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Concise Synthesis of Telmisartan via Decarboxylative Cross-Coupling

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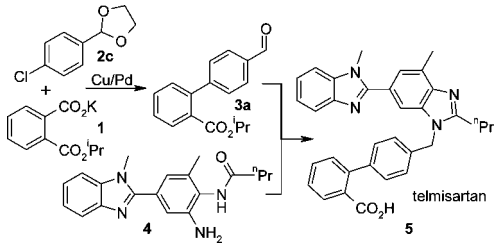


An efficient synthesis of the angiotensin II receptor antagonist telmisartan is presented involving a decarboxylative cross-coupling of isopropyl phthalate (**1**) with 2-(4-chlorophenyl)-1,3-dioxolane (**2c**) as the key step (85% yield). The benzimidazole moiety is constructed regioselectively via a reductive amination−condensation sequence, replacing the previously published route via alkylation of the preformed benzimidazole. The product is obtained in an overall yield of 35% in a convergent synthesis with the longest sequence consisting of eight steps.

Essential hypertension is a major risk factor for cardiovascular disease and is responsible for one-third of global deaths.[1] Most antihypertensive drugs interact with the renin−angiotensin system (RAS), which is the central regulator of blood pressure and electrolyte homeostasis.[2] Renin transforms angiotensinogen into the decapeptide angiotensin I, which is converted by the angiotensin conversion enzyme (ACE) into the octapeptide angiotensin II. The latter binds to its angiotensin receptor (AT_1) and, thereby, becomes a powerful vasoconstrictor.[3]

In the early 1990s, Merck introduced the nonpeptidic orally active angiotensin II receptor antagonist losartan (**6**, Lozaar) as the first member of a new class of antihypertensive drugs called sartans (Figure 1),[4] which all contain a characteristic *ortho*-functionalized biaryl moiety.[5] Telmisartan (**5**, Boehringer Ingelheim, Micardis) (Figure 1) is an important member of this class of top-selling drugs because it has the strongest binding affinity to the AT_1 receptor, an excellent bioavailability, and a once-daily dosage.[6] The first total synthesis of telmisartan as introduced by Ries et al. (Scheme 1) starts with the acylation of the 4-amino-3-methylbenzoic acid methyl ester (**7**) with butyryl chloride, followed by nitration, reduction of the nitro group, and subsequent cyclization of the resulting amine to the benzimidazole derivative **8**. After its saponification, the free carboxyl group is condensed with *N*-methyl-1,2-phenylenediamine to afford the bis-benzimidazole **9**, which is finally alkylated with the 4′-(bromomethyl)-2-biphenylcarboxylic acid *tert*-butyl ester (**13**) to give telmisartan (**5**) after hydrolysis of the ester group in 21% overall yield and eight steps over the longest sequence.[7]

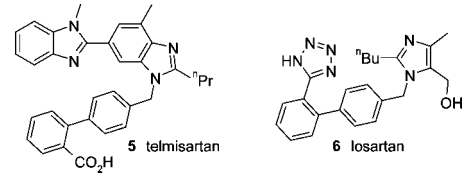
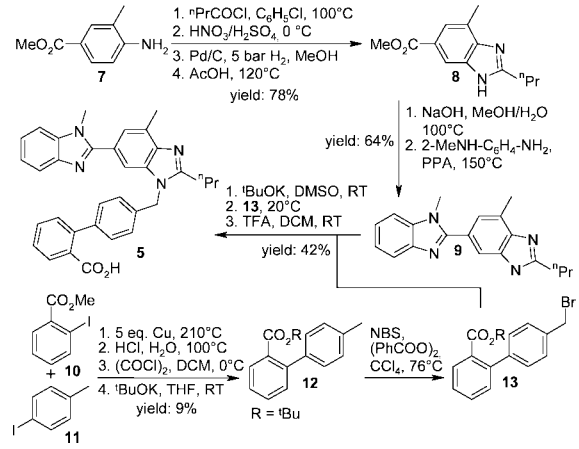


FIGURE 1. Angiotensin II receptor antagonists.

SCHEME 1. First Literature Synthesis of Telmisartan



Several improvements to this reaction seqence have been reported, e.g., the use of KOH instead of potassium *tert*-butoxide in the penultimate step and the use of methanolic HCl solution instead of trifluoroacetic acid in the final step.[8] However, the main shortcomings of the synthesis remained, namely, the unsatisfactory regioselectivity in the alkylation of **9** with **13** and the intricate synthesis of the biaryl intermediate **12**. In the

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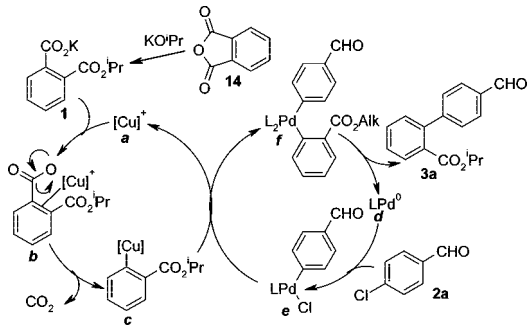
SCHEME 2. Proposed Mechanism of the Decarboxylative Cross-Coupling Reaction

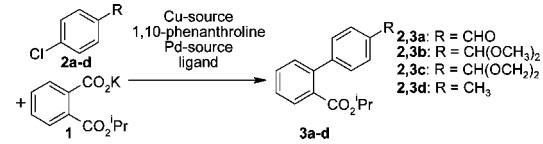


original protocol, it was synthesized via an Ullmann coupling of the aryl iodides **10** and **11** using 5 equiv of copper.[9] Modern syntheses of **12** involve cross-couplings of sensitive arylmagnesium,[10] -zinc,[11] or -boron[12] compounds with alkyl 2-halobenzoates. Since the commercialization of telmisartan, **12** has become easily available at low cost, so that most subsequently published procedures start from this compound.

We realized that the use of our Pd/Cu-catalyzed decarboxylative biaryl synthesis as the key step had the potential to overcome both of these weaknesses.[13] First, the use of an aryl halide (ideally an inexpensive aryl chloride) substituted in the 4-position by an aldehyde or derivative in the cross-coupling would allow a subsequent reductive amination−condensation sequence and, thus, a regioselective entry into the 2-propylbenzimidazole fragment. Second, the use of stoichiometric amounts of organometallic reagents could be avoided because the biaryl would become accessible from a stable potassium monoalkylphthalate (e.g., **1**) instead, which could likely be prepared in one simple step from the bulk chemical phthalic anhydride (**14**) by anhydride esterification with a potassium alkoxide (Scheme in Abstract).

The challenges of adapting the methodology to the synthesis of telmisartan become apparent when considering the mechanism outlined in Scheme 2.[14] A copper/1,10-phenanthroline-catalyzed extrusion of CO_2 would transform a carboxylate salt (e.g., **1**), generated from phthalic anhydride (**14**) and a potassium alkoxide, into an aryl−copper intermediate (***c***). The steric bulk of the ester substituent in the *ortho* position to the Cu can be expected to slow the transmetalation of the aryl group, which may lead to an increased amount of the competing protodecarboxylation. The oxidative addition of an aryl choride (**2**) to the Pd^0 catalyst ***d*** will require an electron-rich phosphine[15] and high reaction temperatures, which may give rise to further side reactions when starting from unprotected 4-chlorobenzaldehyde (**2**). A transmetalation reaction between ***c*** and ***e*** would regenerate the Cu^I catalyst, under formation of diaryl-Pd-complex ***f***, which would liberate the product biaryl **3**, thus, completing the catalytic cycle for the palladium.

TABLE 1. Optimization of the Catalyst System and Conditions for the Key Coupling Step[a]



#	ArCl	Cu source	Pd source	ligand	yield (%)
1	**2d**	CuI	$PdBr_2$	John-Phos[b]	39
2	**2d**	CuF_2	$PdBr_2$	John-Phos[b]	43
3	**2d**	CuBr	$PdBr_2$	John-Phos[b]	49
4	**2d**	Cu_2O	$PdBr_2$	John-Phos[b]	52
5	**2d**	Cu_2O	$Pd(acac)_2$	John-Phos[b]	55
6	**2d**	Cu_2O	$Pd(OAc)_2$	John-Phos[b]	59
7	**2d**	Cu_2O	$Pd(dba)_2$	John-Phos[b]	63
8	**2d**	Cu_2O	$Pd(dba)_2$	John-Phos[c]	65
9	**2d**	Cu_2O	$Pd(dba)_2$	BINAP[c]	11
10	**2d**	Cu_2O	$Pd(dba)_2$	PCy_3[c]	34
11	**2d**	Cu_2O	$Pd(dba)_2$	$P(^tBu)_3$[c]	53
12	**2d**	Cu_2O	$Pd(dba)_2$	Dave-Phos[c]	61
13	**2a**	Cu_2O	$Pd(dba)_2$	John-Phos[c]	64
14	**2b**	Cu_2O	$Pd(dba)_2$	John-Phos[c]	78
15	**2c**	Cu_2O	$Pd(dba)_2$	John-Phos[c]	86

[a] General conditions: 1.5 mmol of potassium monoisopropyl phthalate, 1 mmol of aryl chloride, 10 mol % Cu source (5 mol % for Cu_2O), 2 mol % Pd source, 10 mol % 1,10-phenanthroline, 1.5 mL of NMP, 0.5 mL of quinoline, 170 °C, and 24 h. Yields were determined by GC analysis using *n*-tetradecane as the internal standard. John-Phos, 2-(bis-*tert*-butylphosphino)-biphenyl; BINAP, racemic bis(diphenylphosphino)-1,1′-binaphthyl; and Dave-Phos, 2-dicyclo-hexylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl. [b] At 3 mol % ligand. [c] At 6 mol % ligand (3 mol % for BINAP).

In our search for an optimal combination of starting materials, catalyst components, and conditions for the synthesis of the biaryl intermediate **3**, we started with a catalyst system consisting of CuI/1,10-phenanthroline and $PdBr_2$/2-(bis-*tert*-butylphosphino)-biphenyl (John-Phos), which had proved to be highly efficient for the cross-coupling of potassium 2-nitrobenzoate with 4-chlorotoluene (Table 1, entry 1).[16] An investigation of different monoalkylphthalate salts as coupling partners for 4-chlorotoluene (**2d**) revealed that the isopropyl ester **1** offered the ideal compromise between stability and reactivity. Less stable esters of primary alcohols, like monomethyl phthalate, partially hydrolyzed during reaction workup, while the *tert*-butyl ester was too unreactive (7% and 3% yield, respectively). Next, the catalyst system was optimized using the reaction of **1** and the inert aryl chloride 4-chlorotoluene (**2d**) in order to avoid yields being affected by side reactions of functional groups in the electrophilic coupling partner.

For this substrate combination, Cu^I oxide proved to be the best copper source (Table 1, entries 1−4), while $Pd(dba)_2$ was the optimal palladium precursor (Table 1, entries 5−7). Ex-

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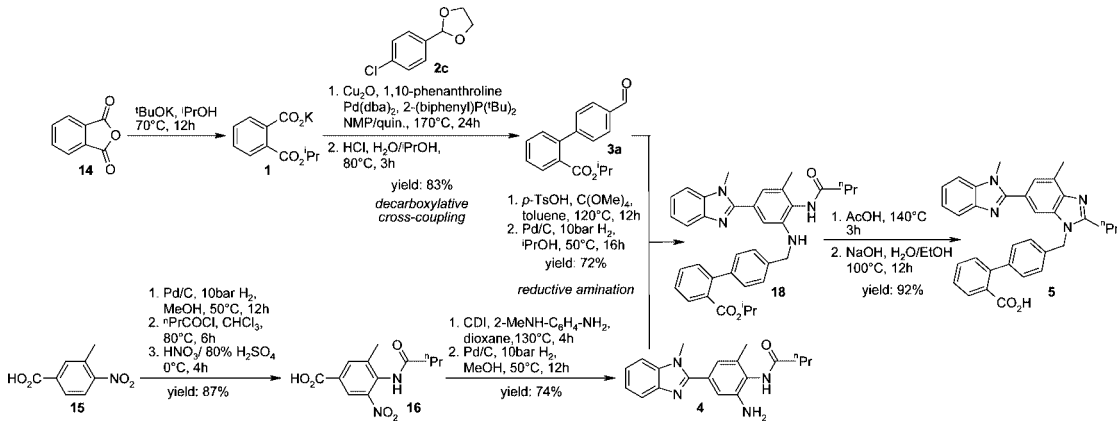
SCHEME 3. New Route to Telmisartan Involving Decarboxylative Biaryl Synthesis and Reductive Amination



pectedly, the choice of phosphine played a critical role; best yields were obtained with the sterically crowded, electron-rich ligand, John-Phos. Unlike for other substrates, the yields were further enhanced when an excess of this phosphine ligand was employed (Table 1, entry 8), and compound **3d** was finally obtained in a satisfactory yield of 65%. A 3:1 NMP/quinoline mixture gave higher yields than NMP (34%) and quinoline (25%) alone. The main side reaction was protodecarboxylation, which we compensated for by employing potassium monoisopropyl phthalate in excess. Under these optimized conditions, still only moderate yields were obtained with 4-chlorobenzaldehyde (**2a**), but we were delighted to see that the corresponding dioxolane (**2c**) was converted in very good yield.

These investigations led to a preparative procedure in which phthalic anhydride (**14**) was treated with potassium *tert*-butoxide in isopropyl alcohol to give **1**. After the protic solvent was exchanged for a mixture of NMP and quinoline, the cross-coupling with 2-(4-chlorophenyl)-1,3-dioxolane (**2c**) was performed in the same vessel and furnished the protected biaryl **3c** in 85% yield based on the aryl chloride. When an isopropyl alcohol solution of the product **3c** was refluxed with dilute aqueous HCl, the aldehyde function of **3a** was quantitatively liberated without hydrolysis of the isopropyl ester. The preparation of the heterocyclic aniline **4**, the coupling partner for the reductive amination of **3a**, is outlined in Scheme 3.

In contrast to the original synthesis, we reduced the nitro group of 3-methyl-4-nitrobenzoic acid (**15**) without previous acid esterification. In the presence of 0.1 mol % palladium on charcoal, this hydrogenation proceeded quantitatively at 10 bar hydrogen pressure. Acylation of the amino group with butyryl chloride followed by nitration afforded compound **16** in an overall yield of 87%. The outcome of the nitration step proved to be highly sensitive to the reaction conditions, and only after thorough optimization with a 1:3 mixture of fuming nitric acid and 80% aqueous sulfuric acid as the nitration agent did we find nearly full conversion and a >99% selectivity for the desired 5-isomer after 4 h at 0 °C. Under most other conditions tested (e.g., concentrated HNO_3/H_2SO_4 or fuming HNO_3/H_2SO_4), the butyryl group was partially hydrolyzed off or the regioselectivity was low.

At this point, our synthetic route deviates from the original pathway via 2-(*n*-propyl)benzimidazole ring closure. We examined the condensation of the carboxyl group of **16** with *N*-methyl-1,2-phenylenediamine. With this substrate, an attempted dehydration with polyphosphoric acid at 150 °C led to substantial side reactions such as cleavage of the butyryl group and butyrylation of the diamine, followed by condensation to 1-methyl-2-(*n*-propyl)benzimidazole. An alternative condensation methodology proved to be more efficient. Activation of the carboxylic acid with 1,1′-carbonyldiimidazole (CDI), coupling with *N*-methyl-1,2-phenylenediamine and in situ cyclization in 1,4-dioxane at 130 °C, afforded the benzimidazole derivative **17** in 82% yield, and hydrogenation to the aniline **4** proceeded smoothly.

The reductive amination of the biaryl aldehyde **3a** with **4** was best carried out in the presence of *p*-toluenesulfonic acid/tetramethyl-*o*-carbonate in toluene, followed by a solvent exchange to isopropyl alcohol and hydrogenation. The amine **18** was thus isolated in 72% yield and was cyclized to the *n*-propylbenzimidazole in refluxing glacial acetic acid. The resulting telmisartan isopropyl ester was saponified with sodium hydroxide in methanol and water, and subsequent acidification led to the precipitation of clean telmisartan in 92% yield over the two final steps.

In conclusion, a concise and selective synthesis of the antihypertensive drug telmisartan has been developed, featuring a decarboxylative cross-coupling for the construction of the biaryl moiety and a regiospecific reductive amination−condensation sequence for the synthesis of the central benzimidazole. It demonstrates the high synthetic potential of decarboxylative coupling reactions, which draw on easily accessible carboxylate salts, rather than sensitive organometallic reagents as sources of carbon nucleophiles.

Experimental Section

4′-(1,3-Dioxolane)-2-biphenylcarboxylic Acid Isopropyl Ester (3c). Phthalic anhydride (**14**, 6.66 g, 45.0 mmol) was added under nitrogen to potassium *tert*-butoxide (5.05 g, 45.0 mmol) in ^{i}PrOH (60 mL). The solution was stirred for 1 h at 70 °C and then concentrated (3×10^{-3} mbar). Chloroform (60 mL) was added, and the resulting mixture was stirred for 5 min and then concentrated (3×10^{-3} mbar). This was repeated twice with *n*-hexane (2 × 60 mL). 2-(4-Chlorophenyl)-1,3-dioxolane (**2c**, 5.54 g, 30.0 mmol), copper(I) oxide (215 mg, 1.50 mmol), 1,10-phenanthroline (541 mg, 3.00 mmol), bis(dibenzylideneacetone)palladium(0) (345 mg, 0.60 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (489 mg, 1.50 mmol), and NMP/quinoline (60 mL, 3:1 ratio) were added. The resulting mixture was stirred for 24 h at 170 °C, cooled to room temperature, and filtered, and the filter cake was rinsed with ethyl acetate (4 × 50 mL). The organic filtrate was washed with aq HCl (1 N, 200 mL), and the washings were re-extracted with ethyl acetate (2 × 60 mL). The combined organic layers were washed

with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The crude brown oil was purified by Kugelrohr distillation (180 °C/3 × 10^{-3} mbar) to yield **3c** as a clear yellow oil (7.97 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (d, ^{3}J = 7.7 Hz, 1H), 7.48−7.50 (m, 2H), 7.43−7.46 (m, 1H), 7.35−7.37 (m, 1H), 7.29−7.33 (m, 3H), 5.83 (s, 1H), 4.96 (h, ^{3}J = 6.4 Hz, 1H), 4.04−4.10 (m, 2H), 3.95−4.00 (m, 2H), 0.99 (d, ^{3}J = 6.4 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 167.9, 142.1, 141.4, 136.7, 131.5, 130.6, 130.2, 129.3, 128.1, 127.0, 125.9, 103.2, 68.2, 64.9, 21.0. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.01; H, 6.49.

4′-Formyl-2-biphenylcarboxylic Acid Isopropyl Ester (3a). A solution of **3c** (3.34 g, 10.7 mmol) in ^{i}PrOH (40 mL) and aq HCl (2 N, 20 mL) was heated to 80 °C for 3 h. After cooling to room temperature, the reaction mixture was poured into saturated aq sodium bicarbonate (150 mL) and extracted with ethyl acetate (100 mL, 2 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated to yield **3a** as a yellow solid (2.82 g, 98%). Mp: 55−57 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.86−7.89 (m, 3H), 7.51 (td, ^3J = 7.5 Hz, ^4J = 1.38 Hz, 1H), 7.42−7.45 (m, 3H), 7.30−7.31 (m, 1H), 4.96 (h, ^3J = 6.3 Hz, 1H), 1.01 (d, ^3J = 6.3 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 191.8, 167.3, 148.0, 141.0, 135.0, 131.1, 130.2, 129.9, 129.3, 129.1 (2C), 127.8, 68.6, 21.2. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.12; H, 5.96.

1-(4-*N*-Butyrylamino-3-methyl-5-nitrophenyl)-3*N*-methylbenzimidazole (17). A solution of *N*-butyryl-4-amino-3-methyl-5-nitrobenzoic acid (**16**, 3.99 g, 15.0 mmol) and 1,1′-carbonyldiimidazole (3.74 g, 23.0 mmol) in 1,4-dioxane (40 mL) was stirred under nitrogen at room temperature until gas evolution ceased. *N*-Methyl-1,2-phenylenediamine (1.83 g, 15.0 mmol, 1.71 mL) was added, and the reaction mixture was refluxed for 2 h, cooled, poured into ice water (200 mL), and basified with concentrated aq ammonia to pH 9. The light yellow precipitate was filtered, washed with Et_2O (2 × 10 mL), and dried in vacuo (3 × 10^{-3} mbar) (2.86 g). The filtrate was extracted with ethyl acetate (3 × 50 mL); the combined organic layers were washed with brine (1 × 50 mL), dried over $MgSO_4$, and concentrated, and the residue was dried in vacuo (3 × 10^{-3} mbar) (1.47 g). The two crops of light yellow solid were combined to yield the title compound **17** (4.33 g, 82%). Mp: 151−153 °C ($CHCl_3$/*n*-hexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.01 (s, 1H), 8.18 (s, 1H), 8.10 (s, 1H), 7.70 (d, ^3J = 7.8 Hz, 1H), 7.63 (d, ^3J = 7.8 Hz, 1H), 7.24−7.33 (m, 2H), 3.92 (s, 3H), 2.41 (s, 3H), 2.35 (t, ^3J = 7.2 Hz, 2H), 1.63 (sext, ^3J = 7.4 Hz, 2H), 0.94 (t, ^3J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.2, 150.5, 146.3, 142.3, 137.1, 136.6, 134.7, 129.8, 127.8, 122.7, 122.5, 122.1, 119.0, 110.6, 37.2, 31.6, 18.3, 17.8, 13.4. Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.54; H, 5.81; N, 15.93.

1-(4-*N*-Butyrylamino-3-methyl-5-aminophenyl)-3*N*-methylbenzimidazole (4). Activated palladium on charcoal (10%, 638 mg, 0.60 mmol) and 1-(4-*N*-butyrylamino-3-methyl-5-nitrophenyl)-3*N*-methylbenzimidazole (**17**, 6.40 g, 18.2 mmol) were suspended in MeOH (100 mL) in a stainless steel autoclave. The mixture was stirred under H_2 pressure (10 bar) for 12 h at 50 °C. The suspension was filtered, the filter cake rinsed with hot ^{i}PrOH (3 × 50 mL), and the filtrate concentrated to dryness (5.76 g). Recrystallization of the crude product from aq MeOH (60%) yielded **4** as its colorless solid monohydrate (5.56 g, 90%). Mp: 187−189 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.08 (s, 1H), 7.65 (d, ^3J = 7.9 Hz, 1H), 7.55 (d, ^3J = 7.9 Hz, 1H), 7.21−7.27 (m, 1H), 7.08 (s, 1H), 6.91 (s, 1H), 4.99 (s, 2H), 3.85 (s, 3H), 2.36 (t, ^3J = 7.3 Hz, 2H), 2.17 (s, 3H), 1.66 (sext, ^3J = 7.2 Hz, 2H), 0.96 (t, ^3J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 171.5, 153.6, 144.9, 142.5, 136.6, 136.0, 128.4, 123.3, 122.2, 121.9, 118.9, 118.8, 114.0, 110.5, 37.6, 31.8, 18.9, 18.4, 13.9. Anal. Calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found: C, 66.81; H, 7.42; N, 16.39.

4′-[(2-Butyrylamino-3-methyl-5-(1*N*-methyl-1*H*-benzimidazole-2-yl)phenylamino)methyl]-biphenyl-2-carboxylic Acid Isopropyl Ester (18). **4** (340 mg, 1.00 mmol), **3a** (269 mg, 1.00 mmol), activated palladium on charcoal (10%, 80.1 mg, 0.08 mmol), and *p*-TsOH (20.4 mg, 0.12 mmol) were suspended in toluene (40 mL) under nitrogen. $C(OMe)_4$ (545 mg, 4.00 mmol) was added, and the mixture was refluxed for 16 h and then concentrated. The residue was diluted with ^{i}PrOH (20 mL), transferred to a stainless steel autoclave, and stirred under H_2 pressure (10 bar) for 16 h at 50 °C, cooled to room temperature, and filtered, and the filter cake was rinsed with ethyl acetate (3 × 25 mL). The filtrate was washed with water, and the aqueous layer was basified to pH 10 with concentrated aq ammonia (1 × 150 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated, and the crude solid was purified by column chromatography (SiO_2, ethyl acetate) to yield **18** as a colorless solid (414 mg, 72%). Mp: 92−94 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.76−7.79 (m, 2H), 7.48 (t, ^{3}J = 7.5 Hz, 1H), 7.30−7.40 (m, 7H), 7.26−7.27 (m, 1H), 7.21 (d, ^{3}J = 7.9 Hz, 1H), 6.76 (s, 1H), 6.56 (s, 1H), 4.92 (h, ^{3}J = 6.2 Hz, 1H), 4.36 (s, 2H), 3.55 (s, 3H), 2.58 (t, ^{3}J = 7.5 Hz, 2H), 2.15 (s, 3H), 1.81 (sext, ^{3}J = 7.4 Hz, 2H), 1.02 (t, ^{3}J = 7.4 Hz, 3H), 0.98 (d, ^{3}J = 6.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 172.8, 168.1, 154.8, 143.8, 142.4, 141.9, 140.3, 137.8, 136.3, 135.8, 131.6, 130.9, 130.6, 129.5, 128.7, 128.4, 127.1, 126.7, 123.7, 122.7, 122.4, 120.1, 119.1, 110.5, 109.8, 68.4, 47.4, 38.5, 31.3, 21.3, 19.7, 18.7, 13.9. Anal. Calcd for $C_{36}H_{38}N_4O_3$: C, 75.24; H, 6.66; N, 9.75. Found: C, 75.01; H, 6.52; N, 9.59.

Telmisartan (5). 18 (575 mg, 1.00 mmol) was diluted with glacial acetic acid (40 mL), and the resulting solution was refluxed for 3 h and then concentrated. Ethanol (10 mL) and aq sodium hydroxide (2 N, 10 mL) were added, and the mixture was refluxed for 12 h, cooled to 80 °C, and acidified to pH 5−6 with aq HCl (6 N, 2.6 mL). The resulting suspension was stirred in an ice bath for 1 h, and filtered, and the filter cake was rinsed with water (2 × 10 mL) and Et_2O (2 × 10 mL) and then dried in vacuo to give **5** as a colorless solid (473 mg, 92%, mp 261−263 °C, >99 area % HPLC purity). The analytical data obtained correspond to those reported for crystal modification A.[8]

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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