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SYNTHESIS OF BOTH ENANTIOMERS OF PROTOBERBERINES *VIA* LATERALLY LITHIATED (*S*)-4-ISOPROPYL-2-(*o*-TOLYL)-OXAZOLINES

Tsutomu Fukuda[a] and Masatomo Iwao[b]*

[a]Graduate School of Science and Technology, and [b]Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan, e-mail: iwao@nagasaki-u.ac.jp

Abstract – The addition of the laterally lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline (**1**) to 6,7-dimethoxy-3,4-dihydroisoquinoline (**2**) proceeded in modest diastereoselectivity. However, the addition products (**3a**) and (**3b**) were easily separated by column chromatography over silica gel. Acid-catalyzed lactamization of **3a** and **3b** followed by $LiAlH_4$-reduction afforded the corresponding optically pure protoberberines (**8a)** and (**8b**), respectively. This procedure was successfully applied to the synthesis of both enantiomers of xylopinine and bharatamine.

INTRODUCTION

Protoberberine alkaloids have attracted considerable attention due to their characteristic structures and a wide range of biological activities.[1] These natural products possess common 6*H*-dibenzo[*a*,*g*]-quinolizine ring system having alkoxy and/or hydroxy groups at A- and D-rings and stereogenic center at C13a position (Figure 1). Although a variety of methods for asymmetric synthesis of protoberberines have been developed so far,[2-6] the protoberberine scaffold was constructed mainly by variants of the Friedel-Crafts reactions such as Picted-Spengler,[3] Bischler-Napieralski,[4] and Pomeranz-Fritsch synthesis.[5]

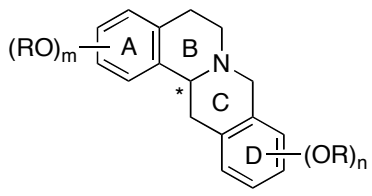


Figure 1 Common scaffold of protoberberine alkaloids

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

Therefore, the synthetically accessible substitution patterns of the protoberberines have been limited due regioselectivity of the conventional aromatic substitution reactions.

In the last three decades, lateral metalation methodology has been developed for the synthesis of a wide range of aromatic and heterocyclic compounds having unique substitution patterns.[7] The sequential nucleophilic addition-lactamization of laterally lithiated *o*-toluamide,[8] phthalide,[9] or 2-(*o*-tolyl)oxazoline[10] with 3,4-dihydroisoquinolines was applied for the synthesis of racemic 8-oxoberbines. Following these basic studies, efficient asymmetric syntheses using chiral *o*-toluamides having a chiral auxiliary in the amine part have been achieved by two groups.[11] In 2003, an alternative asymmetric synthesis via (–)-sparteine mediated enantioselective addition of lithiated nonchiral *o*-toluamides to 3,4-dihydroisoquinoline has also been reported by Liu.[12]

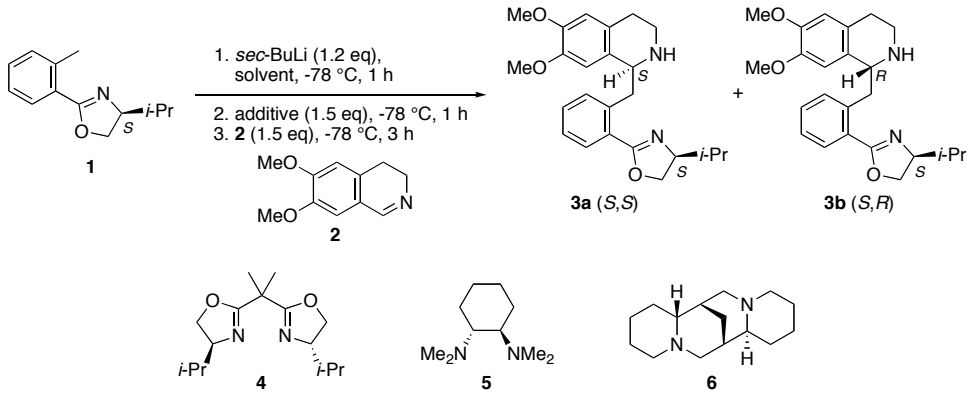
Recently, we reported an asymmetric synthesis of 3-substituted 3,4-dihydroisocoumarins via stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes followed by diastereomer-selective lactonization.[13] In this paper, we report an attempted application of this strategy for the synthesis of optically active protoberberines via addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to 3,4-dihydroisoquinolines.

RESULTS AND DISCUSSION

Initially, we examined the stereoselective addition of laterally lithiated chiral oxazoline (**1**) to 3,4-dihydroisoquinoline (**2**). Treatment of the oxazoline (**1**) with *sec*-BuLi in diethyl ether or THF at –78 °C resulted in the corresponding lateral lithio species as a characteristic burgundy red solution, which upon treatment with 3,4-dihydroisoquinoline (**2**) afforded the addition products (**3a**) and (**3b**) as a diastereomeric mixture. The diastereomeric ratio was determined by integration of ^{1}H NMR absorption of H8 of each diastereomer (δ H8 of **3a**: 6.81; δ H8 of **3b**: 6.75). As shown in Table 1, the stereoselectivities of these reactions are quite modest even in the presence of Lewis basic ligands such as TMEDA, *tert*-BuOK, and chiral diamines (**4-6**).[14] These results are in contrast to the results observed in the reactions of the laterally lithiated **1** to aldehydes.[13a] The low stereoselectivity may be accounted for by assuming that the C=N double bond incorporated in the rigid 3,4-dihydroisoquinoline system may lack flexibility to take the chelation-controlled eight-membered ring transition state[13a] for the stereoselective addition of the laterally lithiated **1**.

In order to produce an enantiomerically enriched 2,3-dimethoxy-8-oxoberbine (**7**), we next examined the diastereomer-selective lactamization of a mixture of addition products (**3a**) and (**3b**) under two different conditions developed for the diastereomer-selective lactonization[13] (Scheme 1). Thus, the diastereomer mixture (**3a**:**3b**= 1.9:1) was treated with TFA in aqueous THF at 0 °C for 24 h at first.[13a] Under these conditions, the lactamization proceeded smoothly, however, the diastereomer-selectivity was quite low.

Table 1. Addition of laterally lithiated oxazoline (**1**) to 3,4-dihydroisoquinoline (**2**)

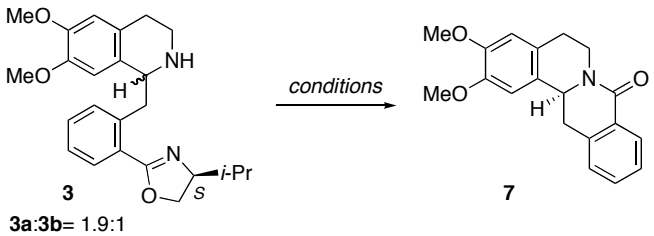


entry	solvent	additive	yield (%)[a]	dr (**3a** : **3b**)[b]
1	Et_2O	none	72	1.2 : 1
2	THF	none	97	1.9 : 1
3	Et_2O	TMEDA	92	1.2 : 1
4	THF	*tert*-BuOK	46	1 : 2.9
5	Et_2O	**4**	72	1.2 : 1
6	Et_2O	**5**	55	1.3 : 1
7	Et_2O	**6**	41	1 : 1.3

[a] Isolated yield.

[b] Diastereomeric ratio was estimated by ^{1}H NMR analysis.

Under silica gel mediated conditions,[13b] no lactamization product (**7**) was obtained, but the starting material (**3**) was recovered quantitatively.

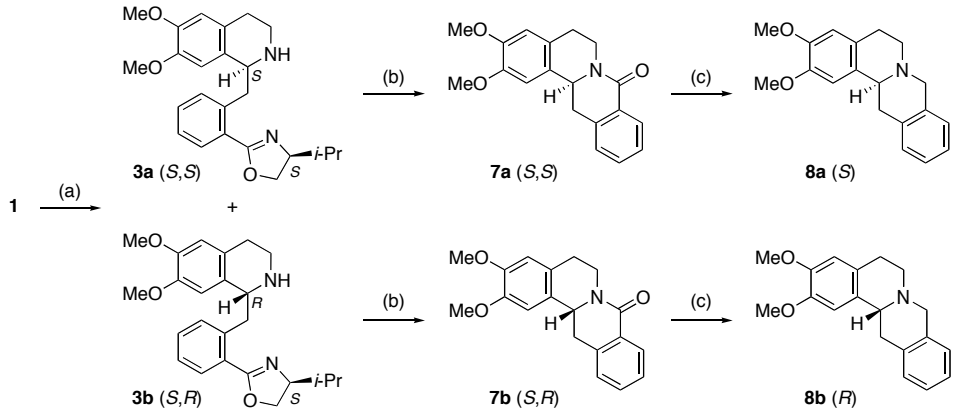


conditions: (a) TFA, THF, water, 0 °C, 24 h [77%, 41% ee (*S*)]
(b) silica gel, CH_2Cl_2, 0 °C, 30 h (0 %)

Scheme 1

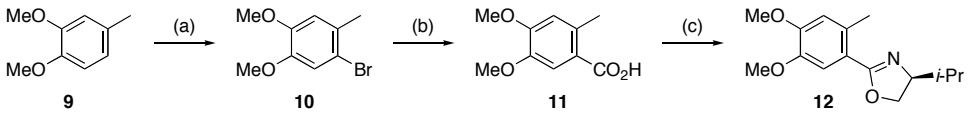
After these disappointing results, we found out fortunately that the diastereomers (**3a**) and (**3b**) could be easily separated by column chromatography. Thus, the crude addition product (**3**), obtained under the conditions shown in entry 2 of Table 1, was separated over silica gel using chloroform-methanol-aq. NH_3= 100:10:1 as an eluent to give **3a** (>95% de) and **3b** (>95% de) in 64% and

33% yields, respectively (Scheme 2). Treatment of **3a** and **3b** with TFA in aqueous THF at 40 °C for 2 days afforded **7a** (98% ee) and **7b** (95% ee) in 94% yields, respectively. Enantiomerically pure samples of **7a** and **7b** could be obtained by single recrystallization from dichloromethane-diethyl ether. Final reduction of **7a** and **7b** with $LiAlH_4$ gave the protoberberines (**8a**) and (**8b**), respectively, without loss of optical purity. The absolute configurations of these products were determined by chiroptical comparison with the previously established data.[11c]



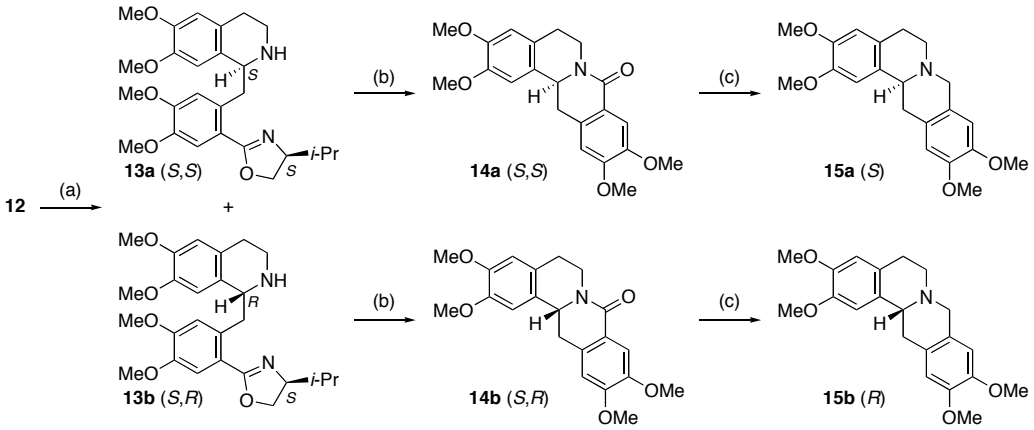
Scheme 2 *Reagents and conditions:* (a) (1) *sec*-BuLi (1.2 equiv.), THF, –78 °C, 1 h, (2) **2** (1.5 equiv.), –78 °C, 3 h, (3) chromatographic separation (**3a**: 64%, >95% de; **3b**: 33%, >95% de); (b) TFA, aqueous THF, 40 °C, 2 d [**7a**: 94%, 98% ee (>99% ee, after recrystallization); **7b**: 94%, 95% ee (>99% ee, after recrystallization)]; (c) $LiAlH_4$, THF, reflux, 2 h (**8a**: 99%, >99% ee; **8b**: 97%, >99% ee).

Next, we applied these procedures for the synthesis of both enantiomers of naturally occurring protoberberine natural products. Xylopinine (**15**), which was isolated from *Xylopia descreta*, was selected as the first target.[15] The synthesis of requisite oxazoline (**12**) was carried out at first (Scheme 3). Commercially available 3,4-dimethoxytoluene (**9**) was regioselectively brominated by *N*-bromosuccinimide (NBS) to give the bromide (**10**) in 96% yield. Bromine-lithium exchange reaction of **10** with 2.1 equiv. of *tert*-BuLi followed by quenching with dry ice afforded benzoic acid (**11**). Conversion of **11** to the oxazoline (**12**) was carried out by using the previously reported procedure.[13b]



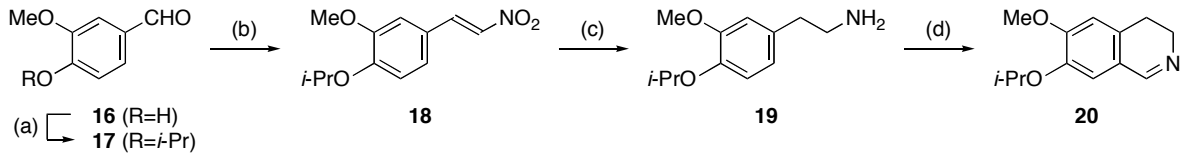
Scheme 3 *Reagents and conditions:* (a) NBS (1.1 equiv.), DMF, rt, 1 h (96%); (b) (1) *tert*-BuLi (2.1 equiv.), THF, –78 °C, 1 h, (2) CO_2 (84%); (c) (1) $SOCl_2$, rt, 9 h, (2) (*S*)-valinol, Et_3N, CH_2Cl_2, 0 °C, 2 h then rt, 1 h, (3) MsCl, 0 °C, 1 h then rt, 15 h (86%).

The synthesis of (*S*)- and (*R*)-xylopinine (**15a**) and **(15b**) is shown in Scheme 4. Lateral lithiation of oxazoline (**12**) using *sec*-BuLi at –78 °C in THF followed by quenching with 3,4-dihydroisoquinoline (**2**) produced the addition product (**13**) as a mixture of diastereomers. The addition product was cleanly separated by column chromatography to give **13a** (>95% de) and **13b** (>95% de) in 52% and 45% yields, respectively. Treatment of **13a** and **13b** with TFA in aqueous THF at 40 °C for 2 days afforded **14a** (98% ee) and **14b** (96% ee) in 94% and 98% yields, respectively. Enantiomerically pure samples of **14a** and **14b** were obtained by single recrystallization from dichloromethane-diethyl ether. Final reduction of **14a** and **14b** with $LiAlH_4$ gave the desired products (**15a**) and (**15b**), respectively, without loss of optical purity. The absolute configurations of these products were determined by chiroptical comparison with previously established data.[3e,3f,16]



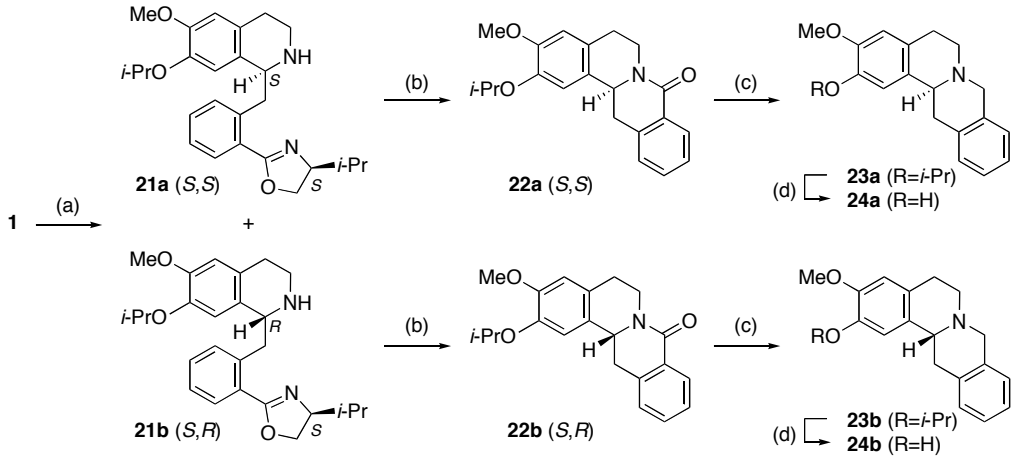
Scheme 4 *Reagents and conditions:* (a) (1) *sec*-BuLi (1.2 equiv.), THF, –78 °C, 1 h, (2) **2** (1.5 equiv.), –78 °C, 3 h, (3) chromatographic separation (**13a**: 52%, >95% de; **13b**: 45%, >95% de); (b) TFA, aqueous THF, 40 °C, 2 d [**14a**: 94%, 98% ee (>99% ee, after recrystallization); **14b**: 98%, 96% ee (>99% ee, after recrystallization)]; (c) $LiAlH_4$, THF, reflux, 2 h (**15a**: 89%, >99% ee; **15b**: 87%, >99% ee).

Bharatamine (**24**) has been isolated as a racemic form from the seeds of *Alangium lamarackii Tii* (Alangiaceae) by Pakrashi, et al.[17] This is the first naturally occurring protoberberine which lacks oxygen functionality in D ring. Although racemic **24** has been synthesized by several groups,[10,18] there is no report on asymmetric synthesis of **24**. Thus, we chose **24** as the next synthetic target. Our synthesis commenced with preparation of the requisite 3,4-dihydroisoquinoline (**20**) as shown in Scheme 5. The hydroxyl group of commercially available vanillin (**16**) was protected by isopropyl ether to give *O*-isopropylvanillin (**17**) in 99% yield. Henry reaction of the resulting aldehyde (**17**) with nitromethane afforded *β*-nitrostyrene (**18**) which was reduced by $LiAlH_4$ to give 2-arylethylamine (**19**). After formylation of **19**, the resulting amide was cyclized to the 3,4-dihydroisoquinoline (**20**) using phosphoryl chloride as a dehydrating agent.



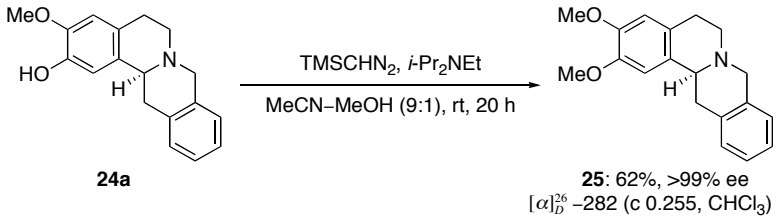
Scheme 5 *Reagents and conditions:* (a) *i*-PrBr, K_2CO_3, DMSO, 55 °C, 12 h (99%); (b) $MeNO_2$, $AcONH_4$, AcOH, 100 °C, 14 h (61%); (c) $LiAlH_4$, THF, reflux, 7 h (45%); (d) (1) HCO_2Et, reflux, 14 h, (2) $POCl_3$, MeCN, reflux, 45 min (54%).

The synthesis of the both enantiomers of bharatamine (**24a**) and (**24b**) is shown in Scheme 6. Lateral lithiation of oxazoline (**1**) using *sec*-BuLi at –78 °C in THF followed by quenching with 3,4-dihydroisoquinoline (**20**) produced the addition product (**21**) as a mixture of diastereomers. The addition product (**21**) was separated by column chromatography to give **21a** (>95% de) and **21b** (>95% de) in 51% and 41% yields, respectively. Further treatment of **21a** and **21b** with TFA in aqueous THF at 40 °C for 2 days afforded **22a** (98% ee) and **22b** (95% ee) in 91% and 94% yields, respectively. Enantiomerically pure samples of **22a** and **22b** were obtained by recrystallization from diethyl ether-pentane. Treatment of **22a** and **22b** with $LiAlH_4$ produced *O*-isopropylbharatamines (**23a**) and (**23b**) in 96% and 96% yields, respectively. Final selective deprotection of the isopropyl group with boron trichloride gave (*S*)- and (*R*)-bharatamines (**24a**) and (**24b**) in good yields without loss of optical purity.



Scheme 6 *Reagents and conditions:* (a) (1) *sec*-BuLi (1.2 equiv.), THF, –78 °C, 1 h, (2) **20** (1.5 equiv.), –78 °C, 3 h, (3) chromatographic separation (**21a**: 51%, >95% de; **21b**: 41%, >95% de); (b) TFA, aqueous THF, 40 °C, 2 d [**22a**: 91%, 98% ee (>99% ee, after recrystallization); **22b**: 94%, 95% ee (>99% ee, after recrystallization)]; (c) $LiAlH_4$, THF, reflux, 2 h (**23a**: 96%, >99% ee; **23b**: 96%, >99% ee); (d) BCl_3, CH_2Cl_2, –78 °C, 15 min then rt, 1 h (**24a**: 90%, >99% ee; **24b**: 88%, >99% ee).

The absolute configuration of **24a** was determined to be *S* by converting it to **25** (Scheme 7).[19] The specific rotation of **25** was identical with that of **8a**.



24a

25: 62%, >99% ee
$[\alpha]_D^{26}$ –282 (c 0.255, $CHCl_3$)

Scheme 7

In conclusion, we have developed an efficient procedure to produce both enantiomers of protoberberines via addition of laterally lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazolines to 3,4-dihydroisoquinolines. This method may be applicable to the synthesis of wide range of protoberberine alkaloids because the diastereomeric addition products could be readily separated by column chromatography in general.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer System 2000 instrument. NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) using tetramethylsilane as an internal standard. High resolution mass spectra were recorded on a JEOL JMS-700N spectrometer. HPLC analyses were performed on a Shimadzu LC-6A apparatus. Optical rotations were measured on a JASCO DPI-1000 digital polarimeter at ambient temperature. Flash chromatography was conducted on Silica Gel 60N, 40-50 μm (Kanto Chemical Co., Inc.). Column chromatography was conducted on Silica Gel 60N, 63-210 μm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd.). *sec*-Butyllithium was purchased from Kanto Chemical Co., Inc. *tert*-Butyllithium was purchased from Aldrich Chemical Co., Inc. The alkyllithiums were used after titration with 2,5-dimethoxybenzyl alcohol. Dry diethyl ether and THF were distilled from Na-benzophenone ketyl under argon immediately before use.

Addition of the laterally lithiated oxazoline (1) to 6,7-dimethoxy-3,4-dihydroisoquinoline (2). General procedure

Under an argon atmosphere, a hexane-cyclohexane solution of *sec*-BuLi (1.20 mmol) was added dropwise to a solution of the oxazoline (**1**) (203 mg, 1.00 mmol) in Et_2O or THF (10 mL) at –78 °C. After being stirred for 1 h, an appropriate additive (1.50 mmol) was added as a Et_2O or THF solution and the mixture was stirred for 15 min at –78 °C. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (**2**)

(287 mg, 1.50 mmol) in Et_2O or THF (2 mL) was added and the solution was stirred for an additional 3 h at –78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl at the same temperature and allowed to warm to rt. The products were extracted with CH_2Cl_2 and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N ($CHCl_3$-MeOH-aq. NH_3= 100:10:1) to give **3** as a mixture of diastereomers. The diastereomeric ratio was determined by integration of ^{1}H NMR absorption of H8 of each diastereomer (δ H8 of **3a**: 6.81; δ H8 of **3b**: 6.75). The results were shown in Table 1.

Preparation of (*S*)- and (*R*)-1-{2-[(*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl]benzyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3a) and (3b)

According to the general procedure, oxazoline (**1**) (203 mg, 1.00 mmol) and 3,4-dihydroisoquinoline (**2**) (287 mg, 1.50 mmol) were reacted under the conditions shown in Table 1, entry 2. After purification by flash chromatography over Silica Gel 60N ($CHCl_3$-MeOH-aq. NH_3=100:10:1), **3a** (251 mg, 64%) and **3b** (131 mg, 33%) were isolated.

Diastereomer (3a): Pale yellow oil. The diastereomeric ratio was estimated to be >95% de by ^{1}H NMR analysis. IR (KBr): 1642, 1612, 1515, 1463, 1260, 1224, 1111, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J*= 6.8 Hz, 3H), 1.02 (d, *J*= 6.8 Hz, 3H), 1.80-1.90 (m, 1H), 1.95 (br s, 1H), 2.68-2.81 (m, 2H), 2.87-2.95 (m, 1H), 3.06 (dd, *J*= 9.5 and 12.9 Hz, 1H), 3.22 (ddd, *J*= 5.3, 6.6 and 11.9 Hz, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 3.88 (dd, *J*= 4.2 and 12.9 Hz, 1H), 4.07-4.20 (m, 2H), 4.31 (dd, *J*= 4.2 and 9.4 Hz, 1H), 4.38 (dd, *J*= 7.6 and 9.0 Hz, 1H), 6.59 (s, 1H), 6.81 (s, 1H), 7.27-7.32 (m, 2H), 7.37-7.42 (m, 1H), 7.87-7.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.39, 19.15, 29.63, 33.02, 40.49, 41.62, 55.82, 55.87, 55.90, 69.37, 73.31, 109.91, 111.63, 126.40, 127.18, 127.32, 130.49, 130.52, 131.32, 132.16, 140.12, 146.88, 147.29, 163.32. $[\alpha]_D^{25}$ +30.5 (c 1.00, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{24}H_{30}N_2O_3$ (M^+): 394.2256. Found: 394.2254.

Diastereomer (3b): Pale yellow oil. The diastereomeric ratio was estimated to be >95% de by ^{1}H NMR analysis. IR (KBr): 1642, 1613, 1514, 1463, 1260, 1225, 1111, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, *J*= 6.8 Hz, 3H), 1.05 (d, *J*= 6.8 Hz, 3H), 1.83-1.93 (m, 1H), 1.88 (br s, 1H), 2.66-2.82 (m, 2H), 2.89 (ddd, *J*= 5.4, 6.4 and 11.8 Hz, 1H), 3.06 (dd, *J*= 9.7 and 12.9 Hz, 1H), 3.21 (ddd, *J*= 5.2, 6.5 and 11.7 Hz, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 3.97 (dd, *J*= 4.2 and 12.9 Hz, 1H), 4.08-4.20 (m, 2H), 4.21 (dd, *J*= 4.2 and 9.7 Hz, 1H), 4.37 (dd, *J*= 7.5 and 9.0 Hz, 1H), 6.59 (s, 1H), 6.75 (s, 1H), 7.26-7.32 (m, 2H), 7.36-7.42 (m, 1H), 7.87-7.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.27, 19.13, 29.62, 32.92, 40.59, 41.52, 55.83, 55.94, 56.19, 69.30, 73.25, 109.85, 111.69, 126.42, 127.26, 127.27, 130.51, 130.57, 131.20, 132.13, 140.19, 146.94, 147.34, 163.37. $[\alpha]_D^{25}$ –30.5 (c 1.00, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{24}H_{30}N_2O_3$ (M^+): 394.2256. Found: 394.2252.

(*S*)-2,3-Dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (7a)

The addition product (**3a**) (464 mg, 1.18 mmol) was dissolved in 14.7 mL of a mixed solvent (THF-H_2O-TFA=10:1.5:0.5) at 40 °C. After being stirred for 2 days, the mixture was quenched with saturated aqueous $NaHCO_3$ and the product was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (EtOAc) to give **7a** (341 mg, 94%) as colorless solid. HPLC (Daicel Chiralcel OD-H, hexane-EtOH=9:1): 98% ee. Recrystallization from CH_2Cl_2-Et_2O gave an optically pure sample as colorless needles. Mp 170.5-172 °C; IR (KBr): 1649, 1518, 1461, 1317, 1256, 1226, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.73-2.84 (m, 1H), 2.90-3.02 (m, 3H), 3.22 (dd, *J*= 3.6 and 15.7 Hz, 1H), 3.90 (s, 3H), 3.91 (s, 3H), 4.86 (dd, *J*= 3.6 and 13.4 Hz, 1H), 4.95-5.06 (m, 1H), 6.70 (s, 1H), 6.72 (s, 1H), 7.26 (d, *J*= 7.5 Hz, 1H), 7.38 (t, *J*= 7.5 Hz, 1H), 7.46 (dt, *J*= 1.5 and 7.5 Hz, 1H), 8.14 (dd, *J*= 1.3 and 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 29.21, 38.12, 38.73, 54.99, 55.94, 56.17, 108.85, 111.47, 126.86, 127.30, 127.32, 127.64, 128.58, 129.08, 131.80, 137.30, 147.96, 148.03, 164.63. $[\alpha]_D^{24}$ –450 (c 0.500, $CHCl_3$) {lit.,[11c] $[\alpha]_D^{20}$ –414 (c 0.359, $CHCl_3$): >99% ee, (*S*)-isomer}. *Anal*. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.86; H, 6.21; N, 4.50.

(*R*)-2,3-Dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (7b)

This compound was prepared from **3b** (120 mg, 0.305 mmol) in a similar manner as described for **7a**. After chromatographic purification over Silica Gel 60N (EtOAc), **7b** was obtained as colorless solid (88.9 mg, 94%). HPLC (Daicel Chiralcel OD-H, hexane-EtOH=19:1): 95% ee. Recrystallization from CH_2Cl_2-Et_2O gave an optically pure sample as colorless needles. Mp 170.5-172 °C. $[\alpha]_D^{25}$ +452 (c 0.500, $CHCl_3$) {lit.,[11c] $[\alpha]_D^{20}$ +428 (c 0.359, $CHCl_3$): >99% ee, (*R*)-isomer}. *Anal*. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.95; H, 6.14; N, 4.79.

(*S*)-2,3-Dimethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine (8a)

Under an argon atmosphere, $LiAlH_4$ (41.0 mg, 1.08 mmol) was added portionwise to a solution of **7a** (61.9 mg, 0.200 mmol) in THF (12 mL) at 0 °C and the mixture was refluxed for 2 h. The mixture was cooled to 0 °C and quenched carefully with water (88 μL) and 10% aqueous NaOH (160 μL). After removal of white precipitates by filtration, the filtrate was dried over K_2CO_3, and evaporated under reduced pressure. The residue was purified by column chromatography over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=3:1) to give **8a** (58.5 mg, 99%) as pale yellow oil. HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): >99% ee. IR (KBr): 1611, 1512, 1461, 1364, 1260, 1230, 1139, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.58-2.72 (m, 2H), 2.91 (dd, *J*= 11.4 and 15.6 Hz, 1H), 3.10-3.20 (m, 2H),

3.33 (dd, *J*= 3.7 and 16.2 Hz, 1H), 3.62 (dd, *J*= 3.7 and 11.2 Hz, 1H), 3.74 (d, *J*= 15.0 Hz, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 4.03 (d, *J*= 15.0 Hz, 1H), 6.62 (s, 1H), 6.75 (s, 1H), 7.06-7.10 (m, 1H), 7.12-7.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 29.06, 36.82, 51.43, 55.83, 56.07, 58.63, 59.57, 108.52, 111.33, 125.82, 126.14, 126.25, 126.74, 128.69, 129.75, 134.39, 134.48, 147.43, 147.47. $[\alpha]_D^{26}$ –303 (c 0.910, $CHCl_3$) {lit.,[11c] $[\alpha]_D^{20}$ –286 (c 0.51, $CHCl_3$): >99% ee, (*S*)-isomer}. HREIMS *m/z*. Calcd for $C_{19}H_{21}NO_2$ (M^+): 295.1572. Found: 295.1578.

(*R*)-2,3-Dimethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine (8b)

This compound was prepared from **7b** (61.9 mg, 0.200 mmol) in a similar manner as described for **8a**. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=3:1), **8b** was obtained as pale yellow oil (57.1 mg, 97%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): >99% ee. $[\alpha]_D^{26}$ +299 (c 0.990, $CHCl_3$) {lit.,[11c] $[\alpha]_D^{20}$ +282 (c 0.32, $CHCl_3$): >99% ee, (*R*)-isomer}. HREIMS *m/z*. Calcd for $C_{19}H_{21}NO_2$ (M^+): 295.1572. Found: 295.1559.

2-Bromo-4,5-dimethoxytoluene (10)

A solution of NBS (2.57 g, 14.5 mmol) in DMF (8 mL) was added dropwise to a solution of 3,4-dimethoxytoluene (2.00 g, 13.1 mmol) in DMF (16 mL) at rt. After being stirred for 1 h, the reaction mixture was quenched with water. The products were extracted with Et_2O and the extract was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation (95-100 °C/0.2 mmHg) to give **10** as colorless oil (2.91 g, 96%). IR (neat): 1508, 1462, 1257, 1215, 1164, 1035, 851, 794 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 6.73 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.34, 56.02, 56.18, 113.56, 114.43, 115.32, 129.63, 147.64, 148.17. HREIMS *m/z*. Calcd for $C_9H_{11}BrO_2$ (M^+): 229.9942. Found: 229.9931.

4,5-Dimethoxy-2-methylbenzoic acid (11)

Under an argon atmosphere, a pentane solution of *tert*-butyllithium (1.45 M, 84.4 mL, 122 mmol) was added dropwise to a solution of **10** (13.3 g, 57.6 mmol) in THF (290 mL) at –78 °C. After being stirred for 1 h, excess amount of dry ice was added and the reaction mixture was allowed to warm to rt. The mixture was quenched with water and evaporated under reduced pressure. To the residue was added 2 M aqueous HCl to adjust the pH to 1 and then the mixture was extract with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Recrystallization from Et_2O gave **11** as colorless cubes (9.51g, 84%). Mp 145.5-146.5 °C; IR (KBr): 1688, 1608, 1575, 1522, 1420, 1355, 1267, 1218, 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 3.92 (s, 3H), 3.94 (s,

3H), 6.72 (s, 1H), 7.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.14, 55.95, 56.02, 114.08, 114.27, 119.73, 136.44, 146.54, 152.61, 172.92. *Anal*. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.06; H, 6.29.

(*S*)-2-(4,5-Dimethoxy-2-methylphenyl)-4-isopropyl-4,5-dihydrooxazole (12)

Thionyl chloride (9.2 mL, ca. 126 mmol) was added as a neat liquid to **11** (3.54 g, 18.1 mmol) at 0 °C. After being stirred for 10 min, the mixture was allowed to warm to rt, stirred for 9 h, and evaporated. The residual thionyl chloride was removed by azeotropic treatment with toluene to give 4,5-dimethoxy-2-methylbenzoyl chloride. The crude acid chloride was dissolved in CH_2Cl_2 (10 mL) and the solution was added dropwise to a mixture of (*S*)-valinol (1.86 g, 18.1 mmol) and triethylamine (8.81 mL, 63.2 mmol) in CH_2Cl_2 (80 mL) at 0 °C. After being stirred for 2 h, the mixture was allowed to warm to rt, stirred for 1 h, and cooled to 0 °C again. Methanesulfonyl chloride (1.54 mL, 19.9 mmol) was added as a neat liquid to the reaction mixture. After being stirred for 1 h, the mixture was allowed to warm to rt and stirred for 15 h. The mixture was quenched with 10% aqueous NaOH and the product was extracted with CH_2Cl_2. The extract was washed successively with 10% aqueous NaOH and brine, dried over Na_2SO_4, and evaporated. The residue was purified by bulb-to-bulb distillation (155-175 °C/ 2.3 mmHg) to give **12** as colorless oil (4.07 g, 86%) and the purified **12** solidified on standing. Mp 60.5-62 °C; IR (KBr): 1643, 1523, 1461, 1365, 1263, 1209, 1149, 992 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J*= 6.8 Hz, 3H), 1.03 (d, *J*= 6.8 Hz, 3H), 1.79-1.91 (m, 1H), 2.56 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.05-4.15 (m, 2H), 4.29-4.39 (m, 1H), 6.71 (s, 1H), 7.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.17, 18.91, 21.46, 32.93, 55.83, 56.01, 69.28, 72.88, 112.62, 113.89, 119.14, 132.43, 146.39, 150.34, 163.60. $[\alpha]_D^{25}$ –52.7 (c 1.00, $CHCl_3$). *Anal*. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.26; H, 8.11; N, 5.12.

Preparation of (*S*)- and (*R*)-1-{2-[(*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl]-4,5-dimethoxybenzyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13a) and (13b)

These compounds were prepared from oxazoline (**12**) (263 mg, 1.00 mmol) and 3,4-dihydroisoquinoline (**2**) (287 mg, 1.50 mmol) in a similar manner as described for **3a** and **3b**. After purification by flash chromatography over Silica Gel 60N ($CHCl_3$-MeOH-aq. NH_3=100:10:1), **13a** (236 mg, 52%) and **13b** (203 mg, 45%) were isolated.

Diastereomer (13a): Pale yellow oil. The diastereomeric ratio was estimated to be >95% de by ^{1}H NMR analysis. IR (KBr): 1639, 1607, 1516, 1463, 1361, 1264, 1213, 1149, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, *J*= 6.7 Hz, 3H), 1.00 (d, *J*= 6.7 Hz, 3H), 1.76-1.90 (m, 1H), 2.04 (br s, 1H), 2.66-2.83 (m, 2H), 2.89 (ddd, *J*= 5.2, 6.7 and 11.9 Hz, 1H), 2.98 (dd, *J*= 9.3 and 13.0 Hz, 1H), 3.17-3.26

(m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.92 (dd, *J*= 4.2 and 13.0 Hz, 1H), 4.05-4.17 (m, 2H), 4.28 (dd, *J*= 4.1 and 9.3 Hz, 1H), 4.36 (dd, *J*= 7.5 and 8.9 Hz, 1H), 6.59 (s, 1H), 6.76 (s, 1H), 6.84 (s, 1H), 7.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.37, 19.18, 29.63, 33.02, 40.90, 41.37, 55.82, 55.91, 55.98, 56.01, 56.16, 69.19, 73.23, 109.88, 111.66, 113.14, 114.67, 119.19, 127.23, 131.24, 133.89, 146.90, 146.96, 147.29, 150.31, 162.98. $[\alpha]_D^{25}$ +23.1 (c 1.00, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{26}H_{34}N_2O_5$ (M^+): 454.2468. Found: 454.2455.

Diastereomer (13b): Pale yellow oil. The diastereomeric ratio was estimated to be >95% de by ^{1}H NMR analysis. IR (KBr): 1638, 1605, 1516, 1463, 1361, 1264, 1217, 1149, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J*= 6.7 Hz, 3H), 1.05 (d, *J*= 6.7 Hz, 3H), 1.80-1.93 (m, 1H), 1.95 (br s, 1H), 2.65-2.84 (m, 2H), 2.88 (ddd, *J*= 5.0, 7.0 and 12.0 Hz, 1H), 3.01 (dd, *J*= 9.4 and 12.9 Hz, 1H), 3.17-3.25 (m, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.96 (dd, *J*= 4.1 and 12.9 Hz, 1H), 4.05-4.17 (m, 2H), 4.20 (dd, *J*= 4.1 and 9.4 Hz, 1H), 4.35 (dd, *J*= 7.4 and 8.8 Hz, 1H), 6.60 (s, 1H), 6.75 (s, 1H), 6.78 (s, 1H), 7.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.27, 19.21, 29.63, 32.94, 40.98, 41.26, 55.84, 55.97, 55.99, 56.01, 56.44, 69.14, 73.15, 109.81, 111.73, 113.21, 114.65, 119.15, 127.32, 131.20, 133.94, 146.95, 146.97, 147.34, 150.32, 163.03. $[\alpha]_D^{25}$ –26.1 (c 1.00, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{26}H_{34}N_2O_5$ (M^+): 454.2468. Found: 454.2471.

(*S*)-2,3,10,11-Tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (14a)

This compound was prepared from **13a** (153 mg, 0.337 mmol) in a similar manner as described for **7a**. After chromatographic purification over Silica Gel 60N (EtOAc), **14a** was obtained as pale yellow solid (117 mg, 94%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): 98% ee. Recrystallization from CH_2Cl_2-Et_2O gave an optically pure sample as colorless powder. Mp 167-168 °C; IR (KBr): 1645, 1603, 1515, 1462, 1429, 1270, 1224, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72-2.81 (m, 1H), 2.87-3.01 (m, 3H), 3.15 (dd, *J*= 3.8 and 15.6 Hz, 1H), 3.90 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 3.95 (s, 3H), 4.84 (dd, *J*= 3.8 and 13.5 Hz, 1H), 4.93-5.03 (m, 1H), 6.70 (s, 1H), 6.72 (s, 1H), 6.73 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 29.26, 37.68, 38.71, 55.28, 55.94, 56.07, 56.14, 56.15, 108.80, 109.21, 110.75, 111.48, 121.68, 127.36, 127.78, 130.00, 147.94, 148.00, 148.23, 151.91, 164.73. $[\alpha]_D^{23}$ –376 (c 0.500, $CHCl_3$) {lit.,[3e] $[\alpha]_D^{23}$ –297 (c 0.95, $CHCl_3$): (*S*)-isomer}. HREIMS *m/z*. Calcd for $C_{21}H_{23}NO_5$ (M^+): 369.1576. Found: 369.1565.

(*R*)-2,3,10,11-Tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (14b)

This compound was prepared from **13b** (166 mg, 0.365 mmol) in a similar manner as described for **7a**. After chromatographic purification over Silica Gel 60N (EtOAc), **14b** was obtained as pale yellow solid (132 mg, 98%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): 96% ee. Recrystallization from

CH_2Cl_2-Et_2O gave an optically pure sample as colorless powder. Mp 167-168 °C. $[\alpha]_D^{23}$ +376 (c 0.500, $CHCl_3$) {lit.,[3e] $[\alpha]_D^{23}$ –297 (c 0.95, $CHCl_3$): (*S*)-isomer}. HREIMS *m/z*. Calcd for $C_{21}H_{23}NO_5$ (M^+): 369.1576. Found: 369.1563.

(*S*)-Xylopinine (15a)

This compound was prepared from **14a** (36.9 mg, 0.100 mmol) in a similar manner as described for **8a**. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=1:1), **15a** was obtained as pale yellow solid (31.7 mg, 89%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): >99% ee. Mp 182-183 °C (sealed capillary); IR (KBr): 1612, 1518, 1455, 1351, 1261, 1144, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.58-2.72 (m, 2H), 2.84 (dd, *J*= 11.3 and 15.7 Hz, 1H), 3.09-3.20 (m, 2H), 3.25 (dd, *J*= 3.7 and 15.7 Hz, 1H), 3.59 (dd, *J*= 3.7 and 11.3 Hz, 1H), 3.68 (d, *J*= 14.5 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 3.95 (d, *J*= 14.5 Hz, 1H), 6.58 (s, 1H), 6.62 (s, 1H), 6.67 (s, 1H), 6.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 29.06, 36.43, 51.38, 55.83, 55.89, 55.94, 56.03, 58.26, 59.60, 108.49, 108.99, 111.32, 111.35, 126.29, 126.35, 126.74, 129.77, 147.37, 147.41, 147.45, 147.60. $[\alpha]_D^{26}$ –273 (c 0.610, $CHCl_3$) {lit.,[3e] $[\alpha]_D^{23}$ –266 (c 0.8, $CHCl_3$): (*S*)-isomer}. HREIMS *m/z*. Calcd for $C_{21}H_{25}NO_4$ (M^+): 355.1784. Found: 355.1789.

(*R*)-Xylopinine (15b)

This compound was prepared from **14b** (36.9 mg, 0.100 mmol) in a similar manner as described for **8a**. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=1:1), **15b** was obtained as pale yellow solid (31.0 mg, 87%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): >99% ee. Mp 182-183 °C (sealed capillary). $[\alpha]_D^{26}$ +266 (c 0.780, $CHCl_3$) {lit.,[3f] $[\alpha]_D^{23}$ +277 (c 0.28, $CHCl_3$): (*R*)-isomer}. HREIMS *m/z*. Calcd for $C_{21}H_{25}NO_4$ (M^+): 355.1784. Found: 355.1784.

4-Isopropoxy-3-methoxybenzaldehyde (17)

A neat liquid of 2-bromopropane (23.1 mL, 247 mmol) was added to a suspension of vanillin (**16**) (25.0 g, 164 mmol) and K_2CO_3 (45.4 g, 329 mmol) in DMSO (350 mL) at the rt and the mixture was heated at 55 °C for 12 h. The reaction mixture was cooled to rt and diluted with water. The mixture was extracted with Et_2O and the extract was washed successively with 10% aqueous NaOH, water, and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by distillation (83-103 °C/ 0.3 mmHg) to give **17** as colorless oil (31.7 g, 99%). IR (neat): 1682, 1588, 1508, 1468, 1389, 1267, 1133, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (d, *J*= 6.1 Hz, 6H), 3.92 (s, 3H), 4.64-4.75 (m, 1H), 6.98 (d, *J*= 8.1 Hz, 1H), 7.41 (d, *J*= 1.9 Hz, 1H), 7.43 (dd, *J*= 1.9 and 8.1 Hz, 1H),

9.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.88, 56.03, 71.36, 109.61, 112.89, 126.61, 129.76, 150.39, 153.13, 190.88. HREIMS *m/z*. Calcd for $C_{11}H_{14}O_3$ (M^+): 194.0943. Found: 194.0932.

(*E*)-β-Nitro-4-isopropoxy-3-methoxystyrene (18)

Nitromethane (14.0 mL, 259 mmol) was added as a neat liquid to a solution of **17** (29.6 g, 152 mmol) and ammonium acetate (35.2 g, 457 mmol) in acetic acid (250 mL) at rt and the solution was heated at 100 °C for 14 h. The mixture was cooled to rt and then poured into ice-cold water. The precipitates thus formed were collected by filtration, washed with water, and dried under reduced pressure. Recrystallization from Et_2O gave **18** as yellow prisms (22.0 g, 61%). Mp 82.0-83.0 °C; IR (KBr): 1627, 1598, 1494, 1334, 1263, 1140, 1111, 950 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (d, *J*= 6.1 Hz, 6H), 3.90 (s, 3H), 4.60-4.70 (m, 1H), 6.92 (d, *J*= 8.4 Hz, 1H), 7.02 (d, *J*= 2.1 Hz, 1H), 7.15 (dd, *J*= 2.1 and 8.4 Hz, 1H), 7.53 (d, *J*= 13.6 Hz, 1H), 7.96 (d, *J*= 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.91, 56.10, 71.40, 111.04, 114.14, 122.51, 124.50, 135.02, 139.46, 150.43, 151.45. *Anal*. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.93; H, 6.36; N, 5.87.

2-(4-Isopropoxy-3-methoxyphenyl)ethylamine (19)

Under an argon atmosphere, **18** (14.4 g, 60.7 mmol) was added portionwise to a suspension of $LiAlH_4$ (7.40 g, 195 mmol) in THF (600 mL) at 0 °C and the mixture was refluxed for 7 h. The mixture was cooled to 0 °C and quenched carefully with water (16 mL) and 10% aqueous NaOH (13 mL). After removal of white precipitates by filtration, the filtrate was dried over K_2CO_3, and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation (160-170 °C/ 2.3 mmHg) to give **19** as pale yellow oil (5.75 g, 45%). IR (neat): 3365, 3302, 1588, 1510, 1466, 1264, 1230, 1140, 1112, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, *J*= 6.1 Hz, 6H), 2.69 (t, *J*= 6.8 Hz, 2H), 2.94 (t, *J*= 6.8 Hz, 2H), 3.84 (s, 3H), 4.43-4.52 (m, 1H), 6.70 (dd, *J*= 1.8 and 8.0 Hz, 1H), 6.72 (d, *J*= 1.8 Hz, 1H), 6.83 (d, *J*= 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.16, 39.66, 43.60, 55.93, 71.57, 112.79, 116.24, 120.75, 132.94, 145.68, 150.42. HREIMS *m/z*. Calcd for $C_{12}H_{19}NO_2$ (M^+): 209.1416. Found: 209.1423.

7-Isopropoxy-6-methoxy-3,4-dihydroisoquinoline (20)

The amine (**19**) (4.19 g, 20.0 mmol) was dissolved in ethyl formate (10.6 mL) and the solution was refluxed for 14 h. The reaction mixture was then cooled to rt and evaporated under reduced pressure. The residual *N*-[2-(4-isopropoxy-3-methoxyphenyl)ethyl]formamide was found to be essentially pure and used for the next reaction without further purification; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, *J*= 6.1 Hz, 6H), 2.78 (t, *J*= 6.8 Hz, 2H), 3.55 (q, *J*= 6.8 Hz, 2H), 3.84 (s, 3H), 4.43-4.52 (m, 1H), 5.80 (br s, 1H),

6.70 (dd, *J*= 2.0 and 8.2 Hz, 1H), 6.72 (d, *J*= 2.0 Hz, 1H), 6.83 (d, *J*= 8.2 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.12, 35.08, 39.29, 55.98, 71.60, 112.62, 116.23, 120.68, 131.44, 146.03, 150.56, 161.34.

A solution of phosphoryl chloride (2.80 mL, 30.0 mmol) in MeCN (11 mL) was added dropwise to a solution of the crude formamide in MeCN (39 mL) at rt and the mixture was refluxed for 45 min. The mixture was cooled to rt and evaporated under reduced pressure. To the residue was added 28% aqueous ammonia to basify and then the mixture was extract with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation (135–150 °C/ 0.6 mmHg) to give **20** as pale yellow oil (2.35 g, 54%). IR (neat): 1629, 1605, 1572, 1509, 1465, 1318, 1281, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, *J*= 6.1 Hz, 6H), 2.67 (t, *J*= 7.8 Hz, 2H), 3.69-3.76 (m, 2H), 3.88 (s, 3H), 4.46-4.56 (m, 1H), 6.67 (s, 1H), 6.83 (s, 1H), 8.20 (t, *J*= 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.08, 24.83, 47.38, 56.03, 71.96, 110.92, 115.32, 121.58, 130.31, 145.92, 152.79, 159.69. HREIMS *m/z*. Calcd for $C_{13}H_{17}NO_2$ (M^+): 219.1259. Found: 219.1260.

Preparation of (*S*)- and (*R*)-7-Isopropoxy-1-{2-[(*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl]benzyl}-6-methoxy-1,2,3,4-tetrahydroisoquinoline (21a) and (21b)

These compounds were prepared from oxazoline (**1**) (1.02 g, 5.00 mmol) and 3,4-dihydroisoquinoline (**20**) (1.65 g, 7.50 mmol) in a similar manner as described for **3a** and **3b**. After purification by flash chromatography over Silica Gel 60N ($CHCl_3$-MeOH-aq. NH_3=100:10:1), **21a** (1.06 g, 51%) and **21b** (862 mg, 41%) were isolated.

Diastereomer (21a): Pale yellow oil. The diastereomeric ratio was estimated to be >95% de by ^{1}H NMR analysis. IR (KBr): 1643, 1509, 1465, 1374, 1324, 1263, 1219, 1109, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J*= 6.7 Hz, 3H), 1.02 (d, *J*= 6.7 Hz, 3H), 1.35 (d, *J*= 6.1 Hz, 3H), 1.35 (d, *J*= 6.1 Hz, 3H), 1.80-1.94 (m, 1H), 2.27 (br s, 1H), 2.68-2.82 (m, 2H), 2.86-2.94 (m, 1H), 3.04 (dd, *J*= 9.8 and 13.0 Hz, 1H), 3.17-3.26 (m, 1H), 3.83 (s, 3H), 3.81-3.87 (m, 1H), 4.08-4.20 (m, 2H), 4.29 (dd, *J*= 3.8 and 9.8 Hz, 1H), 4.39 (dd, *J*= 7.4 and 8.9 Hz, 1H), 4.39-4.49 (m, 1H), 6.60 (s, 1H), 6.90 (s, 1H), 7.26-7.31 (m, 2H), 7.36-7.42 (m, 1H), 7.86-7.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.26, 19.10, 22.17, 22.28, 29.60, 32.93, 40.48, 41.39, 55.84, 55.90, 69.39, 71.86, 73.19, 112.31, 115.30, 126.39, 127.36, 128.01, 130.51, 130.52, 131.28, 132.04, 140.01, 145.15, 149.01, 163.43. $[\alpha]_D^{25}$ +27.0 (c 1.00, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{26}H_{34}N_2O_3$ (M^+): 422.2569. Found: 422.2550.

Diastereomer (21b): Pale yellow oil. The diastereomeric ratio was estimated to be >95% de by ^{1}H NMR analysis. IR (KBr): 1643, 1613, 1510, 1464, 1375, 1324, 1263, 1220, 1109, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, *J*= 6.7 Hz, 3H), 1.05 (d, *J*= 6.7 Hz, 3H), 1.34 (d, *J*= 6.1 Hz, 6H), 1.83-1.96

(m, 1H), 1.92 (br s, 1H), 2.66-2.82 (m, 2H), 2.88 (ddd, *J*= 5.3, 6.5 and 11.8 Hz, 1H), 3.01 (dd, *J*= 10.0 and 13.0 Hz, 1H), 3.20 (ddd, *J*= 5.2, 6.4 and 11.6 Hz, 1H), 3.83 (s, 3H), 3.97 (dd, *J*= 3.8 and 13.0 Hz, 1H), 4.08-4.21 (m, 3H), 4.38 (dd, *J*= 7.6 and 9.0 Hz, 1H), 4.38-4.48 (m, 1H), 6.60 (s, 1H), 6.89 (s, 1H), 7.26-7.32 (m, 2H), 7.36-7.42 (m, 1H), 7.86-7.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.21, 19.14, 22.17, 22.22, 29.67, 32.87, 40.60, 41.39, 55.92, 56.11, 69.30, 71.91, 73.19, 112.36, 115.44, 126.41, 127.26, 128.16, 130.52, 130.58, 131.27, 132.04, 140.20, 145.16, 149.09, 163.41. $[\alpha]_D^{25}$ –36.0 (c 1.00, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{26}H_{34}N_2O_3$ (M^+): 422.2569. Found: 422.2560.

(*S*)-2-Isopropoxy-3-methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (22a)

This compound was prepared from **21a** (947 mg, 2.24 mmol) in a similar manner as described for **7a**. After chromatographic purification over Silica Gel 60N (EtOAc), **22a** was obtained as pale yellow solid (689 mg, 91%). HPLC (Daicel Chiralcel OD-H, hexane-EtOH=19:1): 98% ee. Recrystallization from Et_2O-pentane gave an optically pure sample as colorless needles. Mp 103-104 °C; IR (KBr): 1657, 1512, 1461, 1400, 1314, 1260, 1224, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, *J*= 6.1 Hz, 3H), 1.40 (d, *J*= 6.1 Hz, 3H), 2.73-2.82 (m, 1H), 2.91-3.02 (m, 3H), 3.18 (dd, *J*= 3.6 and 15.7 Hz, 1H), 3.87 (s, 3H), 4.47-4.57 (m, 1H), 4.84 (dd, *J*= 3.6 and 13.4 Hz, 1H), 4.94-5.04 (m, 1H), 6.70 (s, 1H), 6.78 (s, 1H), 7.26 (d, *J*= 7.6 Hz, 1H), 7.39 (t, *J*= 7.6 Hz, 1H), 7.46 (dt, *J*= 1.4 and 7.6 Hz, 1H), 8.14 (dd, *J*= 1.2 and 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.12, 22.17, 29.25, 38.06, 38.77, 54.88, 55.97, 72.12, 112.10, 114.31, 126.88, 127.31, 127.64, 128.05, 128.57, 129.09, 131.79, 137.33, 146.11, 149.61, 164.68. $[\alpha]_D^{23}$ –399 (c 0.500, $CHCl_3$). *Anal*. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.70; H, 6.77; N, 4.07.

(*R*)-2-Isopropoxy-3-methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (22b)

This compound was prepared from **21b** (748 mg, 1.77 mmol) in a similar manner as described for **7a**. After chromatographic purification over Silica Gel 60N (EtOAc), **22b** was obtained as pale yellow solid (560 mg, 94%). HPLC (Daicel Chiralcel OD-H, hexane-EtOH=19:1): 95% ee. Recrystallization from Et_2O-pentane gave an optically pure sample as colorless needles. Mp 103-104 °C. $[\alpha]_D^{23}$ +386 (c 0.500, $CHCl_3$). *Anal*. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.76; H, 6.84; N, 4.08.

(*S*)-2-Isopropoxy-3-methoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine (23a)

This compound was prepared from **22a** (169 mg, 0.500 mmol) in a similar manner as described for **8a**. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=5:1), **23a** was obtained as pale yellow oil (155 mg, 96%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=9:1):

>99% ee. IR (KBr): 1609, 1510, 1462, 1365, 1261, 1138, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, *J*= 6.1 Hz, 3H), 1.38 (d, *J*= 6.1 Hz, 3H), 2.58-2.72 (m, 2H), 2.89 (dd, *J*= 11.3 and 16.1 Hz, 1H), 3.09-3.20 (m, 2H), 3.30 (dd, *J*= 3.7 and 16.1 Hz, 1H), 3.60 (dd, *J*= 3.7 and 11.3 Hz, 1H), 3.73 (d, *J*= 14.9 Hz, 1H), 3.83 (s, 3H), 4.02 (d, *J*= 14.9 Hz, 1H), 4.45-4.55 (m, 1H), 6.62 (s, 1H), 6.80 (s, 1H), 7.05-7.10 (m, 1H), 7.11-7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.15, 22.20, 29.08, 36.73, 51.44, 55.88, 58.63, 59.45, 71.98, 111.96, 114.11, 125.79, 126.12, 126.22, 127.54, 128.69, 129.77, 134.42, 134.46, 145.51, 149.13. $[\alpha]_D^{26}$ –281 (c 0.555, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{21}H_{25}NO_2$ (M^+): 323.1885. Found: 323.1861.

(*R*)-2-Isopropoxy-3-methoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine (23b)

This compound was prepared from **22b** (169 mg, 0.500 mmol) in a similar manner as described for **8a**. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=5:1), **23b** was obtained as pale yellow oil (156 mg, 96%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=9:1): >99% ee. $[\alpha]_D^{26}$ +256 (c 0.520, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{21}H_{25}NO_2$ (M^+): 323.1885. Found: 323.1860.

(*S*)-Bharatamine (24a)

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 330 μL, 0.330 mmol) was added dropwise to a solution of **23a** (35.6 mg, 0.110 mmol) in CH_2Cl_2 (3.0 mL) at –78 °C. After being stirred for 15 min at this temperature, the reaction mixture was allowed to warm to rt and stirred for an additional 1 h. The mixture was quenched with MeOH and saturated aqueous $NaHCO_3$. The product was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-EtOAc=1:1) to give **24a** as yellow solid (28.0 mg, 90%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): >99% ee. Recrystallization from CH_2Cl_2-pentane gave yellow powder. Mp 177-178 °C (sealed capillary); IR (KBr): 3207, 1591, 1517, 1366, 1273, 1226, 1134, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.56-2.70 (m, 2H), 2.88 (dd, *J*= 11.3 and 16.2 Hz, 1H), 3.09-3.19 (m, 2H), 3.29 (dd, *J*= 3.8 and 16.2 Hz, 1H), 3.58 (dd, *J*= 3.8 and 11.3 Hz, 1H), 3.71 (d, *J*= 14.9 Hz, 1H), 3.85 (s, 3H), 4.01 (d, *J*= 14.9 Hz, 1H), 6.58 (s, 1H), 6.82 (s, 1H), 7.04-7.09 (m, 1H), 7.10-7.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 29.07, 36.65, 51.53, 55.85, 58.61, 59.47, 110.61, 111.38, 125.78, 125.95, 126.09, 126.24, 128.77, 130.49, 134.35, 134.47, 143.94, 145.12. $[\alpha]_D^{26}$ –290 (c 0.595, $CHCl_3$). *Anal*. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.78; H, 6.91; N, 4.83.

(*R*)-Bharatamine (24b)

This compound was prepared from **23b** (31.1 mg, 0.0962 mmol) in a similar manner as described for **24a**. After chromatographic purification over Silica Gel 60N (hexane-EtOAc=1:1), **24b** was obtained as pale yellow solid (23.8 mg, 88%). HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): >99% ee. Recrystallization from CH_2Cl_2-pentane gave yellow powder. Mp 176.5-177.5 °C (sealed capillary). $[\alpha]_D^{26}$ +276 (c 0.525, $CHCl_3$). HREIMS *m/z*. Calcd for $C_{18}H_{19}NO_2$ (M^+): 281.1416. Found: 281.1407.

(*S*)-2,3-Dimethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine (25)

Under an argon atmosphere, a hexane solution of (trimethylsilyl)diazomethane (2.0 M, 133 μL, 0.267 mmol) was added dropwise to a solution of **24a** (10.0 mg, 35.5 μmol), *N*,*N*-diisopropylethylamine (51.0 μL, 0.293 mmol) in 2.0 mL of a mixed solvent (MeCN-MeOH=9:1) at rt. After being stirred for 7 h, the mixture was quenched with water and evaporated under reduced pressure. The residue was extract with CH_2Cl_2 and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=3:1) to give **25** (6.5 mg, 62%) as pale yellow oil. HPLC (Daicel Chiralpak AD-H, hexane-EtOH=1:1): >99% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58-2.72 (m, 2H), 2.91 (dd, *J*= 11.4 and 15.6 Hz, 1H), 3.10-3.20 (m, 2H), 3.33 (dd, *J*= 3.7 and 16.2 Hz, 1H), 3.62 (dd, *J*= 3.7 and 11.2 Hz, 1H), 3.74 (d, *J*= 15.0 Hz, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 4.03 (d, *J*= 15.0 Hz, 1H), 6.63 (s, 1H), 6.75 (s, 1H), 7.06-7.10 (m, 1H), 7.12-7.18 (m, 3H). $[\alpha]_D^{26}$ –282 (c 0.255, $CHCl_3$) {lit.,[11c] $[\alpha]_D^{20}$ –286 (c 0.51, $CHCl_3$): >99% ee, (*S*)-isomer}. HREIMS *m/z*. Calcd for $C_{19}H_{21}NO_2$ (M^+): 295.1572. Found: 295.1558.

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