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Diastereo- and Enantioselective Synthesis of Orthogonally Protected 2,4-Diaminocyclopentanecarboxylates: A Flip from β-Amino- to β,γ-Diaminocarboxylates

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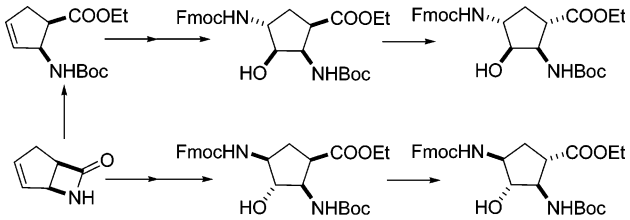

Conformationally restricted, orthogonally protected 2,4-diaminocarboxylates with a cyclopentane skeleton were efficiently synthesized from β-lactam **6**, the syntheses involving strategies of diastereoselective epoxidation of the β-lactam and the corresponding monoprotected amino esters with opposite selectivities followed by regioselective opening of the oxirane ring with sodium azide. The enantiomers were also prepared. This new class of compounds can be regarded not only as conformationally constrained β,γ-diamino acid derivatives but also as potential functionalized carbocyclic nucleoside precursors.

[3]Introduction

Among the large family of γ-amino acids, 4-aminocyclopent-2-ene carboxylic acid **1** and derivatives can serve as conformationally constrained, potentially valuable scaffolds for pharmaceutical assays as anticancer and antiviral agents and as important building blocks in the synthesis of peptides.[1] They may also be regarded as conformationally restricted GABA mimetics.[2] Various mono- and dihydroxylated γ-aminocyclopentanecarboxylic acid diastereomers have been incorporated into tripeptide sequences.[3]

Further, the 3-azido-4-hydroxycyclopentanoic acid moiety has been reported as a synthetic scaffold for β-turn mimetics.[4] These compounds may also be applied as precursors for the synthesis of carbasugars and carbocyclic nucleosides.

Carbocyclic nucleosides are a family of synthetic and naturally occurring compounds which have attracted great interest among chemists and biochemists during recent years. Many of them exert important biological activities[5,6] and are

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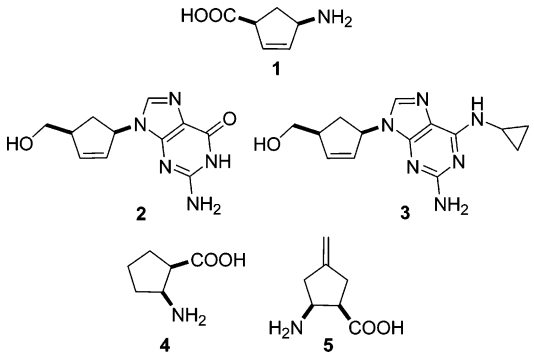
potentially effective therapeutic agents for the treatment of viral infections.[7] A number of synthetic carbocyclic nucleosides exhibit antitumor,[7] cerebroprotective, and cardioprotective[8] effects. Several naturally occurring carbocyclic nucleosides, such as aristeromycin,[9] neplanocin A,[10] and some of their derivatives, display antitumor and antibiotic activity.[11] Synthetic carbocyclic nucleosides with significant therapeutic properties have also been discovered. For example, carbovir (**2**) and abacavir (**3**) with antiviral properties have been reported to inhibit the replication of HIV.[1g,12]



The alicyclic β-amino acids have gained great interest in recent years in view of their pharmacological potential.[13] The natural cispentacin (**4**), an antifungal antibiotic with a cyclopentane skeleton, is one of the most important derivatives. It is additionally a component of the antibiotic amipurimycin.[13a] (1*R*,2*S*)-2-Amino-4-methylenecyclopentanecarboxylic acid (icofungipen) **5** is known as an antifungal agent. Cyclic, conformationally rigid β-amino acids such as *trans*-2-aminocyclopentanecarboxylic acid or 2-amino-3-methoxycyclopentanecarboxylic acid have been used as building blocks in the synthesis of peptides.[14]

The aim of the present work was the synthesis of orthogonally protected 2,4-diaminocyclopentanecarboxylate diastereomers containing both the β- and the γ-amino ester unit on a cyclopentane moiety.

Results and Discussion

Our synthetic strategy was based on the functionalization of the olefinic bond of the readily available azetidinone **6**[15] via its

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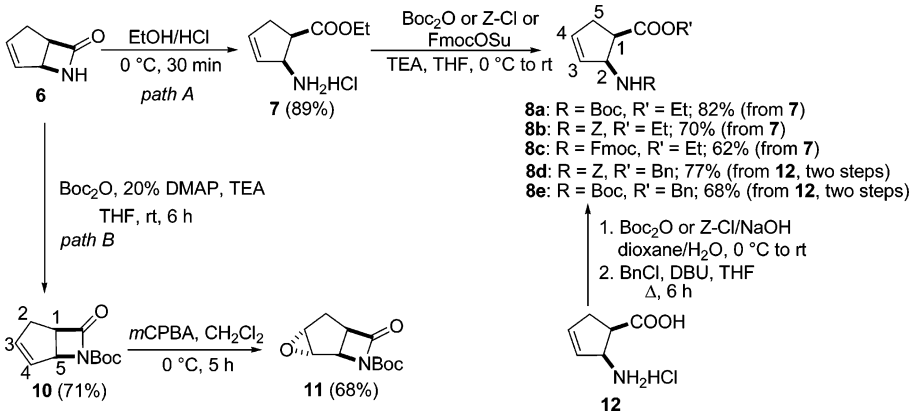
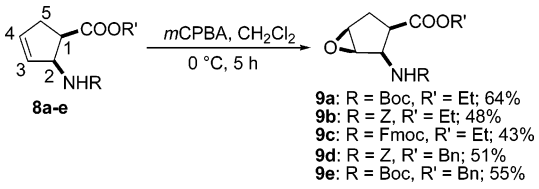
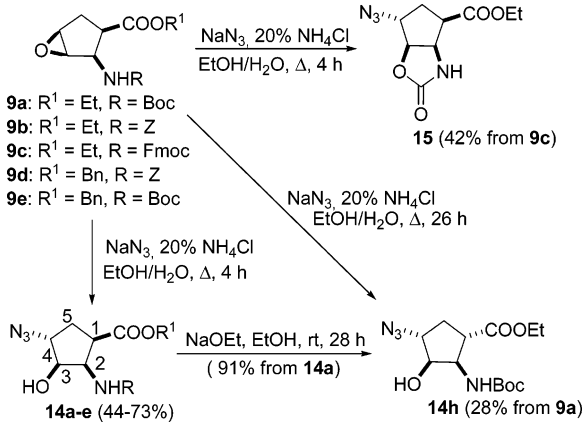
SCHEME 1. Synthesis of Amino Esters 8a−e and Epoxy Lactam 11



SCHEME 2. Synthesis of Epoxy Amino Esters 9a−e



SCHEME 3. Synthesis of 2-Amino-4-azidocarboxylates 14a−e and 14h



epoxidation by two different routes with opposite diastereoselectivities. In the first approach, monoprotected β-amino ethyl esters **8a−c** were prepared in good yields from β-lactam **6** through amino ester **7** (Scheme 1, path A). In the next step, the β-amino esters **8a−c** were submitted to epoxidation of the olefinic bond (Scheme 2). Epoxidation of a mono *N*-protected alkene (carbamate or amide) with peracids is known to give a high degree of cis selectivity, presumably via a hydrogen-bonding interaction of the amide and the peracidic reagent in the transition state of the reaction.[16] We studied the epoxidations of amino ethyl esters **8a−c** with Boc, Fmoc, or Z protecting groups in the presence of *m*-chloroperbenzoic acid in dichloromethane. As expected in all cases, the reaction proceeded diastereoselectively, furnishing the *cis*-epoxides **9a−c** as single diastereoisomers in yields of 43−64% yield (Scheme 2).

In a similar way, *cis*-epoxy derivatives of benzyl aminocarboxylates **9d** and **9e** were synthesized in yields of 51% and 55% by the epoxidation of esters **8d** and **8e** (Scheme 2). Benzyl aminocarboxylates **8d** and **8e** were prepared from lactam **6** via the protected amino acids **13a** and **13b**, whose carboxylic group was benzylated with benzyl chloride in refluxing THF in the presence of DBU (Scheme 1).

With the above epoxidation procedure, the presence of a monoprotected amino group (carbamate) on the cyclopentene skeleton always led to cis selectivity, resulting in the *cis*-epoxy amino esters **9a−e**.

It was expected that introduction of the oxirane skeleton trans to the 5-amino group on the cyclopentanecarboxylic amino ester moiety of **10** would be possible without changing the reaction conditions or the oxidizing agent, but starting from the Boc-protected lactam **10** (Scheme 1, path B). In lactam **10**, the tertiary amine would not exert the cis-stereodirecting effect observed earlier in the transition state of the epoxidation of esters **8a−e**. For this reason, the Boc-protected lactam **10** was treated with *m*-chloroperbenzoic acid at 0 °C for 5 h (Scheme 1, path B). In this case, in consequence of the presence of the bulky Boc group, the "*trans*"-epoxide **11** was formed exclusively. The main reason for the opposite, trans selectivity of the lactam epoxidation may be the fact that in lactam **10** the lone pair of electrons of the nitrogen is distributed between the carbamate and the carbonyl of the lactam, lowering the negative charge on the carbamate oxygen and decreasing the possibility of hydrogen bonding with the peracid. In lactam **10**, therefore, not only steric but also electronic effects account for the trans diastereoselectivity.

An extra amino group was introduced in position 4 on the cyclopentane skeleton of amino esters **8a−e** by opening of the oxirane ring in epoxy aminocarboxylates **9a−e**. For this, the azido group was used as nitrogen source. The reactions with NaN_3 in refluxing EtOH−H_2O in the presence of a catalytic amount of NH_4Cl for 4 h in all cases proceeded regio- and diastereoselectively, giving 4-azido-2-amino esters **14a−e** in yields of 44−73% yield (Scheme 3).

The attack of the azido group took place at position 4 of the cyclopentane ring of **9**, through regioselective opening of the oxirane ring in esters **9a−e** resulting in 4-azido derivatives **14a−e**. The stereochemistry of these azido ester derivatives was proved unambiguously by NMR and X-ray diffraction analyses. These expected results are eloquent proof of the trans relative

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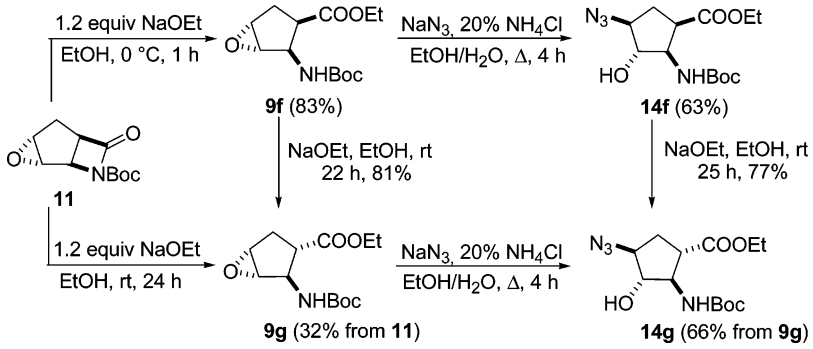
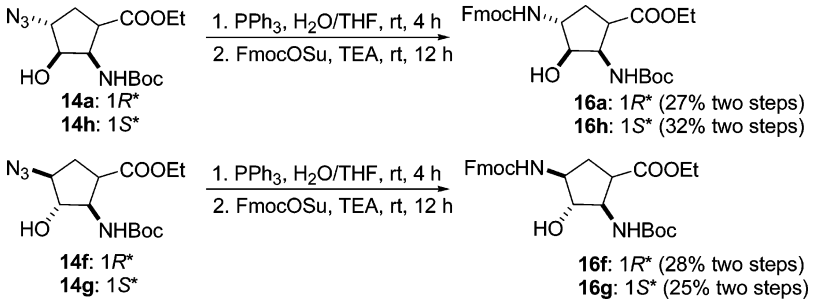
SCHEME 4. Synthesis of 2-Amino-4-azidocarboxylates 14f and 14g



SCHEME 5. Synthesis of the Orthogonally Protected 2,4-Diaminocarboxylates 16a,f−h



stereochemistry of the 2-amino group and the 4-azido group in **14a−e** (see Supporting Information).

When the azide-mediated opening of the oxirane ring in **9a** was effected under similar conditions as previously reported, but for a longer time (26 h) in refluxing EtOH−H_2O, isomerization occurred at position 1 of **9a**, giving the γ-azido diastereomer **14h** in only a modest yield (28%). **14h** was obtained in good yield when **14a** was stirred in EtOH in the presence of 1.2 equiv of NaOEt at room temperature for 28 h, with isomerization occurring at C-1 in **14a** (Scheme 3). Interestingly, after 4 h of heating in EtOH−H_2O, the epoxy amino ester **9c** (Fmoc protecting group) gave not only azido ester **14c** but also oxazolone derivative **15** (Scheme 3), probably via the opening of the oxirane ring with NaN_3 in the first step, followed by the attack of the 3-hydroxy group of **14c** on the carbonyl carbon of the 2-carbamate group. The structure of oxazolone **15** was proved by means of X-ray diffraction analysis (see the Supporting Information).

The preparation of a "*trans*"-epoxy amino ester **9f** was achieved from "*trans*"-epoxy azetidinone **11** by opening of the lactam ring on treatment with 1.2 equiv of NaOEt in EtOH at 0 °C. When the ring opening was performed at room temperature for a longer time (24 h), isomerization occurred at C-1 of **11**, furnishing the epoxy derivative **9g**, which could also be obtained from **9f** by epimerization (Scheme 4).

The stereochemistry of **9f** was determined by means of NMR and X-ray diffraction analysis, and as expected, the trans position of the oxirane ring relative to the 2-amino group was observed (see the Supporting Information).

For epoxides **9f** and **9g**, the attack of the azido group on the oxirane ring occurred from the less hindered face (C-4 of **9**), furnishing γ-azido ester diasteromers **14f** and **14g**, respectively, in good yields (63% and 66%). Azido amino ester **14f** could also be converted to diastereomer **14g** on treatment with 1.2 equiv of NaOEt in EtOH (Scheme 4). The azido function was converted to the Fmoc-protected amino group by reduction in the presence of PPh_3/H_2O in THF, followed by the reaction with FmocOSu in the presence of triethylamine giving the orthogonally protected diaminocarboxylates **16a**,**f−h**, unfortunately in low yields (25−32% in the two steps, Scheme 5). It is noteworthy that when the azido group was reduced by catalytic hydrogenation in the presence of Pd/C, a complex mixture was obtained.

The epoxidation of the amino esters and the ring opening of the resulting epoxides by using NaN_3 were also performed for the enantiomeric substances (Scheme 6). The starting compounds (1*S*,5*R*)-**6** and (1*R*,2*S*)-**12** were prepared through the Lipolase (lipase B from *Candida antarctica*)-catalyzed enantioselective ring opening of 7-azabicyclo[4.2.0]oct-3-en-8-one, using a slightly modified literature procedure.[17] The enantioselective ring cleavage of (±)-**6** was performed successfully ($E > 200$) on the 10 g scale by adding the enzyme in portions to the reaction mixture (see the Supporting Information).

In conclusion, a simple route has been developed for the synthesis of orthogonally protected β,γ-diaminocyclopentanecarboxylate stereoisomers, based on the diastereoselective epoxidation reactions and regioselective opening of the oxirane ring. These new types of compounds are conformationally constrained diamino carboxylates and can be considered as functionalized carbocyclic nucleoside precursors.

Experimental Section

General Procedure for the Epoxidation of Compounds 8a−e and 10. To a solution of amino ester **8a−e** or β-lactam **10** (18 mmol) in CH_2Cl_2 (150 mL) was added *m*-CPBA (21 mmol) at 0 °C. After the mixture was stirred for 5 h, CH_2Cl_2 (120 mL) was added and the resulting mixture was washed with saturated

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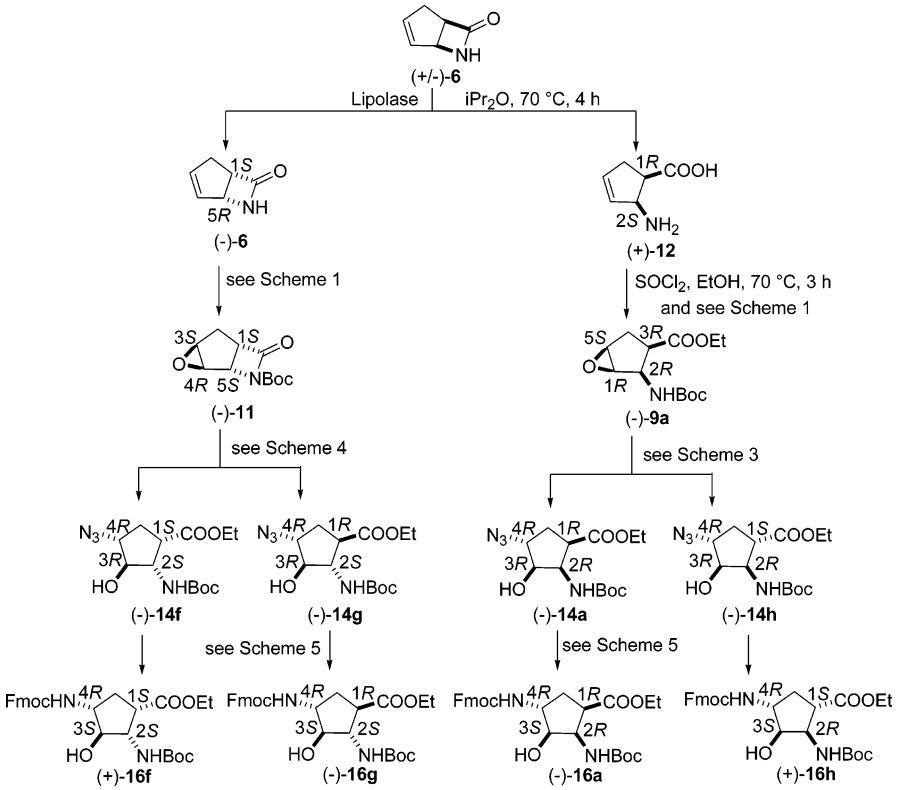
SCHEME 6. Synthesis of the Enantiomers of Aminocarboxylates 14a,f−h and 16a,f−h



$NaHCO_3/H_2O$ (3 × 150 mL). The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was chromatographed on silica gel (*n*-hexane/EtOAc 3:1).

Ethyl (1*R,2*R**,3*R**,5*S**)-2-(*tert*-butoxycarbonylamino)-6-oxabicyclo[3.1.0]hexane-3-carboxylate (9a):** white solid; yield 64%; R_f = 0.35 (*n*-hexane/EtOAc 3:1); mp 50−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.27 (t, J = 7.15 Hz), 1.46 (s, 9H), 1.92−1.99 (m, 1H), 2.65−2.70 (m, 1H), 2.74−2.81 (m, 1H), 3.44−3.45 (m, 1H), 3.53−3.54 (m, 1H), 4.10−4.20 (m, 2H), 4.38−4.45 (m, 1H), 6.40 (brs, 1H). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.81; H, 7.56; N, 5.39.

General Procedure for Opening of the Oxirane Ring in Amino Esters 9a−g. To a solution of amino ester **9a**−**g** (8.9 mmol) in EtOH (30 mL) and water (2 mL) were added NaN_3 (1.2 g, 17.8 mmol, 2 equiv) and NH_4Cl (93 mg, 1.75 mmol, 20 mol %), and the mixture was stirred under reflux for the time indicated in Schemes 3 and 4. The mixture was then concentrated under reduced pressure, and the residue was taken up in EtOAc (150 mL), washed with water (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by crystallization (*n*-hexane/EtOAc) or chromatography on silica gel (*n*-hexane/EtOAc).

Ethyl (1*R,2*R**,3*R**,4*R**)-4-azido-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclopentanecarboxylate (14a):** white crystals; yield 73%; R_f = 0.45 (*n*-hexane/EtOAc 3:1); mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.28 (t, J = 7.15 Hz, 3H), 1.44 (s, 9H), 1.91−1.99 (m, 1H), 2.43−2.50 (m, 1H), 3.33−3.38 (m, 1H), 3.74 (brs, 1H), 3.94−4.00 (m, 1H), 4.01−4.04 (m, 1H), 4.11−4.24 (m, 2H), 4.32−4.42 (m, 1H), 5.25 (brs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δ 14.8, 29.0, 32.7, 45.2, 54.8, 62.5, 66.9, 78.0, 80.6, 156.1, 177.1; MS (ES, pos) *m*/*z* 337 (M + Na). Anal. Calcd for $C_{13}H_{22}N_4O_5$: C, 49.67; H, 7.05; N, 17.82. Found: C, 49.33; H, 7.13; N, 17.52.

General Procedure for Azido Group Reduction and Protection of the Amino Group: Synthesis of Orthogonally Protected Esters 16a,f−h. To a solution of azido ester **14a**, **14f**, **14g**, or **14h** (450 mg, 1.43 mmol) in THF (18 mL) were added PPh_3 (375 mg, 1.43 mmol) and H_2O (70 mg, 3.9 mmol) , and the mixture was stirred for 5 h. Et_3N (433 mg, 4.29 mmol) and FmocOSu (482 mg, 1.43 mmol) were then added to the solution, and stirring was continued for another 12 h. The mixture was then taken up in EtOAc (50 mL), washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 2:1).

Ethyl (1*R,2*R**,3*S**,4*R**)-4-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclopentanecarboxylate (16a):** white solid; yield 27% from **22a**; R_f = 0.40 (*n*-hexane/EtOAc 1:1); mp 186−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.27 (t, J = 7.15 Hz, 3H), 1.44 (s, 9H), 1.66−1.70 (m, 1H), 2.51−2.54 (m, 1H), 3.27−3.30 (m, 1H), 3.60 (brs, 1H), 3.97−4.03 (m, 2H), 4.14−4.30 (m, 4H), 4.43−4.45 (m, 2H), 4.85 (brs, 1H), 5.31 (brs, 1H), 7.27−7.43 (m, 4H), 7.56−7.59 (m, 2H), 7.74−7.78 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$, TMS) δ 14.8, 29.0, 30.4, 45.9, 47.9, 56.0, 58.9, 62.1, 67.5, 78.3, 80.8, 120.7, 125.6, 127.8, 128.4, 129.1, 129.9, 132.8, 165.2, 170.5, 174.4. Anal. Calcd for $C_{28}H_{34}N_2O_7$: C, 65.87; H, 6.71; N, 5.49. Found: C, 65.61; H, 6.83; N, 5.10.

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Supporting Information Available: General information, spectroscopic data for compounds **7**, **8a**−**e**, **9b**−**g**, **10**−**12**, **13a**,**b**, **14b**−**h**, **15**, and **16f**−**h**, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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