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Conformationally Constrained Calcium Channel Blockers: Novel Mimics of 1-Benzazepin-2-ones

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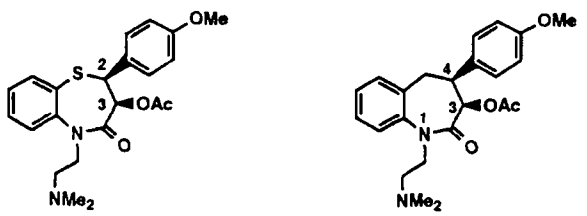
Abstract—In order to test a hypothesis that the seven-membered ring of the benzothiazepinone (diltiazem) and benzazepinone calcium channel blockers serves primarily to orient two critical pharmacophores in space, a series of novel, conformationally constrained bicyclo[2.2.2]octyl amines **3** which severely restrict the relative orientations available to the amine and methoxyphenyl groups was prepared. All compounds which positioned the pharmacophores on the same face of the molecule demonstrated vasorelaxant activity and affinity for the diltiazem receptor equal to or greater than racemic diltiazem **1** or the corresponding benzazepinone **2**. In addition, compound **3d** was equipotent to (+)-diltiazem in its ability to reduce ischemic/reperfusion injury in an *in vitro* model of myocardial ischemia. However, **3d** is significantly less cardiodepressive at an equivalent antiischemic dose. Therefore, the original receptor binding hypothesis led to the design and synthesis of novel calcium channel blockers with unique biological properties.

Calcium Channel Blockers (CCBs) are currently in wide use for the treatment of cardiovascular disease.[1] Diltiazem **1** is a member of the 1,5-benzothiazepin-2-one class of CCBs and has taken a central role in the clinical treatment of hypertension and angina. A series of 1-benzazepin-2-one calcium channel blockers (e.g. **2**) related to diltiazem have been prepared and their pharmacological properties described in detail (Figure 1).[2] A key finding of this work is the demonstration that two pharmacophores are required for the expression of calcium antagonist activity: a basic amino group appended to the amide of the bezazepinone ring and a pendant 4-methoxy group at the C-4 position. In the preceding paper,[3] we presented a hypothetical binding model which defines the spatial relationship between these pharmacophores. In this model, the benzazepinone ring serves primarily as scaffolding from which the pharmacophores are positioned at the required distance for binding to the receptor. However, an accurate description of the distance between the two pharmacophores necessary for binding requires restriction of the basic amine to a limited number (one, if possible) of positions. Due to our inability to construct a benzazepinone which can control the conformational flexibility of the N-1 substituent, we set out to design a replacement for the seven-membered ring. A suitable substitute would permit the synthesis of analogs in which the relative orientation of the pharmacophores could be systematically evaluated. As a test of this model, and with the concurrent goal of obtaining novel compounds with equal or greater intrinsic potency than **1** or **2**, we prepared a series of CCBs in which the seven-membered ring is replaced by a rigid bicyclic framework.[4]

The benzobicyclo[2.2.2]octyl amines **3** are carbocyclic compounds which have a similar overall topology to the low-energy *syn* conformation of the benzazepinones (Figure 2). When a model of **3**[5] is overlaid with the X-ray



1 DILTIAZEM **2**

Figure 1.

crystal structure of **1** or **2** so that the fused phenyl and methoxyphenyl rings are overlapped, the basic amine in **3** is severely restricted to positions that fit the proposed receptor-bound conformations (MI) of **1** and **2**.[3] The analogs **3a** and **3b** rigidly position the amine and methoxyphenyl pharmacophores at distances of 7 Å and 8.5 Å, respectively, while in **3e** and **3f** the groups are held 8 Å and 9 Å apart. The only substantial conformational flexibility available to these compounds is rotation about the bond connecting the pendant methoxyphenyl group to the bicyclic system, but this motion has little effect on the position of the methoxy group. An advantage of conformationally constrained compounds is that the loss of entropy upon binding to the receptor is substantially less than that produced by binding a more flexible molecule, leading to a favorable $\Delta G_{binding}$. However, a disadvantage of this strategy is that the 3-dimensional design of these compounds must be precise for optimal fit to occur. In order to account for the possibility that the limited conformations available to **3a**, **3b** and **3e**, **3f** are incapable of productive binding to the diltiazem receptor, we also prepared analogs which are slightly more flexible; **3c** and **3d** allow the distance between the pharmacophores to range from 6–8 Å and 8–9 Å, respectively.

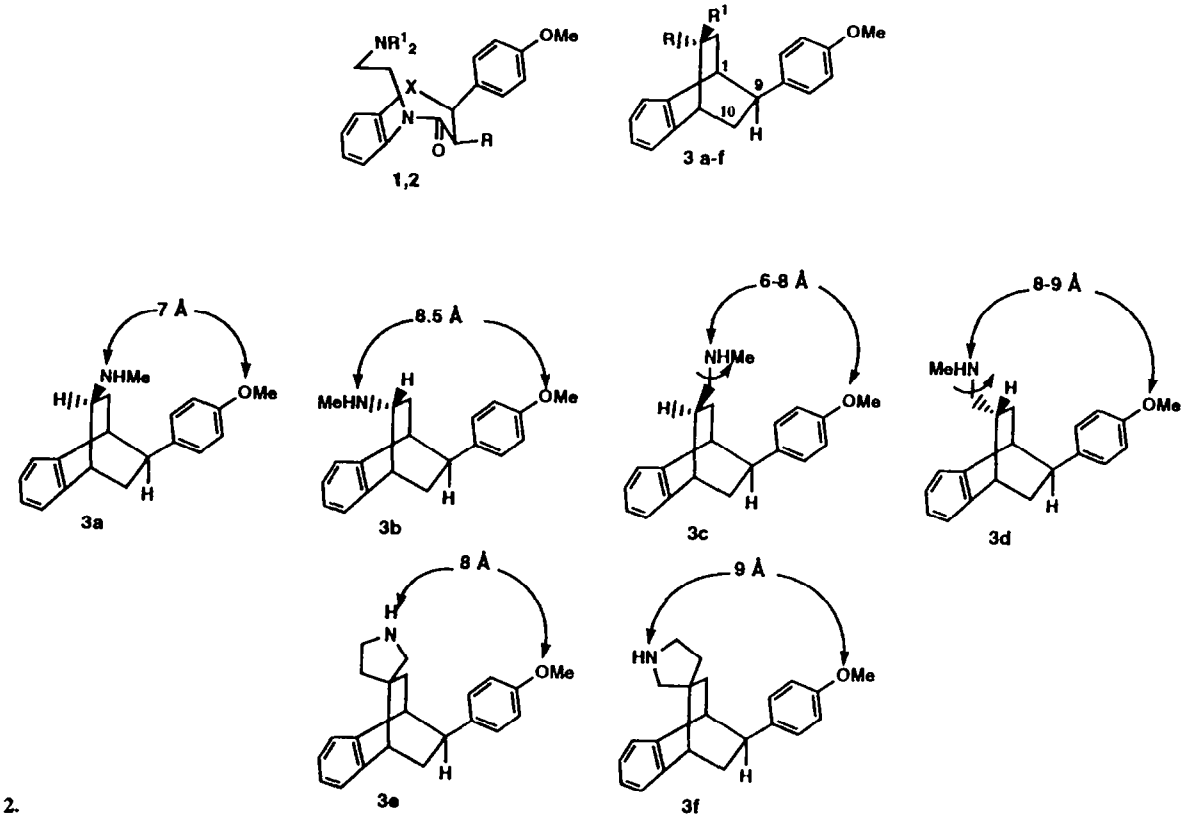


Figure 2.

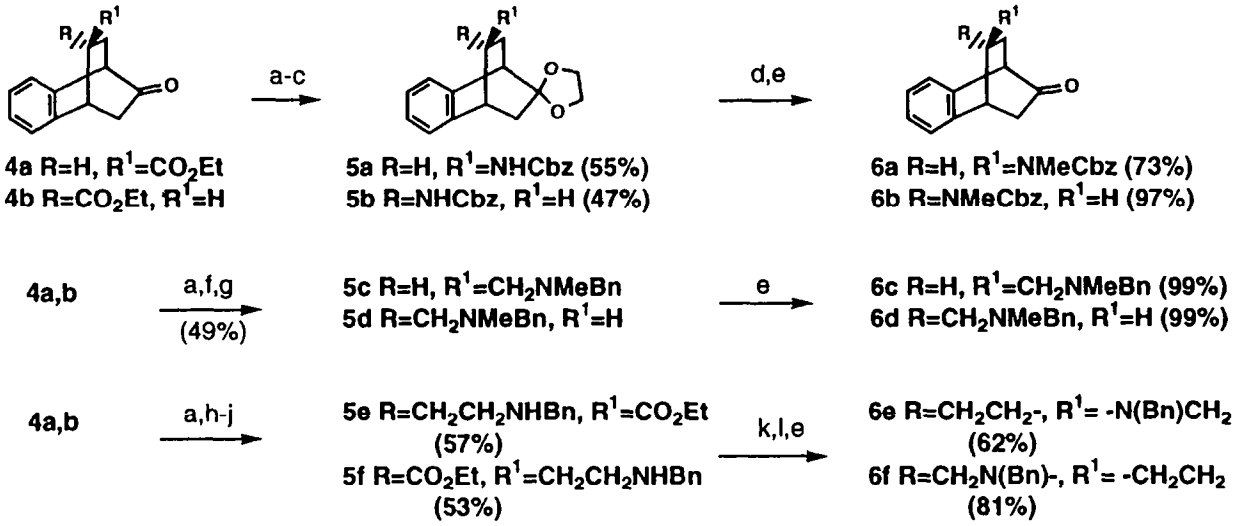
In addition to the C-1 bridge carbon of **3**, there are two other differences between the bicyclic amines and **1** or **2**. Both the amide function and the C-3 substituent of the benzazepinones and benzothiazepinones are absent in **3**. The role that each group plays in providing structural and/or conformational integrity to the seven-membered ring "spacer"[2a] of **1** and **2** is supplanted by the bicyclic ring system of **3**. However, the amide group may also act as a hydrogen bond acceptor and the lipophilicity of the C-3 substituent seems to have a significant effect on the potency of **1** and **2**.[2d] Therefore, we required that the synthetic route to **3** be flexible in order that C-10 could be substituted with an appropriate hydrogen bond acceptor (e.g. C=O) or a lipophilic group for possible future analog synthesis.

Chemistry

We chose as our target molecules the secondary amines due to their inherent metabolic stability in comparison to the corresponding tertiary amines in the case of **2**.[2b] The syntheses of the key intermediates **6a–e** are shown in Scheme I. All of the desired analogs were readily prepared in racemic form from the known bicyclic ketoester **4**.[6] For the synthesis of **6a** and **6b**, the single diastereomers of **4** were isolated by flash chromatography and carried on separately. The relative stereochemical assignment for the diastereomers could readily be made by ^{1}H NMR since in **4b** the carboethoxy group is constrained above the fused benzene ring.[7] Protection of the ketone followed by hydrolysis of the ester and conversion of the resulting carboxylic acid into the carbobenzyloxy (Cbz) protected amine via Curtius rearrangement[8] afforded **5a** and **5b**. Methylation and removal of the ketal group gave **6a** and **6b**.

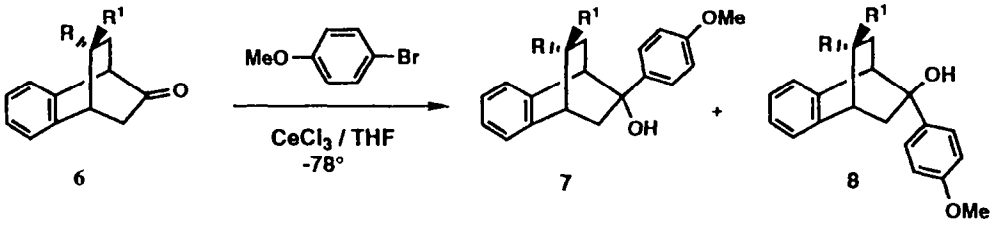
The synthesis of compounds **6c–f** proceeded more conveniently from the mixture of **4a** and **4b**. Conversion of the ketal protected ketoester to the secondary amide by Weinreb methodology[9] followed by reduction to the corresponding amine provided a mixture of diastereomers **5c** and **5d** which were separated by flash chromatography.[10] Hydrolysis of the ketal group gave the diastereomerically pure ketones **6c** and **6d**. Ketalization of a mixture of **4a,4b** followed by alkylation of the ester enolate with allyl bromide afforded a 1:2 mixture of alkylated products[11] which were separated by flash chromatography. Ozonolysis of each isomer and subsequent reductive amination of the resulting aldehydes with benzylamine provided the amino esters **5e** and **5f**. The desired pyrrolidine ring was produced by treatment with base to give the lactam followed by reduction of the carbonyl group. Deprotection as described above gave ketones **6e** and **6f**.

Our strategy for the conversion of **6** to **3** involved introduction of the C_9 aryl substituent with the correct stereochemistry by first, addition of an appropriate organometallic reagent to a C_9 ketone followed by stereoselective reduction of the resulting tertiary alcohol from the sterically less hindered side of the bicyclic ring system. Treatment of **6a** with a 4-methoxyphenyl cerium reagent[12] afforded a 1:2 mixture of **7**:**8** (Table 1); as expected, the major product **8** was derived by addition of the aryl group to the less hindered side of the bicyclic ring system. However, addition of the same reagent to **6b–f** gave tertiary alcohol **7** as the major product.



Scheme I. [a](a) $(CH_2OH)_2$, PhH,80°; (b) aq. NaOH, MeOH, RT; aq. $(CO_2H)_2$; (c) Et_3N, hexane, RT; $(PhO)_2P(O)N_3$; BnOH, 70°; (d) KH, THF, RT; (e) 2N aq. HCl, THF, RT; (f) HNMeBn, Me_3Al, MePh; (g) $LiAlH_4$, Et_2O; (h) LDA, THF, -78°; allyl bromide; (i) O_3, MeOH, $NaHCO_3$, -78°; Me_2S, RT, 20h; (j) $PhCH_2NH_2$, HCl, $NaCNBH_3$; (k) NaOMe, MeOH, reflux; (l) $LiAlH_4$, Et_2O, THF, RT.

Table 1. Addition of organocerium reagents to ketone 6



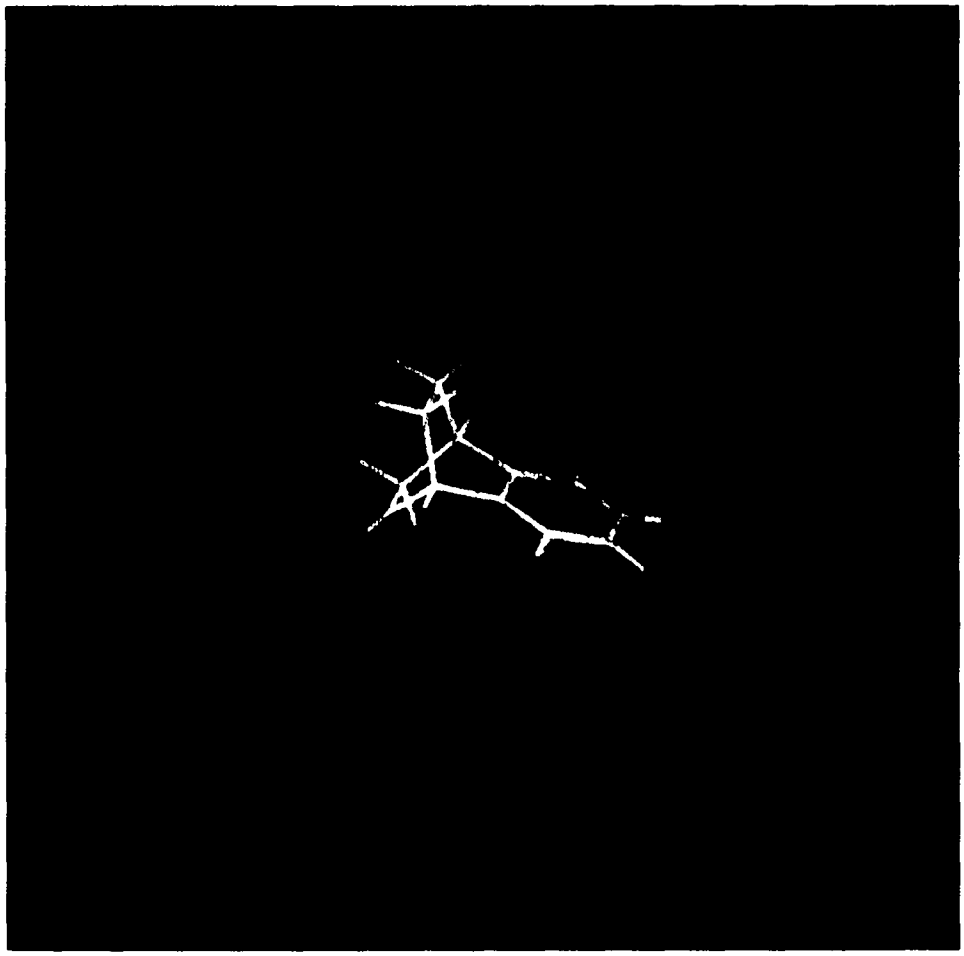
6 7 8

Substrate	R	R¹	7 : 8
6a	H	NHMeCbz	1 : 2
6b	CbzMeN	H	6 : 1
6c	H	CH_2NMeBn	7 : 1
6d	$BnMeNCH_2$	H	20 : 1
6e	CH_2CH_2-	-N(Bn)CH_2	2 : 1
6f	$CH_2N(Bn)$-	-CH_2CH_2	4 : 1

This unexpected π-facial selectivity could be rationalized by consideration of the electronic nature of a related bicyclic ketone (**6g**; R, R^1 = H) derived from *ab initio* calculations.[13] The geometry of **6g** was first optimized with the AM1 method[14] and the MOPAC (5.0) program.[15] The local density functional (LDF) formalism[16] was then applied to the fixed AM1 geometry, using the DMol methodology[17] with a DND (double numerical + d orbitals) basis set, which is analogous to large Gaussian double ζ basis sets with d functions on carbon and oxygen, e.g. the 6-31G* basis set.

The electrostatic potential map (Figure 3) shows a clear and striking division of the space surrounding the molecule into two regions, defined essentially by the two faces of the carbonyl group. Nearly all of the negative electrostatic potential occurs at the less sterically hindered face, and arises from a rather direct combination of negative charge densities associated with the carbonyl oxygen and the π-system of the aromatic ring. Hence, the electronic effect on the long range approach of a nucleophile, represented by a point negative charge, will be to steer it away from the less hindered face of the carbonyl into the more sterically hindered region. Furthermore, the finding that the substrates which place the nitrogen and the carbonyl group on the same side of the bicyclic ring system (**6a**, **6c**, and **6e**) gave lower ratios of **7**:**8** compared to their diastereomers (**6b**, **6d**, and **6f**, respectively) may be explained by complexation of the organocerium reagent with the nitrogen, thereby shielding the ketone more effectively from attack to give **7**. This apparent effect would be expected to be greatest for **6a** where the nitrogen is rigidly held nearest to the carbonyl group.

Although the unusual stereochemical outcome upon addition of the organocerium reagent to **6** provided an interesting diversion in our synthesis, it was inconsequential to the preparation of **3**. The alcohols **7** and **8** could be separated for the purpose of characterization, but were more conveniently carried on as a mixture. Treatment with triethylsilane in the presence of boron trifluoride etherate[18] (Scheme II) gave the desired C_9 stereoisomer as the predominant product along with small amounts of its diastereomer **9** and the olefin **10** (Figure 4) as by-products in certain cases. Hydrogenolysis provided the final products **3a–f** isolated as their hydrochloride salts (Table 2). A crystal structure of compound **3d** was obtained, confirming its relative stereochemistry.[19]



[a] The contours shown are at ±0.002 (- green, + red) and ±0.004 (- blue, + magenta) hartree (1 hartree = 627.51 kcal/mol). Successive contours (not shown here) at higher absolute values of energy, e.g. ±0.006, ±0.008, and so on, enclose progressively smaller volumes within the contour surfaces indicated above.

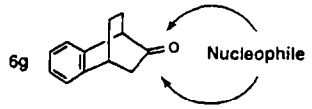
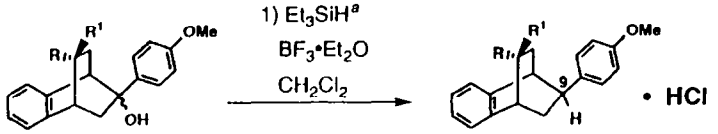


Figure 3. LDF/DND electrostatic potential map for ketone **6g**[a]



3a R=H, R^1=NHMe (65%)
3b R=MeHN, R^1=H (59%)
3c R=H, R^1=CH_2NHMe (72%)
3d R=MeHNCH_2, R^1=H (33%)
3e R=CH_2CH_2-, R^1=-NHCH_2 (40%)
3f R=CH_2HN-, R^1=-CH_2CH_2 (39%)

Scheme II. [a]The C_9 diastereomer **9** was isolated in <5–20% yields. The olefin **10** was detected in the reactions of **7,8c–f** in amounts up to 35% of the reaction mixture. It was routinely carried on in the subsequent reduction step and gave mainly the desired C_9 isomer. [b]For **3a** and **b**, the conditions were H_2, 10% Pd/C, HCO_2NH_4, MeOH; for **3c–f**, the conditions were H_2, $Pd(OH)_2$, HOAc except in the case of **3f** where EtOAc/EtOH was used instead.

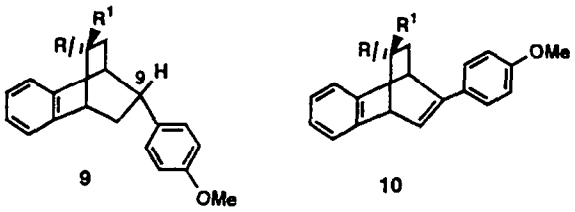
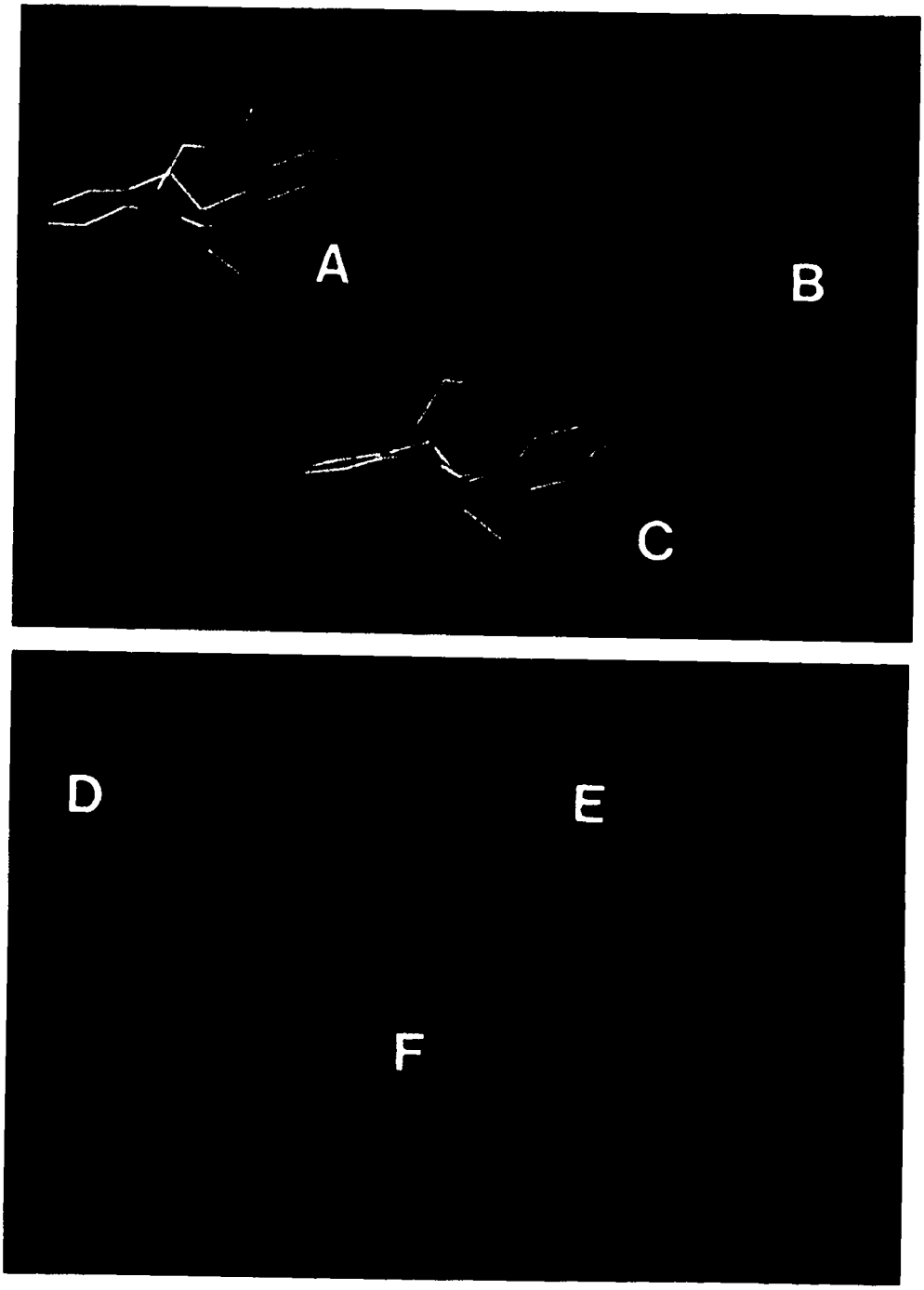


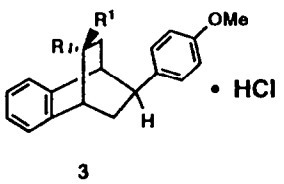
Figure 4.



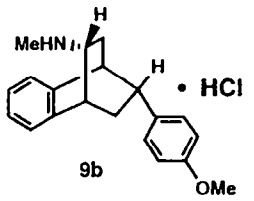
[a] Side view: A = MII conformation of **2** (3-methyl); B = X-ray crystal structure of **3c**; C = overlap of A and B. Top view: C = MII conformation of **2** (3-methyl); D = X-ray crystal structure of **3c**; E = overlap of C and D.

Figure 5. Comparison of the MI conformation of benzazepinone **2** (3-methyl analog) and the X-ray crystal structure of **3c**[a]

Table 2. Physical data for compounds **3** and **9b**



3



9b

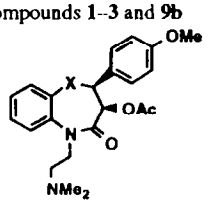
Compound	R	R^1	m.p.	Formula	Analysis
3 a	H	NMeH	254-258°	$C_{20}H_{24}ClNO$	C,H,N,Cl
3 b	HMeN	H	> 275°	$C_{20}H_{24}ClNO \cdot 0.13\ H_2O$	C,H,N,Cl
3 c	H	CH_2NMeH	198-199°	$C_{21}H_{26}ClNO$	C,H,N,Cl
3 d	$HMeNCH_2$	H	209-211°	$C_{21}H_{26}ClNO$	C,H,N,Cl
3 e	CH_2CH_2-	-$NHCH_2$	187-190°	$C_{22}H_{26}ClNO \cdot 0.9\ H_2O$	C,H,N,Cl
3 f	CH_2HN-	-CH_2CH_2	>255°	$C_{22}H_{26}ClNO \cdot 0.2\ H_2O$	C,H,N,Cl
9b	-	-	248-253°	$C_{20}H_{24}ClNO \cdot 0.21\ H_2O$	C,H,N,Cl

Figure 5 shows a comparison of the receptor binding model of **2**[3] (where a methyl group replaces the acetate at C-3) and the crystal structure of **3c**. It is interesting to note that when the structures are overlaid to maximize the overlap of the aromatic rings, the basic amines occupy similar positions in space, corresponding to the previously described MI model. As predicted, the obvious differences between the compounds are the C-3 substituent in **2** and the C-1 bridge methylene group in **3c**.

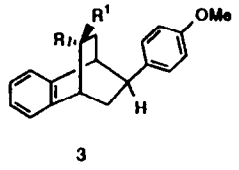
Results and Discussion

The biological data for compounds **1–3** and **9b** are compiled in Table 3. The vasorelaxant effects of compounds in circumferential strips of potassium-depolarized rabbit aorta were measured to determine the potency *in vitro*.[20] The IC_{50} value reported represents the concentration of compound necessary to cause 50% relaxation of a maximal contraction in response to 100 mM KCl. In addition, the affinity of each compound for the diltiazem receptor in isolated guinea pig skeletal muscle microsomal preparations was determined. The k_d values reported were calculated from concentration response curves for the inhibition of specific [^{3}H]-diltazem binding in this preparation.[2b]

Table 3. Biological activity of compounds **1–3** and **9b**



1 X=S
2 X=CH_2



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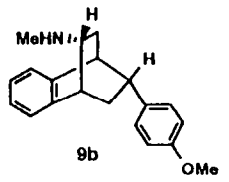


9b

Compound	R	R^1	IC_{50} (μM)[a]	k_d (μM)[b]
3 a	H	NMeH	3.7 (2.6-5.3)	2.1 (±0.63)
3 b	HMeN	H	4.2 (2.9-6.1)	0.89 (±0.20)
3 c	H	CH_2NMeH	0.74 (0.49-1.1)	0.69 (±0.05)
3 d	$HMeNCH_2$	H	0.87 (0.56-1.4)	0.60 (±0.02)
3 e	CH_2CH_2-	-$NHCH_2$	0.95 (0.76-1.2)	0.33 (±0.12)
3 f	CH_2HN-	-CH_2CH_2	2.0 (1.5-2.7)	1.3 (±0.28)
9b	-	-	13 (10.0-18.0)	4.0 (±1.4)
(±)-1	-	-	1.8 (0.74-4.6)	0.38 (±0.04)
(+)-1	-	-	0.21 (0.13-0.36)	0.20 (±0.02)
(±)-2	-	-	4.7 (2.9-7.8)	5.1 (±1.4)

[a] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval)
[b] k_d determined by displacement of radiolabeled diltiazem in guinea pig striated muscle (±SEM).

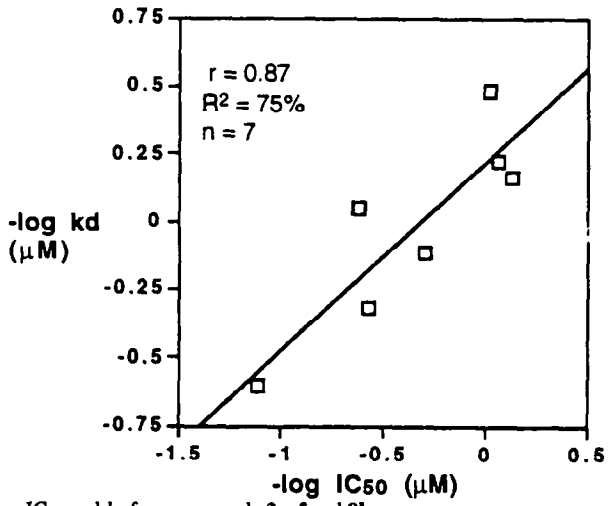


Figure 6. Correlation between IC_{50} and k_d for compounds **3a–f** and **9b**

All of the analogs **3a–f** are at least as potent as the corresponding racemic benzazepinone compound **2** in their ability to inhibit K^+ induced contraction in rabbit aorta. In particular, compounds **3c–f** are equivalent to racemic diltiazem (±)-**1** and 4–5 times more potent than **2** as vasodilators. The radioligand binding data generally seem to follow the rabbit aorta data. Figure 6 shows the correlation between the two *in vitro* tests (log k_d vs log IC_{50}) Although the data set is limited, this good correlation supports the use of the functional assay as a measure of calcium channel blocker activity.[21,22] Analog **3e** is the most potent of the bicyclic compounds in the binding assay with activity equivalent to that of diltiazem. Compound **9b**, the C-9 diastereomer of **3b**, has poor activity in both *in vitro* assays.

While the difference in activity between the least and most potent analogs is not large enough to permit far-ranging conclusions to be drawn, some interesting trends may be observed. The bicyclic compound **3c** is the only analog in which the pharmacophores can attain the 6–7 Å distance postulated in the MI receptor binding hypothesis for the benzazepinones and benzothiazepinones,[3] yet it is not significantly more potent than other analogs such as **3d** and **3e** that cannot conform to the desired model. With the exception of pharmacophore distances ≥ 8.5 Å, all other pharmacophore configurations appear to be tolerated by the receptor. Several explanations are possible to explain this discrepancy. Each of the diastereomeric pairs **3a**, **3b**; **3c**, **3d**; and **3e**, **3f** have essentially the same activity in the functional assay. This interesting finding leads to the possibility that the ideal orientation for the basic amine is somewhere between the two possible locations, directly over C-3. Alternatively, it is conceivable that directionality is not critical for pharmacophore binding and that different configurations can lead to the same productive interactions at the receptor. This conclusion is not unreasonable if we assume that the basic amine associates with the receptor via a charge–charge interaction which is known to be less dependent on directionality or distance between the groups than, for example, a hydrogen bond. Nevertheless, the relative lack of activity of **9b** compared to **3b** does appear to validate the hypothesis that both the amine and the methoxyphenyl group are important for activity and must be on the same face of the molecule for efficient binding to the receptor.

The interesting properties of compounds **3c** and **3d** *in vitro* made them an ideal pair for further biological evaluation. It has been established that all three known chemical classes of calcium channel blockers possess myocardial antiischemic properties.[23] Several explanations have been proposed for this beneficial effect. CCBs can affect the peripheral hemodynamics and contractility of the heart, both of which work to reduce the oxygen demand of the heart.[24] Although it is possible that the cardioprotective effect is due to the cardiodepressive properties of CCBs, it was recently found that diltiazem can reduce the severity of myocardial ischemia at a lower functional cost as compared to verapamil and the dihydropyridine nifedipine.[25,26]

The ability of **3c** and **3d** compared to diltiazem to reduce ischemic/reperfusion injury was examined in rat hearts subjected to total global ischemia. In this study, the time to contracture was taken as a reliable index of the severity of ischemia.[27] Contracture, also known as "stone heart", is the marked increase in diastolic tension which accompanies an ischemic event. It may be caused by inadequate ATP which is therefore unavailable to dissociate the actin–myosin cross bridges, or to insufficient energy reserves which cannot restore resting cytosolic calcium levels.[28] The isolated rat hearts were perfused with buffer and the end diastolic pressure (EDP) was adjusted at the beginning of the experiment. EDP was measured until it reached a value of 25 mm Hg at which point it was assumed that the hearts were in contracture. Cardiac function was determined using the double product of heart rate (HR) x left ventricular developed pressure (LVDP) divided by 1000. The hearts were pretreated with compound before global ischemia was achieved by completely shutting off the perfusate flow.

The results in Table 4 show that **3c**, **3d**, and diltiazem are all equivalent in significantly increasing the time to onset

of contracture compared to vehicle. Although each compound increased coronary flow before the ischemic episode to the same extent, diltiazem dramatically reduced cardiac function whereas **3c** and **3d** had little effect. In a variation of the above experiment, the ischemic episode was allowed to continue for 25 min at which point the hearts were reperfused with non-compound treated buffer for 30 min and the amount of lactate dehydrogenase (LDH) released during the reperfusion measured. LDH release is a sensitive index for loss of cell viability.[29] As shown in Figure 7, compound **3d** and diltiazem **1** are equivalent in their ability to inhibit the release of LDH. However, as in the earlier experiment, compound **3d** is more selective for antiischemic activity than is diltiazem, as demonstrated by the lower ratio of LDH release (antiischemic effect) to post-drug (pre-ischemic) function. Although the significant separation between cardiodepression and antiischemic activity is unusual for diltiazem-like CCBs, a less dramatic but qualitatively similar result for a benzazepin-2-one analog has been observed previously.[30,31] The correlation between cardiodepression and antiischemic activity should not be expected to be 1:1 for any CCB since ischemia can affect receptor binding and may also modulate the gating characteristics of the channel. However, effects of compounds **3c** and **3d** unrelated to their binding to the benzothiazepine receptor cannot be ruled out.

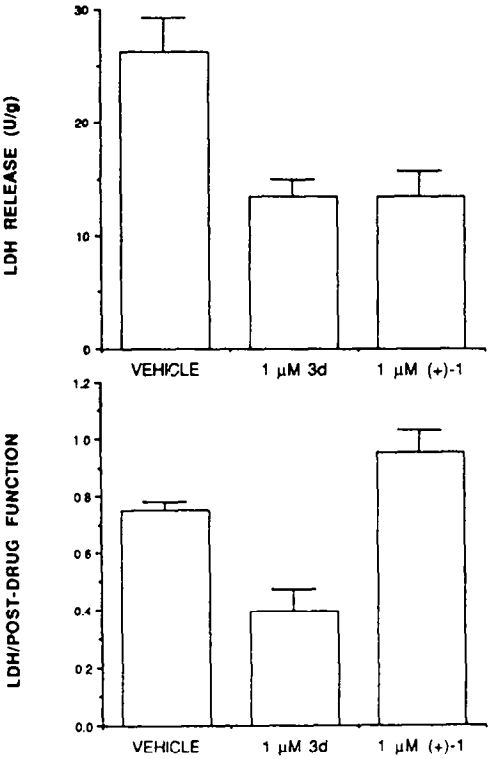
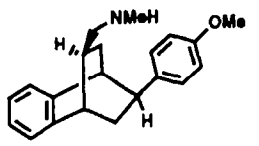
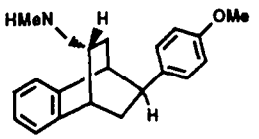


Figure 7. Antiischemic activity (LDH release) and selectivity (LDH/post-drug function) of **1** and **3d**.

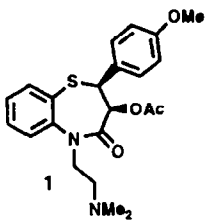
Table 4. Effects of **1**, **3c**, and **3d** on cardiac function and time to contracture in isolated rat hearts



3c



3d



	Pre-Ischemia		Ischemia
	Pre-Drug	Post-Drug	
HR X LVDP/1000[c]			
Vehicle	34.4±0.8	30.0±0.5	-
1 μM 3c	37.9±1.7	32.5±2.0	-
1 μM 3d	36.7±1.6	34.7±1.2	-
1 μM (+)-1	40.0±1.0	16.9±1.7[a,b]	-
Coronary Flow (ml/min/g)			
Vehicle	16.3±1.1	15.0±1.2	-
1 μM 3c	17.8±1.2	22.2±1.6[a,b]	-
1 μM 3d	17.1±1.6	22.8±1.8[b]	-
1 μM (+)-1	19.0±0.6	21.4±1.4[b]	-
Min to Contracture			
Vehicle	-	-	18.4±0.5
1 μM 3c	-	-	21.8±0.5[b]
1 μM 3d	-	-	22.2±0.7[b]
1 μM (+)-1	-	-	23.3±0.2[b]

[a]Significantly different from its respective predrug value.
[b]Significantly different from all of the respective vehicle treated group values.
[c]HR = Heart Rate; LVDP = Left Venticular Developed Pressure.

Summary

We previously proposed that the benzothiazepinone and benzazepirone ring systems in **1** and **2** consist mostly of "scaffolding" which serves to orient the two critical pharmacophores in space.[3] In order to test this hypothesis, we prepared a novel series of conformationally constrained bicyclo[2.2.2]octyl amines **3** which severely restrict the relative orientations available to the amine and methoxy phenyl pharmacophores. These compounds demonstrated vasorelaxant activity and affinity for the diltiazem receptor equal to or greater than racemic diltiazem **1** or the corresponding benzazepinone **2**. Furthermore, compound **3d** was equipotent to (+)-diltiazem in its ability to reduce ischemic reperfusion injury in an *in vitro* model of myocardial ischemia. However, **3d** was significantly less cardiodepressive at an equivalent dose, a distinct advantage over (+)-diltiazem.

Despite the potent biological activity of some of these novel calcium channel blockers, a simple correlation between activity and the relative orientation of the pharmacophores was not revealed. Thus, we have been unable to use the activity of the bicyclic analogs to define the receptor binding conformation for **1** and **2** except to conclude that the pharmacophores must be on the same face of the molecule. Nevertheless, the *in vitro* activity of **3a–f** does appear to validate our optimistic proposal that the receptor binding hypotheses for **1** and **2** could lead to the synthesis of novel CCBs with unique biological properties.

Experimental Section

Biological assays

The *in vitro* vasorelaxant assay and the radioligand binding assay were carried out essentially as described in Ref. 2b.

Myocardial ischemia

Male Sprague–Dawley rats (450–550 g) were used in all experiments. The rats were anesthetized using 30 mg/kg sodium pentobarbital (i.p.). They were incubated and then treated with i.v. heparin (1000 U/kg). While being mechanically ventillated, their hearts were perfused *in situ* via retrograde cannulation of the aorta. The hearts were then excised and quickly moved to a Langendorff apparatus where they were perfused with Krebs–Henseleit bicarbonate buffer (mM: 112 NaCl, 25 $NaHCO_3$, 5 KCl, 1.2 $MgSO_4$, 1 KH_2PO_4, 1.25 $CaCl_2$, 11.5 dextrose, and 2 pyruvate bubbled with 95% O_2–5% CO_2) at a constant perfusion pressure (75 mm Hg). A water filled latex balloon attached to a metal cannula was then inserted into the left ventricle and connected to a Statham pressure transducer for measurement of left ventricular pressure. The hearts were allowed to equilibrate for 15 min at which time end diastolic pressure (EDP) was adjusted to 5 mmHg and this balloon volume was maintained for the duration of the experiment. Pre-ischemia or pre-compound function and heart rate were then measured. Cardiac function was determined using the double product of the heart rate (HR) x left ventricular developed pressure (LVDP) divided by 1000. LVDP was calculated from the difference between left ventricular peak systolic pressure and EDP. Cardiac temperature was maintained throughout the experiment by submerging the hearts in 37 °C buffer which was allowed to accumulate in a stoppered, heated chamber. Once the hearts were stabilized, they were treated either with vehicle or compound. Each group consisted of four hearts. The hearts were pretreated with the respective compound for 10 min before ischemia and function was again measured. Global ischemia was achieved by completely shutting off the perfusate flow. EDP was measured throughout the ischemic period. EDP was recorded as the change in pressure from baseline and was measured until it increased by 25mm Hg. The dependent variable in the study was the time (min) necessary for the changes in EDP to occur during ischemia. The modified procedure used to measure lactate dehydrogenase (LDH) released during ischemia followed by reperfusion is described in Ref. 18.

Crystal structure analysis

Crystals of **3c** were obtained from 95% ethanol/ether (1:5) as colorless hexagonal prisms. Unit cell parameters were obtained through a least squares analysis of the experimental diffractometer settings of twenty-five high angle reflections using Cu Kα monochromatic radiation (λ = 1.5418Å): a = 16.106(2)(2), b = 7.817(2), c = 17.264(2)Å, β = 117.25(1)°, V = 1932(1)Å^3. Space group $P2_1/a$ was assigned on the basis of systematic absences and confirmed by the full structure analysis. The crystal density, D_{obs} = 1.20 g·cm^{-3} was measured by flotation in carbon tetrachloride/hexane mixtures (D_{calc} = 1.21 for Z = 4, $C_{21}H_{26}NOCl$•0.5 H_2O). A total of 3616 reflections were measured on an Enraf–Nonius CAD4 diffractometer at 23 °C with the θ–2θ variable scan technique and were corrected for Lorentz polarization factors. Background counts were collected at the extremes of the scan for half the time of the scan. Two standard reflections were monitored for decay; no decrease of intensity was observed during the course of the measurements. Calculations utilized the SDP program package with minor local modifications.[32] The structure was solved by direct methods and refined on the basis of 1107 "observed" reflections with $I \geq 3\sigma(I)$. Although some hydrogen positions were evident in difference maps, only the hydrogens on N12 were introduced in their observed positions. All other hydrogens were introduced in idealized positions. Although the scattering of hydrogens was included in the terminal stages of refinement, no hydrogen parameters were varied. Least squares weights, $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2 = \varepsilon^2 + (\rho I)^2$ where ε is the statistical counting error and ρ = 0.04. The function minimized in the least squares refinements was $\Sigma_w(|F_o| - |F_c|)^2$. R is defined as $\Sigma\, ||F_o| - |F_c||/\Sigma\, |F_o|$ while $R_w = [\Sigma_w(|F_o| - |F_c|)^2 / \Sigma_w |F_o|^2]^{1/2}$. The refinements converged at R = 0.069, R_w = 0.074. The final difference map contained no significant features. Tables of atomic coordinates, thermal parameters, bond distances and angles are included as supplementary material. The configuration

at the chiral centers C1,C2,C4,C9 is *RRRR* or *SSSS*. In the crystal studied, the water site is 50% occupied.

General chemical procedures

Melting points were recorded on a Thomas-Hoover capillary apparatus and are reported uncorrected. Proton NMR (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were obtained on Jeol FX-270, GX-270, or GX-400 spectrometers and are reported relative to tetramethylsilane (TMS) reference. Accurate mass (HRMS) determinations were performed on a Jeol-SX spectrometer (FAB); sodium iodide was added during some measurements to stabilize the compound. Thin layer chromatography (TLC) was carried out with E. Merck Kieselgel 60 F254 (0.25 mm) plates and flash chromatography was performed using Merck silica gel 60.

(1R, 2S*, 4S*)- and (1R*, 2R*, 4S*)-9-Oxo-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid ethyl ester (4a and 4b)*

A mixture of 33 g (228.9 mmol) of β-naphthol, 48 mL (442.8 mmol) of ethyl acrylate and 0.1 g of 2-hydroxy-4-phenyl phenol as an inhibitor were placed in a resealable bottle and heated at 175–180 °C for 4 days. After cooling to r.t., the reaction mixtures from two separate reactions were combined and the excess ethyl acrylate removed *in vacuo*. The resulting residue was dissolved in 500 mL of Et_2O and poured into a 2 L separatory funnel along with 500 mL of hexanes. The mixture was washed with 2 x 500 mL of 2 N NaOH and 2 x 500 mL of H_2O (any emulsion which forms was filtered through a celite pad on a C-porosity glass frit and the cake washed with 500 mL of 1:1 Et_2O/hexanes). The combined organic extracts were dried ($MgSO_4$) and evaporated to give 15.0 g of a yellow residue. Kugelrohr distillation (175–220 °C; 3 mm) then gave 12.78 g (11.5%) of an oil. The endo (**4a**) and exo (**4b**) isomers could be separated by flash chromatography (10 cm x 50 cm; 4:1 hexane:ethyl acetate) to give 5.975 g of **4a**, 3.445 g of **4b** as well as 4.64 g of mixed fractions which could be rechromatographed. **4a**: R_f: 0.31 (3:1 hexane:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, J = 7 Hz, 3H), 2.02 (ddd, J = 4, 12, 14 Hz, 1H), 2.13 (ddd, J = 2, 3, 19 Hz, 1H), 2.49–2.60 (m, 2H), 2.74 (m, 1H), 3.65 (dd, J = 2, 2 Hz, 1H), 3.73 (dd, J = 3,4 Hz, 1H), 4.23 (q, J = 7 Hz, 2H), 7.20–7.29 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.2, 26.6, 37.6, 39.5, 41.6, 52.3, 61.1, 123.9, 125.8, 127.6 (2), 135.9, 141.9, 173.6, 209.8. **4b**: R_f: 0.23 (3:1 hexane:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.16 (t, J = 7 Hz, 3H), 2.18–2.45 (m, 4H), 3.05 (ddd, J = 2, 8, 8 Hz, 1H), 3.64 (dd, J = 2, 2 Hz, 1H), 3.82 (dd, J = 3, 6 Hz, 1H), 4.00 (q, J = 7 Hz, 1H), 4.03 (q, J = 7 Hz, 1H), 7.21 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.1, 26.6, 40.2, 41.0, 42.2, 52.0, 60.8, 125.1, 125.5, 127.4, 127.6, 136.1, 139.1, 172.9, 210.2.

(1R, 2S*, 4S*)-9,9-[Ethylenebis(oxy)]-1,2,3,4-tetrahydro-N-carbobenzyloxy-1,4-ethanonaphthalen-2-amine (5a)*

To 4.58 g (18.74 mmol) of **4a** dissolved in 300 mL of benzene was added 60 mL (1.075 mol) of ethylene glycol followed by 0.29 g of *p*-toluenesulfonic acid and the mixture stirred at reflux with azeotropic removal of H_2O for 30 h at which point TLC (3:1 hexane:ethyl acetate–UV and PMA) showed only a small amount of **4a** remaining. After cooling to r.t., the reaction mixture was poured into a separatory funnel and the organic layer washed with 200 mL of saturated aq. $NaHCO_3$ and 200 mL of H_2O. The organic layer was dried ($MgSO_4$) and evaporated to give a crude residue which was purified by flash chromatography (4:1 hexanes:ethyl acetate) to give 4.30 g (79%) of a slightly impure oil which solidified on storage at 5 °C. R_f: 0.23 (3:1 hexane:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, J = 7 Hz, 3H), 1.63–1.76 (m, 2H), 2.18 (dd, J = 3, 14 Hz, 1H), 2.44 (m, 1H), 2.62 (ddd, J = 2, 6, 13 Hz, 1H), 3.04 (dd, J = 2, 4 Hz, 1 H), 3.47 (dd, J = 3,6 Hz, 1 H), 3.77–3.99 (m, 4H), 4.22 (q, J = 7 Hz, 2H), 7.20 (m, 4H), ^{13}C NMR ($CDCl_3$): δ 14.3, 24.1, 37.0, 38.2, 41.7, 43.1, 60.6, 64.2, 64.3, 111.0, 123.5, 125.6, 126.8, 139.8, 141.8, 174.1.

To a solution of 5.46 g (18.89 mmol) of the above ketal dissolved in 45 mL of MeOH at r.t. was added a solution of 1.13 g (28.83 mmol) of NaOH dissolved in 22 mL of H_2O. The resulting pink solution was stirred at r.t. for 30 min and at 60 °C for 30 min at which point TLC (3:1 hexane:ethyl acetate—UV and PMA) showed no ester remaining. The reaction mixture was poured into 400 mL of H_2O and extracted with 2 x 150 mL of CH_2Cl_2. The aqueous layer was acidified to pH 2 with saturated aq. oxalic acid and extracted with 2 x 200 mL of CH_2Cl_2. The non-acid impurities were removed by washing the organic layer with aqueous $NaHCO_3$ (18 g dissolved in 300 mL of H_2O). The aqueous layer was washed one additional time with 100 mL of CH_2Cl_2 and then reacidified to pH 2 with aq. oxalic acid. The aqueous layer was then extracted with 2 x 200 mL of CH_2Cl_2 and the organic extracts washed with 150 mL of H_2O, dried ($MgSO_4$) and evaporated to give 4.67 g (95%) of a light-yellow foam. R_f: 0.32 (1:1 hexane:ethyl acetate + 1 % HOAc); ^{1}H NMR ($CDCl_3$): δ 1.76 (m, 2H), 2.26 (dd, J = 2,15 Hz, 1 H), 2.58 (m, 2H), 3.06 (m, 1H), 3.51 (m, 1H), 3.80–4.02 (m, 4H), 7.21 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 23.9, 37.0, 38.0, 41.6, 42.9, 64.1, 64.3, 111.1, 123.5, 125.6, 126.9, 139.6, 141.5, 180.3.

To a suspension of 4.67 g (17.95 mmol) of the above carboxylic acid in 110 mL of hexanes was added 2.74 mL (19.75 mmol) of Et_3N. After stirring for 5 min at r.t. under Ar, 4.24 mL (19.75 mmol) of diphenylphosphoryl azide was added and the resulting mixture stirred at r.t. for 15 min and at reflux for 45 min. At this point, 2.0 mL (19.75 mmol) of benzyl alcohol was added and the reaction mixture stirred at reflux overnight (15 h). The reaction was cooled to r.t. and then poured into 200 mL of 5% citric acid along with 300 mL of Et_2O. The organic layer was washed with 200 mL of H_2O, 200 mL of saturated aq. $NaHCO_3$ and 200 mL of brine and then dried ($MgSO_4$). Evaporation gave an impure residue which was purified by flash chromatography (3:1 hexanes:ethyl acetate) resulting in 4.50 g (68%) of **5a** as a white foam. R_f: 0.11 (3:1

hexane:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.69 (m, 2H), 1.97 (m, 1H), 2.25 (m, 1H), 2.96 (m, 1H), concentrated to afford 4.43 g (99%) of a mixture of the amines **5c** and **5d** as an oil. The isomers were separated by flash chromatography (4:1 hexanes:ethyl acetate). **5c**: ^{1}H NMR ($CDCl_3$): δ 1.53–1.69 (m, 3H), 1.81 (m, 1H), 2.02 (dd, *J* = 2.5, 14 Hz, 1H), 2.19 (s, 3H), 2.40 (dd, *J* = 6.5, 12.5 Hz, 1H), 2.66 (dd, 9.5 Hz, 12.5 Hz, 1H), 2.93 (m, 1H), 3.16 (m, 1H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.58 (d, *J* = 13.5 Hz, 1H), 3.86 (m, 4H), 7.1–7.4 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 27.6, 33.8, 35.9, 38.0, 42.9, 44.0, 61.1, 63.1, 64.4, 64.5, 112.0, 123.7, 125.8, 126.7, 127.1, 127.3, 128.6, 129.6, 140.0, 144.8; HRMS calc. for $C_{23}H_{28}O_2N$: 350.2120; Found: 350.2116 Δ = 1.1 ppm. **5d:** ^{1}H NMR ($CDCl_3$): δ 0.78 (m, 1H), 1.79 (m, 3H), 2.00 (m, 1H), 2.08 (s, 3H), 2.25 (m, 2H), 2.93 (m, 1H), 3.20 (m, 1H), 3.35 (m, 2H), 3.90 (m, 4H), 6.96 (m, 1H), 7.10 (m, 3H), 7.27 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 27.8, 34.1, 38.1, 42.0, 42.2, 43.2, 62.6, 63.4, 64.1, 64.2, 111.8, 124.8, 124.8, 126.2, 126.4, 126.7, 128.1, 129.0, 139.6, 140.2, 140.4; HRMS calc. for $C_{23}H_{28}O_2N$: 350.2120; Found: 350.2108 Δ = 3.4 ppm.

(1R, 2S*, 4R*)-9,9-[Ethylenebis(oxy)]-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-[[2-(phenylmethyl)-amino]-ethyl]-2-carboxylic acid ethyl ester (5e)*

A 2.5 M solution of *n*-BuLi in hexane (5.9 mL; 14.6 mmol) was added to a solution of diisopropyl amine in 25 mL THF at 0 °C. After stirring 10 min at 0 °C, the resulting LDA solution was cooled to -78 °C. The mixture of ethylene ketals of **4a, b** (2.78 g; 9.7 mmol), prepared as described above, was then added dropwise as a solution in 25 mL of THF over 15 min. After stirring for 1 h at -78 °C, allyl bromide was added over 5 min. The reaction was stirred for 3 h during which time the temperature was allowed to rise from -78 °C to -40 °C. After partitioning the reaction mixture between Et_2O (200 mL) and brine (200 mL), the organic layer was dried ($MgSO_4$) and concentrated to an oily residue. This crude mixture of isomers was purified and the diastereomers separated by flash chromatography (85:15 hexanes:ethyl acetate) to afford 2.08g (65%) of **5 (R = $CH_2CH{=}CH_2$, R^1 = CO_2Et)** as a colorless oil and 0.78g (25%) of **5 (R = CO_2Et, R^1 = $CH_2CH{=}CH_2$)** as a colorless solid.

5 (R = CO_2Et, R^1 = $CH_2CH{=}CH_2$): ^{1}H NMR ($CDCl_3$): δ 1.09 (t, *J* = 7, 7.5Hz, 3H), 1.70 (dd, *J* = 3.5, 14.5Hz, 1H), 1.97 (dd, *J* = 2.5, 14.5Hz, 1H), 2.29 (dd, *J* = 3.5, 5.5Hz, 1H), 2.35 (dd, *J* = 3.5, 6Hz, 1H), 2.63 (d, *J* = 7Hz, 2H), 2.99 (m, 1H), 3.32 (m, 1H), 3.90 (m, 6H), 5.07, (m, 2H), 5.70 (m, 1H), 7.15 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.1, 30.8, 36.1, 42.1, 42.9, 43.5, 49.2, 60.4, 64.1, 64.2, 110.9, 117.6, 124.5, 125.4, 126.5, 126.9, 134.0, 139.7, 140.5, 175.2. **5 (R = $CH_2CH{=}CH_2$, R^1 = CO_2Et)**: m.p. 65–67.5 °C; ^{1}H NMR ($CDCl_3$): δ 1.28 (m, 1 H), 1.31 (t, *J* = 7Hz, 3H), 1.61 (t, *J* = 7, 6.5Hz, 1 H), 1.75 (dd, *J* = 3.5, 14.5Hz, 1H), 1.98 (t, *J* = 7.5, 6.5Hz, 1H), 2.06 (dd, *J* = 2.5, 14Hz, 1H), 2.95 (m, 1H), 2.97 (m, 1H), 3.35 (t, *J* = 3Hz, 1H), 3.94 (m, 4H), (q, *J* = 7.5, 14.5Hz, 2H), 4.90 (m, 2H), 5.56 (m, 1H), 7.20 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.4, 30.7, 38.5, 42.7, 43.5, 45.5, 49.2, 60.7, 64.1, 64.3, 110.9, 117.8, 125.4, 125.6, 126.6, 127.0, 133.2, 139.4, 139.8, 175.5.

An ozone/oxygen mixture was bubbled through a suspension of **5 (R = $CH_2CH{=}CH_2$, R^1 = CO_2Et)** (0.68 g; 2.06 mmol) and $NaHCO_3$ (0.02 g; mmol) in MeOH for 10 min at -78 °C. Me_2S (1.5 mL) was added and the reaction mixture was allowed to warm to r.t. After stirring for 20 h, the reaction mixture was concentrated and the residue was partitioned between H_2O and Et_2O (50 mL). The organic layer was washed with brine (2 x 50 mL) and dried ($MgSO_4$). Concentration afforded 0.63 g (94%) of the aldehyde as a colorless oil.

Dilute methanolic HCl (~20 mL) was added to benzyl amine (0.4 mL; 3.64 mmol) with stirring (pH 6). The above aldehyde (0.6 g; 1.82 mmol) was added as a solution in MeOH (~5 mL), followed by 3Å molecular sieves (1 g) and $NaBH_3CN$ (0.12 g; 1.82 mmol). After stirring for 24 h, the cloudy reaction mixture was filtered through celite and the filtrate was concentrated. The residue was partitioned between ethyl acetate (50 mL) and 0.5 N NaOH (30 mL). The organic layer was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (ethyl acetate) to afford 0.59 g (80%) of **5e** as an oily residue. ^{1}H NMR ($CDCl_3$): δ 1.00 (m, 1H), 1.21 (m, 5H), 1.52 (m, 1H), 1.73 (dd, *J* = 3.5, 14.5 Hz, 1H), 1.99 (dd, *J* = 2.5, 14.5 Hz, 1H), 2.45 (m, 2H), 2.94 (m, 1H), 2.99 (s, 1H), 3.30 (m, 1H), 3.63 (s, 2H), 3.86 (m, 4H), 4.20 (m, 2H), 7.20 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 14.5, 31.0, 38.6, 41.5, 43.6, 43.7, 44.8, 48.3, 54.1, 61.0, 64.3, 64.6, 111.0, 125.6, 125.7, 126.9, 127.1, 127.2, 128.2, 128.5, 139.5, 139.9, 140.4, 176.1; HRMS calc. for $C_{26}H_{32}O_4N$: 422.2331; Found: 422.2327 Δ = 0.9 ppm.

(1R, 2R*, 4R*)-9,9-[Ethylenebis(oxy)]-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-[[2-(phenylmethyl)-amino]-ethyl]-2-carboxylic acid ethyl ester (5f)*

Prepared from **5 (R = CO_2Et, R^1 = $CH_2CH{=}CH_2$)**: m.p. 159–162 °C; ^{1}H NMR ($CDCl_3$): δ 1.04 (t, *J* = 7 Hz, 3H), 1.70 (dd, *J* = 3.5, 14.5 Hz, 1H), 1.93 (dd, *J* = 2, 13.5 Hz, 1H), 2.10 (m, 3H), 2.31 (m, 1H), 2.50 (m, 1H), 2.67 (m, 1H), 2.97 (m, 1H), 3.28 (t, *J* = 3 Hz, 1H), 3.76–3.98 (m's, 8H), 7.03–7.34 (m's, 9H); ^{13}C NMR ($CDCl_3$): δ 14.0, 30.7, 36.1, 37.9, 43.5, 43.7, 45.8, 47.9, 54.0, 60.4, 64.1, 64.2, 110.9, 124.5, 125.4, 126.4, 126.9, 128.0, 128.3, 139.5, 140.3, 140.3, 175.5; HRMS calc. for $C_{26}H_{32}O_4N$: 422.2331; Found: 422.2318 Δ = 3.1 ppm.

(1R, 2S*, 4S*)-1,2,3,4-Tetrahydro-*N*-carbobenzyloxy-9-oxo-*N*-methyl-1,4-ethanonaphthalen-2-amine (6a)*

To a suspension of 2.5 mL (19.70 mmol) of KH/mineral oil (~ 8 M) (hexanes washed) in 20 mL of dry THF under Ar at r.t. was added a solution of 2.40 g (6.567 mmol) of **5a** dissolved in 4 mL of THF. After 30 min, 4.41 mL (65.67 mmol) of MeI was added and the mixture immediately warmed to 45–50 °C. After 6 h, the reaction

mixture was carefully poured into 150 mL of H_2O stirring at ~0 °C along with 150 mL of Et_2O. After 5 min, the layers were separated and the aqueous layer extracted with an additional 150 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a crude residue which was purified by flash chromatography (7:3 hexanes:ethyl acetate) resulting in 1.85 g (74%) of a colorless oil. R_f: 0.17 (3:1 hexane:ethyl acetate); ^1H NMR ($CDCl_3$): δ 1.78 (m, 2H), 2.26 (m, 2H), 3.01 (brs, 1H), 3.19 (brs, 4H), 3.84–4.01 (m, 4H), 4.13 (m, 1H), 5.10 (d, J = 13 Hz, 1H), 5.20 (d, J = 13 Hz, 1H), 7.09–7.40 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 23.3, 31.6, 36.1, 41.8, 43.6, 52.9, 64.1, 64.3, 67.1, 111.0, 123.9, 125.4, 126.8, 126.9, 127.7, 127.8, 128.4, 136.9, 139.1, 141.6, 156.9.

To a stirring solution of 2.44 g (6.43 mmol) of the above ketal in 55 mL of THF was added 65 mL of 2 N HCl. The resulting cloudy mixture was stirred at r.t. for 21 h at which point it was poured into 150 mL of brine and extracted with 2 x 175 mL of EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated to give a crude residue which was purified by flash chromatography (7:3 hexanes:ethyl acetate) to give 2.12 g (98%) of **6a** as a viscous oil. R_f: 0.27 (96:4 CH_2Cl_2:Et_2O); ^1H NMR ($CDCl_3$): δ 2.09–2.33 (m, 3H), 2.66 (dd, J = 3, 16 Hz, 1H), 3.01 (s, 3H), 3.54 (dd, J = 2, 5 Hz, 1H), 3.63 (dd, J = 3,3 Hz, 1H), 4.32 (m, 1H), 5.17 (d, J = 12 Hz, 1H), 5.21 (d, J = 12 Hz, 1H), 7.17–7.38 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 26.6, 32.3, 37.6, 42.6, 52.8, 53.2, 67.3, 125.2, 125.6, 127.5, 127.6, 127.9, 128.0, 128.4, 135.7, 136.5, 141.8, 156.8, 210.2; HRMS calc. for $C_{21}H_{22}O_3N$: 336.1599; Found: 336.1613 Δ = 4.2 ppm.

(1R, 2R*, 4S*)-1,2,3,4-Tetrahydro-*N*-carbobenzyloxy-9-oxo-*N*-methyl-1,4-ethanonaphthalen-2-amine (**6b**)*

R_f: 0.16 (3:1 hexane:ethyl acetate); ^1H NMR ($CDCl_3$): δ 1.73 (m, 1H), 2.09 (s, 3H), 2.05–2.19 (m, 1H), 2.34–2.52 (m, 2H), 3.44 (d, J = 2 Hz, 1H), 3.62 (t, J = 3 Hz, 1H), 4.92 (brs, 1H), 5.15 (s, 2H), 7.18–7.43 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 27.5, 29.5, 41.0, 42.4, 52.2, 53.2, 67.3, 125.6, 125.8, 127.7, 127.8, 128.0, 128.5, 136.1, 136.7, 139.8, 156.5, 209.7; HRMS calc. for $C_{21}H_{22}O_3N$: 336.1599; Found: 336.1608 Δ = 2.4 ppm.

(1R, 2R*, 4S*)-1,2,3,4-Tetrahydro-*N*-methyl-9-oxo-*N*-(phenylmethyl)-1,4-ethanonaphthalene-2-methanamine (**6c**)*

A mixture of **5c** (1.53 g; 4.4 mmol) in 2N HCl (48 mL) and THF (40 mL) was stirred at r.t. for 18 h. The volatiles were removed *in vacuo* and the remaining aqueous mixture basified to pH 13. After extracting with EtOAc, the organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 1.32 g (99%) of **6c** as a colorless oil. No further purification of **6c** was necessary. ^1H NMR ($CDCl_3$): δ 1.53 (m, 1H), 2.00 (m, 3H), 2.23 (s, 3H), 2.33 (m, 2H), 2.51 (m,1H), 3.50 (m, 4H), 7.18–7.40 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 29.4, 33.9, 36.1, 38.3, 42.6, 53.0, 60.2, 62.8, 123.6, 125.8, 127.0, 127.2, 127.3, 128.3, 129.0, 136.4, 139.1, 144.5, 211.5; HRMS calc. for $C_{21}H_{24}ON$: 306.1857; Found: 306.1849 Δ = 2.6 ppm.

(1R, 2S*, 4S*)-1,2,3,4-Tetrahydro-*N*-methyl-9-oxo-*N*-(phenylmethyl)-1,4-ethanonaphthalen-2-methanamine (**6d**)*

^1H NMR ($CDCl_3$): δ 1.20 (m, 1H),1.90 (m, 2H), 2.14 (s, 3H), 2.20–2.40 (m, 4H), 3.35 (m, 2H), 3.51 (m, 2H), 7.00–7.40 (m, 9H); HRMS calc. for $C_{21}H_{24}ON$: 306.1857; Found: 306.1852 Δ = 1.6 ppm.

(1R, 2S*, 4R*)-1,2,3,4-Tetrahydro-9-oxo-*N*-(phenylmethyl)-spiro[1,4-ethanonaphthalene-2,3'-pyrrolidine] (**6e**)*

A mixture of **5e** (0.55 g; 1.36 mmol) and 25% NaOMe in MeOH (0.5 mL; 2.0 mmol) was refluxed in 13 mL of MeOH for 3.5 h. After cooling, the reaction mixture was diluted with EtOAc (60 mL) and the mixture washed with 1 N HCl (60 mL), sat. aq. $NaHCO_3$ (60 mL), and brine (60 mL). After drying over $MgSO_4$, the organic layer was concentrated and the resulting material purified by flash chromatography (3:1 to 1:1 hexanes:ethyl acetate) to afford 0.39 g (76%) of the lactam as an oily residue.

A solution of the above lactam (0.34 g; 0.91 mmol) in 5 mL of THF was added dropwise to a suspension of $LiAlH_4$ (0.15 g; 3.8 mmol) in 20 mL of Et_2O at r.t. over 30 min. After stirring 1 h, the reaction mixture was cooled to 0 °C and 0.16 mL of H_2O was added dropwise followed by 0.16 mL of 15% NaOH solution and another 0.48 mL of H_2O. Et_2O and $MgSO_4$ were then added. Filtration of the suspension and concentration of the filtrate gave crude material which was purified by flash chromatography (3:2 ethyl acetate:hexanes) to give 0.27 g (82%) of an oily residue.

A mixture of the above pyrrolidine (1 g; 2.8 mmol), 2 N HCl (32 mL) and THF was stirred at r.t. for 18 h. The THF was removed *in vacuo* and the remaining aqueous mixture was basified to pH > 13 with 3 N KOH. The aqueous layer was extracted with ethyl acetate and the organic extracts washed with brine, dried over $MgSO_4$ and concentrated to afford 0.95 g (~100%) of ketone **6e** as an oil. ^1H NMR ($CDCl_3$): δ 1.09 (m, 1H), 1.71 (m, 1H), 1.85 (dd, J = 3.5, 14 Hz, 1H), 2.10 (dd, J = 3, 19 Hz, 1H), 2.21 (dd, J = 2.5, 14 Hz, 1H), 2.42 (dd, J = 2.5, 19 Hz, 1H), 2.57 (m, 2H), 2.65 (m, 2H), 3.12 (t, J = 2.5, 3 Hz, 1H), 3.55 (m, 1H), 3.61 (d, J = 13.5 Hz, 1H), 3.68 (d, J = 13 Hz, 1H), 7.17–7.37 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 38.6, 41.6, 42.9, 44.3, 46.9, 53.2, 54.0, 60.4, 66.4, 125.2, 125.5, 127.0, 127.1, 128.3, 128.5, 136.2, 139.1, 142.0, 211.3; HRMS calc. for $C_{22}H_{24}ON$: 318.1858; Found: 318.1845 Δ = 4.1 ppm.

(1R, 2R*, 4R*)-1,2,3,4-Tetrahydro-9-oxo-*N*-(phenylmethyl)-spiro[1,4-ethanonaphthalene-2,3'-pyrrolidine] (**6f**)*

^1H NMR ($CDCl_3$): δ 1.80–2.16 (m's, 6H), 2.27 (d, J = 9.5 Hz, 1H), 2.60 (m, 2H), 2.74 (m, 1H), 3.14 (t, J = 2.5, 3 Hz, 1H), 3.51 (m, 3H), 7.13–7.29 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 37.9, 38.6, 42.5, 44.4, 46.8, 53.3, 54.1, 60.0, 68.9, 124.9, 125.6, 126.8, 127.1, 128.1, 128.3, 135.6, 139.1, 142.2, 211.4; HRMS calc. for $C_{22}H_{24}ON$: 318.1858; Found: 318.1855 Δ = 0.9 ppm.

General procedure for the addition of 4-methoxyphenyl cerium reagent to ketone **6**. *Preparation of (1R*, 2S*, 4S*, 9R*)-1,2,3,4,-tetrahydro-9-(4-methoxyphenyl)-2-(carbobenzyloxy)-(methyl)-amino-1,4-ethanonaphthalene-9-ol (***7a***) and (1R*, 2S*, 4S*, 9S*)-1,2,3,4-tetrahydro-9-(4-methoxyphenyl)-2-(carbobenzyloxy)-(methyl)-amino-1,4-ethanonaphthalene-9-ol (***8a***)*

A suspension of 2.27 g (1.5 eq.; 9.20 mmol) of anhydrous cerium (III) chloride was stirred in 17 mL of dry THF at r.t. under Ar for 2 h. During this time, in a separate flask, 3.68 mL (1.5 eq.; 9.20 mmol) of 2.5 M *n*-BuLi/hexane was added to a solution of 1.39 mL (1.8 eq.; 11.058 mmol) of 4-bromoanisole in 20 mL of dry THF at -78 °C under Ar and the resulting cloudy solution stirred at that temperature for 1 h. The cerium chloride/THF slurry was cooled to -78 °C and the aryl lithium reagent prepared above added to it dropwise by means of a cannula. The resulting orange mixture was stirred at -78 °C for 30 min at which point 2.06 g (6.16 mmol) of **6a** dissolved in 23 mL of dry THF was added. After stirring for 1 h, the reaction was quenched with 50 mL of H_2O and warmed to r.t. The mixture was poured into an additional 150 mL of H_2O and extracted with 3 x 150 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a crude residue which was purified by flash chromatography (65:35 hexanes:ethyl acetate) to give 2.10 g (77%) of a white foam. The product consisted of a ~2:1 mixture of **7a:8a** by NMR. These isomers were separated on small scale by preparative TLC (93:7 CH_2Cl_2:Et_2O). **7a**: R_f: 0.33 (93:7 CH_2Cl_2:Et_2O); ^1H NMR ($CDCl_3$): δ 1.73–1.95 (m, 3H), 2.72 (s, 3H), 2.85 (dd, *J* = 2, 15 Hz, 1H), 3.31, (brs, 1H), 3.63 (brs, 1H), 3.83 (s, 3H), 3.93 (m, 1H), 5.07 (d, *J* = 12 Hz, 1H), 5.17 (d, *J* = 12 Hz, 1H), 6.94 (d, *J* = 9 Hz, 2H), 7.19–7.39 (m, 9H), 7.59 (d, *J* = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 24.1, 31.5, 38.1, 40.9, 45.5, 54.3, 55.2, 67.1, 75.4, 113.9, 124.2, 126.9, 127.3, 127.7, 127.9, 128.0, 128.4, 136.2, 136.7, 138.6, 142.0, 156.9, 159.0; HRMS calc. for $C_{28}H_{20}O_4NNa$: 466.1994; Found: 466.1971 Δ = 4.9 ppm. **8a**: R_f: 0.21 (93:7 CH_2Cl_2:Et_2O); ^1H NMR ($CDCl_3$): δ 1.76 (ddd, *J* = 2, 10, 13 Hz, 1H), 2.31 (m, 2H), 3.00 (brs, 1H), 2.97–3.09 (m, 1H), 3.26 (s, 3H), 3.28 (d, *J* = 2 Hz, 1H), 3.70 (s, 3H), 3.98 (m, 1H), 5.13 (d, *J* =13 Hz, 1H), 5.21 (d, *J* = 13 Hz, 1H), 6.60 (d, *J* = 9 Hz, 2H), 6.70 (m, 1H), 6.73 (d, *J* = 9 Hz, 2H), 7.00 (m, 1H), 7.16 (d, *J* = 4 Hz, 2H), 7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.9, 34.4, 38.1, 41.4, 49.5, 55.0, 56.7, 67.1, 75.4, 112.6, 123.5, 126.3, 126.6, 126.7, 127.9, 127.9, 128.5, 136.8, 140.4, 140.6, 141.8, 156.7, 158.0; HRMS calc. for $C_{28}H_{29}O_4NNa$: 466.1994; Found: 466.1992 Δ = 0 ppm.

(1R, 2R*, 4S*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-2-(carbobenzyloxy)-(methyl)-amino-1,4-ethanonaphthalene-9-ol (***7b***)*

R_f: 0.15 (3:1 hexane:ethyl acetate); ^1H NMR ($CDCl_3$): δ 1.26 (m, 1H), 1.69 (dd, *J* = 4, 15 Hz,1H), 1.85–2.04 (m, 1H), 1.98 (s, 3H), 2.82 (brd, *J* = 15 Hz, 1H), 3.17, (m, 1H), 3.28 (m, 1H), 3.82 (s, 3H), 4.71 (brs, 1H), 5.13 (s, 2H), 6.92 (d, *J* = 9 Hz, 2H), 7.15–7.43 (m, 9H), 7.59 (d, *J* = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 25.6, 29.4, 41.3, 43.2, 48.8, 52.8, 55.3, 67.1, 75.3, 113.6, 125.7, 126.5, 127.1, 127.4, 127.6, 127.9, 128.4, 136.6, 136.9, 139.6, 140.0, 156.6, 158.8; HRMS calc. for $C_{28}H_{29}O_4NNa$: 466.1994; Found: 466.1995 Δ = 0.2 ppm.

(1R, 2R*, 4S*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-2-(carbobenzyloxy)-(methyl)-amino-1,4-ethanonaphthalene-9-ol (***8b***)*

7b and **8b** were not separated. **8b**: R_f: 0.10 (3:1 hexane:ethyl acetate); ^1H NMR (partial; $CDCl_3$): δ 2.10 (s, 3H), 3.71 (s, 3H), 3.98 (m, 1H), 6.63 (d, *J* = 9 Hz, 2H), 6.78 (d, *J* = 9 Hz, 2H); HRMS calc. for $C_{28}H_{29}O_4N$: 444.2175; Found: 444.2171 Δ = 0.9 ppm.

(1R, 2R*, 4S*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-2-[[methyl-(phenylmethyl)amino]methyl]-1,4-ethanonaphthalene-9-ol (***7c***)*

^1H NMR ($CDCl_3$): δ 0.92 (ddd, *J* = 2, 6.5, 13.5 Hz,1H),1.48 (m, 3H), 1.70 (m, 1H), 2.07 (dd, *J* = 6.5, 12.5 Hz, 1H),2.22 (s, 3H), 2.37 (dd, *J* = 10,12.5 Hz, 1H), 2.51 (dd, *J* = 2.5, 14.5 Hz,1H), 3.26 (m, 3H), 3.64 (d, *J* = 13 Hz, 1 H), 3.81 (s, 3H), 6.80 (d, *J* = 9 Hz, 2H), 7.23–7.36 (m,11 H); ^{13}C NMR ($CDCl_3$): δ 26.4, 34.1, 35.9, 36.7, 42.8, 48.0, 55.2, 59.6, 63.2, 76.0, 113.5, 123.4, 126.2, 126.9, 127.0, 127.9, 128.2, 129.2, 136.3, 139.5, 139.6, 145.0, 158.6; Anal. ($C_{28}H_{31}NO_2$) C, H, N.

(1R, 2R*, 4S*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-2-[[methyl-(phenylmethyl)amino]methyl]-1,4-ethanonaphthalene-9-ol (***8c***)*

^1H NMR ($CDCl_3$): δ 1.54 (m, 1H), 1.85–2.20 (m, 4H), 2.26 (s, 3H), 2.55 (dd, *J* = 6.5, 13 Hz, 1H), 2.84–2.94 (m, 2H), 3.20 (m, 1H), 3.48 (d, *J* = 13 Hz, 1H), 3.66 (d, *J* = 13 Hz, 1H), 3.70 (s, 3H), 6.60 (d, *J* = 9 Hz, 2H), 6.74 (d, *J* = 9.5 Hz, 2H), 7.00 (dt, *J* = 2.5, 7 Hz, 1H), 7.10–7.42 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 26.2, 33.4, 37.9, 38.6, 42.5, 48.8, 55.1, 60.3, 62.8, 75.7, 112.7, 123.1, 125.9, 126.2, 126.4, 126.7, 127.1, 128.2, 129.4, 139.1, 141.2, 141.3, 144.5, 158.0.

(1R, 2S*, 4S*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-2-[[methyl-(phenylmethyl)amino]-methyl]-1,4-ethanonaphthalene-9-ol (***7d***)*

^1H NMR ($CDCl_3$): δ 0.76 (m, 1H),1.73 (m, 4H), 2.10 (s, 3H), 2.11 (m, 1H), 2.68 (dd, *J* = 2.5, 14.5 Hz, 1H), 3.07 (m, 1H), 3.29 (d, *J* = 13.5 Hz, 1H), 3.36 (m, 1H), 3.40 (d, *J* = 13 Hz, 1H), 3.82 (s, 3H), 6.92 (d, *J* = 9.5 Hz, 2H), 7.08–7.38 (m, 9H), 7.58 (d, *J* = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 27.6, 34.4, 38.0, 42.5, 44.3, 48.8, 55.3, 62.8, 63.6, 76.2, 113.5, 125.9, 126.2, 126.4, 126.8, 127.5, 128.1, 128.9, 137.3, 139.6, 139.8, 140.9, 158.7; Anal. ($C_{28}H_{31}NO_2 \cdot 0.25\ H_2O$) C, H, N.

(1R, 2S*, 4S*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-2-[[methyl-(phenylmethyl)amino]methyl]-1,4-ethanonaphthalene-9-ol (**8d**)*

^{1}H NMR ($CDCl_3$): δ 0.74 (m, 1H), 1.70–2.03 (m, 4H), 2.14 (s, 3H), 2.28 (m, 1H), 2.41 (m, 1H), 2.67 (m, 1H), 3.00 (m, 1H), 3.34 (m, 2H), 3.47 (d, 1H), 3.70 (s, 3H), 6.62 (m, 2H), 6.78 (m,1H), 6.82 (m, 2H), 7.20 (m, 3H), 7.30 (m, 5H).

(1R, 2S*, 4R*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-(phenylmethyl)spiro[2,3'-pyrrolidino]-1,4-ethanonaphthalene-9-ol (**7e**)*

^{1}H NMR ($CDCl_3$): δ 0.83 (m, 1H), 1.43 (m, 1H), 1.53 (m, 2H), 1.72 (m, 2H), 2.47 (m, 2H), 2.70 (m, 2H), 2.90 (m, 1H), 3.30 (m, 1H), 3.59 (m, 2H), 3.83 (s, 3H), 6.89 (d, J = 9 Hz, 2H), 7.28 (m, 9H), 7.52 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 39.5, 40.1, 41.9, 43.9, 45.6, 49.0, 53.0, 55.3, 60.5, 66.7, 75.5, 113.6, 126.8, 127.1, 127.9, 128.2, 128.3, 128.5, 136.7, 139.2, 139.3, 142.4, 158.8; HRMS calc. for $C_{29}H_{32}O_2N$: 426.2433; Found: 426.2436 Δ = 0.7 ppm.

(1R, 2S*, 4R*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-(phenylmethyl)spiro[2,3'-pyrrolidino]-1,4-ethanonaphthalene-9-ol (**8e**)*

^{1}H NMR ($CDCl_3$): δ 1.05 (m, 1H), 1.39 (dd, J = 3, 13.5Hz, 1H), 1.65 (m, 1H), 1.92 (m, 1H), 2.17 (m, 2H), 2.52 (m, 1H), 2.68 (m, 1H), 2.70–2.86 (m, 2H), 2.89 (m, 1H), 3.00 (m, 2H), 3.70 (s, 5H), 6.61 (d, J = 9Hz, 2H), 6.77 (m, 3H), 7.02 (m, 1H), 7.14 (d, J = 4 Hz, 2H), 7.19–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 40.3, 41.7, 42.4, 43.3, 46.2, 49.7, 53.3, 55.1, 60 8, 66.7, 75.1, 112.8, 124.6, 125.9, 126.0, 126.2, 126.7, 126.8, 128.2, 128.7, 139.4, 141.0, 142.2, 144.3, 158.0.

(1R, 2R*, 4R*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-(phenylmethyl)spiro[2,3'-pyrrolidino]-1,4-ethanonaphthalene-9-ol (**7f**)*

^{1}H NMR ($CDCl_3$): δ 1.48–1.72 (m, 5H), 2.08 (m, 1H), 2.12 (d, J = 9Hz, 1H), 2.48 (m, 1H), 2.63 (m, 1H), 2.92 (s, 1H), 2.97 (m, 1H), 3.27 (t, J = 2 Hz, 1H), 3.44 (d, J = 13.5 Hz, 1H), 3.49 (d, J = 13 Hz, 1H), 3.81 (s, 3H), 6.92 (d, J = 9 Hz, 2H), 7.20 (m, 9H), 7.59 (d, J = 9.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 38.7, 38.8, 39.9, 43.9, 45.7, 49.4, 53.6, 55.3, 60.1, 69.5, 75.8, 113.6, 124.9, 126.5, 126.7, 126.8, 127.9, 128.0, 128.3, 136.8, 138.9, 139.3, 142.6, 158.8; Anal. ($C_{25}H_{31}NO_2$) C, H, N.

(1R, 2R*, 4R*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-(phenylmethyl)spiro[2,3'-pyrrolidino]-1,4-ethanonaphthalene-9-ol (**8f**)*

^{1}H NMR ($CDCl_3$): δ 1.43 (dd, J = 3.5, 13.5 Hz, 1H), 1.74 (d, J = 9.5 Hz, 1H), 2.10–2.40 (m's, 4H), 2.65 (m, 4H), 2.92 (t, J = 3 Hz, 1H), 2.99 (t, J = 3, 2.5 Hz, 1H), 3.53 (m, 2H), 3.69 (s, 3H), 6.61 (d, J = 9 Hz, 2H), 6.78 (d, J = 9.5 Hz, 2H), 6.98 (m, 1H), 7.10 (d, J = 5.5 Hz, 2H), 7.25 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 38.5, 39.7, 41.1, 43.4, 46.1, 49.7, 53.8, 55.1, 60.3, 69.7, 76.5, 112.8, 124.3, 125.9, 126.1, 126.2, 126.7, 128.1, 128.6, 139.2, 140.6, 141.0, 142.5, 158.0; HRMS calc. for $C_{29}H_{32}O_2N$: 426.2433; Found: 426.2447 Δ = 3.3 ppm.

*General procedure for the conversion of **7**, **8** to **3**. Preparation of (1R*, 2S*, 4S*, 9S*)-1,2,3,4-tetrahydro-9-(4-methoxyphenyl)-N-methyl-1,4-ethanonaphthalen-2-amine (**3a**)*

To a solution of 1.40 g (3.15 mmol) of a mixture of **7a** and **8a** in 19 mL of dry CH_2Cl_2 at 0 °C under Ar was added 1.0 mL (2 eq.; 6.30 mmol) of Et_3SiH followed by 0.77 mL (2 eq.; 6.30 mmol) $BF_3{\cdot}Et_2O$ dropwise. The resulting orange solution was stirred at 0 °C for 30 min and was then quenched with 50 mL of saturated aq. Na_2CO_3 and warmed to r.t. at which point the mixture was poured into an additional 150 mL of saturated Na_2CO_3 and extracted with 3 x 200 mL of Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a crude residue which appeared to be a 85:10:5 mixture of (***N*-Cbz)3a**:(***N*-Cbz)10a**:(***N*-Cbz)9a** by NMR. This material was purified by flash chromatography (85:15 hexanes:ethyl acetate to 3:1 hexanes:ethyl acetate) to give 0.81 g of pure (***N*-Cbz)3a** and 0.29 g of a mixture which was repurified by preparative TLC to give 1.00 g (75%) overall as a viscous oil. (***N*-Cbz)3a:** R_f: 0.29 (3:1 hexane:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.73 (m, 1H), 1.93–2.08 (m, 2H), 2.17 (ddd, J = 2, 7, 13 Hz, 1H), 2.87 (s, 3H), 2.79–2.93 (m, 1H), 3.23 (dd, J = 2, 2 Hz, 1H), 3.36 (dd, J = 2, 2 Hz, 1H), 3.82 (s, 3H), 3.97 (m, 1H), 5.07 (d, J = 12 Hz, 1H), 5.18 (d, J = 12 Hz, 1H), 6.91 (d, J = 9 Hz, 2H), 7.14–7.39 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 22.3, 26.6, 32.0, 39.1, 40.6, 40.9, 55.3, 55.6, 67.1, 113.9, 123.5, 124.2, 126.4, 126.5, 127.7, 127.9, 128.4, 135.0, 136.9, 142.3, 143.8, 157.0, 157.8.

A suspension of 1.31 g (3.06 mmol) of **(*N*-Cbz)3a,** 0.95 g (5 eq.; 15.30 mmol) of ammonium formate and 0.13 g of 10% Pd/C in 32 mL of MeOH and 5 ml of absolute EtOH was stirred under a hydrogen atmosphere (balloon apparatus) for 3 h. After evacuating and flushing with Ar, the catalyst was filtered off on a pad of celite (MeOH wash) and the filtrate evaporated. The resulting residue was dissolved in 200 mL of 1 N NaOH and extracted with 3 x 100 mL of EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated to give a crude residue which was purified by flash chromatography (93:7 CH_2Cl_2:MeOH) to give 0.85 g (94%) of **3a** as a viscous oil. R_f: 0.4 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR ($CDCl_3$): δ 1.47 (ddd, J = 2, 7, 13 Hz, 1H), 1.54–1.78 (m, 2H), 2.47 (s, 3H), 2.37–2.54 (m, 1H), 2.63 (m, 1H), 2.77–2.90 (m, 1H), 2.88 (dd, J = 2, 4 Hz, 1H), 3.11 (brs, 1H), 3.80 (s, 3H), 6.90 (d, J = 9 Hz, 2H), 7.21 (m, 4H), 7.47 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 23.9, 27.6, 34.6, 39.0, 42.0, 43.2, 55.2, 59.3, 113.6, 123.3, 124.4, 126.1, 126.2, 129.7, 135.9, 142.5, 145.1, 157.9.

3a (0.80 g; 2.726 mmol) was dissolved in 30 mL of dry Et_2O. Saturated HCl/Et_2O was added until no additional

solid formed. The solid was filtered and pumped dry to give 0.83 g (92%) of **3a·HCl** as a white powder. m.p. 254–258 °C; ^{1}H NMR ($CDCl_3$): δ 1.73–2.01 (m, 3H), 2.55–2.80 (m, 1H), 2.74 (s, 3H), 2.87 (m, 1H), 2.95 (m, 1H), 3.04 (d, J = 2 Hz, 1H), 3.69 (brs, 1H), 3.74 (s, 3H), 6.93 (d, J = 9 Hz, 2H), 7.26 (m, 4H), 7.68 (d, J = 9 Hz, 2H), 9.74 (brs, 1H), 10.04 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 22.3, 23.0, 31.9, 37.2, 41.7, 43.7, 55.2, 60.0, 114.0, 123.6, 124.6, 126.9, 127.4, 129.7, 133.0, 139.3, 143.3, 158.3; IR (KBr): 3434, 1513, 1461, 1249, 1031 cm^{-1}; MS (Cl/CH_4; relative intensity): 294 (M + H; 100), 263 (10).

(1R, 2R*, 4S*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-methyl-1,4-ethanonaphthalen-2-amine (3b)*

R_f: 0.25 (93:7 CH_2Cl_2:MeOH + 1% NH_3); ^{1}H NMR ($CDCl_3$): δ 0.58 (brs, 1H–NH), 0.72 (brd, J = 14 Hz, 1H), 1.88–2.05 (m, 2H), 2.22–2.39 (m, 1H), 2.35 (s, 3H), 2.82 (m, 1H), 2.93 (d, J = 3 Hz,1H), 3.03 (m, 1H), 3.34 (brs, 1H), 3.81 (s, 3H), 6.90 (d, J = 9 Hz, 2H), 7.10–7.29 (m, 4H), 7.25 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 30.3, 30.4, 33.1, 38.7, 41.4, 41.8, 55.3, 58.6, 113.8, 123.3, 126.1, 126.21 (CH), 126.5, 128.9, 135.8, 139.2, 144.8, 158.0.

3b·HCl: m.p. >275 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 1.20 (m, 1H), 2.02 (m, 2H), 2.38 (m, 1H), 2.50 (s, 3H), 2.87 (t, J = 9 Hz, 1H), 3.09 (d, J = 2 Hz, 1H), 3.60 (m, 1H), 3.73 (d, J = 3 Hz, 1H), 3.82 (s, 3H), 6.92 (d, J = 9 Hz, 2H), 7.22 (d, J = 9 Hz, 2H). 7.23–7.45 (m, 4H), 9.74 (brs, 1H), 10.04 (brs, 1H); ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 25.6, 29.5, 30.2, 36.7, 40.2, 40.7, 55.2, 57.9, 114.0, 123.9, 126.3, 127.1, 127.8, 128.5, 133.9, 135.4, 143.7, 158.2; IR (KBr): 3432, 1609, 1512, 1461, 1249 cm^{-1}; MS (Cl/CH_4; relative intensity): 294 (M + H; 100).

(1R, 2R*, 4R*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-methyl-1,4-ethanonaphthalene-2-methanamine (3c)*

^{1}H NMR ($CDCl_3$): δ 1.40 (m, 2H), 1.68 (m, 1H), 1.81 (m, 1H), 2.14 (ddd, J = 2, 7, 13.5 Hz, 1H), 2.46 (s, 3H), 2.82 (m, 4H), 3.05 (m, 2H), 3.82 (s, 3H), 6.90 (d, J = 9 Hz, 2H), 7.21 (m, 4H), 7.30 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 24.8, 24.9, 36.1, 36.9, 37.9, 40.9, 42.5, 54.5, 55.3, 113.8, 123.6, 126.0, 126.2, 128.9, 135.3, 144.4, 144.6.

3c·HCl: m.p. 197–199 °C; ^{1}H NMR (DMSO-d^6): δ 1.29 (m, 1H), 1.44 (m, 1H), 1.78 (m, 1H), 2.08 (m, 1H), 2.56 (s, 3H), 3.00 (m, 1H), 3.06 (m, 1H), 3.22 (m, 3H), 3.76 (s, 3H), 6.93 (d, J = 9 Hz, 2H), 7.21 (d, J = 3 Hz, 3H), 7.27 (m, 1H), 7.34 (d, J = 9 Hz, 2H), 8.99 (brs, 2H); ^{13}C NMR (DMSO-d^6): δ 23.6, 23.8, 32.9, 35.4, 40.4, 42.1, 50.7, 55.0, 113.8, 123.4, 123.7, 126.0, 126.1, 129.0, 134.4, 143.4, 143.9, 157.5; IR (KBr): 3437, 1512, 1461, 1249, 1034 cm^{-1}; MS (Cl/CH_4; relative intensity): 308 (100).

(1R, 2S*, 4R*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-methyl-1,4-ethanonaphthalene-2-methanamine (3d)*

^{1}H NMR ($CDCl_3$): δ 0.69 (m, 1H), 1.94 (m, 3H), 2.10 (m, 4H), 2.37 (s, 3H), 2.89 (m, 2H), 3.13 (m, 1H), 3.81 (s, 3H), 6.89 (d, J = 8 Hz, 2H), 7.21 (m, 4H), 7.28 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 26.4, 32.5, 36.3, 37.8, 41.6, 41.8, 55.3, 57.7, 113.8, 123.2, 125.4, 126.0, 126.2, 129.0, 136.0, 140.6, 144.7, 157.9 (1 aliphatic carbon unresolved).

3d·HCl: m.p. 209–211 °C (dec.); ^{1}H NMR (DMSO-d^6): δ 0.74 (m, 1H), 1.78–2.02 (m, 3H), 2.16 (m, 1H), 2.36 (m, 1H), 2.45 (m, 4H), 2.78 (m, 1H), 2.91 (m, 1H), 3.30 (m, 1H), 3.76 (s, 3H), 6.94 (d, J = 9 Hz, 2H), 7.24 (m, 3H), 7.31 (d, J = 9 Hz, 2H) 7.40 (m, 1H); ^{13}C NMR (DMSO-d^6): δ 25.6, 31.4, 32.7, 33.9, 36.0, 40.3, 40.5, 53.4, 55.0, 113.7, 123.3, 125.6, 126.0, 126.4, 128.8, 135.1, 139.3, 144.2, 157.6; IR (KBr): 3435, 1609, 1512, 1249 cm^{-1}; MS (Cl/CH_4; relative intensity): 308 (100).

(1R, 2R*, 4S*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)spiro[1,4-ethanonaphthalene-2,3'-pyrrolidine], monohydrochloride (3e·HCl)*

m.p. 187–189 °C. (dec); ^{1}H NMR (DMSO-d^6): δ 0.81 (m, 1H), 1.15 (m, 1H), 1.44 (m, 1H), 1.78 (m, 1H), 1.88 (m, 1H), 2.09 (m, 1H), 2.73 (m, 1H), 2.98 (m, 2H), 3.15 (m, 3H), 3.37 (m, 1H), 3.76 (s, 3H), 6.94 (d, J = 9 Hz, 2H), 7.22 (m, 3H), 7.31 (m, 1H), 7.34 (d, J = 8 Hz, 2H); ^{13}C NMR (DMSO-d^6): δ 26.8, 32.7, 41.9, 42.6, 45.6, 54.2, 55.0, 113.7, 123.6, 124.6, 126.0, 126.4, 128.8, 134.4, 141.2, 143.3, 157.5 (3 aliphatic carbons unresolved); IR (KBr): 3437, 2934, 2743, 1611, 1512, 1248, 1180 cm^{-1}; Mass spec. (Cl; relative intensity): 320 (100).

(1R, 2S*, 4S*, 9S*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)spiro[1,4-ethanonaphthalene-2,3'-pyrrolidine] (3f)*

^{1}H NMR ($CDCl_3$): δ 1.30 (m, 1H), 1.81 (dd, J = 2, 13.5 Hz, 1H), 1.89 (m, 5H), 2.20 (m, 1H), 2.48 (d, J = 11 Hz, 1H), 2.77 (m, 1H), 2.82 (m, 1H), 3.10 (m, 3H), 3.81 (s, 3H), 6.90 (d, J = 9 Hz, 2H), 7.19 (m, 4H), 7.29 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 27.8, 34.7, 38.2, 41.5, 41.9, 43.9, 45.7, 46.8, 55.3, 60.1, 113.8, 123.5, 124.8, 126.1, 126.4, 128.8, 135.3, 141.9, 143.8, 157.9.

3f·HCl: m.p. > 255 °C; ^{1}H NMR (DMSO-d^6): δ 1.37 (m, 1H), 1.64 (d, J = 12.5 Hz, 1H), 1.80 (m, 1H), 2.94 (m, 2H), 2.15 (m, 2H), 2.54 (m, 1H), 2.72 (m, 1H), 2.98 (m, 1H), 3.18 (brs, 2H), 3.28 (m, 1H), 3.75 (s, 3H), 6.94 (d, J = 8 Hz, 2H), 7.23 (m, 4H), 7.34 (d, J = 9 Hz, 2H), 9.31 (brs, 1H), 9.50 (brs, 1H); ^{13}C NMR (DMSO-d^6): δ 26.5, 32.6, 35.6, 40.8, 41.4, 43.8, 45.7, 55.0, 56.2, 113.7, 123.6, 124.8, 126.0, 126.5, 128.8, 134.4, 141.2, 143.5, 157.5 (1 aliphatic carbon unresolved); IR (KBr): 3402, 1610, 1512, 1460, 1250, 1180 cm^{-1}; Mass spec. (Cl; relative intensity): 320 (100).

(1R, 2R*, 4S*, 9R*)-1,2,3,4-Tetrahydro-9-(4-methoxyphenyl)-N-methyl-1,4-ethanonaphthalene-2-methanamine, monohydrochloride (9b·HCl)*

m.p. 248–253 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.61 (m, 2H), 2.20–2.57 (m, 5H), 3.05 (m, 2H), 3.50–3.75 (m, 2H), 3.70 (s, 3H), 6.42 (d, J = 8 Hz, 2H), 6.62 (d, J = 8 Hz, 2H), 6.97 (d, J = 6 Hz, 1H), 7.22 (d, J = 7 Hz, 1H), 7.31 (d, J = 7 Hz, 1H), 7.40 (d, J = 6 Hz, 1H), 8.79 (brs, 1H), 9.07 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 30.4, 32.4, 34.5, 36.8, 41.3, 41.6, 55.1, 57.2, 113.4, 125.8, 126.7, 127.3, 127.7, 128.3, 136.8, 137.3, 139.9, 158.0; IR (KBr): 3442, 1512, 1251, 1034 cm^{-1}; MS (Cl/CH_4; relative intensity): 294 (M + H; 100).

Supplementary Material Available

Tables of atomic coordinates, thermal parameters, bond distances and angles for **3c** (3 pages).

This data may be obtained from the asterisked author.

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11. ^{1}H NMR (δ) **5e**: OCH_2CH_3 (1.09), $CH{=}CH_2$ (5.07, 5.70); **5f**: OCH_2CH_3 (1.28), $CH{=}CH_2$ (4.9, 5.56).

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31. A 10 μM dose of compound **3c**, above that needed to show an anti-ischemic effect, resulted in a significant reduction in pre-ischemic, post-drug cardiac function (HR x LVDP = 1.9 ± 0.8); compound **3d** was not evaluated at a dose higher than 1 μM.

32. SDP, Structure Determination Package, Enraf-Nonius, Bohemia, NY 11716.