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A novel and facile preparation of bremazocine enantiomers through optically pure *N*-norbremazocines

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Abstract—In order to provide ready access to multigram quantities of the optically pure bremazocines [(−)- and (+)-9,9-dimethyl-5-ethyl-2-hydroxy-2-(1-hydroxy-cyclopropylmethyl)-6,7-benzomorphan)], we have developed an improved non-chromatographic synthesis, and determined the optical purity of their *N*-nor precursors using a rapid and relatively simple ^{1}H NMR method based on diastereomeric derivatization with optically pure 1-phenylethylisocyanate. This method of determining optical purity should be readily amenable to similar systems containing phenolic amino functionalities. Finally, a greatly simplified methodology for introduction of the *N*-(1-hydroxycyclopropylmethyl) substituent in bremazocine is described. The improved synthetic method—the overall yield was increased about 3-fold—combined with the practical methodology to determine optical purity will considerably facilitate the employment of these enantiomers as pharmacological tools for examination of the κ-opioid receptor system, as well as their evaluation as drug abuse treatment agents. This synthesis will also enable the study of these enantiomers for other, non-classical applications (e.g., treatment agents for HIV).
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1. Introduction

It is now widely recognized that the enantiomers of a drug can act on diverse biological systems and thus may have vastly different pharmacological properties (e.g., the morphine enantiomers[1] and the tragic case of thalidomide[2]). Thus any studies with racemates involve the difficult evaluation of two different drugs simultaneously. The enantiomers of bremazocine (Fig. 1) have been found to have very different affinity at opioid receptors, thus possessing very different pharmacological activities and profiles.[3] The opioid effects of racemic bremazocine are due in large measure to the agonist activity of its (−)-enantiomer at the κ-opioid receptor.[3–5]

κ-Agonists have become important pharmacological tools[6–8] and are being examined as treatment agents for cocaine abuse[9,10] due to their ability to lower excessively elevated dopamine levels in the nucleus accumbens. Recently, κ-agonists have been evaluated for their potential usefulness in the treatment for HIV-1[11] and as cardiovascular agents.[12] κ-Agonists such as the prototypic ketocyclazocine, and bremazocine, are members of the 6,7-benzomorphan class of opioids.[13] The (−)-enantiomer of bremazocine is an importamt tool for opioid receptor studies; the (+)-enantiomer, which does not interact well with opioid receptors, can be used to examine non-opioid pharmacological effects. We required substantial quantities of both enantiomers for future pharmacological studies in various primate models of behavior and disease. Since the enantiomers of bremazocine are not commercially available and their only published synthesis is a long, laborious multistep process, described in the patent literature,[14] the development of a simplified synthesis of the pure enantiomers has become extremely important. We now report an improved methodology for the preparation of both enantiomers, optically pure, and in multigram quantities.

2. Results and discussion

Our work focused on shortening the original route,[14] optimizing various steps in the published synthesis that were found to be the most difficult and time-consuming, and eliminating the formerly used 1-oxaspiro[2.2]pentane for the introduction of the *N*-(1-hydroxycyclopropylmethyl) substituent in bremazocine.

Starting from commercially available methyl *p*-methoxyphenylacetate (**1**) the keto compound **2** was

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prepared by a Reformatzky reaction of **1** with methyl-2-bromoisobutyrate as previously described[14] (Scheme 1). However, we developed a distinctly improved workup procedure by changing the extraction conditions, which afforded **2** in 92% yield versus the reported 60–65% yield.[14] After quenching the reaction with sulfuric acid, the solution of **2** in Et_2O was washed with water until the pH was neutral before washing with aqueous base in order to prevent formation of an inorganic salt (Na_2SO_4) and emulsion. This salt formation was found to occur in the original procedure when the organic extract was immediately basified. The elimination of the salt facilitated the work up and precluded loss of product by its entrapment in the salt fraction.

The published route to intermediate **5** was formerly conducted in three steps:[14] (1) conversion of **2** into a benzyliminoester **3** with $TiCl_4$ in toluene, (2) reduction of **3** to benzylamine **4** by catalytic hydrogenation over Pt/C, and (3) a second hydrogenation with Pd as catalyst to afford the debenzylated primary amine **5** (Scheme 1). We simplified the synthesis of **5** to a two-step procedure by a one-pot reductive amination of ketone **2** to benzylamine **4** utilizing $TiCl_4/NaCNBH_3$[15] followed by *N*-debenzylation of **4** to the primary amine **5**. The *N*-debenzylation of compound **4** as described in the original procedure proved troublesome in our hands and did not result in reproducible yields. This problem was overcome by conducting the reaction under catalytic transfer hydrogenolysis conditions[16] employing ammonium formate as the hydrogen source to give the amine **5**. These modifications provided convenient and relatively quick access to intermediate **5** and helped increase the overall yield of **5** from **1** from 22 to 59%.

Compound **6** was prepared by treatment of **5** with methyl acrylate (Scheme 2) followed by acetic acid and formaldehyde in an Eschweiler–Clark reaction, according to the literature.[14] In the next step, sodium hydride in DMF was originally[14] used in the Dieckman cyclization of **6** to **7**. However, we found DMF to be an unsatisfactory solvent for this reaction because it promoted the formation of unidentified by-products. Changing the solvent to toluene and employing catalytic amounts of EtOH to initiate the reaction increased the yield of **7** from **5** from less than 50% to about 60%. Compound **8** was prepared from **7** in five steps as outlined in the original report.[15] Key intermediate **8**, (±)-*N*-norbremazocine, was resolved into its enantiomers, (+)-**8** and (−)-**8**, through diastereomeric salt formation with 3-bromocamphor-8-sulfonic acid (Scheme 3).[14] However, analysis of the optical purity of the enantiomers was not reported.[14] Because optically pure enantiomers were essential at this stage of the synthesis, we devised a simple NMR method for the determination of optical purity as described below.

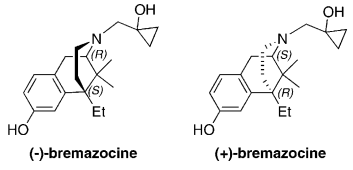
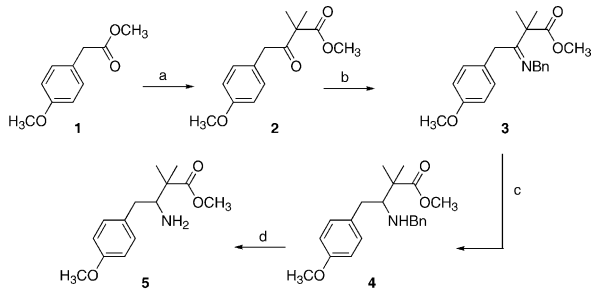


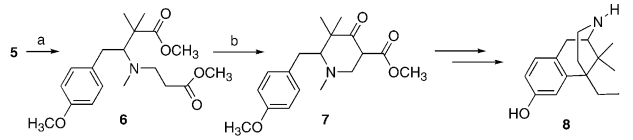
Figure 1. Absolute stereochemistry of bremazocine enantiomers.



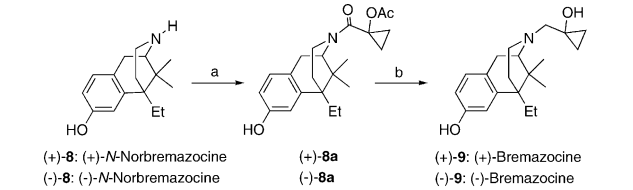
Scheme. 1. Reagents: (a) Zn, methyl 2-bromoisobutyrate, THF; (b) $TiCl_4$, benzylamine, Ch_2Cl_2; (c) $NaCNBH_3$; (d) HCO_2NH_4, Pd/C, MeOH.

In the original synthetic pathway[17] the enantiomers of bremazocine (+)-**9** and (−)-**9** were prepared using 1-oxaspiro[2.2]pentane. This reagent is generated in two steps from methallyl chloride in low overall yield (about 15%).[18] Its preparation is laborious and requires special precautions due to the volatile nature of the intermediate methylenecyclopropane.[18]

In order to avoid the problematic preparation and use of 1-oxaspiro[2.2]pentane, our synthesis of (+)-**9** and (−)-**9** employed 1-acetoxycyclopropanecarboxylic acid, prepared[19] by simple acetylation of the commercially available 1-hydroxycyclopropanecarboxylic acid. The synthesis of bremazocine was then accomplished through 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide (EDCI) mediated coupling of 1-acetoxycyclopropanecarboxylic acid with the enantiopure *N*-norbremazocines (+)-**8** and (−)-**8**, respectively, to give (+)-**8a** and (−)-**8a** as crystalline intermediates. This was followed by simultaneous reduction of the amide and ester groups with AlH_3 to give the bremazocine enantiomers (+)-**9** and (−)-**9**. Our values for optical rotation were comparable with those reported,[17] although the reported values were stated without mention of solvent or concentration. The equal and opposite optical rotations of our enantiomers (+)-**9** and (−)-**9** suggested complete resolution. However, we required an independent determination of enantiopurity of the isomers. Our



Scheme. 2. Reagents: (a) methyl acrylate, cat. HOAc, HCOOH, HCHO; (b) NaH, toluene.

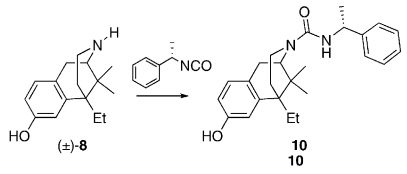


Scheme. 3. Reagents: (a) 1-Acetoxycyclopropanecarboxylic acid, EDCI, CH_2Cl_2; (b) $LiAlH_4$, H_2SO_4, THF.

methodology for evaluation of enantiopurity as described below showed that the *N*-norbremazocine enantiomers (+)-**8** and (−)-**8** were more than 99% pure.

We utilized an NMR method based on spectroscopic enantiodiscrimination that we had previously employed with other phenolic amines.[20] The method relies on derivatization of *N*-norbremazocine enantiomers to give diastereomers selectively on nitrogen (vs phenolic hydroxyl) that show separation of peaks in the ^{1}H NMR spectrum. We used optically pure *R*-(+)-1-phenylethylisocyanate for the reaction with (+)-**8** and (−)-**8** in $CDCl_3$ to give the corresponding ureas **10** (Scheme 4). The quantitative and rapid formation of diastereomers with this reagent offers an excellent alternative to other commonly used reagents such as chiral lanthanide shift reagent or chiral solvating agents. It bears the advantage of rendering both chromatography and isolation of the diastereomers unnecessary.

Well-separated peaks between 1.1 and 1.6 ppm were observed in the ^{1}H NMR spectrum (300 MHz) of the diastereomeric urea mixture **10** (the significant peaks are shown in Fig. 2, trace A). The urea of each enantiomer, formed by reaction with the chiral reagent, displayed a signal that overlapped some of those observed in the diastereomeric ureas of the racemic mixture (Fig. 2, traces B and C). This occurred at δ 1.50, 1.47 and 1.15 ppm for the (−)-isomer and at δ 1.49, 1.46 and 1.14 ppm for the (+)-isomer in the selected area. Little if any enantiomeric contamination was present in the enantiopure samples within the limits of detection. In order to measure the experimental limits of accuracy of this method we deliberately added a mixture containing the opposite isomer together with chiral reagent in steps of 0.5% (wt%) to each sample. Addition of 0.5% of the less predominant enantiomer to the predominant isomer did not cause a detectable change in the signal. After addition of 1% a weak signal of the minor isomer, which was clearly distinguishable from background noise could first be observed (Fig. 2, traces D and E). Continued addition of the minor isomer in 0.5% wt increments produced an increased intensity of its peak. These findings indicate that the detection limit of enantiomeric impurity was between 0.5 and 1%. Thus, our resolved compounds were at least 99% optically pure. In order to avoid misinterpretation of the spectroscopic data and to obtain reproducible and accurate results with this method, it is essential to use optically pure chiral derivatization agent. The absence of optical impurities prevents the formation of peaks due to artifacts in the reagent that would occur when these impurities reacted with optically pure enantiomers. This inexpensive spectroscopic method should prove useful for easily establishing the optical purity of certain opioids and other molecular structures that contain phenolic secondary and possibly primary amino functions.



Scheme. 4. Diastereomeric urea formation employing *R*-(+)-1-phenylethylisocyanate.

3. Conclusion

Our improved synthesis of the two optically pure *N*-norbremazocine enantiomers combined with the facile and rapid determination of their optical purity and the greatly simplified introduction of the *N*-substituent considerably facilitates the availability of bremazocine enantiomers for use as pharmacological tools for the in vitro and in vivo exploration of the κ-opioid receptor system and for other possible applications. In addition, the increased availability of the *N*-nor inter-

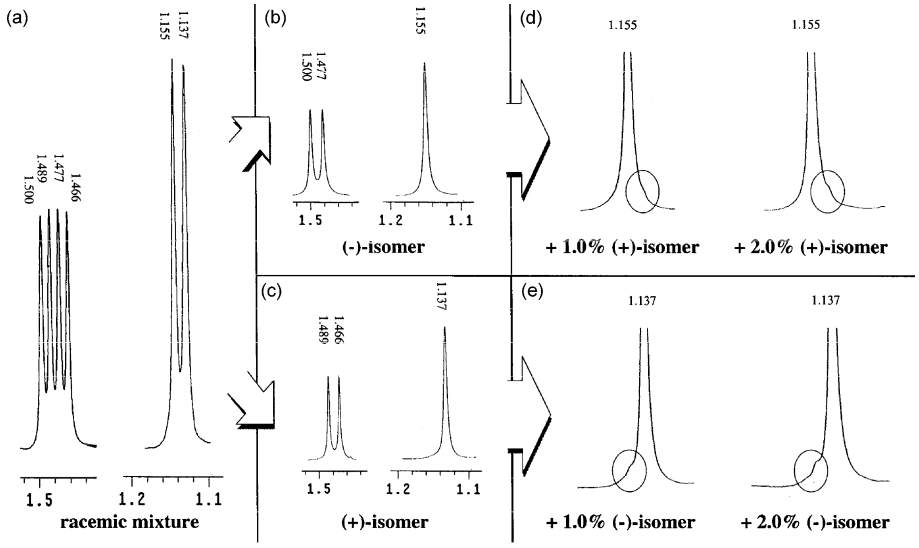


Figure 2. ^{1}H NMR spectra of ureas of (+)-**8** and (−)-**8**: (a) two well separated doublets (δ 1.48 and 1.47 ppm, 2 d, $J = 6.9$ Hz, 3H) and two singlets (δ 1.15 and 1.14 ppm, 2 s, 6H) in the spectrum of diastereomeric urea mixture **10**; (b) and (c) peaks for enantiopure ureas of (+)-**8** and (−)-**8**; (d) and (e) continued addition of the minor isomer produced an increased intensity of its peak.

mediates will further enable future structure–activity studies of novel pharmacological effects. This is particularly important in the opioid area where the pharmacological profile is largely determined by the *N*-substituent.

4. Experimental

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL-300 instrument using DMSO-d_6 or $CDCl_3$ as solvent, δ values in ppm (TMS as internal standard), *J* (Hz) assignments of ^{1}H resonance coupling. Chemical-ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization (EIMS) mass spectra were obtained using a VG-Micro Mass 7070F mass spectrometer. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, USA.

4.1. 2,2-Dimethyl-4-(*p*-methoxyphenyl)acetoacetate (2)

A solution of methyl 2-bromoisobutyrate (583.0 g, 3.2 mol) and methyl *p*-methoxyphenylacetate (**1**) (450.0 g, 2.5 mol) in THF (435 mL) was added to a refluxing suspension of granulated Zn (189 g, 2.9 mol) in THF (435 mL) that was activated with I_2 (0.8 g, 3.5 mmol) under argon atmosphere. After the reaction had started, the addition was continued at such a rate that refluxing was maintained with minimal application of external heat. Stirring was continued at reflux for 5 h. The reaction mixture was cooled in an ice bath and H_2SO_4 (1.25 L, 4 N) was added slowly under vigorous stirring. The organic layer was separated and after filtration from solid material, the aqueous layer was extracted with ether. The combined organic layers were first washed with H_2O until the pH was neutral, then with saturated $NaHCO_3$, brine and dried over Na_2SO_4. Evaporation of the solvent yielded the crude product **2** that was purified by distillation in vacuo (576.0 g, 92%), bp 135 °C/0.7 mm (lit.[14] 145 °C/1 mm).

4.2. 3-Benzylamino-2,2-dimethyl-4-(*p*-methoxyphenyl)-butyrate (4)

$TiCl_4$ (262.0 mL, 0.3 mol, 1 M in CH_2Cl_2) was added slowly to a mixture of **2** (125.0 g, 0.5 mol) and benzylamine (166.0 g, 1.6 mol) in dry CH_2Cl_2 (3 L) under N_2 at such a rate as to keep the reaction mixture warm, but not boiling (45–60 min for addition). Stirring under N_2 was continued for 48 h, then a solution of $NaCNBH_3$ (90.0 g, 1.4 mol) in MeOH (1.2 L) was cautiously added. After 30 min the mixture was filtered through Celite and evaporated to give an oil. This oil was stirred with EtOAc (900 mL) and again filtered through Celite. The yellow gelatinous residue was washed with EtOAc and the filtrate and washings evaporated to an oil under vacuum. Crystallization from 95% EtOH (250 mL) provided product (97.2 g). An additional 23.3 g of product was obtained by evaporating the mother liquor from the first crystallization and dissolving it in EtOAc (800 mL). After washing the solution twice with half saturated $NaHCO_3$ solution and drying with Na_2SO_4 the solvent was removed and the product **4** crystallized from 95% EtOH, (total yield, 120.5 g, 70.6%) mp 60 °C (lit.[14] 58–60 °C).

4.3. 3-Amino-2,2-dimethyl-4-(*p*-methoxyphenyl)butyrate (5)

To a solution of **4** (51.2 g, 0.2 mol) in MeOH (600 mL) was added Pd/C (6.0 g, 10%) under N_2. The mixture was brought to reflux at which time a solution of ammonium formate (37.8 g, 0.6 mol) in H_2O (75 mL) was added. The mixture was heated to reflux for 2 h, cooled, and the catalyst removed by filtration through a pad of Celite. The oil obtained upon removal of solvent was partitioned between ether and saturated $NaHCO_3$ and the aqueous layer was again extracted with ether. The combined ether portions were washed with brine, dried over Na_2SO_4 and evaporated. Crystallization from hexane afforded **5** (34.1 g, 90.5%), mp 46.5 °C (lit.[14] 46–49 °C).

4.4. 3-(*p*-Methoxybenzyl)-2,2-*N*-trimethyl-3,3′-iminodipropionate (6)

A mixture of **5** (62.6 g, 0.25 mol) and methyl acrylate (24.9 mL, 0.3 mol) was stirred vigorously at 50 °C. Acetic acid (6.23 mL) was added rapidly and the temperature was raised to 90 °C at which time it rose spontaneously to 100 °C. After 1 h, the excess of methyl acrylate and acetic acid were removed at 50 °C under aspirator vacuum. Formic acid (49 mL, 95%) and aqueous formaldehyde (49 mL, 35%) were added dropwise successively over a period of 30 min while cooling the reaction with H_2O. Subsequently, the reaction mixture was warmed to 40 °C for 1 h, then stirred at room temperature for 16 h and finally heated to 60 °C for 1 h. The low boiling material was evaporated and the resulting oil was treated with an access of a concentrated aqueous solution of K_2CO_3 and $CHCl_3$ (300 mL). The aqueous layer was extracted with $CHCl_3$ and the combined organic extracts were washed with brine and dried over $MgSO_4$. Removal of solvent provided **6** as an oil (87.7 g) that was used without further purification for the next reaction.

4.5. 2-(*p*-Methoxybenzyl)-4-oxo-1,3,3-trimethyl-5-piperidine-carboxylate hydrochloride (7)

Compound **6** (87.7 g, 9 mmol) was added to a suspension of NaH (18 g, 0.75 mol, 60% dispersion in oil) in toluene (600 mL, dried by azeotropic distillation overnight). The mixture was gradually heated to reflux and EtOH (3 mL) was added to start the reaction after the temperature had reached 50–60 °C. After about 15–30 min, a vigorous evolution of hydrogen occurred. Heating was continued for 3 h. Upon cooling the reaction mixture was washed with half saturated $NaHCO_3$ and brine and dried over Na_2SO_4. After removal of solvent, the residual oil was dissolved in EtOH and made acidic with HCl in ether. Crystallization was induced by cooling to −70 °C. Yield 52 g (59% yield from **5**), mp 169 °C, dec. (lit.[14] 163–164 °C, dec).

4.6. (+) and (−)-9,9-Dimethyl-5-ethyl-2′-hydroxy-6,7-benzomorphan [(+)-norbremazocine, (+)-8 and (−)-norbremazocine, (−)-8]

(+)-8 and (−)-8 were prepared according to the literature[14] in 5 steps from 7.

4.7. Preparation of ^{1}H NMR samples of 9,9-dimethyl-5-ethyl-2′-hydroxy-2-(1-phenylethyl)carbamoyl-6,7-benzomorphan from (+)-8 and (−)-8

R-(+)-1-Phenylethylisocyanate (2.4 μL, 0.017 mmol) was added to a solution of (+)-**8** {$[\alpha]_D^{25} = +75°$ (*c* 2, MeOH)} (4.0 mg, 0.016 mmol) in $CDCl_3$ (0.6 mL). The ^{1}HNMR spectrum of this mixture was determined. Subsequently, a mixture consisting of the other isomer, (−)-**8**, (2.4 mg, 0.01 mmol) and *R*-(+)-1-phenylethylisocyanate (1.44 μL, 0.01 mmol) in exactly 2.5 mL $CDCl_3$ was added in 0.5% (20.8 μL) increments by weight relative to (+)-**8** and analyzed by ^{1}H NMR spectroscopy. An analogous procedure was followed for (−)-**8** {$[\alpha]_D^{25} = -75°$ (*c* 2, MeOH)}.

4.8. Carbamate from (+)-8

^{1}H NMR ($CDCl_3$) δ 7.39–6.56 (m, 8H), 1.47 (d, 3H, *J* = 6.9 Hz), 1.13 (s, 3H), 1.02 (t, 3H, *J* = 7.5 Hz), 0.95 (s, 3H).

4.9. Carbamate from (−)-8

^{1}H NMR ($CDCl_3$) δ 7.39–6.58 (m, 8H), 1.49 (d, 3H, *J* = 6.9 Hz), 1.15 (s, 3H), 1.02 (t, 3H, *J* = 7.2 Hz), 0.95 (s, 3H).

4.10. (−)-2-(1-Acetoxy-cyclopropylcarbonyl)-9,9-dimethyl-5-ethyl-2′-hydroxy-6,7-benzomorphan [(−)-8a]

EDCI (8.97 g, 46.8 mmol) was added portionwise to a stirred mixture of (−)-**8** (4.42 g, 18 mmol) and 1-acetoxycyclopropane-1-carboxylic acid (5.19 g, 36 mmol) in anhyd CH_2Cl_2 (70 mL) at 0 °C. After stirring for 30 min at 0 °C the solution was allowed to come to room temperature and stirring was continued overnight. CH_2Cl_2 was added and the mixture was washed with H_2O, with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was filtered through a short column of silica gel (acetone/*n*-hexane, 3/5) to yield (−)-**8a** as colorless crystals (5.6 g, 84%), mp 168–171 °C; $[\alpha]_D^{25} = -194.2°$ (*c* 1.04, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.07 (s, 1H, OH), 6.91–6.55 (m, 3H ar), 1.83 (q, 2H, *J* = 7.5 Hz), 0.99 (t, 3H, *J* = 7.5 Hz); MS *m*/*z* (FAB) 372 M + 1]$^+$. Anal. calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. C, 71.12; H, 8.11; N, 3.70.

4.11. (+)-2-(1-Acetoxy-cyclopropylcarbonyl)-9,9-dimethyl-5-ethyl-2′-hydroxy-6,7-benzomorphan [(+)-8a]

This material was prepared in 79% yield using the procedure described for (−)-**8a**. Mp 168–170 °C; $[\alpha]_D^{25} = +189.1°$ (*c* 0.97, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.07 (s, 1H, OH), 6.91-6.54 (m, 3H ar), 1.83 (q, 2H, *J* = 7.5 Hz), 0.98 (t, 3H, *J* = 7.5 Hz); MS *m*/*z* (FAB) 372 M + 1]$^+$. Anal. calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.88; H, 8.14; N, 3.69.

4.12. (±)-2-(1-Acetoxy-cyclopropylcarbonyl)-9,9-dimethyl-5-ethyl-2′-hydroxy-6,7-benzomorphan [(±)-8a]

This material was prepared in 86% yield using the procedure described for (−)-**8a**; mp 196–198 °C; ^{1}H NMR (DMSO-d_6) δ 9.08 (s, 1H, OH), 6.91–6.55 (m, 3H), 1.83 (q, 2H, *J* = 7.5 Hz), 0.99 (t, 3H, *J* = 7.5 Hz).

4.13. (−)-9,9-Dimethyl-5-ethyl-2′-hydroxy-2-(1-hydroxycyclopropylmethyl)-6,7-benzomorphan hydrochloride [(−)-bremazocine hydrochloride, (−)-9·HCl]

H_2SO_4 (7.66 g, 75 mmol, 100%) was added dropwise to a solution LAH in THF (150 mmol, 150 mL of 1 M LAH in THF) at 0 °C under argon and the mixture was allowed to stir at room temperature. After 1 h (−)-**8a** (5.6 g, 15 mmol) in dry THF (200 mL) was added in a dropwise manner. After 2 h the reaction was stopped by cautiously adding a mixture of THF/H_2O (15 mL, 1:1) followed by concd NH_4OH (22 mL). The mixture was filtered and the precipitate washed well with $CHCl_3$. The combined filtrates were evaporated and replaced with MeOH (80 mL). After the pH of the solution was adjusted to 3 with ethereal HCl, the product was crystallized by boiling the solution and adding EtOAc to keep the volume constant until crystallization occurred. Yield (3.7 g, 70%), mp 255–256 °C, (lit.[14] 242–246 °C), $[\alpha]_D^{25} = -107°$ (*c* 0.95, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H, OH), 8.45 (s, 1H, NH), 6.97 (d, 1H, *J* = 8.1 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.63 (dd, 1H, *J* = 8.1 Hz, *J* = 2.4 Hz), 6.07 (s, 1H, OH); MS *m*/*z* (FAB) 316 M + 1]$^+$. Anal. calcd for $C_{20}H_{30}NO_2Cl$: C, 68.26; H, 8.59; N, 3.98. C, 68.20; H, 8.66; N, 3.98.

4.14. (+)-9,9-Dimethyl-5-ethyl-2′-hydroxy-2-(1-hydroxycyclopropylmethyl)-6,7-benzomorphan [(+)-bremazocine hydrochloride, (+)-9·HCl]

(+)-**9** was prepared in 67% yield using the procedure described for (−)-**9**, mp 254–256 °C, (lit.[14] 242–246 °C); $[\alpha]_D^{25} = +110.4°$ (*c* 0.90, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H, OH), 8.44 (s, 1H, NH), 6.97 (d, 1H, *J* = 8.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.63 (dd, 1H, *J* = 8.4 Hz *J* = 2.4 Hz), 6.07 (s, 1H, OH); MS *m*/*z* (FAB) 316 M + 1]$^+$. Anal. calcd for $C_{20}H_{30}NO_2Cl$: C, 68.26; H, 8.59; N3.98. C, 68.37; H, 8.62; N3.98.

4.15. (±)-9,9-Dimethyl-5-ethyl-2′-hydroxy-2-(1-hydroxycyclopropylmethyl)-6,7-benzomorphan [(±)-bremazocine, (±)-9]

(±)-**9** was prepared in 68% yield using the procedure described for (−)-**9**, mp 247-249 °C. ^{1}H NMR (DMSO-d_6) δ 9.27 (s, 1H, OH), 8.45 (s, 1H, NH), 6.97 (d, 1H, *J* = 8.1 Hz), 6.70 (d, 1H ar, *J* = 2.1 Hz), 6.64 (dd, 1H, *J* = 8.1, Hz *J* = 2.1 Hz), 6.07 (s, 1H, OH). Anal. calcd for $C_{20}H_{30}NO_2Cl$: C, 68.26; H, 8.59; N 3.98. C, 68.13; H, 8.56; N3.97.

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References and notes

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