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A SIMPLE AND EFFICIENT SYNTHESIS OF GYKI 52466 AND GYKI 52895

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ABSTRACT

The synthesis of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466, **1**), the prototype of a series of noncompetitive AMPA receptor antagonists, and its 3,4-dihydroderivative (GYKI 52895, **2**) is described. The title compounds have been prepared starting from safrole through a quite effective procedure.

The discovery of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466, **1**) as the prototype of selective non-competitive AMPA receptor antagonists endowed with anticonvulsant[1] and neuroprotective properties,[2] induced a wide-ranging research activity focused on 2,3-benzodiazepine derivatives.

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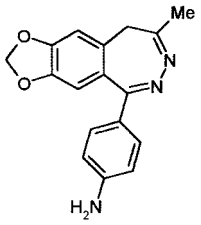
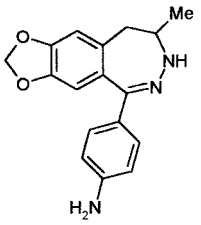
GYKI 52466 has proved to be useful as a tool to investigate the physiological role of the AMPA receptor complex and its involvement in a number of neurodegenerative pathologies. Only few details relating to the preparation of **1** are available[3] and no spectral data were reported in literature.



1: GYKI 52466



2: GYKI 52895

As a part of our ongoing efforts to design new selective noncompetitive AMPA receptor antagonists structurally related to GYKI 52466,[4] we now report a new and simple synthetic approach to compound **1** and to its 3,4-dihydroderivative (GYKI 52895, **2**) which, at variance of **1**, is a selective dopamine uptake inhibitor.[5]

By using natural safrole (**3**) as starting material we have developed an efficient reaction sequence which yielded GYKI 52466 (**1**) in 29% overall yield (Scheme 1).

Alcohol **4** was synthesized in 96% yield from alkene **3** through an oxymercuration–demercuration process. The preparation of methylketone **5** is thus straightforward and was accomplished in 75% yield by a pyridinium chlorochromate (PCC) oxidation of alcohol **4**. Friedel-Craft acylation of **5** with 4-nitrobenzoic acid and subsequent reaction of intermediate diketone **6** with an excess of hydrazine hydrate afforded 4-methyl-7,8-methylenedioxy-1-(4-nitrophenyl)-5*H*-2,3-benzodiazepine **7**, contaminated by minor amounts of 3-methyl-6,7-methylenedioxy-1-(4-nitrophenyl)isoquinoline **8**. A tin(II) chloride reduction of the nitro group of **7** yielded **1** in 80% yield. GYKI 52466 (**1**) was then submitted to a $NaBH_3CN$ reduction to produce GYKI 52895 (**2**) in 83% yield.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba 1106

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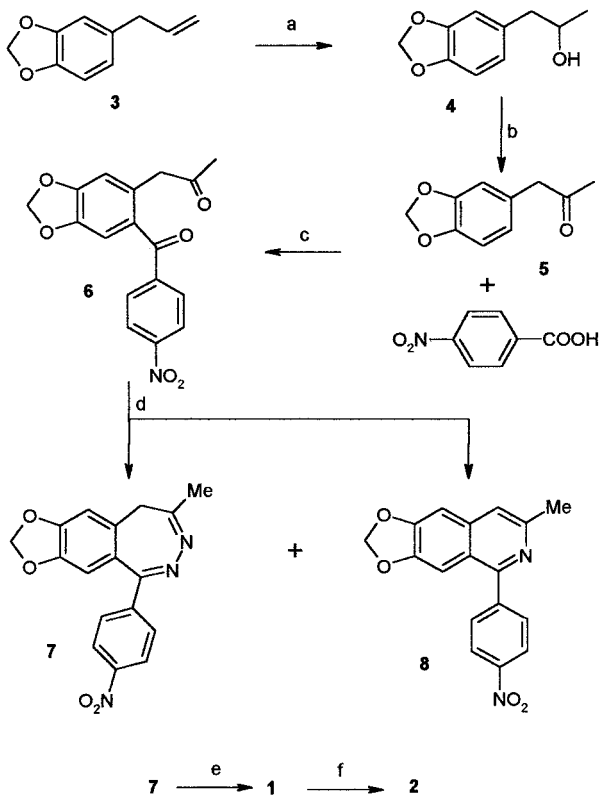

Scheme 1. a) $Hg(OAc)_2/NaBH_4$, THF, rt, 2 h; b) PCC/CH_2Cl_2, rt, 6 h; c) P_2O_5/CH_2Cl_2, rt, 8 h; d) NH_2NH_2, EtOH, rt, 1 h; e) $SnCl_2$, EtOH, 70°C, 1 h; f) $NaBH_3CN$, MeOH/HCl, rt, 1 h.

elemental analyses for C, H, and N, and the results are within ±0.4% of the theoretical values. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ by means of a Varian Gemini-300 spectrometer. Complete ^1H and ^{13}C assignments were made by using direct and long-range heteronuclear chemical shift correlation experiments (HETCOR and LR-HETCOR) carried out by using the standard software package. Chemical shifts are expressed in δ (ppm) relative to TMS and coupling constants (*J*) in Hz. All exchangeable protons were confirmed by addition of D_2O. Mass spectra were recorded under positive electrospray ionization (ESI +) with a ThermoQuest LCQ

mass spectrometer. The relative abundance of the ions is reported in brackets.

1-(3,4-Methylenedioxyphenyl)propan-2-ol (4): Safrole (**3**) (3.1 g, 19.1 mmol) was gradually added to a stirred solution of $Hg(OAc)_2$ (6.25 g, 19.1 mmol) in THF (57 ml)/H_2O (19 ml). After stirring for 1 h at room temperature, the yellow color disappeared. The reaction mixture was alkalinized (3 N NaOH, 20 ml) then a solution of $NaBH_4$ (360 mg, 9.5 mmol) in 3 N NaOH (20 ml) was added dropwise. After 1 h the reaction mixture was saturated with NaCl, the organic layer separated and the aqueous layer was further extracted with EtOAc (4×60 ml). The combined organic extracts were then washed with water (3×25 ml) and the solution dried over anhydrous Na_2SO_4. After evaporation of the solvents under vacuum, alcohol **4** (3.3 g, 96%) was obtained as clear viscous oil. An analytical sample of **4** was obtained by a silica gel column chromatography using cyclohexane/EtOAc (6 : 4) as eluant.

Compound 4: R_f (cyclohexane/EtOAc, 6 : 4) 0.46; ^{1}H NMR: 1.14 (d, 3H, $J = 6.3$ Hz, CH_3), 2.58 (d, 2H, $J = 6.6$ Hz, CH_2), 2.84 (br s, 1H, OH) 3.86 (m, 1H, CH), 5.82 (s, 2H, OCH_2O), 6.57–6.70 (m, 3H, Ar); ^{13}C NMR: 22.22 (CH_3), 44.94 (CH_2), 68.34 (CH), 100.38 (OCH_2O), 107.73 (C-2), 109.31 (C-5), 121.83 (C-6), 132.12 (C-1), 145.56 (C-4), 147.15 (C-3); MS (ESI +): 181 ($M^+ + 1$, 17), 136 (54), 135 (100), 106 (18), 77 (42); Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65, H, 6.71. Found: C, 66.74; H, 6.58.

3,4-Methylenedioxyphenylacetone (5): A mixture of **4** (2.9 g, 16 mmol) and PCC (6.9 g, 32.1 mmol) in dichloromethane (100 ml) was magnetically stirred at room temperature overnight. The slurry was filtered through a Celite pad and the residue washed with dichloromethane (2×60 ml). The clarified solution was washed with water (2×50 ml), dried (Na_2SO_4) and then concentrated at reduced pressure to yield **5** (2.1 g, 75%) as a light brown oil.

Compound 5: R_f (cyclohexane/EtOAc, 6 : 4) 0.56; ^{1}H NMR: 2.14 (s, 3H, CH_3), 3.59 (s, 2H, CH_2), 5.93 (s, 2H, OCH_2O), 6.62–6.77 (m, 3H, Ar); ^{13}C NMR: 28.74 (CH_3), 50.05 (CH_2), 100.71 (OCH_2O), 108.06 (C-2), 109.42 (C-5), 122.17 (C-6), 127.54 (C-1), 146.32 (C-4), 147.53 (C-3); MS (ESI +): 179 ($M^+ + 1$, 37), 135 (100), 122 (61), 102 (50), 91 (80); Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.41, H, 5.66. Found: C, 67.68; H, 5.93.

2-(4-Nitrobenzoyl)-4,5-methylenedioxyphenylacetone (6): To a stirred solution of **5** (1.07 g, 6.0 mmol) in 1,2-dichloroethane (100 ml) was added 4-nitrobenzoic acid (1.3 g, 7.7 mmol) followed by phosphorous pentoxide (8 g, 56.3 mmol). The mixture was stirred at room temperature overnight, then water (60 ml) was cautiously added. The organic layer was separated and sequentially treated with 10% NaOH (60 ml), brine (50 ml) and water (2×50 ml). The organic phase was dried (Na_2SO_4) and the solvent removed

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under reduced pressure to yield crude **6** which was purified by a silica gel column chromatography (eluant: cyclohexane/EtOAc, 6 : 4) to afford pure **6** (1.17 g, 60%) as colorless solid.

Compound 6: R_f (cyclohexane/EtOAc, 6 : 4) 0.49; mp 151–154°C; ^{1}H NMR: 2.25 (s, 3H, CH_3), 4.01 (s, 2H, CH_2), 6.06 (s, 2H, OCH_2O), 6.76 (s, 1H, H-6), 6.81 (s, 1H, H-3), 7.91 (d, 2H, $J = 8.3$ Hz, H-2′,6′), 8.31 (d, 2H, $J = 8.3$ Hz, H-3′,5′); ^{13}C NMR: 29.91 (CH_3), 48.39 (CH_2), 102.11 (OCH_2O), 111.11 (C-6), 112.71 (C-3), 123.47 (C-3′,5′), 129.70 (C-1), 130.82 (C-2′,6′), 131.71 (C-2), 143.66 (C-1′), 146.08 (C-4), 149.79 (C-4′), 150.66 (C-3), 195.0 (C=O), 205.40 ($CH_3C{=}O$); Anal. Calcd. for $C_{17}H_{13}NO_6$: C, 62.39; H, 4.00, N, 4.28. Found: C, 62.58; H, 3.76; H, 4.15.

4-Methyl-7,8-methylenedioxy-1-(4-nitrophenyl)-5*H*-2,3-benzodiazepine (7) and 3-Methyl-6,7-methylenedioxy-1-(4-nitrophenyl)isoquinoline (8): To a solution of **6** (1.095 g, 2.9 mmol) in EtOH (125 ml) was added hydrazine hydrate (2.5 ml, 51.5 mmol) and the resulting mixture was stirred at room temperature for 2 h. Ethanol was removed under vacuum and the residue treated with water (80 ml) and extracted with chloroform (2 × 50 ml). The pooled organic extracts were dried (Na_2SO_4); the solvent was evaporated at reduced pressure to yield a mixture of compounds **7** and **8**. A silica gel column chromatography (eluant: cyclohexane/EtOAc 6 : 4) of the residue gave 535 mg (50%) of **7** and 300 mg (32%) of **8**.

Compound 7: R_f (cyclohexane/EtOAc, 6 : 4) 0.33; mp 200–203°C; ^{1}H NMR: 2.16 (s, 3H, CH_3), 2.90 and 3.29 (dd, 2H, $J = 12.3$ Hz, CH_2), 6.04 (s, 2H, OCH_2O), 6.65 (s, 1H, H-6), 6.77 (s, 1H, H-9), 7.85 (d, 2H, $J = 8.9$ Hz, H-2′,6′), 8.25 (d, 2H, $J = 8.9$ Hz, H-3′,5′); ^{13}C NMR: 22.18 (CH_3), 38.55 (C-5), 101.96 (OCH_2O), 106.51 (C-6), 108.87 (C-9), 122.68 (C-5a), 123.61 (C-3′,5′), 130.29 (C-2′,6′), 134.46 (C-9a), 144.73 (C-1′), 147.14 (C-7), 148.51 (C-4′), 151.17 (C-8), 154.60 (C-4), 156.43 (C-1); Anal. Calcd. for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.0. Found: C, 62.97; H, 4.26; N, 13.15.

Compound 8: R_f (cyclohexane/EtOAc, 6 : 4) 0.56; mp 178–181°C; ^{1}H NMR: 2.69 (s, 3H, CH_3), 6.09 (s, 2H, OCH_2O), 7.08 (s, 1H, H-5), 7.12 (s, 1H, H-8), 7.41 (s, 1H, H-4), 7.82 (d, 2H, $J = 8.9$ Hz, H-2′,6′), 8.38 (d, 2H, $J = 8.9$ Hz, H-3′,5′); ^{13}C NMR: 23.98 (CH_3), 101.68 (OCH_2O), 102.09 (C-5), 102.41 (C-8), 118.95 (C-4), 123.62 (C-3′,5′), 130.71 (C-2′,6′), 121.61 (C-4a), 136.26 (C-8a), 146.46 (C-1′), 147.70 (C-6), 148.29 (C-4′), 150.33 (C-7), 150.83 (C-3), 155.80 (C-1); MS (ESI +): 309 ($M^+ + 1$, 22), 279 (20), 263 (100), 251 (12); Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.41; H, 3.87; N, 9.31.

1-(4-Aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (1): To a solution of **7** (460 mg, 1.42 mmol) in absolute EtOH (80 ml) tin(II) chloride (1.6 g, 6.8 mmol) was added. The mixture was heated at 70°C for 1 h. The solvent was removed *in vacuo* and the residue was treated with a

10% NaOH solution (30 ml), extracted with EtOAc (2 × 30 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by crystallization from EtOH to give 332 mg (80%) of **1**.

Compound 1: R_f ($CHCl_3$/MeOH, 95 : 5) 0.28; mp 235–238°C; ^{1}H NMR: 2.12 (s, 3H, CH_3), 2.99 and 3.20 (dd, 2H, $J = 12.1$ Hz, CH_2), 3.80 (br s, 2H, NH_2), 6.02 (m, 2H, OCH_2O), 6.69 (d, 2H, $J = 8.5$ Hz, H-3′,5′), 6.72 (s, 1H, H-6), 6.80 (s, 1H, H-9), 7.50 (d, 2H, $J = 8.5$ Hz, H-2′,6′); ^{13}C NMR: 22.87 (CH_3), 38.39 (C-5), 101.56 (OCH_2O), 106.0 (C-6), 109.92 (C-9), 114.37 (C-3′,5′), 123.82 (C-5a), 129.06 (C-1′), 130.96 (C-2′,6′), 134.14 (C-9a), 146.56 (C-7), 148.12 (C-4′), 150.28 (C-8), 154.73 (C-4), 157.84 (C-1); Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.83; H, 5.34; N, 4.28.

1-(4-Aminophenyl)-3,4-dihydro-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (2): To a solution of **1** (332 mg, 1.13 mmol) in MeOH (60 ml)/2 N HCl (pH = 3–4) $NaBH_3CN$ (35.1 mg, 5.61 mmol) was added. The mixture was stirred at room temperature for 1 h and, after treatment with 10% KOH (20 ml), was extracted with $CHCl_3$ (2 × 50 ml). The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (eluant: $CHCl_3$/MeOH 95 : 5) to afford 277 mg (83%) of **2**.

Compound 2: R_f ($CHCl_3$/MeOH, 95 : 5) 0.33; mp 116–118°C; ^{1}H NMR: 1.21 (d, 3H, $J = 6.2$ Hz, CH_3), 2.37 (dd, 2H, $J = 4.2$ and 13.8 Hz, H_A-5), 2.81 (dd, 2H, $J = 6.6$ and 13.8 Hz, H_B-5), 3.80 (br s, 2H, NH_2), 4.11 (m, 1H, CH), 5.95 (m, 2H, OCH_2O), 6.63 (d, 2H, $J = 8.7$ Hz, H-3′,5′), 6.61 (s, 1H, H-6), 6.76 (s, 1H, H-9), 7.38 (d, 2H, $J = 8.7$ Hz, H-2′,6′); ^{13}C NMR: 20.85 (CH_3), 38.62 (C-5), 63.43(C-4), 101.16 (OCH_2O), 108.76 (C-6), 109.28 (C-9), 114.41 (C-3′,5′), 128.18 (C-5a), 128.40 (C-1′), 130.04 (C-2′,6′), 134.14 (C-9a), 145.76 (C-7), 147.66 (C-4′), 147.99 (C-8), 163.35 (C-1); Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.95; H, 5.91; H, 14.49.

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