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Chemoenzymatic and Electrochemical Oxidations in the Synthesis of Octahydroisoquinolines for Conversion to Morphine. Relative Merits of Radical vs. Acid-catalyzed Cyclizations.

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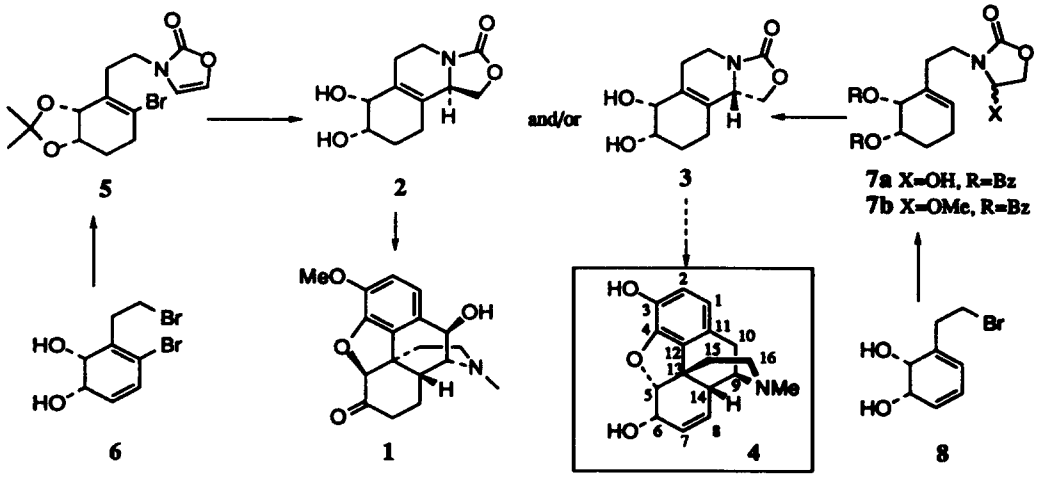
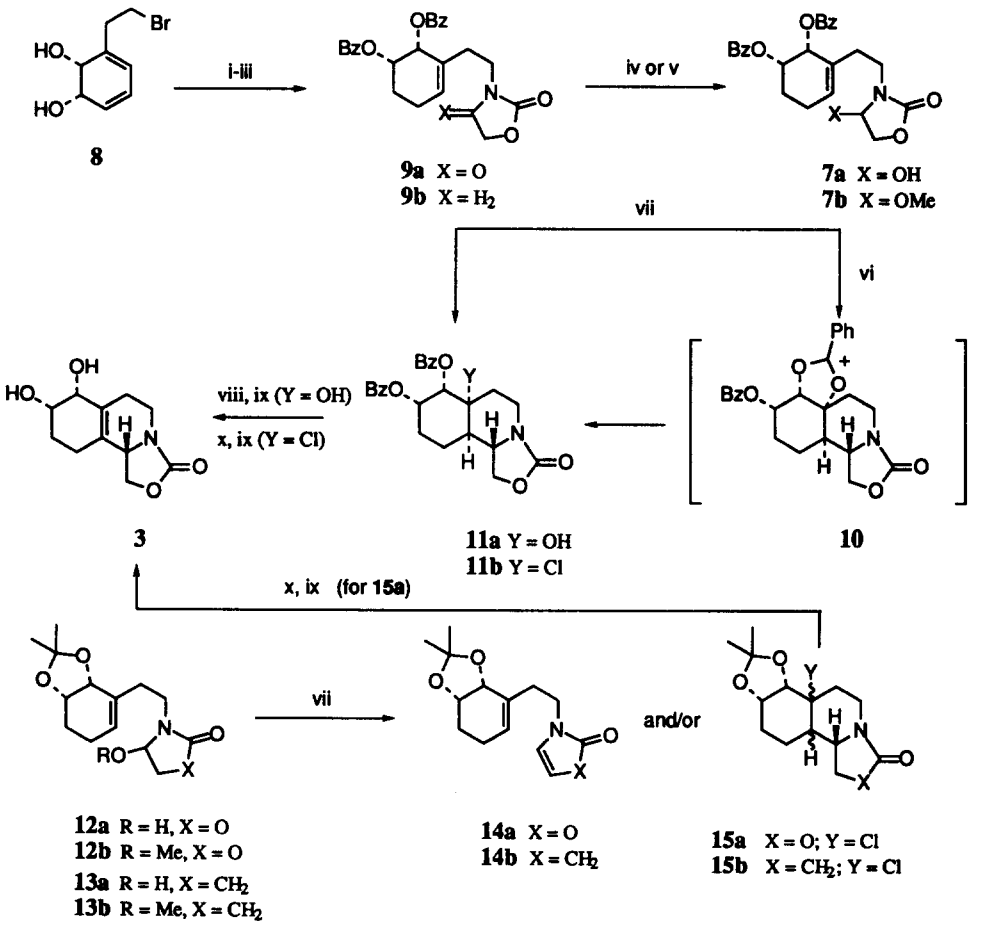
Abstract: Second-generation stereoselective synthesis of octahydroisoquinoline **3**, a potential key intermediate for the projected synthesis of the natural enantiomer of morphine, has been accomplished in five steps from arene *cis*-diol **8**. Electrochemical oxidation of **9b** furnished **7b**, a precursor for the key benzoate-assisted acyl-iminium cyclization. © 1997 Elsevier Science Ltd.

Recently we reported the chemoenzymatic synthesis of *ent*-morphinan **1** in thirteen steps from *o*-bromo-β-bromoethylbenzene by sequential radical cyclizations that established the consecutive formation of the C14–C9 and C12–C13 bonds, respectively.[1] The reverse order of this particular connective strategy was used by Parker (radical cyclization)[2] and by us[1b] whereas Grewe,[3] Beyerman,[4] and Rice[5,6] relied on forming the C12–C13 bond last (cationic cyclization) in their approaches. Analysis of these strategies suggested that isoquinolines such as **2** and **3** might be ideal intermediates for the approach to either enantiomer of morphine as their configurations at C1 correspond to the absolute stereochemistry at C9 of the *ent*-alkaloid and the natural enantiomer **4**, respectively. In our initial investigation of this type of strategy, the radical cyclization of vinyl bromide **5** (obtained in three steps from the known diene diol **6**)[7] furnished isoquinoline derivatives **2** and **3** with low diastereoselectivity (2:1 respectively, 89% combined yield).[1a] The major isomer, whose C1 configuration corresponds to the absolute stereochemistry at C_9 in *ent*-morphine, was converted to *ent*-morphinan **1** in seven steps.[1a] The low stereoselectivity, the use and manipulation of toxic tin reagents, and the relatively cumbersome procurement of diol **6** via biooxidation of the corresponding arene[7] prompted us to seek alternatives to a more concise preparation of either **2** or **3**, preferably controlling selective access to both. In this manuscript we report a new stereoselective synthesis of octahydroisoquinoline **3** by the acid-catalyzed cyclization of (methyl) aminals **7** derived from the more easily accessible diol **8**.[8] In addition, electrochemical methods have been used to



generate selectively **7b** from the cyclic carbamate precursor, thereby effectively obviating the need to expose the base-labile imide to hydride reagents.

The unusually high yield of the biooxidation of β-bromoethylbenzene[8] with *E. coli* JM109(DTG601)[9] made available large quantities of diol **8**, which was converted in four steps to the cyclization precursor **7a** as shown in Scheme 1. Reduction of the less substituted olefin in **8** with potasium azodicarboxylate (PAD/AcOH), proceeded in 80% yield. Benzoylation (DCC, $PhCO_2H$, 83%) followed by displacement with either oxazolidinedione (**7a**, THF, tetramethylguanidine, 77%) or 2-oxazolidone (**7b**, NaH, DMSO, 15%) [1a,7] furnished **9a** or **9b**, respectively. The more reactive amide carbonyl in **9a** was selectively reduced to its hemiaminal with sodium borohydride to generate the precursor for the cyclization of the acyl-iminium species, hemiaminal **7a**, in 80% yield. A wide variety of conditions for the acid-catalyzed generation of the acyl-iminium



Scheme 1.[13] *Reagents and conditions:* **i** PAD/MeOH/HOAc; **ii** $PhCO_2H$/DCC/DMAP/CH_2Cl_2; **iii** for **9a**: oxazolidinedione/tetramethyl guanidine/THF/reflux; for **9b**: oxazolidone/ NaH/DMSO; **iv** $NaBH_4$/MeOH; **v** $Et_4N^+TsO^-$/MeOH/1.850 V vs. Ag/Ag^+; **vi** BF_3/CH_2Cl_2; **vii** $TiCl_4$ or $AlCl_3$/ CH_2Cl_2; **viii** TsOH/PhH/reflux; **ix** LiOH/MeOH; **x** DBU/ CH_2Cl_2.

species[10] was examined for this material, as well as for its carbocyclic analog **13a** (prepared by alkylation of **8** with succinimide, followed by reduction). The well-established formic-acid-catalysis led to cyclization in the case of the succinimide derivative **13a**[11] but failed with **7a**. Of the many Lewis acids that were tested for the cyclization of **7a**, BF_3–ether complex provided the best results and furnished a 55% isolated yield of the perhydrisoquinoline **11a** as a single isomer, whose structure was determined by x-ray analysis.[12] The stereochemistry of this material is noteworthy not only because the stereogenic center corresponding to C9 of morphine has been set in the correct absolute and relative sense, but also because the ring junction stereochemistry has been shown to be *cis*. We invoke the anchimeric assistance of the benzoate, as depicted in the drawing of intermediate **10**, to rationalize this observation.

The use of other Lewis acids led to lower yields of **11b** when applied to dibenzoate **7a**, while parallel experiments with the acetonide derivative **12a** or its methyl hemiaminal **12b** with BF_3 gave lower yields and more complex mixtures.[11] Treatment of **11a** under acid-catalyzed conditions (TsOH/PhH/reflux) provided, after hydrolysis of benzoates, a low yield of **3** (~20%) while the exposure of **11b** to DBU/DMSO at 100 °C furnished the desired olefinic compound (45–60%) whose hydrolysis (aqueous LiOH in methanol, 94%) gave the isoquinoline derivative **3**, identical in all physical and spectral characteristics with the previously reported material.[1a,13] The treatment of succinimide derivatives **13a** with various Lewis acids resulted in moderate yields of octahydroisoquinolines **15b**. On the other hand, the hemiaminal or methyl hemiaminal **12a** or **12b**, respectively, derived from oxazolidinediones afforded under identical conditions mainly the product of elimination, **14a**. The relative stereochemistry of the acetonide-protected cyclized compounds **15a** was not established, and the angular chlorides were converted to the desired isoquinoline derivateive **3** via base-catalyzed elimination/hydrolysis sequence as indicated in Scheme 1. Further treatment of olefins **14a** or **14b** with acids did not result in conversion to **15**. Reasonable yields of **11** as a mixture of stereoisomers have been obtained by treatment of **7b** with $TiCl_4$. Conversion of this mixture to **3** as described above (DBU, followed by LiOH) proceeded in ~50% yield.

Additional improvements can be realized by the incorporation of electrochemical techniques into the preparation of precursors of type **7b** directly from the alkylated oxazolones **9b**. We have had success with the electrooxidations of amides on a medium scale and under mild conditions[14] by employing well-documented conditions.[15] With substrates such as **9b** the question of regioselectivity of the electrooxidation must be addressed. When **9b** was electrooxidized (1.850 V, Ag/Ag^+, MeOH), **7b** was produced as a mixture of anomers (~50%), separable by chromatography, with no detectable trace of the regioisomer resulting from the oxidation of the amino methylene in the alkyl side chain.[16] The crude product was found suitable for further use (as were the anomers generated by the reduction of **9a**). Of additional benefit is the recognition that the regioselective electrooxidation of the ring methylene can be performed at almost any stage of the synthesis and that the *N*-alkyloxazolidone moiety in **9a** is stable to base, thus alleviating the operational restrictions that may be imposed by the base-labile imide functionality (e.g., **9b**).

The aforementioned preparation of **3** was found superior to the one reported in connection with the conversion to the *ent*-morphinan **1**.[1] Although it is slightly longer, the combination of easy accessibility and the high yield of diol **8** from the corresponding arene with the stereospecificity in the formation of **3** bodes well for its preferential use in the quest for the natural isomer of morphine (**4**). These results portend well for the further tuning of reactivity of the cyclization precursors **7** derived from arene *cis*-dihydro diols. The projected endeavor

in this area will now focus on the conversion of **3** to the natural enantiomer of morphine by routes established for the *ent*-isomer.[1a]

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

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