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Model Reactions Targeted at the Synthesis of Carbon-14 Labeled CI-996, a Potent Antagonist of Angiotensin II Receptor (1)

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SUMMARY

A reaction sequence suitable for the preparation of an analog of 2-propyl-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl-4-[2-(trifluoroacetyl)-1H-pyrrol-1-yl]-1H-imidazole-5-carboxylic acid, with ^{14}C at the methylene bridge was developed. The would-be labeled fragment (12) was derived from 4-iodobenzenemethanol (6), which itself was constructed from 1,4-dibromobenzene by the application of silicon chemistry. Pd^0 catalyzed coupling of TBDMS protected 6 and a tetrazole borate 10 gave the compound 12 which upon further transformation to the mesylate 13, N-alkylated an imidazole to furnish target compound.

KEYWORDS: *Angiotensin II receptor, biphenyl tetrazole, imidazole fragment, ipso substitution, and Pd^0 catalyzed coupling.*

Introduction

2-Propyl-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl-4-[2-(trifluoroacetyl)-1H-pyrrol-1-yl]-1H-imidazole-5-carboxylic acid CI-996 (16) is a potent antagonist of angiotensin II receptor (2), and had been in development as potential therapy for hypertension. A labeled analog with ^{14}C at the methylene bridge was required for metabolic and drug disposition studies. Our experiments were modeled from $BaCO_3$ since we intended to use $Ba^{14}CO_3$ as our source of carbon-14 labeled carbon dioxide. We planned to accomplish the preparation of labeled CI-996 in a two part strategy comprising the preparation of a biphenyl fragment, 2′-[2-(triphenylmethyl)-1H-tetrazol-5-yl][1,1′-biphenyl]-4-methanol (11), and the alkylation of an imidazole, 2-propyl-5-[2-(trifluoroacetyl)-1H-pyrrol-1-yl]-1H-imidazole-4-carboxylic acid (14).

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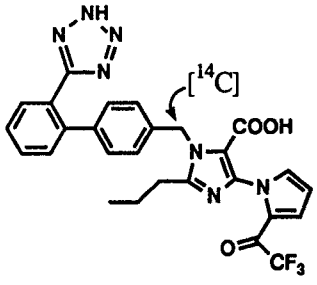
The biphenyl moiety was envisioned as derivable from 4-iodobenzenemethanol, and following conversion to the mesylate, it could N-alkylate the imidazole to furnish CI-996. By employing known reactions, we have developed a high yielding and practical route which is applicable to the synthesis of 4-iodobenzene[^{14}C]methanol, labeled biphenyl group, and CI-996.

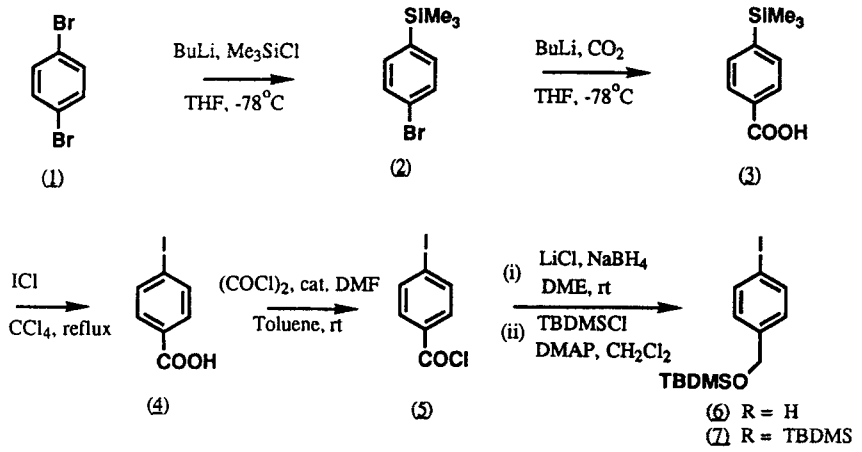


(16) CI-996

Results and Discussion.

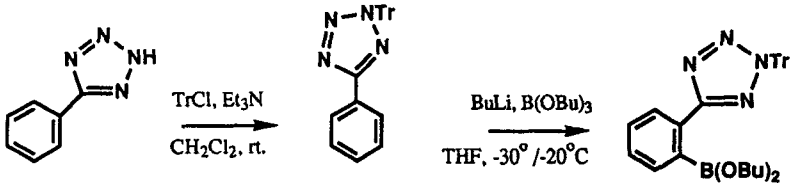
Iodo aryl compounds have commonly been made from nitro derivatives by a sequence of reduction to the amino compounds, diazotization followed by substitution with iodine. Although well established, this approach is not always convenient. An alternative method based on the known replacement of Me3Si group by iodine in the reaction of iodine or iodine monochloride with aryl(trimethyl)silanes (3), offered in our case a ready access to the desired 4-iodobenzenemethanol. These syntheses were rapid and provided high yields of desired products. We began the preparation (**Scheme 1**) by a metal-halogen exchange reaction on 1,4-dibromobenzene (1) with butyllithium at -78°C,

Scheme 1



followed by the addition of chlorotrimethylsilane to give (4-bromophenyl)trimethylsilane (2). By a second metal-halogen exchange reaction (4-lithiophenyl)trimethylsilane was obtained and reacted with carbon dioxide to give 4-(trimethylsilyl)benzoic acid (3) . The compound (3) was subsequently converted by ipso substitution technique to 4-iodobenzoic acid (4). Iodine monochloride under the conditions described by Calas et al (4), was the most effective reagent in this transformation, and afforded a quantitative yield of desired compound (4). Using the reducing reagent combination of LiCl-$NaBH_4$, the acid chloride (5) made from compound (4) by the action of oxalyl chloride, was similarly quantitatively converted to 4-iodobenzenemethanol (6). We protected the alcohol group as the TBDMS ether (7), and turned our attention on making the biphenyl group.

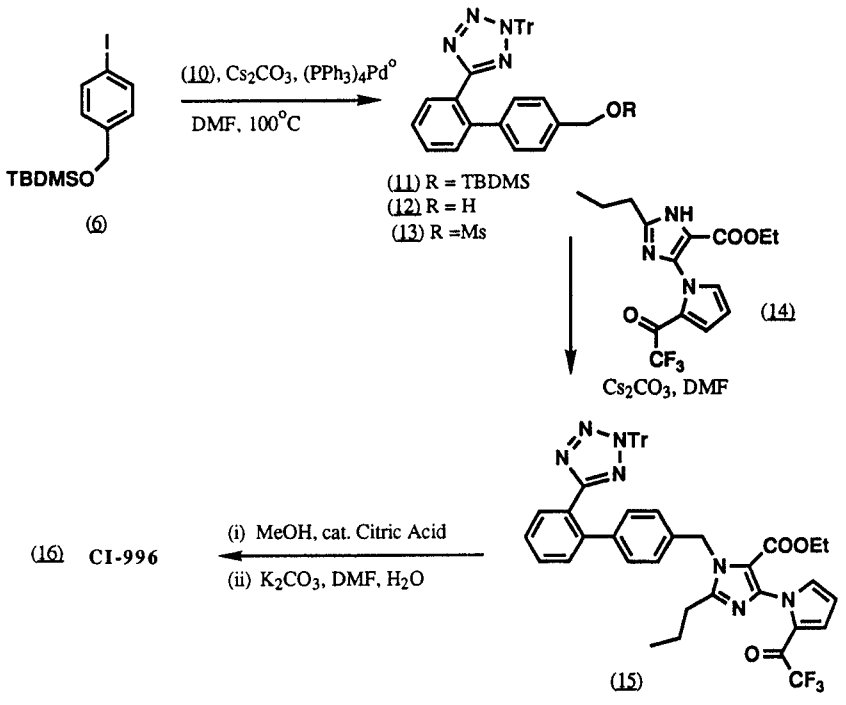
Scheme II



(8) (9) (10)

In the cross-coupling reactions aimed at preparing the biphenyl moiety, we encountered considerable problems. A number of Pd^0 catalyzed coupling reactions (5) and modifications thereof (6), including the use of " Rieke zinc" at best provided very marginal yields of desired biphenyl tetrazole. Coupling was best accomplished under the Suzuki conditions (7) and that approach required us to synthesize (**Scheme II**) the borate (10). A tetrazole directed ortho lithiation of commercially available 5-phenyl-1H-tetrazole (8), protected as the trityl derivative (9), was effected with n-BuLi according to a known method (8). Reaction with tributyl borate furnished compound (10), which in turn was coupled with compound (7) in the presence of Cs_2CO_3 and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) to yield (11). By treating compound (11) with Bu_4NF at 50°C for 45 min, the alcohol (12) was obtained, and subsequently converted to [2′-[2-(triphenylmethyl)-1H-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl sulfonate (13). The mesylate 13 reacted in DMF with the imidazole 14 in the presence

Scheme III



of Cs_2CO_3 to yield a mixture of N-alkylated regio-isomeric products (7), and the preponderant compound 15 was subsequently isolated by column chromatography. The trityl and ethyl protecting groups were removed and compound 16 was obtained pure by column chromatography followed by crystallization. All compounds were characterized by highfield nmr and gave spectra consistent with assigned structures.

In conclusion, this sequence represents an efficient, practical, and potentially inexpensive route that should make the ^{14}C labeled analogs of this therapeutically significant class of compounds readily accessible.

Experimental

General Methods

All reactions involving organometallic compounds were carried out under inert atmosphere and reaction solvents were freshly distilled from appropriate drying agent. ^1H-NMR spectra were recorded on a Gemini 200 MHz or a Varian XL 300 MHz

spectrometer. Column chromatography was carried out on a J.T. Baker Bakerbond octadecyl (C_{18}) prep LC silica gel packing (40mm), and on a Merck Kieselgel 60 (230μ).

(4-Bromophenyl)trimethylsilane (2)

A solution of 1,4-dibromobenzene (1) (50 g, 211.9 mmol) in dry THF (600 mL) was cooled to -78°C for 45 min, and n-BuLi (2.1 molar in hexane, 100.9 mL, 211.9 mmol) was added dropwise over 45 min. The solution was stirred at -78°C for 1 hr, chlorotrimethylsilane (26.89 mL, 211.87 mmol) was added and the reaction was allowed to warm to room temperature. Solvent was stripped and the residue was taken up in ether (400 mL), washed with sat'd NH_4Cl solution, brine and dried. It was filtered, concentrated on a rotary evaporator, and distilled under reduced pressure using a short path condenser to give 48.0 g, (98.5 % g). Proton NMR ($CDCl_3$) δ 7.60 - 7.40, aromatic (4H), 0.30, $(CH_3)_3Si$ (9H).

4-(Trimethylsilyl)benzoic acid (3).

(4-Bromophenyl)trimethylsilane (2) (10 g, 43.66 mmol) in dry THF (200 mL) was cooled to -78°C over 30 min, and n-BuLi (2.1 molar solution in hexane, 20.79 mL, 43.66 mmol) was added dropwise over 30 min with stirring under argon atmosphere. After stirring for additional 1hr CO_2 [pre-generated by the action of excess conc. H_2SO_4 (30 mL) on $BaCO_3$ (8.61 g, 43.62 mmol)] was admitted into the reaction flask. It was stirred for 15 min and allowed to slowly warm to room temperature. The solvent was removed and the residue was taken up in ethyl acetate (300 mL) and washed with sat'd NH_4Cl, brine, and dried. It was filtered, the solvent was removed *in vacuo* and product was crystallized from minimum pet ether to give 6.8 g, (85.6 %). Proton NMR ($CDCl_3$) δ 8.10, d, aromatic (2H); 7.65 , d, aromatic (2H); 0.30, s, $(CH_3)_3Si$ (9H).

4-Iodobenzoic acid (4)

To a solution of (4-trimethylsilyl)benzoic acid (3) (1.5 g, 8.24 mmol) in carbon tetrachloride (20 mL) was slowly added iodine monochloride (1.34 g, 8.24 mmol) in carbon tetrachloride (20 mL) at room temperature with stirring under argon atmosphere. After stirring for 30 min, it was refluxed for 1 hr and then cooled in an ice bath. The solid was separated by filteration and recrystallized from ethyl acetate to give (1.66 g , 95 %). Proton NMR ($CDCl_3$) δ 7.60, dd, aromatic (4H)

4-Iodobenzenemethanol (6)

To a solution of 4-iodobenzoic acid (4) (7.03 g, 28.3 mmol) in dry toluene (120 mL) was added excess oxalyl chloride (15 mL) followed by catalytic amount (20 mL) of anhydrous DMF. It was stirred for 1 hr at room temperature and during which solution was attained. The solvent was removed *in vacuo* and the oil was taken up in anhydrous DME (60 mL) followed by the addition of a mixture of LiCl (1.47 g, 34.0 mmol) and $NaBH_4$ (1.28 g, 34.0 mmol). The suspension was stirred for 1hr, and excess borohydride was destroyed with 1.0 N HCl and the mixture was extracted into 200 mL of ether. The ethereal solution was washed with brine and dried on $MgSO_4$. Product was dissolved in minimum CH_2Cl_2 and diluted with hexane. The dichloromethane was boiled off , and the mixture and compound was crystallized to give 6.04 g, (91%). Proton NMR ($CDCl_3$) δ 7.65, d, aromatic (2H); 7.19, d, aromatic (2H); 4.65, s, (-CH_2OH); 1.80, brs, exc. D_2O, (-CH_2O**H**)

(1,1-Dimethylethyl)[(4-iodophenyl)methoxy]dimethylsilane (7)

4-Iodobenzenemethanol (6) (3.0 g, 12.82 mmol), 4-dimethylaminopyridine (124 mg, 1.026 mmol) and triethylamine (1.557 g, 2.14 mL, 15.39 mmol) in dichloromethane (50 mL) was stirred at room temperature overnight. It was diluted with ether (200 mL) washed with water, brine and dried. Solvent was removed to give an oil which crystallized on standing. Recrystallization from acetone-hexane gave 4.36 g (97.7 %). Proton NMR ($CDCl_3$) δ 7.65, d, aromatic (2H); 7.10, d, aromatic (2H); 4.70, s, (-CH_2O); 0.95, s, t-butyl protons from TBDMS (9H); 0.10, s, CH_3 protons from TBDMS (6H).

5-[4'-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl][1,1'-biphenyl]-2-yl]-2-(triphenylmethyl)-1H-tetrazole (11)

Trityl protected phenyl-1H-tetrazole borate (10) (2.0 g, 3.68 mmol), (1,1-dimethylethyl)[(4-iodophenyl)methoxy]dimethylsilane (7) (1.164 g, 3.34 mmol), cesium carbonate (1.63 g, 5.01 mmol), and $(Ph_3)_4Pd^o$ (77 mg) in DMF (20 mL) was heated under argon overnight. Solvent was removed, product was taken up in CH_2Cl_2, washed with sat'd NH_4Cl solution and brine. It was purified by medium pressure reverse phase (C_{18}) chromatography eluting with acetonitrile:water (80:20 to 90:10) to give desired compound 11 (930 mg, 52 %). Proton NMR ($CDCl_3$) δ 7.90 - 6.90 , m, aromatic protons; 5.70, s, (-CH_2O-); 0.98 , s, t-butyl protons from TBDMS (9H); 0.10 , CH_3 protons from TBDMS (6H).

2'-[2-(Triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-methanol (12)

To 5-[4'-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl][1,1'-biphenyl]-2-yl]-2-(triphenylmethyl)-1H-tetrazole (11) (1.42 mg, 2.24 mmol), in dry THF (25 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF; 6.0 mL, 6.0 mmol) and heated at 50°C for 45 min. The solvent was removed and the residue was taken up in ethyl acetate (80 mL), washed with sat'd $NaHCO_3$, brine, and dried. Product was purified by column chromatography on silica gel eluted with 40 % ethyl acetate in hexane, followed by crystallization from methanol to give 12 (1.10 g, 98.2 %). Proton NMR ($CDCl_3$) δ 8.0 - 6.90 , m, aromatic protons; 4.60, d, (-CH_2OH); 1.40 , tr, exc. D_2O, (O<u>H</u>)

2-Propyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-4-[2-(trifluoroacetyl)-1H-pyrrol-1-yl]-1H-imidazole-5-carboxylic acid CI-996 (16)

To a solution of 2'-[2-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-methanol (12) (1.0 g, 2.02 mmol) in dry CH_2Cl_2 (20 mL) stirred in ice-bath was added triethyl-amine (426 mL, 3.03 mmol), followed by methanesulfonyl chloride (195 mL, 2.5 mmol). After 1.5 hr when reaction was shown to be complete by tlc (EtOAc:Hexane 60:40), it was diluted with ether (150 mL), washed with water, sat'd $NaHCO_3$, brine and dried. Solvent was removed to give a white fluffy solid that was used immediately without further purification. A suspension of the imidazole (14) (746 mg, 2.18 mmol) and Cs_2CO_3 (1.80 g, 5.55 mmol) was stirred for 5 min in anhydrous DMF (10.0 mL) and the above mesylate (calc. 2.02 mmol) in anhydrous DMF (8.0 mL) was added in one portion. It was stirred at room temperature and reaction was monitored by tlc. After 24 hr the reaction was diluted with ethyl acetate and filtered to remove the inorganic material. The filterate was evaporated *in vacuo* and the product was chromatographed on silica gel to afford compound 15, in the trityl protected form. It was dissolved in methanol (20 mL) and treated with 10 % aqueous citric acid (2.0 mL) and heated at reflux for 1.5 hr. It was cooled to room temperature, water (10 mL) and hexane (40 mL) were added and the mixtre was stirred. The methanol layer was separated, washed with hexane and concentrated. The residue was taken up in ethyl acetate and washed with water, dried and evaporated to give de-tritylated compound. The compound was taken up in DMF (10 mL) and treated with K_2CO_3 (2.60 g), and water (0.5 mL) and stirred at room temperature for

48 hr. The insoluble material was removed by filtration, the solid was washed with DMF and the filtrate was acidified with 10 % citric acid solution, followed by extraction with ethyl acetate/hexane (2:1). The organic phase was dried and the residue was crystallized to give 16 (500 mg). Proton NMR ($CDCl_3$) δ 7.67 (m, 3H), 7.57 (t, 2H), 7.37 (s, 3H), 7.08 (q, 4H), 6.53 (q, 1H), 5.69 (s, 2H), 2.58 (t, 2H), 1.57 (m, 2H), 0.85 (t, 3H).

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