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First Total Synthesis of (+)-Epogynolactam, a Novel Autophagy Inducer

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Abstract

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

INTRODUCTION

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

The structure of 1 deduced by spectroscopic analysis resembled to (+)-cerulenin,13 a potent inhibitor of fatty acid synthesis,14-16 and the absolute structure of 1 was assigned by the comparison of its specific rotation with that of (+)-cerulenin.1 To evaluate chemical and biological properties of 1 more precisely, we needed to synthesize enough amount of 1 in enantiomerically pure form. Here we report the first total synthesis, and
thus structural confirmation of 1 by direct comparison of the natural product with the synthetic compound.

RESULT and DISCUSSION

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

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

Finally we devised the most reliable procedure to prepare enantiopure (+)-3 (99 to 100% ee) by treating 3 (89% ee) with PPL in vinyl acetate\textsuperscript{26} as shown in Scheme 1. This type of tandem strategy for preparation of epoxy alcohols could be generally useful
because Sharpless epoxidation has been applied for tremendous number of allylic alcohol but it was difficult to obtain epoxy alcohol having nearly 100% ee. We believe this tandem strategy, Sharpless epoxidation/lipase kinetic resolution for preparation of enantiopure epoxy alcohol becomes one of the standard methods in organic synthesis.

The first total synthesis of (+)-1 was achieved in a straightforward route outlined in Scheme 2. Dess-Martin oxidation\(^27\) of 3 afforded aldehyde 4 in 91% yield. Large-scale preparation of 4 was done by cost-effective TEMPO oxidation\(^28\) whose yield was 85%. Grignard reaction of 4 with \(n\)-BuMgCl in THF at \(-78^\circ C\) followed by deprotection of benzyl group of 5 with hydrogen and palladium/carbon catalyst in EtOAc at room temperature gave desired epoxy diol 6 in 53% yield over two steps. TEMPO oxidation of 6 in the presence of 2.2 eq. of NaOCl\(^29\) at \(0^\circ C\) provided epoxy lactone 7 in 78% yield. Two diastereomers could be separated by silica gel column chromatography (EtOAc : hexane = 1 : 4). Ammonolysis of 7 with NH\(_3\) in MeOH at \(0^\circ C\) furnished desired amide alcohol 8 in 99% yield. All synthetic intermediates 5, 6, 7, and 8 existed as a mixture of two diastereomers, while no inconvenience in the structure determinations of these intermediates by NMR analysis. Oxidation of the both two diastereomeric alcohols should primarily generate the open-chain form 1a. The amide alcohol 8 was successfully converted into (+)-1 by Dess-Martin periodinane in CH\(_2\)Cl\(_2\) at room temperature in 76% yield. Analyses of \(^1\)H and \(^{13}\)C NMR showed that synthetic (+)-1 existed as a ring-chain tautomeric mixture of ketoamide (1a) and diastereomeric hydroxy lactams (1b and 1c) in CD\(_3\)OD as in the case of natural (+)-1. The physicochemical properties and autophagy inducing activity of synthetic (+)-1 were consistent with those of natural epogymnolactam. Therefore, the absolute configuration of natural epogymnolactam was unambiguously confirmed as shown in Fig. 1.

Given the enough amount of synthetic (+)-1, we first decided to clarify the ratio of three isomers, keto isomer 1a, major cyclic isomer 1b, and minor cyclic isomer 1c in CD\(_3\)OD. A tautomeric ratio (1a : 1b : 1c = 4.7 : 4.0 : 1.3) of synthetic epogymnolactam (1) right after dissolving in CD\(_3\)OD changed into a different ratio (1a : 1b : 1c = 2.5 : 6.0 : 1.5) with time. This phenomenon suggests that the keto isomer 1a is most stable in the absence of solvent. The complete NMR assignments of 1a, 1b and 1c are shown in Table 1.

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

Chemicals of the highest commercial purity were used without further purification. Thin-layer and silica gel column chromatography were performed by using Merck Silica Gel 60 F_{254} and Kanto Chemical Co. Silica Gel 60N (spherical, neutral), respectively. A DAICEL Chiralpak AD-H column (ø 0.64 cm x 25 cm) and a Waters 600 System were used for chiral HPLC. $^1$H and $^{13}$C NMR spectra were recorded using a JEOL JNM EX-270 FT-NMR (JEOL, Tokyo, Japan), and HSQC and HMBC spectra were measured with a Bruker AMX-500 (Bruker, MA, USA). Mass spectra were acquired with FI modes using a JMS-T100GCV (JEOL, Tokyo, Japan). ESI-MS spectra of (+)-1 were recorded on a LTQ Orbitrap XL (Thermo Scientific, MA, USA). Optical rotations were determined on a JASCO P-2000 (JASCO, Tokyo, Japan).

(2R,3S)-4-Benzylxy-2,3-epoxybutane-1-ol (3)

To a stirred suspension of activated 4Å molecular sieves (2.29 g) in dry CH$_2$Cl$_2$ (190 ml) were sequentially added Ti(OiPr)$_4$ (7.20 ml, 24.1 mmol) and D-(-)-DIPT (5.03 ml, 24.1 mmol) under argon at -25 ºC. After stirring for 30 min, 2 (4.0 g, 22.5 mmol) in dry CH$_2$Cl$_2$ (34 ml) was slowly added over 90 min and the reaction mixture was continually stirred for another 90 min at -25 ºC. To the solution was added dropwise a nonane solution of t-BuOOH (5.5 M, 8.8 ml) and the solution was stirred for 3 days at -20 ºC. After warming to room temperature, the mixture was diluted with saturated (sat.) aqueous Na$_2$S$_2$O$_3$ (40 ml). The resultant solution was stirred for 2 h and then filtrated. The filtrate was extracted with Et$_2$O and the organic layer was washed with water, dried over Na$_2$SO$_4$, concentrated, and purified by silica gel column chromatography (EtOAc : hexane = 1 : 2) to afford epoxy alcohol 3 (3.26 g, 75%) as a colorless oil. The enantiomeric excess value was determined by HPLC (DICEL Chiralpak AD-H, 0.46 x 25 cm, hexane : EtOH = 9 : 1, 0.8 ml/min).

89% ee; [α]$_D^{25}$ = +23.0 (c 1.00, CHCl$_3$).

$^1$H NMR (270 MHz, CDCl$_3$): δ 2.14 (1H, s, -OH), 3.19-3.32 (2H, m, H-2 and H-3), 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
(5H, m, aromatic).

$^{13}$C NMR (67.5 MHz, CDCl$_3$): $\delta$ 54.7 (C-3), 55.6 (C-2), 60.7 (C-1), 68.0 (C-4), 73.5 (benzyl), 127.9 (aromatic), 128.0 (aromatic), 128.5 (aromatic), 137.4 (aromatic).

FI-MS: $m/z$ 194.1 [M]$^+$. 

**Kinetic resolution of 3**

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

99% ee; $[\alpha]_D^{25} = +24.3$ (c 1.00, CHCl$_3$).

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

To a stirred solution of 3 (1.06 g, 5.47 mmol) in CH$_2$Cl$_2$ (64 ml) were added TEMPO (8.54 mg, 54.7 µmol) and 0.5 M aqueous KBr (1.09 ml) at rt., and then a mixture of 1.96 M aqueous NaOCl (3.35 ml) and sat. aqueous NaHCO$_3$ (3.35 ml) at 0 ºC. After stirring for 4 h at 0 ºC, the reaction mixture was quenched with sat. aqueous Na$_2$S$_2$O$_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, concentrated in vacuo and purified by silica gel column chromatography (EtOAc : hexane = 1 : 2) to afford aldehyde 4 (893 mg, 85%) as a colorless oil.

$[\alpha]_D^{25} = -111.1$ (c 1.00, CHCl$_3$)

$^1$H NMR (270 MHz, CDCl$_3$): $\delta$ 3.39-4.43 (1H, t, $J = 4.5$, H-2), 3.47-3.52 (1H, q, $J = 3.1$, H-3), 3.72-3.86 (2H, m, H-4), 4.55 (2H, s, benzyl), 7.29-7.38 (5H, m, aromatic), 9.42-9.44 (1H, d, $J = 3.7$, H-1).

$^{13}$C NMR (67.5 MHz, CDCl$_3$): $\delta$ 57.3 (C-3), 58.0 (C-2), 66.2 (C-4), 73.5 (benzyl), 127.8 (aromatic), 128.0 (aromatic), 128.5 (aromatic), 137.1 (aromatic), 197.6(C-1).

FI-MS: $m/z$ 192.1 [M]$^+$. 

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

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

[α]D²⁵ = +2.4 (c 1.00, CHCl₃)

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 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), 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).

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 (C-2), 59.1 (C-3), 60.7 (C-1), 69.7(C-4).

FI-MS: m/z 161.1 [M+H]⁺.

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

To a stirred solution of 6 (22.1 mg, 138 µmol) in CH₂Cl₂ (1.8 ml) were added TEMPO (0.23 mg, 1.38 µmol) and 0.5 M aqueous KBr (29 µl) at rt., and then a mixture of 1.96 M aqueous NaOCl (162 µl) and sat. aqueous NaHCO₃ (162 µl) at 0 ºC. After stirring for 4 h at 0 ºC, the reaction mixture was quenched with sat. aqueous Na₂S₂O₃ and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, concentrated in vacuo, and purified by silica gel column chromatography (EtOAc : hexane = 1 : 3) to
afford 7 (78%), which was separable to major isomer (Rf value: 0.4, 14.5 mg, 67%) and
minor isomer (Rf value: 0.3, 1.7 mg, 8%) as a colorless oil respectively.

Major isomer: $[\alpha]_{D}^{25} = +48.9$ (c 1.00, CHCl$_3$)

Minor isomer: $[\alpha]_{D}^{25} = +37.3$ (c 0.13, CHCl$_3$)

$^1$H NMR (270 MHz, CDCl$_3$): δ 0.91-0.96 (3H, t, $J = 6.6$, H-8), 1.26-1.71 (6H, m, H-5, 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 (1H, t, $J = 6.5$, H-4).

$^{13}$C NMR (67.5 MHz, CDCl$_3$): δ 13.8 (C-8), 22.3 (C-2), 26.3 (C-6), 31.8 (C-5), 49.8 (C-3), 58.0 (C-2), 79.8 (C-4), 170.3 (C-1).

FI-MS: m/z 156.1 [M+H]$^+$.  

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

The diastereomeric mixture of 7 (14.2 mg, 91.0 µmol) was dissolved in a solution of
NH$_3$ in MeOH (2.0 M, 3 ml) under nitrogen atmosphere and the mixture was stirred for
2.5 h at 0 ºC. The resulting solution was concentrated in vacuo and purified by silica gel
column chromatography (MeOH : CHCl$_3$ = 7 : 93) to afford a diastereomeric mixture of
amide 8 (15.1 mg, 99%) as a colorless oil.

$[\alpha]_{D}^{25} = +54.4$ (c 1.00, CHCl$_3$)

$^1$H NMR (270 MHz, CDCl$_3$) δ 0.87-0.95 (3H, t, $J = 7.1$, H-8), 1.32-1.69 (6H, m, H-5, 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 (1H, s, -NH$_2$), 6.43 (1H, s, -NH$_2$).

$^{13}$C NMR (67.5 MHz, CDCl$_3$) δ 14.0 (C-8), 22.6 (C-7), 27.0 (C-6), 34.6 (C-5), 54.3 (C-2), 60.1 (C-3), 69.0 (C-4), 170.2 (C-1).

FI-MS: m/z 174.1 [M+H]$^+$.  

(+)-Epogymnolactam  (1)

To a stirred solution of 9 (7.5 mg, 43.4 µmol) in dry CH$_2$Cl$_2$ (1.6 ml) was added
Dess-Martin periodinane (25.7 mg, 60.6 µmol) under argon at 0 ºC. After stirring for 2
h, the mixture was quenched with sat. aqueous Na$_2$S$_2$O$_3$ and sat. aqueous NaHCO$_3$. The solution was extracted with EtOAc and the organic layer was washed with brine, dried over Na$_2$SO$_4$, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc : hexane = 2 : 1) to afford (+)-epogymnolactam (1) (5.6 mg, 76%) as a yellow solid.

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

$^1$H and $^{13}$C NMR: see Table 1.

HR-ESI-MS: $m/z$ 194.07876 [M+Na]$^+$ calcd. for C$_8$H$_{13}$O$_3$NNa, found 194.07887.

Acknowledgements

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References


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Table 1. $^1$H and $^{13}$C NMR data of (+)-epogynolactam in CD$_3$OD (500 MHz for $^1$H and 126 MHz for $^{13}$C, Bruker)

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Legend to figure and schemes

Fig. 1. Ring-chain tautomerism of (+)-epogynolactam (1).

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

Scheme 2. Total synthesis of (+)-epogynolactam (1).
Fig. 1
Scheme 1

D-(-)-DIPT, Ti(OiPr)$_4$, TBHP, CH$_2$Cl$_2$, -20°C → 3 (89% ee) 75%

PPL, vinyl acetate, rt, 6 h → 77%

2

3 (99% ee)

3 (89% ee)
Scheme 2