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NOVEL SYNTHESIS OF 5-OXOMORPHOLINE DERIVATIVE BY CYCLIZATION OF Δ^1-DEHYDRODIPEPTIDE

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Abstract—A convenient synthesis of novel 6-disubstituted 5-oxomorpholine-3-carboxylate derivatives (**5**) by stereoselective cyclization of Δ^1-dehydrodipeptides, Boc-ΔVal-L-AA-OMe (AA=Ser, Thr, HyVal) with *t*-BuOCl or *N*-halosuccinimide is described. Furthermore, the configuration of **5** was determined by single crystal X-Ray analysis.

In previous papers, we have reported many useful synthetic methods for various kinds of dehydropeptide[1] containing one or more α-dehydroamino acids (DHA, ΔAA) and cyclodehydrodipeptides (3-alkylidene- and 3,6-dialkylidene-2,5-piperazinediones: PDO).[2]

In connection with the study on the reactivity of DHA and PDO, the intermolecular additions of protic reagents such as alcohols and amines to the C=C bond by using *N*-bromosuccinimide (NBS) or *t*-BuOCl were hitherto mainly carried out.[3] On the other hand, similarly to the above case, the intramolecular additions of 3-hydroxy- and 3-aminoalkylidene-PDO toward the corresponding 3-spiro and 3,6-macrocyclic PDO derivatives, which were available for the completely chiral synthesis of bicyclomycin,[4] have been also reported.[5] At present, however, study on the additional cyclization to the C=C bond of the linear dehydrodipeptide containing an hydroxy-α-amino acid residue at the C-terminus has not been performed yet.

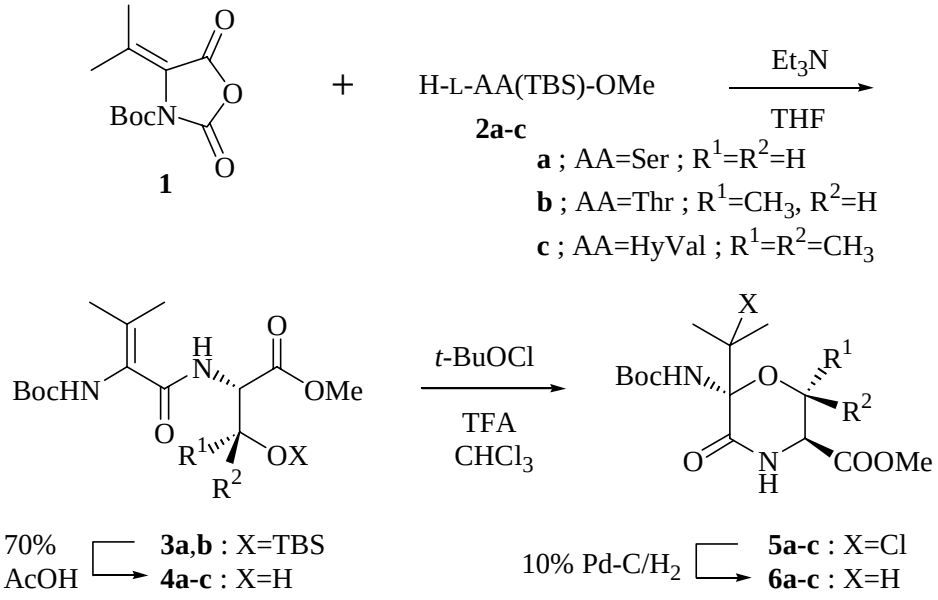
In this paper, we wish to report that the synthesis and intramolecular stereoselective addition of Δ^1-dehydrodipeptides (**4**)[6] (Boc-ΔVal-L-AA-OMe: AA=Ser, Thr, HyVal) gave novel and interesting 6-substituted 5-oxomorpholine-3-carboxylates (**5**). Furthermore, the configuration of **5** could be determined clearly by single crystal X-Ray analysis.

First, after the L-hydroxyvaline (L-HyVal) as a hydroxylated α-amino acid was prepared from *t*-butoxy-

carbonyl (Boc)-L-Ser-OMe in four steps,[7] the substrate Δ^1-dehydrodipeptide,[8,9] *t*-butoxycarbonyl (Boc)-ΔVal-L-AA-OMe (**4a-c**) (AA: **a**; Ser, **b**; Thr, and **c**; HyVal) was synthesized as follows.

Coupling of *N*-Boc-*N*-carboxy-α-dehydrovaline anhydride (Boc-ΔVal·NCA: **1**), derived by protection of ΔVal·NCA with di-*t*-butyl dicarbonate [$(Boc)_2O$] in the presence of dimethylaminopyridine (DMAP),[9] with an appropriate hydroxylated L-α-amino acid methyl ester [**2**: **a**; Ser(TBS), **b**; Thr(TBS), **c**; HyVal] (TBS=*t*-butyldimethylsilyl) using Et_3N was carried out to give Boc-ΔVal-L-Ser(TBS)-OMe (**3a**), Boc-ΔVal-L-Thr(TBS)-OMe (**3b**), and Boc-ΔVal-L-HyVal-OMe (**4c**). Subsequent *O*-deprotection of the TBS group of **3a** and **3b** with 70% acetic acid gave the expected Boc-ΔVal-L-Ser-OMe (**4a**) and Boc-ΔVal-L-Thr-OMe (**4b**).

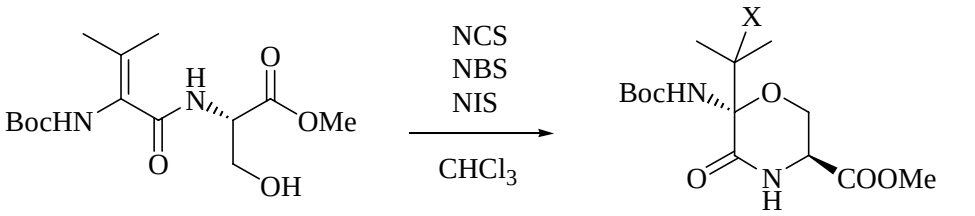
Secondly, according to the method reported earlier,[10] halogenation of **4a-c** with *t*-BuOCl in the presence of trifluoroacetic acid (TFA) in $CHCl_3$ was carried out to give colorless crystals. The products were purified on a silica gel column chromatography and characterized by the IR and ^1H NMR spectral data, and by the X-Ray analysis. From the structural assignment of the obtained crystals as mentioned later, it was found that the cyclization of **4a-c** with *t*-BuOCl occurred to give methyl (3*S*,6*R*)-6-(*N*-Boc)amino-6-(1-chloroisopropyl)-5-oxomorpholine-3-carboxylate (**5a**), methyl (2*R*,3*S*,6*R*)-6-(*N*-Boc)amino-6-(1-chloroisopropyl)-2-methyl-5-oxomorpholine-3-carboxylate (**5b**), and methyl (3*S*,6*R*)-6-(*N*-Boc)amino-6-(1-chloroisopropyl)-2,2-dimethyl-5-oxomorpholine-3-carboxylate (**5c**) in 88%, 63%, and 59% yields, respectively. Subsequently, the hydrogenolysis of the 6-chloro group of **5a** with hydrogen on 10% Pd-C in the presence of Et_3N was tried successfully to give the corresponding 6-isopropyl-5-oxomorpholine derivative (**6a**) in almost quantitative yield, as shown in Scheme 1.



Scheme 1.

Additionally, in the place of *t*-BuOCl, *N*-chlorosuccinimide (NCS) as a similar halogenation reagent was

used in the reaction of **4a**. As a result, additional cyclization of **4a** with NCS in $CHCl_3$ also proceeded readily to give **5a** in 80% yield. Similarly to the case of NCS, reaction of **4a** with NBS or *N*-iodosuccinimide (NIS) gave methyl (3*S*,6*R*)-6-(*N*-Boc)amino-6-(1-bromoisopropyl)- and (3*S*,6*R*)-6-(*N*-Boc)amino-6-(1-iodoisopropyl)-5-oxomorpholine-3-carboxylates (**5d** and **5e**) in 80% and 72% yields, respectively, as shown in Scheme 2.



4a **5a, d, e**

a; X=Cl, **d**; X=Br, **e**; X=I

Scheme 2.

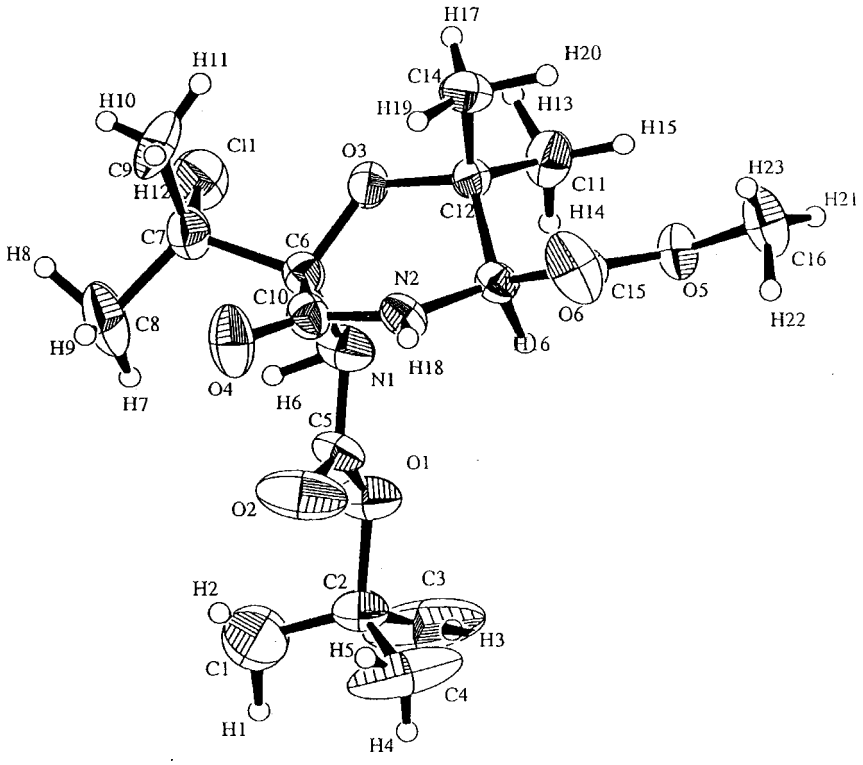
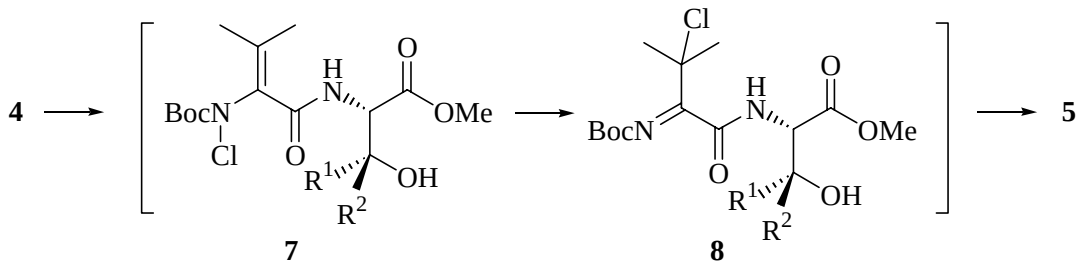


Figure 1. OPTEP drawing of **5c**

Interestingly, based on the ^{1}H NMR spectral analyses of **5**, it was found that the products were obtained in almost 100% diasteromeric excess. The structures of **5** and **6** were confirmed by the spectroscopic (IR and ^{1}H NMR spectrometry) and satisfactory elemental analyses. As a result, in particular, the

ORTEP drawing of **5c** by the single crystal X-Ray analysis shows that the configurations at C-3 and C-6 are unequivocally (*S*) and (*R*), as shown in Figure 1.

From the fact that the reaction of DHA with NBS in a protic reagent, such as alcohol or amine, yielded β-bromoalkyl-α-alkoxy- or -α,α'-diamino acid,[11] it has been already proved that the 1,3-migration of the bromine of the first formed α-(*N*-bromo)-DHA as an intermediate to the corresponding β-bromo-α-imino acid occurred, followed by immediate intermolecular addition of a protic reagent to the C=N bond of the formed α-imino acid.[11,12] Therefore, similarly, in the case using dehydrodipeptide as well, the formation mechanism of **5** from **4** was postulated as follows; the substitution of chlorine to the amino group of **4** and then 1,3-migration of the chlorine of the formed Boc-ΔVal(Cl)-L-AA-OMe (**7**), followed by diastereoselective intramolecular addition of the hydroxy group to the C=N bond of α-iminoacyl amino acid intermediate (**8**), as shown in Scheme 3.



Scheme 3.

In conclusion, it is interesting that the diastereoselective cyclization of the *N*-protected Δ^1-dehydrodipeptide ester occurred by using a halogenation reagent. Furthermore, from the result, wide application of the reaction is expected for the synthesis of various novel morpholine derivatives.

EXPERIMENTAL

The melting points were measured using a Yamato (Model Mp-21) micro-melting point apparatus, and are uncorrected. The IR spectra were recorded using a Hitachi EPI-G3 spectrophotometer in KBr. The NMR spectra were measured with JEOL FX 200 and JNE 500 spectrometers in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane used as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH.

Boc-ΔVal-L-Ser(TBS)-OMe (3a). A solution of ΔVal·NCA (123 mg, 0.87 mmol) and $(Boc)_2O$ (381 mg, 1.75 mmol) in THF (29 mL) in the presence of DMAP (192 mg, 1.57 mmol) was stirred at 0 °C and at rt for 30 min. To the resultant solution was added, with stirring, a solution of H-L-Ser(TBS)-OMe

(**2a**) (2.0 g, 8.65 mmol) in THF (10 mL) in the presence of Et_3N (1.2 g, 11.80 mmol) at 0 ^oC and then at rt for 2 h. Concentration *in vacuo* gave a residue, to which was added EtOAc (30 mL). The reaction mixture was washed with brine (20 mL x 3), 10% citric acid (20 mL), and saturated $NaHCO_3$ aqueous solution (20 mL), and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a residual product, which was purified on a silica gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give **3a** as colorless crystals; Yield 82%. mp 70.5-71.5 ^oC (hexane-EtOAc). $[\alpha]_D^{25}$ +22.2^o (*c* 1.0, MeOH). IR: 3388, 3300, 1715, 1669, 1639 cm^{-1}. ^1H NMR: δ 0.00 (s, 6H, $Si(CH_3)_2$), 0.84 (s, 9H, $SiCH_2(CH_3)_3$, 1.44 (s, 9H, $COC(CH_3)_3$), 1.78 and 2.06 (each s, 6H, ΔVal's CH_3 x 2), 3.72 (s, 3H, OCH_3), 3.81-4.11 (m, 2H, Ser's β-H), 4.57-4.82 (m, 1H, Ser's α-H), 5.75 (br s, 1H, ΔVal's NH), 5.05 (br s, 1H, Ser's NH). *Anal*. Calcd for $C_{20}H_{38}N_2O_6Si$: C, 55.78; H, 8.89; N, 6.51. Found: C, 55.44; H, 9.07; N, 6.51.

Boc-ΔVal-L-Ser-OMe (4a). Treatment of **3a** (0.71 mmol) with 70% AcOH (20 mL) at rt for 6 h gave crude crystals, which were purified on a silica gel column using EtOAc to give **4a** as colorless crystals; Yield 45%. mp 114-115 ^oC (hexane-EtOAc). $[\alpha]_D^{25}$ +6.2^o (*c* 0.8, MeOH). IR: 3268, 2974, 1695, 1509 cm^{-1}. ^1H NMR: δ 1.44 (s, 9H, $C(CH_3)_3$), 1.79 and 2.02 (each s, 6H, ΔVal's CH_3 x 2), 3.48 (br s, 1H, OH), 3.79 (s, 3H, OCH_3), 3.80-4.30 (m, 3H, Ser's α,β-H), 6.03 (br d, 1H, Ser's NH, *J*=7.7 Hz), 6.19 (br s, 1H, ΔVal's NH). *Anal*. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.16; H, 7.65; N, 8.85. Found: C, 52.85; H, 7.71; N, 8.81.

Boc-ΔVal-L-Thr-OMe (4b). Similarly to the case of **3a** and **4a**, reaction of **1** with H-L-Thr(TBS)-OMe was worked up to give Boc-ΔVal-L-Thr(TBS)-OMe (**3b**), which was intact treated with 70% AcOH to give **4b**. Colorless powder; Yield 51%. mp 139-140 ^oC (hexane-EtOAc). $[\alpha]_D^{25}$ +10.0^o (*c* 1.0, MeOH). IR: 3448, 3298, 1758, 1746, 1698, 1623 cm^{-1}. ^1H NMR: δ 1.27 (d, 3H, Thr's CH_3, *J*=6.6 Hz), 1.46 (s, 9H, $C(CH_3)_3$), 1.80 and 2.04 (each s, 6H, ΔVal's CH_3 x 2), 2.61 (br d, 1H, OH, *J*=5.5 Hz), 3.77 (s, 3H, OCH_3), 4.05-4.45 (m, 1H, Thr's β-H), 4.75 (dd, 1H, Thr's α-H, *J*=3.4, 9.0 Hz), 5.80 (br s, 1H, ΔVal's NH), 6.81 (br d, 1H, Thr's NH, *J*=9.0 Hz). *Anal*. Calcd for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.37; H, 7.76; N, 8.52.

Boc-ΔVal-L-HyVal-OMe (4c). Similarly to the case of **3a**, **4c** was obtained from **1** and H-L-HyVal-OMe (**2c**). Colorless powder; Yield 68%. mp 139-140 ^oC (hexane-EtOAc). $[\alpha]_D^{25}$ –4.6^o (*c* 1.0, MeOH). IR: 3453, 3260, 3084, 1758, 1743, 1681, 1625 cm^{-1}. ^1H NMR: δ 1.25 and 1.30 (each s, 6H, HyVal's CH_3 x 2), 1.45 (s, 9H, $C(CH_3)_3$), 1.80 and 2.03 (each s, 6H, ΔVal's CH_3 x 2), 3.10 (br s, 1H, OH), 3.77 (s, 3H, OCH_3), 4.65 (br d, 1H, HyVal's α-H, *J*=8.9 Hz), 5.84 (br s, 1H, ΔVal's NH), 6.91 (br d, 1H, HyVal's NH,

J=8.9 Hz). *Anal*. Calcd for $C_{16}H_{28}N_2O_6$: C, 55.80; H, 8.19; N, 8.13. Found: C, 55.79; H, 8.31; N, 8.16.

Methyl (3*S*,6*R*)-6-*t*-Butoxycarbonylamino-6-(1-chloropropyl)-5-oxomorpholine-3-carboxylate (5a). ***Method A: From 4a and t-BuOCl.*** To a suspension of **4a** (139 mg, 0.44 mmol) in $CHCl_3$ (4 mL) was added, with stirring, TFA (1.0 mg, 0.009 mmol) and then *t*-BuOCl (52.0 mg, 0.48 mmol) at rt. After stirring for 10 h, the reaction mixture was washed with brine (10 mL x 2), 10% citric acid (10 mL), saturated $NaHCO_3$ aqueous solution (10 mL), and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave crude crystals, which were purified on a silica gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give **5a** as colorless plates; Yield 88%. mp 161-162 ^oC (hexane-EtOAc). $[\alpha]_D^{25}$ +55.9^o (*c* 1.0, MeOH). IR: 3385, 3285, 1725, 1687 cm^{-1}. ^1H NMR: δ 1.45 (s, 9H, $C(CH_3)_3$), 1.66 and 1.90 (each s, 6H, $CCl(CH_3)_2$), 3.79 (s, 3H, OCH_3), 4.20 (dt, 1H, NHC*H*, *J*=7.0, 7.4 Hz), 4.33-4.65 (m, 2H, CH_2), 5.73 (br s, 1H, OCONH), 6.69 (br d, 1H, CONH, *J*=7.0 Hz). *Anal*. Calcd for $C_{14}H_{23}N_2O_6Cl$: C, 47.93; H, 6.61; N, 7.99. Found: C, 48.10, H, 6.88; N, 8.12.

Method B: From 4a and NCS. To a suspension of **4a** (139 mg, 0.44 mmol) and TFA (l.0 mg, 0.009mmol) in $CHCl_3$ (4 mL) was added, with stirring, NCS (0.48 mmol) at rt. After stirring for 6 h, the reaction mixture was worked up similarly to the case of Method A. Yield 80%.

Methyl (2*S*,3*S*,6*R*)-6-*t*-Butoxycarbonylamino-6-(1-chloroisopropyl)-2-methyl-5-oxomorpholine-3-carboxylate (5b). Similarly to the case of **5a**, **5b** was also obtained. Colorless plates; Yield 63%. mp 127-128 ^oC (hexane-EtOAc). $[\alpha]_D^{26}$ +6.5^o (*c* 1.0, MeOH). IR: 3279, 3227, 1737, 1680 cm^{-1}. ^1H NMR: δ 1.30 (d, 3H, CHC*H*$_3$, *J*=6.4 Hz), 1.43 (s, 9H, $C(CH_3)_3$), 1.68 and 1.76 (each s, 6H, $CCl(CH_3)_2$), 3.77 (s, 3H, OCH_3), 4.05-4.70 (m, 2H, NHC*H*, C*H*CH_3), 5.62 (br s, 1H, N*H*CH), 7.68 (br s, 1H, OCONH). *Anal*. Calcd for $C_{15}H_{25}N_2O_6Cl$: C, 49.38; H, 6.91; N, 7.68. Found: C, 49.26; H, 7.18; N, 7.32.

Methyl (3*S*,6*R*)-6-*t*-Butoxycarbonylamino-6-(1-chloroisopropyl)-2,2-dimethyl-5-oxomorpholine-3-carboxylate (5c). Similarly to the case of 5a, 5c was obtained. Colorless needles; Yield 59%. mp 154-155 ^oC (hexane-EtOAc). $[\alpha]_D^{23}$ +4.2^o (*c* 1.0, MeOH). IR: 3354, 2988, 1731, 1708 cm^{-1}. ^1H NMR: δ 1.14 (s, 3H, $C(CH_3)CH_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.60 (s, 3H, $C(CH_3)CH_3$), 1.74 and 1.93 (each s, 6H, $CCl(CH_3)_2$), 3.83 (s, 3H, OCH_3), 4.44 (br s, 1H, NHC*H*), 5.57 (br s, 1H, OCONH), 6.34 (br s, 1H, N*H*CH). *Anal*. Calcd for $C_{16}H_{27}N_2O_6Cl$: C, 50.73; H, 7.18; N, 7.39. Found: C, 50.77; H, 7.14; N, 7.36.

X-Ray Structure Determination of 5c. A colorless prismatic crystal of $C_{16}H_{27}N_2O_6Cl$ having approximate dimensions of 0.20 x 0.25 x 0.50 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation. Cell

constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in the range $22.01 < 2\theta < 24.84^{o}$ corresponded to a primitive orthorhombic cell with dimensions: a=9.868(6) $\AA$, b=29.485(7) $\AA$, c=6.787(7) $\AA$, V=1972(1) $\AA^3$. For Z=4 and F.W.=378.85, the calculated density is 1.27 g/cm^3. The systematic absences of: h00: h≠/2n, 0k0: k≠2n, 001: 1≠2n uniquely determine the space group to be $P2_12_12_1$(#19).

The data were collected at a temperature of 23 ± 1^{o} C using the ω–2θ scan technique to a maximum 2θ value of 55.0^{o}. Omega scans of several intense reflections, made prior to data collection, had an average width at half-heigth of 0.37^{o} with a take-off angle of 6.0^{o}. Scans of $(0.73 + 0.30 \tan \theta)^{o}$ were made at a speed of 8.0^{o}/min (in omega). The weak reflections (I<10.0σ(I)) were rescanned (maximum of 5 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to backgroud counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 258 mm, and the detector aperture was 9.0 x 13.0 mm (horizontal x vertical).

A total of 2645 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards increased by 0.8%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Mo-Kα radiation is 2.2 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.96 to 1.00. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full matrix least-squares refinement was based on 1330 observed reflections (I>3.00σ (I)) and 226 variable parameters and converged (largest parameter was 0.07 times its esd) with unweighted and weighted agreement factors of:

$R=\Sigma \| Fo | - | Fc \| / \Sigma | Fo | = 0.055$ $Rw=[(\Sigma w(| Fo | - | Fc |)^2 / \Sigma w Fo^2)]^{1/2} = 0.064$.

The standard deviation of an observation of unit weight was 2.33. The weighting scheme was based on counting statistics and included a factor (p=0.027) to downweight the intense reflections. Plots of $\Sigma w(| Fo | - | Fc |)^2$ versus $| Fo |$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the difference Fourier map corresponded to 0.49 and –0.20 $e^-/\AA^3$, respectively.

Methyl (3*S*,6*R*)-*t*-Butoxycarbonylamino-6-(1-bromoisopropyl)-5-oxomorpholine-3-carboxylate (5d). Similarly to the case of Method B for the synthesis of **5a**. Compound (**5d**) was obtained from **4a** and NBS. Colorless plates; Yield 80%. mp 159.5-160.0 ^{o}C (hexane-EtOAc). $[\alpha]_D^{26}$ $+103.3^{o}$ (*c* 1.0,

MeOH). IR: 3323, 3139, 1730, 1691 cm^{-1}. ^1H NMR: δ 1.36 (s, 9H, $C(CH_3)_3$), 1.73 and 2.01 (each s, 6H, $CBr(CH_3)_2$), 3.70 (s, 3H, OCH_3), 4.07-4.10 (m, 1H, NHC*H*), 4.23-4.57 (m, 2H, OCH_2), 5.65 (br s, 1H, OCONH), 6.37 (br s, 1H, CONH). *Anal*. Calcd for $C_{14}H_{23}N_2O_6Br$: C, 42.54; H, 5.87; N, 7.09. Found: C, 42.30; H, 6.02; N, 7.15.

Methyl (3*S*,6*R*)-*t*-Butoxycarbonylamino-6-(1-iodoisopropyl)-5-oxomorpholine-3-carboxylate (5e). Similarly to the case of Method B for the synthesis of **5a**. Compound **5e** was obtained from **4a** and NIS. Colorless powder; Yield 72%. mp 154-155 °C (hexane-EtOAc). $[\alpha]_D^{26}$ +62.6° (*c* 1.0, MeOH). IR: 3389, 3327, 3134, 1729, 1690 cm^{-1}. ^1H NMR: δ 1.45 (s, 9H, $C(CH_3)_3$), 1.99 and 2.35 (each s, 6H, $CI(CH_3)_2$), 3.79 (s, 3H, OCH_3), 4.14-4.68 (m, 3H, NHC*H* and OCH_2), 5.59 (br s, 1H, OCONH), 6.53 (br d, 1H, CONH, *J*=4.9 Hz). *Anal*. Calcd for $C_{14}H_{23}N_2O_6I$: C, 38.02; H, 5.24; N, 6.33. Found: C, 38.31; H, 5.49; N, 6.23.

Methyl (3*S*,6*R*)-*t*-Butoxycarbonylamino-6-isopropyl-5-oxomorpholine-3-carboxylate (6a). A suspension of **5a** (50 mg, 0.014 mmol) and 10% Pd-C (2 mg) in the presence of Et_3N (1 mL) in MeOH (50 mL) was stirred under H_2 gas stream at rt for 1 h. After Pd/C was filtered off, the filtrate was concentrated *in vacuo* to give a residue, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **6a** as a colorless powder; Yield 99%. mp 142-143 °C (hexane-EtOAc). $[\alpha]_D^{25}$ +29.8° (*c* 1.0, MeOH). IR: 3273, 1752, 1717, 1682, 1531 cm^{-1}. ^1H NMR: δ 0.97, 1.32 (d x 2, 6H, $CH(CH_3)_2$, *J*=4.2 Hz), 1.44 (s, 9H, $C(CH_3)_3$), 2.20-2.33 (m, 1H, $CH(CH_3)_2$), 3.74 (s, 3H, OCH_3), 4.16-4.26 (m, 2H, CH_2), 4.29-4.66 (m, 1H, NHC*H*), 5.33 (br s, 1H, OCONH), 6.65 (br s, 1H, N*H*CH). *Anal*. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.33; H, 7.36; N, 8.99. Found: C, 53.15; H, 7.65; N, 8.86.

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