Benzazepinone Calcium Channel Blockers. 2. Structure-Activity and Drug Metabolism Studies Leading to Potent Antihypertensive Agents. Comparison with Benzothiazepinones

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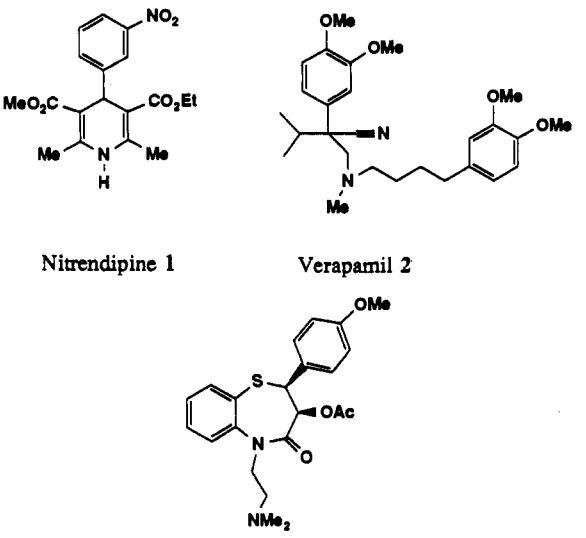
As part of a program to discover potent antihypertensive analogues of diltiazem (3a), we prepared 1-benzazepin-2-ones (4). Benzazepinones competitively displace radiolabeled diltiazem, and show the same absolute stereochemical preferences at the calcium channel receptor protein. Derivatives of 4 containing a trifluoromethyl substituent in the fused aromatic ring show potent and long-acting antihypertensive activity. Studies of the metabolism of 4 lead to the metabolically stable antihypertensive calcium channel blockers 5a and 5c. Benzazepinone 5a is a longer acting and more potent antihypertensive agent than the second generation diltiazem analogue TA-3090 (3e).

Introduction

Calcium channel blockers (CCBs) are important cardiovascular drugs for the management of angina pectoris and hypertension and are being studied in additional therapeutic areas.[1] Currently there are three classes of CCBs that appear to exert their major pharmacological effects by selectively inhibiting the influx of extracellular calcium through the L-type voltage-operated calcium channels.[2] The most studied class of agents are the 1,4-dihydropyridines, e.g., nitrendipine (1), which bind specifically to one of the subunits of the calcium channel (Figure 1).[3] The structural parameters important to potency of dihydropyridines and related compounds in vitro have been described.[4] As a consequence of this interest, several dihydropyridine analogues are currently in clinical development. A second class of compounds are the phenylalkyl amines represented by verapamil (2). The binding site for the phenylalkyl amines appears to be allosterically linked to the dihydropyridine binding site.[4c,5] In contrast



Nitrendipine 1 Verapamil 2

Diltiazem 3a

Figure 1.

to the pharmacological specificity of the dihydropyridines, the phenylalkyl amines appear to possess a variety of ac-

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(3) For a recent review, see: Catterall, W. A.; Seager, J.; Takahashi, M. Molecular Properties of Dihydropyridine-sensitive Calcium Channels in Skeletal Muscle. *J. Biol. Chem.* **1988**, *263*, 3535-3538.

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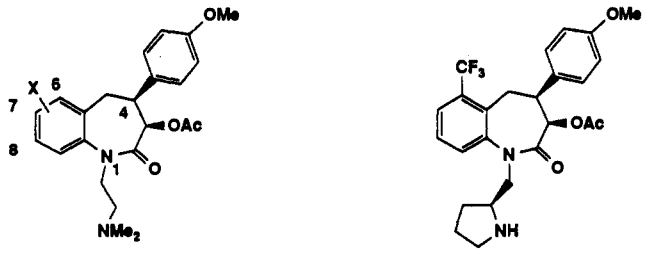

Figure 2. Benzazepinone calcium antagonists.

tions in addition to their ability to block the L-type calcium channel.[6]

A third and structurally distinct class of calcium channel blockers, the 1,5-benzothiazepin-2-ones, is represented by diltiazem (**3a**).[7] Similar to the phenylalkyl amines, diltiazem binds to a site on the calcium channel that is allosterically linked to the dihydropyridine receptor.[8] Although the major pharmacological actions of diltiazem appear to be a function of selective L-type calcium channel blocking activitiy, there are reports of additional intracellular effects on calcium release from the sarcoplasmic reticulum and Na–Ca exchange in mitochondria at pharmacologically relevant concentrations.[9] Compared to the dihydropyridines, however, there has been limited information available on structure–activity relationships in the diltiazem series.[7] Nevertheless, diltiazem is one of the most important calcium channel blocking agents in clinical use for the treatment of angina and hypertension.[1,10] Although diltiazem is widely used in therapy, it has a relatively short duration of action and is known to cause significant prolongation of cardiac P–R intervals.[11] A second generation diltiazem analogue, the 8-chloro derivative (benzothiazepinone numbering) TA-3090, has recently been introduced into the clinic. This compound is a more potent antihypertensive than diltiazem in animals.[12]

The combination of proven clinical utility, the need for improvements in potency and duration of action, and limited structure–activity data made the study of diltiazem and related compounds an attractive area for further research. Our overall goal in this work has been to develop a better understanding of the structural parameters im-

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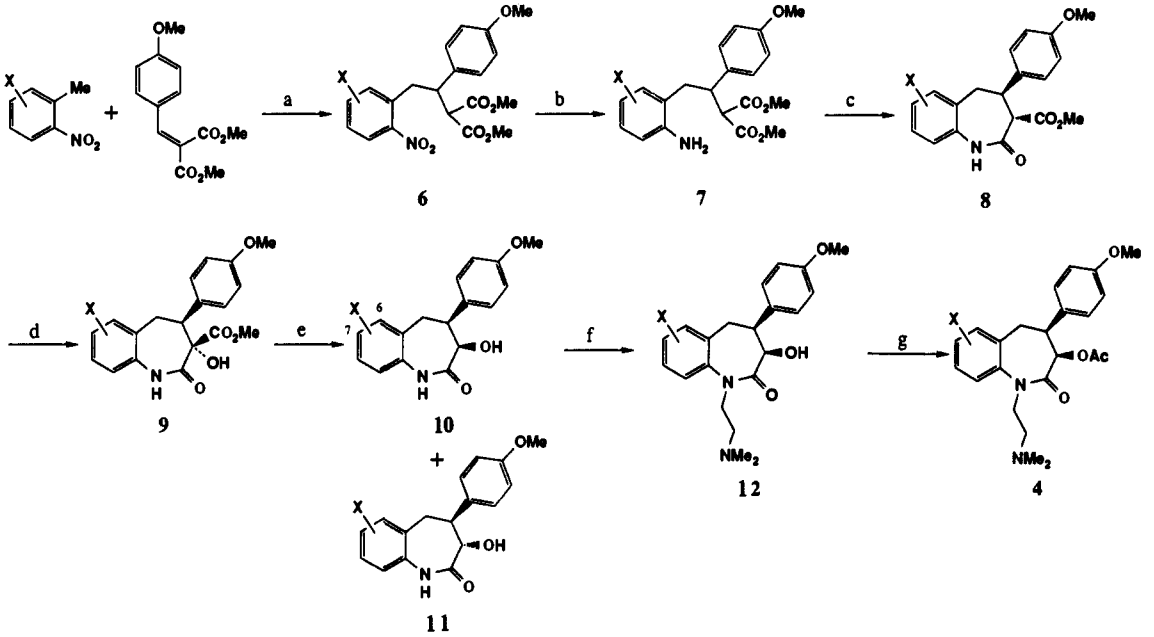
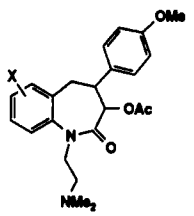
Scheme I[a]



[a] (a) NaH, DMF; (b) H_2, Pd/C; or $SnCl_2$, HCl, MeOH; (c) NaOMe, MeOH, reflux; (d) potassium hexamethyldisilazide, $P(OEt)_3$, O_2; or potassium *tert*-amylate, $P(OMe)_3$, O_2; (e) LiI, pyridine, 100 °C; (f) (*N*,*N*-dimethylamino)ethyl chloride, NaH, DMF, 60 °C; (g) Ac_2O, 100–120 °C.

Table I. Physical Data for Compounds 4



compd	isomer	X	scheme	% yield from 6	mp (°C)	recryst solvent	formula	analysis	optical rotation
4a	racemic (cis)	H	I	38	215–216	$EtOAc/Et_2O$	$C_{23}H_{28}N_2O_4$·HCl	C,H,N,Cl	
4b	racemic (cis)	7-Cl	I	11	217–219	$EtOAc/Et_2O$	$C_{23}H_{27}ClN_2O_4$·HCl	C,H,N,Cl	
4c	racemic (cis)	7-OMe	I	19[a]	215–17	$EtOAc/Et_2O$	$C_{24}H_{30}N_2O_5$·HCl	C,H,N,Cl	
4d	racemic (cis)	6-Cl	I	10	219–22	Et_2O	$C_{23}H_{27}ClN_2O_4$·HCl	C,H,N,Cl	
4e	racemic (cis)	8-Cl	I	6	173–76	$EtOAc/Et_2O$	$C_{23}H_{27}ClN_2O_4$·HCl	C,H,N,Cl	
4f	racemic (cis)	6-OMe	I	29	227–29	$EtOAc/Et_2O$	$C_{24}H_{30}N_2O_5$·HCl	C,H,N,Cl	
4g	racemic (cis)	6-CF_3	I	69	222–24	$EtOAc/Et_2O$	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl,F	
4h	racemic (cis)	7-CF_3	I	12	230–32	Et_2O	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl,F	
4i	3*R*,4*S* (cis)	7-Cl	I	10	252–54	$EtOAc/Et_2O$	$C_{23}H_{27}ClN_2O_4$·HCl	C,H,N,Cl	+131° (*c* = 1, MeOH)
4j	3*S*,4*R* (cis)	7-Cl	I	10	253–55	$EtOAc/Et_2O$	$C_{23}H_{27}ClN_2O_4$·HCl	C,H,N,Cl	−130° (*c* = 1, MeOH)
4k	3*R*,4*S* (cis)	7-CF_3	I	33	257–59	$EtOAc/Et_2O$	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl,F	+143° (*c* = 1, MeOH)
4l	3*S*,4*R* (cis)	7-CF_3	I	30	258–60	$EtOAc/Et_2O$	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl,F	−143° (*c* = 1, MeOH)
4m	3*R*,4*S* (cis)	6-CF_3	I, III	42	180–82	$EtOAc/Et_2O$	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl,F	+97° (*c* = 1, MeOH)
4n	3*S*,4*R* (cis)	6-CF_3	I, III	42	180–82	$EtOAc/Et_2O$	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl,F	−104° (*c* = 1, MeOH)
4o	3*R*,4*R* (trans)	6-CF_3	I, III	74[b]	85–88	$EtOAc/Et_2O$	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl	+129° (*c* = 1, MeOH)
4p	3*S*,4*S* (trans)	6-CF_3	I, III	82[b]	86–89	Et_2O	$C_{24}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl	−130° (*c* = 1, MeOH)

[a] From the 7-*O*-benzyl ether of 6. [b] From 11m.

portant to potency in this class of CCBs as a prelude to the design of new structures. We set as an initial target the discovery of compounds with antihypertensive activity superior to that of diltiazem.

We initially questioned the importance of the sulfur atom in the benzothiazepinone ring system of diltiazem, assuming that its presence was incidental to its synthetic accessibility.[13] Subsequent to the initiation of our studies, reports appeared supporting this assumption, describing the biological activity of benzoxazepinone and benzodiazepinone diltiazem analogues as similar to the benzothiazepinones.[14] In our studies we substituted a methylene

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group for the benzothiazepinone sulfur atom, assuming this change would allow for a wider range of structural modifications than had been achieved with the benzothiazepinones. We sought a method of synthesis employing easily accessible starting materials that would allow substitution in the fused and pendant aromatic rings of benzazepinones 4 (Figure 2). The replacement of sulfur by carbon would also allow us to study the effect of substitution at C-3, as benzazepinones lack a potential leaving group β to the carbonyl. Further, the presence of the benzazepinone ring system could alter the metabolic profile of these compounds relative to that observed with the benzothiazepinones.[15] Therefore, incorporating a methylene group in place of the sulfur atom could result in an improved duration of action. With these considerations we initiated synthetic studies which led to the development of general methods to prepare 1-benzazepin-2-one analogues of diltiazem and allowed us to explore structure–activity relationships in this series.[16]

In this paper we describe additional synthetic studies concerned with the preparation of benzazepinone analogues possessing increased potency in vitro and demonstrating marked antihypertensive activity in the spontaneously hypertensive rat (SHR). This work includes an examination of the effects of both absolute and relative stereochemistry at C-3 and C-4 (benzazepinone numbering) on potency as assessed in isolated, potassium-depolarized rabbit aorta. We have also employed radioligand binding studies to demonstrate that these compounds are antagonists of [^{3}H]diltiazem binding in guinea pig skeletal muscle membrane preparations. Finally, we have investigated the metabolism in vitro and evaluated the biological activity of benzazepinones that are analogous to the known major metabolites of diltiazem resulting from mono-N-demethylation and loss of the C-3 acetyl group.[17] These studies have allowed us to identify metabolically stable 6-(trifluoromethyl)benzazepinone analogues with potent and long-acting antihypertensive activity in the SHR. The most potent of these compounds is *N*-1-pyrrolidinylmethyl analogue **5a**.

Chemistry

As outlined in Scheme I, starting with readily available substituted 2-nitrotoluenes and easily prepared benzylidenemalonates, our procedures allow us to prepare a wide variety of benzazepinone analogues substituted in either aromatic ring. Although the route shown in Scheme I proved to be generally applicable to analogue synthesis, several observations made during this work deserve further comment. Additionally, the previously described synthetic procedures afforded only racemic materials so it was necessary to develop methods for the preparation of nonracemic compounds.

All of the compounds shown in Table I were prepared by the procedures outlined in Scheme I. The addition reaction to form intermediate **6** can be carried out under the previously described conditions, independent of the substitution on either aromatic ring.[16] The only major effect of alterations in the aromatic ring substituents was on reaction time. Thus, stirring a mixture of nitrotoluene and benzylidenemalonate in the presence of sodium hydride at ambient temperature for 6–20 h gave **6** in good yields. In most cases, **6** was isolated by filtration after quenching the reaction mixture with dilute acid in aqueous methanol. In general, a single recrystallization from methanol resulted in analytically pure material. It is important to note again that the order of addition of reagents is very important. Although not investigated in detail, adding 2-nitrotoluene (X = H in Scheme I) to sodium hydride in DMF, in the absence of a benzylidenemalonate, quickly results in a highly exothermic reaction.[18] In the presence of the benzylidenemalonate, only a slight exotherm develops during the addition of the 2-nitrotoluene starting material.

In most cases, reduction of the aromatic nitro group of **6** was accomplished by hydrogenation employing 10% palladium on carbon. For substrates containing aryl chlorides, the reduction of the nitro group was effected with stannous chloride in acidic methanol. Excellent yields of **7** are obtained with either procedure. Cyclization of the amino ester **7** in refluxing methanol in the presence of sodium methoxide affords the desired trans-3,4-disubstituted benzazepinone **8**, also in excellent yield. The pure products from this reaction are generally isolated by filtering the cooled reaction mixture subsequent to the addition of dilute aqueous HCl.

Oxidation at C-3 can be carried out using strong bases and molecular oxygen as the oxidant.[19] Bubbling anhydrous oxygen gas through a cold solution of benzazepinone **8** in tetrahydrofuran that has been pretreated with excess potassium hexamethyldisilazide and triethyl or trimethyl phosphite affords excellent yields of **9**. More

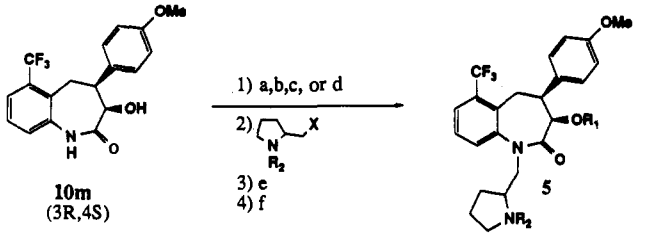
(15) Nakamura, S.; Suzuki, T.; Sugawara, Y.; Usuki, S.; Ito, Y.; Kume, T.; Yoshikawa, M.; Endo, H.; Ohashi, M.; Harigaya, S. Metabolic Fate of Diltiazem. *Arzneim. Forsch.* **1987**, *37*, 1244–1252.

(16) (a) Floyd, D. M.; Moquin, R. V.; Atwal, K. S.; Ahmed, S. Z.; Spergel, S. H.; Gougoutas, J. Z.; Malley, M. F. Synthesis of Benzazepinone and 3-Methylbenzothiazepinone Analogues of Diltiazem. *J. Org. Chem.* **1990**, *55*, 5572–5579. (b) Floyd, D. M.; Krapcho, J. *U.S. Patent 4,748,239*, 1988.

(17) (a) Sugawara, Y.; Ohashi, M.; Nakamura, S.; Usuki, S.; Suzuki, T.; Ito, Y.; Kume, T.; Harigaya, S.; Nakao, A.; Gaino, M.; Inoue, H. Metabolism of Diltiazem. I. Structures of New Acidic and Basic Metabolites in Rat, Dog and Man. *J. Pharmacobio-Dyn.* **1988**, *11*, 211–223. (b) Sugawara, Y.; Nakamura, S.; Usuki, S.; Ito, Y.; Suzuki, T.; Ohashi, M.; Harigaya, S. Metabolism of Diltiazem. II. Metabolic Profile in Rat, Dog and Man. *J. Pharmacobio-Dyn.* **1988**, *11*, 224–233. (c) Sugihara, J.; Sugawara, Y.; Ando, H.; Harigaya, S.; Etoh, A.; Kohno, K. Studies on the Metabolism of Diltiazem in Man. *J. Pharmacobio-Dyn.* **1984**, *7*, 24–32. (d) Montamat, S. C.; Abernethy, D. R.; Mitchell, J. R. High-performance Liquid Chromatographic Determination of Diltiazem and Its Major Metabolites, N-monodemethyldiltiazem and Desacetyldiltiazem, in Plasma. *J. Chromatogr.* **1987**, *415*, 203–207. (e) LeBoeuf, E.; Grech-Belanger, O. Deacetylation of Diltiazem by Rat Liver. *Drug. Metab. Dispos.* **1987**, *15*, 122–126. (f) Montamat, S. C.; Abernethy, D. R. N-monodesmethyldiltiazem is the Predominant Metabolite of Diltiazem in the Plasma of Young and Elderly Hypertensives. *Br. J. Clin. Pharmacol.* **1987**, *24*, 185–189.

(18) Base-induced reactions of 2-nitrotoluenes generally involve the addition of the base to the premixed reagents similar to the conditions we employed for the reaction of 2-nitrotoluenes with benzylidine malonates. We have been unable to find a description of the reaction of 2-nitrotoluenes with strong bases in the literature. The reaction of 4-nitrotoluene with potassium hydride in dimethoxyethane or THF has been described: Buncel, E.; Menon, B. C. Proton-Transfer and Electron-Transfer Processes in Reaction of *p*-Nitrotoluene with Bases. A Spectrophotometric Study. *J. Am. Chem. Soc.* **1980**, *102*, 3499–3507. In this case, mixtures of anionic and radical anionic species are formed although there is no indication that the reaction is violent in nature. We can not exclude a marked solvent effect since we have observed that treatment of 2-nitrotoluene with sodium hydride in THF does not appear to result in a rapid reaction. Nevertheless, *it must be made clear that the reaction of nitrotoluenes with strong bases in DMF, in the absence of trapping reagents, is potentially dangerous.*

Scheme II[a]

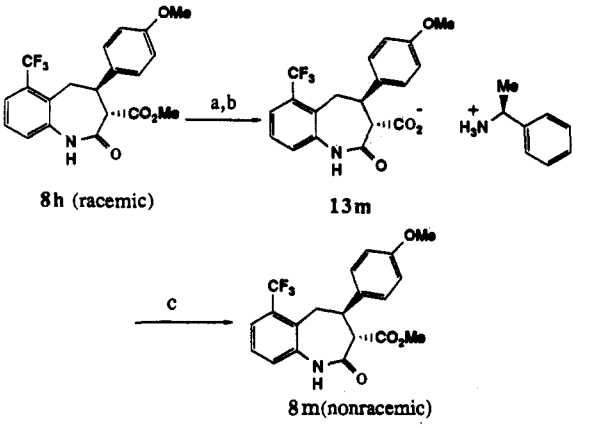


R_2 = CBZ, Me
R_1 = H, Ac
X = Cl, OTs

	R_2	R_1
5g	CBZ	H
5h	CBZ	Ac
5i	Me	H
5j	Me	Ac

[a] (a) NaH/DMF; (b) K_2CO_3/MEK; (c) $Ba(OH)_2/CH_2Cl_2$, phase transfer; (d) Cs_2CO_3/DMF; (e) Ac_2O, DMAP; (f) H_2/Pd–C.

Scheme III[a]



[a] (a) KOH/MeOH; (b) α-methylbenzylamine; (c) MeI/$KHCO_3$/DMF.

conveniently, the reaction can be carried out cleanly on a large scale in toluene–DMF with potassium *tert*-amylate as the base.

Treatment of hydroxy esters **9** (X = H, 7-Cl, 7-CF_3) with excess lithium iodide in hot aqueous pyridine affords a ca. 7:3 mixture of isomeric products **10** and **11** as determined by NMR analysis of the crude product mixture. With the 6-trifluoromethyl-substituted hydroxy ester **9g**, however, we observed that more than 95% of the decarboxylation product was the desired cis isomer **10g**. Interestingly, even under the anhydrous conditions where a predominance of the trans isomer was observed with the unsubstituted and 7-substituted substrates, the 6-trifluoromethyl analogue afforded at most 40% of the trans isomer. Similarly, the reaction of **9d** (X = 6-Cl) under aqueous conditions gave 90% of the cis product **10d**. In almost every example we have encountered, separation of the desired cis isomer **10** from the minor amount of trans alcohol **11** is accomplished by either simple trituration in ether–hexane mixtures or recrystallization of the crude product to afford 50–70% yields of the pure cis alcohol **10**.

The initial assignment of relative stereochemistry for **10** and **11** was based on the ^1H NMR coupling constants for the C-3 and C-4 protons. For example, by analogy to published data for the diltiazem series, we assigned the major isomer **10** as cis with $J_{3,4}$ = 7.9 Hz and the minor isomer **11** as trans with $J_{3,4}$ = 10.0 Hz in the case of the 7-chloro analogues.[13b] Like the benzothiazepinone series, with the 3-hydroxy-substituted benzazepinones the desired cis isomer **10** always has the smaller coupling constant. The cis isomer also elutes faster on silica gel thin-layer chromatography. In several instances, we confirmed our stereochemical assignment by X-ray crystallographic analysis of the alcohol products or subsequently prepared derivatives.[16a]

Once we obtained the desired *cis*-3-hydroxy-4-arylbenzazepinone **10**, the remaining steps proceed by analogy with the benzothiazepinone system.[7b,13b] Accordingly, a variety of published procedures may be followed to incorporate the (*N*,*N*-dimethylamino)ethyl side chain at *N*-1 to afford **12**. We generally employ the reaction of (*N*,*N*-dimethylamino)ethyl chloride in hot DMF using sodium hydride as the base. In the case of the 7-trifluoromethyl-substituted series, however, this procedure gave mainly product resulting from alkylation of the C-3 hydroxyl of **10h** rather than the desired N-1 alkylated material **12h**. With this substrate, we used a phase-transfer procedure and (dimethylamino)ethyl bromide to obtain **12h** in excellent yield. The alkylation of nonracemic (3*R*,4*S*) **10m** by *N*-methyl or *N*-carbobenzyloxy derivatives of prolinol to give nonracemic compounds **5** is shown in Scheme II.

Acetylation of **12** is generally performed in neat acetic anhydride at 100–120 °C. Crude products from this reaction are converted to their hydrochloride salts and purified by recrystallization or simple trituration in ether–hexane. In all cases acetylation affords high yields of **4**.

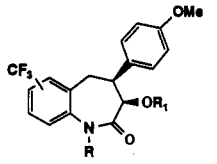
For diltiazem and related benzothiazepinones, maximal calcium channel blocking activity resides in the 2*S*,3*S* isomer (benzothiazepinone numbering).[20] This corresponds to the 3*R*,4*S* absolute configuration in the benzazepinone ring system. To investigate the relationship between biological activity and benzazepinone absolute stereochemistry, resolution procedures were developed. Both the 7-chloro analogue **4b** and the 7-trifluoromethyl analogue **4h** were obtained in nonracemic form by tartaric acid resolution of the corresponding amino alcohol intermediates **12**. The use of *d*-tartaric acid allows the selective crystallization of the 3*R*,4*S* isomers. The respective 3*S*,4*R* enantiomers are obtained from the residue as *l*-tartaric acid salts. Liberation of the free amines followed by acetylation gives the desired resolved enantiomers **4i** and **4k**.

Alternate procedures needed to prepare the enantiomers of the 6-trifluoromethyl analogue **4g** are shown in Scheme III. These involve resolution of the acid resulting from hydrolysis of ester **8g**. Although care is required to avoid decarboxylation of the labile acid, it is possible to effect clean resolution using α-methylbenzylamine. Once the resolution was realized we found it necessary to re-form the methyl ester to continue the synthesis. This was initially accomplished by treatment of the nonracemic acid with methyl iodide in acetone employing a slight excess of 1,8-diazabicyclo[5.4.0]undec-7-ene. Under these conditions, 5%–10% of the resolved material is lost to decarboxylation based on the starting α-methylbenzylamine

(19) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. A One-Step Procedure for the Preparation of Tertiary α-Ketols from the Corresponding Ketones. *J. Org. Chem.* **1968**, *33*, 3294–3297. (b) For leading references on the oxidation of enolates see Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. Synthesis of α-Hydroxy Carbonyl Compounds (Acyloins): Direct Oxidation of Enolates Using 2-Sulfonyloxaziridines. *J. Org. Chem.* **1984**, *49*, 3241–3243.

(20) Sato, M.; Nagao, T.; Yamaguchi, I.; Nakajima, H.; Kiyomoto, A. Pharmacological Studies on a New 1,5-Benzothiazepine Derivative (CRD-401) I. Cardiovascular Actions. *Arzneim. Forsch.* **1974**, *21*, 1338–1343.

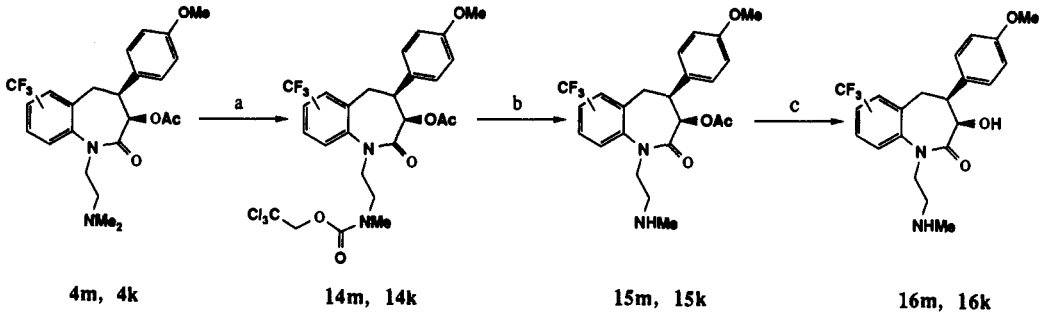
Table II. Physical Data for 3*R*,4*S* Benzazepinones **5**, **12**, **15**–**17**



compd	CF_3	R_1	R	scheme	% yield	mp (°C)	recryst solvent	formula	analysis	optical rotation
5a	6	Ac		II	57[a]	217–19	tol/hex	$C_{25}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl	+78.7° (*c* = 3, MeOH)
5b	6	Ac		II	25[a]	153–57	EtOAc/Et_2O	$C_{25}H_{27}F_3N_2O_4$·HCl	C,H,N,Cl,F	+105° (*c* = 1, MeOH)
5c	6	H		II	75[a]	165–67	Et_2O	$C_{23}H_{25}F_3N_2O_3$·HCl	C,H,N,Cl,F	+75.3 (*c* = 1, MeOH)
5d	6	H		II	8[a]	147–51	Et_2O	$C_{23}H_{25}F_3N_2O_3$·HCl	C,H,N,Cl,F	+108° (*c* = 2.6, MeOH)
5e	6	Ac		II	44[a]	151–54	Et_2O	$C_{26}H_{29}F_3N_2O_4$·HCl	C,H,N,Cl,F	+80.0° (*c* = 3, MeOH)
5f	6	Ac		II	15[a]	158–62	tol/hex	$C_{26}H_{29}F_3N_2O_4$·HCl	C,H,N,Cl,F	+127° (*c* = 3.7, MeOH)
12k	7	H	$CH_2CH_2NMe_2$	I, III	*b*	186–88	EtOAc/Et_2O	$C_{22}H_{25}F_3N_2O_3$·HCl	C,H,N,Cl,F	+156° (*c* = 1, MeOH)
12m	6	H	$CH_2CH_2NMe_2$	I, III	*c*	192–94	Et_2O	$C_{22}H_{25}F_3N_2O_3$·HCl	C,H,N,Cl	+97° (*c* = 1, MeOH)
15k	7	Ac	CH_2CH_2NHMe	IV	62[d]	135–37	EtOAc	$C_{23}H_{25}F_3N_2O_4$·$C_4H_4O_4$	C,H,N,F	+116° (*c* = 1, MeOH)
15m	6	Ac	CH_2CH_2NHMe	I, IV	43[e]	150–55	EtOAc/Et_2O	$C_{23}H_{25}F_3N_2O_4$·HCl	C,H,N,Cl	+95.0° (*c* = 1, MeOH)
16k	7	H	CH_2CH_2NHMe	IV	41[d]	171–72	EtOAc	$C_{21}H_{23}F_3N_2O_3$·$C_4H_4O_4$	C,H,N,F	+125° (*c* = 1.05, MeOH)
16m	6	H	CH_2CH_2NHMe	IV	77[e]	224–26	EtOAc	$C_{21}H_{23}F_3N_2O_3$·HCl	C,H,N,Cl,F	+89.0° (*c* = 1, MeOH)
17a	6		CH_2CHO		50[f]	78–80		$C_{22}H_{20}F_3NO_5$	C,H,N,F	+116° (*c* = 1, MeOH)
17b	6		CH_2CH_2OH		29[g]	199–201		$C_{22}H_{22}F_3NO_5$	C,H,N,F	+106° (*c* = 10, MeOH)
17c	6		CH_2CO_2H		9[g]	129–31	tol	$C_{22}H_{20}F_3NO_6$	C,H,N,F	+114° (*c* = 3.9, MeOH)

[a] From **10m** (3*R*,4*S*). [b] Intermediate in the synthesis of **4k**. [c] Intermediate in the synthesis of **4m**. [d] From **4k**. [e] From **10m** via *N*-methyl, *N*-benzyl derivative. [f] From allyl bromide and ozonolysis. [g] From alkylation of **10m** by THP ether of 2-bromoethanol.

Scheme IV[a]



4m, 4k **14m, 14k** **15m, 15k** **16m, 16k**

[a] (a) 2,2,2-Trichloroethyl chloroformate, toluene, reflux; (b) zinc dust, HOAc, 80 °C; (c) NaOMe, MeOH.

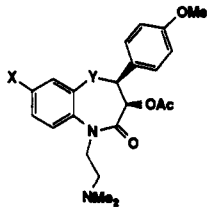
salt. Better conditions involve the formation of the methyl ester directly from the resolved salt **13m**, which eliminates the need to isolate the resolved free acid and reduces the amount of material lost to decarboxylation.[21]

By employing these procedures we were able to obtain large amounts of both enantiomers. In the preparation of trans compounds in both enantiomeric series we used anhydrous decarboxylation conditions to maximize the amount of **11m** formed. Pure trans isomers were isolated by chromatographic techniques and subjected to the remaining steps shown in Scheme I. Thus, in the 6-trifluoromethyl series, all possible diastereoisomers of **4g** (**4m**–**p**) were prepared.

For both the resolved 6- and 7-trifluoromethyl derivatives **4m** and **4k**, we prepared the corresponding mono-*N*-desmethyl analogues **15m** and **15k** by the route shown in Scheme IV. Treatment of the parent dimethylamino compounds with 2,2,2-trichloroethyl chloroformate in refluxing toluene, with azeotropic removal of water, results

(21) Proof of the absolute and relative stereochemistry of 6-trifluoromethyl compounds was established by an X-ray crystal structure of **13m**, described in the following paper in this series (this issue).

Table III. Comparison of Racemic Benzazepinones and Benzothiazepinones in Vitro



compd	Y	X	IC_{50} (μM)[a]	k_d (μM)[b]
3b	S	H	1.8 (0.74–4.6)	0.38 (±0.04)
4a	CH_2	H	4.7 (2.9–7.8)	5.1 (±1.4)
3c	S	Cl	0.24 (0.16–0.38)	0.081 (±0.024)
4b	CH_2	Cl	1.5 (0.84–2.8)	1.4 (±0.51)
3d	S	OMe	0.12 (0.072–0.19)	0.042 (±0.006)
4c	CH_2	OMe	1.9 (0.88–4.0)	1.6 (±0.28)

[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).

in a quantitative conversion to the carbamates **14**. Reduction of **14** with a slight excess of zinc dust in hot glacial acetic acid affords the desired *N*-desmethyl analogues **15m** and **15k** in greater than 75% yields following conversion to either the hydrochloride or fumaric acid salt and recrystallization. The corresponding desacetyl derivatives **16m** and **16k** were prepared by methanolysis of the acetyl group. Physical data for compounds **5**, **12**, and **15–17** are included in Table II.

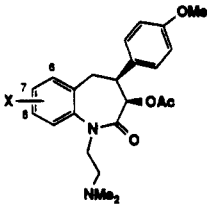
Benzothiazepinones **3a–e** were synthesized as described in the literature.[22]

Structure–Activity Relationships

We have measured the vasorelaxant effects of compounds in circumferential strips of potassium-depolarized rabbit aorta to assess the effects of structural modifications in the 1-benzazepin-2-one series on potency in vitro. 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 some cases we have also determined the affinity of test compounds for the diltiazem receptor in isolated guinea pig skeletal muscle microsomal preparations. The k_d values reported for this test were calculated from concentration response curves for the inhibition of specific [^{3}H]diltiazem binding in this preparation. Antihypertensive activity was calculated as the percent fall in systolic blood pressure from predrug control value and is reported as the mean value acquired from five rats at a standard dose of 135 μmol/kg per os. The maximum antihypertensive effect was noted for the 0–6-h, 6–12-h, and 12–18-h time periods after dosing. These data allow comparison of both the peak potency and duration of action of the test compounds. All blood pressure measurements were obtained by direct recording. Biological test methods are described in the Experimental Section of this paper.

Central to our examination of the benzazepinone series is the effect on potency of exchanging the sulfur atom of the benzothiazepinone (diltiazem) nucleus for a methylene group. We examined this point with three sets of compounds shown in Table III. In each case, the benzothiazepinone derivative was more potent in the functional test than the corresponding benzazepinone analogue. The largest difference occurred with the methoxy derivatives where the benzazepinone **4c** was an order of magnitude less potent compared to the benzothiazepinone **3d**. Similarly, radioligand binding studies demonstrate that benzazepinones possess reduced affinity for the receptor compared to benzothiazepinones. Again, this difference was greatest for the methoxylated analogues **3d** and **4c**. Several aspects of the comparison between receptor affinity and potency in the isolated tissue are of interest. In the benzazepinone series, essentially equivalent results were obtained in either test. There was more of a discrepancy between these two values in the benzothiazepinone series where the compounds appear 3- to 5-fold more potent in receptor binding than in the whole tissue preparation. Although the effects of aromatic substitution on potency in vitro are similar between the two classes of compounds, we conclude that 1-benzazepin-2-ones have a reduced affinity for the receptor relative to analogous benzothiazepinones. However, the results described below demonstrate that appropriate aromatic substitution of benzazepinones results in compounds with significantly improved potency.

Table IV. Activity of Racemic Aryl Substituted Benzazepinones in Vitro and in Vivo



compd	X	IC_{50} (μM)[a]	% decrease in BP @ 135 μmol/kg po[b] 0–6 h	6–12 h	12–18 h
4a	H	4.7 (2.9–7.8)	8	8	13[c]
4d	6-Cl	1.6 (0.71–3.4)	9	8	11
4b	7-Cl	1.5 (0.84–2.8)	13	14	18[c]
4e	8-Cl	7.7 (4.0–15)	7	2	4
4f	6-OMe	2.4 (1.8–3.2)	0	0	1
4c	7-OMe	1.9 (0.88–2.8)	15	8	10
4g	6-CF_3	0.24 (0.13–0.45)	24	26	24
4h	7-CF_3	1.9 (0.95–3.6)	19	19	18

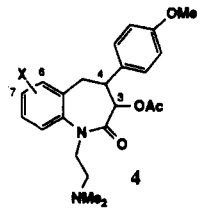
[a] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval). [b] In spontaneously hypertensive rats, n = 5. [c] Dosed at 270 μmol/kg.

The 8-chloro analogue of diltiazem was reported to have enhanced potency in vitro and in vivo relative to unsubstituted diltiazem.[12] Because of the claims made for chloro substitution in the fused aromatic ring of benzothiazepinones, we incorporated chlorine into the 6-, 7-, and 8-position of the 1-benzazepin-2-one aryl ring (Table IV). Substitution of chlorine at both the 6 and 7 positions (**4d**, **4b**) enhanced potency by a factor of 2 relative to unsubstituted **4a**. Substitution at the 8-position (**4e**) decreased the activity of the compound relative to **4a**. Substitution of trifluoromethyl at the 6- or 7-position afforded compounds more potent in vitro than the parent. In addition, these compounds proved to be long-acting antihypertensive agents in the spontaneously hypertensive rat model, with the 6-trifluoromethyl analogue **4g** clearly the most active in vitro and in vivo. From these results, we selected the 6-trifluoromethyl series for further structure–activity studies.

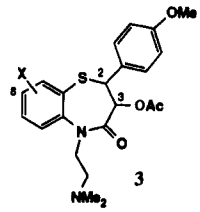
On the basis of analogy with diltiazem, we anticipated that calcium channel blocking activity would reside with

(22) (a) For the synthesis of diltiazem: Kugita, H.; Inoue, H.; Ikezaki, M.; Takeo, S. *U.S. Patent 3,562,257*; 1971. (b) For the synthesis of 8-chloro diltiazem: Takeda, M.; Oh-Ishi, T.; Nakajima, H.; Nagao, T. *Eur. Patent Appl. 0127882 A1*, 1984. (c) For the synthesis of 8-methoxy diltiazem: Takeda, M.; Oh-Ishi, T.; Nakajima, H.; Nagao, T. *Eur. Patent Appl. 0158340 A2*, 1985.

Table V. Comparison of Benzazepinone Diastereomers and Benzothiazepinones



4

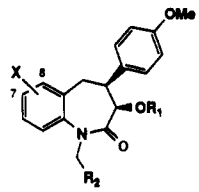


3

compd	X	chirality	IC_{50} (μM)[a]	k_d (μM)[b]	% decrease in BP @ 135 μmol/kg po[c] 0–6 h	6–12 h	12–18 h
4i	7-Cl	3*R*,4*S*-cis	0.82 (0.54–1.3)	0.69 (±0.18)	12	12	12
4j	7-Cl	3*S*,4*R*-cis	14 (8.8–22)	8.2 (±1.4)	1	4	9
4k	7-CF_3	3*R*,4*S*-cis	1.6 (0.87–3.1)	0.18 (±0.036)	19	22	19
4l	7-CF_3	3*S*,4*R*-cis	>10	6.3 (±1.5)	7	8	7
4m	6-CF_3	3*R*,4*S*-cis	0.15 (0.11–0.20)	0.12 (±0.018)	31	27	30
4n	6-CF_3	3*S*,4*R*-cis	4.9 (2.9–5.3)	2.0 (±0.39)	9	9	9
4o	6-CF_3	3*R*,4*R*-trans	>10	3.8 (±0.29)	5	9	11
4p	6-CF_3	3*S*,4*R*-trans	3.9 (3.1–5.0)	1.2 (±0.22)	5	8	7
3a	H	2*S*,3*S*-cis	0.21 (0.13–0.36)	0.20 (±0.017)	23	12	17
3e	8-Cl	2*S*,3*S*-cis	0.10 (0.06–0.18)	0.095 (±0.016)	41	26	24

[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). [c] In spontaneously hypertensive rats, $n = 5$.

Table VI. Comparison of Benzazepinone Metabolites in Vitro and in Vivo



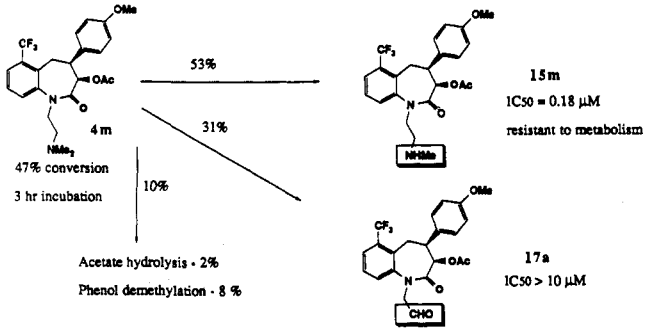
compd	X	R_1	R_2	IC_{50} (μM)[a]	% decrease in BP @ 135 μmol/kg po[b] 0–6 h	6–12 h	12–18 h
4m	6-CF_3	Ac	CH_2NMe_2	0.15 (0.11–0.20)	30	30	29
12m	6-CF_3	H	CH_2NMe_2	0.30 (0.19–0.46)	21	26	28
15m	6-CF_3	Ac	CH_2NHMe	0.18 (0.12–0.28)	32	34	32
16m	6-CF_3	H	CH_2NHMe	0.69 (0.45–1.0)	16	20	22
4k	7-CF_3	Ac	CH_2NMe_2	1.6 (0.87–3.1)	19	22	19
12k	7-CF_3	H	CH_2NMe_2	1.7 (1.0–2.8)	8	9	14
15k	7-CF_3	Ac	CH_2NHMe	0.88 (0.54–1.4)	28	29	31
16k	7-CF_3	H	CH_2NHMe	1.9 (1.2–3.1)	14	15	14
17a	6-CF_3	Ac	CHO	>3	NT		
17b	6-CF_3	Ac	CH_2OH	10 (6.5–15)	1	3	4
17c	6-CF_3	Ac	COOH	>3	6	3	4

[a] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval). [b] In spontaneously hypertensive rats, $n = 5$.

the 3*R*,4*S* cis isomers in the benzazepinone series, which corresponds to the active 2*S*,3*S* (*d*-cis) configuration of the benzothiazepinone system. We examined this effect with three benzazepinone analogues. The data in Table V show that the 3*R*,4*S* enantiomers **4i**, **4k**, and **4m** are active in vitro and in vivo whereas the corresponding 3*S*,4*R* enantiomers **4j**, **4l**, and **4n** are devoid of significant activity. In the case of 6-trifluoromethyl benzazepinones, we also examined the effects of alternate relative stereochemistry. Comparing **4m**, the compound with correct absolute and relative stereochemistry, with its 3*S*,4*S* trans isomer **4p** demonstrates that placing the C-3 substituent in a trans configuration results in a 10-fold decrease in receptor binding potency and a similar loss of potency in the rabbit aorta functional test. The least potent compound is **4o** which possesses the *R* absolute configuration at C-4 and is trans substituted. We interpret these data to indicate that the absolute stereochemistry at C-4 is somewhat more important than that at C-3, and that the cis relative stereochemistry is important to potency in this series. These results are in agreement with data published for diltiazem.[9c]

The data in Table V also show that both of the trifluoromethyl-substituted benzazepinone analogues **4k** and **4m** are superior to diltiazem as antihypertensive agents, especially with regard to the duration of the antihypertensive effect. Although **3e**, the nonracemic 8-chloro analogue of diltiazem (benzothiazepinone numbering), shows a stronger initial antihypertensive effect than **4m**, it is clear that the 6-(trifluoromethyl)benzazepinone maintains its effect over the duration of the test whereas the effect of **3e** diminishes. This suggests that, at similar antihypertensive doses of these compounds, the benzazepinone **4m** will show a longer duration of action. Thus, although the data in Table III shows benzothiazepinone congeners to be more potent than benzazepinones in vitro, appropriate aromatic substitution of benzazepinones affords compounds that are equipotent in vitro, yet superior in vivo relative to known benzothiazepinones.

Scheme V



Metabolism of Benzazepinones in Vitro

There have been many studies published on the metabolism of diltiazem which demonstrate the lability of the *O*-acetyl and *N*-methyl groups.[17] We have synthesized and studied these potential metabolites of both 6- and 7-trifluoromethyl-substituted compounds, **4m** and **4k**. The effects of these modifications on biological activity are shown in Table VI. Comparing the desacetyl compounds **12m** and **12k** to their respective acetylated analogues indicates that the acetyl group does not have a dramatic effect with respect to potency in vitro but does appear to affect antihypertensive activity. Removal of one of the *N*-methyl groups from either **4m** or **4k** does not affect potency in vitro, and the *N*-desmethyl analogues **15m** and **15k** are equipotent antihypertensives when compared with the parent compounds **4m** and **4k**. The *O*-desacetyl-*N*-desmethyl derivatives **16m** and **16k** are similar in potency to their respective desacetyl analogues. While not affecting activity in vitro, removal of the acetyl group consistently lowers the antihypertensive potency of these compounds.

These results are somewhat different from those reported for the corresponding metabolites of diltiazem. In separate studies it has been reported that the order of potency both in vitro and in vivo for diltiazem and its active metabolites is diltiazem = desacetyldiltiazem (M_A) > mono-*N*-desmethyldiltiazem (M_1) > desacetyl, mono-*N*-desmethyldiltiazem (M_2).[23] It is possible that differences in the relative activities of metabolites between the two classes of compounds may be relevant to the apparent longer duration of antihypertensive effect we observe with the benzazepinones compared to diltiazem (**3a**) and TA-3090 (**3e**).

We have also investigated the oxidative metabolism of **4m** by incubating the compound for 3 h with rat liver microsomes. After this incubation period, a 47% conversion to products was observed, as shown in Scheme V. One of the two predominant pathways of oxidative metabolism is oxidative deamination to the aldehyde **17a**. This process represents an inactivation of **4m** in vitro and in vivo. We anticipated that aldehyde **17a** would be unstable to oxidation or reduction in vivo, and we have also prepared and tested the corresponding alcohol **17b** and acid **17c**. Since all the products of the oxidative deamination pathway are much less active than **4m**, this pathway represents an important route for the metabolic inactivation of **4m**.

Oxidative N-demethylation is the major pathway of metabolism observed in vitro, accounting for 53% of the products. In contrast with the results of deamination, demethylation to the secondary amine **15m** afforded a compound with activity equal to that of the parent **4m**. Further, **15m** itself is stable to oxidative deamination. This metabolic pathway therefore represents a stabilization of the calcium channel blocking activity of **4m** by conversion into **15m** in vivo. This finding is consistent with the fact that secondary amines such as **15m** are more basic than their tertiary amine congeners. Enhancing the basicity of the nitrogen should provide greater stability to oxidative metabolism, as the rate-limiting step in this process is believed to involve electron abstraction from the nitrogen lone pair.[24] These in vitro data are consistent with data from in vivo studies in rats (not shown). The finding that **4m** is metabolized in vitro and in vivo to the active calcium channel blocker **15m**, pointed us towards the more basic secondary amines as potentially superior compounds. These studies resulted in the identification of *N*-1-pyrrolidinylmethyl derivatives as compounds of potential interest (Table VII).

Structure–Activity of N-1 Pyrrolidinyl Substitution

The most striking difference between the pyrrolidinylmethyl series and the aminoethyl N-1-substituted series is the discrepancy in potency in vitro between tertiary and secondary amine analogues. In the (*N*,*N*-dimethylamino)ethyl series, the tertiary (dimethylamino)ethyl compound **4m** and its desmethyl analogue **15m** are equipotent in vitro and in vivo. By contrast, the (*N*-methylpyrrolidinyl)methyl analogue **5e** is significantly less active than its secondary amine congener **5a**.

Comparison of tertiary *N*-methylpyrrolidinyl-substituted compounds **5e** and **5f** indicates that the *S* pyrrolidinyl diastereomer is slightly more active in vitro than the *R* diastereomer. This finding is magnified in the case of secondary N-1 pyrrolidinyl benzazepinones, where the difference between the *S* isomers **5a** and **5c**, and their respective *R* isomers **5b** and **5d** in vitro is 7- to 10-fold. The *S* diastereomers **5a**, **5c**, and **5e** also demonstrate consistently superior activity in vivo. It is noteworthy that the 3-hydroxypyrrolidine **5c** retains significant activity in vitro and in vivo, in contrast with the 3-hydroxy metabolites of **4m** shown in Table VI. The fact that **5c** is much less lipophilic than comparably active alkylamino benzazepinones such as **15m** makes it a compound of interest. However, the most outstanding activity profile is found in **5a**. This compound is resistant to oxidative metabolism as measured in vitro (data not shown), and also demonstrates the greatest potency with respect to activity in vivo. We have focused upon **5a** as a potential clinical candidate.

Comparative Antihypertensive Activity

We conducted oral dosing studies in spontaneously hypertensive rats to compare the potencies of benzazepinone

(23) (a) Yabana, H.; Nagao, T.; Sato, M. Cardiovascular Effects of the Metabolites of Diltiazem in Dogs. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 152–157. (b) Schoemaker, H.; Hicks, P. E.; Langer, S. Z. Calcium Channel Receptor Binding Studies for Diltiazem and Its Major Metabolites: Functional Correlation to Inhibition of Portal Vein Myogenic Activity. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 173–180. We have prepared the *N*-desmethyl and desacetyl analogues of both diltiazem and TA-3090. We find that in each case, the corresponding *N*-desmethyl analogues are significantly less potent in vitro than their parent compounds. For the corresponding desacetyl derivatives, our results indicate that desacetyl diltiazem (M_A) is much less potent than diltiazem in vitro, whereas desacetyl TA-3090 appears to be of similar potency to its parent. In spite of its potency in vitro, desacetyl TA-3090 is much less active as an antihypertensive agent in the SHR upon oral dosing.

(24) Guengerich, F. P.; McDonald, R. L. Chemical Mechanisms of Catalysis by Cytochromes P-450: A Unified View. *Acc. Chem. Res.* **1984**, *17*, 9–16.

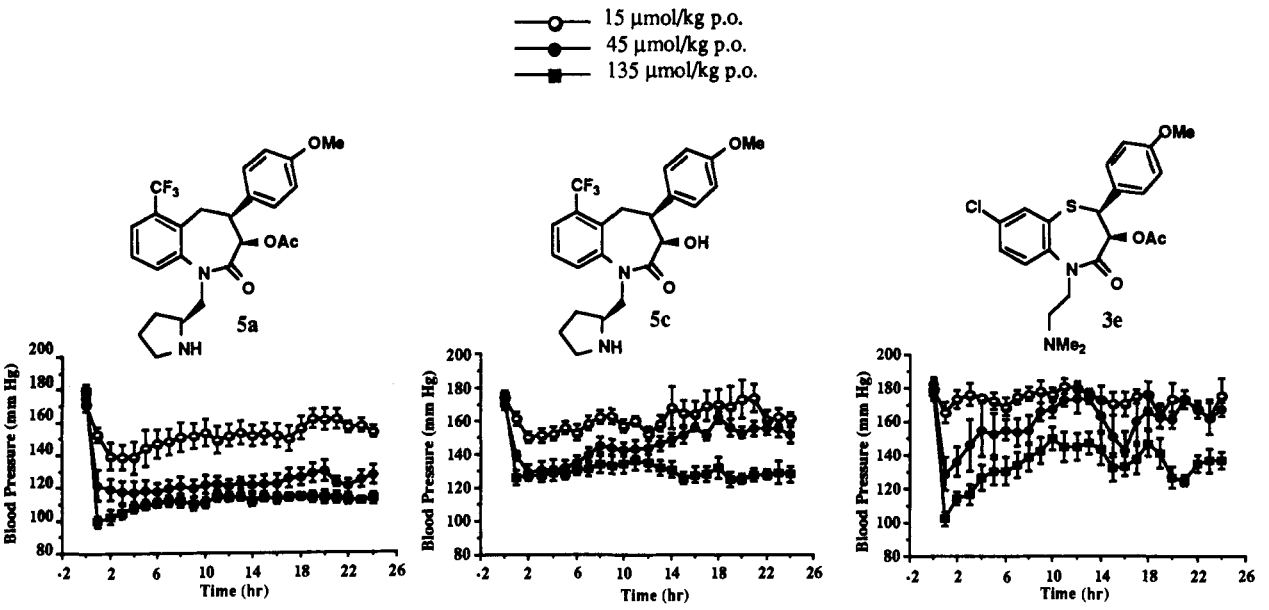
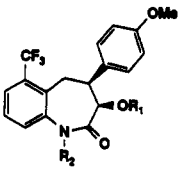


Figure 3. Antihypertensive activity in SHR: comparative oral dose–response.

Table VII. Activity of N-1 Substituted Benzazepinones in Vitro and in Vivo



compd	R_1	R_2	IC_{50} (μM)[a]	% decrease in BP @ 135 μmol/kg po[b] 0–6 h	6–12 h	12–18 h
5a	Ac		0.091 (0.068–0.12)	45	39	38
5b	Ac		0.63 (0.38–1.0)	21	22	26
5c	H		0.095 (0.069–0.13)	30	26	27
5d	H		0.89 (0.60–1.3)	17	18	18
5e	Ac		0.52 (0.29–0.94)	30	29	29
5f	Ac		1.1 (0.61–1.9)	20	21	18

[a] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval). [b] In spontaneously hypertensive rats, $n = 5$.

and benzothiazepinone calcium channel blockers in vivo. Since diltiazem shows relatively little antihypertensive activity in per os dosing regimens, we included for comparison the more potent second generation benzothiazepinone **3e**. The data in Figures 3 and 4 show that **5c** and **3e** are equipotent in the SHR model. While the area over the curve (AOC) is similar, **3e** consistently shows a peak effect that is greater and tails off quickly relative to either **5a** or **5c**. This "shorter duration" may be related to the metabolism of **3e**. In terms of absolute potency and duration of activity, **5a** appears to be 3-fold more potent than the other two compounds. As indicated above, both benzazepinones are superior to diltiazem in this model of hypertension.

Conclusions

We have developed synthetic procedures to prepare a new class of calcium channel blocking agents that are structurally related to diltiazem. Substitution of the sulfur atom of the benzothiazepinone nucleus by a methylene group results in compounds that are of similar potency in

functional tests in vitro in spite of the fact that the benzazepinones demonstrate lower affinity for the skeletal muscle diltiazem receptor compared to analogous benzothiazepinones. The synthetic methods we have developed have allowed us to investigate the effects of aromatic substitution in the benzazepinone series. These studies have lead to the observation that compounds with a trifluoromethyl group at C-6 show excellent potency in vitro and demonstrate pronounced and long-lasting antihypertensive effects in the SHR.

As with the benzothiazepinone diltiazem, both the absolute and relative stereochemistry at C-3 and C-4 of benzazepinones (analogous to C-3 and C-2 in the benzothiazepinone ring system) are important determinants of activity. The requirement for the 3*R*,4*S* absolute configuration in the benzazepinone system corresponds directly with the preferred conformation of these centers in the diltiazem series. Similarly, there is a strong preference for the C-4 aryl ring and the C-3 substituent to be in a cis relationship.

We have observed that compounds having either an (*N*,*N*-dimethylamino)ethyl or (*N*-methylamino)ethyl group at N-1 are equally potent in vitro and in vivo. Acetylation of the C-3 hydroxy group appears to be most important to the antihypertensive activity, although the acetyl group has a small effect on potency in vitro. These results differ somewhat from those observed with diltiazem where N-demethylation attenuates potency and the C-3 acetyl group appears less important to the overall activity.

We have synthesized N-1 pyrrolidinyl derivatives of benzazepinones that are stable to metabolism. The greater basicity of the secondary nitrogen and the steric hindrance afforded by β substitution imbue these compounds with stability towards metabolic degradation. These compounds are equipotent in vitro to the (dimethylamino)ethyl analogues. However, they display significantly greater antihypertensive activity in the spontaneously hypertensive rat.

Oral dosing studies in spontaneously hypertensive rats with **5a**, **5c**, diltiazem (**3a**), and TA-3090 (**3e**) demonstrate that the benzazepinone **5a** is the most potent antihypertensive agent. Although benzazepinone **5c** and benzothiazepinone **3e** are equipotent in the spontaneously hypertensive rat model, the less lipophilic benzazepinone **5c** appears to have a longer duration of action. In this study, diltiazem **3a** displayed little antihypertensive activity.

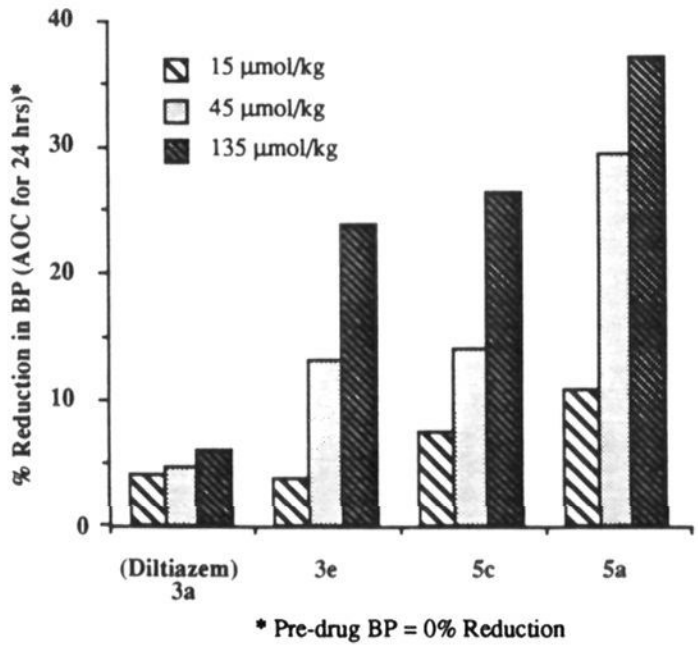


Figure 4. Summary of 24-h blood pressure lowering after oral dose in SHR.

Experimental Section

Vasorelaxant Assay in Vitro. The vasorelaxant assay was conducted as previously described.[25] In brief, circumferential strips of rabbit thoracic aorta were contracted by depolarization with high extracellular concentrations of potassium and then relaxed by exposure to various concentrations of the benzazepinones. IC_{50} values (the concentration of a compound that caused 50% relaxation) were calculated. This test has been shown to be relatively diagnostic for calcium entry blockade.[26]

Antihypertensive Assay. Antihypertensive activity was determined in male spontaneously hypertensive rats, 15 weeks of age, upon administration of drug by oral gavage. Mean arterial blood pressure was recorded via an indwelling polyethylene catheter, implanted in the abdominal aorta, and exteriorized in the intrascapular region.[27] The catheter was connected to a disposable pressure transducer via resistance tubing and a solenoid valve, allowing for intermittent recording of each of 10 animals. Blood pressure data were acquired by a DEC LSI-11 computer over 20-s intervals every 5 min, continuously for 24 h.

Radioligand Binding Assay. Male guinea pigs (350–450 g body weight) were sacrificed by placement in a saturated CO_2 atmosphere. The skin around the hind limbs was removed and muscles (primarily quadriceps and gastrocnemius) rapidly excised and placed in ice-cold 20 mM sodium bicarbonate supplemented with 0.1 mM phenylmethanesulfonyl fluoride (PMSF). Membranes were prepared as described previously,[24] resuspended in 50 mM Tris-HCl buffer at a weight to volume ratio of 1:1 (original wet weight), snap frozen in acetone/dry ice and stored at −70 °C until use.

On the day of the assay, the tissue was thawed and diluted 2-fold with 50 mM Tris-HCl. One hundred microliters of the ice-cold membrane solution (125–250 μg protein) was added to 100 nmol of [^{3}H]-*d*-*cis*-diltiazem from New England Nuclear (NET-847, 60–90 Ci/mmol) and the appropriate concentrations of competing drugs in a final volume of 250 μL of 50 mM Tris-HCl. The binding reaction was carried out at 30 °C for 1 h starting immediately after addition of membrane suspension. At the end of the incubation, the samples were diluted 20-fold by addition of 5 mL of ice-cold 50 mM Tris-HCl buffer and rapidly filtered through Whatman GF/B filters using the Brandel Cell Harvester MB-24. The filters were washed two times with 5 mL of 50 mM Tris-HCl and transferred to scintillation vials. Five milliliters of scintillation cocktail (OPTI-FLUOR, Packard) was added to each vial. Each sample was counted for 5 min in a Packard Tri-Carb 4640 scintillation counter. Specific binding of [^{3}H]-*d*-*cis*-diltiazem was determined as the binding detectable in the absence ("total" binding) minus that in the presence of 100 μM of unlabeled diltiazem ("nonspecific" binding). Specific binding routinely amounted to 70–80% of total binding. Calculation of the equilibrium dissociation constant (k_d) from the observed IC_{50} value (concentration of the compound which causes 50 percent inhibition of specific binding) was performed using the formula: $k_d = IC_{50}/(1 + [RL]/k_{RL})$, where [RL] is the concentration of [^{3}H]-*d*-*cis*-diltiazem and k_{RL} is the affinity of [^{3}H]-*d*-*cis*-diltiazem for its specific binding sites.

Microsomal Oxidations. Rat liver microsomes (12.5 mg of protein) from untreated animals were incubated with **4m** (final concentration 1 mM) and NADPH (3 mM) in potassium phosphate buffer (56 mM, pH 7.4) in a total volume of 2.5 mL at 30 °C for periods of 10, 20, 30, 45, 60, 120, and 180 min. The metabolism of **4m** proceeded at a constant rate of about 0.7 nmol **4m** consumed/min per mg of microsomal protein for the first 2 h. After the indicated incubation periods, the organic compounds

(25) Rovnyak, G.; Andersen, N.; Gougoutas, J. Z.; Hedberg, A.; Kimball, S. D.; Malley, M.; Moreland, S.; Porubcan, M.; Pudzianowsky, A. Studies Directed toward Ascertaining the Active Conformation of 1,4-Dihydropyridine Calcium Entry Blockers. *J. Med. Chem.* **1988**, *31*, 936–944.
(26) Brittain, R. J.; Moreland, S. *Physiologist*, **1985**, *28*, 325.
(27) Laffan, R. J.; Peterson, A.; Hitch, S. W.; Jeunelot, C. A Technique for Prolonged Continuous Recording of Blood Pressure of Unrestrained Rats. *Cardiovasc. Res.* **1972**, *8*, 319–324.

Table VIII. Physical Data for Synthetic Intermediates

compd	substn	scheme	% yield	mp (°C)	recryst solvent	formula	analysis	optical rotation
6a	H	I	71	73–75	MeOH	$C_{20}H_{21}NO_7$	C,H,N	
7a	H	I	91	108–109	MeOH	$C_{20}H_{23}NO_5$	C,H,N	
8a	H	I	84	217–219	MeOH/H_2O	$C_{19}H_{19}NO_4 \cdot 0.26H_2O$	C,H,N	
9a	H	I	78	212–213.5	hexane[a]	$C_{19}H_{19}NO_5 \cdot 0.11H_2O$	C,H,N	
10a	H	I	68	173.5–175.5	Et_2O[a]	$C_{17}H_{17}NO_3$	C,H,N	
12a	H	I	84	248.5–250	MeOH	$C_{21}H_{26}N_2O_3 \cdot HCl \cdot 0.51H_2O$	C,H,N,Cl	
6b	7-Cl	I	79	129–130	MeOH			
7b	7-Cl	I	79	126–127.5	2-PrOH			
8b	7-Cl	I	90	189.5–190	MeOH/H_2O			
9b	7-Cl	I	94	187–188	hexane[a]			
10b	7-Cl	I	59	157–158	EtOAc			
12b	7-Cl	I	59		Et_2O/EtOAc			
6c	7-OMe[b]	I	67	87–89	MeOH	$C_{27}H_{27}NO_8$	C,H,N	
7c	7-OMe[b]	I	100	*c*				
8c	7-OMe[b]	I	72	156–158	EtOAc	$C_{26}H_{25}NO_5$	C,H,N	
9c	7-OMe[b]	I	98	134–137	hexane	$C_{26}H_{25}NO_6 \cdot 0.25H_2O$	C,H,N	
10c	7-OMe[b]	I	55	156–159	EtOH			
12c	7-OMe[b]	I	62	130–132	EtOH	$C_{28}H_{32}N_2O_4 \cdot HCl \cdot 1.5H_2O$	C,H,N,Cl	
6d	6-Cl	I	76	112–114	2-PrOH	$C_{20}H_{20}ClNO_7$	C,H,N,Cl	
7d	6-Cl	I	95	*c*				
8d	6-Cl	I	52	225–227	MeCN	$C_{19}H_{18}ClNO_4$	C,H,N,Cl	
9d	6-Cl	I	44	68–72	hexane	$C_{20}H_{21}ClNO_5$	C,H,N,Cl	
10d	6-Cl	I	50	177–179	EtOH	$C_{17}H_{16}ClNO_3$	C,H,N,Cl	
12d	6-Cl	I	93	239–241	EtOH	$C_{21}H_{25}ClN_2O_3 \cdot HCl$	C,H,N,Cl	
6e	8-Cl	I	61	60–62	2-PrOH	$C_{20}H_{20}ClNO_7$	C,H,N,Cl	
7e	8-Cl	I	100	*c*				
8e	8-Cl	I	46	236–238	MeCN	$C_{19}H_{18}ClNO_4$	C,H,N,Cl	
9e	8-Cl	I	50	168–170	EtOH			
10e	8-Cl	I	38	173–176	MeOH	$C_{17}H_{16}ClNO_3 \cdot H_2O$	C,H,N,Cl	
12e	8-Cl	I	90					
6f	6-OMe	I	50	99–101	2-PrOH	$C_{21}H_{23}NO_8$	C,H,N	
7f	6-OMe	I	95	*c*				
8f	6-OMe	I	70	204–206	MeOH/H_2O	$C_{20}H_{21}NO_5$	C,H,N	
9f	6-OMe	I	78	213–215	MeOH	$C_{20}H_{21}NO_6$	C,H,N	
10f	6-OMe	I	66	213–215	MeCN	$C_{18}H_{19}NO_4$	C,H,N	
12f	6-OMe	I	95	253–255	MeOH/$CHCl_3$	$C_{22}H_{28}N_2O_4$	C,H,N	
6g	6-CF_3	I	82	117–119	MeOH	$C_{21}H_{20}NF_3O_7$	C,H,N,F	
7g	6-CF_3	I	95	112–114	MeOH	$C_{21}H_{22}NF_3O_5$	C,H,N,F	
8g	6-CF_3	I	97	218–220	MeOH	$C_{20}H_{18}NF_3O_4$	C,H,N,F	
9g	6-CF_3	I	97	175–177	hexane	$C_{20}H_{18}NF_3O_5$	C,H,N,F	
10g	6-CF_3	I	100	212–214	MeCN	$C_{18}H_{16}NF_3O_3$	C,H,N,F	
12g	6-CF_3	I	99	148–150	EtOAc	$C_{22}H_{25}N_2F_3O_3 \cdot HCl \cdot 1.25H_2O$	C,H,N,F,Cl[d]	
6h	7-CF_3	I	54	110–112	MeOH	$C_{21}H_{20}NF_3O_7$	C,H,N,F	
7h	7-CF_3	I	91	124–127	MeOH	$C_{21}H_{22}NF_3O_5$	C,H,N,F	
8h	7-CF_3	I	74	161–163	2-PrOH	$C_{20}H_{18}NF_3O_4$	C,H,N,F	
9h	7-CF_3	I	96	196–198	hexane	$C_{20}H_{18}NF_3O_5$	C,H,N,F	
10h	7-CF_3	I	*e*	204–206	Et_2O	$C_{18}H_{16}NF_3O_3$	C,H,N,F	
12h	7-CF_3	I	21[f]		Et_2O			
12i	7-Cl(3*R*,4*S*)	I	46	55–60				+194° (*c* = 1, $CHCl_3$)
8m	6-CF_3(3*S*,4*R*)	I, III	80[g]	136–138		$C_{20}H_{18}NF_3O_4$	C,H,N,F	+10.6° (*c* = 1, MeOH)
9m	6-CF_3(3*S*,4*S*)	I, III	100	*c*				+123° (*c* = 1, MeOH)
10m	6-CF_3(3*R*,4*S*)	I, II, III	66	220–222	MeCN	$C_{18}H_{16}NF_3O_3$	C,H,N,F	+116° (*c* = 1, MeOH)
10n	6-CF_3(3*S*,4*R*)	I, III		221–223	MeCN	$C_{18}H_{16}NF_3O_3$	C,H,N,F	−128° (*c* = 1, MeOH)
10o	6-CF_3(3*R*,4*R*)	I, III	*h*		MeCN			+197° (*c* = 1, MeOH)
12o	6-CF_3(3*R*,4*R*)	I, III	92					+152° (*c* = 1, MeOH)
10p	6-CF_3(3*S*,4*S*)	I, III	*h*	150–154		$C_{18}H_{16}NF_3O_3$	C,H,N,F	−200° (*c* = 1, MeOH)
12p	6-CF_3(3*S*,4*S*)	I, III	92	150–154	MeCN			−154° (*c* = 1, MeOH)

[a] Trituration. [b] Protected as the 7-*O*-benzyl ether. [c] Not crystallized. [d] Analysis indicates excess Cl. [e] Carried through as mixture of cis–trans isomers. [f] From **9h**. [g] Includes resolution. [h] Chromatographed from mother liquors of cis isomer.

in each mixture were concentrated by solid-phase extraction (Bond-Elut cartridges, C_{18}-type; Analytichem, Harbor City, CA) and analyzed by HPLC with UV detection at 230 nm. Components of the reaction mixture were characterized by mass spectrometry and by coelution with available reference compounds. Parent compound and metabolites were quantified by integration of HPLC peak areas and comparison to standards.

General Chemical Procedures. Melting points were recorded on a Thomas-Hoover capillary apparatus and are reported uncorrected. Proton NMR (^{1}H NMR) spectra were obtained on JEOL FX-270 or GX-400 spectrometers and are reported relative to tetramethylsilane (TMS) reference. Carbon NMR (^{13}C NMR) data were obtained on the JEOL FX-270 or FX-60Q spectrometers and are also reported relative to TMS. Optical rotations were recorded with a Perkin-Elmer 241 spectrophotometer. All reactions were conducted under an atmosphere of nitrogen or argon. Table VIII contains physical data for synthetic intermediates.

[1-(4-Methoxyphenyl)-2-(2-nitro-5-chlorophenyl)ethyl]propanedioic Acid, Dimethyl Ester (6b). Sodium hydride (60%, 11.8 g, 295 mmol) was added to a solution of dimethyl (4-methoxybenzylidene)malonate (50 g, 197 mmol) in anhydrous DMF (1 L) at 0 °C. A solution of 5-chloro-2-nitrotoluene (37 g, 216 mmol) in DMF (40 mL) was then added over ca. 1 h, and the resulting solution was allowed to reach room temperature overnight. The reaction was diluted with 300 mL of hexane, and 1.5 L of water was added slowly. The resulting solid was filtered from the reaction mixture and partially air-dried. Recrystallization from 3 L of methanol afforded 69.6 g (79%) of the desired product which was employed in the next step without additional purification: mp 129–130 °C.

[2-(2-Amino-5-chlorophenyl)-1-(4-methoxyphenyl)-ethyl]propanedioic Acid, Dimethyl Ester (7b). A warm suspension of **6b** (11.0 g, 26.1 mmol) in 200 mL of methanol was added to 400 mL of methanol containing stannous chloride dihydrate (30 g, 133 mmol) and 40 mL of concentrated HCl. The resulting mixture was warmed to 50 °C until a homogeneous solution formed (ca. 0.5 h), allowed to cool to room temperature and stirred overnight. The reaction was treated with Celite and diluted with ethyl acetate (500 mL), saturated potassium carbonate (200 mL), and solid potassium carbonate (127 g). The resulting slurry was stirred for 15 min and then filtered through a Celite pad. Partial concentration of the mother liquor afforded a pale yellow solid which was filtered from the mixture. Recrystallization of this material from 2-propanol provided 8.11 g (79%) of crystalline **7b**: mp 126–127.5 °C.

1,3,4,5-Tetrahydro-7-chloro-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (8b). A solution of **7b** (23.2 g, 59.2 mmol) in 200 mL of methanol was treated with 25% sodium methoxide in methanol (16 mL, 70 mmol) and heated to reflux for 3 h. After the reaction was cooled to room temperature, 1 N HCl (200 mL) was slowly added, resulting in the formation of a white precipitate. The solid was filtered from the reaction and washed with water followed by drying in vacuo to afford 19.5 g (90%) of the desired benzazepinone **8b**: mp 189.5–190 °C.

1,3,4,5-Tetrahydro-7-chloro-3-hydroxy-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (9b). A solution of **8b** (15 g, 41.7 mmol) dissolved in anhydrous THF (780 mL) at −78 °C was treated with potassium hexamethyldisilizane (147 mL of 1.13 M, 167 mmol) in THF, and the mixture was allowed to stir for 1 h. Neat triethyl phosphite (28.6 mL, 167 mmol) was then added, and dry oxygen gas was bubbled through the solution (gas dispersion tube) while the temperature of the reaction was raised to 0 °C. TLC analysis indicated the reaction was complete after 30 min, and it was quenched by the addition of 500 mL of glacial acetic acid. The reaction was then concentrated in vacuo and the residue was dissolved in ethyl acetate and washed successively with 1 N HCl, saturated potassium bicarbonate, and brine followed by drying over sodium sulfate and concentration in vacuo to afford a yellow solid. This material was triturated with hexane to provide a beige powder (14.8 g, 94%), which was used without further purification: mp 187–188 °C.

***cis*-1,3,4,5-Tetrahydro-7-chloro-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (10b).** Lithium iodide (5.24 g, 39.17 mmol) and **9b** (3.68 g, 9.79 mmol) were dissolved in wet pyridine (1% water, 64 mL) and heated to reflux under argon for 2.5 h. After the reaction was judged to be complete by TLC, the mixture was cooled and concentrated in vacuo. The residue was suspended in ethyl acetate (200 mL), washed with 1 N HCl (3×), saturated sodium bicarbonate (2×), and brine, dried over magnesium sulfate, and concentrated in vacuo to give 2.82 g of crude product. Recrystallization from ethyl acetate afforded 1.28 g of pure *cis*-**10b**. Flash chromatography of the mother liquor residue (LPS-1 silica gel, 3:1 ethyl acetate/hexane) provided an additional 0.39 g of **10b** for a combined yield of 1.82 g (59%): mp 157–158 °C.

***cis*-3-Hydroxy-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-chloro-2*H*-1-benzazepin-2-one (12b).** To a solution of **10b** (0.83 g, 2.61 mmol) in dry DMF (26 mL) was added sodium hydride (60%, 0.11 g, 2.74 mmol). The reaction was stirred at room temperature for 1 h, a solution of (dimethylamino)ethyl chloride in toluene (1.7 M, 2.30 mL, 3.92 mmol) was added, and stirring was continued at 75 °C for 2 h. The solvents were removed in vacuo and the residue partitioned between ethyl acetate and 1 N hydrochloric acid. The organic phase was washed with 1 N hydrochloric acid, the combined aqueous layers were treated with 6 N sodium hydroxide to adjust the pH to 11, and the product was extracted with ethyl acetate (3 ×), dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was dissolved in ethyl acetate (2 mL) and ether (5 mL) and treated with ethereal hydrochloric acid (1.4 N, 1.2 equiv) at 0 °C. The solid product was isolated by filtration and washed with ether to provide **12b** (0.65 g, 59%).

***cis*-1,3,4,5-Tetrahydro-7-chloro-3-acetoxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (4b).** A solution of **12b** (0.62 g, 1.5 mmol) in dry acetic anhydride (25 mL) was heated to 110 °C under argon until the reaction was judged complete by TLC (8:1:1 methylene chloride/methanol/acetic acid). The solvent was removed in vacuo, the residue was dissolved in ethyl acetate, and saturated ethereal HCl (2 mL) was added. The colorless precipitate was filtered and dried to provide **4b** (0.50 g, 1.07 mmol, 71%): mp 217–219 °C. ^{1}H NMR ($CDCl_3$): δ 7.46 (d, 1 H, J = 8.2), 7.38 (d, 1 H, J = 8.2), 7.28 (s, 1 H), 7.18 (d, 2 H, J = 8.5), 6.90 (d, 2 H, J = 8.5), 5.06 (d, 1 H, J = 8.2), 4.54 (m, 1 H), 4.36 (m, 1 H), 3.82 (s, 3 H), 3.77 (m, 1 H), 3.61 (m, 1 H), 3.33 (m, 1 H), 2.94 (s, 6 H), 2.88 (m, 2 H), 1.89 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.5, 169.2, 159.3, 138.9, 135.3, 133.1, 130.9, 129.9, 129.4, 124.5, 114.3, 72.0, 55.6, 54.8, 50.4, 44.8, 44.1, 43.3, 37.8, 20.8. IR (KBr): 1741, 1679 cm^{-1}. MS (CI): $(M + H)^+$ 431.

(3*R*,4*S*-*cis*)-3-Hydroxy-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-chloro-2*H*-1-benzazepin-2-one (12i). A mixture of recrystallized (MeCN) **12b** (4.5 g, 1.6 mmol) and *d*-(+)-tartaric acid (1.74 g, 11.6 mmol) was dissolved in MeOH (225 mL) with heating, and the hot solution was seeded and allowed to crystallize at room temperature for 2 days. The mother liquors were decanted from the crystalline salt, and the latter was rinsed with fresh MeOH to give 3.22 g ($[\alpha]_D$ +63.1°, c = 1, HOAc). The salt was dissolved in hot MeOH (85 mL), and the solution was seeded and allowed to stand at room temperature for 3 days, to provide a colorless product (2.16 g, $[\alpha]_D$ +106°, c = 1, HOAc). A third crystallization from hot MeOH (65 mL) gave 1.67 g, ($[\alpha]_D$ +119°, c = 1, HOAc): mp 195–197 °C. Further recrystallization of this material did not change the optical rotation. The 1.67 g of *d*-(+)-tartrate was combined with 0.60 g of material from another experiment, suspended in a mixture of water (70 mL) and dichloromethane (70 mL), and treated dropwise with 1 N sodium hydroxide (8.1 mL). The layers were separated, the aqueous phase was extracted with dichloromethane (2 × 50 mL), and the organic phases were combined, washed with water (20 mL), dried over magnesium sulfate, filtered, and evaporated in vacuo to give the free base of **12i** (1.49 g, 46%): mp 55–60 °C; $[\alpha]_D$ +194° (c = 1, $CHCl_3$).

(3*R*,4*S*-*cis*)-3-Acetoxy-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-chloro-2*H*-1-benzazepin-2-one (4i). A solution of **12i** (1.48 g, 3.8 mmol) in EtOH (25 mL) was treated with ethanolic hydrochloric acid (5.7 N, 0.68 mL). The solution was concentrated in vacuo to provide the hydrochloride salt as a colorless solid (1.71 g, $[\alpha]_D$ +143°, c = 1, MeOH). This material was dissolved in acetic anhydride (50 mL) and heated in an oil bath at 110–120 °C for 3 h. The solution was concentrated in vacuo to give a colorless solid which was suspended in ethyl acetate (25 mL), diluted with ether (25 mL), and allowed to crystallize at room temperature for 2 h. The solid was filtered, washed with ether, and dried in vacuo to provide **4i** (1.65 g, 91%): mp 252–254 °C; $[\alpha]_D$ +131° (c = 1, MeOH). ^{1}H NMR (CD_3COOD): δ 7.70 (d, 1 H, J = 8.2), 7.64 (dd, 1 H, J = 1.7, 8.2), 7.61 (s, 1 H), 7.42 (d, 2 H, J = 8.8), 7.08 (d, 2 H, J = 8.8), 5.32 (d, 1 H, J = 8.2), 4.64 (m, 2 H), 3.97 (s, 3 H), 3.85–4.10 (m, 2 H), 3.70–3.85 (m, 1 H), 3.24 (s, 3 H), 3.18 (s, 3 H), 3.07–3.25 (m, 2 H), 2.04 (s, 3 H). ^{13}C NMR (CD_3COOD): δ 178.0, 171.8, 170.9, 160.0, 139.6, 137.0, 133.7, 131.7, 130.5, 130.4, 129.7, 125.6, 114.6, 72.8, 55.7, 55.5, 50.8, 45.4, 44.2, 44.0, 37.3, 20.6. IR (KBr): 1737, 1680 cm^{-1}. MS (CI): $(M + H)^+$ 431.

(3*S*,4*R*-*cis*)-1,3,4,5-Tetrahydro-7-chloro-3-acetoxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (4j). The preparation of **4j** proceeded as described in the preparation of **4i**, except that *l*-(−)-tartaric acid was used to crystallize the product from the mother liquors obtained in the preparation of **4i**: mp 253–255 °C dec; $[\alpha]_D$ −130° (c = 1, MeOH). ^{1}H NMR (CD_3COOD): δ 7.70 (d, 1 H, J = 8.2), 7.64 (d, 1 H, J = 8.2), 7.61 (s, 1 H), 7.42 (d, 2 H, J = 8.8), 7.08 (d, 2 H, J = 8.8), 5.32 (d, 1 H, J = 8.2), 4.64 (m, 2 H), 3.97 (s, 3 H), 3.85–4.10 (m, 2 H), 3.70–3.85 (m, 1 H), 3.24 (s, 3 H), 3.18 (s, 3 H), 3.05–3.25 (m, 2 H), 2.04 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 171.8, 170.9, 160.0, 139.6, 137.0, 133.7, 131.7, 130.5, 130.4, 129.7, 125.6, 114.6, 72.8, 55.7, 55.5, 50.8, 45.4, 44.2, 44.0, 37.3, 20.6. IR (KBr): 1739, 1680 cm^{-1}. MS (CI): $(M + H)^+$ 431.

[1-(4-Methoxyphenyl)-2-[2-nitro-6-(trifluoromethyl)-phenyl]ethyl]propanedioic Acid, Dimethyl Ester (6g). A solution of dimethyl (4-methoxybenzylidene)malonate (52.7 g, 0.21

mmol) in 350 mL of DMF was treated with sodium hydride (11.0 g of 60% dispersion, 0.27 mol). The resulting slurry was treated dropwise with a solution of 2-nitro-6-(trifluoromethyl)toluene (43.0 g, 0.21 mol) in DMF (50 mL) over a period of 30 min while the temperature was maintained at 28–30 °C (internal thermometer). The pale brown mixture was stirred at room temperature for 20 h, cooled in an ice bath, and treated portionwise with acetic acid (20 mL). The pale yellow slurry was poured onto ice water (2 L) and extracted with dichloromethane (500 mL). The aqueous layer was extracted with dichloromethane (250 mL, 2 × 100 mL). The organic phases were combined, washed with water (3 × 500 mL), dried with magnesium sulfate, filtered, and concentrated in vacuo to give 99.1 g of a pale brown granular solid. The latter was digested with hot methanol (150 mL), the suspension allowed to cool to room temperature, chilled overnight, filtered, washed with cold methanol, and dried to give **6g** as a colorless solid (78.3 g, 82%): mp 117–119 °C.

[2-[2-Amino-6-(trifluoromethyl)phenyl]-1-(4-methoxyphenyl)ethyl]propanedioic Acid, Dimethyl Ester (7g). Catalytic reduction of **6g** (20.2 g, 0.044 mol) with Pd–C (2.5 g, 5%) in methanol (250 mL). The reaction was stirred at room temperature under 1 atm hydrogen for 30 min, heated to 50–55 °C for 1 h, and then allowed to stand for 16 h at room temperature. Hydrogen was removed, the mixture was heated to dissolve the product, and the hot solution was filtered through Celite and washed with hot methanol. The colorless filtrate was concentrated in vacuo to give **7g** as a nearly colorless solid (18.5 g, 95%): mp 111–113 °C. A sample crystallized from methanol had mp 112–114 °C.

1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (8g). A suspension of **7g** (34.5 g, 0.081 mol) in methanol (350 mL) was heated to 45 °C and treated with sodium methoxide in methanol (23 mL of 25% solution, 0.106 mol). This mixture was heated at reflux for 1 h. The resulting slurry was cooled to 15 °C and treated with a solution of 6 N HCl (30 mL) in 350 mL of water. After stirring at 0 °C for 2 h, the pale gray solid was filtered and dried to give **8g** (30.8 g, 97%): mp 214–216 °C. A sample crystallized from methanol melted at 218–220 °C.

(3*S*,4*S*-*trans*)-3-Carboxy-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one, (*S*)-α-Methylbenzylamine Salt (13m). Solid **8g** (81.7 g, 0.21 mol) was added portionwise to a stirred, warm solution of KOH (58.0 g, 85%, 0.88 mol) in methanol (500 mL). The mixture was diluted with dioxane (100 mL) and the resulting solution heated to reflux for 6 h. After standing overnight at room temperature, approximately 50% of the solvent was removed in vacuo, and the residue was diluted with cold water (4 L). The insoluble material (mostly **8g**) was filtered and dried (10 g). The filtrate was cooled and treated with acetic acid (270 mL) to give a colorless granular solid. The solid was filtered, washed with cold water, and dried in a desiccator to give the carboxylic acid (69.0 g, 86%) mp 179–181 °C (sintered 128 °C). A solution of the carboxylic acid (67.0 g, 0.176 mol) in ethanol (1 L) was warmed and treated with a solution of (−)-α-methylbenzylamine (21.4 g, 0.176 mol, Aldrich) in ethanol (100 mL). This solution was seeded and allowed to stand undisturbed for 24 h at room temperature. The product separated as well-formed crystals on the walls of the flask. The mother liquor was decanted from the solid, and the latter was suspended in ethanol (70 mL), filtered, and washed with fresh ethanol to give **13m** as a colorless solid (34.6 g, 78%): mp 156 °C dec; $[\alpha]_D$ −10.3° (c = 1, MeOH).

(3*S*,4*R*-*trans*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (8m). A slurry of **13m** (355 g, 0.71 mol) and potassium bicarbonate (284 g, 2.84 mol, powdered) was dissolved in DMF (1.8 L) and cooled to 5 °C. Methyl iodide (165 mL, 2.65 mol) was added dropwise over 5 min, and the reaction was maintained at 0–5 °C for 10 min. The reaction was allowed to warm to room temperature over 5 h, while the disappearance of starting material was monitored. Chilled water (7.1 L) and ethyl acetate (3.5 L) were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 1.75 L). The combined organic extracts were washed with 10% hydrochloric acid (2 × 1.75 L), saturated sodium hydrogen sulfite (2 × 750 mL), water (1 L), and brine (2 L), dried over magnesium sulfate, filtered, and concentrated in vacuo to a thick slurry. To this slurry was added hexane (2.1 L), and the solid was filtered and washed with additional hexane (2.1 L) and dried in vacuo overnight to afford 8m as a colorless solid (274 g, 0.69 mol, 97%): mp 140–141 °C; $[\alpha]_D$ +10.6° (c = 1, MeOH).

(3*S*,4*S*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-hydroxy-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (9m). A solution of **8m** (8.38 g, 21.3 mmol) in tetrahydrofuran (420 mL) at −70 °C was treated with potassium hexamethyldisilazide (17.5 g, 87.7 mmol) and stirred for 1 h. Triethyl phosphite (15.4 mL, 89.8 mmol) was added, the bath was replaced with an ice–water bath, and dry oxygen gas was bubbled through the solution for 2 h at 0 °C. The reaction was then quenched with concentrated HCl (29 mL) at 0 °C, THF was removed in vacuo, and the residue was extracted with ethyl acetate (3 × 100 mL), washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, and was dried over magnesium sulfate and concentrated to give 16.9 g of a yellow oil. The oil was stirred with hexane (175 mL) and cooled overnight, and the hexane liquor was decanted. After the yellow oil was washed again with cold hexane (70 mL), the remaining solvent was concentrated in vacuo to provide crude **9m** (12.85 g): $[\alpha]_D$ +123° (c = 1, MeOH).

(3*R*,4*S*-*cis*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (10m). A stirred solution of **9m** (12.85 g, 21.3 mmol) in pyridine (175 mL) was treated with lithium iodide (11.6 g, 86.7 mmol) and water (1.75 mL), heated to reflux for 2 h, cooled to ambient temperature, and concentrated in vacuo. The residue was dissolved in chloroform (250 mL), washed with 1 N hydrochloric acid (2 × 150 mL) and saturated brine, dried over magnesium sulfate, filtered, and evaporated in vacuo to give 6.85 g of a solid. This material was triturated with ether (75 mL) and cooled overnight to give a colorless solid (5.62 g). Traces of trans isomer were removed by crystallization from acetonitrile (60 mL) to provide **10m** (4.90 g, 14.0 mmol, 66%): mp 220–222 °C; $[\alpha]_D$ +116° (c = 1, MeOH). Additional **10m** could be recovered from the acetonitrile filtrate.

(3*R*,4*S*-*cis*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-hydroxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (12m). A vigorously stirred mixture of **10m** (5.17 g, 14.7 mmol) in dichloromethane (115 mL) and water (19 mL) was treated with pulverized barium hydroxide octahydrate (9.8 g, 31.1 mmol), benzyltrimethylammonium chloride (0.8 g), and (dimethylamino)ethyl bromide hydrobromide (7.9 g, 33.9 mmol) dissolved in water (9.5 mL). After stirring for 18 h, TLC (90:10 dichloromethane–methanol) indicated starting material had been consumed. The reaction was partitioned between ethyl acetate (250 mL) and water (100 mL), the aqueous phase was back-extracted with ethyl acetate (2×), the organic phases were combined, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 6.09 g of colorless solid free base: mp 133–135 °C (sintered 120 °C); $[\alpha]_D$ +135° (c = 1, MeOH). The free base in methanol (200 mL) was treated with ethanolic HCl (5.35 N, 2.8 mL, 15.0 mmol), and the solvents were concentrated to give a sticky foam. The foam was rubbed under ether (200 mL), cooled for 2 h, filtered, and dried in vacuo to provide **12m** (6.65 g, 100%): $[\alpha]_D$ +91.3° (c = 1, MeOH). A sample recrystallized from ether had mp 192–194 °C. ^{1}H NMR (CD_3OD): δ 7.66–7.82 (m, 3 H), 7.29 (d, 2 H, J = 8.8), 6.98 (d, 2 H, J = 8.8), 4.36–4.46 (m, 2 H), 4.34 (d, 1 H, J = 8.8), 3.86 (s, 3 H), 3.58–3.72 (m, 3 H), 3.25 (dd, 1 H, J = 14.1, 5.9), 3.13 (dd, 1 H, J = 13.5, 14.1), 3.02 (s, 6 H). ^{13}C NMR (CD_3OD): δ 175.1, 160.6, 144.0, 134.3, 132.1, 131.0, 129.7, 128.2, 126.0, 125.9, 114.9, 70.6, 56.8, 55.8, 53.8, 45.8, 44.1, 33.6. IR (KBr): 1667 cm^{-1}. MS (CI): $(M + H)^+$ 423.

(3*R*,4*S*-*cis*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-acetoxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (4m). A stirred solution of **12m** (6.5 g, 14.2 mmol) in acetic anhydride (180 mL) was heated in an oil bath at 110–120 °C for 4 h, at which time TLC analysis showed the reaction to be complete. The bulk of acetic anhydride was removed in vacuo, and the syrupy residue (10.6 g) was taken up in ethyl acetate (30 mL); on seeding and rubbing, a solid slowly separated. Ether (90 mL) was added in increments and after cooling for 1 h, the colorless solid was filtered under Ar, washed with ether, and dried in vacuo to provide 4m (6.2 g, 12.4 mmol, 89%): mp 180–182 °C (sintered 178 °C); $[\alpha]_D$ +97.1° (c = 1, MeOH). ^{1}H NMR (CD_3OD): δ 7.88 (d, 1 H, J =

8.8), 7.83 (d, 1 H, J = 7.0), 7.73 (dd, 1 H, J = 7.7), 7.32 (d, 2 H, J = 8.8), 6.98 (d, 2 H, J = 8.8), 5.10 (d, 1 H, J = 8.8), 4.93 (s, 1 H), 4.35–4.55 (m, 2 H), 3.86 (s, 3 H), 3.73–3.92 (m, 1 H), 3.50–3.61 (m, 1 H), 3.30 (d, 1 H, J = 5.3, 14.0), 3.14 (dd, 1 H, J = 14.0), 3.08 (s, 6 H), 1.93 (s, 3 H). ^{13}C NMR (CD_3OD): δ 171.6, 170.6, 160.6, 143.6, 133.9, 131.8, 130.5, 130.0, 128.3, 126.2, 126.1, 114.8, 72.7, 56.2, 55.7, 50.8, 45.7, 44.0, 33.8, 20.3. IR (KBr): 1740, 1686 cm^{-1}. MS (CI): $(M + H)^+$ 465.

(3*R*,4*R*-*trans*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (10o). To a solution of **9n** (3*R*,4*R* stereochemistry, prepared as described for antipode **9m**; 24.7 g, 43.4 mmol) in anhydrous pyridine (40 mL) was added a 100 °C solution of LiI (27.5 g, 206 mmol) in anhydrous pyridine (200 mL). The deep brown mixture was heated to reflux for 6 h. The bulk of the pyridine was removed in vacuo, and the dark syrupy residue was partitioned between ethyl acetate (800 mL) and water (300 mL). The aqueous phase was extracted with ethyl acetate (3 × 200 mL), the combined organic layers were washed with 1 N hydrochloric acid (2 × 300 mL), saturated sodium bicarbonate (120 mL), water, and brine, and dried over magnesium sulfate, and the solvent was evaporated in vacuo to provide a crude yellow solid (13.5 g). Crystallization from MeCN (140 mL) removed 6.59 g of cis alcohol. Chromatography of the filtrate on silica gel provided trans alcohol **10o** (1.64 g): $[\alpha]_D$ +197° (c = 1, MeOH).

(3*R*,4*R*-*trans*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-hydroxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (12o). A vigorously stirred mixture of **10o** (1.55 g, 4.41 mmol) in dichloromethane (55 mL) and water (9 mL) was treated with pulverized $Ba(OH)_2 \cdot 8H_2O$ (2.9 g, 9.2 mmol), benzyltrimethylammonium chloride (0.24 g), and (dimethylamino)ethyl bromide hydrobromide (2.4 g, 10.3 mmol, in 4.5 mL water). The reaction was stirred for 16 h, filtered, and washed with dichloromethane. The organic layer was then washed with water (2×) and shaken with dilute hydrochloric acid, and the acidic aqueous layer was washed with ether. The aqueous phase was treated with excess 1 N sodium hydroxide and extracted with ethyl acetate (4×). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was treated with ethanolic hydrochloric acid to provide **12o** as a pale yellow amorphous solid (1.86 g, 92%): $[\alpha]_D$ +152° (c = 1, MeOH).

(3*R*,4*R*-*trans*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-acetoxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (4o). A stirred solution of **12o** (1.85 g, 4.03 mmol) in acetic anhydride (50 mL) was heated in an oil bath at 117–122 °C for 2.5 h. The acetic anhydride was removed in vacuo to provide an oil (3.5 g) which was dissolved in ethyl acetate, evaporated, and rubbed under ether to give a solid. Repeated cooling and trituration with ether provided **4o** (1.6 g, 80%): mp 85–88 °C; $[\alpha]_D$ +129° (c = 1, MeOH). ^{1}H NMR (CD_3OD): δ 7.75–8.05 (m, 3 H), 6.85–7.50 (m, 4 H), 5.40 (d, 1 H, J = 11.7), 4.44 (m, 1 H), 3.88 and 3.94 (s, 3 H), 3.65–4.05 (m, 2 H), 3.44–3.60 (m, 2 H), 3.30 (d, 1 H, J = 14.6), 3.13 (s, 6 H), 3.14 (m, 1 H), 2.07 and 1.73 (s, 3 H). ^{13}C NMR (CD_3OD): δ 172.0, 171.2, 160.4, 143.5, 132.9, 132.4, 130.3, 129.3, 129.2, 129.0, 115.0, 73.6, 56.4, 55.7, 50.0, 46.2, 44.1, 33.0, 20.2. IR (KBr): 1742, 1684 cm^{-1}. MS (CI): $(M + H)^+$ 465.

(*S*)-*N*-(Benzyloxycarbonyl)-2-[[(*p*-tolylsulfonyl)oxy]methyl]pyrrolidine. *p*-Toluenesulfonyl chloride (102.8 g, 539 mmol) was added in portions to a stirred solution of (*S*)-*N*-(benzyloxycarbonyl)-2-pyrrolidinemethanol (see U.S. Patent 4,902,684; 105.7 g, 449 mmol) in pyridine (400 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 20 h. Most of the pyridine was removed by distillation under reduced pressure. The residue was diluted with water and extracted with ether (3×). The combined ether extracts were washed with aqueous hydrochloric acid (1 N) and saturated copper sulfate solution (3×), dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting viscous syrup was washed with warm hexanes (3×). On standing at 5 °C, (*S*)-*N*-(Benzyloxycarbonyl)-2-[(*p*-toluenesulfonyloxy)methyl]pyrrolidine solidified (147.7 g, 84%): mp 48–49 °C; $[\alpha]_D$ = −49.4° (c = 1, MeOH).

[3*R*-[1(*S),3α,4α]]-1-[[(Benzyloxycarbonyl)-2-pyrrolidinyl]methyl]-1,3,4,5-tetrahydro-3-hydroxy-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one (5g).** A solution of **10m** (25 g, 71.2 mmol), cesium carbonate (34.8 g, 106.7 mmol), and (*S*)-*N*-(benzyloxycarbonyl)-2-[[(*p*-tolylsulfonyl)oxy]methyl]pyrrolidine (34.6 g, 89 mmol) in DMF (200 mL) was heated to 50 °C. After 8 h, additional (*S*)-*N*-(benzyloxycarbonyl)-2-[[(*p*-tolylsulfonyl)oxy]methyl]pyrrolidine (2.8 g, 7.2 mmol) was added. The reaction mixture was stirred at 50 °C for 20 h, cooled to room temperature and diluted with ether. It was extracted with ethyl acetate (3× 300 mL). The combined organic extracts were washed with 10% aqueous lithium chloride (3×), dried over magnesium sulfate, filtered, and concentrated in vacuo to afford a pale yellow solid. The solid was suspended in ether (100 mL) and stirred for 30 min, hexanes (100 mL) were added, and the suspension was stirred for an additional 30 min. The solid was filtered and dried in vacuo to afford **5g** (34.5 g, 85%): mp 181 °C; $[\alpha]_D$ = 144.7° (c = 1, MeOH).

[3*R*-[1(*S),3α,4α]]-3-(Acetyloxy)-1-[[(benzyloxycarbonyl)-2-pyrrolidinyl]methyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one (5h).** Acetyl chloride (14.7 mL, 206.7 mmol) was added dropwise to a stirred solution of **5g** (25 g, 44 mmol) in ethyl acetate (200 mL). The solution was heated to 70 °C for 22 h, cooled to 0 °C, and treated with methanol (6.6 mL, 162.5 mmol). The reaction mixture was washed with saturated potassium bicarbonate solution (2×) and water. The aqueous extracts were combined and back-extracted with ethyl acetate (200 mL). The combined organic extract was dried over magnesium sulfate, filtered, and concentrated in vacuo to provide the crude 3-acetyl derivative (27.7 g) which was used in the next step without further purification.

[3*R*-[1(*S),3α,4α]]-3-(Acetyloxy)-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-(2-pyrrolidinylmethyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (5a).** A mixture of **5h** (27.7 g, 44 mmol), 20% palladium hydroxide on carbon (Pearlman's catalyst, 5.4 g), and trifluoroacetic acid (12 mL) in ethyl acetate (300 mL) was hydrogenated under 1 atm of hydrogen for 1 h. The mixture was filtered through a pad of anhydrous magnesium sulfate, and the solids were washed with ethyl acetate. The filtrate was concentrated, dissolved in ethyl acetate (300 mL), and washed with saturated potassium bicarbonate solution (2×) and water. The ethyl acetate extract was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in methanol (75 mL), and fumaric acid (5.1 g, 44 mmol) was added to the stirred solution. Upon concentration of the mixture, the fumarate salt precipitated out as a white solid. The precipitate was filtered, washed with ethyl acetate, and dried to provide the fumarate salt (18.14 g), which was dissolved in ethyl acetate/dichloromethane and washed with saturated potassium bicarbonate solution. The organic extract was dried over magnesium sulfate, filtered, and concentrated in vacuo to afford the free base of **5a**. The free base was dissolved in ether, treated with an excess of ethereal hydrogen chloride solution, and concentrated to a white foam, which was triturated with ethyl/dichloromethane (98:2) to provide **5a** as a white powder (15.02 g, 67% overall yield from the alcohol): mp 218–220 °C; $[\alpha]_D$ = 80° (c = 1, MeOH). ^{1}H NMR ($CDCl_3$): δ 10.20 (bs, 1 H), 9.30 (bs, 1 H), 7.77 (d, 1 H, J = 8.0), 7.62 (d, 1 H, J = 8.0), 7.51 (t, 1 H, J = 7.9), 7.21 (d, 2 H, J = 8.7), 6.90 (d, 2 H, J = 8.7), 5.06 (d, 1 H, J = 8.4), 4.54–4.38 (m, 2 H), 3.99–3.67 (m, 5 H), 3.42–3.17 (m, 3 H), 2.93–2.75 (t, 1 H, J = 12.2), 2.26–1.79 (m, 4 H), 1.87 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 169.9, 169.5, 158.9, 141.3, 132.3, 130.5, 129.1, 128.7, 126.8, 113.9, 71.1, 58.4, 55.2, 49.5, 48.4, 44.9, 33.2, 28.8, 23.1, 20.4. IR (KBr): 1740, 1689 cm^{-1}. MS: $(M + H)^+$ 477.

[3*R*-[1(*S)],3α,4α]-3-Hydroxy-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-(2-pyrrolidinylmethyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (5c).** A mixture of **5g** (35 g, 61.6 mmol), palladium hydroxide on carbon (7 g), and acetyl chloride (35 mL) in absolute ethanol (700 mL) was placed in a Parr shaker apparatus and hydrogenated for 100 min at a pressure of 50 psi of hydrogen. After evacuation of the hydrogen, magnesium sulfate was added, and the reaction mixture was filtered to remove the catalyst. The solids were washed well with absolute ethanol, the filtrate was concentrated, and the residue was diluted with saturated aqueous potassium bicarbonate and extracted with ethyl acetate (3×). The combined extract was dried over magnesium sulfate, filtered, and concentrated in vacuo to provide a pale yellow foam, which was dissolved in methanol

(350 mL) and filtered. Fumaric acid (7.15 g, 61.6 mmol) was added, and the mixture was heated on a steam bath to form a homogeneous solution and allowed to cool and crystallize overnight. The white crystalline solid was filtered and washed well with ethyl acetate to provide the fumarate salt of **5c** (29.76 g). The fumarate salt was converted to its free base by washing with saturated aqueous potassium bicarbonate and extracting with ether/ethyl acetate (3×). To the solution of free base was added excess ethereal hydrochloric acid. The white precipitate was collected and dried to provide **5c** (21.6 g, 88%): mp 163–7 °C; $[\alpha]_D$ = +75.1° (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$): δ 9.4 (bs, 1 H), 9.1 (bs, 1 H), 7.56 (dd, 2 H, *J* = 9.5, 7.9), 7.44 (t, 1 H, *J* = 7.9), 7.13 (d, 2 H, *J* = 8.4), 6.84 (d, 2 H, *J* = 8.4), 4.78 (dd, 1 H, *J* = 9), 4.27 (d, 1 H, *J* = 8.4), 3.90–3.45 (m, 4 H), 3.77 (s, 3 H), 3.38 (m, 1 H), 3.22 (m, 1 H), 3.00 (m, 1 H), 2.84 (dd, 1 H, *J* = 13.7), 2.12–1.97 (m, 2 H), 1.96–1.75 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 175.0, 159.0, 142.3, 132.5, 130.5, 129.8, 128.2, 126.1, 124.7, 113.7, 69.6, 60.5, 55.2, 51.4, 49.6, 45.6, 31.8, 28.8, 22.4. IR (KBr): 1665 cm^{-1}. MS: $(M + H)^+$ 435.

(*S*)-2-(Chloromethyl)-1-methylpyrrolidine Hydrochloride. Thionyl chloride (3.28 mL, 45 mmol) was added dropwise to a stirred solution of (*S*)-1-methyl-2-pyrrolidinemethanol (1.73 g, 15 mmol, Aldrich) in chloroform (15 mL) at 0–5 °C. The mixture was heated under reflux for 2 h and was then concentrated. The residue was crystallized from acetone/ether to provide (*S*)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride (1.48 g, 57%).

[3*R*-[1(*S),3α,4α]]-1-[(1-Methyl-2-pyrrolidinyl)methyl]-3-hydroxy-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one (5i).** A mixture of **10m** (700 mg, 2.0 mmol) and sodium hydride (130 mg, 5.4 mmol) in dry DMF (20 mL) was stirred at room temperature for 1 h and cooled to 0 °C, and (*S*)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride (520 mg, 3 mmol) was added. Additional sodium hydride (12 mg, 0.5 mmol) was added after 1 h. The mixture was allowed to come to room temperature for 3 h, quenched with water, and extracted with ethyl acetate. The ethyl acetate extract was washed with 10% aqueous lithium chloride solution, dried over magnesium sulfate, filtered, and concentrated. The crude product was chromatographed on silica gel and eluted with 2–5% methanol in dichloromethane to provide **5i** (650 mg, 72%) as a foam.

[3*R*-[1(*S),3α,4α]]-3-(Acetyloxy)-1-[(1-methyl-2-pyrrolidinyl)methyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (5e).** A solution of **5i** (750 mg, 1.67 mmol), (*N*,*N*-dimethylamino)pyridine (410 mg, 3.34 mmol), and acetic anhydride (0.79 mL, 8.4 mmol) in dichloromethane (18 mL) was stirred at room temperature for 24 h. The mixture was absorbed on silica gel and was chromatographed on a silica gel column. Elution with 2–3% methanol in dichloromethane afforded the free base of **5e** which was dissolved in ether and treated with an excess of ethereal hydrogen chloride solution. The precipitated white solid was filtered and dried in vacuo at 70 °C to provide **5e** (536 mg, 1.0 mmol, 60%): mp 151–154 °C. $[\alpha]_D$ = +80° (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 1 H, *J* = 7.9), 7.64 (d, 1 H, *J* = 7.9), 7.55 (dd, 1 H, *J* = 7.9), 7.21 (d, 2 H, *J* = 8.5), 6.91 (d, 2 H, *J* = 8.5), 5.01 (d, 1 H, *J* = 8.5), 4.64–4.80 (m, 1 H), 4.28–4.44 (m, 1 H), 3.68–3.92 (m, 2 H), 3.82 (s, 3 H), 3.30 (m, 1 H), 2.78–3.00 (m, 2 H), 2.91 (s, 3 H), 2.03–2.60 (m, 5 H), 1.90 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.0, 169.3, 158.9, 142.3, 131.9, 130.3, 129.1, 128.7, 127.0, 124.8, 113.8. 71.3, 66.4, 56.0, 55.1, 50.0, 49.5, 39.7, 33.2, 29.5, 21.5, 20.3. IR (KBr): 1741, 1687 cm^{-1}. MS: $(M + H)^+$ 491.

***cis*-3-Hydroxy-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one (12h).** A vigorously stirred suspension of **10h** (7.0 g, 20 mmol), prepared as described for **10b**, in dichloromethane (140 mL) and water (25 mL) was treated with pulverized barium hydroxide (13.3 g, 42 mmol) and benzyltrimethylammonium chloride (10 mol %). A solution of 2-(dimethylamino)ethyl bromide hydrobromide (10.5 g, 45 mmol) in water (12 mL) was then added, and the resulting mixture was stirred for 16 h. After filtration of residual solid material from the reaction, the phases were separated and the dichloromethane layer was washed with water (2 × 75 mL) and then washed with water (750 mL) containing 1 N HCl (42 mL). The aqueous phase was washed once with ether, treated with 1 N NaOH (56 mL), and extracted with ethyl acetate (250 mL), and the phases were separated. The aqueous phase was back-extracted with ethyl acetate (3 × 150 mL), and the combined organic phases were dried over magnesium sulfate and concentrated in vacuo to afford **12h** (7.87 g, 18.6 mmol, 93%): mp 136–138 °C.

(3*R*,4*S*-*cis*)-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one (4k). Racemic **12h** (15.8 g, 37.4 mmol) and (+)-tartaric acid (5.7 g, 38 mmol) were dissolved in hot methanol (500 mL). The warm solution was then seeded with the desired salt obtained from a previous small-scale resolution and allowed to stand at room temperature for 3 days. The resulting crystals were filtered, washed with cold methanol (50 mL), and dried in vacuo to give the (+)-tartrate salt (11.7 g, $[\alpha]_D$ +59.7° (*c* = 1, HOAc)). This material was dissolved in hot methanol (275 mL), allowed to recrystallize as above, filtered, and washed with cold methanol to give (+)-tartrate salt (5.43 g) with mp 165–167 °C, $[\alpha]_D$ +117° (*c* = 1, HOAc). The salt thus obtained was combined with additional material (1.74 g) from another resolution (7.17 g total, 12.1 mmol), suspended in dichloromethane (200 mL), treated with 1 N NaOH (25 mL), and stirred until all of the solid had dissolved. The aqueous phase was back-extracted with dichloromethane (2 × 100 mL), and the combined organic phases were washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue obtained from the organic phase was dissolved in methanol (150 mL) and treated with ethanolic HCl (2.3 mL of 5.35 N). Concentration in vacuo afforded **12k** (5.57 g, 11.7 mmol, 96%): $[\alpha]_D$ +144° (*c* = 1, MeOH).

This material was acetylated under the conditions described for the preparation of **4m** to afford **4k** (5.60 g, 10.8 mmol, 92%): mp 257–259 °C dec; $[\alpha]_D$ +143° (*c* = 1, MeOH). ^{1}H NMR (CD_3COOD): δ 7.90–7.95 (m, 3 H), 7.42 (d, 2 H, *J* = 8.8), 7.09 (d, 2 H, *J* = 8.8), 5.32 (d, 1 H, *J* = 8.2), 4.71 (m, 2 H), 3.70–4.10 (m, 3 H), 3.97 (s, 3 H), 3.15–3.35 (m, 2 H), 3.24 (s, 3 H), 3.18 (s, 3 H), 2.04 (s, 3 H). ^{13}C NMR (CD_3COOD): δ 171.8, 170.8, 160.0, 144.3, 135.9, 131.6, 130.4, 127.6, 126.7, 124.7, 114.6, 72.8, 55.5, 50.9, 45.3, 44.1, 44.0, 37.4, 20.3. IR (KBr): 1742, 1684 cm^{-1}. MS (CI): $(M + H)^+$ 465.

(3*S*,4*R*-*cis*)-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one (4l). Combining the mother liquors and wash solutions from the resolution of **12k** gave 10.5 g of salt enriched in the 3*S*,4*R* isomer (**12l**). This was liberated and resolved as described for **4k** to afford enantiomerically pure (−)-tartaric acid salt (4.57 g): mp 163–165 °C; $[\alpha]_D$ −118° (*c* = 1, HOAc). This material was combined with 2.11 g of salt from an earlier resolution (6.68 g total, 11.3 mmol) and subjected to the procedures described above to provide the pure (3*S*,4*R*-*cis*)-3-acetoxy isomer as the hydrochloride salt (5.08 g, 9.79 mmol, 87% from tartrate): mp 258–260 °C dec; $[\alpha]_D$ −143° (*c* = 1, MeOH). ^{1}H NMR (CD_3COOD): δ 7.90–7.95 (m, 3 H), 7.42 (d, 2 H, *J* = 8.8), 7.09 (d, 2 H, *J* = 8.8), 5.32 (d, 1 H, *J* = 8.2), 4.71 (m, 2 H), 3.70–4.10 (m, 3 H), 3.97 (s, 3 H), 3.15–3.35 (m, 2 H), 3.24 (s, 3 H), 3.18 (s, 3 H), 2.04 (s, 3 H). ^{13}C NMR (CD_3COOD): δ 171.8, 170.8, 160.0, 144.3, 135.9, 131.6, 130.4, 127.6, 126.7, 124.7, 114.6, 72.8, 55.5, 50.9, 45.3, 44.1, 44.0, 37.4, 20.3. IR (KBr): 1742, 1684 cm^{-1}. MS (CI): $(M + H)^+$ 465.

(3*R*,4*S*-*cis*)-3-(Acetyloxy)-1-[2-(methylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one, Fumarate (1:1) Salt (15k). Compound **4k** (4.08 g, 8.16 mmol) was partitioned between saturated sodium bicarbonate (100 mL) and ethyl acetate (100 mL). The separated aqueous phase was washed with additional ethyl acetate (50 mL), and the combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in toluene (100 mL) and heated to reflux for 2 h with azeotropic removal of water. Trichloroethyl chloroformate (1.46 mL, 10.6 mmol) was then added via syringe, and the mixture was heated at reflux for 16 h. The cooled toluene solution was diluted with ethyl acetate (50 mL), washed with 1 N HCl (3 × 50 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated in vacuo. Trituration of the residue in diethyl ether gave 4.67 (91%) of **14k**.

This material was slurried in glacial acetic acid (50 mL) with zinc dust (0.65 g, 10 mmol) and heated to 50 °C for 24 h. Additional zinc dust (0.75 g, 11.5 mmol) was added to the reaction

mixture, and heating was continued for 2 h, whereupon the reaction was cooled and filtered. The clear filtrate was concentrated in vacuo, and the residue was dissolved in ethyl acetate (100 mL), washed with saturated sodium bicarbonate (100 mL) and brine, and dried over magnesium sulfate. The dry ethyl acetate solution was treated with a solution of fumaric acid (0.87 g, 7.5 mmol) in methanol (10 mL). The solution was concentrated in vacuo, and the residue was recrystallized from ethyl acetate (100 mL) and washed with diethyl ether to give **15k** (3.34 g, 6.00 mmol, 74%): mp 135–137 °C; $[\alpha]_D$ +116.2° (c = 1, MeOH). ^{1}H NMR (CD_3OD): δ 7.68 (s, 1 H), 7.66 (d, 1 H, J = 8.4), 7.54 (d, 1 H, J = 8.4), 7.15 (d, 2 H, J = 8.7), 6.79 (d, 2 H, J = 8.7), 6.56 (s, 2 H), 4.96 (d, 1 H, J = 8.4), 4.20 (m, 2 H), 3.77 (m, 1 H), 3.40 (m, 1 H), 3.21 (m, 1 H), 3.00 (m, 2 H), 2.67 (s, 3 H), 1.75 (s, 3 H). ^{13}C NMR (CD_3OD): δ 171.8, 171.3, 171.0, 160.5, 145.1, 136.6, 136.2, 132.2, 130.7, 128.1, 128.0, 126.8, 124.4, 114.8, 71, 55.7, 51.2, 48.2, 46.5, 37.8, 33.9, 20.3. IR (KBr): 1743, 1689 cm^{-1}. MS (CI): $(M + H)^+$ 451.

(3*R*,4*S*-*cis*)-3-Hydroxy-1-[2-(methylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one, Fumarate (1:1) Salt (16k). Compound **15k** (3.92 g, 6.92 mmole) was dissolved with stirring in methanol (60 mL). Treatment of the solution with 25% NaOMe (3.0 mL, 13.8 mmol) resulted in the immediate formation of a white heterogeneous suspension. TLC analysis (10% methanol/dichloromethane) showed complete disappearance of starting material after 5 min. The mixture was concentrated, dissolved in ethyl acetate (75 mL), washed with water (75 mL) and brine (75 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in methanol (10 mL), treated with 1 equiv of fumaric acid, and concentrated in vacuo to a colorless solid. The solid was triturated with hot ethyl acetate, giving **16k** (2.40 g, 4.58 mmol, 66%): mp 171–172 °C dec; $[\alpha]_D$ = +125° (c = 1.05, MeOH). ^{1}H NMR (CD_3OD): δ 7.73 (s, 1 H), 7.71 (d, 1 H, J = 7.9), 7.56 (d, 1 H, J = 7.9), 7.21 (d, 2 H, J = 8.4), 6.89 (d, 2 H, J = 8.4), 6.68 (s, 2 H), 4.35 (m, 1 H), 4.31 (d, 1 H, J = 7.9), 4.18 (m, 1 H), 3.77 (s, 3 H), 3.70 (m, 1 H), 3.44 (m, 1 H), 3.35 (m, 1 H), 3.02 (m, 2 H), 2.68 (s, 3 H). ^{13}C NMR (CD_3OD): δ 175.5, 171.4, 160.5, 145.5, 137.0, 136.2, 132.4, 131.1, 127.8, 127.7, 126.5, 124.4, 114.8, 71.0, 55.8, 54.1, 46.7, 37.6, 34.1. IR (KBr): 1672 cm^{-1}. MS (CI): $(M + H)^+$ 409.

(3*R*,4*S*-*cis*)-1-(Formylmethyl)-1,3,4,5-tetrahydro-6-(trifluoromethyl)-3-acetoxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (17a). To a solution of **10m** (5.00 g, 14.2 mmol) in dry DMF (50 mL) was added sodium hydride (60%, 0.54 g, 13.5 mmol). The mixture was stirred at room temperature for 20 min and cooled to 0 °C, and allyl bromide (1.17 mL, 13.5 mmol) was added. The reaction was stirred for 16 h as it warmed to room temperature, quenched with water, and extracted with ether (3×). The ether layer was washed with 1 N hydrochloric acid (3×) and brine, dried over magnesium sulfate, and evaporated in vacuo. Flash chromatography provided the *N*-allyl derivative of **10m**.

The N-allylated derivative (5.32 g, 13.59 mmol) in MeOH (140 mL) and dichloromethane (70 mL) was cooled to −78 °C and treated with O_3. The blue mixture was allowed to stir for 10 min and was then flushed with O_2. The solution was treated with dimethyl sulfide (2 mL), and the solvent was distilled off in the hood. The crude material was chromatographed to provide the aldehyde (4.50 g, 84%): mp 64–68 °C; $[\alpha]_D$ +143° (c = 8, MeOH).

The *N*-acetaldehyde derivative (0.50 g, 1.3 mmol) was dissolved in acetic anhydride (5 mL) and heated to 100 °C for 3 h. Acetic anhydride was distilled off, and the residue was purified by preparative TLC to provide **17a** as a foamy solid (0.34 g, 61% from **10m**): mp 78–80 °C; $[\alpha]_D$ +116° (c = 1.01, MeOH). ^{1}H NMR ($CDCl_3$): δ 9.74 (s, 1 H), 7.62 (d, 1 H, J = 7.4), 7.45 (m, 1 H), 7.36 (d, 1 H, J = 7.4), 7.26 (d, 2 H, J = 8.5), 6.90 (d, 2 H, J = 8.5), 5.18 (d, 1 H, J = 7.9), 5.06 (d, 1 H, J = 18), 4.52 (d, 1 H, J = 18), 3.81 (s, 3 H), 3.78 (m, 1 H), 3.61 (m, 1 H), 3.37 (m, 1 H), 1.89 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 195.0, 170.1, 167.7, 158.9, 142.3, 130.7, 129.4, 128.0, 126.2, 113.9, 71.0, 58.8, 55.2, 49.7, 32.4, 20.5. MS (CI): $(M + H)^+$ 436. IR (KBr): 1738, 1686 cm^{-1}.

(3*R*,4*S*-*cis*)-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-acetoxy-1-(2-hydroxyethyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (17b). To a solution of **10m** (4.0 g, 11.4 mmol) in DMF (75 mL) was added sodium hydride (0.33 g, 13.8 mmol). The mixture was stirred at room temperature for 1 h, the THP ether of bromoethanol (3.57 g, 17.1 mmol) was added, and the mixture was heated to 90 °C for 2 h. The reaction mixture was cooled, quenched with water, and extracted with ethyl acetate (2×), and the combined ethyl acetate extracts were washed with lithium chloride solution (10%, 2×) and saturated potassium bicarbonate, dried over magnesium sulfate, and evaporated in vacuo. The resulting oil was purified by chromatography (20–50% ethyl acetate/hexane) to give the N-alkylated product (3.52 g, 7.34 mmol, 64%).

The N-alkylated material (3.52 g, 7.34 mmol) in dichloromethane (70 mL) was treated with acetic anhydride (3.46 mL, 36.7 mmol) and DMAP (1.79 g, 14.7 mmol). The reaction was stirred at room temperature for 29 h, the solvent was evaporated, and the residue was flash chromatographed on silica gel (2:3 ethyl acetate/hexane) to provide the acetate in quantitative yield. The THP acetate (5.47 g, 10.2 mmol) in THF (70 mL) was treated with 1 N hydrochloric acid (28 mL) at room temperature for 24 h. The solvent was removed in vacuo, and the residue was extracted with ethyl acetate (2×). The combined extracts were washed with saturated potassium bicarbonate, dried over magnesium sulfate, filtered, and evaporated in vacuo. The resulting colorless solid was purified by flash chromatography (1:1 ethyl acetate/hexane) to provide **17b** (2.01 g, 4.60 mmol, 45%, 29% yield from **10m**): mp 199–201 °C; $[\alpha]_D$ +106° (c = 10, MeOH). ^{1}H NMR ($CDCl_3$): δ 7.62 (m, 2 H), 7.48 (m, 1 H), 7.27 (d, 2 H, J = 8), 6.88 (d, 2 H, J = 8), 5.10 (d, 1 H, J = 8), 4.45 (m, 1 H), 3.70–3.95 (m, 5 H), 3.80 (s, 3 H), 3.15–3.35 (m, 2 H), 2.25–2.45 (bs, 1 H), 1.90 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.2, 168.7, 158.9, 142.9, 133.2, 130.8, 129.3, 128.0, 127.2, 124.4, 124.3, 113.8. 71.3, 60.7, 55.2, 51.8, 49.7, 32.6, 20.4. MS (CI): $(M + H)^+$ 438. IR (KBr): 1716, 1677 cm^{-1}.

(3*R*,4*S*-*cis*)-1-(Carboxymethyl)-1,3,4,5-tetrahydro-6-(trifluoromethyl)-3-acetoxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (17c). To a solution of **17b** (0.88 g, 2.0 mmol) in dry DMF (5 mL) was added pyridinium dichromate (3.78 g, 10 mmol), and the reaction was stirred for 5 h at room temperature. Additional pyridinium dichromate (3.78 g, 10 mmol) was added, and the reaction mixture was stirred for 20 h. The reaction was partitioned between ethyl acetate and water, the organic layer was separated, and the aqueous layer was back-extracted with ethyl acetate (2×). The combined organic extracts were washed with aqueous LiCl (10%), dried over magnesium sulfate, filtered, and concentrated in vacuo to provide a crude solid. The crude product was chromatographed on silica gel (5–10% methanol/dichloromethane), dissolved in ethyl acetate, washed with 1 N hydrochloric acid, and evaporated in vacuo. This material was recrystallized from toluene to provide **17c** as a colorless solid (0.27 g, 30%): mp 129–131 °C; $[\alpha]_D$ +114° (c = 3.9, MeOH). ^{1}H NMR ($CDCl_3$): δ 7.66–7.60 (m, 1 H), 7.49–7.40 (m, 2 H), 7.24 (d, 2 H), 6.87 (d, 2 H), 5.18 (d, 1 H, J = 8.0), 5.00 (d, 1 H, J = 18), 4.39 (d, 1 H, J = 18), 3.78–3.61 (m, 5 H), 3.29 (dd, 1 H), 1.88 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 172.6, 170.2, 168.2, 158.9, 142.3, 133.4, 130.7, 129.4, 129.0, 128.2, 128.1, 126.3, 113.9, 71.7, 55.2, 50.2, 50.0, 32.2, 20.5. IR (KBr): 1742, 1691 cm^{-1}.

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