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Synthesis of (−)-Morphine

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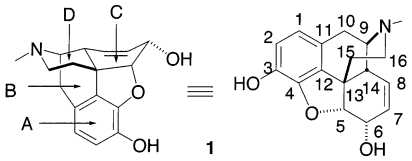
Morphine **(1)** is the principal alkaloid of opium, derived from *Papaver somniferum L.*, or *P. album Mill*, *Papaveraceae*.[1] Morphine is also found in normal brain, blood, and liver tissue.[2] The morphine alkaloids comprise a family of structurally related natural products of unique clinical importance in medicine.[3] The unusual architecture of morphine has offered a continuing challenge to the art and science of organic synthesis.[4−6]



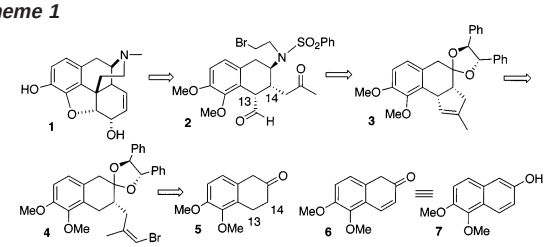
We envisioned that (−)-morphine **1** could ultimately be constructed from the easily prepared 5,6-dimethoxy-β-tetralone **5** (Scheme 1). A key step in this approach was the bis-intramolecular cyclization of the keto aldehyde **2**. The challenge was the introduction of the formyl substituent at C-13 (morphine numbering). Conjugate addition to an enone such as **6** would not be possible, as the enone **6** would tautomerize to the β-naphthol **7**. We hypothesized that initial alkylation of **5** at the C-14 position followed by ketalization with (*S*,*S*)-(−)-hydrobenzoin would give the bromoalkene **4**. Intramolecular alkylidene C−H insertion[7] would then convert bromoalkene **4** to the cyclopentene **3**, and thus give access to **2**.

Our approach to the synthesis of (−)-morphine **1** began with the preparation of β-tetralone **13** (Scheme 2). Using modifications of the published procedures,[8] we alkylated 1,6-dibromo-2-naphthol **8** with iodomethane to give the methoxynaphthalene **9**. Ullman coupling with sodium methoxide then gave the desired trimethoxynaphthalene **10**. Dissolving metal reduction followed by hydrolysis led to the desired β-tetralone **5**. The β-tetralone **5** would tend to alkylate at the benzylic position. The procedure of Aristoff,[9] methoxycarbonylation, dianion alkylation using *cis*-1,3-dibromo-2-methyl-1-propene,[10] and decarboxylation, was therefore employed to obtain the alkylated β-tetralone **13**.

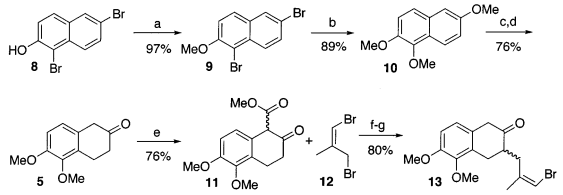
Protection of the β-tetralone **13** (Scheme 3) with (*S*,*S*)-(−)-hydrobenzoin gave the diastereomeric ketals **14** and **4**, which, as anticipated, were separable by silica gel chromatography. The undesired diastereomer **14** was readily recycled to the racemic β-tetralone **13**. Cyclization of ketal **4** via alkylidene carbene C−H insertion[7] followed by hydrolysis led to the enantiomerically pure ketone **15**. The beauty of this approach is that while β-tetralone **13** can readily racemize, β-tetralone **15** cannot.

The sterically congested ketone **15** was selectively reduced to the cis alcohol **16**. Direct displacement of the alcohol by a functionalized amine could not be achieved. Fortunately, the alcohol

Scheme 1

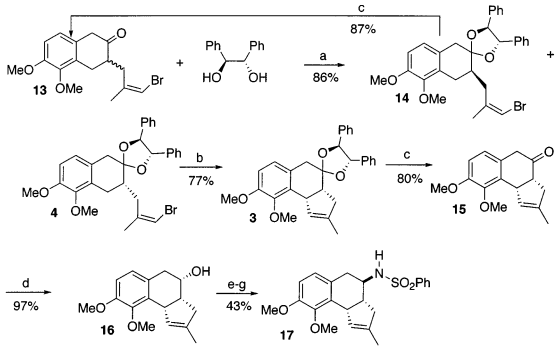


Scheme 2 [a]



[a] Conditions: (a) CH_3I, K_2CO_3, DMF; (b) $NaOCH_3$, collidine, CuI, MeOH, reflux; (c) Na, EtOH, reflux; (d) HCl, H_2O, reflux; (e) $(CH_3O)_2CO$, NaOMe, MeOH, reflux; (f) LDA (2 equiv), THF, 0 °C; (g) LiCl, DMSO, H_2O, reflux.

Scheme 3 [a]



[a] Conditions: (a) *p*-TSA, $HC(OEt)_3$, CH_2Cl_2; (b) KHMDS, Et_2O; (c) AcOH, H_2O, reflux; (d) L-selectride, THF, 0 °C; (e) $(PhO)_2P(O)N_3$, DEAD, Ph_3P, THF; (f) LAH/EtOH − (1/1), Et_2O; (g) $PhSO_2Cl$, Et_3N, CH_2Cl_2.

16 was smoothly converted to the azide via Mitsunobu coupling. Reduction and protection then gave sulfonamide **17**.

The key to the assembly of morphine was the anticipated selective bis-cyclization of keto aldehyde **2** (Scheme 4). Alkylation of the sulfonamide **17** with 1,2-dibromoethane under phase-transfer conditions provided **18**, which upon ozonolysis gave the desired keto aldehyde **2**. The benzylic proton α to the aldehyde in **2** is the most acidic, so we expected to obtain the aldehyde enolate selectively. Although the keto aldehyde **19** could be isolated after brief exposure to base, it was more practical to continue heating, to cleanly obtain the tetracycle **20**. The final conversion to complete the core structure of morphine **1** was the construction of the ether ring. Reduction of the enone **20** gave a single alcohol **21** (Scheme

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§ For X-ray analysis.

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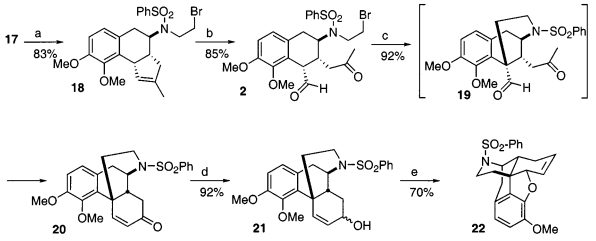
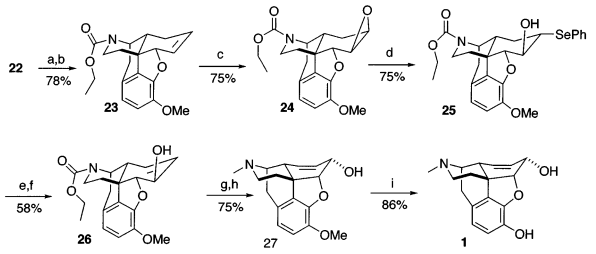
Scheme 4 [a]



[a] Conditions: (a) $BrCH_2CH_2Br$, 1 N NaOH, TBAB, toluene, reflux; (b) O_3, CH_2Cl_2, −78 °C, Ph_3P; (c) K_2CO_3, TBAB, toluene, reflux; (d) $NaBH_4$, EtOH; (e) BBr_3, CH_2Cl_2, −40 °C.

Scheme 5 [a]



[a] Conditions: (a) Red-Al, toluene, reflux; (b) ClCOOEt, Et_3N, CH_2Cl_2; (c) $[(C_8H_{17})_3NCH_3]^+{}_3[PO_4[W(O)(O_2)_2]_4{}^{3-}$, H_2O_2, DCE, reflux; (d) PhSeSePh, $NaBH_4$, EtOH, reflux; (e) $NaIO_4$, THF, H_2O; (f) Na_2CO_3, toluene, H_2O; (g) MnO_2, CH_2Cl_2; (h) $LiAlH_4$, THF, reflux; (i) BBr_3.

4), which upon brief exposure to BBr_3 gave clean cyclization to **22**, having the pentacyclic morphine skeleton.

The next challenge (Scheme 5) was the removal of the robust phenylsulfonyl protecting group. Although dissolving metal conditions failed, we found that Red-Al was very effective[11] for this difficult deprotection. Reprotection immediately followed to give the carbamate **23**.

To effect the final oxidation to the allylic alcohol of morphine, we first epoxidized the alkene **23** with H_2O_2.[12] Regioselective ring opening of the epoxide **24** then gave the selenide **25**. The expected selectivity exhibited in both the epoxidation and the epoxide opening was controlled by the strong steric influence of the arene ring, which effectively blocks both the lower face of the C ring and the backside attack at the C-6 position. Oxidation of the selenide **25** followed by elimination yielded the allylic alcohol **26** with the configuration at C-6 opposite to that of morphine. Manganese dioxide oxidation followed by $LiAlH_4$ reduction proceeded with the reported[13] high diastereocontrol to deliver codeine **27**. Finally, O-demethylation[14] gave morphine **1**, identical (TLC, ^1H NMR, ^{13}C NMR, $[\alpha]_D$) with natural material.

A β-tetralone-based approach to the synthesis of (−)-morphine **1** has been achieved, in 23 steps from **5**, with an overall yield of 0.77%. This synthesis opens the way to the preparation of a variety of C-10, C-15, and C-16 substituted morphine analogues that have previously not been available. The strategy outlined here for the enantioselective construction of three contiguous stereogenic centers and the novel ring cyclizations that followed will have many applications in target-directed organic synthesis.

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Note Added after Print Publication: Due to a production error, the graphics were incomplete in the version published on the Web 09/28/2002 (ASAP) and in the October 23, 2002 issue (Vol. 124, No. 42, pp 12416−12417); the correct electronic version of the paper was published on 11/27/02 and an Addition and Correction appears in the December 25, 2002 issue (Vol. 124, No. 51).

Supporting Information Available: Details for the preparation of compounds **1**−**27** (PDF), and X-ray data for compound ***i*** (CIF).[15] This material is available free of charge via the Internet at http://pubs.acs.org.

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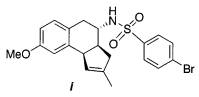
(15) β-Tetralone **13** was initially ketalized with (*R*,*R*)-(+)-hydrobenzoin. The first ketal diastereomer to elute via chromatography was converted to the *p*-bromobenzenesulfonamide *i*. This was determined by X-ray analysis to have the configuration at C-9, C-13, and C-14 shown.



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