A Highly Diastereoselective Approach to Conformationally Constrained Serine Analogues: Synthesis of an α-Amino-β-hydroxycyclohexenecarboxylic Acid and Derivatives

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Received November 2, 1998

A diastereospecific synthesis of α-amino-β-hydroxycyclohexenecarboxylic acid (**7**) was found starting from 4-chloromethylene-5(4*H*)-oxazolone (**1**) which reacted with 2,3-dimethylbutadiene in the presence of $EtAlCl_2$. The Diels−Alder reaction gave two diastereoisomeric cycloadducts **2** and **3**, depending on the configuration of the starting dienophile **1**. Compounds **2a** and **3** were transformed into the ester **4** and the oxazoline **6**, respectively, by reaction with MeOH and *p*-TSA. The reaction of **2a** and **3** with dimethylamine in ethanol solution gave the corresponding amides **8** and **9**, respectively, which were transformed into the bicyclic oxazoline **10** on reaction with Na_2CO_3 in acetonitrile. On acidic hydrolysis both oxazolines **6** and **10** were transformed into α-amino-β-hydroxycyclohexenecarboxylic acid (**7**) that includes the serine skeleton.

Introduction

Much attention in recent years was focused on the synthesis of conformationally restricted α-amino acids because their incorporation into peptides is an effective approach to generate modified peptides having a modulated biological activity.[1] The growing interest in the synthesis of 1-aminocyclohexanecarboxylic acid derivatives, which are constrained nonproteinogenic amino acids, is documented by recent literature.[2]

The key reaction for their preparation was the Diels−Alder reaction using different dienes and, as dienophiles, 1-aminoacrylate derivatives[3] or 4-arylidene-5(4*H*)-oxazolones,[2,4] the latter being masked amino acids. Final products were obtained by reduction of the cyclohexene ring. In particular, many efforts are now directed to the preparation of 1-aminocyclohexanecarboxylic acids having one or more hydroxy groups in specific positions.[5]

The introduction of serine in peptides or proteins is an important tool one can use to study the role of the hydroxy group in a variety of enzymatic transformations and biochemical signal transductions in the cell.[6] Accordingly, the preparation of constrained serine analogues is of interest to clarify the conformational role of this group when these amino acids are incorporated into peptides or proteins instead of normal serine.[7] Notwithstanding their importance, the preparation of β-hydroxycyclohexaneamino acids is still scarcely considered. To our knowledge, such compounds have been synthesized only using the Strecker method[8] and only recently an asymmetric synthesis has been developed.[9]

As a part of our continuing research program on the synthetic potential of 5(4*H*)-oxazolones, and in the preparation of constrained cyclic amino acids functionalized on the ring with a substituent linked by a heteroatom,[10] we now report on a new synthesis of the cyclohexeneamino acid **7** which bears a hydroxy group at the β-carbon and in which the serine skeleton is included. In our synthesis 4-chloromethylene-5(4*H*)-oxazolone (**1**) was chosen as the ideal starting material to prepare compound **7** because it appeared that the chlorine could be converted into a hydroxy group after Diels−Alder reaction had generated the cyclic skeleton. Compound **7** was obtained with high diastereoselectivity independent of the configuration of the starting oxazolone.

Results and Discussion

Oxazolone **1** was obtained by the method described in the literature[11] and to the product the (*Z*) configuration was assigned as reported below.

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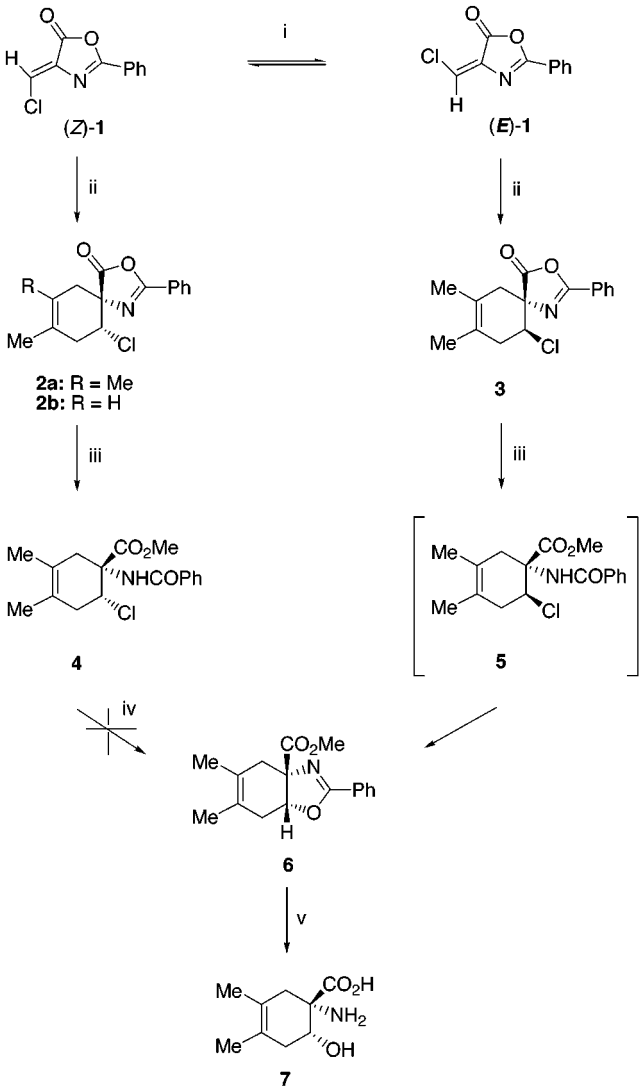
10.1021/jo9821877 CCC: $18.00
Published on Web 07/14/1999

Scheme 1[a]



[a] Key: (i) hν, CH_2Cl_2; (ii) diene, $EtAlCl_2$, CH_2Cl_2; (iii) MeOH/*p*-TSA; (iv) Na_2CO_3, MeCN; (v) EtOH/HCl, then propylene oxide.

Previous literature reports the use of oxazolone (*Z*)-**1** in the Diels−Alder reaction as unsuccessful.[4] However, this is true only under classical conditions. Instead, in the presence of a Lewis acid, which catalyzed the cycloaddition reaction,[2] 2,3-dimethylbutadiene was readily reacted with (*Z*)-**1** affording the Diels−Alder adduct **2a**. Several Lewis acids, $ZnCl_2$, $SnCl_4$, $TiCl_4$, and $EtAlCl_2$, were tried, but the use of the first three catalysts gave only moderate results (20−35% yields of cycloadduct **2a** and long reaction times). Good results were obtained using ethylaluminum dichloride (0.35 equiv) and operating in dichloromethane at room temperature. The reaction proceeded quickly (30 min), and the spirooxazolone **2a** was isolated in 70% yield. The diastereoisomeric cycloadduct **3** was present only in trace amounts (1%) (Scheme 1).

As shown, the cycloaddition reaction is characterized by high diastereoselectivity, practically occurring without any appreciable isomerization of the dienophile, and the final configuration is the same as in the starting dienophile. To obtain larger amounts of diastereoisomer **3**, the starting oxazolone (*Z*)-**1** was isomerized to the corresponding (*E*)-**1** oxazolone in dichloromethane solution by UV light. After 1-h exposition, a mixture of the (*Z*)/(*E*) isomers was obtained (52:48, 90% purity). When the reaction time was prolonged, only an increase of decomposition products was observed.

Our results about configurational assignment to oxazolones (*Z*)-**1** and (*E*)-**1** are not in agreement[12] with those reported in the literature[11] where signals for vinyl protons at $\delta = 7.25$ and $\delta = 5.30$ ($CDCl_3$) are reported and assigned to the (*Z*) and (*E*) isomers, respectively. In our case signals at $\delta = 7.31$ and $\delta = 7.20$ (CD_2Cl_2) were observed and assigned with the (*E*) and (*Z*) isomers, respectively. Two facts are in favor of this conclusion: (i) it is known that (*Z*)-oxazolones are more stable than the (*E*) isomers and are photoisomerized to the less stable (*E*)-isomers and (ii) for all (*Z*)/(*E*) couples the chemical shifts of the vinyl protons are in the range of $\delta = 6.8-8.0$ for both isomers and the signal associated with the (*E*) isomer is found consistently.[14]

The reaction solution of the two isomers was used without further elaboration for the cycloaddition reaction under the same conditions as described for (*Z*)-**1**. Cycloadducts **2a** and **3** (54:46) were obtained in 67% total yield, and this gave further confirmation that the reaction occurs without appreciable isomerization of the dienophile (Scheme 1).

The cycloaddition reaction was also performed starting from (*Z*)-**1** and 2-methylbutadiene with the same conditions as those reported above. The cycloadduct **2b** was isolated in 50% yield as a single regio- and diastereoisomer (Scheme 1).

The structures of compounds **2a** and **3** were confirmed by spectroscopic data. In the IR spectra the characteristic absorption of the lactone ring (1800 cm^{-1}) is present. ^1H NMR spectra showed a signal associated to the CH group ($\delta = 4.43$ and 4.40, for **2a** and **3**, respectively) and multiplets in the $\delta = 3.00-2.28$ region (CH_2). Spectroscopic data for spirocompound **2b** are in agreement to those observed for **2a**. The ^1H NMR and the COSY experiments allowed to assign unequivocally the regiochemistry of this compound.

It is well-known that nucleophiles easily react with oxazolones cleaving the ring. Accordingly, before attempting nucleophilic substitutions of the chlorine atom, oxazolone **2** was transformed into the corresponding ester **4** by reaction with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 1).

The ^1H NMR spectrum of **4** is in agreement with the structure proposed and shows the expected signals associated with NH ($\delta = 6.60$), CH ($\delta = 4.48$), and CH_2 (multiplets in the $\delta = 3.04-2.37$ region).

(12) Former establishment of configuration of the starting oxazolone was based on the X-ray structural determination of a cyclopropanation and subsequent ring opening product assuming that both reactions occurred without isomerization.[11] As demonstrated in our previous work[10] and in the literature[13] cyclopropanation of pure oxazolones is accompanied by isomerization, both stereoisomeric products being obtained. Accordingly, it is impossible to safely correlate the configuration of the starting oxazolone with the configuration of the isomeric mixture.

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All attempts to perform a direct substitution of the chlorine atom in compound **4** failed, both using different nucleophiles and changing the reaction conditions, very likely because of steric hindrance. It is known[15] that cyclic trans β-chloro amides can be cycled under basic or acidic conditions to the corresponding oxazolines, so the possibility to perform the intramolecular nucleophilic substitution, taking advantage of the assistance of the amide group, was considered. It was expected that the alcoholysis reaction of oxazolone **3**, which should occur through intermediate **5** in which is present the correct trans relationship of the amide and chlorine substituents, would result in intramolecular nucleophilic substitution, thus overcoming the low reactivity of chlorine. In fact, compound **3** was directly transformed into the bicyclic oxazoline **6** on reaction with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid. The intermediate ester **5** could not be isolated. Expectedly, ester **4** did not give this reaction because of its incorrect stereochemistry and could not be transformed into the corresponding oxazoline by anhydrous sodium carbonate in acetonitrile at reflux (Scheme 1).

The structure of the oxazoline **6** was confirmed by analytical and spectroscopic data. In the ^{1}H NMR spectrum a low-field signal is associated with CH ($\delta = 5.63$). A positive NOESY effect is observed between this proton and the methoxy group confirming the cis junction of the rings.

Compound **6** was readily hydrolyzed by acqueous HCl in ethanol affording the amino acid **7** in 54% yield.

The structure of the amino acid **7** is confirmed by its ^{1}H NMR spectrum in which the signal of H-6 is present at $\delta = 4.3$ (dd, $J = 6.9$, 9.9 Hz).[9]

The synthesis of the amino acid **7** by the above approach suffers from the limitation that only oxazolone **3** is an useful precursor. However, as said above, compound **3** is unavoidably obtained in mixture with the "wrong" stereoisomer **2a**. The following modification of the synthetic pathway permits the use of compound **2a**, for the preparation of the target products. By reaction of **2a** and **3** with an ethanolic solution of dimethylamine the corresponding *N*,*N*-dimethylcarboxamides **8** and **9** were prepared (Scheme 2). For compound **8**, it was expected that the neighboring *N*,*N*-dimethylcarboxamido group, acting as internal nucleophile, would produce anchimeric assistance in the nucleophilic substitution of the chlorine atom by the enolate anion of the benzoylamino group, eventually leading to oxazoline **10** by a two-step process, as shown in Scheme 2 (intermediate **A**). In fact, by reacting amide **8** with anhydrous sodium carbonate in acetonitrile at reflux, the oxazoline **10** was formed and isolated in good yield. Clearly, the same product **10** was also obtained directly from the diastereoisomeric amide **9** under the same reaction conditions (Scheme 2).

The spectroscopic data of oxazoline **10** were in fair agreement with those of ester **6**, and the cis junction of the rings was confirmed in this case, too, by a NOESY experiment (positive Overhauser effect between the CH and *N*-Me$_2$).

Finally, oxazoline **10** was hydrolyzed in the same conditions used for **6** giving the corresponding acid **7** (Scheme 2).

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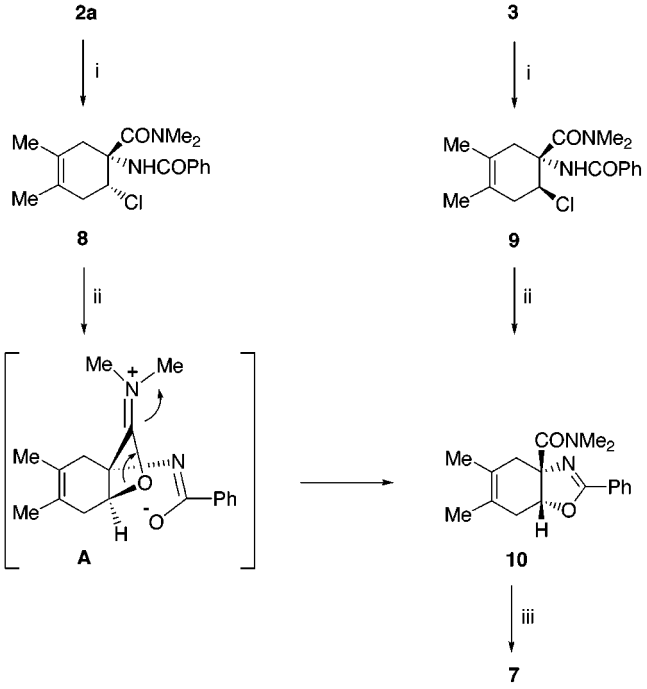
Scheme 2[a]



[a] Key: (i) Me_2NH, EtOH; (ii) Na_2CO_3, MeCN; (iii) EtOH/HCl, then propylene oxide.

In conclusion it was possible to prepare the 1-(*S**),6-(*R**) form of 1-amino-6-hydroxy-3,4-dimethylcyclohex-3-enecarboxylic acid (**7**) by a highly diastereoselective reaction sequence starting from readily available 4-chloromethylene-5(4*H*)oxazolone (**1**) independently from the configuration of this reagent. By using other diene reactants, the synthetic scheme appears to be of general scope for the preparation of carbocyclic serine analogues with controlled substitution on the ring.

Experimental Section

General. Melting points are uncorrected. IR spectra of the Nujol method were measured using NaCl plates. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ at 200 and 300, and 50 and 75 MHz, respectively, with $CHCl_3$ as internal standard. Coupling constants (*J*) are given in hertz. Ethanol-free CH_2Cl_2 was used in all experiments. Oxazolone **1**[11] is a known compound.

General Procedure for the Preparation of (5*R,10*R**)-10-Chloro-2-phenyl-3-oxa-1-azaspiro[4.5]deca-1,7-dien-4-ones 2.** To a stirred solution of oxazolone (*Z*)-**1** (207 mg, 1 mmol) and butadiene derivative (4 mmol) in anhydrous CH_2Cl_2 (5 mL), under nitrogen at room temperature, $EtAlCl_2$ (21.7 μL, 0.2 eq) was added. After the time indicated the solvent was evaporated, and the crude reaction mixture was chromatographed (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) giving **2**.

(5*R,10*R**)-10-Chloro-7,8-dimethyl-2-phenyl-3-oxa-1-azaspiro[4.5]deca-1,7-dien-4-one (2a):** reaction time, 1 h; yield 70%; mp 94 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 1800, 1640 cm^{-1}; ^{1}H NMR δ 1.69, 1.74 (s, 6 H), 2.19 (d, $J = 17.2$, 1 H), 2.41−2.51 (m, 1 H), 2.71−2.85 (m, 2 H), 4.43 (dd, $J = 5.7$, 11.2, 1 H), 7.44−8.10 (m, 5 H); ^{13}C NMR δ 18.6, 19.3, 38.7, 41.5, 58.8, 73.7, 121.9, 125.4, 126.2, 128.8, 129.2, 133.4, 162.4, 178.9. Anal. Calcd: C, 66.42; H, 5.58; N, 4.84. Found: C, 66.76; H, 5.78; N, 4.67.

(5*R,10*R**)-10-Chloro-8-methyl-2-phenyl-3-oxa-1-azaspiro[4.5]deca-1,7-dien-4-one (2a):** reaction time, 2.30 h; yield 50%; oil; IR ν_{max} 1800, 1640 cm^{-1}; ^{1}H NMR δ 1.80 (s, 3 H), 2.32 (dd, $J = 17.2$, 4.6, 1 H), 2.50 (dd, $J = 15.0$, 5.9, 1 H), 2.60−2.90 (m, 2 H), 4.45 (dd, $J = 5.9$, 10.8, 1 H), 5.40−5.45

(m, 1 H), 7.40−8.20 (m, 5 H). Anal. Calcd: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.51; H, 5.00; N, 5.22.

(5*R,10*R**)- and (5*R**,10*S**)-10-Chloro-7,8-dimethyl-2-phenyl-3-oxa-1-azaspiro[4.5]deca-1,7-dien-4-ones (2a and 3).** A solution of oxazolone (*Z*)-**1** (300 mg, 1.45 mmol) dissolved in anhydrous CH_2Cl_2 (80 mL) was irradiated with a Pyrex-filtered light from a high-pressure Hg lamp (HPK-125 W Philips) for 1 h. [An amount of this solution was analyzed by ^{1}H NMR (CD_2Cl_2): ratio of isomers (*Z*)/(*E*) = 52:48; 90% purity.] This solution was transferred into a flask under nitrogen, and 2,3-dimethylbutadiene (492 mg, 6 mmol) and $EtAlCl_2$ (43.4 μL, 0.4 eq) were added at room temperature under stirring. After 1 h the solvent was evaporated, and the crude reaction mixture was chromatographed (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) giving two fractions. The first contained pure **2a** (142 mg, 37%). The second contained compound **3** (113 mg, 30%) as colorless crystals: mp 108 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 1800, 1640 cm^{-1}; ^{1}H NMR δ 1.66, 1.74 (s, 6 H), 2.34 (d, J = 17.6, 1 H), 2.56−3.01 (m, 3 H), 4.40 (dd, J = 6.1, 10.5, 1 H), 7.45−8.05 (m, 5 H); ^{13}C NMR δ 18.7, 19.1, 38.4, 39.8, 58.6, 72.2, 121.0, 125.4, 126.1, 128.6, 129.3, 133.4, 162.2, 176.1. Anal. Calcd: C, 66.42; H, 5.58; N, 4.84. Found: C, 66.60; H, 5.60; N, 4.51. The ^{1}H NMR spectrum of the crude reaction mixture shows the signals for *cis*-**2** and *trans*-**3** in the ratio of 54:46.

Methyl (1*R,6*R**)-1-(Benzoylamino)-6-chloro-3,4-dimethylcyclohex-3-enecarboxylate (4).** A solution of spirooxazolone **2a** (570 mg, 1.97 mmol) and a catalytic amount of *p*-TSA in MeOH (15 mL) was refluxed for 45 min. After solvent evaporation, the crude reaction mixture was recrystallized giving pure **4** (200 mg). A further crop of **4** was obtained after chromatographic separation (*n*-pentane/CH_2Cl_2, 1:0 to 0:1): total yield, 550 mg (87%); colorless crystals; mp 105 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3280, 1715, 1620 cm^{-1}; ^{1}H NMR δ 1.63 (s, 6 H), 2.37−2.76 (m, 2 H), 2.94 (dd, J = 18.2, 2 H), 3.74 (s, 3 H), 4.48 (t, J = 5.7, 1 H), 6.60 (s, 1 H), 7.37−7.79 (m, 5 H); ^{13}C NMR δ 18.5, 18.6, 36.7, 38.9, 53.1, 60.7, 62.5, 120.8, 123.2, 127.2, 128.7, 131.9, 134.2, 167.4, 171.0. Anal. Calcd: C, 63.53; H, 6.28; N, 4.36. Found: C, 63.30; H, 6.36; N, 4.32.

Methyl (3*aS,7*aR**)-5,6-Dimethyl-2-phenyl-7,7*a*-dihydro-4(*H*)-benzoxazole-3*a*-carboxylate (6).** A solution of spirooxazolone **3** (127 mg, 0.44 mmol) and a catalytic amount of *p*-TSA in MeOH (4 mL) was refluxed for 6 h. After solvent evaporation, the crude reaction mixture was recrystallized giving pure **6** (80 mg). A further crop of **6** was obtained after chromatographic separation (*n*-pentane/CH_2Cl_2, 1:0 to 0:1): total yield, 100 mg (80%); colorless crystals; mp 162 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 1715 cm^{-1}; ^{1}H NMR δ 1.68 (s, 3 H), 1.78 (s, 3 H), 2.29−2.65 (m, 3 H), 3.20 (d, J = 16.6, 1 H), 3.86 (s, 3 H), 5.63 (t, J = 3.6, 1 H), 7.55−8.52 (m, 5 H); ^{13}C NMR δ 19.7, 19.8, 34.7, 35.6, 54.5, 71.9, 88.4, 119.7, 123.9, 127.2, 130.0, 131.7, 137.4, 170.3, 171.3. Anal. Calcd: C, 71.54; H, 6.72; N, 4.91. Found: C, 71.66; H, 6.99; N, 4.72.

(1*R,6*R**)-*N*-(6-Chloro-1-(dimethylcarbamoyl)-3,4-dimethylcyclohex-3-enyl)benzamide (8).** A solution of spirooxazolone **2a** (1 g, 3.46 mmol) in $(Me)_2NH$ (20 mL, 33% in EtOH) was stirred at room temperature. After 15 min a solid corresponding to amide **8** was separated and filtered. A further crop of **8** was obtained after chromatographic separation (*n*-pentane/CH_2Cl_2/Et_2O, 1:0 to 0:1): total yield, 1.1 g (95%); colorless crystals; mp 170 °C (EtOH); IR ν_{max} 3300, 1720, 1640 cm^{-1}; ^{1}H NMR δ 1.63, 1.68 (s, 6 H), 2.36−3.02 (m, 4 H), 3.07 (s, 6 H), 4.90 (t, J = 4.4, 1 H), 6.75 (s, 1 H), 7.41−7.81 (m, 5 H). Anal. Calcd: C, 64.64; H, 6.94; N, 8.38. Found: C, 64.40; H, 6.93; N, 8.20.

(1*R,6*S**)-*N*-(6-Chloro-1-(dimethylcarbamoyl)-3,4-dimethylcyclohex-3-enyl)benzamide (9).** A solution of spirooxazolone **3** (1 g, 3.46 mmol) in $(Me)_2NH$ (20 mL, 33% in EtOH) was stirred at room temperature. After 15 min a solid corresponding to amide **9** was separated and filtered. A further crop of **9** was obtained after chromatographic separation (*n*-pentane/CH_2Cl_2/Et_2O, 1:0 to 0:1): total yield, 1.1 g (95%); colorless crystals; mp 104 °C (EtOH); IR ν_{max} 3300, 1720, 1640 cm^{-1}; ^{1}H NMR δ 1.71 (s, 6 H), 2.41−2.76, 3.15−3.26 (m, 4 H), 3.10 (s, 6 H), 4.87 (t, J = 3.9, 1 H), 6.46 (s, 1 H), 7.42−7.72 (m, 5 H). Anal. Calcd: C, 64.64; H, 6.94; N, 8.38. Found: C, 64.43; H, 6.88; N 8.25.

(3*aS,7*aR**)-5,6-Dimethyl-2-phenyl-7,7a-dihydro-4(*H*)-benzoxazole-3*a*-*N*,*N*-dimethylcarboxamide 10.** (a) To a solution of amide **8** (500 mg, 1.5 mmol) in anhydrous MeCN (7 mL) was added anhydrous Na_2CO_3 (475 mg, 4.48 mmol), and the reaction mixture was refluxed under nitrogen and stirred for 4 h. After solvent evaporation, the crude reaction mixture was taken up with CH_2Cl_2 (15 mL) and washed with H_2O (15 mL), and the organic layer was dried over Na_2SO_4. After recrystallization, oxazoline **10** (426 mg, 95%) was isolated as colorless crystals. (b) Amide **9** (114 mg, 0.33 mmol) in anhydrous MeCN (2 mL) was reacted with anhydrous Na_2CO_3 (108 mg, 1.02 mmol) giving, after workup as described in part a, compound **10** (89.4 mg, 91%): mp 90 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 1620 cm^{-1}; ^{1}H NMR δ 1.57, 1.61 (s, 6 H), 2.17−2.49 (m, 4 H), 2.89, 3.51 (s, 6 H), 5.63 (t, J = 3.2, 1 H), 7.30−7.83 (m, 5 H); ^{13}C NMR δ 20.1, 20.2 37.8, 38.7, 35.7, 39.8, 80.4, 83.4, 125.1, 125.6, 125.7, 128.6, 128.7, 131.6, 163.4, 173.7. Anal. Calcd: C, 72.44; H, 7.44; N, 9.39. Found: C, 72.28; H, 7.45; N, 9.19.

(1*S,6*R**)-1-Amino-6-hydroxy-3,4-dimethylcyclohex-3-enecarboxylic Acid 7.** (a) A mixture of oxazoline **6** (285 mg, 1 mmol) in EtOH (1 mL) and HCl (1 mL, 20%) was refluxed for 24 h. After solvent evaporation, the crude reaction mixture was dissolved in EtOH (2 mL) and propylene oxide (1 mL), and the solution was refluxed for 1 h after which a solid was separated, filtered, and washed with EtOH giving acid **7** (96 mg, 52%) as colorless crystals. (b) A mixture of oxazoline **10** (298 mg, 1 mmol) reacted as described in part a. Amino acid **7** was isolated as colorless crystals (93 mg, 50%): mp (dec); IR ν_{max} 1620 cm^{-1}; ^{1}H NMR (D_2O/CF_3CO_2D) δ 1.54 (s, 6 H), 1.81−2.00 (m, 1 H), 2.42 (dd, J = 6.7, 18.3, 1 H), 2.19, 2.75 (AB system, J = 18.3, 2 H), 4.30 (dd, J = 6.7, 9.9, 1 H). Anal. Calcd: C, 58.35; H, 8.17; N, 7.56. Found: C, 58.19; H, 8.30; N, 7.40.

JO9821877