SYNTHESIS OF 4-METHYL-2-BENZAZEPIN-3-ONE ANALOGS OF DILTIAZEM

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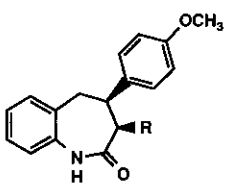
Abstract- An efficient method for the preparation of an alternative benzazepinone ring fusion, the *cis* and *trans* isomers of 4-methyl-5-(4-methoxyphenyl)-1,2,4,5-tetrahydro-3H-2-benzazepin-3-one (**3**), is described. The key reaction involved the $ZnCl_2$-catalyzed alkylation of 3-(4-methoxyphenyl)phthalide (**4**) with the trimethylsilylketene acetal of ethyl propionate to form **5** as a mixture of diastereomers. Selective reduction of the carboxylic acid, conversion of the primary alcohol to the primary amine and cyclization produced the isomers of **3**, which were separated by crystallization. The solid state conformation of the *cis* isomer (**10**) and a related 1-benzazepin-2-one were compared.

We have been engaged in a program to develop analogs of the 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one nucleus (**1**) as antihypertensive agents related to diltiazem (**2**).[1] In order to explore the activity of analogs containing alternative benzazepinone ring fusions, we sought the *cis* and *trans* isomers of 4-methyl-5-(4-methoxyphenyl)-1,2,4,5-tetrahydro-3H-2-benzazepin-3-one (**3**). Derivatives of the 1,2,4,5-tetrahydro-3H-2-benzazepin-3-one nucleus have been patented for the treatment of memory disorders[2] but compounds containing the pharmacophores important for antihypertensive activity have not been prepared. In particular, we were interested in derivatives of this nucleus which contained a 4-substituent as well as a 4-methoxyphenyl group at the 5-position.



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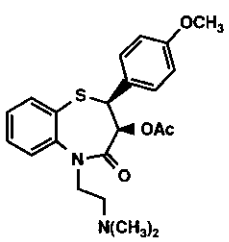

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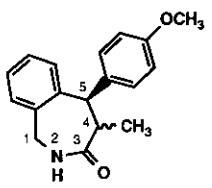

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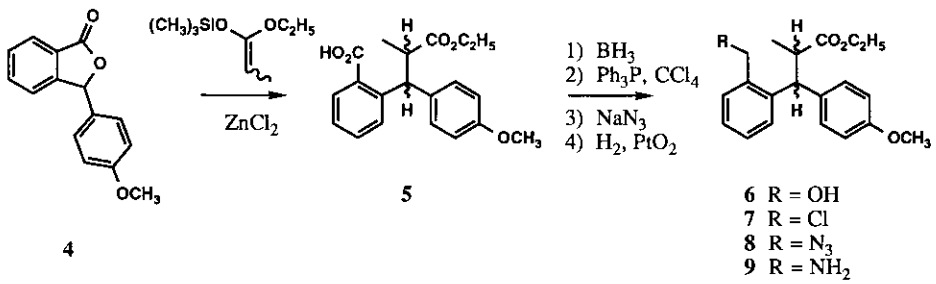
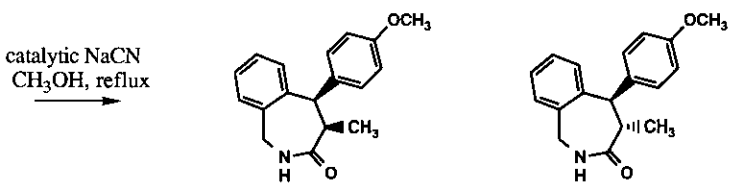
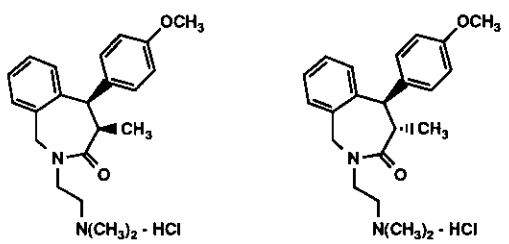
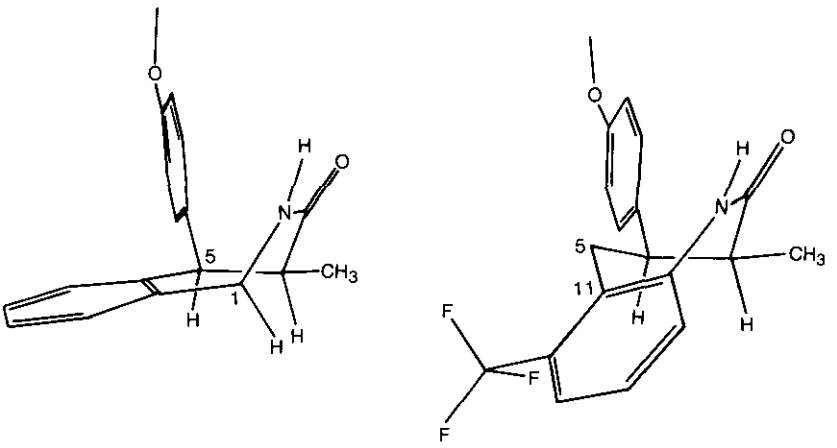
The synthetic route previously used to prepare 5-phenyl-1,2,4,5-tetrahydro-3H-2-benzazepin-3-one employed a low yielding final step involving $AlCl_3$-catalyzed cyclization of N-hydroxymethyl-3,3-diphenylpropionamide.[2] This route was not suitable for our purposes because with non-identical phenyl rings, the electron-rich methoxyphenyl group would cyclize to become part of the fused ring system. Our route to the target ring system began with the readily available phthalide (**4**).[3] The key carbon-carbon bond forming reaction involved the Lewis acid catalyzed alkylation of **4** ($ZnCl_2$ in CH_2Cl_2) with the trimethylsilylketene acetal of ethyl propionate to afford an 86% yield of **5** as an approximately 3:2 mixture of diastereomers. Similar reactions involving the alkylation of benzhydryl chloride and 1-naphthol acetate have been reported[4] but the alkylation of a lactone, where the leaving group remains attached to the electrophile, appears to be novel. With the two carboxyl groups differentially protected, **5** is a versatile intermediate which allows access to a number of heterocyclic systems.







Synthesis of the 2-benzazepin-3-one ring system required selective reduction of the carboxylic acid in the presence of the carboxylic ester and this transformation was achieved using borane to produce **6** in 84% yield. In order to facilitate analysis of the ^1H nmr spectrum, the diastereomers were separated on a small scale by flash chromatography. On a larger scale, the diastereomers were carried through the remainder of the sequence and separated after cyclization to the benzazepinone. Conversion of the hindered benzylic hydroxyl group to the amine (**9**) was accomplished by chlorination with Ph_3P/CCl_4 (74%), displacement with sodium azide in DMF (87%), and catalytic hydrogenation with PtO_2 (100%). Cyclization of **9** to the mixture of lactams (**3**) was effected in refluxing methanol containing 20 mole percent NaCN[5] and produced an approximately 3:2 ratio of *cis* product (**10**) to *trans* product (**11**). Crystallization of the reaction product afforded a 34% yield of the slower moving isomer (R_f = 0.24, 80% ethyl acetate/hexane) which was assigned *cis* stereochemistry based on the small coupling constant of 3.29 Hz between H-4 and H-5. The stereochemistry of **10** was confirmed by X-ray crystallographic analysis, which indicated a dihedral angle between H-4 and H-5 of ~55°. Chromatography of the mother liquor afforded 26% of the faster moving isomer (R_f = 0.34, 80% ethyl acetate/ hexane) which was assigned *trans* stereochemistry (see below).



10 **14**

Figure 1. The observed solid-state conformations of **10** and **14**.

Figure 1 presents a comparison of the observed solid-state conformations of **10** and 3-methyl-4-(4-methoxyphenyl)-6-trifluoromethyl-1-benzazepin-2-one (**14**).[6] Without exception, the equatorial C3-substituent and the twist-boat heptagonal ring conformation of **14** have also been observed in about twenty other crystal structures of

various C3-*cis* substituted derivatives of the 1-benzazepin-2-one nucleus and diltiazem.[6] The extensive twist about the C5-C11 bond of the twist-boat conformation of **14** (73°) clearly cannot be realized for the isomeric ring fusion of **10**. Instead **10** adopts a half-chair conformation. However, as in the structure of **14**, the methyl of **10** is equatorial and the amide and methoxyphenyl ring are *syn* with respect to the mean heptagonal ring plane. Given the close (2.2 Å) transannular diaxial approach of H-1 and H-4 in **10**, it is likely that the *trans* methyl group of **11** is also equatorial while the methoxyphenyl ring and H-5 are interchanged to give an *anti* half-chair conformation with a calculated *trans* dihedral angle for H4-C4-C5-H5 of about 170° (for **11**, J_{obs} = 10.99 Hz).

The dimethylaminoethyl group, an important pharmacophore in the diltiazem-like calcium channel antagonists, was appended to the amide nitrogen of both the *cis* and *trans* nuclei using NaH and N,N-dimethyl-2-chloroethylamine to form **12** and **13**.[7]

Table 1. Crystallographic Data for **10** and **14**

Structure	**10**	**14**
Crystallization Solvent	EtOAc	acetone
mp (°C)	204-205	204-205
a, Å	21.875(3)	14.381(1)
b, Å	14.510(3)	9.983(1)
c, Å	10.425(5)	12.791(6)
β°	114.01(2)	110.10(4)
V, Å^3	3023(2)	1725(1)
Space Group	C2/c	$P2_1/c$
Formula	$C_{18}H_{19}NO_2$	$C_{18}H_{18}NO_2F_3$
Z	8	4
d_{obs}, g-cm^{-3}	1.23	1.29
d_{calc},g-cm^{-3}	1.24	1.3
λ, Å	1.5418	1.5418
NUNI[a]	1843	2066
NOBS[b]	1129	1241
NV[c]	200	233
R	0.037	0.042
R_w	0.043	0.047

[a] Number of symmetry-independent measured reflections. [b] Total number of "observed" reflections with I≥ 3σ(I) used in least squares refinements. [c] Number of refined variables.

Table 2. Positional Parameters And Their Estimated Standard Deviations for **10**

Atom	X	Y	Z
C1	-0.0811(1)	0.1452(2)	-0.0739(3)
N2	-0.0311(1)	0.1143(2)	0.0613(2)
C3	0.0337(1)	0.1047(2)	0.0921(3)
O3	0.07294(9)	0.0735(1)	0.2063(2)
C4	0.0565(1)	0.1359(2)	-0.0202(3)
C5	0.0537(1)	0.2433(2)	-0.0356(3)
C6	-0.0162(2)	0.3838(2)	-0.1087(3)
C7	-0.0754(2)	0.4328(2)	-0.1667(3)
C8	-0.1350(2)	0.3882(2)	-0.1993(3)
C9	-0.1345(2)	0.2959(2)	-0.1671(3)
C10	-0.0751(1)	0.2455(2)	-0.1070(3)
C11	-0.0149(1)	0.2897(2)	-0.0813(3)
C12	0.1070(1)	0.2900(2)	0.0903(3)
C13	0.1025(1)	0.2988(2)	0.2183(3)
C14	0.1531(1)	0.3386(2)	0.3342(3)
C15	0.2096(1)	0.3708(2)	0.3212(3)
C16	0.2148(1)	0.3652(2)	0.1941(3)
C17	0.1646(1)	0.3248(2)	0.0820(3)
O18	0.2638(1)	0.4103(2)	0.4281(2)
C19	0.2636(2)	0.4116(3)	0.5643(4)
C20	0.1262(2)	0.0997(2)	0.0059(3)
H1	-0.081(1)	0.102(2)	-0.153(3)
H4	0.025(1)	0.112(2)	-0.110(2)
H5	0.066(1)	0.255(2)	-0.112(2)

Table 3. Positional Parameters and Their Estimated Standard Deviations for **14**

Atom	X	Y	Z
N1	0.1393(2)	0.5175(3)	0.0496(2)
C2	0.1259(2)	0.4399(4)	0.1302(3)
O2	0.0414(2)	0.4151(3)	0.1289(2)

C3	0.2172(2)	0.3858(4)	0.2171(3)
C4	0.2754(2)	0.4961(4)	0.3006(3)
C5	0.2861(2)	0.6238(4)	0.2387(3)
C6	0.3973(2)	0.6333(4)	0.1190(3)
C7	0.4088(3)	0.6213(5)	0.0158(3)
C8	0.3305(3)	0.5783(5)	-0.0744(3)
C9	0.2419(3)	0.5439(4)	-0.0629(3)
C10	0.2320(3)	0.5531(4)	0.0407(3)
C11	0.3079(2)	0.6013(4)	0.1327(3)
C12	0.2336(3)	0.5276(4)	0.3915(3)
C13	0.2809(3)	0.4846(5)	0.4997(3)
C14	0.2433(3)	0.5107(5)	0.5825(3)
C15	0.1564(3)	0.5813(4)	0.5598(3)
C16	0.1078(3)	0.6275(4)	0.4536(3)
C17	0.1468(3)	0.5994(4)	0.3708(3)
O18	0.1241(2)	0.6003(3)	0.6481(2)
C19	0.0326(3)	0.6669(4)	0.6276(3)
C20	0.1941(3)	0.2646(4)	0.2751(3)
C21	0.4821(3)	0.6851(5)	0.2134(4)
F22	0.5037(2)	0.6090(3)	0.3051(2)
F23	0.5657(2)	0.6933(4)	0.1916(2)
F24	0.4669(2)	0.8072(3)	0.2471(2)
H3	0.259(2)	0.348(3)	0.174(2)
H4	0.341(2)	0.454(3)	0.333(2)

EXPERIMENTAL SECTION

General Experimental Procedures. Tetrahydrofuran was distilled from sodium/benzophenone. Dimethylformamide was dried over 3Å molecular sieves. Melting points are uncorrected. ^{1}H Nmr spectra were recorded at 270 MHz and ^{13}C nmr spectra at 67.5 MHz on a JEOL GX-270 Nmr spectrometer in $CDCl_3$ solution with Me_4Si as internal standard (unless otherwise noted). Ir spectra were measured on a Perkin-Elmer 137 spectrometer. Mass spectra were measured on a Finnigan TSQ-4600 mass spectrometer using ammonia as the reagent gas for chemical ionization. High resolution mass spectra were measured on a VG ZAB-HF mass spectrometer with $M/\Delta M = 12,500$ using a dithiothreitol-dithioerythritol (3:1) matrix and polyethylene glycol or

polypropylene glycol as internal standard. Because fast atom bombardment of **8** produced loss of N_2, NaI was added to produce an intact quasi-molecular ion and the $(M + Na)^+$ ion was measured.

Crystal Structure Analyses. Crystal cell parameters and some details of data collection and refinement are summarized in Table 1. Unit cell parameters were obtained through a least squares analysis of more than fifteen high angle reflections. Crystal densities were measured by flotation in carbon tetrachloride/hexane mixtures. Reflections were measured diffractometrically at 23°C with the θ-2θ variable scan technique and were corrected for Lorentz polarization factors. Background counts were collected at the extremes of the scan for half the time of the scan. Two standard reflections were monitored for decay; no decrease of intensity was observed during the course of the measurements.

Structures were solved by direct methods and refined on the basis of "observed" reflections with $I \geq 3\sigma$ (I). All calculations utilized the SDP program package with minor local modifications.[8] Least squares weights, $w^{-1} = \sigma^2(F_o)$ were calculated with the assumption that $\sigma^2 = \varepsilon^2 + (pI)^2$ where ε is the statistical counting error and p = 0.04. The function minimized in the least squares refinements was $\Sigma w(|F_o| - |F_c|)^2$. R is defined as $\Sigma ||F_o| - |F_c|| / \Sigma |F_o|$ while $R_w = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w |F_o|^2]^{1/2}$. All hydrogens were included in structure factor calculations at positions consistent with peaks in difference maps; however, only hydrogens H1, H4, and H5 of **10** and H3 and H4 of **14** were refined (coordinates only). Final difference Fourier maps for **10** had no peaks larger than ±0.06(1) e/Å^3 (±0.13(3) for **14**). Atomic positional parameters are given in Tables 2 and 3. Atomic thermal parameters, hydrogen positional parameters, bond distances and angles are available from the authors.[9]

Ethyl β-(2-carboxyphenyl)-4-methoxy-α-methylbenzenepropanoate (5). To a mixture of the trimethylsilylketene acetal of ethyl propionate[10] (2.25 g, 13 mmol) and dry, free-flowing $ZnCl_2$ (1.77 g, 13 mmol) in CH_2Cl_2 (75 ml) at 0°C was added 3-(4-methoxyphenyl)phthalide[3] (2.60 g, 10.8 mmol) as a solid. The mixture was allowed to warm to room temperature over 1 h. Aqueous 5% $KHSO_4$ was added and the mixture was partitioned. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to afford 4.82 g of thick, clear oil. The oil was dissolved in 100 ml of 3:1 hexane:ether and the solution was washed 7 times with 10% aq. $NaHCO_3$. The combined aqueous layers were acidified with solid $KHSO_4$, extracted 3 times with ether and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to afford **5** (3.68 g, 86%) as a light yellow gum, consisting of a 3:2 ratio of diastereomers. ^{1}H Nmr δ 5.25 (1H, d, J = 11.6 Hz, PhC<u>H</u>Ph), 5.44 (1H, d, J = 11.6 Hz, PhC<u>H</u>Ph). ^{13}C Nmr 13.79, 13.91 ($\underline{C}H_3CH$); 16.67, 17.13 ($CH_2\underline{C}H_3$); 45.52, 45.61 ($CH_3\underline{C}H$); 47.34, 47.80 (Ph<u>C</u>HPh); 55.12 ($O\underline{C}H_3$); 60.27, 60.50 ($\underline{C}H_2CH_3$); 172.81, 173.24 ($\underline{C}O_2H$); 175.60, 176.03 ppm ($\underline{C}O_2Et$). *High resolution ms: Calcd for* $C_{20}H_{23}O_5$ 343.1545; Found 343.1528.

Ethyl β-(2-(hydroxymethyl)phenyl)-4-methoxy-α-methylbenzenepropanoate (6). To a solution of **5** (2.56 g, 7.48 mmol) in dry THF (50 ml) at 0°C was added a 1M solution of BH_3 in THF (37 ml, 37 mmol) dropwise over 20 min. The solution was allowed to warm to room temperature over 90 min. An additional aliquot

of BH_3 solution (10 ml) was added and the solution was stirred for an additional 30 min. The reaction was quenched carefully with water and the mixture was extracted twice with ether. The combined organic layers were washed with brine, dried and evaporated to afford 3.76 g of an oily semisolid. This material was passed through a pad of silica with 75% ether/hexane to afford **6** (2.06 g, 84%), as a mixture of diastereomers, as a colorless oil. The diol resulting from overreduction was also obtained in about 3% yield. ^{1}H Nmr Isomer A: δ 4.40 (1H, d, J = 11.08 Hz, PhC<u>H</u>Ph), 4.56 (1H, dd, J = 7.91, 11.60 Hz, C<u>H</u>$_2$OH), 4.96 (1H, dd, J = 2.64, 11.60 Hz, C<u>H</u>$_2$OH); Isomer B: 4.45 (1H, d, J = 11.07 Hz, PhC<u>H</u>Ph), 4.80 (2H, s, C<u>H</u>$_2$OH). ^{13}C Nmr 13.88, 13.97 (<u>C</u>H$_3$CH); 16.70, 17.31 (CH$_2$<u>C</u>H$_3$); 45.27, 45.70 (CH$_3$<u>C</u>H); 48.32, 47.41 (Ph<u>C</u>HPh); 55.20 (O<u>C</u>H$_3$); 60.27, 60.62 (<u>C</u>H$_2$CH$_3$); 63.24, 63.61 (<u>C</u>H$_2$OH); 175.83, 176.78 ppm (<u>C</u>O$_2$Et). Ms (M+NH$_4$)$^+$ 346; (M+H)$^+$ 329; (M+H-OH)$^+$ 311. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37; Found: C, 72.71; H, 7.63.

Ethyl β-(2-(chloromethyl)phenyl)-4-methoxy-α-methylbenzenepropanoate (7). A solution of **6** (2.06 g, 6.27 mmol) and triphenylphosphine (2.50 g, 9.52 mmol) in CCl_4 (75 ml) was refluxed for 24 h. The insoluble triphenylphosphine oxide was removed by filtration, rinsed twice with CCl_4 and the combined filtrates were evaporated to afford a semisolid which was flash chromatographed on silica with 25% ether/hexane to afford **7** (1.60 g, 74%; 82% based on unrecovered starting material), as a mixture of diastereomers, as a colorless oil. Elution of the column with ether afforded 0.22 g (11%) of recovered **6**. ^{1}H Nmr δ 4.40-4.75 (2H, m, PhC<u>H</u>Ph). ^{13}C Nmr 13.78, 13.92 (<u>C</u>H$_3$CH); 16.60, 17.04 (CH$_2$<u>C</u>H$_3$); 44.09 (CH$_3$<u>C</u>H); 45.47, 45.61 (Ph<u>C</u>HPh); 48.29, 48.49 (<u>C</u>H$_2$Cl); 55.07 (O<u>C</u>H$_3$); 60.15 (<u>C</u>H$_2$CH$_3$); 175.35, 175.43 ppm (<u>C</u>O$_2$Et). High resolution ms: Calcd for $C_{20}H_{24}ClO_3$ 347.1414; Found 347.1422.

Ethyl β-(2-(azidomethyl)phenyl)-4-methoxy-α-methylbenzenepropanoate (8). A mixture of **7** (1.72 g, 4.96 mmol) and NaN_3 (0.48 g, 7.43 mmol) in dry DMF (8 ml) was heated at 65°C for 1.75 h. The solvent was removed under high vacuum with gentle warming and the residue was partitioned between ether and water. The organic layer was washed twice with water, once with brine, dried ($MgSO_4$) and evaporated to afford crude **8** (1.53 g, 87%), as a mixture of diastereomers, as a light yellow oil. ^{1}H Nmr δ 4.25-4.50 (2H, m, PhC<u>H</u>Ph). ^{13}C Nmr 13.81, 13.95 (<u>C</u>H$_3$CH); 16.60, 17.13 (CH$_2$<u>C</u>H$_3$); 45.44, 45.61 (CH$_3$<u>C</u>H); 48.71, 48.79 (Ph<u>C</u>HPh); 52.67 (<u>C</u>H$_2$N$_3$); 55.13 (O<u>C</u>H$_3$); 60.20 (<u>C</u>H$_2$CH$_3$); 175.37, 175.51 ppm (<u>C</u>O$_2$Et). Ir (neat) 2110 cm^{-1} (N_3); 1740 cm^{-1} (CO_2Et). Ms (M+NH$_4$)$^+$ 371; (M+H)$^+$ 354; (M+H-N$_2$)$^+$ 326. High resolution ms: Calcd for $C_{20}H_{23}NaN_3O_3$ 376.1638; Found 376.1651.

Ethyl β-(2-(aminomethyl)phenyl)-4-methoxy-α-methylbenzenepropanoate (9). A mixture of **8** (1.53 g, 4.33 mmol) and PtO_2 (260 mg) in absolute ethanol (30 ml) was hydrogenated for 5 h. The mixture was filtered through a pad of celite and the celite was rinsed twice with absolute ethanol. The combined filtrates were evaporated to afford crude **9** (1.50 g, 100%) as an oil. ^{1}H Nmr Isomer A: δ 4.40 (1H, d, J = 11.54 Hz, PhC<u>H</u>Ph); Isomer B: δ 4.30 (1H, d, J = 11.5 Hz, PhC<u>H</u>Ph). ^{13}C Nmr 13.75, 13.81 (<u>C</u>H$_3$CH); 16.60, 17.18 (CH$_2$<u>C</u>H$_3$); 42.15, 42.82

($\underline{C}H_2NH_2$); 45.03, 45.56 ($CH_3\underline{C}H$); 48.37 (Ph$\underline{C}$HPh); 55.01 ($O\underline{C}H_3$); 60.04, 60.62 ($\underline{C}H_2CH_3$); 175.51, 176.65 ppm ($\underline{C}O_2Et$). High resolution ms: Calcd for $C_{20}H_{26}NO_3$ 328.1913; Found 328.1916.

(*cis*)-1,2,4,5-Tetrahydro-5-(4-methoxyphenyl)-4-methyl-3H-2-benzazepin-3-one (10). A mixture of crude **9** (1.50 g, 4.33 mmol) and NaCN (50 mg) in methanol (125 ml) was heated to reflux for 48 h and evaporated. The residue was dissolved in boiling ethyl acetate (125 ml) and the solution was filtered through celite and cooled to afford 27 mg of **10** as large hexagonal prisms, mp 204-205°C. Concentration of the mother liquor afforded an additional 215 mg of **10**. Flash chromatography of the mother liquor on silica with 95% ethyl acetate/hexane afforded an additional 166 mg of **10** (total 0.41 g, 34% overall yield from the azide). ^{1}H Nmr ($CDCl_3$-CD_3OD) δ 1.15 (3H, d, J = 6.59 Hz, $C\underline{H}_3CH$), 3.61 (1H, m, H-4), 3.73 (3H, s, $OC\underline{H}_3$), 4.09 (1H, d, J = 17 Hz, H-1), 4.16 (1H, d, J = 3.29 Hz, H-5), 4.96 (1H, d, J = 17 Hz, H-1). ^{13}C Nmr 15.09 ($\underline{C}H_3CH$); 38.44 (C-4); 46.30 (C-1); 51.69 (C-5); 55.06 ($O\underline{C}H_3$); 113.40, 126.07, 127.60, 128.06, 128.34, 128.52, 130.59, 131.83, 131.97, 132.12, 132.75, 133.90, 134.36, 141.42, 158.38; 176.41 ppm ($\underline{C}ONH$). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98; Found: C, 76.73; H, 6.84; N, 4.91.

(*trans*)-1,2,4,5-Tetrahydro-5-(4-methoxyphenyl)-4-methyl-3H-2-benzazepin-3-one (11). Fractions from the chromatography of **10** which were enriched in the faster moving isomer (R_f = 0.34 in 50% ethyl acetate/hexane) were pooled and evaporated and the residue was recrystallized from ethyl acetate to afford 0.32 g of **11** (26%) as a translucent crystalline solid, mp 183-184°C. ^{1}H Nmr δ 1.06 (3H, d, J = 6.60, $C\underline{H}_3CH$), 3.49 (1H, m, H-4), 3.78 (3H, s, $OC\underline{H}_3$), 3.94 (1H, dd, J = 6.60, 15.93 Hz, H-1), 3.94 (1H, d, J = 10.99 Hz, H-5), 4.96 (1H, dd, J = 6.60, 15.93 Hz, H-1). ^{13}C Nmr 16.50 ($\underline{C}H_3CH$); 41.93 (C-4); 46.22 (C-1); 52.32 (C-5); 55.20 ($O\underline{C}H_3$); 114.06, 126.10, 128.03, 128.43, 129.35, 132.84, 135.72, 137.18, 141.62, 158; 177.10 ppm ($\underline{C}ONH$). High resolution ms: Calcd for $C_{18}H_{20}NO_2$ 282.1494; Found 282.1502

(*cis*)-2-[2-(Dimethylamino)ethyl]-1,2,4,5-tetrahydro-5-(4-methoxyphenyl)-4-methyl-3H-2-benzazepin-3-one, monohydrochloride (12). To a solution of **10** (0.16 g, 0.57 mmol) in dry DMF (4 ml) was added NaH (27 mg of a 60% oil dispersion). The mixture was stirred for 45 min and N,N-dimethyl-2-chloroethylamine (0.32 ml of a 1.9 M solution in toluene, 0.63 mmol) was added. The mixture was heated to 65°C for 135 min. Additional NaH (10 mg) and N,N-dimethyl-2-chloroethylamine (0.08 ml) were added and the mixture was heated for an additional 55 min and quenched with aq. K_2CO_3. Solvent was removed under vacuum with gentle warming and the residue was partitioned between 10% aq. K_2CO_3 and ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The resulting oil was dissolved in ether, the solution was filtered through celite and HCl-saturated ether was added to the filtrate. The resulting white solid was collected by filtration, rinsed twice with ether and air-dried to afford 0.15 g of white solid. The white solid was dissolved in methanol and the solution was filtered and evaporated. The solid was dissolved in 4 ml of warm methanol, diluted with 40 ml of ether and the solution was allowed to cool. The resulting white solid was collected by filtration and dried to afford 0.12 g of **12** (55%), mp 134-136°C. ^{1}H Nmr δ 1.15 (3H, d, J = 6.59 Hz, $C\underline{H}_3CH$), 2.96 (6H, s,

$N(C\underline{H}_3)_2$), 3.51 (2H, m, $C\underline{H}_2N(CH_3)_2$), 3.74 (3H, s, $OC\underline{H}_3$), 3.89 (1H, m, H-4), 4.16-4.32 (3H, m, $NC\underline{H}_2CH_2$, H-5, H-1), 5.36 (1H, d, J = 15.93 Hz, H-1). ^{13}C Nmr 15.97 ($\underline{C}H_3CH$); 40.22 (C-4); 43.18, 45.14 ($N(\underline{C}H_3)_2$); 44.08 ($\underline{C}H_2N(CH_3)_2$); 52.69 (C-5); 53.46 ($N\underline{C}H_2CH_2$); 55.68 ($O\underline{C}H_3$); 57.18 (C-1); 114.37, 127.24, 129.03, 129.78, 131.88, 133.75, 134.35, 135.56, 142.76, 159.90; 177.98 ppm ($\underline{C}ONH$). Anal. Calcd for $C_{22}H_{29}N_2O_2Cl$. 1.50 H_2O: C, 63.46; H, 7.76; N, 6.73; Cl, 8.51; Found: C, 63.40; H, 7.97; N, 6.73; Cl, 8.92.

(*trans*)-2-[2-(Dimethylamino)ethyl]-1,2,4,5-tetrahydro-5-(4-methoxyphenyl)-4-methyl-3H-2-benzazepin-3-one, monohydrochloride (13). Prepared as a white crystalline solid, mp 131-134°C, in 53% yield from **11** as described for **12**. ^1H Nmr 1.02 (3H, d, J = 5.49 Hz, $C\underline{H}_3CH$), 2.92 (6H, s, $N(C\underline{H}_3)_2$), 3.2-3.3 (1H, m, H-4), 3.43 (2H, m, $C\underline{H}_2N(CH_3)_2$), 3.74 (3H, s, $OC\underline{H}_3$), 3.82 (2H, m, $NC\underline{H}_2CH_2$), 4.15 (1H, m, H-5), 4.14 (1H, d, J = 16.48 Hz, H-1), 5.63 (1H, d, J = 16.48 Hz, H-1). ^{13}C Nmr 16.59 ($\underline{C}H_3CH$); 43.11, 43.97 (C-4, $\underline{C}H_2N(CH_3)_2$); 43.28 ($N(\underline{C}H_3)_2$); 53.13, 53.99 (C-5, $N\underline{C}H_2CH_2$); 55.75 ($O\underline{C}H_3$); 57.08 (C-1); 115.19, 127.05, 129.44, 130.13, 130.62, 134.14, 135.43, 139.20, 142.86, 159.88; 178.42 ppm ($\underline{C}ONH$). Anal. Calcd for $C_{22}H_{29}N_2O_2Cl$. 0.95 H_2O: C, 65.08; H, 7.67; N, 6.90; Cl, 8.73; Found: C, 65.08; H, 7.65; N, 6.67; Cl, 8.50.

(*cis*)-1,3,4,5-Tetrahydro-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2H-1-benzazepin-2-one, (14). mp 203.5-204.5°C. ^1H Nmr δ 0.80 (3H, d, J = 6.96 Hz, $C\underline{H}_3CH$), 2.76 (1H, m, H-3), 2.99 (1H, t, J = 13.6 Hz, H-5β), 3.30 (1H, dd, J = 5.49, 13.6 Hz, H-5α), 3.42 (1H, m, H-4). ^{13}C Nmr 13.42 ($\underline{C}H_3CH$); 35.95 (C-5); 38.23 (C-3); 53.04 (C-4); 55.11 ($O\underline{C}H_3$); 113.82, 122.52, 122.92, 125.32, 127.14, 129.02, 132.20, 133.31, 140.19, 158.70; 176.56 ppm ($\underline{C}ONH$). Anal. Calcd for $C_{19}H_{18}NO_2F_3$: C, 65.33; H, 5.19; N, 4.01; F, 16.31; Found: C, 65.44; H, 5.22; N, 3.96; F, 16.02.

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Chem., submitted for publication. The CF_3 group of **14** does not appreciably affect the pucker of the twist-boat conformation.

7. Neither **12** or **13** were effective calcium channel blockers as measured by their ability to relax rabbit aorta strips which were precontracted with 110 mM K^+ (R. J. Brittain and S. Moreland, Physiologist, 1985, **24**, 325). Whereas 1.8 μM diltiazem produced 50% relaxation, **12** produced 16% relaxation and **13** produced 2% relaxation at 1μM.
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