ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/51637313

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

ARTICLE *in* ORGANIC LETTERS · SEPTEMBER 2011

Impact Factor: 6.36 · DOI: 10.1021/ol2021862 · Source: PubMed

CITATIONS
3

READS
50

4 AUTHORS:

Hwan Jung Lim
Korea Research Institute of Chemical Techno…
23 PUBLICATIONS **230** CITATIONS

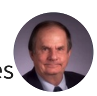
SEE PROFILE

Jeffrey R Deschamps
United States Naval Research Laboratory
309 PUBLICATIONS **4,955** CITATIONS

SEE PROFILE

Arthur E Jacobson
U.S. Department of Health and Human Services
344 PUBLICATIONS **6,850** CITATIONS

SEE PROFILE



Kenner C Rice
National Institutes of Health
894 PUBLICATIONS **25,703** CITATIONS

SEE PROFILE

Available from: Jeffrey R Deschamps
Retrieved on: 24 January 2016

NIH Public Access
Author Manuscript
Org Lett. Author manuscript; available in PMC 2012 October 07.

Published in final edited form as:
Org Lett. 2011 October 7; 13(19): 5322–5325. doi:10.1021/ol2021862.

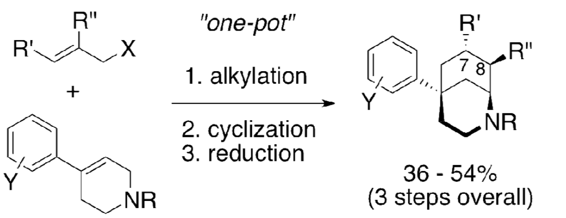
Diastereoselective One-Pot Synthesis of 7- and 8-Substituted 5-Phenylmorphans☐

Hwan Jung Lim[†,≠], **Jeffrey R. Deschamps**[§], **Arthur E. Jacobson**[†], and **Kenner C. Rice**[*,†]
Drug Design and Synthesis Section, CBRB, 5625 Fishers Lane, Room 4N03, National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, DHHS, Rockville, Maryland 20852, and Center for Biomolecular Science and Engineering, Naval Research Laboratory, Washington, D.C. 20375, United States

[†]Drug Design and Synthesis Section, CBRB, NIDA-NIAA

[§]Naval Research Laboratory

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**, Fig. 1) was conceptualized[1] as a structurally simplified fragment of morphine or heroin (Fig. 1), and some N-substituted 5-phenylmorphans were found to have morphine-like activity.[2] Recently Hiebel et al.,[3] synthesized a C9βOH *N*-phenethyl-5-phenylmorphan (the 1*R*,5*R*,9*S*-enantiomer of **2**, Fig. 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

☐Probes for Narcotic Receptor Mediated Phenomena. 45

*kr21f@nih.gov.
≠Present address: LG Chem Research Park, 104-1 Munji-dong, Yuseong-gu, Daejeon, 305-380 South Korea

Supporting Information Available. Detailed experimental procedures, spectroscopic data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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 deposit@ccdc.cam.ac.uk.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

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 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 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 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 toluene cyclized the ene-enamine **6b** giving a single diastereomer in higher yields within a shorter time than 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

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

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 (**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 (Fig. 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.

In the report of 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 no evidence for this hypothesis nor can it explain 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 **(1)** alkylation on the *Re*-face of the olefin that occurred relatively fast because of the more favored Zimmerman-Traxler chair-like 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 **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, 8g**. 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 non-selective alkylation, it would give the diastereomeric mixture **8h** (Scheme 2).

In summary, our improved series of reactions, alkylation, cyclization, 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, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Acknowledgments

The work of the Drug Design and Synthesis Section was supported by the NIH Intramural Research Programs of the National Institute on Drug Abuse (NIDA) and the National Institute of Alcohol Abuse and Alcoholism (NIAAA). The X-ray crystallographic work was supported by NIDA through an Interagency Agreement #Y1-DA1101 with the Naval Research Laboratory. We thank Dr. K. Gawrisch and Dr. W. Teague (NIAAA), for NMR data, N. Whittaker and Dr. H. Yeh (Mass Spectrometry Facility, NIDDK), for MS and ^{1}H NMR data, and Dr. Jason A. Deck (Division of Food Contact Notifications, Office of Food AdditiveSafety, Center for Food Safety and Applied Nutrition, FDA) for discussions and suggestions.

References

(1). May EL, Murphy JG. J. Org. Chem. 1954; 19:618.

(2). May EL, Murphy JG. J. Org. Chem. 1955; 20:1197.

(3). Hiebel AC, Lee YS, Bilsky EJ, Giuvelis D, Deschamps JR, Parrish DA, Aceto MD, May EL, Harris EM, Coop A, Dersch CM, Partilla JS, Rothman RB, Jacobson AE, Rice KC. J. Med. Chem. 2007; 50:3765. [PubMed: 17625813]

(4). Thomas JB, Atkinson RN, Namdev N, Rothman RB, Gigstad KM, Fix SE, Mascarella SW, Burgess JP, Vinson NA, Xu H, Dersch CM, Cantrell BE, Zimmerman DM, Carroll FI. J. Med. Chem. 2002; 45:3524. [PubMed: 12139463]

(5). Bertha CM, Flippen-Anderson JL, Rothman RB, Porreca F, Davis P, Xu H, Becketts K, Cha X-Y, Rice KC. Journal of Medicinal Chemistry. 1995; 38:1523. [PubMed: 7739011]

(6). Zimmerman, DM. U. S. Patent 4,278,797. 1981. p. 1

(7). Rogers ME, May EL. J. Med. Chem. 1974; 17:1328. [PubMed: 4473552]

(8). Bonjoch J, Casamitjana J, Bosch J. Tetrahedron. 1988; 44:1735.

(9). Lim, HJ. unpublished results

(10). Evans DA, Mitch CH, Thomas RC, Zimmerman DM, Robbey RL. J. Am. Chem. Soc. 1980; 102:5955.

(11). Burke TR Jr. Jacobson AE, Rice KC, Weissman BA, Huang HC, Silverton JV. J. Med. Chem. 1986; 29:748. [PubMed: 3009813]

(12). Yamada K, Flippen-Anderson JL, Jacobson AE, Rice KC. Synthesis-Stuttgart. 2002:2359.

(13). Cheng K, Kim IJ, Lee MJ, Adah SA, Raymond TJ, Bilsky EJ, Aceto MD, May EL, Harris LS, Coop A, Dersch CM, Rothman RB, Jacobson AE, Rice KC. Org. Biomolec. Chem. 2007; 5:1177.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

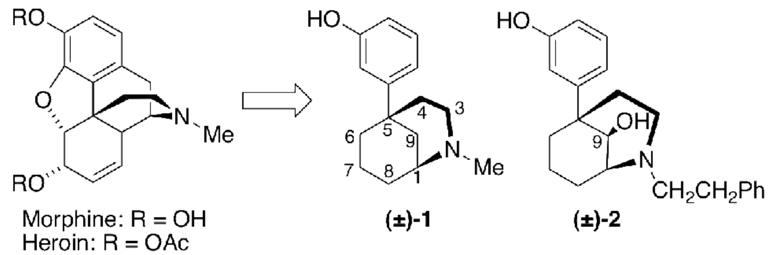


Figure 1.
5-Phenylmorphan fragment **±-1** of morphine or heroin, and potent analogue **±-2**

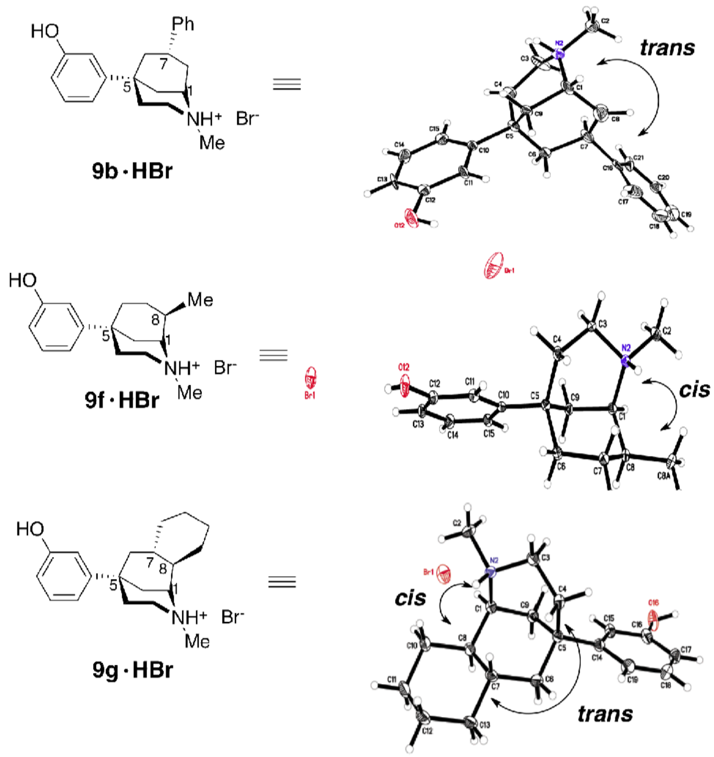


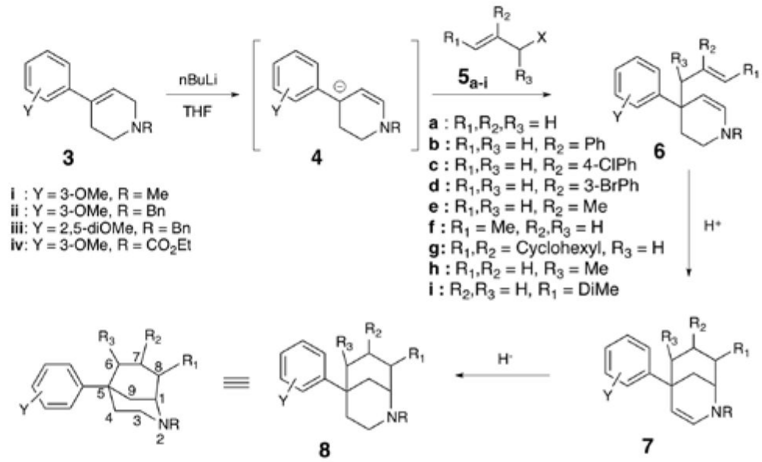
Figure 2.
Ortep plots of **9b, f, g** (one enantiomer was drawn for **9f**)

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript



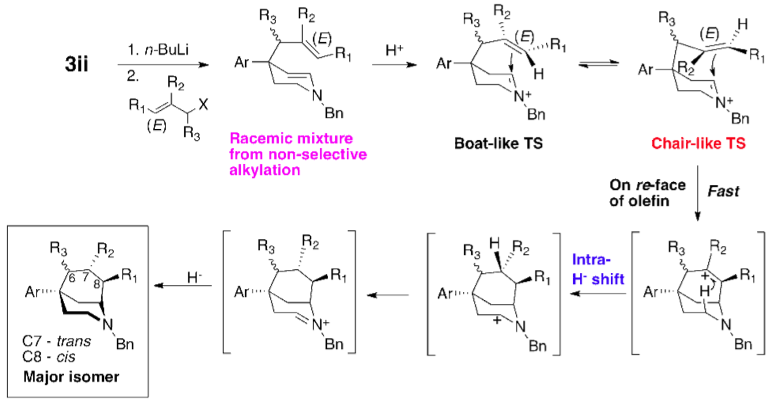
Scheme 1.

Substituted 5-phenylmorphans via series of alkylation, cyclization, and ($NaBH_4$) reduction reactions

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

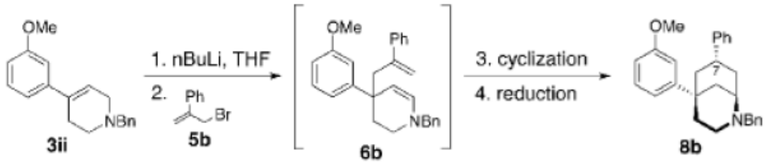


Scheme 2.
Possible mechanism of the highly stereoselective cyclization

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Alternative cyclization conditions



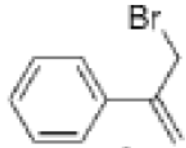
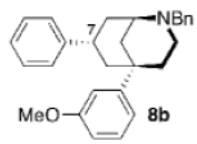
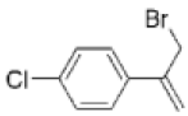
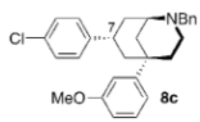
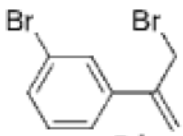
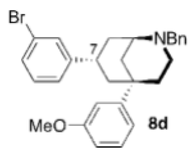
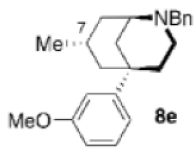
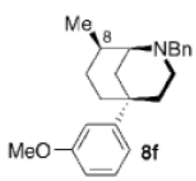
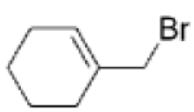
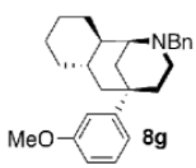
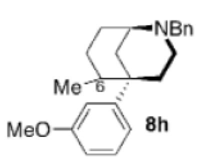
entries	cyclization conditions	temperature (°C), time (in days)	yield (%)[a]
1	HCO_2H/H_3PO_4 (1:1)	rt, 7	48
2	***p*-TsOH (2 equiv), toluene**	**reflux, 2[b]**	**56**
3	*p*-TsOH (0.2 equiv), CH_2Cl_2	rt, 3	41
4	TfOH (0.2 equiv), CH_2Cl_2	rt, 3	38
5	30% TFA in CH_2Cl_2	rt, 3	44

[a]Isolated yields of 8b (3 steps overall).;

[b]Prolonged reaction time did not increase the yield.

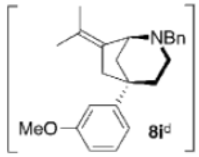
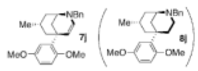
Table 2

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**

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

entry	allyl halide	yield (%)	product
8	 **5i**	60 (0)[c]	
9	 **5e**	36[d] (31)[e]	

[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**.