Synthesis of Benzazepinone and 3-Methylbenzothiazepinone Analogues of Diltiazem

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One of the most important calcium channel blocking agents in clinical use is diltiazem, a 1,5-benzothiazepin-2-one derivative. Synthetic methods to prepare both benzazepinone and novel benzothiazepinone analogues have been developed. The initial step in the synthesis of the 1-benzazepin-2-one analogues of diltiazem involves the base-induced addition of 2-nitrotoluene to a benzylidenemalonate to afford the addition product **1**. This reaction has not been previously described in the literature. Critical to the success of this synthetic scheme was the observation that the decarboxymethylation of **4** with LiI in aqueous pyridine affords predominantly the desired *cis*-3-hydroxybenzazepinone **5**. The importance of a proton source during this reaction is discussed. With the use of X-ray crystallographic methods, C-3/C-4 relative stereochemistry was found to impart a profound effect on molecular shape, which is, most likely, ultimately relevant to the differences in biological activity between cis and trans isomers in this series. The conversion of intermediate **1** to the 3-methyl analogue **12** is also described, which, again, relies on a decarboxylation reaction to set the desired cis relationship between the substituents on C-3 and C-4. The results obtained in these studies were applied to the development of a new method to prepare **18**, the *cis*-3-methylbenzothiazepinone analogue of diltiazem. The key step in this process involves the two-step decarboxylation of **15**, affording a good yield of the *cis*-2-aryl-3-methylbenzothiazepinone **17**. Both **8** and **12** have potency in vitro similar to diltiazem, whereas the benzothiazepinone **18** was found to be significantly more potent than diltiazem and the benzazepinone derivatives. The procedures described in this paper represent general methods to prepare cis-3,4-disubstituted-1-benzazepin-2-ones and analogous 3-methylbenzothiazepinones.

Introduction

Calcium ion is a ubiquitous second messenger in the mammalian cell and, consequently, its intracellular concentration is tightly regulated.[1] Under a variety of physiological conditions, cell membrane depolarization results in the rapid influx of calcium ion through voltage-operated calcium channels. Alterations of this calcium gating mechanism are thought to be important in a number of disease states including hypertension and various cardiac disorders.[2] It is not surprising then that compounds which block the influx of calcium ion through the voltage-operated channels, calcium channel blockers, have found widespread utility in the area of cardiovascular medicine.[3] One of the most important agents in clinical use is the 1,5-benzothiazepin-4-one derivative diltiazem shown in Figure 1.[4] However, little information is available concerning structure–activity relationships for the benzothiazepinone calcium channel blocking agents.[5] Our interest in this area prompted us to explore synthetic methods to prepare 1-benzazepin-2-one analogues of diltiazem to initially examine the effects of substituting a methylene group for the sulfur atom of diltiazem and, subsequently, explore structure–activity relationships in this series. In connection with this work we report the development of a versatile method for the synthesis of 3- and 4-substituted 1-benzazepin-2-ones that has allowed us to prepare analogues of diltiazem containing both acetoxy and methyl substituents on C3 (benzazepinone numbering). We also report on the application of these methods to the preparation of the *cis*-3-methylbenzothiazepinone analogue of diltiazem, which has not been previously described.

Results and Discussion

Analogous to the procedures used to prepare the corresponding benzothiazepinones and, subsequently, benzoxazepinone and benzodiazepinones, we envisioned the critical step of a general synthesis as the formation of the 4–5 (benzazepinone numbering) carbon–carbon bond.[6] To our knowledge, the only general method described for the preparation of the desired ring system employed the same strategy with the Michael addition of a metalated toluene isocyanide to an α,β-unsaturated ester.[7] Although this method was attractive, it seemed simpler to employ a 2-nitrotoluene as the nucleophile. Based on a consideration of our need to further functionalize C3 of the benzazepinone ring once formed, we chose to employ a benzylidenemalonate as the electrophile. Therefore, successful formation of the C4–C5 connection followed by reduction of the nitro group and cyclization was expected to give the 3-(alkoxycarbonyl)-4-arylbenzazepinone nucleus. The presence of the C3 carboxy group was anticipated to expedite either oxidation of C3 or the incorporation of additional functionality.[8] In a final step, the C3 carboxyl auxiliary could be disposed of by decarboxylation.

Despite significant precedent for the reaction of 2-nitrotoluenes with a variety of imines, aromatic aldehydes, as well as the classical Reissert reaction, we were unable to find reference to general conditions for carbon–carbon

(1) Rubin, R. P.; Weiss, G. R.; Putney, J. W. *Calcium in Biological Systems*; Plenum Press: New York and London, 1985.
(2) For a comprehensive review, see: Godfraind, T.; Miller, R.; Wibo, M. *Pharmocol. Rev.* **1986**, *38*, 321.
(3) Vanhoutte, P. M. *Am. J. Cardiol.* **1987**, *59*, 3a.
(4) For a recent review, see: *Diltiazem*; Tanabe Seiyaku Co. Ltd.: Higashiku, Osaka, Japan, 1987; Chapter 1.
(5) (a) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Chem. Pharm. Bull.* **1973**, *21*, 92. (b) Takeda, M.; Oh-Ishi, T.; Nagao, H. U.K. Patent Appl. 2-154-757 A, 1985; (c) 2-154-758 A, 1985. (d) Takeda, M.; Oh-Ishi, T.; Nakajima, H.; Nagao, H. European Patent Appl. 84106187.2, 1984; (e) 85101713.7, 1985. (f) Mohacsi, E.; O'Brien, J. P. U.S. Patent 4,652,561, 1987; (g) U.S. Patent 4,640,930, 1987.
(6) (a) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* **1971**, *19*, 595. (b) Hashiyama, T.; Watanabe, A.; Inoue, H.; Konda, M.; Takeda, M.; Murata, S.; Nagao, T. *Chem. Pharm. Bull.* **1985**, *33*, 634. (c) Hashiyama, T.; Inoue, H.; Takeda, M.; Murata, S.; Nagao, T. *Chem. Pharm. Bull.* **1985**, *33*, 2348.
(7) Ito, Y.; Kobayshi, K.; Maeno, M.; Saegusa, T. *Chem. Lett.* **1980**, 487.
(8) For leading references on the oxidation of enolates, see: (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.

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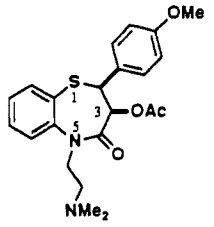
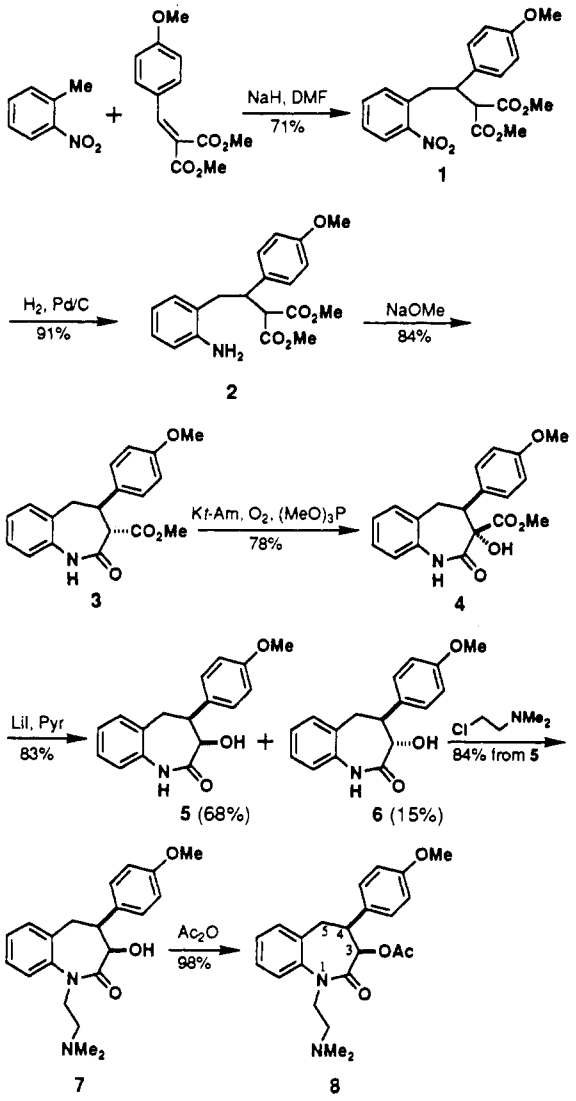


Diltiazem

Figure 1.

Scheme I



bond formation applicable to the process we desired.[9] As shown in Scheme I, however, we found that the addition of 2-nitrotoluene to a solution of (4-methoxybenzylidene)malonate and sodium hydride in DMF gave the desired adduct **1** in ca. 70% yield after removal of much of the dark byproducts by filtration of the crude product through silica gel followed by recrystallization from methanol. The order of addition of the reagents is very important in this reaction. *The addition of nitrotoluene to a slurry of sodium hydride in DMF, in the absence of the benzylidenemalonate, results in a very vigorous reaction.* Therefore, the success of the reaction depends on the stability of the benzylidenemalonate to sodium hydride. The reaction failed if alkoxide bases were employed or when THF was substituted for DMF.

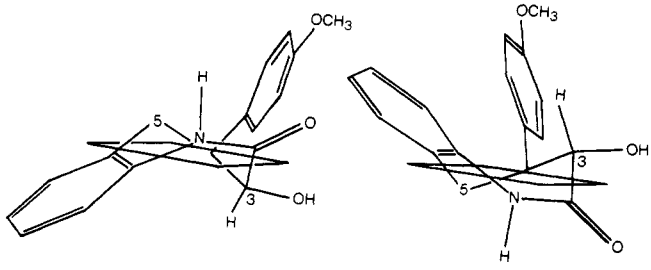


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Figure 2.

The conversion of **1** to the desired benzazepinone **3** was easily accomplished. Catalytic reduction of the nitro group gave the desired aniline **2** in high yield. Without purification this material was cyclized in refluxing methanol in the presence of 1 equiv of sodium methoxide. From this reaction, pure *trans*-3-carbomethoxybenzazepinone **3** was isolated by filtration of the reaction mixture after it had been cooled in an ice bath and diluted with aqueous 1 N HCl. As discussed below, the trans stereochemical assignment for **3** is consistent with the observed NMR coupling constant between the C3 and C4 protons ($J_{3,4}$ = 9.5 Hz). This assignment was also confirmed by single-crystal X-ray analysis, which shows **3** to possess a ring conformation identical with that of the trans alcohol **6** (see Figure 2).

At the outset, we made no provisions to control the relative stereochemistry associated with the introduction of the oxygen functionality onto C3. Treatment of the benzazepinone ester **3** with excess potassium hexamethyldisilazide in THF at low temperature followed by the addition of triethylphosphite and finally bubbling the mixture with anhydrous oxygen gas gave near quantitative crude yields of the desired product **4**. Analysis of ^1H and ^{13}C NMR spectra for this material indicated the presence of a single isomer. Assignment of relative stereochemistry was made by single-crystal X-ray analysis of **4**.[10] The stereochemical results of this reaction appear to be a consequence of virtually complete blockade of one face of the planar β-dicarbonyl anion intermediate by the C4 aromatic ring. Alternate, and simpler, procedures to effect the oxidation were also developed. These involved the use of potassium *tert*-amylate as the base in toluene–DMF mixtures, again employing molecular oxygen as the oxidant in the presence of triethyl or trimethyl phosphite. Omission of the phosphite results in greatly reduced yields of the desired product and is accompanied by the appearance of numerous byproducts that were difficult to remove from the desired material.

Treatment of hydroxy ester **4** with excess lithium iodide in refluxing pyridine afforded a variable mixture of isomeric products **5** and **6** as determined by NMR analysis of the crude product mixture. Assignment of the relative

(9) (a) Bakke, J. *Acta. Chem. Scand.* **1967**, *21*, 19. (b) Wesslen, B. *Acta. Chem. Scand.* **1967**, *21*, 718. (c) Bakke, J. *Acta. Chem. Scand. B* **1974**, *28*, 134. (d) Gupton, J. T.; Lizzi, M. J.; Polk, D. *Synth. Commun.* **1982**, *12*, 939. (e) Bartloli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1986**, *51*, 3694. (f) Bartloli, G.; Bosco, M.; Caretti, D.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1987**, *52*, 4381.

(10) Crystallographic data for **3**, **4**, **5**, **6**, and **10** are supplied as supplementary material to this paper. We have examined the solid state structures of over 30 benzazepinone and benzothiazepinone derivatives. Without exception, monosubstituted cis derivatives crystallize in the "M" twist-boat configuration with the C3 substituent in an equatorial position. For C3 disubstituted derivatives, greater variation has been observed. For example, whereas **10** adopts the "M" twist-boat configuration of **5**, **4** has a flat conformation in which all of the cyclic atoms of the fused benzazepinone nucleus except C4 are nearly coplanar.

stereochemistry for **5** and **6** was initially based on an analysis of ^{1}H NMR coupling constants for the C3 and C4 protons. By analogy to the diltiazem series, we assigned the major isomer **5** as cis with $J_{3,4}$ = 7.9 Hz and the minor isomer **6** as trans with $J_{3,4}$ = 10.0 Hz.[6,11]

These stereochemical assignments were confirmed by single-crystal X-ray analysis of both **5** and **6** (Figure 2). The heptagonal ring of each isomer adopts a twist-boat conformation, which is nearly torsionally symmetric with respect to a 2-fold axis passing through C4 and the midpoint of the N1–aryl bond. The two twist-boat conformations are enantiomeric, the cis isomer **5** having an equatorial OH with the ring in an "M" configuration and the trans isomer **6** possessing a ring-inverted "P" configuration with an equatorial OH.[12] Since the axial and equatorial orientation of ring substituents are interchanged upon ring inversion, isomers **5** and **6** differ markedly in overall shape.[13] As shown in Figure 2, the C4 *p*-methoxyphenyl ring and the amide group are in a syn relationship, relative to the mean plane of the heptagonal ring, in the "M" conformer of **5** and anti to each other in the ring-inverted "P" conformer of **6**.[13] As will be reported elsewhere, we have determined that the two critical pharmacophores are the *p*-methoxy group of the C4 aromatic ring and the basic amino group contained in the amide substituent, vis-a-vis, **8** and diltiazem. We believe the observation that only the product derived from **5** possesses activity in vitro is related to the differing spacial relationship of these pharmacophores as a consequence of the major differences in molecular shape between **5** and **6**.

The observation that the major product from the decarboxymethylation reaction was the desired cis isomer prompted a further investigation of reaction conditions. We found that the addition of 1–2% water resulted in a very reproducible isomer ratio of 7:3 in favor of the cis isomer **5**. Under these conditions the reaction proceeds to completion (as judged by TLC) in about 1 h at reflux. Different results were obtained under anhydrous conditions. Azeotropic removal of water from the reaction mixture prior to the addition of the substrate resulted in a significantly faster reaction, yielding a 6:4 mixture of **6** to **5**. This indicated that the presence of a proton source facilitated the formation of the desired cis isomer. Based on these observations, we routinely add 1% water to the reaction mixture, although a slightly improved isomer ratio can be obtained by the addition of acid (see below). Almost complete separation of the desired cis isomer **5** from the minor amount of trans alcohol **6** was accomplished by simple trituration in ether–hexane mixtures. Thus, the significant difference in solubility between the two isomers allowed us to easily obtain **5** on large scale and negated the need to search for more stereoselective procedures or resort to an oxidation and reduction sequence to set the desired C3 relative stereochemistry.[14]

The preponderance of the desired cis isomer is in agreement with the stereochemical results of the oxidation reaction and indicates that, in the presence of water, **5** is the kinetic product of this reaction. Since the oxidation reaction is a nonreversible process, **4** is the kinetic product resulting from the least hindered attack on the planar β-dicarbonyl anion. While the decarboxymethylation reaction also proceeds through a planar intermediate, the amide enol/enolate, there is a possibility for isomerization of the product due to the presence of a proton on C3, adjacent to the amide carbonyl. We investigated this possibility by subjecting pure cis alcohol to various reaction conditions. Under the anhydrous reaction conditions, an analogue of **5** containing a 7-chloro substituent was converted to a mixture containing 72% of the trans isomer following 16 h of heating. Since additional reaction times failed to alter this isomer ratio (ca. 7:3 trans–cis), we conclude that this represents thermodynamic equilibrium. This is identical with the isomer ratio obtained when the decarboxylation is conducted under anhydrous conditions. The same experiment conducted in the presence of 1% water gave only 45% conversion to the trans isomer. Most importantly, TLC examination of the isomerization experiment conducted in the presence of water after 2 h of heating, the normal reaction period, showed that only a trace of the trans isomer had been formed. These results indicate that the aqueous reaction conditions do not yield a thermodynamic mixture of products and that the desired cis product is not extensively isomerized to its trans isomer during the reaction. We conclude that the presence of a proton source such as water results in rapid and slowly reversible protonation of C3 from the least hindered face of the planar enol/enolate primary intermediate.

As a further test of the importance of water as a proton source, we examined the decarboxylation reaction in the presence of added acid. Under the aqueous reaction conditions, the addition of pyridinium iodide (equivalent to the amount of LiI employed) increased the reaction time to 6.5 h but afforded a somewhat improved isomer ratio, ca. 4:1 of **5** and **6**, respectively. In the presence of added pyridinium iodide, even the reaction under anhydrous conditions gave **5** as ca. 80% of the isomer mixture. In this case, however, we observed that the reaction was complete in 1.5 h. The last reaction substantiates the important role of water as a proton source in the original aqueous conditions but, interestingly, indicates that water actually retards the overall rate of reaction. In total, we conclude from our investigations that the desired cis isomer **5** results from kinetic protonation of C3, which is facilitated by the addition of a proton source to the reaction, i.e., water and/or pyridinium iodide.

Once we obtained the desired *cis*-3-hydroxy-4-arylbenzazepinone **5**, the remaining steps proceeded as described for the benzothiazepinone system. Accordingly, the reaction of (dimethylamino)ethyl chloride in hot DMF using sodium hydride as the base gave **7** in 84% yield. Acetylation of **7** was performed in neat acetic anhydride at 100–120 °C. The crude product from this reaction was converted to its hydrochloride salt in a mixture of ether and ethyl acetate to yield **8**, the desired racemic benz-

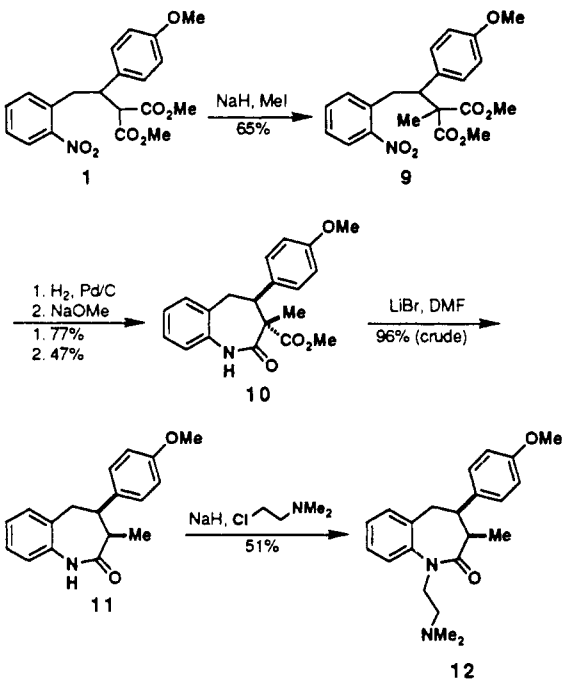
(11) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* **1970**, *18*, 2284.

(12) We have adopted nomenclature previously employed to describe ring conformations of diltiazem. See: Glaser, R.; Sklarz, B. *J. Chem. Soc., Perkin Trans. II* **1989**, 1031. Although the benzazepinone analogues are racemic, we limit our discussion to enantiomers having the *S* configuration at C4 to facilitate a comparison of their structures to that of diltiazem (*S,S* absolute configuration). The twist-boat conformation of diltiazem in the solid state has been designated as "M" on the basis of the negative cyclic torsional angle S1–C2–C3–C4. We have applied the "M" and "P" descriptors to the benzazepinone series *independent of the priority of the substituent at C3 and C4* to simply identify the minus or plus sign of the C2–C3–C4–C5 torsional angle. The "M" conformation of **5** is very similar to the (M, 2*S*,3*S*) twist-boat conformation described for the solid-state conformation of diltiazem. Although previously unobserved in the solid state, the P twist-boat conformation has been suggested for the minor (1:12) conformational component noted during NMR studies with diltiazem.

(13) Substituents at C4 cannot be designated as axial or equatorial since they are oriented symmetrically with respect to the 2-fold axis and the mean plane of the two enantiomeric twist-boat conformations.

(14) Derwent Abstracts 84-185470/30, 84-185471/30, and 85-0709034/13. These abstracts of Japanese Patents describe the reduction of a benzothiazepin-3,4-dione with sodium borohydride to give predominantly the cis 2-aryl-3-hydroxy precursor of diltiazem.

Scheme II



azepinone analogues of diltiazem.

With a general procedure for the preparation of benzazepinone analogues of the benzothiazepinone calcium channel blockers, we were interested in extending our analogue series by incorporating alternate functionalities at C3. Of these, perhaps most difficult to obtain in the benzothiazepine series are the *cis*-3-alkyl derivatives.[15] Based on the observation of significant control of C3 stereochemistry during the decarboxymethylation reaction described above, it appeared feasible to employ the malonate derivative **1** as a starting point, assuming that cyclization of the tetrasubstituted diester would be feasible.

As shown in Scheme II, the proposed route proved successful, although we did not maximize the yield of products in each step. Alkylation of **1** with methyl iodide in the presence of sodium hydride went smoothly to afford **9** in 65% yield after recrystallization. Reduction of the nitro group of **9** under catalytic conditions gave the corresponding aniline derivative, which was subjected to standard cyclization conditions. Contrary to the cyclization of **2** to **3**, the cyclization involving a quaternary center proceeded extremely slowly. Additionally, it was necessary to add DMF to the reaction to effect complete solution of the starting aniline. Under these conditions it took 4 days to effect conversion of most of the starting material (by TLC) to the desired benzazepinone **10**. Although the reaction appeared clean by TLC analysis, recrystallization of the crude product to remove the small amount of remaining starting material accounts for the relatively low yield of pure product obtained in this reaction. Additionally, NMR analysis of the crude product indicated the presence of ca. 10% of the diastereomer, which was also removed during purification. The stereochemical assignment shown in Scheme II is based on single-crystal X-ray data, which show **10** to possess the "M" twist-boat ring conformation noted for the cis alcohol **5** with the C3 methyl group assuming the equatorial position.[10]

Although the approach to C3-alkylated derivatives through this route was predicated on the control of relative stereochemistry observed in the C3-hydroxylated series described above, we found the conditions employed in the former decarboxylation unsuitable for this application. Employing lithium iodide in pyridine gave nearly equal quantities of the desired **11** and the corresponding trans isomer. Changing the solvent to DMF gave significantly better results, affording approximately 95% selectivity for **11**. However, in this solvent an additional problem arose. In the absence of an effective trap for the methyl iodide generated in the reaction, as much as 30% of the product was accounted for as the *N*-methylbenzazepinone. Although substituting lithium bromide for lithium iodide decreased, to some extent, the amount of undesired N-methylation, we found it necessary to also incorporate *p*-aminothiophenol as a trap for the methyl halide byproduct. Under these conditions, **11** was obtained in 96% crude yield, contaminated by less than 3% of its trans isomer and a small amount of starting material. Alkylation of crude **11** with (dimethylamino)ethyl chloride under conditions essentially identical with those described above for the conversion of **5** to **7** gave **12** in 51% yield after conversion to its HCl salt and recrystallization from ethyl acetate–methanol.

We have employed this synthetic scheme to prepare a number of additional analogues of 3-alkylbenzazepinones. In general, the route described represents the first general approach to diltiazem-like molecules containing 3-alkyl substituents with the preferred relative stereochemistry on the heptagonyl ring. With the development of these procedures it appeared possible to apply these to the synthesis of the analogous *cis*-3-methylbenzothiazepinone **18**, which had not been previously reported in the literature.[16] Additionally, this appeared to be an important compound with respect to gaining further insight into the structure–activity associated with modifications of the C3 substituent.

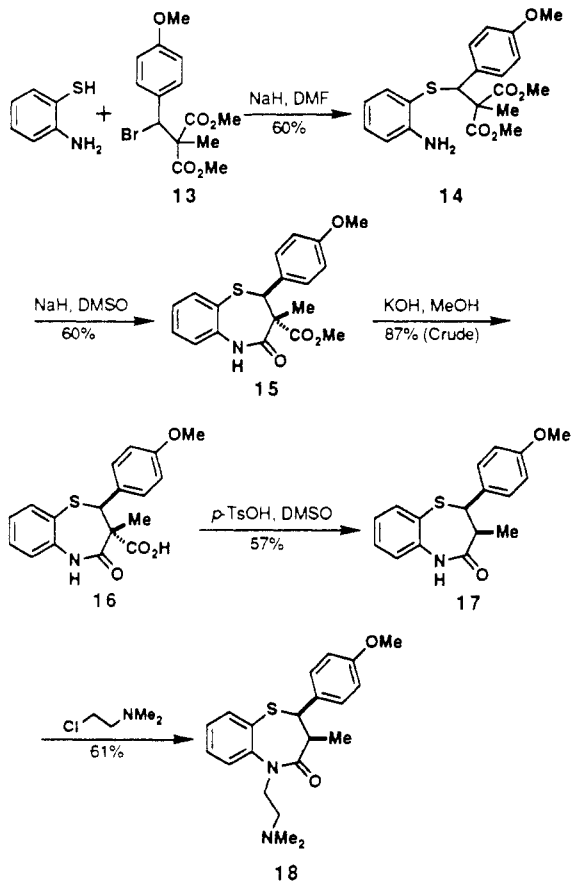
Based on our experience with the benzazepinone synthesis, we believed that the desired cis stereochemistry of the substituents on C-2 and C-3 (benzothiazepinone numbering) could be set by a decarboxylation reaction. Although, β-elimination of the thiolate from the expected intermediate enol/enolate was a potential problem, it seemed possible that performing the reaction in the presence of a proton source could retard this process. If this proved to be the case, kinetic protonation at C-3 should afford predominantly the desired cis relative stereochemistry. Again, due to the possibility for β-elimination of the thiolate, incorporation of the C-3 alkyl group by the procedures used to prepare the corresponding benzazepinone did not appear useful. With these considerations, we focused on assembling the requisite benzothiazepinone intermediate by a process that would preclude β-elimination of the thiophenol moiety prior to cyclization.

The most likely approach appeared to be construction of the carbon–sulfur bond by a nucleophilic displacement resulting in an intermediate that could not suffer subse-

(15) (a) Kraphco, J.; Spitzmiller, E. R.; Turk, C. *J. Med. Chem.* **1963**, *6*, 544. (b) Kraphco, J.; Turk, C. *J. Med. Chem.* **1966**, *9*, 191. (c) Levai, A.; Duddeck, H. *Pharm.* **1983**, *38*, 827. (d) Kuchar, M.; Brunova, B.; Rejholec, V.; Roubal, Z.; Grimova, J.; Nemecek, O. *Collect. Czech. Chem. Commun.* **1975**, *40*, 3545. (e) Ohno, S.; Izumi, K.; Mizukoshi, K.; Kato, K.; Hori, M. *Chem. Pharm. Bull.* **1983**, *31*, 1780. (f) Ohno, S.; Mizukoshi, K.; Izumi, K.; Kato, K.; Hori, M. *Chem. Pharm. Bull.* **1988**, *36*, 551.

(16) Predicated on the report of Ohno et al. (see ref 15f) that thermal condensation of 2-aminothiophenol with 2-methyl-3-phenylpropenoic acid gave *cis*-3-methyl-4-phenylbenzothiazepinone as a minor component (6.7%), we attempted the identical reaction employing 2-methyl-3-(4-methoxyphenyl)propenoic acid. In our hands, we were only able to isolate *trans*-**17** in less than 15% yields. Additionally, conversion of *trans*-**17** to its 5-(dimethylamino)ethyl derivative followed by attempted epimerization of the methyl substituent under a variety of conditions was not found to be a useful method to prepare **18**.

Scheme III



quent elimination. The benzylic bromide **13** was prepared in two steps from dimethyl methylmalonate to examine this approach. As shown in Scheme III, treatment of this material with the sodium salt of 2-aminothiophenol gave the desired adduct **14** in 60% yield. Cyclization of **14** using sodium hydride in DMSO at room temperature gave the 3,3-disubstituted benzothiazepinone **15**, again in 60% yield following trituration of the crude product in isopropyl ether. Analysis of the crude product by ^{1}H NMR, prior to the isopropyl ether trituration, indicated a 9:1 mixture of isomers with benzylic proton resonances at δ 5.55 (major) and 4.65 (minor). By analogy to the identical reaction in the benzazepinone series, we assume that the major isomer from this reaction is **15**. However, this cyclization appeared to be more facile than that observed in the benzazepinone series.[17] In general, separation of the isomers was not necessary since the stereochemical results obtained in the decarboxylation (**16** → **17**) reaction are independent of starting material relative stereochemistry.

Completing the synthesis of **18** involved the determination of conditions to decarboxylate **15** while setting the desired relative stereochemistry at C-3 and, subsequently, appending the N-5 substituent. We found that the conditions used to decarboxylate benzazepinone methyl esters **4** and **10** were unsuccessful when applied to the benzothiazepinone **15**. Although we did not investigate the products of these attempts in detail, all evidence indicated that the major products resulted from cleavage of the benzothiazepinone ring. These results clearly indicated the need to find decarboxylation conditions employing more acidic conditions. To accomplish this, we resorted to a two-step process. Hydrolysis of **15** with KOH in methanol at reflux gave the acid **16** in 87% crude yield. Without purification, **16** was decarboxylated with *p*-toluenesulfonic acid in DMSO at 75 °C to give **17** in 57% yield. Assignment of relative stereochemistry was based on comparison of NMR spectra between **17** and its trans isomer.[16] Consistent with literature precedent, $J_{2,3}$ for **17** was observed to be 7 Hz, whereas this coupling constant for *trans*-**17** was 12 Hz.[15f]

Inspection of the crude decarboxylation reaction products failed to demonstrate the presence of *trans*-**17** as a byproduct, indicating that protonation of the planar enol intermediate occurred from the side of the molecule opposite to the C-2 aromatic ring. The importance of the additional acid during the decarboxylation reaction was demonstrated by the observation that attempted thermal decarboxylation of **16** led to greatly reduced yields of **17**, with the major products appearing to arise from cleavage of the benzothiazepinone ring.

As anticipated, alkylation of **17** with (dimethylamino)-ethyl chloride using potassium carbonate in refluxing methyl ethyl ketone gave the desired product **18** in 61% yield after conversion to its hydrochloride salt.[6c] Although we have not investigated the generality of these procedures to the preparation of other *cis*-3-alkyl-2-aryl-1,5-benzothiazepinones, these methods may represent a more general route than previously described in the literature.[15f]

Employing testing methods in vitro, the C3 acetoxybenzazepinone analogue **8** (IC_{50} = 4.7 μM) is slightly less potent than racemic diltiazem (IC_{50} = 1.8 μM), whereas the C-3 methyl derivative **12** (IC_{50} = 1.1 μM) has the same level of potency in vitro.[18] Interestingly, the increase in potency of the 3-methylbenzothiazepinone **18** (IC_{50} = 0.08 μM) over its 3-acetoxy analogue, racemic diltiazem, is significantly greater than that observed for the corresponding benzazepinone analogues **8** and **12**. We also prepared the trans isomer of **8** from **6** by employing the same procedures used to convert **5** to **8**. In agreement with the diltiazem series, *trans*-**8** was devoid of significant activity in vitro.[5]

We have described synthetic methods to prepare several new analogues of the important clinical agent diltiazem. In our study of the benzazepinone system, we have also demonstrated what appears to be a general approach to the preparation of 1-benzazepin-2-ones, which allows for significant latitude in the substitution at both C3 and C4.[19] The studies described with the benzothiazepinone system represents a potential improvement in the synthesis of *cis*-3-alkylbenzothiazepinone analogues of diltiazem, although these studies have not been pursued in depth. Using the synthetic procedures described in the benz-

(17) This may be related to the different conditions used for this cyclization reaction. In additional studies with the benzazepinone system, we have found that alterations in the solvent and base strength can have a marked effect on both the rate and stereoselectivity of cyclization with these alkylated diester intermediates. Floyd, D. M.; Moquin, R. V. Unpublished results.

(18) Determination of the concentration of test compound necessary to cause 50% relaxation of 110 mM K^+ contracted rabbit aorta (IC_{50} value) were made in the laboratory of S. Moreland, Squibb Institute for Medical Research Pharmacology Department; see: Brittain, R. J.; Moreland, S. *Physiologist* **1985**, *24*, 325.

(19) Alkylidenemalonates can be employed in the initial reaction with nitrotoluene. For example, the reaction between cyclohexylidenemalonate and 5-chloro-2-nitrotoluene gave a 78% yield of product, which was converted by the procedures described in this work to an analogue of **8** containing a cyclohexyl ring at C4 in place of the *p*-methoxyphenyl group, mp 238.5–239.5 °C dec. Anal. Calcd for $C_{22}H_{31}N_2O_3$·HCl·0.25 H_2O: C, 58.98; H, 7.31; N, 6.26; Cl, 15.83. Found: C, 58.98; H, 7.28; N, 6.22; Cl, 15.64. Derivatives of the 3-hydroxybenzazepines have been used to prepare analogues with a variety of 3-thio and amino analogues. Additionally, 3-allyl analogues, prepared by the procedures described above, have been converted into functionalized 3-alkyl derivatives. Das, J.; Floyd, D. M. U.S. Patent 4,767,756, 1988. Das, J. U.S. Patents 4,771,047 and 4,774,239, 1988.

azepinone system, many analogues have been prepared. This work has resulted in significant improvements in the yields of many of the reactions described above. The results of these studies, including methods to prepare nonracemic benzazepinones and additional examples of racemic 3-alkylbenzothiazepinones, will be reported in connection with our structure–activity studies.[20]

Experimental Procedures

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 relatie 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. Mass spectra were measured on a Finnigan TSQ-4600 mass spectrophotometer using ammonia as the reagent gas for chemical ionization. Analysis by TLC was performed on E. Merck kieselgel 60, F-254 silica-gel plates. Flash chromatography was done on either Whatman LPS-1 or E. Merck kieselgel 60 (240-400 mesh) silica gel.

Unless otherwise stated, concentrations of solutions were done in vacuo. All reactions were conducted under an atmosphere of argon, employing reagent grade solvents. The DMF and DMSO were dried by storage over 3A molecular sieves. Anhydrous THF was prepared by distillation from sodium–benzophenone prior to use.

Experimental procedures and tables of crystal cell parameters are supplied in the supplementary material section to this paper.

[1-(4-Methoxyphenyl)-2-(2-nitrophenyl)ethyl]-propanedioic Acid, Dimethyl Ester (1). Dimethyl (4-methoxybenzylidene)malonate (25.0 g, 100 mmol) was added to a slurry of NaH (3.6 g, 150 mmol; obtained by removing the oil from 6.0 g of 60% dispersion with diethyl ether) in 375 mL of DMF and allowed to dissolve. A solution of 2-nitrotoluene (15.1 g, 110 mmol) in 25 mL of DMF was added dropwise over a 1-h period. The reaction was stirred overnight and judged complete by TLC (4:1 hexane–ethyl acetate, disappearance of starting malonate). The reaction was quenched by the addition of 20 mL of acetic acid in 50 mL of methanol followed by the addition of 1 L of water. The mixture was extracted with ethyl acetate (3 × 250 mL), and the combined organic extracts were washed successively with 1 N HCl, saturated $KHCO_3$, and brine. The dark organic solution was dried over $MgSO_4$, concentrated, dissolved in warm methanol, and cooled to room temperature. The solution was seeded with the desired product and allowed to crystallize overnight. The crystalline material was collected by filtration and recrystallized from methanol to yield 22.2 g of the desired product. The mother liquors from both crystallizations were combined and concentrated. The residue was dissolved in 1:1 hexane–ethyl acetate and passed through a 50 × 35 cm pad of silica gel to remove much of the dark, polar byproducts. Concentration and recrystallization of the residue from methanol afforded an additional 6.4 g of material, giving a total of 28.6 g (71% combined yield) of tan crystalline product: mp 73–75 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (1 H, dd, J = 7.9 and 1.6 Hz), 7.35–7.21 (2 H, m), 7.05 (1 H, dd, J = 7.4 and 1.0 Hz), 6.94 (2 H, d, J = 8.4 Hz), 6.73 (2 H, d, J = 8.4 Hz), 3.81 (1 H, d, J = 11.3 Hz), 3.79 (3 H, s), 3.74 (3 H, s), 3.65 (1 H, m), 3.45 (3 H, s), 3.41 (1 H, dd), 3.23 (1 H, dd, J = 13.7 and 10.6 Hz); ^{13}C NMR ($CDCl_3$) δ 168.4, 167.8, 158.6, 133.9, 132.7, 132.2, 131.1, 129.1, 127.2, 124.4, 113.8, 79.1, 58.0, 55.1, 52.6, 52.3, 45.8, 36.8. Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.63. Found: C, 61.80; H, 5.55; N, 3.47.

[2-(2-Aminophenyl)-1-(4-methoxyphenyl)ethyl]-propanedioic Acid, Dimethyl Ester (2). Hydrogenation of 1 (7.44 g, 19.2 mmol) was conducted at 40 psi in 60 mL of glacial acetic acid in the presence of 750 mg of 10% Pd on carbon. The reaction was terminated after 40 min and shown to be complete by TLC (1:1 hexane–ethyl acetate). The reaction was filtered and concentrated. Recrystallization from methanol gave 6.27 g (91%) of 2: mp 108–109 °C; ^{1}H NMR ($CDCl_3$) δ 6.99 (2 H, d, J = 8.4 Hz), 6.96–6.90 (1 H, m), 6.75 (2 H, d, J = 8.4 Hz), 6.62 (1 H, d, J = 8.4 Hz), 6.42–6.40 (2 H, m), 4.04 (1 H, br s), 3.81 (3 H, s), 3.83 (1 H, d, J = 11.1 Hz), 3.75 (3 H, s), 3.57 (1 H, ddd, J = 3.2, 11.1, and 11.1 Hz), 3.41 (3 H, s), 3.04 (1 H, dd, J = 13.7 and 3.2 Hz), 2.65 (1 H, dd, J = 2.65 and 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ 169.6, 168.1, 158.3, 144.8, 131.7, 131.0, 129.2, 127.3, 122.6, 117.4, 115.2, 113.4, 57.3, 54.9, 52.6, 52.1, 44.0, 37.3. Anal. Calcd for $C_{20}H_{22}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.07; H, 6.61; N, 3.88.

1,3,4,5-Tetrahydro-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (3). A solution of 2 (12.0 g, 33 mmol) in 80 mL of anhydrous methanol was treated with sodium methoxide (9.2 mL of 25% in methanol, 40 mmol) and refluxed for 1.5 h. The solution was cooled to room temperature, and a large excess of 1 N aqueous HCl was added. The resulting white precipitate was filtered from the mixture, washed with additional water, and dried in vacuo to afford 9.2 g (84%) of pure product: mp 217–219 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (1 H, s), 7.30 (1 H, dt, J = 7.7 and 1.1 Hz), 7.16 (1 H, m), 7.06 (2 H, m), 7.05 (2 H, d, J = 8.8 Hz), 6.80 (2 H, d, J = 8.8 Hz), 4.16 (1 H, m), 3.77 (3 H, s), 3.74 (1 H, d, J = 9.5 Hz), 3.54 (3 H, s), 3.34 (1 H, dd, J = 13.9 and 7.3 Hz), 2.75 (1 H, dd, J = 3.7 and 13.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.4, 158.1, 137.6, 135.0, 131.6, 130.6, 127.8, 125.2, 122.0, 113.9, 55.0, 51.7, 46.8, 37.6. Anal. Calcd for $C_{19}H_{19}NO_4 \cdot 0.26H_2O$: C, 69.37; H, 5.67; N, 4.26. Found: C, 69.56; H, 6.09; N, 4.22.

1,3,4,5-Tetrahydro-3-hydroxy-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (4). Potassium *tert*-amylate (9.6 mL of 1.6 M in toluene, 15.37 mmol) was added to a −78 °C suspension of 3 (2.0 g, 6.15 mmol) in 20 mL of 2:1 anhydrous toluene–DMF, and the resulting turbid solution was stirred for 0.5 h. Trimethyl phosphite (1.81 mL, 15.37 mmol) was added followed by the introduction of dry oxygen gas via a gas dispersion tube. The reaction temperature was raised to 0 °C and maintained for 1.5 h, whereupon TLC analysis (1:1 hexane–ethyl acetate) indicated that all the starting material had been consumed. The reaction was quenched by the addition of 1 N HCl and the mixture was extracted twice with ethyl acetate. The organic phase was washed sequentially with 1 N HCl (3×), saturated $NaHCO_3$ (2×), and brine and dried over Na_2SO_4. Concentration gave 2.35 g of colorless solid. Trituration of this material in hexane afforded 1.63 g (78%) of 4: mp 212–213.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (1 H, s), 7.31 (2 H, d, J = 8.8 Hz), 7.25 (2 H, m), 7.13 (1 H, dd, J = 6.1 and 1.1 Hz), 6.95 (1 H, d, J = 7.7 Hz), 6.85 (2 H, d, J = 8.8 Hz), 4.53 (1 H, s), 3.79 (3 H, s), 3.66 (1 H, dd, J = 15.2 and 7.9 Hz), 3.55 (1 H, dd, J = 5.0 and 3.4 Hz), 3.43 (3 H, s) 3.29 (1 H, dd, J = 15.2 and 4.95 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 169.4, 158.6, 135.4, 132.5, 131.7, 130.1, 127.6, 125.3, 121.1, 113.2, 81.4, 74.9, 55.1, 52.5, 51.7, 35.2. Anal. Calcd for $C_{19}H_{19}NO_5 \cdot 0.11H_2O$: C, 66.45; H, 5.64; N, 4.08. Found: C, 66.36; H, 5.62; N, 4.09.

***cis*-1,3,4,5-Tetrahydro-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (5).** A mixture of 5.3 g (14.6 mmol) of 4 and 19.6 g (146 mmol) of LiI was dissolved in 150 mL of 1% aqueous pyridine and heated to reflux for 1 h. After cooling, the solution was concentrated, slurried in 1 N HCl, and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed once each with 6 N HCl, saturated $KHCO_3$ solution, and brine and then dried over Na_2SO_4. Concentration gave a solid which, upon trituration in diethyl ether, afforded 2.81 g (68%) of the desired cis isomer 5: mp 173.5–175.5 °C; ^{1}H NMR ($CDCl_3$, D_2O exchanged) δ 7.33–7.17 (4 H, m), 7.06 (2 H, d, J = 7.9 Hz), 6.90 (2 H, d, J = 7.9 Hz), 4.34 (1 H, d, J = 8.4 Hz), 3.80 (3 H, s), 3.75 (1 H, m), 3.14 (1 H, t, J = 13.2 Hz), 2.97 (1 H, dd, J = 13.2 and 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9, 158.8, 136.4, 132.8, 131.3, 129.5, 127.7, 126.1, 121.7, 113.8, 69.3, 55.0, 53.4, 37.2. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.00; H, 6.13; N, 4.73.

***trans*-1,3,4,5-Tetrahydro-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (6).** Concentration of the ether solution from the trituration of 5, followed by flash chromato-

(20) Some of the structure–activity studies and a brief description of the synthetic procedures described in this paper were presented at the 198th National Meeting of the American Chemical Society, Miami Beach, September 10–15, 1989. See: Floyd, D. M.; Kimball, S. D.; Krapcho, J.; Das, J.; Moreland, S.; Hedberg, S. A.; White, R. E. *Abstracts of Papers*; American Chemical Society: Washington, DC, 1989; Med Chem, 86 and Das, J.; Floyd, D. M.; Moreland, S.; Hedberg, S. A. *Abstracts of Papers*; American Chemical Society: Washington, DC, 1989; Med Chem 93.

graphic purification of the residue (7:3 hexane–ethyl acetate) gave 0.62 g (15%) of the trans isomer **6**: mp 168–170 °C; ^{1}H NMR ($CDCl_3$, D_2O exchanged) δ 7.31 (1 H, t, J = 7.4 Hz), 7.19 (1 H, t, J = 6.6 Hz), 7.14 (1 H, d, J = 5.8 Hz), 7.11 (2 H, d, J = 8.4 Hz), 7.07 (1 H, d, J = 8.4 Hz), 6.86 (2 H, d, J = 8.4 Hz), 4.28 (1 H, d, J = 10.0 Hz), 3.78 (3 H, s), 3.40 (2 H, m), 2.68 (1 H, d, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$) δ 175.2, 158.5, 136.0, 135.3, 131.9, 131.0, 128.3, 127.9, 126.0, 122.0, 114.0, 72.3, 55.1, 53.9, 36.4. Anal. Calcd for $C_{17}H_{17}NO_3 \cdot 0.09H_2O$: C, 71.63; H, 6.08; N, 4.93. Found: C, 71.57; H, 6.04; N, 4.93.

***cis*-3-Hydroxy-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (7).** A solution of **6** (1.0 g, 3.5 mmol) in 35 mL of anhydrous DMF was treated with NaH (0.15 g of 60% dispersion in mineral oil, 3.7 mmol). After stirring for 1 h, a solution of 1-(dimethylamino)-2-chloroethane in toluene (3.1 mL of 1.7 M solution, 5.3 mmol) was added, and the reaction was heated to 75 °C for 1.5 h. The mixture was then cooled and concentrated. The residue was slurried in ethyl acetate and extracted three times with 1 N HCl. The combined aqueous layers were adjusted to ca. pH 11 with solid NaOH and extracted with ethyl acetate (3×). The resulting organic solution was dried over Na_2SO_4 and concentrated. The residue was dissolved in a small amount of chloroform and cooled in an ice bath, whereupon excess HCl-saturated diethyl ether was added, resulting in the formation of a white, hygroscopic solid. Filtration and drying gave 1.27 g (84%) of **7**: mp 248.5–250 °C dec; ^{1}H NMR (CD_3OD) δ 7.41–7.32 (4 H, m), 7.24 (2 H, d, J = 7.4 Hz), 6.90 (2 H, d, J = 7.4 Hz), 4.31 (2 H, d, J = 7.9 Hz), 3.79 (3 H, s), 3.67–3.50 (s H, m), 2.99 (6 H, s), 3.78 (3 H, s), 2.96 (2 H, m); ^{13}C NMR (DMSO-d_6) δ 172.4, 158.0, 140.1, 134.3, 132.3, 129.8, 128.1, 126.7, 122.4, 113.2, 68.9, 53.1, 52.2, 42.1. Anal. Calcd for $C_{21}H_{26}N_2O_3 \cdot HCl \cdot 0.51H_2O$: C, 63.04; H, 7.06; N, 7.00; Cl, 8.86. Found: C, 63.03; H, 6.84; N, 7.01; Cl, 8.86.

***cis*-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (8).** A slurry of **7** (1.27 g, 2.83 mmol) in 28 mL of acetic anhydride was heated to 100 °C for 3 h, during which time a clear solution was formed. The solution was cooled and concentrated and the residue was dissolved in ethyl acetate. A small amount of HCl-saturated ether was added and crystallization commenced. The mixture was filtered to yield 1.25 g (98%) of **8** as an off-white powder: mp 215–216 °C; ^{1}H NMR (CD_3OD) δ 7.48–7.35 (4 H, m), 7.62 (2 H, d, J = 8.4 Hz), 6.89 (2 H, d, J = 8.4 Hz), 5.07 (1 H, d, J = 8.4 Hz), 4.33 (2 H, m), 3.79 (1 H, m), 3.64 (1 H, m), 3.42 (1 H, m), 3.10–2.98 (8 H, m), 1.85 (3 H, s); ^{13}C NMR (CD_3OD) δ 171.8, 171.1, 141.4, 135.5, 132.6, 131.0, 130.6, 130.0, 128.9, 123.8, 114.7, 73.2, 55.7, 56.6, 51.5, 44.4, 44.2, 44.0, 38.0, 20.4. Anal. Calcd for $C_{23}H_{28}N_2O_4 \cdot HCl \cdot 0.40H_2O$: C, 62.76; H, 6.82; N, 6.36; Cl, 8.05. Found: C, 62.76; H, 6.65; N, 6.40; Cl, 7.97.

[1-(4-Methoxyphenyl)-2-(2-nitrophenyl)ethyl]-2-methylpropanedioic Acid, Dimethyl Ester (9). Sodium hydride (0.5 g of 60% dispersion in mineral oil, 12.4 mmol) was added to an ice-bath cooled solution of **1** (4.0 g, 10.33 mmol) in 20 mL of DMF, and the mixture was stirred for 5 min. The resulting deep orange solution was treated with methyl iodide (3.21 mL, 51.63 mmol). The ice bath was removed and the mixture allowed to stir at room temperature for 2.25 h. The reaction was then quenched by the addition of 10 mL of acetic acid, diluted with several volumes of water, and extracted with ethyl acetate. The organic phase was washed twice with 1 N HCl, dried over $MgSO_4$, and concentrated to yield a viscous yellow oil. This material was triturated three times with small portions of hexane to yield a yellow, oily solid. Recrystallization from methanol gave, in two crops, 2.69 g (65%) of the desired product. An additional 1.06 g of crude product was obtained by concentration of the mother liquors from each crop of pure material: mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (1 H, d, J = 7.90 Hz), 7.35–7.15 (3 H, m), 6.92 (2 H, d, J = 8.4 Hz), 6.92 (2 H, d, J = 8.4 Hz), 3.78 (3 H, s), 3.74–3.36 (3 H, m), 3.72 (2 H, s), 3.58 (3 H, s), 1.42 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 171.5, 158.6, 148.8, 134.6, 132.1, 131.8, 130.2, 129.3, 126.6, 123.8, 113.4, 58.4, 54.9, 52.3, 51.2, 30.0, 18.42. Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.84; H, 5.78: N, 3.49. Found: C, 62.88; H, 5.80; N, 3.50.

[2-(2-Aminophenyl)-1-(4-methoxyphenyl)ethyl]-2-methylpropanedioic Acid, Dimethyl Ester. A solution of **9** (2.47 g, 6.38 mmol) in 25 mL of trifluoroacetic acid was charged with 10% Pd on carbon (0.25 g, 10% by weight) and placed under 42 psi of hydrogen on a Parr hydrogenation apparatus. After 1.5 h the reaction was vented and judged complete by TLC analysis (1:1 hexane–ethyl acetate). The mixture was filtered through Celite and concentrated to an oil. The crude product was dissolved in ethyl acetate and washed with saturated K_2CO_3, during which time a precipitate formed. The solid material obtained from filtration of the mixture was combined with the residue obtained after separation, drying, and concentration of the ethyl acetate layer. Recrystallization from methanol gave 1.82 g (77% obtained in three crops): mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 6.98 (2 H, d, J = 8.96 Hz), 6.86 (1 H, m), 6.78 (2 H, d, J = 8.96 Hz), 6.58 (1 H, d, J = 8.0 Hz), 6.40 (1 H, m), 6.33 (1 H, d, J = 8.0 Hz), 4.57 (2 H, br s), 3.80 (3 H, s), 3.72 (3 H, s), 3.62 (1 H, dd, J = 11.0 Hz, J = 1.6 Hz), 3.58 (3 H, s), 3.12 (1 H, dd, J = 11.0 Hz, J = 1.6 Hz), 2.86 (1 H, t, J = 12 Hz), 1.48 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 172.7, 171.9, 158.6, 145.1, 131.3, 130.3, 126.9, 123.3, 117.2, 115.1, 113.2, 58.2, 54.9, 52.5, 52.3, 48.2, 34.3, 17.5. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.73; H, 7.05; N, 3.70.

1,3,4,5-Tetrahydro-3-methyl-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (10). The starting aniline from the above reaction (1.73 g, 4.66 mmol) was slurried in 15 mL of methanol and treated with sodium methoxide (2.66 mL of 25% by weight in methanol, 11.64 mmol). The mixture was brought to reflux and ca. 3 mL of DMF was added to effect complete solution. After 2.5 h the reaction had not proceeded by TLC analysis (1:1 hexane–ethyl acetate) and an additional 2.66 mL of sodium methoxide solution was added. The mixture was then refluxed for 4 days, after which only a small amount of starting material remained by TLC analysis. The mixture was cooled in an ice bath and diluted with enough 1 N HCl to precipitate the product. Filtration and washing the solid with 10% methanol in water followed by drying in vaccuo gave 1.77 g of crude product. Recrystallization from ethyl acetate–hexane gave 0.74 g (47%) of white solid in two crops: mp 198–200.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (1 H, br s), 7.26–7.16 (6 H, m), 6.90 (1 H, d, J = 7.39 Hz), 6.87 (2 H, d, J = 8.97 Hz), 4.25 (1 H, dd, J = 6.86 Hz, J = 12.66 Hz), 3.80 (3 H, s), 3.19 (1 H, t, J = 13.26 Hz), 2.92 (1 H, dd, J = 6.90 Hz, J = 13.2 Hz), 0.98 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 173.6, 173.1, 158.7, 136.8, 134.3, 133.6, 129.9, 129.5, 127.7, 126.2, 122.3, 113.9, 55.2, 54.5, 52.5, 51.0, 39.3, 32.5. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.56; H, 6.24; N, 4.08.

***cis*-1,3,4,5-Tetrahydro-3-methyl-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (11).** A mixture of **10** (0.67 g, 1.97 mmol), LiBr (0.98 g, 11.25 mmol), and *p*-aminothiophenol (0.49 g, 3.94 mmol) was dissolved in 6 mL of DMF and heated at 137 °C for 5 h. The reaction was cooled to room temperature and diluted with 1 N HCl. The mixture was extracted twice with ethyl acetate and the combined organic phases were washed with 1 N HCl (3×), saturated K_2CO_3 (2×), and once with brine and dried over $MgSO_4$. Concentration gave 0.53 g (96%) of crude product. NMR analysis demonstrated the presence of ca. 2.0% starting material and 2.5% of the trans isomer. This material was employed crude in the following reaction: ^{1}H NMR ($CDCl_3$) δ 7.62 (1 H, br s), 7.30–7.15 (5 H, m), 7.21 (2 H, d, J = 8.44 Hz), 7.01 (1 H, d, J = 7.38 Hz), 3.80 (3 H, s), 3.37 (1 H, dd, J = 6.30 Hz, J = 13.2 Hz), 3.06 (1 H, t, J = 13.2 Hz), 2.89 (1 H, dd, J = 6.3 Hz, J = 13.2 Hz), 2.84 (1 H, m), 0.78 (3 H, d, J = 6.85 Hz); ^{13}C NMR ($CDCl_3$) δ 176.2, 175.9, 158.4, 138.1, 133.9, 133.2, 129.1, 129.0, 127.5, 125.4, 121.6, 113.7, 55.1, 53.7, 40.3, 38.2, 13.6.

***cis*-3-Methyl-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (12).** Crude **11** (0.37 g, 1.32 mmol) was dissolved in 13 mL of DMF and treated with NaH (0.06 g of 60% dispersion in mineral oil, 1.5 mmol). After stirring for 0.5 hour, 1-(dimethylamino)-2-chloroethane in toluene (1.38 mL of 2.15 M solution, 2.97 mmol) was added, and the solution was heated at 85 °C. After 4 h the reaction was judged complete by TLC analysis (9:1 methylene chloride–methanol), cooled to room temperature, and concentrated. The residue was diluted with water and extracted twice with ethyl acetate. The combined organic phases were washed once with water followed by brine and dried over Na_2SO_4. After concentration, the residue was dissolved in ether and treated with and excess of HCl-saturated ether. The resulting solid was filtered and recrystallized from ethyl acetate–methanol

mixtures to afford 0.24 g (51%) of final product: mp 211–216 °C; ^{1}H NMR ($CDCl_3$) δ 7.45–7.28 (4 H, m), 7.17 (2 H, m), 6.88 (2 H, m), 4.27 (2 H, t, J = 7.0 Hz), 3.79 (3 H, s), 3.62–3.55 (1 H, m), 3.48–3.43 (1 H, m), 3.41–3.29 (1 H, m), 3.00 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 174.8, 158.5, 141.0, 134.6, 133.1, 129.2, 128.4, 126.8, 122.5, 113.7, 55.1, 54.4, 53.3, 43.3, 43.1, 39.9, 38.3, 13.7. Anal. Calcd for $C_{22}H_{28}N_2O_2$·HCl: C, 66.58; H, 7.59; N, 7.06; Cl, 8.93. Found: C, 66.26; H, 7.30; N, 6.92; Cl, 9.28.

2-[Bromo(4-methoxyphenyl)methyl]-2-methylpropanedioic Acid, Dimethyl Ester (13). A mixture of NaH (1.44 g of 50% dispersion in mineral oil, 30 mmol) and dimethyl methylmalonate (4.38 g, 30 mmol) in DMF (100 mL) was stirred for 40 min, after which *p*-methoxybenzyl chloride (5.2 g, 3.3 mmol) was added and the mixture stirred for an additional 4 h. The reaction was then poured into water (100 mL) and extracted with a 1:1 mixture of ether and hexanes (3 × 200 mL). The combined organic layers were washed with water (2 × 100 mL), dried over $MgSO_4$, and concentrated. Purification by flash chromatography (10% ethyl acetate in hexane) gave 6 g (75%) of 2-[(4-methoxyphenyl)methyl]-2-methylpropanedioic acid, dimethyl ester as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.0 (2 H, d, J = 9.0 Hz), 6.8 (2 H, d, J = 9.0 Hz), 3.75 (3 H, s), 3.7 (6 H, s), 3.25 (2 H, s), 1.3 (3 H, s); MS $(M + H)^+$ 267.

A mixture of the above product (2.66 g, 10 mmol), *N*-bromosuccinimide (1.8 g, 10 mmol), and azobis(isobutyrylnitrile) (10 mg) in anhydrous carbon tetrachloride (75 mL) was heated with a sun lamp for 3 h. After being cooled to room temperature, the mixture was filtered and the filtrate was concentrated to give 3.4 g (87%) of **13** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.4 (2 H, d, J = 10 Hz), 6.8 (2 H, d, J = 10 Hz), 5.8 (1 H, s), 3.78 (3 H, s), 3.75 (3 H, s), 3.55 (3 H, s), 1.65 (3 H, s); MS $(M + H)^+$ 343, 345.

2-[[(2-Aminophenyl)thio](4-methoxyphenyl)methyl]-2-methylpropanedioic Acid, Dimethyl Ester (14). To a suspension of NaH (0.57 g of material obtained from hexane wash of a 50% dispersion in mineral oil, 11.8 mmol) in DMF (10 mL) was added slowly 2-aminothiophenol (1.5 g, 11.8 mmol). After being stirred for 30 min, a solution of **13** (3.4 g, 9.8 mmol) in DMF (2 mL) was added, and the reaction mixture was allowed to stir at room temperature overnight. It was then poured into water and extracted with ether (3 × 150 mL). The combined organic extracts were washed with water and brine, dried over MgSO4, and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in hexane) and the combined product was triturated with isopropyl ether to provide 2.3 g (60%) of a colorless solid: mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 7.2 (2 H, d, J = 9.0 Hz), 7.0 (1 H, t, J = 8.0 Hz), 6.9 (1 H, d, J = 8.0 Hz), 6.75 (2 H, d, J = 9.0 Hz), 6.6 (1 H, d, J = 8.0 Hz), 6.4 (1 H, t, J = 8.0 Hz), 4.6 (1 H, s), 4.5 (2 H, br s), 3.8 (3 H, s), 3.75 (3 H, s), 3.6 (3 H, s), 1.55 (3 H, s). Anal. Calcd for $C_{20}H_{23}NO_5S$: C, 61.83; H, 5.71; N, 3.61. Found: C, 61.13; H, 5.83; N, 3.70.

1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-3-methyl-4-oxo-1,5-benzothiazepine-3-carboxylic Acid, Methyl Ester (15). A solution of **14** (1.6 g, 4.1 mmol) in anhydrous DMSO (2 mL) was added to a suspension of NaH (0.2 g of 50% dispersion in mineral oil, 4.1 mmol) in anhydrous DMSO (5 mL). After being stirred for 16 h, the reaction was poured into water (25 mL) and extracted with ether (3 × 150 mL). The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was triturated with isopropyl ether to give 0.85 g (58%) of **15**: mp 198–199 °C; ^{1}H NMR ($CDCl_3$) δ 8.3 (1 H, s), 7.6 (1 H, d, J = 7.0 Hz), 7.45 (2 H, d, J = 9.0 Hz), 7.35 (1 H, d, J = 7.0 Hz), 7.2 (1 H, t, J = 7.0 Hz), 7.1 (1 H, d, J = 8.0 Hz), 6.85 (2 H, d, J = 9.0 Hz), 5.6 (1 H, s), 3.8 (3 H, s), 3.2 (3 H, s), 1.1 (3 H, s). Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.54; H, 5.36; N, 3.92; S, 8.95. Found: C, 64.28; H, 5.55; N, 3.80; S, 8.91.

1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-3-methyl-4-oxo-1,5-benzothiazepine-3-carboxylic Acid (16). Solid KOH (0.56 g, 10 mmol) was added to a solution of **15** (0.36 g, 1.0 mmol) in anhydrous methanol (2 mL), and the reaction was heated at reflux for 24 h. The reaction was cooled, poured into water (50 mL), and extracted with ethyl ether (2 × 50 mL). The aqueous layer was then acidified with 5 N HCl and extracted with chloroform (3 × 100 mL). The combined organic phases were washed with water and brine and dried over $MgSO_4$. Concentration of the dried solution gave 0.3 g (86.7%) of product as a light yellow solid, which was submitted to the next reaction without further purification: ^{1}H NMR (DMSO-d_6) δ 10.1 (1 H, s), 7.4 (2 H, m), 6.9 (2 H, d, J = 10.0 Hz), 5.48 (1 H, s), 3.75 (3 H, s), 0.9 (3 H, s).

***cis*-2,3-Dihydro-2-(4-methoxyphenyl)-3-methyl-1,5-benzothiazepin-4(5*H*)-one (17).** Solid *p*-TsOH·H_2O (0.5 g, 2.6 mmol) was added to a solution of **16** (0.3 g, 0.9 mmol) in DMSO (2 mL), and the mixture was heated at 75 °C for 2 h. After being cooled to room temperature, the reaction was poured into water (50 mL) and extracted with chloroform (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated to give **17** (0.15 g, 57%): mp 188–190 °C (recrystallized from isopropyl ether–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 7.8 (1 H, s), 7.65 (1 H, dd, J = 3.0 and 8.0 Hz), 7.4 (2 H, d, J = 9.0 Hz), 7.35 (1 H, d, J = 3.0 Hz), 7.2 (1 H, t, J = 9 Hz), 7.1 (1 H, d, J = 9.0 Hz), 6.85 (2 H, d, J = 10 Hz), 4.8 (1 H, d, J = 7.0 Hz), 3.8 (3 H, s), 3.05 (1 H, m), 0.85 (3 H, d, J = 7.0 Hz). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.43; H, 5.41; N, 4.70. Found: C, 67.99; H, 5.83; N, 4.68.

***cis*-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-3-methyl-1,5-benzothiazepin-4(5*H*)-one Hydrochloride (18).** Powdered K_2CO_3 (0.03 g, 0.2 mmol) and 1-(dimethylamino)-2-chloroethane hydrochloride (0.03 g, 0.2 mmol) were added to a solution of **17** (0.04 g, 0.13 mmol) in methyl ethyl ketone (4 mL). The reaction was heated under reflux for 18 h and then cooled to ambient temperature. The mixture was diluted with ethyl acetate and filtered, and the filtrate was washed with water and brine. After drying over $MgSO_4$, the solvent was evaporated and the residue was dissolved in dichloromethane and treated with HCl-saturated diethyl ether. Concentration and recrystallization from acetonitrile gave 0.03 g (61%) of **18**: mp 167–168 °C; ^{1}H NMR (DMSO-d_6) δ 7.55–7.6 (3 H, m), 7.35 (1 H, m), 7.3 (2 H, s), 6.9 (2 H, d, J = 8 Hz), 6.8 (2 H, d, J = 8 Hz), 4.75 (1 H, d, J = 6 Hz) 4.4 (1 H, m), 4.0 (1 H, m), 3.75 (3 H, s), 3.2 (1 H, m), 2.9 (2 H, m), 2.7 (6 H, s), 0.6 (3 H, d, J = 6.0 Hz). Anal. Calcd for $C_{21}H_{26}N_2O_2S$·HCl·0.16H_2O: C, 61.55; H, 6.71; N, 6.85; S, 7.80; Cl, 8.66. Found: C, 61.55; H, 6.65; N, 7.21; S, 7.75; Cl, 8.66.

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Supplementary Material Available: Tables of crystallographic data and ORTEP drawings for **3**, **4**, **5**, **6**, and **10** (37 pages). Ordering information is given on any current masthead page.