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Diastereoselective One-Pot Synthesis of 7- and 8-Substituted 5-Phenylmorphans[||]

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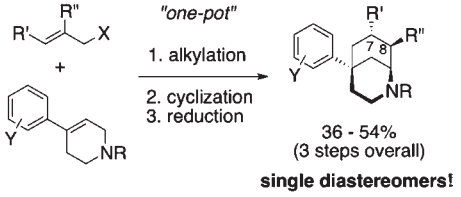
ABSTRACT



Novel 7- and 8-alkyl and aryl substituted 5-phenylmorphans were synthesized from substituted allyl halides and *N*-benzyl-4-aryl-1,2,3,6-tetrahydropyridine by a highly efficient and diastereoselective reaction series, "one-pot" alkylation and ene-imine cyclization followed by sodium borohydride reduction. Mild cyclization conditions gave the desired substituted 5-phenylmorphans in good yield as a single diastereomer.

The molecular structure of the 5-phenylmorphans (**1**, Figure 1) was conceptualized[1] as a structurally simplified fragment of morphine or heroin (Figure 1), and some N-substituted 5-phenylmorphans were found to have morphine-like activity.[2] Recently Hiebel et al.[3] synthesized a C9β−OH *N*-phenethyl-5-phenylmorphan (the 1*R*,5*R*,9*S*-enantiomer of **2**, Figure 1) that had extremely high affinity for the μ-opioid receptor and was far more potent than morphine in vivo; its epimer (1*R*,5*R*,9*R*) had 230-fold less affinity. This is a remarkable effect of the stereochemistry at a single OH group. In order to determine what pharmacological profile would be conferred by substituents at the C-7 or C-8 positions we needed to find a synthetic path to these less accessible compounds. Only 7-amino[4] and 6,7- and 7,8-fused indole derivatives[5] synthesized from 7-keto-5-phenylmorphan, and C3 and C7-alkyl or alkenyl 5-phenylmorphans have been reported thus far, the latter by Zimmerman[6] who used a phosphoric acid/formic acid mixture and did not assign the stereochemistry of his products.

Although synthetic strategies have been developed for 5-phenylmorphans,[1,2,7,8] we hoped to find a concise synthesis of the desired target molecules. We thought that a 7-keto derivative might be used as an intermediate, but found that the 7-keto group had unexpectedly low reactivity toward C−C bond forming reactions such as Wittig olefination.[9] Among available strategies, a 3-step

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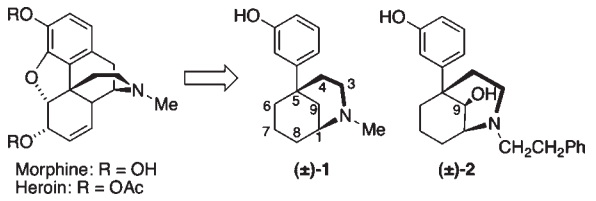
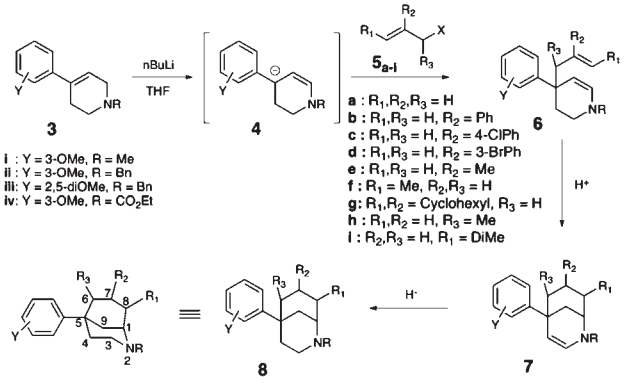


Figure 1. 5-Phenylmorphan fragment ±**-1** of morphine or heroin, and potent analogue ±**-2**.

synthesis using allyl bromide reported by Evans et al. brought our attention to the possibility of applying that methodology in a novel way to prepare 6-, 7-, and 8-substituted 5-phenylmorphans.[10,11] However, after the original report,[10] the reaction scope and mechanism were not studied. We decided to investigate the methodology of Evans et al., to see whether it could be applied to the synthesis of the C-7 or C-8 substituted 5-phenylmorphans.

In the original report[10] the *N*-methyl tetrahydropiperidine **3i** was alkylated using allyl bromide **5a** to generate an all-carbon quaternary center (**6a**, Scheme 1). A mixture of

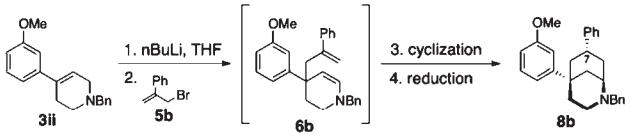
Scheme 1. Substituted 5-Phenylmorphans via Series of Alkylation, Cyclization, and ($NaBH_4$) Reduction Reactions



neat acids (1:1 HCO_2H and H_3PO_4) was used for the cyclization of the crude alkylated product **6a** (where $R_1 = R_2 = R_3 = H$). The cyclized enamine **7a** ($R_1 = R_2 = R_3 = H$) of Evans et al. was then isolated from a strong acid and reduced. Although the cyclization worked well, the reaction was slow (66 h at rt), there were problems isolating the cyclized product from the highly acidic media, and no substituted allyl bromides were tested.

For our functionalized allylic substrates we explored more practical and efficient cyclization conditions and examined milder acids in organic solvents. To test the scope of the reaction, β-phenyl-substituted allyl bromide **5b** was used. The original conditions were initially applied, and the desired product **8b** was obtained in moderate yield (entry 1, Table 1). We then screened organic acids for the cyclization. *p*-Toluenesulfonic acid (*p*-TsOH) in refluxing

Table 1. Alternative Cyclization Conditions



entries	cyclization conditions	temp (°C), time (in days)	yield (%)[a]
1	HCO_2H/H_3PO_4 (1:1)	rt, 7	48
2	***p*-TsOH (2 equiv), toluene**	**reflux, 2**[b]	**56**
3	*p*-TsOH (0.2 equiv), CH_2Cl_2	rt, 3	41
4	TfOH (0.2 equiv), CH_2Cl_2	rt, 3	38
5	30% TFA in CH_2Cl_2	rt, 3	44

[a] Isolated yields of **8b** (3 steps overall). [b] Prolonged reaction time did not increase the yield.

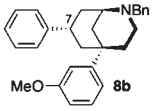
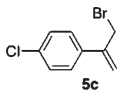
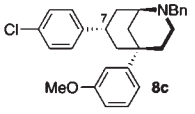
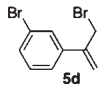
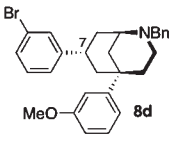
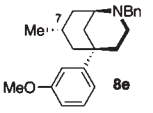
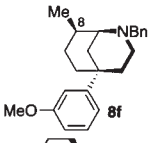
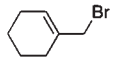
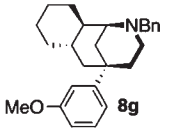
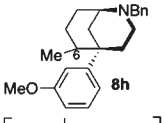
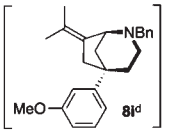
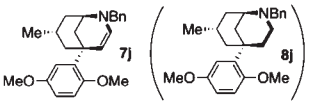
toluene cyclized the ene-enamine **6b** giving a single diastereomer in higher yields within a shorter time than the case with the mixed acid conditions (entry 2, Table 1). In contrast to the acidic conditions of Evans et al., the crude cyclized enamine **7b** under our modified conditions could be directly reduced with sodium borohydride to give the desired amine **8b**.[8] Thus, the use of *p*-TsOH eliminated the necessity of removing the acid before the reduction. Not only did the use of a stoichiometric amount of the reagent at elevated temperature work for the reaction, but a catalytic amount of *p*-TsOH at room temperature also gave the desired product with only a small reduction in yield (entry 3, Table 1). Other, stronger, acids also gave the desired product at room temperature, albeit with lower yields (entries 4−5, Table 1).

Using our optimized conditions, other substituted allyl bromides and chlorides were tested (**5c**−**h**, Scheme 1). The unsubstituted phenyl moiety **5b** and the bromo- and chloro-compounds **5c,d** all underwent the desired reaction in good yields (entries 1−3, Table 2). The simple methyl substituted **5e** also worked well, providing the desired 7-methyl 5-phenylmorphan **8e** (entry 4, Table 2).

All of these R_2-(β)-substituted allyl bromides gave only single diastereomers **8b**−**e**. Reaction with the R_1-(γ)-methyl substituted (*E*)-1-bromobut-2-ene, **5f**, provided 8-methyl substituted 5-phenylmorphan **8f** as a single diastereomer in good yield (entry 5, Table 2). Moreover, cyclohexyl-fused 5-phenylmorphan **8g** was synthesized as a single compound (entry 6, Table 2).

However, the R_3-(α)-methyl substituted compound (**5h**) gave **8h** as an inseparable diasteromeric mixture of the C6-methyl isomers (entry 7, Table 2) with 20% of the diastereomerically pure C8-methyl isomer **8f** arising from γ-alkylation. When the R_1-(γ)-disubstituted compound (1-bromo-3-methylbut-2-ene) **5i** was used, a 5-membered cyclization product **8i** formed. Under the original conditions of Evans et al., a mixture of cyclization adducts were obtained from **5i**. Interestingly, the reaction of 2,5-dimethoxy substituted compound **3iii** with 3-bromo-2-methylprop-1-ene

Table 2. Synthesis of 5-Phenylmorphans **8b–j** Using Substituted Allyl Halides **5b–i**

entry	allyl halide	yield (%)	product
1	 **5b**	56	 **8b**
2	 **5c**	49	 **8c**
3	 **5d**	41	 **8d**
4	 **5e**	65	 **8e**
5	 **5f**	64	 **8f**
6	 **5g**	52	 **8g**
7	 **5h**	39[a,b]	 **8h**
8	 **5i**	60 (0)[c]	 **8i**[d]
9	 **5e**	36[e] (31)[f]	 **7j** **8j**

[a] Diastereomeric mixture. [b] 20% of **8f** was also obtained. [c] When the original reaction conditions (HCO_2H/H_3PO_4, 1:1) were used, the desired product was not obtained. [d] Not isolated - NMR and MS indicated product. [e] Yield of the cyclized enamine **7i**. [f] Yield of **8j** after reduction of **7j**.

(**5e**) gave enamine **7j** (entry 9, Table 2), structurally similar to an intermediate in the synthesis of a *para*-a oxide-bridged phenylmorphan.[12] The enamine was further reduced to obtain the amine **8j** (entry 9, Table 2).

Allyl bromides such as cinnamyl bromide **5k**, bromocyclohex-2-ene **5l**, and *O*-TBDPS protected substrate **5m** did not undergo the cyclization. Moreover, *N*-carbethoxy protected substrate **3iv**, instead of *N*-Bn, did not undergo the desired cyclization reaction. In order to examine the relative stereochemistry of the substituents in the cyclized products, representative products **8b,f,g** were converted into their phenolic relatives **9b,f,g** using known procedures.[13] Crystalline HBr salts of **9b,f,g** were obtained for X-ray crystallographic structure analyses to determine the relative stereochemistry of substituents at C-7 and C-8 with regard to the piperidine ring (Figure 2). For clarity, if a substituent is on the same side of the cyclohexane ring as the piperidine ring, it is called *cis*; otherwise it is *trans*. X-ray analyses showed that substituents at C-7 were *trans*-oriented and those at C-8 were *cis*. Substituents such as a methyl group did not show selectivity at C-6. These selectivities provided information that enabled us to postulate a possible mechanism for this highly selective cyclization.

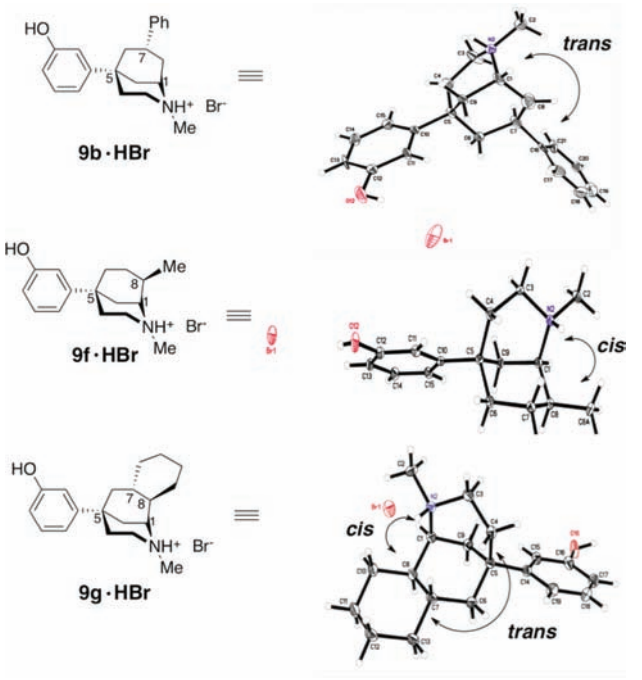


Figure 2. Ortep plots of **9b,f,g** (one enantiomer was drawn for **9f**).

In the report by Evans et al.,[10] it was briefly noted that this cyclization might occur by ene-imine cyclization followed by a hydride shift. Although this appeared to reasonably explain the formation of the obtained products, there was neither evidence for this hypothesis nor explanation for why this reaction was highly diastereoselective *for β-and γ-substituted allylic groups with ene-enamine substrates, which are not* α*-substituted.*

We hypothesized that the exceptional diastereoselectivities were due to the following: (1) Alkylation on the *Re*-face of the olefin that occurred relatively fast because of the more favored Zimmerman-Traxler chairlike TS.[10] It would have to be the most rapid alkylation to obtain, as was found, a single stereoisomer at the C-8-position, as in

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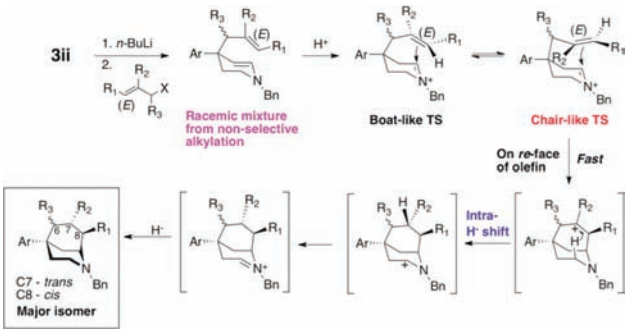
8f−**g**. (2) The hydride shift after cyclization must only occur intramolecularly to obtain the stereochemistry found at the 7-position, i.e., the *trans* products **8b**−**e,g**. If the hydride came from an intermolecular source, the opposite stereochemistry would have been found; moreover, the intramolecular hydride shift is the most likely way to generate an imine after the cyclization. (3) If the chiral center at C-6 was generated via a nonselective alkylation, it would give the diastereomeric mixture **8h** (Scheme 2).

Scheme 2. Possible Mechanism of the Highly Stereoselective Cyclization



In summary, our improved series of reactions, alkylation, cyclization, and then reduction, were successfully applied to the synthesis of new 7- and 8-substituted 5-phenylmorphans in good yields as single diastereomers. The stereochemistry of the products was confirmed by X-ray crystallographic analyses. A possible mechanism, based on the analyses, that explains the obtained data suggests 6-membered *Re*-face C−C bond formation and an intramolecular hydride shift as key aspects of the highly diastereoselective cyclization that gave *trans* selectivity at C-7 and *cis* selectivity at C-8. Further evidence to support our hypothesis can come from the use of more diversely substituted allyl bromides, and these will be tested in future work. Also, pharmacological data for structure−activity relationship (SAR) studies will be carried out and reported in subsequent publications using compounds **8** and **9** with *N*-substituents other than *N*-benzyl or *N*-methyl.

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Supporting Information Available. Atomic coordinates for **9b**, **9f**, and **9g** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 837805, 837804, and 837806, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk. Detailed experimental procedures, spectroscopic data, and X-ray crystallographic data are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.