Sequential Double C–H Functionalization of 2,5-Norbornadiene in Flow

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Contents:

1. General information

Reagents: *n*-Butyllithium (2.65 M in hexane) was purchased from Kanto Chemical. Tetrahydrofuran (THF) was purchased from Wako as a dry solvent and used without further purification. Ether was purchased from Wako as a dry solvent and used without further purification. All electrophiles were purchased from Sigma-Aldrich, TCI, or Wako and used without further purification.

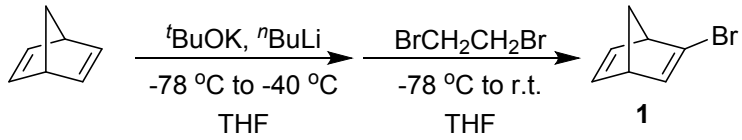
Devices: Stainless steel (SUS316) tube reactors with inner diameter of 1 mm were purchased from GL Science and were cut into appropriate lengths. Stainless steel (SUS316) T-shaped micromixers with inner diameter of 500 μm were manufactured by Sanko Seiki Co., Ltd. The micromixer and tube reactors were connected with stainless steel fittings (GL Science, 1/16" OUW) to construct the flow reactor system in the laboratory.

Reaction procedure: The flow reactor system was immersed in a cooling bath to control the temperature. Solutions were continuously introduced to the flow microreactor system using syringe pumps (Harvard Model PHD ULTRA™ Syringe Pumps), equipped with gastight syringes (50 mL, inner diameter: 27.58 mm; 100 mL, inner diameter: 34.96 mm) purchased from SGE Analytical Science. After a steady state was reached, the product solution was collected for 30 s.

Spectrometric identification: ^{1}H and ^{13}C NMR spectra were recorded on a JEOL REASONANCE JNM-ECZ400S spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer with TMS as a standard in $CDCl_3$ or CD_2Cl_2. Gel-permeation chromatography (GPC) was performed on a JAI Recycling Preparative HPLC LC-908W with a JAIGEL 1H and 2H using $CHCl_3$ as an eluent. TLC analysis was performed using Merck silica gel 60 F_{254}, and the preparative TLC (PTLC) purification was conducted using Wakogel B-5F PTLC plates. High resolution MS analyses (HRMS) were measured on a (GC-MS: JMS-700 MStation Mass Spectrometer) at the Analysis Center in Osaka University. Melting points (m.p.) were recorded on OptiMelt MPA100 Automated Melting Point System (Measured range: 30 ℃ to 300 ℃, Heating Rate: 1.0 ℃/min)

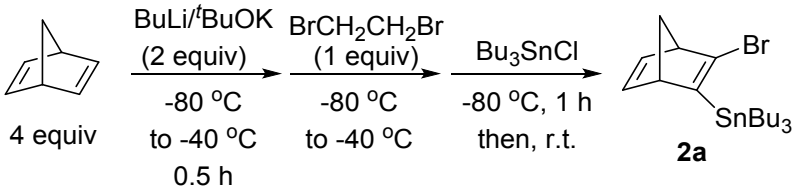
2. Flask reactions for the synthesis of compounds **1** and **2a**

2-1. Preparation of 2-bromonorbornadiene (**1**) in flask



To a three-necked round-bottomed flask equipped a magnetic stirrer bar and glass septa was added *t*-BuOK (6.73 g, 60 mmol, 1 equiv) and THF (90 mL). After the mixture was cooled to –78 °C, 2,5-norbornadiene (11.1 mL, 120 mmol, 2 equiv) was added. Then *n*-BuLi (1.6 M in hexane, 60 mmol, 1 equiv) was added dropwise over 1 h. After stirring for 30 min at –40 °C, the solution was cooled again to –78 °C. Then, 1,2-dibromoethane (11.28 g, 60 mmol, 1 equiv) was added dropwise. The mixture was stirred at –78 °C for 30 min and gradually warmed to room temperature. After quenching the mixture with water (150 mL), the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed sequentially with water (100 mL) and brine (100 mL) and dried over sodium sulfate. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography (hexane) to give pure compound **1** (8.2 g, 48 mmol, 80%) as colorless oil. The spectroscopic data were identical to those reported in the literature (*1*).

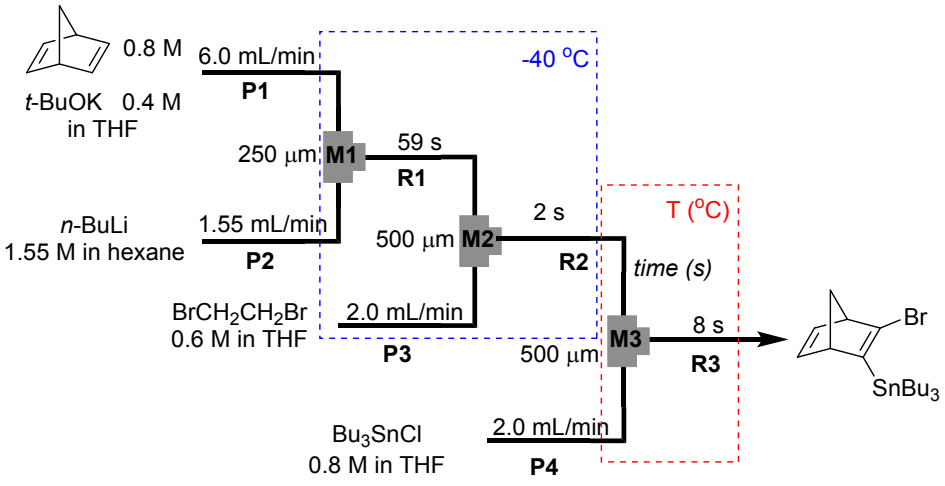
2-2. Preparation of 2-bromo-3-tributylstannylnorbornadiene (**2a**) in flask



To a three-necked round-bottomed flask equipped a magnetic stirrer bar and glass septa was added *t*-BuOK (6.73 g, 60 mmol, 2 equiv) and THF (90 mL). After the mixture was cooled to –78 °C, 2,5-norbornadiene (11.1 mL, 120 mmol, 4 equiv) was added. Then *n*-BuLi (2.65 M in hexane, 60 mmol, 2 equiv) was added dropwise over 1 h. After stirring for 30 min at –40 °C, the solution was cooled to –78 °C. 1,2-Dibromoethane (5.64 g, 30 mmol, 1 equiv) was added dropwise, then the mixture was stirred at –40 °C for 90 min. After the solution was chilled again to –78 °C, tributyltin chloride (11.4 g, 35 mmol, 1.17 equiv) was added. After stirring for 1 h at –78 °C, the mixture was gradually warmed to room temperature for 12 h. After quenching the mixture with water (100 mL), the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed sequentially with water (100 mL) and brine (100 mL) and dried over

sodium sulfate. The solvent was removed by rotary evaporation and the crude product was purified by high vacuum evaporation and column chromatography (hexanes) to give pure compound **2a** (10.8 g, 23.4 mmol, 78%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dd, 1H, J = 5.1, 3.1 Hz), 6.64 (dd, 1H, J = 5.1, 2.9 Hz), 3.73 (br s, 1H), 3.50 (br s, 1H), 2.17 (dm, 1H, J = 6.0 Hz), 1.97 (dm, 1H, J = 6.0 Hz), 1.46 (m, 6H), 1.29 (m, 6H), 0.99 (t, 6H, J = 8.0 Hz), 0.87 (t, 9H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 148.9, 142.6, 141.3, 73.2, 60.3, 57.5, 29.1, 27.3, 13.8, 9.8 ppm. The spectroscopic data were identical to those reported in the literature (*2*).

3. Flow synthesis of compound **2a** under unoptimized conditions

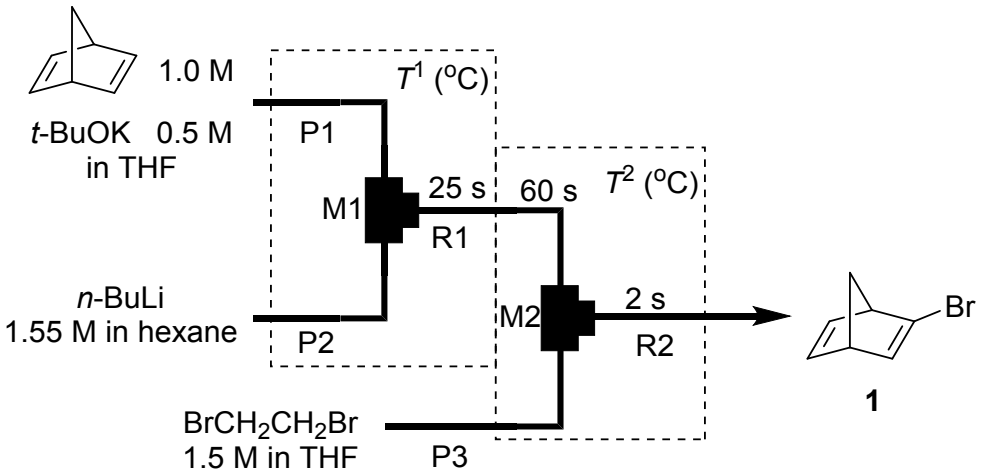


A flow reactor system consisting of three T-shaped micromixers (M1, M2 and M3), three tube reactors (R1 R2 and R3; inner diameter ϕ = 1 mm) and four tube pre-temperature-retaining units (P1, P2, P3 and P4, inner diameter ϕ = 1 mm, length L = 1 m) was used. The whole system was immersed in two cooling baths. A solution of 2,5-norbornadiene and potassium *tert*-butoxide (0.8 M and 0.4 M in THF, flow rate: 6.0 mL/min) and a solution of *n*-BuLi (1.55 M in hexane, flow rate: 1.55 mL/min) were introduced to M1 (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through R1 (L = 950 cm, at –40 °C) and was mixed with a solution of 1,2-dibromoethane (0.6 M in THF, flow rate: 1.8 or 2.0 mL/min) in M2 (ϕ = 500 μm). The resulting solution was passed through R2 (L = 420 to 1000 cm at –40 °C and T °C) and was mixed with a solution of Bu_3SnCl (0.8 M in THF, flow rate: 2.0 mL/min) in M3 (ϕ = 500 μm). The resulting solution was passed through R3 (L = 200 cm at T °C). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH_4Cl aqueous solution (2 mL). Then, Et_2O (10 mL), brine (2 mL), and 1,3,5-trimethoxybenzene (50 mg) were added, and then an aliquot (2mL) of the organic phase was analyzed by GC (Table S1)

Table S1. Flow synthesis of compound **2a** under unoptimized conditions

Entry	T [°C]	Time [s]	Equiv of BuLi/^{t}BuOK	Yield of **2a** [%]
1	0	19	1.0	26
2	0	47	1.0	39
3	23	19	1.0	40
4	23	47	1.0	46
5	23	48	1.1	49
6	23	49	1.25	53

4. Flow synthesis of 2-bromonorbornadiene (**1**)

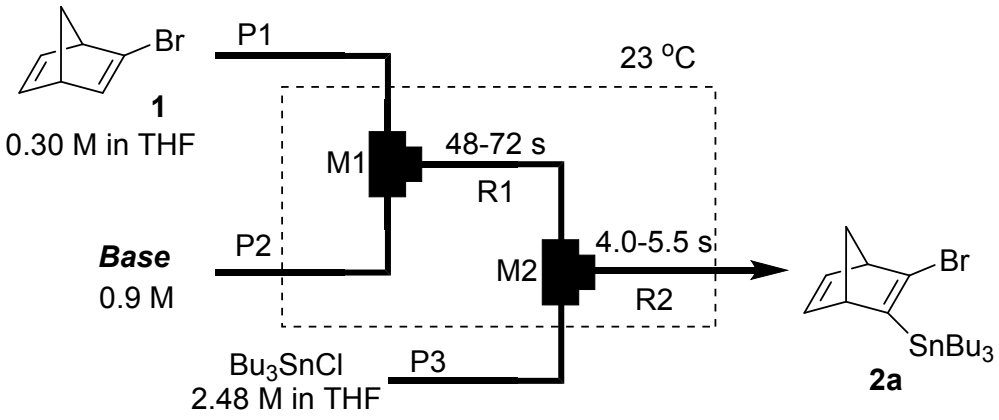


A flow microreactor system consisting of two T-shaped micromixers (M1, and M2), two tube reactors (R1 and R2; inner diameter ϕ = 1 mm) and three tube pre-temperature-retaining units (P1, P2, and P3; inner diameter ϕ = 1 mm, length L = 1 m) was used. The whole system was immersed in two cooling baths. A solution of 2,5-norbornadiene and potassium *tert*-butoxide (1.0 M and 0.05 M in THF, flow rate: 3.0 mL/min) and a solution of *n*-BuLi (1.55 M in hexane, flow rate: 0.97 mL/min) were introduced to M1 (ϕ = 500 μm) by syringe pumps. The resulting solution was passed through R1 (L = 200 cm at T^1 °C and 500 cm at T^2 °C) and was mixed with a solution of 1,2-dibromoethane (1.5 M in THF) in M2 (ϕ = 500 μm). The resulting solution was passed through R2 (L = 50 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH_4Cl aqueous solution (2 mL). Then, Et_2O (10 mL), brine (2 mL), and 1,3,5-trimethoxybenzene (50 mg) were added, and then an aliquot (2mL) of the organic phase was analyzed by GC spectroscopy (Table S1).

Table S1. Deprotonation of norbornadiene and following reaction with 1,2-dibromoethane using a microreactor.

Entry	T^1 [°C]	T^2 [°C]	Flow rate of 1,2-dibromoethane [ml/min]	Yield of **1** [%]
1	23	23	1	0
2	0	23	1	77
3	0	0	1	59
4	-40	0	1	81
5	-40	-40	1	92
6	-70	-40	1	82
7	-70	-70	1	44
8	**-40**	**-40**	**0.9**	**94**
9	-70	-40	0.9	91

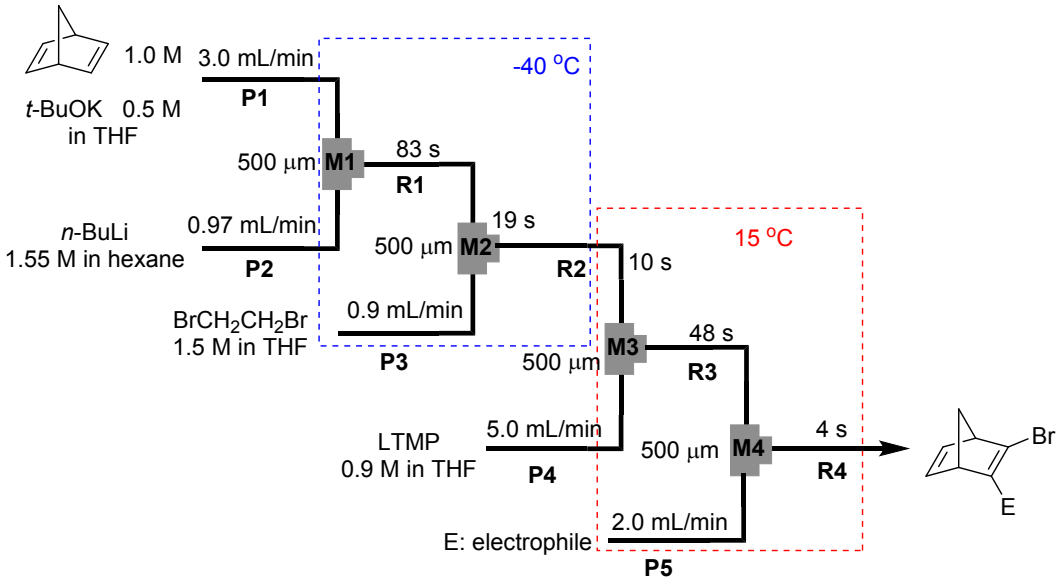
5. Flow synthesis of 2-bromo-3-tributylstannylnorbornadiene (**2a**)



A flow microreactor system consisting of two T-shaped micromixers (M1, and M2), two tube reactors (R1 and R2; inner diameter ϕ = 1 mm) and three tube pre-temperature-retaining units (P1, P2, and P3; inner diameter ϕ = 1 mm, length L = 1 m) was used. The whole system was immersed in two cooling baths. A solution of 2-bromonorborna-2,5-diene (**1**; 0.3 M in THF, flow rate: 4.87 mL/min) and a solution of base (0.9 M in THF and hexane, flow rate: 1.67 mL/min for 1.0 equiv; 3.34 mL/min for 2.0 equiv; 5.0 mL/min for 3 equiv) were introduced to M1 (ϕ = 500 μm) by syringe pumps. The resulting solution was passed through R1 (L = 1000 cm) at 23 °C and was mixed with a solution of tributyltin chloride (2.48 M in THF, flow rate: 2.0 mL/min) in M2 (ϕ = 500 μm). The resulting solution was passed through R2 (L = 100 cm). After a steady state was reached, the product solution was collected for 30 s while being quenched with sat.

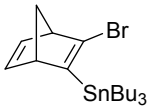
NH_4Cl aqueous solution (2 mL). Then, Et_2O (10 mL), brine (2 mL), and 1,3,5-trimethoxybenzene (50 mg) were added, and then an aliquot (2mL) of the organic phase was analyzed by GC spectroscopy.

6. Integrated synthesis of difunctionalized norbornadienes in flow microreactors

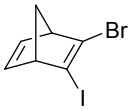


A flow microreactor system consisting of four T-shaped micromixers (M1, M2 M3 and M4), four tube reactors (R1 R2 R3 and R4; inner diameter ϕ = 1 mm) and five tube pre-temperature-retaining units (P1, P2, P3 P4 and P5, inner diameter ϕ = 1 mm, length L = 1 m) was used. The whole system was immersed in two cooling baths. A solution of 2,5-norbornadiene and *t*-BuOK (1.0 M and 0.5 M in THF, flow rate: 3.0 mL/min) and a solution of *n*-BuLi (1.55 M in hexane, flow rate: 0.97 mL/min) were introduced to M1 (ϕ = 500 μm) by syringe pumps. The resulting solution was passed through R1 (L = 700 cm, at –40 °C) and was mixed with a solution of 1,2-dibromoethane (1.5 M in THF, flow rate: 0.9 mL/min) in M2 (ϕ = 500 μm). The resulting solution was passed through R2 (L = 200 cm at –40 °C and 100 cm at 15 °C) and was mixed with a solution of LTMP (0.9 M in THF, flow rate: 5.0 mL/min) in M3 (ϕ = 500 μm). The resulting solution was passed through R3 (L = 1000 cm). The resulting solution was mixed and reacted with a solution of an electrophile in M3 (ϕ = 500 μm) and R4 (L = 100 cm). For the reaction with hexachloroethane or *i*-PrOB(pin), the resulting solution from reactor R3 was directly quenched with a solution of electrophile in a vial, without the use of M4 and R4. For the synthesis of product **2a**, **2b** or **2f**, a solution of tributyltin chloride, iodine or benzaldehyde in THF (0.75 M) was used, respectively. For the synthesis of product **2c**, **2d**, **2g** or **2h**, a solution of hexachloroethane, *i*-PrOB(pin), phenyl isocyanate, or ethyl chloroformate in THF (2.2 M) was used, respectively. For the synthesis of product **2e**, a solution of trimethylsilyl triflate in ether (2.2 M) was used. After a steady state was reached, the product solution was collected for 30 s while being quenched with sat. NH_4Cl aqueous solution (2 mL). Then, ether (10 mL), brine (2 mL), and 1,3,5-trimethoxybenzene

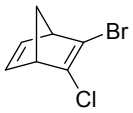
(50 mg) were added, and then an aliquot (2mL) of the organic phase was analyzed by GC or NMR spectroscopy. Several crude products were purified by high vacuum evaporation and column chromatography to give corresponding compounds.



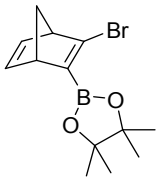
2-Bromo-3-tributylstannylnorbornadiene (2a). 89 % GC yield; a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dd, 1H, *J* = 5.1, 3.1 Hz), 6.64 (dd, 1H, *J* = 5.1, 2.9 Hz), 3.73 (br s, 1H), 3.50 (br s, 1H), 2.17 (dm, 1H, *J* = 6.0 Hz), 1.97 (dm, 1H, *J* = 6.0 Hz), 1.46 (m, 6H), 1.29 (m, 6H), 0.99 (t, 6H, *J* = 8.0 Hz), 0.87 (t, 9H, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 148.9, 142.6, 141.3, 73.2, 60.3, 57.5, 29.1, 27.3, 13.8, 9.8 ppm. The spectroscopic data were identical to those reported in the literature (*2*).



2-Bromo-3-iodonorbornadiene (2b). 59% isolated yield (118.3 mg, 0.40 mmol); a pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.86 (m, 2H), 3.71 (m, 1H), 3.61 (m, 1H), 2.43 (dt, 1H, *J* = 6.2, 1.4 Hz), 2.13 (dt, 1H, *J* =6.2, 1.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.1, 141.5, 140.9, 105.2, 72.7, 61.9, 59.0 ppm. The spectroscopic data were identical to those reported in the literature (*2*).

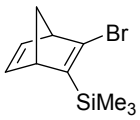


2-Bromo-3-chloronorbornadiene (2c). 91% ^{1}H NMR yield; a colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.89 (m, 2H), 3.60 (m, 1H), 3.52 (m, 1H), 2.43 (dtd, 1H, *J* = 6.3, 1.6, 0.3 Hz), 2.19 (dt, 1H, *J* = 6.3, 1.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.0, 141.6, 141.1, 128.3, 71.5, 57.8, 56.8 ppm. The spectroscopic data were identical to those reported in the literature (*2*).

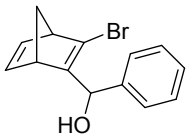


2-Bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)norbornadiene (2d). 88% GC yield; a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.80 (m, 2H), 3.84 (m, 1H), 3.56 (m, 1H), 2.20 (dt, 1H, *J* = 6.2 1.6 Hz), 1.99 (dt, 1H, *J* = 6.1 1.3 Hz) 1.27 (s, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.37, 143.82, 140.34, 83.50,

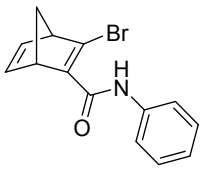
73.18, 61.51, 54.34, 25.03, 24.88 ppm; HRMS (EI) cald. for $[M]^+$: 296.0583; found: 296.0581; M.p. = 61.7–63.3 °C.



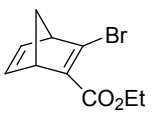
2-Bromo-3-trimethylsilylnorbornadiene (2e). 74% NMR yield; a colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.83 (dd, 1H, *J* = 5.0, 3.2 Hz), 6.70 (dd, 1H, *J* = 5.0, 3.2 Hz), 3.73 (br. s, 1H), 3.54 (br. s, 1H), 2.14 (dt, 1H, *J* = 6.1, 1.5 Hz), 1.94 (dt, 1H, *J* = 6.1, 1.5 Hz), 0.15 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.6, 147.2, 142.7, 141.0, 72.3, 61.4, 55.7, –1.7 ppm. The spectroscopic data were identical to those reported in the literature (*2*).



2-Bromo-3-(1-hydroxybenzyl)norbornadiene (2f). 80% isolated yield (149.7 mg, 0.54 mmol); a colorless liquid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.31–7.17 (m, 5H), 6.56 (dd, 1H, *J* = 5.0, 3.1 Hz), 6.21 (dd, 1H, *J* = 5.0, 2.9 Hz), 5.66 (d, 1H, *J* = 2.9 Hz), 3.58 (m, 1H), 3.52 (m, 1H), 2.15 (dm, 2H, *J* = 6.3 Hz), 1.96 (dt, 1H, *J* = 6.4, 1.8 Hz); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ: 151.5, 142.5, 139.6, 139.1, 130.6, 129.7, 128.2, 127.4, 125.6, 115.2, 70.6, 70.3, 58.3, 49.7. The spectroscopic data were identical to those reported in the literature (*2*).



2-Bromo-3-(1-carboxamide-*N*-phenyl)norbornadiene (2g). 65 % isolated yield (127.3 mg, 0.44 mmol); a pale-yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (bs, 1H), 7.56 (dm, 2H, *J* = 8.3), 7.32 (tm, 2H, *J* = 8.3), 7.10 (tm, 1H, *J* = 7.3), 6.98 (dd, 1H, *J* = 5.1, 3.0 Hz), 6.88 (dm, 1H, *J* = 5.1 Hz), 4.20 (m, 1H), 3.73 (m, 1H), 2.33 (dt, 1H, *J* = 1.4, 6.6 Hz), 2.12 (dt, 1H, *J* = 6.6, 1.7 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.23, 146.07, 143.44, 140.38, 139.81, 137.78, 129.11, 124.42, 119.88, 71.37, 61.68, 52.70 ppm; HRMS (EI) cald. for $[M]^+$: 289.0102; found: 289.0104.



2-Bromo-3-ethoxycarbonylnorbornadiene (2h). 44% isolated yield (72.2 mg, 0.30 mmol); a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, 1H, *J* =5.1, 3.1 Hz), 6.84 (m, 1H), 4.21 (m, 2H), 3.99 (m, 1H), 3.67 (m, 1H), 2.31 (dt, 1H, *J* = 6.7, 1.7 Hz), 2.11 (dt, 1H, *J* = 6.4, 1.4 Hz), 1.30 (t, 3H, *J* = 7.3 Hz). ppm; ^{13}C NMR (CDCl3, 100 MHz) δ: 163.9, 148.6, 143.2, 142.2, 140.5, 71.9, 61.8, 60.6, 52.2, 14.3. ppm; HRMS (EI) cald. for $[M]^+$: 241.9942; found: 241.9939.

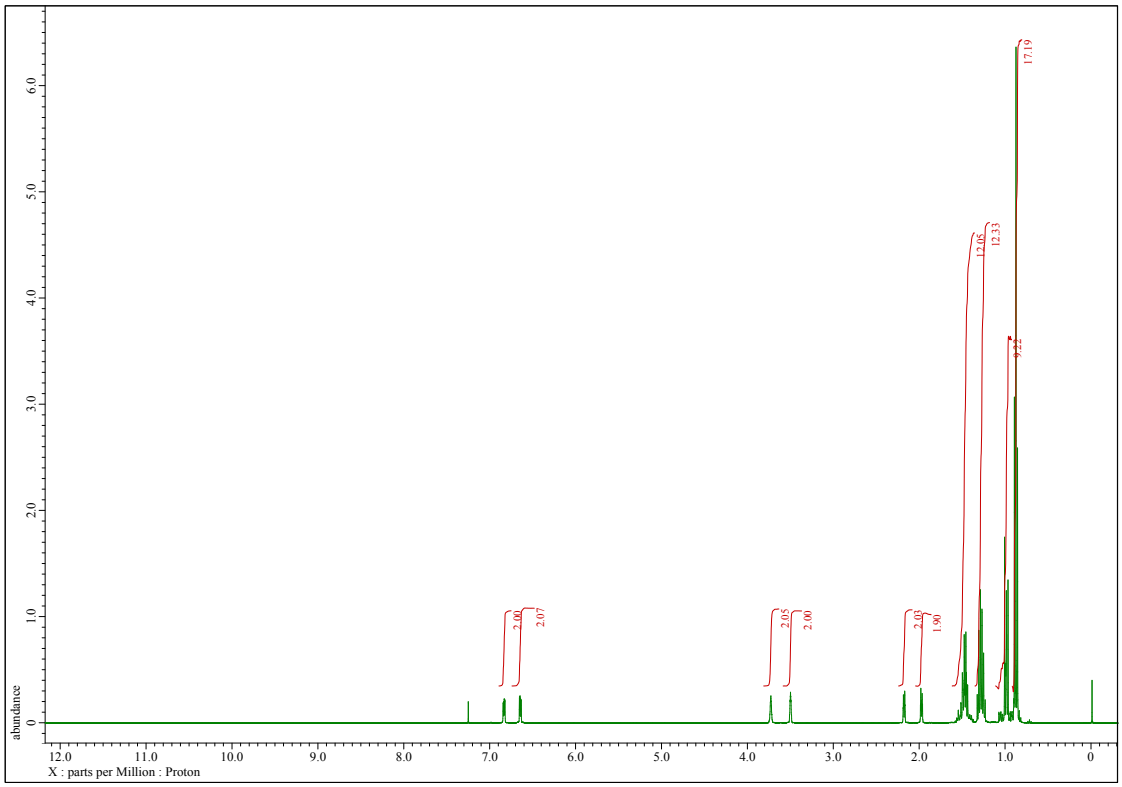
7. References

[1] (a) J. Kenndoff, K. Polborn, G. Szeimies, *J. Am. Chem. Soc.***1990**, *112*, 6117; (b) G. K. Tranmer, C. Yip, S. Handerson, R.W. Jordan, W. Tam, *Can. J. Chem.* **2000**, *78*, 527.

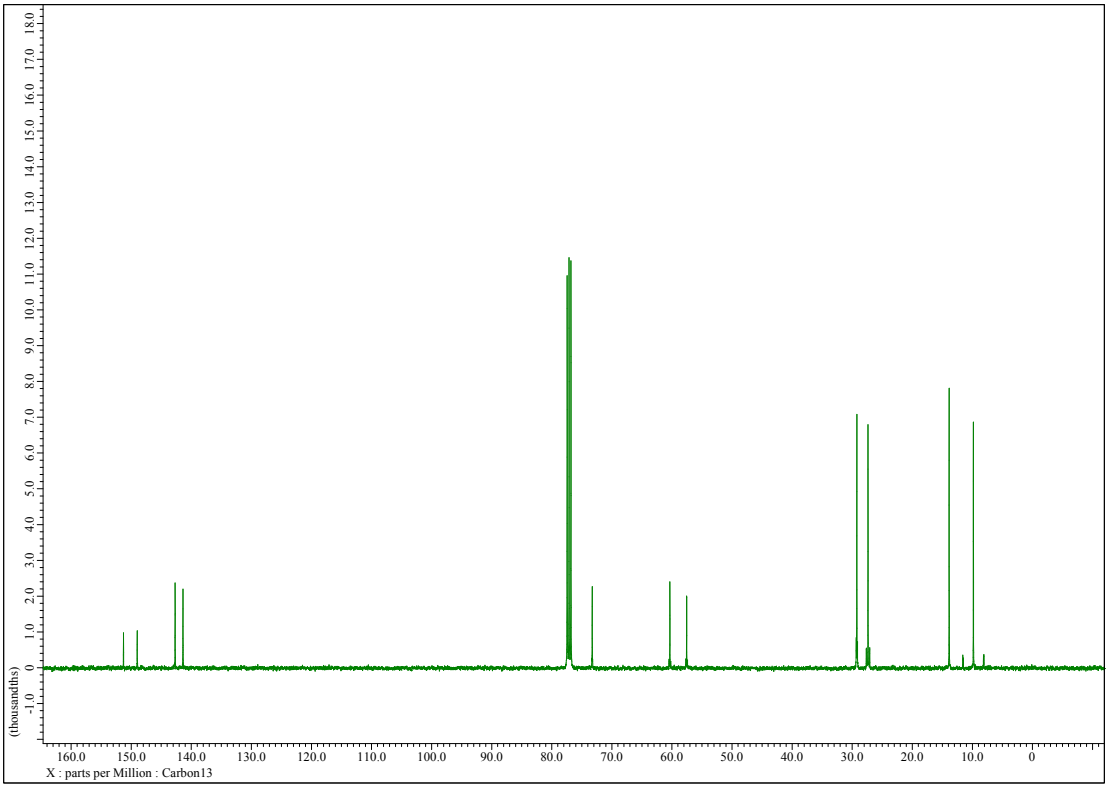
[2] G. K. Tranmer, C. Yip, S. Handerson, R. W. Jordan, W. Tam, *Can. J. Chem.* **2000**, *78*, 527.

8. ^{1}H NMR and ^{13}C Spectra

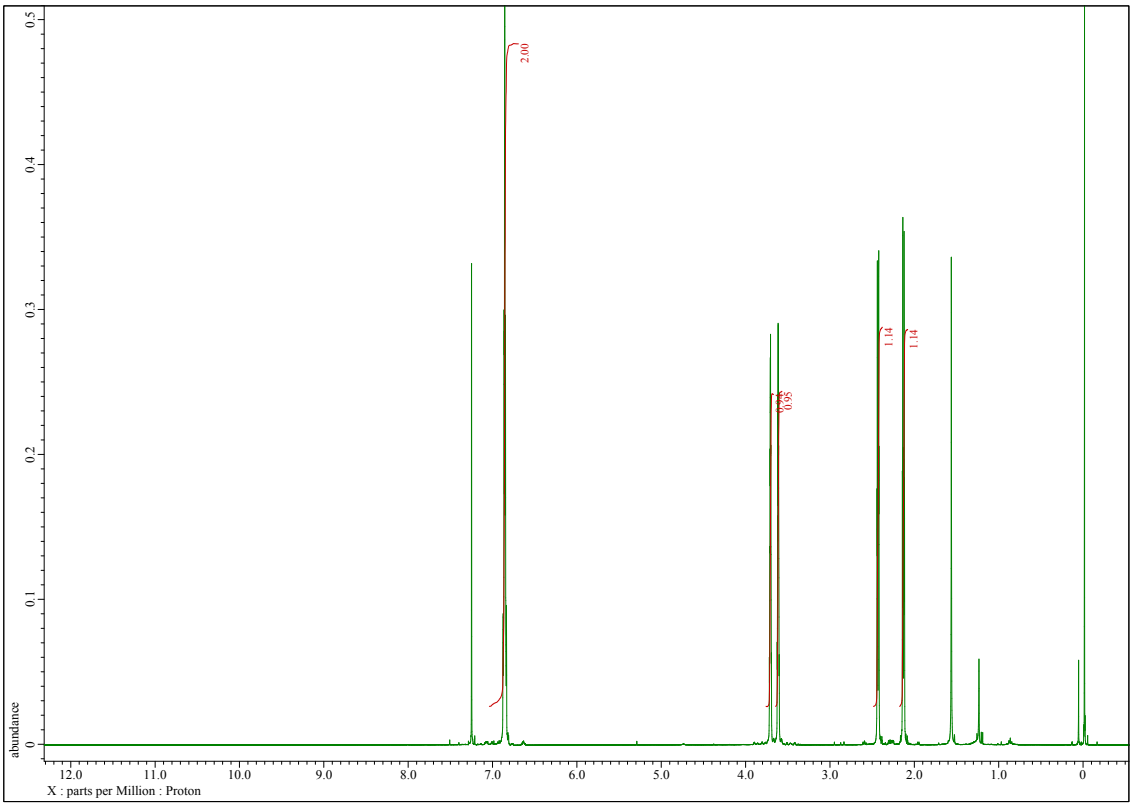
^{1}H NMR (400 MHz, $CDCl_3$) of 2-bromo-3-tributylstannylnorbornadiene (**2a**)



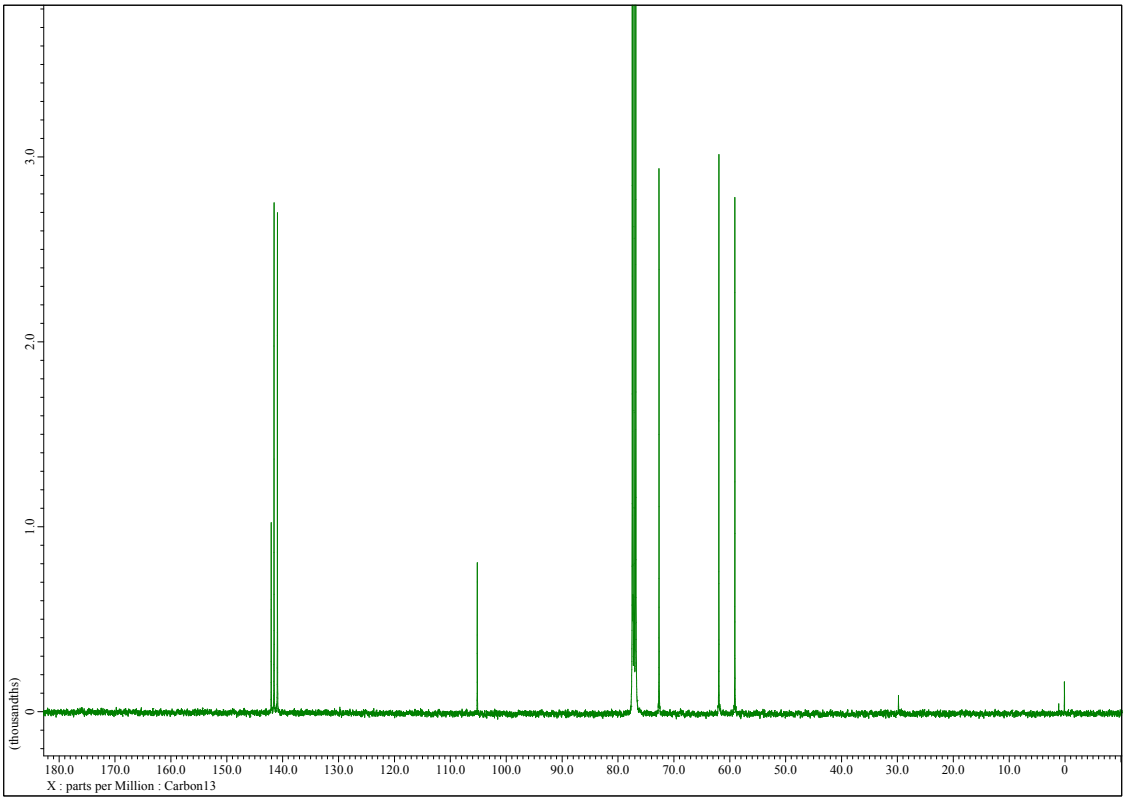
^{13}C NMR (100 MHz, $CDCl_3$) of 2-bromo-3-tributylstannylnorborna-2,3-diene (**2a**)



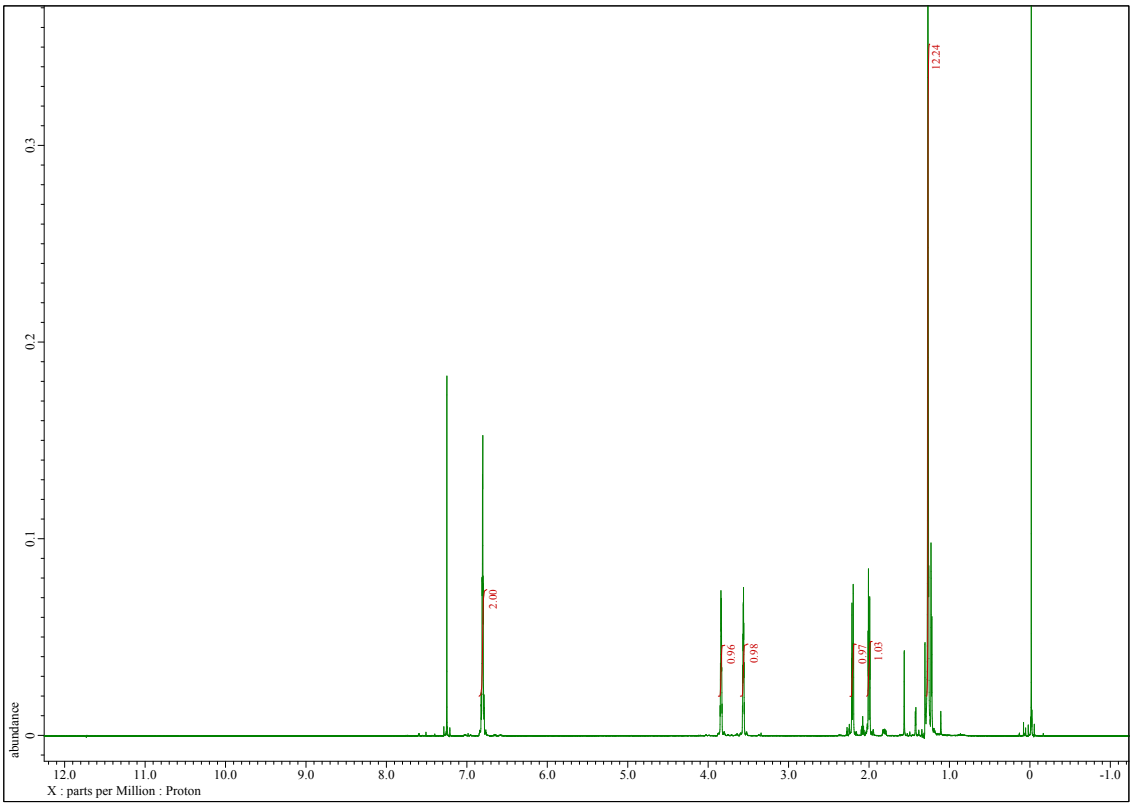
^{1}H NMR (400 MHz, CDCl3) of 2-bromo-3-iodonorbornadiene (**2b**)



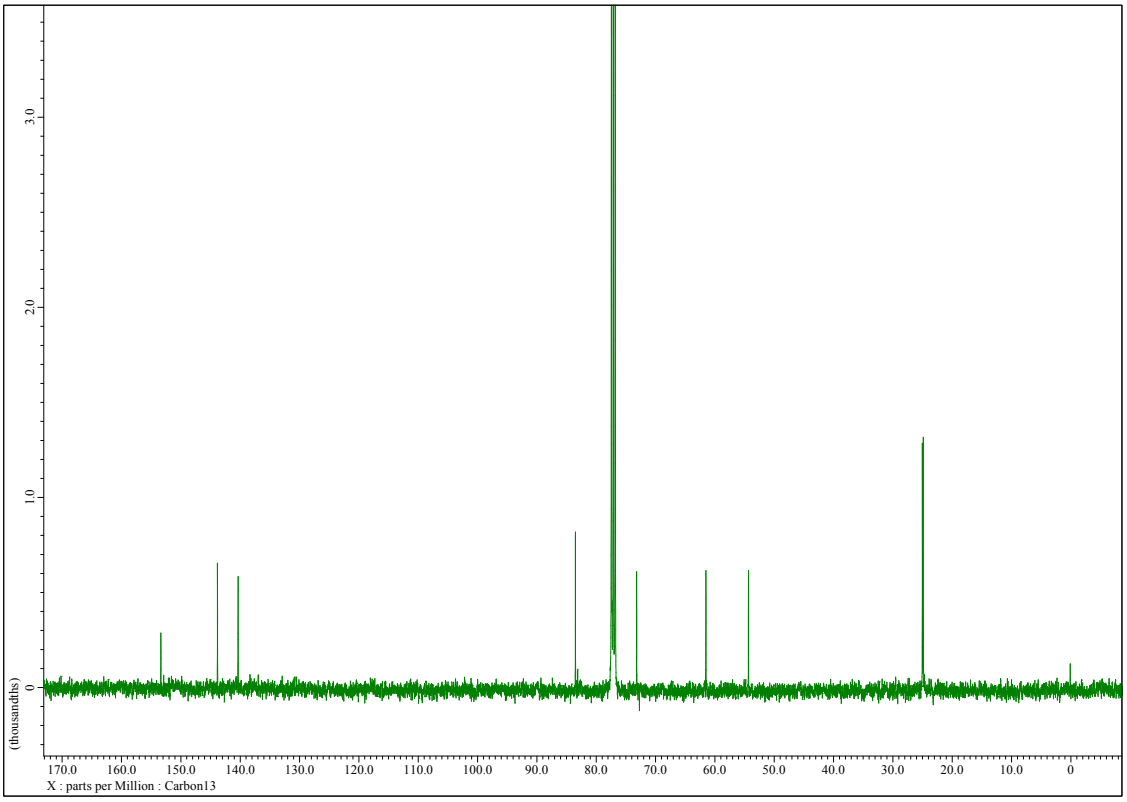
^{13}C NMR (100 MHz, CDCl3) of 2-bromo-3-iodonorbornadiene (**2b**)



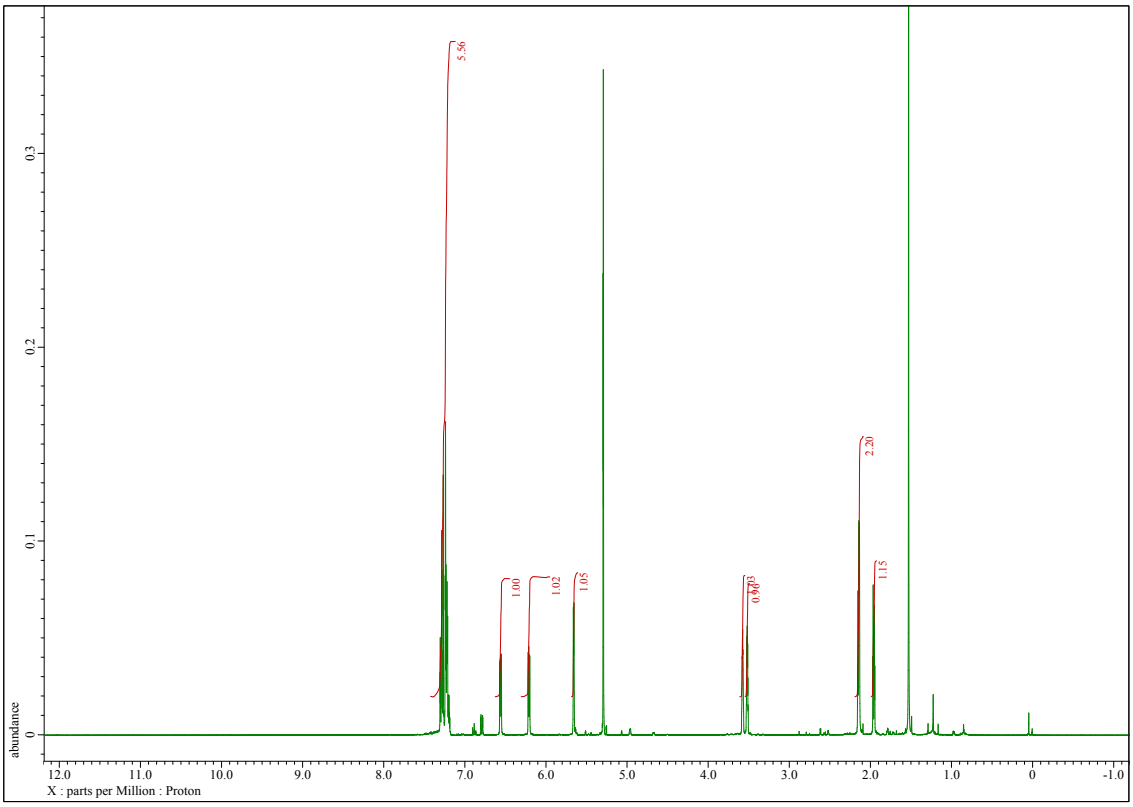
^{1}H NMR (400 MHz, CDCl3) of 2-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)norbornadiene (**2d**)



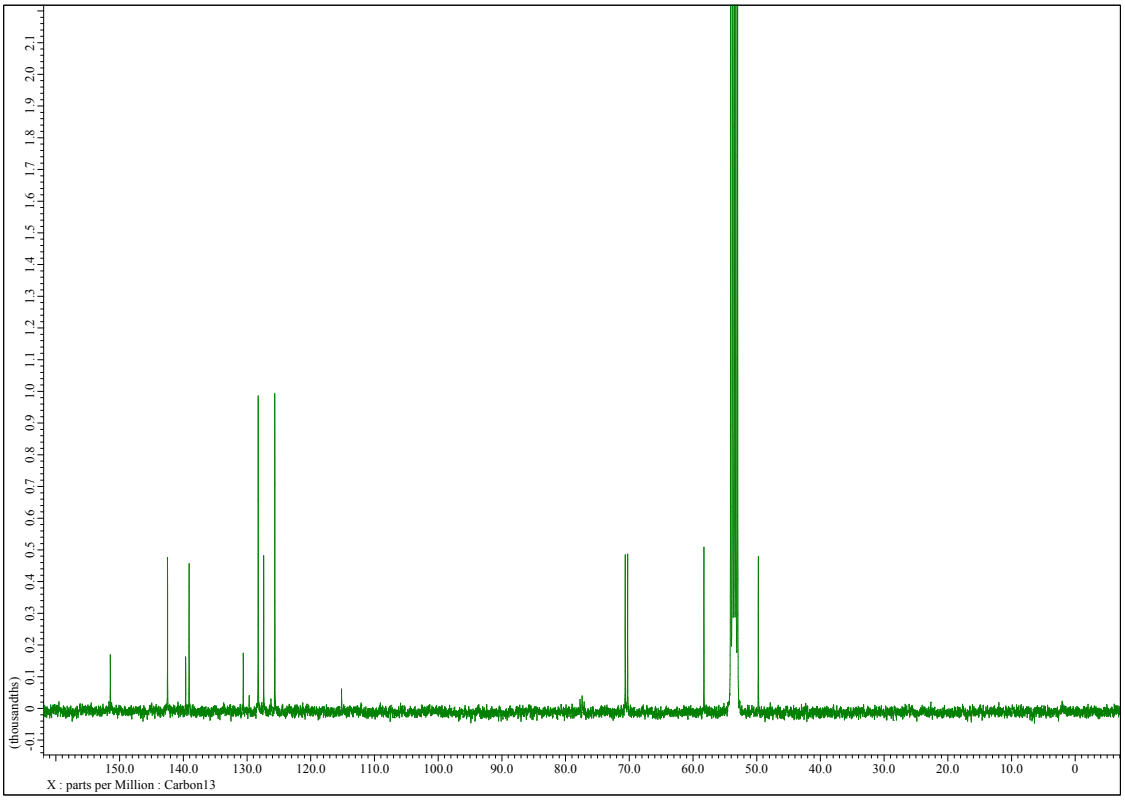
^{13}C NMR (100 MHz, CDCl3) of 2-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)norbornadiene (**2d**)



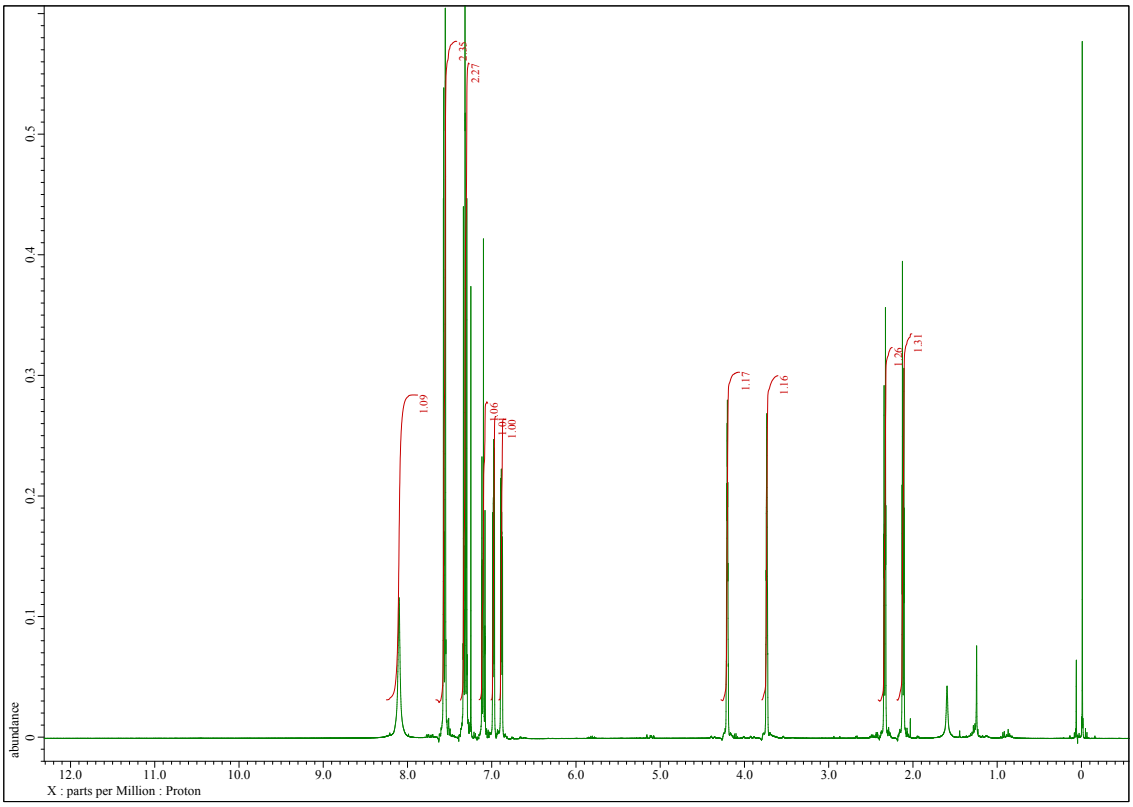
^{1}H NMR (400 MHz, CD_2Cl_2) of 2-bromo-3-(1-hydroxybenzyl)norbornadiene (**2f**)



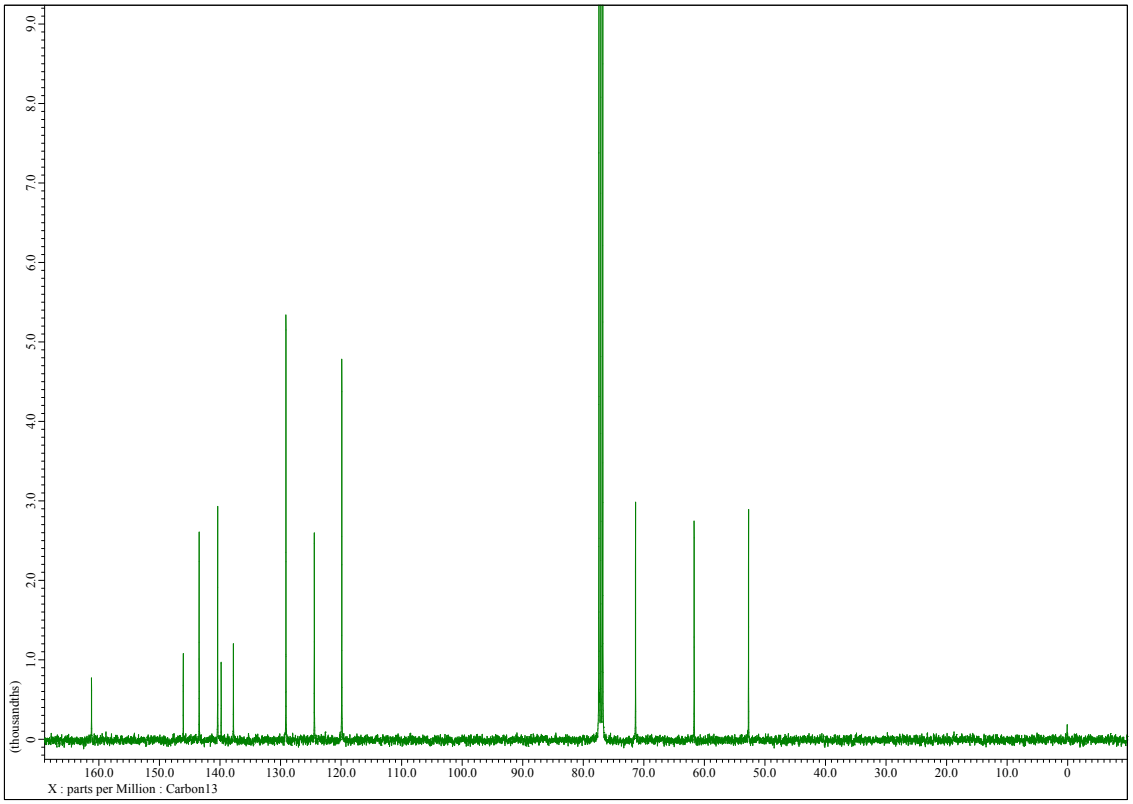
^{13}C NMR (100 MHz, CD_2Cl_2) of 2-bromo-3-(1-hydroxybenzyl)norbornadiene (**2f**)



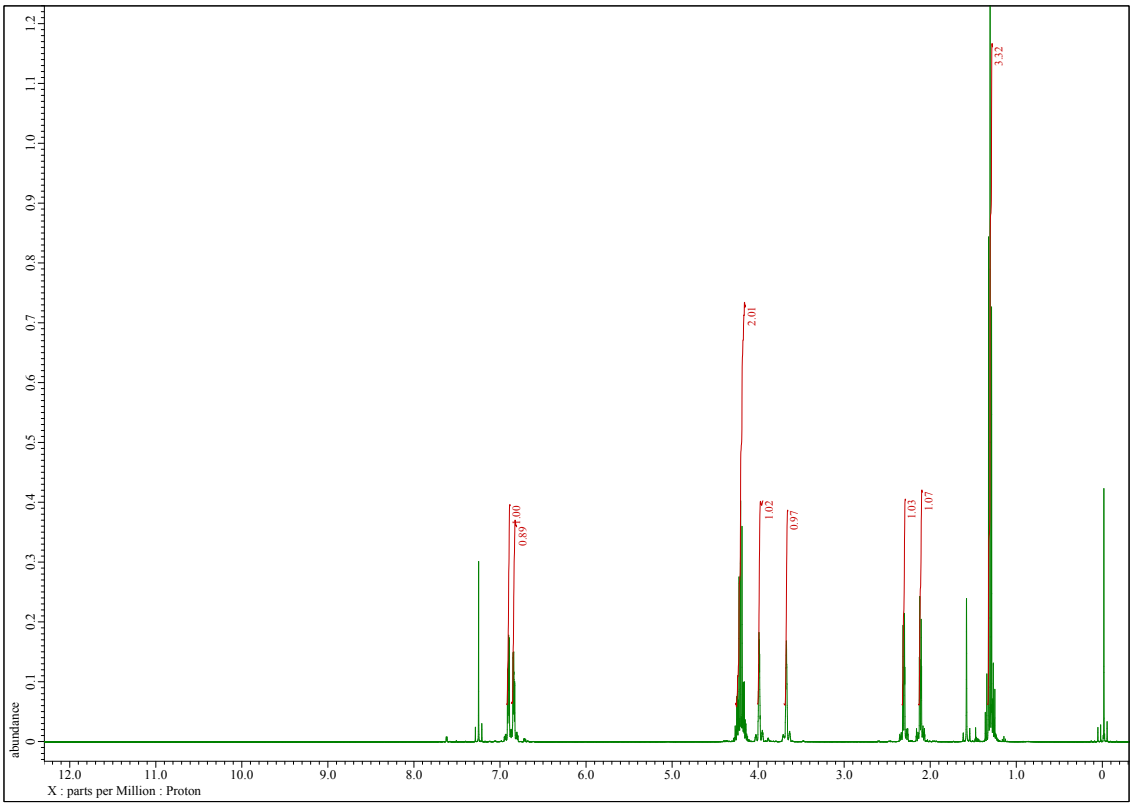
^{1}H NMR (400 MHz, $CDCl_3$) of 2-bromo-3-(1-carboxamide-N-phenyl)norbornadiene (**2g**)



^{13}C NMR (100 MHz, $CDCl_3$) of 2-bromo-3-(1-carboxamide-N-phenyl)norbornadiene (**2g**)



^{1}H NMR (400 MHz, $CDCl_3$) of 2-bromo-3-ethoxycarbonylnorbornadiene (**2h**)



^{13}C NMR (100 MHz, $CDCl_3$) of 2-bromo-3-ethoxycarbonylnorbornadiene (**2h**)