# Formal Synthesis of (±)-Peduncularine: Use of the [3 + 2] Annulation of Allylic Silanes and Chlorosulfonyl Isocyanate

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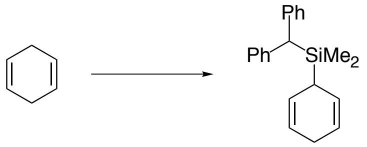
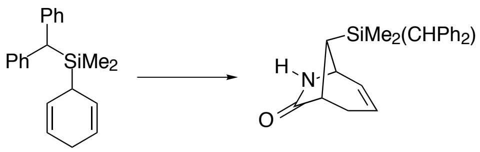
## Supporting Information

**General.** $^1$H NMR and $^{13}$C NMR spectra were recorded at ambient temperature at 500 and 125 MHz, respectively, using Bruker DRX 500 spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the $\delta$ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were acquired on a VG Analytical 7070E or Fisons Autospec spectrometer, and were obtained by peak matching. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on EM Reagents 0.25 mm silica gel 60-F plates. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM Reagents silica gel ($SiO_2$) 60 (230-400) mesh. All reactions were carried out under an atmosphere of nitrogen in glassware which had been flame-dried under a stream of nitrogen. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Toluene, THF, $Et_2O$, and $CH_2Cl_2$ were dried by filtration through alumina according to the procedure of Grubbs.[1] Chlorosulfonyl isocyanate was purchased from Aldrich and distilled over $K_2CO_3$ prior to use. *s*-BuLi was titrated with 2-butanol (1.00 M in xylenes) using *o*-phenanthroline as an indicator.



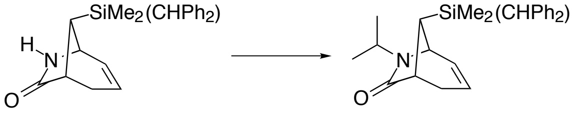
**6**

**3-Dimethyl(diphenylmethyl)silyl-1,4-cyclohexadiene (6).** To a cooled (-78 °C) solution of 1,4-cyclohexadiene (0.055 mL, 0.60 mmol) in 1 mL of THF were added *s*-BuLi (0.625 mL, 0.96 M in cyclohexane, 0.60 mmol), and TMEDA (0.100 mL, 0.60 mmol). The yellow solution was warmed to -45 °C, and after 2.5 h was treated with $(Ph_2CH)Me_2SiCl$ **5**[2] (0.160 g, 0.613 mmol) in 1 mL of THF. After 10 min at -45 °C, the solution was warmed to 23 °C and treated with 6 mL of saturated aqueous $NH_4Cl$ solution. The organic phase was diluted with 3 mL of $Et_2O$, separated from the aqueous phase, washed with 6 mL of brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography (hexanes) provided **6** as an oil (0.139 g, 76%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.25 (m, 8H), 7.12 (m, 2H), 5.53-5.48 (m, 4H), 3.67 (s, 1H), 2.69-2.56 (m, 2H), 2.25 (m, 1H), 0.08 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.3, 128.7, 128.4, 125.8, 125.2, 122.0, 43.6, 29.5, 26.3, -5.5; IR (thin film) 3023, 2819, 1665, 1622, 1600 cm$^{-1}$; HRMS (CI/isobutane) *m/z* calcd for $C_{21}H_{24}Si$ $(M)^+$ 304.1647, found 304.1647. Anal. Calcd for $C_{21}H_{24}Si$: C, 82.83; H, 7.94. Found: C, 82.83; H, 7.87.



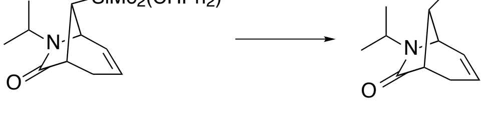
**6** **7**

**(1*S**,5*S**,8*R**)-8-[Dimethyl(diphenylmethyl)silyl]-6-aza-bicyclo[3.2.1]oct-3-en-7-one (7).** To a cooled (-78 ºC) solution of **6** (0.030 g, 0.099 mmol) in 1.5 mL of $CH_2Cl_2$ was added chlorosulfonyl isocyanate (0.020 mL, 0.230 mmol). The solution was warmed to -40 ºC. After 24 h at -40 ºC, the solution was treated with 2 mL of 25 % aqueous $Na_2SO_3$. The biphasic mixture was warmed to 23 ºC and stirred for 16 h. The organic phase was separated from the aqueous phase, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography (1:1 EtOAc:hexanes) provided **7** and **8** (0.026 g, 76%) in an 82 : 18 ratio by $^1$H NMR. Recrystallization provided a pure sample of **7** as a white solid: mp 154-156 ºC; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 8H), 7.15 (m, 2H), 6.14 (br s, 1H), 6.04 (m, 1H), 5.59 (m, 1H), 3.54 (s, 1H), 3.25 (t, *J* = 4.1, 1H), 2.39 (m, 1H), 2.23 (m, 2H), 1.86 (t, *J* = 3.8, 1H), 0.15 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 182.4, 142.01, 141.95, 131.5, 128.7, 128.6, 128.52, 128.47, 125.6, 51.2, 45.7, 41.7, 34.8, 27.0, -2.7, -2.8; IR (KBr) 3168, 3021, 2961, 1734, 1716, 1700, 1684, 1676, 1670, 1653 cm$^{-1}$; HRMS (CI/isobutane) *m/z* calcd for $C_{22}H_{26}NOSi$ $(M+H)^+$ 348.1784, found 348.1779. Anal. Calcd for $C_{22}H_{25}NOSi$: C, 76.03; H, 7.25; N, 4.03. Found: C, 75.80; H, 7.24; N, 4.01.



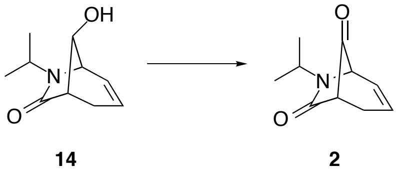
**7** **13**

**(1*S**,5*S**,8*R**)-6-Isopropyl-8-[dimethyl(diphenylmethyl)silyl]-6-aza-bicyclo[3.2.1]oct-3-en-7-one (13).** To a solution of **7** (0.410 g of 84 : 16 ratio of **7** : **8** by GC, 0.991 mmol of **7**) in 20 mL of $CH_3CN$ were added 2,2-dimethoxypropane (0.580 mL, 4.72 mmol), triethylsilane (0.754 mL, 4.72 mmol), and trifluoroacetic acid (0.364 mL, 4.72 mmol). After 16 h, the solution was diluted with 50 mL of $Et_2O$ and treated with 50 mL of saturated aqueous $NaHCO_3$ solution. The organic phase was separated from the aqueous phase, washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography (1:3 EtOAc:hexanes) provided **13** (0.239 g, 62%) as an oil which solidified on standing: mp 100-102 ºC; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 8H), 7.16 (m, 2H), 5.98 (m, 1H), 5.52 (m, 1H), 4.11 (septet, *J* = 6.8, 1H), 3.53 (s, 1H), 3.04 (t, *J* = 4.5, 1H), 2.52 (m, 1H), 2.27-2.03 (m, 2H), 1.64 (t, *J* = 3.9, 1H), 0.97 (d, *J* = 6.8, 3H), 0.92 (d, *J* = 6.8, 3H), 0.14 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 177.5, 142.1, 141.9, 132.1, 128.7, 128.51, 128.49, 128.3, 127.8, 125.51, 125.48, 51.3, 45.8, 43.0, 42.5, 34.8, 26.4, 21.7, 20.5, -2.5, -3.0; IR (KBr) 3035, 2968, 1682, 1635 cm$^{-1}$; HRMS (CI/isobutane) *m/z* calcd for $C_{25}H_{32}NOSi$ $(M+H)^+$ 390.2253, found 390.2258. Anal. Calcd for $C_{25}H_{31}NOSi$: C, 77.07; H, 8.02; N, 3.59. Found: C, 77.08; H, 8.10; N, 3.57.



**13** **14**

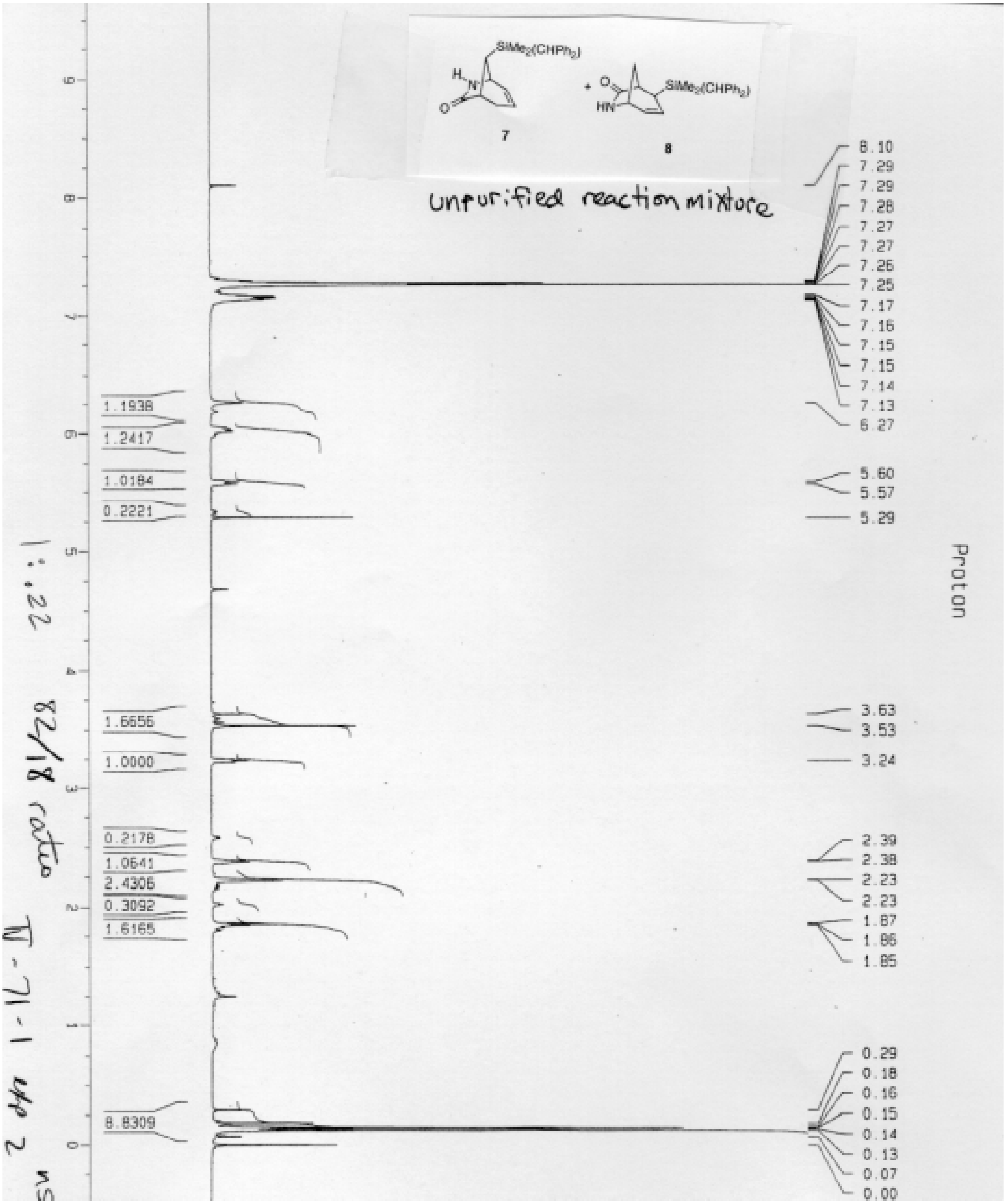
**(1*R**,5*S**,8*R**)-8-Hydroxy-6-isopropyl-6-aza-bicyclo[3.2.1]oct-3-en-7-one (14).** To a solution of **13** (0.060 g, 0.173 mmol) in 2 mL of THF was added TBAF (0.207 mL, 1.0 M in THF, 0.207 mmol). After 10 min, the solution was concentrated *in vacuo*. The residue was dissolved in 3 mL of DMF. To this solution was added KF (0.050 g, 0.865 mmol), $KHCO_3$ (0.019 g, 0.190 mmol), and $H_2O_2$ (0.235 mL, 30% solution in $H_2O$, 2.08 mmol). The solution was heated at 65 ºC for 17 h. The reaction mixture was cooled to 23 ºC, diluted with 4 mL of $CH_2Cl_2$, and treated with 4 mL of saturated aqueous $NaHSO_3$. The organic phase was separated from the aqueous phase, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography (9:1 EtOAc:hexanes) provided **14** (0.021 g, 67%) as a white solid: mp 101-103 °C; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.04-5.97 (m, 2H), 4.42-4.33 (m, 2H), 3.67 (m, 1H), 2.64 (m, 1H), 2.43-2.32 (m, 2H), 2.33 (d, $J$ = 10.1, 1H), 1.15 (d, $J$ = 6.8, 3H), 1.13 (d, $J$ = 6.8, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 173.6, 131.2, 128.4, 68.4, 51.4, 43.8, 42.2, 23.4, 22.2, 20.6; IR (KBr) 3248, 3037, 2969, 1651 $cm^{-1}$; HRMS (CI/isobutane) *m/z* calcd for $C_{10}H_{16}NO_2$ $(M+H)^+$ 182.1181, found 182.1178. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.28; H, 8.33; N, 7.61.



**(1*R**,5*S**)-6-Isopropyl-6-aza-bicyclo[3.2.1]oct-3-en-7,8-dione (2).** To a cooled (-78 °C) solution of oxalyl chloride (0.032 mL, 0.366 mmol) in 3 mL of $CH_2Cl_2$ was added DMSO (0.052 mL, 0.731 mmol). After 20 min, a solution of **14** (0.039 g, 0.215 mmol) in 3 mL of $CH_2Cl_2$ was added. Triethylamine (0.225 mL, 1.61 mmol) was added to the solution after 1 h at -78 °C. The reaction mixture was allowed to warm to 23 °C, was stirred for 16 h, and was poured into 10 mL of $H_2O$. The organic phase was separated from the aqueous phase, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography (1:1 EtOAc:hexanes) gave **2** (0.033 g, 86%) as a white solid, whose data match that of the known compound:[3] mp 67-69 °C; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.24 (m, 1H), 5.84 (dm, $J$ = 9.1, 1H), 4.55 (septet, $J$ = 6.8, 1H), 3.81 (d, $J$ = 5.7, 1H), 3.02-2.84 (m, 3H), 1.24 (d, $J$ = 6.8, 3H), 1.16 (d, $J$ = 6.8, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 204.0, 170.1, 132.4, 130.9, 56.3, 50.8, 42.8, 33.8, 22.3, 20.3; HRMS (CI/isobutane) *m/z* calcd for $C_{10}H_{13}NO_2$ $(M)^+$ 179.0946, found 179.0941.

## References

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.
(2) To prepare compound **5**, diphenylmethane (100 mmol) was deprotonated by *n*-BuLi (130 mmol) in 100 mL of $Et_2O$ (35 °C, 48 h) and then added to $Cl_2Me_2Si$ (500 mmol) in 200 mL of hexanes (-78 °C to 0 °C, 4 h). Filtration followed by purification by distillation (130 - 132 °C, 0.10 mmHg) provided **5** in 70 % yield.
(3) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588-2595.

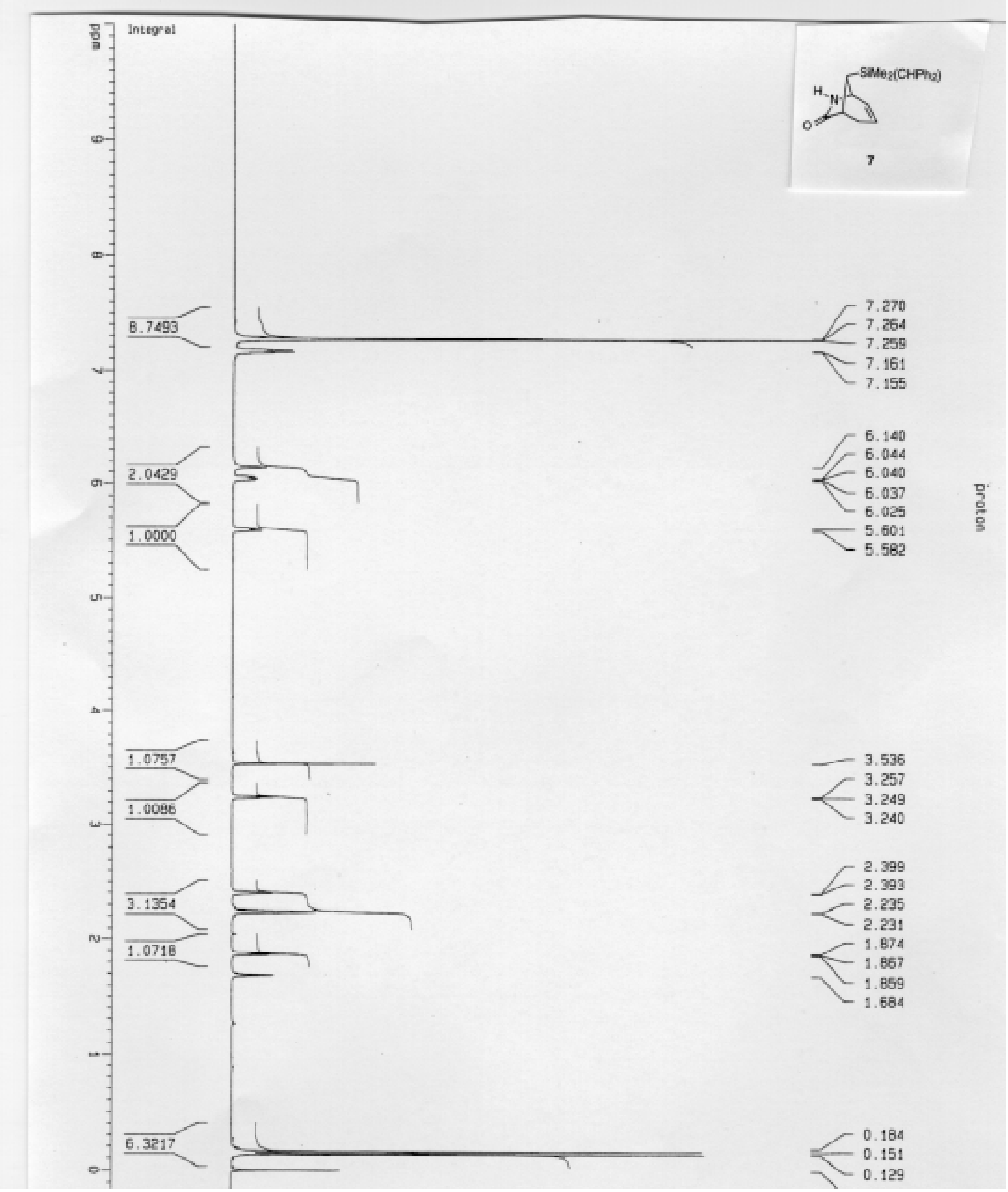


unpurified reaction mixture

1:.22

82/18 ratio

IV-71-1 exp 2 nS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N
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7
ppm
Integral
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7
6
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4
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7.161
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3.257
3.249
3.240
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2.235
2.231
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230-270° 5° per min
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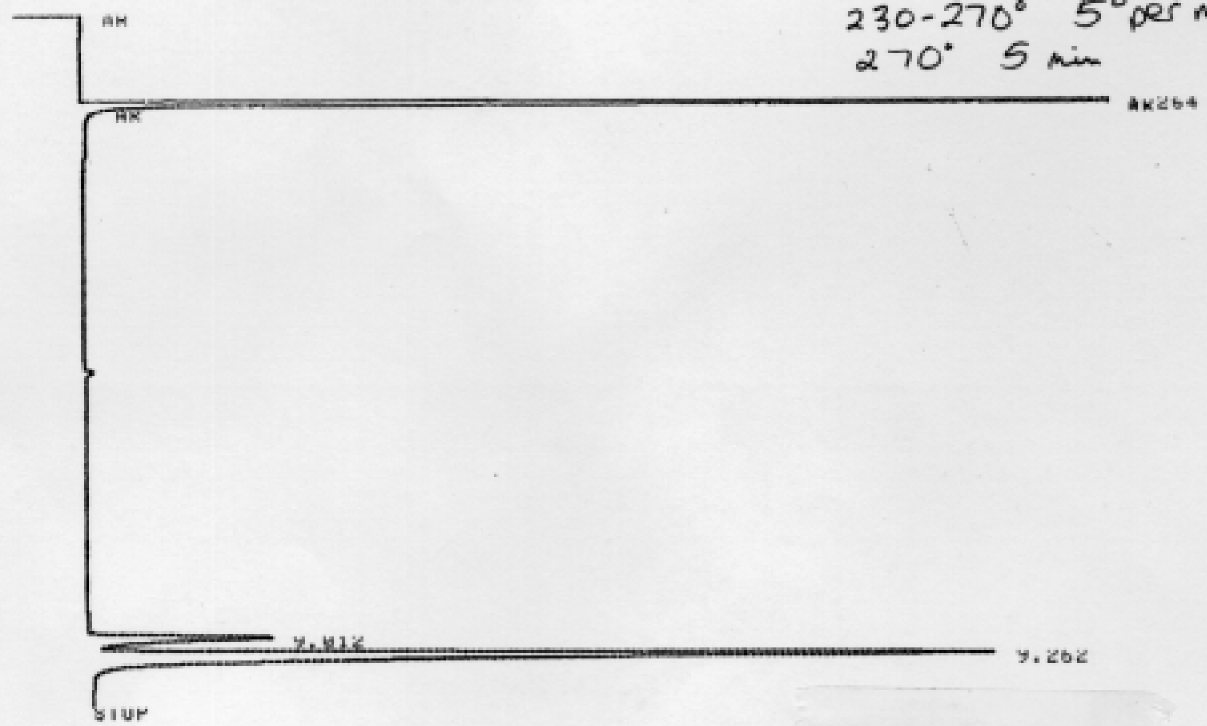

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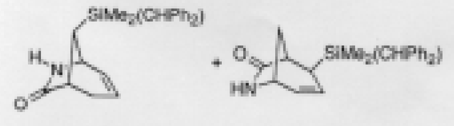
II-10-3 mixture used [illegible] to make 13



7 8