A Novel Synthetic Approach to the 8,10-Dimethyl *Anti-Syn-Anti* Perhydrophenanthrene Skeleton

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Supporting Information

General Considerations: Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see later) and under a slight static pressure of Ar (pre-purified quality), that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 140 °C for at least 3 h prior to use and then either cooled in a dessicator cabinet over Drierite, or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 140 °C for at least 3 h prior to use then cooled in a dessicator cabinet over Drierite. Commercially available Norm-Ject disposable syringes were used. Dry benzene, toluene, Et₂O, CH₂Cl₂, THF were obtained using a Solv-Tek, Inc. solvent purification system. All other dry solvents were of anhydrous quality purchased from Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et₃N, pyridine, *i*-Pr₂NEt, 2,6-lutidine, *i*-Pr₂NH were distilled from CaH₂ under a N₂ atmosphere prior to use.

35% HClO₄ (4 mL) was added to a stirred solution of ketal **15** (3.3211 g; 15.79 mmol) in THF (20 mL). The mixture was stirred for 1 h and then partitioned between Et₂O and water. The organic phase was washed with water, saturated aqueous NaHCO₃ (twice), water, saturated aqueous NaCl, dried (MgSO₄), and evaporated under reduced pressure to give a colorless oil (2.5999 g; 15.67 mmol; 99%). Spectroscopic data was identical to that reported previously.¹

PPTS (0.1491 g; 0.59 mmol) was added to a stirred solution of ketone **16** (2.5612 g, 15.40 mmol) and *p*-TsNHNH₂ (2.8677 g; 15.40 mmol) in THF (30 mL) (Ar atmosphere). The mixture was stirred for 11 h, by which time all of the ketone was consumed (TLC control: silica gel; 5:95 and 30:70 EtOAc-hexanes), and was then evaporated to approximately 10 mL under reduced pressure. The resulting residue was partitioned between Et₂O and water and the organic phase was washed with water, saturated aqueous NaCl, dried (MgSO₄), and evaporated under reduced pressure. Flash chromatography of the resulting white solid over silica gel using 30:70 EtOAc-hexanes (material loaded onto column as a CH₂Cl₂ solution) gave **17** (4.7364 g; 14.16 mmol; 92%) as a white solid: FTIR (CH₂Cl₂ cast) 3215, 2928, 1334, 1166 cm⁻¹; ¹H NMR (CD₂Cl₂, 400 MHz) δ 0.92 (s, 3 H), 1.13-1.50 (m, 9 H), 1.55-1.69 (m, 3H), 1.79-1.88 (m, 1 H), 1.93-2.03 (m, 1 H), 2.42 (s, 3 H), 2.46-2.54 (m, 1 H), 7.22 (bs, 1 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.79 (d, *J* = 8.1 Hz, 2 H); ¹³C NMR (CD₂Cl₂, 400 MHz) δ 17.32, 21.88, 22.21, 23.16, 25.82, 26.85, 28.44, 29.02, 35.25, 43.15, 46.23, 128.66, 129.82, 135.96, 144.57, 169.03; ESIMS *m/z* calcd for C₁₈H₂₆N₂NaO₂S 357.2, found 356.7.

n-BuLi (4.70 mL of a 2.5 M solution in hexanes; 11.75 mmol) was added via syringe pump over ca. 20 min to a stirred and cooled (-78 °C) solution of hydrazone **17** (1.7811 g, 5.33 mmol) in THF (50 mL) (Ar atmosphere). Once addition was complete, the resulting deep red solution was stirred for 5 min, transferred to a -40 °C bath, stirred for 10 min, and cooled to -78 °C. A solution of phenyl disulfide (1.4011 g, 6.42 mmol) in THF (7 mL) was added by cannula over ca. 5 min. Once addition was complete, the resulting yellow solution was stirred for 5 min, transferred to a -40 °C bath, and stirred for 1h, by which time a colorless solution had formed. Saturated aqueous NH₄Cl was added, and the mixture was warmed to room temperature over ca. 5 min with the aid of a water bath, and then concentrated under reduced pressure to approximately 20 mL and partitioned between water and Et₂O. The organic phase was washed with saturated aqueous NaCl, dried (MgSO₄) and evaporated under reduced pressure. Flash chromatography of the resulting light-yellow oil over silica gel using 30:70 Et₂O-hexanes gave **18** (2.2159 g; 5.01 mmol; 94%) as a white foam: FTIR (CH₂Cl₂ cast) 3212, 2928, 2858, 1340, 1169 cm⁻¹; ¹H NMR (CD₂Cl₂, 400 MHz) δ 0.87-1.08 (m, 1 H, including a s at δ 0.9, and a s at δ 1.07), 1.15-1.29 (m, 2 H), 1.30-1.57 (m, 5 H), 1.58-1.88 (m, 4 H), 1.89-2.04 (m, 2 H), 3.98-4.20 (m, 1 H, including a dd at δ 4.00 (*J* = 4.2, 1.9 Hz), and a d at δ

4.18 ($J = 5.4$ Hz), 7.28-7.49 (m, 7 H), 7.72-8.29 (m, 3 H, including a s at δ 7.74, a t at 7.80 ($J = 8.0$ Hz), and a s at δ 8.27); ^{13}C NMR (CD_2Cl_2 , 400 MHz) δ 18.51, 18.92, 21.90, 21.96, 22.39, 22.54, 22.90, 24.17, 26.48, 26.72, 28.87, 29.48, 30.41, 35.53, 36.62, 37.99, 40.61, 42.52, 42.71, 43.88, 44.63, 128.65, 128.70, 129.02, 129.30, 129.85, 129.87, 129.96, 130.10, 130.14, 132.79, 132.99, 133.72, 133.84, 133.94, 135.76, 135.87; ESIMS m/z calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{NaO}_4\text{S}_2$ 465.2, found 465.1.

n-BuLi (1.05 mL of a 1.6 M solution in hexanes; 1.68 mmol) was added via syringe pump over ca. 20 min to a stirred and cooled (-78 $^\circ\text{C}$) solution of hydrazone **18** (0.3379 g; 0.76 mmol) in THF (7 mL) (Ar atmosphere). The resulting deep red solution was stirred for 5 min and the mixture was transferred to a -20 $^\circ\text{C}$ bath and stirred for 16 h. Saturated aqueous NH_4Cl was added and the mixture was partitioned between Et_2O and water. The organic phase was washed with saturated aqueous NaCl, dried (MgSO_4), and evaporated under reduced pressure. Flash chromatography of the resulting light-yellow oil over silica gel using hexanes gave **19** (0.0819 g; 0.32 mmol; 42%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2925, 2854, 1583, 1475, 739, 691 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.94 (s, 3 H), 1.20-1.58 (m, 11 H), 1.68-1.77 (m, 1 H), 2.08-2.17 (m, 1 H), 2.17-2.27 (m, 1 H), 5.91 (s, 1 H), 7.11-7.16 (m, 1 H), 7.22-7.28 (m, 4 H); ^{13}C NMR (CD_2Cl_2 , 400 MHz) δ 18.78, 21.74, 26.65, 27.06, 28.15, 31.19, 37.00, 38.91, 42.77, 126.28, 128.83, 129.03, 129.80, 135.91, 146.34; ESIMS m/z calcd for $\text{C}_{17}\text{H}_{22}\text{NaS}$ 281.1, found 281.2, and gave **18** (0.1483 g; 0.43 mmol). Yield corrected for recovered **18** is 74%.

SeO_2 (2.9899 g, 26.95 mmol) was added to a stirred solution of thioenol ether **19** (1.1603, 4.49 mmol) in 95:5 EtOH-water (20 mL) and pyridine (2.91 mL) (Ar atmosphere). The mixture was stirred at reflux for 5 h, by which time all of the starting material was consumed (TLC control: silica gel; hexanes). The mixture was allowed to cool to room temperature and was filtered through celite and partitioned between EtOAc and water. The organic phase was washed with saturated aqueous NaHCO_3 , saturated aqueous NaCl, dried (MgSO_4), and evaporated under reduced pressure. Flash chromatography of the resulting light-yellow oil over silica gel using 10:90 EtOAc-hexanes gave **20** (0.9506 g; 3.50 mmol; 78%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3556, 2934, 1571, 1470 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.91 (s, 3 H), 1.18-1.38 (m, 4 H), 1.39-1.54 (m, 3 H), 1.54-1.74 (m, 4 H), 2.20 (bs, 1 H), 3.89 (dd, $J = 3.3, 1.9$ Hz, 1 H), 6.06 (s, 1 H), 7.12-7.17 (m, 1 H), 7.19-7.29 (m, 4 H); ^{13}C NMR (CD_2Cl_2 , 400 MHz) δ

17.24, 21.41, 26.59, 27.35, 34.03, 37.04, 37.54, 37.96, 66.04, 126.61, 129.06, 129.71, 131.16, 134.79, 150.23; ESIMS m/z calcd for $C_{17}H_{22}NaOS$ 297.4, found 297.0.

m-CPBA (0.6871 g (77% maximum purity), approximately 3.07 mmol) was added to a stirred and cooled (ice-water bath) solution of **20** (0.3775 g, 1.39 mmol) in CH_2Cl_2 (12 mL) (Ar atmosphere). The cooling bath was removed and stirring was continued for 2 h. The mixture was partitioned between EtOAc and 1M aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with 1M aqueous $\text{Na}_2\text{S}_2\text{O}_3$, saturated aqueous NaHCO_3 (twice), saturated aqueous NaCl, dried (MgSO_4), evaporated under reduced pressure and then stored under high vacuum for 1 h to give a colorless oil. DMP (0.7081 g, 1.67 mmol) was added to a stirred and cooled (ice-water bath) solution of the above oil in CH_2Cl_2 (10 mL) and pyridine (0.40 mL) (Ar atmosphere). The cold bath was removed and stirring was continued for 2 h. The mixture was partitioned between EtOAc and 1M aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The organic phase was washed with saturated aqueous NaHCO_3 , saturated aqueous NaCl, dried (MgSO_4), and evaporated under reduced pressure. Flash chromatography of the resulting light-yellow oil over silica gel using 25:75 EtOAc-hexanes gave **21** (0.3877 g; 1.27 mmol; 91%) as a white solid: FTIR (CH_2Cl_2 cast) 2932, 2859, 1691, 1308, 1160 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 400 MHz) δ 1.14 (s, 3 H), 1.21-1.47 (m, 3 H), 1.48-1.56 (m, 1 H), 1.60-1.71 (m, 2 H), 1.72-1.84 (m, 2 H), 1.88-1.98 (m, 1 H), 2.23 (dd, $J = 17.6, 4.5$ Hz, 1 H), 2.31 (dd, $J = 17.6, 13.8$ Hz, 1 H), 7.49-7.56 (m, 2 H), 7.58-7.65 (m, 1 H), 7.93-7.97 (m, 2 H), 7.98, (s, 1 H); ^{13}C NMR (CD_2Cl_2 , 400 MHz) δ 16.00, 21.73, 26.03, 27.52, 37.22, 38.29, 42.34, 42.44, 129.17, 129.26, 133.89, 138.42, 140.82, 168.68, 192.45; ESIMS m/z calcd for $C_{17}H_{20}NaO_3S$ 327.4, found 327.0.

Dienophile **21** (0.3720 g, 1.22 mmol) was combined with diene **22** (1.5 mL) in a sealed glass tube and stirred at 130 $^\circ\text{C}$ for 20 h, and then allowed to cool to room temperature. Flash chromatography of the resulting light-yellow oil over silica gel, using 10:90 EtOAc-hexanes gave **23** (0.4485 g; 0.89 mmol; 73%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2928, 2857, 1703, 1303, 1141, 838 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 400 MHz) δ 0.15 (s, 3 H), 0.17 (s, 3 H), 0.92 (s, 3 H), 0.97 (s, 9 H), 1.1-1.25 (m, 2 H), 1.36-1.45 (m, 2 H), 1.46-1.57 (m, 4 H, including a s at 1.53), 1.57-1.72 (m, 3 H), 1.88-1.97 (m, 1 H), 2.01 (dd, $J = 18.2, 10.9$ Hz, 1 H), 2.09 (d, $J = 15.2$ Hz, 1 H), 2.24 (dd, $J = 18.2, 7.0$ Hz, 1 H),

2.29 (dd, $J = 15.4, 6.2$ Hz, 1 H), 2.45 (dd, $J = 15.4, 4.4$ Hz, 1 H), 2.73 (d, $J = 15.2$ Hz, 1 H), 2.93 (dd, $J = 6.2, 4.4$ Hz, 1 H), 7.54 (m, 2 H), 7.64 (m, 1 H), 8.02 (m, 2 H); ^{13}C NMR (CD_2Cl_2 , 400 MHz) δ -3.78, -3.61, 16.03, 18.47, 20.19, 22.50, 26.04, 26.29, 30.11, 31.70, 35.57, 37.23, 37.61, 38.73, 43.17, 48.25, 78.91, 106.12, 128.75, 132.07, 134.02, 139.03, 147.11, 208.45; ESIMS m/z calcd for $\text{C}_{28}\text{H}_{42}\text{NaO}_4\text{SSi}$ 525.2, found 525.3. Continued chromatography using 25:75 EtOAc-hexanes gave **21** (0.0769 g; 0.25 mmol). Yield corrected for recovered **21** is 92%.

Lithium naphthalenide was prepared as follows:² Li (0.1001g, 14.42 mmol) was added to a mixture of naphthalene (0.5433 g, 4.24 mmol) and THF (10 mL) (Ar atmosphere). The mixture was sonicated for 20 min, producing a dark green mixture, and then additional THF (15 mL) was added. Sonication was continued for 1h, and the resulting dark green mixture was used as such.

A solution of cycloadduct **23** (0.0690 g, 0.137 mmol) in benzene (3 mL) was evaporated under reduced pressure using a rotovap connected to a dry N_2 source, and was then placed under high vacuum for 1 h. The process was repeated once, and the resulting white solid was then dissolved in benzene (3 mL), the solution was frozen, and then evaporated under high vacuum for 11 h. The resulting fluffy white material was dissolved in THF (1 mL), and freshly prepared lithium naphthalenide (approximately 1.3 mL) was added drop-wise by syringe over ca. 15 min, until the reaction mixture just maintained the dark green color of the lithium naphthalenide solution. The mixture was stirred for an addition 5 min, and MeI (freshly distilled from CaH_2 under a N_2 atmosphere) (0.40 mL; 6.42 mmol) was injected all at once. The mixture was stirred for 10 min, the cold bath was removed, and stirring was continued for 6 h. The reaction was quenched with saturated aqueous NaHCO_3 , and then partitioned between EtOAc and water. The organic phase was washed with saturated aqueous NaCl , dried (MgSO_4), and evaporated under reduced pressure. Flash chromatography of the resulting light-yellow oil over silica gel using 4:96 EtOAc-hexanes gave **24** (0.0341 g; 0.091 mmol; 66 %) as a colorless oil: FTIR (CH_2Cl_2 cast) 2929, 2856, 1710, 1251, 1176, 838 cm^{-1} ; ^1H NMR (CD_2Cl_2 , 400 MHz) δ 0.13 (s, 3 H), 0.14 (s, 3 H), 0.93 (s, 3 H), 0.96 (s, 9 H), 1.16 (s, 3 H), 1.24-1.46 (m, 4 H), 1.49-1.63 (m, 7 H, including a s at δ 1.54), 1.70-1.76 (m, 2 H, including a dd at δ 1.73 ($J = 12.8, 4.9$ Hz)), 1.81 (d, $J = 16.7$ Hz, 1 H), 2.00-2.08 (m, 3 H), 2.13 (d, $J = 3.3$ Hz, 1 H), 2.3 (dd, $J = 17.2, 14.1$ Hz, 1 H); ^{13}C NMR (CD_2Cl_2 , 400 MHz) δ -3.69, -3.31, 16.60, 18.61, 20.10, 20.98, 22.57, 26.21, 26.96, 28.03, 29.31, 35.48, 35.90, 39.68, 42.22, 42.89, 46.62, 48.17, 109.27, 142.96, 217.66; ESIMS m/z calcd for $\text{C}_{23}\text{H}_{40}\text{NaO}_2\text{Si}$ 399.3, found 399.2.

LiAlH₄ (0.32 mL of a 1.0 M solution in Et₂O; 0.32 mmol) was injected into a stirred and cooled (-78 °C) solution of ketone **24** (0.0806 g, 0.21 mmol) in Et₂O (6 mL) (Ar atmosphere). The mixture was stirred for 1 h, transferred to an ice-water bath, and stirred for an additional 1 h. Saturated aqueous NaHCO₃ was added and the mixture was partitioned between EtOAc and water. The organic phase was washed with saturated aqueous NaCl, dried (MgSO₄), evaporated under reduced pressure, and stored under high vacuum for 1 h to give a colorless oil. TBAF (0.32 mL of a 1.0 M solution in THF; 0.32 mmol) was injected into a stirred solution of the above oil in THF (6 mL) (Ar atmosphere). The resulting solution was stirred for 1 h and then partitioned between EtOAc and water. The organic phase was washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated under reduced pressure. Flash chromatography of the resulting light-yellow oil over silica gel using 20:80 EtOAc-hexanes gave **25** (0.0463 g; 0.18 mmol; 86 %) as a white solid: FTIR (CH₂Cl₂ cast) 3313, 2927, 2856, 1703 cm⁻¹; ¹H NMR (CD₂Cl₂ plus 1 drop D₂O, 400 MHz) δ 0.83 (s, 3 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 1.03 (apparent t, *J* = 12.8 Hz, 1 H), 1.15-1.27 (m, 3 H), 1.28 (s, 3 H), 1.29-1.42 (m, 4 H), 1.45-1.55 (m, 2 H), 1.62-1.73 (m, 1 H), 1.83 (apparent dt, *J* = 14.2, 8.8 Hz, 1 H), 1.91-1.99 (m, 1 H), 2.08 (dd, *J* = 12.8, 5.8 Hz, 1 H), 2.33 (dd, *J* = 14.0, 3.9 Hz, 1 H), 2.43 (apparent t, *J* = 14.0 Hz, 1 H), 2.47 (q, *J* = 6.5 Hz, 1 H), 3.53 (dd, *J* = 8.8, 4.7 Hz, 1 H); ¹³C NMR (CDCl₃, 400 MHz) δ 14.66, 15.62, 21.54, 22.22, 26.56, 28.24, 35.44, 35.91, 36.52, 38.31, 39.40, 40.13, 40.61, 51.03, 53.10, 76.08, 213.97; ESIMS *m/z* calcd for C₁₇H₂₈NaO₂ 287.2, found 287.0.

Hydrazine monohydrate (0.5 mL) was added to a stirred solution of **24** (0.0291 g; 0.077 mmol) in tri(ethylene glycol) (1.5 mL), and the resulting solution was heated at 110 °C for 1 h. The solution was cooled to room temperature and KOH (0.0273 g; 0.49 mmol) was added. The mixture was heated to 200 °C for 2.5 h, cooled to room temperature, and partitioned between Et₂O and water. The aqueous phase was extracted with Et₂O (thrice) and the combined organic extracts were washed with saturated aqueous NaCl, dried (MgSO₄), and evaporated under reduced pressure. Flash chromatography of the resulting oil over silica gel using hexanes gave **26** (0.0139 g; 0.059 mmol; 77 %) as a

colorless oil: FTIR (CH₂Cl₂ cast) 2926, 2861, 1456, 1374 cm⁻¹; ¹H NMR (CD₂Cl₂, 400 MHz) δ 0.78 (d, *J* = 6.5 Hz, 3 H), 0.84 (s, 3 H) 0.86-0.94 (m, 2 H), 1.07 (s, 3 H), 1.14-1.60 (m, 16 H), 1.63-1.79 (m, 3 H); ¹³C NMR (CDCl₃, 400 MHz) δ 20.20, 22.84, 23.13, 23.41, 24.75, 25.29, 27.57, 28.24, 28.88, 34.70, 34.87, 36.07, 37.25, 39.50, 40.54, 52.72, 56.12; ESIMS *m/z* calcd for C₁₇H₃₀Cl 269.2, found 269.1.

¹ Mewshaw, R. E.; Taylor, M. D.; Smith, III, A. B. *J. Org. Chem.* **1989**, *54*, 3449-3462.

² *Cf.* Azuma, T.; Yanagida, S.; Sakurai, H.; Sasa, S.; Yoshino, K. *Synthetic Commun.* **1982**, *12*, 137-140.