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Chemoenzymatic Synthesis of the Morphine Skeleton via Radical Cyclization and a C_{10}–C_{11} Closure.

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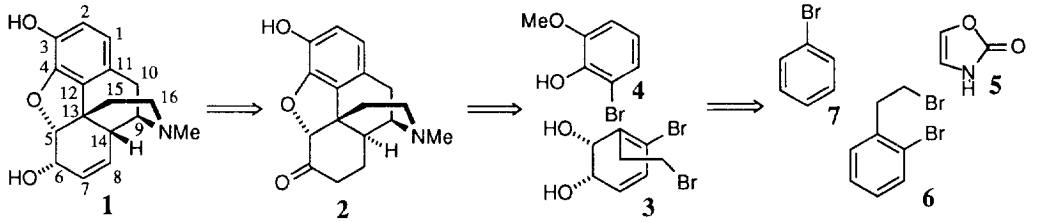
Abstract: A short synthesis of a morphinan skeleton has been accomplished. The key steps involve enzymatic dihydroxylation of β-bromoethyl benzene, vinyl and aryl radical cyclizations, and Friedel-Crafts closure of an aziridinium ion or an acid-catalyzed closure of an aldehyde to form the C_{10}-C_{11} bond.

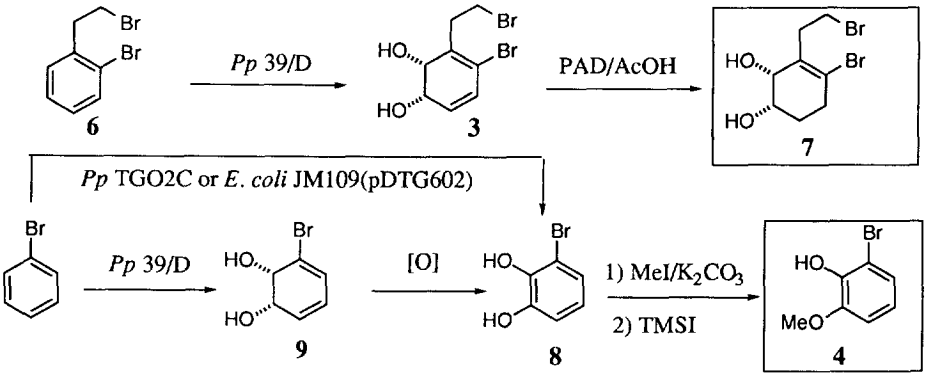
In 1954, Gates[1] reported the first total synthesis of morphine **1** by an ingenious yet simple route, utilizing a β-dihydrothebainone–dihydrothebainone isomerization sequence in order to adjust the C_{14} stereocenter. Since Gates's original approach, a total of 16 syntheses have been reported.[2] The majority (nine of them), including the most recent one of Overman,[2b] proceed *via* 1-benzylisoquinoline intermediates, with the crucial step being C_{12}–C_{13} bond formation. These syntheses are formalized by intercepting Gates's dihydrothebainone (or β-dihydrothebainone) or by producing thebaine. The most efficient routes to date, those of Rice[2c] and Beyerman,[2d] have also used this strategy. Despite a number of attempts, only one successful synthesis (Evans)[2e] utilized a C_{10}–C_{11} closure late in the synthesis in order to complete the morphinan skeleton, followed by adjustment of stereochemistry at C_{14}.



In 1994, Parker reported the full details[2f, g] of a radical cascade approach (published in a preliminary form in 1992)[2h] to racemic **1**. Parallel to Parker's effort, we designed a similar strategy, and during our first-generation approach to the synthesis of enantiomerically pure **1** we also encountered problems with low yields in the radical cascades.[3] In this manuscript, we report the second-generation approach in which both the yields and the stereoselectivity have been addressed.

Our strategy is based on the exploitation of microbial dioxygenase-mediated degradation of toluene, elucidated by Gibson in 1969.[4] In the arene degradation pathway, elimination of catechol dehydrogenase synthesis by mutation of the wild strain yields an organism *Pseudomonas putida* 39/D[4] that converts aromatic compounds to cyclohexadiene *cis*-diols, which accumulate in the fermentation broth. We have taken advantage of this process by converting 2-(2-bromoethyl)bromobenzene **6** to diol **3**.[5] Even though 2-bromo-6-methoxyphenol **4** is directly available via bromination of guaiacol, we have shown that the precursor, catechol **8**, is also accessible from bromobenzene via full biooxidation of bromobenzene (*Pp* TGO2C or *E. coli* JM 109, pDTG602, where both

toluene dioxygenase and catechol dehydrogenase are expressed)[6] or partial biooxidation (*Pp* 39/D; Jones oxidation). Exhaustive methylation (MeI/K_2CO_3) followed by selective demethylation (TMSI) yields **4**, Scheme 1. In this fashion two of the three fragments required for synthesis are available via biocatalysis; the third, oxazolone **5**,[7] is prepared electrochemically, thus contributing to the environmentally benign nature of the synthesis.



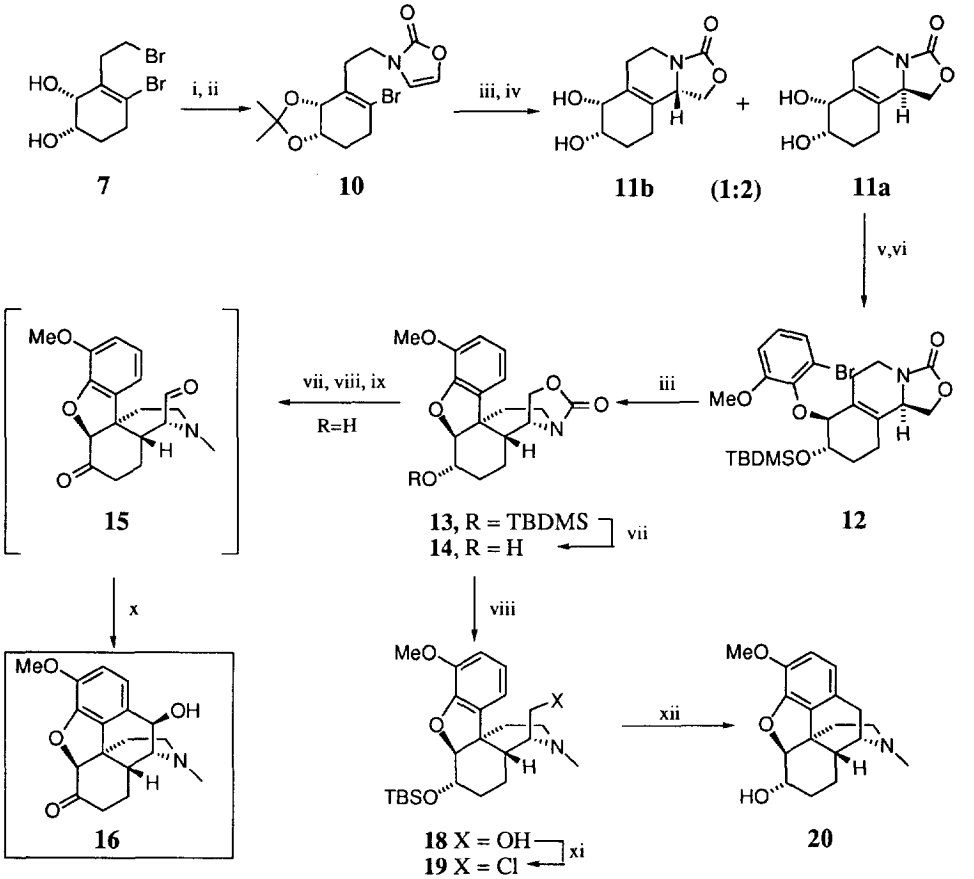
Scheme 1

The chirality, set enzymatically in **3**, is propagated though the synthesis by the directing effects of the *cis*-diol moiety. Diol **3** ($t_{1/2}$ = one week in $CDCl_3$ solution) was reduced with diimide (50% yield) in order to minimize the tendency toward aromatization, protected as an acetonide (2,2-dimethoxy propane, methylene chloride, cat. *p*TsOH, 95%), and coupled with oxazolone **5**[7] (39%) to give[8] the precursor to the first radical closure, vinyl bromide **10**. Exposure of this material to Bu_3SnH and AIBN in refluxing benzene gave a 2:1 mixture of **11a** and **11b** in a combined yield of 89% after deprotection of the acetonide with Dowex 50X8-100 acidic resin in aqueous methanol. ^1H- and ^{13}C-NMR analysis and nOe, confirmed by x-ray of **11a**,[9] led to the assignment of absolute stereochemistry as shown. As the only center in morphine not subject to facile manipulation is C_9 corresonding to C_1 in isoquinolines **11**, we chose to pursue the route using the more abundant **11a**, leading ultimately to ent-morphinan skeleton.

Diol **11a** was selectively protected with TBDMSOTf (86%) and subjected to Mitsunobu protocol using the monomethyl ether of bromocatechol **4** to yield **12** (94%), which contains all of the carbons for codeine. This material smoothly cyclized to **13** (49%). The combined yields of both ring closures were higher than those of the radical cascade from the first generation, and the second cyclization proceeded stereospecifically giving only the diastereomer **13**. The absolute stereochemistry at C_{14} corresponds to that of the enantiomer of β-thebainone. The closure of the free alcohol, derived from **12**, did not affect the absolute stereochemistry[10] of C_{14}, and the pentacyle **14** was isolated in 29% yield.

The TBDMS protected pentacycle **13** was reduced with DIBAL to **18** (95%) to furnish the *N*-methyl functionality and to establish the C_{10} eletrophilic center by mesylation with in situ displacement to **19** (81%). Exposure of **19** to $AlCl_3$ in benzene gave material whose analysis suggested a mixture of morphinan **20** and the corresponding free phenol[11] resulting from the aluminum-chloride-catalyzed demethylation. To our knowledge this would be the first instance of a direct C_{10}–C_{11} closure of a compound already containing the furan ring and a

C_{10} sp^3-hybridized center.[12] Poor reproducibility of this reaction on small scale (<5 mg) compelled us to search for alternatives.



Reagents and conditions: (i) DMP, *p*-TSA; (ii) **5**, NaH, DMSO; (iii) $^{n}Bu_3SnH$, AIBN, benzene, reflux; (iv) Dowex 50X8-100, MeOH, H_2O; (v) TBDMSOTf, $^{i}Pr_2EtN$, THF, –78 °C; (vi) **4**, DEAD, $^{n}Bu_3P$, THF, 0 °C; (vii) TBAF, THF; (viii) DIBAL-H, CH_2Cl_2, 0 °C; (ix) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, –78 to 0 °C; (x) CF_3SO_3H; (xi) MsCl, Et_3N, THF; (xii) $AlCl_3$, benzene, reflux.

Scheme 2

Reduction of **14** with DIBAL-H followed by a double Swern oxidation yielded the ketoaldehyde **15** (70%), which upon exposure to trifluoromethyl sulfonic acid furnished the C_{10}-hydroxy morphinan **16** (70%), as evidenced by the appearance of two upfield doublets, (δ 6.84, 6.68 in benzene-d6, or 6.97, 6.79 in chloroform-d), corresponding to the aromatic protons of a complete morphinan skeleton.[13] Reduction of **16**, epimerization at C_{14} based on a known procedure,[14] and demethylation would formalize the synthesis of ent-morphine.

In summary, the synthesis of a complete morphinan skeleton has been accomplished with reasonable stereoselectivity in 13 steps from 2-(2-bromoethyl)bromobenzene. Further refinement of this strategy is currently in progress in our laboratory and will be reported in due course.

Acknowledgments: The authors thank Mallinckrodt Chemicals, Inc., and TDC Research, Inc., for funding.

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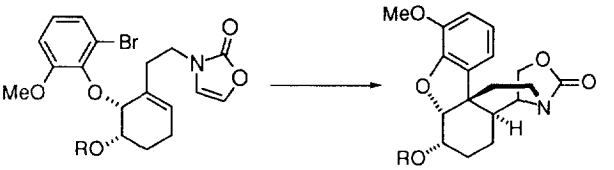
3. The following sequence was carried out in our laboratories in the natural enantiomer series (ca. 10 % yield):



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6. In *E. coli* JM109 (pDTG 602) the catechol dehydrogenase is still synthesized but the expression of enzymes for the next step in the degradation, namely the ortho-scission, has been blocked. See: Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *164*, 14940.

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8. The alkylation of oxazolone yielded a substantial amount (55 %) of (3aR,7aS)-5-bromo-2,2-dimethyl-4-vinylbenzodioxol, which, after hydroboration/oxidation (9BBN, H_2O_2) and mesylation (MsCl/iPr_2NEt), was coupledwith oxazolone to yield **10**.

9. Full x-ray crystallography data will be published in *Acta Cryst.* by Khalil Abboud, University of Florida.

10. Work of Gates, Evans, and others suggests that the unnatural absolute stereochemistry at C_{14} predominates (or is sterically feasible) when either the C_5-O bond (β-thebainone) or C_{10}-C_{11} bonds are disconnected. For recent reference see: Cheng, C.-Y., Hsin, L.-W., Liou, J.-P. Tetrahedron, **1996**, *52*, 10935.

11. The mass spectrum of the mixture indicated the presence of ions 302.1800 ($C_{18}H_{24}NO_3$, δ = 4.4 ppm) and 288.1590 ($C_{17}H_{22}NO_3$, δ = 0.9 ppm), corresponding to morphinan **20** and the free phenol derived from its the $AlCl_3$-catalyzed demethylation, respectively. This result indicates that a C_{10}-C_{11} closure is possible with compound containing the complete benzofuran unit.

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13. All analytical and spectral data obtained were consistent with the structural assignments.

14. Weller, D. D.; Rappoport, H. *J. Med. Chem.* **1976**, *19*, 1171.

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