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SYNTHESIS OF ^{14}C-LABELED S-(-)-1-PHENYLETHYLAMINE AND ITS APPLICATION TO THE SYNTHESIS OF [^{14}C] CI-1021, A POTENTIAL ANTIEMETIC AGENT(1)

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SUMMARY

S-(-)-1-[U-ring-^{14}C]phenylethylamine **3** was synthesized through the enantioselective borane reduction of E-[U-ring-^{14}C]acetophenone oxime methyl ether derived from [U-ring-^{14}C]acetophenone. The overall radiochemical yield was 66.7%. The enantiomeric excess (ee) was 96.60%. Coupling the labeled amine **3** with (R)-N-[(benzo[b]furan-2-ylmethoxy)-carbonyl-2-methyltryptophan **4** provided [R-(R*, S*)]{1-(1H-indole-3-ylmethyl)-1-methyl-2-oxo-2-[(1-[U-ring-^{14}C]phenylethyl) amino]ethyl} carbamic acid benzo[b]furan-2-ylmethyl ester (CI-1021), a potential antiemetic agent.

Keywords: S-(-)-1-[U-ring-^{14}C]phenylethylamine, enantioselective borane reduction, [^{14}C] CI-1021, antiemetic agent

INTRODUCTION

[R-(R*, S*)]{1-(1H-Indole-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenyl-ethyl)amino]ethyl} carbamic acid benzo[b]furan-2-ylmethyl ester (CI-1021,

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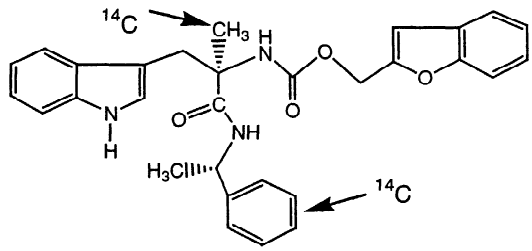

Fig. 1 CI-1021

PD-0154075) is a selective, specific, and high affinity NK_1 receptor antagonist being developed as a potential antiemetic drug (2). Further pharmacokinetic and metabolic studies require synthesis of the ^{14}C-labeled forms of the compound. CI-1021 was ^{14}C-labeled previously by using the synthetically more difficulty [^{14}C]α-methyltryptophan route (6 steps) (2). Since we have seen no evidence of the *in vivo* hydrolysis of S-(-)-1-phenylethylamine from the molecule, we decided to radiolabel S-(-)-1-phenylethylamine, which is an important moiety in drug design and relatively easy to synthesize. In this paper we wish to report an efficient, enantioselective synthesis of (S)-(-)-1- [U-ring-^{14}C] phenylethylamine, and its applications to the preparation of ^{14}C labeled CI-1021, a potential antiemetic agent.

RESULTS AND DISCUSSION

Isotopically labeled chiral phenylethylamine has not been reported in the literature. However, several asymmetric syntheses of unlabeled S-(-)-1-phenylethylamine were reported (3a-g). Among the reported methods, Didier's enantioselective borane reduction of the E-oxime methyl ether of acetophenone in the presence of a chiral ligand is straightforward, and provides chiral phenylethylamine in higher enantioselectivity (up to 94.5% ee based on HPLC analysis of 3,5-dinitrobenzamides) (3e). Using the same reaction conditions (see table 1, entry 1) as described by Didier, we were able to obtain 93.0% ee of the isolated amine based on chiral HPLC analysis (4). According to previous studies on the asymmetric borane reduction reaction, the improvement of enantioselectivity of the reaction could be

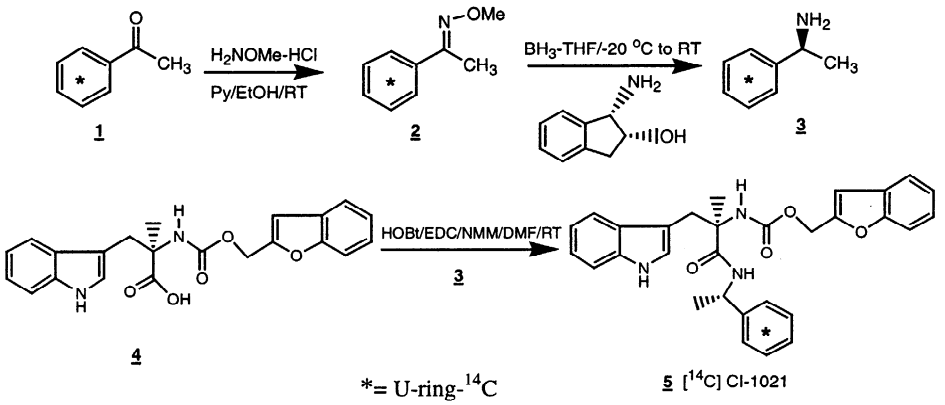

Fig. 2

Table 1. Enantioselective reduction reaction of E-acetophoneneoxime methyl ether (2)

Entry	Equiv. 2 : Ligand : Borane	Reaction temperature (°C)	% ee	Isolated Yield
1	1 : 1.25 : 2.8	0 to 22	93.0	55.5
2	1 : 1.6 : 2.8	0 to 22	93.9	57.0
3	1 : 1.6 : 3.2	-20 to 22	95.0	68.0
4	1 : 2.2 : 3.2	-20 to 22	96.6	71.0

achieved by increasing the amount of chiral ligand and lowering the reaction temperature (5). Table 1 shown that by decreasing the reaction temperature from 0° to –20°C and increasing molar ratio of ligand from 1.25 to 2.2, we were able to achieve an enantiomeric excess (ee) of 96.60 % and an isolated yield of 71% for both labeled and unlabeled S-(-)-1-phenylethylamine. The ligand, 1S, 2R-1-amino-indan-2-ol, was recovered in 90% yield and could be reused. During the work-up, the ligand precipitated out from the ether solution as nice crystals. The separation of the product, S-(-)-1-phenylethylamine, from a small amount of the ligand was carried out by flash column chromatography. However, in larger scale preparations the separation can be achieved by simple distillation.

E-Acetophenone oxime methyl ether **2** was prepared as the major product in 88% yield by the treatment of [U-ring-^{14}C]acetophenone **1** with O-methyl hydroxylamine hydrochloride in pyridine and ethanol (6). Addition of a small amount of $MgSO_4$ has improved the yield from 88% to 94%. The crude product from enantioselective reduction of the ether **2** has a radiochemical purity of 96.7% by TLC , and was purified by flash chromatography to get 99.1% radiochemical purity. The final Coupling reaction between S-(-)-1-[U-ring-^{14}C] phenylethylamine **3** and chiral acid **4** was performed with two kinds of coupling reagents, N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU)/diiso-propylethylamine (7) and 1-hydroxybenzotriazole hydrate (HOBt)/1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)/ N-methylmorpholine (NMM) (2). The latter coupling reagent afforded a higher yield (74% vs. 61%) in this case.

EXPERIMENTAL

All reactions were carried out under an atmosphere of nitrogen unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz or 400 MHz. Radiochemical purity of all labeled compounds was determined on silica gel plates by TLC radiochromatogram with Bioscan 200 imaging scanner. [U-ring-^{14}C]Acetophenone was purchased from Amersham Co., and diluted to required activity. Chiral acid **4** was provided by Preps Laboratory of Chemical Development, Parke-Davis Pharmaceutical Research. HPLC analysis of S-(-)-1-[U-ring-^{14}C]phenylethylamine and final product were performed on a Waters Associates 600E solvent delivery system with in line PDA 996 photodiode array detector and an IN/US β-RAM radioactivity flow detector. Purification was done by flash column chromatography on Biotage Flash 40 system.

Anti-[U-ring-14C]Acetophenone oxime methyl ether 2

To a suspension of [U-ring-^{14}C]acetophenone (600 mg, 5.0 mmol, 0.5 mCi/mg), pyridine (482 mg, 6.1 mmol), $MgSO_4$ (400 mg) and dry ethanol (12 mL) was added O-methylhydroxylamine hydrochloride (507 mg, 6.0

mmol). The mixture was stirred at room temperature for 20 h, filtered to remove the solid, and the filtrate was concentrated to dryness. To the colorless residue was added ether (30 mL) and water (15 mL). The ether layer was washed with brine, dried with $MgSO_4$ and concentrated. A flash column chromatography purification of crude material (Biotage 40M, eluent: petroleum ether/ether 40:1 v/v) afforded 700 mg (94%) of anti-[U-ring-^{14}C]acetophenone oxime methyl ether **2** as a colorless liquid. (TLC RCP >99%, R_f = 0.42, silica gel, petroleum ether/ether 30:1 v/v)

S-(-)-1-[U-ring-^{14}C]Phenylethylamine 3

To a suspension of 1S, 2R-1-aminoindan-2-ol (1.54 g, 10.32 mmol) in THF (15 mL, freshly distilled) was added BH_3-THF (1M, 15.0 mL, 15 mmol) at –20 °C. The resulting mixture was stirred for 7 h to form a homogeneous solution. To this cold solution was then added a solution of E-[U-ring-^{14}C]acetophenone oxime methyl ether **2** (0.70 g, 4.7 mmol) in dry THF (6 ml). The mixture was stirred at –20 °C for 15 h and then at room temperature for 16 h. After complete consumption of oxime ether **2**, additional BH_3-THF (1M, 15 mL) was added and the mixture was heated at 70 °C for 4 h. The reaction mixture was cooled to –10 °C, and then 2N HCl (15 mL) solution was added to acidify the mixture. The acidic solution was evaporated to remove THF in vacuum, and then extracted with ether (2 x 15 mL). The aqueous layer was cooled to 5 °C, the pH was adjusted to 9 with concentrated NH_4OH, and it was extracted with ether (4 x 15 mL). The combined ether layers were dried over $MgSO_4$, and concentrated. After cold ether (20 mL) was added to the residue, crystals (ligand) formed immediately and were filtered off. The mother liquor containing product and a small amount of ligand was evaporated and purified by flash column chromatography (Biotage 40M, eluent: $CHCl_3$/2 M NH_3 in MeOH, 30:1 v/v). [U-ring-^{14}C] S-(-)-1-phenylethylamine **3** was obtained as a colorless liquid (400.4 mg, 71%, TLC: RCP > 98%, R_f = 0.22, silica gel, $CHCl_3$/2 M NH_3 in MeOH, 25:1 v/v).

[R-(R*, S*)]{1-(1H-Indole-3-ylmethyl)-1-methyl-2-oxo-2-[(1-[U-ring-^{14}C]phenylethyl) amino]ethyl} carbamic acid benzo[b]furan-2-ylmethyl ester 5 (CI 1021)

A suspension of (R)-N-[(benzo[b]furan-2-yl-methoxy)carbonyl-2-methyl tryptophan 4 (450 mg, 1.15 mmol), 1-hydroxybenzotriazole hydrate (HOBt, 190 mg, 1.41 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 270 mg, 1.41 mmol) and N-methylmorpholine (NMM, 285 mg, 2.82 mmol) in dry DMF (2 mL) was stirred for 15 min. To this yellowish solution was added a solution of S-(-)-1-[U-ring-^{14}C]phenyl-ethylamine in dry DMF (1.5 mL). The resulting mixture was stirred at room temperature for 30 h, and then evaporated in vacuum. To the residue was added water (10 mL) and ethyl acetate (30 mL). The organic layer was washed with brine (10 mL), 5% citric acid (3 x 10 mL), 10% K_2CO_3 (3 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by flash column chromatography (Biotage 40M, eluent: CH_2Cl_2/Acetone 25:1) to provide 427 mg of [^{14}C] CI-1021 5 as a white powder (74%). The product was further purified by recrystallization from CH_2Cl_2 (5 ml) and hexane (8 ml) to give analytically pure product 5 (TLC: RCP > 99%, R_f = 0.52, silica gel, CH_2Cl_2/Acetone 20:1). ^{1}H and ^{13}C NMR ($CDCl_3$) spectra agreed with those of authentic material, and HPLC retention time matched that of authentic material (Column: Waters Symmetry C18, 5µm, 43.9x150 mm. Mobile Phase: 0.05M $NH_4H_2PO_4$ pH 3.5 w/H_3PO_4 : MeCN 42:58; Flow Rate: 1.0 mL/min; UV Detection: 220 nm; Retention Time: 7.71 minutes); 98.55% radiochemical purity; 99.5% chemical purity. Specific Activity: 98.2 µCi/mg, 48.7 mCi/mmol (based on MW of 495.6).

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