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SYNTHESIS OF A PSEUDOENANTIOMER OF β-ISOCUPREIDINE (β-ICD), A CHIRAL AMINE CATALYST FOR ASYMMETRIC BAYLIS-HILLMAN REACTIONS†

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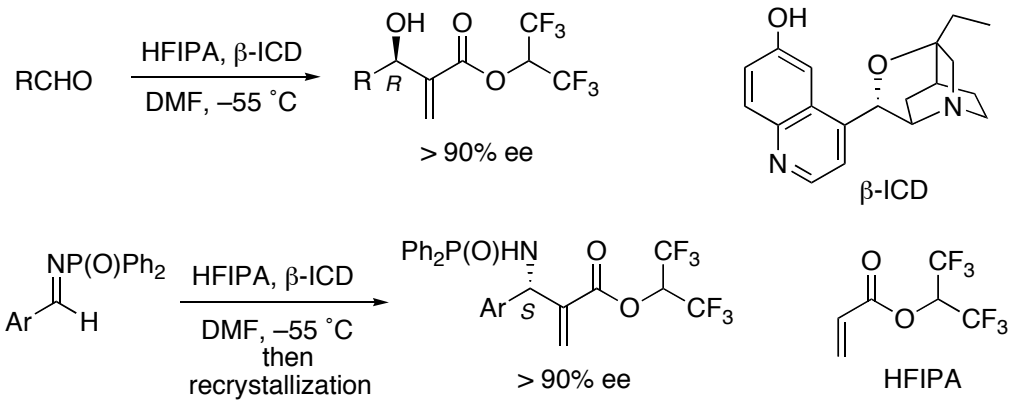
Abstract – (3*S*,8*S*,9*R*)-3,9-Epoxy-6'-hydroxy-11-norcinconane (**23**), a pseudoenantiomer of β-isocupreidine (β-ICD), was synthesized starting with a fragmentation reaction of 10-bromo-10,11-dihydroquinine, prepared from quinine. Baylis-Hillman reaction of benzaldehyde with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) using **23** as a chiral amine catalyst gave the corresponding *S*-enriched adduct in high optical purity (93% ee) in contrast to the β-ICD-catalyzed reaction which affords *R*-enriched adducts.

INTRODUCTION

The Morita-Baylis-Hillman reaction, an organocatalytic three component reaction leading to coupling of aldehydes or imines with activated alkenes, has attracted considerable interest due to the atom economical efficacy and the promising utility of the multifunctional products. However, the major problems associated with this reaction are its slow reaction rate and difficulty in realization of a high level of asymmetric induction. This situation has brought about recent great progress in rate acceleration as well as asymmetric induction based on various imaginative ideas.[1] Recently, we have developed a highly enantioselective asymmetric Baylis-Hillman reaction of aldehydes[2] as well as imines[3] by use of β-isocupreidine (β-ICD)[4,5] as a chiral amine catalyst and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as an activated alkene. In addition, we have successfully demonstrated the synthetic utility of this reaction *via* syntheses of biologically intriguing natural products.[6] This β-ICD-HFIPA method has remarkable advantages in terms of the high enantionselectivity, the broad applicability, and the availability of both β-ICD and HFIPA. However, one serious drawback is that this method cannot be

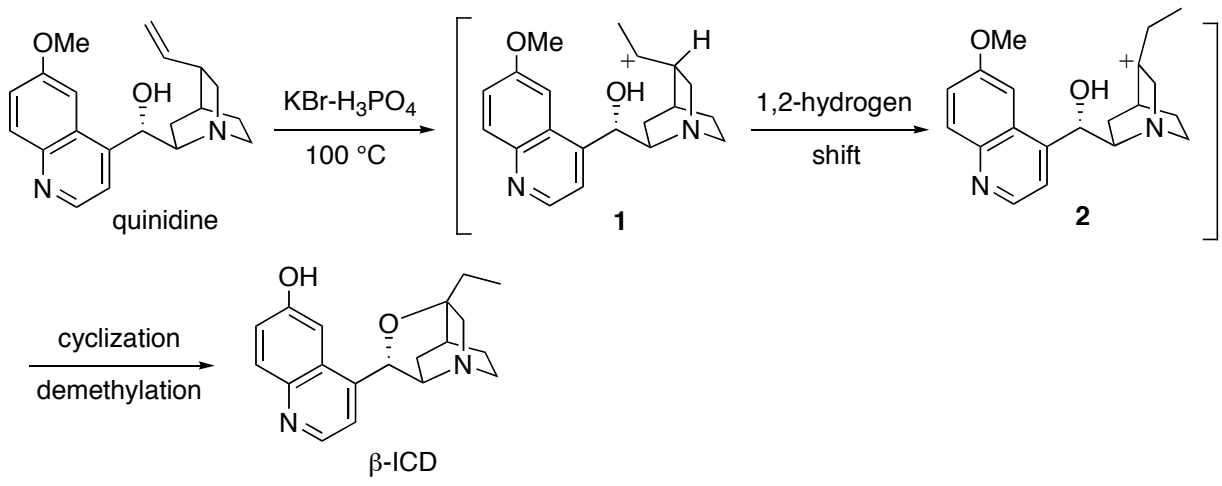
† Dedicated to the memory of the late Professor Kenji Koga.

applied to the synthesis of the products with opposite absolute configuration because the required enantiomer of β-ICD is not easily available.[7] As one solution to this problem, we investigated the synthesis of an enantio-complementary catalyst of β-ICD.[8]



Scheme 1. β-ICD-HFIPA method

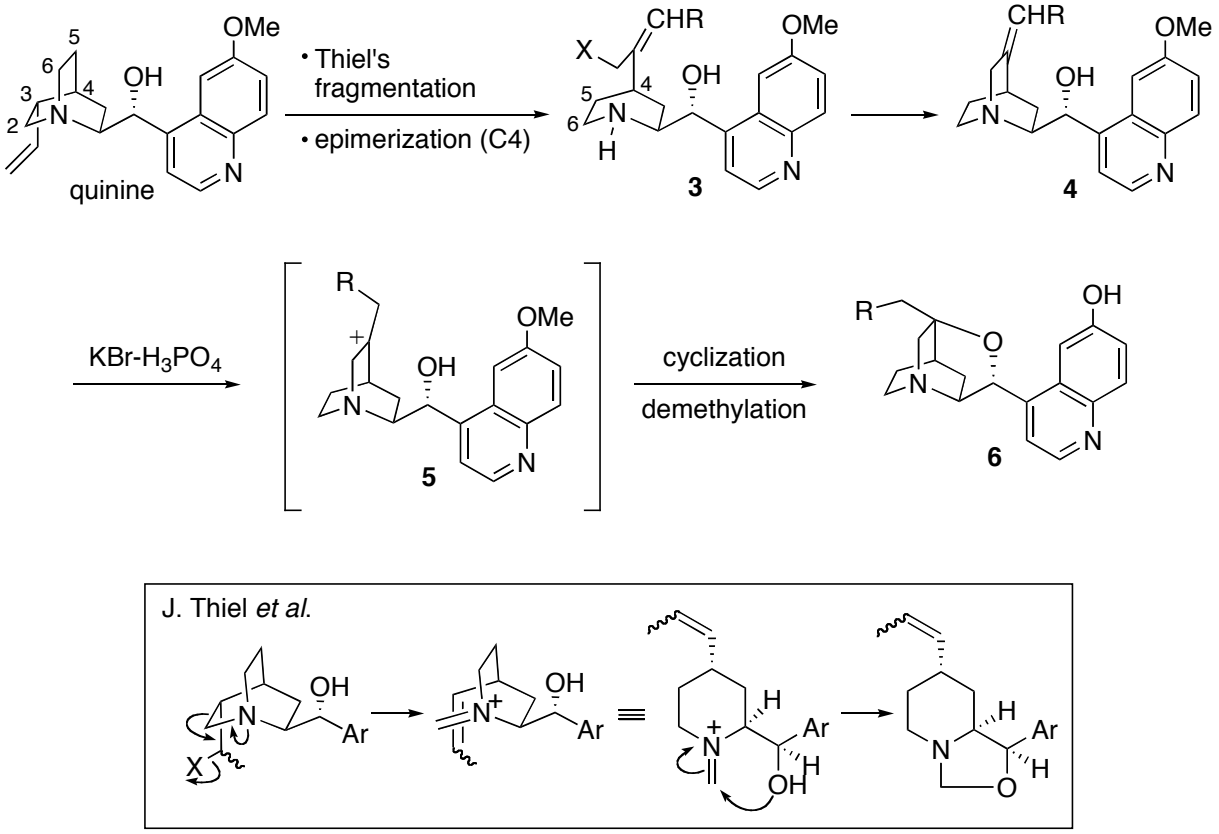
β-ICD can be prepared in one step from quinidine by treatment with aqueous KBr-H_3PO_4 at 100 °C.[2] In this process, together with demethylation, acid-induced cycloisomerization of quinidine takes place *via* carbocations (**1**) and (**2**) as reported by Hoffmann *et al*. (Scheme 2)[9]



Scheme 2. Cycloisomerization of quinidine leading to β-ICD

This transformation suggests that if carbocation (**5**) is accessible from quinine, a pseudoenantiomer of quinidine, then the synthesis of **6**, a pseudoenantiomer of β-ICD, would also become possible. Thus, we envisaged alkene (**4**) as a precursor of carbocation (**5**) and postulated that this intermediate could be accessed via cyclization of piperidine (**3**), accessible from quinine *via* cleavage of the C2-C3 bridge by

taking advantage of the fragmentation reaction developed by Thiel *at al.*[10] and a suitable functionalization of the resulting C4-substituent involving epimerization. (Scheme 3)

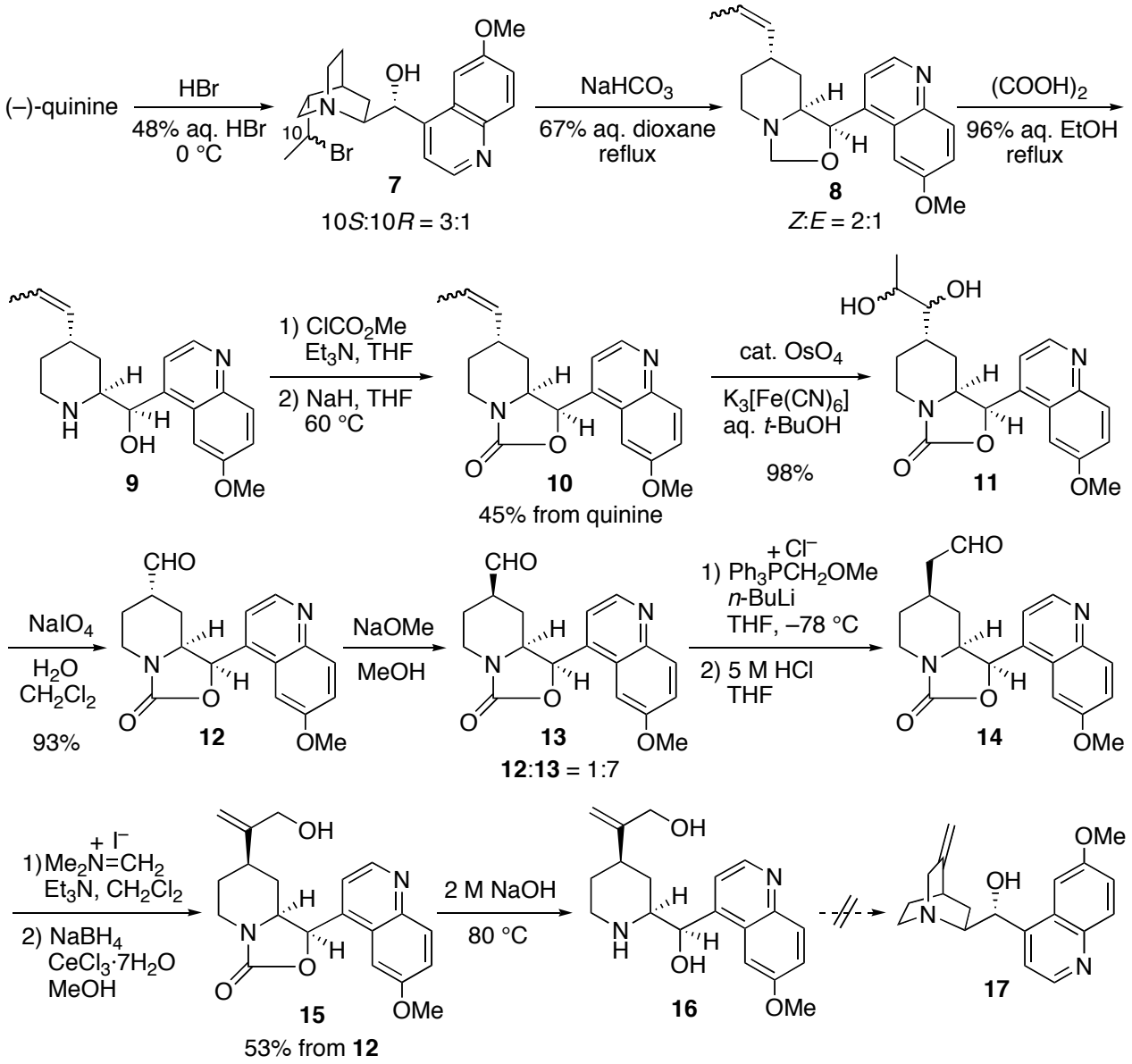


Scheme 3. Strategy for the synthesis of a pseudoenantiomer of β-ICD

RESULTS AND DISCUSSION

Following the strategy mentioned above, the synthesis of a psudoenantiomer of β-ICD started from cleavage of the C2-C3 bridge of quinine by Thiel's fragmentation reaction (Scheme 4). Thus, treatment of 10-bromo-10,11-dihydroquinine (**7**),[11] prepared as a 3:1 epimeric mixture by the reaction of quinine with hydrogen bromide, with aqueous $NaHCO_3$ in boiling dioxane caused fragmentation reaction to give alkene (**8**) as a 2:1 *Z*- and *E*-mixtures. Hydrolysis of the N,O-acetal of **8** followed by protection of **9** as its cyclic carbamate afforded carbamate (**10**). To invert the C4 stereocenter, carbamate (**10**) was successively subjected to dihydroxylation,[11] $NaIO_4$-oxidation, and base-catalyzed epimerization to give a 1:7 equilibrium mixture of aldehydes (**12**) and (**13**). Without separation, this mixture was converted to piperidine (**15**) *via* **14** by a four-step sequence involving Wittig reaction employing methoxymethylenetriphenylphosphorane,[12] acidic hydrolysis, Mannich reaction employing Eschenmoser's salt,[13] and Luche reduction.[14] Alkaline hydrolysis of **15** produced quantitatively amino

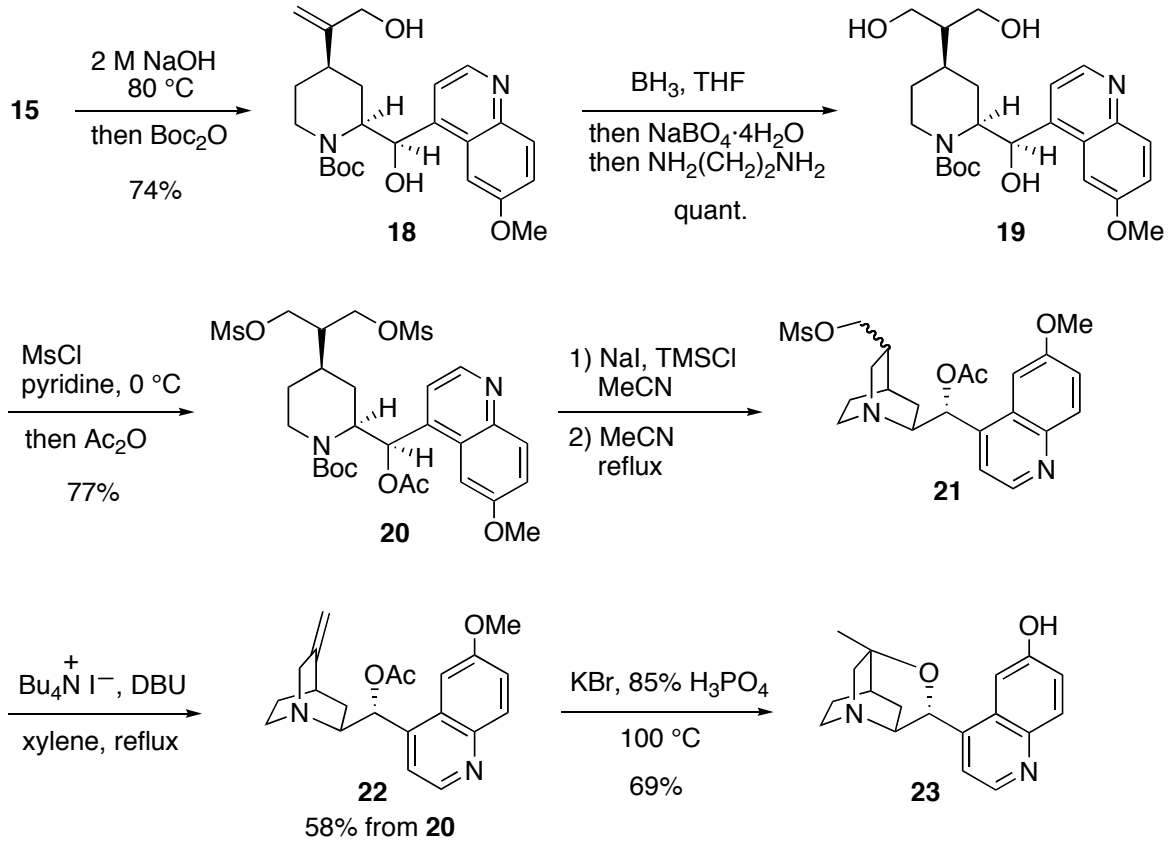
diol (**16**), intramolecular N-alkylation of which was then investigated to obtain quinuclidine (**17**). However, all attempts including the Stork's procedure[15] employed in the synthesis of quinine were unsuccessful.



Scheme 4. Attempt to synthesize the key intermediate

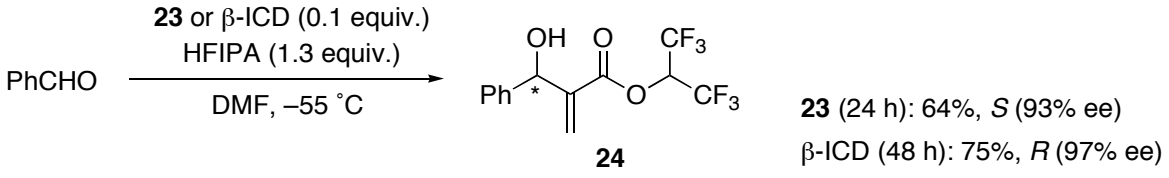
The above-mentioned failure of the quinuclidine ring formation is attributed possibly to severe strain caused by the existence of the exo-methylene. Therefore, we alternatively examined the route shown in Scheme 5. Thus, compound (**15**) was converted to **18** by alkaline hydrolysis followed by *tert*-butoxycarbonylation. Successive hydroboration of **18**, oxidation of the resulting alkylborane using $NaBO_4$,[16] and decomplexation of the corresponding quinoline-borane complex with ethylenediamine afforded triol (**19**) quantitatively. Triol (**19**) was then converted to dimesylate (**20**) by mesylation

followed by acetylation. The *tert*-butoxycarbonyl group of **20** was removed cleanly by the reaction with *in situ* generated trimethylsilyl iodide[17] to give the corresponding amino dimesylate, which underwent cyclization smoothly in boiling acetonitrile to produce quinuclidine (**21**) as an inseparable epimeric mixture. Without purification, **21** was directly treated with DBU and tetra-*n*-butylanmonium iodide in boiling xylene to give alkene (**22**) cleanly. Finaly, **22** was directly exposed to the conditions[2] employed for the synthesis of β-ICD to furnish compound (**23**), a pseudoenantiomer of β-ICD.



Scheme 5. Synthesis of a pseudoenantiomer of β-ICD

In order to evaluate the ability of **23** as a chiral amine catalyst complementary to β-ICD, we examined the Baylis-Hillman reaction of benzaldehyde with HFIPA using **23** as a catalyst. As a result, compound (**23**) catalyzed Baylis-Hillman reaction as effectively as β-ICD and resulted in opposite enantioselectivity.



Scheme 6. Baylis-Hillman reaction of benzaldehyde using **23** and β-ICD

In conclusion, we have synthesized chiral amine (**23**) starting from quinine and proved that it behaves as an enantio-complementary catalyst to β-ICD in the asymmetric Baylis-Hillman reaction of aldehydes with HFIPA. Efforts toward improving the synthetic route are now underway in this laboratory.

EXPERIMENTAL

Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. All extracts were dried over K_2CO_3 and concentrated by rotary evaporation below 30 °C at *ca*. 25 Torr unless otherwise noted. TLC was performed with Merck F-254 TLC plates. Column chromatography was performed employing silica gel 60 (230-400 mesh ASTM, Merk). Commercial reagents and solvents including anhydrous tetrahydrofuran (THF) (stabilizer free) were used as supplied with the following exceptions. Dichloromethane (CH_2Cl_2), *N*,*N*-dimethyformamide (DMF), acetonitrile (MeCN), triethylamine, pyridine, and xylene were distilled from CaH_2. All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter at ambient temperature. IR spectra were measured on a JASCO FT/IR-230 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 300, JEOL JNM-AL 400, or a Varian Unity plus 500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) in δ units and coupling constants are given in hertz. TMS was defined as 0 ppm for ^{1}H NMR spectra and the center of the triplet of $CDCl_3$ was also defined as 77.10 ppm for ^{13}C NMR spectra. HRMS (EI) spectra were measured on a JEOL JMS-DX303 or a JEOL JMS-700N.

(1*R*,7*S*,8a*S*)-Tetrahydro-1-(6-methoxyquinolin-4-yl)-7-prop-1-enyl-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (10) (2:1 *Z*- and *E*-mixture). HBr gas, generated by the addition of Br_2 (45 mL) to tetraline (48 mL), was passed slowly through an ice-cooled solution of quinine (11.1 g, 34.3 mmol) in 48% HBr (22 mL) over 3 h. The reaction mixture was basified with 10 M NaOH (130 mL), extracted with Et_2O, washed with brine, dried, concentrated to give bromide **7** (11.5 g) as a yellow amorphous solid, which was used for the next reaction without purification. The ratio of the 10*S* and 10*R*-isomer was determined to be 3:1 by ^{1}H NMR spectrum of **7** which was identical with that reported.[11]

A mixture of crude bromide **7** (11.5 g) and $NaHCO_3$ (5.79 g, 68.7 mmol) in 33% aqueous 1,4-dioxane (807 mL) was heated at 120 ˚C for 6 h. The reaction mixture was concentrated, extracted with $CHCl_3$, washed with brine, dried, and concentrated to give **8** (8.60 g) as a yellow amorphous solid, which was used for the next reaction without purification. The *Z*/*E*-ratio was determined to be 2:1 by ^{1}H NMR spectrum of **8** which was identical with that reported.[10]

A solution of crude **8** (8.60 g) and oxalic acid (3.10 g, 34.4 mmol) in 96% EtOH (550 mL) was refluxed for 3 h. The reaction mixture was basified with 10% K_2CO_3 with cooling in an ice bath, extracted with

$CHCl_3$, washed with brine, dried, and concentrated to give **9** (10.3 g), the ^{1}H NMR spectrum of which was identical with that reported.[10]

To a stirred solution of crude **9** (10.3 g) in THF (200 mL) at rt were added triethylamine (6.74 mL, 48.0 mmol) and methyl chloroformate (3.18 mL, 41.2 mmol). After being stirred at rt for 15 h, H_2O (4 mL) was added and the reaction mixture was concentrated. The residue was extracted with AcOEt, and the extract was washed with brine, dried, and concentrated to give the corresponding carbamate (10.1 g).

To an ice-cooled solution of crude carbamate (10.1 g) in THF (120 mL) was added NaH (60% in mineral oil, 1.60 g, 40.0 mmol) and the mixture was heated at 60 °C for 1.5 h. The reaction was quenched with H_2O (10 mL) with cooling in an ice bath and most of the THF was removed by evaporation. The residue was extracted with Et_2O, washed with brine, dried, concentrated, and chromatographed (SiO_2, $CHCl_3$) to give **10** (5.18 g, 45% from quinine) as a colorless amorphous solid: $[\alpha]_D^{24}$ –250.0° (*c* 1.008, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, *J* = 4.5 Hz, 1H), 8.10 (d, *J* = 9.6 Hz, 0.67H), 8.09 (d, *J* = 9.6 Hz, 0.33H), 7.62 (d, *J* = 4.5 Hz, 1H), 7.45-7.39 (m, 1H), 6.86 (d, *J* = 2.7 Hz, 0.67H), 6.83 (d, *J* = 2.7 Hz, 0.33H), 6.19 (d, *J* = 8.1 Hz, 0.33H), 6.16 (d, *J* = 7.8 Hz, 0.67H), 5.71-5.35 (m, 2H), 4.54-4.45 (m, 1H), 3.95 (s, 2H), 3.93 (s, 1H), 3.89-3.82 (m, 1H), 3.31-3.19 (m, 1H), 2.81 (br s, 0.33H), 2.49 (br s, 0.67H), 1.69 (d, *J* = 1.5 Hz, 2H), 1.68 (d, *J* = 1.5 Hz, 1H), 1.64 (br d, *J* = 4.5 Hz, 1H), 1.49 (br d, *J* = 15.3 Hz, 0.33H), 1.44 (dd, *J* = 1.5, 6.6 Hz, 0.67H), 1.26 (t, *J* = 7.2 Hz, 0.33H), 1.14 (dt, *J* = 4.2, 12.9 Hz, 0.67H), 0.93 (br d, *J* = 14.1 Hz, 0.67H), 0.81 (br d, *J* = 11.7 Hz, 0.33H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 156.3, 148.0, 144.0, 139.1, 132.3, 130.6, 128.5, 126.8, 126.5, 125.8, 121.7, 118.3, 100.3, 100.2, 74.4, 55.7, 55.6, 53.8, 53.6, 38.0, 32.7, 30.8, 30.3, 28.7, 28.4, 28.3, 18.2, 13.0; FT-IR (neat) 2935, 1757, 1622, 1508, 1427, 1238, 1061, 970, 860, 725 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}N_2O_3$ (M^+): 338.1630, found 338.1631.

(1*R*,7*S*,8a*S*)-Tetrahydro-7-(1,2-dihydroxypropyl)-1-(6-methoxyquinolin-4-yl)-1*H*-oxazolo[3,4-*a*]-pyridin-3(5*H*)-one (11) (diastereoisomeric mixture). To a stirred solution of **10** (1.20 g, 3.53 mmol) in 50% aqueous *tert*-BuOH (36 mL) at rt were added K_2CO_3 (1.37 g, 9.90 mmol), $K_3[Fe(CN)_6]$ (3.26 g, 9.90 mmol), and an aqueous solution of OsO_4 (0.15 M, 0.48 mL, 0.072 mmol). After 13 h, saturated $Na_2S_2O_3$ (7 mL) was added and the mixture was stirred at rt for 10 min. The reaction mixture was basified with 10% K_2CO_3, extracted with $CHCl_3$, and the extract was washed with brine, dried, concentrated, and chromatographed (SiO_2, $CHCl_3$/MeOH = 30/1) to give **11** (1.29 g, 98%) as a colorless amorphous solid: $[\alpha]_D^{24}$ –205.9° (*c* 1.195, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81-8.67 (m, 1H), 8.12-7.98 (m, 1H), 7.65-7.54 (m, 1H), 7.46-7.34 (m, 1H), 6.94-6.82 (m, 1H), 6.22-6.10 (m, 1H), 4.85-4.70 (m, 0.8H), 4.70-4.60 (m, 0.13H), 4.57-4.47 (m, 0.07H), 4.01-3.15 (m, 4H), 3.95, 3.94 (s x 2, 3H), 2.96-2.50 (m, 1H), 2.30 (br s, 1H), 2.05-1.38 (m, 3H), 1.30-0.84 (m, 2H), 1.16, 1.14, 1.06, 0.99 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 158.3, 156.6, 156.5, 156.5, 147.5, 147.4, 143.5, 139.6, 139.5, 139.4, 132.0, 131.8, 131.5, 125.9, 125.8, 122.1, 122.0, 121.9, 121.7, 118.3, 118.2, 118.1, 100.5, 100.4, 100.3, 75.5, 74.7,

74.7, 74.6, 74.4, 72.5, 72.3, 68.4, 68.2, 68.0, 67.9, 55.7, 54.2, 53.9, 53.8, 39.2, 38.5, 38.3, 38.2, 33.1, 32.3, 29.3, 27.8, 26.8, 26.6, 26.4, 25.7, 24.4, 23.8, 20.5, 20.2, 16.3, 15.8; FT-IR (neat) 3417, 2931, 1751, 1624, 1510, 1435, 1240, 1065 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}N_2O_5$ (M^+): 372.1685, found 372.1674.

(1*R*,7*S*,8a*S*)-Hexahydro-1-(6-methoxyquinolin-4-yl)-3-oxo-1*H*-oxazolo[3,4-*a*]pyridine-7-carbaldehyde (12). To a solution of the above-mentioned diol (978.7 mg, 2.63 mmol) in CH_2Cl_2 (30 mL) were added H_2O (3 mL) and $NaIO_4$ (731.5 mg, 3.42 mmol), and the mixture was stirred at rt for 1 h. The reaction mixture was basified with saturated $NaHCO_3$ (10 mL) and filterd through a pad of Celite. The pad was washed with CH_2Cl_2, and the filtrate was washed with brine, dried, concentrated, and chromatographed (SiO_2, $CHCl_3$/MeOH = 50/1) to give **12** (795.1 mg, 93%) as a yellow amorphous solid: $[\alpha]_D^{23}$ –283.7° (*c* 1.055, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.0 Hz, 1H), 8.83 (d, *J* = 4.0 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 4.5 Hz, 1H), 7.43 (dd, *J* = 2.5, 9.0 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.17 (d, *J* = 8.5 Hz, 1H), 4.53 (ddd, *J* = 4.0, 8.5, 12.5 Hz, 1H), 4.03 (s, 3H), 3.98 (dd, *J* = 5.5, 16.5 Hz, 1H), 2.99 (ddd, *J* = 3.5, 13.5, 13.5 Hz, 1H), 2.68-2.64 (m, 1H), 2.16-2.10 (m, 1H), 1.83 (dddd, *J* = 6.0, 6.0, 14.0, 14.0 Hz, 1H), 1.49-1.43 (m, 1H), 1.10 (ddd, *J* = 5.5, 13.0, 13.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 202.5, 158.3, 155.7, 147.6, 143.8, 138.4, 132.0, 125.4, 122.0, 118.0, 99.8, 74.3, 55.5, 53.9, 44.0, 38.7, 24.1, 22.4; FT-IR (neat); 2935, 1757, 1620, 1510, 1427, 1238, 1063 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}N_2O_4$ (M^+); 326.1267, found 326.1252.

(1*R*,7*R*,8a*S*)-Tetrahydro-7-(1-hydroxyprop-2-en-2-yl)-1-(6-methoxyquinolin-4-yl)-1*H*-oxazolo-[3,4-*a*]pyridin-3(5*H*)-one (15). To a solution of **12** (192.1 mg, 0.589 mmol) in MeOH (3.9 mL) was added NaOMe (6.4 mg, 0.118 mmol), and the mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with $CHCl_3$, washed with brine, dried, and concentrated to give **13** (223.3 mg), a yellow amorphous solid, as a 7:1 epimeric mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 0.1H), 9.38 (s, 0.7H), 8.83 (d, *J* = 4.5 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 4.2 Hz, 1H), 7.45 (dd, *J* = 2.7, 9.3 Hz, 1H), 6.90 (d, *J* = 2.7 Hz, 1H), 6.25 (d, *J* = 8.1 Hz, 0.88H), 6.23-6.15 (m, 0.12H), 4.59-4.47 (m, 0.12H), 4.29 (ddd, *J* = 3.6, 7.8, 12.3 Hz, 0.88H), 4.18 (br dd, *J* = 4.5, 13.2 Hz, 0.88H), 4.03 (s, 0.36H), 4.02-3.88 (m, 0.12H), 3.97 (s, 2.64H), 3.08 (ddd, *J* = 3.6, 13.2, 13.2 Hz, 0.88H), 2.99 (br dd, *J* = 13.5, 13.5 Hz, 0.12H), 2.67 (m, 0.12H), 2.46-2.32 (m, 0.88H), 2.18-2.09 (m, 0.12H), 2.02-1.91 (m, 0.88H), 1.90-1.75 (m, 0.12H), 1.51-1.30 (m, 1H), 1.18 (br d, *J* = 13.5 Hz, 0.88H), 1.12-0.95 (m, 0.12H), 0.87 (ddd, *J* = 12.6, 12.6, 12.6 Hz, 0.88H).

To a stirred suspension of methoxymethyltriphenylphosphonium chloride (427.6 mg, 1.25 mmol), dried at 80 ˚C under vacuum for 5 h, in THF (4.2 mL) at –78 ˚C was added *n*-butyllithium (1.54 M in hexane, 0.77 mL, 1.18 mmol). After the mixture was stirred at 0 ˚C for 0.5 h and cooled to –78 ˚C, a solution of crude **13** (223.3 mg) in THF (5.0 mL), pre-cooled at –78 ˚C, was added *via* cannula, and the mixture was gradually allowed to warm to –40 ˚C. After being stirred at –40 °C for 1 h, at –20 °C for 1 h, and at rt for

12 h, the reaction mixture was diluted with AcOEt, washed with H_2O and saturated $NaHCO_3$, dried, and concentrated. The residue was dissolved in $CHCl_3$ and filtered through SiO_2 pad and the filter pad was thoroughly washed with 100:1 $CHCl_3$-MeOH. Concentration of the filtrate and washings gave the corresponding enol ether (500.2 mg) as a yellow viscous oil.

To a solution of the crude enol ether (500.2 mg) in THF (2.6 mL) was added 5 M HCl (1.3 mL), and the mixture was stirred at rt for 2 h. The reaction mixture was diluted with H_2O (10 mL) and washed with Et_2O thoroughly. The aqueous layer was basified with $NaHCO_3$, extracted with $CHCl_3$, washed with brine, dried, and concentrated to give **14** (230.4 mg) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.82 (d, *J* = 4.5 Hz, 1H), 8.09 (d, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 4.2 Hz, 1H), 7.43 (dd, *J* = 2.4, 9.3 Hz, 1H), 6.89 (d, *J* = 2.7 Hz, 1H), 6.20 (d, *J* = 8.1 Hz, 1H), 4.28 (m, 1H), 4.11-3.98 (m, 1H), 4.00 (s, 3H), 3.11-2.98 (m, 1H), 2.33-2.02 (m, 3H), 1.69 (br d, *J* = 15.3 Hz, 1H), 1.20-1.04 (m, 1H), 0.94-0.83 (m, 1H), 0.69-0.54 (m, 1H).

To a stirred solution of crude **14** (230.4 mg) in CH_2Cl_2 (2.0 mL) at rt was added a solution of *N*,*N*-dimethylmethyleneiminium iodide (Eschenmoser's salt) (490.3 mg, 2.65 mmol) and triethylamine (0.74 mL, 5.30 mmol) in CH_2Cl_2 (3.0 mL). After 4 h, an additional Eschenmoser's salt (109.0 mg, 0.59 mmol) was added and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O, saturated $NaHCO_3$, and brine, dried, and concentrated to give the corresponding methylenated aldehyde (378.5 mg) as a yellow amorphous solid.

To an ice-cooled solution of the crude methylenated aldehyde (378.5 mg) and $CeCl_3 \cdot 7H_2O$ (658.3 mg, 1.767 mmol) in MeOH (12 mL) was added $NaBH_4$ (200 mg, 5.29 mmol), and the mixture was stirred at 0 °C for 3h. H_2O (5 mL) was added and the mixture was stirred at rt for 10 min. After most of the MeOH was evaporated, the residue was basified with $NaHCO_3$, diluted with $CHCl_3$, and filtered through a pad of Celite. The filtrate was washed with brine, dried, concentrated, and chromatographed (SiO_2, $CHCl_3$/MeOH = 50/1) to give **15** (110.8 mg, 53% from **12**) as a white solid: $[\alpha]_D^{23}$ –373.6° (*c* 0.720, MeOH); mp 147-150 °C (toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.8 Hz, 1H), 8.09 (d, *J* = 9.3 Hz, 1H), 7.63 (d, *J* = 4.5 Hz, 1H), 7.44 (dd, *J* = 2.7, 9.0 Hz, 1H), 6.91 (d, *J* = 2.7 Hz, 1H), 6.23 (d, *J* = 7.8 Hz, 1H), 4.91 (s, 1H), 4.59 (s, 1H), 4.27 (ddd, *J* = 3.9, 7.8, 11.7 Hz, 1H), 4.10 (dd, *J* = 3.6, 13.2 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 2H), 3.06 (ddd, *J* = 3.6, 13.2, 13.2 Hz, 1H), 2.23-2.15 (m, 1H), 2.10 (br s, 1H), 1.37 (dddd, *J* = 12.6, 12.6, 12.6, 4.8 Hz, 1H), 0.96-0.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 156.2, 150.9, 147.8, 143.8, 138.8, 132.2, 125.8, 121.5, 118.3, 110.3, 100.6, 74.1, 64.5, 57.9, 55.5, 42.0, 37.2, 31.3, 29.7; FT-IR (neat) 3379, 2937, 1749, 1622, 1514, 1431, 1236, 1028 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{22}N_2O_4$ (M^+): 354.1580, found 354.1570.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-hydroxy(6-methoxyquinolin-4-yl)methyl]-4-(1-hydroxyprop-2-en-2-yl)piperidine (18). A mixture of **15** (215.7 mg, 0.609 mmol) and 2 M NaOH (1.5 mL) in MeOH

(1.5 mL) was heated at 80 ˚C for 3 h. After most of the MeOH was evaporated, H_2O (1.5 mL) and THF (1.5 mL) were added to the residue. To this mixture at 0 °C was added di-*tert*-butyl dicarbonate (0.49 mL, 2.13 mmol) and the mixture was stirred at rt for 7 h. The reaction mixture was diluted with $CHCl_3$, washed with brine, dried, concentrated, and chromatographed (SiO_2, Hex/AcOEt = 2/1) to give **18** (258.5 mg, 74%) as a colorless amorphous solid: $[\alpha]_D^{24}$ –91.5° (*c* 1.060, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.8 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.26 (dd, *J* = 2.7, 9.0 Hz, 1H), 5.79 (s, 1H), 5.00 (s, 1H), 4.79 (s, 1H), 4.07-3.78 (m, 3H), 4.01 (s, 3H), 3.67-3.51 (m, 2H), 2.13-2.00 (m, 1H), 2.00-1.72 (m, 4H), 1.50 (s, 9H), 1.50-1.31 (m, 1H), 1.31-1.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 157.9, 156.0, 152.9, 146.9, 143.5, 130.5, 126.7, 122.0, 118.4, 108.5, 102.2, 80.0, 70.7, 64.5, 58.9, 55.9, 41.4, 34.9, 29.4, 28.5, 24.8; FT-IR (neat); 2927, 1676, 1419, 1244, 1149, 1036 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{32}N_2O_5$ (M^+); 428.2312, found 428.2299.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-hydroxy(6-methoxyquinolin-4-yl)methyl]-4-(1,3-dihydroxypropan-2-yl)piperidine (19). To an ice-cooled solution of **18** (71.6 mg, 0.167 mmol) in THF (0.84 mL) was added BH_3·THF complex (1.0 M in THF, 1.0 mL, 1.00 mmol), and the mixture was stirred at rt for 1 h. H_2O (1.8 mL) and $NaBO_4$·$4H_2O$ (30.8 mg, 0.200 mmol) were added with cooling in an ice bath and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with $CHCl_3$, washed with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$, dried, and concentrated. The residue was dissolved in ethylenediamine (0.56 mL) and the mixture was stirred at rt for 3 h. The reaction mixture was concentrated and chromatographed (SiO_2, $CHCl_3$/MeOH = 50/1) to give **19** (77.7 mg, 100%) as a colorless amorphous solid: $[\alpha]_D^{24}$ –29.5° (*c* 1.330, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 7.94 (br d, *J* = 8.7 Hz, 1H), 7.76 (br d, *J* = 2.7 Hz, 1H), 7.53 (br s, 1H), 7.32 (br d, *J* = 9.0 Hz, 1H), 5.83 (br s, 1H), 4.01 (s, 3H), 4.01-3.92 (m, 1H), 3.79-3.63 (m, 5H), 3.50-3.40 (m, 2H), 1.90-1.75 (m, 2H), 1.68-1.41 (m, 12H), 1.31-1.17 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.0, 146.9, 146.8, 143.3, 130.3, 126.8, 122.2, 118.4, 102.3, 80.0, 70.7, 63.9, 58.8, 56.0, 46.8, 41.2, 29.9, 28.5, 27.5, 23.0; FT-IR (neat) 3375, 2933, 1670, 1419, 1363, 1242, 1153, 1032 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{34}N_2O_6$ (M^+): 446.2417, found 446.2439.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-Acetoxy(6-methoxyquinolin-4-yl)methyl]-4-(1,3-dimethanesulfonyloxypropan-2-yl)piperidine (20). To an ice-cooled solution of **19** (44.5 mg, 0.100 mmol) in pyridine (2.0 mL) was added methanesulfonyl chloride (0.04 mL, 0.500 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with AcOEt, washed with H_2O and brine, dried, concentrated. The residue was dissolved in pyridine (2.0 mL) and acetic anhydride (0.25 mL, 2.650 mmol) was added to the mixture with cooling in an ice bath. After being stirred at rt for 7 h, the reaction mixture was quenched with MeOH (0.1 mL), extracted with AcOEt, washed with brine, dried, concentrated, and chromatographed (SiO_2, $CHCl_3$/MeOH = 50/1) to give **20** (49.5 mg, 77%) as a yellow

amorphous solid: $[\alpha]_D^{23}$ +2.6° (*c* 1.030, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.5 Hz, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.39 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.29 (d, *J* = 4.5 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 4.38 (ddd, *J* = 2.4, 6.6, 11.4 Hz, 1H), 4.29 (dd, *J* = 4.2, 10.5 Hz, 1H), 4.24-4.15 (m, 2H), 4.12-4.06 (m, 2H), 4.10 (s, 3H), 3.98 (dd, *J* = 7.4, 13.8 Hz, 1H), 3.17 (ddd, *J* = 6.6, 11.4, 14.1 Hz, 1H), 2.96 (s, 3H), 2.87 (s, 3H), 2.26 (s, 3H), 2.08-1.94 (m, 1H), 1.87-1.56 (m, 3H), 1.48 (s, 9H), 1.42-1.33 (m, 1H), 1.26-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 158.5, 155.3, 147.1, 144.4, 141.8, 131.2, 126.5, 122.8, 117.4, 102.3, 80.5, 73.0, 66.7, 66.4, 56.2, 55.4, 42.9, 38.5, 37.4, 37.3, 29.5, 28.4, 26.7, 23.2, 21.2; FT-IR (neat) 2974, 1745, 1678, 1624, 1412, 1354, 1236, 1169 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{40}N_2O_{11}S_2$ (M^+): 644.2073, found 644.2070.

(2*S*,4*R*)-2-[(*R*)-Acetoxy(6-methoxyquinolin-4-yl)methyl]-5-methylenequinuclidine (22). To an ice-cooled solution of **20** (42.3 mg, 0.066 mmol) in MeCN (1.3 mL) were added NaI (29.7 mg, 0.198 mmol) and chlorotrimethylsilane (0.03 mL, 0.198 mmol). After being stirred at rt for 1 h, the reaction mixture was diluted with $CHCl_3$, washed with 10% Na_2CO_3 and brine, dried, and concentrated to give the corresponding amine (38.9 mg) as a yellow amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.2 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.47-7.37 (m, 3H), 6.33 (d, *J* = 6.0 Hz, 1H), 4.41-4.20 (m, 4H), 3.99 (s, 3H), 3.23-3.09 (m, 2H), 3.03 (s, 3H), 3.01 (s, 3H), 2.65-2.53 (m, 1H), 2.19 (s, 3H), 2.05-1.58 (m, 5H), 1.39-1.16 (m, 2H).

A solution of the crude amine (38.9 mg) in MeCN (5.0 mL) was refluxed for 6 h. After cooling, the reaction mixture was diluted with $CHCl_3$, washed with 10% Na_2CO_3 and brine, dried, concentrated to give **21** (32.0 mg), a yellow viscous oil, as a 7:3 epimeric mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.5 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 7.42-7.27 (m, 3H), 6.55 (d, *J* = 6.3 Hz, 0.3H), 6.52 (d, *J* = 6.3 Hz, 0.7H), 4.34 (dd, *J* = 3.9, 8.1 Hz, 0.6H), 4.19 (dd, *J* = 6.0, 7.8 Hz, 1.4H), 3.96 (s, 3H), 3.45-3.25 (m, 2H), 3.07 (s, 0.9H), 3.03 (s, 2.1H), 3.01-2.49 (m, 3H), 2.36-1.12 (m, 6H), 2.18 (s, 0.9H), 2.16 (s, 2.1H).

A mixture of crude **21** (32.0 mg), tetra-*n*-butylammonium iodide (27.0 mg, 0.073 mmol) and DBU (0.04 mL, 0.264 mmol) in xylene (6.0 mL) was refluxed for 9 h. The reaction mixture was concentrated and purified with preparative TLC ($CHCl_3$/MeOH = 10/1) to give **22** (13.4 mg, 58% from **20**) as a colorless viscous oil: $[\alpha]_D^{24}$ –12.8° (*c* 0.670, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 9.3 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 2.4, 9.3 Hz, 1H), 7.34 (d, *J* = 4.8 Hz, 1H), 6.51 (d, *J* = 6.9 Hz, 1H), 4.83 (s, 1H), 4.70 (s, 1H), 3.97 (s, 3H), 3.77 (br dd, *J* = 1.8, 16.8 Hz, 1H), 3.43 (ddd, *J* = 8.1, 8.1, 8.1 Hz, 1H), 3.30 (br d, *J* = 17.7 Hz, 1H), 2.87-2.71 (m, 2H), 3.51 (br t, *J* = 3.0 Hz, 1H), 2.12 (s, 3H), 1.84 (br dd, *J* = 3.0, 8.7 Hz, 2H), 1.69-1.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 158.0, 151.4, 147.5, 144.8, 143.7, 131.9, 127.0, 121.9, 118.8, 103.9, 101.5, 73.8, 58.8, 55.7, 51.2, 50.7, 33.1, 29.8, 27.2, 21.1; FT-IR (neat) 2940, 1741, 1622, 1508, 1466, 1367, 1230, 1078, 1028 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{24}N_2O_3$ (M^+): 352.1787, found 352.1784.

(3*S*,8*S*,9*R*)-3,9-Epoxy-6'-hydroxy-11-norcinconane (23). A solution of crude **22** (28.2 mg, 0.080 mmol) and KBr (428.4 mg, 3.600 mmol) in 85 % aqueous H_3PO_4 (2.7 mL) was heated at 100 ˚C for 12 days. The reaction mixture was basified to pH 9 with 4 M KOH, extracted with $CHCl_3$, washed with brine, dried, concentrated, and chromatographed (SiO_2, $CHCl_3$/MeOH = 50/1) to give **23** (16.4 mg, 69%) as a colorless amorphous solid: $[\alpha]_D^{22}$ +19.5° (*c* 0.195, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.5 Hz, 1H), 8.16 (d, *J* = 2.1 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.23 (dd, *J* = 2.4, 9.0 Hz, 1H), 6.08 (s, 1H), 3.73 (d, *J* = 13.5 Hz, 1H), 3.48 (d, *J* = 6.3 Hz, 1H), 3.25 (dd, *J* = 12.6, 8.4 Hz, 1H), 3.17-3.04 (m, 1H), 2.81 (d, *J* = 13.5 Hz, 1H), 2.16 (m, 1H), 1.97-1.87 (m, 1H), 1.87-1.72 (m, 1H), 1.72-1.60 (m, 1H), 1.36 (s, 3H), 1.31-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 146.9, 143.2, 141.8, 131.2, 127.3, 122.1, 119.0, 106.8, 75.0, 73.0, 66.0, 56.4, 55.6, 46.7, 35.0, 23.4, 21.0; FT-IR (neat) 3600-3200, 2958, 1620, 1506, 1238, 1138, 1014 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{20}N_2O_2$ (M^+): 296.1525, found 296.1527.

1,1,1,3,3,3-Hexafluoroisopropyl (*S*)-3-Hydroxy-2-methylene-3-phenylpropanoate (24). To a solution of benzaldehyde (23.7 mg, 0.223 mmol) and **23** (6.6 mg, 0.022 mmol) in DMF (0.45 mL) at –55 °C was added HFIPA (48 μL, 0.290 mmol). After stirring at –55 °C for 24 h, the reaction was quenched by the addition of 0.1 M HCl (0.5 mL). The reaction mixture was extracted with AcOEt, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and chromatographed (SiO_2, AcOEt/hexane) to give **24** (46.9 mg, 64%) as a colorless oil. The spectral data (^{1}H and ^{13}C NMR, IR, HRMS) were identical with those reported.[2] The optical purity and absolute configuration of **24** were determined by HPLC analysis using a chiral column of the corresponding methyl ester, a colorless oil (93% *ee*): $[\alpha]_D^{28}$ +105.6° (*c* 1.29, MeOH); Daicel Chiralcel OJ, 2-propanol:hexane = 1:5 (0.5 mL/min), t_R = 26.4 min (*R*) and 32.4 min (*S*).

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