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Stereoselective total synthesis of (+)-radicamine B via *anti,syn,syn*-oxazine

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ABSTRACT

The stereoselective total synthesis of (+)-radicamine B was achieved using commercially available D-4-hydroxy-phenylglycine via chiral 1,3-oxazine, which has been applied to synthesis of amino polyols such as DAB-1, D-fagomine, and phytosphingosines. The key steps in this strategy were the palladium(0)-catalyzed stereoselective intramolecular oxazine formation, an extension of the chirality of *anti,syn*-oxazine with Lewis acid and vinylmagnesium bromide, and pyrrolidine ring formation via hydrogenation reaction. The chiral extension is also applicable to other chiral 1,3-oxazine derived from D-4-hydroxy-phenylglycine.

1. Introduction

Several structurally related polyhydroxylated pyrrolidines have been reported to be biologically active as antiviral agents, acaricides, and competitive inhibitors of glycosidases (Fig. 1).[1] (+)-Radicamine A **1**[2] and (+)-radicamine B **2**[3] were extracted from *Lobelia chinensis* Lour, which was used as a diuretic, antidote, hemostat, and carcinostatic agent for stomach cancer in Chinese folk medicine.[2c,4] Their relative configurations are similar to those of (−)-codonopsine (**3**)[5] and (−)-codonopsinine **4**;[5] accordingly, their absolute configuration was proposed both to be (2*S*,3*S*,4*S*,5*S*). After the first synthesis of radicamines by Yu and Huang, the absolute configurations were revised to be (2*R*,3*R*,4*R*,5*R*).[3j] Cheng et al. described the biological effects of radicamine B **2** and related polyhydroxylated pyrrolidine derivatives.[2a] (−)-Codonopsine (**3**) and (−)-codonopsinine **4** were extracted from *Codonopsis clematidea*, which show hypotensive pharmacological efficacy without causing any effect on the central nervous system in animals.[6] Due to their biological activities and structures, which include four contiguous stereocenters, many synthetic routes to these molecules have been reported over the last decade.[2,3,5]

We have previously described the syntheses of chiral natural aminopolyols, such as DAB-1, D-fagomine, phytosphingosines, and daunosamine.[7] Recently we developed a novel chiral building block, *anti,syn,syn*-oxazine derived from D-serine and reported its application in the total syntheses of (−)-conduramine F-1,[8a] (+)-hyacinthacine A_2,[8b] (−)-sphingofungin B,[8b] (+)-1-deoxynojirimycin,[8c] and (+)-DMDP.[8c] In order to expand the synthetic utility of chiral *anti,syn,syn*-oxazine derived from various amino acids, we herein describe the stereoselective total synthesis of (+)-radicamine B **2** using *anti,syn,syn*-oxazine derived from D-4-hydroxy-phenylglycine (Fig. 2).

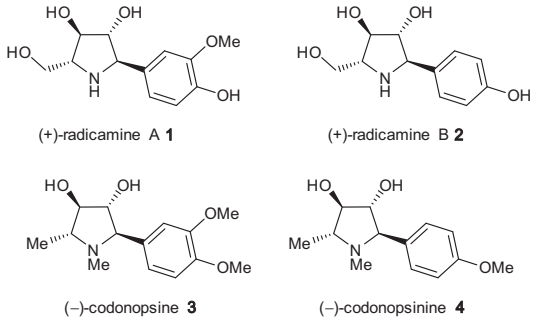

Figure 1. Chemical structures of (+)-radicamines, A **1**, B **2**, (−)-codonopsine **3**, and (−)-codonopsinine **4**.

2. Results and discussion

The retrosynthetic analysis shown in Scheme 1 indicates that (+)-radicamine B **2** could be obtained by deprotection of pyrrolidine **5**, which could be generated from *anti,syn,syn*-oxazine **6**.

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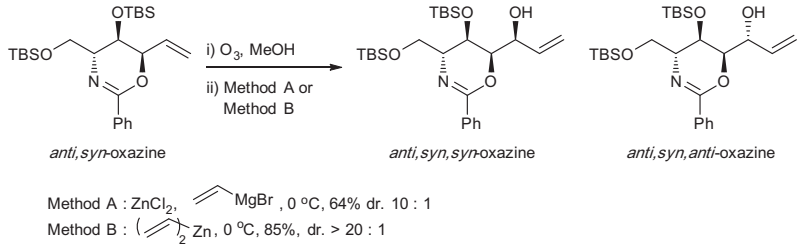
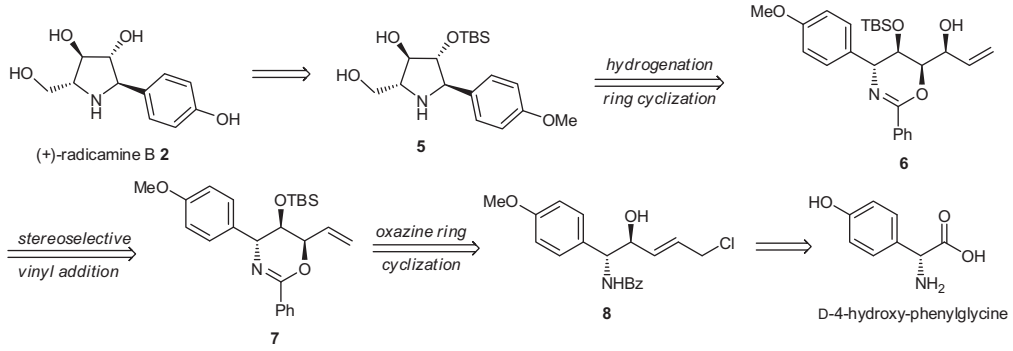


Figure 2. Previous report of chiral extension of *anti,syn*-oxazine derived from D-serine.



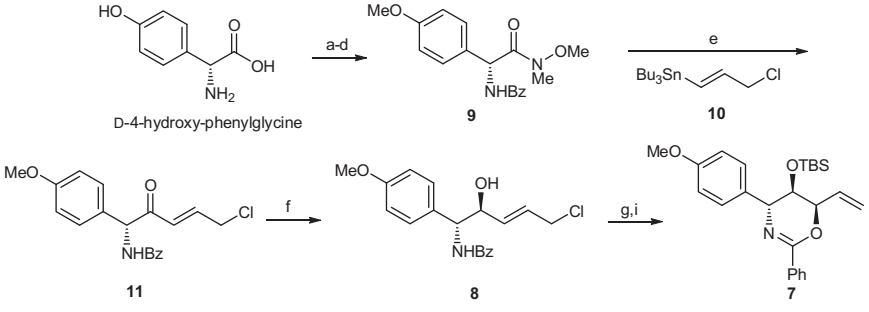
Scheme 1. Retrosynthetic analysis for (+)-radicamine B **2**.

anti,syn,syn-Oxazine **6** could in turn be prepared from *anti,syn*-oxazine **7** via stereoselective nucleophilic addition. The key intermediates, *anti,syn*-oxazine **7**, could be achieved from *anti*-amino alcohol **8**, which could be obtained from commercially available D-4-hydroxy-phenylglycine.

The preparation of *anti,syn*-oxazine **7** from D-4-hydroxy-phenylglycine is shown in Scheme 2. The Weinreb amide **9** was obtained by successive esterification, benzoyl protection of amino group, *O*-methylation of the phenolic OH, and Weinreb amide formation using MeHNOMe·HCl, $AlMe_3$ in CH_2Cl_2. Treatment of Weinreb amide **9** with vinyltin **10** and MeLi·LiBr complex solution in THF at −78 °C gave α,β-unsaturated ketone **11** in 86% yield. Chelation controlled hydride reduction of amino ketone **11** with $LiAlH(t\text{-}OBu)_3$ in EtOH at −78 °C, gave *anti*-amino alcohol **8** in 90% yield with excellent stereoselectivity (ds. >90%, as determined by ^1H NMR). Protection of *anti*-amino alcohol **8** with TBSCl in DMF and subsequent oxazine ring cyclization with Pd(0) cat. afforded *anti,syn*-oxazine **7** in good yield and with excellent diastereoselectivity (75% and ds. >97% as determined by ^1H NMR).

To increase the stereogenic centers of *anti,syn*-oxazine **7**, various conditions were explored (Table 1). Ozonolysis of the pendant olefin gave the corresponding aldehyde, which was subsequently reacted with vinylmagnesium bromide in the absence of Lewis acid to give the adduct *anti,syn,syn*-oxazine **6** with low diastereoselectivity (1.6:1 mixture of *syn*/*anti* isomers at 0 °C and 1:1 mixture at −78 °C; entries 1 and 7). Divinylzinc was also tested but unexpectedly gave low selectivity (entry 2).[8b] After extensive screening of reaction conditions, we established that the reaction of the aldehyde, $ZnCl_2$, and vinylmagnesium bromide in a 1:1:3 ratio delivered *anti,syn,syn*-oxazine **6** with good diastereoselectivity in good yield (entries 3 and 8). In entries 4 and 9, it is interesting to note that moderate *anti*-selectivity was obtained via the reaction with $TiCl_4$. We also found that $SnCl_4$ and $BF_3{\cdot}OEt_2$ gave low selectivities (entries 5, 6, 10, and 11). A low temperature led to improved diastereomeric ratios but gave low yields.

The total synthesis of (+)-radicamine B **2** is shown in Scheme 3. After mesylation of *anti,syn,syn*-oxazine **6**, subsequent ozonolysis



Reagents and conditions: (a) $SOCl_2$, MeOH, reflux; (b) BzCl, Et_3N, MeOH, 0 °C; (c) K_2CO_3, MeI, DMF; (d) MeNHOMe·HCl, $AlMe_3$, CH_2Cl_2, 82% over four steps; (e) **10**, MeLi·LiBr, −78 °C, 86%; (f) $LiAlH(tBuO)_3$, EtOH, −78 °C, 90%, ds. >90%; (g) TBSCl, imidazole, DMF, 93%; (i) $Pd(PPh_3)_4$, TBAI, NaH, THF, 0 °C, 75%, ds. >97%

Scheme 2. Preparation of *anti,syn*-oxazine **7** from D-4-hydroxy-phenylglycine.

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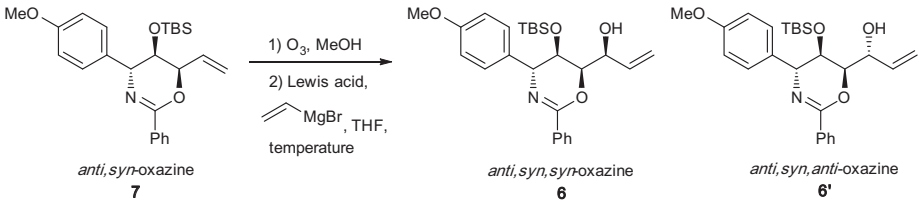
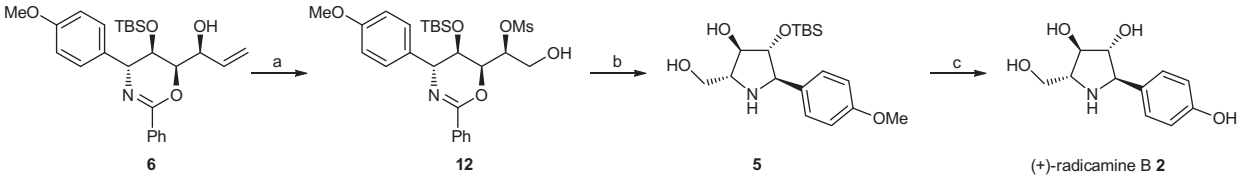
Table 1
anti,syn,syn-Oxazine **6** formation from *anti,syn*-oxazine **7**



Entry	Temp (°C)	Lewis acid	Ratio (**6**/**6′**)[a,b]	Yield[c] (%)
1	0	N/A	1.6:1	54
2[d]	0	N/A	1:1	—
3	0	$ZnCl_2$	8:1	83
4	0	$TiCl_4$	1:3	48
5	0	BF_3OEt_2	1.2:1	55
6	0	$SnCl_4$	1.1:1	48
7	−78	N/A	1:1	60
8	−78	$ZnCl_2$	8.5:1	64
9	−78	$TiCl_4$	1:3.5	50
10	−78	BF_3OEt_2	1:1	45
11	−78	$SnCl_4$	1:2	45

[a] Ratio was determined by ^{1}H NMR.
[b] The relative stereochemistry was established on the basis of the R_f value of the TLC analysis and comparison with ^{1}H and ^{13}C NMR of *anti,syn,syn*-oxazine and *anti,syn,anti*-oxazine in Ref. 8a.
[c] Two-step yield was indicated.
[d] Divinylzinc was employed instead of vinylmagnesium bromide.



Reagents and Conditions : (a) i) MsCl, Et_3N, CH_2Cl_2, 98.6%; ii) O_3, MeOH, –78 °C, then $NaBH_4$, 82%; (b) $Pd(OH)_2$, H_2, MeOH/AcOH(9:1), 78%; (c) BBr_3, CH_2Cl_2, 80%

Scheme 3. Stereoselective total synthesis of (+)-radicamine B **2**.

and hydride reduction afforded the corresponding primary alcohol **12**. Hydrogenolysis of resulting alcohol **12** with $Pd(OH)_2$ and H_2 in the presence of methanol and acetic acid afforded pyrrolidine derivative **5**. Under these conditions, cyclization of the mesylate formed pyrrolidine ring **5** as a single isomer as well as cleavage of the oxazine ring. Finally, treatment of **5** with boron tribromide afforded **2**·**HBr**. All spectroscopic data were similar to those reported for **2**·**HCl** except for the specific rotation.[3f,9] To confirm the identity of **2**·**HBr**, the product was purified by ion-exchange chromatography through Dowex 50WX8 (H^+) to give (+)-radicamine B **2**. The specific rotation of synthetic **2**, $[\alpha]_D^{19}$ = +42.8 (*c* 0.04, MeOH),[9] is similar to the reported value, $[\alpha]_D^{20}$ = +48.1 (*c* 0.34, EtOH),[3b] which confirms the identity of the absolute configuration. Thus, (+)-radicamine B **2** was synthesized from *anti,syn,syn*-oxazine **6** in 40.6% yield over four steps and from D-4-hydroxy-phenylglycine in 18.6% yield over 12 steps.

3. Conclusion

We have demonstrated that (+)-radicamine B **2** could be readily obtained from homochiral *anti,syn,syn*-oxazine **6** derived from D-4-hydroxy-phenylglycine. The key features in this strategy were stereoselective intramolecular oxazine formation, stereoselective addition of vinylmagnesium bromide in the presence of a Lewis acid, and cyclization by catalytic hydrogenolysis of oxazine. It is important to note that we controlled the fourth stereocenter with high stereoselectivity via Lewis acid mediated nucleophilic addition.

4. Experimental

4.1. General

Optical rotations were measured using a polarimeter in the solvent specified. ^{1}H and ^{13}C NMR spectroscopic data were recorded a 500/125, or 700/175 MHz FT-NMR spectrometer, respectively. The chemical shift values are reported in parts per million relative to TMS or $CDCl_3$ as the internal standards, and the coupling constants are reported in Hertz. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were measured using an FT-IR spectrometer. Mass spectroscopic data were obtained using a Jeol JMS 700 high resolution mass spectrometer with a magnetic sector–electric sector double focusing analyser. Flash chromatography was carried out using mixtures of ethyl acetate and hexane as the eluents. Unless otherwise noted, all non-aqueous reactions were carried out under an argon atmosphere using commercial grade reagents and solvents. Tetrahydrofuran (THF) was distilled from sodium and benzophenone ketyl (indicator). Dichloromethane (CH_2Cl_2) was distilled from calcium hydride.

4.2. (*R*)-*N*-(2-(Methoxy(methyl)amino)-1-(4-methoxyphenyl)-2-oxoethyl) benzamide 9

To a solution of *N,O*-dimethyl-hydroxylamine hydrochloride (4.19 g, 42.92 mmol) in CH_2Cl_2 (51 mL) was added trimethylaluminum (21.46 mL of a 2.0 M solution in hexane, 42.92 mmol) at 0 °C (Caution: CH_4 evolution). The mixture was stirred for 30 min

at room temperature. Subsequently, a solution of methyl ester (4.28 g, 14.31 mmol) in CH_2Cl_2 (21 mL) was added dropwise. The mixture was stirred at room temperature for 1 h, after which time TLC analysis indicated complete reaction. The reaction mixture was cooled to 0 °C and carefully quenched with 10% sodium potassium tartrate. After being stirred for 1 h at room temperature, the resulting suspension was filtered through a Celite pad and washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give the crude product, which upon purification by column chromatography on silica gel gave the Weinreb amide **9** (4.23 g, 90% yield) as a colorless oil; $[\alpha]_D^{25} = -115.30$ (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3327, 1644, 1585, 1514, 1484, 1391, 1309,1253, 1182, 1033, 996 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.22 (s, 3H), 3.50 (s, 3H), 3.79 (s, 3H), 6.13 (d, *J* = 6.5 Hz, 1H), 6.88 (m, 2H), 7.39–7.49 (m, 5H), 7.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.12, 53.85, 55.50, 61.46, 76.66, 114.45, 127.36, 128.70, 129.44, 131.81, 134.31, 159.71, 166.47; HRMS (FAB) calcd for $C_{18}H_{21}N_2O_4$ 329.1501, found 329.1501.

4.3. (*R*,*E*)-*N*-(5-Chloro-1-(4-methoxyphenyl)-2-oxopent-3-enyl) benzamide 11

Vinyltin **10** (14.17 g, 38.65 mmol) was dissolved in dry THF (90 mL) and cooled to −78 °C. Next, 1.5 M MeLi·LiBr in hexane (25.76 mL, 38.65 mmol) was added dropwise. The mixture was stirred for 30 min at the same temperature. Subsequently, a solution of Weinreb amide **9** (4.23 g, 12.88 mmol) in dry THF (40 mL) was added dropwise and stirring was continued for 30 min, after which time TLC analysis indicated complete reaction. The reaction was quenched by aqueous sat. NH_4Cl, and then warmed to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was concentrated in vacuo. The resulting substance was purified by silica gel column chromatography and gave amino ketone **11** (3.81 g, 11.08 mmol, 86% yield); $[\alpha]_D^{25} = -191.7$ (*c* 0.1, $CHCl_3$): IR (neat) ν_{max}: 3394, 3063, 3003, 2959, 2933, 2840, 1711, 1640, 1607, 1581, 1514, 1484, 1424, 1346, 1305, 1253, 1179, 1115, 1033, 978, 836, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 1H), 4.12 (dd, *J* = 6.0, 1.5 Hz, 2H), 5.87 (d, *J* = 6.0 Hz, 1H), 6.41 (td, *J* = 15.5, 1.5 Hz, 1H), 6.91 (m, 2H), 7.02 (td, *J* = 15.0, 6.0 Hz, 1H), 7.32 (m, 2H), 7.41–7.50 (m, 3H), 7.52 (d, *J* = 6.5, 1H), 7.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.12, 42.82, 55.53, 61.99, 76.68, 115.04, 127.36, 127.97, 128.78, 129.99, 131.97, 134.08, 142.10, 160.19, 166.58, 194.06; HRMS (FAB) calcd for $C_{19}H_{19}ClNO_3$ 344.1053, found 344.1053.

4.4. *N*-((1*R*,2*S*,*E*)-5-Chloro-2-hydroxy-1-(4-methoxyphenyl)pent-3-enyl) benzamide 8

To a solution of amino ketone **11** (3.81 g, 11.08 mmol) in ethanol (110 mL) was added lithium tri-*tert*-butoxyaluminohydride (1.0 M solution in THF, 27.71 mL, 27.71 mmol) at −78 °C. After the reaction mixture was stirred at the same temperature for 2 h, a 10% aqueous solution of citric acid was added. The resulting mixture was warmed to room temperature and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude products. Column chromatography on silica gel gave *anti*-amino alcohol **8** (3.45 g, 9.98 mmol, 90% yield); $[\alpha]_D^{25} = -45.7$ (*c* 0.1, $CHCl_3$); IR (neat) ν_{max}: 3309, 3003, 2936, 2836, 1633, 1585, 1532, 1518, 1491, 1465, 1447, 1313, 1283, 1249, 1182, 1119, 1082, 1033, 970, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 1H), 4.02 (dd *J* = 6.0, 1.0 Hz, 2H), 4.58 (m, 1H), 5.27 (dd, *J* = 6.0, 3.5 Hz, 1H), 5.75 (td, *J* = 6.0, 1.0 Hz, 1H), 5.92 (m, 1H), 6.75 (d, *J* = 7.5, Hz, 1H), 6.90 (m, 2H), 7.29 (m, 2H), 7.43–7.54 (m, 3H), 7.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.13, 44.23, 55.53, 58.47, 74.77, 114.39, 124.18, 127.25, 128.87, 131.98, 131.99, 133.24, 133.26, 134.37, 134.38, 134.40, 159.59, 167.72; HRMS (FAB) calcd for $C_{19}H_{21}ClNO_3$ 346.1210, found 346.1210.

4.5. *N*-((1*R*,2*S*,*E*)-2-(*tert*-Butyldimethylsilyloxy)-5-chloro-1-(4-methoxyphenyl)pent-3-enyl)benzamide

Imidazole (1.02 g, 14.96 mmol) and *tert*-butyldimethylchlorosilane (3.01 g, 19.95 mmol) were added to a stirred solution of *anti*-amino alcohol **8** (3.45 g, 9.98 mmol) in DMF (6.9 mL) at room temperature, after which stirring was continued for 2 h. The reaction mixture was quenched with H_2O and then extracted twice with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification by silica gel chromatography gave TBS ether (4.2 g, 9.13 mmol, 93%); $[\alpha]_D^{25} = -46.9$ (*c* 0.1, $CHCl_3$); IR (neat) ν_{max}: 3432, 3298, 2955, 2933, 2899, 2858, 1637, 1540, 1514, 1491, 1465, 1447, 1309, 1249, 1182, 1115, 1082, 1033, 974, 873, 836, 780, 698, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.92 (s, 9H), 3.80 (s, 3H), 3.98 (m, 2H), 4.62 (m, 1H), 5.13 (td, *J* = 8.0, 4.0 Hz, 1H), 5.53 (m, 1H), 5.88 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.86 (m, 2H), 7.28 (m, 2H), 7.41-7.51 (m, 3H), 7.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.74, −4.04, 18.35, 26.05, 30.80, 44.24, 55.48, 58.00, 74.93, 76.67, 113.97, 127.07, 128.52, 128.81, 129.30, 130.56, 131.72, 134.43, 134.80, 159.29, 166.67; HRMS (FAB) calcd for $C_{25}H_{35}ClNO_3Si$ 460.2075, found 460.2073.

4.6. (4*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine 7

At first, NaH (55% in mineral oil, 430 mg, 18.26 mmol) and *n*-Bu_4NI (3.38 g, 9.13 mmol) were added to a stirred solution of allyl chloride (4.20 g, 9.13 mmol) in anhydrous THF (450 mL) at 0 °C. After stirring for 5 min, $Pd(PPh_3)_4$ (2.11 g, 1.83 mmol) was added to the mixture and stirring was continued for 12 h at the same temperature. The reaction mixture was filtered through a pad of silica and then evaporated under reduced pressure to give a crude product. Purification of this material by silica gel chromatography (hexanes/EtOAc = 30/1) gave **7** (2.90 g, 6.846 mmol, 75% yield); $[\alpha]_D^{25} = -8.0$ (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 2955, 2929, 2858, 1659, 1614, 1585, 1514, 1465, 1365, 1324, 1302, 1283, 1249, 1179, 1115, 1074, 1037, 1011, 996, 929, 870, 836, 780, 702, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.22 (s, 3H), −0.03 (s, 3H), 0.87 (s, 3H), 3.83 (s, 3H), 3.84 (dd, *J* = 6.5, 4.0 Hz, 1H), 4.51 (d, *J* = 6.5 Hz, 1H), 4.73 (ddd, *J* = 6.5, 4.0, 1.5 Hz, 1H), 5.35 (d, *J* = 1.5 Hz, 1H), 5.38 (dt, *J* = 6.5, 1.5 Hz, 1H), 6.11 (ddd, *J* = 8.5, 5.25, 4.5 Hz, 1H), 6.90 (m, 2H), 7.21 (m, 2H), 7.40-7.49 (m, 3H), 8.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.01, −4.62, 18.22, 25.96, 55.57, 61.04, 71.41, 75.65, 113.94, 117.76, 127.75, 128.28, 129.24, 130.77, 133.40, 134.25, 154.16, 159.12; HRMS (FAB) calcd for $C_{25}H_{34}NO_3Si$ 424.2308, found 424.2306.

4.7. (*S*)-1-((4*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)prop-2-en-1-ol 6

anti,*syn*-Oxazine **7** (2.90 g, 6.846 mmol) was dissolved in dry methanol (103 mL) and cooled to −78 °C. Ozone was then passed through the solution until the reaction was complete. The reaction mixture was quenched with $(CH_3)_2S$ (5.0 mL, 68.46 mmol) and allowed to warm to room temperature. The solvents were evaporated under reduced pressure. The crude aldehyde was immediately employed in the next step without further purification. Next, $ZnCl_2$ (1.0 M solution in diethyl ether; 6.85 mL, 6.85 mmol) and vinylmagnesium bromide (1.0 M solution in THF; 34.23 mL, 34.23 mmol) were added to a solution of the aldehyde in THF

(145 mL) at −78 °C over 12 h. The reaction was quenched by a saturated aqueous solution of NH_4Cl and then warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting substance was purified by silica gel column chromatography to obtain **6** as a colorless oil; $[\alpha]_D^{25}$ = +5.1 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3435, 2988, 2955, 2933, 2858, 2702, 1659, 1477, 1402, 1309, 1212, 1179, 1074, 1041, 970, 844, 776, 702, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.17 (s, 3H), 0.18 (s, 3H), 0.89 (s, 9H), 2.90 (d, *J* = 2.6 Hz, 1H), 3.79 (s, 3H), 3.84 (dd, *J* = 5.8, 0.9 Hz, 1H), 4.06 (t, *J* = 2.0 Hz, 1H), 4.48 (tt, *J* = 5.8, 1.2 Hz, 1H), 4.85 (d, *J* = 2.6 Hz, 1H), 5.27 (dt, *J* = 10.5, 1.3 Hz, 1H), 5.43 (dt, *J* = 17.5, 1.5 Hz, 1H), 5.84 (ddd, *J* = 17.1, 10.6, 6.2 Hz, 1H), 6.88 (m, 2H), 7.11 (m, 2H), 7.41–7.44 (m, 2H), 7.46–7.48 (m, 1H), 8.04–8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.15, −3.92, 18.28, 25.94, 31.13, 55.52, 62.63, 70.37, 72.90, 74.77, 114.26, 118.37, 127.67, 128.35, 128.51, 130.88, 133.21, 135.52, 159.12; HRMS (FAB+): calcd. for $C_{26}H_{36}NO_4Si$ $[M+H]^+$ 454.2414, found 454.2414.

4.8. (*R*)-1-((4*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)prop-2-en-1-ol 6′

Crude oil; $[\alpha]_D^{25}$ = +30.3 (*c* 0.4, $CHCl_3$); IR (neat) ν_{max} 3342, 2955, 2929, 2858, 1652, 1614, 1585, 1514, 1465, 1365, 1343, 1283, 1249, 1201, 1179, 1115, 1078, 1033, 952, 929, 884, 866, 836, 806, 780, 747, 702, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 0.08 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 2.50 (br s, 1H), 3.79 (s, 3H), 3.85 (dd, *J* = 7.8, 2.3 Hz, 1H), 4.21 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.47–4.52 (m, 1H), 4.82 (d, *J* = 3.5 Hz, 1H), 5.30 (dt, *J* = 10.6, 1.5 Hz, 1H), 5.42 (dt, *J* = 17.5, 1.5 Hz, 1H), 5.84 (dt, *J* = 17.1, 1.6 Hz, 1H), 6.03 (dd, *J* = 10.6, 5.5 Hz, 2H), 6.06 (dd, *J* = 10.5, 5.6 Hz, 1H), 6.85–6.89 (m, 2H), 7.12–7.16(m, 2H), 7.38–7.42 (m, 2H), 7.44–7.48 (m, 1H), 8.00–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −15.23, −0.4336, 18.25, 25.96, 31.13, 55.54, 62.15, 69.40, 71.33, 74.30, 114.20, 117.14, 127.71, 128.29, 128.72, 130.84, 133.46, 133.58, 137.72, 155.13, 159.12, 207.05; HRMS (FAB+): calcd. for $C_{26}H_{36}NO_4Si$ $[M+H]^+$ 454.2414, found 454.2414.

4.9. (*S*)-1-((4*R*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)allyl methanesulfonate

Triethylamine (0.29 mL, 2.058 mmol) and methanesulfonyl chloride (0.11 mL, 1.372 mmol) were successively added to a solution of *anti,syn,syn*-oxazine **6** (0.31 g, 0.686 mmol) in dichloromethane (13.7 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature over 1 h. After the addition of water, the aqueous layer was extracted with dichloromethane. The dichloromethane extracts were washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine, and then dried and evaporated. Flash column chromatography on silica gel (ethyl acetate/hexane = 1:4) gave mesylate (0.36 g, 0.677 mmol) as a colorless oil; $[\alpha]_D^{25}$ = +17.7 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 2955, 2933, 2858, 1659, 1614, 1585, 1514, 1465, 1421, 1361, 1305, 1287, 1253, 1201, 1179, 1115, 1074, 1037, 940, 870, 836, 780, 702, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.14 (s, 3H), 0.19 (s, 3H), 0.89 (s, 9H), 3.04 (s, 3H), 3.80 (s, 3H), 3.95 (m, 1H), 4.00 (d, *J* = 8.5 Hz, 1H), 4.88 (d, *J* = 1.5 Hz, 1H), 5.37 (t, *J* = 8.0 Hz, 1H), 5.48 (m, 1H), 5.62 (m, 1H), 5.64–5.80 (m, 2H), 6.88 (m, 2H), 7.09 (m, 2H), 7.40–7.49 (m, 3H), 8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −3.98, −3.74, 18.35, 25.96, 31.13, 39.49, 55.53, 62.22, 68.52, 82.54, 114.36, 123.39, 127.76, 128.42, 130.41, 130.95, 133.55, 159.21, 207.06.

4.10. (*S*)-1-((4*R*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)-2-hydroxyethyl methanesulfonate 12

Mesylate (0.36 g, 0.677 mmol) was dissolved in dry methanol (27 mL) and cooled to −78 °C. Ozone was then passed through the solution until the reaction was complete. Next, $NaBH_4$ (40 mg, 1.016 mmol) was added to the reaction mixture, which was then warmed to room temperature. The mixture was washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine, and then dried over $MgSO_4$ and evaporated. Flash column chromatography on silica gel (ethyl acetate/hexane = 1:2) gave primary alcohol **12** as a colorless oil; $[\alpha]_D^{25}$ = +28.5 (*c* 0.3, $CHCl_3$); IR (neat) ν_{max} 3312, 2955, 2929, 2858, 1655, 1614, 1514, 1465, 1354, 1290, 1253, 1201, 1179, 1119, 1078, 1033, 966, 937, 866, 836, 784, 739, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.14 (s, 3H), 0.15 (s, 3H), 0.88 (s, 9H), 3.11 (s, 3H), 3.83 (m, 1H), 4.01 (ddd, *J* = 21.5, 11.0, 6.0 Hz, 1H), 4.09 (m, 1H), 4.28 (td, *J* = 8.0, 1.5 Hz, 1H), 4.85 (d, *J* = 3.0 Hz, 1H), 5.03 (m, 1H), 6.88 (m, 2H), 7.12 (m, 2H), 7.40–7.49 (m, 3H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.21, −3.98, 18.27, 25.89, 31.13, 38.85, 55.53, 61.83, 68.81, 72.04, 82.94, 114.35, 127.70, 128.46, 130.99, 132.66, 155.28, 159.26; $C_{26}H_{38}NO_7SSi$ $[M+H]^+$ 536.2138; found 536.2137.

4.11. (2*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)- 5-(4-methoxyphenyl) pyrrolidin-3-ol 5

A suspension of synthesized mesylate compound **12** (300 mg, 0.56 mmol) in MeOH/AcOH (7.5 mL:0.83 mL) in the presence of 20% $Pd(OH)_2/C$ (300 mg) at room temperature was hydrogenated at atmospheric pressure for 48 h. The catalyst was then removed by filtration through a Celite pad, and the filtrate was evaporated to dryness. After washing with EtOAc, the residue was neutralized with $NaHCO_3$ in water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to give **5** as a crude oil (220 mg, 75%). R_f = 0.48 (ethyl acetate/hexane = 1:1); $[\alpha]_D^{25}$ = +7.6 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3346, 2955, 2929, 2858, 1737, 1614, 1588, 1518, 1465, 1447, 1413,1391, 1365, 1253, 1182, 1153, 1041, 944, 840, 784, 732, 713, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ −0.28 (s, 3H), −0.07 (s, 3H), 0.81 (s, 9H), 3.35 (br s, 1H), 3.65-3.70 (m, 2H), 3.81 (s, 3H), 3.92 (d, *J* = 7.1 Hz, 1H), 3.98-4.02 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.97, −4.63, 17.88, 25.69, 25.74, 55.29, 62.45, 63.54, 66.43, 79.29, 85.64, 114.02, 128.35, 133.60, 159.20; HRMS (FAB+): calcd. for $C_{18}H_{31}NO_3Si$ $[M+H]^+$ 354.2101; found 354.2102.

4.12. (2*R*,3*R*,4*R*,5*R*)-4-(Hydroxy)-2-(hydroxymethyl)-5-(4-hydroxyphenyl) pyrrolidin-3-ol 2

Boron tribromide (1.0 M solution in CH_2Cl_2; 0.427 mL, 0.427 mmol) was added dropwise at 0 °C to a solution of pyrrolidine **3** (30.2 mg, 0.0854 mmol) in CH_2Cl_2 (1.71 mL). The reaction mixture was stirred for 5 h at room temperature and then quenched with MeOH. The mixture was diluted with H_2O and washed with EtOAc. The aqueous layer was evaporated, and the residue was purified by flash column chromatography (silica gel, chloroform/methanol = 1:1) to give **2·HBr**. $[\alpha]_D^{25}$ = +41.3(*c* 0.1, MeOH); IR(neat) ν_{max} 3353, 2959, 2929, 2854, 1640, 1525, 1462, 1417, 1253, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 3.52 (br s, 1H), 3.85 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.90 (dd, *J* = 12.8, 3.6 Hz, 1H), 4.12 (t, *J* = 7.7 Hz, 1H), 4.23 (br s, 1H), 4.35 (br s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 60.13, 61.55, 63.08, 75.33, 79.37, 115.96, 129.62, 156.38. Further purification with Dowex 50WX8 afforded **2** as a white solid

(11.3 mg, 0.0683 mmol, 59%); $[\alpha]_D^{19}$ = +42.8 (*c* 0.04, MeOH); HRMS (FAB+): calcd. for $C_{11}H_{16}NO_4$ $[M+H]^+$ 226.1079, found 226.1073.

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