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The Synthesis Of A Conformationally Rigid Calcium Channel Blocker[1]

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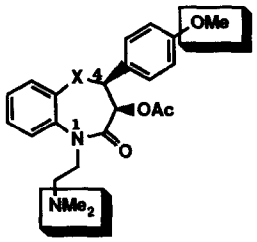
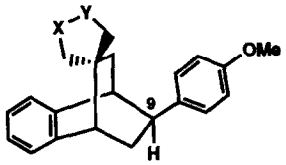
Abstract: *The preparation of (±)-3 and 4, conformationally rigid calcium channel blockers related to diltiazem, is described starting from the known bicyclic ketone 5. The syntheses include the addition of an aryl organometallic reagent to the ketones 9 and 13a respectively, which occurs with unexpected π-facial selectivity.*

Calcium Channel Blockers (CCBs) have recently found wide use in the treatment of cardiovascular disease.[2] Diltiazem **1**, a representative example of the 1,5-benzothiazepin-2-one class of CCBs, is an important therapeutic agent in the treatment of angina. Recently, a series of substituted 1-benzazepin-2-ones **2** were prepared as antihypertensive CCBs related to diltiazem.[3] It was determined that both benzothiazepinones and benzazepinones require two pharmacophores to demonstrate activity *in vitro* and *in vivo*; the N_1 substituent must contain a basic nitrogen attached to the seven-membered ring nucleus *via* an appropriately substituted carbon linkage and the C_4 phenyl moiety must be substituted by an alkyl ether group at the 4' position. The synthesis of analogs of **2** in which the N_1 substituent is conformationally constrained[4] led us to the hypothesis that the benzazepinone (and presumably the benzothiazepinone) nucleus may simply be acting as a spacer to hold the pharmacophores at the required distance for binding to the receptor. In this paper, we describe the synthesis of two CCBs, **3** and **4**, in which the seven-membered ring is replaced by a rigid bicyclic framework.



1 X = S (DILTIAZEM)
2 X = CH_2

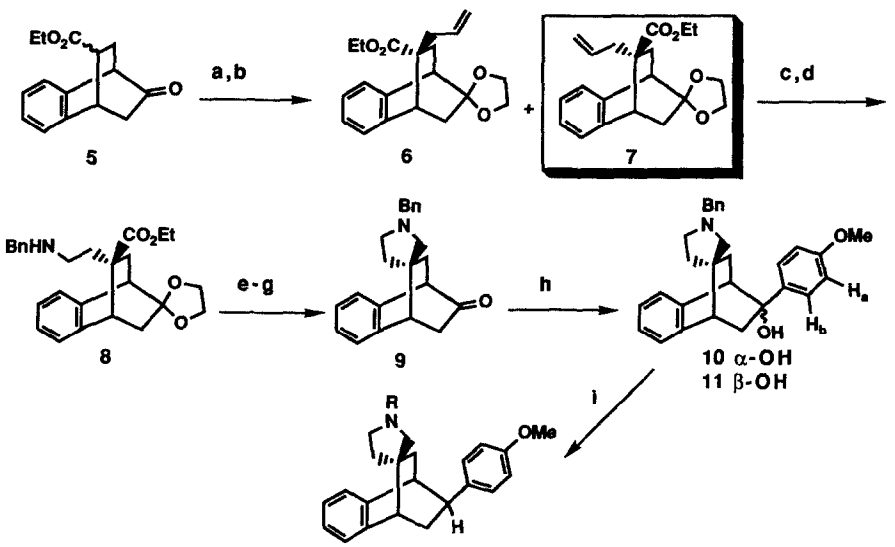


3 X = CH_2, Y = NH
4 X = NH, Y = CH_2

Our strategy for the synthesis of **3** and **4** involved, as a key step, introduction of the C_9 aryl substituent with the correct stereochemistry by first, addition of an appropriate organometallic reagent to a C_9 ketone followed by stereoselective reduction of the resulting tertiary alcohol from the less sterically hindered side of the bicyclic ring system. The entire carbon framework of the benzobicyclo[2.2.2]octane system is available in one step from the Diels-Alder cycloaddition of β-naphthol and ethyl acrylate[5] (2 equiv. acrylate, 180°, 4d) to give **5** (**Scheme**), albeit in low (12-15%) yield. However, the reaction was readily performed on 0.25 mole scale to give >10 g of the ketone (2:1 endo:exo) after distillation. The diastereomers can be separated by flash

chromatography but were more efficiently carried on as the mixture. Protection of the ketone followed by alkylation of the ester enolate gave a 1:2 mixture of **6** and **7**[6] which were separated by flash chromatography. Ozonolysis of **7** and subsequent reductive amination of the resulting aldehyde with benzylamine gave the amino ester **8**. The desired spiropyrrolidine ring was produced in excellent yield by treatment of **8** with base to give the lactam followed by reduction of the carbonyl group.

Scheme

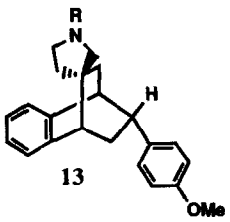


a. $(CH_2OH)_2$,PhH,80° (79%); b. LDA,THF,-78°; allyl bromide (90%); c. O_3,MeOH,$NaHCO_3$,-78°; Me_2S,RT,20h (94%); d. $PhCH_2NH_2$,HCl,MeOH, $NaCNBH_3$ (80%); e. NaOMe,MeOH,reflux (76%); f. $LiAlH_4$,Et_2O,THF,RT (82%); g. 2N aq. HCl,THF,RT (99%); h. n-BuLi,4-(MeO)PhBr,THF,-78°; $CeCl_3$; **9**,-78° (77%); i. 1) Et_3SiH,BF_3•Et_2O,CH_2Cl_2,0°; 2) H_2,$Pd(OH)_2$/C,HOAc; 3) HCl/Et_2O (40%).

After removal of the ketal, the resulting ketone **9** was added to a solution of the arylcerium reagent[7] derived from 4-bromoanisole to give a mixture of alcohols **10** and **11** in 77% yield. The corresponding Grignard reagent gave mostly recovered **9** due to enolization of the ketone. Interestingly, a 2:1[8] ratio of **10**:**11** was formed in this reaction; the major product was derived by addition of the aryl group from the more hindered side of the bicyclic system. Addition of the same reagent to five related ketones[9] gave similar results in all but one case. Further studies directed towards determining the origin of this unusual selectivity are described elsewhere.[10]

The alcohols **10** and **11** were separated for the purpose of characterization but could be conveniently carried on as a mixture by treatment with triethylsilane in the presence of boron trifluoride etherate[11] to give **12** along with its diastereomer **13** (R=Bn) and the olefin **14** (R=Bn) in a 14:1:6 ratio.[12] The crude mixture was reduced using Pearlmans' catalyst[13] in acetic acid to give **3** isolated as its hydrochloride salt along with a small

amount of the C_9 diastereomer.[14] By a similar route, **6**, the minor product derived from alkylation of **5**, was converted to **4** (8 steps; 37% overall).



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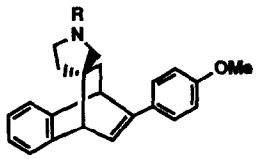

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Both (±) - **3** and **4** are equivalent to diltiazem (**1**) as inhibitors of the K^+ induced contraction of rabbit aorta (I_{50} (**3**): 0.95 μM; I_{50} (**4**): 2.0 μM; I_{50} (± **1**): 1.8 μM).[15] In addition, we have determined their affinity for the diltiazem receptor in isolated guinea pig skeletal muscle microsomal preparations by measuring their ability to inhibit specific binding of [^{3}H]-*d*-cis-diltiazem.[3,16] Compound **3** is equivalent to diltiazem (k_d (**3**): 0.33 μM; k_d (± **1**): 0.38 μM) and four times more potent than its diastereomer **4** (k_d (**4**): 1.26 μM) in this assay.

In conclusion, we have prepared two tricyclic amines **3** and **4** as potential calcium channel blockers in nine steps each starting from the known bicyclic ketone **5**. Detailed SAR and pharmacological studies of this series of compounds will be reported in due course.

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Notes and References

1. Presented at the 202nd American Chemical Society National Meeting, New York City, NY, MEDI 188, ORGN 114, August 25-30, 1991.

2. T. Godfraind, R. Miller, M. Wibo, *Pharmacological Reviews* **1986**, *38*, 321.

3. D. M. Floyd, R. V. Moquin, K. S. Atwal, S. Z. Ahmed, S. H. Spergel, *J. Org. Chem.* **1990**, *55*, 5572; D. M. Floyd, S. D. Kimball, J. Krapcho, J. Das, C. F. Turk, R. V. Moquin, M. W. Lago, K. J. Duff, V. G. Lee, R. E. White, R. E. Ridgewell, S. Moreland, R. J. Brittain, S. A. Hedberg, G. C. Cucinotta, *J. Med. Chem.*, in press; J. Das, D. M. Floyd, S. D. Kimball, K. J. Duff, T. C. Vu, M. W. Lago, R. V. Moquin, J. Z. Gougoutas, M. F. Malley, S. Moreland, R. J. Brittain S. A. Hedberg, G. C. Cucinotta, *J. Med. Chem.*, in press; S. D. Kimball, D. M. Floyd, J. Das, J. Krapcho, J. T. Hunt, G. Rovnyak, K. J. Duff, V. G. Lee, R. V. Moquin, C. F. Turk, S. A. Hedberg, S. Moreland, R. J. Brittain, D. M. McMullen, D. E. Normandin, G. C. Cucinotta, *J. Med. Chem.*, in press.

4. S. D. Kimball, J. C. Barrish, J. T. Hunt, D. M. Floyd, J. Das, J. Z. Gougotas, J. Krapcho, M. Lago, V. Lee, M. Malley, A. Pudzianowski, G. Rovnyak, S. Spergel, S. Moreland, S. A. Hedberg, unpublished results.

5. M. Nakazaki, K. Naemura, H. Yoshihara, *Bull. Chem. Soc. Jap.* **1975**, *48*, 3278.

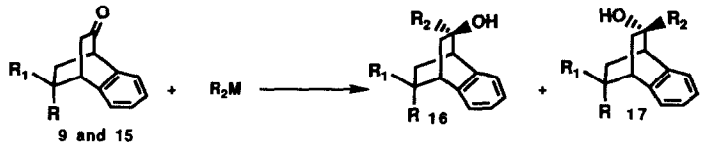
6. All new compounds displayed satisfactory spectral and analytical data. NMRs were taken in deutereochloroform unless otherwise noted. ^{1}H NMR (δ): **6** OCH_2CH_3 (1.09), $CH{=}CH_2$ (5.07, 5.70); **7** OCH_2CH_3 (1.28), $CH{=}CH_2$ (4.90, 5.56).

7. T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233; T. Imamoto, N. Takiyama,

K. Nakamura, *Tetrahedron Lett.* **1985**, *26*, 4763.

8. ^{1}H NMR (δ): **10** H_a (6.89), H_b (7.52), CH_3O (3.83); **11** H_a (6.61), H_b (7.14), CH_3O (3.70); The methoxyphenyl group of **11** is rigidly held over the fused benzene ring resulting in shielding of the hydrogens of the methoxyphenyl group relative to those of **10**.

9.



Entry	Substrate	R	R_1	R_2	M	16:17
1	9	CH_2CH_2-	-N(Bn)CH_2	4-(OMe)Ph	$CeCl_2$	2:1
2	15a	$CH_2N(Bn)$-	-CH_2CH_2	4-(OMe)Ph	$CeCl_2$	4:1
3	15b	H	$CH_2N(Bn)Me$	4-(OMe)Ph	$CeCl_2$	7:1
4	15c	$CH_2N(Bn)Me$	H	4-(OMe)Ph	$CeCl_2$	20:1
5	15d	H	N(Cbz)Me	4-(OMe)Ph	$CeCl_2$	1:2
6	15e	N(Cbz)Me	H	4-(OMe)Ph	$CeCl_2$	6:1

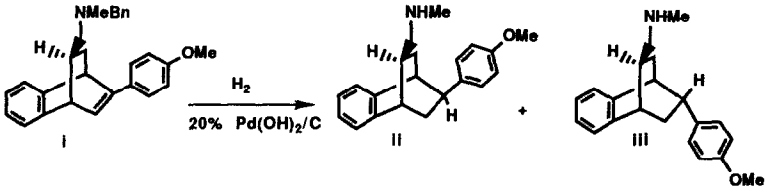
The finding that the substrates which place the nitrogen and the carbonyl group on the same side of the bicyclic ring system (**9**, **15b**, **15d**) gave lower ratios of **16**:**17** than their diastereomers (**15a**, **15c**, **15e**) may be explained by complexation of the organocerium reagent with the the nitrogen, thereby shielding the ketone more effectively from attack to give **16**. This apparent effect would be greatest in the case of **15d** where the nitrogen is rigidly held nearest to the carbonyl group. The synthesis of **15b-e** will be described in the full report.

10. A. Puzianowski, J. C. Barrish, S. Spergel, *Tetrahedron Letters*, in press.

11. M. Orfanopoulus, I. Smonou, *Synth. Commun.* **1988**, *18*, 833.

12. The olefin by-product was also formed during similar reductions of the alcohols **16/17 a-c** but was not seen in the reductions of the analogs **16/17 d** and **16/17 e**.

13. In one case, the olefin **i** derived from **15b** was isolated and gave on reduction a 7:1 mixture of **ii**:**iii**. The structure of **ii** was confirmed by x-ray crystallography.



14. **3** (Free base): ^{1}H NMR (δ): 6.81 (Ha), 7.23 (Hb); **14** (R=H): ^{1}H NMR (δ): 6.46 (Ha), 6.63 (Hb).
3 • HCl: ^{1}H NMR (DMSO-d^6): δ 0.81 (m, 1H), 1.15 (m, 1H), 1.44 (m, 1H), 1.78 (m, 1H), 1.88 (m, 1H), 2.09 (m, 1H), 2.73 (m, 1H), 2.98 (m, 2H), 3.15 (m, 1H), 3.37 (m, 1H), 3.76 (s, 3H), 6.94 (d, J=9 Hz, 2H), 7.22 (m, 3H), 7.31 (m, 1H), 7.34 (d, J=8Hz, 2H); ^{13}C NMR (DMSO-d^6): δ 157.5, 143.3, 141.2, 134.4, 128.8, 126.4, 126.0, 124.6, 123.6, 113.7, 55.0, 54.2, 45.6, 42.6, 41.9, 32.7, 26.8.

15. K. S. Atwal, J. L. Bergey, A. Hedberg, S. Moreland, *J. Med. Chem.* **1987**, *30*, 635.

16. F. P. Guengerich, R. L. McDonald, *Accts. Chem. Res.* **1984**, *17*, 9.