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Ring Closing Metathesis Mediated Synthesis of 4a-Aryloxodecahydroisoquinolines, Intermediates in the Preparation of Novel Opiates

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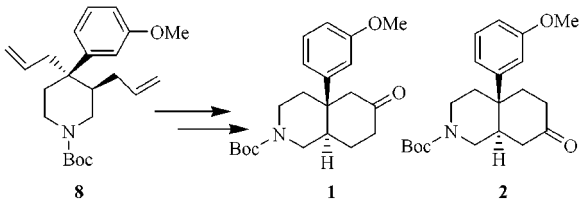
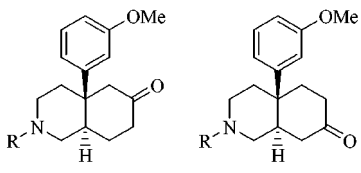
ABSTRACT



The concise syntheses of the 4a-aryldecahydroisoquinolines 1 and 2 through a uniform strategy starting from *N*-methyl-3-allyl-4-piperidinone are reported in this Letter. Key transformations include a ring closing metathesis reaction to prepare a *trans*-octahydroisoquinoline common intermediate and a regiocontrolled hydroboration–oxidation sequence.

The 4a-aryldecahydroisoquinolines **1** and **2** (Scheme 1)-represent structural fragments of morphine with significant pharmacological activity. The compounds exhibit potent affinity for the μ opioid receptor and possess antinociceptive properties consistent with those of μ receptor agonists.[3] The pharmaceutical importance of these compounds is further enhanced by their utility as advanced intermediates for the synthesis of novel selective ligands for the δ opioid receptor.[4] Synthetic efforts toward the 4a-aryldecahydroisoquinoline **1** have been previously reported.[5] In contrast, the synthesis of compound **2** has been the subject of fewer reports.[6] As part of a program that aimed at the design and synthesis of novel δ opioid receptor ligands, we sought to develop concise syntheses for substrates **1** and **2**. In this Letter we report a uniform approach to the targeted 4a-aryldecahydroisoquinolines through common intermediates highlighted by a ring closing metathesis reaction and a regiochemically controlled hydroboration−oxidation step.

Scheme 1



R = Boc

(1) CNS medicinal chemistry.
(2) Exploratory Medicinal Sciences, computational chemistry.
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(4) For recent examples, see: (a) Dondio, G.; Ronzoni, S.; Eggleston, D. S.; Artico, M.; Petrillo, P.; Petrone, G.; Visentin, L.; Farina, C.; Vecchietti, V.; Clarke, G. D. *J. Med. Chem.* **1997**, *40*, 3192. (b) Nagase, H.; Kawai, K.; Hayakawa, J.; Wakita, H.; Mizusuna, A.; Matsuura, H.; Tajima, C.; Takezawa, Y.; Endoh, T. *Chem. Pharm. Bull.* **1998**, *46*(11), 1695.

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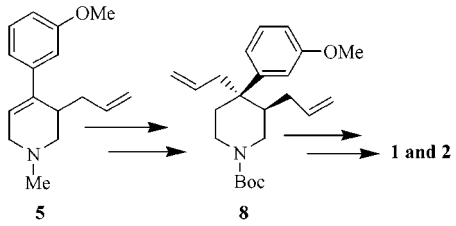
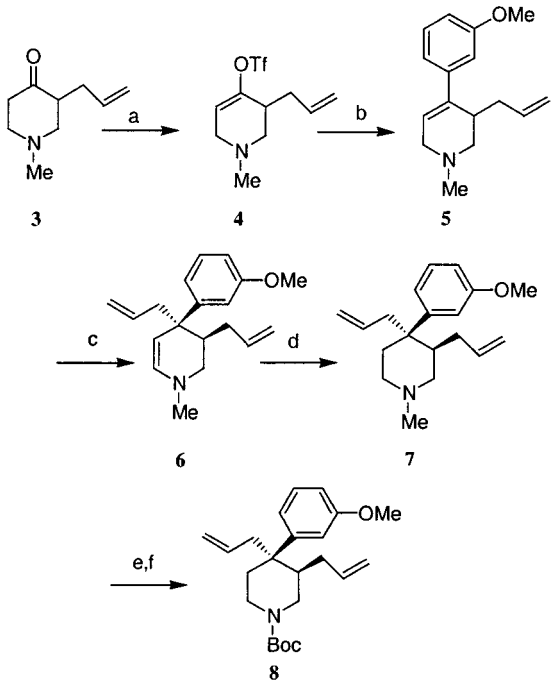
Scheme 2



For the syntheses of both substrates, we envisioned an approach as described in Scheme 2. The diallyl piperidine **8**, precursor to the ring closing metathesis reaction, would be accessed following an allylation reaction of the metalloenamine generated from compound **5**. A ring closing metathesis of compound **8** would furnish a *trans* octahydroisoquinoline with a quaternary carbon center, which after a regioselective hydroboration−oxidation sequence would be converted to the target compounds **1** and **2**. The regiochemical preference of the hydroboration−oxidation step could be predicted on the basis of molecular orbital calculations.

The reduction of this plan to practice commenced with the multigram preparation of 3-allyl-*N*-methyl-4-piperidinone **3** according to literature procedures.[7] Related piperidinones have been converted to the 3-alkyl-4-aryltetrahydropyridines similar to **5** via aryl Grignard or aryllithium additions followed by regioselective dehydration.[8] As an alternative to this strategy, we envisioned the preparation of compound **5** from a precursor vinyl triflate utilizing organopalladium chemistry (Scheme 3). Thus, the piperidinone **3** was transformed with exclusive regiocontrol to the vinyl triflate **4** in 92% yield with LiHMDS and *N*-phenyl triflamide[9] in THF at −78 °C. The vinyl triflate was converted to the desired tetrahydropyridine **5** after Suzuki coupling with the commercially available 3-methoxyphenylboronic acid. The yields for the Suzuki coupling ranged from 48% to 94%. Optimum reaction conditions for this step were discovered when the vinyl triflate and boronic acid were treated with KBr, K_3PO_4, and $Pd(PPh_3)_4$ as catalyst in dioxane solvent at 85 °C to afford compound **5** in 94% yield.[10] With tetrahydropyridine **5** available, our attention was turned to the formation of diallylpiperidine **7**. The preparation of diallylpiperidine **7** was achieved via a metalloenamine generation−alkylation sequence. This sequence was first reported in the context of

Scheme 3[a]



[a] (a) LiHMDS, *N*-phenyltrifluoromethanesulfonimide, THF −78 °C to rt, 92%; (b) 3-methoxyphenylboronic acid, KBr, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, 85 °C, 94%; (c) sec-Buli, allyl bromide, THF, −45 °C to −78 °C to rt; (d) $NaBH_4$, MeOH, rt, 88% for steps c and d; (e) ACE-Cl, 1,2-dichloroethane, reflux, then methanol, reflux; (f) di-*tert*-butyl dicarbonate, Et_3N, dichloromethane, rt, 80% for steps e and f.

the synthesis of related morphinoid alkaloids.[11] In the event, treatment of compound **5** with sec-BuLi in THF at −45 °C followed by addition of allyl bromide produced enamine **6** in quantitative yield. The crude enamine was reduced with $NaBH_4$ in methanol to afford piperidine **7** in 88% yield for the two steps. The *N*-methylpiperidine was subsequently converted to the *N*-Boc equivalent to ultimately produce a compound with an easily removable nitrogen-protecting group, suitable for analogue formation. Thus, after treatment of **7** with 1-chloroethyl chloroformate in dichloroethane at reflux, subsequent carbamate methanolysis and treatment of the crude hydrochloride salt with di-*tert*-butyl dicarbonate and triethylamine compound **8** was obtained in 80% overall yield.

With the synthesis of diallylpiperidines **7** and **8** completed, our attention was turned to the ring closing metathesis transformation (Scheme 4). The diallylpiperidine **8** was converted to the cyclic olefin **11** after treatment with 0.1 equiv of the Grubbs catalyst **9** in dichloroethane at 60 °C in 93% yield. Similarly, the hydrochloride salt of compound **7** was converted to the corresponding olefin **10** in 88% yield.[12]

The regioselective functionalization of the olefin in compound **11** was predicted on the basis of molecular orbital interactions. Restricted Hartree−Fock calculations were carried out for the transition states corresponding to

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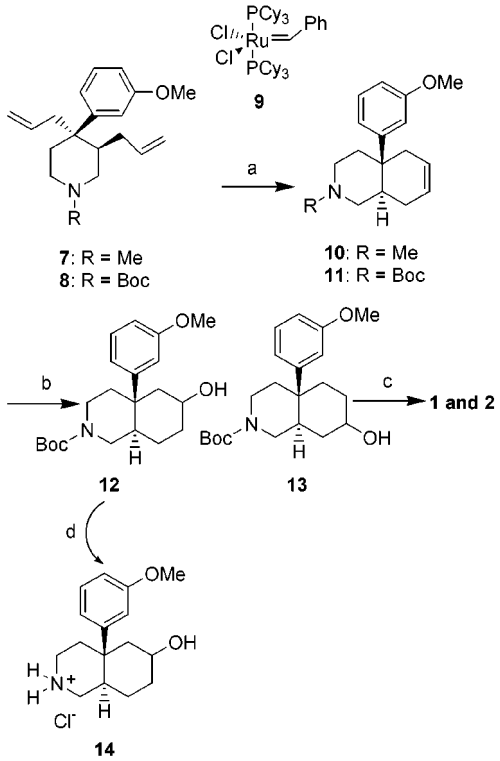
Scheme 4[a]



[a] (a) Grubbs catalyst **9**, 1,2-dichloroethane, 60 °C, 93% for compound **11**, 88% for compound **10**; (b) 9-BBN, THF, reflux, 30% aqueous H_2O_2, EtOH, 6 N NaOH, quantitative yield for **12** and **13** (3:1 ratio); (c) TPAP, NMO, dichloromethane, rt, 88% for **1** and 84% for **2**; (d) HCl, EtOAc, rt, 85%.

the hydroboration of **11** with both 9-BBN and borane. The geometries for this series of molecules were fully optimized by means of analytical energy gradients[13] with the 6-31G-(d)-basis set[14] in the gas phase. The ab initio molecular orbital calculations were carried out with the Gaussian 94 series of programs on a Silicon Graphics computer.[15] Comparison of the transition state energies for the reaction of **11** with 9-BBN shows a preference for product **12** over **13** of 0.616 kcal/mol, corresponding to a ratio of 2.83:1. The reaction of **11** with borane is predicted to favor the regioisomer, **13**, by 0.767 kcal/mol (predicted ratio 1:3.65). Our findings are consistent with prior ab initio calculations that implicate

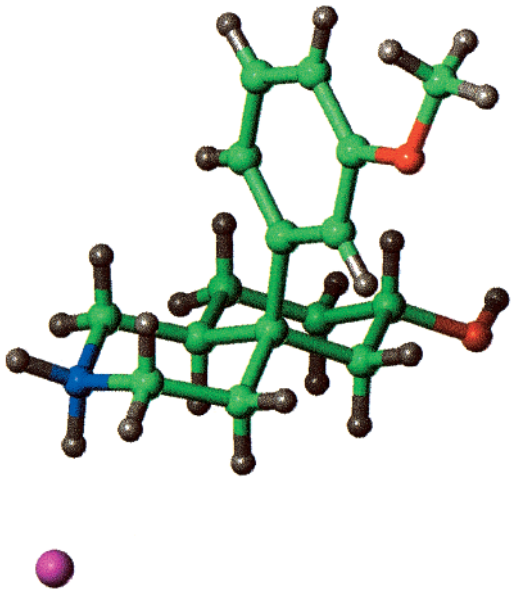


Figure 1.

both steric and electronic factors in the regioselectivity.[16] Experimental results supported the computational chemistry predictions. Thus, treatment of olefin **11** with a sterically hindered borane such as 9-BBN in refluxing THF, followed by oxidation of the organoborane species, yielded in quantitative yield a 3:1 ratio of the separable, isomeric alcohols **12** and **13**. Conversely, treatment of **11** with the smaller borane−dimethyl sulfide reagent complex yielded a 3:1 ratio of alcohols **13** and **12** in a not optimized 52% yield. The final step for the preparation of isoquinolines **1** and **2** was the oxidation of the secondary hydroxyl groups. Typically, Swern oxidation reactions had been employed for this transformation in good yields. In this instance, oxidation of alcohols **12** and **13** with TPAP and *N*-morpholine oxide afforded ketones **1** and **2** in 88% and 84% yields, respectively.

The stereochemistry of the major product **12** was confirmed from a crystal structure obtained from its hydrochloride salt **14** (Figure 1). Compound **14** was produced after removal of the nitrogen-protecting group with HCl in ethyl acetate at room temperature in 85% yield.

In conclusion, the efficient syntheses of the 4a-aryldecahydroisoquinolines **1** and **2** through a uniform strategy were reported in this Letter. The desired compounds exhibit significant pharmacological activity at opioid receptors and provide useful intermediates for the synthesis of novel and selective δ opioid receptor ligands. Key synthetic steps in this approach include a highly efficient ring closing metathesis reaction to form a *trans* octahydroisoquinoline substrate and a regioselective hydroboration−oxidation reaction sequence.

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Supporting Information Available: Representative experimental procedures for the preparation of compounds **4**, **5**, **7**, **8**, **11**, **12**, **13**, **1**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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