Efficient Synthesis of Losartan, A Nonpeptide Angiotensin II Receptor Antagonist

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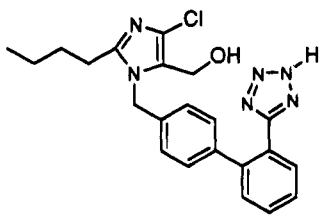
A highly efficient, convergent approach to the synthesis of the angiotensin II receptor antagonist losartan (**1**) is described. Directed ortho-metalation of 2-trityl-5-phenyltetrazole provides the key boronic acid intermediate **10** for palladium-catalyzed biaryl coupling with bromide **5** obtained from the regioselective alkylation of the chloroimidazole **2**. This methodology overcomes many of the drawbacks associated with previously reported syntheses.

Introduction

The renin–angiotensin system (RAS) plays a critical role in the regulation of blood pressure.[1] This cascade begins with the cleavage by renin of angiotensinogen to the decapeptide angiotensin I. Subsequently, angiotensin converting enzyme (ACE) produces the powerful vasoconstrictor angiotensin II (AII) by clipping a dipeptide unit. To control hypertension the ACE inhibitors captopril, enalapril, and lisinopril function by monitoring the formation of AII.[2] Since ACE is also involved in the catabolism of bradykinin, an alternative means for controlling blood pressure has been sought through the antagonism of the AII receptor, thereby overcoming the side effects associated with ACE inhibitors. This has led to the design and discovery of the nonpeptide angiotensin II receptor antagonist losartan (**1**).[3]



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losartan

The majority of AII antagonists have as a common structural feature a biphenyl moiety with a heterocycle in the 4-position and an acid group in the 2′-position; losartan is substituted with an imidazolylmethyl and a tetrazole group, respectively. The key step in the syntheses of these AII antagonists is the aryl–aryl coupling reaction to form the biphenyl moiety. Previous approaches to the synthesis of the requisite substitution pattern have employed the Ullmann coupling between 4-iodotoluene and 2-iodobenzoate,[3b] nucleophilic aromatic substitution at the ortho position of a suitably activated benzoic acid derivative,[3b,4c] and Ni-catalyzed coupling of (4-methylphenyl)magnesium bromide and 2-bromobenzonitrile.[4a,b] The syntheses were then completed by conversion of the carboxy equivalent to the tetrazole and subsequent free-radical bromination of the methyl group for alkylation by the heterocycle. Problems with these approaches have been (1) the need for a trialkyltin azide in the conversion of the benzonitrile intermediate to the tetrazole, (2) the nonselective and moderately yielding free-radical bromination of a late intermediate, (3) poor separation of the regioisomers of **1**, and (4) the waste and recovery issues of spent metallic species.

In designing an alternative synthesis of losartan our goal was to minimize the use of expensive and hazardous metals, circumvent the tetrazole formation and bromination steps, and increase the overall efficiency of the synthesis. This was accomplished by reversing the order of the major bond disconnections. Alkylation of the imidazole first with commercially available 4-bromobenzyl bromide obviated the free-radical bromination; this offered a suitable substrate for metal-catalyzed biaryl coupling. In order to avoid the use of tin azides in the synthesis of the tetrazole moiety, commercially available 5-phenyltetrazole was converted to an ortho-substituted boronic acid for coupling to the bromide. We would now like to disclose this highly efficient, convergent synthesis of the free acid of losartan in three linear steps in 80% overall yield from the chloroimidazole **2**.

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(1) (a) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312.

(2) Wyvratt, M. J.; Patchett, A. A. *Med. Res. Rev.* **1985**, *5*, 483.

(3) (a) Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395. (b) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525. (c) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149.

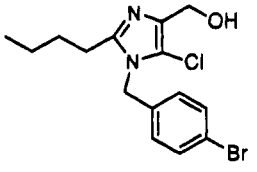
(4) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2922. (c) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, W.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525. (d) Russel, R. K.; Murray, W. V. *J. Org. Chem.* **1993**, *58*, 5023.

0022-3263/94/1959-6391$04.50/0

Results and Discussion

The first segment of this convergent synthesis was the construction of the benzylated imidazole **5** (Scheme 1). The chloroimidazole **2**[5] was benzylated in dimethylacetamide (DMAC) at −10 °C with K_2CO_3 as base to provide a 97:3 mixture of regioisomers **4a** and **4b**. The aldehyde was necessary for providing the high ratio of the desired regioisomer **4a** and a suitable rate of reaction; for example, the alcohol derivative of **2** alkylated 100 times slower and provided a higher ratio of the undesired isomer **6** (17:83; **5**/**6**).

As part of a one-pot procedure the aldehyde was reduced directly, since **4a** is a low-melting solid, with methanol added to provide a protic medium for $NaBH_4$. Unexpectedly, a synergistic effect was observed with the DMAC/MeOH mixture: the benzylated imidazole dimerized via an aldol reaction to form 13−19% of a 9:1 mixture of the diastereomers **7**. To avoid this the potassium salts from the alkylation containing residual K_2CO_3 were filtered and methanol was then added to the filtrate. Addition of 0.3 equiv of $NaBH_4$ at 0 °C provided a quantitative yield of the alcohols **5** and **6**. The desired isomer of the benzylated imidazole alcohol was now separated from the regioisomer by crystallization from the reaction mixture by adding water. An 89−92% yield of **5** was obtained as a white crystalline solid containing <0.3% of the regioisomer **6**.



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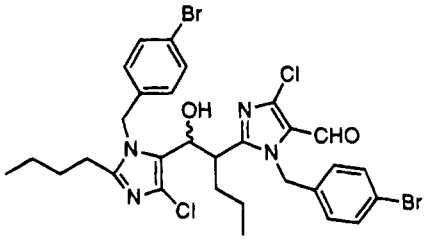

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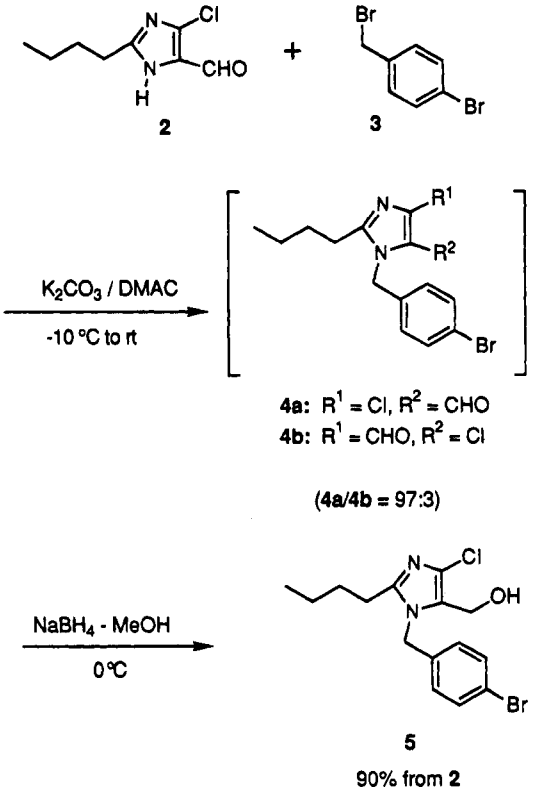
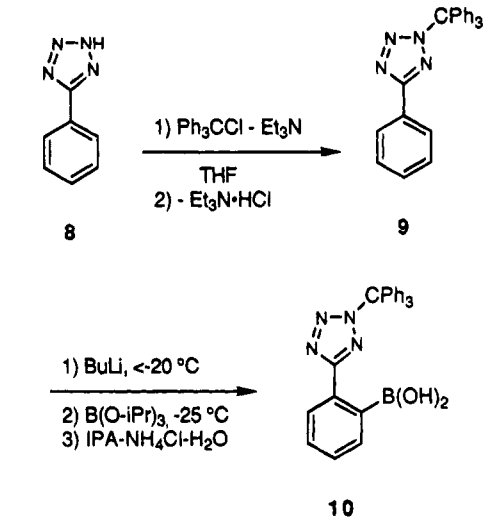
Coupling of the phenyltetrazole component of losartan with the bromide **5** required a selective functionalization of the ortho position. Snieckus[6] has shown the power of the Suzuki coupling[7] when combined with directed ortho metalation.[8] During the development of the L-159,809 synthesis in these same laboratories King[9a] demonstrated

Scheme 1



Scheme 2



the feasibility of the ortho-directed lithiation of 5-phenyltetrazole[9b] for the synthesis of the biphenylyltetrazole moiety using nickel-catalyzed coupling after transmetalation with zinc. With the implementation of a selective ortho-coupling sequence on 5-phenyltetrazole (**8**) not only was an ortho-substituted benzoic acid derivative not necessary, but trialkyltin azides were avoided since **8** can be prepared from benzonitrile and sodium azide.[9a] In the synthesis of losartan we have applied this directed ortho metalation to palladium-catalyzed coupling by conversion of 5-phenyltetrazole to the boronic acid **10** (Scheme 2).

Protection of the tetrazole was necessary since the free tetrazole group acted as a poison with palladium reagents. The triphenylmethyl (trityl) group was optimal for a number of reasons: it was easily added and removed under mild conditions, formed specifically one isomer on

(5) (a) Watson, S. P. *Synth. Commun.* **1992**, *22*, 2971. (b) Shi, Y. J.; Frey, L. F.; Tschaen, D. M.; Verhoeven, T. R. *Synth. Commun.* **1993**, *23*, 2623.

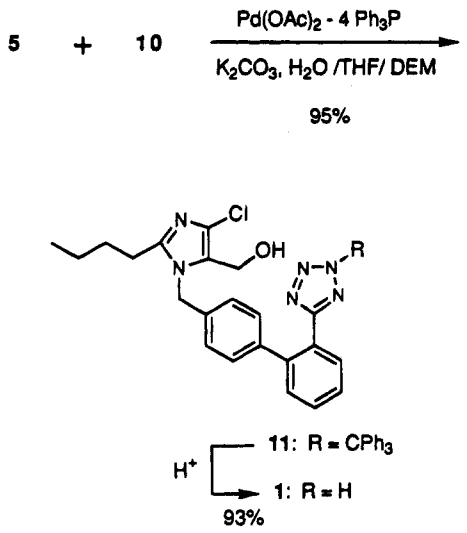
(6) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997. (b) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763. (c) C. Unrau, C. M.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2773.

(7) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (c) For a review of palladium-catalyzed carbon−carbon bond formation see: Kalinin, V. N. *Synthesis* **1992**, 413.

(8) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(9) (a) Schuman, R. F.; King, A. O.; Anderson, R. K. U.S. Patent 5,039,814, 1991. (b) During the filing of this work a paper on the ortho-lithiation of unprotected 5-phenyltetrazole was published: Flippin, L. *Tetrahedron Lett.* **1991**, *32*, 6857.

Scheme 3



the N-2 position, and was inert to the basic conditions of the coupling reaction. The tritylation was carried out by addition of trityl chloride to a mixture of **8** and Et_3N at 30–35 °C so as to keep the substrates dissolved. The resultant triethylammonium hydrochloride was then removed by filtration to provide a THF solution of trityl 5-phenyltetrazole **9**.

In the synthesis of **1** the intermediate **9**[9a] was not isolated but was converted to the boronic acid as a through process. The filtrate containing **9** was cooled to <−20 °C and butyllithium was added until the mixture remained red from conversion of the excess trityl chloride to triphenylmethyl anion; the color acted as an indicator for the consumption of residual water and hydrogen chloride. Subsequently, the addition of 1.05 equiv of butyllithium generated the ortho lithium anion in >98% conversion by methyl iodide assay. Quenching the anion with 1.3 equiv of triisopropyl borate at <−25 °C produced the diisopropyl borate ester of **10**; the more hindered boron reagent prevented partial formation of the diarylborinic acid as was observed with trimethyl borate. The boronic acid **10** was isolated by the sequential addition of isopropyl alcohol as a cosolvent, 20% aqueous NH_4Cl to catalyze the hydrolysis of the ester and neutralize the lithium isopropoxide, and water to complete the crystallization.[10] It was necessary to keep the pH of the mixture between 8–11 to prevent detritylation and decomposition of the product; the addition of 1.8 equiv of NH_4Cl maintained this range. The boronic acid **10** was isolated in 89% overall yield from **8** as a mono tetrahydrofuran solvate.

The key biaryl coupling of the boronic acid **10** with the bromide **5** required an explicit set of reaction conditions to attain a high yield (Scheme 3). In general, the coupling between a boronic acid and a halide is catalyzed with a palladium(0) reagent in the presence of a base and often water at temperatures >70 °C in an inert solvent. Although tetrakis(triphenylphosphine)palladium(0) was suitable for this coupling reaction, its sensitivity to air and expense required an in-situ generation of the catalyst. By heating $Pd(OAc)_2$ and 4 equiv of triphenylphosphine in deoxygenated THF an active catalyst was prepared. THF, however, did not boil high enough to provide an effective rate of reaction. Although toluene was promising, poor mixing of the water/base (K_2CO_3) system was problematic. Diethoxymethane (DEM) proved to be an excellent medium for the coupling. The catalyst preparation, however, was unsatisfactory in DEM alone; a 1:4 mixture of THF/DEM was suitable for the catalyst preparation and did not affect the rate of reaction.

The order of addition of the reagents was critical to the success of this reaction. First, triphenylphosphine and palladium acetate (1 mol %) were added sequentially to the thoroughly degassed THF/DEM mixture, and the precatalyst was aged for 30 min at rt. The boronic acid **10** as the THF solvate (1.05–1.1 equiv) was added followed by 2.3 equiv of water. The charge of water was critical to the rate of reaction: a deficit caused the reaction to cease and an excess resulted in agglomeration of the K_2CO_3. The mixture was stirred for 30 min to allow displacement of the THF solvate by water. Once this was achieved the active potassium borate species was generated by adding 2.5 equiv of potassium carbonate. Addition of the bromide **5** (1.0 equiv) was followed by heating the mixture at reflux (~80 °C) for 3–6 h to effect >99% conversion of **5** to the biaryl compound. Workup provided a 93% yield of the penultimate intermediate **11** to losartan.[11]

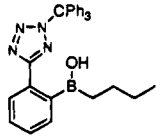
A novel method for removing residual palladium from the isolated product was developed by adding tributylphosphine (10 mol %) to the organic layer after aqueous extraction. This served to stabilize the palladium(0) in solution such that <50 ppm of elemental palladium remained in trityllosartan (**11**).

Deprotection of trityllosartan was achieved by adding the substrate to 0.7 M H_2SO_4 in acetonitrile/water (50:50). In 1.5 h a slurry of trityl alcohol was obtained. The spent protecting group was removed by addition of the slurry to aqueous sodium hydroxide so as to solubilize the tetrazole as the sodium salt. The insoluble trityl alcohol was filtered and the pH of the filtrate was adjusted to 3.8 to crystallize the free acid of losartan (**1**) in 93% yield containing <0.05% of the **6**-derived regioisomer of losartan. The age of the slurry in acid was minimized due to the propensity of the hydroxymethyl group to undergo intermolecular displacement by the tetrazole-forming dimers.

Summary

An extremely efficient, convergent approach to the biphenyltetrazole structure of the AII antagonists has been developed by employing a combination of the directed ortho metalation and Suzuki coupling methodologies. Application of this technology to the synthesis of losartan provided a high-yielding (80% overall in three steps) procedure that rivaled all previous approaches.

(10) A byproduct of the boronic acid synthesis was the butylphenylborinic acid **i**. The compound is not formed by attack of butyllithium on the phenylborate ester; rather, it results from the reaction of excess butyllithium with triisopropyl borate to form diisopropyl butylborate.



i

(11) A detailed study of the mechanism of this reaction has been carried out and will be reported shortly.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AM-250 instrument (^{1}H NMR at 250 MHz, ^{13}C NMR at 63 MHz).

2-*n*-Butyl-4-chloro-1-(4-bromobenzyl)-1*H*-imidazole-5-methanol (5). 2-*n*-Butyl-4-chloro-1*H*-imidazole-5-carboxaldehyde (**2**) (30.5 g, 0.163 mol) and 4-bromobenzyl bromide (41.5 g, 0.16 mol) were dissolved in DMAC (200 mL). At −10 °C under a nitrogen atmosphere powdered K_2CO_3 (23.7 g, 0.168 mol) was added portionwise over 10 min maintaining the temperature at −10 to −5 °C. The slurry was stirred at −10 °C for 2 h, warmed to room temperature, and stirred for 2 h. The slurry was filtered and the cake was washed with DMAC (60 mL). The filtrate was diluted with MeOH (80 mL). This mixture was cooled to −10 °C and $NaBH_4$ (1.85 g, 48 mmol) was added portionwise over 0.5 h. The mixture was then warmed to rt and stirred for 1 h. Aqueous acetic acid (50%, 5.76 mL) was added over 10 min at 20−25 °C to quench the excess hydride. **Hydrogen is evolved!** The mixture was stirred for 0.5 h. Water (160 mL) was added over 1 h and the mixture was seeded. After aging the seed mixture for 1 h at rt, additional water (160 mL) was added over 1 h. The crystallization mixture was stirred at rt for 2 h and at 5−10 °C for 0.5 h. The solid was filtered, washed with water (320 mL), and suction-dried to afford 52.8 g (92.5%) of the benzylated imidazole **5** as a white solid containing <0.5% of the regioisomer **6**. An analytical sample was prepared by recrystallization from methyl isobutyl ketone: mp 92.5−93.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 8.3 Hz, 2 H), 6.9 (d, J = 8.8 Hz, 2 H), 5.2 (s, 2 H), 4.45 (d, J = 6.0 Hz, 2 H), 2.75 (t, J = 6.0 Hz, 1 H), 2.5 (t, J = 7.9 Hz, 2 H), 1.6 (m, 2 H), 1.3 (m, 2 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 148.5, 135.1, 132.1, 127.6, 127.2, 124.8, 121.8, 53.0, 46.9, 29.6, 26.6, 22.4, 13.7. Anal. Calcd for $C_{15}H_{18}BrClN_2O$: C, 50.36; H, 5.08; N, 7.83. Found: C, 50.62; H, 4.85; N, 7.71.

5-(2′-Boronophenyl)-2-(triphenylmethyl)-2*H*-tetrazole (10). 5-Phenyltetrazole (**8**) (14.9 g, 100 mmol) was slurried in THF (120 mL, dried over 3 Å molecular sieves), and Et_3N (14.8 mL, 105 mmol) was added. The temperature of the solution was increased to 40 °C and trityl chloride (29.9 g, 105 mmol) in THF (60 mL) was added. The mixture was aged for 15−30 min. The precipitated triethylammonium chloride was filtered at 0 °C and washed with cold THF (40 mL). The combined filtrates were degassed and cooled to −25 °C. The residual HCl, H_2O, and TrCl were quenched with n-BuLi (1.6 M in hexanes; ~6.5 mL); once the mixture remained red for 5 min the addition was stopped. The main charge of BuLi (65.6 mL,105 mmol) was then added at <−15 °C. The red slurry was stirred at −10 to −20 °C for 1 h. The reaction mixture was cooled to −25 °C and triisopropyl borate (30.6 mL, 130 mmol) was added at <−20 °C. The mixture was aged for 30 min and warmed to 10 °C over 1 h. The mixture was then concentrated under vacuum (50−75 mmHg) to remove ~200 mL of volatiles or until <4% hexanes remained in the THF. The concentrate was diluted to 160 mL with THF, and isopropyl alcohol (IPA) (60 mL) was added. The mixture was cooled to 0 °C and saturated aqueous NH_4Cl (40 mL, 180 mmol) was added at <10 °C. The slurry of boronic acid was warmed to rt and was aged for 30 min. Water (100 mL) was added over 15−20 min and the mixture was aged for 2 h. The solid was filtered, washed with a 50:50:2 mixture of IPA/H_2O/Et_3N (100 mL), and suction dried with a stream of nitrogen. The boronic acid **10** was obtained as an off-white solid (54 g, 90% yield; 80 wt %). The crude solid contained 2−5 area % of the unreacted **9**, 1−2 area % of the butylborinic acid impurity, 1−2 area % trityl alcohol, and ~1 equiv of THF as solvate. The material was used directly in the coupling reaction. An analytical sample was prepared by recrystallization twice from THF−H_2O: mp 118−120 °C. The boronic acid **10** was isolated as a 1:0.5 THF−H_2O solvate: ^{1}H NMR (DMSO-d_6) δ 7.95 (s, 2 H), 7.82 (m, 1 H), 7.53−7.35 (m, 12 H), 7.07 (m, 6 H), 3.58 (m, 4 H) 3.33 (s, 1H), 1.75 (m, 4 H). Anal. Calcd for $C_{26}H_{21}N_4O_2B{\cdot}C_4H_8O{\cdot}^1/_2H_2O$: C, 70.18; H, 5.89; N, 10.91. Found: C, 70.44; H, 5.61; N, 11.04.

2-*n*-Butyl-4-chloro-1-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-1,1′-biphenyl-4-yl]methyl]-1*H*-imidazole-5-methanol (11). A mixture of DEM (80 mL) and THF (20 mL) was degassed by vacuum/nitrogen purges (3×). Triphenylphosphine (262 mg, 1.0 mmol) was added. Once the reagent had dissolved, palladium acetate (56 mg, 0.25 mmol) was added and this mixture was degassed (3×). The mixture was then stirred at rt for 30 min. The boronic acid **10** (14.2 g as 80 wt %, 26.3 mmol) was suspended in the mixture and this slurry was stirred for 30 min. Water (1.1 mL, 61 mmol) was added and the slurry was stirred at rt for 30 min. Powdered K_2CO_3 (8.6 g, 62.2 mmol) and the aryl bromide **5** (8.97 g, 25.0 mmol) were then added sequentially. This mixture was degassed (3×). The reaction mixture was then heated at reflux for 3−6 h. The product mixture was cooled to <76 °C, and THF (25 mL) and H_2O (30 mL) were added. This mixture was stirred at 55−60 °C and the layers were separated. The organic layer was washed again at 55−60 °C with water (15 mL). Tributylphosphine (0.62 mL, 10 mmol) was added, and this mixture was filtered and concentrated *in vacuo* (16 in mmHg) at 50−65 °C to 50 mL to remove the THF. DEM (50 mL) was added and the volume was again reduced by 50 mL to bring the THF concentration to <5%. The concentrate was then diluted to 75 mL with DEM and the slurry was heated at reflux for 30 min. Water (0.5 mL, 27.8 mmol) was added and the mixture was cooled to −15 to −10 °C over 2 h. The slurry was aged for 1 h. The solid was filtered, washed with cold DEM (25 mL) and vacuum dried at 40 °C. The product **11** was obtained as a white solid (15.5 g, 93% yield) containing only 7−18 ppm residual Pd. An analytical sample was recrystallized from THF−DEM (1:4): mp 171−172 °C dec (lit.[3b] mp 167−169 °C); ^{1}H NMR ($CDCl_3$) δ 8.02−7.9 (m, 1 H), 7.56−7.42 (m, 2 H), 7.42−7.32 (m, 4 H), 7.32−7.19 (m, 6 H), 7.14 (d, J = 8.1 Hz, 2 H), 7.01−6.88 (m, 6 H), 6.8 (d, J = 8.1 Hz, 2 H), 5.15 (s, 2 H), 4.32 (s, 2 H), 3.4 (s, 1 H), 2.5 (t, J = 7.41 Hz, 2H), 1.72−1.57 (m, 2 H), 1.39−1.2 (m, 2 H), 0.86 (t, J = 7.32 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.8, 148.3, 141.2, 141.1, 140.7, 134.5, 130.6, 130.1, 130.06, 129.9, 129.7, 128.2, 127.6, 127.5, 126.8, 126.0, 125.2, 124.9, 82.8, 52.7, 47.0, 29.5, 26.5, 22.2, 13.6. Anal. Calcd for $C_{41}H_{37}ClN_6O$: C, 74.01; H, 5.62; N, 12.64; Cl, 5.32. Found: C, 74.25; H, 5.64; N, 12.68; Cl, 5.32.

2-*n*-Butyl-4-chloro-1-[[2′-(2*H*-tetrazol-5-yl)-1,1′-biphenyl-4-yl]methyl]-1*H*-imidazole-5-methanol (1). The trityl derivative **11** (3.93 g, 5.9 mmol) was slurried in a mixture of 0.75 M H_2SO_4 in 1:1 CH_3CN/H_2O (20 mL). The mixture was stirred at rt for 35 min. The slurry of the free acid and trityl alcohol was transferred to a solution of 1.5 N NaOH (30 mL) over 3 min. The basic mixture was stirred for 1.5 h. The trityl alcohol was filtered and washed with 20:80 CH_3CN/H_2O (10 mL). The filtrate was diluted with CH_3CN (11 mL) and 1.5 M H_2SO_4 (3.85 mL) was added followed by seed crystals (10 mg). The crystallization mixture was aged for 15 min and the pH was adjusted to 3.6−3.9 with 1.5 M H_2SO_4 (1.65 mL). The mixture was aged for 1 h. The solid was filtered, washed with 20:80 CH_3CN/H_2O (10 mL) and H_2O (25 mL), and dried under vacuum at 35−40 °C for 24 h. The free acid of **1** was obtained as a white solid (2.38 g) in 95% yield. An analytical sample was recrystallized from CH_3CN: mp 188−189 °C (gas evolution) (lit.[3b] mp 183.5−184.5 °C); ^{1}H NMR (DMSO-d_6) δ 7.68 (dd, J = 7.9, 1.9 Hz, 1 H), 7.65 (d, J = 6.5 Hz, 1 H), 7.58 (d, J = 6.5 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 2 H), 7.01 (d, J = 8.3 Hz, 2 H), 5.23 (s, 2 H), 4.3 (s, 1 H), 2.43 (t, J = 7.4 Hz, 2 H), 1.44 (m, 2 H), 1.22 (m, 2 H), 0.8 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 147.3, 140.9, 138.3, 136.1, 130.9, 130.4, 129.0, 127.7, 126.1, 125.5, 125.1, 123.4, 112.2, 51.2, 46.3, 28.9, 25.7, 21.5, 13.5. Anal. Calcd for $C_{22}H_{23}ClN_6O$: C, 62.47; H, 5.49; N, 19.87. Found: C, 62.38; H, 5.54; N, 19.95.