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An efficient synthesis of carbazole-based secretory phospholipase A_2 ($sPLA_2$) inhibitors LSN433771 and LSN426891

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Abstract—The flexible and efficient synthesis of two structurally similar carbazole derivatives is described. This general strategy features an intramolecular palladium-mediated biaryl coupling reaction to join two aromatic domains of the target molecules. Formation of the carbazole core is accomplished via nitrene insertion. The synthesis of secretory phospholipase A_2 ($sPLA_2$) inhibitors LSN433771 (**1**) and LSN426891 (**2**) is detailed.

Phospholipase A_2 is an enzyme critical to the formation of arachidonic acid from membrane phospholipids as part of the body's inflammatory response cascade.[1] Elevated levels of human non-pancreatic secretory phospholipase A_2 ($sPLA_2$) have been observed in patients suffering from a number of conditions including acute pancreatitis, respiratory distress syndrome, bacterial peridonitis, and septic shock.[2] In conjunction with a program aimed at identifying selective $sPLA_2$ inhibitors, two molecules of particular interest were identified, carbazoles LSN433771 (**1**) and LSN426891 (**2**).

The initial synthetic routes toward **1** and **2** were independent and somewhat labor intensive. Since both compounds were required on large scale for toxicology studies, an efficient and unified strategy was highly desirable. In this letter, we report such a unified strategy for synthesis of both LSN433771 (**1**) and LSN426891 (**2**) starting from 2-bromo-3-nitrobenzoic acid (**6**) and an appropriately substituted phenol (**5**).

The goal of this new synthetic route toward **1** and **2** was to incorporate flexibility into the synthetic design such that the same general strategy could be applied to both molecules. From a processing standpoint, this new route focused on minimizing the use of protecting groups as well as isolation of products via crystallization in lieu of chromatography. The strategy that was envisioned (Fig. 1) focused on a nitrene insertion reaction wherein

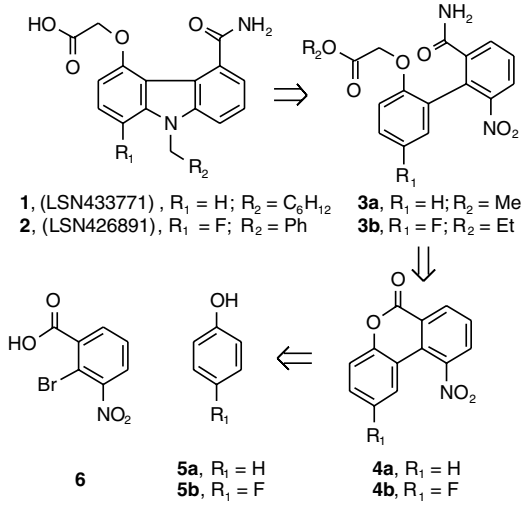

Figure 1. Retrosynthetic analysis.

functionalized biaryls **3** could be converted into the carbazole core structure. This method allows for the two aryl portions of the molecule to be assembled in the correct oxidation state. Formation of the fully functionalized biaryls (**3**) was thought to occur via amination/alkylation of benzocoumarin **4**. In this fashion, no protecting groups are required for elaboration to **1** and **2**. The synthesis of benzocoumarin could be formed through intramolecular biaryl coupling of the corresponding aryl 2-bromo-3-nitrobenzoate, which is simply constructed by coupling the appropriate phenol **5** with carboxylic acid **6**.

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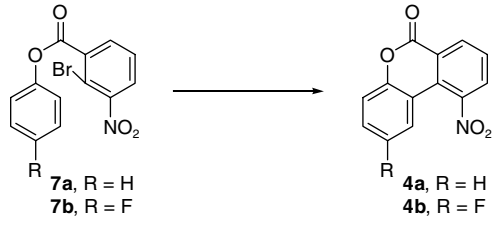
We sought to examine the intramolecular biaryl coupling using conditions originally described by Ames and Opalko.[3] The required benzoates (**7a**,**b**) were prepared in straightforward fashion via DCC coupling reactions between 2-bromo-3-nitrobenzoic acid[4] and phenol or 4-fluorophenol. The corresponding aryl benzoates **7a** (92%) and **7b** (80%) were obtained in good yield after crystallization from the crude reaction mixtures. The initial coupling conditions [$Pd(OAc)_2$, DMA, NaOAc, PPh_3, 170 °C, 2 h] with benzoate **4a** afforded the desired coumarin **4b** in ~50% isolated yield. While this result was encouraging, especially in light of the modest yields reported in the literature for these types of reactions,[5] the yield was still modest. It was subsequently found that simply removing the phosphine ligand and lowering the temperature to 125 °C allowed for a higher yield of the desired product. Under more optimized conditions, **7a** and **7b** afforded the corresponding benzocoumarins **4a** (76%) and **4b** (73%) after crystallization (Scheme 1).

Elaboration of benzocoumarins **4a** and **4b** into fully functionalized biaryls **3a** and **3b** is described in Scheme 2. Treatment of **4a**,**b** with anhydrous ammonia in methanol afforded phenoxy amides **8a**,**b**, which were typically processed as crude solutions after workup. Smooth alkylation with ethyl or methylbromoacetate provided biarlys **3a** (74%) and **3b** (77%) after simply treating the crude reaction mixture with water and isolating the precipitate by filtration (Scheme 2). Another more streamlined approach involved direct treatment of the crude benzocoumarin (**4a**,**b**) solution in DMF from the biaryl-coupling with anhydrous ammonia. The resulting hydroxyamides were then processed by removal of the excess ammonia and in situ alkylation as described above. For example, phenyl 2-bromo-3-nitrobenzoate **7a** was converted into the fully functionalized biaryl **3a** in 75% yield with a single isolation.



Scheme 1. Reagents and conditions: $Pd(OAc)_2$, DMF, DMA, NaOAc (73–76%).

With biaryl amides **3a** and **3b** in hand, two strategies for carbazole formation were considered (Fig. 2). Path 'a' featured a Cadogen-type[6] cyclization wherein heating **3a** or **3b** in the presence of a phosphite would afford the carbazole core structure **10** directly via in situ nitrene formation. Path 'b' featured conversion to and isolation of azides **11** followed by thermal decomposition to afford **10**.

Since the Cadogen-type reaction appeared less lengthy, this was examined first. Accordingly, compounds **3a** and **3b** were heated to 160 °C in trimethylphosphite. After several hours of reaction, HPLC analysis showed near complete consumption of the starting materials and numerous products. The same poor results were obtained when triethylphosphite was used. However, when the reactions were conducted in triphenylphosphite [180 °C for 16 h] HPLC analysis revealed a relatively clean reaction profile (Scheme 3). Isolation of the new product and careful evaluation indicated that they were not the desired products **10a** and **10b**, but rather dehydration products **12a** (40%) and **12b** (56%). Despite extensive efforts to improve the yield of this reaction, 40–55% was the optimal result in both cases and isolation was challenging.

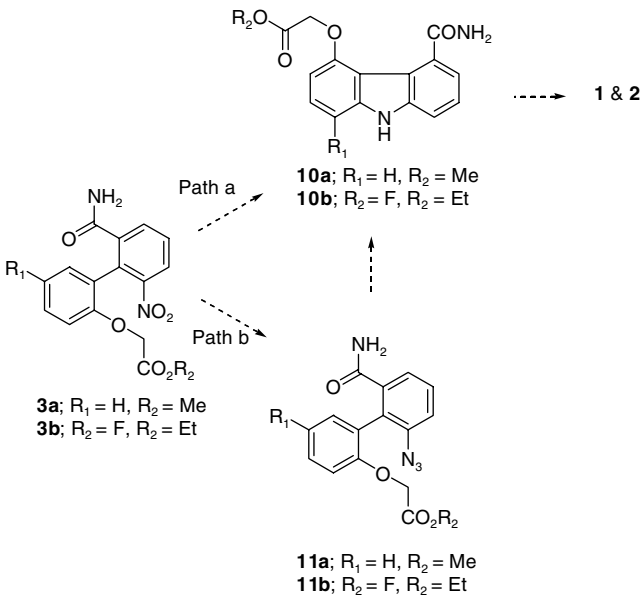
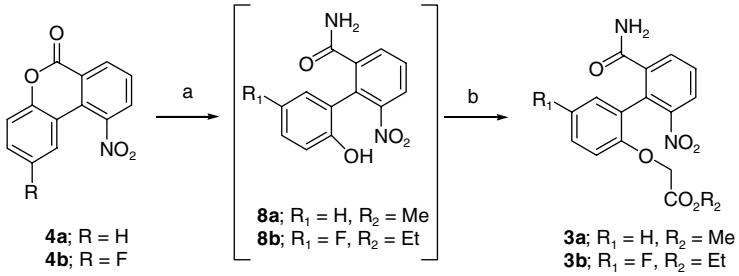


Figure 2. Strategies for carbazole formation.



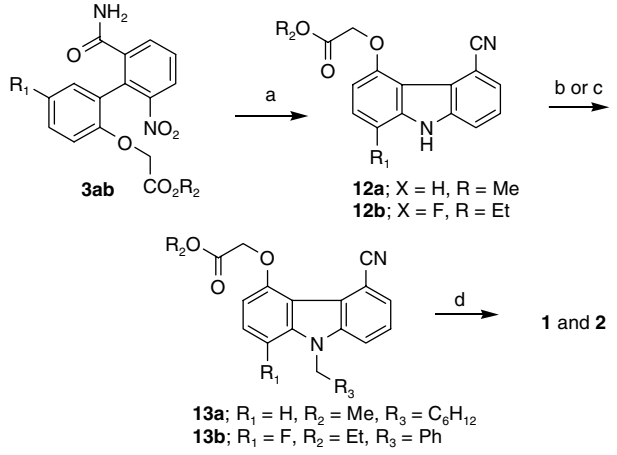
Scheme 2. Reagents and conditions: (a) NH_3, MeOH, rt, 1 h; (b) methyl or ethylbromoacetate, K_2CO_3, DMF, rt, 15 min, 74–77%.

Intermediates **12a**,**b** were alkylated at nitrogen with (bromomethyl)cyclohexane to afford **13a** (90%) and with benzylbromide to afford **13**,**b** (96%). Carbazoles **13a**,**b** were converted directly to the target molecule products LSN433771 (**1**, 98%) and LSN426891 (**2**, 86%) under the conditions described by Hall (Scheme 3).[7]

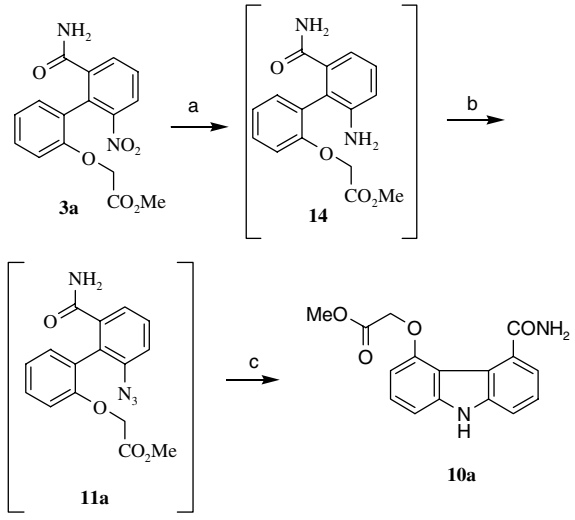
The amide dehydration that was observed in Scheme 2 (**3a**,**b**→**12a**,**b**) is likely promoted by triphenylphosphate, which is generated during the nitrene formation. Mechanistically, this would be similar to that of $POCl_3$[8] and likely enabled by the vigorous reaction conditions (180 °C, 18 h). To our knowledge, however, this type of dehydration of primary amides in the presence of phosphates alone has not been reported in the literature.[9]

Since the Cadogen-based pathway suffered from long reaction times and low yields, the thermal decomposition of the aryl azides was examined as an alternative with biaryl **3a** (Scheme 4). Thus, reduction of **3a** under the standard conditions (H_2, Pd/C, MeOH, 2.5 h) afforded the corresponding amine **14**. The crude amine was carried directly into the azide formation [$NaNO_3$, HCl, 0 °C, 5 min then NaN_3, CH_2Cl_2]. After isolation of azide **11a** as an organic solution in 1,2-dichlorobenzene, the solution was heated to 165 °C. Slow nitrogen evolution indicated decomposition to the nitrene and after 2 h the reaction was complete. The product **10a** crystallized from the reaction solvent upon cooling to room temperature and was isolated by filtration in 74% yield from biaryl **3a**.[10] The synthesis of **1** could be completed by alkylation with excess (bromomethyl)-cyclohexane and saponification akin to the examples in Scheme 3.

In conclusion, an efficient and robust synthesis of LSN433771 (**1**) and LSN426891 (**2**) has been described. The new synthetic route is nine linear steps (four isolations) from 2-bromo-3-nitrobenzoic acid. This new strategy employs a palladium mediated intramolecular biaryl coupling and allows for effective elaboration in the core carbazole framework rapidly. It is important



Scheme 3. Reagents and conditions: (a) $P(OPh)_3$, 180 °C, 16 h, 40–56%; (b) (bromomethyl)cyclohexane, NaI, Cs_2CO_3, DMF, 12 h, 65 °C, 90%; (c) benzylbromide, K_2CO_3, DMF, 1 h, rt, 96%; (d) KOH, *t*-BuOH, 86%.



Scheme 4. Reagents and conditions: (a) H_2, Pd/C, MeOH, rt, 2 h; (b) $NaNO_2$, HCl, 0 °C, 5 min then NaN_3, 15 min; (c) 1,2-dichlorobenzene, 165 °C, 2 h, 74% from **3a**.

to note that all intermediates can be isolated by precipitation from crude reaction mixtures. Further studies are underway to expand the scope of this chemistry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.043.

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9. The details of this reaction are currently under investigation and will be reported in due course.
10. While no alarming results were observed during this reaction sequence, future scale up work via this route would undoubtedly require a thorough hazard evaluation.