SUPPORTING INFORMATION

First synthesis of an ABCE ring substructure of daphnicyclidin A

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EXPERIMENTAL PROCEDURES

I General Information

Experimental

Sodium benzoate and methyltriphenylphosphonium iodide were purchased from AmBeed and used as received. Sodium bicarbonate was purchased from Fisher and used as received. Hexanes, ethyl acetate, and methylene chloride for flash chromatography purposes were purchased from Fisher and used as received. Argon cylinder was purchased from AirGas and used as received. *Tert*-butyldimethylchlorosilane, tetra-*n*-butylammonium fluoride (1.0 M solution in THF), propane-1,3-diol, and 4-dimethylaminopyridine were purchased from Oakwood and used as received. Triethylamine and 2,6-lutidine were distilled over CaH_2 prior to use. Cyclopentanone was first dried over 4 Å molecular sieves and Na_2SO_4 overnight, then freshly distilled prior to use. Tetrahydrofuran was purchased from Fisher and distilled over sodium with benzophenone as an indicator prior to use. *n*-Butyl lithium (2.5 M solution in hexane), benzonitrile, methylene chloride, diisopropylamine, and imidazole were purchased from Sigma-Aldrich and used as received. Trifluoromethanesulfonic anhydride was purchased from TCI and used as received. TLC silica gel 60 F254 aluminum sheets were purchased from Sigma-Aldrich. SiliaFlash® F60 (and P60) 230-400 silica gel for column chromatography was purchased from SiliCycle. All reactions were carried out in oven-dried glassware, capped with a Precision Seal® rubber septum, and purged with argon (balloon) unless otherwise stated. All (4+3) cycloadditions were conducted in CG-1880-21 pressure vessels (sealed tube) unless otherwise stated. When necessary, syringes and needles were used to transfer all liquid reagents. A NE-300 syringe pump was used for all dropwise addition of reagents.

Analytical

TLC spotting was observed under a SPECTROLINE® ENF-260C UV lamp using short wave mode (254 nm). For non-UV absorbing products, visualization of the TLC is possible with either vanillin stain or Seebach's magic stain followed by gentle heating with a heat gun to reveal Rf value. Nuclear Magnetic Resonance (NMR) spectroscopy was measured by Bruker AVANCE III HD 500 (500 MHz) or Bruker AVANCE III HD 600 (600 MHz) for ^{1}H (proton) and ^{13}C (carbon). Norell® 508-up NMR tubes were used to measure NMR spectroscopy. ^{1}H NMR are reported in δ units, parts per million (ppm), relative to tetramethylsilane (TMS) as an internal standard (0.00 ppm). ^{13}C NMR are reported in ppm relative to chloroform-d (77.16 ppm). Infrared spectra were measured by a ThermoScientific Nicolet Summit PRO FTIR spectrometer equipped with an Everest™ Diamond ATR Accessory. Samples were prepared

either as a neat sample or dissolved in chloroform-d. Samples were further characterized by High-Resolution Mass Spectrometry (HR-MS) using an Apollo II ion source on a Bruker 12 Tesla APEX-Qe FTICR-MS.

Abbreviations

EtOAc = ethyl acetate
DMAP = 4-dimethylaminopyridine
RBF = round-bottom flask
TBSCl = *tert*-butyldimethylchlorosilane
THF = tetrahydrofuran, *n*BuLi = *n*-butyllithium
TBAF = tetra-*n*-butylammonium fluoride
TEA = triethylamine
DMSO = dimethylsulfoxide
LDA = lithium diisopropylamide.

II Tables for Optimizations of Reaction Conditions

II.1 Temperature Study of ABCE Ring 31 Formation

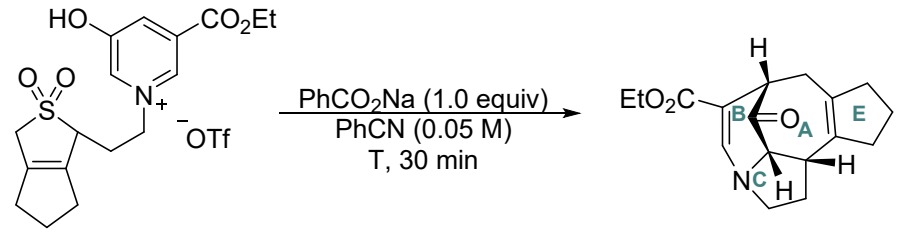


Table S1. Temperature Study of ABCE Ring Formation.

Entry	T °C	Yield (%)
1	125[a]	8[c]
2	170[a]	25
3	180[a]	28
4	180[b]	22
5	190[a]	22
6	200[a]	11

[a] Carried out with a closed-cap sealed tube.
[b] Carried out with an open-cap sealed tube to vent SO_2 gas.
[c] Reaction time = 3 hours.

II.2 Time Study of ABCE Ring 31 Formation

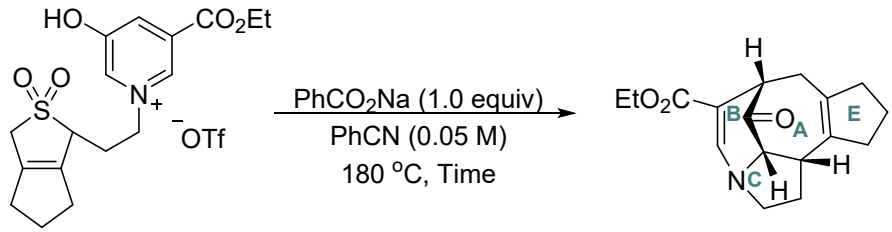


Table S2. Time Study of ABCE Ring Formation.

Entry	Time (min)	Yield (%)
1	30	28
2	60	70[a]
3	60[b]	62
4	90	38

[a] Repeated 3 times to verify accuracy of yield.
[b] Reaction carried out on larger scale (1.07 mmol).

III Stability Studies

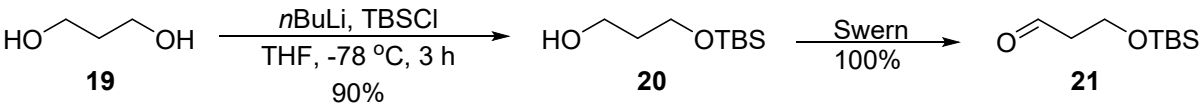
1. To a CG-1880-01 15 mL sealed tube, cycloadduct **31** (18 mg) was dissolved in PhCN (1 mL), and the solution was heated to 180 ^{o}C for 6 hours. After cooling to room temperature, the reaction mixture was passed through a plug of silica gel (Hexane : EtOAc = 2 : 1) to remove most of the PhCN and collect the crude product (containing a small amount of PhCN). ^{1}H NMR revealed compound **31** was recovered with a 50% yield (9 mg).

2. To a CG-1880-01 15 mL sealed tube, cycloadduct **31** (18 mg) was dissolved in PhCN (1 mL), followed by addition of gaseous SO_2 (trace), trifluoromethanesulfonic acid (1 equiv) and sodium benzoate (1 equiv). The mixture was heated to 180 ^{o}C for 4 hours to give a burnt, sticky residue.

Conclusion: Cycloadduct **31** is thermally unstable, explaining the increased time of reaction and reduced yield of cycloaddition (Table S2).

IV Synthetic Procedures and Characterization

IV.1 Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)propanal 21

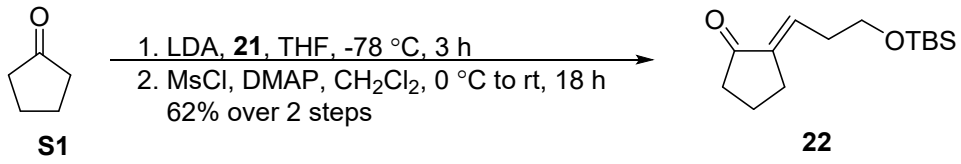


Following a known procedure.[1] To a 500 mL, 24/40 single-neck RBF was added propane-1,3-diol **19** (10 mL, 140 mmol, 1.0 equiv) and freshly distilled THF (250 mL). The solution was cooled to -78 °C followed by dropwise addition of *n*BuLi (2.5 M in hexanes, 56 mL, 140 mmol, 1.0 equiv). The mixture stirred at -78 °C for 30 minutes followed by slow addition of a solution of TBSCl (21 g, 140 mmol, 1.0 equiv) in THF (20 mL). The mixture was then slowly warmed to room temperature by removing the cold bath, then stirred for 3 hours at room temperature before quenching with water (300 mL). The reaction mixture was extracted with Et_2O (300 mL x 3), and the combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude **20** in 90% yield (24 g). The crude **20** was used in the next step without further purification.

Following a known procedure.[1,2] To a 250 mL, 24/40 single-neck RBF was first added CH_2Cl_2 (50 mL) then oxalyl chloride (2.4 mL, 31.22 mmol, 1.4 equiv). The solution was cooled to -78 °C followed by dropwise addition of DMSO§ (3.6 mL, 51.29 mmol, 2.3 equiv) in CH_2Cl_2 (5 mL). The mixture stirred for 15 minutes at the same temperature before dropwise addition of a solution of **20** (4.24 g, 22.30 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL). TEA (15.4 mL, 111.50 mmol, 5.0 equiv) is added dropwise to the mixture followed by immediate removal of the cold bath to allow the temperature to slowly warm to room temperature over 2 hours before quenching with water (50 mL). The organic layer was separated and washed sequentially with 1 N HCl (50 mL), sat. $NaHCO_3$ aq. (50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford crude **21** without further purification.

§DMSO should be dissolved in CH_2Cl_2 to prevent its freezing during syringe pump addition

IV.2 Synthesis of (*E*)-2-(3-((*tert*-butyldimethylsilyl)oxy)propylidene)cyclopentan-1-one 22



S1 **22**

To a 100 mL, 24/40 single-neck RBF was added diisopropylamine (1.83 mL, 12.5 mmol, 1 equiv) and freshly distilled THF (12.5 mL). The mixture was cooled to -78 °C followed by slow addition of *n*BuLi (2.5 M in hexanes, 5 mL, 12.5 mmol, 1.0 equiv). The mixture stirred at the same temperature for 30 minutes to afford a solution of LDA.

To a 100 mL, 24/40 single-neck RBF was added cyclopentanone **S1** (1.05 g, 12.5 mmol, 1.0 equiv) and freshly distilled THF (12.5 mL). The solution was cooled to -78 °C followed by dropwise addition of the freshly made LDA solution via syringe. The mixture stirred at -78 °C for 30 minutes before dropwise addition of a solution of **21** (2.36 g, 12.5 mmol. 1.0 equiv) in THF (12.5 mL). The reaction stirred at -78 °C for 1.5 hours before removing the cold bath and quenching the reaction with sat. $NaHCO_3$ aq. (25 mL). The mixture was extracted with EtOAc (25 mL x 4), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was used without further purification for the next step.

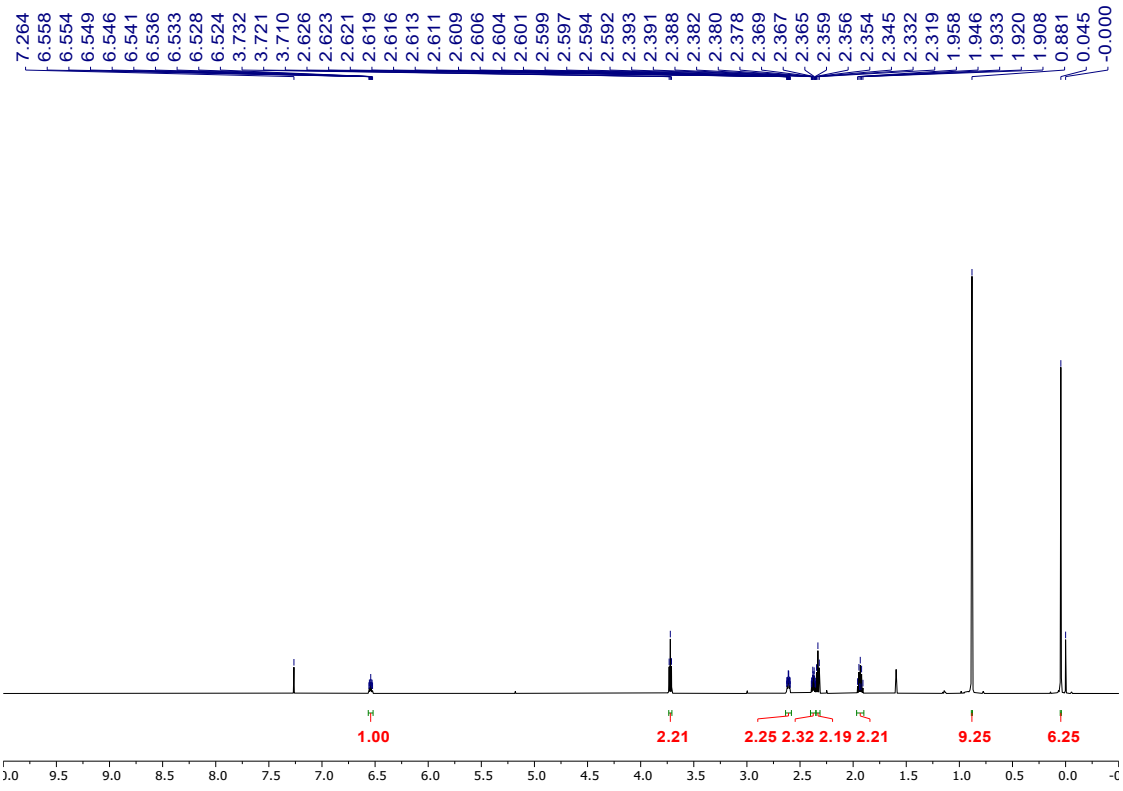
To a 250 mL, 24/40 single-neck RBF was added the residue, CH_2Cl_2 (50 mL) and DMAP (6.1 g, 50 mmol, 4 equiv). The mixture was cooled to 0 °C followed by dropwise addition of methanesulfonyl chloride (1.1 mL, 31 mmol, 2.5 equiv). The reaction stirred at 0 °C for 16 hours before quenching with sat. $NaHCO_3$ aq. (50 mL). The mixture was extracted with CH_2Cl_2 (25 mL x 3), and the combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane : EtOAc = 100 : 1) to afford (*E*)-2-(3-((*tert*-butyldimethylsilyl)oxy)propylidene)-cyclopentane-1-one **22** in 62% yield (1.97 g) over 2 steps as a light-yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) = 6.54 (tt, *J* = 7.6, 2.7 Hz, 1H), 3.72 (t, *J* = 6.6 Hz, 2H), 2.61 (tdt, *J* = 7.3, 2.6, 1.5 Hz, 2H), 2.37 (dtt, *J* = 7.6, 6.6, 1.5 Hz, 2H), 2.33 (t, *J* = 7.8 Hz, 2H), 1.93 (tt, *J* = 7.6, 7.5 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H).

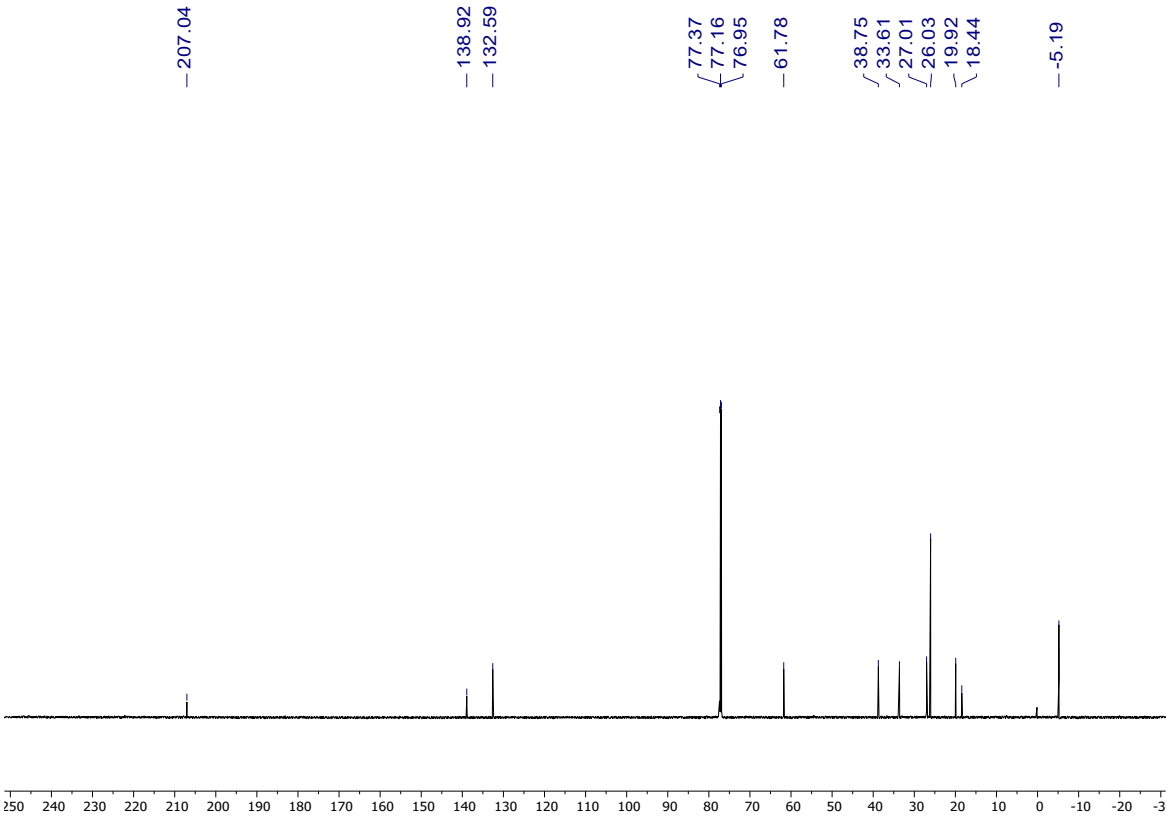
^{13}C NMR (151 MHz, $CDCl_3$): δ_C (ppm) = 207.0, 138.9, 132.6, 61.8, 38.8, 33.6, 27.0, 26.0, 19.9, 18.4, -5.2.

FTICR-MS (m/z): Calcd for ($[M+Na]^+$) 277.1594; found 277.1592.

IR (neat): $\tilde{\nu}$ = 2955, 2936, 2887, 2858, 1717, 1650, 1473, 1256, 1190, 1100, 904 cm^{-1}.

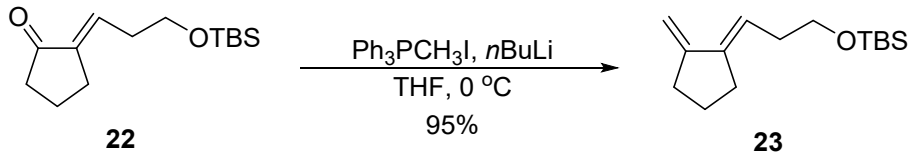


^{1}H NMR (600 MHz, $CDCl_3$) of **22**



^{13}C NMR (151 MHz, $CDCl_3$) of **22**

IV.3 Synthesis of (*E*)-*tert*-butyldimethyl(3-(2-methylenecyclopentylidene)propoxy)-silane 23



22 **23**

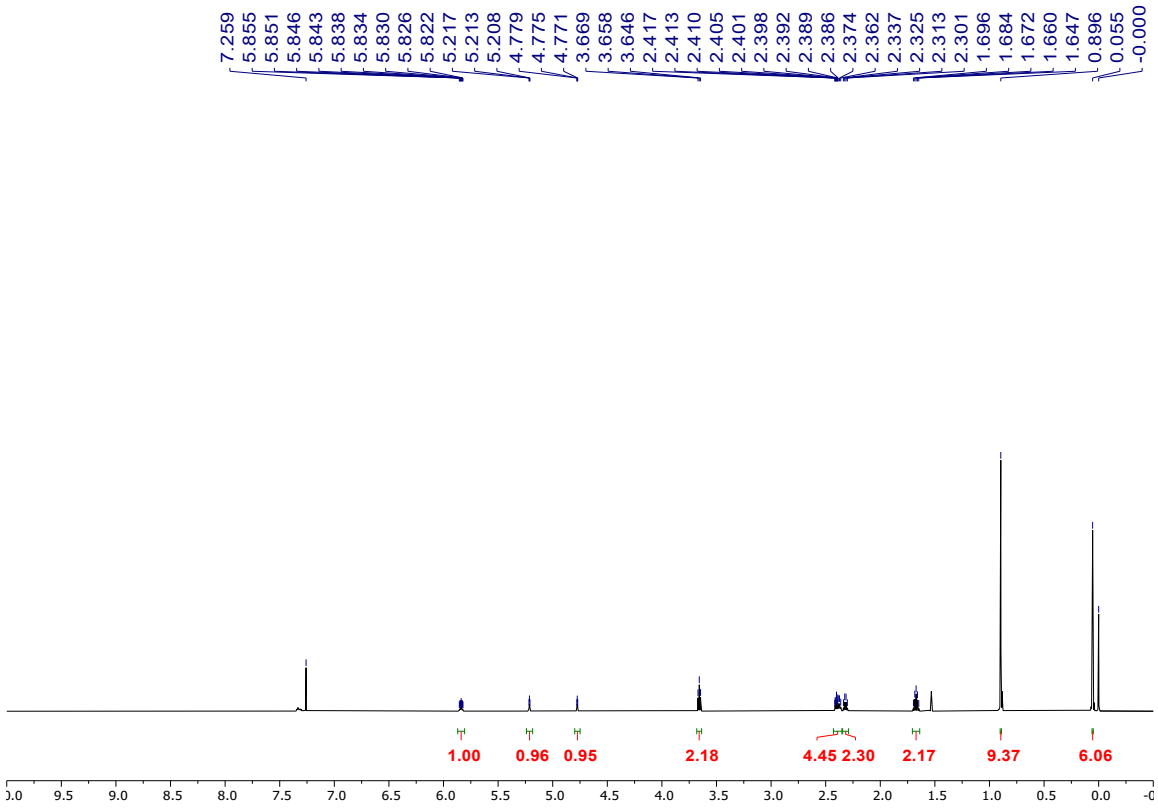
To a 250 mL, 24/40 single-neck RBF was added methyltriphenylphosphonium iodide (7 g, 17.4 mmol, 2.0 equiv) and freshly distilled THF (100 mL). The solution was cooled to 0 °C followed by dropwise addition of *n*BuLi (2.5 M in hexanes, 7 mL, 17.4 mmol, 2.0 equiv). The mixture stirred at 0 °C for 60 minutes before dropwise addition of a solution of **22** (2.21 g, 8.68 mmol, 1.0 equiv) in THF (50 mL). The ice bath was removed, and the reaction slowly warmed to room temperature over 60 minutes before quenching with water (5 mL) followed by addition of sat. NH_4Cl aq. (100 mL). The reaction mixture was extracted with EtOAc (100 mL x 2), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexanes) to afford (*E*)-*tert*-butyldimethyl(3-(2-methylenecyclopentylidene)propoxy)silane **23** in 95% yield (2.1 g) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) = 5.84 (tt, *J* = 7.4, 2.5 Hz, 1H), 5.21 (dd, *J* = 2.6, 2.5 Hz, 1H), 4.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 3.66 (t, *J* = 7.0 Hz, 2H), 2.40 (ddt, *J* = 7.3, 7.3, 2.1 Hz, 2H), 2.39-2.39 (m, 2H), 2.32 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.67 (tt, *J* = 7.3, 7.3 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H).

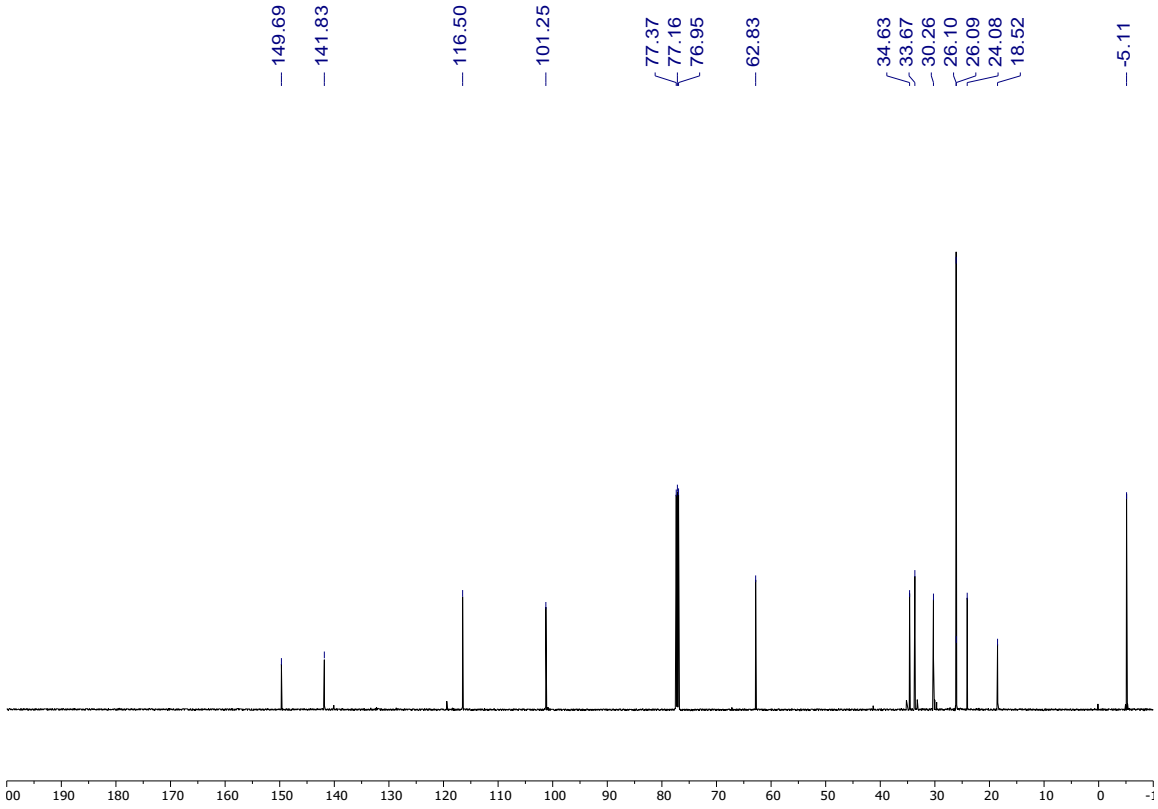
^{13}C NMR (151 MHz, $CDCl_3$): δ_C (ppm) = 149.7, 141.8, 116.5, 101.2, 62.8, 34.6, 33.7, 30.3, 26.1, 24.1, 18.5, -5.1.

FTICR-MS (m/z): Calcd for ($[M+Na]^+$) 275.1802; found 275.1801.

IR (neat): $\tilde{\nu}$ = 2957, 2934, 2857, 1625, 1472, 1440, 1255, 1100, 912 cm^{-1}.

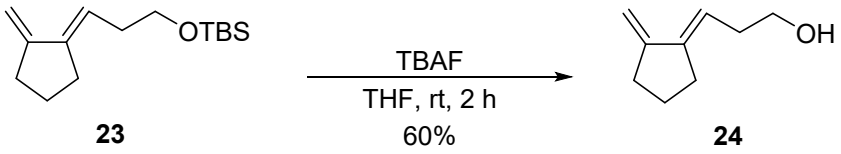


^{1}H NMR (600 MHz, $CDCl_3$) of **23**



^{13}C NMR (151 MHz, $CDCl_3$) of **23**

IV.4 Synthesis of (*E*)-3-(2-methylenecyclopentylidene)propan-1-ol 24



23 **24**

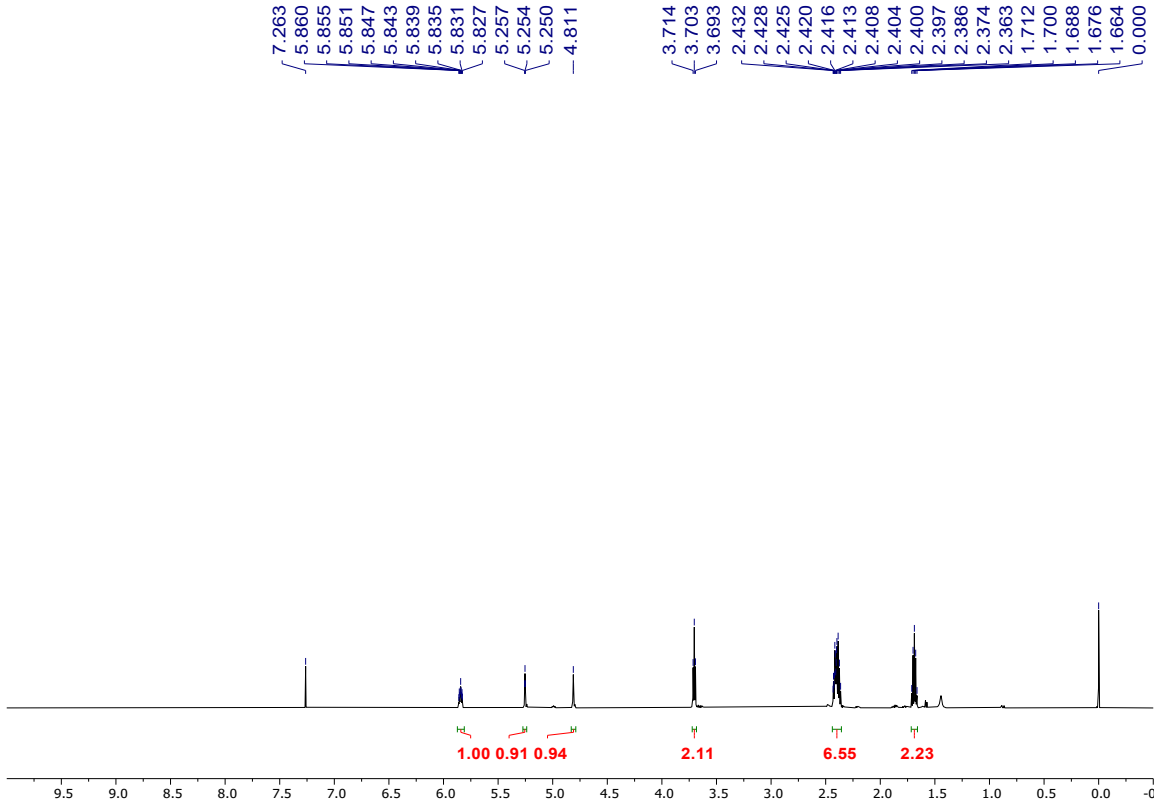
To a 50 mL, 14/20 single-neck RBF was added **23** (611 mg, 2.4 mmol, 1.0 equiv) and freshly distilled THF (20 mL). The solution was cooled to 0 °C followed by dropwise addition of TBAF (1.0 M in THF, 2.5 mL, 2.5 mmol, 1.04 equiv). The mixture stirred at 0 °C for 2 hours before quenching with sat. NH_4Cl aq. (3 mL). The reaction mixture was extracted with EtOAc (10 mL x 3), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane : EtOAC = 1 : 1) to afford (*E*)-3-(2-methylenecyclopentylidene)propan-1-ol **24** in 60% yield (200 mg) as a colorless oil. The product is unstable and begins to decompose immediately after isolation.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) = 5.84 (tt, *J* = 7.5, 2.5 Hz, 1H), 5.25 (dd, *J* = 2.0, 2.0 Hz, 1H), 4.81 (s, 1H), 3.70 (t, *J* = 6.5 Hz, 2H), 2.43-2.36 (m, 6H), 1.69 (tt, *J* = 7.3, 7.2 Hz, 2H).

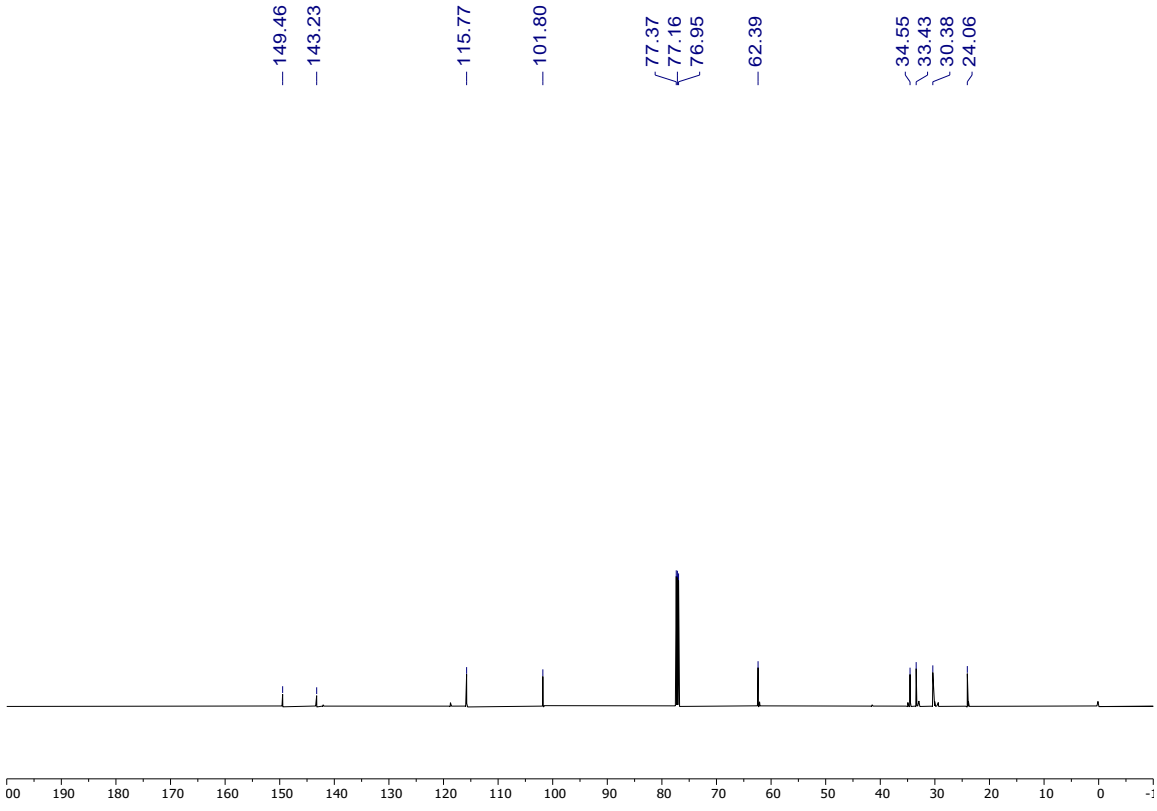
^{13}C NMR (151 MHz, $CDCl_3$): δ_C (ppm) = 149.5, 143.2, 115.8, 101.8, 62.4, 34.6, 33.4, 30.4, 24.1.

FTICR-MS (m/z): Calcd for ([M+Na]$^+$) 161.0937; not observed.

IR (neat): $\tilde{\nu}$ = 3437, 2956, 2933, 2894, 2857, 1728, 1458, 1443, 1392, 1365, 1303, 1249, 1174, 1072, 990 cm^{-1}.

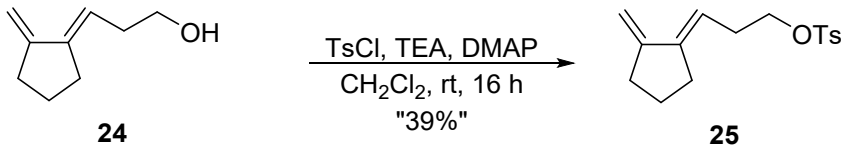


^{1}H NMR (600 MHz, $CDCl_3$) of **24**



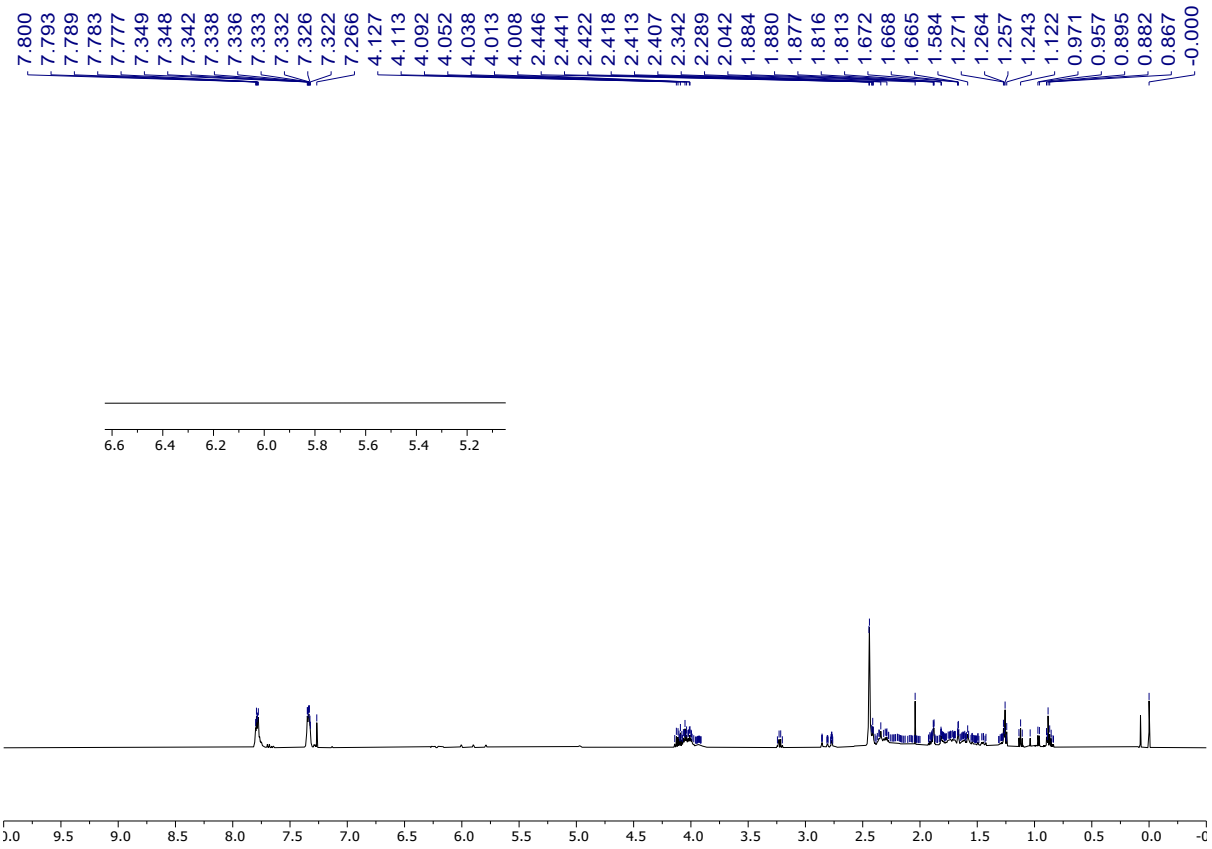
^{13}C NMR (151 MHz, $CDCl_3$) of **24**

IV.5 Synthesis of (*E*)-3-(2-methylenecyclopentylidene)propyl tosylate 25



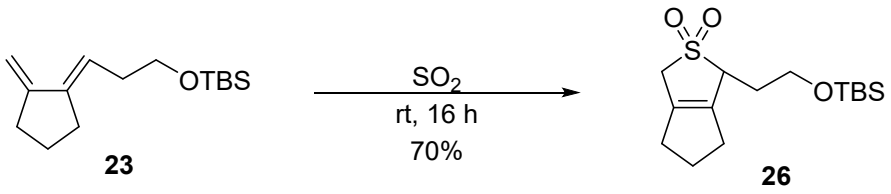
24 **25**

To a 10 mL, 14/20 single-neck RBF was added **24** (45 mg, 0.33 mmol, 1.0 equiv), tosyl chloride (76 mg, 0.4 mmol, 1.2 equiv), TEA (0.06 mL, 0.5 mmol, 1.5 equiv) and DMAP (4.5 mg, 0.03 mmol, 0.1 equiv) in dry CH_2Cl_2 (30 mL). The mixture stirred at room temperature for 16 hours before quenching with water (3 mL). The organic layer was separated and analyzed by TLC (Hexane : EtOAc = 4:1) to give one spot (R_f = 0.75), which we suspect to be the tosylate, according to our previous paper.[3] The aqueous layer was then extracted with CH_2Cl_2 (3 mL x 2), and the combined organic layers were dried over anhydrous Na_2SO_4. TLC was again performed to ensure only one spot remained before concentration of the mixture. The solvent was removed under reduced pressure and the residue was loaded on a CG-1203-21 column for flash chromatography [SiliaFlash® F60 230-400 silica gel, slurry method, packed with hexanes, eluted with Hexane : EtOAC = 9 : 1, and collected with FISHERbrand® Borosilicate Disposable Culture Tubes (13x100mm)]. The colorless fractions containing the desired TLC spot were combined in a 20 mL disposable scintillation vial (transparent). When concentrated under reduced pressure, the original colorless solution produced a dark brown residue once stripped of the solvent. This residue was then exposed to a high vacuum system (oil pump) for 30 minutes, leaving 37 mg of material to give a “39%” yield. The dark brown residue was then dissolved in chloroform-d and analyzed by TLC (Hexane : EtOAc = 4:1) to reveal a plate with messy spots, none of which had R_f = 0.75, indicating the product is extremely unstable and quickly decomposes after isolation. NMR was then performed to show the decomposition of the tosylate. The observed color (before decomposition) should be ‘colorless,’ while its consistency should be in the form of an ‘oil’ for (*E*)-3-(2-methylenecyclopentylidene)propyl tosylate **25**.



^{1}H NMR (500 MHz, $CDCl_3$) of combined fractions of **25**, which showed a total decomposition.

IV.6 Synthesis of 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophene 2,2-dioxide 26



23 **26**

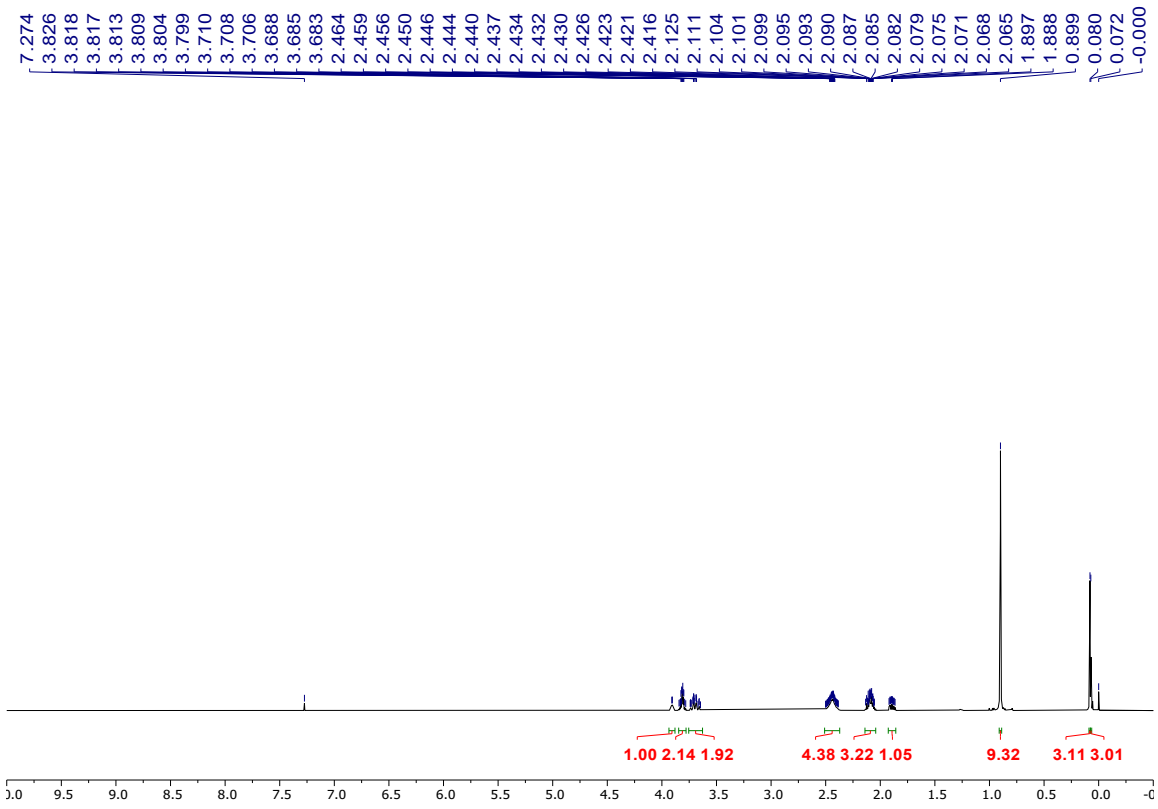
To a CG-1880-21 seal tube was added **23** (250 mg, 0.99 mmol, 1.0 equiv) and freshly condensed SO_2 (~1 mL, ~45 mmol, ~45 equiv) at room temperature. The seal tube was covered with aluminum foil to avoid exposure to UV light. The mixture stirred at room temperature for 16 hours, at which time the reaction mixture was chilled to 0 °C with an ice bath (Note: the cooling process is important to prevent the reaction mixture from venting violently.) The cap was then removed slowly, and the excess SO_2 was removed under reduced pressure. The residue was purified by flash chromatography (Hexane : EtOAc = 9 : 1) to afford 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophene 2,2-dioxide **26** in 71% yield (224 mg) as a colorless oil. The product is unstable and begins to decompose after isolation.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) = 3.93-3.88 (m, 1H), 3.84-3.78 (m, 2H), 3.75-3.65 (m, 2H), 2.51-2.38 (m, 4H), 2.14-2.04 (m, 3H), 1.89 (dddd, *J* = 13.9, 7.5, 6.2, 5.1 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

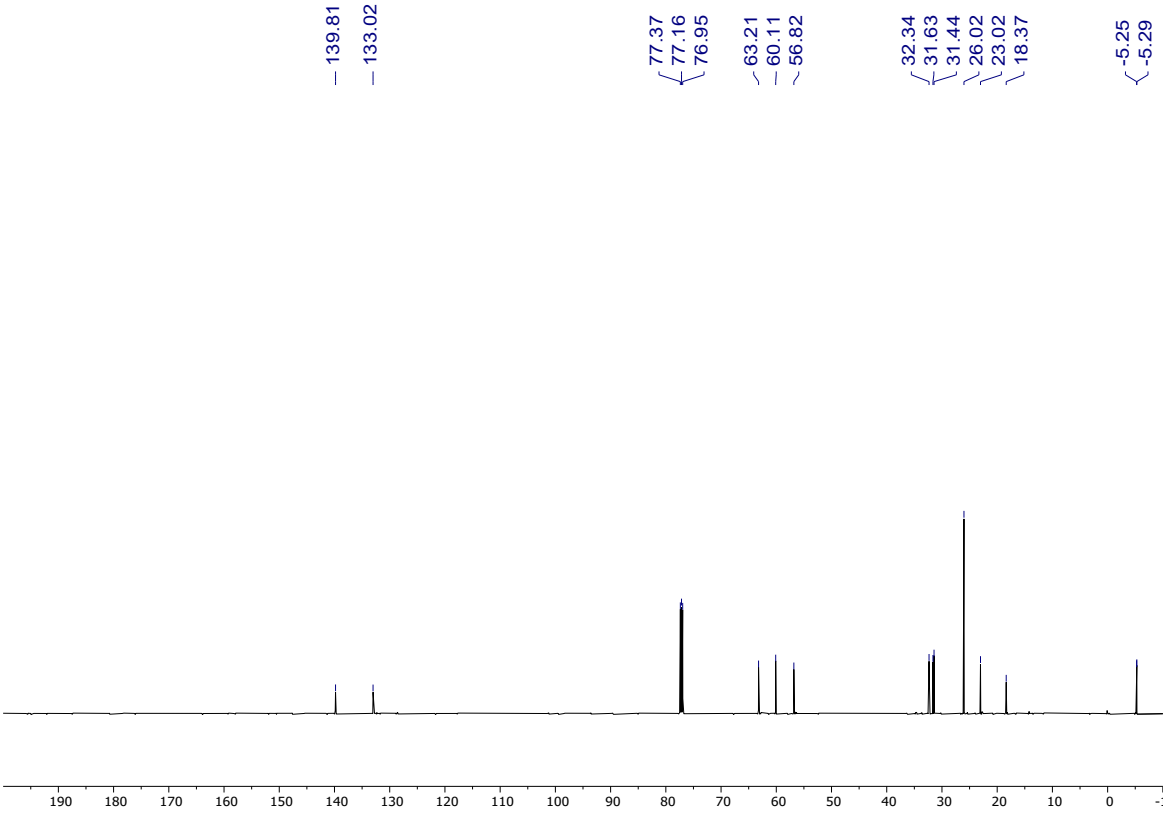
^{13}C NMR (151 MHz, $CDCl_3$): δ_C (ppm) = 139.8, 133.0, 63.2, 60.1, 56.8, 32.3, 31.6, 31.4, 26.0, 23.0, 18.4, -5.2, -5.3.

FTICR-MS (m/z): Calcd for ($[M+Na]^+$) 339.1421; found 339.1420.

IR (neat): $\tilde{\nu}$ = 2954, 2930, 2856, 1474, 1311, 1258, 1171, 1106, 912 cm^{-1}.

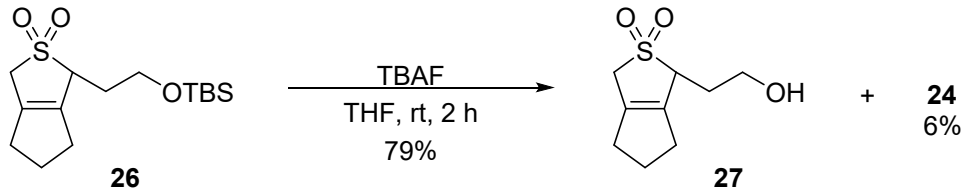


^{1}H NMR (600 MHz, $CDCl_3$) of **26**



^{13}C NMR (151 MHz, $CDCl_3$) of **26**

IV.7 Synthesis of 1-(2-hydroxyethyl)-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophene 2,2-dioxide 27



26 **27**

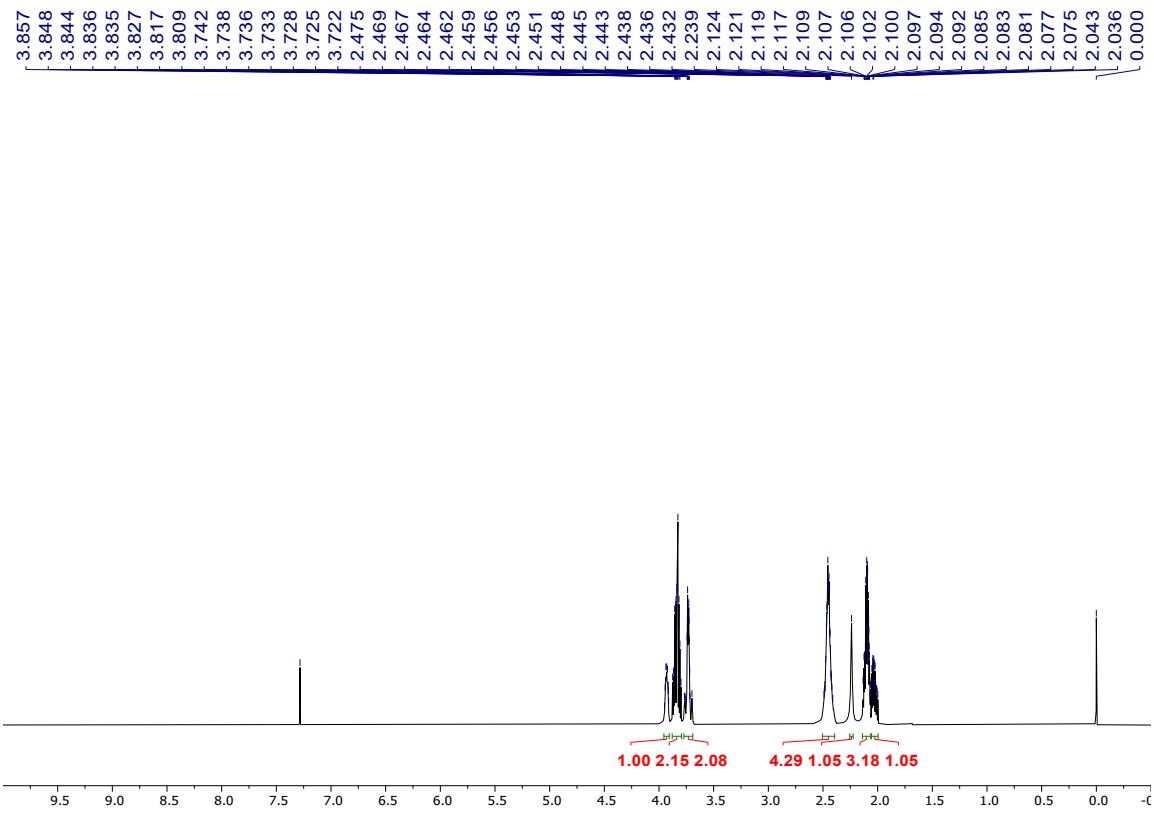
To a 50 mL, 14/20 single-neck RBF was added **26** (600 mg, 1.89 mmol, 1.0 equiv) and freshly distilled THF (20 mL). The solution was cooled to 0 °C followed by dropwise addition of TBAF (1.0 M in THF, 2.08 mL, 2.08 mmol, 1.1 equiv). The mixture stirred at 0 °C for 2 hours before quenching with sat. NH_4Cl aq. (3 mL). The reaction mixture was extracted with EtOAc (10 mL x 3), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (Hexane : EtOAC = 1 : 1) to afford 1-(2-hydroxyethyl)-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophene 2,2-dioxide **27** in 79% yield (300 mg) as a colorless oil. This reaction also gave **24** in 6% yield (15 mg) as a byproduct. The product is unstable and begins to decompose after isolation.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) = 3.95-3.91 (m, 1H), 3.88-3.80 (m, 2H), 3.77-3.69 (m, 2H), 2.50-2.40 (m, 4H), 2.24 (s, 1H), 2.13-2.07 (m, 3H), 2.05-2.00 (m, 1H), 3.70 (t, *J* = 6.5 Hz, 2H), 2.43-2.36 (m, 6H), 1.69 (tt, *J* = 7.3, 7.2 Hz, 2H).

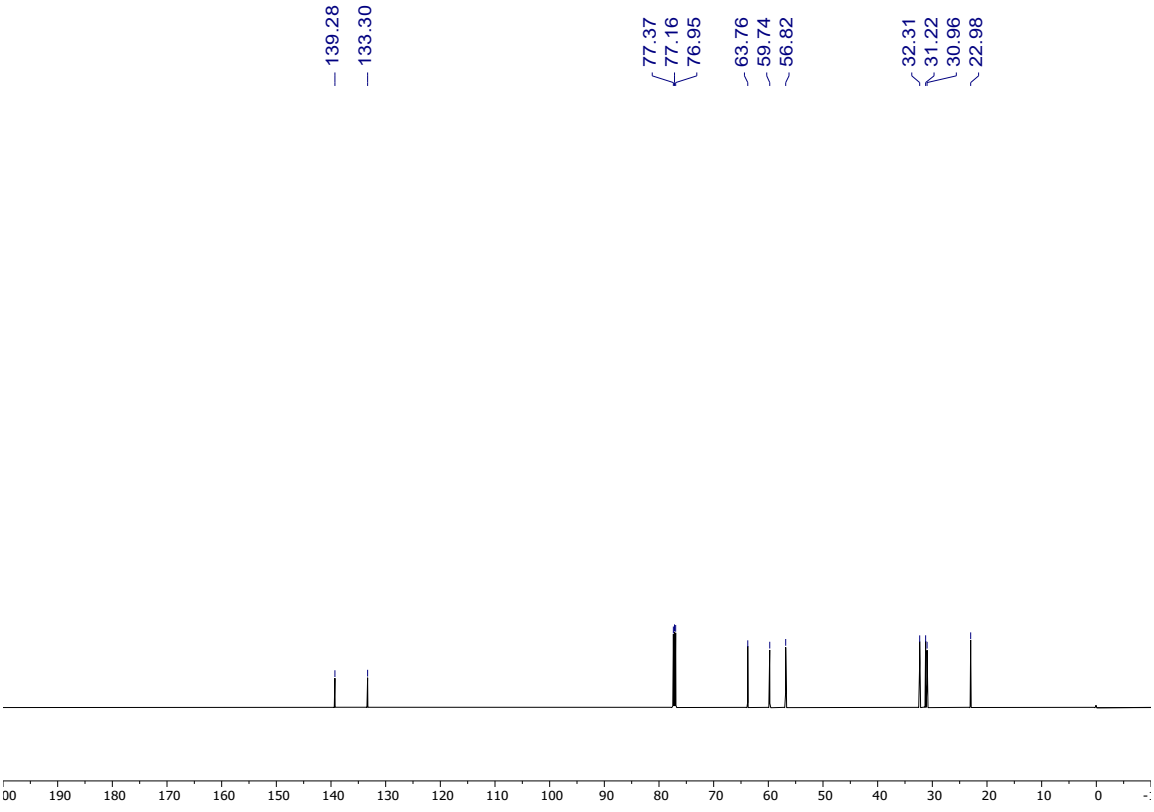
^{13}C NMR (151 MHz, $CDCl_3$): δ_C (ppm) = 139.3, 133.3, 63.8, 59.7, 56.8, 32.3, 31.2, 31.0, 23.0.

FTICR-MS (m/z): Calcd for ([M+Na]$^+$) 225.0556; found 225.0557.

IR (neat): $\tilde{\nu}$ = 3519, 2953, 2857, 1440, 1307, 1171, 1105, 1078, 921 cm^{-1}.

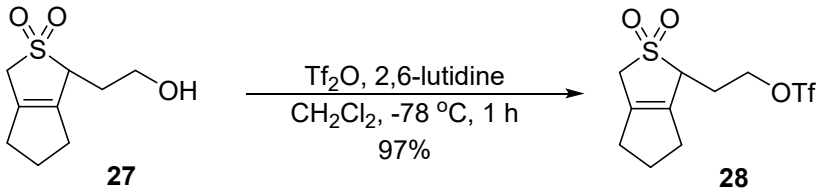


^{1}H NMR (600 MHz, $CDCl_3$) of **27**



^{13}C NMR (151 MHz, $CDCl_3$) of **27**

IV.8 Synthesis of 2-(2,2-dioxido-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophen-1-yl)ethyl trifluoromethanesulfonate 28



27 **28**

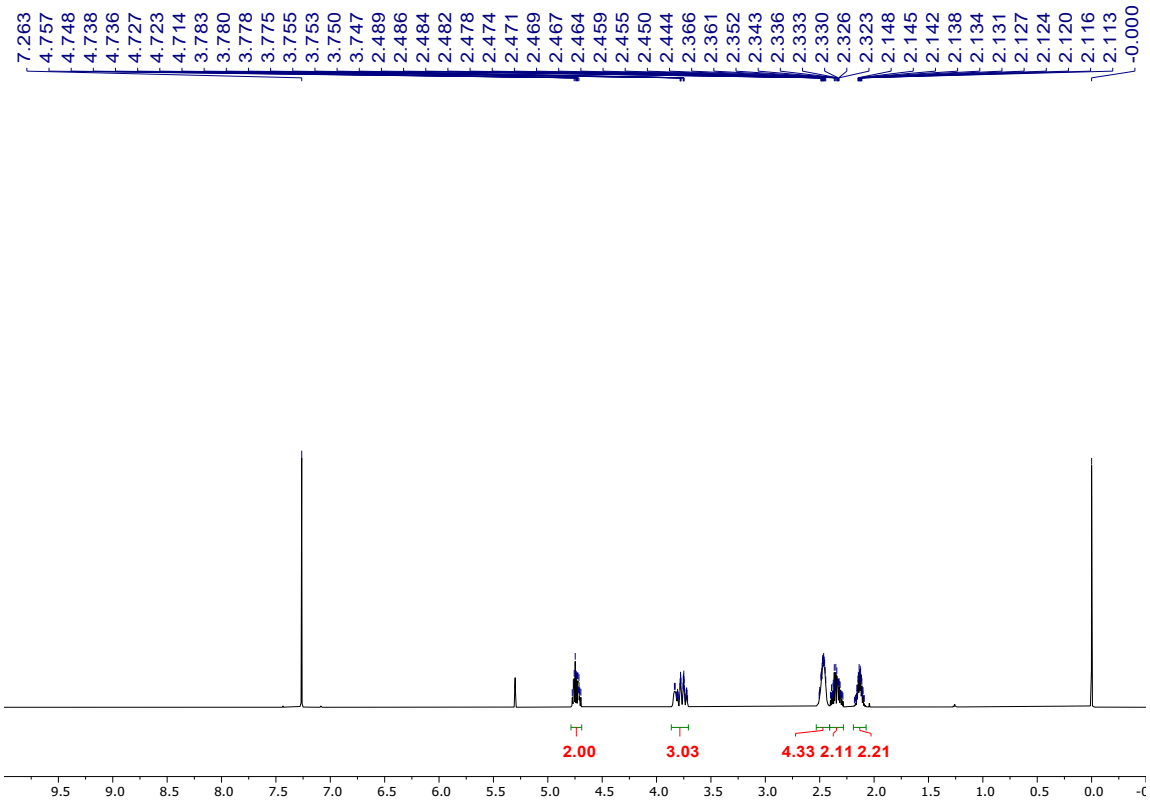
To a 50 mL, 14/20 single-neck RBF was added **27** (145 mg, 0.71 mmol, 1.0 equiv) and 2,6-lutidine (0.14 mL, 1.28 mmol, 1.8 equiv) in CH_2Cl_2 (15 mL). The mixture was cooled to -78 °C followed by dropwise addition of triflic anhydride (0.2 mL, 1.2 mmol, 1.7 equiv). The mixture stirred at -78 °C for 1 hour before quenching with water (10 mL). The reaction mixture was extracted with CH_2Cl_2 (15 mL x 2), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2) to afford 2-(2,2-dioxido-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophen-1-yl)ethyl trifluoromethane-sulfonate **28** in 97% yield (226 mg) as a colorless oil. This reaction was repeated on a larger scale (1.18 mmol) to give **28** in 95% yield (377 mg). The product is extremely unstable and begins to decompose after isolation.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) = 4.78-4.69 (m, 2H), 3.85-3.71 (m, 3H), 2.52-2.41 (m, 4H), 2.40-2.29 (m, 2H), 2.18-2.07 (m, 2H).

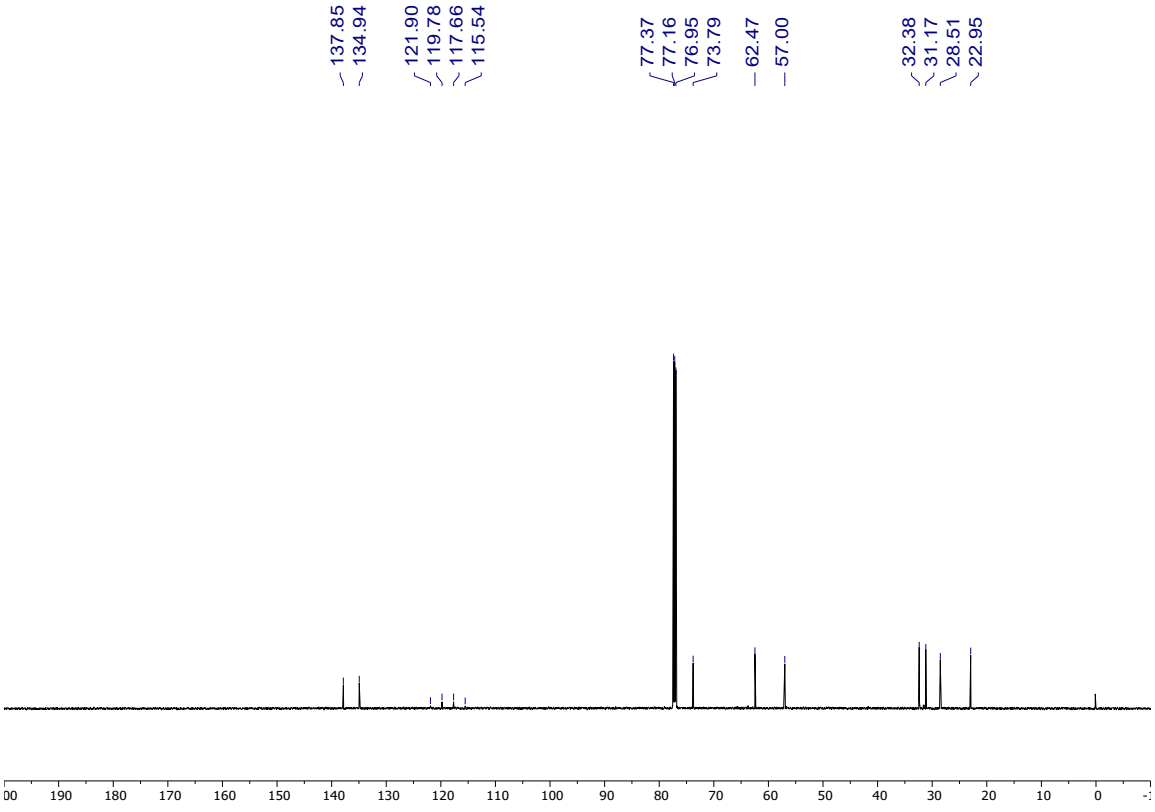
^{13}C NMR (151 MHz, $CDCl_3$): δ_C (ppm) = 137.9, 134.9, 118.6 (q, J = 319.8 Hz), 73.8, 62.5, 57.0, 32.4, 31.2, 28.5, 23.0.

FTICR-MS (m/z): Calcd for ([M+Na]$^+$) 357.0049; found 357.0053.

IR ($CDCl_3$): $\tilde{\nu}$ = 2935, 2864, 1661, 1409, 13120, 1219, 1148, 1114, 913 cm^{-1}.

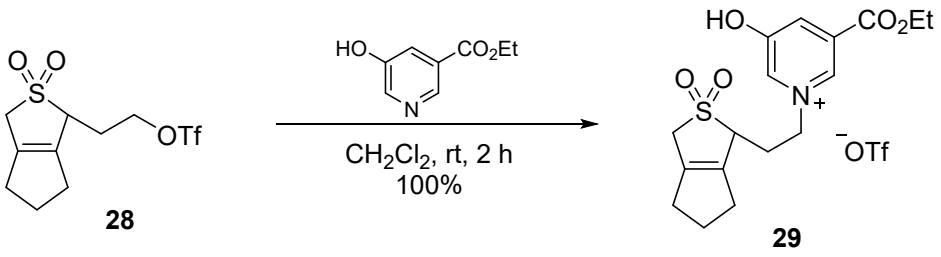


^{1}H NMR (600 MHz, $CDCl_3$) of **28**



^{13}C NMR (151 MHz, $CDCl_3$) of **28**

IV.9 Synthesis of 1-(2-(2,2-dioxido-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophen-1-yl)ethyl)-3-(ethoxycarbonyl)-5-hydroxypyridin-1-ium trifluoromethanesulfonate 29



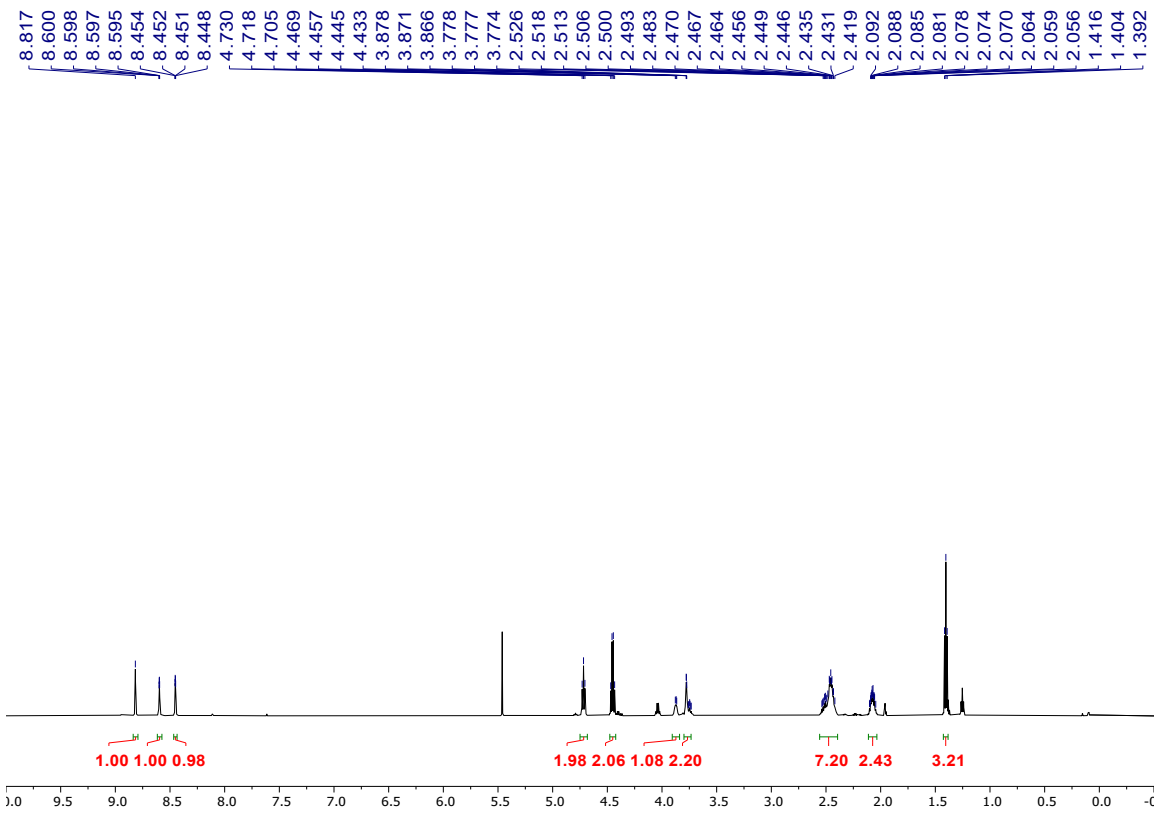
To a 25 mL, 14/20 single-neck RBF was added **28** (210 mg, 0.63 mmol, 1.0 equiv), ethyl 5-hydroxynicotinate (105 mg, 0.63 mmol, 1.0 equiv), and CH_2Cl_2 (10 mL). The mixture stirred at room temperature for 2 hours and then concentrated under reduced pressure to give 1-(2-(2,2-dioxido-3,4,5,6-tetrahydro-1*H*-cyclopenta[*c*]thiophen-1-yl)ethyl)-3-(ethoxycarbonyl)-5-hydroxypyridin-1-ium trifluoromethanesulfonate **29** in quantitative yield (315 mg) as a white ionic liquid. This reaction was repeated on a larger scale (1.13 mmol) to give **29** in quantitative yield (566 mg). The product is unstable and begins to decompose upon formation.

^{1}H NMR (600 MHz, CD_3CN): δ_H (ppm) = 8.82 (s, 1H), 8.60 (dd, *J* = 2.2, 1.2 Hz, 1H), 8.45 (dd, *J* = 2.3, 1.2 Hz, 1H), 4.72 (t, *J* = 7.7 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.89-3.85 (m, 1H), 3.79-3.73 (m, 2H), 2.18-2.07 (m, 2H) 2.55-2.40 (m, 7H), 2.11-2.03 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

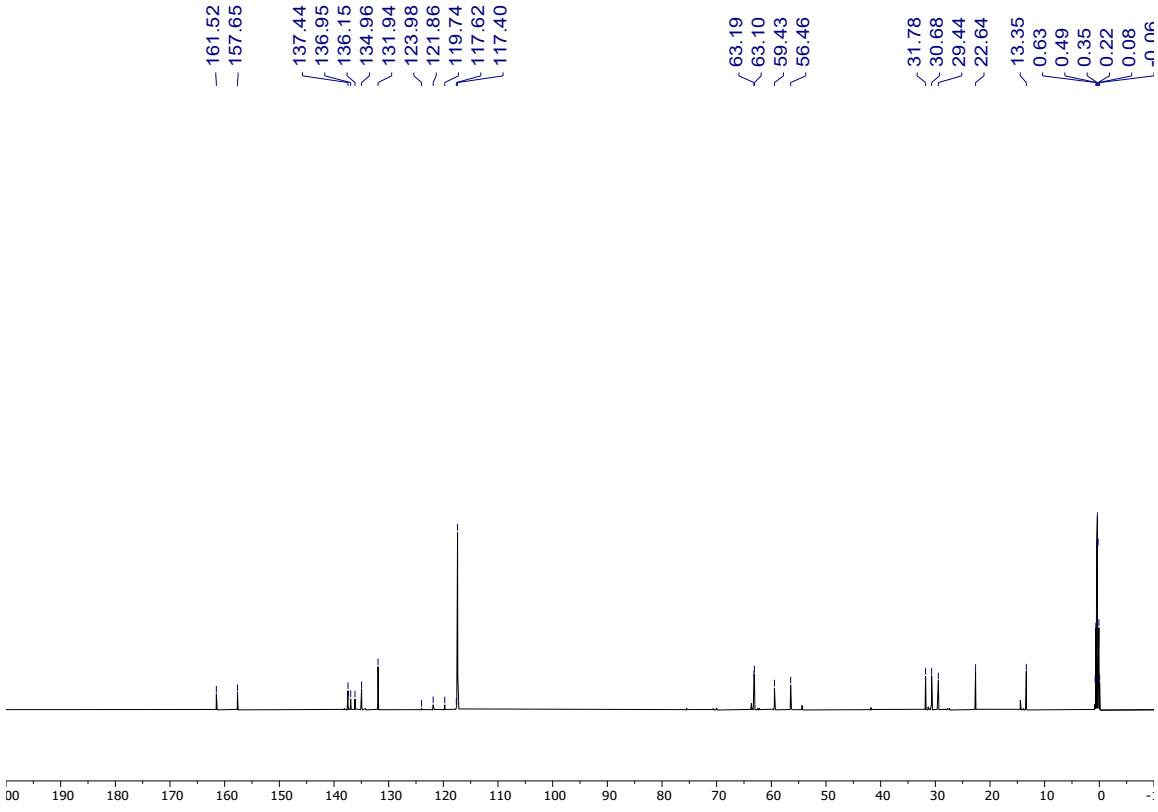
^{13}C NMR (151 MHz, CD_3CN): δ_C (ppm) = 161.5, 157.6, 137.4, 137.0, 136.2, 135.0, 131.9, 120.7 (q, *J* = 319.8 Hz), 117.4, 63.2, 63.1, 59.4, 56.5, 31.8, 30.7, 29.4, 22.6, 13.4.

FTICR-MS (m/z): Calcd for ([cation]$^+$) 352.1213; found 352.1213.

IR (neat): $\tilde{\nu}$ = 3500, 3081, 2933, 2860, 1737, 1605, 1455, 1377, 1240, 1163, 1030, 916 cm^{-1}.

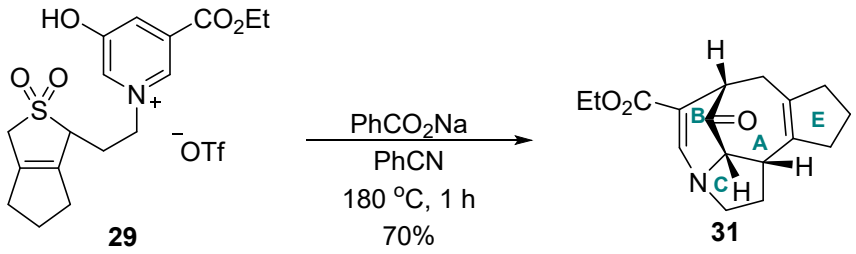


^{1}H NMR (600 MHz, CD_3CN) of **29**



^{13}C NMR (151 MHz, CD_3CN) of **29**

IV.10 Synthesis of ethyl (3a*S*,5*S*,9b*S*)-4-oxo-1,2,3a,4,5,6,7,8,9,9b-decahydro-3,5-ethenoazuleno[5,4-*b*]pyrrole-10-carboxylate 31



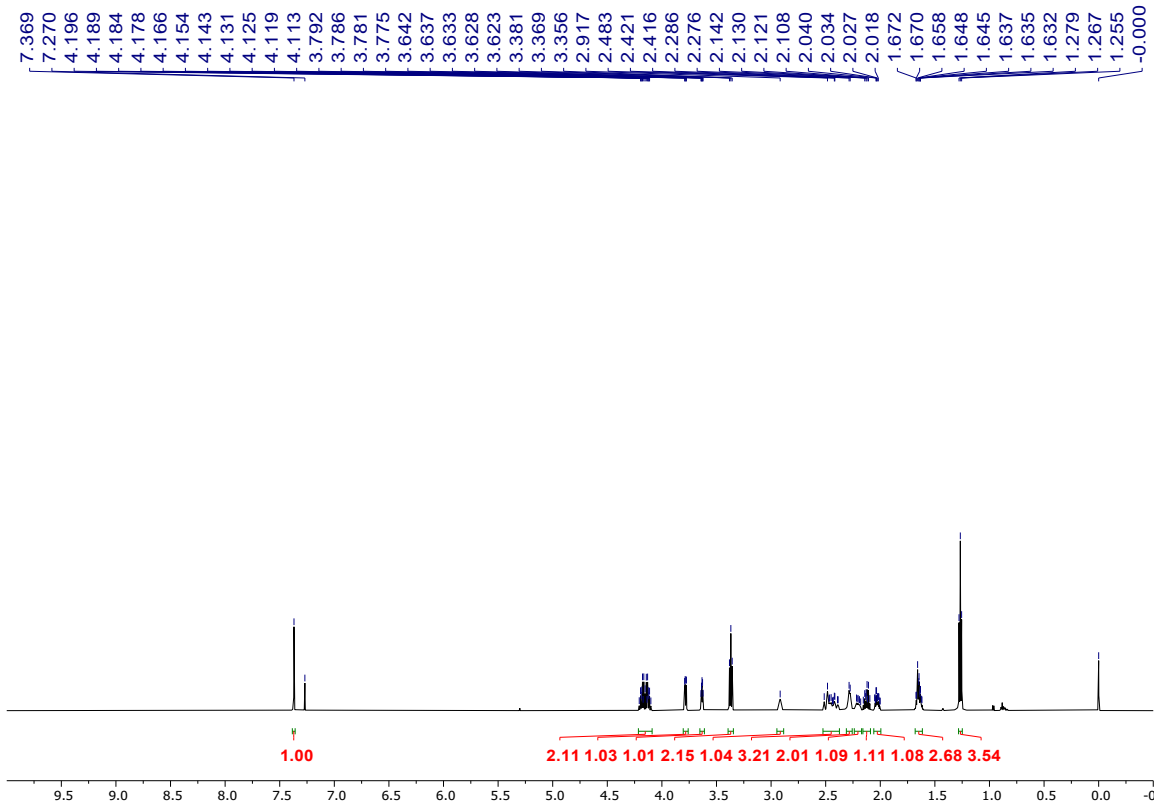
To a CG-1880-21 seal tube was added **29** (55 mg, 0.11 mmol, 1.0 equiv), sodium benzoate (16 mg, 0.11 mmol, 1.0 equiv), and benzonitrile (2.2 mL). The mixture stirred at 180 °C for 1 hour, at which point it was immediately placed in a room temperature water bath to cease the reaction. The mixture was purified by flash chromatography (Hexane : EtOAc = 2 : 1) to afford an inseparable mixture of ethyl (3a*S*,5*S*,9b*S*)-4-oxo-1,2,3a,4,5,6,7,8,9,9b-decahydro-3,5-ethenoazuleno[5,4-*b*]pyrrole-10-carboxylate **31** and benzoic acid. The fractions were combined and washed with sat. $NaHCO_3$ aq. (2.2 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure to afford pure **31** in 70% yield (22 mg) as a colorless oil. This reaction was repeated on a larger scale (1.07 mmol) to give **31** in 62% yield (190 mg). **31** is thermally unstable.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) = 7.37 (s, 1H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.13 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.78 (dd, *J* = 6.6, 3.2 Hz, 1H), 3.63 (dt, *J* = 5.8, 2.9 Hz, 1H), 3.37 (t, *J* = 7.2 Hz, 3H), 2.94-2.89 (m, 1H), 2.51-2.38 (m, 3H), 2.30-2.26 (m, 2H), 2.24-2.17 (m, 1H), 2.12 (dtd, *J* = 12.8, 7.8, 7.4 Hz, 1H), 2.03 (dtd, *J* = 12.8, 7.3, 3.1 Hz, 1H), 1.67-1.62 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

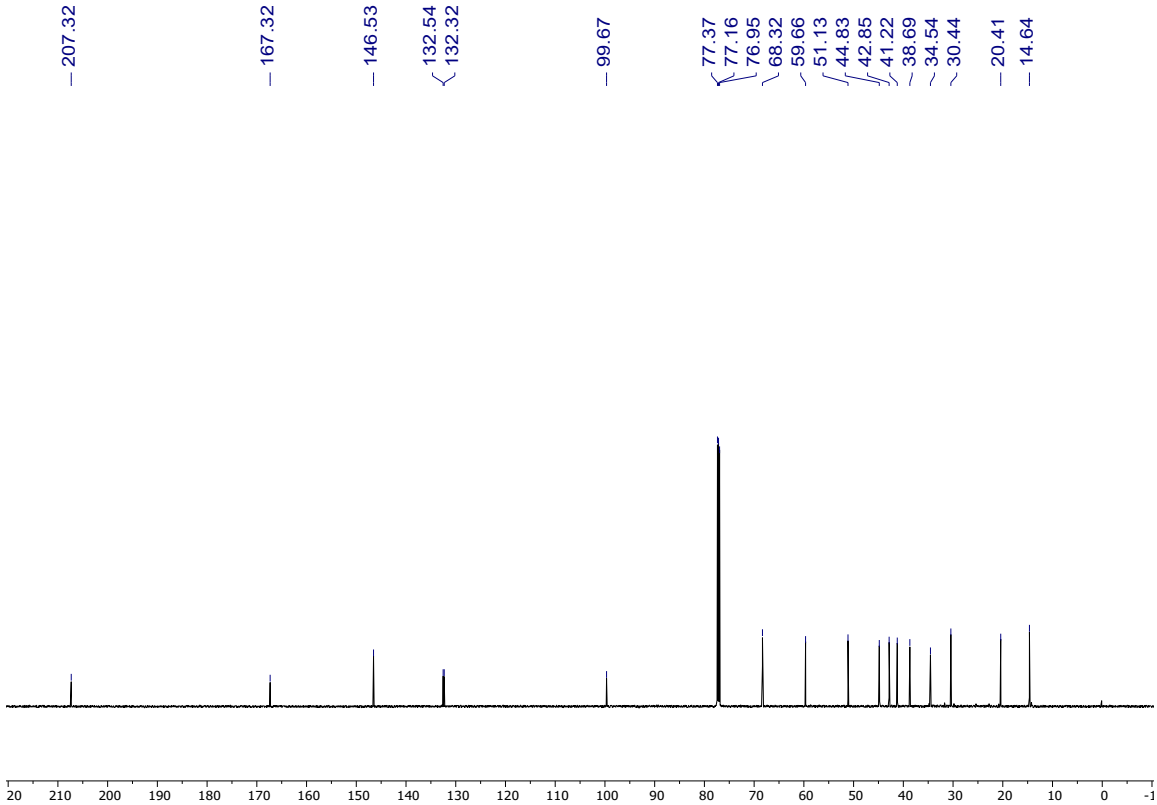
^{13}C NMR (151 MHz, $CDCl_3$): δ_C (ppm) = 207.3, 167.3, 146.5, 132.5, 132.3, 99.7, 68.3, 59.7, 51.1, 44.8, 42.8, 41.2, 38.7, 34.5, 30.4, 20.4, 14.6.

FTICR-MS (m/z): Calcd for ([M+Na]$^+$) 310.1414; found 310.1413.

IR (neat): $\tilde{\nu}$ = 2953, 2889, 2845, 1717, 1682, 1621, 1393, 1277, 1247, 1113, 923 cm^{-1}.



^{1}H NMR (600 MHz, $CDCl_3$) of **31**



^{13}C NMR (151 MHz, $CDCl_3$) of **31**

V References

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[3] J. Tu, R. A. Ripa, S. P. Kelley and M. Harmata, *Chem. Eur. J.*, 2022, (doi.org/10.1002/chem.202200370).