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 alkyldiene C–H insertion7 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 trimethoxy-naphthalene 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 alkyldiene carbene C–H insertion7 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...
4), which upon brief exposure to BBr₃ 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 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 H₂O₂. 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-9, C-13, and C-14 shown. p-Tert-butyldimethylsilyl protection 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 by elimination yielded the allylic alcohol 26.

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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). This material is available free of charge via the Internet at http://pubs.acs.org.

References

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(2) Benshy, S. Life Sci. 1994, 55, 969.
(8) (a) Gold, E. H.; Babad, E. J. Org. Chem. 1972, 37, 2208. (b) Sodium bis(2-methoxyethoxy)aluminum hydride is sold as both Red-Al and Vinylide.
(9) (a) Venturrello, C.; D’Aloio, R. J. Org. Chem. 1988, 53, 1553. (b) Attempted epoxidation with peracids led to extensive decomposition.
(11) B-β-Tetralone 1a initially was ketalized with (R)-(+)-hydrobenzo. The first ketal diastereomer to elute via chromatography was converted to the p-bromobenzencesulfonamide. This was determined by X-ray analysis to have the configuration at C-9, C-13, and C-14 shown.