Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Oxetanes as Promising Modules in Drug Discovery

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General:

All non-aqueous reactions were carried out using oven-dried (90 °C) or flame dried glassware under a positive pressure of dry nitrogen unless otherwise noted. Tetrahydrofuran, diethyl ether, toluene, and methylene chloride were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content < 30 ppm, *Karl–Fischer* titration).[1] Dioxane was distilled from calcium hydride under an inert atmosphere. Triethylamine was distilled from KOH under an atmosphere of dry nitrogen. All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel 60 F_{254} or Merck Aluminum oxide 60 F_{254} plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain. Chromatographic purification of products (flash chromatography) was performed on E. Merck Silica Gel 60 (230-400 mesh) or Machery Nagel neutral Aluminium Oxide (Brockmann activity 1, deactivated with 6 w% water) using a forced flow of eluant at 0.3-0.5 bar.[2] Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure, unless otherwise stated. Purified compounds were further dried for 12-72 h under high vacuum (0.01-0.05 Torr). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Melting points: measured on a Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected.

NMR spectra: NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for 1H and 13C acquisitions, respectively Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26) for 1H, and chloroform (δ 77.0) for 13C. All 13C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz.

IR spectra: recorded on a PerkinElmer Spectrum RXI FT-IR spectrophotometer. Absorptions are given in wavenumbers (cm^{-1}).

Mass spectra: recorded by the MS service at ETH Zürich. EI-MS (*m*/*z*): VG-TRIBRID spectrometer. MALDI-MS (*m*/*z*): IonSpec Ultima Fourier Transform Mass Spectrometer.

Elemental analyses: performed at the Mikrolabor der ETH Zürich.

Chemical names: generated with AutoNom 2.02 (Beilstein Informationssysteme GmbH) or ChemDraw Ultra 9.0 (CambridgeSoft) and modified where appropriate.

Determination of solubilities at thermodynamic equilibrium

For each compound, a sample of approximately 2 mg was added to ca 150 µL of a 50 mM aqueous phosphate buffer and transferred to a standard 96-well plate at room temperature (22.5±1°C). The pH of each drug suspension was adjusted by using a concentrated NaOH solution and the 96-well plate was placed on a plate shaker which agitated the suspensions over night. At the next day the samples were filtered with a micronic filter plate (MSGVN2250) to separate the solid material from the solution. After confirming unchanged pH of the solutions by way of micro-pH-meter measurements, the solution concentrations were determined by calibrated HPLC. The calibrations were obtained by HPLC analysis of different concentrations of each compound in DMSO.

Determination of lipophilicities ($logD^{pH=7.4}$)

The high-throughput assay method is derived from the conventional 'shake flask' method:
The compound of interest is distributed between a 50mM aqueous TAPSO buffer at pH 7.4 and 1-octanol. The distribution coefficient is then calculated from the difference in concentration in the aqueous phase before and after partitioning and the volume ratio of the two phases.
To measure logD values within the range of -1 to 3.5, it is necessary to carry out the procedure at four different octanol/water ratios.
The "one-phase-analysis" experiment starts with 2 or 9 µL of a pure DMSO-solution of the compound, which is dispensed into, respectively, 38 or 171 µL of the aqueous buffer solution, bringing the compound concentration to approximately c = 0.5 mM. A small part of this solution is then analyzed by UV. The observed optical density corresponds to the concentration of the substance before partitioning.
To a measured aliquot of the aqueous solution a matching aliquot of 1-octanol is added, and the mixture is incubated by quiet shaking for 2 hours at 23±1°C. The emulsion is allowed to stand over night at the same temperature to ensure that the partition

equilibrium is reached. Then, thorough centrifugation at 3000 rpm for 10 min is applied to separate the layers, and the concentration of the compound in the aqueous phase is determined again by measuring the UV-absorption under the same conditions as the reference.

High-throughput measurement of ionization constants (pKa)

Ionization constants are determined at 23±1°C by spectrophotometry using a ProfilerSGA SIRIUS instrument in buffered water solution at ionic strength of 150 mM To this end the UV-spectrum of a compound is measured at different pH values. The solution of the sample is injected at constant flow rate into a flowing pH gradient. Changes in UV absorbance are monitored as a function of the pH gradient. The pKa values are found and determined where the rate of change of absorbance is at a maximum.
The pH gradient is established by proportionally mixing two flowing buffer solutions. The buffer solutions contain mixtures of weak acids and bases that are UV-spectroscopically transparent above 240 nm.
It is necessary to calibrate the gradient in order to know exactly the pH at any given time. This is achieved by introducing standard compounds with known pKa values.

Measurement of amphiphilicity *via* the measurement of surface tension:

An aqueous solution of the compound of known concentration at the limit of its solubility is diluted 1:1 (v/v) with aqueous MOPSO buffer 11 times in sequence. Samples of 5 µL of compound solution are taken at each dilution step and transferred to a 96-well plate containing 45 µL pure aqueous MOPSO buffer in each well. This plate is then placed into a MULTI PI WS1 instrument of KIBRON Inc. The determination of amphiphilicity involves (i) the measurement of the surface tension of the compound solution at different concentrations based on the well known Du Nouy maximum pull force method , and (ii) the determination of the critical micelle concentration (CMC) which is obtained at the intersection of two experimental lines, the first being the correlation line of decreasing surface tension with increasing sample concentration, the second being the plateau line where the surface tension no longer changes with increasing sample concentration. All measurements are done at 22.5±1°C. From the experimental data, the free energies of transfer from aqueous solution to the air-water interface and from aqueous solution to micelles are obtained. The difference of free energies is taken as a measure of amphiphilicity (Fischer, H, Kansy, M., Bur, D., Chimia, 54, 640-645, 2000).

Determination of metabolic stability in liver microsomes

Microsomal incubations were carried out in 96-well plates in 200 µL of liver microsome incubation medium containing potassium phosphate buffer (50mM, pH 7.4), $MgCl_2$ (10mM), EDTA (1mM), $NADP^+$ (2mM), glucose-6-phosphate * 2 H_2O (20 mM), glucose-6-phosphate dehydrogenase (4 units/ml) with 0.1mg of liver microsomal protein per mL. Test compounds were incubated at 2 µM for up to 30 min at 37°C under vortexing at 500 rpm. The reaction was stopped by transferring 30 µL incubation aliquots to 90 µL of ice-cold methanol. Levels of un-metabolized drug were determined by high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (LC/MS/MS). The system consisted of a Shimadzu binary gradient HPLC system, a Waters XTerra® MS C18 column (1mm * 50mm) and a Sciex API 2000 mass spectrometer. A two-component mobile phase pumped at 0.15 mL/min contained the following solvents: solvent A (1% aqueous formic acid and MeOH 80:20) and solvent B (MeOH). An initial isocratic step of 0.5 min solvent A was followed by a gradient of 0 to 80% solvent B within 1 min. Detection was performed in positive mode. The intrinsic clearance (CL_{int}) was determined in semi-logarithmic plots of compound concentrations *versus* time.

Determination of chemical stability in aqueous solutions

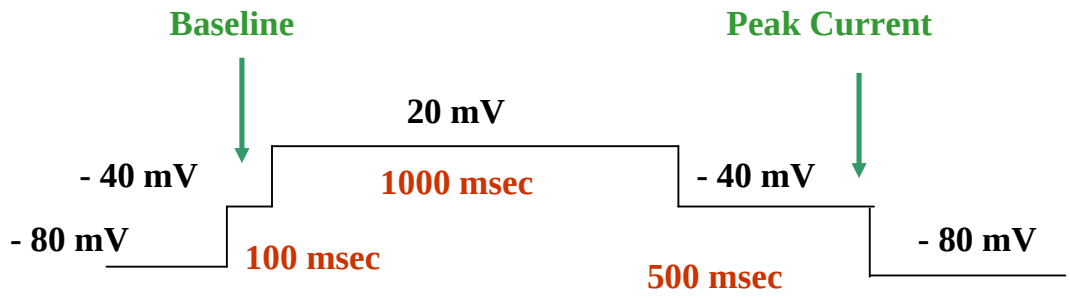
The chemical stability of a given compound is determined in aqueous solutions at pH 1, 4, 6, 8, 10. Commercial available buffer systems from Merck KGaA, Darmstadt (Catalog numbers 109881, 109884, 109886, 109888, 109890) are used. An aqueous stock solution of 10 mM of each sample is prepared and diluted at a ratio of 1:20 (v/v) with buffer solution before they are shaken for 10 minutes at 37°C. Next, the solutions are transferred to a filter plate (Millipore MSGVN2250, pore size 0.22 µm) and filtrated into V-bottom plates (from ABGene, AB-0800) that are heat-sealed prior to analysis by HPLC. Samples are taken at time points 0h and 2h and analyzed by HPLC. The percentage of recovered unchanged compound is determined by calibrated HPLC. A compound is classified as “chemically unstable” if after 2 hours less than 90% of the initial concentration is detected.

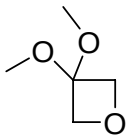
Automated patch clamp procedure for the hERG current measurement at PatchXpress 7000A

Electrophysiologcal recordings of K^+ currents (IK_{hERG}) were conducted at room temperature (22-25°C) using Aviva Bioscience *Seal*Chip$_{16}$™ (Molecular Devices Corporation, Cat SealChip™16). CHO cells stably expressing hERG K^+ channels (Roche Palo Alto, USA) were added by the integrated Cavro robot to each well of the sealchip. Cells were held at a resting voltage of –80 mV and they were stimulated by a voltage pattern to activate hERG channels and conduct outward IK_{hERG} current (Figure 1) at a stimulation frequency of 0.1 Hz (6 bpm). Cell health and membrane parameters (access resistance (Ra), membrane resistance (Rm) and membrane capacitance (Cm)) were monitored on-line. After the cells stabilized and the currents were steady, the amplitude and kinetics of IK_{hERG} were recorded under control conditions. Thereafter, the solution of the test compound in the extracellular buffer (NaCl 150 mM, KCl 4 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 1 mM, HEPES 10 mM, pH 7.4 with NaOH, 300-310 mOsm) was directly added by the robot to each well at increasing concentrations. Double addition of each compound concentration was performed at 1 min interval to ensure the full exchange of the solution in the well. Currents were monitored continuously during the exposure to compounds.

Offline analysis of the peak tail current was performed using DataXpress2 software (Molecular Devices Corporation, USA). The amplitude and kinetics of IK_{hERG} were recorded in each concentration of drug and they were compared to the control values (taken as 100%) to define fractional blocks. The hERG current was measured as the average current from 10 sweeps collected at the end of vehicle or compound addition. Data were expressed as mean±SEM. Concentration-response curves were fitted by non-linear regression analysis and the IC_{50} values were reported.

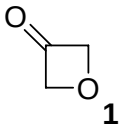
Figure 1 Pulse pattern used to elicit outward K^+ currents.





3,3-dimethoxyoxetane: To a solution of dihydroxy acetone dimer (60.0 g, 0.34 mol, 1.00 equiv and trimethyl orthoformate (70.0 g, 0.66 mol, 2.00 equiv) in 900 mL methanol was added *p*TSA (240 mg, 1.26 mmol, 0.004 equiv) at room temperature. After stirring for 10 h, the reaction was quenched by addition of 13.2 g dried Ambersep 900 OH ion exchanger. After stirring for 15 minutes, the ion exchanger resin was filtered off and the filtrate evaporated. The residual slightly yellow oil was dried under high vacuum for further 4 h to give crude dihydroxy acetone dimethylketal as a white solid which was used without further purification[3, 4]. This material was dissolved in 900 mL THF and cooled to 0°C. A 2.5 M solution of *n*BuLi in hexanes (270 mL, 0.64 mol, 1.90 equiv) was added slowly over 45 min using a transfer cannula. After stirring for further 45 minutes, a solution of p-toluenesulfonyl chloride (122 g, 0.64 mol, 1.90 equiv) in 300 mL THF was added dropwise over 1 h[5]. After stirring for 1 h, the mixture was evaporated under reduced pressure (bath-temp <35°C) to a volume of ~200 mL and mixed with 300 mL diethyl ether. Water was added and the aqueous phase extracted with diethyl ether (200 mL) twice. The combined organic phases were dried over magnesium sulfate, filtered, evaporated and the residue dissolved in 1.6 L THF. The solution was cooled to 0°C and sodium hydride (60% dispersion in mineral oil, 24.2 g, 0.61 mol, 1.80 equiv) was added in 4 portions. After stirring for 1 h at 0°C, the mixture was allowed to warm to room temperature and stirred for further 48 h. The mixture was poured on ice and diluted with 200 mL diethyl ether. The aqueous phase was extracted with diethyl ether (200 mL) twice. The combined organic phases were dried over magnesium sulfate for 20 minutes, filtered, evaporated under reduced pressure (bath temperature 25°C, 100 mbar) and the residue distilled (20 mbar, b_p = 40°C) to give 3 fractions containing 29.87 g product (37.6%, calculated on the amount of dihydroxy acetone dimer used) as a clear colorless liquid.

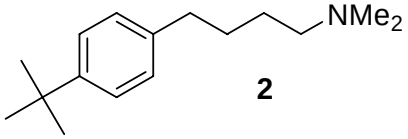
R_f = 0.41 (hexane/EtOAc 2:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.55 (s, 4H), 3.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 100.6, 79.8, 49.4; IR (thin film) ν 2954, 2878, 2835, 1473, 1716, 1453, 1352, 1204, 1134, 1044, 980 cm^{-1}; Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 51.07; H, 8.45;



1

Oxetan-3-on: 3,3-dimethoxyoxetane (15.8 g, 0.13 mol) was dissolved in 7 L dichloromethane and 99.1 g Montmorillonite K10 clay was added. The mixture was refluxed for 70 h, cooled to room temperature, filtered through a plug of celite and the plug washed with three times 50 mL dichloromethane. The Dichloromethane was removed from the filtrate by distillation employing a 30 cm Vigreux column to prevent product from distilling over. The residue was transferred to a 100 mL flask and distilled under reduced pressure (b_p = 50-56°C, 68 mm, bath temperature = 87°C) to give 5.96 g (62%) product in 2 fractions. One containing 5.37 g product (~90w% by NMR) being a clear slightly yellowish liquid, another containing 0.59 g product (30 w%) together with dichloromethane. The material should be stored in the freezer, where it solidifies.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.40 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ.199.7, 92.6; The proton NMR had been reported before[6] and is identical with the one observed.

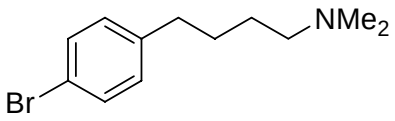


2

4-(4-*tert*-butylphenyl)-N,N-dimethylbutan-1-amine[7]: To a suspension of the hydro bromide salt of (3-(dimethylamino)propyl)triphenylphosphonium bromide[8] (3.8 g, 7.5 mmol, 1.0 equiv) in 100 mL dry THF was added *n*BuLi (1.6 M in hexanes, 9.9 mL, 15 mmol, 2.0 equiv) at 0°C. After stirring for 40 min at 0°C, a solution of *p*-*t*Bu-benzaldehyde (1.2 g, 7.5 mmol, 1.0 equiv) in 5 mL dry THF was added slowly. The mixture was stirred at 60°C over night, cooled to 0°C; water was added, followed by concentrated aqueous HCl. The clear yellowish solution was freed from THF by evaporation and washed twice with 50 mL toluene. The aqueous phase was extracted five times with 40 mL chloroform. The combined chloroform phases were dried over magnesium sulfate, evaporated and the residue dissolved in 100 mL methanol. After

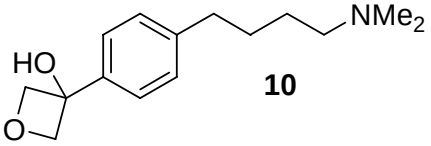
addition of 60 mg Pd/C (10 w%), hydrogen was bubbled through the solution for 45 min and the mixture vigorously stirred for 24 h. The mixture was filtered through a pad of celite, the filtrate evaporated and the residue taken up in ~25 mL water. Diethyl ether (50 mL) was added, followed by excess sodium hydroxide (cooling) to free the amine. The aqueous phase was extracted 3 times with diethyl ether, the combined organic phases were dried over magnesium sulfate, filtered, the filtrate evaporated and the residue distilled to give 1.044 g (60%) pure product as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, J=8.3 Hz), 7.13 (d, 2H, J=8.2 Hz), 2.61 (m, 2H), 2.27 (m, 2H), 2.22 (s, 6H), 1.56 (m, 4H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 139.3, 127.9, 125.0, 59.7, 45.5, 35.2, 34.2, 31.3, 29.2, 27.5; IR (thin film) ν 2939, 2858, 2813, 2762, 1515, 1461, 1392, 1363, 1268, 1042, 828, 570 cm^{-1}; Anal. Calcd for $C_{16}H_{27}N$: C, 82.34; H, 11.66; N, 6.00 . Found: C, 82.27; H, 11.63.; N, 5.95; HRMS (EI) calcd for $C_{16}H_{27}N$ $[M]^+$, 233.2139, found, 233.2139.



[4-(4-Bromo-phenyl)-butyl]-dimethyl-amine[7]: To a suspension of the hydro bromide salt of (3-(dimethylamino)propyl)triphenylphosphonium bromide[8] (12.2 g, 24.0 mmol, 1.00 equiv) in 150 mL dry THF was added *n*BuLi (1.6 M in hexanes, 17 mL, 43 mmol, 1.8 equiv) at 0°C. After stirring for 40 min at 0°C, a solution of *p*-bromobenzaldehyde (5.3 g, 29 mmol, 1.2 equiv) in 15 mL dry THF was added slowly. The mixture was stirred at 60°C over night, cooled to 0°C; water was added, followed by concentrated aqueous HCl. The clear yellowish solution was freed from THF by evaporation and washed twice with 50 mL toluene. The aqueous phase was extracted five times with 40 mL chloroform. The combined chloroform phases were dried over magnesium sulfate, evaporated and the residue dissolved in 100 mL methanol. After addition of 540 mg Rh/C (5 w%), hydrogen was bubbled through the solution for 45 min and the mixture vigorously stirred for 19 h. The mixture was filtered through a pad of celite, the filtrate evaporated and the residue taken up in ~25 mL water. Diethyl ether (50 mL) was added, followed by excess sodium hydroxide (with cooling) to free the amine. The aqueous phase was extracted 3 times with diethyl ether, the combined organic phases were dried over magnesium sulfate, filtered, the filtrate evaporated and the residue distilled (bp ~98°C at 0.5 mm) to give 5.15 g (84%) pure product as a colorless oil.

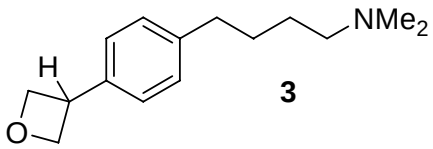
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, 2H, J=8.4 Hz), 7.05 (d, 2H, J=8.3 Hz), 2.63 (m, 2H), 2.27 (m, 2H), 2.21 (s, 6H), 1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 131.2, 130.1, 119.3, 59.6, 45.6, 35.3, 29.2, 27.4; IR (thin film) ν 2937, 2858, 2818, 2762, 1488, 1462, 1072, 1011 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}BrN$ $[M]^+$, 255.0613, found, 255.0614.



10

3-[4-(4-Dimethylamino-butyl)-phenyl]-oxetan-3-ol: To a solution of [4-(4-Bromo-phenyl)-butyl]-dimethyl-amine (0.89 g, 3.48 mmol, 1.30 equiv.) in 10 mL dry THF was added a solution of *n*BuLi (2.5 M in hexanes, 1.4 mL, 3.5 mmol, 1.3 equiv) at –78°C. After stirring for 10 min, a solution of oxetan-3-on (193 mg, 2.68 mmol, 1.0 equiv.) in 4 mL dry THF was added dropwise. The mixture was stirred for 10 min, before it was allowed to warm to RT. Water was added and the aqueous phase extracted three times with ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered, evaporated and the residue purified by flash chromatography (SiO_2; 10% to 40% MeOH in methylene chloride, 0.1% NEt_3) to give 480 mg (71%) pure product as a viscous colorless oil which solidified upon cooling (m_p=57-58°C).

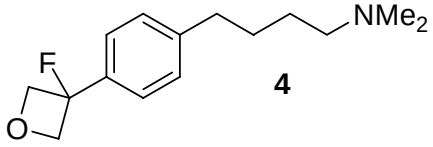
R_f = 0.17 (SiO_2, 40% MeOH in CH_2Cl_2, 0.1% NEt_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 2H, J=8.3 Hz), 7.23 (d, 2H, J=8.2 Hz), 4.92 (d, 2H, J=6.9 Hz), 4.89 (d, 2H, J=6.9 Hz), 2.65 (m, 2H), 2.26 (m, 2H), 2.20 (s, 6H), 1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 139.9, 128.5, 124.4, 85.5, 75.5, 59.6, 45.4, 35.4, 29.3, 27.3; IR (thin film) ν 3373, 2940, 2859, 2780, 1467, 1175, 981 cm^{-1}; Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.13; H, 9.30; N, 5.54; HRMS (EI) calcd for $C_{15}H_{23}NO_2$ $[M]^+$, 249.1729, found, 249.1723



3

Dimethyl-[4-(4-oxetan-3-yl-phenyl)-butyl]-amine: To a solution of tertiary alcohol **10** (135 mg, 0.54 mmol, 1.00 equiv) in 8 mL dry diethyl ether was added NaH (60% dispersion in mineral oil, 45 mg, 1.1 mmol, 2.1 equiv) at 0°C. After stirring for 1 h at RT, *p*TosCl (135 mg, 0.71 mmol, 1.30 equiv.) was added at 0°C. After stirring for 1 h at 0°C, the mixture was cooled to –78°C and a solution of lithium aluminum hydride (1.0 mL, 4.0 mmol, 7.4 equiv, 4.0 M solution in diethyl ether) was added slowly. After stirring for 1 h, the reaction was quenched at this temperature by dropwise addition of 2 M aqueous NaOH. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were washed once with brine, dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Al_2O_3; 20/1 to 1/1 cyclohexane/ethyl acetate) to give 73 mg (58%) pure product as a colorless oil.

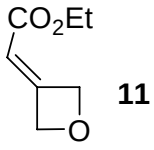
R_f = 0.44 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, J=8.1 Hz), 7.18 (d, 2H, J=8.0 Hz), 5.05 (dd, 2H, J=5.9 Hz, J=8.4 Hz), 4.77 (dd, 2H, J=6.1 Hz, J=6.7 Hz), 4.20 (m, 1H), 2.63 (m, 2H), 2.26 (m, 2H), 2.20 (s, 6H), 1.63 (m, 2H), 1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 138.7, 128.7, 126.6, 79.1, 59.8, 45.7, 40.1, 35.5, 29.4, 27.6; IR (thin film) ν 2937, 2868, 2813, 2763, 1515, 1463, 983 cm^{-1}; Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.87; N, 6.00. Found: C, 76.99; H, 9.87; N, 5.98; HRMS (EI) calcd for $C_{15}H_{23}NO$ $[M]^+$, 233.1775, found, 233.1776.



4

{4-[4-(3-Fluoro-oxetan-3-yl)-phenyl]-butyl}-dimethyl-amine: To a solution of tertiary alcohol **10** (135 mg, 0.54 mmol, 1.00 equiv) in 8 mL dry methylene chloride was added DAST (86 µL, 0.65 mmol, 1.20 equiv) at –78°C. The mixture was allowed to warm to 0°C over 2 h and quenched by adding 1 M aqueous NaOH at –5°C. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were washed once with brine, dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Al_2O_3; 20/1 to 1/1 cyclohexane/ethyl acetate) to give 54 mg (40%) pure product as a colorless oil.

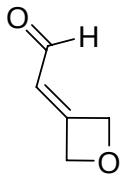
R_f = 0.43 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, J=8.0 Hz), 7.25 (d, 2H, J=8.0 Hz), 5.08 (ddd, 2H, J=1.1 Hz, J=7.8 Hz, J=21.2 Hz), 4.88 (ddd, 2H, J=1.1 Hz, J=7.8 Hz, J=21.5 Hz), 2.65 (t, 2H, J=7.5 Hz), 2.26 (m, 2H), 2.20 (s, 6H), 1.64 (m, 2H), 1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 135.6 (d, J=23.8Hz), 128.6, 124.0 (d, J=8.2Hz), 83.2 (d, J=25.5Hz), 95.2 (d, J=206.3Hz), 59.72, 45.64, 35.6, 29.30, 27.5; IR (thin film) ν 1940, 2858, 2814, 2764, 1518, 1460, 1299, 1174, 982, 820 cm^{-1}; Anal. Calcd for $C_{15}H_{22}FNO$: C, 71.68; H, 8.82; N, 5.57. Found: C, 71.44; H, .8.93; N, 5.77; HRMS (EI) calcd for $C_{15}H_{22}FNO$ $[M]^+$, 251.1680, found, 251.1682



11

Oxetan-3-ylidene-acetic acid ethyl ester: To a solution of oxetan-3-on (0.22 g, 3.0 mmol, 1.0 equiv) in 6 mL dry methylene chloride was added Carboethoxymethylene triphenylphosphorane (1.2 g, 3.3 mmol, 1.1 equiv) at 0°C. The solution was allowed to warm to room temperature and after stirring for 15 min filtered through silica gel (2/1 Cyclohexane/EtOAc) to give 388 mg (89%) product (97 w% by NMR) as a colorless oil.

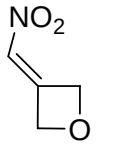
R_f = 0. 0.33 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.47 (m, 2H), 5.27 (m, 2H), 4.13 (q, 2H, J=7.1 Hz), 1.24 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 159.3, 111.3, 81.2, 78.6, 60.5, 14.4; IR (thin film) ν 2983, 2927, 2858, 1722, 1698, 1446, 1372, 1346, 1298, 1266, 1206, 1100, 1038, 961, 870, 833 cm^{-1}; Anal. Calcd for $C_7H_{10}O_3$: C, 77.21; H, 9.87; N, 6.00. Found: C, 76.99; H, 9.87; N, 5.98.



12

Oxetan-3-ylidene-acetaldehyde: To a solution of oxetan-3-on (441 mg, 6.12 mmol, 1.00 equiv) in 8 mL dry methylene chloride was added formylmethylene triphenylphosphorane (2.6 g, 8.6 mmol, 1.4 equiv) at RT. The solution was stirred over night and filtered through silica gel (1/1 pentane/diethyl ether) to give 537 mg product (~90 w% by NMR) as an orange oil (yield 81% assuming 90% purity).

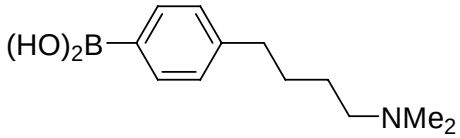
R_f = 0.33 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.52 (d, 1H, J=5.8 Hz), 5.92 (m, 1H), 5.58 (m, 2H), 5.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 168.0, 163.4, 119.8, 80.0, 79.7; IR (thin film) ν 2918, 2856, 2747, 1693, 1650, 1149, 962, 865 cm^{-1}; HRMS (EI) calcd for $C_5H_6O_2$ $[M]^+$ 98.0368, found: 98.0359



13

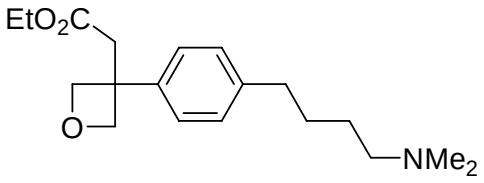
3-Nitromethylene-oxetane: To a solution of oxetane-3-on (188 mg, 2.61 mmol, 1.00 equiv) in 3 mL nitro methane was added a catalytic amount of triethyl amine (6 drops) at RT. After stirring for 20 minutes, the mixture was evaporated and the residue dissolved in 10 mL dry methylene chloride. The mixture was cooled to –78°C, triethyl amine (1.6 mL, 12 mmol, 4.4 equiv) was added followed by dropwise addition of mesyl chloride (600 µL, 7.75 mmol, 3.00 equiv) over 10 min (pink color). After stirring for 20 min, the mixture was directly put on a column packed with silica gel and eluted with 1/1=diethyl ether /pentane to give 243 mg (81%) of product as a white solid (m_p=41-43°C).

R_f = 0.28 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (m, 1H), 5.66 (m, 2H), 5.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 130.0, 79.6, 75.5; IR (thin film) ν 3092, 2925, 2848, 1698, 1525, 1421, 1350, 1319, 1186, 1125, 960, 947, 904, 828, 777, 725 cm^{-1}; HRMS (EI) calcd for $C_4H_5NO_3$ $[M-H]^+$ 114.0186, found: 114.0184.



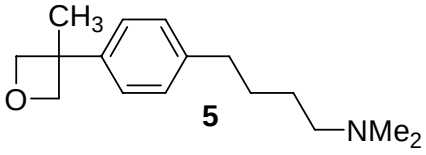
2-(4-(4-(dimethylamino)butyl)phenyl) boronic acid: To a solution of [4-(4-Bromo-phenyl)-butyl]-dimethyl-amine (0.97 g, 3.8 mmol, 1.0 equiv) in 30 mL of a 1/1-mixture of diethyl ether and THF was slowly added *n*BuLi (1.6 M in hexanes, 3.0 mL, 4.8 mmol, 1.3 equiv) at –78°C. After stirring for 45 minutes, freshly distilled triisopropyl borate (1.5 mL, 6.0 mmol, 1.6 equiv) was added and the mixture was allowed to warm to RT over night. 6 mL 2 M aqueous HCl were added and the mixture vigorously stirred for 20 minutes. The mixture was basified with 5 M aqueous NaOH and the aqueous phase was washed 2 times with diethyl ether. The pH was adjusted to 9-10 with aqueous HCl. The aqueous phase was saturated with sodium chloride and extracted 5 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered, evaporated and the residue (white foam) used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, 2H, J=7.7Hz), 7.22 (d, 2H, J=7.9Hz), 2.68 (t, 2H, J=6.7Hz), 2.43 (m, 2H), 2.28 (s, 6H), 1.62 (m, 4H).



Ethyl 2-(3-(4-(4-(dimethylamino)butyl)phenyl)oxetan-3-yl)acetate: To a solution of $[Rh(cod)Cl]_2$ (25.0 mg, 0.05 mmol, 0.05 equiv) in 3 mL dry dioxane was added aqueous KOH (1.5 M, 0.9 mL, 1.3 mmol, 1.3 equiv), followed by the α,β-unsaturated ester **11** (137 mg, 0.96 mmol, 1.00 equiv) and a solution of 2-(4-(4-(dimethylamino)butyl)phenyl) boronic acid (320 mg, 1.45 mmol, 1.50 equiv) in ~5 mL dry dioxane. After stirring for 6 h, diethyl ether and brine were added. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Al_2O_3; 8/1 to 2/1 cyclohexane/ethyl acetate) to give 256 mg (83%) pure product as colorless oil.

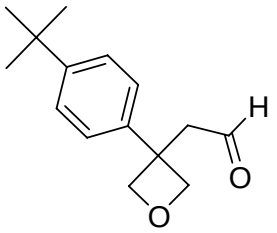
R_f = 0.29 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, 2H, J=8.2Hz), 7.06 (d, 2H, 8.2Hz), 4.99 (d, 2H, J=6.1Hz), 4.84 (d, 2H, J=6.1Hz), 3.99 (q, 2H, J=7.1Hz), 3.08 (s, 2H), 2.60 (m, 2H), 2.25 (m, 2H), 2.19 (s, 6H), 1.52 (m, 4H), 1.10 (t, 3H, J=7.1Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 141.1, 128.7, 125.8, 82.2, 60.5, 59.9, 45.7, 45.3, 45.0, 35.6, 29.4, 27.6, 14.2; IR (thin film) ν 2933, 2867, 2762, 1798, 1463, 1372, 1191, 1029, 989 cm^{-1}; HRMS (MALDI) calcd for $C_{19}H_{29}NO_3$ $[M]^+$ 319.2142, found: 319.2142.



5

N,N-dimethyl-4-(4-(3-methyloxetan-3-yl)phenyl)butan-1-amine: To a solution of Ethyl 2-(3-(4-(4-(dimethylamino)butyl)phenyl)oxetan-3-yl)acetate (232 mg, 0.73 mmol, 1.00 equiv) in 10 mL diethyl ether was added a solution of DIBALH (20 w% in hexanes, 2.2 mL, 2.2 mmol, 3.0 equiv) at –78°C over 45 minutes. After stirring for 1 h at this temperature, the solution was poured into ice cold 1 M HCl. The aqueous phase was basified with KOH (cooling) and extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in ~30 mL toluene. $[(Ph_3P)_3RhCl]$ (2.0 g, 2.2 mmol, 3.0 equiv) were added and the mixture stirred at 105°C for 16 h. After cooling to RT, the mixture was filtered, washed with diethyl ether and 2 M aqueous NaOH. The aqueous phase was extracted 3 times with ethyl acetate, dried over magnesium sulfate, filtered, evaporated and the residue purified by flash chromatography (Al_2O_3; 20/1 to 4/1 cyclohexane/ethyl acetate) to give 66 mg (33%) pure product as colorless oil.

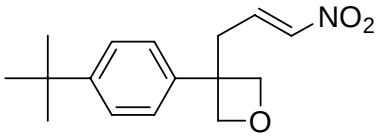
R_f = 0.45 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, 2H, J=8.2Hz), 7.10 (d, 2H, J=8.3Hz), 4.95 (d, 2H, J=5.5Hz), 4.61 (d, 2H, J=5.5Hz), 2.61 (m, 2H), 2.27 (m, 2H), 2.21 (s, 6H), 1.71 (s, 3H), 1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 140.7, 128.7, 125.1, 84.1, 59.9, 45.8, 43.3, 35.6, 29.5, 28.0, 27.7; IR (thin film) ν 2935, 2865, 2814, 2763, 1517, 1461, 1041, 985, 821 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{25}NO$ $[M]^+$ 247.1931, found: 247.1933.



[3-(4-*tert*-Butyl-phenyl)-oxetan-3-yl]-acetaldehyde: A catalytic amount (~2 mg, ~0.004 mmol, 0.01 equiv)of $[Rh(cod)Cl]_2$ was dissolved in 1.6 mL dry dioxane within 10 min. 1.5 M aqueous KOH (0.17 mL, 0.25 mmol, 0.5 equiv) was added and the mixture was stirred for 5 minutes before *p*-*t*Bu-phenylboronic acid (198 mg, 1.11 mmol, 2 equiv) was added. A solution of α,β-unsaturated aldehyde **12** (49 mg, 0.5 mmol, 1.0 equiv) in 0.6 mL dry dioxane was added and the mixture stirred for 20 minutes at RT. Another 170 mg of *p*-*t*Bu-phenylboronic acid (0.96 mmol, 1.9 equiv) were added to drive the reaction to completion. After further stirring for 1 h, diethyl ether (20 mL) and water was added. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by

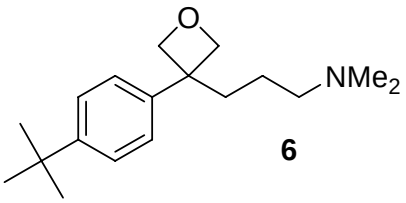
flash chromatography (SiO_2; 8/1 to 2/1 cyclohexane/ethyl acetate) to give 90 mg (78%) pure product as a white solid (m_p=66-67°C).

R_f = 0.35 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (t, 1H, J=1.7 Hz), 7.38 (d, 2H, J=8.6 Hz), 7.10 (d, 2H, J=8.5 Hz), 5.06 (d, 2H, J=6.2 Hz), 4.77 (m, 2H), 3.25 (d, 2H, J=1.7 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 149.7, 140.2, 125.5, 125.4, 82.0, 53.3, 44.6, 34.6, 31.4; IR (thin film) ν 3092, 2925, 2848, 1698, 1525, 1421, 1350, 1319, 1186, 1125, 960, 947, 904, 828, 777, 725 cm^{-1}; Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.60; H, 8.72.



3-(4-*tert*-Butyl-phenyl)-3-(3-nitro-allyl)-oxetane: To a solution of [3-(4-tert-Butyl-phenyl)-oxetan-3-yl]-acetaldehyde (90 mg, 0.4 mmol), 1.0 equiv) in 4 mL nitromethane was added triethyl amine (8.0 µL, 58 µmol, 0.2 equiv). After stirring for 3 h, the solvent was evaporated, the residue dissolved in 10 mL dry methylene chloride and cooled to –78°C. Triethyl amine (162 µL, 1.16 mmol, 3.00 equiv) was added, followed by mesyl chloride (90 µL, 1.2 mmol, 3.0 equiv). After stirring for 30 minutes at –78°C, triethyl amine (162 µL, 1.16 mmol, 3.00 equiv) was added and the mixture slowly allowed to warm to 0°C. This solution was added to cold brine and the aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (SiO_2; 8/1 to 4/1 cyclohexane/ethyl acetate) to give 62 mg (58%) almost pure product as a yellowish oil that solidified in the freezer (m_p= 69-72°C).

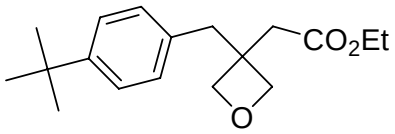
R_f = 0.40 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, 2H, J=8.4 Hz), 7.06 (m, 2H), 6.93 (d, 2H, J=8.5 Hz), 5.01 (d, 2H, J=6.1 Hz), 4.63 (d, 2H, J=6.2 Hz), 3.00 (d, 2H, J=7.5 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0, 141.3, 139.4, 137.4, 125.7, 125.1, 80.8, 46.6, 39.4, 34.6, 31.4; IR (thin film) ν 3098, 2963, 2906, 2872, 1912, 1650, 1526, 1464, 1396, 1352, 1270, 1202, 1116, 982, 835, 736 cm^{-1}; Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.00; H, 7.68; N, 4.91.



6

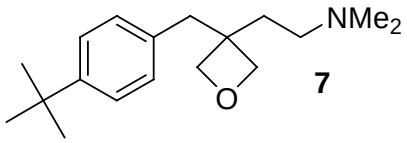
{3-[3-(4-*tert*-Butyl-phenyl)-oxetan-3-yl]-propyl}-dimethyl-amine: To a solution of nitro 3-(4-tert-Butyl-phenyl)-3-(3-nitro-allyl)-oxetane (250 mg, 0.91 mmol, 1.00 equiv) in 15 mL methanol was added $Pd(OH)_2$/C (20w%, 600 mg). Hydrogen was bubbled through this mixture for 45 minutes under vigorous stirring, before formaldehyde (37 w% in water, 1.7 mL, 21 mmol, 23 equiv) and acetic acid (0.2 mL) were added. After stirring for 72 h, the mixture was filtered through a pad of celite, the filtrate evaporated, treated with aqueous NaOH and extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered, evaporated and the residue dissolved in 10 mL methanol. Formaldehyde (37 w% in water, 2.0 mL, 25 mmol, 27 equiv) and acetic acid (34 µL) were added. The mixture was stirred over night, evaporated, taken up in diethyl ether and basified with aqueous NaOH (cooling). The aqueous phase was extracted 3 times with ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Al_2O_3; 20/1 to 2/1 cyclohexane/ethyl acetate) to give 84 mg (34%) pure product as a white solid (m_p = 36-37°C).

R_f = 0.53 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 2H, J=8.5 Hz), 6.95 (d, 2H, J=8.4 Hz), 4.96 (d, 2H, J=5.6 Hz), 4.64 (m, 2H), 2.18 (m, 2H), 2.14 (s, 6H), 2.06 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 141.7, 125.3, 125.2, 82.0, 59.8, 47.0, 45.5, 38.9, 34.5, 31.5, 23.0; IR (thin film) ν 2961, 2867, 2814, 2763, 1511, 1462, 11364, 1269, 1114, 986, 828 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M]^+$, 275.2249, found, 275.2247.



[3-(4-*tert*-Butyl-benzyl)-oxetan-3-yl]-acetic acid ethyl ester: To a suspension of CuI (38 mg, 0.2 mmol, 0.1 equiv) and Oxetan-3-ylidene-acetic acid ethyl ester **11** (309 mg, 2.17 mmol, 1.00 mmol) in 4 mL dry THF was added freshly distilled TMSCl (0.3 mL, 2.4 mmol, 1.1 equiv) at RT. After stirring for 5 minutes, the mixture was cooled to –15°C in a methanol/ice bath. A solution of 4-*t*Bu-BnMgBr (4 mL, 1 M in diethyl ether) was dropwise added over 1 h. After stirring for 2 h, saturated aqueous $KHSO_4$ was added. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (SiO_2; 8/1 to 2/1 cyclohexane/ethyl acetate) to give 439 mg (70%) pure product as a colorless oil.

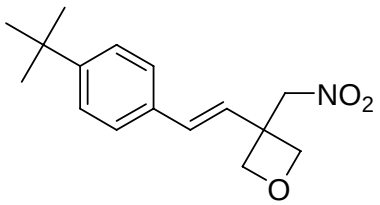
R_f = 0.53 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, 2H, J=8.3 Hz), 7.06 (d, 2H, J=8.3 Hz), 4.65 (d, 1H, J=6.2 Hz), 4.52 (d, 2H, J=6.2 Hz), 4.16 (q, 1H, J=7.1 Hz), 3.10 (s, 2H), 2.65 (s, 2H), 1.31(s, 9H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 149.4, 134.2, 129.3, 125.3 80.9, 60.5, 41.8, 41.3, 40.1, 34.5, 31.5, 14.4,; IR (thin film) ν 2967, 2871, 1733, 1509, 1371, 1177, 1028, 981, 668 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{26}O_3$ $[M]^+$ 290.1882, found: 290.1880.



7

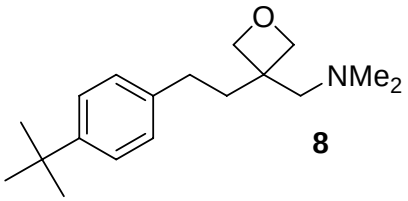
{2-[3-(4-*tert*-Butyl-benzyl)-oxetan-3-yl]-ethyl}-dimethyl-amine: To a solution of ester **11** (359 mg, 1.23 mmol, 1.00 equiv) in 10 mL diethyl ether was added a solution of DIBALH (20 w% in hexanes, 2.0 mL, 5.2 mmol, 1.7 equiv) at –78°C over 45 minutes. After stirring for 1 h at this temperature, the solution was poured into ice cold 4 M HCl. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in 50 mL methanol, before triethyl amine (0.3 mL, 1.8 mmol, 1.5 equiv) and dimethylammonium chloride (1.04 g, 12.8 mmol, 10.4 equiv) were added. Acetic acid was added until the pH was between 4 and 5. The mixture was stirred for 1.5 h, before $NaCNBH_3$ (785 mg, 12.3 mmol, 10.0 equiv) was added. The mixture was stirred over night at RT, concentrated and taken up with diethyl ether. Water was added, followed by NaOH with cooling. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Al_2O_3; 20/1 to 4/1 cyclohexane/ethyl acetate) to give 95 mg (28%) pure product as yellowish oil.

R_f = 0.39 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 2H, J=8.2 Hz), 7.06 (d, 2H, J=8.2 Hz), 4.59 (d, 2H, J=5.9 Hz), 4.43 (d, 2H, J=5.9 Hz), 2.94 (s, 2H), 2.37 (m, 2H), 2.24 (s, 6H), 1.80 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 134.5, 129.0, 125.2, 81.0, 55.1, 45.8, 42.5, 41.5, 34.4, 33.3, 31.4; IR (thin film) ν 2961, 2866, 1463, 1365, 1267, 981, 835 cm^{-1}; Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.38; H, 10.83; N, 4.96; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M]^+$, 275.2249, found, 275.2241.



3-[2-(4-*tert*-Butyl-phenyl)-vinyl]-3-nitromethyl-oxetane: To a solution of $[Rh(cod)Cl]_2$ (10.0 mg, 0.02 mmol, 0.03 equiv)in 4 mL dry dioxane was added aqueous KOH (1.5 M, 0.6 mL, 0.9 mmol, 1.3 equiv) at RT. After stirring for 2 minutes, nitromethylene oxetane **13** (0.1 g, 0.9 mmol, 1.0 equiv) was added, followed by a solution of (E)-4-*tert*-butylstyrylboronic acid (0.2 g, 1.1 mmol, 1.2 equiv) in 3 mL dry dioxane. After stirring for 30 min, additional (*E*)-4-*tert*-butylstyrylboronic acid (75 mg, 0.4 mmol, 0.4 equiv) was added. After stirring for further 20 min, diethyl ether and brine were added. The aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (SiO_2; 8/1 to 4/1 cyclohexane/ethyl acetate) to give 137 mg (55%) pure product as a white solid (m_p=108-110°C).

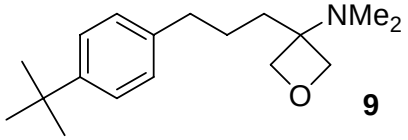
R_f = 0.40 (SiO_2, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (q, 4H, J=8.4 Hz), 6.55 (d, 1H, J=16.3 Hz), 6.30 (d, 1H, J=16.3 Hz), 4.89 (s, 2H), 4.85 (d, 2H, J=6.5 Hz), 4.74 (d, 2H, J=6.5 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.4, 132.9, 131.7, 126.1, 126.0, 125.5, 80.2, 78.7, 44.6, 34.7, 31.3; IR (thin film) ν 2953, 2919, 2868, 1547, 1377, 1270, 1108, 976, 814 cm^{-1}; Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.50; H, 7.96; N, 5.00; HRMS (EI) calcd for $C_{16}H_{21}NO_3$ $[M]^+$, 275.1521, found, 275.1515.



8

{3-[2-(4-*tert*-Butyl-phenyl)-ethyl]-oxetan-3-ylmethyl}-dimethyl-amine: Through a mixture of 3-[2-(4-tert-Butyl-phenyl)-vinyl]-3-nitromethyl-oxetane (164 mg, 0.60 mmol, 1.00 equiv) and $Pd(OH)_2$/C (20 w%, 70 mg) was bubbled hydrogen for 50 minutes. The mixture was then vigorously stirred over night. After filtration through a pad of celite, aqueous formaldehyde (37 w%, 1.6 mL, 2.0 mmol, 3.3 equiv) and the solution adjusted to a pH between 4 and 5 with acetic acid. After stirring for 30 minutes, $NaCNBH_3$ (120 mg, 1.90 mmol, 3.20 equiv) was added. The mixture was stirred for 5.5 h, evaporated to ~1 mL and diethyl ether and aqueous NaOH (cooling) were added. The aqueous phase was saturated with NaCl and extracted 3 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Al_2O_3; 20/1 cyclohexane/ethyl acetate) to give 109 mg (67%) pure product as a yellowish oil that solidified in the freezer (m_p = 40-42°C).

R_f = 0.74 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 2H, J=8.3 Hz), 7.18 (d, 2H, J=8.2 Hz), 4.46 (d, 2H, J=5.9 Hz), 4.40 (d, 2H, J=5.9 Hz), 2.58 (m, 4H), 2.17 (s, 6H), 2.12 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 139.1, 127.9, 125.1, 81.0, 64.3, 46.3, 46.3, 42.7, 36.6, 34.4, 31.5, 29.8; IR (thin film) ν 2961, 2859, 2817, 2765, 1517, 1458, 1364, 1266, 1036, 989, 823, 772 cm^{-1}; Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H 10.61, N, 5.09. Found: C, 78.41, H, 10.60, N, 5.16; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M]^+$, 275.2249, found, 275.2245.



9

{3-[3-(4-*tert*-Butyl-phenyl)-propyl]-oxetan-3-yl}-dimethyl-amine: To a solution of a catalytic amount of DBU in 1.5 mL dry THF was added dimethyl amine (0.5 M in diethyl ether, 2.4 mL, 1.2 mmol, 1.0 equiv) followed by a solution of α,β-unsaturated aldehyde **12** (117 mg, 1.20 mmol, 1.00 equiv) in 1 mL dry THF at –15°C. The solution was stirred for 50 minutes, before it was added to a solution of *p*-*t*Bu-phenylmethylene triphenylphosphorane in 20 mL dry THF (This solution was made by adding *n*BuLi (1.6 M solution in hexanes, 3.0 mL, 4.8 mmol, 4.0 equiv) at 0°C to a dispersion of (4-*tert*-Butyl-benzyl)-triphenyl-phosphonium bromide (2.8 g, 4.8 mmol, 4.0 equiv) in 20 mL dry THF at 0°C and stirring this mixture for 30 minutes at 0°C.). The reaction mixture was stirred for 30 minutes at 0°C, and then warmed for 30 minutes to 60°C. After cooling to 0°C, 1 M aqueous HCl was added and the THF evaporated under reduced pressure. The residue was washed 3 times with toluene, and then extracted 4 times with chloroform. The combined chloroform phases were washed once with brine (acidified with HCl), dried over magnesium sulfate, filtered, evaporated and the residue dissolved in 20 mL methanol. To this solution Pd/C (10 w%, 100 mg) was added and the atmosphere exchanged with hydrogen. Hydrogen was bubbled through the mixture for 30 minutes and the mixture was vigorously stirred over night and filtered through a plug of celite. The filtrate was evaporated and the residue mixed with water and diethyl ether. Aqueous NaOH (2 M, 2.5 mL) was added (with cooling) and the aqueous phase extracted 4 times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Al_2O_3; 8/1 cyclohexane/ethyl acetate) to give 120 mg (36%) pure product as a colorless oil.

R_f = 0.60 (Al_2O_3, 2/1 Cyclohexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 2H, J=8.3 Hz), 7.15 (d, 2H, J=8.1 Hz), 4.64 (d, 2H, J=6.2 Hz), 4.32 (d, 2H, J=6.3 Hz), 2.66 (t, 2H, J=7.0 Hz), 2.24 (s, 6H), 1.81 (m, 4H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 138.9, 127.9, 125.1, 77.9, 63.4, 38.2, 35.8, 34.3, 31.3, 30.7, 25.8; IR (thin film) ν 2952, 2870,

2782, 1902, 1511, 1476, 1462, 1364, 1269, 1109, 1046, 1019, 984, 830, 573 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{29}NO$ $[M\text{-}CH_3]^+$, 260.2009, found, 260.2007.

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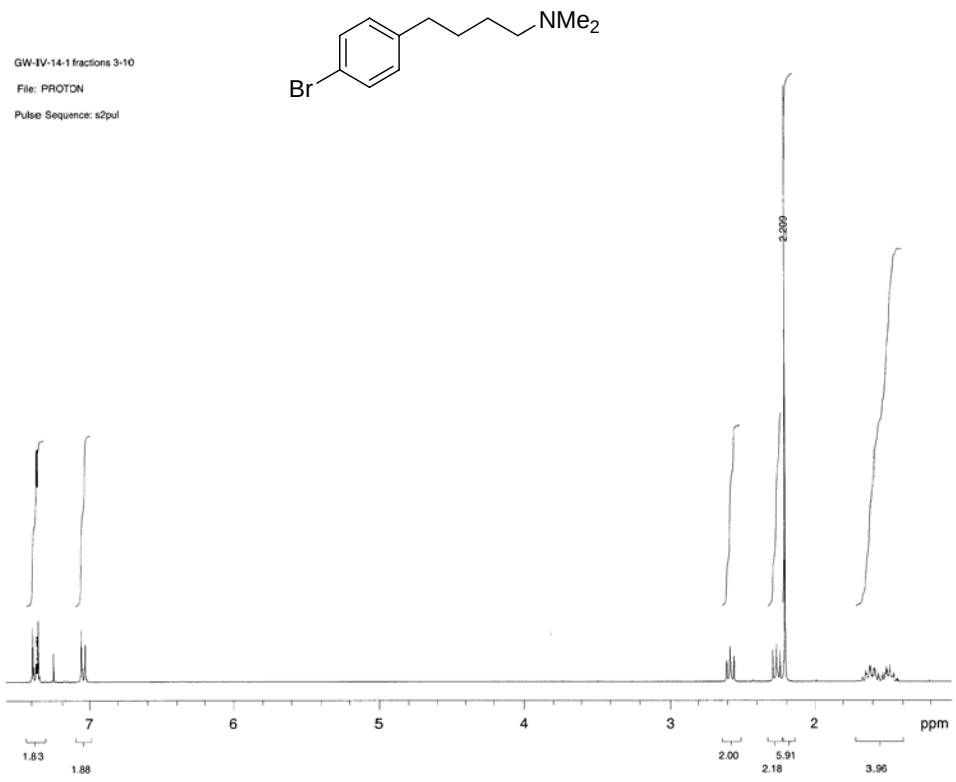
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7
6
5
4
3
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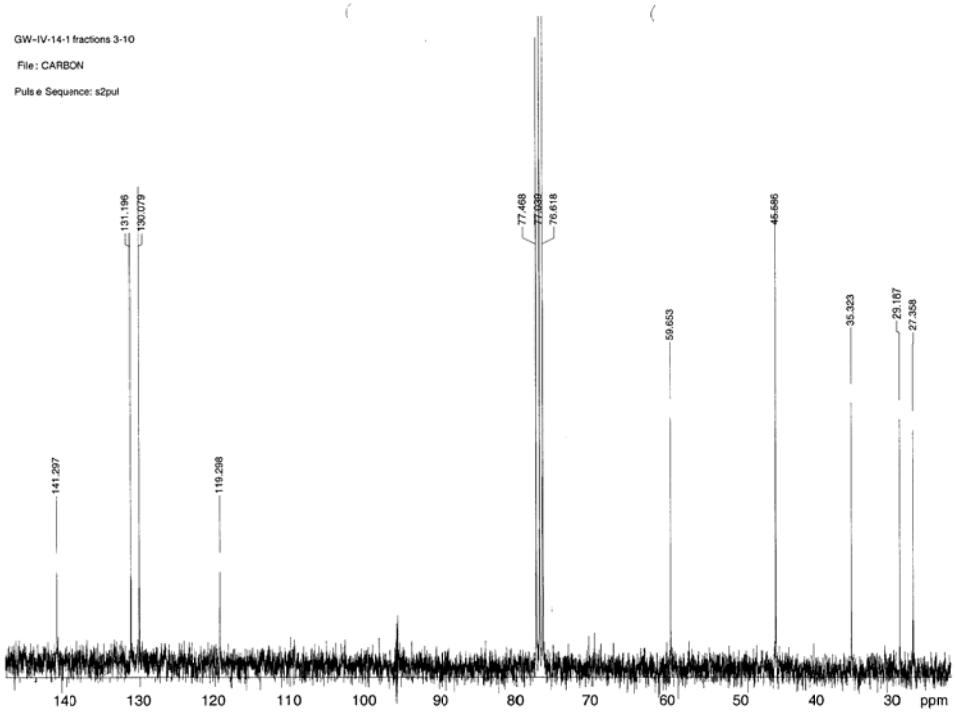
1.83
1.88
2.00
5.91
2.18
3.96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Pulse Sequence: s2pul
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131.196
130.079
119.298
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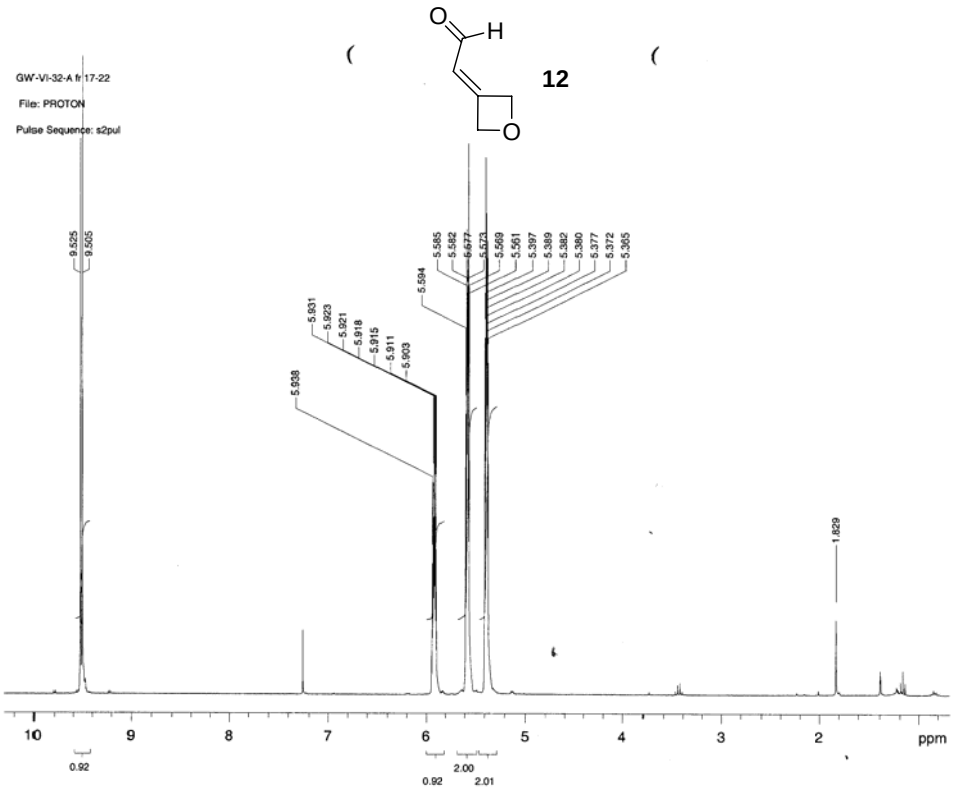
77.039
76.618
59.653
45.656
35.323
29.167
27.358
140
130
120
110
100
90
80
70
60
50
40
30
ppm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O
H
O
12
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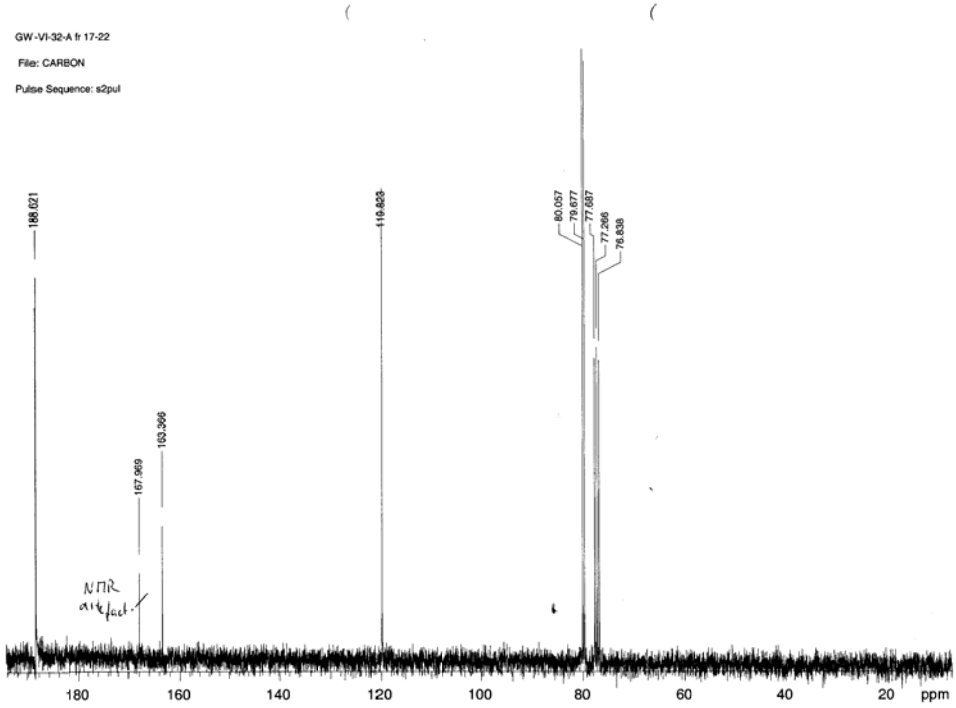
9.505
5.938
5.931
5.923
5.921
5.918
5.915
5.911
5.903
5.594
5.585
5.582
5.577
5.573
5.569
5.561
5.397
5.389
5.382
5.380
5.377
5.372
5.365
1.629
10
9
8
7
6
5
4
3
2
ppm
0.92
0.92
2.00
2.01


GW-VI-32-A fr 17-22
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Pulse Sequence: s2pul
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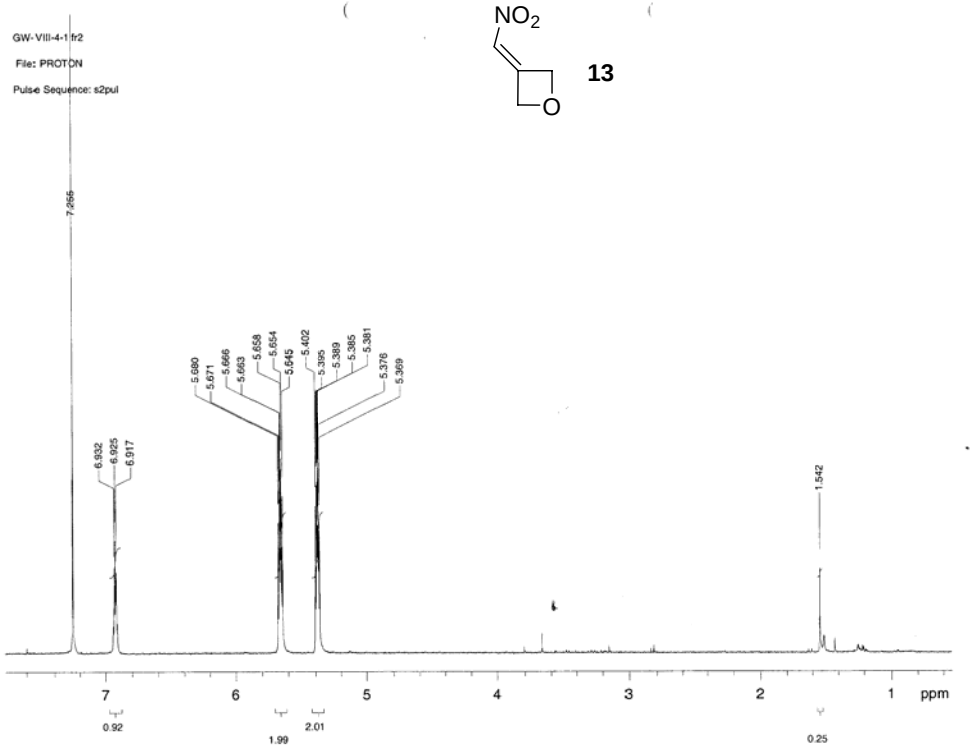
167.969
163.366
119.823
80.057
79.677
77.687
77.266
76.838
NMR
artefact
180
160
140
120
100
80
60
40
20
ppm


GW-VIII-4-1 fr2
File: PROTON
Pulse Sequence: s2pul
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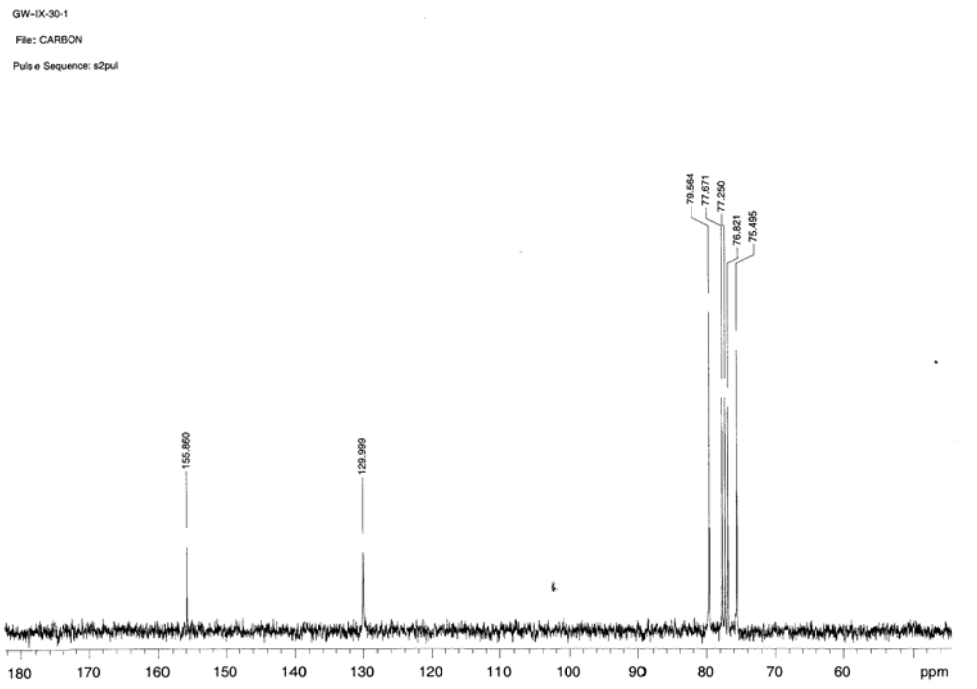
6.925
6.917
5.680
5.671
5.666
5.663
5.658
5.654
5.645
5.402
5.395
5.389
5.385
5.381
5.376
5.369
1.542
7
6
5
4
3
2
1
ppm
0.92
1.99
2.01
0.25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79.564
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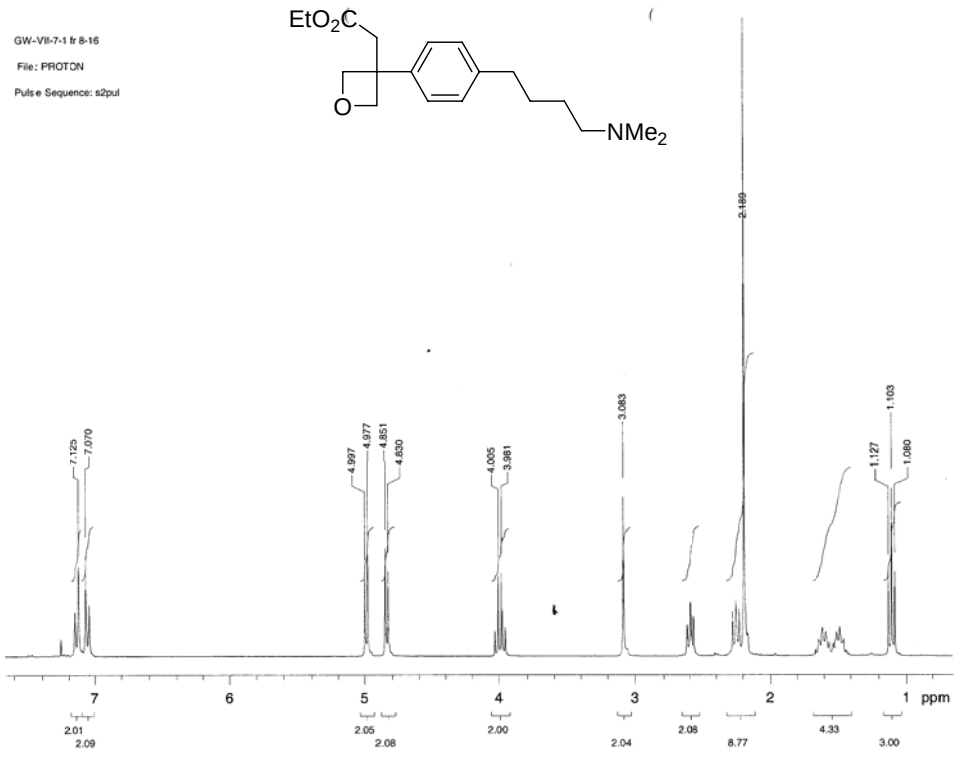
77.250
76.821
75.495
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm

13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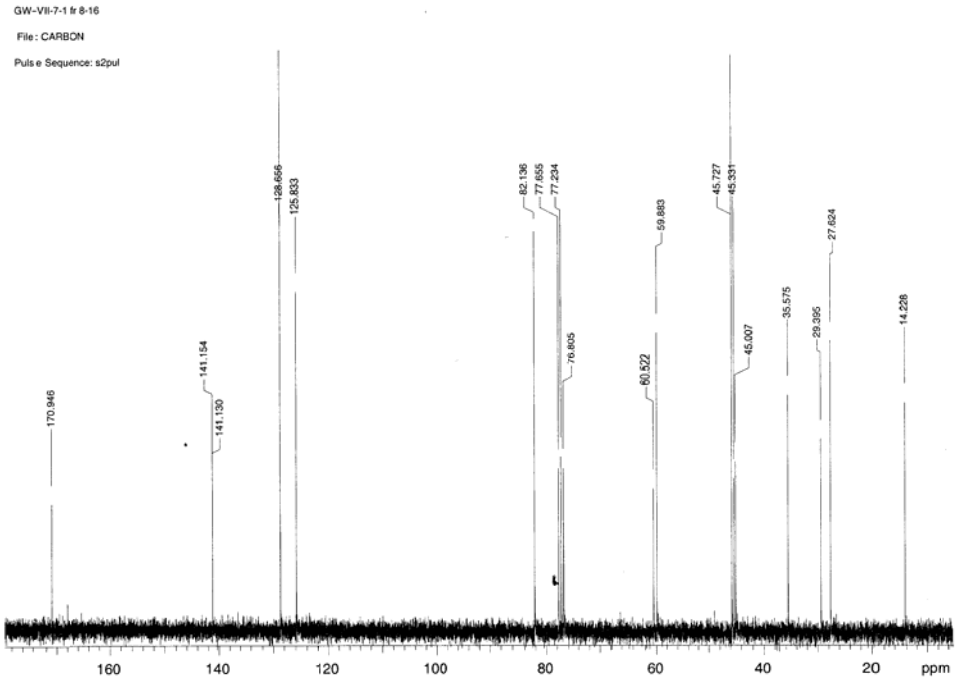
O
NMe2
7.125
7.070
4.997
4.977
4.851
4.830
4.005
3.981
3.083
2.189
1.127
1.103
1.080
7
6
5
4
3
2
1 ppm
2.01
2.09
2.05
2.08
2.00
2.04
2.08
8.77
4.33
3.00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Pulse Sequence: s2pul
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60.522
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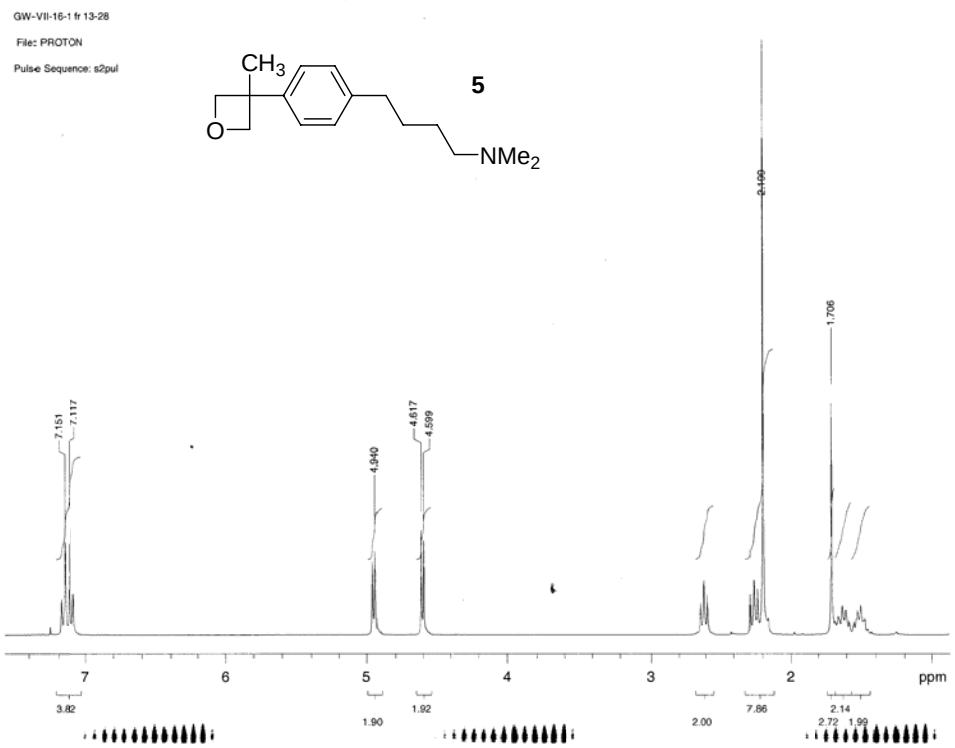
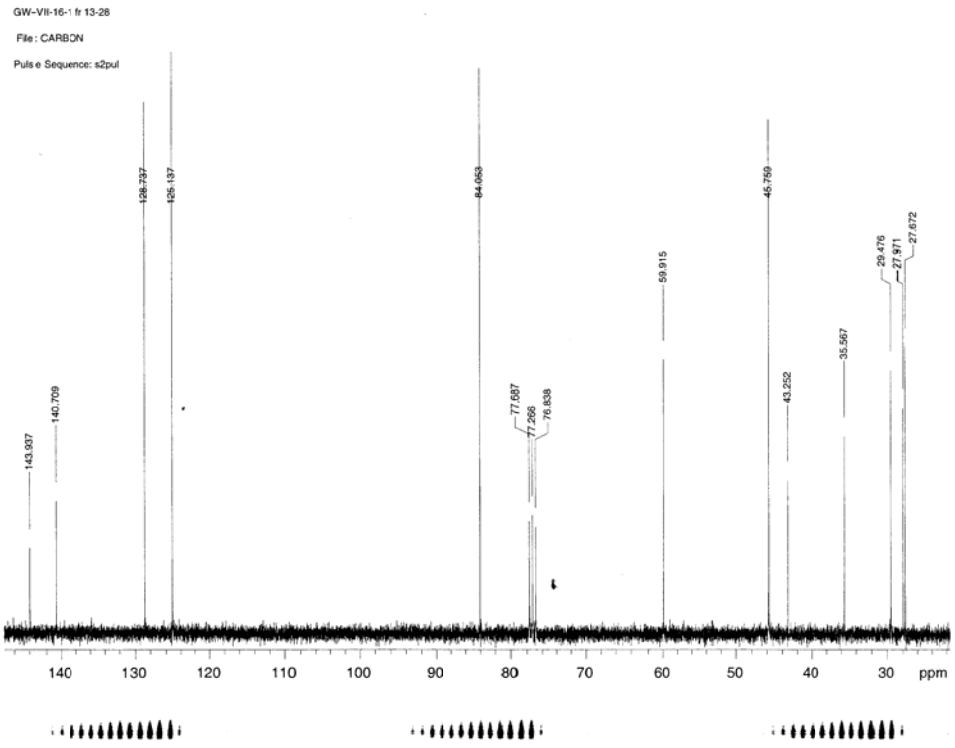
35.575
29.395
27.624
14.228
160
140
120
100
80
60
40
20
ppm


GW-VII-16-1 fr 13-28
File: PROTON
Pulse Sequence: s2pul
CH3
O
NMe2
5
7.151
7.117
4.640
4.617
4.599
2.100
1.706
7
6
5
4
3
2
ppm
3.82
1.90
1.92
2.00
7.86
2.14
2.72
1.99


GW-VII-16-1 fr 13-28
File: CARBON
Pulse Sequence: s2pul
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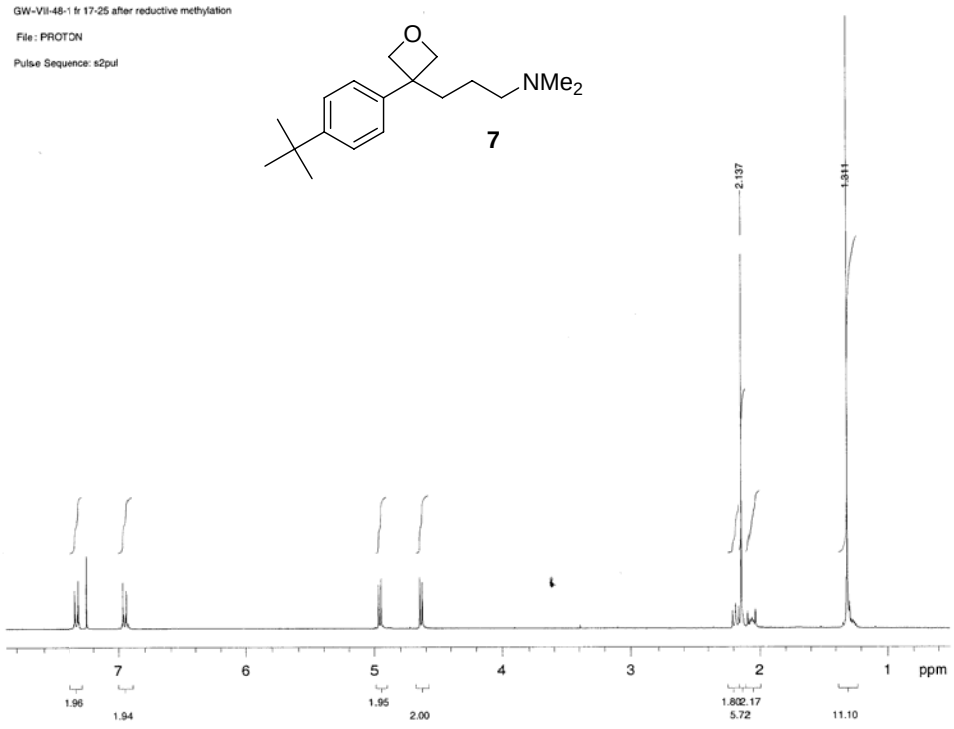
140.709
128.737
125.137
84.063
77.087
77.266
76.838
59.915
45.769
43.252
35.567
29.476
27.971
27.672
140
130
120
110
100
90
80
70
60
50
40
30
ppm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File : PROTON
Pulse Sequence: s2pul
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NMe2
7
2.137
1.311
7
6
5
4
3
2
1
ppm
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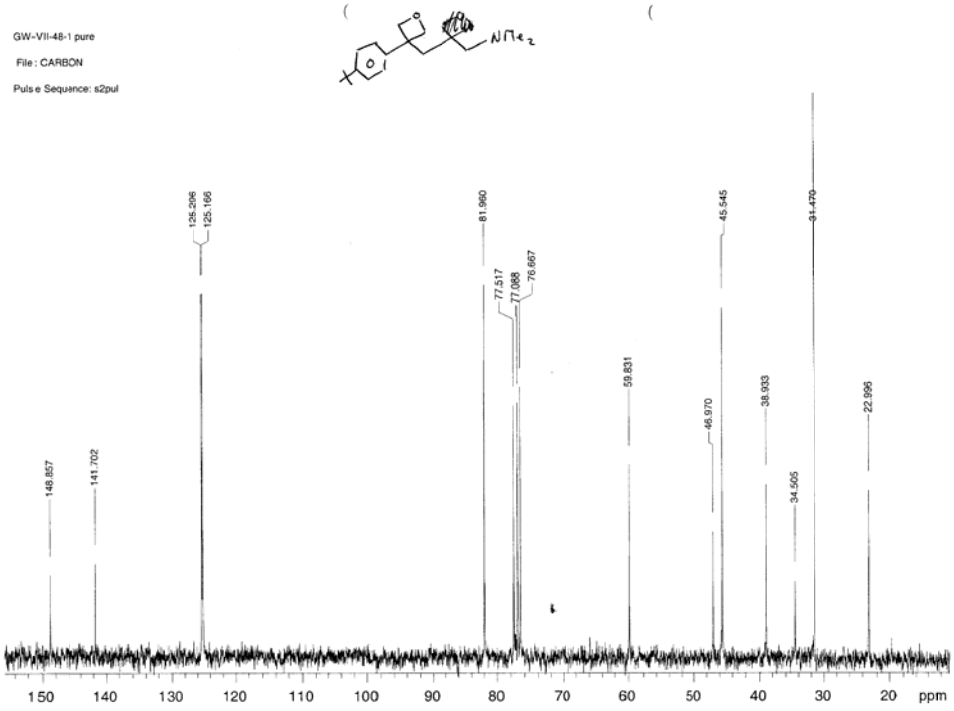
1.94
1.95
2.00
1.80
2.17
5.72
11.10


GW-VII-48-1 pure
File : CARBON
Pulse Sequence: s2pul
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126.206
125.166
81.960
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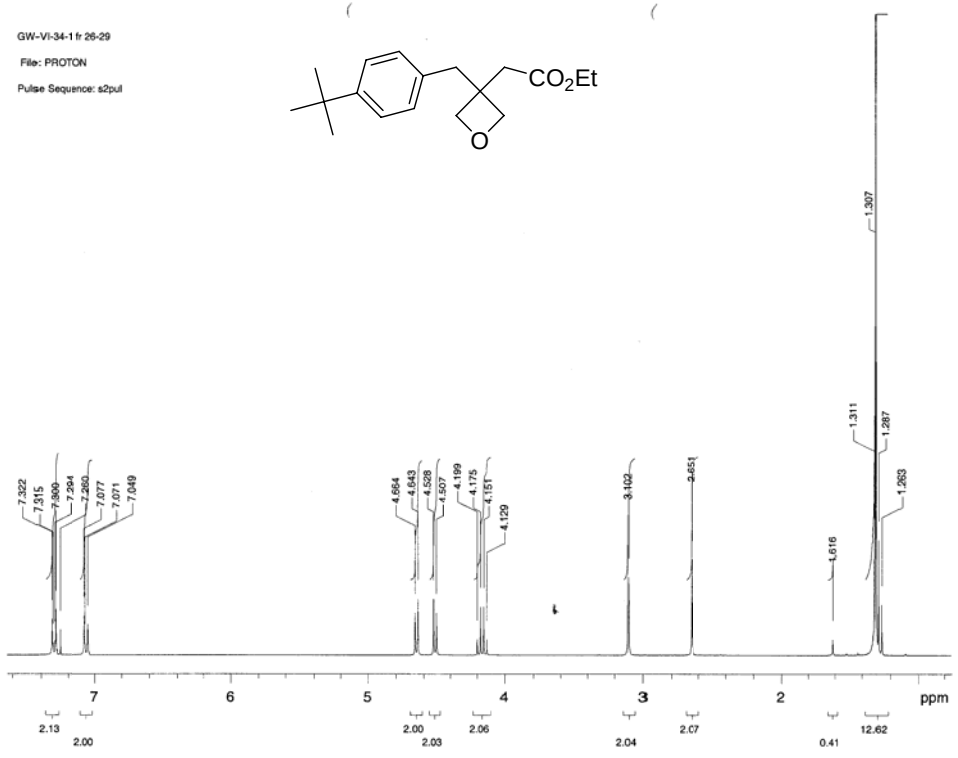
76.667
59.831
45.970
45.545
38.933
34.505
31.470
22.996
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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CO2Et
O
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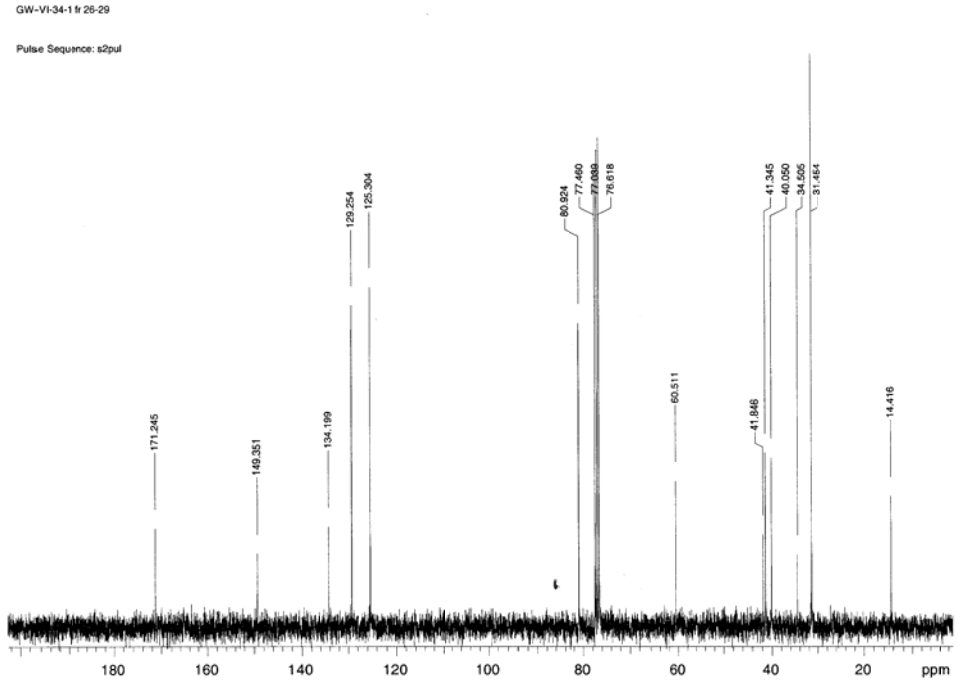
7.300
7.294
7.260
7.077
7.071
7.049
4.664
4.643
4.526
4.507
4.199
4.175
4.151
4.129
3.102
2.651
1.616
1.311
1.307
1.287
1.263
7
6
5
4
3
2
ppm
2.13
2.00
2.00
2.03
2.06
2.04
2.07
0.41
12.62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125.304
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77.089
76.618
60.511
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40.050
34.505
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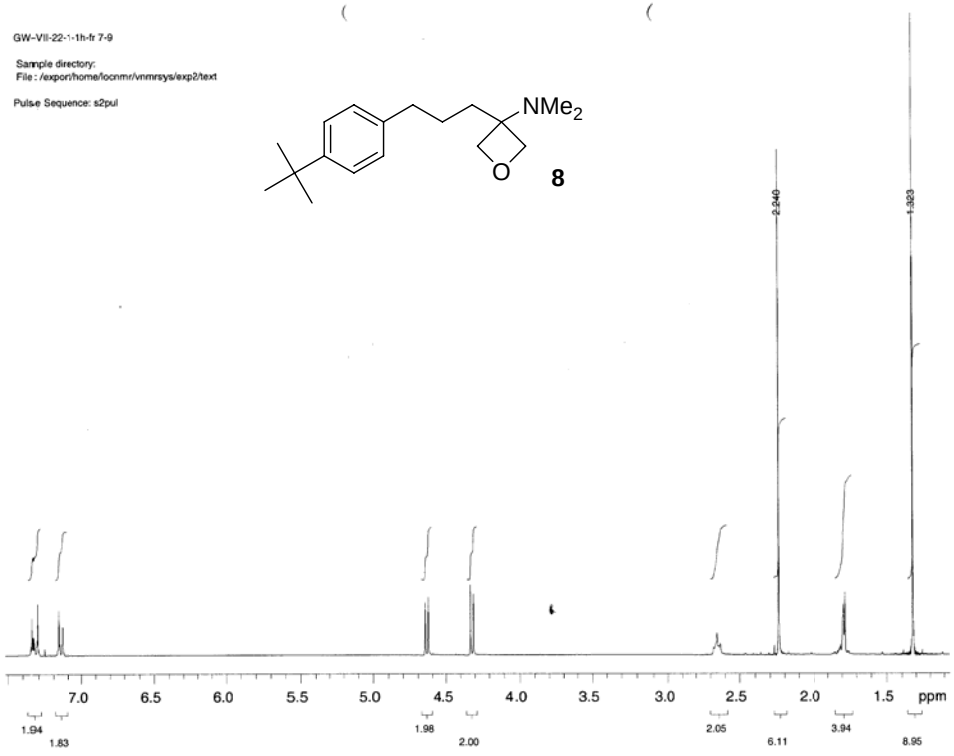
14.416
180
160
140
120
100
80
60
40
20
ppm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Pulse Sequence: s2pul
NMe2
O
8
2.240
1.323
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.94
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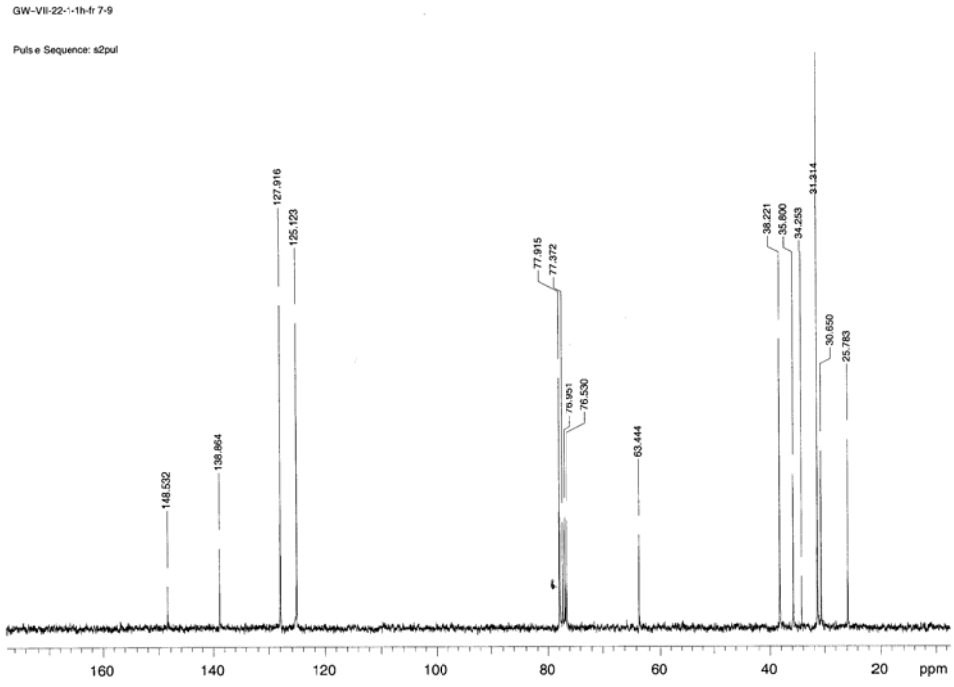
1.98
2.00
2.05
6.11
3.94
8.95


GW-VII-22-1-1h-fr 7-9
Pulse Sequence: s2pul
148.532
138.864
127.916
125.123
77.915
77.372
76.951
76.530
63.444
38.221
35.800
34.253
31.314
30.650
25.783
160
140
120
100
80
60
40
20
ppm