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A synthesis of abemaciclib utilizing a Leuckart–Wallach reaction

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ABSTRACT

A concise total synthesis of CDK 4/6 inhibitor abemaciclib is described. The synthesis uses a Suzuki coupling, followed by a Hartwig–Buchwald amination to join three of the four subunits. The final step is a reductive amination utilizing Leuckart–Wallach conditions. Key to the Leuckart–Wallach reaction was the addition of trimethyl orthoformate to remove water formed during the reaction, allowing the reaction to go to completion.

Cyclin-dependent kinases play a key role in regulating cell cycle progression. In many cancers, there is a loss of control in regulating the cell cycle in response to increased signaling from CDK 4/6. As a result, there is uncontrolled growth of cancer cells.[1] Abemaciclib (**1**) is a cell-cycle inhibitor, designed to block the growth of cancer cells by specifically inhibiting CDK 4 and 6. Abemaciclib has shown evidence of single-agent activity in patients with advanced non-small cell lung cancer and breast cancer in a Phase I study. It is also under investigation as a combination therapy for breast cancer. Retrosynthetically, we planned to break the molecule in three places giving commercially available building blocks **2**, **3**, **4,** and **5** (Fig. 1). We envisioned connecting building blocks **2** and **3** through a Suzuki coupling reaction,[2] building blocks **3** and **4** through a Buchwald–Hartwig type coupling,[3] and building blocks **4** and **5** through a reductive amination.

It is well documented in the literature that the chloride in the 4-position of dichloro-pyrimidine **2** is generally the most reactive in palladium mediated reactions,[4] so this bond was targeted first through a Suzuki coupling between boronic ester **3** and pyrimidine **2** (Scheme 1). Use of $PdCl_2(PPh_3)_2$ with Na_2CO_3 in DME at 80 °C provided the desired biaryl compound **6** in 66% yield.[5] To form the carbon–nitrogen bond, we explored a Buchwald–Hartwig amination. The choice of solvent was important for this reaction due to solubility limitations. While alcohols provided adequate solubility, unhindered alcohols such as MeOH and EtOH displaced the chloride and provided the corresponding ethers as unwanted by-products. Use of the more hindered *t*AmylOH fortunately allowed the reaction to work well without observing any of the undesired *t*Amyl ether by-product. Ligand choice was also important, as PPh_3 was not active enough to provide full conversion and generally resulted in stalled reactions. We, fortunately, found DPEPhos was a sufficiently active catalyst,[6] to provide the desired product **7** in 99% yield.[7]

The final reaction in the synthesis was a reductive amination between aldehyde **7** and *N*-ethylpiperazine **5**. Initially, we explored $NaBH(OAc)_3$ as the reductant (Table 1, entry 1).[8] Although complete conversion was observed, product (**1**) was obtained as a 97:3 mixture with the corresponding alcohol (**8**) and could ultimately not be further purified through crystallization. Typical hydrogenative conditions (hetero- and homogeneous catalysts with H_2)[9] caused similar problems with reduction to the alcohol (**8**, results not listed). These setbacks led to the exploration of Leuckart–Wallach conditions,[10,11] utilizing formic acid as the reducing agent without the use of a catalyst. Given the presumed reaction mechanism,[12] we theorized that reduction of the alcohol would not be observed. This was indeed the case, and running the reaction with 2 equiv of formic acid and 1.5 equiv of *N*-ethylpiperazine **5** gave 73% conversion, with no alcohol (**8**) observed and the remainder being starting aldehyde **7** (entry 2). Increasing equivalents of both formic acid and *N*-ethylpiperazine (**5**) improved conversion (entries 3–5), but ultimately the reaction stalled. We hypothesized that water formed during the course of the reaction was ultimately causing the reaction to stall, so we explored ways to remove the water in situ.[13] Trimethyl orthoformate is known to facilitate the removal of water when added either as a solvent,[14] or co-solvent[15] driving the formation of an imine to completion, but to our knowledge, this has not been explored with one-step

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0040-4039/

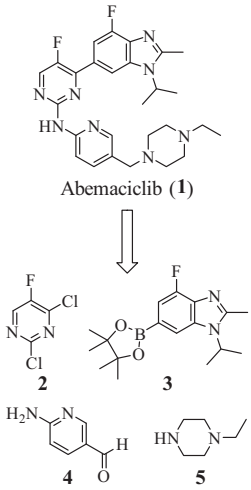
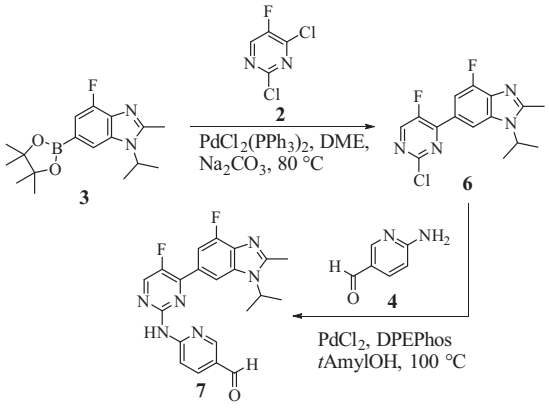
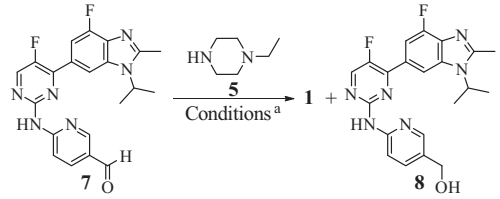


Figure 1.



Scheme 1.

Table 1



Entry	Conditions	Conversion	1:8	Isolated yield
1	$NaBH(OAc)_3$ (3 equiv), **5** (2 equiv), DCM[b]	100	97:3	69
2	Formic acid (2 equiv), **5** (1.5 equiv), ACN[c]	73	100:0	N/A
3	Formic acid (4 equiv), **5** (1.5 equiv), ACN[c]	86	100:0	N/A
4	Formic acid (2 equiv), **5** (3 equiv), ACN[c]	92	100:0	N/A
5	Formic acid (4 equiv), **5** (3 equiv), ACN[c]	95	100:0	N/A
6	Formic acid (4 equiv), **5** (2 equiv), ACN[c,d]	100	100:0	74

[a] Reactions run on 0.1 mmol scale except entry 6 (1.0 mmol).
[b] At 22 °C.
[c] At 80 °C.
[d] 2 equiv trimethyl orthoformate added.

reductive aminations, or more specifically with the Leuckart–Wallach reaction. Fortunately, adding 2 equiv of trimethyl orthoformate facilitated driving the reaction to completion affording an isolated yield of 74% for abemaciclib (**1**).[16]

In conclusion, we have developed a short, 3-step synthesis of drug candidate abemaciclib (**1**) from commercially available starting materials. Key to the synthesis was a Leuckart–Wallach reductive amination to avoid reduction of the aldehyde, which relied on trimethyl orthoformate to trap the water generated and allowed the reaction to go to completion.

Acknowledgments

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5. Procedure for the synthesis of biaryl compound **6**: To a 250 mL 3-neck round bottom flask equipped with a N_2 inlet, overhead stirrer, reflux condenser and temperature probe was charged 5-fluoro-2,4-dichloropyrimidine (**2**, 5.17 g, 31.0 mmol, 1.4 equiv), Na_2CO_3 (5.86 g, 55.3 mmol, 2.5 equiv), water (9 mL), and DME (45 mL). The solution was degassed by sparging N_2 subsurface for 30 min. After subsurface sparging, $PdCl_2(PPh_3)_2$ (46.6 mg, 66 μmol, 0.03 equiv) was added in one portion. The resulting solution was heated to 80 °C. In a separate 100 mL round bottom flask was charged boronic ester **3** (7.04 g, 22.1 mmol, 1.0 equiv) and DME (40 mL). The resulting solution was added to the heated solution by syringe pump over the course of 1.5 h. After all of boronic ester **3** was added, the reaction solution was stirred at 80 °C for an additional 4 h, at which time the reaction was complete as judged by HPLC analysis. The reaction mixture was then cooled to ambient temperature and diluted with ice cold water (300 mL) and stirred for 25 min. The resulting slurry was collected by filtration and the resulting wetcake was slurried in IPA (105 mL) and heated to 80 °C for 3.5 h. The heated slurry was then allowed to cool to ambient temperature over 16 h and the solid was collected by filtration and washed with IPA (35 mL). The wetcake was dried in a vacuum oven at 45 °C for 18 h to obtain the desired biaryl compound **6** in 66% yield. Compound **6**: IR (film) ν_{max} = 3413, 2972, 2940, 2892, 1567, 1507, 1401, 1388, 1348, 1210 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.50 (d, J = 3.4 Hz, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.77 (d, J = 11.7 Hz, 1H), 4.74 (septet, J = 7.0 Hz, 1H), 2.69 (s, 3H), 1.69 (d, J = 7.0 Hz, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 154.8, 154.2, 153.9, 153.2, 148.4, 136.6, 134.7, 125.5, 108.8, 108.2, 48.7, 21.5, 15.2 ppm; HR-MS [ESI]: Calcd for $C_{15}H_{14}N_4ClF_2$ [M+H$^+$]: 323.0870, found 323.0864.
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7. Procedure for the synthesis of aldehyde **7**: To a 250 mL 3-neck round bottom flask equipped with a N_2 inlet, overhead stirrer and temperature probe was charged aminoaldehyde **4** (6.13 g, 50.2 mmol, 1.25 equiv), biaryl compound **6** (12.96 g, 40.2 mmol, 1.0 equiv), $PdCl_2$ (214 mg, 1.21 mmol, 0.03 equiv), K_2CO_3 (5.6 g, 40.2 mmol, 1.0 equiv), and 2-methyl-2-butanol (130 mL). The resulting slurry was heated to 100 °C for 18 h at which point the reaction was deemed complete by HPLC analysis. The slurry was then cooled to ambient temperatures and the solid was collected by filtration. The wetcake was washed with water (30 mL) followed by acetone (30 mL) and then dried in a vacuum oven at 45 °C for 16 h to afford aldehyde **7** (16.3 g, 40.1 mmol, 99% yield) as an off-white solid. Compound **7**: IR (film) ν_{max} = 3229, 3173, 3041, 1973, 1681, 1576, 1421, 1370, 1292, 1222, 1117 cm^{-1}; ^1H NMR (600 MHz, TFA-d): δ = 9.94 (s, 1H), 8.90 (s, 1H), 8.68 (s, 1H), 8.65 (d, J = 9.2 Hz, 1H), 8.42 (s, 1H), 8.07 (d, J = 10.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 5.00 (m, 1H), 2.92 (s, 3H), 1.74 (d, J = 6.7 Hz, 6H) ppm; ^{13}C NMR (150 MHz, TFA-d): δ = 192.6, 155.8, 155.7, 155.3, 155.0, 154.3, 151.9, 149.0, 145.5, 144.2, 135.4, 133.2, 128.9, 124.4, 119.4, 115.8, 114.1, 55.4, 21.9, 13.7 ppm; HR-MS [ESI]: Calcd for $C_{21}H_{18}F_2N_6OH^+$ [M+H$^+$]: 409.1583, found 409.1579.
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16. Procedure for the synthesis of abemaciclib **1**: To a 20 mL reaction vessel equipped with a stir bar was charged aldehyde **7** (500 mg, 1.22 mmol, 1.0 equiv), *N*-ethylpiperazine (0.31 mL, 2.45 mmol, 2.0 equiv), ACN (5 mL), trimethyl orthoformate (0.27 mL, 2.45 mmol, 2.0 equiv), and formic acid (0.187 mL, 4.9 mmol, 4.0 equiv). The reaction vessel was sealed and the stirring mixture was heated to 80 °C for 16 h. The resulting slurry was cooled to ambient temperatures and the solid was collected by filtration. The wetcake was then washed with ACN (5 mL) and then dried in the vacuum oven at 45 °C for 16 h to afford abemaciclib **1** (456 mg, 0.90 mmol, 74% yield) as an off-white solid. Compound **1**: IR (film) ν_{max} = 3232, 3167, 3089, 3030, 2970, 2936, 2810, 1584, 1533, 1477, 1434, 1398, 1291 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, 1H), 8.47 (d, *J* = 6.0 Hz, 1H), 8.38 (d, *J* = 12.0 Hz, 1H), 8.30 (d, *J* = 3.0 Hz, 1H), 8.16 (d, *J* = 1.5 Hz, 1H), 7.75 (dd, *J* = 12.0, 1.5 Hz, 1H), 7.66 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.70 (septet, *J* = 6.0 Hz, 1H), 3.47 (s, 2H), 2.65 (s, 3H), 2.48 (br m, 8H), 2.39 (q, *J* = 12.0 Hz, 2H), 1.68 (d, *J* = 6.0 Hz, 6H), 1.05 (t, *J* = 12.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 153.7, 153.5, 152.4, 151.5, 151.1, 148.9, 147.4, 139.2, 136.6, 134.2, 127.7, 127.3, 111.6, 108.9, 108.3, 60.0, 53.1, 52.9, 52.5, 48.8, 21.6, 15.2, 12.2 ppm; HR-MS [ESI]: Calcd for $C_{27}H_{32}F_2N_8H^+$ [M+H$^+$]: 507.2791, found 507.2789.