

A Model Study Directed Towards a Practical Enantioselective Total Synthesis of (–)-Morphine

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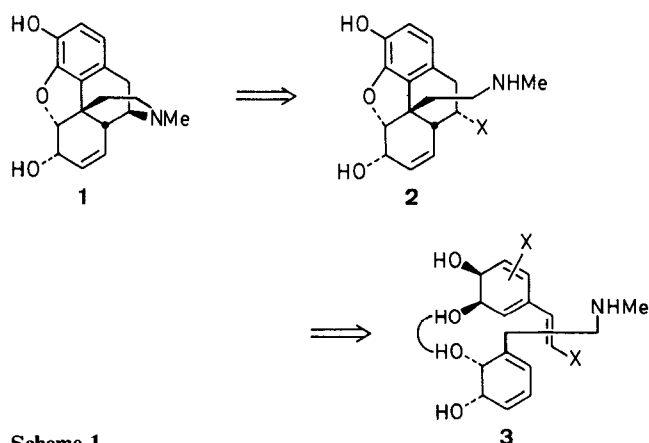
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A tricyclic ring system **10** containing the stereogenic centers of the nonaromatic portion of morphine (**1**) has been prepared in eight steps from toluene by the combination of microbial oxidation and intramolecular Diels–Alder cycloaddition followed by a Cope rearrangement. Experimental and spectral data are provided for all key compounds and potential for a short synthesis of morphine is indicated.

Introduction

The elements of control over synthetic transformations have been refined over the years so that methodologies are now available to provide outstanding degrees of selectivity in the regio-, stereo-, and enantiomeric domains of synthesis. Increasingly, the issues of brevity, efficiency, and therefore overall practicality have also surfaced and will soon dominate those synthetic endeavors that are destined to furnish real solutions to current problems defined by pharmaceutical and medicinal communities.

Examples of recent union of artful design with the utmost in chemical efficiency can be seen in the synthesis of cedrene in four steps by Wender and Howbert,¹ the preparation of lycopodine² and daphnilactone A³ by Heathcock et. al. in eight steps and eleven steps, respectively, the formation of the taxane skeleton in five steps by Holton,⁴ and the preparation of both enantiomers of pinitol in six steps in our laboratories.⁵ From simple consideration of yields of chemical reactions, especially when such considerations are realistic,⁶ it becomes obvious that an arbitrary limit of about ten operations can be placed on any total synthesis in order for it to be practical. With these criteria in mind we approached a significant challenge; namely, a practical synthesis of morphine. In this manuscript we report on the first two model studies designed to provide information about the topology of the intermediates and the disposition of their stereogenic centers. The strategic disconnection from morphine to two optically pure subunits that form the intermediate **3** is shown in Scheme 1. These subunits may ultimately be derived from styrenes by biocatalytic means.⁷

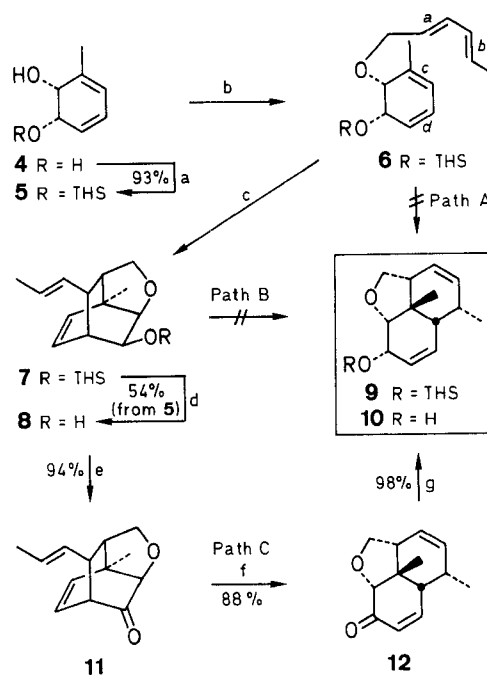


Scheme 1

Results and Discussion

Morphine (**1**) remains a formidable target for total synthesis. None of the published syntheses^{8a–n} are suitable for commercial application.^{8o} We envisioned an approach to **1** by an intramolecular union of two fragments in **3** using a 4 + 2 cycloaddition (Scheme 1). The two halves would be accessible via microbial oxidation of the corresponding arenes by *Pseudomonas putida*. To test the steric integrity and the overall viability of this plan, we chose to perform a simple model study which would yield appropriate information with regard to the five stereogenic centers in the nonaromatic region of **1**. We assumed that the formation of the ethylamino bridge would be one of the last operations, and therefore the target of this study would contain the asymmetric centers present in **2**.

For this model study (Scheme 2), we chose to use the *cis*-diol **4** which is obtained in enantiomerically pure form in multigram quantities from the microbial oxidation of toluene by *Pseudomonas putida* strain 39D.^{9,10} The diol **4** was selectively protected at the less-hindered hydroxy group by treatment with imidazole and dimethylhexylsilyl chloride (THSCl) to yield **5** (93%) as the only protection product (Scheme 2). Treatment of **5** with sodium hydride in THF followed by addition of sorbyl bromide¹¹ provided ether **6**.



THS = dimethylhexylsilyl = dimethyl(1,1,2-trimethylpropyl)silyl

(a) THSCl/imidazole/DMF, 0°C, 18 h. (b) NaH/sorbyl bromide/THF, 0°C, then r.t., 30 h. (c) CCl₄, 77°C, 7 h. (d) Bu₄NF · 3 H₂O/THF, r.t., 24 h. (e) PCC/CH₂Cl₂, r.t., 21 h. (f) xylenes, 250°C (sealed tube), 22 h. (g) NaBH₄/CeCl₃ · 7 H₂O/MeOH, r.t., 15 min.

Scheme 2

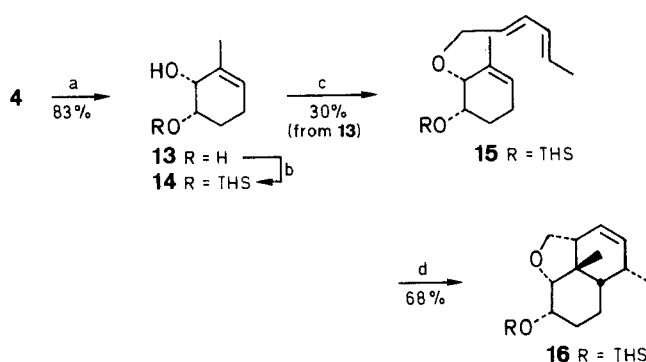
Two possibilities for intramolecular Diels–Alder reactions exist in **6**: (1) combination of the diene *a,b* with dienophile *c*, or (2) reaction of the more proximal side-chain olefin *a* with the diene *c,d* of the ring. A Diels–Alder reaction similar in regiochemistry to the latter was applied in the total synthesis of zeylena.⁷ When a ca. 0.02 M solution of **6** was refluxed in CCl₄ (77 °C) for several hours, the adduct **7** was obtained and none of adduct **9** (Path A, Scheme 2) was detected. It remains to investigate whether transition-metal-catalyzed [4 + 2] cycloadditions^{12,13} will alter this regiochemistry.

Despite the observed regiochemistry in the intramolecular cycloaddition of **6**, we noted that adduct **7** could undergo a Cope rearrangement restricted to a boat-like transition state geometry to yield the desired framework in **9** (Path B, Scheme 2). Unfortunately, even the most vigorous attempts at this conversion were unsuccessful, and it became evident that some driving force would be necessary in order for the reaction to proceed. The simplest method seemed to be the oxidation of the hydroxy group in the deprotected adduct **8**, allowing the formation of an α,β -unsaturated ketone **12** as a result of the Cope rearrangement.

To this end, **7** was treated with tetrabutylammonium fluoride in THF to yield the alcohol **8** (82%) which was oxidized in 94% yield to ketone **11** with pyridinium chlorochromate in dichloromethane. As anticipated, **11** underwent the Cope rearrangement to provide the enone **12** (88%, Path C, Scheme 2). It is interesting to note that the overall topology observed in the synthesis of **12** (a regiochemistry not favored in the intramolecular cycloaddition of **6**) is ultimately derived by a sigmatropic rearrangement via the observed regioisomer **7**. The absolute stereochemistry of the five chiral centers in **12** was determined by NOE experiments, extrapolating from the known stereochemistry of the chiral centers in the starting *cis*-diol **4**. Reduction of the enone **12** with sodium borohydride in the presence of CeCl₃ · 7H₂O¹⁴ proceeded with great facility providing a single diastereomeric alcohol **10** (98%). The stereochemistry illustrated for **10** is based on the reasonable assumption that hydride ion is delivered on the less hindered convex face of **12** which was also supported by NOE experiments.

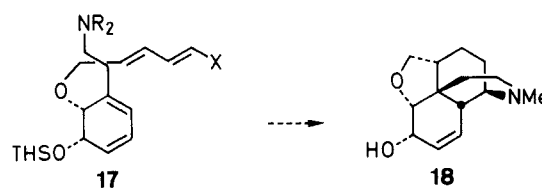
A simplified model study which eliminates regiochemistry problems has been accomplished as shown in Scheme 3. In a preliminary experiment, triene **15**, prepared from **4** via diimide reduction,¹⁵ hydroxy group protection, and subsequent alkylation, underwent intramolecular cycloaddition at 210 °C to the adduct **16** (68%). Optimum conditions for this transformation, including nickel-¹² and rhodium-mediated¹³ cyclizations, are being pursued.

The feasibility of paths A and B (Scheme 2) remains to be investigated in detail in order to shorten the synthesis of **10**. A third model study (**17** → **18**; Scheme 4) is planned to establish the intramolecular alkylation protocol and hence the formation of the ethylamino bridge prior to the effort toward the synthesis of **3** and application to the total synthesis of morphine (**1**).



(a) KO₂CN=NCO₂K/HOAc/MeOH, 0 °C to r. t. (b) THSCl/imidazole/DMF, 0 °C, 18 h. (c) NaH/sorbyl bromide/THF, 0 °C, then r. t., 48 h. (d) toluene, 210 °C (sealed tube), 24 h.

Scheme 3



Scheme 4

Conclusion

In summary, an interesting tandem Diels–Alder/Cope strategy proved to be a viable stereo- and regioselective route to the desired ring system in **9**, **10**, and **12** which contain the necessary stereogenic centers, thus serving as models for the synthesis of **1**. Assuming an internal S_N2-like displacement for the formation of the ethylamino bridge in **18**, the completion of these studies will allow a focused pursuit of the synthesis of **1** as outlined in Scheme 1.

¹H NMR spectra were recorded in CDCl₃ (ref. δ = 7.24) at 200, 270 and 400 MHz on Brüker WP-200, Brüker WP-270, and Varian Unity 400 instruments, respectively. ¹³C NMR spectra were recorded in CDCl₃ (ref. δ = 77.0) at 50 and 100 MHz on Brüker WP-200 and Varian Unity 400 instruments, respectively, and multiplicities were determined by DEPT experiments. THF and Et₂O were distilled from sodium/benzophenone. CH₂Cl₂ and hexanes were distilled from CaH₂. EtOAc and CCl₄ were HPLC grade. Flash column chromatography was performed on Merck silica gel (grade 60, 230–400 mesh). Air- and moisture-sensitive reactions were carried out in flame-dried reaction vessels under argon using oven-dried syringes. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

(2*R*,3*S*)-*cis*-1-Methylcyclohexa-4,6-diene-2,3-diol (**4**):

Pseudomonas putida strain 39-D (Pp 39D) were grown in a B. Braun Biostat E 15 L fermenter in 8 L of mineral salts broth modified from that of Gibson:⁹ Solution A (320 mL), Solution B (160 mL), Solution C (120 mL), and L-arginine (40 g) were combined and diluted to 6200 mL with distilled water and sterilized. D-Fructose (160 g) was diluted to 2000 mL with distilled water and sterilized before being combined with the mineral salts broth. The pH was maintained at nominally 7.2 during the course of the oxidation by the automated addition of 5 M aq NH₃. The stirring rate was 250 rpm, and toluene (125 mL) was bubbled through the fermenter over a period of 41.5 h when massive cell death occurred. About 2 L of broth were lost during the course of the reaction to foaming. (Later fermentations utilized the addition of oxygen gas during the fermentation to maintain the oxygen level at about 50% of the initial

dissolved oxygen content. This decreased foaming significantly and increased the rate of cell growth.) The remaining 6 L (pH = 7.8) were processed by continuous centrifugation to remove cells, basification with 10 M aq NaOH to pH = 8.8, saturation with NaCl, and extraction with base-washed EtOAc (12 × 300 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo to yield 23.1 g of crude **4** which was recrystallized from EtOAc and hexanes.

(2R,3S)-cis-3-Dimethyl(1,1,2-trimethylpropyl)siloxy-1-methylcyclohexa-4,6-dien-2-ol (5):

The diol **4** (1.36 g, 10.79 mmol) was dissolved in DMF (20 mL). Imidazole (0.854 g, 12.56 mmol) was added followed by chlorodimethyl(1,1,2-trimethylpropyl)silane (dimethylhexylsilyl chloride, 2.24 g, 12.56 mmol), and the resulting solution allowed to stand at 0°C for 18 h. The mixture was diluted with Et₂O (60 mL) and washed with brine (3 × 25 mL). The brine was back-extracted with Et₂O (3 × 15 mL), and the combined organic layers were washed with sat. CuSO₄ (3 × 30 mL), H₂O (1 × 30 mL), and brine (1 × 30 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo to give **5** as a yellow oil (3.1 g) which was chromatographed on silica gel (10% deactivated with H₂O) eluting with 5% base-washed EtOAc/hexanes to provide pure **5** as a colorless oil; yield: 2.69 g (93%); [α]_D + 86.11° (c = 1.26, CHCl₃).

HRMS: *m/z*, C₁₅H₂₈O₂Si calcd: 268.1859; found: 268.1860.

IR (neat): ν = 3557, 2958, 2867, 1465, 1396, 1252, 1091, 832, 777 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.13 (s, 6H), 0.84 (s, 6H), 0.87 (d, 6H, *J* = 6.8 Hz), 1.62 (septet, 1H, *J* = 6.8 Hz), 1.90 (dd, 3H, *J* = ca. 0.6 Hz), 2.58 (d, 1H, *J* = 4.8 Hz), 3.85 (t, 1H, *J* = 5.3 Hz), 4.40 (m, 1H), 5.58 (dd, 1H, *J* = 9.6, 2.7 Hz), 5.70 (m, 1H), 5.83 (ddd, 1H, *J* = 9.6, 5.3, 1.7 Hz).

(5S,6R)-cis-5-Dimethyl(1,1,2-trimethylpropyl)siloxy-6-(2,4-hexadienyl)-1-methylcyclohexa-1,3-diene (6):

A solution of the THS-protected diol **5** (2.94 g, 10.95 mmol) in THF (25 mL) was added dropwise to a stirring slurry of NaH (460 mg, 19.16 mmol) in THF (5 mL) cooled to -5°C. The resulting mixture was stirred for 10 min at this temperature followed by the rapid addition of sorbyl bromide (2.31 g, 14.34 mmol) in THF (20 mL). The mixture was allowed to warm to r.t. and was stirred an additional 30 h during which time a thick orange precipitate formed. The reaction was quenched with H₂O (25 mL) and extracted with Et₂O (3 × 40 mL). The combined Et₂O extracts were washed with H₂O (50 mL) and brine (50 mL) and dried (Na₂SO₄). Filtration and concentration in vacuo provided 4.7 g of clear orange oil which was carried immediately on to the next step. Partially purified **6** was obtained by repeated flash chromatography on silica gel (deactivated with 10% water) using hexanes/EtOAc.

¹H NMR (CDCl₃): δ = 0.13 (s, 6H), 0.86 (s, 6H), 0.89 (d, 6H, *J* = 6.9 Hz), 1.66 (m, 1H), 1.72 (d, 1H, *J* = 6.8 Hz), 1.87 (s, 3H), 3.57 (d, 1H, *J* = 6.0 Hz), 4.03 (dd, 1H, *J* = 12.5, 7.2 Hz), 4.21 (dd, 1H, *J* = 12.5, 6.0 Hz), 4.47 (m, 1H), 5.56 (dd, 1H, *J* = ca. 6.7 Hz), 5.63 (dd, 1H, *J* = 6.5, 6.1 Hz), 5.77–5.69 (m, 2H), 5.80 (ddd, 1H, *J* = 8.7, 5.2, 2.1 Hz), 5.98 (dq, 1H, *J* = 10.3, 1.4 Hz), 6.13 (dd, 1H, *J* = 12.9, 10.3 Hz).

¹³C NMR (CDCl₃): δ = -2.6 (2 × CH₃), 17.9 (CH₃), 18.7 (2 × CH₃), 20.4 (2 × CH₃), 20.8 (CH₃), 25.1 (C), 34.3 (CH), 70.9 (CH₂), 71.1 (CH), 77.8 (CH), 121.2 (CH), 123.3 (CH), 128.0 (CH), 129.2 (CH), 130.0 (CH), 131.2 (CH), 132.6 (CH), 136.0 (C).

(1R,2S,3R,6R,7S,10R)-2-Dimethyl(1,1,2-trimethylpropyl)siloxy-7-methyl-10-(1-propenyl)-4-oxatricyclo[4.3.1.0^{3,7}]dec-8-ene (7):

A solution of the crude **6** (4.70 g) in CCl₄ (650 mL) was refluxed (77°C) for 7 h and then cooled to r.t. Concentration in vacuo provided an orange oil which was passed through a column of silica gel eluting with 3.5% EtOAc/hexanes to provide the adduct **7** in reasonably pure form; yield 2.55 g (68% crude yield). Analytically pure **7** was obtained as a colorless oil by HPLC (C₁₈ semipreparative column, 100% MeOH); [α]_D - 14.88° (c = 1.08, CHCl₃).

C₂₁H₃₆O₂Si calcd. C 72.35 H 10.41
(348.6) found 72.25 10.37

IR (neat): ν = 3041, 2955, 2876, 1250, 1127, 1105, 883, 831, 777 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.05 (s, 3H), 0.08 (s, 3H), 0.83 (s, 3H), 0.84 (s, 3H), 0.89 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 1.21 (s, 3H), 1.68–1.50 (m, 1H), 1.59 (br d, 3H, *J* = 5.4 Hz), 2.26 (m, 1H), 2.52 (m, 1H), 3.29 (d, 1H, *J* = 6.8 Hz), 3.40 (dd, 1H, *J* = 6.8, 2.3 Hz), 3.59 (d, 1H, *J* = 7.7 Hz), 3.98 (dd, 1H, *J* = 7.7, 4.6 Hz), 5.51–5.44 (m, 2H), 5.69 (dd, 1H, *J* = 8.2, 1.4 Hz), 6.09 (dd, 1H, *J* = 8.2, 6.8 Hz).

¹³C NMR (CDCl₃): δ = -3.2 (CH₃), -2.6 (CH₃), 17.7 (CH₃), 18.5 (CH₃), 18.7 (CH₃), 20.4 (CH₃), 20.6 (CH₃), 21.3 (CH₃), 25.3 (C), 34.6 (CH), 43.8 (CH), 46.3 (C), 48.6 (CH), 48.7 (CH), 72.7 (CH), 73.8 (CH₂), 77.0 (CH), 123.6 (CH), 132.4 (CH), 132.8 (CH), 135.6 (CH).

(5S,6R)-cis-5-Dimethyl(1,1,2-trimethylpropyl)siloxy-6-(2,4-hexadienyl)-1-methylcyclohexa-1,3-diene (6):

A solution of the THS-protected diol **5** (2.94 g, 10.95 mmol) in THF (9.51 mmol) in THF (15 mL) was stirred at r.t. for 24 h. The resulting brown solution was concentrated in vacuo, and Et₂O (20 mL) and H₂O (10 mL) were added. The layers were separated, and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined Et₂O extracts were washed with H₂O (15 mL) and brine (15 mL) and dried (MgSO₄). Filtration and concentration in vacuo provided a crude oil which was purified by flash chromatography on silica gel (7% EtOAc/hexanes) providing pure **8** as a colorless oil; yield: 409 mg (82%, 54% from **5**); [α]_D + 42.03° (c = 1.04, CHCl₃).

C₁₃H₁₈O₂ calcd. C 75.69 H 8.80
(206.3) found 75.66 8.83

IR (neat): ν = 3483, 3042, 2938, 2886, 1372, 1074, 1048, 1030, 987, 969, 771, 710 cm⁻¹.

¹H NMR (CDCl₃): δ = 1.26 (s, 3H), 1.58 (dd, 3H, *J* = 5.7, 1.0 Hz), 1.67–1.53 (m, 1H), 2.47–2.33 (m, 2H), 3.31 (dt, 1H, *J* = 6.9, 1.9 Hz), 3.45 (dd, 1H, *J* = 6.9, 2.0 Hz), 3.62 (d, 1H, *J* = 8.1 Hz), 4.02 (dd, 1H, *J* = 8.1, 4.0 Hz), 5.20 (ddd, 1H, *J* = 15.2, 7.8, 1.0 Hz), 5.38 (dq, 1H, *J* = 15.2, 5.7 Hz), 5.70 (dd, 1H, *J* = 8.1, 1.2 Hz), 6.16 (dd, 1H, *J* = 8.1, 7.3 Hz).

¹³C NMR (CDCl₃): δ = 17.8 (CH₃), 21.1 (CH₃), 43.0 (CH), 45.6 (C), 47.5 (CH), 48.7 (CH), 70.5 (CH), 74.2 (CH₂), 76.8 (CH), 124.1 (CH), 131.8 (CH), 133.5 (CH), 134.6 (CH).

MS (EI): *m/z* = 206 (6), 188 (6), 175 (7), 147 (40), 132 (60), 119 (30), 105 (100), 97 (30), 91 (50), 81 (45), 77 (30), 55 (55).

(1R,3R,6R,7S,10R)-7-Methyl-10-(1-propenyl)-4-oxatricyclo[4.3.1.0^{3,7}]dec-5-en-2-one (11):

To a solution of the alcohol **8** (235 mg, 1.14 mmol) in CH₂Cl₂,⁷ (8.5 mL) was added PCC (993 mg, 4.61 mmol), and the resulting mixture was stirred at r.t. for 21 h. The mixture was diluted with Et₂O (20 mL) and vacuum filtered through a plug of silica gel washing with Et₂O. Concentration in vacuo of the filtrate provided the essentially pure ketone **11** as a light yellow oil; yield: 219 mg (94%). Analytically pure **11** was obtained as a colorless oil by flash chromatography; [α]_D - 243° (c = 0.96, CHCl₃).

C₁₃H₁₆O₂ calcd. C 76.44 H 7.90
(204.3) found 76.38 7.95

IR (neat): ν = 3064, 2936, 2887, 1741, 1453, 1041, 986, 969, 801, 690 cm⁻¹.

¹H NMR (CDCl₃): δ = 1.33 (s, 3H), 1.61 (dd, 3H, *J* = 6.3, 1.5 Hz), 1.83 (d, 1H, *J* = 4.1 Hz), 2.49 (dd, 1H, *J* = 8.3, 3.1 Hz), 2.99 (br dd, 1H, *J* = 6.7, 3.1 Hz), 3.25 (s, 1H), 3.79 (d, 1H, *J* = 8.4 Hz), 4.15 (dd, 1H, *J* = 8.4, 4.1 Hz), 5.25 (ddq, 1H, *J* = 15.2, 8.3, 1.5 Hz), 5.46 (ddq, 1H, 15.2, 6.3, 0.6 Hz), 5.96 (d, 1H, *J* = 8.1, 1.3 Hz), 6.13 (dd, 1H, *J* = 8.1, 6.7 Hz).

¹³C NMR (CDCl₃): δ = 17.8 (CH₃), 20.0 (CH₃), 47.3 (C), 48.0 (CH), 48.7 (CH), 51.2 (CH), 75.5 (CH₂), 78.8 (CH), 126.3 (CH), 128.1 (CH), 131.2 (CH), 134.9 (CH), 205.6 (C).

(2aR,5S,5aR,8aR,8bS)-2a,5,5a,8,8a,8b-Hexahydro-5,8b-dimethyl-8-oxo-2H-naphtho[1,8-bc]furan (12):

The ketone **11** (32 mg, 0.157 mmol) was dissolved in xylenes (9.5 mL) in a thick-walled glass tube which was sealed after degassing. The tube was heated to 250 °C for 22 h. After cooling and breaking the seal, the solution was concentrated in vacuo and the residue purified by column chromatography on silica gel (0–25 % EtOAc/hexanes gradient) to provide pure enone **12** as a light yellow residue; yield: 28 mg (88 %); $[\alpha]_D - 96.12^\circ$ ($c = 0.34$, CHCl₃).

HRMS: m/z , C₁₃H₁₆O₂ calcd: 204.1150; found: 204.1118.

IR (neat): $\nu = 3026, 2961, 2873, 1682, 1454, 1377, 1084, 1042, 946$ cm⁻¹.

¹H NMR (CDCl₃): $\delta = 1.26$ (d, 3 H, $J = 7.6$ Hz), 1.37 (s, 3 H), 2.25 (m, 1 H), 2.50 (m, 1 H), 2.60 (m, 1 H), 3.50 (dd, 1 H, $J = 8.8, 7.1$ Hz), 3.98 (s, 1 H), 4.27 (t, 1 H, $J = 8.8$ Hz), 5.46 (dt, 1 H, $J = 9.3, 3.2$ Hz), 5.61 (dt, 1 H, $J = 9.3, 2.3$ Hz), 6.07 (dd, 1 H, $J = 10.3, 2.3$ Hz), 6.67 (dd, 1 H, $J = 10.3, 3.3$ Hz).

¹³C NMR (CDCl₃): $\delta = 17.3$ (CH₃), 29.4 (CH₃), 33.1 (CH), 45.9 (CH), 46.6 (CH), 48.1 (C), 72.3 (CH₂), 85.0 (CH), 129.8 (CH), 131.7 (CH), 133.8 (CH), 148.6 (CH), 197.6 (C).

(2aR,5S,5aR,8S,8aR,8bS)-2a,5,5a,8,8a,8b-Hexahydro-5,8-dimethyl-8-hydroxy-2H-naphtho[1,8-bc]furan (10):

The enone **12** (12.6 mg, 0.0617 mmol) and CeCl₃ · 7H₂O (30 mg, 0.081 mmol) were dissolved in MeOH (0.2 mL) at r. t., and NaBH₄ (3 mg, 0.079 mmol) was added in two portions with stirring. Stirring was continued for 15 min at which point the reaction was quenched with 4 N HCl (1 mL) and extracted with CHCl₃ (4 × 5 mL), vacuum filtering the CHCl₃ extracts through MgSO₄. The filtrate was concentrated in vacuo and the resulting oil purified by chromatography on silica gel eluting with a 0 → 50 % EtOAc/hexanes solvent gradient which provided pure **10** as a colorless oil; yield: 12.5 mg (98 %); $[\alpha]_D - 33.5^\circ$ ($c = 1.04$, CHCl₃).

HRMS: m/z , C₁₃H₁₈O₂ calcd: 206.1307; found: 206.1300.

IR (neat): $\nu = 3429, 3016, 2960, 2873, 1455, 1395, 1377, 1095, 1078, 1059, 1029, 770$ cm⁻¹.

¹H NMR (CDCl₃): $\delta = 1.14$ (d, 3 H, $J = 7.3$ Hz), 1.30 (s, 3 H), 1.82 (m, 1 H), 2.45 (ddq, 1 H), 2.54 (m, 1 H), 2.74 (d, 1 H, $J = 10.5$ Hz), 3.36 (dd, 1 H, $J = 10.2, 7.9$ Hz), 3.90 (dd, 1 H, $J = 8.4, 7.9$ Hz), 4.07 (br d, 1 H, $J = 9.7$ Hz), 4.14 (dd, 1 H, $J = 3.8, 1.7$ Hz), 5.50 (dt, 1 H, $J = 10.0, 2.9$ Hz), 5.55 (m, 1 H), 5.67 (dt, 1 H, $J = 9.8, 3.0$ Hz), 5.87 (m, 1 H).

¹³C NMR (CDCl₃): $\delta = 18.0$ (CH₃), 27.3 (CH₃), 28.5 (CH), 42.2 (CH), 44.9 (C), 48.3 (CH), 69.0 (CH), 74.7 (CH₂), 91.6 (CH), 125.3 (CH), 129.0 (CH), 132.1 (CH), 134.5 (CH).

(2R,3S)-cis-1-methylcyclohex-6-ene-2,3-diol (13):

A solution of **4** (1.02 g, 8.07 mmol) in MeOH (70 mL) was cooled to 0 °C and potassium azodicarboxylate (PAD) (5.42 g, 27.9 mmol) was added via spatula. Glacial HOAc (3.33 g, 55.4 mmol) in MeOH (70 mL) was then added dropwise over a period of 1 h. The reaction mixture was allowed to warm to r. t., and an additional 1 equiv of PAD and 2 equiv of HOAc (neat) were added. Stirring continued for 3 h. The mixture was concentrated in vacuo to remove the MeOH and diluted with brine (20 mL) followed by extraction with Et₂O (4 × 50 mL). The combined Et₂O layers were washed with brine (1 × 50 mL), dried (Na₂SO₄), filtered and concentrated in vacuo to provide the essentially pure diol **13** as a white solid; yield: 0.858 g (83 %). An analytical sample was obtained by sublimation (50–60 °C/1 Torr); mp 82–83 °C; $[\alpha]_D - 151.7^\circ$ ($c = 0.6$, CHCl₃).

C₇H₁₂O₂ calc. C 65.60 H 9.44
(128.1) found 65.69 9.46

HRMS: m/z , C₇H₁₂O₂ calcd: 128.0837; found: 128.0847.

IR (KBr): $\nu = 3345, 2936, 1451, 1083, 1051, 983$ cm⁻¹.

¹H NMR (CDCl₃): $\delta = 1.66$ (m, 2 H), 1.78 (q, 3 H, $J = 1.8$ Hz), 2.02 (m, 1 H), 2.15 (m, 1 H), 2.20 (br s, 2 H), 3.73 (ddd, 1 H, $J = 9.2, 5.0, 4.0$ Hz), 3.90 (d, 1 H, $J = 4.0$ Hz), 5.54 (m, 1 H).

¹³C NMR (CDCl₃): $\delta = 20.8$ (CH₃), 23.9 (CH₂), 25.2 (CH₂), 69.7 (CH), 70.1 (CH), 125.4 (CH), 133.5 (C).

(2R,3S)-cis-3-Dimethyl(1,1,2-trimethylpropyl)siloxy-1-methylcyclohex-6-en-2-ol (14):

By the procedure used to prepare **5**, **14** was obtained as a colorless oil and carried directly to the next step without purification. An analytical sample was obtained by flash chromatography on silica gel eluting with 5 % EtOAc/hexanes providing **14** as a colorless oil; $[\alpha]_D - 61.5^\circ$ ($c = 1.52$, CHCl₃).

IR (neat): $\nu = 3559, 2957, 2868, 1467, 1452, 1377, 1252, 1086, 831, 777$ cm⁻¹.

¹H NMR (CDCl₃): $\delta = 0.11$ (s, 3 H), 0.12 (s, 3 H), 0.84 (s, 6 H), 0.87 (d, 3 H, $J = 6.9$ Hz), 0.88 (d, 3 H, $J = 6.9$ Hz), 1.51 (m, 1 H), 1.62 (septet, 1 H, $J = 6.9$ Hz), 1.69 (dd, 1 H, $J = 10.7, 5.8$ Hz), 1.72 (ddd, 1 H, $J = 10.7, 5.8, 2.0$ Hz), 1.78 (q, 3 H, $J = 1.9$ Hz), 1.95 (br m, 1 H), 2.09 (br m, 1 H), 3.76 (dt, 1 H, $J = 10.7, 3.9$ Hz), 3.79 (br d, 1 H, $J = 3.9$ Hz), 5.50 (m, 1 H).

¹³C NMR (CDCl₃): $\delta = -2.9$ (CH₃), -2.4 (CH₃), 18.5 (CH₃), 18.6 (CH₃), 20.2 (CH₃), 20.4 (CH₃), 21.2 (CH₃), 24.2 (CH₂), 24.9 (C), 25.3 (CH₂), 34.2 (CH), 70.2 (CH), 71.1 (CH), 124.8 (CH), 133.5 (C).

(5S,6R)-cis-5-Dimethyl(1,1,2-trimethylpropyl)siloxy-6-(2,6-hexadienyl)-1-methylcyclohex-1-ene (15):

A solution of **14** (0.397 g, 1.47 mmol) in THF (4 mL) was added rapidly to a stirring suspension of NaH (70.5 mg, 2.94 mmol) in THF (2 mL) cooled to 0 °C. Stirring was continued for 5 min and sorbyl bromide (0.414 g, 2.57 mmol) in THF (4 mL) was added dropwise. Stirring was continued for 10 min at 0 °C and the mixture was allowed to warm to r. t. and stirred an additional 48 h. Work-up was performed as described for **6**. Purification by flash chromatography on silica gel eluting with 1 % EtOAc/hexanes provided **15** as a colorless oil pure enough for use in the next step; yield: 0.204 g (30 % from **13**).

HRMS: m/z , C₁₅H₂₉O₂Si [M⁺ - C₆H₉O] calcd: 253.1988; found: 253.1980.

¹H NMR (CDCl₃): $\delta = 0.102$ (s, 3 H), 0.105 (s, 3 H), 0.84 (s, 3 H), 0.85 (s, 3 H), 0.880 (d, 3 H, $J = 6.8$ Hz), 0.883 (d, 3 H, $J = 6.8$ Hz), 1.52 (m, 1 H), 1.65 (septet, 1 H, $J = 6.8$ Hz), 1.716 (s, 3 H), 1.724 (d, 3 H, $J = 6.5$ Hz), 1.87 (m, 1 H), 1.93 (m, 1 H), 2.10 (m, 1 H), 3.50 (br d, 1 H, $J = 3.2$ Hz), 3.76 (dt, 1 H, $J = 11.6, 3.2$ Hz), 4.10 (dd, 1 H, $J = 12.4, 7.2$ Hz), 4.44 (dd, 1 H, $J = 12.4, 6.2$ Hz), 5.40 (m, 1 H), 5.62 (m, 1 H), 5.65 (dq, 1 H, $J = 14.5, 6.5$ Hz), 6.03 (ddd, 1 H, $J = 14.5, 10.6, 1.5$ Hz), 6.14 (dd, 1 H, $J = 15.3, 10.6$ Hz).

¹³C NMR (CDCl₃): $\delta = -2.5$ (2 × CH₃), 18.1 (CH₃), 18.5 (CH₃), 18.6 (CH₃), 20.2 (CH₃), 20.3 (CH₃), 21.3 (CH₃), 24.9 (C), 25.5 (CH₂), 34.0 (CH), 72.6 (CH), 73.4 (CH₂), 78.5 (CH), 124.7 (CH), 128.3 (CH), 129.3 (CH), 131.1 (CH), 132.5 (CH), 133.3 (C).

(2aR,5S,5aR,8S,8aR,8bS)-8-Dimethyl(1,1,2-trimethylpropyl)siloxy-2a,5,5a,6,7,8,8a,8b-octahydro-5,8b-dimethyl-2H-naphtho[1,8-bc]furan (16):

The triene **15** (25 mg, 0.0713 mmol) was dissolved in toluene (8 mL) and the solution sealed in a thick-walled glass tube. The tube was heated to 210 °C and maintained at that temperature for 24 h. After cooling and breaking the seal, the solution was concentrated in vacuo and the residue purified by flash chromatography on silica gel (0 → 4 % EtOAc/hexanes solvent gradient) to provide the adduct **16** as a colorless oil; yield: 17 mg (68 %); $[\alpha]_D + 4.04^\circ$ ($c = 0.57$, CHCl₃).

HRMS (CI): m/z , C₂₁H₃₉O₂Si [M + 1] calcd: 351.2719; found: 351.2701.

¹H NMR (CDCl₃): $\delta = 0.06$ (s, 3 H), 0.11 (s, 3 H), 0.81 (s, 6 H), 0.83 (s, 3 H), 0.85 (d, 6 H, $J = 6.9$ Hz), 1.10 (d, 3 H, $J = 7.6$ Hz), 1.27 (m, 4 H), 1.38 (m, 1 H), 1.62 (m, 2 H), 1.86 (m, 1 H), 3.50 (d, 1 H, $J = 4.7$ Hz), 3.51 (dd, 1 H, $J = 11.1, 7.0$ Hz), 3.90 (m, 1 H), 4.06 (dd, 1 H, $J = 8.5, 7.0$ Hz), 5.51 (dt, 1 H, $J = 9.6, 2.9$ Hz), 5.64 (dt, 1 H, $J = 9.6, 2.5$ Hz).

¹³C NMR: $\delta = -3.2$ (CH₃), -2.5 (CH₃), 18.50 (CH₃), 18.54 (C), 18.6 (CH₃), 20.1 (CH₃), 20.2 (CH₃), 23.10 (CH₃), 23.13 (CH₂), 23.2 (CH₃), 30.4 (CH₂), 34.0 (CH), 37.3 (CH), 39.0 (CH), 43.2 (C), 47.9 (CH), 68.1 (CH), 69.0 (CH₂), 84.0 (CH), 123.7 (CH), 134.5 (CH).

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- (1) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688.
- (2) (a) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *J. Am. Chem. Soc.* **1978**, *100*, 8036.
(b) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054.
- (3) Ruggeri, R. B.; McClure, K. F.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 1530.
- (4) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731.
- (5) Hudlicky, T.; Price, J. D.; Fan, R.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439.
- (6) This table shows the overall yields calculated for 10, 20, 30, and 40 step syntheses based on an average 90% yield for each step (common publishing practice) vs. 75% yield (a realistic assumption).
- | # steps | overall yield | |
|---------|---------------|-------|
| | (75%) | (90%) |
| 10 | 5.63 | 34.9 |
| 20 | 0.32 | 12.2 |
| 30 | 0.018 | 4.2 |
| 40 | 0.001 | 1.5 |
- (7) For preparation and use of styrene diol see: Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239.
- (8) For a recent total synthesis of (\pm -morphine) (**1**) and earlier synthetic approaches to **1** see:
(a) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380.
(b) Elad, D.; Ginsburg, D. *J. Chem. Soc.* **1954**, 3052.
(c) Barton, D. H. R.; Bhakuni, D. S.; James, R.; Kirby, G. W. *J. Chem. Soc. C* **1967**, 128.
(d) Kametani, T.; Ihara, M.; Fukumoto, K.; Yagi, H. *J. Chem. Soc. C* **1969**, 2030.
(e) Schwartz, M. A.; Mami, I. S. *J. Am. Chem. Soc.* **1975**, *97*, 1239.
(f) Beyerman, H. C.; Lie, T. S.; Maat, L.; Bosman, H. H.; Buurman, E.; Bijsterveld, E. J. M.; Sinnige, H. J. M. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 24.
(g) Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135.
(h) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261.
(i) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285.
(j) Szantay, C.; Barczai-Beke, M.; Pechy, P.; Blasko, G.; Dornyey, G. *J. Org. Chem.* **1982**, *47*, 594.

- (k) Moos, W. H.; Gless, R. D.; Rapoport, H. J. *J. Org. Chem.* **1983**, *48*, 227.
- (l) Weller, D. D.; Stirchak, E. P.; Weller, D. L. *J. Org. Chem.* **1983**, *48*, 4597.
- (m) McMurry, J. E.; Farina, V.; Scott, W. J.; Davidson, A. H.; Summers, D. R.; Shenvi, A. *J. Org. Chem.* **1984**, *49*, 3803.
- (n) Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 4694.
- (o) The cost of morphine available from natural opium concentrate is approximately \$250/kg. While it is difficult to envision a chemical synthesis that could compete with this cost, it is appropriate to design a suitable synthesis of the morphine skeleton for the preparation of commercially useful morphine analogs the majority of which are produced from natural morphine at the present time.
- (9) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* **1970**, *9*, 1626. The mineral salts broth used in our labs is constituted of the following: Solution A— KH_2PO_4 136.1 gL^{-1} , $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ 268.1 gL^{-1} . Solution B—Nitrilotriacetic acid (NTA) 10 gL^{-1} , KOH 7.5 gL^{-1} , $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 29.6 gL^{-1} , $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 3.3 gL^{-1} , $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ 9.3 mgL^{-1} , $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ 99.0 mgL^{-1} , Metals Solution 50 mL L^{-1} . The first four materials are each dissolved separately in distilled water. The NTA and KOH solutions are then mixed, and the magnesium and calcium solutions are slowly added successively with stirring to prevent formation of insoluble precipitates. The iron and molybdate salts are dissolved together in distilled water, and this solution is added. No precipitation is observed here, but a pale yellow color should obtain. The solution is diluted to the final desired volume, and 10 M NaOH is added in mL aliquots with stirring until pH 6.8. If the pH exceeds 7, insoluble precipitates will form. Solution C— $(\text{NH}_4)_2\text{SO}_4$ 200 gL^{-1} . Metals Solution (100 mL)—EDTA 250 mg, $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 1.095 g, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ 500 mg, $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ 154 mg, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 39.2 mg, $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ 24.8 mg, $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ 17.7 mg, 1M H_2SO_4 3 drops to retard precipitation.
- (10) Ziffer, H.; Jerina, D. M.; Gibson, D. T.; Kobal, V. M. *J. Am. Chem. Soc.* **1973**, *95*, 4048.
- (11) Mori, K. *Tetrahedron* **1974**, *30*, 3807.
- (12) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432.
- (13) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965.
- (14) Luche, J. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
- (15) van Tamelen, E. E.; Dewey, R. S.; Timmons, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 3725.