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Iodine(III)-mediated ring expansion: an efficient and green pathway in the synthesis of a key precursor for the design of aminopeptidase (APN or CD13) inhibitors

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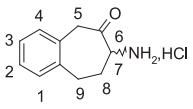
ABSTRACT

Iodine(III)-mediated ring expansion of a methylidenebenzocyclohexane derivative into the corresponding benzosuberone was used as a key reaction for the obtention of an important precursor for the design of aminopeptidase (APN or CD13) inhibitors. It represents the first application of this environmentally friendly rearrangement to medicinal chemistry.

1. Introduction

Aminopeptidase N (APN)/CD13 (EC 3.4.11.2) is an ectopeptidase that belongs to the class of metalloenzymes from the M1 family with a zinc ion essential for catalysis.[1] The expression of this ubiquitous proteolytic enzyme has been shown to be dysregulated in many diseases and is known to play an important role in tumor angiogenesis and metastasis.[1b,2] Although many inhibitors of aminopeptidases are available, most of them are poorly selective.[3] The development of highly specific and potent inhibitors remains a challenge since most aminopeptidases are zinc-dependent enzymes that share a broad substrate specificity.[1] Specific inhibitors would be undoubtely crucial biological tools since little is known about the precise role and mechanism of action of APN in the physiological and pathological processes, in particular in angiogenesis-dependent pathologies.[2] Structural requirements for APN inhibition were previously determined[4,5] and led to the discovery of (±)-7-amino-6-benzosuberone scaffold **1** as a lead structure, showing a remarkable inhibitory potency and selectivity toward APN, with a Ki value of 1 μM.[5] In view of its minimal size, this compound displayed an excellent ligand efficiency of 0.63 according to the definition by Hopkins et al.[6]



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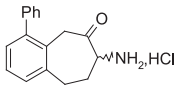

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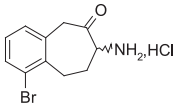

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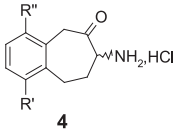

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This scaffold therefore appeared as an excellent candidate for further chemical elaboration and derivatization and we already pointed out the outstanding inhibitory activity and selectivity toward APN of the racemic 4-phenyl and 1-bromo derivatives **2** and **3**, paving thus the way to the elaboration of (±)-1,4-difunctionalized derivatives **4**. Our synthesis of **2** and **3** started from *ortho*-xylenic precursors and relied on a non-regioselective step of modest yield.[5] We present here a straightforward synthesis of the (±)-1,4-disubstituted aminobenzosuberone **5**, which potentially represents an ideal precursor to compounds of the series **4**.[7] As indicated Fig. 1, our synthesis started from natural L-tryptophane **10**

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and was based on the transformation in two steps of the 1-tetralone derivative **8** into the corresponding β-benzosuberone **6**. This overall transformation, which is based in a first step on the conversion of a six-membered ring ketone into the corresponding exomethylene derivative followed by a step of oxidative rearrangement, has been originally reported from 1-tetralone and some of its methyl or methoxy derivatives, using thallium nitrate in methanol for the ring expansion.[8] More recently, after a first report that implied non-cyclic ketones,[9a] Justik and Koser published, again from simple 1-tetralones, an analogous sequence in which [hydroxy(tosyloxy)iodo]benzene (HTIB) was employed as an excellent green alternative to the very toxic thallium salt in the rearrangement step.[9b] As reported here, this latter procedure proved very convenient for the preparation of the functionalized benzosuberone **6** from its exomethylenic precursor **7**. To the best of our knowledge, this represents the first application of Koser's procedure to medicinal chemistry.[10]

saponification and protection of the primary amine function as a trifluoroacetamide.

The preparation of 1-oxo-tetrahydronaphthalenic compound **8** required at first the tricky reduction of the carbonyl function in trifluoroacetaniline **9**. As shown in Scheme 2, this could be achieved by prolonged hydrogenation in acetic acid at 110 °C. Under these conditions, both the *N*-trifluoroacetyl and the *N*-ethoxycarbonyl protecting groups were preserved.[11] The acid chloride derivative of **15** was then submitted to a $AlCl_3$-mediated Friedel–Crafts reaction[12] yielding **8** and the lactam derivative **16** arising from prior $AlCl_3$-induced partial deprotection of the $NHCOCF_3$ moiety.

Access to the precursor **7** of the rearranged compound implied the methylenation of the oxo derivative **8**. This step required extensive trials as a Wittig reaction[13] or the use of a Tebbe reagent[14] proved quite unsatisfactory. Finally, a two-steps procedure implying the addition of methylmagnesium bromide followed by the dehydratation of the tertiary alcohol appeared much

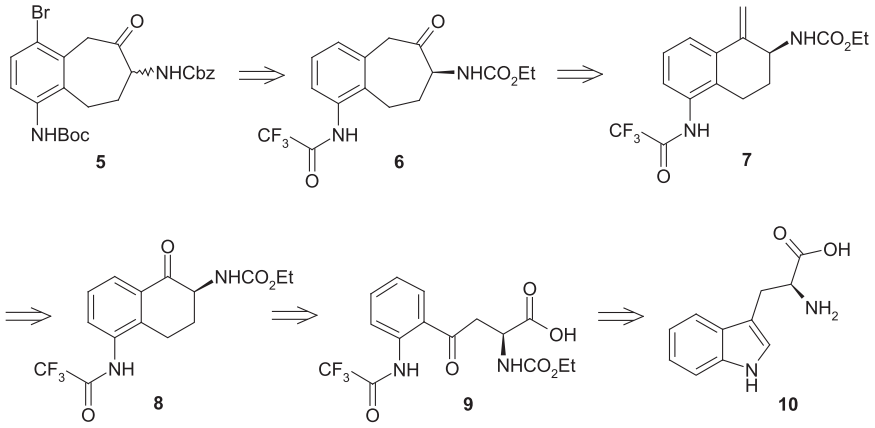


Fig. 1. Retrosynthesis of 4-bromo-1-*tert*-butylbenzyloxycarbonylamino benzosuberone derivative **5**.

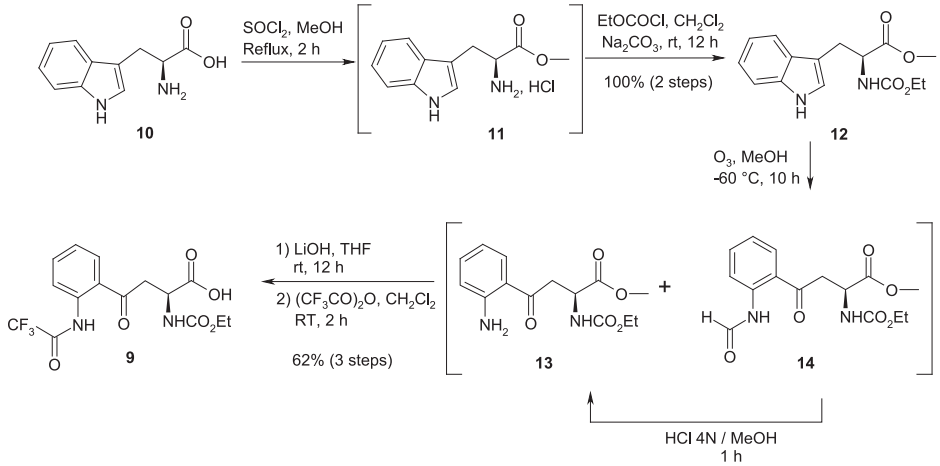
2. Results and discussion

Our synthesis started with the preparation of the 4-phenylbutanoic acid derivative **9**. This compound was readily obtained with an overall yield of 62% from natural L-tryptophane as indicated Scheme 1. After protection as a methyl ester and as a *N*-ethoxycarbonyl derivative, intermediate **12** was submitted to ozonolysis leading to an equimolar mixture of the expected *N*-formyl compound **14** and its deprotected partner **13**. A full access to **13** was possible by the treatment of **14** with methanolic HCl. The aniline derivative **13** was finally converted into **9** after more suitable and allowed us to obtain the desired intermediate in 55% overall yield.

Methylenic derivative **7** was then submitted to HTIB in methanol at rt according to Koser and Justik.[9] Under these conditions, we were pleased to isolate after 1 h the desired β-benzocycloalkanone **6** in a good yield as shown in Scheme 3.

Our key-precursor **5** carrying bromo- and NHBoc subtituents for further chemical derivatization on the aromatic ring was finally prepared from **6** according to Scheme 4.

Switching the trifluoroacetyl protection of **6** to a *tert*-butyloxycarbonyl was easily accomplished using mild basic conditions to



Scheme 1. Synthesis of 2-ethoxycarbonylamino-4-oxo-4-[2-(2,2,2-trifluoroacetylamino)-phenyl]-butanoic acid **9**.