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USEFUL SYNTHESIS OF 2,3,6-TRI- AND 2,3,5,6-TETRASUBSTITUTED PYRIDINE DERIVATIVES FROM ASPARTIC ACID

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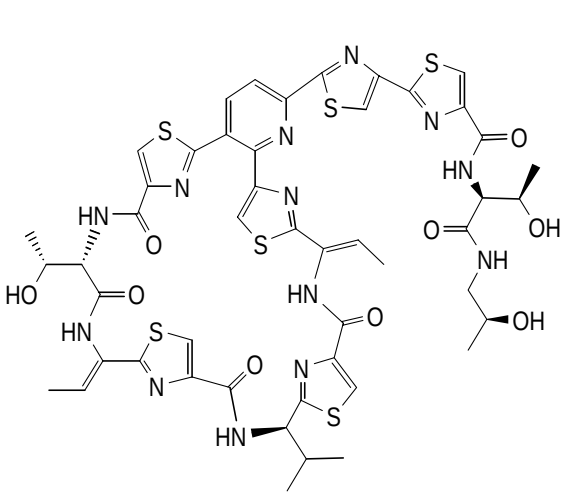
Abstract—New synthetic methods for 2,3,6-tri- and 2,3,5,6-tetrasubstituted pyridine skeletons, which are the essential main central segments of thiostrepton-type macrocyclic antibiotics, were developed from L-α-aspartic acid (Asp) *via* the Asp-derived α-dehydroamino acid ester.

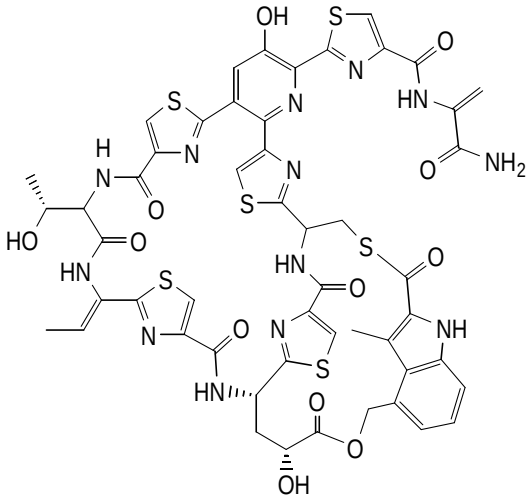
Most thiostrepton-type macrocyclic antibiotics, such as micrococcins P (**1**)[1] and nosiheptide (**2**)[2] (Figure 1), are constituted of a 2,3,6-tri- or 2,3,5,6-tetrasubstituted pyridine skeleton as the main central segment. So far, two kinds of polysubstituted 6-pyridone derivatives as the promising starting materials for the above-mentioned pyridines for **1** and **2** have been already synthesized from 1,1-dimethoxypropane *via* 5-cyano-2- dimethoxymethyl-6-pyridone[3] and from 2,3,5-trisubstituted 6-pyridone *via* the corresponding pyridine derivative, respectively.[4] However, unfortunately, the yield of the former 6-pyridone derivative was very low (23% yield in two steps) and the latter synthetic route needed many steps. Therefore, it is necessary to develop newly an alternative efficient method for the preparation of the required polysubstituted pyridine derivatives.

In particular, concerning the possible formation of the polysubstituted pyridine segment constructing the thiostrepton-type antibiotics, it was presumed that the pyridine skeletons mentioned above were produced by an appropriate oxidation and cyclization of a peptide sequence constituted of an L-*α*-aspartic acid (Asp) residue through the biosynthetic pathway. Here, to verify and realize chemically the above presumption, the synthesis of the polysubstituted pyridine derivatives from the Asp *via* the Asp-derived α-dehydroamino acid derivative was tried successfully.

First of all, esterification of the authentic benzyloxycarbonyl (Cbz)-L-Asp(OMe)-OH (**3**), derived from L-Asp-OH in two steps, with DCC and *N*-hydroxybenzotriazole (HOBt), followed by selective reduction of the formed activated α-ester with $NaBH_4$ afforded the corresponding primary alcohol derivative (**4**).[5] The two functional groups of both the (*N*-Cbz)amino and hydroxyl groups of **4**[5] were protected with an



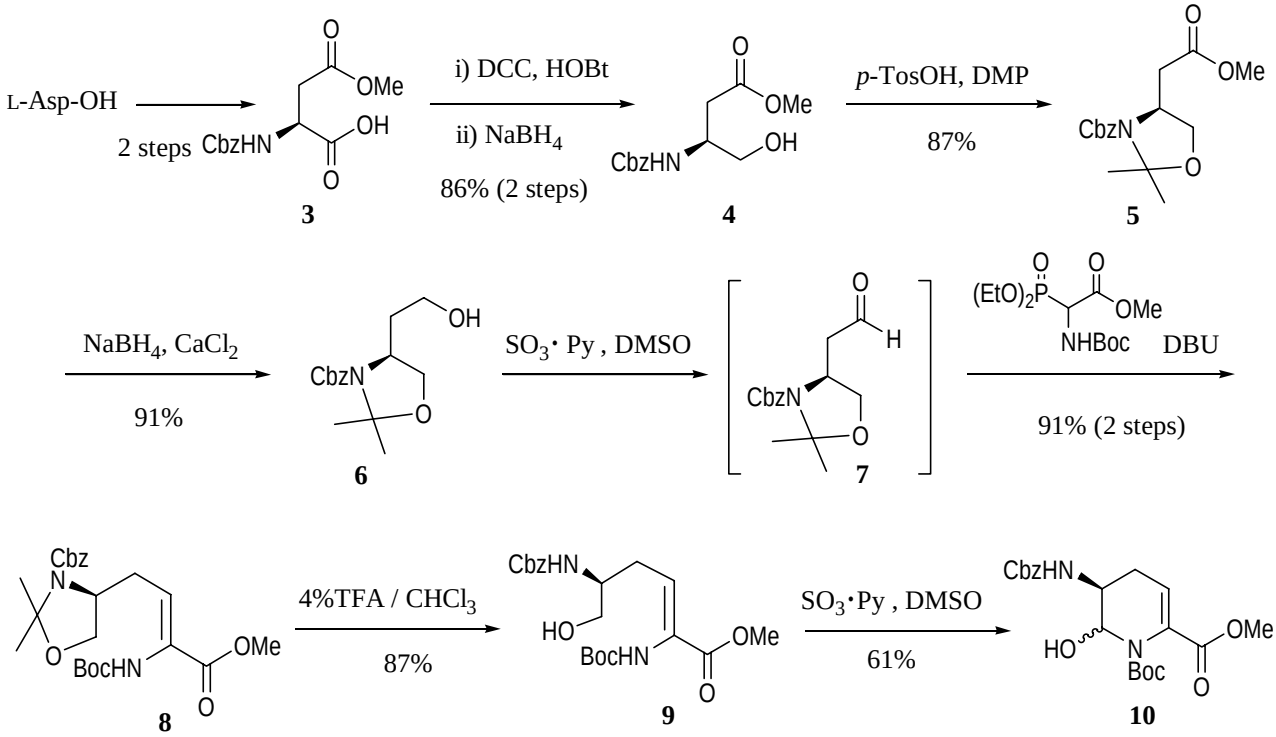
Micrococcin P (**1**)



Nosiheptide (**2**)

Figure 1

isopropylidene (Ip) group by using acetone dimethyl acetal (DMP) in the presence of *p*-toluenesulfonic acid hydrate (*p*-TosOH·H_2O) to give methyl [(4*S*)-3-(*N*-Cbz)-2,2-dimethyl-1,3-oxazolidin-4-yl]acetate (**5**). Subsequently, reduction of the methyl ester (**5**) with $NaBH_4$ in the presence of $CaCl_2$ gave the corresponding primary hydroxyl derivative (**6**), which was oxidized with SO_3·pyridine in DMSO to form



Scheme 1

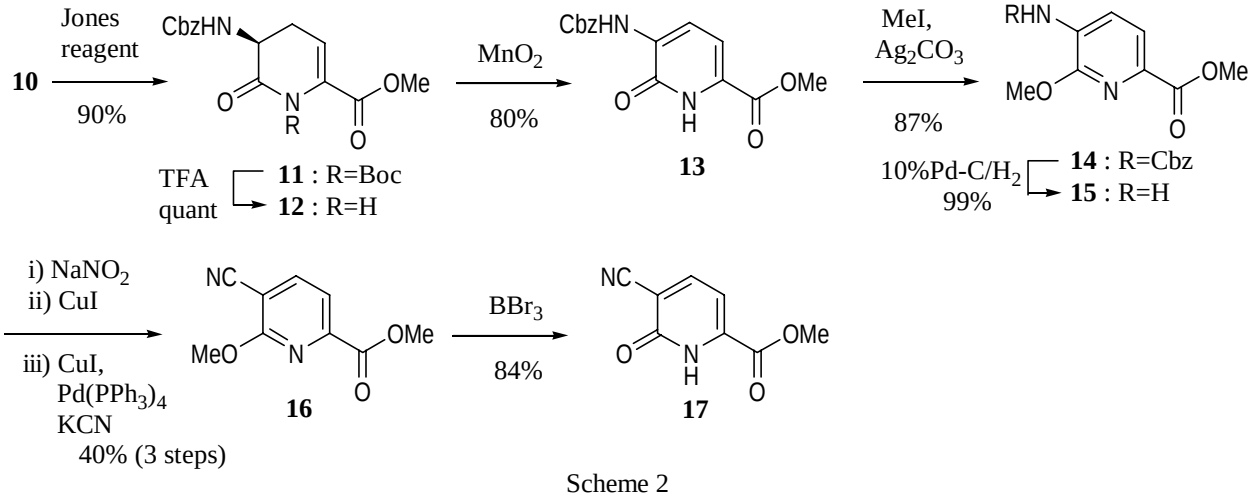
the corresponding formyl derivative (**7**) as an intermediate. Without purification, Wittig reaction of the formyl group of **7** with *N*-Boc-α-diethoxyphosphorylglycine methyl ester in the presence of DBU was

intact performed to give the required (*Z*)-α-dehydroamino acid; methyl (5*S*,2*Z*)-2-(*N*-Boc)amino-4-[3-(*N*-Cbz)-2,2-dimethyl-1,3-oxa-zolidin-4-yl]-2-butenoate (**8**). Deprotection of the isopropylidene (Ip) group with 4% trifluoroacetic acid (TFA) proceeded smoothly to give the corresponding 6-hydroxy-2-hexenoate derivative (**9**), which was then cyclized with SO_3·pyridine in DMSO to give the expected methyl (5*S*,6*RS*)-5-(Cbz)amino-6-hydroxy-1-(*N*-Boc)-4,5,6-trihydropyridine-2-carboxylate (**10**), as shown in Scheme 1.

From the fact that compound (**9**) could cyclize, the geometric structures of **8** and **9** could be determined to be (*Z*)-isomer. Furthermore, in the ^{1}H NMR spectrum, the appearance of β-olefin protons at δ 6.44 and δ 6.55 ppm for **8** and **9** supported also the above structural confirmation by comparing with the chemical shifts of the (*E*)-isomers of appropriate α-dehydroamino acid esters.[6] In general, it is well-known that the olefinic protons of (*E*)-isomer of α-dehydroamino acids resonate at a lower magnetic field.

Secondly, to synthesize the desired 2,5-disubstituted 6-pyridone derivative for the 2,3,6-trisubstituted pyridine, the hydroxyl compound (**10**) was oxidized with 2.67 Jones reagent to give methyl 1-(*N*-Boc)-5-(Cbz)amino-6-oxo-4,5,6-trihydropyridine-2-carboxylate (**11**). After deprotecting the Boc group by using TFA, the obtained 6-oxo-1,3,4-trihydropyridine derivative (**12**) was again oxidized with MnO_2 to give the corresponding 6-pyridone derivative (**13**). Furthermore, to transform the 6-pyridone ring into the pyridine skeleton, *O*-methylation of **13** with MeI and Ag_2CO_3 was carried out to give 5-(*N*-Cbz)amino- pyridine derivative (**14**), the Cbz group of which was deprotected with 10% Pd-C/H_2 to give methyl 5-amino-6-methoxypyridine-2-carboxylate (**15**).

Finally, the amino group of **15** was subjected to cyanization by the method of Anderson and co-workers.[7] That is, to replace the 5-amino group of **15** to a cyano group, treatment of **15** with $NaNO_2$ and CuI, followed by cyanization of the formed 5-iodopyridine derivative as an intermediate with CuI, $Pd(PPh_3)_4$, and KCN gave the corresponding 5-cyanopyridine derivative (**16**). Furthermore, treatment of **16** with BBr_3 gave the expected methyl 5-cyano-6-pyridone-2-carboxylate (**17**), as shown in Scheme 2. As a

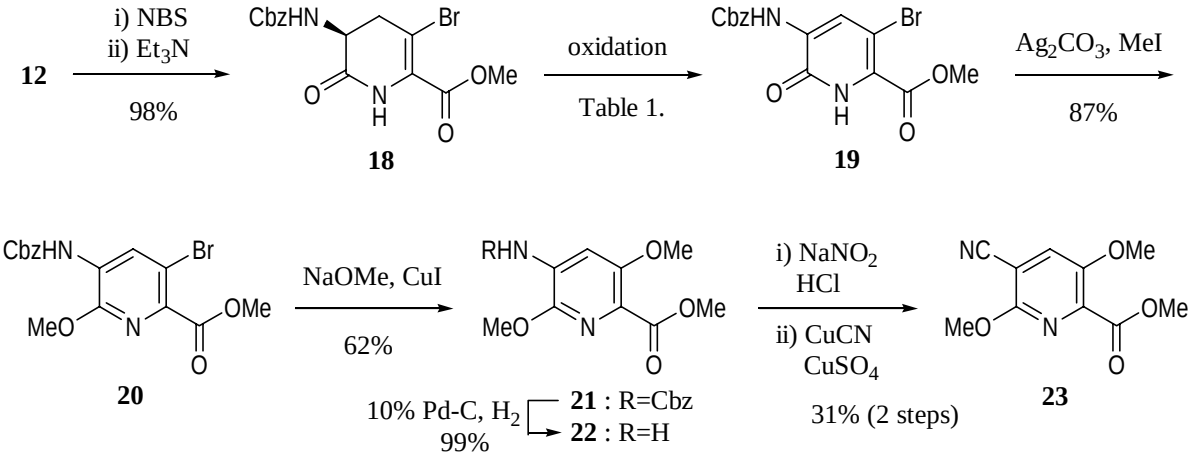


Scheme 2

result, compound (**17**) was thought to be the most important substance for the thiostrepton-type antibiotics, because the reverse conversion of the 6-methoxycarbonyl compound (**17**) to the corresponding thioamide derivative proceeds easily.[8]

On the other hand, with regard to the synthesis of the 2,3,5,6-tetrasubstituted pyridine derivative constructing **2**, firstly, bromination of the 3-position of **12** with NBS and then Et_3N gave the corresponding 3-bromo-6-oxo-1,4,5-trihydropyridine derivative (**18**), by the method reported earlier.[7]

Subsequently, oxidation of the ring of **18** to the 6-pyridone ring system was performed under various conditions, as shown in Table 1. As a result, in the case using DBU, $CuBr_2$, and hexamethylene-tetramine (HMTA) as an oxidizing agent system, it was found that the reaction of **18** in CH_2Cl_2 at 0 ^oC for 4 h proceeded rapidly and the yield of the required 6-pyridone (**19**) reached 84%.



Scheme 3

Furthermore, similarly to the case of **14**, *O*-methylation of the carbonyl group of **19** with MeI and Ag_2CO_3, followed by further substitution at the 3 position of the formed 6-methoxypyridine (**20**) with CuI and MeONa gave 3,6-dimethoxypyridine derivative (**21**). To form the 5-cyanopyridine derivative, deprotection of the Cbz group of **21** with H_2 on 10% Pd/C gave 5-aminopyridine derivative (**22**), the amino compound (**22**) which was cyanized with $NaNO_2$ and HCl and then CuCN and Na_2CO_3 to give the

Table 1. Oxidation of **18** to 6-Pyridone (**19**)

Entry	Reagent	Time (h)	Temp. (^oC)	Solvent	Yield (%)
1	DDQ, AcOH	96	50	Dioxane	10
2	MnO_2	48	rt.	$CHCl_3$	75
3	DBU, $CuBr_2$, HMTA[1)]	4	0	CH_2Cl_2	84

1) Hexamethylenetetramine

required 5-cyanopyridine derivative (**23**), as shown in Scheme 3. Consequently, it was found that the promising **23** for the synthesis of **2** could be synthesized.

In conclusion, although the synthetic route needs multiple steps, it is important that the main central polysubstituted pyridine skeleton in antibiotics (**1**) and (**2**) were readily derived from L-α-aspartic acid *via* α-dehydroamino acid derivative. Furthermore, this synthetic method is thought to be widely applicable to the synthesis of various polysubstituted pyridine derivatives.

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EXPERIMENTAL

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

Methyl (3*S*)-Benzyloxycarbonylamino-4-hydroxybutanoate (4). To a solution of **3** (30.0 g, 106.66 mmol) in THF (150 mL) was added, with stirring, a solution of HOBt (21.62 g, 160.01 mmol) and DCC (26.41 g, 127.99 mmol) in THF (150 mL) at 0 ^{o}C. After stirring for 30 min, the DCC salt precipitated was filtered off and the filtrate was stirred with $NaBH_4$ (4.29 g, 117.32 mmol) at 0 ^{o}C for 30 min. To the reaction mixture was added saturated NH_4Cl aqueous solution (100 mL) and then THF was evaporated. The aqueous solution was extracted with $CHCl_3$ (100 mL x 3) and the combined extracts were washed with saturated $NaHCO_3$ aqueous solution (100 mL x 3) and brine (100 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a crude syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 3 v/v) to give **4** as a colorless syrup. Yield 86% (23.94 g). $[\alpha]_D^{25}$ –10.4^{o} (*c* 1.07, MeOH). IR (KBr) 3568, 3370, 2956, 1728 cm^{-1}. ^{1}H NMR : δ 2.58 (d, 2H, α-H, *J*=5.9 Hz), 3.62 (s, 3H, $COOCH_3$), 3.70-3.75 (m, 2H, C*H*$_2$OH), 3.90-4.05 (m, 1H, β-H), 5.11 (s, 2H, Cbz's CH_2), 5.50 (br d, 1H, NH, *J*=8.6 Hz), 7.32 (s, 5H, Ph). *Anal*. Calcd for $C_{13}H_{17}NO_5$: C, 58.43; H, 6.41; N, 5.24. Found: C, 58.27; H, 6.59; N, 5.24.

Methyl (4*S*)-(3-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl)acetate (5). To a solution of **4**

(2.32 g, 8.75 mmol) in acetone (50 mL) were added, with stirring, acetone dimethyl acetal (2.15 mL, 17.49 mmol) and *p*-toluenesulfonic acid hydrate (0.33 g, 1.75 mmol) at rt. After stirrng overnight, the reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution and then evaporated. The aqueous solution was extracted with EtOAc (100 mL x 3), the combined extracts were washed with brine (100 mL x 3) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a crude syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **5** as a colorless syrup. Yield 87% (1.72 g). $[\alpha]_D^{25}$ +21.7^o (*c* 1.04, MeOH). IR (KBr) 3449, 2988, 1717 cm^{-1}. ^{1}H NMR: δ 1.52, 1.62 (each s, 3H x 2, Ip's CH_3), 2.48-2.98 (m, 2H, α-H), 3.65 (s, 3H, $COOCH_3$), 3.86-3.90 (m, 2H, CH_2), 4.02-4.31 (m, 1H, NCH), 5.44 (s, 2H, Cbz's CH_2), 7.36 (s, 5H, Ph). *Anal*. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.37; H, 6.84; N, 4.32.

2-[(4*S*)-(3-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl)]ethanol (6). To a solution of $NaBH_4$ (3.30 g, 87.12 mmol) and $CaCl_2$ (3.30g, 29.73 mmol) in EtOH (100 mL) was added, with stirring, a solution of **5** (22.24 g, 72.60 mmol) in EtOH (150 mL) at 0 ^{o}C. The reaction mixture was treated with saturated NH_4Cl aqueous solution (200 mL) and EtOH was evaporated. The aqueous solution was extracted with EtOAc (100 mL x 3), the combined extracts were washed with brine (100 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a crude syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **6** as a colorless syrup. Yield 91% (18.45 g). $[\alpha]_D^{25}$ +9.4^o (*c* 0.66, MeOH). IR (KBr) 3448, 2980, 2944, 2878, 1698 cm^{-1}. ^{1}H NMR: δ 1.49, 1.55 (each s, 3H x 2, Ip's CH_3), 1.68-l.96 (m, 2H, β-H), 3.45-4.39 (m, 6H, NCH, CH_2 x 2, OH), 5.16 (s, 2H, Cbz's CH_2), 7.35 (s, 5H, Ph). *Anal*. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.42; H, 7.52; N, 4.96.

Methyl (5*S*,2*Z*)-4-(3-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl)-2-*t*-butoxycarbonyl-amino-2-butenoate (8). To a solution of **6** (5.50 g, 19.70 mmol) in $CHCl_3$ (20 mL) was added, with stirring, Et_3N (21.87 mL, 157.50 mmol) at 0 ^{o}C and then a solution of SO_3·pyridine (15.67 g, 98.50 mmol) in DMSO (40 mL). After stirring for 1 h at 0 ^{o}C, ether (20 mL) and EtOAc (20 mL) were further added. The reaction mixture was washed with 10% citric acid (50 mL x 3) and brine (50 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a cude syrup, to which was added, with stirring, a solution of *N*-Boc-α-ethoxyphosphorylglycine methyl ester (6.41 mg, 19.7 mmol) in $CHCl_3$ (20 mL) and then DBU (4.40 mL, 29.53 mmol). The whole was stirred for 30 min at 0 ^{o}C and then overnight at rt. The reaction mixture was dissolved in ether (50 mL) and the resulting solution was washed successively with 10% citric acid (50 mL x 3), brine (50 mL x 3), and saturated $NaHCO_3$ aqueous solution (50 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a crude syrup, which was purified

on a silica gel column using a mixture of hexane and EtOAc (2.5 : 1 v/v) to give **8** as colorless syrup. Yield 91% (8.0 g). $[\alpha]_D^{28}$ +66.8° (*c* 4.04, MeOH). IR(KBr) 3334, 2980, 1710, 1500, 1455 cm^{-1}. ^1H NMR: δ 1.38 (s, 9H, Boc's *t*-Bu), 1.44, 1.56 (each s, 3H x 2, Ip's CH_3), 2.47-2.52 (m, 2H, CH_2), 3.68 (s, 3H, $COOCH_3$), 3.87-4.08 (m, 3H, NCH, CH_2), 5.08 (s, 2H, Cbz's CH_2), 6.00 (br s, 1H, NH), 6.44 (t, 1H, olefin-H, *J*=7.3 Hz), 7.28 (s, 5H, Ph). *Anal*. Calcd for $C_{23}H_{32}N_2O_7$: 61.59; H, 7.19; N, 6.25. Found: C, 61.68; H, 7.25; N, 6.40.

Methyl (5*S*,2*Z*)-5-Benzyloxycarbonylamino-2-*t*-butoxycarbonylamino-6-hydroxy-2-hexenoate (9). A solution of **8** (318 mg, 0.71 mmol) in a mixture of $CHCl_3$ and TFA (96 : 4 v/v, 6 mL) was stirred overnight at rt. The resultant solution was made to weak alkali with Et_3N and then concentrated *in vacuo* to give a residual syrup, which was dissolved in EtOAc (10 mL). The reaction mixture was washed with 10% citric acid (20 mL x 3) and brine (20 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a crude syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **9** as a colorless syrup. Yield 87% (252 mg). $[\alpha]_D^{26}$ +23.7° (*c* 3.38, MeOH). IR (KBr) 3406, 2974, 1713, 1524 cm^{-1}. ^1H NMR: δ 1.45 (s, 9H, Boc's *t*-Bu), 2.50-2.55 (m, 2H, CH_2), 3.53-3.91 (m, 4H, NCH, CH_2, OH), 3.77 (s, 3H, $COOCH_3$), 5.10 (s, 2H, Cbz's CH_2), 5.81 (br d, 1H, NH, *J*=7.7 Hz), 6.38 (br s, 1H, BocNH), 6.55 (t, 1H, olefin-H, *J*=7.7 Hz), 7.34 (s, 5H, Ph). *Anal*. Calcd for $C_{20}H_{28}N_2O_7$: C, 58.81; H, 6.91; N, 6.86. Found: C, 58.40; H, 7.33; N, 6.83.

Methyl (6*RS*,5*S*)-5-Benzyloxycarbonylamino-6-hydroxy-1-*t*-butoxycarbonyl-4,5,6-trihydro-pyridine-2-carboxylate (10). To a solution of **9** (278 mg, 0.682 mmol) in $CHCl_3$ (10 mL) was added, with stirring, Et_3N (0.764 mL, 5.456 mmol) and then a solution of SO_3·pyridine (543 mg, 3.41 mmol) in DMSO (20 mL) at 0 °C. After stirring for 30 min and for 1 h at rt, the reaction mixture was mixed to ether (10 mL) and the resulting solution was washed with 10% citric acid (30 mL x 3) and brine (30 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave crude crystals, which were recrystallized from $CHCl_3$-hexane to give **10** as colroelss needles. Yield 61% (168 mg). mp 169-170 °C. $[\alpha]_D^{28}$ –67.6° (*c* 0.82, MeOH). IR (KBr) 3484, 3316, 1722, 1689, 1647, 1536 cm^{-1}. ^1H NMR: δ 1.40 (s, 9H, Boc's *t*-Bu), 1.96-2.24 (m, 1H, H-4a), 2.58-2.91 (m, 1H, H-4b), 3.19 (d, 1H, OH, *J*=3.7 Hz), 3.61 (s, 3H, $COOCH_3$), 3.95-4.l8 (m, 1H, H-5), 5.08 (s, 2H, Cbz's CH_2), 5.87 (m, 2H, H-3, H-6), 7.32 (s, 5H, Ph). *Anal*. Calcd for $C_{20}H_{26}N_2O_7$: C, 59.10; H, 6.45; N, 6.89. Found: C, 59.19; H, 6.29; N, 6.84.

Methyl (5*S*)-5-Benzyloxycarbonylamino-6-oxo-1-*t*-butoxycarbonyl-4,5,6-trihydropyridine-2-carboxylate (11). To a solution of **10** (70 mg, 0.17 mmol) in acetone (10 mL) was added, with stirring, 2.67 M Jones reagent (0.13 mL) at 0 °C. After stirring for 30 min and overnight at rt, to the resulting solution was added 2-propanol (10 mL) at 0 °C for 10 min. The precipitates were filtered off and the

filtrate was neutralized with saturated $NaHCO_3$ aqueous solution and then acetone was evaporated *in vacuo*. The aqueous solution was extracted with EtOAc (5 mL x 3) and the combined extracts were washed with saturated $NaHCO_3$ aqueous solution (5 mL x 3) and brine (5 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave crude crystals, which were recrystallized from hexane-EtOAc to give **11** as colorless needles. Yield 90% (62 mg). mp 158-160 ^oC. $[\alpha]_D^{25}$ –9.3^o (*c* 0.67, MeOH). IR (KBr) 3448, 2980, 1785, 1728, 1707, 1656, 1521 cm^{-1}. ^1H NMR: δ 1.53 (s, 9H, Boc's *t*-Bu), 2.32-2.44 (m, 1H, H-4a), 2.96-3.08 (m, 1H, H-4b), 3.81 (s, 3H, $COOCH_3$), 4.23-4.33 (m, 1H, H-5), 5.10 (s, 2H, Cbz's CH_2), 5.83 (br d, 1H, NH, *J*=4.5 Hz), 6.51 (dd, 1H, H-3, *J*=2.6, 7.6 Hz), 7.37 (s, 5H, Ph). *Anal*. Calcd for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.34; H, 5.99; N, 7.32.

Methyl (5*S*)-Benzyloxycarbonylamino-6-oxo-1,4,5-trihydropyridine-2-carboxylate (12). A solution of **11** (2.255 g, 5.58 mmol) in a mixture of $CHCl_3$ and TFA (1 : 1 v/v, 30 mL) was stirred for 1 h at rt. The reaction mixture was made to weak alkali with Et_3N and then the solvent was evaporated *in vacuo*. The residual substance was dissolved in EtOAc (50 mL) and the resulting solution was washed successively with 10% citric acid (25 mL x 2), brine (25 mL x 3), and saturated $NaHCO_3$ aqueous solution (25 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave crude crystals, which were recrystallized from a EtOAc-hexane to give **12** as colorless needles. Yield 99 % (1.697 g). mp 111-112 ^oC. $[\alpha]_D^{25}$ –40.2^o (*c* 0.86, MeOH). IR (KBr) 3448, 3334, 1716, 1683, 1536 cm^{-1}. ^1H NMR: δ 2.33 (ddd, 1H, H-4a, *J*=2.9, *J*=14.7, 17.6 Hz), 3.05 (ddd, 1H, H-4b, *J*=7.2, 7.3 Hz, 17.6 Hz), 3.81 (s, 3H, $COOCH_3$), 4.28 (ddd, 1H, H-5, *J*=5.5, 7.3, 14.7 Hz), 5.11 (s, 2H, Cbz's CH_2), 5.96 (br d, 1H, CbzNH, *J*=5.5 Hz), 6.27 (dd, 1H, H-3, *J*=2.9, 7.2 Hz), 7.33 (s, 5H, Ph), 7.92 (br s, 1H, H-1). *Anal*. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 58.94; H, 5.13; N, 8.97.

Methyl 5-Benzyloxycarbonylamino-6-oxo-1-hydropyridine-2-carboxylate (13). A suspension of **12** (0.50 g, 1.64 mmol) and MnO_2 (4.28 g, 49.29 mmol) in $CHCl_3$ (20 mL) was stirred under sonication for 6 h at rt. The MnO_2 was filtered off and the residue was concentrated *in vacuo* to give crude crystals. Recrystallization from a EtOAc-hexane gave **13** as colorless needles. Yield 80% (397 mg). mp 185-186 ^oC. IR 3430, 3404, 1737, 1716, 1650, 1632, 1569, 1524 cm^{-1}. ^1H NMR: δ 3.39 (s, 3H, $COOCH_3$), 5.22 (s, 2H, Cbz's CH_2), 7.10 (d, 1H, H-3, *J*=7.6 Hz), 7.37 (s, 5H, Ph), 8.10 (d, 1H, H-4, *J*=7.6 Hz), 8.13 (br s, 1H, CbzNH), 10.18 (br s, 1H, H-1). *Anal*. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.55; H, 4.29; N, 9.15.

Methyl 5-Benzyloxycarbonylamino-6-methoxypyridine-2-carboxylate (14). A suspension of **13** (320 mg, 0.84 mmol), Ag_2CO_3 (116 mg, 0.42 mmol), and MeI (0.1 mL, 1.68 mmol) in $CHCl_3$ (15 mL) was

stirred 48 h at rt. The Ag salt was filtered off and the filtrate concentrated *in vacuo* to give crude crystals, which were recrystallized from a EtOAc-hexane to give **14** as colorless needles. Yield 87% (288 mg). mp 90-92 ^{o}C. IR (KBr) 3431, 2941, 1734, 1714, 1587, 1521, 1467 cm^{-1}. ^{1}H NMR: δ 3.86 (s, 3H, $COOCH_3$), 4.00 (s, 3H, OCH_3), 5.12 (s, 2H, Cbz's CH_2), 7.26-7.33 (m, 6H, Ph, H-3), 7.69 (d, 1H, H-4, *J*=8.3 Hz), 8.34 (d, 1H, NH). *Anal*. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.87; H, 5.59; N, 8.60.

Methyl 5-Amino-6-methoxypyridine-2-carboxylate (15). A suspension of **14** (88 mg, 0.278 mmol) and 10% Pd/C (l0 mg) in MeOH (10 mL) was stirred under H_2 gas atmosphere for 2 h at rt. The Pd/C was filtered off and the filtrate was concentrated *in vacuo* to give crude crystals, which were recrystallized from a EtOAc-hexane to give **15** as colorless needles. Yield 99% (50 mg). mp 161-163 ^{o}C. IR (KBr) 3487, 3346, 2360, 2341, 1716, 1618, 1581, 1566 cm^{-1}. ^{1}H NMR: δ 3.91 (s, 3H, $COOCH_3$), 4.07 (s, 3H, OCH_3), 4.84 (br s, 2H, NH_2), 6.85 (d, 1H, H-3, *J*=7.7 Hz), 7.65 (d, 1H, H-4, *J*=7.7 Hz). *Anal*. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.68; H, 5.20; N, 14.94.

Methyl 5-Cyano-6-methoxypyridine-2-carboxylate (16). To a solution of **14** (24 mg, 0.131 mmol) in THF (1 mL) and 3M HCl (5 mL) was added, with stirring, a solution of $NaNO_2$ (11 mg, 0.158 mmol) in water (2 mL) at 0 ^{o}C for 5 min. After stirring for 15 min, further for 15 min at rt, and then 2 h at 60 ^{o}C, the reaction mixture was made to weak alkali with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc (10 mL x 2). The combined extracts were washed with saturated $Na_2S_2O_3$ aqueous solution (5 mL x 3), brine (5 mL x 3), and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a residual substance, to which were added CuI (2 mg, 1.317 x 10^{-2} mmol), Pd(0) $(PPh_3)_4$ (7 mg, 6.587 x 10^{-2} mmol), and KCN (17 mg, 0.263 mmol) and then CH_3CN (10 mL). After refluxing for 12 h, the precipitates were filtered off and the filtrate was washed with water (10 mL x 2) and brine (10 mL x 2) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave crude crystals, which were purified on a silica gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give colorless crystals. Recrystallization from EtOAc-hexane gave **16** as colorless needles. Yield 40% (10 mg). mp 125-126 ^{o}C. IR (KBr) 3097, 3072, 3039, 3007, 2229, 1730, 1712 cm^{-1}. ^{1}H NMR: δ 3.99 (s, 3H, $COOCH_3$), 4.15 (s, 3H, OCH_3), 7.76 (d, 1H, H-3, *J*=7.6 Hz), 8.02 (d, 1H, H-4, *J*=7.6 Hz). *Anal*. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.33; H, 4.00; N, 14.62.

Methyl 5-Cyano-6-oxohydropyridine-2-carboxylate (17). To a solution of **16** (100 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) and was added, with stirring, a solution of BBr_3 (1 M solution in CH_2Cl_2, 0.78 mL, 0.78 mmol) under Ar gas atmosphere at -20 ^{o}C for 30 min. After stirring for 1 h, further for and then 1 h

at 0 ^{o}C, the reaction mixture was poured into H_2O (30 mL) and the resulting solution was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were washed with saturated brine (10 mL x 3), and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave crude crystals, which were purified on a silica gel column using a EtOAc to give colorless solids. Recrystallization from EtOAc gave **17** as colorless crystals. Yield 84% (78 mg). mp 261-263 ^{o}C (from EtOAc). IR (KBr) 3095, 2225, 1737, 1658, 1610 cm^{-1}. ^{1}H NMR: δ in DMSO-d6 3.31 (br s,1H, NH or OH), 3.88 (s, 3H, $COOCH_3$), 7.10 (br d, 1H, H-3, *J*=7.5 Hz), 8.27 (d, 1H, H-4, *J*=7.5 Hz). *Anal*. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 54.12; H, 3.41; N, 15.68.

Methyl (5*S*)-5-Benzyloxycarbonylamino-3-bromo-6-oxo-1,4,5-trihydropyridine-2-carboxylate (18). To a solution of **12** (200 mg, 0.66 mmol) in $CHCl_3$ (10 mL) was added, with stirring, NBS (129 mg, 0.72 mmol) at rt for 1 h. After adding Et_3N (0.09 mL, 0.72 mmol), the resulting solution was stirred overnight at rt. The precipitated material was filtered off and the filtrate was concentrated *in vacuo* to give crude crystals. Recrystallization from $CHCl_3$-hexane gave **18** as pale yellow crystals. Yield 98% (227 mg). mp 141-143 ^{o}C. $[\alpha]_D^{26}$ –36.1^{o} (*c* 1.44, MeOH). IR 3316, 3244, 1743, 1674, 1536 cm^{-1}. ^{1}H NMR: δ 2.88 (dd, 1H, H-4a, *J*=17.5, 14.5 Hz), 3.48 (dd, 1H, H-4b, *J*=17.5, 6.8 Hz), 3.90 (s, 3H, $COOCH_3$), 4.41 (ddd, 1H, H-5, *J*=6.8, 14.5, 5.3 Hz), 5.13 (s, 2H, Cbz's CH_2), 5.67 (br d, 1H, CbzNH, *J*=5.3 Hz), 7.36 (s, 5H, Ph), 7.75 (br s, 1H, H-1). *Anal*. Calcd for $C_{15}H_{15}N_2O_5Br$: C, 47.02; H, 3.95; N, 7.31. Found: 47.32; H, 3.91; N, 7.13.

Methyl (5*S*)-5-Benzyloxycarbonylamino-3-bromo-6-oxo-1-hydropyridine-2-carboxylate (19). To a solution of $CuBr_2$ (473 mg, 2.12 mmol) and hexamethylentetramine (297 mg, 2.12 mmol) in CH_2Cl_2 (10 mL) was added, with stirring, DBU (0.30 mL, 2.12 mmol) at 0 ^{o}C under Ar gas atmosphere. After stirring for 10 min, to the resulting solution was further added a solution of **18** (203 mg, 0.53 mmol) in CH_2Cl_2 (2 mL). After stirring for 4 h at rt, the reaction mixture was poured into EtOAc (50 mL) and the resulting solution was washed with saturated $NaHCO_3$ aqueous solution (30 mL) and brine (30 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave crude crystals, which were recrystallized from EtOAc-hexane to give **19** as colorless needles. Yield 84% (170 mg). mp 201-203 ^{o}C. IR 3388, 1722, 1656, 1608, 1551, 1527 cm^{-1}. ^{1}H NMR: δ 3.98 (s, 3H, $COOCH_3$), 5.23 (s, 2H, Cbz's CH_2), 7.39 (s, 5H, Ph), 8.00 (br s, 1H, CbzNH), 8.29 (s, 1H, H-4), 9.79 (br s, 1H, H-1). *Anal*. Calcd for $C_{15}H_{13}N_2O_5Br$: C, 47.27; H, 3.44; N, 7.35. Found: C, 47.12; H, 3.43; N, 7.21.

Methyl 5-Benzyloxycarbonylamino-3-bromo-6-methoxypyridine-2-carboxylate (20). To a solution of **19** (320 mg, 0.84 mmol) in toluene (15 mL) were added, with stirring, Ag_2CO_3 (116 mg, 0.42 mmol)

and MeI (0.1 mL, 1.68 mmol). The resulting solution was further stirred at 60 ^{o}C overnight. After Ag salt was filtered off, the filtrate was concentrated *in vacuo* to give crude crystals, which were recrystallized from EtOAc-hexane to give **20** as colorless needles. Yield 87% (288 mg). mp 155-156 ^{o}C. IR 3448, 2984, 1722, 1698 cm^{-1}. ^{1}H NMR: δ 3.95 (s, 3H, $COOCH_3$), 4.02 (s, 3H, OCH_3), 5.21 (s, 2H, Cbz's CH_2), 7.31 (s, 5H, Ph), 8.12 (br s, 1H, CbzNH), 8.17 (s, 1H, H-4). *Anal*. Calcd for $C_{16}H_{15}N_2O_5Br$: C, 48.63; H, 3.83; N, 7.09. Found: C, 48.59; H, 3.73; N, 7.12.

Methyl 5-Benzyloxycarbonylamino-3, 6-dimethoxypyridine-2-carboxylate (21). To a solution of **20** (174 mg, 0.44 mmol) in DMF (5 mL) was added, with stirring, a solution of MeONa (29 mg, 0.53 mmol) in MeOH (5 mL) under 0 ^{o}C . After adding CuI (16.8 mg, 0.09 mmol), the resulting solution was refluxed for 3 h. Precipitated Cu salt was filtered off and the residue was extracted with EtOAc (5 mL x 3). The combined extracts were washed with brine (5 mL x 3) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a crude substance, which was purified on a silica gel column using a mixture of EtOAc and hexane (1 : 3 v/v) to give **21** as colorless crystals. Yield 62% (95 mg). mp 134-135 ^{o}C. IR 3448, 2980, 2236, 1731 cm^{-1}. ^{1}H NMR: δ 3.83 (s, 3H, 3-OCH_3), 3.98 (s, 3H, $COOCH_3$), 4.07 (s, 3H, 6-OCH_3), 5.19 (s, 2H, $PhCH_2$), 7.32 (s, 5H, Ph), 7.81 (s, 1H, H-4), 8.08 (br s, 1H, CbzNH). *Anal*. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 59.21; H, 5.17; N, 7.86.

Methyl 5-Amino-3,6-dimethoxypyridine-2-carboxylate (22). A suspension of **21** (217 mg, 0.63 mmol) and 10% Pd-C (21 mg) in EtOH (15 mL) was stirred under H_2 gas atmosphere at rt for 2 h. The Pd-C was filtered off and the filtrate was concentrated *in vacuo* to give crude crystals, which were recrystallized from EtOAc-hexane to give **22** as colorless prisms. Yield 99% (133 mg). mp 162-164 ^{o}C. IR 3298, 2932, 2860, 1734, 1659 cm^{-1}. ^{1}H NMR: δ 3.84 (s, 3H, 3-OCH_3), 3.97 (s, 3H, $COOCH_3$), 4.10 (s, 3H, 6-OCH_3), 4.31 (br s, 2H, NH_2), 7.31 (s, 1H, H-4). *Anal*. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.88; H, 5.67; N, 13.45.

Methyl 5-Cyano-3,6-dimethoxypyridine-2-carboxylate (23). A buffer solution was prepared from a mixture of $CuSO_4{\cdot}5H_2O$ (146 mg, 0.58 mmol) and CuCN (209 mg, 2.34 mmol) in H_2O (10 mL), and a small amount of Na_2CO_3. On the other hand, to a solution of a concentrated HCl (0.1 mL, 1.64 mmol) and H_2O (1 mL) was added a solution of **22** (133 mg, 0.63 mmol) in THF (3 mL) at 0 ^{o}C and then added slowly a solution of $NaNO_2$ (40 mg, 584 mmol) in H_2O (3 mL). To the latter solution was added, with stirring, the former buffer at 0 ^{o}C, the resulting solution was stirred at 0 ^{o}C for 1 h and then 50 ^{o}C for 4 h. The reaction mixture was mixed with EtOAc (5 mL) and then the resulting solution was washed with saturated aquous $NaHCO_3$ solution (3 mL x 5) and brine (5 mL x 3) and then dried over anhydrous

Na_2SO_4. Concentration *in vacuo* gave a crude residue, which was purified on a silica gel column using a mixture of EtOAc and hexane (1 : 2 v/v) to give colorless crystals. Recrystallization from EtOAc-hexane gave **23** as colorless needles. Yield 31% (43 mg). mp 159-160 ^{o}C. IR 3448, 2944, 2224, 1731 cm^{-1}. ^{1}H NMR: δ 3.87 (s, 3H, 3-OCH_3), 3.97 (s, 3H, $COOCH_3$), 4.04 (s, 3H, 6-OCH_3), 7.58 (s, 1H, H-4). *Anal*. Calcd for $C_{19}H_{10}N_2O_4$: C, 54.05; H, 4.53; N, 12.61. Found: C, 53.78; H, 4.44; N, 12.51.

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