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Practical Synthesis and Regioselective Alkylation of Methyl 4(5)-(Pentafluoroethyl)-2-propylimidazole-5(4)-carboxylate To Give DuP 532, a Potent Angiotensin II Antagonist

Michael E. Pierce,* David J. Carini, George F. Huhn, Gregory J. Wells, and John F. Arnett

Chemical Process R&D Department, Process Research Facility, The DuPont Merck Pharmaceutical Company, Deepwater, New Jersey 08023-0999, and Cardiovascular Sciences Department, Experimental Station, The DuPont Merck Pharmaceutical Company, Wilmington, Delaware 19880-0402

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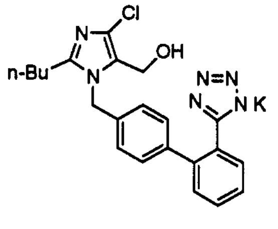
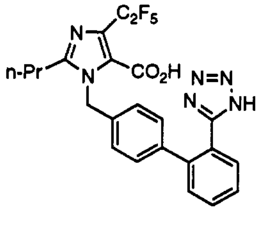
DuP 532 (**2**), which is a potent angiotensin II receptor antagonist, has been prepared by two different routes. One route, which is more practical for large-scale synthesis, required the preparation of methyl 4(5)-(pentafluoroethyl)-2-propylimidazole-5(4)-carboxylate (**9**). This imidazole was synthesized in five steps from commercially available **11** in 32% overall yield. Alternate perfluoroalkylation methods of the iodoimidazole precursor **14** are presented. Imidazole **9** is remarkably stable to basic conditions and is alkylated by 2-[*N*-(triphenylmethyl)tetrazol-5-yl]-4′-(bromomethyl)-1,1′-biphenyl (**8**), giving only the desired regioisomer. A comparison of the alkylation of the trisubstituted precursors and analogues to **9** with **8** indicate that even under mildly basic conditions (K_2CO_3/DMF), the mechanism is S_E2cB (anionic), except for 2-propyl-4(5)-(hydroxymethyl)imidazole (**11**) which alkylates as a neutral species (S_E2').

DuP 753 (**1**, losartan) is a nonpeptide angiotensin II antagonist which is in phase III clinical trials as an orally active antihypertensive agent.[1,2] Its major active metabolite, the imidazole-5-carboxylic acid, is not orally active.[3] DuP 532 (**2**) is under development as an analogue that does not require metabolic activation and has been found to be longer acting and about three times more potent than DuP 753 when given orally to renal hypertensive rats.[4,5]



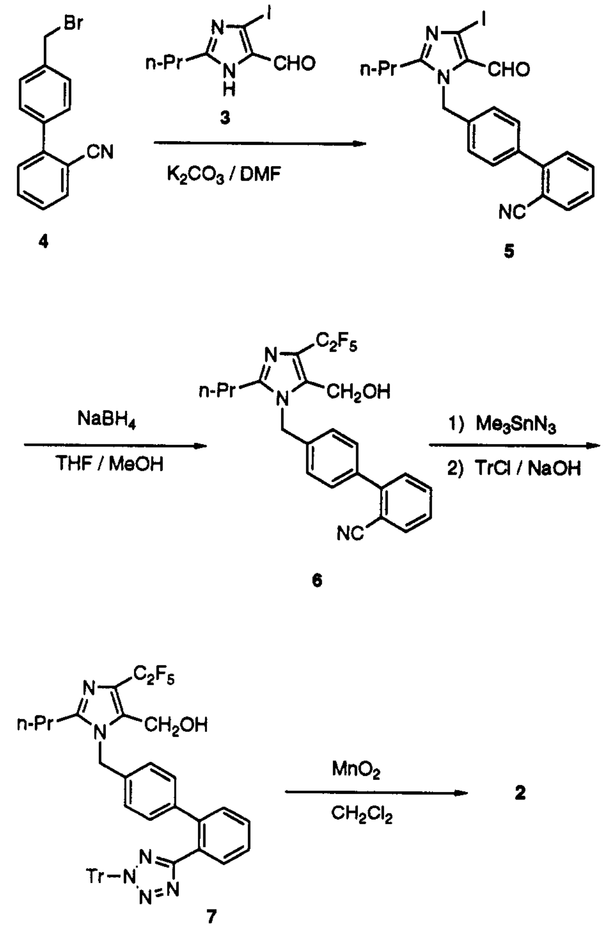
(1) DuP 753



(2) DuP 532

Our original synthesis of DuP 532 is shown in Scheme I.[6] Although the alkylation of iodoimidazolecarboxaldehyde **3** with the bromomethyl biphenyl nitrile **4** was highly regioselective, there were a number of scaleup problems that made this route unattractive. First, the conversion to the pentafluoroethyl imidazolyl alcohol **6** was circuitous, involving reduction of the aldehyde, protection as its MEM ether, pentafluoroethylation, and then MEM hydrolysis. Second, conversion of the highly hindered nitrile **6** to the protected tetrazole **7** required the use of expensive and highly toxic trimethyltin azide. Finally, oxidation of the hindered alcohol **7** gave a mixture of the acid **2** and corresponding aldehyde, requiring chromatography for purification.

Scheme I



In order to develop a practical large-scale process, we chose to alter the synthetic sequence by preparing the

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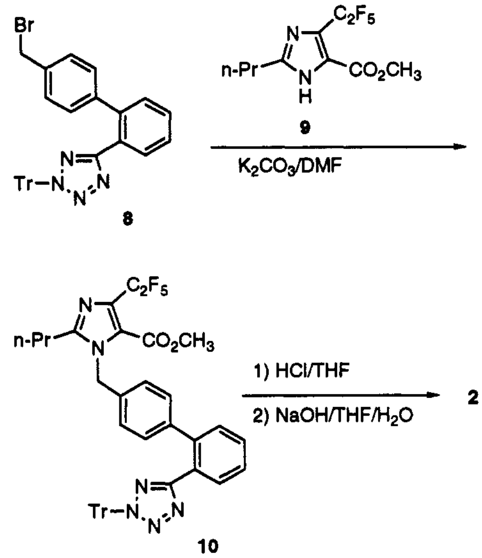
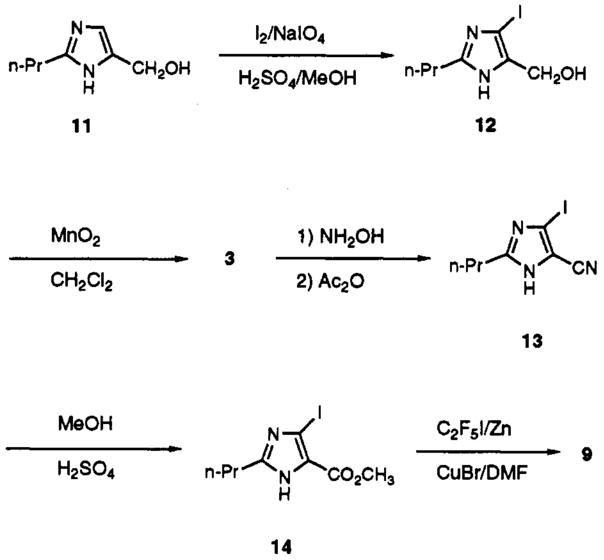
Scheme II



Scheme III



trityl-protected biphenyl tetrazole **8** as well as the fully functionalized imidazole **9** prior to alkylation (Scheme II). Aside from making the synthesis more convergent, **8** was a common intermediate with the DuP 753 process and its synthesis from *o*-anisic acid had previously been demonstrated on large scale.[1,2,7,8]

The major concerns with this route were the uncertain degree of regioselectivity in the alkylation step and the expected instability of the pentafluoroethyl imidazole **9** to the reaction conditions. Also, development of a perfluoroalkylation method that avoided the use of cadmium, a highly toxic carcinogen suspect, was required.

Imidazole **9** was synthesized as shown in Scheme III. Imidazole **11** is commercially available or may be prepared by reaction of methyl butyrimidate with dihydroxyacetone and ammonia.[9,10] Iodination of **11** with either *N*-iodosuccinimide or $I_2/NaIO_4$ proceeds in good yield; however, the latter method is preferred because it is more economical. After oxidation of **12** to aldehyde **3** with MnO_2, the compound was further oxidized to the nitrile **13** by reaction with hydroxylamine followed by dehydration with acetic anhydride. Reaction of **13** with $MeOH/H_2SO_4$ gave the ester **14**. Although **3** can be converted directly to **14** by the conventional $NaCN/HOAc/MnO_2/MeOH$ procedure,[11] the nitrile method avoids generation of HCN. The overall yield of **14** from **11** on a kilogram scale is 42%.

Our initial synthesis of **9** was based on the formation of a pentafluoroethyl cadmium reagent[12] and transmetalation with a copper(I) salt. The trifluoromethyl copper reagent had previously been used for perfluoroalkylation of iodoaromatics in DMF/HMPA, but not with haloimidazoles.[13] We found that the analogous chemistry worked with the pentafluoroethyl reagent and that HMPA was unnecessary in this case. Using 3 equiv of the reagent, we obtained a good yield (73% without HMPA, 78% with HMPA), and prepared enough **9** to evaluate the regioselective alkylation; however, we still needed to eliminate the use of cadmium from the process.

Previous work suggested that we could prepare the copper reagent directly from pentafluoroethyl iodide and copper metal in DMSO.[14] Although we could produce the reagent and successfully couple it with **14**, the high volatility of pentafluoroethyl iodide (bp 12–13 °C) and the high temperature required for formation of the reagent (110 °C), required the use of a pressure vessel. Additionally, after preparation of the reagent, insoluble salts had to be removed prior to coupling with **14**, and the yield of **9** varied considerably.

It has been reported that aryl iodides react with sodium pentafluoropropionate in DMF or *N*-methyl-2-pyrrolidinone at 150–170 °C in the presence of CuI to give the pentafluoroalkyl compounds.[15,16] We attempted unsuccessfully to convert **14** to **9** by this method. Attempts to react pentafluoroethyl iodide with **13** under photochemical[17] or electron-transfer conditions[18] also failed to give **9** as the major product.

We have since found that a pentafluoroethyl zinc reagent is easily prepared by direct reaction of pentafluoroethyl iodide with zinc, and although unreactive in itself, can be exchanged to give a copper reagent which reacts with **14** to give **9** in 75–85% yields. The reaction conditions have been optimized and we have found that DMF is preferable to DMSO or DMAC and that HMPA is unnecessary. Zinc of 20–30 mesh works well (acid washing is unnecessary), and technical grade perfluoroethyl iodide and various copper(I) salts are acceptable. As with the previous methods, a relatively large excess (3–4 equiv) of pentafluoroethyl zinc reagent is required to obtain a high conversion. Copper(I) bromide can be employed catalytically (0.4 equiv); however, the best yields are obtained when 1.8 equiv are used. Although **9** forms an insoluble copper complex, simply adjusting the pH to 2 on workup, followed by extraction of the relatively nonbasic imidazole (pK_a = 1.3) into 1-chlorobutane gives good recovery. Although preferable for large-scale synthesis, the pentafluoroethyl copper reagent prepared by this method is considerably

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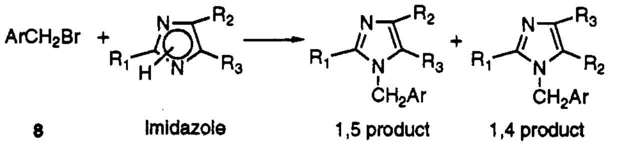
Table I. Ratios of Isomers from Alkylation of Imidazoles with 8 under Neutral or Basic Conditions

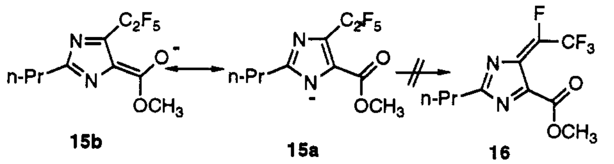


imidazole	R1	R2	R3	1,5/1,4[a,b]	1,5/1,4[c]
11	propyl	H	CH_2OH	14/86	10/90
12	propyl	I	CH_2OH	51/49	21/79
3	propyl	I	CHO	89/11	no reaction
13	propyl	I	CN	58/42	no reaction
14	propyl	I	CO_2CH_3	62/38	25/75
9	propyl	C_2F_5	CO_2CH_3	~99/1	no reaction
17	butyl	Cl	CH_2OH	60/40	27/73
18	butyl	Cl	CHO	93/7	no reaction

[a] The ratio of 1,5/1,4 products indicates the position of alkylation with respect to the R3 substituents. [b] Alkylation conditions: 5 mmol of 8 and 5 mmol of imidazole in 12 mL of DMF with 6 mmol of K_2CO_3 at ambient temperature for 1–3 days. [c] Alkylation conditions: 2.5 mmol of 8 and 5 mmol each of imidazole in 10 mL of DMF at ambient temperature for 1–14 days.

less reactive than those prepared by transmetalation of pentafluoroethyl cadmium or directly from copper powder. Under comparable conditions (~3.0–3.7 equiv reagent, 1.0–1.2 M) the reactions via the zinc reagent required 6–9 h at 65 °C for completion versus 1 h for the other reagents. The reagent prepared directly from copper powder in DMSO is the most reactive and coupling occurs even at room temperature.

Imidazoles can be N-alkylated under either neutral conditions (S_E2' mechanism) which often gives considerable amounts of quaternary byproducts, or through their reactive salts (S_E2cB mechanism). Depending on the mechanism and the substituents present, the regioselectivity of N-alkylation can be controlled to some extent.[19] The direction of predominating alkylation can generally be predicted by the steric bulk of the substituents and their electronic effects. Electron-withdrawing groups favor formation of 1,4-disubstituted products by the S_E2cB mechanism and somewhat favor 1,5-disubstituted products by the S_E2' mechanism, though the neutral, electron-poor imidazoles are not very reactive. A strong electronic effect has been demonstrated in the alkylation of imidazole-4-carboxaldehyde with dimethyl sulfate under neutral conditions, which gives 1-methylimidazole-5-carboxaldehyde as the major regioisomer.[20] We used this as the basis for the alkylation step in losartan where we found that alkylation of aldehyde 18 proceeds with much higher regioselectivity than alkylation of the hydroxymethyl analogue 17 (Table I). A weak base, K_2CO_3, was added to scavenge the HBr generated. For the corresponding alkylation of 9 with 8, we were concerned not only with the regioselectivity, but also the known instability of pentafluoroethyl imidazoles to base, resulting in conversion via the diazafulvene intermediate 16 to the trifluoroacetyl derivative.[17,21] We hoped that the steric bulk of the pentafluoroethyl group and use of a weak base would lead to 1,5 regioselectivity with respect to the methyl ester. To our delight, not only is 9 completely stable to the alkylation conditions (K_2CO_3/DMF/25 °C), but only the desired alkylation isomer 10 is formed. We now believe that the high regioselectivity in the alkylation of 9 with 8 is due to anion **15a** being the reactive species (S_E2cB mechanism). This is supported by the high acidity of this imidazole (pK_a ~10.1) and the fact that no alkylation takes place with $NaHCO_3$ or excess 9 as HBr scavengers. Although the inductive effect of the pentafluoroethyl moiety stabilizes the nitrogen anion **15a**, thereby favoring alkylation at the desired site, contribution of resonance form **15b** may explain the unexpected stability of 9 to base.



15b **15a** **16**

The ratios of regioisomers from the alkylation of several imidazoles (17, 18, 9 and its precursors) with 8, are listed in Table I.[22] Under identical alkylation conditions, none of the precursors to 9 gave comparable regioselectivity and would not have been attractive alternatives had 9 been unstable to base. The more basic imidazoles 11, 12, 14, and 17 alkylate 8 without potassium carbonate; however, other than for 11, the rates are greatly diminished and the regioselectivities reversed. Therefore, under our standard conditions, they too alkylate via their salts. Reconsidering the alkylation of 18 in the losartan synthesis, it now seems clear that the anion is the reactive species and that the inductive effect of the chlorine atom directs the site of alkylation, not the aldehyde. In this case, the main effects of the aldehyde in 18, compared to the hydroxymethyl moiety in 17, must be in lowering the pK_a of the imidazole and possibly being less sterically demanding than the hydroxymethyl group. Note that alkylation with iodo aldehyde 3 is somewhat less regioselective than 18, indicating the greater importance of the inductive (Cl > I) versus the steric (I > Cl) effect. Although it is not possible to separate inductive, resonance, or steric components from this limited data in Table I, the relative ability to direct alkylation toward 1,4-substituted isomers by the anionic mechanism is C_2F_5 > Cl > I > H, which is what one would expect by the inductive effect. However, CH_2OH > CN > CO_2CH_3 > CHO is not easily reconcilable by inductive field effects alone.

Following the alkylation of 9 with 8, the synthesis of DuP 532 was readily completed by detritylation of the tetrazole followed by saponification of the methyl ester. Initially we precipitated the product as an amorphous solid, by neutralization of the basic aqueous solution. This product was then recrystallized as an anhydrous form from ethyl acetate/heptane. This form was somewhat difficult to crystallize and tended to retain organic solvents. An alternate, shorter method was then devised where the basic aqueous solution was diluted with ethanol before acidification. Under these conditions the product crystallized directly as a stable dihydrate. The presence of two water molecules in the crystal lattice, as well as the regiochemical assignment of DuP 532, was confirmed by single crystal X-ray crystallography.

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(22) The regioisomer ratios were determined by ^1H NMR integration of the benzylic protons and are assigned by analogy with the results of alkylations reported in ref 9. For imidazoles 9, 14, 17, and 18, the products were converted to DuP 753 or DuP 532, whose structures have been determined by X-ray crystallography. The author has deposited atomic coordinates for this structure with the CCDC. The coordinates can be obtained on request from the Director, CCDC, 12 Union Rd., Cambridge, CB2 1EZ, U.K.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were determined at 300 MHz. ^{19}F NMR spectra were determined at 282.2 MHz. High resolution mass specta were obtained on a VG 70-VSE mass spectrometer. All reactions were run under nitrogen and all reagents were reagent grade unless otherwise noted.

2-Propyl-4(5)-(hydroxymethyl)-5(4)-iodoimidazole (12). To a solution of 2.4 M aqueous H_2SO_4 (450 mL) and MeOH (2.75 L) were added 2-propyl-4(5)-(hydroxymethyl)imidazole[23] (450.0 g, 3.21 mol), I_2 (331.7 g, 1.31 mol), and $NaIO_4$ (127.5 g, 0.60 mol). After rinsing the addition funnel with 200 mL of MeOH, the mixture was heated at 70 °C for 5 h. After cooling the mixture to 20 °C, a solution of $NaHSO_3$ (54.6 g, 52 mmol) in water (2.68 L) was added, keeping the temperature below 25 °C. The pH was adjusted to 8.1 with 30% NaOH and the mixture diluted with 3.0 L of H_2O. The product was filtered, washed with water, and dried *in vacuo* at 60–80 °C to yield 659.5 g (77%) of **12**: mp 167.5–168.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.60 (s, 2H), 2.68 (t, 2H, J = 7.5 Hz), 1.75 (brs, 1H), 1.73 (sext, 2H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.5 Hz).

2-Propyl-4(5)-iodoimidazole-5(4)-carboxaldehyde (3). MnO_2 (2.0 kg, 23.0 mol) and **12** (1.267 kg, 4.76 mol) were slurried in refluxing CH_2Cl_2 (9.5 L) for 48 h. The mixture was cooled and filtered. The solids were reslurried with 4.0 L of hot CH_2Cl_2 and refiltered. The combined filtrates were solvent exchanged with *n*-butyl chloride (12.0 L). After crystallization, the product was dried *in vacuo* at 40 °C to yield 946 g (75%) of **3**: mp 138–142 °C; ^{1}H NMR ($CDCl_3$) δ 9.45 (s, 1H), 2.82 (t, 2H, J = 7.5 Hz), 1.83 (sext, 2H, J = 7.5 Hz), 0.95 (t, 3H, J = 7.5 Hz).

2-Propyl-4(5)-cyano-5(4)-iodoimidazole (13). To a solution of **3** (770 g, 2.92 mol) in pyridine (1.55 L) was added hydroxylamine hydrochloride (228 g, 3.28 mol), in portions and with cooling to keep the temperature below 40 °C. After stirring 2 h at rt to complete oxime formation, the solution was heated to 60 °C, Ac_2O (540 mL, 5.51 mol) was added, and the warm solution was stirred for 2 h, diluted with water (3.85 L), cooled to rt, and titrated to pH 7.9 with 30% NaOH. The solution was concentrated by distilling 3.6 L of solvent, diluted with MeOH (0.96 L), and cooled to give, after filtration and drying, 706 g (93%) of **13**: mp 148.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.97 (t, 2H, J = 7.5 Hz), 1.8 (brs, 1H), 1.77 (sext, 2H, J = 7.5 Hz), 0.98 (t, 3H, J = 7.5 Hz).

Methyl 2-Propyl-4(5)-iodoimidazole-5(4)-carboxylate (14). To a solution of **13** (662 g, 2.54 mol) in MeOH (2.40 L) and water (47 mL) was added concd H_2SO_4 (850 mL), maintaining the temperature below 45 °C. The solution was then refluxed for 66 h, occasionally adding fresh MeOH to maintain the volume. The mixture was cooled to 10 °C and neutralized with 3 N NaOH to pH 7.6, keeping the temperature below 30 °C. The mixture was cooled to 10 °C and the product filtered, washed with water, and dried with Na_2SO_4 to give 624 g (84%) of **14**: mp 158.5–160 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 2.73 (t, 2H, J = 7.5 Hz), 1.8 (brs, 1H), 1.77 (sext, 2H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.5 Hz); HRMS (NH_3-CI) calcd for $C_8H_{11}IN_2O_2$ $(M + H)^+$, 294.9944, found 294.9948.

Methyl 4(5)-(Pentafluoroethyl)-2-propylimidazole-5(4)-carboxylate (9). (Method A). Pentafluoroethyl iodide[24] (872 g, 3.55 mol) was bubbled through an alumina scrubber[25] into a mixture of 20-mesh zinc (220 g, 3.36 mol, 3.6 equiv) and DMF (825 mL) over 3 h, keeping the temperature at 30–40 °C. After dissolution of the zinc, the solution was pumped into a slurry of 98% cuprous bromide (275 g, 2.05 mol) and DMF (825 mL) over 30 min, keeping the temperature below 30 °C. After stirring the mixture for 15 min, **14** (275 g, 0.94 mol) was added and the resulting mixture was heated at 65 °C for 6 h. The mixture was cooled to rt and poured into a mixture of water (3.0 L), 32% HCl (305 mL), and 1-chlorobutane (3.3 L). After phase separation, the organic phase was washed with 1.5-L portions of 0.1 N HCl, 0.03 N aqueous $NaHSO_3$, and water and then dried with Na_2SO_4. After distilling 3.5 L of solvent, while adding 2.4 L of heptanes, the mixture was cooled below 10 °C and the product was isolated by vacuum filtration to afford, after drying *in vacuo* at 40 °C, 209 g (78%) of **9**: mp 105–108 °C; ^{1}H NMR ($CDCl_3$) δ 10.6 (brs, 1H), 3.92 (s, 3H), 2.77 (t, 2H, J = 7.5 Hz), 1.79 (sext, 2H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.5 Hz); ^{19}F NMR ($CDCl_3$) δ −84.2 (s, 3F), −111.8 (s, 2F); HRMS (NH_3-CI) calcd for $C_{10}H_{12}F_5N_2O_2$ $(M + H)^+$, 287.0819, found 287.0827.

Methyl 4(5)-(Pentafluoroethyl)-2-propylimidazole-5(4)-carboxylate (9). (Method B). Copper powder (1.59 g, 0.025 mol) and DMSO (10 mL) were charged to a resealable pressure tube and cooled to 0 °C. Predistilled pentafluoroethyl iodide (1.50 mL, 3.13 g, 12.7 mmol) was added and the mixture was heated at 110–120 °C for 4 h. After cooling to rt, the blue-green supernatant reagent was removed by syringe, 8 mL was added to **14** (0.78 g, 2.65 mmol), and the mixture was heated to 65 °C for 1 h. The cooled mixture was poured into dilute aqueous HCl and Et_2O. The organic phase was separated, washed with water, dried with Na_2SO_4, concentrated, and chromatographed on a short florisil column (elution: 0–50% Et_2O/CH_2Cl_2). Concentration and trituration of the residue with hexane afforded 0.67 g (88%) of **9**: mp 106–107 °C. Physical properties were identical with product produced by method A.

Methyl 4-(Pentafluoroethyl)-2-propyl-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate (10). A mixture of **8**[26] (10.7 kg, 17.3 mol, 1.05 equiv), K_2CO_3 (2.74 kg, 19.8 mol, 1.20 equiv), and **9** (4.7 kg, 16.4 mol, 1.00 equiv) was stirred in 37.7 kg of DMF at ambient temperature for 16 h. The mixture was clarified and the filtrate warmed to 50 °C, diluted with 7 L of H_2O, and then cooled below 10 °C as the product crystallized. The product was filtered, reslurried twice with water, and dried *in vacuo* to afford 11.9 kg of crude **10**. The product was recrystallized from 23.3 kg of *n*-butyl chloride giving 9.3 kg of pure **10** (74%): mp 150–151.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (dd, 1H, J = 7.5, 2 Hz), 7.47 (m, 2H), 7.34 (m, 4H), 7.26 (t, 6H, J = 7.5 Hz), 7.10 (d, 2H, J = 7.5 Hz), 6.93 (d, 6H, J = 7.5 Hz), 6.75 (d, 2H, J = 7 Hz), 5.41 (s, 2H), 3.72 (s, 3H), 2.53 (t, 2H, J = 7 Hz), 1.65 (sext, 2H, J = 7 Hz), 0.88 (t, 3H, J = 7 Hz); ^{19}F NMR (DMSO-d_6) δ −83.5 (s, 3F), −110.2 (s, 2F); HRMS (FAB-NBA/TFA) calcd for $C_{43}H_{36}F_5N_6O_2$ $(M + H)^+$, 763.2820 , found 763.2811.

4-(Pentafluoroethyl)-2-*n*-propyl-1-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxylic Acid (2). A mixture of **10** (8.1 kg, 10.6 mol, 1.00 equiv), 32% HCl (4.0 kg, 34.5 mol), water (2.2 L), and THF (24.7 kg) was stirred at ambient temperature for 3 h, after which 30% NaOH (7.9 kg, 59 mol, 5.6 equiv) was added. After distilling 27.9 L of solvent and adding 24.3 L of H_2O, the mixture was cooled and trityl alcohol removed by filtration. EtOH (20 kg), followed by 32% HCl (3.3 kg, 29 mol, 2.7 equiv), was added to the filtrate and the resulting mixture cooled to 0 °C, held 2 h, and filtered. The crude wet product was dissolved in EtOH (21 kg), clarified, and then recrystallized by the addition of 18.1 L of H_2O. The yield of **2** as the dihydrate was 4.9 kg (90%): mp 116–118 °C; ^{1}H NMR (DMSO-d_6) δ 7.71–7.63 (m, 2 H), 7.59 (d, 1H, J = 7.5 Hz), 7.54 (d,1H, J = 7.5 Hz), 7.09 (d, 2H, J = 7.5 Hz), 6.98 (d, 2H, J = 7.5 Hz), 5.58 (s, 2H), 2.59 (t, 2H, J = 7 Hz), 1.56 (sext, 2H, J = 7 Hz), 0.85 (t, 3H, J = 7 Hz); ^{19}F NMR (DMSO-d_6) δ −81.3 (s, 3F), −106.9 (s, 2F); HRMS (EI) calcd for $C_{23}H_{19}F_5N_6O_2$, 506.1490, found 506.1488. An analytical sample of the anhydrous polymorph was prepared by crystallization from ethyl acetate/ heptane: mp 172–173 °C. Anal. Calcd for $C_{23}H_{19}F_5N_6O_2$: C, 54.55; H, 3.78; F, 18.76; N, 16.69. Found: C, 54.26; H, 3.65, F, 18.78; N, 16.40.

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(23) 2-Propyl-4(5)-(hydroxymethyl)imidazole was purchased from Finorga, SA and was assayed as 95.5 weight % pure by HPLC.

(24) Technical grade C_2F_5I is manufactured by E. I. Du Pont de Nemours and is >90% pure, containing IF_6, perfluorobutane, and chloroethane as the major impurities. The alumina column traps IF_6, which is corrosive.

(25) The scrubber was constructed by loosely filling a 15 × 2.5 cm polyethylene drying tube with 150-mesh basic alumina and plugging the ends with glass wool. To assist the transfer of perfluoroethyl iodide, a t-tube connected to a nitrogen outlet was inserted before the scrubber.

(26) Compound 8 was prepared as described in ref 2 and further purified by reslurrying in EtOAc. Purity by HPLC was 95%.