Asymmetric Synthesis of a Selective Endothelin A Receptor Antagonist

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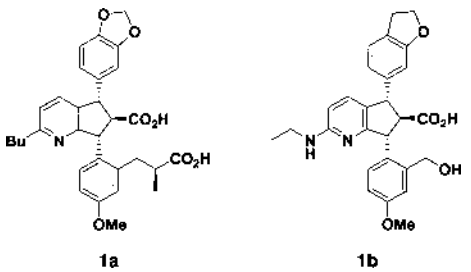
An asymmetric synthesis of a selective endothelin A receptor antagonist 1b is described. Asymmetric conjugate addition of aryllithium derived from 18 to the chiral oxazoline 17 followed by hydrolysis afforded 15 in 96% ee *via* purification as (*S*)-(−)-1-phenylethylamine salt. Pd(OAc)$_2$/dppf (1,1′-bis(diphenylphosphino)ferrocene) catalyzed carbonylation followed by chemoselective addition of aryllithium derived from 23 which gave ketone 24. Diastereoselective reduction of the ketone with catecholborane followed by concomitant activation of the resulting alcohol and cyclization gave the late intermediate 26. Introduction of amino moiety on the pyridine ring by imidoyl rearrangement followed by deprotection and purification by crystallization furnished the enantiomerically pure target molecule 1b in 8% overall yield from 16.

Key words endothelin antagonist; asymmetric conjugate addition; oxazoline; thiomicamine; phosphate mediated cyclization

Endothelin receptor antagonists are currently being evaluated as potential therapeutic agents for the treatment of hypertension, congestive heart failure and renal diseases.[1)] Medicinal chemistry efforts led to the discovery of the earlier drug candidate **1a**, which is a relatively non-selective antagonist for the receptor subtypes.[2—4)] Recently, a more selective endothelin A receptor antagonist **1b** was identified and is being developed as a potentially more effective drug.[5)]

Synthetically, these are quite challenging target molecules. The main common structural feature is the fused five-membered ring with three contiguous stereocenters. Two general approaches can be envisioned as outlined in Chart 1. Both of them require chiral conjugate addition utilizing chiral auxiliary and stereospecific cyclization as the key steps. Earlier work on the synthesis of **1a** showed that both are viable approaches.[6,7)] We have recently disclosed a practical asymmetric synthesis of **1b** utilizing the "bottom to top" approach A.[8)] We have also disclosed an alternative asymmetric synthesis of **1b** starting from amino substituted pyridine utilizing the "top to bottom" approach B.[9)] In this paper, we wish to report another "top to bottom" approach B starting from non-amino substituted pyridine, which can be utilized to further derivatization study of the alkyl amino moiety on the pyridine ring. In this approach, the major challenge is to carry out a series of asymmetric reactions to build the fused cyclopentane ring with three stereocenters. The key steps will include an asymmetric conjugate addition of the top aryl metal to the Michael acceptor **5** or its equivalents, construction of the chiral alcohol **7** followed by the stereospecific cyclization to form the fused five-membered ring with three consecutive stereocenters.

A number of methods have been reported for the stereoselective conjugate additions of chiral α,β-unsaturated esters or their equivalents[10)] including Meyers' oxazoline,[11)] Evans' oxazolidone,[12,13)] and Oppolzer's sultam.[14)] First, several oxazolidinones were evaluated. α,β-Unsaturated carboxylic acid **11** was synthesized from commercially available 2-chloro-3-cyanopyridine **9** *via* DIBAL-H (diisobutylaluminum hydride) reduction of the nitrile group to the aldehyde **10**, Horner–Emmons reaction with $(EtO)_2P(O)CH_2COOEt$ followed by hydrolysis of the ester. Acid chloride of the acid **11** was treated with various oxazolidinone lithium salts to give α,β-



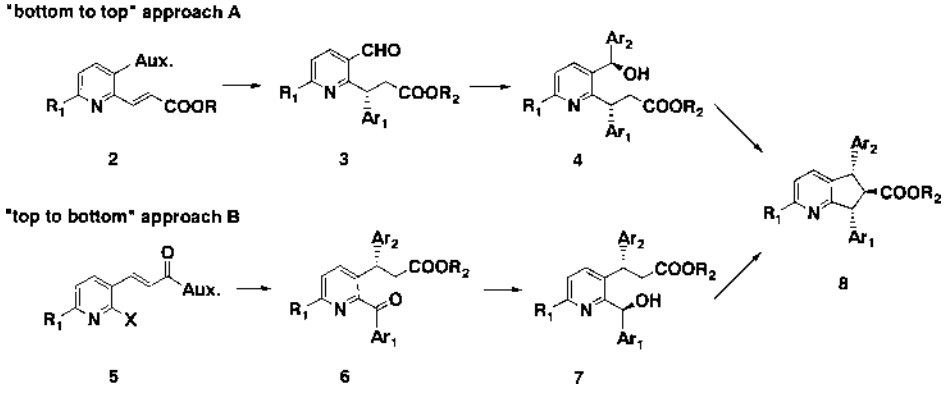


Chart 1

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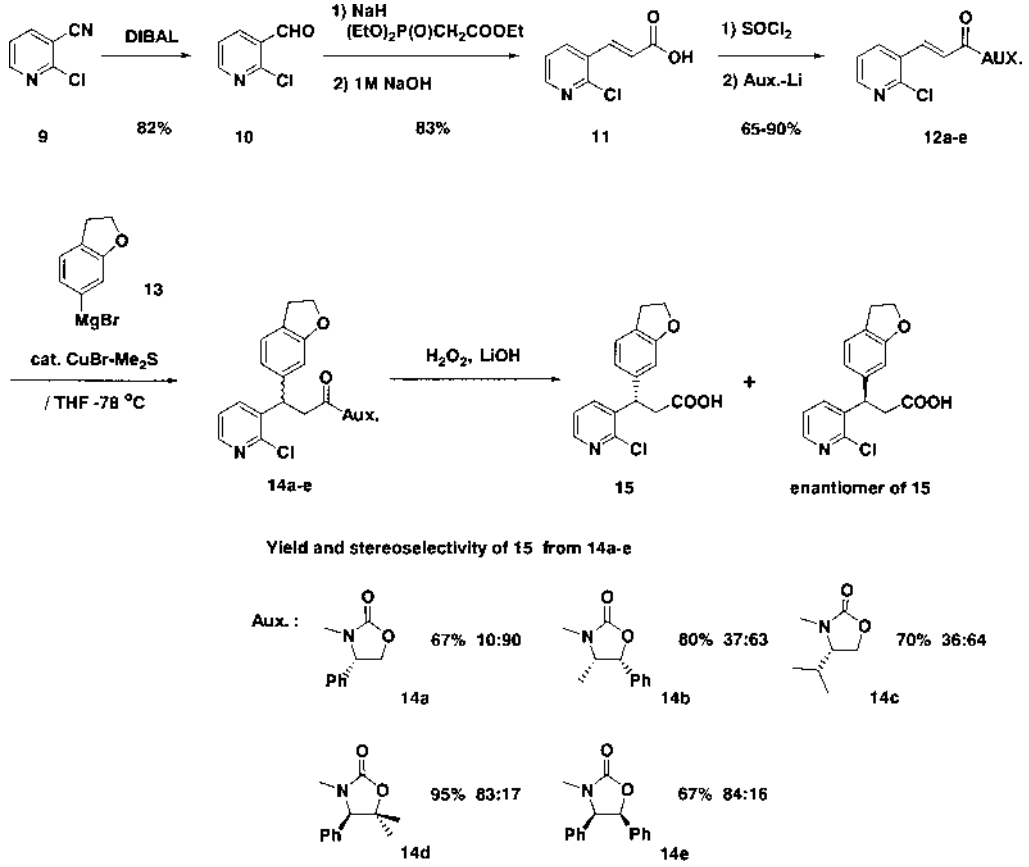

Chart 2

unsaturated oxazolidinones **12a**—**e** with *E*-stereochemistry. The conjugate addition was carried out with a Grignard reagent **13** prepared from 6-bromo-2,3-dihydrobenzofuran **18**[8] in the presence of a catalytic amount of CuBr–Me_2S at −78 °C. The stereoselectivity was determined by chiral HPLC after hydrolysis to the acid **15**. For our substrate, 4-phenyl-2-oxazolidinone **14a** gave good stereoselectivity (80% de) with moderate yield, and 5,5-dimethyl-4-phenyl-2-oxazolidinone **14d** showed moderate stereoselectivity (66% de) with good yield (Chart 2).

However, the result of oxazolidinones was not satisfactory, and an oxazoline derived from inexpensive (1*S*,2*S*)-(+)-thiomicamine was much more economical and thus preferred. Therefore, aldehyde **10** was coupled with the Horner–Emmons reagent generated *in situ* from the oxazoline **16** and $(EtO)_2P(O)Cl$ in the presence of 2 eq of LDA (lithium diisopropylamide) to give the conjugate addition precursor **17** with *E*-stereochemistry. The efficient synthesis of the top aryl bromide **18** (6-bromo-2,3-dihydrobenzofuran) has been reported.[8] The conjugate addition was carried out by 1.5 eq of aryllithium from **18** and the Michael acceptor **17** at −78 °C in THF (tetrahydrofuran) to give the Michael product **19** in 85% de with 63% assay yield. The stereoselectivity was determined by chiral HPLC after hydrolysis to the acid **15**. A significant amount (13%) of double Michael product **20** generated in the reaction was the cause of the lower yield. After many attempts, we found that addition of 1.5—3.0 eq of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) reduced the double Michael product (*ca.* 6%) to give **19** in better assay yield (76%) with 85% de (Chart 3).

The Michael addition product **19** was then hydrolyzed by treatment with sulfuric acid in dioxane–H_2O followed by crystallization from 2-propanol/isopropyl ether to give the optically pure carboxylic acid **15** in <50% yield. A large amount of mother liquor loss was the cause of the lower isolation yield, and no appropriate solvent system had been found to give good isolation yield with satisfactory optical purity. Several amine salt were then evaluated for the isolation, and we found both (*S*) and (*R*)-1-phenylethylamine salt gave good results. Unfortunately, commercially inexpensive racemic 1-phenylethylamine showed no purification effect. Once fairly pure amine salt was isolated in good yield without chromatography, it was treated under acidic conditions and extracted to the organic solvent to give free acid in quantitative recovery yield from the amine salt. Finally, conjugate addition, hydrolysis, amine salt formation and salt break was carried out successively to give pure acid **15** (96% ee) in 60% yield from **17**. The absolute configuration of **15** was determined after converting to **1b**, and the stereochemistry of **1b** was determined by X-ray as the HCl salt. The carboxyl group was then protected by esterification with *tert*-BuOH to give **21** in 91% yield. With the intermediate **21** in hand, methoxycarbonylation of **21**[15] was accomplished with CO (1 kg/cm^2) in methanol in the presence of $NaHCO_3$ and a catalytic amount of $Pd(OAc)_2$ and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) in 97% yield. From the readily accessible 4-bromo-3-hydroxymethylanisole,[6,7] the bottom aryl bromide **23** was prepared by introduction of the PMB (*p*-methoxybenzyl) protecting group to the hydroxymethyl group under standard conditions. Chemoselective addition of aryllithium

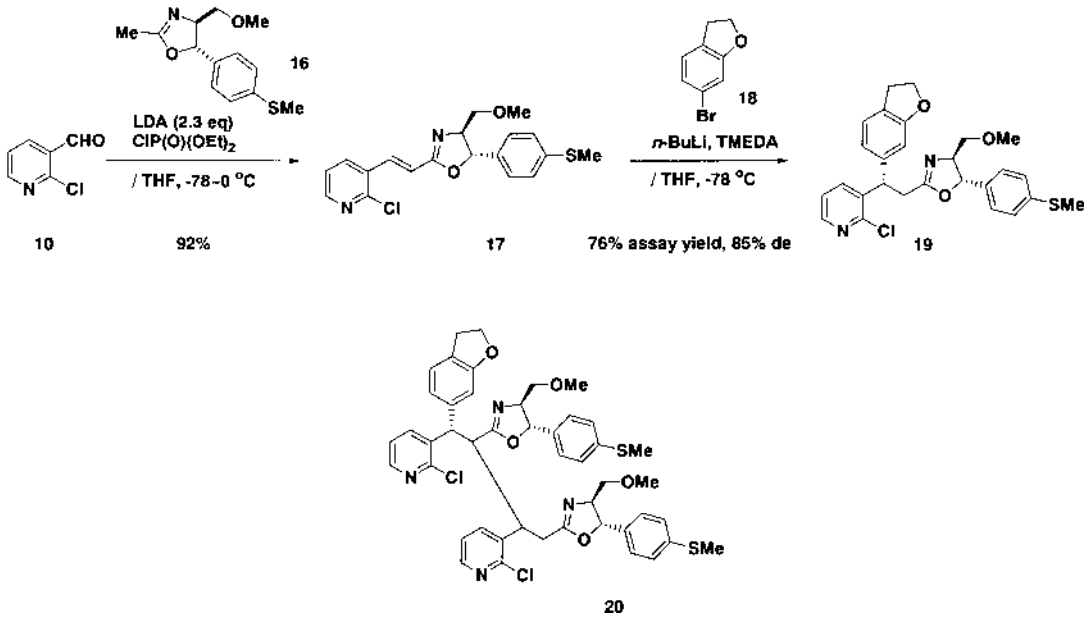

Chart 3

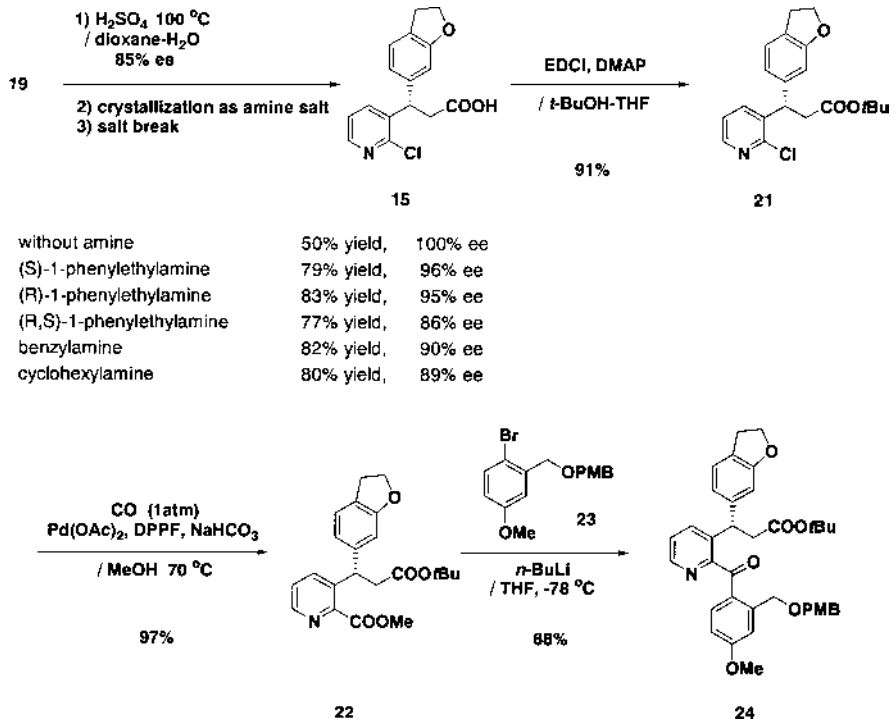

Chart 4

from **23** to the methyl ester of **22** at low temperature afforded ketone **24** in 88% yield (Chart 4).

In order to set up the alkylative cyclization, the ketone needs to be stereoselectively reduced and the resulting alcohol activated. A variety of reducing agents were screened and the results are summarized in Table 1. Catechol borane and 9-BBN gave good selectivity (9/1) in 78—79% yields. BH_3–THF complex, DIBAL-H and Red-Al® gave the same selectivity (4—5/1) in good to moderate yield (47—82%). $Zn(BH_4)_2$, Li-9-BBN-H and LAH (lithium aluminum hydride) also offered essentially the same selectivity (1.2—1.6/1). L-Selectride® offered no selectivity at all (1/1) and $NaBH_4$ gave a slightly opposite selectivity (1/1.4). We chose catecholborane for this reaction and the 9/1 mixture of diastereoisomer was subjected to the next reaction without further purification.

With the crude alcohol **25** in hand, the key cyclization step was then investigated. Based on the experience with earlier drug candidate **1a**, we opted to use a phosphate for activation of the alcohol. Mesylate and tosylate are probably too active and will likely decompose or scramble the stereochemistry of the carbinol. Indeed, the activation of the alcohol and the cy-

clization was accomplished in one step by sequential treatment of **25** with $(EtO)_2POCl$ and LiHMDS [lithium bis-(trimethylsilyl)amide] to give the late intermediate **26**. The reaction presumably involves deprotonation of the alcohol, formation of the phosphate intermediate, enolization of the ester and alkylation of the enolate by the phosphate. The stereospecificity (S_N2 inversion) of this type of cyclization was demonstrated in the synthesis of the **1a**.[6] This also was the basis for the stereochemical assignment for the alcohol stereogenic center in **25**. The isopropyl amino moiety was then introduced on the pyridine ring of the crude intermediate **26** by imidoyl rearrangement[16] *via* pyridine *N*-oxide to give the pure compound **27** after chromatography in 38% yield from alcohol **25**. With the intermediate **27** in hand, all that remained to be done was to remove the three protecting groups. Hydrogenolysis of the PMB ether followed by DIBAL-H reduction gave compound **28** in 87% yield. Then, **28** was treated with TFA (trifluoroacetic acid) and purified by crystallization from MeOH (methanol) to afford the target molecule **1b** in 71% yield with >99% purity as a single enantiomer. (Chart 5).

Table 1. Reduction of Ketone **24**

Reducing agent	Selectivity (desired/undesired)	Yield (%)
Catecholborane	9/1	79
9-BBN	9/1	78
BH_3–THF	5/1	47
DIBAL-H	4/1	82
Red-Al®	4/1	58
$Zn(BH_4)_2$	1.6/1	65
Li-9-BBN-H	1.2/1	94
LAH	1.2/1	85
L-Selectride®	1/1	52
$NaBH_4$	1/1.4	86

The ratio of diastereoisomer was determined by ^{1}H-NMR.

In conclusion, a new asymmetric synthesis of **1b** was accomplished in 8% overall yield from chiral oxazoline **16** in a highly stereo- and regio-controlled manner.

Experimental

Melting points were determined with a Yanaco MP micromelting point apparatus and were not corrected. The ^{1}H-NMR spectra were recorded on a Varian VXR-300 (300 MHz) spectrometer and a JEOL JNM-EX270 (270 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a BRUKER AVANCE500 (125 MHz). IR absorption spectra were recorded on a Horiba FT-200 spectrometer. Specific rotations were measured on a Jasco DIP-370 polarimeter, and mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. The silica gel used for column chromatography was WAKO gel C-300. All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere.

2-Chloro-3-formylpyridine (10) To a suspension of 2-chloro-3-cyanopyridine **9** (173 g, 1.25 mol) in toluene (600 ml) was added 1.0 M DIBAL-H in toluene (1.5 l, 1.5 mol) at −40 °C, and the mixture was warmed to 0 °C. The reaction mixture was poured into a mixed solution of conc. H_2SO_4 (400 ml, 14.4 mol) and ice-cold water (3.6 l), and was stirred vigorously at room temperature until the imine intermediate was consumed completely. The product was extracted with toluene (2×400 ml), and the combined organic layers were washed with water (1 l), sat. $NaHCO_3$ (1 l), then water again (1 l). The organic layer was subjected to the azeotropic distillation with toluene and concentrated to give the crude product (145 g assay) in 82% yield which could be used for the next reaction without further purification. Pure product **10** (117 g) was obtained by crystallization with heptane (200 ml) in 66% yield from **9**. HPLC: column, YMC ODS A-303: eluent, CH_3CN/H_2O (40/60): flow rate, 1.0 ml/min; t_R for **9**, 5.7 min; t_R for **10**, 6.4 min. mp 80 °C. IR (KBr) cm^{-1}: 3043, 2883, 1695, 1572, 1414, 1373, 1261, 1184, 1124, 1065, 824, 808, 725, 621. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.43 (dd, J=7.6, 4.7 Hz, 1H), 8.24 (dd, J=7.6, 2.0 Hz, 1H), 8.62 (dd, J=4.7, 2.0 Hz, 1H), 10.46 (s, 1H). High resolution (HR)-MS electron impact ((EI)) calcd for C_6H_4ClNO $(M)^+$ 140.9981, found 140.9958.

3-(-2-Chloro-3-pyridinyl)-(*E*)-2-propenoic Acid (11) To a suspension of 60% sodium hydride (18.0 g, 0.45 mol) in THF (1400 ml) was added $(EtO)_2P(O)CH_2CO_2Et$ (89.3 ml, 0.45 mol) under nitrogen at 5 °C for 30 min. The mixture was stirred at 1 °C for 30 min and a solution of 2-chloro-3-formylpyridine **10** (42.5 g, 0.30 mol) in THF (100 ml) was added to the mixture at 5—7 °C. The mixture was stirred at 1—3 °C for 1 h and the reaction was quenched with sat. NH_4Cl (300 ml). The product was extracted with *tert*-butyl methyl ether (2×300 ml) and the combined organic solution was

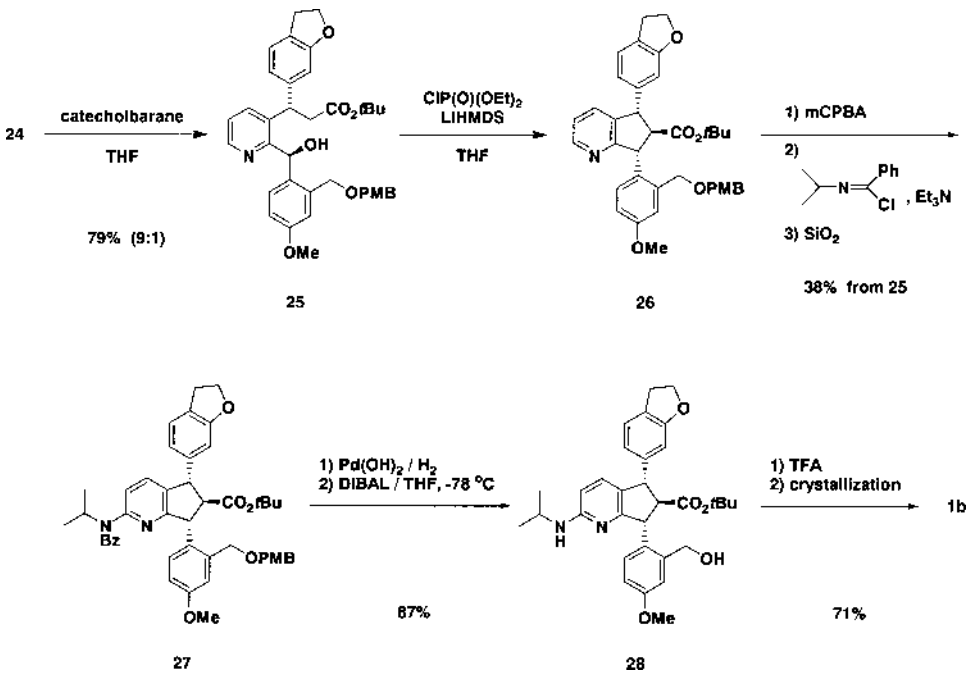

Chart 5

washed with brine (300 ml). After concentration, the product was crystallized from methanol–water to give crystalline ethyl ester of compound **11** (56.2 g) in 89% yield. HPLC: column, YMC ODS A-303: eluent, CH_3CN/H_2O (50/50): flow rate, 1.0 ml/min; t_R for **11**, 8.30 min. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.28 (t, 3H), 4.22 (q, 2H), 6.38 (d, 1H), 7.22 (dd, 1H), 7.85 (dd, 1H), 7.90 (d, 1H), 8.32 (dd, 1H).

To a solution of the above ester (56.2 g, 0.266 mol) in methanol (600 ml) was added 1 M NaOH (400 ml, 0.40 mol), and the mixture was stirred at 50 °C for 1 h. After cooling to room temperature, the mixture was washed with *tert*-butyl methyl ether (1700 ml). The product in the organic layer was extracted with 1 M NaOH (2×400 ml) and the combined aqueous layer was adjusted to pH 2 with 6 M HCl. The product was extracted with ethyl acetate (4×1000 ml) and the combined organic layer was washed with brine (700 ml) and concentrated to dryness to give compound **11** (45.6 g) in 93% yield (83% yield from **10**). HPLC: column, YMC ODS A-303: eluent, CH_3CN/H_2O (50/50): flow rate, 1.0 ml/min; t_R for **11**, 1.88 min. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.48 (d, 1H), 7.33 (dd, 1H), 7.42 (dd, 1H), 8.06 (d, 1H), 8.43 (dd, 1H).

Oxazolidinone Derivatives (12a—e) To a solution of compound **11** (29.9 g, 0.163 mol) in $CHCl_3$ (300 ml) was added $SOCl_2$ (33.5 ml, 0.459 mol) and the mixture was refluxed for 2 h. After cooling to room temperature, the mixture was concentrated and residual $SOCl_2$ was eliminated by azeotropic distillation with toluene. The residue was dissolved in THF (50 ml) and the solution was used as 1.5 M solution of acid chloride of compound **11**.

(*S*)-(+)-4-Phenyl-2-oxazolidinone (3.56 g, 21.8 mmol) was dissolved in THF (70 ml) under nitrogen and cooled to −72 °C. To the solution was added *n*-BuLi (*n*-butyl lithium, 1.40 M in hexane, 15.6 ml, 21.8 mmol) keeping the temperature below −66 °C, and then the acid chloride solution (1.5 M, 21.8 ml, 32.7 mmol) keeping the temperature below −72 °C. After stirring at −72 °C for 30 min, water (500 ml) was added and the mixture was stirred vigorously at room temperature. The product was extracted with ethyl acetate (4×70 ml) and the combined organic layer was washed with sat. $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$, and concentrated to dryness to give the crude product. The yellow solid was crystallized from toluene–heptane to give the crystalline compound **12a** (6.07 g) in 85% yield. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.29 (dd, 1H), 4.36 (dd, 1H), 5.57 (dd, 1H), 7.44—7.26 (m, 6H), 7.93 (d, 1H), 8.04 (dd, 1H), 8.06 (d, 1H), 8.40 (m, 1H).

In a similar manner, compounds **12b**—**e** were prepared.

12b was prepared from **11** and (4*S*,5*R*)-(−)-4-methyl-5-phenyl-2-oxazolidinone in 65% yield. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.94 (d, 3H), 0.97 (d, 3H), 2.29 (m, 1H), 4.25 (dd, 1H), 4.29 (dd, 1H), 4.60 (ddd, 1H), 7.24 (dd, 1H), 7.95 (d, 1H), 8.06 (dd, 1H), 8.14 (d, 1H), 8.40 (m, 1H).

12c was prepared from **11** and (4*S*)-(−)-4-isopropyl-2-oxazolidinone in 32% yield. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.00 (d, 3H), 4.88 (dq, 1H), 5.74 (d, 1H), 7.46—7.28 (m, 6H), 7.94 (d, 1H), 8.08 (dd, 1H), 8.17 (d, 1H), 8.42 (dd, 1H).

12d was prepared from **11** and (4*R*)-5,5-dimethyl-4-phenyl-2-oxazolidinone in 83% yield. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.06 (s, 3H), 1.65 (s, 3H), 5.20 (s, 1H), 7.43—7.20 (m, 6H), 8.03 (d, 1H), 8.07 (dd, 1H), 8.10 (d, 1H), 8.40 (m, 1H).

12e was prepared from **11** and (4*R*,5*S*)-4,5-diphenyl-2-oxazolidinone in 90% yield. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.80 (d, 1H), 6.00 (d, 1H), 7.13—6.89 (m, 10H), 7.33 (dd, 1H), 8.05 (d, 1H), 8.08 (dd, 1H), 8.14 (d, 1H), 8.40 (m, 1H).

Michael Addition to Oxazolidinone Derivatives (12a—e) Followed by Hydrolysis A suspension of magnesium granules (2.08 g, 85.6 mol) in THF (20 ml) was refluxed under the nitrogen atmosphere. To the mixture was added a solution of 6-bromo-2,3-dihydro-1-benzofuran **18** (14.2 g, 71.3 mmol) in THF (55 ml) for 40 min, and the mixture was stirred at 70 °C for 2 h. After cooling, titration of the mixture showed 0.76 M of the Grignard reagent **13**.

To a solution of $CuBr\cdot Me_2S$ (93.7 mg, 0.46 mmol) in THF (2.8 ml) was added the above Grignard reagent (0.76 M, 3 ml, 2.28 mmol) at 5 °C under the nitrogen atmosphere, and the mixture was stirred for 20 min. The mixture was cooled to −78 °C and a solution of oxazolidinone derivatives (**12a**—**e**) (1.52 mmol) in THF was added at −78 °C for 10 min. After stirring at −78 °C for 1 h, the reaction was quenched with sat. NH_4Cl (30 ml) and the mixture was stirred vigorously at room temperature for 1 h. The product was extracted with *tert*-butyl methyl ether (3×40 ml), and the combined organic layer was washed with water (20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$, and concentrated to dryness. The product was subjected to the next reaction without further purification.

The above residue was dissolved in THF (6 ml) and water (6 ml). After cooling to 0 °C, 30% H_2O_2 (0.54 ml, 4.76 mol) and LiOH (99.9 mg, 2.38 mmol) was added to the solution, and the mixture was stirred at room temperature for 40 min. After cooling to 0 °C, the reaction was quenched with 1 M sodium sulfate (6 ml) and sat $NaHCO_4$ (10 ml). Heptane (10 ml) was added to the mixture and the aqueous layer was separated and washed with *tert*-butyl methyl ether (20 ml). The aqueous layer was acidified (pH 1) with 6 M HCl, and the product was extracted with *tert*-butyl methyl ether (3×30 ml). The combined organic layer was washed with brine (20 ml) and concentrated to dryness to give enantiomeric mixture of compound **15**. The stereoselectivity was determined by chiral HPLC at this stage. HPLC: column, DAICEL CHIRALCEL OJ: eluent, 2-propanol/ethanol/TFA (600/400/1): flow rate, 0.5 ml/min; t_R for **15**, 16.0 min; t_R for enantiomer, 14.5 min.

2-Chloro-3-{(*E*)-[2-(4*S*,5*S*)-4-methoxymethyl-5-(4-methylthiophenyl)-4,5-dihydro-1,3-oxazol-2-yl]vinyl}pyridine (17) To a solution of diisopropylamine (149 ml, 1.06 mol) in THF (600 ml) was added *n*-BuLi (1.66 M in hexane, 583 ml, 968 mmol) at −78 °C. A solution of (4*S*,5*S*)-4-methoxymethyl-2-methyl-5-(4-methylthiophenyl)-4,5-dihydro-1,3-oxazole **16** (106 g, 422 mmol) in THF (200 ml) was added dropwise to the LDA solution at the same temperature and stirred at −78 °C for 30 min. $ClPO(OEt)_2$ (66.9 ml, 463 mmol) was added at −78 °C, then the reaction mixture was warmed to 0 °C and stirred for 30 min. A solution of **10** (65.5 g, 463 mmol) in THF (200 ml) was added dropwise to the reaction mixture and the mixture was stirred for 30 min at 0 °C. The reaction was quenched with 10% NH_4Cl and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by silica gel column chromatography (C-300, hexane/ethyl acetate=1/1) to give pure compound **17** (146 g) in 92% yield as a solid. HPLC: column, YMC ODS A-303: eluent, CH_3CN/H_2O (80/20): flow rate, 1.0 ml/min; t_R for **17**, 5.34 min. mp 63—69 °C. $[\alpha]_D^{20}=+157°$ (c=1.0, $CHCl_3$). IR (KBr) cm^{-1}: 2918, 2887, 1655, 1605, 1560, 1406, 1325, 1126, 1084, 1063, 974, 808. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.49 (3H, s), 3.44 (3H, s), 3.60 (dd, J=9.7, 6.0 Hz, 1H), 3.67 (dd, J=9.7, 4.5 Hz, 1H), 4.21—4.30 (m, 1H), 5.40 (d, J=7.2 Hz, 1H), 6.72 (d, J=16.4 Hz, 1H), 7.22—7.32 (m, 4H), 7.30 (dd, J=7.8, 4.7 Hz, 1H), 7.75 (d, J=16.4 Hz, 1H), 7.93 (dd, J=7.8, 1.9 Hz, 1H), 8.37 (dd, J=4.7, 1.9 Hz, 1H). HR-MS (FAB) calcd for $C_{19}H_{20}ClN_2O_2S$ $(M+1)^+$ 375.0934, found 375.0927.

(3*S*)-3-(-2-Chloro-3-pyridinyl)-3-(2,3-dihydro-1-benzofuran-6-yl)-propanoic Acid (15) To a solution of 6-bromo-2,3-dihydro-1-benzofuran **18** (47.9 g, 0.241 mol) in THF (1.2 l), was added dropwise *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (72.7 ml, 0.482 mol) and *n*-BuLi (1.53 M in hexane, 158 ml, 0.242 mol) at −78 °C, and the mixture was stirred for 30 min. A solution of oxazoline **17** (60.2 g, 0.161 mol) in THF (200 ml) was added dropwise for 15 min. The reaction was quenched by addition of acetic acid (41 ml) and water (1.2 l), and the product was extracted with *tert*-butyl methyl ether (720 ml). HPLC assay showed 76% assay yield of compound **19** in the solution. After concentration of the organic layer, the residue was dissolved in a mixed solution of 1,4-dioxane (276 ml) and water (276 ml). conc. H_2SO_4 (128 ml) was added to the mixture and the mixture was stirred at 110 °C for 1.5 h. The reaction mixture was cooled to room temperature and the solution was adjusted to pH 2 with 6 N NaOH (642 ml). Once the product was extracted with ethyl acetate (513 ml) and extracted again with 0.2 N NaOH (2×321 ml) from the organic layer, the combined aqueous layer was acidified (pH 3) with 2 N HCl and the product was extracted with ethyl acetate (321 ml). The organic layer was washed with water, dried over $MgSO_4$, and concentrated to 149 g. Chiral HPLC showed 85% ee of the stereoselectivity in this stage. The solution was diluted with ethyl acetate (74.9 g) and (*S*)-(−)-1-phenylethylamine (19.0 ml, 147 mmol) was added. The mixture was stirred at room temperature overnight and the resulting crystal was filtered, washed with *tert*-butyl methyl ether, and dried to give (*S*)-(−)-1-phenylethylamine salt of compound **15** (41.1 g, 96% ee) in 60% yield from **17**. IR (KBr) cm^{-1}: 2935, 1620, 1541, 1385, 1244, 1184, 1074, 987, 752, 700. The amine salt (15.7 g, 36.9 mmol) was suspended in ethyl acetate (100 ml) and water (100 ml), and the pH was adjusted to 3.0 with 2 N HCl (19 ml). The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated to dryness to give crystalline compound **15** (11.2 g) in quantitative yield from amine salt. HPLC: column, YMC ODS A-303: eluent, CH_3CN/0.1 M H_3PO_4 (40/60): flow rate, 1.0 ml/min; t_R for **15**, 8.25 min. mp 156—158 °C. $[\alpha]_D^{20}=+20.6°$ (c=1.000, DMSO). IR (KBr) cm^{-1}: 2908, 2517, 1709, 1578, 1495, 1408, 1331, 1238, 1186, 1095, 984, 955, 802. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.01 (dd, J=16.3, 8.1 Hz, 1H), 3.07 (dd, J=16.3, 7.8 Hz, 1H), 3.16 (t, J=8.6 Hz, 2H), 4.55 (t, J=8.6 Hz, 2H), 4.92 (dd, J=8.1, 7.8 Hz, 1H), 6.64 (d, J=1.3 Hz, 1H), 6.73 (dd, J=7.6, 1.3 Hz, 1H), 7.11 (d, J=7.6 Hz, 1H), 7.21 (dd, J=7.7,

4.6 Hz, 1H), 7.59 (dd, *J*=7.7, 1.7 Hz, 1H), 8.26 (dd, *J*=4.6, 1.7 Hz, 1H). HR-MS (FAB) calcd for $C_{16}H_{15}ClNO_3$ $(M+1)^+$ 304.0740, found 304.0757.

***tert*-Butyl (3*S*)-3-(2-Chloro-3-pyridinyl)-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (21)** To a solution of compound **15** (9.29 g, 30.6 mmol) in THF (69 ml) was added *tert*-butyl alcohol (19.8 ml), 4-dimethylaminopyridine (5.59 g, 45.8 mmol) and EDCl (8.79 g, 45.9 mmol), and the mixture was stirred at room temperature for 5 h. *tert*-Butyl methyl ether (70 ml) was added to the reaction mixture, and the organic solution was washed with 10% citric acid (80+50 ml), sat. $NaHCO_4$ (50 ml), water (50 ml) and brine (50 ml) successively. The organic layer was dried over $MgSO_4$ and concentrated to dryness to give crystalline compound **21** (10.0 g) in 91% yield. HPLC: column, YMC ODS A-303: eluent, CH_3CN/H_2O (70/30): flow rate, 1.0 ml/min; t_R for **21**, 9.21 min. Chiral HPLC: column, DAICEL CHIRALPAK AD: eluent, hexane/2-propanol (85/15): flow rate, 1.0 ml/min; t_R for ester **21**, 6.8 min; t_R for enantiomer, 8.2 min. mp 49 °C. $[\alpha]_D^{20}=-16.6°$ (c=1.000, $CHCl_3$). IR (KBr) cm^{-1}: 2974, 1724, 1566, 1493, 1404, 1365, 1211, 1147, 1068, 987, 951, 770. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 9H), 2.90 (dd, *J*=15.4, 8.0 Hz, 1H), 2.97 (dd, *J*=15.4, 8.4 Hz, 1H), 3.17 (t, *J*=8.6 Hz, 2H), 4.55 (t, *J*=8.6 Hz, 2H), 4.90 (dd, *J*=8.4, 8.0 Hz, 1H), 6.65 (d, *J*=1.5 Hz, 1H), 6.74 (dd, *J*=7.6, 1.5 Hz, 1H), 7.11 (d, *J*=7.6 Hz, 1H), 7.21 (dd, *J*=7.8, 4.7 Hz, 1H), 7.64 (dd, *J*=7.8, 1.9 Hz, 1H), 8.26 (dd, *J*=4.7, 1.9 Hz, 1H). HR-MS (FAB) calcd for $C_{20}H_{23}ClNO_3$ $(M+1)^+$ 360.1366, found 360.1362.

***tert*-Butyl (3*S*)-3-(2-Methoxycarbony-3-pyridinyl)-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (22)** A mixture of compound **21** (3.00 g, 8.34 mmol), $NaHCO_3$ (840 mg, 10.0 mmol), $Pd(OAc)_2$ (187 mg, 0.833 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (462 mg, 0.833 mmol) in methanol (30 ml) was treated under CO (1 kg/cm^2) at 70 °C for 18 h. The reaction mixture was filtered through celite®, and the filtrate was diluted with ethyl acetate. The organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by silica gel column chromatography (C-300, hexane/ethyl acetate=7/3) to give pure compound **22** (3.09 g) in 97% yield as an oil. HPLC: column, YMC ODS A-303: eluent, CH_3CN/H_2O (70/30): flow rate, 1.0 ml/min; t_R for **22**, 6.63 min. $[\alpha]_D^{20}=-82.5°$ (c=1.0, MeOH). IR (KBr) cm^{-1}: 1720, 1614, 1427, 1296, 1198, 1140, 1093, 987, 955, 770, 627, 500. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (s, 9H), 2.95 (d, *J*=8.2 Hz, 2H), 3.16 (t, *J*=8.6 Hz, 2H), 3.99 (s, 3H), 4.55 (t, *J*=8.6 Hz, 2H), 5.35 (t, *J*=8.2 Hz, 1H), 6.70 (d, *J*=0.9 Hz, 1H), 6.77 (dd, *J*=7.6, 0.9 Hz, 1H), 7.10 (d, *J*=7.6 Hz, 1H), 7.38 (dd, *J*=8.0, 4.6 Hz, 1H), 7.73 (dd, *J*=8.0, 1.4 Hz, 1H), 8.54 (dd, *J*=4.6, 1.4 Hz, 1H). HR-MS (FAB) calcd for $C_{22}H_{26}NO_5$ $(M+1)^+$ 384.1811, found 384.1826.

***tert*-Butyl (3*S*)-3-{2-[4-Methoxy-2-(4-methoxy-benzyloxymethyl)benzoyl]-3-pyridinyl}-3-(2,3-dihydro-1-benzofuran-6yl)propanoate (24)** To a solution of 4-Bromo-3-(4-methoxybenzyloxymethyl)anisole **23** (1.55 g, 4.60 mmol) in THF (16 ml) was added dropwise *n*-BuLi (1.63 M in hexane, 2.82 ml, 4.60 mmol) at −78 °C, and the mixture was stirred for 30 min. The mixture was added dropwise to a cold solution of compound **22** (1.59 g, 4.15 mmol) in THF (28 ml) at −78 °C for 2 min and the whole was stirred for 10 min. The reaction was quenched with sat. NH_4Cl and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by silica gel column chromatography (C-300, hexane/ethyl acetate=7/3) to give pure compound **24** (2.23 g) in 88% yield as an oil. $[\alpha]_D^{20}=-77.4°$ (c=1.0, MeOH). IR (KBr) cm^{-1}: 1722, 1655, 1601, 1566, 1502, 1433, 1290, 1198, 1140, 1034, 949, 812, 758, 623, 498. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (s, 9H), 2.88 (dd, *J*=15.5, 8.8 Hz, 1H), 2.98 (dd, *J*=15.5, 7.3 Hz, 1H), 3.04 (t, *J*=8.6 Hz, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 4.46 (t, *J*=8.6 Hz, 2H), 4.62 (s, 2H), 4.74 (dd, *J*=8.8, 7.3 Hz, 1H), 5.06 (s, 2H), 6.54 (d, *J*=1.4 Hz, 1H), 6.55—6.65 (m, 2H), 6.87—6.97 (m, 3H), 7.08 (d, *J*=8.7 Hz, 1H), 7.12—7.44 (m, 4H), 7.73 (dd, *J*=8.1, 1.5 Hz, 1H), 8.44 (dd, *J*=4.7, 1.5 Hz, 1H). HR-MS (FAB) calcd for $C_{37}H_{40}NO_7$ $(M+1)^+$ 610.2805, found 610.2806.

***tert*-Butyl (3*S*)-3-{2-{(*S*)-Hydroxy[4-methoxy-2-(4-methoxybenzyloxymethyl)phenyl]methyl-3-pyridinyl}-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (25)** To a solution of compound **24** (7.78 g, 12.8 mmol) in THF (60 ml) was added catecholborane (1.0 M in THF, 40 ml, 40 mmol) at −10 °C and the mixture was stirred at room temperature for 1 h. The reaction was quenched with 30% H_2O_2 and 1 N NaOH by stirring at room temperature for 1 h, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated to dryness to give compound **25** (9 : 1 mixture of diastereomer, 6.19 g) in 79% yield as an oil. A pure sample of **25** was obtained through silica gel column chromatography (C-300, hexane/ethyl acetate=7/3). IR (KBr) cm^{-1}: 1722, 1608, 1502, 1431, 1363, 1292, 1209, 1151, 1032, 814, 629, 503. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 9H), 2.29 (dd, *J*=15.8, 6.7 Hz, 1H), 2.58 (dd, *J*=15.8, 9.2 Hz, 1H), 3.13 (t, *J*=8.6 Hz, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 3.95—4.10 (m, 1H), 4.29 (dd, *J*=9.2, 6.7 Hz, 1H), 4.40—4.63 (m, 4H), 4.67 (d, *J*=12.5 Hz, 1H), 4,82 (d, *J*=12.5 Hz, 1H), 6.11 (s, 1H), 6.46 (d, *J*=1.5 Hz, 1H), 6.52 (dd, *J*=7.6, 1.5 Hz, 1H), 6.59—6.71 (m, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 6.99 (d, *J*=7.6 Hz, 1H), 7.08 (d, *J*=2.3 Hz, 1H), 7.33 (d, *J*=8.8 Hz, 2H), 7.38 (dd, *J*=7.9, 4.9 Hz, 1H), 7.76 (dd, *J*=7.9, 1.2 Hz, 1H), 8.58 (dd, *J*=4.9, 1.2 Hz, 1H). HR-MS (FAB) calcd for $C_{37}H_{42}NO_7$ $(M+1)^+$ 612.2961, found 612.2966.

Diastereomer (Less Polar): IR (KBr) cm^{-1}: 3417, 1720, 1614, 1504, 1433, 1209, 1149, 1032, 814, 764, 636, 505. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 9H), 2.68 (dd, *J*=15.5, 7.6 Hz, 1H), 2.75 (dd, *J*=15.5, 9.2 Hz, 1H), 3.03 (t, *J*=8.6 Hz, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 4.19 (br s, 1H), 4.44 (t, *J*=8.6 Hz, 2H), 4.37—4.72 (m, 4H), 5.00 (d, *J*=12.1 Hz, 1H), 5.95—6.04 (m, 2H), 6.39—6.50 (m, 3H), 6.79 (d, *J*=7.3 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.00 (d, *J*=2.3 Hz, 1H), 7.29—7.40 (m, 3H), 7.69 (dd, *J*=7.7, 1.1 Hz, 1H), 8.54 (dd, *J*=4.8, 1.1 Hz, 1H). HR-MS (FAB) calcd for $C_{37}H_{42}NO_7$ $(M+1)^+$ 612.2961, found 612.2966.

***tert*-Butyl (5*S*,6*R*,7*R*)-2-(*N*-Benzoyl-*N*-isopropylamino)-5-(2,3-dihydro-1-benzo-furan-6-yl)-7-[4-methoxy-2-(4-methoxybenzyloxymethyl)-phenyl]-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-6-carboxylate (27)** To a solution of compound **25** (9 : 1 mixture of diastereomer, 5.53 g, 9.04 mmol) in THF (70 ml) was added $(EtO)_2POCl$ (2.0 ml, 13.8 mmol) and LiHMDS (1.0 M in THF, 45 ml, 45 mmol) at −10 °C under nitrogen. The reaction mixture was stirred for 30 min at room temperature then quenched with sat. NH_4Cl. The product was extracted with EtOAc, and the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated to dryness. HPLC assay indicated 84% assay yield of **26** in the residue. Analytical data of pure **26**: IR (KBr) cm^{-1}: 1718, 1610, 1583, 1504, 1427, 1205, 1147, 1038, 989, 816, 766. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 9H), 3.22 (t, *J*=8.6 Hz, 2H), 3.32 (t, *J*=10.0 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.40—4.65 (m, 6H), 4.72 (br, 1H), 4.94 (d, *J*=10.2 Hz, 1H), 6.67 (s, 1H), 6.76 (d, *J*=7.6 Hz, 1H), 6.82 (d, *J*=9.0 Hz, 1H), 6.83 (d, *J*=8.2 Hz, 2H), 6.96—7.08 (m, 2H), 7.09 (d, *J*=4.8 Hz, 1H), 7.15 (d, *J*=7.6 Hz, 1H), 7.27 (s, 1H), 7.28 (d, *J*=8.2 Hz, 2H), 8.42 (d, *J*=4.8 Hz, 1H). HR-MS (FAB) calcd for $C_{37}H_{40}NO_6$ $(M+1)^+$ 594.2856, found 594.2831.

The crude **26** was dissolved in $CHCl_3$ (60 ml), and 3-chloroperoxybenzoic acid (5.46 g, 31.6 mmol) was added to the solution at 0 °C under nitrogen. The mixture was stirred at 0 °C for 12 h, and the reaction was quenched with sodium thiosulfate solution. The product was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated to dryness. The residue was dissolved in $CHCl_3$ (60 ml) again, and triethylamine (7.6 ml, 54.5 mmol) and Isopropylbenzimidoyl chloride (4.90 g, 27.0 mmol) were added to the solution. The mixture was stirred at 70 °C for 7 h, and the reaction was quenched with water. The product was extracted with ethyl acetate, and the organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$, concentrated to dryness, and purified by silica gel column chromatography (C-300, hexane/ethyl acetate=8/2) to give compound **27** (2.60 g) in 38% yield from **25**. IR (KBr) cm^{-1}: 3369, 1714, 1641, 1581, 1502, 1439, 1942, 1200, 1142, 708, 631, 498. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.09 (d, *J*=6.9 Hz, 3H), 1.17 (d, *J*=6.9 Hz, 3H), 1.31 (s, 9H), 3.19 (t, *J*=8.6 Hz, 2H), 3.26 (dd, *J*=9.9, 8.6 Hz, 1H), 3.76 (s, 3H), 3.83 (s, 3H), 4.46 (d, *J*=8.6 Hz, 1H), 4.51 (s, 2H), 4.57 (t, *J*=8.6 Hz, 2H), 4.41—4.63 (m, 1H), 4.81 (d, *J*=15.5 Hz, 1H), 4.88—5.05 (m, 1H), 5.02 (d, *J*=9.9 Hz, 1H), 6.50—6.55 (m, 2H), 6.63 (d, *J*=7.6 Hz, 1H), 6.71—6.87 (m, 4H), 6.96—7.04 (m, 2H), 7.06—7.33 (m, 8H). HR-MS (FAB) calcd for $C_{47}H_{51}N_2O_7$ $(M+1)^+$ 755.3696, found 755.3673.

***tert*-Butyl (5*S*,6*R*,7*R*)-5-(2,3-Dihydro-1-benzofuran-6-yl)-7-[2-(hydroxymethyl)-4-methoxy-phenyl]-2-(isopropylamino)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-6-carboxylate (28)** To a solution of compound **27** (2.60 g, 3.44 mmol) in ethyl acetate (30 ml) and methanol (30 ml) was added 20% $Pd(OH)_2$ (4.00 g), and the mixture was hydrogenated at ambient temperature under H_2 (1 kg/cm^2) for 2 d. The reaction mixture was filtered through Celite® and the filtrate was concentrated to dryness. The residue was dissolved in THF (34 ml), and DIBAL (1.01 M in toluene, 17 ml, 17.2 mmol) was added to the solution under nitrogen at −78 °C for 10 min. After stirring at −78 °C for 1 h, the reaction was quenched with sat. NH_4Cl, and the product was extracted with ethyl acetate. The organic layer was washed with 1 N $KHSO_4$ and brine, dried over $MgSO_4$, and concentrated to dryness to give compound **28** (1.59 g) in 87% yield as a solid. mp 72 °C. $[\alpha]_D^{20}=+37.8°$ (c=1.0, MeOH). IR (KBr) cm^{-1}: 3250, 2964, 2359, 1713, 1603, 1495, 1435, 1367, 1201, 1142, 764, 631, 500. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.09 (d, *J*=6.3 Hz, 3H), 1.14 (d, *J*=6.3 Hz, 3H), 1.36 (s, 9H), 3.23 (t, *J*=8.6 Hz, 2H), 3.46 (dd, *J*=8.5, 7.7 Hz, 1H), 3.60—3.75 (m, 1H), 3.81 (s, 3H), 4.29 (d,

J=7.9 Hz, 1H), 4.46 (d, J=11.5 Hz, 1H), 4.52 (d, J=7.7 Hz, 1H), 4.60 (t, J=8.6 Hz, 2H), 4.98 (d, J=8.5 Hz, 1H), 5.03 (d, J=11.5 Hz, 1H), 6.15 (d, J=8.5 Hz, 1H), 6.73—6.85 (m, 3H), 6.98 (d, J=2.0 Hz, 1H), 7.04—7.14 (m, 2H), 7.18 (d, J=7.6 Hz, 1H). HR-MS (FAB) calcd for $C_{32}H_{39}N_2O_5$ $(M+1)^+$ 531.2859, found 531.2866.

(5*S*,6*R*,7*R*)-5-(2,3-Dihydro-1-benzofuran-6-yl)-7-[2-(hydroxymethyl)-4-methoxy-phenyl]-2-(isopropylamino)-6,7-dihydro-5*H*-cyclopenta[*b*]-pyridine-6-carboxylic Acid (1b) Compound **27** (21.0 g, 39.6 mmol) was treated with TFA (63 ml) at the ambient temperature for 1 h, and the mixture was concentrated to dryness. Water (100 ml) and ethyl acetate (200 ml) were added to the residue and the mixture was neutralized with $NaHCO_3$. After separation, the product was extracted with ethyl acetate (2×100 ml). The combined organic layer was dried over $MgSO_4$, and concentrated to dryness. The solid residue was crystallized from ethanol to give the title compound **1b** (13.3 g, 99.9% ee) as a white crystalline solid in 71% yield. HPLC: column, DAICEL CHIRALPAK AD: eluent, hexane/2-propanol/CF_3COOH (700/300/1): flow rate, 1.0 ml/min; t_R for **1b**, 8.5 min; t_R for enantiomer, 13.5 min. mp 203 °C (dec.). $[\alpha]_D^{20}=+63°$ (c=1.002, DMF). IR (KBr) cm^{-1}: 2966, 1670, 1618, 1500, 1394, 1250, 1171, 1034, 999, 814, 721. ^{1}H-NMR (300 MHz, DMSO) δ: 0.98 (d, J=6.4 Hz, 3H), 1.04 (d, J=6.4 Hz, 3H), 3.01 (dd, J=8.8, 8.6 Hz, 1H), 3.15 (t, J=8.8 Hz, 2H), 3.58—3.75 (m, 1H), 3.73 (s, 3H), 4.33 (d, J=8.6 Hz, 1H), 4.40—4.56 (m, 3H), 4.57—4.73 (m, 2H), 6.25 (d, J=8.3 Hz, 1H), 6.60 (d, J=1.4 Hz, 1H), 6.71 (dd, J=7.6, 1.4 Hz, 1H), 6.75 (dd, J=8.5, 2.9 Hz, 1H), 6.87—6.97 (m, 2H), 7.02 (d, J=2.8 Hz, 1H), 7.18 (d, J=7.6 Hz, 1H). ^{13}C-NMR (125 MHz, DMSO) δ: 22.6, 22.8, 29.2, 42.2, 50.0, 51.5, 55.3, 61.1, 62.0, 71.3, 108.7, 112.5, 120.4, 124.1, 125.3, 126.2, 129.6, 132.0, 134.0, 142.6, 144.2, 158.1, 160.5, 161.9, 175.6. HR-MS (FAB) calcd for $C_{28}H_{31}N_2O_5$ $(M+1)^+$ 475.2233, found 475.2247; *Anal.* Calcd for $C_{28}H_{30}N_2O_5$: C, 70.87; H, 6.37; N, 5.90. Found: C, 70.39; H, 6.43; N, 5.83.

References and Notes

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