# Progress Toward the Total Synthesis of Kalihinane Diterpenoids

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## Material and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether ($Et_2O$) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Methylene chloride ($CH_2Cl_2$), and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 nm) purchased from Bodman. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker Avance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform ($^1H$, $\delta$ 7.26 ppm, $^{13}C$ $\delta$ 77.0 ppm), benzene ($^1H$, $\delta$ 7.30 ppm), dimethyl sulfoxide ($^{13}C$, $\delta$ 40.5 ppm), or methanol ($^{13}C$, $\delta$ 49.9 ppm). Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

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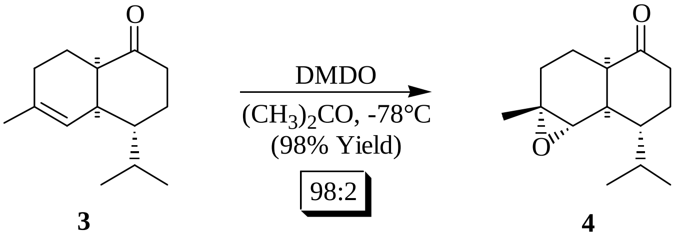
## Preparation of epoxide 4.



**3** **4**

To a 0.09 M solution of dimethyl dioxirane in acetone (145 mL) at –78°C, was added olefin **3** (1.52 g, 7.29 mmol) in acetone (10mL). After 2h, the solution was warmed to 25°C and the solvent was removed in vacuo. The resulting oil was purified by silica gel column chromatography (hexanes:EtOAc, 15:1 then hexanes:EtOAc, 8:1) to give epoxide **4** (1.55 g, 95% yield) as a colorless oil. **$^1$H NMR** (400 MHz, $CDCl_3$) 2.67 (s, 1H), 2.43 (t, *J*=7.1 Hz, 3H), 2.17 (m, 1H), 1.96-1.70 (comp. m, 6H), 1.43 (m, 1H), 1.36-1.22 (comp. m, 4H), 1.03 (d, *J*= 7.0 Hz, 3H), 0.96 (d, *J*=7.0 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 213.3, 64.3, 58.4, 44.7, 42.3, 38.7, 38.4, 28.4, 26.2, 23.9, 23.3, 21.7, 19.5, 19.1; **IR** (thin film/NaCl) 2958 (s), 2872 (s), 1708 (s), 1463 (m), 1420 (m), 1379 (m), 1223 (w), 963 (w),880 (w), 794 (m) cm$^{-1}$; **HRMS** (EI) *m/z* found: 223.1698 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

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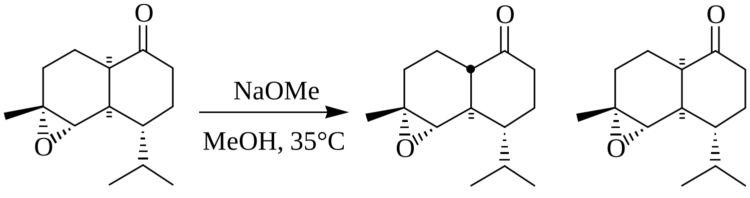
## Preparation of trans-decalin 4A.



**4** **4A** **4**

**3:1**

To a solution of epoxide **4** (4.69 g, 20.9 mmol) in MeOH (50 mL) at 35°C was added NaOMe (60 mg, 1.11 mmol). After 36 h the solution was cooled to 25°C, the volume was reduced in vacuo (ca.10 mL), diluted with $CH_2Cl_2$ (100 mL), and washed with $H_2O$ (2 x 25 mL) and brine (25 mL). After drying ($Na_2SO_4$), concentration in vacuo gave a 3:1 mixture of **4A:4** which could be used without further purification or purified by silica gel chromatography (hexanes:EtOAc, 15:1 then hexanes:EtOAc, 8:1) to afford pure **4A** (3.42 g, 70% yield) as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) 2.98 (s, 1H), 2.40-2.24 (comp. m, 3H), 2.10-1.98 (m, 2H), 1.93 (br t, *J*= 11.9 Hz, 1H), 1.84-1.71 (m, 2H), 1.70-1.46 (m, 3H), 1.31 (s, 3H), 1.29-1.15 (m, 1H), 1.02 (d, *J*=7.0 Hz, 3H), 0.85 (d, *J*=7.0 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 211.7, 61.2, 58.8, 50.4, 44.7, 43.9, 40.5, 29.7, 27.1, 25.1, 23.9, 21.9, 19.3, 15.9; **IR** (thin film/NaCl) 2958 (s), 2874 (s), 1715 (s), 1452 (m), 1424 (m), 1370 (m), 1301 (w), 1019 (w), 888 (m), 791 (m) cm$^{-1}$; **HRMS** (EI) *m/z* found: 223.1698 [calc'd for $C_{14}H_{23}O_2$ (M+H): 223.1698].

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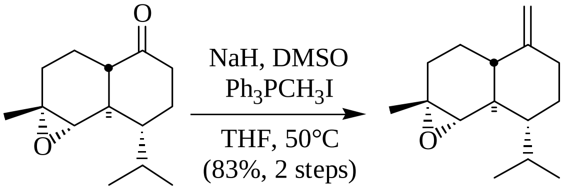
**Preparation of olefin 5.**



**4A:4**
(3:1)

**5**

To a solution of DMSO (16.2 mL) and THF (10 mL) was added 60% NaH (1.8 g, 42 mmol). The resulting mixture was heated at 60°C for 4 h then cooled to 25°C before adding a solution of methyltriphenylphosphonium iodide (16.92 g, 42.0 mmol) in THF (40 mL) over 5 minutes. To the yellow mixture was added a crude solution of decalins **4A**:**4**, 3:1 (4.64 g, 20.7 mmol) in THF (100 mL). After heating at 50°C for 3 h, then 25°C for an additional 3 h, the reaction was quenched with $H_2O$ (50 mL) and diluted with hexanes (100 mL). The aqueous layer was separated and extracted with hexanes (3 x 25 mL) and the combined organic fractions were washed with $H_2O$ (3 x 50 mL), dried ($NaSO_4$), and concentrated. The resulting residue was purified by silica gel column chromatography (Pentane:$Et_2O$, 9:1) to give 3.50 g ( 76% yield from **4**) of olefin **5** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.64 (d, 1.5 Hz, 1H), 4.48 (d, 1.5 Hz, 1H), 2.95 (s, 1H), 2.34 (dt, *J*=12.5, 6.7 Hz, 1H), 2.26 (m, 1H), 2.09 (m, 1H), 1.97 (dt, *J*=13.0, 4.3 Hz), 1.82 (ddd, *J*=12.7, 6.8, 3.5 Hz, 1H), 1.65 (ddd, *J*=13.5, 12.6, 5.7 Hz, 1H), 1.60 (ddt, *J*=12.8, 6.0, 2.0 Hz, 1H), 1.51 (br t, *J*=11.5 Hz, 1H), 1.44 (tt, *J*=12.0, 3.5Hz, 1H), 1.36-1.24 (comp. m, 5H), 1.14 (dq, *J*=13.0, 4.1 Hz, 1H), 0.96 (d, *J*=7.0, 3H), 0.91 (d, *J*=7.0 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 152.6, 104.6, 61.5, 58.6, 46.2, 45.2, 44.0, 36.4, 30.6, 27.2, 26.7, 24.1, 22.9, 22.0, 15.9; **IR** (thin film/NaCl) 2957 (s), 2933 (s), 2875 (m), 2842 (m), 1649 (w), 1449 (w), 1378 (w), 887 (m), 807 (w) cm$^{-1}$; **HRMS** (EI) *m/z* found: 221.1905 [calc'd for $C_{15}H_{25}O$ (M+H): 221.1905].

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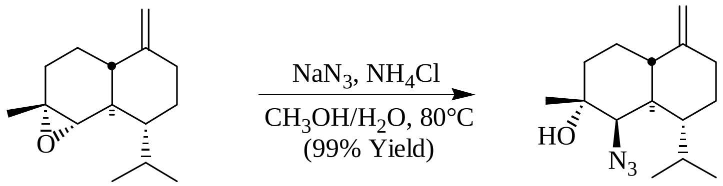
**Preparation of azide 6.**



**5** **6**

To a solution of olefin **5** (3.45 g, 15.7 mmol) in 8:1 $MeOH/H_2O$ (150 mL), was added $NaN_3$ (6.11 g, 94.0 mmol) and $NH_4Cl$ (2.51 g, 47.0 mmol). The mixture was heated to 80°C. After 36 h, the mixture was cooled to 25°C and the solvent volume reduced to ca. 50 mL and diluted with hexanes (50 mL) and EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (2 x 25 mL) and the combined organic fractions were washed with brine (2 x 25 mL), dried ($NaSO_4$), and concentrated to give spectroscopically pure azide **6** (4.12 g, 99% yield) as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.68 (d, 1.5 Hz, 1H), 4.56 (d, 1.5 Hz, 1H), 3.50 (s, 1H), 2.36 (dt, *J*=13.0, 3.5 Hz, 1H), 2.02-1.93 (m, 2H), 1.88 (br t, *J*=11.2 Hz, 1H), 1.82 (ddd, *J*=18.6, 7.0, 3.5 Hz, 1H), 1.73-1.63 (comp. m, 3H), 1.62-1.47 (comp. m, 3H), 1.42 (br s, 1H), 1.36 (s, 3H), 1.13 (dq, *J*=12.4, 3.5 Hz, 1H), 0.99 (d, *J*=7.0, 3H), 0.76 (d, *J*=7.0 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 152.7, 105.4, 72.8, 68.5, 44.4, 43.6, 38.8, 36.6, 33.3, 29.2, 26.5, 26.3, 24.3, 21.8, 15.7; **IR** (thin film/NaCl) 3439 (br w), 2959 (m), 2935 (m), 2868 (m), 2104 (vs), 1644 (w), 1465 (w)1280 (m), 890 (m) cm$^{-1}$; **HRMS** (EI) *m/z* found: 264.2075 [calc'd for $C_{15}H_{26}N_3O$ (M+H): 264.2076].

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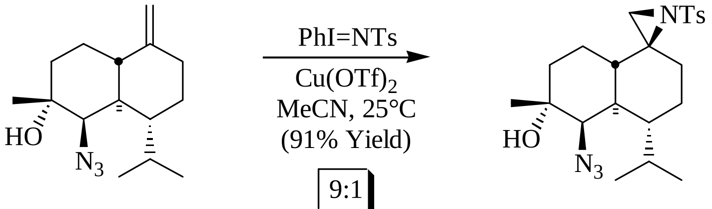
**Preparation of aziridine 7.**



**6** **7**

To a solution of azide **6** (1.26 g, 4.80 mmol) in dry MeCN (250 mL) with 4 Å sieves (ca. 3 g) at 25°C, was added *N*-tosyliminophenyliodinane (3.59 g, 9.61 mmol). After 5 minutes, Cu(Otf)$_2$ (87 mg, 0.24 mmol) was added and the mixture was vigorously stirred for 8 h. EtOAc (50 mL) was added and the mixture was filtered through a short silica gel plug. After solvent removal in vacuo, the resulting residue, a 9:1 mixture of aziridine diastereomers, was purified by silica gel column chromatography (hexanes:EtOAc, 11:1) to afford aziridine **7** (1.65 mg, 82% yield) as a white solid. m.p. >143°C (dec). **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.80 (d, 8.5 Hz, 2H), 7.30 (d, 8.5 Hz, 2H), 3.49 (br s, 1H), 2.50 (s, 1H), 2.43 (s, 3H), 2.37 (d, *J*=1.7 Hz, 1H), 2.27 (dt, *J*=13.3, 3.5 Hz, 1H), 2.11 (m, 1H), 2.02-1.89 (comp. m, 2H), 1.78 (dt, *J*=11.2, 2.5 Hz, 1H), 1.61-1.46 (comp. m, 5H), 1.40-1.34 (comp. m, 1H), 1.34 (s, 3H), 1.19 (dq, *J*=13.1, 3.5 Hz, 1H), 1.00 (d, *J*=13.1 Hz, 3H), 0.99-0.88 (comp. m, 1H), 0.79 (d, *J*=13.1 Hz, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 144.0, 138.7, 129.8, 127.6, 72.5, 68.2, 55.7, 42.9, 42.2, 38.1, 36.9, 32.8, 31.6, 29.3, 26.3, 24.1, 22.0, 21.7, 20.5, 15.7; **IR** (thin film/NaCl) 3507 (br w), 2958 (m), 2870 (w), 2099 (s), 1313 (m), 1288 (m), 1156 (m)1094 (w), 718 (m) cm$^{-1}$; **HRMS** (EI) *m/z* found: 433.2274 [calc'd for $C_{22}H_{33}N_4O_3S$ (M+H): 433.2273].

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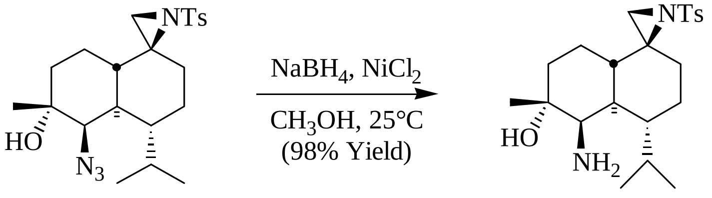
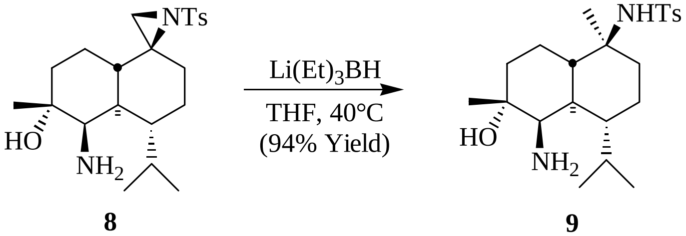
**Preparation of amine 8.**



**7** **8**

To a solution of aziridine **7** (617 mg, 1.43 mmol) in 3:1 MeOH/THF (30 mL) at 0°C was added $NiCl_2 \cdot 6H_2O$ (542 mg, 2.28 mmol) followed by $NaBH_4$ (248 mg, 6.57 mmol) over 10 minutes. After 30 minutes the black mixture was allowed to warm to 25°C, diluted with EtOAc (40 mL), and filtered through celite. The solution was further diluted with EtOAc (50 mL) and washed with brine (2 x 25 mL) and 0.01M EDTA solution (1 x 25 mL, pH 7.5, K-phosphate buffer). After solvent removal in vacuo, the resulting oil was purified by silica gel column chromatography (EtOAc, 100% then EtOAc: MeOH, 12:1) to give 569 mg (98% yield) of amine **8**. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, 8.5 Hz, 2H), 7.30 (d, 8.5 Hz, 2H), 2.76 (br s, 1H), 2.52 (s, 1H), 2.43 (s, 1H), 2.42(s, 3H), 2.28 (dt, *J*=13.2, 3.5 Hz, 1H), 2.10 (br t, *J*=13.0 Hz, 1H), 1.92 (comp. m, 3H), 1.73 (br t, *J*=11.3 Hz, 1H), 1.62 (br t, *J*=11.6 Hz, 1H), 1.52-1.14 (comp. m, 9H), 0.98 (m, 1H), 0.96 (d, *J*=7.8 Hz, 3H), 0.77 (d, *J*=7.8 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.9, 138.8, 129.8, 127.6, 56.3, 55.7, 42.6, 41.8, 37.4, 37.2, 32.1, 31.9, 29.2, 25.8, 24.3, 22.0, 21.9, 20.8,15.8; **IR** (thin film/NaCl) 3522 (br w), 2955 (m), 2870 (m), 1598 (w), 1465 (w), 1384 (w), 1369 (w),1156 (s), 1094 (m),1005 (m),716 (s) cm$^{-1}$; **HRMS** (EI) *m/z* found: 407.2368 [calc'd for $C_{22}H_{35}N_2O_3S$ (M+H): 407.2368].

**Preparation of amine 9.**



To a solution of amine **8** (703 mg, 1.73 mmol) in THF (30 mL) at 0°C was added 1M $Li(Et)_3BH$ in THF (8.7 mL, 8.7 mmol). The reaction mixture was stirred at 0°C for 1 h, then warmed to 40°C. After 10 h, the mixture was cooled to 0°C and diluted with EtOAc (50 mL) and $H_2O$ (15 mL). The organic layer was separated, washed with brine (2 x 20 mL), and dried ($Na_2SO_4$). After solvent removal in vacuo, the residue was purified by silica gel column chromatography (EtOAc then EtOAc:MeOH, 10:1) to afford amine **9** (664 mg, 94% yield) as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.67 (d, 17.0 Hz, 2H), 7.18 (d, 17.0 Hz, 2H), 4.41 (s, 1H), 2.62 (s, 1H), 2.33 (s, 3H), 1.82-1.71 (m, 2H), 1.63 (dt, *J*=20.0, 6.0 Hz, 1H), 1.52-1.04 (comp. m, 16H), 1.02 (s, 3H), 0.96 (m, 1H), 0.79 (d, *J*=13.0 Hz, 3H), 0.63 (d, *J*=13.0 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.2, 141.3, 129.8, 128.7, 127.4, 72.6, 61.1, 55.7, 42.4, 42.2, 39.8, 38.3, 32.7, 29.2, 25.7, 22.0, 21.9, 21.5, 20.4, 19.9, 15.7; **IR** (thin film/NaCl) 3503 (br w), 3276 (m), 2955 (s), 2933 (s), 2870 (s), 1598 (w), 1456 (m), 1384 (m), 1322 (m), 1150 (s), 1093 (s), 732 (s) cm$^{-1}$; **HRMS** (EI) *m/z* found: 409.2526 [calc'd for $C_{22}H_{37}N_2O_3S$ (M+H): 409.2525].

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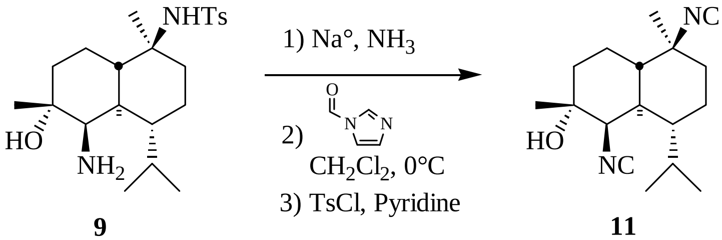
**Preparation of bis-isonitrile 11.**



**9** **11**

To condensed ammonia (40 mL) at –78°C was added sodium (300 mg, 13 mmol) followed by **9** (530 mg, 1.30 mmol) in THF (8 mL). After 3 h, the blue mixture was warmed to reflux for an additional 2 h. The ammonia was allowed to evaporate until the reaction mixture volume was ca. 10 mL, then the reaction was quenched with saturated ammonium chloride (5 mL) and diluted with EtOAc (30 mL). The organic layer was washed with 0.1 M NaOH (2 x 10 mL), brine (1 x 10 mL) and dried ($Na_2SO_4$). After concentration, the resulting oil was dissolved in THF (10 mL) to which a 0.5 M solution of N-formyl imidazole in $CH_2Cl_2$ (4 ml) was added. After 8 h at room temperature, the solvent was removed in vacuo and the residue taken up in $Et_2O$ (3 mL) and filtered through celite. After concentration, the resulting oil was diluted with $CH_2Cl_2$ (15 mL). To this solution was added pyridine (80 µL, 0.99 mmol) followed by p-toluenesulphonyl chloride (189 mg, 0.990 mmol). After 12 h at room temperature, the solvent was removed in vacuo and the residue purified by silica gel column chromatography (hexanes:EtOAc, 9:1) to afford 270 mg (76% yield from **9**) of isonitrile **11** as a white solid. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.49 (s, 1H), 1.92 (dt, *J*= 12.9, 3.4 Hz, 1H), 1.79-1.29 (comp. m, 10H), 1.29 (s, 3H), 1.22 (br s, 1H), 1.18 (t, *J*=2.3 Hz, 3H), 0.98 (dq, *J*=12.7, 3.4 Hz, 1H), 0.80 (d, *J*=7.0 Hz, 3H), 0.59 (d, *J*=7.0 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 158.8 (t, *J*=5.0 Hz), 153.2 (t, *J*=5.0 Hz), 70.6, 61.2, (t, *J*=5.0 Hz), 60.6, (t, *J*=5.0 Hz), 43.1, 42.6, 40.7, 36.4, 33.0, 29.1, 25.8, 21.7, 21.4, 21.2, 19.5, 15.4; **IR** (thin film/NaCl) 3419 (br m), 2955 (s), 2873 (m), 2273 (w), 2133 (vs), 1467 (w), 1385 (m), 1179 (w), 1125 (w), 1002 (m), 733 (w) cm$^{-1}$; **HRMS** (EI) *m/z* found: 275.2123 [calc'd for $C_{17}H_{27}N_2O$ (M+H): 275.2124].