Goyet for his help in the binding studies reported in this paper.

Registry No. 1, 98900-25-5; 2, 60398-45-0; 3, 133851-82-8; 4·TFA, 133851-84-0; 5, 133851-85-1; 6·TFA, 133851-87-3; 7, 98900-29-9; 8, 109953-94-8; 9, 133851-88-4; 10, 133851-89-5; 11·AcOH, 133851-91-9; 11 (free base), 133851-90-8; 12, 98900-24-4; 13, 69676-65-9; 14, 133851-92-0; 15·AcOH, 133851-94-2; 16, 133851-95-3; 17·TFA, 133907-21-8; 17 (free base), 98900-28-8; BOC-Phe-OH, 13734-34-4; H-pGlu-OH, 98-79-3; H-Gly-Phe-Leu-NH_2·TFA, 133851-96-4; H-Phe-Leu-NH_2·HCl, 81638-86-0; BOC-Tyr-OH, 3978-80-1; H-Leu-Met-NH_2·TFA, 84552-48-7.

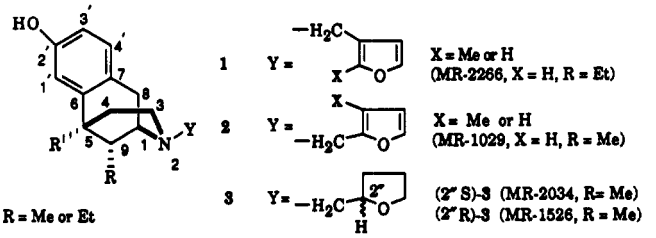
Electrophilic γ-Lactone κ-Opioid Receptor Probes. Analogues of 2′-Hydroxy-2-tetrahydrofurfuryl-5,9-dimethyl-6,7-benzomorphan Diastereomers

Peter Klein and Wendel L. Nelson*

Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, Washington 98195.
Received January 7, 1991

Benzomorphans with an electrophilic group in the nitrogen substituent were prepared as potentially irreversible ligands for the κ-opioid receptor. These were synthesized from products of the reaction of normetazocine with the enantiomers of 5-(iodomethyl)-γ-butyrolactone (11). α-Methylene γ-lactones **5** and **7** and endocyclic α,β-unsaturated γ-lactones **8** and **9** were prepared from the corresponding saturated γ-lactones **13** and **23** possessing the "active" (1*R*,5*R*,9*R*)-benzomorphan stereochemistry. Only γ-lactones **8**, **9**, **13**, and **23**, lacking the exocyclic methylene group, retain significant affinities for opioid receptor binding sites when compared with the reference compounds (2″*S*)-**3** and (2″*R*)-**3**. As observed with these references compounds, greater binding affinity is also seen with γ-lactone diastereomers having the 2″*S* stereochemistry in the nitrogen substituent. Although the γ-lactones do not bind irreversibly in opioid receptor preparations, they do show κ-receptor selectivities comparable to those observed for the reference compounds.

A series of *N*-(furanylmethyl)- and *N*-tetrahydrofurfurylbenzomorphans (**1**–**3**), reported by Merz and coworkers,[1-5] have very interesting pharmacological profiles. Among these are the *N*-furanylmethyl series of compounds (**1** and **2**) and related compounds which, depending on the location of the attachment of the substituted or unsubstituted furan ring, show mixed agonist antagonist effects or even agonist effects, but have no ability to substitute for morphine in dependent monkeys. The corresponding *N*-2-furanylethyl homologue is a potent analgesic (25 × morphine in the writhing assay).[1,6] In the more recently reported *N*-tetrahydrofurfuryl series (**3**), introduction of a new chiral center in the N-substitutent greatly influences activity. The new 2″*S* chiral center confers primarily potent analgesic properties (up to 50 × morphine on a molar basis) and no ability to substitute for morphine in dependent monkeys to (2″*S*)-**3** (R = Me), while its diastereomer with the 2″*R* chiral center had primarily antagonist properties.[4,5] Compound (2″*R*)-**3** (R = Me) showed weak analgesic properties in the writhing assay and was not analgesic in the tail-clip and hot-plate assays. The effects of these agents have been assigned primarily to interaction at the κ-receptor subclass of opioid receptors where **1** (X = H, R = Et, MR-2266) is believed to be a selective antagonist.[7-9] Although the *N*-tetrahydrofurfuryl compounds displace κ-receptor ligands, they also displace μ-receptor ligands.

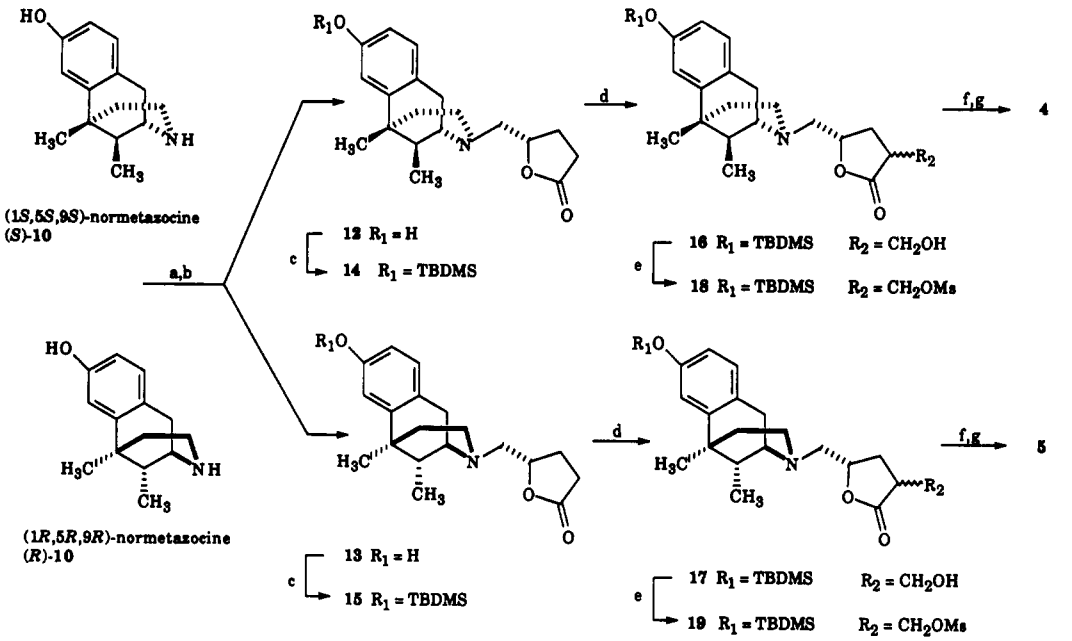


Based on this information, we prepared the diastereomeric N-substituted α-methylene γ-lactone derivatives that have an electrophilic group incorporated into the tetrahydrofurfuryl substituent in order to obtain possible affinity ligands for κ-receptors. We thought that replacement of the (2″*S*)-tetrahydrofurfuryl substituent on the basic benzomorphan nitrogen with the analogous (2″*S*)-α-methylene γ-lactone substituent (as in **5**) would provide minimal structural distortion, thereby maintaining a high degree of affinity for opioid binding sites, while simultaneously incorporating a potentially useful electrophile[10-13]

(1) Merz, H. In *X-ray Crystallography and Drug Action*; Horn, A. S., De Ranter, C. J., Eds.; Clarendon Press: Oxford, England, 1984; Chapter 17, pp 302–331. Merz, H.; Langbein, A.; Stockhaus, K.; Walther, G.; Wick, H. In Narcotic Antagonists. *Advances in Biochemical Psychopharmacology*; Braude, M. C., Harris, L. S., May, E. L., Smith, J. P., Villarreal, J. E., Eds.; Raven Press: New York, 1974; Vol 8, pp 91–107.
(2) Casy, A. F. *Advances in Drug Research*; Testa, B., Ed.; Academic Press: London, 1989; Vol. 18, pp 177–289.
(3) Casy, A. F.; Parfitt, R. T. *Opioid Analgesics. Chemistry and Receptors*; Plenum Press: New York, 1986; Chapter 12, pp 405–444; Chapter 4, pp 153–214.
(4) Merz, H.; Stockhaus, K.; Wick, H. *J. Med. Chem.* **1975**, *18*, 996–1000.
(5) Merz, H.; Stockhaus, K. *J. Med. Chem.* **1979**, *22*, 1475–1483.
(6) Gordon, M.; Lafferty, J. J. U.S. Patent. 2,924,604; *Chem. Abstr.* **1960**, *54*, 18556g.
(7) Kosterlitz, H.; Paterson, S. J.; Robson, L. E. *Br. J. Pharmacol.* **1981**, *73*, 939–949.
(8) Magnan, J.; Paterson, S. J.; Tavani, A.; Kosterlitz, H. W. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1982**, *319*, 197–205.
(9) Robson, L. E.; Foote, R. W.; Maurer, R.; Kosterlitz, H. W. *Neuroscience* **1984**, *12*, 621–627.
(10) Koolpe, G. A.; Nelson, W. L.; Gioannini, T. L.; Angel, L.; Simon, E. J. *J. Med. Chem.* **1984**, *27*, 1718–1723.
(11) Koolpe, G. A.; Nelson, W. L.; Gioannini, T. L.; Angel, L.; Appelmans, N.; Simon, E. J. *J. Med. Chem.* **1985**, *28*, 949–957.
(12) Klein, P.; Nelson, W. L.; Yao, Y.-H.; Simon, E. J. *J. Med. Chem.* **1990**, *33*, 2286–2296.

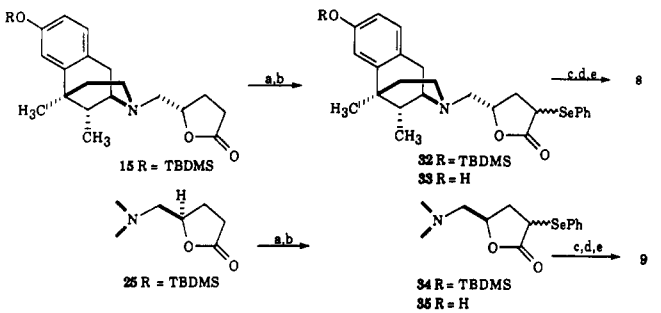
0022-2623/91/1834-2438$02.50/0

Scheme I[a]



[a] Reagents: (a) (5S)-11; (b) separation; (c) *tert*-butyldimethylsilyl chloride; (d) LDA, then CH_2O; (e) MsCl; (f) pyridine, heat; (g) $(n\text{-}Bu)_4N^+F^-$.

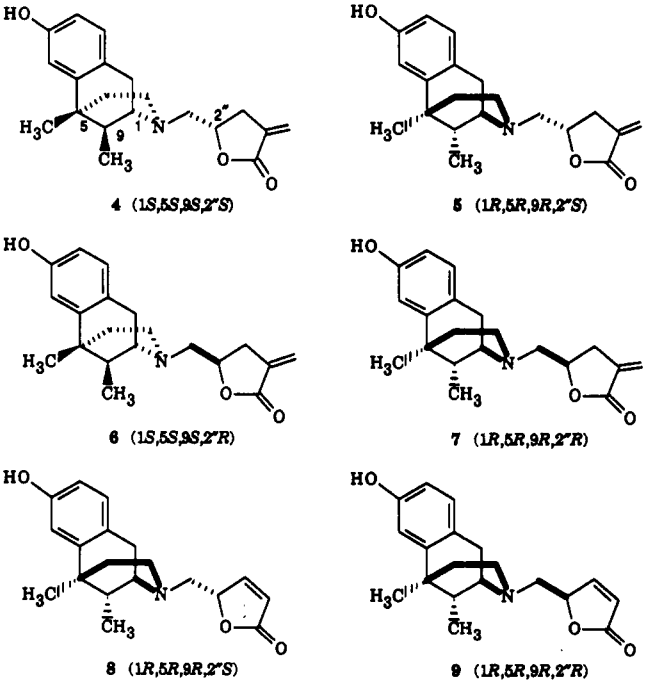
Scheme II[a]



[a] Reagents: (a) $Li^+N^-(SiMe_3)_2$; (b) PhSeBr; (c) $(n\text{-}Bu)_4N^+F^-$; (d) HCl, ether; (e) MCPBA.

into the molecule. A number of highly selective electrophilic ligands for various subtypes of opioid receptors have been reported,[14-16] including some for the κ-receptor.[17-19] Although various electrophiles have been incorporated into a number of locations in the skeletal framework of the ligands, few have these substituents at the basic nitrogen. The location of the electrophilic α-methylene γ-lactone functionality on the basic nitrogen would probe for the presence of a receptor bound nucleophile in the region of opioid receptor site(s) associated with binding of the N-substituent.

The corresponding endocyclic (2″*S*)- and (2″*R*)-α,β-unsaturated γ-lactones **8** and **9**, based on the active (1*R*,5*R*,9*R*)-benzomorphan stereochemistry,[20] were also prepared from intermediates in the synthesis. These compounds incorporate the electrophilic α,β-unsaturated γ-lactone system at the same N-substituent, but they lack the additional exocyclic carbon atom. The corresponding saturated γ-lactones, intermediates **13** and **23**, were also tested for their binding affinity at opioid receptors.

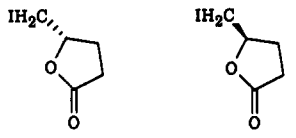


Chemistry. The α-methylene γ-lactones **4–7** were synthesized from intermediate tertiary amines prepared

(13) Olsen, L. D.; Klein, P.; Nelson, W. L.; Yao, Y.-H.; Simon, E. J. *J. Med. Chem.* **1990**, *33*, 737–741.
(14) Takemori, A. E.; Portoghese, P. S. *Ann. Rev. Pharmacol. Toxicol.* **1985**, *25*, 193–223.
(15) Simon, E. J.; Hiller, J. M. In *The Opiate Receptors*; Pasternak, G. W., Ed.; Humana Press: Clifton, NJ, 1988; Chapter 6, pp 165–194.
(16) Newman, A. H. *Ann. Rep. Med. Chem.* **1990**, *25*, 271–280.
(17) de Costa, B. R.; Rothman, R. B.; Bykov, V.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **1989**, *32*, 281–283.
(18) de Costa, B. R.; Rothman, R. B.; Bykov, V.; Band, L.; Pert, A.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **1990**, *33*, 1171–1176.
(19) de Costa, B. R.; Thurkauf, A.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Labelled Comp. Radiopharm.* **1990**, *28*, 1257–1264.

(20) Active benzomorphans have the 1*R*,5*R* and the 9*R*/*S* stereochemistry.[1-5] In this series, compounds with the 1*R*,5*R*,9*R* stereochemistry and compounds enantiomeric at these centers were prepared.

by N-alkylation of racemic normetazocine (**10**)[21] with the enantiomeric iodo γ-lactones (5*S*)- and (5*R*)-**11**[22] (Scheme I). The enantiomeric iodo γ-lactones are readily available



(5*S*)-**11** (5*R*)-**11**

from the enantiomers of glutamic acid.[22] When racemic normetazocine (**10**) and iodo γ-lactone (5*S*)-**11** were heated at 95 °C in DMF in the presence of $NaHCO_3$, the two diastereomeric tertiary amines **12** and **13** were obtained. These diastereomers were readily separated by flash column chromatography. The levorotatory γ-lactone **13** is the 2″*S* diastereomer incorporating the "active" (1*R*,5*R*,9*R*)-benzomorphan stereochemistry.[20]

γ-Lactones **12** and **13** were converted to the corresponding α-methylene γ-lactones **4** and **5**, respectively, in five steps. The phenolic hydroxyl group of γ-lactone **12** was first protected as its *tert*-butyldimethylsilyl ether **14**. α-Methylenation of γ-lactone **14** was achieved in three steps by hydroxymethylation, methanesulfonation, and elimination[11] (intermediates **16** and **18**) to provide the silyl-protected α-methylene γ-lactone **20**. Removal of the silyl protecting group with tetrabutylammonium fluoride provided phenolic α-methylene γ-lactone **4**. In a similar manner, the phenolic α-methylene γ-lactone **5** was obtained from γ-lactone **13** through analogous intermediates **15**, **17**, **19**, and **21**.

Similarly, when a mixture of racemic normetazocine (**10**) and iodo γ-lactone (5*R*)-**11** was heated at 95 °C in DMF in the presence of $NaHCO_3$, the diastereomeric tertiary amines **22** and **23** were obtained. All spectral data from **22** were identical with those from **13** except the optical rotations, indicating they are enantiomers. Similarly, **23** and **12** are enantiomers. γ-Lactones **22** and **23** were then converted to the phenolic α-methylene γ-lactones **6** and **7**, respectively, as described above for the conversions of **12** and **13** to **4** and **5**, respectively.

α,β-Unsaturated lactone **8** was prepared from O^3-silylated saturated lactone **15** (Scheme II). Selenation produced a mixture of diastereomeric α-phenyl selenides (**32**). Completion of the sequence was accomplished by fluoride ion deprotection followed by oxidation and elimination of the phenyl selenides. The order of these steps was critical because if the conversion was attempted in the reverse order, decomposition occurred. The oxidation step using *m*-chloroperbenzoic acid required conversion of the tertiary amine to its hydrochloride salt to prevent its participation in the oxidative decomposition of the selenides. The 2″*R* diastereomeric γ-lactone **9** was prepared from O^3-silylated saturated γ-lactone **25** by the same method (Scheme II).

Opioid Receptor Binding. α-Methylene γ-lactones **4**–**7** were examined for their ability to displace [^{3}H]bremazocine, a universal ligand with significant κ-receptor affinity, from binding sites on cell membranes prepared from whole guinea pig brain minus cerebellum (Table I). Only lactone **5** exhibited activity (IC_{50} = 380 nM) in the assay for total opioid sites labeled by [^{3}H]bremazocine. Compound **5** was not more potent when the radioligand displacement assays were run in the presence of unlabeled DAGO [D-Ala^2-NMe-Phe^4-Gly-ol^5-enkephalin] and DPDPE [D-Pen^2-D-Pen^5-enkephalin] to block μ and δ sites, respectively; thus, it is not selective for κ-sites.

Compound **5**, having the "active" 1*R*,5*R*,9*R* absolute configuration and the 2″*S* configuration in the side chain, is 16-fold less potent than naloxone, and approximately 120-fold less potent than the *N*-tetrahydrofurfuryl standard (2″*S*)-**3** (MR-2034). Compound **7**, having the "active" 1*R*,5*R*,9*R* absolute configuration and the 2″*R* configuration in the side chain is devoid of activity. Clearly the change from tetrahydrofuran ring to 5′-oxo-4′-methylenetetrahydrofuran moiety is detrimental to opioid receptor binding. Steric and/or electronic effects appear to be logical reasons for this difference.

In the displacement assay, the diastereomeric saturated lactones with the 1*R*,5*R*,9*R* stereochemistry without the α-methylene group (**13** and **23**), and their unsaturated analogues **8** and **9** were more potent. Those with the 2″*S* stereochemistry were about 3–5 times less potent than (2″-*S*)-**3**. The 2″*R* diastereomers, although about 12–50 times less potent than the 2″*S* compounds, were more potent than the (2″*S*)-α-methylene γ-lactones by ca. 3–5-fold. There was no significant difference between the saturated and unsaturated lactones having the 2″*S* stereochemistry. However, in the lactones with the 2″*R* configuration, the endocyclic unsaturated γ-lactone was 5–7 times more potent than the corresponding saturated lac-

Table I. Opioid Receptor Binding against 0.5 nM [^{3}H]Bremazocine of γ-Lactones in the Guinea Pig Brain Membrane Preparation

compounds	IC_{50}[a] total sites	IC_{50}[a] κ-sites[b]
α-Methylene γ-lactones		
4 (1*S*,5*S*,9*S*,2″*S*)	1300	–
5 (1*R*,5*R*,9*R*,2″*S*)	380	400
6 (1*S*,5*S*,9*S*,2″*R*)	1800	–
7 (1*R*,5*R*,9*R*,2″*R*)	>3000	–
α,β-Unsaturated γ-Lactones		
8 (1*R*,5*R*,9*R*,2″*S*)	7.4	5.4
9 (1*R*,5*R*,9*R*,2″*R*)	89	74
Saturated γ-Lactones		
13 (1*R*,5*R*,9*R*,2″*S*)	12	7.3
23 (1*R*,5*R*,9*R*,2″*R*)	620	400
Reference Compounds		
(2″*S*)-**3** (MR-2034) (1*R*,5*R*,9*R*,2″*S*)	2.3	1.7
enant-(2″*S*)-**3** (MR-2035) (1*S*,5*S*,9*S*,2″*R*)	1000	–
(2″*R*)-**3** (MR-1526) (1*R*,5*R*,9*R*,2″*R*)	84	70
2 (MR-1029) (1*R*,5*R*,9*R*)	6.8	5.7
1 (MR-2266) (1*R*,5*R*,9*R*)	2.9	1.6
enant-**1** (MR-2267) (1*S*,5*S*,9*S*)	2200	–
naloxone	23	–
naltrexone	5.7	9.5

[a] Values are averages of duplicate determinations (±10–15%). [b] Binding assay done in presence of 100 nM DAGO and 100 nM DPDPE to block μ- and δ-receptors.

Table II. Irreversibility of Opioid Receptor Binding and Protection by Naloxone

drug (concn)[b]	% recovery of specific binding of 0.5 nM [^{3}H]bremazocine binding[a] unwashed	washed	protected
naloxone (1000 nM)	0	100	
lactone **5** (1000 nM)	50	83	82
lactone **8** (60 nM)	9	96	97
lactone **9** (100 nM)	25	93	94
lactone **13** (50 nM)	0	96	97

[a] Values are averages of duplicate determinations (±10–15%). [b] The concentrations of displacing ligands are chosen to approximate a 70–85% decrease in binding of [^{3}H]bremazocine (see Table I).

(21) Normetazocine was obtained from the National Institute on Drug Abuse.

(22) Mori, K. *Tetrahedron* **1975**, *31*, 3011–3012.

tone. This result suggests the greater degree of unsaturation, and perhaps the planarity of the furfuryl substituent, the less the binding is restricted to the 2″S diastereomer. The greater the degree of unsaturation in the five-membered ring, the more closely the compounds resemble the most potent analogue 1.

The most potent unsaturated lactones 5, 8, and 9, and saturated lactone 13, the 2″-oxo analogue of (2″S-3), were screened for irreversible effects in the binding assay (Table II). After preincubation, the receptor preparations were washed to remove unbound ligand, and the binding assay was repeated. Washing restored 80–95% of binding of [^{3}H]bremazocine, clearly indicating no irreversible effects of the test compounds. Because washing of the more potent ligands restores 93–96% of the binding [^{3}H]bremazocine, it seems unlikely that irreversible binding occurs at any of the opioid receptor types that specifically bind bremazocine.

Conclusion. We conclude that altering of the *N*-tetrahydrofuranyl group is detrimental to opioid receptor affinity. The 2″S-oxo analogues, both with and without the 3″,4″-double bond are potent ligands at opioid receptors, but 2–5 times less potent than (2″S)-3 (MR-2034) or 1 (MR-2266), a 3-furanyl analogue. The *exo*-methylene unit at C-4″ clearly reduces binding, suggesting significant sensitivity to steric effects at this position, although the tested series did not include the α-methyl compounds to separate steric and electronic effects.

A moderate degree of selectivity for κ-sites was observed with unsaturated γ-lactones 8 and 9 and with saturated γ-lactones 13 and 23. This selectivity was comparable to that observed for (2″S)-3 in our assay. These results suggest κ-selectivity imparted by the benzomorphan skeleton of the molecule to a large extent dictates the selectivity for κ-sites observed with these agents.

The lack of irreversible effect appears to indicate a lack of sufficiently reactive nucleophilic groups of the receptor near the termini of either the α-methylene unit in 5 or the β-carbon atoms in 8 or 9. Thus far, we have not obtained ligands with irreversible activity where the electrophile is in the N-substituent.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 spectrometer or a Perkin-Elmer 1610 FTIR. NMR spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as the internal standard. Electron impact (EI) mass spectra were obtained on a VG-7070 mass spectrometer and FAB mass spectra on a VG-70 SEQ mass spectrometer both by direct insertion probe. Optical rotations were measured on a JASCO-DIP-4 digital polarimeter. Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel HLF glass plates. Flash chromatography[23] was performed using Merck silica gel 60 (230–400 mesh). Dichloromethane and dimethylformamide (DMF) were stored over 3-Å molecular sieves prior to use. Diisopropylamine, pyridine, and triethylamine were stored over KOH. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. All reactions were performed in flame-dried flasks under an argon atmosphere. Microanalyses were determined by Galbraith Laboratories, Knoxville, TN, or by Desert Analytics, Tucson, AZ. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

(1*S*,5*S*,9*S*,2″*S*)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (12) and (1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (13). A mixture of racemic normetazocine (10)[21] (694 mg, 3.2 mmol), (5*S*)-(iodomethyl)-γ-butyrolactone[22] [(5*S*)-11] (790 mg, 3.5 mmol), and $NaHCO_3$ (591 mg, 7.0 mmol) in DMF (9 mL) was heated at 95 °C for 22 h. After cooling, the mixture was treated with half-saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4), and the solvents were evaporated. The residue was purified by flash chromatography (200 g silica gel), eluting with 7% methanol–ethyl acetate (2 L) to give 12 (280 mg, 28% yield) as a viscous oil, $[\alpha]_D$ = +90.0° (*c* = 1.00, CH_2Cl_2), followed by 13 (350 mg, 35% yield) as a viscous oil, $[\alpha]_D$ = −54.0° (*c* = 1.00, CH_2Cl_2). 12: ^{1}H NMR ($CDCl_3$) δ 0.81 (d, *J* = 7.0 Hz, 3 H, C-9 CH_3), 1.25–1.35 (m, 1 H, C-4 H), 1.30 (s, 3 H, C-5 CH_3), 1.78 (dt, *J* = 4.9 and 12.7 Hz, 1 H, C-4 H), 1.85–2.05 (m, 2 H, C-9 H and C-3″ H), 2.2–2.4 (m, 2 H, C-3 H and C-3″ H), 2.4–2.65 (m, 2 H, C-4″ CH_2), 2.65–2.75 (m, 1 H, C-3 H), 2.75–2.9 (m, 4 H, C-8 CH_2 and NCH_2 lactone), 2.9–3.0 (m, 1 H, C-1 H), 4.65–4.75 (m, 1 H, C-2″ H), 6.62 (dd, *J* = 2.4 and 8.2 Hz, 1 H, C-3′ H), 6.71 (d, *J* = 2.4 Hz, 1 H, C-1′ H), 6.90 (d, *J* = 8.2 Hz, 1 H, C-4′ H); ^{13}C NMR ($CDCl_3$) δ 14.03, 24.58, 25.22, 26.24, 28.39, 35.83, 41.12, 41.73, 46.31, 59.20, 59.59, 80.05, 112.20, 113.00, 127.06, 127.83, 142.59, 154.38, 177.46; FTIR (neat) 3600–2900 (OH), 1770, 1610, 1582, 1498 cm^{-1}; HREIMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1840. 13: ^{1}H NMR ($CDCl_3$) δ 0.82 (d, *J* = 6.9 Hz, 3 H, C-9 CH_3), 1.25–1.3 (m, 1 H, C-4 H), 1.30 (s, 3 H, C-5 CH_3), 1.80 (dt, *J* = 4.9 and 12.5 Hz, 1 H, C-4 H), 1.85–2.05 (m, 2 H, C-9 H and C-3″ H), 2.2–2.35 (m, 2 H, C-3 H and C-3″ H), 2.45–2.65 (m, 3 H, C-3 H and C-4″ CH_2), 2.65–2.9 (m, 3 H, NCH_2 lactone and C-8β H), 2.94 (d, *J* = 20.4 Hz, 1 H, C-8α H), 2.95–3.05 (m, 1 H, C-1 H), 4.6–4.75 (m, 1 H, C-2″ H), 6.62 (dd, *J* = 2.5 and 8.2 Hz, 1 H, C-3′ H), 6.71 (d, *J* = 2.5 Hz, 1 H, C-1′ H), 6.90 (d, *J* = 8.0 Hz, 1 H, C-4′ H), 7.1 (br s, 1 H, movable, OH); ^{13}C NMR ($CDCl_3$) δ 14.08, 24.14, 25.28, 26.20, 28.59, 35.84, 41.20, 41.64, 46.92, 58.07, 58.72, 80.00, 112.16, 112.97, 127.39, 127.90, 142.62, 154.26, 177.35; FTIR (neat) 3600–2900 (OH), 1771, 1610, 1582, 1498 cm^{-1}; HREIMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1835. Anal. ($C_{19}H_{25}NO_3 \cdot 1.33H_2O$) C, H, N.

(1*S*,5*S*,9*S*,2″*S*)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (14). A solution of phenol 12 (250 mg, 0.79 mmol), *tert*-butyldimethylsilyl chloride (143 mg, 0.95 mmol), and imidazole (129 mg, 1.90 mmol) in DMF (1.5 mL) was stirred for 40 h and then treated with half-saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (36 g silica gel), eluting with 4% triethylamine–ether (700 mL) to give silyl ether 14 (210 mg, 62% yield) as white crystals (mp 118–120 °C): $[\alpha]_D$ = +74.0° (*c* = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.18 [s, 6 H, $Si(CH_3)_2$] 0.81 (d, *J* = 7.1 Hz, 3 H, C-9 CH_3), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.25–1.35 (m, 1 H, C-4 H), 1.31 (s, 3 H, C-5 CH_3), 1.75 (dt, *J* = 4.8 and 12.7 Hz, 1 H, C-4 H), 1.85–2.05 (m, 2 H, C-9 H and C-3″ H), 2.2–2.4 (m, 2 H, C-3 H and C-3″ H), 2.45–2.9 (m, 7 H, C-3 H, C-8 CH_2, NCH_2 lactone, and C-4″ CH_2), 2.9–3.0 (m, 1 H, C-1 H), 4.6–4.75 (m, 1 H, C-2″ H), 6.60 (dd, *J* = 2.4 and 8.2 Hz, 1 H, C-3′ H), 6.69 (d, *J* = 2.3 Hz, 1 H, C-1′ H), 6.90 (d, *J* = 8.2 Hz, 1 H, C-4′ H); ^{13}C NMR ($CDCl_3$) δ −4.37 (silyl dimethyl), 14.09, 18.18, 24.89, 25.35, 25.69 (silyl *tert*-butyl), 26.08, 28.39, 35.90, 41.57, 42.26, 46.45, 59.02, 59.59, 80.10, 116.76, 117.19, 127.66, 128.75, 142.68, 153.56, 177.10; FTIR (KBr) 1763, 1609, 1495 cm^{-1}; FAB MS $[M + 1]^+$ calcd for $C_{25}H_{40}NO_3Si$ 430.2774, found 430.2750.

(1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (15). Silyl ether 15 was prepared from phenol 13 as described above for the synthesis of 14 from 12. Silyl ether 15 was obtained in 66% yield as a viscous oil: $[\alpha]_D$ = −38.5° (*c* = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.18 [s, 6 H, $Si(CH_3)_2$], 0.82 (d, *J* = 7.0 Hz, 3 H, C-9 CH_3), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.25–1.35 (m, 1 H, C-4 H), 1.31 (s, 3 H, C-5 CH_3), 1.76 (dt, *J* = 4.8 and 12.5 Hz, 1 H, C-4 H), 1.8–1.95 (m, 1 H, C-9 H), 1.95–2.1 (m, 1 H, C-3″ H), 2.15–2.35 (m, 2 H, C-3 H and C-3″ H), 2.4–2.9 (m, 7 H, C-3 H, C-8 CH_2, NCH_2 lactone, and C-4″ CH_2), 2.9–3.0 (m, 1 H, C-1 H), 4.6–4.7 (m, 1 H, C-2″ H), 6.60 (dd, *J* = 2.4 and 8.0 Hz, 1 H, C-3′ H), 6.69 (d, *J* = 2.4 Hz, 1 H, C-1′ H), 6.91 (d, *J* = 8.2 Hz, 1 H, C-4′ H); ^{13}C NMR ($CDCl_3$) δ −4.38 (silyl dimethyl), 14.12, 18.17, 24.57, 25.38, 25.70 (silyl *tert*-butyl), 25.98, 28.61, 35.89, 41.57, 42.15, 46.91, 58.52,

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923–2925.

58.89, 80.12, 116.71, 117.18, 127.68, 128.86, 142.65, 153.54, 177.06; FTIR (neat) 1778, 1608, 1573, 1494 cm^{-1}; FAB MS $[M + 1]^+$ calcd for $C_{25}H_{40}NO_3Si$ 430.2774, found 430.2766.

(1*S*,5*S*,9*S*,2″*S*)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (20). To a solution of diisopropylamine (172 μL, 1.22 mmol) in THF (1.5 mL), cooled in an ice bath, was added a 2.5 M solution of *n*-BuLi in hexanes (0.45 mL, 1.12 mmol) dropwise. After the mixture was cooled at −78 °C, a solution of lactone **14** (190 mg, 0.44 mmol) in THF (4 mL) was added over 12 min. The solution was stirred at −78 °C for 35 min and then warmed to −25 °C (dry ice–CCl_4). Formaldehyde gas, generated from paraformaldehyde (126 mg, 9.5 equivalents) by heating at about 190 °C, was bubbled into the solution under a stream of argon over 12 min. After the mixture was stirred at −25 °C for an additional 35 min, half-saturated aqueous $NaHCO_3$ solution (30 mL) was added, and then the cooling bath was removed. The mixture was stirred for 90 min and then extracted with CH_2Cl_2 (3 × 12 mL). The combined extracts were dried (Na_2SO_4), and the volatiles were evaporated. The residue was purified by flash chromatography (20 g of silica gel), eluting with 4% triethylamine–ethyl acetate (600 mL) to give a mixture of two diastereomeric hydroxymethyl lactones **16** (110 mg) as a viscous oil. The proton NMR in $CDCl_3$ showed a complex multiplet at 3.6–4.0 ppm for the 2 sets of CH_2OH protons.

To a solution of hydroxymethyl lactones **16** (110 mg, 0.24 mmol) and methanesulfonyl chloride (22 μL, 0.29 mmol) in CH_2Cl_2 (1.5 mL), cooled in an ice bath, was added triethylamine (50 μL, 0.36 mmol) dropwise. After 5 min the cooling bath was removed and the mixture was stirred for 30 min. Half-saturated aqueous $NaHCO_3$ solution (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4), and the volatiles were evaporated to give a mixture of two diastereomeric methanesulfonates **18** (130 mg) as a beige foam. The residue was dissolved in pyridine (1 mL) and then heated at 105 °C for 150 min. The pyridine was evaporated, and the residue was treated with half-saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4), and volatiles were evaporated to give α-methylene γ-lactone **20** (110 mg, 57% yield from lactone **14**) as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.17 [s, 6 H, $Si(CH_3)_2$], 0.80 (d, *J* = 6.9 Hz, 3 H, C-9 CH_3), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.2–1.35 (m, 1 H, C-4 H), 1.30 (s, 3 H, C-5 CH_3), 1.73 (dt, *J* = 5.0 and 12.6 Hz, 1 H, C-4 H), 1.8–1.9 (m, 1 H, C-9 H), 2.25 (dt, *J* = 2.9 and 12.1 Hz, 1 H, C-3 H), 2.45–2.55 (m, 1 H, C-3 H), 2.65–2.85 (m, 6 H, C-1 H, C-8 CH_2, NCH_2 lactone, and C-3″ H), 3.01 (ddt, *J* = 7.8, 17.2, and 2.7 Hz, 1 H, C-3″ H), 4.55–4.65 (m, 1 H, C-2″ H), 5.61 (t, *J* = 2.4 Hz, 1 H, vinylic H), 6.20 (t, *J* = 2.8 Hz, 1 H, vinylic H), 6.60 (dd, *J* = 2.5 and 8.1 Hz, 1 H, C-3′ H), 6.69 (d, *J* = 2.4 Hz, 1 H, C-1′ H), 6.90 (d, *J* = 8.3 Hz, 1 H, C-4′ H); ^{13}C NMR ($CDCl_3$) δ −4.4 (silyl dimethyl), 14.06, 18.17, 24.99, 25.33, 25.68 (silyl *tert*-butyl), 31.74, 35.86, 41.41, 42.14, 46.46, 59.14, 59.67, 76.41, 116.74, 117.18, 121.05, 127.67, 128.72, 134.46, 142.62, 153.54, 170.07; IR (neat) 1775, 1615, 1580, 1500 cm^{-1}; FAB MS $[M + 1]^+$ calcd for $C_{26}H_{40}NO_3Si$ 442.2777, found 442.2795.

(1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (21). α-Methylene γ-lactone **21** was prepared from lactone **15** as described above for the synthesis of **20** from **14**. α-Methylene γ-lactone **21** was obtained (44% yield) as a viscous oil: ^1H NMR ($CDCl_3$) δ 0.18 [s, 6 H, $Si(CH_3)_2$], 0.81 (d, *J* = 7.0 Hz, 3 H, C-9 CH_3), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.2–1.3 (m, 1 H, C-4 H), 1.30 (s, 3 H, C-5 CH_3), 1.76 (dt, *J* = 4.8 and 12.5 Hz, 1 H, C-4 H), 1.8–1.9 (m, 1 H, C-9 H), 2.24 (dt, *J* = 3.0 and 12.1 Hz, 1 H, C-3 H), 2.4–2.5 (m, 1 H, C-3 H), 2.6–2.9 (m, 6 H, C-1 H, C-8 CH_2, NCH_2 lactone, and C-3″ H), 2.99 (ddt, *J* = 7.8, 17.1, and 2.6 Hz, 1 H, C-3″ H), 4.6–4.7 (m, 1 H, C-5″ H), 5.61 (t, *J* = 2.4 Hz, 1 H, vinylic H), 6.20 (t, *J* = 2.8 Hz, 1 H, vinylic H), 6.60 (dd, *J* = 2.5 and 8.2 Hz, 1 H, C-3′ H), 6.69 (d, *J* = 2.4 H, 1 H, C-1′ H), 6.90 (d, *J* = 8.2 Hz, 1 H, C-4′ H); ^{13}C NMR ($CDCl_3$) δ −4.4 (silyl dimethyl), 14.11, 18.18, 24.83, 25.37, 25.69 (silyl *tert*-butyl), 31.58, 35.87, 41.30, 42.04, 46.91, 58.64, 58.84, 76.52, 116.74, 117.17, 120.91, 127.67, 128.78, 134.60, 142.66, 153.54, 170.07; IR (neat) 1775, 1615, 1580, 1500 cm^{-1}; FAB MS $[M + 1]^+$ calcd for $C_{26}H_{40}NO_3Si$ 442.2777, found 442.2795.

(1*S*,5*S*,9*S*,2″*S*)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (4). To a solution of silyl ether **20** (106 mg, 0.24 mmol) in THF (2 mL) was added a 1 M solution of tetrabutylammonium fluoride in THF (0.37 mL). The solution was stirred for 1 h and then treated with half-saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 12 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (21 g silica gel), eluting with 4% triethylamine–ether (300 mL) to give phenolic α-methylene γ-lactone **4** (70 mg, 89%) as a viscous oil, which crystallized on standing (mp 179–184 °C): $[\alpha]_D$ = +93.0° (*c* = 0.90, 10% methanol–CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.79 (d, *J* = 6.9 Hz, 3 H, C-9 CH_3), 1.2–1.35 (m, 1 H, C-4 H), 1.28 (s, 3 H, C-5 CH_3), 1.74 (dt, *J* = 4.5 and 12.7 Hz, 1 H, C-4 H), 1.8–1.9 (m, 1 H, C-9 H), 2.26 (dt, *J* = 2.9 and 12.2 Hz, 1 H, C-3 H), 2.55–2.65 (m, 1 H, C-3 H), 2.65–2.8 (m, 5 H, C-8 CH_2, NCH_2 lactone, and C-3″ H), 2.8–2.9 (m, 1 H, C-1 H), 3.01 (ddt, *J* = 7.8, 17.2, and 2.6 Hz, 1 H, C-3″ H), 4.6–4.7 (m, 1 H, C-2″ H), 5.62 (t, *J* = 2.4 Hz, 1 H, vinylic H), 6.21 (t, *J* = 2.7 Hz, 1 H, vinylic H), 6.62 (dd, *J* = 2.5 and 8.1 Hz, 1 H, C-3′ H), 6.72 (d, *J* = 2.5 Hz, 1 H, C-1′ H), 6.89 (d, *J* = 8.2 Hz, 1 H, C-4′ H); ^{13}C NMR ($CDCl_3$) δ 14.05, 24.78, 25.27, 31.87, 35.88, 41.18, 41.79, 46.43, 59.42, 59.75, 76.61, 112.24, 112.99, 121.62, 127.39, 127.91, 134.16, 142.73, 154.18, 170.41; FTIR (neat) 3600–3000 (OH) 1762, 1611, 1583, 1498 cm^{-1}; FAB MS $[M + 1]^+$ calcd for $C_{20}H_{26}NO_3$ 328.1913, found 328.1900. Anal. ($C_{20}H_{25}NO_3$) C, H, N.

(1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (5). Phenolic α-methylene γ-lactone **5** was prepared from silyl ether **21** as described above for the synthesis of **4** from **20**. Phenolic α-methylene γ-lactone **5** was obtained (92% yield) as a white powder (mp 198–203 °C): $[\alpha]_D$ = −33.0° (*c* = 0.90, 10% methanol–CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.80 (d, *J* = 7.1 Hz, 3 H, C-9 CH_3), 1.2–1.3 (m, 1 H, C-4 H), 1.28 (s, 3 H, C-5 CH_3), 1.77 (dt, *J* = 4.9 and 12.7 Hz, 1 H, C-4 H), 1.8–1.9 (m, 1 H, C-9 H), 2.25 (dt, *J* = 2.9 and 12.1 Hz, 1 H, C-3 H), 2.45–2.55 (m, 1 H, C-3 H), 2.6–2.9 (m, 5 H, C-8 CH_2, NCH_2 lactone, and C-3″ H), 2.9–3.05 (m, 2 H, C-1 H and C-3″ H), 4.6–4.7 (m, 1 H, C-2″ H), 5.62 (t, *J* = 2.4 Hz, 1 H, vinylic H), 6.21 (t, *J* = 2.7 Hz, 1 H, vinylic H), 6.61 (dd, *J* = 2.5 and 8.2 Hz, 1 H, C-3′ H), 6.71 (d, *J* = 2.4 Hz, 1 H, C-1′ H), 6.90 (d, *J* = 8.2 Hz, 1 H, C-4′ H); ^{13}C NMR ($CDCl_3$) δ 14.12, 24.49, 25.34, 31.74, 35.89, 41.09, 41.70, 46.92, 58.30, 58.83, 76.69, 112.22, 112.98, 121.42, 127.55, 127.93, 134.29, 142.73, 154.18, 170.40; FTIR (neat) 3600–3000 (OH), 1762, 1611, 1583, 1498 cm^{-1}; FAB MS $[M + 1]^+$ calcd for $C_{20}H_{26}NO_3$ 328.1913, found 328.1928. Anal. ($C_{20}H_{25}NO_3 \cdot 0.25H_2O$) C, H, N.

(1*R*,5*R*,9*R*,2″*R*)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (23) and (1*S*,5*S*,9*S*,2″*R*)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (22). Lactones **22** and **23** were prepared from racemic normetazocine (**10**)[21] and (5*R*)-(iodomethyl)-γ-butyrolactone [(5*R*)-**11**][22] as described above for the synthesis of **12** and **13**. Lactone **23** was obtained (28% yield) as a viscous oil, $[\alpha]_D$ = −94.5° (*c* = 0.91, 9% methanol–CH_2Cl_2), followed by lactone **22** (16% yield), also as a viscous oil, which crystallized on standing (mp 162–169 °C), $[\alpha]_D$ = +55.0° (*c* = 1.00, CH_2Cl_2). **23**: the ^1H NMR, ^{13}C NMR, and FTIR spectra of **23** were identical in all respects with those of **12**; HREIMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1842. Anal. ($C_{19}H_{25}NO_3 \cdot 0.5H_2O$) C, H, N. **22**: the ^1H NMR, ^{13}C NMR, and FTIR spectra of **22** were identical in all respects with those of **13**; HREIMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1834.

(1*S*,5*S*,9*S*,2″*R*)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (24). Silyl ether **24** was prepared from phenol **22** as described above for the synthesis of **14** from **12**. Silyl ether **24** was obtained (68% yield) as a viscous oil: the ^1H NMR, ^{13}C NMR, and FTIR spectra of **24** were identical in all respects with those of **15**; FAB MS $[M + 1]^+$ calcd for $C_{25}H_{40}NO_3Si$ 430.2774, found 430.2774.

(1*R*,5*R*,9*R*,2″*R*)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxotetrahydrofurfuryl)-6,7-benzomorphan (25). Silyl ether **25** was prepared from phenol **23** as described above for the synthesis of **14** from **12**. Silyl ether **25** was obtained (75% yield) as a viscous oil that crystallized on standing (mp 109–118 °C): the ^1H NMR, ^{13}C NMR, and FTIR spectra of **25**

were identical in all respects with those of 14; FAB MS $[M + 1]^+$ calcd for $C_{25}H_{40}NO_3Si$ 430.2774, found 430.2794.

(1S,5S,9S,2″R)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (30). α-Methylene γ-lactone **30** was prepared from lactone **24** as described above for the synthesis of **20** from **14**. α-Methylene γ-lactone **30** was obtained (38% yield) as a viscous oil: the ^1H NMR, ^{13}C NMR, and IR spectra of **30** were identical in all respects with those of **21**; FAB MS $[M + 1]^+$ calcd for $C_{26}H_{40}NO_3Si$ 442.2777, found 442.2760.

(1R,5R,9R,2″R)-5,9-Dimethyl-2′-[(*tert*-butyldimethylsilyl)oxy]-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (31). α-Methylene γ-lactone **31** was prepared from lactone **25** as described above for the synthesis of **20** from **14**. Lactone **31** was obtained (27% yield) as a viscous oil: the ^1H NMR, ^{13}C NMR, and IR spectra of **31** were identical in all respects with those of **20**; FAB MS $[M + 1]^+$ calcd for $C_{26}H_{40}NO_3Si$ 442.2777, found 442.2760.

(1S,5S,9S,2″R)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (6). α-Methylene γ-lactone **6** was prepared from silyl ether **30** as described above for the synthesis of **4** from **20**. Lactone **6** was obtained (87% yield) as white crystals (mp 202–207 °C): $[\alpha]_D$ = +36.0° (c = 0.90, 10% methanol–CH_2Cl_2); the ^1H NMR, ^{13}C NMR, and FTIR spectra of **6** were identical in all respects with those of **5**; FAB MS $[M + 1]^+$ calcd for $C_{20}H_{26}NO_3$ 328.1913, found 328.1900. Anal. ($C_{20}H_{25}NO_3 \cdot 0.25H_2O$) C, H, N.

(1R,5R,9R,2″R)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxo-4″-methylenetetrahydrofurfuryl)-6,7-benzomorphan (7). α-Methylene γ-lactone **7** was prepared from silyl ether **31** as described above for the synthesis of **4** from **20**. Lactone **7** was obtained (60% yield) as a viscous oil that crystallized on standing (mp 176–180 °C): $[\alpha]_D$ = −98.5° (c = 0.90, 10% methanol–CH_2Cl_2); the ^1H NMR, ^{13}C NMR, and FTIR spectra of **7** were identical in all respects with those of **4**; FAB MS $[M + 1]^+$ calcd for $C_{20}H_{26}NO_3$ 328.1913, found 328.1915. Anal. ($C_{20}H_{25}NO_3 \cdot 0.25H_2O$) C, H, N.

(1R,5R,9R,2″S)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxo-2″,5″-dihydrofurfuryl)-6,7-benzomorphan (8). To a solution of hexamethyldisilazane (157 μL, 0.74 mmol) in THF (1 mL), cooled in an ice bath, was added a 2.5 M solution of *n*-BuLi in hexanes (285 μL, 0.71 mmol) dropwise. The solution was cooled to −78 °C, and then a solution of lactone **15** (290 mg, 0.68 mmol) in THF (2 mL) was added dropwise. The solution was stirred at −78 °C for 30 min, and then a solution of phenylselenenyl bromide (168 mg, 0.71 mmol) in THF (0.5 mL) was added in one portion. After 5 min the cooling bath was removed and the solution was treated with saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted with ether (3 × 20 mL), and the combined extracts were dried ($MgSO_4$). The volatiles were evaporated, giving a residue that was purified by flash chromatography (20 g silica gel), eluting with hexanes (150 mL) followed by 50% ether–hexanes (100 mL) and finally with ether (100 mL) to give a diastereomeric mixture of two selenides **32** (360 mg, 91%) in a ratio of 4:1 as a viscous oil. The proton NMR in $CDCl_3$ showed two multiples at 3.9–4.1 ppm for the C-4″ protons in the ratio of 4:1.

To a solution of diastereomeric selenides **32** (450 mg, 0.77 mmol) in THF (5 mL), cooled in an ice bath, was added a 1 M solution of tetrabutylammonium fluoride in THF (0.92 mL) dropwise. After 15 min the cooling bath was removed. The solution was stirred for 15 min and then treated with half-saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with ether (3 × 20 mL). The combined extracts were washed with water (20 mL) and dried ($MgSO_4$), and then the volatiles were evaporated. The residue was purified by flash chromatography (60 g silica gel), eluting with ethyl acetate (300 mL) to give a mixture of two diastereomeric phenols **33** (307 mg, 85%) as a viscous oil. The mixture was dissolved in CH_2Cl_2 (10 mL) and then treated with a saturated solution of HCl in ether (2 mL), and then volatiles were evaporated to give the HCl salts of **33** as a white powder.

To a solution of HCl salts of **33** (60 mg, 0.12 mmol) in CH_2Cl_2 (5 mL), cooled in an ice bath, was added a solution of 50–60% *m*-chloroperbenzoic acid (45 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) dropwise. After stirring at 0 °C for 30 min the cooling bath was removed. The mixture was stirred for 45 min and then treated with half-saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4), and then a saturated solution of HCl in ether (2 mL) was added. Volatiles were evaporated, and the residue was triturated with ether (2 × 10 mL) to give the HCl salt of unsaturated lactone **8** (40 mg, 97%) as a white powder (mp 126–129 °C dec): $[\alpha]_D$ = −74.5° (c = 0.91, 9% 2-propanol–CH_2Cl_2); ^1H NMR of free amine **8** ($CDCl_3$) δ 0.82 (d, *J* = 7.0 Hz, 3 H, C-9 CH_3), 1.2–1.3 (m, 1 H, C-4 H), 1.30 (s, 3 H, C-5 CH_3), 1.7–1.9 (m, 2 H, C-4 H and C-9 H), 2.27 (dt, *J* = 3.0 and 12.1 Hz, 1 H, C-3 H), 2.4–2.5 (m, 1 H, C-3 H), 2.67 (dd, *J* = 5.0 and 13.8 Hz, 1 H, C-1″ H), 2.7–3.09 (m, 4 H, C-1 H, C-8 CH_2, C-1″ H), 4.9 (br s, movable, 1 H, OH), 5.1–5.2 (m, 1 H, C-2″ H), 6.14 (dd, *J* = 1.9 and 5.6 Hz, 1 H, C-3″ H), 6.61 (dd, *J* = 2.4 and 8.2 Hz, 1 H, C-3′ H), 6.71 (d, *J* = 2.2 Hz, 1 H, C-1 H), 6.91 (d, *J* = 8.2 Hz, 1 H, C-4′ H), 7.49 (dd, *J* = 1.4 and 5.7 Hz, 1 H, C-4″ H); ^{13}C NMR ($CDCl_3$) δ 14.12, 24.66, 25.38, 35.92, 41.29, 41.85, 46.85, 57.01, 57.90, 82.91, 112.25, 113.01, 121.71, 127.48, 127.97, 142.76, 154.33, 155.43, 173.07; FTIR of HCl salt (KBr) 3700–2400 (OH and NH), 1774, 1758, 1612, 1584 cm^{-1}; FABMS $[M + H]^+$ calcd for $C_{19}H_{23}NO_3$ 314.1754, found 314.1743. Anal. ($C_{19}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$) C, N; H: calcd 7.02, found 7.46.

(1R,5R,9R,2″R)-5,9-Dimethyl-2′-hydroxy-2-(5″-oxo-2″,5″-dihydrofurfuryl)-6,7-benzomorphan (9). Selenides **34** were prepared from **25** as described above for the synthesis of **32** from **15**. Selenides **34** were obtained (76% yield) as a viscous oil. The proton NMR in $CDCl_3$ showed a pair of multiplets at 4.0–4.5 ppm for the C-4″ protons.

Phenolic selenides **35** were prepared from **34** as described above for the synthesis of **33** from **32**. Phenolic selenides **35** were obtained (66% yield) as a viscous oil. The HCl salts of **35** were prepared as described above for HCl salts of **33**.

Unsaturated lactone **9** was prepared from **35** as described above for the synthesis of **8** from **33**. Unsaturated lactone·HCl **9** was obtained (41% yield) as a white powder (mp 145–147 °C dec): $[\alpha]_D$ = −48.0° (c = 0.91, 9% 2-propanol–CH_2Cl_2); ^1H NMR of free amine **9** ($CDCl_3$) δ 0.81 (d, *J* = 7.0 Hz, 3 H, C-9 CH_3), 1.2–1.3 (m, 1 H, C-4 H), 1.31 (s, 3 H, C-5 CH_3), 1.74 (dt, *J* = 4.7 and 12.6 Hz, 1 H, C-4 H), 1.8–1.95 (m, 1 H, C-9 H), 2.25 (dt, *J* = 3.0 and 12.2 Hz, 1 H, C-3 H), 2.5–2.6 (m, 1 H, C-3 H), 2.7–2.9 (m, 5 H, C-1 H, C-8 CH_2, C-1″ CH_2), 4.0 (br s, movable, 1 H, OH), 5.05–5.15 (m, 1 H, C-2″ H), 6.14 (dd, *J* = 1.9 and 5.6 Hz, 1 H, C-3″ H), 6.61 (dd, *J* = 2.0 and 7.9 Hz, 1 H, C-3′ H), 6.71 (d, *J* = 2 Hz, 1 H, C-1′ H), 6.90 (d, *J* = 7.9 Hz, 1 H, C-4′ H), 7.55 (dd, *J* = 1.5 and 5.6 Hz, 1 H, C-4″ H); ^{13}C NMR ($CDCl_3$) δ 14.06, 25.20, 25.30, 35.95, 41.51, 42.01, 46.21, 57.77, 59.78, 82.62, 112.19, 112.86, 121.42, 127.77, 128.00, 142.90, 153.99, 155.74, 173.04; FTIR (neat) 3700–2700 (OH), 1747, 1610, 1583 cm^{-1}; FABMS $[M + H]^+$ calcd for $C_{19}H_{23}NO_3$ 314.1754, found 314.1743. Anal. ($C_{19}H_{23}NO_3 \cdot HCl$) C, H, N.

Opioid Receptor Binding. Guinea pig brain homogenate was prepared as described by Lin and Simon.[24] The radioligand used was [^3H]bremazocine (New England Nuclear) (37.0 Ci/mmol) at a concentration of 0.5 nM for determination of total opioid binding sites. For κ-binding sites 0.5 nM [^3H]bremazocine was used in the presence of 100 nM unlabeled DAGO [D-Ala^2-NMePhe^4-Gly-ol^5-enkephalin] and 100 nM unlabeled DPDPE [D-Pen^2-D-Pen^5-enkephalin] to block μ- and δ-sites, respectively. Nonspecific binding was determined with naloxone (10 μM). Nine concentrations of each ligand to be tested were examined in competition experiments with radioligand (with and without μ- and δ-site blockers). The samples were incubated in 50 mM Tris-HCl buffer (pH 7.4) at 25 °C for 1 h and then rapidly filtered through Whatman GF/B filters, rinsed three times with cold buffer (2 mL each), and after standing overnight in Aquasol II scintillation fluid (10 mL) were counted in a scintillation counter. IC_{50} values were determined using log-probit analysis.

Irreversibility and Protection Studies. These studies were carried out as described previously.[13] Membrane preparations were incubated with drug to be tested for 1 h at 25 °C. For protection studies, naloxone was added at a concentration of 1 μM (recovery was checked with naloxone alone). After incubation, the samples were diluted 4-fold with buffer and centrifuged for 15 min at 20000*g*. The supernatant was removed, and the pellet

(24) Lin, H.-K.; Simon, E. J. *Nature (London)* **1978**, *271*, 383–384.

was resuspended in 3 times the original volume of buffer and incubated at 37 °C for 15 min, centrifuged again, and resuspended in the original volume of buffer. A binding assay using [^{3}H]-bremazocine (0.5 nM) was carried out as described above.

Acknowledgment. We greatly appreciate receiving samples of benzomorphan standards **1**, its enantiomer, **2**, (2′*R*)- and (2″*S*)-**3**, and the enantiomer of (2″*S*)-**3** from Dr. Herbert Merz, Boehringer Ingelheim KG, Germany. We acknowledge the support of this work by the National Institute on Drug Abuse through research grants DA-03933 and DA-06675.

Registry No. **4**, 134133-69-0; **5**, 134233-45-7; **6**, 134233-46-8; **7**, 134233-47-9; **8**, 134133-70-3; **8**·HCl, 134233-67-3; **9**, 134233-48-0; **9**·HCl, 134308-16-0; (±)-**10**, 52079-30-8; (5*R*)-**11**, 58879-35-9; (5*S*)-**11**, 58879-36-0; **12**, 134133-71-4; **13**, 134233-49-1; **14**, 134133-72-5; **15**, 134233-50-4; **16** (isomer 1), 134133-73-6; **16** (isomer 2), 134233-51-5; **18** (isomer 1), 134133-74-7; **18** (isomer 2), 134233-52-6; **20**, 134133-75-8; **21**, 134233-53-7; **22**, 134233-54-8; **23**, 134233-55-9; **24**, 134233-56-0; **25**, 134233-57-1; **30**, 134233-58-2; **31**, 134233-59-3; **32** (isomer 1), 134133-76-9; **32** (isomer 2), 134233-60-6; **33** (isomer 1), 134133-77-0; **33** (isomer 2), 134233-61-7; **33** (isomer 1)·HCl, 134233-62-8; **33** (isomer 2)·HCl, 134308-15-9; **34** (isomer 1), 134233-63-9; **34** (isomer 2), 134233-64-0; **35** (isomer 1), 134233-65-1; **35** (isomer 2), 134233-66-2.

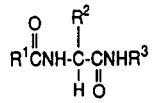
Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids

Harold Kohn,*,† Kailash N. Sawhney,† Philippe LeGall,† David W. Robertson,‡ and J. David Leander‡

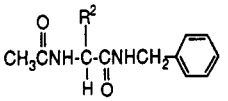
Department of Chemistry, University of Houston, Houston, Texas 77204-5641, and Lilly Research Laboratories, Eli Lilly Company, Indianapolis, Indiana 46285. *Received December 4, 1990*

Potent anticonvulsant activity has been reported for (*R,S*)-2-acetamido-*N*-benzyl-2-methylacetamide (**2a**). Select α-heteroatom substituted derivatives of **2a** have been prepared (26 examples) in which the α-methyl group has been replaced by nitrogen (**3a–q**), oxygen (**3r–u**), and sulfur (**3v–z**) containing moieties. The functionalized amino acid derivatives were evaluated in the maximal electroshock seizure (MES) and horizontal screen (tox) tests in mice. The most active compounds were (*R,S*)-2-acetamido-*N*-benzyl-2-(methoxyamino)acetamide (**3l**), and (*R,S*)-2-acetamido-*N*-benzyl-2-(methoxymethylamino)acetamide (**3n**). After ip administration, the MES ED_{50} values for **3l** (6.2 mg/kg) and **3n** (6.7 mg/kg) compared favorably with phenytoin (9.50 mg/kg).

Nonnaturally occurring amino acids have become increasingly important in the design of pharmacologically active peptides and peptidomimetics.[1] Recently we reported the excellent anticonvulsant activity of certain functionalized amino acid derivatives **1**.[2-6] Potent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing both an *N*-benzylamide moiety and an acetylated amino group. Systematic variation of the α-substituent revealed that stringent steric and electronic requirements must be met for optimal activity. The median effective dose (ED_{50}) for the α-methyl (**2a**) (76.5 mg/kg) and α-phenyl (**2b**) (20.3 mg/kg) derivatives[4] compared favorably with that observed for phenobarbital[7] (21.8 mg/kg), while those of the α-pyrrolyl (**2c**) (16.1 mg/kg) and α-furanyl (**2d**) (10.3 mg/kg) adducts[6] rivaled that reported for phenytoin[7] (9.50 mg/kg). Furthermore, comparison of the two individual enantiomers of **2a,b,d** revealed that in each case the anticonvulsant activity resided primarily in the *R* stereoisomer.[2,5,6]



1



2a R^2 = CH_3
b R^2 = Ph
c R^2 = 2-pyrrolyl
d R^2 = 2-furanyl

In the present study, the synthesis and anticonvulsant properties of a novel series of α-heteroatom-substituted amino acid derivatives (26 examples) are presented. Included in this survey are selected oxygen, nitrogen, and sulfur-functionalized amino acids. Analysis of the composite data set disclosed trends that further define the structure–activity relationships for this class of amino acid derived anticonvulsant agents.

Selection of Compounds

(*R,S*)-2-Acetamido-*N*-benzyl-2-methylacetamide[3] (**2a**) represented the parent compound in this study wherein the α-methyl group was replaced by select functionalized nitrogen, oxygen, and sulfur substituents (Table I). In all cases, the racemates were prepared and tested. No attempts were made at this stage to resolve the enantiomeric mixtures. The α-nitrogen-substituted adducts consisted of the parent amino **3a**, the monoalkylamino **3b,c**, the dialkylamino **3d,e**, and the trialkylammonium **3f** derivatives, as well as the corresponding monoaryl analogues **3g** and **3h**. Included in our α-nitrogen subset of compounds were three classes of functionalized amino derivatives. These were the monoacyl derivatives **3i** and **3j**, the *N*-hydroxyamino adducts **3k–o**, and the *N*-hydrazino compounds **3p** and **3q**. The second set of structurally modified amino acid derivatives were the

* Author to whom correspondence should be addressed to at the University of Houston.
† University of Houston.
‡ Lilly Research Laboratories.

(1) For leading references, see: (a) Shuman, R. T.; Ornstein, P. L.; Paschal, J. W.; Gesellchen, P. D. *J. Org. Chem.* **1990**, *55*, 738. (b) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770 and references therein.
(2) Kohn, H.; Conley, J. D. *Chem. Br.* **1988**, *24*, 231.
(3) Cortes, S.; Liao, Z.-K.; Watson, D.; Kohn, H. *J. Med. Chem.* **1985**, *28*, 601.
(4) Conley, J. D.; Kohn, H. *J. Med. Chem.* **1987**, *30*, 567.
(5) Kohn, H.; Conley, J. D.; Leander, J. D. *Brain Res.* **1988**, *457*, 371.
(6) Kohn, H.; Sawhney, K. N.; LeGall, P.; Conley, J. D.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1990**, *33*, 919.
(7) Porter, R. J.; Cereghino, J. J.; Gladding, G. D.; Hessie, B. J.; Kupferberg, H. J.; Scoville, B.; White, B. G. *Cleveland Clin. Q.* **1984**, *51*, 293.

0022-2623/91/1834-2444$02.50/0