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A C_2-Symmetric Pool Based Flexible Strategy: An Enantioconvergent Synthesis of (+)-Valiolamine and (+)-Valienamine

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A new enantioconvergent strategy directed toward the synthesis of glucosidase inhibitors was developed by using a C_2-symmetric element within the chiral pool and by applying an iodine-promoted cyclization of an unsaturated carbonimidothioate for the regio- and diastereocontrolled installation of amino and hydroxy units. Not only does this simple flexible strategy provide a convergent concise approach to (+)-valiolamine (**1**), but it can also be readily adopted for the synthesis of (+)-valienamine (**2**). Commercially available and cheap C_2-symmetric D-tartaric acid served as the chiral building block.

Introduction

Both natural products (+)-valiolamine (**1**) and (+)-valienamine (**2**) are found as components of pseudo-oligosaccharides,[1,2] which are potent glucosidase inhibitors and have therapeutic value. Valiolamine (**1**) is the most potent α-glucosidase inhibitor among the amino pseudosugars.[3] Its potent activity has stimulated much synthetic activity and has increased the interest to simplify its synthesis. An enantiospecific synthesis of valiolamine and its diastereomers from (–)-quinic acid and carbohydrate-derived diketones has appeared in the literature.[4] A total synthesis of racemic and optically pure valienamine based upon Pd-catalyzed desymmetrization and *cis*-hydroxyamination has been reported by Trost.[5] Several chiral pool based syntheses of (+)-valienamine (**2**) employ the cyclitol quebrachitol,[6] D-glucose derivatives,[7] or (–)-quinic acid[8a,8b] as the chiral building block, wherein new stereogenic centers are introduced into compounds bearing preexisting ones. Some of the reported syntheses involve lengthy protecting group manipulation and employ expensive chiral substrates such as tetra-*O*-benzyl-D-glucopyranose[7d] and quebrachitol[6] as starting materials. The chiral pool approach to synthesize chiral targets can be extremely attractive if nature happens to provide an abundant supply of an inexpensive starting material appropriate for the synthetic target. The importance of C_2-symmetric tartaric acid in asymmetric synthesis was detailed decades ago.[9] We have previously described a flexible synthetic strategy from C_2-symmetric L-tartaric acid leading to many aminocyclitol analogs.[10] The successful creation of this convenient general strategy illustrates the importance of the C_2-symmetric element in the development of new strategies for the asymmetric synthesis of natural products.[11] To further evaluate the capacity of C_2-symmetric chiral substrates, we developed a new concise approach to both (+)-valiolamine (**1**) and (+)-valienamine (**2**) by using commercially available D-tartaric acid as the chiral building block (Figure 1).

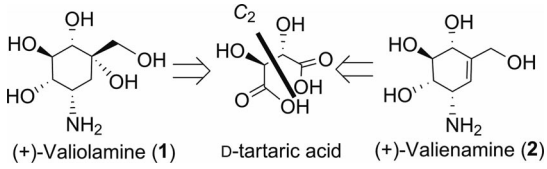

Figure 1. (+)-Valiolamine (**1**) and (+)-valienlamine (**2**).

Results and Discussion

The ready availability of enantiomerically pure vinyl carbinol **5**[9] suggested that an effective strategy might emerge through its ring-closing metathesis (RCM) by using Grubbs catalyst. By combining this RCM reaction with an iodine-assisted cyclization[12] of unsaturated carbonimidothioate **9** to introduce the amino unit with complete regio- and stereoselectivity, a simple, concise, flexible, and readily scalable enantioconvergent synthesis of (+)-valiolamine (**1**) and (+)-valienamine (**2**) could be possible (Figure 2).

Following the reported procedures, the synthesis commenced with commercially available D-tartaric acid (**3**, Scheme 1). Reduction of dimethyl 2,3-*O*-isopropylidene-D-tartrate (**4**) with DIBALH, followed by a highly diastereoselective divinylzinc addition to the in situ generated dialdehyde afforded desired vinyl carbinol **5**.[9a–9e] Subsequent

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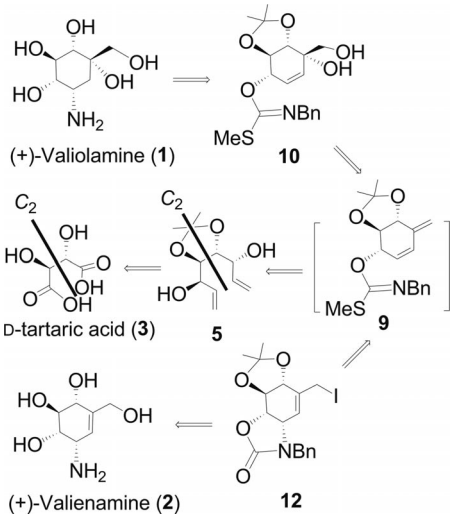
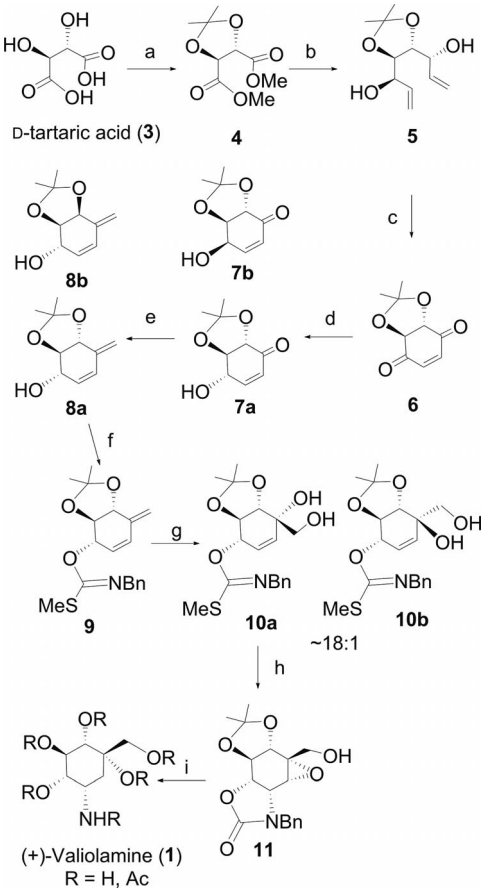


Figure 2. Retrosynthesis of (+)-valiolamine (**1**) and (+)-valienlamine (**2**).

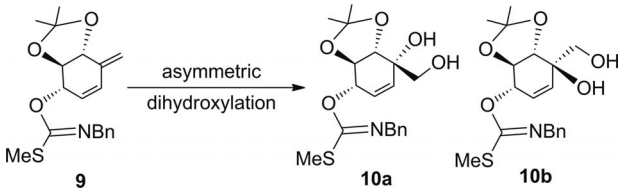
RCM with the use of the second-generation Grubbs catalyst and oxidation with Dess–Martin periodinane proceeded without complication to give cyclic enedione **6**. Gratifyingly, by simple modification of the reaction conditions, we found that the two-step process from vinyl carbinol **5** to enedione **6** could be carried out in a single vessel without isolation of the cyclic diol. Most fortunately, purification of enedione **6** could be achieved by silica gel chromatography at 0 °C. Enedione **6** was isolated in 82% overall yield. We suggest that the keto form of enedione **6** is stabilized by the *trans*-fused ring system. It has also been noted by Sulikowski[9a] that the enantiomer of **6** is stable to silica gel chromatography and could serve as a stable dienophile at 40 °C for several days. Controlled reduction of enedione **6** with $Zn(BH_4)_2$ in DME/Et_2O at –78 °C gave a chromatographically separable mixture of hydroxyenones **7a** and **7b** in 92% yield with >13:1 diastereoselectivity. Next, we examined the carbonyl methylenation of **7a**. Surprisingly, methylenation of **7a** turned out to be challenging. All attempts to perform the carbonyl methylenation promoted by the ylide derived from phosphonium bromide or the α-silyl carbanion led to an inseparable mixture of **8a** and **8b**. Finally, when this hydroxyenone was subjected to methylenation with the ylide derived from phosphonium iodide,[13] only desired dienol **8a** was obtained. With enantiomerically pure dienol **8a** in hand, the stage was set for installation of the amino and hydroxy units. For introduction of the C-1 and C-7 hydroxy groups and the C-3 and C-4 vicinal amino alcohol units, we pursued the conversion of the hydroxy group into the carbonimidothioate, followed by the regio- and diastereocontrolled dihydroxylation of the diene and an iodine-assisted cyclization of the unsaturated carbonimidothioate. Treatment of **8a** with sodium hydride in THF at 0 °C followed by addition of benzyl isothiocyanate (1.5 equiv.) and methyl iodide resulted in efficient formation of desired carbonimidothioate **9** in 88% yield.[12] For the regio- and diastereocontrolled introduction of the dihydroxy groups, compound **9** was subjected to osmium-catalyzed asymmetric dihydroxylation.[14] Surprisingly, all attempts to perform the dihydroxylation by using OsO_4/NMO or $K_2OsO_4{\cdot}2H_2O$ mediated by chiral ligands such as $(DHQD)_2$-PHAL, $(DHQD)_2$-PYR, $(DHQ)_2$-PHAL, $(DHQ)_2$-PYR, and $(DHQ)_2$-AQN led to disappointing results (DHQD = dihydroquinidine, PHAL = 1,3-phthalazinediyl, PYR = pyrimidine, DHQ = dihydroquinine, AQN = anthraquinone; Table 1). On the other hand, asymmetric dihydroxylation of **9** by using K_2OsO_4 mediated by $(DHQD)_2$-AQN led to unsaturated dihydroxycarbonimidothioates **10a** and **10b** with complete regioselectivity and good diastereoselectivity (>13:1). Interestingly, decreasing the amount of $(DHQD)_2$-AQN to 0.01 equiv. increased the diastereoselectivity to 18.1:1. The desired stereochemical outcome of this dihydroxylation was confirmed by the elab-



Scheme 1. Asymmetric synthesis of (+)-valiolamine (**1**). Reagents and conditions: (a) TsOH (0.02 equiv.), $Me_2C(OMe)_2$/MeOH (3:1), reflux, 48 h, 83%; (b) DIBALH (2.3 equiv. 20 wt.-% in hexane), –78 °C, 2 h, then $ZnCl_2/H_2C{=}CHMgBr$, –78 to 25 °C, 8 h, 83%; (c) Grubbs II (2% equiv.), CH_2Cl_2, reflux, 2 h; then Dess–Martin periodinane, 0 °C, 12 h, 82%; (d) $Zn(BH_4)_2$ (0.25 equiv.), DME/Et_2O (1:1), –78°C, 92% (>13:1 diastereoselectivity); (e) Ph_3PCH_3I, *n*BuLi, THF, 0 °C, 1 h, 88%; (f) NaH, THF, 0 °C, 30 min; then $PhCH_2NCS$, 3 h; then CH_3I, 10 min, 88%; (g) $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, 1,4-bis(dihydroquinidinyl)anthraquinone [$(DHQD)_2$-AQN] (1 mol-%), K_2CO_3, $MeSO_2NH_2$, H_2O/*t*BuOH, 94% (>18:1 diastereoselectivity); (h) I_2, THF, K_2CO_3, 25 °C, 18 h, 72%; (i) Li, NH_3, THF, –78 °C, 45 min; then LiOH, H_2O, EtOH, 80 °C, 30 min; then HOAc, 50 °C; then Ac_2O, pyridine, DMAP, 25 °C, 18 h, 53%.

oration of **10a** into (+)-valiolamine (**1**). The availability of **10a** allowed for direct construction of epoxy carbonate **11** by iodine-promoted N-cyclization in the presence of K_2CO_3. This simple procedure afforded **11** very efficiently. Finally, reductive cleavage of the epoxide and the *N*-benzyl group in carbamate **11** with Li/NH_3 followed by LiOH-promoted carbamate hydrolysis and HOAc-assisted acetal deprotection resulted in efficient formation of **1**. Comparison of the physical properties of the N,O-acetyl derivative of **1** to those recorded confirmed its identity.[4c,15] By simple modification of the reaction conditions, we found that this one-pot reductive cleavage, deprotection, and acylation sequence under conditions reported by Trost[16] proceeded in 53% overall yield in a single vessel without isolation of any intermediates. Thus, this sequence required only nine steps to synthesize (+)-valiolamine (**1**) and proceeded in 12.6% overall yield from commercially available and cheap C_2-symmetric D-tartaric acid.

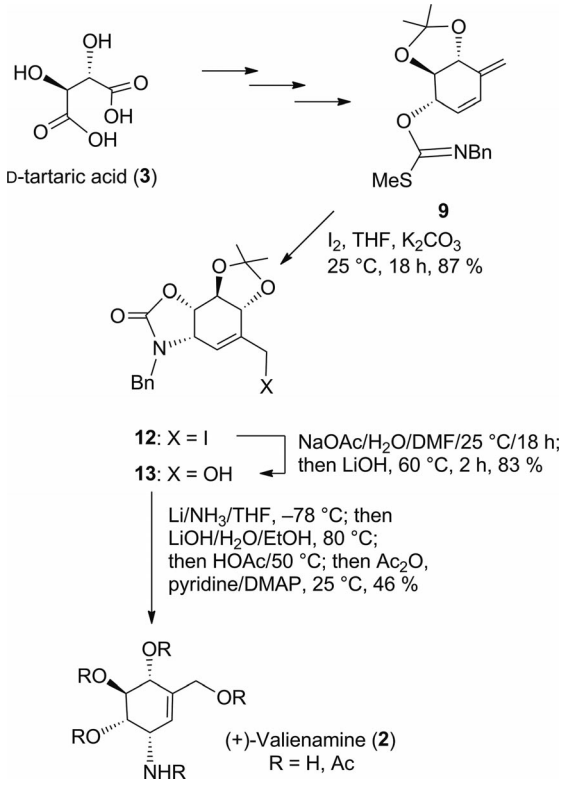
Table 1. Asymmetric dihydroxylation of **9**.



Entry	Chiral ligand (equiv.)	**10a/10b**[a]	Yield [%]
1	0[b]	1:1.8	75
2	$(DHQD)_2$-PHAL (0.05)[c]	1.7:1	78
3	$(DHQ)_2$-PHAL (0.05)[c]	4.2:1	87
4	$(DHQ)_2$-PYR (0.05)[c]	1:6.2	84
5	$(DHQD)_2$-PYR (0.05)[c]	1:3.5	79
6	$(DHQ)_2$-AQN (0.05)[c]	1:3.3	89
7	$(DHQD)_2$-AQN (0.09)[c]	13.7:1	82
8	$(DHQD)_2$-AQN (0.07)[c]	16.6:1	88
9	$(DHQD)_2$-AQN (0.03)[c]	17.3:1	92
10	$(DHQD)_2$-AQN (0.01)[c]	18.1:1	94

[a] Determined by ^{1}H NMR spectroscopy. [b] The reaction was run by using OsO_4 (0.02 equiv.) and NMO (8 equiv.) in acetone/H_2O (9:1) at 0 to 25 °C. [c] The reaction was run by using $K_2OsO_4 \cdot 2H_2O$ (0.01 equiv.), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), and $MeSO_2NH_2$ (1 equiv.) in *t*BuOH/H_2O (1:1) at 0 °C.

Unsaturated carbonimidothioate **9** not only serves as a pivotal intermediate to approach (+)-valiolamine (**1**), but it can also be readily adopted for the synthesis of (+)-valienamine (**2**, Scheme 2). For **2**, we must install the C-3 amino and C-7 hydroxy groups. Envisioning iodide **12** as the precursor to **1** suggests a regiospecific iodocyclization of dienylcarbonimidothioate **9** to create **12**. Fortunately, exposure of **9** to I_2 in THF at room temperature smoothly and cleanly effected the desired cyclization to afford 7-iodooxazolidinone **12** in 87% yield. Sequential exposure of iodide **12** to sodium acetate in DMF and hydrolysis under basic conditions resulted in efficient formation of allylic alcohol **13**. Simple removal of the *N*-benzyloxazolidinone and acetal groups completed the synthesis of **2**, which was characterized as its penta-*N*,*O*-acetyl derivative.[5] In nine steps, cheap C_2-symmetric D-tartaric acid was converted into (+)-valienamine (**2**) in 12.4% overall yield.



Scheme 2. Completion of the total synthesis of (+)-valienamine (**2**).

Conclusions

In summary, this C_2-symmetric chiral pool synthesis represents an economic and flexible enantioconvergent approach to both (+)-valiolamine (**1**) and (+)-valienamine (**2**). The success of this efficient synthetic strategy illustrates the importance of the presence of a C_2-symmetric element within the chiral pool. The key to our successes in the synthesis was the melding of several key reactions. Thus, the successful application of the iodine-promoted regio- and diastereocontrolled cyclization of cyclohexadienyl carbonimidothioate illustrated its extension to highly functionalized unsaturated systems. In addition, this study opened the question about the nature of the lithium salt and its importance in Wittig methylenation. This simple convergent strategy can readily be adopted for the construction of various structurally related natural products and other members of the aminocyclitol class. Modification of this route should be able to provide access to interesting analogs.

Experimental Section

General: Dichloromethane, dichloroethane, and DME (1,2-dimethoxyethane) were distilled from P_2O_5 prior to use. Commercially available ketones and aldehydes were used as received. Titanium tetrachloride and magnesium powder (ca 50 mesh) were used as

received. Chromatography was performed on silica gel 60 (230–400 mesh). All reactions were carried out under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR-400 MHz spectrometer at ambient temperature. High-resolution mass spectra were determined with a Jeol JMS-HX 110 spectrometer. Optical rotations were obtained with an Optical Activity AA-100 polarimeter.

Dimethyl 2,3-*O*-Isopropylidene-D-tartrate (4):[9h,10] D-Tartaric acid (**3**; 101 g, 673 mmol) was added to a solution of methanol (40 mL) and *p*-toluenesulfonic acid (400 mg, 2.1 mmol) in dimethoxypropane (190 mL) at room temperature. The mixture was stirred for 1.5 h at reflux, an additional amount of dimethoxypropane (95 mL) was added, and the stirring was continued at reflux for an additional 12 h. All volatile compounds (dimethoxypropane, acetone, and methanol) were removed by simple distillation, and the resulting crude product was washed with saturated aqueous potassium carbonate (2 × 30 mL). The combined organic layer was dried and purified by vacuum distillation to yield dimethyl tartrate (**4**; 121.9 g, 558.6 mmol, 83%) as a colorless oil. B.p. 110–112 °C (2 mm) [ref.[1] b.p. 100–110 °C (0.7 mm); ref.[2] b.p. 82–90 °C (0.02 mm)]. R_f = 0.5 (silica gel; hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.76 (s, 2 H), 3.81 (s, 6 H), 1.48 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (C), 113.9 (C), 77.0 (CH), 52.8 (CH_3), 26.3 (CH_3,CH_3) ppm.

4,5-*O*-Isopropylidene-1,7-octadiene-3,6-diol (5):[9,10] To a solution of D-tartrate **4** (8.0 g, 36.6 mmol) in toluene (96 mL) at –78 °C was added DIBALH (20% in hexane, 84.3 mL, 84.3 mmol) over 15 min. The mixture was stirred at –78 °C for 2 h, and a solution of divinylzinc (0.4 M in THF, 337 mL, 135 mmol) was then added dropwise over 45 min. The stirring was continued for 1 h at –78 °C, and the solution was then warmed to room temperature and stirred for another 6 h. The mixture was carefully quenched with H_2O and filtered through Celite to remove the solids. The eluate was concentrated in vacuo and extracted with EtOAc (3 × 300 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 3:1) to give vinyl carbinol **5** (6.51 g, 30.4 mmol, 83%). R_f = 0.6 (silica gel; hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (ddd, *J* = 16.8, 10.4, 6.0 Hz, 2 H), 5.37 (ddd, *J* = 17.6, 1.6, 1.6 Hz, 2 H), 5.25 (ddd, *J* = 10.8, 1.6, 1.6 Hz, 2 H), 4.18–4.15 (m, 2 H), 3.88–3.87 (m, 2 H), 2.68 (br., 1 H), 1.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 117.0, 109.4, 81.9, 73.5, 26.8 ppm.

(5*S*,6*S*)-5,6-(Isopropylidenedioxy)-2-cyclohexene-1,4-dione (6):[9a] To a solution of vinyl carbinol **5** (1.07 g, 5.0 mmol) in CH_2Cl_2 (250 mL) at room temperature was added a solution of the second-generation Grubbs catalyst (94.8 mg, 0.10 mmol) in CH_2Cl_2 (5 mL). After stirring for 2 h at reflux, the mixture was cooled to 0 °C. A solution of Dess–Martin periodinane (8.49 g, 20 mmol) in CH_2Cl_2 (67 mL) was added dropwise. The mixture was stirred at 0 °C for 12 h, and the solvent was then removed in vacuo. The residue was purified by flash chromatography at 0 °C (hexane/EtOAc, 2:1) to give enedione **6** (746 mg, 4.1 mmol, 82%). R_f = 0.5 (silica gel; hexane/EtOAc, 1:1). $[\alpha]_D^{25}$ = –253.0 (*c* = 2.3, $CHCl_3$) {enantiomer of **6**: ref.[9a] $[\alpha]_D^{20}$ = +263.5 (*c* = 2.1, $CHCl_3$)}. IR (film): $\tilde{\nu}$ = 2990, 1714, 1377, 1220, 1148, 1051, 814 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (s, 2 H), 4.58 (s, 2 H), 1.52 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 140.1, 114.3, 80.5, 26.4 ppm. HRMS (EI): calcd for $C_9H_{10}O_4$ $[M]^+$ 182.0579; found 182.0574.

(4*S*,5*R*,6*S*)-4-Hydroxy-5,6-(isopropylidenedioxy)cyclohex-2-en-1-one (7a): To a solution of enedione **6** (2.3 g, 12.6 mmol) in DME (35 mL) and ether (24 mL) at –78 °C was added $Zn(BH_4)_2$ (0.283 M in ether, 11 mL, 3.2 mmol). The mixture was stirred at –78 °C for 1 h and then acetone (5 mL) was added dropwise. After the mixture was stirred at –78 °C for 2 min, saturated aqueous ammonium chloride was carefully added at –78 °C and stirring was continued for an additional 10 min at room temperature. The mixture was extracted with EtOAc (3 × 150 mL). The combined organic layer was dried, filtered, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 2:1) to give a mixture of enedione **7a** and **7b** (2.14 g, 11.6 mmol, 92%). The title compound was obtained as a mixture of diastereomers (>13:1) and the ratio was determined by NMR integration of the olefinic protons (1 H in total): δ = 6.78 (dd, ≈0.929 H, **7a**) and 6.84(dd, ≈0.071 H, **7b**) ppm. Data for **7a**: R_f = 0.3 (silica gel; hexane/EtOAc, 1:1). $[\alpha]_D^{25}$ = –28.3 (*c* = 6.6, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 3420, 2988, 1710, 1378, 1227, 1137, 1052, 844 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (dd, *J* = 10.4, 2.0 Hz, 1 H), 6.05 (dd, *J* = 10.4, 2.4 Hz, 1 H), 4.75–4.71 (m, 1 H), 4.09 (d, *J* = 10.8 Hz, 1 H), 3.85 (dd, *J* = 10.8, 8.4 Hz, 1 H), 2.51 (br., 1 H), 1.50 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0, 149.9, 128.3, 112.7, 81.9, 79.3, 71.6, 26.7, 26.4 ppm. HRMS (EI): calcd for $C_9H_{12}O_4$ $[M]^+$ 184.0736; found 184.0729. Data for **7b**: R_f = 0.2 (silica gel; hexane/EtOAc, 1:1). $[\alpha]_D^{25}$ = –263.6 (*c* = 1.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3431, 2988, 1712, 1378, 1229, 1139, 1080, 817 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (dd, *J* = 10.0, 5.2 Hz, 1 H), 6.07 (d, *J* = 10.0 Hz, 1 H), 4.79–4.77 (m, 1 H), 4.71 (d, *J* = 10.4 Hz, 1 H), 3.88–3.83 (m, 1 H), 2.61 (br., 1 H), 1.49 (s, 3 H), 1.48 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 143.3, 130.5, 112.1, 77.2, 75.9, 64.2, 26.6, 26.5 ppm. HRMS (EI): calcd for $C_9H_{12}O_4$ $[M]^+$ 184.0735; found 184.0736.

(1*S*,5*R*,6*R*)-5,6-(Isopropylidenedioxy)-4-methylenecyclohex-2-en-1-ol (8a): To a suspension of methyltriphenylphosphonium iodide (7.1 g, 17.6 mmol) in THF (30 mL) at 0 °C was added *n*BuLi (1.6 M in hexane, 7.7 mL, 12.4 mmol). The mixture was stirred at 0 °C for 30 min, and then a solution of enone **7a** (650 mg, 3.5 mmol) in THF (10 mL) was added dropwise, The stirring was continued for 1 h at 0 °C, and saturated aqueous ammonium chloride (10 mL) was then carefully added at 0 °C. The resulting mixture was filtered through Celite to remove the solids, and the eluate was concentrated in vacuo. The residue was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 3:1) to give dienol **8a** (563 mg, 3.1 mmol, 88%). R_f = 0.4 (silica gel; hexane/EtOAc, 3:1). $[\alpha]_D^{25}$ = –96.2 (*c* = 2.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3430, 2986, 1648, 1374, 1232, 1060, 848 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.11 (dd, *J* = 10.0, 1.6 Hz, 1 H), 5.62 (d, *J* = 10.0 Hz, 1 H), 5.13 (s, 1 H), 5.03 (s, 1 H), 4.57–4.53 (m, 1 H), 4.04 (d, *J* = 10.0 Hz, 1 H), 3.54 (dd, *J* = 10.0, 8.4 Hz, 1 H), 2.85 (d, *J* = 5.2 Hz, 1 H), 1.48 (s, 3 H), 1.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7, 131.1, 128.8, 111.6, 109.3, 83.1, 76.7, 71.5, 27.0, 26.9 ppm. HRMS (EI): calcd for $C_{10}H_{14}O_3$ $[M]^+$ 182.0943; found 182.0935.

(1*S*,5*S*,6*S*)-*O*-[5,6-(Isopropylidenedioxy)-4-methylene-2-cyclohexenyl] *S*-Methyl *N*-Benzylcarbonimidothioate (9): To a suspension of NaH (277 mg, 6.9 mmol) in THF (20 mL) at 0 °C was added a solution of dienol **8a** (631 mg, 3.5 mmol) in THF (30 mL). The mixture was stirred at 0 °C for 30 min, and a solution of benzyl isothiocyanate (1.0 M in THF, 3.5 mL, 3.5 mmol) was then added dropwise. The mixture was further stirred for 3 h at room temperature, and a solution of methyl iodide (1.0 M in THF, 7.0 mL, 7.0 mmol) was then added. The stirring was continued at room temperature for 20 min, and the solvent was then removed in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 30:1) to give carbonimidothioate **9** (1047 mg, 3.0 mmol, 88%). R_f

= 0.6 (silica gel; hexane/EtOAc, 9:1). $[\alpha]_D^{25}$ = –64.3 (c = 4.9, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2986, 1635, 1584, 1494, 1452, 1372, 1230, 1168, 1094, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 4 H), 7.24–7.20 (m, 1 H), 6.16 (d, J = 10.0, Hz, 1 H), 5.93 (d, J = 8.8 Hz, 1 H), 5.82 (d, J = 10.0, Hz, 1 H), 5.17 (s, 1 H), 5.06 (s, 1 H), 4.43 (s, 2 H), 4.18 (d, J = 10.0 Hz, 1 H), 3.80 (dd, J = 8.8, 8.8 Hz, 1 H), 2.42 (s, 3 H), 1.50 (s, 3 H), 1.49 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 140.2,140.3, 129.2, 128.2, 128.1, 127.3, 126.5, 111.6, 109.3, 79.7, 76.8, 76.0, 52.6, 27.1, 27.0, 13.4 ppm. HRMS (EI): calcd for $C_{19}H_{23}NO_3S$ $[M]^+$ 345.1398; found 345.1400.

(*Z*)-(3a*R*,4*S*,7*S*,7a*S*)-*O*-[5,6-(Isopropylidenedioxy)-4-hydroxy-4-(hydroxymethyl)cyclohex-2-enyl] *S*-Methyl *N*-Benzylcarbonimidothioate (10): To a solution of carbonimidothioate **9** (947 mg, 2.7 mmol) in *t*BuOH (15 mL) and H_2O (15 mL) at 0 °C was added $K_3Fe(CN)_6$ (2.72 g, 8.2 mmol), K_2CO_3 (1.14 g, 8.2 mmol), $(DHQD)_2$-AQN (24 mg, 0.027 mmol), $K_2OsO_4{\cdot}2H_2O$(9 mg, 0.027 mmol), and $MeSO_2NH_2$(262 mg, 2.7 mmol). The mixture was stirred for 48 h at 0 °C, and then 20% aqueous sodium thiosulfate (5 mL) was added at 0 °C. The resulting mixture was then extracted with EtOAc (4 × 20 mL). The combined organic layer was washed with brine (5 mL). Flash chromatography (hexane/EtOAc, 1:2) gave dihydroxycarbonimidothioate **10a** (978 mg, 2.6 mmol, 94%). The title compound was obtained as a mixture of diastereomers (>18:1), and the ratio was determined by NMR integration of the olefinic protons (1 H in total): δ = 6.01 (dd, ≈0.948 H, **10a**) and 5.48 (dd, ≈0.052 H, **10b**) ppm. R_f = 0.5 (silica gel; hexane/EtOAc, 1:2). $[\alpha]_D^{25}$ = +77.4 (c = 2.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3422, 1634, 1495, 1453, 1431, 1373, 1229, 1168, 1114, 1047, 980, 868, 792, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 4 H), 7.23–7.19 (m, 1 H), 6.01 (dd, J = 10.0, 1.6 Hz, 1 H), 5.78 (d, J = 10.0 Hz, 1 H), 5.71 (dd, J = 10.0, 1.6 Hz, 1 H), 4.40 (s, 2 H), 4.20 (dd, J = 9.6, 9.6 Hz, 1 H), 3.73 (d, J = 10.8 Hz, 1 H), 3.57 (dd, J = 9.6, 9.6 Hz, 1 H), 3.52 (d, J = 10.8 Hz, 1 H), 2.88 (s, 1 H), 2.42 (s, 3 H), 1.99 (d, J = 9.6 Hz, 1 H), 1.46 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 140.3, 131.6, 128.5, 128.2, 127.3, 126.5, 111.9, 78.5, 75.3, 74.9, 71.5, 68.6, 52.7, 27.2, 26.7, 13.4 ppm. HRMS (EI): calcd for $C_{19}H_{25}NO_5S$ $[M]^+$ 379.1454; found 379.1459.

(3a*S*,4*R*,5*R*,6*S*,7*R*,7a*S*)-3-Benzyl-4,5-epoxy-5-hydroxymethyl-6,7-(isopropylidenedioxy)hexahydrobenzoxazol-2-one (11): Potassium carbonate (106 mg, 0.69 mmol) and iodine (195 mg, 0.69 mmol) were added sequentially to a solution of **10** (146 mg, 0.38 mmol) in THF (4 mL) at room temperature. After 24 h of stirring at room temperature, saturated aqueous sodium sulfite (5 mL) was added. The mixture was extracted with EtOAc (4 × 10 mL). The combined organic layer was dried, filtered, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 1:2) to give epoxy carbonate **11** (95 mg, 0.27 mmol, 72%). R_f = 0.5 (silica gel; hexane/EtOAc, 1:2). $[\alpha]_D^{25}$ = +56.7 (c = 0.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2987, 1746, 1542, 1500, 1453, 1228, 1098, 1065, 913, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H), 5.00 (d, J = 15.2 Hz, 1 H), 4.57 (dd, J = 9.6, 9.6 Hz, 1 H), 4.22–4.15 (m, 2 H), 4.07 (dd, J = 9.6, 2.4 Hz, 1 H), 4.01 (dd, J = 12.8, 4.0 Hz, 1 H), 3.90 (dd, J = 12.8, 9.2 Hz, 1 H), 3.84 (d, J = 9.2 Hz 1 H), 3.36 (d, J = 2.4 Hz, 1 H), 1.71 (dd, J = 4.0, 9.2 Hz, 1 H), 1.43 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 134.7, 129.1, 128.3, 128.2, 112.9, 76.1, 74.3, 73.9, 62.3, 59.5, 54.1, 53.4, 46.6, 26.7, 26.5 ppm. HRMS (EI): calcd for $C_{18}H_{21}NO_6$ $[M]^+$ 347.1368; found 347.1372.

(+)-Valiolamine (1) and Its Pentaacetate: Small pieces of lithium were added to a solution of *N*-benzyl epoxycarbamate **11** (73 mg, 0.21 mmol) in THF (2 mL) and liquid ammonia (10 mL) at –78 °C until the blue color persisted. The mixture was stirred for 3 h at –60 °C, and a small amount of H_2O (0.5 mL) was then carefully added to destroy the excess amount of lithium. The reaction mixture was warmed to room temperature, at which point a solution of LiOH (24 mg, 1.0 mmol) in ethanol/H_2O (3:7, 3 mL) was added. The mixture was stirred at 80 °C for 1 h, and a solution of HOAc/H_2O (4:1, 1 mL) was then added. After stirring for 18 h at 50 °C, the reaction mixture was allowed to cool to room temperature and concentrated in vacuo to gave **1**. To crude product **1** was added acetic anhydride (1 mL), pyridine (2 mL), and DMAP (5 mg) sequentially. After stirring overnight at room temperature, the reaction mixture was concentrated in vacuo, diluted with EtOAc, and filtered through Celite. The eluate was washed with saturated sodium carbonate and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc) to give valiolamine pentaacetate (45 mg, 0.11 mmol, 53%). R_f = 0.56 (silica gel; methanol/EtOAc, 2:1). $[\alpha]_D^{25}$ = –19.6 (c = 0.2, $CHCl_3$) {ref.[15] $[\alpha]_D^{20}$ = –18.0 (c = 1.0, $CHCl_3$), ref.[4c] $[\alpha]_D^{20}$ = –17.8 (c = 2.0, $CHCl_3$), ref.[2b] $[\alpha]_D^{25}$ = –14.8 (c = 1.0, $CHCl_3$)}. IR (film): $\tilde{\nu}$ = 3356, 1747, 1662, 1227 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (d, J = 8.8 Hz, 1 H), 5.49 (dd, J = 10.0, 10.0 Hz, 1 H), 5.06 (d, J = 10.0 Hz, 1 H), 4.90 (dd, J = 4.4, 10.8 Hz, 1 H), 4.75–4.70 (m, 1 H), 3.93 (d, J = 11.6 Hz, 1 H, *A*Bq), 3.82 (d, J = 11.6 Hz, 1 H, A*B*q), 3.00 (s, 1 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.94–1.93 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (C), 170.3 (C), 170.2 (C), 169.9 (C), 169.2 (C), 74.9 (CH), 72.9 (CH), 71.9 (CH), 68.8 (CH), 66.3 (CH_2), 44.9 (C), 32.7 (CH_2), 23.5 (CH_3), 20.7 (2 C, CH_3,CH_3), 20.6 (CH_3), 20.4 (CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 172.7 (C), 172.1 (C), 171.8 (C), 171.7 (C), 171.5 (C), 75.2 (CH), 74.0 (CH), 73.8 (CH), 70.4 (CH), 67.0 (CH_2), 46.9 (C), 33.8 (CH_3), 33.1 (CH_3), 20.7 (CH_3), 20.6 (2 C, CH_3,CH_3), 20.5 (CH_3) ppm. HRMS (EI): calcd for $C_{17}H_{25}NO_{10}$ $[M]^+$ 403.1479; found 403.1476.

(3a*S*,6*R*,7*S*,7a*S*)-3-Benzyl-3a,6,7,7a-tetrahydro-5-iodomethyl-6,7-(isopropylidenedioxy)benzoxazol-2-one (12): Potassium carbonate (623 mg, 4.5 mmol) and iodine (577 mg, 2.3 mmol) were added sequentially to a solution of carbonimidothioate **9** (519 mg, 1.5 mmol) in THF (5 mL) at room temperature. After 18 h of stirring at room temperature, saturated aqueous sodium sulfite (10 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried, filtered, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 3:1) to give tetrahydrobenzoxazolin-2-one **12** (577 mg, 1.3 mmol, 87%). R_f = 0.7 (silica gel; hexane/EtOAc, 1:1). $[\alpha]_D^{25}$ = +33.5 (c = 6.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2985, 1731, 1495, 1449, 1411, 1336, 1230, 1170, 1099, 1057, 1022, 836, 730, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 5 H), 5.66 (s, 1 H), 4.85 (d, J = 15.2 Hz, 1 H), 4.71 (dd, J = 10.4,10.4 Hz, 1 H), 4.21 (d, J = 8.8 Hz, 1 H), 4.16 (d, J = 8.8 Hz, 1 H), 4.11 (d, J = 15.2 Hz, 1 H), 4.08 (d, J = 9.6 Hz, 1 H), 3.85–3.79 (m, 2 H), 1.48 (s, 3 H), 1.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 139.7, 134.9, 129.0, 128.2, 128.0, 118.0, 113.7, 79.9, 73.4, 72.4, 54.8, 46.4, 26.7, 26.6, –0.1 ppm. HRMS (EI): calcd for $C_{18}H_{20}INO_4$ $[M]^+$ 441.0437; found 441.0439.

(3a*S*,6*R*,7*S*,7a*S*)-3-Benzyl-3a,6,7,7a-tetrahydro-5-hydroxymethyl-6,7-(isopropylidenedioxy)benzoxazol-2-one (13): NaOAc (293 mg, 1.2 mmol) was added to a solution of 7-iodooxazolidinone **12** (526 mg, 1.2 mmol) in DMF (2.0 mL) at room temperature. After 18 h of stirring at room temperature, LiOH (428 mg, 17.9 mmol) and H_2O (3 drops) were added sequentially. After stirring for 2 h at 60 °C, the reaction was cooled and H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and evapo-

rated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 1:1) to give alcohol **13** (327 mg, 0.99 mmol, 83%). $[\alpha]_D^{25}$ = +37.1 (*c* = 1.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3442, 2987, 1743, 1496, 1417, 1376, 1228, 1112, 1027, 846, 736, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 5.56 (s, 1 H), 4.90 (d, *J* = 15.6 Hz, 1 H), 4.70 (dd, *J* = 9.2, 9.2 Hz, 1 H), 4.30–4.22 (m, 3 H), 4.10 (d, *J* = 15.6 Hz, 1 H), 4.10–4.08 (m, 1 H), 3.80 (dd, *J* = 9.2, 9.2 Hz, 1 H), 1.99 (dd, *J* = 7.2, 5.2 Hz, 1 H), 1.45 (s, 6 H) ppm. ^{13}C (100 MHz, $CDCl_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 140.6, 134.9, 129.0, 128.3, 128.2, 114.9, 113.8, 80.3, 74.5, 72.7, 61.5, 54.1, 46.2, 26.7, 26.6 ppm. HRMS (EI): calcd for $C_{18}H_{21}NO_5$ $[M]^+$ 331.1420; found 331.1428.

(+)-Valienamine (2) and Its Pentaacetate: Small pieces of lithium were added to a solution of tetrahydrobenzoxazolin-2-one **13** (66 mg, 0.2 mmol) in THF (2 mL) and liquid ammonia (10 mL) at –78 °C until the blue color persisted. The mixture was stirred for 45 min at –78 °C, and a small amount of H_2O (0.5 mL) was then carefully added to destroy the excess amount of lithium. The reaction mixture was warmed to room temperature, at which point a solution of LiOH (24 mg, 1.0 mmol) in ethanol/H_2O (3:7, 3 mL) was added, and the mixture was stirred at 80 °C for 0.5 h. To the resulting mixture was then added a solution of HOAc/H_2O (4:1, 1 mL). After stirring for 18 h at 50 °C, the reaction mixture was allowed to cool to room temperature and was then concentrated in vacuo to give (+)-valienamine (**2**). To crude product **2** was added acetic anhydride (1 mL), pyridine (2 mL), and DMAP (5 mg) sequentially. After stirring overnight at room temperature, the reaction mixture was concentrated in vacuo, diluted with EtOAc, and filtered through Celite. The eluate was washed with saturated sodium carbonate and brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by flash chromatography (acetone/toluene, 1:2) to give valienamine pentaacetate (35 mg, 0.09 mmol, 46%). R_f = 0.19 (silica gel, acetone/toluene, 1:2). $[\alpha]_D^{25}$ = +22.6 (*c* = 2.3, $CHCl_3$) {ref.[8b] $[\alpha]_D^{20}$ = +20.1 (*c* = 0.8, $CHCl_3$), ref.[5] $[\alpha]_D^{28}$ = +23.8 (*c* = 0.5, $CHCl_3$)}. IR (film): $\tilde{\nu}$ = 3321, 3210, 1735, 1620 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.85 (d, *J* = 4.0 Hz, 1 H), 5.80 (d, *J* = 8.4 Hz, 1 H), 5.41 (dd, *J* = 9.6, 6.4 Hz, 1 H), 5.34 (d, *J* = 6.4 Hz, 1 H), 4.98–5.06 (m, 2 H), 4.61 (d, *J* = 13.2 Hz, 1 H, *A*Bq), 4.35 (d, *J* = 13.2 Hz, 1 H, A*B*q), 2.02–2.05 (m, 12 H) 1.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (C), 170.1 (C), 170.0 (C), 169.8 (C), 169.7 (C), 134.2 (C), 126.1 (CH), 71.0 (CH), 69.0 (CH), 68.4 (CH), 62.9 (CH_2), 44.8 (CH), 23.2 (CH_3), 20.7 (CH_3), 20.6 (2 C, CH_3,CH_3), 20.5 (CH_3) ppm. HRMS (ESI): Calcd for $C_{17}H_{23}NO_9$: 385.1373; found 385.1377.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H NMR and ^{13}C NMR spectra for all key intermediates and final products.

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