A Facile Synthesis of an Oxidation Product of Terfenadine

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Terfenadine (11), a selective H_1-histamine receptor antagonist,[2] is a widely used antihistamine[3] which is devoid of CNS effects.[4] The compound is almost completely biotransformed by hepatic cytochrome P450[3] to the pharmacologically active acid metabolite 10[3] and the inactive metabolite azacyclonol (α,α-diphenyl-4-piperidinemethanol) in the first pass.[3,5] Recently, there have been reports which suggest that terfenadine is responsible for a serious ventricular arrhythmia, torsades de pointes, when it is taken concomitantly with drugs known to alter hepatic oxidative metabolism (e.g. erythromycin, ketoconazole, and macrolide antibiotics).[3,6] Terfenadine is considered to be a pro-drug with the acid metabolite 10 being the active agent.[3,5,7,8] It is postulated that drugs which alter hepatic oxidative metabolism cause an accumulation of terfenadine by preventing its metabolism to carboxyterfenadine (10). This accumulation of terfenadine is believed to be responsible for the cardiac irregularities experienced by patients.[3] In this note, we describe the first synthesis of carboxyterfenadine.

Results and Discussion

In approaching the synthesis of the metabolite 10, it appeared that the most straightforward route would involve the attachment of a four-carbon chain to the phenylacetic acid moeity followed by coupling with the piperidine ring, analogous to the method that was employed in the synthesis of terfenadine.[2] We initially attempted to perform the first step by the Friedel–Crafts acylation[9] of methyl α,α-dimethyl-α-phenylacetate. The desired para-disubstituted product, however, could not be separated from the other regioisomers that were also formed in appreciable quantities. An alternate strategy employing a Pd(0)-catalyzed coupling of terminal alkyne and aromatic bromide followed by regioselective hydration proved very successful.

Thus, commercially available 4-bromophenylacetic acid (1) was quantitatively esterified by Chan's method[10] (2.2 equiv of Me_3SiCl/MeOH/rt/15 h) followed by methylation of the benzylic carbon employing 2.4 equiv of methyl iodide (3 equiv of NaH/THF/rt), which afforded the ester 3 in 71% yield (Scheme 1). The Pd(0)/Cu_2Br_2-catalyzed coupling[11] of bromide 3 and 3-butyne-1-ol, carried out in refluxing triethylamine, gave the alkyne 4 in 97% yield. Mesylation of the primary hydroxyl of 4 (2 equiv of MsCl/9 equiv of pyridine/CH_2Cl_2/rt/12 h) proceeded to give 5 in a quantitative manner. Attempts to convert this alkyne to the ketone via a mercury-catalyzed hydration, however, resulted in the loss of the mesyl group and formation of the hemiketal 6.

To circumvent this, the piperidine was attached prior to formation of the benzylic alcohol. The displacement of the mesyl group by azacyclonol (1.1 equiv of amine·HCl/3.3 equiv of K_2CO_3/MeCN) afforded the tertiary amine 7 in 82% yield. The mercury-catalyzed hydration[12] was successfully carried out on this alkyne ($Hg^{II}O/H_2SO_4/H_2O$/MeOH/55 °C), affording the benzylic ketone 8 in 75% yield, contaminated by < 5% of what appeared to be dehydration product 12. Whereas ketone 8 could be obtained pure after careful chromatography, the dehydration product 12 could not be completely separated in a pure form. Its presence was inferred, on the basis of mass spectral data and an ultraviolet spectrum which exhibited much greater molar absorbtivity than that for the pure ketone 8. Ketone 8 was reduced (1.5 equiv of $NaBH_4$/MeOH/rt/20 h) to the secondary alcohol 9 in virtually quantitative yield, contaminated by <5% of what again appeared to be dehydration products. These contaminants were detected in the crude product, again, by mass spectrometry and UV spectroscopy. The alcohol 9 was obtained in a pure form by careful chromatography. Finally, cleavage of the methyl ester required that a solution of 9 in 1:1 (v/v) 1 N NaOH/MeOH be heated overnight at 80 °C. The treatment afforded the zwitterionic product 10 in 76% yield, which precipitated out of the reaction mixture upon lowering of the pH to 7. The structure and purity of the final product, the oxidized metabolite 10, is supported by ^{1}H-NMR and ^{13}C-NMR, mass spectrometry and elemental analysis, as well as by HPLC comparison with an authentic sample. We are presently involved in the synthesis of enantiomerically pure carboxyterfenadine (10) as there have been suggestions that (*S*)-terfenadine may have improved therapeutic characteristics compared to the racemate.[6] If so, it is most probable that the (*S*)-isomer of carboxyterfenadine (10) will be superior to racemic 10.

Experimental Section

Melting points are uncorrected. HPLC was performed on a HP ODS Hypersil column and pre-column. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. (Guelph, Ontario). All compounds were shown to be homogeneous by TLC and high-field NMR and to have a purity of >95% by elemental analysis. ^{1}H-NMR spectra were recorded at 200 and 300 MHz and the peak assignments were made, in some cases, with the aid of homonuclear decoupling and/or COSY experiments. The residual proton signals of chloroform and methanol (assigned values of δ 7.24 and 3.30 ppm) were used as references in these solvents. ^{13}C-NMR spectra were all obtained at 75.4 MHz. The $^{13}CDCl_3$, $^{13}CD_3OD$, and $^{13}CD_2Cl_2$ signals (assigned values of δ 77.00, 49.00, and 53.80 ppm, respectively) were used as references in these solvents. Peak assigments were, in some cases, made with the aid of APT or HETCOR experiments. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was

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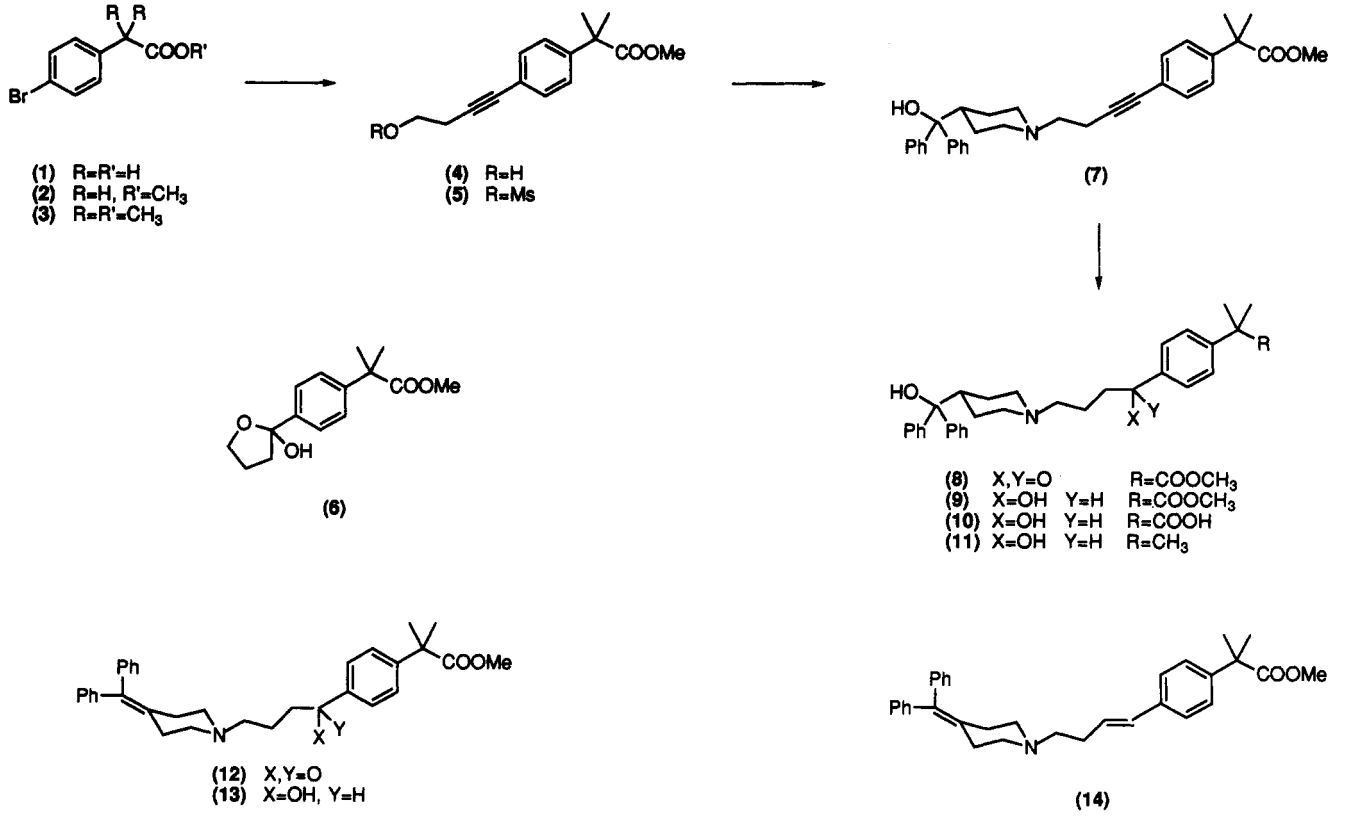
Scheme 1



distilled from P_2O_5. Acetonitrile, ethyl acetate, hexanes, pentane, pyridine, and triethylamine were distilled from CaH_2. Methanol was distilled from magnesium. TLC was performed using kieselgel 60 F_{254} aluminum-backed plates (0.2 mm thickness) and visualized by UV and/or dipping in a solution of ammonium molybdate (2.5 g) and ceric sulfate (1 g) in 10% v/v aqueous sulfuric acid (100 mL), followed by heating. Kieselgel 60 (Merck, 230–400 mesh) silica gel was employed for column chromatography.[13]

Methyl 2-(4-Bromophenyl)-2,2-dimethylacetate (3). Chlorotrimethylsilane (26.0 mL, 0.205 mol) was added dropwise to a stirred solution of commercially available carboxylic acid 1 (20.0 g, 0.093 mol) in freshly distilled methanol (240 mL). After being stirred under a nitrogen atmosphere at ambient temperature for 15 h, the solution was evaporated *in vacuo* to yield ester 2 as a clear, slightly yellow oil (21.4 g, 100%). A solution of unpurified ester 2 (21.3 g, 93.0 mmol) in dry THF (100 mL) was added dropwise to a stirred suspension of sodium hydride (8.37 g, 80% in oil dispersion, 0.279 mol) in dry THF (350 mL). To the resulting suspension was then added dropwise methyl iodide (13.9 mL, 0.223 mol), and the reaction was stirred under nitrogen at rt. (**CAUTION**: The reaction is highly exothermic, requiring the use of a condenser.) After 15 h, Florisil (10 g) was added to the reaction and the solids were then filtered through Celite. Evaporation of the filtrate *in vacuo* afforded a yellow solid, which was extracted with pentane (3 × 250 mL). The oily residue obtained upon removal of the solvent *in vacuo* was chromatographed on silica gel (10:1 to 8:1 hexanes–ethyl acetate, v/v) to afford the dimethylated ester 3 as a colorless oil (16.9 g, 71% yield).

4-(4-Hydroxy-1-butynyl)-α,α-dimethylbenzeneacetic Acid, Methyl Ester (4). Tetrakis(triphenylphosphine)palladium(0) (166 mg, 0.144 mmol) and cuprous bromide (62 mg, 0.43 mmol) were successively added to a stirred solution of bromo ester 3 (933 mg, 3.63 mmol) and 3-butyn-1-ol (550 μL, 7.27 mmol) in freshly distilled triethylamine (15 mL), and the resulting solution was heated to reflux under nitrogen. After 3.5 h, the dark suspension was cooled and the solvent was removed *in vacuo* to yield a solid which was extracted with ethyl ether (100 mL) and washed with saturated aqueous NH_4Cl (2 × 125 mL). The organic phase was then dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a green syrup which was chromatographed on silica gel (2:1 hexanes–ethyl acetate, v/v) to afford alkyne 4 as a slightly yellow syrup (866 mg, 97% yield).

4-[4-(Methanesulfonyloxy)-1-butynyl]-α,α-dimethylbenzeneacetic Acid, Methyl Ester (5). Methanesulfonyl chloride (326 mL, 4.22 mmol) was added to a stirred solution of alkyne 4 (520 mg, 2.11 mmol) in dry CH_2Cl_2 (6.5 mL) containing pyridine (1.48 mL). After the solution was stirred under a nitrogen atmosphere for 20 h, the reaction was diluted with CH_2Cl_2 (100 mL), washed with aqueous sulfuric acid (1% w/v, 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), and reextracted with CH_2Cl_2 (100 mL). The combined organic phases were then dried ($MgSO_4$), and the solvent was removed *in vacuo* to afford mesylate 5 as a colorless syrup (684 mg, 100%).

4-[4-[4-Hydroxydiphenylmethyl)-1-piperidinyl]-1-butynyl]-α,α-dimethylbenzeneacetic Acid, Methyl Ester (7). A solution of mesylate 5 (625 mg, 1.93 mmol), azacyclonol hydrochloride (644 mg, 2.12 mmol), and anhydrous K_2CO_3 (800 mg) in dry acetonitrile (10 mL) was refluxed under nitrogen for 12 h. The reaction mixture was then cooled and filtered, and the solids were washed repeatedly with CH_2Cl_2. The filtrate was then evaporated *in vacuo* and the resulting white solid chromatographed on silica gel (2:1 hexanes–ethyl acetate, v/v) to afford amino alcohol 7 as an amorphous white solid (750 mg, 75% yield).

4-[1-Oxo-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethylbenzeneacetic Acid, Methyl Ester (8). A solution of HgO in aqueous sulfuric acid (10 mL of a solution of 75 mg of HgO in 12 mL of 4% w/v sulfuric acid) was added to a solution of alkyne 7 (583 mg, 1.18 mmol) in methanol (2 mL), resulting in the precipitation of the alkyne. The resulting mixture was then heated at 55 °C for 3 h (**NOTE:** proportionately longer reaction times are required for larger scale preparations). The reaction was diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were then washed with brine (100 mL), dried (Na_2SO_4), and evaporated *in vacuo* to yield a brown solid. Chromatography over silica gel (1:2 → 3:1 ethyl acetate–hexanes, then 15:1 CH_2Cl_2–methanol, v/v) afforded ketone 8 as a white solid (456 mg,

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75% yield). Analysis by HPLC indicated the presence of only one compound.

4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethylbenzeneacetic Acid, Methyl Ester (9). Sodium borohydride (38 mg, 1.0 mmol) was slowly added to a stirred solution of ketone 8 (350 mg, 0.681 mmol) in methanol (5 mL), and the resulting suspension was stirred at rt under a nitrogen atmosphere. After 20 h, the excess hydride was destroyed using aqueous sulfuric acid (3% w/v, 10 mL), and saturated aqueous sodium bicarbonate was then added. The product was extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic fractions were washed with brine (200 mL). The organic phase was then dried (Na_2SO_4) and evaporated *in vacuo*, yielding crude alcohol 9. Chromatography over silica gel (1:5 hexanes–acetone, v/v) afforded pure alcohol 9 as a white solid (342 mg, 95% yield). Analysis by HPLC indicated the presence of only one compound.

4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethylbenzeneacetic Acid (10). Aqueous KOH (1N, 3.0 mL) was slowly added to a stirred solution of ester 9 (256 mg, 0.496 mmol) in methanol (3.0 mL), resulting in a suspension which was heated to 80 °C. After 16 h of stirring, the resulting homogeneous solution was cooled and 1 N aqueous HCl was carefully added until the precipitate remained and a pH of 7.0 was attained (~2.6 mL). The resulting gummy solid was dispersed using ultrasound and allowed to stand overnight. The resulting fine solid was filtered and dried in a dessicator (**NOTE:** when the reaction was carried out on a 5 mmol or larger scale, sonication transformed the gum into a solid lump which had to be broken up by stirring). Recrystallization from methanol afforded the amino acid 10 as white crystals (189 mg, 76% yield, mp 142–143 °C). The compound's purity was also ascertained by HPLC to be >99%.

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Supplementary Material Available: Spectral and analytical data (^1H NMR, ^{13}C NMR, MS, UV and elemental analysis) for all new compounds (5 pages). This material is contained in libraries on microfiche, immediately follows this paper in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.