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A Novel Stereo- and Enantioselective Synthesis of trans-9-Alkyl-2-benzyl-5-methyl-6,7-benzomorphans

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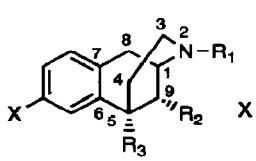
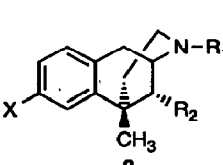
Abstract: The first stereo- and enantioselective syntheses of trans-9-alkyl-2-benzyl-5-methyl-6,7-benzomorphans (**12**) are described. The addition of alkyl magnesium halides to (*R*)-2-naphthyl-4-phenyl-1,3-oxazolidine (**7**) followed by treatment with iodomethane and quenching with acid gave (1*S*,2*S*)-2-alkyl-1-methyl-1,2-dihydronaphthalenecarboxaldehyde (**10**). Homologation of **10** followed by reductive amination using benzylamine gave (1*S*,2*S*)-trans-2-alkyl-1-benzylaminoethyl-1-methyl-1,2-dihydronaphthalene (**11**). Mercuric acetate-assisted cyclization of **11** followed by LAH reduction afforded (1*S*,5*S*,9*R*)-**12**.

Recently, we reported the synthesis and the sigma, PCP, and μ opioid receptor binding affinity of a series of (+)- and (-)-cis-2-substituted-2'-hydroxy-5,9-dimethyl-6,7-benzomorphans (**1a**, cis-N-substituted N-normetazocines).[1,2] In a later study, we reported that cis-2-substituted-5,9-dimethylbenzomorphans (**1b**, cis-N-substituted-2'-deoxy-N-normetazocines) also possessed high affinity to the sigma binding site.[3] As a continuation of this structure activity relationship (SAR) study, we were interested in evaluating the binding affinity of the (+)- and (-)-trans-2-substituted-5-methyl-9-alkyl-6,7-benzomorphans (**2**).



1a, X = OH, $R_2 = R_3 = CH_3$
b, X = H, $R_2 = R_3 = CH_3$



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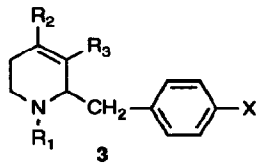

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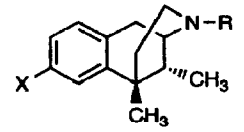
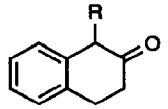


15a, R = H; X = OH



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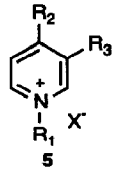

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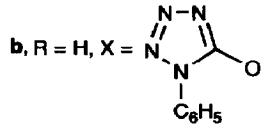
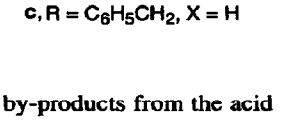


b, R = H, X =



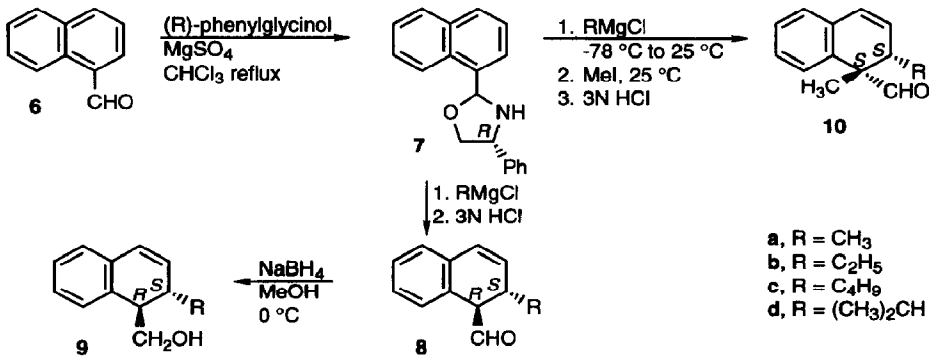
c, $R = C_6H_5CH_2$, X = H

(±)-trans-2,5,9-Trisubstituted benzomorphans (**2**) have been obtained as by-products from the acid catalyzed cyclization of 1,3,4-trisubstituted 2-benzyltetrahydropyridines (**3**) which yields the (±)-cis-isomer (**1**) as the major product.[4] In some cases, if aluminum bromide is used as the acid catalyst, **2** can be the major product.[5] The trans isomers of **2** have also been obtained via multistep synthesis starting with 1-alkyl-2-tetralones (**4**)[6,7] or 1,3,4-trisubstituted pyridinium salts (**5**).[8] However, all of the methods reported gave

racemic material, and none provided a convenient synthesis of **2**. In this report, we describe a new stereo- as well as enantioselective synthesis of the (+)-isomers of trans-9-alkyl-2-benzyl-5-methyl-6,7-benzomorphans (**2**, X = H, R_1 = Bn).

In 1992, Pridgen *et al.*[9] reported that optically active trans-2-alkyl-1-hydroxymethyl-1,2-dihydronaphthalenes (**9**) could be prepared in high chemical and optical purity by the addition of alkyl magnesium halides to the oxazolidine (**7**) derived from (*R*)- or (*S*)-phenylglycinol and naphthaldehyde (**6**). Acid quenching and cleavage of the chiral auxiliary gave the trans-2-alkyl-1,2-dihydronaphthalenecarboxaldehyde (**8**) which was reduced, without isolation, with sodium borohydride to give **9**. The asymmetric synthesis based on the *R*-isomer is illustrated in Scheme 1. We found that quenching the alkyl magnesium chloride reaction with

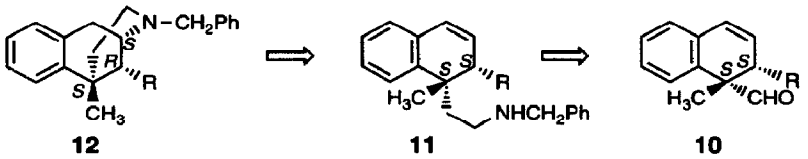
Scheme 1



methyl iodide before removal of the chiral auxiliary gave 2-alkyl-1-methyl-1,2-dihydronaphthalenecarboxaldehyde (**10**) in high yield and excellent enantiomeric excess. Recently, Pridgen *et al.*[10] reported a similar finding. The relative configuration of **10** was established by NOE experiments. For example, when the 2-methyl group at 1.20 ppm ($CDCl_3$) of the aldehyde **10a** was irradiated at room temperature, NOEs were observed at 2.70 ppm (H-2, 42%), 9.79 ppm (CHO, 32%), and 5.85 ppm (H-4, 26%). Also irradiation of the 1-methyl group at 1.42 ppm ($CDCl_3$) at room temperature showed NOEs at 2.70 ppm (H-2, 34%). These observations show that the H-2 and the 1-methyl groups are cis to each other, whereas the 1-methyl and 2-methyl groups are trans oriented.

The easy availability of the aldehydes **10** in high yield and optical purity suggested the retrosynthesis shown in Scheme 2 for the synthesis of the (1*S*,5*R*,9*S*)-N-benzylbenzomorphans (**12**). We found that the

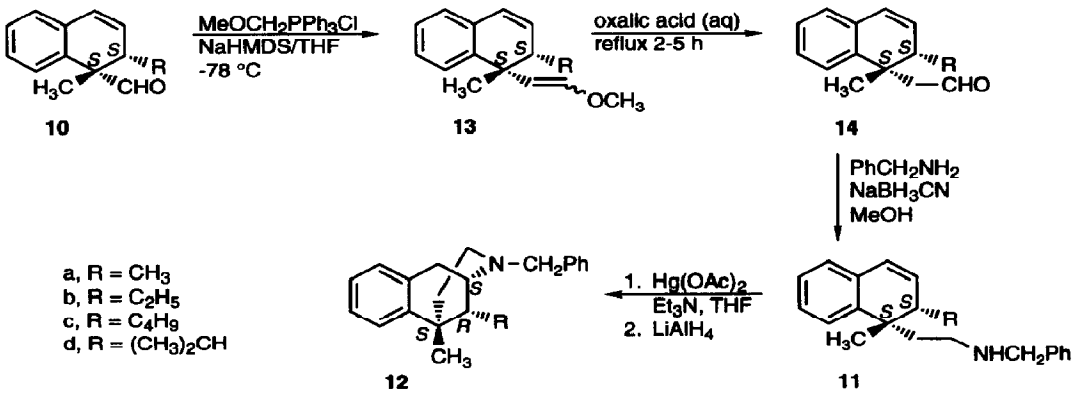
Scheme 2



benzomorphans (**12**) could be prepared in high yield and excellent optical purity by the general route shown in Scheme 3. For instance, the Wittig reaction of aldehyde (1*S*,2*S*)-**10a** with the ylid prepared from (methoxy-

methyl)triphenylphosphonium chloride in THF at -78 °C afforded the methyl vinyl ether [(1*S*,2*S*)-**13a**: $[\alpha]_D^{22}$ +204°(*c* 0.28, $CHCl_3$), -CH=CH-OCH_3, 5.88 ppm (d, J = 7.20 Hz), 4.60 ppm (d, J = 7.20 Hz), 91% yield]. Acid hydrolysis of the vinyl ether **13a** resulted in the formation of the aldehyde [(1*S*,2*S*)-**14a**: $[\alpha]_D^{22}$ +138.2°(*c* 0.685, $CHCl_3$), -CH_2-CHO, 2.79 ppm (dd, J = 2.90, 14.16 Hz), 2.32 ppm (dd, J = 3.60, 14.16 Hz), 72% yield]. Reductive amination of aldehyde **14a** in the presence of benzylamine hydrochloride in MeOH at room temperature followed by sodium cyanoborohydride reduction provided the amine [(1*S*,2*S*)-**11a**: $[\alpha]_D^{22}$ +73°(*c* 0.735, $CHCl_3$), -CH_2-CH_2-NH-CH_2-Ph, 1.53-1.64 ppm (m), 2.08-1.96 ppm (m), 2.44-2.30 ppm (m), 3.65 ppm (s), 92% yield]. Mercuric acetate-assisted cyclization of this amine in the presence of triethylamine in THF at room temperature followed by addition of lithium aluminum hydride afforded the desired product **12a**: $[\alpha]_D^{24}$ +33.6°(*c* 0.145, $CHCl_3$), 80% yield, 99% ee].[12] The formation of **12a** was indicated by the loss of the resonances at 6.37 ppm (dd, J = 2.10, 9.50 Hz) and 5.73 ppm (dd, J = 3.65, 9.59 Hz) which are due to the vinyl 3-H and 4-H vinyl protons of (1*S*,2*S*)-**11a** and the appearance of the typical benzylic H-1 methylene protons in the spectrum of (1*S*,5*S*,9*R*)-**12a** [2.72 ppm (dd, J = 6.0, 18.0 Hz) and 3.20 ppm (d, J = 18.0 Hz)].

Scheme 3



The absolute configuration of the starting aldehydes (**10**) obtained by the method shown in Scheme 1 has been previously established.[11] The stereochemistry of all three stereogenic centers in the benzomorphans **12a** is determined by the stereochemistry of the aldehyde **10a**. To further confirm the structural assignment of benzomorphan **12a**, an authentic sample of (±)-trans-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan **15a**[13] was treated with an acetone solution of 5-chloro-1-phenyl-1H-tetrazole in the presence of potassium carbonate to give the 2'-phenyltetrazoyl ether **15b**. Hydrogenolysis of **15b** in the presence of palladium hydroxide catalyst in ethanol followed by N-benzylation with benzyl bromide in acetone containing potassium carbonate afforded (±)-N-benzyl-trans-5,9-dimethyl-6,7-benzomorphan (**15c**). The ^1H and ^{13}C NMR spectra of (±)-**15c** and (+)-**12a** were identical.

Since Pridgen et al.[10] showed that **10a** was greater than 98% optically pure, **12a** would be expected to possess similar optical purity. HPLC analysis of **12a** on a chiral column confirmed that this compound possessed a 99% ee (Table). The benzomorphans **12b-12d** were synthesized by methods analogous to those used for **12a** by using the appropriate alkyl magnesium chloride in place of methyl magnesium chloride. The overall yields as well as physical data for the benzomorphans are listed in the table.

Table

benzo-morphans	overall yield[a] %	% ee[b]	mp[c] °C	$[\alpha]_D^{24}$ ($CHCl_3$)[c]
12a	33 (80)	99	159-160	+33.6 (c 0.145)
12b	48 (91)	99	147-148	+61.1 (c 0.155)
12c	41 (95)	>99	130-131	+59.3 (c 0.045)
12d	53 (89)	>99	135-136	+84.1 (c 0.170)

[a] The number in the parentheses is the % yield in the last step. [b] The enantiomeric purity was determined on the free base via the chiral HPLC on a Sumichiral OA-4900 column (Rainin Instrument, Inc.). [c] The mp and optical rotation are for the hydrochloride salt. The C, H, and N analyses of the hydrochloride salts of **12a-d** agreed to ±0.4% with theoretical values.

In summary, we have developed the first stereo- and enantioselective synthesis of (+)-trans-2-benzyl-5-methyl-9-alkyl-6,7-benzomorphans (**12**). N-Debenzylation of **12** followed by N-alkylation will provide easy access to the synthesis of other N-substituted benzomorphan analogues. Using 7-methoxynaphthaldehyde in place of naphthaldehyde (Scheme 3) will lead to 2'-methoxy substituted analogues of **12** which are important for their opioid activity. The investigation of the sigma binding properties of **12a-d** is currently in progress.

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References and Notes

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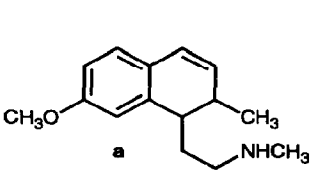
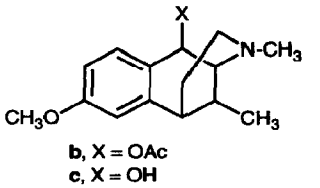
12. Inoue and May found that mercuric acetate-sodium borohydride cyclization of racemic trans-1,2-dihydro-2-methyl-7-methoxy-1-(2-dimethylaminoethyl)naphthalene (**a**) gave a mixture of 8α-acetoxy- and 8α-hydroxy-2,9α-dimethyl-2'-methoxy-6,7-benzomorphan (**b** and **c**) (Inoue, H.; May, E. L. *J. Med. Chem.* **1976**, *19*, 259.



a



b, X = OAc
c, X = OH

13. We thank Dr. John Mallamo from Sterling Winthrop Pharmaceuticals Research Branch, Rensselaer, NY, for supplying **15a**.

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