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(*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate: chiral building block for the synthesis of optically active α-substituted α-amino acid derivatives

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Abstract—(*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate was efficiently obtained by lipase-catalyzed asymmetrization of the prochiral diol. (*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate was converted to (*R*)-2-(hydroxymethyl)glutamic acid and a synthetic intermediate of (−)-deoxydysibetaine.

1. Introduction

Recently, compounds containing highly functionalized α-substituted α-amino acid moieties have been reported to possess intriguing biological activity (Fig. 1). For example, myriocin (also known as thermozymocidin and ISP-1) is an α-substituted α-amino acid derivative isolated from the culture broth of *Myriococcum albomyces*, *Mycelia sterilia* and *Isaria sinclairii*, and has reported to possess antifungal and immunosuppressive activity.[1–3] Lactacystin is an α-substituted α-amino acid derivative isolated from the culture broth of *Streptomyces* sp. OM-6519 and first attracted interest due to its ability to inhibit cell proliferation and induce nerve outgrowth in mouse neuroblastoma. The compound exhibits significant neurotropic activity due to its ability to inhibit the 20S proteasome.[4] (*R*)-2-(Hydroxymethyl)glutamic acid is a selective agonist of metabotropic glutamate receptor group II (mGluR3).[5] Dysibetaine is an α-substituted α-amino acid derivative isolated from the marine sponge *Dysidea herbacea* collected in Yap (Micronesia). As this compound is able to induce convulsive behavior in mice, it was suspected of acting on glutamate receptors in the central nervous system.[6] These biological features have prompted many groups to pursue synthetic studies of compounds containing highly functionalized α-substituted α-amino acid moieties.[5,7–9]

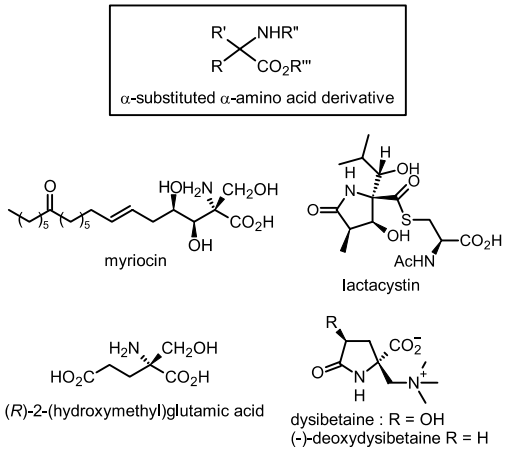

Figure 1. Structure of biologically active compounds containing α-substituted α-amino acid moieties.

The chiral α-substituted α-amino acid derivatives were synthesized using a number of methods including alkylation of chiral enolates,[5a,f,7f,8a–c,e,g,h,k,l] Strecker synthesis,[5c,e,8m] rearrangement of chiral trichloroacetimidates,[7i,8d,f] chiral epoxide-opening with azide[7e,g] or trichloroacetimidates,[7h,8o] and desymmetrization of prochiral compounds.[10]

The synthetic method employed to generate biologically active chiral compounds using chiral building block represents one of the useful methods. Although many chiral building blocks, prepared by enzymatic methods or from the chemical conversion of natural sources (sugars, amino acids etc.), have been developed for the synthesis of versatile

Keywords: Lipase; Chiral building block; α-Substituted α-amino acid; (*R*)-2-(Hydroxymethyl)glutamic acid; (−)-Deoxydysibetaine.
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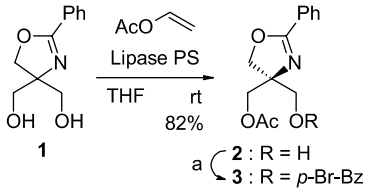
chiral compounds, only a few chiral building blocks have been prepared for the synthesis of highly functionalized α-substituted α-amino acid derivatives.[10]

The authors previously reported the development of chiral building blocks using lipase[11] and the successful synthesis of biologically active natural products from these chiral building blocks.[12] In this paper, the authors developed useful a novel chiral building block for the synthesis of α-substituted α-amino acid derivatives using lipase-catalyzed asymmetrization of the prochiral diol. The chiral building block was converted to (*R*)-2-(hydroxymethyl)-glutamic acid and a synthetic intermediate of (−)-deoxydysibetaine.

2. Results and discussion

Prochiral diol **1**,[13] prepared from 2-amino-2-hydroxymethylpropane-1,3-diol and benzoic acid, was treated with vinyl acetate in THF at rt for 5 days in the presence of Lipase PS® (from *Pseudomonas cepacia*) and gave mono acetate **2** in 82% yield (Scheme 1). Enantiomeric excess of acetate **2** was >99% ee as determined by HPLC using a chiral column. In the case of using Lipase AY® (from *Candida rugosa*) or Lipase AK® (from *Pseudomonas fluorescence*), enantiomeric excess of acetate **2** was 16 or 87% ee. The absolute configuration of acetate **2** was determined by X-ray analysis of *p*-bromobenzoate **3** (Fig. 2),[14] which was derived from **2** and *p*-bromobenzoic acid. The configuration of the chiral center in **2** was thus concluded to be in the *R* configuration. For the assessment of optically active **2** as a potential chiral building block of α-substituted α-amino acid derivatives, (*R*)-2-(hydroxymethyl)glutamic acid and a synthetic intermediate of (−)-deoxydysibetaine were synthesized from acetate **2**.



Scheme 1. Reagents and conditions: (a) *p*-Br–BzOH, DCC, DMAP, CH_2Cl_2, rt, quant.

The primary alcohol **2** was oxidized by DMSO/$(COCl)_2$ to give the aldehyde.[15] This was followed by a Horner–Wadsworth–Emmons reaction to afford (*E*)-α,β-unsaturated ester **4** as the sole product (Scheme 2). Ethanolysis of the acetyl group in ester **4** was carried out by treatment with K_2CO_3 in EtOH to give alcohol **5**. Hydrogenation of the carbon–carbon double bond in **5** in the presence of 10% Pd/C in EtOH gave alcohol (*S*)-**6**. Primary alcohol (*S*)-**6** was oxidized by treatment with 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and bis(acetoxy)iodobenzene (BAIB) to give the carboxylic acid.[16] Finally, hydrolysis of oxazoline by treatment with 6 M HCl under reflux afforded (*R*)-2-(hydroxymethyl)glutamic acid, $[\alpha]_D^{25}$ −11.9 (*c* 1.17, H_2O).[5]

The primary hydroxy group of acetate **2** was protected to give TBS ether **7** and methanolysis of the acetate

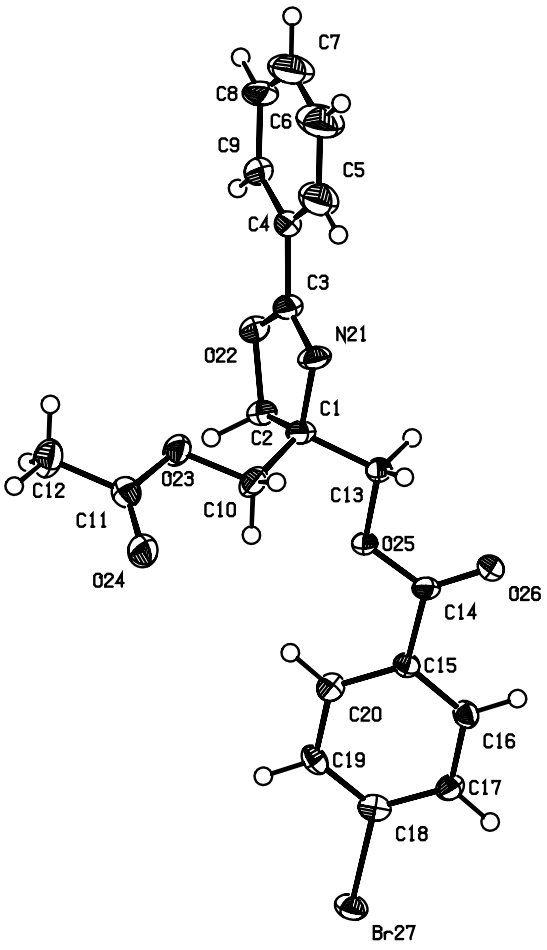
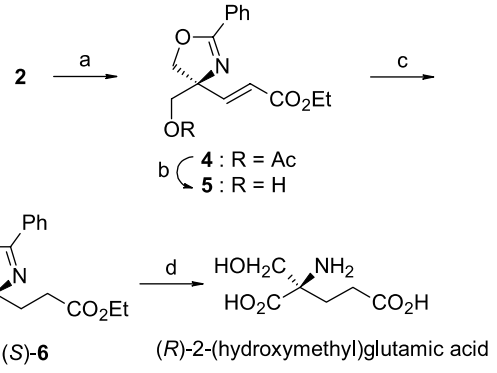
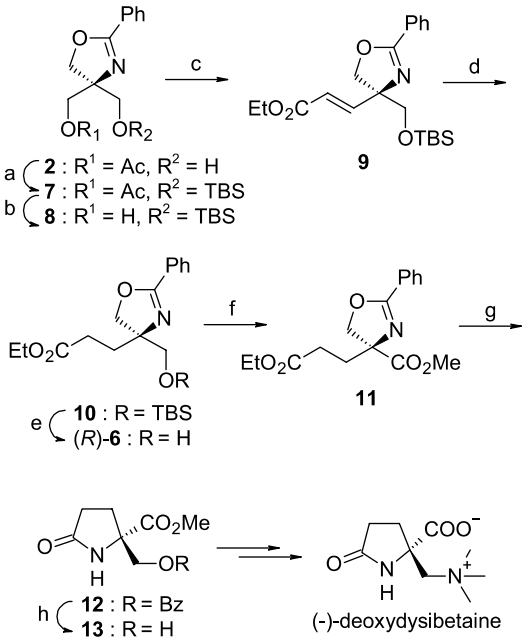


Figure 2. ORTEP drawing of *p*-bromobenzoate **3**.



Scheme 2. Reagents and conditions: (a) (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, (ii) $(^iPrO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 to 0 °C, 86% (two steps); (b) K_2CO_3, EtOH, rt, 96%; (c) H_2, Pd/C, EtOH, rt, quant.; (d) (i) TEMPO, BAIB, H_2O–CH_2Cl_2, rt, (ii) 6 M HCl, reflux, 96% (two steps).

by treatment with K_2CO_3 in MeOH to give alcohol **8** (Scheme 3). Alcohol **8** was oxidized by DMSO/TFAA oxidation followed by a Horner–Wadsworth–Emmons reaction to give (*E*)-α,β-unsaturated ester **9** as a sole product. Hydrogenation of the carbon–carbon double bond in **9** in the presence of 10% Pd/C in EtOH gave ester **10**. Deprotection of the TBS group in ester **10** was carried out by treatment with TBAF in THF to give alcohol (*R*)-**6**. Primary alcohol (*R*)-**6** was oxidized directly into the



Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, quant.; (b) K_2CO_3, MeOH, rt, 98%; (c) (i) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C to rt, (ii) $(^iPrO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 to 0 °C, 95% (two steps); (d) H_2, Pd/C, EtOH, rt, 98%; (e) TBAF, THF, rt, 79%; (f) (i) TEMPO, BAIB, H_2O–CH_2Cl_2, rt, (ii) CH_2N_2, MeOH, 0 °C, 77% (two steps); (g) 1 M HCl, MeOH, 80 °C, 81%; (h) K_2CO_3, MeOH, rt, 81%.

carboxylic acid using TEMPO and BAIB.[16] This was followed by esterification of the carboxylic acid by treatment with CH_2N_2 to afford methyl ester **11**. Hydrolysis of oxazoline in ester **11** by treatment with 1 M HCl gave lactam **12**. Finally, lactam **12** was treated with K_2CO_3 in MeOH at rt to afford alcohol **13**, $[\alpha]_D^{25}$ +34.3 (*c* 0.46, $CHCl_3$), which is a synthetic intermediate of (−)-deoxydysibetaine.[9b,d]

A lipase-catalyzed method for the preparation of optically active oxazoline **2** was established. The present method of desymmetrization of prochiral diol can easily be conducted under mild conditions even in a large-scale experiment. Enantiomeric excess of oxazoline **2** is higher than enantiomeric excess of the chiral compounds provided by the reported enzymatic desymmetrization of prochiral compounds. The optically active oxazoline **2** was clearly shown to be useful as a chiral building block for the synthesis of biologically active chiral compounds containing α-substituted α-amino acid moieties.

3. Experimental

3.1. General

Melting points (mp) were measured using a Yazawa melting point apparatus BY-2 and are uncorrected. Optical rotations were measured using a Jasco P-1030 polarimeter or a Jasco DIP-360 polarimeter. IR spectra were recorded using a Jasco FT-IR/620 spectrometer. UV spectra were recorded using a Jasco V-550 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer. Chemical shifts are given on the δ (ppm) scale using tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad). ESIMS and high-resolution ESIMS (HRESIMS) spectra were obtained using a Micromass LCT spectrometer. Elemental analysis data were obtained using an Elemental Vavio EL. X-ray diffraction was measured on Bruker MXC18 KHF22 and Rigaku RAXIS-RAPID diffractometers. Flash column chromatography was carried out using Kanto Chemical Silica Gel 60 N (spherical, neutral) 40–50 μm. Reversed phase column chromatography was carried out using Wakosil 25C18 (spherical) 15–30 μm.

3.1.1. (*R*)-4-Hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate (2). To a solution of diol **1**[12] (33.0 g, 159 mmol) and vinyl acetate (147 mL, 1.59 mol) in THF (318 mL) was added Lipase PS® (6.36 g) and the mixture was stirred for 5 days at rt. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give a crude solid (40.7 g, >99% ee). The crude solid was purified by recrystallization from acetone–hexane to yield acetate **2** (32.5 g, 82% yield) as colorless plates. Enantiomeric excess of acetate **2** was >99% ee as determined by HPLC analysis (CHIRALPAK AS®, 0.46×25 cm, hexane/2-propanol=93:7, flow rate: 1.0 mL/min, **2**: t_R=22.6 min, *ent*-**2**: t_R=16.8 min), mp: 128 °C; $[\alpha]_D^{26}$ −18.6 (*c* 1.08, $CHCl_3$); IR (KBr) cm^{-1}: 3199, 2962, 1731, 1634; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80 (2H, m), 7.44 (1H, m), 7.32 (2H, m), 4.39 (1H, d, *J*=8.6 Hz), 4.30 (1H, d, *J*=8.6 Hz), 4.22 (1H, d, *J*=11.3 Hz), 4.18 (1H, d, *J*=11.3 Hz), 3.85 (1H, br dd, *J*=9.2, 15.3 Hz), 3.63 (1H, br dd, *J*=8.1, 15.3 Hz), 3.62 (1H, br s), 2.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 165.9, 131.7, 128.4, 128.2, 126.8, 74.7, 71.4, 66.2, 64.7, 20.7; ESIMS *m/z*: 250 (M^++H, 100); HRESIMS *m/z*: 250.1071 (Calcd for $C_{13}H_{16}NO_4$: M^++H, 250.1079). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.73; H, 6.12; N, 5.33.

3.1.2. (*R*)-4-Acetoxymethyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl 4-bromobenzoate (3). To a solution of alcohol **2** (99.8 mg, 400 μmol) in CH_2Cl_2 (2.00 mL) were added *p*-bromobenzoic acid (88.4 mg, 440 μmol), DCC (90.8 mg, 440 μmol) and DMAP (4.9 mg, 40.0 μmol). Following stirring at rt for 1 h, the reaction mixture was filtered through a thin silica gel pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=4:1) to give *p*-bromobenzoate **3** (173 mg, quantitative yield) as colorless pillars: mp: 118–120 °C; $[\alpha]_D^{25}$ −28.3 (*c* 1.08, $CHCl_3$); IR (KBr) cm^{-1}: 2984, 1739, 1709, 1650; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96 (2H, m), 7.82 (2H, m), 7.52 (3H, m), 7.42 (2H, m), 4.54 (1H, d, *J*=11.3 Hz), 4.45 (1H, d, *J*=11.3 Hz), 4.44 (1H, d, *J*=9.0 Hz), 4.38 (1H, d, *J*=11.4 Hz), 4.37 (1H, d, *J*=9.0 Hz), 4.32 (1H, d, *J*=11.4 Hz), 2.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 165.7, 165.4, 131.9, 131.8 (×2), 131.1 (×2), 128.5, 128.4, 127.0, 73.0, 72.0, 65.9, 66.3, 20.8; ESIMS *m/z*: 432 (M^++H, 100); HRESIMS *m/z*: 432.0421 (Calcd for $C_{20}H_{19}^{79}BrNO_5$: M^++H, 432.0447). Anal. Calcd for $C_{20}H_{18}BrNO_5$: C, 55.57; H, 4.20; N, 3.24. Found: C, 55.58; H, 4.28; N, 3.09.

3.1.3. Ethyl (*R*,*E*)-3-(4-acetoxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)acrylate (4). To a cold (−78 °C) solution of oxalyl chloride (210 μL, 2.41 mmol) in

CH_2Cl_2 (6.0 mL) was added DMSO (230 μL, 3.21 mmol). Following stirring at −78 °C for 10 min, a solution of alcohol **2** (200 mg, 802 μmol) in CH_2Cl_2 (2.0 mL) was added. Following stirring at −78 °C for 30 min, Et_3N (560 μL, 4.01 mmol) was added. The mixture was warmed to rt for over 15 min and then stirred for 30 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde. The crude aldehyde was subsequently used without further purification.

To a suspension of NaH (55%, 49 mg, 1.12 mmol) in THF (2.0 mL) was added $(^iPrO)_2P(O)CH_2CO_2Et$ (270 μL, 1.20 mmol) at 0 °C and the mixture was stirred at 0 °C for 30 min. A solution of the above crude aldehyde in THF (2.0 mL) was added to the mixture at −78 °C and then the mixture was warmed to 0 °C for over 30 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=5:2) to give α,β-unsaturated ester **4** (219 mg, 86% yield, two steps) as a colorless oil: $[\alpha]_D^{25}$ −75.9 (*c* 1.56, $CHCl_3$); IR (neat) cm^{-1}: 3064, 2981, 2902, 1745, 1719, 1644, 1603, 1496; UV (EtOH) nm: 242 (ε 11,900); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 (2H, m), 7.51 (1H, m), 7.42 (2H, m), 7.07 (1H, d, *J*=15.7 Hz), 6.15 (1H, d, *J*=15.7 Hz), 4.46 (1H, d, *J*=8.7 Hz), 4.26 (1H, d, *J*=8.7 Hz), 4.25 (2H, s), 4.20 (2H, q, *J*=7.1 Hz), 2.06 (3H, s), 1.28 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 166.1, 165.3, 146.5, 131.9, 128.6, 128.4, 127.0, 122.8, 74.0, 73.7, 67.6, 60.7, 20.8, 14.2; ESIMS *m/z*: 318 (M^++H, 100); HRESIMS *m/z*: 318.1345 (Calcd for $C_{17}H_{20}NO_5$: M^++H, 318.1341). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.29; H, 5.98; N, 4.29.

3.1.4. Ethyl (*S*,*E*)-3-(4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)acrylate (5). To a solution of acetate **4** (34.6 mg, 109 μmol) in EtOH (550 μL) was added K_2CO_3 (5.5 mg, 39.8 μmol). After stirring at rt for 40 min, the reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=3:2) to give alcohol **5** (28.8 mg, 96% yield) as a colorless oil: $[\alpha]_D^{25}$ −56.9 (*c* 0.96, $CHCl_3$); IR (neat) cm^{-1}: 3241, 2980, 2932, 1717, 1641, 1604, 1496; UV (EtOH) nm: 242 (ε 8050); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (2H, m), 7.47 (1H, m), 7.35 (2H, m), 7.00 (1H, d, *J*=15.7 Hz), 6.09 (1H, d, *J*=15.7 Hz), 4.59 (1H, d, *J*=8.4 Hz), 4.28 (1H, d, *J*=8.4 Hz), 4.19 (2H, q, *J*=7.1 Hz), 3.87 (1H, dd, *J*=11.6, 4.8 Hz), 3.64 (1H, dd, *J*=11.6, 9.2 Hz), 3.25 (1H, m), 1.27 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1, 165.8, 147.5, 131.8, 128.4, 128.2, 126.5, 122.4, 75.9, 73.0, 66.1, 60.6, 14.2; ESIMS *m/z*: 276 (M^++H, 100); HRESIMS *m/z*: 276.1217 (Calcd for $C_{15}H_{18}NO_4$: M^++H, 276.1236). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.34; H, 6.24; N, 4.90.

3.1.5. Ethyl (*S*)-3-(4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)propionate ((*S*)-6). A solution of α,β-unsaturated ester **5** (158 mg, 574 μmol) in EtOH (5.74 mL) was hydrogenated with 10% Pd/C (57.4 mg). The mixture was stirred at rt under a balloon pressure of H_2 for 1 h. The reaction mixture was diluted with AcOEt and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=2:3) to give ester (*S*)-**6** (159 mg, quantitative yield) as a colorless oil: $[\alpha]_D^{25}$ +13.4 (*c* 1.20, $CHCl_3$); IR (neat) cm^{-1}: 3376, 2927, 1732, 1644, 1579, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86 (2H, m), 7.46 (1H, m), 7.38 (2H, m), 4.44 (1H, d, *J*=8.5 Hz), 4.15 (1H, d, *J*=8.5 Hz), 4.11 (2H, dq, *J*=1.7, 7.2 Hz), 3.77 (1H, dd, *J*=11.4, 3.0 Hz), 3.53 (1H, dd, *J*=11.4, 7.8 Hz), 2.38 (2H, m), 2.09 (1H, ddd, *J*=14.2, 8.4, 7.6 Hz), 1.85 (1H, ddd, *J*=14.2, 8.6, 6.6 Hz), 1.20 (3H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 164.7, 131.5, 128.3, 128.2, 127.0, 74.4, 72.8, 66.9, 60.6, 31.1, 28.6, 14.1; ESIMS *m/z*: 278 (M^++H, 100); HRESIMS *m/z*: 278.1404 (Calcd for $C_{15}H_{20}NO_4$: M^++H, 278.1392). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.89; H, 6.89; N, 4.78.

3.1.6. (*R*)-2-(Hydroxymethyl)glutamic acid. To a solution of alcohol (*S*)-**6** (57.2 mg, 206 μmol) in H_2O–CH_2Cl_2 (2/1, 630 μL) were added TEMPO (9.7 mg, 61.8 μmol) and BAIB (199 mg, 618 μmol). After stirring at rt for 75 min, the reaction mixture was diluted with $CHCl_3$ and then washed with saturated aqueous $Na_2S_2O_3$ and 1 M HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with $CHCl_3$–MeOH (69/1) and filtered through silica gel using $CHCl_3$–MeOH (69/1–4/1). The filtrate was concentrated under reduced pressure to give the crude carboxylic acid. The crude carboxylic acid was used for the next reaction without further purification.

A solution of the above crude carboxylic acid in 6 M HCl (1.03 mL) was refluxed for 12 h. The reaction mixture was washed with Et_2O. The aqueous layer was concentrated under reduced pressure. The residue was purified by reversed phase column chromatography (H_2O) to give the hydrochloride salt. The hydrochloride salt was passed through a DOWEX® 50W-X8 ion-change resin. Elution with 5% aqueous NH_4OH furnished (*R*)-2-(hydroxymethyl)glutamic acid (35.2 mg, 96% yield, two steps) as colorless needles: $[\alpha]_D^{25}$ −11.9 (*c* 1.17, H_2O). The physical and spectral properties were consistent with the literature values.[5]

3.1.7. (*R*)-4-(*tert*-Butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-ylmethyl acetate (7). To a solution of alcohol **2** (2.51 g, 10.1 mmol) in DMF (10.1 mL) were added imidazole (1.31 g, 19.2 mmol) and *tert*-butylchlorodimethylsilane (2.28 g, 15.1 mmol). After stirring at rt for 1 h, the reaction mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=6:1) to give alcohol TBS ether **7** (3.66 g, quantitative yield) as a colorless oil: $[\alpha]_D^{25}$ −20.6

(c 1.04, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2930, 2858, 1746, 1649, 1604, 1580, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93 (2H, m), 7.48 (1H, m), 7.40 (2H, m), 4.44 (1H, d, J=8.6 Hz), 4.28 (1H, d, J=11.4 Hz), 4.25 (1H, d, J=11.4 Hz), 4.23 (1H, d, J=8.6 Hz), 3.84 (1H, d, J=10.0 Hz), 3.63 (1H, d, J=10.0 Hz), 2.05 (3H, s), 0.85 (9H, s), 0.06 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 164.9, 131.5, 128.4, 128.3, 127.5, 74.7, 71.9, 66.5, 65.9, 25.7, 20.9, 18.1, −5.5. −5.5; ESIMS m/z: 364 (M^++H, 100); HRESIMS m/z: 364.1948 (Calcd for $C_{19}H_{30}NO_4Si$: M^++H, 364.1944). Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.76; H, 7.87; N, 3.75.

3.1.8. (*S*)-[4-(*tert*-Butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]methanol (8). To a solution of acetate **7** (3.61 g, 9.93 mmol) in MeOH (49.7 mL) was added K_2CO_3 (497 mg, 3.60 mmol). After stirring at rt for 10 min, the reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=2:1) to give alcohol **8** (3.14 g, 98% yield) as colorless needles: mp: 90 °C; $[\alpha]_D^{25}$ −6.6 (c 1.01, $CHCl_3$); IR (KBr) cm^{-1}: 3214, 2954, 2929, 2657, 1640, 1604, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84 (2H, m), 7.45 (1H, m), 7.35 (2H, m), 4.46 (1H, d, J=8.4 Hz), 4.36 (1H, d, J=8.4 Hz), 3.82 (1H, dd, J=11.3, 4.0 Hz), 3.81 (1H, d, J=9.8 Hz), 3.73 (1H, dd, J=11.3, 6.2 Hz), 3.61 (1H, d, J=9.8 Hz), 0.86 (9H, s), 0.07 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.4, 131.5, 128.3, 128.2, 127.3, 76.2, 72.0, 66.6, 65.9, 25.7, 18.1, −5.5, −5.5; ESIMS m/z: 322 (M^++H, 100); HRESIMS m/z: 322.1866 (Calcd for $C_{17}H_{28}NO_3Si$: M^++H, 322.1838). Anal. Calcd for $C_{17}H_{27}NO_3Si$: C, 63.51; H, 8.47; N, 4.36. Found: C, 63.28; H, 8.43; N, 4.08.

3.1.9. Ethyl (*S*,*E*) 3-[4-(*tert*-butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]acrylate (9). To a cold (−78 °C) solution of TFAA (65.9 μL, 474 μmol) in CH_2Cl_2 (1.0 mL) was added DMSO (44.8 μL, 632 μmol). Following stirring at −78 °C for 30 min, a solution of alcohol **8** (50.7 mg, 158 μmol) in CH_2Cl_2 (580 μL) was added. Following stirring at −78 °C for 30 min, Et_3N (110 μL, 790 μmol) was added. The mixture was warmed to rt for over 15 min and then stirred for 20 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde. The crude aldehyde was used for the next reaction without further purification.

To a suspension of NaH (55%, 20.7 mg, 474 μmol) in THF (1.0 mL) was added $(^iPrO)_2P(O)CH_2CO_2Et$ (120 μL, 553 μmol) at 0 °C. Following stirring at 0 °C for 45 min, a solution of the above crude aldehyde in THF (580 μL) was added to this mixture at −78 °C. The mixture was subsequently warmed to 0 °C for over 15 min. The reaction mixture was diluted with Et_2O and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=10:1) to give α,β-unsaturated ester **9** (56.0 mg, 95% yield, two steps) as a colorless oil: $[\alpha]_D^{25}$ +47.6 (c 1.11, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2930, 2857, 1722, 1647, 1580, 1496; UV (EtOH) nm: 242 (ε 15,300); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (2H, m), 7.49 (1H, m), 7.41 (2H, m), 7.15 (1H, d, J=15.8 Hz), 6.11 (1H, d, J=15.8 Hz), 4.61 (1H, d, J=8.4 Hz), 4.19 (2H, q, J=7.1 Hz), 4.19 (1H, d, J=8.4 Hz), 3.76 (1H, d, J=9.9 Hz), 3.71 (1H, d, J=9.9 Hz), 1.28 (3H, t, J=7.1 Hz), 0.84 (9H, s), 0.06 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 164.8, 148.1, 131.6, 128.4, 128.3, 127.5, 121.9, 75.9, 74.0, 67.6, 60.4, 25.7, 18.1, 14.2, −5.4, −5.5; ESIMS m/z: 390 (M^++H, 100); HRESIMS m/z: 390.2089 (Calcd for $C_{21}H_{32}NO_4Si$: M^++H, 390.2101). Anal. Calcd for $C_{21}H_{31}NO_4Si$: C, 64.75; H, 8.02; N, 3.60. Found: C, 64.47; H, 8.06; N, 3.47.

3.1.10. Ethyl (*S*)-3-[4-(*tert*-butyldimethylsiloxymethyl)-2-phenyl-4,5-dihydrooxazol-4-yl]-propionate (10). A solution of α,β-unsaturated ester **9** (114 mg, 305 μmol) in EtOH (3.05 mL) was hydrogenated with 10% Pd/C (30.5 mg). The mixture was stirred at rt under a balloon pressure of H_2 for 30 min. The reaction mixture was diluted with Et_2O, filtered through Celite, and the filtrate concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=8:1) to give ester **10** (112 mg, 98% yield) as a colorless oil: $[\alpha]_D^{25}$ −6.2 (c 1.04, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2930, 2857, 1737, 1649, 1604, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.91 (2H, m), 7.47 (1H, m), 7.39 (2H, m), 4.44 (1H, d, J=8.6 Hz), 4.10 (2H, dq, J=7.1, 2.2 Hz), 4.08 (1H, d, J=8.6 Hz), 3.68 (1H, d, J=9.9 Hz), 3.61 (1H, d, J=9.9 Hz), 2.42 (1H, ddd, J=16.3, 10.1, 6.3 Hz), 2.36 (1H, ddd, J=16.3, 9.9, 6.3 Hz), 2.07 (1H, ddd, J=14.0, 10.1, 6.3 Hz), 1.95 (1H, ddd, J=14.0, 9.9, 6.3 Hz), 1.20 (3H, t, J=7.1 Hz), 0.84 (9H, s), 0.05 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 163.8, 131.3, 128.3, 128.2, 127.8, 74.4, 73.5, 68.2, 60.4, 31.0, 29.0, 25.7, 18.1, 14.1, −5.4, −5.5; ESIMS m/z: 392 (M^++H, 100); HRESIMS m/z: 392.2265 (Calcd for $C_{21}H_{34}NO_4Si$: M^++H, 392.2257). Anal. Calcd for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found: C, 64.53; H, 8.47; N, 3.47.

3.1.11. Ethyl (*R*)-3-(4-hydroxymethyl-2-phenyl-4,5-dihydrooxazol-4-yl)propionate ((*R*)-6). To TBS ether **10** (66.0 mg, 176 μmol) was added TBAF (1.0 M in THF, 530 μL, 527 μmol). After stirring at rt for 5 min saturated aqueous NH_4Cl was added to the reaction mixture. The mixture was diluted with AcOEt and then washed with water and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt=2:1) to give alcohol (*R*)-**6** (38.6 mg, 79% yield) as a colorless oil: $[\alpha]_D^{25}$ −14.6 (c 1.23, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.11; H, 7.09; N, 4.90.

3.1.12. Methyl (*S*)-4-(2-ethoxycarbonylethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate (11). To a solution of alcohol (*R*)-**6** (28.8 mg, 104 μmol) in H_2O–CH_2Cl_2 (2/1, 330 μL) were added TEMPO (4.9 mg, 31.2 μmol) and BAIB (100 mg, 312 μmol). After stirring at rt for 75 min, the reaction mixture was diluted with $CHCl_3$ and then

washed with saturated aqueous $Na_2S_2O_3$ and 1 M HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with $CHCl_3$–MeOH (69/1) and filtered through silica gel using $CHCl_3$–MeOH (69/1–4/1). The filtrate was concentrated under reduced pressure to give the crude carboxylic acid. The crude carboxylic acid was subsequently used without further purification.

To a cold (0 °C) solution of the above crude carboxylic acid in MeOH (1.0 mL) was added a solution of CH_2N_2 in Et_2O until the mixture turned yellow. After stirring at 0 °C for 5 min and then at rt for 50 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=3:1) to give diester **11** (24.5 mg, 77% yield, two steps) as a colorless oil: $[\alpha]_D^{25}$ +18.6 (*c* 0.66, $CHCl_3$); IR (neat) cm^{-1}: 2981, 1735, 1643, 1603, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.98 (2H, m), 7.50 (1H, m), 7.41 (2H, m), 4.75 (1H, d, J=9.1 Hz), 4.28 (1H, d, J=9.1 Hz), 4.11 (2H, dq, J=1.0, 7.1 Hz), 3.80 (3H, s), 2.52–2.35 (3H, m), 2.19 (1H, m), 1.22 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 172.7, 165.1, 131.9, 128.6, 128.3, 126.9, 77.1, 74.1, 60.6, 52.8, 33.2, 29.0, 14.1; ESIMS *m*/*z*: 306 (M^++H, 100); HRESIMS *m*/*z*: 306.1348 (Calcd for $C_{16}H_{20}NO_5$: M^++H, 306.1341). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.73; H, 6.26; N, 4.46.

3.1.13. Methyl (*S*)-2-benzoyloxymethyl-5-oxopyrrolidine-2-carboxylate (12). To a solution of diester **11** (752 mg, 2.46 mmol) in MeOH (18.3 mL) was added 1 M HCl (6.1 mL). After stirring at 80 °C for 2.5 h, the reaction mixture was diluted with AcOEt and then washed with saturated aqueous $NaHCO_3$, water and finally saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:3) to give lactam **12** (552 mg, 81% yield) as colorless needles: mp: 140 °C; $[\alpha]_D^{25}$ +37.6 (*c* 0.37, $CHCl_3$); IR (KBr) cm^{-1}: 3232, 2959, 1751, 1723, 1702; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 (2H, m), 7.58 (1H, m), 7.44 (2H, m), 6.40 (1H, br s), 4.68 (1H, d, J=11.1 Hz), 4.36 (1H, d, J=11.1 Hz), 3.80 (3H, s), 2.50–2.40 (3H, m), 2.25 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.6, 172.0, 165.7, 133.6, 129.7, 129.0, 128.6, 68.5, 64.7, 53.2, 29.2, 27.7; ESIMS *m*/*z*: 278 (M^++H, 100); HRESIMS *m*/*z*: 278.1054 (Calcd for $C_{14}H_{16}NO_5$: M^++H, 278.1028). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.52; H, 5.58; N, 4.90.

3.1.14. Methyl (*S*)-2-hydroxymethyl-5-oxopyrrolidine-2-carboxylate (13). To acetate **12** (9.9 mg, 35.7 μmol) was added K_2CO_3 (0.5 g/L in MeOH, 360 μL). After stirring at rt for 1.5 h, the reaction mixture was diluted with $CHCl_3$ and then washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=20:1) to give alcohol **13** (5.0 mg, 81% yield) as colorless pillars: mp: 133°C; $[\alpha]_D^{25}$ +34.3 (*c* 0.46, $CHCl_3$). The physical and spectral properties were consistent with the literature values.[9d]

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References and notes

1. (a) Kluepfel, D.; Bagli, J.; Baker, H.; Charest, M.-P.; Kudelski, A.; Sehgal, S. N.; Vézina, C. *J. Antibiot.* **1972**, *25*, 109–115. (b) Bagli, J. F.; Kluepfel, D.; Jacques, M. S. *J. Org. Chem.* **1973**, *38*, 1253–1260.
2. (a) Craveri, R.; Manachini, P. L.; Aragozzini, F. *Experientia* **1972**, *28*, 867–868. (b) Aragozzini, F.; Manachini, P. L.; Craveri, R.; Rindone, B.; Scolastico, C. *Experientia* **1972**, *28*, 881–882. (c) Aragozzini, F.; Manachini, P. L.; Craveri, R.; Rindone, B.; Scolastico, C. *Tetrahedron* **1972**, *28*, 5493–5498. (d) Destro, R.; Colombo, A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 896–899.
3. (a) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Yoneta, M.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 208–215. (b) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Yoneta, M.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 216–224. (c) Sasaki, S.; Hashimoto, R.; Kikuchi, M.; Inoue, K.; Ikumoto, T.; Hirose, R.; Chiba, K.; Hoshino, Y.; Okumoto, T.; Fujita, T. *J. Antibiot.* **1994**, *47*, 420–433.
4. (a) Ōmura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113–116. (b) Ōmura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, T.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117–118.
5. (a) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555–7559. (b) Choudhury, P. K.; Le Nguyen, B. K.; Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 463–464. (c) Kawasaki, M.; Namba, K.; Tsujishima, H.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2003**, *44*, 1235–1238. (d) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611–2613. (e) Tang, G.; Tian, H.; Ma, D. *Tetrahedron* **2004**, *60*, 10547–10552. (f) Lee, J.; Lee, Y.-I.; Kang, M. J.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, M.-J.; Choi, J.-y.; Ku, J.-M.; Park, H.-g.; Jew, S.-s. *J. Org. Chem.* **2005**, *70*, 4158–4161. (g) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-s.; Park, H.-g. *Org. Lett.* **2005**, *7*, 3207–3209.
6. Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941–6944.
7. For total and formal synthesis of myriocin (thermozymocidin, ISP-1), see: (a) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1982**, 488–490. (b) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613–1619. (c) Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. *Tetrahedron Lett.* **1993**, *34*, 1653–1656. (d) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 4783–4786. (e) Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*,

994–996. (f) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097–2100. (g) Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Tetrahedron* **1995**, *51*, 6209–6228. (h) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887–7890. (i) Oishi, T.; Ando, K.; Chida, N. *Chem. Commun.* **2001**, 1932–1933. (j) Lee, K.-Y.; Oh, C.-Y.; Kim, Y.-H.; Joo, J.-E.; Ham, W.-H. *Tetrahedron Lett.* **2002**, *43*, 9361–9363.

8. For total and formal synthesis of lactacystin, see: (a) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677–10678. (b) Sunazuka, T.; Nagamitsu, T.; Matsuzaka, K.; Tanaka, H.; Ōmura, S.; Smith, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 5302. (c) Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139–2140. (d) Chida, N.; Takeoka, J.; Tsutsumi, N.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1995**, 793–794. (e) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Ōmura, S.; Sprengeler, P. A.; Smith, A. B. *J. Am. Chem. Soc.* **1996**, *118*, 3584–3590. (f) Chida, N.; Takeoka, J.; Ando, K.; Tsutsumi, N.; Ogawa, S. *Tetrahedron* **1997**, *53*, 16287–16298. (g) Corey, E. J.; Li, W.; Reichard, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 2330–2336. (h) Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1676–1679. (i) Kang, S. H.; Jun, H.-S.; Youn, J.-H. *Chem. Commun.* **1998**, 1929–1930. (j) Kang, S. H.; Jun, H.-S.; Youn, J.-H. *Synlett* **1998**, 1045–1046. (k) Panek, J. S.; Masse, C. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 1093–1095. (l) Soucy, F.; Grenier, L.; Behnke, M. L.; Destree, A. T.; McCormack, T. A.; Adams, J.; Plamondon, L. *J. Am. Chem. Soc.* **1999**, *121*, 9967–9976. (m) Iwama, S.; Gao, W.-G.; Shinada, T.; Ohfune, Y. *Synlett* **2000**, 1631–1633. (n) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609–6611. (o) Brennan, C. J.; Pattenden, G.; Rescourio, G. *Tetrahedron Lett.* **2003**, *44*, 8757–8760. (p) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765–7768. (q) Wardrop, D. J.; Bowen, E. G. *Chem. Commun.* **2005**, 5106–5108.
9. For total synthesis of dysibetaine and (−)-deoxydysibetaine, see: (a) Snider, B. B.; Gu, Y. *Org. Lett.* **2001**, *3*, 1761–1763. (b) Nguyen, B. K. L.; Langlois, N. *Tetrahedron Lett.* **2003**, *44*, 5961–5963. (c) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230–1231. (d) Langlois, N.; Nguyen, B. K. L. *J. Org. Chem.* **2004**, *69*, 7558–7564.
10. (a) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449–8450. (b) Sano, S.; Hayashi, K.; Miwa, T.; Ishii, T.; Fujii, M.; Mima, H.; Nagao, Y. *Tetrahedron Lett.* **1998**, *39*, 5571–5574. (c) Lane, J. W.; Halcomb, R. L. *J. Org. Chem.* **2003**, *68*, 1348–1357.
11. (a) Miyaoka, H.; Sagawa, S.; Inoue, T.; Nagaoka, H.; Yamada, Y. *Chem. Pharm. Bull.* **1994**, *42*, 405–407. (b) Miyaoka, H.; Sagawa, S.; Nagaoka, H.; Yamada, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 587–594. (c) Miyaoka, H.; Kajiwara, Y.; Hara, M.; Suma, A.; Yamada, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 3189–3196.
12. (a) Mitome, H.; Miyaoka, H.; Yamada, Y. *Tetrahedron Lett.* **2000**, *41*, 8107–8110. (b) Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. *J. Org. Chem.* **2001**, *66*, 1429–1435. (c) Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y. *J. Org. Chem.* **2003**, *68*, 3476–3479.
13. (a) Billman, J. H.; Parker, E. E. *J. Am. Chem. Soc.* **1945**, *67*, 1069–1070. (b) Pierce, J. S.; Lunsford, C. D. *J. Am. Chem. Soc.* **1951**, *73*, 2596–2598. (c) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353–9372.
14. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre with deposition number CCDC 290624.
15. It was determined from the optical purity of **4** from HPLC analysis using a chiral column that migration of an acetyl group in **2** had not taken place in the Swern oxidation process.
16. Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295.