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Asymmetric synthesis of a selective endothelin A receptor antagonist

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Abstract—An asymmetric synthesis of a selective endothelin A receptor antagonist **1b** is described. A highly substituted pyridine intermediate **11a** was efficiently prepared via a mono-amination of inexpensive 2,6-dichloropyridine followed by a Vilsmeier formylation. Asymmetric conjugate addition of aryl lithium **14** to the chiral oxazoline **13** followed by hydrolysis afforded **15** in 90% ee. $Pd(OAc)_2$/dppf catalyzed carbonylation followed by chemoselective addition of aryl lithium **18** gave ketone **19**. Diastereoselective reduction of the ketone with LS-Selectride® followed by concomitant activation of the resulting alcohol and cyclization gave the late intermediate **21**. Deprotection and purification by crystallization furnished the enantiomerically pure target molecule **1b** in 10% overall yield from **11a**.

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] Recently, a more selective endothelin A receptor antagonist **1b** was identified and is being developed as a potentially more effective drug.[3]

Synthetically, these are quite challenging target molecules. The main common structural feature is the fused five-member ring with three contiguous chiral centers. Two general approaches can be envisioned as outlined in Scheme 1. Both of them require chiral conjugate addition and stereospecific cyclization as the key steps. Earlier work on the synthesis of **1a** showed that both are viable approaches.[4] We have recently disclosed a practical asymmetric synthesis of **1b** utilizing the 'bottom to top' approach A[5] (Scheme 1). In this paper, we wish to report an alternative synthesis of **1b** adopting the 'top to bottom' approach B. In this approach, the major challenge is to carry out a series of asymmetric reactions to build the fused cyclopentane ring with three chiral centers. The key steps will include preparation of the highly substituted pyridine **8** to access the Michael acceptor **7**, an asymmetric conjugate addition of the top aryl metal to the Michael acceptor **7** or its equivalents, construction of the chiral alcohol **5** followed by the stereospecific cyclization to form the fused five-member ring with three consecutive chiral centers.

The highly substituted pyridine intermediate **11a** was efficiently prepared from inexpensive 2,6-dichloropyridine (**9a**).[6] Amination of **9a** with *i*-Pr(Bn)NH in the presence of catalytic $Pd(DPPF)Cl_2$, DPPF and sodium *tert*-pentoxide in THF at refluxing temperature gave **10a** in only 23–45% yield. Surprisingly, the reaction with *i*-$PrNH_2$ under the same conditions proceeded smoothly to afford 2-chloro-6-isopropylaminopyridine in 96% yield. Subsequent benzylation with BnBr and NaH in THF–DMF at 50°C gave the desired product **10a** in 90%-quant. yield. This two step sequence was replaced by a more efficient process by direct treatment of **9a** with 1.3 equiv. of *i*-Pr(Bn)NLi in toluene to give mono-amination product **10a** in 99% yield. Regioselective Vilsmeier formylation of **10a** by treatment with slight excess of $POCl_3$ in DMF at 70°C gave aldehyde **11a** (Scheme 2). Similar sequence of amination and formylation starting from 2,6-dibromopyridine **9b** gave comparable results.[5,7]

A number of methods have been reported for the stereoselective conjugate additions of chiral α,β-unsaturated esters or their equivalents[8] including Meyers' oxazoline,[9]

Keywords: endothelin antagonist; substituted pyridine; amination; asymmetric conjugate addition; oxazoline; thiomicamine; phosphate mediated cyclization.

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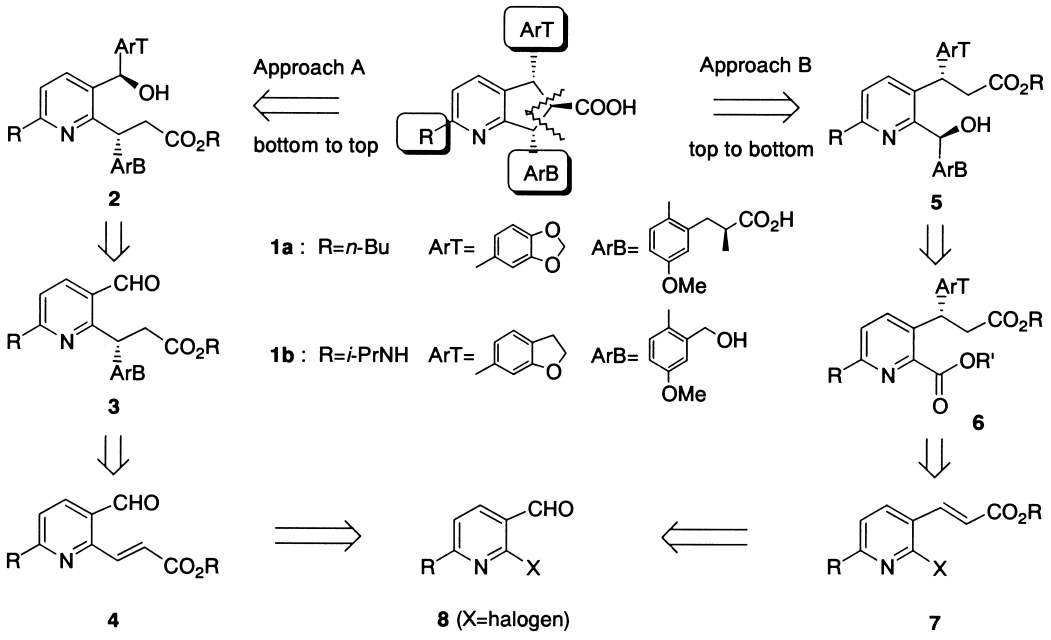


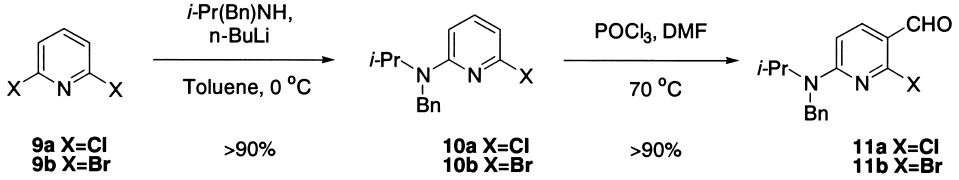
Scheme 1.

Evans' oxazolidone,[10] and Oppolzer's sultam.[11] For our substrate, only (*R*)-4-phenyl-2-oxazolidinone gave satisfactory stereoselectivity and chemical yield among chiral oxazolidinones and sultams evaluated. However, the oxazoline derived from inexpensive (1*S*,2*S*)-(+)-thiomicamine was much more economical and thus preferred. Therefore, aldehyde **11a** was coupled with the Horner–Emmons reagent, generated in situ from the oxazoline **12** and $(EtO)_2P(O)Cl$ in the presence of 2 equiv. of LDA, to give the conjugate addition precursor **13** with *E*-stereochemistry. The efficient synthesis of the top aryl bromide **14**, 6-bromo-2,3-dihydrobenzofuran, has been reported.[5] The conjugate addition was carried out by first reacting *n*-butyl lithium with the aryl bromide **14** at −78°C in THF followed by addition of the Michael acceptor **13**. The addition product was then hydrolyzed by treatment with sulfuric acid in dioxane/H_2O to give the carboxylic acid **15** in 72% isolated yield. The carboxyl group was then protected by esterification with *tert*-BuOH to give **16**. The enantiomeric excess was determined to be 90% ee at this stage by chiral HPLC.

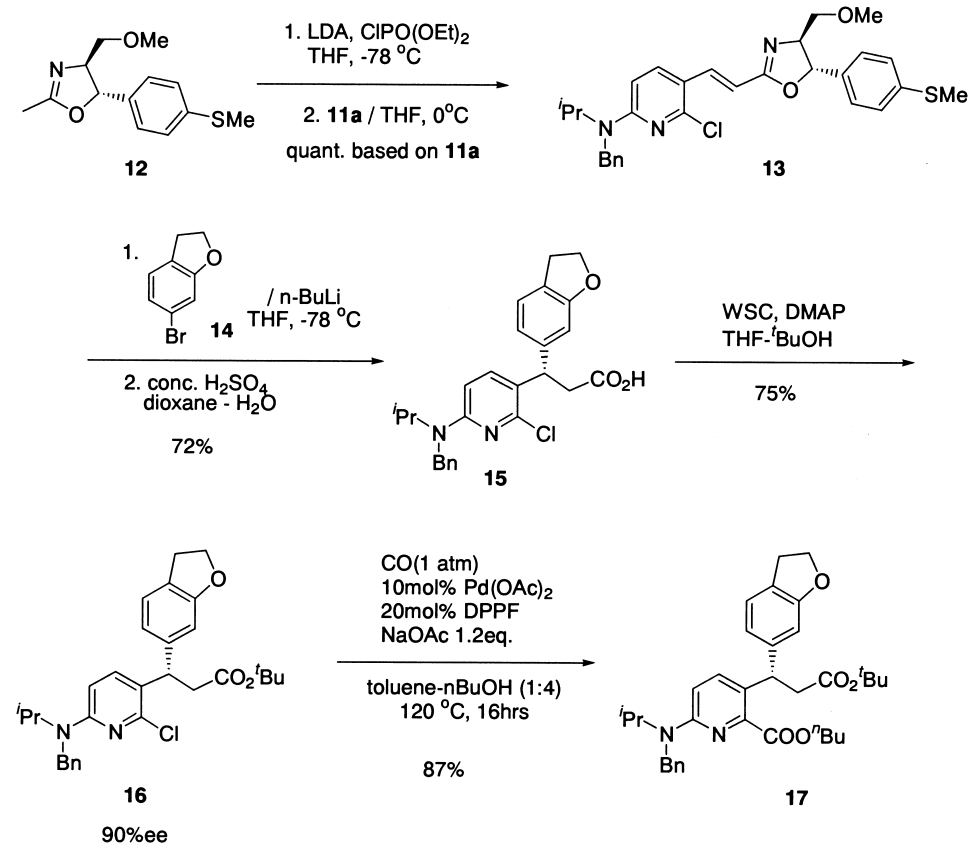
Efforts were then directed to carbonylation of the chloropyridine **16**.[12] Methoxycarbonylation of **16** with various palladium catalysts, ligands, bases etc. afforded only 10–30% of the product. Obviously, the chloropyridine **16** was much less reactive than the corresponding bromo-substrate[13] since the latter gave 90% yield of the product under similar conditions. After many attempts, we found that the reaction of **16** with *n*-BuOH at a higher reaction temperature in the presence of catalytic $Pd(OAc)_2$ and DPPF produced the *n*-butyl ester **17** in 87% yield (Scheme 3).

From the readily accessible 4-bromo-3-hydroxymethylanisole,[4] the bottom aryl bromide **18** was prepared by introduction of PMB protecting group to the hydroxymethyl group under standard conditions. Chemoselective addition of ArLi from **18** to the *n*-butyl ester of **17** at low temperature afforded ketone **19** in 75% yield (Scheme 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. L-Selectride gave a 3/1 mixture of product in 63% combined yield. Lithium 9-BBN hydride and BH_3/THF complex gave essentially the same selectivity (2/1) and yield (80%). As expected, $NaBH_4$ offered no selectivity at all (1/1) but gave a very clean reaction (96% yield). Interestingly, Dibal-H selectively reduced the *tert*-butyl ester over the ketone! The best result was obtained with LS-Selectride®. The stereoselectivity was satisfactory (5/1) and yield was very good (84%) (Table 1). Purification of the crude product by crystallization gave alcohol **20** in 66% yield with enhanced diastereomeric purity (>99.5% de). The chiral alcohol stereochemistry was assigned based on subsequent chemistry (see later).

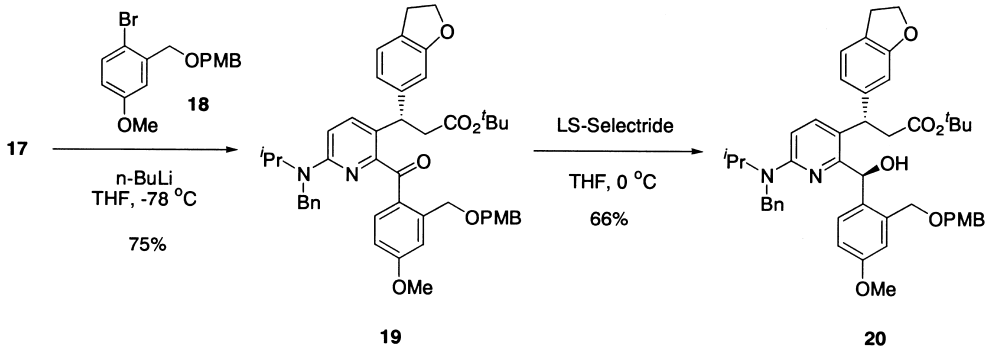
With the alcohol **20** in hand, the key cyclization step was then investigated. Based on the experience with earlier drug candidate **1a**, we opted for using a phosphate for the



Scheme 2.



Scheme 3.

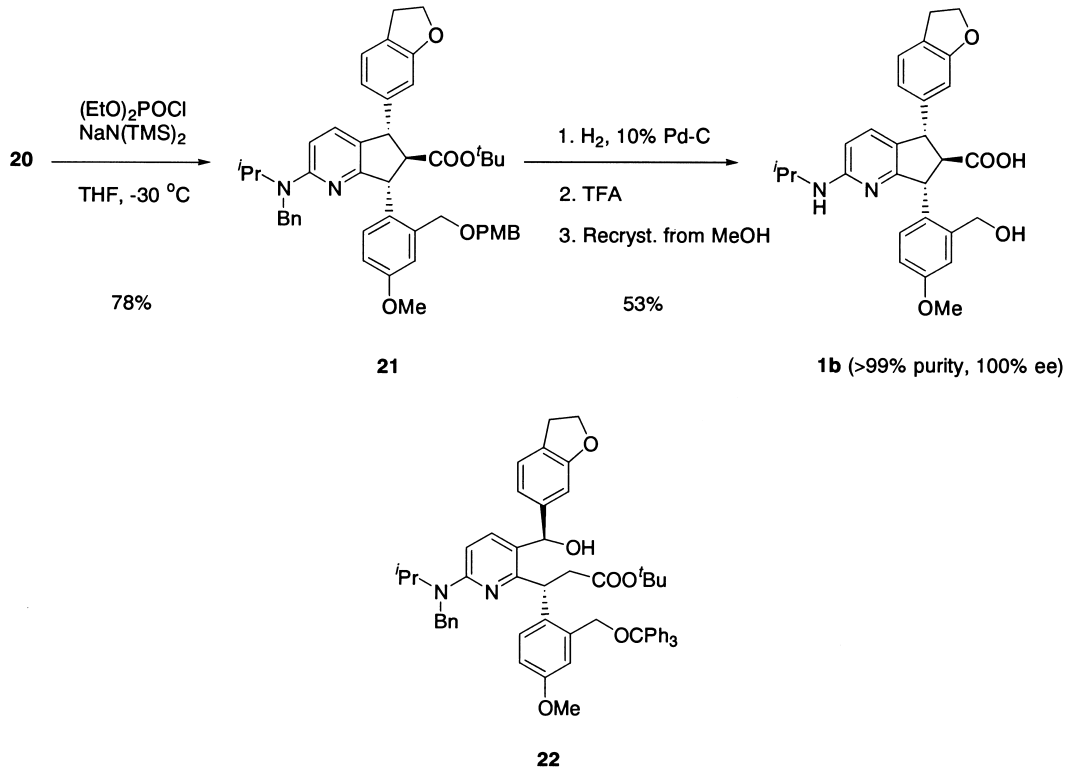


Scheme 4.

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 cyclization was accomplished in one step by sequential treatment of **20** with $(EtO)_2POCl$ and NaHMDS to give the late intermediate **21** in 78% yield. 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**.[4a] This was also the basis for the stereochemical assignment for the chiral alcohol center in **20**. The success of this phosphate mediated cyclization is in sharp contrast to the failure of phosphate to mediate similar cyclization of intermediate **22** used in the alternate route, probably due to much less stability (thus decomposition) of the desired phosphate intermediate.[14] The fact that the isopropylbenzylamino group is at the *para* position to the alcohol in **22** but at the *meta* position in **20** must be the main reason.

Table 1. Reduction of ketone **19**

Reducing agent	Selectivity	Yield (%)
L-Selectride	3/1	63
Li 9-BBNH	2/1	81
BH_3/THF	2/1	79
$NaBH_4$	1/1	96
9-BBN	No reaction	
Dibal-H	Reduction of *tert*-butyl ester	
LS-Selectride®	5/1	84



Scheme 5.

With the intermediate **21** in hand, all that remained to be done was to remove three protecting groups. Hydrogenolysis removed both the PMB and the *N*-benzyl groups. Subsequent treatment of the crude product with TFA gave the final product **1b**. It was purified by crystallization from MeOH to afford the target molecule **1b** in 53% yield from **21** with >99% purity as a single enantiomer (Scheme 5).

In conclusion, a new asymmetric synthesis of **1b** was accomplished in 10% overall yield from the pyridine intermediate **11a** in a highly stereo- and regio-controlled manner. Highly functionalized pyridine **11a** was also efficiently synthesized from inexpensive 2,6-dichloropyridine via mono-amination with the lithium amide and Vilsmeier formylation.

1. Experimental

1.1. General

1.1.1. 2-(*N*-Benzylisopropylamino)-6-chloropyridine (10a). To a solution of *N*-benzylisopropylamine (989 mL, 5.91 mol) in toluene (989 mL) was added 1.58 M solution of *n*-BuLi in hexane (3.60 L, 5.68 mol) keeping the temperature below −64°C under N_2 atmosphere. The temperature was allowed to warm to 0°C after the addition of *n*-BuLi. The pink suspension was added dropwise to a solution of 2,6-dichloropyridine (700 g, 4.73 mol) in toluene (3.5 L) below 4°C and then was allowed to warm to ambient temperature. The reaction was quenched with water (2 L), and the organic layer was washed with 10% citric acid twice (2.5 and 2.9 L) and water (2 L). The organic layer was concentrated and subjected to the azeotropic distillation with toluene (2×2 L) to give the crude product (1.88 kg). HPLC assay indicated 1.23 kg (99% yield) of the title compound in the crude mixture, which was used for the next reaction without further purification. A pure sample of **10a** was isolated as an oil after silica gel column chromatography. IR (KBr) 3433, 2975, 1593, 1546, 1474, 1415, 1365, 1135, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.1–7.4 (m, 6H), 6.51 (d, J=7.6 Hz, 1H), 6.12 (d, J=8.3 Hz, 1H), 5.09 (m, 1H), 4.50 (s, 2H), 1.19 (d, J=6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.56, 46.58, 46.86, 105.45, 111.26, 126.60, 127.14, 128.78, 139.48, 139.75, 149.55, 158.86. LC-HRMS (APCI) calcd for $C_{15}H_{18}ClN_2$ (M+1) 261.1159, found 261.1184.

1.1.2. 2-(*N*-Benzylisopropylamino)-6-chloro-5-formylpyridine (11a). $POCl_3$ (477 mL, 5.12 mol) was added to DMF (1584 mL) below 8°C under N_2 atmosphere, and the mixture was allowed to warm to 20°C. After stirring at 20°C for 30 min, a solution of **10a** (1213 g assay, 4.65 mol) in toluene (1.5 L) was added at ambient temperature. The mixture was stirred at 70°C for 8 h, cooled to 20°C, and poured into chilled water (13.5 L) keeping the temperature below 15°C. Toluene (1.5 L) was added to the mixture, and the organic layer was separated and washed with sat. $NaHCO_3$ (2 L) and water (3 L). The organic layer was concentrated and subjected to the azeotropic distillation with toluene (3×1 L) to give the crude product (1.59 kg). HPLC assay indicated 1.33 kg (99% yield) of the title compound in the crude mixture, which was used for the next reaction without further purification. A pure sample of **11a** was isolated as an oil after silica gel column chromatography (C-300, hexane/EtOAc=95/5). IR (KBr) 1666, 1583, 1483, 1392, 1350, 1198, 1140, 1041, 500 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.85 (d,

J=8.9 Hz, 1H), 7.10–7.40 (m, 5H), 6.27 (d, J=8.6 Hz, 1H), 5.00–5.30 (br, 1H), 4.64 (s, 2H), 1.24 (d, J=6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.20, 46.62, 47.55, 106.02, 118.36, 126.08, 127.21, 128.78, 137.42, 138.37, 154.33, 160.15, 188.06. LC-HRMS (APCI) calcd for $C_{16}H_{18}ClN_2O$ (M+1) 289.1108, found 289.1120.

1.1.3. 2-(*N*-Benzylisopropylamino)-6-chloro-5-{(*E*)-[2-(4*S*,5*S*)-4-methoxymethyl-5-(4-methylthiophenyl)-4,5-dihydro-1,3-oxazol-2-yl]vinyl}pyridine (13). To a solution of diisopropylamine (18.5 mL, 133 mmol) in THF (81.6 mL), was added *n*-BuLi (1.63 M in hexane, 81.6 mL, 133 mmol) at −78°C. A solution of (4*S*,5*S*)-4-methoxymethyl-2-methyl-5-(4-methylthiophenyl)-4,5-dihydro-1,3-oxazole (**12**) (16.3 g, 64.8 mmol) in THF (36 mL) was added dropwise to the LDA solution at the same temperature and the mixture was stirred at −78°C for 30 min. $ClPO(OEt)_2$ (9.19 mL, 63.6 mmol) was added to the mixture, then the reaction mixture was warmed to 0°C and stirred for 30 min. A solution of **11a** (16.7 g, 57.8 mmol) in THF (34 mL) was added dropwise to the reaction mixture and the mixture was stirred at 0°C for 30 min. 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. HPLC assay indicated 30.2 g (quant.) of the title compound **13** in the crude product. It was used for the next reaction without further purification. A pure sample of **13** was isolated as an oil after silica gel column chromatography (C-300, hexane/acetone=8/2). $[\alpha]_D^{20}$=+115° (c=1.000, $CHCl_3$). IR (KBr) 3329, 1635, 1589, 1475, 1388, 1353, 1198, 1138, 627, 496 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J=16.2 Hz, 1H), 7.57 (d, J=8.7 Hz, 1H), 7.10–7.35 (m, 9H), 6.40 (d, J=16.2 Hz, 1H), 6.23 (d, J=8.7 Hz, 1H), 5.34 (d, J=6.9 Hz, 1H), 5.00–5.20 (m, 1H), 4.56 (s, 2H), 4.20 (ddd, J=6.9, 6.4 and 4.5 Hz, 1H), 3.65 (dd, J=9.6 and 4.5 Hz, 1H), 3.55 (dd, J=9.6 and 6.4 Hz, 1H), 3.42 (s, 3H), 2.48 (s, 3H), 1.21 (d, J=6.8 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.66, 20.03, 46.29, 46.64, 59.16, 74.17, 74.48, 82.87, 106.14, 112.36, 116.51, 125.98, 126.08, 126.67, 126.80, 128.49, 135.55, 136.03, 137.55, 138.22, 138.40, 149.53, 157.86, 164.01. HRMS (FAB) calcd for $C_{29}H_{33}ClN_3O_2S$ (M+1) 522.1982, found 522.1986.

1.1.4. (3*S*)-3-[6-(*N*-Benzyl-*N*-isopropylamino)-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 **14** (8.00 g, 40.2 mmol) in THF (240 mL), was added dropwise *n*-BuLi (1.63 M in hexane, 24.7 mL, 40.2 mmol) at −78°C, and the mixture was stirred for 1 h. A solution of oxazoline **13** (15.4 g, 29.5 mmol) in THF (140 mL) was added dropwise in 1 h. The reaction was quenched with methanol and sat. NH_4Cl. The product was extracted with ethyl acetate and the organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness to give the crude conjugate addition product. It was dissolved in 1,4-dioxane/water (72/24 mL), and conc. H_2SO_4 was added dropwise to the mixture at 0°C. The mixture was heated to 100°C and stirred for 1.5 h, then cooled to room temperature. The reaction mixture was diluted with $CHCl_3$ and the product was extracted with 2N NaOH. The aqueous layer was separated and acidified with 5N HCl, and the product **15** was extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated to dryness to give the title compound (9.58 g, 72% yield) as a solid. The enantiomeric excess was determined to be 90% by chiral HPLC after the esterification with *tert*-BuOH. Recrystallization (ethyl acetate/hexane) of the crude acid product gave optically pure white crystalline solid (99% ee) in 60% crystallization yield. Mp 161°C; $[\alpha]_D^{20}$=−15.6° (c=1.0, $CHCl_3$). IR (KBr) 2976, 1741, 1603, 1539, 1483, 1255, 1063, 945, 868, 797, 725 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.35 (m, 5H), 7.13 (d, J=8.6 Hz, 1H), 7.07 (d, J=7.6 Hz, 1H), 6.73 (dd, J=7.6 and 1.5 Hz, 1H), 6.63 (d, J=1.5 Hz, 1H), 6.10 (d, J=8.6 Hz, 1H), 5.02 (qq, J=6.8 and 6.8 Hz, 1H), 4.78 (t, J=7.7 Hz, 1H), 4.52 (t, J=8.6 Hz, 2H), 4.45 (s, 2H), 3.13 (t, J=8.6 Hz, 2H), 2.93 (d, J=7.7 Hz, 2H), 1.17 (d, J=6.8 Hz, 3H), 1.15 (d, J=6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.56, 29.85, 39.96, 42.28, 46.66, 46.97, 71.76, 106.18, 109.04, 120.30, 123.61, 125.20, 125.82, 126.63, 127.13, 128.95, 138.29, 139.61, 142.79, 148.53, 157.24, 160.78, 177.55. HRMS (FAB) calcd for $C_{26}H_{28}ClN_2O_3$ (M+1) 451.1788, found 451.1784. Anal. Calcd for $C_{26}H_{27}ClN_2O_3$: C, 69.25; H, 6.03; N, 6.21. Found: C, 69.24; H, 6.03; N, 6.18.

1.1.5. *tert*-Butyl (3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-chloro-3-pyridinyl]-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (16). To a solution of compound **15** (87.7 g, 194 mmol) in THF (500 mL) and *tert*-BuOH (500 mL), was added EDCl (44.6 g, 233 mmol) and 4-dimethylaminopyridine (28.5 g, 233 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was diluted with ethyl acetate and hexane, and the organic solution was washed with 0.5N HCl, sat. $NaHCO_3$, and brine. The organic solution was dried over $MgSO_4$, and concentrated to dryness to give the title compound **16** (73.8 g assay, 90% ee, 75% yield) as an oil. A pure sample of **16** was isolated through silica gel column chromatography (C-300, hexane/ethyl acetate=9/1) as a yellow oil. HPLC: column, DAICEL CHIRALPAK AD: eluent, hexane/2-propanol (95/5): flow rate, 1.0 mL min^{-1}; t_R for ester **16**, 12.5 min; t_R for enantiomer, 13.9 min. $[\alpha]_D^{20}$=−6.80° (c=1.00, $CHCl_3$). IR (KBr) 1720, 1595, 1470, 1354, 1198, 1138, 129, 689, 617, 494 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.35 (m, 6H), 7.07 (d, J=7.6 Hz, 1H), 6.74 (dd, J=7.6 and 1.5 Hz, 1H), 6.65 (d, J=1.5 Hz, 1H), 6.13 (d, J=8.6 Hz, 1H), 4.95–5.15 (m, 1H), 4.75 (t, J=8.4 Hz, 1H), 4.52 (t, J=8.6 Hz, 2H), 4.46 (s, 2H), 3.13 (t, J=8.6 Hz, 2H), 2.83 (d, J=8.4 Hz, 2H), 1.29 (s, 9H), 1.161 (d, J=6.7 Hz, 3H), 1.155 (d, J=6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.50, 28.27, 29.85, 41.93, 42.85, 46.62, 46.84, 71.72, 81.00, 106.12, 109.01, 120.31, 123.79, 125.02, 125.50, 126.61, 127.09, 128.91, 138.43, 139.66, 143.37, 148.70, 157.07, 160.71, 171.11. HRMS (FAB) calcd for $C_{30}H_{36}ClN_2O_3$ (M+1) 507.2414, found 507.2396. Anal. Calcd for $C_{30}H_{35}ClN_2O_3$: C, 71.06; H, 6.96; N, 5.52. Found: C, 70.96; H, 7.13; N, 5.50.

1.1.6. *tert*-Butyl (3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbony-3-pyridinyl]-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (17). A mixture of **16** (1.00 g, 1.97 mmol), sodium acetate (194 mg, 2.37 mmol), $Pd(OAc)_2$ (44.2 mg, 0.197 mmol), DPPF (218 mg, 0.394 mmol) in *n*-butanol (4 mL) and toluene (2 mL) was

stirred under 1 atm of CO atmosphere (1 kg cm^{-2}) at 120°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 to give the title compound **17** (983 mg, 87% yield) as an oil. A pure sample of **17** was obtained through silica gel column chromatography (C-300, hexane/ethyl acetate=9/1). IR (KBr) 2968, 1726, 1601, 1485, 1354, 1248, 1151, 1072, 987, 949, 810, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.32 (m, 6H), 7.04 (d, J=7.6 Hz, 1H), 6.74 (dd, J=7.6 and 1.4 Hz, 1H), 6.67 (d, J=1.4 Hz, 1H), 6.31 (d, J=9.0 Hz, 1H), 4.95–5.10 (m, 1H), 4.91 (t, J=8.2 Hz, 1H), 4.40–4.58 (m, 4H), 4.26–4.38 (m, 2H), 3.12 (t, J=8.6 Hz, 2H), 2.82 (d, J=8.2 Hz, 2H), 1.65–1.80 (m, 2H), 1.35–1.54 (m, 2H), 1.27 (s, 9H), 1.16 (d, J=6.8 Hz, 6H), 0.94 (t, J=7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.15, 19.58, 20.55, 28.25, 29.85, 31.04, 41.22, 42.39, 46.55, 47.01, 65.45, 71.65, 80.81, 109.11, 109.71, 120.36, 124.90, 125.23, 126.13, 126.73, 126.97, 128.82, 137.81, 140.17, 144.04, 146.74, 156.59, 160.67, 167.96, 171.17. HRMS (FAB) calcd for $C_{35}H_{45}N_2O_5$ (M+1) 573.3328, found 573.3316. Anal. Calcd for $C_{35}H_{44}N_2O_5$: C, 73.40; H, 7.74; N, 4.89. Found: C, 73.64; H, 7.87; N, 4.98.

1.1.7. *tert*-Butyl (3*S*)-3-{6-(*N*-benzyl-*N*-isopropylamino)-2-[4-methoxy-2-(4-methoxy-benzyloxymethyl)benzoyl]-3-pyridinyl}-3-(2,3-dihydro-1-benzofuran-6yl)propanoate (19). To a solution of 4-bromo-3-(4-methoxybenzyloxymethyl)anisole **18** (530 mg, 1.57 mmol) in THF (4 mL) was added dropwise *n*-BuLi (1.63 M in hexane, 0.96 mL, 1.57 mmol) at −78°C, and the mixture was stirred for 30 min. To the mixture was added dropwise a solution of compound **17** (600 mg, 1.05 mmol) in THF (8 mL) at −78°C for 2 min and the mixture 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 to give the title compound **19** (598 mg, 75% yield) as an oil. A pure sample of **19** was obtained through silica gel column chromatography (C-300, hexane/ethyl acetate=85/15). IR (KBr) 1720, 1655, 1595, 1466, 1352, 1298, 1192, 1132, 955, 814, 619, 459 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.12–7.40 (m, 10H), 6.85–6.95 (m, 3H), 6.51–6.63 (m, 3H), 6.32 (d, J=9.0 Hz, 1H), 5.05 (s, 2H), 4.80 (qq, J=6.8 and 6.6 Hz, 1H), 4.61 (s, 2H), 4.55 (dd, J=8.9 and 7.3 Hz, 1H), 4.40–4.50 (m, 4H), 3.85 (s, 3H), 3.81 (s, 3H), 3.04 (t, J=8.6 Hz, 2H), 2.83 (dd, J=15.5 and 7.3 Hz, 1H), 2.82 (dd, J=15.5 and 8.9 Hz, 1H), 1.25 (s, 9H), 1.07 (d, J=6.6 Hz, 3H), 1.06 (d, J=6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.04, 27.89, 29.37, 41.06, 41.86, 46.15, 46.50, 55.27, 55.36, 70.48, 71.18, 72.42, 80.31, 107.84, 108.84, 110.82, 111.71, 113.78, 120.12, 124.35, 124.70, 125.19, 126.29, 126.46, 127.34, 128.36, 129.28, 130.80, 135.94, 137.26, 139.97, 143.41, 145.02, 153.59, 155.55, 159.10, 160.10, 162.71, 170.77, 196.50. HRMS (FAB) calcd for $C_{47}H_{53}N_2O_7$ (M+1) 757.3835, found 757.3865.

1.1.8. *tert*-Butyl (3*S*)-3-{6-(*N*-benzyl-*N*-isopropylamino)-2-(*S*)-hydroxy[4-methoxy-2-(4-methoxybenzyloxymethyl)-phenyl]methyl-3-pyridinyl}-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (20). To a solution of compound **19** (681 mg, 0.900 mmol) in THF (3.6 mL) was added LS-Selectride® (1.0 M in THF, 1.80 mL, 1.80 mmol) at 0°C and the mixture was stirred for 5 h. The reaction was quenched with 30% H_2O_2 and 4N NaOH, 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 crystallized from 2-propanol to give the title compound **20** (451 mg, >99.5% de, 66% yield) as a white crystal. Mp 124–128°C. IR (KBr) 2974, 1728, 1605, 1491, 1358, 1294, 1244, 1147, 1072, 1034, 812, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.40 (m, 8H), 7.08 (d, J=2.4 Hz, 1H), 6.97 (d, J=7.6 Hz, 1H), 6.88 (d, J=8.7 Hz, 2H), 6.61–6.73 (m, 2H), 6.57 (dd, J=7.6 and 1.3 Hz, 1H), 6.51 (d, J=1.3 Hz, 1H), 6.35 (d, J=8.9 Hz, 1H), 5.85 (s, 1H), 5.71 (br s, 1H), 4.76–4.93 (m, 1H), 4.82 (d, J=12.9 Hz, 1H), 4.70 (d, J=12.9 Hz, 1H), 4.46–4.60 (m, 6H), 4.09 (dd, J=9.9 and 6.2 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.11 (t, J=8.6 Hz, 2H), 2.48 (dd, J=15.5 and 9.9 Hz, 1H), 2.08 (dd, J=15.5 and 6.2 Hz, 1H), 1.24 (d, J=6.7 Hz, 3H), 1.23 (d, J=6.6 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.61, 20.71, 28.17, 29.83, 40.60, 41.66, 47.18, 55.60, 55.67, 68.60, 69.45, 71.69, 72.46, 80.55, 106.25, 108.92, 113.35, 113.97, 114.16, 120.26, 123.81, 124.96, 125.45, 126.45, 127.00, 128.96, 129.51, 129.80, 131.11, 133.35, 138.10, 139.50, 140.36, 143.88, 154.57, 155.55, 159.49, 159.51, 160.75, 170.66. HRMS (FAB) calcd for $C_{47}H_{55}N_2O_7$ (M+1) 759.4001, found 759.3994. Anal. Calcd for $C_{47}H_{54}N_2O_7$: C, 74.38; H, 7.17; N, 3.69. Found: C, 74.35; H, 7.27; N, 3.68.

1.1.9. *tert*-Butyl (5*S*,6*R*,7*R*)-2-(*N*-benzyl-*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 (21). To a solution of compound **20** (152 mg, 0.200 mmol) in THF (1 mL) was added $(EtO)_2POCl$ (37.6 mL, 0.260 mmol) under nitrogen. The mixture was cooled to −30°C, and NaHMDS (1.0 M in THF, 1.00 mL, 1.00 mmol) was added. The reaction mixture was stirred for 30 min and then quenched with sat. NH_4Cl. The product was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness to give the title compound **21** (115 mg, 78% yield) as an oil. A pure sample of **21** was isolated through silica gel column chromatography (C-300, hexane/ethyl acetate=5/1). IR (KBr) 1714, 1597, 1464, 1354, 1192, 1138, 810, 741, 582, 478 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.06–7.32 (m, 8H), 6.92–7.16 (m, 3H), 6.84 (d, J=8.6 Hz, 2H), 6.72–6.80 (m, 2H), 6.69 (d, J=1.2 Hz, 1H), 6.13 (d, J=8.6 Hz, 1H), 4.86 (d, J=9.6 Hz, 1H), 4.50–4.78 (m, 3H), 4.56 (t, J=8.6 Hz, 2H), 4.35–4.48 (m, 5H), 3.80 (s, 3H), 3.79 (s, 3H), 3.12–3.25 (m, 3H), 1.32 (s, 9H), 1.04 (d, J=6.7 Hz, 3H), 1.01 (d, J=6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.79, 20.23, 28.06, 29.53, 46.37, 46.82, 51.48, 55.21, 55.25, 62.79, 69.68, 71.34, 71.49, 80.59, 105.22, 109.05, 113.19, 113.34, 113.68, 120.62, 124.54, 124.61, 125.40, 126.29, 126.49, 128.24, 129.46, 130.74, 134.03, 138.49, 140.54, 144.41, 157.92, 159.05, 159.16, 160.45, 162.35, 173.27. HRMS (FAB) calcd for $C_{47}H_{53}N_2O_6$ (M+1) 741.3904, found 741.3892.

1.1.10. (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). To a solution of compound **21** (2.22 g,

3.00 mmol) in EtOAc (20 mL) and methanol (20 mL) was added 10% Pd–C (300 mg), and the mixture was hydrogenated at ambient temperature under H_2 (1 kg cm^{-2}) for 20 h. The reaction mixture was filtered through Celite® and the filtrate was concentrated to dryness. The residue was treated with TFA (20 mL) at the ambient temperature for 1 h, and the mixture was neutralized with 1N NaOH. The product was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The solid residue was crystallized from methanol to give the title compound **1b** (749 mg, 100% ee) in 53% yield as a white crystalline solid. HPLC: column, DAICEL CHIRALPAK AD: eluent, hexane/2-propanol/CF_3COOH (700/300/1): flow rate, 1.0 mL min^{-1}; 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) 2966, 1670, 1618, 1500, 1394, 1250, 1171, 1034, 999, 814, 721 cm^{-1}. ^1H NMR (300 MHz, DMSO) δ 7.18 (d, J=7.6 Hz, 1H), 7.02 (d, J=2.8 Hz, 1H), 6.87–6.97 (m, 2H), 6.75 (dd, J=8.5 and 2.9 Hz, 1H), 6.71 (dd, J=7.6 and 1.4 Hz, 1H), 6.60 (d, J=1.4 Hz, 1H), 6.25 (d, J=8.3 Hz, 1H), 4.57–4.73 (m, 2H), 4.40–4.56 (m, 3H), 4.33 (d, J=8.6 Hz, 1H), 3.73 (s, 3H), 3.58–3.75 (m, 1H), 3.15 (t, J=8.8 Hz, 2H), 3.01 (dd, J=8.8 and 8.6 Hz, 1H), 1.04 (d, J=6.4 Hz, 3H), 0.98 (d, J=6.4 Hz, 3H). ^{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. HRMS (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.

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7. In order to obtain good yield for the amination of **9b**, premixing at least 1 equiv. of *i*-Pr(Bn)NH with 2,6-dibromopyridine was required and 1.5 equiv. of *i*-Pr(Bn)NLi was used. Additionally, chloride–bromide exchange caused formation of small amount of chloro-compound in the formylation. So, excess $POCl_3$ at lower temperature was used to suppress this side reaction.[5]
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13. Bromo-substrate corresponding to **16** was prepared from **11b** in a similar manner as **16**.
14. Less reactive $(Me_2N)_2POCl$ was used for cyclization of **22**.[5]