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First chiral synthesis of the N-terminal amino acid congener of nikkomycin Z based on lipase-catalyzed enantioselective acetylation of a primary alcohol possessing two stereogenic centers

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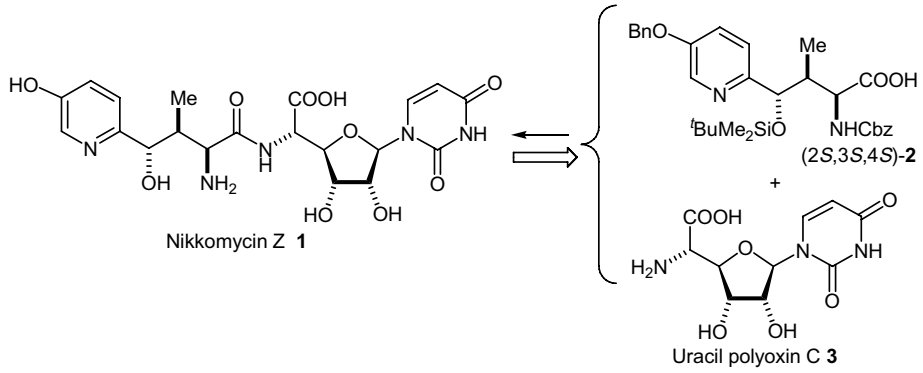
Abstract—A stereoselective synthesis of a versatile chiral synthon possessing two stereogenic centers, (2*S*,3*S*)-3-[2-(5-benzyloxypyridyl)]-2-methyl-1,3-propane diol **12** (>99% ee), was achieved by using a chemo-enzymatic method. The conversion of (2*S*,3*S*)-**12** to the homochiral intermediate (2*S*,3*S*,4*S*)-2-benzyloxycarbonylamino-4-[2-(5-benzyloxypyridyl)]-4-*tert*-butyldimethylsilyloxy-3-methylbutanoic acid **2** corresponding to the N-terminal amino acid congener of nikkomycin Z **1** is described.

1. Introduction

Nikkomycins are peptidyl nucleoside antibiotics which have been isolated from the culture broths *Streptomyces tendae*[1] and *Streptomyces cacaoi* subsp. *Asoensis*.[2] These antibiotics are potent competitive inhibitors of chitin synthetase and exhibit antifungal, insecticidal, and acaricidal activities. The synthesis of nikkomycin Z **1** has already been achieved based upon the separation of a diastereomeric mixture of products, which were obtained by the condensation of (±)-α-amino-γ-hydroxy-β-methylbutanoic acid congener **2** and uracil polyoxin C **3**.[3] A convenient synthesis of **3** from D-(−)-ribose was already reported by us.[4] We now report the first stereoselective synthesis of (2*S*,3*S*,4*S*)-**2** based on a combination of chemical diastereoselectivity and enzymatic enantioselectivity (Scheme 1).

2. Results and discussion

Benzylation of **4** followed by successive treatment with *m*-chloroperbenzoic acid (MCPBA) and Ac_2O gave acetate



Scheme 1.

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6, which was deacetylated to afford alcohol **7** in 43% overall yield (four steps). Swern oxidation of **7** provided aldehyde **8** in 95% yield, which was subjected to the Reformatsky reaction to afford a 1:1 mixture of β-hydroxy-α-methyl esters (±)-*anti*-**9** and (±)-*syn*-**10** in 89% yield. Oxidation of this mixture furnished β-keto ester (±)-**11** (99% yield), which was reduced with *n*-Bu_4NBH_4[5] to give the (±)-*anti*-**9** (76% yield) together with the (±)-*syn*-**10** (7% yield) with high *anti*-diastereoselectivity (*anti*/*syn* = 10:1). In order to confirm the stereochemistry of the reaction products, both (±)-**9** and (±)-**10** were reduced to diols (±)-**12** (81% yield) and (±)-**13** (64% yield), respectively, which were converted to acetonides (±)-**14** (80% yield) and (±)-**15** (81% yield), respectively. The 2,3-*trans* configuration in (±)-**14** and the 2,3-*cis* configuration in (±)-**15** were confirmed by the fact that coupling constants due to the C_2- and C_3-hydrogens of (±)-**14** and (±)-**15** were 10.3 and 2.8 Hz, respectively. Consequently, it was found that β-hydroxy esters (±)-**9** and (±)-**10** possessed the *anti*- and *syn*-structures, respectively. This high *anti*-diastereoselectivity in *n*-Bu_4NBH_4 mediated reduction of (±)-**11** was explained by a Felkin–Anh model[6] as shown in Figure 1 (Scheme 2).

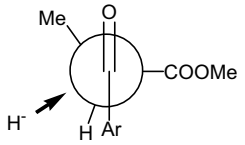
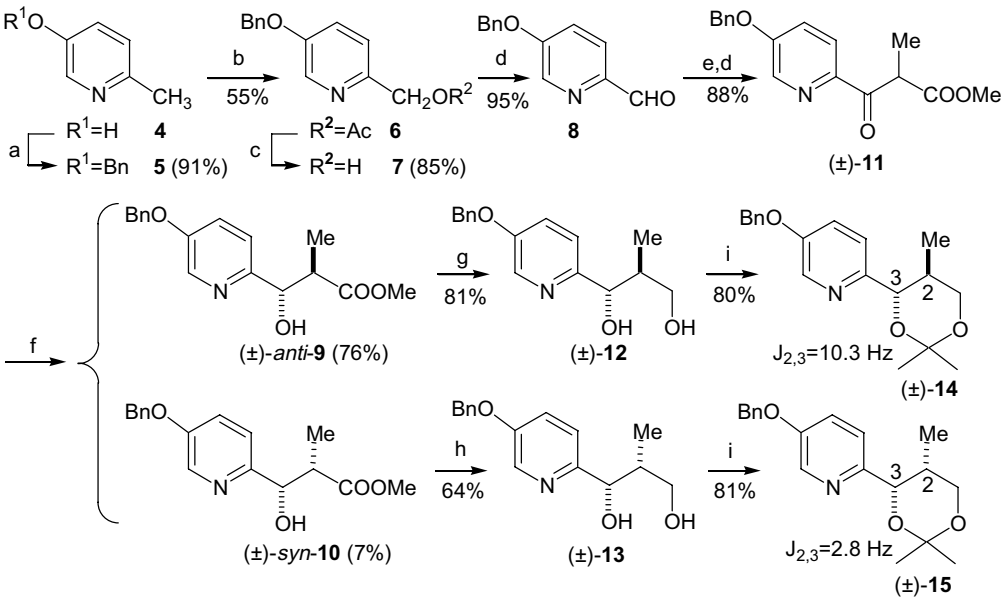


Figure 1.

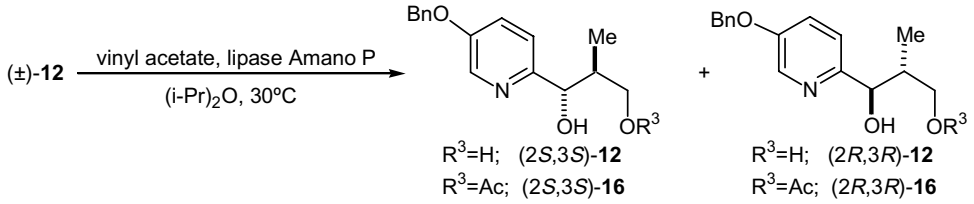
For the purpose of obtaining the optically active diol **12**, (±)-**12** was subjected to screening experiments using several kinds of commercially available lipases. Among them, lipase Amano P from *Pseudomanas* sp. was found to give the (2*R*,3*R*)-monoacetate **16** (59%, 59% ee) and the unchanged (2*S*,3*S*)-**12** (38%, 97% ee) in the presence of vinyl acetate as an acyl donor in diisopropyl ether as shown in Table 1 (entry 1). The *E* value of the present enzymatic esterification was found to be 15.2. The recovered (2*S*,3*S*)-**12** having 97% ee was again subjected to the same enzymatic acetylation as in the case of entry 1 for 2.5 h to give (2*S*,3*S*)-**12** (65%, $[\alpha]_D^{26} = -28.6$ (*c* 0.92, $CHCl_3$), >99% ee by HPLC analysis) and (2*S*,3*S*)-**16** (32%, 93% ee) (entry 2). On the other hand, (2*R*,3*R*)-**12** (59% ee) derived from (2*R*,3*R*)-**16** possessing 59% ee was again subjected to the same enzymatic acetylation as in the case of entry 1 for 1 h to afford (2*R*,3*R*)-**16** (66%, 95% ee) and (2*S*,3*S*)-**12** (27%, 32% ee) (entry 3). Furthermore, (2*R*,3*R*)-**12** (95% ee) derived from (2*R*,3*R*)-**16** possessing 95% ee was again subjected to the same enzymatic acetylation as in the case of entry 3 for 1 h to afford (2*R*,3*R*)-**16** (74%, $[\alpha]_D^{29} = +19.6$ (*c* 0.98, $CHCl_3$), >99% ee by HPLC analysis) and (2*R*,3*R*)-**12** (24%, 80% ee) (entry 4). The enantiomeric excess of the enzymatic reaction products was determined by HPLC on CHIRALCEL OD (250 × 4.6 mm) for (2*S*,3*S*)-**12** and AS (250 × 4.6 mm) for (2*R*,3*R*)-**16** columns.

In order to confirm the absolute structure of (+)-(2*R*,3*R*)-**16**, (+)-(2*R*,3*R*)-**16** was successfully converted to diacetate (2*R*,3*R*,4*R*)-**28**. Silylation of (+)-(2*R*,3*R*)-**16** followed by deacetylation and oxidation gave aldehyde **19** in 37% overall yield (three steps). Treatment of **19** with $LiC(SMe)_3$ followed by Hg^{2+} provided a 10:1 mixture of 2-hydroxy esters (**20** and **21**, **20**:**21** = 10:1) in 72% yield. Treatment of this mixture with fluoride ion furnished γ-lactones **22** (74% yield) and **23** (7% yield). The C_2-configurations of (±)-**22** and (±)-**23** were confirmed by NOE studies as shown in Figure 2. The high 2,3-*syn*-diastereoselectivity in the reaction of **19** and $LiC(SMe)_3$ was explained by a Felkin–



Scheme 2. Reagents and conditions: (a) BnBr, NaH, MeOH; (b) i. MCPBA, CH_2Cl_2; ii. Ac_2O, reflux; (c) K_2CO_3, MeOH; (d) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N, −78 °C; (e) MeCH(Br)COOMe, Zn, PhH, reflux; (f) *n*-Bu_4NBH_4, MeOH, −78, −40, 0 °C; (g) $LiAlH_4$, THF; (h) $NaBH_4$, MeOH; (i) $Me_2C(OMe)_2$, CSA, PhH.

Table 1. Enantioselective acetylation of (±)-**12** in the presence of lipase Amano P



Entry	Substrate (g)	Time (h)	Product (%, % ee)	
1	(±)-**12** (10.32 g)	2.5	(2*S*,3*S*)-**12** (38%, 97% ee)	(2*R*,3*R*)-**16** (59%, 59% ee)
2	(2*S*,3*S*)-**12** (97% ee, 3.922 g)	2.5	(2*S*,3*S*)-**12** (65%, >99% ee)	(2*S*,3*S*)-**16** (32%, 93% ee)
3	(2*R*,3*R*)-**12** (59% ee, 5 g)[a]	1	(2*S*,3*S*)-**12** (27%, 32% ee)	(2*R*,3*R*)-**16** (66%, 95% ee)
4	(2*R*,3*R*)-**12** (95% ee, 3.3 g)[b]	1	(2*R*,3*R*)-**12** (24%, 80% ee)	(2*R*,3*R*)-**16** (74%, >99% ee)

[a] (2*R*,3*R*)-**12** (59% ee) was obtained by deacylation of (2*R*,3*R*)-**16** (59% ee) with K_2CO_3 in MeOH.
[b] (2*R*,3*R*)-**12** (95% ee) was obtained by deacylation of (2*R*,3*R*)-**16** (95% ee) with K_2CO_3 in MeOH.

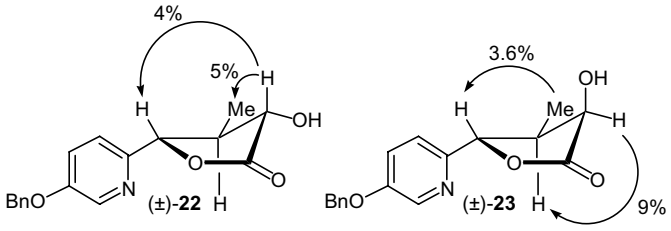


Figure 2.

Anh model[6] as shown in Figure 3. Conversion of the hydroxyl group in **22** to an amino group in **27** was achieved in 53% overall yield (three steps). Treatment of **22** with I_2/Ph_3P gave the corresponding iodide, which was treated with NaN_3 to afford **24** (58%), **25** (9%), and **26** (29%). Treatment of **24** with Ph_3P/H_2O gave the desired amine **27** in 91% yield. Deprotection of **27** followed by acetylation gave the desired diacetate **28** {$[\alpha]_D = -13.5$ (*c* 0.2, MeOH)} in 80% overall yield (two steps), which was identical with an authentic sample (2*S*,3*S*,4*S*)-**28**[2] {$[\alpha]_D = +13.9$ (*c* 0.5, MeOH)} obtained from the degradation product of natural nikkomycin Z **1** except for the sign of specific rotation. From these conversion experiments, the configuration of the enzymatic acetylation product (+)-**16** was determined to be 2*R*,3*R*, and thence that of (−)-**12** was confirmed to be 2*S*,3*S*. Enzymatic acetylation of (2*S*,3*S*)-**12** with vinyl acetate provided acetate (2*S*,3*S*)-**16** in 87% yield, which was converted to γ-lactone (2*S*,3*S*,4*S*)-**27** {$[\alpha]_D^{26} = -18.0$ (*c* 0.7, $CHCl_3$)} in 14% overall yield (nine steps) in the same way as in the case of (2*R*,3*R*,4*R*)-**27**. Alkaline treatment of (2*S*,3*S*,4*S*)-**27** followed by ion-exchange resin gave the intermediary carboxylic acid, which was converted to the desired (2*S*,3*S*,4*S*)-2-benzyloxycarbonylamino-4-[2-(5-benzyloxypyridyl)]-4-*tert*-butyldimethylsilyloxy-3-methylbutanoic acid **2**[9] {$[\alpha]_D^{28} = -5.4$ (*c* 0.79, $CHCl_3$), 69% overall yield from (2*S*,3*S*,4*S*)-**27**)} by applying the reported method.[3] The NMR data of the (2*S*,3*S*,4*S*)-**2** synthesized were identical with those of the reported (±)-**2**.[3] In this process, epimerization at the C_2-position of (±)-**27** was found not to occur because amino protection of (±)-**27** as a benzyloxycarbonyl group and desilylation of (±)-**2** followed by γ-lactonization furnished the same compound (±)-**28**, respectively (Scheme 3).

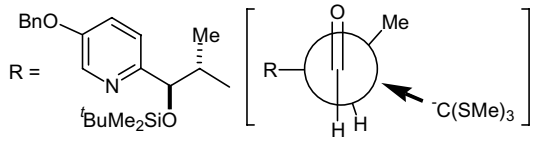


Figure 3.

In conclusion, *n*-Bu_4NBH_4 reduction of β-keto ester (±)-**11** afforded the (±)-*anti*-β-hydroxy ester **9** (83% yield) with 10:1 *anti*-diastereoselectivity. An enantioselective esterification of (±)-*anti*-diol **12** derived from (±)-**9** using lipase Amano P provided the enantiomerically pure (2*S*,3*S*)-**12**, which was converted to the N-terminal amino acid congener (2*S*,3*S*,4*S*)-**2** for the synthesis of nikkomycin Z **1** in 9% overall yield (fourteen steps).

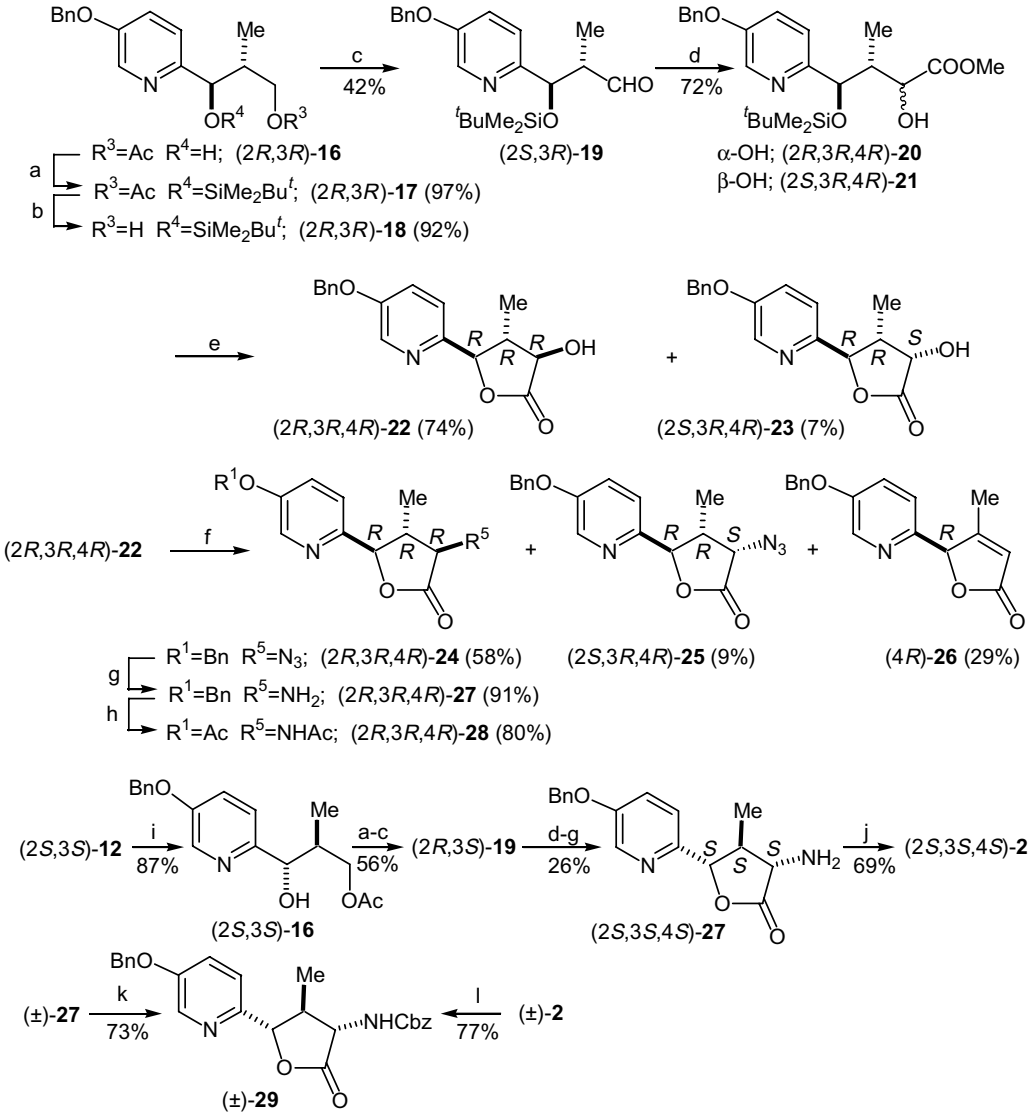
3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL EX 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB-MS) were obtained with JEOL JMS-DX 303 spectrometer. IR spectra were recorded with JASCO FT/IR-300 spectrometer. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

3.2. 5-Benzyloxy-2-methylpyridine 5

To a well-stirred solution of 5-hydroxy-2-methylpyridine **4** (10 g, 92 mmol) in DMF (50 ml) at 0 °C, NaH in oil



Scheme 3. Reagents and conditions: (a) $^{t}BuMe_2SiCl$, imidazole, DMF; (b) K_2CO_3, MeOH; (c) PCC; (d) i. *n*-BuLi, $CH(SMe)_3$, −78 °C; ii. $HgCl_2$, HgO, MeOH, H_2O; (e) $Bu_4N^+F^-$, THF; (f) i. Ph_3P, I_2, THF; ii. NaN_3, DMF; (g) Ph_3P, H_2O, 60 °C; (h) i. H_2, 5% Pd–C; ii. Ac_2O, pyridine; (i) vinyl acetate, lipase Amano P, 30 °C, 12 h; (j) i. KOH, THF, H_2O, 0 °C; ii. Dowex-50WX8-400; iii. *N*-methyl-*N*-(^{t}butyldimethylsilyl)trifluoroacetamide, iv. *N*-(benzyloxycarbonyloxy)-succinimide; (k) CbzCl, $NaHCO_3$, dioxane; (l) i. $Bu_4N^+F^-$; ii. DCC.

(55–75%, 4.63 g) and benzyl bromide (17.3 g, 101 mmol) were added and the whole mixture was stirred for 30 min. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (300 g, *n*-hexane/EtOAc = 1:1) to give **5** (16.64 g, 91%) as a colorless oil. **5**: IR (neat): 1255 cm^{-1}. NMR: δ 2.47 (3H, s), 5.05 (2H, s), 7.03 (1H, d, $J = 8.8$ Hz), 7.15 (1H, dd, $J = 2.9$, 8.3 Hz), 8.25 (1H, d, $J = 2.9$ Hz). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.19; H, 6.80; N, 6.87.

3.3. 2-Acetoxymethyl-5-benzyloxypyridine 6

To a well stirred solution of **5** (33.48 g, 168 mmol) in $CHCl_3$ (300 ml) at 0 °C, *m*-chloroperbenzoic acid (40.94 g 237 mmol) was added and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and the organic layer was separated. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was used without further purification. A mixture of the crude residue and Ac_2O (35.74 g, 350 mmol) was heated at 120 °C for 40 min, and the reaction mixture was diluted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (300 g, *n*-hexane/EtOAc = 9:1) to give **6** (23.88 g, 55%) as a colorless oil. **6**: IR (neat): 1739 cm^{-1}. NMR: δ 2.13 (3H, s), 5.11 (2H, s), 5.15 (2H, s), 7.25 (1H, dd, $J = 2.9$, 8.3 Hz), 7.28 (1H, d, $J = 8.3$ Hz), 7.34–7.44 (5H, m), 8.37 (1H, d, $J = 2.9$ Hz). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.09; H, 6.47; N, 5.24.

3.4. 5-Benzyloxy-2-hydroxymethylpyridine 7

To a well-stirred solution of **6** (11.01 g, 42.8 mmol) in MeOH (300 ml) at 0 °C, K_2CO_3 (5.94 g, 43 mmol) was added and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was evaporated and a residue was diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (100 g, *n*-hexane/EtOAc = 1:1) to give **7** (7.86 g, 85%) as colorless needles (*n*-hexane/EtOAc). Compound **6**: mp 67–68 °C, IR (KBr): 3196 cm^{-1}. NMR: δ 4.68 (2H, s), 5.09 (2H, s), 7.20 (1H, d, $J = 8.8$ Hz), 7.26 (1H, dd, $J = 2.4$, 8.8 Hz), 8.29 (1H, d, $J = 2.4$ Hz). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.40; H, 6.00; N, 6.51.

3.5. 5-Benzyloxy-2-formylpyridine 8

To a well-stirred solution of DMSO (19.6 ml, 276 mmol) in CH_2Cl_2 (100 ml) was added oxalyl chloride (11.7 ml, 138 mmol) at −78 °C, and the mixture was stirred for 30 min. A solution of **7** (14.84 g, 69 mmol) in CH_2Cl_2 (30 ml) was added and the mixture was stirred for 30 min, Et_3N (76.3 ml, 552 mmol) was added and the mixture was stirred at room temperature for 1 h. The mixture was diluted with 1 M aqueous HCl and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (200 g, *n*-hexane/EtOAc = 4:1) to give **8** (13.96 g, 95%) as colorless needles (*n*-hexane/EtOAc). Compound **8**: mp 64–66 °C, IR (KBr): 1703 cm^{-1}. NMR: δ 5.20 (2H, s), 7.36 (1H, dd, $J = 2.9$, 8.8 Hz), 7.95 (1H, d, $J = 8.8$ Hz), 8.51 (1H, d, $J = 2.4$ Hz), 8.99 (1H, d, $J = 1.0$ Hz). FAB-MS *m*/*z*: 214 (M^++1).

3.6. (±)-Methyl *anti*-3-[2-(5-benzyloxypyridyl)]-3-hydroxy-2-methylpropanoate 9 and (±)-methyl *syn*-3-[2-(5-benzyloxypyridyl)]-3-hydroxy-2-methylpropanoate 10

(1) A stirred mixture of **8** (11.71 g, 55 mmol), methyl α-bromopropanoate (11 g, 65.9 mmol) and activated Zn dust [prepared from Zn (7 g)] in dry benzene (200 ml) was refluxed for 90 min. The reaction mixture was diluted with H_2O and 1 M aqueous HCl, and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent provided a crude oily product, which was chromatographed on silica gel (300 g, *n*-hexane/EtOAc = 5:1) to afford a 1:1 mixture (14.72 g, 89%) of (±)-*anti*-**9** and (±)-*syn*-**10**. (2) To a well-stirred solution of DMSO (13.9 ml, 196 mmol) in CH_2Cl_2 (100 ml) was added oxalyl chloride (12.8 ml, 147 mmol) at −78 °C, and the mixture was stirred for 30 min. A solution of the above-mentioned mixture (14.72 g, 48.9 mmol) in CH_2Cl_2 (30 ml) was added and the mixture was stirred for 30 min, Et_3N (40.6 ml, 293 mmol) was added and the mixture was stirred at room temperature for 1 h. The mixture was diluted with 1 M aqueous HCl and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (200 g, *n*-hexane/EtOAc = 10:1) to give **11** (14.48 g, 99%) as colorless needles (*n*-hexane/EtOAc). Compound **11**: mp 57–58 °C, IR (KBr): 1738, 1216 cm^{-1}. NMR: δ 1.47 (3H, d, $J = 7.0$ Hz), 3.66 (3H, s), 4.74 (1H, q, $J = 7.0$ Hz), 5.17 (2H, s), 7.33 (1H, dd, $J = 2.9$, 8.8 Hz), 7.34–7.43 (5H, m), 8.06 (1H, d, $J = 8.8$ Hz), 8.37 (1H, d, $J = 2.9$ H). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 67.78; H, 6.03; N, 4.55. FAB-MS *m*/*z*: 300 (M^++1). (3) To a well-stirred solution of *n*-Bu_4BH_4 (4.34 g, 16.8 mmol) in MeOH (70 ml) was added a solution of **11** (5.0 g, 16.7 mmol) in MeOH (30 ml) at −78 °C, and the mixture was stirred at −40 °C for 1 h and at 0 °C for 30 min. After acetone (20 ml) was added to the reaction mixture, the whole mixture was stirred at 0 °C for 1 h. The mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (100 g, *n*-hexane/EtOAc = 4:1) to give (±)-*syn*-**10** (0.383 g, 7%) as colorless needles (*n*-hexane/EtOAc) and (±)-*anti*-**9** (3.83 g, 76%) as colorless needles (*n*-hexane/EtOAc) in elution order. Compound (±)-*syn*-**10**: mp 50–51 °C, IR (KBr): 3228, 1728 cm^{-1}. NMR: δ 1.04 (3H, d, $J = 7.3$ Hz), 2.92 (1H, dq, $J = 4.4$, 7.3 Hz), 3.68 (3H, s), 4.20 (1H, br s), 5.07 (2H, s), 5.10 (1H, d, $J = 4.0$ Hz), 7.26 (2H, s), 7.31–7.42 (5H, m), 8.29 (1H, s). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.48; H, 6.43; N, 4.64. Compound (±)-*anti*-**9**: mp 87–88 °C, IR (KBr): 3323, 1731 cm^{-1}. NMR: δ 1.09 (3H, d, $J = 7.1$ Hz), 2.99 (1H, dq, $J = 7.1$ Hz), 3.68 (3H, s), 4.14 (1H, br s), 4.80 (1H, d, $J = 7.0$ Hz), 5.10 (2H, s), 7.21–7.44 (7H, m), 8.31 (1H, d, $J = 2.4$ Hz). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 68.00; H, 6.29; N, 4.68.

3.7. (±)-*anti*-3-[2-(5-Benzyloxypyridyl)]-2-methyl-1,3-propanediol 12

To a suspension of $LiAlH_4$ (1.89 g, 49.8 mmol) in dry THF (150 ml) was added a solution of (±)-**10** (14.1 g, 46.8 mmol) in dry THF (90 ml) at room temperature, and the reaction mixture was stirred for 1 h at the same temperature. After the addition of acetone (11 ml) and EtOAc (150 ml), the whole mixture was filtered with the aid of Celite and the precipitate was washed with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was crystallized from benzene to give crystals (±)-**12** (10.32 g, 81%) as colorless needles (*n*-hexane/EtOAc). Compound (±)-**12**: mp 64–65 °C; IR (KBr): 3351 cm^{-1}. NMR: δ 0.86 (3H, d, $J = 7.3$ Hz), 2.06–2.13 (1H, m), 3.62 (1H, dd, $J = 6.8$, 11.2 Hz), 3.69 (1H, dd, $J = 3.9$, 11.2 Hz), 4.67 (1H, d, $J = 6.4$ Hz), 5.11 (2H, s), 7.24 (1H, d, $J = 8.8$ Hz), 7.28 (1H, dd, $J = 2.5$, 8.8 Hz), 7.35–7.44 (5H, m), 8.29 (1H, d, $J = 2.5$ Hz). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 69.96; H, 7.05; N, 5.16.

3.8. Acetonide formation of (±)-12

A mixture of (±)-**12** (0.521 g, 1.9 mmol), 2,2-dimethoxypropane (4 ml) and camphorsulfonic acid (CSA; 0.177 g, 0.76 mmol) in benzene (5 ml) was stirred for 12 h at room

temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (30 g, *n*-hexane/EtOAc = 3:1) to afford (±)-**14** (0.478 g, 80%) as colorless needles (*n*-hexane/EtOAc). Compound (±)-**14**: mp 74–75 °C; IR (KBr): 1237, 1277, 1022 cm^{-1}. NMR: δ 0.66 (3H, d, $J = 6.8$ Hz), 1.48 (3H, s), 1.56 (3H, s), 1.97–2.06 (1H, m), 3.71 (1H, dd, $J = 6.4$, 11.7 Hz), 3.82 (1H, dd, $J = 4.9$, 11.7 Hz), 4.59 (1H, d, $J = 10.3$ Hz), 5.10 (2H, s), 7.26–7.43 (2H, m), 8.30 (1H, d, $J = 2.4$ Hz). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.38; H, 7.43; N, 4.47.

3.9. (±)-*syn*-3-[2-(5-Benzyloxypyridyl)]-2-methyl-1,3-propanediol 13

To a solution of (±)-**10** (0.811 g, 2.7 mmol) in MeOH (12 ml) was added $NaBH_4$ (0.205 g, 5.4 mmol) in MeOH at 0 °C, and the reaction mixture was stirred for 1 h at the same temperature. After the addition of acetone (2 ml) and EtOAc (50 ml), the whole mixture was filtered with the aid of Celite and the precipitate was washed with EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (30 g, *n*-hexane/EtOAc = 2:1) to afford (±)-**13** (0.472 g, 64%) as colorless needles (*n*-hexane/EtOAc). Compound (±)-**13**: mp 77–78 °C; IR (KBr): 3339 cm^{-1}. NMR: δ 0.71 (3H, d, $J = 7.0$ Hz), 2.06–2.12 (1H, m), 3.69 (1H, dd, $J = 4.4$, 10.8 Hz), 3.75 (1H, dd, $J = 6.6$, 10.8 Hz), 4.98 (1H, d, $J = 3.1$ Hz), 5.09 (2H, s), 7.24 (1H, d, $J = 8.6$ Hz), 7.29 (1H, dd, $J = 2.8$, 8.6 Hz), 7.31–7.43 (5H, m), 8.26 (1H, d, $J = 2.8$ Hz). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.07; H, 7.02; N, 5.10.

3.10. Acetonide formation of (±)-13

A mixture of (±)-**13** (0.367 g, 1.3 mmol), 2,2-dimethoxypropane (4 ml) and camphorsulfonic acid (CSA; 0.125 g, 0.54 mmol) in benzene (5 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane/EtOAc = 3:1) to afford (±)-**15** (0.341 g, 81%) as colorless needless (*n*-hexane/EtOAc). Compound (±)-**15**: mp 78–79 °C; IR (KBr): 1240, 1198, 1014 cm^{-1}. NMR: δ 0.78 (3H, d, $J = 7.0$ Hz), 1.52 (3H, s), 1.54 (3H, s), 2.02–2.08 (1H, m), 3.70 (1H, dd, $J = 1.3$, 11.5 Hz), 4.31 (1H, dd, $J = 2.8$, 11.5 Hz), 5.10 (2H, s), 5.16 (1H, d, $J = 2.8$ Hz), 7.24–7.43 (7H, m), 8.31 (1H, d, $J = 2.9$ Hz). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.59; H, 7.50; N, 4.54.

3.11. (±)-*anti*-1-Acetoxy-3-[2-(5-benzyloxypyridyl)]-2-methyl-3-propanol 16

A mixture of (±)-**12** (0.521 g, 1.91 mmol) and Ac_2O (0.193 ml, 2.0 mmol) in pyridine (2 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with 1 M aqueous HCl and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane/EtOAc = 3:1) to afford diacetate (0.102 g, 14.9%) from *n*-hexane/EtOAc = 5:1 elution, (±)-**16** (0.292 g, 48.6%) and monoacetate (0.026 g, 4.4%) from *n*-hexane/EtOAc = 4:1 elution, and (±)-**12** (0.156 g, 30%) from *n*-hexane/EtOAc = 1:1 elution. Compound (±)-**16**: colorless oil. IR (neat): 3418, 1732, 1247 cm^{-1}. NMR: δ 0.95 (3H, d, $J = 6.8$ Hz), 1.91 (3H, s), 2.22–2.28 (1H, m), 4.02 (1H, br s), 4.06 (1H, dd, $J = 5.9$, 1.0 Hz), 4.10 (1H, dd, $J = 5.9$, 11.0 Hz), 4.59 (1H, d, $J = 5.4$ Hz), 5.11 (2H, s), 7.16–7.43 (7H, m), 8.29 (1H, d, $J = 2.9$ Hz). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.57; H, 6.67; N, 4.44. Found: C, 68.19; H, 6.86; N, 4.38.

3.12. HPLC analysis of the racemic alcohol (±)-12 and acetate (±)-16 by using a chiral column

Two racemates (±)-**12** and (±)-**16** gave individually two well separated peaks. Compound (±)-**12**; 75.1 and 85.0 min corresponding to each enantiomer under the following analytical conditions (column, CHIRALCEL OD (250 × 4.6 mm); eluent, *n*-hexane/EtOH = 40:1; detection, UV at 254 nm; flow rate, 1 ml/min). Compound (±)-**16**; 38.6 and 56.9 min corresponding to each enantiomer under the following analytical conditions (column, CHIRALCEL AS (250 × 4.6 mm); eluent, *n*-hexane/EtOH = 40:1; detection, UV at 254 nm; flow rate, 1 ml/min).

3.13. Enzymatic resolution

(1) A mixture of (±)-**12** (5.00 g, 18.3 mmol), vinyl acetate (3.1 g, 36 mmol) and lipase 'Amano P' (2.5 g) in diisopropyl ether (1000 ml) was stirred at 33 °C for 2.5 h. This enzymatic reaction was carried out twice and the total amount of the used substrate (±)-**12** was 10.32 g. The reaction mixture was filtered with the aid of Celite and the precipitate was washed with EtOAc. The combined organic solvent was evaporated to give a residue, which was chromatographed on silica gel (100 g) to afford (2*R*,3*R*)-**16** (7.058 g, 59%, 59% ee) from *n*-hexane/EtOAc = 2:1 elution and (2*S*,3*S*)-**12** (3.922 g, 38%, 97% ee) from *n*-hexane/EtOAc = 1:2 elution. Enantiomeric excess (ee) of (2*R*,3*R*)-**16** and (2*S*,3*S*)-**12** was analyzed by HPLC. (2) A mixture of (2*S*,3*S*)-**12** (97% ee, 3.922 g, 14.4 mmol), vinyl acetate (2.473 g, 28.8 mmol) and lipase 'Amano P' (2 g) in diisopropyl ether (800 ml) was stirred at 33 °C for 2.5 h. The reaction mixture was worked up in the same way as for case (1) to afford (2*S*,3*S*)-**16** (1.448 g, 32%, 93% ee) and (2*S*,3*S*)-**12** (2.549 g, 65%, $[\alpha]_D^{26} = -28.6$ (*c* 0.92, $CHCl_3$); corresponds to >99% ee). (3) A mixture of (2*R*,3*R*)-**16** (59% ee, 7.0851 g, 22.4 mmol), K_2CO_3 (6.194 g, 44.8 mmol) in MeOH (80 ml) was stirred for 40 min at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave crude (2*R*,3*R*)-**12** (6.117 g, >99%). A mixture of (2*R*,3*R*)-**12** (5 g, 18.3 mmol),

vinyl acetate (3.1 g, 36 mmol) and lipase 'Amano P' (2.5 g) in diisopropyl ether (1000 ml) was stirred at 33 °C for 1 h. The reaction mixture was worked up in the same way as for case (1) to afford (2*R*,3*R*)-**16** (3.808 g, 66%, 95% ee) and (2*R*,3*R*)-**12** (1.35 g, 27%, 32% ee). (4) A mixture of (2*R*,3*R*)-**16** (95% ee, 3.808 g, 12.1 mmol), K_2CO_3 (3.344 g, 24.2 mmol) in MeOH (40 ml) was stirred for 40 min at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave crude (2*R*,3*R*)-**12** (3.30 g, >99%). A mixture of (2*R*,3*R*)-**12** (3.30 g, 12.1 mmol), vinyl acetate (2.081 g, 24.2 mmol) and lipase 'Amano P' (1.65 g) in diisopropyl ether (700 ml) was stirred at 33 °C for 1 h. The reaction mixture was worked up in the same way as for case (1) to afford (2*R*,3*R*)-**16** (2.817 g, 74%, $[\alpha]_D^{29} = +19.6$ (*c* 0.98, $CHCl_3$); corresponds to >99% ee) and (2*R*,3*R*)-**12** (0.768 g, 24%, 80% ee).

3.14. (2*R*,3*R*)-1-Acetoxy-3-[2-(5-benzyloxypyridyl)]-3-*tert*-butyldimethylsilyloxy-2-methyl-propane 17

A mixture of (2*R*,3*R*)-**16** (2.895 g, 9.2 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl; 2.77 g, 18.4 mmol), and imidazole (1.87 g, 27.6 mmol) in DMF (10 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (60 g, *n*-hexane/EtOAc = 15:1) to afford (2*R*,3*R*)-**17** (3.835 g, 97%) as a colorless oil. Compound (2*R*,3*R*)-**17**: $[\alpha]_D^{27} = +52.3$ (*c* 0.77, $CHCl_3$); IR (neat): 1739, 1246 cm^{-1}. NMR: δ −0.26 (3H, s), 0.03 (3H, s), 0.84 (3H, d, $J = 6.8$ Hz), 0.88 (9H, s), 1.95 (3H, s), 2.17–2.24 (1H, m), 4.04 (1H, dd, $J = 6.4$, 10.7 Hz), 4.12 (1H, dd, $J = 4.4$, 10.7 Hz), 4.68 (1H, d, $J = 6.4$ Hz), 5.09 (2H, s), 7.24–7.44 (7H, m), 8.25 (1H, d, $J = 2.4$ Hz). FAB-MS *m*/*z*: 430 (M^++1). Anal. Calcd for $C_{24}H_{35}NO_4Si$: C, 67.13; H, 8.16; N, 3.26. Found: C, 66.94; H, 8.62; N, 3.07.

3.15. (2*R*,3*R*)-3-[2-(5-Benzyloxypyridyl)]-3-*tert*-butyldimethylsilyloxy-2-methyl-1-propanol 18

A mixture of (2*R*,3*R*)-**17** (3.835 g, 8.9 mmol), K_2CO_3 (4.95 g, 35.8 mmol) in MeOH (50 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (60 g, *n*-hexane/EtOAc = 5:1) to afford (2*R*,3*R*)-**18** (3.173 g, 92%) as a colorless oil. Compound (2*R*,3*R*)-**18**: $[\alpha]_D^{27} = +54.2$ (*c* 0.886, $CHCl_3$); IR (neat): 2943, 1255 cm^{-1}. NMR: δ −0.13 (3H, s), 0.08 (3H, s), 0.82 (3H, d, $J = 7.3$ Hz), 0.91 (9H, s), 2.16–2.18 (1H, m), 3.34 (1H, dd, $J = 7.3$, 11.7 Hz), 3.62 (1H, dd, $J = 4.4$, 11.7 Hz), 3.90 (1H, br s), 4.91 (1H, d, $J = 5.4$ Hz), 5.10 (2H, s), 7.26–7.44 (7H, m), 8.25 (1H, d, $J = 2.9$ Hz). FAB-MS *m*/*z*: 388 (M^++1). Anal. Calcd for $C_{22}H_{33}NO_3Si$: C, 68.22; H, 8.53; N, 3.62. Found: C, 68.01; H, 9.00; N, 3.54.

3.16. (2*R*,3*R*)-3-[2-(5-Benzyloxypyridyl)]-3-*tert*-butyldimethylsilyloxy-2-methylpropanal 19

A mixture of (2*R*,3*R*)-**18** (3.173 g, 8.2 mmol), PCC (3.59 g, 16.3 mmol) in CH_2Cl_2 (150 ml) was stirred for 10 h at room temperature. The reaction mixture was directly subjected to chromatography on Florisil (40 g, AcOEt) to afford a residue, which was again chromatographed on silica gel (40 g, *n*-hexane/EtOAc = 8:1) to afford (2*R*,3*R*)-**19** (1.311 g, 42%) as a colorless oil. Compound (2*R*,3*R*)-**19**: $[\alpha]_D^{27} = +84.2$ (*c* 0.92, $CHCl_3$); IR (neat): 1725 cm^{-1}. NMR: δ −0.12 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 0.96 (3H, d, $J = 6.8$ Hz), 2.78–2.85 (1H, m), 5.04 (1H, d, $J = 5.9$ Hz), 5.10 (2H, s), 7.28–7.44 (7H, m), 8.27 (1H, d, $J = 2.4$ Hz), 9.78 (1H, s). FAB-MS *m*/*z*: 386 (M^++1).

3.17. (2*R*,3*R*,4*R*)-4-[2-(5-Benzyloxypyridyl)]-2-hydroxy-3-methyl-butano-4-lactone 22 and (2*S*,3*R*,4*R*)-4-[2-(5-benzyloxypyridyl)]-2-hydroxy-3-methyl-butano-4-lactone 23

(1) To a solution of tris(methylthio)methane (0.80 g, 5.09 mmol) in THF (15 ml) at −78 °C was added *n*-BuLi (1.53 M in hexane, 2.9 ml (4.4 mmol)) under an argon atmosphere, and the reaction mixture was stirred at −78 °C for 20 min and at −20 °C for 1 h. To the generated carbanion solution was added a solution of aldehyde **19** (1.31 g, 3.39 mmol) in THF (5 ml) at −78 °C, and the whole mixture was stirred at −78 °C for 2 h and at 0 °C for 2 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with saturated brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in a mixed solvent (MeOH (12 ml) and H_2O (1 ml)), and $HgCl_2$ (4.2 g, 15.3 mmol) and HgO (3.3 g, 15.3 mmol) were added to the above solution at room temperature and the mixture was stirred for 4 h at the same temperature. The reaction mixture was filtered with the aid of Celite and the filtrate was condensed to give a residue, which was treated with saturated NH_4Cl and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (45 g, *n*-hexane/EtOAc = 10:1) to afford a 10:1 mixture of α-hydroxy esters (**20** and **21**, 1.09 g, 72%) as a colorless oil. (2) To a solution of α-hydroxy esters (**20** and **21**, 1.09 g, 2.45 mmol) in THF (20 ml) was added tetrabutylammonium fluoride TBAF (1.28 g, 4.9 mmol), and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (25 g, *n*-hexane/EtOAc = 5:1) to afford (2*S*,3*R*,4*R*)-**23** (0.049 g, 7%) from *n*-hexane/EtOAc = 3:1 elution as colorless oil and (2*R*,3*R*,4*R*)-**22** (0.544 g, 74%) as colorless needles from *n*-hexane/EtOAc = 1:1 elution. Compound (2*R*,3*R*,4*R*)-**22**: mp 114–115 °C (*n*-hexane/EtOAc); $[\alpha]_D^{27} = -3.1$ (*c* 0.707, $CHCl_3$); IR (neat): 3109, 1801 cm^{-1}. NMR: δ 1.27 (3H, d, $J = 6.4$ Hz), 2.57–2.67 (1H, m), 4.17 (1H, dd, $J = 6.4$, 8.3 Hz), 4.70 (1H, d, $J = 7.8$ Hz), 4.97 (1H, d, $J = 7.8$ Hz), 5.12 (2H, s), 7.29–7.43 (7H, m), 8.35 (1H, d, $J = 2.9$ Hz). FAB-MS *m*/*z*: 300 (M^++1). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.09;

H, 5.75; N, 4.66. Compound (2*S*,3*R*,4*R*)-**23**: $[\alpha]_D^{28} = -36.1$ (*c* 0.676, $CHCl_3$); IR (neat): 3218, 1784, 1262 cm^{-1}. NMR: δ 1.24 (3H, d, $J = 6.8$ Hz), 2.95–3.03 (1H, m), 4.71 (1H, d, $J = 7.3$ Hz), 5.12 (2H, s), 5.18 (1H, d, $J = 3.4$ Hz), 7.23–7.43 (7H, m), 8.35 (1H, dd, $J = 1.5$, 2.0 Hz). FAB-MS *m*/*z*: 300 (M^++1). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 68.21; H, 5.73; N, 4.68. Found: C, 67.87; H, 5.69; N, 4.70.

3.18. (2*R*,3*R*,4*R*)-2-Azido-4-[2-(5-benzyloxypyridyl)]-3-methyl-butano-4-lactone 24, (2*S*,3*R*,4*R*)-2-azido-4-[2-(5-benzyloxypyridyl)]-3-methyl-butano-4-lactone 25, and (4*R*)-4-[2-(5-benzyloxypyridyl)]-3-methyl-2-buteno-4-lactone 26

To a solution of (2*R*,3*R*,4*R*)-**22** (0.30 g, 1 mmol), triphenylphosphine (Ph_3P; 0.525 g, 2 mmol) and imidazole (0.136 g, 2 mmol) in THF (10 ml) was added a solution of I_2 (0.381 g, 1.5 mmol) in THF (3 ml) at 0 °C, and the reaction mixture was stirred for 30 min. After addition of one drop of H_2O, the reaction mixture was directly chromatographed on silica gel (20 g, *n*-hexane/EtOAc = 5:1) to afford 2-iodo compound. To a mixture of sodium azide (NaN_3; 0.095 g, 1.47 mmol) in DMF (10 ml) was added a solution of the above iodo compound in THF (1 ml), and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (25 g, *n*-hexane/EtOAc = 5:1) to afford (2*S*,3*R*,4*R*)-**25** (0.028 g, 9%) as colorless needles and (2*R*,3*R*,4*R*)-**24** (0.189 g, 58%) as colorless oil from *n*-hexane/EtOAc = 9:1 elution and (4*R*)-**26** (0.082 g, 29%) as colorless needles from *n*-hexane/EtOAc = 7:1 elution. Compound (2*R*,3*R*,4*R*)-**24**: $[\alpha]_D^{29} = +107.8$ (*c* 0.55, $CHCl_3$); IR (neat): 2111, 1784 cm^{-1}. NMR: δ 1.28 (3H, d, $J = 6.3$ Hz), 2.53–2.63 (1H, m), 4.03 (1H, d, $J = 11.7$ Hz), 4.97 (1H, d, $J = 9.8$ Hz), 5.12 (2H, s), 7.25–7.44 (7H, m), 8.35 (1H, d, $J = 2.9$ Hz). FAB-MS *m*/*z*: 325 (M^++1). Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.28. Found: C, 63.02; H, 5.05; N, 17.01. Compound (2*S*,3*R*,4*R*)-**25**: mp 107–109 °C (*n*-hexane/EtOAc); $[\alpha]_D^{30} = -139.1$ (*c* 0.675, $CHCl_3$); IR (KBr): 2106, 1771, 1210 cm^{-1}. NMR: δ 1.20 (3H, d, $J = 6.8$ Hz), 2.95–3.05 (1H, m), 4.65 (1H, d, $J = 7.3$ Hz), 5.10 (1H, d, $J = 4.9$ Hz), 5.12 (2H, s), 7.33–7.43 (7H, m), 8.34 (1H, d, $J = 1.5$ Hz). FAB-MS *m*/*z*: 300 (M^++1). Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.28. Found: C, 63.18; H, 4.95; N, 16.97. Compound (4*R*)-**26**: mp 89–90 °C (*n*-hexane/EtOAc); $[\alpha]_D^{30} = +2.0$ (*c* 0.94, $CHCl_3$); IR (KBr): 3443, 2921, 1752, 1646, 1291 cm^{-1}. NMR: δ 2.01 (3H, s), 5.11 (2H, s), 5.82 (1H, s), 5.89 (1H, s), 7.21–7.44 (7H, m), 8.35 (1H, d, $J = 2.5$ Hz). FAB-MS *m*/*z*: 282 (M^++1). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.40; H, 5.38; N, 5.03.

3.19. (2*R*,3*R*,4*R*)-2-Amino-4-[2-(5-benzyloxypyridyl)]-3-methyl-butano-4-lactone 27

A mixture of (2*R*,3*R*,4*R*)-**24** (0.175 g, 0.54 mmol) and Ph_3P (0.17 g, 0.65 mmol) in THF (5 ml) was stirred for 30 min at room temperature. After addition of 0.7 ml of H_2O, the reaction mixture was directly chromatographed on silica gel (20 g, $CHCl_3$/MeOH = 50:1) to afford (2*R*,3*R*,4*R*)-**27** (0.146 g, 91%) as a colorless oil. Compound (2*R*,3*R*,4*R*)-**27**: $[\alpha]_D^{29} = +18.1$ (*c* 0.52, $CHCl_3$); IR (KBr): 3436, 1770, 1268 cm^{-1}. NMR: δ 1.27 (3H, d, $J = 6.4$ Hz), 1.71 (2H, br s), 2.30–2.40 (1H, m), 3.40 (1H, d, $J = 11.2$ Hz), 4.92 (1H, d, $J = 9.8$ Hz), 5.13 (2H, s), 7.26–7.44 (7H, m), 8.34 (1H, d, $J = 2.9$ Hz). FAB-MS *m*/*z*: 299 (M^++1).

3.20. (2*R*,3*R*,4*R*)-2-Acetoamino-4-[2-(5-acetoxypyridyl)]-3-methyl-butano-4-lactone 28

A solution of (2*R*,3*R*,4*R*)-**27** (0.125 g, 0.42 mmol) in MeOH (5 ml) was subjected to catalytic hydrogenolysis using 5% Pd–C (0.085 g) at ordinary temperature, and the reaction mixture was filtered with the aid of Celite. The filtrate was condensed to give a residue, which was treated with Ac_2O (0.25 g, 2.45 mmol) in pyridine (0.5 ml). The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (10 g, $CHCl_3$/MeOH = 70:1) to afford (2*R*,3*R*,4*R*)-**28** (0.114 g, 80%) as colorless needles. Compound (2*R*,3*R*,4*R*)-**28**: mp 205–207 °C ($CHCl_3$/MeOH); $[\alpha]_D^{27} = -13.5$ (*c* 0.2, MeOH); IR (KBr): 3292, 1787, 1198 cm^{-1}. NMR: δ 1.30 (3H, d, $J = 6.8$ Hz), 2.09 (3H, s), 2.35 (3H, s), 2.58–2.65 (1H, m), 4.62 (1H, dd, $J = 7.8$, 11.2 Hz), 5.05 (1H, d, $J = 9.3$ Hz), 6.26 (1H, d, $J = 7.8$ Hz), 7.53 (2H, dd, $J = 2.4$, 8.3 Hz), 8.39 (1H, d, $J = 2.4$ Hz). FAB-MS *m*/*z*: 293 (M^++1). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.14; H, 5.70; N, 9.21.

3.21. (2*S*,3*S*)-1-Acetoxy-3-[2-(5-benzyloxypyridyl)]-2-methyl-3-propanol 16

A mixture of (2*S*,3*S*)-**12** (>99% ee, 2.05 g, 7.5 mmol), vinyl acetate (2.07 g, 24.0 mmol) and lipase 'Amano P' (1.02 g) in diisopropyl ether (400 ml) was stirred at 33 °C for 12 h. The reaction mixture was worked up in the same way as (±)-**12** to afford (2*S*,3*S*)-**16** (2.06 g, 87%). Spectral data of (2*S*,3*S*)-**16** were identical with those of (±)-**16**. Compound (2*S*,3*S*)-**16**: $[\alpha]_D^{29} = -19.7$ (*c* 0.98, $CHCl_3$).

3.22. (2*S*,3*S*)-1-Acetoxy-3-[2-(5-benzyloxypyridyl)]-3-*tert*-butyldimethylsilyloxy-2-methyl-propane 17

A mixture of (2*S*,3*S*)-**16** (2.75 g, 8.7 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl; 2.63 g, 17.4 mmol) and imidazole (1.78 g, 26.2 mmol) in DMF (10 ml) was stirred for 12 h at room temperature. The reaction mixture was worked up in the same way as (2*R*,3*R*)-**17** to afford (2*S*,3*S*)-**17** (3.5 g, 93%). Spectral data of (2*S*,3*S*)-**17** were identical with those of (2*R*,3*R*)-**17**. Compound (2*S*,3*S*)-**17**: $[\alpha]_D^{28} = -52.8$ (*c* 0.98, $CHCl_3$).

3.23. (2*S*,3*S*)-3-[2-(5-Benzyloxypyridyl)]-3-*tert*-butyldimethylsilyloxy-2-methyl-1-propanol 18

A mixture of (2*S*,3*S*)-**17** (2.58 g, 6.0 mmol), K_2CO_3 (3.32 g, 24.4 mmol) in MeOH (50 ml) was stirred for 2 h at room

temperature. The reaction mixture was worked up in the same way as (2*R*,3*R*)-**18** to afford (2*S*,3*S*)-**18** (2.3 g, 98%). Spectral data of (2*S*,3*S*)-**18** were identical with those of (2*R*,3*R*)-**18**. Compound (2*S*,3*S*)-**18**: $[\alpha]_D^{28} = -54.3$ (*c* 0.975, $CHCl_3$).

3.24. (2*S*,3*S*)-3-[2-(5-Benzyloxypyridyl)]-3-*tert*-butyldimethylsilyloxy-2-methylpropanal 19

A mixture of (2*S*,3*S*)-**18** (3.06 g, 7.9 mmol), PCC (3.46 g, 15.7 mmol) in CH_2Cl_2 (30 ml) was stirred for 10 h at room temperature. The reaction mixture was worked up in the same way as (2*R*,3*R*)-**19** to afford (2*S*,3*S*)-**19** (1.83 g, 60%). Spectral data of (2*S*,3*S*)-**19** were identical with those of (2*R*,3*R*)-**19**. Compound (2*S*,3*S*)-**19**: $[\alpha]_D^{28} = -84.3$ (*c* 0.99, $CHCl_3$).

3.25. (2*S*,3*S*,4*S*)-4-[2-(5-Benzyloxypyridyl)]-2-hydroxy-3-methyl-butano-4-lactone 22 and (2*R*,3*S*,4*S*)-4-[2-(5-benzyloxypyridyl)]-2-hydroxy-3-methyl-butano-4-lactone 23

(1) To a solution of tris(methylthio)methane (0.76 g, 4.8 mmol) in THF (10 ml) at −78 °C was added *n*-BuLi (1.53 M in hexane, 2.7 ml (4.2 mmol)) under argon atmosphere, and the reaction mixture was stirred at −78 °C for 20 min and at −20 °C for 1 h. To the carbanion solution generated was added a solution of (2*S*,3*S*)-**19** (1.24 g, 3.21 mmol) in THF (5 ml) at −78 °C, and the whole mixture was stirred at −78 °C for 2 h and at 0 °C for 2 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with saturated brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in a mixed solvent (MeOH (24 ml) and H_2O (2 ml)) and $HgCl_2$ (3.94 g, 14.5 mmol) and HgO (3.14 g, 14.5 mmol) were added to the above solution at room temperature and the mixture was stirred for 4 h at the same temperature. The reaction mixture was worked up in the same way as α-hydroxy esters (**20** and **21**) to afford a mixture of α-hydroxy esters (**20** and **21**, 0.944 g, 66%). (2) To a solution of α-hydroxy esters (**20** and **21**, 0.918 g, 2.1 mmol) in THF (17 ml) was added TBAF (1.1 g, 4.1 mmol), and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was worked up in the same way as preparation of (2*R*,3*R*,4*R*)-**22** and (2*S*,3*R*,4*R*)-**23** to afford (2*R*,3*S*,4*S*)-**23** (0.045 g, 7%) and (2*S*,3*S*,4*S*)-**22** (0.456 g, 74%). Compound (2*S*,3*S*,4*S*)-**22**: mp 115–116 °C (*n*-hexane/EtOAc); $[\alpha]_D^{26} = +3.15$ (*c* 0.825, $CHCl_3$). Compound (2*R*,3*S*,4*S*)-**23**: $[\alpha]_D^{27} = +36.9$ (*c* 0.453, $CHCl_3$).

3.26. (2*S*,3*S*,4*S*)-2-Azido-4-[2-(5-benzyloxypyridyl)]-3-methyl-butano-4-lactone 24, (2*R*,3*S*,4*S*)-2-azido-4-[2-(5-benzyloxypyridyl)]-3-methyl-butano-4-lactone 25, and (4*S*)-4-[2-(5-benzyloxypyridyl)]-3-methyl-2-buteno-4-lactone 26

To a solution of (2*S*,3*S*,4*S*)-**22** (0.30 g, 1 mmol), triphenylphosphine (Ph_3P, 0.525 g, 2 mmol) and imidazole (0.136 g, 2 mmol) in THF (10 ml) was added a solution of I_2 (0.381 g, 1.5 mmol) in THF (3 ml) at 0 °C, and the reaction mixture was stirred for 30 min. After addition of one drop of H_2O, the reaction mixture was worked up in the same way as (2*R*,3*R*,4*R*)-**22** to afford 2-iodo compound. To a mixture of sodium azide (NaN_3, 0.095 g, 1.47 mmol) in DMF (10 ml) was added a solution of the above iodo compound in THF (1 ml) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as preparation of (2*R*,3*R*,4*R*)-**24**, (2*S*,3*R*,4*R*)-**25**, and (4*R*)-**26** to afford (2*R*,3*S*,4*S*)-**25** (0.028 g, 10%) as colorless needles, (2*S*,3*S*,4*S*)-**24** (0.195 g, 60%) as a colorless oil and (4*R*)-**26** (0.084 g, 30%) as colorless needles. Compound (2*S*,3*S*,4*S*)-**24**: $[\alpha]_D^{29} = -107.3$ (*c* 0.545, $CHCl_3$), (2*R*,3*S*,4*S*)-**25**: mp 110–111 °C (*n*-hexane/EtOAc); $[\alpha]_D^{30} = +139.1$ (*c* 0.58, $CHCl_3$), (4*S*)-**26**: mp 90–91 °C (*n*-hexane/EtOAc); $[\alpha]_D^{30} = -2.1$ (*c* 0.91, $CHCl_3$).

3.27. (2*S*,3*S*,4*S*)-2-Amino-4-[2-(5-benzyloxypyridyl)]-3-methyl-butano-4-lactone 27

A mixture of (2*S*,3*S*,4*S*)-**24** (0.165 g, 0.51 mmol) and Ph_3P (0.16 g, 0.61 mmol) in THF (5 ml) was stirred for 30 min at room temperature. After addition of 0.7 ml of H_2O, the reaction mixture was directly chromatographed on silica gel (20 g, $CHCl_3$/MeOH = 50:1) to afford (2*S*,3*S*,4*S*)-**27** (0.139 g, 92%) as a colorless oil. Compound (2*S*,3*S*,4*S*)-**27**: $[\alpha]_D^{26} = -18.0$ (*c* 0.7, $CHCl_3$). FAB-MS *m*/*z*: 299 (M^++1).

3.28. (2*S*,3*S*,4*S*)-2-Benzyloxycarbonylamino-4-[2-(5-benzyloxypyridyl)]-4-*tert*-butyldimethylsilyloxy-3-methylbutanoic acid 2

To a solution of (2*S*,3*S*,4*S*)-**27** (0.13 g, 0.44 mmol) in THF (1 ml) was added aqueous KOH (KOH (0.086 g)–H_2O (1 ml)) at 0 °C, and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was directly subjected to chromatography (Dowex 50WX8-400 (4 g; 1 M aqueous NH_3) and elution and was evaporated under reduced pressure. The resulting residue (crude γ-hydroxy-β-methyl-α-amino acid) was dried for 12 h. To a solution of the resulting residue in MeCN (4 ml) was added *N*-methyl-*N*-(*t*-butyldimethylsilyl)-trifluoroacetamide, and the whole mixture was stirred for 36 h at room temperature. Then *N*-(benzyloxycarbonyl)-succinimide (0.16 g, 0.64 mmol) was added to the above reaction mixture and the whole mixture was further stirred for 36 h at room temperature. To the reaction mixture were added 5% aqueous KH_2PO_4 (30 ml) and brine (20 ml), and the reaction mixture was extracted with AcOEt (20 ml × 3). The organic layer was dried over $MgSO_4$ and evaporated to afford a residue. A mixture of the above residue and K_2CO_3 (0.05 g) in a mixed solvent (THF (2 ml)/MeOH (2 ml)/H_2O (2 ml)) was stirred for 30 min at room temperature. The reaction mixture was diluted with H_2O (10 ml) and brine (20 ml), and extracted with AcOEt (20 ml × 2). The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (7 g, $CHCl_3$/MeOH = 50:1–20:1) to afford a colorless amorphous product (2*S*,3*S*,4*S*)-**2** (0.169 g, 69%). Compound (2*S*,3*S*,4*S*)-**2**: mp 60–61 °C; $[\alpha]_D^{28} = -5.44$ (*c* 0.79, $CHCl_3$). IR (KBr): 2938, 1722, 1250, 1079 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.14 (3H, s), 0.06 (3H, s), 0.80 (3H, d, *J* = 6.8 Hz), 0.89 (9H, s), 2.24 (1H, m), 4.19 (1H, dd, *J* = 7.8, 8.3 Hz), 5.03–5.08 (3H, m), 5.12 (2H, s), 5.68

(1H, d, $J = 7.8$ Hz), 7.2–7.6 (12H, m), 8.26 (1H, d, $J = 2.4$ Hz). ^{13}C NMR ($CDCl_3$): δ 173.5 (s), 156.3 (s), 154.8 (s), 152.5 (s), 136.5 (s), 135.6 (s), 134.0 (d), 128.8 (d), 128.5 (d), 128.5 (d), 128.0 (d), 127.9 (d), 127.6 (d), 124.7 (d), 123.2 (d), 73.6 (d), 70.8 (t), 66.9, (t), 56.7 (d), 44.6 (d), 25.8 (q), 18.0 (s), 10.9 (q), −5.0, (q), −5.2 (q). FAB-MS *m*/*z*: 565 (M^++1). Anal. Calcd for $C_{31}H_{40}N_2O_6Si$: C, 65.93; H, 7.14; N, 4.96. Found: C, 65.45; H, 7.27; N, 4.64.

3.29. (±)-(2,3)-*trans*-(3,4)-*trans*-2-Benzyloxycarbonylamino-4-[2-(5-benzyloxypyridyl)]-3-methyl-butano-4-lactone 29

(1) To a solution of (±)-**27** (0.085 g, 0.29 mmol) in dioxane (3 ml) were added 7% aqueous $NaHCO_3$ (1 ml) and 30% carbobenzyloxy chloride (CbzCl)–toluene solution (0.25 ml), and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt (20 m × 3). The organic layer was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (5 g, *n*-hexane/EtOAc = 2:1) to give (±)-**29** (0.090 g, 73%) as colorless oil. Compound (±)-**29**: IR (KBr): 3330, 2927, 1785, 1532 cm^{-1}. NMR ($CDCl_3$): δ 1.26 (d, $J = 7.4$ Hz, 3H), 2.60–2.70 (1H, m), 4.36 (1H, t, $J = 9.2$ Hz), 4.97 (1H, d, $J = 9.5$ Hz), 5.11 (2H, s), 5.45 (1H, d, $J = 8.2$ Hz), 7.32–7.44 (12H, m), 8.34 (1H, d, $J = 2.2$ Hz). FAB-MS *m*/*z*: 433 (M^++1). (2) To a solution of (±)-**2** (0.05 g, 0.09 mmol) in THF (4 ml) was added TBAF (0.102 g, 0.32 mmol) and the reaction mixture was stirred for 3 h at 50 °C. The reaction mixture was evaporated under reduced pressure and the resulting residue was dried for 2 h. To a mixture of the above residue in MeCN (6 ml) was added 1,3-dicyclohexylcarbodiimide (DCC; 0.072 g, 0.35 mmol), and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (5 g, *n*-hexane/EtOAc = 2:1) to afford (±)-**29** (0.029 g, 74%) as a colorless oil. The NMR data of the present (±)-**29** were identical with those of the previous (±)-**29** described in (1).

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