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Analogues of the 2-carboxyl-6-hydroxyoctahydroindole (CHOI) unit from diverging Pd-catalyzed allylations: Selectivity as a function of the double bond position

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ABSTRACT

Pd-catalyzed allylations of cyclic bis-allylic substrates, carried out either as two separate steps or in a pseudo-domino fashion, can generate 2-carboxyl-hexahydroindoles bearing an unsaturation in different positions. Sequential homologation, and epoxidation or *syn*-dihydroxylation steps were investigated to access analogues of the bicyclic 2-carboxyl-6-hydroxyoctahydroindole motif of aeruginosins, a family of peptides displaying serine protease inhibitor activity.

Introduction

Aeruginosins[1] constitute a family of structurally related molecules found in cyanobacteria (blue-green algae). These peptidic structures that incorporate the 2-carboxyl-6α-hydroxyoctahydroindole (CHOI) bicyclic structure hydroxylated at 5 and/or 6 positions, display inhibitory actions against several serine proteases such as thrombin and trypsin (Fig. 1).[2] Since the discovery of their potent anticoagulant action, structure-activity relationship (SAR) studies on aeruginosin family are constantly and intensively pursued.[3] Although synthetic routes of some of these structures have been recently reported, further studies are still desirable, especially those focusing on the common bicyclic CHOI fragment and access to analogues of it.

Some years ago, we anticipated that analogues of the CHOI motif could be ideal targets, achievable through palladium chemistry developed in our laboratory.[4,5] In the present study we developed a double Pd-catalyzed allylation (amination and alkylation) of the cyclic bis-allylic substrate **I**, which, as a function of the *modus operandi*, provided the desired bicyclic advanced intermediates **II** and **III** that differ by the double bond location (Scheme 1). After an appropriate one-carbon homologation at position 2, diastereoselective post-functionalizations (epoxidation and *syn*-dihydroxylation) of the resulting hexahydroindoles **IV** and **V** were carried out to evaluate the selectivity of these transformations, which provided CHOI analogues as a function of the transformation and the position of the unsaturation.

Results and discussion

*"Separated allylations" strategy-based approach to the bicyclic tetrahydroindolone **6***

This strategy is based on the construction of the bicyclic tetrahydroindolone structure **6** starting from 1,3-cyclohexadiene **1**. This was achieved through a five-step sequence (Scheme 2) previously described by us.[4b] Two key steps of this synthetic sequence are based on palladium catalysis. First, 1,3-cyclohexadiene **1** was converted into the corresponding chloroacetate ***cis*-2** according to Bäckvall's protocol.[6] Then, palladium-catalyzed allylation of

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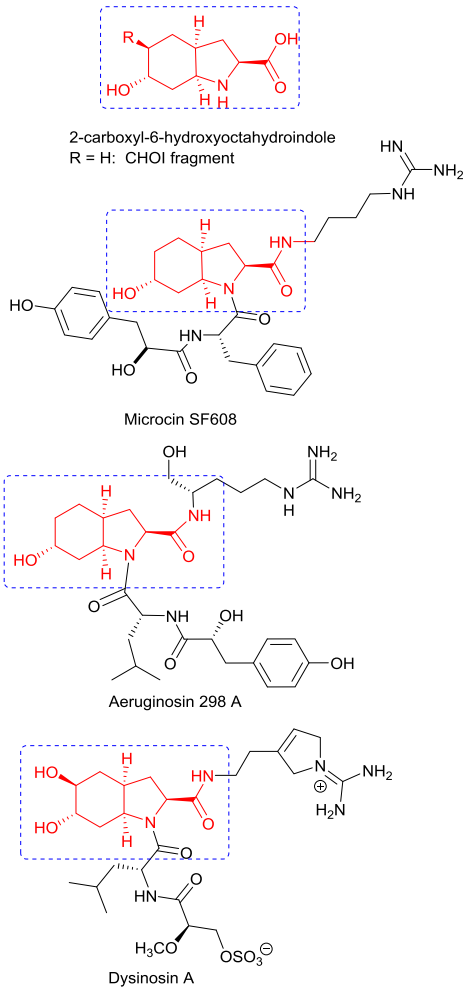
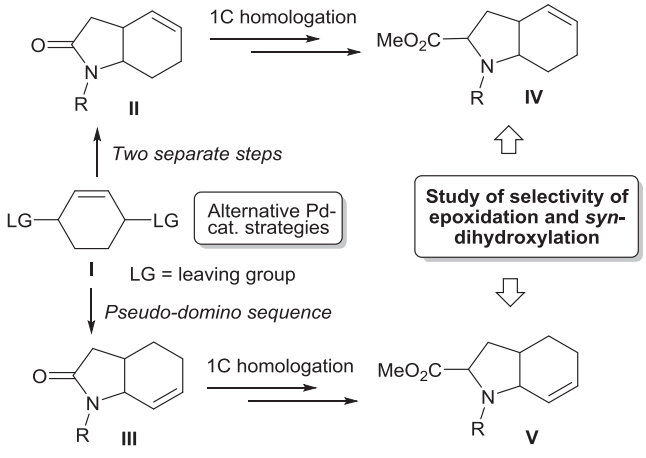
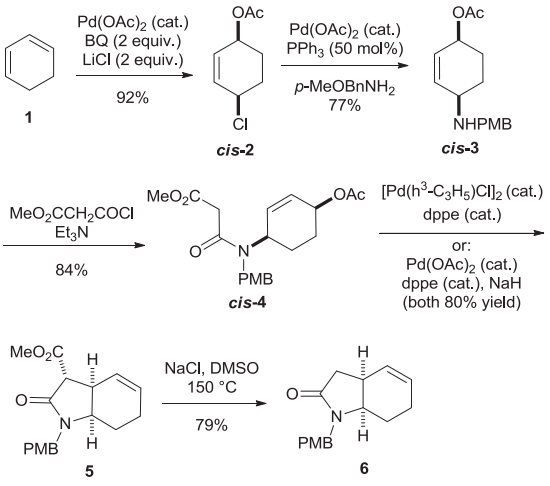


Fig. 1. CHOI motif and representative members of the Aeruginosin family.



Scheme 1. CHOI aim of the project.

p-methoxybenzylamine with the allylic chloride *cis*-**2** afforded *cis*-**3**. Standard treatment of this amine with methyl 3-chloro-3-oxopropionate gave the 1,4-disubstituted amide *cis*-**4**, which underwent a smooth intramolecular allylic alkylation. Two different palladium-based catalytic systems can be used, both leading to bicyclic lactam **5** in 80% yield as a single diastereoisomer.[7] Finally, demethoxycarbonylation of **5** under Krapcho conditions[8] led to lactam **6**.



Scheme 2. Previous synthesis of the bicyclic tetrahydroindolone **6**.

*Transformation of lactam **6** to the methoxycarbonylated derivative **12***

Introduction of the carboxyl substituent at position 2 of the hexahydroindole bicycle was planned through α-aminoether homologation. However, this type of strategy is viable only when the nitrogen atom of the aminoether function is electron poor. Accordingly, a PMB-to-Boc *N*-protection switch was accomplished through treatment with CAN, followed by standard Boc protection of the resulting secondary amide **7**. DIBAL-H reduction of **8** led to hemiaminal **9**, whose treatment with MeOH in the presence of a catalytic amount of *p*-TsOH gave the desired *N*,*O*-acetal **10** as a 3:1 diastereomeric mixture. C1-homologation was achieved through trimethylsilylcyanide (TMSCN) addition to **10** in the presence of $BF_3{\cdot}Et_2O$.[9] Finally, nitrile methanolysis[10] (K_2CO_3, MeOH, rt; then 7% HCl) gave methyl ester **12** as an inseparable 1.5:1 diastereoisomeric mixture (Scheme 3).[11]

Different epimerization attempts, in the hope of obtaining a single (or at least highly prevalent) diastereoisomer of **12** were carried out. However, treatment of ester **12** with catalytic amount of DBU at room temperature or reflux (in the aim of reaching the thermodynamic regime), or treatment with a stoichiometric amount of a lithium amide (LDA or $LiNEt_2$) followed by kinetic quenching, led only to recovered starting material with unchanged diastereoisomeric ratio, or degradation products. Furthermore, preliminary studies of epoxidation of intermediate **6** showed to be rather non-selective (*dr* = 1.3:1),[12] while epoxidation and dihydroxylation of diastereomeric mixtures of **11** (*dr* = 1.6:1) and **12** (*dr* = 1.5:1) under various conditions gave complex products/diastereomers.[12]

Judging that unsaturation at position 4,5 of the hexahydroindole bicycle was likely intrinsically unbiased for diastereoselective functionalizations, we passed to tackle an alternative way of generating this bicyclic unit, so as to obtain the unsaturation at position 6,7. This objective was achieved through a modified palladium-catalyzed strategy, featuring this time a domino sequence.[13]

*Domino sequence-based approach to N-tosyl bicyclic tetrahydroindolone **17***

This second strategy exploits the double Pd-catalyzed allylation of a malonamide with a cyclohexenyl bis-allylic system, according to a *C*-allylation/*N*-allylation *pseudo*-domino[14] sequence (Scheme 4).[15]

N-Tosyl malonamide **16**[16] was selected as the appropriate C/N double nucleophile, and its reaction with *cis*-OBz cyclohexene