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An efficient synthesis of 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-((2,2-methylpropyl)carbamoyl)benzoic acid: a factor VIIa inhibitor discovered by the Ono Pharmaceutical Company

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Abstract

A small molecule factor VIIa inhibitor has recently been reported by the Ono Pharmaceutical Company. Herein, we outline an efficient and convergent, synthetic route that relies upon a palladium-catalyzed Stille coupling reaction as a key step for the synthesis of the inhibitor.

Keywords: Factor VIIa; anticoagulant; palladium catalyzed cross-coupling; Stillie coupling.

It is the abnormal coagulation and inappropriate thrombus formation within blood vessels that precipitates many acute cardiovascular diseases. As a result, there has been an intense effort to discover small molecule anticoagulants that work to specifically inhibit serine proteases in the blood coagulation cascade. The direct inhibition of thrombin has been intensively investigated leading to the development of potent and selective inhibitors, but clinical trials have met with disappointing results.[1,2] The specific inhibition of factor Xa, which is a key enzyme in the production of thrombin and subsequent formation of a blood clot, has also received increased attention owing to its central position in linking the extrinsic and intrinsic coagulation pathways.[1,2]

Recently, the extrinsic clotting system has been recognized as the major pathway for activation of coagulation.[3] Formation of a blood clot via the extrinsic pathway results from vascular injury

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and exposure of cell surface tissue factor (TF) to circulating factor VII (FVII) forming an FVII/TF complex. This complex activates FVII to factor VIIa (FVIIa) which, when combined with tissue factor in the presence of Ca^{2+} and phospholipids, ultimately converts factor X into factor Xa.[3]

Due to the importance of FVIIa in the hemostasis/thombosis balance, its inhibition is believed to be useful as a treatment for disease states associated with the extrinsic system such as acute myocardial infarction, stroke, disseminated intravascular coagulation (DIC) and thrombolytic disease.[3a] Also, the specific inhibition of FVIIa, while interrupting thrombus formation, should not effect the function of normal hemostasis.[4] Thus, specific inhibitors of FVIIa may reduce the risk of hemorrhagic complications observed with current heparin and warfarin therapies. Despite its significant role in coagulation, few small molecule FVIIa inhibitors have been reported.[5]

Recently, the Ono Pharmaceutical Company reported that 2-(3-(4-amidinophenylcarbamoyl)-naphthalen-2-yl)-5-((2,2-methylpropyl)carbamoyl)benzoic acid–methane sulfonate **1** was a potent inhibitor of FVIIa with an IC_{50} of 12 nM.[5b] As part of our program to develop small molecule anticoagulants, inhibitor **1** was prepared to evaluate the potential of a FVIIa inhibitor as a pharmaceutical agent. Unfortunately it was not evident from the Ono patent application[5b] as to how certain key intermediates were prepared or, in fact, the actual synthetic strategy that was utilized for construction of the inhibitor. Therefore, it was necessary to develop an independent synthesis of **1**. In this communication, we report the implementation of an efficient, scalable and convergent synthetic strategy for the preparation of **1** that relies on a palladium-catalyzed Stille coupling reaction of the naphthyliodide **2** with organostannane **3** (Fig. 1).[6]

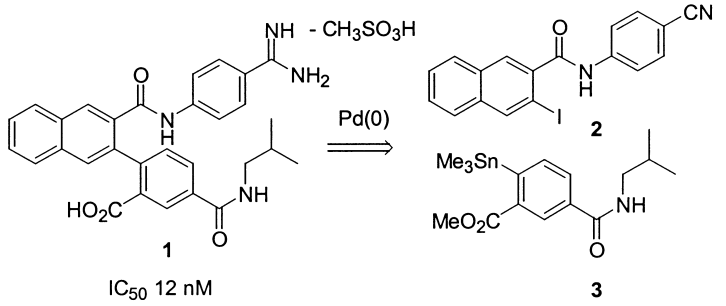
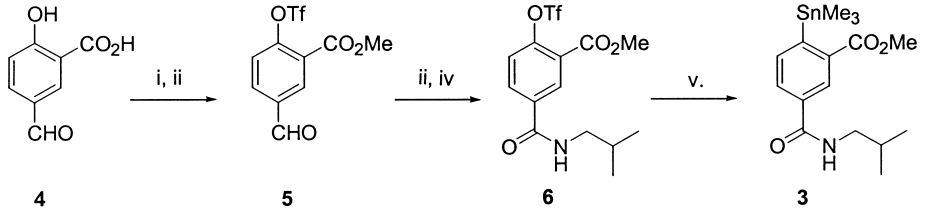


Figure 1.

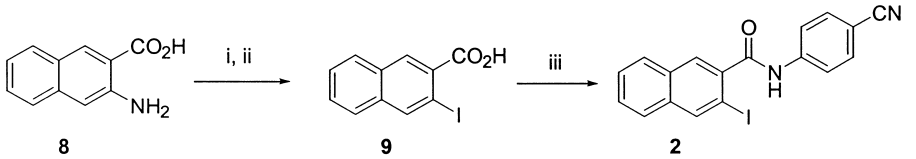
Chemistry: The synthesis of **1** started with the esterification of commercially available 5-formylsalicylic acid **4** under literature conditions to form the corresponding methyl ester,[7] which was then converted to triflate **5** with triflic anhydride under standard conditions.[8] Oxidation of the aldehyde to the carboxylic acid with a buffered solution of sodium hypochlorite followed by a benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) mediated amide coupling with isobutylamine provided the amide **6** in a 95% yield over two-steps.[9] Triflate **6** was converted to trimethylstannane **3** in excellent yield via palladium-catalyzed coupling with hexamethylditin (Scheme 1).[10]

Formation of the naphthyliodide **2** started with 3-amino-2-napthanoic acid which was subjected to Sandmeyer conditions to form the iodo-acid **9**.[11] The coupling of **9** and 4-aminobenzonitrile required vigorous dehydrating conditions[12a] in which catalytic 4-dimethylaminopyridine (DMAP) was found necessary for formation of amide **2** (Scheme 2). Standard carbodiimide, BOP



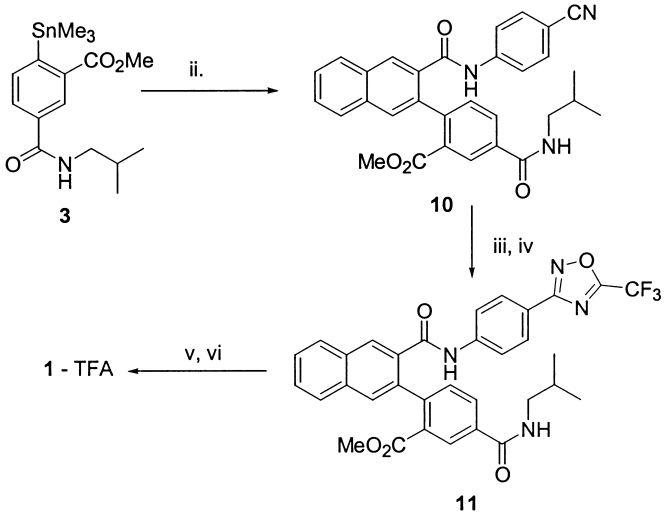
Scheme 1. Conditions: (i) H_2SO_4, MeOH, reflux, 24 h, 78%; (ii) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78°C–rt, 5 h, 65%; (iii) $NaClO_2$, H_2O_2, NaH_2PO_4, H_2O, MeCN, 0°C–rt, 18 h; (iv) isobutylamine, diisopropylethylamine, BOP, DMF, rt, 4 h, 95% (two-steps); (v) hexamethylditin, LiCl, $PdCl_2(PPh_3)_2$, THF, reflux, 14 h, 75%

and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate/1-hydroxy-7-azabenzotriazole (HATU/HOAT)[12b] mediated amide coupling reactions failed to yield any of the desired product.



Scheme 2. Conditions: (i) H_2SO_4, H_2O, $NaNO_2$, 100–110°C; (ii) Kl, H_2SO_4, H_2O, 100°C–rt, 75% (two-steps); (iii) 4-aminobenzonitrile, PCl_3, DMAP, xylenes, 150°C, 1.5 h, 71%

Using a palladium-catalyzed Stille coupling procedure which relied upon the use of both catalytic copper(I) iodide and triphenylarsine, stannane **3** and iodo-amide **2** were coupled to form **10** in 55% yield.[6] Failure to use both copper(I) iodide and triphenylarsine resulted only in trace yields of the coupled product. Completion of the synthesis required conversion of the nitrile into



Scheme 3. Conditions: (ii) **2**, $Pd_2(dba)_3$, Ph_3As, Cul, DMF, 60°C, 6 h, 55%; (iii) NH_2OH–HCl, MeOH, 12 h, rt; (iv) TFA, TFAA, 4 h, 100% (two-steps); (v) RaNi, H_2, Et_3N, MeOH, 14 h; (vi) LiOH, MeOH, THF, H_2O (1:1:1), rt, 4 h, 62% (two-steps)

an amidine which was accomplished via a high yielding, two-step procedure for the formation of trifluoromethyloxadiazole **11** followed by a Raney nickel-catalyzed hydrogenation.[13] The final hydrolysis of the methyl ester with lithium hydroxide and purification of the resulting amidinocarboxylic acid by reversed-phase preparative HPLC revealed the inhibitor **1**, as a trifluoroacetate salt, in a combined 62% yield over the final two steps (Scheme 3).

Scheme 3 allows for facile preparation of the factor VIIa inhibitor **1** in quantities sufficient for further pharmacological evaluation. The above structure was fully characterized by high-resolution proton NMR, mass spectrometry, and CHN combustion analysis as the trifluoroacetate salt.[14] When synthetic **1** was tested in our in-vitro assay for FVIIa/TF inhibition, an IC_{50} of 9 nM with a K_i of 6.4 nM was determined, which compared favorably with the published values.[5b]

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14. 2-(3-(4-Amidinophenylcarbamoyl)naphthalen-2-yl)-5-((2,2-methylpropyl)carbamoyl)benzoic acid–trifluoromethane acetate **1**: HPLC (% A: 0.1% TFA:H_2O; B: 0.1% TFA:CH_3CN; gradient: 20–86% B over 22 min; Vydac 218TP54) $R_t = 12.5$ min; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.11 (broad s, 2H) 8.86 (broad s, 2H), 8.65 (1H, t, $J = 5.8$ Hz), 8.31 (1H, s), 8.26 (1H, s), 8.08–7.96 (3H, m), 7.78–7.70 (5H, m), 7.64–7.60 (2H, m), 7.39 (1H, d, $J = 8.0$ Hz), 3.06 (2H, broad t, $J = 6.4$ Hz), 1.84 (1H, m), 0.86 (6H, d, $J = 6.6$ Hz); MS (APCI) $m/e = 509$ $(M+1)^+$, 492 $(M–OH)^+$, 448 $(M–H_2O,CO, NH_3)^+$; anal. calcd for $C_{30}H_{28}N_4O_4$–1.10 $(C_2F_3O_2)$–0.7 (H_2O): % C = 59.81, % H = 4.75, % N = 8.66, % F = 9.70, % H_2O = 1.95. Found: % C = 59.61, % H = 4.78, % N = 8.59, % F = 9.67, % H_2O = 1.94.