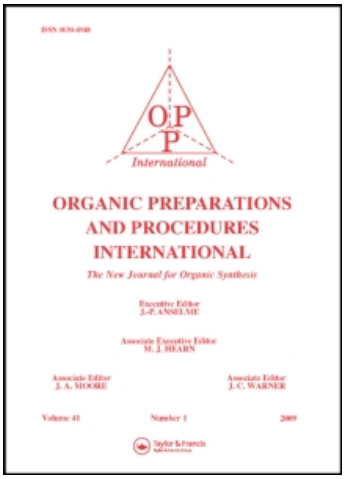

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SYNTHESIS OF A SPIROCYCLIC OXENDOLE ANALOGUE AS A PUTATIVE REPLACEMENT FOR PR0²-PRO³-GLY⁴-PHE⁵ IN BRADYKININ ANTAGONISTS

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SYNTHESIS OF A SPIROCYCLIC OXINDOLE ANALOGUE AS A PUTATIVE REPLACEMENT FOR PRO^2-PRO^3-GLY^4-PHE^5 IN BRADYKININ ANTAGONISTS

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(5/23/95)

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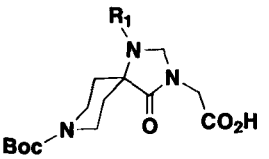
As part of a program for the synthesis of bradykinin antagonists, we recently investigated the use of 1,3,8-triazaspiro[4.5]decan-4-one-3-acetic acids (**1**) as amino acid surrogates for the Pro^2-Pro^3-Gly^4-Phe^5 section of the bradykinin B2 receptor-selective antagonist, D-Arg^0-Arg^1-Pro^2-Pro^3-Gly^4-Phe^5-Ser^6-D-Tic^7-Oic^8-Arg^9.[1] As a variation on this theme, we proposed to prepare **2** as a rotationally constrained analogue of **1a** in which the aromatic ring is in the same approximate plane as the 5-membered ring. Herein, we wish to describe the success of these synthetic efforts which provides **2** in six steps from commercially available materials.



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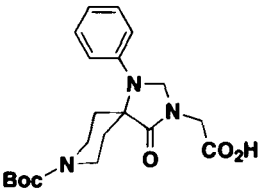
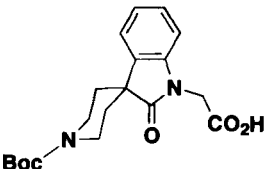
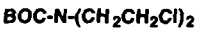


1a

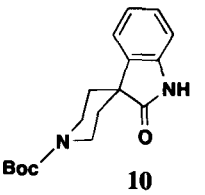


2

Treatment of oxindole **3** with excess sodium hexamethyldisilazide in THF gave the oxindole dianion[2] which was alkylated with N-methyl*bis*(2-chloroethyl)amine[3] to give the spirocyclic oxindole **4** in 66% yield. It is worth noting that, in our hands, attempts to alkylate the oxindole dianion with **9**

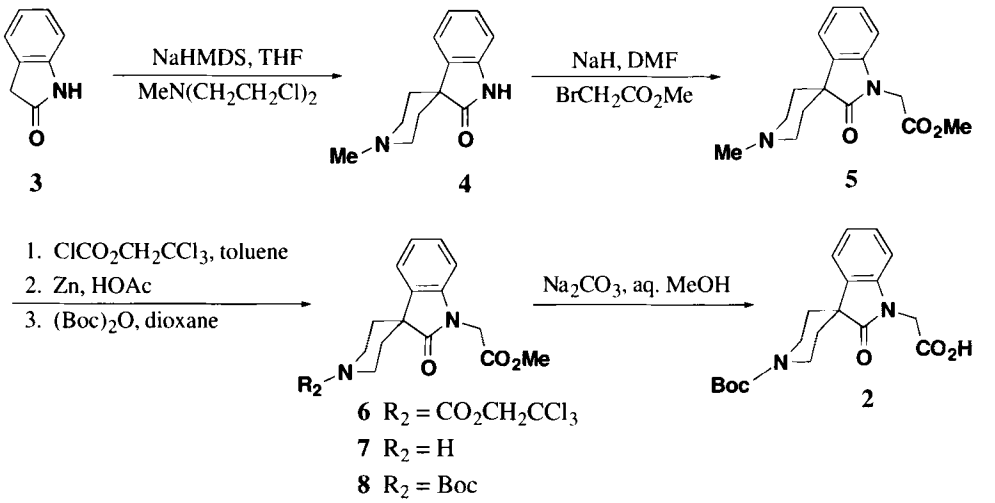


9



10

to prepare **10** (and potentially shorten the synthesis) met with no success. The acetic acid side chain was introduced by deprotonation with sodium hydride in DMF followed by alkylation with methyl bromoacetate to give **5** in 84% yield. The N-methyl group in **5** could be replaced with a Boc group *via* a three step procedure involving demethylation with 2,2,2-trichloroethyl chloroformate,[4] cleavage of the carbamate **6** with zinc to give the secondary amine **7**, which was protected by reaction with $(Boc)_2O$ to provide **8** in 90% overall yield from **5**. Finally, saponification of the methyl ester gave a 74% yield of the desired Boc protected amino acid **2**.



Incorporation of **2** into putative bradykinin receptor antagonists and the pharmacological profiles of the resulting pseudopeptides will be reported in due course.

EXPERIMENTAL SECTION

All reaction mixtures were stirred magnetically under an atmosphere of argon. Reagents and chemicals were purchased from common commercial suppliers and used without purification. Solutions of crude products were dried over anhydrous Na_2SO_4, and the solvents removed using a rotary evaporator. Chromatography refers to flash column chromatography on silica gel.[5] Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer Model 1625 FT-IR. ^{1}H NMR spectra were recorded on a Bruker AC-400 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

1,2-Benzo-8-methyl-3,8-diazaspiro[4.5]decan-4-one (4).- A solution of oxindole (**3**) (6.65 g, 50 mmol) in THF (100 mL) was cooled to -78° and a 1*M* solution of sodium hexamethyldisilazide in THF (250 mL, 250 mmol) was added dropwise. After stirring at -78° for 30 min, N-methylbis(2-chloroethyl)amine hydrochloride (9.63 g, 50 mmol) was added, as a solid. The reaction mixture was stirred at -78° for 30 min and at room temperature for 18 hrs. After quenching with H_2O (100 mL) the mixture was extracted with Et_2O (3 x 50 mL). The organic extracts were washed with brine (25 mL), dried and the solvent removed *in vacuo*. Chromatography (5-50% MeOH/CH_2Cl_2, gradient) gave 7.17 g (66%) of **4** as a tan crystalline solid, mp. 200-205° (dec); R_f = 0.26 (SiO_2, 50% MeOH/CH_2Cl_2, UV or $KMnO_4$); ^{1}H NMR ($CDCl_3$): δ 2.00 (br t, 4H, J = 8.3Hz), 2.50 (s, 3H), 2.70-2.80 (m, 2H), 2.99-3.05 (m, 2H), 6.95 (d, 1H, J = 7.6Hz), 7.02 (t, 1H, J = 7.6Hz), 7.21 (t, 1H, J = 7.4Hz), 7.35 (d, 1H, J = 7.4Hz), 9.71 (br s, 1H); IR: 3415, 3057, 1692, 1620, 1471, 1234, 1193, 764 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}N_2O$•0.25 H_2O: C, 70.72; H, 7.53; N, 12.69
Found: C, 70.78; H, 7.51; N, 12.81

1,2-Benzo-8-methyl-3,8-diazaspiro[4.5]decan-4-one-3-acetic Acid Methyl Ester (5).- Sodium hydride (60 wt%, 1.60 g, 40.0 mmol) was washed with hexanes (3 x 5 mL), suspended in DMF (10 mL) and cooled to 0°. A solution of **4** (7.07 g, 32.7 mmol) in DMF (50 mL) was added dropwise. After stirring at 0° for 30 min, methyl bromoacetate (3.80 mL, 40.0 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 5 hrs and poured into H_2O (500 mL). After extracting with Et_2O (5 x 50 mL) the organic extracts were washed with H_2O (3 x 25 mL), brine (25 mL), dried and the solvent removed *in vacuo*. Chromatography (1-25% MeOH/CH_2Cl_2, gradient) gave 7.93 g (84%) of **5** as a crystalline solid, mp. 100-103°; R_f = 0.29 (SiO_2, 10% MeOH/CH_2Cl_2, UV or $KMnO_4$); ^1H NMR ($CDCl_3$): δ 1.90-2.13 (m, 4H), 2.48 (s, 3H), 2.68-2.83 (m, 2H), 2.90-3.10 (m, 2H), 3.75 (s, 3H), 4.46 (s, 2H), 6.72 (d, 1H, J = 7.7Hz), 7.08 (t, 1H, J = 7.2Hz), 7.25 (t, 1H, J = 7.8Hz), 7.37 (d, 1H, J = 7.3Hz); IR: 2931, 1738, 1702, 1612, 1355, 1219, 1178, 980, 753 cm^{-1}.

Anal. Calcd. for $C_{16}H_{20}N_2O_3 \cdot 0.25\ H_2O$: C, 65.62; H, 7.06; N, 9.57

Found: C, 65.90; H, 7.04; N, 9.66.

1,2-Benzo-8-Boc-3,8-diazaspiro[4.5]decan-4-one-3-acetic Acid Methyl Ester (8).- To a solution of **5** (3.26 g, 11.3 mmol) in toluene (100 mL) was added 2,2,2-trichloroethyl chloroformate (7.5 mL, 45.1 mmol) and the mixture heated to reflux for 18 hrs. After cooling to room temperature the mixture was diluted with Et_2O (200 mL), washed with H_2O (2 x 25 mL), brine (25 mL), dried and the solvent removed *in vacuo*. The crude **6** (oil) was used directly in the next step.

Crude **6** from the previous step was dissolved in HOAc (30 mL) and zinc dust (10 g) was added. After the initial exothermic reaction subsided, the reaction mixture was stirred for 1 hr, diluted with CH_2Cl_2 (50 mL) and the mixture filtered through Celite. The filtrate was diluted with H_2O (50 mL), cooled to 0° and made basic with conc. NH_4OH. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (25 mL), dried and the solvent removed *in vacuo*. This crude product (**7**) was again used directly in the next step.

Crude **7** was dissolved in 1,4-dioxane (50 mL), cooled to 0° and a solution of di-tert-butyl dicarbonate (2.54 g, 11.6 mmol) in 1,4-dioxane (10 mL) was added in one portion. After stirring at room temperature for 16 hrs, the reaction mixture was diluted with Et_2O (100 mL) and H_2O (25 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with H_2O (25 mL), brine (25 mL), dried and the solvent removed *in vacuo*. Chromatography (0-5% MeOH/CH_2Cl_2, gradient) gave 3.82 g (90%) of **8** as a white crystalline solid, mp. 135-136°; R_f = 0.71 (SiO_2, 5% MeOH/CH_2Cl_2, UV); ^1H NMR ($CDCl_3$): δ 1.51 (s, 9H), 1.75-1.93 (m, 4H), 3.75 (s, 3H), 3.77-3.86 (m, 4H), 4.47 (s, 2H), 6.74 (d, 1H, J = 7.8Hz), 7.09 (t, 1H, J = 7.6Hz), 7.20-7.35 (m, 2H); IR: 2962, 1743, 1707, 1687, 1250, 1165 cm^{-1}.

Anal. Calcd. for $C_{20}H_{26}N_2O_5 \cdot 0.25\ H_2O$: C, 63.39; H, 7.05; N, 7.39

Found: C, 63.55; H, 7.02; N, 7.34.

1,2-Benzo-8-Boc-3,8-diazaspiro[4.5]decan-4-one-3-acetic Acid (2).- A mixture of **8** (3.76 g, 10.0 mmol), Na_2CO_3 (4.24 g, 40.0 mmol), MeOH (50 mL) and H_2O (50 mL) was heated to reflux for 2 hrs and cooled to room temperature. The MeOH was removed *in vacuo* and the resulting aqueous solution

diluted with H_2O (100 mL), cooled to 0° and carefully acidified with conc. HCl. After extracting with EtOAc (5 x 25 mL), these organic extracts were washed with brine (25 mL), dried and the solvent removed *in vacuo*. Crystallization from 95% EtOH gave 2.67 g (74%) of **2** as a white crystalline solid, mp. 225-228° (dec); R_f = 0.57 (SiO_2, 10% MeOH/CH_2Cl_2 + 1% HOAc, UV or I_2); ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 9H), 1.63-1.80 (m, 4H), 3.58-3.78 (m, 4H), 4.43 (s, 2H), 6.99 (d, 1H, J = 8.2Hz), 7.03 (t, 1H, J = 8.6Hz), 7.25 (t, 1H, J = 7.6Hz), 7.48 (d, 1H, J = 7.3Hz); IR: 3430, 3098, 1761, 1710, 1643, 1173 cm^{-1}.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.19; H, 6.77; N, 7.67

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