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Synthesis of A-79175: a second generation 5-lipoxygenase inhibitor

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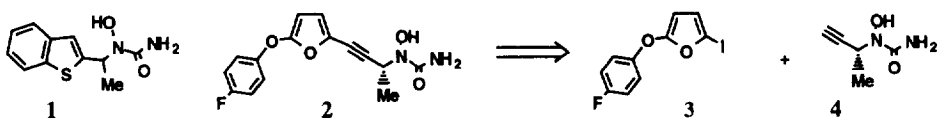
Abstract: A convergent, high yielding, and scalable synthesis of A-79175, with a key step involving a mild and efficient Cu–Pd catalyzed coupling reaction of a terminal acetylene with a substituted 2-iodofuran is discussed. © 1997 Elsevier Science Ltd

Inhibition of the 5-lipoxygenase (5-LO) enzyme has been shown to have therapeutic value in the treatment of inflammatory and allergic disorders such as asthma.[1] The success of zileuton (**1**) in this regard has prompted the discovery of even more effective *N*-hydroxyurea inhibitors of this enzyme, which block the biosynthesis of leukotrienes. The second generation 5-LO inhibitor (+) A-79175 (**2**) has improved potency and longer duration of action than **1**.[2] Herein we report a synthesis that has been used to prepare multikilogram quantities of **2**.



An initial synthesis of **2** involved a linear sequence of synthetic steps followed by a resolution, to provide it optically pure.[3] A new approach to the synthesis of **2** was examined where the optically pure chiral moiety could be introduced at a different stage of the synthesis. A potentially attractive method to couple an acetylenic moiety onto a halo-aromatic ring involved the use of a palladium–copper catalyzed coupling reaction of a halo-arene to a terminal acetylene.[4] Such an approach would be advantageous due to the mild conditions under which the coupling step could be effected as well as the convergent nature of the synthetic sequence.

Several methods were evaluated to synthesize both iodofuran (**3**) and butynyl hydroxyurea (**4**) moieties. The synthesis of **3** (Scheme 1) began with 5-nitro-2-furaldehyde dimethyl acetal (**5**), which was treated with 2 equivalents potassium *p*-fluorophenolate[5] to give aldehyde (**6**) in 70% yield. Oxidation of aldehyde (**6**) to the furoic acid (**7**) was accomplished with $NaH_2PO_4/NaClO_2$/DMSO[6] in 75% yield. We next turned our attention to convert **7** to **3** in one step. Such reactions are precedented, but are known to occur in low yield.[7] This reaction was explored in great detail.[8] It was critical that the conversion of **7** to **3** be performed in a biphasic (ethyl acetate/water) rapidly stirred solution with 1.2 eq KOH, 2.2 eq, KI, and 1.0 eq I_2. Under these conditions, product yields routinely exceeded 90% on large scale (>50 kg).

The previously reported methods[9] to prepare **4** were problematic on large scale. The synthesis of (R)-*N*-3-butyn-2-yl-*N*-hydroxyurea (**4**, Scheme 2), suitable for the preparation of up to 50 kg, begins with the mixture of (S)-trimethylsilyl-3-butyn-2-ol (**8**) and the corresponding acetate (R)-**9**.[10] The mixture was treated with *N,O*-bis(phenoxycarbonyl)hydroxylamine[11] under Mitsunobu conditions to provide

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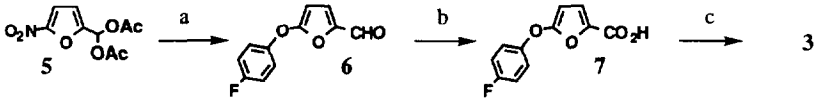
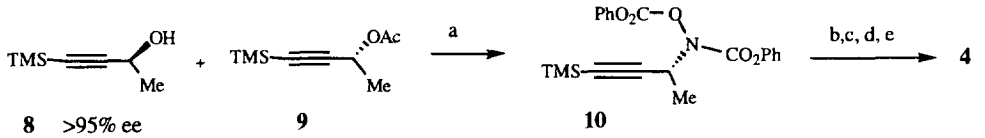


[a]reagents and conditions: a) 2.0 eq 4-fluorophenol, 2.0 eq KOt-Bu, THF (rt, 5h) b) $NaClO_2$, NaH_2PO_4 DMSO[6] c) 1.2 eq aq KOH, 2.2 eq KI, 1.0 eq I_2 water-ethyl acetate, 50-60 °C, 2h

Scheme 1. [a]

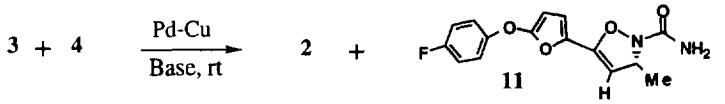
the (R) urethane derivative (**10**) in 95% yield. Conversion of **10** to **4** was accomplished as shown below with the overall yield of **8** to (R)-**4** being 75% (99% ee) after crystallization from acetonitrile.



[b]reagents and conditions: a) $PhO_2CNHOCO_2Ph$, Ph_3P,DIAD, THF, b) aq. NH_3, THF, rt, c) remove THF, filter solid, d) wash aq. layer with toluene, e) add NaCl to aq. layer and extract with ethyl acetate.

Scheme 2. [b]

With efficient methods to prepare both **3** and **4** several palladium–copper catalyzed reactions were evaluated to form **2**. When terminal acetylene (**4**) was allowed to react with iodofuran (**3**) in the presence of 2 mol% $(MeCN)_2PdCl_2$, 4 mol% Ph_3P, 4 mol% CuI, 1.2 eq iPr_2NH in ethyl acetate (ambient temperature), **2** was formed in 98% yield after 2 h. When triethylamine was substituted for di-isopropylamine **2** was formed in only 60% yield after 8 h. In the latter case, the crude mixture contained approximately 20% of unreacted **3**, **4**, and 10–15% isoxazole **11**.



In conclusion, a short, convergent, and high-yielding synthesis of A-79175 in greater than 99% optical purity, in 4 steps from **5**, has been developed that has produced **2** in multi-kilogram quantities by application of an efficient decarboxylative–iodination procedure to yield **3**, a short synthetic sequence to provide **4**, followed by an efficient and mild copper–palladium coupling of **3** and **4** to give A-79175.

Experimental

General experimental

Melting points were determined by using a Thomas Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured using a Perkin Elmer 241 Polarimeter. IR spectra were obtained by using pressed KBr pellets, thin film on a sodium chloride plate, or in solution on a Nicolet 5SXC IR Spectrometer as noted. ^1H and ^{13}C spectra were recorded on either a General Electric QE 300 at 300 MHz and 75.5 MHz or a Bruker AMX400 at 400 MHz and 100.6 MHz, respectively with the chemical shifts reported in ppm (δ) downfield from TMS. Mass Spectra were obtained with a Hewlett Packard HP5985 spectrometer (DCI/NH_3). Elemental Analyses were performed on a JEOL SX102Q/FAB high resolution mass spectrometer.

5-(4-Fluorophenoxy)-2-furaldehyde ***6***

To a 250 mL round bottom flask with magnetic stir bar was added 5-nitro-2-furaldehyde diacetate (**5**) Aldrich (4.35 g, 17.89 mmol, 1.00 eq) and THF (30 mL). The resulting solution was cooled to 0°C in an ice–water bath. To this solution was added a stirred solution of 4-fluorophenol (4.21 g, 37.55 mmol, 2.1 eq), potassium tert-butoxide (4.26 g, 37.55 mmol, 2.1 eq) in THF (40 mL) over a period

of 0.5 h while maintaining the internal temperature of the reaction mixture below 10°C. After the addition of potassium 4-fluorophenolate in THF was complete, the resulting solution was allowed to warm to ambient temperature and stir for an additional 3 h. It was then concentrated under vacuum to afford a dark brown solid, which was allowed to stir over heptane (100 mL) for 3 h. The solid was removed by filtration and it was allowed to stir over water (100 mL) for 3 h. The solid was removed by suction filtration and was allowed to dry yielding 2.63 g of **6** (71%) as a light brown solid. mp 76–77°C. IR KBr (cm^{-1}) 765, 1499, 1661. ^1H NMR (300 MHz, DMSO-δ6) δ 5.81 (d,1H, J=3.8 Hz), 7.29–7.41 (m,4H), 7.59 (d,1H, J=3.8 Hz), 9.35 (s,1H). ^{13}C NMR (75.5 MHz, DMSO-δ6) δ 90.0, 117.0 (d, J=24.4 Hz), 121.1 (d, J=9.8 Hz), 127.5 (brs), 144.5, 149.9 (d, J=2.4 Hz), 159.5 (d, J=242.9 Hz), 162.0, 176.2. ms (DCI/NH_3) m/z 149, 207 $(m+H)^+$, 224 $(m+NH_4)^+$. Anal: Cal m/z for $(M+H)^+$: $C_{11}H_8FO_3$ 207.0457; Found 207.0460.

5-(4-Fluorophenoxy)-2-furoic acid 7

The compound was prepared according to the published procedure[6] in 75% yield. mp 159°C. IR KBr (cm^{-1}) 1502, 1703. ^1H NMR (300 MHz, DMSO-δ6) δ 5.79 (d,1H, J=3.6 Hz), 7.23 (d,1H, J=3.6 Hz), 7.26–7.31 (m,4H), 12.9–13.1 (brs,1H). ^{13}C NMR (75.5 MHz, DMSO-δ6) δ 90.3, 116.8 (d, J=23.2 Hz), 120.2 (d, J=8.5 Hz), 120.5, 136.7, 150.8 (d, J=2 Hz), 158.7, 158.9, 159.1 (d, J=240.7 Hz). ms (DCI/NH_3) m/z 179, 240 $(m+NH_4)^+$. Anal: Cal m/z for $(M+K)^+$: $C_{11}H_7FO_4K$ 260.9965; Found 260.9964.

5-(4-Fluorophenoxy)-2-iodofuran 3

To a 250 mL round bottom flask with magnetic stir bar was added sodium hydroxide (1.22 g, 30 mmol, 1.2 eq), water (35 mL) and acid **7** (5.5 g, 25 mmol, 1.0 eq). The mixture was allowed to stir at room temperature until a clear homogeneous solution was formed. After all **7** was in solution, the mixture was heated to 50°C and isopropyl acetate (40 mL) was added. To this stirring mixture, a *homogeneous* solution of potassium iodide (8.3 g, 50 mmol, 2.0 eq), iodine (6.35 g, 25 mmol, 1.0 eq) in water (100 mL) was added over 0.75 h while maintaining the internal temperature of the reaction mixture between 50–55°C. After stirring at this temperature for an additional 2 h, the solution was cooled to room temperature and transferred to a separatory funnel where the solution was extracted with 2×50 mL portions of ethyl acetate. The combined organic layers were washed with a 4% aqueous sodium thiosulfate solution (100 mL) and were dried over sodium sulfate. The organic solution was concentrated in vacuo to give 6.9 g of **3** (95%) as an oil. **Caution**: compound **3** is extremely unstable when it is stored neat. Upon heating as a neat oil, **3** has decomposed violently to iodine and polymeric tars. Compound **3** is best stored as a 5–10% solution in ethyl acetate. IR NaCl/film (cm^{-1}) 780. ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 (d,1H, J=3.3 Hz), 6.50 (d,1H, J=3.3 Hz), 6.9–7.1 (m,4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 92.3, 116.2 (d, J=23.7 Hz), 118.4 (d, J=8.3 Hz), 121.9, 152.4 (d, J=2.5 Hz), 159.2 (d, J=242 Hz), 159.8. Anal: Cal m/z for M^+: $C_{10}H_6FIO_2$ 303.9397; Found 303.9408.

(R)-N-3-Butyn-2-yl-N-hydroxyurea 4

To a 0°C solution of 4-TMS–3-butyn-2-ol[10] (10.0 g, 70.4 mmol), triphenylphosphine (18.5 g, 70.4 mmol) and N,O di(phenoxycarbonyl) hydroxylamine[11] (17.8 g, 70.4 mmol) in THF (200 ml) was added a solution of diisopropylazodicarboxylate (13.9 ml, 70.4 mmol) in 50 ml THF, dropwise with stirring. After stirring at 0°C for 1.5 h, the reaction mixture was warmed to room temperature. The volatiles were removed in vacuo, and the remaining oil was taken up in 100 ml of methanol and 200 ml NH_4OH then stirred at room temperature for 2 days. The methanol was removed in vacuo and the aqueous reaction mixture was further diluted with water and extracted two times with CH_2Cl_2 or toluene. These organic extracts contain the by-products from the reaction and are discarded. The desired product remains in the aqueous portion, which was saturated with NaCl and extracted four times with ethyl acetate, or until TLC indicates all of the product is out of the aqueous layer. These washings were combined, dried over $MgSO_4$ and concentrated to give a light orange oil which solidifies on cooling. The product may be purified in one of two ways. Flash chromatography (9:1 $CHCl_3$:

MeOH) provides a solid which can be further purified by recrystallization from CH_2Cl_2/methanol (mp=130.5–131.5°C; $[\alpha]_D$=+54.5 (c=1.15, MeOH). The crude solid may be directly recrystallized to give material of high purity; the mother liquors from the recrystallization are then chromatographed as above and recrystallized. The aminolysis takes a significantly longer period of time (2–3 days) due to the formation of a carbamoyl intermediate, which is very slowly converted to product under these conditions. In order to monitor the progress of the aminolysis and visualize the above intermediates, elute TLC plates with 20% methanol/$CHCl_3$ and develop plates with ninhydrin/heat. Spectral data were identical to those reported for the known compound.[9a,b]

*(R)-(+)-*N*-[3-[5-[(4-Fluorophenoxy)methyl]-2-furyl]-1-methyl-2-propynyl-*N*-hydroxy-urea* **2**

To a solution of **3** (35 g, 109 mmol) in ethyl acetate (200 mL) was added **4** (14 g, 109 mmol) at 20°C. The internal temperature of the reaction vessel was maintained at 20°C throughout the course of the reaction by water bath cooling. To this solution was added palladium (II) bis(acetonitrile)dichloride (0.259 g, 1 mmol), cuprous iodide (0.380 g, 1 mmol), triphenyl phosphine (0.524 g, 2 mmol), and diisopropyl amine (15 mL, 1 eq). The reaction was allowed to stir between 20–25°C for 1.5 h. It was then poured into an ice cold mixture of water:heptane (250 mL:600 mL) and was stirred for 0.4 h, filtered, and washed with water. The solid was triturated with 25% dichloromethane/heptane, filtered and washed with 50 mL of heptane to give 26.13 g of **2** 86% as a colorless solid. Spectral characteristics and optical rotation were identical to those reported.[3] The percent enantiomeric excess of **2** was determined to be greater than 99 by use of a Chiralpak AD 4.6×250 HPLC column from Chiral Technologies, Exton, PA. The mobile phase employed was 93:7 hexane:ethanol and the flow rate was 1.0 mL/min at ambient temperature and 254 nm. The retention times of the enantiomers were 19 and 21.5 min. Substitution of triethyl amine for diisopropyl amine resulted in a much slower reaction (16 h) and the appearance of **11**, (10–15%) as a high rF TLC spot, using 5% methanol/chloroform as the eluent, was observed. Data for compound **11** amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d,3H, J=6.4 Hz), 5.22 (d,q,1H, J_1=6.4 Hz,J_2=2.8 Hz), 5.28 (d,1H, J=2.7 Hz), 5.64–5.50 (brs,2H), 5.53 (d,1H, J=3.7 Hz), 6.47 (d,1H, J=3.4 Hz), 7.0–7.1 (m,4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3, 61.6, 89.5, 98.6, 110.3, 116.4 (d, J=24.4 Hz), 119.1 (d, J=8.5 Hz), 135.1, 143.7, 151.9 (d, J=2.5 Hz), 157.8, 159.5 (d, J=242 Hz), 162.3. ms (DCI/NH_3) m/z 104, 247, 262, 305 $(M+H)^+$, 322 $(M+NH_4)^+$.

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