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Cyclodimerization by ring-closing metathesis: synthesis, computational, and biological evaluation of novel bis-azetidinyl-macrocycles

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ABSTRACT

During our research on novel, non-traditional, bicyclic β-lactams as potential inhibitors of Penicillin Binding Proteins (PBPs), we focused on the synthesis of 1,3-bridged 2-azetidinones by RCM reaction from 1,3-bis-ω-alkenoyl-3(S)-amino-2-azetidinone precursors. Submitting the precursors to RCM, we faced an unexpected problem: cyclodimerization was the preferred outcome. This peculiar reactivity, explained by a computational study, led to unprecedented bis-azetidinyl-macrocycles acting as potent inhibitors of R39 D,D-carboxypeptidase, a bacterial model enzyme for PBPs.

1. Introduction

Ring-closing metathesis (RCM) of α,ω-dienes is nowadays a very common reaction used for the construction of medium-sized and macrocyclic organic compounds. Its wide scope and use as the key-step in numerous total syntheses of complex target molecules have been reviewed[1] recently. The thermodynamic and kinetic aspects of the RCM and related reactions catalyzed by ruthenium/carbene complexes have been discussed as well.[2]

Despite an increasing amount of technical reports, there are still no clear rules available for planning a new RCM synthesis: different catalysts and loading, different substrate concentrations, addition, and reaction times, different solvents, additives, and temperatures have to be tested for maximizing the yield of the desired cyclic product. Beside the experimental conditions, the ring size to be formed, the substrate structure, its substitution pattern, steric, and conformational factors will also influence the outcome of the reaction, i.e., the product *E*/*Z* ratio, the formation of isomerized or/and oligomerized by-products. In general, oligomerization is considered detrimental to the RCM reaction[2] and the corresponding products are neither isolated nor characterized. But in few cases, dimers, and in particular cyclic dimers, are highly desired products.[3] Recently, a double-centered catalyst has been designed to favor the dimer ring-closing metathesis reaction[4] and the competitive pathways leading to the cyclic monomer, and dimer have been theoretically studied with 1,7-octadiene as model substrate.[5]

We have previously applied the RCM reaction for the preparation of 1,3-bridged bicyclic β-lactams **A** (i.e., 2-azetidinones) derived from the commercial acetoxy-azetidinone used as the chiral precursor of carbapenem antibiotics[6] (Fig. 1, Eq. (a)). Series of

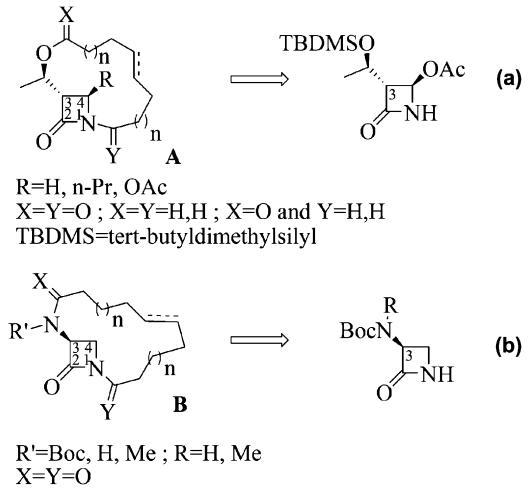

Fig. 1. Two families of 1,3-bridged 2-azetidinones.

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compounds featuring 12 and 13-membered rings (including HC=CH double bond or the reduced motif) have been obtained and evaluated as potential inhibitors of Penicillin Binding Proteins (PBPs). The weak activities recorded were attributed, among other factors, to the steric effect of the macrocycles, which hinders the so-called α-face of the azetidinone ring and thus might prevent nucleophilic attack by the active serine of PBPs. This hypothesis derives from a theoretical investigation of the reactivity of the bridged azetidinones **A** when processed into a model of serine protease active site.[6] To further our research on novel, non-traditional, bicyclic β-lactams, we have focused on 1,3-bridged compounds **B** derived from 3-amino-2-azetidinone featuring the amino substituent and the chirality of penicillins, and cephalosporins at the C(3) carbon (Fig. 1, Eq. (b)). This inversion of configuration regarding the carbapenem chiron (see Eq. (a)) should position the macrocycle above the β-face of the azetidinone ring and consequently make the serine nucleophilic attack easier on the α-face during the processing of molecules **B** by PBPs.

In this article, we describe our synthetic efforts toward the target molecules **B** belonging to the bis-acylated family (X=Y=O). From the 3-amino-2-azetidinone chiron, three series of RCM precursors have been prepared (R′=Boc, H or Me) varying by the length of the ω-alkenoyl chain fixed on the N(1) and N–C(3) atoms. Surprisingly, under RCM conditions, the isolated products were all cases but one the cyclic dimers instead of the expected cyclic monomers **B**. These observations stimulated a theoretical investigation of the possible cyclization reactions. Our study highlights the dramatic effect of accessible conformations and flexibility of precursors on the intra- or intermolecular ring closure, particularly when the substrates possess amide, imide, and carbamate functions.

The inhibition potential of our compounds (precursors and RCM products) has been tested against R39 D,D-carboxypeptidase, which is a commonly used model for bacterial enzymes.

2. Results and discussion

2.1. Synthesis

The RCM reaction was chosen as the key-step for the synthesis of 1,3-bridged bicycles B, a strategy, which has already been successfully used for the preparation of 1,3-bridged derivatives A.[6] The precursors are chiral azetidin-2-ones C equipped with ω-alkenoyl chains on the positions N(1) and C(3)–N (Fig. 2). The starting chirons, i.e., (*S*)-3-(*tert*-butyloxycarbonyl)amino-2-azetidinone and (*S*)-3-*N*-methyl(*tert*-butyloxycarbonyl)amino-2-azetidinone, derived from commercially available Boc-L-serine and Boc-Me-L-serine, respectively.

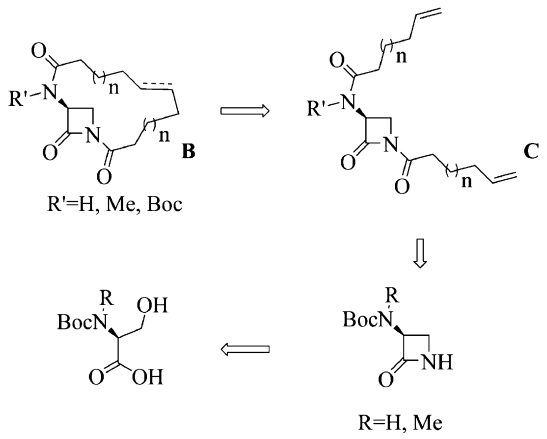
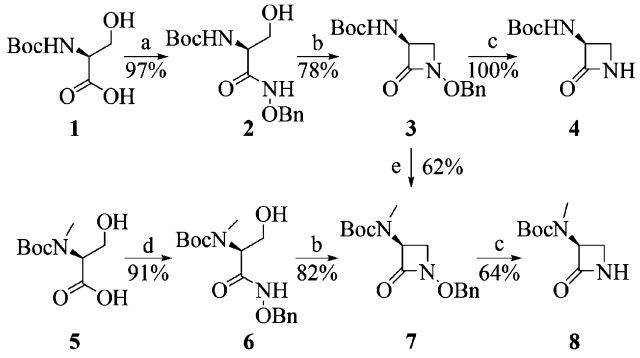


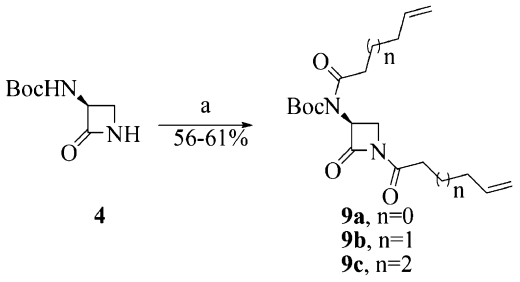
Fig. 2. General RCM strategy.

Boc-L-serine **1** was converted, in nearly quantitative yield, into the corresponding hydroxamate **2**, employing *O*-benzylhydroxylamine and DCC.[7] Intramolecular cyclization was performed with the method proposed by Miller et al.,[7] in the presence of PPh_3 and CCl_4, and afforded the β-lactam **3** in 78% yield. Subsequent hydrogenation in the presence of Raney nickel[8] gave the desired chiron **4**[9] in quantitative yield (Scheme 1). In the first attempt to obtain the corresponding N–Me chiron **8**, we considered the direct methylation[10] of **3** into the desired intermediate **7**. This reaction proceeded with 62% yield at the mmol scale, but the scaling-up was not successful. So we developed a similar route toward the N–Me derivatives as for the N–H derivatives, starting from Boc-Me-L-serine **5**. This compound was converted into hydroxamate **6** employing EDCI in 91% yield. The β-lactam **7** was obtained in 82% yield and subsequent hydrogenation afforded the chiron **8** in 64% yield.



Scheme 1. Synthesis of chirons **4** and **8**. Reagents and conditions: (a) DCC, NH_2OBn, THF, 0 °C to rt; (b) PPh_3, CCl_4, TEA, CH_3CN, 0 °C to rt; (c) H_2, Raney-Ni, MeOH, rt; (d) EDCI, NH_2OBn, CH_2Cl_2, 0 °C to rt; (e) Me_2SO_4, LiHMDS, THF, −78 °C to rt.

The *N*-Boc bis-acylated monocyclic azetidinones **9a**–**c** were obtained in one step by treatment of the chiron **4** with 2 equiv of alkenoyl chlorides in the presence of 2 equiv of lithium hexamethyldisilazide (Scheme 2). 4-Butenoyl chloride (*n*=0) is commercially available, while 5-hexenoyl chloride (*n*=1) and 6-heptenoyl chloride (*n*=2) have been previously synthesized starting from the corresponding commercial carboxylic acid.[11]



Scheme 2. Synthesis of bis-acylated **9**. Reagents and conditions: (a) alkenoyl chloride, LiHMDS, THF, −78 °C to rt.

For the preparation of N–H and N–Me bis-acylated precursors, a three-step sequence was used (Scheme 3). The chiron **4** was mono-acylated at the N(1) position regioselectively under mild conditions giving the series of compounds **10a**–**c**. Then, the Boc protecting group was removed with trifluoroacetic acid and the free amine function was acylated with the alkenoyl chlorides affording the series of compounds **12a**–**c**. Similarly, the chiron **8** was mono-acylated (compounds **11a**–**c**), *N*-deprotected and acylated again to produce the N–Me precursors **13a**–**c**.

The first attempts at RCM were performed on bis-acylated compounds with *n*=0 (i.e., **9a**, **12a**, and **13a**) with the view to form 12-membered macrocycles, under standard reaction conditions (CH_2Cl_2, 40 °C, 5 mM) in the presence of second generation Grubbs'