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2-Butyl-4-iodoimidazole-5-carboxaldehyde: A Versatile Intermediate for the Synthesis of Highly Functionalized Imidazoles

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2-BUTYL-4-IODOIMIDAZOLE-5-CARBOXALDEHYDE: A VERSATILE INTERMEDIATE FOR THE SYNTHESIS OF HIGHLY FUNCTIONALIZED IMIDAZOLES

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Abstract: The facile preparation of 2-butyl-4-iodoimidazole-5-carboxaldehyde **1** is described. The versatility of this intermediate in the synthesis of highly functionalized imidazoles is demonstrated with the synthesis of two potent and selective angiotensin II receptor antagonists.

Angiotensin II (AII) is the octapeptide responsible for the peripheral effects of the renin-angiotensin system.[1] These effects include the regulation of blood pressure, volume homeostasis, and salt retention. Activity has been intense in the area of developing novel nonpeptide AII antagonists, spurred initially by the discovery of Furukawa et al.[2,3] and

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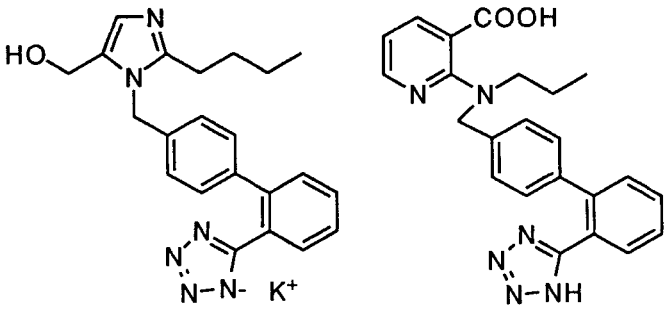


DuP 753 **A-81988**

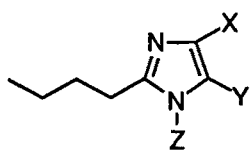
Figure 1.

recently accelerated by reports from workers at DuPont-Merck detailing their structure-activity relationship studies that have resulted in the clinical candidate DuP 753.[4,5] A large number of companies have subsequently disclosed structures of non-peptidic AII receptor antagonists.[6] We have prepared a number of these compounds for evaluation versus our own recently disclosed candidate A-81988.[7] In this report we describe the syntheses of two such imidazole containing AII inhibitors that utilize 2-butyl-4-iodoimidazole-5-carboxaldehyde **1** as a common intermediate. The preparation of this intermediate is short, reliably high yielding, and amenable to multi-gram scale.

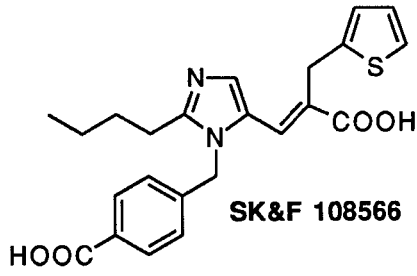
2-Butyl-4-chloroimidazole-5-carboxaldehyde[8] **2** had been prepared by the oxidation of 2-butyl-4-chloro-5-(hydroxymethyl)imidazole[2] **3**, however, in our hands the high pressure condensation of imidate ester **4** with 1,3-dihydroxyacetone and ammonia to produce this compound proceeded in low and variable yield (0-30%). A report by Groziak[9] prompted us to investigate the regioselective halogen-metal exchange of 1-[(benzyloxy)methyl]-2-butyl-4,5-diiodoimidazole **6**. We anticipated that

the resultant 2-butyl-4-iodoimidazole-5-carboxaldehyde **1** would be a versatile intermediate allowing for regioselective N^1-imidazole alkylation and functionalization of the aryl iodide into more elaborate polyfunctional imidazoles. Recently both Groziak[10] and Lipshutz[11] have independently described methodology involving sequential halogen-metal exchange / functionalization of 2,4,5-trihaloimidazoles applicable to the synthesis of a variety of 2,4,5-trisubstituted imidazoles, in some cases in a single pot.

2-Butylimidazole was prepared by oxidation of 2-butylimidazoline[12] according to the method of Knapp and Schugar.[13] Diiodination was carried out using a slightly modified version of the procedure of Pauley[14] to give **5** in 97% yield. The (benzyloxy)methyl moiety was introduced under standard conditions[9] (**6** in 99% yield). Halogen-metal exchange was accomplished by treatment of a THF solution of the diiodide **6** at -78°C with 1.4 equivalents *n*-butyllithium. Addition of a THF solution of *N*-methyl-*N*-(2-pyridyl)formamide[15] to the resulting imidazol-5-yllithium species followed by aqueous work up provided a mixture of the desired imidazole-5-carboxaldehyde **7** (66% yield) and 1-[(benzyloxy)methyl]-2-butyl-4-iodoimidazole **8** (19% yield). The (benzyloxy)methyl protecting group proved to be more resistant to acid hydrolysis than anticipated. Treatment of the N^1-[(benzyloxy)methyl]-imidazole-5-carboxaldehyde **7** with HOAc/THF/water, aqueous 10% HCl in THF/methanol, or 6M HCl/methanol resulted in recovered starting material. Reflux of an ethanolic solution of the *N*-[(benzyloxy)methyl]imidazole **7** and concentrated hydrochloric acid removed the (benzyloxy)methyl moiety and partially acetalized the aldehyde to give a mixture of **1** and **9**. This mixture was converted to the aldehyde **1** by stirring in an acetone solution with pTsOH-H_2O (98% yield).



1 X=I; Y=CHO; Z=H
2 X=Cl; Y=CHO; Z=H
3 X=Cl; Y=CH_2OH; Z=H
5 X,Y=I; Z=H
6 X,Y=I; Z=CH_2OCH_2Ph
7 X=I; Y=CHO; Z=CH_2OCH_2Ph
8 X=I; Y=H; Z=CH_2OCH_2Ph
9 X=I; Y=$CH(OEt)_2$; Z=H



SK&F 108566

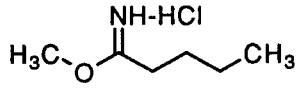


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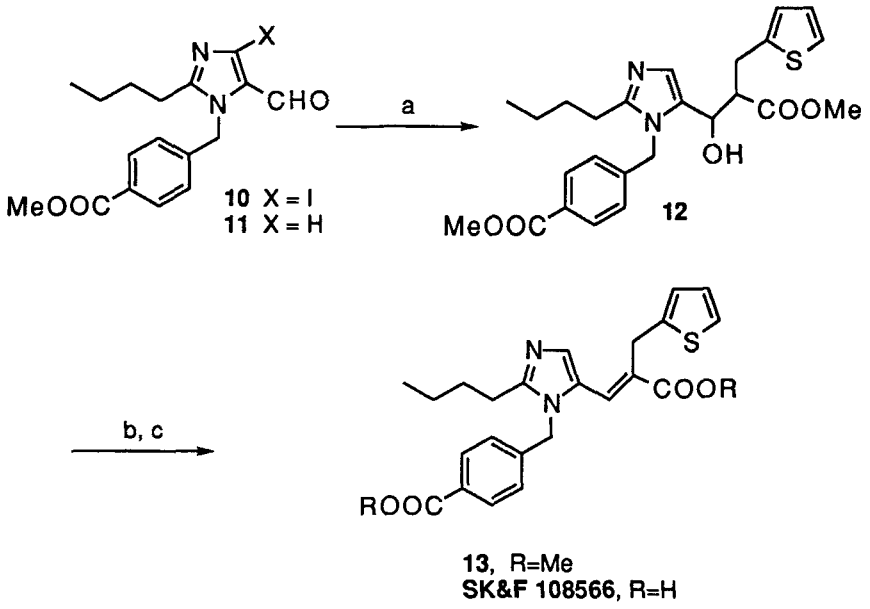
Figure 2.

In a recent communication SK&F 108566 was described as a potent and selective AII receptor antagonist.[16] We were able to substitute the iodoimidazole for the chloroimidazole in the synthesis of SK&F 108566 which was carried out as described[16] without incident (Scheme 1). Alkylation of iodoimidazole **1** with methyl 4-(bromomethyl)benzoate gave the *N*[1]-benzyl-4-iodoimidazole **10** (91% yield) with no trace of the regioisomer. The des-haloimidazole was reported to give a 1:1 ratio of regioisomeric products.[16] Hydrogenolysis on 10% Pd/C followed by condensation with the lithium enolate derived from treatment of methyl 3-(2-thienyl)propionate with LDA gave a mixture of aldol products **12**. Acetylation and based induced elimination provided the diester **13** (35% yield from aldehyde **10**) which was hydrolyzed to the required diacid SK&F 108566.

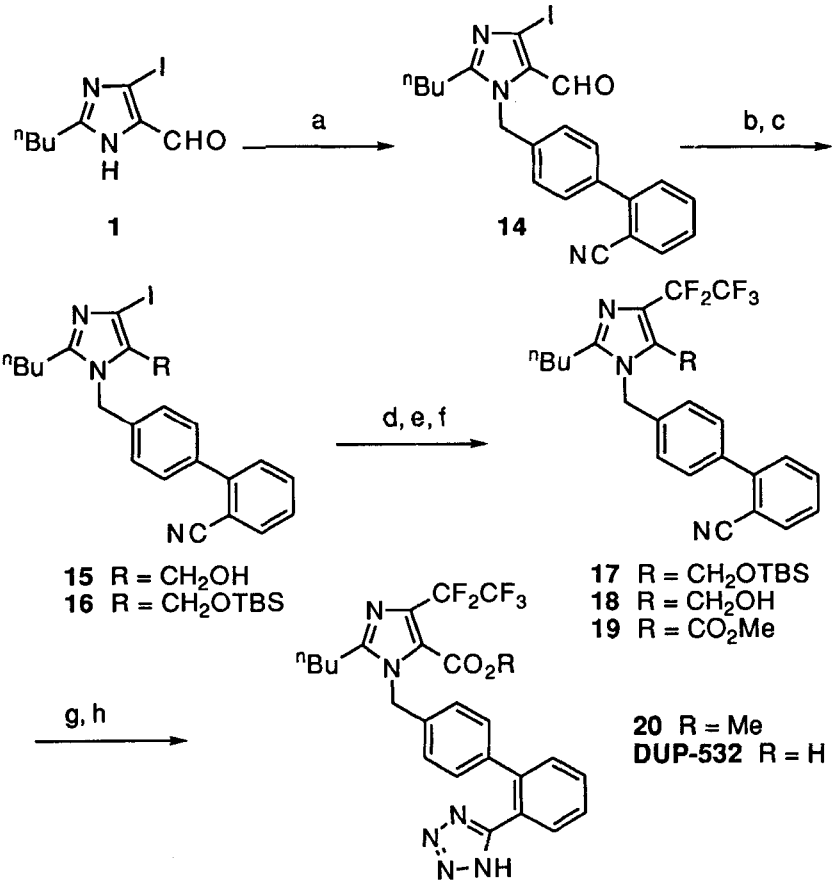
Recently Carini *et al* [8] have disclosed a series of perfluoroalkyl imidazoles to be potent AII receptor antagonists. The iodoimidazole **1**



a) (i) 10% Pd/C, H_2 (1 atm), NaOAc, MeOH, (ii) LDA, methyl 3-(2-thienyl)propionate, THF, -78°C, then **10**; b) (i) Ac_2O,DMAP, CH_2Cl_2, (ii) DBU, $PhCH_3$, reflux; c) NaOH, EtOH, H_2O.

Scheme 1.

again lends itself to a relatively simple synthesis of these compounds (Scheme 2). Reaction of the free imidazole **1** with the 2-[4-(bromomethyl)-phenyl]benzonitrile gave aldehyde **14**. Reduction with sodium borohydride followed by reaction of the resultant alcohol **15** with t-butyl-dimethylchlorosilane gave the silyl ether **16**. Copper-catalyzed cross coupling afforded the perfllluoroethyl imidazole **17**. Deprotection of the alcohol, and direct oxidation to the methyl ester employing MnO_2-NaCN failed in our hands. We resorted to the reliable three step sequence of oxidation to the aldehyde, subsequent chlorite oxidation to the acid, and



Reagents and Conditions: a, BFN-Br, K_2CO_3, DMF; b, $NaBH_4$, EtOH-CH_2Cl_2; c, $^tBuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2; d, $Cd(CF_2CF_3)_2$, DMF-HMPA, 70°C;e, aq.HCl-THF; f, (i) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, then Et_3N and up to rt, (ii)$NaClO_2$, KH_2PO_4, $MeCH{=}CMe_2$, ^tBuOH, H_2O, (iii) CH_2N_2, Et_2O; g, Bu_2SnO (cat.), Me_3SiN_3, PhMe, 110°C; h, LiOH, THF, H_2O.

Scheme 2.

conversion to the methyl ester **19** with diazomethane. The nitrile moiety was converted to the tetrazole **20** utilizing the catalytic dibutyltin oxide-trimethylsilyl azide procedure.[17] Ester hydrolysis was effected under standard conditions with lithium hydroxide to afford the target tetrazolo-acid DUP-532. Using this synthetic scheme we were readily able to prepare gram-scale quantities of material for in vivo evaluation.

We have described a short reliable preparation of 2-butyl-4-iodoimidazole-5-carboxaldehyde **1** that has proven to be a veristle intermediate in the synthesis of two distinct nonpeptide angiotensin II antagonists. We foresee the use of similar 2-substituted-4-iodoimidazole-5-carboxaldehydes (e.g. **1**) or their precursors the 1-(benzyoxymethyl)-2-butyl-4,5-diiodoimidazoles (e.g. **6**) as valuble intermediates in the synthesis of a variety of highly functionalized imidalozes.

Experimental Section

General. Reagents and solvents were used as received from commercial suppliers without further purification unless otherwise noted. Melting points were taken on an automated Mettler FP62 apparatus and are uncorrected. NMR spectra were recorded with tetramethylsilane as an internal standard. NMR and mass spectra were measured by the Structural Chemistry Department at Abbott Laboratories. Elemental analyses were performed by either the Structural Chemistry Department at Abbott Laboratories or Oneida Research Services, Whitesboro, NY. Flash chromatography was performed on silica gel 60, 0.04-0.063 mm (E. Merck).

2-Butyl-4,5-diiodoimidazole (5)

To a solution of 2-butylimidazole[13] (0.73 g, 5.9 mmol) in a dioxane-water mixture (1:1, 20 mL) was added sodium carbonate (1.89 g, 17.8 mmol) and iodine (3.30 g, 13.0 mmol). The reaction mixture was stirred,

protected from the light, at rt for 23 h Ethyl acetate was added (ca. 50 mL) and the mixture was twice washed with aqueous $Na_2S_2O_3$ solution. The aqueous portions were extracted twice with ethyl acetate, and the combined organics were washed with brine then dried ($MgSO_4$). Filtration and solvent evaporation left 2.16 g **5** (97% yield) as a white solid. An analytical sample was obtained by recrystallization from ether. mp 164-165°C (dec); ^{1}H NMR (300 MHz, D^6-DMSO) δ 12.5 (br s, 1H), 2.58 (t, *J*= 7 Hz, 2H), 1.63-1.5 (m, 2H), 1.34- 1.20 (m, 2H), 0.76 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, D^6-DMSO) δ 154.1, ca. 94.5, ca. 76.0, 29.8, 27.6, 21.5, 13.5; MS (DCI-NH_3) *m/z* 377 $(M+H)^+$; HRMS for $C_7H_{11}N_2I_2$, calc. 375.8931, found 375.8932; Anal. for $C_7H_{10}N_2I_2$, calc. C, 22.36, H, 2.68, N, 7.45, found C, 22.35, H, 2.65, N, 7.28.

1-(Benzyloxymethyl)-2-butyl-4,5-diiodoimidazole (6)

To a mixture of imidazole **5** (2.15 g, 5.71 mmol) and anhydrous potassium carbonate (7.7 g, 56 mmol) in dry DMF (20 mL) was added dropwise chloromethyl benzyl ether (0.88 mL, 6.3 mmol). The reaction was vigorously stirred 19 h. The solids were filtered off and rinsed with DMF. The filtrate was concentrated and the residue was subject to flash chromatography on silica gel eluting with 10% ethyl acetate - hexanes to provide 2.80 g **6** (99% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.37 (s,2H), 4.53 (s, 2H), 2.8-2.7 (m, 2H), 1.8-1.65 (m, 2H), 1.45- 1.30 (m, 2H), 0.91 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 136.3, 128.6, 128.3, 127.8, 95.5, 81.5, 75.8, 70.5, 30.0, 27.7, 22.4, 13.7; MS (DCI-NH_3) *m/z* 497 $(M+H)^+$; HRMS for $C_{15}H_{19}N_2OI_2$, calc. 496.9600, found 496.9593; Anal. for $C_{15}H_{18}N_2OI_2$, calc. C, 36.31, H, 3.66, N, 5.65, found C, 36.26, H, 3.61, N, 5.58.

1-(Benzyloxymethyl)-2-butyl-4-iodoimidazole-5-carboxaldehyde (7)

To a solution of the diiodoimidazole **6** (19.1 g, 38.5 mmol) in THF (170 mL) at -78°C was added a solution of *n*-BuLi (2.16 M hexanes, 25.0 mL, 54 mmol) over 30 min. After 25 min a solution of *N*-methyl-*N*-(2-pyridyl)formamide (9.75 g, 71.6 mmol) in THF (15 mL) was added. After 30 min the reaction was quenched with saturated aqueous ammonium chloride solution (125 mL) and allowed to warm to rt over approximately

30 min. Ethyl acetate (125 mL) was added and the layers separated. Following a standard extractive work-up the organic portion was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel eluting with 8% to 10% to 15% ethyl acetate - hexanes provided first the desired aldehyde **7** 10.17 g (66% yield) followed by the more polar reduction product **8** 2.68 g (19% yield). **7**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.4-7.2 (m, 5H), 5.81 (s, 2H), 4.58 (s, 2H), 2.76 (m, 2H), 1.81-1.68 (m, 2H), 1.45-1.35 (m, 2H), 0.92 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 159.0, 136.6, 129.2, 128.5, 128.1, 127.7, 102.7, 72.5, 71.2, 29.6, 27.0, 22.5, 13.7; MS (DCI-NH_3) *m/z* 399 $(M+H)^+$; HRMS for $C_{16}H_{20}N_2O_2I$, calc. 399.0600, found, 399.0569; Anal. for $C_{16}H_{19}N_2O_2I$, calc. C, 48.26, H, 4.81, N, 7.03, found C, 48.28, H, 4.84, N, 7.00. **8**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.4-7.25 (m, 5H), 7.0. (s, 1H), 5.21 (s, 2H), 4.46 (s, 2H), 2.72-2.65 (m, 2H), 1.80-1.65 (m, 2H), 1.45-1.30 (M, 2H), 0.92 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 136.0, 128.7, 128.3, 127.9, 125.0, 80.6, 73.8, 70.2, 30.3, 26.6, 22.5, 13.7; MS (DCI-NH_3) *m/z* 371 $(M+H)^+$; HRMS for $C_{15}H_{20}N_2OI$, calc. 371.0600, found, 371.0621; Anal. for $C_{15}H_{19}N_2OI \cdot 0.5H_2O$, calc. C, 47.51, H, 5.32, N, 7.39, found C, 47.83, H, 5.03, N, 7.36.

2-Butyl-4-iodoimidazole-5-carboxaldehyde (1)

A mixture of **7** (10.17 g, 25.5 mmol), concentrated hydrochloric acid (13 mL, 161 mmol) and 95% ethanol (75 mL) was heated at reflux for 1.25 h. The reaction flask was immersed in an ice/water bath and solid sodium carbonate (20 g, 189 mmol) was added in portions. The mixture was stirred and allowed to warm to rt over 30 min. The solids were filtered off and rinsed with ethanol. The filtrate was concentrated, taken up in ethyl acetate (100 mL), and washed with saturated sodium carbonate solution (125 mL). The aqueous phase was extracted with ethyl acetate (2x 50 mL) and the combined organics were washed with brine and dried ($MgSO_4$). Filtration and evaporation to dryness left 9.94 g of *a ca.* 6:1 mixture of aldehyde **1** and acetal **9**. This material was dissolved in acetone (100mL) and treated with p-toluenesulfonic acid monohydrate (ca. 10 mg) and stirred over ca. 2 days. Following aqueous work-up, 8.14 g oily orange solid was obtained. Direct crystallization from ether - hexanes

gave 4.87 g **1**. The mother liquor was subject to flash chromatography on silica gel eluting with 20% ethyl acetate - hexanes. The product containing fractions were pooled and yielded upon recrystallization an additional 2.12 g **1** (98% total yield). mp 103.5°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.0 (br s, 1H), 9.43 (s, 1H), 2.83 (t, *J*= 7 Hz, 2H), 1.82-1.70 (m, 2H), 1.46-1.32 (m, 2H), 0.95 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 157.8, 131.7, ca.99.6, 29.9, 28.5, 22.2, 13.6; MS (DCI-NH_3) *m/z* 279 $(M+H)^+$; Anal. for $C_8H_{11}N_2OI$, calc. C, 34.55, H, 3.99, N, 10.07, found C, 34.66, H, 3.97, N, 10.07.

2-Butyl-1-(4-carbomethoxybenzyl)-4-iodoimidazole-5-carboxaldehyde (10)

A mixture of imidazole **1** (0.87 g, 3.13 mmol), potassium carbonate (1.07 g, 7.75 mmol), and methyl 4-(bromomethyl)benzoate (0.85 g, 3.71 mmol) in DMF (7.0 mL) was heated at ca. 80°C for 17 h. After cooling to rt the solids were filtered off, rinsed with ethyl acetate, and the filtrate was concentrated. The residue was taken up in ethyl acetate (50 mL) and washed with water (50 mL). The aqueous portion was extracted with ethyl acetate (2x 25 mL) and the combined organics were washed with brine and dried ($MgSO_4$). Flash chromatography on silica gel eluting with 15% ethyl acetate - hexanes gave 1.21 g **10** (91% yield). A sample for analysis was recrystallized form ether - hexane. mp 83°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.00 (d, *J*= 8 Hz, 2H), 7.08 (d, *J*= 8 Hz, 2H), 5.63, (s, 2H), 3.91 (s, 2H), 2.63 (dd, *J*= 6, 7 Hz, 2H), 1.72-1.60 (m, 2H), 1.40-1.28 (m, 2H), 0.88 (t, *J*= 7 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 166.4, 157.9, 140.6, 130.2, 129.8, 129.1, 126.1, 101.9, 52.2, 47.6, 29.4, 26.5, 22.4, 13.6; MS (DCI-NH_3) *m/z* 427 $(M+H)^+$; Anal. for $C_{17}H_{19}N_2O_3I$, calc. C, 47.90, H, 4.49, N, 6.57, found C, 47.63, H, 4.50, N, 6.48.

2-Butyl-1-(4-carbomethoxybenzyl)imidazole-5-carboxaldehyde (11)

Iodide **10** (4.25 g, 9,97 mmol), sodium acetate (1.02 g, 2.69 mmol), and 10% Pd/C (0.93 g, 0.87 mmol) in methanol (80 mL) was stirred under an atmosphere of hydrogen for ca. 18 h. Following filtration of the catalyst and evaporation, the residue was partitioned between ethyl acetate (75

mL) and water (50 mL). The aqueous portion was extracted with ethyl acetate (2x 25 mL) and the combined organics were washed with brine the dried ($MgSO_4$). Flash chromatography on silica gel eluting with 60% ethyl acetate - hexanes gave 2.60 g **11** (96% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.98 (d, *J*= 9 Hz, 2H), 7.82 (s, 1H), 7.07 (d, *J*= 9 Hz, 2H), 5.63 (s, 2H), 3.90, (s, 2H), 2.64 (t, *J*= 7 Hz, 2H), 1.75-1.65 (m, 2H), 1.40-1.27 (m, 2H), 0.88 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 166.3, 156.6, 143.5, 141.1, 131.2, 130.0, 129.6, 126.0, 52.0, 47.8, 29.2, 26.3, 22.2, 13.5; MS (DCI-NH_3) *m/z* 301 $(M+H)^+$; Anal. for $C_{17}H_{20}N_2O_3$, calc. C, 67.98, H, 6.71, N, 9.33, found C, 68.05, H, 6.64, N, 9.30.

2-Butyl-1-(4-carbomethoxybenzyl)-5-[2-carbomethoxy-1-hydroxy-3-(2-thienyl)propyl]imidazole (12)

To LDA (prepared in THF (50 mL) from diisopropylamine (4.0 mL, 28.5 mmol) and *n*-BuLi (2.16 M hexanes, 12.7 mL, 27.4 mmol)) at -78°C was added methyl 3-(2-thienyl)propionate (4.68 g, 27.5 mmol) in THF (22 mL). Following the addition, the reaction was stirred for 30 min before a solution of the aldehyde **11** (2.79 g, 9.29 mmol) in THF (17 mL) was added. After 30 min the reaction mixture was partitioned between ethyl acetate (125 mL) and saturated ammonium chloride solution (125 mL). The layers were separated and the organics washed with saturated ammonium chloride solution (125 mL). The combined aqueous portions were extracted with ethyl acetate (2x 50 mL). The combined organics were washed with brine and dried ($MgSO_4$). Flash chromatography on silica gel eluting with ethyl acetate gave 4.96 g **12** (113% of theory) as a yellow foam used directly in the following step.

2-Butyl-1-(4-carbomethoxybenzyl)-5-[2-carbomethoxy-3-(2-thienyl)prop-1-enyl]imidazole (13)

To the crude aldol reaction product **12** (4.95 g, ca. 9.2 mmol) and DMAP (ca. 20 mg) in methylene chloride (50 mL) was added acetic anhydride (1.0 mL, 10.6 mmol). After 2 h at rt water (5 mL) was added, the mixture was stirred for 10 min and then was washed with saturated sodium bicarbonate solution (2x 50 mL). The combined aqueous portions were

extracted with methylene chloride (2x 25 mL) and combined organics were washed with brine and dried ($MgSO_4$). Solvent evaporation left 5.06 g crude acetates which were taken up in toluene (50 mL), treated with DBU (3.0 mL, 20 mmol), and heated at 80°C for 3 h. Following usual extractive aqueous work-up, flash chromatography on silica gel eluting with 30% to 50% ethyl acetate - hexanes gave 1.46 g **13** (35% yield from aldehyde **11**) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J*= 9 Hz, 2H), 7.45 (s, 1H), 7.43 (s, 1H), 7.11 (dd, *J*= 2, 5 Hz, 1H), 7.03 (d, *J*= 9 Hz, 2H), 6.89 (dd, *J*= 3, 5 Hz, 1H), 6.79 (dd, *J*= 2, 3 Hz, 1H), 5.23 (s, 2H), 4.09 (s, 2H), 3.92 (s, 3H), 3.73 (s, 3H), 2.64 (t, *J*= 7 Hz, 2H), 1.75-1.65 (m, 2H), 1.41-1.30 (m, 2H), 0.88 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 166.4, 151.6, 141.0, 140.9, 132.0, 130.4, 130.0, 128.3, 127.1, 126.8, 125.8, 125.5, 124.6, 123.6, 52.2 (2C), 46.5, 29.6, 28.9, 27.0, 22.4, 13.7; MS (DCI-NH_3) *m/z* 453 $(M+H)^+$; HRMS for $C_{25}H_{29}N_2O_4S$, calc.453.1848 , found, 453.1844; Anal. for $C_{25}H_{28}N_2O_4S \cdot 0.5H_2O$, calc. C, 65.05, H, 6.33, N, 6.07, S, 6.95, found C, 65.28, H, 6.00, N, 6.03, S, 7.06.

SK&F 108566

The diester **13** (1.32 g, 2.91 mmol) was stirred a rt in a mixture of 95% ethanol (14 mL) and 3.75 M NaOH solution (7.0 mL, 26 mmol) for 4 h. Acetic acid (1.54 mL, 26.9 mmol) was added and the mixture was concentrated in vacuo. The residue was partitioned between 10% i-PrOH - chloroform and brine (50 mL each). Following extractive work-up and solvent removal, the residue (0.93 g) was purified by recystallization from methylene chloride - methanol yielding 0.72 g **SK&F 108566** (58 % yield). *mp* 258°C (*dec*); ^1H NMR (300 MHz, D_6-DMSO) δ 12.8 (br s, 2H), 7.93 (d, *J*= 9 Hz, 2H), 7.45, (s, 1H), 7.32-7.27 (m, 2H), 7.08 (d, *J*= 9 Hz, 2H), 6.93 (dd, *J*= 3, 5 Hz, 1H), 6.82 (dd, *J*= 1, 3 Hz, 1H), 5.43 (s, 2H), 4.00 (s, 2H), 2.66 (t, *J*= 7 Hz, 2H), 1.62-1.50 (m, 2H), 1.35-1.20 (m, 2H), 0.83 (t, *J*= 7 Hz, 3H); ^{13}C NMR (75 MHz, D_6-DMSO) δ 168.3, 166.8, 151.2, 141.9, 141.3, 131.3, 130.0, 129.8, 127.6, 126.8, 126.7, 125.9, 125.0, 124.5, 123.8, 45.7, 29.1, 28.3, 26.0, 21.6, 13.5; MS (DCI-NH_3) *m/z* 425 $(M+H)^+$; HRMS for $C_{23}H_{25}N_2O_4S$, calc. 425.1535, found, 425.1525; Anal. for $C_{23}H_{24}N_2O_4S$, calc. C, 65.08, H, 5.70, N, 6.60, S, 7.52, found C, 65.17, H, 5.64, N, 6.56, S, 7.75.

2-Butyl-4-iodo-1-[4-(2-cyanophenyl)phenyl]methyl-imidazole-5-carbox-aldehyde (14).

The imidazole **1** (2.47 g, 8.9 mmol) was dissolved in dry DMF (18 mL) and to the stirred solution was added successively anhydrous potassium carbonate (2.47 g, 17.7 mmol, 2 equiv.) and 2-[4-(bromomethyl)phenyl]benzonitrile (2.47 g, 9.1 mmol, 1.02 equiv.). After 60 h, the mixture was filtered through Celite, and evaporated. Flash chromatography on silica gel eluting with 20% ethyl acetate - hexanes gave compound **14** (2.89 g, 70%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.77 (d, *J*=8 Hz, 1H), 7.64 (td, *J*=8, 3 Hz, 1H), 7.53, (d, *J*=8 Hz, 2H), 7.45 (m, 2H), 7.15 (d, *J*=8 Hz, 2H), 5.62 (s, 2H), 2.69 (t, *J*=7, 6 Hz, 2H), 1.70 (m, 2H), 1.38 (m, 2H), 0.89 (t, *J*=7 Hz, 3H). MS (DCI-NH_3) *m/z* 470 $(M+H)^+$, 344, 226.

2-Butyl-5-hydroxymethyl-4-iodo-1-[4-(2-cyanophenyl)phenyl]methyl-imidazole (15).

To a stirred solution of the aldehyde **14** (2.89 g, 6.16 mmol) in 20% methylene chloride - ethanol (20 mL) at 0°C was added powdered sodium borohydride (58 mg, 1.54 mmol). The mixture was stirred at 0°C for 30 min then most of the solvent was evaporated. The residue was partitioned between water and ethyl acetate, and the organic solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography on silica gel eluting with 50% ether - hexanes gave the alcohol **15** (2.85 g, 98%) as colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J*=8, 3 Hz, 1H), 7.65 (td, *J*=8, 3 Hz, 1H), 7.53 (d, *J*=8 Hz, 2H), 7.46 (td, *J*=8, 3 Hz, 1H), 7.11 (d, *J*=8 Hz, 2H), 5.33 (s, 2H), 4.52 (s, 2H), 2.63 (dd, *J*=7, 6 Hz, 2H), 1.67 (m, 2H), 1.35 (m, 2H), 0.87 (t, J=7 Hz, 3H). MS (DCI-NH_3) *m/z* 472 $(M+H)^+$, 211, 197.

2-Butyl-5-(t-butyldimethylsilyloxy)methyl-4-iodo-1-[4-(2-cyanophenyl) phenyl]methylimidazole (16).

To a suspension of the alcohol **15** (2.85 g, 6.05 mmol) in dry methylene chloride (10 mL) was added successively dry 2,6-lutidine (0.98 mL, 8.47 mmol, 1.4 equiv) and *tert*-butyldimethylsilyl trifluoromethane sulfonate (1.52 mL, 6.65 mmol, 1.1equiv). After 2 h the mixture was diluted with

ether and washed successively with sat. aq. sodium bicarbonate, 1N hydrochloric acid, water, and sat. aq. sodium chloride. The solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel eluting with 30% ether - hexanes gave the silyl ether **16** (3.23 g, 91%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, *J*= 8, 3 Hz, 1H), 7.65 (td, *J*=8, 3 Hz, H), 7.54 (d, *J*=8 Hz, 2H), 7.52 (dd, *J*=8, 3 Hz, 1H), 7.46 (td, *J*=8, 3 Hz, 1H), 7.11 (d, *J*=8 Hz, 2H), 5.33 (s, 2H), 4.52 (s, 2H), 2.62 (dd, *J*=7, 6 Hz, 2H), 1.68 (m, 2H), 1.38 (m, 2H), 0.89 (t, *J*=7 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H). MS (DCI-NH_3) *m/z* 586 $(M+H)^+$, 459, 395, 228, 211, 197.

2-Butyl-5-(t-butyldimethylsilyloxy)methyl-4-pentafluoroethyl-1-[4-(2-cyanophenyl)phenyl]methylimidazole (17).

To a stirred solution of bis(pentafluoroethyl)cadmium (14 mL, 14 mmol, 2.5 equiv., 1M in DMF) at 0°C was added successively hexamethylphosphoramide (18.75 mL), copper (I) bromide (2.0 g, 14 mmol, 2.5 equiv.), and a solution of the iodoimidazole **16** (3.23 g, 5.53 mmol), in DMF (5 mL). The resultant was heatced at 70-75°C for 3h, after which the mixture was poured into water (50 mL) and extracted with ether (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel eluting with 30% ether - hexanes gave the perfluoroethylimidazole **17** (2.67 g, 84%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J=8, 3 Hz, 1H), 7.65 (td, J=8, 3 Hz, 1H), 7.54 (d, J=8 Hz, 2H), 7.46 (m, 2H), 7.09 (d, J=8 Hz, 2H), 5.33 (s, 2H), 4.64 (s, 2H), 2.62 (dd, J=7, 6 Hz, 2H), 1.64 (m, 2H), 1.33, (m, 2H), 0.89 (t, J=7 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 6H). MS (DCI-NH_3) *m/z* 578 $(M+H)^+$, 387, 226, 211.

2-Butyl-5-hydroxymethyl-4-pentafluoroethyl-1-[4-(2-cyanophenyl)phenyl] methylimidazole (18).

The silyl ether **17** (2.67 g, 4.62 mmol) was dissolved in THF (20 mL), and to the stirred solution at room temperature was added 3 N hydrochloric acid (10 mL). After 3h, most of the THF was removed in vacuo, and the residue poured into a mixture of ethyl acetate and sat. aq. sodium bicarbonate. The layers were separated and the aqueous portion was

extracted once with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude alcohol was purified by flash chromatography on silica gel eluting with 40% ethyl acetate - hexanes to yield **18** as colorless crystals (2.14 g, 100%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, J=8, 3 Hz, 1H), 7.66 (td, J=8, 3 Hz, 1H), 7.56 (d, J=8 Hz, 2H), 7.48 (m, 2H), 7.10 (d, J=8 Hz, 2H), 5.34 (s, 2H), 4.62 (bs, 2H), 2.66 (dd, J=7, 6 Hz, 2H), 1.68 (m, 2H), 1.36 (m, 2H), 0.89 (t, J=7 Hz, 3H). MS (DCI-NH_3) *m/z* 464 $(M+H)^+$, 421, 192. Anal calcd for $C_{24}H_{22}F_5N_3O$: C, 62.20; H, 4.78; N, 9.06; Found: C, 62.12; H, 4.64; N, 9.00;

Methyl 2-butyl-4-pentafluoroethyl-1-[4-(2-cyanophenyl)phenyl]methyl imida-zole-5-carboxylate (19).

To a stirred solution of dry dimethyl sulfoxide (1.1 mL, 15.3 mmol, 3.6 equiv.) in anhydrous methylene chloride (20 mL) at -78°C was added a solution of oxalyl chloride (0.67 mL, 7.69 mmol, 1.8 equiv.) in CH_2Cl_2 (0.33 mL) such that the temperature did not exceed -68°C. After 15 min a solution of the alcohol **18** (1.98 g, 4.27 mmol) in CH_2Cl_2 (12 mL) was added, again maintaining the temperature below -68°C. After 50 min, dry triethylamine (2.38 mL, 17.08 mmol, 4 equiv.) was added, and the mixture was warmed to room temperature. The mixture was poured into ether (150 mL), was washed with water (30 mL) and brine (3o mL). The ethereal solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the crude aldehyde (1.98g, 100%). The crude aldehyde was dissolved in tert-butanol (88 mL), and to this solution was added successively 2-methylbut-2-ene (21.3 mL), potassium dihydrogen phosphate (4.0 g, 29.5 mmol, 6.9 equiv.) and a solution of 80% sodium chlorite (4.44 g, 39 mmol) in water (35 mL). The two-phase mixture was stirred 1h, then the solvents were removed in vacuo. The residue was adjusted to pH 11 by careful addition of 1N sodium hydroxide, washed with ether, and then acidified to pH 2 by addition of sodium bisulfate. The mixture was partitioned into ether (5 x 30 mL), and the combined organics then dried over Na_2SO_4, filtered, and concentrated to yield the crude acid as a white foam (1.65 g, 80%). The crude acid was esterified with ethereal diazomethane to afford, after flash chromatography on silica gel

eluting with 50% ethyl acetate - hexane, the ester **19** (1.68 g, 80% overall yield from the alcohol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J=8, 3 Hz, 1H), 7.65 (td, J=8, 3 Hz, 1H), 7.54 (d, J=8 Hz, 2H), 7.47 (m, 2H), 7.10 (d, J=8 Hz, 2H), 5.58 (s, 1H), 3.83 (s, 3H), 2.69 ((dd, J=7, 6 Hz, 2H), 1.68 (m, 2H), 1.37 (m, 2H), 0.89 (t, J=7 Hz, 3H). MS (DCI-NH_3) *m/z* 492 $(M+H)^+$, 462, 301, 211, 197.

Methyl 2-butyl-4-pentafluoroethyl-1-{4-[2-(5-tetrazyl)phenyl]phenyl-methyl-imidazole-5-carboxylate (20).

To a stirred solution of the nitrile **19** (1.68 g, 3.45 mmol) in anhydrous toluene (7 mL) was added successively dibutyltin oxide (86 mg, 0.34 mmol, 10 mol%) and trimethylsilyl azide (0.9 mL, 6.90 mmol, 2 equiv.). The resultant was heated under reflux for 18 h, after which time the volatiles were removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with 5% methanol - methylene chloride to yield the tetrazole **20** (1.16g, 64%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, J=8, 3 Hz, 1H), 7.61 (td, J=8, 3 Hz, 1H), 7.55 (td, J=8, 3 Hz, 1H), 7.41 (dd, J=8, 3 Hz, 2H), 7.32 (d, J=8 Hz, 2H), 7.04 (d, J=8 Hz, 2H), 5.53 (s, 1H), 3.84 (s, 3H), 2.69 (dd, J=7, 6 Hz, 2H), 1.69 (m, 2H), 1.36 (m, 2H), 0.88 (t, J=7 Hz, 3H). MS (DCI-NH_3) *m/z* 535 $(M+H)^+$, 301.

2-Butyl-4-pentafluoroethyl-1-{4-[2-(5-tetrazolo)phenyl]phenyl}methyl-imidazole-5-carboxylic acid (DUP-532).

To a solution of the ester **20** (1.06 g, 1.98 mmol) in tetrahydrofuran (4 mL) was added a solution of lithium hydroxide monohydrate (183 mg, 4.36 mmol, 2.2 equiv.) in water (3 mL). The mixture was stirred at room temperature for 3 h, then most of the THF was removed in vacuo. The residue was poured into a mixture of ethyl acetate and 1N sodium bisulfate. The phases were separated, and the aqueous extracted with ethyl acetate (3 x 5 mL). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel eluting with 10% methanol - methylene chloride containing 0.5% TFA gave the acid **DUP-532** (817 mg, 80%) as an amorphous solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.64 (m, 2H), 7.53 (m, 2H), 7.10, (d, J=8 Hz,

2H), 7.01 (d, J=8 Hz, 2H), 5.57 (s, 2H), 2.63 (dd, J=7, 6 Hz, 2H), 1.53 (m, 2H), 1.32 (m, 2H), 0.88 (t, J=7 Hz, 3H). MS (DCI-NH_3) *m/z* 521 $(M+H)^+$, 477, 216. Anal calcd for $C_{24}H_{21}F_5N_6O_2 \cdot 0.3TFA$: C, 53.07; H, 3.85; N, 15.06; Found: C, 52.99; H, 3.54; N, 14.97.

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