Synthesis of Optically Active Vasicinone Based on Intramolecular Aza-Wittig Reaction and Asymmetric Oxidation[1]

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Both optical isomers of a quinazoline alkaloid, vasicinone, were synthesized by two different methods. The first method used (3*S*)-3-hydroxy-γ-lactam as a chiral synthon, which was, after *O*-TBDMS protection, *o*-azidobenzoylated followed by treatment with tri-*n*-butylphosphine to afford (*S*)-(−)-vasicinone *via* the tandem Staudinger/intramolecualr aza-Wittig reaction. The second method utilized asymmetric oxygenation of deoxyvasicinone with (1*S*)-(+)- or (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (the Davis reagent), respectively. The aza-enolate anion of deoxyvasicinone was treated with (*S*)-(+)-reagent to afford (*R*)-(+)-vasicinone in 71% ee, while the reaction with (*R*)-(−)-reagent gave (*S*)-(−)-vasicinone in 62% ee. The optical purity was analyzed by HPLC on specially modified cellulose as a stationary phase. These results provided a facile method to prepare both optical isomers of vasicinone and confirmed the recently reversed stereochemistry of natural (−)-vasicinone.

Introduction

Vasicinone is known as one of the pyrrolo[2,1-*b*]-quinazoline alkaloids isolated from the leaves and the inflorescence of *Adhatada vasica* Nees, which is an evergreen subherbaceous bush and is used in indigenous medicine as a remedy for cold, cough, bronchitis, and asthma, etc.[2] Vasicinone has also been found to be identical with an alkaloid isolated from the seeds of *Pegamum harmala* Linn.[2] Related pyrrolo[2,1-*b*]quinazoline alkaloids containing, for example, (−)-vasicine (peganine), (+)-vasicinol (7-hydroxyvasicine), and adhavasinone (5-methoxyvasicinone), etc., have been reported as well. It is shown that (−)-vasicinone can be derived from (−)-vasicine by autooxidation or by oxidation with 30% H_2O_2.[2] In view of the pharmacological activity of these molecules, the determination of the absolute stereochemistry and development of convenient synthetic method are important. However, the reported stereochemical assignment and the optical rotation of natural vasicinone and related compounds seem to be somewhat confusing.[3,4] Very recently, Joshi and co-workers[4] reversed the previously assigned 3*R* configuration of (−)-vasicinone to the 3*S* configuration on the bas of the X-ray crystallographic analysis of (+)-vasicinone hydrobromide derived from (−)-vasicinone. The previously assigned 3*R* stereochemistry of (−)-vasicine has also been reversed to 3*S*. Several syntheses of vasicinone and deoxyvasicinone have been reported;[5] however, these syntheses targeted the *dl* racemic mixture. Therefore, we investigated synthesis of optically active vasicinone by two methods *via* the tandem Staudinger/intramolecular aza-Wittig reaction and/or asymmetric oxidation of deoxyvasicinone with the Davis oxidation reagent. This aza-Wittig methodology has received increased attention for its utility in the formation of C═N bond-containing compounds (*e.g.*, imines, imidates, amidines, *etc.*), and in particular, nitrogen heterocyclic compounds.[6,7] For example, we and other workers have recently demonstrated that the intramolecular aza-Wittig reaction is a powerful tool for the synthesis of 5- to 7-membered nitrogen heterocycles including natural products, such as oxazoles,[8] imidazolinone,[9] iminolactam,[10] 4(3*H*)-quinazolinones,[9,11] 1,4-benzodiazepin-5-ones,[12] 1,3-benzoxazepines,[13] 1,3-benzodiazepines,[13] and pyrazino[2,3-*e*][1,4]-diazepines.[14] On the other hand, the intermolecular aza-

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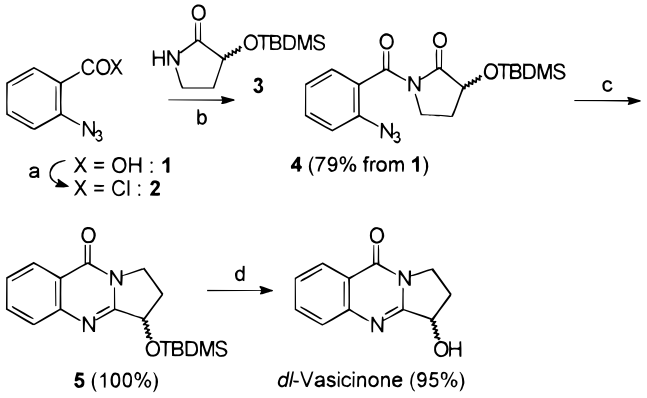
Scheme 1. Synthesis of *dl*-Vasicinone *via* Intramolecular Aza-Wittig Reaction[a]



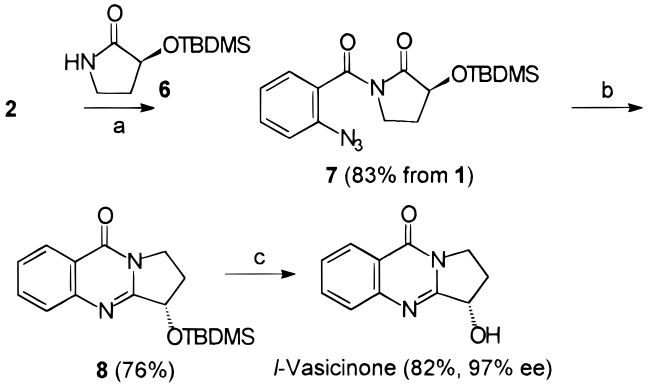
[a] Reagents and conditions: (a) $SOCl_2$ (neat), reflux, 2 h; (b) NaH, THF, 0 °C → rt, 3 h; (c) *n*-Bu_3P, toluene, rt, 1 h → reflux, 2 h; (d) TBAF, THF, 0 °C → rt, 15 h. TBAF = tetra-*n*-butylammonium fluoride.

Wittig reaction followed by electrocyclization, intramolecular cycloaddition, or heterocyclization, *i.e.*, the tandem aza-Wittig reaction and cyclization sequence, has been utilized for synthesis of pyridines and pyrimidines, etc.[6c,15−19] We wish to report here two methods of synthesis of optically active vasicinone by utilizing the tandem Staudinger/intramolecular aza-Wittig reaction and/or asymmetric oxidation of deoxyvasicinone with the Davis reagent.

Results and Discussion

Several examples of the synthesis of deoxyvasicinone **9**, 9-pyrrolo[2,1-*b*]quinazolinone, from anthranilic acid have been reported,[5] whereby *dl*-vasicinone was synthesized from **9** by NBS/benzoyl peroxide bromination, followed by acetolysis and hydrolysis.[5a] Our previous synthesis of **9** was applied to an alternative synthesis of *dl*-vasicinone from 3-hydroxy γ-lactam and anthranilic acid *via* the intramolecular aza-Wittig reaction. At first, according to previous literature,[20] 3-hydroxy γ-lactam was prepared from 3-hydroxy γ-lactone and then the hydroxyl group was protected by TBDMSCl to give **3** (Scheme 1). Next, *o*-azidobenzoic acid **1** derived from anthranilic acid by the usual method was converted into *o*-azidobenzoyl chloride **2**, followed by condensation with **3** by treatment with sodium hydride in THF to afford the precursor *N*-(*o*-azidobenzoyl)-3-(*tert*-butyldimethylsiloxy) γ-lactam **4**. The addition of tri-*n*-butylphosphine to **4** initiated the tandem Staudinger/intramolecular aza-Wittig reaction to give *O*-*tert*-butyldimethylsilyl vasicinone **5** (see the Experimental Section.). The deprotection of the siloxy substituent by tetra-*n*-butylammonium fluoride (TBAF) in THF gave *dl*-vasicinone in 95% yield (Scheme 1).

Scheme 2. Synthesis of *l*-Vasicinone *via* Intramolecular Aza-Wittig Reaction[a]



[a] Reagents and conditions: (a) NaH, THF, 0 °C → rt, 3 h; (b) *n*-Bu_3P, toluene, rt, 1 h → reflux, 2 h; (c) TBAF, THF, 0 °C → rt, 15 h.

In the next stage, we investigated the synthesis of (*S*)-(−)-vasicinone as follows. The chiral synthon, (3*S*)-3-hydroxy γ-lactam derived from L-aspartic acid in five steps,[21] was protected by TBDMSCl to prepare **6** in the same way. Employing the above-mentioned method for synthesis of *dl*-vasicinone enabled (*S*)-(−)-vasicinone to be synthesized in 52% overall yield from anthranilic acid (Scheme 2), ($[\alpha]^{28}_D$ −58° (*c* 0.45 $CHCl_3$), 97% ee). The optical purity of the enantiomers was analyzed by HPLC on specially modified cellulose as a stationary phase.[22]

We considered the thus obtained (*S*)-(−)-vasicinone as an authentic sample of the defined stereochemistry and investigated asymmetric oxidation with deoxyvasicinone **9** as a more convenient route by employing (1*S*)-(+)- or (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine, *i.e.*, the Davis reagents.[23] Although, heretofore, the asymmetric oxidation reactions have been mainly reported on achiral enolates, there have been no reports, except for only one case,[24] on aza-enolates, *i.e.*, imine enolate. This was 3-(phenylthio)-4,5-dihydroisoxazole where 50% ee was obtained using the LDA−TMEDA system as a base. Aza-enolate was generated from **9** with various bases in THF at −78 °C followed by addition of (*S*)- or (*R*)-reagents in THF solution to afford the optically active vasicinone (Scheme 3). The results are summarized in Table 1.

We obtained the best result for asymmetric oxidation of imine **9** by Davis reagents using the LDA−TMEDA system (Table 1, entries 1−4). Asymmetric oxidation of **9** was dependent upon the geometry of Davis reagents as expected. The results of the entries 1 and 2 suggest that the intermediate, lithium aza-enolate of **9** was

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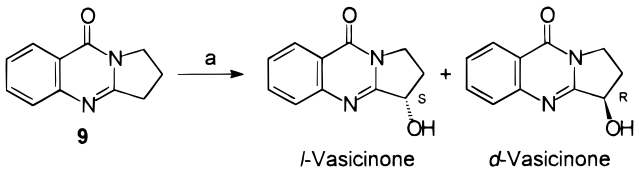
Scheme 3. Synthesis of Vasicinone by Davis Reagent[a]



[a] Reagents and conditions: (a) base, Davis reagent (see Table 1), −78 °C.

Table 1. Asymmetric Oxidation of Deoxyvasicinone 9 with (*R*)- and (*S*)-Davis Reagent

entry	base[a]	oxidant (equiv)	RT[b]	yield[c] (%)	absolute config[d] (ee, %)
1	LDA, TMEDA	*S* (1.5)	1.5 h	36	*R* (62)
2	LDA, TMEDA	*R* (1.5)	1.5 h	34	*S* (62)
3	LDA, TMEDA	*S* (1.0)	1.5 h	30	*R* (66)
4	LDA, TMEDA	*S* (0.5)	1.5 h	24	*R* (64)
5	LDA	*S* (1.5)	1.5 h	23	*R* (40)
6	LDA	*S* (1.0)	1.5 h	18	*R* (66)
7	LDA	*S* (0.5)	1.5 h	25	*R* (40)
8	NaHMDS	*S* (1.5)	1.5 h	57	*R* (38)
9	NaHMDS	*S* (1.0)	1.5 h	46	*R* (46)
10	NaHMDA	*S* (0.5)	1.5 h	37	*R* (62)
11	LDA, TMEDA	*S* (1.0)	15 min	17	*R* (66)
12	NaHMDS	*S* (0.5)	30 min	39	*R* (71)

[a] 1.5 equiv was used. NaHMDS = sodium bis(trimethylsilyl)-amide. [b] Reaction time. [c] Isolated yield. [d] Stereochemical assignment and ee were determined by HPLC on specially modified cellulose as a stationary phase.

thoroughly planar (Table 1, entry 1, *R* 62% ee; entry 2, *S* 62% ee). Also, the PM3 semiempirical level calculation indicated that the lithium aza-enolate of **9** is completely planar. Taking these results into consideration, **9** was successfully converted into (*R*)-vasicinone with (*S*)-Davis reagents. However, in the LDA−TMEDA system, the amount of oxidative reagents had little influence on the yield and ee of vasicinone (Table 1, entries 1, 3, and 4). With simple LDA system as the base, the results of yield and ee were not consistent (Table 1, entries 5−7). In the case where sodium bis(trimethylsilyl)amide (NaHMDS) instead of LDA was used, the yields decreased (57% → 46% → 37%) but the stereoselectivity increased (38% ee → 46% ee → 62% ee) with decreasing amount of Davis reagents (Table 1, entries 8−10, respectively). Furthermore, when the reaction time was shortened, no change of ee was observed in the LDA−TMEDA system (Table 1, entries 3 and 11) but the improvement of ee was observed in the NaHMDS system (Table 1, entries 10 and 12). Bach and co-workers[25] previously have reported a mechanism for oxidation of the lithium enolate of acetaldehyde by oxaziridine on the basis of molecular orbital calculations at the HF/6-31+G*//HF/4-31+G level and interpreted the oxidation of the lithium enolate of acetaldehyde to proceed by S_N2 attack of the β-carbon on the enolate along the O−N bond of the parent oxaziridine and that the lithium cation is coordinated to both nitrogen and oxygen of oxaziridine but not to oxygen of enolate in the transition state. Taking the above mechanism and our results into consideration, the transition state of asymmetric oxidation of **9** with Davis reagent is proposed as follows. The β-carbon on the aza-enolate attacks along the O−N bond of the oxaziridine and the metal cation (Li^+ or Na^+) had apparently some minor controlling effects, and furthermore, the steric repulsion between the quinazoline and camphor skeletons should be operating considerably.

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Conclusions

In conclusion, we have reported the synthesis of racemic vasicinone from 3-hydroxy-γ-lactam and anthranilic acid and the synthesis of (*S*)-vasicinone (97% ee) from L-aspartic acid and anthranilic acid utilizing intramolecular aza-Wittig reaction as the key step. In addition, we investigated the asymmetric oxidation of deoxyvasicinone **9** by employing (*R*)- and (*S*)-Davis reagents to provide a convenient route to both (*S*)- and (*R*)-vasicinone. We have clarified that *l*-vasicinone has the (*S*)-configuration by comparison of the optical rotation value of synthetic product in accordance with the recently reversed stereochemistry of natural vasicinone based on X-ray crystallographic analysis.[4]

Experimental Section

General Methods. Most of the general experimental methods have been reported previously.[12b] Optical rotations were measured with a JASCO DIP-1000 polarimeter. Flash chromatography was performed with a silica gel column (Fuji Davison BW-300 silica gel or ICN Alumina N, Akt. I.) eluted with mixed solvents (hexane, ethyl acetate). All reagents were of commercial quality. Solvents were dried prior to use when deemed necessary: THF was freshly distilled from Na and benzophenone. Toluene was dried over Na. Pyridine was dried over KOH.

Synthesis of *dl*-Vasicinone *via* Intramolecular aza-Wittig Reaction. *N*-(2-Azidobenzoyl)-3-(*tert*-butyldimethylsiloxy)-2-pyrrolidinone (4). To a stirred solution of 3-(*tert*-butyldimthylsiloxy) γ-lactam **3** (280 mg, 1.30 mmol), prepared from 3-hydroxy γ-lactam[20] and *tert*-butyldimethylsilylation by standard procedure in THF (5.0 mL) under nitrogen at 0 °C was added sodium hydride (60% dispersion in mineral oil; 57 mg, 1.43 mmol). The stirring was continued for 15 min followed by addition of *o*-azidobenzoyl chloride **2**, which was prepared from *o*-azidobenzoic acid **1** (318 mg, 1.95 mmol) and thionyl chloride (0.75 mL, 10.3 mmol) in THF (5.0 mL), and then this mixture was stirred at room temperature for 3 h. The mixture was poured into ice-cooled water and extracted with dichloromethane (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (AcOEt:hexane 1:6 as the eluent) to gain azidobenzoyl derivative **4** (367 mg, 79%): yellow solid; mp 117−119.5 °C; IR (KBr) 2141, 1761, 1690, 1251, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.12 (6H, s), 0.90 (9H, s), 2.05 (1H, ddd, J = 12.6, 9.6, 1.7 Hz), 2.36−2.51 (1H, m), 3.68 (1H, ddd, J = 11.8, 9.6, 7.0 Hz), 4.09 (1H, ddd, J = 8.9, 6.0, 1.4 Hz), 4.43 (1H, dd, J = 9.4, 1.8 Hz), 7.16−7.31 (3H, m), 7.49 (1H, ddd, J = 8.2, 7.0, 1.8 Hz); MS m/z 275 (M^+ − 85, N_2 and *t*-Bu), 259, 158, 146. Anal. Calcd for $C_{17}H_{24}N_4O_3Si$: C, 56.64; H, 6.71; N, 15.54. Found: C, 56.99; H, 6.76; N, 15.17.

***dl*-*O*-(*tert*-Butyldimethylsilyl)vasicinone (5).** To a stirred solution of azide derivative **4** (520 mg, 1.44 mmol) in toluene (10 mL) was added dropwise tri-*n*-butylphosphine (315 mg, 1.56 mmol), and the mixture was stirred for 1 h at room temperture and 2 h at reflux under nitrogen. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt:hexane 1:6 as the eluent) to give **5** (455 mg, 100%): white solid; mp 41−42.5 °C; IR (KBr) 1687, 1631, 1253, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.20 (3H, s), 0.26 (3H, s), 0.93 (9H, s), 2.12−2.27 (1H, m), 2.46 (1H, dddd, J = 13.2, 7.8, 6.6, 6.4 Hz), 4.09 (1H, ddd, J = 12.2, 7.8, 5.5 Hz), 4.27 (1H, ddd, J = 12.2, 7.8, 6.4 Hz),

5.10 (1H, dd, J = 6.6, 5.0 Hz), 7.44−7.54 (1H, m), 7.73−7.76 (2H, m), 8.31 (1H, dt, J = 8.0, 1.0 Hz); MS m/z (relative intensity) 301 (M^+ − 15, 4.0), 260 (31), 259 (100), 185 (11). Anal. Calcd for $C_{17}H_{24}N_2O_2Si$: C, 64.52; H, 7.64; N, 8.85. Found: C, 64.34; H, 7.69; N, 8.98.

***dl*-Vasicinone.** To a stirred solution of **5** (197 mg, 0.622 mmol) in THF (3.0 mL) was added TBAF (1.0 M solution in THF, 0.63 mL, 0.63 mmol) at 0 °C, and the mixture was stirred for 15 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt:hexane 10:1 as the eluent) to give *dl*-vasicinone (119 mg, 95%): white solid; mp 205−207 °C (lit.[2a] mp 212−213 °C); IR (KBr) 3423, 1686, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.23−2.41 (1H, m), 2.60−2.77 (2H, m), 4.05 (1H, dt, J = 12.4, 7.6 Hz), 4.38 (1H, ddd, J = 12.4, 8.6, 4.4 Hz), 5.28 (1H, t, J = 7.2 Hz), 5.95 (1H, br), 7.46−7.54 (1H, m), 7.76 (1H, s), 7.78 (1H, s), 8.32 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.51, 43.71, 71.93, 121.31, 126.90, 127.02, 127.37, 134.89, 148.84, 160.99, 161.07; MS m/z (relative intensity) 202 (M^+, 100), 146 (69), 119 (45). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.24; H, 5.07; N, 13.78.

(3*S*)-3-(*tert*-Butyldimethylsiloxy)-2-pyrrolidinone (6). To a solution of (3*S*)-3-hydroxy-2-pyrrolidinone[21] (75 mg, 0.75 mmol) in pyridine (0.5 mL) was added TBDMSCl (145 mg, 0.96 mmol) in dichloromthane (1.5 mL). The reaction mixture was stirred under nitrogen at room temperature overnight, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (Et_2O as the eluent) to give **6** as a colorless solid (81 mg, 51%): $[\alpha]^{26}_D$ −44° (*c* 0.34 $CHCl_3$); mp 54−55 °C; IR (KBr) 3432, 3219, 2932, 2893, 1703 (C═O), 1294, 1254 (SiC), 1154, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.15 (3H, s), 0.16 (3H, s), 0.92 (9H, s), 2.03 (1H, m), 2.37 (1H, m), 3.32 (2H, m), 4.27 (1H, t, J = 7.7 Hz), 6.46 (1H, s). MS m/z (relative intensity) 200 (M^+ − 15, 7.7), 158 (100). Anal. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50. Found: C, 55.94; H, 9.45; N, 6.72.

(3*S*)-*N*-(2-Azidobenzoyl)-3-(*tert*-butyldimethylsiloxy)-2-pyrrolidinone (7). To a stirred solution of (3*S*)-3-(*tert*-butyldimethylsiloxy) γ-lactam **6** (120 mg, 0.56 mmol) in THF (3.0 mL) under nitrogen at 0 °C was added sodium hydride (60% dispersion in mineral oil, 25 mg, 0.63 mmol). The stirring was continued for 15 min followed by addition of *o*-azidobenzoyl chloride **2**, which was derived from *o*-azidobenzoic acid **1** (137 mg, 0.84 mmol) and thionyl chloride (0.61 mL, 8.40 mmol), in THF (2.0 mL0, and then this mixture was stirred at room temperature for 3 h. The mixture was poured into ice-cooled water and then extracted with dichloromethane (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford a residue that was purified by silica gel column chromatography (AcOEt:hexane 1:1 as the eluent) to gain azidobenzoyl derivative **7** (168 mg, 83%): yellowish solid; $[\alpha]^{28}_D$ −25° (*c* 3.1 $CHCl_3$); mp 86−87 °C; IR (KBr) 2131, 1765, 1680, 1249, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.12 (6H, s), 0.90 (9H, s), 2.04 (1H, dddd, J = 12.6, 9.6, 9.4, 8.8 Hz), 2.43 (1H, dddd, J = 12.6, 7.8, 6.8, 2.6 Hz), 3.68 (1H, ddd, J = 11.7, 9.6, 6.8 Hz), 4.09 (1H, ddd, J = 11.7, 8.8, 2.6 Hz), 4.43 (1H, dd, J = 9.4, 7.8 Hz), 7.19 (2H, m), 7.31 (1H, m), 7.48 (1H, ddd, J = 8.1, 7.2, 1.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3, −4.7, 18.3, 25.7, 28.3, 41.0, 72.0, 118.6, 125.2, 128.2, 128.9, 131.9, 137.7, 167.9, 173.3. Anal. Calcd for $C_{17}H_{24}N_4O_3Si$: C, 56.64; H, 6.71; N, 15.54. Found: C, 56.82; H, 6.42; N, 15.64.

(3*S*)-*O*-(*tert*-Butyldimethylsilyl)vasicinone (8). To a stirred solution of azide derivtaive **7** (160 mg, 0.44 mmol) in toluene (3.0 mL) was added dropwise tri-*n*-butylphosphine (98 mg, 0.48 mmol), and the mixture was stirred for 1 h at room temperature and 2 h at reflux under nitrogen. After being cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt:hexane 1:2 as the eluent) to give **8** (106 mg, 76%): white solid; mp 44−46 °C; IR (KBr) 1672, 1636, 839, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.19 (3H, s), 0.26 (3H, s), 0.93 (9H, s), 2.19 (1H, dddd, J = 13.0, 7.8, 5.4, 5.4 Hz), 2.46 (1H, dddd, J = 13.1, 7.8, 6.6, 6.6 Hz), 4.08 (1H, ddd, J = 12.2, 7.8, 5.6 Hz), 4.25 (1H, ddd, J = 12.2, 7.8, 6.2 Hz), 5.10 (1H, dd), 7.45 (1H, ddd, J = 7.8, 4.4, 3.9 Hz), 7.75 (2H, m), 8.31 (1H, ddd, J = 7.8, 1.2, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −4.91, −4.26, 18.4, 25.9, 31.3, 43.6, 73.8, 121.4, 126.7, 127.0, 128.1, 134.4, 149.9, 159.2, 161.5; MS m/z (relative intensity) 316 (M^+, 2.0), 259 (100), 185 (36). Anal. Calcd for $C_{17}H_{24}N_2O_2Si$: C, 64.52; H, 7.64; N, 8.85. Found: C, 64.48; H, 7.69; N, 8.84.

***l*-Vasicinone.** To a stirred solution of **8** (21 mg, 0.066 mmol) in THF (1.5 mL) was added TBAF (1.0 M solution in THF, 0.066 mL, 0.066 mmol) at 0 °C, and the mixture was stirred for 15 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt as the eluent) to give *l*-vasicinone (11 mg, 82%, 97% ee): white solid; $[\alpha]^{28}_D$ −57.8° (*c* 0.45 $CHCl_3$) (lit.[2b] natural vsaicinone $[\alpha]^{25}_D$ −58° (*c* 0.5 $CHCl_3$); different values have been reported also, see ref 2b−4); mp 200−202 °C (lit.[2b] mp 201−202 °C); IR (KBr) 1667, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.32 (1H, dddd, J = 13.4, 8.6, 7.4, 7.4 Hz), 2.68 (1H, dddd, J = 13.2, 7.4, 7.2, 4.6 Hz), 4.05 (1H, ddd, J = 12.4, 7.4, 7.4 Hz), 4.38 (1H, ddd, J = 12.4, 8.6, 4.6 Hz), 5.27 (1H, dd, J = 7.2, 7.2 Hz), 5.98 (1H, brs), 7.50 (1H, ddd, J = 8.0, 4.0, 4.0 Hz), 7.76 (2H, m), 8.31 (1H, ddd, J = 8.0, 1.2, 1.0 Hz); MS m/z (relative intensity) 202 (M^+, 100), 146 (95), 119 (50); HRMS calcd for $C_{11}H_{10}N_2O_2$ 202.0742, found 202.0745.

Asymmetric Oxidation of Deoxyvasicinone. To a solution of prepared base (LDA and NaHMDS, 0.75 mmol) in THF (1.0 mL) at −78 °C was added deoxyvasicinone[9] (93 mg, 0.50 mmol) in THF (3.0 mL), and the mixture was stirred for 1 h at the same temperature followed by addition of (*R*)- or (*S*)-Davis reagent (0.5−1.5 equiv), which was purchased from Aldrich Chemical, Inc., in THF (4.0 mL). The reaction was qunched at −78 °C by addition of saturated aqueous NH_4Cl (1.0 mL) and warmed to room temperature. The mixture was diluted with AcOEt (10 mL), and the combined organic layers were washed with water (2.0 mL) and saturated aqueous NaCl (4.0 mL). The aqueous layer was extracted with AcOEt (2 × 5.0 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt as the eluent) to give vasicinone. Furthermore, the optical purity of enantiomers was analyzed by HPLC on tris(4-chloro-3-methylphenyl carbamate) or tris(4-fluoro-3-methylphenyl carbamate) of cellulose as a stationary phase using hexane/2-propanol (85/15) as the eluent.[22] The results are summarized in Table 1.

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