The Power of Visual Imagery in Drug Design. Isopavines as a New Class of Morphinomimetics and Their Human Opioid Receptor Binding Activity†

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The importance of visual imagery and relational thinking manifests itself in a heuristic approach to the design and synthesis of potential morphinomimetics as agonists of the human μ-receptor. The well-known class of alkaloids represented by the isopavine nucleus has a topological resemblance to the morphine skeleton, especially when viewed in a particular way. Enantiopure isopavines can be readily obtained from a 1,2 Stevens rearrangement of 13-substituted dihydromethanodibenzoazocines, prepared in four steps from D- and L-amino acids. Consideration of the topology and the expected orientation of the nitrogen lone pair for a better overlap with morphine necessitates the utilization of D-amino acids. By variation of the substituents on the aromatic rings and a judicious choice of ring substituents, it is possible to obtain low nanomolar binding to the human μ receptor while maintaining good to excellent μ/δ selectivity. Agonist-like activity is indicated in a functional assay for one of the analogues originally derived from D-alanine as a precursor. X-ray crystal structures of several compounds corroborate stereochemistries and overall topologies.

Introduction

The potent analgesic properties of morphine, a prominent constituent of the opiate class of alkaloids, has been recognized since the time of Helen of Troy.[1] Considerably more potent than its close analogue codeine, it is used in a hospital environment for temporary alleviation of extreme pain associated with a host of disease conditions. Morphine is one of the most widely investigated natural products, with a rich history in chemistry and pharmacology.[2−4]

The analgesic properties of opioids are now better understood in the context of their interaction with three major types of receptors, namely, δ, κ, and μ,[5] which belong to the G-protein-coupled receptor superfamily.[6] Although X-ray structural data are still unavailable for these receptors, several studies proposing three-dimensional models using computational methods have been reported over the years.[7−11] The identification of specific amino acid sequences in the cloned receptors[5,12,13] has greatly expanded the understanding of ligand−receptor interactions, offering insights into the molecular determinants for effective binding.[14] While specific details are still elusive, it is generally accepted that morphine and its congeners interact with the δ, κ, and μ receptors on the basis of a three-dimensional pharmacophore model that involves four sites, namely, a protonated amine, two (or three) hydrophobic groups, and an H-bond donor to a complementary site.[14−19] Indeed, numerous efforts concerned with the synthesis of analogues,[20] the chemical modification of the natural opioid alkaloids,[21−23] and the synthesis of peptide[24−26] and non-peptide analogues[27] have relied on these principles during the recent past.

In view of the nonspecific recognition of the opioid receptors, morphine and many of its congeners have serious side effects such as physical dependence, respiratory depression, and muscle rigidity.[28−31] Strategies that capitalize on different levels of agonist efficacy vis-à-vis these receptors have been advocated as a means of diminishing side effects.[14] A large proportion of opioid ligands have centered around the 4,5-epoxymorphinan, dihydromorphone, and dihydromorphindole structures.[32] Morphine, nalorphine, naltrexone, natrindole, oxymorphindole, and their variants are representative opioids that belong to these classes. Tricyclic structures have included morphinans, benzomorphans, aminotetralins, and cyclazocines, to mention a few. The cyclazocines have received considerable attention as clinical candidates in the early 1970s[33,34] and continue to be interesting pharmacological probes for the functional requirements of the opioid receptors.[35] For historical reasons,[36] peptidic compounds have also been pursued as a backdrop to non-peptidic counterparts.[24,37,38]

Major advances in identifying receptor subtypes and pharmacophore recognition sites through site-directed mutagenesis and other structural tools have provided convincing biochemical evidence for the existence of homo- and heterodimers among opioid receptors.[39] For example, "message" and "address" sequences[40] have been identified and morphinan structures synthesized as probes for heterodimeric δ, κ, and μ recognition sites.[41,42] Perhaps one of the more intriguing consequences of these studies was the synthesis of a C_2 centrosymmetric "dimeric" morphine analogue, norbin-

† Dedicated to Professor Philip Portoghese for his seminal contributions to the chemistry of opioids.

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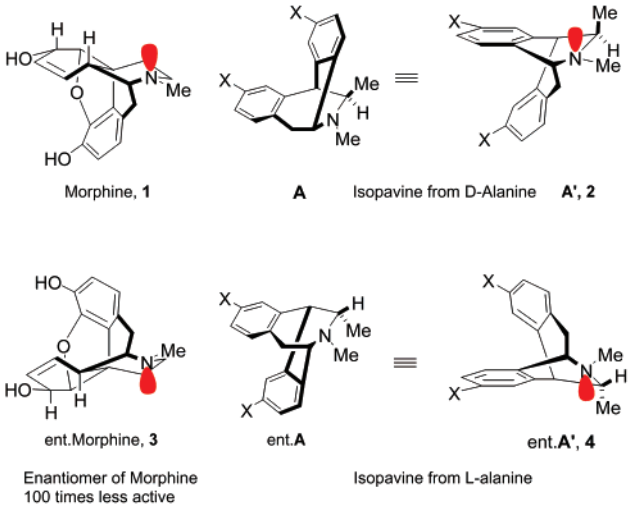


Figure 1. Morphine and isopavine perspectives.

altrophimine (BNI).[43] Further studies revealed that half of the dimer served as a scaffold to rigidly hold the basic nitrogen in a favorable position to interact with one of the receptors.[44−46] While rigid structures such as morphine itself are not absolute requirements for favorable binding, the proper alignment of pharmacophores and the all too important orientation of the nitrogen lone pair[47,48] are critical. Fentanyl, containing a piperidine moiety, represents an example of a "flexible" monocyclic opioid receptor ligand with considerable history.[16]

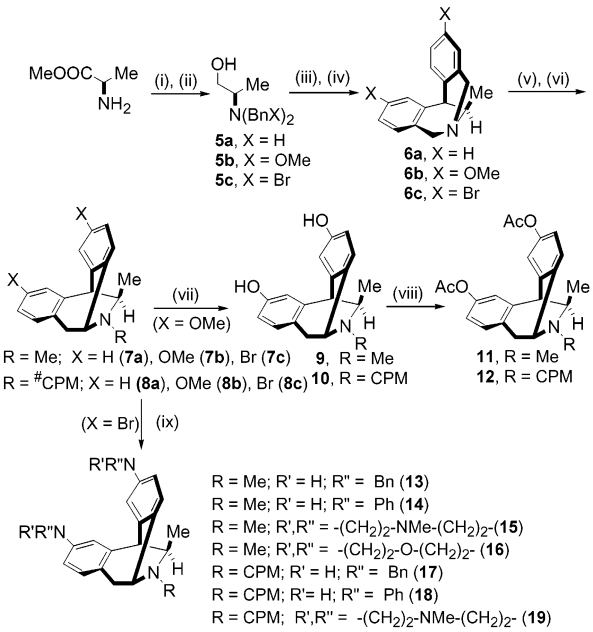
Morphinomimetic Design through Visual Imagery

The power of visual association especially in a three-dimensional sense is an ongoing challenge in our daily encounters with molecular entities.[49] Much like eye-teasing Dalièsque paintings of motifs that are "the same and not the same,[50] the surrealism of molecular similarities and of pharmacophore juxtapositions can be just as intriguing. The isopavines, readily available from the corresponding dihydromethanodibenzoazocines (see below),[51−53] represent examples of rigid molecules, with exquisitely deployed topology and functionality anchored around a tertiary nitrogen atom originally derived from a natural amino acid. Thus, the isopavine prepared from D-alanine is shown in two perspective drawings represented by **A** and **A′** (Figure 1). At first glance, the topological resemblance of isopavine **A** to morphine **1** is not obvious. However, a view in another perspective such as **A′** (**2**) reveals a skeletal convergence with morphine, where some of the desired pharmacophoric elements that are required for μ opioid receptor binding and activation are present. Likewise, the enantiomeric isopavine, ent.**A** (or **A′**, **4**) derived from L-alanine,[51,52] is topologically related to the enantiomer of morphine **3**, which is 100 times less active than the natural product. The perspective-based design and synthesis of isopavines and the choice of a D- rather than an L-amino acid[51] as a preferred chiral progenitor to achieve potential morphine-like receptor binding activity are the objectives of this paper.

Synthesis

The general protocol for the synthesis of *p*-aryl-substituted isopavines involved a highly stereocontrolled

Scheme 1[a]



[a] (i) 4-(X)-Benzyl bromide, $NaHCO_3$, THF/DMSO, reflux, (ii) LAH, THF, 0 °C to room temp, (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, (iv) $AlCl_3$, CH_2Cl_2, 0 °C to room temp, (v) RX, acetone, reflux, (vi) *t*-BuOK, dioxane, 80 °C, (vii) aqueous HBr, reflux, (viii) Ac_2O, Et_3N, CH_2Cl_2, (ix) BINAP, $Pd(dba)_3$, *t*-BuONa, R′R″NH, or R″NH_2, toluene, 80 °C. [#]Cyclopropylmethyl.

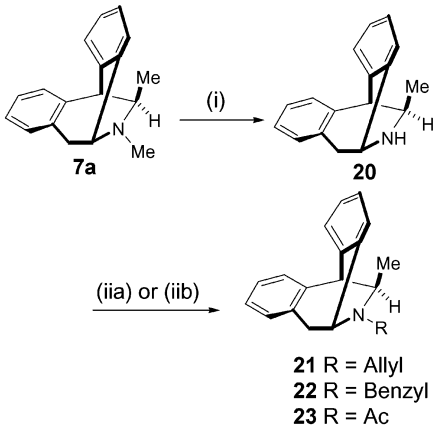
1,2 Stevens rearrangement[54,55] of the corresponding 13-substituted dihydromethanodibenzoazocines.[52] The latter compounds were in turn prepared from the appropriate *N*,*N*-dibenzylamino aldehydes (derived from the corresponding amino acids)[56] by a two-stage intramolecular Friedel−Crafts reaction. Symmetrical unsubstituted dihydromethanodibenzoazocines have been known for some time,[57,58] but their desymmetrized enantiopure analogues were not previously described. Their pharmacological properties have remained largely unexplored.[59]

Scheme 1 illustrates the synthesis of dihydromethanodibenzoazocines **6a**−**c** from D-alanine with variations in the benzyl substituent. Treatment with methyl iodide or cyclopropylmethyl iodide in refluxing acetone afforded the corresponding *N*-methyl or *N*-cyclopropylmethyl quaternary salts, which were subjected to rearrangement in the presence of *t*-BuOK in refluxing dioxane.[60] The corresponding isopavines **7a**−**c** and **8a**−**c** were obtained in good to excellent yields. The methoxy groups were cleaved with aqueous HBr at reflux temperature[61] to afford the free bis-phenols **9** and **10**. Acetylation led to **11** and **12**, which are formally related to heroin by analogy with the diacetylmorphine structure as shown in Figure 1.

The *p*-bromoarylisopavines were transformed to the corresponding bis-*N*-alkyl and bis-*N*-phenyl analogues **13**−**19** by versatile Pd-catalyzed insertion reactions of appropriate substituted amines.[62] Scheme 2 shows the oxidative demethylation[63] of **7a** to yield the corresponding des-*N*-methyl analogue **20**. Allylation, benzylation, and acetylation afforded the respective *N*-substituted compounds **21**−**23**.

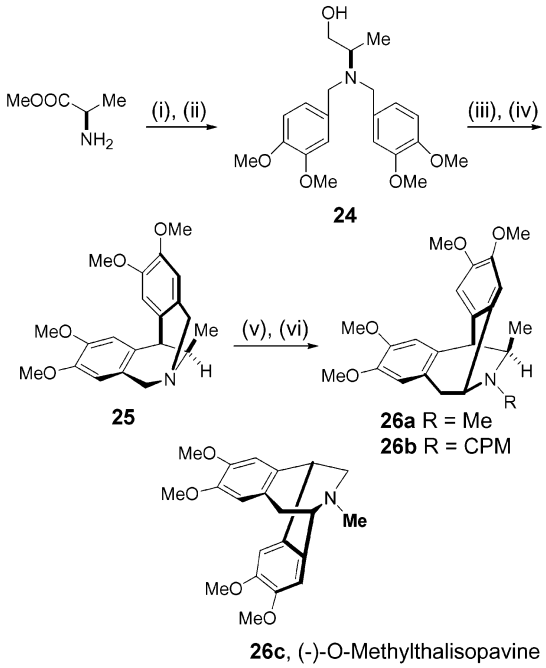
Unlike the dihydromethanodibenzoazocines, there are numerous natural products belonging to the isopavine group of alkaloids.[53,64] *O*-Methylthalisopavine, **26c**, has

Scheme 2[a]



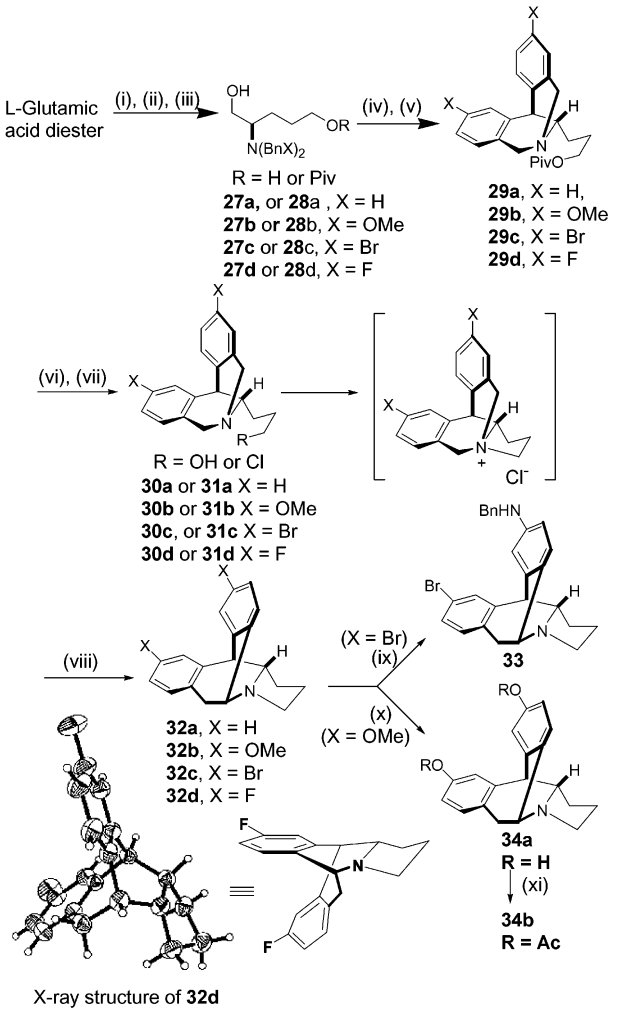
[a] (i) Pd-C, MeOH, Air, (iia) RX, Na_2CO_3, THF, reflux, or (iib) Ac_2O, Et_3N, CH_2Cl_2, room temp.

Scheme 3[a]



[a] (i) (3,4)-Dimethoxybenzyl bromide, $NaHCO_3$, THF/DMSO, reflux, (ii) LAH, THF, 0 °C to room temp, (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, (iv) $AlCl_3$, CH_2Cl_2, 0 °C to room temp, (v) RX, acetone, reflux, (vi) *t*-BuOK, dioxane, 80 °C.

Scheme 4[a]

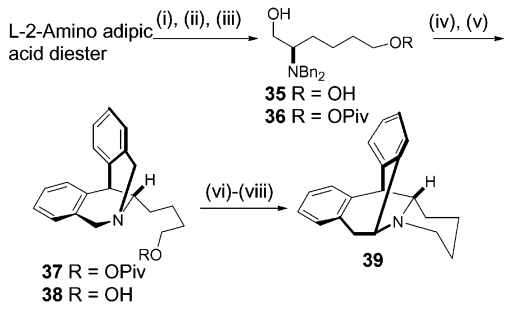


[a] (i) 4-(X)-Benzyl bromide, $NaHCO_3$, THF/DMSO, reflux, (ii) LAH, THF, 0 °C to room temp, (iii) PivCl, Et_3N, CH_2Cl_2, −10 to 0 °C, (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, (v) $AlCl_3$, CH_2Cl_2, 0 °C to room temp, (vi) DIBALH, toluene, −78 °C, (vii) $SOCl_2$, benzene, reflux, (viii) *t*-BuOK, dioxane, 80 °C, (ix) BINAP, Pd(dba)$_3$, *t*-BuONa, R′R″NH, toluene, 80 °C, (x) aqueous HBr, reflux, (xi) Ac_2O, Et_3N, CH_2Cl_2.

been synthesized in enantiomerically pure form by two groups[65,66] and in racemic form also.[67] A 13-methyl *ent*-*O*-methylthalisopavine **26a** and its *N*-cyclopropylmethyl analogue **26b** were prepared by the same methodology described above as shown in Scheme 3.

The importance of the proper orientation of the nitrogen lone pair in the isopavine series was recognized when we compared the μ receptor binding affinities[52] of a constrained tricyclic isopavine, with a similar analogue derived from L-alanine (Figure 1, ent.**A**/**A**′). The synthetic sequence for the tricyclic analogues in this series is shown in Scheme 4, which starts with the chemoselective modification of L-glutamic acid to afford the *N*,*N*-dibenzyl-2-aminopentane-1,5-diol monopivaloate analogues **28a**−**d**. Oxidation to the corresponding aldehyde and Friedel−Crafts cyclization proved to be successful (especially utilizing a pivaloate ester) to give the aryl-substituted dihydromethanodibenzoazocines **29a**−**d**. Intramolecular quaternization via the chlorides **31a**−**d** followed by Stevens rearrangement led to the bridged tricyclic isopavines **32a**−**d**, respectively. Pd-catalyzed insertion[62] of amines into the dibromo analogue **32c** took place only partially to afford the monobenzylamino derivative **33** (or its alternative isomer in which the aromatic substituents are interchanged). Treatment of **32b** with aqueous HBr at reflux afforded the corresponding bis-phenolic analogue **34a**, which was converted to the diacetate **34b**. The stereochemical course of the Stevens rearrangement to give the expected isopavines was corroborated by a single-crystal X-ray analysis of the difluoro analogue **32d** (Scheme 4). The tetracyclic fused piperidine analogue **39** was synthesized according to the protocol shown in Scheme 5 and proceeding via the 13-hydroxypropyldihydromethanodibenzoazocine **38**. Selected isopavine analogues were also prepared starting from L-amino acids using the same methods described for the D-enantiomer.

Scheme 5[a]



[a] (i) Benzyl bromide, $NaHCO_3$, THF/DMSO, reflux, (ii) LAH, THF, 0 °C to room temp, (iii) PivCl, Et_3N, CH_2Cl_2, −10 to 0 °C, (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, (v) $AlCl_3$, CH_2Cl_2, 0 °C to room temp, (vi) DIBALH, toluene, −78 °C, (vii) $SOCl_2$, benzene, reflux, (viii) *t*-BuOK, dioxane, 80 °C.

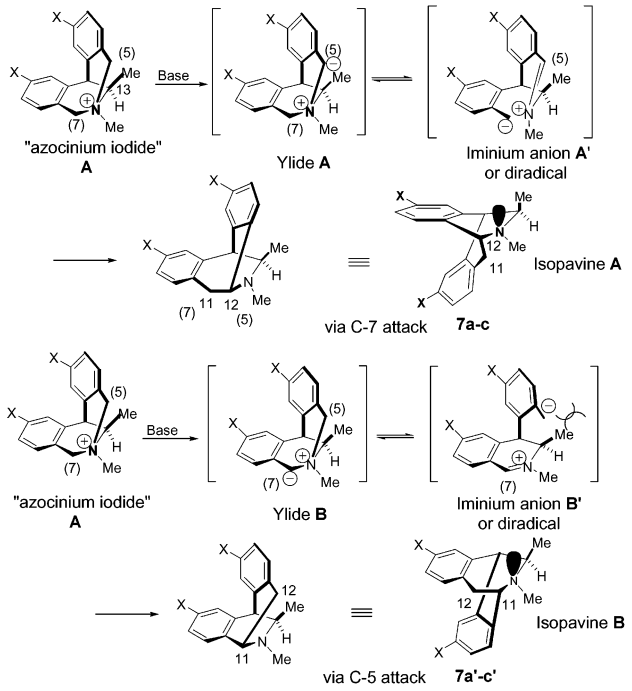


Figure 2. Proposed pathway for [1,2] Stevens rearrangement.

Mechanistic Issues

Before presentation of the receptor binding activities of the isopavines, it is of interest to discuss the stereochemical issues related to the Stevens rearrangement as illustrated in Figure 2. Abstraction of one of the diastereotopic C-5 benzylic protons from the dihydromethanodibenzoazocinium iodide **A** leads to ylid **A**, then to iminium ion **A′** (or its diradical equivalent).[68] Intramolecular closure via a C-7 attack affords isopavine **A**, which is the observed diastereomer as confirmed by X-ray crystallography.[51] Alternatively, abstraction of a C-7 benzylic proton will lead to ylid **B** and to iminium ion **B′** (or its diradical equivalent). Ring closure via a C-5 attack leading to the isopavine **B** is apparently not favored. On the other hand, the tricyclic iminium ion resulting from **31a**−**d** (Scheme 4) via intramolecular alkylation will cyclize via a preferred pathway that leads to a type **B** isopavine (where a pyrrolidine ring is appended).[51] Thus, to achieve the desired topological convergence and nitrogen lone pair orientation with morphine, one must use D-amino acids to access the bridged isopavines of type **A** via *N*-methylation. To differentiate the two pathways leading to isopavines **A** and **B** in the D-alanine series, the starting dihydromethanodibenzoazocines must carry different substituents on the aryl portion.[51,52]

In Vitro Receptor Binding Affinities

In vitro binding affinities of the synthetic isopavines were determined with the use of cloned human δ, κ, and μ opioid receptors.[69] The IC_{50} values and selectivities for the bridged bicyclic isopavines derived from D-alanine and for the bridged tricyclic isopavines derived from L-glutamic and 2-aminoadipic acids are listed in Table 1.

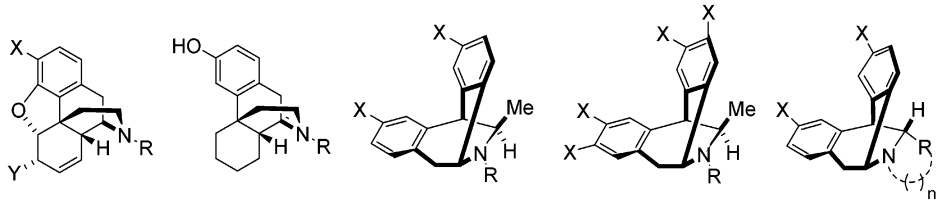
Our original design principle relied on a topological and functional convergence with morphine itself while maintaining a favorable orientation of the nitrogen lone pair in the synthetic compounds. Those analogues in which the phenyl rings were unsubstituted in the **7a** and **8a** series exhibited 200−100 nM binding affinity to the μ receptor with no activity at δ or κ receptors (Table 1, entries 4 and 5).

Introduction of *p*-bromo or *p*-methoxy groups in the phenyl rings resulted in compounds that retained the μ binding and selectivity (Table 1, entries 10−13). However, the bis-phenolic analogues **9** and **10** (Table 1, entries 14 and 15) showed a significant improvement in binding with IC_{50} values of 16 and 6.4 nM, respectively. The δ and κ binding was also improved compared to the analogues described above. The corresponding bis-phenolic acetates **11** and **12** (Table 1, entries 16 and 17) maintained the same trend, with the *N*-cyclopropylmethyl analogues being about 3−5 times more active than the *N*-methyl analogues.

The introduction of amino groups in cyclazocines has proven to be beneficial for μ and κ receptor binding.[35] In this regard the bis-aminophenyl analogues **14** and **18** (Table 1, entries 18 and 19) had higher affinity for the μ and δ receptors than for κ. Low nanomolar μ binding was observed for the bis-aminobenzyl analogues **13** and **17**, with the former being approximately 2 and 20 times as selective vs δ and κ, respectively. Changing the phenyl substituent to bis-*N*-methylpiperazine in the *N*-methyl and *N*-cyclopropylmethyl series (compounds **15**, **19**, Table 1, entries 22 and 23) resulted in a lower affinity of μ receptor binding compared to the corresponding bis-*N*-aminobenzyl analogues **13** and **17**. Removal of the *N*-methyl or *N*-cyclopropylmethyl group as in the case of the secondary amine analogue **20** retained selectivity; i.e., the resulting compound still had no detectable binding to δ and κ (Table 1, entry 6).

As previously mentioned, we had surmised that introduction of a third ring such as in the bridged tricyclic analogue **32a** would nicely converge with the morphine skeleton.[51] The rigidity of the ring system would also place the nitrogen lone pair in a favorable orientation. This topology could only be accessible from L-amino acids precursors via cyclic quaternary salts. We were indeed pleased that **32a**[51] showed an IC_{50} of 59 nM toward the μ opioid receptor with excellent selectivity toward the δ and κ receptors (Table 1, entry 27). The piperidine analogue **39** maintained the selectivity but showed lower affinity for the μ opioid receptor (Table 1, entry 28). Bis-bromo, bis-methoxy, and bis-fluoro (X-ray crystal structure) analogues **32b**−**d** (Table 1, entries

Table 1. Binding Affinities of Synthetic Isopavines for the Human Opioid Receptors

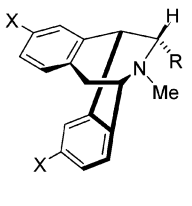


entry	compd	R	X	Hδ IC50,[a] nM	Hδ SEM[b]	Hκ IC50,[a] nM	Hκ SEM[b]	Hμ IC50,[a] nM	Hμ SEM[b]	μ selectivity vs δ (-fold)[c]
1	(−)-morphine	Me	OH	150	13	170	35	0.57	0.10	265
2	levorphanol	Me	OH	5.1	0.4	4.0	0.2	0.13	0.03	39
3	codeine	Me	OMe	>9300	9335 to >10000	15000	2000	105	20	>89
4	**7a**	Me	H	>10000		>7500	7500 to >10000	230	19	>43
5	**8a**	CPM[d]	H	>10000		>10000		1080	78	>9.3
6	**20**	H	H	>10000		>10000		650	81	>15
7	**21**	allyl	H	>9700	9700 to >10000	>4000	4000 to >10000	2000	190	>5
8	**22**	benzyl	H	>8800	8900 to >10000	>5800	5800 to >10000	>10000		NA
9	**23**	acetyl	H	>10000		>10000		>9500	9500 to >10000	NA
10	**7c**	Me	Br	8840	500	6920	864	360	130	25
11	**8c**	CPM	Br	>10000		>4900	4900 to >10000	2050	72	>5
12	**7b**	Me	OMe	>10000		>10000		420	96	NA
13	**8b**	CPM	OMe	6630	1190	5330	1220	1030	190	6.4
14	**9**	Me	OH	1300	110	961	18	16	2	80
15	**10**	CPM	OH	460	55	204	20	6.4	1.4	72
16	**11**	Me	OAc	>4700	4700 to >10000	>9500	9500 to >10000	200	44	>23
17	**12**	CPM	OAc	3300	740	2020	460	44	10	74
18	**14**	Me	NHPh	530	55	3600	470	56	13	9.5
19	**18**	CPM	NHPh	890	65	1200	190	82	14	11
20	**13**	Me	NHBn	120	12	640	77	8	1.5	15
21	**17**	CPM	NHBn	49	6	31	2	7	1.6	7.0
22	**15**	Me	*N*-Me piperazine	2500	300	3200	400	53	14	47
23	**19**	CPM	*N*-Me piperazine	2040	120	1600	360	690	200	3.0
24	**16**	Me	morpholine	7500	520	>10000		690	170	11
25	**26a**	Me	OMe	>10000		>10000		>10000		NA
26	**26b**	CPM	OMe	>10000		>10000		>10000		NA
27	**32a**	$-(CH_2)_3-$	H	>7800	7800 to >10000	6100	260	59	12	>131
28	**39**	$-(CH_2)_4-$	H	>10000		7400	1100	390	130	>25
29	**32b**	$-(CH_2)_3-$	Br	5020	470	7400	1800	500	110	10
30	**32c**	$-(CH_2)_3-$	OMe	4040	380	>10000		160	32	25
31	**32d**	$-(CH_2)_3-$	F	>10000		>6400	6400 to >10000	103	6	>97
32	**34a**	$-(CH_2)_3-$	OH	3800	400	7200	740	130	37	29
33	**34b**	$-(CH_2)_3-$	OAc	2900	550	>6000	6000 to >10000	220	70	13
34	**33**	$-(CH_2)_3-$	Br, NHBn[e]	5300	340	7000	1000	120	5	44

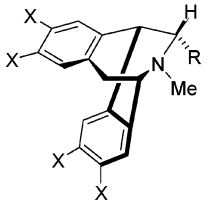
[a] IC_{50} values represent the arithmetic mean of 3−10 determinations except for compounds **7a** and **8a**. [b] Standard error of the mean. Blank SEM indicates all replicates were >10000. Range is shown instead of SEM if one or more value is >10000. [c] μ selectivity calculated as δ IC_{50}/μ IC_{50}. NA indicates insufficient binding potency at μ to obtain a selectivity value. [d] CPM = cyclopropylmethyl. [e] Specific location of 4-aryl substituent not known.

29−31) maintained the same selectivity trend with small variations. The significant improvement in μ receptor binding in the bis-phenol bridged bicyclic series **9** compared to **7a** (and **10** compared to **8a**) can be intuitively ascribed to a closer relationship to morphine (Figure 1, isopavine **A** or **A′**, X = H, OH). The binding affinity is of the order that would be expected theoretically for an additional dipolar H-bond interaction.[70] We were, however, surprised that the binding of bis-phenolic analogue **34a** to the μ receptor was not improved compared to the unsubstituted precursor **32a**. An IC_{50} of 130 nM for the μ receptor is the same as those for the corresponding bis-methoxy and bis-fluoro analogues (Table 1, entries 30−32). The bis-acetate **34b**, like its bis-phenolic precursor **34a**, lost some μ/δ selectivity compared to the bis-fluoro analogue (Table 1, entry 33). Finally, a mixed *p*-bromophenyl, *p*-aminobenzyl analogue **33** showed significant μ-receptor binding at IC_{50} = 120 nM, with 44- and 58-fold selectivity versus δ and κ receptors (Table 1, entry 34). We cannot ascertain if the para substituents are as shown in **33** or if they are interchanged. A perspective drawing of

Table 2. Binding Affinities of Synthetic Isopavines from L-Alanine for the Human Opioid Receptors



40a-40g



40h

				Hδ		hκ		Hμ		μ selectivity
entry	compd	R	X	IC_{50},[a] nM	SEM[b]	IC_{50},[a] nM	SEM[b]	IC_{50},[a] nM	SEM[b]	vs δ (-fold)[c]
1	**40a**	Me	H	>10000		>10000		611	28	>16
2	**40b**	*i*-Pr	H	>10000		3410	264	695	60	>14
3	**40c**	*i*-Bu	H	>8700	8700 to >10000	2970	500	1010	153	>8.6
4	**40d**	Bn	H	3442	273	1710	190	1050	100	3.3
5	**40e**	CH_2OH	H	>10000		>10000		404	14	>25
6	**40f**	$(CH_2)_2OH$	H	>10000		>9960	9965 to >10000	764	77	>13
7	**40 g**	$(CH_2)_3OH$	H	>10000		>10000		1150	91	>8.7
8	**40h**	Me	OMe	>5700	5700 to >10000	>10000			>10000	NA

[a] IC_{50} values represent the arithmetic mean of 3−5 determinations. [b] Standard error of the mean. Blank SEM indicates all replicates were >10000. Range is shown instead of SEM if one or more value is >10000. [c] μ selectivity calculated as δ IC_{50}/μ IC_{50}. NA indicates insufficient binding potency at μ to obtain a selectivity value.

the tricyclic bridged series **32a**−**d** and **34a**,**b**, based on the single-crystal structure of the bis-fluoro analogues **32d**, is shown in Scheme 4. Clearly, the substitution patterns and electronic properties of the bis-phenyl rings of these isopavines are important features in the relative binding affinities to the three opioid receptors. These functional features are better correlated with activity in the series morphine, its monomethyl ether (codeine), and its dimethyl ether (thebaine). The phenolic hydroxyl group in morphine is a key functional feature for binding to the μ receptor and for in vivo opioid activity. Indeed, the binding of 3-deoxymorphine was 30-fold less than the binding of morphine,[71] and the monomethyl ether codeine had a 200-fold lower affinity.[72] On the other hand, it has been recently shown that the introduction of other pharmacophores in morphine as in the 14β-cinnamoylamino derivative of morphinone (clocinnamox) can compensate for the absence of a phenolic group.[23] Table 2 lists the binding affinities of isopavine analogues derived from L-amino acids (see Figure 1).[51] Not surprisingly, **40a**, which is enantiomeric with **7a**, showed 3-fold weaker μ receptor binding but maintained excellent selectivity (Table 2, entry 1). As the size of the side chain was increased to isopropyl, isobutyl, and benzyl, little effect was seen on μ affinity (which diminished slightly) or κ affinity (which increased slightly) (Table 2, entries 2−4). Introduction of polar side chains seemed to have a similar effect with respect to μ receptor binding but not with δ and κ (Table 2, entries 5−7). The bis-methoxyphenyl analogue **40h**, enantiomeric with *O*-methylthalisopavine **26a**, showed no binding to the three receptors (Table 2, entry 8).

Several isopavines showed μ opioid receptor binding that was selective over δ by up to 80-fold (Table 1, compounds **9**, **10**, **12**, **13**). Compound **13**, which had lower selectivity than these but retained excellent μ affinity, showed agonist activity in stimulation of the human μ receptor with an EC_{50} of 4.3 ± 1 μM. It showed a higher maximal effect in stimulating the μ receptor (100% vs 56% for morphine), but it was 10 times less potent.

Conclusion

Diversely substituted dihydromethanodibenzoazocines, which are readily available from D- and L-amino acid precursors, undergo a stereocontrolled 1,2 Stevens rearrangement to the corresponding isopavines. The product originating from D-alanine and represented in perspective drawings of isopavines **A** and **A′** in Figure 1 are topologically related to morphine. A series of substituted isopavines derived from D- and L-amino acids with and without aromatic substituents were synthesized and tested for their binding affinities toward human opioid receptors.

Several analogues showed high affinity for the μ opioid receptor, as well as good selectivity over δ and κ receptors. The importance of the orientation of the nitrogen lone pair to achieve morphine-like structural features becomes evident when comparing isopavines derived from D- and L-alanine. A mechanistic rationale for the stereocontrolled 1,2 Stevens rearrangement is presented. A functional assay on a representative μ receptor selective analogue **13** showed agonist activity at EC_{50} = 4.3 μM and proved to be more efficacious than morphine though less potent. Isopavines were shown to be novel potential novel mimetics of morphine.

Experimental Section

Solvents were distilled under positive pressure of dry nitrogen before use and dried by standard methods: THF and ether, from K/benzophenone; CH_2Cl_2 and toluene from $CaCl_2$. All commercially available reagents were used without further purification. All reactions were performed under nitrogen atmosphere. NMR (^1H, ^{13}C) spectra were recorded on AMX-300 and ARX-400 spectrometers in $CDCl_3$ or CD_3OD with tetramethylsilane as the internal standard. In some cases, carbon resonances were coincident. Low- and high-resolution mass spectra were recorded on VG Micromass, AEI-MS 902, and Kratos MS-50 spectrometers using fast atom bombardement (FAB) or electrospray techniques. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ precoated silica gel plates. Visualization was performed by UV or by development using $KMnO_4$ or $FeCl_3$ solutions. Flash column chromatography was

performed using silica gel (40−60 μm) at increased pressure. Melting points recorded were uncorrected.

***N,N*-Dibenzyl-(*R*)-2-amino-1-propanol (5a).**[56] D-Alanine methyl ester (8.5 g, 60 mmol) and $NaHCO_3$ (20.8 g, 240 mmol, 4.0 equiv) suspended in THF/DMSO (160 mL, 4:1) were treated with benzyl bromide (14.3 mL, 120 mmol) at room temperature, and the solution was heated at reflux for 20 h. After completion, the solid materials were removed by filtration, the resulting filtrate was evaporated, and the residue was diluted with EtOAc (80 mL). The organic phase was washed with water and brine, dried over Na_2SO_4, concentrated in vacuo to give the crude *N*,*N*-dibenzylated product as a viscous oil (16.5 g, 99%). The crude product was subjected to the next step without purification. To a suspension of lithium aluminum hydride (3.2 g, 84 mmol, 2.0 equiv) in dry THF (80 mL) was added the above crude ester (16.2 g, 60 mmol, 1.0 equiv) in THF (20 mL) at 0 °C, and the mixture was warmed to room temperature. After 12 h of being stirred, the mixture was cooled to 0 °C, excess hydride was quenched with EtOAc (3 mL), and then water (3 mL) and a 15% NaOH aqueous solution (3 mL) were slowly added. Finally, water (9 mL) was added and the mixture was filtered and washed with hot EtOAc. The filtrates were concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc 1:1, then neat EtOAc) to give the desired alcohol **5a** (12.8 g, 84%) as a viscous oil.

(2*R*)-2-[Bis(4-methoxybenzyl)]aminopropane-1-ol (5b). From D-alanine methyl ester (8.5 g, 61.0 mmol), **5b** was obtained in two steps (14.8 g, 83%) as a colorless, viscous oil: $[\alpha]_D$ −46.6° (*c* 1, $CHCl_3$); TLC R_f = 0.32 (40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 4H, *J* = 8 Hz), 7.16 (d, 4H, *J* = 7.9 Hz), 3.78 (m, 2H), 3.75 (s, 6H), 3.73 (d, 2H, *J* = 13 Hz), 3.25 (d, 2H, *J* = 13.5 Hz), 2.94 (q, 1H, *J* = 5.8 Hz), 1.76 (bs, 1H, −*OH*), 0.94 (d, 3H, *J* = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (2C), 131.7 (2C), 130.5 (4C), 114.3 (4C), 65.4, 62.9, 55.7, 55.6, 54.2, 52.4, 9.0; HRMS calcd for $C_{19}H_{25}NO_3$ 315.411 43 $(M)^+$, found 315.418 12.

(2*R*)-2-[Bis(4-bromobenzyl)]aminopropane-1-ol (5c). From D-alanine methyl ester (10 g, 71.0 mmol), **5c** was obtained in two steps (22.5 g, 79%) as a colorless, viscous oil: $[\alpha]_D$ −20.6° (*c* 3, $CHCl_3$); TLC R_f = 0.36 (40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, 2H, *J* = 8.0 Hz), 7.18 (m, 4H), 7.09 (d, 2H, *J* = 7.8 Hz), 3.83 (m, 1H), 3.77 (d, 2H, *J* = 16.8 Hz), 3.42 (t, 1H, *J* = 10.3 Hz), 3.29 (d, 2H, *J* = 17.0 Hz), 2.89 (m, 1H), 0.95 (d, 3H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (2C), 131.0 (4C), 131.1 (4C), 127.8 (2C), 63.2, 54.9, 54.7, 52.8, 9.1; LRMS (FAB, NBA, *m*/*z*, %) 412 (50) $(M - H^+)$, 382 (45), 207 (35), 169 (100), 147 (80).

Swern Oxidation of (5a). To a solution of oxalyl chloride (9.0 mL, 100 mmol, 2.0 equiv) in dry dichloromethane (80 mL) was added DMSO (14.7 mL, 200 mmol, 4.0 equiv) at −78 °C. After 5 min of strirring, the α-*N*,*N*-dibenzylamino alcohol **5a** (50 mmol, 12.5 g) diluted in dry dichloromethane (30 mL) was added dropwise. The mixture was stirred for 30 min at −78 °C, and then triethylamine (57 mL, 400 mmol, 8.0 equiv) was added and the mixture was warmed to room temperature for 30 min. Water (30 mL) was added, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic layers were sequentially washed with 1% HCl solution, water, saturated $NaHCO_3$ solution, and brine and dried over Na_2SO_4. Evaporation of solvent give the desired α-*N*,*N*-dibenzylamino aldehyde, which was used immediately in the next reaction.

(13*R*)-13-Methyl-7,12-dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocine (6a). To a suspension of $AlCl_3$ (26.2 g, 200 mmol, 4.0 equiv) in dry dichloromethane (120 mL) at 0 °C was added via cannula the crude aldehyde obtained from the corresponding alcohol (40 mmol, 1.0 equiv) in dry dichloromethane (40 mL). The mixture was stirred for 1 h at 0 °C. The red reaction mixture was diluted with dichloromethane (50 mL) and quenched with saturated aqueous $NaHCO_3$. After the pH became basic (pH 8), the layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% MeOH/EtOAc as the eluent system to give the desired azocine **6a** (9.2 g, 78%) as a white solid: mp 100−101 °C; $[\alpha]_D$ −37.7° (*c* 1.0, $CHCl_3$); TLC R_f = 0.50 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 2H), 7.08 (m, 2H), 6.98 (m, 2H), 4.64 (d, 1H, *J* = 17.7 Hz), 4.54 (d, 1H, *J* = 18.4 Hz), 4.02 (d, 1H, *J* = 17.8 Hz), 3.89 (d, 1H, *J* = 18.0 Hz), 3.64 (bs, 1H), 3.53 (dq, 1H, *J* = 1.6, 6.8 Hz), 1.22 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.2, 133.7, 133.4, 128.3, 127.5, 126.2, 126.1, 126.0, 125.9, 125.8, 125.6, 59.7, 52.4, 52.1, 41.6, 17.5; HRMS calcd for $C_{17}H_{18}N$ 236.143 92 $(M)^+$, found 236.142 90.

(13*R*)-13-Methyl-(2,10-bismethoxy)-7,12-dihydro-5*H*-6,-12-methanodibenzo[*c*,*f*]azocine (6b). By use of the above procedure, **5b** (12.6 g) was subjected to Swern oxidation and Friedel−Crafts cyclization to afford **6b** (4.1 g, 35%) as a white solid: mp 146−147 °C; $[\alpha]_D$ −34.1° (*c* 1.0, $CHCl_3$); TLC R_f = 0.32 (20% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (t, 2H, *J* = 6.8 Hz), 6.71 (d, 2H, *J* = 8.0 Hz), 6.59 (d, 2H, *J* = 7.5 Hz), 4.51 (d, 1H, *J* = 18.0 Hz), 4.46 (d, 1H, *J* = 18.3 Hz), 3.94 (d, 1H, *J* = 17.9 Hz), 3.71 (d, 1H, *J* = 18.0 Hz), 3.69 (s, 3H), 3.68 (s, 3H), 3.48 (s, 1H), 3.46 (m, 1H), 1.12 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 158.3, 142.7, 139.4, 127.4, 127.1, 125.6, 125.3, 113.9, 113.2, 112.4, 112.2, 59.5, 55.7, 55.6, 52.6, 52.2, 42.7, 17.8; HRMS calcd for $C_{19}H_{21}NO_2$ 295.380 42 $(M)^+$, found 295.315 77.

(13*R*)-13-Methyl-(2,10-bisbromo)-7,12-dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocine (6c). By use of the above procedure, **5c** (18.1 g) was subjected to Swern oxidation and Friedel−Crafts cyclization to afford **6c** (12.97 g, 74%) as a white solid: mp 196−197 °C; $[\alpha]_D$ −82.3° (*c* 1.0, $CHCl_3$); TLC R_f = 0.32 (5% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.32 (s, 1H), 7.24 (dd, 2H, *J* = 6.0, 8.0 Hz), 7.21 (dd, 2H, *J* = 5.7, 8.0 Hz), 4.53 (d, 1H, *J* = 18 Hz), 4.39 (d, 1H, *J* = 18.5 Hz), 3.94 (d, 1H, *J* = 17.6 Hz), 3.76 (d, 1H, *J* = 18.3 Hz), 3.48 (s, 1H), 3.43 (dq, 1H, *J* = 6.8, 2 Hz), 1.16 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 139.7, 132.6, 132.3, 130.9, 130.2, 129.3, 129.2, 127.8, 127.4, 119.6, 119.5, 59.1, 51.9, 51.5, 41.0, 17.3; HRMS calcd for $C_{17}H_{15}Br_2N$ 392.120 33 $(M - H)^+$, found 392.195 61.

(5*S*,6*R*,12*R*)-*N*-Methyl-6-methylisopavine (7a). To a solution of **6a** (0.95 g, 4.0 mmol, 1.0 equiv) in dry acetone (5 mL) was added iodomethane (0.75 mL, 12.0 mmol, 3.0 equiv) at room temperature. The mixture was refluxed with stirring for 1 h. Evaporation of solvent and an excess of iodomethane gave the desired quaternary salt, which was diluted with dry 1,4-dioxane (10 mL), and potassium *tert*-butoxide (700 mg, 6.0 mmol, 1.5 equiv) was added. The mixture was warmed to 80 °C for 3 h. After the mixture was diluted with water, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography using 5−10% MeOH/EtOAc as an eluent to give **7a** (0.84 g, 85%) as a white solid: mp 82−83 °C; TLC R_f = 0.5 (5% MeOH in EtOAc); $[\alpha]_D$ +149.8° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.08 (m, 8H), 4.10 (t, 1H, *J* = 3.3 Hz), 3.80 (dd, 1H, *J* = 3.5, 17.8 Hz), 3.58 (s, 1H), 3.21 (q, 1H, *J* = 6.5 Hz), 2.94 (dd, 1H, *J* = 3.0, 18.0 Hz), 2.68 (s, 3H), 1.15 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.6, 138.9, 134.6, 131.5, 127.5, 127.3, 126.4, 126.3, 126.2, 125.6, 124.8, 62.7, 61.5, 54.2, 40.3, 31.7, 22.8; HRMS calcd for $C_{18}H_{19}N$ 249.151 75 (M^+), found 249.150 62.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bismethoxy)-6-methylisopavine (7b). By use of the same procedure, **6b** (1.24 g) was subjected to Stevens rearrangement to give **7b** (820 mg, 70%) as a white solid: mp 72−73 °C; $[\alpha]_D$ +136° (*c* 1.0, $CHCl_3$); TLC R_f = 0.4 (20% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 1H, *J* = 8.0 Hz), 6.91 (d, 1H, *J* = 7.8 Hz), 6.88−6.70 (m, 4H), 4.16 (t, 1H, *J* = 3 Hz), 3.71 (s, 1H), 3.70 (s, 3H), 3.62 (dd, 1H, *J* = 3.0, 17.5 Hz), 3.47 (s, 1H), 3.29 (q, 1H, *J* = 6.3 Hz), 2.89 (dd, 1H, *J* = 3.0, 18 Hz), 2.62 (s, 3H), 1.12 (d, 3H, *J* = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 157.5, 143.5, 139.2, 132.0, 130.3, 126.5, 125.4, 112.9, 112.6, 112.1, 111.6,

63.8, 61.3, 55.2, 53.8, 40.3, 30.7, 21.8; HRMS calcd for $C_{20}H_{23}NO_2$ 309.467 51 (M^+), found 309.417 37.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bisbromo)-6-methylisopavine (7c). By use of the same procedure, **6c** (790 mg) was subjected to Stevens rearrangement to give **7c** (570 mg, 72%) as an amorphous solid: mp 138−140 °C; $[\alpha]_D$ +111.7° (*c* 1.0, $CHCl_3$); TLC R_f = 0.34 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37(m, 4H), 7.02 (d, 1H, *J* = 7.5 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 4.02 (t, 1H, *J* = 3 Hz), 3.64 (dd, 1H, *J* = 3.0, 17.6 Hz), 3.47 (s, 1H), 3.12 (q, 1H, *J* = 6.4 Hz), 2.82 (dd, 1H, *J* = 3.3 Hz, 18.0 Hz), 2.60 (s, 3H), 1.09 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 140.3, 139.1, 133.6, 132.8, 130.2, 129.5, 129.4, 126.5, 120.7, 119.2, 62.1, 60.7, 53.2, 39.9, 31.2, 22.6; LRMS (FAB, NBA, *m*/*z*, %) 408 (M + H^+) (60), 328 (30), 236 (35), 154 (20), 136 (25); HRMS calcd for $C_{18}H_{17}Br_2N$ 407.147 02 (M^+), found 407.198 40.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl-6-methylisopavine (8a). To a solution of **6a** (200 mg, 0.85 mmol, 1.0 equiv) and *n*-BuN_4I (36 mg, 0.1 mmol) in dry acetone (2 mL) was added cyclopropylmethyl bromide (0.30 mL, 3.0 mmol, 4.0 equiv) at room temperature. The mixture was refluxed with stirring for 1 h. Evaporation of solvent and an excess of the bromide gave the desired quaternary salt, which was diluted with dry 1,4-dioxane (10 mL), and potassium *tert*-butoxide (230 mg, 2.0 mmol, 2.5 equiv) was added. The mixture was warmed to 80 °C for 6 h. After the mixture was diluted with water, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography using 50−80% EtOAc/hexane as the eluent to give the desired isopavine **8a** (219 mg, 89%) as a viscous oil: $[\alpha]_D$ +154.7° (*c* 1.0, $CHCl_3$); TLC R_f = 0.7 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12−7.38 (m, 10H), 4.51 (t, 1H, *J* = 3.6 Hz), 3.75 (dd, 1H, *J* = 3.3, 18.0 Hz), 3.61 (s, 1H), 3.32 (q, 1H, *J* = 6.5 Hz), 2.96 (dd, 1H, *J* = 3.0, 18.0 Hz), 2.82 (dd, 1H, *J* = 6.0, 14.0 Hz), 2.62 (dd, 1H, *J* = 6.3, 13.8 Hz), 1.18 (d, 3H, *J* = 6.0 Hz), 1.08 (m, 1H), 0.63 (m, 1H), 0.59 (m, 1H), 0.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.3, 139.4, 135.0, 131.1, 127.7, 127.1, 126.6, 126.4, 126.3, 125.7, 125.0, 61.9, 58.5, 58.1, 54.4, 32.8, 24.1, 10.7, 4.5, 3.7; HRMS calcd for $C_{21}H_{23}N$ 289.419 40 (M^+), found 289.418 43.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bismethoxy)-6-methylisopavine (8b). By use of the same procedure, **6b** (320 mg) was subjected to Stevens rearrangement to give **8b** (256 mg, 84%) as a yellow oil: $[\alpha]_D$ +54.7° (*c* 1.0, $CHCl_3$); TLC R_f = 0.5 (20% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, 1H, *J* = 8.0 Hz), 6.88 (d, 1H, *J* = 8.0 Hz), 6.64 (m, 4H), 4.43 (t, 1H, *J* = 3.3 Hz), 3.75 (s, 3H), 3.74 (s, 3H), 3.52 (dd, 1H, *J* = 3.0, 18.0 Hz), 3.47 (s, 1H), 3.32 (q, 1H, *J* = 6.5 Hz), 2.79 (dd, 1H, *J* = 3.3, 17.8 Hz), 2.69 (dd, 1H, *J* = 3.3, 18.0 Hz), 2.53 (dd, 1H, *J* = 6.0, 13.5 Hz), 1.13 (d, 3H, *J* = 6 Hz), 0.96 (m, 1H), 0.53 (m, 2H), 0.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.3, 143.9, 140.1, 132.0, 126.6, 125.9, 114.2, 112.9, 112.6, 111.8, 111.3, 61.6, 58.3, 57.8, 55.1, 54.7, 32.2, 23.9, 10.5, 4.2, 4.0, 3.6; HRMS calcd for $C_{23}H_{27}NO_2$ 349.600 83 (M^+), found 349.602 30.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bisbromo)-6-methylisopavine (8c). By use of the same procedure, **6c** (600 mg) was subjected to Stevens rearrangement to give **8c** (540 mg, 81%) as a yellow oil: $[\alpha]_D$ +110.4° (*c* 1.0, $CHCl_3$); TLC R_f = 0.9 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−6.89 (m, 6H), 4.42 (t, 1H, *J* = 3.3 Hz), 3.55 (dd, 1H, *J* = 3.3, 18.0 Hz), 3.48 (s, 1H), 3.24 (q, 1H, *J* = 6. Hz), 2.80 (dd, 1H, *J* = 3.3, 17.8 Hz), 2.71 (m, 1H), 2.62 (m, 1H), 1.13 (d, 3H, *J* = 6.4 Hz), 0.89 (m, 1H), 0.62 (m, 1H), 0.56 (m, 1H), 0.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 140.7, 132.8, 130.4, 129.7, 129.5, 129.4, 129.3, 127.7, 126.5, 120.6, 119.2, 61.5, 57.8, 53.5, 32.2, 23.8, 10.4, 4.4 (2C), 3.5; HRMS calcd for $C_{21}H_{21}Br_2N$ 448.211 63 (M + H^+), found 448.201 08.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bishydroxy)-6-methylisopavine (9). A solution of **7b** (165 mg, 0.5 mmol) in 48% aqueous HBr (3 mL) was heated to reflux at 120 °C for 3−4 h. The resulting dark-brown solution was evaporated to dryness and diluted with 10% $NaHCO_3$, and the aqueous phase was continuously extracted with dichloromethane (5 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered, and condensed in vacuo. The crude product was purified by flash column chromatography (eluent: MeOH/$CHCl_3$, 1:4) to give the bis-phenol **9** (106 mg, 76%) as a white solid: mp 195−196 °C; $[\alpha]_D$ +93.6° (*c* 1.0, MeOH); TLC R_f = 0.30 (30% MeOH in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 7.12 (d, 1H, *J* = 8.5 Hz), 6.81 (d, 1H, *J* = 7.9 Hz), 6.76−6.71 (m, 4H), 4.26 (bs, 1H), 3.60 (dd, 1H, *J* = 3.0, 18 Hz), 3.49 (s, 1H), 3.42 (q, 1H, *J* = 6.3 Hz), 3.24 (bs, 2H), 2.90 (dd, 1H, *J* = 3.3, 18 Hz), 2.74 (s, 3H), 1.20 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 158.2, 155.7, 143.5, 139.6, 132.2, 127.3, 126.8, 123.2, 114.3, 114.2, 114.0, 113.9, 65.7, 62.5, 52.6, 39.5, 30.6, 19.9; HRMS calcd for $C_{18}H_{19}NO_2$ 281.353 62 (M^+), found 281.314 13.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bishydroxy)-6-methylisopavine (10). By use of the same procedure, **8c** (106 mg) was refluxed in 3 mL of aqueous HBr for 3 h to give **10** (52 mg, 61%) as a pale-yellow solid: mp 160−162 °C; $[\alpha]_D$ −20.6° (*c* 2.0, MeOH); TLC R_f = 0.4 (30% MeOH in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 7.09 (d, 1H, *J* = 8.0 Hz), 6.87 (d, 1H, *J* = 7.5 Hz), 6.85−6.46 (m, 4H), 4.34 (bs, 1H), 3.40 (dd, 1H, *J* = 3.0, 18 Hz), 3.29 (s, 1H), 3.24 (m, 1H), 2.70 (dd, 1H, *J* = 3.0, 18 Hz), 2.68 (m, 2H), 1.10 (d, 3H, *J* = 6.5 Hz), 0.89 (m, 1H), 0.54 (m, 2H), 0.21 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.3, 155.4, 143.9, 140.6, 132.1, 126.8, 124.5, 114.2, 113.9, 113.8, 113.3, 63.5, 59.2, 58.9, 53.9, 31.7, 22.2, 8.9, 3.9, 3.6; HRMS calcd for $C_{21}H_{23}NO_2$ 321.418 20 (M^+), found 321.417 34.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bisacetoxy)-6-methylisopavine (11). To a mixture of **9** (28 mg, 0.1 mmol) and DMAP (2 mg) in CH_2Cl_2 (5 mL) was added Et_3N (0.070 mL, 0.5 mmol) and pyridine (1 mL). The reaction mixture was cooled to 0 °C and treated with acetic anhydride (0.050 mL, 0.5 mmol). The resulting solution was warmed to room temperature for 12 h. After completion, the reaction mixture was diluted with dichloromethane (20 mL), washed with water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude diacetate was purified by flash column chromatography using MeOH/EtOAc (1:4) as the eluent to give the pure diacetate **11** (31.7 mg, 89%) as a colorless oil: $[\alpha]_D$ +114.8° (*c* 1.0, $CHCl_3$); TLC R_f = 0.70 (30% MeOH in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1H, *J* = 8.0 Hz), 6.98 (d, 1H, *J* = 7.8 Hz), 6.93−6.76 (m, 4H), 4.07 (t, 1H, *J* = 3 Hz), 3.66 (dd, 1H, *J* = 3.0, 18 Hz), 3.42 (s, 1H), 3.14 (q, 1H, *J* = 6.3 Hz), 2.85 (dd, 1H, *J* = 3.3, 17.8 Hz), 2.58 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.06 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8, 150.2, 148.7, 144.7, 140.1, 138.2, 132.7, 132.6, 126.2, 120.7, 120.2, 120.0, 119.9, 62.6, 61.3, 54.1, 40.4, 31.7, 23.0, 21.6, 21.5; HRMS calcd for $C_{22}H_{23}NO_4$ 365.428 04 (M^+), found 365.416 14.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bisacetoxy)-6-methylisopavine (12). By use of the above procedure, **10** (20 mg) was subjected to acetylation to give **12** (23 mg, 79%) as a viscous oil: $[\alpha]_D$ +85.2° (*c* 2.0, $CHCl_3$); TLC R_f = 0.8 (20% MeOH in EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 7.18 (d, 1H, *J* = 8.0 Hz), 6.89 (d, 1H, *J* = 7.5 Hz), 6.86−6.75 (m, 4H), 4.38 (bs, 1H), 3.57 (dd, 1H, *J* = 3.2, 18 Hz), 3.43 (s, 1H), 3.20 (q, 1H, *J* = 6.3 Hz), 2.83 (dd, 1H, *J* = 3.3, 18.2 Hz), 2.64 (dd, 1H, *J* = 6.3, 14.5 Hz), 2.58 (dd, 1H, *J* = 6.0, 13.2 Hz), 2.24 (s, 3H), 2.21 (s, 3H), 1.08 (d, 3H, *J* = 6.5 Hz), 0.89 (m, 1H), 0.53 (m, 2H), 0.13 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.0, 169.8, 150.2, 148.7, 144.2, 140.6, 132.9, 132.6, 126.5, 120.9, 120.2, 120.1, 119.9, 61.9, 58.4, 58.1, 54.4, 32.6, 30.1, 24.3, 21.5, 10.9, 4.9, 4.0; HRMS calcd for $C_{25}H_{27}NO_4$ 405.492 63 (M^+), found 405.491 43.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bisbenzylamino)-6-methylisopavine (13). Into a flame-dried flask were placed sodium *tert*-butoxide (15 mg, 0.15 mmol), tris(dibenzylidene acetone)-dipalladium (3 mg, 0.0025 mmol, 5 mol %), and BINAP (4.6 mg, 0.0075 mmol) in toluene (2 mL). To the above pink solution was added isopavine bis-bromide **7b** (41 mg, 0.1 mmol) in toluene (2 mL) followed by benzylamine (0.032 mL, 0.3 mmol), which was introduced dropwise. The resulting solution was

stirred at 80 °C for 24−36 h. The reaction mixture was diluted with water and extracted with dicholoromethane, and the combined organic layers were washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude bis-amine was purified by flash column chromatography (MeOH/EtOAc, 1:4) to give isopavine **13** (40 mg, 87%) as yellow viscous oil: $[\alpha]_D$ −10.4° (*c* 4.0, $CHCl_3$); TLC R_f = 0.30 (10% MeOH in EtOAC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.04 (m, 9H), 6.98 (d, 2H, J = 8.0 Hz), 6.80 (d, 2H, J = 7.8 Hz), 6.39 (m, 3H), 4.24 (d, 4H, J = 4.5 Hz), 3.98 (bs, 1H), 3.81 (bs, 2H, −*NH*), 3.62 (dd, 1H, J = 3.3, 18.2 Hz), 3.27 (s, 1H), 3.06 (q, 1H, J = 6.0 Hz), 2.72 (dd, 1H, J = 3.0, 17.8 Hz), 2.60 (s, 3H), 1.09 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 146.6, 139.9, 139.8, 132.5, 129.1 (3C), 129.0 (3C), 128.1 (3C), 128.0 (3C), 127.7, 127.6, 126.4, 112.2, 111.7, 110.9, 63.8, 61.6, 54.9, 48.9 (2C), 40.9, 31.9, 22.8; LRMS (FAB, NBA, *m*/*z*, %) 460.3 (60) (M + H$^+$), 355 (25), 263 950), 154 (100), 137 (80); HRMS calcd for $C_{32}H_{33}N_3$ 459.632 81 (M)$^+$, found 459.632 21.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bisanilino)-6-methylisopavine (14). By use of the above procedure, **7b** (43 mg) was subjected to amination to give **14** (30 mg, 66%) as a pink solid: mp 79−80 °C; $[\alpha]_D$ −36.0° (*c* 1.0, $CHCl_3$); TLC R_f = 0.34 (10% MeOH in EtOAC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−6.78 (m, 16H), 3.97 (bs, 1H), 3.36 (dd, 1H, J = 3.3, 18.0 Hz), 3.32 (s, 1H), 3.09 (q, 1H, J = 6.5 Hz), 2.82 (dd, 1H, J = 3.0, 18.0 Hz), 2.59 (s, 3H), 2.01 (bs, 2H, −*NH*), 1.08 (d, 3H, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 143.9, 143.8, 142.4, 132.6, 129.8 (3C), 129.7 (3C), 127.9, 126.7, 126.3, 121.0, 120.9, 117.8 (2C), 117.7 (2C), 117.4, 117.1, 116.8, 116.5, 63.1, 61.6, 54.7, 39.9, 31.8, 23.2; LRMS (FAB, NBA, *m*/*z*, %) 432 (25) (M + H$^+$), 341 (30), 325 (15), 249 (45), 219 (80), 147 (100); HRMS calcd for $C_{30}H_{29}N_3$ 431.282 25 (M)$^+$, found 431.282 02.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bis-*N*-methylpiperazineamino)-6-methylisopavine (15). By use of the above procedure, **7b** (40 mg) was subjected to amination to give **15** (31 mg, 69%) as a yellow solid: mp 72−74 °C; $[\alpha]_D$ −11.9° (*c* 1.4, $CHCl_3$); TLC R_f = 0.23 (10% MeOH in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65−7.08 (m, 6H), 4.01 (t, 1H, J = 3.3 Hz), 3.66 (dd, 1H, J = 3.3, 18.0 Hz), 3.43 (s, 1H), 3.13 (m, 9H), 2.89 (dd, 1H, J = 3.0, 18.0 Hz), 2.59 (s, 6H), 2.54 (m, 8H), 2.31 (s, 3H), 1.09 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 144.0, 139.9, 135.3, 132.3, 131.6, 128.1, 126.8, 126.2, 126.1, 115.5, 114.3, 63.6, 61.3, 55.5 (4C), 54.9 (2C), 49.7 (2C), 46.4, 40.8, 32.7, 22.9; LRMS (FAB, NBA, *m*/*z*, %) 443 (40) (M − H_2^+), 385 (15), 281 (25), 207 (50), 191 (40), 147 (100); HRMS calcd for $C_{30}H_{29}N_3$ 445.6496 (M$^+$), found 445.6491.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bismorpholineamino)-6-methylisopavine (16). By use of the above procedure, **7b** (42 mg) was subjected to amination to afford **16** (46 mg, 99%) as a yellow solid: mp 102−104 °C; $[\alpha]_D$ +59.6° (*c* 4.0, $CHCl_3$); TLC R_f = 0.53 (10% MeOH in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06−6.60 (m, 6H), 3.97 (bs, 1H), 3.79 (d, 8H, J = 4.5 Hz), 3.59 (dd, 1H, J = 3.3, 18.0 Hz), 3.36 (s, 1H), 3.06 (d, 8H, J = 4.9 Hz), 2.79 (dd, 1H, J = 3.0, 18.0 Hz), 2.57 (s, 3H), 1.05 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 149.6, 144.8, 139.9, 132.4 (2C), 126.7, 126.0, 115.4, 115.2, 114.4, 114.0, 67.4 (4C), 63.3, 61.3, 55.5, 50.3 (2C), 50.1 (2C), 40.8, 31.7, 23.2; LRMS (FAB, NBA, *m*/*z*, %) 420 (50) (M + H$^+$), 335 (35), 243 (65), 154 (90), 136 (100); HRMS calcd for $C_{26}H_{33}N_3O_2$ 419.565 62 (M$^+$), found 419.565 59.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bisbenzylamino)-6-methylisopavine (17). By use of the above procedure, **7b** (41 mg) was subjected to amination to give **17** (33 mg, 66%) as a viscous oil: $[\alpha]_D$ +138° (*c* 1.0, $CHCl_3$); TLC R_f = 0.50 (10% MeOH in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−6.96 (m, 11H), 6.75 (d, 2H, J = 8.0 Hz), 6.36 (m, 3H), 4.24 (bs, 4H), 3.79 (bs, 1H), 3.46 (dd, 1H, J = 3.0, 18.0 Hz), 3.21 (s, 1H), 3.14 (q, 1H, J = 4.8 Hz), 2.53 (dd, 1H, J = 3.0, 18.5 Hz), 2.51 (m, 1H), 2.49 (m, 1H), 1.84 (bs, 2H, −*NH*), 1.09 (d, 3H, J = 6.0 Hz), 0.86 (m, 1H), 0.51 (m, 2H), 0.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 146.5, 140.0, 132.9, 132.8, 132.5, 132.4, 129.0 (2C), 128.9 (2C), 128.4, 128.2, 128.1 (2C), 128.0 (2C), 127.6 127.5, 126.2, 112.4, 112.1, 111.6, 110.8, 62.3, 59.0, 58.5, 55.5, 49.0 (2C), 32.8, 24.6, 11.1, 4.7, 4.2; LRMS (FAB, NBA, *m*/*z*, %) 500 (100) (M + H$^+$), 339 (20), 303 (85), 201 (50), 154 (80); HRMS calcd for $C_{35}H_{37}N_3$ 500.697 45 (M + H$^+$), found 500.697 40.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bisanilino)-6-methylisopavine (18). By use of the above procedure, **7b** (41 mg) was subjected to amination to give **18** (20 mg, 48%) as a viscous oil: $[\alpha]_D$ −34.7° (*c* 1.0, $CHCl_3$); TLC R_f = 0.30 (10% MeOH in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−6.68 (m, 16H), 4.30 (bs, 1H), 3.60 (dd, 1H, J = 3.3, 18.0 Hz), 3.28 (s, 1H), 3.18 (q, 1H, J = 6.0 Hz), 2.86 (dd, 1H, J = 3.0, 18.0 Hz), 2.68 (m, 1H), 2.54 (m, 1H), 1.96 (bs, 2H, −*NH*), 1.12 (d, 3H, J = 6.5 Hz), 0.86 (m, 1H), 0.56 (m, 2H), 0.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 143.0, 141.3, 133.3 (2C), 131.6, 130.9, 130.8, 130.3, 129.9 (2C), 129.8, 129.6, 128.8, 128.2, 127.7, 127.6, 127.4, 127.3, 127.0, 126.4, 125.6, 121.2, 119.7, 61.8, 58.6, 54.0, 32.8, 30.1, 24.4, 10.9, 4.9, 4.0; LRMS (FAB, NBA, *m*/*z*, %) 472 (25) (M + H$^+$), 381 (75), 289 (35), 147 (40); HRMS calcd for $C_{33}H_{33}N_2$ 471.990 12 (M)$^+$, found 471.989 41.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bis-*N*-methylpiperazineamino)-6-methylisopavine (19). By use of the above procedure, **7b** (41 mg) was subjected to amination to give **19** (30 mg, 61%) as a yellow viscous oil: $[\alpha]_D$ +7.2° (*c* 1.0, $CHCl_3$); TLC R_f = 0.58 (10% MeOH in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−6.68 (m, 6H), 4.41 (bs, 1H), 3.52 (dd, 1H, J = 3.0, 18.0 Hz), 3.49 (s, 1H), 3.23 (q, 1H, J = 6.5 Hz), 3.12 (bs,-8H), 2.71 (dd, 1H, J = 3.0, 18.0 Hz), 2.68 (m, 2H), 2.49 (bs, 8H), 2.36 (s, 6H), 1.14 (d, 3H, J = 6.0 Hz), 0.99 (m, 1H), 0.59 (m, 2H), 0.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 143.5, 138.9, 131.7, 128.3, 127.1, 126.8, 126.5, 126.4, 125.0, 115.3, 114.2, 61.9, 58.7, 58.1, 54.9 (4C), 54.6 (2C), 49.0 (2C), 45.8 (2C), 31.7, 23.7, 10.3, 3.7 (2C), 3.5; LRMS (FAB, NBA, *m*/*z*, %) 466 (15) (M − NH_3^+), 388 (100), 290 (25), 198 (50), 154 (50); HRMS calcd for $C_{31}H_{43}N_5$ 485.714 23 (M)$^+$, found 485.714 12.

(5*S*,6*R*,12*R*)-6-Methylisopavine (20). To a solution of **7a** (410 mg, 1.6 mmol) in MeOH (10 mL) was added Pd/C (1.0 g, 10%) at 0 °C, and the reaction mixture was stirred at room temperature in open-air atmosphere for 24 h.[63] The mixture was filtered through Celite and washed with 30% MeOH in EtOAc. The combined filtrates were dried over Na_2SO_4 and concentrated in vacuo. The crude product was flash-chromatographed on silica gel to give pure amine **20** (298 mg, 84%) as a colorless oil: $[\alpha]_D$ +99.3° (*c* 1.0, $CHCl_3$); TLC R_f = 0.32 (10% MeOH in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.01 (m, 8H), 4.28 (t, 1H, J = 3.6 Hz), 3.91 (q, 1H, J = 6.5 Hz), 3.49 (dd, 1H, J = 3.0, 18.0 Hz), 3.46 (bs, 1H, −*NH*), 3.33 (s, 1H), 3.20 (dd, 1H, J = 3.7 Hz, 18.0 Hz), 1.05 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 140.0, 139.8, 135.3, 131.7, 128.2, 127.8, 127.5, 127.3, 127.1, 126.3, 125.1, 56.2, 55.3, 53.3, 40.0, 24.2; LRMS (FAB, NBA, *m*/*z*, %) 236 (100) (M)$^+$, 219 (25), 192 (30), 91 (10); HRMS calcd for $C_{17}H_{17}N$ 236.328 02 (M)$^+$, found 236.319 60.

(5*S*,6*R*,12*R*)-*N*-Allyl-6-methylisopavine (21). A mixture of **20** (25 mg, 0.1 mmol), Na_2CO_3 (106 mg, 1 mmol), and *n*-BuN_4I (36 mg, 0.01 mmol) in EtOH (3 mL) was treated with allyl bromide (0.045 mL, 0.5 mmol), and the resulting solution was heated to reflux for 12 h. The solvent was evaporated, and the crude product was diluted with ether (20 mL) and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The pure product was obtained by flash chromatography to give *N*-allylisopavine **21** (27 mg, 98%) as a highly viscous oil: $[\alpha]_D$ +148.8° (*c* 2.6, $CHCl_3$); TLC R_f = 0.70 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.02 (m, 8H), 5.97 (m, 1H), 5.12 (dd, 2H, J = 9.0, 34 Hz), 4.16 (t, 1H, J = 3.3 Hz), 3.67 (dd, 1H, J = 3.0, 18.0 Hz), 3.53 (s, 1H), 3.44 (d, 2H, J = 6.5 Hz), 3.26 (q, 1H, J = 6.0 Hz), 2.86 (dd, 1H, J = 3.0, 18.0 Hz), 1.04 (d. 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 140.7, 139.8, 135.4, 131.6, 128.2, 127.7, 127.1, 127.0, 126.8, 126.3, 125.4, 117.6, 62.2, 58.2, 56.8, 54.7, 33.0, 24.0; LRMS (FAB, NBA, *m*/*z*, %) 276.2 (100) (M + H$^+$), 260 (30), 236 (15), 219 (30), 192.2 (75), 91 (20); HRMS calcd for $C_{20}H_{21}N$ 275.392 63 (M)$^+$, found 275.316 78.

(5*S*,6*R*,12*R*)-*N*-Benzyl-6-methylisopavine (22). A mixture of **20** (25 mg, 0.1 mmol), Na_2CO_3 (106 mg, 1.0 mmol), and *n*-BuN_4I (36 mg, 0.01 mmol) in EtOH (3 mL) was treated with benzyl bromide (0.035 mL, 0.3 mmol), and the resulting solution was refluxed for 12 h. The solvent was evaporated, and the crude product was diluted with ether (20 mL) and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The pure product was obtained by flash chromatography to give **22** (36.8 mg, 99%) as a white solid: mp 165−166 °C; $[\alpha]_D$ +111° (*c* 1.0, $CHCl_3$); TLC R_f = 0.80 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.03 (m, 13H), 3.97 (bs, 3H), 3.75 (dd, 1H, J = 3.0, 18 Hz), 3.60 (s, 1H), 3.42 (q, 1H, 6.0 Hz), 2.83 (dd, 1H, J = 2.9, 18.0 Hz), 1.08 (d, 3H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 139.9, 135.6, 131.7, 129.2, 128.9, 128.8, 128.2, 128.1, 127.9, 127.5, 127.4, 127.2, 127.0, 126.8, 126.3, 125.1, 73.2, 62.5, 54.9, 32.9, 24.0, 15.7; LRMS (FAB, NBA, *m*/*z*, %) 326 (100) (M + H$^+$), 234 (30), 192 (25), 154 (45), 91 60); HRMS calcd for $C_{24}H_{23}N$ 325.452 41 (M)$^+$, found 325.418 23.

(5*S*,6*R*,12*R*)-*N*-Acetyl-6-methylisopavine (23). To a mixture of isopavine **20** (30 mg, 0.14 mmol) and DMAP (2 mg) in CH_2Cl_2 (5 mL) was added Et_3N (0.10 mL, 0.75 mmol) and pyridine (0.5 mL). The reaction mixture was cooled to 0 °C and treated with acetic anhydride (0.050 mL, 0.5 mmol). The resulting solution was warmed to room temperature for 12 h. After completion, the mixture was diluted with dichloromethane (20 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude acetate was purified by flash column chromatography using MeOH/EtOAc (1:4) as the eluent to give the pure diacetate **23** (37.7 mg, 97%) as an amorphous solid: mp 63−64 °C; $[\alpha]_D$ +198.7° (*c* 8.0, $CHCl_3$); TLC R_f = 0.70 (10% MeOH in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 7.27−6.97 (m, 8H), 6.01 (t, 1H, J = 2.5 Hz), 4.06 (q, 1H, J = 3.0 Hz), 4.02 (dd, 1H, J = 3.0, 12.0 Hz), 3.51 (s, 1H), 2.83 (d, 1H, J = 12 Hz), 1.81 (s, 3H), 0.78 (d, 3H, J = 4.8 Hz, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (rotamer B, minor, amide) 7.29−6.99 (m, 8H), 5.13 (q, 1H, J = 3.0 Hz), 4.66 (t, 1H, J = 2.8 Hz), 3.56 (s, 1H), 3.16 (dd, 1H, J = 3.3, 18.0 Hz), 2.71 (d, 1H, J = 12 Hz), 2.01 (s, 3H), 1.28 (d, 3H, J = 4.6 Hz, 33%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 139.3, 137.1, 135.5, 132.1, 129.3, 128.2, 128.0, 127.9, 127.7, 126.9, 126.5, 126.2, 58.1, 56.3, 54.7, 39.8, 22.6, 22.1; LRMS (FAB, NBA, *m*/*z*, %) 278 (100) (M + H$^+$), 234 910), 219 (20), 192 (20), 154 (30), 107 (10); HRMS calcd for $C_{19}H_{19}NO$ 277.365 23 (M$^+$), found 277.314 73.

(2*R*)-2-[Bis-3,4-dimethoxybenzyl)]aminopropane-1-ol (24). By use of the reported procedure,[56] D-alanine methyl ester (from 5 g, 35.0 mmol) was subjected to dimethoxybenzylation and LAH reduction to give **24** (10.8 g, 78%) as a clear viscous oil: $[\alpha]_D$ −29° (*c* 1, $CHCl_3$); TLC R_f = 0.36 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82−6.66 (m, 6H), 3.78 (s, 4H), 3.76 (s, 6H), 3.74 (s, 6H), 3.36 (m, 2H), 2.92 (m, 1H), 0.91 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 148.7, 148.5, 147.5, 134.2, 133.8, 132.2, 120.8, 119.6, 112.2, 111.3, 110.7, 65.3, 62.9, 56.2, 53.9, 52.9, 9.2; HRMS calcd for $C_{21}H_{29}NO_5$ 376.463 83 (M + H$^+$), found 376.421 35.

(13*R*)-13-Methyl-(2,10-bismethoxy)-7,12-dihydro-5*H*-6,-12-methanodibenzo[*c*,*f*]azocine (25). The general procedure as described for **6b** was followed. A quantity of **24** (8.3 g) was subjected to Swern oxidation and Friedel−Crafts cyclization to give **25** as a yellow amorphous solid (3.9 g, 48%): mp 94−95 °C; $[\alpha]_D$ −15.5° (*c* 1, $CHCl_3$); TLC R_f = 0.30 (20% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, 2H, J = 10 Hz), 6.34 (d, 2H, J = 3.5 Hz), 4.37 (d, 1H, J = 18.0 Hz), 4.26 (d, 1H, J = 18.0 Hz), 3.74 (d, 1H, J = 17.5 Hz), 3.72 (s, 3H), 3.69 (s, 3H), 3.60 (d, 1H, J = 18.0 Hz), 3.58 (s, 6H), 3.30 q, 1H, J = 6.5 Hz), 3.19 (s, 1H), 1.03 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8 (2C), 147.6, 134.4, 131.0, 125.8, 125.5, 111.6, 110.8, 109.3, 109.1, 59.9, 56.4 (4C), 56.1, 52.8, 52.6, 40.9, 17.6; HRMS calcd for $C_{21}H_{25}NO_4$ 356.432 81 (M + H$^+$), found 356.418 87.

(5*S*,6*R*,12*R*)-*N*-Methyl(3,8-bismethoxy)-6-methylisopavine (26a). Typical procedure described for **7b** was followed. From **25** (525 mg), after Stevens rearrangement, **26a** was obtained as a white solid (417 mg, 76%): mp 122−123 °C; $[\alpha]_D$ +111.0° (*c* 1, $CHCl_3$); TLC R_f = 0.35 (20% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, 2H, J = 4.8 Hz), 6.54 (s, 1H), 6.45 (s, 1H), 3.91 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.52 (dd, 1H, J = 3.0, 18.0 Hz), 3.28 (s, 1H), 3.0 (q, 1H, J = 6.0 Hz), 2.76 (dd, 1H, J = 3.0, 18.0 Hz), 2.51 (s, 3H), 0.99 (d, 3H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.8, 147.7, 146.8, 136.8, 132.8, 132.0, 126.7, 114.6, 111.4, 110.7, 109.7, 63.6, 61.6, 56.3 (3C), 56.2, 53.5, 40.6, 32.0, 23.2; HRMS calcd for $C_{22}H_{27}NO_4$ 370.459 63 (M + H$^+$), found 370.420 53.

(5*S*,6*R*,12*R*)-*N*-Cyclopropylmethyl(3,8-bismethoxy)-6-methylisopavine (26b). Typical procedure as described for **8b** was followed. From **25** (360 mg), after Stevens rearrangement, **26b** was obtained as a viscous oil (345 mg, 87%): $[\alpha]_D$ +114° (*c* 1, $CHCl_3$); TLC R_f = 0.35 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.73 (s, 1H), 6.56 (s, 1H), 6.45 (s, 1H), 4.26 (bs, 1H), 3.80 (s, 3H), 3.79 (s, 6H), 3.69 (s, 3H), 3.52 (dd, 1H, J = 3.3, 18.0 Hz), 3.31 (s, 1H), 3.15 (q, 1H, J = 6.0 Hz), 2.75 (dd, 1H, J = 3.0, 18.0 Hz), 2.64 (dd, 1H, J = 6.0, 14.0 Hz), 2.54 (dd, 1H, J = 6.0, 14.0), 1.04 (d, 3H, J = 6.0 Hz), 0.91 (m, 1H), 0.49 (t, 2H, J = 10.0 Hz), 0.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.8, 147.7, 146.9, 136.4, 132.7, 132.4, 126.9, 114.5, 111.5, 110.8, 109.9, 62.8, 58.9, 58.7, 56.5, 56.4, 56.3, 56.2, 53.8, 32.9, 24.5, 11.2, 4.8, 4.1; LRMS (FAB, NBA, *m*/*z*, %) 410 (100) (M + H$^+$), 339 (45), 258 (80), 154 (90); HRMS calcd for $C_{25}H_{31}NO_4$ 409.524 21 (M)$^+$, found 409.512 87.

Typical Procedure for *N*-*N*-Dibenzyl-(*S*)-2-amino-1,5-pentanediol (27a). A mixture of L-glutamic acid diester (10 g, 41.8 mmol) and $NaHCO_3$ (13.8 g, 167 mmol, 4.0 equiv) suspended in THF/DMSO (100 mL, 4:1) was treated with benzylbromide (9.98 mL, 84 mmol) at room temperature and allowed to reflux for 20 h. After completion, the solid materials were removed by filtration and the resulting filtrate was concentrated and then diluted with EtOAc (80 mL). The organic phase was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo to give the crude *N*,*N*-dibenzylated product as a viscous oil (16.1 g, 99%), which was used in the next step without purification.

To a suspension of lithium aluminum hydride (3.2 g, 84 mmol, 2.0 equiv) in dry THF (80 mL) was added the above crude diester (16.2 g, 41 mmol, 1 equiv) in THF (20 mL) at 0 °C, and the mixture was warmed to room temperature. After 12 h of being stirred, the mixture was cooled to 0 °C. Excess hydride was quenched with EtOAc (3 mL) and then water (3 mL), and a 15% NaOH aqueous solution (3 mL) was slowly added. Finally, water (9 mL) was added and the mixture was filtered and washed with hot EtOAc. The filtrates were concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc 1:1, then neat EtOAc) to give the desired diol **27a** (11.2 g, 90%) as a viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 10H), 3.83 (d, 2H, J = 18.0 Hz), 3.65 (t, 2H, J = 6.5 Hz), 3.51−3.49 (m, 4H), 2.83 (m, 1H), 1.89 (m, 1H), 1.52 (m, 3H), 1.36 (m, 1H). The crude diol **27a** was used in the next step.

(2*S*)-2-[Bis-(4-methoxybenzyl)amino]pentane-1,5-diol (27b). By use of the above procedure, 15.5 g of L-glutamic acid diester was subjected to 4-methoxybenzylation and $LiAlH_4$ reduction to give **27b** as a viscous oil: $[\alpha]_D$ +44.2° (*c* 1, $CHCl_3$); TLC R_f = 0.35 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, 4H, J = 8.5 Hz), 6.85 (d, 4H, J = 8.7 Hz), 3.78 (s, 3H), 3.74 (s, 3H), 3.68 (d, 2H, J = 12.9 Hz), 3.62 (t, 2H, J = 6.5 Hz), 3.45 (m, 2H), 3.37 (d, 2H, J = 13.1 Hz), 2.80 (q, 1H, J = 4.5 Hz), 1.80 (m, 1H), 1.50 (m, 2H), 1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (4C), 130.0 (4C), 113.7 (4C), 62.5, 60.5, 58.3, 55.1 (2C), 52.2 (2C), 30.0, 21.2; LRMS (FAB, NBA, *m*/*z*, %) 360 (20) (M + H$^+$), 328 (25), 281 (15), 207 (45), 190 (45); HRMS calculated for $C_{21}H_{30}NO_4$ (M + H$^+$): 360.217 50, found 360.216 30.

(2*S*)-2-[Bis-(4-bromobenzyl)amino]pentane-1,5-diol(27c). By use of the same procedure, 2.3 g of L-glutamic acid diester was subjected to 4-bromobenzylation and $LiAlH_4$ reduction to

give **27c** (1.34 g, 74%) as a viscous oil: $[\alpha]_D$ +13.8° (*c* 1, $CHCl_3$); TLC R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 4H, *J* = 8.5 Hz), 7.08 (d, 4H, *J* = 8.0 Hz), 3.69 (d, 2H, *J* = 17.5 Hz), 3.58 (t, 2H, *J* = 6.8 Hz), 3.51 (m, 2H), 3.47 (d, 2H, *J* = 16.8 Hz), 2.71 (m, 1H), 1.79 (m, 1H), 1.52 (m, 2H), 1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (2C), 131.5 (4C), 130.4 (4C), 121.0 (2C), 62.3 (2C), 60.8, 58.8, 52.6 (2C), 29.9, 21.4; LRMS (FAB, NBA, *m*/*z*, %) 458 (80) (M + H^+), 426 (100), 169 (95), 136 (25), 91 (15).

(2*S*)-2-[Bis(4-fluorobenzyl)amino]pentane-1,5-diol (27d). By use of the same procedure, 4.8 g of L-glutamic acid diester was subjected to 4-fluorobenzylation and $LiAlH_4$ reduction to give **27d** (1.9 g, 89%) as a viscous oil: $[\alpha]^{20}_D$ +67.0° (*c* 1, $CHCl_3$); TLC R_f = 0.38 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 4H), 6.99 (m, 4H), 3.74 (d, 2H, *J* = 13.3 Hz), 3.63 (t, 2H, *J* = 6.3 Hz), 3.50 (m, 2H), 3.43 (d, 2H, *J* = 13.3 Hz), 2.90 (bs, 1H, −*OH*), 2.78 (m, 1H), 1.83 (m, 1H), 1.52 (m, 3H), 1.32 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 160.8, 158.4, 132.9 (2C), 127.9 (4C); 112.7 (2C), 112.5 (2C), 59.3, 58.5, 56.1, 50.0 (2C), 27.4, 19.7; LRMS (EI, *m*/*z*, %) 336 (100) (M + H^+), 304 (30), 165 (10), 136 (40), 109 (80), 80.9 (15); HRMS calcd for $C_{19}H_{22}NO_2F_2$ (M − H^+) 334.161 87, found 334.162 90.

(4*S*)-2,2-Dimethylpropionic Acid 4-Dibenzylamino-5-hydroxypentyl Ester (28a). To a solution of diol **27a** (11.2 g, 38.0 mmol) Et_3N (5.67 mL, 41.0 mmol, 1.1 equiv) in dichloromethane was treated with pivaloyl chloride (5.09 mL, 41 mmol, 1.1 equiv) dropwise at 0 °C. After 3 days at 0 °C, water was added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to afford the desired monopivaloyl ester **28a** as a viscous oil (4.96 g, 32%): $[\alpha]_D$ +36.4° (*c* 1.0, $CHCl_3$); TLC R_f = 0.45 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.23 (m, 10H), 4.40 (t, 2H, *J* = 5.5 Hz), 3.82 (d, 2H, *J* = 13.0 Hz), 3.52 (m, 2H), 3.44 (d, 2H, *J* = 13.0 Hz), 3.10 (bs, 1H, −*OH*), 2.82 (m, 1H), 1.81 (m, 1H), 1.62 (m, 2H), 1.30 (m, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 278.9, 138.6 (2C), 129.4 (4C), 128.9 (4C), 127.7 (2C), 64.5, 61.2, 59.0, 53.7 (2C), 39.2, 27.7 (3C), 26.8, 22.0; LRMS (EI, *m*/*z*, %) 384 (80) (M + H^+), 352 (30), 132 (15), 91 (100); HRMS calculated for $C_{24}H_{34}NO_3$ (M^++1): 384.253 88, found 384.252 70. An amount (6.5%) of the other regioisomeric pivaloate was also obtained and separated.

(4*S*)-2,2-Dimethylpropionic Acid 4-[Bis-(4-methoxybenzyl)amino]-5-hydroxypentyl Ester (28b). By use of the same procedure, **27b** (12.3 g) was subjected to monopivaloylation to give **28b** (5.8 g, 38%) as a viscous oil: $[\alpha]_D$ +32.1° (*c* 1.05, $CHCl_3$); TLC R_f = 0.40 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, 4H, *J* = 8.0 Hz), 6.82 (d, 4H, *J* = 8.5 Hz), 4.04 (t, 2H, *J* = 6.5 Hz), 3.74 (s, 6H), 3.68 (d, 2H, *J* = 13.0 Hz), 3.38 (m, 2H), 3.27 (d. 2H, *J* = 13.0 Hz), 2.80 (bs, 1H, −*OH*), 2.74 (q, 1H, *J* = 4.6 Hz), 1.79 (m, 2H), 1.52 (m, 2H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 159.2 (2 C), 131.6 (2C), 130.5 (4C), 114.3 (4C), 64.5, 61.1, 58.6, 55.6 (2C), 52.8 (2C), 39.2, 27.7 (3C), 26.8, 21.9; LRMS (FAB, NBA, *m*/*z*, %) 444 (30) (M + H^+), 412 (10), 121 (100); HRMS calcd for $C_{26}H_{38}NO_5$ (M + H^+): 444.274 99, found 444.273 60.

(4*S*)-2,2-Dimethylpropionic Acid 4-[Bis(4-bromobenzyl)amino]-5-hydroxypentyl Ester (28c). By use of the same procedure, **27c** (1.52 g) was subjected to monopivaloylation to give **28c** (0.57 g, 32%) as a viscous oil: $[\alpha]_D$ +26.2° (*c* 1, $CHCl_3$); TLC R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, 4H, *J* = 7.9 Hz), 7.10 (d, 4H, *J* = 8.6 Hz), 4.01 (t, 2H, *J* = 6.5 Hz), 3.70 (d, 2H, *J* = 17.5 Hz), 3.47 (m, 2H), 3.35 (d, 2H, *J* = 17.5 Hz), 2.72 (q, 1H, *J* = 4.5 Hz), 1.74 (m, 1H), 1.66 (m, 2H), 1.55 (m, 1H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 138.5 (2C), 132.4 (4C), 131.0 (4C), 121.8 (2C), 64.3, 61.3, 59.2, 53.1, 39.2, 27.6 (3C), 26.7, 22.1; LRMS (FAB, NBA, *m*/*z*, %) 542 (20) (M + H^+), 510 (30), 169 (100), 147 (15), 91 (15).

(4*S*)-2,2-Dimethylpropionic Acid 4-[Bis(4-fluorobenzyl)amino]-5-hydroxypentyl Ester (28d). By use of the same procedure, **27d** (1.48 g) was subjected to monopivaloylation to give **28d** (2.09 g, 50%) as a viscous oil: $[\alpha]_D$ +65.3° (*c* 1, $CHCl_3$); TLC R_f = 0.46 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 4H), 7.02 (m, 4H), 4.05 (t, 2H, *J* = 6.3 Hz), 3.75 (d, 2H, *J* = 13.3 Hz), 3.52 (m, 2H), 3.40 (d, 2H, *J* = 13.3 Hz), 2.79 (m, 1H), 1.78 (m, 1H), 1.60 (m, 2H), 1.30 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 163.1, 160.7, 134.6 (2C), 130.3 (2C), 130.2 (2C), 115.3 (2C), 115.1 (2C), 63.8, 60.7, 58.5, 52.3 (2C), 38.6, 27.0 (3C), 26.2, 21.5; LRMS (EI, *m*/*z*, %) 418 (60) (M − H^+), 388 (40), 109 (75); HRMS calculated for $C_{24}H_{30}NO_3F_2$ (M − H^+): 418.219 36, found 418.220 00.

(13*S*)-2,2-Dimethylpropionic Acid 3-(7,12-Dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocin-13-yl)propyl Ester (29a). To a solution of oxalyl chloride (5.2 mL, 60.0 mmol, 5 equiv) in dry dichloromethane (30 mL) was added, at −78 °C, DMSO (8.43 mL, 120 mmol, 10 equiv). After 5 min of stirring, the α-*N*,*N*-dibenzylamino alcohol (4.78 g, 120.0 mmol, 1.0 equiv) diluted in dry dichloromethane (30 mL) was added. The mixture was stirred for 30 min at −78 °C, and then triethylamine (24.2 mL,175.0 mmol, 15 equiv) was added and the mixture was warmed to room temperature for 30 min. Water (20 mL) was added, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic layers were successfully washed with 1% HCl solution, water, saturated $NaHCO_3$ solution, and brine and dried over Na_2SO_4. Evaporation of solvent give the desired α-*N*,*N*-dibenzylamino aldehyde, which was used immediately in the next reaction.

To a suspension of $AlCl_3$ (4.8 g, 36.0 mmol, 3.0 equiv) in dry dichloromethane (60 mL) at 0 °C was added via cannula the crude aldehyde obtained from the corresponding alcohol (12 mmol, 1.0 equiv) in dry dichloromethane (40 mL). The mixture was stirred for 12 h at room temperature. $AlCl_3$ (2.4 g, 18.0 mmol, 1.5 equiv) was added to complete the reaction. After 2 h of being stirred, the red reaction mixture was diluted with dichloromethane and quenched with saturated aqueous sodium hydrogen carbonate solution. After the pH became basic (pH 8), the layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography to give **29a** (3.6 g, 85%) as a white solid: $[\alpha]_D$ +26.5° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.12 (m, 4H), 7.00 (m, 2H), 4.62 (d, 1H, *J* = 17.7 Hz), 4.47 (d, 1H, *J* = 18.4 Hz), 4.05 (m, 3H), 3.85 (d, 1H, *J* = 18.4 Hz), 3.65 (s, 1H), 3.35 (m, 1H), 1.90 (m, 1H), 1.82 (m, 1H), 1.61 (m, 1H), 1.50 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 141.2, 138.1, 133.9, 133.6, 128.0, 127.5, 126.2, 126.1, 126.0, 125.9, 125.8, 125.5, 64.0, 59.9, 56.4, 52.3, 40.4, 38.5, 27.4, 27.0 (3C), 25.6; LRMS (EI, *m*/*z*, %): 364 (100) (M + H^+), 278 (30), 262 (15), 218 (20), 192 (40), 154 (20), 91 (60); HRMS calculated for $C_{24}H_{30}NO_2$ (M + H^+): 364.227 66, found 364.226 40.

(13*S*)-2,2-Dimethylpropionic Acid 3-(2,10-Dimethoxy-7,12-dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocin-13-yl)-propyl Ester (29b). By use of the same procedure, **28b** (4.8 g) was subjected to Swern oxidation and Friedel−Crafts reaction to give **29b** (1.36 g, 33%) as a viscous oil: $[\alpha]_D$ +13.1° (*c* 1, $CHCl_3$); TLC R_f = 0.20 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (2d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 7.8 Hz), 6.59 (d, 2H, *J* = 8.3 Hz), 4.49 (d, 1H, *J* = 17.5 Hz), 4.39 (d, 1H, *J* = 17.5 Hz), 4.05 (t, 2H, *J* = 4.6 Hz), 3.93 (d, 1H, *J* = 18.0 Hz), 3.83 (d, 1H, *J* = 18.0 Hz), 3.74 (s, 3H), 3.72 (s, 3H), 3.51 (s, 1H), 3.26 (t, 1H, *J* = 6.5 Hz), 1.84 (m, 1H), 1.73 (m, 1H), 1.49 (m, 1H), 1.47 (m, 1H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 159.1, 158.9, 142.3, 138.9, 128.2, 127.9, 126.4, 126.2, 114.2, 113.9, 112.7, 112.3, 64.3, 59.2 (2C), 56.7, 54.9, 52.5, 41.9, 38.6, 27.8, 27.2 (3C), 26.1; LRMS (EI, *m*/*z*, %): 424 (100) (M + H^+), 338 (25), 280 (15), 258 (45), 165 (20); HRMS calculated for $C_{26}H_{34}NO_4$ (M + H^+) 424.551 03, found 424.524 78.

(13*S*)-2,2-Dimethylpropionic Acid 3-(2,10-Dibromo-7,-12-dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocin-13-yl)-propyl Ester (29c). By use of the same procedure, **28c** (1.0 g) was subjected to Swern oxidation and Friedel−Crafts

reaction to give **29c** (0.42 g, 45%) as a viscous oil: $[\alpha]_D$ +15.1° (*c* 1, $CHCl_3$); TLC R_f = 0.20 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 2H, *J* = 7.9 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 6.84 (t, 2H, *J* = 6.9 Hz), 4.48 (d, 1H, *J* = 18.0 Hz), 4.28 (d, 1H, *J* = 18.0 Hz), 4.08 (m, 2H), 3.87 (d, 1H, *J* = 17.5 Hz), 3.69 (d, 1H, *J* = 18.0 Hz), 3.52 (s, 1H), 3.22 (t, 1H, *J* = 4.8 Hz), 1.78 (m, 1H), 1.59 (m, 1H), 1.52 (m, 1H), 1.34 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 142.9, 140.0, 133.0, 132.7, 131.2, 130.9, 130.0, 129.9, 128.4, 128.0, 120.4, 120.2, 64.3, 59.6, 56.4, 52.3, 40.3, 39.1, 27.6, 27.5 (3C), 26.0; HRMS calculated for $C_{24}H_{27}NO_2Br_2$ (M^+) 521.290 83, found 521.284 36.

(13*S*)-2,2-Dimethylpropionic Acid 3-(2,10-Difluoro-7,-12-dihydro-5*H*-6,12-methanodibenzo[*c,f*]azocin-13-yl)-propyl Ester (29d). By use of the same procedure, **28d (**2.0 g) was subjected to Swern oxidation and Friedel−Crafts reaction to give **29d** (455 mg, 57%) as an amorphous solid: $[\alpha]_D$ +24.6° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (m, 4H), 6.70 (m, 2H), 4.51 (d, 1H, *J* = 17.5 Hz), 4.36 (d, 1H, *J* = 18.3 Hz), 4.05 (m, 2H), 3.94 (d, 1H, *J* = 17.5 Hz), 3.76 (d, 1H, *J* = 18.3 Hz), 3.52 (s, 1H), 3.23 (m, 1H), 1.85 (m, 1H), 1.76 (m, 1H), 1.53 (m, 1H), 1.42 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 162.0 (2C), 142.5, 139.5, 129.3, 129.0, 127.4, 127.1, 114.3, 113.9, 113.3, 113.1, 63.8, 59.2, 55.8, 51.6, 40.4, 38.5, 27.2, 26.9 (3C), 25.5; LRMS (EI, *m*/*z*, %) 399 (80) (M^+), 290 (70), 233 (30), 124 (20); HRMS calculated for $C_{24}H_{27}NO_2F_2$ (M^+) 399.200 98, found 399.200 22.

(13*S*)-3-(7,12-Dihydro-5*H*-6,12-methanodibenzo[*c,f*]azocin-13-yl)propan-1-ol (30a). To a solution of pivaloyl ester **29a** (3.0 g, 8.2 mmol) in dry toluene (30 mL) was added DIBAl-H solution (1.5 M in toluene, 16.4 mL, 24.5 mmol, 3.0 equiv) at −78 °C. The mixture was stirred for 1 h at − 78 °C. Then methanol (3.5 mL) was added and the mixture was warmed to room temperature. A saturated solution of potassium and sodium tartrate tetrahydrate was added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography to give **30a** (2.2 g, 99%) as a viscous oil: $[\alpha]_D$ +37.5° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14−6.78 (m, 6H), 4.60 (d, 1H, *J* = 17.6 Hz), 4.50 (d, 1H, *J* = 18.5 Hz), 4.0 (d, 1H, *J* = 17.6 Hz), 3.90 (d, 1H, *J* = 18.5 Hz), 3.73 (dt, 1H, *J* = 8.9, 4.4 Hz), 3.60 (s, 1H), 3.56 (dt, 1H, *J* = 8.8, 3.2 Hz), 3.30 (dd, 1H, *J* = 5.1, 3.3 Hz), 1.73−1.60 (m, 3H), 1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 138.0, 132.6, 132.5, 127.8, 127.6, 126.5, 126.4, 126.2, 126.1, 126.0, 125.6, 63.0, 59.4, 57.5, 52.0, 41.8, 31.7, 30.6; LRMS (EI, *m*/*z*, %) 279 (100) (M^+); HRMS calculated for $C_{19}H_{21}NO$ (M^+): 279.162 31, found 279.162 50.

(13*S*)-3-(2,10-Dimethoxy-7,12-dihydro-5*H*-6,12-methanodibenzo[*c,f*]azocin-13-yl)propan-1-ol (30b). By use of the above procedure, from **29b** (0.72 g), **31b** (0.573 g, 99%) was obtained as a viscous oil: $[\alpha]_D$ +37.7° (*c* 1.0, $CHCl_3$); TLC R_f = 0.30 (5% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (2d, 2H, *J* = 8.5 Hz), 6.88 (d, 1H, *J* = 2.5 Hz), 6.79 (d, 1H, *J* = 2.5 Hz), 6.64 (2dd, 2H, *J* = 2.8, 8.0 Hz), 4.49 (d, 1H, *J* = 17.8 Hz), 4.40 (d, 1H, *J* = 18.0 Hz), 4.13 (t, 1H, *J* = 4.8 Hz), 3.94 (d, 1H, *J* = 17.5 Hz), 3.82 (d, 1H, *J* = 18.0 Hz), 3.72 (s, 3H), 3.70 (s, 3H), 3.57 (m, 2H), 3.50 (s, 1H), 3.20 (bs, 1H, −*OH*), 1.76 (m, 2H), 1.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 (2C), 141.5 138.7, 127.1, 126.6, 123.8 (2C), 113.0, 112.7, 112.2, 111.9, 63.2, 58.7, 57.8 (2C), 55.1, 51.4, 42.6, 31.5, 30.8; HRMS calculated for $C_{21}H_{25}NO_3$ (M + H^+) 339.433 42, found 339.418 24.

(13S)-3-(2,10-Dibromo-7,12-dihydro-5*H*-6,12-methanodibenzo[*c,f*]azocin-13-yl)propan-1-ol (30c). By use of the above procedure, from **29c** (110 mg), **30c** (76 mg, 87%) was obtained as a viscous oil: $[\alpha]_D$ +36° (*c* 1, $CHCl_3$); TLC R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−6.82 (m, 6H), 4.42 (d, 1H, *J* = 18.0 Hz), 4.36 (d, 1H, *J* = 18.5 Hz), 3.84 (d, 1H, *J* = 17.8 Hz), 3.68 (d, 1H, *J* = 17.6 Hz), 3.66 (m, 2H), 3.51 (s, 1H), 3.22 (d, 1H, *J* = 10.0 Hz), 2.32 (bs, 1H, −*OH*), 1.76 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.1, 132.2, 131.1, 130.9, 130.1, 129.5, 128.7, 128.5, 128.0, 125.8, 120.5, 63.6, 59.6, 57.6, 52.2, 41.9, 32.1, 31.0; HRMS calculated for $C_{19}H_{19}NOBr_2$ (M^+) 437.173 24, found 437.165 41.

(13*S*)-3-(2,10-Difluoro-7,12-dihydro-5*H*-6,12-methanodibenzo[*c,f*]azocin-13-yl)propan-1-ol (30d). By use of the above procedure, from **29d** (450 mg), **30d** (255 mg, 81%) was obtained as a viscous oil: $[\alpha]_D$ +52.7° (*c* 1, $CHCl_3$); TLC R_f = 0.35 (5% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 4H), 6.74 (m, 2H), 5.60 (bs, 1H), 4.50 (d, 1H, *J* = 17.5 Hz), 4.46 (d, 1H, *J* = 18.3 Hz), 3.95 (d, 1H, *J* = 17.5 Hz), 3.83 (d, 1H, *J* = 18.3 Hz), 3.72 (m, 1H), 3.52 (m, 2H), 3.27 (m, 1H), 1.70 (m, 3H), 1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 142.2, 139.3, 128.1, 128.0, 127.6, 127.2, 114.5, 113.8, 113.5, 113.3, 63.0, 58.8, 56.9, 51.4, 41.8, 31.5, 30.3; LRMS (EI, *m*/*z*, %) 315 (100) (M^+), 285 (80), 254 (30), 218 (60), 254 (20), 218 (15), 206 (20), 163 (50), 147 (20); HRMS calculated for $C_{19}H_{19}NOF_2$ (M^+) 315.143 47, found 315.143 65.

Stevens Rearrangement. Typical Procedure for Isopavine (32a). To a solution of **30a** (1.4 g, 5.0 mmol) in dry benzene (20 mL) was added thionyl chloride (0.79 mL, 10.0 mmol, 2.0 equiv), and the mixture was refluxed for 1 h. Evaporation of solvent gave the corresponding chloride in quantitative yield as an amorphous solid. The chloride was dissolved in dry 1,4-dioxane (20 mL), potassium *tert*-butoxide (1.68 g, 15.0 mmol, 3 equiv) was added, and the mixture was warmed to 80 °C. After 1 h, water was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography to give pure **32a** (0.98 g, 75%) as a white solid: $[\alpha]_D$ +180.1° (*c* 1, $CHCl_3$); TLC R_f = 0.40 (5% MeOH in EtOAc); ^{1}H NMR (400 MHz, C_6D_6) δ 7.05−6.82 (m, 7H), 6.80 (m, 1H), 4.20 (dd, 1H, *J* = 1.7, 4.6 Hz), 3.72 (ddd, 1H, *J* = 3.0, 6.3, 9.5 Hz), 3.52 (d, 1H, *J* = 3.0 Hz), 3.47 (dd, 1H, *J* = 4.6, 17.8 Hz), 2.82 (dd, 1H, *J* = 11.2, 7.2 Hz), 2.70 (ddd, 1H, *J* = 5.5, 8.1, 10.6 Hz), 2.64 (d, 1H, *J* = 17.8 Hz), 1.73 (m, 1H), 1.62 (m, 1H), 1.50 (m, 1H), 1.22 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 140.1, 138.7, 136.9, 132.9, 128.7, 127.6, 124.3, 124.1, 124.0, 123.1, 122.7 (2C), 61.7, 55.4, 50.5, 46.2, 33.3, 26.8, 24.1; LRMS (EI, *m*/*z*, %) 261 (100) (M^+), 192 (40); HRMS calculated for $C_{19}H_{19}N$ (M^+): 261.151 75, found 261.152 16.

Isopavine (32b). By use of the same procedure, **31b** (570 mg) was subjected to Stevens rearrangement to give **32b** (350 mg, 72%) as an amorphous solid: mp 118−120 °C; $[\alpha]^{20}_D$ +106.8° (*c* 1, $CHCl_3$); TLC R_f = 0.50 (10% MeOH in $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.23 (d, 1H, *J* = 8.5 Hz), 6.94 (d, 1H, *J* = 8.0 Hz), 6.76 (d, 1H, *J* = 7.9 Hz), 6.72 (d, 1H, *J* = 8.0 Hz), 6.64 (d, 1H, *J* = 8.0 Hz), 6.62 (d, 1H, *J* = 8.5 Hz), 4.56 (t, 1H, *J* = 3.0 Hz), 3.96 (ddd, 1H, *J* = 3.0, 6.3, 9.5 Hz), 3.77 (s, 3H), 3.74 (s, 3H), 3.68 (dd, 1H, *J* = 3.5, 18.0 Hz), 3.36 (t, 1H, *J* = 6.5 Hz), 2.95 (dd, 1H, *J* = 6.5, 13.0 Hz), 2.92 (m, 1H), 2.02 (m, 2H), 1.81 (m, 1H), 1.42 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.3, 157.8, 141.6, 138.6, 132.0, 127.1, 124.8, 115.5, 112.7, 112.3, 111.4, 64.9, 57.5, 55.2 (2C), 51.0, 49.6, 34.2, 28.3, 25.7; HRMS calculated for $C_{21}H_{23}NO_2$ 321.172 87 (M^+), found 321.172 00.

Isopavine (32c). By use of the same procedure, **31c (**75 mg) was subjected to Stevens rearrangement to give **32c** (30 mg, 39%) as an amorphous solid: $[\alpha]_D$ +155.2° (*c* 1, $CHCl_3$); TLC R_f = 0.50 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.08 (m, 6H), 4.91 (bs, 1H), 4.12 (m, 1H), 3.87 (s, 1H), 3.59 (m, 1H), 3.53 (d, 1H, *J* = 18.0 Hz), 3.12 (d, 1H, *J* = 17.8 Hz), 2.89 (q, 1H, *J* = 3.0 Hz), 2.18 (m, 2H), 1.89 (m, 1H), 1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 140.3, 133.2 (2C), 130.8 (2C), 129.0 (2C), 127.9 (2C), 121.8, 120.4, 64.7, 57.7, 51.5, 49.4, 35.0, 29.3, 26.6; LRMS (FAB, NBA, *m*/*z*, %) 419 (100) (M^+), 340 (45); HRMS calculated for $C_{19}H_{17}NBr_2$ (M^+) 419.158 05, found 419.197 86.

Isopavine (32d). By use of the same procedure, **31d** (250 mg) was subjected to Stevens rearrangement to give **32d** (119 mg, 80%) as an amorphous solid: $[\alpha]_D$ +178° (*c* 1, $CHCl_3$); TLC R_f = 0.6 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, C_6D_6) δ 7.30 (m, 1H), 6.85−6.50 (m, 5H), 4.07 (d, 1H, *J* = 4.4 Hz), 3.54

(ddd, 1H, J = 3.1, 6.2, 9.4 Hz), 3.28 (dd, 1H, J = 4.4, 17.9 Hz), 3.13 (d, 1H, J = 3.1 Hz), 2.80 (dd, 1H, J = 7.3, 13.8 Hz), 2.59 (ddd, 1H, J = 5.5, 8.3 Hz), 2.40 (d, 1H, J = 17.9 Hz), 1.69 (m, 1H), 1.45 (m, 2H), 1.01 (m, 1H); LRMS (EI, *m*/*z*, %) 297 (80) (M^+), 295 (60), 228 (15); HRMS calculated for $C_{19}H_{17}NF_2$ (M^+): 297.132 90, found 297.132 99.

Isopavine (33). Typical procedure described for **13** was followed. From **32c** (20 mg), **33** was obtained as a viscous oil (105 mg, 48%): $[\alpha]_D$ −38.1° (*c* 1, $CHCl_3$); TLC R_f = 0.26 (10% MeOH in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 7.5 Hz), 6.34 (dd, 1H, J = 3.0, 8.0 Hz), 6.31 (d, 1H, J = 3.0 Hz), 4.43 (bs, 1H), 4.27 (s, 2H), 3.71 (m, 1H), 3.61 (s, 1H), 3.55 (d, 1H, J = 18.0 Hz), 3.09 (t, 1H, J = 3.0 Hz), 2.88 (m, 1H), 2.77 (d, 1H, J = 18.0 Hz), 2.04 (m, 1H), 1.88 (m, 2H), 1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 139.5, 32.4, 130.4, 129.1 (4C), 128.9 (2C), 128.0 (4C), 127.8 (2C), 114.7, 112.6, 64.6, 58.0, 52.1, 49.4, 48.8, 34.5, 29.2, 26.7; LRMS (FAB, NBA, *m*/*z*, %) 445 (100) (M^+), 375 (45), 284 (20), 154 (80), 136 (100); HRMS calcd for $C_{26}H_{25}N_2Br$ 445.400 96 (M^+).

Isopavine (34a). Typical procedure described for **9** was followed. A solution of **32b** (100 mg) was refluxed at 120 °C with 3.0 mL of aqueous HBr for 3 h to give **34a** as a pale-yellow solid (41 mg, 49%): mp 240−242 °C; $[\alpha]_D$ +42° (*c* 1, MeOH); TLC R_f = 0.23 (30% MeOH in $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 7.21 (d, 1H, J = 8.5 Hz), 6.87 (d, 1H, J = 8.0 Hz), 6.74−6.40 (m, 4H), 4.56 (bs, 1H), 4.02 (dd, 2H, J = 4.5, 17.7 Hz), 3.60 (d, 1H, J = 17.0 Hz), 3.46 (q, 1H, J = 4.8 Hz), 3.21 (s, 1H), 3.03 (d, 1H, J = 16.8 Hz), 1.94 (m, 2H), 1.51 (q, 1H, J = 4.6 Hz), 1.17 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 158.8, 156.4, 142.0, 137.9, 132.3, 128.0, 124.4, 122.5, 116.7, 115.4, 114.6, 113.2, 68.1, 60.0, 50.8, 32.8, 27.8, 25.5; HRMS calcd for $C_{19}H_{19}NO_2$ 293.364 62 (M^+), found 293.314 20.

Isopavine (34b). Typical procedure described for **11** was followed. An amount of **34a** (30 mg) was subjected to acetylation to give **34b** as a viscous oil (31 mg, 89%): $[\alpha]_D$ −18.3° (*c* 1, $CHCl_3$); TLC R_f = 0.50 (20% MeOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 8.5 Hz), 6.92−6.72 (m, 4H), 4.45 (t, 1H, J = 3.0 Hz), 3.78 (m, 2H), 3.72 (d, 1H, J = 18.5 Hz), 3.12 (t, 1H, J = 6.0 Hz), 2.94 (s, 1H), 2.90 (d, 1H, J = 17.5 Hz), 2.27 (s, 3H), 2.25 (s, 3H), 1.82 (m, 2H), 1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.7, 150.3, 149.1, 142.7, 139.6, 132.5, 132.2, 127.2, 123.3, 120.7, 120.5, 119.2, 64.7, 57.7, 52.0, 49.4, 35.2, 29.3, 26.7, 21.6 (2C); HRMS calcd for $C_{23}H_{23}NO_4$ 377.439 04 (M^+), found 377.416 35.

(2*S*)-2-Dibenzylaminohexane-1,6-diol (35). To a solution of L-2-aminoadipic acid (1 g, 6.2 mmol) in a 20% aqueous solution of potassium carbonate (20 mL) was added benzyl bromide (4.4 mL, 37 mmol, 6.0 equiv), and the mixture was refluxed with stirring for 12 h. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 80/20) to give crude dibenzyl diester (2.63 g, 81%) as an oil: $[\alpha]_D$ −66.5° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.18 (m, 20H), 5.31 (d, 1H, J = 12.2 Hz), 5.19 (d, 1H, J 12.4 Hz), 5.10 (s, 2H), 3.94 (d, 2H, J = 13.8 Hz), 3.55 (d, 2H, J = 13.8 Hz), 3.41 (dd, 1H, J = 6.0, 8.8 Hz), 2.24 (t, 2H, J = 7.2 Hz), 1.90 (m, 2H), 1.72 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.4, 139.3 (2C), 135.9 (2C), 128.7 (2C), 128.5 (2C), 128.4 (4C), 128.3 (4C), 128.2 (4C), 128.0 (2C), 126.9 (2C), 65.9 (2C), 60.0, 54.3 (2C), 33.5, 28.5, 21.4; LRMS (EI, *m*/*z*, %) 522 (100) (M + H^+), 446 (15), 386 (40), 296 (20), 181 (15), 91 (80), 77 (30); HRMS calculated for $C_{34}H_{36}NO_4$ (M + H^+): 522.264 40, found 522.263 20.

The general procedure as described for **27a** was followed. From 2.63 g of dibenzylamino adipic diester subjected to LAH reduction was obtained **35** as a yellow amorphous solid (1.39 g, 89%): $[\alpha]_D$ +70.6° (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.20 (m, 10H), 3.82 (d, 2H, J = 13.2 Hz), 3.61 (m, 2H), 3.52 (m, 1H), 3.45 (m, 3H), 2.80 (m, 1H), 2.35 (bs, 1H), 1.75 (m, 1H), 1.53 (m, 2H), 1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.9 (4C), 128.4 (4C), 128.3 (2C), 127.1 (2C), 62.2, 60.7, 58.8, 53.0 (2C), 32.7, 24.8, 23.3; LRMS (EI, *m*/*z*, %) 314 (80) (M + H^+), 282 (30), 192 (65); HRMS calculated for $C_{20}H_{28}NO_2$ (M + H^+) 314.212 00, found 314.211 71.

(5*S*)-2,2-Dimethylpropionic Acid 5-Dibenzylamino-6-hydroxyhexyl Ester (36). Typical procedure described for **28a** was followed. Monopivaloylation of **35** (1.39 g) gave **36** as a viscous oil (1.98 g, 50%): $[\alpha]_D$ +54.0° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 10H), 4.05 (t, 2H, J = 7.3 Hz), 3.82 (d, 2H, J = 13.5 Hz), 3.50 (m, 2H), 3.43 (d, 2H, J = 13.5 Hz), 2.79 (m, 1H), 1.75 (m, 1H), 1.62 (m, 2H), 1.30 (m, 3H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 139.1 (2C), 128.9 (4C), 128.3 (4C), 127.1 (2C), 63.7, 60.6, 58.6, 53.1 (2C), 38.6, 28.7, 27.1 (3C), 24.6, 23.3; LRMS (EI, *m*/*z*, %) 398 (100) (M + H^+), 320 (35), 276 (60), 240 920), 181 (15), 104 (40), 91 (80); HRMS calculated for $C_{25}H_{36}NO_3$ (M + H^+) 398.269 53, found 398.268 40.

(13*S*)-2,2-Dimethylpropionic Acid 4-(7,12-Dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocin-13-yl)butyl Ester (37). Typical procedure described for **29a** was followed. A two-step Swern oxidation and Friedel−Crafts cyclization on **36** (1.95 g) gave **37** as an amorphous solid (535 mg, 71%): $[\alpha]_D$ +26.7° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 2H), 7.10 (m, 4H), 6.95 (m, 2H), 4.63 (d, 1H, J = 17.8 Hz), 4.47 (d, 1H, J = 18.5 Hz), 4.10−4.01 (m, 3H), 3.84 (d, 1H, J = 18.4 Hz), 3.65 (s, 1H), 3.31 (m, 1H), 1.70−1.40 (m, 6H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 141.4, 138.2, 134.0, 133.7, 128.0, 127.6, 126.2, 126.1, 126.0, 125.9, 125.8, 125.6, 64.1, 59.9, 56.7, 52.5, 40.3, 38.7, 30.7, 28.5, 27.1 (3C), 22.9; LRMS (EI, *m*/*z*, %) 377 (M^+) (100), 335 (35), 276 (40), 205 (60), 77 (15); HRMS calculated for $C_{25}H_{31}NO_2$ (M^+) 377.235 48, found 377.234 59.

(13*S*)-4-(7,12-Dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocin-13-yl)butan-1-ol (38). Typical procedure described for **30a** was followed. From **37** (530 mg), **38** was obtained as a viscous oil (235 mg, 81%): $[\alpha]_D$ +29.7° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2H), 7.08 (m, 4H), 6.97 (m, 2H), 4.60 (d, 1H, J = 17.7 Hz), 4.46 (d, 1H, J = 18.5 Hz), 4.02 (d, 1H, J = 17.7 Hz), 3.83 (d, 1H, J = 18.4 Hz), 3.63 (m, 3H), 3.45 (m, 1H), 2.55 (bs, 1H), 1.60 (m, 5H), 1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 138.2, 133.7, 133.4, 128.0, 127.5, 126.3, 126.1, 126.0, 125.9, 125.8, 125.6, 62.5, 59.8, 56.7, 52.4, 40.3, 32.3, 30.8, 22.6; LRMS (EI, *m*/*z*, %) 293 (M^+) (80), 202 (40); HRMS calculated for $C_{20}H_{23}NO$ (M^+) 293.177 96, found 293.178 29.

Isopavine (39). Typical procedure described for **31a** was followed. Rearrangement of **38** (230 mg) gave **39** as a viscous oil (99 mg, 72%): $[\alpha]_D$ −44.3° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.15−6.88 (m, 8H), 3.71 (dd, 1H, J = 2.2, 4.5 Hz), 3.50 (s, 1H), 3.39 (dd, 1H, J = 2.2, 17.8 Hz), 2.91 (dd, 1H, J = 2.2, 10.9 Hz), 2.82 (m, 1H), 2.72 (dd, 1H, J = 4.5, 17.8 Hz), 2.62 (dt, 1H, J = 3.1, 10.9 Hz), 1.73−1.40 (m, 5H), 1.23 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 144.4, 139.0, 138.7, 132.9, 128.7 (2C), 124.3, 124.0, 123.2, 123.1, 122.9, 121.3, 63.0, 60.5, 50.2, 49.6, 30.6, 29.3, 23.6, 22.9; LRMS (EI, *m*/*z*, %) 275 (80) (M^+), 273 (20), 219 (15), 205 (40), 163 (25), 147 (60), 77 (40); HRMS calculated for $C_{20}H_{21}N$ (M^+): 275.167 40, found 275.167 83.

Biological Assays. Procedures described in ref 69 were followed. In brief, human HEK-293S cells expressing the human μ, δ, κ receptor were harvested and P2 membrane preparations were produced. In receptor binding assays, membranes were combined with test compounds (5 or 10 concentrations in duplicate per curve), ∼0.07 nM of the appropriate radioligand [^{125}I]-[D-Ala^2]-deltorphin II (K_d = 0.93 nM), [^{125}I]-FK33824 (K_d = 1.14 nM), and [^{125}I]-D-Pro^{10}-dynorphin A[1−11] (K_d = 0.16 nM) in 50 mM Tris, 3 mM $MgCl_2$, 1 mg/mL BSA, pH 7.4. The amounts of bound radioactivity were determined at equilibrium by filtration. The nonspecific (NS) binding was defined in the presence of 10 μM naloxone. The IC_{50} values of test compounds were determined from two-parameter logistic curve fits of the percentage of specific binding vs log(molar ligand), solving for IC_{50} and hill slope. Reference compounds showed expected IC_{50} values for the μ (DAMGO IC_{50} = 0.6 nM), δ (deltorphin II IC_{50} = 1.3 nM), and κ (U69593 IC_{50} = 2.2 nM) receptors. In functional assays, GTP-

[γ]^{35}S binding was used as an indicator of receptor/G-protein activation. Membranes expressing hμ receptors (0.2 pmol/mg protein) were combined with test compounds (10 concentrations in duplicate per curve) and ~0.2 nM GTP[γ]^{35}S in 50 mM Hepes, 20 mM NaOH, pH 7.4, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM EDTA, 1 mM DTT, 0.1% BSA, 15 μM GDP. The bound radioactivity was determined after 1 h by filtration. Control and stimulated binding were determined respectively in the absence and presence of reference agonist (30 μM DAMGO). Values of EC_{50} and E_{max} for ligands were obtained from three-parameter logistic curve fits of the percentage of stimulated GTP[γ]^{35}S binding vs log(molar ligand), solving for EC_{50} and hill slope, and % E_{max} DAMGO had an EC_{50} of 220 nM.

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Supporting Information Available: Selected HRMS data, ^{1}H NMR and ^{13}C NMR spectra, and X-ray structure data of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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