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Enantioselective Synthesis of *N*-Boc-2,2-Dimethyloxazolidine-5-Carbaldehydes, Versatile Precursors of Dipeptide Isosteres

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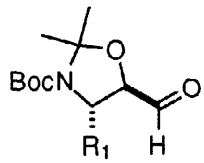
Abstract. Highly enantioenriched *cis* and *trans* *N*-Boc-2,2-dimethyl-oxazolidine-5-carbaldehydes have been efficiently prepared from *N*-Boc-3-amino-1,2-alkanediols, readily available in enantiopure or enantioenriched form by Sharpless epoxidation methodology. These compounds have been converted into *N*-Boc-(*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones which are key intermediates of hydroxyethylene dipeptide isosteres. © 1998 Elsevier Science Ltd. All rights reserved.

The successful development of aspartic protease inhibitors acting on renin or on the HIV protease has stimulated the research in the use of enzyme inhibitors as therapeutic agents.[1] The most usual strategy so far employed has been the replacement of the scissile amide bond in a peptidic substrate by hydrolytically stable functionality with isosteric character.[2] From the perspective of starting materials, most of the approaches to dipeptide mimics in enantiomerically pure form are based on natural sugars or amino acids. Taking into account that the stereochemistry of the peptidomimetic fragment is key to inhibitory action, stereoselective methodologies devoted to the synthesis of those fragments are of fundamental importance for the development of new drugs belonging to this class.

Oxazolidine-5-carbaldehydes *trans*-**1a-c**, which have been prepared from α-amino acids,[3-5] are precursors to several types of important dipeptide isosteres.[3-6] It is evident that the development of stereoselective methodology of wide applicability for the synthesis of these and related compounds would overcome the limitations inherent to the use of natural products as starting materials and would allow the control of the configuration of the stereogenic centres.



trans-**1**

1a: R = $CH_2CH(CH_3)_2$
1b: R = CH_2Ph
1c: R = $CH_2C_6H_{11}$
1d: R = CH_3
1e: R = Ph

During the last years we have shown how *anti*-*N*-Boc-3-amino-1,2-alkanediols **2**, available in high enantiomeric purity through the use of a catalytic asymmetric Sharpless epoxidation of (*E*)-allyl alcohols followed by nucleophilic ring opening, can be efficiently converted into enantiomerically pure α-amino acids[7], β-amino acids[8], α-hydroxy-β-amino acids[9] and β-hydroxy-γ-amino acids,[10] which are important components of peptides and other biologically active compounds. We describe in the present paper an efficient stereoselective synthesis of *N*-Boc-2,2-dimethyloxazolidine-5-carbaldehydes **1c-e** of any relative configuration from *N*-Boc-3-amino-1,2-alkanediols **2c-e**. Moreover, as an illustration of the synthetic potential of these

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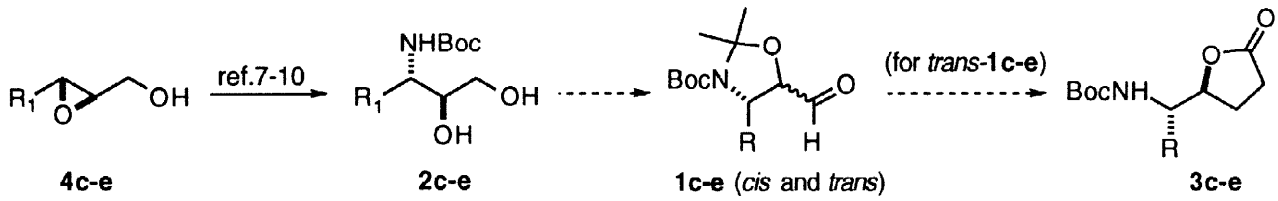
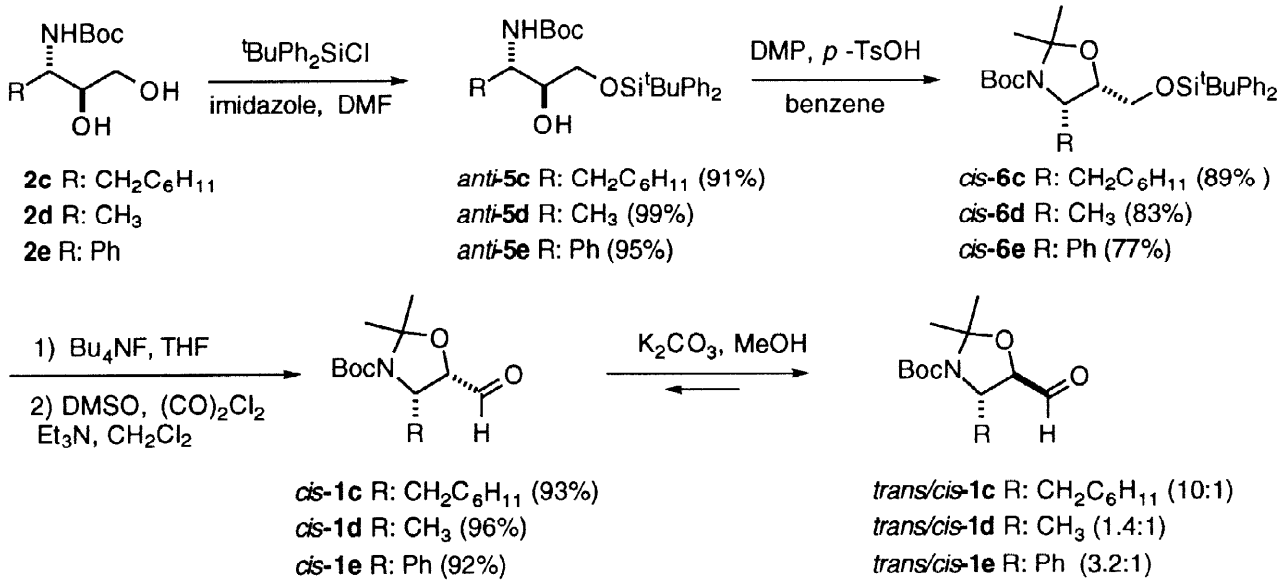
compounds, *trans*-**1c-e** have been converted into *N*-Boc-(*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones **3c-e**, key intermediates in the synthesis of important hydroxyethylene dipeptide isosteres.[11]



anti-*N*-Boc aminodiols **2c-e** were selected as starting materials since they cover a representative variety of side chains: The cyclohexylmethyl radical present in **2c** is a non proteinogenic fragment found in many dipeptide isosteres and is a representative example of a large alkyl group, whereas **2d** contains a small alkyl group and **2e** an aromatic substituent. All of them are readily available in high enantiomeric purity and can be prepared in multigram amounts by our reported methodology[7-10] from epoxides **4c-e**.

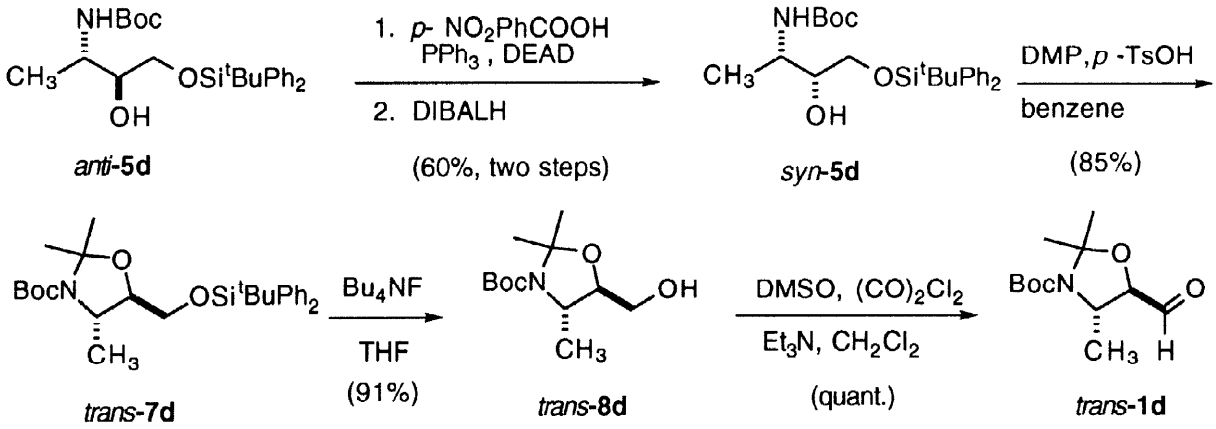
4,5-*Cis* disubstituted oxazolidines *cis*-**1** would be simply prepared from *N*-Boc-3-amino-1,2-alkanediols **2** through the following sequence: protection of the primary hydroxyl group, formation of the oxazolidine ring, deprotection and oxidation. Our first attempts in this direction involving the use of the *tert*-butyldimethylsilyl protecting group failed due to its (in our hands) unavoidable acidolysis during the formation of the oxazolidine ring. This fact prompted us to use the more acid resistant *tert*-butyldiphenylsilyl protecting group. Thus, treatment of *N*-Boc-3-amino-1,2-alkanediols **2c-e** with *tert*-butyldiphenylsilyl chloride/imidazole in DMF afforded chemoselectively the corresponding primary *tert*-butyldiphenylsilyl ethers *anti*-**5c-e** in excellent yield (Scheme 1). Subsequent treatment with excess 2,2-dimethoxypropane (DMP) in the presence of a catalytic amount of *p*-toluenesulfonic acid[12] in benzene solution provided silyloxymethyloxazolidines *cis*-**6c-e** also in high yield. The primary hydroxy group was then selectively deprotected by treatment with tetrabutylammonium fluoride in THF and oxidized under Swern conditions[13] to afford the target aldehydes *cis*-**1c-e** in almost quantitative yield.



Scheme 1

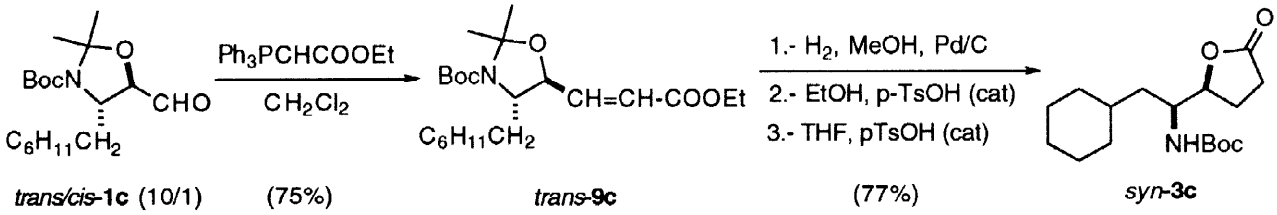
In order to prepare the even more interesting *N*-Boc-2,2-dimethyl-oxazolidine-5-carbaldehydes **1** with *trans* configuration, which are precursors of *syn* dipeptide isosteres[1,2] the simplest solution would involve a base catalyzed epimerization of the corresponding *cis* derivative. Although this turned out to be satisfactory

for the preparation of *trans*-**1c** (Scheme 1), where a 10:1 mixture (by GC) of *trans* and *cis* isomers was obtained in almost quantitative yield when *cis*-**1c** was treated with potassium carbonate in methanol, the strategy was not applicable to **1d** or **1e** due to low equilibrium *trans/cis* ratios. Consequently, a completely stereoselective alternative route to *trans* oxazolidine-5-carbaldehydes was developed. In this route, the *trans* stereochemistry is secured by performing an inversion of the configuration of the secondary alcohol in the *tert*-butyldiphenylsilyl ether *anti*-**5d**. Thus, *via* a two step sequence consisting of Mitsunobu reaction,[14] and DIBALH reduction, *syn*-**5d** was obtained from *anti*-**5d** in good yield. (Scheme 2). With *anti*-**5d** in hand, application of the previously developed sequence provided carbaldehyde *trans*-**1d** in good yield and complete stereoselectivity.



Scheme 2

Although oxazolidine-5-carbaldehydes **1** have already been used as precursors of dipeptide isosteres, its synthetic potential has not been fully developed yet. As a straightforward demonstration of this potential, we envisaged that a simple sequence of Wittig olefination, catalytic hydrogenation of the double bond and acidic treatment would afford *N*-Boc-(*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones **3**. As a representative example, an isomerized mixture of *trans* and *cis*-**1c** (10/1) was submitted to Wittig olefination to afford a 70:30 mixture of *Z* and *E*-*trans*-**9c** in good yield. It is important to notice that the small amount of *cis* isomers arising from the minor stereoisomer *cis*-**1c** were easily removed at this point by column chromatography. The alkene mixture *trans*-**9c** was then hydrogenated over Pd/C in MeOH to give a diastereomerically pure product that was submitted to an acidic treatment (MeOH, cat. *p*-TsOH) in order to hydrolyse the oxazolidine ring. Under these conditions, lactonization of the intermediate hydroxyester took place to some extent, being completed by an additional acidic treatment in THF. In this way, diastereomerically pure (4*S*,5*S*)-5-*N*-Boc-amino-6-cyclohexyl-4-hydroxyhexanoic acid lactone[11d] *syn*-**3c** was obtained in excellent yield (Scheme 3). Interestingly, the enantiomeric purity is maintained along the route from **2c** to *syn*-**3c**. A similar sequence, applied to *trans*-**1d-e** afforded lactones *syn*-**3d-e** in 57 and 46% overall yields respectively.



Scheme 3

In summary, we have developed a versatile, stereoselective synthesis of *N*-Boc-2,2-dimethyl-oxazolidine-5-carbaldehydes **1**, a catalytic Sharpless epoxidation being the sole source of chirality. Our methodology provides an enantioselective access to both diastereomeric series (*cis* and *trans*) and allows ample variation of the R substituent. Moreover, both enantiomeric series are equally available by simply adjusting the configuration of the tartrate employed in the Sharpless epoxidation step. The synthetic potential of the oxazolidine-5-carbaldehydes **1** has been expanded with a simple procedure for the preparation of *N*-Boc-(*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones **3** which are key intermediates in the preparation of hydroxyethylene dipeptide isosteres.

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