Enantioselective Synthesis of Pentacycloanammoxic Acid

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Supporting Information

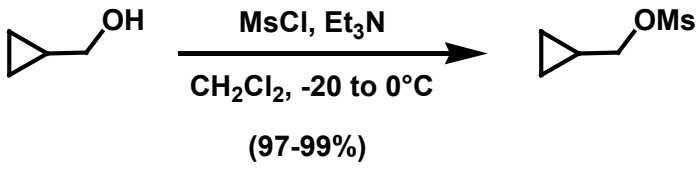
Materials and methods

Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of nitrogen using freshly distilled solvent. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone before use. Dichloromethane, benzene, toluene and acetonitrile were distilled from CaH_2. Methanol was distilled over magnesium methoxide. Thin-layer chromatography (TLC) was performed using E. Merck® silica gel 60 F_{254} pre-coated plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 or 366 nm), anisaldehyde stain or ethanolic phosphomolybdic acid stain. Column chromatography was performed using Bakerbond® silica gel (40 μm particle size) using the indicated solvent system as eluent. NMR spectra were recorded in deuteriochloroform on Varian® Inova-600 (^{1}H: 600 MHz), Inova-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) or Mercury-400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) instruments. ^{1}H chemical shifts are reported in parts per million (ppm) on δ scale using residual undeuterated solvent as an internal standard (7.26 ppm). The abbreviations used for the multiplicity are: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. ^{13}C chemical shifts are reported in parts per million (ppm) on δ scale using the central peak of deuteriochloroform as an internal

standard (77 ppm). IR spectra were recorded on an Avatar® 360 FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Only the most important and relevant frequencies are reported. High-resolution mass spectral analyses were performed at Harvard University Mass Spectrometry Center. Melting points (m.p.) are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus. X-ray data were collected at Harvard University using a Bruker SMART CCD (charge coupled device) based diffractometer equipped with an LT-3 low-temperature apparatus operating at 213 K.

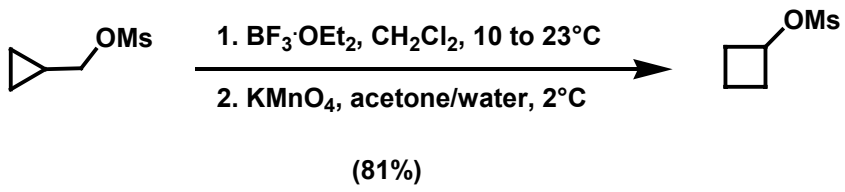
Experimental part

Cyclopropylmethyl Methanesulfonate



To a mechanically stirred solution of cyclopropanemethanol (50 mL, 632 mmol) in CH_2Cl_2 (250 mL) cooled at -30°C (internal temperature) was added MsCl (73 mL, 1.5 equiv.) in one portion. Distilled Et_3N (141 mL, 1.6 equiv.) was then added dropwise rapidly via dropping funnel over 30 min so that the internal temperature remained between -25 to -20°C (after addition of 20 to 40 mL of Et_3N a white precipitate remained). The resulting mixture was stirred 45 min. more allowing the internal temperature to rise from -20 to 0°C (the reaction mixture turned slightly yellow). 85 mL of cold 3M HCl aqueous solution and 100 mL of cold brine were added dropwise via the dropping funnel while the reaction mixture was gently stirred to avoid any emulsion (the internal temperature rose to 4°C). The resulting biphasic mixture was poured into a separatory funnel and the yellow organic phase separated. The aqueous phase was diluted with 200 mL of cold brine and extracted twice with CH_2Cl_2 (2 x 300 mL). The combined organic phase was washed with cold brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow liquid was then dried under reduced pressure to afford 94.2 g (99%) of cyclopropylmethyl methanesulfonate. ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm): 4.07 (d, 2H, J = 7.3 Hz), 3.02 (s, 3H), 1.23 (m, 1H), 0.68 (m, 2H), 0.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 75.3, 37.9, 10.1, 3.8 (x2).

Cyclobutyl Methanesulfonate

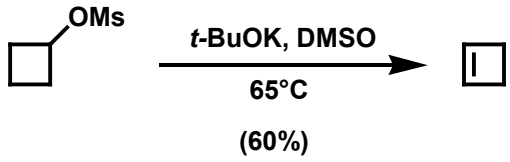


(81%)

To a solution of cyclopropylmethyl methanesulfonate (94.2 g, 627 mmol) in anhydrous CH_2Cl_2 (300 mL) cooled in a water bath (10°C, external temperature) was added dropwise $F_3B{\cdot}OEt_2$ (4.8 mL, 0.06 equiv.). The resulting solution was warmed to room temperature (22-23°C) and stirred for 12 hrs. 100 mL of a cold saturated aqueous solution of NH_4Cl was added, the resulting biphasic mixture was poured into a separatory funnel and shaken vigorously. The organic phase was separated and concentrated under reduced pressure to afford a 10-11/1 mixture of cyclobutyl methanesulfonate and but-3-enyl methanesulfonate in quantitative yield as a brown oil.

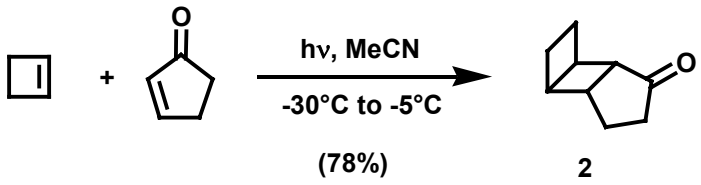
To a mechanically stirred solution of the former mixture (627 mmol) in acetone (200 mL) cooled in an ice bath (2°C, external temperature) was added dropwise (using a dropping funnel) a aqueous solution of $KMnO_4$ (16.5 g, 2 equiv./olefin, in 120 mL of water). After about 5 to 10 min. the purple color disappeared and a brown precipitate formed. The reaction mixture was stirred 2 hrs. more and filtered through a bed of celite®. The reaction flask and the cake were then rinsed with 1 L of Et_2O and 300 mL of cold water. The filtrate was poured into a separatory funnel, shaken vigorously and the two phases separated. The aqueous phase was extracted with 200 mL of Et_2O. The combined organic phase was dried over $MgSO_4$, filtered and concentrated to afford 76.3 g (81%, 2 steps) of cyclobutyl methanesulfonate as a yellowish liquid. ^1H NMR (600 MHz, $CDCl_3$); δ (ppm): 4.96 (qt apparent, 1H, J = 7.5 Hz), 2.97 (s, 3H), 2.43-2.37 (m, 2H), 2.34-2.26 (m, 2H), 1.85 (m, 1H), 1.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm): 73.8, 38.3, 31 (x2), 12.9.

Cyclobutene



The procedure of Salaün and Fadel for the conversion of cyclobutyl tosylate to cyclobutene was used[1]. In a typical experiment 60 g (0.4 mol) of cyclobutyl mesylate gave cyclobutene in 60% yield (13 g). Cyclobutene which was not used immediately was stored in a -78°C freezer under inert atmosphere without any decomposition. ^{1}H NMR (600 MHz, $CDCl_3$); δ (ppm): 6.01 (s, 2H), 2.56 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 136.8, 31.1.

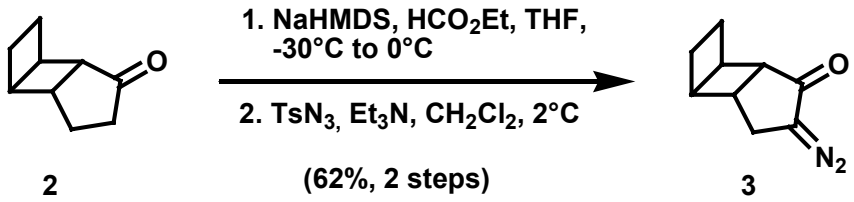
Ketone 2



A solution 2-cyclopenten-1-one (35 mL, 1.5 equiv.) in anhydrous MeCN (50 mL) placed in a photoreactor was cooled at 0°C (internal temperature measured by a thermocouple immersed into the solution) and degassed for 1 hour by bubbling N_2 (passed through a cartridge of drierite and sodium hydroxide) through the solution. A positive pressure of N_2 was then maintained in the reaction vessel and the photoreactor was cooled to -30°C (internal temperature) using an external bath. Cyclobutene (15 g, 277 mmol) was then cannulated as a cold liquid to this solution and the irradiation started (use of a Pyrex® cooling jacket and a medium pressure mercury lamp 450W Hanovia® UV lamp; the tap water used to cool the jacket was first passed through a 50' copper coil [1/4" O.D. x 0.030" wall] immersed in child water). During the irradiation the internal temperature was maintained between -30°C and -5°C. After 8 hours of irradiation 12 mL (0.5 equiv.) more of 2-cyclopenten-1-one was added and the irradiation pursued until ^{1}H NMR analysis of an aliquot showed the complete consumption of cyclobutene (about 20 to 24 hours of irradiation). The reaction mixture was warmed to room temperature, concentrated and purified by flash chromatography over silica

gel (hexanes/Et_2O : 9/1) to give 29.3 g (78%) of photoadduct **2** as a colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$); δ (ppm): 2.96 (dd, 1H, *J* = 7.0 and 5.9 Hz), 2.76 (d, 1H, *J* = 5.3 Hz), 2.62 (m, 1H), 2.58-2.48 (m, 4H), 2.26 (ddt, 1H, *J* = 17.9, 9.1 and 1.8 Hz), 2.19-2.11 (m, 2H), 2.04 (m, 1H), 1.93 (ddt, 1H, *J* = 13.2, 9.4 and 1.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 221.5 (HMBC), 52.9, 42.8, 40.9, 37.8, 36.7, 28.7, 26.9, 26.6. IR (film, cm^{-1}): 2935, 2856, 1731, 1455, 1412, 1326, 1279, 1229, 1169, 1138.

α-Diazo Ketone 3

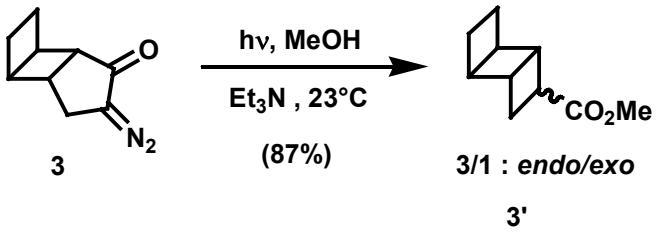


To a solution of NaHMDS (48 mL, 1M in THF, 1.2 equiv.) at -45°C was added dropwise (using a dropping funnel) over 20 minutes a solution of ketone **2** (5.44 g, 40 mmol) in 60 mL of THF. The resulting solution was stirred 30 minutes more during which time the temperature of the cooling bath was allowed to rise to -30°C. Freshly distilled ethyl formate (9.7 mL, 3 equiv.) was then added rapidly in one portion. The resulting mixture was stirred 2 hours more during which time the temperature was allowed to rise to 0°C. At this point TLC indicated the complete consumption of the starting ketone. Et_2O (100 mL) was added and the reaction was quenched at 0°C by dropwise addition of 77 mL of a 1M HCl aqueous solution (until pH 5-6). The resulting two phases were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give an orange/brown oil. The crude α-hydroxymethylene ketone obtained was used in the next step without further purification.

To a solution of the former α-hydroxymethylene derivative in CH_2Cl_2 (60 mL) was added at 2°C a solution of tosyl azide (7.9 g, 1 equiv.) in 20 mL of CH_2Cl_2 followed by Et_3N (11.2 mL, 2 equiv.). The resulting orange/yellow solution was stirred at this temperature for 30 minutes then concentrated and purified by flash chromatography over silica gel (hexanes/EtOAc : 8/2) to give the α-diazo ketone **3** (4.02 g, 62% over 2 steps) as a yellow oil that solidifies upon standing. ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm): 3.37 (dd, 1H, *J* = 13.7 and 8.8 Hz), 3.02 (d,

1H, *J* = 5.8 Hz), 2.90 (m,1H), 2.86 (d,1H, *J* = 13.7 Hz), 2.79 (m, 1H), 2.56 (m,1H), 2.52-2.42 (m, 2H), 2.15 (m,1H), 1.98 (m,1H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 201.7, 59.2, 54.7, 43.1, 40.1, 39.3, 31.1, 26.6, 26.5. IR (film, cm^{-1}): 2937, 2854, 2084, 1663, 1459, 1339, 1301, 1254, 1227.

Mixture of Methyl Esters 3'

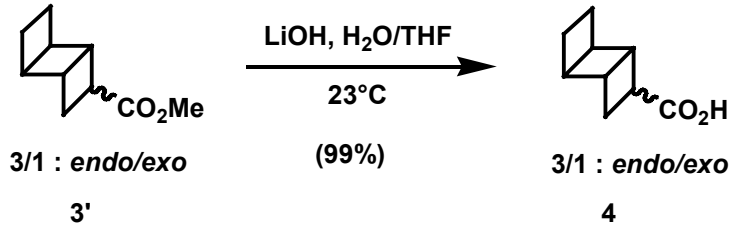


3 **3/1 : *endo/exo***

3'

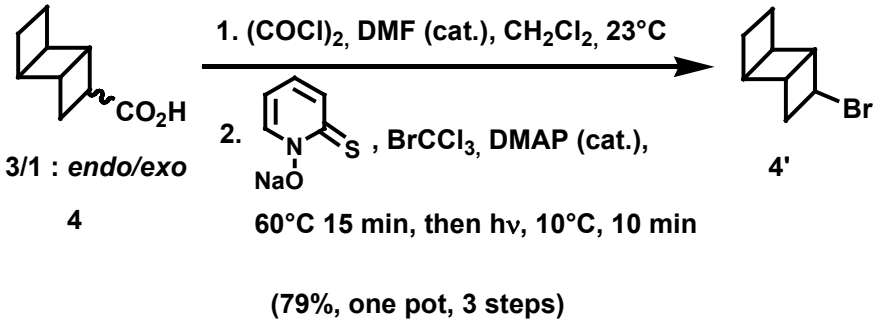
To a solution of α-diazo ketone **3** (2 g, 12.3 mmol) in anhydrous MeOH (110 mL) placed in a photoreactor was added Et_3N (1.72 mL, 1 equiv.). The solution was degassed for 1 hour by bubbling N_2 (passed through a cartridge of drierite and sodium hydroxide) through the solution. A positive pressure of N_2 was then maintained in the reaction vessel and the irradiation was started (use of a Pyrex® cooling jacket and a medium pressure mercury lamp 450W Hanovia® UV lamp). The solution was irradiated at 23°C until TLC indicated the complete consumption of the starting material (1 hour) and concentrated. The crude product was purified by flash chromatography over silica gel (hexanes/CH_2Cl_2 : 6/4) to give a ~ 3:1 mixture of *endo* and *exo* esters **3'** (1.78 g, 87%). *Data for the mixture of epimers at C2 (from a ca 3/1 : endo/exo mixture). Determination based also on HMQC data*. ^{1}H NMR (600 MHz, $CDCl_3$); δ (ppm): 3.69 (s, 1H, minor), 3.67 (s, 3H, major), 3.60 (m, 1H, major), 3.06 (m, 1.33H, 1H major + 1H minor), 2.90 (bs, 0.33H, minor), 2.83-2.74 (m, 2.4H, 1H major + 4H minor), 2.70 (m, 1H, major), 2.66 (m, 1H, major), 2.62-2.42 (m, 3.8H, 3H major + 2H minor), 2.36 (m, 1H, major), 2.18 (m, 0.33H, minor), 2.00-1.88 (m, 2.7H, 2H major + 2H minor). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): *endo isomer*: 174.2, 51.1, 45.5, 43.3, 39.6, 39.3, 38.5, 27.4, 25.9, 25.7. *exo isomer*: 176.1, 51.6, 46.4, 43.0, 42.7, 42.4, 40.9, 29.0, 25.8, 25.5. IR (film, cm^{-1}): 2937, 2852, 1733, 1436, 1343, 1243, 1229, 1196, 1171, 1073, 1054.

Mixture of Carboxylic Acids 4



To a solution of the mixture of esters **3'** (3.43 g, 20.6 mmol) in THF (8.2 mL) cooled at 2°C was added dropwise rapidly an aqueous solution of LiOH (41 mL, 2M, 4 equiv.). The resulting mixture was stirred at 23°C for 4 hours at which point TLC indicated the complete consumption of the starting material. The solution was cooled to 2°C, 60 mL of Et_2O was added followed by dropwise addition of 33 mL of a 3M HCl aqueous solution (~ 1.2 equiv./base). The two phases were separated and the aqueous phase was extracted again with Et_2O (3 x 40 mL). The combined organic phase was washed with cold brine (20 mL), dried over Na_2SO_4, filtered and concentrated to afford 3.10 g (99%) of a 3/1 : *endo*/*exo* mixture of acids **4** as a colorless oil which solidifies upon cooling. *Data for the mixture of epimers at C2 (from a ca 3/1 : endo/exo mixture). Determination based also on HMQC data*. ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm): 3.66 (m, 1H, major), 3.10 (m, 1.31H, 1H major + 1H minor), 2.96 (bs, 0.36H, minor), 2.92 (m, 1H, major), 2.86-2.75 (m, 1.51H, 4H minor), 2.73 (m, 1H, major), 2.67 (m, 1H, major), 2.64-2.42 (m, 3.9H, 3H major + 2H minor), 2.33 (m, 1H, major), 2.21 (m, 0.4H, minor), 2.02-1.90 (m, 2.8H, 2H major + 2H minor). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): *endo isomer*: 180.5, 45.5, 43.2, 39.6, 39.3, 38.5, 27.3, 26.0, 25.8. *exo isomer*: 182.3, 46.4, 43.0, 42.8, 42.5, 41.0, 29.0, 25.8, 25.6. IR (film, cm^{-1}): 2937, 2854, 2738, 2636, 2553, 1696, 1418, 1328, 1287, 1250, 1227, 1192, 1179, 1069.

Alkyl Bromide 4'

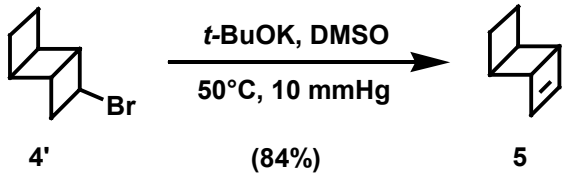


To a solution of the mixture of acids **4** (1.93 g, 12.7 mmol) in CH_2Cl_2 (12 mL) cooled at 2°C was added dropwise oxalyl chloride (2.2 mL, 2 equiv.) followed by a catalytic amount of DMF (10 μL, 0.01 equiv.) and the resulting yellow solution was stirred at 2°C for 10 minutes then warmed to 23°C and stirred for an additional 20 minutes (until the gas evolution stopped). The solution was then concentrated under reduced pressure and stirred under vacuum for 30 minutes more. The crude mixture of acid chlorides (2.1 g, 97%) was used in the next step without further purification. IR (film, cm^{-1}): 2941, 2854, 1796, 1441, 1250, 1231, 1173, 1057.

The next reaction was conducted in an environment avoiding as much light as possible.

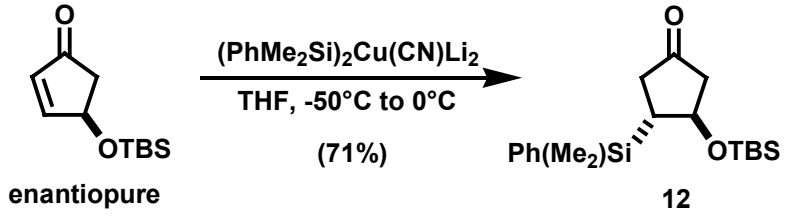
To a solution of the former mixture of acid chlorides (~ 12.7 mmol) in 5 mL of $BrCCl_3$ placed in a round bottom flak covered with aluminum foil and cooled at 2°C with an ice bath was added in one portion 2-mercaptopyridine-1-oxide sodium salt (2.28 g, 1.2 equiv.) followed by a catalytic amount of DMAP (78 mg, 0.05 equiv.). The aluminium foil was removed and the flak equipped with a reflux condenser. The mixture was **slowly** warmed to 60°C and stirred at this temperature for 15 minutes (*caution: the radical chain reaction is exothermic; extreme care should be exercised*). At this point TLC indicated the complete consumption of the starting material. The mixture was cooled at 10°C with an ice bath and irradiated for 10 minutes at this temperature using a sun lamp placed at 10 cm of the flask (to ensure the complete consumption of the Barton ester intermediate). The crude mixture was filtered over neutral alumina and the cake was washed with pentane (50 mL). The filtrate was concentrated and purified by passage through a short plug of neutral alumina using pentane as eluent. Concentration under reduced pressure of the less polar fractions gave the desired alkyl bromide **4'** (1.87 g, 79 % starting from **4**) as a colorless liquid. This material was stored under N_2 in a -78°C freezer. ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm): 4.45 (m, 1H), 3.13 (bs, 1H), 3.00-2.93 (m, 2H), 2.84 (m, 1H), 2.76 (m, 1H), 2.68 (m, 1H), 2.58-2.44 (m, 2H), 1.98-1.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm): 55.5, 48.6, 42.2, 41.7, 41.1, 40.8, 25.4, 25.3. IR (film, cm^{-1}): 2966, 2931, 2852, 1428, 1250, 1235, 1223, 1210, 1183, 1135.

Alkene 5



A 50 mL two neck flask was equipped with a 10 mL dropping funnel and connected by mean of a glass connection to a two neck 25 mL flask equipped with a cold finger whose top was connected to a manometer and a vacuum pump by mean of tubing. Anhydrous DMSO (4.3 mL) was added to the first flask followed by KO*t*-Bu (1.46 g, 2.6 equiv.). A solution of alkyl bromide **4'** (934 mg, 5 mmol) in 2.5 mL of DMSO was then added to the dropping funnel and the internal pressure in the assembly was adjusted precisely to 9-10 mmHg. The receiving flask as well as the cold finger were cooled to -78°C using acetone/dry ice and the reaction flask heated to 50°C. The solution of alkyl bromide was then added dropwise over 20 minutes to the solution of base (as soon as the addition starts, a burgundy color formed which darkened during the addition). The mixture was stirred two hours more at this temperature, then the reaction flask was cooled down to 23°C and the internal pressure carefully adjusted to 760 mmHg. The receiving flask contained 523 mg of crude alkene **5** contaminated with some *t*-BuOH (product / *t*-BuOH : 4.2/1 in molar equiv.) as well as traces of DMSO (product / DMSO : 152/1 in molar equiv.). This corresponds to 446 mg (84%) of pure **5** obtained. No attempt was made to remove the *t*-BuOH from the alkene since it had no deleterious influence in the following [2+2]-photocycloadditions. ^{1}H NMR (600 MHz, $CDCl_3$); δ (ppm): 6.29 (bs, 2H), 3.19 (bs, 2H), 2.51-2.43 (m, 4H), 1.81-1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm): 140.6, 52.0, 38.4, 23.8.

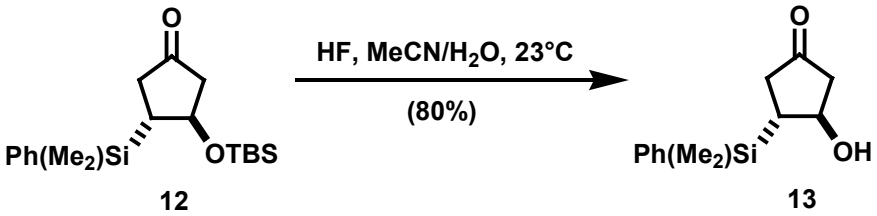
Ketone 12



To a suspension of CuCN (337 mg, 1.2 equiv.) in THF (3.8 mL) cooled at -50°C was added a solution of $Ph(Me_2)SiLi$ in THF[2] (9.4 mL, 2.4 equiv., 0.8M) and the resulting dark red solution was stirred at this temperature for 40 minutes. A precooled solution of 4-(R)-(+)-*tert*-butyldimethylsilyloxy-2-cyclopenten-1-one[3] (667 mg, 3.14 mmol) in THF (3.2 mL) was then added via canula over 5 minutes and the mixture stirred 1 hour more during which time the temperature was warmed up to –20°C. Et_2O (20 mL) was added followed by the dropwise addition of an aqueous solution of NH_4Cl/NH_4OH (1/1 vol., 20 mL). The two phases were

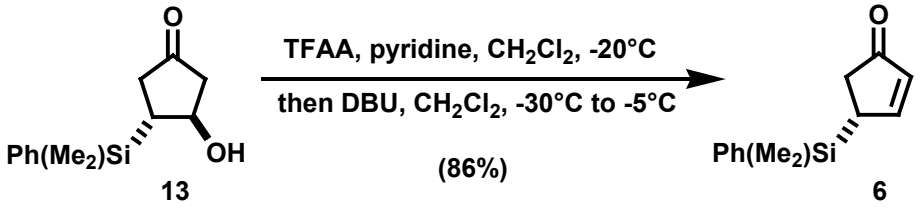
stirred at 23°C for 10 minutes and separated. The organic phase was washed with NH_4Cl/NH_4OH (1/1 vol., 3 x 20 mL) and brine (2 x 20 mL), then dried over $MgSO_4$. Filtration, concentration and purification of the crude product by chromatography over silica gel (hexanes/EtOAc : 95/5) gave ketone **12** (774 mg, 71%). $[\alpha]_D$ -22.5 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$); δ (ppm): 7.51-7.48 (m, 2H), 7.40-7.34 (m, 3H), 4.36 (q, 1H, *J* = 5.2 Hz), 2.53 (dd, 1H, *J* = 18.6 and 9.8 Hz), 2.28 (dd, 1H, *J* = 18.1 and 5.9 Hz), 2.20 (dd, 1H, *J* = 18.1 and 4.9 Hz), 2.04 (dd, 1H, *J* = 19.0 and 8.3 Hz), 1.74 (m, 1H), 0.85 (s, 9H), 0.36 (s, 3H), 0.34 (s, 3H), 0.00 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): quaternary carbon not detected, 136.6, 133.8 (x2), 129.4, 128.0 (x2), 71.9, 49.1, 38.4, 33.5, 25.7 (x3), 17.8, -3.9, -4.4, -4.5, -4.8. IR (film, cm^{-1}): 2956, 2929, 2896, 2858, 1746, 1472, 1428, 1362, 1250, 1189, 1148, 1108, 1055, 1019.

β-Hydroxyketone 13



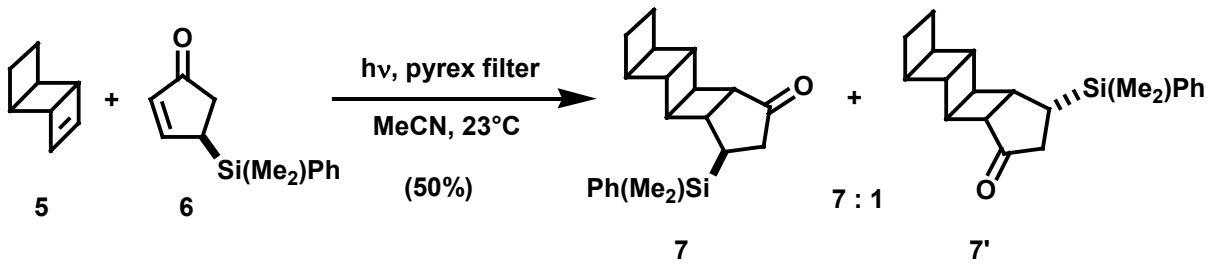
To a solution of ketone **12** (727 mg, 2.09 mmol) in acetonitrile (3 mL) placed in a polypropylene flask was added aqueous HF (160 μL, 2 equiv., 48%) and the resulting solution was stirred at 23°C for 12 hours. EtOAc (10 mL) was added and the crude solution was transferred into a separatory funnel containing solid $NaHCO_3$ (700 mg, 2 equiv./HF) and 5 mL of distilled water. The two phases were separated. The organic phase was washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography through a short plug of silica gel (hexanes/EtOAc : 70/30) to give β-Hydroxyketone **13** as an oil (390 mg, 80%). $[\alpha]_D$ -67.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$); δ (ppm): 7.54-7.51 (m, 2H), 7.41-7.36 (m, 3H), 4.39 (q, 1H, *J* = 6.5 Hz), 2.55 (dd, 1H, *J* = 18.6 and 9.8 Hz), 2.42 (dd, 1H, *J* = 18.6 and 6.4 Hz), 2.17 (dd, 1H, *J* = 17.6 and 7.1 Hz), 2.06 (dd, 1H, *J* = 19.0 and 9.8 Hz), 1.75 (bs, 1H), 1.66 (m, 1H), 0.38 (s, 3H), 0.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): quaternary carbon not detected, 136.4, 133.7 (x2), 129.7, 128.2 (x2), 71.6, 48.3, 39.3, 33.0, -4.2, -4.6. IR (film, cm^{-1}): 3450, 2958, 2925, 2854, 1744, 1428, 1252, 1119, 1055.

(4R)-(+)-(dimethyl(phenyl)silyl)-2-cyclopenten-1-one 6



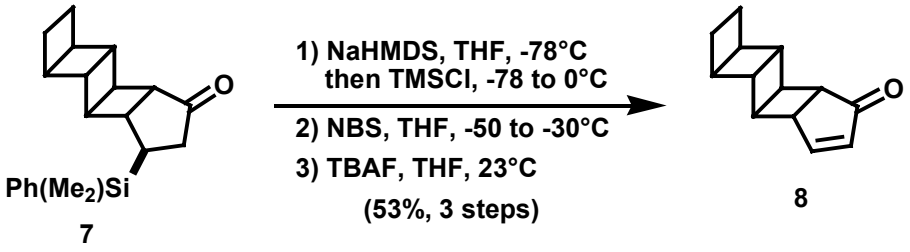
To a solution of β-hydroxyketone **13** (188 mg, 802 μmol) in CH_2Cl_2 (2.5 mL) cooled at -20°C was added trifluoroacetic anhydride (150 μL, 1.35 equiv.) followed by anhydrous pyridine (180 μL, 2.7 equiv.). The solution turned slightly yellow and a white precipitate formed. After stirring for 20 minutes more at this temperature, the mixture was cooled at -30°C and DBU (320 μL, 2.7 equiv.) was added dropwise (the reaction mixture turned brown/red). After stirring at –30°C for 5 minutes more, the reaction mixture was warmed to –5°C over 5 minutes and an aqueous solution of $CuSO_4$ (72 mg/mL, 6 equiv.) was added followed by CH_2Cl_2 (7 mL). The two phases were shaken vigorously and separated. The organic phase was washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography over silica gel (hexanes/EtOAc : 75/25) to give enone **6** as an oil (149 mg, 86%). $[\alpha]_D$ +417.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm): 7.72 (dd, 1H, *J* = 5.9 and 2.9 Hz), 7.50-7.47 (m, 2H), 7.42-7.36 (m, 3H), 6.12 (dd, 1H, *J* = 5.9 and 2.4 Hz), 2.61 (m, 1H), 2.53 (dd, 1H, *J* = 19.5 and 6.3 Hz), 2.29 (dd, 1H, *J* = 19.5 and 1.0 Hz), 0.32 (s, 3H), 0.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): quaternary carbon not detected, 168.6, 135.7, 133.6 (x2), 131.9, 129.8, 128.1 (x2), 37.3, 33.5, -4.9, -5.3.

Ketone 7



A solution of alkene **5** (56 mg, 528 μmol) and (4R)-(+)-(dimethyl(phenyl)silyl)-2-cyclopenten-1-one **6** (143 mg, 1.25 equiv.) in acetonitrile (200 μL) in a quartz test tube was degassed (vacuum/N_2; 10 times). A positive pressure of N_2 was then maintained in the reaction vessel and the tube was placed at about 5 cm of the Pyrex® cooling jacket of a 450W Hanovia® UV lamp (medium pressure mercury lamp). The solution was irradiated at room temperature under N_2 atmosphere for 12 hours. The solution was concentrated and the crude product was purified by flash chromatography over silica gel (hexanes/EtOAc : 92/8) to give a 7/1 mixture of ketones **7** and **7'** (85 mg, 50%). Ketone **7** was obtained in pure form by separation by preparative TLC (hexanes/Et_2O : 95/5). $[\alpha]_D$ +136 (*c* 1.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$); δ (ppm): 7.50-7.46 (m, 2H), 7.39-7.33 (m, 3H), 2.79 (m, 2H), 2.75 (bs, 1H), 2.70-2.60 (m, 4H), 2.59-2.52 (m, 3H), 2.42 (m, 1H, [appears as a broad singlet]), 2.21 (ddd, 1H, *J* = 18.1, 7.3 and 1.5 Hz), 2.03 (m, 2H, [appears as a broad doublet]), 1.57 (m, 1H), 0.28 (s, 3H), 0.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): quaternary carbon not detected, 136.8, 133.8 (x2), 129.3, 127.9 (x2), 51.6, 50.8, 50.0, 48.6, 43.8, 41.9, 41.2, 41.1, 39.2, 28.2, 26.3, 26,2, -4.8, -5.1. IR (film, cm^{-1}): 2923, 2852, 1733, 1465, 1428, 1250, 1231, 1175, 1115.

Enone 8



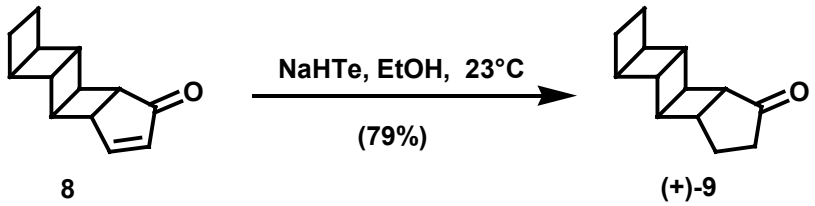
To a solution of NaHMDS (160 μL, 1M in THF, 2 equiv.) in THF (400 μL) at -78°C was added dropwise a solution of ketone **7** (26 mg, 81 μmol) in 800 μL of THF. The resulting solution was stirred 30 minutes more at this temperature. TMSCl (40 μL, 4 equiv.) was added dropwise, the solution stirred at –78°C 20 minutes before being stirred at 0°C for 20 minutes. Et_2O (5 mL) was added and the reaction was quenched at 0°C by dropwise addition of 2 mL of a saturated $NaHCO_3$ aqueous solution. The resulting two phases were separated and the aqueous phase was extracted with Et_2O (5 mL). The combined organic phase was dried over

Na_2SO_4, filtered, concentrated and dried under reduced pressure for 15 minutes to give an oil. The crude TMS-enol ether obtained was used in the next step without further purification.

To a cooled solution of the crude TMS-enol ether in THF (800 μL) at -50°C was added NBS (22 mg, 1.5 equiv.) in one portion and the resulting solution was warmed up to -30°C over 30 minutes. Et_2O (5 mL) was added and the reaction was quenched by dropwise addition of 2 mL of a saturated NH_4Cl aqueous solution. The resulting two phases were separated and the aqueous phase was extracted with Et_2O (5 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated and dried under reduced pressure for 10 minutes to give an oil. The crude α-bromoketone obtained was used in the next step without further purification.

To a solution of the crude α-bromoketone in THF (800 μL) at 23°C was added TBAF (160 μL, 1M in THF, 2 equiv.) and the resulting solution was stirred at this temperature for 5 minutes. Et_2O (5 mL) was added followed by dropwise addition of 2 mL of a saturated $NaHCO_3$ aqueous solution. The resulting two phases were separated and the aqueous phase was extracted with Et_2O (5 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography over silica gel (hexanes/Et_2O : 9/1) to give enone **8** as a solid (8 mg, 53%). The solid was recrystallized from EtOAc/heptane to furnish X-ray quality colorless crystals (plate shape) m.p. = 91-99°C. $[\alpha]_D$ +259 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ (ppm): 7.80 (dd, 1H, *J* = 5.6 and 3.2 Hz), 6.45 (d, 1H, *J* = 5.3 Hz), 3.40 (m, 1H), 2.93 (d, 1H, *J* = 3.5 Hz), 2.88 (d, 1H, *J* = 1.5 Hz), 2.85 (d, 1H, *J* = 1. 5 Hz), 2.70-2.64 (m, 2H), 2.63-2.55 (m, 2H), 2.50 (m, 1H, [appears as a singlet]), 2.40 (m, 1H, [appears as a singlet]), 2.10-2.04 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): quaternary carbon not detected, 166.0, 136.2, 50.2, 50.2, 49.6, 46.9, 46.2, 42.4, 41.1 (x2), 26.1, 26.0. IR (film, cm^{-1}): 2927, 2852, 1702, 1578, 1343, 1237, 1192, 1177, 1146.

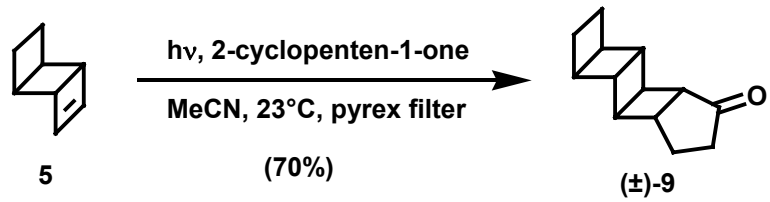
Ketone (+)-9 (from enone 8)



8 **(+)-9**

To a suspension of tellurium powder (17 mg, 3 equiv.) in EtOH (500 μL) at -40°C was added $NaBH_4$ (12 mg, 2.33 equiv./Te) and the mixture was degassed at this temperature (vacuum/N_2; 10 times). The resulting suspension was then heated at reflux for 30 minutes (all the Te powder dissolved and apparition of a purple coloration). The solution was cooled at 23°C and a degassed solution of enone **8** (8 mg, 43 μmol) in EtOH (200 μL) was added dropwise. The mixture was stirred at this temperature for 5 hours, filtered over a plug of celite® and concentrated. The crude product was purified by chromatography over silica gel (hexanes/Et_2O : 9/1) to give ketone (+)-**9** (6.3 mg, 79%) as an oil which solidifies upon cooling. $[\alpha]_D$ +407 (*c* 0.35, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$), δ (ppm): 2.92 (t, 1H, *J* = 6.6 Hz), 2.87 (d, 1H, *J* = 1.2 Hz), 2.80-2.78 (m, 2H), 2.70-2.65 (m, 2H), 2.64-2.53 (m, 4H), 2.45 (m, 1H, [appears as a singlet]), 2.30 (ddt, 1H, *J* = 18.0, 9.6 and 1.5 Hz), 2.18 (m, 1H), 2.08-2.02 (m, 2H); 2.00 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 221.6 (HMBC), 51.5, 50.7, 50.4, 46.3, 43.2, 41.4, 41.2, 40.6, 36.5, 29.1, 26.4, 26.3. IR (film, cm^{-1}): 2925, 2852, 1737, 1457, 1169. HRMS calcd for $C_{13}H_{20}NO$ (M+ NH_4^+) 206.1545, found 206.1554.

Ketone (±)-9 (from alkene 3 and 2-cyclopenten-1-one)



A solution of alkene **5** (695 mg, 6.55 mmol) and 2-cyclopenten-1-one (1.1 mL, 2 equiv.) in acetonitrile (1.5 mL) in a quartz test tube was degassed for 20 minutes by bubbling N_2 (passed through a cartridge of drierite and sodium hydroxide) through the solution. A positive pressure of N_2 was then maintained in the reaction vessel and the tube was placed at about 5 cm of the Pyrex® cooling jacket of a 450W Hanovia® UV lamp (medium pressure mercury lamp). The solution was irradiated at room temperature under N_2 atmosphere for 42 hours. ^1H NMR of an aliquot indicated 90% conversion of **5** to the desired ketone (±)-**9**. The solution was concentrated and the crude product was purified by flash chromatography over silica gel (hexanes/Et_2O : 9/1) to give ketone (±)-**9** (772 mg, 70% at 90% conversion) as an oil which solidifies upon cooling.

Chiral HPLC Separation of (+)-9 and (-)-9

A mixture of enantiomeric ketones **9** was separated by preparative chiral HPLC using a CHIRALPAK AD column.

Mobile phase: Hexanes/*i*-PrOH : 99.5/0.5.

Flux: 5 mL.min^{-1}.

UV detector: λ = 306 nm.

(+)- **9**: R_{time} = 46 min 52 s.

(-)- **9**: R_{time} = 66 min 17 s.

On an analytical CHIRALPAK AD column:

Mobile phase: Hexanes/*i*-PrOH : 99.5/0.5.

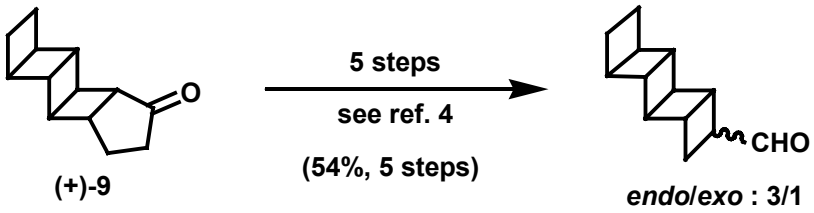
Flux: 1 mL.min^{-1}.

UV detector: λ = 306 nm.

(+)- **9**: R_{time} = 11 min 14 s.

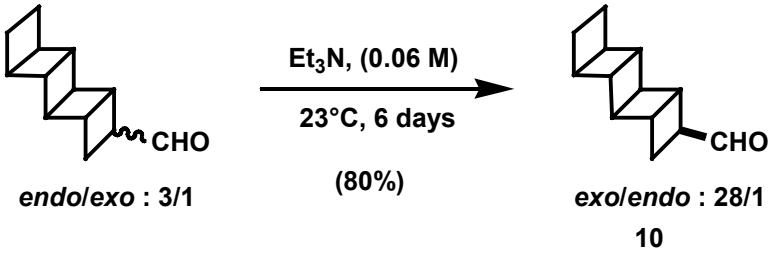
(-)- **9**: R_{time} = 14 min 53 s.

Mixture of Pentacyclic Aldehydes



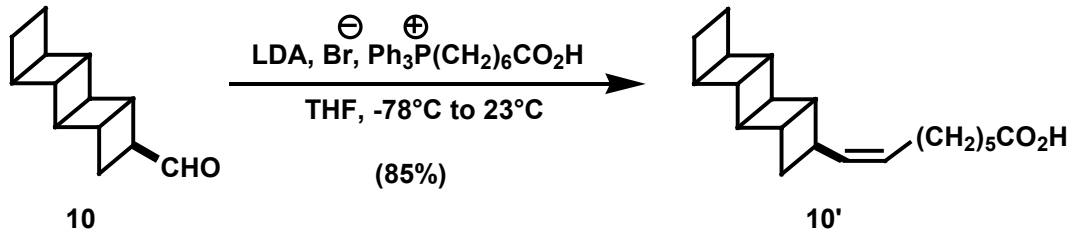
See reference 4.

***Exo* Aldehyde 10**



The *endo*/*exo* mixture of aldehydes (97 mg, 515 μmol) was dissolved in Et_3N (9 mL), degassed and stirred under N_2 atmosphere at room temperature in the dark for 6 days. Concentration under reduced pressure afforded a 15/1 : *exo*/*endo* mixture (determined by ^1H NMR) of aldehydes. Passage through a short plug of silica gel (hexanes/EtOAc : 95/5) gave a 28/1 : *exo*/*endo* mixture of aldehydes (78 mg, 80%). *Data for the exo aldehyde* **10**: ^1H NMR (600 MHz, $CDCl_3$), δ (ppm): 9.77 (d, 1H, *J* = 1.2 Hz), 3.25 (m, 1H, [appears as a triplet, *J* = 7.6 Hz]), 2.97 (m, 1H, [appears as a singlet]), 2.87 (dt, 1H, *J* = 12.9 and 6.6 Hz), 2.80-2.74 (m, 3H), 2.74-2.69 (m, 3H), 2.68 (bs, 1H), 2.62-2.54 (m, 2H), 2.18 (ddd, 1H, *J* = 12.9, 8.5 and 2.3 Hz), 2.09-2.02 (m, 2H, [appears as a doublet]).

Δ^7-Dehydro-(+)-pentacycloanammoxic Acid 10'

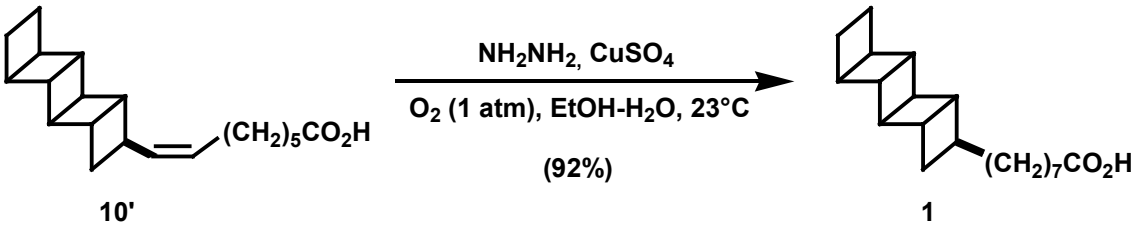


10 **10'**

To a solution of (*i*-Pr)$_2$NH (260 μL, 4.16 equiv.) in THF (12 mL) at -78°C was added dropwise a solution of *n*-BuLi (1.16 mL, 4.16 equiv., 1.6 M) in hexanes and the resulting solution was stirred at this temperature for 30 min. A fine powder of (Br,$Ph_3P(CH_2)_6CO_2H$)[5] (421 mg, 2 equiv.) [dried overnight under reduced pressure in a desiccator over P_2O_5] was then added in one portion and the mixture warmed to 0°C over 30 minutes. The mixture was stirred 2 hours more at room temperature (23°C) before being cooled to -50°C. A solution of the pentacyclic *exo*-aldehyde **10** (84 mg, 446 μmol) in THF (2.2 mL) was added dropwise (disappearance of the orange color within a minute after addition; only a yellowish color remained). The reaction mixture was warmed to 0°C over 1.5 hours and then stirred at room temperature for another 3 hours. The reaction mixture was cooled to 2°C and 25 mL of Et_2O were added followed by dropwise addition of 15 mL of a 1 M HCl aqueous solution. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography over silica gel (hexanes/EtOAc : 75/25) afforded Δ^7-dehydro-(+)-pentacycloanammoxic acid **10'** (114 mg, 85%). $[\alpha]_D$ +4.16 (*c* 1.25,

CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm): 5.64 (dd, 1H, *J* = 10.3 and 9.3 Hz), 5.23 (m, 1H), 3.19 (m, 1H), 2.74 (m, 2H), 2.70-2.64 (m, 3H), 2.64 (bs, 2H), 2.60-2.52 (m, 2H), 2.48 (bs, 1H), 2.34 (m, 1H), 2.33 (t, 2H, *J* = 7.5 Hz), 2.26 (m, 1H), 2.04 (m, 2H, [appears as a broad doublet]), 1.96 (m, 2H), 1.62 (m, 2H, [appears as a broad quintuplet, *J* = 7.2 Hz]), 1.36-1.28 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 178.5 (HMBC), 136.2, 127.3, 49.5, 49.2, 49.1, 48.6, 48.5, 41.8, 41.7, 38.5, 37.6, 34.5, 33.7, 29.3, 28.6, 27.3, 26.5, 26.4, 24.5. IR (film, cm^{-1}): 3438, 2923, 2854, 1710, 1465. MS (AP +) m/z (%): 300.5 (M^+, 100).

(+)-Pentacycloanammoxic Acid 1

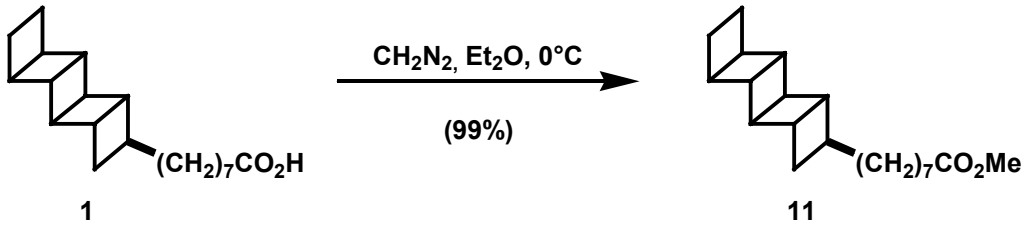


10' **1**

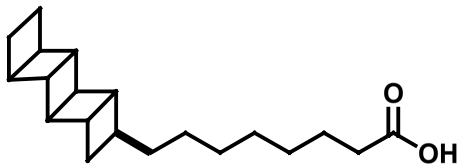
To a solution of the above unsaturated acid **10'** (25mg, 83.2 μmol) in 95% EtOH (5 mL) was added anhydrous hydrazine (1 mL) followed by dropwise addition of an aqueous solution of $CuSO_4$ (50 μL, 72 mg/mL). The resulting mixture was vigorously stirred in the dark under O_2 (1 atm) until the gas evolution stopped (~ 1 hour). 50 μL of the solution of aqueous $CuSO_4$ were then added every hour (for 12 hours), the solution being vigorously stirred in the dark under O_2 (1 atm). The reaction mixture was then cooled to 8°C, diluted with Et_2O (30 mL) and acidified by dropwise addition of a 2 M HCl aqueous solution. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with 2 M HCl (10 mL), brine (10 mL) and dried over $MgSO_4$. Concentration and purification by flash chromatography over silica gel (hexanes/EtOAc : 8/2) afforded (+)-pentacycloanammoxic acid **1** (23 mg, 92%) as a white powder. m.p. = 113-114 °C; $[\alpha]_D$ +16.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm): 2.73 (bd, 2H), 2.63 (bs, 2H), 2.62 (m, 1H), 2.59 (bs, 1H), 2.57 (bs, 1H), 2.58-2.52 (m, 2H), 2.35 ([appears as a broad triplet], 1H + 2H, *J* = 7.3 Hz), 2.20 (m, 1H), 2.18 (m, 1H), 2.04 (m, 2H, [appears as a broad doublet]), 2.00 (m, 1H), 1.63 (m, 2H, [appears as a broad quintuplet, *J* = 7.4 Hz]), 1.50-1.38 (m, 2H), 1.36-1.26 (m, 6H), 1.22 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 179.7, 49.4, 49.3, 49.2, 48.3, 47.3, 41.8 (x2), 39.9, 38.5, 37.3, 34.0, 33.3, 29.4, 29.3, 29.0, 26.5 (x2), 26.4, 24.7. IR (film, cm^{-1}): 3429, 2919, 2850, 1700, 1465. MS (AP

+) m/z (%): 302.6 (M^+, 100). R_f = 0.5 (hexanes/EtOAc : 7/3); R_f = 0.27 (hexanes/*i*-PrOH : 9/1); R_f = 0.27 (hexanes/Et_2O : 7/3).

(+)-Pentacycloanammoxic Acid Methyl Ester 11

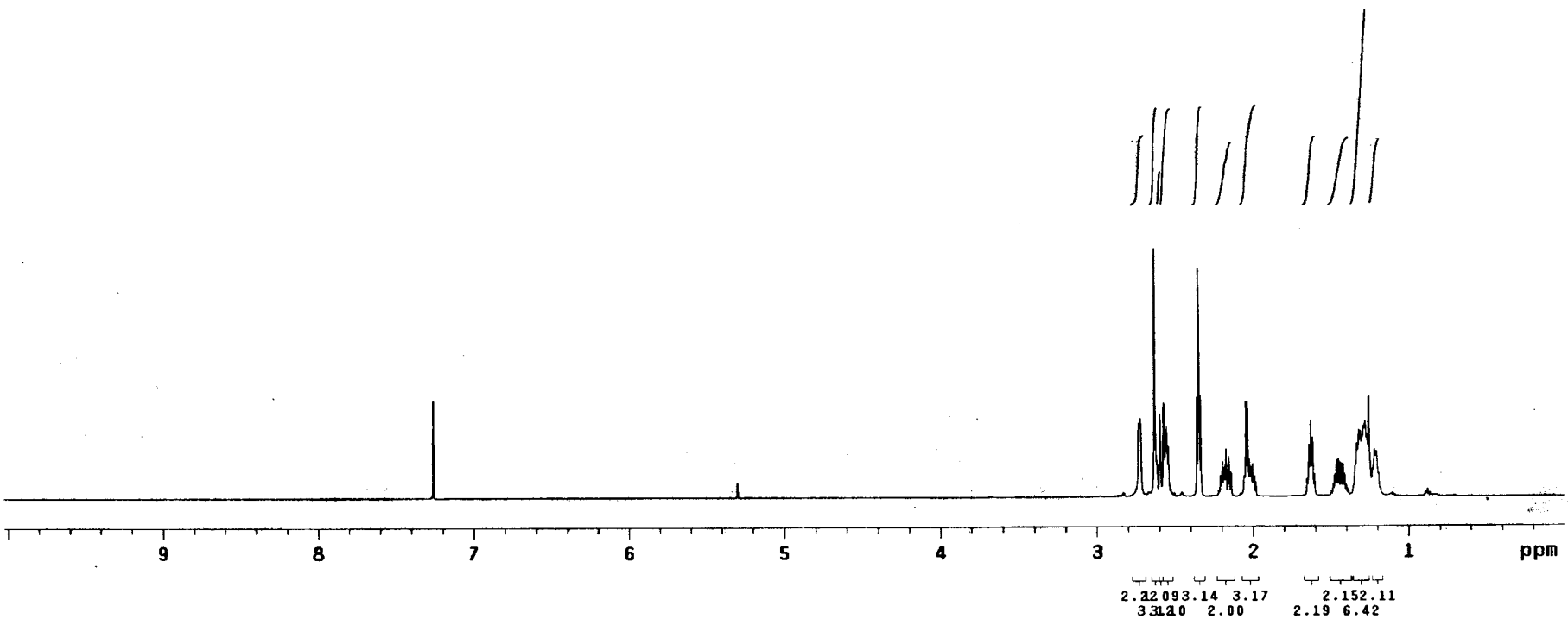


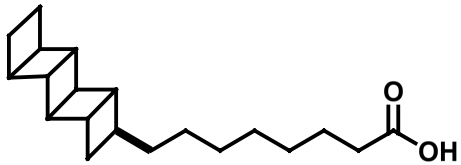
To a solution of (+)-pentacycloanammoxic acid **1** (20 mg, 66.1 μmol) in Et_2O (1 mL) was added at 0°C a solution of diazomethane in Et_2O (until a yellow color remained). The resulting solution was stirred at this temperature for 2 hours then N_2 was bubbled into the solution for 10 min. Concentration and purification by flash chromatography over silica gel (hexanes/Et_2O : 95/5) afforded (+)-pentacycloanammoxic acid methyl ester **11** (21 mg, >99%) as colorless needles. m.p. = 55-57 °C; $[\alpha]_D$ +15.0 (*c* 1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$); δ (ppm): 3.66 (s, 3H), 2.73 (bd, 2H), 2.63 (bs, 2H), 2.63 (m, 1H), 2.59 (bs, 1H), 2.57 (bs, 1H), 2.58-2.52 (m, 2H), 2.34 (bs, 1H), 2.30 (t, 2H, *J* = 7.5 Hz), 2.19 (m, 1H), 2.17 (m, 1H), 2.04 (m, 2H, [appears as a doublet]), 2.00 (m, 1H), 1.61 (m, 2H, [appears as a broad quintuplet, *J* = 7.3 Hz]), 1.49-1.37 (m, 2H), 1.32-1.26 (m, 6H), 1.22 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 174.3, 51.4, 49.4, 49.3, 49.2, 48.3, 47.3, 41.8 (x2), 39.9, 38.5, 37.3, 34.1, 33.3, 29.5, 29.3, 29.1, 26.5 (x2), 26.4, 25.0. IR (film, cm^{-1}): 2921, 2852, 1742, 1465, 1437, 1378, 1260, 1167. HRMS calcd for $C_{21}H_{33}O_2$ ($M+H^+$) 317.2480, found 317.2475. R_f = 0.43 (hexanes/EtOAc : 95/5); R_f = 0.28 (hexanes/*i*-PrOH : 98/2); R_f = 0.36 (hexanes/Et_2O : 95/5).



(+)-Pentacycloanammoxic Acid

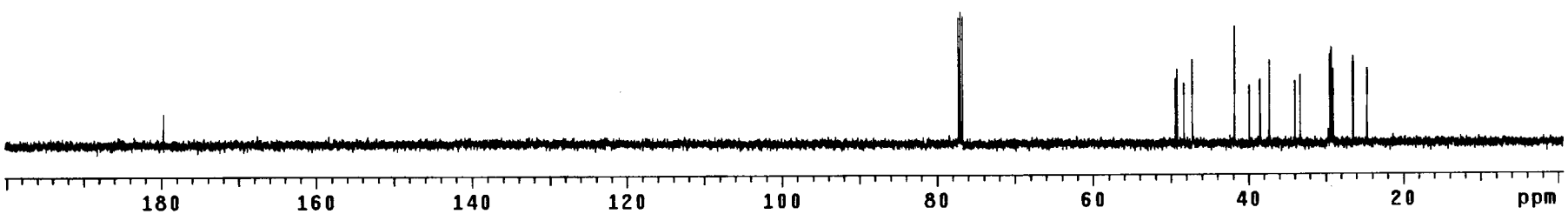
(600 MHz, $CDCl_3$)

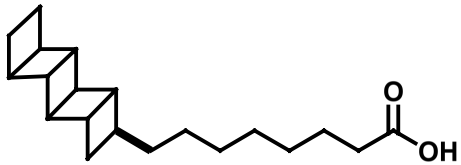




(+)-Pentacycloanammoxic Acid

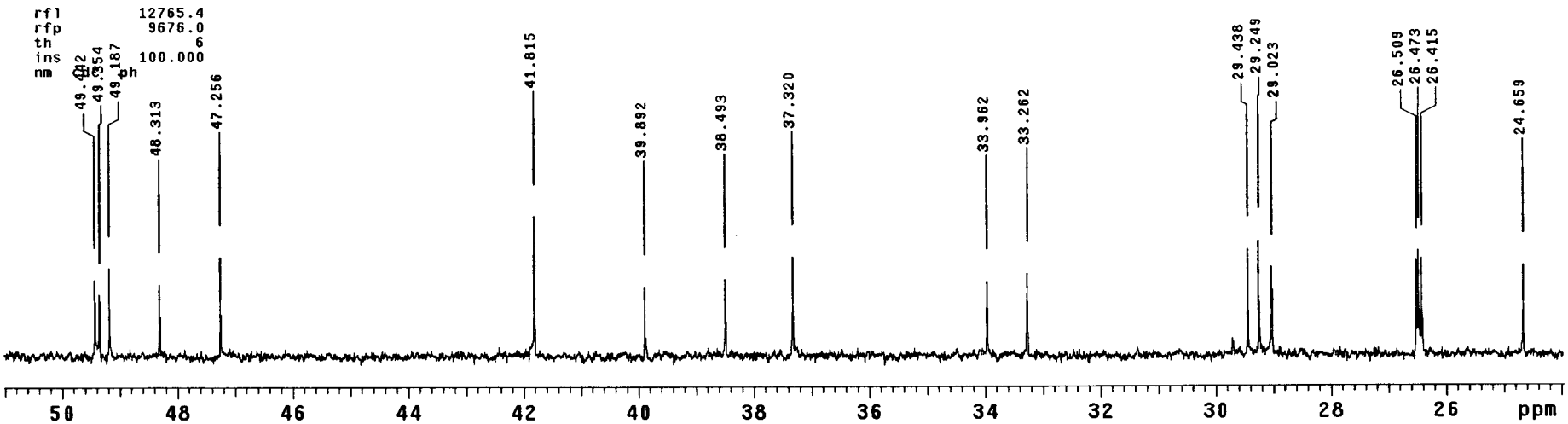
(125 MHz, $CDCl_3$)

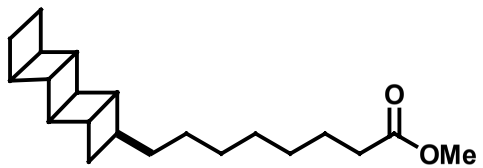




(+)-Pentacycloanammoxic Acid

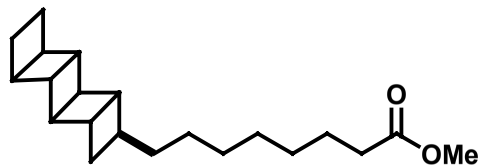
(125 MHz, $CDCl_3$)





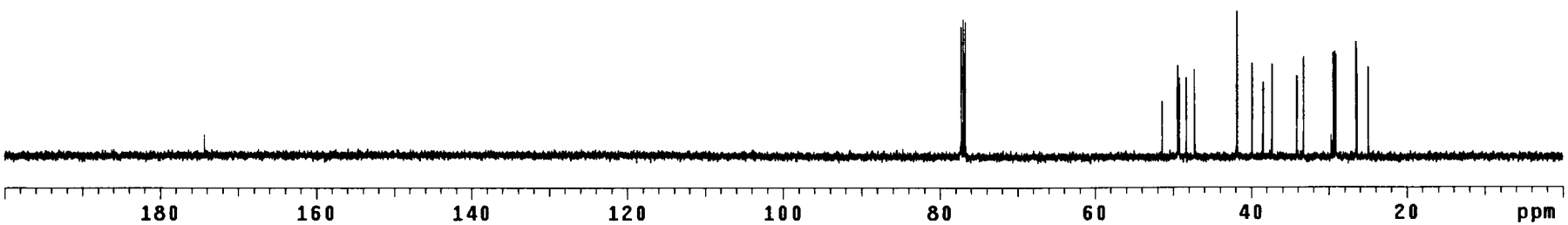
(+)-Pentacycloanammoxic Acid Methyl Ester

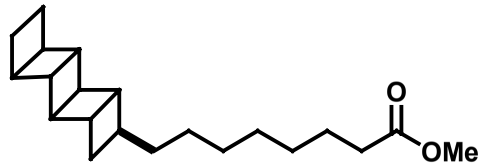
(600 MHz, $CDCl_3$)



(+)-Pentacycloanammoxic Acid Methyl Ester

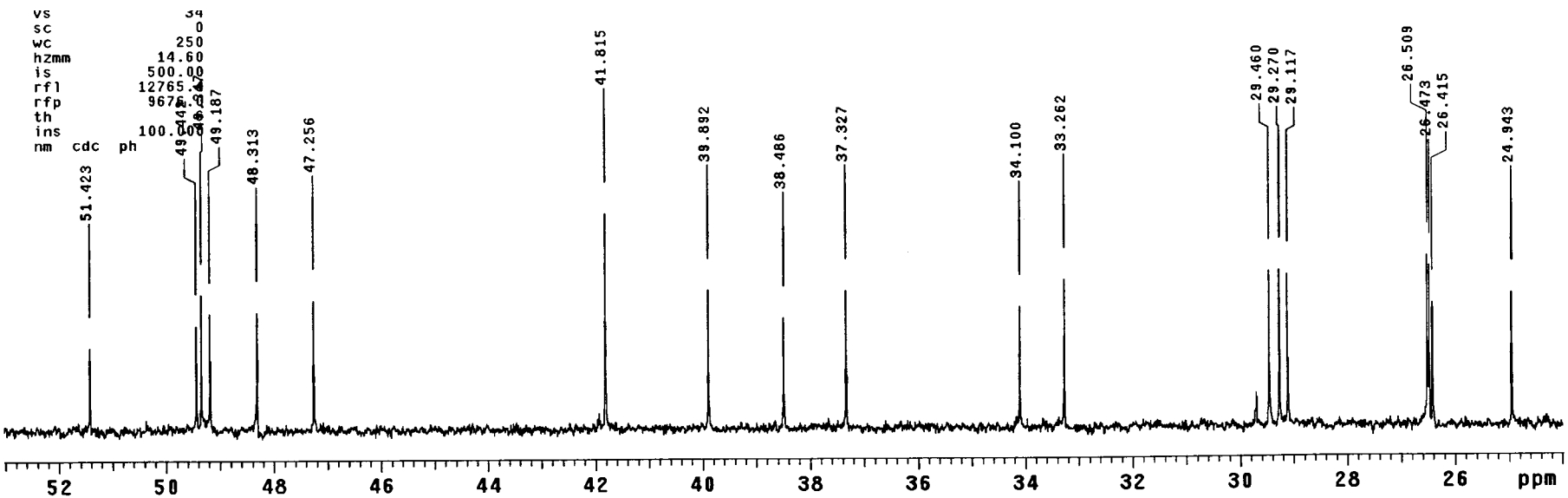
(125 MHz, $CDCl_3$)



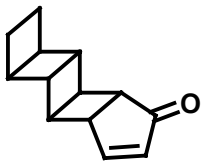


(+)-Pentacycloanammoxic Acid Methyl Ester

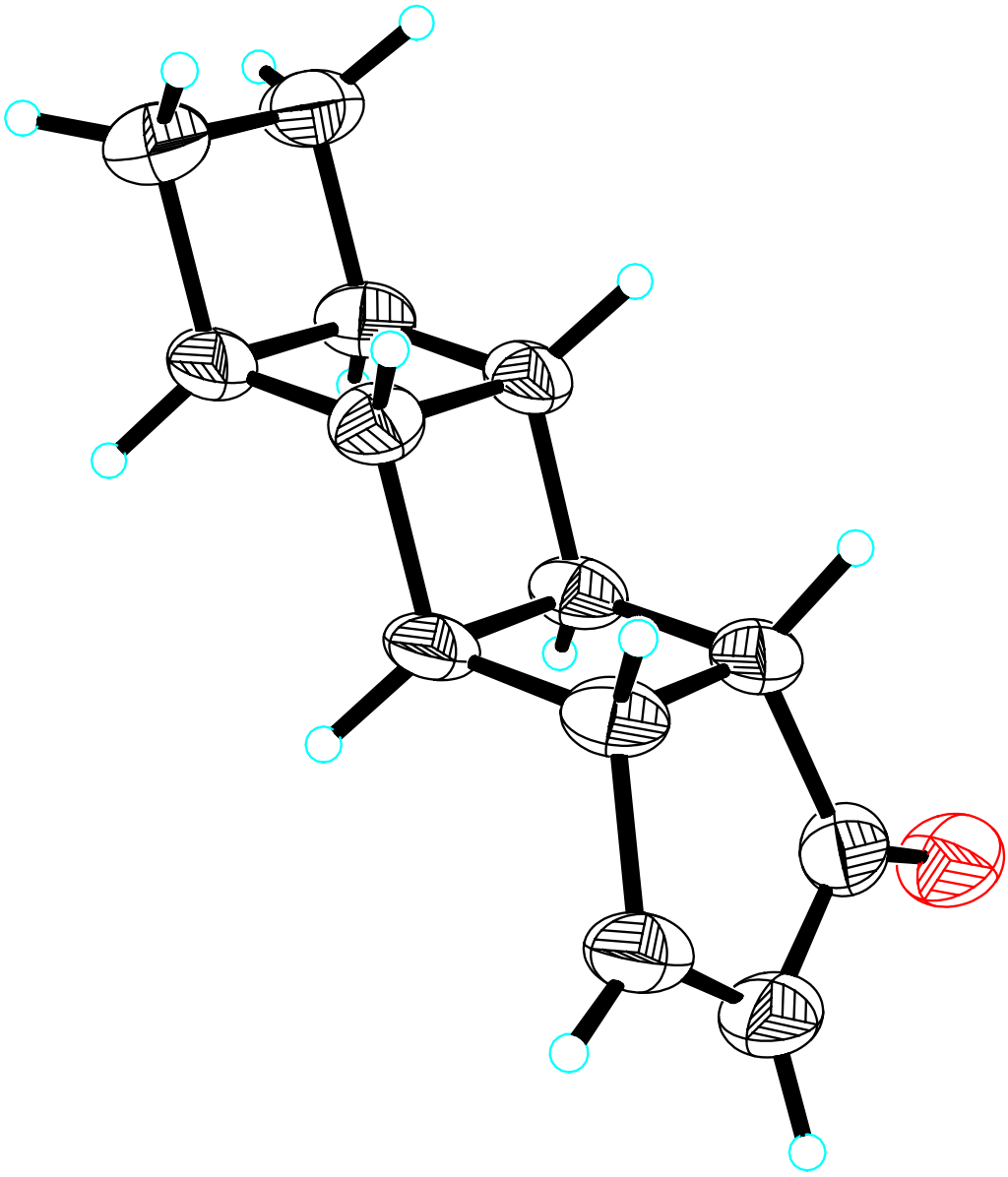
(125 MHz, $CDCl_3$)



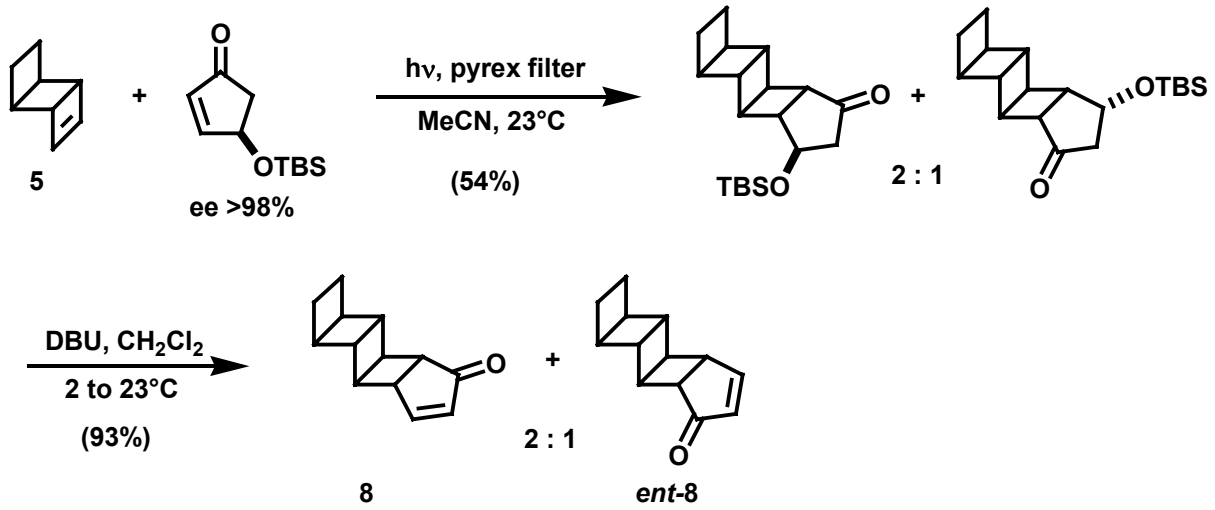
X-ray data for compound 8



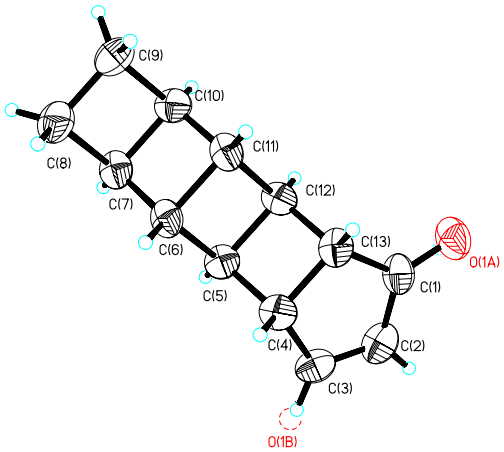
8



The sample (**8**/*ent*-**8** : 2/1) used for the single-crystal X-ray diffraction analysis was obtained according to the following scheme.



The solid was recrystallized from EtOAc/heptane to furnish X-ray quality colorless crystals (plate shape) m.p. = 91-99°C. The structure was solved in the space group $P2_12_12_1$ (# 19) by analysis of systematic absences. All non-hydrogen atoms were refined anisotropically. Hydrogens were found by difference Fourier methods and refined except for the disorder hydrogens on C3 and C1. The crystal proved to be twinned and disordered. The disorder distorts the bond length for C2. The bond distances C2 to C3 and C2 to C1 are a percentage average of the real distances due the disorder which places the double bond in two different locations, dependant on the position of the oxygen atom. This ratio of disorder is that of 0.89/0.11, O1a/O1b. Attempts to separate the carbon atom (C2) into two distinct positions failed to yield a reasonable structure. The crystal used for the diffraction study showed no decomposition during data collection. All drawing are done at 50% ellipsoids.



Picture with all the labels shown and the dotted representation of the disorder.

Table 1. Crystal data and structure refinement for rak48o.

Identification code	rak48o	
Empirical formula	C13 H14 O	
Formula weight	186.24	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.501(5) Å	α= 90°.
	b = 10.385(9) Å	β= 90°.
	c = 16.917(14) Å	γ = 90°.
Volume	966.4(14) $Å^3$	
Z	4	
Density (calculated)	1.280 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	400	
Crystal size	0.08 x 0.1 x 0.4 mm^3	
Theta range for data collection	2.30 to 27.94°.	
Index ranges	-7<=h<=6, -13<=k<=5, -22<=l<=22	
Reflections collected	6239	
Independent reflections	2297 [R(int) = 0.2288]	
Completeness to theta = 27.94°	99.3 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2297 / 0 / 183	
Goodness-of-fit on F^2	0.945	
Final R indices [I>2sigma(I)]	R1 = 0.0745, wR2 = 0.1506	
R indices (all data)	R1 = 0.1857, wR2 = 0.1948	
Absolute structure parameter	-5(5)	
Largest diff. peak and hole	0.217 and -0.199 $e.Å^{-3}$	

References

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