# Progress toward the Total Synthesis of Frondosin C

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*Supporting Information*

**General Experimental.**

$^{1}H$ and $^{13}C$ NMR spectra were obtained using a Varian INOVA NMR 500 MHz spectrometer. Chemical shifts are reported in units of parts per million (ppm), relative to tetramethylsilane at $\delta = 0.00$ ppm. Coupling constants *J* are reported in hertz (Hz).

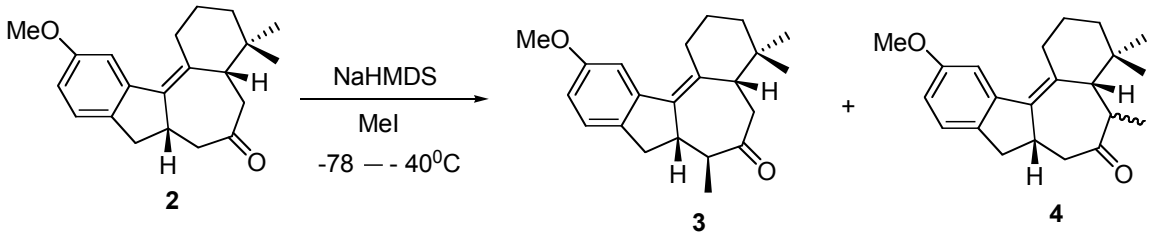
Infrared spectra were recorded on a Pelkin Elmer 1600 series FT-IR and reported in $cm^{-1}$. Melting points were observed using a Melt-Temp in an open Pyrex capillary tube and are uncorrected. High resolution mass spectra were analyzed by the Mass Spectrometry Laboratory at the University of Illinois, Urbana Champaign, Illinois.

All microwave experiments were conducted in a CEM Focused Microwave™ Synthesis System, Model Discover microwave oven, equipped with an infrared temperature control system. All microwave reactions were performed in sealed 10 mL microwave vials.

THF was freshly distilled under $N_2$ from dark blue solutions of sodium benzophenone ketyl. PhOEt (Phenetole), $CH_2Cl_2$, TMSCl, and $Et_3N$ were freshly distilled from calcium hydride. Bulk solvents were purchased from Fisher or VWR.

All starting reagents were purchased from Aldrich, Acros or Strem. The concentrations of solutions of *n*-BuLi were determined by titrations with *sec*-butyl alcohol using 1,10-phenantroline as the indicator following the method of Watson and Eastham.[1] All glassware was flame-dried under an inert atmosphere and all reactions were performed under an atmosphere of dry argon or nitrogen.

**Preparative Procedures.**




**(4a*S**,7*S**,7a*S**)-11-Methoxy-4,4,7-trimethyl-1,2,3,4,4a,5,7a,8-octahydro-7*H*-dibenzo[*a*,*h*]azulen-6-one 3.**
**(4a*S**,7a*S**)-11-Methoxy-4,4,5-trimethyl-1,2,3,4,4a,5,7a,8-octahydro-7*H*-dibenzo[*a*,*h*]azulen-6-one 4.**

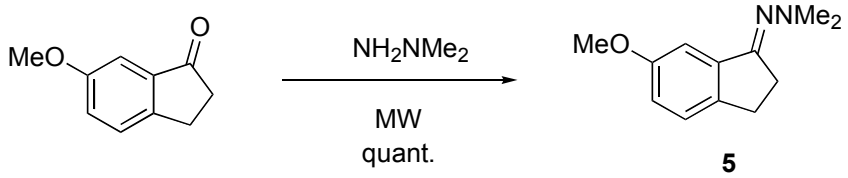
To a solution of **2** (20 mg, 0.065 mmol) in 2mL THF at –78$^0$C was added NaHMDS (1.0M in THF, 97 μL, 0.097 mmol). The resulting solution was stirred at this temperature for 20 min, then at –40 $^0$C for 30 min. To this was then added MeI (18 mg, 0.13 mmol) and stirring of the reaction mixture was continued for 30 min at -40 $^0$C. The reaction was quenched by the addition saturated aq. $NH_4Cl$ solution, the aqueous solution was diluted with ether and the layers were separated. The aqueous layer was extracted twice with diethyl ether and the combined ethereal layers were washed successively with water and brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The

[1] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem*. **1967**, *9*, 165-168.

product was purified by column chromatography (5% EtOAc in hexane) to give two unseparable regioisomers as a yellow oil (14.7 mg, 70% yield, **3**:**4**=2.4:1 ratio).

Compound **3**. IR (neat): 2933, 1698, 1601, 1485, 1240, 1040, 807, 737 $cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 500 MHz) δ 7.15 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 2.5, 1H), 6.75 (dd, J = 8.5, 2.5 Hz, 1H), 3.80 (s, 3H), 3.28-3.23 (m, 1H), 3.14-3.09 (q, J = 16, 8.0 Hz, 1H), 2.90 (dd, J = 14.5, 5.5 Hz, 1H), 2.80-2.71 (m, 3H), 2.62 (dd, J = 15, 5.0 Hz, 1H), 2.55 (q, J = 14.5, 9.5 Hz, 1H), 2.42-2.37 (m, 1H), 1.67-1.62 (m, 2H), 1.51-1.46 (m, 1H), 1.40-1.33 (m, 1H), 1.26 (d, J = 7.0 Hz, 3H), 1.04 (s, 3H), 0.92 (s, 3H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 214.5, 158.3, 142.4, 139.7, 137.6, 136.6, 125.2, 112.6, 111.4, 55.5, 53.0, 48.0, 47.3, 42.3, 37.3, 37.3, 33.9, 29.2, 28.8, 25.7, 21.4, 15.7; HRMS (EI) calcd for $C_{22}H_{28}O_2$ ($M^+$) *m/z* 324.2089, found 324.2085.

Compound **4.** $^{1}$HNMR ($CDCl_3$, 500 MHz) δ 7.15 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 2.5, 1H), 6.75 (dd, J = 8.5, 2.5 Hz, 1H), 3.81(s, 3H), 3.38-3.34 (m, 1H), 3.14-3.09 (m, 1H), 2.90 (dd, J = 14.5, 5.5 Hz, 1H), 2.80-2.68 (m, 3H), 2.63-2.50 (m, 2H), 2.42-2.37 (m, 1H), 1.67-1.62 (m, 2H), 1.51-1.46 (m, 1H), 1.40-1.33 (m, 1H), 1.34 (d, J = 7.0 Hz, 3H), 1.04 (s, 3H), 0.94 (s, 3H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 214.5, 158.4, 144.0, 137.1, 136.6, 133.9, 124.9, 112.4, 112.1, 57.3, 55.6, 48.1, 47.9, 42.5, 41.6, 39.5, 36.8, 32.8, 30.4, 24.2, 23.5, 18.9.

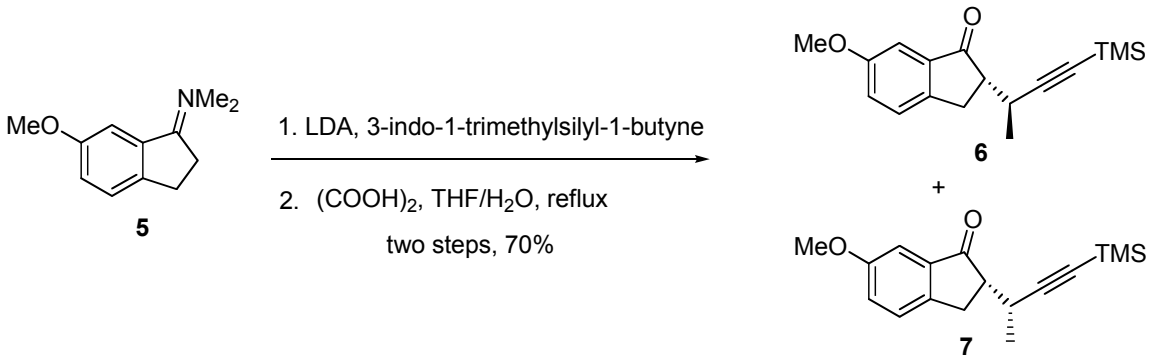



**5**

***N*-(6-methoxyindan)-1-ylidene-*N*,*N*-dimethylhydrazine 5.**

6-Methoxy-1-indanone (.500 g, 3.08 mmol) and N,N-dimethylhydrazine (1.5 mL) were placed in a sealed reaction vial equipped with a magnetic stir bar and heated under microwave irradiation at 140°C for 20 minutes. The reaction mixture was then concentrated under reduced pressure to remove excess *N,N*-dimethylhydrazine to yield 0.630 g of the crude hydrazone (quant.) as a yellow oil which was used without purification for the subsequent step. IR (neat): 3402, 2953, 2856, 1710, 1608, 1229, 1028, 975, 834, 748 $cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J = 2.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 6.95 (dd, J = 8.5, 2.5 Hz, 1H), 3.83 (s, 3H), 2.97-2.96 (m, 2H), 2.93-2.90

(m, 2H), 2.65 (s, 6H); $^{13}$CNMR ($CDCl_3$, 125MHz) δ 169.4, 159.1, 140.9, 129.2, 126.0, 119.5, 104.3, 55.6, 47.0, 47.0, 29.5, 28.0; HRMS (EI) calcd for $C_{12}H_{16}N_2O$ ($M^+$) *m/z* 204.1263, found 204.1265.

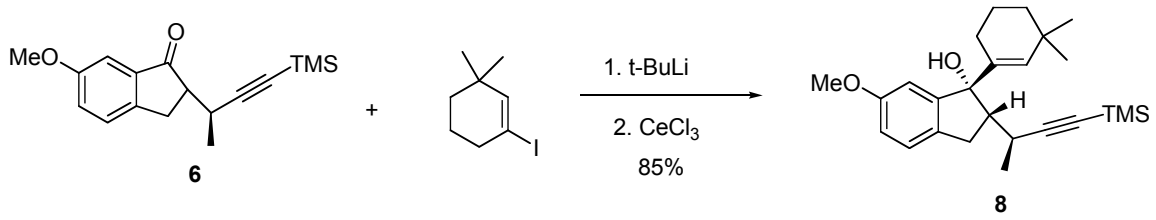



**(2*S**)-6-methoxy-2-[(*R**)-1-methyl-3-trimethylsilyl-2-propynyl]indan-1-one and (2*S**)-6-methoxy-2-[(*S**)-1-methyl-3-trimethylsilyl-2-propynyl]indan-1-one 6 and 7**. To a solution of diisopropylamine (1.70g, 16.8 mmol) in 100 mL of THF 0°C was added *n*-BuLi (1.6M in hexane, 10.1 mL, 16.1 mmol) and the resulting mixture was stirred at 0°C for 1 h and then cooled to –40°C. A solution of hydrazone **5** (2.86 g, 14.0 mmol) in THF (20 mL), which had been dried over activated molecular sieves for 15 min was then added in a dropwise fashion *via* teflon cannula and the reaction mixture was allowed to stir at -40°C for three hours. A solution of 3-iodo-1-trimethyl-silyl-1-butyne (5.29 g, 21.0 mmol) in THF (15 mL), which had been dried over activated molecular sieves for 15 min was added to the reaction vessel in a dropwise fashion *via* teflon cannula. The reaction mixture was allowed to stir at -40°C overnight. The reaction was quenched with water (3 mL) and the mixture was concentrated under reduced pressure. The residue was then dissolved in diethyl ether (100 mL) and the solution was washed successively with water (2 x 50 mL) and brine (2 x 50) and dried over $MgSO_4$. Filtration and solvent evaporation under reduced pressure afforded the crude product which was passed through a short column of silica gel eluting with 5% EtOAc/hexanes to remove the most polar impurities. The product thus obtained was then mixed with THF (50 mL) and aqueous oxalic acid solution (4.55 g in 25 mL $H_2O$, 50.5 mmol), and the resulting heterogeneous mixture was heated at reflux for 6 hours. The solvents were then removed under reduced pressure and the aqueous solution was extracted with ether (2 x 100 mL). The combined

organic layers were then washed successively with water and brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The product was purified by column chromatography (2% to 5% EtOAc in hexane) to give two separable diastereomers **6** and **7** in a 1.5:1 ratio as a yellow amorphous solid (2.80 g, 70% yield).

**isomer 6** (more polar):[2] IR (neat): 2960, 1702, 1492, 1276, 1162, 1026, 841, 759 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 500 MHz) δ 7.38(d, J = 8.0 Hz, 1H), 7.20-7.18 (m, 2H), 3.83 (s, 3H), 3.28-3.23 (m, 1H), 3.13-3.11 (m, 2H), 2.68-2.65 (m, 1H), 1.33(d, J = 7.0 Hz, 3H), -0.14 (s, 9H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 206.7, 159.1, 147.3, 137.9, 126.8, 124.0, 106.9, 104.7, 85.8, 55.3, 52.3, 28.5, 28.3, 19.7, -0.4; HRMS (EI) calcd for $C_{17}H_{22}O_2Si$ ($M^+$) *m/z* 286.1389, found 286.1384.

**isomer 7** (less polar):[2] IR (neat): 2959, 1711, 1616, 1492, 1277, 1163, 1029, 843, 760; $^1$HNMR ($CDCl_3$, 500 MHz) δ 7.38 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0, 2.0 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 3.83 (s, 3H), 3.26-3.18 (m, 2H), 3.04-2.96 (m, 2H), 1.06 (d, 7.0 Hz, 3H), 0.10 (s, 9H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 206.4, 159.4, 147.1, 138.5, 127.2, 124.3, 109.3, 104.8, 85.1, 55.6, 51.5, 28.7, 27.7, 15.7, 0.04.

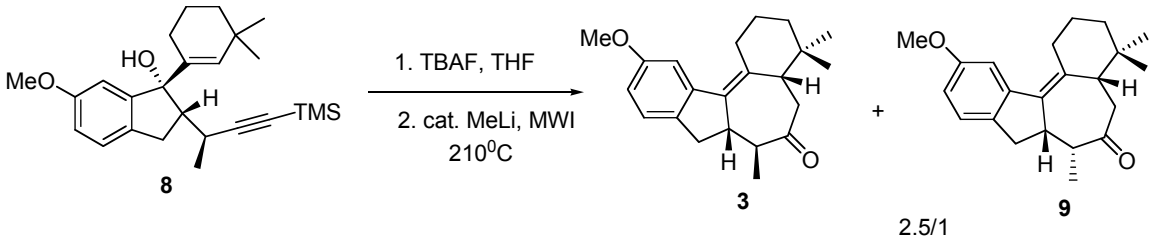



**(1*S**,2*S**)-2,3-dihydro-6-methoxy-1-(3,3-dimethylcyclohex-1-enyl)-2-((*S**)-1-methyl-3-trimethylsilyl-2-propynyl)-1*H*-inden-1-ol 8.**

*t*-BuLi (1.27M in pentane, 6.86 mL, 5.40 mmol) was added dropwise to a solution of 1-iodo-3,3-dimethylcyclohexene (0.700 g, 2.96 mmol) in $Et_2O$ (10 mL) at –78 $^0$C. The resulting solution was first stirred at –78 $^0$C for 30 min, then at 0 $^0$C for additional 15 min to destroy excess *t*-BuLi and finally re-cooled to –78 °C. In a separate flask, a slurry of anhydrous $CeCl_3$ (740 mg, 3.00 mmol) in THF (20 mL) was stirred for 1h at room temperature and then cooled to –78°C. To the slurry at –78°C was then rapidly added the vinyllithium solution via cannula and the resulting solution was stirred for one hour at

[2] The stereochemical configurations of the propargyl carbons in compounds **6** and **7** and could not be determined with certainty and are drawn in random.

this temperature. A solution of ketone **6** (286 mg, 0.998 mmol) in THF (5 mL) was then added via cannula to the resulting vinylcerium species dropwise at –78 $^0$C. The resulting solution was stirred for 2 hours at –78 $^0$C followed by the addition of water (2 mL) to quench the reaction. The solvents were then evaporated under reduced pressure, the residue was diluted with ether and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic extracts were washed with saturated aq. $NH_4Cl$ solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (5% EtOAc in hexane) to give compound **8** as a pale yellow oil (337 mg, 85%). IR (neat): 3525, 2954, 1708, 1612, 1488, 1248, 1033, 842, 655 cm$^{-1}$; $^1$HNMR ($CDCl_3$, 500 MHz) δ 7.15 (d, J = 8.5 Hz, 1H), 6.81 (dd, J = 8.5, 2.5 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 5.78 (s, 1H), 3.76 (s, 3H), 3.04-2.90 (m, 3H), 2.51 (dd, J = 15, 8.5 Hz, 1H), 1.88-1.83 (m, 1H), 1.63-1.46 (m, 5H), 1.41-1.35 (m, 1H), 1.26 (d, J = 7.0 Hz, 3H), 1.06 (s, 3H), 1.02 (s, 3H), 0.10 (s, 9H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 159.0, 148.8, 136.8, 135.0, 132.5, 125.3, 114.7, 111.0, 107.8, 85.6, 85.5, 55.3, 51.4, 37.3, 33.6, 31.8, 30.4, 30.1, 26.8, 26.2, 20.2, 19.8, 0.1; HRMS (EI) calcd for $C_{25}H_{36}O_2Si$ ($M^+$) *m/z* 396.2485, found 396.2479.



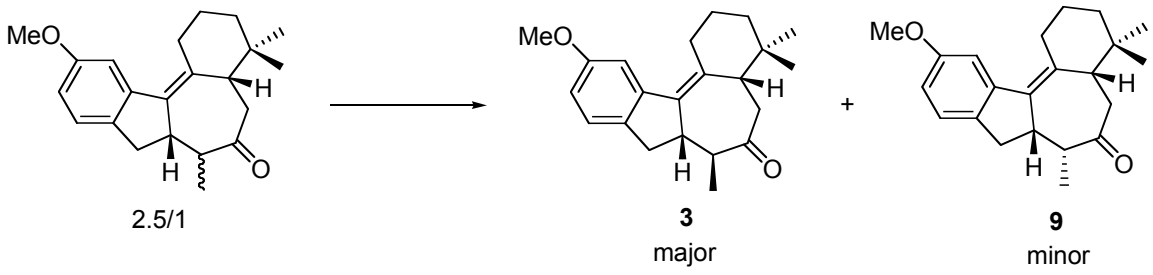

**(4a*S**,7*S**,7a*S**)-11-Methoxy-4,4,7-trimethyl-1,2,3,4,4a,5,7a,8-octahydro-7*H*-dibenzo[*a*,*h*]azulen-6-one 3 and (4a*S**,7*R**,7a*S**)-11-Methoxy-4,4,7-trimethyl-1,2,3,4,4a,5,7a,8-octahydro-7*H*-dibenzo[*a*,*h*]azulen-6-one 9.**

To a solution of **8** (337 mg, 0.85 mmol) in THF (10 mL) was added TBAF (1.0M in THF, 1.28 mL, 1.28 mmol) at room temperature and the resulting solution was stirred for 30 min. Water (3 mL) was added to quench the reaction, the layers were separated and the aqueous solution was extracted with ether (2 x 30 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under

reduced pressure. The crude product was transferred to a 10 mL flame dried microwave vial with anhydrous phenetole (1 mL). A ca. 10 mol% MeLi in $Et_2O$ was added and the solution was heated at 210 $^0$C for 45 min in the microwave oven. The product was purified by column chromatography (10% EtOAc in hexane) to give two unseparable compounds **3** and **9** as a yellow amorphous solid (207 mg, 75%).

Compound **3**: IR (neat): 2933, 1698, 1601, 1485, 1240, 1040, 807, 737 cm$^{-1}$; $^1$HNMR ($CDCl_3$, 500 MHz) δ 7.15 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 2.5, 1H), 6.75 (dd, J = 8.5, 2.5 Hz, 1H), 3.80 (s, 3H), 3.28-3.23 (m, 1H), 3.14-3.09 (q, J = 16, 8.0 Hz, 1H), 2.90 (dd, J = 14.5, 5.5 Hz, 1H), 2.80-2.71 (m, 3H), 2.62 (dd, J = 15, 5.0 Hz, 1H), 2.55 (q, J = 14.5, 9.5 Hz, 1H), 2.42-2.37 (m, 1H), 1.67-1.62 (m, 2H), 1.51-1.46 (m, 1H), 1.40-1.33 (m, 1H), 1.26 (d, J = 7.0 Hz, 3H), 1.04 (s, 3H), 0.92 (s, 3H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 214.5, 158.3, 142.4, 139.7, 137.6, 136.6, 125.2, 112.6, 111.4, 55.5, 53.0, 48.0, 47.3, 42.3, 37.3, 37.3, 33.9, 29.2, 28.8, 25.7, 21.4, 15.7; HRMS (EI) calcd for $C_{22}H_{28}O_2$ ($M^+$) *m/z* 324.2089, found 324.2085.

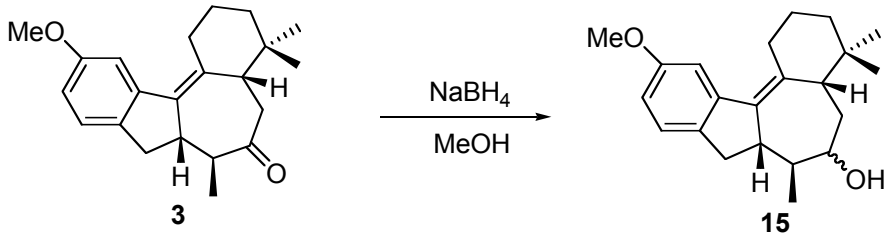
Compound **9**: $^1$HNMR ($CDCl_3$, 500 MHz) δ 7.19 (d, J = 2.5 Hz, 1H), 7.14 (d, J = 8.5, 1H), 6.75-6.73 (m, 1H), 3.82 (s, 3H), 3.51-3.47 (m, 1H), 3.28-3.23 (m, 1H), 3.14-3.09 (m, 1H), 2.80-2.68 (m, 3H), 2.63-2.50 (m, 2H), 2.42-2.37 (m, 1H), 1.67-1.62 (m, 2H), 1.51-1.46 (m, 1H), 1.40-1.33 (m, 1H), 1.01 (s, 3H), 0.98 (s, 3H), 0.76 (d, J = 7.0 Hz, 3H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 214.5, 158.4, 142.8, 138.5, 137.7, 137.6, 124.9, 112.2, 110.8, 55.5, 53.0, 47.2, 43.0, 42.4, 37.3, 35.3, 34.8, 33.2, 30.3, 26.1, 24.9, 19.3.




To a mixture of **3** and **9** (20 mg, 0.062 mmol) in dry THF (3 mL) was added KHMDS (0.5M in toluene, 0.160 μL, 0.080 mmol) at room temperature and the resulting solution was stirred for 30 min. Then the solution was cooled down to -78$^0$C and 0.05 mL AcOH (dissolved in 0.5 mL THF) was then added to the quench the reaction. The solvents were

evaporated under reduced pressure and the residue was diluted with diethyl ether. The ethereal solution was washed with saturated aq. $NH_4Cl$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give two isomers **3** and **9** in a ratio of 10.3:1 (quantitative yield).

To a mixture of **3** and **9** (20mg, 0.062mmol) in dry $^t$BuOH (3 mL) was added $^t$BuOK (14 mg, 0.13mmol) and the resulting solution was heated to reflux for 3.5h. Saturated aq. $NH_4Cl$ solution (1 mL) was then added to quench the reaction, the solvent was evaporated under reduced pressure and the residue was taken up in water and diethyl ether. The layers were separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined ethereal extracts were washed with saturated aq. $NH_4Cl$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give two isomers **3** and **9** in a ratio of 14.6:1 (quantitative yield).

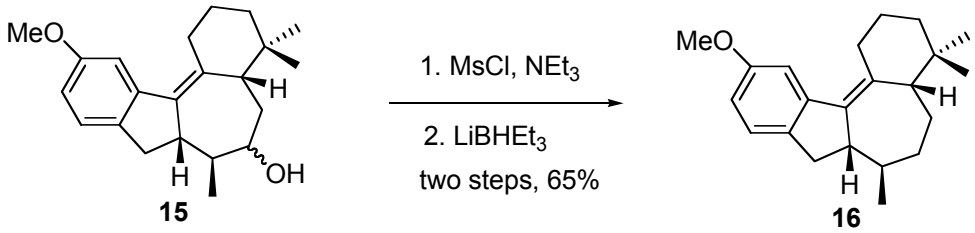



**(4a*S**,7*S**,7a*S**)-11-Methoxy-4,4,7-trimethyl-1,2,3,4,4a,5,6,7,7a,8-decahydro-dibenzo[*a*,*h*]azulen-6-ol 15.**

To a solution of compound **3** (101 mg, 0.311 mmol) in MeOH (5 mL), was added $NaBH_4$ (24.0 mg, 0.634 mmol) at $0^0$C. After 30 min, water (1 mL) was added to quench the reaction. Most of the methanol was then evaporated under reduced pressure, the residue was diluted with water (5 mL) and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic extracts were washed with saturated aq. $NH_4Cl$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc in hexane) to give two separable isomers **15** as a colorless oil (99 mg, overall 98%).

**15** (less polar): IR (neat) 3392, 2932, 1601, 1481, 1294, 1157, 1038, 733 $cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 500 MHz) δ 7.14-7.12 (m, 2H), 6.74 (dd, J = 8.5, 2.5 Hz, 1H), 3.81(s, 3H), 3.44 (dd, J = 12.5, 7.5 Hz, 1H), 3.12-3.07 (m, 3H), 2.77 (d, J = 16.0 Hz, 1H), 2.52-2.45 (m, 1H), 2.39 (d, J =10.5, 1H), 2.10-2.05(m, 1 H), 1.76-1.65 (m, 3H), 1.49-1.41 (m, 2H), 1.32-1.25 (m, 2H), 1.12 (d, J = 7.0 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H); $^{13}$CNMR($CDCl_3$, 125 MHz): δ 158.3, 141.7, 139.6, 138.9, 138.3, 125.3, 112.1, 111.1, 78.5, 55.5, 46.3, 46.0, 42.6, 35.4, 34.7, 34.2, 32.1, 30.0, 26.6, 25.2, 19.5, 17.6.

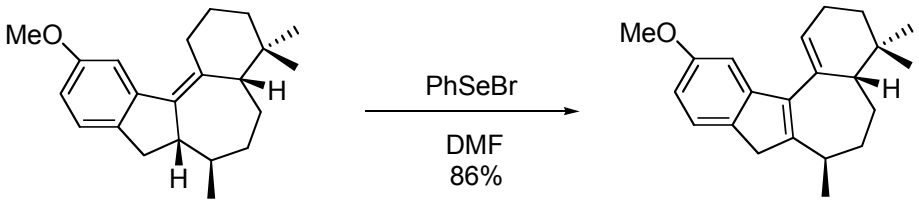
**15** (more polar): IR (neat) 3390, 2934, 1600, 1479, 1246, 1035, 732 $cm^{-1}$; $^{1}$HNMR ($CDCl_3$, 500 MHz) δ 7.15-7.13 (m, 2H), 6.73 (dd, J = 8.5, 2.5 Hz, 1H), 3.81(s, 3H), 3.56-3.52 (m, 1H), 3.22 (q, J=16, 8.5 Hz, 1H), 3.05-3.00 (m, 2H), 2.57 (dd, J = 16.5, 2.5 Hz, 1H), 2.47-2.43 (m, 1H), 2.40-2.33 (m, 1 H), 1.77-1.69 (m, 1H), 1.67-1.63 (m, 3H), 1.60-1.51 (m, 2H), 1.28-1.24(m, 2H), 1.05 (d, J = 7.0 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H); $^{13}$CNMR($CDCl_3$, 125 MHz): δ 158.4, 141.9, 139.0, 138.4, 134.5, 125.6, 112.0, 110.9, 72.1, 55.5, 46.6, 45.9, 41.2, 37.5, 33.9, 32.2, 30.4, 29.4, 27.8, 26.4, 20.3,13.3.




**(4a*S**,7*R**,7a*S**)-11-Methoxy-4,4,7-trimethyl-1,2,3,4,4a,5,6,7,7a,8-decahydro-dibenzo[*a*,*h*]azulene 16.**

To a 0°C solution of **15** (mixture of two isomers, 99 mg, 0.31mmol) in $CH_2Cl_2$ (10 mL) was added $NEt_3$ (157 mg, 1.55 mmol) followed by MsCl (13.5 mg, 0.930 mmol). After 1h at $0^0$C, the solution was filtered through Celite and the solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL), the aqueous layer was extracted with ether (3 x 20 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mesylate was dissolved in THF (10 mL), $LiHBEt_3$ (1.0M in THF, 2.48 mL, 2.48 mmol) was added, the solution was heated at reflux overnight. The reaction mixture was then poured into saturated aq. $NaHCO_3$ solution and the aqueous layer was extracted with

ether (30 mL x 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (2% EtOAc in hexane) to give compound **16** as a colorless oil (59.6 mg, 65% yield two steps). IR (neat): 2924, 1601, 1479, 1260, 1097, 780 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 500 MHz) δ 7.18 (d, J = 2.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 3.82 (s, 3H), 3.13 (q, J = 16, 8.5 Hz, 1H), 3.01-2.89 (m, 2H), 2.54 (dd, J = 16, 3.0 Hz, 1H), 2.47-2.36 (m, 2H), 1.68-1.64 (m, 3H), 1.50-1.46 (m, 3H), 1.26-1.22 (m, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H); $^{13}$CNMR($CDCl_3$, 125 MHz): δ 158.3, 142.6, 139.5, 139.0, 135.5, 125.4, 111.7, 111.0, 55.5, 49.2, 49.1, 37.0, 35.0, 34.9, 32.7, 30.3, 29.8, 27.4, 27.0, 22.1, 20.6, 19.5; HRMS (EI) calcd for $C_{22}H_{30}O$ ($M^+$) *m/z* 310.2297, found 310.2298.

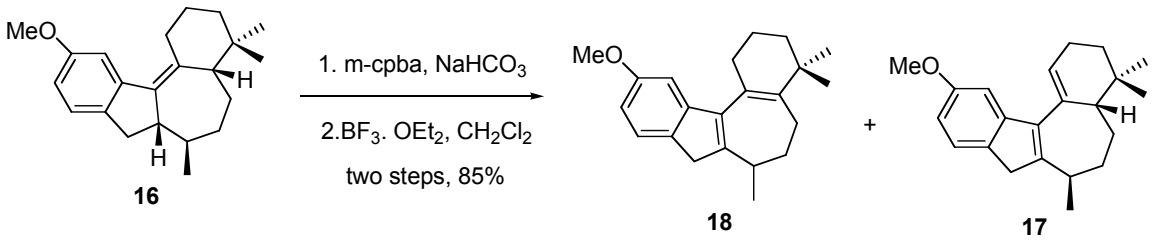



**16** **17**

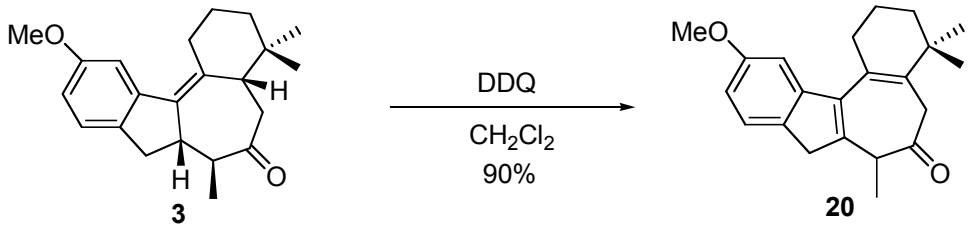
**(4a*S*,7R**)-11-Methoxy-4,4,7-trimethyl-2,3,4,4a,5,6,7,8-octahydro-dibenzo[*a*,*h*]azulene 17.**

To a solution of **16** (20.0 mg, 0.0645 mmol) in DMF (1 mL) was added PhSeBr (38.0 mg 0.161 mmol) and the resulting solution was stirred at room temperature overnight. The reaction mixture was then filtered through Celite, eluting with diethyl ether, and the filtrate was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (2% EtOAc in hexanes) to give compound **17** as a colorless oil (17.2 mg, 86% yield). IR (neat): 2930, 1617, 1475, 1264, 1105, 1037, 739 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 500 MHz): δ 7.26 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 2.5 Hz, 1H), 6.68 (dd, J = 8.0, 2.5 Hz, 1H), 5.92 (t, J = 3.5 Hz, 1H), 3.82 (s, 3H), 3.43 (d, J = 23 Hz, 1H), 3.18 (d, J = 23 Hz, 1H), 2.86-2.84 (m, 1H), 2.22 (d, J=4.5 Hz, 1H), 2.37-2.31 (m, 1H), 2.22-2.15 (m, 1H), 2.00-1.94 (m, 2H), 1.90-1.88 (m, 1H), 1.67-1.61 (m, 2H), 1.47-1.38(m, 1H), 1.24 (d, J = 7.0 Hz, 3H), 0.97 (s, 3H), 0.91 (s, 3H); $^{13}$CNMR($CDCl_3$, 125 MHz): δ 158.6, 150.1, 147.5, 140.0, 135.0, 134.3, 124.1,

123.6, 108.2, 106.4, 55.5, 48.3, 39.7, 34.6, 32.1, 31.7, 29.3, 27.9, 27.9, 26.9, 23.5, 19.0; HRMS (EI) calcd for $C_{22}H_{28}O$ ($M^+$) *m/z* 308.2140, found 308.2137.



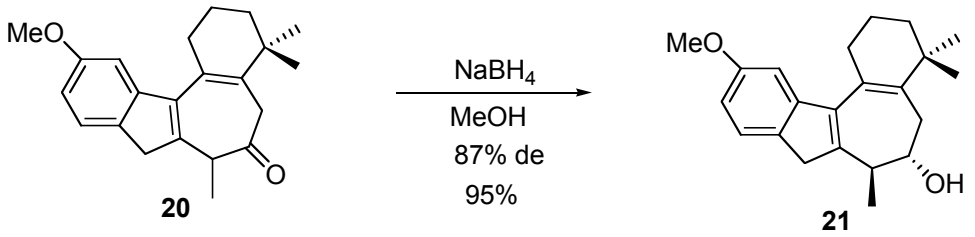

To a 0°C solution of **16** (30.1 mg, 0.0969 mmol) in $CH_2Cl_2$ (3 mL) was added $NaHCO_3$ (24.4 mg, 0.290 mmol) followed by *m*-CPBA (25.0 mg, 0.145 mmol), the resulting solution was stirred at 0°C for 30 min. The solution was then diluted with ether, washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The unstable crude epoxide product was immediately dissolved in dry $CH_2Cl_2$ (3 mL) and the solution was treated with $BF_3{\cdot}OEt_2$ (27.5 mg, 0.194 mmol) at room temperature. After stirring the mixture for 5 minutes, saturated aq. $NaHCO_3$ solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (2% EtOAc in hexane) to give compound **18** and **17** as a colorless oil (25.4 mg, 85% overall yield, the ratio is: **18**/**17**=2.3/1).




**11-Methoxy-4,4,7-trimethyl-1,2,3,4,5,8-hexahydro-7*H*-dibenzo[*a*,*h*]azulen-6-one 20.** To a solution of compound **3** (80.0 mg, 0.247 mmol) in $CH_2Cl_2$ (4 mL) was added DDQ (84.0 mg, 0.370 mmol) and the mixture was stirred for 30 minutes at $0^0$C. The reaction mixture was then filtered through Celite, eluting with diethyl ether, and the filtrate was

diluted with ether, washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% EtOAc in hexane) to give compound **20** as a colorless oil (71.6 mg, 90% yield). IR (neat): 2934, 1712, 1607, 1286, 1219, 1159, 1036, 858, 795 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 500 MHz) δ 7.33 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 6.74 (dd, J = 8.0, 2.5 Hz, 1H), 3.85 (s, 3H), 3.41-3.32 (m, 2H), 3.22 (br s, 1H), 2.94 (br s, 1H), 2.22 (br s, 2H), 1.73-1.60 (m, 5H), 1.39 (d, J = 6.5 Hz, 3H), 1.11 (s, 3H), 1.08 (s, 3H); $^{13}$CNMR($CDCl_3$, 125 MHz): δ 215.3, 158.7, 145.6, 142.2, 140.4, 139.1, 134.8, 129.8, 124.1, 109.5, 107.2, 55.6, 47.7, 44.8, 39.6, 37.5, 35.7, 29.7, 28.9, 28.2, 19.8, 11.1;

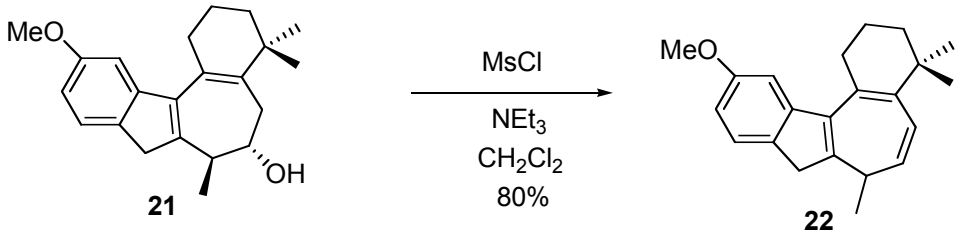
HRMS (EI) calcd for $C_{22}H_{26}O_2$ ($M^+$) *m/z* 322.1933, found 322.1938.




**(6*S**,7*S**)-11-Methoxy-4,4,7-trimethyl-1,2,3,4,5,6,7,8-octahydro-dibenzo[*a*,*h*]azulen-6-ol 21.**

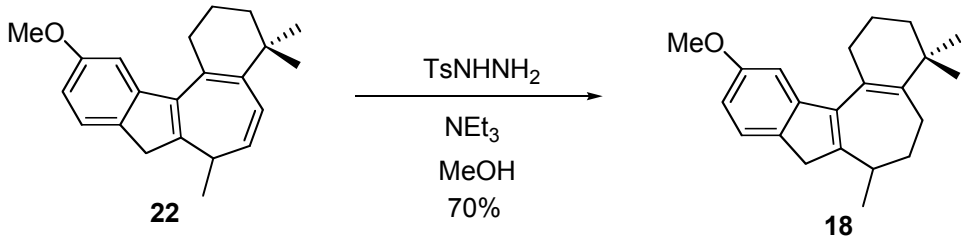
To a solution of compound **20** (50.0 mg, 0155 mmol) in MeOH (4 mL), was added $NaBH_4$ (7.2 mg, 0.190 mmol) at $0^0$C. After 30 min, water (1 mL) was added to quench the reaction. Most of the methanol was then evaporated under reduced pressure, the residue was diluted with water (4 mL) and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic extracts were washed with saturated aq. $NH_4Cl$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc in hexane) to give compound **21** as a colorless oil (47.7 mg, 95% yield, 87% de). IR (neat): 3436, 2930, 1618, 1472, 1285, 1218, 1148, 1037, 988, 792, 734 $cm^{-1}$; $^1$HNMR ($CDCl_3$, 500 MHz): δ 7.31 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 2.5, 1H), 6.70 (dd, J = 8.0, 2.5 Hz, 1H), 5.78 (s, 1H),

3.92-3.89 (m, 1H), 3.83 (s, 3H), 3.46 (d, J = 23 Hz, 1H), 3.38 (d, J = 23 Hz, 1H), 2.52-2.49 (m, 2H), 2.22 (d, J = 4.5 Hz, 1H), 1.76-1.71(m, 2H), 1.67-1.63 (m, 2H), 1.61-1.54 (m, 2H), 1.31(d, J = 7 Hz, 3H), 1.19 (s, 3H), 1.09 (s, 3H); $^{13}$CNMR ($CDCl_3$, 125 MHz) δ 158.5, 148.7, 146.5, 139.8, 135.1, 129.7, 123.9, 123.9, 108.8, 106.9, 86.1, 55.5, 42.1, 39.8, 38.7, 38.7, 36.3, 34.6, 29.1, 28.8, 28.8, 19.9; HRMS (EI) calcd for $C_{22}H_{28}O_2$ ($M^+$) *m/z* 324.2089, found 324.2092.




**11-Methoxy-4,4,7-trimethyl-1,2,3,4,7,8-hexahydro-dibenzo[*a*,*h*]azulene 22.**

To a 0°C solution of **21** (27.0 mg, 0.0833 mmol) in $CH_2Cl_2$ (4 mL) was added $NEt_3$ (42.5 mg, 0.420 mmol) followed by MsCl (28.6 mg, 0.25 mmol). After 1h at $0^0$C, the solution was filtered through celite and the solvent was evaporated under reduced pressure. The residue was diluted with water (3 mL), the aqueous layer was extracted with ether (2 x 15 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (2% EtOAc in hexane) to afford compound **22** as a pale yellow oil (20 mg, 80%). IR (neat): 2931, 1617, 1470, 1283, 1221, 1148, 1038, 856, 774, 667 $cm^{-1}$; $^1$HNMR($CDCl_3$, 500 MHz): δ 7.27(d, J = 8.5 Hz, 1H), 7.12(d, J = 2.5 Hz, 1H), 6.67 (dd, J = 8.5, 2.5 Hz, 1H), 6.04 (d, J = 9.0 Hz, 1H), 5.40 (brs, 1H), 3.83 (s, 3H), 3.38 (s, 2H), 3.10-3.06 (m, 1H), 2.60-2.53 (m, 2H), 1.84-1.81 (m, 1H), 1.70-1.66 (m, 3H), 1.42-1.40 (m, 3H) 1.27 (s, 3H), 1.11 (s, 3H); $^{13}$CNMR($CDCl_3$, 125 MHz): δ 158.4, 148.4, 146.3, 135.8, 135.0, 132.1, 131.8, 124.5, 123.9, 123.9, 108.5, 107.6, 55.5, 39.8, 34.6, 34.6, 33.2, 31.6, 30.6, 29.8, 29.8, 19.9; HRMS (EI) calcd for $C_{22}H_{26}O$ ($M^+$) *m/z* 306.1984, found 306.1978.




**22** **18**

**11-Methoxy-4,4,7-trimethyl-1,2,3,4,5,6,7,8-octahydro-dibenzo[*a*,*h*]azulene 18.**

To a solution of compound **22** (20.0 mg, 0.0654 mmol) in anhydous MeOH (3 mL) was added $NEt_3$ (0.18 mL, 1.31 mmol) followed by $TsNHNH_2$ (123 mg, 0.66 mmol). The resulting solution was heated at reflux for 16 h, then poured into brine. The aqueous mixture was extracted with ether (2 x 15 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography (1% EtOAc in hexanes) to give compound **18** as a colorless oil (14.0 mg, 70%). IR (neat): 2926, 1617, 1472, 1285, 1143, 1038, 838, 803, 722 $cm^{-1}$; $^1$HNMR($CDCl_3$, 500 MHz): δ 7.33 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.69 (dd, J = 8.0, 2.5 Hz, 1H), 3.84 (s, 3H), 3.44 (d, J = 23 Hz, 1H), 3.36 (d, J = 23 Hz, 1H), 2.73-2.69 (m, 2H), 2.26-2.23 (m, 1H), 2.03-1.99 (m, 2H), 1.91-1.84 (m, 1H), 1.80-1.69 (m, 3H), 1.64-1.59 (m, 2H), 1.20 (d, J = 7.0 Hz, 3H), 1.17 (s, 3H), 1.07 (s, 3H); $^{13}$CNMR($CDCl_3$, 125 MHz): δ 158.5, 151.4, 146.8, 145.5, 139.4, 135.2, 128.4, 123.8, 108.4, 106.4, 55.5, 46.7, 39.7, 37.2, 35.2, 32.0, 30.4, 28.3, 28.3, 26.5, 19.8, 18.2; HRMS (EI) calcd for $C_{22}H_{28}O$ ($M^+$) *m/z* 308.2140, found 308.2147.