-2.25 (m, 12 H, 2, 3, 10, 14, 15, 16); 2.61-3.02 (m, 4 H, 1, 9, 12, 17); 3.21 (s, 3 H, 8); 3.34-3.78 (2 mult + m, 5 H, 1, 18); 4.04-4.11 (m, 2 H, 13, OH); 4.18-4.24 (m, 1 H, 4)

\textbf{\textsuperscript{13}C NMR} (CDCl_3, 75 MHz): 14.1 (15); 14.8 and 15.1 (19); 21.0 and 21.4 (6, 7); 24.6, 26.1 and 26.6 (2, 3, 16); 30.9 (14); 36.4 (17); 38.0 (10); 49.0 (8); 49.3 (12); 50.2 (1); 56.7 and 58.4 (18); 60.4, 64.7 and 65.4 (4, 9, 13); 78.2 (5); 109.2 (11)

\textbf{IR} (liquid film, cm\textsuperscript{-1}): 1060 (C-O); 1135 (NSO_2); 1340 (NSO_2); 2975 (C-H); 3510 (O-H)
7.1.4 Synthesis of 7-hydroxy-3-\{((2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-yl)sulfonyl\}octahydro-1H-inden-1-one 133

M.F.: C\textsubscript{17}H\textsubscript{29}NO\textsubscript{5}S (M.W. 359.482)


In a flask, 82 mg (189.1 µmol; 1 eq.) of 3,3-bis(ethyloxy)-1-\{((2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-yl)sulfonyl\}octahydro-1H-inden-4-ol 132 were dissolved in a mixture of 1 ml of acetone and 1 ml of water. The mixture was cooled to 0°C and 14 mg (56.73 µmol; 0.3 eq.) of pyridinium \textit{para}-toluenesulfonate were added. It was stirred for 30 minutes at 0°C and for 60 minutes at room temperature. The reaction was quenched by the addition of a few ml of a saturated solution of NaHCO\textsubscript{3}. The aqueous phase was extracted 5 times with CH\textsubscript{2}Cl\textsubscript{2}. The organic phase was washed with water and with a saturated solution of NaCl, dried over MgSO\textsubscript{4}, filtered and evaporated under reduced pressure.

Yield: 45 mg of a mixture containing 133 and 134.

7.1.5 Synthesis of 7-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one 134

M.F.: C\textsubscript{9}H\textsubscript{12}O\textsubscript{2} (M.W. 152.190) RN: 190510-64-6


The crude product of 7.1.4 was passed on a flash chromatography column (petroleum ether : ether 25 : 75) to yield 7-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one 134.

Yield: 9 mg (47 %)

TLC: Rf = 0.26 (petroleum ether : ether 25 : 75)
\textbf{H NMR} (CDCl$_3$, 200 MHz): 1.05-2.05 (m, 6 H, 5, 6, 7); 2.77 (t, $^3J_{9,8} = ^3J_{9,4} = 5.9$, 1 H, 9); 3.10 (mult, 1 H, 4); 4.11 (mult, 1 H, 8); 6.18 (dd, $^3J_{2,3} = 5.7$, $^4J_{2,4} = 1.4$, 1 H, 2); 7.76 (dd, $^3J_{3,2} = 5.7$, $^3J_{3,4} = 3.0$, 1 H, 3)

\textbf{C NMR} (CDCl$_3$, 50 MHz): 20.1 (6); 27.3 and 30.3 (5, 7); 42.1 (4); 49.1 (9); 69.8 (8); 132.9 (2); 169.6 (3); 216.3 (1)

\textbf{IR} (liquid film, cm$^{-1}$): 1595 (C=C); 1700 (C=O); 2945 (C-H); 3455 (O-H)

\section*{7.2 Cyclization of 2,2-dimethylhex-4-en-3-one 75 with 10}

\textit{7.2.1 Synthesis of (2S)-(1-methoxy-1-methylethyl)-1-(1,1,1-triethoxy-4,7,7-trimethyl-6-trimethylsilyloxyoct-5-ene-3-sulfonyl)pyrrolidine 135}

\textbf{M.F.:} C$_{28}$H$_{57}$NO$_7$SSi (M.W. 579.9)

Following the general procedure described in 6.1 with:

- 500 mg (1.31 mmol; 1 eq.) of (2S)-2-(1-methoxy-1-methylethyl)-1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 10
- 550 µl (1.376 mmol; 1.05 eq.) of n-BuLi, 2.5M solution in hexane
- 182 mg (1.441 mmol; 1.1 eq.) of (E)-2,2-dimethylhex-4-en-3-one 75
- 642 µl (467 mg; 4.617 mmol; 3.52 eq.) of Et$_3$N
- 642 µl (549 mg; 5.056 mmol; 3.85 eq.) of TMSCl
- 1.824 ml (1.878 g; 10.48 mmol; 8 eq.) of HMPA
- 12.3 ml of THF

quenched with a saturated solution of NH$_4$Cl

\textbf{Yield:} 671 mg (88 %) crude product sufficiently pure to be used in the next step.

\textbf{H NMR} (CDCl$_3$, 300 MHz): 0.27 (s, 9 H, 20); 1.04 (s, 9 H, 18); 1.12-1.22 (mult, 18 H, 6, 7, 13, 19); 1.78-1.99 (m, 5 H, 2, 3, 14); 2.17 (dd, $^2J_{10,10'} = 14.4$, $^3J_{10,9} = 8.0$, 1 H, 10); 2.50 (dd, $^2J_{10,10'} = 14.4$, $^3J_{10,9} = 2.0$, 1 H, 10); 2.95-3.05 (m, 1 H, 1); 3.18 (s, 3 H,
8); 3.39-3.47 (m, 1 H, 1); 3.50-3.69 (m, 7 H, 9, 12); 4.19-4.25 (m, 1 H, 4); 4.96 (d, $^3J_{15-14} = 8.9$, 1 H, 15)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 1.4 (20); 15.3 (13); 20.1 (19); 21.8 and 22.1 (6, 7); 26.5 and 27.0 (2, 3); 28.8 (18); 30.5 (14); 36.5 (17); 49.2 (8); 50.4 (1); 57.4 (12); 63.0 (9); 65.4 (4); 77.8 (5); 107.0 (15); 113.8 (11); 157.2 (16)

IR (liquid film, cm$^{-1}$): 844 (C-Si); 1070 (C-O); 1137 (NSO$_2$); 1320 (NSO$_2$); 1654 (C=C-O); 2974 (C-H)

7.2.2 Synthesis of 1-[2,2-bis(ethyloxy)-5-methyl-4-({(2S)-2-[1-methyl-1-(methyloxy)ethyl]pyrrolidin-1-yl}sulfonyle)cyclopentyl]-2,2-dimethylpropan-1-one 138

M.F.: C$_{23}$H$_{43}$NO$_6$S (M.W. 461.65)

In a flame-dried two-necked flask equipped with a magnetical stirrer, 625 mg (1.157 mmol; 1 eq.) of (2S)-(1-methoxy-1-methylethyl)-1-(1,1,1-triethoxy-4,7,7-trimethyl-6-trimethylsilyloxyoct-5-ene-3-sulfonyl)pyrrolidine 135 were dissolved in 7.1 ml of CH$_2$Cl$_2$. The mixture was cooled to -45°C and 22 µl (25 mg; 115.7 µmol; 0.1 eq.) of trimethylsilyl trifluoromethanesulfonate were slowly added. The mixture was stirred for 60 minutes at -45°C. The reaction was then quenched by the addition of a few ml of a saturated solution of NaHCO$_3$ and the mixture was allowed to come to room temperature. The aqueous phase was extracted 3 times with CH$_2$Cl$_2$. The organic phase was washed with water and with a saturated solution of NaCl, dried over MgSO$_4$, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 85 : 15).

Yield: 294 mg (55 %)

Aspect: colorless oil

TLC: $R_f = 0.39$ (petroleum ether : AcOEt 80 : 20)
1H NMR (CDCl₃, 300 MHz): 1.13 and 1.15 (2 s, 15 H, 6, 7, 16); 1.22 and 1.26 (2 t, 3J₁₉₋₁₈ = 7.1, 6 H, 19); 1.24 (d, 3J₁₇₋₁₃ = 7.0, 3 H, 17); 1.76-2.00 (m, 5 H, 2, 3, 13); 2.26 (dd, 2J₁₀₋₁₀’ = 11.5, 3J₁₀₋₉ = 6.6, 1 H, 10); 2.65 (dd, 2J₁₀₋₉ = 12.5, 2J₁₀₋₁₀’ = 11.4, 1 H, 10); 2.80 (mult, 1 H, 12); 3.00-3.11 (m, 1 H, 1); 3.18 (s, 3 H, 8); 3.32 (mult, 1 H, 9); 3.45 and 3.55 (2 mult, 4 H, 18); 3.67-3.76 (m, 1 H, 1); 4.21-4.27 (m, 1 H, 4)

13C NMR (CDCl₃, 50 MHz): 14.7 and 15.2 (19); 21.2 and 21.5 (6, 7, 17); 25.8 (16); 26.4 and 26.5 (2, 3); 37.8 (10); 37.9 (13); 44.8 (15); 49.1 (8); 50.3 (1); 55.8 (12); 55.9 and 58.6 (18); 65.6 and 66.3 (4, 9); 77.7 (5); 109.1 (11); 214.2 (14)

IR (liquid film, cm⁻¹): 1135 (NSO₂); 1304 (NSO₂); 1705 (C=O); 2975 (C-H)

Mass (Cl –Q1MS): 460 ([M-H]⁻, 100%)

7.2.3 Synthesis of 1-(2,2-diethoxy-4-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl]-5-methylcyclopentyl)-2,2-dimethylpropan-1-ol 140

M.F.: C_{23}H_{45}NO_{6}S (M.W. 463.67)

In a flame-dried two-necked flask, a solution of 183 mg (396.3 µmol; 1 eq.) of 1-(2,2-diethoxy-4-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl]-5-methylcyclopentyl)-2,2-dimethylpropan-1-one 138 in 5 ml of Et₂O was slowly added to a suspension of 7.5 mg (198.1 µmol; 0.5 eq.) of lithium aluminum hydride in Et₂O at 0°C. The mixture was stirred for 20 minutes at 0°C. A few ml of a saturated solution of NaHCO₃ were added. The aqueous phase was extracted with Et₂O. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

Yield: 145 mg (79 %)

Aspect: colorless oil

1H NMR (CDCl₃, 300 MHz): 0.98 (s, 9 H, 8); 1.15 and 1.17 (2 s, 15 H, 9, 17, 18); 1.24 (mult, 9 H, 9, 11); 1.75-2.03 (m, 6 H, 2, 13, 14); 2.30-2.48 (m, 2 H, 4, 5); 2.52-2.61
Experimental part

\[(\text{m, 1 H, 3}); 2.96-3.06 (\text{m, 1 H, 12}); 3.20 (\text{s, 3 H, 19}); 3.28 (\text{dd, } ^3J_{6,\text{OH}} = 7.7, ^3J_{6,5} = 5.0, \text{1 H, 6}); 3.45 (\text{mult, 4 H, 10}); 3.71-3.79 (\text{m, 1 H, 12}); 4.18-4.25 (\text{m, 1 H, 15}); 4.33 (\text{d, } ^3J_{\text{OH,6}} = 7.7, \text{1 H, OH})\]

\[13C \text{ NMR (CDCl}_3, 75 \text{ MHz}): 15.0 \text{ and 15.2 (11); 20.6 \text{ and 21.1 (17, 18); 21.7 (9); 27.0 (8); 26.6 \text{ and 28.9 (13, 14); 36.3 (7); 38.8 (2); 40.1 (4); 49.2 (19); 50.3 (12); 50.6 (5); 56.2 \text{ and 58.7 (10); 65.0 \text{ and 66.0 (3, 15); 77.8 (16); 82.3 (6); 109.7 (1)}\]

\[\text{IR (liquid film, cm}^{-1}\): 1055 (C-O); 1145 (NSO \text{2}); 1323 (NSO \text{2}); 2975 (C-H); 3441 (O-H)

\[\text{Mass (Cl/CH}_4\text{N}_2\text{O): 84 (35\%); 125 (100\%); 211 ([M-\text{OEt-SO}_2\text{N}^+]^+, 64\%); 464 ([M+H]^+, 2\%)}\]

7.2.4 Synthesis of 2-(1-hydroxy-2,2-dimethylpropyl)-4-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl]-3-methylcyclopentanone 142

M.F.: C_{19}H_{35}NO_5S (M.W. 389.55)

In a two-necked flask, 134 mg (288.9 µmol; 1 eq.) of 1-(2,2-diethoxy-4-[(2S)-2-(1-methoxy-1-methylethyl)pyrrolidin-1-yl]sulfonyl]-5-methylcyclopentyl)-2,2-dimethylpropan-1-ol 140 were dissolved in a mixture of 1.5 ml of acetone and 1.5 ml of H_2O. The mixture was cooled to 0°C and 22 mg (86.69 µmol; 0.3 eq) of pyridinium para-toluenesulfonate were added. The mixture was stirred for 30 minutes at 0°C and for 60 minutes at room temperature. A few ml of a saturated solution of NaHCO_3 were then added. The aqueous phase was extracted 5 times with CH_2Cl_2. The organic phase was washed with water and with a saturated solution of NaCl, dried over MgSO_4, filtered and evaporated under reduced pressure.

Yield: 88 mg of a mixture of 142 and 144

Aspect: colorless oil

\[1^H \text{ NMR (CDCl}_3, 300 \text{ MHz): 0.96 (s, 9 H, 8); 1.10 \text{ and 1.12 (2 s, 6 H, 6, 7); 1.21 (d, } ^3J_{9,4} = 7.2, 3 \text{ H, 9}); 1.68-2.26 (\text{m, 8 H, 2, 4, 5, 11, 12}); 2.60-3.75 (\text{m, 4 H, 3, 6, 10}); 3.17 (\text{s, 3 H, 17}); 4.15-4.28 (\text{m, 1 H, 13})\]
Experimental part

13C NMR (CDCl₃, 75 MHz): 18.9 (9); 21.4 and 22.9 (15, 17); 25.8 and 26.6 (11, 12); 26.2 (8); 36.0 (7); 37.9 (2); 38.0 (4); 49.5 (17); 50.4 (1); 65.7, 66.4 and 66.7 (3, 5, 13); 77.7 (14); 79.8 (6); 214.2 (1)

7.2.5 Synthesis of 5-(1-hydroxy-2,2-dimethylpropyl)-4-methylcyclopent-2-en-1-one 144

M.F.: C₁₁H₁₈O₂ (M.W. 182.26)

The crude product of 7.2.4 was passed on a flash chromatography column (petroleum ether : ether 55 : 45) to yield 5-(1-hydroxy-2,2-dimethylpropyl)-4-methylcyclopent-2-en-1-one 144.

Yield: 32 mg (78 %)

Aspect: colorless oil

TLC: \( R_f = 0.50 \) (petroleum ether : ether 50 : 50)

¹H NMR (CDCl₃, 300 MHz): 1.00 (s, 9 H, 8); 1.27 (d, \(^3 J_{9,4} = 7.2\), 3 H, 9); 2.10 (dd, \(^3 J_{5,6} = 5.25\), \(^3 J_{5,4} = 2.7\), 1 H, 5); 2.92 (mult, 1 H, 4); 3.39 (dd, \(^3 J_{6,OH} = 6.8\), \(^3 J_{6,5} = 5.25\), 1 H, 6); 3.70 (d, \(^3 J_{OH,6} = 6.8\), 1 H, OH); 6.11 (dd, \(^3 J_{2,3} = 5.7\), \(^4 J_{2,4} = 1.9\), 1 H, 2); 7.60 (dd, \(^3 J_{3,2} = 5.7\), \(^3 J_{3,4} = 2.4\), 1 H, 3)

¹³C NMR (CDCl₃, 50 MHz): 18.9 (9) 26.2 (8); 36.0 (7); 42.7 (4); 55.4 (5); 80.0 (6); 132.5 (2); 169.5 (3); 212.3 (1)

IR (liquid film, cm⁻¹): 1687 (C=O); 2959 (C-H); 3441 (O-H)

Mass (Cl/CH₄-N₂O): 165 ([M-OH]⁺, 100%); 183 ([M+H]⁺, 43%)

Chiral GC (70/0/5/200/10): 21.70 min (major); 22.10 min (minor); ratio 95.6 : 4.4

\([\alpha]_{D}^{20} = +45.2^\circ\) (c=0.177; CHCl₃)

HRMS: calculated for C₁₁H₁₉O₂⁺: 183.138505; found: 183.137882

7.3 Cyclization of 2,2-dimethylhex-4-en-3-one 75 with 52

7.3.1 Synthesis of 1-(1,1,1-triethoxy-4,7,7-trimethyl-6-trimethylsilyloxyoct-5-ene-3-sulfonyl)pyrrolidine 136

M.F.: C₂₂H₄₃NO₆SSi (M.W. 477.73)
Following the general procedure described in 6.1 with:
500 mg (1.616 mmol; 1 eq.) of 1-[(3,3,3-triethoxypropyl)sulfonyl]pyrrolidine 52
875 µl (1.697 mmol; 1.05 eq.) of n-BuLi, 1.94M solution in hexane
224 mg (1.777 mmol; 1.1 eq.) of (E)-2,2-dimethylhex-4-en-3-one 75
790 µl (576 mg; 5.688 mmol; 3.52 eq.) of Et₃N
790 µl (677 mg; 6.222 mmol; 3.85 eq.) of TMSCl
2.250 ml (2.317 g; 12.93 mmol; 8 eq.) of HMPA
15.2 ml of THF
quenched with a saturated solution of NH₄Cl

Yield: 650 mg (84 %) crude product sufficiently pure to be used in the next step.

Aspect: yellow oil

\[ \text{H NMR (CDCl}_3, 300 MHz): 0.27 (s, 9 H, 14); 1.05 (s, 9 H, 12); 1.18 (t, }^{3}J_{7,6} = 7.2, 9 H, 7); 1.21 (d, }^{3}J_{13,8} = 8.1, 3 H, 13); 1.85-1.95 (m, 4 H, 2); 2.17 (dd, }^{3}J_{4,4'} = 15.3, }^{3}J_{4,3} = 6.3, 1 H, 4); 2.30 (dd, }^{2}J_{4,4'} = 14.4, }^{3}J_{4,3} = 1.7, 1 H, 4); 3.14-3.20 (m, 1 H, 3); 3.32-3.44 (m, 1 H, 1); 3.58 (m, 6 H, 6); 4.96 (d, }^{3}J_{9,8} = 9.0, 1 H, 9) \]

\[ \text{C NMR (CDCl}_3, 75 MHz): 1.3 (14); 15.4 (7); 20.4 (13); 26.0 (2); 28.8 (12); 30.8 (4); 31.1 (8); 36.5 (11); 47.7 (1); 57.5 (6); 63.1 (3); 107.0 (9); 113.9 (5); 157.4 (10) \]

\[ \text{IR (liquid film, cm}^{-1}): 845 \text{ (C-Si); 1070 \text{ (C-O); 1141 \text{ (NSO}_2); 1325 \text{ (NSO}_2); 1654 \text{ (C=C-O); 2974 \text{ (C-H)}}) \]

7.3.2 Synthesis of 1-[2,2-bis(ethyloxy)-5-methyl-4-(pyrrolidin-1-ylsulfonyl)-cyclopentyl]-2,2-dimethylpropan-1-one 139

M.F.: C₁₉H₃₅NO₅S (M.W. 389.55)

In a flame-dried two-necked flask equipped with a magnetical stirrer, 625 mg (1.308 mmol; 1 eq.) of 1-(1,1,1-triethoxy-4,7,7-trimethyl-6-trimethylsilyloxyoct-5-
ene-3-sulfonyl)pyrrolidine 136 were dissolved in 8.1 ml of CH$_2$Cl$_2$. The mixture was cooled to -45°C and 25 µl (29 mg; 130.8 µmol; 0.1 eq.) of trimethylsilyl trifluoromethanesulfonate were slowly added. The mixture was stirred for 60 minutes at -45°C. The reaction was then quenched by the addition of a few ml of a saturated solution of NaHCO$_3$ and the mixture was allowed to come to room temperature. The aqueous phase was extracted 3 times with CH$_2$Cl$_2$. The organic phase was washed with water and with a saturated solution of NaCl, dried over MgSO$_4$, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 85 : 15).

Yield: 340 mg (67 %)

Aspect: colorless oil

TLC: R$_f$ = 0.41 (petroleum ether : AcOEt 80 : 20)

$^1$H NMR (CDCl$_3$, 300 MHz): 1.09 and 1.22 (2 t, $^3$J$_{13-12}$ = 7.2, 6 H, 13); 1.14 (s, 9 H, 10); 1.25 (d, $^3$J$_{11-17}$ = 7.0, 3 H, 11); 1.81-1.90 (m, 5 H, 2, 7); 2.26 (dd, $^2$J$_{4-4'}$ = 11.4, $^2$J$_{4-3}$ = 6.0, 1 H, 4); 2.60 (t, $^3$J$_{4-3}$ = $^2$J$_{4-4'}$ = 11.4, 1 H, 4); 2.60-2.78 (m, 1 H, 6); 3.26-3.60 (m, 9 H, 1, 3, 12)

$^{13}$C NMR (CDCl$_3$, 50 MHz): 14.9 and 15.3 (13); 21.4 (11); 26.0 (2); 26.1 (10); 37.4 (4); 36.2 (7); 45.0 (9); 48.4 (1); 56.0 (6); 56.1 and 58.9 (12); 67.0 (3); 77.7 (5); 109.4 (5); 214.2 (8)

IR (liquid film, cm$^{-1}$): 1142 (NSO$_2$); 1324 (NSO$_2$); 1702 (C=O); 2975 (C-H)

Mass (Cl –Q1MS): 153 (100%); 388 ([M-H], 25%)

### 7.3.3 Synthesis of 1-[2,2-bis(ethyloxy)-5-methyl-4-(pyrrolidin-1-ylsulfonyl)-cyclopentyl]-2,2-dimethylpropan-1-ol 141

M.F.: C$_{19}$H$_{37}$NO$_5$S (M.W. 391.56)

In a flame-dried two-necked flask, a solution of 300 mg (770.1 µmol; 1 eq.) of 1-[2,2-bis(ethyloxy)-5-methyl-4-(pyrrolidin-1-ylsulfonyl)cyclopentyl]-2,2-dimethylpropan-1-
one 139 in 9.7 ml of Et₂O was slowly added to a suspension of 14 mg (385 µmol; 0.5 eq.) of lithium aluminum hydride in Et₂O at 0°C. The mixture was stirred for 20 minutes at 0°C. A few ml of a saturated solution of NaHCO₃ were added. The aqueous phase was extracted with Et₂O. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

**Yield:** 260 mg (86 %)

**Aspect:** colorless oil

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\text{NH} & \quad \text{S} \\
\text{OH-6} & \quad \text{O} \\
\end{align*}
\]

**¹H NMR** (CDCl₃, 300 MHz): 0.98 (s, 9 H, 9); 1.22 (mult, 12 H, 8, 9); 1.75-1.98 (m, 4 H, 12); 2.38 and 2.50 (2 mult, 2 H, 4, 5); 3.15-3.58 (m, 9 H, 6, 10, 12); 4.28 (d, \(^3J_{OH-6} = 7.8\), 1 H, OH)

**¹³C NMR** (CDCl₃, 75 MHz): 15.1 and 15.4 (11); 26.1 (9); 26.3 (13); 27.1 (8); 36.4 (7); 38.3 (2); 40.5 (4); 48.1 (12); 50.5 (5); 56.3 and 58.8 (10); 64.7 (3); 82.7 (6); 109.4 (1)

**IR** (liquid film, cm⁻¹): 1145 (NSO₂); 1324 (NSO₂); 2975 (C-H); 3490 (O-H)

**Mass** (Cl/CH₄-N₂O): 84 (77%); 125 (100%); 167 ([M-OEt-SO₂NC₄H₈]⁺, 27%); 211 ([M-OEt-SO₂NC₄H₈]⁺, 73%); 374 ([M-OH]⁺, 1%)

### 7.3.4 Synthesis of 2-(1-hydroxy-2,2-dimethylpropyl)-3-methyl-4-(pyrrolidin-1-ylsulfonyl)cyclopentanone 143

**M.F.:** C\(_{15}\)H\(_{27}\)NO\(_4\)S (M.W. 317.44)

In a two-necked flask, 200 mg (511 µmol; 1 eq.) of 141 were dissolved in a mixture of 2.7 ml of acetone and 2.7 ml of H₂O. The mixture was cooled to 0°C and 38 mg (153.2 µmol; 0.3 eq) of pyridinium para-toluenesulfonate were added. The mixture was stirred for 30 minutes at 0°C and for 60 minutes at room temperature. A few ml of a saturated solution of NaHCO₃ were then added. The aqueous phase was extracted 5 times with CH₂Cl₂. The organic phase was washed with water and with a
saturated solution of NaCl, dried over MgSO₄, filtered and evaporated under reduced pressure.

**Yield:** 123 mg (76 %)

**Aspect:** colorless oil

![Chemical structure](image)

**H NMR** (CDCl₃, 300 MHz): 0.89 (s, 9 H, 8); 1.33 (d, 3 H, 9); 1.82-1.93 (m, 4 H, 11); 2.13 (mult, 1 H, 4); 2.52-2.68 (m, 3 H, 2, 5); 3.21-3.42 (m, 6 H, 3, 10, OH)

**13C NMR** (CDCl₃, 50 MHz): 18.4 (9); 25.8 (11); 26.1 (8); 35.6 (7); 38.4 (4); 41.1 (2); 48.4 (10); 57.6 and 61.9 (3, 5); 79.1 (6); 212.3 (1)

7.3.5 *Synthesis of 5-(1-hydroxy-2,2-dimethylpropyl)-4-methylcyclopent-2-en-1-one* 144

**M.F.:** C₁₁H₁₈O₂ (M.W. 182.26)

The crude product of 7.3.4 was passed on a flash chromatography column (petroleum ether : ether 55 : 45) to yield 5-(1-hydroxy-2,2-dimethylpropyl)-4-methylcyclopent-2-en-1-one 144.

**Yield:** 53 mg (75 %)

Analyses were identical to that of 7.2.5
8 Phase-transfer catalysis: sulfur-containing nucleophiles

8.1 Sulfones as nucleophiles

8.1.1 Synthesis of ethylphenylsulfone 157

M.F.: C₈H₁₀O₂S (M.W. 170.22)  RN: 599-70-2

To a solution of 1 ml (1.021 g; 7.386 mmol; 1 eq.) of ethylphenylsulfide in 25 ml of CH₂Cl₂ were added 4 g (16.25 mmol; 2.2 eq.) of 3-chloroperoxybenzoic acid dissolved in CH₂Cl₂. After 2 hours of reaction, the mixture was poured into a saturated solution of NaHCO₃. The aqueous phase was extracted with CH₂Cl₂. The organic phase was washed with a solution of 10% KOH, dried over MgSO₄, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 1.263 g (quant.)

TLC: Rₓ = 0.63 (petroleum ether : AcOEt 60 : 40)

¹H NMR (CDCl₃, 200 MHz): 1.28 (t, ³J₁₂ = 7.4, 3 H, 1); 3.13 (q, ³J₂₁ = 7.4, 2 H, 2); 7.53-7.72 (m, 3 H, 5, 6); 7.92 (mult, 2 H, 4)
¹³C NMR (CDCl₃, 50 MHz): 7.3 (1); 50.4 (2); 128.1 (4); 129.2 (5); 133.6 (6); 138.6 (3)
IR (liquid film, cm⁻¹): 1145 (S=O); 1307 (S=O); 2983 (C-H); 3065 (C-Harom.)
Mass (Cl +Q1MS): 171 ([M+H]⁺, 100%); 341 ([2M+H]⁺, 33%)
GC (100/0/10/290/15): tᵣ = 9.00 min

Elemental analysis:
calculated (%): C: 56.44; H: 5.92; O: 18.79; S: 18.83
found (%): C: 56.6; H: 5.83; O: 18.82; S: 18.75

8.1.2 Synthesis of ethylphenylsulfone d₂ 228

M.F.: C₈H₈D₂O₂S (M.W. 172.234)
A mixture of 50 mg (293.7 µmol; 1 eq.) of ethylphenylsulfone 157, 90 ml (881.1 µmol; 3 eq.) of sodium deuteroxide, 30% solution in D₂O, 99+ atom % d, 7 mg (29.37 µmol; 0.1 eq.) of benzyltriethylammonium chloride and 0.7 ml of CH₂Cl₂ was stirred for 5 hours at room temperature. After that time, 1 ml of a dilute solution of D₂SO₄ in D₂O was added. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

¹H NMR showed that the protons α to the sulfone had been replaced by deuterium.

¹H NMR (CDCl₃, 200 MHz): 1.27 (s, 3 H, 1); 7.61 (mult, 3 H, 5, 6); 7.92 (mult, 2 H, 4)

### 8.2 α-Sulfonylcarboxylic esters as nucleophiles

#### 8.2.1 Synthesis of methyl 2-(phenylsulfanyl)propanoate 160

**M.F.:** C₁₀H₁₂O₂S (M.W. 196.26)  
**RN: 21673-18-7**

In a flame-dried two-necked flask, 1 ml (1.497 g; 8.963 mmol; 1 eq.) of methyl 2-bromopropionate, 920 µl (987 mg; 8.963 mmol; 1 eq.) of thiophenol and 1.245 ml (907 mg; 8.963 mmol; 1 eq.) of Et₃N were mixed together in 23 ml of Et₂O and stirred for 16 hours. After this time, the mixture was filtered and the solvent was removed under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 90 : 10).

**Yield:** 1.629 g (93 %)

**Aspect:** colorless oil

**TLC:** Rᵢ = 0.37 (petroleum ether : AcOEt 95 : 5); 0.8 (petroleum ether : AcOEt 90 : 10)

¹H NMR (CDCl₃, 300 MHz): 1.49 (d, ³J₁-₂ = 7.1, 3 H, 1); 3.67 (s, 3 H, 4); 3.79 (q, ³J₂-₁ = 7.1, 1 H, 2); 7.31 (mult, 3 H, 6, 8); 7.45 (mult, 2 H, 7)
8.2.2 Synthesis of methyl 2-(phenylsulfonyl)propanoate 158

**M.F.:** C$_{10}$H$_{12}$O$_4$S (**M.W.** 228.26)  
**RN:** 85979-85-7

8.345 g (33.85 mmol; 2.2 eq.) of 3-chloroperoxybenzoic acid dissolved in CH$_2$Cl$_2$ were added to a solution of 3.02 g (15.38 mmol; 1 eq.) of methyl 2-(phenylsulfonyl)propanoate 160 in 52 ml of CH$_2$Cl$_2$. After 2 hours, the reaction mixture was poured into a saturated solution of NaHCO$_3$. The aqueous phase was extracted with CH$_2$Cl$_2$. The organic phase was dried over MgSO$_4$, filtered and evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 2.99 g (85 %)

**TLC:** $R_f = 0.18$ (petroleum ether : AcOEt 80 : 20)

$^1$H NMR (CDCl$_3$, 300 MHz): 1.57 ($d$, $^3J_{1,2} = 7.2$, 3 H, 1); 3.68 ($s$, 3 H, 4); 4.17 ($q$, $^3J_{2,1} = 7.2$, 1 H, 2); 7.58 ($mult$, 2 H, 7); 7.70 ($tt$, $^3J_{8,7} = 7.4$, $^4J_{8,6} = 1.26$, 1 H, 8); 7.87-7.90 ($m$, 2 H, 6)

$^{13}$C NMR (CDCl$_3$, 50 MHz): 11.8 (1); 52.9 (4); 65.3 (2); 129.0 and 129.3 (6, 7); 134.3 (8); 137.0 (5); 166.7 (3)

**IR** (liquid film, cm$^{-1}$): 1454; 1585; 1734 (C=O); 2955 (C-H); 3003; 3066

**Mass** (Cl$^+$+Q1MS): 89 (100%); 229 ([M+H]$^+$, 20%)

**GC** (100/0/10/290/15): $t_R = 13.29$ min
8.2.3 Synthesis of methyl 2-(phenylsulfonyl)butanoate 161

**M.F.:** C\textsubscript{11}H\textsubscript{14}O\textsubscript{4}S (M.W. 242.28) \hspace{1cm} **RN:** 129585-56-4

A mixture of 780 µl (1 g; 4.667 mmol; 1 eq.) of methyl phenylsulfonylacetae, 373 µl (728 mg; 4.667 mmol; 1 eq.) of iodoethane and 645 mg (4.667 mmol; 1 eq.) of potassium carbonate in 17 ml of acetone was refluxed for 88 hours. After that time, the reaction was complete and the mixture was passed through a short pad of celite. The solvent was removed under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 70 : 30).

**Yield:** 930 mg (82 %)

\[
\begin{align*}
\text{1H NMR (CDCl}_3, 300 MHz):} & 0.97 (t, \ ^3J_{5,4} = 7.5, 3 H, 5); 2.02 (\text{mult}, 2 H, 4); 3.69 (s, 3 H, 1); 3.89 (dd, \ ^3J_{3,4} = 11.4, \ ^3J_{3,4} = 4.2, 1 H, 3); 7.59 (\text{mult}, 2 H, 8); 7.68 (\text{mult}, 1 H, 9); 7.88 (\text{mult}, 2 H, 7) \\
\text{13C NMR (CDCl}_3, 75 MHz):} & 11.3 (5); 20.5 (4); 52.8 (1); 72.1 (3); 128.9 and 129.2 (7, 8); 134.2 (9); 136.9 (6); 166.2 (2) \\
\text{Mass (Cl +Q1MS):} & 89 (100%); 243 ([M+H]^{+}, 87%)
\end{align*}
\]

8.2.4 Synthesis of [(1-(phenylsulfonyl)propyl)sulfonyl]benzene 162

**M.F.:** C\textsubscript{15}H\textsubscript{16}O\textsubscript{4}S\textsubscript{2} (M.W. 324.40) \hspace{1cm} **RN:** 110945-04-5

In a flask equipped with a reflux condenser, a mixture of 100 mg (337.4 µmol; 1 eq.) of bis(phenylsulfonyl)methane, 27 µl (52 mg; 337.4 µmol; 1 eq.) of iodoethane, 47 mg (337.4 µmol; 1 eq.) of potassium carbonate and 8 mg (33.74 µmol, 0.1 eq.) of benzyltriethylammonium chloride in 1.2 ml of acetone was refluxed for 16 hours. After that time, the reaction was complete and the mixture was passed through a short pad of celite. The solvent was removed under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).
Yield: 105 mg (96%)

TLC: $R_f = 0.59$ (petroleum ether : AcOEt 60 : 40)

$\text{H NMR (CDCl}_3, 300 \text{ MHz)}$: 1.17 ($t$, $^3J_{3-2} = 7.5$, 3 H, 3); 2.21 ($\text{mult}$, 2 H, 2); 4.35 ($t$, $^3J_{1-2} = 5.7$, 1 H, 1); 7.58 ($\text{mult}$, 4 H, 6); 7.71 ($\text{mult}$, 2 H, 7); 7.97 ($dd$, $^3J_{5-6} = 7.2$, $^4J_{5-7} = 1.2$, 4 H, 5)

$\text{C NMR (CDCl}_3, 75 \text{ MHz)}$: 12.9 (3); 19.5 (2); 85.0 (1); 129.0 and 129.4 (5, 6); 134.5 (7); 137.8 (4)

Mass (CI +Q1MS): 84 (100%); 87 (100%); 325 ([M+H]$^+$, 50%)

GC (100/0/10/290/15): $t_R = 20.64$ min

8.2.5 Synthesis of methyl 2-methyl-3-phenyl-2-(phenylsulfonyl)propanoate 163

M.F.: C$_{17}$H$_{18}$O$_4$S (M.W. 318.38)

A mixture of 50 mg (219 µmol; 1 eq.) of methyl 2-(phenylsulfonyl)propanoate 158, 123 mg (2.19 mmol; 10 eq.) of potassium hydroxyde and 5 mg (21.9 µmol; 0.1 eq.) of benzytriethylammonium chloride in 0.5 ml of CH$_2$Cl$_2$ was stirred for 15 minutes. Then 130 µl (187 mg; 1.095 mmol; 5 eq.) of benzyl bromide were added and the mixture was stirred for 3 hours. It was then passed through a small pad of celite. The solvent was removed under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 80 : 20).

Yield: 60 mg (86 %)

Aspect: colorless oil

TLC: $R_f = 0.33$ (AcOEt : petroleum ether 20 : 80)
8.2.6 *Synthesis of methyl 2-(3-oxocyclohexyl)-2-(phenylsulfonyl)propanoate*

**M.F.:** C_{16}H_{20}O_{5}S (M.W. 324.39)

A mixture of 100 mg (438 µmol; 1 eq.) of methyl 2-phenylsulfonylpropanoate 158, 6 mg (43.8 µmol; 0.1 eq.) of potassium carbonate and 11 mg (43.8 µmol; 0.1 eq.) of 18-crown-6 in 2.75 ml of acetone was stirred for 15 minutes. 55 ml (55 mg, 569.5 µmol; 1.3 eq.) of 2-cyclohexen-1-one were added. As there was no reaction after 24 hours, 54 mg (394.2 µmol; 0.9 eq.) of potassium carbonate were added and the mixture was stirred for another 24 hours. It was the passed through a short pad of celite and the solvent was removed under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 113 mg (79 %)

**Aspect:** white solid

**TLC:** R_f = 0.51 and 0.62 (petroleum ether : AcOEt 60 : 40) (2 diastereomers)
**Experimental part**

**H NMR** (CDCl₃, 300 MHz):

1ˢᵗ diastereomer: 1.51-1.75 (m, 3 H, 13, 14); 1.64 (s, 3 H, 1); 1.85-1.98 (m, 1 H, 13, 14); 2.04 (mult, 1 H, 10); 2.10-2.49 (m, 2 H, 12); 2.50-2.62 (m, 1 H, 10); 2.94 (mult, 1 H, 9); 3.56 (s, 3 H, 4); 7.55 (mult, 2 H, 7); 7.65 (mult, 1 H, 8); 7.75 (mult, 2 H, 6)

2ⁿᵈ diastereomer: 1.45-1.52 (m, 2 H, 13 or 14); 1.64 (s, 3 H, 1); 2.00-2.10 (m, 2 H, 13 or 14); 2.25 (mult, 1 H, 10); 2.30-2.45 (m, 2 H, 12); 2.80-2.95 (m, 1 H, 9); 3.03 (mult, 1 H, 10); 3.59 (s, 3 H, 4); 7.55 (mult, 2 H, 7); 7.67 (mult, 1 H, 8); 7.82 (mult, 2 H, 6)

**C NMR** (CDCl₃, 50 MHz):

1ˢᵗ diastereomer: 12.3 (1); 24.4 and 26.3 (13, 14); 40.7 (9); 41.0 (12); 43.5 (10); 53.0 (4); 76.6 (2); 128.8 and 130.0 (6, 7); 134.3 (8); 136.7 (5); 168.1 (3); 208.6 (11)

2ⁿᵈ diastereomer: 12.5 (1); 24.4 and 27.4 (13, 14); 40.6 (9); 40.7 (12); 42.8 (10); 52.9 (4); 76.5 (2); 128.8 and 130.2 (6, 7); 134.2 (8); 136.5 (5); 168.4 (3); 208.6 (11)

**Mass** (CI +Q1MS): 69 (75%); 87 (100%); 193 (56%); 229 (24%); 325 ([M+H]+, 28%)

**GC** (100/0/10/290/20): tᵣ = 21.78 min and tᵣ = 22.08 min (2 diastereomers)

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8.2.7 **Synthesis of methyl (3-oxocyclohexyl)(phenylsulfonyl)acetate 229**

**M.F.:** C₁₅H₁₈O₅S (M.W. 310.36)

A mixture of 100 mg (466.7 µmol; 1 eq.) of methyl phenylsulfonylacetate, 161 mg (1.166 mmol; 2.5 eq.) of potassium carbonate and 11 mg (46.67 µmol; 0.1 eq.) of benzyltriethylammonium chloride in 2.6 ml of CH₂Cl₂ was stirred for 15 minutes at room temperature before 59 µl (58 mg; 606.8 µmol; 1.3 eq.) of 2-cyclohexen-1-one and 19 µl (14 mg; 466.7 µmol; 1 eq.) of MeOH were added. The mixture was stirred for 3 hours. It was then passed through a short pad of celite and the solvent was evaporated under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 94 mg (65 %)
Experimental part

\[1^H \text{NMR} (\text{CDCl}_3, 300 \text{ MHz}): 1.52-2.46 (2 \text{ m}, 8 \text{ H}, 9, 11, 12, 13); 2.58-2.89 (2 \text{ m}, 2 \text{ H}, 8); 3.51 \text{ and } 3.58 (2 \text{ s}, 3 \text{ H}, 1); 3.91 \text{ and } 3.97 (2 \text{ d}, ^3J_{3,3'} = 8.1, ^2J_{3,8} = 7.8, 1 \text{ H}, 3); 7.58 (\text{ mult}, 2 \text{ H}, 6); 7.70 (\text{ mult}, 1 \text{ H}, 7); 7.91 (\text{ mult}, 2 \text{ H}, 5)\]

\[13C \text{NMR} (\text{CDCl}_3, 50 \text{ MHz}): 24.2 (12); 28.3 \text{ and } 29.2 (13); 37.0 \text{ and } 37.05 (8); 40.7 \text{ and } 40.75 (11); 44.4 \text{ and } 45.5 (9); 52.6 \text{ and } 52.7 (1); 74.7 \text{ and } 74.8 (3); 128.9 \text{ and } 129.0 (5, 6); 134.3 (7); 138.0 (4); 165.4 (2); 207.9 (10)\]

\[\text{Mass (Cl/CH}_4\text{-N}_2\text{O): 83 (100\%); 101 (35\%); 311 ([M+H]^+}, 2\%\)

8.2.8 Synthesis of methyl 2-(3-oxocyclohexyl)-2-(phenylsulfonyl)butanoate

**M.F.:** C\(_{17}\)H\(_{22}\)O\(_5\)S (**M.W.** 338.41)

A mixture of 75 mg (308.2 µmol; 1 eq.) of methyl 2-phenylsulfonylbutanoate 161, 106 mg (770.6 µmol; 2.5 eq.) of potassium carbonate and 7 mg (30.82 µmol; 0.1 eq.) of benzyltriethylammonium chloride in 3 ml of \(N,N\)-dimethylformamide was stirred for 15 minutes before 39 µl (38 mg; 400.7 µmol; 1.3 eq.) of 2-cyclohexen-1-one and 12 µl (9.877 mg; 308.2 µmol; 1 eq.) of MeOH were added. The mixture was stirred for 90 minutes. It was then passed through a short pad of celite and the solvent was removed under reduced pressure.

The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 31 mg (30 \%) 

**TLC:** \(R_f = 0.52\) (petroleum ether : AcOEt 60 : 40)
8.2.9 Synthesis of 3-[bis(phenylesulfonyl)methyl]cyclohexanone 231

M.F.: C₁₉H₂₀O₅S₂ (M.W. 392.48)

A mixture of 100 mg (337.4 µmol; 1 eq.) of bis-(phenylsulfonyl)methane, 116 mg (843.5 µmol; 2.5 eq.) of potassium carbonate and 8 mg (33.74 µmol; 0.1 eq.) of benzyltriethylammonium chloride in 3 ml of acetone was stirred for 15 minutes at room temperature before 42 µl (42 mg; 438.6 µmol; 1.3 eq.) of 2-cyclohexen-1-one and 14 µl (10 mg; 337.4 µmol; 1 eq.) of MeOH were added. The mixture was stirred for 16 hours. As no reaction occurred after this time, the mixture was heated to reflux for 24 hours. After being cooled to room temperature, it was passed through a short pad of celite and the solvent was removed under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 28 mg (21 %)
9 Phase-transfer catalysis: nitro-containing nucleophiles

9.1 Synthesis of ketals

9.1.1 Synthesis of 3-nitropropanal 166

M.F.: C₃H₅NO₃ (M.W. 103.07)  
RN: 58657-26-4


In a flame-dried two-necked flask equipped with a reflux condenser, 20 ml (16.78 g; 299.2 mmol; 1 eq.) of acrolein and 25.83 g (374.3 mmol; 1.25 eq.) of sodium nitrite were dissolved in 120 ml of THF. The mixture was cooled to 0°C and 21.4 ml (22.44 g; 373.8 mmol; 1.24 eq.) of acetic acid were slowly added over a period of 30 minutes. The mixture was stirred for 3 hours. After that time, water was added to dissolve the salts that had formed. The aqueous phase was extracted 4 times with CH₂Cl₂. The organic phase was washed twice with a saturated solution of NaHCO₃, twice with a saturated solution of NaCl and once with water, then dried over MgSO₄, filtered and evaporated under reduced pressure.

The product was purified by bulb-to-bulb distillation (60°C at 9·10⁻³ mbar).

Yield: 11.02 g (36 %)
**9.1.2 Synthesis of 2-(2-nitroethyl)-1,3-dioxolane 167**

**M.F.:** C₅H₉NO₄ (M.W. 147.13)  \hspace{1cm} **RN: 82891-99-4**

In a flask equipped with a Dean-Stark apparatus, 500 mg (4.85 mmol; 1 eq.) of 3-nitropropanal 166, 297 µl (331 mg; 5.335 mmol; 1.1 eq.) of ethylene glycol and 46 mg (242.5 µmol; 0.05 eq.) of para-toluenesulfonic acid monohydrate were put into 11 ml of benzene. The mixture was heated to reflux until a constant volume of water was collected. It was then cooled to room temperature and the solvent was removed under reduced pressure.

The product was purified by flash chromatography (mounting: petroleum ether : AcOEt 80 : 20 + 5% Et₃N; elution: petroleum ether : AcOEt 80 : 20).

**Yield:** 485 mg (68 %)

**Aspect:** yellow liquid

**1H NMR** (CDCl₃, 200 MHz): 2.44 (dt, 3J₁₂ = 6.8, 2H, 2); 3.97 and 3.89 (2 mult, 4 H, 4); 4.51 (t, 3J₁₂ = 6.8, 2H, 1); 5.04 (t, 3J₃₂ = 3.7, 1 H, 3)

**13C NMR** (CDCl₃, 50 MHz): 30.7 (2); 65.1 (4); 69.9 (1); 101.0 (3)

**IR** (liquid film, cm⁻¹): 1045; 1141; 1377; 1556 (NO₂); 1735; 2982 (C-H)

**Mass** (Cl/CH₄-N₂O): 73 (85%); 101 ([M-NO₂]⁺, 100%); 148 ([M+H]⁺, 87%)

**GC** (100/0/10/290/20): tᵣ = 5.74 min

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**9.1.3 Synthesis of 1,1-diethoxy-3-nitropropane 168**

**M.F.:** C₇H₁₅NO₄ (M.W. 177.2)  \hspace{1cm} **RN: 107833-73-8**

In a flame-dried two-necked flask equipped with a tube of silicagel, 1.192 g (11.56 mmol; 1 eq.) of freshly distilled 3-nitropropanal 166 dissolved in 9 ml of EtOH were reacted with 2.308 ml (2.056 g; 13.87 mmol; 1.2 eq.) of triethyl orthoformate and 69 mg (364.7 µmol; 0.0315 eq.) of para-toluenesulfonic acid monohydrate for 16 hours. The volatile compounds were removed under reduced pressure. The residue was neutralized with a saturated solution of NaHCO₃. The aqueous phase was extracted with Et₂O. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by bulb-to-bulb distillation (65°C at 2.6·10⁻² mbar).

Yield: 2.019 g (98 %)

Aspect: yellow liquid

\[ \text{1H NMR (CDC\textsubscript{3}, 300 MHz): } 1.22 (t, ^3J_{5,4} = 6.6, 6 \text{ H, 5}); 2.32 (q, ^3J_{2,1} = ^3J_{2,3} = 5.1, 2 \text{ H, 2}); 3.69-3.51 (2 \text{ mult}, 4 \text{ H, 4}); 4.49 (t, ^3J_{1,2} = 6.9, 2 \text{ H, 1}); 4.61 (t, ^3J_{3,2} = 5.4, 1 \text{ H, 3})\]

\[ \text{13C NMR (CDC\textsubscript{3}, 50 MHz): } 15.1 (5); 31.6 (2); 62.5 (4); 71.3 (1); 100.0 (3)\]

IR (liquid film, cm⁻¹): 1055; 1375; 1558 (NO₂); 1739; 3981 (C-H)

Mass (Cl/CH₄-N₂O): 85 (100%); 132 ([M-OEt]⁺, 29%)  

b.p.: 65°C (2.6·10⁻² mbar)

GC (100/0/10/290/20): tR = 5.72 min

### 9.1.4 Synthesis of 2-(2-nitroethyl)-1,3-dioxane 169

M.F.: C₆H₁₁NO₄ (M.W. 161.15)  

RN: 146073-16-7

In a flame-dried two-necked flask, 297 mg (4.312 mmol; 1.17 eq.) of sodium nitrite were dissolved in 3.7 ml of DMSO. 0.5 ml (715 mg; 3.668 mmol; 1 eq.) of 2-(2-bromoethyl)-1,3-dioxane were added. The mixture was stirred for 27 hours and then poured into an Erlenmeyer containing a mixture of ice and Et₂O. The aqueous phase was extracted with Et₂O. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (mounting: petroleum ether : AcOEt 80 : 20 + 5% Et₃N; elution: petroleum ether : AcOEt 80 : 20).
Yield: 438 mg (74 %)

Aspect: colorless liquid

$^1$H NMR (CDCl$_3$, 300 MHz): 1.35 (mult, 1 H, 5$_{ax}$); 2.05 (mult, 1 H, 5$_{eq}$); 2.30 (dt, 3$J_{2,1}$ = 6.6, 3$J_{2,3}$ = 4.8, 2 H, 2); 3.76 (dt, 3$J_{4,5}$ = 12; 2$J_{4,4'}$ = 2.1, 2 H, 4$_{ax}$); 4.10 (mult, 2 H, 4$_{eq}$); 4.52 (t, 3$J_{1,2}$ = 6.9, 2 H, 1); 4.72 (t, 3$J_{3,2}$ = 4.8, 1 H, 3)

IR (liquid film, cm$^{-1}$): 1141; 1241; 1377; 1555 (NO$_2$); 1738; 2978 (C-H)

Mass (CI/CH$_4$-N$_2$O): 87 (19%); 115 ([M-NO$_2$]$^+$, 100%); 162 ([M+H]$^+$, 11%)

GC (100/0/10/290/20): $t_R$ = 8.01 min

9.2 Synthesis of orthoester

9.2.1 Synthesis of 3-nitropropanal dimethylhydrazone 173

M.F.: C$_5$H$_{11}$N$_3$O$_2$ (M.W. 145.16)


A mixture of 2 g (19.4 mmol; 1 eq.) of 3-nitropropanal 166, 1.547 ml (1.224 g; 20.37 mmol; 1.05 eq.) of 1,1-dimethylhydrazine and 2.101 g (17.46 mmol; 0.9 eq.) of magnesium sulfate in 31.5 ml of CH$_2$Cl$_2$ was stirred for 6 hours at 0°C. It was then filtered and the solvent was removed under reduced pressure.

The product, highly unstable, is obtained sufficiently pure to be used without purification.

Yield: 2.755 g (98 %)

$^1$H NMR (CDCl$_3$, 300 MHz): 2.75 (s, 6 H, 4); 2.91 (dt, 3$J_{2,1}$ = 6.6, 3$J_{2,3}$ = 3.9, 2 H, 2); 4.61 (t, 3$J_{1,2}$ = 6.6, 2 H, 1); 6.55 (t, 3$J_{3,2}$ = 3.9, 1 H, 3)
9.2.2 Synthesis of 3-nitropropanenitrile 171

M.F.: C₃H₄N₂O₂ (M.W. 100.07) RN: 35461-45-1

References:

To an ice-cooled solution of 22.53 g (36.44 mmol; 2.5 eq.) of monoperoxyphthalic acid, magnesium salt hexahydrate, 80% in 114 ml of MeOH were added 2.116 g (14.57 mmol; 1 eq.) of 3-nitropropanal dimethylhydrazone 173 dissolved in 14.2 ml of MeOH. The solution was stirred for 5-10 minutes and then poured into a mixture of 355 ml of water and 355 ml of CH₂Cl₂. The organic phase was washed once with a saturated solution of NaCl, twice with water, then dried over MgSO₄, filtered and evaporated under reduced pressure. As only a small quantity of product was found in the organic phase, the aqueous phases were extracted with CHCl₃. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.
The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 921 mg (63 %)

¹H NMR (CDCl₃, 200 MHz): 3.09 (t, ³J₂,₁ = 6.8, 2 H, 2); 4.66 (t, ³J₁,₂ = 6.7, 2 H, 1)
¹³C NMR (CDCl₃, 50 MHz): 15.6 (2); 69.1 (1); 115.4 (3)
IR (liquid film, cm⁻¹): 1380; 1560 (NSO₂); 2260 (C=N); 2980 (C-H)
Mass (CI/CH₄-N₂O): 82 (48%); 101 ([M+H]+, 100%); 154 (17%); 201 ([2M+H]+, 21%)
GC (100/0/10/290/15): tᵣ = 4.19 min

9.2.3 Synthesis of 3-ethyloxetan-3-yl 3-bromopropanoate 176

M.F.: C₉H₁₅BrO₃ (M.W. 251.12)


1 ml (1.019 g; 8.772 mmol; 1eq.) of 3-ethyl-3-oxetanemethanol was solubilized in 17.5 ml of THF and 852 µl (833 mg; 10.53 mmo; 1.2 eq.) of pyridine. The mixture was cooled to 0°C and 975 µl (1.66 g; 9.684 mmoles; 1.1 eq.) of 3-bromopropionyle
chloride were added. The mixture was stirred for 2 hours and the reaction was quenched by the addition of water. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was obtained sufficiently pure to be used without purification.

Yield: 2.194 (quant.)

\[
\begin{align*}
\text{H NMR} \ (\text{CDCl}_3, \ 300 \text{ MHz}): & \ 0.93 \ (t, \ 3J_{6-7} = 7.5, \ 3 \text{ H}, \ 8); \ 1.78 \ (q, \ 3J_{7,8} = 7.2, \ 2 \text{ H}, \ 7); \\
& \ 2.99 \ (t, \ 3J_{2,1} = 6.6, \ 2 \text{ H}, \ 2); \ 3.61 \ (t, \ 3J_{1,2} = 6.9, \ 2 \text{ H}, \ 1); \ 4.30 \ (s, \ 2 \text{ H}, \ 4); \ 4.43 \text{ and } 4.50 \\
& \ (2d, \ 2J_{6,6'} = 6.0, \ 4 \text{ H}, \ 6) \\
\text{IR} \ (\text{liquid film}, \ \text{cm}^{-1}): & \ 1740 \ (\text{C=O}); \ 2965 \ (\text{C-H}) \\
\text{Mass} \ (\text{Cl/CH}_4\cdot\text{N}_2\text{O}): & \ 99 \ ([\text{M-BrCH}_2\text{CH}_2\text{CO}_2]^+, \ 78\%); \ 251 \ ([\text{M+H}]^+ (^{79}\text{Br}), \ 96\%); \ 253 \\
& \ ([\text{M+H}]^+ (^{81}\text{Br}), \ 100\%)
\end{align*}
\]

9.2.4 Synthesis of 1-(2-bromoethyl)-4-ethyl-2,6,7-trioxabicyclo[2,2,2]octane

M.F.: C₉H₁₅BrO₃ (M.W. 251.12)


In a flame-dried two-necked flask, 9 g (35.83 mmol; 1 eq.) of (3-ethyloxetan-3-yl)methyl 3-bromopropionate were dissolved in 38.6 ml of CH₂Cl₂. The mixture was cooled to 0°C and 1.262 ml (1.424 g; 10.03 mmol; 0.28 eq.) of trifluoroborane diethyl etherate were added. After 3 hours of stirring at 0°C the reaction was quenched by the addition of 5.579 ml (4.061 g; 40.14 mmol; 1.12 eq.) of Et₃N. Et₂O was added and the precipitate that formed was eliminated by filtration. The filtrate was evaporated under reduced pressure.

The product was purified by flash chromatography (mounting: petroleum ether : AcOEt 80 : 20 + 10% Et₃N; elution: petroleum ether : AcOEt 80 : 20).

Yield: 5.949 g (66 %)
Experimental part

$^1$H NMR (CDCl$_3$, 300 MHz): 0.83 ($t, 3J_{7,6} = 7.8, 3$ H, 7); 1.24 ($q, 3J_{6,7} = 7.8, 2$ H, 6); 2.26 ($mult, 2$ H, 2); 3.42 ($mult, 2$ H, 1); 3.91 (s, 6 H, 4)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 7.6 (7); 22.5 (6); 26.1 (2); 33.2 (5); 40.5 (1); 71.0 (4); 108.0 (3)

Mass (Cl/CH$_4$N$_2$O): 99 (28%); 171 ([M-Br]$^+$, 44%); 251 ([M+H]$^+$ ($^{79}$Br), 95%); 253 ([M+H]$^+$ ($^{81}$Br), 100%)

Elemental analysis:
calculated (%): C: 43.05; H: 6.02; Br: 31.82
found (%): C: 43.69; H: 6.23; Br: 32.59

9.2.5 Attempted synthesis of 4-ethyl-1-(2-nitroethyl)-2,6,7-trioxabicyclo[2.2.2]octane 232


In a flame-dried flask, 97 mg (1.404 mmoles; 1.17 eq.) of sodium nitrite were put into 1.2 ml of DMSO. 300 mg (1.194 mmol; 1 eq.) of 1-(2-bromoethyl)-4-ethyl-2,6,7-trioxabicyclo[2,2,2]octane were added and the mixture was stirred for 27 hours. It was then poured into an Erlenmeyer containing a mixture of ice and Et$_2$O. The aqueous phase was extracted with Et$_2$O. The organic phase was dried over MgSO$_4$, filtered and evaporated under reduced pressure.
The product obtained resulted from the substitution of the bromide by the nitrite and simultaneous hydrolysis of the orthoester function.

9.3 Michael addition of nitro-compounds: racemic

9.3.1 General procedure

A mixture of 1 eq. of the corresponding nitro-compound, 2.5 eq. of potassium carbonate and 0.1 eq. of the catalyst in the desired solvent were stirred for 15 minutes at room temperature before 1.3 eq. of the Michael acceptor were added. The mixture was stirred for x hours and then passed through a short pad of celite. The solvent was removed under reduced pressure.
The product was purified by flash chromatography.
9.3.2 Addition of nitroethane to cyclohexenone

Following the general procedure described in 9.3.1 with:
50 µl (52 mg; 696 µmol; 1 eq.) of nitroethane
240 mg (1.74 mmol; 2.5 eq.) of potassium carbonate
16 mg (69.6 µmol; 0.1 eq.) of benzyltriethylammonium chloride
88 µl (86 mg; 904.8 µmol; 1.3 eq.) of 2-cyclohexen-1-one
3.8 ml of CH₂Cl₂
Reaction time: 4 hours
Flash chromatography: petroleum ether : AcOEt 60 : 40
Yield: 80 mg (67%) as a mixture of 2 diastereomers

3-(1-nitroethyl)cyclohexanone 177
M.F.: C₈H₁₃NO₃ (M.W. 171.19)  RN: 59969-93-6

Aspect: yellow oil
TLC: Rᵥ = 0.5 (petroleum ether : AcOEt 60 : 40)

¹H NMR (CDCl₃, 300 MHz): 1.53 (t, J₂₁ = 6.6, 3 H, 2); 1.58-2.49 (m, 9 H, 3, 4, 6, 7, 8); 4.49 (mult, 1 H, 1)
¹³C NMR (CDCl₃, 75 MHz): 16.1 (2'); 16.3 (2); 24.2 and 26.9 (7, 8); 24.3 and 27.4 (7', 8'); 40.8 (6); 42.3 (3'); 42.4 (3); 43.2 (4'); 43.6 (4); 86.9 (1); 208.3 (5)
IR (liquid film, cm⁻¹): 1547 (NO₂); 1715 (C=O); 2950 (C-H)
Mass (Cl +Q₁MS): 125 ([M-NO₂]⁺, 28%); 172 ([M+H]⁺, 24%); 296 ([2M-NO₂]⁺, 35%); 343 ([2M+H]⁺, 100%)
Mass (Cl -Q₁MS): 57 (100%); 170 ([M-H], 85%)
GC (100/0/10/290/15): tᵣ = 8.38 min; tᵣ = 8.77 min

9.3.3 Addition of nitropropane to cyclohexenone

Following the general procedure described in 9.3.1 with:
62 µl (62 mg; 696 µmol; 1 eq.) of 1-nitropropane
240 mg (1.74 mmol; 2.5 eq.) of potassium carbonate
16 mg (69.6 µmol; 0.1 eq.) of benzyltriethylammonium chloride
88 µl (86 mg; 904.8 µmol; 1.3 eq.) of 2-cyclohexen-1-one
3.8 ml of CH₂Cl₂
Reaction time: 4 hours
Flash chromatography: petroleum ether : AcOEt 50 : 50

Yield: 136 mg (quant.) as a mixture of 2 diastereomers

3-(1-nitropropyl)cyclohexanone 178
M.F.: C₉H₁₅NO₃ (M.W. 185.22)  RN: 71759-65-4

Aspect: yellow oil
TLC: Rᵣ = 0.54 (petroleum ether : AcOEt 60 : 40)

¹H NMR (CDCl₃, 300 MHz): 0.94 (t, 3J₃,₂ = 7.5, 3 H, 3); 1.34-2.5 (m, 11 H, 2, 4, 5, 7, 8, 9); 4.31 (mult, 1 H, 1)
¹³C NMR (CDCl₃, 75 MHz): 10.1 (3); 10.3 (3'); 23.9 and 24.1 (2, 8); 24.0 and 24.3 (2', 8'); 27.4 (9'); 27.5 (9); 40.8 (7); 41.2 (4); 41.4 (4'); 43.3 (5'); 43.7 (5); 94.6 (1); 208.6 (6)
IR (liquid film, cm⁻¹): 1547 (NO₂); 1716 (C=O); 2943 (C-H)
Mass (CI +Q1MS): 139 ([M-NO₂]⁺, 3%); 186 ([M+H]⁺, 4%); 324 ([2M-NO₂]⁺, 45%); 357 (31%); 371 ([2M+H]⁺, 100%)
GC (100/0/10/290/15): tᵣ = 9.21 min; tᵣ = 9.89 min

9.3.4 Addition of nitropropane to 2,2-dimethylhex-4-en-3-one 75

Following the general procedure described in 9.3.1 with:
60 µl (59 mg; 672 µmol; 1 eq.) of 1-nitropropane
232 mg (1.68 mmol; 2.5 eq.) of potassium carbonate
15 mg (67.2 µmol; 0.1 eq.) of benzyltriethylammonium chloride
110 mg (873.7 µmol; 1.3 eq.) of (E)-2,2-dimethylhex-4-en-3-one
3.7 ml of CH₂Cl₂
Reaction time: 4 hours
Flash chromatography: petroleum ether : AcOEt 70 : 30

**Yield:** 79 mg (55 %)

*2,2,5-trimethyl-6-nitrooctan-3-one 179*

**M.F.:** C\textsubscript{11}H\textsubscript{21}NO\textsubscript{3} (M.W. 215.29)

\[\text{H NMR (CDCl}_3, 300 \text{ MHz): 0.95 (d, } ^3J_{9.5} = 7.8, 3 \text{ H, 9); 0.96 (t, } ^3J_{8.7} = 6.9, 3 \text{ H, 8); 1.13 and 1.15 (2 s, 9 H, 1); 1.65-2.15 (2 mult, 3 H, 5, 7); 2.56 (mult, 2 H, 4); 4.44 (mult, 1 H, 6)\]

\[\text{^13C NMR (CDCl}_3, 75 \text{ MHz): 10.4 (8); 10.5 (8'); 14.6 (9); 16.7 (9'); 24.2 (7); 24.3 (7'); 26.1 (1'); 26.3 (1); 31.7 (5); 32.2 (5'); 38.7 (4'); 40.1 (4); 44.1 (2); 93.0 (6); 94.5 (6'); 214.3 (3)\]

**IR (liquid film, cm\textsuperscript{-1}):** 808; 1368; 1548 (NO\textsubscript{2}); 1706 (C=O); 2972 (C-H)

**Mass (Cl +Q1MS):** 85 ([\((\text{CH}_3)_3\text{CC}=\text{O}])^+, 35%); 169 ([M-NO\textsubscript{2}])^+, 100%; 216 ([M+H]^+, 14%)

**GC (60/10/290/10):** t\textsubscript{R} = 5.13 min

**HRMS:** calculated for C\textsubscript{11}H\textsubscript{22}NO\textsubscript{3}: 216.159969; found: 216.160446

### 9.3.5 Addition of nitropropane to N,N-dimethylacrylamide

Following the general procedure described in 9.3.1 with:

- 62 µl (62 mg; 696 µmol; 1 eq.) of 1-nitropropane
- 240 mg (1.74 mmol; 2.5 eq.) of potassium carbonate
- 16 mg (69.6 µmol; 0.1 eq.) of benzyltriethylammonium chloride
- 93 µl (89 mg; 904.8 µmol; 1.3 eq.) of N,N-dimethylacrylamide
- 3.8 ml of CH\textsubscript{2}Cl\textsubscript{2}

Reaction time: 20 hours

Flash chromatography: AcOEt : CH\textsubscript{2}Cl\textsubscript{2} 50 : 50

**Yield:** 109 mg (83 %)

*N,N-dimethyl-4-nitrohexanamide 180*

**M.F.:** C\textsubscript{8}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3} (M.W. 188.22)
TLC: $R_f = 0.36$ (CH$_2$Cl$_2$ : AcOEt 50 : 50)

$^1$H NMR (CDCl$_3$, 300 MHz): 0.98 ($t$, $^3J_{7.6} = 7.5$, 3 H, 7); 1.85 and 2.01 ($2$ mult, 2 H, 6); 2.16-2.28 ($m$, 2 H, 4); 2.33 ($mult$, 2 H, 3); 2.96 and 2.97 ($2s$, 6 H, 1); 4.56 ($mult$, 1 H, 5)

$^{13}$C NMR (CDCl$_3$, 75 MHz): 10.1 (7); 27.3 (6); 28.5 (4); 28.7 (3); 35.3 and 36.8 (1); 89.6 (5); 170.6 (2)

IR (liquid film, cm$^{-1}$): 1265 (NO$_2$); 1547 (NO$_2$); 1647 (C=O); 2974 (C-H)

Mass (Cl/CH$_4$-N$_2$O): 142 ([M-NO$_2$]$^+$, 91%); 189 ([M+H]$^+$, 100%); 377 ([2M+H]$^+$; 20%)

HRMS: calculated for C$_8$H$_{17}$N$_2$O$_3$+$^+$: 189.123918; found: 189.123025

9.3.6 Addition of nitropropane to ethyl acrylate

Following the general procedure described in 9.3.1 with:
62 µl (62 mg; 696 µmol; 1 eq.) of 1-nitropropane
240 mg (1.74 mmol; 2.5 eq.) of potassium carbonate
16 mg (69.6 µmol; 0.1 eq.) of benzyltriethylammonium chloride
98 µl (90 mg; 904.8 µmol; 1.3 eq.) of ethyl acrylate
3.8 ml of CH$_2$Cl$_2$
Reaction time: 4 hours
Flash chromatography: petroleum ether : AcOEt 60 : 40

Yield: 157 mg (quant.)

ethyl 4-nitrohexanoate 181

M.F.: C$_8$H$_{15}$NO$_4$ (M.W. 189.21)

$^1$H NMR (CDCl$_3$, 200 MHz): 0.98 ($t$, $^3J_{8.7} = 7.4$, 3 H, 8); 1.26 ($t$, $^3J_{1.2} = 7.2$, 3 H, 1); 1.72-2.41 ($m$, 6 H, 4, 5, 7); 4.15 ($q$, $^3J_{2.1} = 6.3$, 2 H, 2); 4.49 ($mult$, 1 H, 6)
**9.3.7 Addition of nitropropane to methyl crotonate**

Following the general procedure described in 9.3.1 with:

- 62 µl (62 mg; 696 µmol; 1 eq.) of 1-nitropropane
- 240 mg (1.74 mmol; 2.5 eq.) of potassium carbonate
- 16 mg (69.6 µmol; 0.1 eq.) of benzyltriethylammonium chloride
- 96 µl (90 mg; 904.8 µmol; 1.3 eq.) of methyl crotonate
- 3.8 ml of CH₂Cl₂

Reaction time: 24 hours

Flash chromatography: petroleum ether : AcOEt 50 : 50

**Yield:** 53 mg (40 %)

*methyl 3-methyl-4-nitrohexanoate* 182

M.F.: C₈H₁₅NO₄ (M.W. 189.21)  
RN: 16507-08-7

**9.3.8 Addition of nitropropane to methyl methacrylate**

Following the general procedure described in 9.3.1 with:

- 60 µl (59 mg; 672 µmol; 1 eq.) of 1-nitropropane
232 mg (1.68 mmol; 2.5 eq.) of potassium carbonate
15 mg (67.2 µmol; 0.1 eq.) of benzyltriethylammonium chloride
93 µl (87 mg; 873.7 µmol; 1.3 eq.) of methyl methacrylate
3.7 ml of CH₂Cl₂
Reaction time: 4 hours
Flash chromatography: petroleum ether : AcOEt 80 : 20

Yield: 69 mg (54 %) as a mixture of 2 diastereomers

**methyl 2-methyl-4-nitrohexanoate 183**

**M.F.:** C₈H₁₅NO₄ (M.W. 189.21)

**RN:** 16507-05-4

**TLC:** Rᵣ = 0.64; 0.71 (petroleum ether : AcOEt 80 : 20)

**¹H NMR** (CDCl₃, 200 MHz): 0.96 and 0.97 (2 t, 3J₇-₆ = 7.2, 3 H, 7); 1.20 and 1.23 (2 d, 3J₆-₃ = 6.6, 3 H, 8); 1.70-2.09 (m, 4 H, 4, 6); 2.45 (mult, 1 H, 3); 3.69 and 3.71 (2 s, 3 H, 1); 4.49 (mult, 1 H, 5)

**¹³C NMR** (CDCl₃, 50 MHz): 10.0 and 10.1 (7); 16.4 and 18.0 (8); 27.3 and 27.7 (6); 36.2 and 36.3 (3); 36.5 and 36.9 (4); 51.8 and 51.9 (1); 87.6 and 88.5 (5); 175.3 and 175.6 (2)

**IR** (liquid film, cm⁻¹): 1550 (NO₂); 1737 (C=O); 2978 (C-H)

**Mass** (Cl +Q1MS): 143 ([M-NO₂]⁺, 100%); 158 ([M-OMe]⁺, 24%); 190 ([M+H]⁺, 6%)

### 9.3.9 Addition of 2-(2-nitroethyl)-1,3-dioxolane 167 to cyclohexenone

Following the general procedure described in 9.3.1 with:
100 mg (679.6 µmol; 1 eq.) of 2-(2-nitroethyl)-1,3-dioxolane 167
235 mg (1.699 mmol; 2.5 eq.) of potassium carbonate
15 mg (67.96 µmol; 0.1 eq.) of benzyltriethylammonium chloride
85 µl (84 mg; 883.5 µmol; 1.3 eq.) of 2-cyclohexen-1-one
3.7 ml of CH₂Cl₂
Reaction time: 3 hours
Flash chromatography: mounting: petroleum ether : AcOEt 80 : 20 + 5% Et₃N; elution: petroleum ether : AcOEt 80 : 20
Yield: 133 mg (80%) as a mixture of 2 diastereomers

3-[2-(1,3-dioxolan-2-yl)-1-nitroethyl]cyclohexanone 184
M.F.: C_{11}H_{17}NO_{5} (M.W. 243.25)  RN: 215236-84-3 (R,R)

\[
\begin{array}{c}
\text{O} \\
8 \\
7 \\
6 \\
5 \\
4 \\
3 \\
2 \\
\text{NO}_2 \\
1 \\
9 \\
10
\end{array}
\]

\(^1\)H NMR (CDCl\(_3\), 300 MHz): 1.39-1.76 (m, 4 H, 9, 10); 1.82-2.27 (m, 4 H, 6, 8); 2.35-2.58 (m, 2 H, 2); 2.82 (\textit{mult}, 1 H, 5); 3.95 (\textit{mult}, 4 H, 4); 4.65 (\textit{mult}, 1 H, 1); 4.95 (\textit{mult}, 1 H, 3)

\(^13\)C NMR (CDCl\(_3\), 75 MHz): 24.1 and 24.2 (10); 26.8 and 27.6 (9); 33.9 (2); 40.7 (8); 41.6 and 41.7 (5); 42.9 and 43.9 (6); 65.1 (4); 86.4 and 86.6 (1); 100.8 and 100.9 (3); 208.1 (7)

Mass (Cl/CH\(_4\)-N\(_2\)O): 59 (100%); 73 (29%); 79 (52%); 197 ([M-NO\(_2\)]^+, 53%); 244 ([M+H]^+, 12%)

GC (100/0/10/290/20): t\(_R\) = 15.49 min; t\(_R\) = 15.77 min

9.3.10 Addition of 2-(2-nitroethyl)-1,3-dioxane 169 to cyclohexenone

Following the general procedure described in 9.3.1 with:
100 mg (620.5 µmol; 1 eq.) of 2-(2-nitroethyl)-1,3-dioxane 169

214 mg (1.551 mmol; 2.5 eq.) of potassium carbonate

14 mg (62.05 µmol; 0.1 eq.) of benzyltriethylammonium chloride

78 µl (77 mg, 806.6 µmol; 1.3 eq.) of 2-cyclohexen-1-one

3.4 ml of CH\(_2\)Cl\(_2\)

Reaction time: 3 hours

Flash chromatography: mounting: petroleum ether : AcOEt 70 : 30 + 5% Et\(_3\)N; elution: petroleum ether : AcOEt 70 : 30

Yield: 153 mg (96%) as a mixture of 2 diastereomers

3-[2-(1,3-dioxan-2-yl)-1-nitroethyl]cyclohexanone 185
M.F.: C\(_{12}\)H\(_{19}\)NO\(_5\) (M.W. 257.28)
Aspect: yellow oil

\[
\text{H NMR (CDCl}_3\text{, 300 MHz): 1.30-1.72 (m, 4 H, 10, 11); 1.83-2.56 (m, 8 H, 2, 5, 7, 9); 3.72 and 4.07 (2 mult, 4 H, 4); 4.58 (mult, 1 H, 3); 4.70 (mult, 1 H, 1)\
\text{C NMR (CDCl}_3\text{, 75 MHz): 24.3 and 24.35 (10); 25.4 (5); 27.0 and 27.7 (11); 35.4 and 35.5 (2); 40.9 (9); 41.7 and 41.8 (6); 43.1 and 44.0 (7); 66.8 (4); 86.8 and 87.0 (1); 98.3 (3); 208.4 (8)\
\text{IR (liquid film, cm}^{-1}\text{): 1047; 1244; 1375 (NO}_2\text{); 1551 (NO}_2\text{); 1731 (C=O); 2979 (C-H)\
\text{Mass (Cl/CH}_4\text{-N}_2\text{O): 83 (100%); 85 (73%); 87 (84%); 101 (31%); 103 (22%); 211 ([M-NO}_2]^+, 30%); 258 ([M+H]^+, 15%)\
\text{GC (100/0/10/290/20): t}_R = 17.58 \text{ min; } t_R = 17.93 \text{ min}\
\text{Chiral GC (150/0/0.4/200/10): } t_R = 65.65 \text{ min and 66.00 min (1}\text{st diastereomer); 69.08 \text{ min and 69.80 min (2}\text{nd diastereomer)\
\text{HRMS: calculated for C}_{12}\text{H}_{20}\text{NO}_5^+: 258.134148; found: 258.134773}
\]

**9.3.11 Addition of 1,1-diethoxy-3-nitropropane 168 to cyclohexenone**

Following the general procedure described in 9.3.1 with:
100 mg (564.3 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 168
195 mg (1.41 mmol; 2.5 eq.) of potassium carbonate
13 mg (56.43 µmol; 0.1 eq.) of benzyltriethylammonium chloride
71 µl (70 mg; 733.6 µmol; 1.3 eq.) of 2-cyclohexen-1-one
3.1 ml of CH\text{}_2\text{Cl}_2
Reaction time: 3 hours
Flash chromatography: mounting: petroleum ether : AcOEt 70 : 30 + 5% Et\text{}_3\text{N}; elution: petroleum ether : AcOEt 70 : 30

**Yield:** 126 mg (82 %) as a mixture of 2 diastereomers

**3-(3,3-diethoxy-1-nitropropyl)cyclohexanone 186**

**M.F.: C\text{}_{13}\text{H}_{23}\text{NO}_5** (**M.W.** 273.32)

**Aspect:** yellow oil

**TLC:** R\text{f} = 0.54 (petroleum ether : AcOEt 70 : 30)
9.3.12 Addition of 1,1-diethoxy-3-nitropropane 168 to cyclopentenone

Following the general procedure described in 9.3.1 with:
100 mg (564.3 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 168
195 mg (1.41 mmol; 2.5 eq.) of potassium carbonate
13 mg (56.43 µmol; 0.1 eq.) of benzyltriethylammonium chloride
61 µl (60 mg; 733.6 µmol; 1.3 eq.) of 2-cyclopentenone
3.1 ml of CH₂Cl₂
Reaction time: 3 hours
Flash chromatography: mounting: petroleum ether : AcOEt 60 : 40 + 5% Et₃N;
elution: petroleum ether : AcOEt 60 : 40

Yield: 148 mg (quant.) as a mixture of 2 diastereomers

2-(3,3-diethoxy-1-nitropropyl)cyclopentenone 198
M.F.: C₁₂H₂₁NO₅ (M.W. 259.3)
**Experimental part**

$^1$H NMR (CDCl$_3$, 300 MHz): 1.19 and 1.20 (2 t, $^3$J$_{5.4}$ = 7.1, 6 H, 5); 1.62-2.55 (m, 7 H, 2, 7, 9, 10); 2.57-2.78 (m, 2 H, 2); 3.49 and 3.68 (2 mult, 4 H, 4); 4.46 (mult, 1 H, 3); 4.62 (mult, 1 H, 1)

$^{13}$C NMR (CDCl$_3$, 50 MHz): 15.0 and 15.1 (5); 25.9 and 26.2 (10); 35.8 and 36.6 (2); 38.0 and 38.2 (9); 40.4 and 40.5 (6); 41.3 and 41.5 (7); 62.7 and 63.2 (4); 88.1 and 88.2 (1); 99.9 and 99.95 (3); 215.1 (8)

IR (liquid film, cm$^{-1}$): 1548 (NO$_2$); 1740 (C=O); 2975 (C-H)

Mass (Cl/CH$_4$-N$_2$O): 59 (39%); 83 ([C$_5$H$_7$O]$^+$, 100%); 103 (34%); 141 (26%); 167 (80%); 183 (34%); 187 (35%); 214 ([M+OEt]$^+$, 17%)

GC (100/0/10/290/10): $t_R$ = 13.79 min; $t_R$ = 14.04 min

Chiral GC (100/010/150/0.5/225/5): $t_R$ = 43.97 min and 44.62 min (1$^{st}$ diastereomer); 47.06 min (2$^{nd}$ diastereomer)

### 9.4 Synthesis of catalysts

#### 9.4.1 General procedure


A mixture of 1 eq. of amine and 1 eq. of aryl chloride was refluxed for 3 hours in toluene or methanol. Once cooled to room temperature, the mixture was poured into an important volume (~10 times the volume of the solvent) of Et$_2$O to precipitate the product. Filtration and drying under vacuum allowed to isolate the product.

#### 9.4.2 Monobenzylation of 1,4-diazabicyclo[2.2.2]octane

Following the general procedure described in 9.4.1 with:

- 200 mg (1.782 mmol; 1 eq.) of 1,4-diazabicyclo[2.2.2]octane
- 427 µl (469 mg; 3.708 mmol; 2.08 eq.) of benzyl chloride
- 5.3 ml of toluene

**Yield:** 425 mg (quant.)
**Experimental part**

1-(phenylmethyl)-4-aza-1-azoniabicyclo[2.2.2]octane chloride 187

**M.F.:** C_{13}H_{19}ClN_{2} (M.W. 238.756)  
**RN: 42790-42-1**

**Aspect:** white solid

\[
\text{N}^+\text{N}^+\text{Cl}^-
\]

**H NMR** (CDCl\(_3\), 300 MHz): 3.17 (t, \(3J_{1-2} = 7.5\), 6 H, 1); 3.77 (t, \(3J_{2-1} = 7.2\), 6 H, 2); 5.13 (s, 2 H, 3); 7.43 (mult, 3 H, 6, 7); 7.64 (d, \(3J_{5-6} = 7.5\), 2 H, 5)

**C NMR** (CD\(_3\)OD, 50 MHz): 46.2 (1); 53.6 (2); 69.4 (3); 127.8 (4); 130.0 (6); 131.8 (7); 134.3 (5)

**Mass** (Cl/CH\(_4\)-N\(_2\)O): 59 (79%); 91 (100%); 203 ([M]+, 7%)

9.4.3 **Dibenzylation of 1,4-diazabicyclo[2.2.2]octane**

Following the general procedure described in 9.4.1 with:
- 200 mg (1.782 mmol; 1 eq.) of 1,4-diazabicyclo[2.2.2]octane
- 410 µl (451 mg; 3.565 mmol; 2 eq.) of benzyl chloride
- 2.7 ml of MeOH

**Yield:** 651 mg (quant.)

1,4-bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane dichloride 188

**M.F.:** C\(_{20}\)H\(_{26}\)Cl\(_2\)N\(_2\) (M.W. 365.345)  
**RN: 42790-43-2**

**Aspect:** white solid

\[
\text{N}^+\text{N}^+\text{Cl}^-
\]

**H NMR** (CD\(_3\)OD, 300 MHz): 3.98 (s, 12 H, 1); 4.83 (s, 4 H, 2); 7.55-7.61 (m, 10 H, 4, 5, 6)

**C NMR** (CD\(_3\)OD, 50 MHz): 52.2 (1); 69.6 (2); 127.0 (3); 130.9 (5); 132.6 (6); 134.4 (4)

**Mass** (Cl/CH\(_4\)-N\(_2\)O): 59 (100%); 91 (63%); 131 (58%); 203 ([M-CH\(_2\)C\(_6\)H\(_5\)]+, 28%)
9.4.4  
**Reaction of cinchonidine with 9-(chloromethyl)anthracene**

Following the general procedure described in 9.4.1 with:
- 410 mg (1.391 mmol; 1 eq.) of cinchonidine
- 328 mg (1.446 mmol; 1.04 eq.) of 9-(chloromethyl)anthracene
- 4 ml of toluene

**Yield:** 633 mg (87 %)

*N-(9-anthrylmethyl)cinchonidinium chloride* 189

**M.F.:** C_{34}H_{33}ClN_{2}O (M.W. 521.10)  
**RN:** 199588-80-2

Spectral data identical to a commercial sample.  
**Mass (APCI):** 191 ([CH_{3}C_{14}H_{8}]^{+}, 21%); 295 ([M-CH_{2}C_{14}H_{8}]^{+}, 100%); 485 (M^{+}, 7%)

9.4.5  
**Reaction of quinine with 9-(chloromethyl)anthracene**

Following the general procedure described in 9.4.1 with:
- 451 mg (1.391 mmol; 1 eq.) of quinine
- 328 mg (1.446 mmol; 1.04 eq.) of 9-(chloromethyl)anthracene
- 4 ml of toluene

**Yield:** 499 mg (65 %)

*N-(9-anthrylmethyl)quininium chloride* 156

**M.F.:** C_{35}H_{35}ClN_{2}O_{2} (M.W. 551.12)  
**RN:** 199588-84-6
Experimental part

9.4.6 Reaction of quinidine with 9-(chloromethyl)anthracene

Following the general procedure described in 9.4.1 with:
451 mg (1.391 mmol; 1 eq.) of quinidine
328 mg (1.446 mmol; 1.04 eq.) of 9-(chloromethyl)anthracene
4.2 ml of toluene

Yield: 363 mg (47 %)

N-(9-anthrylmethyl)quinidinium chloride 155

M.F.: C_{35}H_{35}ClN_{2}O_{2} (M.W. 551.12)  
RN: 199588-78-8

^{13}C NMR (CDCl_{3}, 50 MHz): 17.6 and 23.4 (2, 8); 27.6 (3), 37.5 (4); 48.4, 49.2 and 54.5 (1, 9, 21); 56.8, 60.0 and 66.3 (7, 10, 20); 99.6 (18); 117.7 and 118.3 (6, 19); 118.5, 122.2, 124.9, 125.0 and 131.2 (24, 25, 26, 27, 29); 120.6 and 121.2 (12, 16); 125.1 (22); 130.5 and 133.1 (23, 28); 136.3 (5); 143.6 and 144.1 (11, 14); 147.0 (13); 158.0 (17)
Mass (APCI): 282 (35%); 325 ([M-CH$_2$C$_8$H$_8$]+, 100%); 515 (M$^+$, 2%)

9.4.7 Reaction of cinchonine with 1-(chloromethyl)naphthalene

Following the general procedure described in 9.4.1 with:
409 mg (1.391 mmol; 1 eq.) of cinchonine
232 µl (255 mg; 1.446 mmol; 1.04 eq.) of 1-(chloromethyl)naphthalene
4.2 ml of toluene

Yield: 537 mg (82%)

N-(1-naphthylmethyl)cinchoninium chloride 190

M.F.: C$_{30}$H$_{31}$ClN$_2$O (M.W. 471.03)

Aspect: white solid

$^1$H NMR (CDCl$_3$, 300 MHz): 0.65-0.80 (m, 2 H); 2.06 (mult, 2 H); 2.62 (mult, 1 H); 3.26 (t, J = 12.0, 1 H); 4.07 (mult, 2 H); 4.12-4.23 (m, 1 H); 4.54 (t, J = 10.4, 1 H); 5.13 (d, J = 16.8, 1 H); 5.18 (d, J = 9.6, 1 H); 5.58 (d, J = 11.2, 1 H); 5.81 (mult, 1 H); 6.42 (d, J = 11.2, 1 H); 6.52-6.61 (m, 1 H); 7.01 (mult, 2 H); 7.18 (mult, 1 H); 7.23-7.38 (m, 3 H); 7.50-7.62 (m, 4 H); 7.85-7.94 (m, 2 H); 8.28 (d, J = 8.0, 1 H); 8.80 (d, J = 4.0, 1 H)

$^{13}$C NMR (CDCl$_3$, 50 MHz): 22.0 and 23.9 (2, 8); 26.7 (3); 37.9 (4); 49.9, 54.8 and 56.4 (1, 9, 20); 66.3 and 66.5 (7, 10); 117.7 (6); 119.6 (12); 122.5 and 123.6 (19, 21); 123.4, 124.3, 124.7 and 125.6 (18, 26, 27, 28); 126.9, 127.3, 128.1, 128.5, 129.1 and 130.2 (16, 17, 22, 23, 24, 28); 132.7 and 133.0 (25, 30); 134.3 (15); 135.3 (5); 145.2 (11); 146.8 (14); 149.3 (13)

Mass (APCI): 141 ([CH$_2$C$_{10}$H$_7$]+, 25 %); 295 ([M-(CH$_2$C$_{10}$H$_7$]+, 100%); 435 (M$^+$, 43%)

[α]$_{20}^0$ : 196° (c=0.240; MeOH)

m.p.: 228°C (decomposition)
9.4.8 Reaction of cinchonine with 4-(chloromethyl)biphenyl

Following the general procedure described in 9.4.1 with:
400 mg (1.358 mmol; 1 eq.) of cinchonine
286 mg (1.413 mmol; 1.04 eq.) of 4-(chloromethyl)biphenyl
4.1 ml of toluene

Yield: 484 mg (72 %)

N-([1,1'-biphenyl]-4-ylmethyl)cinchoninium chloride 191

M.F.: C_{32}H_{33}ClN_{2}O (M.W. 497.07)

Aspect: purple solid

\[ \begin{align*}
\text{H NMR} (\text{CDCl}_3, 300 \text{ MHz}): & 0.65-0.76 \ (m, 2 \text{ H}); \ 2.02-2.21 \ (m, 2 \text{ H}); \ 2.65-2.78 \ (m, 1 \text{ H}); \ 3.34 \ (t, J = 10.5, 1 \text{ H}); \ 3.92-4.18 \ (m, 2 \text{ H}); \ 4.52 \ (\text{mult}, 1 \text{ H}); \ 5.20 \ (\text{mult}, 4 \text{ H}); \ 5.82 \ (\text{mult}, 1 \text{ H}); \ 6.39 \ (d, J = 11.7, 1 \text{ H}); \ 6.51 \ (\text{broad s}, 1 \text{ H}); \ 7.00 \ (\text{mult}, 2 \text{ H}); \ 7.19-7.29 \ (m, 3 \text{ H}); \ 7.30-7.36 \ (m, 3 \text{ H}); \ 7.54 \ (\text{mult}, 3 \text{ H}); \ 7.60-7.69 \ (m, 2 \text{ H}); \ 7.89 \ (d, J = 4.2, 1 \text{ H}); \\
\text{C NMR} (\text{CDCl}_3, 50 \text{ MHz}): & 21.7 \text{ and } 23.7 \ (2, 8); \ 27.1 \ (3); \ 38.0 \ (4); \ 49.7, 53.5 \text{ and } 56.3 \ (1, 9, 20); \ 65.7 \text{ and } 67.0 \ (7, 10); \ 118.0 \ (6); \ 119.6 \ (12); \ 123.1 \ (18); \ 123.5 \ (19); \ 126.1 \ (21); \ 126.8, 127.8, 128.3 \text{ and } 128.9 \ (22, 23, 26, 27); \ 129.2 \text{ and } 130.1 \ (16, 17); \ 134.3 \text{ and } 135.3 \ (5, 15); \ 139.4 \text{ and } 142.2 \ (24, 25); \ 144.7 \text{ and } 146.8 \ (11, 14); \ 149.3 \ (13) \\
\text{Mass} (\text{APCI}): & 167 \ ([\text{CH}_2\text{C}_6\text{H}_4\text{C}_6\text{H}_3]^+, 67\%); \ 295 \ ([\text{M-CH}_2\text{C}_6\text{H}_4\text{C}_6\text{H}_3]^+, 80\%); \ 461 \ (\text{M}^+, 100\%) \\
[\alpha]_D^{20} : & 107^\circ \ (c=0.225; \text{MeOH}) \\
\text{m.p.}: & 192^\circ \ (\text{decomposition}) \end{align*} \]
9.4.9 Reaction of cinchonine with 2-(chloromethyl)naphthalene

Following the general procedure described in 9.4.1 with:
400 mg (1.358 mmol; 1 eq.) of cinchonine
250 mg (1.413 mmol; 1.04 eq.) of 2-chloromethylnaphtalene
4.1 ml of toluene

Yield: 440 mg (69%)  

N-(2-naphthylmethy)cinchoninium chloride 192

M.F.: C_{30}H_{31}ClN_{2}O (M.W. 471.04)

Aspect: white solid

\[
\begin{align*}
\text{1H NMR (CDCl}_3, 300 MHz):} & \ 0.63-0.75 (m, 2 H); 2.02 (\text{mult}, 2 H); 2.64 (\text{mult}, 2 H); \\
& 3.13 (\text{mult}, 1 H); 3.99-4.11 (m, 1 H); 4.12-4.22 (m, 2 H); 4.52 (\text{mult}, 1 H); 5.03 (\text{mult}, 2 H); \\
& 5.57 (d, J = 11.7, 1 H); 6.54-6.60 (m, 1 H); 7.03 (\text{mult}, 2 H); 7.14-7.21 (m, 1 H); \\
& 7.26-7.37 (m, 3 H); 7.43-7.71 (m, 4 H); 7.89 (m, 2 H); 8.37 (d, J = 9.3, 1 H); 8.80 (d, J = 4.2, 1 H) \\
\text{13C NMR (CDCl}_3, 50 MHz):} & \ 21.5 \text{ and } 23.5 \text{ (2, 8)}; 26.9 \text{ (3)}; 37.9 \text{ (4)}; 49.4, 53.6 \text{ and} \\
& 56.2 \text{ (1, 9, 20)}; 65.5 \text{ and } 66.7 \text{ (7, 10)}; 117.8 \text{ (6)}; 119.6 \text{ (12)}; 123.0 \text{ (18)}; 123.7 \text{ and} \\
& 124.0 \text{ (19, 21)}; 126.3, 126.6, 127.1, 127.2, 127.3, 127.9, 128.0, 128.6 \text{ and } 128, 7 \text{ (16,} \\
& 17, 22, 24, 25, 26, 27, 29, 30); 132.2 \text{ and } 133.0 \text{ (23, 28)}; 133.9 \text{ and } 135.2 \text{ (5, 15)}; \\
& 145.1 \text{ and } 147.4 \text{ (11, 14); 149.0 (13)} \\
\text{Mass (APCI):} & \ 141 ([\text{CH}_2\text{C}_{10}\text{H}_7]^+, 29\%); 295 ([\text{M-CH}_2\text{C}_{10}\text{H}_7]^+, 100\%); 435 (M^+, 27\%) \\
[\alpha]_D^{20}: \ 139^\circ \text{ (c=0.237; MeOH)} \\
\text{m.p.:} & \ 213^\circ \text{C (decomposition)}
\end{align*}
\]

9.4.10 Reaction of cinchonidine with 1,3-bis(bromomethyl)benzene

A mixture of 500 mg (1.698 mmol; 2.03 eq.) of cinchonidine and 220 mg (833.4 µmol; 1 eq.) of 1,3-bis(bromomethyl)benzene in 1.5 ml of DMF and 0.5 ml of CHCl₃ was heated to 100°C for 6 hours. Once cooled down to room temperature it was diluted with 10 ml of MeOH. Then 50 ml of ether were slowly added to precipitate the product. The precipitate was filtered and dried under high vacuum.

**Yield:** 701 mg (99 %)

**Catalyst 194**

**M.F.:** C₄₆H₅₂Br₂N₄O₂ (M.W. 852.75)  
**RN:** 473410-07-0

\[
\begin{array}{c}
\text{C NMR (CDCl}_3, 75 \text{ MHz):} & 21.6 \text{ and } 24.6 (2, 8); 26.3 (3); 37.2 (4); 51.0, 60.6 \text{ and } 62.3 (1, 9, 20); 64.5 \text{ and } 68.2 (7, 10); 117.1 (6); 119.6 (12); 122.4 (18); 124.1 (19); 127.9 (21); 127.9 (22); 129.2 \text{ and } 129.5 (16, 17, 23); 135.4 \text{ and } 136.4 (5, 15); 139.0 (22); 145.2 \text{ and } 147.0 (11, 15); 149.2 (13) \\
\text{Mass (APCI):} & 397 ([M-cinchonidinium]^+; 67\%); 506 (100\%); 530 (54\%); 673 ([M-H₃O]^+; 93\%); 692 ([M-H]^+; 1\%) \\
[\alpha]_{20}^D & -169^\circ (c=0.189; \text{MeOH}) \text{ [lit.: } -171^\circ (c=0.276; \text{MeOH})]\n\end{array}
\]

9.4.11 Reaction of N-benzylcinchonidinium chloride 196 with allyl bromide


742 mg (1.727 mmol; 1 eq.) of N-benzylcinchonidinium chloride were put into suspension in 6.5 ml of CH₂Cl₂. 249 µl (509 mg; 9.074 mmol; 5.25 eq.) of allyl bromide and an aqueous solution of 50% of KOH (509 mg (9.074 mmol; 5.25 eq.) of potassium hydroxide in 433.5 µl of water) were then added. The mixture was stirred vigorously for 4 hours. A homogenization of the organic phase occurred. The mixture
was then diluted with water and extracted with CH$_2$Cl$_2$. The organic phase was dried over MgSO$_4$, filtered and evaporated under reduced pressure.

**Yield:** 1.101 g (quant.)

*O-allyl-N-benzylcinchonidinium bromide 197*

**M.F.:** $C_{29}H_{33}BrN_2O$ (**M.W.** 505.49)  
**RN:** 158195-40-5

![Structure of O-allyl-N-benzylcinchonidinium bromide](structure.png)

Spectral data identical to a commercial sample  
**Mass (APCI):** 282 (26%); 335 ([M-CH$_2$C$_8$H$_14$]$^+$, 100%); 425 ($M^+$, 2%)

**9.4.12 Reaction of N-(9-anthrylmethyl)cinchonidinium chloride 189 with allyl bromide**


1000 mg (1.727 mmol; 1 eq.) of N-(9-anthrylmethyl)cinchonidinium chloride were put into suspension in 6.6 ml of CH$_2$Cl$_2$. 249 µl (509 mg; 9.074 mmol; 5.25 eq.) of allyl bromide and an aqueous solution of 50% of KOH (509 mg (9.074 mmol; 5.25 eq.) of potassium hydroxide in 433.5 µl of water) were then added. The mixture was stirred vigorously for 4 hours. A homogenization of the organic phase occurred. The mixture was then diluted with water and extracted with CH$_2$Cl$_2$. The organic phase was dried over MgSO$_4$, filtered and evaporated under reduced pressure.

**Yield:** 917 mg (88 %)

*O-allyl-N-(9-anthrylmethyl)cinchonidinium bromide 195*

**M.F.:** $C_{37}H_{37}BrN_2O$ (**M.W.** 605.61)  
**RN:** 200132-54-3
**Experimental part**

**13C NMR** (CDCl₃, 50 MHz): 23.2 and 25.5 (2, 8); 26.0 (3); 38.3 (4); 50.8 and 54.8 (1, 23); 61.3 (9); 66.8 (7); 70.1 (20); 70.2 (10) 117.9, 118.0 and 118.3 (6, 19, 22); 123.2, 124.9, 125.6, 126.6, 127.6, 128.4, 128.9, 129.9 (12, 16, 18, 26, 27, 28, 29, 31); 131.2, 133.1, 133.6 (24, 25, 30); 132.1, 132.6 (15, 17); 136.2 and 136.5 (5, 21); 139.6 and 140.1 (11, 14); 148.5 (13)

**Mass** (APCI): 282 (28%); 335 ([M-CH₂C₁₄H₈]⁺, 100%); 525 (M⁺, 2%)

### 9.5 Michael addition of nitro-compounds: asymmetric

#### 9.5.1 Addition to cyclopentenone

Following the general procedure described in 9.3.1 with the following quantities:
- 75 mg (423.2 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 168
- 146 mg (1.058 mmol; 2.5 eq.) of potassium carbonate
- 0.1 eq of catalyst
- 46 µl (45 mg; 550.2 µmol; 1.3 eq.) of 2-cyclopentene none
- 3.9 ml of toluene
### 9.5.2 Addition to cyclohexenone

Following the general procedure described in 9.3.1 with the following quantities:
- 75 mg (423.2 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 168
- 146 mg (1.058 mmol; 2.5 eq.) of potassium carbonate
- 0.1 eq of catalyst
- 53 µl (52 mg; 550.2 µmol; 1.3 eq.) of 2-cyclohexenone
- 3.9 ml of toluene

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<td>11%</td>
<td>S</td>
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<tr>
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<td>21%</td>
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$^a$ reaction time until complete conversion
10 Michael addition of nitro-compounds: other catalytic methods

10.1 Silylated nitronates

10.1.1 Synthesis of propylidene[(trimethylsilyl)oxy]azane oxide (1-aci-nitropropane trimethylsilylester) 207

M.F.: C_6H_{15}NO_2Si (M.W. 161.27)  
RN: 51146-38-4


In a flame-dried two-necked flask, to a solution of 2 ml (1.996 g; 22.4 mmol; 1 eq.) of 1-nitropropane in 45 ml of benzene were added 3.114 ml (2.267 g; 22.4 mmol; 1 eq.) of Et_3N, then 2.843 ml (2.433 g; 22.4 mmol; 1 eq.) of TMSCl. The mixture was stirred for 64 hours, then filtered and evaporated under reduced pressure. The product was purified by bulb-to-bulb distillation (75°C at 16 mmHg).

Yield: 2.158 g (60 %)

\[
\begin{align*}
N &\quad O \\
\quad &\quad O \\
\quad &\quad Si
\end{align*}
\]

^1H NMR (CDCl_3, 300 MHz): 0.32 (s, 9 H, 4); 1.09 (t, 3J_{3,2} = 7.8, 3 H, 3); 2.32 (quint, 3J_{2,1} = 3J_{2,3} = 7.8, 3 H, 2); 6.10 (t, 3J_{1,2} = 6.3, 1 H, 1)

^13C NMR (CDCl_3): -0.15 (4); 10.1 (3); 19.9 (2); 118.1 (1)

b.p.: 75°C (16 mmHg)

10.1.2 Synthesis of {[tert-butyl(dimethyl)silyl]oxy}(propylidene)azane oxide (1-aci-nitropropane tert-butyl(dimethyl)silylester) 208

M.F.: C_{9}H_{21}NO_2Si (M.W. 203.35)  
RN: 77242-14-9

In a flame-dried two-necked flask, to a solution of 2 ml (1.996 g; 22.4 mmol; 1 eq.) of 1-nitropropane in 25 ml of toluene were added 3.114 ml (2.267 g; 22.4 mmol; 1 eq.) of Et₃N, then 3.376 g (22.4 mmol; 1 eq.) of tert-butyldimethylsilyl chloride. The mixture was stirred for 64 hours, then filtered and evaporated under reduced pressure.

The product was purified by bulb-to-bulb distillation (75°C at 9·10⁻³ mbar).

**Yield:** 1.483 g (33 %)

**1H NMR** (CDCl₃, 200 MHz): 0.32 (s, 6 H, 4); 0.94 (s, 9 H, 6); 1.09 (t, ³J₃-2 = 7.6, 3 H, 3); 2.31 (dq, ³J₂-3 = 7.6, ³J₂-1 = 6.3, 2 H, 2); 6.10 (t, ³J₁-2 = 6.2, 1 H, 1)

**13C NMR** (CDCl₃, 50 MHz): -3.7 (4); 9.7 (3); 18.5 (5); 22.0 (2); 25.4 (6); 107.8 (1)

**b.p.:** 75°C (9·10⁻³ mbar)

10.1.3 *Synthesis of 7-ethoxy-2,2-dimethyl-3,8-dioxa-4-aza-2-siladec-4-ene 4-oxide (1-aci-nitro-3,3-diethoxypropane trimethylsilylester)* 209

**M.F.:** C₁₀H₂₃NO₄Si (M.W. 249.38)


In a flame-dried two-necked flask, to a solution of 500 mg (2.821 mmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 168 in 5.6 ml of benzene were added 392 µl (285 mg; 2.821 mmol; 1 eq.) of Et₃N, then 358 µl (306 mg; 2.821 mmol; 1 eq.) of TMSCl. The mixture was stirred for 64 hours, then filtered and evaporated under reduced pressure.

The product was purified by bulb-to-bulb distillation (75°C at 2.1·10⁻² mbar).

**Yield:** 549 mg (78 %)

**Aspect:** colorless oil
Experimental part

\[ \text{N} + \text{O}_\text{Si}^{-} \]

\[ \text{O} \]

1H NMR (CDCl\textsubscript{3}, 200 MHz): 0.31 (s, 9 H, 6); 1.21 (t, \( ^2J_{5-4} = 6.9, 6 \) H, 5); 2.64 (t, \( ^3J_{2-1} = ^3J_{2-3} = 6.1, 2 \) H, 2); 3.65 and 3.51 (2 mult, 4 H, 4); 4.68 (t, \( ^3J_{3-2} = 5.6, 1 \) H, 3); 6.18 (t, \( ^3J_{1-2} = 6.3, 1 \) H, 1)

b.p.: 75°C (2.1 x 10\textsuperscript{-2} mbar)

10.1.4 Synthesis of N-benzylcinchonidinium fluoride 210

M.F.: C\textsubscript{26}H\textsubscript{29}FN\textsubscript{2}O (M.W. 404.52)             RN: 174626-65-4


A mixture of 100 mg (201.9 µmol; 1 eq.) of benzylcinchonidinium chloride and 26 mg (201.9 µmol; 1 eq.) of silver fluoride in 5 ml of water was stirred overnight. The solution was evaporated under reduced pressure. Acetonitrile was added to the residue and the solvent was evaporated under reduced pressure. To separate the product from AgCl, acetone was added to the residue and the suspension was filtered. The filtrate was evaporated under reduced pressure and the resulting residue was dried under high vacuum.

Yield: 105 mg (quant.)

\[ \text{H} \text{NMR} \text{ (CDCl}_{3} \text{, 300 MHz): 1.03-1.16 (m, 1 H); 1.51-1.65 (m, 1 H); 1.90-2.19 (m + s, 4 H); 2.42-2.52 (m, 1 H); 3.02 (dt, J = 11.8, J = 3.1, 1 H); 3.18 (t, J = 11.8, 1 H); 3.57 (d, J = 12.6, 1 H); 3.83 (t, J = 8.6, 1 H); 4.80-4.91 (m, 1 H); 4.93 (d, J = 11.0, 1 H); 5.09 (d, J = 16.5, 1 H); 5.31 (d, J = 11.8, 1 H); 5.84 (d, J = 11.8, 1 H); 6.34 (s, 1 H); 6.95 (mult, 3 H); 7.45 (d, J = 7.1, 1 H); 7.59 (mult, 2 H); 7.84 (d, J = 3.9, 1 H); 7.98 (mult, 1 H); 8.05 (mult, 1 H); 8.83 (d, J = 3.9, 1 H) \]
**Experimental part**

**10.1.5 Michael addition of 207: TBAF**


In a flame-dried flask, 16 mg (62 µmol; 0.1 eq.) of tetrabutylammonium fluoride and 63 µl (62 mg; 651 µmol; 1.05 eq.) of 2-cyclohexen-1-one were put into solution in 5 ml of THF. 100 mg (620 µmol; 1 eq.) of 1-aci-nitropropan-trimethylsilylester 207 dissolved in a small quantity of THF were then slowly added and the mixture was stirred for 4 hours. The reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 87 mg (76 %) of 3-(1-nitropropyl)cyclohexanone 178

Physical data as described in 9.3.3.

**10.1.6 Michael additon of 207: KF and benzyltriethylammonium chloride or N-(1-naphthylmethyl)cinchoninium chloride 190**

In a flame-dried flask, 3 mg (62 µmol; 0.1 eq.) of potassium fluoride and catalyst (7 mg (31 µmol; 0.05 eq.) of benzyltriethylammonium chloride or 29 mg (62 µmol; 0.1 eq.) of N-(1-naphthylmethyl)cinchoninium chloride) were put into suspension in 6.6 ml of toluene. 63 µl (62 mg; 651 µmol; 1.05 eq.) of 2-cyclohexen-1-one were added, followed by 100 mg (620 µmol; 1 eq.) of 1-aci-nitropropan-trimethylsilyl ester 207 in solution in a small quantity of toluene. The mixture was stirred for 4 hours before the reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

No product was obtained by this method.
10.1.7 General procedure for the Michael addition of silylated nitronates catalyzed by N-benzylcinchonidinium fluoride 210

In a flame-dried flask, 0.1 eq. of N-benzylcinchonidinium fluoride 210 and 1.05 eq. of enone were dissolved in the solvent. 1 eq. of silylated nitronate dissolved in a small quantity of solvent was added. The mixture was stirred for x hours before the reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

10.1.8 Michael addition of 207 to cyclohexenone: N-benzylcinchonidinium fluoride 210

Following the general procedure described in 10.1.7 with:
100 mg (620 µmol; 1 eq.) of 1-aci-nitropropan-trimethylsilylester 207
63 µl (62 mg; 651 µmol; 1.05 eq.) of 2-cyclohexen-1-one
25 mg (62 µmol; 0.1 eq.) of N-benzylcinchonidinium fluoride 210
5.1 ml of THF
reaction time: 1 hour

Yield: 120 mg (quant.) of 3-(1-nitropropyl)cyclohexanone 178

Physical data as described in 9.3.3.

10.1.9 Michael addition of 209 to cyclopentenone: N-benzylcinchonidinium fluoride 210

Following the general procedure described in 10.1.7 with:
100 mg (400.9 µmol; 1 eq.) of 1-aci-nitro-3,3-diethoxypropane trimethylsilylester 209
35 µl (34 mg; 421 µmol; 1.05 eq.) of 2-cyclopentenone
16 mg (40.09 µmol; 0.1 eq.) of N-benzylcinchonidinium fluoride 210
3.3 ml of THF
reaction time: 1 hour

Complete conversion to 2-(3,3-diethoxy-1-nitropropyl)cyclopentenone 198
Adduct 198 was obtained with 7% de and 7% ee.
10.1.10 *Michael addition of 209 to cyclohexenone: N-benzylcinchonidinium fluoride 210*

Following the general procedure described in 10.1.7 with:
100 mg (400.9 µmol; 1 eq.) of 1-aci-nitro-3,3-dioethoxypropane trimethylsilyl ester 209
41 µl (40 mg; 421 µmol; 1.05 eq.) of 2-cyclohexen-1-one
16 mg (40.09 µmol; 0.1 eq.) of N-benzylcinchonidinium fluoride 210
3.3 ml of THF
reaction time: 2 days

Only 30% conversion were observed after 2 days. Reagent 209 had been transformed to 1,1-diethoxy-3-nitropropane 168.
Adduct 186 was obtained with 4% de and 30% ee.

10.1.11 *Michael addition of 209 to cyclopentenone: N-benzylcinchonidinium fluoride 210*

Following the general procedure described in 10.1.7 with:
100 mg (400.9 µmol; 1 eq.) of 1-aci-nitro-3,3-dioethoxypropane trimethylsilyl ester 209
35 µl (34 mg; 421 µmol; 1.05 eq.) of 2-cyclopentenone
16 mg (40.09 µmol; 0.1 eq.) of N-benzylcinchonidinium fluoride 210
4.3 ml of toluene
reaction time: 1 hour

Complete conversion to 2-(3,3-diethoxy-1-nitropropyl)cyclopentenone 198
Adduct 198 was obtained with 7% de and 2% ee.

10.1.12 *Michael addition of 209 to cyclohexenone: N-benzylcinchonidinium fluoride 210*

Following the general procedure described in 10.1.7 with:
100 mg (400.9 µmol; 1 eq.) of 1-aci-nitro-3,3-dioethoxypropane trimethylsilyl ester 209
41 µl (40 mg; 421 µmol; 1.05 eq.) of 2-cyclohexen-1-one
16 mg (40.09 µmol; 0.1 eq.) of N-benzylcinchonidinium fluoride 210
4.3 ml of toluene
reaction time: 2 days
Only 30% conversion were observed after 2 days. Reagent 209 had been transformed to 1,1-diethoxy-3-nitropropane 168. Adduct 186 was obtained with 8% de and 50% ee.

10.2 AlLi[(R)-binaphthoxide]₂ complex as catalyst

10.2.1 Preparation of a 0.1M solution of AlLi[(R)-binaphthoxide]₂ ((R)-ALB)


To a suspension of 24 mg (625 µmol; 1 eq.) of lithium aluminum hydride in 2.5 ml of THF at 0°C were added 358 mg (1.25 mmol; 2 eq.) of (R)-(+) -1,1' -bi-2-naphthol dissolved in 2.5 ml of THF followed by 2x 625 µl of THF. After 30 minutes of stirring at 0°C, the mixture was stirred for 1 hour at room temperature, then left standing without stirring overnight. The supernatant was used as 0.1M solution of (R)-ALB in THF.

10.2.2 Michael addition of 168 to cyclopentenone


To 35 µl (34 mg; 423.2 µmol; 1 eq.) of 2-cyclopentenone contained in a flame-dried two-necked flask were added 423 µl (42.32 µmol; 0.1 eq.) of the previously prepared 0.1M solution of AlLi[(R)-binaphthoxide]₂. The mixture was stirred for 10 minutes, cooled to -40°C and stirred for another 10 minutes before 43 mg (380.9 µmol; 0.9 eq.) of potassium tert-butoxide dissolved in 78 µl of THF were added followed by 75 mg (423.2 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane. The mixture was stirred for 48 hours at -40°C. The reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted by CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

Quantitative yield of racemic 2-(3,3-diethoxy-1-nitropropyl)cyclopentenone 198 was obtained.
10.3 Rubidium prolinate as catalyst

10.3.1 Synthesis of rubidium prolinate 211

M.F.: C\textsubscript{5}H\textsubscript{8}NO\textsubscript{2}Rb (M.W. 199.59) \hspace{1cm} RN: 151600-44-1


A mixture of 2 g (17.37 mmol; 1 eq.) of L-proline and 2.093 g (17.37 mmol; 1 eq.) of rubidium hydroxyde hydrate in 36 ml of MeOH was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the product was dried at high vacuum.

Quantitative yield of rubidium prolinate 211 was obtained.

\[
\begin{align*}
\text{NH} &\quad \text{COORb} \\
1 &\quad 2 &\quad 3 &\quad 4 &\quad 5
\end{align*}
\]

\(^1\text{H NMR}\) (D\textsubscript{2}O, 200 MHz): 1.72-1.92 (m, 3 H, 2, 3), 2.06-2.29 (m, 1 H, 3); 2.85-3.01 (m, 1 H, 1); 3.09-3.22 (m, 1 H, 1); 3.67 (dd, \(^3\text{J}_{4,3} = 8.4, \(^3\text{J}_{4,3} = 6.3\), 1 H, 4)

\(^{13}\text{C NMR}\) (D\textsubscript{2}O, 75 MHz, acetone as internal reference (29.9 ppm)): 23.9 (2); 29.4 (3); 45.2 (1); 60.6 (4); 179.0 (5)

10.3.2 Michael addition of 209 to cyclopentenone


A mixture of 75 mg (423.2 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 209, 35 µl (34 mg; 423.2 µmol; 1 eq.) of 2-cyclopentenone and 8 mg (42.32 µmol; 0.1 eq.) of rubidium prolinate 211 in 500 µl of CHCl\textsubscript{3}, previously passed through a column of basic alumina, was stirred for 72 hours at room temperature. The reaction was quenched by the addition of a saturated solution of NH\textsubscript{4}Cl. The aqueous phase was extracted by CH\textsubscript{2}Cl\textsubscript{2}. The organic phase was dried over MgSO\textsubscript{4}, filtered and evaporated under reduced pressure.

Quantitative yield of adduct 198 was obtained.

Diastereoselectivity: 4% de; enantioselectivity: 59% ee.
10.3.3 Michael addition of 209 to cyclohexenone


A mixture of 75 mg (423.2 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 209, 41 µl (40 mg; 423.2 µmol; 1 eq.) of 2-cyclohexen-1-one and 8 mg (42.32 µmol; 0.1 eq.) of rubidium prolinate 211 in 500 µl of CHCl₃, previously passed through a column of basic alumina, was stirred for 72 hours at room temperature. The reaction was quenched by the addition of a saturated solution of NH₄Cl. The aqueous phase was extracted by CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

Quantitative yield of adduct 186 was obtained.
Diastereoselectivity: 4% de; enantioselectivity: 57% ee.

10.4 L-proline as catalyst

10.4.1 Michael addition of 209 to cyclopentenone


A mixture of 75 mg (423.2 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 209, 35 µl (34 mg; 423.2 µmol; 1 eq.) of 2-cyclopentenone, 49 mg (430.5 µmol; 1.01 eq.) of trans-2,5-dimethylpiperazine and 1 mg (15.65 µmol; 0.0369 eq.) of L-proline in 3.3 ml of CHCl₃, previously passed through a column of basic alumina, was stirred for 46 hours. It was then diluted with CH₂Cl₂, washed with a 3% solution of HCl, dried over MgSO₄, filtered and evaporated under reduced pressure.

Quantitative yield of adduct 198 was obtained.
Diastereoselectivity: 1% de; enantioselectivity: 77% ee.
10.4.2 *Michael addition of 209 to cyclohexenone*


A mixture of 75 mg (423.2 µmol; 1 eq.) of 1,1-diethoxy-3-nitropropane 209, 41 µl (40 mg; 423.2 µmol; 1 eq.) of 2-cyclohexen-1-one, 49 mg (430.5 µmol; 1.01 eq.) of *trans*-2,5-dimethylpiperazine and 1 mg (15.65 µmol; 0.0369 eq.) of *L*-proline in 3.3 ml of CHCl₃, previously passed through a column of basic alumina, was stirred for 46 hours. It was then diluted with CH₂Cl₂, washed with a 3% solution of HCl, dried over MgSO₄, filtered and evaporated under reduced pressure.

Quantitative yield of adduct 186 was obtained.  
Diastereoselectivity: 25% de; enantioselectivity: 69% ee.

11 **Chemical modification of adducts**

11.1 **Cyclization**

11.1.1 *Cyclization of adduct 186*


A mixture of 200 mg (731.7 µmol; 1 eq.) of 3-(3,3-diethoxy-1-nitropropyl)cyclohexanone 186, 3.3 ml of THF and 100 µl (90 mg; 1.25 mmol; 1.7 eq.) of a 12.5N solution of hydrochloric acid was stirred for 2 hours at room temperature. It was then neutralized with a 5% solution of NaHCO₃ and diluted with Et₂O. The organic phase was washed 3 times with water and once with a saturated solution of NaCl. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.  
The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

**Yield:** 87 mg (66 %) as a mixture of 2 diastereomers

*1-nitro-1,2,5,6,7,7a-hexahydro-4H-inden-4-one 218*  
**M.F.:** C₉H₁₁NO₃ (**M.W.** 181.19)  
**RN:** 182298-16-4
1H NMR (CDCl₃, 200 MHz): 1.12-2.75 (m, 6 H, 6, 7, 8); 3.05 and 3.18 (2 mult, 2 H, 2); 3.34-3.56 (m, 1 H, 9); 4.92 (q, 3J₁₋₂ = 3J₁₋₉ = 8.7, 1 H, 1); 5.32 (dt, 3J₁₋₂ = 7.4, 3J₁₋₉ = 1.2, 1 H, 1); 6.50 (mult, 1 H, 3); 6.69 (mult, 1 H, 3)

13C NMR (CDCl₃, 50 MHz): major isomer: 22.9 (8); 29.8 (7); 36.8 (2); 39.7 (6); 50.3 (9); 90.7 (1); 132.7 (3); 140.8 (4); 196.7 (5); minor isomer: 25.5 (8); 29.8 (7); 36.2 (2); 39.6 (6); 49.7 (9); 88.3 (1); 135.0 (3); 140.7 (4); 197.1 (5)

Mass (Cl/CH₄-N₂O): 59 (58%); 63 (37%); 89 (100%); 135 ([M-NO₂]⁺, 69%); 151 (28%); 166 (12%); 182 ([M+H]⁺, 5%)

11.1.2 Cyclization of 198

A mixture of 100 mg (385.6 µmol; 1 eq.) of 2-(3,3-diethoxy-1-nitropropyl)cyclopentenone 198, 1.7 ml of THF and 0.263 ml (658.8 µmol; 1.7 eq.) of a 2.5N solution of hydrochloric acid was stirred for 2 hours at room temperature. It was then neutralized with a 5% solution of NaHCO₃ and diluted with Et₂O. The organic phase was washed 3 times with water and once with a saturated solution of NaCl. The aqueous phase was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 55 mg (77%)

6-hydroxy-4-nitrohexahydrosentalen-1(2H)-one 219

M.F.: C₈H₁₁NO₄ (M.W. 185.18)

1H NMR (CDCl₃, 200 MHz): 1.94-2.66 (mult + m, 8 H, 2, 4, 6, 7, 8); 3.30-3.46 (m, 1H, 3); 4.69-4.80 (m, 1 H, 1)

13C NMR (CDCl₃, 50 MHz): 26.2 (7); 39.8 (2); 41.6 (6); 47.0 (8); 56.3 (4); 72.4 (3); 90.2 (1); 213.2 (5)

Mass (Cl/CH₄-N₂O): 121 ([M-NO₂-OH]⁺, 100%); 139 ([M-NO₂]⁺, 77%); 168 ([M-OH]⁺, 60%); 186 ([M+H]⁺, 16%)
11.2 The Nef reaction

11.2.1 Nef reaction of adduct 178


In a flask equipped with a reflux condenser 400 mg (2.159 mmol; 1 eq.) of 3-(1-nitropropyl)cyclohexanone 178 were dissolved in 2.2 ml (1.708 g) of MeOH. 1.99 g (16.19 mmol; 7.5 eq.) of chromium(II) chloride dissolved in 54 ml of a 3% solution of HCl were added and the mixture was refluxed for 2 hours. After being cooled to room temperature the reaction mixture was extracted with Et₂O. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure.

Yield: 298 mg (89 %)

3-propionylcyclohexanone 221

M.F.: C₉H₁₄O₂ (M.W. 154.2)  RN: 88017-43-0

TLC: Rᵣ = 0.37 (petroleum ether : AcOEt 70 : 30)

¹H NMR (CDCl₃, 300 MHz): 1.07 (t, ³J₃-2 = 7.2, 3 H, 3); 1.62-1.82 (m, 2 H, 8); 2.00-2.16 (m, 2 H, 9); 2.25-2.62 (m, 6 H, 2, 5, 7); 2.82-2.98 (m, 1 H, 4)

¹³C NMR (CDCl₃, 50 MHz): 7.5 (3); 24.8 and 27.3 (8, 9); 34.1 (2); 40.7 and 42.5 (5, 7); 49.8 (4); 209.6 (6); 210.8 (1)

Mass (Cl/CH₄-N₂O): 155 ([M+H]+, 100%)

GC (100/0/10/290/15): tᵣ = 7.4 min

11.2.2 Nef reaction of 186

In a flame-dried two-necked flask 147 mg (539.8 µmol; 1 eq.) of 3-(3,3-diethoxy-1-nitropropyl)cyclohexanone 186 and 290 mg (1.328 mmol; 2.46 eq.) of phenyl disulfide were dissolved in 2.175 ml of THF. 507 µl (412 mg; 2.036 mmol; 3.77 eq.) of tri-n-butylphosphine were added to this mixture, which was stirred for 3 hours at room temperature. After this time 435 µl of water were added and the mixture was stirred overnight at room temperature. The solvents were removed under reduced pressure. The product was purified by flash chromatography (petroleum ether : AcOEt 60 : 40).

Yield: 88 mg (67 %)

3-(3,3-diethoxypropanoyl)cyclohexanone 222
M.F.: C_{13}H_{22}O_{4} (M.W. 242.31)

TLC: R_f = 0.38 (petroleum ether : AcOEt 70 : 30)

\[\begin{align*}
&1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
&O & O & O & & & & & & & \\
\end{align*}\]

^1H NMR (CDCl₃, 300 MHz): 1.18 and 1.19 (2 t, \(^3J_{5,4} = 6.6\), 6 H, 5); 1.61-1.81 (m, 2 H, 11); 2.01-2.13 (m, 2 H, 10); 2.25-2.56 (m, 4 H, 7, 9); 2.79 (d, \(^3J_{2,3} = 6.0\), 2 H, 2); 2.88-2.99 (m, 1 H, 6); 3.53 and 3.66 (2 mult, 4 H, 4); 4.89 (t, \(^3J_{3,2} = 5.7\), 1 H, 3)

^13C NMR (CDCl₃, 50 MHz): 15.2 (5); 24.7 and 26.7 (10, 11); 40.9 and 42.1 (7, 9); 46.0 (2); 51.0 (6); 62.6 and 62.7 (4); 100.2 (3); 207.7 (8); 209.9 (1)

Mass (Cl/CH₄-N₂O): 103 (37%); 111 (29%); 151 ([M-2OEt]⁺, 52%); 197 ([M-OEt]⁺, 100%); 242 (M**, 3%)

GC (100/0/10/290/15): t_R = 13.24 min
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