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A Facile and Practical Synthesis of Capsazepine, a Vanilloid Receptor Antagonist

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SYNTHETIC COMMUNICATIONS, 29(23), 4127–4140 (1999)

A FACILE AND PRACTICAL SYNTHESIS OF CAPSAZEPINE, A VANILLOID RECEPTOR ANTAGONIST

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ABSTRACT: A facile and practical synthesis of capsazepine, a vanilloid receptor antagonist, has been accomplished from isovanillin in 8 steps *via* an efficient intramolecular Mannich cyclization.

Capsazepine is a vanilloid receptor antagonist which inhibits agonistic cellular responses to capsaicin, the pungent component of hot peppers, and to resiniferatoxin, a daphnane diterpene, by blocking their binding to the receptor in a competitive manner.[1] Even though capasazepine has been used as an important biochemical tool in vanilloid receptor research and

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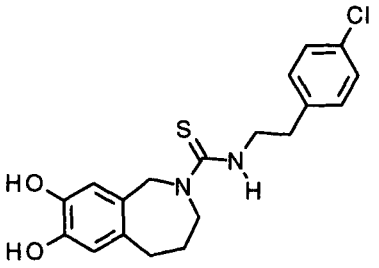
is considered as a lead compound for developing potential analgesics with novel modes of action, it is still a very expensive chemical commercially available.[2] As regards its synthesis, the first report by the Sandoz group is the only reference to it, to our knowledge.[3]



Capsazepine

In our efforts to investigate the interaction of capsazepine derivatives with the vanilloid receptor, and hence to develop novel analgesics, we required a reasonable method for the large-scale synthesis of capsazepine and its benzazepine nucleus.

This report herein describes a facile and practical synthesis of capsazepine involving an efficient intramolecular Mannich cyclization as a key step.

In a previous synthesis of the key intermediate, 7,8-dihydroxy-2,3,4,5-tetrahydro-2-benzazepine hydrobromide

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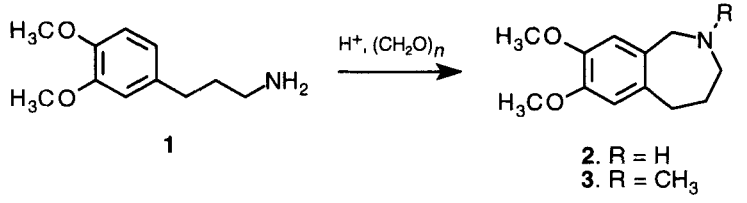
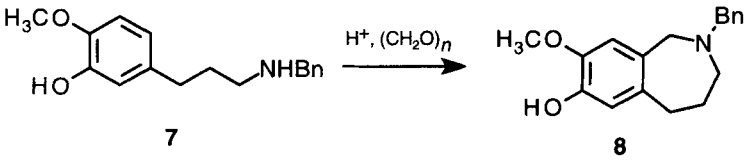
(**10**), 3-(3,4-dimethoxyphenyl)propylamine (**1**) was cyclized *via* the isocyanate to yield the intermediate benzazepinone, which was then reduced and demethylated.[3] Our studies on the direct cyclization of amine **1** to benzazepine (**2**) through intramolecular Mannich reaction[4] indicated that cyclization to a 7-membered ring proceeded sluggishly and was accompanied by reductive methylation on the nitrogen atom as a consecutive reaction, resulting in production of N-methyl benzazepine (**3**) as a major product.[5]



1

2. R = H
3. R = CH_3



7 **8**

In order to overcome the above problems in the cyclization of **1**, we chose an intermediate **7** for the intramolecular Mannich reaction, since nucleophilicity of C(6) in this Mannich reaction acceptor is reinforced by the 3-hydroxy group, a more electron-donating group, and the amine function is protected by the

benzyl group. As expected, the cyclization of **7** proceeded smoothly to produce in high yield benzazepine **8** as the sole product.

Thus, the synthesis of capsazepine was started from commercially available isovanillin (**4**). Horner-Emmons reaction of **4** with trimethyl phosphonoacetate followed by hydrogenation, produced methyl ester **5**. The ester (**5**) was converted into *N*-benzyl amide **6** by direct condensation with benzylamine or in two steps including alkaline hydrolysis and condensation with benzylamine. Reduction of amide **6** with lithium aluminum hydride gave benzylamine **7**, a key intermediate for intramolecular Mannich cyclization. Of several conditions investigated,[4] treatment of **7** with paraformaldehyde (1.1 eq) and methanesulfonic acid (1.1 eq) in refluxing acetonitrile afforded the best yield of *N*-benzylbenzazepine **8** as sole product. *N*-Benzylbenzazepine **8** was then subjected to debenzylation followed by demethylation to give 7,8-dihydroxybenzazepin (**10**), a known compound. Finally, benzazepine **10** was condensed with 2-(4-chlorophenyl)ethyl isothiocyanate (prepared from 2-(4-chlorophenyl)ethylamine

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and 1,1'-thiocarbonyldi-2(1*H*)-pyridone)[6] to complete the synthesis of capsazepine whose spectra were identical with those previously reported.[3]

In summary, we accomplished the synthesis of capsazepine on a large scale by practical methods including an efficient intramolecular Mannich cyclization of **7** as a key step. This method will also be applied to the synthesis of capsazepine derivatives as potent vanilloid receptor antagonists.

EXPERIMENTAL

General Experimental

All chemical reagents were commercially available. Melting points were determined on a Melting Point B-540 apparatus, Büchi, Switzerland, and are uncorrected. Silica gel column chromatography was performed on silica gel 60, 230-400 mesh, Merck. Proton NMR spectra were recorded on a Bruker Avance 400 at 400 MHz. Chemical shifts are reported in ppm downfield internal tetramethylsilane as reference standard. Mass spectra were recorded on a VG Trio-2, GC-MS. Elemental analyses were

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performed with EA 1110 Automatic Elemental Analyzer, CE Instruments, Italy.

Methyl 3-(3-Hydroxy-4-methoxyphenyl)propanoate (5)

A cooled solution of trimethyl phosphonoacetate (12.95 mL, 80 mmol) in THF (20 mL) at 0 °C was treated dropwise with a 1 M solution of potassium *tert*-butoxide in THF (80 mL, 80 mmol), and the mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C, and a solution of isovanillin (**4**) (6.08 g, 40 mmol) in THF (20 mL) was added dropwise. After refluxing for 2 h, the mixture was cooled and concentrated *in vacuo*. The residue was purified by flash chromatography [silica gel, EtOAc/hexane (1:2)] to give methyl 3-(3-hydroxy-4-methoxyphenyl)propenoate (6.83 g, 82%) as a white solid: mp 72.4 °C (recrystallized from hexane); ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1H, J = 16.0 Hz, C<u>H</u>=CHCO$_2$Me), 7.14 (d, 1H, J = 2.0 Hz, H-2), 7.03 (dd, 1H, J = 8.3 and 2.0 Hz, H-6), 6.84 (d, 1H, J = 8.3 Hz, H-5), 6.30 (d, 1H, J = 16.0 Hz, CH=C<u>H</u>CO$_2$Me), 5.71 (br s, 1H, OH), 3.92 (s, 3H, OCH_3), 3.79 (s, 3H, CO_2CH_3). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.70 ; H, 5.83.

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A suspension of 10% palladium on charcoal (1.36 g) in a solution of unsaturated ester (6.83 g, 32.8 mmol) in MeOH (80 mL) was hydrogenated under a balloon of hydrogen for 2 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give **5** (6.89 g, 100%) as a white solid which was pure enough to be used for the next step without further purification: mp 72.4 °C (recrystallized from hexane); ^{1}H NMR ($CDCl_3$) δ 6.74-6.82 (m, 2H, H-2 and H-5), 6.69 (dd, 1H, J = 8.2 and 1.8 Hz, H-6), 5.60 (s, 1H, OH), 3.88 (s, 3H, OCH_3), 3.69 (s, 3H, CO_2CH_3), 2.87 (t, 2H, J = 7.6 Hz, $C\underline{H}_2CH_2CO_2CH_3$), 2.61 (t, 2H, J = 8.1 Hz, $CH_2C\underline{H}_2CO_2CH_3$); IR (KBr) 3385, 1727, 1517 cm^{-1}; MS (EI) *m/z* 210 (M^+). *Anal.* Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.94; H, 6.73.

N-Benzyl-3-(3-hydroxy-4-methoxyphenyl)propanamide (6)

<Method A>

A mixture of **5** (6.73 g, 32 mmol) and 15% NaOH solution (32 mL) in THF (20 mL) was stirred for 16 h at room temperature. The reaction mixture was acidifed with 1 N aqueous HCl and

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extracted with CH_2Cl_2 several times. The combined organic layers were washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude acid. A mixture of the acid, benzylamine (7 mL, 64 mmol), and 4Å molecular sieves (3 g) was heated at 150 °C for 4 h. The resulting mixture was cooled and diluted with CH_2Cl_2. The organic layer was washed successively with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography [silica gel, EtOAc/hexane (2:1)] to give **6** (6.94 g, 76%) as a white solid: mp 117.1 °C (recrystallized from EtOAc-Hexane); ^1H NMR ($CDCl_3$) δ 7.14-7.32 (m, 5H, phenyl), 6.77 (d, 1H, J = 2.0 Hz, H-2), 6.74 (d, 1H, J = 8.2 Hz, H-5), 6.67 (dd, 1H, J = 8.2 and 2.0 Hz, H-6), 5.67 (br s, 2H, OH and NH), 4.39 (d, 2H, J = 5.6 Hz, $NHCH_2Ph$), 3.86 (s, 3H, OCH_3), 2.90 (t, 2H, J = 7.5 Hz, $C\underline{H}_2CH_2CONH$), 2.47 (t, 2 H, J = 7.5 Hz, $CH_2C\underline{H}_2CONH$); IR (KBr) 3443, 1648, 1510 cm^{-1}; MS (EI) m/z 285 (M^+). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.71; H, 6.68; N, 4.88.

<Method B>

A mixture of **5** (6.73 g, 32 mmol) and benzylamine (7 mL, 64

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mmol) in toluene (50 mL) was refluxed for 24 h. After adding additional benzylamine (7 mL, 64 mmol), the reaction mixture was refluxed for 24 h and concentrated. The residue was diluted with CH_2Cl_2, washed successively with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography [silica gel, EtOAc/hexane (2:1)] to give **6** (6.48 g, 71.3%) as a white solid, whose melting point and ^{1}H-NMR were identical with those by method A.

N-Benzyl-3-(3-hydroxy-4-methoxyphenyl)propylamine (7)

To a suspension of lithium aluminum hydride (1.82 g, 48 mmol) in THF (100 mL) was added dropwise a solution of **6** (6.85, 24 mmol) in THF (50 mL), and the mixture was refluxed for 16 h. The reaction mixture was cooled in an ice bath, quenched by successive addition of H_2O (1.8 mL), 15% aqueous NaOH (3.6 mL), and H_2O (5.4 mL), and stirred for 30 min. The resulting suspension was filtered, the residue was washed with EtOAc, and the combined filtrate and washings were concentrated *in*

vacuo. The residue was purified by flash chromatography [silica gel, CH_2Cl_2/MeOH (8:1)] to give **7** (4.82 g, 74%) as a white solid: mp 117 °C (recrystallized from dichloromethane); ^1H NMR ($CDCl_3$) δ 7.2-7.35 (m, 5H, phenyl), 6.73-6.76 (m, 2H, H-2 and H-5), 6.67 (dd, 1H, J = 8.1 and 1.4 Hz, H-6), 3.85 (s, 3H, OCH_3), 3.78 (s, 2H, $NHCH_2Ph$), 2.66 (t, 2H, J = 7.1 Hz, CH_2NH), 2.56 (t, 2H, J = 7.5 Hz, $ArCH_2$), 1.81 (m, 2H, CH_2CH_2NH); IR (KBr) 3440, 1509 cm^{-1}; MS (EI) *m/z* 271 (M^+). *Anal.* Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.13. Found: C, 74.98; H, 7.82; N, 5.15.

2-Benzyl-7-hydroxy-8-methoxy-2,3,4,5-tetrahydro-2-benzazepine (8)

A mixture of **7** (4.61 g, 17 mmol), paraformaldehyde (0.57 g, 19 mmol), and methanesulfonic acid (1.23 mL, 19 mmol) in acetonitrile (150 mL) was refluxed for 16 h and then concentrated *in vacuo*. The residue was diluted with H_2O, basified with solid $NaHCO_3$, and extracted with CH_2Cl_2 several times. The combined organic layers were washed successively with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography [silica gel,

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CH_2Cl_2/MeOH (10:1)] to give **8** (3.95 g, 82%) as a yellow solid: mp 117.5 °C (recrystallized from EtOAc-Hexane); ^{1}H NMR ($CDCl_3$) δ 7.2-7.35 (m, 5H, phenyl), 6.74 (s, 1H, H-6), 6.41 (s, 1H, H-9), 3.80 (s, 2H, $ArCH_2NBn$), 3.79 (s, 3H, OCH_3), 3.54 (s, 2H, $NHCH_2Ph$), 3.12 (t, 2H, *J* = 5.3 Hz, $CH_2C\underline{H}_2N$), 2.81 (t, 2H, *J* = 5.4 Hz, $ArC\underline{H}_2CH_2$), 1.73 (m, 2H, $ArCH_2C\underline{H}_2$); IR (KBr) 3445, 1588, 1513 cm^{-1}; MS (EI) *m/z* 283 (M^+). *Anal.* Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.32; H, 7.43; N, 4.89.

7-Hydroxy-8-methoxy-2,3,4,5-tetrahydro-2-benzazepine (9)

A suspension of 10% palladium on charcoal (0.8 g) in a solution of **8** (3.85 g, 13.6 mmol) in MeOH (40 mL) was hydrogenated under a ballon of hydrogen for 3 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give **9** (2.57 g, 98%) as a pink solid which was pure enough to be used for the next step. For analytical purpose, it was recrystallized from EtOAc-MeOH to give a pure **9** as a white solid: mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 6.74 (s, 1H, H-6), 6.66 (s, 1H, H-9), 3.87 (s, 2H, $ArCH_2NH$), 3.86 (s, 3H, OCH_3), 3.18 (t, 2H, *J* = 5.2 Hz, $CH_2C\underline{H}_2N$),

2.84 (t, 2H, J = 4.5 Hz, $ArCH_2CH_2$), 1.70 (m, 2H, $ArCH_2CH_2$); IR (KBr) 3445, 1508 cm^{-1}; MS (EI) m/z 193 (M^+). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.10; H, 7.85; N, 7.22.

7,8-Dihydroxy-2,3,4,5-tetrahydro-2-benzazepine Hydrobromide (10)

A mixture of **9** (2.32 g, 12 mmol) and 48% hydrobromic acid (30 mL) was refluxed for 24 h. After cooling, the mixture was concentrated *in vacuo*. The brown residue was suspended in a small volume of MeOH, the suspension was filtered, and the insoluble solid collected was washed with ether to give **10** (1.72 g, 80%) as a gray solid: mp 219 °C (recrystallized from MeOH); ^1H NMR (DMSO-d_6) δ 9.07 (s, 1H, OH), 8.89 (s, 1H, OH), 8.61 (br s, 2H, NH_2^+), 6.76 (s, 1H, H-6), 6.63 (s, 1H, H-9), 4.11 (s, 2H, $ArCH_2NH$), 3.28 (m, 2H, CH_2CH_2N), 2.76 (m, 2H, $ArCH_2CH_2$), 1.79 (m, 2H, $ArCH_2CH_2$); ; MS (EI) m/z 193 (M^+). *Anal.* Calcd for $C_{10}H_{14}BrNO_2$: C, 46.17; H, 5.42; N, 5.38. Found: C, 46.34; H, 5.62; N, 5.25.

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N-[[[2-(4-Chlorophenyl)ethyl]amino]thiocarbonyl]-7,8-dihydroxy-2,3,4,5-tetrahydro-2-benzazepine (Capsazepine)

By following literature procedure,[3] **10** was converted to capsazepine by the reaction with 2-(4-chlorophenyl)ethyl isothiocyanate, which was prepared from 2-(4-chlorophenyl)ethylamine and 1,1'-thiocarbonyldi-2(1*H*)-pyridone.[6] Its ^{1}H NMR, melting point, and TLC behavior were identical with those of commercially available capsazepine.

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