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AN EFFICIENT SYNTHESIS OF [ring-^{14}C]-L-TYROSINE FROM [U-^{14}C]-PHENOL

John T. Kendall

Wyeth-Ayerst Research

401 North Middletown Road, Pearl River, NY 10965

Summary

The title compound was prepared in good overall yield and high enantiopurity *via* a five step route beginning with [U-^{14}C]-phenol, **4**. Benzyl ether **5** was prepared from **4** under standard conditions and underwent selective iodination at the 4-position in the presence of iodine and mercuric oxide. Palladium catalysed cross coupling of the resulting aryl iodide **6** and the organozinc intermediate derived from N-*tert*-butoxycarbonyl-3-iodo-alanine methyl ester, **7**, proceeded smoothly to give **8**. Debenzylation and acid hydrolysis afforded the deprotected amino acid as the hydrochloride salt. Purification (flash chromatography) was necessary in only two of the five steps in the synthesis.

Key Words: [U-^{14}C]-phenol, L-tyrosine, carbon-14, iodination, palladium

Introduction

A quick and economical synthesis of 100-200 mCi of [ring-^{14}C]-L-tyrosine, **1**, in the specific activity range 20-30 mCi/mmol was needed for a multistep radiosynthesis. A review of the literature revealed two reports

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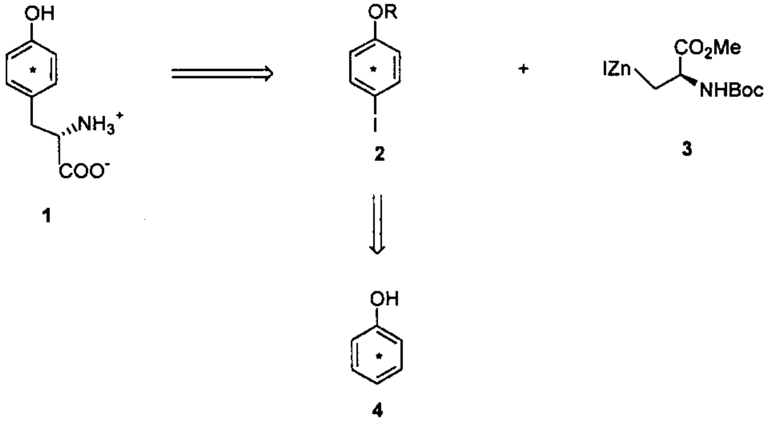
describing the direct synthesis of ^{13}C and ^{17}O enriched *L*-tyrosine derivatives *via* microorganism (*Erwina Herbicola*) mediated coupling of the C and/or O labelled phenols and *L*-serine[1,2]. More recent work by Jackson and coworkers[3] (unlabelled precedents) showed that **1** could also be assembled in an expedient manner by palladium catalyzed cross coupling of subunits **2** and **3**, followed by removal of the protecting groups (Scheme 1). The strategy was appealing in that **2** should be easily obtained from **4**, and the source of the stereogenic center in **1**, is derived from a readily accessible member of the chiral pool, thus eliminating the need for asymmetric synthesis.

SCHEME 1

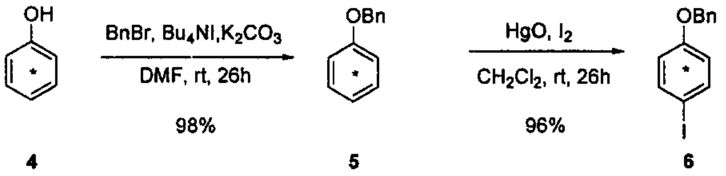


Results and Discussion

Sodium iodide in conjuction with either Chloramine T[4] or commercial bleach[5] can be used to iodinate phenol directly. However, treatment of phenol with these reagent systems is known to produce multicomponent mixtures (2-iodo and polyiodinated products accompany the desired *para* isomer)[5]. Similar results were obtained in this laboratory with both phenol and its TBS ether. Orito and coworkers recently reported that anisole and benzyl phenyl ether were selectively iodinated in high yield in the presence of one equivalent each of mecuric oxide (red) and iodine[6].

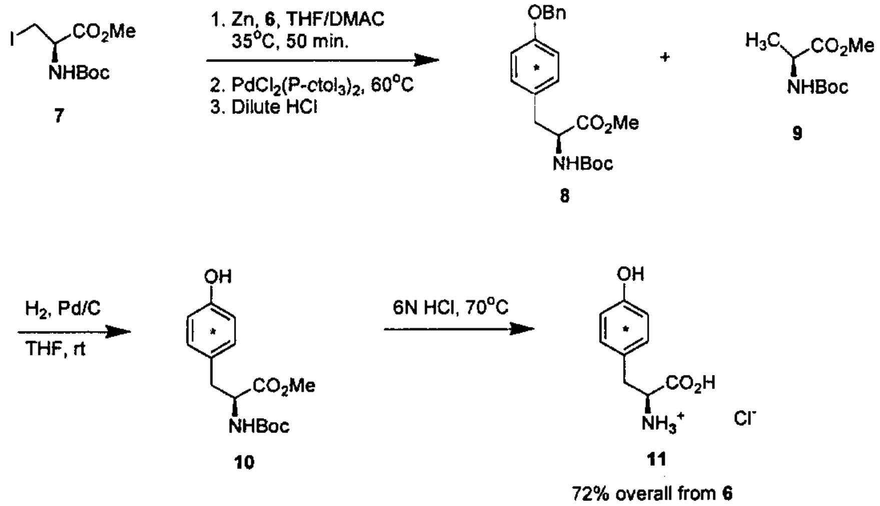
Iodide **6** (Scheme 2) was therefore selected as the aryl coupling partner because benzyl ethers are compatible[7] with the Jackson[3] reaction conditions and easily cleaved upon hydrogenolysis[7]. [U-^{14}C] phenol, **4**, was converted to **5** in nearly quantitative yield using benzyl bromide, K_2CO_3, and tetrabutylammonium iodide[7] in DMF. Iodination of **5** with HgO/I_2 occurred selectively at the 4-position in 96% yield; none of the *ortho* isomer was detected by ^{1}H NMR. It should be noted however that *two* equivalents of each reagent were necessary in order to achieve 100% conversion.

SCHEME 2



The reaction conditions used for the palladium mediated coupling of **6** with **7** were modeled after those reported by Jung and Starkey[7] (Scheme 3). Thus, a solution containing both **6** and **7** (1.5 equivalents) was added to activated (Knochel[8] procedure) zinc and stirred at 35°C for 50 minutes; the catalyst was added, and the temperature increased to 60°C. The coupling reaction was monitored by radio TLC and was complete after three hours. The inseparable mixture of **8** and **9** (formed upon protonolysis of **3**) was carried forward into the hydrogenolysis step, whereupon the more polar **10** could easily be separated from **9** by flash chromatography. Hydrolysis of the remaining protecting groups afforded 150 mCi of **11** (26.7 mCi/mmol) as a crystalline solid in 72% yield from **6**. HPLC analysis of the final material revealed that both the radiochemical and optical purity were >99%.

SCHEME 3



Conclusion

Ring labelled L-tyrosine hydrochloride **11** was prepared in five steps in an overall chemical yield of 65%. The selectivity of the aryl ether iodination and efficiency of the subsequent carbon-carbon bond forming reaction allowed for the rapid assembly of enantiomerically pure radiolabelled material from simple and readily available building blocks.

Experimental

[U-^{14}C]-Phenol (Amersham Pharmacia Biotech, Code CFQ11071) was obtained from Amersham Life Science. Compound **7** was made according to a literature procedure[9]. All other reagents were obtained from J. T. Baker or Aldrich and used without further purification. Flash chromatography was performed on a Biotage FlashElute™ chromatography system with the same manufacturer's prepacked silica gel cartridges. All chromatography solvents were obtained from BrandNu Laboratories and were used without further purification. Radiochemical purity of intermediates **5-8,10** was determined as follows: A sample of the purified material was adsorbed onto a 5 x 20 cm silica gel coated TLC plate and developed. A Bioscan TLC Scanner (P10 counting gas) was used to measure total counts for each of the components; peak integrals and radiochemical purity were then determined from the above data using Winscan (LabLogic) software. An IN/US β-ram radiochemical flow detector (IN/US INFLOW-3 counting cocktail) and Winflow (LabLogic) software were used to assay HPLC samples for radiochemical purity. The R_f's exhibited by compounds **5-8, 10** and the HPLC R_T for **11** were identical to those of authentic, unlabelled samples in side by side comparisons and co-spotted or co-injected samples. Liquid scintillation counting was performed on a Packard 2500 TR Liquid Scintillation Counter using 3a70B counting cocktail from Research Products International Corporation. NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer by Mr. George Morton, Discovery Analytical Chemistry, Wyeth-Ayerst Research, Pearl River, NY.

[U-^{14}C]-Benzyl Phenyl Ether (5). To a stirred solution of [U-^{14}C] phenol **4** (250 mCi @ 131 mCi/mmol) and unlabelled phenol (0.596 g, 6.33 mmol, Aldrich ReagentPlus™) in 12 mL of DMF were added 1.33 g (9.64 mmol) of K_2CO_3, 0.756 g (2.05 mmol) of tetrabutylammonium iodide, and 1.07 mL (9.03 mmol) of benzyl bromide. The reaction mixture was stirred for 26 h at room temperature then diluted with water (165 mL) and extracted with hexanes (1 x 50 mL, 2 x 40 mL, 1 x 30 mL). The combined extracts were washed with water (1 x 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure (aspirator) to give 1.53 g, (98%) of **5** as a light yellow solid. ^{1}H NMR[10] (300 MHz, $CDCl_3$,): δ 7.4-7.2 (7H, m), 7.0-6.9 (3H, m), 5.06 (2H, s); analytical TLC on silica gel, 85:15 hexane:ethyl acetate, R_f = 0.53; radiochemical purity: 99%. The product was used directly in the next step without further purification.

Benzyl-(4-iodo-[U^{14}C]-phenyl) ether (6). To a well stirred solution of **5** (1.53 g, 8.22 mmol) in 34 mL of methylene chloride were added 3.51 g (16.3 mmol) HgO and 4.10 g (16.3 mmol) iodine pellets. The reaction mixture was stirred vigorously in the dark for 26 h then filtered through a 1 cm layer of Celite. The filter cake was washed with an additional 140 mL of methylene chloride, and the combined filtrates were washed with 5% $Na_2S_2O_3$ (2 x 60 mL) and water (1 x 60 mL), dried ($MgSO_4$), and evaporated (aspirator) to give 2.40 g (96%) of **6** as a tan solid. ^{1}H NMR[6] (300 MHz, $CDCl_3$): δ 7.54 (2H, d, J = 7.0 Hz), 7.4-7.2 (5H, m), 6.74 (2H, d, J = 7.0 Hz), 5.03 (2H, s); analytical TLC on silica gel, 85:15 hexane:ethyl acetate, R_f = 0.65; radiochemical purity: 99%. The product was used directly in the next step without further purification.

[U-^{14}C]-(8). An oven dried, 3-necked, 100 mL round-bottomed flask was equipped with an addition funnel, rubber septum, and condenser fitted with a nitrogen inlet adaptor. The apparatus was evacuated and filled with nitrogen (3 cycles). The flask was charged with 2.03 g (31.1 g-atom) of zinc dust, 3.5 mL of anhydrous THF, and 130 μL (1.50 mmol) of 1,2-dibromoethane. The mixture was warmed with a heat gun until the solvent began to boil vigorously; it was then stirred for three minutes. The reflux/cool cycle was repeated four times *and performed under nitrogen.* The suspension was treated with trimethylsilyl chloride (40 μL, 0.31 mmol) and heated in an oil bath maintained at 35°C for 35 min.; a solution of **6** (2.40 g, 7.67 mmol) and **7** (5.08 g, 15.4 mmol) in 40 mL of 1:1 THF:DMAC was added dropwise over a 25 min. period and the reaction was stirred at 35°C for an additional 50 min. Finally, $PdCl_2[P(o\text{-tol})_3]$ (0.300 g, 0.381 mmol) was added, and the reaction mixture was heated at 60°C for 3 h. The dark brown mixture was cooled, diluted with ethyl acetate (800 mL), and filtered through Celite. The filtrate was washed with 0.1N HCl (1 x 400 mL), water (3 x 400 mL), dried ($MgSO_4$) and concentrated under reduced pressure (aspirator). The crude mixture (4.4 g) was purified by flash chromatography [95:5 hexane:ethyl acetate (60 x 8 mL fractions), then 4:1 hexane:ethyl acetate (84 x 8 mL fractions)]. Fractions 97-138 were combined and concentrated under reduced pressure (aspirator) to give 2.97 g of a dark red oil which contained **8** (85% by weight)[11]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4-7.2 (5H, m), 7.03 (2H, d, J = 8.6 Hz), 6.89 (2H, d, J =

8.6 Hz), 5.03 (2H, s), 4.96 (1H, br d, J = 8.3 Hz), 4.5-4.4 (1H, m), 3.73 (3H, s), 3.1-2.9 (2H, m), 1.42 (9H, s); analytical TLC on silica gel, 85:15 hexane:ethyl acetate, $R_f = 0.07$ along with **9** (15% by weight)[11].

[U-^{14}C]-(10). A 3-necked, 50 mL round-bottomed flask was equipped with two gas inlet adapters and a rubber septum. The apparatus was charged with 0.59 g of 10% palladium on carbon then evacuated and filled (*via* balloon) with hydrogen (5 cycles). A solution of **8** (2.97 g) above in 28 mL of THF was then introduced, and the reaction mixture stirred under an atmosphere of hydrogen for 21 h at ambient temperature. The mixture was filtered through Celite, and the filter cake washed with THF (3 x 28 mL). The filtrate was concentrated under reduced pressure, and the residue (2.4 g) purified by flash chromagraphy (7:3 hexane:ethyl acetate, 144 x 8 mL fractions). Fractions 55-96 were combined and concentrated under reduced pressure (aspirator) to give 1.80 g of **10** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (2H, d, J = 8.6 Hz), 6.74 (2H, d, J = 8.6 Hz), 5.99 (1H, br s), 5.01 (1H, br d, J = 7.8 Hz), 4.6-4.4 (1H, m), 3.72 (3H, s), 3.1-2.9 (2H, m), 1.42 (9H, s); analytical TLC on silica gel, 1:1 hexane:ethyl acetate, $R_f = 0.27$; radiochemical purity: >99%.

[U-^{14}C]-(11). A suspension of **10** (1.80 g, 6.08 mmol) in 88 mL of 6N HCl was heated at 70°C for 12 h. The water was removed by azeotropic distillation (760 torr) with benzene (350 mL) to give **11** (1.22g, 150 mCi

72% from **6**) as a light tan crystalline solid. Both optical and radiochemical purity were determined using a Phenomenex™ Chirex™ chiral HPLC column [CSP 3126, (D)-penicillamine ligand exchange]. Conditions: sample concentration 0.35 mg/mL in 4:1 H_2O:MeOH, 30 μL injection; isocratic run (65.0 min): mobile phase 85:15 2 mM aqueous $CuSO_4$:MeOH @ 1 mL/min, UV detection (230 nm); R_T = 37.2 min (R_T = 54.2 min for D based on assay of authentic racemic mixture); enantiomeric excess: >99%; radiochemical purity: >99%; specific activity: 26.7 mCi/mmol.

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