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PAPER

Synthesis of manzacidin A and C: efficient construction of quaternary carbon stereocenters bearing nitrogen substituents†

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An efficient synthetic method for stereoselective construction of asymmetric quaternary carbon stereocenters, bearing nitrogen in the form of Boc-protected allyl amines, has been developed. This methodology is employed in the synthesis of marine alkaloids, manzacidin A and C.

Introduction

Stereoselective synthesis of quaternary stereocenters is one of the most challenging problems in modern organic chemisry.[1] Among quaternary stereocenters, nitrogen-substituted quaternary chiral centres have attracted our continuous interest, because they serve as important architectural elements in a variety of nitrogen-containing natural products.[2] In order to address the problems associated with installation of quaternary stereocenters bearing nitrogen, we have focused on the allyl cyanate-to-isocyanate rearrangement, which is a highly stereoselective carbon–nitrogen bond forming process at sterically encumbered positions.[3] Recent investigations aimed at developing the preparative utility of this process led us to explore stereoselective routes for the synthesis of marine alkaloids, manzacidin A and C.

In 1991, Kobayashi and his co-workers reported the isolation of a novel class of bromopyrrole alkaloids, manzacidin A (**1**) and C (**2**) (Fig. 1), from the marine sponge *Hymeniacidon* sp. collected at the Manza beach of Okinawa island in Japan.[4] Ohfune and co-workers reported the first syntheses of manzacidin A and C that served to confirm the relative and absolute stereochemistry of these compounds.[5]

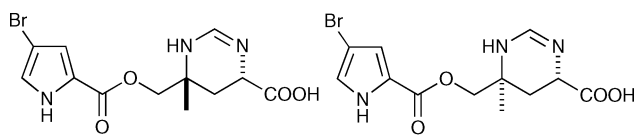
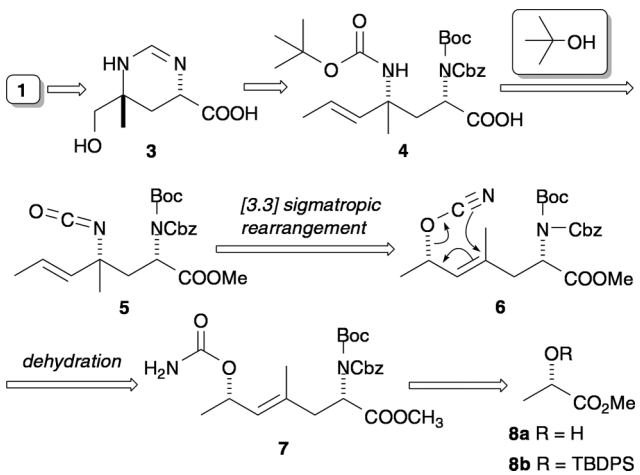


Fig. 1 Manzacidin A (**1**) and C (**2**).

Their unique structures coupled with their scarcity from the natural sources make manzacidin A and C attractive targets for total synthesis. The most critical problem confronted in the synthesis of these targets is the construction of a quaternary stereogenic carbon center bearing nitrogen. Previous syntheses present elegant approaches to this problem and, as a result, syntheses of manzacidins have showcased the power of novel synthetic methodologies.[6]

Results and discussion

Retrosynthetic analysis of manzacidin A (**1**) is shown in Scheme 1. The structure of manzacidin A (**1**) can be simplified to tetrahydropyrimidine **3** by removal of the 3-bromopyrrole-5-carboxylic acid moiety. Consideration of preparing α,γ-diamino-δ-hydroxy acid **3** by employing allyl cyanate-to-isocyanate rearrangement led to the identification of Boc-carbamate **4** as a key intermediate. We envisioned that dehydration of carbamate **7** could generate the allyl cyanate **6**, which could then undergo [3,3] sigmatropic rearrangement attended by [1,3]-chiral transfer to produce **5**



Scheme 1 Retrosynthetic plan of manzacidin A (**1**).

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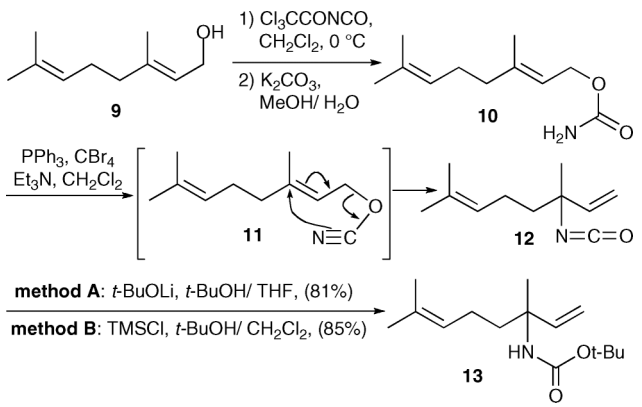
that contains a quaternary carbon bearing nitrogen in the form of an isocyanate.[7] Isocyanate **5** could be transformed to the Boc-carbamate **4** by reaction with *tert*-butyl alcohol. Further retrosynthesis of γ,δ-unsaturated α-amino acid **7** sets up **8b** as a chiral starting material, which would derive from commercially available (−)-methyl L-lactate **8a** by silylation.

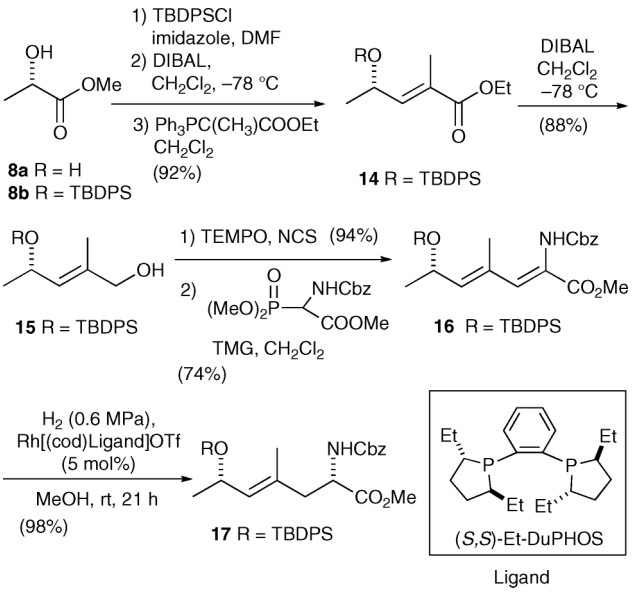
We believed that the development of this strategy would lead to a significant expansion of the utility of the allyl cyanate-to-isocyanate rearrangement to access valuable allyl amine derivatives. However, two key questions needed to be addressed in order to assess the feasibility of our approach to manzacidin A (**1**). Firstly, the ally cyanate **6** would have to be generated from **7** without disturbing the *N*,*N*-dicarbamoyl-protected amine, methyl ester and the stereogenic center in the racemization prone N-protected α-amino acid ester. Secondly, the Boc-carbamate **4** would need to be prepared by reaction of the sterically encumbered isocyanate **5** with *t*-butyl alcohol without affecting the functional groups within **5**.

Our initial studies focused on the conversion of sterically crowded isocyanates into the Boc-carbamates. For this purpose, the model isocyanate **12** was prepared from geraniol (**9**) (Scheme 2) and its reaction with *tert*-butyl alcohol was examined. Disappointingly, our previously reported protocols using stannous alkoxide (Bu_3SnO*t*-Bu)[8] and catalyst (dibutyltin maleate)[9] gave the Boc-carbamate **13** in only low yields; however, screening several alkoxides led to the finding that reaction of isocyanate **12** with lithium *t*-butoxide provided the Boc-carbamate **13** in 81% yield (method A).[10] Furthermore, it was found that addition of *tert*-butyl alcohol to isocyanate **12** proceeded smoothly in the presence of chlorotrimethylsilane (TMSCl) to furnish **13** in 85% yield (method B).[11] The two methods are complementary (basic *vs.* acidic conditions) and have the merit of utilizing commonly available reagents.[12]



Scheme 2 Transformation of a sterically crowded model isocyanate into a Boc-carbamate.

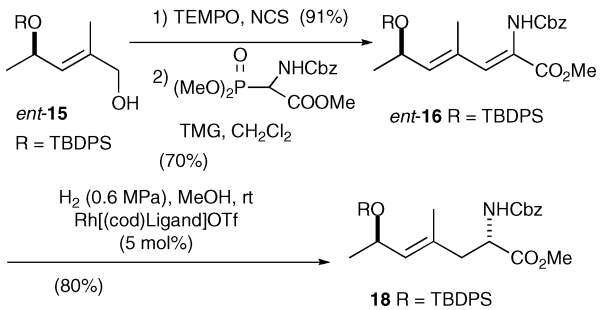
Having established conditions for the conversion of sterically crowded isocyanates into the Boc-carbamates, we initiated the synthesis of manzacidin A starting with commercially available (−)-methyl L-lactate **8a** (Scheme 3). Protection of the hydroxyl group in **8a** as TBDPS ether, followed by diisobutylaluminium hydride (DIBAL) reduction of **8b** and Wittig olefination produced the (*E*)-α,β-unsaturated ester **14** exclusively in 92% yield. Installation of the γ,δ-unsaturated α-amino acid moiety was performed using enantioselective catalytic hydrogenation of α,γ-dienamide esters



Scheme 3 Synthesis of the γ,δ-unsaturated α-amino acid **17** by diastereoselective hydrogenation.

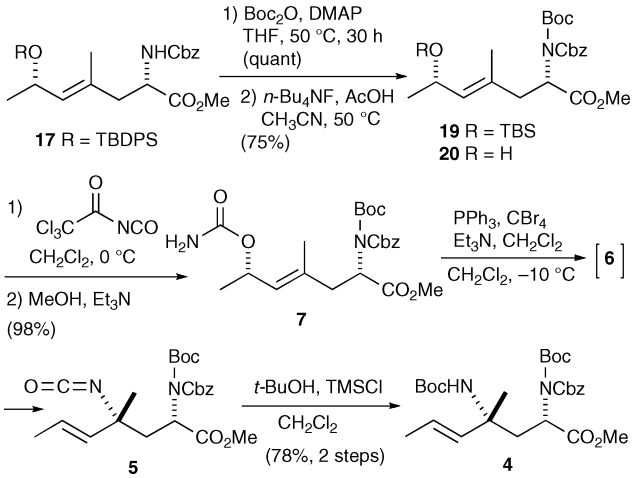
with DuPHOS-Rh catalyst reported by Burk and co-workers.[13] Accordingly, dienamide **16** was prepared by a three-step sequence involving DIBAL reduction, TEMPO oxidation and Horner–Emmons olefination using Schmidt's reagent[14] to afford **16** in 61% yield over three steps. Initially, we had little confidence that diastereoselective hydrogenation of **16** would be successful, because Burk noted that N-Cbz protected α,γ-dienamide esters do not undergo asymmetric hydrogenation with DuPHOS-Rh catalysts. Contrary to our apprehension, enamide **16** was found to undergo hydrogenation in the presence of 5 mol% catalyst in methanol under hydrogen (0.6 MPA) to furnish the desired γ,δ-unsaturated amino acid **17** predominantly.[15]

In order to check the diastereoselectivity of the hydrogenation of **16** and to prepare the intermediate for manzacidin C, *ent*-allyl alcohol **15**, prepared from (+)-methyl D-lactate,[16] was elaborated to **18** (Scheme 4) in a manner that is identical to that described in Scheme 3. Importantly, no signals corresponding to **18** were observed in the ^{1}H NMR spectrum of **17**.



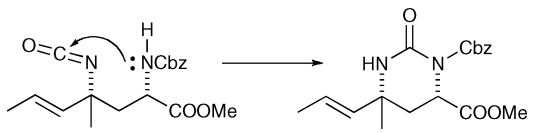
Scheme 4 Synthesis of the diastereomer **18** from the *ent*-allyl alcohol **15**.

With **17** in hand, we were positioned to examine installation of the key quaternary asymmetric carbon center exploiting allyl cyanate-to-isocyanate rearrangement (Scheme 5). Initial efforts showed that a problem existed in that a urea was formed by



Scheme 5 Allyl cyanate-to-isocyanate rearrangement of **6** and conversion to Boc-carbamate **4**.

intramolecular capture of the formed isocyanate by the nitrogen in the Cbz group (eqn (1)).

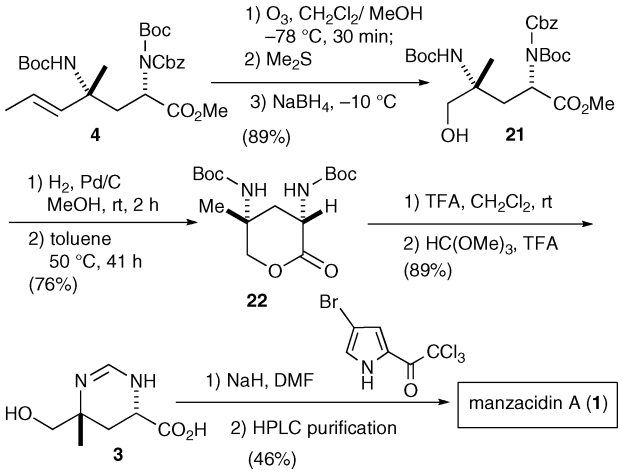


(1)

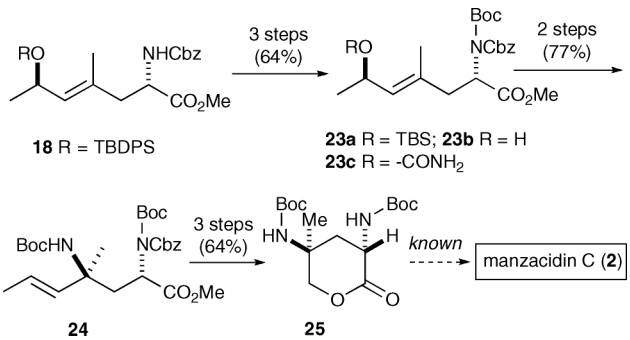
To prevent this process, the nitrogen in the Cbz group was masked as the bis-carbamate protected amine **19** by treatment of **17** with Boc_2O and DMAP.[17] Deprotection of the TBDPS group in **19** followed by carbamoylation of the resulting allyl alcohol **20** by treatment with trichloroacetyl isocyanate and methanolysis of the resulting *N*-trichloroacetylcarbamate produced allyl carbamate **7**. Dehydration of **7** utilizing triphenylphosphine, carbon tetrabromide and triethylamine in CH_2Cl_2 at –10 °C generated the allyl cyanate **6**, which uneventfully underwent rearrangement to form the allyl isocyanate **5**. After careful isolation, isocyanate **5** was immediately transformed to the Boc-carbamate **4** in 78% yield employing method B described in Scheme 2.

The remaining tasks were synthesis of the lactone intermediate **22** and its conversion to manzacidin A (**1**). To this end, ozonolysis of **4** was carried out at –78 °C in a mixture of CH_2Cl_2 and methanol. Without isolation, the resulting aldehyde was reduced with sodium borohydride to afford **21** in 89% yield. Hydrogenolysis to remove the Cbz group in **21** followed by heating a solution of the resulting methyl ester in toluene provided the crystalline lactone **22** in 76% yield over two steps. Following the procedures reported by Ohfune and co-workers,[5,6k] sequential deprotection of the Boc group in **22** with trifluoroacetic acid (TFA) in CH_2Cl_2 and treatment of the hydrolysate with a mixture of methyl orthoformate and TFA was carried out in one flask to give rise to the tetrahydropyrimidine **3** after ion exchange chromatography in 89% yield. Finally, coupling of **3** with 2-(trichloroacetyl)-4-bromopyrrole with sodium hydride in DMF and HPLC purification furnished manzacidin A (**1**) in 46% yield.

In addition, we carried out a synthesis of manzacidin C (**2**) (Scheme 7). The procedures used for conversion of **17** to **4** (Scheme 5) and from **4** to **22** (Scheme 6) were repeated using **18** and **24**, respectively, to furnish the lactone **25** in 32% overall yield from **18** in 8 steps. Since lactone **25** was employed as an intermediate in the



Scheme 6 Synthesis of manzacidin A (**1**).



Scheme 7 Formal synthesis of manzacidin C (**2**).

synthesis of manzacidin C by Ohfune,[5] this sequence represents a formal synthesis of manzacidin C.

Conclusions

In summary, we have developed a practical procedure for stereoselective construction of asymmetric quaternary carbon stereocenters bearing nitrogen in the form of Boc-protected allyl amines. In addition, this process served as a key step in the synthesis of marine alkaloids, manzacidin A and C. Importantly, generation of the allyl cyanate **6**, its rearrangement and transformation of the sterically encumbered cyanate **5** into the Boc-carbamate **4** were carried out in the presence of labile functionality as well as an α-stereogenic center present in the α-amino acid moiety.[18]

Experimental

General

Melting points were recorded on a micro melting point apparatus and are not corrected. Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. Infrared spectra are reported in wave number (cm^{-1}). ^1H NMR data are reported with the solvent resonance as the internal standard relative to chloroform (δ 7.27), methanol (δ 3.31) and DOH (δ 4.80) as follows; chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, m = multiplet), coupling constants (J, given in Hz) and integration. ^{13}C NMR

chemical shifts (δ) are recorded in parts per million (ppm) relative to $CDCl_3$ (δ 77.0), CD_3OD (δ 49.0) and *t*-BuOH (δ 30.29 in D_2O) as internal standards. High-resolution mass spectra (HRMS) are reported in *m*/*z*. Reactions were run under atmosphere of argon when the reactions were sensitive to moisture or oxygen. Dichloromethane was dried over 3 Å molecular sieves. Pyridine and triethylamine were stocked over anhydrous KOH. All other commercially available reagents were used as received.

(*E*)-3,7-Dimethylocta-2,6-dienyl carbamate (10). To a solution of geraniol (**9**) (1.78 g, 11.5 mmol) in CH_2Cl_2 (115 mL) cooled to 0 °C was added trichloroacetyl isocyanate (1.40 mL, 17.3 mmol). After stirring at 0 °C for 30 min, the solution was concentrated under reduced pressure. The resulting residue was dissolved in a mixture of MeOH (70 mL) and 1 M aqueous potassium carbonate (45 mL). After stirring at room temperature for 3 h, the separated aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Purification by silica gel chromatography (AcOEt–hexane 1 : 4 to 1 : 2) afforded carbamate **10** (2.33 g, 102%), which was used for the next reaction without further purification; IR (NaCl) ν_{max} 3439, 3344, 2967, 2918, 2855, 1712, 1606, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.62 (s, 3H), 1.69 (s, 3H), 1.71 (s, 3H), 2.00–2.15 (4H), 4.59 (d, J = 7.0 Hz, 2H), 4.92 (br, 2H), 5.09 (brt, J = 7.0 Hz, 1H), 5.35 (t, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 17.6, 25.6, 26.2, 39.5, 61.9, 118.4, 123.7, 131.8, 142.1, 157.2; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{19}NO_2Na$ (M+ Na)$^+$ 220.13135, found 220.1315.

***tert*-Butyl 3,7-dimethylocta-1,6-dien-3-ylcarbamate (13) prepared using method A.** To a solution of allyl carbamate **10** (200 mg, 1.01 mmol), triphenylphosphine (665 mg, 2.53 mmol) and triethylamine (0.45 mL, 3.24 mmol) in CH_2Cl_2 (6.0 mL) at –10 °C was added a solution of carbon tetrabromide (941 mg, 2.84 mmol) in CH_2Cl_2 (4.0 mL) dropwise. After being stirred at –10 °C for 30 min, the reaction mixture was diluted with hexane. The mixture was washed with H_2O (3 times) and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude allyl isocyanate **12**, which was immediately used for subsequent reaction.

A mixture of *tert*-butyl alcohol (5.0 mL) and dry THF (3.0 mL) at 0 °C was treated with *n*-butyllithium (1.58 M solution in hexane, 1.30 mL, 2.03 mmol), and then allowed to warm to room temperature. After stirring at room temperature for 30 min, the reaction mixture was recooled to –10 °C and then a solution of crude allyl isocyanate in THF (2.0 mL) was added. The reaction mixture was stirred at –10 °C for 20 min, and then diluted with H_2O. The separated aqueous layer was extracted with Et_2O (3 times). The combined organic layers were washed with H_2O, brine, and dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt–hexane 1 : 20) to afford Boc-carbamate **13** (206 mg, 81% from geraniol **9**) as a colorless liquid.

***tert*-Butyl 3,7-dimethylocta-1,6-dien-3-ylcarbamate (13) prepared using method B.** To a solution of allyl carbamate **10** (200 mg, 1.01 mmol), triphenylphosphine (665 mg, 2.53 mmol) and triethylamine (0.45 mL, 3.24 mmol) in CH_2Cl_2 (6.0 mL) at –10 °C was added a solution of carbon tetrabromide (941 mg, 2.84 mmol) in CH_2Cl_2 (4.0 mL) dropwise. After being stirred at –10 °C for 30 min, the reaction mixture was diluted with hexane. The mixture was washed with H_2O (3 times) and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude allyl isocyanate **12**, which was immediately used for the subsequent reaction.

Crude allyl isocyanate **12** was dissolved in CH_2Cl_2 (5.0 mL), and then treated with trimethylchlorosilane (3 μL, 0.03 mmol) and *tert*-butyl alcohol (0.48 mL, 5.1 mmol) at room temperature. After being stirred at room temperature for 25 h, the solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (AcOEt–hexane 1 : 20) to afford Boc-carbamate **13** (109 mg, 85% from geraniol **9**) as a colorless liquid; IR (NaCl) ν_{max} 3450, 3361, 2975, 2929, 1725, 1698, 1492, 1249, 1169, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (s, 3H), 1.43 (s, 9H), 1.59 (s, 3H), 1.68 (s, 3H), 1.95 (brq, J = 7.5 Hz, 2H), 4.62 (br, 1H), 5.03–5.13 (3H), 5.89 (dd, J = 17.0, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.5, 22.5, 24.8, 25.6, 28.4, 39.5, 56.1, 78.8, 78.8, 111.9, 124.0, 131.8, 143.6, 154.3; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{28}NO_2$ (M+ H)$^+$ 254.21200, found 254.2114.

(*S*)-Methyl 2-(*tert*-butyldiphenylsilyloxy)propanoate (8b). To a solution of L-(–)-lactic acid methyl ester (**8a**) (4.36 g, 41.9 mmol) and imidazole (8.5 g, 0.12 mol) in DMF (23.0 mL) was added *tert*-butylchlorodiphenylsilane (10.9 mL, 41.9 mmol) portionwise. The reaction mixture was stirred at room temperature for 48 h, and then diluted with Et_2O (120 mL) and H_2O (100 mL). The separated organic layer was washed with H_2O, brine, and dried over Na_2SO_4. Concentration under reduced pressure provided the crude silyl ether **8b** (14.8 g), which was used for the next reaction without further purification; $[\alpha]_D^{16}$ –44.7 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 2952, 2933, 1758, 1739, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H), 1.36 (d, J = 7.0 Hz, 3H), 3.55 (s, 3H), 4.28 (quin, J = 7.0 Hz, 1H), 7.45–7.34 (m, 6H), 7.70–7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 21.2, 26.8, 51.5, 68.9, 127.5, 127.6, 129.7, 133.1, 133.5, 135.7, 135.8, 174.1; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{26}O_3SiNa$ [M+ Na]$^+$ 365.15489, found 365.1520.

(*S*,*E*)-Ethyl 4-(*tert*-butyldiphenylsilyloxy)-2-methylpent-2-enoate (14). To a solution of silyl ether **8b** (6.00 g, 17.5 mmol) in CH_2Cl_2 (140 mL) cooled to –78 °C was added a solution of diisobutylaluminium hydride (0.99 M in toluene, 21 mL, 21.0 mmol) dropwise. After being stirred at –78 °C for 1 h, several drops of methanol were added to quench the reaction, and aqueous potassium sodium (+)-tartrate tetrahydrate solution was added. After stirring at room temperature for 30 min, the separated aqueous layer was extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude aldehyde (6.63 g), which was immediately used for the subsequent reactions.

To a solution of aldehyde in CH_2Cl_2 (140 mL) was added ethyl 2-(triphenylphosphoranylidene)propionate (19.0 g, 52.5 mmol). After being stirred at room temperature for 18 h, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (AcOEt–hexane 1 : 10) to give (*E*)-unsaturated ester **14** (6.35 g, 92%) as a colorless liquid; $[\alpha]_D^{16}$ –53.6 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 2693, 2931, 1714, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 1.20 (d, J = 6.5 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H) 1.42 (s, 3H) 4.16 (quin, J = 7.0 Hz, 2H), 4.56 (dq, J = 8.5, 6.5 Hz, 1H) 6.72

(d, J = 8.5 Hz, 1H) 7.45–7.31 (m, 6H), 7.68–7.60 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.2, 14.2, 19.1, 23.1, 26.9, 60.5, 66.7, 125.7, 127.3, 127.4, 127.6, 129.6, 129.6, 133.8, 134.1, 135.7, 135.8, 144.9, 168.0; HRMS (ESI): m/z calcd for $C_{24}H_{33}O_3Si$ $(M+H)^+$ 397.21990, found 397.2198.

(*S*,*E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylpent-2-en-1-ol (15). To a solution of unsaturated ester **14** (3.70 g, 9.34 mmol) in CH_2Cl_2 (93 mL) cooled to −78 °C was added a solution of diisobutylaluminium hydride (0.99 M in toluene, 22 mL, 21.5 mmol) dropwise. After being stirred at −78 °C for 1 h, MeOH and aqueous potassium sodium (+)-tartrate solution were added. After stirring at room temperature for 30 min, the separated aqueous layer was extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt–hexane 1 : 4) to afford allyl alcohol **15** (2.91 g, 88%) as a colorless liquid; $[\alpha]_D^{24}$ −6.6 (c 1.00, $CHCl_3$); IR (NaCl) ν_{max}; 3344, 2964, 2930, 2857 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.08 (s, 9H), 1.23 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 1.0 Hz, 3H), 3.80 (s, 2H), 4.60 (dq, J = 8.0, 6.0 Hz, 1H), 5.43 (dq, J = 8.0, 1.0 Hz, 1H), 7.33–7.73 (10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.5, 19.1, 24.2, 26.9, 66.4, 68.2, 127.3, 127.4, 129.36, 129.44, 130.5, 133.5, 134.4, 134.6, 135.7, 135.9; HRMS (ESI): m/z calcd for $C_{22}H_{30}O_2SiNa$ $[M+Na]^+$ 377.1913, found 377.1921.

(*S*,2*Z*,4*E*)-Methyl 2-(benzyloxycarbonylamino)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhepta-2,4-dienoate (16). To a solution of allyl alcohol **15** (2.90 g, 8.19 mmol) dissolved in a mixture of CH_2Cl_2 (82.0 mL) and aqueous solution (82.0 mL) of $NaHCO_3$ (0.5 M) and K_2CO_3 (0.05 M) were added TEMPO (128 mg, 0.82 mmol) and tetrabutylammonium chloride (227 mg, 0.82 mmol). After vigorously stirring at room temperature for 10 min, *N*-chlorosuccinimide (1.90 g, 14.3 mmol) was added. After being stirred at room temperature for 5 h, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt–hexane 1 : 20) to afford a α,β-unsaturated aldehyde (2.71 g, 94%) as a colorless liquid.

To a solution of α,β-unsaturated aldehyde (2.39 g, 6.79 mmol) in CH_2Cl_2 (23.0 mL) cooled to 0 °C were added methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate (7.40 g, 22.3 mmol) and 1,1,3,3-tetramethylguanidine (3.40 mL, 27.2 mmol). The reaction mixture was stirred at room temperature for 4 days and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt–hexane 1 : 5) to afford *Z*-dienamide ester **16** (2.64 g, a colorless liquid, 74%, calculated based on the consumed starting material), recovered starting aldehyde (129 mg, 6%), and *E*-isomer (282 mg, 7%). $[\alpha]_D^{16}$ −85.9 (c 0.90, $CHCl_3$); IR (NaCl) ν_{max} 3317, 2931, 2857, 1715, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 9H), 1.17 (d, J = 6.0 Hz, 3H), 1.40 (s, 3H), 3.76 (brs, 3H), 4.56 (dq, J = 8.0, 6.0 Hz, 1H), 5.12 (s, 2H), 5.85 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 7.29–7.43 (6H), 7.60–7.69 (4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 19.1, 23.6, 26.9, 52.4, 66.3, 67.3, 122.4, 127.47, 127.52, 128.04, 128.16, 128.5, 129.41, 129.53, 129.56, 133.9, 134.2, 135.72, 135.79, 136.0, 137.4, 144.2, 154.4, 165.9; HRMS (ESI): m/z calcd for $C_{33}H_{39}NO_5SiNa$ $(M+Na)^+$ 580.24952, found 580.2502.

(2*S*,6*S*,*E*)-Methyl 2-(benzyloxycarbonylamino)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhept-4-enoate (17). Dry Schlenk tube is charged with dienamide ester **16** (1.00 g, 1.79 mmol) and methanol (20.0 mL). The mixture is degassed by three freeze–thaw cycles and [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf (65 mg, 0.09 mmol, 5 mol%) was added. The resulting orange solution was further degassed by three freeze–thaw cycles and then transferred by syringe to a 50 mL glass autoclave equipped with a gas inlet tube and pressure gauge. The gas inlet tube was attached to a hydrogen source and then the autoclave was replaced by evacuation (to *ca.* 20 mmHg) and refilling with hydrogen three times. Hydrogen was introduced into the reaction vessel until the pressure gauge indicated 0.6 MPa. After stirring at room temperature for 21 h, the hydrogen was vented and the solvent was evaporated. The crude material was purified by silica gel chromatography (AcOEt–hexane 1 : 4) to afford γ,δ-unsaturated amino acid methyl ether **17** (0.98 g, 98%) as a colorless liquid; $[\alpha]_D^{16}$ −22.6 (c 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3429, 3345, 2961,2930, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9H), 1.11 (d, J = 6.5 Hz, 3H), 1.22 (brs, 3H), 2.20 (dd, J = 13.5, 8.0 Hz, 1H), 2.39 (dd, J = 13.5, 6.5 Hz, 1H), 3.70 (s, 3H), 4.36 (q, J = 6.5 Hz, 1H), 4.44 (dq, t, J = 8.0, 6.5 Hz, 1H), 5.02–5.13 (3H), 5.31 (d, t, J = 8.0 Hz, 1H), 7.29–7.42 (11H), 7.58–7.68 (4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 19.0, 24.2, 26.8, 42.1, 52.2, 66.4, 67.0, 127.39, 127.45, 128.12, 128.18, 128.44, 128.55, 129.5, 134.1, 134.4, 134.6, 135.70, 135.76136.1, 155.7, 172.8; HRMS (ESI): m/z calcd for $C_{33}H_{41}O_5NSiNa$ $[M+Na]^+$ 582.26517, found 582.2655.

(2*S*,6*S*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhept-4-enoate (19). To a solution of **17** (2.05 g, 3.67 mmol) and 4-dimethylaminopyridine (0.45 g, 3.67 mmol) in dry THF (37.0 mL) was added di-*tert*-butyl dicarbonate (3.80 mL, 16.4 mmol) at room temperature. After being stirred at 50 °C for 28 h, the reaction mixture was diluted with water, and then extracted with Et_2O (3 times). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt–hexane 1 : 10) to afford biscarbamate **19** (2.41 g, quant) as a colorless liquid; $[\alpha]_D^{16}$ −44.9 (c 1.00, $CHCl_3$); IR (NaCl) ν_{max} 2965, 2931, 1748, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (s, 9H), 1.04 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 1.0 Hz, 3H), 1.43 (s, 9H), 2.49 (dd, J = 14.5, 9.5 Hz, 1H), 2.75 (dd, J = 14.5, 5.5 Hz, 1H), 3.66 (s, 3H), 4.45 (dq, J = 8.0, 6.0 Hz, 1H), 5.10 (dd, t, J = 9.5, 5.5 Hz, 1H), 5.35 (brd, J = 8.0 Hz, 1H), 5.17–5.24 (2H), 7.29–7.42 (11H), 7.59–7.70 (4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 19.1, 24.2, 26.9, 27.9, 39.1, 52.2, 57.2, 66.7, 68.8, 83.5, 127.42, 127.43, 128.21, 128.29, 128.44, 129.32, 129.38, 129.8, 133.6, 134.2, 134.8, 135.2, 135.2, 135.75, 135.8, 151.2, 153.9, 170.9; HRMS (ESI): m/z calcd for $C_{38}H_{49}O_7NSiNa$ $[M+Na]^+$ 682.31760, found 682.3185.

(2*S*,6*S*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)-amino)-6-hydroxy-4-methylhept-4-enoate (20). To a solution of

biscarbamate **19** (2.30 g, 3.49 mmol) and AcOH (1.20 mL, 20.9 mmol) in CH_3CN (35.0 mL) was added dropwise tetrabutylammonium fluoride (1.0 M solution in THF, 21.0 mL, 21.0 mmol) at 0 °C. After stirring at 50 °C for 36 h, the reaction mixture was cooled to room temperature and then diluted with water. The aqueous layer was extracted with Et_2O (3 times). The combined organic extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude material was purified by silica gel chromatography (AcOEt–hexane 1 : 2) to afford allyl alcohol **20** (1.11 g, 75%) as a colorless liquid; $[\alpha]_D^{16}$ −40.2 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3535, 2976, 1790, 1745, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, J = 6.5 Hz, 3H), 1.44 (s, 9H), 1.64 (s, 3H), 2.62–2.73 (2H), 3.68 (s, 3H), 4.43 (m, 1H), 5.09 (dd, J = 10.0, 5.5 Hz, 1H), 5.03 (d, J = 8.5, 6.0 Hz, 1H), 5.23 (s, 2H), 7.33–7.42 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 23.0, 27.8, 39.2, 52.3, 56.4, 64.3, 68.9, 128.46, 128.49, 128.52, 132.9, 133.6, 151.4, 153.8, 170; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{31}O_7NNa$ $[M+Na]^+$ 444.19982, found 444.2011.

(2*S*,6*S*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)-amino)-6-(carbamoyloxy)-4-methylhept-4-enoate (7). To a solution of allyl alcohol **20** (1.04 g, 2.47 mmol) in CH_2Cl_2 (15.0 mL) cooled to 0 °C was added trichloroacetyl isocyanate (0.44 mL, 3.70 mmol). After stirring at 0 °C for 1 h, the solution was concentrated under reduced pressure. The resulting residue was dissolved in MeOH (15.0 mL) and then treated with triethylamine (2.10 mL, 14.8 mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with AcOEt (3 times). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt–hexane 1 : 2) to afford allyl carbamate **7** (1.12 g, 98%) as a colorless liquid; $[\alpha]_D^{17}$ −45.4 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3488, 3381, 2979, 1793, 1742, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 6.5 Hz, 3H), 1.46 (s, 9H), 1.69 (s, 3H), 2.65 (dd, J = 14.0, 10.5 Hz, 1H), 2.74 (dd, J = 14.0, 5.0 Hz, 1H), 3.67 (s, 3H), 4.38 (brs, 2H), 5.11–5.16 (2H), 5.23 (s, 2H), 5.42 (dq, J = 8.5, 6.5 Hz, 1H), 7.32–7.43 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 20.8, 27.8, 39.2, 52.3, 56.4, 68.2, 68.7, 83.5, 128.2, 128.3, 128.5, 129.0, 134.6, 135.2, 151.0, 153.5, 156.4, 170.7; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{32}O_8N_2Na$ $[M+Na]^+$ 487.20563, found 487.2068.

(2*S*,4*R*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino)-4-(*tert*-butoxycarbonylamino)-4-methylhept-5-enoate (4). To a solution of allyl carbamate **7** (1.80 g, 3.88 mmol), triphenylphosphine (2.54 g, 19.7 mmol) and triethylamine (1.90 mL, 14.0 mmol) in CH_2Cl_2 (37 mL) at −10 °C was added a solution of carbon tetrabromide (3.60 g, 10.9 mmol) in CH_2Cl_2 (2.0 mL) dropwise. After being stirred at −10 °C for 20 min, the reaction mixture was diluted with hexane. The mixture was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude allyl isocyanate **5**, which was immediately used for the subsequent reaction.

Crude allyl isocyanate **5** was dissolved in a mixture of *tert*-butyl alcohol (3.70 mL, 38.8 mmol) and CH_2Cl_2 (39.0 mL), and then treated with trimethylchlorosilane (50 μL, 0.39 mmol) at room temperature. After being stirred at room temperature for 7 days, the reaction mixture was poured into aqueous saturated $NaHCO_3$. The separated aqueous layer was extracted with ether, and the combined organic extracts were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure followed by purification by silica gel chromatography (AcOEt–hexane 1 : 4) afforded Boc-carbamate **4** (1.58 g, 78%) as a colorless liquid; $[\alpha]_D^{17}$ −14.1 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3378, 2977, 1796, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 1.41 (s, 9H), 1.44 (s, 9H), 1.62 (d, J = 5.0 Hz, 3H), 2.18 (dd, J = 15.0, 6.5 Hz, 1H), 2.65 (dd, J = 15.0, 3.5 Hz, 1H), 3.65 (s, 3H), 5.20–5.28 (2H), 5.35–5.46 (2H), 7.33–7.44 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8, 26.1, 27.9, 28.3, 41.0, 52.6, 54.9, 55.3, 68.8, 83.6, 123.2, 128.33, 128.37, 128.5, 135.2, 135.5, 151.1, 153.6, 171.9; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{40}O_8N_2Na$ $[M+Na]^+$ 543.26823, found 543.2729.

(2*S*,4*R*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)-amino)-4-(*tert*-butoxycarbonylamino)-5-hydroxy-4-methylpentanoate (21). A stream of ozone in oxygen was bubbled through a solution of Boc-carbamate **4** (481 mg, 0.92 mmol) and a trace amount of Sudan IV in a mixture of CH_2Cl_2 and MeOH (6 : 1, 48 mL) at −78 °C for 5 min. Oxygen was bubbled through the solution for 30 min and then dimethyl sulfide (0.68 ml, 9.2 mmol) was added. After being stirring at −78 °C for 60 min and at room temperature for 60 min, reaction mixture was cooled to −78 °C and then treated with a solution of sodium borohydride (699 mg, 18.5 mmol). The reaction mixture was warmed to −10 °C and stirred at −10 °C for 30 min. Saturated aqueous $NaHCO_3$ was added at −78 °C, and the cooling bath was removed. After stirring at room temperature for 60 min, the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt–hexane 1 : 10 followed by 1 : 2) to afford alcohol **21** (430 mg, 89%) as a colorless liquid; $[\alpha]_D^{27}$ −2.8 (*c* 1.02, $CHCl_3$), $[\alpha]_D^{27}$ −8.5 (*c* 0.96, MeOH); IR (NaCl) ν_{max} 3393, 2978, 1793, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (s, 3H), 1.39 (s, 9H), 1.46 (s, 9H), 2.36 (dd, J = 15.5, 4.5 Hz, 1H), 3.53 (brd, J = 12.0 Hz, 1H), 3.60–3.65 (1H), 3.65 (s, 3H), 5.04–5.11 (2H), 5.21 (d, J = 12.0 Hz, 1H), 5.30 (d, J = 12.0 Hz, 1H), 7.30–7.44 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 27.8, 28.3, 37.0, 52.7, 54.8, 55.8, 69.0, 69.3, 79.6, 84.0, 128.2, 128.4, 128.5, 135.0, 150.9, 153.7, 155.8, 172.1; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{39}O_5N_2O_9$ $[M+H]^+$ 511.26556, found 511.2647.

***tert*-Butyl (3*S*,5*R*)-5-methyl-2-oxotetrahydro-2*H*-pyran-3,5-diyldicarbamate (22).** A mixture of alcohol **21** (207 mg, 0.406 mmol) and palladium on carbon (10%, 23 mg) in MeOH (4.0 mL) was stirred vigorously under a hydrogen atmosphere for 2 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to provide a mixture of deprotection product and lactone **22**, which was immediately dissolved in toluene (4.0 mL). The solution was heated at 60 °C for 40 h and then concentrated to afford the residue, which was purified by silica gel chromatography (AcOEt–hexane 1 : 10 followed by 2 : 1) to provide lactone **22** (106 mg, 76%) as a white solid; Mp 178–179 °C (lit.[1] Mp 177 °C); $[\alpha]_D^{18}$ = +120.3 (*c* 1.05, $CHCl_3$) (lit.[5] $[\alpha]_D^{27}$ = +128, *c* 1.05, $CHCl_3$); IR (NaCl) ν_{max} 3317, 3053, 2978, 1755, 1687, 1536 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 1.45 (s, 9H), 1.47 (s, 3H), 1.91 (dd, J = 14.0, 10.5 Hz, 1H), 2.65 (dd, J = 14.0, 8.5 Hz, 1H), 4.07 (d, J = 12.0 Hz, 1H), 4.42 (m, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.77

(brs, 1H), 5.37 (brd, J = 5.5 Hz, 1H) (lit.[5] $CDCl_3$, 300 MHz, δ 1.42 (s, 9H), 1.45 (s, 9H), 1.47 (s, 3H), 1.93 (dd, J = 13.8, 11.4 Hz, 1H), 2.64 (dd, J = 13.8, 8.2 Hz, 1H), 4.08 (d, J = 11.9 Hz, 1H), 4.39 (m, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.76 (s, 1H), 5.36 (d, J = 5.5 Hz, 1H)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 28.20, 28.27, 40.7, 47.3, 51.5, 72.7, 77.2, 79.9, 80.3, 154.4, 155.3, 172.0. (lit.[5] $CDCl_3$, 75 MHz, δ 23.54, 28.30, 28.36, 40.91, 47.41, 51.56, 72.80, 80.07, 80.44, 154.44, 155.30, 171.99); Anal. Calcd for $C_{28}H_{28}N_2O_6$: C, 55.80; H, 8.19; N, 8.13. Found: C, 55.98; H, 8.47; N, 8.07.

(4*S*,6*R*)-6-(Hydroxymethyl)-6-methyl-3,4,5,6-tetrahydropyrimidine-4-carboxylic acid (3). To a solution of **22** (124 mg, 0.36 mmol) in CH_2Cl_2 (3.6 mL) cooled to 0 °C was added TFA (2.4 mL) and the cooling bath was removed. After stirring at room temperature for 30 min, the mixture was concentrated under reduced pressure to afford the residue, which was dissolved in trimethyl orthoformate (3.0 mL). The solution was treated with TFA (0.90 mL) at 0 °C, and was stirred at room temperature for 20 h. After concentration under reduced pressure, the resulting residue was dissolved in 2 N HCl. After stirring at room temperature for 2 h followed by concentration, the crude **3** was purified by ion exchange chromatography (Dowex 50 W × 8, 100–200 mesh, H^+ form, eluted with H_2O, then 1 N aqueous NH_3) to afford tetrahydropyrimidine **3** (55 mg, 89%), which was considered to be pure enough for the subsequent reaction by ^{1}H NMR analysis; $[\alpha]_D^{23}$ = +45.7 (*c* 0.60, H_2O) (lit.[5] $[\alpha]_D^{22}$ = +57.3 (*c* 0.53, H_2O)); ^{1}H NMR (H_2O, 500 MHz) δ 1.25 (s, 3H), 1.83 (dd, J = 14.0, 11.0 Hz, 1H), 2.08 (dd, J = 14.0, 5.0 Hz, 1H), 3.48 (d, J = 11.5 Hz, 1H), 3.57 (d, J = 11.5 Hz, 1H), 4.05 (dd, J = 11.0, 5.0 Hz, 1H), 7.89 (s, 1H) (lit.,[5] D_2O, 500 MHz, δ 1.28 (s, 3H), 1.86 (dd, J = 13.5, 10.7 Hz, 1H), 2.11 (dd, J = 13.5, 4.9 Hz, 1H), 3.51 (d, J = 11.8 Hz, 1H), 3.59 (d, J = 11.8 Hz, 1H), 4.08 (dd, J = 10.7, 4.9 Hz, 1H), 7.92 (s, 1H)); ^{13}C NMR (D_2O, 125 MHz) δ 23.4, 31.0, 50.9, 54.6, 67.3, 150.8, 176.1 (lit.,[5] D_2O, 100 MHz, δ 22.78, 30.46, 50.31, 54.09, 66.78, 150.28, 175.44); HRMS (ESI): *m*/*z* calcd for $C_7H_{13}N_2O_3$ (M+ H)$^+$ 173.0926, found 173.0934.

Manzacidin A (1). To a solution of **3** (55 mg, 0.32 mmol) in DMF (3.0 mL) cooled to 0 °C was added sodium hydride (64 mg, 60% dispersion in mineral oil, washed with hexane before use, 1.6 mmol). After stirring at 0 °C for 1 h, bromopyrrole (465 mg, 1.60 mmol) was added in one portion, and the cooling bath was removed. After stirring at room temperature for 3 h, the reaction mixture was quenched with 2 N HCl and washed with AcOEt to remove excess bromopyrrole. The aqueous layer was concentrated under reduced pressure to afford the residue, which was subjected to reversed-phase chromatography (flash column of Cosmosil 75C_{18}-OPN eluted with water–acetonitrile 1 : 0 to 7 : 3, and HPLC with Develosil ODS-UG-5, Nomura Chemical eluted with acetonitrile–water–TFA = 22 : 78 : 0.1) to furnish manzacidin A (**1**) (50 mg, 46%); $[\alpha]_D^{24}$ −23.1 (*c* 0.50, CH_3OH) (lit.[4] $[\alpha]_D^{27}$ −28, *c* 0.67, CH_3OH; lit.[5] $[\alpha]_D^{27}$ −22.4, *c* 0.52, CH_3OH; lit.[6a] $[\alpha]_D^{27}$ −26.5, *c* 0.65, CH_3OH; lit.[6a] $[\alpha]_D^{29}$ −23.0, *c* 0.50, CH_3OH; lit.[6e] $[\alpha]_D^{25}$ −26.3, *c* 0.30, CH_3OH; lit.[6j] $[\alpha]_D^{29}$ −21.8, *c* 1.09, CH_3OH); IR (KBr) ν_{max} 3198, 2984, 1676, 1319, 1202 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.46 (s, 3H), 2.22 (dd, J = 14.0, 10.0 Hz, 1H), 2.38 (dd, J = 14.0, 5.0 Hz, 1H), 4.23 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 4.48 (dd, J = 10.0, 5.0 Hz, 1H), 6.92 (d, J = 1.4 Hz, 1H), 7.03 (d, J = 1.4 Hz, 1H), 8.08 (s, 1H). (lit.:[5] CD_3OD, 75 MHz, δ 1.47 (s, 3H), 2.20 (dd, J = 13.7, 10.0 Hz, 1H), 2.38 (dd, J = 13.7, 5.2 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 4.47 (dd, J = 10.0, 5.2 Hz, 1H), 6.92 (d, J = 1.6 Hz, 1H), 7.02 (d, J = 1.6 Hz, 1H), 8.07 (s, 1H)); ^{13}C NMR (CD_3OD, 125 MHz) δ 24.0, 31.0, 49.6, 53.8, 68.8, 98.2, 118.6, 123.2, 125.3, 152.1, 160.5, 171.3. (lit.:[5] CD_3OD, 75 MHz, δ 24.05, 31.05, 53.82, 68.80, 98.18, 118.63, 123.24, 125.36, 152.19, 160.59; lit.:[6e] CD_3OD, 75 MHz, δ 24.1, 31.2, 53.8, 68.7, 98.1, 118.4, 123.1, 125.2, 151.9, 160.4, 172.8); HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}BrN_3O_4$ (M+ H)$^+$ 346.0246 and 346.0267, found 344.0253 and 346.0245.

***ent*-16.** Starting from allyl alcohol *ent*-**15** (1.60 g, 4.52 mmol), CH_2Cl_2 (45.0 mL), aqueous solution (45.0 mL) of $NaHCO_3$ (0.5 M) and K_2CO_3 (0.05 M), TEMPO (71 mg, 0.45 mmol), tetrabutylammonium chloride (125 mg, 0.45 mmol) and *N*-chlorosuccinimide (1.10 g, 7.9 mmol), α,β-unsaturated aldehyde was obtained as a colorless liquid (1.45 g, 91%); $[\alpha]_D^{15}$ = +29.4 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3071, 2961, 2930, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 9H), 1.27 (d, J = 6.5 Hz, 3H), 1.33 (brs, 3H), 4.73 (dq, t, J = 8.0, 6.5 Hz, 1H), 6.40 (dd, J = 7.5, 1.0 Hz, 1H), 7.30–7.47 (6H), 7.58–7.70 (4H), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.9, 19.1, 22.9, 26.8, 66.5, 127.58, 127.65, 129.79, 129.83, 133.5, 133.6, 135.7, 136.2, 156.5, 195.1.

Starting from α,β-unsaturated aldehyde (1.35 g, 3.83 mmol), CH_2Cl_2 (38.0 mL), methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate (4.20 g, 12.6 mmol) and 1,1,3,3-tetramethylguanidine (1.90 mL, 15.3 mmol), a mixture of dienamide ester was obtained, which was purified by silica gel chromatography (AcOEt–hexane 1 : 5) to afford *Z*-dienamide ester *ent*-**16** (1.22 g, a colorless liquid, 70%, calculated based on the consumed starting material), a 1 : 1 mixture of *Z*- and *E*-isomers (0.16 g, 8%), *E*-isomer (35 mg, 2%) and recovered starting material (243 mg, 18%). The calculated selectivity (*Z* : *E*) is approximately 91 : 9; $[\alpha]_D^{27}$ = +83.7 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3317, 2931, 2857, 1715, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 9H), 1.18 (d, J = 6.0 Hz, 3H), 1.41 (s, 3H), 3.76 (brs, 3H), 4.56 (dq, J = 8.0, 6.0 Hz, 1H), 5.12 (s, 2H), 5.85 (d, J = 8.0 Hz, 1H), 5.95 (br, 1H), 6.84 (s, 1H), 7.29–7.43 (6H), 7.60–7.69 (4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 19.1, 23.6, 26.8, 52.4, 66.3, 67.3, 122.4, 127.47, 127.53, 128.05, 128.18, 128.5, 129.40, 129.54, 129.57, 133.9, 134.2, 135.73, 135.80, 136.0, 137.4, 144.1, 154.4, 165.9; HRMS (ESI): *m*/*z* calcd for $C_{33}H_{39}O_5NSiNa$ [M+ Na]$^+$ 582.26517, found 582.2657.

(2*S*,6*R*,*E*)-Methyl 2-(benzyloxycarbonylamino)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhept-4-enoate (18). Starting from dienamide ester *ent*-**16** (1.01 g, 1.81 mmol), methanol (18.0 mL) and [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf (65 mg, 0.091 mmol, 5 mol%), γ,δ-unsaturated amino acid methyl ether **18** (0.81 g, 80%) was obtained as a colorless liquid; $[\alpha]_D^{27}$ = +27.2 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3423, 3344, 2961, 2930, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (s, 9H), 1.10 (d, J = 6.5 Hz, 3H), 1.23 (brs, 3H), 2.17 (dd, J = 13.5, 8.5 Hz, 1H), 2.38 (dd, J = 13.5, 4.5 Hz, 1H), 3.71 (s, 3H), 4.39 (td, J = 8.5, 4.5 Hz, 1H), 4.46 (dq, J = 8.0, 6.5 Hz, 1H), 5.00–5.11 (3H), 5.29 (brd, J = 8.5 Hz, 1H), 7.29–7.44 (11H), 7.60–7.69 (4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 19.1, 24.2, 26.9, 42.5, 52.1, 52.3, 66.5, 66.9, 127.37, 127.46, 128.03, 128.10, 128.4, 128.7, 129.4, 129.5, 134.2, 134.4, 134.7, 135.73, 135.76, 136.2, 155.6, 172.6; HRMS (ESI): *m*/*z* calcd for $C_{33}H_{41}O_5NSiNa$ [M+ Na]$^+$ 582.26517, found 582.2657.

(2*S*,6*R*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-4-methylhept-4-enoate (23a). Carbamate **18** (708 mg, 1.27 mmol) was transformed into biscarbamate **23a** (0.66 g, 79%) by employing 4-dimethylaminopyridine (155 mg, 1.27 mmol), di-*tert*-butyl dicarbonate (1.30 mL, 5.70 mmol) and THF (13.0 mL); $[\alpha]_D^{19}$ −11.9 (*c* 1.25, $CHCl_3$); IR (NaCl) ν_{max} 2965, 2932, 1747, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.02 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H), 1.14 (brs, 3H), 1.42 (s, 9H), 2.50 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.59 (dd, *J* = 13.5, 4.5 Hz, 1H), 3.66 (s, 3H), 4.39 (dq, *J* = 8.5, 6.5 Hz, 1H), 5.01 (dd, t, *J* = 11.0, 4.5 Hz, 1H), 5.14–5.09 (3H), 7.28–7.44 (11H), 7.60–7.68 (4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5, 19.1, 24.2, 26.9, 27.8, 39.3, 52.2, 56.2, 66.5, 68.7, 83.4, 127.3, 127.4, 128.34, 128.37, 128.44, 129.33, 129.40, 129.46, 134.3, 134.4, 134.5, 135.1, 135.7, 135.8, 151.2, 153.7, 170.9; HRMS (ESI): *m*/*z* calcd for $C_{38}H_{49}O_7NSiNa$ $[M+Na]^+$ 682.31760, found 682.3184.

(2*S*,6*R*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino)-6-hydroxy-4-methylhept-4-enoate (23b). Starting from biscarbamate **23a** (203 mg, 0.31 mmol), AcOH (0.11 mL, 1.85 mmol), CH_3CN (3.1 mL) and tetrabutylammonium fluoride (1.0 M solution in THF, 1.80 mL, 1.80 mmol), allyl alcohol **23b** was obtained as a colorless liquid (112 mg, 86%); $[\alpha]_D^{18}$ −23.1 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3524, 3418, 2976, 1747, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (d, *J* = 6.5 Hz, 3H), 1.44 (s, 9H), 1.65 (d, *J* = 1.0 Hz, 3H), 2.64–2.73 (2H), 3.68 (s, 3H), 4.46 (m, 1H), 5.09–5.16 (2H), 5.21 (s, 2H), 7.31–7.41 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 23.3, 27.8, 39.3, 52.3, 56.4, 64.5, 68.7, 83.6, 128.39, 128.41, 128.5, 132.6, 133.5, 135.0, 151.2, 153.7, 170.7; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{31}O_7NNa$ $[M+Na]^+$ 444.19982, found 444.2016.

(2*S*,6*R*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino)-6-(carbamoyloxy)-4-methylhept-4-enoate (23c). Allyl alcohol **23b** (91 mg, 0.22 mmol) was transformed into allyl carbamate **23c** (94 mg, 94%) by employing CH_2Cl_2 (1.30 mL), trichloroacetyl isocyanate (40 µL, 0.32 mmol), MeOH (1.30 mL) and triethylamine (0.18 mL, 1.30 mmol); $[\alpha]_D^{24}$ −27.2 (*c* 1.08, $CHCl_3$); IR (NaCl) ν_{max} 3481, 3380, 2979, 1792, 1730, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, *J* = 6.5 Hz, 3H), 1.44 (s, 9H), 1.69 (d, *J* = 1.0 Hz, 3H), 2.68–2.74 (2H), 3.68 (s, 3H), 4.53 (br, 2H), 5.08 (dd, *J* = 8.5, 1.0 Hz, 1H), 5.12 (dd, *J* = 8.5, 7.0 Hz, 1H), 5.22 (s, 2H), 5.38 (dq, *J* = 8.5, 6.5 Hz, 1H), 7.30–7.42 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2, 20.7, 27.8, 39.4, 52.3, 56.2, 68.4, 68.8, 83.5, 128.36, 128.43, 128.46, 129.3, 134.5, 135.0, 151.1, 153.6, 156.4, 170.6; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{32}N_2O_8Na$ $[M+Na]^+$ 487.20563, found 487.2052.

(2*S*,4*S*,*E*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino)-4-(*tert*-butoxycarbonylamino)-4-methylhept-5-enoate (24). Starting from allyl carbamate **23c** (94 mg, 0.22 mmol), triphenylphosphine (146 mg, 0.56 mmol), triethylamine (0.11 mL, 0.80 mmol), CH_2Cl_2 (2.20 mL), carbon tetrabromide (207 mg, 0.62 mmol) in CH_2Cl_2 (2.0 mL), crude allyl isocyanate was obtained. Without purification, crude allyl isocyanate was transformed into Boc-carbamate **24** (90 mg, 77%) using CH_2Cl_2 (2.20 mL), trimethylchlorosilane (3 µL, 0.02 mmol) and *tert*-butyl alcohol (0.43 mL, 4.46 mmol); $[\alpha]_D^{26}$ −16.0 (*c* 1.05, $CHCl_3$); IR (NaCl) ν_{max} 3433, 3383, 2977, 1798, 1746, 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 12H), 1.46 (s, 9H), 1.64 (d, *J* = 5.0 Hz, 3H), 2.39 (br, 1H), 2.53 (brd, *J* = 14.5 Hz, 1H), 3.64 (s, 3H), 5.01 (dd, *J* = 7.0, 3.0 Hz, 1H), 5.18–5.32 (2H), 5.39–5.46 (2H), 7.30–7.44 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8, 25.6, 27.9, 28.3, 39.9, 52.5, 55.2, 55.7, 68.8, 78.9, 83.6, 123.5, 128.28, 128.33, 128.5, 151.1, 153.6, 154.4, 171.6; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{41}N_2O_8$ $[M+H]^+$ 521.2863, found 521.2857.

(2*S*,4*S*)-Methyl 2-((benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino)-4-(*tert*-butoxycarbonylamino)-5-hydroxy-4-methylpentanoate. Boc-carbamate **24** (90 mg, 0.17 mmol) was transformed into alcohol (66 mg, 75%) employing CH_2Cl_2 (7.7 mL), MeOH (1.3 mL), ozone, dimethyl sulfide (0.13 mL, 1.7 mmol) and a solution of sodium borohydride (131 mg, 3.46 mmol) in MeOH (1.0 mL); $[\alpha]_D^{18}$ −15.5 (*c* 1.05, $CHCl_3$); IR (NaCl) ν_{max} 3500, 3416, 2978, 1791, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (s, 3H), 1.42 (s, 9H), 1.45 (s, 9H), 1.97 (dd, *J* = 15.5, 5.0 Hz, 1H), 2.74 (dd, *J* = 15.5, 5.0 Hz, 1H), 3.50–3.60 (2H), 3.66 (s, 3H), 5.10 (br, 1H), 5.12 (t, *J* = 5.0 Hz, 1H), 5.22–5.30 (2H), 7.32–7.43 (5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 27.8, 28.3, 38.2, 52.7, 54.8, 55.9, 69.0, 79.6, 84.0, 128.3, 128.41, 128.48, 135.1, 151.2, 153.7, 155.7, 172.3; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{39}ON_2O_9$ $[M+H]^+$ 511.2656, found 511.2647.

***tert*-Butyl (3*S*,5*S*)-5-methyl-2-oxotetrahydro-2*H*-pyran-3,5-diyldicarbamate (25).** Starting from alcohol **24** (56 mg, 0.11 mmol), palladium on carbon (10%, 6 mg), MeOH (2.0 mL) and toluene (2.0 mL), lactone **25** was produced as a white solid (32 mg, 85%); Mp 171–172 °C; $[\alpha]_D^{24}$ = +19.1 (*c* 1.10, $CHCl_3$) (lit.[5] $[\alpha]_D^{27}$ = +21.5, *c* 1.10, $CHCl_3$); IR (NaCl) ν_{max} 3332, 2978, 2932, 1713, 1692, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 3H), 1.45 (s, 9H), 1.44 (s, 9H), 1.67 (t, *J* = 12.5 Hz, 1H), 2.72 (br, 1H), 4.24 (br, 1H), 4.44–4.62 (2H), 4.74 (br, 1H), 5.29 (br, 1H) (lit.[5] $CDCl_3$, 300 MHz, δ 1.38 (s, 3H), 1.43 (s, 9H), 1.44 (s, 9H), 1.66 (t, *J* = 12.9 Hz, 1H), 2.71 (m, 1H), 4.23 (m, 1H), 4.57 (m, 2H), 4.78 (s, 1H), 5.30 (brs, 1H)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8, 28.3, 39.7, 47.8, 50.7, 73.7, 80.3, 154.5, 155.1, 173.0 (lit.[5] $CDCl_3$, 100 MHz, δ 28.29, 29.66, 39.66, 47.78, 50.67, 73.65, 80.30, 154.52, 155.16, 172.05); Anal. Calcd for $C_{28}H_{28}N_2O_6$: C, 55.80; H, 8.19; N, 8.13. Found: C, 55.91; H, 8.43; N, 7.96; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{29}N_2O_6$ $[M+H]^+$ 345.20256, found 345.2022.

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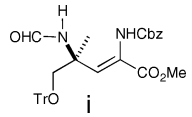

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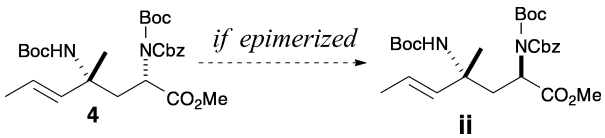
17 D. L. Flynm, R. E. Zelle and P. A. Grieco, *J. Org. Chem.*, 1983, **48**, 2424.
18 If epimerization of the α-stereogenic center in the α-amino acid ester **4** (Scheme 5) occurred, diastereomer **ii** should be formed. On the other hand, **ii** is an enantiomer of **24** (Scheme 7). ^{1}H NMR analysis of the product **4** showed that no signals corresponding to those of **24** were presented, which confirmed that the α-stereocenter in the α-amino acid ester **7** did not epimerize in the conversion of **7** to **4**.



4 ii

