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Synthesis of (−)-β conhydrine and analogues using *N*-Boc-2-acyl oxazolidine methodology and ring closing metathesis

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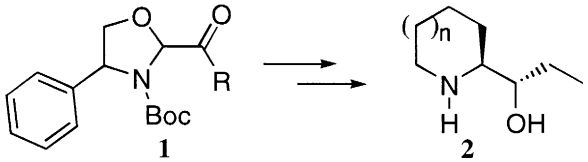
Abstract

Two key-steps involving: (i) a stereoselective reduction of an *N*-Boc-2-acyl oxazolidine; and (ii) an RCM performed on enantiopure *trans*-3,4,5-trisubstituted oxazolidin-2-ones account for the synthesis of unsaturated bicyclic oxazolidin-2-ones with various sizes of ring. One of these bicyclic compounds was transformed into (−)-β-conhydrin. An unsaturated and a dihydroxylated analogue of this alcaloid were also prepared from the same starting material. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: oxazolidines; asymmetric synthesis; ring closing metathesis.

N-Boc-2-acyl oxazolidines **1**, prepared either from commercialy available (*R*) or (*S*)-phenylglycinol are recognized as useful chiral protected forms of 1,2-dicarbonyl compounds and were recently used by our group for the asymmetric synthesis of homochiral 1,2-diols,[1] amino acids[2] or piperidinic alkaloids.[3] It was indeed observed that reduction of the keto moiety adjacent to the heterocyclic ring occurs with high diastereoselectivity and that the direction of the hydride attack can be chosen depending on the nature of the reducing agent.

We wish to describe in this letter that this methodology can be used, combined with ring closing metathesis (RCM),[4] in order to provide a new access to piperidinic alkaloids, as exemplified by the synthesis of (−)-β-conhydrin **2** (*n*=1) and analogous compounds.[5]



1 **2**

To this end, Weinreb amide **3**[3] prepared from (*S*)-phenylglycinol was treated with ethylmagnesium bromide (Scheme 1), to provide ethyl ketone **4**. This crude ketone was then reduced with sodium boro-

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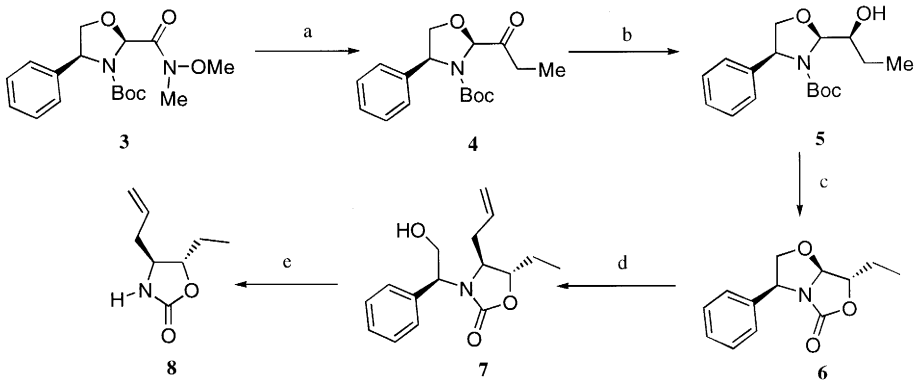
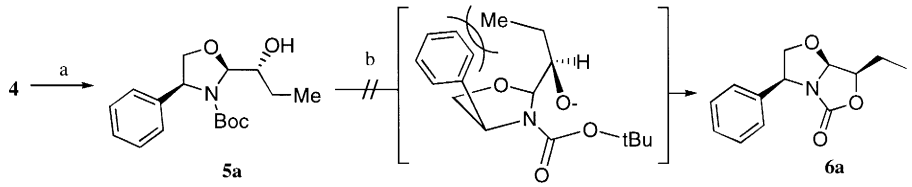
hydride at −78°C to give α-hydroxy oxazolidine **5** showing a 86:14 isomeric ratio on the newly created stereogenic center. Although stereoselectivity was quite modest, pure isomer **5** could be conveniently isolated with an overall yield of 49% from **3**. The same stereochemical course of $NaBH_4$-mediated reductions on similar substrates was explained on the basis of a Felkin–Ahn control.[3] Oxazolidine **5** was then treated with sodium hydride in THF in order to induce a transcarbamation and to provide bicyclic heterocycle **6**. This compound was then reacted with allyltrimethylsilane in the presence of $TiCl_4$ and gave allylated oxazolidinone **7** with a high stereoselectivity (98% de).[6] Finally, reductive debenzylation with a controlled amount of sodium[7] gave diastereoisomerically pure oxazolidinone **8** in good yield.



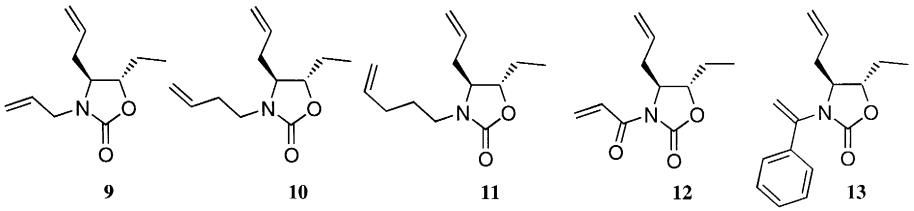
Scheme 1. Reagents and conditions. a. Ethylmagnesiumbromide, Et_2O, rt; b. $NaBH_4$, EtOH, −78°C, 49% overall; c. NaH, THF, reflux, 98%; d. allyltrimethylsilane, $TiCl_4$, −78°C, CH_2Cl_2, 71%; e. Na (3.5 equiv.), EtOH, THF, NH_3, 93%

From a mechanistical point of view, it should be pointed out that an attempt to prepare *ent*-**8** from the same Weinreb amide **3** (Scheme 2) was unsuccessful: although reduction of **4** with sodium borohydride in the presence of $CeCl_3$ occurred with the anticipated opposite diastereoselectivity,[8] the intramolecular nucleophilic attack in **5a** to give bicyclic oxazolidinone **6a** was not operative, probably because of a severe steric crowding between the ethyl and the phenyl groups during the cyclization step.

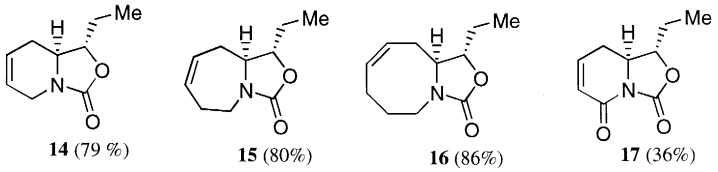


Scheme 2. Reagents and conditions. a. $NaBH_4/CeCl_3$, EtOH, −78°C, 45% overall from **3**; b. NaH, THF, reflux

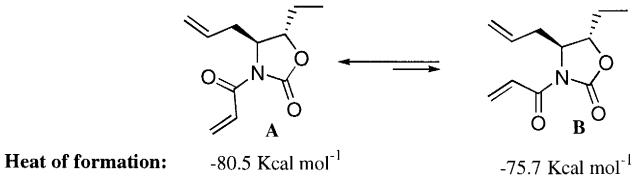
In order to synthesize substrates for the ring closing metathesis, oxazolidinone **8** was transformed into unsaturated compounds **9**–**12**, and oxazolidine **7** was transformed into **13** (Scheme 3). The modest yield obtained in the case of the preparation of compound **10** (alkylation of the sodium amide derived from **6** with 4-bromo-1-butene) can be explained by a competitive elimination of the unsaturated bromoalkene.These unsaturated oxazolidinones were then subjected to ring closing metathesis using Grubb's catalyst (4% molar ratio added in two portions in refluxing CH_2Cl_2 during 8 h). Whereas oxazolidinones **9**–**11** gave the expected bicyclic heterocycles **14**–**16** in good yields, compound **12** sluggishly yielded **17** along with unreacted starting material and substrate **13** only gave intermolecular reactions under forcing conditions.



Scheme 3. Reagents and conditions. From **8**; **9**: NaH, DMF, C_3H_7Br, 74%; **10**: NaH, DMF, C_4H_9Br, 42%; **11**: NaH, DMF, $C_5H_{10}Br$, 72%; **12**: EtMgBr, THF, $ClCH_2CH_2COCl$, then Et_3N, CH_2Cl_2 67%. From **7**; **13**: (i) $SOCl_2$, THF (ii) DBU, CH_2Cl_2, 79%

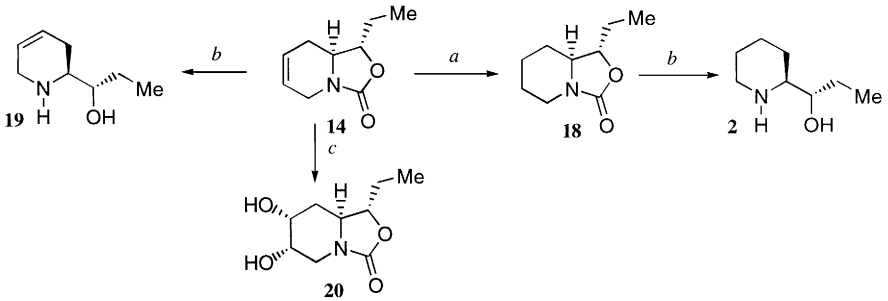


Compared to oxazolidinones **9**–**11,** the lower reactivity of substrate **12** towards RCM can be explained on the basis of a conformational analysis. In fact, AM1 calculations show that conformer **A** of **12** is ca. 5 kcal mol^{-1} more stable than the reactive conformer **B**, probably because of a dipolar repulsion between C=O moieties, thus lowering the population of the reactive conformer (Scheme 4). Notwithstanding, attempts to use a Lewis acid ($Ti(Oi\text{-}Pr)_4$, 20% molar ratio)[9] in order to increase the population of conformer by chelation with the C=O moieties only led to degradation products.



Scheme 4.

The reactivity of bicyclic urethane **14** was then briefly examinated (Scheme 5).[10] It was observed that its hydrogenation gave quantitatively **18** which was hydrolyzed to give (−)-β-conhydrine **2**. On the other hand, basic hydrolysis of **14** furnished the conhydrine unsaturated analogue **19**. Dihydroxylation of **14** was highly stereoselective yielding, albeit in modest isolated yield, compound **20** as a unique stereoisomer, whose structure was secured by an X-ray radiocrystallography. The stereoselectivity of this dihydroxylation can be easily understood by considering the spatial structure of **12**, which shows a less crowded *exo* diastereoface (Fig. 1).



Scheme 5. Reagents and conditions. a. Pd/C, EtOH, 92%; b. LiOH, EtOH, THF, reflux, 45% (**2**), 54% (**19**); c. OsO_4, NMO, acetone/water, 45%

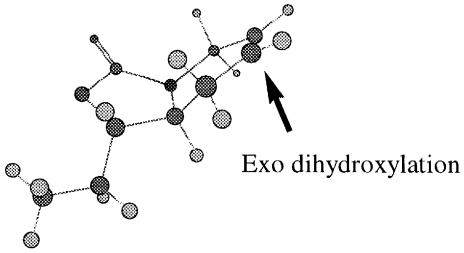


Fig. 1. Chem3D view of compound **14** showing the preferred *exo* dihydroxylation

Compound **20** belongs to the class of azasugars, intensively studied because of the biological activities displayed by some of its members. Interestingly, recently reported hydroxylated 2-oxaindolizidines related to **20** were found to be highly selective inhibitors of glycosidases.[11]

In summary, the strategy reported above provides a new entry for the synthesis of hydroxylated piperidinic alkaloids and efforts are ongoing in our laboratory in order to synthesize other representative targets belonging to this class of compounds.

Acknowledgements

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