Preparation of Fused Polycyclic Vinylcyclopropanes via Radical Cascade Reactions

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Supplementary Material

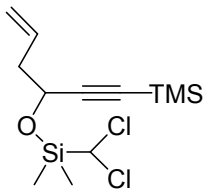
The following includes representative experimental procedures and details for isolation of compounds.

^{1}H NMR were recorded using Bruker instruments at 200, or 400 MHz, and ^{13}C NMR were recorded using Bruker instruments at 50, or 100 MHz. NMR shifts are reported relative to the residual solvent signal (7.27 ppm for $CDCl_3$, and 7.15 for C_6D_6) for proton NMR and relative the residual solvent central peak for carbon spectra (77.0 ppm for $CDCl_3$ and 128.0 ppm for C_6D_6. IR spectra were obtained using a Tensor 27 ATR diamond PKE Bruker instrument. Mass spectra (MS) were obtained on a GC-MS Hewlett-Packard HP 5971 apparatus and on a NERMAG R 30-10 apparatus in the Laboratoire de Chimie Structurale Organique et Biologique, Universite Pierre et Marie Curie. Elemental analysis were performed by the Service Regional de Microanalyzse de l'Universite Pierre et Marie Curie. Melting points were determined using a Reichert melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone. CH_2Cl_2, benzene and toluene were distilled from calcium hydride or used as ACS reagents if noted.

All reactions were performed under an atmosphere of argon in flame dried glassware using standard syringe-septum techniques unless otherwise noted.

Representative Procedure for Formation of Dichloromethylsilyl ethers:

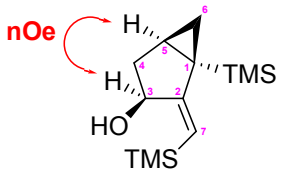


(2) (+/-)-(Dichloromethyl)(dimethyl)({1-[(trimethylsilyl)ethynyl]but-3-enyl}oxy)silane.

(+/-)-1-(Trimethylsilyl)hex-5-en-1-yn-3-ol **1** (842 mg, 5 mmol) was diluted with 5 mL CH_2Cl_2 to which triethylamine (1.39 mL, 10 mmol) and DMAP (122 mg, 1 mmol). Dichloromethyldimethylsilyl chloride (0.75 mL, 5 mmol) was added dropwise (exotherm

noted) and the reaction mixture left stirring for three hours. The reaction mixture was quenched with brine and transferred to a separatory funnel with ether. The organic layer was isolated and the aqueous layer back extracted with ether, and the combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then purified by flash chromatography (5% Et_2O/PE ~ 3 minutes) to afford the product as a colorless oil (1.38 g, yield = 89%); R_f = 0.21 (PE); ^{1}H NMR (400 MHz, C_6D_6) δ = 6.11 – 6.00 (m, 1H), 5.44 (s, 1H), 5.26 – 5.20 (m, 2H), 4.62 (dd, J = 6.6 Hz, 6.6 Hz, 1H), 2.64 – 2.55 (m, 2H), 0.54 (s, 3H), 0.47 (s, 3H), 0.32 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ = 133.9, 118.5, 106.8, 91.1, 64.6, 62.4, 43.3, 0.1, -3.8, -4.2; IR (neat) υ 2961, 2174, 1643, 1337, 1081, 839, 798; Elemental analysis: (Found: C, 46.42; H, 7.29. $C_{12}H_{22}OCl_2Si_2$ requires C, 46.59; H = 7.17).

Representative Procedure for Radical Cyclization of Dichloromethylsilyl ethers:



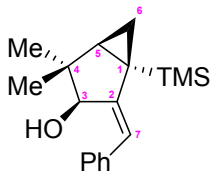
(4) (1*S,2*E*,3*S**,5*S**)-1-(Trimethylsilyl)-2-[(trimethylsilyl)methylene]bicyclo [3.1.0]hexan-3-ol.**[1]

(+/-)-(Dichloromethyl)(dimethyl)({1-[(trimethylsilyl)ethynyl]but-3-enyl}oxy)silane (**2**, 155 mg, 0.5 mmol) was diluted with PhH (10 mL, distilled and degassed – 20 minutes argon). To this was added Et_3N (1.4 mL, 10 mmol) and AIBN (5 mg, 0.03 mmol) and the reaction mixture subsequently heated to reflux. To the hot solution was added a PhH (5 mL, distilled and degassed – 20 minutes argon) solution of Ph_3SnH (228 mg, 0.65 mmol) and AIBN (20 mg, 0.12 mmol) *via* syringe pump (0.21 mmol/hr). After the addition was complete, the mixture was stirred for 30 minutes at reflux then cooled to 0 ^oC and MeLi (1.6 M in Et_2O, 2.5 mL, 4 mmol) was added *via* syringe. The reaction was left stirring for 30 minutes at 0 ^oC then warmed to room temperature for 2 hours. An approximately equal amount of brine was added and the reaction contents transferred to a separatory funnel with ether and the organic layer isolated. The aqueous layer was back extracted with ether, the combined organics dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (0 to 5% Et_2O/PE) to afford the desired product as a colorless oil (98 mg, yield = 77%); R_f = 0.41 (10% Et_2O/PE); dr > 20 : 1 (^{1}H NMR crude); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.60 (s, 1H, H_7), 4.55 (d, J = 7.3 Hz, 1H, H_3), 2.15- 2.07 (m, 1H, H_4), 1.91 (d, J = 14.1 Hz, 1H, H_4), 1.54 (ddd, J = 7.6 Hz, 4.8 Hz, 4.5 Hz, 1H, H_5), 1.37 (brs, 1H, OH), 1.13 (dd, J = 4.2 Hz, 4.2 Hz, 1H, H_6), 0.91 – 0.87 (m, 1H, H_6), 0.13 (s, 9H, vinyl TMS), 0.01 (s, 9H, cyclopropyl TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0 (C_2), 123.6 (C_7), 75.0 (C_3), 37.0 (C_4), 25.9 (C_5), 23.3 (C_1), 19.0 (C_6), 0.6 (vinyl TMS), -2.09 (cyclopropyl TMS); IR (neat) υ 3439, 2952, 1610, 1247, 988, 830, 746, 687 cm^{-1};

[1] Relative configuration of stereocenters determined by nOe results. Assignment of spectra made with assistance of 2 D NMR.

Elemental analysis: (Found: C, 61.41; H, 10.37. $C_{13}H_{26}OSi_2$ requires C, 61.35; H = 10.30).

Representative Procedure for Radical Cyclization/Cross-Coupling of Dichloromethylsilyl ethers:

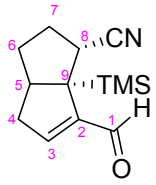


(17) (1*S,2*E*,3*S**,5*R**)-2-Benzylidene-4,4-dimethyl-1-(trimethylsilyl)bicyclo[3.1.0] hexan-3-ol.**

(+/-)-(Dichloromethyl)({2,2-dimethyl-1-[(trimethylsilyl)ethynyl]but-3-enyl}oxy) dimethylsilane (**5**, 338 mg, 1.0 mmol) was diluted with PhH (20 mL, distilled and degassed – 20 minutes argon). To this was added Et_3N (2.8 mL, 20 mmol) and AIBN (10 mg, 0.06 mmol) and the reaction mixture subsequently heated to reflux. To the hot solution was added a PhH (10 mL, distilled and degassed – 20 minutes argon) solution of Ph_3SnH (456 mg, 1.3 mmol) and AIBN (40 mg, 0.24 mmol) *via* syringe pump (0.21 mmol/hr). After the addition was complete the mixture was stirred for 30 minutes at reflux then cooled to room temperature and the solvent removed *in vacuo*. Pentane (15 mL) was added and the heterogeneous mixture stirred vigorously for 10 minutes then filtered through a short pad of celite using additional pentane (~100 mL total volume). The solvent was removed *in vacuo* to afford a heterogenous mixture which was triturated with pentane (10 + 5 mL) with the supernate removed *via* a Pasteur pipette and placed in a separate round bottom flask. The solvent was removed *in vacuo* and the residue dried for 15 minutes under high vacuum. To this was added TBAF (1 M in THF, 4 mL, 4 mmol). After 2 minutes $Pd(dba)_2$ (29 mg, 0.05 mmol) and PhI (223 μL, 2.0 mmol) were added and the mixture heated to 45 ^oC where it was stirred for 48 hours. The reaction mixture was cooled to room temperature and 30% EtOAc/Hex (3 mL) was added and the reaction filtered through a short column of silica (6 inches, total volume of elutant 300 mL – 30% EtOAc/Hex). The solvent was removed *in vacuo* and the crude residue purified by flash chromatography (0 to 2.5% Et_2O/PE) to afford the product as a light yellow oil that solidified on standing (158 mg, yield = 55%); R_f = 0.2 (5% EtOAc/Hex); melting point = 79 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ= 7.54 – 7.46 (m, 2H, ArH), 7.41 – 7.32 (m, 2H, ArH), 7.29 – 7.23 (m, 1H, ArH), 6.70 (s, 1H, H_7), 4.11 (d, J = 2.3 Hz, 1H, H_3), 1.70 (d, J = 2.3 Hz, 1H, OH), 1.38 – 1.30 (m, 2H, H_5 and H_6), 1.25 (s, 3H, Me), 0.93 (s, 3H, Me), 0.86 (dd, J = 6.8 Hz, 3.8 Hz, 1H, H_6), 0.17 (s, 9H, cyclopropyl TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 150.8 (C_2), 137.8 (ArH), 128.6 (ArH), 128.5 (ArH), 126.9 (C_7), 126.6 (ArH), 78.9 (C_3), 42.7 (C_4), 36.5 (C_5), 29.2 (Me), 21.1 (C_1), 20.6 (Me), 16.5 (C_6), -1.9 (cyclopropyl TMS); IR (neat) υ 3424, 2952, 1248, 1017, 833, 701 cm^{-1}; Elemental analysis: (Found: C, 75.43; H, 9.11. $C_{18}H_{26}OSi$ requires C, 75.46; H = 9.15).

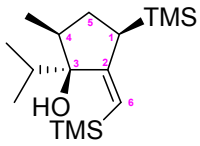
Representative Procedure for Radical Cyclization of Dichloromethylsilyl ethers Involving an External Acceptor:

(18) 8-cyano-2-formyl-1-(trimethylsilyl)bicyclo[3.3.0] oct-2-ene.



(+/-)-(Dichloromethyl)(dimethyl)({1-[(trimethylsilyl)ethynyl]but-3-enyl}oxy)silane (**2**, 155 mg, 0.5 mmol) was diluted with PhH (10 mL, distilled and degassed – 20 minutes argon). To this was added acrilonitrile (330 µL, 5 mmol) and AIBN (5 mg, 0.03 mmol) and the reaction mixture subsequently heated to reflux. To the hot solution was added a PhH (5 mL, distilled and degassed – 20 minutes argon) solution of Ph_3SnH (296 mg, 1 mmol) and AIBN (20 mg, 0.12 mmol) *via* syringe pump (0.21 mmol/hr). After the addition was complete, the mixture was stirred for 30 minutes at reflux then cooled at room temperature and concentrated *in vacuo*. The crude residue was engaged in the next step without further purification. ^{1}H NMR of the crude product revealed a conversion rate of 60%, and a 30% yield (calibrated by an internal standard). The crude product was then diluted with 1.5 mL of THF and 1.5 mL of MeOH. $KHCO_3$ (100 mg, 1 mmol), KF (56mg, 1 mmol) and H_2O_2 (250 µL, 7.5 mmol, 30% in H_2O) were added. The reaction was left stirring for 2 hours at room temperature then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude, which was purified by flash chromatography on silica gel (20% Et_2O/pentane) to afford the desired product as a colorless oil (13 mg, yield =11%, dr 80:20); R_f= 0.65 (40% Et_2O/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ= 9.81 (s, 1H, H_1), 6.83 (t, J = 2.5 Hz, 1H, H_3), 3.11- 3.09 (m, 1H, H_8), 2.83-2.70 (m, 2H, H_4, H_5), 2.43 (dt, J = 19.7 Hz, 2.7 Hz, 1H, H_4), 2.04- 1.97 (m, 2H, H_6), 1.87- 1.76 (m, 2H, H_7), 0.05 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 189.4 (C_1), 152.6 (C_3), 149.5 (C_2), 122.0 (C nitrile), 50.4 (C_9), 46.8 (C_5), 39.5 (C_4), 35.5 (C_8), 33.9 (C_6), 33.1 (C_7),-2.4 (CH_3 TMS); IR (neat) υ 2925, 2854, 2235, 1685, 1607, 1251, 840 cm^{-1}.

Representative Procedure for Radical Cyclization of Dichloromethylsilyl ethers Involving a 1,5-Hydrogen Transfer:



(20) (1*S,2*E*,3*R**,5*S**)-1-Isopropyl-5-methyl-3-(trimethylsilyl)-2-[(trimethylsilyl) methylene]cyclopentanol**

(Dichloromethyl){[1,1-diisopropyl-3-(trimethylsilyl)prop-2-ynyl]oxy} dimethylsilane (**19**, 177 mg, 0.5 mmol) was diluted with PhH (30 mL, distilled and degassed – 20 minutes argon). To this was added Et_3N (1.4 mL, 10 mmol) and AIBN (5 mg, 0.03 mmol) and the reaction mixture subsequently heated to reflux. To the hot solution was added a PhH (7 mL, distilled and degassed – 20 minutes argon) solution of Bu_3SnH (175 μL, 0.65 mmol) and AIBN (20 mg, 0.12 mmol) *via* syringe pump (0.21 mmol/hr). After the addition was complete the mixture was stirred for 30 minutes at reflux then cooled to 0 ^oC and MeLi (1.6 M in Et_2O, 2.5 mL, 4 mmol) was added *via* syringe. The reaction was left stirring for 30 minutes at 0 ^oC then warmed to room temperature for 2 hours. An approximately equal amount of brine was added and the reaction contents transferred to a separatory funnel with ether and the organic layer isolated. The aqueous layer was back extracted with ether, the combined organics dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (PE) to afford the desired product as a colorless oil (113 mg, yield = 80%); R_f = 0.88 (4% Et_2O/PE); ^1H NMR (400 MHz, $CDCl_3$) δ = 5.41 (d, J = 2.8 Hz, 1H, H_6), 2.12 – 2.02 (m, 2H), 1.92 – 1.76 (m, 2H), 1.16 – 1.12 (m, 1H), 1.15 (brs, OH), 0.99 (d, J = 6.8 Hz, 3H, Me), 0.94 (d, J = 6.8 Hz, 3H, Me), 0.88 (d, J = 6.8 Hz, 3H, Me), 0.16 (s, 9H, vinyl TMS), 0.06 (s, 9H, TMS); ^{13}C NMR (100 MHz, C_6D_6) δ = 170.4 (C_2), 121.7 (C_6), 85.4 (C_3), 37.1, 36.5, 34.6, 34.4 (C_5), 18.5 (Me), 17.5 (Me), 16.6 (Me), 1.9 (vinyl TMS), -1.8 (TMS); IR (neat) υ 2953, 1614, 1247, 1050, 968, 844, 748 cm^{-1}. Elemental analysis: (Found: C, 65.39; H, 11.50. $C_{16}H_{34}OSi_2$ requires C, 64.35; H = 11.48).

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Selected Spectra

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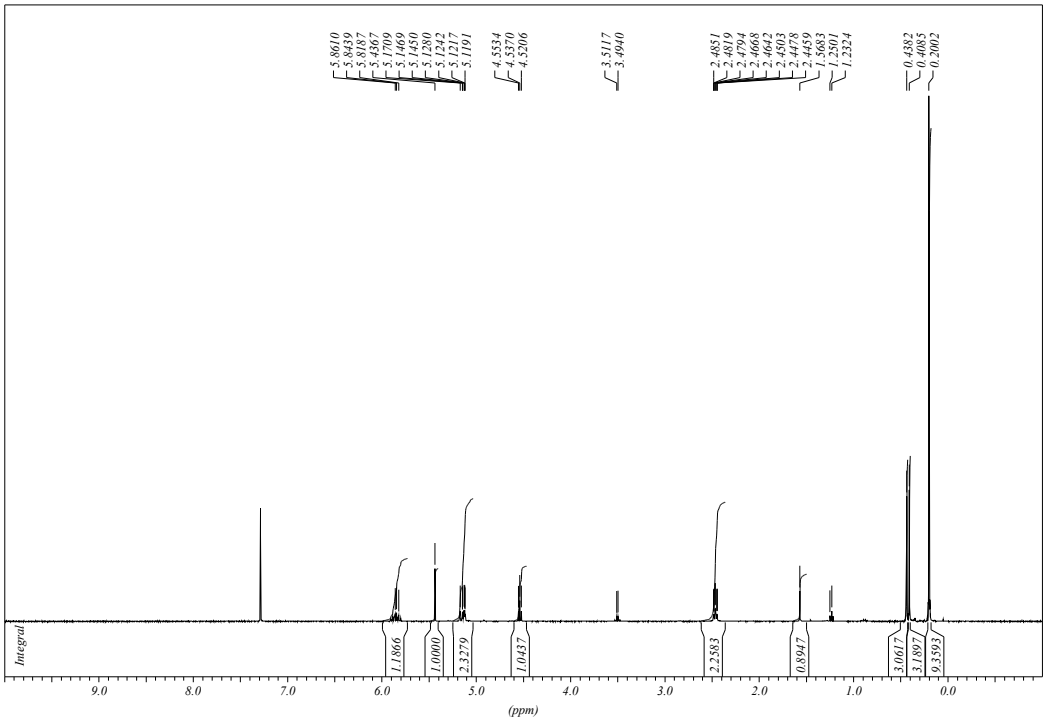
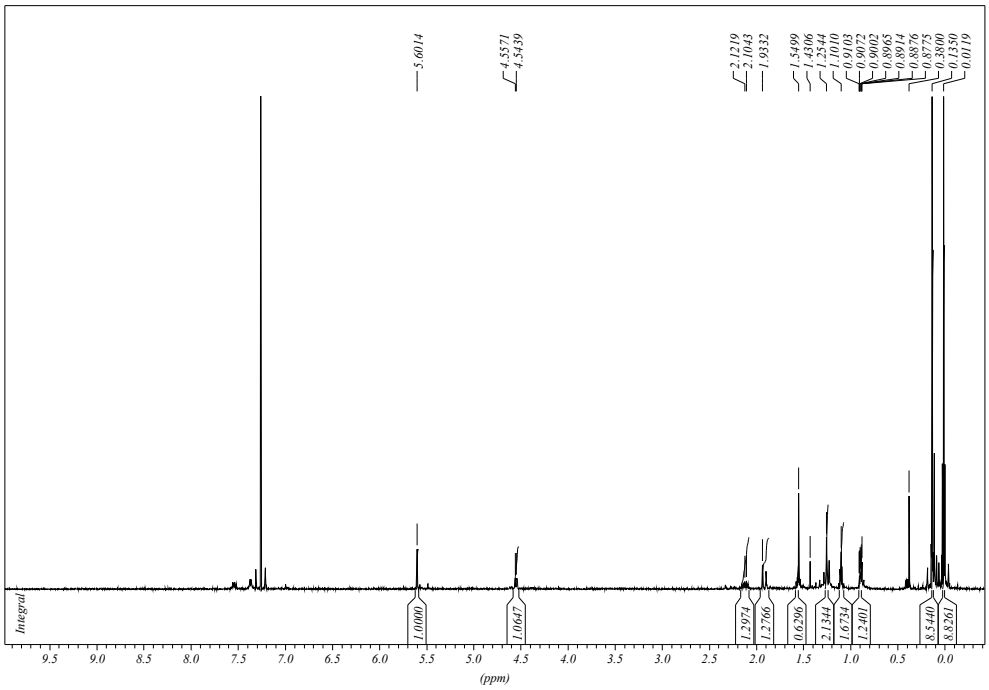
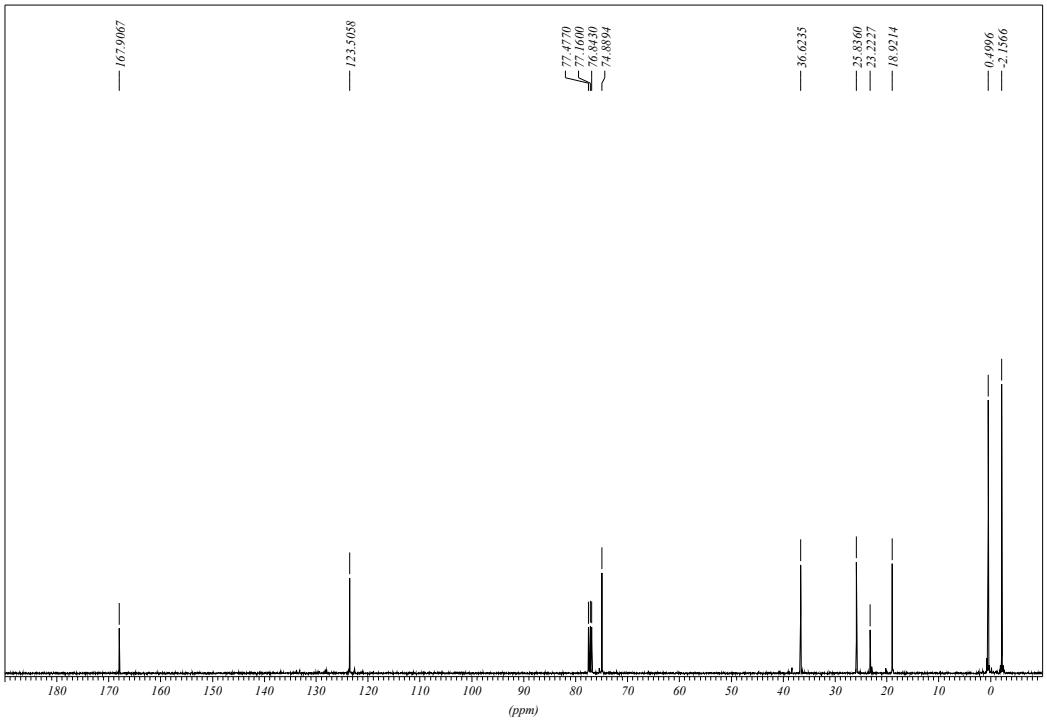
(**2**) (+/-)-(Dichloromethyl)(dimethyl)({1-[(trimethylsilyl)ethynyl]but-3 enyl}oxy)silane

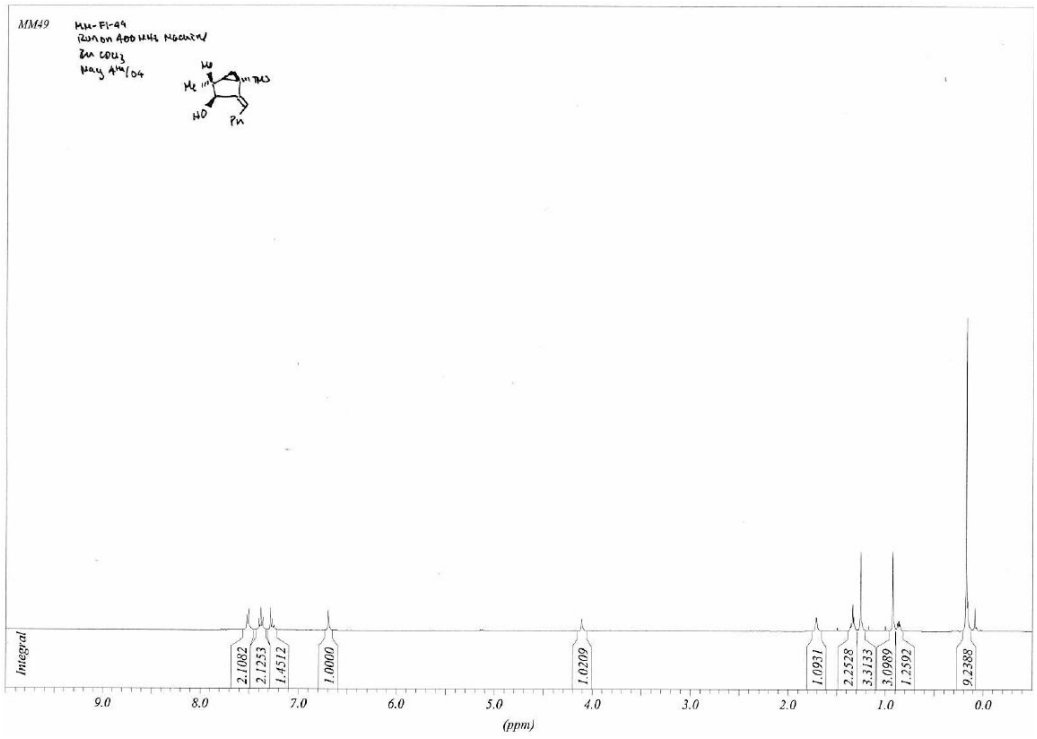


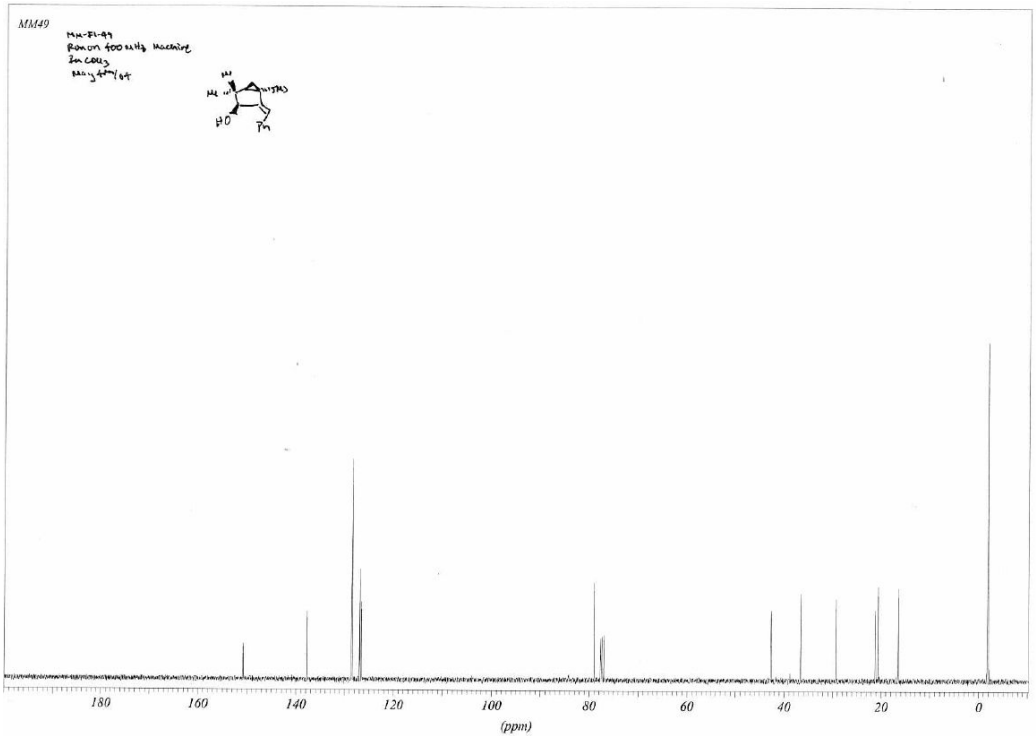
(**4**) (1*S**,2*E*,3*S**,5*S**)-1-(Trimethylsilyl)-2-[(trimethylsilyl)methylene]bicyclo [3.1.0]hexan-3-ol



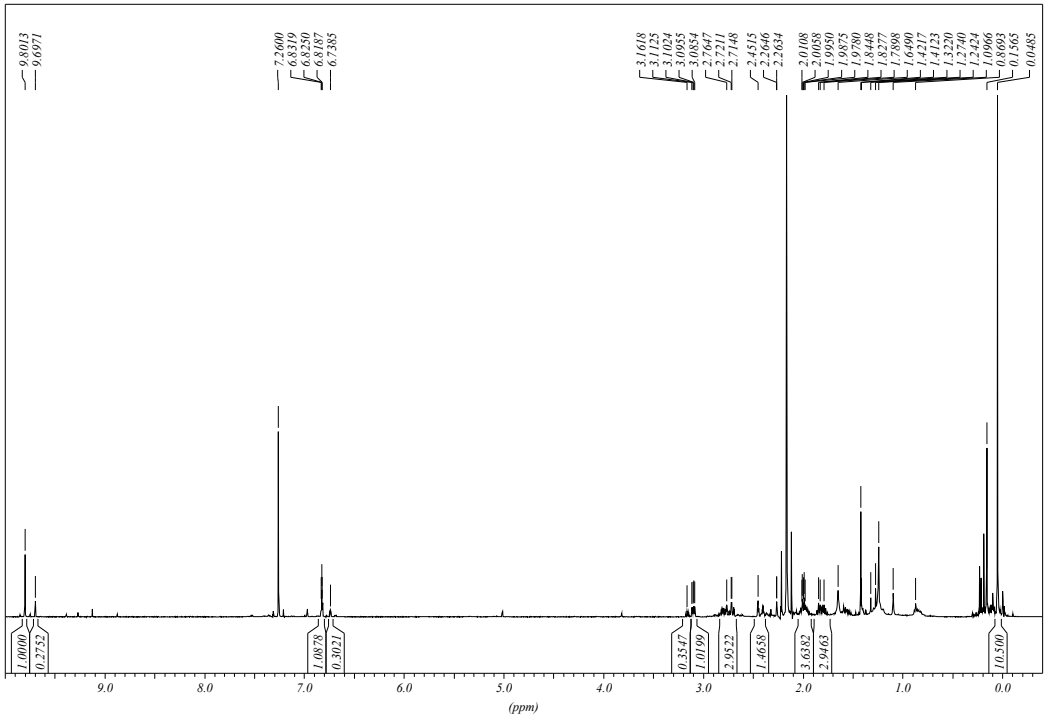


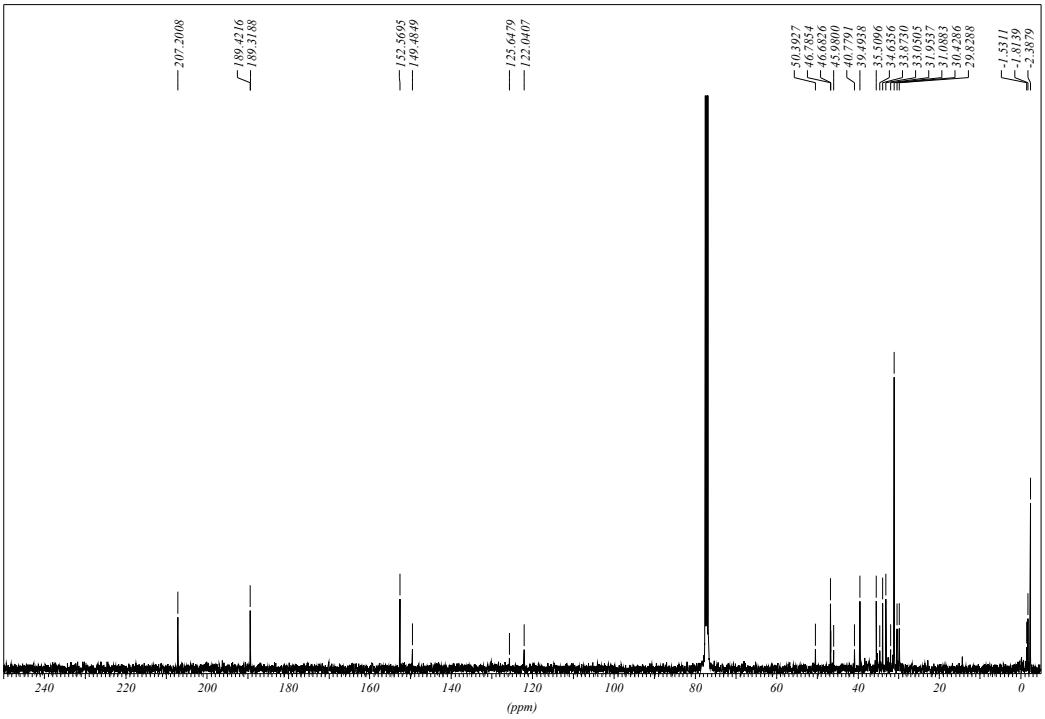
(**17**) (1*S**,2*E*,3*S**,5*R**)-2-Benzylidene-4,4-dimethyl-1-(trimethylsilyl)bicyclo[3.1.0] hexan-3-ol





(**18**): 8-cyano-2-formyl-1-(trimethylsilyl)bicyclo[3.3.0] oct-2-ene





(**20**) (1*S**,2*E*,3*R**,5*S**)-1-Isopropyl-5-methyl-3-(trimethylsilyl)-2-[(trimethylsilyl) methylene]cyclopentanol