A Short Efficient Synthesis of (S)-4-Amino-5-hexenoic Acid [(S)-Vigabatrin]

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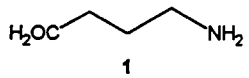
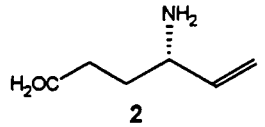
Received September 28, 1992

The brain concentrations of the excitatory L-glutamate and inhibitory γ-aminobutyric acid (GABA, 1) neurotransmitters are regulated primarily by the two pyridoxyl 5′-phosphate dependent enzymes L-glutamic acid decarboxylase (GAD) that catalyzes the conversion of L-glutamate to GABA and GABA-aminotransferase (GABA-T) which degrades GABA to succinic semialdehyde.[1] When the concentration of GABA diminishes below a theshold level in brain, seizures develop.[2] GABA would be an ideal anticonvulsant agent, but peripheral administration of GABA is ineffective since it does not cross the blood-brain-barrier (BBB), presumably due to its low lipophilicity.[3] Alternatively, a more lipophilic compound that is able to cross the BBB and selectively inhibit GABA-T would block the degradation of GABA. GABA levels would be expected to rise, provided inhibition of GAD does not occur, to provide an anticonvulsant effect. There is precedent for this approach since a number of in vitro GABA-T inhibitors elevate whole-brain GABA levels in vivo and exhibit anticonvulsant properties.[4,5]



1
GABA



2
(S)-Vigabatrin

Vigabatrin (γ-vinyl-GABA, 4-amino-5-hexenoic acid, 2), which is a highly selective enzyme-activated inhibitor of GABA-T in mammalian brain,[6] crosses the BBB and is used clinically primarily to control seizures refractory to other anticonvulsant drugs.[7] In connection with a study involving the design and synthesis of a novel chemical delivery system, the pharmacologically active enantiomer (S)-(+)-vigabatrin was required. Methodologies for the synthesis of (S)-2, that are sparse,[8] start with L-glutamic acid which is converted to pyroglutamic acid as a method to protect both the amino and γ-carboxyl groups. The vinyl group was then introduced by pyrolysis of an *N*-oxide[8a] or an ester[8b] moiety, or by a Wittig reaction,[8c,d] respectively. These procedures[8a,b] have certain diadvantages which include a large number of reaction steps, low yields, specialized equipment, and/or nonroutine procedures. Accordingly, we now report a simple high yield procedure for the synthesis of (S)-vigabatrin (2).

L-Glutamic acid (3) was selectively protected as the ω-monoethyl ester 4 using concentrated sulfuric acid in EtOH (Scheme I). Although this selective monoesterification reaction has been carried out previously using hydrogen chloride gas,[9] or timethylsilyl chloride,[10] in our hands it was difficult to achieve selective monoesterification. Since the subsequent reaction to protect the amino group of 4 using methyl chloroformate could be carried out directly in water, it was not necessary to separate the intermediate ω-monoethyl ester 4 and (S)-5-ethyl *N*-(methoxycarbonyl)glutamate (5) was obtained in 93% yield in this one-pot procedure. Reduction of the carboxyl group of N-protected amino acids to the alcohol has been effected using $BH_3{\cdot}SMe_2$ at −15 °C in dry THF[11] or via the $NaBH_4$ reduction of a mixed anhydride.[12–14] Since the latter procedure appeared to be a superior method, the reaction of 5 with *i*-BuOC(O)Cl to form the mixed anhydride and reduction with $NaBH_4$ was used to prepare the alcohol 6. Swern oxidation[15] of the alcohol 6 afforded the aldehyde 7. Since chiral α-amino aldehydes such as 7 may racemize, the subsequent olefination of 7 using $Ph_3P^+Me\ Br^-/TMS_2NNa$ was carried out immediately to give the vinyl analog 8 in 64% yield from the alcohol 6. When *n*-BuLi was used in place of TMS_2NNa, the Wittig reaction was very sluggish. Removal of the *N*-(methoxycarbonyl)amino protective group using TMSI[16] and hydrolysis of the ester group using 3 N HCl afforded the target (S)-(+)-4-amino-5-hexenoic acid (2) (89%) with an optical rotation of +11.4° (lit.[8a] $[\alpha]_D$ = +12.4 ± 0.6° (*c* 0.515, H_2O)). The (S)-acid 2 was obtained from L-glutamate in 38% overall yield. The optical purity of the (S)-acid 2 was determined by conversion to its ethyl ester which was then condensed with Moshers (S)-acid chloride.[17] The ^{19}F NMR spectrum of the diastereomeric amides obtained showed ^{19}F resonances at δ 92.35 and 92.44 (relative to C_6F_6) in a ratio of 95:5, respectively, indicating that the diastereomeric excess of (S)-2 was 90%. The ^{19}F NMR spectrum of the same amides prepared from racemic γ-vinyl-GABA showed two resonances of equal intensity, corresponding to the two stereoisomers at the α-center, which indicates that the two diastereomers were resolved.

In conclusion, an efficient synthesis of (S)-vigabatrin (2) has been developed. Advantages of this methodology include high optical and chemical yields, ease of operation, commercially available L-glutamate, and a short synthetic sequence. In addition, this procedure is applicable to the synthesis of other chiral (S)-GABA analogs, which may also be useful as GABA-T inhibitors, since the vinyl moiety was introduced by the versatile Wittig olefination reaction.

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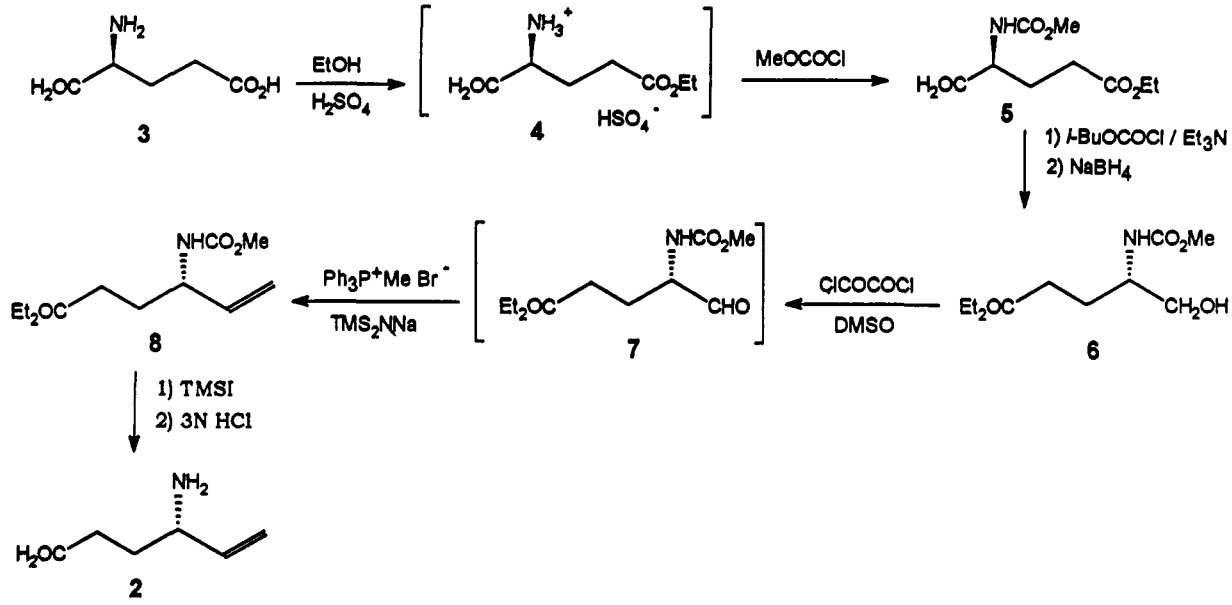
Scheme I



Experimental Section

All moisture-sensitive reactions were carried out under a positive pressure of argon. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl. Dichloromethane and triethylamine were distilled from powdered calcium hydride prior to use. Ethanol was distilled from the corresponding magnesium alkoxide. Most chemical reagents were purchased from the Aldrich Chemical Co. Nuclear magnetic resonance spectra (^{1}H, ^{13}C NMR) were acquired on a Bruker AM-300 spectrometer. Infrared spectra were recorded using a Nicolet 5DX spectrometer, and only selected resonances are reported. Mass spectra were recorded on an AEI MS-50 mass spectrometer. Optical rotations were obtained using a Perkin-Elmer 241 polarimeter at 25 °C. Melting points were determined using a capillary melting point apparatus and are uncorrected.

(*S*)-5-Ethyl *N*-(Methoxycarbonyl)glutamate (5). Concentrated sulfuric acid (5 mL) was added slowly to a stirred suspension of L-glutamic acid (14.7 g, 100 mmol) in dry ethanol (100 mL) and the mixture was refluxed for 2 h (or longer to obtain a clear solution). The solvent was removed in vacuo to give a residue which was dissolved in water (200 mL) and the aqueous solution was basified by addition of potassium carbonate (13.8 g, 0.1 mol) and sodium bicarbonate (16.8 g, 0.2 mmol). To this solution was added methyl chloroformate (11.3 g, 0.12 mol) at rt, and the mixture was refluxed for 2 h. After extraction with ether (3 × 200 mL), the aqueous phase was cooled in an ice bath, the pH was adjusted to 2.5 using concentrated hydrochloric acid, and the resulting solution was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine solution (50 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo gave 21.7 g (93%) of **5** as an oil: IR 3337 (m), 3025 (s), 2984 (s), 1721 (s), 1516 (m), 1450 (w), 1376 (m), 1220 (s), 1064 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 1.9–2.1 (m, 1 H), 2.14–2.3 (m, 1 H), 2.33–2.54 (m, 2 H), 3.63 (s, 3 H), 4.07 (q, J = 7.2 Hz, 2 H), 4.35–4.52 (m, 1 H), 5.76 (br s, 1 H), 9.08 (br s, 1 H); HRMS m/z 233.0893 (M^+ 233.0899 calcd for $C_9H_{15}NO_6$), 215, 188, 174, 169, 156, 142, 128, 114, 102, 84.

(*S*)-Ethyl 4-[*N*-(Methoxycarbonyl)amino]-5-hydroxypentanoate (6). A solution of isobutyl chloroformate (7.5 g, 55 mmol) in dry tetrahydrofuran (10 mL) was added to a solution of the carboxylic acid **5** (11.7 g, 50 mmol) and triethylamine (6.1 g, 60 mmol) in dry THF (40 mL) at −23 °C during 20 min, and the mixture was warmed to 0 °C. The white precipitate of triethylammonium chloride was filtered off and washed with THF (50 mL), and the combined filtrates and the washings were added to a solution of sodium borohydride (3.8 g, 0.1 mol) in water (40 mL) at −10 °C. Rapid evolution of carbon dioxide gas was observed. After the addition was complete, the reaction mixture was stirred at 0 °C for 4 h prior to acidification with hydrochloric acid. The reaction mixture separated into two layers. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the combined ethyl acetate extracts and the tetrahydrofuran layer were washed with saturated brine solution (50 mL) and dried over $MgSO_4$. The residue obtained on evaporation of the solvent was purified by silica gel column chromatography using ethyl acetate:hexane (60:40, v/v) as eluant to give 7.9 g (72%) of the alcohol **6** as an oil: IR 3353 (s), 2951 (s), 1721 (s), 1532 (m), 1450 (w), 1253 (m), 1187 (m), 1073 (m), 917 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 1.7–1.96 (m, 2 H), 2.34 (t, J = 7.2 Hz, 2 H), 3.35 (br s, 1 H), 3.59 (s, 3 H), 3.5–3.75 (m, 3 H), 4.06 (q, J = 7.2 Hz, 2 H), 5.37 (d, J = 8.2 Hz, 1 H); HRMS m/z 220.1188 (M + 1, 220.1185, calcd for $C_9H_{18}NO_5$), 215, 188, 174, 156, 149, 142, 128, 114, 102, 98, 86.

(*S*)-[*N*-(Methoxycarbonyl)amino]-4-(ethoxycarbonyl)butyraldehyde (7). Oxalyl chloride (3 mL, 33 mmol) was dissolved in dry dichloromethane (50 mL), the mixture was cooled to −63 °C, and a solution of dry DMSO (5.6 mL, 66 mmol) in dichloromethane (10 mL) was then added dropwise during 15 min. The alcohol **6** (4.38 g, 20 mmol) in dichloromethane (20 mL) was then added during 10 min, the resulting slightly cloudy solution was stirred for 10 min at −63 °C, and a solution of triethylamine (13.3 g, 132 mmol) in dichloromethane (50 mL) was added dropwise during 15 min. After 15 min, the reaction was quenched by adding water (4 mL) to the rapidly stirred reaction mixture at −63 °C. The resulting slurry was immediately poured into ether (300 mL) and washed with 20% aqueous $KHSO_4$ (2 × 100 mL). The layers were separated and the aqueous layer was back-extracted with ether (2 × 150 mL). The combined organic layers were washed with brine solution (2 × 50 mL), dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo to afford the crude aldehyde **7** as an oil, which was immediately used in the next reaction; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 1.7–2.7 (m, 4 H), 3.64 (s, 3 H), 4.1 (q, J = 7.2 Hz, 2 H), 4.05–4.2 (m, 1 H), 5.9 (br s, 1 H), 9.7 (br s, 1 H).

(*S*)-Ethyl 4-[*N*-(Methoxycarbonyl)amino]-5-hexenoate (8). To a stirred suspension of methyltriphenylphosphonium bromide (10.7 g, 30 mmol) in dry THF (80 mL) at 0 °C was added TMS_2NNa (30 mL of a 1 M solution in THF, 30 mmol) during 30 min. The mixture was stirred for 1 h at 0 °C, and then a solution of the crude aldehyde **7**, obtained in the previous reaction, in THF (20 mL) was added. The reaction was allowed to proceed for 1 h at 0 °C, water (30 mL) was added, and the mixture was washed with brine solution (50 mL), dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo and purification of the product by silica gel column chromatography using ethyl acetate:hexane (15:85, v/v) as eluant gave 2.75 g (64%) of the olefin **8** as an oil: IR 3337 (s), 2984 (s), 1721 (s), 1647 (m), 1532 (s), 1450 (s),

1196 (m), 1089 (m), 925 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 1.7–1.95 (m, 2 H), 2.35 (t, J = 7.4 Hz, 2 H), 3.64 (s, 3 H), 4.1 (q, J = 7.2 Hz, 2 H), 4.05–4.2 (m, 1 H), 4.8 (br s, 1 H), 5.09–5.19 (m, 2 H), 5.67–5.78 (m, 1 H); HRMS m/z 215.1157 (M^+, 215.1157, calcd for $C_{10}H_{17}NO_4$), 188, 183, 170, 156, 141, 127, 114, 99, 95.

(*S*)-4-Amino-5-hexenoic Acid (2). To a stirred solution of the olefin 8 (0.75 g, 3.5 mmol) in dry dichloromethane (10 mL) at 0 °C was added iodotrimethylsilane (0.7 g, 3.5 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 4 h at 0 °C and then 8 h at rt, and then methanol (2 mL) was added. Removal of the solvent in vacuo gave a residue which was dissolved in 3 N HCl (5 mL). The mixture was stirred for 16 h at 50 °C and cooled to rt, and the solvent was removed in vacuo to give an oil. This oil was dissolved in water (2 mL) and the solution was applied to the top of a Dowex 50X2-200 (H^+ form, 100–200 mesh) column. The column was eluted with water until the eluant was neutral. Further elution with 2 N aqueous ammonium hydroxide and removal of the solvent from the eluant in vacuo afforded 0.4 g (89%) of (*S*)-4-amino-5-hexenoic acid (2): mp 162–163 °C; $[\alpha]_D$ = +11.4° (*c* 0.515, H_2O) (lit.[8a] $[\alpha]_D$ = +12.4 ± 0.6° (*c* 0.515, H_2O)); IR 3427 (m), 2935 (s), 1639 (s), 1573 (s), 1524 (s), 1393 (s), 1122 (s), 991 (s) cm^{-1}; ^1H NMR (D_2O) δ 1.58–1.74 (m, 1 H), 1.74–1.92 (m, 1 H), 1.98–2.14 (m, 2 H), 3.68 (m, 1 H), 4.7 (br s, 3 H), 5.19–5.25 (m, 2 H), 5.56–5.68 (m, 1 H); ^{13}C NMR (D_2O) δ 29.4, 33.9, 54.5, 121.6, 133.4, 181.9.

Acknowledgment. We are grateful to the Medical Research Council of Canada (Grant No. MT-4888) for financial support of this research and to the Pharmaceutical Manufacturers of Canada and the Medical Research Council of Canada for a joint fellowship to one of us (Z.W).

Supplementary Material Available: ^1H NMR spectra for compounds 5, 6, 8, and 2 and ^{13}C NMR spectrum for compound 2 (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.