Synthesis of Carbon-14 Labeled 1-(4-Methoxybenzoyl)-5-oxo-2-pyrrolidinepropanoic acid (CI-933)

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SUMMARY

1-(4-Methoxybenzoyl)-5-oxo-2-pyrrolidinepropanoic acid (CI-933) (17), a new cognition activating agent, was radiolabeled with carbon-14. The synthesis was accomplished using bromo[1-14C]acetic acid as the starting material. A facile one-pot synthesis of an α,β-unsaturated ester 10 from an alcohol 2 and a Wittig reagent 15 in the presence of Dess-Martin periodinane was developed.

Key Words: CI-933, ^{14}C, 1-(4-methoxybenzoyl)-5-oxo-2-pyrrolidinepropanoic acid, cognition activator

A number of pyrrolidine derivatives have shown good cognition activity in animals.[1-4] Some of these such as CI-911[5,6] and CI-879[7] have been radiolabeled for metabolic and binding studies. One of the recent candidates in this series which has been shown to exhibit good amnesia-reversal activity is 1-(4-methoxybenzoyl)-5-oxo-2-pyrrolidinepropanoic acid (CI-933).[3,4] The carbon-14 labeled compound 17 was synthesized as reported herein for metabolic and pharmacokinetic studies.

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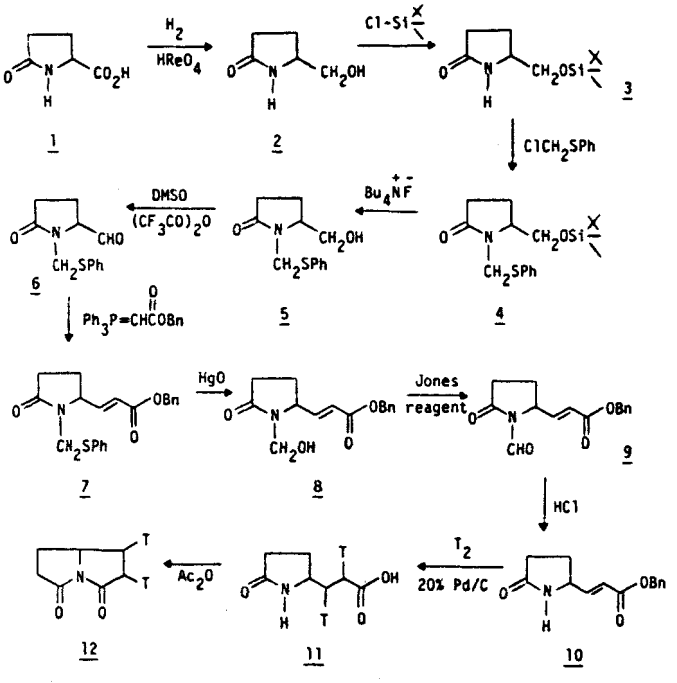
RESULTS AND DISCUSSION

The original synthesis of CI-933 involved the ring opening of CI-911 (dihydro-1H-pyrrolizine-3,5(2H,6H)-dione) to 5-oxo-2-pyrrolidinepropanoic acid followed by N-acylation of the pyrrolidine ring nitrogen.[3] Since our supply of ^{14}C-labeled CI-911 was depleted, the synthesis of labeled CI-933 from labeled nitromethane using the original CI-911 synthesis would be too lengthy and give poor overall yield. Furthermore, a large amount of expensive labeled nitromethane would have to be used. Consequently a new synthetic route was developed. The synthesis of tritium-labeled CI-911 was reported previously (Scheme 1).[5] However, this eleven-step sequence, involving oxidation, Wittig reaction, and many protection/deprotection steps, was very tedious. It was reasoned that if much milder conditions could be found, there would be no need for the protection and deprotection steps, hence the sequence could be considerably shortened. Several oxidation reagents and conditions, such as PDC, PCC, Swern reagent, and Dess-Martin periodinane, were examined for conversion of the unprotected 5-(hydroxymethyl)-2-pyrrolidinone (2) to the corresponding aldehyde, but no desired product was isolated.

Scheme 1



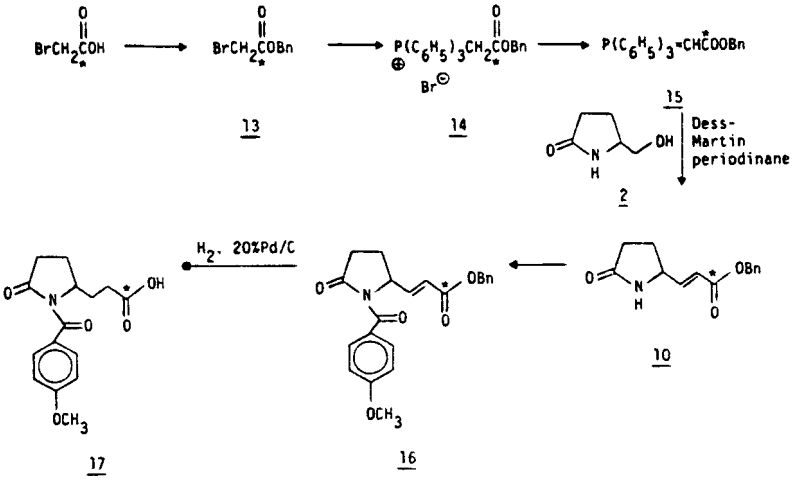
Suprisingly, when ethyl (triphenylphosphoranylidene) acetate was mixed with 5-(hydroxymethyl)-2-pyrrolidinone (2) in CH_2Cl_2 followed by addition of the Dess-Martin periodinane,[8] the corresponding α,β-unsaturated ester was isolated in a 20% yield. Use of the phenylmethyl ester instead of the ethyl ester increased the yield of the unsaturated ester 10 to 78%. Obviously the alcohol 2 was oxidized by periodinane to the corresponding aldehyde in situ, which then immediately underwent a Wittig reaction with the phosphorus ylide. The same conversion (2 to 10) in the original tritium labeled synthesis of CI-911 precursor (Scheme 1) required eight steps in an overall yield of 20%. NMR analysis showed that the Wittig reaction gave the trans-unsaturated ester exclusively in agreement with the previous report.[9]

Besides providing a much better yield, the use of the phenylmethyl ester also eliminated the need for subsequent hydrolytic cleavage, since it undergoes simultaneous hydrogenolysis during the hydrogenation step required for the conversion of 16 to the target compound 17 (Scheme 2).

The facile one pot reaction of the combined oxidation and Wittig reaction could have many synthetic applications for the synthesis of α,β-unsaturated ester from an alcohol, especially when the intermediate aldehyde is either unstable or too reactive.

Compound 10 was acylated with p-methoxybenzoyl chloride at 95°C for 40 hours to give the N-acylated product 16 in a 91% yield. The α,β-unsaturated ester 16 was hydrogenated in the presence of 20% Pd/C to give the final target compound 17. The hydrogenation was done twice since it did not work the first time, probably because of the presence of catalyst poison which inhibited the catalytic activity. Once the mixture was filtered and fresh catalyst was added, the hydrogenation proceeded smoothly. TLC showed that 99% of the radioactivity of the crude material was associated with the product spot. However, repeated recrystallizations were required to remove uncharacterized chemical impurities, resulting in low yield (37%) of the final product obtained in high radiochemical and chemical purity.

Scheme 2



EXPERIMENTAL

^{1}H-NMR spectra were determined on a Varian XL-200 (200 mHz) spectrometer. Chemical shifts were reported in δ (ppm) downfield from tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Liquid scintillation counting was performed with a Packard Tri-Carb 4530 liquid scintillation counter using Beckman Ready-Solv MP scintillation cocktail. Microanalyses were performed in-house by the Physical and Analytical Section of Warner-Lambert/Parke-Davis.

Thin layer chromatography (TLC) was performed on Kodak chromatogram slilica gel sheets or Whatman reversed phase KC18F plates. Radiochemical purity determinations using TLC plates were performed on a Berthold LB2832 automatic TLC linear analyzer. Column chromatography was carried out on Merck Kieselgel 60 (40-63 nm). High pressure liquid chromatography (HPLC) was performed using a Spectra Physics SP8700 solvent delivery system, Kratos Spectroflow 773 variable wavelength UV detector, Hewlett-Packard 3390 integrator, and United Technologies Packard Tri-Carb RAM 7500 radioactivity monitor.

Unlabeled 5-(hydroxymethyl)-2-pyrrolidinone (2), phenylmethyl 3-(5-oxo-2-pyrrolidinyl)-2-propenoate[5] (10), and CI-933 were synthesized in-house. Dess-Martin periodinane is commercially available from Aldrich Chemical Company but was synthesized in-house according to the procedures of Dess and Martin.[8] Bromo[1-14C]acetic acid was purchased from Pathfinder Laboratories, St. Louis, MO.

Phenylmethyl bromo[1-^{14}C]acetate (13)

A mixture of bromo[1-14C]acetic acid (1.10 g; 200 mCi at 25.2 mCi/mmol), phenylmethyl alcohol (0.80 g, 7.95 mmol), 1,3-dicyclohexylcarbodiimide (1.65 g, 8.00 mmol), 4-pyrrolidinepyridine (0.10 g, 0.67 mmol) in CH_2Cl_2 (35 mL) was stirred for two hours at room temperature. The mixture was chromatographed on a silica gel column with CH_2Cl_2. Removal of the solvent gave the ester 13 as a colorless liquid (1.60 g, 88% chemical yield, 100% radiochemically pure).

Phenylmethyl (triphenylphosphoranylidene)[1-^{14}C]acetate (15)

A mixture of the bromo ester 13 (1.60 g, 6.98 mmol) and triphenylphosphine (1.85 g, 7.05 mmol) in toluene (20 mL) was stirred at room temperature for four days, and heated to 70°C for 30 minutes. n-Heptane (80 mL) was added to the cooled mixture. The precipitate was filtered, washed with n-heptane to give the phosphonium bromide 14 as a white solid (3.16 g, 92%).

The phosphonium bromide 14 was partitioned between 0.28 N NaOH (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with additional CH_2Cl_2 (3 x 30 mL). The CH_2Cl_2 layers were combined, dried ($MgSO_4$), filtered, and concentrated to give 15 (2.68 g, 100%).

Phenylmethyl 3-(5-oxo-2-pyrrolidinyl)-[1-^{14}C]-2-trans-propenoate (10)

To a solution of 15 (2.68 g, 6.53 mmol) and 5-(hydroxymethyl)-2-pyrrolidinone (2) (0.93 g, 8.03 mmol) in CH_2Cl_2 (50 mL) at 0°C was added Dess-Martin periodinane (3.82 g, 9.00 mmol) in one portion. The mixture was allowed to warm up to room temperature and stirred overnight. The mixture was

chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc/Et_2O (4:2:1) followed by EtOAc gave an oil 10 (1.23 g, 78%, 99% radiochemically pure).

Phenylmethyl 3-[1-(4-methoxybenzoyl)-5-oxo-2-pyrrolidinyl]-[1-^{14}C]-2-trans-propenoate (16)

To the α,β-unsaturated ester 10 (0.81 g, 3.3 mmol) in toluene (5 mL) was added 4-methoxybenzoyl chloride (0.62 g, 3.6 mmol) in toluene (10 mL). Triethylamine (0.37 g, 3.6 mmol) in toluene (12 mL) was added dropwise to the solution in a three-hour period at 90°C under N_2, and the solution was stirred at 95°C for 40 hours. The solution was cooled and poured into a silica gel column. Eluting with hexane and CH_2Cl_2 followed by concentration gave 16 as an oil (1.14 g, 91%).

1-(4-Methoxybenzoyl)-5-oxo-2-pyrrolidine[1-^{14}C]propanoic acid; CI-933 (17)

The phenylmethyl ester 16 (1.14 g, 3.00 mmol) was hydrogenated in THF (30 mL) and MeOH (10 mL) overnight in the presence of 20% Pd/C at an initial pressure of 51 psi. The mixture was filtered through a bed of Celite and concentrated in vacuo. The residue was redissolved in THF (30 mL) and MeOH (10 mL), and the hydrogenation process was repeated. After filtration and concentration in vacuo, the oily residue was mixed with 200 mg of unlabeled carrier and recrystallized from Et_2O/CH_3CN. The resulting solid was recrystallized again with CH_3CN/hexane once and CH_3CN/Et_2O twice to give 439 mg (25.33 mCi, 37% chemical yield, overall radiochemical yield 12.7%) of 17 as a white solid, mp 128.0-129.5°C; specific activity 16.81 mCi/mmol; ^{1}H-NMR (200 mHz, $CDCl_3$) δ 1.8-2.0 (m, 2H); 2.2-2.7 (m, 6H); 3.87 (s, 3H); 4.5-4.6 (m, 1H); 6.92 (d, 2H); 7.67 (d, 2H); IR (KBr) 1739, 1699, 1664, 1603 cm^{-1}. TLC: RCP>99%, (a) SiO_2, 1.3% HOAc in EtOAc, R_f = 0.18; (b) SiO_2, EtOAc/MeOH (2:1), R_f = 0.28; (c) Whatman KC18F, 60% MeOH, R_f = 0.80; HPLC: Alltech C-18 column, 10 μ, 4.6 mm x 25 cm, 40% CH_3CN, 60% 0.05M $PO_4^{=}$(pH=3), flow rate 1 mL/min, UV 215 nm, R_t = 5.18 min, RCP>99%; Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.84; H, 5.89; N, 4.81; Found: C, 61.57; H, 5.90; N, 4.93.

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