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The second generation synthesis of (±)-berkeleyamide D

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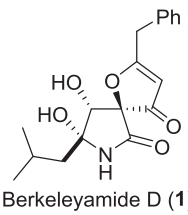
ABSTRACT

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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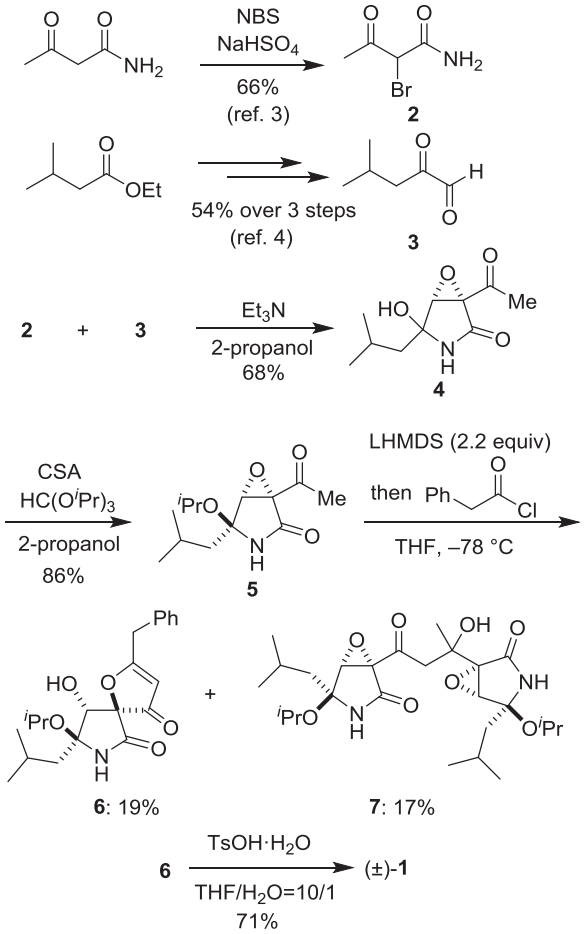
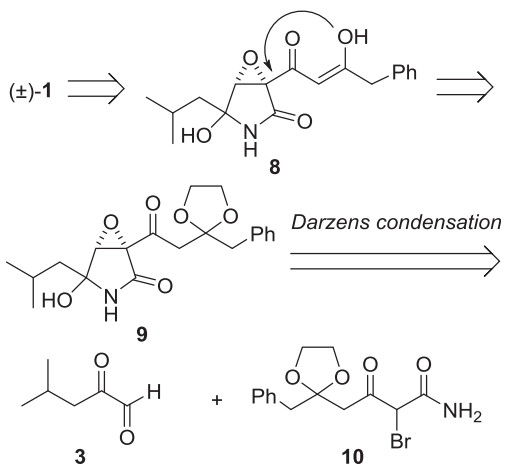
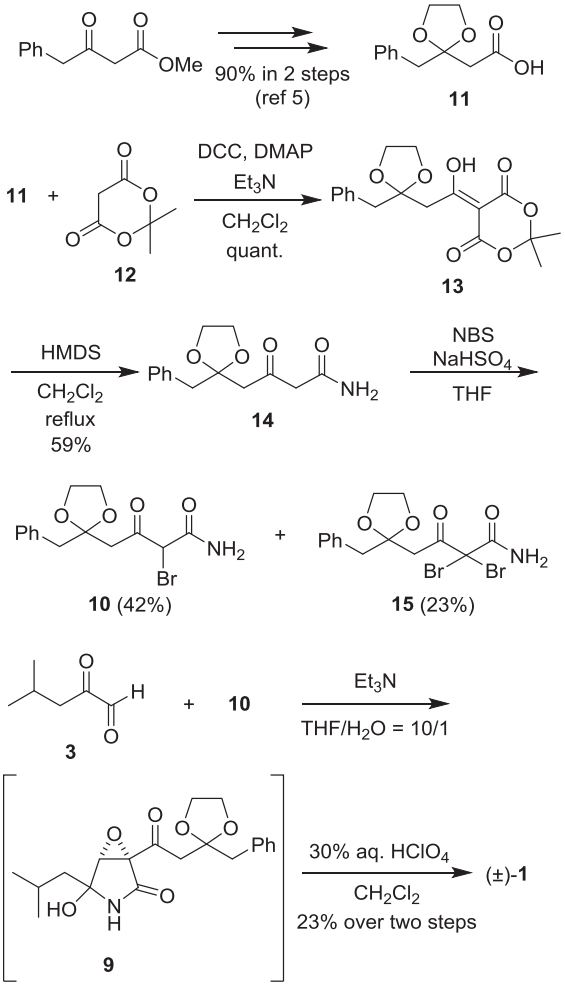


Scheme 1. Our previous synthesis of (±)-berkeleyamide D (**1**).



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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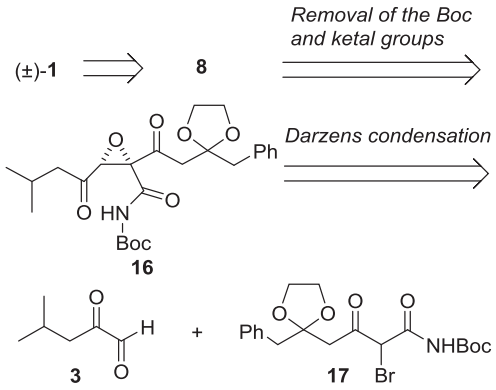
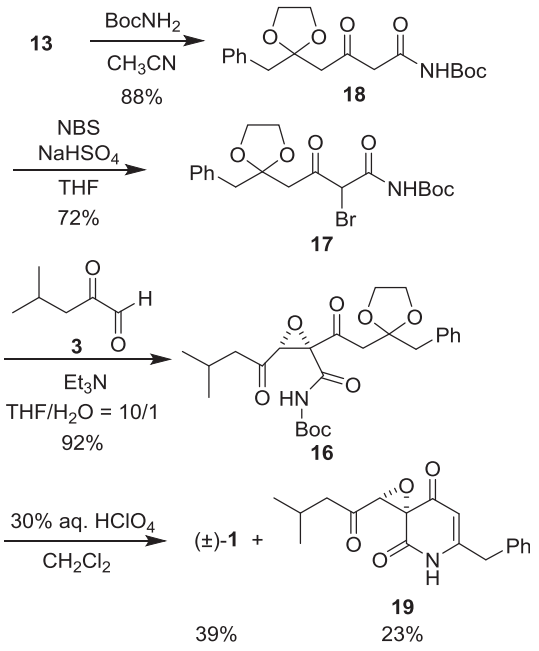
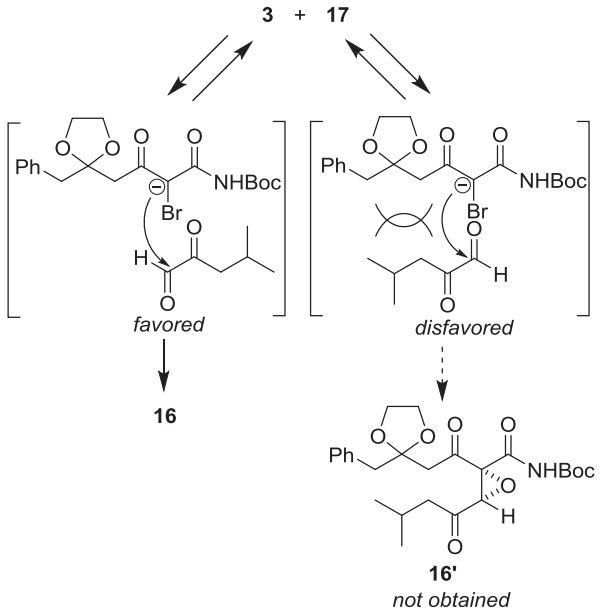


Scheme 4. Alternative retrosynthetic approach toward (±)-**1**.

The synthesis of (±)-**1** according to the alternative retrosynthetic plan is shown in Scheme 5. Treatment of **13** with *tert*-butyl carbamate gave **18** in a high yield. Bromination of **18** with NBS under acidic conditions gave monobromide **17** in 72% yield. Excess bromination was prevented by the steric effect of the bulky Boc group in **17**. Darzens condensation of **17** with **3** gave the desired epoxyimide **16** in a high yield with perfect stereoselectivity. Compound **16** was stable and easily purified by silica gel chromatography. The high stereoselectivity of the Darzens condensation between **3** and **17** is explained by the steric repulsion between the substituents on **3** and **17** (Scheme 6). The formation of isomer **16**′ is disfavored by the steric hindrance between the isobutyl group in **3** and the side-chain moiety in **17**.[2] Finally, treatment of **16** with 30% aqueous perchloric acid in dichloromethane afforded (±)-**1** and **19** in 39% and 23% yields, respectively. The synthetic route presented in Scheme 5 provided (±)-**1** in a total of 10 steps and 11% overall yield from commercially available ethyl isovalerate and methyl 3-oxo-4-phenylbutyrate. Compared with the previous synthesis, the overall yield was improved.

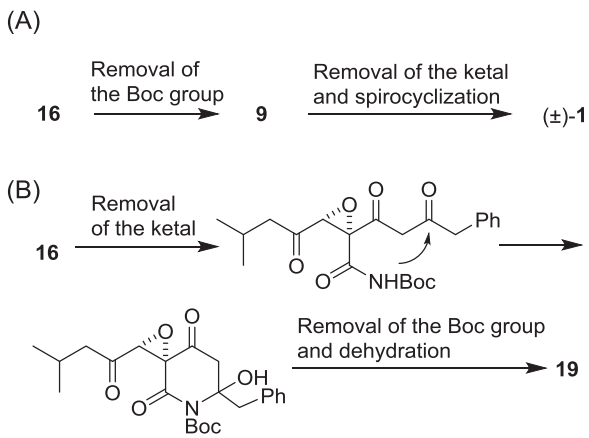


Scheme 5. Synthesis of (±)-**1** by the alternative synthetic plan.

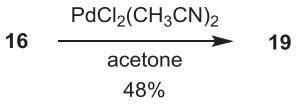


Scheme 6. Explanation for the stereoselectivity of the Darzens condensation between **3** and **17**.

The proposed reaction pathways for the formation of (±)-**1** and **19** from **16** are outlined in Scheme 7A and B, respectively. Removal of the Boc group in **16** furnishes **9**, which is followed by removal of the ketal group and subsequent spirocyclization to produce (±)-**1** (Scheme 7A). The order of the deprotection steps is critical. When the ketal group is removed before the Boc group, **19** is formed instead of (±)-**1** (Scheme 7B). The intermediate *δ*-lactam formed after the removal of the ketal and cyclization undergoes deprotection of the Boc group and subsequent dehydration.[8] This alternative reaction was separately confirmed by deprotection of the ketal in **16** with bis(acetonitrile)dichloropalladium(II)[9] in acetone to furnish **19** in 48% yield (Scheme 8). Bis(acetonitrile)dichloropalladium(II) is a mild Lewis acid, which is reported to catalyze acetal/ketal hydrolysis/exchange reactions.[9] Under these conditions, cleavage of the ethylene glycol ketal in **16** will occur first, then deprotection of the Boc group and dehydration will proceed to give **19**. Compound **19** is a derivative of (−)-flavipucine, an alkaloid from Aspergillus flavipes (Fig. 2).[10]



Scheme 7. Proposed mechanism for the formation of (±)-**1** (A) and **19** (B).



Scheme 8. Transformation of **16** into **19**.

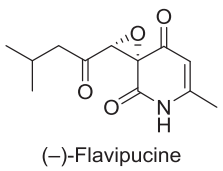


Fig. 2. Structure of (−)-flavipucine.

3. Conclusion

In this paper, the second generation synthesis of (±)-berkeleyamide D (**1**) is reported. This synthesis provides (±)-**1** in a total of 10 steps and 11% overall yield from commercially available starting materials. Compared with our previous synthesis, the overall yield was improved. The key feature of the improved synthesis includes a stereoselective Darzens condensation between **3** and **17** and subsequent transformation of the resultant epoxyimide **16** into (±)-**1**. Further investigations toward the asymmetric version of the Darzens condensation are currently underway and will be reported in due course.

4. Experimental section

4.1. General experimental procedures

Melting point (Mp) data were determined with a Yanaco MP-3S instrument and were uncorrected. IR spectra were recorded on a Horiba FT210 spectrometer, using NaCl (neat) or KBr pellets (solid). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Biospin Avance 400 (400 and 100 MHz, respectively) using $CDCl_3$ or CD_3OD as the solvent. Chemical shift values are expressed in δ (ppm) relative to tetramethylsilane (TMS, δ 0.00 ppm) or the residual solvent resonance ($CDCl_3$: δ 77.0 for ^{13}C NMR; CD_3OD: δ 3.30 for ^{1}H NMR; CD_3OD: δ 49.0 for ^{13}C NMR). Data are reported as follows: chemical shifts, multiplicity (s=singlet, d=doublet, dd=double doublet, br=broad, m=multiplet), coupling constants (*J*; Hz), and integration. MS spectrum were obtained on a Fourier transformation-ion cyclotron resonance-mass spectrometer, Bruker solariX (FT-ICR-MS), by using electrospray ionization (ESI) or a JEOL JMS-SX102A using fast atom bombardment (FAB).

4.2. Preparation of known compounds

*4.2.1. Isobutylglyoxal (**3**).* The titled compound was prepared by the procedure reported by Wendler and co-workers.[4] 2-Hydroxy-5-methyl-1-(methylsulfinyl)hexan-3-one was synthesized from ethyl isovalerate (35 g, 0.269 mol) and sodium methylsulfinylmethylide.[11] Without purification, the crude ester was treated with concentrated HCl solution (97 mL) in H_2O (614 mL) to give 1-hydroxy-4-methyl-1-(methylthio)-2-pentanone (31 g, 71%).[12] Treatment of 1-hydroxy-4-methyl-1-(methylthio)-2-pentanone (4.60 g, 28.4 mmol) with copper(II) acetate monohydrate (5.72 g, 28.6 mmol) in CH_2Cl_2 (130 mL) afforded **3** (2.45 g, 76%).[12]

*4.2.2. 2-(2-Benzyl-1,3-dioxolan-2-yl)acetic acid (**11**).* The titled compound was prepared by the procedure reported by Blackwell and co-workers.[5] Treatment of methyl 3-oxo-4-phenylbutyrate (8.95 g, 46.6 mmol) with ethylenedioxybis(trimethylsilane) (13.5 mL, 58.3 mmol) in the presence of trimethylsilyl triflate (1.72 mL, 9.32 mmol) in CH_2Cl_2 (110 mL) gave methyl 2-(phenylmethyl)-1,3-dioxolane-2-acetate (10.6 g, 96%). Hydrolysis of the ester (6.0 g, 25.4 mmol) with a 1 M aqueous NaOH solution (150 mL) in MeOH (75 mL) gave **11** (5.31 g, 94%).

4.3. Synthesis and characterization of new compounds

*4.3.1. 5-{2-(2-Benzyl-1,3-dioxolan-2-yl)-1-hydroxyethylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (**13**).* DCC (960 mg, 4.95 mmol) was added to a solution of **11** (1.00 mg, 4.50 mmol), triethylamine (0.63 mL, 4.52 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (**12**) (649 mg 4.50 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 16 h. The precipitated *N*,*N*′-dicyclohexylurea was filtered off and washed with $CHCl_3$. The filtrate was diluted with a 0.5 M aqueous HCl solution (40 mL) and $CHCl_3$. After the layers were separated, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give **13** (1.58 g, quant.) as pale yellow solid. Mp=45–46 °C; IR (KBr) ν_{max}=2983, 2960, 2893, 1736, 1653, 1587, 1437, 1404, 1298, 1255, 1207, 1176, 1157, 1165, 1039, 955, 923, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.3 (s, 1H), 7.27, (m, 5H), 3.89 (m, 2H), 3.61 (m, 2H), 3.55 (s, 2H), 3.09 (s, 2H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 170.3, 160.4, 135.5, 130.8 (2C), 127.8 (2C), 126.5, 109.7, 104.7, 94.0, 65.4 (2C), 44.5, 42.6, 26.6 (2C); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{20}NO_7Na$ ([M+Na]$^+$) 371.1011, found 371.1098.

*4.3.2. 4-(2-Benzyl-1,3-dioxolan-2-yl)-3-oxobutanamide (**14**).* A solution of **13** (1.58 g, 4.54 mmol) and HMDS (1.00 mL, 4.50 mmol) in CH_2Cl_2 (45 mL) was stirred under reflux for 30 min. The reaction mixture was cooled to room temperature. MeOH (15 mL) was added to a solution and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc=1/1–1/4) to give **14** (691 mg, 59%) as a 8:1 mixture of keto form and enol form as a white solid. Mp=63–64 °C; IR (neat) ν_{max}=3442, 3352, 3199, 3030, 2978, 2893, 1714, 1678, 1608, 1495, 1454, 1429, 1381, 1323, 1257, 1225, 1190, 1103, 1030, 951, 754, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) keto form: δ 7.26 (m, 5H), 6.98 (br s, 1H), 6.05 (br s, 1H), 3.92 (m, 2H), 3.75 (m, 2H), 3.48 (s, 2H), 2.99 (s, 2H), 2.82 (s, 2H); enol form: δ 13.8 (br s, 1H), 7.26 (m, 5H), 4.99 (s, 1H), 3.87 (m, 2H), 3.61 (m, 2H), 3.02 (s, 2H), 2.49 (s, 2H), two exchangeable NH peaks were not observed; ^{13}C NMR (100 MHz, $CDCl_3$) keto form: δ 203.6, 168.1, 135.5, 130.6 (2C), 128.0 (2C), 126.7, 109.2, 65.0 (2C), 50.7, 50.0, 43.9; enol form: δ 173.0 (2C),136.0, 130.8 (2C), 127.8 (2C), 126.4, 109.7, 92.4, 65.3 (2C), 44.1, 43.9; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{17}NO_4Na$ ([M+Na]$^+$) 262.1074, found 262.1086.

*4.3.3. 4-(2-Benzyl-1,3-dioxolan-2-yl)-2-bromo-3-oxobutanamide (**10**) and 4-(2-benzyl-1,3-dioxolan-2-yl)-2,2-dibromo-3-oxobutanamide (**15**).* NBS (466 mg, 2.62 mmol) was added in several portions to a solution of **14** (690 mg, 2.62 mmol) and $NaHSO_4$ (79.0 mg 0.660 mmol) in THF (30 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc=2/1) to give **10** (376 mg, 42%) as a 5:1 mixture of keto form and enol form as a white solid and **15** (249.9 mg, 23%) as a white solid.

10: Mp=88–89 °C, IR (KBr) ν_{max}=3346, 3180, 2895, 1741, 1666, 1618, 1400, 1360, 1342, 1277, 1228, 1153, 1128, 1028, 959 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) keto form: δ 7.26 (m, 5H), 6.67 (br s, 2H), 5.01 (s, 1H), 3.90 (m, 2H), 3.71 (s, 2H), 3.09 (m, 2H), 3.01 (s, 2H); enol

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form: δ 14.6 (br s, 1H), 7.26 (m, 5H), 6.35 (br s, 2H), 3.09 (m, 2H), 3.59 (m, 2H), 3.09 (m, 2H), 2.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) keto form: δ 197.2, 166.5, 135.3, 130.6 (2C), 128.0 (2C), 126.7, 109.3, 65.2, 65.1, 49.6, 47.6, 44.0; enol form: δ 171.7, 171.6, 135.8, 130.9 (2C), 127.7 (2C), 126.4, 110.0, 88.0, 65.2, 65.3, 44.2, 43.1; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}{}^{79}BrNO_4Na$ ($[M+Na]^+$) 364.0155, found 364.0155.

15: Mp=110–112 °C, IR (KBr) ν_{max}=3446, 3299, 3236, 3056, 3029, 3004, 2962, 2929, 2881, 1737, 1689, 1583, 1496, 1436, 1389, 1365, 1346, 1313, 1259, 1215, 1145, 1113, 1080, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 6.72 (br s, 1H), 6.13 (br s, 1H), 3.93 (m, 2H), 3.69 (s, 2H), 3.28 (s, 2H), 3.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 165.4, 135.8, 130.8 (2C), 128.0 (2C), 126.7, 109.3, 65.4 (2C), 62.6, 43.9, 43.2; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{15}{}^{79}Br_2NO_4Na$ ($[M+Na]^+$) 441.9260, found 441.9262.

*4.3.4. (±)-Berkeleyamide D (**1**).* Triethylamine (9.4 μL, 67.4 μmol) was added to a solution of **10** (23.0 mg, 67.2 μmol) and isobutylglyoxal (**3**) (8.4 mg, 73.6 μmol) in a 10:1 mixture of THF and H_2O (2.2 mL). The mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of water, and the mixture was diluted with CH_2Cl_2. After the layers were separated, the organic layer was washed with water twice, brine, dried over Na_2SO_4, and concentrated to a volume of 2 mL.

A 30% aqueous $HClO_4$ solution (0.10 mL, 52.8 μmol) was added to the solution of the crude product in CH_2Cl_2 (2 mL) at room temperature, and the mixture was stirred for 3 days. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC (hexane/EtOAc=1/1) to give (±)-**1** (5.1 mg, 23% over two steps) as a white solid. Mp=142–143 °C, IR (KBr) ν_{max}=3396, 3210, 3034, 2951, 1732, 1674, 1574, 1454, 1387, 1352, 1277, 1180, 1149, 1126, 964, 852, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.77 (br s, 1H), 5.51 (d, *J*=0.8 Hz, 1H), 5.37 (d, *J*=0.4 Hz, 1H), 4.43 (d, *J*=10.4 Hz, 1H), 4.02 (d, *J*=17.6 Hz, 1H), 3.96 (d, *J*=17.6 Hz, 1H), 3.06 (d, *J*=10.4 Hz, 1H), 1.94 (m, 1H), 1.88 (m, 1H), 1.61 (m, 1H), 1.02 (d, *J*=6.4 Hz, 3H) 1.01 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 197.8, 164.0, 133.2, 129.2 (2C), 129.0 (2C), 127.8, 104.4, 95.3, 84.9, 75.2, 45.5, 37.4, 24.0, 23.9, 23.8; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{21}NO_5Na$ ($[M+Na]^+$) 354.1312, found 354.1312.

*4.3.5. tert-Butyl {4-(2-benzyl-1,3-dioxolan-2-yl)-3-oxobutanoyl}carbamate (**18**).* A solution of **13** (1.54 g, 4.42 mmol) and *tert*-butyl carbamate (518 mg, 4.42 mmol) in acetonitrile (45 mL) was stirred under reflux for 30 min. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography (hexane/$CHCl_3$/EtOAc=6/3/1) to give **18** (1.41 g, 88%) as a 2:1 mixture of keto form and enol form as a white solid. Mp=65–67 °C, IR (KBr) ν_{max}=3248, 3209, 2978, 2895, 1753, 1622, 1485, 1456, 1371, 1336, 1292, 1232, 1149, 1091, 1064, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) keto form: δ 7.90 (br s, 1H), 7.26 (m, 5H), 3.95 (m, 4H), 3.72 (m, 2H), 3.01 (s, 2H), 2.86 (s, 2H), 1.47 (s, 9H); enol form: δ 13.82 (br s, 1H), 7.39 (br s, 1H), 7.26 (m, 5H), 6.27 (s, 1H), 3.95 (m, 2H), 3.62 (m, 2H), 3.05 (s, 2H), 2.60 (s, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) keto form: δ 200.9, 167.9, 150.3, 135.8, 130.7 (2C), 128.0 (2C), 126.6, 109.2, 82.8, 65.1 (2C), 52.0, 50.6, 43.8, 27.9 (3C); enol form: δ 178.1, 172.1, 150.0, 135.9, 130.7 (2C), 128.0 (2C), 126.4, 109.6, 92.6, 82.5, 65.3 (2C), 44.4, 44.2, 28.0 (3C); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{25}NO_6Na$ ($[M+Na]^+$) 386.1574, found 386.1574.

*4.3.6. tert-Butyl (4-(2-benzyl-1,3-dioxolan-2-yl)-2-bromo-3-oxobutanoyl)carbamate (**17**).* NBS (608 mg, 3.42 mmol) was added in several portions to a solution of **18** (1.31 g, 3.60 mmol) and $NaHSO_4$ (108 mg 0.900 mmol) in THF (50 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=6/1) to give **17** (1.14 g, 72%) as colorless oil. IR (neat) ν_{max}=3392, 3269, 3020, 2981, 2935, 2985, 1784, 1474, 1713, 1493, 1456, 1394, 1369, 1319, 1234, 1145, 1078, 1032, 848 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (m, 5H), 3.89 (m, 2H), 3.67 (m, 2H), 3.11 (d, *J*=16.0 Hz, 1H), 3.04 (d, *J*=16.0 Hz, 1H), 3.04 (s, 2H), 1.50 (s, 9H), the peak derived from H-2 was not observed; ^{13}C NMR (100 MHz, CD_3OD) δ 196.7, 167.2, 152.8, 137.4, 131.9 (2C), 128.9 (2C), 127.6, 110.3, 83.9, 66.2, 66.1, 47.7, 44.5, 28.2 (3C), the peak derived from C-2 was not observed; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{24}{}^{79}BrNO_6Na$ ($[M+Na]^+$) 464.0679, found 464.0680.

*4.3.7. tert-Butyl [(2RS,3RS)-2-{2-(2-benzyl-1,3-dioxolan-2-yl)acetyl}-3-(3-methylbutanoyl)oxirane-2-carbonyl]carbamate (**16**).* Triethylamine (15.3 μL, 0.110 mmol) was added to a solution of **17** (48.3 mg, 0.109 mmol) and isobutylglyoxal (**3**) (15.1 mg, 0.132 mmol) in a 10:1 mixture of THF and H_2O (2 mL). The mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=5/1) to give **16** (47.8 mg, 92%) as a colorless solid. Mp=34–38 °C; IR (KBr) ν_{max}=3276, 2960, 2933, 1788, 1753, 1716, 1493, 1458, 1396, 1369, 1315, 1236, 1151, 1065, 1032, 854, cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (m, 5H), 4.14 (s, 1H), 3.88 (m, 2H), 3.67 (m, 2H), 3.06 (d, *J*=18.0 Hz, 1H), 3.02 (d, *J*=18.0 Hz, 1H), 2.89 (d, *J*=15.6 Hz, 1H), 2.72 (d, *J*=15.6 Hz, 1H), 2.49 (dd, *J*=18.0, 7.2 Hz, 1H), 2.45 (dd, *J*=18.0, 6.4 Hz, 1H), 2.09 (m, 1H), 1.46 (s, 9H), 0.92 (d, *J*=7.2 Hz, 3H), 0.90 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 203.3, 200.0, 166.3, 152.6, 137.4, 131.9 (2C), 128.9 (2C), 127.6, 110.6, 83.8, 68.9, 66.2, 66.1, 62.0, 50.3, 44.9, 42.9, 28.2 (3C), 24.7, 22.84, 22.80; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{33}NO_8Na$ ($[M+Na]^+$) 489.2099, found 489.2097.

*4.3.8. (±)-Berkeleyamide D (**1**) and (2RS,3RS)-6-benzyl-2-(3-methylbutanoyl)-1-oxa-5-azaspiro[2.5]oct-6-ene-4,8-dione (**19**).* A 30% aqueous $HClO_4$ solution (0.10 mL, 52.8 μmol) was added to a solution of **16** (21.4 mg, 45.0 μmol) in CH_2Cl_2 (2 mL) at room temperature, and the mixture was stirred for 3 days. The reaction was quenched by the addition of water, and the mixture was diluted with $CHCl_3$. After the layers were separated, the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=4/1) to give (±)-**1** (5.80 mg, 39%) and **19** (3.20 mg, 23%).

19: Mp=55–62 °C; IR (KBr) ν_{max}=3479, 3375, 3089, 2958, 1732, 1714, 1651, 1612, 1508, 1456, 1421, 1396, 1363, 1340, 1267, 1144, 1030, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.63 (m, 3H), 7.23 (m, 2H), 5.64 (s, 1H), 3.84 (s, 1H), 3.75 (d, *J*=16.4 Hz, 1H), 3.69 (d, *J*=16.4 Hz, 1H), 2.71 (dd, *J*=17.2 Hz, 5.6 Hz, 1H), 2.66 (dd, *J*=17.2, 7.2 Hz, 1H), 2.16 (m, 1H), 0.96 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 186.3, 167.2, 156.8, 132.6, 129.5 (2C), 129.3 (2C), 128.5, 107.0, 68.6, 59.9, 49.4, 40.4, 23.8, 22.8, 22.3; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}NO_4Na$ ($[M+Na]^+$) 336.1206, found 336.1207.

*4.3.9. Transformation of **16** into **19**.* $PdCl_2(CH_3CN)_2$ (44.0 mg, 0.170 mmol) was added to a solution of **16** (61.0 mg, 0.128 mmol) in acetone (3 mL) at room temperature, and the mixture was stirred for 4 days. The reaction was quenched by the addition of water, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and

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concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=9/2) to give **19** (19.3 mg, 48%).

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Supplementary data

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