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Synthetic Studies on an Antitumor Antibiotic, Bleomycin. XIV.[1] The Synthesis of Boc-Pyrimidoblamic Acid

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New methodology was developed for the introduction of an acetate unit into the Schiff base **2**, based on the reaction of the Schiff base **2** with malonic acid monoester or vinyloxyborane. Furthermore, the synthesis of Boc-pyrimidoblamic acid, a key fragment for the total synthesis of bleomycin, was achieved by utilizing these two methods.

Keywords——bleomycin; pyrimidobleonic acid; Boc-pyrimidoblamic acid; ethyl hydrogen malonate; vinyloxyborane; Schiff base; β-amino acid

In the preceding papers, we have described practical methods for the preparation of formylpyrimidine **3** and (*S*)-3-amino-2-*tert*-butoxycarbonylaminopropionamide (Boc-L-DAPA, **4**).[1] The subject of the present paper is the synthesis of Boc-pyrimidoblamic acid **1**. Our strategy for obtaining Boc-pyrimidoblamic acid was to obtain the Schiff base **2** from formylpyrimidine **3** and Boc-L-DAPA (**4**), and then to introduce an acetic acid unit into the carbon–nitrogen double bond to construct the pyrimidoblamic acid skeleton.[2] Although a β-amino acid skeleton is commonly found in many biologically significant antibiotics, synthesis from the Schiff base is relatively unexplored. The few methods reported include the reaction of the Schiff base with the Reformatsky reagent[3] and malonic acid diester.[4] Recently, Ojima reported the reaction of the Schiff base with *O*-alkyl-*O*-trimethylsilyl ketene acetal in the presence of titanium tetrachloride, giving the β-amino ester and/or β-lactam depending on the structural features of the reactants.[5] We initially examined such a reagent with the model Schiff base **7**, prepared from 2-formyl-6-methoxycarbonylpyridine and β-alanine methyl ester. However, the desired addition product was not obtained. The reaction of the lithium enolate

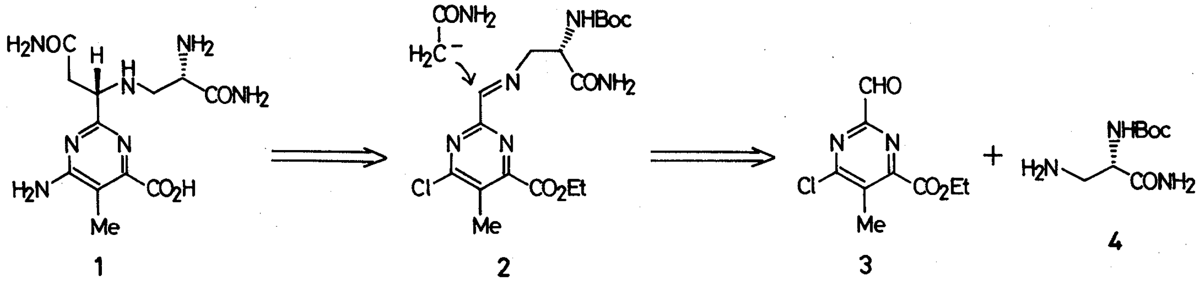

Chart 1

of ethyl acetate was also tried in an attempt to obtain the β-amino ester, but proceeded only in low yield.

Schöpf has reported that sodium acetoacetate adds to the Schiff base **5** through decarboxylative acetonylation to give the β-amino ketone **6** in a high yield.[6] Although no analogous reaction with malonic acid derivatives has been reported, the mild conditions of the reaction, which proceeds without any assistance of a strong acid or base, were attractive, considering the various functional groups present in pyrimidoblamic acid.

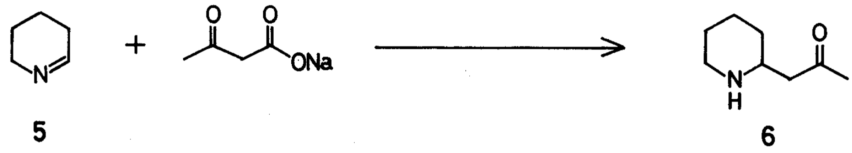

Chart 2

After a number of experiments, the desired β-amino ester **8** was obtained in 31% yield by treatment of the model Schiff base **7** with a large excess of monomethyl malonate (5 eq) in acetonitrile.[2] In this reaction, the undesired α,β-unsaturated ester **9** was also formed in 20% yield.

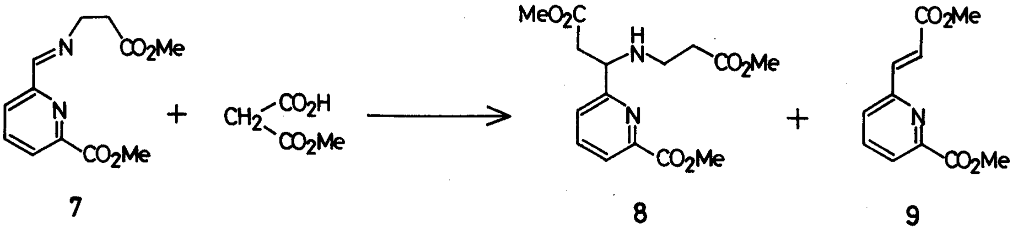

Chart 3

All attempts to further improve the yield of **8** by varying the solvent and the reaction temperature were unsuccessful. Initially, we thought that the reaction would proceed through the six-membered-ring cyclic transition state with synchronous decarboxylation, and that the undesired α,β-unsaturated ester **9** might be derived from the β-amino ester **8** by β-elimination. However, the β-amino ester **8** does not undergo β-elimination on retreatment with monomethyl malonate in acetonitrile. Furthermore, monitoring of the reaction by thin-layer chromatography (TLC) showed that the reaction seemed to proceed by the initial addition of malonate to **7** to form the amino acid **10**, followed by decarboxylation of **10** to afford both the β-amino ester **8** (path a) and the α,β-unsaturated ester **9** (path b).

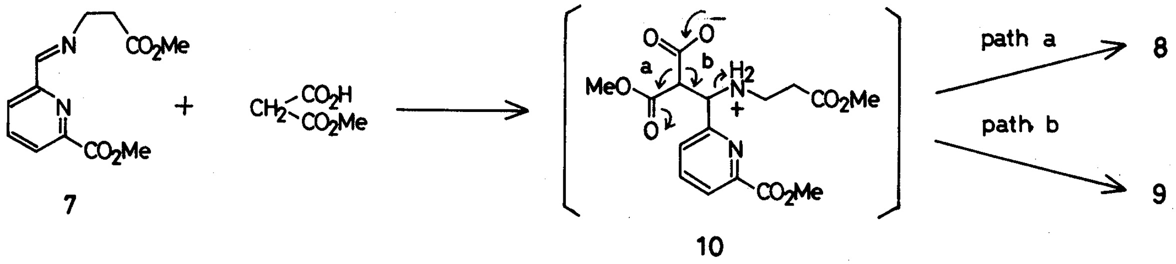

Chart 4

Thus, the step-by-step mechanism is more likely than the synchronous mechanism we initially expected. Although we could not obtain the β-amino ester **8** selectively in a good yield, this method is very simple, needing only the mixing of the reactants in acetonitrile, and proceeds under very mild conditions. Therefore, the application of this method to pyrimidoblamic acid was examined. The Schiff base **2** was found to be formed from equimolar amounts of formylpyrimidine **3** and Boc-L-DAPA **4** in acetonitrile in the presence of activated molecular sieves 3A (MS-3A). The addition of MS-3A is critical for the dehydration of aminal to the Schiff base. Unfortunately, all attempts to isolate the Schiff base **2** were unsuccessful, and we obtained only the aminal. Therefore, the Schiff base was directly used for the next C–C bond formation. After formylpyrimidine **3** and Boc-L-DAPA **4** had been stirred in acetonitrile in the presence of MS-3A for 22 h, monoethyl malonate was added; the reaction mixture was then stirred for another 24 h. We thus obtained the desired β-amino ester **11** in 23% yield as an almost 1 : 1 epimeric mixture, along with the undesired α,β-unsaturated ester **12** in 46% yield.[2)]

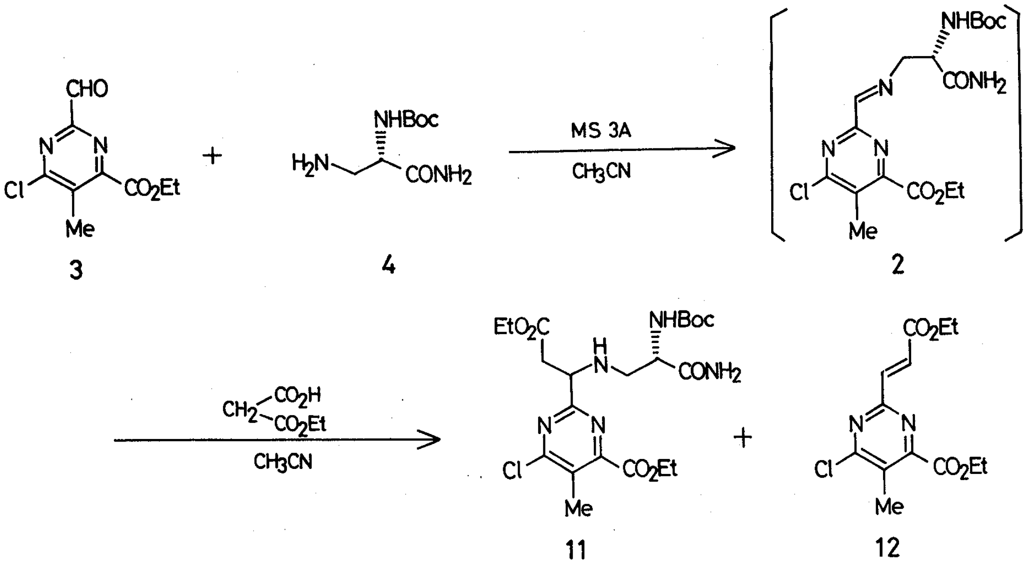

Chart 5

The epimeric mixture could be separated by silica-gel thin-layer chromatography (Merck, HPTLC Art. 5642) to afford the desired *S*,*S*-isomer **11*S*** (less polar, *Rf* 0.48, benzene : EtOH = 9 : 1) and the *S*,*R*-isomer **11*R*** (more polar, *Rf* 0.44, benzene : EtOH = 9 : 1). The absolute configuration of the newly formed chiral center was unambiguously established by correlating the less polar isomer **11*S*** to pyrimidobleonic acid **13**, the degradation product of bleomycin, as shown in the following scheme. Each isomer, **11*S*** and **11*R***, was separately treated with ammonia, followed by acid hydrolysis, thus giving pyrimidobleonic acid **13** and epi-pyrimidobleonic acid **14**, respectively.

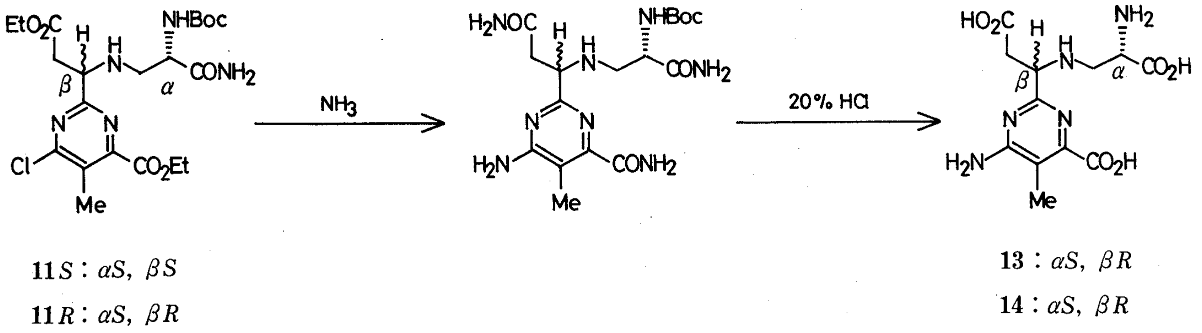

Chart 6

Although **13** and **14** have almost the same retention times on high performance liquid chromatography (HPLC) analysis (RADIAL PAK-A, Waters Ltd., eluted with 0.1 M KH_2PO_4, 1.0 ml/min), their copper complexes, prepared by treatment with cupric acetate, were found to be cleanly separated on HPLC. The copper complex derived from the less polar **11***S* showed the same retention time (5.5 min) as that of pyrimidobleonic acid of natural origin,[7] while the copper complex of epipyrimidobleonic acid[8] had a retention time of 6.5 min. It was thus established that the less polar **11***S* has the same absolute configuration as bleomycin. However, during the above operations we observed some epimerization at the newly formed chiral center. For example, HPLC analysis showed that the complex derived from **11***S* is a 79 : 21 mixture of *S*,*S*- and *S*,*R*-isomers, while the copper complex derived from **11***R* is a 27 : 73 epimeric mixture. This epimerization has already been observed in the degradation of bleomycin, and has been utilized to obtain epipyrimidobleonic acid.[8] Therefore, we decided to separate the epimeric mixture at a later stage. By treatment of the epimeric mixture with 1.1 eq of NaOH in $EtOH-H_2O$ at 0 °C for 1 h, selective hydrolysis of the ester group attached to the pyrimidine ring was effected to give the acid **15** in a 93% yield. Exhaustive amination of the acid **15** gave rise to a 1 : 1 epimeric mixture of Boc-pyrimidoblamic acid **16** and Boc-epipyrimidoblamic acid **17** in 25% yield. Although HPLC separation was possible with the copper complexes, it was very gratifying to find that recrystallization from anhydrous EtOH afforded the desired Boc-pyrimidoblamic acid **16** from **11** in 8% yield.

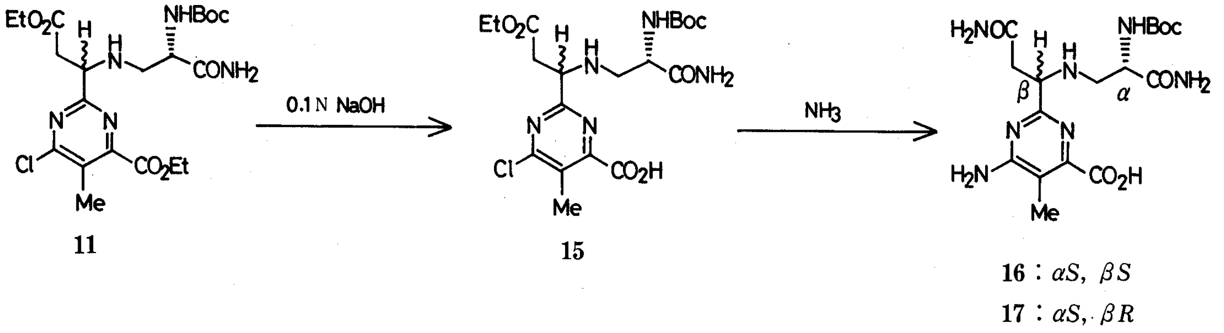

Chart 7

The Boc-pyrimidoblamic acid thus synthesized was identical (proton nuclear magnetic resonance (^{1}H-NMR), infrared (IR), optical rotatory dispersion (ORD), field disorption mass spectrum (FD-MS), and optical rotation) with the Boc-pyrimidoblamic acid derived from natural bleomycin.[9] We thus achieved the first synthesis of Boc-pyrimidoblamic acid by the reaction of the Schiff base **2** and monoethyl malonate. However, the yield was low, and the product was always accompanied by the undesired unsaturated ester, despite the experimental simplicity of the reaction. We have, therefore, reinvestigated another method for the introduction of the acetate unit into the Schiff base **2**. Recent developments in aldol chemistry have revealed the importance of metal enolates.[10] The most noteworthy development is the vinyloxyborane methodology, first introduced by Mukaiyama[11] and then developed by Masamune.[10a] Vinyloxyborane reacts with carbonyl compounds through a six-membered cyclic transition state, where boron enolate not only acts as a nucleophile, but activates carbonyl compounds at the same time. Althoug there were no precedents for the reaction of vinyloxyborane and the Schiff base, it seemed reasonable to expect that vinyloxyborane would add to the Schiff base through a similar cyclic transition state, considering the strong affinity of borane for nitrogen as well as oxygen. Thus, the model Schiff base **7** was treated with vinyloxyborane **18**, prepared from *tert*-butyl thioacetate and di-*n*-butylboryltriflate according to Masamune's procedure,[12] to afford the *β*-amino thiolester **19** in 81% yield.[13]

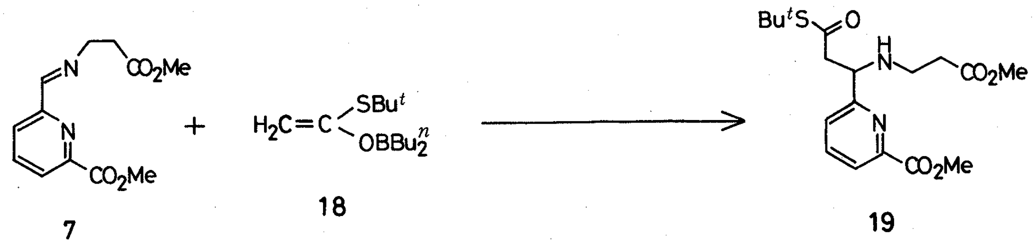

Chart 8

The formation of the elimination product, always seen in the monomethyl malonate method, could be completely suppressed by the present method. In a similar manner, the Schiff base **2**, prepared from formylpyrimidine **3** and Boc-L-DAPA **4** in ether in the presence of activated MS-3A, was reacted with vinyloxyborane **18** to afford the β-amino thiolester **20** in 40% yield as an almost 1 : 1 epimeric mixture. This was then converted into Boc-pyrimidoblamic acid **16** by the same procedure; alkaline hydrolysis, followed by exhaustive amination, afforded a mixture of **16** and **17** from **20** in 28% yield.

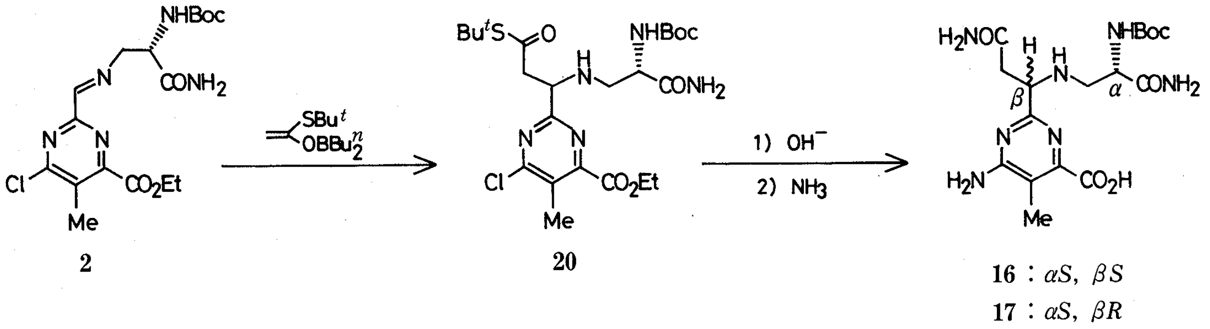

Chart 9

In conclusion, we have developed two methods for the introduction of an acetate unit into the Schiff base **2**. By applying these two methods, the first synthesis of pyrimidobleonic acid and Boc-pyrimidoblamic acid was achieved. This result confirms the structure of the pyrimidine moiety of bleomycin. Furthermore, the Boc-pyrimidoblamic acid thus synthesized was successfully utilized in the first total synthesis of bleomycin.[14)]

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a JEOL FX-100 spectrometer and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a JASCO DS-402G spectrometer. Electron impact mass spectra (EI-MS), and FD-MS were measured with a Hitachi RMU-7M spectrometer. Ultraviolet (UV) spectra were measured with a Hitachi 124 spectrometer. Optical rotations were measured with a JASCO DIP-181 digital polarimeter.

Methyl 6-[[(2-Methoxycarbonylethyl)imino]methyl]pyridine-2-carboxylate (7)——A mixture of methyl 6-formylpyridine-2-carboxylate (1.65 g, 10.0 mmol) β-alanine methylester hydrochloride (1.40 g, 10.0 mmol), triethylamine (2.05 g, 20.3 mmol), and anhydrous magnesium sulfate (2.40 g, 20 mmol) in CH_2Cl_2 (100 ml) was stirred at room temperature overnight. After filtration of the reaction mixture, the filtrate was concentrated. The residue was dissolved in Et_2O, and the Et_2O solution was washed with sat. NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give **7** (2.21 g, 88%) as a syrup. This was used for the next reaction without further purification. IR (neat): 2950, 1740, 1650, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.78 (2H, t, $J=7$ Hz), 3.74 (3H, s), 4.00 (2H, dt, $J=2$, 7 Hz), 4.08 (3H, s), 7.8—8.3 (3H, m), 8.61 (1H, br). MS m/e: 251 ($M^+ + 1$), 250 (M^+), 219 ($M^+ - OMe$), 191 ($M^+ - CO_2Me$), 177 ($M^+ - CH_2CO_2Me$).

Methyl 3-[(2-Methoxycarbonylethyl)amino]-3-(6-methoxycarbonylpyridin-2-yl)propionate (8)——A mixture of **7** (127.2 mg, 0.50 mmol) and monomethyl malonate (297.0 mg, 2.52 mmol) in CH_3CN (8 ml) was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with sat. $NaHCO_3$ to remove excess monomethyl malonate, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel to give **8** (51.1 mg, 31%) and **9** (22.5 mg, 20%). **8**; IR (neat): 3340, 2960, 1740, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.5—2.8 (7H, m), 3.65 (3H, s), 3.67 (3H, s), 3.97 (3H, s), 4.34 (1H, dd, $J=7.5$, 9 Hz), 7.8 (3H, m). MS *m/e*: 325 ($M^+ + 1$), 293 ($M^+ - OMe$).

Ethyl 2-[1-[[(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-(carbamoyl)ethyl]amino]-2-(ethoxycarbonyl)ethyl]-6-chloro-5-methylpyrimidine-4-carboxylate (11)——A mixture of formylpyrimidine **3** (114 mg, 0.5 mmol), Boc-L-DAPA **4** (102 mg, 0.5 mmol) and activated MS-3A in CH_3CN (4 ml) was stirred at room temperature for 22 h. Then monoethyl malonate (330 mg, 2.5 mmol) in CH_3CN (0.5 ml) was added, and the reaction mixture was stirred at room temperature for 24 h. MS-3A was filtered off, the filtrate was concentrated and the residue was dissolved in AcOEt. The AcOEt solution was washed with sat. $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (eluted with (1) benzene, (2) benzene–AcOEt (10 : 1), and (3) benzene–EtOH (25 : 1)) to give **11** (57 mg, 23%) and **12** (58 mg, 46%). The epimeric mixture of **11** was separated by silica gel TLC (Merck, Art. 5628) developed with benzene–EtOH (9 : 1).

11*S*: $[\alpha]_D^{20} - 3.5°$ ($c=2.0$, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t), 1.42 (3H, t), 1.44 (9H, s), 2.47 (3H, s), 2.5—2.8 (2H, m), 2.7—3.2 (2H, m), 4.14 (2H, q), 3.98—4.15 (1H, m), 4.17—4.37 (1H, m), 4.46 (2H, q), 5.79 (1H, br d), 5.82 (1H, br s), 7.20 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 173.8 (s), 168.2 (s), 164.6 (s), 163.9 (s), 157.5 (s), 155.8 (s), 126.8 (s), 79.9 (s), 62.6 (t), 60.8 (t), 60.7 (d), 53.8 (d), 49.4 (t), 40.1 (t), 28.4 (q × 3), 15.0 (q), 14.2 (q), 14.1 (q). EI-MS *m/e*: 502 ($M^+ + 1$), 428 ($M^+ - CO_2Et$).

11*R*: $[\alpha]_D^{24} + 29.5°$ ($c=2.0$, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t), 1.42 (3H, t), 1.44 (9H, s), 2.47 (3H, s), 2.65—3.15 (2H × 2, m), 3.99—4.15 (1H, m), 4.14 (2H, q), 4.3—4.5 (1H, m), 4.46 (2H, q), 5.70 (1H, br d), 5.84 (1H, br s), 7.25 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 173.9 (s), 171.2 (s), 168.2 (s), 164.6 (s), 163.8 (s). 157.5 (s), 155.6 (s), 126.8 (s), 79.9 (s), 62.6 (t), 60.8 (t), 60.0 (d), 53.6 (d), 49.1 (t), 40.0 (t), 28.3 (q × 3), 15.0 (q), 14.2 (q), 14.1 (q). EI-MS *m/e*: 502 ($M^+ + 1$), 428 ($M^+ - CO_2Et$).

Pyrimidobleonic Acid 13 from 11*S*——The ethanol solution (25 ml) of **11***S* (3.0 mg) was saturated with NH_3 at 0 °C, and allowed to stand for 1 week. After removal of the solvent, the residue was dissolved in methanol (25 ml), and the slution was saturated with NH_3 at −20 °C. The mixture was stirred at 40 °C for 3 d. After removal of the solvent, 20% HCl (3 ml) was added to the residue, and the mixture was heated at 50 °C for 5 d. The solvent was removed under reduced pressure, and the residue was dissolved in H_2O (5 ml). The aqueous solution was charged on a column of Dowex 1 × 8 (acetate form, 100—200 mesh, 2 ml). The column was washed with H_2O, then elution with 6% AcOH in H_2O afforded pyrimidobleonic acid **13** (1.0 mg, 46%).

Epipyrimidobleonic Acid 14 from 11*R*—— In a similar manner, **11***R* (3.0 mg) was converted into epi-pyrimidobleonic acid **14** (1.1 mg, 50%).

Boc-Pyrimidoblamic Acid 16 from 11——**11** (491 mg, 0.98 mmol) was dissolved in EtOH (10 ml), and then H_2O (5 ml) and 0.1 N NaOH (10.8 ml, 1.08 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then neutralized with 0.1 N HCl (10.8 ml). EtOH was removed under reduced pressure. Unreacted **11** was removed by extraction with AcOEt, and the aqueous solution was concentrated to dryness to afford the crude acid **15** 493 mg, containing NaCl (63 mg, calculated amount).

15: ^{1}H-NMR (CD_3OD) δ: 1.23 (3H, t), 1.45 (9H, s), 2.49 (3H, s), 2.6—3.2 (4H, m), 4.19 (2H, q). MS *m/e*: 429 ($M^+ - CO_2$), 328, 257. FD-MS *m/e*: 474 ($M^+ + 1$). UV $\lambda_{max}^{2.5\%\ EtOH\text{-}H_2O}$ nm (ε): 266 (7570). The crude acid **15** containing NaCl was dissolved in anhydrous EtOH (15 ml). The solution was cooled to −70 °C, and NH_3 gas was passed until the total volume reached 25 ml. The mixture was heated in a sealed tube at 40 °C for 6 d. After removal of NH_3 and EtOH, the residue was chromatographed on Dowex 1 × 8 (acetate form, 100—200 mesh, 150 ml) to afford a crude mixture (108 mg, 25%) of Boc-pyrimidoblamic acid **16** and Boc-epipyrimidoblamic acid **17**. Recrystallization from anhydrous EtOH gave pure Boc-pyrimidoblamic acid **16** (31 mg, 8% overall yield from **11**) as white crystals.

16: mp 223—225 °C (dec.), $[\alpha]_D^{28} - 32.8°$ ($c=0.75$, H_2O). ^{1}H-NMR (D_2O) δ: 1.94 (9H, s), 2.61 (3H, s), 3.4—3.6 (2H, m), 3.6—4.1 (2H, m), 4.98 (1H, dd). FD-MS *m/e*: 426 ($M^+ + 1$).

***S*-*tert*-Butyl 3-[(2-Methoxycarbonylethyl)amino]-3-(6-methoxycarbonylpyridin-2-yl)propanethioate (19)**——The vinyloxyborane **18** was prepared from *S*-*tert*-butyl thioacetate (137 mg, 1.04 mmol), di-*n*-butylboryltriflate (284 mg, 1.04 mmol) and diisopropylethylamine (148 mg, 1.15 mmol) in Et_2O (6 ml) according to Masamune's procedure.[12] The Schiff base **7** (208 mg, 0.83 mmol) in Et_2O (2 ml) was added to the vinyloxyborane in Et_2O (6 ml), and the mixture was stirred at room temperature for 2 h, cooled to 0 °C and treated with 30% H_2O_2 (4 ml) for 30 min. The Et_2O solution was successively washed with 1 N NaOH, H_2O and sat, NaCl, then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel to afford **19** (257 mg, 81%). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 2.40 (1H, s), 2.47 (2H, t, $J=6.6$ Hz), 2.71 (2H, t, $J=6.6$ Hz), 2.89 (2H, d, $J=7.5$ Hz), 3.63 (3H, s), 4.03 (3H, s), 4.34 (1H, q; $J=7.5$ Hz), 7.8 (m, 3H). MS *m/e*: 383 ($M^+ + 1$).

Ethyl 2-[1-[[(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-carbamoylethyl]amino]-2-[(*tert*-butylthio)carbonyl]ethyl]-6-chloro-5-methylpyrimidine-4-carboxylate (20)——The vinyloxyborane **18** was prepared from *S*-*tert*-butyl thioacetate

(370 mg, 2.80 mmol) and di-*n*-butylboryltriflate (770 mg, 2.81 mmol), and diisopropylethylamine (400 mg, 3.09 mmol) in Et_2O (18 ml) by the same procedure as described above. In another flask, the Schiff base **2** was prepared from formylpyrimidine **3** (172 mg, 0.75 mmol) and Boc-L-DAPA **4** (152 mg, 0.75 mmol) in Et_2O (10 ml) in the presence of MS-3A. The Schiff base **2** in Et_2O (10 ml) and CH_2Cl_2 (5 ml) was added to the vinyloxyborane **18** in Et_2O, and the reaction mixture was stirred at room temperature for 2 h. The solution was cooled to 0 °C and 30% H_2O_2 (12 ml) was added. The mixture was stirred at 0 °C for 30 min, then the organic layer was successively washed with sat. $NaHCO_3$, H_2O, and sat. NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with benzene–MeOH (5 : 1)) to give an almost 1 : 1 epimeric mixture of **20** (164 mg, 40%). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t), 1.44 (18H, s × 2), 2.48 (3H, s), 2.6—3.2 (4H, m), 4.1 (1H, m), 4.3 (1H, m), 4.46 (2H, q), 5.60 (2H). IR ($CHCl_3$): 1730, 1680 cm^{-1}.

Boc-Pyrimidoblamic Acid 16 from 20——**20** (34 mg, 0.062 mmol) was dissolved in EtOH (1 ml) and H_2O (0.5 ml), then 0.1 N NaOH (0.68 ml, 0.068 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h, then neutralized with 0.1 N HCl (0.68 ml, 0.068 mmol). The solvent was removed under reduced pressure to afford the crude acid containing NaCl. The crude acid was treated with NH_3 by the same procedure as described above to give a mixture of Boc-pyrimidoblamic acid **16** and Boc-epipyrimidoblamic acid **17** (7.4 mg, 28%).

References and Notes

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