Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXVI, No. 5

An Efficient Synthesis of Carbon-14 Labelled Vigabatrin

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SUMMARY

Vigabatrin-[6-^{14}C] ((*R,S*)-4-amino-5-hexenoic-[6-^{14}C] acid) was synthesized by employing Wittig condensation of 1-(1-butenyl)-2-oxo-5-pyrrolidinecarboxaldehyde with methyl-[^{14}C]-triphenylphosphonium iodide as the key step. The synthetic sequence involved 3 steps and produced the title compound in 70% overall yield with a radiochemical purity of 100%.

Key Words: Vigabatrin-[6-^{14}C], antiepileptic, Wittig Reaction, methyl-[^{14}C]-triphenyl-phosphonium iodide.

INTRODUCTION

GABA (γ-aminobutyric acid) is a major inhibitory neurotransmitter in the mammalian central nervous system. Deficiency of GABA in the brain has been associated with various neurological disorders like epilepsy, schizophrenia, and Parkinson's disease (1). GABA is metabolized by pyridoxal phosphate dependent aminobutyrate-2-oxoglutarate aminotransferase (GABA-T) to succinic semialdehyde and thus leads to decreased levels of GABA in the central nervous system and brain. Vigabatrin which is a highly selective enzyme-activated inhibitor of GABA-T has been introduced into the European market as a successful antiepileptic drug (2). A relatively large amount of carbon-14 labelled vigabatrin was needed for the metabolism and pharmacokinetic studies and this led to development of the alternative synthesis of the title compound.

CCC 0362–4803/95/050425–06

Received 20 July, 1994
Revised 31 October, 1994

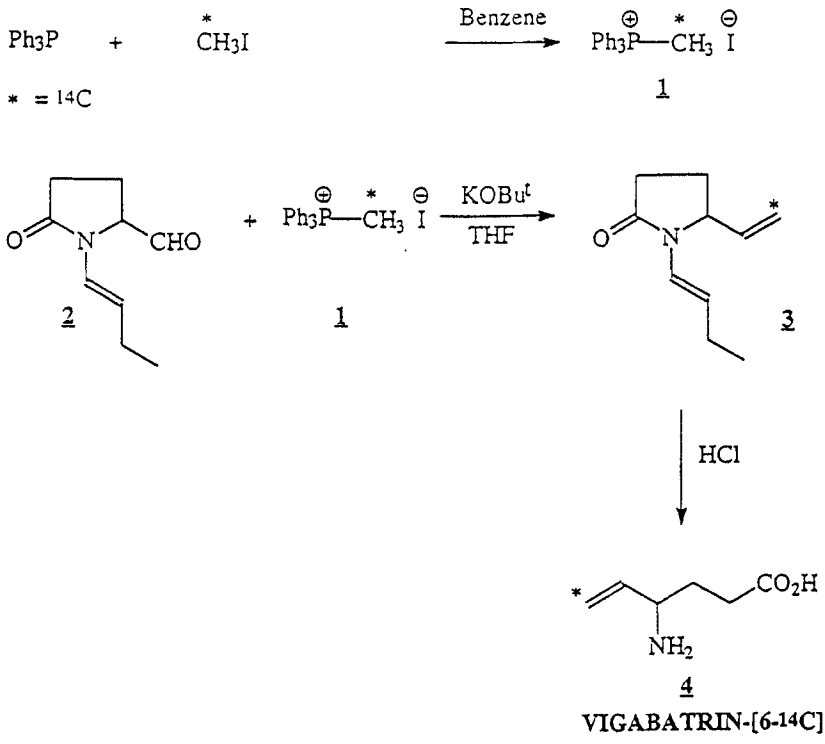
RESULTS AND DISCUSSION

Several syntheses of vigabatrin, involving different methodologies for introduction of the vinyl group, have been reported (3-7). Metcalf introduced the double bond either by reduction of racemic 4-amino-5-hexynoic acid with Na/NH_3, or by hydrogenation of 4-acetamido-5-hexynoic acid methyl ester over Lindlar's catalyst (3). Frieben and Gerhart employed a Cope elimination of the N-oxide to prepare 5-ethenyl-2-pyrrolidinone which was hydrolysed with HCl to produce (*S*)-vigabatrin (4). Gerhart's synthesis has been used to prepare vigabatrin-[6-^{14}C] in 5 steps and 22% overall yield from 5-hydroxymethyl-2-pyrrolidinone tosylate and carbon-14 labelled sodium cyanide (5).

Recently stereoselective syntheses of (*S*)-vigabatrin were reported which employed Wittig reaction for introduction of the vinyl group in the target molecule (6,7). The Wittig approach seemed very attractive for the synthesis of carbon-14 labelled vigabatrin, however, 3 equivalents of methyltriphenylphosphonium bromide were used to react with (*S*)-1-(1-butenyl)-2-oxo-5-pyrrolidinecarboxaldehyde to produce (*S*)-5-ethenyl-2-pyrrolidinone in 77% yield (6). The higher cost of the carbon-14 labelled intermediate and the need to reduce radioactive waste discouraged the use of excess ylide. It was found, however, that one equivalent of methyltriphenylphosphonium iodide was sufficient to provide the Wittig product in a high yield.

Methyl-[^{14}C]-triphenylphosphonium iodide (**1**) was prepared in 100% yield by treating methyl-[^{14}C] iodide with triphenylphosphine (Scheme). The ylide, generated from **1** by deprotonation with potassium *tert*-butoxide, was treated with 1-(1-butenyl)-2-oxo-5-pyrrolidinecarboxaldehyde (6) (**2**) to provide 1-(1-butenyl)-5-ethenyl-[1'-^{14}C]-2-pyrrolidinone (**3**) in quantitative yield after purification by flash chromatography. Compound **3** was hydrolysed with 6M HCl and the product was purified by ion exchange chromatography to give vigabatrin-[6-^{14}C] (**4**) in 70% yield with a specific activity of 19.8 mCi/mmol (153.2 μCi/mg) and radiochemical purity of 100%. The highly efficient 3 step synthesis of carbon-14 labelled vigabatrin described herein produced the title compound in an overall yield of 70%. This synthesis is a big improvement over the previously reported synthesis (4) which employed 5 steps to produce 22% overall yield of carbon-14 labelled vigabatrin.

SCHEME



VIGABATRIN-[6-^{14}C]

EXPERIMENTAL

All chemicals and reagents were used as received from the suppliers. Methyl-[^{14}C] iodide was purchased from Chemsyn Science Laboratories, Lenexa, Kansas. Thin layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} (0.25 mm) plates. Visualization of the spots on TLC plates was accomplished by I_2 or UV light (254 nm). Amino acid spots on TLC plates were visualized by a 3% solution of ninhydrin in abs. ethanol. Flash chromatography was performed by using silica gel (230-400 mesh) from EM Science, Gibbstown, New Jersey. TLC plates used in the analysis of radioactive samples were scanned on a Digital Diagnostics Vanguard Autoscanner using 1.3% isobutane in helium.

Analysis by HPLC was performed on a Beckman 114M Solvent Delivery System, Beckman 421 Controller, Waters WISP 712B Autosampler, Spectroflow 757 Variable

Wavelength Spectrophotometer and a Beta-RAM Radioactive Flow-Through Monitor System, Model 2 (IN/US Systems Inc.). Radiochemical purity was determined by HPLC using a Spherisorb C_6, 5 μm, 250 x 4.6 mm i.d. HPLC column in series with a Partisil SCX, 10 μm, 250 x 4.6 mm i.d. HPLC column, eluting with a 2.5/97.5 CH_3CN/H_2O mobile phase containing 1.0 g NaH_2PO_4 H_2O and 0.67 g of H_3PO_4 (85%) per 1000 mL, a flow rate of 1.0 mL/min. The specific activity was determined on a Packard Minaxi Tri-Carb Liquid Scintillation Counter. A Varian Gemini 300 NMR spectrometer operating at 300 MHz was used for ^1H NMR.

Methyl-[^{14}C]-triphenylphosphonium iodide (1)

Methyl-[^{14}C] iodide (100 mCi, 1.75 mmol) in C_6H_6 (2 mL) was diluted with unlabelled methyl iodide (0.461 g, 3.25 mmol) to adjust the specific activity to 20 mCi/mmol. The diluted methyl-[^{14}C] iodide (100 mCi, 5 mmol) was added to a solution of triphenylphosphine (1.31 g, 5 mmol) in C_6H_6 (3 mL). The reaction flask was sealed and the mixture was stirred at 22 °C for 37 h. The mixture was filtered and the white solid washed with benzene (20 mL) and dried under vacuum (0.1 mm Hg, 22 °C) to provide 2.165 g (100% yield) of methyl-[^{14}C]-triphenylphosphonium iodide (**1**).

1-(1-Butenyl)-5-ethenyl-[1'-^{14}C]-2-pyrrolidinone (3)

Methyl-[^{14}C]-triphenylphosphonium iodide, (**1**) (2.165 g, 5 mmol) was stirred with THF (10 mL) and potassium *tert*-butoxide (5 mL, 5 mmol, 1M in THF) was added dropwise in 5 min under nitrogen. The yellow colored ylide solution was stirred for 25 min at 22 °C and 1-(1-butenyl)-2-oxo-5-pyrrolidinecarboxaldehyde (6), (**2**, 0.898 g, 5.37 mmol) in THF (13 mL) was added over 15 min. After stirring the reaction mixture for 16 h at 22 °C, ether (40 mL) and water (10 mL) were added, and the organic layer was separated. The aqueous layer was extracted with ether (120 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure (20 mm Hg, 22 °C). The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 10/0.3) to provide 0.853 g (quantitative yield) of **3** as an oil. The vinylpyrrolidinone **3** comigrated on TLC (silica gel, CH_2Cl_2/MeOH, 10/0.3; $R_f = 0.51$) with the standard sample of unlabelled **3**.

Vigabatrin-[6-^{14}C](4-Amino-5-hexenoic-[6-^{14}C] acid), (4)

A mixture of vinylpyrrolidinone **3** (0.826 g, 5 mmol) and 10% HCl (40 mL) was heated at 95 °C for 5 h. The aqueous layer was separated and the oily layer was extracted with water (10 mL). The combined aqueous extracts were concentrated under reduced pressure (0.1 mm Hg, 40 °C). The crude product was dissolved in water (5 mL) and purified by an ion exchange chromatography on a Dowex 50X2-200 (100-200 mesh, H^+) resin (100 g). The ion exchange column was eluted with water till the effluent was neutral, then the product was eluted with 2M NH_4OH. To remove the last traces of ammonia, the solid product was dissolved in 2-propanol (10 mL) and water (10 mL) and the solvent was removed under reduced pressure (0.1 mm Hg, 40 °C) . The residue was dissolved in water (10 mL), the mixture filtered and concentrated to 1 mL with a nitrogen stream and by heating in a water bath at 60 °C. Acetone (15 mL) was added to the solution, the mixture filtered and the solid washed consecutively with an acetone-water mixture (20/1, 10 mL), abs. ethanol (3 mL) and 2-propanol (3 mL).The solid was dissolved in hot water (2 mL) and acetone (15 mL) was added to induce crystallization. Crystallized solid was washed successively with acetone (15 mL), abs. ethanol (3 mL) and 2-propanol (3 mL), and was dried under vacuum (0.1 mm Hg, 22 °C) to provide 0.458 g (70.16 mCi, 70% yield) of **4** as a white solid. Amino acid **4** comigrated on TLC (silica gel, n-BuOH/AcOH/H_2O, 8/2/3; R_f = 0.48) and HPLC (retention time, 17.5 min) with the standard sample of unlabelled **4**. The ^{1}H NMR (DMSO-d_6) of **4** displayed signals at δ 1.79-2.14 (m, 2H, H-3), 2.26 (m, 2H, H-2), 3.78 (m, 1H, H-4), 5.43 (m, 2H, H-6) and 5.70-5.93 (m, 1H, H-5).

ACKNOWLEDGEMENT

The author wishes to thank N.W. Brake, R.J. Barbuch, and E.W. Huber of Analytical and Structural Sciences, Cincinnati, for the analyses by HPLC and ^{1}H NMR respectively.

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