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A concise synthesis of biaryl PDE4D allosteric modulators

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ABSTRACT

The optimization and synthesis of biaryl PDE4D allosteric modulator D159687 was achieved on gram scale via a concise two-step process. The synthesis features sequential chemoselective Suzuki coupling reactions taking advantage of different reactivity profiles of benzyl versus aryl halides. The method was then applied to the synthesis of two additional PDE4D allosteric modulators, D159404 and D159153. The efficient synthesis of these PDE4 allosteric modulators will allow for further biological evaluation of these compounds and the method developed will empower rapid analog formation through combinatorial chemical means.

Phosphodiesterase 4 (PDE4) is the major cAMP-metabolizing enzyme found in inflammatory and immune cells. PDE4 is a therapeutic target of high interest for central nervous system (CNS), inflammatory, respiratory diseases, and stroke.[1] PDE4 inhibitors have also been reported to have antidepressant effects and have been proposed as antipsychotics and cognition enhancers.[2] Numerous PDE4 inhibitors have been elevated to development status by the pharmaceutical industry; however, none have become marketable entities as these development candidates have been hampered by the side effects of nausea, emesis, and diarrhea.[3]

PDE4 is represented by four sets of protein isoforms (PDE4A–D).[4] Recently Burgin et al. reported on a series of selective PDE4D inhibitors whose inhibition of this enzyme was documented as occurring through binding at non-catalytic sites and exhibited partial inhibition kinetics.[5] As a result of their partial inhibition, these novel PDE4D allosteric modulators displayed efficacy of improved cognition in animal models with an increased therapeutic index relative to emesis (nausea and vomiting). Three compounds were identified as partial allosteric PDE4D modulators; D159687, D159404, and D159153.[5] Herein, we describe highly convergent syntheses of these three compounds whose chemical economy is derived from differentiation of benzylic and aryl halides in sequential Suzuki couplings.

The original six-step synthesis of D159687 is shown in Scheme 1.[6] Aldehyde **1** is reduced to alcohol **2** with $NaBH_4$. The 3-chlorophenyl group is introduced by Suzuki coupling to obtain **3**. The alcohol is then converted into bromide **4** and the second aryl group is introduced using another Suzuki reaction. The urea functionality is introduced by reduction of the nitro group followed by urea formation. The yields are modest to good for this reaction sequence, with an overall yield of 8%. Our initial challenge for improving the availability of these compounds focused on streamlining the synthesis of D159687.

For the synthesis of D159687, we envisioned a two-step procedure in which the product could be prepared via sequential Suzuki coupling reactions involving benzyl aryl dibromides (i.e., **8**). Generating an efficient synthesis of these compounds via this route focused on controlling the Suzuki coupling process selectivity for the benzylic versus the aryl bromide functionality. Literature precedent supported that the first Suzuki coupling would occur at the benzylic carbon.[8]

Initial attempts to prepare **10** from coupling of **8**[7a] with **9**[7b] suffered from low chemical conversion and production of a significant quantity of side products. Thus, optimization of the reaction sequence was undertaken by varying the Pd catalyst and equivalents, solvent, and base.

The two-step synthesis for D159687 is shown in Scheme 2 and the conditions attempted in optimization of step 1 of this sequence are listed in Table 1. The reactions that run in anhydrous DMF (entries 10, 16, and 25) suffered from very low conversion, resulting in the disappearance of compound **8** and the recovery of compound **9**. The identity of the base proved to exert little effect on the reaction conversions (compare Table 1 entry pairs 3/4, 7/8, 5/9, 12/1, 14/15, 17/18, 19/20, 22/23, and 24/26). Reduction of the amount of catalyst used increased the conversion of **10** (compare entry pair 1/2), but not in all cases (entries 15 vs 17) Higher catalyst loading generally increased the number of low level impurities, which was typically present in less than 2%. In addition, the use of higher catalyst loading introduced larger quantities of the catalytic ligand

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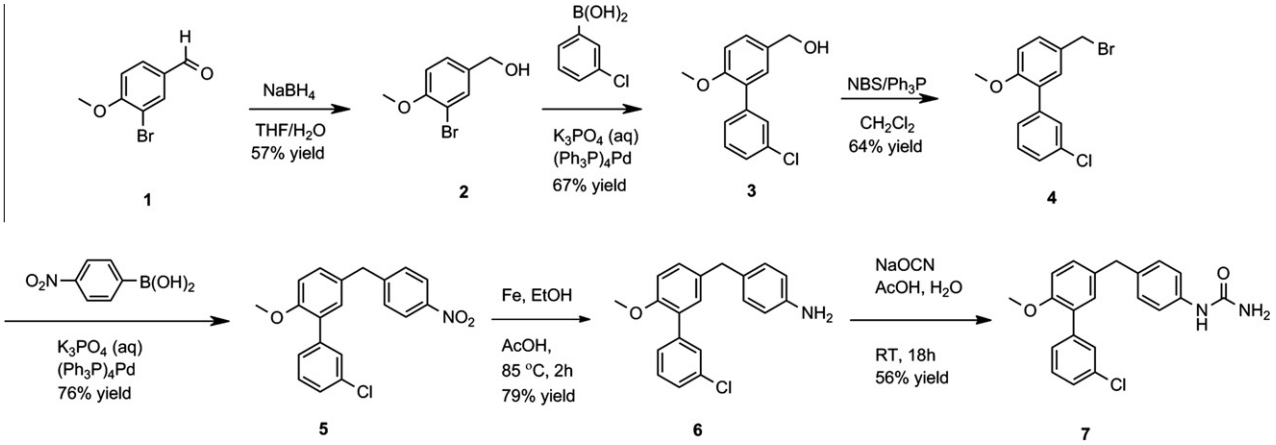
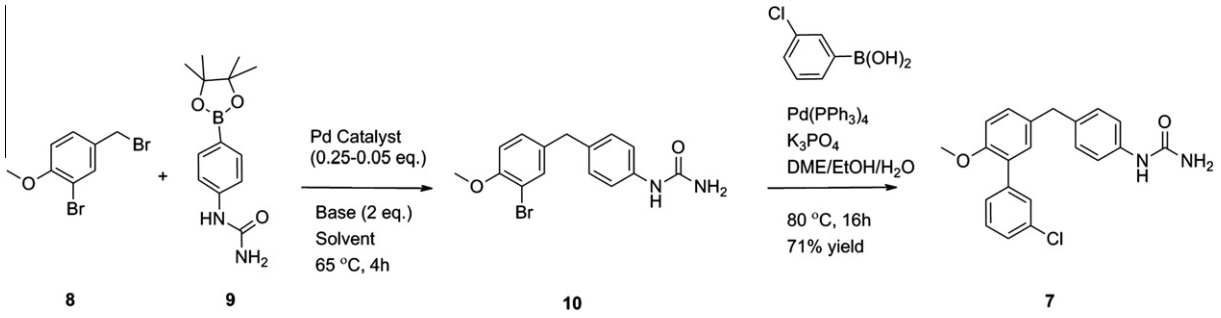


Scheme 1. Six-step synthesis of D159687 (**7**), overall yield of 8%.



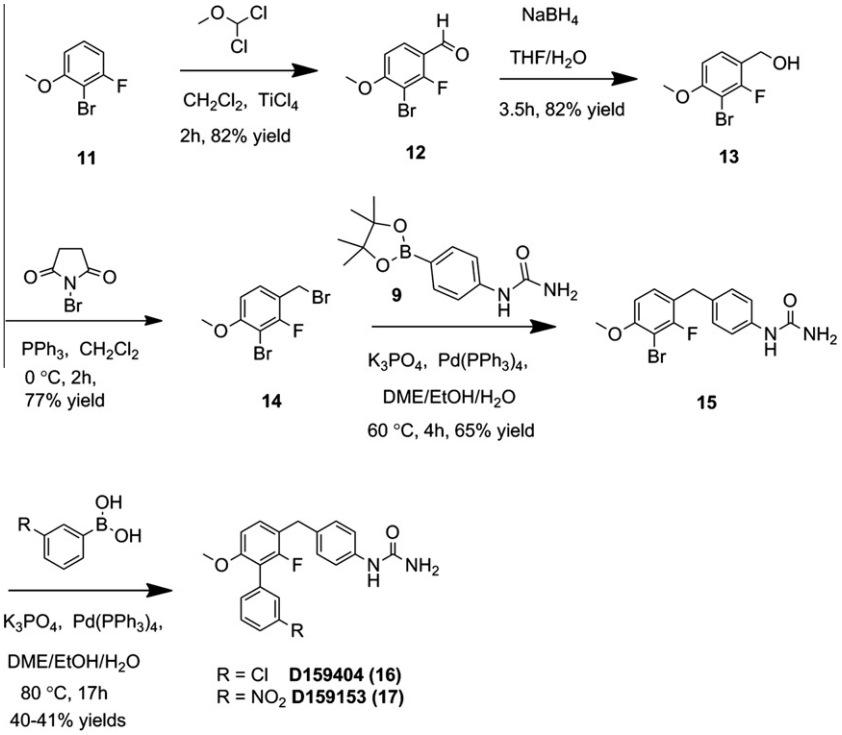
Scheme 2. Synthesis of D159687 (**7**).

Table 1
Optimization of conditions for the first Suzuki coupling

Entry	Catalyst	Equiv cat.	Base	Solvent	10[a,b] (%)
1	$Pd(PPh_3)_4$	0.25	K_3PO_4	DME/EtOH/H_2O (4:1:1)	54
2	$Pd(PPh_3)_4$	0.08	K_3PO_4	DME/EtOH/H_2O (4:1:1)	72, 66[c]
3	$Pd(PPh_3)_4$	0.15	K_2CO_3	DME/EtOH/H_2O (4:1:1)	41
4	$Pd(PPh_3)_4$	0.15	Na_2CO_3	DME/EtOH/H_2O (4:1:1)	50
5	$Pd(PPh_3)_4$	0.05	Na_2CO_3	Dioxane/H_2O (3:1)	40
6	$Pd(PPh_3)_4$	0.25	Cs_2CO_3	DME/EtOH/H_2O (4:1:1)	59
7	$Pd(PPh_3)_4$	0.15	K_3PO_4	Dioxane/H_2O (3:1)	62, 33[c]
8	$Pd(PPh_3)_4$	0.15	Cs_2CO_3	Dioxane/H_2O (3:1)	53
9	$Pd(PPh_3)_4$	0.05	K_2CO_3	Dioxane/H_2O (3:1)	57
10	$Pd(PPh_3)_4$	0.05	K_3PO_4	DMF	1
11	$PdCl_2(PPh_3)_2$	0.05	Na_2CO_3	Dioxane/H_2O (3:1)	44
12	$PdCl_2(PPh_3)_2$	0.25	K_3PO_4	DME/EtOH/H_2O (4:1:1)	62, 21[c]
13	$PdCl_2(PPh_3)_2$	0.25	Cs_2CO_3	DME/EtOH/H_2O (4:1:1)	56
14	$PdCl_2(PPh_3)_2$	0.15	K_3PO_4	Dioxane/H_2O (3:1)	60
15	$PdCl_2(PPh_3)_2$	0.15	Cs_2CO_3	Dioxane/H_2O (3:1)	64
16	$PdCl_2(PPh_3)_2$	0.05	K_3PO_4	DMF	6
17	$PdCl_2(PPh_3)_2$	0.05	Cs_2CO_3	Dioxane/H_2O (3:1)	59
18	$PdCl_2(PPh_3)_2$	0.05	K_2CO_3	Dioxane/H_2O (3:1)	61, 49[c]
19	$Pd(OAc)_2/PPh_3$ (1:4)	0.25	K_3PO_4	DME/EtOH/H_2O (4:1:1)	55
20	$Pd(OAc)_2/PPh_3$ (1:4)	0.25	Cs_2CO_3	DME/EtOH/H_2O (4:1:1)	52
21	$Pd(OAc)_2/PPh_3$ (1:4)	0.15	K_2CO_3	DME/EtOH/H_2O (4:1:1)	55
22	$Pd(OAc)_2/PPh_3$ (1:4)	0.15	K_3PO_4	Dioxane/H_2O (3:1)	60
23	$Pd(OAc)_2/PPh_3$ (1:4)	0.15	Cs_2CO_3	Dioxane/H_2O (3:1)	57
24	$Pd(OAc)_2/PPh_3$ (1:4)	0.05	K_2CO_3	Dioxane/H_2O (3:1)	60
25	$Pd(OAc)_2/PPh_3$ (1:4)	0.05	K_3PO_4	DMF	1
26	$Pd(OAc)_2/PPh_3$ (1:4)	0.05	Na_2CO_3	Dioxane/H_2O (3:1)	53

[a] Determined by HPLC analysis. For HPLC conversions, the absorbance was measured at 254 nm for both reagents and product.
[b] The yields are reported as an average of two experiments.
[c] Isolated yield and 3 h reaction time.

(PPh_3) into the reaction mixture, further complicating purification of the product of the reaction. The optimal conditions chosen were those of entry 2, 0.08 equiv $Pd(Ph_3)_4$, K_3PO_4, DME/EtOH/H_2O (4:1:1), based on the observed HPLC yield and the comparative



Scheme 3. Synthesis of D159404 (**16**) and D159153 (**17**).

overall cleanliness of the HPLC trace versus those of alternative conditions examined. The second Suzuki coupling (conversion of compound **10** to **7**) was conducted under the same stoichiometric reaction conditions, altering only the temperature under which the coupling was conducted and the duration of the reaction. Application of these conditions allowed for generation of product **7** (D159687) to be conducted on gram scale.

Now armed with an efficient process for assembling this class of compounds, the applicability of the sequential Suzuki couplings was tested with the synthesis of the two other identified PDE4D partial allosteric modulators, D159404 and D159153. The syntheses of these two compounds required preparation of pivotal fluoro substituted intermediate **14** (Scheme 3). The commercially available 2-bromo-3-fluoroanisole **11** was converted into aldehyde **12** then reduced to alcohol **13** with sodium borohydride.[9] Alcohol **13** was converted into dibromide **14** using NBS. The initial Suzuki coupling of dibromide **14** with boronic ester **9** proceeded as expected to provide urea **15**. Urea **15** undergoes Suzuki coupling with 3-chlorophenylboronic acid to give D159404 (**16**) and 3-nitrophenyl boronic acid to give D159153 (**17**), albeit in modest isolated yields of 40 and 41%.

We report a concise two-step synthesis of D159687, a partial PDE4D allosteric modulator. The reaction conditions were optimized and the overall yield is 47% on gram scale. This sequence also allows for the synthesis of the additional two PDE4D partial allosteric modulators D159404 (**16**) and D159153 (**17**). Development of this synthetic process will allow for further biological evaluation of these important PDE4 partial allosteric modulators. The chemoselectivity observed in this synthetic scheme is currently being applied in the development of combinatorial processes for focused analog production.

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Supplementary data

Supplementary data (experimental procedures and characterization data for compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.063.

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