TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION OF RADIOSUMIN, A STRONG TRYP SIN INHIBITOR FROM THE BLUE-GREEN ALGA PLECTONEMA RADIOSUM

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Dedicated to Prof. A. I. Meyers on the occasion of his 70th birthday.

Abstract-Radinosumin (1), a strong trypsin inhibitory dipeptide isolated from the freshwater blue-green alga Plectonema radiosum (NIES-515), was synthesized for the first time by use of the hetero Diels-Alder reaction, the Horner-Wadsworth-Emmons reaction, the Corey-Winter reaction, regioselective hydrogenation, and reduction with zinc and formic acid as key steps, which unambiguously determined the absolute configuration of the structurally unique and biologically intriguing aquatic natural product (1).

Radinosumin was isolated by Murakami and co-workers from the freshwater blue-green alga Plectonema radiosum (NIES-515).1 Its structure was elucidated to be the dipeptide composed of two unusual amino acids: (2S,7R)-Aayp (2-amino-3-(4-amino-2-cyclohexen-1-ylidene)propionic acid) and (2S,7aR or S)-Aacp (2-amino-3-(4-amino-2-cyclohexylidene)propionic acid). Radinosumin was revealed to be a protease inhibitor, which inhibited trypsin with an IC₅₀ of 0.14 μg/mL, plasmin with an IC₅₀ of 6.2 μg/mL, but did not inhibit chymotrypsin, elastase, or papain at 200 μg/mL.1 We have been quite interested in the synthesis of aquatic natural products having unusual amino acids,2 and the structural curiosity as well as its interesting biological activities stimulated us to synthesize radinosumin.3

![Figure 1](image-url)
We now describe the first total synthesis of radiosumin which clearly identified the configuration at C-7 position of Aacp to be \((aS)\) and culminated in the determination of the absolute stereostructure of this interesting molecule to be 1, as shown in Figure 1.

Before the construction of the whole molecule of radiosumin (1), two components, Aayp and Aacp, had to be synthesized by a stereodefined manner. Since these two amino acids have \((S)\)-configuration at each C-2 position, use of proteinogenic \((S)\)-\(\alpha\)-amino acids as starting materials would be feasible. Furthermore, since the absolute configuration at the C-7 position of Aacp remained to be determined, both \((aR)\)- and \((aS)\)-isomers should be prepared in a convenient way. According to these considerations, we thought that the two \((S)\)-alanine synthons (2) \(^4\text{a}\) or (3) would react with the carbonyl compounds (4 or 5) or the anion (6) to give Aayp or Aacp, as shown in Figure 2.

First attempt of the synthesis of Aacp started from 4-tert-butyloxy carbonylaminocyclohexanone (8), easily prepared from 4-aminocyclohexanol hydrochloride (7•HCl), as shown in Scheme 1. However, condensation of 8 with \(^9\text{a-d}\) \(^4\text{b-e}\) equivalents of the alanine anion synthon (2), mostly resulted in the recovery of the starting materials without the formation of the desired products.

In another attempt, the alanine cation equivalent (10a)\(^5\text{a,b}\) or (10b) \(^5\text{c}\) corresponding to 3 was allowed to react with the lithium salt from the diselenoacetal (11), but the reaction took a complicated course. Thus the direct use of \((S)\)-\(\alpha\)-amino acids proved to be fruitless (Scheme 2).
Next, we designed a synthetic route using an asymmetric olefination followed by the asymmetric hydrocyanation then amination or the Strecker synthesis. Thus, trans-4-aminocyclohexanol (7) was first converted to the DBT-ketone (12), which was transformed to the 1,2-unsaturated DBT-aldehyde (13) by the Horner-Wadsworth-Emmons reaction, reduction with diisobutylaluminum hydride, followed by oxidation with chemical manganese dioxide (CMD), as shown in Scheme 3. The racemic DBT-aldehyde (13) thus obtained underwent the asymmetric catalytic hydrocyanation by use of Oguni’s protocol. The desired cyanohydrin was obtained in 94% yield as a diastereoisomeric mixture of 15a and 15b with enantiomeric ratio of ca. 8 : 1 by use of the Schiff base (14) as a chiral catalyst. The enantiomeric ratio of each diastereomer was determined by 1H NMR spectra of the (S)-MTPA esters of 15a and 15b. However, conversion of the cyanohydrins (15a, b) to the corresponding amino compounds could not be brought about. The attempted Strecker synthesis by use of the aldehyde (13) was also unsuccessful.

Figure 3 shows the alternative approaches, routes A and B, to Aacp. The route A might enable construction of the stereogenic centers at both the C-2 and C-7 positions by isomerization of the double bond when...
asymmetric hydrazination is carried out.\textsuperscript{12} In the route B, the stereogenic center at the C-2 position might be stereoselectively introduced.

In the route A, the aldehyde (17) was first prepared from the amino acid (16) by amine protection, methyl esterification, and then reduction with disobutyraluminum hydride, as shown in Scheme 4. The aldehyde (17) reacted with the keto phosphorane (19) prepared from the bromide (18) to give the coupling product (20a) in 91\% yield. Boc protected 20a was transformed to the N-acetyl compounds which were separated to furnish 20b (the less polar isomer) in 77\% yield and 20c (the more polar isomer) in 23\% yield. Unfortunately, however, addition of di-\textit{tert}-butyl azodicarboxylate to 20b under basic conditions failed to give the desired Aacp derivative (21).

To realize the route B, the \(\beta,\gamma\)-unsaturated carboxylic acid (26) was prepared from the phosphonium salt (22) and the ketone (8) via 23-25, as shown in Scheme 5. Conversion of 26 to the Evans amide (28) with the enolate (27) followed by replacement of the Boc group with the acetyl moiety afforded the N-acetyl Evans
amide (29). Addition of di-tert-butyl azodicarboxylate to 29 proceeded to give the desired hydrazino derivative (30). However, separation of the diastereomers in 30 failed and removal of the chiral auxiliary from 30 was found to be difficult without epimerization at the C-2 stereogenic center. Thus this route again had to be abandoned.

Next, we investigated the synthesis of racemic β,γ-unsaturated trisubstituted α-amino acids according to the method of Elder and co-workers13 followed by optical resolution, as shown in Scheme 6. The Elder’s phosphonate (32a), obtained from bromopyruvic acid (31) by oximation and then Arbuzov reaction, was

![Scheme 5](image)

![Scheme 6](image)
lithiated and reacted with the DBT-ketone (12) to give the Horner-Wadsworth-Emmons product (33). Attempted kinetically controlled optical resolution by AD-mix\textsuperscript{14} failed to give the optically active product whereas the asymmetric reduction of the oxime\textsuperscript{15} resulted in the formation of an uncharacterized product. Reduction of 33 with zinc and formic acid\textsuperscript{13} followed by treatment with Boc\textsubscript{2}O afforded 34\textsubscript{a} and 34\textsubscript{b}, the protected forms of Aacp, in almost equal ratio. After their chromatographic separation, attempted optical resolution of these isomers and their derivatives was unfortunately unsuccessful.

Alternatively, the oxazine (36) was prepared from the hetero Diels-Alder reaction of 1,3-cyclohexadiene and the α-nitroso-α-chloro sugar derivative (35) according to the literature,\textsuperscript{16} shown in Scheme 7. Treatment of 36 with benzoxycarbonyl chloride (ZCl), reductive cleavage of the N-O bond,\textsuperscript{17} followed by oxidation with CMD\textsuperscript{9} gave 38. Coupling of 38 with the Elder’s phosphonate (32\textsubscript{b}) was attempted under reaction conditions analogous to the coupling of the methyl ester (32\textsubscript{a}) with the ketone (12), giving the ethyl ester (39) in lower yield as a mixture of (E)- and (Z)-isomers in preference of the undesired Z isomer. Although the reduction of the oxime function in 39 followed by amine protection with Boc\textsubscript{2}O afforded the desired Aayp derivative (40), it was revealed to be impossible to separate each isomer in pure state.

Based on these numerous unsuccessful attempts, we designed the alternative route that first introduced the C-7 amino function in a stereoselective manner, as shown in Figure 4. As an electrophile which would react with the Elder’s phosphonate (32\textsubscript{a}), we employed optically active aminocyclitol (41), which could be prepared from 42,\textsuperscript{18} the hetero Diels-Alder adduct from the nitroso sugar derivative (35) and the diene (43) analogously as the conversion of 35 to 36. The acetonide group in the cyclitol (41) was expected to function as followed: (1) protection of the double bond, (2) increase of stereoselectivity and chemical yield during the Horner-Wadsworth-Emmons reaction, and (3) easiness of separation of diastereomers. After preparation of (7R)-Aayp, selective reduction of the disubstituted double bond would give (7aS)-Aacp. The synthetic works according to this retrosynthetic consideration culminated in the successful synthesis of radiosumin and the determination of its absolute configuration.

Thus, the asymmetric hetero Diels-Alder reaction\textsuperscript{16} of the α-chloro-α-nitro compound (35) and cis-dihydrocatechol (43)\textsuperscript{18,19} afforded the adduct (42), whose amino group was protected with Boc\textsubscript{2}O to give
the Boc-adduct (44) in 90% yield in 2 steps, as shown in Scheme 8. The oxazine ring of 44 was reductively cleaved with sodium amalgam in a buffered solution17 to give the cyclohexenol (45). Catalytic hydrogenation of 45 over Pd/C followed by the Swern oxidation of the resulting cyclohexanol derivative (46a) afforded the desired aminocyclitol (41) in excellent yield.

Analogously, 46b antipodal to 46a was prepared from the Diels-Alder adduct (36), as shown in Scheme 9. The successive Boc protection, dihydroxylation with osmium, acetalization followed by amalgam reduction afforded 46b. The both cyclohexanols (46a) and (46b) were respectively converted to the corresponding 3,5-dinitrobenzoates (53a) and (53b) to determine the enantiomeric excess of each isomer. Comparison of the both compounds on chiral HPLC revealed their enantiomeric excess to be 94% for 53a and 96% for 53b. The corresponding benzyloxycarbonyl derivative (52) was similarly prepared from 37, and converted to the Z-ketone (54).

Utilizing the aminocyclitols (41) and (54), the Horner-Wadsworth-Emmons reaction with the Elder’s phosphonates (32a) was investigated under various reaction conditions, as summarized in Table 1. The use of butyllithium in 1,2-dimethoxyethane (DME) gave the best result, and the product (55a) was obtained in
Scheme 9

Table 1

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<th>entry</th>
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<th>temp.</th>
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<th>yield (%)</th>
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<tr>
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<td>41</td>
<td>n-BuLi</td>
<td>THF</td>
<td>-78°C to rt</td>
<td>20</td>
<td>88</td>
<td>82 : 18</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>LDA</td>
<td>THF</td>
<td>-78°C to -20°C</td>
<td>18</td>
<td>66</td>
<td>83 : 17</td>
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<tr>
<td>4</td>
<td>41</td>
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<td>-78°C to rt</td>
<td>15</td>
<td>90</td>
<td>78 : 22</td>
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<td>15</td>
<td>71</td>
<td>87 : 13</td>
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<td>-78°C to rt</td>
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<td>75 : 25</td>
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NMO : N-methylmorpholine N-oxide; DMP : 2,2-dimethoxypropane;  
DNB : 3,5-dinitrobenzoyl; DMAP : 4-(N,N-dimethylamino)pyridine
preference of the E-isomer (94 : 6) in 86% yield (see entry 7 in Table 1).
The compound (55a) underwent the acidic removal of the acetonide function to give the diol (56) together
with a small amount of the lactone (57), whose separation was easily achieved on a silica gel column.
Treatment of the diol (56) with 1,1′-thiocarbonyldiimidazole (58) gave the thionocarbonate (59), which
smoothly gave the diene (61) by the action of the phospholidine (60) according to the Corey-Winter
protocol.20 Replacement of the Boc function of 61 with the benzyloxy carbonyl one afforded the Aayp
equivalent (62), as shown in Scheme 10.

Toward the synthesis of the (7aS)-Aacp derivative (65), the common intermediate (61) was first transformed to
its N-acetyl derivative (63), whose double bond in the ring was selectively hydrogenated by use of the Lindlar
catalyst to give the cyclohexane derivative (64).21 Reduction of the oxime ether group with zinc in formic acid
and then treatment with Boc₂O afforded the protected form (65) of (7aS)-Aacp as a mixture of
diastereoisomers at the C-2 position, shown in Scheme 11.

With the (7R)-Aayp equivalent (62) and (7aS)-Aacp derivative (65) in hand, we synthesized radiosumin (1) as
summarized in Scheme 12. After each protective group of 62 and 65 was removed, coupling by use of diethyl
phosphorocyanidate (DEPC, (EtO)₂P(O)CN)²² efficiently afforded the dipeptide as a mixture of
diastereoisomers (66a) and (66b) in a ratio of 55:45, which were separated by precipitation with chloroform
and ether. The dipeptides (66a) and (66b) thus obtained were respectively reduced with zinc in formic acid,
and the N-acetylation of the reduction products afforded the protected forms (67a-d). The diastereomeric ratio
of 67a and 67b was 55:45 while that of 67c and 67d was 44:56.

On the other hand, natural radiosumin (1) was converted to the protected form (67) by treatment with
benzyloxy carbonyl chloride and then trimethylsilyldiazomethane in methanol.²³
Comparison of the product on HPLC clearly revealed that 67a was identical with 67 derived from natural radiosumin. In addition, the synthetic 67a was identified with the naturally derived 67 by spectral comparisons as well as the optical rotation.

Thus the absolute configuration of the C-7 position in the Aacp unit of radiosumin (1) was determined clearly and proved to be the (αS)-configuration hence the absolute stereostructure of radiosumin was determined as shown in the structure (1).

Finally, conversion of the Z-radiosumin methyl ester (67a) to radiosumin (1) was achieved by use of bis(tri-n-butyltin)oxide in refluxing benzene under neutral conditions, giving radiosumin (1) together with the corresponding methyl ester and the starting material (67a). The synthetic radiosumin was identified with the natural one by comparison of their $^1$H NMR spectra and HPLC behavior. Radiosumin thus obtained was actually its trifluoroacetic acid (TFA) salt because 8% aqueous acetonitrile-0.05% TFA was used as an eluent for purification of the crude product on HPLC. The synthetic sample showed $[\alpha]_D^{20}+74.4^\circ$ (c 0.1, H$_2$O) while $[\alpha]_D^{20}+96^\circ$ (c 0.77, H$_2$O) was reported for the natural sample. This discrepancy may be attributed to the content of TFA attached to radiosumin because the natural sample showed $[\alpha]_D^{20}+79.2^\circ$ (c 0.1, H$_2$O) after retreatment with 8% aq. MeCN-0.05% TFA on HPLC.

Thus, we have succeeded in the first total synthesis of radiosumin (1) which determined the unidentified stereogenic center to be (αS) and hence the whole absolute stereostructure. The method employed here will be useful for the synthesis of radiosumin B, isolated recently, and other biologically interesting molecules.

**EXPERIMENTAL**

**General:** All melting and boiling points are uncorrected. Distillation was carried out by a Kugelrohr apparatus. IR spectra were measured with a SHIMADZU FTIR-8100 spectrophotometer. $^1$H NMR spectra were recorded on a JEOL EX-270 or GSX-400 spectrometer in CDCl$_3$ with tetramethylsilane or CHCl$_3$ as an internal standard, unless otherwise stated. MS spectra were obtained on a JEOL DX-300 spectrometer. Optical rotations were measured on a JASCO DIP-140 or DIP-1000 automatic polarimeter. Silica gel BW-820MH, BW-200, or BW-300 (purchased from Fuji Davison Co. Ltd.) and Silica gel 60-C$_{18}$ (purchased from NACALAI TESQUE, INC) were used for column chromatography. Analytical TLC was carried out.
Scheme 12
on a silica gel plate (Merck Art. 5715). THF and DME were dried by distillation from benzophenone ketyl. CH₂Cl₂, MeCN, Et₃N, DBU, and HMPA were dried by distillation from CaH₂. Benzene and toluene were dried by distillation from LiAlH₄. MeOH and EtOH were dried by distillation from magnesium alcoholate.

4-tert-Butoxycarbonylaminocyclohexanone (8). A solution of trans-4-aminocyclohexanol hydrochloride (7·HCl, 25.66 g, 169.19 mM) in H₂O-dioxane (170 mL·510 mL) was neutralized with 1N aq. NaOH (170 mL, 170 mmol), and Boc₂O (40.62 g, 186.11 mmol) was added at 0°C. After being stirred at ambient temperature for 2 h, the mixture was quenched with 1M KHSO₄. The whole was extracted with CHCl₃ (x 2) and washed with brine. The extracts were dried over Na₂SO₄, then concentrated in vacuo to give a white solid. The crude solid was recrystallized from CHCl₃-hexane to give trans-4-t-butoxycarbonylaminocyclohexanol (33.75 g, 93%) as colorless needles, mp 146-148°C. IR νmax (KBr): 4000-3000, 3847, 1684, 1534, 1456, 1387, 1366, 1320, 1273, 1254, 1231, 1183, 1071, 1042, 1026, 1005, 968, 953, 907, 891, 862, 801, 783, 764, 743 cm⁻¹. ¹H NMR δ 1.06-1.28 (m, 2H), 1.29-1.55 (m, 3H), 1.43 (s, 9H), 1.98 (m, 4H), 3.40 (br, 1H), 3.60 (m, 1H), 4.34 (br, 1H). Anal. Calcd for C₁₁H₂₁NO₃: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.18; H, 9.78; N, 6.38.

To a stirred solution of (COCl)₂ (8.05 mL, 92.23 mmol) in CH₂Cl₂ (400 mL) was added dropwise DMSO (7.85 mL, 110.5 mmol) at -78°C under argon and the mixture was stirred for 30 min. A solution of the above alcohol (13.22 g, 61.4 mmol) in CH₂Cl₂ (100 mL) was added and the mixture was stirred for 30 min. After addition of Et₃N (42.8 mL, 307 mmol), the whole was warmed to rt and stirred for 1 h. The mixture was quenched with H₂O, and extracted with CH₂Cl₂ (x 2). The extracts were washed with H₂O and saturated brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was recrystallized from CHCl₃-hexane to give 8 (12.86 g, 98%) as a white solid, mp 97-98°C. IR νmax (KBr): 3364, 1719, 1680, 1526, 1474, 1458, 1448, 1389, 1373, 1364, 1314, 1260, 1234, 1167, 1105, 1051, 1032, 1001, 941, 882, 760 cm⁻¹. ¹H NMR δ 1.45 (s, 9H), 1.70 (br, 2H), 2.24 (m, 2H), 2.42 (m, 4H), 3.92 (br, 1H). Anal. Calcd for C₁₁H₁₉NO₃: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.90; H, 9.05; N, 6.57.

4-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)cyclohexanone (12). A mixture of trans-4-aminocyclohexanol (7) (6.15 g, 53.375 mmol), formalin (53.4 mL), and i-Pr₂NEt (9.3 mL, 53.375 mmol) was stirred at ambient temperature for 10 min. The mixture was diluted with toluene and concentrated in vacuo. This work-up was repeated three times. The residue was dried under reduced pressure (2.0 mmHg) at rt for 5 h, dissolved in THF (267 mL), and then N, N'-dibenzylurea (12.81 g, 53.375 mmol) was added. After being refluxed for 3 h, the mixture was concentrated in vacuo. The residue was extracted with EtOAc (x 2), and washed with H₂O (x 3). The extracts were dried over Na₂SO₄, then concentrated in vacuo. The residual oil was purified by silica gel column chromatography (BW-200, 250 g, acetone:hexane=2:3) to give trans-4-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)cyclohexanol (20.18 g, 100%) as a colorless prism, mp 187-189°C. IR νmax (CHCl₃): 3418, 1622, 1504, 1455, 1358, 1298, 1250, 1215, 1161, 1140, 1123, 1065, 1028, 1019, 972, 951, 804, 758, 704, 669 cm⁻¹. ¹H NMR δ 0.94 (m, 4H), 1.35 (m, 3H), 1.75 (br d, 2H, J=10.6 Hz), 2.42 (m, 1H), 3.40 (m, 1H), 4.18 (s, 4H), 4.53 (s, 4H), 7.33 (m, 10H). Anal. Calcd for C₂₃H₂₉N₃O₂ 3/4H₂O: C, 70.29; H, 7.82; N, 10.69. Found: C, 69.90; H, 7.49; N, 10.59.
The above alcohol (3.50 g, 9.235 mmol) was oxidized as described for 4-t-butoxycarbonylamino-cyclohexanone (8) to give crude 12, which was purified by silica gel column chromatography (BW-200, 200 g, EtOAc:hexane=2:5 to 1:2) to furnish 12 (3.295 g, 95%) as a white waxy solid, mp 79-82°C. IR \( \nu_{\text{max}} \) (CHCl\(_3\)): 1717, 1640, 1497, 1455, 1429, 1358, 1330, 1296, 1291, 1258, 1188, 1148, 1132, 1075, 1028, 1013, 981, 953, 939, 887, 805, 750, 706, 668 cm\(^{-1}\). \( ^1 \text{H NMR} \) \( \delta \) 1.35 (m, 2H), 1.50 (br, 2H), 1.95 (ddd, 2H, \( J=15.2, 9.9, 5.3 \) Hz), 2.15 (m, 2H), 2.87 (ddd, 1H, \( J=11.8, 8.3, 3.3 \) Hz), 4.23 (s, 4H), 4.55 (s, 4H), 7.35 (m, 10H). Anal. Calcd for C\(_{23}\)H\(_{27}\)N\(_3\)O\(_2\): C, 73.18; H, 7.21; N, 11.13. Found: C, 72.93; H, 7.29; N, 10.93.

4-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)cyclohexylidenacetaldehyde (13). To a suspension of NaH (60% oil dispersion, 131 mg, 3.282 mmol) in THF (10.0 mL) was added dropwise a solution of trimethyl phosphononacetate (531 \( \mu \)L, 3.282 mmol) in THF (5.0 mL) at 0°C under argon, and the mixture was stirred for 30 min. A solution of 12 (1.125 g, 2.984 mmol) in THF (15.0 mL) was added to the mixture. After being stirred at rt for 1 h, the mixture was quenched with 10% aq. citric acid. The whole mixture was extracted with EtOAc twice, and the extracts were washed with H\(_2\)O and brine, dried over Na\(_2\)SO\(_4\), then concentrated in vacuo. The crude residue was purified by silica gel column chromatography (BW-200, 300 g, EtOAc:hexane=3:2 to 2:1) to give methyl 4-DBT-cyclohexylidenacetate (1.282 g, 97%) as a white waxy solid, mp 52-54°C. IR \( \nu_{\text{max}} \) (neat): 1715, 1640, 1497, 1455, 1296, 1244, 1196, 1163, 1146, 1076, 1028, 941, 862, 808, 749, 704 cm\(^{-1}\). \( ^1 \text{H NMR} \) \( \delta \) 1.0-1.2 (br, 2H), 1.3-1.5 (br, 2H), 1.7-1.9 (m, 2H), 2.0-2.2 (br d, 1H, \( J=14.2 \) Hz), 2.67 (m, 1H), 3.39 (br d, 1H, \( J=15.2\)Hz), 3.65 (s, 3H), 4.20 (s, 4H), 4.54 (s, 4H), 5.52 (s, 1H), 7.34 (m, 10H). Anal. Calcd for C\(_{26}\)H\(_{31}\)N\(_3\)O\(_3\): C, 72.03; H, 7.21; N, 9.69. Found: C, 72.25; H, 7.33; N, 9.55.

To a solution of the above ester (1.937 g, 4.37 mmol) in CH\(_2\)Cl\(_2\) (20 mL) was added diisobutylaluminum hydride (1.5 M in toluene, 8.7 mL, 13.12 mmol) at \(-78^\circ\)C under argon. After being stirred at this temperature for 3 h, the mixture was quenched with MeOH, followed by the addition of 1M KHSO\(_4\). The whole mixture was extracted with CH\(_2\)Cl\(_2\) (x 2), and the extracts were washed with sat. aq. NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 200 g, EtOAc) to give the allyl alcohol (1.705 g, 94%) as a white solid, mp 109-111°C. IR \( \nu_{\text{max}} \) (CHCl\(_3\)): 3700-3100, 3015, 2940, 1628, 1504, 1454, 1441, 1356, 1298, 1252, 1217, 1150, 1132, 1075, 1012, 943, 701, 668 cm\(^{-1}\). \( ^1 \text{H NMR} \) \( \delta \) 0.8-1.1 (br, 2H), 1.3-1.6 (m, 4H), 1.74 (br, 1H), 2.02 (br d, 1H, \( J=10.9 \) Hz), 2.35 (br d, 1H, \( J=13.2 \) Hz), 2.61 (m, 1H), 4.05 (d, 2H, \( J=7.33\)Hz), 4.19 (s, 4H), 4.53 (ABq, 4H, \( J=15.2 \) Hz), 5.28 (t, 1H, \( J=7.3 \) Hz), 7.33 (m, 10H). Anal. Calcd for C\(_{25}\)H\(_{31}\)N\(_3\)O\(_2\) \( \frac{1}{2} \text{H}_2\text{O}: \) C, 73.23; H, 7.74; N, 10.25. Found: C, 73.57; H, 7.77; N, 10.12.

To a solution of the above alcohol (1.605 g, 3.867 mmol) in CH\(_2\)Cl\(_2\) (40 mL) was added CMD (6.72 g, 77.34 mmol). After being stirred at ambient temperature for 8 h, the mixture was filtered through the pad of celite. The filtrate was concentrated in vacuo to give a yellow oily residue. The crude oil was purified by silica gel column chromatography (BW-820MH, 150 g, EtOAc:hexane= 7:3) to give 13 (1.467 g, 92%) as a white solid, mp 132-134°C. IR \( \nu_{\text{max}} \) (CHCl\(_3\)): 3019, 1672, 1630, 1499, 1455, 1354, 1298, 1252, 1217, 1184, 1115, 1076, 1012, 982, 943, 887, 808, 706, 668 cm\(^{-1}\). \( ^1 \text{H NMR} \) \( \delta \) 1.1 (m, 2H), 1.4 (m, 2H), 1.90 (dt, 2H,
J=10.7, 2.3 Hz), 2.17 (br d, 1H, J=13.9 Hz), 2.68 (m, 1H), 2.94 (br d, 1H, J=13.9 Hz), 4.20 (s, 4H), 4.54 (ABq, 4H, J=16.86 Hz), 5.72 (d, 1H, J=7.9 Hz), 7.35 (m, 10H), 9.88 (d, 1H, J=8.3 Hz). Anal. Calcd for C_{25}H_{29}N_{3}O_{2}: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.13; H, 7.28; N, 10.36.

2-Hydroxy-3-[4-(1,3-Dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)cyclohexylidene]propionitrile (15). To a solution of 14 (33 mg, 0.11 mmol) in CH_{2}Cl_{2} (0.5 mL) was added Ti(ORi)_{4} (28 µL, 0.1 mmol) at 0°C under argon, and the mixture was stirred for 1 h, then cooled to -78°C. A solution of 13 (207 mg, 0.5 mmol) in CH_{2}Cl_{2}-MeCN (2.0 mL-0.8 mL) was added dropwise to the mixture over 5 min period, followed by the addition of TMSCN (143 µL, 1.15 mmol) at -78°C. After being stirred at -50°C for 3 days and at -40°C for 5 days, the mixture was quenched with sat. aq. NaHCO_{3}. The whole mixture was extracted with EtOAc twice and washed with brine. The extracts were combined and dried over Na_{2}SO_{4} and concentrated in vacuo to give a yellow oil. The crude oil was treated with 10% aq. citric acid-MeOH (1.0 mL-3.0 mL) at ambient temperature for 1 h. The whole mixture was extracted with EtOAc (x 2), and washed with sat. aq. NaHCO_{3} and brine. The extracts were combined and dried over Na_{2}SO_{4}, then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 20g, EtOAc:hexane=3:1 to 4:1) to give 15a (less polar diastereomer, 75 mg, 34%) and 15b (polar diastereomer, 133 mg, 60%), respectively. The enantiomeric ratio of each diastereomer was determined by {\textsuperscript{1}}H NMR spectroscopy after conversion to their (S)-MTPA esters.

**Compound (15a):** a white solid, mp 128-130°C. IR ν_{max} (CHCl_{3}): 3140, 2247, 1640, 1504, 1455, 1439, 1356, 1344, 1298, 1260, 1215, 1154, 1132, 1121, 1076, 1028, 1007, 943, 933, 910, 839, 810 cm^{-1}. {\textsuperscript{1}}H NMR δ 0.93 (m, 2H), 1.26 (br, 2H), 1.59 (br t, 1H, J=12.9 Hz), 1.63 (br t, 1H, J=11.5 Hz), 2.02 (br d, 1H, J=12.9 Hz), 2.25 (br d, 1H, J=14.2 Hz), 2.59 (m, 1H), 3.7 (br, 1H), 4.18 (s, 4H), 4.52 (ABq, 4H, J=16.5 Hz), 5.00 (d, 1H, J=8.6 Hz), 5.27 (d, 1H, J=8.6 Hz), 7.33 (m, 10H). Anal. Calcd for C_{26}H_{30}N_{4}O_{2}: C, 72.53; H, 7.02; N, 13.01. Found: C, 72.36; H, 7.09; N, 12.97. (S)-MTPA ester of 15a: a viscous oil. IR ν_{max} (CHCl_{3}): 2361, 2342, 1759, 1632, 1501, 1455, 1354, 1298, 1217, 1188, 1173, 1123, 1109, 1080, 1013, 945, 918, 704, 667 cm^{-1}. {\textsuperscript{1}}H NMR δ 1.02 (m, 2H), 1.35 (m, 2H), 1.5-1.9 (m, 2H), 2.08 (br d, 1H, J=13.9 Hz), 2.08 (br d, 1H, J=14.2 Hz), 2.62 (m, 1H), 3.52 and 3.55 (d, J=1.0 Hz and br s, 3H), 4.18 (s, 4H), 4.53 (ABq, 4H, J=15.5 Hz), 5.22 and 5.31 (d, 12H, J=8.9 Hz and d, 0.88H, J=8.9 Hz), 6.06 and 6.08 (d, J=8.9 Hz and d, J=8.9 Hz; 1H), 7.33 (m, 10H), 7.44 (m, 5H).

**Compound (15b):** a white solid, mp 104-106°C. IR ν_{max} (CHCl_{3}): 3250, 2253, 1619, 1509, 1454, 1437, 1360, 1352, 1298, 1259, 1215, 1146, 1134, 1103, 1076, 1030, 1013, 939, 908, 833 cm^{-1}. {\textsuperscript{1}}H NMR δ 0.92 (m, 2H), 1.26 (br, 2H), 1.55 (br t, 1H, J=11.2 Hz), 1.72 (br t, 1H, J=11.2 Hz), 1.99 (br d, 1H, J=13.9 Hz), 2.24 (br d, 1H, J=13.9 Hz), 2.57 (m, 1H), 4.16 (s, 4H), 4.3 (br, 1H), 4.50 (ABq, 4H, J=18.2 Hz), 4.98 (d, 1H, J=8.3 Hz), 5.24 (d, 1H, J=8.3 Hz), 7.32 (m, 10H). (S)-MTPA ester of 15b: a viscous oil. IR ν_{max} (CHCl_{3}): 2361, 2343, 1759, 1636, 1499, 1455, 1354, 1298, 1236, 1186, 1173, 1123, 1107, 1080, 1015, 945, 930, 806, 706, 668 cm^{-1}. {\textsuperscript{1}}H NMR δ 0.90 (m, 2H), 1.36 (m, 2H), 1.5-1.9 (m, 2H), 2.07 (br d, 1H, J=15.8 Hz), 2.36 (br d, 1H, J=14.2 Hz), 2.59 (m, 1H), 3.48 and 3.54 (d, J=1.0 Hz and br s, 3H), 4.17 (s, 4H), 4.53 (ABq, 4H, J=15.5 Hz), 5.19 and 5.30 (d, 0.17H, J=9.2 Hz and d, 0.83H, J=9.2 Hz), 6.09 and 6.10 (d, J=9.2 Hz and d, J=9.2 Hz; 1H), 7.3 (m, 10H), 7.4 (m, 5H).
4-t-Butoxyaminocyclohexanaldehyde (17). To a solution of 4-aminoacyclohexanecarboxylic acid (16) (8.407 g, 56 mmol) in H2O-dioxane (90 mL-280 mL) was added 1N aq. NaOH (56 mL, 56 mmol) and Boc2O (13.4 g, 61.6 mmol) at 0°C. After being stirred at rt for 3 h, the mixture was concentrated in vacuo. 1M KHSO4 was added to the mixture, which was extracted with EtOAc (x 2). The extracts were washed with brine, dried over Na2SO4, and concentrated in vacuo to give a white powder. The crude acid was used for the next step without further purification.

The above acid was dissolved in DMF (200 mL) and K2CO3 (8.17 g, 59 mmol), and MeI (3.68 mL, 59 mmol) were added at ambient temperature. After being stirred at rt for 12 h, the mixture was diluted with EtOAc. The whole mixture was extracted with EtOAc (x 2). The extracts were washed with H2O and brine, dried over Na2SO4, then concentrated in vacuo. The residual oil was purified by silica gel column chromatography (BW-200, 300 g, EtOAc:hexane=1:4) to give methyl 4-t-butoxycarbonylamino-cyclohexanecarboxylate (13.89 g, 97%) as a viscous oil. IR νmax (neat): 3400, 1732, 1701, 1518, 1366, 1248, 1171, 1043, 1026 cm⁻¹. 1H NMR δ 1.44 (s, 9H), 1.4-2.0 (m, 8H), 2.47 (m, 1H), 3.6-3.7 (m, 1H), 3.68 (s, 3H), 4.58 (br, 1H). Anal. Calcd for C13H23NO4: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.55; H, 8.94; N, 5.46.

To a solution of methyl 4-t-butoxycarbonylamino-cyclohexanecarboxylate (1.515 g, 5.895 mmol) in CH2Cl2 (60 mL) was added diisobutylaluminum hydride (1.5M solution in toluene, 4.3 mL, 6.484 mmol) at -78°C under argon. After being stirred at -78°C for 2.5 h, diisobutylaluminum hydride (0.4 mL, 0.6 mmol) was added again to the mixture, which was stirred at this temperature for 1 h. The whole mixture was quenched with 1M KHSO4, warmed to rt, and extracted with CH2Cl2 (x 2). The extracts were washed with brine, dried over Na2SO4, then concentrated in vacuo to give an oily residue. Purification of the residue by silica gel column chromatography (BW-200, 100 g, EtOAc:hexane=1:4) afforded 17 (845 mg, 63%) as a colorless viscous oil. IR νmax (CHCl3): 3343, 1721, 1686, 1520, 1450, 1391, 1368, 1246, 1040, 1026, 877 cm⁻¹. 1H NMR δ 1.2-1.6 (m, 2H), 1.44 (s, 9H), 1.6-1.9 (m, 4H), 1.9-2.1 (m, 2H), 2.38 (br, 1H), 3.69 (br, 1H), 4.45 (br, 1H), 9.67 (s, 1H).

3-(4S)-4-Phenylmethyl-2-oxazolidinoyl)carbonylmethylmethylenetriphenylphosphorane (19). To a solution of (4S)-3-(2-bromoacetyl)-4-phenylmethyl-2-oxazolidinone (18) (2.365 g, 8.842 mmol) in toluene (30 mL) was added Ph3P (2.551 g, 9.746 mmol). After being stirred at ambient temperature for 5 days, the mixture was filtered and the precipitates were washed with Et2O. The precipitates were dissolved in H2O and added to 1N aq. NaOH. The mixture was triturated from Et2O-1N aq. NaOH to give crude 19 (3.18 g, 75%) as a pale brown powder, a part of which was purified by silica gel column chromatography (BW-200, EtOAc:hexane=3:2) to give 19 (50% from (4S)-3-(2-bromoacetyl)-4-phenylmethyl-2-oxazolidinone) as a white powder, which was used for analyses, mp 187-188°C. [α]D23 +44.1° (c=1.0, CHCl3). IR νmax (CHCl3): 3019, 1751, 1582, 1570, 1439, 1367, 1107 cm⁻¹. 1H NMR δ 2.84 (dd, 1H, J=13.2, 9.2 Hz), 3.28 (dd, 1H, J=13.2, 3.6 Hz), 4.02 (dd, 1H, J=8.9, 3.0 Hz), 4.10 (m, 1H), 4.78 (m, 2H), 7.2-7.7 (m, 20H). Anal. Calcd for C30H26NO3P: C, 75.14; H, 5.47; N, 2.92. Found: C, 74.92; H, 5.55; N, 3.08.
(4S)-3-[trans-4-t-Butoxycarbonylamino-cyclohexyl][propenoyl]-4-phenylmethyl-2-oxazolidinone (20a) and (4S)-3-[cis-4-t-Butoxycarbonylaminocyclohexyl][propenoyl]-4-phenylmethyl-2-oxazolidinone (20a’). A mixture of 17 (6.103 g, 26.885 mmol) and 19 (12.878 g, 26.885 mmol) in toluene (150 mL) was refluxed for 30 h. After cool, the mixture was concentrated in vacuo to give a yellow oily residue. The residual oil was purified by silica gel column chromatography (BW-200, 150 g, Et2O:hexane=1:3 to 1:1) to give 20a (10.462 g, 91%) and its isomer (20a’) (120 mg, 1%), respectively.

**Compound (20a):** a less polar geometric mixture of the cyclohexane ring, a white solid, mp 121-123°C. IR \(\nu_{\text{max}}\) (CHCl3): 3340, 1779, 1707, 1690, 1632, 1499, 1354, 1169, 1047, 1028, 928, 669 cm\(^{-1}\). \(^1\)H NMR \(\delta\): 1.1-1.6 (m, 2H), 1.45 (s, 9H), 1.6-1.8 (m, 4H), 1.8-2.5 (m, 3H), 2.79 (dd, 1H, \(J=13.2, 9.6\) Hz), 3.35 (dd, 1H, \(J=13.5, 3.2\) Hz), 3.73 (br, 1H), 4.20 (m, 2H), 4.40 and 4.60 (br and br, 1H), 7.05-7.38 (m, 7H). Anal. Calcld for C\(_{24}\)H\(_32\)N\(_2\)O\(_5\): C, 67.27; H, 7.53; N, 6.54. Found: C, 67.03; H, 7.57; N, 6.36.

**Compound (20a’):** a more polar geometric mixture of the cyclohexane ring, a pale brown solid, mp 115-120°C. IR \(\nu_{\text{max}}\) (CHCl3): 3339, 1784, 1713, 1674, 1609, 1499, 1454, 1366, 1246, 926, 702 cm\(^{-1}\). \(^1\)H NMR \(\delta\): 1.1-1.4 (m, 1H), 1.44 (s, 9H), 1.4-1.6 (m, 3H), 1.65 (m, 3H), 2.05 (br, 1H), 2.27 (br, 1H), 2.66 (dd, 1H, \(J=13.9, 8.9\) Hz), 3.14 (dd, 1H, \(J=13.9, 5.6\) Hz), 3.70 (br, 1H), 3.95-4.24 (m, 2H), 4.44 (m, 1H), 4.56 (br, 1H), 5.96 and 5.99 (d, \(J=15.8\) and d, \(J=16.2\) Hz; 1H), 6.50 and 6.57 (dd, \(J=19.8, 7.6\) Hz, and dd, \(J=18.8, 6.3\) Hz; 1H), 7.2-7.4 (m, 5H).

(4S)-3-[trans-3-(trans-4-Acetaminocyclohexyl)[propenoyl]-4-phenylmethyl-2-oxazolidinone (20b) and (4S)-3-[trans-3-(cis-4-Acetaminocyclohexyl)[propenoyl]-4-phenylmethyl-2-oxazolidinone (20c). To a solution of 20 (831 mg, 1.94 mmol) in CH\(_2\)Cl\(_2\) (4.85 mL) was added TFA (1.75 mL) at ambient temperature. After being stirred at rt for 6 h, the mixture was concentrated in vacuo to give a pale yellow oil. Toluene was added to the mixture, which was concentrated in vacuo. This work-up was repeated three times to complete removal of the excess of TFA. The crude amine TFA salt was dissolved in pyridine (3 mL) and treated with Ac\(_2\)O (275 \(\mu\)L, 2.91 mmol). After being stirred at rt for 10 h, the mixture was added to an ice-cooled 1N aq. HCl. The whole was extracted with EtOAc (x 2), and the extracts were washed with sat. NaHCO\(_3\) and brine, dried over Na\(_2\)SO\(_4\), then concentrated in vacuo. The residual oil was purified by silica gel column chromatography (BW-200, 80 g, EtOAc to EtOAc:MeOH=35:1 to 50:3) to give 20b (555 mg, 77%) and 20c (165 mg, 23%).

**Compound (20b):** a less polar geometric isomer of the cyclohexane ring, a white amorphous powder, mp 47-54°C. [\(\alpha\)]\(_D\)\(^{23}\) +44.8° (c=1.0, CHCl3). IR \(\nu_{\text{max}}\) (CHCl3): 3430, 1779, 1732, 1682, 1634, 1520, 1455, 1354, 1111, 1007, 930, 853 cm\(^{-1}\). \(^1\)H NMR \(\delta\): 1.5-1.8 (m, 7H), 1.98 (s, 3H), 2.0-2.1 (br, 1H), 2.45 (m, 1H), 2.80 (dd, 1H, \(J=13.2, 9.6\) Hz), 3.36 (dd, 1H, \(J=13.2, 3.3\) Hz), 4.25 (br, 1H), 4.22 (m, 2H), 4.74 (dd, 1H, \(J=13.2, 6.9, 3.3\) Hz), 5.48 (br, 1H), 7.1-7.4 (m, 7H). Anal. Calcld for C\(_{21}\)H\(_{26}\)N\(_2\)O\(_4\): C, 68.09; H, 7.07; N, 7.56. Found: C, 67.59; H, 7.34; N, 7.46.

**Compound (20c):** a more polar geometric isomer of the cyclohexane ring, a white powder, mp 152-155°C. [\(\alpha\)]\(_D\)\(^{23}\) +53.3° (c=1.0, CHCl3). IR \(\nu_{\text{max}}\) (CHCl3): 3440, 1777, 1700, 1683, 1632, 1518, 1453, 1354, 1107, 1007, 930, 861 cm\(^{-1}\). \(^1\)H NMR \(\delta\): 1.16 (dt, 1H, \(J=12.5, 3.3\) Hz), 1.20 (dt, 1H, \(J=11.9, 3.0\) Hz), 1.35 (br t, 1H, \(J=13.2\) Hz), 1.40 (br t, 1H, \(J=13.2\) Hz), 1.88 (br d, 1H, \(J=13.2\) Hz), 1.96 (s, 3H), 2.07 (br
Diphenyl-3-tetrahydropyranoyloxypropylphosphine oxide (23). 3-Hydroxypropyltriphenylphosphonium chloride (22) (12.0 g, 33.66 mmol) was treated with 30% aq. NaOH (50 mL) at 100°C for 4 h. After cooling, the mixture was extracted with CH₂Cl₂ three times. The extracts were dried over Na₂SO₄ and concentrated in vacuo to give a pale yellow viscous oil. The crude oil was used for the next step without further purification. The above oil was dissolved in CH₂Cl₂ (110 mL), then 2,3-dihydropyran (3.7 mL, 40.39 mmol) and pyridinium p-toluenesulphonate (846 mg, 3.37 mmol) was added to the mixture at rt. After being stirred at rt for 20 h, the mixture was washed with H₂O and brine. The CH₂Cl₂ layer was dried over Na₂SO₄, and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (BW-200, 200 g, CHCl₃:MeOH=30:1) to give 23 (10.285 g, 89%) as a white waxy solid, mp 98-100°C. IR νmax (CHCl₃): 1439, 1176, 1120, 1028 cm⁻¹. ¹H NMR δ 1.5-2.0 (m, 8H), 2.3-2.4 (m, 2H), 3.4-3.5 (m, 2H), 3.7-3.8 (m, 2H), 4.50 (brs, 1H), 7.4-7.5 (m, 6H), 7.7-7.8 (m, 4H). Anal. Calcd for C₂₀H₂₅O₃P: C, 69.75; H, 7.32. Found: C, 69.66; H, 7.32.

3-(4-t-Butoxycarbonylaminocyclohexylidene)-1-tetrahydropyranol (24). To a solution of 23 (722 mg, 2.11 mmol) in THF (8.0 mL) was added n-BuLi (1.63 M solution in hexane, 1.35 mL, 2.2 mmol) at -78°C under argon. After 10 min, a solution of 8 (215 mg, 1.0 mmol) in THF (2.0 mL) was added and the mixture was stirred at -78°C for 10 min, warmed to rt, and stirred for 30 min. Sat. aq. NH₄Cl was added to this mixture and the mixture was extracted with EtOAc (x 2). The extracts were washed with H₂O and brine, dried over Na₂SO₄, and then concentrated in vacuo. The crude residual oil was purified by silica gel column chromatography (BW-200, 40 g, EtOAc:hexane=4:1 to EtOAc to EtOAc:MeOH=10:1) to give the adduct (327 mg, 59%) as a white solid, mp 72-76°C. IR νmax (CHCl₃): 3700-3100, 3340, 1700, 1505, 1439, 1366, 1167 cm⁻¹. Anal. Calcd for C₃₁H₄₄N₀₆P /₄H₂O: C, 66.23; H, 7.98; N, 2.49. Found: C, 66.12; H, 8.02; N, 2.56.

The above adduct (2.436 g, 4.327 mmol) in THF (45 mL) was added NaH (60% oil dispersion, 525 mg, 13.12 mmol) at ambient temperature under argon. After being refluxed for 1.5 h, the mixture was quenched with sat. aq. NaHCO₃. The whole mixture was extracted with EtOAc (x 2). The extracts were washed with brine, dried over Na₂SO₄, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 80 g, Et₂O:hexane=2:5) to give 24 (1.013 g, 68%) as a white waxy solid, mp 47-48°C. IR νmax (CHCl₃): 3445, 1705, 1502, 1368, 1315, 1169, 1028 cm⁻¹. ¹H NMR δ 1.1-1.3 (m, 3H), 1.44 (s, 9H), 1.4-2.7 (m, 10H), 2.30 (br q, 2H, J=7.3 Hz), 2.53 (br d, 1H, J=5.5 Hz), 3.37 (m, 1H), 3.4-3.7 (m, 3H), 3.8-3.9 (m, 1H), 4.47 (br, 1H), 4.59 (t, 1H, J=3.0 Hz), 5.15 (t, 1H, J=7.3 Hz).

3-(4-t-Butoxycarbonylaminocyclohexylidene)-1-propanol (25). To a solution of the tetrahydropyranol ether (24) (998 mg, 2.944 mmol) in 90% aq. MeOH (30 mL) was added p-TsOH □₂O
(112 mg, 0.589 mmol) at rt. After being stirred at rt for 12 h, the mixture was neutralized with Et$_3$N (82 mL, 0.589 mmol), then concentrated in vacuo. The residue was extracted with EtOAc (x 2), and the extracts were washed with H$_2$O and brine, dried over Na$_2$SO$_4$, and then concentrated in vacuo to give a colorless oil. The oil was purified by silica gel column chromatography (BW-200, 80 g, EtOAc:hexane=1:1) to give a white waxy solid 25, mp 97-99°C. IR $\nu_{\text{max}}$ (CHCl$_3$): 3700-3100, 3445, 1700, 1505, 1368, 1316, 1169, 1045, 880 cm$^{-1}$. $^1$H NMR $\delta$ 1.1-1.3 (m, 2H), 1.45 (s, 9H), 1.62 (br, 1H), 1.8-2.1 (m, 3H), 2.1-2.3 (m, 2H), 2.27 (br q, 2H), 2.54 (br d, 1H), 3.61 (br t, 3H, $J$=7.5 Hz), 4.42 (br, 1H), 5.13 (t, 1H, $J$=7.5 Hz). Anal. Calcd for C$_{14}$H$_{25}$NO$_3$: C, 65.85; H, 9.87; N, 5.49. Found C, 65.68; H, 9.74; N, 5.49.

3-(4-t-Butoxy carbonylaminocyclohexylidene)propionic Acid (26). To a solution of the above alcohol (25) (44 mg, 0.171 mmol) in DMF (2.0 mL) was added PDC (322 mg, 0.855 mmol) at rt. The mixture was stirred at rt for 2 h, and then 1N aq. NaOH was added. The mixture was washed with Et$_2$O and the aqueous layer was acidified with 1M KHSO$_4$. The aqueous layer was extracted with EtOAc (x 2), and the extracts were washed with H$_2$O and brine, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, EtOAc:hexane=2:5) to give 26 (23 mg, 50%) as a white solid, mp 102-104°C. IR $\nu_{\text{max}}$ (CHCl$_3$): 3700-3200, 3355, 1709, 1651, 1505, 1368, 1166, 1047, 926, 880, 853 cm$^{-1}$. $^1$H NMR $\delta$ 1.1-1.4 (m, 2H), 1.45 (s, 9H), 1.8-2.4 (m, 5H), 2.47 (br d, 1H), 3.08 (br d, 2H, $J$=6.9 Hz), 3.61 (br, 1H), 4.44 (br, 1H), 5.30 (t, 1H, $J$=7.3 Hz), 5.4-5.8 (br, 1H). Anal. Calcd for C$_{14}$H$_{23}$NO$_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.18; H, 8.59; N, 5.19.

(4S)-3-[1-Oxo-3-(4-(t-butoxy carbonylamino)cyclohexylidene)propyl]-4-phenylmethyl-2-oxazolidinone (28). To a solution of the acid (26) (184 mg, 0.684 mmol) and Et$_3$N (124 $\mu$L, 0.889 mmol) in THF (6 mL) was added pivaloyl chloride (93 $\mu$L, 0.752 mmol) at -78°C under argon. After being stirred at this temperature for 15 min, the mixture was warmed to rt and stirred for 45 min. The lithiated oxazolidinone (27) (prepared as follows; to a solution of (4S)-benzyl-2-oxazolidinone (436 mg, 2.463 mmol) in THF (8 mL) was added $n$-BuLi (1.61 M solution in hexane, 1.53 mL, 2.467 mmol) at -78°C under argon, and the mixture was stirred for 15 min) was added to the mixture at -78°C by cannula. After being stirred at -78°C for 15 min, the mixture was warmed to rt during 2 h. The mixture was quenched with 1M KHSO$_4$ and concentrated in vacuo. The residue was extracted with CH$_2$Cl$_2$ (x 3), and the extracts were washed with sat. aq. NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and then concentrated in vacuo to give an oily residue. The residue was purified by silica gel column chromatography (BW-200, 50 g, EtOAc:hexane=12:5 to acetone:hexane=3:2 to 2:1) to give 28 (150 mg, 51%) as a colorless oil. IR $\nu_{\text{max}}$ (neat): 3370, 1777, 1713, 1684, 1505, 1391, 1367, 1316, 1171, 1105, 1048, 881, 758 cm$^{-1}$. $^1$H NMR $\delta$ 1.1-1.4 (m, 2H), 1.44 (s, 9H), 1.9-2.1 (m, 2H), 2.1-2.5 (m, 3H), 2.5-2.6 (m, 1H), 2.79 (dd, 1H, $J$=13.2, 9.6 Hz), 3.27 (dd, 1H, $J$=13.2, 3.3 Hz), 3.67 (m, 3H), 4.20 (m, 2H), 4.53 (br, 1H), 4.66 (m, 1H), 5.39 (t, 1H, $J$=6.9 Hz), 7.18-7.36 (m, 5H).

(4$\overline{S}$)-3-[1-Oxo-3-(4-acetamidocyclohexylidene)propyl]-4-phenylmethyl-2-oxazolidinone (29). To a solution of 28 (141 mg, 0.329 mmol) in CH$_2$Cl$_2$ (876 $\mu$L) was added trifluoroacetic acid (315
µL) at rt. After being stirred at rt for 9 h, the mixture was concentrated in vacuo to give an oily residue. Toluene was added to the residual oil and the mixture was concentrated in vacuo. This work-up was repeated three times. The residue was used for the next step without further purification. The above amine TFA salt was treated with pyridine-acetic anhydride (2.0 mL-47 µL) at rt for 12 h. The mixture was added to the ice-cooled 1N aq. HCl, and extracted with EtOAc (x 2). The extracts were washed with sat. aq. NaHCO3 and brine, dried over Na2SO4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 20 g, acetone:hexane=5:6) to give 29 (120 mg, 98%) as a white solid. IR νmax (CHCl3): 3440, 1779, 1703, 1659, 1538, 1445, 1389, 1309, 1211, 1111, 1047, 986 cm⁻¹. 1H NMR δ 1.1-1.4 (m, 2H), 1.9-2.1 (m, 2H), 1.96 (s, 3H), 2.1-2.4 (m, 3H), 2.57 (m, 1H), 2.80 (dd, 1H, J=13.5, 9.3 Hz), 3.27 (dd, 1H, J=13.5, 3.3 Hz), 3.68 (m, 2H), 3.95 (m, 1H), 4.21 (m, 2H), 4.67 (ddd, 1H, J=9.3, 3.6, 3.3 Hz), 5.40 (t, 1H, J=6.9 Hz), 5.81 (br d, 1H, J=7.9 Hz), 7.2-7.4 (m, 5H).

(4S)-3-[1-Oxo-2-(N,N’-bis-t-butoxycarbonylhydrazino)-3-(4-acetamidocyclohexylidene)-propyl]-4-phenylmethyl-2-oxazolidinone (30). To a solution of 29 (54 mg, 0.164 mmol) in THF (3.0 mL) was added KHMD (0.5 M solution in toluene, 613 µL, 0.307 mmol) at -78°C under argon. After being stirred at this temperature for 30 min, the mixture was added a precooled (-78°C) solution of tert-butyl azodicarboxylate (40 mg, 0.175 mmol) in CH2Cl2 (1.0 mL). After 3 min, the mixture was quenched with AcOH (100 µL), and a phosphate buffer (pH=7) was added to this mixture and then the mixture was warmed to rt. The whole mixture was extracted with EtOAc (x 2), and the extracts were washed with sat. aq. NaHCO3 and brine, dried over Na2SO4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 20 g, acetone:hexane=5:6) to give 30 (46 mg, 53%) as a colorless oil. IR νmax (CHCl3): 3401, 1784, 1740, 1701, 1659, 1510, 1392, 1370, 1242, 1157, 1109, 1051, 855 cm⁻¹. 1H NMR δ 1.1-1.4 (br, 2H), 1.43 and 1.45 (s and s; 9H), 1.468 and 1.474 (s and s; 9H), 1.92 and 1.93 (s and s; 3H), 1.8-2.3 (br, 5H), 2.65-2.9 (m, 2H), 3.1-3.4 (br, 1H), 3.96 (br, 1H), 4.17 (m, 2H), 4.5-4.8 (m, 1H), 5.06 (br, 1H), 5.40 (br, 1H), 6.49 (m, 2H), 7.1-7.4 (m, 5H).

Methyl 3-Bromo-2-methoxyiminopropionate. A mixture of bromopyruvic acid (31) (13.09 g, 78.38 mmol) in 10% HCl-MeOH (80 mL) was stirred at ambient temperature for 15 h. MeONH2 ⋅ Cl (9.82 g, 117.58 mmol) was added to the mixture and the whole was stirred for 6 h, then concentrated in vacuo. The residue was extracted with Et2O (x 2) and washed with H2O and brine. The extracts were dried over Na2SO4, and then concentrated in vacuo. The residual crude oil was distilled under reduced pressure (bp 94-96°C /19 mmHg) to give methyl 2-methoxyimino-3-bromopropionate13 (12.43 g, 76%) as a colorless oil.

Ethyl 3-Bromo-2-methoxyiminopropionate. To a solution of ethyl 3-bromopyruvate (1.95 g, 10 mmol) in EtOH (30 mL) was added MeONH2 ⋅ Cl (1.25 g, 15 mmol) and the mixture was stirred for 3 h, and then concentrated in vacuo. The residue was extracted with Et2O (x 2) and washed with H2O and brine. The extracts were dried over Na2SO4, and then concentrated in vacuo. The crude oil was distilled under reduced pressure (bp 80-85°C /4 mmHg), to give ethyl 2-methoxyimino-3-bromopropionate13 (2.06 g, 92%) as a colorless oil. IR νmax (neat): 1722, 1597, 1375, 1333, 1177, 1049, 855 cm⁻¹. 1H NMR δ 1.35 (t, 3H,
J=7.3 Hz), 4.16 (s, 1H), 4.17 (s, 3H), 4.20 (s, 1H), 4.33 (q, 2H, J=7.3 Hz).

**Trimethyl Phosphono-2-methoxyiminopropionate (32a).** A mixture of methyl methoxyimino-3-bromopropionate (6.80 g, 32.38 mmol) and P(OMe)₃ (5.73 mL, 48.57 mmol) was refluxed for 48 h. After cooling, the mixture was concentrated in vacuo. The crude oil was distilled under reduced pressure (119-121°C/0.8 mmHg) to give 32a (8.01 g, quant.) as a colorless oil. IR νmax (neat): 1728, 1609, 1443, 1345, 1264, 1210, 1171, 1040, 845, 776 cm⁻¹. [lit., IR νmax (film): 1720, 1270, 1210, 1170, 1040, 850, 780 cm⁻¹]. ¹H NMR δ 3.34 (d, 2H, J=23.4 Hz), 3.75 (d, 6H, J=11.2 Hz), 3.89 (s, 3H), 4.13 (s, 3H). [lit., ¹H NMR (250 MHz, CDCl₃) δ 3.34 (d, 2H, J=23.5 Hz), 3.75 (d, 6H, J=11.2 Hz), 3.89 (s, 3H), 4.13 (s, 3H)].

**Ethyl Dimethylphosphono-2-methoxyiminopropionate (32b).** Ethyl 3-bromo-2-methoxyiminopropionate (1.70 g, 7.603 mmol) was treated as described for 32a to give 32b (1.96 g, quant.) as a colorless oil, bp 120°C/1.5 mmHg. IR νmax (neat): 1721, 1607, 1466, 1333, 1266, 1179, 1040, 936, 857, 775 cm⁻¹.

**Methyl 2-Methoxyimino-3-[4-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)cyclohexylidene]propionate (33).** To a solution of 32a (7.61 g, 31.83 mmol) in THF (100 mL) was added dropwise n-BuLi (1.61 M in hexane solution, 19.8 mL, 31.83 mmol) over 15 min period at -78°C under argon. The mixture was stirred for 1 h, then a solution of 12 (10.0 g, 26.53 mmol) in THF (30 mL) was added to the mixture over 20 min period. After being stirred at -78°C for 2 h, the mixture was warmed to rt during 2 h, and then stirred at rt for 12 h. The whole was quenched with sat. aq. NH₄Cl and extracted with EtOAc (x 2). The extracts were washed successively with 10% aq. citric acid, sat. aq. NaHCO₃, and brine. The extracts were dried over Na₂SO₄, then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 200 g, acetone:hexane=1:2) to give 33 (10.53 g, 81%) as a pale yellow oil, which was used for the next step. IR νmax (CHCl₃): 1732, 1689, 1499, 1455, 1298, 1254, 1202, 1148, 1015, 914, 706 cm⁻¹. ¹H NMR δ 0.8-1.2 (m, 2H), 1.3-1.7 (m, 3H), 1.7-2.0 (m, 2H), 2.05-2.1 (m, 1H), 2.57 (m, 1H), 3.82 (s, 3H), 4.01 (s, 3H), 4.18 (s, 4H), 4.52 (s, 4H), 5.67 (s, 1H), 7.21-7.36 (s, 10H).

**Methyl 2-ter-Butoxycarbonylamo-3-[4-(1,3-dibenzylhexahydro-2-oxo-1,3,5-triazin-5-yl)cyclohexylidene]propionate (34).** To a solution of 33 (443 mg, 0.904 mmol) in THF (10 mL) were added Zn dust (296 mg, 45.204 mmol) and HCO₂H (3.4 mL, 90.405 mmol) at ambient temperature. After being stirred at rt for 1.5 h, the mixture was filtered through a pad of celite, then the filtrate was concentrated in vacuo to give a yellow oil. Toluene was added to the crude oil and the mixture was concentrated in vacuo. This work-up was repeated three times to complete removal of the excess of HCO₂H. The crude amine formic acid salt was dissolved in H₂O-dioxane (1.0 mL-3.0 mL) and neutralized with Et₃N (189 µL, 1.356 mmol). Boc₂O (296 mg, 1.356 mmol) was added to the whole at ambient temperature and stirred for 12 h. The mixture was quenched with 1M KHSO₄, and extracted with EtOAc (x 2). The extracts were washed with sat. aq. NaHCO₃ and brine, then dried over Na₂SO₄. The mixture was concentrated in vacuo, and the
residue was purified by silica gel column chromatography (BW-200, 80 g, EtOAc:hexane=2:1) to give **34a** (less polar diastereomer, 170 mg, 33%) and **34b** (polar diastereomer, 169 mg, 33%), respectively.

**Compound (34a):** a white amorphous powder, mp 48-52°C. IR \( \nu_{\text{max}} \) (CHCl3): 3445, 1744, 1709, 1632, 1501, 1454, 1298, 1252, 1161, 1049, 1028, 943, 928 cm\(^{-1}\). \(^1\)H NMR \( \delta \) 0.8-1.1 (m, 2H), 1.43 (s, 9H), 1.3-1.5 (m, 2H), 1.5-2.1 (m, 4H), 2.4-2.7 (m, 2H), 3.71 (s, 3H), 4.18 (s, 4H), 4.53 (ABq, 4H, \( J=15.2 \) Hz), 4.89 (brs, 2H), 5.02 (br, 1H). 7.24-7.35 (m, 10H). Anal. Calcd for C\(_{32}\)H\(_{43}\)N\(_4\)O\(_5\): C, 68.30; H, 7.52; N, 9.96. Found: C, 67.96; H, 7.38; N, 9.79.

**Compound (34b):** a white amorphous powder, mp 48-56°C. IR \( \nu_{\text{max}} \) (CHCl3): 3443, 1746, 1705, 1634, 1505, 1455, 1298, 1252, 1163, 1049, 1028, 943, 929 cm\(^{-1}\). \(^1\)H NMR \( \delta \) 0.8-1.05 (m, 2H), 1.44 (s, 9H), 1.3-1.5 (m, 2H), 1.55-1.8 (m, 2H), 1.98 (m, 1H), 2.47 (br d, 1H, \( J=14.2 \) Hz), 2.62 (m, 1H), 3.66 (s, 3H), 4.19 (s, 4H), 4.53 (ABq, 4H, \( J=15.2 \) Hz), 4.88 (br s, 2H), 5.06 (br, 1H). 7.23-7.35 (m, 10H). Anal. Calcd for C\(_{32}\)H\(_{42}\)N\(_4\)O\(_5\): C, 68.30; H, 7.52; N, 9.96. Found: C, 67.94; H, 7.39; N, 9.97.

**\((1R,4S)-3\text{-}\text{Aza}\text{-2-oxabicyclo[2.2.2]oct-5-ene Hydrochloride (36).}** To a solution of **35** (9.2 g, 29.897 mmol) in CHCl\(_3\) (85 mL) was added a solution of 1,3-cyclohexadiene (5.7 mL, 59.794 mmol) in EtOH (28 mL) at -78°C over 30 min period. After being stirred at this temperature for 4 h, the mixture was quenched with 1N aq. HCl. The whole was washed with CHCl\(_3\) (x 3), and the H\(_2\)O layer was concentrated in vacuo. The residue was recrystallized from hot EtOH to give **36** (3.648 g, 93%) as colorless prisms, mp 134-136°C (decomp) [lit.,\(^{16c}\) mp 135°C (decomp)]. [\( \alpha \)]\(_D\)\(^{25}\) +25.9° (c=1.0, MeOH) [lit.,\(^{16b}\) [\( \alpha \)]\(_D\)\(^{20}\) +24.0° (c=5.0, MeOH)]. IR \( \nu_{\text{max}} \) (KBr) 3600-3300, 3050-2000, 1560, 1452, 1435, 1390, 1363, 1315, 1277, 1210, 1163, 1120, 1065, 1026, 990, 941, 922, 860, 821, 802, 777, 656 cm\(^{-1}\). [lit.,\(^{16c}\) IR \( \nu_{\text{max}} \) (KBr) 3600-3300, 3025-2330, 1540, 1452, 1415, 1381, 1359, 1310, 1280, 1265, 1220, 1164, 1120, 1080, 1058, 1022, 1005, 988, 959, 940, 920, 856, 810, 798, 773, 661, 650 cm\(^{-1}\)]. \(^1\)H NMR (TMS/CD\(_3\)OD) \( \delta \) 1.5-1.7 (m, 2H), 2.1-2.4 (m, 2H), 4.56 (br, 1H), 4.98 (m, 1H), 6.65 (ddd, 1H, \( J=8.2,6.3,1.7 \) Hz), 6.93 (ddd, 1H, \( J=8.2,5.9,1.7 \) Hz). [lit.,\(^{16c}\) \(^1\)H NMR (200 MHz, D\(_2\)O) \( \delta \) 1.60 (m, 2H), 2.16 (m, 1H), 2.25 (m, 1H), 4.60 (ddd, 1H, \( J=6.3,3.5,1.5 \) Hz), 5.01 (ddd, 1H, \( J=5.8,3.8,1.5 \) Hz), 6.63 (ddd, 1H, \( J=8.4,6.3,1.5 \) Hz), 6.90 (ddd, 1H, \( J=8.4,5.8,1.5 \) Hz)].

**\((1R,4S)-3\text{-\text{t-\text{Benzyloxycarbonyl-3-aza-2-oxabicyclo[2.2.2]oct-5-ene (37).}}** To a solution of **36** (9.4 g, 63.69 mmol) in H\(_2\)O-dioxane (60 mL-180 mL) were added NaHCO\(_3\) (12.85 g, 152.85 mmol) and ZCl (11.0 mL, 76.43 mmol) at 0°C. After being stirred at 0°C for 1.5 h, the mixture was added to Et\(_2\)O. The whole mixture was extracted with Et\(_2\)O (x 2) and washed with H\(_2\)O and brine. The extracts were dried over Na\(_2\)SO\(_4\), then concentrated in vacuo to give oily residue. The crude oil was purified by silica gel column chromatography (BW-200, 300 g, EtOAc:hexane=2:7) to give **37** (15.45 g, 99%) as a white solid, mp 46-47°C. [\( \alpha \)]\(_D\)\(^{25}\) +7.3° (c=3.3, CHCl\(_3\)). IR \( \nu_{\text{max}} \) (neat): 2970, 2940, 2897, 2867, 1716, 1497, 1454, 1395, 1372, 1292, 1266, 1233, 1215, 1167, 1109, 1076, 1051, 959, 899, 894, 830, 753, 698 cm\(^{-1}\). \(^1\)H NMR \( \delta \) 1.3-1.6 (m, 2H), 2.0-2.3 (m, 2H), 4.77 (br, 1H), 4.82 (br, 1H), 5.17 (ABq, 2H, \( J=12.2 \) Hz), 6.55 (m, 2H), 7.34 (m, 5H). Anal. Calcd for C\(_{14}\)H\(_{15}\)NO\(_3\): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.62; H,
6.26; N, 5.69.

**4S-Benzyloxy carbonylamino-2-cyclohexenone (38).** To a mixture of 37 (1.227 g, 5.008 mmol) in dry MeOH (100 mL) were added Na2HPO4 (3.55 g, 25.041 mmol) and freshly crushed 5% Na(Hg) (18.4 g, 15 times weight of 37) at -10°C under argon. After being stirred at -10°C for 4 h, THF-Et2O (200 mL-200 mL) was added to the mixture and the mixture was stirred at ambient temperature for 10 min. The whole was decanted to a silica gel short column and eluted with THF. The eluate was concentrated *in vacuo* to give a pale yellow oil, which was extracted with EtOAc (x 2), and washed with H2O and brine. The extracts were dried over Na2SO4, then concentrated *in vacuo* to give an oily residue. The crude oil was purified by silica gel column chromatography (BW-200, 100 g, EtOAc:hexane=1:1) to give (4S)-benzyloxy carbonylamino-2-cyclohexenol (1.2 g, 97%) as a colorless oil. [α]D25 ±38.9° (c=1.3, CHCl3). IR νmax (neat): 3320, 1694, 1530, 1456, 1406, 1306, 1250, 1124, 1065, 1028, 990, 949, 839, 741, 698 cm⁻¹. 1H NMR δ 1.58 (br, 1H), 1.6-1.8 (m, 2H), 1.8-2.0 (m, 2H), 4.18 (br, 2H), 4.80 (br, 1H), 5.11 (s, 2H), 5.75 (dd, 1H, J=10.2, 2.3 Hz), 5.88 (br d, 1H, J=8.9 Hz), 7.36 (s, 5H). Anal. Calcd for C14H17NO3: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.76; H, 7.05; N, 5.51.

To a solution of the above alcohol (953 mg, 3.86 mmol) in CH2Cl2 (40 mL) was added CMD (6.7 g, 77.17 mmol) at ambient temperature. After being stirred at rt for 12 h, the mixture was filtered through a pad of celite. The filtrate was concentrated *in vacuo* to give a pale yellow oil. The residual oil was purified by silica gel column chromatography (BW-200, 80 g, EtOAc:hexane=1:2) to give 38 (815 mg, 86%) as a white solid, mp 91-93°C. [α]D25 ±109.0° (c=1.1, CHCl3). IR νmax (CHCl3): 3339, 1710, 1684, 1510, 1455, 1418, 1300, 1217, 1055, 1026, 930, 876, 849, 777, 669 cm⁻¹. 1H NMR δ 1.8-2.0 (ddd, 1H, J=22.4, 12.2, 5.0 Hz), 2.3-2.4 (m, 1H), 2.4-2.6 (m, 2H), 4.58 (br, 1H), 5.12 (br s, 3H), 5.99 (dd, 1H, J=10.2, 2.0 Hz), 6.81 (br d, 1H, J=10.2 Hz), 7.35 (s, 5H). Anal. Calcd for C14H15NO3: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.41; H, 6.23; N, 5.71.

**Ethyl 2-Methoxyimino-3-(4S-benzyloxy carbonylamino-2-cyclohexenylidene)propionate (39).** To a solution of LDA (prepared from (i-Pr)2NH (350 μL, 2.5 mmol) and n-BuLi (1.61 M solution in hexane, 1.55 mL, 2.5 mmol) in THF (10.0 mL)) was added a solution of 32b (633 mg, 2.5 mmol) in THF (2.0 mL) at -78°C under argon. A solution of 38 (245 mg, 1.0 mmol) in THF (2.0 mL) was added to the mixture at -78°C, and the mixture was stirred at this temperature for 1 week. The whole mixture was quenched with sat. aq. NH4Cl, and extracted with EtOAc (x 2). The extracts were washed with H2O and brine and combined. The whole was dried over Na2SO4 and concentrated *in vacuo* to give a dark brown oil, which was purified by silica gel column chromatography (BW-200, 30 g, EtOAc:hexane=2:5) to give 39 (80 mg, 22%; E/Z=1:2.7 mixture) as a colorless oil. IR νmax (neat): 3441, 1732, 1698, 1630, 1525, 1456, 1371, 1156, 1053, 1024, 930, 845, 738, 698 cm⁻¹. 1H NMR δ 1.34 and 1.35 (t, J=7.3 Hz and t, J=7.3 Hz; 3H), 1.5-1.7 (m, 1H), 2.0-2.2 (m, 1H), 2.26 and 2.51 (br t, J=4.9 Hz and br t, J=6.3 Hz), 4.05 and 4.07 (s and s; 3H), 4.33 and 4.32 (q, J=7.3 Hz and q, J=7.3 Hz), 4.40 (br m, 1H), 5.76 (br d, 1H, J=8.6 Hz), 5.11 (s, 2H), 5.79-5.91 (m, 2H), 5.86 (br s, 0.73H), 5.99 (br s, 0.27H), 6.09 (dd, J=9.6, 1.7 Hz, 0.73Hz), 6.24 (dd, J=9.9, 2.0 Hz, 0.27H), 7.37 (s, 5H).
Ethyl 2-(t-Butoxycarbonylamino)-3-(4S-benzylxoy carbonylamino-2-cyclohexenylidene)-propionate (40). To a solution of 39 (80 mg, 0.215 mmol) in THF (2.0 mL) were added Zn dust (703 mg, 10.752 mmol) and HCO2H (811 µL, 21.51 mmol) at ambient temperature. After being stirred at rt for 1 h, the mixture was filtered through the pad of celite. The filtrate was concentrated in vacuo. Toluene was added to the residue and concentrated in vacuo to give an oily residue. This work-up was repeated three times to complete removal of the excess of HCO2H. The crude residue was used for the next step without further purification. The crude amine formic acid salt was dissolved in H2O-dioxane (0.3 mL-1.0 mL) and neutralized with Et3N (45 mL, 0.323 mmol). Boc2O (70 mg, 0.323 mmol) was added to the mixture, which was stirred at ambient temperature for 20 h. The mixture was quenched with 1M KHSO4, and extracted with EtOAc (x 2). The extracts were washed with sat. aq. NaHCO3 and brine. The extracts were dried over Na2SO4, then concentrated in vacuo. The residual oil was purified by silica gel column chromatography (BW-200, 20 g, EtOAc:hexane=1:2) to give 40 (48 mg, 50%) as a colorless oil. 1H NMR δ 1.24 (t, 3H, J=7.3 Hz), 1.43 (s, 9H), 1.5-1.7 (br m, 1H), 2.0-2.1 (br m, 1H), 2.34 (br m, 2H), 4.17 (q, 2H, J=7.3 Hz), 4.3-4.4 and 4.8-4.9 (br and br; 1H), 5.11 (br s, 2H), 4.9-5.1 (br m, 3H), 5.74 and 6.0-6.1 (m and m; 1H), 5.84 and 5.86 (d, J=10.2 Hz and d, J=10.2 Hz; 1H), 6.65 (br d, 1H, J=10.2 Hz), 7.35 (s, 5H).

(1S,4R,7S,8S)-7,8-O-Isopropylidenedioxy-3-t-butoxycarboylnyl-3-aza-2-oxabicyclo-[2.2.2]oct-5-ene (44). To a solution of 35 (22.53 g, 73.26 mmol) in Et2O-CH2Cl2-EtOH (200 mL-110 mL-8 mL) was added dropwise a solution of 43 (11.14 g, 73.26 mmol) in 22 mL of Et2O at -40°C over 30 min period. After being stirred at -30°C for 1 week, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 300 g, EtOAc:hexane=2:3 to MeOH:EtOAc=2:5) to give an oily 42, which was used for the next reaction without further purification. The above crude 42 was treated with Boc2O (19.2 g, 87.91 mmol), Et3N (12.3 mL, 87.91 mmol) in dioxane-H2O (210 mL-70 mL). The mixture was stirred at ambient temperature for 10 h, then quenched with 1M KHSO4. The whole was extracted with EtOAc (x 2), and washed with sat. aq. NaHCO3 and brine. The extracts were dried over Na2SO4, then concentrated in vacuo. The white solid was purified by silica gel column chromatography (BW-200, 300 g, Et2O:hexane=1:2) to give 44 (18.65 g, 90% in 2 steps) as a white solid, mp 118-121 °C. [α]D24 +24.7° (c=1.0, CHCl3). IR νmax (CHCl3): 1713, 1458, 1385, 1372, 1330, 1252, 1211, 1074, 1022, 994, 885, 870 cm⁻¹. 1H NMR δ 1.31 (s, 3H), 1.32 (s, 3H), 1.47 (s, 9H), 4.53 (m, 2H), 4.88 (m, 1H), 4.99 (m, 1H), 6.44 (m, 2H). Anal. Calcd for C14H21NO5: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.33; H, 7.49; N, 4.74.

(1S,2R,3S,4R)-2,3-O-I sopropylidenedioxy-4-t-butoxycarbonylamino-5-cyclohexenol (45). To a mixture of 44 (2.567 g, 9.071 mmol) in dry MeOH (180 mL) were added Na2HPO4 (6.44 g, 45.35 mmol) and freshly crushed 5% Na(Hg) (38.50 g, 15 times weight of 40) at -10°C under argon. After being stirred at -10°C for 18 h, THF-Et2O (200 mL-200 mL) was added to the mixture and the mixture was stirred at ambient temperature for 10 min. The whole was decanted to a silica gel short column and eluted with THF. The eluate was concentrated in vacuo to give a pale yellow oil, which was extracted with EtOAc (x 2)
and washed with H₂O and brine. The extracts were dried over Na₂SO₄, then concentrated \textit{in vacuo} to give an oily residue. The crude oil was purified by silica gel column chromatography (BW-200, 200 g, \text{Et}_2\text{O:hexane}=2:1) to give 45 (2.667 g, quant.) as a white solid, mp 121-122°C. \([\alpha]D^{25} = -44.2^\circ\text{c=1.1}, \text{CHCl}_3\). IR \(v_{\text{max}}\) (\text{CHCl}_3): 3441, 3386, 1698, 1514, 1456, 1370, 1254, 1163, 1061, 876 cm⁻¹. \(1^H\) NMR \(\delta\) 1.35 (s, 3H), 1.45 (s, 12H), 2.54 (br, 1H), 4.02 (m, 1H), 4.21 (m, 3H), 5.00 (br, 1H), 5.80 (ddd, 1H, J=9.9, 3.3, 1.3 Hz), 6.10 (ddd, 1H, J=9.9, 2.6, 2.3 Hz). Anal. Calcd for \text{C}_{14}\text{H}_{23}\text{NO}_5: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.70; H, 8.11; N, 4.93.

(1S,2R,3S,4R)-2,3-\textit{O}-Isopropylidenedioxy-4-t-butoxycarbonylaminocyclohexanol (46a). A mixture of 45 (17.44 g, 61.19 mmol), 5% \text{Pd/C} (1.75 g) in MeOH (1.22 L) was stirred at ambient temperature for 2 h under H₂. The mixture was filtered through the pad of celite, and the precipitates were washed with MeOH. The filtrate and washed solution were combined and concentrated \textit{in vacuo} to give a colorless oil. The crude oil was purified by silica gel column chromatography (BW-200, 300 g, \text{EtOAc:hexane}=1:1) to give 46a (17.79 g, quant.) as a hygroscopic oil. \([\alpha]D^{25} = -7.1^\circ\text{c=1.1}, \text{CHCl}_3\). IR \(v_{\text{max}}\) (\text{CHCl}_3): 3441, 3385, 1705, 1505, 1456, 1370, 1244, 1165, 1022, 994, 874 cm⁻¹. \(1^H\) NMR \(\delta\) 1.36 (s, 3H), 1.45 (s, 9H), 1.52 (s, 3H), 1.5-1.7 (m, 2H), 1.8-2.0 (m, 2H), 2.12 (br, 1H), 3.81 (m, 1H), 4.03 (m, 3H), 4.68 (br d, 1H, J=7.9 Hz). Anal. Calcd for \text{C}_{14}\text{H}_{25}\text{NO}_5: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.22; H, 8.87; N, 4.86.

(2S,3S,4R)-2,3-\textit{O}-Isopropylidenedioxy-4-t-butoxycarbonylaminocyclohexanone (41). The alcohol (46a) (5.834 g, 18.951 mmol) was oxidized as described for the oxidation of \textit{trans}-4-t-butoxycarbonylaminocyclohexanol to give crude 41, which was purified by silica gel column chromatography (BW-200, 300 g, \text{EtOAc:hexane}=2:3, then acetone:hexane=1:3) to give 41 (5.07 g, 94%) as a hygroscopic viscous oil. \([\alpha]D^{28} = +26.9^\circ\text{c=2.6, CHCl}_3\). IR \(v_{\text{max}}\) (neat): 3352, 1717, 1684, 1530, 1369, 1244, 1163, 1076, 868 cm⁻¹. \(1^H\) NMR \(\delta\) 1.38 (s, 3H), 1.46 (s, 9H), 1.47 (s, 3H), 1.98 (m, 1H), 2.24 (m, 1H), 2.49 (br t, 2H, J=7.9 Hz), 3.93 (m, 1H), 4.4-4.5 (m, 2H), 4.80 (br, 1H). Anal. Calcd for \text{C}_{14}\text{H}_{23}\text{NO}_5: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.70; H, 8.19; N, 4.85.

(1R,4S)-3-t-Butoxycarbonyl-3-aza-2-oxabicyclo[2.2.2]oct-5-ene (47). The oxazine (36) (4.96 g, 33.627 mmol) was protected as described for the protection of 42 to give 47 (6.91 g, 97%) as a colorless oil, bp 120°C / 3 mmHg. \([\alpha]D^{22} = +21.3^\circ\text{c=1.5, CHCl}_3\). IR \(v_{\text{max}}\) (neat): 1703, 1617, 1456, 1368, 1260, 1074, 1053, 991, 959, 916, 880 cm⁻¹. \(1^H\) NMR \(\delta\) 1.1-1.6 (m, 2H), 1.46 (s, 9H), 2.17 (m, 2H), 4.73 (br, 2H), 6.54 (m, 2H). Anal. Calcd for \text{C}_{11}\text{H}_{17}\text{NO}_3: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.18; H, 8.12; N, 6.63.

(1R,4S,5R,6R)-5,6-Dihydroxy-3-t-butoxycarbonyl-3-aza-2-oxabicyclo[2.2.2]octane (48). To a solution of 47 (6.29 g, 29.81 mmol) in 90% aq. acetone (298 mL) were added OsO₄ (0.1 M solution in toluene, 29.8 mL, 2.98 mmol) and 50% aq. NMO (17.5 mL, 74.526 mmol). After being stirred at rt for 2 h, the mixture was added to 1M Na₂SO₃ and stirred at ambient temperature for 30 min. NaCl was added to the
mixture, and the mixture was extracted with EtOAc (x 3) and washed with brine. The extracts were dried over Na₂SO₄ then concentrated in vacuo. The residue was recrystallized from EtOAc-acetone-hexane to give 48 (2.982 g, 41%) as colorless needles. Then the mother liquid was purified by silica gel column chromatography (BW-200, 200 g, EtOAc:hexane=7:11) to give 48 (2.172 g, 30%) as a colorless solid, mp 117-119°C. [α]D²⁰ -5.4° (c=0.5, CHCl₃). IR νmax (CHCl₃) 3750-3100, 1705, 1458, 1370, 1256, 1167, 1121, 1088, 937, 839 cm⁻¹. ¹H NMR δ 1.50 (s, 9H), 1.87 (br, 2H), 2.05 (m, 2H), 3.55 (br, 2H), 4.10 (br, 1H), 4.16 (br, 1H), 4.22 (br, 2H). Anal. Calcd for C₁₁H₁₉NO₅: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.73; H, 7.84; N, 5.79.

(1R,4S,5R,6R)-5,6-Dihydroxy-3-benzylloxycarbonyl-3-aza-2-oxabicyclo[2.2.2]octane (49). The olefin (37) (7.058 g, 28.808 mmol) was dihydroxylated as described for the oxidation of 47 to give crude 49, which was purified by silica gel column chromatography (BW-200, 300 g, EtOAc:hexane=2:1) to give 49 (6.528 g, 81%) as a colorless viscous oil. [α]D²³ -3.6° (c=1.0, CHCl₃). IR νmax (neat): 3700-3100, 1700, 1499, 1456, 1399, 1341, 1273, 1243, 1118, 1087, 1069 cm⁻¹. ¹H NMR δ 1.8-1.9 (m, 2H), 1.9-2.1 (m, 2H), 3.0-3.7 (br, 2H), 4.14 (m, 4H), 5.21 (s, 2H), 7.36 (s, 5H).

(1R,4S,5R,6R)-5,6-O-Isopropylidenedioxy-3-t-butoxyoxycarbonyl-3-aza-2-oxabicyclo-[2.2.2]octane (50). To a solution of 49 (4.994 g, 20.38 mmol) in CH₂Cl₂ (160 mL) were added 2,2-dimethoxypropane (DMP) (20 mL, 160.30 mmol) and pyridinium p-toluenesulfonate (410 mg, 1.63 mmol) at ambient temperature. After being stirred at ambient temperature for 12 h, the mixture was added to H₂O. The whole mixture was extracted with CH₂Cl₂ (x 2), and washed with H₂O and brine. The extracts were dried over Na₂SO₄, then concentrated in vacuo. The crude residue was purified by silica gel column chromatography (BW-200, 250 g, EtOAc:hexane=1:5) to give 50 (5.723 g, 99%) as a white solid, mp 64-65°C. [α]D²⁰ -4.2° (c=1.3, CHCl₃). IR νmax (CHCl₃): 1698, 1456, 1368, 1266, 1210, 1161, 1127, 1063, 934, 866 cm⁻¹. ¹H NMR δ 1.39 (s, 3H), 1.51 (s, 9H), 1.54 (s, 3H), 1.7-2.1 (m, 4H), 4.28 (br, 2H), 4.43 (m, 2H). Anal. Calcd for C₁₄H₂₃NO₅: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.91; H, 8.18; N, 4.92.

(1R,4S,5R,6R)-5,6-O-Isopropylidenedioxy-3-benzylloxycarbonyl-3-aza-2-oxabicyclo-[2.2.2]octane (51). The diol (49) (6.414 g, 22.989 mmol) was protected as described for the protection of 48 to give crude 51, which was purified by silica gel column chromatography (BW-200, 250 g, EtOAc:hexane=1:4) to give 51 (6.618 g, 90%) as a white solid, mp 66-69°C. [α]D²³ -4.1° (c=1.1, CHCl₃). IR νmax (CHCl₃): 1700, 1499, 1385, 1347, 1267, 1209, 990, 870, 754, 698 cm⁻¹. ¹H NMR δ 1.37 (s, 3H), 1.53 (s, 3H), 1.7-2.1 (m, 4H), 4.3-4.5 (m, 4H), 5.23 (s, 2H), 7.36 (s, 5H). Anal. Calcd for C₁₇H₂₁NO₅: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.87; H, 6.69; N, 4.40.

(1R,2S,3R,4S)-2,3-O-Isopropylidenedioxy-4-((t-butoxycarbonylamino)cyclohexanol (46b). The oxazine (50) (5.65 g, 19.825 mmol) was reduced as described for the reduction of 44 to give 46b (6.22 g, quant.) as a hygroscopic viscous oil. [α]D²⁰ +7.5° (c=1.0, CHCl₃). Anal. Calcd for
C_{14}H_{25}NO_5 \cdot \frac{1}{2}H_2O: C, 56.74; H, 8.84; N, 4.73. Found: C, 56.65; H, 8.60; N, 4.88.

(1R,2S,3R,4S)-2,3-O-Isopropylidenedi-oxy-4-benzyloxy-carbonylamino-cyclohexanol (52). The oxazine (51) (6.57 g, 20.60 mmol) was reduced as described for the reduction of 44 to give crude residue, which was purified by silica gel column chromatography (BW-200, 200 g, EtOAc:hexane=3:2) to give 52 (6.377 g, 96%) as a white solid, mp 74-77°C. [α]D^{20} +15.3° (c=1.0, CHCl_3). IR ν\text{max} (CHCl_3): 3432, 3341, 1701, 1541, 1456, 1374, 1296, 1244, 1057, 997, 876, 754 cm\(^{-1}\). 1H NMR δ 1.35 (s, 3H), 1.52 (s, 3H), 1.59 (m, 2H), 1.82 (m, 2H), 2.16 (br, 1H), 3.86 (m, 1H), 4.04 (m, 3H), 4.99 (d, 1H, J=8.3 Hz), 5.10 (ABq, 2H, J=12.2 Hz) 7.35 (s, 5H). Anal. Calcd for C_{17}H_{23}NO_5: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.48; H, 7.27; N, 4.38.

(1R,2R,3R,4S)-1-(3,5-Dinitrobenzoyloxy)-2,3-O-isopropylidenedi-oxy-4-t-butoxy-carbonylamino-cyclohexane (53b). To a solution of 46b (29 mg, 0.102 mmol) in CH_2Cl_2 (1.0 mL) were added 3.5-dinitrobenzoyl chloride (28 mg, 0.123 mmol), Et_3N (21 μL, 0.153 mmol), and DMAP (1 mg, 0.01 mmol) at rt. After being stirred at ambient temperature for 2 h, H_2O was added to the mixture. The whole mixture was extracted with Et_2O, and washed with H_2O and brine. The extracts were dried over Na_2SO_4, then concentrated in vacuo to give pale yellow oil. The residue was purified by silica gel column chromatography (BW-200, 15 g, EtOAc:hexane=2:3) to give 53b (44 mg, 89%) as a pale yellow amorphous solid. [α]D^{20} -27.21° (c=0.9, CHCl_3). IR ν\text{max} (CHCl_3): 3443, 1732, 1703, 1630, 1549, 1507, 1456, 1347, 1275, 1215, 1165, 1065, 922 cm\(^{-1}\). 1H NMR δ 1.39 (s, 3H), 1.47 (s, 9H), 1.57 (s, 3H), 1.7-1.8 (m, 2H), 1.9-2.1 (m, 2H), 4.00 (br, 1H), 4.22 (br t, 1H, J=5.3mHz), 4.31 (brmt, 1H, J=5.60Hz), 4.71 (br, 1H), 5.39 (br, 1H), 9.15 (d, 2H, J=2.3 Hz), 9.24 (t, 1H, J=2.3 Hz).

(1S,2S,3S,4R)-1-(3,5-Dinitrobenzoyloxy)-2,3-O-Isopropylidenedi-oxy-a-4-t-butoxy-carbonylamino-cyclohexane (53a). The alcohol 46a (31 mg, 0.108 mmol) was condensed as described for 46b to give 53a (30 mg, 58%) as a pale yellow amorphous solid. [α]D^{20} +28.1° (c=1.3, CHCl_3).

HPLC analysis for 53b and 53a: column, DIACEL CHIRALCEL OD-H; eluate, i-PrOH: hexane=1:3; detect, UV (254 nm); flow, 0.75 ml/min; retention time, 53b: 21.7 min, 53a: 25.9 min. From 46b; 98:2 (96%ee). From 46a: 3:97 (94%ee).

(2R,3R,4S)-2,3-O-Isopropylidenedi-oxy-(benzyloxy-carbonylamino)-cyclohexanone (54). The alcohol 52 (6.34 g, 19.75 mmol) was oxidized as described for the oxidation of trans-4-t-butoxycarbonylamino-cyclohexanol to give the crude 54, which was purified by silica gel column chromatography (BW-200, 300 g, acetone:hexane=5:12) to give 54 (5.907 g, 94%) as a colorless viscous oil. [α]D^{23} -18.9° (c=2.1, CHCl_3). IR ν\text{max} (neat) 3445, 1728, 1700, 1538, 1534, 1456, 1388, 1379, 1310, 1242, 1225, 1163, 1040, 980, 895, 876 cm\(^{-1}\). 1H NMR δ 1.37 (s, 3H), 1.47 (s, 3H), 1.99 (m, 1H), 2.22 (br, 1H), 2.47 (d, 1H, J=7.9 Hz), 2.49 (d, 1H, J=5.9 Hz), 3.99 (m, 1H), 4.40 (d, 1H, J=6.6 Hz), 4.45 (m, 1H), 5.12 (ABq, 2H, J=12.5 Hz), 5.1-5.2 (m, 1H), 7.36 (s, 5H). Anal. Calcd for C_{17}H_{21}NO_5 \cdot \frac{1}{2}H_2O: C, 62.18; H, 6.75; N, 4.27. Found: C, 61.82; H, 6.51; N, 4.33.
Methyl 2-Methoxyimino-3-[(2R,3S,4R)-2,3-O-isopropylidenedioxy-4-t-butoxycarbonylamino cyclohexyldene]propionate (55a). To a solution of 32a (10.42 g, 43.60 mmol) in DME (150 mL) was added n-BuLi (1.56 M in hexane, 28.0 mL, 43.60 mmol) at -78°C under argon. The mixture was stirred for 1 h, then a solution of 41 (4.97 g, 17.44 mmol) in DME (50 mL) was added. After being stirred at -78°C for 2 h, the mixture was warmed to rt during 2 h, and stirred at rt for 11 h. The mixture was quenched with sat. aq. NH₄Cl and extracted with EtOAc (x 2). The extracts were washed successively with 10% aq. citric acid, sat. aq. NaHCO₃, and brine. The extracts were dried over Na₂SO₄, then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 300 g, EtOAc:hexane=2:5 and BW-300, 300 g, Et₂O:hexane=3:2) to give 55a (5.95 g, 86%; E:Z=94:6) as a colorless waxy solid, mp. 35-39°C. [α]D²⁵ +60.3° (c=1.1, CHCl₃, pure E isomer). IR νmax (CHCl₃): 3391, 1709, 1507, 1439, 1368, 1313, 1163, 927, 868 cm⁻¹. 1H NMR δ 1.38 (s, 3H), 1.44 (s, 9H), 1.54 (s, 3H), 1.4-1.6 (m, 1H), 2.0-2.2 (m, 2H), 2.2-2.4 (m, 1H), 3.79 (m, 1H), 3.86 and 3.87 (s and s; 3H), 4.06 and 4.09 (s and s; 3H), 4.0-4.2 (m, 1H), 4.54 (d, 0.06H, J=4.3 Hz), 4.61 (d, 0.94H, J=8.3Hz), 4.93 (br d, 1H, J=8.3 Hz), 6.06 (s, 0.06H), 6.17 (s, 0.94H). Anal. Calcd for C₁₉H₃₀N₂O₇: C, 57.27; H, 7.59; N, 7.03. Found: C, 57.12; H, 7.70; N, 6.97.

Methyl 2-Methoxyimino-3-[(2S,3R,4S)-2,3-O-isopropylidenedioxy-4-benzyl oxycarbonylamino cyclohexyldene]propionate (55b). The ketone (54) (75 mg, 0.235 mM) was condensed with 32a as described for the preparation of 55a to give an oily residue, which was purified by silica gel column chromatography (BW-200, 20 g, EtOAc:hexane=1:2) to give 55b (59 mg, 58%) as a viscous oil. In addition, 13 mg of the starting material (54) (17%) was recovered.

Compound (55b): a colorless viscous oil. IR νmax (CHCl₃): 3440, 1720, 1518, 1456, 1439, 1385, 1373, 1289, 1159, 1134, 1030, 930 cm⁻¹. 1H NMR δ 1.2-1.6 (m, 2H), 1.30 and 1.38 (s and s, 3H), 1.47 and 1.55 (s and s, 3H), 2.0-2.2 (m, 2H), 2.2-2.4 (m, 1H), 3.76 and 3.7-4.0 (dd, J=12.2, 6.9 Hz and m; 1H), 3.85 (br s, 3H), 3.95 and 4.05 (s and s; 3H), 4.17 and 4.33 (m and dd, J=14.2, 7.3Hz; 1H), 4.52 (d, 0.14H, J=6.6 Hz), 4.62 (d, 0.86H, J=6.3 Hz), 5.12 (m, 2H), 5.0-5.2 and 5.35 (m and br; 1H), 6.05 (s, 0.14H), 6.16 (d, 0.86H, J=1.3 Hz), 7.35 (s, 5H). DIFNOE: 9.4% δ 6.16 (C3-H) to 4.62 (C5-H).

Methyl 2-Methoxyimino-3-[(2R,3S,4R)-2,3-dihydroxy-4-t-butoxycarbonylamino cyclohexyldene]propionate (56) and (7R,8S,8'R)-3-Methoxyimino-7-t-butoxycarboxylamin o-8-hydroxy-3,5,6,7,8,8a-hexahydro-4-dehydrocoumarin (57). To a solution of 55a (14.8 g, 37.19 mmol) in 90% aq. MeOH (372 mL) was treated with p-TsOH · H₂O (3.54 g, 18.59 mmol) at ambient temperature. After being stirred at rt for 3 days, the mixture was concentrated in vacuo. The whole residue was extracted with EtOAc (x 2) and washed with H₂O and brine. The extracts were combined and dried over Na₂SO₄, then concentrated in vacuo to give an oily residue. The residue was purified by silica gel column chromatography (BW-300, 300 g, EtOAc:hexane=2:1) to give 56 (12.49 g, 83%) and 57 (879 mg, 6%).

Compound (56): a hygroscopic viscous oil. [α]D²⁷ +72.56° (c=1.0, CHCl₃). IR νmax (CHCl₃): 3750-3100, 3400, 1732, 1715, 1510, 1439, 1367, 1165, 1051, 949, 926 cm⁻¹. 1H NMR δ 1.1-1.3 (m, 1H), 1.46 (s, 9H), 1.9-2.1 (m, 2H), 2.3-2.5 (m, 1H), 2.80 (br, 1H), 3.49 (m, 1H), 3.86 (s, 3H), 3.7-4.0 (m,
1H), 4.06 (s, 3H), 4.31 (br, 2H), 4.53 (br, 1H), 6.03 (s, 1H). Anal. Calcd for C_{16}H_{26}N_{2}O_{7}: C, 53.62; H, 7.31; N, 7.82. Found: C, 53.48; H, 7.63; N, 7.47.

**Compound (57):** a white solid, mp 189°C (decomp). [α]p{27} -12.37° (c=1.0, CHCl₃). IR ν{max} (CHCl₃): 3750-3100, 3445, 1732, 1700, 1568, 1507, 1446, 1395, 1367, 1320, 1248, 1165, 1078, 939, 911, 877 cm⁻¹. ¹H NMR δ 1.46 (s, 9H), 1.77 (m, 1H), 2.0-2.2 (m, 1H), 2.2-2.6 (m, 2H), 2.70 (br, 1H), 3.99 (br, 1H), 4.12 (s, 3H), 4.43 (d, 1H, J=3.6 Hz), 4.66 (br, 1H), 5.16 (br, 1H), 6.82 (s, 1H). Anal. Calcd for C_{15}H_{22}N_{2}O_{6} [4/4H_{2}O]: C, 54.45; H, 6.85; N, 8.47. Found: C, 54.70; H, 6.87; N, 8.08.

**Methyl 2-Methoxyimino-3-[(2R,3S,4R)-2,3-O-thiocarbonyldioxy-4-tert-butoxycarbonylaminocyclohexylidene]propionate (59).** To a solution of 56 (3.3 g, 9.23 mmol) in benzene (92 mL) was added 1,1'-thiocarbonyldimidazole (TCD1 58) (1.87 g, 10.16 mmol) at ambient temperature under argon. After being stirred at rt for 12 h, the mixture was quenched with 10% aqueous citric acid. The whole was extracted with EtOAc (x 2), and washed with sat. aq. NaHCO₃ and brine. The extracts were dried over Na₂SO₄, then concentrated in vacuo. The whole residue was purified by silica gel column chromatography (BW-200, 250 g, EtOAc:hexane=4:5) to give 59 (3.371 g, 91%) as a colorless amorphous solid, mp 45-52°C. [α]D{25} +122.7° (c=1.0, CHCl₃). IR ν{max} (CHCl₃): 3391, 1713, 1510, 1441, 1316, 1275, 1248, 1159, 1051, 910 cm⁻¹. ¹H NMR δ 1.45 (s, 9H), 1.83 (m, 1H), 1.9-2.2 (m, 1H), 2.2-2.5 (m, 2H), 3.90 (s, 3H), 3.8-4.0 (m, 1H), 4.13 (s, 3H), 5.08 (br, 1H), 5.35 (br d, 2H, J=7.9 Hz), 5.26 (d, 1H, J=1.3 Hz). Anal. Calcd for C_{17}H_{24}N_{2}O_{7}S: C, 50.99; H, 6.04; N, 7.00. Found: C, 51.09; H, 6.04; N, 6.90.

**Methyl 2-Methoxyimino-3-(4R-tert-butoxycarbonylamino-2-cyclohexenylidene)propionate (61).** To a solution of 59 (635 mg, 1.588 mmol) in CH₂Cl₂ (7 mL) was added the phosphine (60) (923 mg, 4.763 mmol) at ambient temperature under argon. After being stirred at rt for 12 h, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 80 g, Et₂O:hexane=4:5) to give 61 (479 mg, 93%) as a colorless viscous oil. [α]D{28} +34.8° (c=1.2, CHCl₃). IR ν{max} (CHCl₃): 3443, 1705, 1499, 1439, 1368, 1320, 1242, 1217, 1163, 1051, 1015, 926 cm⁻¹. ¹H NMR δ 1.45 (s, 9H), 1.54 (m, 1H), 1.9-2.1 (m, 1H), 2.25 (m, 2H), 3.87 (s, 3H), 4.07 (s, 3H), 4.32 (br, 1H), 4.52 (br, 1H), 5.89 (dd, 1H, J=9.9, 3.3 Hz), 5.98 (s, 1H), 6.22 (dd, 1H, J=9.9, 1.7 Hz). Anal. Calcd for C_{16}H_{24}N_{2}O_{5}: C, 59.24; H, 7.46; N, 8.64. Found: C, 58.95; H, 7.60; N, 8.35.

**Methyl 2-Methoxyimino-3-(4R-benzylxycarbonylamino-2-cyclohexenylidene)propionate (62).** A solution of 61 (1.82 g, 5.617 mmol) in CH₂Cl₂ (14.0 mL) was treated with TFA (5.06 mL) at ambient temperature for 1.5 h. The mixture was concentrated in vacuo, and toluene was added to the residue, then the mixture was concentrated in vacuo. This work-up was repeated three times. The residue was dissolved in CHCl₃ (56.2 mL), and Et₃N (1.88 mL, 13.48 mmol) and ZCl (963 µL, 6.741 mmol) were added at 0°C. After being stirred at 0°C for 2 h, the mixture was extracted with EtOAc (x 2). The extracts were washed with 10% aqueous citric acid, sat. aq. NaHCO₃, and brine. The extracts were dried over Na₂SO₄, then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 200 g, Et₂O:hexane=3:2) to give 62 (1.823 g, 91%) as a colorless viscous oil. [α]D{27} +46.9° (c=1.1, CHCl₃). IR
\[ \nu_{\text{max}} (\text{CHCl}_3): 3440, 1721, 1717, 1504, 1439, 1320, 1302, 1157, 1024, 926 \text{ cm}^{-1}. \]  
\[ ^1\text{H} \text{ NMR } \delta 1.5-1.7 \text{ (m, 1H)}, 1.9-2.1 \text{ (m, 1H)}, 2.25 \text{ (br, 2H)}, 3.86 \text{ (s, 3H)}, 4.07 \text{ (s, 3H)}, 4.39 \text{ (br, 1H)}, 4.86 \text{ (br d, 2H, J=8.3 Hz)}, 5.10 \text{ (s, 2H)}, 5.88 \text{ (dd, 1H, J=9.9, 3.3 Hz)}, 5.98 \text{ (s, 1H)}, 6.22 \text{ (dd, 1H, J=9.9, 1.7 Hz)}, 7.35 \text{ (s, 5H)}. \]  
Anal. Calcd for C_{19}H_{22}N_{2}O_{5}: C, 59.55; H, 5.78; N, 7.22. Found: C, 59.43; H, 5.94; N, 7.39. FABMS m/z=359 (MH\(^+\)).

**Methyl 2-Methoxyiminono-3-,(4R-acetamido-2-cyclohexenylidene) propionate (63).** A solution of 61 (2.01 g, 6.20 mmol) in CH_{2}Cl_{2} (15.5 mL) was treated with TFA (5.6 mL) at ambient temperature for 1 h. The mixture was concentrated in vacuo, and toluene was added to the residue, then the mixture was concentrated in vacuo. This work-up was repeated three times. The residue was dissolved in CH_{2}Cl_{2} (62 mL), and then Et_{3}N (2.15 mL, 15.51 mmol), Ac_{2}O (704 µL, 7.45 mmol), and DMAP (76 mg, 0.62 mmol) were added. After being stirred at rt for 7 h, H_{2}O was added to the mixture and the mixture was extracted with EtOAc (x 2). The extracts were washed with 10% aq. citric acid, sat. aq. NaHCO_{3}, and brine. The extracts were dried over Na_{2}SO_{4}, then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 200 g, EtOAc:hexane=6:1) to give 63 (1.632 g, 99%) as a white solid, mp 105-108°C. \[ [\alpha]D_{25}^{27} +22.6° \text{ (c=1.0, CHCl}_3). \] IR \nu_{\text{max}} (CHCl_{3}): 3440, 1732, 1657, 1539, 1439, 1372, 1318, 1157, 1051, 962, 841 cm\(^{-1}\). \[ ^1\text{H} \text{ NMR } \delta 1.52 \text{ (m, 1H)}, 1.99 \text{ (s, 3H)}, 1.9-2.1 \text{ (m, 1H)}, 2.25 \text{ (m, 2H)}, 3.87 \text{ (s, 3H)}, 4.08 \text{ (s, 3H)}, 4.65 \text{ (m, 1H)}, 5.59 \text{ (br d, 1H, J=8.3 Hz)}, 5.86 \text{ (dd, 1H, J=9.6, 3.3 Hz)}, 5.99 \text{ (s, 1H)}, 6.26 \text{ (dd, 1H, J=9.6, 1.3 Hz)}. \] Anal. Calcd for C_{13}H_{18}N_{2}O_{4}: C, 58.65; H, 6.81; N, 10.52. Found: C, 58.44; H, 6.68; N, 10.53.

**Methyl 2-Methoxyiminono-3-,(4aS-acetamidocyclohexylidene) propionate (64).** To a solution of 63 (100 mg, 0.376 mmol) in MeOH (10 mL) was added 5% Pd-CaCO_{3} poisoned with Pb (Lindlar catalyst: 50 mg), and the mixture was stirred at rt for 5 h under H_{2} (1 atm). The mixture was filtered through the pad of celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-300, 20 g, acetone:hexane=3:2) to give 64 (63 mg, 63%) as a colorless viscous oil. \[ [\alpha]D_{25}^{27} +8.0° \text{ (c=1.1, CHCl}_3). \] IR \nu_{\text{max}} (CHCl_{3}): 3438, 1732, 1651, 1549, 1439, 1372, 1320, 1217, 1148, 1109, 972, 912, 735 cm\(^{-1}\). \[ ^1\text{H} \text{ NMR } \delta 1.2-1.5 \text{ (m, 2H)}, 1.96 \text{ (s, 3H)}, 1.9-2.2 \text{ (m, 4H)}, 2.2-2.5 \text{ (m, 2H)}, 3.85 \text{ (s, 3H)}, 3.98 \text{ (m, 1H)}, 4.05 \text{ (s, 3H)}, 5.64 \text{ (br, 1H)}, 5.79 \text{ (s, 1H)}. \] Anal. Calcd for C_{13}H_{20}N_{2}O_{4}: C, 57.92; H, 7.64; N, 9.65. Found: C, 57.86; H, 7.68; N, 9.75. FABMS: m/z=269 (MH\(^+\)).

**Methyl 2-\(t\)-Butoxycarbonylamino-3-,(4aS-acetamidocyclohexylidene) propionate (65).** The oxime (64) (250 mg, 0.933 mmol) was converted to the Boc amino acid in two step sequence, as described for the preparation of 34 to give crude 65, which was purified by silica gel column chromatography (BW-300, 10 g, CHCl_{3}:MeOH=30:1) to give 65 (275 mg, 87%) as an amorphous powder, mp 51-57°C. IR \nu_{\text{max}} (CHCl_{3}): 3440, 3305, 1743, 1700, 1659, 1539, 1447, 1368, 1254, 1169, 1049, 1026, 914, 864, 772 cm\(^{-1}\). \[ ^1\text{H} \text{ NMR } \delta 1.2-1.4 \text{ (m, 2H)}, 1.43 \text{ (s, 4.5H)}, 1.44 \text{ (s, 4.5H)}, 1.96 \text{ (s, 3H)}, 1.9-2.3 \text{ (m, 5H)}, 2.6-2.8 \text{ (m, 1H)}, 3.72 \text{ (s, 1.5H)}, 3.74 \text{ (s, 1.5H)}, 3.8-4.1 \text{ (m, 1H)}, 4.9-5.3 \text{ (m, 3H)}, 5.64
(br, 1H). Anal. Calcd for C17H28N2O5 [2/5CHCl3 [2/4H2O: C, 56.02; H, 7.84; N, 7.60. Found: C, 56.36; H, 7.94; N, 7.60. FABMS: m/z=341 (MH+).

2-Methoxyimino-3-(4R-benzoxycarbonylamino-2-cyclohexenylidene)propionyl-(2S,7aS)-Aacp(Ac)-OME (66a) and 2-Methoxyimino-3-(4R-benzoxycarbonylamino-2-cyclohexenylidene)propionyl-(2R,7aS)-Aacp(Ac)-OME (66b). To a solution of 62 (101 mg, 0.283 mmol) in THF-H2O (2.5 mL-0.8 mL) was added a solution of 0.5N aq. LiOH (847 µL, 0.424 mmol) at 0°C and the mixture was stirred for 1 h. After the mixture was washed with EtOAc, the aqueous layer was acidified with 1M KHSO4 (pH=3), extracted with EtOAc (x 2), and washed with brine. The extracts were dried over Na2SO4, then concentrated in vacuo to give the crude acid (90 mg). The crude acid was used for the condensation without further purification.

A solution of 65 (80 mg, 0.235 mmol) in CH2Cl2 (588 µL, 2.5 mL/mmol) was treated with TFA (212 µL, 0.9 mL/mmol) at ambient temperature for 1 h. The mixture was concentrated in vacuo to give a pale yellow residue. Toluene was added to the residue and the mixture was concentrated in vacuo. This work-up was repeated three times to remove the excess of TFA completely. The crude amine TFA salt (116 mg) was used for condensation without further purification.

The above acid and the amine TFA salt were dissolved in DMF (700 µL) and cooled to 0°C. DEPC (43 µL, 0.283 mmol) and then i-Pr3NET (90 µL, 0.517 mmol) were added to the solution. After being stirred at 0°C for 4 h, then rt for 3 days, the mixture was quenched with 10% aq. citric acid. The whole mixture was extracted with CHCl3 (x 3) and washed with sat. aq. NaHCO3 and brine. The extracts were dried over Na2SO4 and concentrated in vacuo to give a yellow residue. The residue was triturated with CHCl3-Et2O to give 66a as a white amorphous powder. The mother liquid was purified by silica gel column chromatography (BW=300, 20 g, acetone:hexane=10:9) to give 66b as a colorless amorphous solid. The yield of 66 was 113 mg, 85%, and the ratio was determined by HPLC analysis (DAICEL CHIRALCEL OJ, eluate: i-PrOH:hexane=1:3, flow rate: 0.5 mL/min, detect: UV 254 nm, 66a:66b=55:45; 18.1 min:10.9 min). Each diastereomer was used for the next step after complete separation.

**Compound (66a):** a white amorphous powder, mp 215-219°C. [α]D24 +25.5° (c=2.1, CHCl3). IR νmax (CHCl3): 3441, 3330, 1749, 1682, 1647, 1528, 1508, 1456, 1307, 1199, 1169, 1055, 1026 cm⁻¹. ¹H NMR δ 1.27 (m, 2H), 1.57 (m, 1H), 1.97 (s, 3H), 2.06 (m, 4H), 2.24 (m, 4H), 2.75 (br d, 1H), 3.75 (s, 3H), 3.97 (m, 1H), 4.02 (s, 3H), 4.38 (br, 1H), 4.77 (br d, 1H, J=8.6 Hz), 5.10 (s, 2H), 5.14 (d, 1H, J=9.2 Hz), 5.2-5.4 (m, 2H), 5.85 (dd, 1H, J=9.9, 3.3 Hz), 5.91 (s, 1H), 6.23 (dd, 1H, J=9.9, 1.3 Hz), 7.10 (d, 1H, J=6.9 Hz), 7.36 (s, 5H). Anal. Calcd for C30H38N4O7 [2/5CHCl3 [2/2CH3OH: C, 60.79; H, 6.68; N, 9.24. Found: C, 60.43; H, 6.54; N, 9.54. HRFABMS Calcd for C30H39N4O7 (MH+): 567.2819. Found: 567.2779.

**Compound (66b):** a colorless amorphous solid. [α]D24 +70.6° (c=1.1, CHCl3). IR νmax (CHCl3) 3440, 1740, 1707, 1676, 1509, 1458, 1439, 1217, 1207, 1174, 1053 cm⁻¹. ¹H NMR δ 1.2-1.4 (m, 2H), 1.4-1.7 (m, 1H), 1.94 (s, 3H), 1.8-2.4 (m, 8H), 2.81 (brd, 1H), 3.75 (s, 3H), 4.00 (m, 1H), 4.03 (s, 3H), 4.36 (br, 1H), 4.80 (brd, 1H), 5.10 (m, 3H), 5.30 (dd, 1H, J=9.3, 1.7Hz), 5.48 (br, 1H), 5.86 (dd, 1H, J=9.9, 3.3Hz), 5.94 (s, 1H), 6.24 (dd, 1H, J=9.9, 1.7Hz), 7.18 (m, 1H), 7.35 (s, 5H). HRFABMS Calcd for

(2S,7R)-Ac-Aap(Z)-(2S,7aS)-Aacp(Ac)-OMe (67a) and (2R,7R)-Ac-Aap(Z)-(2S,7aS)-Aacp(Ac)-OMe (67b).

i) From 66a: The oxime (66a) (178 mg, 0.315 mmol) was reduced as described for the preparation of 65 to give crude (2S,R,7R)-H-Aap(Z)-(2S,7aS)-Aacp(Ac)-OMe HCO₂H, which was treated with Ac₂O-pyridine (0.4 mL-2.0 mL) at ambient temperature for 10 h. The mixture was concentrated in vacuo to give a yellow residue. The crude residue was purified by silica gel column chromatography (BW-300, 20 g, CHCl₃:MeOH=35:1 to 15:1) to give 67a and 67b (173 mg, 95%) as a white powder, in a ratio of 55:45 diastereomixture. The diastereomer was separated by preparative HPLC (YMC Pack R&D D-SIL-5-06, 250 x 20 mm; eluate: (CH₂Cl₂):EtOH=8:1, flow rate: 10 mL/min, detect: UV 254 nm 67a: 31 min; 67b: 33 min).

ii) From radiosumin (1): A solution of 1 (16.5 mg, 0.03 mmol) in H₂O-dioxane (0.5 mL-0.5 mL) was treated with NaHCO₃ (6.4 mg, 0.076 mmol) and ZCl (6.5 µL, 0.045 mmol) at 0°C. After being stirred vigorously at 0°C for 2 h, the mixture was washed with Et₂O (x 3). The H₂O layer was neutralized with AcOH and concentrated in vacuo to give pale yellow residue. The residue was dissolved in MeOH (2.0 mL) and TMSCHN₂ (1.59 M in hexane solution, 190 µL, 0.3 mmol) was added at ambient temperature. After being stirred at rt for 2 h, the mixture was concentrated in vacuo, to give a yellow residue. The crude residue was purified by silica gel column chromatography (BW-300, 10 g, CHCl₃:MeOH=35:1 to 15:1) to give 67a (6.7 mg, 38%) as a white amorphous solid.

**Compound (67a) from 66a:** a white amorphous powder. [α]D¹⁷ +118.5° (c=0.1, CHCl₃:MeOH=9:1). IR υmax (nujol): 3304, 1742, 1687, 1684, 1651, 1636, 1539, 1310, 1252, 1061, 1026, 847 cm⁻¹. ¹H NMR δ 1.1-1.4 (m, 2H), 1.60 (m, 2H), 1.96 (s, 3H), 2.01 (s, 3H), 1.9-2.2 (m, 3H), 2.2-2.3 (m, 2H), 2.3-2.5 (m, 1H), 2.6-2.9 (m, 2H), 3.74 (s, 3H), 3.95 (m, 1H), 4.40 (m, 1H), 4.77 (br d, 1H, J=8.6 Hz), 5.03 (br d, 1H, J=9.9 Hz), 5.11 (s, 2H), 5.1-5.2 (m, 2H), 5.31 (br d, 2H, J=7.9 Hz), 5.76 (dd, 1H, J=9.9, 3.3 Hz), 6.10 (dd, 1H, J=9.9, 1.0 Hz), 6.26 (br d, 1H, J=7.3 Hz), 6.40 (br d, 1H, J=6.3 Hz), 7.36 (s, 5H). HRFABMS Calcd for C₃₁H₄₁N₄O⁷ (MH⁺): 581.2975. Found: 581.2950.

**Compound (67a) from 1:** a white amorphous powder. [α]D²¹ +117.2° (c=0.07, CHCl₃:MeOH=9:1). ¹H NMR δ 1.1-1.4 (m, 2H), 1.60 (m, 2H), 1.96 (s, 3H), 2.01 (s, 3H), 1.9-2.2 (m, 3H), 2.2-2.3 (m, 2H), 2.3-2.5 (m, 1H), 2.6-2.9 (m, 2H), 3.74 (s, 3H), 3.95 (m, 1H), 4.40 (m, 1H), 4.77 (br d, 1H, J=8.6 Hz), 5.03 (br d, 1H, J=9.2 Hz), 5.11 (s, 2H), 5.1-5.2 (m, 2H), 5.3 (m, 2H changed with D₂O), 5.32 (br d, 2H, J=7.9 Hz), 5.76 (dd, 1H, J=9.9, 3.3 Hz), 6.10 (dd, 1H, J=9.9, 1.0 Hz), 6.32 (br d, 1H, J=6.6 Hz), 6.45 (br d, 1H, J=6.6 Hz), 7.36 (s, 5H).

**Compound (67b):** a white amorphous powder. [α]D²⁰ -68.6° (c=0.08, CHCl₃:MeOH= 9:1). IR υmax (nujol): 3291, 1742, 1693, 1684, 1645, 1636, 1317, 1252, 1202, 1138, 1059, 1026, 868, 802, 722, 696, 670 cm⁻¹. ¹H NMR δ 1.1-1.4 (m, 2H), 1.4-1.7 (m, 2H), 1.95 (s, 3H), 2.00 (s, 3H), 2.05 (m, 3H), 2.20 (m, 2H), 2.55 (m, 2H), 2.70 (m, 1H), 3.73 (s, 3H), 3.95 (s, 3H), 4.37 (m, 1H), 4.79 (br d, 1H, J=7.6 Hz), 5.04 (br d, 1H, J=8.9 Hz), 5.11 (s, 2H), 5.1-5.2 (m, 2H), 5.30 (d, 1H, J=8.3 Hz), 5.39 (d, 1H, J=9.6 Hz), 5.78 (dd, 1H, J=9.9, 3.6 Hz), 6.12 (dd, 2H, J=9.9, 1.3 Hz), 6.47 (br d, 1H, J=6.9 Hz), 7.36 (s, 5H).
(2S,7R)-Ac-Aayp(Z)-(2R,7aS)-Aacp(AC)-OMe (67c) and (2R,7R)-Ac-Aayp(Z)-(2R,7aS)-Aacp(AC)-OMe (67d). The oxime (66b) (23 mg, 0.04 mmol) was converted as described for the conversion of 66a to give crude 67c and 67d. The crude residue was purified by silica gel column chromatography (BW-300, 20 g, CHCl3:MeOH=20:1 to 15:1) to give 67c and 67d (17.4 mg, 74 %) as a white powder, a 44:56 ratio diastereomixture.


HPLC analysis for 67a-d: column, DAICEL CHIRALPAK AD; eluate: i-PrOH:hexane=1:2; flow rate: 0.5 ml/min; detect: UV (254 nm). 67a: 9.5 min; 67b: 12.4 min; 67c: 16.2 min; 67d: 19.6 min.

(2S,7R)-Ac-Aayp-(2S,7aS)-Aacp(AC)-OH § TFA, (1, radiosumin). To a suspension of 67a (29 mg, 0.05 mmol) in benzene (30 mL) was added (Bu₃Sn)₂O (150 µL, 0.3 mmol) and the mixture was refluxed for 3 days under argon. After cooling, the mixture was quenched with AcOH and concentrated in vacuo. The residue was washed with Et₂O (x 3), and CHCl₃-MeOH-EtOAc was added to the precipitates, then the whole was centrifuged (2000 rpm, 3 min). The supernatant was separated from the precipitates, and concentrated in vacuo to give crude 67a. The precipitate was passed through the ODS column (ODS, 5 g, H₂O to H₂O:MeOH=4:1) to give 15 mg of the crude product. The crude product was separated by preparative HPLC (YMC-Pack R&D, D-ODS-5-A, 250 x 20 mm, aq. 8% MeCN:0.05% TFA) to give 1 (7 mg, 26%), and radiosumin methyl ester (6 mg, 22%) after lyophilized, respectively. In addition to these, starting material (67a) (12 mg, 41%) was recovered after purification.

Synthetic (1): a white amorphous powder, [α]D¹⁷ +74.4° (c=0.1, H₂O). [lit.,¹ [α]D²⁰ +96° (c=0.77, H₂O)]. IR νmax (nujol): 3700-2000, 3283, 1717, 1684, 1653, 1636, 1559, 1541, 1509, 1204, 1136, 1043, 841, 801, 723, 669 cm⁻¹.¹H NMR (270 MHz, DMSO-d₆) δ 1.21 (m, 2H), 1.53 (m, 1H), 1.76 (s, 3H), 1.7-2.0 (m, 3H), 1.82 (s, 3H), 2.0-2.4 (m, 4H), 2.54 (m, 1H), 2.72 (m, 1H), 3.71 (br m, 1H), 3.86 (brm, 1H), 4.85 (dd, 1H, J=8.9, 7.3 Hz), 5.13 (d, 1H, J=9.2 Hz), 5.16 (dd, 1H, J=8.9, 5.6 Hz), 5.33 (d, 1H, J=9.2 Hz), 5.68 (br dd, 1H, J=9.2, 2.3 Hz), 6.25 (d, 1H, J=9.2 Hz), 7.75 (d, 1H, J=7.5 Hz), 7.91 (br d, 3H, J=3.6 Hz), 8.26 (d, 1H, J=7.9 Hz), 8.46 (d, 1H, J=6.9 Hz). HRFABMS Calcd for C₂₂H₃₃N₄O₅ (MH⁺): 433.2451. Found: 433.2438.

Natural 1: a white amorphous powder. [α]D¹⁴ +99.9° (c=0.06, H₂O) and [α]D¹⁶ +79.2° (c=0.1, H₂O; after preparative HPLC).¹H NMR (270 MHz, DMSO-d₆) δ 1.20 (m, 2H), 1.53 (m, 1H), 1.76 (s, 3H), 1.7-2.0 (m, 3H), 1.82 (s, 3H), 2.0-2.4 (m, 4H), 2.4-2.6 (m, 1H), 2.75 (m, 1H), 3.7 (br m, 1H), 3.86 (br m, 1H), 4.85 (dd, 1H, J=8.6, 7.9 Hz), 5.13 (d, 1H, J=8.9 Hz), 5.16 (dd, 1H, J=8.6, 4.6 Hz), 5.33 (d, 1H, J=9.2 Hz), 5.68 (br dd, 1H, J=9.2, 2.6 Hz), 6.25 (d, 1H, J=9.2 Hz), 7.76 (d, 1H, J=7.9 Hz), 7.95 (br, 3H), 8.26 (d, 1H, J=7.9 Hz), 8.46 (d, 1H, J=7.3 Hz). [lit.,¹⁹¹H NMR (500 MHz, DMSO-d₆)δ 1.19 (m, 2H), 1.52 (m, 1H), 1.76 (s, 3H), 1.77 (m, 2H), 1.82 (s, 3H), 1.85 (m, 1H), 2.00 (m, 1H), 2.02 (m, 1H), 2.16 (m, 1H), 2.31 (m, 1H), 2.53 (m, 1H), 2.71 (m, 1H), 3.70 (m, 1H), 3.85 (br m, 1H), 4.86 (dd, 1H, J=9.1, 6.6 Hz), 5.13 (d, 1H, J=9.1 Hz), 5.15 (dd, 1H, J=9.3, 7.9 Hz), 5.33 (d, 1H, J=9.3 Hz), 5.70 (br dd, 1H, J=9.7, 2.8 Hz), 6.23 (d, 1H, J=9.7 Hz), 7.75 (d, 1H, J=7.6 Hz), 8.08 (br d, 3H, J=7.6 Hz), 8.24 (d, 1H, J=7.9 Hz), 8.40 (d, 1H, J=6.6 Hz).
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REFERENCE AND NOTES

2. For a recent review, see T. Shioiri and Y. Hamada, Synlett, 2001, 184.
21. Catalytic hydrogenation of **63** over 5% Pd/C mainly gave the overreduction product and the desired cyclohexane derivative (**64**) was obtained in 32% yield. Only the overreduction product was formed in the analogous hydrogenation of **61**. The imide reduction did not proceed at all, and only the starting material was recovered.
25. During the preparation of this manuscript, radiosumin B, composed of Aayp and N-Me-Aayp, was isolated from the blue-green alga *Microcystis aeruginosa* Kützing: J. E. Coleman and J. L. C. Wright, *J. Nat. Prod.*, 2001, **64**, 668.