SYNTHESIS OF DEUTERIUM-LABELED ACRIVASTINE AND AN ACRIVASTINE METABOLITE

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SUMMARY

The antihistamine acrivastine and a metabolite dihydroacrivastine were prepared as their [$^2H_7$]-congeners from [$^2H_8$]-tolualdehyde for use as internal standards in gas chromatography/mass spectroscopy of biological samples.

Key words: acrivastine, antihistamine, deuterium labeling.

INTRODUCTION

Acrivastine is a recently introduced antihistaminic agent (H_1-antagonist) with minimal sedative properties (1). Because of its zwitterionic character, acrivastine does not cross the blood-brain-barrier readily and exerts its therapeutic actions in peripheral tissues with little or no effect on central nervous system function.

In the course of clinical studies, samples of deuterium-labeled acrivastine and a prominent metabolite **2** were needed as internal standards for quantitative analysis of biological samples via gas chromatography/mass spectroscopy (GC/MS) (2). A minimum of four deuterium atoms was desired to provide unambiguous instrumental resolution. Considerations of synthetic simplicity prompted the incorporation of seven deuterium atoms. Herein we report the syntheses of [$^2H_7$]-acrivastine **1** and the acrivastine metabolite (E)-3-(6-(3-(1-pyrrolidinyl)-1-([$^2H_7$]-4-tolyl)-1-propenyl)-2-pyridyl)propionic acid **2**.

RESULTS AND DISCUSSION

The syntheses of both compounds proceeded by similar routes through a common intermediate (Scheme 1). Addition of pyridyllithium **3** to [$^2H_8$]-tolualdehyde provided alcohol **4** which was oxidized to ketone **5** with pyridinium chlorochromate (3). Palladium catalyzed Heck reaction (4) of **5** with ethyl acrylate proceeded smoothly to afford ketoester **6**. Wittig reaction of **6** with 2-(1-pyrrolidino)ethyltriphenylphosphonium bromide **7** (5) gave a mixture of E and Z isomers. After

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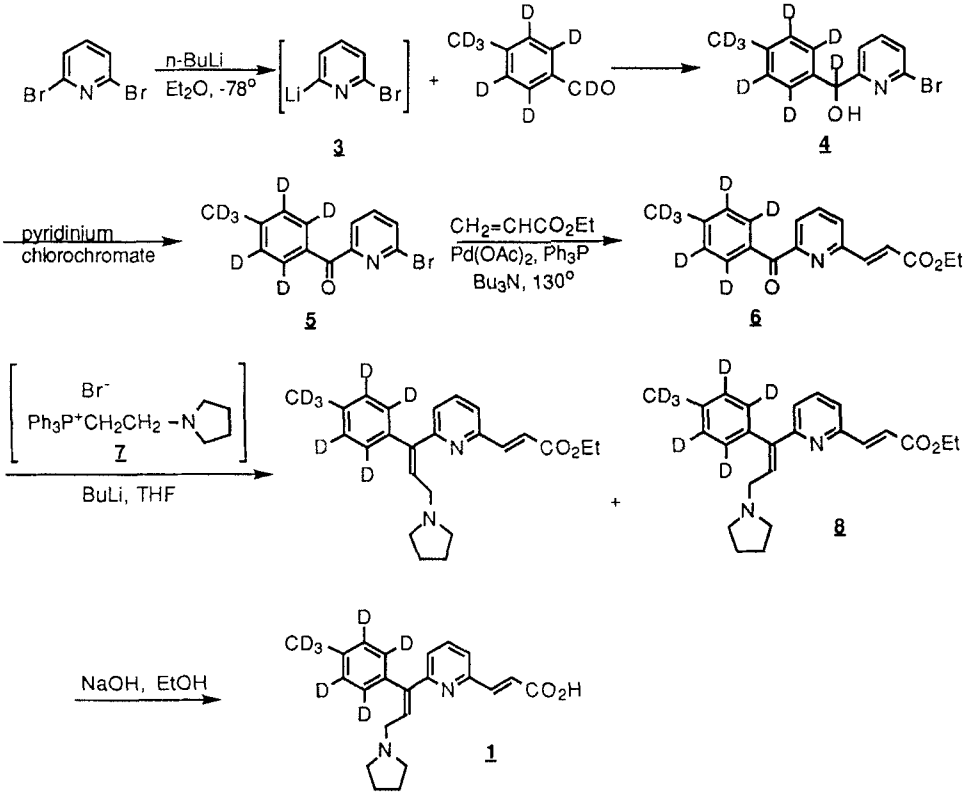
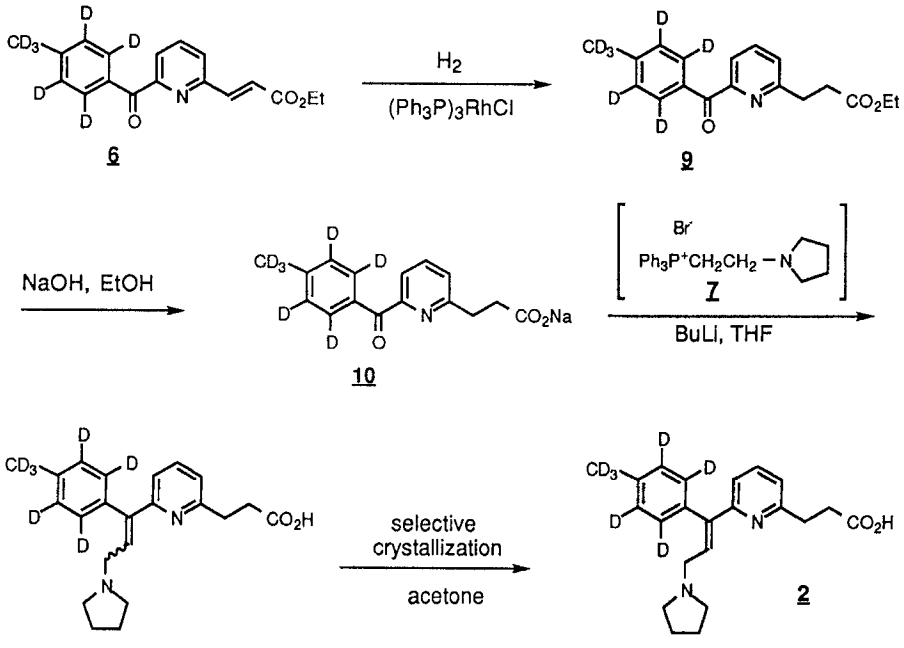
isomer separation by chromatography, the desired E isomer **8** was hydrolyzed to provide [$^2H_7$]-acrivastine **1**.

Scheme 1.



Preparation of metabolite **2** (Scheme 2) required selective reduction of intermediate ketoester **6**. Catalytic hydrogenation with palladium proved to be non-selective, with reduction of the alkene and ketone functions occurring at comparable rates. However, hydrogenation in the presence of Wilkinson's catalyst [(Ph3P)3RhCl] (6) proceeded with complete chemoselectivity to afford **9**. Despite concerns that isotopic exchange at the toluene methyl group might be a complication during the Heck reaction or catalytic reduction (7), deuterium NMR and GC/MS confirmed that the isotopic purity of intermediate **9** was >99%. Attempted reaction of **9** with the pyrrolidinoethyl Wittig reagent proved troublesome. Although the preceding Wittig reaction with **6** (Scheme 1) produced only the expected isomeric products, the corresponding reaction with **9** resulted in a complex mixture under a variety of conditions. In order to eliminate participation of the flexible ester sidechain, ketoester **9** was hydrolyzed to ketoacid **10**, and subsequent Wittig reaction on the sodium salt of **10** proceeded without difficulty. The resulting E/Z isomer mixture was purified by chromatography and the deuterium-labeled acrivastine metabolite **2** was isolated by selective crystallization.

Scheme 2.



Analysis by gas chromatography/mass spectroscopy indicated that the deuterium-labeled **1** and **2** were obtained in >99% isotopic purity. Use of the compounds in quantitative analysis of biological samples has been reported elsewhere (2).

EXPERIMENTAL

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. TLC was performed on Whatman 250 μ MK6F plates of silica gel with fluorescent indicator; spots were detected with UV light. HPLC was performed on a Waters 840 Data System with two Waters Model 510 pumps, WISP injector and Waters 490 UV detector set at 230, 254, 280 nm (maxplot mode) using a β-cyclodextrin Cyclobond I column (4.6 x 250 mm, 5 μ, 0.75 ml/min) or Versa- pack C_{18} column (4.6 x 250 mm, 10 μ). NMR spectra were recorded using a Varian XL-200 spectrometer. Preparative column chromatography was done using the flash chromatography technique[8] on Silica Gel 60 (40-63 μ, E. Merck No. 9385). Elemental analyses were performed by Atlantic Microlab, Inc. and mass spectra by Oneida Research Services, Inc.

α-(6-Bromo-2-pyridyl)-[$^2H_8$]-4-methylbenzyl alcohol (**4**). A stirred solution of 2,6-dibromopyridine (93.3 g, 0.39 mol) in Et_2O (2.0 L) under N_2 was cooled to -78° C and 2.22 M n-BuLi in hexane (173.5 mL) was added dropwise during 1 h. The resulting green solution was slowly added to a solution of [$^2H_8$]-4-tolualdehyde (49.5 g, 0.39 mol; Cambridge Isotope Laboratories, Inc.) in Et_2O (1.5 L) under N_2 and stirring at -78° C. After 1.5 h, the mixture was warmed to

ambient temperature and quenched by slowly adding saturated aq NH_4Cl solution (150 mL). The reaction solution was washed with H_2O (800 mL), with saturated NaCl solution (800 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to a yellow oil. Chromatography (5-10% EtOAc/hexane) gave the alcohol (4, 70.3 g, 64%), TLC: one spot with 25% EtOAc/hexane, R_f=0.40; HPLC: one major peak on Versapack C_{18} with 40% MeOH/H_2O/0.1% F_3CCOOH, K'=11.33; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 4.33 (s, 1H, OH), 7.13 (d, J=7.4 Hz, 1H, H-3), 7.36 (d, J=7.8 Hz, 1H, H-5), 7.46 (t, 1H, H-4); MS (CI/CH_4) m/z: 286 (67.2, M+1), 268 (52.2, M-17). Anal Calcd for $C_{13}H_4D_8BrNO$: C, 54.56; H+D as H, 4.23; N, 4.89; Br, 27.92. Found: C, 54.50; H+D as H, 4.29; N, 4.85; Br, 27.86.

6-Bromo-2-pyridyl-[$^2H_7$]-4-tolyl ketone (5). A mixture of 4 (44.5 g, 0.16 mol) and pyridinium chlorochromate (69.0 g, 0.32 mol) in CH_2Cl_2 (650 mL) was stirred at room temperature for 20 h. The black mixture was filtered through a bed of silica gel and further eluted with Et_2O (2.0 L) to give 5 as pale yellow crystals (40.5 g, 92%), M.P. = 94-96° C, TLC: one spot with 25% EtOAc/hexane, R_f=0.55; HPLC: one major peak on Versapack C_{18} with 60% MeOH/H_2O/0.1% F_3CCOOH, K'=6.54; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.63-7.78 (m, 2H, arom), 7.93-8.02 (m, 1H, arom); MS (CI/CH_4) m/z: 311 (7.1, M+29), 283 (100.0, M+1).
Anal Calcd for $C_{13}H_3D_7BrNO$: C, 55.14; H+D as H, 3.56; N, 4.95; Br, 28.22. Found: C, 55.13; H+D as H, 3.60; N, 4.97; Br, 28.17.

(E)-Ethyl 3-(6-([$^2H_7$]-4-toluoyl)-2-pyridyl)acrylate (6). A stirred mixture of 5 (40.0 g, 0.14 mol), tributylamine (33.4 mL, 0.14 mol), triphenylphosphine (3.7 g, 0.014 mol), palladium(II) acetate (1.6 g, 7 mmol) and ethyl acrylate (37 mL, 0.34 mol) under N_2 was heated at 130° C for 8 h (additional 18 mL of ethyl acrylate was added after 4 h). The mixture was dissolved in CH_2Cl_2 (1.0 L), washed with 0.2M HCl and H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated to a nm (maxplot mode) using a β-cyclodextrin Cyclobond I column (4.6 x 250 mm, 5 μ, 0.75 ml/min) or Versa- pack C_{18} column (4.6 x 250 mm, 10 μ). NMR spectra were recorded using a Varian XL-200 spectrometer. Preparative column chromatography was done using the flash chromatography technique[8] on Silica Gel 60 (40-63 μ, E. Merck No. 9385). Elemental analyses were performed by Atlantic Microlab, Inc. and mass spectra by Oneida Research Services, Inc.

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(E)-Ethyl 3-(6-([$^2H_7$]-4-toluoyl)-2-pyridyl)acrylate (**6**). A stirred mixture of **5** (40.0 g, 0.14 mol), tributylamine (33.4 mL, 0.14 mol), triphenylphosphine (3.7 g, 0.014 mol), palladium(II) acetate (1.6 g, 7 mmol) and ethyl acrylate (37 mL, 0.34 mol) under N_2 was heated at 130° C for 8 h (additional 18 mL of ethyl acrylate was added after 4 h). The mixture was dissolved in CH_2Cl_2 (1.0 L), washed with 0.2M HCl and H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated to a dark oily residue. Crystallization from cyclohexane gave pale yellow crystals of **6** (22.0 g, 52%), M.P.=109-111° C, TLC: one spot with 25% EtOAc/hexane, R_f=0.40; HPLC: one major peak on Versapack C_{18} with 70% MeOH/H_2O/0.1% F_3CCOOH, K'=3.11; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.33 (t, 3H, $COOCH_2CH_3$), 4.27 (q, 2H, $COOCH_2CH_3$), 6.89, 7.72 (d, J=15.7 Hz, 1H each, -CH=CH-), 7.58 (d of d, J=1.4, 7.4 Hz, 1H, arom), 7.81-8.05 (m, 2H, arom); MS (CI/CH_4) m/z: 331 (9.0, M+29), 303 (100.0, M+1). Anal Calcd for $C_{18}H_{10}D_7NO_3$: C, 71.50; H+D as H, 5.67; N, 4.63. Found: C, 71.42; H+D as H, 5.70; N, 4.62.

(E)-Ethyl 3-(6-((E)-3-(1-pyrrolidinyl)-1-([$^2H_7$]-4-tolyl)-1-propenyl)-2-pyridyl)acrylate (**8**). A solution of 2.14M n-BuLi in hexane (42 mmol) was added dropwise to a suspension of pyrrolidinoethylphosphonium bromide (5) (**7**, 17.5 g, 40 mmol) in THF (300 mL) at 0° C with stirring under N_2. The resulting dark colored solution was stirred for 2 h at 0° C, treated with a solution of **6** (12.0 g, 40 mmol) in THF (150 mL) and heated at reflux for 2 h. The mixture was concentrated and chromatography (EtOAc - 8% MeOH/EtOAc) gave two fractions. The first fraction was crystallized from acetone to give tan crystals of **8** (2.0 g, 14%), M.P.=112-113° C, TLC: one spot with MeOH, R_f=0.45; HPLC: one peak on β-cyclodextrin Cyclobond I with 50% MeOH/0.1M NH_4OAc, retention time=8.15 min; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.35 (t, 3H, $COOCH_2CH_3$, 1.77 (m, 4H, $CH_2CH_2NCH_2CH_2$), 2.53 (m, 4H, CH_2NCH_2), 3.19 (d, J=7 Hz, 2H, NCH_2CH=), 4.27 (q, 2H, $COOCH_2CH_3$), 6.83 (d, J=8 Hz, 1H, arom), 7.04, 7.67 (d, J=15.6 Hz, 2H, CH=CHCOOEt), 7.22 (m, 2H, arom), 7.50 (t, 1H, NCH_2CH=); MS (CI/CH_4) m/z: 412 (9.0, M+29), 383 (100.0, M^+).
Anal Calcd for $C_{24}H_{21}D_7N_2O_2$: C, 75.16; H+D as H, 7.36; N, 7.30. Found: C, 75.20; H+D as H, 7.36; N, 7.26.

The second fraction was the Z-isomer (4.6 g, 30%), TLC: one major spot with MeOH, R_f=0.27; HPLC: one major peak on β-cyclodextrin Cyclobond I with 50% MeOH/0.1M NH_4OAc, retention time=9.66 min; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.34 (t, 3H, $COOCH_2CH_3$), 2.09 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.33 (m, 4H, CH_2NCH_2), 3.93 (d, J=7.2 Hz, 2H, NCH_2CH=), 4.28 (q, 2H, $COOCH_2CH_3$), 6.43 (m, 1H, arom), 6.85, 7.55 (d, J=15.6 Hz, 2H, CH=CHCOOEt), 7.09, 7.41 (d, J=8 Hz, 2H, arom), 7.71 (t, 1H, NCH_2CH=).

(E)-3-(6-((E)-3-(1-Pyrrolidinyl)-1-([$^2H_7$]-4-tolyl)-1-propenyl)-2-pyridyl)acrylic acid ([$^2H_7$]-acrivastine, **1**). A mixture of **8** (675 mg, 1.8 mmol) and 2M NaOH (1.8 mL) in ethanol (9 mL) was stirred at room temperature for 16 h. The resulting pale yellow solution was concentrated to remove ethanol. The aqueous residue was acidified to pH 4 by adding 1M H_2SO_4 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous Na_2SO_4, filtered and concentrated to a beige foam. Crystallization from isopropanol gave **1** (378 mg, 59%) as off-white crystals, M.P.=219-M.P.=219-220° C (dec), TLC: one spot with MeOH, R_f=0.48; HPLC: one peak on β-cyclodextrin Cyclobond I with 50% MeOH/0.1M NH_4OAc, retention time=7.89 min; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.06 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.27 (m, 4H, CH_2NCH_2), 3.77 (d, J=7.2 Hz, 2H, NCH_2CH=), 6.77 (d, J=7.2 Hz, 1H, arom), 7.21-7.64 (m 5H, arom, CH=CHCOOH, NCH_2CH=); MS (CI/CH_4) m/z: 356 (13.1, M+1), 97 (45.6, $C_6H_{11}N$·).
Anal Calcd for $C_{22}H_{17}D_7N_2O_2$: C, 74.33; H+D as H, 6.80; N, 7.88. Found: C, 74.24; H+D as H, 6.89; N, 7.85.

Ethyl 3-(6-([$^2H_7$]-4-toluoyl)-2-pyridyl)propionate (**9**). Tris(triphenylphosphine)rhodium(I) chloride (11.1 g, 12.0 mmol) and **6** (8.0 g, 26.4 mmol) were combined in benzene (300 mL) and the resulting mixture was stirred under hydrogen (1 atm) for 24 h at room temperature. Hydrogen uptake was 812 mL (theoretical volume, 592 mL). The mixture was concentrated and purified by chromatography (CH_2Cl_2) to give **9** as a greenish-yellow oil (6.8 g, 85%), TLC: one spot with 25% EtOAc/hexane, R_f=0.40; HPLC: one peak on Versapack C_{18} with 60% MeOH/H_2O/0.1% F_3CCOOH, K'=2.98; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.21 (t, 3H, $COOCH_2CH_3$), 2.82 (t, 2H, CH_2CH_2COOEt), 3.18 (t, 2H, CH_2CH_2COOEt), 4.06 (q, 2H, $COOCH_2CH_3$), 7.34-7.38 (m, 1H, arom), 7.73-7.85 (m, 2H, arom); MS (CI/CH_4) m/z: 333 (11.6, M+29), 305 (100.0, M+1).
Anal Calcd for $C_{18}H_{12}D_7NO_3$: C, 71.03; H+D as H, 6.29; N, 4.60. Found: C, 71.13; H+D as H, 6.33, N, 4.58.

3-(6-([$^2H_7$]-4-Toluoyl)-2-pyridyl)propionic acid sodium salt (**10**). To a stirred mixture of ester **9** (2 g, 6.6 mmol) in EtOH (30 mL) was added 2M NaOH (6.6 mL) and the mixture was stirred at room temperature for 20 h. After concentrating to remove the EtOH, the aqueous residue was diluted with H_2O, adjusted to pH 2 by adding 1N HCl and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to a tan solid. The solid was dissolved in EtOH (50 mL), adjusted to pH 7.98 (the predetermined inflection point) by adding 0.1N NaOH and the solution was concentrated to a tan solid (**10**, 1.5 g, 71%), M.P.=179-181° C, HPLC: one peak on Versapack C_{18} with 50% MeOH/H_2O/0.1 % F_3CCOOH, K'=2.64; ^{1}H-NMR (D_2O, 200 MHz) δ: 2.62 (t, 2H, CH_2CH_2COONa), 3.10 (t, 2H, CH_2CH_2COONa), 7.59 (d, J=7.9 Hz, 1H, arom), 7.69 (d, J=7.8

Hz, 1 H, arom), 7.97 (t, 1H, arom); MS (FABNEG) m/z: 298 (M^-), 275 (M-Na).
Anal Calcd for $C_{16}H_7D_7NO_3Na$: C, 64.42; H+D as H, 4.73; N, 4.70; Na, 7.71. Found: C, 64.46; H+D as H, 4.74; N, 4.68; Na, 7.67.

(E)-3-(6-(3-(1-Pyrrolidinyl)-1-([$^2H_7$]-4-tolyl)-1-propenyl)-2-pyridyl)propionic acid (2).

A solution of 2.14M n-BuLi in hexane (16 mmol) was added dropwise to a suspension of pyrrolidinoethylphosphonium bromide (7, 6.6 g, 15 mmol) in THF (35 mL) with stirring under N_2 at 0° C. The resulting dark colored solution was stirred for an hour at 0° C and treated with **10** (4.5 g, 15 mmol). The reaction was allowed to warm to room temperature during 2 h and then heated at reflux for 2 h. The reaction was diluted with H_2O, extracted with Et_2O (discarded) and the aqueous solution was acidified to pH 5-6 by adding 1N HCl. Extraction with $CHCl_3$ gave a beige foam (5.7 g) after drying and concentration. Chromatography of the foam (25% MeOH/EtOAc - MeOH) gave 2.4 g of product. Crystallization from acetone gave white crystals of **2** (0.8 g, 15%), M.P.=154-156° C, TLC: one spot with MeOH, R_f=0.35; HPLC: one peak on β-cyclodextrin Cyclobond I with 50% MeOH/0.1M NH_4OAc, retention time=7.01 min; ^{1}H-NMR ($CDCl_3$, 200MHz) δ: 2.02 (m, 4H, $CH_2CH_2NCH_2CH_2$), 2.72-2.86 (m, 2H, CH_2CH_2COOH), 3.12-3.30 (m, 6H, CH_2NCH_2, CH_2CH_2COOH), 3.68 (d, J=7.1 Hz, 2H, NCH_2CH=), 6.61 (d, J=7.6Hz, 1H, arom), 7.04 (d, J=7 Hz, 1H, arom), 7.25 (t, 1H, arom), 7.40 (t, 1H, NCH_2CH=); MS (CI/CH_4) m/z: 386 (7.2, M+29), 358 (100.0, M+1), 296 (86.1, M-61).
Anal Calcd for $C_{22}H_{19}D_7N_2O_2$: C, 73.91; H+D as H, 7.33; N, 7.84. Found: C, 73.70; H+D as H, 7.37; N, 7.80.

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