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EFFICIENT AND CONVERGENT SYNTHESIS OF TELMISARTAN

A Sanjeev Kumar, Samir Ghosh, GN Mehta*

Applied Chemistry Department, Sardar Vallabhbhai National Institute of Technology, Surat-395 007, India.

ABSTRACT

A highly efficient, convergent approach to the synthesis of the angiotensin II receptor antagonist telmisartan (**1**) is described. Involving a Suzuki coupling of 4-(hydroxymethyl)phenylboronic acid with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline as the key step (95% yield). The bisbenzimidazole moiety is constructed alternatively via an *N*-alkylation-condensation sequence, replacing the previously published route. The product is obtained in an overall yield of 46% in this convergent synthesis with the sequence consisting of six steps.

Keywords: Telmisartan, antihypertensive drug, Suzuki coupling, oxazoline hydrolysis

Corresponding author
E-mail: drgnmehta@rediffmail.com

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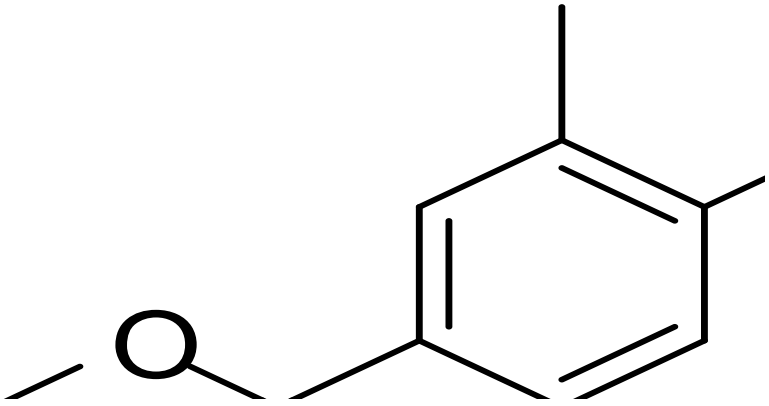
INTRODUCTION

Telmisartan **1** is an angiotensin II receptor antagonist useful in the treatment of hypertension, heart diseases, heart strokes, and bladder diseases [1]. Telmisartan is currently available in the market as an antihypertensive drug [2] under the brand name of MICARDIS.®

Figure 1: The Angiotensin II receptor antagonist telmisartan

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 **2** with butyryl chloride, followed by nitration, reduction of the nitro group, and subsequent cyclization of the resulting amine to the benzimidazole derivative **3**. After its saponification, the free carboxyl group is condensed with *N*-methyl-1,2-phenylenediamine to afford the bis-benzimidazole **4**, which is finally alkylated with the 4′-(bromomethyl)-2-biphenylcarboxylic acid *tert*-butyl ester **8** to give telmisartan **1** after hydrolysis of the ester group in 21% overall yield and eight steps over the longest sequence [3].

First literature synthesis of telmisartan



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Scheme 1: (a) ^{n}PrCOCl, C_6H_5Cl, 100 ^{o}C (b) HNO_3/H_2SO_4, 0 ^{o}C (c) Pd/C, 5 bar, H_2, MeOH (d) AcOH, 120 ^{o}C, yield : 78% (e) NaOH, MeOH/H_2O, 100 ^{o}C (f) 2- MeNH-C_6H_4- NH_2, PPA, 150 ^{o}C, yield 64% (g) ^{t}BuOK, DMSO, RT (h) TFA, DCM, RT, yield: 42% (i) Cu (5 eq), 210 ^{o}C, (j) HCl, H_2O, 100 ^{o}C (k) $(COCl)_2$, DCM, 0 ^{o}C, (l) ^{t}BuOK, THF, RT, yield: 9% (m) NBS, $(PhCOO)_2$, CCl_4, 76 ^{o}C.

Several improvements to this reaction sequence 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 [4]. However, the main shortcomings of the synthesis remained, namely, the unsatisfactory regioselectivity in the alkylation of **8** with **4**, the poor stability and shorter shelf life of 4'-bromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **8**, the non selective and moderately yielding free radical bromination of expensive intermediate **8** and the intricate synthesis of the biaryl intermediate **7**. In the original protocol, the biaryl intermediate **7** was synthesized via an Ullmann coupling of the aryl iodides **5** and **6** using 5 equiv of copper [5]. Modern syntheses of **7** involve cross-couplings of sensitive aryl magnesium, [6] zinc, [7] or boron [8, 9] compounds with alkyl 2-halobenzoates.

EXPERIMENTAL

All solvents and reagents were purchased from the commercial suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin layer chromatography was performed on Merck precoated Silica-gel $60F_{254}$ plates. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS (Tetra methyl silane). The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Melting points were obtained by using the open capillary method and are uncorrected.

[2'-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-yl]-methanol (14)

To a mixture of 4-(hydroxymethyl)phenylboronic acid (**13**, 5.0 g, 0.032 mol) and 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline [10] (**12**, 10.0 g, 0.039 mol) in tetrahydrafuran (50 mL), 2M aqueous sodium carbonate solution (20 mL) was added at room temperature. The resulting biphase solution was degassed with nitrogen gas for 20 minutes. Tetrakis(triphenylphosphine)palladium (0) (0.25 g) was added and heated to reflux (64 ^{o}C). The reaction mixture was maintained under reflux up to 12 h. After completion of the reaction, the reaction mixture was cooled to 26 ^{o}C and added saturated ammonium chloride solution (50 mL) and ethyl acetate (50 mL). Separated organic layer and washed twice with water (2 x 25 mL). Organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with hexane /ethyl acetate 50:50 to get the title compound as a white solid (8.8g, 95%). Mp: 98-100 °C (lit [11] Mp: 98-100 °C); MS (m/z): 282 [M^+ + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.74 (m, 1H, ArH), 7.49 (m, 1H, ArH), 7.40 -7.39 (m,

2H, ArH), 7.38 (d, 2H, J = 8.0 Hz, ArH), 7.35 (d, 2H, J = 8.0 Hz, ArH), 4.75 (s, 2H, -CH_2), 3.80 (s, 2H, -CH_2), 1.30 (s, 6H, 2 x -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 28.7, 66.3, 68.1, 78.9, 127.1, 126.9,127.7, 128.5,129.4, 129.4, 130.2, 137.2, 140.2, 141.2, 164.9.

***2-(4'-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole* (15)**

To a solution of [2'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]methanol (**14**, 4 g, 0.014 mol) in methylene chloride (40 mL), was added thionyl chloride (2 g, 0.017 mol) drop wisely at 0-5 ^{o}C and maintained for 2 h. The reaction mixture was poured into an aqueous solution of 20 % of sodium hydrogen carbonate solution (40 mL). Separated the organic layer was washed twice with water (50 mL). The organic layer was concentrated under pressure to get the title compound **5** as a white solid (4.2 g, 99%). Mp: 73-75 °C (lit [11] Mp: 73-75 °C); MS (m/z): 300 [M^+ + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.75 (1H, d, J = 7.4 Hz, ArH), 7.62 (1H, m, ArH), 7.43-7.35 (6H, m, ArH), 4.64 (2H, s, -CH_2), 3.81 (2H, s, -CH_2), 1.29 (6H, s, 2 x -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm); 32.1, 50.2, 71.7, 83.6, 131.4, 132.0, 132.4, 132.9, 134.2, 134.3, 134.6, 140.5, 145.1, 145.4, 167.7.

***1-((2'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)biphenyl-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]-imidazole-6-carboxylic acid* (17)**

A solution of methyl 4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxylate (**3**, 4.0 g, 0.017 mol) in dimethylacetamide (10 mL) and THF (30 mL) was added dropwise to the mixture of 60% sodium hydride (0.8 g, 0.034 mol) in THF (30 mL) under inert atmosphere. The reaction mixture was stirred for 30 min at room temperature. 2-[4'-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**15**, 5.7 g, 0.018 mol) in THF (30 mL) was added to the reaction mixture. Heated the reaction mixture to reflux and maintained for 8 h. After cooling the reaction mixture to 25-35 °C, this was poured into a solution of saturated aqueous ammonium chloride (50 mL). Product was extracted twice with ethyl acetate (2 x 25 mL) and evaporated under vacuum at 55 °C. To the obtained residue **16,** methanol (30 mL), water (30 mL) was added followed by sodium hydroxide (3.4 g, 0.086 mol) and heated to reflux temperature for about 5 h. After completion, the reaction mass was cooled to 25-35 °C, the pH of the reaction mass was adjusted to 4.5 -5.0 using concentrated hydrochloric acid, and then the reaction mass continued stirring for 45- 60 min. The crystalline solid obtained was filtered, washed with water (20 mL), and dried at 55-60 °C for 2-3 h to obtain **17** as an off white crystalline powder (6.6 g, 80%). Mp: 112-116 °C; MS (m/z): 482 [M + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.86 (1H, s, ArH), 7.62- 7.51 (3H, m, ArH), 7.43 -7.37 (2H, m, ArH), 7.28- 7.26 (2H, d, J = 8.0 Hz, ArH), 7.08- 7.06 (2H, d, J = 8.0 Hz, ArH), 5.60 (2H, s, -CH_2), 3.72 (2H, s, -CH_2), 2.87 (2H, t, J = 7.6 Hz, -CH_2), 2.56 (3H, s, -CH_3), 1.88 (2H, m, J = 7.6 Hz, -CH_2), 1.12 (6H, s, 2 x -CH_3), 0.97 (3H, t, J = 7.6 Hz, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 14.2, 16.9, 21.6, 28.6, 29.6, 31.5, 47.0, 67.6, 79.0, 112.3, 126.1, 126.3, 127.0, 127.2, 127.5, 127.7, 128.8, 129.1, 130.2, 136.9, 137.1, 139.4, 140.6, 143.8, 154.2, 164.1, 171.3.

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3'-{[2'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]methyl}-1,7'-dimeth-yl-2'-propyl-1H,- 3'H-2,5'-bibenzimidazole (18)

A solution of 1-((2'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)biphenyl-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxylic acid (**17**, 4.0 g, 0.0083 mol) and 1,1′-carbonyldiimidazole (2.0 g, 0.012 mol) in 1,4-dioxane (40 mL) was stirred under nitrogen at room temperature. *N*-Methyl-1,2-phenylenediamine (1.5 g, 0.012 mol) was added, and the reaction mixture was refluxed for 4 h, cooled, poured into ice water (200 mL), and basified with aq ammonia to pH 9. Product was extracted twice with ethyl acetate (2 x 25 mL) and evaporated under vacuum at 55 °C. The obtained residue was triturated with n-hexane (50 mL) to get the solid material and filtered, dried at 50-55 °C for 3-4 h to obtain **18** as a white crystalline powder (4.0 g, 85%). Mp: 191-193 °C; MS (m/z): 568 [M^+ + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.78 (1H, d, J = 8.0 Hz, ArH), 7.68 (1H, s, ArH), 7.64 (1H, s, ArH), 7.62- 7.60 (2H, d, J = 8.0 Hz, ArH), 7.59 (1H, d, J = 8.0 Hz, ArH), 7.47- 7.17 (6H, m, ArH), 7.09- 7.07 (2H, d, J = 8.0 Hz, ArH), 5.45 (2H, s, -CH_2), 3.82 (3H, s, -CH_3), 3.58 (2H, s, -CH_2), 2.97 (2H, t, J = 7.6 Hz, -CH_2), 2.74 (3H, s, -CH_3), 1.92 (2H, m, J = 7.6 Hz, -CH_2), 1.29 (6H, s, 2 x -CH_3), 1.04 (3H, t, J = 7.6 Hz, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 13.9, 16.7, 21.6, 27.6, 29.6, 31.6, 46.9, 67.2, 79.0, 108.8, 109.2, 119.3, 122.1, 122.2, 123.5, 123.6, 125.6, 127.0, 127.2, 128.8, 129.1, 129.7, 129.9, 130.2, 134.4, 134.8, 136.4, 140.6, 140.8, 142.6, 142.8, 154.2, 156.2, 163.1.

4'-[(1,7'-Dimethyl-2'-propyl-1H,3'H-2,5'-bibenzimidazol-3'-yl)methyl] biphenyl-2-carboxylic acid (1)

A mixture of (**18**, 4.0 g, 0.007 mol), concentrated hydrochloric acid (40 mL) was heated to reflux (100-105 ^{o}C) for about 30 h. The reaction mass was cooled to 0-5 ^{o}C. 20% sodium hydroxide solution was added until the reaction mixture pH attained to 9-10 and further stirred at room temperature for 2 h. Precipitated solid was filtered and washed with water (50 mL). The wet cake was dissolved in a mixture of water (60 mL) and acetonitrile (20.0 mL) and then heated to 60-65 °C. The pH of the resulting clear solution was adjusted to 5.0-5.5 using 5% acetic acid, and stirring continued for 2 h. The precipitated solid was filtered and washed with water (50 mL). Dried at 70-75 °C for 4-5 h under a vacuum to obtain telmisartan as a white crystalline powder (3.0 g, 85 %). Mp: 260-262 °C (lit [4] Mp: 260-262 °C); IR (KBr, cm^{-1}) 2300-3500 (broad), 1680 (C=O); MS (m/z): 515 [M^+ + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 12.8 (1H, s, -COOH), 8.42 (1H, d, J = 8.0 Hz, ArH), 8.02 (1H, d, J = 8.0 Hz, ArH), 7.52-7.28 (8H, m, ArH), 7.20 (2H, d, J = 8.0 Hz, ArH), 7.05 (1H, s, ArH), 6.96 (1H, s, ArH), 5.42 (2H, s, -CH_2), 3.82 (3H, s, -CH_3), 2.97 (2H, t, J = 7.6 Hz, -CH_2), 2.74 (3H, s, -CH_3), 1.92 (2H, m, J = 7.6 Hz, -CH_2), 1.04 (3H, t, J = 7.6 Hz, -CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) (δ ppm): 13.5, 16.7, 20.6, 27.6, 32.7, 47.1, 51.7, 112.0, 112.7, 114.7, 118.6, 125.3, 125.7, 125.8, 127.0, 127.4, 128.6, 129.3, 130.4, 130.6, 131.5, 132.3, 133.1, 133.2, 133.7, 134.5, 140.2, 140.5, 150.2, 157.3, 168.1.

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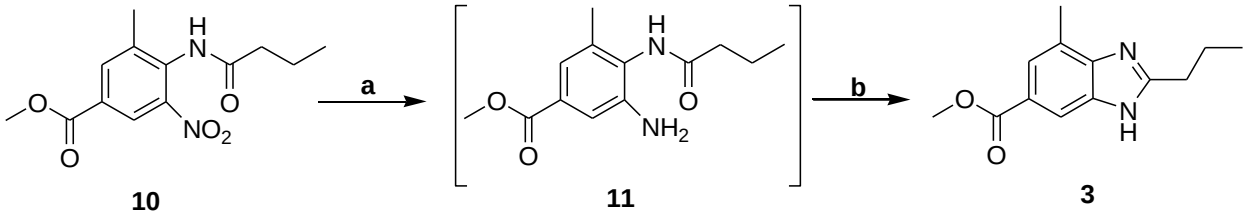
RESULTS AND DISCUSSION

We opted for 4-butyrylamino-3-methyl-5-nitro-benzoic acid methyl ester **10** as a starting material due to its commercial availability. In our approach, after the reduction of nitro compound **10** to obtain amine **11**, the resulting reaction mass was filtered to remove Pd-C catalyst and the filtrate was concentrated to thick syrup which was directly treated with glacial acetic acid to furnish benzimidazole intermediate **3** in a single step with 90% yield (Scheme 2). The workup involves evaporation of the acetic acid and cooling the reaction mass to room temperature followed by adjusting the pH of the reaction mass between 9.0 and 9.5 with concentrated ammonia to afford compound **3** as crystalline brown powder.



Scheme 2: (a) Pd/C, 5 bar, H_2, MeOH, rt, 4h (100%) (b) AcOH, 100-110 ^{o}C, 1.5 h, (90%).

At this point, our synthetic route deviates from the original pathway via bis benzimidazole formation with *N*-methyl-1,2-phenylenediamine. We examined the *N*-alkylation of methyl-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxylate **3** with 2-(4'-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole **15** with sodium hydride as base and in situ hydrolysis of ester to afforded the 1-((2'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)biphenyl-4-yl)methyl)-4-methyl-2-propyl-1H-ben- zo[d]-imidazole-6-carboxylic acid **17** in 80% yield.

Suzuki coupling was employed for the preparation of biaryl intermediate by the reaction of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline [10] **12** with 4-(hydroxymethyl)phenyl boronic acid **13** in presence of aqueous sodium carbonate and tetrakis(triphenylphospine) palladium (0) produced [2'-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-yl]-methanol **14** in 95% yield. Treatment of [2'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-biphenyl-4-yl]-methanol with thionyl chloride at low temperature afforded the key intermediate 2-(4'-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole **15** in 99% yield (Scheme 3).

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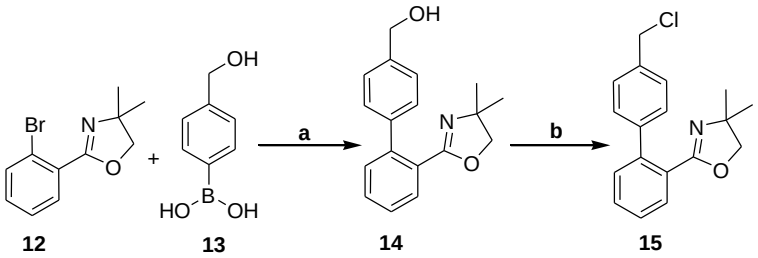
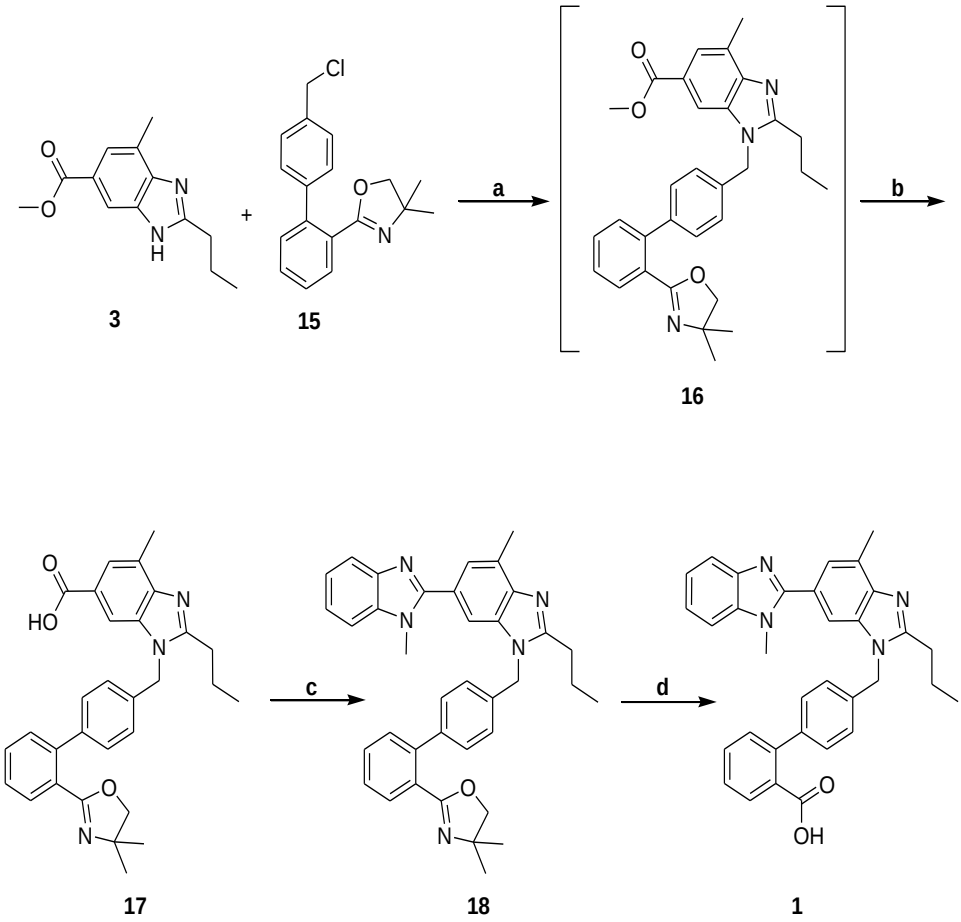


Scheme 3: (a) $Pd(Ph_3P)_4$, aq Na_2CO_3, THF, 60-65 ^oC, 2 h (95%) (b) $SOCl_2$, CH_2Cl_2, rt, 2 h (99%).

The substrate **17**, an attempted dehydration with polyphosphoric acid at 150 °C led to substantial side reactions such as cleavage of the butyryl group, butyrylation of the diamine and cleavage of oxazoline group afforded the intermediate **18** with 30% isolated yield after repeated purifications. An alternative condensation methodology proved to be more efficient. Activation of the carboxylic acid **17** with 1,1'-carbonyldiimidazole (CDI) followed by coupling with *N*-methyl-1,2-phenylenediamine and in situ cyclization in 1,4-dioxane at 130 ^oC, afforded the bis benzimidazole derivative **18** in 85% yield. Finally oxazoline intermediate was cleaved by concentrated hydrochloric acid to afford telmisartan **1** (Scheme 4).



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Scheme 4: (a) NaH, THF, 75-80 ^{o}C, 60-65 ^{o}C (100%) (b) NaOH, MeOH/H_2O, 70 ^{o}C, 5h (80%) (c) CDI, 2- MeNH-C_6H_4- NH_2, 1,4- Dioxane, 130 ^{o}C, 4h (85%) (d) Conc. HCl, 100-110 ^{o}C, 30h (85%).

CONCLUSION

In conclusion, a greatly efficient and convergent approach to the biphenyloxazoline structure of the A-II antagonists has been developed by employing a combination of the Suzuki coupling method. Application of this approach provided a practical procedure to the synthesis of telmisartan, which is a potent, orally active antagonist of the angiotensin II AT_1-receptor subtype.

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