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# The second generation synthesis of (±)-berkeleyamide D

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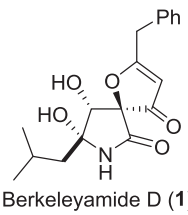
ABSTRACT

Previously, our group reported the first synthesis of (±)-berkeleyamide D, optical resolution of both enantiomers, and determination of their absolute configuration. The synthesis provided (±)-berkeleyamide D in a total of eight steps from commercially available materials. However, the synthesis included an inefficient acylation for the construction of the spirocyclic system, resulting in an overall yield of only 2.8%. In this paper, the second generation and improved synthesis of (±)-berkeleyamide D is reported. The present synthesis provides (±)-berkeleyamide D without the problematic acylation step. This synthesis requires 10 steps and proceeds in 11% overall yield from commercially available starting materials.


## 1. Introduction

Berkeleyamide D (**1**) was isolated in an optically active form from the acid lake fungus *Penicillium rubrum Stoll* (Fig. 1).[1] The specific rotation was reported to be $[\alpha]_D^{25}=-56.9$ (*c* 0.007, MeOH). This compound inhibits matrix metalloproteinase-3 and caspase-1. Our group reported the first synthesis of (±)-**1**, optical resolution of both enantiomers by chiral HPLC, and determination of their absolute configuration by the VCD exciton chirality method.[2] The synthesis is depicted in Scheme 1. According to the reported procedures, α-bromo-β-ketoamide **2**[3] and isobutylglyoxal (**3**)[4] were prepared from commercially available acetoacetamide and ethyl isovalerate, respectively. Darzens reaction of **2** with **3** gave α,β-epoxy-γ-lactam **4**. Hemiaminal **4** was protected as its isopropyl ether **5**. Acylation of **5** with phenylacetyl chloride gave the spirolactam **6**, together with the homodimer **7**. Finally, acidic hydrolysis of **6** afforded (±)-**1**. Although the total synthesis of (±)-**1** was achieved in only eight steps from commercially available starting materials, the overall yield was only 2.8% due to the low yield of **6** and the formation of byproduct **7** in the acylation of **5**. Herein, an improved synthesis of (±)-**1** is reported. Although the total steps of this improved synthesis increased from eight to ten, the overall yield increased from 2.8% to 11%.



Berkeleyamide D (**1**)

**Fig. 1.** Structure of berkeleyamide D (**1**).

## 2. Results and discussion

The modified retrosynthetic plan for (±)-**1** is shown in Scheme 2. Compound (±)-**1** can be prepared by deprotection of the ketal in **9**, followed by intramolecular spirocyclization of resultant **8**. Compound **9** may be synthesized by a Darzens reaction of α-bromo-β-ketoamide **10** with isobutylglyoxal (**3**). The use of **10** as a substrate for the Darzens reaction would enable us to avoid the problematic acylation in the previous synthesis.

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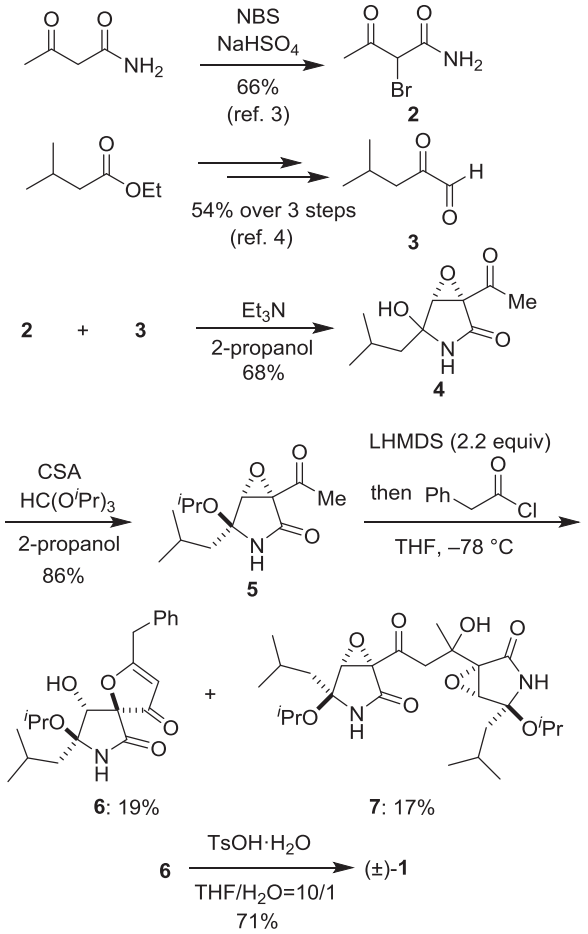
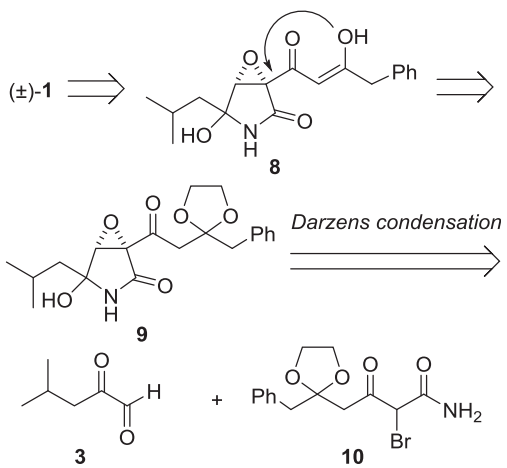
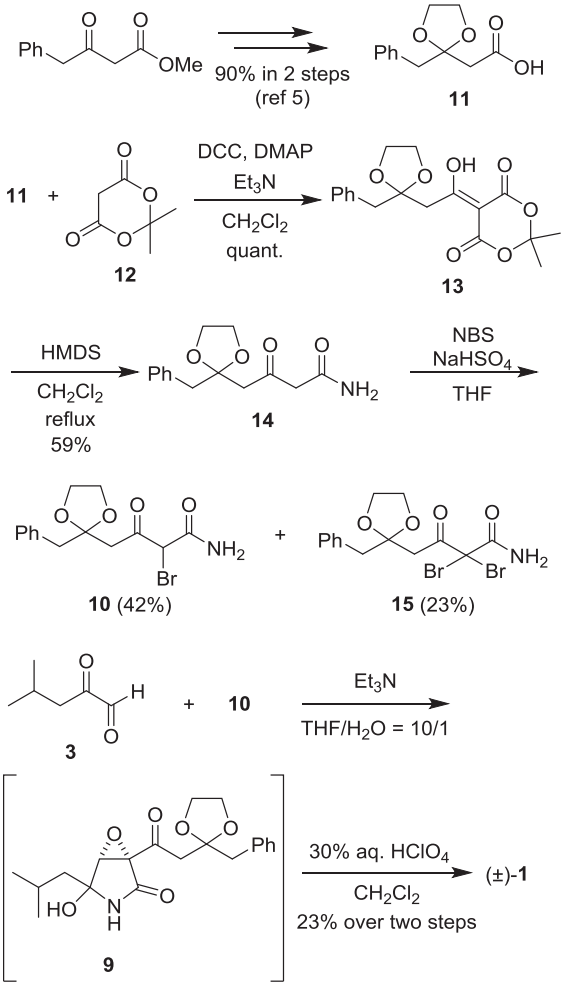



**Scheme 1.** Our previous synthesis of (±)-berkeleyamide D (**1**).




**Scheme 2.** Modified retrosynthetic approach toward (±)-**1**.

The forward synthesis of (±)-**1** according to the modified retrosynthetic plan is depicted in Scheme 3. Carboxylic acid **11** was prepared from commercially available methyl 3-oxo-4-phenylbutyrate according to the reported protocol.[5] Coupling of **11** with 2,2-dimethyl-1,3-dioxane-4,6-dione (**12**) in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) furnished **13**.[6] Amidation of **13** with hexamethyldisilazane (HMDS) gave β-ketoamide **14**. Bromination of **14** with *N*-bromosuccinimide (NBS) in the presence of sodium hydrogen sulfate afforded monobromide **10** and dibromide **15** in 42% and 23% yields, respectively. Darzens condensation between **3** and **10** with triethylamine gave **9**. Judging from thin layer chromatography (TLC) analysis, the reaction provided **9** in only a moderate yield, together with unidentified byproducts. Furthermore, compound **9** was unstable and decomposed during evaporation of the solvent under vacuum. Thus, after the reaction was quenched by the addition of water, compound **9** was extracted with dichloromethane. Then, the organic layer was concentrated to a certain volume, and the resultant solution was used in the next reaction. Treatment of the crude product with 30% aqueous perchloric acid[7] afforded (±)-**1** in 23% yield. The synthetic route presented in Scheme 3 provided (±)-**1** in 10 steps and in 2.8% overall yield from commercially available ethyl isovalerate and methyl 3-oxo-4-phenylbutyrate. Compared with the previous synthesis, neither the total step count nor overall yield was improved. Because the preparation of (±)-**1** from **3** and **10** suffered from low yield, we further investigated an alternative synthetic route to (±)-**1**.




**Scheme 3.** Synthesis of (±)-**1** by the modified synthetic approach.

To improve the overall yield of (±)-**1**, an alternative retrosynthetic approach toward (±)-**1** was planned (Scheme 4).[8] Compound (±)-**1** can be prepared from an intramolecular spirocyclization of **8**, which in turn can be obtained by removal of the Boc and ketal groups in epoxyimide **16**. Compound **16** can be synthesized by a Darzens condensation between **3** and **17**.

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