Enantioselective Total Synthesis of (–)-Nardoaristolone B *via* a Gold(I)-Catalyzed Oxidative Cyclization

Anna Homs, Michael E. Muratore and Antonio M. Echavarren*

Institute of Chemical Research of Catalonia (ICIQ), Tarragona, Spain

E-mail: aechavarren@iciq.es

Supporting Information

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1. General Information

Unless otherwise stated, reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv^{TM} solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck GF_{234}) using UV light as the visualizing agent and an acidic solution of vanillin or anisaldehyde in ethanol as the developing agent. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-63 μm). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

NMR spectra were recorded at 298 K on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatuses. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

Crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = –173 ºC). Full-sphere data collection was used with w and j scans. *Programs used*: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solutions were achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

HPLC analysis was carried out in an Agilent Tehcnologies instrument HPLC 1100 series with VWD detector or HPLC 1200 series with DAD detector. The column used was a Chiralpack IC (4.6 mm x 250 mm) eluting with hexane:isopropanol (99:1), 0.85 mL/ min flow, 5 μL injection and λ = 210 nm.

2-methylcyclohexenone,[1] phosphoramidite L*,[2] methallyl iodide[3] and 2-*tert*-butylpyridine *N*-oxide (PNO6)[4] were prepared according to the literature whereas the other reagents were purchased from SigmaAldrich or Alfa Aesar. $RhCl_3 \cdot xH_2O$ was purchased from Strem Chemicals.

[1] Baker, L.; Minehan, T. *J. Org. Chem.* **2004**, *69*, 3957–3960.

[2] Smith, C. R.; RajanBabu, T. V. *Org. Lett.* **2008**, *10*, 1657–1659.

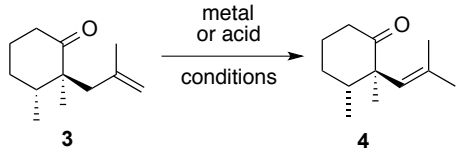
[3] Smith, A. B., III,; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299.

[4] Bell, T. W.; Hu, L. H.; Patel, S. V. *J. Org. Chem.* **1987**, *52*, 3847–3850.

2. Screening of Conditions

a) Isomerization of the *exo*-olefin **3** into trisubstituted *endo*-olefin **4**

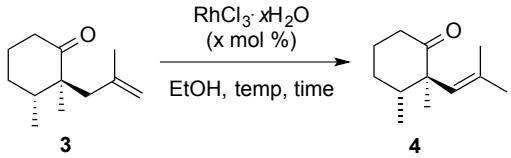
Preliminary screening of conditions



Entry	Metal or acid	Conditions	Outcome
1	$RhCl(PPh_3)_3$	EtOH, reflux, 52 h	No reaction
2	$PdCl_2(PhCN)_2$	$(CH_2Cl)_2$, reflux, 20 h	Traces of **3**
3	$RhCl_3 \cdot xH_2O$[a]	EtOH, sealed tube 115 ºC, 1 h	42% of **3** + 10% usm
4	CF_3SO_3H	dioxane, 95 ºC, 30 h	Decomposition

usm = unreacted starting material

Optimization of conditions

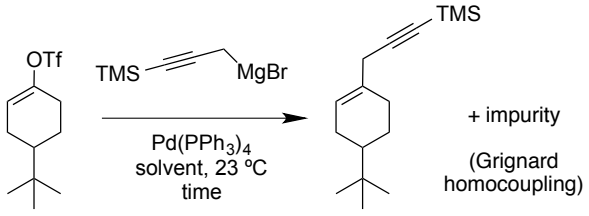


Entry	$RhCl_3 \cdot xH_2O$ (mol %)	Temp.	Time	[*c*]	Yield 4 + 3 [a]
1	30	23 ºC	24 h	0.019 M	< 1% + >95%
2	30	40 ºC	24 h	0.019 M	4% + > 90%
3	30	60 ºC	24 h	0.019 M	74% + 5%
4	30	60 ºC	4 h	0.019 M	83% + 10%
5	30	75 ºC	4 h	0.019 M	68% + <3%
6	20	75 ºC	5 h	0.019 M	86% + < 3% (71%)[b]
7	20	90 ºC	2 h	0.019 M	64% + 4%
8	10	75 ºC	10 h	0.019 M	64% + 5%
9	10	90 ºC	2 h	0.019 M	72% + 9%
10	10	90 ºC	2 h	0.048 M	66% + 2%
11	5	75 ºC	2 h	0.037 M	65% + 6%
12	**5**	**75 ºC**	**4.5 h**	**0.078 M**	**83% + < 3% (74%)**[b]

[a] GC-MS yield determined using diphenylmethane as internal standard; [b] Yields isolated after purification by column chromatography.

b) Kumada Cross-Coupling

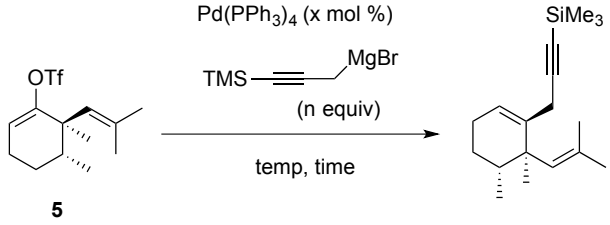
Optimization on model enol triflate



Entry	Solvent	Catalyst loading	Equiv Grignard	Time	Outcome[a] GC yield (ratio product/impurity)
1	THF/Et_2O	5%	4	14 h	73% (2/3)
2	THF/Et_2O	1%	4	14 h	71% (1/1)
3	THF/Et_2O	5%	2.1	14 h	78% (2/1)
4	THF/Et_2O	2.5%	1.2	14 h	Low conversion
5	THF/Et_2O	2.5%	1.5	14 h	29% (1/2) + 62% **5**
6	Et_2O	5%	2.1	4 h	80% (2/1)
7	Et_2O	4%	2.1	4 h	82% (2/1)
8	Et_2O	3%	2.1	4 h	78% (5/3)
9	**Et_2O**	**2%**	**2.1**	**2 h**	**84% (7/3) 63% isolated product**

[a] Calibrated GC yields against 1,3,5-tribromobenzene as internal standard; GC ratio of areas product/impurity (uncalibrated).

Optimization on substrate **5**

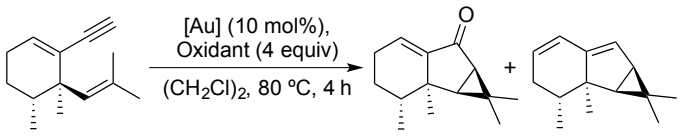


5

Entry	Solvent	Catalyst loading	Equiv Grignard	Temp.	Time	Outcome
1	THF/Et_2O	4%	2.1	23 ºC	16 h	28:72[a]
2	Et_2O	10%	3	23 ºC	60 h	5:1[a]
3	Et_2O	10%	4	23 ºC	60 h	9:1[a]
4	Et_2O	10%	4	55 ºC	9 h	95:5[a]
5	Et_2O	10%	4	55 ºC	16 h	68%[b,c]
9	**Et_2O**	**20%**	**4**	**23 ºC**	**20 h**	**72%[b,d]**

[a] Ratio of areas product:starter determined by GC-MS (uncalibrated); [b] Yield isolated after column chromatography; [c] Contains *ca.* 50% of inseparable impurity originating from the dimerization of the Grignard reagent; [d] Contains *ca.* 10% of inseparable impurity originating from the dimerization of the Grignard reagent.

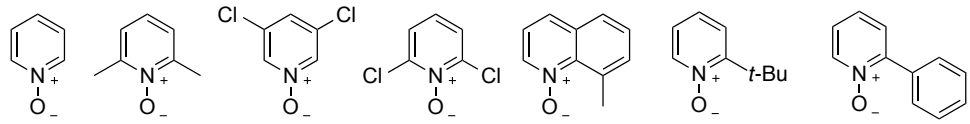
c) Optimization of the Au(I)-catalyzed oxidative cyclization of 1,5-enyne **6**



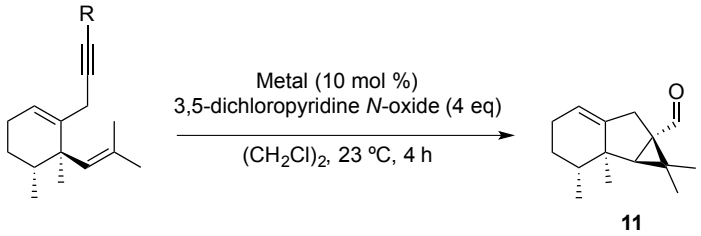
6 **7** **9**

Entry	Oxidant	Yield 7/9 [a]
1	PNO1	31/5
2	PNO2	20/36
3	PNO3	74/15 (isolated products)
4	PNO4	0/55
5	PNO5	20/25
6	PNO6	0/44
7	PNO7	21/9
8	No oxidant	Decomposition

[a] Unless otherwise stated, yield determined by ^{1}H-NMR using diphenylmethane as internal standard



d) Screening of conditions for the Au(I)-catalyzed oxidative cyclization of 1,6-enynes

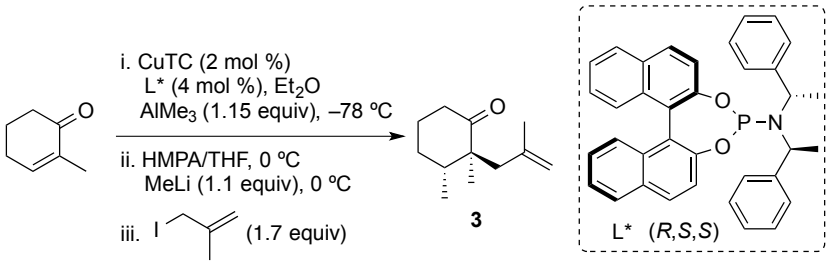


Entry	Metal	R	Yield[a]
1	$IPrAuNTf_2$	H	65% isolated
2	AuCl	H	86%
3	$AuBr_3$	H	80%
4	$PtCl_2$	H	70% + 25% cycloisomerized product
5	$IPrAuNTf_2$	TMS	50% (24 h, 50% conversion)
6	$PtCl_2$	TMS	No reaction

[a]Unless otherwise stated, yield determined by ^{1}H-NMR using diphenylmethane as internal standard

3. Procedures for the synthesis of (–)nardoaristolone B and compounds 8 and 10

(2*S*,3*R*)-2,3-dimethyl-2-(2-methylallyl)cyclohexan-1-one (3)



To a stirred suspension of copper(I)-thiophene-2-carboxylate (69 mg, 0.36 mmol, 0.02 equiv) in 15 mL Et_2O was added (*R*,*S*,*S*)-(+)-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)bis(1-phenylethyl) amine (392 mg, 0.72 mmol, 0.04 equiv). After stirring for 15 min at 23 ºC, the resulting suspension was cooled to –35 ºC and 2-methylcyclohex-2-en-1-one (2.1 mL, 18.2 mmol, 1 equiv) was added. Subsequently, $AlMe_3$ (2M in heptane, 10.4 mL, 20.9 mmol, 1.15 equiv) was added slowly over a period of 15 min and allowed to react for 3 h at –35 ºC (the mixture turns milky bright yellow upon addition of $AlMe_3$).

After 3 h at –35 ºC, dry THF (15 mL) and HMPA (12 mL) were added and the mixture allowed to warm to –5 ºC. MeLi (1.6 M in Et_2O, 12.7 mL, 20.3 mmol, 1.07 equiv) was added dropwise over 5 min from –5 ºC to 0 ºC (the reaction turns greenish upon addition of MeLi). After 20 min stirring, methallyl iodide (3.5 mL, 32.7 mmol, 1.7 equiv) was slowly added over 5 min. The reaction mixture was left at 0 ºC for 30 min and slowly warmed to 23 ºC and left stirring at this temperature for 60 h. The reaction was then quenched with a saturated aqueous solution of potassium sodium tartrate and extracted with dichloromethane (5 × 100 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (200 mL) and brine (200 mL) and finally dried over Na_2SO_4. The volatiles were removed under vacuum and the crude mixture was purified by column chromatography on silica gel eluting with pentane/Et_2O 100:1 to 30:1 to afford a colorless liquid (3:1 mixture of diastereomers **3** and **3'**, 1.8 g, 10 mmol, 55% yield, 90% ee). The desired diastereomer **3** could be separated after several chromatography columns eluting with pentane/Et_2O 80:1 in essentially pure form (> 30:1 *dr*).

The *dr* was determined by integrating the olefinic protons in the ^{1}H-NMR of both diastereomers. The *ee* was determined by HPLC.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 – 4.77 (m, 1H), 4.67 – 4.63 (m, 1H), 2.65 (d, *J* = 13.9 Hz, 1H), 2.50 (dddd, *J* = 15.1, 7.0, 5.8, 1.5 Hz, 1H), 2.41 – 2.28 (m, 2H), 2.00 – 1.84 (m, 3H), 1.80 – 1.68 (m, 1H), 1.60 (s, 3H), 1.57–1.45 (m, 1H), 0.98 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 215.7, 142.9, 114.5, 52.0, 44.3, 38.4, 38.3, 28.8, 24.2, 23.5, 19.7, 15.8. **$[\alpha]_D$** ($CHCl_3$, *c* 1.02, 26 ºC) = –10.0 º. **MS** (GSMS) *m/z* 180.1.

HPLC Chiralpack IC (4.6 mm × 250 mm); hexane:IPA 99:1; 0.85 mL/min; λ = 210 nm, 5 μL injection; t_R (major) 7.5–7.6 min, t_R (minor) 7.8–8.0 min, 91–92% *ee*.

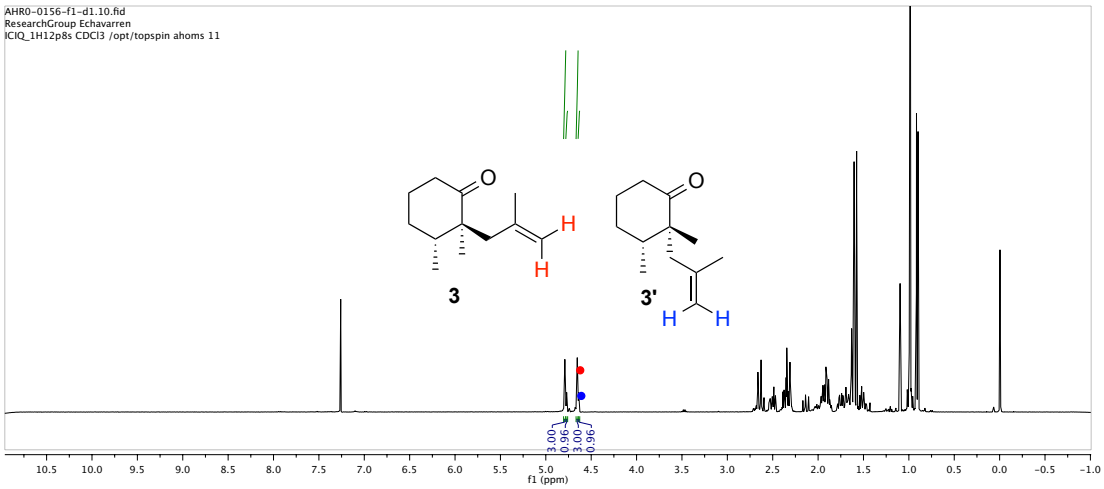
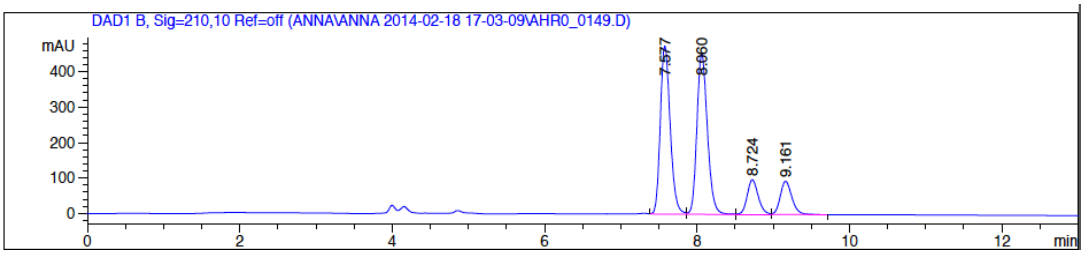
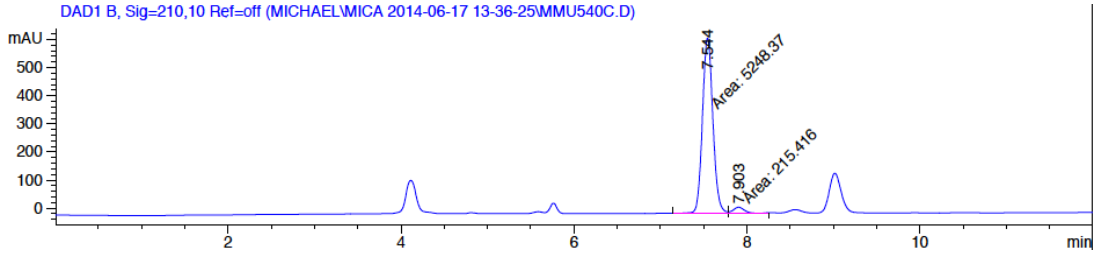


Figure S1 Diastereomeric mixture of **3**+**3´**: *ca.* 3:1 *dr*



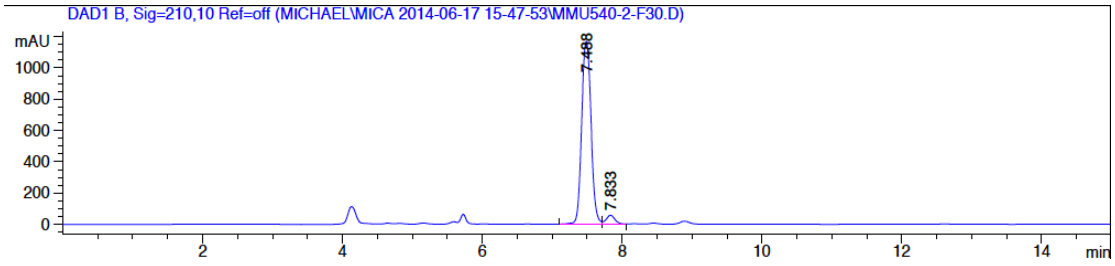
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.577	VV	0.1410	4277.24756	475.08759	40.3521
2	8.060	VV	0.1498	4332.19971	452.15582	40.8706
3	8.724	VV	0.1534	986.34308	98.01797	9.3053
4	9.161	VB	0.1624	1004.01105	94.13841	9.4720

Figure S2 HPLC chromatogram of racemic **3**+**3´**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.544	MF	0.1400	5248.36621	625.01849	96.0574
2	7.903	FM	0.1609	215.41559	22.31853	3.9426
Totals :				5463.78180	647.33702	

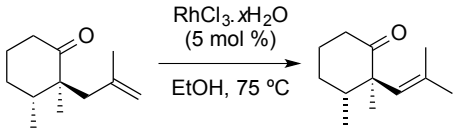
Figure S3 Enantioenriched mixture of **3**+**3´**: *ca.* 92% *ee*



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.488	BV	0.1488	1.09079e4	1169.62219	95.5011
2	7.833	VV	0.1332	513.85321	58.07860	4.4989
Totals :				1.14218e4	1227.70079	

Figure S4 Enantioenriched pure **3**: *ca.* 91% *ee*

(2*R*,3*R*)-2,3-dimethyl-2-(2-methylprop-1-en-1-yl)cyclohexan-1-one (4)



3 **4**

3 (70 mg, 0.38 mmol, 1 equiv) was placed in a 20 mL microwave vial and dissolved in 20 mL of HPLC analytical grade EtOH and $RhCl_3 \cdot xH_2O$ (64 mg, 0.117 mmol, 38% Rh, 0.3 equiv) was added. The vial was sealed and heated at 75 ºC for 4 h.

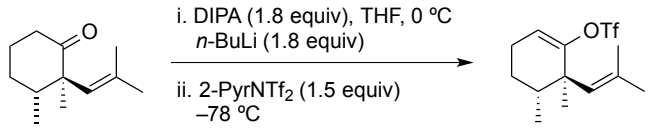
Six experiments were conducted and after cooling to 23 ºC, the combined mixtures were poured on 400 mL of brine and extracted with pentane (5 × 400 mL). After drying over Na_2SO_4, the solvent was concentrated and the crude residue was purified by column chromatography eluting with pentane/Et_2O 50:1 to afford **4** as a colorless liquid (314 mg, 1.74 mmol, 75% yield) as a 15:1 mixture of **4**:**3**.

The reaction was also performed decreasing the amount of catalyst to *ca.* 5% and increasing the concentration. Thus, **3** (58 mg, 0.322 mmol, 1 equiv) was placed in a 5 mL microwave vial and dissolved in HPLC analytical grade EtOH (5 mL) and $RhCl_3 \cdot xH_2O$ (10 mg, 0.019 mmol, 38% Rh, 0.056 equiv) was added. The vial was sealed and heated at 75 ºC for 4.5 h. The work-up and purification were the same as previously stated.

4 was isolated as a colorless oil (43 mg, 0.238 mmol, 74% > 97:3 mixture of **4**:**3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (p, J = 1.4 Hz, 1H), 2.73 – 2.60 (m, 1H), 2.21 – 2.11 (m, 2H), 2.11 – 2.03 (m, 1H), 1.91 – 1.78 (m, 2H), 1.71 (d, J = 1.4 Hz, 3H), 1.45 – 1.38 (m, 1H), 1.42 (d, J = 1.3 Hz, 3H), 1.07 (s, 3H), 0.83 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 216.5, 133.8, 132.4, 54.6, 45.0, 39.3, 28.8, 27.1, 23.9, 20.7, 18.5, 14.4. **$[\alpha]_D$** ($CHCl_3$, *c* 0.50, 26 ºC) = 60.5 º. **MS** (GSMS) *m/z* 180.1

(5*R*,6*R*)-5,6-dimethyl-6-(2-methylprop-1-en-1-yl)cyclohex-1-en-1-yl trifluoromethanesulfonate (5)

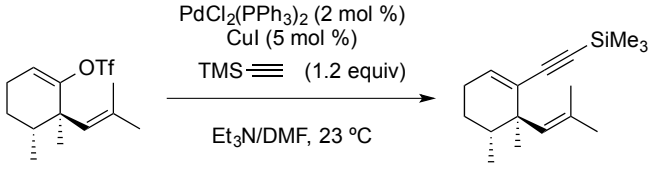


4 **5**

A solution of distilled diisopropylamine (0.35 mL, 2.50 mmol) in anhydrous THF (10 mL) was cooled to 0 ºC and *n*-BuLi (2.5 M in hexane, 1.0 mL, 2.50 mmol) was added dropwise. After 10 min at 0 ºC, the solution was cooled to –78 ºC and **4** (240 mg, 1.33 mmol) was added as a solution in anhydrous THF (2 mL). After 1 h stirring at –78 ºC, a solution of *N*-(2-pyridyl)bis(trifluoromethanesulfonimide) (800 mg, 2.24 mmol) in anhydrous THF (1 mL) was added. The resulting mixture was allowed to warm to 0 ºC for 1 h and then stirred at room temperature for 16 hours. It was then poured on brine (100 mL) and extracted with pentane (5 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude mixture was purified by column chromatography on silica gel eluting with pentane to afford **5** as a colorless oil (340 mg, 1.09 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dd, *J* = 5.2, 3.1 Hz, 1H), 4.94 (app. pent, *J* = 1.5 Hz, 1H), 2.32 – 2.14 (m, 2H), 2.05 (app. dqd, *J* = 11.9, 6.9, 3.1 Hz, 1H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.58 – 1.37 (m, 2H), 1.14 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.7, 135.0, 127.7, 118.3 (q, $J_{C\text{-}F}$ 319.2 Hz), 115.4, 43.1, 39.2, 27.4, 26.1, 23.8, 21.0, 18.4, 16.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F –75.4. **HRMS** (ESI+) calculated mass for $[C_{13}H_{19}F_3O_3SNa]^+$ (M+Na^+) *m*/*z* 335.0899, measured mass *m*/*z* 335.0899. **$[\alpha]_D$** ($CHCl_3$, *c* 0.67, 25 ºC) = –7.17 º.

(((5*R*,6*R*)-5,6-dimethyl-6-(2-methylprop-1-en-1-yl)cyclohex-1-en-1-yl)ethynyl)trimethylsilane (6a)



5 **6a**

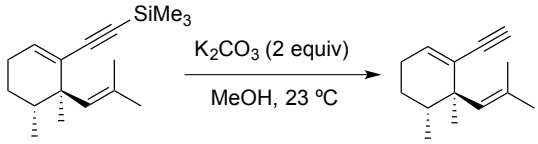
$PdCl_2(PPh_3)_2$ (9 mg, 0.013 mmol, 0.02 equiv) and CuI (6 mg, 0.032 mmol, 0.05 equiv) were suspended in degassed Et_3N (1.43 mL, 10.2 mmol, 16 equiv). To this suspension was added **5** (200 mg, 0.64 mmol, 1 equiv) dissolved in 1 mL of degassed DMF immediately followed by addition of TMS-acetylene (0.11 mL, 0.77 mmol, 1.2 equiv). The mixture was stirred at 23 ºC for 3 h, then poured on brine (50 mL) and extracted with pentane (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

Note: alternatively this enyne can be purified by column chromatography on silica gel eluting with pentane to afford analytically pure material.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, *J* = 4.3, 3.4 Hz, 1H), 5.06 (app. pent, *J* = 1.2 Hz, 1H), 2.16 – 2.09 (m, 2H), 1.89 – 1.78 (m, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.65 (d, *J* = 1.3 Hz, 3H), 1.53 – 1.36 (m,

2H), 1.09 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.6, 132.6, 132.4, 131.2, 107.1, 91.0, 42.3, 37.6, 27.5, 26.6, 26.1, 22.9, 18.5, 17.2, 0.2. **HRMS** (APCI+) calculated mass for $[C_{17}H_{29}Si]^+$ ($M+H^+$) *m/z* 261.2033, measured mass *m/z* 261.2033. **$[\alpha]_D$** ($CHCl_3$, *c* 0.75, 25 ºC) = –17.5 º.

(5*R*,6*R*)-1-ethynyl-5,6-dimethyl-6-(2-methylprop-1-en-1-yl)cyclohex-1-ene (6)

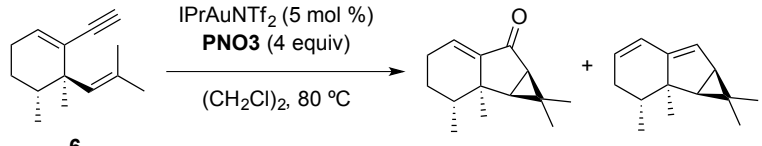


6

The crude material obtained previously was dissolved in MeOH (2 mL) and K_2CO_3 (177 mg, 1.28 mmol, theor. 2 equiv) was added. The resulting suspension was stirred at 23 ºC for 5 h (monitored by GC-MS) and poured on half-saturated brine (100 mL) and extracted with pentane (5 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was concentrated. Purification by column chromatography on silica gel eluting with pentane afforded **6** as a pale yellow oil (90 mg, 0.48 mmol, 74% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (dd, *J* = 4.8, 3.4 Hz, 1H), 5.12 (app. pent, *J* = 1.4 Hz, 1H), 2.67 (app. s, 1H), 2.17 – 2.10 (m, 2H), 1.86 (dqd, *J* = 11.9, 6.8, 3.1 Hz, 1H), 1.72 (d, *J* 1.5 Hz, 3H), 1.66 (d, *J* 1.4 Hz, 3H), 1.54 – 1.47 (m, 1H), 1.45 – 1.36 (m, 1H), 1.11 (s, 3H), 0.89 (d, *J* 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.5, 133.0, 132.0, 130.0, 84.9, 74.2, 41.9, 37.5, 27.4, 26.5, 26.0, 22.8, 18.2, 17.0. **HRMS** (APCI+) calculated mass for $[C_{14}H_{21}]^+$ ($M+H^+$) *m/z* 189.1638, measured mass *m/z* 189.1645. **$[\alpha]_D$** ($CHCl_3$, *c* 0.60, 26 ºC) = 19.0 º.

(1a*S*,1b*R*,2*R*,6a*R*)-1,1,1b,2-tetramethyl-1a,1b,2,3,4,6a-hexahydrocyclopropa[*a*]inden-6(1*H*)-one (7)



6 **7** **9**

To a solution of **6** (65 mg, 0.345 mmol, 1 equiv) in $(CH_2Cl)_2$ (1.5 mL) were added 3,5-dichloropyridine *N*-oxide (226 mg, 1.381 mmol, 4 equiv) and $IPrAuNTf_2$ (15 mg, 0.017 mmol, 0.05 equiv). The resulting mixture was stirred at 80 ºC for 5 h. After cooling to 23 ºC, the mixture was poured on a saturated solution of $CuSO_4$ and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under vacuum. The crude material was purified by column chromatography on silica gel eluting with pentane/Et_2O 10:1 to afford **7** as a pale yellow oil (52 mg, 0.255 mmol, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (t, *J* = 3.5 Hz, 1H), 2.30 – 2.10 (m, 2H), 1.79 – 1.70 (m, 1H), 1.73 (d, *J* = 5.7 Hz, 1H), 1.61 (dd, *J* = 5.5, 0.7 Hz, 1H), 1.58 – 1.51 (m, 1H), 1.50 – 1.40 (m, 1H), 1.14 (s,

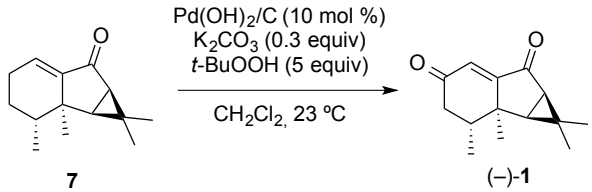
3H), 1.06 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.2, 146.8, 131.6, 42.4, 42.2, 39.2, 33.5, 30.2, 28.9, 26.5, 25.9, 22.5, 16.9, 16.1. **HRMS** (APCI+) calculated mass for $[C_{14}H_{21}O]^+$ ($M+H^+$) *m/z* 205.1587, measured mass *m/z* 205.1590. **$[\alpha]_D$** ($CHCl_3$, *c* 0.53, 26 ºC) = –39.0 º.

(1a*S*,1b*R*,2*R*,6a*R*)-1,1,1b,2-tetramethyl-1,1a,1b,2,3,6a-hexahydrocyclopropa[*a*]indene (9)

Along with **7**, side product **9** (9 mg, 0.048 mmol, 15% yield contaminated with 10% of an unknown impurity) was also isolated.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (dd, *J* = 9.5, 2.4 Hz, 1H), 5.60 (ddd, *J* = 9.7, 5.4, 2.1 Hz, 1H), 5.33 (d, *J* = 1.4 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.97 – 1.84 (m, 2H), 1.67 (dd, *J* = 6.0, 2.0 Hz, 1H), 1.03 – 1.01 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.1 Hz, 1H), 0.95 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.5, 128.7 123.4, 121.8, 49.0, 37.1, 34.9, 33.0, 32.8, 27.8, 24.7, 21.2, 17.1, 16.7. **HRMS** (EI+) calculated mass for $[C_{14}H_{20}]^+$ (M^+) *m/z* 188.1565, measured mass *m/z* 188.1563.

(1a*S*,1b*R*,2*R*,6a*R*)-1,1,1b,2-tetramethyl-1,1a,1b,2,3,6a-hexahydrocyclopropa[*a*]indene-4,6-dione, (–)-nardoaristolone B (1)



7 (–)-**1**

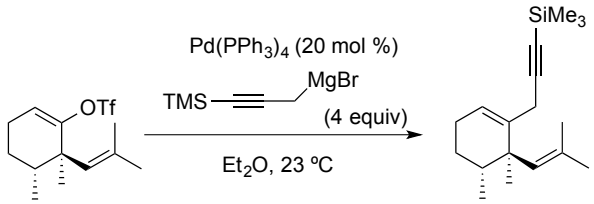
To a suspension of **7** (15 mg, 0.073 mmol, 1 equiv) in CH_2Cl_2 (0.4 mL) and K_2CO_3 (3 mg, 0.022 mmol, 0.3 equiv) were added $Pd(OH)_2/C$ (5 mg, 0.007 mmol, 20% Pd, 0.1 equiv) and *t*-BuO_2H (5M in decane, 74 μL, 0.367 mmol, 5 equiv). The reaction was stirred for 5 h at 23 ºC. The crude was filtered though Celite and the solvent was concentrated. Purification by column chromatography on silica gel eluting with pentane/Et_2O 2:1 afforded the natural product (–)-**nardoaristolone B** (**1**) as a pale yellow solid (15 mg, 0.069 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 1H), 2.50 – 2.37 (m, 2H), 2.29 (dd, *J* = 18.0, 13.5 Hz, 1H), 1.99 (d, *J* = 5.5 Hz, 1H), 1.83 (dd, *J* = 5.5, 0.8 Hz, 1H), 1.23 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.3, 199.7, 164.9, 123.3, 44.1, 42.1, 42.0, 40.0, 35.3, 31.9, 28.6, 20.6, 17.6, 15.6. **HRMS** (ESI+) calculated mass for $[C_{14}H_{19}O_2]^+$ ($M+H^+$) *m/z* 219.1380, measured mass *m/z* 219.1371. **$[\alpha]_D$** (MeOH, *c* 0.50, 26 ºC) = –7.40 º.[5] **M.p.** 96–97 ºC.[6] Structure confirmed by **X-Ray**: CCDC 1037494.

(3-((5*R*,6*R*)-5,6-dimethyl-6-(2-methylprop-1-en-1-yl)cyclohex-1-en-1-yl)prop-1-yn-1-yl)trimethylsilane

[5] The reported α_D of the isolated natural product is the following: $[\alpha]_D$ (MeOH, *c* 0.5, 26 ºC) = – 19.60º (Liu, M.-L.; Duan, Y.-H.; Hou, Y.-L.; Li, C.; Gao, H.; Dai, Y.; Yao, X.-S. *Org. Lett.* **2013**, *15*, 1000–1003).

[6] Melting point of the racemate: 60–62 ºC (Handore, K. L.; Reddy, D. S. *Org. Lett.* **2014**, *16*, 4252–4255).

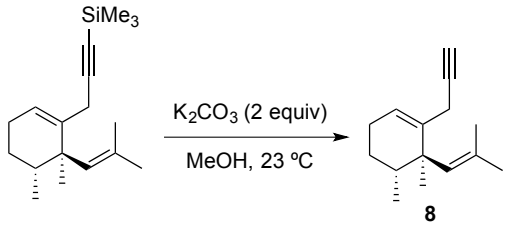


5

A dry 2-neck round-bottom flask equipped with a condenser, was charged with activated magnesium tunings (315 mg, 13.0 mmol, 1.5 equiv) that were covered with anhydrous diethyl ether (8 mL). Dibromoethane (10 μL, 4.6 μmol, catalytic) was added followed by trimethylsilylpropargyl bromide (0.5 mL, 2.9 mmol, 0.33 equiv). The reaction was initiated by warming to reflux. A gentle reflux was then maintained by slow addition of the remaining bromide (1 mL, 5.8 mmol, 0.66 equiv). After addition the mixture was heated to reflux for 20 additional minutes. The Grignard reagent was titrated and used in the following reaction.

A dry Schlenk tube was charged with $Pd(PPh_3)_4$ (148 mg, 0.128 mmol, 0.2 equiv) which was suepended in anhydrous Et_2O (8 mL). The suspension was stirred vigorously and **5** (200 mg, 0.64 mmol, 1 equiv) was added as a solution in anhydrous Et_2O (2 mL) immediately followed by addition of the solution of Grignard reagent freshly prepared (0.37 M, 6.9 mL, 2.56 mmol, 4 equiv) were added dropwise. The resulting reaction was stirred for 20 h at 23 ºC (monitored by GC-MS). The mixture was poured on brine (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent concentrated. The crude material was used in the next step without further purification.

(5*R*,6*R*)-5,6-dimethyl-6-(2-methylprop-1-en-1-yl)-1-(prop-2-yn-1-yl)cyclohex-1-ene (8)



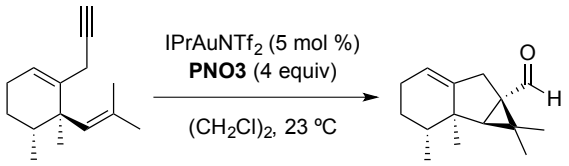
8

The crude material from the reaction described above (theor. 0.64 mmol, 1 equiv) was dissolved in MeOH (1.5 mL) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) was added. The resulting suspension was stirred at 23 ºC for 6 h (monitored by GC-MS) and then poured on brine (50 mL) and extracted with pentane (5 × 30 mL). The combined organic layers were dried over Na_2SO_4,filtered and solvent was concentrated. Purification by column chromatography on silica gel eluting with pentane afforded **8** as a colourless oil (100 mg, 0.494 mmol, 77% yield over 2 steps).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.20 – 6.12 (m, 1H), 5.57 (t, *J* = 1.2 Hz, 1H), 3.19 – 3.10 (m, 1H), 3.09 – 3.00 (m, 1H), 2.38 (t, *J* = 2.7 Hz, 1H), 2.38 – 2.33 (m, 2H), 2.19 – 2.04 (m, 1H), 1.93 (d, *J* = 1.4 Hz, 3H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.74 – 1.66 (m, 2H), 1.24 (s, 3H), 1.12 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 140.1, 133.5, 132.9, 123.4, 83.8, 71.0, 43.0, 39.1, 27.5, 27.3, 26.2, 22.5, 22.4,

18.2, 17.4. **HRMS** (EI+) calculated mass for $[C_{15}H_{22}]^+$ (M^+) *m/z* 202.1722, measured mass *m/z* 202.1721. **[α]$_D$** ($CHCl_3$, *c* 0.37, 23 ºC) = –2.3 º.

(1a*S*,1b*R*,2*R*,6a*S*)-1,1,1b,2-tetramethyl-1a,1b,2,3,4,6-hexahydrocyclopropa[*a*]indene-6a(1*H*)-carbaldehyde (10)

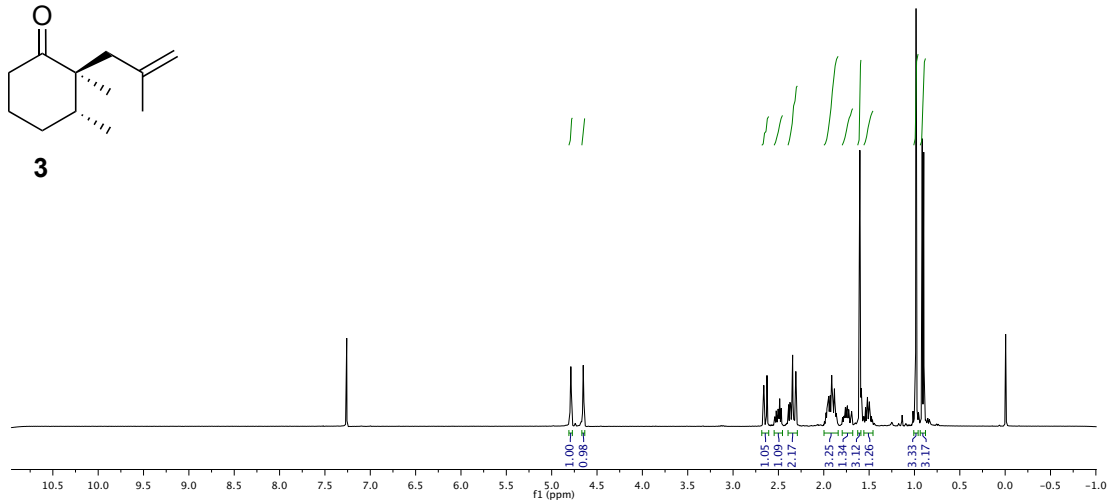


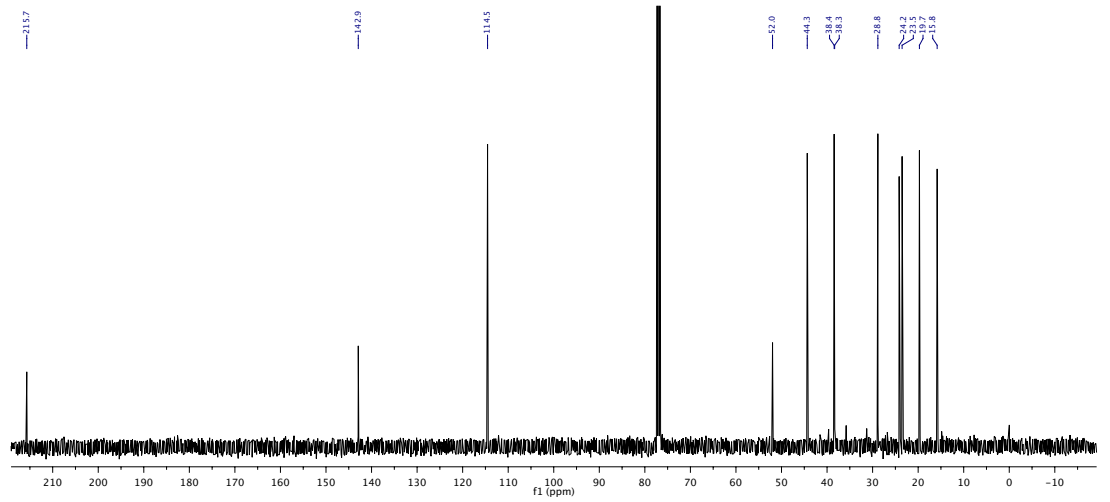
8 **10**

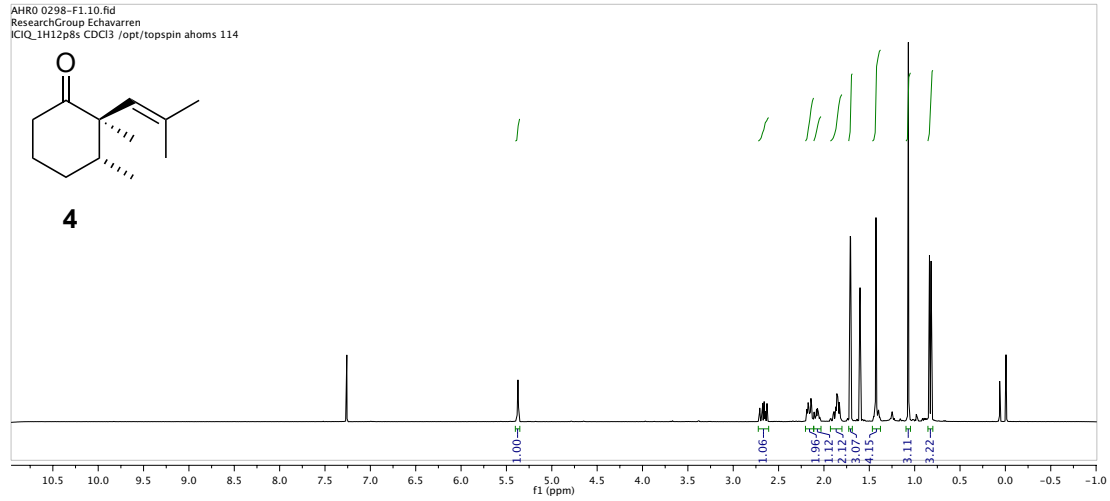
To a solution of **8** (10 mg, 0.049 mmol, 1 equiv) in $(CH_2Cl)_2$ (0.5 mL) was added 3,5-dichloropyridine *N*-oxide (32 mg, 0.198 mmol, 4 equiv) and $IPrAuNTf_2$ (4 mg, 4.9 μmol, 0.1 equiv). The resulting mixture was stirred at 23 ºC for 4 h. After cooling to 23 ºC, the mixture was poured on a saturated solution of $CuSO_4$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography on silica gel eluting with pentane/Et_2O 20:1 to afford **10** as a pale yellow oil (7 mg, 0.032 mmol, 65% yield).

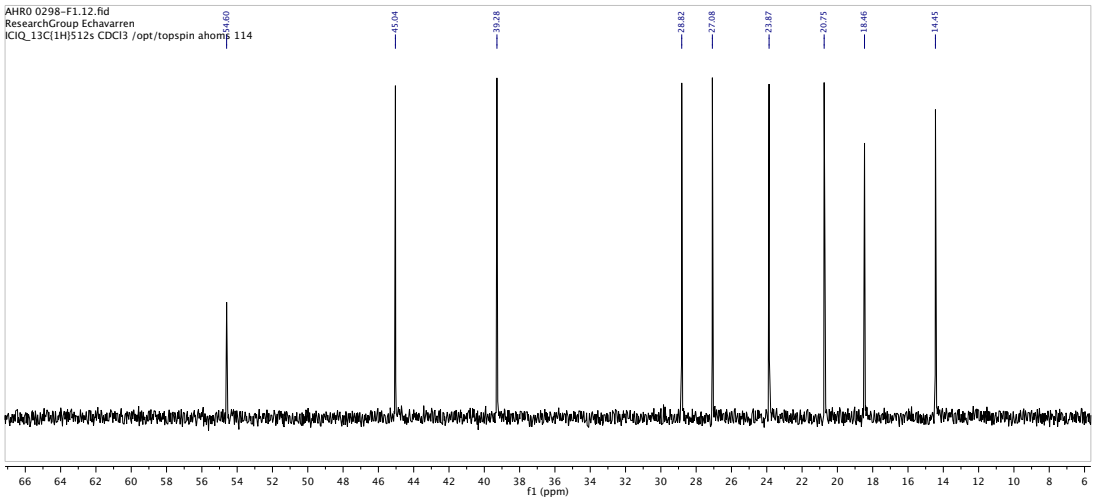
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 5.29 (d, *J* = 3.1 Hz, 1H), 3.30 – 3.23 (m, 1H), 2.28 (dd, *J* = 16.6, 1.5 Hz, 1H), 2.07 – 2.00 (m, 2H), 1.93 (s, 1H), 1.63 – 1.55 (m, 1H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.52 – 1.38 (m, 2H), 1.37 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.3, 146.4, 119.0, 51.4, 46.4, 45.6, 35.0, 34.7, 29.8, 26.9, 25.6, 24.8, 21.1, 17.3, 17.1. **HRMS** (ESI+) calculated mass for $[C_{15}H_{22}NaO]^+$ ($M+Na^+$) *m/z* 241.1563, measured mass *m/z* 241.1555. **[α]$_D$** ($CHCl_3$, *c* 0.57, 26 ºC) = –73.9 º.

4. NMR Spectra





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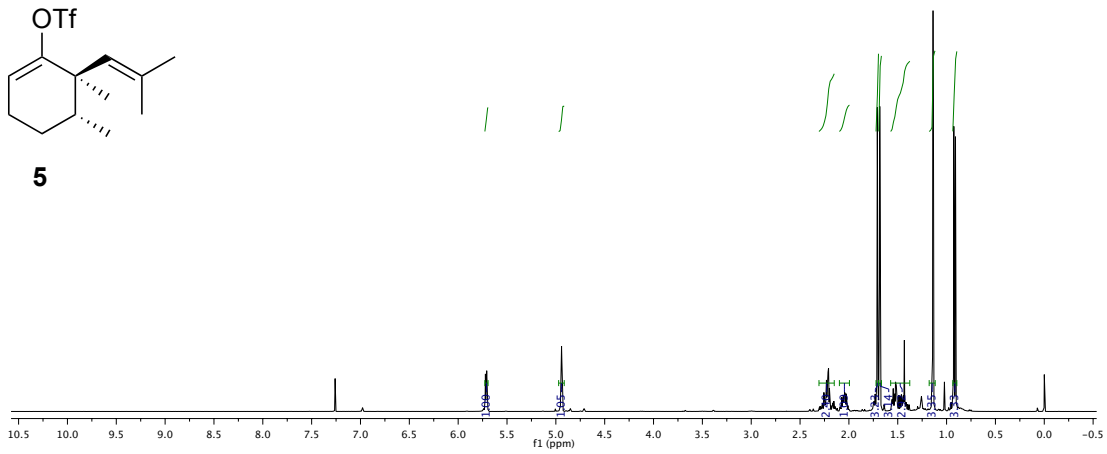
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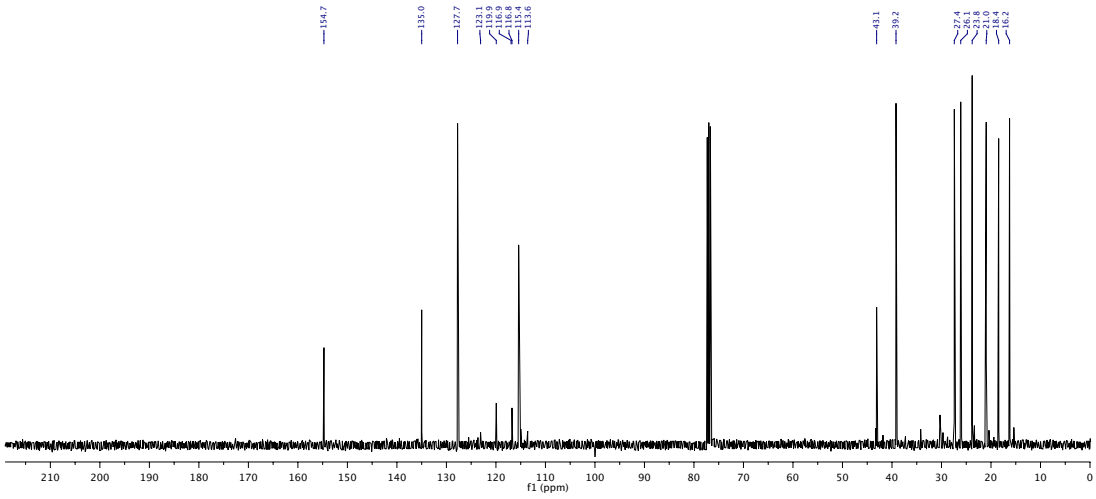
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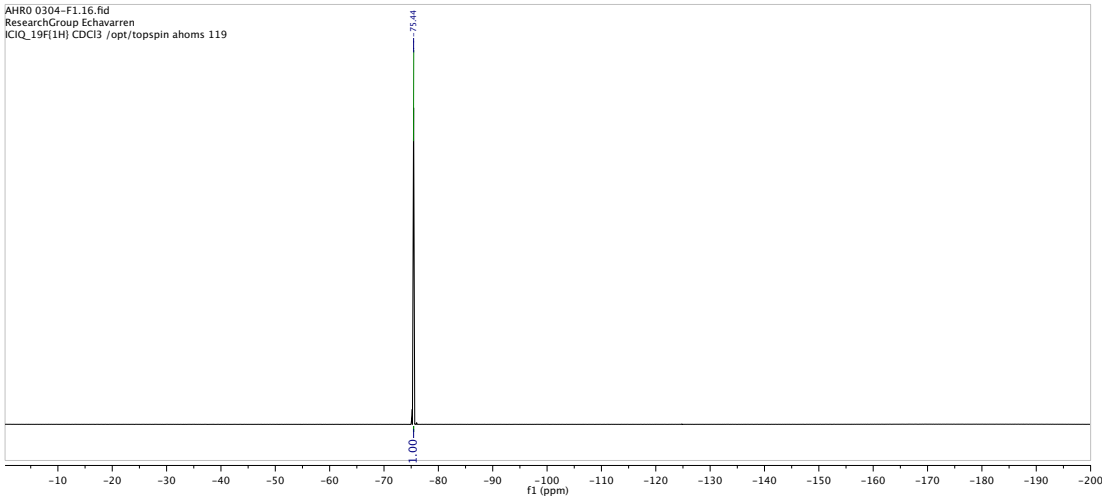
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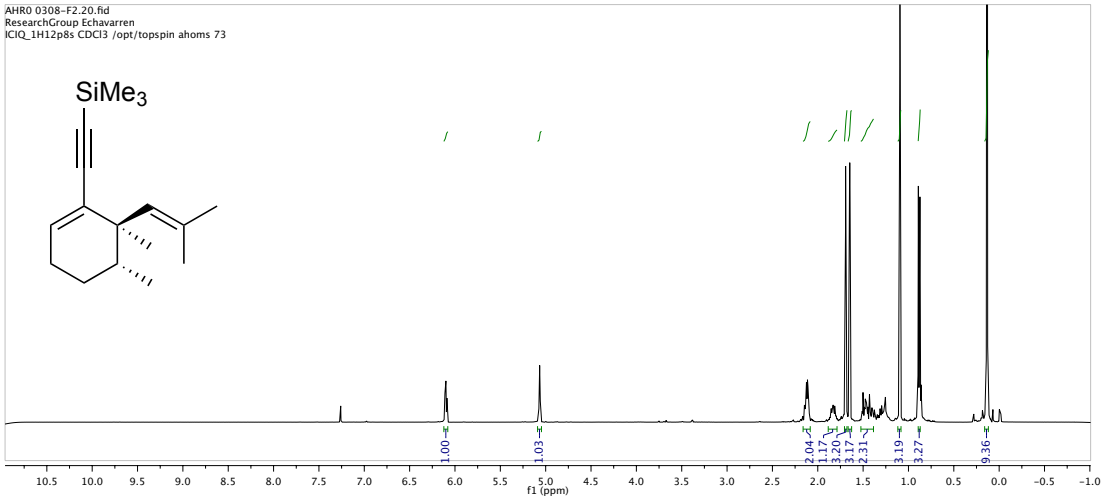
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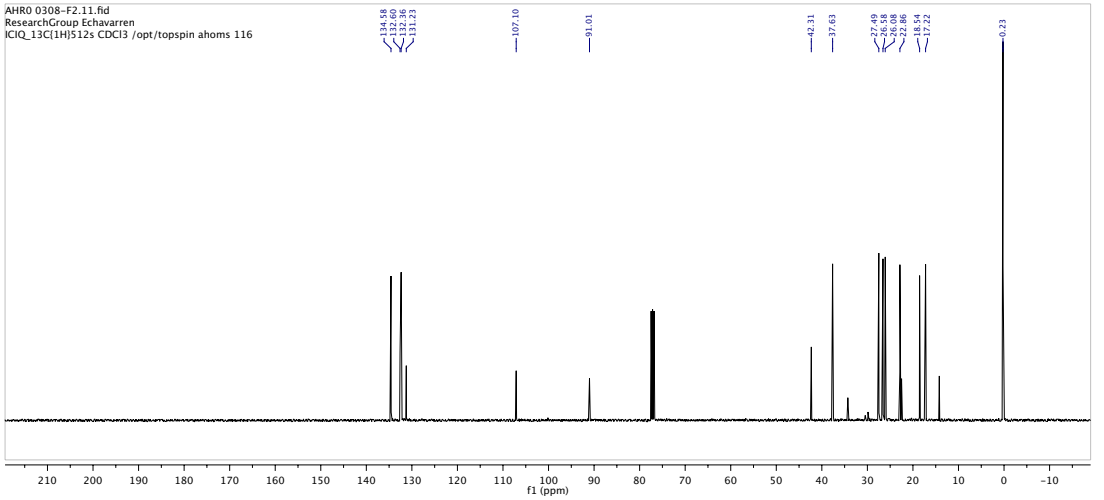
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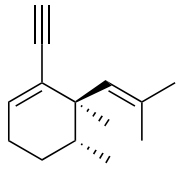

6

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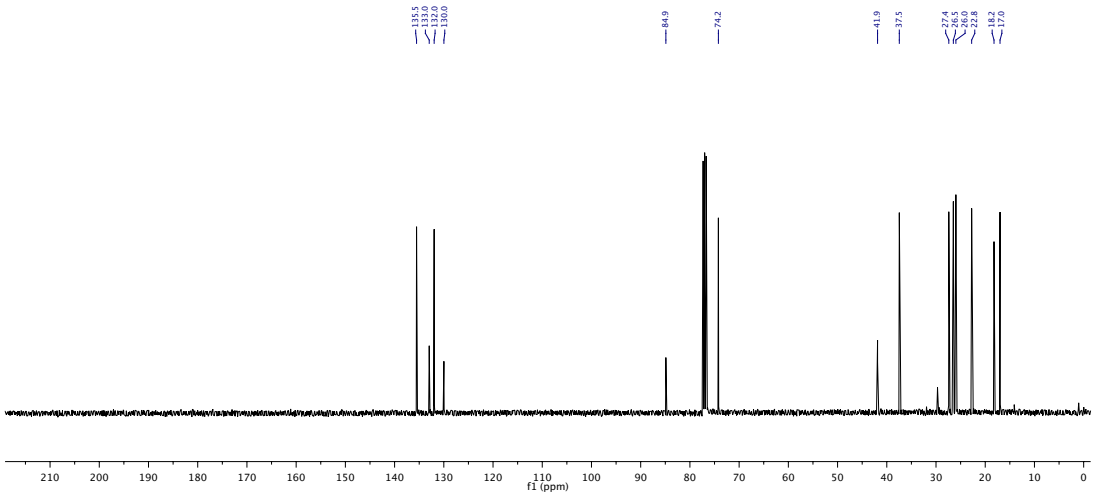
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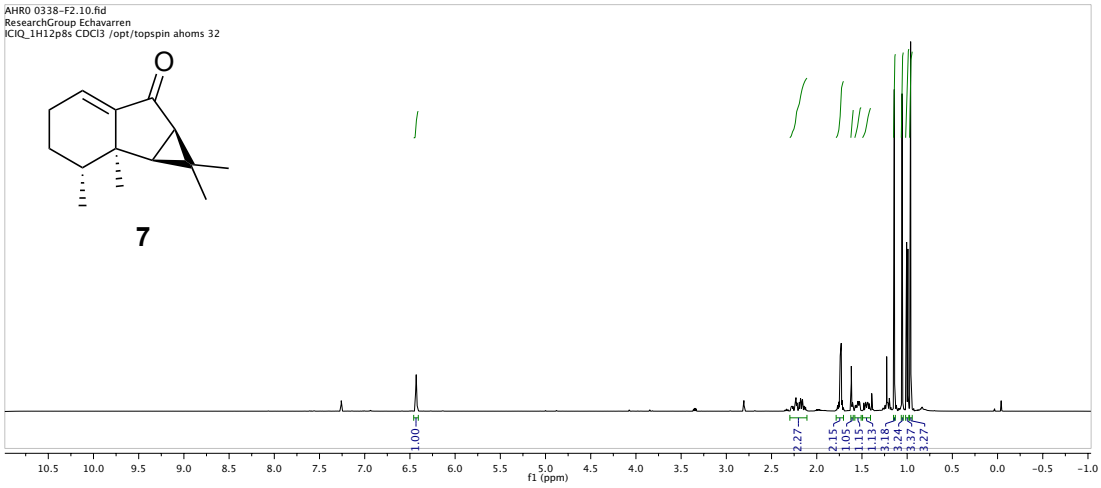
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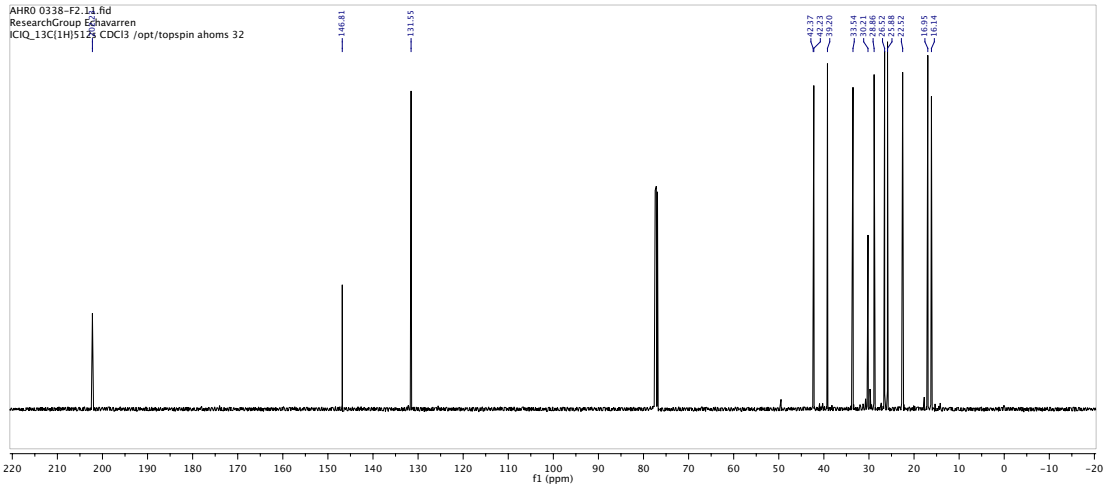
7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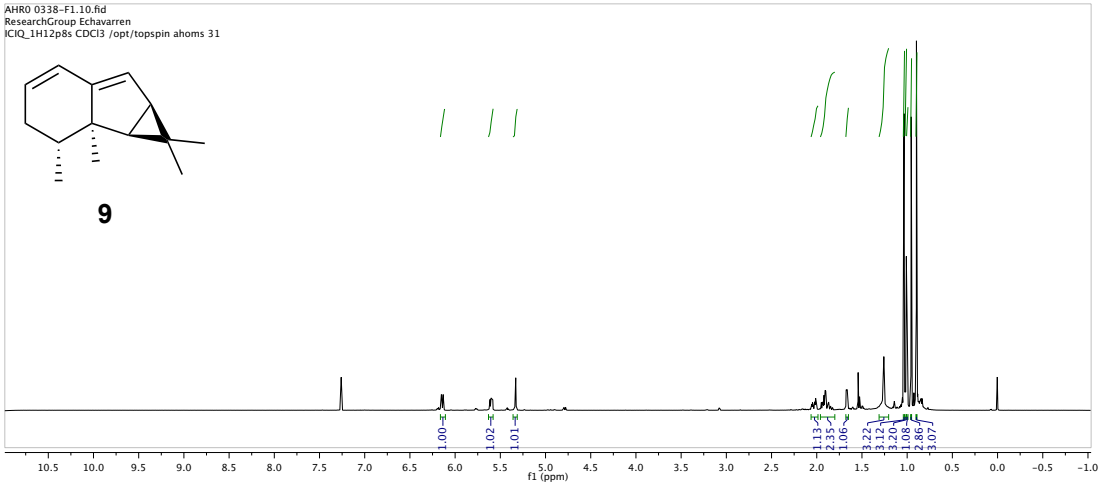
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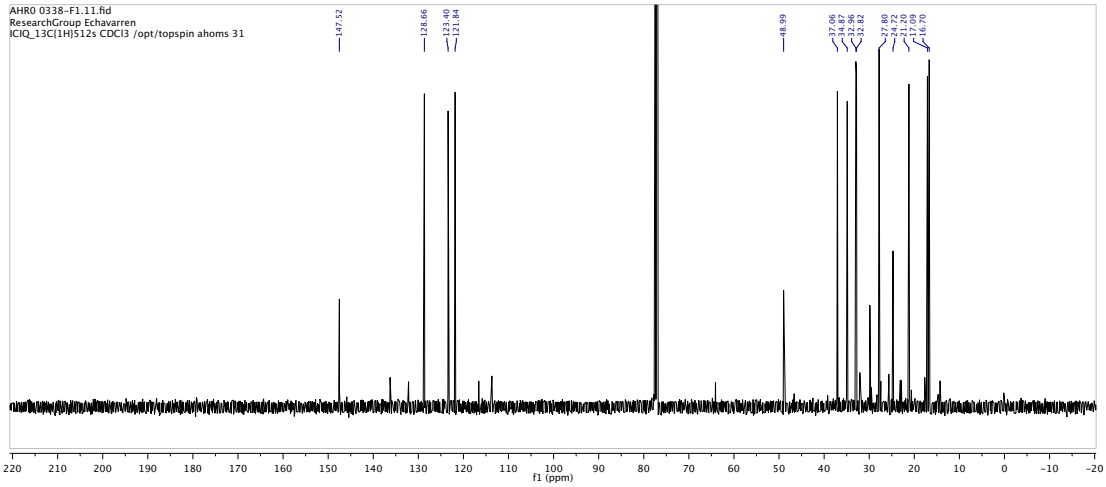
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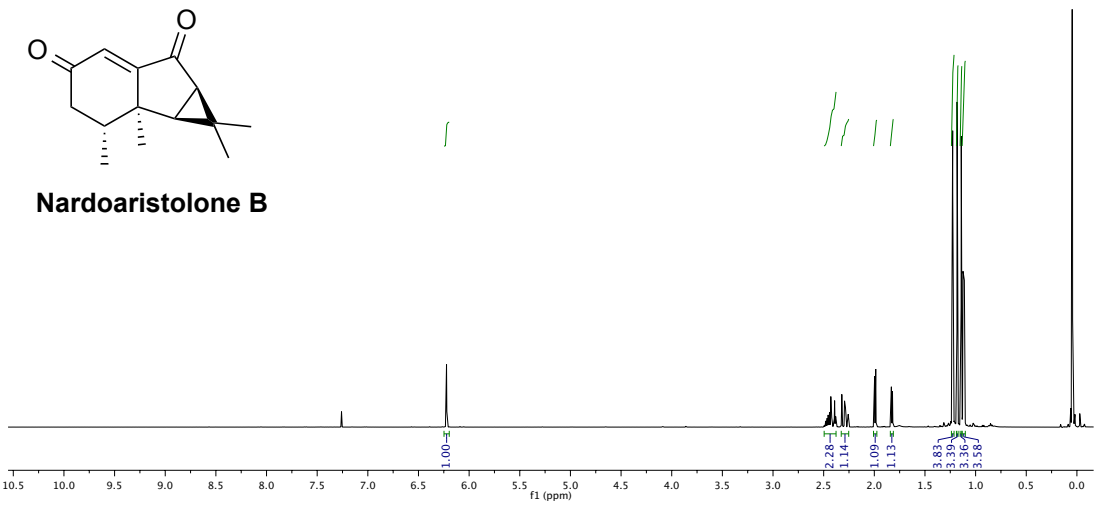
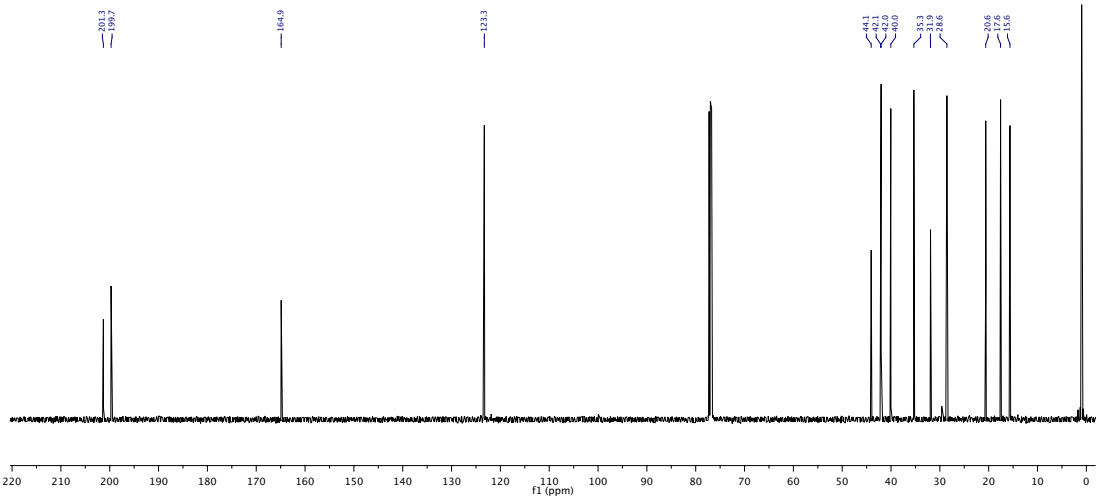
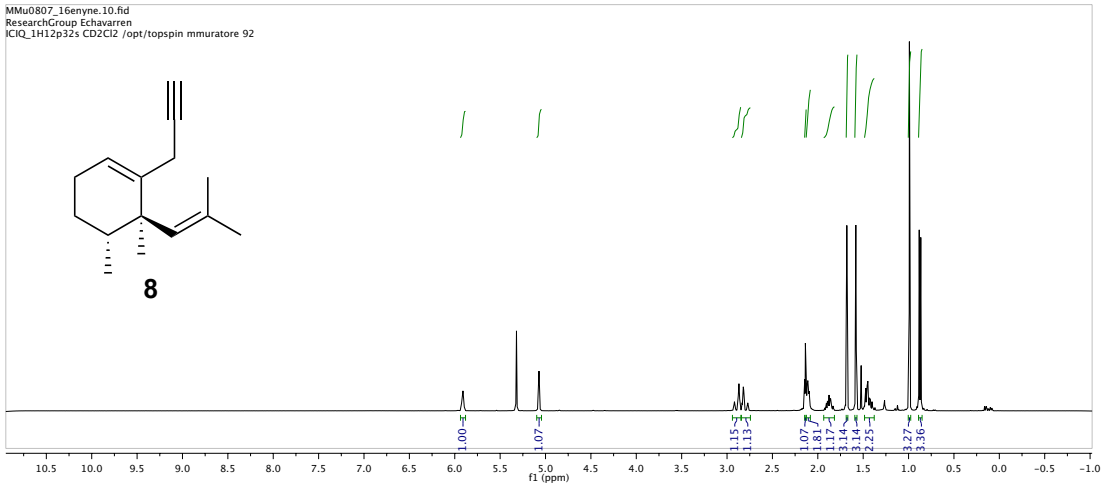
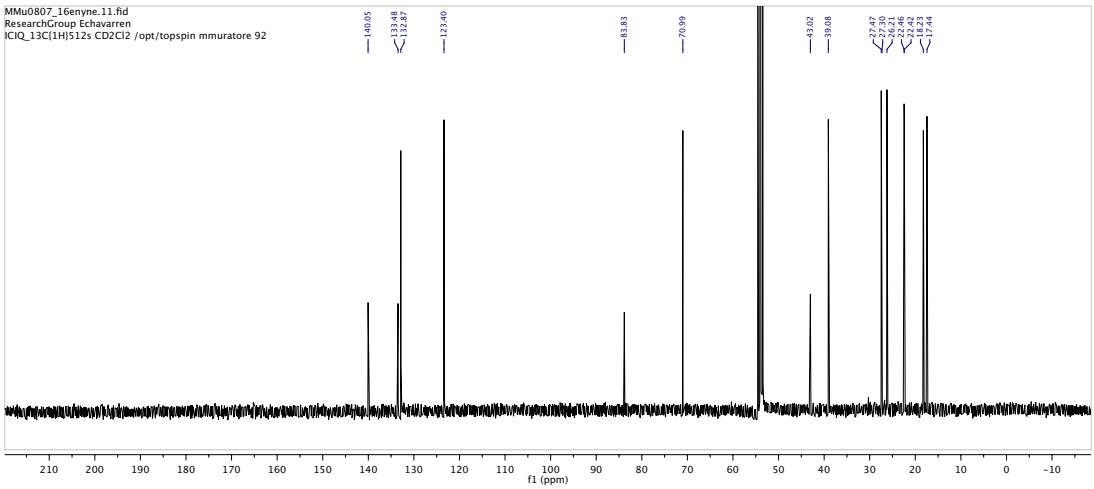
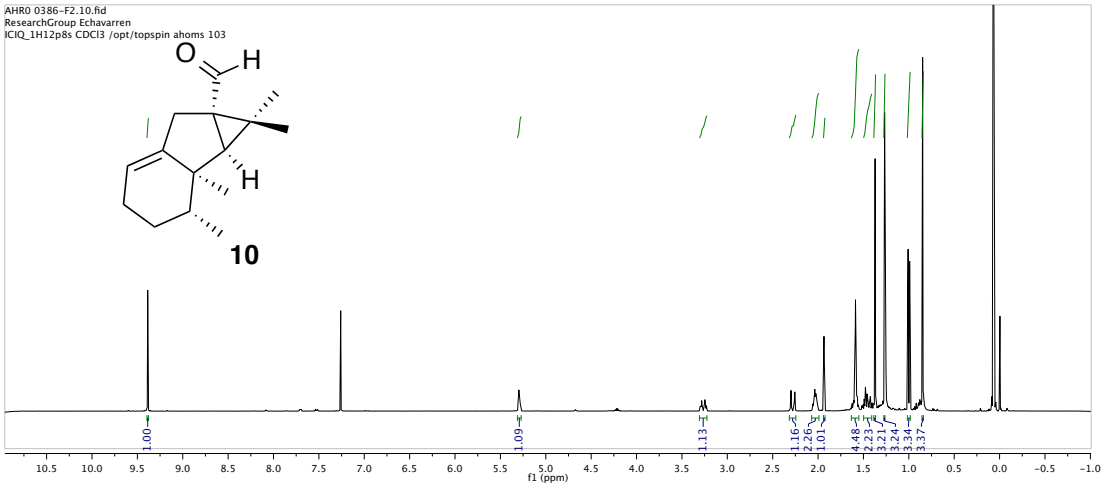
17.09
16.70
f1 (ppm)

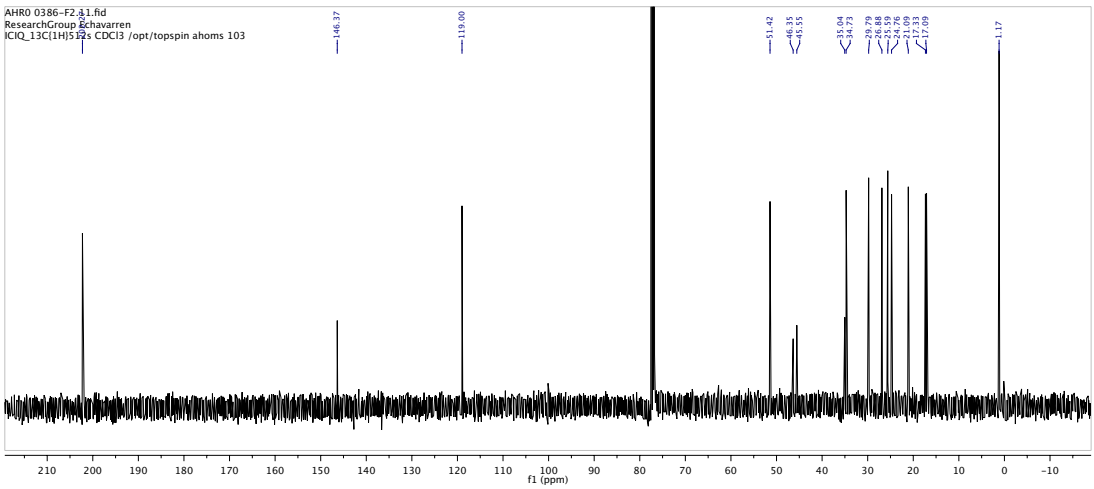

O
O
Nardoaristolone B
1.00
2.28
1.14
1.09
1.13
3.83
3.39
3.36
3.58
f1 (ppm)


201.3
199.7
164.9
123.3
44.1
42.1
42.0
40.0
35.3
31.9
28.6
20.6
17.6
15.6
f1 (ppm)

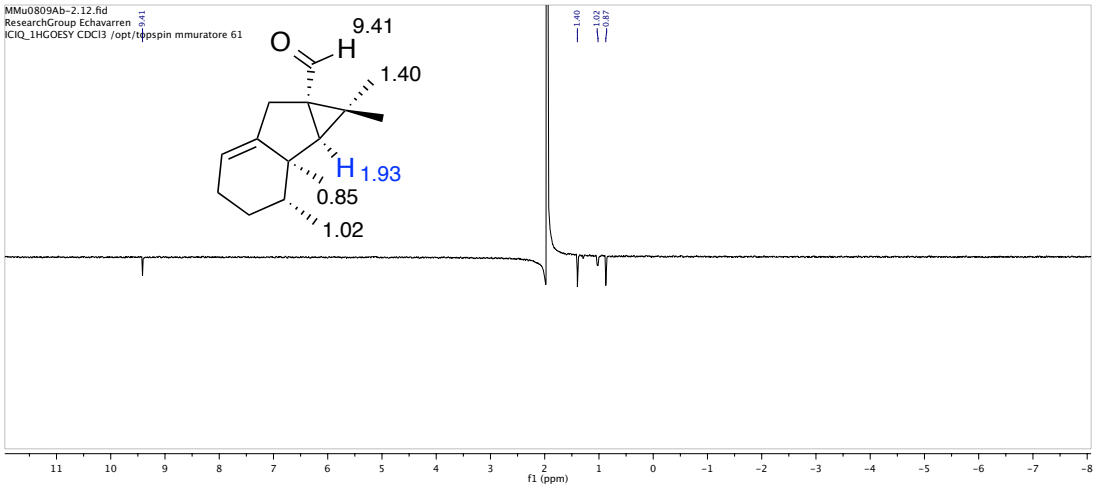

MMu0807_16enyne.10.fid
ResearchGroup Echavarren
ICIQ_1H12p32s CD2Cl2 /opt/topspin mmuratore 92
8
1.00
1.07
1.15
1.13
1.07
1.81
1.17
3.14
3.14
2.25
3.27
3.36
f1 (ppm)


MMu0807_16enyne.11.fid
ResearchGroup Echavarren
ICIQ_13C{1H}512s CD2Cl2 /opt/topspin mmuratore 92
140.05
133.48
132.87
123.40
83.83
70.99
43.02
39.08
27.47
27.30
26.21
25.46
22.42
18.23
17.44
f1 (ppm)

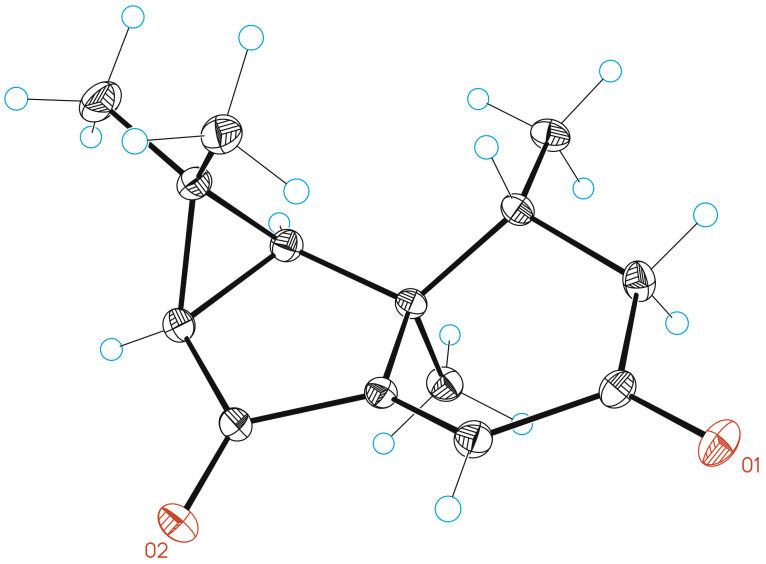

AHR0 0386-F2.10.fid
ResearchGroup Echavarren
ICIQ_1H12p8s CDCl3 /opt/topspin ahoms 103
O
H
H
10
1.00
1.09
1.13
1.16
2.26
1.01
4.48
2.23
3.21
3.24
3.34
3.37
f1 (ppm)


AHR0 0386-F2.11.fid
ResearchGroup Echavarren
ICIQ_13C{1H}512s CDCl3 /opt/topspin ahoms 103
152.21
146.37
119.00
51.42
46.35
45.55
35.04
34.73
29.79
26.88
25.59
24.76
21.09
17.33
17.09
1.17
f1 (ppm)

GOESY (irradiation at 1.93 ppm)



5. X-Ray

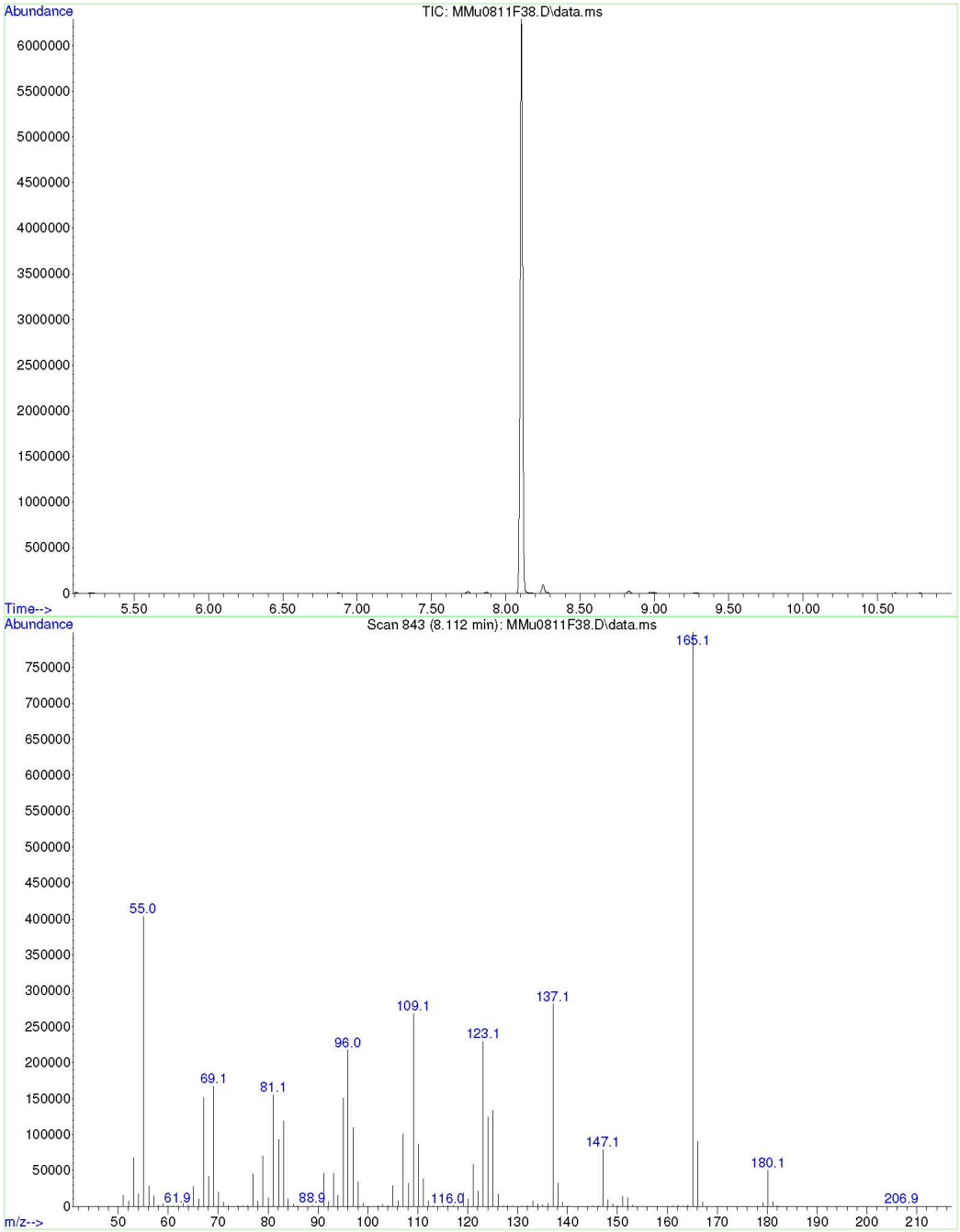


Identification code	mo_MMuNardo_0m	
Empirical formula	C14 H18 O2	
Formula weight	218.28	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.0591(4)Å	α = 90°.
	b = 9.6081(5)Å	β = 90°.
	c = 15.5767(8)Å	γ = 90°.
Volume	1206.15(11) $Å^3$	
Z	4	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	472	
Crystal size	0.40 x 0.15 x 0.15 mm^3	
Theta range for data collection	2.491 to 43.527°.	
Index ranges	-14<=h<=9,-18<=k<=11,-23<=l<=29	
Reflections collected	29745	
Independent reflections	7025[R(int) = 0.0261]	
Completeness to theta =43.527°	82.5%	
Absorption correction	Empirical	
Max. and min. transmission	0.988 and 0.834	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7025/ 0/ 149
Goodness-of-fit on F^2	1.102
Final R indices [I>2sigma(I)]	R1 = 0.0331, wR2 = 0.0893
R indices (all data)	R1 = 0.0355, wR2 = 0.0915
Flack parameter	x =-0.30(18)
Largest diff. peak and hole	0.334 and -0.378 e.$Å^{-3}$

MS for compound 3

```
File       :D:\MassHunter\GCMS\1\data\Echavarren\Michael\MMu0811F38.D
Operator   : GCMS5977A\admin
Acquired   : 27 Oct 2014  18:15     using AcqMethod Michael60-210_50-350-11min.M
Instrument :    GCMS5977A
Sample Name: MMu0811F38
Misc Info  :
Vial Number: 42
```



MS for compound 4

```
File       :D:\MassHunter\GCMS\1\data\Echavarren\Michael\MMu0814col.D
Operator   : GCMS5977A\admin
Acquired   : 07 Dec 2014  11:58     using AcqMethod Michael60-210_50-350-11min.M
Instrument :    GCMS5977A
Sample Name: MMu0814col
Misc Info  :
Vial Number: 4
```