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Chiral Bipyrindine and Biquinoline Ligands: Their Asymmetric Synthesis and Application to the Synthesis of *trans*-Whisky Lactone

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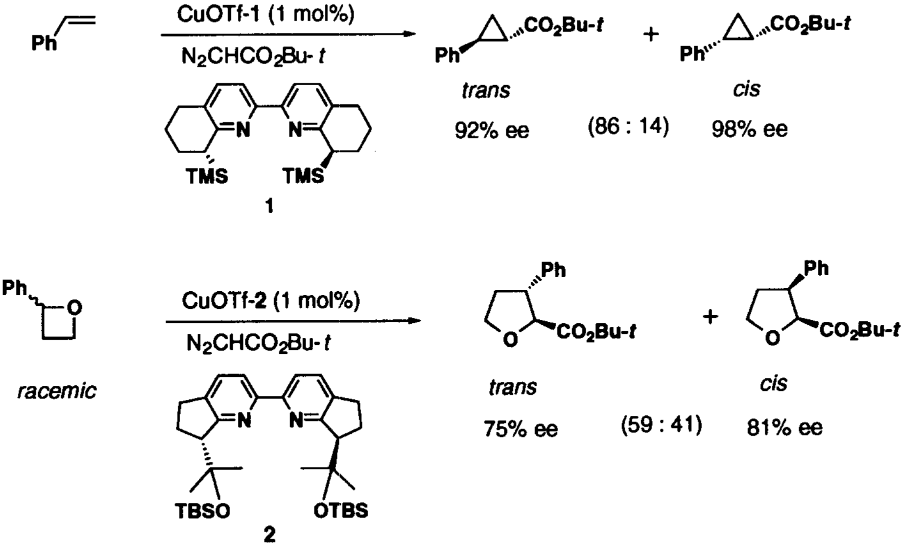
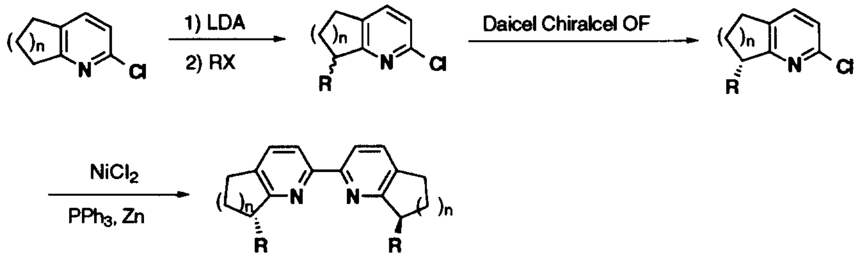
Abstract: Chiral bipyrindine and biquinoline which have been reported to be efficient ligands for the construction of chiral copper catalysts, were synthesized enantioselectively by using Mn-salen catalyzed asymmetric epoxidation as a key step. Enantioselective synthesis of *trans*-whisky lactone was then achieved by way of enantiospecific ring expansion reaction of oxetane with a chiral copper catalyst bearing the bipyrindine ligand as a chiral source.

Chiral nitrogen ligands have recently aroused chemist's attention due to their high asymmetric induction and various types of nitrogen ligands have been reported to date.[1] We recently reported that newly designed chiral C_2-symmetric bipyrindine and biquinoline ligands served as effective chiral sources in copper-catalyzed asymmetric cyclopropanation and enantiospecific ring expansion of oxetane (Scheme 1).[2] These binitrogen ligands could be prepared in a short step according to the procedure described in Scheme 2. However, their synthesis in bulk met difficulty, since the resolution of the intermediary 2-chloro-7-alkyl-6,7-dihydro-5*H*-1-pyrindine and 2-chloro-8-alkyl-5,6,7,8-tetrahydroquinoline could be achieved only with the aid of HPLC using optically active column. Thus, we examined the alternative method for the general asymmetric synthesis of bipyrindine and biquinoline ligands of various types.



Scheme 1

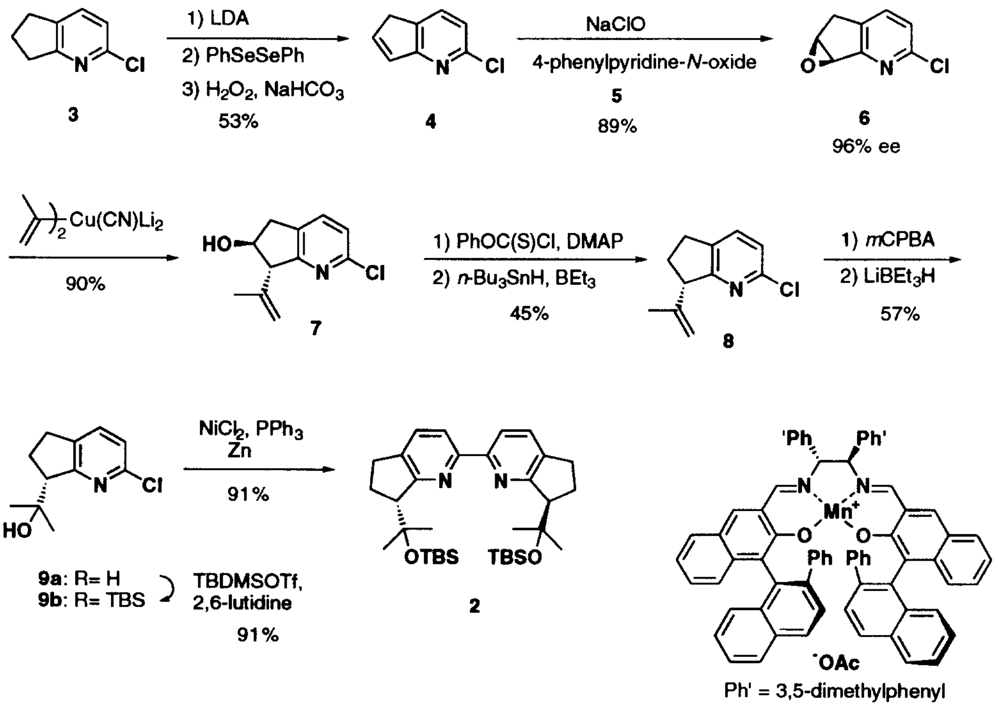


Scheme 2

Asymmetric synthesis of chiral bipyrindine and biquinoline ligands

Recently, we developed Mn-salen catalyzed epoxidation of simple olefins, which showed extremely high level of enantioselectivity in the epoxidation of conjugated *cis*-disubstituted and trisubstituted olefins.[3] With this reaction as a key step, we examined the enantioselective synthesis of chiral bipyrindine and biquinoline ligands which could be carried out in quantities.

Synthesis of chiral bipyrindine **2** started with 2-chloro-6,7-dihydro-5*H*-1-pyrindine, which was prepared according to the literature procedures (Scheme 3).[4] Compound **3** was successively treated with LDA and



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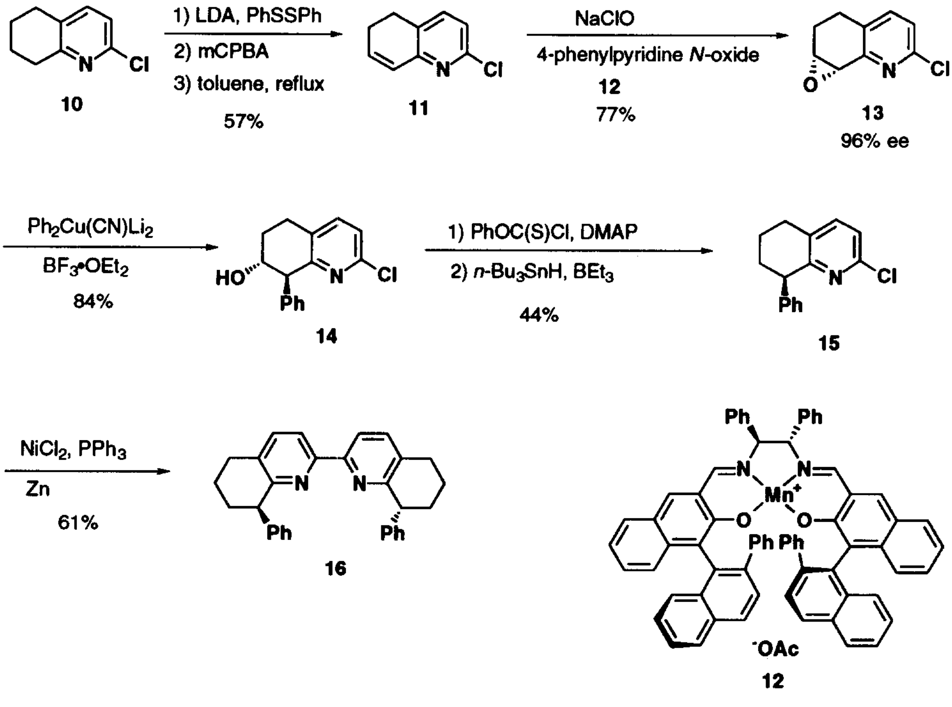
Scheme 3

diphenyldiselenide and the resulting selenide was oxidized with H_2O_2 to give 2-chloro-5*H*-1-pyrindine (**4**). Asymmetric epoxidation of **4** with catalyst **5** proceeded smoothly with high enantioselectivity of 96% ee to give epoxide **6**. Treatment of epoxide **6** with higher order cuprate provided alcohol **7** as a single isomer. No regioisomeric epoxide-opening product was detected. The absolute configuration of **7** was determined to be 6*S*,7*S* by the modified Mosher method.[5] This assignment is consistent to the empirical rule on the enantioface selectivity in Mn-salen catalyzed epoxidation.[3b] Reaction of **7** with phenyl chlorothionoformate in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), followed by treatment of the resulting thiocarbonate with tributyltinhydride in the presence of triethylborane (Barton reduction)[6] gave **8**. Compound **8** was converted into bipyrindine **2** by the sequence: i) epoxidation of **8** with *m*-chloroperbenzoic acid (*m*CPBA), ii) reduction of the resulting epoxide with super hydride to give alcohol **9a**, the NMR spectrum of which was identical with the authentic sample prepared before as described previously,[2d] iii) Protection of hydroxy group as TBS ether **9b** and the subsequent nickel-catalyzed coupling reaction according to the reported procedure.[2d,e] Although the optical purity of **2** could not be determined by ^{1}H NMR or HPLC analysis, its optical purity was presumed to be 99.9% ee by calculation: If *R*-**9b** couples with *R*-**9b** and with *S*-**9b** in an equal rate, the homocoupling of **9b** should give *R*,*R*-**2**, *S*,*S*-**2** and *meso*-**2** in a ratio of 96.04 : 0.04 : 3.92. This means that the enantiomeric excess of **2** is 99.92% and that the ratio of [*R*,*R*-**2** +*S*,*S*-**2**] and *meso*-**2** is 96.08 : 3.92. Actually, the observed ratio of [*R*,*R*-**2** +*S*,*S*-**2**] and *meso*-**2** is 95.4 : 4.6.

Next we examined the asymmetric synthesis of biquinoline derivative **16**.

Synthesis of compound **16** started with 2-chloro-5,6,7,8-tetrahydroquinoline (**10**), which was prepared



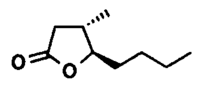
Scheme 4

according to the literature procedures (Scheme 4).[7] Compound **10** was converted to 2-chloro-5,6-dihydroquinoline (**11**) by the sequence: i) treatment of **10** with LDA and diphenyldisulfide successively, ii) *m*CPBA oxidation, and iii) refluxing the resulting sulfoxide in toluene. Asymmetric epoxidation of **11** with catalyst **12** proceeded smoothly with high enantioselectivity of 96% ee to give epoxide **13**. Treatment of epoxide **13** with higher order cuprate in the presence of $BF_3{\bullet}OEt_2$ provided alcohol **14** as a single isomer. The absolute configuration of **14** was also determined to be 7*R*,8*R* by the modified Mosher method.[5] This assignment is consistent to the empirical rule on the enantioface selectivity in Mn-salen catalyzed epoxidation.[3b] Barton reduction of **14** gave **15**, which was then subjected to nickel-mediated homocoupling reaction[8] to give biquinoline ligand **16**. The optical purity of **16** was presumed to be 99.9% ee by calculation. In the homocoupling reaction, the ratio of [*R*,*R*-**16** +*S*,*S*-**16**] and *meso*-**16** was 96.3 : 3.7.

Enantioselective synthesis of *trans*-whisky lactone

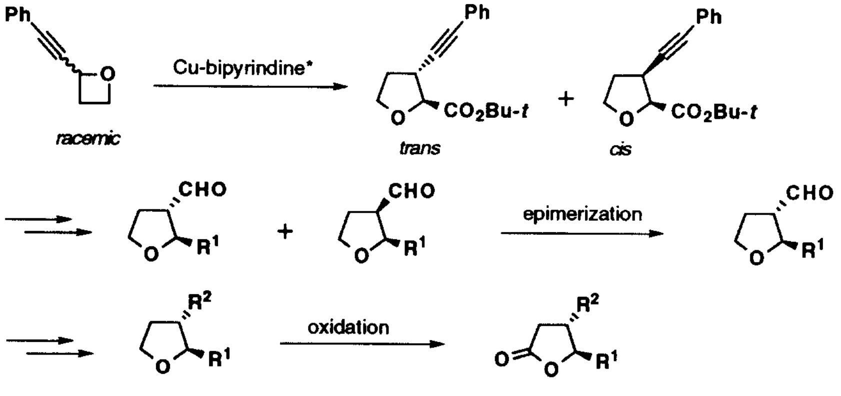
Since we could develop the straightforward asymmetric synthesis of bipyrindine and biquinoline ligands, we next examined the application of Cu-catalyzed enantiospecific ring expansion of oxetane (Scheme 1)[2d,e] which provided a useful entry to catalytic asymmetric synthesis of tetrahydrofuran and γ-butyrolactone derivatives, to the synthesis of natural products. As a successful example, we describe herein the enantioselective synthesis of *trans*-whisky lactone using ring expansion of 2-alkynyloxetane as a key step.[9]

trans-Whisky lactone (**17**) is found along with *cis*-whisky lactone in whisky, brandy and wine stored in oak barrel, because they are extracted from the barrels under maturing.[10] Although several syntheses of optically active *trans*-whisky lactone have been reported, most of them used stoichiometric amount of chiral sources as starting materials or chiral auxiliaries,[11] except for a few examples.[12]



trans-Whisky lactone (17)

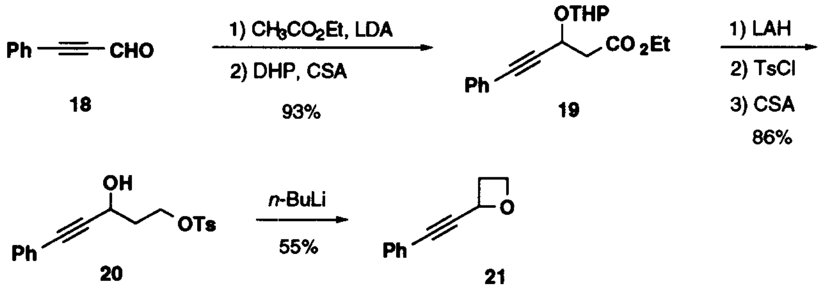
trans-Whisky lactone has a *trans*-disubstituted γ-butyrolactone ring. On the other hand, the reaction of



Scheme 5

(±)-2-substituted oxetane with diazoacetate in the presence of bipyrindine-copper complex gives a mixture of *trans*- and *cis*-tetrahydrofuran-2-carboxylate derivatives which are diastereomeric at C3-carbon to each other (Scheme 5). Accordingly, if the desired sense of epimerization at C3 is possible at an appropriate stage, (±)-oxetane is readily converted into optically active 2,3-disubstituted tetrahydrofuran derivative which is amenable to further functionalization such as oxidation giving γ-lactone. Along this line, (±)-2-alkynyloxetane was planned to be subjected to asymmetric ring expansion reaction toward the synthesis of *trans*-whisky lactone (**17**), since alkynyl group was considered to be a chemical equivalent of aldehyde group and the configuration of the carbon α to aldehyde was considered to be readily inverted.

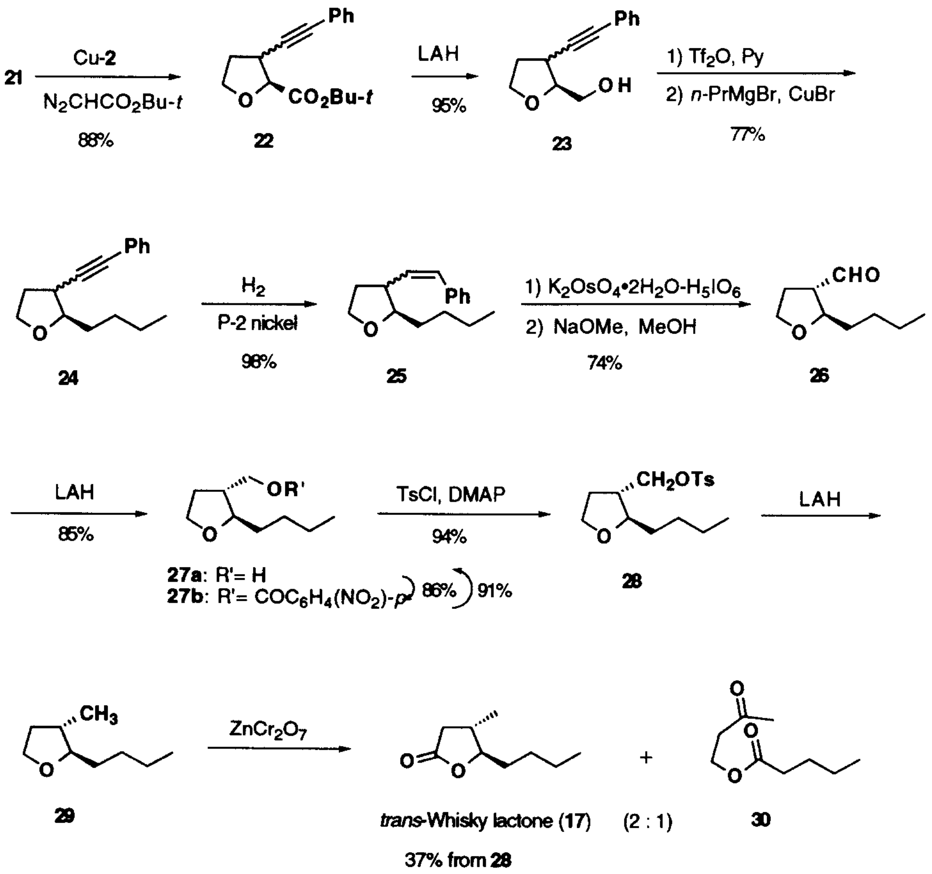
According to the above analysis, our synthesis of **17** started from (±)-2-(phenylethynyl)oxetane (**21**), which was prepared in 6 steps from propargyl aldehyde in a conventional manner (Scheme 6).



Scheme 6

We next examined the reaction of **21** with equimolar amount of *t*-butyl diazoacetate in the presence of catalytic amount of copper complexes bearing **2**, **16**, or some other bipyrindines and the reaction using Cu-**2** complex as a catalyst was found to proceed smoothly with the highest enantioselectivity, giving a 1:1 mixture of *trans*- and *cis*-*t*-butyl tetrahydrofuran-2-carboxylates (**22**, 75 and 71% ee, respectively[2d,e]). The reaction using Cu-**16** was sluggish. The mixture of the resulting *trans*- and *cis*-tetrahydrofurans was subjected to lithium aluminum hydride reduction (LAH) without separation to give alcohol **23** (Scheme 7). Three carbon extension of the side chains of **23** was effected according to Kotsuki's procedure[13] (Tf_2O, pyridine, then CuBr, *n*-PrMgBr) to give compound **24**. Hydrogenation of **24** with P2-Ni[14] as a catalyst gave *cis*-olefin **25** exclusively. Formation of *trans*-isomer was not observed by ^1H NMR analysis (270 MHz). Oxidative cleavage of double bond under modified Lemieux-Johnson conditions[15] (cat. K_2OsO_4-H_5IO_6) and subsequent epimerization at C-3 carbon with NaOMe gave preferentially *trans*-aldehyde **26** (*trans* : *cis* = 95:5) which was used for the next reaction without separation. In this procedure, no epimerization due to elimination-addition of the alkoxide β to the aldehyde, was detected. LAH reduction of aldehyde **26** followed by *p*-nitrobenzoylation afforded **27b**. The optical purity of **27b** was determined to be 73% ee by HPLC analysis using DAICEL (Chiralcel, OJ). The compound **27b** was subjected to recrystallization from hexane at -20 °C. The resulting crystals showed the reduced optical purity of 49% ee, but **27b** obtained from the filtrate showed the considerably improved optical purity of 89% ee. This procedure was repeated and **27b** of 98% ee was obtained in 33% yield. Although this material still contained a small amount of *cis*-isomer (7%), it was directly used for the next reaction, since *trans*- and *cis*-whisky lactones were known to be chromatographically separable.[10] Reductive cleavage of *p*-nitrobenzoyl group with LAH followed by tosylation of the resulting alcohol afforded tosylate **28**. Reduction of **28** with LAH gave **29**. Compound **29** was first subjected to RuO_4 oxidation using aqueous $NaIO_4$ as a terminal oxidant. However, the reaction did not give the desired γ-lactone but 4-ketocarboxylic acid exclusively. In contrast to this, the oxidation with $ZnCr_2O_7$[16] gave **17** preferentially, which was separated from the undesired side product **30** and a small amount of *cis*-whisky lactone by gel permeation chromatography. Compound **17** gave the satisfactory spectroscopic data which were identical with that reported by Ebata *et al.*[11j] The specific rotation of **2** was $[\alpha]_D^{25}$ +81.8° (*c* 0.41, MeOH) [Lit.[11j] $[\alpha]_D^{23}$ +79.5° (*c* 1.0, MeOH)]. The minor side product **30** was considered to be generated by the sequence, i) oxidation of α-methine carbon, ii) dehydration, and iii) oxidative cleavage of the resulting double bond.

In conclusion, we could achieve the asymmetric synthesis of chiral bipyrindine and biquinoline ligands by using Mn-salen catalyzed asymmetric epoxidation and the enantioselective synthesis of *trans*-whisky lactone by using enantiospecific ring expansion of oxetane as a key step. These results demonstrate the high utility of the asymmetric ring expansion reaction using Cu-**2** catalyst in organic synthesis.



Scheme 7

Experimental

NMR spectra were recorded at 270 MHz on a JEOL EX-270 instrument. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in $CDCl_3$). IR spectra were obtained with a SHIMADZU FTIR-8600 instrument. Optical rotation was measured with a JASCO DIP-360 automatic digital polarimeter. High-resolution mass spectra were recorded on a JEOL JMS-SX/SX 102A instrument. Column chromatography was conducted on Silica Gel BW-820MH, 70-200 mesh ASTM, available from FUJI SILYSIA CHEMICAL LTD. Preparative thin layer chromatography was performed on 0.5 mm x 20 cm x 20 cm E. Merck silica gel plate (60 F-254). Solvents were dried and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen or argon if necessary.

2-Chloro-5*H*-1-pyrindine (4)

n-Butyllithium (4.1 ml, 1.68 mol dm^{-3} in hexane) was added to a solution of *N*,*N*-diisopropylamine (0.96 ml, 6.88 mmol) in THF (7 ml) at 0 °C. After being stirred for 30 min, the mixture was cooled to -78 °C. To this solution was added 2-chloro-6,7-dihydro-5*H*-1-pyrindine (**3**)[4] (1.06 g, 6.88 mmol) in THF (7 ml) dropwise and the mixture was gradually raised to -20 °C. After stirred for another 1 h at the temperature, the mixture was cooled to -78 °C and added to a pre-cooled solution (-20 °C) of diphenyldiselenide (2.36 g, 7.57 mmol) in THF (14 ml) *via* cannula. After being stirred for 10 min, the mixture was quenched with saturated aqueous NH_4Cl, allowed to raise to room temperature, and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1) gave the corresponding selenide (1.56 g, 73%). ^1H NMR (270 MHz): δ 7.52-7.48 (m, 2H), 7.37 (d, *J*= 7.9 Hz, 1H), 7.31-7.19 (m, 3H), 7.07 (d, *J*= 7.9 Hz, 1H), 4.77 (dd, *J*= 7.3 and 7.6 Hz, 1H), 2.76-2.52 (m, 3H), 2.36-2.26 (m, 1H).

The selenide (1.56 g, 5.05 mmol) was dissolved in AcOEt-THF (51 ml, 2:1) and cooled to 0 °C. To this solution was successively added $NaHCO_3$ (1.2 g, 18.6 mmol) and 31% H_2O_2 (1.1 ml). After vigorous stirring for 30 min at the temperature, the mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 19:1) gave olefin **4** (549 mg, 72%) as colorless crystals. M.p. 58-59 °C. ^1H NMR (270 MHz): δ 7.68 (d, *J*= 7.9 Hz, 1H), 7.14 (d, *J*= 7.9 Hz, 1H), 7.00 (brs, 2H), 3.43 (brs, 2H). IR (KBr): 3449, 3051, 1595, 1572, 1545, 1406, 1381, 1215, 1180, 1111, 1059, 941, 895, 831, 758, 739, 700, 675, 613, 573, 453. HREIMS m/z Calcd for C_8H_6ClN: 151.0189. Found 151.0193 (M^+).

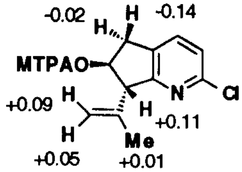
(6*S*,7*R*)-2-Chloro-6,7-epoxy-5*H*-1-pyrindine (6)

Mn-salen complex **5** (28.9 mg, 26.4 μmol) was added to a solution of olefin **4** (400 mg, 2.64 mmol) and 4-phenylpyridine *N*-oxide (90 mg, 0.53 mmol) in dichloromethane (4.4 ml) at 0 °C. To this solution was added aqueous NaOCl (4.4 ml, 1.2 M) adjusted at pH 12 with phosphate buffer at the temperature. After vigorous stirring for 3 h, the solution was diluted with water (50 ml) and the resulting mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 8:2) gave epoxide **6** (392 mg, 89%) as colorless crystals. The enantiomeric excess of **6** was determined to be 96% ee by GC analysis (SUPELCO α-DEX fused silica capillary column, 30 m x 0.25 mm ID, 0.25 μm film). **6**: M.p. 85-86 °C. $[\alpha]_D^{25}$ -38.0° (*c* 0.33, $CHCl_3$). ^1H NMR (270 MHz): δ 7.50 (d, *J*= 8.3 Hz, 1H), 7.21 (d, *J*= 8.3 Hz, 1H), 4.30 (dd, *J*= 1.0 and 3.0 Hz, 1H), 4.17 (dd, *J*= 3.0 and 3.0 Hz, 1H), 3.22 (d, *J*= 18.2 Hz, 1H), 3.00 (ddd, *J*= 1.0, 3.0 and 18.2 Hz, 1H). IR (KBr): 3449, 3053, 1568, 1421, 1234, 1211, 1178, 1121, 1099, 988, 883, 824, 783, 756, 692, 635, 575, 449. HREIMS m/z Calcd for C_8H_6ClNO: 167.0138. Found 167.0133 (M^+).

(6*S*,7*S*)-2-Chloro-6-hydroxy-7-(2-propenyl)-6,7-dihydro-5*H*-1-pyrindine (7)

t-Butyllithium (8.7 ml, 1.56 mol dm^{-3} in pentane) was added to a solution of 2-bromopropene (0.61 ml, 6.82 mmol) in THF (4.7 ml) at -78 °C and gradually raised to -10 °C. This solution was added to a suspension of CuCN (305 mg, 3.41 mmol) in THF (3.1 ml) at -78 °C with vigorous stirring and gradually raised to -10 °C. After stirring for 5 min at the temperature, the mixture was re-cooled to -78 °C. A solution of epoxide **6** (260 mg, 1.55 mmol) in THF (1.5 ml) was added to the mixture at -78 °C and gradually raised to -10 °C. The mixture was stirred at the temperature for 10 min, quenched with saturated aqueous NH_4Cl, and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 8:2~7:3) gave alcohol **7** (294 mg, 90%) as colorless crystals. M.p. 132-133 °C. $[\alpha]_D^{25}$ -0.5° (*c* 1.01, $CHCl_3$). ^1H NMR (270 MHz): δ 7.49 (d, *J*= 8.3 Hz, 1H), 7.13 (d, *J*= 8.3 Hz, 1H), 4.96 (brs, 1H), 4.54 (brs, 1H), 4.51 (ddd, *J*= 4.6, 5.0 and 6.6 Hz, 1H), 3.70 (d, *J*= 5.0 Hz, 1H), 3.24 (dd, *J*= 6.6 and 16.5 Hz, 1H), 2.84 (dd, *J*= 4.6 and 16.5 Hz, 1H), 1.76 (brs, 3H). IR (KBr): 3346, 3078, 2918, 1647, 1570, 1429, 1331, 1267, 1234, 1175, 1121, 1063, 941, 905, 827, 532. HREIMS m/z Calcd for $C_{11}H_{12}ClNO$: 209.0607. Found 209.0600 (M^+).

A small amount of **7** was converted into the corresponding (*S*)- and (*R*)-MTPA esters as described by Kusumi[5b] to determine its configuration. (*S*)-MTPA ester: ^1H NMR (270 MHz): δ 7.59-7.36 (m, 6H), 7.17 (d, *J*= 8.3 Hz, 1H), 5.33 (ddd, *J*= 3.8, 4.3 and 7.0 Hz, 1H), 5.01 (brs, 1H), 4.65 (brs, 1H), 3.93 (d, *J*= 4.3 Hz, 1H), 3.52 (s, 3H), 3.43 (dd, *J*= 7.0 and 16.8 Hz, 1H), 2.84 (dd, *J*= 3.8 and 16.8 Hz, 1H), 1.84 (s, 3H). (*R*)-MTPA ester: ^1H NMR (270 MHz): δ 7.51-7.36 (m, 6H), 7.17 (d, *J*= 7.9 Hz, 1H), 5.65 (ddd, *J*= 3.3, 4.0 and 6.6 Hz, 1H), 4.96 (brs, 1H), 4.56 (brs, 1H), 3.82 (d, *J*= 4.0 Hz, 1H), 3.50 (s, 3H), 3.45 (dd, *J*= 6.6 and 17.2 Hz, 1H), 2.98 (dd, *J*= 3.3 and 17.2 Hz, 1H), 1.83 (s, 3H). The $\Delta\delta$ (δ_S-δ_R) (ppm) values are indicated in the following figure. From this result, it was determined that the absolute configuration of the C6-carbon in **7** was *S* and, in turn, the configuration of **7** was 6*S*,7*S*.[5]



(7*S*)-2-Chloro-7-(2-propenyl)-6,7-dihydro-5*H*-1-pyrindine (8)

Phenyl chlorothionoformate (181 μl, 1.31 mmol) was added to a solution of alcohol **7** (250 mg, 1.19 mmol) and DMAP (407 mg, 3.33 mmol) in acetonitrile (5 ml) at room temperature. After being stirred for 3 h, the mixture was concentrated. Silica gel chromatography of the residue (hexane-ether = 9:1) gave the corresponding thiocarbonate (267 mg, 65%), which was immediately used for the next reaction.

Tributyltinhydride (0.62 ml, 2.32 mmol) and triethylborane (230 μl, 1.0 mol dm^{-3} in THF) was added to a solution of the above thiocarbonate (267 mg, 0.77 mmol) in benzene (3.8 ml) at room temperature. After being stirred for 12 h, the mixture was directly subjected to silica gel chromatography (hexane-dichloromethane = 2:1) to give olefin **8** (91 mg, 61%) as an oil. $[\alpha]_D^{24}$ -6.5° (c 0.57, $CHCl_3$). ^1H NMR (270 MHz): δ 7.47 (d, J= 7.9 Hz, 1H), 7.09 (d, J= 7.9 Hz, 1H), 4.88 (brs, 1H), 4.74 (brs, 1H), 3.83 (dd, J= 6.3 and 8.6 Hz, 1H), 3.01-2.78 (m, 2H), 2.45-2.30 (m, 1H), 2.13-2.00 (m, 1H), 1.71 (brs, 3H). IR (KBr): 3460, 2968, 1647, 1568, 1420, 1167, 1121, 1086, 899, 818, 532. HREIMS m/z Calcd for $C_{11}H_{12}ClN$: 193.0658. Found 193.0667 (M^+).

(7*R*)-2-Chloro-7-(1-hydroxy-1-methylethyl)-6,7-dihydro-5*H*-1-pyrindine (9a)

*m*CPBA (18 mg, 74.4 μmol) was added to a solution of olefin **8** (10 mg, 51.6 μmol) in dichloromethane (0.6 ml) at 0 °C. After being stirred at the temperature for 2.5 h, the mixture was filtered through a pad of silica gel and aluminum oxide to give the corresponding epoxide (8.2 mg, 76%), which was immediately used for the next reaction without further purification.

Super hydride® (76 μl, 1.0 mol dm^{-3} in THF) was added to a solution of the above epoxide (8.2 mg, 39.1 μmol) in THF (0.2 ml) at 0 °C. After being stirred at the temperature for 1 h, the mixture was cooled to 0 °C and quenched with water. To this solution was added saturated aqueous $NaHCO_3$ and 30% H_2O_2. After vigorous stirring for 30 min, the mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 8:2) gave alcohol **9a** (6.5 mg, 79%) as an oil. The ^1H NMR spectrum of alcohol **9a** was identical with the authentic sample prepared as described before.[2d,e] **9a**: $[\alpha]_D^{26}$ -38.6° (c 0.49, $CHCl_3$).

Compound **9a** was converted into bipyrindine ligand **2** in the same manner as described in the literature.[2d,e]

2-Chloro-5,6-dihydroquinoline (11)

n-Butyllithium (18.2 ml, 1.68 mol dm^{-3} in hexane) was added to a solution of *N,N*-diisopropylamine (4.2 ml, 30 mmol) in THF (30 ml) at 0 °C. After being stirred for 30 min, the mixture was cooled to -78 °C. To this solution was added 2-chloro-5,6,7,8-tetrahydro-quinoline (**10**)[7] (5.03 g, 30 mmol) in THF (30 ml) dropwise and the mixture was gradually raised to -20 °C. After stirred for 1 h at the temperature, the mixture was cooled to -78 °C. This solution was added to a pre-cooled (-20 °C) solution of diphenyldisulfide (7.2 g, 33 mmol) in THF (30 ml) *via* cannula. After being stirred for 10 min, the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 30:1) gave the corresponding sulfide (7.83 g, 95%) as an oil. ^1H NMR (270 MHz): δ 7.53-7.10 (m, 7H), 4.61 (t, J= 4.0 Hz, 1H), 2.86-2.60 (m, 2H), 2.28-1.73 (m, 4H).

*m*CPBA (7.01 g, 28.4 mmol) was added to a solution of the above sulfide (7.83 g, 28.4 mmol) in dichloromethane (284 ml) at 0 °C. After being stirred at the temperature for 30 min, the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The extract was washed three times with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 30:1) gave the corresponding diastereomeric sulfoxide (7.2 g, 87%) as crystals.

The above sulfoxide (7.2 g, 24.7 mmol) was dissolved in toluene (25 ml) and refluxed for 1 h. After cooled to room temperature, the mixture was concentrated *in vacuo*. Silica gel chromatography of the residue (hexane-benzene = 1:1) gave olefin **11** (2.82 g, 69%) as an oil. ^1H NMR (270 MHz): δ 7.32 (d, J= 7.9 Hz, 1H), 7.04 (d, J= 7.9 Hz, 1H), 6.58 (dt, J= 2.0 and 9.9 Hz, 1H), 6.36 (dt, J= 4.3 and 9.9 Hz, 1H), 2.82 (t, J= 8.3 Hz, 2H), 2.37 (dddd, J= 2.0, 4.3, 8.3 and 8.3 Hz, 2H). IR (KBr): 3449, 3045, 2936, 2887, 2831, 1580, 1556, 1437, 1196, 1126, 1107, 1011, 937, 856, 804, 700, 629, 530. Anal. Calcd for C_9H_8ClNO: C, 65.27; H, 4.87; N, 8.46. Found: C, 65.27; H, 4.89; N, 8.43.

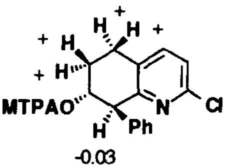
(7*R*,8*S*)-2-Chloro-7,8-epoxy-5,6,7,8-tetrahydroquinoline (13)

Mn-salen complex **12** (15.2 mg, 14.7 μmol) was added to a solution of olefin **11** (240 mg, 1.45 mmol) and 4-phenylpyridine *N*-oxide (24 mg, 0.14 mmol) in dichloromethane (4 ml). To this solution was added aqueous NaOCl (3.6 ml, 0.79 M) adjusted at pH 12 with phosphate buffer at the temperature. After vigorous stirring for 3 h, the mixture was diluted with water (20 ml), extracted with ether, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 19:1~9:1) gave epoxide **13** (193 mg, 73%) as an oil. $[\alpha]_D^{24}$ -124.0° (*c* 1.08, $CHCl_3$). ^1H NMR (270 MHz): δ 7.36 (d, *J*= 7.9 Hz, 1H), 7.23 (d, *J*= 7.9 Hz, 1H), 4.03 (d, *J*= 4.0 Hz, 1H), 3.80-3.78 (m, 1H), 2.75 (ddd, *J*= 6.6, 13.2 and 15.8 Hz, 1H), 2.58-2.41 (m, 2H), 1.78 (dddd, *J*= 1.0, 5.94, 13.2 and 13.2 Hz, 1H). IR (KBr): 3449, 3001, 2937, 2851, 1570, 1443, 1192, 1134, 1117, 982, 939, 874, 831, 775, 737, 671, 648, 621, 565. Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.54; H, 4.51; N, 7.66.

(7*R*,8*R*)-2-Chloro-7-hydroxy-8-phenyl-5,6,7,8-tetrahydroquinoline (14)

Phenyllithium (2.6 ml, 1.8 mol dm^{-3} in cyclohexane/ether 7:3) was added to a suspension of CuCN (209.5 mg, 2.3 mmol) in THF (5.3 ml) at -78 °C and gradually raised to -10 °C. After stirring for 5 min at the temperature, the mixture was cooled to -78 °C. To the mixture were added $BF_3 \bullet OEt_2$ (0.29 ml, 2.3 mmol) and a solution of epoxide **13** (193 mg, 1.06 mmol) in THF (1 ml). After being stirred for another 2 h at the temperature, the mixture was raised to room temperature, quenched with saturated aqueous NH_4Cl, and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3~6:4) gave alcohol **14** (204 mg, 74%) as colorless crystals. M.p. 172-173 °C. $[\alpha]_D^{25}$ -1.8° (*c* 0.90, $CHCl_3$). ^1H NMR (270 MHz): δ 7.45 (d, *J*= 8.3 Hz, 1H), 7.34-7.17 (m, 3H), 7.13 (d, *J*= 8.3 Hz, 1H), 7.20-6.94 (m, 3H), 4.25-4.15 (m, 2H), 3.07-2.80 (m, 2H), 2.12-1.79 (m, 3H). IR (KBr): 3454, 2939, 1570, 1493, 1443, 1258, 1200, 1138, 1107, 1063, 1001, 953, 930, 843, 785, 758, 702, 631, 530. Anal. Calcd for $C_{15}H_{14}ClNO$: C, 69.37; H, 5.43; N, 5.39. Found: C, 69.28; H, 5.48; N, 5.36.

A small amount of **14** was converted into the corresponding (*S*)- and (*R*)-MTPA esters as described by Kusumi[5b] to determine its configuration. (*S*)-MTPA ester: ^1H NMR (270 MHz): δ 7.42-7.18 (m, 9H), 7.13 (d, *J*= 7.9 Hz, 1H), 7.00-6.96 (m, 2H), 5.57-5.53 (m, 1H), 4.52 (d, *J*= 3.3 Hz, 1H), 3.45 (s, 3H), 2.90-2.85 (m, 2H), 2.14-1.95 (m, 2H). (*R*)-MTPA ester: ^1H NMR (270 MHz): δ 7.57-7.15 (m, 10H), 7.02-6.99 (m, 2H), 5.57-5.53 (m, 1H), 4.55 (d, *J*= 3.6 Hz, 1H), 3.42 (s, 3H), 2.86-2.81 (m, 2H), 2.09-1.79 (m, 2H). The Δδ (δ_S-δ_R) (ppm) values are described in the following figure. [The signals of protons at the ethylene moiety in (*R*)-ester appear in the upper field than those in (*S*)-ester. However, these signals appear as multiplet and the correct measurement of Δδ was difficult. Accordingly only the signs of Δδ's are given.] This result indicated that the absolute configuration of the C7-carbon in **14** was *R* and, therefore, the configuration of **14** was determined to be 7*R*,8*R*.[5]



(8*R*)-2-Chloro-8-phenyl-5,6,7,8-tetrahydroquinoline (15)

Phenyl chlorothionoformate (120 µl, 0.86 mmol) was added to a solution of alcohol **14** (204 mg, 0.786 mmol) and DMAP (269 mg, 2.2 mmol) in acetonitrile (3 ml) at room temperature. After being stirred for 3 h, the mixture was concentrated. Silica gel chromatography of the residue (hexane-ether = 9:1~5:1) gave thiocarbonate (212 mg, 68%) as an oil. ^{1}H NMR (270 MHz): δ 7.51 (d, *J*= 8.3 Hz, 1H), 7.42-7.20 (m, 8H), 7.08-7.04 (m, 3H), 5.82 (dt, *J*= 2.6 and 4.6 Hz, 1H), 4.81 (brs, 1H), 3.12-2.85 (m, 2H), 2.22-2.00 (m, 2H).

Tributyltinhydride (216 µl, 0.8 mmol) and triethylborane (107 µl, 1.0 mol dm^{-3} in THF) was added to a solution of the above thiocarbonate (212 mg, 0.54 mmol) in benzene (2.7 ml) at room temperature. After being stirred for 12 h, the mixture was directly subjected to silica gel chromatography (hexane-dichloromethane = 2:1) to give **15** (75 mg, 58%) as an oil. $[\alpha]^{24}_{D}$ +21.7° (*c* 0.60, $CHCl_3$). ^{1}H NMR (270 MHz): δ 7.42 (d, *J*= 8.3 Hz, 1H), 7.30-7.13 (m, 3H), 7.11 (d, *J*= 8.3 Hz, 1H), 6.97-6.90 (m, 2H), 4.30 (t, *J*= 5.3 Hz, 1H), 2.93-2.72 (m, 2H), 2.30-2.13 (m, 1H), 2.05-1.95 (m, 1H), 1.90-1.64 (m, 2H). IR (KBr): 3449, 3060, 2934, 2860, 1564, 1493, 1441, 1200, 1182, 1136, 1101, 858, 816, 754, 700, 642, 584. Anal. Calcd for $C_{15}H_{14}ClN$: C, 73.92; H, 5.79; N, 5.75. Found: C, 73.87; H, 5.82; N, 5.72.

(8*R*,8*R*')-8,8'-Diphenyl-5,5',6,6',7,7',8,8'-octahydro-2,2'-biquinoline (16)

To a stirred solution of $NiCl_2{\bullet}6H_2O$ (72.7 mg, 0.31 mmol) and triphenylphosphine (320 mg, 1.23 mmol) in DMF (1.5 ml) was added zinc powder (19.7 mg, 0.31 mmol) at 50 °C. After the mixture was stirred for 1 h, a solution of **15** (75 mg, 0.31 mmol) in DMF (0.5 ml) was added at the same temperature. After another 12 h, the mixture was poured into a mixture of aqueous 10% NH_3 and $CHCl_3$. The organic layer was separated, washed three times with water, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ether = 9:1~5:1) gave biquinoline **16** (39 mg, 61%) as colorless crystals. M.p. 144-145 °C. $[\alpha]^{25}_{D}$ +150.7° (*c* 0.14, $CHCl_3$). ^{1}H NMR (270 MHz): δ 7.85 (d, *J*= 7.9 Hz, 2H), 7.39 (d, *J*= 7.9 Hz, 2H), 7.34-7.03 (m, 10H), 4.36 (t, *J*= 5.9 Hz, 2H), 2.96-2.75 (m, 4H), 2.32-2.21 (m, 2H), 2.10-1.99 (m, 2H), 1.92-1.72 (m, 4H). IR (KBr): 3449, 3062, 2936, 2860, 1603, 1551, 1445, 1427, 1373, 1240, 1119, 826, 754, 723, 694, 523. HREIMS m/z Calcd for $C_{30}H_{28}N_2$: 416.2252. Found 416.2254 (M^+).

Ethyl *dl*-5-phenyl-3-(2-tetrahydropyranyloxy)-4-pentynoate (19)

Butyllithium (29 ml, 1.69 mol dm^{-3} in hexane) was added to a solution of *N,N*-diisopropylamine (6.9 ml, 49 mmol) in THF (74 ml) at 0 °C. After being stirred for 30 min, the mixture was cooled to -78 °C. To this solution was added ethyl acetate (4.8 ml, 49 mmol) at the temperature. After 1h, a solution of phenylpropargylaldehyde (**18**, 6.4 g, 49 mmol) in THF (12 ml) was added to the solution dropwise. After being stirred for another 10 min, the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 8:2) gave β-hydroxy ester (9.61 g, 96%) as an oil. ^{1}H NMR (270 MHz): δ 7.44-7.27 (m, 5H), 4.99 (dt, *J*= 5.9 and 5.9 Hz, 1H), 4.22 (q, *J*= 7.3 Hz, 2H), 3.21 (d, *J*= 5.9 Hz, 1H), 2.84 (d, *J*= 5.9 Hz, 2H), 1.29 (t, *J*= 7.3 Hz, 3H). IR (KBr): 3450, 2984, 1734, 1491, 1445, 1373, 1275, 1174, 1028, 758, 692. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.35; H, 6.48.

To a solution of the above β-hydroxy ester (9.61 g, 46.7 mmol) and *dl*-camphorsulfonic acid (217 mg, 0.9 mmol)) in dichloromethane (93 ml) was added dihydropyran (4.5 ml, 49.0 mmol) at room temperature. After being stirred for 30 min, triethylamine (1 ml) was added and the mixture was concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1) gave ester (**19**, 12.47 g, 88%) as an oil. IR (KBr): 3450, 2943, 1740, 1491, 1373, 1283, 1175, 1121, 1022, 978, 872, 758, 692. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.40; H, 7.35.

dl-1-Phenyl-5-(*p*-toluenesulfonyloxy)-1-pentyn-3-ol (20)

To a solution of ester (**19**, 12.47 g, 41.2 mmol) in THF (90 ml) was added LAH (1.56 g, 41.2 mmol) at 0 °C. After being stirred for 15 min, the mixture was quenched with MeOH (1 ml) and warmed to room temperature. Saturated aqueous potassium sodium tartrate (90 ml) was added to the mixture and vigorously stirred for 30 min. The mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated to give the corresponding alcohol which was used for the next reaction without further purification. IR (KBr): 2943, 2874, 2228, 1491, 1443, 1189, 1119, 1022, 758, 692. HREIMS m/z Calcd for $C_{16}H_{20}O_3$: 260.1412. Found 260.1412 (M^+).

p-Toluenesulfonyl chloride (10.16 g, 53.3 mmol) was added to a solution of 4-(*N*,*N*-dimethylamino)pyridine (50 mg, 0.41 mmol), triethylamine (7.4 ml, 53.3 mmol), and the above alcohol (10.5 g, 40.3 mmol) in dichloromethane (80 ml). After being stirred for 30 min, the mixture was concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1~8:2) gave the corresponding tosylate, (15.71 g, 92% for 2 steps) as an oil. IR (KBr): 3450, 2928, 1738, 1650, 1355, 1244, 1177, 918, 760, 692, 555. HREIMS m/z Calcd for $C_{23}H_{26}O_5S$: 414.1501. Found 414.1509 (M^+).

To a solution of the above tosylate (15.71 g, 37.9 mmol) in MeOH (400 ml) was added (*dl*)-camphorsulfonic acid (440 mg, 1.9 mmol) at room temperature. After being stirred for 3h, triethylamine (2 ml) was added and the mixture was concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1~7:3) gave tosylate (**20**, 11.37 g, 91%) as colorless crystals. ^{1}H NMR (270 MHz): δ 7.80 (d, *J*= 8.3 Hz, 2H), 7.38-7.27 (m, 7H), 4.73 (dt, *J*= 6.3 and 6.3 Hz, 1H), 4.32 (dt, *J*= 6.3 and 9.9 Hz, 1H), 4.23 (dt, *J*= 6.3 and 9.9 Hz, 1H), 2.40 (s, 3H), 2.16 (d, *J*= 6.3 Hz, 1H), 2.14 (dt, *J*= 6.3 and 6.3 Hz, 2H). IR (KBr): 3883, 3074, 3011, 1600, 1443, 1360, 1288, 1173, 1094, 1026, 926, 841, 779, 696, 554. Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.44; H, 5.49. Found: C, 65.21; H, 5.56.

dl-2-(2-Phenylethynyl)oxetane (21)

Butyllithium (4.2 ml, 1.69 mol dm^{-3} in hexane) was added to a solution of tosylate (**20**, 2.35 g, 7.12 mmol) in THF (35 ml) at 0 °C and gradually raised to 50°C. After being stirred for 3 h at the temperature, the mixture was cooled to room temperature, quenched with water (50 ml), and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Kugel Rohr distillation (160°C, 2 mmHg) gave oxetane **21** (622 mg, 55%) as an oil. ^{1}H NMR (270 MHz): δ 7.43-7.22 (m, 5H), 5.50 (t, *J*= 7.3 Hz, 1H), 4.63 (t, *J*= 7.3 Hz, 2H), 2.76-3.01 (m, 2H). IR (KBr): 3450, 3011, 2887, 2224, 1491, 1445, 1340, 1229, 1070, 961, 916, 758, 692, 554. HREIMS m/z Calcd for $C_{11}H_{10}O$: 158.0732. Found 158.0731 (M^+).

tert-Butyl (2*S*,3*RS*)-3-(2-phenylethynyl)tetrahydrofuran-2-carboxylate (22)

To a suspension of CuOTf•0.5C_6H_6 (2.9 mg, 11.4 μmol) in CH_2Cl_2 (2.1 ml) was added a solution of **2** (7.3 mg, 12.6 μmol) in CH_2Cl_2 (0.5 ml). After 30 min, the mixture was filtered through a packed adsorbent cotton under argon and to the filtrate was added *dl*-2-(2-phenylethynyl)oxetane (352 mg, 2.2 mmol). To the solution was added dropwise a solution of *tert*-butyl diazoacetate (295 μl, 2.2 mmol) in CH_2Cl_2 (1 ml) over a period of 30 min at room temperature. The mixture was concentrated and purified by silica gel chromatography (hexane-*i*-Pr_2O = 5:1) to give a mixture of *trans*- and *cis*-**22** (482 mg, 88%) as an oil, which was used for the following reaction without separation. IR (KBr): 3450, 2984, 2930, 2230, 1740, 1738, 1491, 1371, 1367, 1248, 1157, 1103, 843, 760, 696, 540. HREIMS m/z Calcd for $C_{17}H_{20}O_3$: 272.1412. Found 272.1407 (M^+).

(2*S*,3*RS*)-2-Hydroxymethyl-3-(2-phenylethynyl)tetrahydrofuran (23)

To a solution of ester **22** (320 mg, 1.3 mmol) in THF (5.2 ml) was added LAH (49 mg, 1.3 mmol) at 0 °C. After being stirred for 30 min, the mixture was quenched with MeOH and warmed to room temperature. Saturated aqueous potassium sodium tartrate (5 ml) and ethyl acetate (5 ml) were added to the mixture and vigorously stirred for 30 min. The mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3) gave alcohol **23** (250 mg, 95%) as an oil. IR (KBr): 3430, 2928, 2878, 1800, 1512, 1491, 1069, 758, 692. HREIMS m/z Calcd for $C_{13}H_{14}O_2$: 202.0994. Found 202.0989 (M^+).

(2*R*,3*RS*)-2-Butyl-3-(2-phenylethynyl)tetrahydrofuran (24)

To a solution of alcohol **23** (516 mg, 2.6 mmol) and pyridine (619 µl, 7.7 mmol) in dichloromethane (7.6 ml) was added trifluoromethanesulfonic anhydride (644 µl, 3.8 mmol) in dichloromethane (3.0 ml) dropwise at -15 °C. After being stirred for 30 min, the mixture was raised to room temperature, diluted with dichloromethane (20 ml), and washed successively with aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered through a pad of silica gel, and concentrated to give the corresponding triflate which was used without further purification for the next reaction after toluene azeotrope (x 2).

To a suspension of CuBr (73 mg, 0.51 mmol) in THF (6.5 ml) was added *n*-propylmagnesium bromide (1.9 ml, 2.0 mol dm^{-3} in THF) at 0 °C. To this mixture was added the above triflate (767 mg, 2.3 mmol) in THF (4.3 ml) at the temperature. After being stirred at this temperature for 2h, the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 19:1) gave **24** (450 mg, 77%) as an oil. IR (KBr): 3445, 2957, 2982, 2860, 1638, 1498, 1130, 756, 692. HREIMS m/z Calcd for $C_{16}H_{20}O$: 228.1514. Found 228.1510 (M^+).

(2*R*,3*RS*)-2-Butyl-3-[(Z)-2-phenylethenyl]tetrahydrofuran (25)

To a solution of ethanol (3 ml) and 2*N* aqueous NaOH was added $NaBH_4$ (125 mg, 3.3 mmol) at room temperature. After being stirred for 10 min, the mixture was filtered through a pad of celite. A portion (0.62 ml) of the filtrate was added dropwise to a vigorously stirred suspension of $Ni(OAc)_2 \cdot 4H_2O$ (122.6 mg, 0.49 mmol) in ethanol (11.8 ml) under hydrogen. To this mixture was added ethylenediamine (99 µl, 1.48 mmol) and **24** (450 mg, 1.97 mmol) in ethanol (5 ml). After being stirred for 3h, the mixture was diluted with water and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 19:1) gave **25** (445 mg, 98%) as an oil. IR (KBr): 3440, 2981, 2957, 2361, 1651, 1510, 1456, 1072, 770, 700. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.14; H, 9.58.

(2*R*,3*R*)-2-Butyltetrahydrofuran-3-carboxaldehyde (26)

Potassium osmate (7.3 mg, 0.02 mmol) was added to a solution of **25** (450 mg, 1.95 mmol) in THF-H_2O (2:1, 12 ml) at room temperature. After 5 min, periodic acid (1.12 g, 4.92 mmol) was added and the mixture was stirred for another 3h. The mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (pentane-ether = 9:1) gave a mixture of (2*R*,3*R*)- and (2*R*,3*S*)-aldehydes (305 mg, 77%) as an oil.

The mixture of aldehydes (269 mg, 1.72 mmol) was dissolved into a methanol solution of NaOMe (6.9 ml, 0.25 mol dm^{-3}) and stirred for 30 min. The mixture was diluted with water (50 ml) and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and concentrated to give a 95:5 mixture of (2*R*,3*R*)- and (2*R*,3*S*)-aldehydes by ^1H NMR analysis. This product **26** was immediately used for the next reaction without further purification because it was very sensitive to air oxidation. **26**: ^1H NMR (270 MHz, only the signals relating to (2*R*,3*R*)-aldehyde are described.): δ 9.66 (d, *J*= 3.0 Hz, 1H), 4.03 (dt, *J*= 6.3 and 7.3 Hz, 1H), 3.94 (ddd, *J*= 6.3, 7.3 and 8.6 Hz, 1H), 3.86-3.70 (m, 1H), 2.70 (ddd, *J*= 3.0, 6.3 and 15.8 Hz, 1H), 2.28-1.95 (m, 2H), 1.68-1.20 (m, 6H), 0.91 (t, *J*= 6.6 Hz, 3H).

(2*R*,3*R*)-2-Butyl-3-hydroxymethyltetrahydrofuran (27a)

To a solution of aldehyde **26** (181 mg, 1.16 mmol) in THF (4.6 ml) was added LAH (44 mg, 1.16 mmol) at 0 °C. After being stirred for 30 min, the mixture was quenched with MeOH and warmed to room temperature. Saturated aqueous potassium sodium tartrate (5 ml) and ethyl acetate (10 ml) were added to the mixture and vigorously stirred for 30 min. The mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3) gave alcohol **27a** (*trans*:*cis*=95:5, 152 mg, 85%) as an oil. ^1H NMR (270 MHz): δ 4.14-3.58 (m, 5H), 2.14-2.00 (m, 2H), 1.76-1.24 (m, 7H), 0.91 (t, *J*= 6.9 Hz, 3H).

p-Nitrobenzoyl chloride (732 mg, 3.94 mmol) was added to a solution of 4-(*N*,*N*-dimethylamino)pyridine (10 mg, 0.08 mmol), triethylamine (0.55 ml, 3.94 mmol), and alcohol **27a** (156 mg, 0.99 mmol) in dichloromethane (4 ml). After being stirred for 1 h, the mixture was concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1~8:2) gave *p*-nitrobenzoate **27b** (260 mg, 86%) as an oil. The optical purity of **27b** was determined to be 73% ee by HPLC analysis (Daicel Chiralcel OJ; 0.46 cm x 25 cm, hexane/*i*-PrOH=9:1, flow rate 0.5 ml/min, UV detector 254 nm; t_{cis}= 43.50 min, $t_{trans(2R,3R)}$= 53.36 min, $t_{trans(2S,3S)}$= 62.35 min). Recrystallization from hexane at -20 °C gave crystals (49% ee) and a filtrate containing **27b** of 89% ee and a small amount of the *cis*-isomer. The filtrate was concentrated and the resulting crystals were subjected to recrystallization from hexane again at -20 °C. Compound **27b** of 98% ee containing the 7% of *cis*-isomer was obtained from the filtrate in 33% yield. $[\alpha]_D^{27}$ +13.9° (*c* 0.47, $CHCl_3$). ^1H NMR (270 MHz): δ 8.33-8.18 (m, 4H), 4.42-4.31 (m, 2H), 3.93 (ddd, *J*= 5.9, 7.3 and 8.9 Hz, 1H), 3.82 (dt, *J*= 7.3 and 8.9 Hz, 1H), 1.13 (q, *J*= 5.9 Hz, 1H), 2.40-2.13 (m, 2H), 1.84-1.72 (m, 1H), 1.60-1.32 (m, 6H), 0.89 (t, *J*= 6.9 Hz, 3H). IR (KBr): 3450, 2950, 2855, 1728, 1529, 1348, 1275, 1103, 1015, 874, 719. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.63; H, 6.99; N, 4.51.

The *p*-nitrobenzoate **27b** (85 mg, 0.28 mmol) was dissolved in THF (2.7 ml) and cooled to 0 °C. To this solution was added LAH (21 mg, 0.55 mmol) at the temperature. After being stirred for 30 min, the mixture was quenched with MeOH and warmed to room temperature. Saturated aqueous potassium sodium tartrate (3 ml) and ethyl acetate (3 ml) were added to the mixture and vigorously stirred for 30 min. The mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3) gave the enantiomerically enriched alcohol **27a** (39.9 mg, 91%, 98% ee) as an oil that contained 7% of the *cis*-isomer.

(2*R*,3*R*)-2-Butyl-3-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran (28)

p-Toluenesulfonyl chloride (105 mg, 0.55 mmol) was added to a solution of 4-(*N*,*N*-dimethylamino)pyridine (5 mg, 0.04 mmol), triethylamine (77 μl, 0.55 mmol), and alcohol **27a** (containing 7% of the *cis*-isomer) (39.9 mg, 0.25 mmol) in dichloromethane (2.8 ml) at room temperature. After being stirred for 30 min, the mixture was concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1~8:2) gave tosylate **28** (74 mg, 94%) as an oil. $[\alpha]_D^{27}$ +23.4° (*c* 0.71, $CHCl_3$). ^1H NMR (270 MHz): δ 7.79 (d, *J*= 7.9 Hz, 2H), 7.36 (d, *J*= 7.9 Hz, 2H), 3.98 (d, *J*= 6.6 Hz, 2H), 3.82 (ddd, *J*= 5.9, 7.6 and 8.6 Hz, 1H), 3.68 (ddd, *J*= 6.6, 7.6 and 8.6 Hz, 1H), 3.47 (q, *J*= 5.9 Hz, 1H), 2.46 (s, 3H), 2.21-2.0 (m, 2H), 1.67-1.20 (m, 7H), 0.88 (t, *J*= 6.6 Hz, 3H). IR (KBr): 3450, 2982, 2957, 2860, 1599, 1466, 1364, 1190, 1177, 1097, 951, 816, 667, 556. Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74. Found: C, 61.67; H, 7.72.

trans-Whisky lactone (17)

To a solution of tosylate **28** (containing 7% of the *cis*-isomer) (56.9 mg, 0.182 mmol) in ether (2 ml) was added LAH (20 mg, 0.53 mmol) at 0 °C and gradually raised to room temperature. After being stirred for 3 h, the mixture was quenched with 1N HCl and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and ether was carefully distilled off to give **29** (30 mg, containing a trace amount of ether). This compound **29** was immediately used for the next reaction without further purification.

Zinc dichromate[16] (420 mg, 1.25 mmol) was added in small portions to a solution of the tetrahydrofuran **29** (30 mg, containing a trace amount of ether) in dichloromethane (3.6 ml) at room temperature. After being stirred for 1h, the mixture was filtered through a pad of silica gel and concentrated. Gel permeation chromatography of the residue ($CHCl_3$) gave *trans*-whisky lactone **17** (10.5 mg, 37% from tosylate **28**) as an oil. $[\alpha]_D^{25}$ +81.8° (*c* 0.41, MeOH). ^1H NMR (270 MHz): δ 4.10 (m, 1H), 2.75-2.58 (m, 1H), 2.32-2.13 (m, 2H), 1.73-1.17 (m, 6H), 1.13 (d, *J*= 6.3 Hz, 3H), 0.91 (t, *J*= 6.6 Hz, 3H). CIGCMS (isobutane) m/z 157 (M^++1)

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