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Model Study for a General Approach to Morphine and Noroxymorphone via a Rare Heck Cyclization

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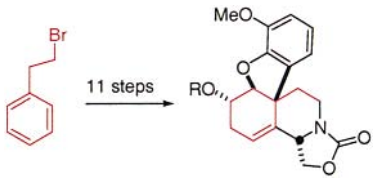
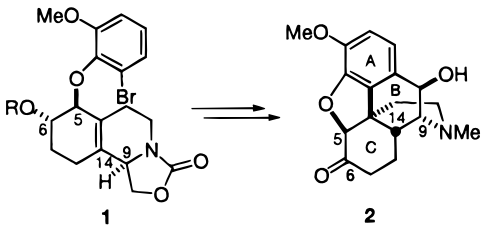
ABSTRACT



***β*-Bromoethylbenzene was converted to the pentacycle 6 in 11 steps. The key features of this model were the toluene dioxygenase catalyzed production of diol 13 and the stereospecific Heck closure of 5 to 6.**

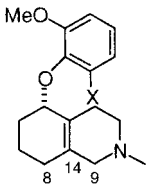
Several years ago we reported the synthesis of a complete morphinan skeleton via a radical cyclization of aryl halide **1**.[1] The pentacyclic ketone **2** was obtained as shown in the *ent* series, as a consequence of the configuration at C5 and C9 (morphine numbering) in the precursor **1**. The radical



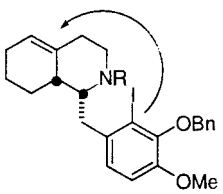
1 **2**

cyclization produced the incorrect stereochemistry at C14 because of unfavorable conformation of the radical prior to hydrogen abstraction, and it is clear that the same fate would be expected for similar closures performed in the natural series from precursors having the opposite configuration at C5 and C9. These results, fully disclosed in a recent publication,[2] indicated that the approach based on radical cyclization of intermediates already containing the C9−C14 bond cannot be successful in producing the correct C14 stereochemistry. (Compare this approach with that of Parker[3] in which the C14 is set correctly as a consequence of a conformationally more flexible system.)

We considered the Heck reaction[4] for this closure, despite the fact that cyclizations onto highly substituted olefins are rare. To our knowledge there is only one example of a successful Heck cyclization onto a tetrasubstituted olefin related to isoquinoline derivatives such as **1**: that of **3**. Cheng successfully performed the Heck cyclization of **3** (X = Br, 48%; X = I, 72%), but the olefin was generated at C14−C9 (morphine numbering). When C9 was functionalized as a lactam, the *β*-hydride elimination furnished C8−C14 unsaturation.[5] Overman employed the Heck closure onto a trisubstituted olefin in **4** during his recent synthesis of



3 X = Br, I
Cheng, 1997



4
Overman, 1993

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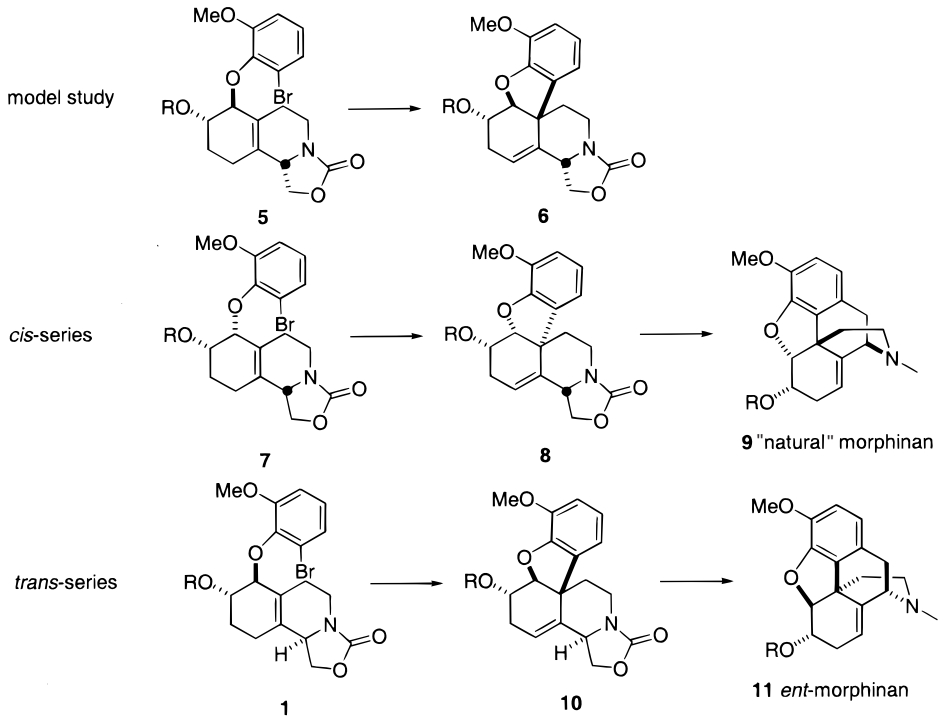


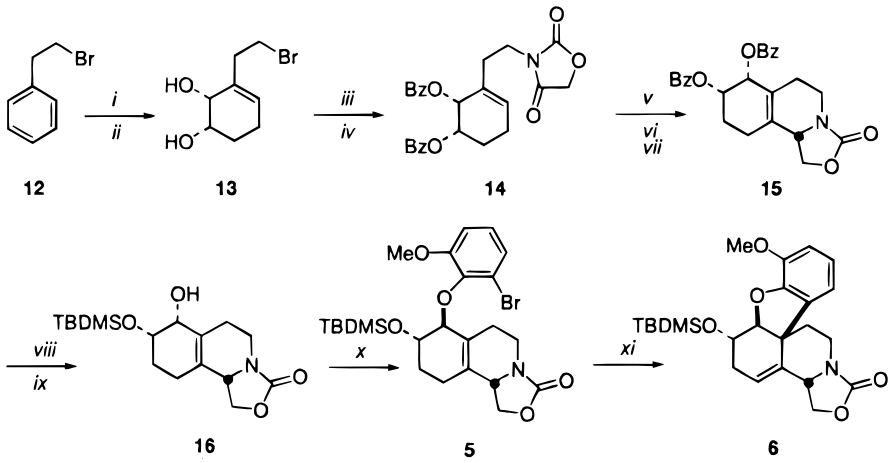
Figure 1. Heck cyclization strategy for morphinan synthesis.

morphine.[6] On the basis of this precedent we felt that the issue of C14 stereochemistry could be successfully resolved by using the Heck closure on intermediates such as **1**. Furthermore, β-hydride elimination of the organopalladium intermediate would "return" the necessary oxidation state to ring C of morphine, allowing control of C14 at that stage.

The strategy is illustrated in Figure 1. We chose isoquinoline derivative **5**, which has the "natural" configuration at C9, with the expectation that the Heck cyclization of this substrate could produce **6** as well as its regioisomer because of the steric requirements for *syn* β-hydride elimination and the *syn* arrangement of the organopalladium intermediate and the hydrogen at C9.

In the actual applications to either **7** or **11**, no regioisomers would be expected because the C9 center will always remain *trans* to the organopalladium functionality. Conversion of **1**

Scheme 1

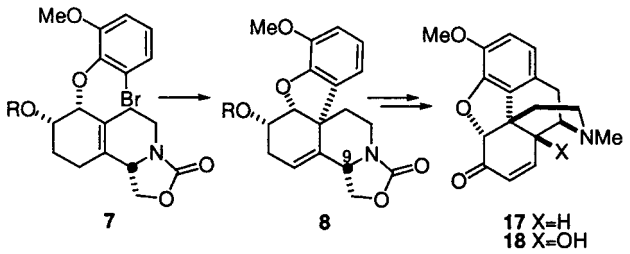


Reagents: i. *E. coli* JM109 (pDTG601); ii. PAD/AcOH/MeOH, 80% yield; iii. $PhCO_2H$/DCC/DMAP/CH_2Cl_2, 83% yield; iv. Oxazolidinedione/tetramethylguanidine/ THF/reflux, 77% yield; v. $NaBH_4$/MeOH; vi. $AlCl_3/CH_2Cl_2$; vii. DBU/DMSO/reflux, 13% yield; viii. LiOH/MeOH; ix. TBDMSOTf/ imidazole/DMF, yield 20%, 40% recovered SM; x. Bu_3P/DEAD/bromoguiacol/THF, 53% yield xi. $Pd(PPh_3)_4$/Proton sponge/ toluene/reflux, yield 57%.

to **10** or **7** to **8** would eventually ensure the correct C14 stereochemistry, once the C10−C11 closure, performed by previously established methods,[1,2] is completed. The synthesis of **5** was accomplished as shown in Scheme 1 and followed, with few adjustments, the previously reported synthesis of dibenzoate **14**.[7]

Biooxidation of (2-bromoethyl)benzene (**12**)[8] with *Escherichia coli* JM109 (pDTG601) followed by the reduction of the less substituted double bond with diimide afforded diol **13** in 80% yield. Esterification of the two hydroxyl groups with DCC/$PhCO_2H$ in CH_2Cl_2 followed by the displacement of bromine with oxazolidine-2,4-dione in the presence of tetramethylguanidine (TMG) in THF furnished the protected diol **14** in 77% yield. Following reduction of the more reactive amide carbonyl with $NaBH_4$,[9] *N*-acyliminium ion−olefin cyclization ($AlCl_3$ in CH_2Cl_2), and the elimination of the alkyl chloride with DBU in DMSO under reflux afforded the cyclized product **15**.[10] The deprotection of the dibenzoate groups with LiOH in MeOH followed by the selective protection of the distal (homoallylic) hydroxyl group furnished the monoprotected diol **16**. Mitsunobu inversion of the secondary alcohol with 6-bromo-2-methoxyphenol provided the Heck reaction substrate **5**. Heck cyclization of the sterically hindered tetrasubstituted olefin proceeded in the presence of tetrakis(triphenylphospine)-palladium(0) catalyst with Proton Sponge in refluxing toluene for 48 h to give the tetracyclic product **6** as the only identifiable product in a 57% yield along with 15% recovered starting material.[11]

The successful preparation of **6** allows the formulation of a new approach to both morphine and noroxymorphone since the issue of C10−C11 closure has been previously solved by the acid-catalyzed cyclization.[1,2] What remains to complete the synthesis of both enantiomeric series is the application of a double Mitsunobu inversion to produce **7** and convert it to the reduced neopine intermediate **9**. Rice has demonstrated successful conversion of codeine, via neopinone, to 14-hydroxycodeinone.[12]



We have shown that the Heck reaction provides stereo- and regiospecifically the neopine-type intermediate even in the case of **5** where there is a possibility of alternate β-hydride elimination. In both the natural and the *ent* series such a possibility is removed. Therefore, olefin **8**, to be obtained from the "natural" precursor **7**, should be easily converted to neopine **9** (R = H) and then to either **17**(X = H) or **18** (X = OH) by an oxidation/isomerization or epoxidation/oxidation sequence, respectively,[11] and can therefore be converted to both morphine and noroxymorphone. Studies on the realization of this protocol are ongoing and will be reported in due course.

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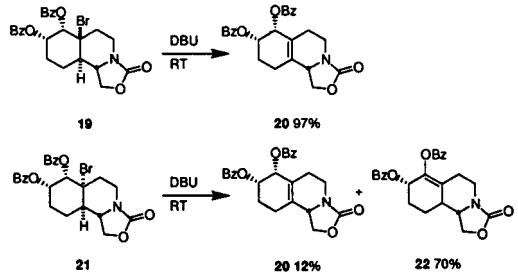
(10) In a study to determine the regiochemistry of elimination, the two isomers of intermediate halides from the cyclization of **14**, **19**, and **21** were subjected to elimination conditions with neat DBU. Isomer **19** gave selectively **20** in 97% yield, while isomer **21** produced enol ester **22** as a major product.



(11) All compounds were fully characterized by physical and spectral data.

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