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Stereoselective Synthesis of All Stereoisomers of Orthogonally Protected Cyclobutane-1,2-diamine and Some Chemoselective Transformations

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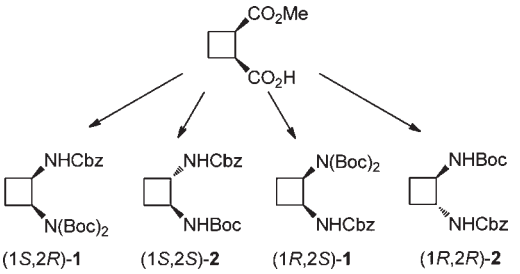
ABSTRACT



The four stereoisomers of protected cyclobutane-1,2-diamine have been prepared in an enantio- and diastereocontrolled manner through stereodivergent synthetic routes starting from a half-ester as a common chiral precursor. Orthogonal protection allows the chemoselective manipulation of both amino groups as shown in this work.

In recent years, compounds that incorporate a 1,2-diamine functionality have attracted attention due to their plentiful applications. Some of them have important biological activities, and many are medicinal agents. Among them are antidepressant and antianxiety agents, antiarrythmics, and especially chemotherapy drugs. These molecules have also been described as chiral auxiliaries, ligands, and organocatalysts, with relevant applications in stereoselective synthesis.[1] When the vicinal amine functionalities are linked to a carbocyclic ring,[2] the most studied compounds are cyclohexyl-1,2-diamines,[3] whose *trans*-diastereoisomer has been used, for instance, in the preparation of nanostructured hybrid materials.[4]

As a part of our research program on the synthesis of chiral cyclobutane scaffolds and their use in the preparation of designed foldamers,[5] organogelators,[6] enzime inhibitors,[7] and organoconducting materials,[8] among other interesting products, in this paper we describe the

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enantio- and diastereocontrolled synthesis of the four stereoisomers of orthogonally protected cyclobutane-1,2-diamine in view of opening a new access for a wide range of useful enantiopure molecules containing this moiety. Three syntheses of racemic *trans*-cyclobutane-1,2-diamine had been reported previously, but in most cases, yields were low.[9] Resolution of the racemic mixture was accomplished in one instance also in modest yield by using L-tartaric acid.[9a]

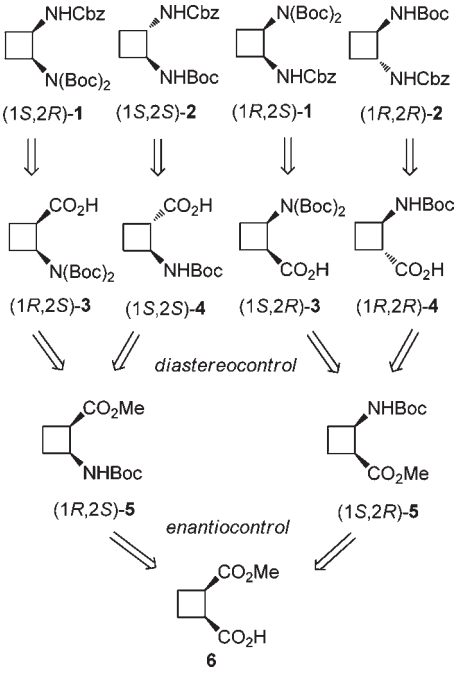
The retrosynthetic analysis of the target molecules points to readily available optically pure half-ester **6**[5c,10] as the only chiral precursor (Scheme 1). From **6**, enantiodivergent synthetic routes lead to the two enantiomers of the key intermediate diprotected cyclobutane β-amino acid, (1*R*,2*S*)- and (1*S*,2*R*)-**5**. These compounds allow the preparation of enantiomeric *cis*-derivatives **1** through acids **3** by hydrolysis and subsequent Curtius rearrangement. In turn, *trans*-diastereoisomers **2** come from *trans*-acids **4**, which result from epimerization of the α-carbonyl position in both enantiomers of **5**.

Orthogonal protection in target molecules **1** and **2** is crucial for further chemoselective manipulation of the two amino groups. This allows retention of the chirality in *cis*-diastereomers **1** that, otherwise, would become *meso*. Therefore, the sequential order of the synthetic transformations is the key to successfully accomplish the stereocontrolled synthesis of both enantiomers of *cis*-**1** and *trans*-**2** diamine derivatives.

The two enantiomers of *cis*-**1** were obtained from **5**.[5c] First, the diprotection of the amino group was necessary in order to avoid the formation of cyclic ureas during Curtius rearrangement of monoprotected amines (Scheme 2). These byproducts are formed through intramolecular nucleophilic attack of the carbamate nitrogen to the carbon of the transient isocyanate with concomitant ring-closure, due to the kinetically favorable cyclization to the five-membered urea ring.[11] This process is not favorable with *trans*-derivatives so they do not need amine diprotection.

Scheme 2 shows the diastereodivergent synthetic pathways for the preparation of *cis*-(1*S*,2*R*)-**1** and *trans*-(1*S*,2*S*)-**2** from *cis*-amino acid derivative (1*R*,2*S*)-**5**. The double protection was achieved by treating **5** with Boc anhydride (2 equiv) in the presence of DMAP and triethylamine. Saponification of the methyl ester was carried out to obtain quantitatively *cis*-**3**. After that, the carboxylic acid was activated as a mixed anhydride by reaction with ethyl chloroformate and then sodium azide was added to form an acyl azide that was not isolated. This intermediate was submitted to Curtius rearrangement by heating to reflux in toluene and in the presence of benzyl alcohol. In this way,

Scheme 1. Retrosynthetic Analysis of the Orthogonally Protected Four Stereoisomers of Cyclobutane-1,2-diamine (**1** and **2**)



both enantiomers of orthogonally protected *cis*-diamine **1** were obtained in 48% and 50% yields, respectively (three steps) (see the Supporting Information).

The syntheses of both enantiomers of *trans*-diamine **2** were also conducted from amino acid derivative **5**. Activation of the carboxylic acid as a mixed anhydride by reaction with ethyl chloroformate and subsequent treatment with ammonium hydrogencarbonate in pyridine yielded an amide,[12] which was heated under strong basic conditions to afford monoprotected *trans*-amino acid **4**. From this intermediate and following procedures similar to those described above for *cis*-diastereomers, both enantiomers of orthogonally protected *trans*-**2** were obtained in 67% and 69% overall yield (three steps), respectively.

For the purpose of proving that the synthesized orthogonally protected cyclobutane 1,2-diamine derivatives could be used for further functionalization, their selective deprotections were carried out (Scheme 3). Thus, elimination of the two *tert*-butoxycarbonyl groups in *cis*-diamine (1*S*,2*R*)-**1** was achieved quantitatively giving amine hydrochloride (1*S*,2*R*)-**10**. In a similar way, both enantiomers of *trans*-amine hydrochloride **10** were obtained in quantitative yield from diprotected *trans*-diamines (1*R*,2*R*)- and (1*S*,2*S*)-**2**, respectively. Alternatively, the benzyl carbamate group in (1*S*,2*S*)-**2** was hydrogenolyzed in the presence of $Pd(OH)_2/C$ to afford (1*S*,2*S*)-**12** in 82% yield.

Products **10** and **12** are suitable for the chemoselective introduction of structural units containing additional functional groups. As a preliminary instance,

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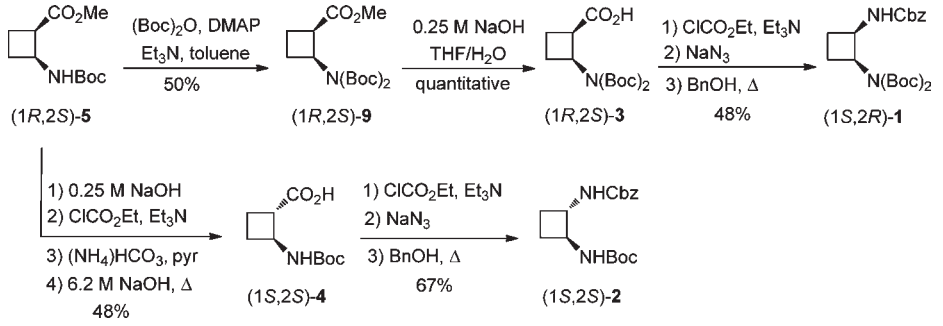
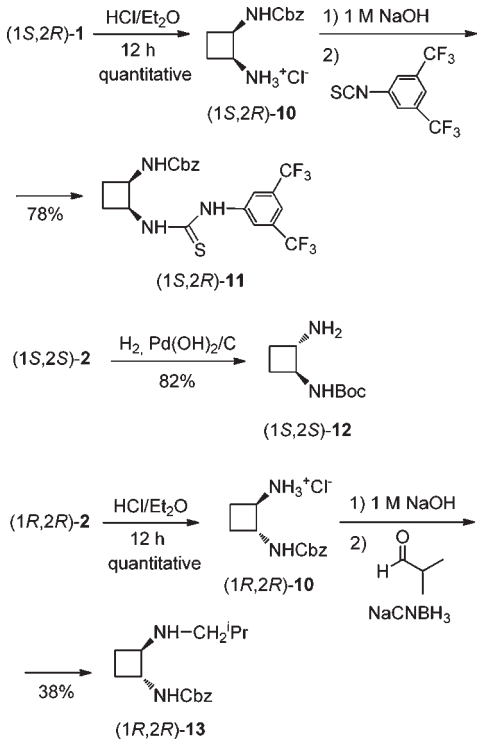
Scheme 2. Diastereoselective Synthesis of Compounds (1*S*,2*R*)-**1** and (1*S*,2*S*)-**2**



Scheme 3. Some Examples on Deprotection and Chemoselective Functionalization of Diamines



cis-aminothiourea (1*S*,2*R*)-**11** was synthesized from the free amine obtained under treatment of the ammonium salt (1*S*,2*R*)-**10** with 1 M sodium hydroxide and subsequent reaction with bis(trifluoromethyl)phenyl thioisocyanate (78% yield, Scheme 3). Similarly, *trans*-thiourea (1*S*,2*S*)-**11** was prepared in 74% yield from the corresponding stereoisomer of amine **10**. The preparation of an alkyl derivative was achieved from (1*R*,2*R*)-**2** by removal of *N*-Boc protection giving salt (1*R*,2*R*)-**10**, neutralization with 1 M NaOH, and reductive amination of isobutyraldehyde in the presence of $NaCNBH_3$ to afford compound (1*R*,2*R*)-**13** in 38% yield (two steps, yield not optimized).

In summary, we have achieved the enantio- and diastereocontrolled synthesis of the four stereoisomers of orthogonally protected cyclobutane-1,2-diamine. The versatility of these scaffolds is illustrated by the preliminary examples presented herein. Their use for the preparation of functional products with applications in remarkable fields such as hetero- and homogeneous catalysis as metal ligands or organocatalysts, surfactants, etc., is under active investigation.

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Supporting Information Available. Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.