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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7389–7393

ε-Amino acids based on bicyclic skeleton: bicyclo[3.3.0]octane-5-amino-1-carboxylic acids

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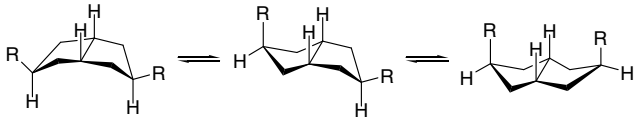
Received 4 July 2006; accepted 27 July 2006
Available online 28 August 2006

Abstract—Tsc-protected ε-amino acids, bicyclo[3.3.0]octane-5-amino-1-carboxylic acids (**1**), ready to use in the solid-phase synthesis, are prepared from 4,4-diethylcarboxylic bicyclo[3.3.0]oct-2-enone (**3**), which is available in bulk from **2** through the catalytic Pauson-Khand reaction.

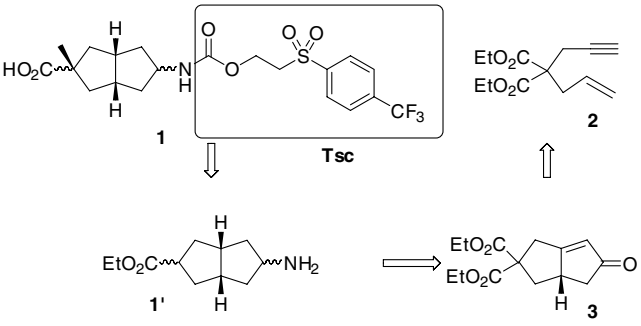
Unnatural α-amino acids[1] and their homologous amino acids have been the intensive research interests in recent years because of their utilities as surrogates for natural amino acids. β-Amino acids are a notable class in that their oligomers have been the subject of folding studies.[2] Much less is known of γ- and δ-amino acids, but the studies on this class of compounds are growing substantially.[3,4] ε-Amino acids are seldom used in this line.[5] A recent report revealed the synthesis of triazole-incorporated ε-amino acids and its application for the preparation of a cyclic hexapeptide.[6]

The skeleton of bicyclo[3.3.0]octane is interesting because it has a rigid ring junction as well as conformationally flexible side ends. One of the notable applications of this bicyclic system in peptide chemistry was bisguanidinium-bicyclo[3.3.0]octane.[7] It was used to induce the α-helix secondary structure from the oligopeptide bearing properly positioned aspartic amino acids. We are interested in ε-amino acid based on bicyclo-[3.3.0]octane because it can serve as a novel controller of the secondary structure of oligopeptides. Depending on substituents, it will select one of the possible conformers in a given circumstance (Scheme 1).



Scheme 1. The possible conformers of bicyclo[3.3.0]octane.

Meantime, we have been involved in the development of Pauson-Khand reaction. We realized that the bicyclic compound **3**, which is produced from the most-commonly used bench-marking substrate **2** for the test of the newly developed conditions, can be modified easily to give the desired ε-amino acids (Scheme 2). This approach will be practical since the catalytic Pauson-Khand reaction is well optimized to afford the compound **3** in more than 100 g at a batch.[8] Herein, we present the preparation of all possible stereoisomers of the



Scheme 2. Retrosynthetic analysis of **1**.

Keywords: Unnatural amino acid; ε-Amino acid; Bicyclic amino acid; Pauson-Khand reaction; Solid phase synthesis; Tsc amine-protecting group.
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✠ Deceased on February 6, 2006.

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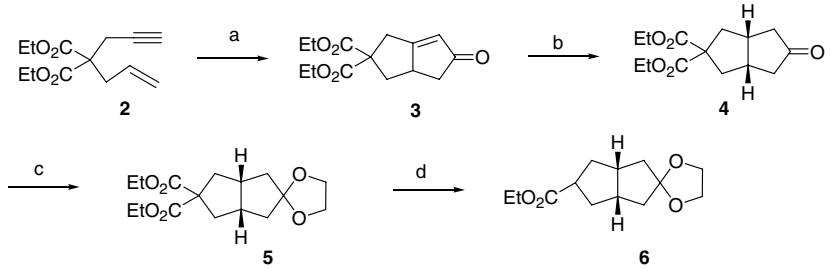
doi:10.1016/j.tetlet.2006.07.137

ε-amino acids **1** bearing Tsc (2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl) amine-protecting group and their use in the solid-phase peptide synthesis.

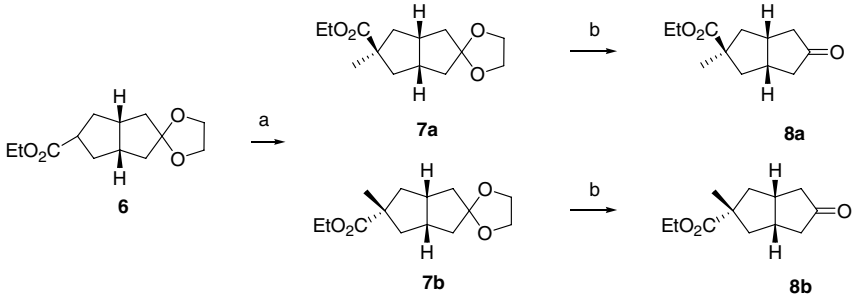
Tsc recently introduced by us is a nice substitute for Fmoc as amine-protecting group because it is compatible with Fmoc chemistry, but exhibits higher thermal and chemical stability.[9] In addition, Tsc could be installed on amine groups via base- and acid-resistant Ttc (2-(4-trifluoromethylphenylthio)ethoxycarbonyl) group, thereby allowing more options for ester hydrolysis of troublesome quaternary esters.

The precursors for ε-amino acids were prepared according to Scheme 3. The catalytic Pauson-Khand reaction of enyne **2** provided bicyclopentenone **3** in 60% on a 100 g scale. Upon hydrogenation of **3** over Pd/C in ethanol, **4** was obtained in almost quantitative yield. After protection of ketone in **4** as ketal in **5**, monodecarboxylation of **4** was successfully achieved providing compound **6** in 74% over two steps.

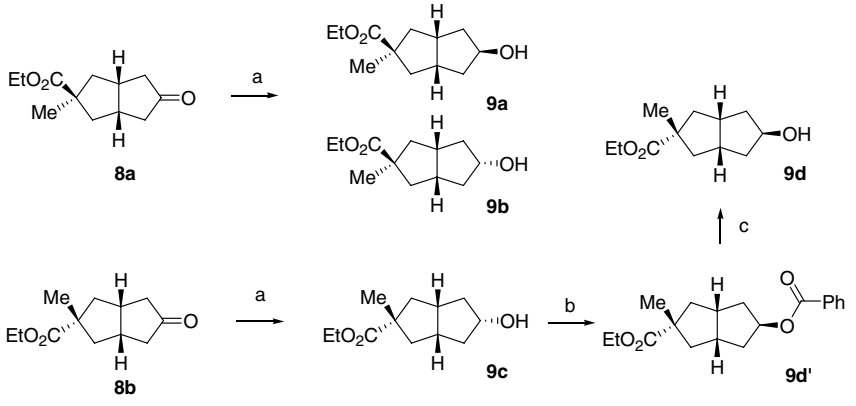
At this point, methyl group was introduced at α-position to the ester to prevent potential complication by epimerization in due course (Scheme 4). A mixture of **7a** and **7b** was obtained by treating **6** with LDA at −78 °C followed by quenching with iodomethane and then was subjected to column chromatography giving **7a** and **7b** in 17% and 77% yields, respectively. Since we wanted to have all four isomers, we did not try to optimize the selectivity to favor one over the other at this moment. Instead, each isomer was subjected to aqueous



Scheme 3. Reagents and conditions: (a) $Co_2(CO)_7[P(OPh)_3]$ (3 mol %), CO (1 atm), DME, 120 °C, 60% (100 g scale); (b) H_2, Pd/C, EtOH, rt, 95%; (c) TMSOTf, 1,2-bis(trimethylsiloxy)ethane, CH_2Cl_2, −78 °C and then rt, 97%; (d) NaCl, H_2O, DMSO, 200 °C, 76%.



Scheme 4. Reagents and conditions: (a) LDA, MeI, THF, −78 °C, (**7a**, 17%; **7b**, 77%); (b) pyridinium *p*-toluene sulfonate, H_2O/acetone, reflux, (**8a** from **7a**, 89%; **8b** from **7b**, 99%).



Scheme 5. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, (**9a** from **8a**, 27%; **9b** from **8a**, 57%; **9c** from **8b**, 93%); (b) DEAD, PPh_3, benzoic acid, THF, 0 °C, 74%; (c) NaOH, H_2O/EtOH, rt, 76%.

acid hydrolysis to yield the corresponding ketones **8a** and **8b**, respectively.

In initial attempts to obtain the amines from ketones **8** by direct reductive-amination, we were not successful in obtaining clean reaction mixtures. We decided to detour rather lengthy, but sure pathways. Sodium borohydride reduction of **8a** provided a mixture again (Scheme 5). Alcohols **9a** and **9b** were obtained in 27% and 57% yields, respectively. On the other hand, reduction of **8b** provided an alcohol **9c** exclusively in 93% yield. The other isomer **9d** was obtained by inversion of alcohol of **9c** under Mitsunobu condition with benzoic acid followed by the hydrolysis of the resultant ester **9d′**.[10]

The introduction of Tsc amine-protecting group was followed. The procedure exemplified with **9a** according to the previously described methods is given in Scheme 6. Mitsunobu reaction with **9**s in the presence of phthalimide provided the corresponding phthalimides **10** with inversion of the stereochemistry in excellent yield. Hydrolysis of the imide **10a** to the amine **11a** (**1′**) by employing hydrazine followed by trapping with Ttc-Cl provided **12a** in 56% yield over two steps. Hydrolysis of the quaternary ester **12a** in the presence of the carbamate has been troublesome under acidic conditions in use for the deprotection of *t*-Boc group. Fortunately, since this thiophenol-substituted carbamate **12a** is stable to basic condition, **12a** was treated with potassium *t*-butoxide in aqueous ethanol to give the free acid **13a** in reasonable yield (70%). Compound **13a** was then oxidized to *N*-Tsc amino acid **1a** with sodium molybdate in 70% yield.[11] The same series of conditions have been applied to afford the rest of the possible stereoisomers uneventfully (Fig. 1).

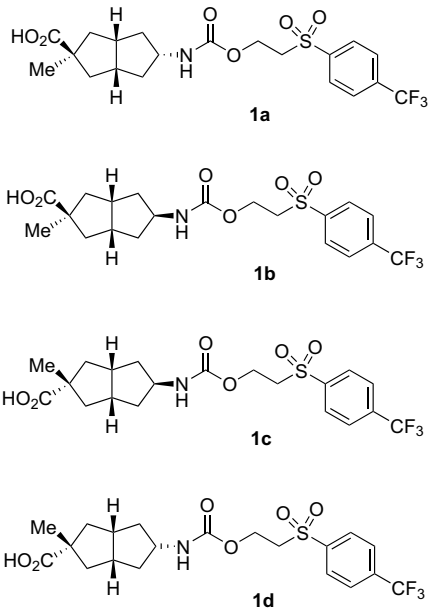
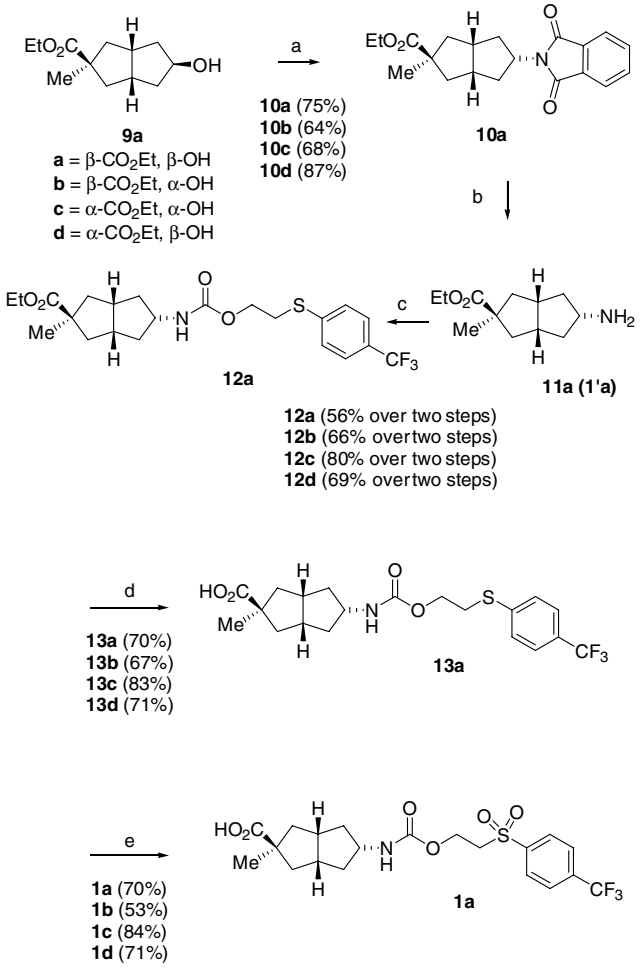


Figure 1. All four isomers of bicyclo[3.3.0]octane-5-amino-1-carboxylic acids.



Scheme 6. Reagents and conditions: (a) DEAD, PPh_3, phthalimide, THF, 0 °C; (b) H_2NNH_2–H_2O, EtOH/CH_2Cl_2, rt; (c) Ttc-Cl, TEA, THF/DMF, rt; (d) *t*-BuOK, H_2O, EtOH, rt; (e) Na_2MoO_4, H_2O_2, acetone, rt.

At the stage of **10**, we tried to make sure of our assignment of stereochemistry of all isomers (Fig. 2). Since compounds **10** were crystalline, **10b** and **10c** were recrystallized to generate single crystals suitable for the X-ray diffraction study.[12] The stereochemistry of all four isomers was assigned unambiguously based on these two structures.

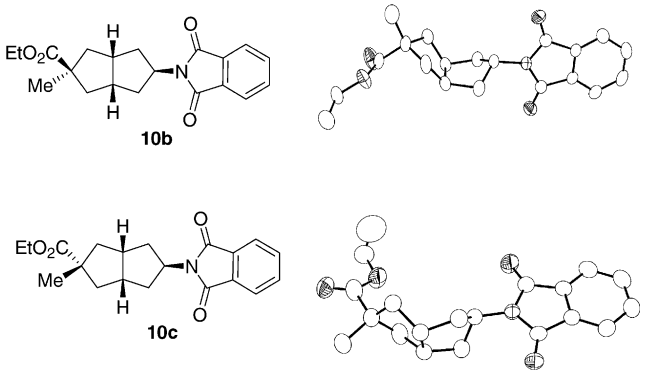
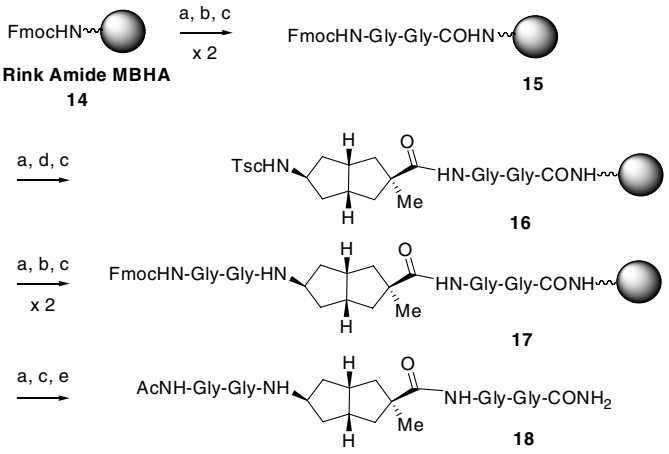


Figure 2. ORTEP diagram of **10b** and **10c**.[12]



Scheme 7. Reagents and conditions: (a) 50% piperidine/DMF, rt; (b) Fmoc-Gly-OH, PyBOP, DIEA, DMF, rt; (c) Ac_2O, DIEA, CH_2Cl_2, rt; (d) **1b**, PyBOP, DIEA, DMF, rt; (e) TFA, rt.

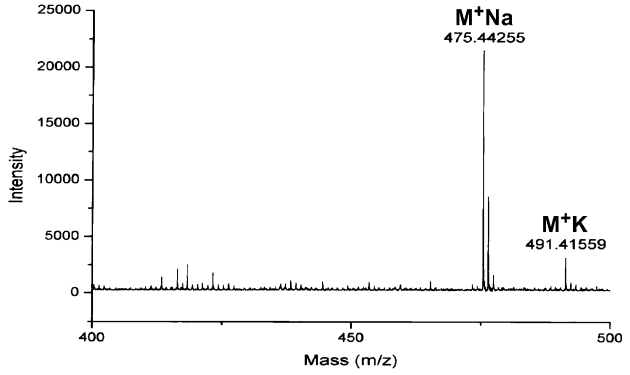


Figure 3. MALDI-TOF analysis of purified peptide **18**.

The utility of these amino acids in the solid-phase synthesis is well demonstrated by the synthesis of oligopeptide **18**, AcNH-Gly-Gly-1b-Gly-Gly-$CONH_2$ (Scheme 7). The synthesis was successfully carried out on the Fmoc-Rink Amide MBHA resin in a stepwise fashion by a manual solid-phase method. The crude peptide was purified by reverse-phase HPLC, giving an overall 73% recovery of **18**. Mass and NMR data are in good accord with the projected structure (Fig. 3). A further study about the oligopeptide structures will be described in due course.

In conclusion, we successfully provide a reliable synthetic way for Tsc-protected ε-amino acids based on the bicyclo[3.3.0]octane skeleton and their incorporation into oligopeptides by the solid-phase synthesis. The efficiency of the pathway relies on a couple of key results. First, bicyclic compounds are available in bulk by the catalytic Pauson-Khand reaction. Second, Tsc as an amine-protecting group allows us to have a versatile synthetic pathway. Ttc, an immediate precursor of Tsc, is inert enough to tolerate the strong basic conditions for the hydrolysis of quaternary esters. Ttc was thereafter oxidatively converted into Tsc that is labile enough to be eliminated under mild basic condition compatible with Fmoc chemistry. Third, the quaternary carboxylic acid of bicyclic amino acids can be coupled to amines of amino acids on the resin without using acyl halide coupling scheme with high efficiency.

Acknowledgments

This work was financially supported by the Basic Research Program (R02-2002-000-00128-0) and CMDS from KOSEF to N.J. and the Korea Research Foundation Grant (KRF-2003-015-C00377) CRM to H.H. S.J.Y. and K.S.J. are grateful to the BK21 program for the fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.137.

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11. The order of the reaction sequences is critical. Ester hydrolysis has to precede the oxidation of sulfide. Otherwise, the elimination of the Tsc is inevitable during the base-catalyzed ester hydrolysis. Tsc is vulnerable even in the presence of a weak base like piperidine. Please refer to Ref. 9 for the details.
12. (a) Crystal data for **10b**: A colorless needle crystal, $C_{20}H_{23}NO_4$, $M_r = 341.39$, orthorhombic, *Pbcm* (No. 57), $a = 8.4578(4)$, $b = 28.6810(12)$, $c = 7.3916(3)$ Å, $V = 1793.04(13)$ Å^3, $Z = 4$, $T = 296(2)$ K, $d_{calcd} = 1.265$ g/cm^3, μ(Mo K$_\alpha$) $= 0.088$ mm^{-1}, 26,960 total reflections, 2202 unique reflections, $R_{int} = 0.0743$, $R1 = 0.0710$, and $wR2 = 0.1314$ for 1282 observed reflections ($I > 2.00\sigma(I)$), GOF = 1.125. CCDC-294651; (b) Crystal data for **10c**: A colorless rectangular crystal, $C_{20}H_{23}NO_4$, $M_r = 341.39$, triclinic, $P(-1)$ (No. 2), $a = 7.9975(10)$, $b = 9.5843(12)$, $c = 13.0250(17)$ Å, $\alpha = 77.305(1)$, $\beta = 77.614(1)$, $\gamma = 83.751(1)$, $V = 946.9(2)$ Å^3, $Z = 2$, $T = 296(2)$ K, $d_{calcd} = 1.197$ g/cm^3, μ (Mo K$_\alpha$) $= 0.083$ mm^{-1}, 6444 total reflections, 3109 unique reflections, $R_{int} = 0.0653$, $R1 = 0.1237$, and $wR2 = 0.2160$ for 1564 observed reflections ($I > 2.00\sigma(I)$), GOF = 1.408. CCDC-294650.