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1 **First Total Synthesis of (+)-Epogymnolactam, a Novel Autophagy Inducer**

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1 **Abstract**

2 A novel autophagy inducer, (+)-epogymnolactam (**1**) was first synthesized from
3 *cis*-4-benzyloxy-2-butene-1-ol (**2**) in 8 steps. A reliable preparation of optically pure
4 epoxy alcohol (+)-**3** from monobenzyl derivative (**2**) was established by a tandem
5 strategy, Sharpless epoxidation/lipase kinetic resolution.

6
7 **INTRODUCTION**

8 (+)-Epogymnolactam (**1**) was discovered as a novel autophagy inducer from a mycelial
9 culture of *Gymnopus* sp. in our laboratory (Fig. 1).¹ Autophagy is one of the major
10 intracellular degradation systems in eukaryotic cells, eliminating damaged organelles
11 and protein aggregates to maintain cytoplasmic homeostasis. This degradation pathway
12 plays important roles in such diseases as cancer, neurodegenerative and infectious
13 diseases. Thus, the application of autophagy inducer would help to understand the
14 regulatory roles of autophagy in human diseases, and provide insight into the
15 development of therapeutic agents that target autophagy.²⁻⁵ As an example of the effort
16 for the development of autophagy-inducing drug, a peptide has been reported to have
17 benefits in the clearance of a model polyglutamine expansion protein aggregates in
18 HeLa/htt103Q cells, inhibition of intracellular survival of the bacterium, *Listeria*
19 *monocytogenes*, inhibition of HIV-1 replication in human monocyte-derived
20 macrophages, and a reduction in the mortality of neonatal mice infected chikungunya
21 virus and West Nile virus.⁶ Although researchers have identified different types of
22 autophagy inducers, e.g. rapamycin, an inhibitor of mTORC1;⁷ lithium L-690330, an
23 inhibitor of IMPase;⁸ verapamil, Ca²⁺ channel blocker;⁹ resveratrol, activator of sirtuin 1
24 and inhibitor of S6 kinase;¹⁰ clonidine, an imidazole-1 receptor agonist;⁹ minoxidil, a
25 K⁺ATP channel opener;⁹ spermidine, endogenous anti-aging mediator;¹¹ α -ketoglutarate,
26 inhibitor of ATP synthase¹² and so on, none of these compounds is similar to **1** in
27 chemical structure.

28
29 The structure of **1** deduced by spectroscopic analysis resembled to (+)-cerulenin,¹³ a
30 potent inhibitor of fatty acid synthesis,¹⁴⁻¹⁶ and the absolute structure of **1** was assigned
31 by the comparison of its specific rotation with that of (+)-cerulenin.¹ To evaluate
32 chemical and biological properties of **1** more precisely, we needed to synthesize enough
33 amount of **1** in enantiomerically pure form. Here we report the first total synthesis, and

1 thus structural confirmation of **1** by direct comparison of the natural product with the
2 synthetic compound.

3

4 **RESULT and DISCUSSION**

5 Among the total syntheses of (+)-cerulenin, the concise synthesis by Townsend group¹⁷
6 seemed to be most effective. Optically pure (+)-cerulenin was synthesized with use of
7 the coupling reaction of a chiral oxiranyl lithium with a side-chain aldehyde as a key
8 step. (+)-Epogymnolactam (**1**) would be synthesized in 10 steps starting from propargyl
9 alcohol, and the number of reaction steps in the synthetic route was shorter than any
10 other known synthetic methods from glucose,^{18,19} tartaric acid,²⁰ or a four-carbon
11 synthon obtained by Sharpless epoxidation.²¹ We decided, however, to develop the
12 straightforward synthesis of (+)-**1** which could be achieved in fewer steps by using the
13 enantiomer of Sudalai's epoxy alcohol (96% ee, as TBS-alternate of (-)-**3**)²²
14 synthesized via Sharpless asymmetric epoxidation using (+)-DET as a chiral source.
15 Nevertheless, we could not reproduce such a high enantioselectivity in the synthesis of
16 TBS alternate of (+)-**3** using (-)-DET. In general, Sharpless epoxidation of *cis* allylic
17 alcohol has been shown not to give high enantiomeric excess especially in the
18 large-scale preparation in a reproducible fashion. Sharpless epoxidation of
19 *cis*-4-benzyloxy-2-buten-1-ol **2** resulted in 89% ee similar to the observation by
20 Terashima group.²³ We tried to obtain enantiopure (+)-**3** by a recrystallization of
21 3,5-dinitrobenzoate of **3** followed by alkaline hydrolysis,²⁴ whereas we could not
22 obtain an acceptable result, and abandoned optimization of this procedure, because a
23 three-step process involving dinitrobenzoylation, recrystallization, and hydrolysis was
24 needed in any case.

25 Next we searched for the best conditions to obtain enantiopure (+)-**3** by a
26 lipase-mediated kinetic resolution of the corresponding acetate prepared by acetylation
27 of **3** (89% ee). Epoxy alcohol (+)-**3** could be obtained with up to 96% ee by hydrolysis
28 of the acetylated precursor with porcine pancreatic lipase (PPL), unfortunately this
29 procedure did not give reproducible results and gave mostly unsatisfactory
30 enantioselectivity less than 90% ee.²⁵

31 Finally we devised the most reliable procedure to prepare enantiopure (+)-**3** (99 to
32 100% ee) by treating **3** (89% ee) with PPL in vinyl acetate²⁶ as shown in Scheme 1.
33 This type of tandem strategy for preparation of epoxy alcohols could be generally useful

1 because Sharpless epoxidation has been applied for tremendous number of allylic
2 alcohol but it was difficult to obtain epoxy alcohol having nearly 100% ee. We believe
3 this tandem strategy, Sharpless epoxidation/lipase kinetic resolution for preparation of
4 enantiopure epoxy alcohol becomes one of the standard methods in organic synthesis.

5 The first total synthesis of (+)-**1** was achieved in a straightforward route outlined
6 in Scheme 2. Dess-Martin oxidation²⁷ of **3** afforded aldehyde **4** in 91% yield.
7 Large-scale preparation of **4** was done by cost-effective TEMPO oxidation²⁸ whose
8 yield was 85%. Grignard reaction of **4** with *n*-BuMgCl in THF at $-78\text{ }^{\circ}\text{C}$ followed by
9 deprotection of benzyl group of **5** with hydrogen and palladium/carbon catalyst in
10 EtOAc at room temperature gave desired epoxy diol **6** in 53% yield over two steps.
11 TEMPO oxidation of **6** in the presence of 2.2 eq. of NaOCl²⁹ at $0\text{ }^{\circ}\text{C}$ provided epoxy
12 lactone **7** in 78% yield. Two diastereomers could be separated by silica gel column
13 chromatography (EtOAc : hexane = 1 : 4). Ammonolysis of **7** with NH₃ in MeOH at $0\text{ }^{\circ}\text{C}$
14 furnished desired amide alcohol **8** in 99% yield. All synthetic intermediates **5**, **6**, **7**,
15 and **8** existed as a mixture of two diastereomers, while no inconvenience in the structure
16 determinations of these intermediates by NMR analysis. Oxidation of the both two
17 diastereomeric alcohols should primarily generate the open-chain form **1a**. The amide
18 alcohol **8** was successfully converted into (+)-**1** by Dess-Martin periodinane in CH₂Cl₂
19 at room temperature in 76% yield. Analyses of ¹H and ¹³C NMR showed that synthetic
20 (+)-**1** existed as a ring-chain tautomeric mixture of ketoamide (**1a**) and diastereomeric
21 hydroxy lactams (**1b** and **1c**) in CD₃OD as in the case of natural (+)-**1**. The
22 physicochemical properties and autophagy inducing activity of synthetic (+)-**1** were
23 consistent with those of natural epogymnolactam. Therefore, the absolute configuration
24 of natural epogymnolactam was unambiguously confirmed as shown in Fig. 1.

25 Given the enough amount of synthetic (+)-**1**, we first decided to clarify the ratio
26 of three isomers, keto isomer **1a**, major cyclic isomer **1b**, and minor cyclic isomer **1c** in
27 CD₃OD. A tautomeric ratio (**1a** : **1b** : **1c** = 4.7 : 4.0 : 1.3) of synthetic epogymnolactam
28 (**1**) right after dissolving in CD₃OD changed into a different ratio (**1a** : **1b** : **1c** = 2.5 :
29 6.0 : 1.5) with time. This phenomenon suggests that the keto isomer **1a** is most stable in
30 the absence of solvent. The complete NMR assignments of **1a**, **1b** and **1c** are shown in
31 Table 1.

32 In conclusion, we accomplished the first total synthesis of (+)-epogymnolactam
33 (**1**), and determined the absolute configuration of **1** unambiguously.

1

2 **EXPERIMENTAL**

3 Chemicals of the highest commercial purity were used without further purification.
4 Thin-layer and silica gel column chromatography were performed by using Merck
5 Silica Gel 60 F₂₅₄ and Kanto Chemical Co. Silica Gel 60N (spherical, neutral),
6 respectively. A DAICEL Chiralpak AD-H column (ϕ 0.64 cm x 25 cm) and a Waters
7 600 System were used for chiral HPLC. ¹H and ¹³C NMR spectra were recorded using a
8 JEOL JNM EX-270 FT-NMR (JEOL, Tokyo, Japan), and HSQC and HMBC spectra
9 were measured with a Bruker AMX-500 (Bruker, MA, USA). Mass spectra were
10 acquired with FI modes using a JMS-T100GCV (JEOL, Tokyo, Japan). ESI-MS spectra
11 of (+)-**1** were recorded on a LTQ Orbitrap XL (Thermo Scientific, MA, USA). Optical
12 rotations were determined on a JASCO P-2000 (JASCO, Tokyo, Japan).

13

14 **(2R,3S)-4-Benzoyloxy-2,3-epoxybutane-1-ol (3)**

15 To a stirred suspension of activated 4Å molecular sieves (2.29 g) in dry CH₂Cl₂ (190
16 ml) were sequentially added Ti(O^{*i*}Pr)₄ (7.20 ml, 24.1 mmol) and D-(–)-DIPT (5.03 ml,
17 24.1 mmol) under argon at -25 °C. After stirring for 30 min, **2** (4.0 g, 22.5 mmol) in dry
18 CH₂Cl₂ (34 ml) was slowly added over 90 min and the reaction mixture was continually
19 stirred for another 90 min at -25 °C. To the solution was added dropwise a nonane
20 solution of *t*-BuOOH (5.5 M, 8.8 ml) and the solution was stirred for 3 days at -20 °C.
21 After warming to room temperature, the mixture was diluted with saturated (sat.)
22 aqueous Na₂S₂O₃ (40 ml). The resultant solution was stirred for 2 h and then filtrated.
23 The filtrate was extracted with Et₂O and the organic layer was washed with water, dried
24 over Na₂SO₄, concentrated, and purified by silica gel column chromatography (EtOAc :
25 hexane = 1 : 2) to afford epoxy alcohol **3** (3.26 g, 75%) as a colorless oil. The
26 enantiomeric excess value was determined by HPLC (DICE L Chiralpak AD-H, 0.46 x
27 25 cm, hexane : EtOH = 9 : 1, 0.8 ml/min).

28 89% ee; $[\alpha]_D^{25} = +23.0$ (*c* 1.00, CHCl₃).

29 ¹H NMR(270 MHz, CDCl₃): δ 2.14 (1H, s, -OH), 3.19-3.32 (2H, m, H-2 and H-3),
30 3.62-3.75 (4H, m, H-1 and H-4), 4.51-4.64 (2H, dd, *J* = 24.7, 11.9, benzyl), 7.28-7.39

1 (5H, m, aromatic).
2 ¹³C NMR (67.5 MHz, CDCl₃): δ 54.7 (C-3), 55.6 (C-2), 60.7 (C-1), 68.0 (C-4), 73.5
3 (benzyl), 127.9 (aromatic), 128.0 (aromatic), 128.5 (aromatic), 137.4 (aromatic).
4 FI-MS: *m/z* 194.1 [M]⁺.

5

6 **Kinetic resolution of 3**

7 To a stirred solution of **3** (1.39 g, 7.17 mmol) in vinyl acetate (73.8 ml) was added 403
8 mg of PPL (L3126-25G, Sigma, USA) at room temperature (rt.). The reaction mixture
9 was stirred for 6 h, filtered with Celite pad to remove PPL, and the residue on Celite
10 pad was washed with EtOAc. The combined filtrate and washings were concentrated *in*
11 *vacuo*, and the resultant residue was purified by silica gel column chromatography
12 (EtOAc : hexane = 1 : 2) to give 1.07 g of enantiopure (+)-**3** (1.07 g, 77%).
13 99% ee; [α]_D²⁵ = +24.3 (*c* 1.00, CHCl₃).

14

15 **(2R,3S)-4-Benzyloxy-2,3-epoxy-1-butanal (4)**

16 To a stirred solution of **3** (1.06 g, 5.47 mmol) in CH₂Cl₂ (64 ml) were added TEMPO
17 (8.54 mg, 54.7 μmol) and 0.5 M aqueous KBr (1.09 ml) at rt., and then a mixture of
18 1.96 M aqueous NaOCl (3.35 ml) and sat. aqueous NaHCO₃ (3.35 ml) at 0 °C. After
19 stirring for 4 h at 0 °C, the reaction mixture was quenched with sat. aqueous Na₂S₂O₃
20 and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄,
21 concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc :
22 hexane = 1 : 2) to afford aldehyde **4** (893 mg, 85%) as a colorless oil.

23 [α]_D²⁵ = -111.1 (*c* 1.00, CHCl₃)

24 ¹H NMR (270 MHz, CDCl₃): δ 3.39-4.43 (1H, t, *J* = 4.5, H-2), 3.47-3.52 (1H, q, *J* = 3.1,
25 H-3), 3.72-3.86 (2H, m, H-4), 4.55 (2H, s, benzyl), 7.29-7.38 (5H, m, aromatic),
26 9.42-9.44 (1H, d, *J* = 3.7, H-1).

27 ¹³C NMR (67.5 MHz, CDCl₃): δ 57.3 (C-3), 58.0 (C-2), 66.2 (C-4), 73.5 (benzyl), 127.8
28 (aromatic), 128.0 (aromatic), 128.5 (aromatic), 137.1 (aromatic), 197.6(C-1).

29 FI-MS: *m/z* 192.1 [M]⁺.

1

2 **(2R,3S)-2,3-epoxy-1,4-octandiol (6)**

3 To a stirred solution of **5** (44.7 mg, 0.233 mmol) in dry THF (1.0 ml) was added
4 dropwise a solution of *n*-BuMgCl in THF (2.0 M, 129 μ l) under argon at -78 $^{\circ}$ C. The
5 reaction mixture was stirred for 1.5 h, and quenched with MeOH. After warming to
6 room temperature, sat. aqueous NH₄Cl was added to the solution. The mixture was
7 stirred vigorously and extracted with Et₂O. The organic layer was dried over Na₂SO₄,
8 concentrated *in vacuo*, and subjected to silica gel column chromatography (EtOAc :
9 hexane = 1 : 3) to give crude alcohol **5**. To a solution of crude **5** (50.3 mg) in EtOAc
10 (5.8 ml) was added Pd/C (66 mg) and the mixture was stirred vigorously under H₂
11 overnight. The resulting solution was filtered, concentrated and purified by silica gel
12 column chromatography (EtOAc : hexane = 1 : 1) to afford a diastereomeric mixture of
13 diol **6** (19.7 mg, 53% over 2 steps) as a colorless oil.

14 $[\alpha]_{\text{D}}^{25} = +2.4$ (*c* 1.00, CHCl₃)

15 ¹H NMR (270 MHz, CDCl₃): δ 0.90-0.95 (3H, m, H-8), 1.31-1.77 (6H, m, H-5, H-6 and
16 H-7), 2.93-3.30 (4H, m, H-2, H-3 and (-OH) x 2), 3.55-3.62 (1H, q, *J* = 6.7, H-4),
17 3.68-3.75 (1H, dd, *J* = 12.1, 3.3, H-1), 3.99-4.06 (1H, dd, *J* = 12.0, 2.8, H-1).

18 ¹³C NMR (67.5 MHz, CDCl₃): δ 13.9 (C-8), 22.6 (C-7), 27.1 (C-6), 35.2 (C-5), 55.6
19 (C-2), 59.1 (C-3), 60.7 (C-1), 69.7(C-4).

20 FI-MS: *m/z* 161.1 [M+H]⁺.

21

22 **(1R,5R)-4-Butyl-3,6-dioxabicyclo[3.1.0]hexan-2-one (7)**

23 To a stirred solution of **6** (22.1 mg, 138 μ mol) in CH₂Cl₂ (1.8 ml) were added TEMPO
24 (0.23 mg, 1.38 μ mol) and 0.5 M aqueous KBr (29 μ l) at rt., and then a mixture of 1.96
25 M aqueous NaOCl (162 μ l) and sat. aqueous NaHCO₃ (162 μ l) at 0 $^{\circ}$ C. After stirring for
26 4 h at 0 $^{\circ}$ C, the reaction mixture was quenched with sat. aqueous Na₂S₂O₃ and extracted
27 with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, concentrated
28 *in vacuo*, and purified by silica gel column chromatography (EtOAc : hexane = 1 : 3) to

1 afford **7** (78%), which was separable to major isomer (Rf value: 0.4, 14.5 mg, 67%) and
2 minor isomer (Rf value: 0.3, 1.7 mg, 8%) as a colorless oil respectively.

3 Major isomer : $[\alpha]_{\text{D}}^{25} = +48.9$ (*c* 1.00, CHCl₃)

4 Minor isomer : $[\alpha]_{\text{D}}^{25} = +37.3$ (*c* 0.13, CHCl₃)

5 ¹H NMR (270 MHz, CDCl₃): δ 0.91-0.96 (3H, t, *J* = 6.6, H-8), 1.26-1.71 (6H, m, H-5,
6 H-6 and H-7), 3.77-3.78 (1H, d, *J* = 1.6, H-2), 3.96-3.97 (1H, d, *J* = 2.3, H-3), 4.55-4.59
7 (1H, t, *J* = 6.5, H-4).

8 ¹³C NMR (67.5 MHz, CDCl₃): δ 13.8 (C-8), 22.3 (C-7), 26.3 (C-6), 31.8 (C-5), 49.8
9 (C-3), 58.0 (C-2), 79.8 (C-4), 170.3 (C-1).

10 FI-MS: *m/z* 156.1 [M+H]⁺.

11

12 **(2*R*,3*R*)-2,3-epoxy-4-hydroxyoctanamide (8)**

13 The diastereomeric mixture of **7** (14.2 mg, 91.0 μ mol) was dissolved in a solution of
14 NH₃ in MeOH (2.0 M, 3 ml) under nitrogen atmosphere and the mixture was stirred for
15 2.5 h at 0 °C. The resulting solution was concentrated *in vacuo* and purified by silica gel
16 column chromatography (MeOH : CHCl₃ = 7 : 93) to afford a diastereomeric mixture of
17 amide **8** (15.1 mg, 99%) as a colorless oil.

18 $[\alpha]_{\text{D}}^{25} = +54.4$ (*c* 1.00, CHCl₃)

19 ¹H NMR (270 MHz, CDCl₃) δ 0.87-0.95 (3H, t, *J* = 7.1, H-8), 1.32-1.69 (6H, m, H-5,
20 H-6 and H-7), 3.07-3.21 (2H, m, H-2 and H-3), 3.45-3.58 (2H, m, H-4 and -OH), 6.28
21 (1H, s, -NH₂), 6.43 (1H, s, -NH₂).

22 ¹³C NMR (67.5 MHz, CDCl₃) δ 14.0 (C-8), 22.6 (C-7), 27.0 (C-6), 34.6 (C-5), 54.3
23 (C-2), 60.1 (C-3), 69.0 (C-4), 170.2 (C-1).

24 FI-MS: *m/z* 174.1 [M+H]⁺.

25

26 **(+)-Epogymnolactam (1)**

27 To a stirred solution of **9** (7.5 mg, 43.4 μ mol) in dry CH₂Cl₂ (1.6 ml) was added
28 Dess-Martin periodinane (25.7 mg, 60.6 μ mol) under argon at 0 °C. After stirring for 2

1 h, the mixture was quenched with sat. aqueous Na₂S₂O₃ and sat. aqueous NaHCO₃. The
2 solution was extracted with EtOAc and the organic layer was washed with brine, dried
3 over Na₂SO₄, concentrated *in vacuo*, and purified by silica gel column chromatography
4 (EtOAc : hexane = 2 : 1) to afford (+)-epogymnolactam (**1**) (5.6 mg, 76%) as a yellow
5 solid.

6 $[\alpha]_D^{25} = +25.6$ (c 0.49, MeOH)

7 ¹H and ¹³C NMR: see Table 1.

8 HR-ESI-MS: *m/z* 194.07876 [M+Na]⁺ calcd. for C₈H₁₃O₃NNa, found 194.07887.

9

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11

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17

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2 **Table 1.** ^1H and ^{13}C NMR data of (+)-epogymnolactam in CD_3OD (500 MHz for ^1H and 126 MHz for ^{13}C , Bruker)

Position	1a		1b (major)		1c (minor)	
	δ_{C} , type	δ_{H} (<i>J</i> in Hz)	δ_{C} , type	δ_{H} (<i>J</i> in Hz)	δ_{C} , type	δ_{H} (<i>J</i> in Hz)
1	170.5, s	—	174.4, s	—	172.9, s	—
2	55.8, d	3.70, d (5.2)	53.1, d	3.57, d (2.6)	54.3, d	3.56, d (2.7)
3	59.4, d	3.88, d (5.2)	59.0, d	3.80, d (2.6)	58.1, d	3.84, d (2.7)
4	205.8, s	—	87.2, s	—	86.8, s	—
5	41.0, t	2.68, ddd (17.6, 8.2, 6.6) 2,56, ddd (17.6, 8.1, 6.5)	36.3, t	1.72, m	38.9, t	1.78, m
6	26.1, t	1.55, m	27.0, t	1.51, m	25.9, t	1.41, m
7	23.2, t	1.31, sext (7.4)	24.0, t	1.37, sext (7.4)	23.9, t	1.38, sext (7.4)
8	14.1, q	0.90, t (7.4)	14.3, q	0.94, t (7.4)	14.3, q	0.94, t (7.4)

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Legend to figure and schemes

Fig. 1. Ring-chain tautomerism of (+)-epogymnolactam (**1**).

Scheme 1. A tandem strategy for preparation of enantiopure (+)-**3**.

Scheme 2. Total synthesis of (+)-epogymnolactam (**1**).

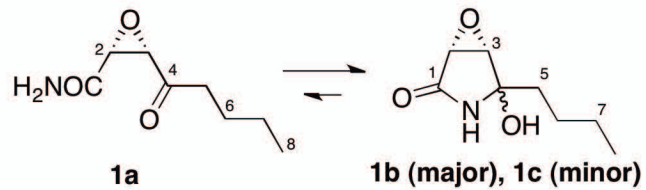
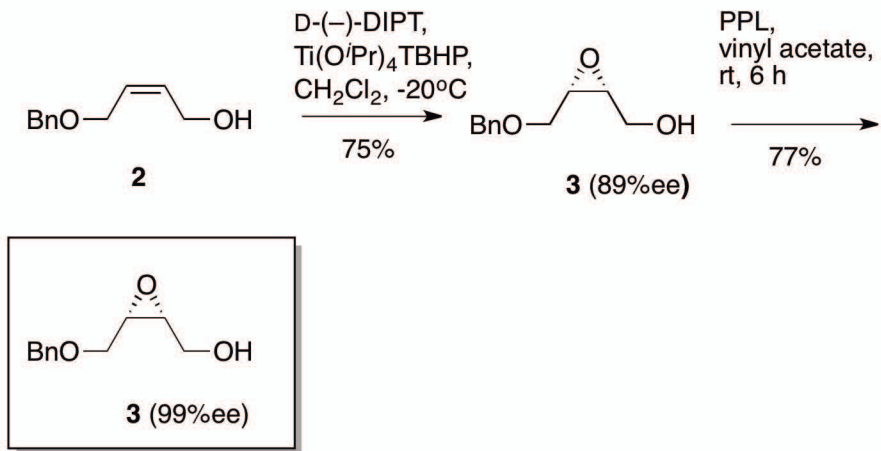
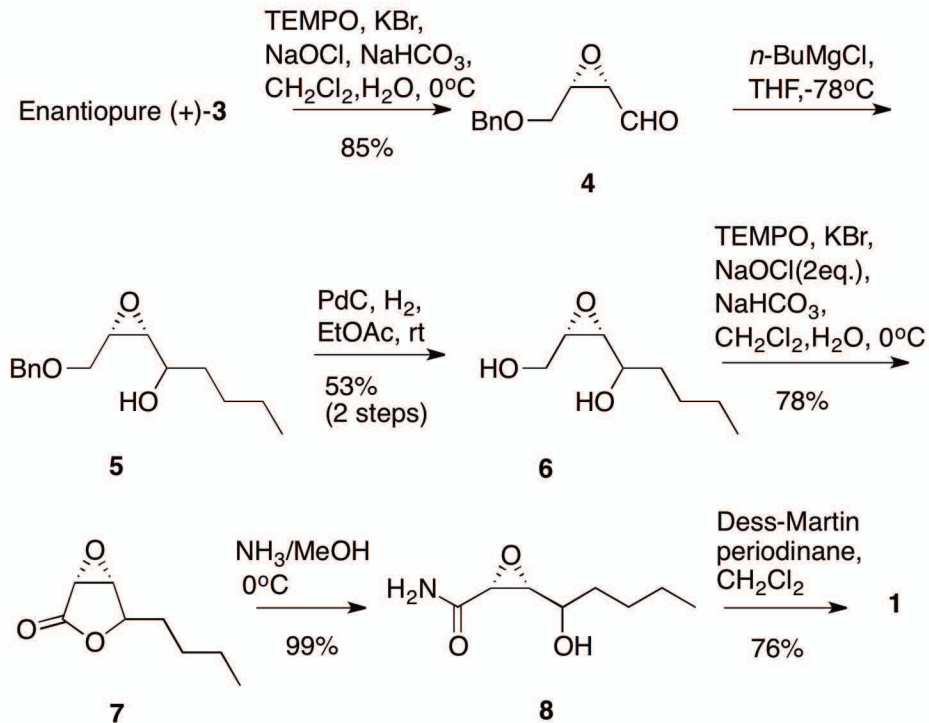


Fig. 1



Scheme 1



Scheme 2