Orally Active, Nonpeptide Oxytocin Antagonists†

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The first nonpeptide antagonists of the neurohypophyseal hormone, oxytocin (OT) are described. Derivatives of the spiroindenepiperidine ring system, these compounds include L-366,509, an orally bioavailable OT antagonist with good in vivo duration. The potential use of these agents for treatment of preterm labor and their significance as new nonpeptide ligands for peptide receptors are discussed.

Introduction

Premature birth is a leading cause of infant morbidity and mortality.[1] Its direct consequence, low birth weight, is a strong predictor of serious health problems or death in the neonate.[2] The risk factors for the premature onset of labor are either unknown or difficult to eliminate in every case (e.g., poor prenatal care),[2] so treatment has focused on methods for stopping premature labor once it has begun and for holding the process in abeyance until an acceptable term of gestation has been reached. Current approaches to this end are less than satisfactory.[1] The only agent presently approved by the U.S. Food and Drug Administration for treatment of premature labor is the β-adrenergic agonist, Ritodrine.[3] On the basis of its ability to relax uterine smooth muscle, Ritodrine has been used extensively in attempts to suppress premature labor. Recent studies have concluded, however, that despite widespread application, Ritodrine has had little effect in reducing the nationwide incidence of low birth weight.[3] More effective treatments are needed.

While the physiological mechanism of labor remains to be fully elucidated, several lines of evidence indicate that a key mediator in the process is the peptide hormone, oxytocin (OT):[4] (1) plasma levels of oxytocin increase coincidentally with the onset of labor;[5] (2) the concentration of OT receptors on the uterine myometrium increases sharply near the end of pregnancy, bringing uterine sensitivity to oxytocin to a maximum at about the time labor begins;[4,6] (3) exogenous oxytocin is a proven stimulant of uterine contractions and is frequently employed for artificial induction of labor.[7] On the basis of the hypothesis that oxytocin is an essential element in the initiation and maintainance of preterm labor, antagonists of oxytocin have been investigated as agents for arresting the process. Recent studies with peptide oxytocin antagonists in animals and in humans[1,8-11] have shown that these agents can successfully block both uterine contractions induced by exogenous oxytocin and the spontaneous nocturnal uterine contractions which occur naturally late in pregnancy. The clinical utility of these peptide antagonists for treatment of preterm labor is currently under investigation.

Studies reported with peptide oxytocin antagonists describe compounds which require iv administration and which have relatively short durations of action in vivo.[1,10,11] These attributes are suitable for an agent to be used in a controlled, hospital environment for management of acute situations, cases where the effect of an antagonist might require rapid application and equally rapid reversal. For chronic use, such as might be required to preempt the start of labor for several weeks in an outpatient setting, however, an agent which is long-acting and orally bioavailable might be more suitable. The purpose of the present investigation has been to develop an agent for both iv and oral use, and in this paper, we describe structure–activity studies leading to a successful example, the compound L-366,509 (1). As detailed elsewhere,[12]

† Presented in honor of Dr. Ralph F. Hirschmann on the occasion of his 70th birthday. His leadership in the development of chemical sample collections for broad-based screening of bioactivity has had significant impact on the discovery of new leads. His continuing support for and active participation in the pursuit of nonpeptide ligands for peptide receptors have been vindicated in part through screening of such sample collections, as reflected in this manuscript.

‡ Department of New Lead Pharmacology.

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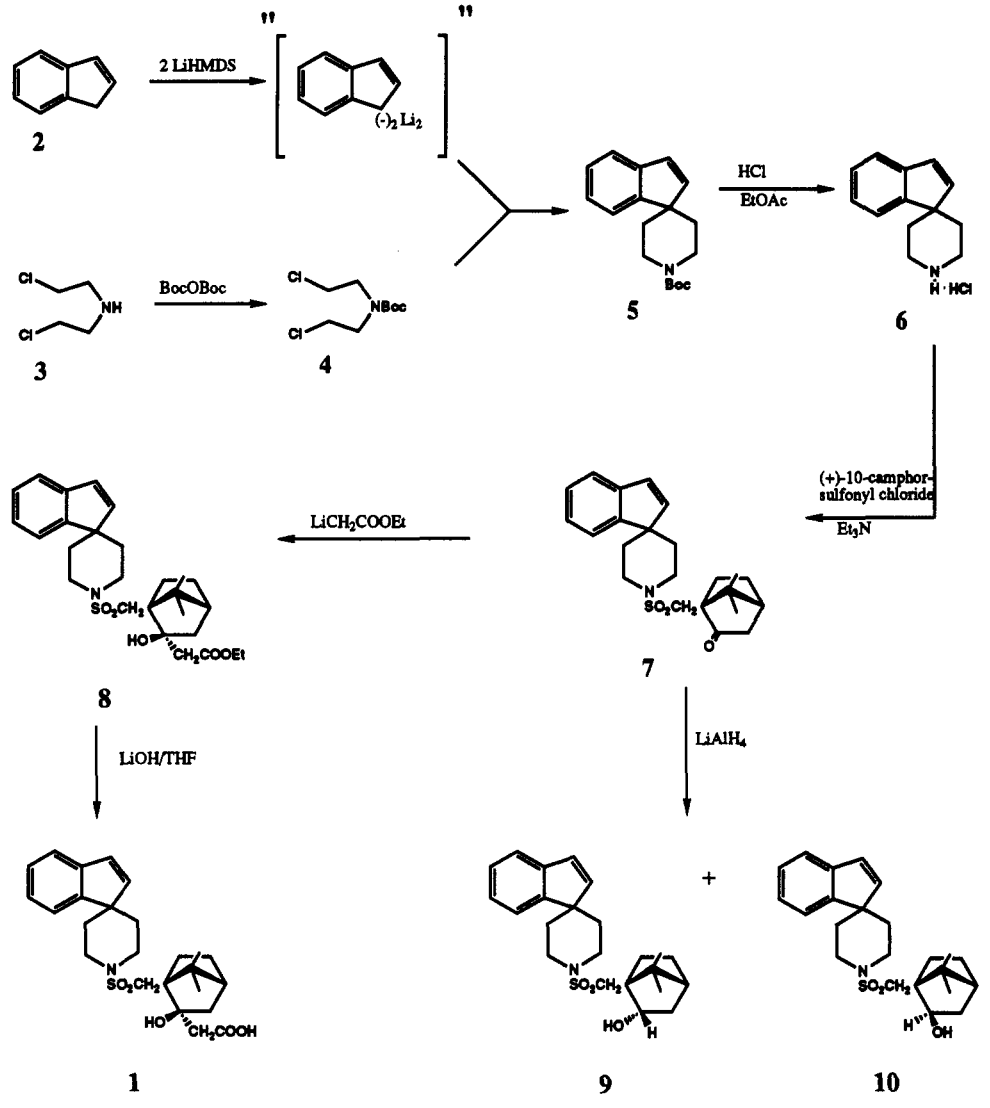
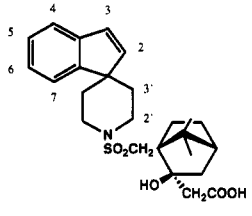
Scheme I



L-366,509 is a long-acting, orally bioavailable, nonpeptide oxytocin antagonist effective in vivo.



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Chemistry

L-366,509 (1) belongs to a class of spiroindenepiperidines of which only a few examples appear in the literature. The 3-keto-*N*-methyl[13] and 3-phenyl[14] analogs have been reported, as has the *N*-methyl derivative of the parent heterocycle.[15] None of these reports provides the efficient synthetic approach to the parent amine 6 required for the present investigation, however, and we therefore developed the synthesis outlined in Scheme I. Here, indene (2) is converted to the anion with 2 equiv of lithium hexamethyldisilazide and then spiroalkylated with an N-protected bis(2-chloroethyl)amine (e.g., 4) to provide the spiroindenepiperidine nucleus 5. Formally, this alkylation proceeds through an indene dianion. It seems likely, however, that the process is in fact stepwise, a result of the sequence, deprotonation-alkylation-deprotonation-spiroalkylation.

Of the several N-protecting groups examined (Boc, *p*-toluenesulfonyl, methyl, benzyl) in this alkylation reaction, Boc proved consistently superior in the ease of insertion and removal and in the yield and purity of the resulting spiroindenepiperidine 6. Similarly, commercial lithium hexamethyldisilazide/THF provided consistently higher yields of purer spiroalkylation product than did LDA/THF.

The sulfonamides, carboxamides, and ureas of Tables I–VII, (e.g., compound 7, Scheme I) were prepared by acylation of a spiroindenepiperidine (e.g., 6; Tables I, II,

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VI, VII) or other base (Tables III–V) with the appropriate sulfonyl chloride, acyl chloride, or isocyanate, respectively. Secondary (e.g., **9**, **10**, **80**, **81**) or tertiary (e.g., **88–91**) camphor carbinols were obtained by lithium aluminum hydride reduction or organometal (organolithium or organomagnesium halide) addition, respectively, to the parent ketone **7**. The reductions generally proceeded with only limited regioselectivity, so that the individual stereoisomers of the secondary carbinols (e.g., **9**, **10**) were obtainable by chromatographic separation (silica gel) of the resulting mixtures. The configurations of these carbinols were assigned based on several lines of NMR evidence, as described in the Experimental Section. The organometal additions appeared considerably more regioselective: the sole product obtained in each case was the *exo*-carbinol, with no significant amount of the endo derivative observed. The acetonitrile addition (compound **91**), for example, provided the pure *exo*-carbinol as a crystalline solid in greater than 85% yield. Minor components in these more complex product mixtures were not exhaustively investigated, however.

L-366,509 (**1**) was prepared by saponification of the ethyl ester **8** with lithium hydroxide in THF. Interestingly, attempted saponification in methanol produced only the product of transesterification, the methyl ester **92**, which was resistant to subsequent saponification. Assignment of the exo configuration was again based on chemical shift perturbation of one of the C-7 methyl groups by the exo hydroxyl substituent and on NOE's observed at the C-3 and C-6 endo hydrogens upon irradiation of the CH_2 proton region in the endo acetic acid side chain (see Experimental Section). α-Methyl derivatives of L-366,509 (**93**, **94**) were prepared by analogous addition of propionate ester to ketone **7** using lithium *N*-isopropyl-*N*-cyclohexylamide[16] in place of the silazide base.

α-Aminocamphor derivatives (**86**, **87**) were prepared from the corresponding amine which, in turn, was synthesized from the parent ketone **7** by α-nitrosation with potassium hydride/isoamyl nitrite (cf. the procedure of Claisen and Manasse[17] for nitrosation of camphor) followed by catalytic hydrogenation of the resulting oxime mixture over 10% palladium/charcoal. The latter hydrogenation procedure simultaneously reduced the indene to an indan. Other indan derivatives (see Tables I, II, V, VII) were prepared by similar hydrogenation of the corresponding indenes.

The α-methyl (**82**) and α,α-dimethyl (**83**) compounds were separated from the mixture of mono- and dialkylation products produced upon treatment of the parent ketone **7** with sodium amide or lithium hexamethyldisilazide in THF followed by iodomethane. The monomethyl ketone obtained was a mixture of isomers which varied from 4:1 α:β with sodium amide to 1:2 α:β with the silane base. The absolute stereochemistries at camphor C_3 in these monomethyl compounds were not determined. As above, lithium aluminum hydride reduction of the ketones provided carbinols such as **84** and **85**.

Substituted piperidine analogs such as **35** and **36** were prepared by substituting (2-chloroethyl)(2-chloro-2-phenylethyl)amine or (2-chloroethyl)(2-chloropropyl)-amine, respectively, for bis(2-chloroethyl)amine **3** in Scheme I. The fused indenes (**37** and **38**) were obtained by substitution of fluorene for indene **2** in Scheme I, and variously substituted indenes (**42–47**) were prepared by similar substitution for indene in Scheme I with 5-methoxy-,[18] 6-chloro-,[19] 6-fluoro-,[20] 4/7-monomethyl-, 4/7-monochloro-, and 5/6-monophenylindene, respectively. The latter three indenes were prepared from 4-methylindanone, 2-chlorocinnamic acid, and 4-phenylcinnamic acid, respectively, using the procedures reported for the 6-chloro- and 6-fluoro- analogs.[19,20] The carbinols (**48–51**) were prepared by lithium aluminum hydride reduction, as described above for the unsubstituted analogs (e.g., **9**, **10**).

For preparation of (aminoethyl)indan analogs (**63–65**), indene was converted to the anion with butyllithium and then alkylated with chloroacetonitrile to provide (cyanomethyl)indene. This nitrile was reduced (nitrile and indene bonds) by catalytic hydrogenation over 5% rhodium on alumina in 10% ammonia/ethanol solution. The resulting 1-(2-aminoethyl)indan was acylated with 4-toluenesulfonyl chloride (**63**) or (*S*)-camphorsulfonyl chloride (**64**). The former (**63**) was N-ethylated with sodium hydride/DMF/ethyl iodide to provide the tertiary sulfonamide **65**.

The spirotetralinpiperidine **53** was prepared by acylation of the parent base,[21] a gift of Dr. David Billington, Merck Research Laboratories, Terlings Park, U.K. Reduction to and separation of the carbinols **54** and **55** were carried out as described above for the corresponding indene compounds. The pyrrolidone **56** was prepared by substitution for indene (**2**) in Scheme I with the parent base, 1-methylspiro[3*H*-indole-3,4′-piperidin]-2(1*H*)-one,[22] a gift of Dr. David Remy, Merck Research Laboratories, West Point, PA.

The compounds of Table IV were prepared by acylation of 4-phenylpiperidine (**57**), 4,4-diphenylpiperidine[23] (**58**, **60**), *N*-phenylpiperazine (**59**), or 4-carbethoxy-4-phenylpiperidine (**61**, **62**) with the appropriate sulfonyl halide.

For preparation of the isomer **95** of ketone **7**, fenchone-10-sulfonyl chloride[24–26] was used in place of the 10-camphorsulfonyl chloride. Reduction to carbinol **96** (stereochemistry undetermined) was carried out as above.

Biology

The methods for determination of oxytocin (OT) and vasopressin (AVP; rat liver = V_1, and rat kidney = V_2)

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receptor binding are described in detail in a separate publication.[12] This source also describes the in-depth in vitro and in vivo evaluation of the compound L-366,509 (1), results of which are summarized below.

Results

Structure–Activity. The characteristics of oral bioavailability and long duration in vivo which we sought in an oxytocin receptor antagonist are not commonly found in peptides. The peptide oxytocin antagonists cited above, for example, are iv agents with short in vivo lifetimes.[1,10,11] Structural constraints such as cyclization can sometimes improve in vivo duration, as has been accomplished in the oxytocin field with cyclic hexapeptide OT antagonists, such as L-365,209.[27-31] The problem of oral bioavailability, however, is seldom overcome in the peptide manifold. As a consequence, we concentrated our search for an orally bioavailable OT antagonist around the nonpeptide L-342,643 (11), a screening lead with 4 μM affinity for rat uterine oxytocin receptors (Table I). Structure–activity studies were carried out on this compound with the aim of improving potency and acquiring aqueous solubility (for iv use) and oral bioavailability with acceptable duration in vivo.

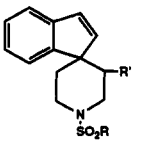
The focus of initial modification studies of the screening lead 11 was the toluenesulfonamide appendage. Variation of the substitution pattern in the aryl ring produced little if any enhancement of OT receptor affinity, as illustrated by the selected analogs 13 to 23 in Table I. The most potent compound in the series was the 4-bromo 16, a modest 3-fold improvement over the 4-methyl lead 11. More substantive changes in the arylsulfonamide produced wide variations in oxytocin receptor affinity. The pared-down methanesulfonyl compound 24, for example, proved essentially inactive, as did the larger alkyl congener 25.

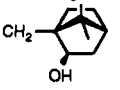
Addition of a methylene spacer to the arylsulfonamide structure caused a decrease in OT receptor affinity (compounds 26 and 27 vs 15 and 21), a decrease which was reversed upon extension of the spacer unit to the *Z*-olefin (28 vs 15). Other aryl units, such as thienyl (29), proved comparable to phenyl, while larger rings (e.g., 30) provided modest enhancements. In general, bulky, lipophilic groups at this site seemed to provide the better OT receptor ligands. In keeping with this observation, the nonaryl polycycle of the camphor ring formed the basis for one of the most promising compounds to emerge from this preliminary examination, the ketone 7. The OT receptor affinity of this compound was slightly sensitive to inversion of stereochemistry (32) and somewhat more so to excision of the camphor 7,7-dimethylmethylene bridge (34). More importantly, reduction to the carbinol 10 provided a substantial receptor affinity enhancement. Detailed examination of this structural modification is discussed below.

In the five-membered ring portion of the indene substructure, compounds such as 11 and 7 could be saturated with little change in oxytocin receptor affinity (cf. 12 and 33, respectively), but other fusions (37 and 38 vs 7 and 11, respectively) and substitutions (39–41 vs 7) in the indene ring proved detrimental (Table II). Substitution (42–51) or saturation (52) in the benzene portion of the indene ring produced mostly negative variations in oxytocin receptor affinity, with only the fluoro derivatives (44, 48, 49) rivaling the unsubstituted compounds as oxytocin receptor ligands.

Expansion of the indene five-membered ring to the six-membered spirotetralin proved compatible with full receptor affinity in the camphor ketone series (53 vs 7, Table III). The potency enhancement upon reduction of the camphor ketone to the (*S*)-*exo*-carbinol seen in the

Table I. Oxytocin (OT) and Vasopressin (AVP) Receptor Binding Affinities for Spiroindenepiperidine Sulfonamides[a]



compd	R	R'	IC50, μM OT	V_1	V_2
11	4-methylphenyl	H	4.0	35	100
12[b]	4-methylphenyl	H	5.7	80	100
13	3-methylphenyl	H	>10	>10	>10
14	2-methylphenyl	H	10	>10	>10
15	phenyl	H	10	ND[c]	ND
16	4-bromophenyl	H	1.2	>10	>10
17	3-bromophenyl	H	>10	>10	>10
18	2-bromophenyl	H	>10	>10	>10
19	4-fluorophenyl	H	7.1	>100	>100
20	4-methoxyphenyl	H	6.0	>100	>100
21	4-nitrophenyl	H	16	ND	ND
22	3-nitrophenyl	H	>10	>100	>100
23	2-nitrophenyl	H	>10	>100	>100
24	methyl	H	>100	>100	>100
25	*n*-butyl	H	>30	ND	ND
26	benzyl	H	>10	ND	ND
27	4-nitrobenzyl	H	>10	>10	>10
28	*trans*-cinnamyl	H	10	ND	ND
29	2-thienyl	H	10	ND	ND
30	2-naphthyl	H	3.0	ND	ND
31	2-(methoxycarbonyl)phenyl	H	3.0	ND	ND
7	(1*S*)-camphor-10-yl	H	1.8	>100	>100
32	(1*R*)-camphor-10-yl	H	2.4	>100	>100
33[b]	(1*S*)-camphor-10-yl	H	1.1	>10	>10
34	(2-oxocyclohexyl)methyl	H	6.4	>100	>100
10		H	0.47	8.4	>10
35	(1*S*)-camphor-10-yl	Ph	8.5	0.79	>10
36	(1*S*)-camphor-10-yl	CH_3	3.7	>10	>10

[a] Receptor binding is expressed as IC_{50}, the concentration (μM) of compound required for half-maximal inhibition of binding of [^{3}H]OT to rat uterine tissue (OT) or of [^{3}H]AVP to rat liver (V_1) or rat kidney (V_2) tissues as described by Pettibone et al.[12] [b] The indene bond is saturated (indan) in these compounds. [c] ND = not determined.

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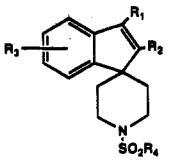
Table II. Oxytocin (OT) and Vasopressin (AVP) Receptor Binding Affinities for Indene-Substituted Spiroindenepiperidine Sulfonamides[a]



compd	R_1	R_2	R_3	R_4[c]	IC_{50}, μM OT	V_1	V_2
37	phenyl		H	A	>10	>10	>10
38	phenyl		H	D	>100	>100	>100
39	Ph	H	H	A	>10	>100	>100
40[b]	OH	OH	H	A	>100	>100	>100
41[b]	Br	Br	H	A	4.5	>100	>100
42	H	H	5/6-CH_3O	A	>10	>100	>100
43	H	H	5/6-Cl	A	7.6	>10	>10
44	H	H	5/6-F	A	2.3	>10	>10
45	H	H	4/7-CH_3	A	6.2	>10	>10
46	H	H	4/7-Cl	A	>10	>10	>10
47	H	H	5/6-Ph	A	>10	>100	>100
48	H	H	5/6-F	B	0.56	8.2	>10
49	H	H	5/6-F	C	1.9	>10	>10
50	H	H	5/6-CH_3O	B	>10	10	>10
51	H	H	5/6-CH_3O	C	>10	>10	>10
52[b]	hexahydroindane			B	>10	>10	>10

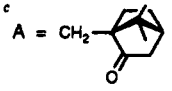
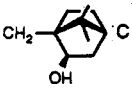
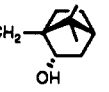
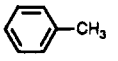
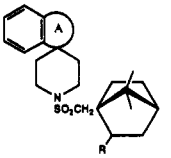
[a] Binding affinities defined as in Table I, footnote *a*. [b] The indene double bond is saturated (indan) in these compounds. [c] A =  B =  C =  D = 

Table III. Oxytocin (OT) and Vasopressin (AVP) Receptor Affinities for Spiropiperidines[a]



compd	A-ring	R	IC_{50}, μM OT	V_1	V_2
53		O=	1.1	7.9	>10
54		*exo*-OH	1.0	3.7	>10
55		*endo*-OH	2.0	3.0	>10
56		O=	6.5	100	>10

[a] Binding affinities defined as in Table I, footnote *a*.

indene series (**7** to **10**) was not observed in the tetralins, however (**53** to **54**). Other replacements for the five-membered ring, such as pyrrolidone (**56**), proved less efficacious.

Deletion of the indene five-membered ring entirely, as in the 4-phenylpiperidines (**57**, **58**, **60**; Table IV) and -piperazines (**59**), generally caused a substantial drop in OT receptor affinity. An exception was the Meperidine analog **62**[32] which proved equally effective compared with its spiroindenepiperidine counterpart (**11**). The effectiveness of compound **62** proved highly dependent on its piperidine 3-methyl substituent, however (**61** vs **62**).

In the piperidine portion of the spiroindenepiperidine, various substitutions failed to enhance oxytocin receptor binding affinity (Table I, **35**, **36**; cf. **7**). Interestingly, one of these substitutions, the 3-phenyl (compound **35**), did enhance vasopressin V_1 receptor affinity, giving a compound with 10-fold selectivity for V_1 vs oxytocin receptors. A precise comparison of compounds **35** and **36** based on the data in Table I must be made with caution, however, since the methyl compound **36** is a single isomer, while the phenyl derivative **35** is a mixture of diastereomers (80:20).

The effect of scission of the piperidine ring (Table V) on oxytocin receptor affinity was either detrimental or neutral. Thus, removal of one ethylene unit from the piperidine ring significantly reduced OT receptor affinity in the toluenesulfonate series (**63** vs **11**) and left it unchanged in the camphor ketone series (**64** vs **7**). Even the less drastic single bond cleavage represented by compound **65** occasioned a serious loss of affinity in the toluenesulfonamide class (cf. **11**). Replacement of the sulfonamide linkage to the piperidine with alternatives (Table VI) such as amide (**66–69**; **75–78**) and urea (**70–74**) similarly decreased affinity for the OT receptor almost uniformly. The only exceptions to this generalization were the phenylacetate **69** (cf. **26**) and the camphor ketone **77**. The latter compound again failed to provide the subsequent potency enhancements obtained by modification in the camphorsulfonamide series.[33]

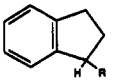
On the basis of these studies, the unsubstituted camphorsulfonamide **7** was selected for further, detailed

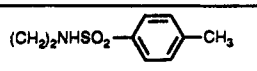
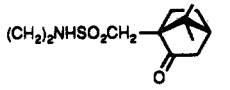
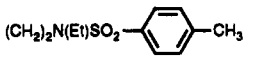
Table IV. Oxytocin (OT) and Vasopressin (AVP) Receptor Affinities for Monocyclic OT Antagonists[a]

compd	X	R	R′	IC_{50}, μM OT	V_1	V_2
57	PhCH	4-methylphenyl	H	>10	ND[b]	ND
58	Ph_2C	4-methylphenyl	H	>10	ND	ND
59	PhN	4-methylphenyl	H	>100	ND	ND
60	Ph_2C	(1*S*)-camphor-10-yl	H	>10	>100	>10
61	EtOOCCPh	4-methylphenyl	H	>30	>30	>30
62	EtOOCCPh	4-methylphenyl	CH_3	5.4	>100	>100

[a] Binding affinities defined as in Table I, footnote *a*. [b] ND = not determined.

Table V. Oxytocin (OT) and Vasopressin (AVP) Receptor Affinities for 1-Substituted Indan[a]



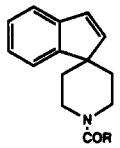
compd	R	IC_{50}, μM OT	V_1	V_2
63		>10	>100	>100
64		2.2	>10	>10
65		>10	>100	>100

[a] Binding affinities defined as in Table I, footnote *a*.

(32) Casy, A. F.; Chatten, L. G.; Khullar, K. K. Synthesis and stereochemistry of 3-methyl analogues of pethidine. *J. Chem. Soc. C* 1969, 2491–2495.

(33) Hobbs, D. W.; Gould, N. P. Unpublished results.

Table VI. Oxytocin (OT) and Vasopressin (AVP) Receptor Affinities for Spiroindenepiperidine Carboxamides and Ureas[a]



compd	R	IC_{50}, μM		
		OT	V_1	V_2
66	phenyl	10	ND	ND
67	4-bromophenyl	>10	>10	>10
68	4-methoxyphenyl	>10	>10	>100
69	benzyl	5.0	>10	>100
70	phenylamino	10	ND	ND
71	(4-methylphenyl)amino	10	ND	ND
72	(4-nitrophenyl)amino	>10	>100	>100
73	1-adamantylamino	>10	ND	ND
74	2-adamantylamino	10	ND	ND
75	(2-oxocyclohexyl)methyl	>10	>100	>100
76	cyclooctylmethyl	22	>10	>10
77	(1S)-camphor-10-yl	0.76	>10	>10
78	(1R)-camphor-10-yl	8.7	>10	>10

[a] Binding affinities defined as in Table I, footnote a. [b] ND = not determined.

investigation (Table VII). As noted above, the series of carbinols obtained by reduction of this ketone, compounds **9, 10, 80, 81**, included one analog (**10**) with enhanced OT receptor affinity over the parent ketone **7**. The relative potencies of the (*S*)- and (*R*)-carbinols (see Table VII), (*S*)-exo (**10**) > (*S*)-endo (**9**) ≃ (*R*)-endo (**81**) > (*R*)-exo (**80**), conjures a vision of the camphor ring as an amorphous ball wherein rotation about the camphor ring-to-piperidine linkage places the key hydroxyl group of the more potent of the (*R*)-carbinols (endo: **81**) in approximately the same location as in the more potent of the *S*-isomers (exo: **10**). Such a view is an oversimplification, however, for the OT receptor exhibits considerable selectivity for various features specific to the camphor ring. Thus, shift of the camphor 7-methyl groups to the 3 position, as in the fenchone-derived compounds **95** and **96**, occasions a considerable loss in OT receptor affinity compared with 3-substitution in the camphor itself (cf. **7, 82, 83, 86, 87, 95**) or the camphor *exo*-carbinol (cf. **9, 10, 84, 85, 96**).

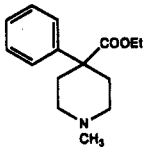
Success of the secondary carbinol **10** prompted investigation of a series of tertiary analogs formed by carbanion addition to the parent ketone (Table VII). In these compounds, oxytocin receptor affinity was relatively insensitive to the added substituent, allowing considerable variation at this site for the purpose of optimization of physical properties. Thus, side chains such as methyl (**88**), ethyl (**89**), phenyl (**90**), and methyl ester (**92**) all provided comparably effective oxytocin receptor ligands. This tolerance was used to advantage in L-366,509 (**1**) which incorporates an acetic acid side chain at this site. This modification gives the resulting oxytocin antagonist **1** a combination of good OT receptor affinity and considerably improved solubility in aqueous media at physiological pH (2.5 mg/mL, pH 7.4) compared with other members of this series (e.g., compound **10**, 0.0001 mg/mL, pH 7.4). Compound **1** was selected for detailed biological examination.

In Vitro/in Vivo. The results of in vitro and in vivo examination of L-366,509 are presented in detail in a separate publication.[12] These studies indicate that the compound is an effective, orally bioavailable oxytocin receptor antagonist with good duration of action in vivo. L-366,509 has 460 nM affinity for the human uterine oxytocin receptor, with 3.5-fold and 5.4-fold selectivities vs human liver ($AVP\text{-}V_1$) and kidney ($AVP\text{-}V_2$) vasopressin receptors, respectively. In the isolated rat uterus, L-366,509 acts as a pure, competitive antagonist with no agonist properties, and in the rat, it causes significant and long-lasting (>2 h) inhibition of oxytocin-stimulated uterine activity when administered iv (10 mg/kg) or intraduodenally (10–50 mg/kg). In the pregnant rhesus monkey, L-366,509 given orally (20 mg/kg) or iv (6 mg/kg) effectively blocks oxytocin-induced uterine contractions.[12]

Discussion

In the past several years, it has become clear that the earlier general view of peptides and nonpeptides as mutually exclusive classes of receptor ligands was inaccurate.[34] Our development of the CCK antagonist, L-364,718,[34-37] provided an early and convincing example of how a nonpeptide could be devised to bind a peptide hormone receptor every bit as effectively as the native peptide ligand. In the intervening years, numerous additional examples of such nonpeptide ligands for peptide receptors have been described.[38]

Another principle demonstrated by L-364,718 was that certain, select ligands for one receptor can serve as templates for construction of ligands for other receptors: the benzodiazepine nucleus was made selective for either benzodiazepine (Diazepam) or CCK (L-364,718) receptors by appropriate functionalization.[34,37] Elements of this principle are evident in the present development of L-366,509. The lead compound for this endeavor was the spiroindenepiperidine **11**. Formally a fused 4-phenylpiperidine, this compound bears a structural resemblance to well-known 4-phenylpiperidine analgesics such as Meperidine (**97**).[39] In fact, the Meperidine analog **62** of



MEPERIDINE 97

spiroindenepiperidine **11** is an oxytocin receptor ligand of comparable affinity. The spirotetralinpiperidine ring present in the OT antagonists **53–55** (Table III) has served as the base for a variety of opioid receptor ligands.[15,21]

(34) Evans, B. E.; Bock, M. G. Promiscuity in Receptor Ligand Research. In *Advances in Medicinal Chemistry*; Maryanoff, B. E., Maryanoff, C. A., Eds.; JAI Press, Inc.: Greenwich, CT, 1992; Vol. 2, in press.

(35) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. Design of potent, orally effective, nonpeptidal antagonists of the peptide hormone cholecystokinin. *Proc. Nat. Acad. Sci. U.S.A.* **1986**, *83*, 4918–4922.

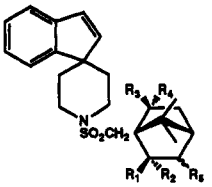
(36) Chang, R. S. L.; Lotti, V. J. Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist. *Proc. Nat. Acad. Sci. U.S.A.* **1986**, *83*, 4923–4926.

(37) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. Methods for drug discovery: Development of potent, selective, orally effective cholecystokinin antagonists. *J. Med. Chem.* **1988**, *31*, 2235–2246.

(38) Hirschmann, R. Medicinal Chemistry in the golden age of biology: Lessons from steroid and peptide research. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1278–1301.

(39) Smissman, E. E.; Hite, G. The quasi-Favorskii rearrangement. I. The preparation of demerol and β-pethidine. *J. Am. Chem. Soc.* **1959**, *81*, 1201–1203.

Table VII. Oxytocin (OT) Receptor Affinities Spiroindenepiperidine Camphorsulfonamides[a]



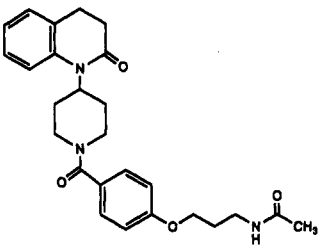
compd	R_1	R_2	R_3	R_4	R_5	IC_{50}, μM OT	V_1	V_2
7		=O	H	H	H	1.8	>100	>100
33[b]		=O	H	H	H	1.1	>10	>10
32	H	H	=O		H	2.4	>100	>100
10	OH	H	H	H	H	0.47	10	>10
79[b]	OH	H	H	H	H	0.34	45	30
9	H	OH	H	H	H	2.2	>10	>100
80	H	H	OH	H	H	3.9	>100	>10
81	H	H	H	OH	H	2.5	>10	>10
82		=O	H	H	CH_3	1.3	10	>10
83		=O	H	H	$(CH_3)_2$	3.4	>10	>10
84	OH	H	H	H	*exo*-CH_3	0.98	13	10
85	H	OH	H	H	*endo*-CH_3	0.59	6.7	10
86[b]		=O	H	H	$NHCOCH_3$	3.4	>100	>100
87[b]		=O	H	H	$NHCOCH(CH_3)_2$	3.0	>100	>100
88	OH	Me	H	H	H	0.60	10	>10
89	OH	Et	H	H	H	0.63	4.4	>10
90	OH	Ph	H	H	H	0.46	10	>10
91	OH	CH_2CN	H	H	H	0.77	>10	>10
92	OH	CH_2COOMe	H	H	H	0.35	10	>10
93	OH	$CH(CH_3)COOEt$	H	H	H	0.89	>10	>10
1	OH	CH_2COOH	H	H	H	0.78	89	83
94	OH	$CH(CH_3)COOH$	H	H	H	1.4	>100	>100
95[c]		=O	H	H	$(CH_3)_2$	>10	>100	>100
96[c]	OH[d]	H[d]	H	H	$(CH_3)_2$	3.0	>10	>100

[a] Binding affinities defined as in Table I, footnote *a*. [b] The indene double bond is saturated (indan) in these compounds. [c] These compounds lack the camphor 7-methyl groups. [d] The exo/endo stereochemistry in this compound is undetermined.

This crossover of one ligand base is not limited to two receptors. Benzodiazepine-based ligands have been found for at least three separate receptors—CCK, benzodiazepine, and opioid—and in a subsequent paper, we will describe benzodiazepines which bind to the oxytocin receptor as well. Customizing a suitable base system with appropriate functionality can apparently tailor that system to bind each one of a number of different receptors selectively. While subsequent optimization remains a major undertaking, this principle provides a useful method for facilitating the discovery of new receptor ligand leads.

The discovery of the lead compound for this effort, spiroindenepiperidine 11, underscores as well the value of receptor-based screening for uncovering new drug leads. The development of that lead as described here illustrates yet another lesson from the L-364,718 work,[34-37] namely that the precision of receptor–ligand interactions dictates considerable caution in attempts to extrapolate structure–activity profiles from one base lead to another, even to one closely related in structure and in target receptor affinity. This discussion presents several examples—7 → 10 vs 53 → 54; 63 and 64 vs 11 and 7—where a feature or change which enhanced receptor affinity in one base structure failed to do so in a closely related analog.

The limited selectivity of L-366,509 for human OT vs human vasopressin (AVP) receptors[12] implies that the compound is a reasonably effective nonpeptide ligand for the AVP receptor. In this capacity, L-366,509 is not unique, for nonpeptide vasopressin antagonists such as OPC-21268 (98) have been reported.[40] These compounds



OPC-21268 = 98

bear some structural resemblance to the spiroindenepiperidines of the present work. Detailed biological profiles of compounds such as 98, particularly their effect on OT receptors, have not yet been published, however. Ongoing development of L-366,509 will focus on enhancement of OT receptor affinity and of selectivity vs the vasopressin receptors.

Conclusion

In this paper, we have described the development of the spiroindenepiperidine, L-366,509 (1). This compound is the first reported example of a nonpeptide antagonist for the oxytocin receptor, and it has achieved the important goals of oral bioavailability and long duration of action in an OT receptor antagonist. Such properties are absent in

(40) Yamamura, Y.; Ogawa, H.; Chihara, T.; Kondo, K.; Onogawa, T.; Nakamura, S.; Mori, T.; Tominaga, M.; Yabuuchi, Y. OPC-21268, An orally effective, nonpeptide vasopressin V1 receptor antagonist. *Science* 1991, 252, 572–574.

currently available peptide compounds. L-366,509 has demonstrated the ability of a nonpeptide agent to effectively suppress uterine contractions, either artificially induced or naturally occurring, and to do so whether administered iv, orally, or intraduodenally.[12] This compound is a prototype for orally effective, long-acting OT antagonists suitable for outpatient use. Enhancement of its potency and selectivity are key goals for future development.

Experimental Section

Melting points (Thomas-Hoover melting point apparatus) are uncorrected. Spectra were obtained as follows: EI mass spectra on a VG MM 7035 mass spectrometer, FAB mass spectra on a VG MM/ZAB-HF spectrometer, ^{1}H NMR spectra on a Varian XL-300, Nicolet NT-360, or Varian VXR 400S spectrometer with Me_4Si as internal standard. HPLC was carried out on a Hewlett-Packard Model 1084B liquid chromatograph using a Waters C-18 column (30 × 0.39 cm). Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer. Analytical TLC was carried out on 250-μm, 5 × 20 cm silica gel plates (60 F-254, E. Merck) with ultraviolet light and/or phosphomolybdic acid for visualization.

Syntheses. The specific examples presented below illustrate the synthetic methods used in preparing the compounds of Tables I–VII in general and L-366,509 (1) in particular. All new compounds gave NMR spectra consistent with the reported structures. HPLC purities, mass spectral molecular ion determinations, and C, H, N analytical data for new compounds are given in the supplementary material. In general, samples prepared for physical and biological studies were dried in high vacuum (<5 torr) over P_2O_5 for 18 h at temperatures ranging from ambient to 110 °C, depending on the sample melting point. Despite these measures, some compounds remained solvated. Where analytical data have been presented for such solvates, the presence and approximate stoichiometry of all indicated solvents have been verified by NMR.

Method A. Spiroindenepiperidines: Spiro(1*H*-indene-1,4′-piperidine) Hydrochloride (6). Di-*tert*-butyl dicarbonate (62 g, 0.28 mol) and bis(2-chloroethyl)amine (3) hydrochloride (55 g, 0.31 mol) were stirred together in methylene chloride (400 mL). Triethylamine (42 mL, 0.3 mol) was added dropwise but briskly to the stirred suspension. After 10 min, additional triethylamine (ca. 5–6 mL) was added to adjust the pH of the mixture (E. Merck pH 5–10 colorpHast sticks, moistened with water) to 9–9.5. The mixture was stirred for 1 h at ambient temperature and then filtered. The filtrate was chromatographed on a silica column packed with 3:2 (v:v) methylene chloride/hexane and eluted with 9:1 methylene chloride/hexane. Evaporation of the combined product fractions in vacuo provided *N*,*N*-bis(2-chloroethyl)-*tert*-butyl carbamate (4) (70 g) as a colorless oil. The oil was twice dissolved in dry THF and evaporated in vacuo to remove methylene chloride.

To a solution of indene (2) (36.2 g, 310 mmol) in dry tetrahydrofuran (THF, 40 mL) cooled in an ice bath and maintained under a nitrogen blanket was added lithium bis(trimethylsilyl)amide (620 mL of a 1.0 M solution in THF; 620 mmol) over 30 min. The mixture was stirred in the cold for 30 min, then transferred by cannula over 20 min to a solution of *N*,*N*-bis(2-chloroethyl)-*tert*-butyl carbamate (4) (70 g, 290 mmol) in THF (40 mL), and stirred in an ice bath. The mixture was stirred for 2 h in the cold and for 30 min at ambient temperature under nitrogen and then evaporated in vacuo to a foam. Methylene chloride (400 mL) was added and the resulting mixture chromatographed on silica (1:1 followed by 1:4 hexane/CH_2Cl_2). The product fractions were evaporated to dryness in vacuo to provide 1′-(*tert*-butyloxycarbonyl)spiro(indene-1,4′-piperidine) (5) (90 g) as a crude yellow solid. The solid was recrystallized from hexane, giving a total of 54 g of pure product in several crops. The residue was rechromatographed to provide another 6.7 g (60.7 g total) of 5: ^{1}H NMR ($CDCl_3$) δ 1.33 (2 H, br d, J = 13.2 Hz), 1.42 (9 H, s), 2.02 (2 H, dt, J_1 = 13.2 Hz, J_2 = 5.1 Hz), 3.12 (2 H, br t, J = 13.2 Hz), 4.19 (2 H, br s), 6.79 (1 H, d, J = 6 Hz), 6.86 (1 H, d, J = 6 Hz), 7.16–7.37 (4 H, m).

1′-(*tert*-Butyloxycarbonyl)spiro(1*H*-indene-1,4′-piperidine) (5) (60.7 g) in ethyl acetate (700 mL) was stirred in an ice bath and saturated with HCl (g) for 30 min, keeping the internal temperature ≤12 °C. The mixture was stirred in the cold an additional 30 min and then evaporated to dryness. Ethyl acetate was added and removed in vacuo three times, and the residue was triturated with diethyl ether and filtered to provide spiro(1*H*-indene-1,4′-piperidine) hydrochloride (6): ^{1}H NMR (free base; $CDCl_3$) δ 1.4 (2 H, d, J = 13.8 Hz), 2.2 (2 H, dt, J_1 = 13.5 Hz, J_2 = 4.8 Hz), 3.09 (2 H, dt, J_1 = 13.5 Hz, J_2 = 3.6 Hz), 3.35 (2 H, dt, J_1 = 3.6 Hz, J_2 = 13.8 Hz), 5.3 (2 H, br s), 6.78 (1 H, d, J = 6 Hz), 6.86 (1 H, d, J = 6 Hz), 7.18–7.42 (4 H, m), 9–11 (br s).

Method B. Acylations: (1*S*)-1′-[[(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]-sulfonyl]spiro(1*H*-indene-1,4′-piperidine) (7). Spiro(1*H*-indene-1,4′-piperidine) hydrochloride (6) (45.4 g, 0.2 mol) and (*S*)-(+)-10-camphorsulfonyl chloride (62.5 g, 0.25 mol) were combined in CH_2Cl_2 (700 mL) and treated with triethylamine to adjust the pH of the mixture to 9–9.5 (moistened E. Merck colorpHast sticks). The mixture was stirred at ambient temperature for 1 h, then poured onto a silica gel column packed with CH_2Cl_2, and eluted with 1:1 Et_2O/CH_2Cl_2. The product fractions were combined and evaporated to dryness in vacuo to provide 7 as a solid which was recrystallized from petroleum ether and dried 6 h in vacuo at ambient temperature: ^{1}H NMR ($CDCl_3$) δ 0.8 (3 H, s), 1.3 (3 H, s), 1.5–1.9 (m), 2.12 (1 H, d, J = 19 Hz), 2.12–2.26 (2 H, m), 2.35 (2 H, dt, J_1 = 13.2 Hz, J_2 = 5.4 Hz), 2.56 (1 H, dt, J_1 = 5.4 Hz, J_2 = 19 Hz), 2.73 (1 H, dt, J_1 = 15 Hz, J_2 = 5 Hz), 3.0 (1 H, d, J = 15 Hz), 3.3 (1 H, dt, J_1 = 12 Hz, J_2 = 3 Hz), 3.42 (1 H, dt, J_1 = 12 Hz, J_2 = 3 Hz), 3.58 (1 H, d, J = 15 Hz), 4.1 (2 H, br d, J = 13 Hz), 6.95 (1 H, d, J = 7 Hz), 7.03 (1 H, d, J = 7 Hz), 7.3–7.55 (4 H, m). Anal. Calcd for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.51; found: C, 68.97; H, 7.2; N, 3.38.

Method C. Reductions: *endo*-(9) and *exo*-(10) 1′-[[(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl]-sulfonyl]spiro(1*H*-indene-1,4′-piperidine). A solution of (1*S*)-1′-[[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl]-spiro(1*H*-indene-1,4′-piperidine) (7) (2.0 g, 5.2 mmol) in dry THF (20 mL) was stirred at ambient temperature under a nitrogen atmosphere and treated with a 1.0 M solution of lithium aluminum hydride (5.1 mL, 5.1 mmol) in THF, and the mixture was stirred overnight. The mixture was carefully quenched with 1 N HCl, diluted with water, and extracted with Et_2O. The ether layer was washed with water, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with CH_2Cl_2. The faster eluting, major component was evaporated in vacuo and the residue recrystallized from ether to give the *exo*-carbinol 10 (1.2 g, 60%): ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, s), 1.1 (3 H, s), 1.2 (1 H, m), 1.47 (2 H, br d, J = 16 Hz), 1.5–1.9 (6 H, m), 2.22 (2 H, dt, J_1 = 13 Hz, J_2 = 5 Hz), 2.78 (1 H, d, J = 14 Hz), 3.13 (2 H, tt, J_1 = 13 Hz, J_2 = 2.5 Hz), 3.29 (1 H, d, J = 5 Hz), 3.34 (1 H, d, J = 14 Hz), 3.94 (2 H, br d, J = 14 Hz), 4.13 (1 H, p, J = 3.5 Hz), 6.82 (2 H, s), 7.2–7.4 (4 H, m).

The slower eluting component was eluted from the column with 2% MeOH/CH_2Cl_2, and the product obtained upon evaporation in vacuo was recrystallized from ether to give *endo*-carbinol 9 (0.7 g, 35%): ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, s), 0.96 (3 H, s), 1.16 (1 H, dd, J_1 = 14 Hz, J_2 = 3 Hz), 1.45 (ca. 4 H, d, J = 16 Hz), 1.5–1.7 (m), 1.72 (1 H, t, J = 5 Hz), 1.82 (1 H, m), 2.15–2.43 (4 H, m), 2.47–2.57 (1 H, m), 2.98 (2 H, s), 3.13 (2 H, tt, J_1 = 13 Hz, J_2 = 3 Hz), 3.65 (1 H, s), 3.92 (2 H, d, J = 13 Hz), 4.32 (1 H, br d, J = 11 Hz), 6.82 (2 H, s), 7.2–7.4 (4 H, m).

The configurations of carbinols 9 and 10 were assigned based on several lines of NMR evidence. The exo hydroxy orientation in carbinol 10 was suggested by the perturbation of the chemical shift of one of the two camphor methyl peaks by the proximate exo hydroxyl group in this compound (CH_3: δ = 0.88 and 1.1 in 10; cf. δ = 0.95 and 0.96 in 9). This assignment was supported by observation of a nuclear Overhauser effect (NOE) at C-2 hydrogen in *endo*-carbinol 9 upon irradiation of the C-7 methyl region, indicating an exo orientation for this hydrogen, placing it in proximity to the C-7 methyl substituent. In the *exo*-carbinol 10, irradiation of C-7 methyl produced no NOE at the C-2 endo hydrogen. Finally, in a 2-D COSY experiment, the C-2 proton

in *endo*-carbinol **9** showed a correlation with the C-6 exo hydrogen, supporting the exo orientation of the former (i.e., W-coupling of C-2 exo and C-6 exo hydrogens).

Method D. Organolithium Additions: [1*S*-(1α, 2α, 4α)]-2-Hydroxy-7,7-dimethyl-1-[[spiro(1*H*-indene-1,4′-piperidin)-1′-ylsulfonyl]methyl]bicyclo[2.2.1]heptane-2-acetic Acid (1). Lithium hexamethyldisilazide (48.5 mL of a 1.0 M solution in THF; 48.5 mmol) was stirred under a nitrogen atmosphere at −78 °C for 10 min. Dry, distilled ethyl acetate (4.55 mL, 4.09 g, 46.5 mmol) was added over 2 min, and the mixture was stirred another 15 min in the cold. A solution of (1*S*)-1′-[[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl]spiro(1*H*-indene-1,4′-piperidine) (**7**) (9.1 g, 22.8 mmol) in dry THF (60 mL) was added over 4 min, and the mixture was stirred an additional 10 min in the cold. 6 N HCl (18 mL) was added in one bolus, and the mixture was warmed to ambient temperature. After addition of water (60 mL), the mixture was separated and the aqueous layer extracted with ether. The combined organic layers were dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was treated with 55 mL of THF followed by 60 mL of a 0.2 M solution of $LiOH·H_2O$ (12 mmol) in water. The mixture was stirred at ambient temperature for 18 h, evaporated in vacuo, and treated with water to a total volume of ca. 600 mL. The solution was washed with ether (3×), acidified with 6 N HCl, and then extracted with ether (3×). The ether layer was reextracted with 0.5 M NaOH and the aqueous layer acidified with 1 N HCl and extracted with ether. White solids not dissolving in either layer during the extractions were identified (TLC) as the desired product. These were extracted into a large volume of ether and the combined, product-containing ether layers were filtered and evaporated to dryness in vacuo to give **1** as a white solid (2.84 g). Final purification by chromatography on silica gel (900:10:1:1 CH_2Cl_2/MeOH/HOAC/H_2O elution) provided material: mp 128–130 °C; ^{1}H NMR (DMSO-d_6) δ 0.92 (3 H, s), 1.1 (3 H, s), 1.2 (2 H, d, 14 Hz), 1.55 (1 H, br t, J = 12 Hz), 1.7 (3 H, d, J = 12 Hz + m), 1.9–2.08 (2 H, m), 2.12 (2 H, dt, J_1 = 13 Hz, J_2 = 5 Hz), 2.46 (1 H, d, J = 15 Hz), 2.5 (1 H, m), 2.8 (1 H, d, J = 15 Hz), 3.0 (1 H, d, J = 15 Hz), 3.1–3.3 (2 H, m), 3.53 (1 H, d, J = 15 Hz), 3.73 (2 H, br d, J = 14 Hz), 4.7 (1 H, s), 6.83 (1 H, d, J = 6 Hz), 7.28 (1 H, d, J = 6 Hz), 7.18–7.28 (2 H, m), 7.35 (1 H, d, J = 7 Hz), 7.48 (1 H, d, J = 7 Hz), 12.3 (br).

The separation of the camphor methyl groups (δ = 0.92 and 1.1) in compound **1** indicated an exo orientation for the 2-hydroxy substituent on the camphor ring, as in *exo*-carbinol **10** above. NOE's observed in C-3 endo and C-6 endo hydrogens of compound **1** upon irradiation of the CH_2 protons of the acetic acid side chain support the endo assignment for the latter substituent.

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