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Use of chiral-pool approach into *epi*-thieno analogues of the scarce bioactive phenanthroquinolizidine alkaloids

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ABSTRACT

The stereoselective synthesis of *epi*-thieno analogues of the phenanthroquinolizidine bioactive alkaloids (−)-Cryptopleurine and (−)-(15*R*)-Hydroxycryptopleurine was achieved in five steps starting from easily available enantiopure (*S*)-2-aminoadipic acid used as chiral pool and nitrogen atom source. During these investigations, both π-cationic cyclization of chiral *N*-thienylmethyl-6-oxopipecolinic acids into pure (*S*)-keto-lactams and theirs regioselective and diastereoselective reduction, considered as key steps of this sequence, were studied. Of particular interest, the Friedel–Crafts cyclization using $(CF_3CO)_2O/BF_3{\cdot}Et_2O$ show that near the expected keto-lactams, enamides and enamidones containing trifluoromethyl residue were isolated. A mechanism leading to the latter products with high synthetic potential was discussed.

1. Introduction

2,3-Fused quinolizidine framework is an important motif which is found in numerous compounds among which the scarce phenanthroquinolizidines extract from three plants families.[1] The small family of pentacyclic alkaloids (Scheme 1), is represented by the bioactive (−)-Cryptopleurine (R=H, **1**),[1a] (−)-(15*R*)-Hydroxycryptopleurine (R=OH, **2**),[1a,b] Cryptopleuridine (**3**),[1c] Boehmeriasin-A (R=OMe, **4**),[1d] and Boehmeriasin-B (R=OH, **5**).[1d]

Based on the success of similar alkaloids with simpler skeleton, the phenanthroindolizidines, most of which demonstrate remarkable biological and pharmacological profiles, anticancer notably. In the light of these results, numerous efforts were undertaken to carry out quantitative structure–activity relationship (QSAR) studies (Scheme 1). The results of certain phenanthroquinolizidine derivatives show inhibitory activity in three human cancer cell lines with appreciable IC_{50} (104–130 nM),[2] the potential to treat coronavirus infection,[3] good to excellent in vivo antiviral activity against tobacco mosaic virus (TMV)[4] and anti-proliferative and selective antitumor properties.[5] While these studies were based essentially on Cryptopleurine (**1**) as the alkaloid model, the more recent Boehmeriasin-A (**4**) based compounds have shown in in vitro study anti-proliferative activity in three cancer cell lines (CEM, HeLa, and L1210) and in two endothelial cell lines (HMEC-1, BAEC) at concentration near the nanomolar range. Interestingly, during these studies, topoisomerases and SIRT2 were identified to be biological targets of these structures.[6]

Out of such considerations, the synthesis of these natural products and derivatives has been an appealing area of research. Most of the hitherto reported approaches into these types of compounds rely on a small number of strategies; the majority of which centers on the construction of the aza-six-membered ring **E** from cheap educts, which used subsequently as a chiral pool and a nitrogen atom source (Scheme 1). The ring closure of the central ring **D** proceeded then by Friedel–Crafts cyclization as pioneered by Rapoport et al.,[6,7] the Parham-type cycloacylation[8] and intramolecular aldol-type condensation.[6,9] Beyond other racemic experimental protocols[10] an alternative and interesting approach based on the construction first of chiral polycyclic systems containing piperidine-2-methanol (**A**–**D**) was also developed.[11] These key intermediates, when involved in a ring-closing metathesis afford a way to vary the nature and the size of the cycle at the end of

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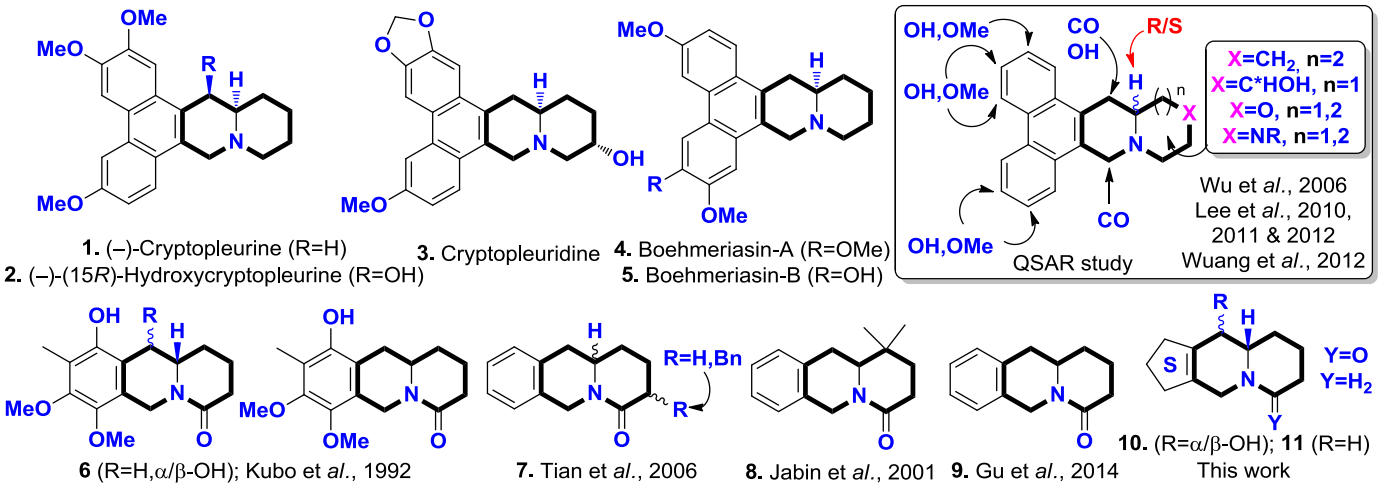


Scheme 1. Structure of the phenanthroquinolizidine alkaloids, their aromatic analogues and our targeted products **10** and **11**.

the targets enchainment **E** and are used to produce the molecular diversity.[5]

Curiously, no QSAR studies based on the modulation at the aromatic phenanthrene residue of these alkaloids have been described to this day. Along this line of reasoning, small aromatic analogues of these described phenanthroquinolizidines have been used as intermediates in the synthesis of the potent anticancer Saframycin-A (**6**)[7b] and precursors of enantiopure and non-proteogenic aromatic-δ-amino acids (**7**).[12]

Other structures, exemplified by compounds **8** and **9** were also found procreative. Their preparation is based on an imine Michael reaction followed by a radical cyclization[13] and intramolecular Schmidt reaction of acyl chlorides with alkyl azides, the last proceeding via *N*-acyliminium species as intermediates.[14]

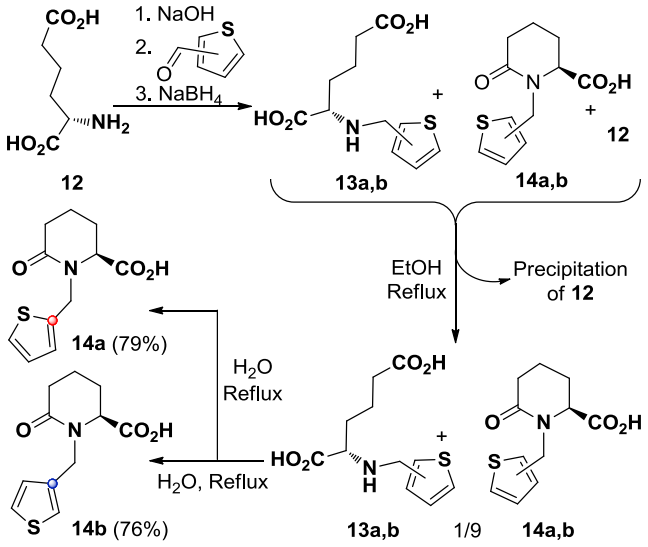
In keeping with our longstanding interest in the synthesis of indolizidinones and quinolizidinones fused to sulfur heterocyclic systems,[15] and their use for the elaboration of alkyl(or aryl) bicyclic iminosugars and their salts,[16] we herein report our findings on synthesis and properties of chiral thienoquinolizidindiones starting from chiral 6-oxopiperidine-carboxylic acid (6-oxopipecolinic acid). Their sequential stereoselective reduction led to the targeted thieno analogues of the bioactive phenanthroquinolizidine alkaloids **10** (R=OH) and **11** (R=H) (Scheme 1).

2. Results and discussion

2.1. Preparation of *N*-thienylmethyl-6-oxopipecolinic acids 14a,b

We firstly planned access to the requisite *N*-thienylmethyl-6-oxopipecolinic acids **14a**,**b** for the Rapoport cyclization by the known protocol.[7,17] This comprises *N*-reductive amination by mixing commercially available (*S*)-2-aminoadipic acid (**12**) and 2(or 3)-thienaldehyde in aqueous alkaline media (NaOH 2 M), addition of sodium borohydride to the same media, followed by intramolecular N-acylation of the resulting *N*-thienylmethyl-aminoadipic acids **13a**,**b** (Scheme 2).

The cyclization of dicarboxylic acids **13a**,**b** was performed by refluxing in ethanol for 8 h. To our surprise and contrary to the reaction profile obtained in the literature for similar sequences,[7,17] the reaction was incomplete (after cooling a small amount of unreacted (*S*)-2-aminoadipic acid (**12**) was obtained) and we observed after processing of the reaction mixture the expected carboxylic acids **14a**,**b** (in 79% and 76% isolated yields, respectively) in



Scheme 2. Synthesis scheme of oxopipecolinic acids **14a**,**b** precursors of the π-cationic cyclization.

addition to N-substituted amino acids **13a**,**b** in 9/1 ratio. Complete cyclization of **13a**,**b** to **14a**,**b** was carried out by heating in water at reflux for 4 h.

Interestingly, the structure of both carboxylic acids **14a** and **14b** was secured by an X-ray crystallographic analysis[18] (see also the ORTEP drawing of **14a**,**b** in the ESI part). Hence the possible epimerisation at the α-position of the cyclic lactam-acid under alkaline and thermal conditions can be excluded.

2.2. π-Cyclization of *N*-thienylmethyl-6-oxopipecolinic acids 14a,b

In the first set of Friedel–Crafts cyclization attempts of *N*-thienylmethyl-6-oxopipecolinic acids **14a**,**b**, standard Rapoport conditions were used.[7a] In stereospecific syntheses of the bioactive alkaloids (+)-Tylophorine and the piperidine analogue (−)-Cryptopleurine the reaction conditions were optimized. To our surprise, no reaction occurred, rather a complete polymerization of the reactants was observed under all reaction conditions tried.

Standard Rapoport conditions[7] having failed to produce the expected tricyclic keto-lactams **15a**,**b**, other cyclization conditions