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Short Synthesis of Berkeleyamide D and Determination of the Absolute Configuration by the Vibrational Circular Dichroism Exciton Chirality Method

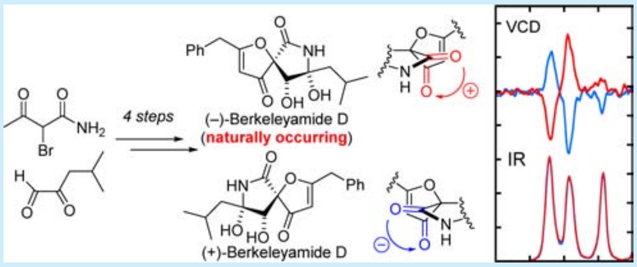
Kenta Komori,[†] Tohru Taniguchi,[‡] Shoma Mizutani,[†] Kenji Monde,[‡] Kouji Kuramochi,*[,†] and Kazunori Tsubaki[†]

[†]Graduate School for Life and Environmental Sciences, Kyoto Prefectural University, 1-5 Shimogamo Hangi-cho, Sakyo-ku, Kyoto 606-8522, Japan

[‡]Faculty of Advanced Life Science, Frontier Research Center for Post-Genome Science and Technology, Hokkaido University, Kita 21 Nishi 11, Sapporo 001-0021, Japan

Supporting Information

ABSTRACT: The first synthesis of (±)-berkeleyamide D has been accomplished. The key features of this synthesis include the formation of an α,β-epoxy-γ-lactam via a Darzens reaction and the construction of a spirocyclic ring system by a C-acylation reaction followed by an intramolecular spirocyclization via an epoxide-opening reaction. Following optical resolution by chiral HPLC, the absolute configurations of both enantiomers of berkeleyamide D were determined by the vibrational circular dichroism exciton chirality method.



Berkeleyamide D (**1**) was originally isolated by Stierle et al.[1] in 2008 from the acid lake fungus *Penicillium rubrum* Stoll (Figure 1) and was shown to inhibit matrix metalloproteinase-3 and caspase-1. Although the structure of **1** has been confirmed by detailed NMR studies, its relative and absolute configurations remain undetermined. Several related natural spiroheterocyclic γ-lactams have also been reported in the literature including pseurotin A (**2**)[2] and azaspirene (**3**).[3] The interesting biological activities and structural complexities of compounds **2** and **3** have attracted considerable interest from synthetic chemists, which culminated in their total syntheses.[4] The absolute configuration of **2** was determined by X-ray crystallographic analysis of its 12,13-dibromo derivative.[2a,b] The absolute configuration of **3** was determined by Hayashi et al.[4a] during their total synthesis of the same compound. The spirocenters at the C-5 positions in compounds **2** and **3** exist in the *S* configuration. Recent developments in the vibrational circular dichroism (VCD) exciton chirality method have made this a powerful tool for determining absolute configuration.[5] In a similar manner to the exciton chirality method in electronic circular dichroism (ECD),[6] the VCD exciton chirality method is based on the through-space coupling of two or more IR chromophores in chiral substrates. The interaction of two IR chromophores yields a bisignate VCD couplet (a pair of VCD signals with opposite signs around the absorption regions of the chromophores) whose sign reflects the absolute configuration of the molecule. Herein, we report the first synthesis of (±)-**1** as well as the determination of the absolute configuration of (−)-**1** and (+)-**1** by the VCD exciton chirality method.

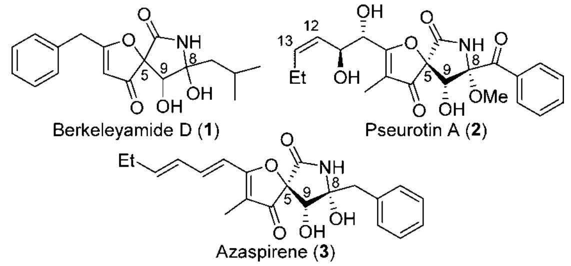


Figure 1. Structures of berkeleyamide D (**1**), pseurotin A (**2**), and azaspirene (**3**). Selected carbon atoms have been labeled using the IUPAC numbering system.

Our retrosynthetic analysis of berkeleyamide D (**1**) is depicted in Scheme 1. It was envisaged that (±)-**1** could be prepared by the intramolecular epoxide ring-opening reaction of the enolate derived from β-diketone **4**, which could be prepared by the protection of the hemiaminal in α,β-epoxy-γ-lactam **5**, followed by C-acylation with phenylacetyl chloride. The α,β-epoxy-γ-lactam **5** could itself be prepared by the Darzens reaction of α-bromo-β-ketoamide **6a**[7] with isobutylglyoxal **7**.[8]

The formation of an α,β-epoxy-γ-lactam was initially investigated using α-bromo-β-ketoamide **6b**[9] and commercially available methylglyoxal (40% aqueous solution) as model substrates (Table 1). The treatment of a mixture of **6b** and methylglyoxal (2.1 equiv) with sodium carbonate (1.0 equiv) in

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Scheme 1. Retrosynthetic Analysis of Berkeleyamide D (1)

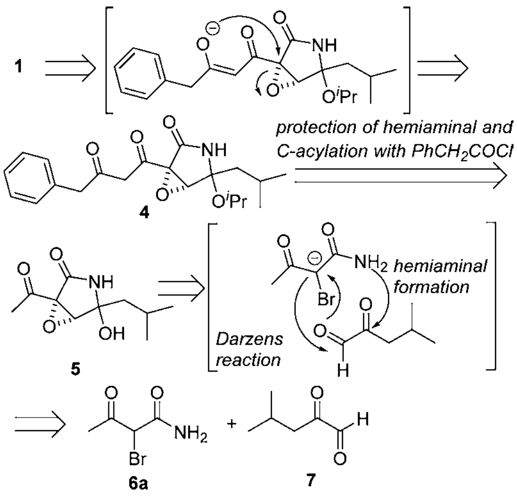
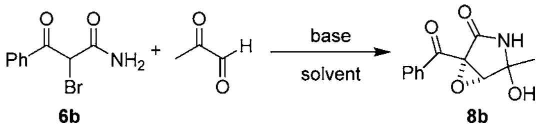


Table 1. Formation of *α*,*β*-Epoxy-*γ*-lactam by the Darzens Reaction Using Model Substrates[a]



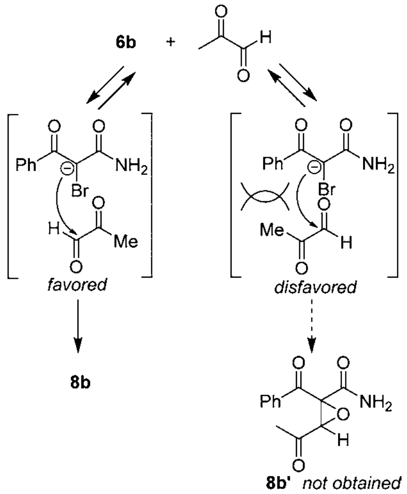
entry	base	solvent	temp (°C)	yield[b] (%)
1	Na_2CO_3	THF	40	0−69[c]
2	Na_2CO_3	THF/H_2O (10:1)	rt	54
3	Et_3N	THF/H_2O (10:1)	rt	69

[a] Reaction conditions: **6b** (0.12 mmol), methylglyoxal (0.25 mmol) and base (0.12 mmol) in solvent (3.3 mL). Based on the ^1H NMR spectrum, product **8b** existed as a 7:1 diastereomeric mixture at the *γ*-position in CD_3OD. [b] Isolated yield. [c] Poor reproducibility.

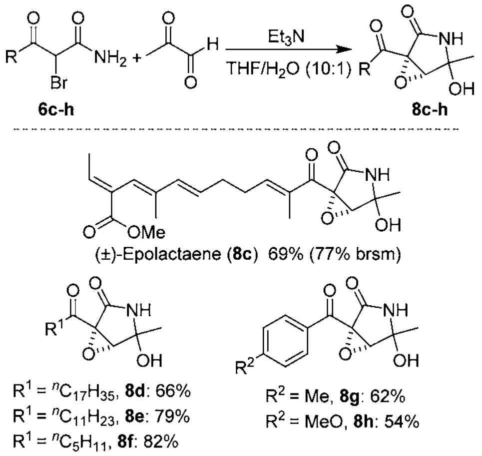
THF at 40 °C afforded **8b** (Table 1, entry 1), although the reaction suffered from poor reproducibility, which was attributed to the poor solubility of sodium carbonate in THF and the decomposition of product **8b** under the reaction conditions. When the reaction was performed in a 10:1 mixture of THF and H_2O at room temperature, **8b** was obtained in 54% yield with good reproducibility. The use of triethylamine as a base led to further improvements in the yield of **8b** (Table 1, entry 3). It is noteworthy that *trans*-epoxide **8b**′ was not observed in any of the reactions described in Table 1 (Scheme 2). The formation of **8b**′ would be disfavored by steric hindrance between the phenyl group in **6b** and the methyl group in methylglyoxal.

This transformation was found to be effective for the preparation of (±)-epolactaene, which is a microbial metabolite isolated from *Penicillium* sp. BM1689-P[10] and its derivatives (Scheme 3).[11] The *α*-bromo-*β*-ketoamides **6c−h** were prepared by the bromination of the corresponding *β*-ketoamides (Supporting Information, Schemes S1−S3). The reaction of **6c** with methylglyoxal in the presence of triethylamine in a 10:1 mixture of THF and H_2O gave (±)-epolactaene (**8c**) in 69% yield (77% yield based on the recovered **6c**). The epolactaene derivatives **8d−h** bearing either an aliphatic or aromatic side-chain were readily prepared by the reaction of the corresponding *α*-bromo-*β*-ketoamides **6d−h** with methylglyoxal.

Scheme 2. Proposed Mechanism for the Stereoselectivity of the Key Darzens Reaction



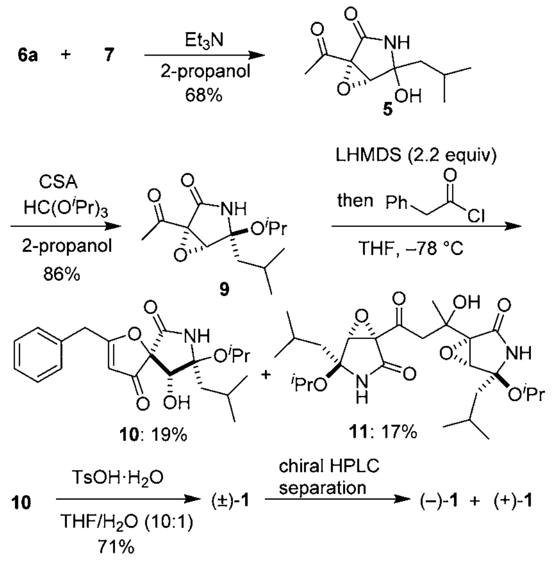
Scheme 3. Application of Darzens Reaction for the Synthesis of Epolactaene (8c) and Its Derivatives 8d−h[a]

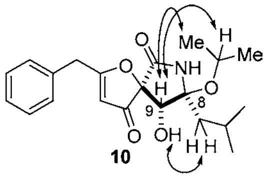


[a] Reaction conditions: **6** (0.15 mmol), methylglyoxal (0.30 mmol) and triethylamine (0.17 mmol) in solvent (4.5 mL) at room temperature. Based on the ^1H NMR spectrum, (±)-epolactaene (**8c**) existed as a 4.7:1 diastereomeric mixture at the *γ*-position in CD_3OD. Although compounds **8d-f** were observed as single diastereomers in CD_3OD, compounds **8g** and **8h** were observed as 7:1 diastereomeric mixtures.

We proceeded to apply our newly developed synthetic strategy to the synthesis of berkeleyamide D (**1**) (Scheme 4). The reaction of *α*-bromo-*β*-ketoamide **6a**[7] with isobutylglyoxal **7**[8] in the presence of triethylamine in 2-propanol gave *α*,*β*-epoxy-*γ*-lactam **5** in 68% yield. Subsequent treatment of **5** with 10-camphorsulfonic acid (CSA) and triisopropyl orthoformate in 2-propanol gave **9** as a single diastereomer in 86% yield.[12] The treatment of **9** with lithium hexamethyldisilazide (LHMDS) (2.2 equiv) followed by phenylacetyl chloride (1.0 equiv) gave the spiro lactam **10** in 19% yield, together with the homodimer **11**, which was isolated in 17% yield. The relative configuration in **10** was determined by NOESY correlations between H-9 and the methine proton of the isopropyl group at C-8, between H-9 and the methyl protons of the isopropyl group, and between 9-OH and the methylene protons at the isobutyl group (Figure 2). The formation of **10** could rationalized by the sequential C-acylation of **9**, enolization of

Scheme 4. Synthesis of (±)-Berkeleyamide D (1)

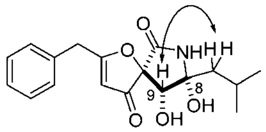




10

Figure 2. Selected NOESY correlations in **10**. Selected carbon atoms have been labeled using the IUPAC numbering system.

the resulting 1,3-diketone, and intramolecular spirocyclization via an epoxide ring-opening reaction (Scheme 1). Although the inclusion of a variety of different bases and additives was examined in detail, it was not possible to improve the yield of **10** (Supporting Information, Table S-1). Hydrolysis of **10** with *p*-toluenesulfonic acid (TsOH) in THF–H_2O gave (±)-**1** in 71% yield.[13] The ^{1}H and ^{13}C NMR spectra for synthetic (±)-**1** were in agreement with those reported for natural **1**.[1,14] NOESY correlations between H-9 and the methylene protons of the isobutyl group at C-8 in (±)-**1** indicated that there was a *cis* relationship between H-9 and the isobutyl group (Figure 3).



(±)-**1**

Figure 3. Selected NOESY correlations in (±)-**1**. Selected carbon atoms have been labeled using the IUPAC numbering system.

Optical resolution of synthetic (±)-**1** by chiral HPLC using a CHIRALPAK IC column gave both enantiomers of **1**, which possessed almost equal and opposite specific rotation values [i.e., $[\alpha]^{17}_{D}$ = +84.6 and −85.7, respectively (*c* 0.25, MeOH)]. The specific rotation of natural **1** was reported to be $[\alpha]^{25}_{D}$ = −55.9 (*c* 0.003, MeOH).[1]

With both (−)-**1** and (+)-**1** in hand, we proceeded to measure their VCD and IR spectra in $CDCl_3$ to determine their absolute configuration (Figure 4). The IR spectra of (−)-**1** and (+)-**1** contained strong absorptions at 1744 and 1686 cm^{-1}, which were derived from the C═O stretching vibrations of the lactam at C-6 and the ketone at C-4, respectively (Figure 4A). The VCD spectra of (−)-**1** and (+)-**1** exhibited strong bisignate VCD signals in the C═O stretching region (Figure 4B). The VCD spectrum of (−)-**1** showed a positive-negative couplet going from the lower to higher frequencies, indicating a clockwise orientation between the two adjacent carbonyl groups at C-4 and C-6 (Figure 4C). Taken together with the NOESY correlations, these data indicated that the absolute configuration of (−)-**1** was 5*S*,8*R*,9*R*.[15] Thus, natural **1** has the same absolute configuration for the spirocenter at its C-5 position as the structurally related compounds pseurotin A (**2**) and azaspirene (**3**). The VCD spectrum of (+)-**1** showed a negative–positive couplet going from the lower to higher frequencies, indicating a counterclockwise orientation between the two adjacent carbonyl groups. These data therefore indicated that the absolute configuration of (+)-**1** was 5*R*,8*S*,9*S*.

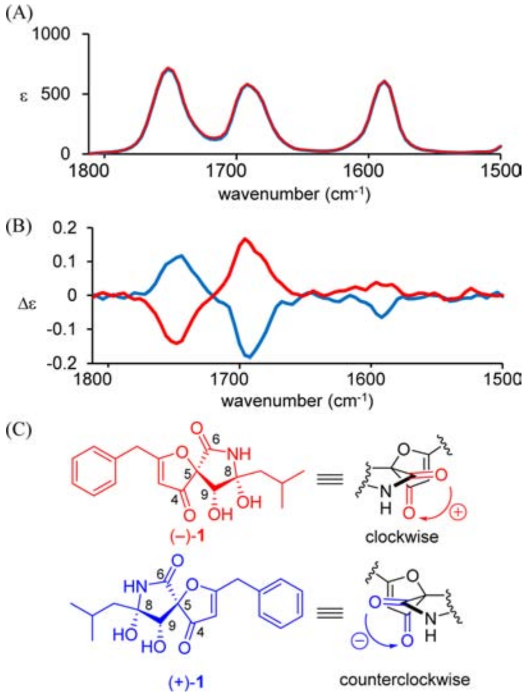


Figure 4. Determination of absolute configurations of (−)-**1** and (+)-**1**. IR (A) and VCD (B) spectra of (−)-**1** (red) and (+)-**1** (blue). The IR and VCD spectra were measured in $CDCl_3$ (3.3×10^{-2} M, *l* = 100 μm) for 2 and 90 min, respectively. (C) Schematic structures for (−)-**1** and (+)-**1**.

In conclusion, we have developed an efficient method for the construction of *α*,*β*-epoxy-*γ*-lactams via the Darzens reaction of *α*-bromo-*β*-ketoamides with glyoxals. This method has been successfully applied to several *γ*-lactam derivatives, including (±)-epolactaene and the key intermediate for berkeleyamide D. The key features of our newly developed synthesis of berkeleyamide D include the construction of the core spiro ring system by a C-acylation reaction followed by spirocyclization involving an epoxide ring-opening reaction. After separation by optical resolution of synthetic (±)-**1** using chiral HPLC, the absolute configurations of (+)-**1** and (−)-**1** were determined by the VCD exciton chirality method.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: kuramoch@kpu.ac.jp.

Notes

The authors declare no competing financial interest.

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(12) Because of the steric hindrance, 2-propanol should attack the iminium ion from the opposite side of the adjacent epoxide.

(13) The 8,9-*cis*-diol (±)-**1** was solely obtained by hydrolysis of aminal **10**. Formation of (±)-**1** can be explained by the difference in thermodynamic stability between **1** and 8-*epi*-**1**. Given that the hemiaminal formation is a reversible process, the thermodynamically stable product should be obtained. Density functional theory (DFT) calculations at the B3LYP/6-311+G(d,p) level indicated that the lowest energy conformation of **1** was more stable than that of 8-*epi*-**1** by 7.2 kcal/mol following zero-point energy corrections.

(14) The ^{1}H and ^{13}C NMR spectra of synthetic **1** were in agreement with those of natural **1**, which are provided in the Supporting Information of ref 1. The ^{1}H NMR assignments for the methine (δ 1.95, m) and methylene (δ 1.90, m and 1.61, m) protons of the isobutyl group in our synthetic **1** were different from those reported in natural berkeleyamide D (δ 1.92, m for the methine, and δ 1.88, m, 2H for the methylene); see ref 1. Because a peak at 1.6 ppm appears in the ^{1}H NMR spectrum of natural **1**, the signals derived from the methylene protons of the isobutyl group have been incorrectly assigned in natural **1**.

(15) The absolute configuration of (−)-**1** was supported by a comparison of the experimental and calculated VCD spectra. See the Supporting Information.