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Tetrahedron 61 (2005) 8456–8464

# Novel stereocontrolled approach to conformationally constrained analogues of L-glutamic acid and L-proline via stereoselective cyclopropanation of 3,4-didehydro-L-pyroglutamic ABO ester

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Received 7 June 2005; revised 20 June 2005; accepted 20 June 2005

Available online 11 July 2005

**Abstract**—A new stereocontrolled approach to L-(carboxycyclopropyl)glycines (L-CCGs) and 3,4-methano-L-prolines, conformationally constrained analogues of L-glutamic acid and L-proline, respectively, was developed using a 3,4-didehydro-L-pyroglutamate derivative as a common chiral template. The unsaturated L-pyroglutamate derivative employed in this work is a novel chiral synthon in which the carboxyl functionality is protected as a 2,7,8-trioxabicyclo[3.2.1]octyl group (ABO ester). Stereospecific cyclopropanation of the olefin using diazomethane followed by appropriate functional group interconversion gave L-CCG-III and *trans*-3,4-methano-L-proline with complete stereocontrol. Synthesis of other diastereomers of L-CCG and *cis*-3,4-methano-L-proline was accomplished by alteration of the 3,4-methanoglutamic acid framework via carboxycyclopropanation of the olefin with sulfur ylide and subsequent Barton decarboxylation reaction of the original γ-carboxyl group included in the pyroglutamate skeleton.


## 1. Introduction

L-Glutamic acid is the most widely used α-amino acid in asymmetric synthesis because of its versatility as a chiral starting material and its availability at low cost.[1] Among a wide variety of chiral synthons derived from L-glutamic acid, L-pyroglutamic acid, easily prepared by the intramolecular dehydration of L-glutamic acid, occupies an important place in the field of natural product synthesis.[2] For the functionalization at the 3- or 3,4-positions of the lactam ring, it is necessary to employ 3,4-didehydropyroglutamic acid derivatives. Although there are some reports concerning the reactivity of the unsaturated pyroglutamates,[3] they could not be used as a chiral template due to their tendency to racemize and isomerize via a double-bond shift. For example, Ezquerra and co-workers reported the first trapping reaction of the olefin with cyclopentadiene where the Diels–Alder adduct was obtained only in 50% ee.[3b] To circumvent the above problems, the corresponding pyroglutaminol derivatives are often employed as the chiral template; however, the procedure necessitates the reduction of the carboxyl group and its regeneration after the desired modification has been completed.

In an effort to overcome the problems encountered by the above approaches, we opted to explore an alternative chiral template involving the unsaturated pyroglutamate skeleton. Recently, Lajoie and co-workers have developed a new methodology for the synthesis of a wide range of nonproteinogenic α-amino acids based on the elaboration of a chiral serine aldehyde in which Corey's 2,6,7-trioxabicyclo[2.2.2]octyl group (OBO ester)[4] was used as a protective group for the carboxylic acid.[5] The bulky OBO moiety was found to reduce the acidity of the α-proton allowing several transformations without racemization and to induce high diastereoselectivity in the addition reactions performed on the aldehyde moiety.

In the present work, we adopted a 2,7,8-trioxabicyclo[3.2.1]octyl group (ABO ester)[6] as a protective group for the carboxyl functionality of the unsaturated pyroglutamate derivative because the pyroglutamic ABO ester is easier to prepare than the corresponding OBO ester. During the course of our investigation, synthesis of an unsaturated L-pyroglutamic OBO ester has been published;[7] however, the overall yield of the olefin from the starting L-pyroglutamic acid was very low (8.4%) and the reaction of the olefin was limited to Michael additions. In our preliminary communication,[8] we demonstrated an efficient synthesis of a 3,4-didehydropyroglutamic ABO ester **1** (49.8% overall yield) and its reactions, such as catalytic hydrogenation, Diels–Alder reaction, cyclopropanation, dihydroxylation,

*Keywords*: Amino acids; Asymmetric synthesis; Cyclopropanation; Ortho ester; Pyroglutamic acid.
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doi:10.1016/j.tet.2005.06.051

and Michael addition, which were found to proceed with excellent π-facial diastereoselectivity to the olefin without loss of enantiomeric purity at the α-position. As part of our ongoing development of the unsaturated orthopyroglutamate methodology for the asymmetric synthesis of unusual amino acids, we report herein a full account of the synthesis of L-(carboxycyclopropyl)glycines (L-CCGs) and 3,4-methano-L-prolines, the conformationally restricted analogues of L-glutamic acid and L-proline, respectively, via stereoselective cyclopropanation of 3,4-didehydro-L-pyroglutamic ABO ester **1**. Recently, considerable interest has been drawn to such conformationally constrained α-amino acids containing a cyclopropyl ring in their structure on account of their diverse biological activities.[9] In particular, L-CCGs are recognized as useful pharmacological tools for analyzing glutamate neurotransmitter systems.[10]

## 2. Results and discussion

### 2.1. Synthetic strategy

Since the first synthesis of racemic CCG-I by Ohfune and co-workers,[11] several enantioselective syntheses of L-CCGs have been reported mainly on the basis of cyclopropanation of chiral olefinic precursors,[12] where an appropriate choice of the geometrical isomer of the olefin or the starting olefin itself was necessary depending upon the desired diastereomer of CCGs. On the other hand, the first synthetic 3,4-methano-L-proline was obtained as a mixture of *cis* and *trans* isomers by Fujimoto and co-workers via addition of carbene to the corresponding dehydroproline derivative.[13] Later, several synthetic methods leading to the 3,4-methanoproline have appeared in the literature;[14] however, most of them were not enantioselective and gave a mixture of *cis* and *trans* isomers. To our knowledge, there are only two enantioselective routes to *cis*-3,4-methano-L-proline using chiral cyclopropane derivatives as starting materials.

This paper presents a novel stereocontrolled approach to L-CCGs and 3,4-methano-L-prolines from a common chiral olefinic precursor **1** as outlined in Figure 1. In general, an unsaturated lactam such as compound **1** can become a precursor only to L-CCG-III and *trans*-3,4-methano-L-proline because the cyclopropanation of the olefin is expected to occur exclusively from *trans* to the resident substituent at the 5-position (path A). The present strategy enables an alteration of the 3,4-methanoglutamic acid framework by carboxycyclopropanation of the olefin to introduce a new γ-carboxyl group into the cyclopropane ring as in path B followed by decarboxylation of the original γ-carboxyl group included in the pyroglutamate skeleton. Consequently, it becomes possible to obtain L-CCG-IV and *cis*-3,4-methano-L-proline, which can be formally accessible via *cis*-selective cyclopropanation of the olefin, from the *endo* adduct. Furthermore, it is feasible to obtain L-CCG-II, an extended derivative of CCGs, provided the corresponding *exo* adduct can be isolated in pure form. Usually, the extended form of CCGs can not be secured from the cyclopropanation of the cyclic olefin.

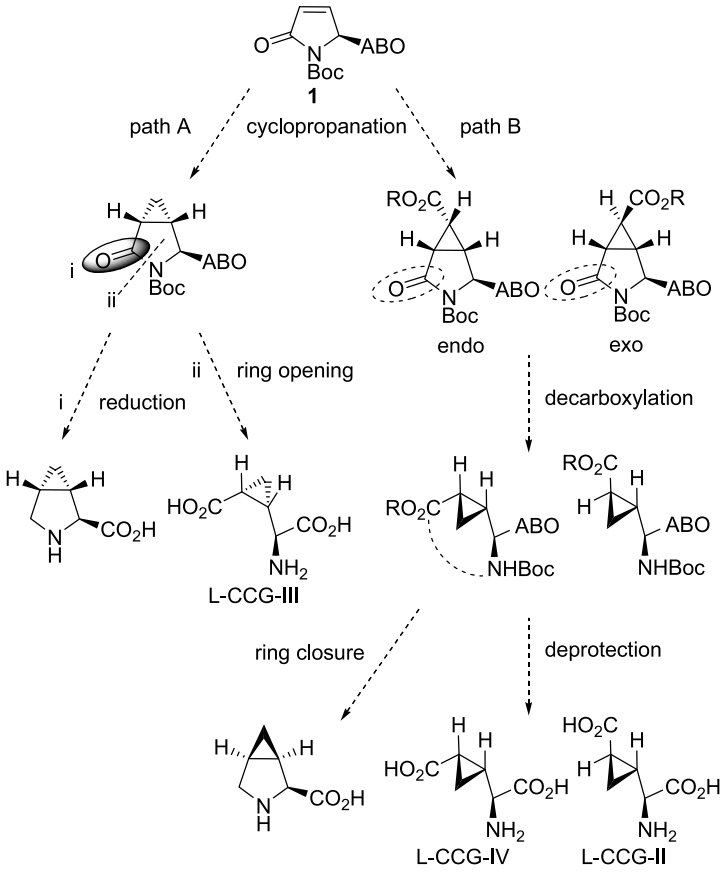
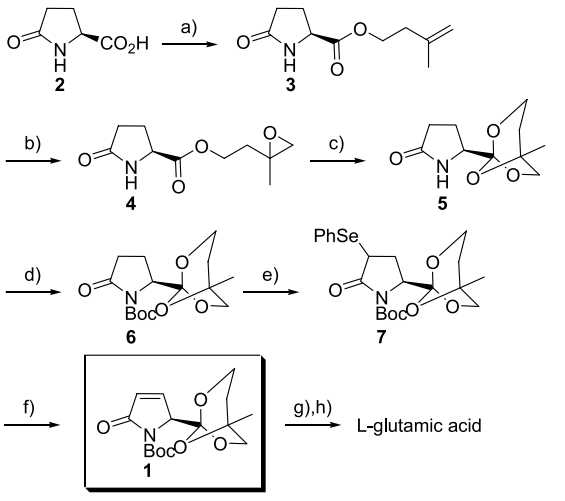



**Figure 1.** Stereocontrolled approach to L-CCGs and 3,4-methano-L-prolines.

### 2.2. Synthesis of unsaturated orthopyroglutamate 1

Construction of the 2,7,8-trioxabicyclo[3.2.1]octane (ABO) skeleton relied on zirconocene-catalyzed rearrangement of the epoxy ester toward the ortho ester reported by Wipf and co-workers.[6] According to the procedure shown in Scheme 1, the epoxy ester **4** was prepared from L-pyroglutamic acid **2** via condensation with 3-methyl-3-buten-1-ol in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) followed by epoxidation with 3-chloroperoxybenzoic acid (*m*CPBA). The obtained epoxy ester **4** was then treated with zirconocene catalyst, prepared in situ from zirconocene dichloride and silver perchlorate, to give an ABO ester **5**. Since the epoxidation of the chiral olefin **3** was non-stereoselective, the orthopyroglutamate **5** was obtained as a 1:1 mixture of diastereomers. In Scheme 1, only one enantiomeric form of the ABO skeleton is depicted for clarity. After protection of the amide proton with a *tert*-butoxycarbonyl (Boc) group, the orthopyroglutamate **6** was converted to a 3,4-didehydro-L-pyroglutamic ABO ester **1** using the well-established procedure involving phenylselenenylation and oxidative deselenenylation by hydrogen peroxide. The unsaturated orthopyroglutamate **1** was isolated in 49.8% yield based on the starting L-pyroglutamic acid (six steps) as a colorless crystalline solid, which was stable at room temperature for several months.

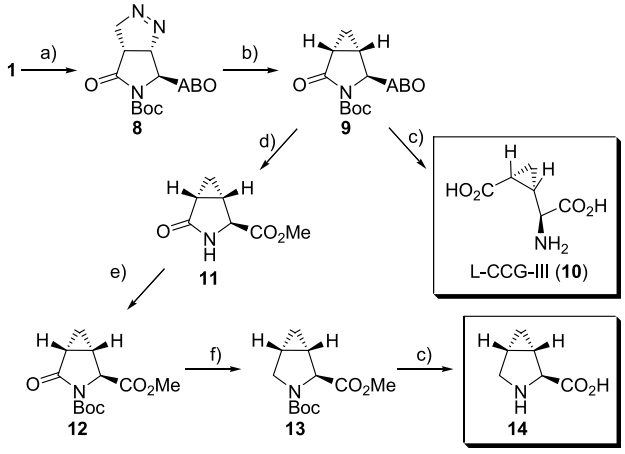



**Scheme 1.** Preparation of 3,4-didehydro-L-pyroglutamic ABO ester (**1**). Reagents and conditions: (a) $CH_2{=}C(Me)CH_2CH_2OH$, DCC, DMAP, $CH_2Cl_2$, quant; (b) *m*CPBA, $CH_2Cl_2$, 0 °C; (c) $Cp_2ZrCl_2$, $AgClO_4$, $CH_2Cl_2$; (d) $(tert\text{-}BuOCO)_2O$, DMAP, MeCN, 60% (three steps); (e) $NaN(SiMe_3)_2$, PhSeCl, DMPU–THF, −78 °C; (f) 30% $H_2O_2$, THF, 83% (two steps); (g) $H_2$, 10% Pd/C, MeOH; (h) 1 M HCl reflux; then Dowex 50W-X8, 77% (two steps).

In order to evaluate the chiral integrity at the α-position of the unsaturated orthopyroglutamate **1**, the olefin **1** was hydrogenated in the presence of 10% palladium on carbon followed by acidic hydrolysis in refluxing 1 M HCl to give L-glutamic acid in 77% yield. The enantiomeric purity of the obtained L-glutamic acid was found to be >99% ee by HPLC analysis using a chiral stationary column (MCIGEL CRS10W), suggesting that no racemization at the α-position occurred during the chemical transformations shown in Scheme 1.

### 2.3. Synthesis of L-CCG-III (10) and *trans*-3,4-methano-L-proline (14)

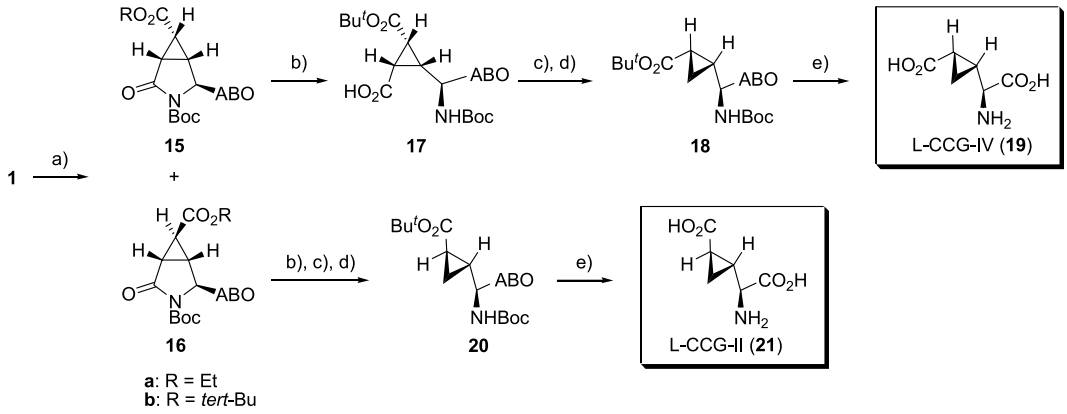
The synthetic course of (2*S*,1′*S*,2′*R*)-(carboxycyclopropyl) glycine (L-CCG-III, **10**) and *trans*-3,4-methano-L-proline (**14**) based on stereospecific cyclopropanation of the unsaturated orthopyroglutamate **1** is illustrated in Scheme 2. First of all, we investigated direct cyclopropanation of the unsaturated lactam **1** using a sulfoxonium ylide[15] as an alkylidene transfer reagent; however, the desired cycloadduct **9** could be obtained in only 32% yield. The cyclopropanation of the olefin **1** was next carried out by 1,3-dipolar cycloaddition of diazomethane followed by photolysis of the resultant pyrazoline **8** in the presence of benzophenone as a photosensitizer,[5b] affording the cycloadduct **9** in 61% yield. We could not detect the corresponding *cis* adduct in the reaction mixture, suggesting that exclusive addition of diazomethane to the olefin **1** opposite to the bulky ABO group occurred. In this case, the $Pd(OAc)_2$-catalyzed cycloaddtion of diazomethane to the olefin **1** gave no cycloadduct.




**Scheme 2.** Preparation of L-CCG-III (**10**) and *trans*-3,4-methano-L-proline (**14**). Reagents and conditions: (a) $CH_2N_2$, ether; (b) Hg-lamp (400 W), benzophenone, MeCN, 0 °C, 64% (two steps); (c) 1 M HCl reflux; then Dowex 50W-X8, **10**: 61%, **14**: 89%; (d) HCl–MeOH, 0 °C; (e) $(tert\text{-}BuOCO)_2O$, DMAP, MeCN, 56% (two steps); (f) $BH_3$–THF, 64%. ABO= 5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl.

Acidic hydrolysis of the cyclopropane derivative **9** in refluxing 1 M HCl and subsequent ion exchange operation afforded 61% yield of enantiomerically pure (>99% ee) L-CCG-III (**10**) in a single step, where ring-opening of the lactam skeleton, deprotection of the *N*-Boc group, and regeneration of the carboxyl functionality from the ABO ester occurred simultaneously. The stereochemistry of L-CCG-III (**10**) was determined by comparison of the $^1H$ NMR spectrum and specific rotation with the reported data.[12d]

To access the *trans*-3,4-methano-L-proline (**14**), we next investigated the chemoselective reduction of the lactam carbonyl moiety. Several attempts to reduce directly the carbonyl group of the bicyclic lactam **9** by borane or $LiEt_3BH$ were unsuccesfull. We eventually found that the corresponding methyl ester **12**, prepared by methanolysis of the ABO ester **9** followed by reprotection with the Boc group, underwent chemoselective reduction by borane–THF




**Scheme 3.** Preparation of L-CCG-II (**21**) and L-CCG-IV (**19**). Reagents and conditions: (a) $Me_2S{=}CHCO_2R$, DMSO, **15a**: 56%, **16a**: 40%, **15b**: 54%, **16b**: 29%; (b) 1 M LiOH, THF; (c) 4-methylmorpholine, $ClCO_2Bu^i$, THF; then 2-mercaptopyridine *N*-oxide, $Et_3N$, THF; (d) *tert*-BuSH, W-lamp (100 W), **18**: 85% (three steps), **20**: 51% (three steps); (e) 1 M HCl reflux; then Dowex 50W-X8, **19**: 86%, **21**: 84%. ABO=5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl.

to afford 3,4-methanoproline derivative **13** in 63% yield. Deprotection of compound **13** in refluxing 1 M HCl followed by treatment with Dowex 50W-X8 gave enantiomerically pure (>99% ee) *trans*-3,4-methano-L-proline (**14**) in 89% yield; and the structure was also confirmed by $^1$H NMR data and specific rotation.[13]

The present protocol provides an extremely facile and straightforward approach to L-CCG-III and *trans*-3,4-methano-L-proline with unprecedented complete stereocontrol.

### 2.4. Synthesis of L-CCG-IV (19) and L-CCG-II (21)

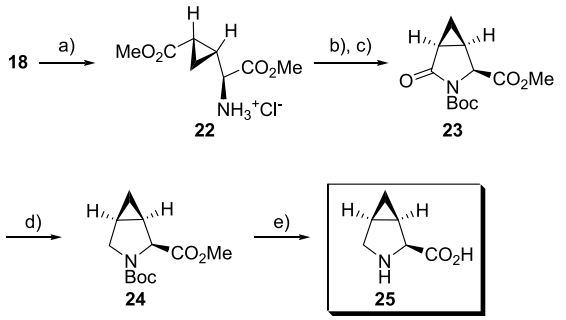
Scheme 3 shows the synthetic course of (2*S*,1′*R*,2′*S*)-(carboxycyclopropyl)glycine (L-CCG-IV, **19**) and (2*S*,1′*R*,2′*R*)-(carboxycyclopropyl)glycine (L-CCG-II, **21**) via alteration of the 3,4-methanoglutamic acid framework by a combination of carboxycyclopropanation of the olefin with sulfur ylides[16] and Barton decarboxylation reaction. When a solution of the unsaturated pyroglutamate **1** and ethyl dimethylsulfuranylideneacetate[17] in dimethyl sulfoxide was stirred at room temperature overnight, a mixture of *endo* and *exo* adducts, **15a** and **16a**, respectively, was obtained in a 57:42 ratio. Similar treatment of the olefin **1** with *tert*-butyl dimethylsulfuranylideneacetate[18] slightly improved the *endo* selectivity, giving a 67:33 mixture of **15b** and **16b**. This stereochemical outcome observed in the conjugate addition of sulfur ylides toward the unsaturated lactam **1** can be rationalized by considering a synclinal-like transition state proposed by Meyers and co-workers.[19] We also investigated the cyclopropanation using ethyl and *tert*-butyl diazoacetate in the presence or absence of a catalytic amount of $Pd(OAc)_2$; however, the expected cycloadducts could not be detected in the reaction mixture. The reason for the lower reactivity of the diazoacetates compared to diazomethane itself is probably due to the steric hindrance. Several efforts to obtain either diastereomer as a major product utilizing thermodynamic equilibration of the two products by treatment with a weak base or kinetic protonation of the corresponding enolate were unsuccessful. While the addition of the sulfur ylides across the carbon–carbon double bond is stereospecific, we could not obtain either an *endo* or *exo* adduct as a major product with overwhelming selectivity.

With the basic and nucleophilic reaction conditions employed in the succeeding processes in mind, only the *tert*-butyl ester derivatives **15b** and **16b** were adopted in this synthesis. The obtained *endo* and *exo* adducts **15b** and **16b** were chromatographically separable and were isolated in 54 and 29% yields, respectively. The chemoselective ring-opening of the lactam **15b** was carried out with 1 M LiOH to give crude carboxylic acid **17**. The acid **17** was then subjected to Barton decarboxylation reaction[20] using mercatopyridine *N*-oxide as a derivatizing reagent of the carboxyl group to afford fully protected (carboxycyclopropyl)glycine derivative **18** in 85% yield for the three steps. Finally, deprotection of compound **18** in refluxing 1 M HCl followed by the standard ion exchange operation afforded 86% yield of enantiomerically pure (99% ee) L-CCG-IV (**19**).

In order to obtain the corresponding extended form, similar treatment of the *exo* adduct **16b**, even though it was obtained as a minor product in the carboxycyclopropanation reaction, was carried out and afforded L-CCG-II (**21**) in 43% yield based on the adduct **16b** (four steps). The structures of L-CCG-IV (**19**) and L-CCG-II (**21**) were established by comparing their physical and spectral data with those reported in the literature.[12d]

### 2.5. Synthesis of *cis*-3,4-methano-L-proline (25)

Since the *cis*-3,4-methano-L-proline (**25**) is regarded as a cyclic analogue of L-CCG-IV (**19**), it is reasonable to employ a common precursor to these amino acids. There has been only one enantioselective route to *N*-Boc derivatives of L-CCG-IV and *cis*-3,4-methano-L-proline from a common key intermediate.[14b] In this work, we planned to prepare the methanoproline **25** via intramolecular cyclization of compound **18**, the precursor of L-CCG-IV, as shown in Scheme 4. Treatment of compound **18** with dry hydrogen chloride in methanol gave a crude dimethyl ester of L-CCG-IV as the hydrochloride salt **22**. The obtained hydrochloride **22** was neutralized to effect intramolecular cyclization reaction and subsequent protection of the resultant pyroglutamate derivative with the Boc group afforded 3,4-methano-L-pyroglutamate **23** in 40% yield based on compound **18** (three steps). According to the procedure for the synthesis of *trans*-3,4-methanoproline (**14**), the bicyclic




**Scheme 4.** Preparation of *cis*-3,4-methano-L-proline (**25**). Reagents and conditions: (a) HCl–MeOH, 0 °C; (b) aqueous $NaHCO_3$–THF; (c) (*tert*-$BuOCO)_2O$, DMAP, MeCN, 40% (three steps); (d) $BH_3$–THF, 31%; (e) 1 M HCl reflux; then Dowex 50W-X8, 70%.

lactam **23** was converted to the corresponding *cis*-3,4-methano-L-proline (**25**) via chemoselective reduction of the lactam carbonyl group followed by the standard deprotection protocol. The structure and enantiomeric purity (>99% ee) of the final product **25** were determined by comparison of their $^1H$ NMR data and the specific rotation with those reported.[13]

## 3. Conclusion

In this paper, we have demonstrated a novel approach to some pharmacologically important cyclopropane amino acids, such as L-CCGs and 3,4-methano-L-prolines, via stereoselective cyclopropanation of 3,4-didehydro-L-pyroglutamic ABO ester **1**.

Among the four possible diastereomers of L-CCGs, two folded and one extended forms, L-CCG-III, -IV, and -II, respectively, were prepared from a common starting olefin **1** in a stereodivergent way using a combination of cyclopropanation with diazomethane or sulfur ylides and Barton decarboxylation reaction. The *trans*- and *cis*-3,4-methano-L-prolines, which are considered to be cyclic derivatives of the folded L-CCGs, were also prepared from the precursors of L-CCG-III and -IV, respectively.

As expected, the ABO group serves as an efficient protective group, which completely prevents racemization at the α-position. Furthermore, the bulky ABO group provides steric hindrance that limits the approach of reagents from the β-face of the olefin, thus realizing stereospecific cyclopropanation. The ABO moiety can resist various reaction conditions employed in the present work and is amenable to regeneration of the carboxyl functionality through acidic treatment in the final stage of the synthetic processes.

## 4. Experimental

### 4.1. General

Melting points are uncorrected. $^1H$ and $^{13}C$ NMR spectra were measured at 400 and 100 MHz, respectively. All chemical shifts are reported as $\delta$ values (ppm) relative to residual chloroform ($\delta_H$ 7.26), sodium 3-(trimethylsilyl)[2,2,3,3-$D_4$]propionate ($\delta_H$ 0.00), or the central peak of deuteriochloroform ($\delta_C$ 77.0). High-resolution mass spectra (HRMS) were determined using perfluorokerosene as an internal standard. Optical rotations were measured on a HORIBA SEPA-200 polarimeter. Solvents and reagents were of commercial grade and were purified if necessary.

**4.1.1. (5*S*)-2-Pyrrolidone-5-carboxylic acid 3-methyl-3-butenyl ester (3).** To a solution of 1,3-dicyclohexylcarbodiimide (DCC, 12.3 g, 59.7 mmol), 4-dimethylaminopyridine (DMAP, 610 mg, 5.00 mmol) and 3-methyl-3-buten-1-ol (5.17 g, 60.1 mmol) in dichloromethane (150 mL) was added L-pyroglutamic acid (**2**, 6.45 g, 50.0 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. After removal of the precipitated 1,3-dicyclohexylurea, the filtrate was washed with saturated aqueous $NH_4Cl$ and concentrated. The residue was dissolved in ether and extracted several times with water. The combined aqueous extracts were evaporated and the residue was dissolved in chloroform. The organic layer was dried over $MgSO_4$ and concentrated to give quantitative yield of the title compound **3** (9.85 g, 50.0 mmol) as an oil. $^1H$ NMR ($CDCl_3$) $\delta$ 1.75 (s, 3H), 2.17–2.51 (m, 6H), 4.21–4.32 (m, 3H), 4.73 (br s, 1H), 4.82 (br s, 1H), 6.15 (s, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.4, 24.1, 28.5, 35.8, 54.9, 62.4, 111.7, 140.5, 171.6, 177.9. HRMS (EI, 70 eV) *m/z* 197.1052 ($M^+$, calcd for $C_{10}H_{15}NO_3$ 197.1031).

**4.1.2. (5*S*)-1-*tert*-Butoxycarbonyl-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-2-pyrrolidone (6).** To a solution of 3-chloroperoxybenzoic acid (*m*CPBA, 13.0 g, 75.0 mmol) in dichloromethane (150 mL) was added a solution of ester **3** (9.85 g, 50.0 mmol) in dichloromethane (50 mL) at 0 °C and the reaction mixture was stirred for 4 h. After removal of the solvent, the residue was chromatographed on silica gel (chloroform/methanol=90:10) to give epoxide **4** (10.7 g) in quantitative yield. Although the obtained epoxide **4** was still contaminated with 3-chlorobenzoic acid, the sample could be used in the next step without further purification.

To a suspension of bis(cyclopentadienyl)zirconium dichloride (1.47 g, 5.03 mmol) and $AgClO_4$ (1.10 g, 5.31 mmol) in dichloromethane (60 mL) was added a solution of the obtained crude epoxide **4** in dichloromethane (40 mL) and the mixture was stirred for 2 days. After addition of saturated aqueous $NaHCO_3$, the insoluble materials were filtered off. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated to afford crude orthopyroglutamate **5**.

The obtained orthoester **5** was then treated with di-*tert*-butyl dicarbonate (13.2 g, 60.6 mmol) and DMAP (6.20 g, 50.8 mmol) in acetonitrile (80 mL) at room temperature for 1.5 h. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous $KHSO_4$ and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate=50:50) to afford 9.40 g (60%, three steps) of the title compound **6** as an oil. $^1H$ NMR ($CDCl_3$) $\delta$ 1.34 and 1.35 (2s, 3H), 1.43–1.48 (m, 1H), 1.51 (s, 9H), 1.98–2.35 (m, 4H), 2.74–2.84 (m, 1H), 3.45–3.49 (m, 1H), 3.85–3.91 (m,

1H), 3.97–4.14 (m, 2H), 4.44 and 4.48 (2d, $J=9$ Hz, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 19.2 and 19.6, 21.2, 27.1 and 27.2, 31.2, 33.05 and 33.08, 57.9 and 58.5, 58.75 and 58.83, 72.9 and 73.2, 78.5 and 78.6, 81.59 and 81.61, 119.6 and 119.7, 149.09 and 149.12, 174.6. HRMS (EI, 30 eV) *m/z* 313.1525 ($M^+$, calcd for $C_{15}H_{23}NO_6$ 313.1556).

**4.1.3. (5*S*)-1-*tert*-Butoxycarbonyl-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-5*H*-2-pyrrolinone (1).** A solution of 1 M sodium bis(trimethylsilyl)amide in THF (61 mL, 61 mmol) was treated with *N*,*N*′-dimethylpropyleneurea (8.2 mL, 68 mmol) at 0 °C under an argon atmosphere for 20 min, cooled to −78 °C, and treated with a solution of compound **6** (7.90 g, 25.2 mmol) in THF (50 mL). After 0.5 h, a solution of phenylselenenyl chloride (5.30 g, 27.7 mmol) in THF (50 mL) was added and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous $NH_4Cl$ and the mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give 3-phenylseleno-2-pyrrolidone derivative **7**.

To a solution of the obtained crude phenylselenide **7** in THF (300 mL) was added dropwise 30% $H_2O_2$ (15 mL, 132 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel. Elution with a mixture of hexane and ethyl acetate (50:50) afforded 6.48 g (83%, two steps) of the title compound **1** as a colorless solid, mp 110–112 °C. $^1$H NMR ($CDCl_3$) $\delta$ 1.34 and 1.35 (2s, 3H), 1.43–1.48 (m, 1H), 1.52 (s, 9H), 1.99 and 2.08 (2m, 1H), 3.45 and 3.47 (2d, $J=2$ Hz, 1H), 3.84–4.1 (m, 3H), 4.97 and 5.03 (2dd, $J=2$, 2 Hz, 1H), 6.11 (m, 1H), 7.19 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 21.6 and 21.7, 27.7 and 27.8, 33.6, 59.4 and 59.5, 63.3 and 63.9, 73.4 and 73.5, 79.1 and 79.5, 82.6 and 82.7, 117.9 and 118.0, 127.3, 146.1, 149.1, 169.8. HRMS (EI, 30 eV) *m/z* 312.1447 [$(M+1)^+$, calcd for $C_{15}H_{22}NO_6$ 312.1485].

**4.1.4. (1*R*,4*S*,5*S*)-3-*tert*-Butoxycarbonyl-4-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-3-azabicyclo[3.1.0]hexan-2-one (9).** To a solution of olefin **1** (3.11 g, 10 mmol) in ether (50 mL) was added an excess ethereal solution of diazomethane (ca. 8.3 equiv) at 0 °C and the mixture was stirred at room temperature in the dark for 3.5 h. The reaction was quenched by addition of anhydrous $CaCl_2$ and, after filtration, evaporation of the solvent gave very unstable pyrazoline derivative **8** (3.53 g).

An acetonitrile solution (500 mL) of the obtained pyrazoline **8** in the presence of benzophenone (1.87 g, 10.3 mmol) was irradiated with a 400 W medium-pressure mercury lamp at 0 °C under an argon atmosphere for 20 min. After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate=50:50) to afford the title compound **9** (2.09 g, 64%) as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.65–0.69 (m, 1H), 1.08–1.13 (m, 1H), 1.35 and 1.37 (2s, 3H), 1.45–1.50 (m, 1H), 1.47 and 1.48 (2s, 9H), 1.93–2.14 (m, 3H), 3.47–3.51 (m, 1H), 3.88–4.13 (m, 3H), 4.38 and 4.42 (2s, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 10.8, 12.0 and 12.3, 20.2, 21.7 and 21.8, 27.8, 33.8, 59.4 and 59.5, 60.0, 73.6 and 73.8, 79.0 and 79.3, 82.3, 119.3, 150.3, 174.3. HRMS (EI, 70 eV) *m/z* 326.1604 [$(M+1)^+$, calcd for $C_{16}H_{24}NO_6$ 326.1648].

**4.1.5. (2*S*,1′*S*,2′*R*)-2-(Carboxycyclopropyl)glycine (10, L-CCG-III).** A mixture of compound **9** (318 mg, 0.978 mmol) and 1 M HCl (30 mL) was heated to reflux for 3 h. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on Dowex 50W-X8 and elution with 1 M $NH_4OH$ to give the ammonium salt of compound **10**. The salt was then dissolved in water and the solution was acidified to pH 3 with 1 M HCl. The precipitated solids were collected by filtration and recrystallized from water–acetone to give the title compound **10** (95.0 mg, 61%) as colorless crystals, mp 205–207 °C (lit.[12d] mp 192–197 °C dec). $[\alpha]_D^{23}$ +20.7 (*c* 0.54, $H_2O$) (lit.[12d] $[\alpha]_D^{22}$ +20.8 (*c* 0.52, $H_2O$)). $^1$H NMR ($D_2O$) $\delta$ 1.37 (ddd, $J=6$, 6, 7 Hz, 1H), 1.52 (ddd, $J=6$, 9, 9 Hz, 1H), 1.77 (dddd, $J=7$, 8, 9, 11 Hz, 1H), 1.99 (ddd, $J=6$, 8, 9 Hz, 1H), 4.21 (d, $J=11$ Hz, 1H).

**4.1.6. (1*R*,4*S*,5*S*)-3-*tert*-Butoxycarbonyl-4-methoxycarbonyl-3-azabicyclo[3.1.0]hexan-2-one (12).** A solution of compound **9** (534 mg, 1.64 mmol) in methanol (40 mL) was cooled in an ice bath and a slow stream of HCl was introduced with stirring to saturation. After being stirred at room temperature for 3 h, the solution was concentrated and the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give crude methyl pyroglutamate derivative **11** (187 mg).

The obtained ester **11** was treated with di-*tert*-butyl dicarbonate (640 mg, 2.94 mmol) and DMAP (310 mg, 2.54 mmol) in acetonitrile (20 mL) at room temperature overnight. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous $KHSO_4$ and brine, dried over $MgSO_4$, and concentrated to give 233 mg (56%, two steps) of the title compound **12** as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.84 (ddd, $J=4$, 4, 5 Hz, 1H), 1.24 (ddd, $J=5$, 8, 9 Hz, 1H), 1.45 (s, 9H), 1.95 (ddd, $J=4$, 6, 8 Hz, 1H), 2.06 (dddd, $J=1$, 4, 6, 9 Hz, 1H), 3.79 (s, 3H), 4.51 (s, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 12.0, 14.9, 20.4, 27.8, 52.7, 60.2, 83.4, 149.5, 170.6, 172.6. HRMS (EI, 70 eV) *m/z* 255.1107 ($M^+$, calcd for $C_{12}H_{17}NO_5$ 255.1124).

**4.1.7. (1*S*,2*S*,5*R*)-3-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-azabicyclo[3.1.0]hexane (13).** To a solution of compound **12** (83.0 mg, 0.325 mmol) in THF (10 mL) was added a 1 M solution of borane in THF (1 mL, 1 mmol) under an argon atmosphere and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of methanol and, after being stirred for 1 h, the mixture was diluted with dichloromethane. The organic layer was then dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate=50:50) to afford the title compound **13** (50.0 mg, 64%) as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.319 (ddd, $J=5$, 9, 9 Hz, 1H), 0.742 (ddd, $J=5$, 7, 15 Hz, 1H), 1.39 and 1.44 (2s, 9H), 1.49–1.56 (m, 1H), 1.57–1.62 (m, 1H), 3.54 (d, $J=2$ Hz, 1H), 3.58 (d, $J=4$ Hz, 1H), 3.74

and 3.75 (2s, 3H), 4.27 and 4.39 (2s, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 8.84 and 9.13, 14.9 and 15.4, 18.9 and 19.8, 28.3 and 28.4, 48.3 and 48.4, 52.0 and 52.1, 60.9 and 61.5, 80.0, 154.7 and 155.2, 172.7 and 172.9. HRMS (EI, 70 eV) *m/z* 241.1314 ($M^+$, calcd for $C_{12}H_{19}NO_4$ 241.1313).

**4.1.8. (2*S*,3*S*,4*R*)-3,4-Methanoproline (14).** A mixture of compound **13** (255 mg, 1.06 mmol) and 1 M HCl (26 mL) was heated to reflux for 3 h. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on Dowex 50W-X8 and elution with 1 M $NH_4OH$ to give the title compound **14** (120 mg, 89%) as colorless crystals (water–acetone), mp 263–265 °C (lit.[13] mp 245–250 °C). $[\alpha]_D^{20}$ −94.8 (*c* 0.5, $H_2O$) (lit.[13] $[\alpha]_D^{20}$ −94 (*c* 1.0, $H_2O$)). $^1$H NMR ($D_2O$) $\delta$ 0.38–0.42 (m, 1H), 0.93–0.99 (m, 1H), 1.80–1.86 (m, 1H), 1.99–2.04 (m, 1H), 3.45 (d, *J*=11 Hz, 1H), 3.58 (dd, *J*=4, 12 Hz, 1H), 4.13 (s, 1H).

**4.1.9. (1*S*,4*S*,5*R*,6*R*)-3,6-Di-*tert*-butoxycarbonyl-4-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-3-azabicyclo-[3.1.0]hexan-2-one (15b) and (1*S*,4*S*,5*R*,6*S*)-isomer (16b).** A solution of olefin **1** (5.07 g, 16.3 mmol) and *tert*-butyl dimethylsulfuranylideneacetate (5.70 g, 32.4 mmol) in DMSO (100 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl acetate, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (hexane/ethyl acetate=50:50) to give compound **16b** (1.99 g, 29%) as colorless crystals, mp 173–178 °C. $^1$H NMR ($CDCl_3$) $\delta$ 1.35 and 1.37 (2s, 3H), 1.43 (s, 9H), 1.47 (s, 9H), 1.57–1.67 (m, 1H), 1.71 (dd, *J*=3, 3 Hz, 1H), 2.00–2.14 (m, 1H), 2.41 (d, *J*=3 Hz, 1H), 2.45 and 2.47 (2d, *J*=3 Hz, 1H), 3.46–3.51 (m, 1H), 3.88–4.13 (m, 3H), 4.44 and 4.48 (2s, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 20.0 and 20.3, 21.7, 25.6, 27.7, 27.9, 28.4 and 28.5, 33.7, 59.3 and 59.4, 59.6 and 59.9, 73.6 and 73.8, 79.2 and 79.4, 81.8, 82.7 and 82.8, 118.8, 149.5, 168.7 and 168.8, 171.3. HRMS (EI, 70 eV) *m/z* 426.2128 [$(M+1)^+$, calcd for $C_{21}H_{32}NO_8$ 426.2169].

Further elution with a mixture of hexane and ethyl acetate (50:50) afforded the compound **15b** (3.75 g, 54%) as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 1.31 and 1.32 (2s, 3H), 1.36 (s, 9H), 1.42 (s, 9H), 1.45–1.47 (m, 1H), 1.94–2.08 (m, 2H), 2.19–2.27 (m, 2H), 3.45–3.46 (m, 1H), 3.83–4.09 (m, 3H), 4.51 and 4.54 (2s, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 18.9 and 19.1, 21.4, 24.7, 25.9 and 26.0, 27.4 and 27.5, 27.6, 33.5, 56.9 and 57.4, 59.1 and 59.3, 73.2 and 73.5, 77.2, 78.8 and 79.1, 81.4 and 81.8, 118.9 and 119.0, 149.0, 166.1 and 166.2, 170.3. HRMS (EI, 70 eV) *m/z* 425.2050 ($M^+$, calcd for $C_{21}H_{31}NO_8$ 425.2056).

**4.1.10. (2*S*,1′*R*,2′*S*)-*N*-*tert*-Butoxycarbonyl-2-((*tert*-butoxycarbonyl)cyclopropyl)glycine ABO ester (18).** To a solution of compound **15b** (2.37 g, 5.58 mmol) in THF (60 mL) was added a solution of 1 M aqueous LiOH (20 mL) and the mixture was stirred at room temperature overnight. The solution was then acidified to pH 4 with 10% aqueous citric acid and extracted with chloroform. The organic layer was dried over $MgSO_4$ and concentrated to give compound **17** (2.47 g) in quantitative yield.

To a solution of the obtained acid **17** (912 mg, 2.06 mmol) in THF (40 mL) were added 4-methylmorpholine (250 mg, 2.47 mmol) and isobutyl chloroformate (337 mg, 2.47 mmol) at −15 °C under an argon atmosphere. After 5 min, a solution of 2-mercaptopyridine *N*-oxide (326 mg, 2.56 mmol) and triethylamine (259 mg, 2.56 mmol) in THF (20 mL) was added and the mixture was stirred in the dark for 1 h. After removal of the precipitated triethylamine hydrochloride, the filtrate was concentrated and the residue was chromatographed on silica gel in the dark. Elution with a mixture of hexane and ethyl acetate (50:50) gave quantitative yield (1.14 g) of the corresponding ester, which was very unstable and used immediately in the next step.

A solution of the obtained ester and 2-methyl-2-propanethiol (1.88 g, 20.8 mmol) in THF (40 mL) was irradiated with a 100 W tungsten lamp at room temperature under an argon atmosphere for 1 h. After removal of the solvent, the residue was extracted with ethyl acetate, washed successively with 0.1 M aqueous $NaHCO_3$, 0.5 M aqueous $KHSO_4$, and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate=70:30) to afford the title compound **18** (701 mg, 85%, three steps) as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.86–0.91 (m, 1H), 1.16–1.22 (m, 1H), 1.35 and 1.36 (2s, 3H), 1.40–1.42 (dd, *J*=4, 4 Hz, 1H), 1.45 (s, 18H), 1.60–1.70 (m, 2H), 1.99–2.08 (m, 1H), 3.44–3.50 (m, 1H), 3.82–3.88 (m, 1H), 3.99–4.08 (m, 2H), 4.26 (br s, 1H), 4.85 (br s, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 10.4, 20.3 and 20.4, 21.8, 21.9, 28.2, 28.3, 33.8, 51.4, 59.1 and 59.2, 73.7, 73.9, 78.9, 79.9, 119.6, 155.4, 171.4. HRMS (EI, 70 eV) *m/z* 399.2257 ($M^+$, calcd for $C_{20}H_{33}NO_7$ 399.2291).

**4.1.11. (2*S*,1′*R*,2′*S*)-2-(Carboxycyclopropyl)glycine (19, L-CCG-IV).** A mixture of compound **18** (219 mg, 0.549 mmol) and 1 M HCl (30 mL) was heated to reflux for 3 h. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on Dowex 50W-X8 and elution with 1 M $NH_4OH$ to give the ammonium salt of compound **19**. The salt was then dissolved in water and the solution was acidified to pH 3 with 1 M HCl. The precipitated solids were collected by filtration and recrystallized from water–acetone to give the title compound **19** (75.0 mg, 86%) as colorless crystals, mp 180–182 °C (lit.[12d] mp 178–180 °C). $[\alpha]_D^{22}$ +103.7 (*c* 0.2, $H_2O$) (lit.[12d] $[\alpha]_D^{26}$ +103.4 (*c* 0.5, $H_2O$)). $^1$H NMR ($D_2O$) $\delta$ 1.13 (ddd, *J*=6, 6, 7 Hz, 1H), 1.29 (ddd, *J*=6, 9, 9 Hz, 1H), 1.66 (dddd, *J*=7, 9, 9, 10 Hz, 1H), 2.02 (ddd, *J*=6, 9, 9 Hz, 1H), 3.83 (d, *J*=10 Hz, 1H).

**4.1.12. (2*S*,1′*R*,2′*R*)-*N*-*tert*-Butoxycarbonyl-2-((*tert*-butoxycarbonyl)cyclopropyl)glycine ABO ester (20).** According to the procedure for the preparation of compound **18**, ring-opening of lactam **16** (504 mg, 1.14 mmol) followed by the Barton decarboxylation reaction afforded 51% (three steps) yield of the title compound **20** (233 mg) as an oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.86–0.91 (m, 1H), 0.96–1.02 (m, 1H), 1.20–1.26 (m, 1H), 1.35 and 1.37 (2s, 3H), 1.42 (s, 9H), 1.43 (s, 9H), 1.51–1.62 (m, 2H), 1.99–2.08 (m, 1H), 3.45–3.51 (m, 1H), 3.67–3.73 (m, 1H), 3.84–3.91 (m, 1H), 4.01–4.09 (m, 2H), 4.65–4.76 (br s, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 10.9, 19.5 and 19.7, 21.8, 28.1, 28.3, 29.6, 33.8, 54.8, 59.3,

73.9 and 74.0, 79.0 and 79.1, 79.5, 79.9, 119.6, 155.9, 173.3. HRMS (EI, 70 eV) *m/z* 400.2335 [$(M+1)^+$, calcd for $C_{20}H_{34}NO_7$ 400.2341].

**4.1.13. (2*S*,1′*R*,2′*R*)-2-(Carboxycyclopropyl)glycine (21, L-CCG-II).** According to the procedure for the preparation of compound **19**, hydrolysis and deprotection of compound **20** (293 mg, 0.734 mmol) gave the title compound **21** (98.0 mg, 84%) as colorless crystals (water–acetone), mp 265–270 °C dec (lit.[12d] mp 255–258 °C dec). $[\alpha]_D^{23}$ −20.0 (*c* 0.1, $H_2O$) (lit.[12d] $[\alpha]_D^{25}$ −20.2 (*c* 0.51, $H_2O$)). $^1H$ NMR ($D_2O$) $\delta$ 1.04 (ddd, $J=5$, 7, 9 Hz, 1H), 1.21 (ddd, $J=5$, 5, 9 Hz, 1H), 1.67 (dddd, $J=4$, 7, 9, 9 Hz, 1H), 1.80 (ddd, $J=4$, 5, 9 Hz, 1H), 3.39 (d, $J=9$ Hz, 1H).

**4.1.14. (1*S*,4*S*,5*R*)-3-*tert*-Butoxycarbonyl-4-methoxycarbonyl-3-azabicyclo[3.1.0]hexan-2-one (23).** A solution of compound **18** (1.32 g, 3.31 mmol) in methanol (300 mL) was cooled in an ice bath and a slow stream of HCl was introduced with stirring to saturation. After being stirred at room temperature overnight, the solution was concentrated and the residue was dissolved in water. The aqueous layer was washed with chloroform and concentrated to give quantitative yield of crude methyl ester **22**.

The obtained ester was then dissolved in a mixture of water (100 mL) and THF (100 mL) and the pH was adjusted to 8 by adding $NaHCO_3$. After being stirred at room temperature overnight, the mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$ and concentrated to give a crude lactam (372 mg). The obtained lactam was then treated with di-*tert*-butyl dicarbonate (631 mg, 2.89 mmol) and DMAP (297 mg, 2.43 mmol) in acetonitrile (30 mL) at room temperature overnight. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous $KHSO_4$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate=50:50) to give 341 mg (40%, three steps) of the title compound **23** as an oil. $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (ddd, $J=5$, 8, 9 Hz, 1H), 1.14 (ddd, $J=5$, 6, 6 Hz, 1H), 1.37 (s, 9H), 2.02 (ddd, $J=4$, 6, 9 Hz, 1H), 2.12 (dddd, $J=4$, 6, 6, 8 Hz, 1H), 3.72 (s, 3H), 4.61 (d, $J=6$ Hz, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 8.8, 14.6, 21.2, 27.7, 52.4, 58.5, 83.4, 149.1, 169.8, 172.4. HRMS (EI, 70 eV) *m/z* 255.1107 ($M^+$, calcd for $C_{12}H_{17}NO_5$ 255.1101).

**4.1.15. (1*R*,2*S*,5*S*)-3-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-azabicyclo[3.1.0]hexane (24).** According to the procedure for the preparation of compound **13**, reduction of lactam **23** (341 mg, 1.34 mmol) afforded the title compound **24** (101 mg, 31%) as an oil. $^1H$ NMR ($CDCl_3$) $\delta$ 0.62 (m, 1H), 0.72 (m, 1H), 1.35 and 1.40 (2s, 9H), 1.56–1.61 (m, 1H), 1.77–1.83 (m, 1H) 3.49–3.58 (m, 2H), 3.71 and 3.72 (2s, 3H), 4.30 and 4.34 (2d, $J=5$ Hz, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 8.26 and 8.38, 15.8 and 16.5, 19.7 and 20.6, 28.1 and 28.3, 49.7, 51.8 and 51.9, 60.3 and 60.5, 80.0 and 80.1, 154.2, 171.8. HRMS (EI, 70 eV) *m/z* 241.1314 ($M^+$, calcd for $C_{12}H_{19}NO_4$ 241.1355).

**4.1.16. (2*S*,3*R*,4*S*)-3,4-Methanoproline (25).** According to the procedure for the preparation of compound **14**, hydrolysis and deprotection of compound **24** (101 mg, 0.419 mmol) gave the title compound **25** (37.0 mg, 70%) as colorless crystals (water–acetone), mp 224–230 °C (lit.[13] mp 235–245 °C). $[\alpha]_D^{20}$ −130 (*c* 0.12, $H_2O$) (lit.[13] $[\alpha]_D^{20}$ −131 (*c* 0.1, $H_2O$)). $^1H$ NMR ($D_2O$) $\delta$ 0.508 (ddd, $J=4$, 5, 6 Hz, 1H), 0.804 (ddd, $J=6$, 7, 8 Hz, 1H), 1.83–1.89 (m, 1H), 2.01–2.05 (m, 1H), 3.51 (d, $J=2$ Hz, 2H), 4.32 (d, $J=5$ Hz, 1H).

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