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A modular, general and enantiospecific strategy for the synthesis of CVS 1778 analogs: inhibitors of factor Xa

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Abstract—A modular synthetic route has been developed for the synthesis of a series of complex benzalactams which are potent inhibitors of factor Xa. The route produces fused benzalactams of varying ring size via a key-step ring-closing metathesis reaction. The route also facilitates the synthesis of discrete enantiomers using readily available commercial building blocks.

The blood clotting cascade mechanism in the body reacts to both intrinsic and extrinsic stimuli to maintain a healthy cardiovascular system. This mechanism is highly complex with a number of factors that play a role in regulating the depolymerization of fibrinogin to fibrin that leads to platelet aggregation and blood clotting. It has been proposed that factor Xa converts prothrombin to thrombin in response to vascular injury and in fact this action is the penultimate step of the extrinsic pathway. In healthy individuals, this extrinsic pathway poses little concern and in fact it is necessary to prevent excessive bleeding from injury. However, in heart attack and stroke patients, who may have suffered vessel damage from the event itself, blood clotting can prove fatal. Thus, such patients are usually placed on blood thinners or anticoagulants. At present, compounds used in the treatment and prevention of thromboembolic diseases include Coumadin, heparins, hirudin and Aspirin. Some problems associated with these agents include parenteral administration (injection), the need to carefully titrate drug dosage, excessive bleeding and gastrointestinal irritation. These problems are especially acute when the patients are elderly and most people requiring these drugs are older. To combat the oral availability issues, many research groups utilize peptidomimetics,[1] and in particular those containing lactams and heterocyclic motifs have proven to be quite efficacious.

One group of peptidomimetics that is attractive for our purposes is the series of benzalactams (**1b**) developed around CVS 1778 (**1a**) by the research group at Corvas International Inc. (Fig. 1).[2] We are developing a new screening platform and are using factor Xa as a model enzyme with which to assess the efficacy of the method. In order to probe the platform we required a group of structurally-related compounds with a range of binding efficiencies, yet, ideally, high selectivity for factor Xa. With these criteria in mind, **1b** served as an ideal structure to build a library around for a number of reasons. First, the structure contains a number of chiral centers which allow for not only the assessment of differently substituted pharmacophores, but to evaluate how well the screening platform distinguishes between

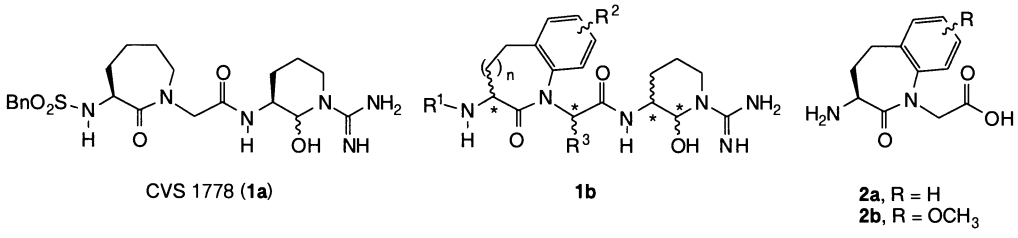

Figure 1. Lactam-containing peptidomimetic inhibitors of factor Xa.

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enantiomers and diastereomers. Also, despite the complexity of the core structure, we felt that we could devise a reasonably modular approach to the library using solution-phase synthesis with the option of moving readily to solid phase if a larger number of compounds were required. With these things in mind, we sought to develop one single strategy to produce a variety of optically-pure synthetic templates that could serve as the diversification point from which to build benzalactams of varying ring size and substitution pattern.

The basic template (**2a**) used by the group at Corvas was obtained commercially in racemic form and the diastereomers of **1b** that ultimately were derived from **2a** were purified by preparative HPLC. When substituted benzalactams were prepared, a new synthetic route was developed and each substituted template (i.e. **2b**) was prepared de novo. Each template was individually resolved to obtain enantiomerically pure **2b** that was then elaborated to optically pure drug candidates (ignoring the hemiaminal center which is in the open form when it reacts with the enzyme). Despite these issues, we still viewed a protected amino acid template resembling **2** as an ideal diversification point. Thus, we decided to use this template, but opted to develop a new and more general synthetic strategy that would allow for the preparation of all templates in the series in optically pure form (Fig. 2). Ring-closing metathesis (RCM) facilitates bond formation that takes place at a remote position in the lactam ring.[3] This chiron-type approach allows for the use of commercially-available chiral building blocks (e.g. amino acids) to produce the chiral center in the lactam. Further, this approach can be used to prepare any medium-sized ring by varying the length of the tethers (i.e. m and p) on the RCM precursor **5**. In this report we detail the preparation of **2** and how we plan to build a library around this general structure.

Construction of the left-hand piece (**12**) of the RCM precursor began from commercially-available (L) methionine methyl ester (**9**) (the D isomer is also available) (Scheme 1).[4] Amine protection, oxidation and sulfoxide elimination proceeded smoothly (70% yield over three steps) providing the requisite olefin (**11**).[5] The ester was readily modified into the stable acid chloride **12** in two steps with excellent recovery.

Preparation of the phenyl-containing right-hand piece (**16**) began with an aza Claisen rearrangement of **13** to provide **14** (Scheme 2).[6] Alkylation of anilines **14** presented some unexpected and interesting product stability issues. While alkylation of the three compounds proceeded smoothly, only **15b** proved to be stable enough to handle. Compound **15c** decomposed during silica gel chromatography, although as the crude product it was effectively carried through amide bond formation to provide **16c** which was a stable compound. Compound **15a** appeared to be stable enough to silica gel, but upon sitting it oxidized to give **15d** and by 48 h the oxidation was complete. However, like **15c**,

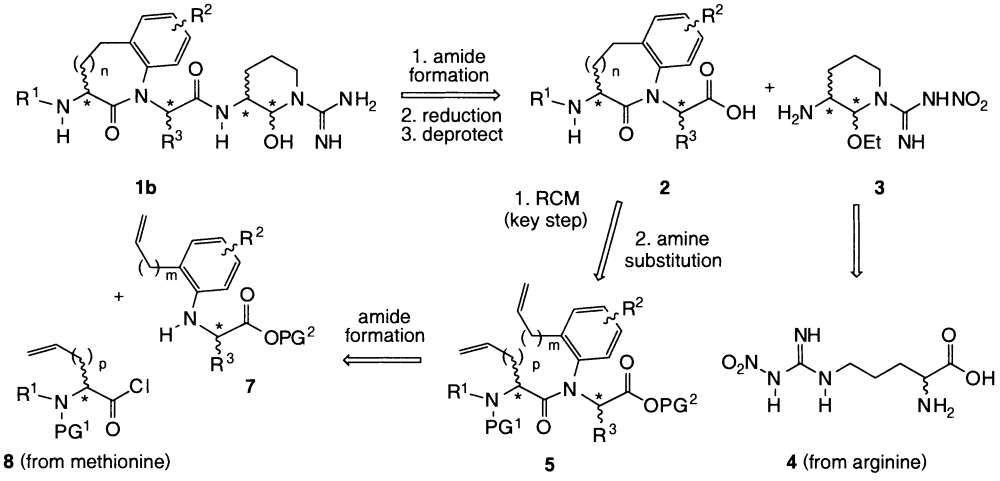
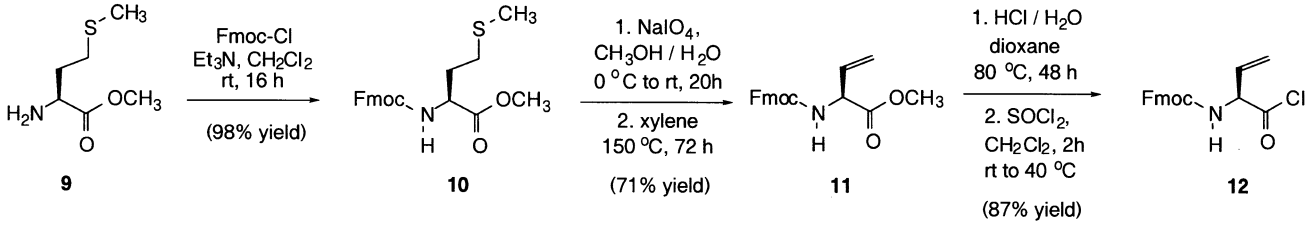
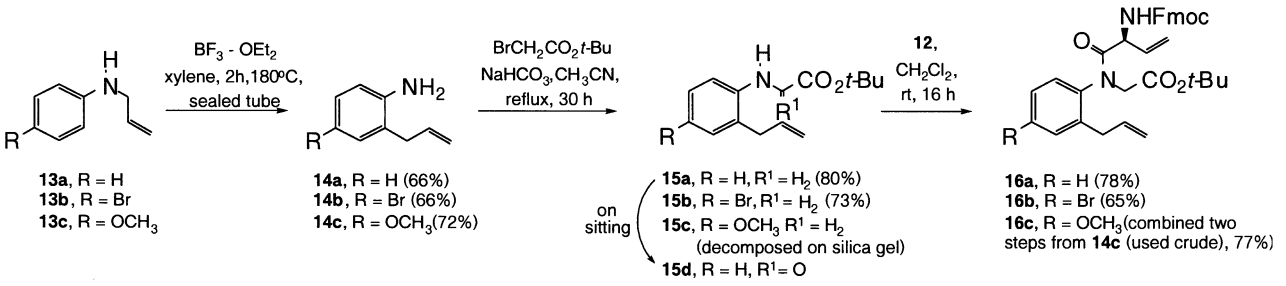


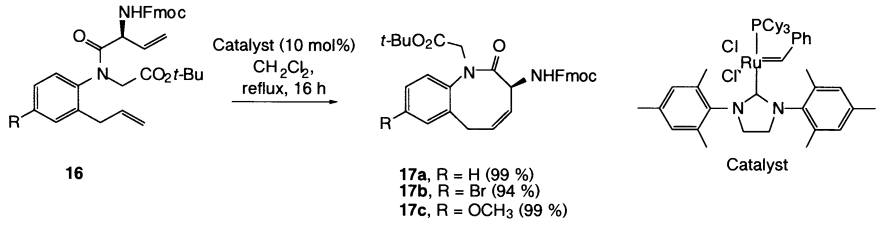
Figure 2. Retrosynthetic analysis of a benzalactam peptidomimetic library of factor Xa inhibitors using RCM as the key step to provide the intermediate template **2**.



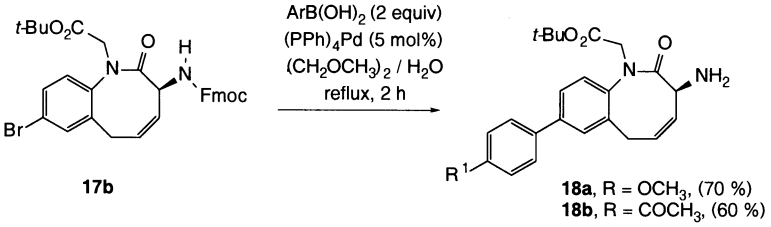
Scheme 1.



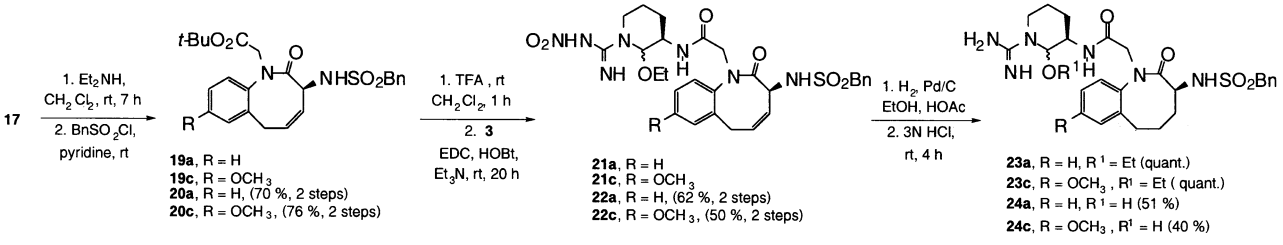
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

once **15a** was converted to the more electron-deficient amide (i.e. **16a**) the methylene group was no longer readily oxidizable, either in **16** or in any other similar compounds further along in this synthetic route.

The RCM step,[7] which was pivotal in this approach as a general strategy for making the inhibitor library, proceeded very cleanly and essentially quantitatively in all cases (Scheme 3). However, we did discover that while the reaction was faster at higher temperature (refluxing benzene), it was accompanied by double bond isomerization toward the phenyl ring. There was no observed movement of the olefin under conditions of refluxing CH_2Cl_2. Thus, with this step worked out, we had the desired templates in hand for adding the diversity elements to the library.

As a proof of principle, elaboration of the core template to the desired drug candidate structure is discussed here. Template **17b** was further diversified with a Suzuki coupling at the bromide site before we continued on with the synthesis (Scheme 4). Although we have not tested a wide variety of boronic acids to date, the coupling proceeded cleanly with both an electron-rich and an electron-poor phenylboronic acid. Under these reaction conditions, the Fmoc group was also deprotected which was convenient because the next step diversifies the primary amine site.

The Fmoc group on templates **17** were removed with diethylamine to provide **19** and the free amine was capped as a sulfonamide in very good recovery (**20**, Scheme 5). A variety of sulfonyl chlorides will be used in the final library preparation.[8] Carboxylic acids **21**

were liberated using trifluoroacetic acid and then they were condensed with amine **3**[9] to provide **22**, once again in good yield over the two steps. Catalytic hydrogenation of **22** under mild conditions simultaneously reduced the lactam olefin and deprotected of the nitro-protected guanidinium moiety. Treatment of the reduced product (**23**) with strong acid liberated the biologically active hemiaminal (**24**). Although the yield from the final step is not fully optimized, we have succeeded in the development of a modular and enantiomerically pure strategy to make compounds possessing the general structure contained in compound **1**.

In summary, we have developed a concise and general strategy for the synthesis of compounds containing a complex fused benzalactam that have demonstrated potency against factor Xa. This modular approach allows for the synthesis of enantiomerically-pure materials using a key RCM reaction.

Acknowledgements

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