

学校编码: 10384

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厦 门 大 学

硕 士 学 位 论 文

多羟基环己基 β -氨基酸衍生物的合成

Synthesis of Polyhydroxylated
2-Aminocyclohexanecarboxylic Acids Derivatives

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专 业 名 称: 有机化学

论文提交日期: 2006 年 10 月

论文答辩时间: 2006 年 10 月

学位授予日期: 2006 年 月

答辩委员会主席: _____

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摘要

多羟基环己基手性 β -氨基酸及其衍生物具有重要的药物、生物和合成用途。其中, 2-氨基环己基羧酸及其衍生物的寡聚体已经被发现具有与蛋白质相似的二级结构, 成为扩展已知蛋白质结构和稳定性的有用工具。

本文开辟了一种合成多羟基取代的、具有光学活性的多羟基 2-氨基环己基羧酸的衍生物的方法。该合成法以内消旋的 *cis*-1,2,3,6-四氢邻苯二甲酸酐 **I** 为起始原料, 以奎宁为手性试剂, 通过去对称化、Curtius 重排、醇解以及分子内立体选择性碘内酯化和消除反应等五步反应, 以近 40% 的总产率简捷地合成光学活性多羟基环己基 β -氨基酸的关键中间体 **II** (图 1)。

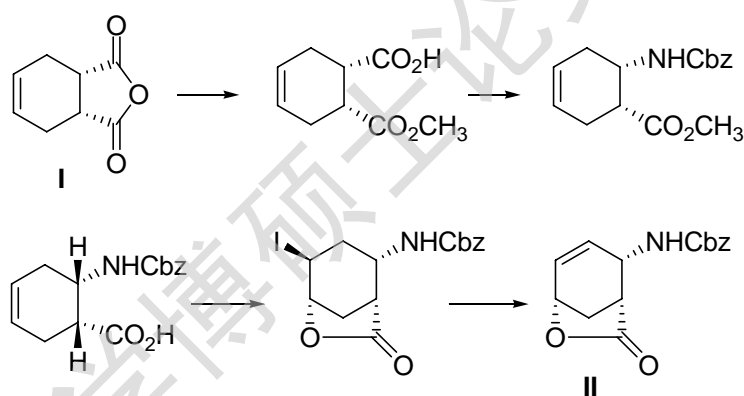


图 1

从中间体 **II** 出发, 一方面经邻二羟基化、开环, 以 45.0% 的收率得到 (3*S*,4*R*,5*S*)-3,4,5-三羟基-环己基- β -氨基酸衍生物 **III**。另一方面, 经 **II** 的开环、环氧化、水解, 以 55.3% 的收率得到 3,4,5-三羟基-环己基- β -氨基酸衍生物 **IV** (图 2)。

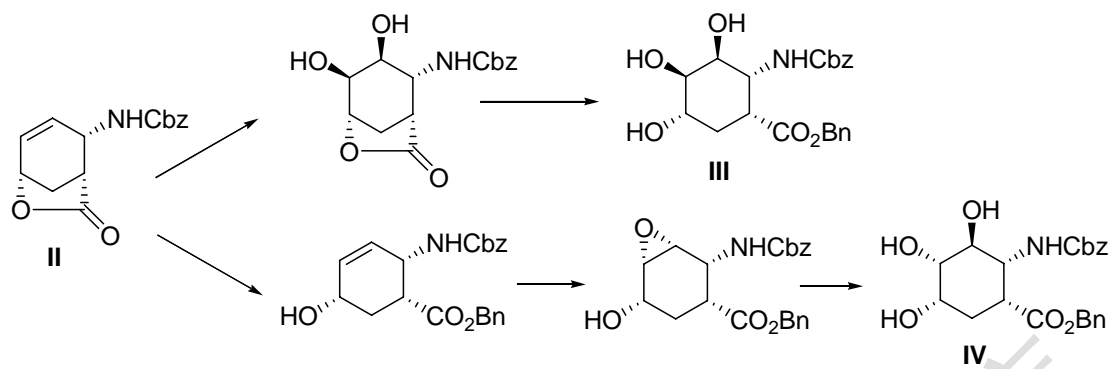


图 2

关键词：去对称化；邻二羟基化；环氧化

Abstract

Chiral polyhydroxy β -amino cyclohexane carboxylic acid have important pharmaceutical, biological and synthetic applications. Among these, oligmeric 2-amino cyclohexane carboxylic acid and their derivatives have been found to form secondary structures similar to those of proteins and used useful tools for the study of the known structure and stability of proteins.

This thesis describes a novel approach for the synthesis of chiral polyhydroxy β -amino cyclohexane carboxylic acid derivatives. This method is based on the desymmetrisation of *cis meso*-1, 2, 3, 6-tetrahydrophthalic anhydride **I** using quinine as the chiral reagent. The desymmetrized intermediate is then subjected to Curtius rearrangement, alcoholysis with benzyl alcohol, stereoselective intramolecular iodolactonization and elimination to form the key intermediate **II** in 5 steps in 40% overall yield (**Fig. 1**).

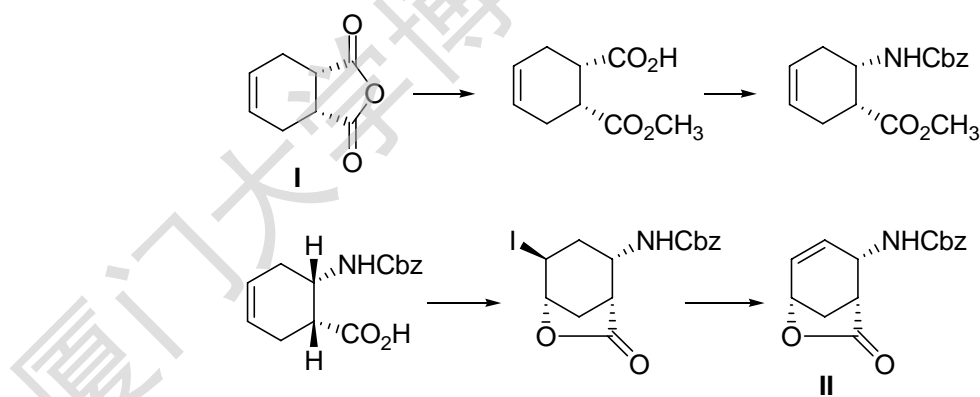


Fig. 1 Synthesis of the key chiral intermediate **II** for chiral polyhydroxy β -amino cyclohexane carboxylic acid derivatives

This key intermediate is then transformed into chiral polyhydroxy β -amino cyclohexane carboxylic acid derivatives by two divergent routes. On the one hand, osmium catalysed dihydroxylation followed by lactone ring opening gave (3*S*, 4*R*, 5*S*)-3, 4, 5- trihydroxy β -amino cyclohexane carboxylic acid derivatives **III** in 45.0%

overall yield. On the other hand, hydrolysis of the lactone moiety followed by epoxidation on the double bond of and epoxide ring opening afforded the trihydroxy β -amino cyclohexane carboxylic acid derivatives **IV** in 55.3% overall yield (**Fig. 2**).

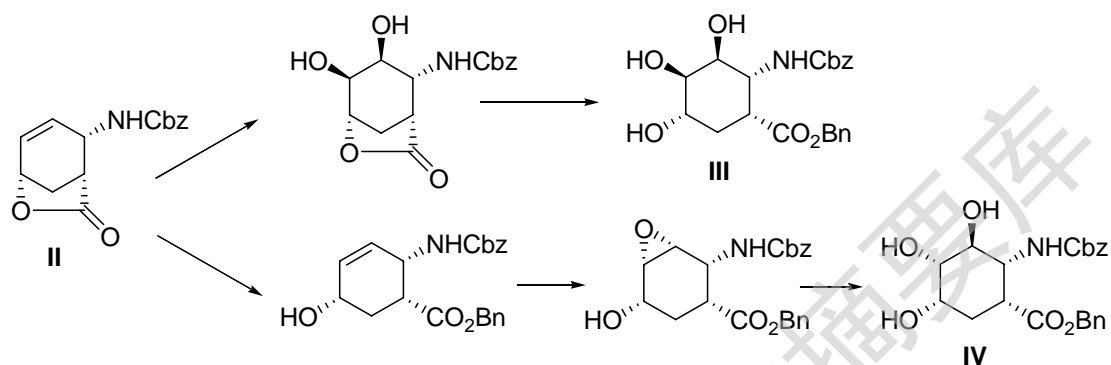


Fig. 2 synthesis of trihydroxy β -amino cyclohexane carboxylic acid derivatives **III** and **IV** from common intermediate **II**

Keyword: desymmetrization; dihydroxylation; epoxidation

化合物缩写对照表

| | |
|----------|---|
| ACAC | amino cycloalkane carboxylic acids |
| ACHC | amino cyclohexane carboxylic acid |
| ACPC | amino cyclopentane carboxylic acid |
| BINAL | binaphthol modified aluminum hydride |
| DBU | 1,5-diazabicyclo[5.4.0]undec-5-ene |
| DMAP | 4-dimethyl aminopyridine |
| DPPA | diphenyl phosphoryl azide |
| KHMDS | potassium hexamethyldisilyl amide |
| LDA | lithium diisopropyl amide |
| LHMDS | lithium hexamethyldisilylamide |
| mCPBA | <i>m</i> -chloroperbenzoic acid |
| NMO | <i>N</i> -methyl morpholine <i>N</i> -Oxide |
| TMSCN | trimethylsilyl cyanide |
| Z or Cbz | benzyloxycarbonyl |

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