Synthesis M. Seki Paper

2,4-Dimethoxybenzyl Group for the Protection of Tetrazole: An Efficient Synthesis of Olmesartan Medoxomil through C–H Arylation

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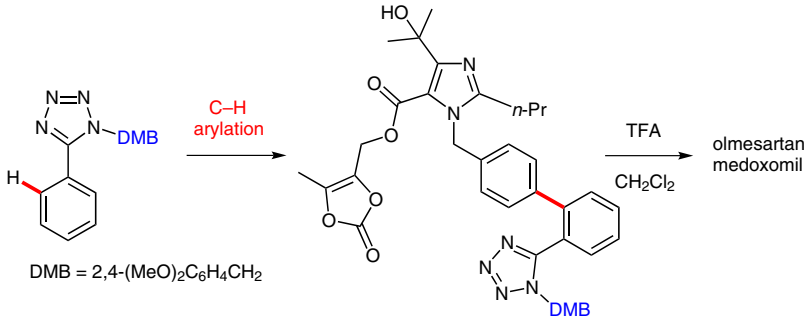


Received: 06.05.2015
Accepted after revision: 19.05.2015
Published online: 10.07.2015
DOI: 10.1055/s-0034-1378848; Art ID: ss-2015-f0291-op

Abstract The 2,4-dimethoxybenzyl (DMB) group was found to be effective for protecting tetrazoles. The DMB group is inert to various conditions, including those for ruthenium-catalyzed C–H arylation, but is readily cleaved under mild conditions. The use of a DMB protecting group permitted a synthesis of highly functionalized olmesartan medoxomil in a few steps.

Key words protecting groups, arylations, heterocycles, biaryls, drugs, tetrazoles

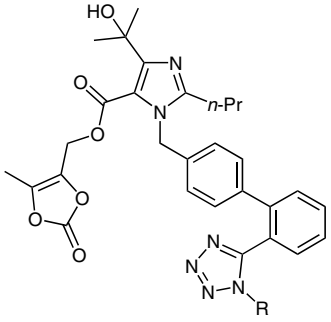


Figure 1 Olmesartan medoxomil (**1**) and its protected derivatives

Developing an efficient protecting group is crucial, especially in syntheses of multifunctional bioactive compounds such as drugs or natural products.[1] In the course of process development for angiotensin II receptor blockers (ARBs) through C–H arylation,[2,3] we generally used a benzyl group for the protection of tetrazole. However, in the synthesis of olmesartan medoxomil (**1**; Olmecip, Benicar; Figure 1) from the corresponding *N*-benzyl derivative **2a**, the medoxomil ester moiety was cleaved under the deprotection conditions. Hence, a better protecting group had to be developed that would be stable under the conditions for C–H arylation and would not affect the labile medoxomil ester group during deprotection. Described herein is the use of the 2,4-dimethoxybenzyl group for protection of tetrazole and its use in an efficient synthesis of olmesartan medoxomil (**1**) through C–H arylation.

In the synthesis of ARBs, we used a ruthenium-catalyzed C–H arylation to form a biphenyl tetrazole, a key structural feature of ARBs. Previous syntheses of ARBs generally used a trityl group for the protection of the tetrazole moiety.[4] However, the trityl group is not resistant to the reaction conditions for C–H arylation and is not atom-economical[5] because of its high molecular weight. Consequently, we used a benzyl group in our syntheses of such ARBs as losartan, valsartan, and candesartan cilexetil.[2] However, in marked contrast to the behavior of these compounds, the removal of a benzyl group from N-benzylated olmesartan medoxomil (**2a**) under deprotection conditions of transfer hydrogenation resulted in exclusive cleavage of the medoxomil ester moiety rather than the benzyl group.

To address this problem, we screened various protecting groups for tetrazole (Table 1). First, we tested the 4-methoxybenzyl (PMB) group.[6] Heating 4-methoxybenzylated olmesartan medoxomil (**2c**) in trifluoroacetic acid (5% v/v) at 40 °C for 12 hours resulted in complete consumption of **2c**. However, olmesartan medoxomil (**1**) was obtained in a poor yield (66%) and low purity (68.6%) (Table 1, entry 1). When the reaction temperature was reduced from 40 °C to 25 °C, a much longer period (72 h) was required to complete the reaction and the purity of the product **1** was still unsatisfactory (72.3%; entry 2). Raising the temperature from 40 °C to 60 °C accelerated the reaction, but decreased

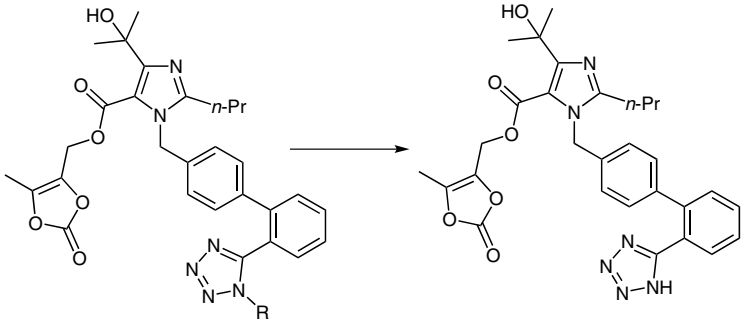
the purity of the product **1** to 66.4% (entry 3). Removal of a 3,4-methylenedioxybenzyl group from derivative **2d** proceeded much faster (12 h at 25 °C), but the purity of product **1** was still poor (45.3%; entry 4). Dilution of the mixture with dichloromethane or toluene did not improve the quality of product **1** (entries 5 and 6). Finally, we tested the 2,4-dimethoxybenzyl (DMB) group for protection of the tetrazole moiety. Cleavage of DMB-protected olmesartan medoxomil (**2b**) proceeded smoothly in the presence of small amount of trifluoroacetic acid in dichloromethane to give the product **1** in high yield (98%) and with excellent purity (98.1%) (entry 9).

The entire scheme for the synthesis of olmesartan medoxomil (**1**) by means of C–H arylation and the use of a DMB protecting group is shown in Scheme 1. The key step of the synthesis is the ruthenium-catalyzed C–H arylation of the DMB-protected 5-phenyltetrazole **3** with the aryl bromide **4**. The reaction took place according to our previously reported procedure.[1] Although the yield was moderate (55%), the use of a sterically more demanding DMB group prevented the formation of a diarylation byproduct, even when potassium pivalate[7] was used as the co-catalyst, so that the desired monoarylation product **5** was formed exclusively.

Removal of the benzoyl group from benzoate **5** and subsequent chlorination gave the corresponding chloro compound **6** as a stable solid. Coupling of **6** with the imidazole derivative **7**, followed by hydrolysis and esterification with medoxomil chloride, gave the *N*-(2,4-dimethoxybenzyl) derivative of olmesartan medoxomil **2b**. Finally, deprotection of **2b** by using the procedure described above gave the target compound **1** in 98% yield.

In conclusion, we have identified the DMB group as an efficient protecting group for tetrazoles. It is effective in terms of its stability toward various conditions, including those for ruthenium-catalyzed C–H arylation, and is ready removed, even from highly functionalized substrates such as **2b**. The high selectivity toward monoarylation in the C–H arylation when the DMB is used is beneficial as well. The use of a DMB group for the protection of tetrazoles could find widespread use in syntheses of tetrazole-containing compounds of pharmaceutical importance.

Table 1 Deprotection of Protected Olmesartan Medoxomil

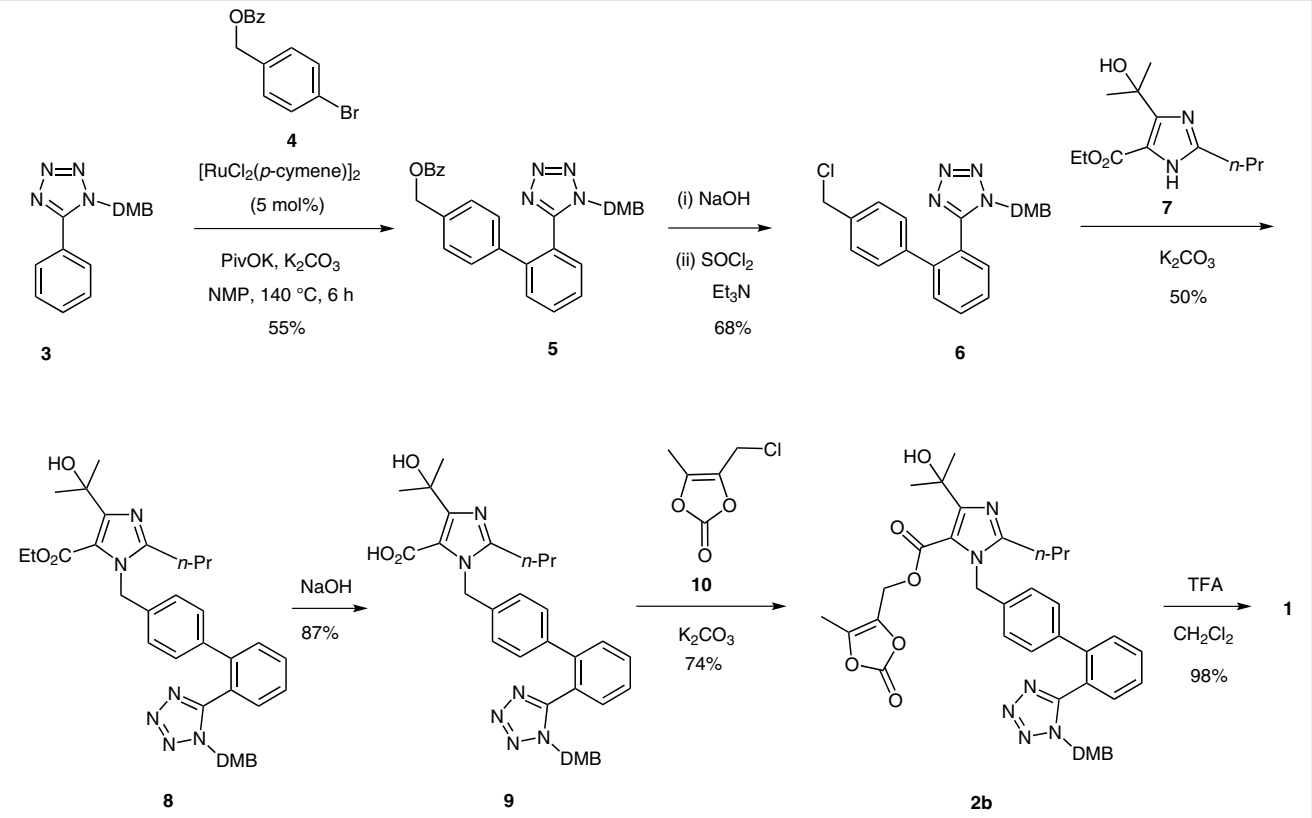


2b: R = 2,4-$(MeO)_2C_6H_4CH_2$ (DMB)
2c: R = 4-$MeOC_6H_4CH_2$ (PMB)
2d: R = 3,4-$OCH_2OC_6H_4CH_2$ (PIP)

1

Entry	R	TFA[a]	Solvent (v/w)[a]	Temp (°C)	Time (h)	Conv. (%)	Yield[b] (%)	HPLC (area%)
1	PMB	5	–	40	12	100	66	68.6
2	PMB	5	–	25	72	100	83	72.3
3	PMB	15	–	60	4	100	quant	66.4
4	PIP[c]	10	–	25	12	64	–[d]	45.3
5	PIP	5	CH_2Cl_2 (5)	40	8	86	–[d]	53.7
6	PIP	5	toluene (5)	40	8	81	–[d]	44.2
7	PIP	10	–	40	8	75	–[d]	45.1
8	DMB[e]	1	CH_2Cl_2 (4)	25	2	99.2	84	93.9
9	DMB	1	CH_2Cl_2 (5)	25	6	99.8	98	98.1

[a] Volume (mL) per gram of substrate.
[b] Isolated yield
[c] PIP = 3,4-methylenedioxybenzyl.
[d] Not determined.
[e] DMB = 2,4-dimethoxybenzyl.



Scheme 1 Synthesis of olmesartan medoxomil (**1**) through C–H arylation with a 2,4-dimethoxybenzyl protecting group

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer with TMS as the internal standard. Column chromatography was performed on Kieselgel 60 (E. Merck). TLC was carried out on 0.25 mm precoated glass-backed plates (60 F_{254}; E. Merck); development was accomplished by using 5% phosphomolybdic acid in EtOH followed by heating or spots were visualized by UV irradiation where feasible. Mass spectra were recorded on a Shimadzu 8030 LC mass spectrometer operated in the ESI mode. High-resolution mass spectra were recorded on a Micromass ESI-TOF mass spectrometer in the ESI-TOF mode.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-Hydroxy-1-methylethyl)-1-({2′-[1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl}methyl)-2-propyl-1*H*-imidazole-5-carboxylate (2c); Typical Procedure

A solution of PMBCl (6.61 g, 44.8 mmol) in $CHCl_3$ (125 mL) was added dropwise over 1 h to a solution of tetrazole **1** (25 g, 44.8 mmol), Na_2CO_3 (7.12 g, 67 mmol), and TBAB (0.32 g, 0.98 mmol) in H_2O (25 mL) at 10 °C, and the mixture was stirred at 55 °C for 11 h. The aqueous phase was extracted with $CHCl_3$, and the organic extracts were combined, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography [silica gel, hexane–EtOAc (3:1)] to give a colorless solid; yield: 12.5 g (20.6%); mp 126.8 °C.

IR (KBr): 3388, 2965, 1817, 1742, 1677, 1613, 1530, 1515, 1245, 1149, 1002, 766 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.74 (t, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 6.77 (s, 4 H), 5.41 (s, 2 H), 5.21 (s, 1 H), 5.04 (s, 2 H), 5.0 (s, 2 H), 3.67 (s, 3 H), 2.59 (t, *J* = 7.6 Hz, 2 H), 2.07 (s, 3 H), 1.58–1.50 (m, 2 H), 1.47 (s, 6 H), 0.85 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 160.6, 159.2, 157.5, 153.8, 151.6, 151.0, 141.1, 140.4, 137.6, 137.0, 132.8, 131.6, 130.8, 130.3, 129.4, 128.6, 127.9, 125.7, 125.5, 122.3, 116.2, 114.0, 69.6, 55.0, 54.11, 49.9, 47.9, 29.7, 28.2, 20.5, 13.5, 08.7.

MS: *m/z* = 679 [M + H]$^+$.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{37}H_{38}N_6NaO_7$: 701.2700; found: 701.2700.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-({2′-[1-(1,3-Benzodioxol-5-ylmethyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl}methyl)-4-(1-hydroxy-1-methylethyl)-2-propyl-1*H*-imidazole-5-carboxylate (2d)

Prepared by a similar procedure to **2c** from **1** (10 g); yield: 3.6 g (14.5%); mp 156.3 °C.

IR (KBr): 3389, 2965, 1817, 1741, 1676, 1492, 1399, 1312, 1238, 1149, 1034, 1002, 956, 767 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.73 (d, *J* = 7.2 Hz, 1 H), 7.61–7.56 (m, 2 H), 7.52 (d, *J* = 7.2 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 8 Hz, 2 H). 6.73 (d, *J* = 8 Hz, 1 H), 6.31 (d, *J* = 7.6 Hz, 2 H), 5.96 (s, 2 H), 5.40 (s, 2 H), 5.20 (s, 1 H), 5.01 (s, 2 H), 4.96 (s, 2 H), 2.59 (t, *J* = 7.6 Hz, 2 H), 2.07 (s, 3 H), 1.58–1.52 (m, 2 H), 1.47 (s, 6 H), 0.85 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 160.6, 157.5, 153.9, 151.6, 151.0, 147.4, 147.2, 141.1, 140.4, 137.5, 137.1, 132.8, 131.7, 131.6, 130.8, 130.3, 128.7, 127.9, 127.1, 125.7, 122.3, 121.8, 116.2, 108.2, 108.1, 101.2, 69.6, 67.4, 54.1, 50.1, 47.9, 29.8.

MS: *m/z* = 693 [M + H]$^+$.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{37}H_{36}N_6NaO_8$: 715.2492; found: 715.2491.

{2′-[1-(2,4-Dimethoxybenzyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl}methyl Benzoate (5)

An oven-dried flask was sequentially charged with tetrazole **3** (5.0 g, 16.87 mmol), benzoate **4** (5.4 g, 18.56 mmol), K_2CO_3 (2.33 g, 16.87 mmol), PvOK (0.47 g, 3.37 mmol), and NMP (25 mL) at 25 °C under N_2. The mixture was heated to 138 °C, and [$(RuCl_2)$(*p*-cymene)]$_2$ (0.52 g, 0.84 mmol) was added in one portion with stirring. The mixture was kept at 138 °C for 6 h then cooled to 25 °C. MTBE (25 mL) was added, and the mixture was filtered through a sintered funnel. The residue was washed with MTBE (50 mL), and the organic layers were combined and washed with H_2O (2 × 25 mL). The separated aqueous layer was extracted with MTBE (2 × 25 mL). The organic layers were again combined and washed successively with H_2O (2 × 25 mL) and brine (25 mL) then dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel 2.0–8.0% EtOAc–hexane) to give a colorless solid; yield: 4.70 g (55%); mp 132 °C.

IR (KBr): 3424, 3064, 3034, 3011, 2967, 2945, 2935, 2838, 1722, 1617, 1587, 1509, 1469, 1453, 1272, 1208/, 1159, 1126 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ = 8.09 (d, *J* = 7.6 Hz, 2 H), 7.64–7.56 (m, 3 H), 7.50–7.44 (m, 4 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 6.28–6.24 (m, 2 H), 5.36 (s, 2 H), 4.68 (s, 2 H), 3.73 (s, 3 H), 3.46 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.2, 161.3, 157.9, 154.3, 141.3, 138.8, 135.7, 133.0, 131.2, 131.1, 130.9, 130.0, 129.8, 129.6, 128.8, 128.3, 128.2, 127.5, 123.2, 113.9, 104.1, 98.14, 65.8, 55.2, 54.9, 45.73.

MS: *m/z* = 507 [M + H]$^+$.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{30}H_{26}N_4NaO_4$: 529.1852; found: 529.1852.

5-[4′-(Chloromethyl)biphenyl-2-yl]-1-(2,4-dimethoxybenzyl)-1*H*-tetrazole (6)

A solution of benzoate **5** (3.74 g, 7.38 mmol) in MeOH (27 mL) was treated with 20% aq NaOH (13.6 mL) at 25–30 °C. TBAB (0.043 g, 0.134 mmol) was added at 25–30 °C, and the mixture was stirred at 60–65 °C for 4 h. When the reaction was complete, the mixture was cooled to 40–45 °C and concentrated. H_2O (10 mL) was added to the residue, and the mixture was neutralized with 2 M aq HCl (15 mL, pH 6.5–7.5) at 0–10 °C. The mixture was then extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined and washed with brine (10 mL). The separated organic layer was distilled under reduced pressure to give a residue that was purified by column chromatography (silica gel, 50–60% EtOAc–hexane). The appropriate fractions were distilled to give the corresponding alcohol (2.5 g) as a black thick mass.

The alcohol was dissolved in a mixture of Et_3N (1.3 mL, 9.32 mmol) and CH_2Cl_2 (25 mL) at 25–30 °C and the solution was cooled to 0–5 °C. $SOCl_2$ (0.443 g, 3.72 mmol) was added at 0–5 °C during 15 min, and the mixture was heated to 25–30 °C and stirred at this temperature for 4 h. When the reaction was complete, H_2O (10 mL) was added and the mixture was stirred for 10 min. The layers were separated and the organic layer was washed successively with 5% aq $NaHCO_3$ (20 mL) and brine (20 mL) then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 40–50% EtOAc–hexane). The appropriate fractions were collected and distilled to give **6** as a brown solid; yield: 2.1 g (68%); mp 108–109 °C.

IR (KBr): 2927, 1707, 1616, 1510, 1367, 1040, 777 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.67–7.62 (m, 1 H), 7.57 (d, *J* = 9.0 Hz, 1 H), 7.52–7.43 (m, 2 H), 7.31 (d, *J* = 9.0 Hz, 2 H), 7.12 (d, *J* = 9.0 Hz, 2 H), 6.77 (d, *J* = 9.0 Hz, 1 H), 6.31–6.23 (m, 2 H), 4.67 (s, 2 H), 4.56 (s, 2 H), 3.74 (s, 3 H), 3.46 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 161.3, 157.8, 154.2, 141.1, 139.0, 137.0, 131.2, 131.1, 130.9, 130.0, 128.96, 128.9, 127.6, 123.2, 113.9, 104.2, 98.1, 55.2, 55.0, 45.7, 45.5.

MS: *m/z* = 421 [M + H]$^+$.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{21}ClN_4NaO_2$: 443.1251; found: 443.1251.

Ethyl 1-({2′-[1-(2,4-Dimethoxybenzyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl}methyl)-4-(1-hydroxy-1-methylethyl)-2-propyl-1*H*-imidazole-5-carboxylate (8)

A dried flask was charged with imidazole **7** (0.91 g, 3.79 mmol), K_2CO_3 (1.047 g, 7.58 mmol), and TBAB (0.0122 g, 0.038 mmol). Acetone (4 mL) was added at 25–30 °C, and the mixture was cooled to 0–5 °C. A solution of chloro compound **6** (1.6 g, 3.8 mmol) in acetone (4 mL) was added over 10–15 min at 0–5 °C, and the mixture was heated to 60–65 °C and stirred for 89 h at 60–65 °C. When the reaction was complete, the mixture was concentrated and the residue was treated with H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, washed with brine (10 mL), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 1–5% MeOH–CH_2Cl_2). The appropriate fractions were collected and distilled to give a thick brown mass; yield: 1.2 g (50%).

IR (KBr): 3409, 2964, 2937, 1707, 1698, 1511, 1031 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.66–7.60 (m, 1 H), 7.53–7.38 (m, 3 H), 7.08 (d, *J* = 6.0 Hz, 2 H), 6.81 (dd, *J* = 15.0, 9.0 Hz, 3 H), 6.29 (dd, *J* = 6.0, 3.0 Hz, 1 H), 6.21 (d, *J* = 3.0 Hz, 1 H), 5.78 (s, 1 H), 5.42 (s, 2 H), 4.65 (s, 2 H), 4.21 (dd, *J* = 9.0, 15.0 Hz, 2 H), 3.73 (s, 3 H), 3.45 (s, 3 H), 2.64 (t, *J* = 6.0 Hz, 2 H), 1.77–1.66 (m, 2 H), 1.63 (s, 6 H), 1.17 (t, *J* = 6.0 Hz, 3 H), 0.96 (t, *J* = 9.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 161.5, 161.4, 158.8, 157.8, 154.2, 151.2, 141.2, 138.3, 136.8, 131.1, 131.0, 130.9, 129.9, 129.0, 127.6, 125.7, 123.2, 116.8, 113.8, 104.2, 98.1, 70.2, 61.2, 55.2, 54.9, 48.6, 45.6, 29.2, 21.2, 14.0, 13.9, 13.7.

MS: *m/z* = 625 [M + H]$^+$.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{35}H_{40}NaN_6O_5$: 647.2958; found: 647.2959.

1-({2′-[1-(2,4-Dimethoxybenzyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl}methyl)-4-(1-hydroxy-1-methylethyl)-2-propyl-1*H*-imidazole-5-carboxylic Acid (9)

NaOH (158.4 mg, 3.96 mmol) was added to a stirred solution of ester **8** (0.6 g, 0.96 mmol) in MeOH (2.4 mL) and H_2O (1.2 mL) at 25–30 °C, and the mixture was stirred at 70–75 °C for 4 h. When the reaction was complete, the mixture was concentrated and the residue was treated with H_2O (10 mL), The mixture was then was neutralized with 2 M HCl (15 mL, pH 6.5–7.5) and extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined and washed with brine (10 mL).

The separated organic layer was distilled under reduced pressure and then co-distilled with toluene (5 mL) to give an off-white solid; yield: 0.5 g (87%); mp 105–106 °C.

IR (KBr): 3436, 2929, 1718, 1614, 1511, 1467, 1032 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.76–7.71 (m, 1 H), 7.63–7.55 (m, 3 H), 7.00–6.94 (m, 4 H), 6.86 (d, *J* = 9.0 Hz, 1 H), 6.41 (s, 1 H), 6.37 (d, *J* = 3.0 Hz, 1 H), 5.65 (s, 2 H), 4.76 (s, 2 H), 3.70 (s, 3 H), 3.44 (s, 3 H), 2.71 (br s, 2 H), 1.57 (s, 6 H), 1.50 (dd, *J* = 15.0, 6.0 Hz, 2 H), 0.85 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 161.1, 160.4, 157.8, 153.8, 149.9, 140.8, 137.8, 136.5, 131.4, 131.1, 130.9, 130.1, 128.6, 127.8, 126.2, 122.6, 118.3, 113.6, 104.7, 98.2, 70.1, 55.2, 47.7, 45.6, 29.3, 27.2, 20.6, 13.4.

MS: *m/z* = 597 $[M + H]^+$.

HRMS: *m/z* $[M + Na]^+$ calcd for $C_{33}H_{36}N_6NaO_5$: 619.2645; found: 619.2645.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-({2′-[1-(2,4-Dimethoxybenzyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl}methyl)-4-(1-hydroxy-1-methylethyl)-2-propyl-1*H*-imidazole-5-carboxylate (2b)

An oven-dried flask was sequentially charged with carboxylic acid **9** (5.8 g, 7.98 mmol), Na_2CO_3 (1.1 g, 10.4 mmol), KI (0.0133 g, 0.08 mmol), and acetone (20.0 mL), and the mixture was stirred for 10 min. A solution of medoxomil chloride (**10**; 1.66 g, 11.2 mmol) in acetone (9.0 mL) was added over 10 min at 25 °C, and the mixture was heated at 45–50 °C until the reaction was complete (11 h). The mixture was then cooled to 25 °C and the acetone was removed under reduced pressure. To the resulting mixture were added 10% aq NaCl (29.0 mL) and toluene (29.0 mL). The pH of the solution was adjusted to 7–8 by using 5% aq HCl (6.3 mL), and the mixture was stirred for 10 min. The two layers were separated and the aqueous layer was extracted with toluene (2 × 15.0 mL). The organic layers were combined and washed with 10% aq NaCl (29.0 mL). The toluene was distilled off under reduced pressure to give a crude product that was purified by column chromatography (silica gel, 0.4–0.5% MeOH–CH_2Cl_2) to give a colorless solid; yield: 4.19 g (74%); mp 139.8 °C.

IR (KBr): 3392, 2965, 2872, 2836, 1817, 1744, 1678, 1589, 1490, 1466, 1312, 1231, 1149, 1034, 1003, 956, 767 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.74 (dt, *J* = 7.6, 7.2 Hz, 1 H), 7.62–7.55 (m, 3 H), 6.94 (d, *J* = 8 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 3 H), 6.41–6.37 (m, 2 H), 5.42 (s, 2 H), 5.21 (s, 1 H), 5.05 (s, 2 H), 4.76 (s, 2 H), 3.70 (s, 3 H), 3.45 (s, 3 H), 2.62 (t, *J* = 7.2 Hz, 2 H), 2.07 (s, 3 H), 1.59–1.51 (m, 2 H), 1.47 (s, 6 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 161.6, 161.1, 158.3, 157.9, 154.3, 152.1, 151.4, 141.4, 140.8, 138.1, 137.5, 133.2, 131.9, 131.5, 131.3, 130.5, 129.0, 128.2, 126.2, 123.1, 116.7, 114.1, 105.2, 98.6, 70.0, 55.7, 54.6, 48.4, 46.0, 30.1, 28.7, 21.0, 14.0, 9.1.

MS: *m/z* = 709 $[M + H]^+$.

HRMS: *m/z* $[M + Na]^+$ calcd for $C_{38}H_{40}N_6NaO_8$: 731.2805; found: 731.2802.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-imidazole-5-carboxylate (1; Olmesartan Medoxomil)

An oven-dried flask was sequentially charged with CH_2Cl_2 (1.0 mL), ester **2b** (0.2 g, 0.28 mmol), and TFA (0.2 g, 1.82 mmol, 0.14 mL) at 25 °C, and the mixture was stirred at 25 °C for 6 h. When the reaction was complete, the mixture was evaporated under reduced pressure then co-evaporated with CH_2Cl_2 (2 × 5.0 mL). CH_2Cl_2 (5.0 mL) was added to the residue, and the mixture was filtered through Celite, which was washed with CH_2Cl_2 (2 × 2.0 mL). The organic layer was treated with 0.5 M aq KH_2PO_4 buffer (4.0 mL), and the mixture was stirred for 0.5 h. The pH of the mixture was adjusted to 4–5 by using 5% aq Na_2CO_3 (0.4 mL). The organic layer was washed with H_2O (5.0 mL), dried (Na_2SO_4), filtered, and concentrated. Heptane was added and the product was collected by filtration then dried under vacuum at 45 °C for 1 h to give colorless crystals; yield: 0.154 g (98%); mp 173.6 °C.

HPLC: Column: Unisol C18 (4.6 × 150 mm; 3 µm); Buffer: $NaH_2PO_4·H_2O$ (2.76 g) in H_2O (1 L) + TEA (1 mL); pH adjusted to 3.3 with H_3PO_4; Buffer–MeCN (80:20); Gradient program (% B/T): 50:0, 95:02, 95:20, 50:22, 50:25; Flow: 1.0 mL/min; Injection vol.: 10 µL; Column temp: 30 °C; Diluent: MeCN–H_2O (90:10); Sample concentration: 500 ppm; Purity (area%): 98.1%.

IR (KBr): 3292, 2972, 1832, 1740, 1707 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.55–7.70 (m. 4 H), 7.04 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 5.42 (s, 2 H), 5.21 (s, 1 H), 5.06 (s, 2 H), 2.61 (t, *J* = 7.5 Hz, 2 H), 2.08 (s, 3 H), 1.54–1.63 (m, 2 H), 1.47 (s, 6 H), 0.88 (t, *J* = 7.5 Hz, 3 H).

MS: *m/z* = 559 $[M + H]^+$.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378848.

References

(1) (a) *The Art of Process Chemistry*; Yasuda, N., Ed.; Wiley-VCH: Weinheim, **2011**. (b) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, **2000**. (c) *Green Chemistry in the Pharmaceutical Industry*; Dunn, P.; Wells, A.; Williams, M. T., Eds.; Wiley-VCH: Weinheim, **2010**.

(2) (a) Seki, M. WO 2011061996, **2010**. (b) Seki, M. *ACS Catal.* **2011**, *1*, 607. (c) Seki, M.; Nagahama, M. *J. Org. Chem.* **2011**, *76*, 10198. (d) Seki, M. *Synthesis* **2012**, *44*, 3231. (e) Seki, M. *Yuki Gosei Kagaku Kyokaishi* **2012**, *70*, 1295. (f) Kocienski, P. *Synfacts* **2013**, *9*, 0006. (g) Seki, M. In *Science of Synthesis: Catalytic Transformations via C–H Activation*; Vol. 1; Yu, J.-Q., Ed.; Thieme: Stuttgart, **2015**, in press. (h) Seki, M. WO 2014034868, **2014**. (i) Seki, M. WO 2014051008, **2014**. (j) Seki, M. *RSC Adv.* **2014**, *4*, 29131. (k) Seki, M. *Synthesis* **2014**, *46*, 3249. (l) Seki, M. *ACS Catal.* **2014**, *4*, 4047. (m) Seki, M. *Synthesis* **2015**, *47*, 1423.

(3) For selected reviews on C–H activation (arylation), see: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (d) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (e) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (f) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (g) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2096. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (i) Sun, S.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (j) Peng, H. M.; Dai, L.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2010**, *49*, 5826. (k) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (l) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.

(4) For examples, see: (a) 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. *J. Med. Chem.* **1991**, *34*, 2525. (b) Bernhart, C. A.;

Perreaut, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J. L. A.; Clement, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E. *J. Med. Chem.* **1993**, *36*, 3371. (c) Kubo, K.; Kohara, Y.; Yoshimura, Y.; Inada, Y.; Shibouta, Y.; Furukawa, Y.; Kato, T.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 2343. (d) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1996**, *39*, 625. (e) Kurup, A.; Garg, R.; Carini, D. J.; Hansch, C. *Chem. Rev.* **2001**, *101*, 2727.

(5) Trost, B. M. *Science* **1991**, *254*, 1471.

(6) A PMB group was used for the protection of losartan: see refs. 2a and 2c.

(7) The use of PvOK for C–H arylation of unsubstituted benzyl-protected 1-benzyl-5-phenyl-1*H*-tetrazole resulted in a higher extent of diarylation (~14%); see ref. 2m. For original papers that describe the use of PvOK for C–H arylation, see: (a) Arockiam, P. B.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871. (b) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 6629.