Aziridinium Cation Mediated Cyclizations. New Routes to the Morphinan Ring System

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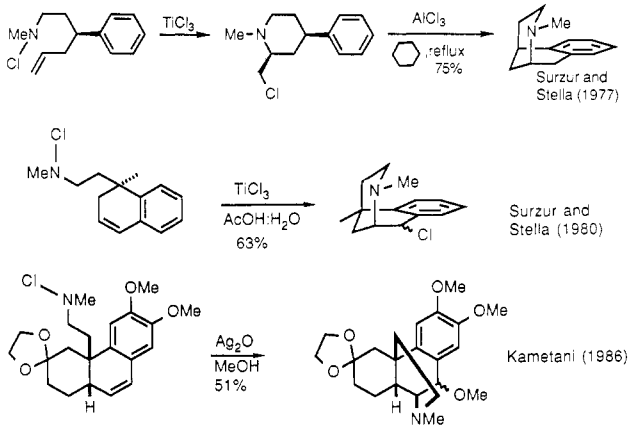
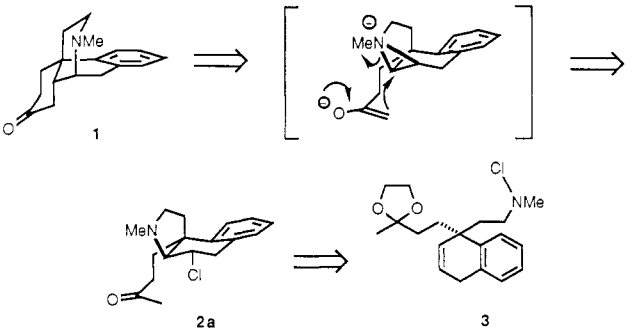
A concise route to the morphinan **1** has been developed which relies upon the intramolecular trapping of an aziridinium cation by an internal carbon nucleophile. The aziridinium cation intermediate is generated in situ by the treatment of pyrrolidine **20** with $AgBF_4$ or $AgSbF_6$ in toluene. Compound **20** is, in turn, derived from the readily available 1,4-dihydronaphthalene intermediate **3** by means of a copper(I)-promoted nitrogen radical cation cyclization followed by silylation. The success of the critical aziridinium cation alkylation reaction depends upon the nature of the internal nucleophile, and in the present case, dimethyl-*tert*-butylsilyl enol ether **20** was found to be the substrate of choice. The structure of **1** was established by its conversion to the known morphinan **18**.

As part of an effort aimed at exploiting the unique potential of nitrogen radical cation cyclizations (NRCC)[1] in the context of alkaloid total synthesis,[2] we became interested in utilizing this chemistry for the construction of simple morphinans. We were not the first to conceive this general idea. Surzur and Stella[3] took advantage of a $TiCl_3$-promoted NRCC reaction to generate a precursor to the benzomorphan ring system. They later approached a related compound from a different direction, using similar chemistry.[4] More recently, Kametani[5] has prepared an oxygenated morphinan system by means of an NRCC reaction, this time using silver(I)[6-8] to promote the cyclization.

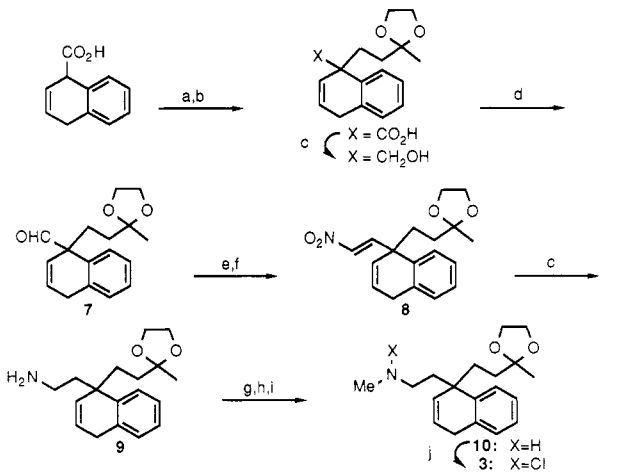


In the first of these approaches, the heteroatom substituent which accompanies nitrogen onto the double bond is utilized profitably in the next step (Friedel-Crafts alkylation). In the other two it must be reductively removed afterwards. We approached the problem of morphinan synthesis differently by asking whether the initial NRCC product could, by way of its derived aziridinium cation, function as a substrate for intramolecular alkylation. Our chosen target was morphinan **1**, and our retrosynthetic analysis is outlined in Scheme I.

Scheme I



Scheme II[a]



[a] (a) LDA (2 equiv); (b) **5**, HMPA; (c) LAH; (d) $(COCl)_2$, DMSO; (e) CH_3NO_2, KF; (f) Ac_2O, DMAP; (g) $(TFA)_2O$; (h) KH, MeI, 18-crown-6; (i) KOH, aqueous MeOH; (j) NCS, Et_2O.

Dihydronaphthalene **3** promised to be an easily obtainable starting material, and our aziridinium cation mediated rearrangement-alkylation sequence would, if successful, enable us to overcome the NRCC reaction's inherent preferences for the 5-exo cyclization mode, generating both the required piperidine ring of **1**[9,10] and a new

(1) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.

(2) NRCC reactions have also been used in the total synthesis of *Chinchona* alkaloids (Grete, G.; Lee, H. L.; Mitt, T.; Uskoković, M. *J. Am. Chem. Soc.* **1978**, *100*, 581); 8-*epi*-dendrobine (Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 1612); and gephyrotoxin-223AB (Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043).

(3) Stella, L.; Raynier, B.; Surzur, J. M. *Tetrahedron* **1981**, *37*, 2843 and references cited therein.

(4) See ref 1 and: Bougeois, J. L. Thesis, Marseille, 1980.

(5) Kametani, T.; Suzuki, Y.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1373.

(6) (a) Edwards, O. E.; Vocelle, D.; ApSimon, J. W. *Can. J. Chem.* **1972**, *50* 1167. (b) Edwards, O. E.; Bernath, G.; Dixon, J.; Paton, J. M.; Vocelle, D. *Can. J. Chem.* **1974**, *52*, 2123.

(7) Bastable, J. W.; Hobson, J. D.; Riddell, W. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2205.

(8) Furstoss, R.; Tadayoni, R.; Waegell, B. *Nouv. J. Chim.* **1977**, 167.

(9) Monković (Monković, I.; Conway, T. T. *J. Am. Chem. Soc.* **1973**, *95*, 7910) has utilized an aziridinium cation mediated rearrangement-dehydrobromination to effect a similar transposition of nitrogen in a system already containing all four rings of the morphinan system. Monković's rearrangement was used recently in a synthesis of 3-methyl-8,14-dehydromorphinan (Tius, M. A.; Thurkauf, A. *Tetrahedron Lett.* **1986**, *27*, 4541). An aziridinium cation mediated piperidine to pyrrolidine transformation in a thebaine derived system has also been observed (Mokotoff, M. *J. Org. Chem.* **1968**, *33*, 3556).

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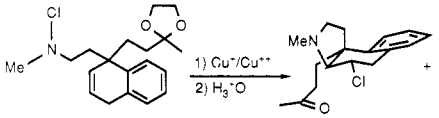
carbocyclic ring in a single operation. Beyond enabling us to obtain **1** from the readily available **3**, our interest in the proposed rearrangement–alkylation sequence derived from its uniqueness and its potential for broadly increasing the applicability of NRCC chemistry to problems in alkaloid synthesis. This paper describes the successful implementation of our strategy and the total synthesis of morphinan **1**.

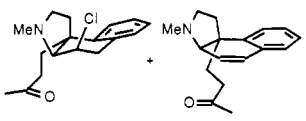
Results and Discussion

Synthesis and NRCC Reaction of 3. The construction of cyclization substrate **3** did prove to be straightforward. 1,4-Dihydronaphthoic acid[11] was deprotonated with LDA (2 equiv) to give an orange solution of its dianion, which was alkylated with the ethylene ketal of 1-bromo-3-butanone (**5**) in the presence of HMPA (Scheme II).[12] Since the resulting acid was not stable to chromatography, the crude product was reduced directly to the alcohol **6** (LAH, THF) prior to purification. Swern oxidation of **6** produced the labile aldehyde **7**, which was converted into nitro olefin **8** and thence to primary amine **9** by using the chemistry developed by Kametani.[5] Methylation of **9** was accomplished by using the general procedure of Norlander.[13]

Treatment of the resulting secondary amine **10** with NCS in ether provided **3** in excellent yield.[14] A number of reducing metal systems were examined to find the one most suitable for effecting the cyclization of **3**.[15] The best results were achieved by using CuCl (0.1 equiv)/$CuCl_2$ (1.0 equiv) in THF/AcOH/H_2O.[16] Under these conditions,



3 **2a** : 44%



2b : 20% 11 : 5%

(10) For different approaches to morphine which also involve the ring opening of aziridinium cations, see: Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285. McMurry, J. E.; Farina, V.; Scott, W. J.; Davidson, A. H.; Summers, D. R.; Shenvi, A. *J. Org. Chem.* **1984**, *49*, 3803.

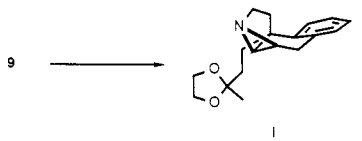
(11) Rabideau, P. W.; Burkholder, E. G.; Yates, M. J. *Synth. Commun.* **1980**, *10*, 627.

(12) Since 1,4-dihydronaphthoic acid is prepared by Birch reduction of 1-naphthoic acid, it should be possible to perform this alkylation directly without the isolation of 1,4-dihydronaphthoic acid itself. However, our efforts to do so have met with little success and we prefer the two-step approach. This alternative to the direct trapping of Birch reduction products has precedent (Plieninger, H.; Ege, G. *Chem. Ber.* **1961**, *94*, 2095).

(13) Norlander, J. E.; Catalane, D. B.; Eberlein, T. H.; Farkas, L. V.; Howe, R. S.; Stevens, R. M.; Tripoulas, N. T. *Tetrahedron Lett.* **1978**, 4987.

(14) *N*-Chloroamine **3** is not stable and should be cyclized immediately after preparation for the best results.

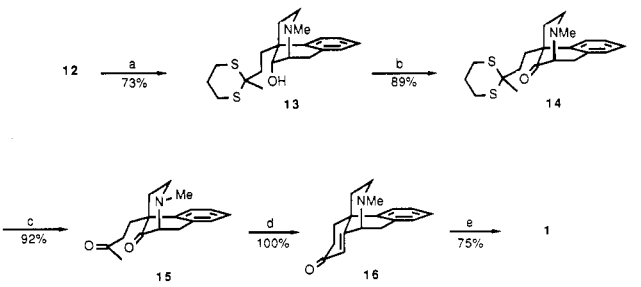
(15) We also attempted to prepare aziridine i from **9** using both NCS and LTA as described by Nagata (Nagata, W.; Hirai, S.; Kawata, K.; Aoki, T. *J. Am. Chem. Soc.* **1967**, *89*, 5045) as well as the modified procedure employing NCS and CuCl which has been described by Inubushi (Harayama, T.; Ohtani, M.; Oki, M.; Inubushi, Y. *Chem. Pharm. Bull.* **1975**, *23*, 1511). In no case were we successful.



i

(16) Bougeois, J.-L.; Stella, L.; Surzur, J.-M. *Tetrahedron Lett.* **1981**, *22*, 61.

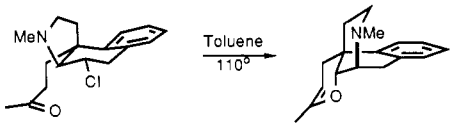
Scheme III[a]



[a] (a) 1,3-Propanedithiol, BF_3·Et_2O; (b) Ac_2O, DMSO; (c) NCS, acetone; (d) NaOMe, MeOH; (e) H_2/Pd–C.

the desired pyrrolidine **2a** was obtained in 44% yield along with its syn isomer **2b** (20%) and the elimination product **11** (5%) after hydrolysis of the ketal moiety with HCl in aqueous methanol. When the cyclization was carried out by using $FeCl_2/FeCl_3$, the ratio of anti to syn product dropped to 1.3:1. When $TiCl_3$ was used, an even more satisfactory 1:1 ratio was obtained. The structures of **2a** and **2b** could be inferred from their ^1H NMR spectra[17] and chemical behavior (vide infra).

Rearrangement–Alkylation Sequence. Thermal Reactions. Only the anti isomer (**2a**), in which departure of chloride can be assisted by the nitrogen lone pair, underwent reaction in refluxing toluene. In an experiment in which a solution of **2a** in toluene was refluxed in a Soxhlet-like apparatus with the cup filled with K_2CO_3 to remove HCl generated during the course of the reaction, the starting material disappeared over 8 h to afford a single product (yield 80%). The ^1H NMR spectrum of this product showed one vinylic proton (4.37 ppm), oxymethine and azamethine protons (at 4.09 and 3.31 ppm, respectively), and an allylic methyl singlet (1.54 ppm). The two benzylic protons could also be observed (as doublets of doublets), and their geminal and vicinal coupling constants (see Experimental Section) were close to those normally observed in morphinans. Accordingly structure **12** could be assigned to the thermolysis product of **2a**.



2a **12**

In order to verify the structure of **12**, we carried it on to morphinan **1** by treatment with 1,3-propanedithiol to give the ring-opened thioketal **13**, which, upon Albright–Goldman oxidation,[18] produced the ketone **14**. Removal of the protecting group and base-catalyzed cyclization gave enone **16**. Hydrogenation of this compound took place stereoselectively to give **1** as the sole product (Scheme III).

The structure of **1** was, in turn, established by its reduction to the corresponding alcohols **17** (equatorial/axial ratio 12:1) followed by deoxygenation. Conversion of **17** to the thiocarbonyl imidazolide[19] followed by treatment with Bu_3SnH in refluxing toluene[20] gave **18**, identical in

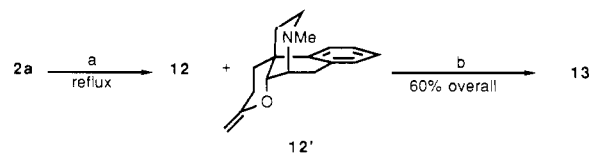
(17) The chloromethine proton of **2b** appears downfield (δ 4.51) from that of **2a** (δ 4.07), as would be expected on the basis of its transoid relationship to the neighboring C–N bond.

(18) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416.

(19) Staab, H. A. *Angew. Chem.* **1961**, *73*, 148.

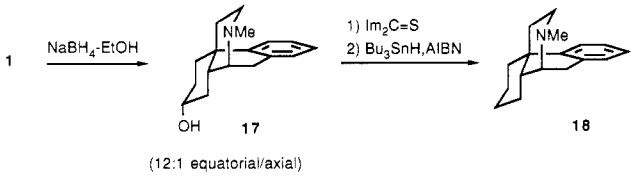
(20) For a review of radical deoxygenations, see: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

Scheme IV[a]



[a] (a) $NaHCO_3$, toluene, reflux; (b) 1,3-propanedithiol, $BF_3 \cdot Et_2O$.

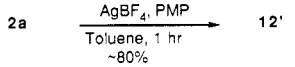
all respects, save optical rotation, with an authentic sample kindly provided by Prof. A. I. Meyers.[21]



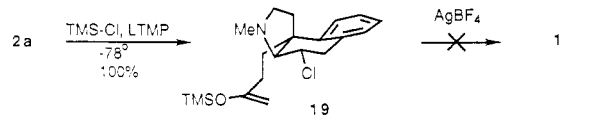
(12:1 equatorial/axial)

The thermally promoted rearrangement–trapping sequence which converts **2a** into **12**, while an interesting reaction in its own right,[22] did not enable us to achieve our goal, which was the *direct* synthesis of **1** from **2a**. Of course, this outcome was not particularly surprising. Very little of the enolized form of **2a** is present at equilibrium; thus, when the aziridinium cation is generated, it is opened by the available carbonyl oxygen lone pair with C–O rather than C–C bond formation taking place. We also found that the thermal conversion of **2a** into **12**, under the conditions described above, was not highly reproducible. Initial reactions, performed on a small (30 mg) scale, appeared to work well enough. However, when the reaction was scaled up, it proceeded only partially to completion or not at all. More consistent results were obtained when **2a** was refluxed in toluene containing excess $NaHCO_3$. Under these conditions, all reactions went to completion in 7–9 h and gave **12** and its exocyclic double bond isomer **12'** (ratio ~1:1) along with small amounts of the hemiketal corresponding to **12** (water being produced by the reaction of $NaHCO_3$ with HCl). These products were generally carried on to **13** without isolation. In this manner **2a** could be transformed into **13** in good and completely reproducible yield (Scheme IV).

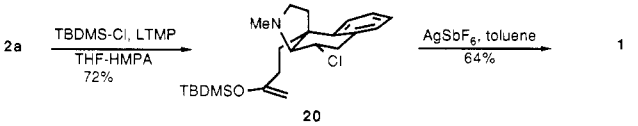
Silver-Promoted Reactions. We next turned our attention to a different strategy for effecting aziridinium cation formation from **2a**. Treatment of this material, in toluene solution, with $AgBF_4$ and 1,2,2,6,6-pentamethylpiperidine (PMP) led to a rapid reaction, which produced **12'** in about 80% yield.[23] The presence of PMP, which serves to deprotonate the oxonium ion intermediate formed upon opening of the aziridinium cation, was found to be essential to the success of this reaction.



Now in possession of an efficient and dependable means for generating the necessary aziridinium cation intermediates, we set out to modify the O vs C selectivity of the internal nucleophile. One obvious strategy involved preparation of the trimethylsilyl enol ether of **2a**. This goal was achieved by utilizing the approach of Rickborn.[24] A solution of **2a** in THF was added, at −78 °C, to a mixture of lithium tetramethylpiperidide (LTMP) and TMS-Cl. In this way **19** could be obtained in quantitative yield.



Treatment of **19** with $AgBF_4$ under a variety of conditions led to no formation of **1**. The only products that could be isolated from these reactions, generally in poor yield, were oxamorphinans **12** and **12'** along with varying amounts of their decomposition products. We then prepared the dimethyl-*tert*-butylsilyl (TBDMS) enol ether **20** from **2a**. The synthesis of **20** proved difficult, in comparison with that of **19**, owing to the lower reactivity of TBDMS-Cl. When not trapped quickly, the enolate derived from **2a** has a tendency to suffer dehydrochlorination giving **11**, and considerable experimentation was required to find a way around this difficulty. The procedure that worked best involved the addition of a stock solution of LTMP in THF to a mixture of **2a** and excess TBDMS-Cl in THF/HMPA at −25 °C. The base was added in small portions with continuous monitoring of the reaction by TLC. Once the starting material **2a** had been entirely consumed, the reaction mixture was worked up and the relatively stable TBDMS ether **20** isolated in 70–75% yield after silica gel chromatography.



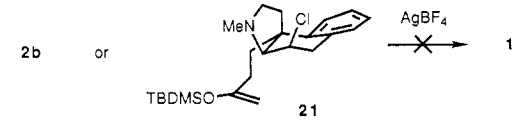
We were pleased to find that treatment of TBDMS ether **20** with $AgBF_4$ (toluene, 20 min, 20 °C) did, in fact, lead to **1** in 56% yield, demonstrating that our proposed rearrangement–alkylation sequence (Scheme I) could be rendered workable. Using THF or CH_3CN as the solvent, we again obtained **1**, although in slightly diminished yield. Even better results were achieved by using $AgSbF_6$ in toluene. Treatment of **20** with AgOAc or AgF failed to afford **1**. Refluxing enol ethers **19** and **20** in toluene also failed to bring about their conversion into **1**.

The factors responsible for the difference in behavior of **19** and **20** cannot be identified with certainty. It may be that the rather labile enol ether **19** suffers desilylation or undergoes other side reactions[25] in the presence of $AgBF_4$ before reaction with the aziridinium cation can occur. On the other hand, Tidwell[26] has shown that the acid-catalyzed hydrolysis of TMS enol ethers quite likely involves protonation on oxygen whereas, in the hydrolysis of TBDMS enol ethers, protonation on carbon is the rate-determining step. While it is true that many electrophiles react with TMS enol ethers at carbon, it may be that our aziridinium cation, responding to differences in steric encumbrance or acting as a rather hard electrophile, mimics the behavior of a proton by reacting, in the case of **19**, on oxygen, and in the case of **20**, on carbon.

The syn-series pyrrolidine **2b** and its TBDMS enol ether **21** were examined briefly as substrates for the silver-promoted rearrangement. The ketone **2b**, on treatment with $AgBF_4$ in toluene, did yield small amounts of oxamor-

(21) Meyers, A. I.; Bailey, T. R. *J. Org. Chem.* **1986**, *51*, 872.
(22) Some oxamorphinans analogous to **12** show interesting and potent biological activity; see, for example: Lemaire, S.; Dumont, M.; Jolicoeur, F.; Belleau, B. *Can. J. Physiol. Pharmacol.* **1986**, *64*, 707.
(23) It did not prove possible to isolate this enol ether chromatographically since exposure to silica gel resulted in its partial isomerization to **12** as well as in some decomposition. The yield was estimated from the NMR of the crude product.
(24) Mirsadeghi, S.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 986.
(25) For the Ag_2O-promoted dimerization of TMS enol ethers, see: Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 649.
(26) Novice, M.; Seikaly, H. R.; Seiz, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1980**, *102*, 5835.

phinans as verified by TLC and NMR as well as by conversion of these products to **13** upon reaction with 1,3-propanedithiol. However, the yields obtained (10–20%) were not synthetically useful. As might be expected, the reaction of this compound with $AgBF_4$ was exceedingly slow in comparison with that of **2a** (considerable amounts of starting material remained after 3 h). The TBDMS enol ether of **2b** (**21**) treated with $AgBF_4$ (toluene, 20 °C, 14 h) gave **2b** as the principle product of another slow reaction.



Conclusion

The direct synthesis of morphinan **1** from **20** demonstrates that intramolecular ring opening of in situ generated aziridinium cations by carbon nucleophiles can be a viable strategy for the formation of new carbon–carbon bonds and for the elaboration of complex ring systems. Examination of the behavior of compounds **2a,b** and **19–21** leads to several conclusions regarding requirements for the success of reactions of this type. One of these concerns the nature of the internal nucleophile. In the systems studied, C-alkylation could be achieved only through the use of the TBDMS enol ether. The parent ketone **2a** and its derived TMS enol ether **19** gave, instead, the products of O-alkylation. As to the means of bringing about formation of the aziridinium cation itself, we have found the use of $AgBF_4$ or $AgSbF_6$ (in toluene) to be the method of choice. Thermolysis serves to generate the necessary electrophilic intermediates in some cases but does not appear to be compatible with the use of TBDMS enol ethers as nucleophiles. Lastly, the neighboring N–C and C–Cl bonds of the substrate must be able to achieve an antiperiplanar disposition in order for the facile expulsion of chloride to take place. The syn-series compounds **2b** and **21** proved unsuitable as substrates for both the thermal and silver-promoted reactions.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 (300 MHz), a Nicolet NT-360 (360 MHz), or a GN-500 (500 MHz) NMR spectrometer in $CDCl_3$ or benzene-d_6 with tetramethylsilane or $CHCl_3$ as internal standard. Chemical shifts relative to TMS are reported as follows: chemical shift (δ) in ppm, multiplicity, number of protons, and coupling constants, when measured. Infrared spectra were obtained on an IBM Instruments IR/32 FT-IR spectrophotometer. All spectra were obtained on neat films. Peaks are reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a Finnigan-Matt 731 spectrometer using electron-impact (EI) ionization and on a VG-70 SE spectrometer using chemical-ionization (CI) or electron-impact ionization. THF and ether were distilled from sodium benzophenone. CH_2Cl_2 was distilled from calcium hydride, and benzene and toluene were distilled from sodium. Other reagents and solvents were purified as needed. Brine refers to a saturated solution of aqueous sodium chloride. $NaHCO_3$ (aqueous) refers to a saturated aqueous solution. Column chromatography was performed using Brinkman 0.05–0.2-mm silica gel. Preparative TLC was done on glass plates measuring 20 cm × 10 cm with a layer of Merck Kieselgel 60 PF 1.2 mm thick. Analytical TLC was done with Merck 60 F_{254} glass backed (0.25 mm) silica gel plates. TLC plates were visualized with fluorescence quenching and developed with I_2 or anisaldehyde reagent. Anisaldehyde reagent was prepared from 90% aqueous EtOH (330 mL), AcOH (3.7 mL), H_2SO_4 (12.3 mL), and *p*-anisaldehyde (9.1 mL). All reactions, unless indicated otherwise, were performed in oven-dried (135 °C) glassware under argon.

1-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-1,4-dihydro-1-naphthoic Acid. A solution of LDA (254 mmol, 2.1 equiv) was prepared by adding 1.5 M *n*-butyllithium (169 mL, 254 mmol) to a solution of $HN(i\text{-}Pr)_2$ (35.6 mL, 254 mmol) in 840 mL of THF at 0 °C and stirring for 30 min. To this solution, at −30 °C, was added 1,4-dihydronaphthoic acid (21.1 g, 121 mmol) dissolved in 93 mL of THF. After the mixture was stirred for 30 min at −30 °C, HMPA (63.4 mL) was added, followed by the bromo ketal **5** (26.56 g, 135 mmol). The mixture was warmed to room temperature and stirred for 14 h. Three-fourths of the solvent was evaporated. The remaining solution was acidified by pouring into 800 mL of ice-cold water containing 15 mL of concentrated H_2SO_4. This solution was extracted with ether. The combined organic extracts were washed with water and dried over Na_2SO_4. Solvents were removed to give the crude product, which was unstable to purification on silica gel.

1-(Hydroxymethyl)-1-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]-1,4-dihydronaphthalene (6). The crude acid from the preceding reaction (39.4 g) was dissolved in 100 mL of THF and added slowly to LAH (17 g, 448 mmol) in 400 mL of THF at 0 °C. The mixture was stirred for 2 h at room temperature, then cooled to 0 °C, and diluted with Et_2O (1100 mL). Water (16.5 mL) was added dropwise, followed by 20% NaOH (16.5 mL) and then water (37 mL). The mixture was filtered. The filter cake was washed with CH_2Cl_2. Concentration of the filtrate in vacuo followed by column chromatography (eluting with a gradient of 20–37% EtOAc/hexane) yielded 19.0 g of **6** (57% yield overall from 1,4-dihydronaphthoic acid) as a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.15 (m, 4 H), 6.17 (dt, 1 H, J = 10.2, 3.5 Hz), 5.53 (dt, 1 H, J = 10.2, 2.0 Hz), 3.91–3.76 (m, 5 H), 3.56–3.53 (c, 1 H), 3.43–3.40 (m, 2 H), 1.94 (td, 1 H, J = 13.1, 4 Hz), 1.63–1.47 (m, 2 H), 1.28–1.2 (m, 1 H), 1.23 (s, 3 H); IR 3460, 2950, 2880, 1490, 1450, 1370, 1040; HRMS calcd for $C_{17}H_{23}O_3$ (m + 1)/z 275.1648, found (CI) 275.1650.

1-Formyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,4-dihydronaphthalene (7). To DMSO (21.2 mL, 299 mmol) in 176 mL of CH_2Cl_2 at −78 °C was added oxalyl chloride (11.75 mL, 135 mmol). After 10 min at −78 °C, the alcohol **6** (10.56 g, 38.5 mmol) dissolved in 59 mL of CH_2Cl_2 was added. After a further 10 min at −78 °C, triethylamine (70 mL, 13 equiv) was added, and the mixture was warmed to −40 °C and stirred for 30 min. The mixture was poured into $NaHCO_3$ (aqueous) and extracted with ether. The combined ether extracts were washed with water and then brine and dried (Na_2SO_4). The ether was removed. The yield was essentially quantitative. The product **7** can be purified by column chromatography (eluting with a gradient of 0–10% AcOEt/hexane). This product is unstable and should be used immediately for the next reaction: ^1H NMR ($CDCl_3$, 30 MHz) δ 9.41 (s, 1 H), 7.28–7.09 (m, 4 H), 6.28 (dt, 1 H, J = 10.3, 3.5 Hz), 5.49 (dt, 1 H, J = 10.3, 2.0 Hz), 3.93–3.80 (m, 4 H), 3.48 (m, 2 H), 2.21 (td, 1 H, J = 13.8, 4.5 Hz), 1.94 (td, 1 H, J = 13.4, 4.5 Hz), 1.54 (td, 1 H, J = 13.4, 4.0 Hz), 1.32–1.21 (m, 1 H), 1.24 (s, 3 H); IR 2980, 2880, 1720, 1490, 1450, 1370, 1040; HRMS calcd for $C_{17}H_{21}O_3$ (m + 1)/z 273.1491, found (CI) 273.1495. Anal. Calcd for $C_{17}H_{21}O_3$: C, 74.96; H, 7.41. Found: C, 74.49; H, 7.69.

(*E*)-1-(2-Nitroethenyl)-1-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]-1,4-dihydronaphthalene (8). The crude aldehyde **7** (10.5 g, 38 mmol) was dissolved in 378 mL of 2-propanol, treated with $KF{\cdot}2H_2O$ (3.73 g, 39 mmol) and CH_3NO_2 (12.34 mL, 228 mmol), and stirred for 9 h at room temperature. The solution was concentrated in vacuo until the volume decreased to 160 mL, then diluted with 160 mL of CH_2Cl_2, filtered, and concentrated to give the intermediate nitro aldol with a crude weight of 11.16 g.

The crude nitro aldol (11.16 g, 33.5 mmol) was dissolved in 158 mL of CH_2Cl_2. DMAP (10.29 g, 84.2 mmol) was added, and the solution was cooled to 0 °C. Acetic anhydride (3.63 mL, 38.5 mmol) was added dropwise. The mixture was stirred at 0 °C for 10 min. The solution was poured into $NaHCO_3$, and brine was added. The mixture was extracted with CH_2Cl_2. The product was concentrated, applied to a silica gel column, with enough CH_2Cl_2 to dissolve the residue, and then eluted with a gradient of 15–25% EtOAc/hexane to yield 7.42 g (61% overall from the alcohol **6**) of **8** as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, 1 H, J = 13.4 Hz), 7.29–7.16 (m, 4 H), 6.81 (d, 1 H, J = 13.4 Hz), 6.17 (dt, 1 H, J = 10.1, 3.6 Hz), 5.52 (dt, 1 H, J = 10.1, 2.1 Hz), 3.94–3.81 (m, 4 H), 3.41 (m, 2 H), 2.19 (td, 1 H, J = 12.9, 4.4 Hz), 1.84 (td, 1 H, J = 12.9, 4.0 Hz), 1.59–1.52 (m, 1 H), 1.30–1.24 (m, 1 H), 1.24 (s, 3 H); IR 2980, 2880, 1640, 1520, 1490,

1450, 1370, 1340, 1060, 1040; HRMS calcd for $C_{18}H_{22}NO_4$ (m + 1)/z 316.1550, found (CI) 316.1555.

1-(2-Aminoethyl)-1-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]-1,4-dihydronaphthalene (9). The nitro olefin **8** (2.84 g, 8.5 mmol) was dissolved in 88 mL of THF and added slowly to LAH (1.15 g, 3.3 equiv) in 60 mL of THF at 0 °C. The mixture was stirred for 9 h at room temperature, then cooled to 0 °C, and diluted with 150 mL of ether. Water (1.8 mL) was added dropwise, followed by 20% NaOH (1.8 mL), then more water (4 mL). The mixture was filtered and dried ($MgSO_4$). The filter cake was washed with CH_2Cl_2. Removal of solvents gave crude **9**, which was purified by column chromatography [eluting with a gradient of 0.5–6% (12% NH_3/MeOH)/$CHCl_3$] to yield 1.77 g (68%) of **9** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.06 (m, 4 H), 5.98 (dt, 1 H, J = 10.2, 3.4 Hz), 5.43 (dt, 1 H, J = 10.2, 2.0 Hz), 3.93–3.73 (m, 4 H), 3.34 (m, 2 H), 2.62–2.53 (m, 1 H), 2.32–2.22 (m, 1 H), 2.02–1.81 (m, 2 H), 1.76–1.67 (m, 1 H), 1.60 (td, 1 H, J = 13.0, 4.0 Hz), 1.48 (td, 1 H, J = 13.4, 4.0 Hz), 1.21 (s, 3 H), 1.10 (td, 1 H, J = 13.3, 4.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.55, 134.41, 132.69, 128.03, 126.21, 125.33, 124.43, 109.76, 64.12, 47.75, 41.38, 38.20, 37.75, 33.46, 29.73, 23.46; IR 3372, 3312, 2938, 2874, 1662, 1489, 1453, 1375, 1217, 1046; HRMS calcd for $C_{18}H_{25}NO_2$ m/z 287.1886, found (EI) 287.1885.

1-[2-(N-Methylamino)ethyl]-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,4-dihydronaphthalene (10). To the amine **9** (1.75 g, 6.1 mmol) in 36 mL of pyridine at 0 °C was added trifluoroacetic anhydride (3.58 mL, 25.4 mmol). After 20 min, methanol (1.5 mL) was added. The pyridine was removed under vacuum. The residue was partitioned between Et_2O and $NaHCO_3$ (aqueous) and then purified by column chromatography (eluting with a gradient of 5–20% EtOAc/hexane) to yield 2.04 g (87%) of the amide.

The amide was dissolved in 38 mL of THF containing 18-crown-6 (0.10 g, 0.38 mmol), and KH (0.39 g, 9.75 mmol) was added. This mixture was stirred at room temperature for 10 min. Iodomethane (1.07 mL, 17.2 mmol) was added, and the solution was stirred for 1 h at room temperature and then refluxed for 30 min. The solution was diluted with water and extracted with CH_2Cl_2. Removal of solvent yielded the crude methylated amide, as a mixture of rotamers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.05 (m, 4 H), 6.10–6.03 (m, 1 H), 5.48–5.39 (m, 1 H), 3.92–3.71 (m, 4 H), 3.37 (m, 2 H), 3.2 (m, 1 H), 2.90, 2.86 (2 s, 3 H), 2.8 (m, 1 H), 2.18–1.07 (m, 6 H), 1.21, 1.20 (2 s, 3 H).

The methylated amide was dissolved in 2:1 MeOH/H_2O (90 mL) containing 3 g of KOH. The solution was stirred for 30 min. Methanol was removed under vacuum. The reaction mixture was partitioned between water and CH_2Cl_2. The product **10** was purified by column chromatography [eluting with 0.4% (12% NH_3/MeOH)/CH_2Cl_2]. Overall yield from **9** to **10** was 87%: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.07 (m, 4 H), 5.98 (dt, 1 H, J = 10.2, 3.4 Hz), 5.43 (dt, 1 H, J = 10.2, 1.8 Hz), 3.93–3.75 (m, 4 H), 3.35 (s, 2 H), 2.43 (td, 1 H, J = 11.7, 5.0 Hz), 2.27 (s, 3 H), 2.16–2.00 (m, 2 H), 1.93 (td, 1 H, J = 12.9, 4.3 Hz), 1.78–1.68 (m, 1 H), 1.68 (td, 1 H, J = 12.9, 4.0 Hz), 1.48 (td, 1 H, J = 13.2, 4.0 Hz), 1.21 (s, 3 H), 1.10 (td, 1 H, J = 13.2, 4.3 Hz); IR 3324, 2948, 2884, 1692, 1489, 1453, 1375, 1004; HRMS calcd for $C_{19}H_{27}NO_2$ m/z 301.2043, found (EI) 301.2035.

1-[2-(N-Chloro-N-methylamino)ethyl]-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,4-dihydronaphthalene (3). The amine **10** (1.49 g, 4.94 mmol) was dissolved in 90 mL of Et_2O and cooled to 0 °C. NCS (797 mg, 5.97 mmol) was added, and the solution was stirred for 30 min. More NCS (66 mg, 0.49 mmol) was added, and the solution was stirred for an additional 30 min. The solvent was removed and the product purified on a short silica gel column (eluting with a gradient of 10–20% EtOAc/hexane) to obtain 86% of **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.07 (m, 4 H), 6.00 (dt, 1 H, J = 10.3, 3.5 Hz), 5.43 (dt, 1 H, J = 10.3, 1.9 Hz), 3.90–3.72 (m, 4 H), 3.45 (s, 2 H), 2.8–2.71 (m, 1 H), 2.79 (s, 3 H), 2.38 (td, 1 H, J = 12.1, 4.5 Hz), 2.23 (td, 1 H, J = 12.3, 4.5 Hz), 1.96 (dd, 1 H, J = 13.1, 4.3 Hz), 1.89 (dd, 1 H, J = 13.1, 4.2 Hz), 1.64 (td, 1 H, J = 12.9, 3.9 Hz), 1.49 (td, 1 H, J = 13.2, 3.9 Hz), 1.21 (s, 3 H), 1.10 (td, 1 H, J = 13.3, 4.3 Hz).

Pyrrolidines 2a and 2b and Elimination Product 11. The chloroamine **3** (311 mg, 0.93 mmol) was dissolved in 24 mL of THF and cooled to −10 °C. To this solution was added dropwise 12 mL of 1:1 AcOH/H_2O containing CuCl (18.4 mg, 0.185 mmol) and $CuCl_2 \cdot 2H_2O$ (158 mg, 0.9 mmol). The solution became heterogeneous and took on a greenish color. After the reaction mixture was stirred for 15 min, it was cooled to −40 °C and 20% NaOH (aqueous) (50 mL) was added. The resulting solution was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to obtain the crude ketals. These could be separated by column chromatography on silica gel (eluting with a gradient of 15–40% EtOAc/hexane) to obtain, in order of decreasing R_f, 141 mg (45%) of the ethylene ketal of **2a** and 61 mg (20%) of the ethylene ketal of **2b**. Ketal of **2a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.03 (m, 4 H), 4.02–3.95 (m, 1 H), 3.92–3.78 (m, 4 H), 3.16–3.09 (m, 2 H), 3.02–2.94 (dd, 1 H, J = 15.3, 9.9 Hz), 2.76–2.62 (m, 2 H), 2.70 (s, 3 H), 2.06–1.92 (m, 2 H), 1.89–1.70 (m, 2 H), 1.54 (td, 1 H, J = 12, 4.5 Hz), 1.29–1.19 (m, 1 H), 1.24 (s, 3 H). Ketal of **2b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.04 (m, 4 H), 4.51–4.46 (m, 1 H) 3.92–3.77 (m, 4 H), 3.30–3.22 (ee, 1 H, J = 15.5, 7.7 Hz), 3.10–3.01 (m, 4 H), 2.80 (d, 1 H, J = 3.3 Hz), 2.71–2.6 (m, 1 H), 2.62 (s, 3 H), 2.13–2.07 (m, 2 H), 1.83–1.76 (m, 2 H), 1.57–1.47 (m, 1 H), 1.35–1.24 (m, 1 H), 1.23 (s, 3 H). A small amount (ca. 5%) of the ketal of **11** eluted after the two major products.

The anti ketal (444.5 mg, 1.32 mmol) was dissolved in 6 mL of MeOH. To this was added 3 mL of H_2O containing concentrated HCl (16 drops). After being stirred for 1 h, the solution was poured into $NaHCO_3$ (aqueous) and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to give 386 mg (100%) of pyrrolidine **2a**. The same hydrolysis procedure could be applied to the syn ketal and the elimination product.

In practice, the crude cyclization products were usually subjected to hydrolysis (as above) and chromatographed on silica gel since separation is accomplished more easily at this point.

Pyrrolidine **2a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.09 (m, 4 H), 4.10–4.04 (m, 1 H, J = 9.0, 6.7, 3.6 Hz), 3.20 (dd, 1 H, J = 15.5, 3.6 Hz), 3.17–3.09 (m, 1 H), 2.99 (dd, 1 H, J = 15.5, 9.0 Hz), 2.74–2.7 (m, 1 H), 2.68 (s, 3 H), 2.61 (d, 1 H, J = 6.7 Hz), 2.48–2.37 (m, 1 H), 2.16–1.91 (m, 5 H), 2.04 (s, 3 H); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25–7.10 (m, 4 H), 4.06–4.03 (m, 1 H, J = 8.9, 6.6, 3.5 Hz), 3.19 (dd, 1 H, J = 15.4, 3.5 Hz), 3.13–3.10 (m, 1 H), 2.98 (dd, 1 H, J = 15.4, 8.9 Hz), 2.70–2.63 (m, 1 H), 2.66 (s, 3 H), 2.60 (d, 1 H, J = 6.6 Hz), 2.46–2.39 (m, 1 H), 2.14–1.91 (m, 5 H), 2.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 208.48, 141.24, 133.83, 128.53, 127.43, 126.19, 125.69, 75.48, 61.27, 54.49, 45.76, 43.95, 41.59, 38.87, 37.54, 34.22, 30.05; IR 2938, 2851, 2791, 1715, 1453, 1362, 1191; TLC R_f 0.58 (50% EtOAc/hexane); HRMS calcd for $C_{17}H_{22}NOCl$ m/z 291.1392, found (EI) 291.1391. Anal. Calcd for $C_{17}H_{22}NOCl$: C, 69.97; H, 7.60; N, 4.80; Cl, 12.15. Found: C, 70.07; H, 7.67; N, 4.60; Cl, 12.30. Pyrrolidine **2b**: ^{1}H NMR ($CDCl_3$) δ 7.28–7.06 (m, 4 H), 4.53–4.49 (m, 1 H, J = 7.0, 3.4, 3.0 Hz), 3.24 (dd, 1 H, J = 15.7, 7.0 Hz), 3.12–3.02 (m, 1 H), 3.06 (dd, 1 H, J = 15.7, 3.0 Hz), 2.75 (d, 1 H, J = 3.4 Hz), 2.72–2.6 (m, 1 H), 2.60 (s, 3 H), 2.34–2.25 (m, 1 H), 2.16–1.91 (m, 5 H), 2.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 207.95, 141.46, 133.48, 128.58, 127.17, 126.35, 125.96, 72.79, 58.88, 54.36, 49.70, 42.85, 39.50, 39.12, 36.31, 36.15, 29.89; IR 2934, 2838, 2791, 1715, 1453, 1362, 1161; TLC R_f 0.34 (50% EtOAc/hexane); HRMS calcd for $C_{17}H_{22}NOCl$ m/z 291.1392, found (EI) 291.1392. Elimination product **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.08 (m, 4 H), 6.62 (d, 1 H, J = 9.8 Hz), 6.07 (dd, 1 H, J = 9.8, 5.0 Hz), 2.91 (m, 1 H), 2.45–1.81 (m, 8 H), 2.42 (s, 3 H), 1.99 (s, 3 H); IR 2926, 2853, 2772, 1711, 1451, 1362, 1161; TLC R_f 0.45 (10% MeOH/CH_2Cl_2); HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1624, found (EI) 255.1619.

Preparation of Enol Ether 12. (Note: This procedure has not, in our hands, led to reproducible results.) The pyrrolidine **2a** (44.4 mg, 0.152 mmol) was dissolved in 3 mL of toluene and heated for 8 h at reflux. The toluene was refluxed up the side arm of an addition funnel and allowed to filter back down through a layer of K_2CO_3. TLC showed no starting material and only one product.[27] The solution was concentrated to give the crude product, which was purified by preparative TLC (10% MeOH/CH_2Cl_2), to give **12** (31 g, 80%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.11 (m, 4 H), 4.37 (d, 1 H, J = 5.7 Hz), 4.09 (d, 1 H, J = 4.2 Hz), 3.32 (m, 1 H), 3.08–2.93 (m, 2 H), 2.69 (dd, 1 H,

(27) Identification of **12** and **12'** is facilitated by the fact that these compounds stain a very bright magenta with anisaldehyde reagent.

J = 16.8, 5.7 Hz), 2.53–2.04 (m, 3 H), 2.46 (s, 3 H), 1.76 (td, 1 H, J = 12.7, 4.7 Hz), 1.60–1.58 (m, 1 H), 1.54 (d, 3 H, J = 0.9 Hz); ^{1}H NMR (benzene-d_6, 300 MHz) δ 7.21–7.02 (m, 4 H), 4.35 (d, 1 H, J = 5.7 Hz), 4.22 (d, 1 H, J = 4.2 Hz), 3.30 (m, 1 H), 3.03 (dd, 1 H, J = 18.0, 5.7 Hz), 2.89 (d, 1 H, J = 18.0 Hz), 2.56 (dd, 1 H, J = 16.8, 5.7 Hz), 2.23–1.97 (m, 3 H), 2.19 (s, 3 H), 1.64 (td, 1 H, J = 12.5, 4.9 Hz), 1.49 (d, 3 H, J = 1.8 Hz), 1.4 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.42, 138.17, 137.93, 127.42, 126.09, 125.74, 125.00, 93.41, 56.16, 46.62, 42.59, 39.48, 34.16, 31.50, 23.89, 19.74 (one peak is obscured by $CDCl_3$ resonances); ^{13}C NMR (benzene-d_6, 75.5 MHz) δ 151.16, 139.06, 138.76, 94.20, 77.99, 56.87, 47.01, 42.99, 40.10, 34.83, 32.35, 24.71, 20.25 (four peaks are in the solvent absorption region); IR 2921, 2851, 1741, 1684, 1449, 1648; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1624, found (EI) 255.1622.

(9α)-9-Hydroxy-5-[2-(2-methyl-1,3-dithian-2-yl)ethyl]-2-methyl-6,7-benzomorphan (13). The enol ether **12** (29 mg, 0.15 mmol) was dissolved in 1.5 mL of AcOH. 1,3-Propanedithiol (61 μL, 0.61 mmol) was added followed by BF_3·Et_2O (32 μL, 0.26 mmol). The solution was stirred at 60 °C for 5 h, then poured into $NaHCO_3$ (aqueous), and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to obtain the crude product. Preparative TLC (10% MeOH/CH_2Cl_2) yielded 40.4 mg (73%) of the thioketal alcohol **13** as a yellow oil: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.35–7.12 (m, 4 H), 4.08 (d, 1 H, J = 4.1 Hz), 3.27 (m, 1 H), 3.03–2.77 (m, 6 H), 2.53–2.39 (m, 2 H), 2.47 (s, 3 H), 2.28–1.92 (m, 8 H), 1.65 (s, 3 H); ^{13}C NMR ($CDCl_3$, 91 MHz) δ 138.22, 135.27, 126.52, 125.68, 125.20, 125.09, 71.59, 59.10, 50.04, 49.96, 42.92, 40.59, 38.23, 36.16, 32.26, 28.63, 27.47, 27.40, 26.17, 24.08; IR 3060, 2922, 2855, 1451, 1424, 1277, 1055; HRMS calcd for $C_{20}H_{29}NOS_2$ m/z 363.1693, found (EI) 363.1694. Anal. Calcd for $C_{20}H_{29}NOS_2$: C, 66.07; H, 8.04; N, 3.85; S, 17.64. Found: C, 65.73; H, 7.99; N, 3.67; S, 17.65.

Direct Preparation of 13 from 2a. A solution of **2a** (80 mg, 0.27 mmol) in 5 mL of toluene containing 500 mg of $NaHCO_3$ was refluxed for 7 h, then cooled, and diluted with CH_2Cl_2. After filtration, the solvent was removed to afford a residue consisting almost entirely of **12** and **12′**. The crude enol ethers were dissolved in 3 mL of acetic acid and treated with 1,3-propanedithiol (130 μL, 1.30 mmol) and BF_3·Et_2O (60 μL, 0.48 mmol). After the mixture was stirred for 6 h at 60 °C, workup as before provided **13** (59 mg, 60%).

9-Keto-5-[2-(2-methyl-1,3-dithian-2-yl)ethyl]-2-methyl-6,7-benzomorphan (14). The thioketal alcohol **13** (46 mg, 0.13 mmol) was dissolved in 4 mL of DMSO, and Ac_2O (500 μL) was added. The solution was stirred for 36 h at room temperature, then poured into $NaHCO_3$ (aqueous), stirred for 30 min, and then extracted with Et_2O. The organic extracts were washed with water. Preparative TLC (12% MeOH/CH_2Cl_2) yielded 41 mg (89%) of the thioketal ketone **14** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.17 (m, 4 H), 3.50 (d, 1 H, J = 16.2 Hz), 3.31 (d, 1 H, J = 5.7 Hz), 3.17 (dd, 1 H, J = 18.2, 5.7 Hz), 3.06–2.97 (m, 1 H), 2.93–2.87 (m, 1 H), 2.85–1.70 (m, 12 H), 2.45 (s, 3 H), 1.63 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 211.21, 138.95, 135.76, 127.37, 127.07, 126.62, 125.53, 66.51, 51.66, 49.20, 46.23, 44.03, 41.63, 35.19, 32.06, 28.34, 27.42, 26.49, 27.27, 25.00; IR 2930, 1728, 1450, 1422, 1275, 760, 735; HRMS calcd for $C_{20}H_{27}NOS_2$ m/z 361.1536, found (EI) 361.1531.

9-Keto-5-(3-ketobutyl)-2-methyl-6,7-benzomorphan (15). The thioketal ketone **14** (17.4 mg, 0.0481 mmol) was dissolved in 0.2 mL of 9:1 acetone/water. NCS (7.1 mg, 0.0529 mmol, 1.1 equiv), dissolved in 1.0 mL of 9:1 acetone/water, was added. After being stirred for 6 min at room temperature, the solution was poured into 15 mL of $NaHCO_3$ (aqueous) and extracted with CH_2Cl_2. Preparative TLC (10% MeOH/CH_2Cl_2) yielded 12 mg (92%) of the diketone **15** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.07 (m, 4 H), 3.54 (d, 1 H, J = 18.3 Hz), 3.35 (d, 1 H, J = 5.8 Hz), 3.16 (dd, 1 H, J = 18.3, 5.8 Hz), 2.80–2.5 (m, 3 H), 2.46 (s, 3 H), 2.30–2.12 (m, 4 H), 2.09 (s, 3 H), 1.70 (d, 1 H, J = 12.9 Hz); IR 2932, 1713, 1449, 1354, 1163, 1115, 760; HRMS calcd for $C_{17}H_{21}NO_2$ m/z 271.1573, found (EI) 271.1588.

8,14-Didehydro-17-methylmorphinan-7-one (16). Sodium (41.7 mg) was dissolved in 25 mL of MeOH. Argon was bubbled gently through this solution for 15 min. To 12 mg (0.044 mmol) of the diketone **15** was added 5.0 mL of this solution (containing 8.34 mg of Na, 0.363 mmol, 8.2 equiv). The solution was refluxed for 65 min. (Prior to completion of the reaction, a possible aldol intermediate of lower R_f was observed.) Three drops of AcOH were then added, and the mixture was partitioned between water and CH_2Cl_2 to give 9.5 mg (85%) of the crude enone **16**, which was obtained in good purity: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.14 (m, 4 H), 6.00 (s, 1 H), 3.64 (d, 1 H, J = 6 Hz), 3.46 (d, 1 H, J = 18.0 Hz), 3.03 (dd, 1 H, J = 18.0, 6.0 Hz), 2.70–2.12 (m, 7 H), 2.50 (s, 3 H), 1.58 (d, 1 H, J = 12.8 Hz); IR 2928, 2853, 1713, 1678, 1451, 1173, 758; HRMS calcd for $C_{17}H_{19}NO$ m/z 253.1468, found (EI) 253.1468.

17-Methylmorphinan-7-one (1). The enone **25** (8 mg) was dissolved in 2 mL of MeOH, and 5% Pd/C (20 mg) was added. The mixture was stirred under a hydrogen atmosphere for 1 h, at which time TLC showed the reaction to be complete. The crude product was purified by column chromatography (eluting with a gradient of 3–10% MeOH in CH_2Cl_2) to give morphinan **1** (6 mg, 75%): mp 92–93 °C (white crystals from Et_2O/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, 1 H, J = 9 Hz), 7.27–7.16 (m, 3 H), 3.14 (d, 1 H, J = 18 Hz), 2.89 (m, 1 H), 2.72 (m, 1 H), 2.53–2.12 (m, 9 H), 2.43 (s, 3 H), 1.78 (m, 2 H), 1.50 (m, 1 H); IR 2924, 1713, 1449, 1169, 1125, 764, 722; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1624, found (EI) 255.1617. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.48. Found: C, 79.57; H, 8.14; N, 5.43.

Deoxygenation of Morphinan 1 To Yield 18. A solution of **1** (25 mg, 0.10 mmol) in 4 mL of EtOH was treated with excess $NaBH_4$ (100 mg) and stirred for 45 min. The solution was then partitioned between water and CH_2Cl_2 and the organic phase dried over K_2CO_3 and then evaporated to give 7-hydroxy-*N*-methylmorphinan (**17**) (25 mg, 100%). ^{1}H NMR showed the material to be a 12:1 mixture of the equatorial and axial epimers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.09 (m, 4 H), 3.70 (m, 1 H), 3.05 (d, 1 H, J = 18 Hz), 2.83 (m, 1 H), 2.65 (dd, 1 H, J = 18, 6 Hz), 2.63–2.30 (m, 2 H), 2.36 (s, 3 H), 2.03 (dt, 1 H, J = 12, 3 Hz), 1.89–1.11 (m, 9 H); the oxymethine proton of the axial epimer was discernible at δ 3.95, and it was from the relative areas of this peak and the peak at δ 3.70 that the epimer ratio is estimated. The other axial epimer resonances could not be observed.

Alcohol **17** (25 mg, 0.10 mmol) was dissolved in 0.5 mL of CH_2Cl_2 and treated with 1,1′-thiocarbonyldiimidazole (38 mg, 0.21 mmol). After being stirred overnight, the reaction mixture was applied directly to a preparative TLC plate and eluted with 12% MeOH/CH_2Cl_2. In this way the equatorial thiocarbonyl imidazolide was obtained (29 mg, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 7.52 (s, 1 H), 7.30–7.16 (m, 4 H), 6.96 (s, 1 H), 5.56 (m, 1 H), 3.12 (d, 1 H, J = 18.9 Hz), 3.04 (m, 1 H), 2.79 (dd, 1 H, J = 18.9, 5.7 Hz), 2.65–2.42 (m, 2 H), 2.48 (s, 3 H), 2.20–2.04 (m, 4 H), 1.83 (dt, 1 H, J = 12, 3 Hz), 1.58–1.25 (m, 4 H). The axial epimer (2 mg, 5%) could also be obtained and had an R_f lower than that of the major product. This compound was not carried on further.

A solution of the equatorial thiocarbonyl imidazolide (29 mg, 0.08 mmol), Bu_3SnH (43 μL, 0.16 mmol), and 2 mg of AIBN in 4 mL of toluene was refluxed for a period of 1.5 h. The reaction mixture was then partitioned between Et_2O and dilute aqueous HCl. The aqueous layer was basified with NH_4OH and thoroughly extracted with CH_2Cl_2. The organic extracts were dried (K_2CO_3) and evaporated to give **18**, which then was purified by preparative TLC on silica gel (12% MeOH/CH_2Cl_2) (12 mg, 63%). The chromatographic behavior and 300-MHz ^{1}H NMR and IR spectra of **18** were identical with those of an authentic sample.[21]

Exocyclic Enol Ether 12′. A solution of **2a** (34 mg, 0.12 mmol) and PMP (27 μL, 0.15 mmol) in 1 mL of toluene was cooled to 0 °C. A solution of $AgBF_4$ (25 mg, 0.13 mmol) in 1 mL of toluene was added and the reaction allowed to proceed for 30 min with exclusion of light. An additional 25 mg of $AgBF_4$ in 1 mL of toluene followed by 27 μL of PMP was added and the reaction mixture stirred for 30 min longer. The mixture was then diluted with $NaHCO_3$ (aqueous) and CH_2Cl_2 and filtered through Celite. The aqueous phase was thoroughly extracted with CH_2Cl_2, and the CH_2Cl_2 layers were dried over K_2CO_3 and evaporated. In this way was obtained **12′** (30 mg) judged to be >80% pure by ^{1}H NMR: δ 7.25–7.12 (m, 4 H), 4.29 (d, 1 H, J = 1.5 Hz), 4.02 (d, 1 H, J = 1.5 Hz), 3.81 (d, 1 H, J = 3.9 Hz), 3.23 (t, 1 H, J = 4.0 Hz), 3.04 (d, 1 H, J = 18 Hz), 2.91 (dd, 1 H, J = 18, 4 Hz), 2.65–2.01 (m, 4 H), 2.43 (s, 3 H), 1.74–1.20 (m, 4 H). This compound was not stable to silica gel chromatography.

Silyl Enol Ether 19. A solution of lithium tetramethylpiperidide (LTMP) was prepared by addition of 1.5 M *n*-BuLi in hexane (145 μL, 0.22 mmol) to a solution of tetramethylpiperidine (TMP) (37 μL, 0.22 mmol) in 0.5 mL of THF at 0 °C. After the reaction mixture was stirred for 15 min, the solution was cooled to −78 °C and TMS-Cl (31 μL, 0.24 mmol) was injected by syringe. The pyrrolidine **2a** (24 mg, 0.08 mmol), dissolved in 0.5 mL of THF, was added dropwise, over a period of 1 min. The solution was stirred for 15 min before quenching at −78 °C with Et_3N followed by $NaHCO_3$ (aqueous). The solution was poured into $NaHCO_3$ (aqueous) and extracted with CH_2Cl_2. The solution was dried (K_2CO_3) and concentrated to give 30 mg (100%) of silyl enol ether **19**. The product, being hydrolyzed rapidly on silica gel, could not be purified further: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.05 (m, 4 H), 4.01–3.94 (m, 1 H), 3.97 (m, 2 H), 3.18–3.09 (m, 1 H), 3.12 (dd, 1 H, J = 15.3, 4.0 Hz), 3.02 (dd, 1 H, J = 15.3, 10.0 Hz), 2.75 (d, 1 H, J = 8.0 Hz), 2.71 (s, 3 H), 2.7–2.63 (m, 1 H), 2.09–1.1 (m, 6 H), 0.16 (s, 9 H).

Silyl Enol Ether 20. A solution (0.2 M) of LTMP was prepared by adding *n*-BuLi (1.55 M in hexane, 750 μL, 1.16 mmol) to TMP (205 μL, 1.22 mmol) in 5 mL of THF at 0 °C and stirring the mixture at this temperature for 30 min. A separate solution of **2a** (32 mg, 0.11 mmol) and TBDMS-Cl (130 mg, 0.86 mmol) in 2.2 mL of THF/HMPA (10:1) was prepared and cooled to −25 °C. A 500-μL portion of the LTMP solution was added dropwise to the stirred mixture of **2a** and silyl chloride. A 250-μL portion was added after 15 min, and after 15 min more, a further 200 μL was added. After the mixture was stirred for an additional 10 min, TLC indicated the reaction to be complete. The reaction mixture was diluted with NEt_3 (2 mL) and partitioned between $NaHCO_3$ (aqueous) and Et_2O. The organic layer was washed with water and brine and then evaporated. The product was purified by preparative TLC on silica gel (25% EtOAc/hexane) to obtain **20** (32 mg, 72%): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.05 (m, 4 H), 3.98 (m, 1 H), 3.95 (m, 2 H), 3.17–3.00 (m, 3 H), 2.78–2.62 (m, 2 H), 2.70 (s, 3 H), 2.03–1.58 (m, 6 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 159.3, 142.1, 134.1, 128.1, 127.3, 126.1, 126.0, 89.8, 75.4, 62.5, 54.8, 51.0, 44.3, 41.3, 39.5, 38.3, 31.8, 25.7, 18.0, −4.7 (2 C); IR 2955, 2856, 1290, 1253.

Synthesis of Morphinan 1 from 20. A. Using $AgBF_4$. To a solution of **20** (54 mg, 0.13 mmol) in 3 mL of toluene was added $AgBF_4$ (56 mg, 0.29 mmol) in 2 mL of toluene. A precipitate of AgCl began to form immediately. The mixture was stirred in the dark for 20 min and then diluted with CH_2Cl_2 and $NaHCO_3$ (aqueous). The mixture was then filtered through Celite and the aqueous phase extracted with additional CH_2Cl_2. The organic phase was dried (K_2CO_3), evaporated, and the product purified by preparative TLC on silica gel (eluting with 12% MeOH/CH_2Cl_2) to obtain **1** (19 mg, 56%) identical in all respects with that prepared from enone **16**.

B. Using $AgSbF_6$. A solution of **20** (24 mg, 0.06 mmol) in toluene (2 mL) was treated with $AgSbF_6$ (50 mg, 0.14 mmol) and stirred for 30 min at 25 °C. Product isolation was accomplished in the same manner as described for the $AgBF_4$-mediated reaction (part A). The yield of **1** was 9.7 mg (64%).

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Registry No. (±)-**1**, 113777-44-9; (±)-**2a**, 113777-45-0; (±)-**2a** (ketal), 113777-69-8; (±)-**2b**, 113830-02-7; (±)-**2b** (ketal), 113830-03-8; (±)-**3**, 113777-46-1; **5**, 37865-96-6; (±)-**6**, 113777-48-3; (±)-**6** (acid), 113777-63-2; (±)-**7**, 113777-49-4; (±)-**8**, 113777-50-7; **8** (nitro-aldol), 113777-64-3; (±)-**9**, 113777-51-8; (±)-**9** (*N*-trifluoroacetyl deriv), 113777-65-4; (±)-**10**, 113777-52-9; (±)-**10** (X = $COCf_3$), 113777-66-5; (±)-**11**, 113777-53-0; (±)-**11** (ketal), 113777-70-1; (±)-**12**, 113777-54-1; (±)-**12′**, 113777-68-7; (±)-**13**, 113777-55-2; (±)-**14**, 113777-56-3; (±)-**15**, 113777-57-4; (±)-**16**, 113777-58-5; (±)-7β-**17**, 113777-59-6; (±)-7α-**17**, 113777-47-2; (±)-7β-**17** (thiocarbonylimidazolide), 113777-67-6; (±)-**18**, 63783-50-6; (±)-**19**, 113777-60-9; (±)-**20**, 113777-61-0; (±)-1,4-dihydro-1-naphthoic acid, 113777-62-1.

An ab Initio Molecular Orbital Study of Acetyl Ions XCH_2CO^+, H_3CCS^+, H_3SiCO^+, and H_3CSiO^+

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Structures and energies of acetyl cations XCH_2CO^+, where X is H, CH_3, NH_2, OH, and F, have been obtained by using ab initio molecular orbital calculations with a 6-31G* basis set. With the exception of $H_2NCH_2CO^+$, which dissociates into CO and $H_2CNH_2^+$, all XCH_2CO^+ ions are the global minima on their respective surfaces. The MP2/6-31G**//6-31G* energy for elimination of CO from H_3CCO^+ is 81.8 kcal/mol (experimental 84.6 kcal/mol) but substitution of one hydrogen greatly decreases the dissociation energy. At the Hartree–Fock 6-31G* level the dissociation energy of $HOCH_2CO^+$ is close to zero but inclusion of correlation energy (MP2/6-31G*) has the effect of shortening the C–C bond and increasing the dissociation energy to 12.8 kcal/mol. The thioacetyl ion is the global minimum on the $C_2H_3S^+$ surface and cleavage of the C–C bond to form CH_3^+ and CS has a higher energy (125.6 kcal/mol). On the $SiCH_3O^+$ surface structures have been optimized for six isomers and for three pairs of dissociation products. The β-sila acetyl ion, H_3SiCO^+, is higher in energy than the global minimum H_3CO^+=Si by 25.8 kcal/mol. For 1,2-shifts of SiH_3 in H_3SiCO^+ and CH_3 in H_3CSiO^+ the transition structures have very long bonds and are close in energy to the dissociation products.

Acylium ions RCO^+ have long been thought to be the intermediates in Friedel–Crafts acylation reactions[1] and in the decarbonylation of carboxylic acids in concentrated mineral acids. More recently many acylium ions have been observed under stable ion conditions in superacid solutions.[2] Acylium ions are also common species in the gas phase. They are produced in the mass spectrometric decomposition of most ions containing carbonyl groups and the simplest acylium ion, HCO^+, along with the isomeric

(1) *Friedel-Craft and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, 1963; Vol. 1.

(2) Olah, G. A.; Germain, A.; White, A. M. *Carbonium Ions*; Olah, G. A.; Schleyer, P. v. R. Eds.; Wiley Interscience: New York, 1976; Vol V, p 2049.

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