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Total Synthesis of (±)-Berkeleyone A

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Supporting Information

ABSTRACT: A 13-step total synthesis of the fungal meroterpenoid berkeleyone A is reported. The molecular skeleton is formed using the first examples of two critical construction reactions: (1) an epoxide-initiated, β-ketoester-terminated polycyclization, and (2) an isomerization−cyclization cascade to generate the remaining bicyclo[3.3.1]nonane framework. The resulting 6-step synthesis of the carbocyclic core of the berkeleyone natural products has been used to access protoaustinoid A and berkeleyone A, and will aid future biosynthetic investigations into the origin of related natural products.

Extremophiles isolated from the Berkeley Pit lake in Butte, Montana thrive in the remnants of an abandoned open-pit copper mine that has since filled with water, now pH 2.6 and discolored by toxic heavy metals.[1] This EPA Superfund site has facilitated the accelerated evolution of dozens of bacteria and fungi, including *Penicillium rubrum*, which produces the meroterpenoid berkeleyone A (**1**) when grown in the toxic environment of the Berkeley Pit lake.[2] Additionally, a number of related downstream metabolites have been shown to arise from dioxygenase-catalyzed oxidative skeletal reorganizations of berkeleyones, as determined through the pioneering genome mining and mechanistic studies of Abe,[3] Wang,[4] and others.[5,6]

Subtle differences in the sequences of nonheme iron-dependent dioxygenases lead to dramatically different chemical outcomes, including the transformation of berkeleyone A (**1**) to either the 7-membered ring containing berkeleydione (**3**),[3d] also isolated from the Berkeley Pit,[2a] or the spirocyclic preaustinoid A3 (**4**)[3b] and ultimately austinol (**5**) (Figure 1).[3b,4] These divergent pathways are each hypothesized to initiate by oxidation of C5, but as Abe and co-workers have noted, understanding the precise roles of these dioxygenases has been impeded by limited access to molecular analogs that could be cocrystallized with the dioxygenase enzymes.[3d] The structural diversity of this class of meroterpenoids leads to attendant disparate functional activities of the berkeleyone family of natural products.[6] Among the most exciting observations is that berkeleyone A inhibits caspase-1,[2b] a protein involved in neuroinflammation associated with Alzheimer's and Parkinson's diseases,[7] as well as a number of other conditions.[8]

Although biological synthesis has provided laboratory methods for producing these naturally occurring compounds,[3−6] chemical synthesis[9,10] provides a complementary approach to access unnatural derivatives that can be used to aid biosynthetic mechanistic studies, and may lead to improved caspase-1 inhibition through structure−activity relationship studies. Therefore, a synthetic route to access the carbocyclic architecture of the

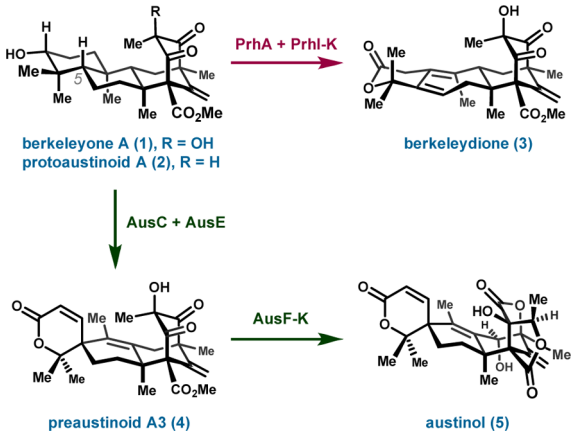

Figure 1. Protoaustinoid A (**2**) is a biosynthetic precursor to berkeleyone A (**1**), berkeleydione (**3**), preaustinoid A3 (**4**), and austinol (**5**).

berkeleyone natural products by a concise chemical process would allow the core structure to be altered to a range of natural and unnatural materials. From a chemical synthesis perspective, the most challenging aspects of berkeleyone A (**1**) include the three quaternary centers about the C-ring, two of which are vicinal, and a highly oxidized D-ring lacking a single hydrogen atom substituent.

The highly oxidized D-ring of berkeleyone A (**1**), derived from the aromatic polyketide 3,5-dimethylorsellinic acid (DMOA), was retrosynthetically reduced to the tetracyclic structure **6** (Figure 2). In a forward sense, intermediate **6** would serve as a branching point for introducing the distinguishing functionality of the berkeleyone D-ring, to access alternative structures with improved ability to mitigate neuroinflammation, as well as provide materials to aid biosynthetic investigations.

Removal of two of the three quaternary centers about the C-ring of tetracycle **6** via sequential cleavage of the central two carbon−carbon bonds of the DMOA-derived segment was envisioned through identification of (1) the oxidative radical cyclization transform keyed by the ancillary carbomethoxy group,[11] and (2) the subsequently revealed Claisen and allylation retrons[12] leading to tricycle **7**. Topological analysis of **7** suggested the strategic use of a polyene cyclization,[13] although disconnection directly to the acyclic precursor **8** clarifies that an epoxide initiating group and a β-ketoester terminating group would be the most logical functional groups to employ.[14,15]

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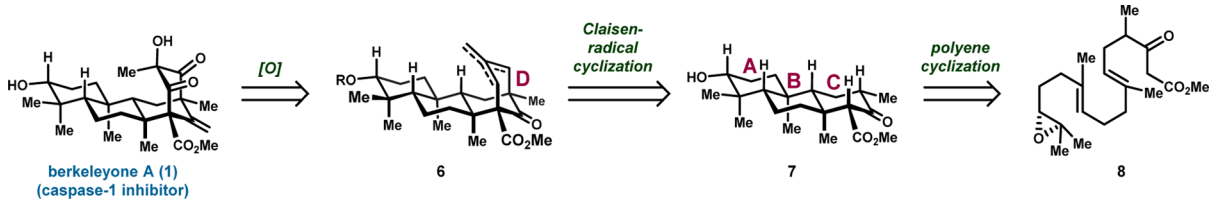

Figure 2. Retrosynthetic analysis of berkeleyone A (**1**) to the polycyclization precursor **8**.

Unfortunately, polycyclization events that initiate with epoxide groups are most commonly conducted using Lewis-acids, whereas β-ketoester terminating groups generally require Brønsted-acids to facilitate carbon-based, rather than oxygen-based, nucleophilic attack by the β-ketoester.[16] Perhaps because of these opposing requirements, analysis of the literature indicates that, to the best of our knowledge, no such cyclization reactions have previously been reported, and instead multistep solutions are pursued.[16] Such a transformation, were it possible, would rapidly lead to the necessary tricycle **7** from readily available starting materials.

Following this logic, we advanced a strategy that included the above tricyclization reaction. We commenced our studies by synthesizing the linear polyolefin **8** from commercially available farnesyl bromide (**9**) and the Weiler dianion derived from methyl 3-oxopentanoate. Treatment of the allylation product with *meta*-chloroperbenzoic acid (*m*-CPBA) resulted in a selective epoxidation reaction to produce the epoxide **8** in 51% yield (Scheme 1). It is noteworthy that the most distal, most electron-rich alkene underwent selective oxidation to produce **8**, while leaving the oxidation-prone β-ketoester intact.[17] Although the alternate order of experimental operations is viable (i.e., allylation with 10,11-epoxyfarnesyl bromide) and would be amenable to enantioselective synthesis, the racemic route used this convenient approach.

With the precursor **8** in hand, a broad examination of Lewis- and Brønsted-acid promoters was conducted, but our initial efforts were plagued by the formation of a range of undesired byproducts consistent with previous reports on similar cyclization reactions.[16] It was ultimately found that the yellow ether-solvated complex of $HFeCl_4$,[18] prepared in situ by treating a heterogeneous mixture of $FeCl_3$ in CH_2Cl_2 with anhydrous HCl in Et_2O, elicited the desired cyclization reaction to afford tricyclic compound **7** in 39% yield. This unique Brønsted acid with the noncoordinating $[FeCl_4]^-$ anion was found to be superior to either $FeCl_3$ or anhydrous HCl alone, in addition to the numerous other conditions explored. The majority of the berkeleyone scaffold, 3 carbon−carbon bonds and 6 stereogenic centers, is constructed in this key cyclization. To the best of our knowledge, this transformation is the first example of an epoxide-initiated, β-ketoester terminated polycyclization that provides the desired mode of cyclization at carbon.[16]

The early introduction of the carbomethoxy group conveniently allows for both the direct introduction of the farnesyl-derived component using the Weiler dianion, and the formation of the remaining carbon ring using the β-ketoester functional group. Assembly of the final ring began with forming the starting material for the Claisen cyclization through O-allylation to afford the conjugated isomer **11** after treatment of TBS-protected **10** with Cs_2CO_3 and 3-bromo-2-methylpropene in *N*,*N*-dimethylacetamide (DMA). However, to utilize the propensity of β-ketoester-derived enolates to undergo single-electron oxidation during the ring-forming radical cyclization,[11] the alternative β,γ-alkene isomer was required. If an alkene isomerization could be promoted, then the ensuing Claisen rearrangement would reveal the desired enolizable β-ketoester, as opposed to the ketone that would result from Claisen cyclization without olefin transposition. Thus, the material obtained from the O-allylation after simple aqueous workup was dissolved in AcOH and heated to 120 °C: this resulted in double bond transposition to form **12** and Claisen rearrangement to provide intermediate **13**, which was poised to undergo radical cyclization. Gratifyingly, when freshly prepared $Mn(OAc)_3{\cdot}2H_2O$[19] was added to the reaction mixture, oxidative cyclization occurred to provide the product **6** in 44% yield as a mixture of alkene isomers that possess the bicyclo[3.3.1]nonane structure of berkeleyone A (**1**). This isomerization−cyclization approach forges the challenging vicinal quaternary centers of the C-ring and completes the essential framework of berkeleyone A (**1**) in two steps from tricycle **10**. This 6-step route to the carbocyclic skeleton of berkeleyone A (**1**) may serve as a suitable platform to access a library of berkeleyone structures for biosynthetic and biological investigation.

At this juncture, installation of the α-hydroxy-1,3-diketone was necessary and envisioned to occur through sequential allylic oxidations after olefination of ketone **6**. The mixture of isomers that results from the radical cyclization was subjected to Wittig olefination under modified salt-free ylide conditions to form the 1,1-disubstituted olefin in 44% yield as a single olefin isomer after chromatographic purification.[20] Standard methylene triphenylphosphorane preparations resulted in poor yields (0−17%). The Wittig product was then subjected to allylic oxidation by the complex derived from CrO_3 and 3,5-dimethylpyrazole (3,5-DMP),[21] to form enone **14** in 59% yield.

Conversion of the enone to the corresponding enoxysilane by conjugate reduction and trapping with a suitable electrophile would provide the substrate for the second allylic oxidation using Corey−Yu conditions.[22,23] However, reduction of enone **14** proved to be a significant challenge owing to chemoselectivity concerns arising from the 1,1-disubstitued alkene. In addition, the steric hindrance of the enone inflicted by the highly substituted bicyclic substrate led to low levels of reactivity and competitive 1,2-reduction. Conjugate reduction strategies using transition-metal or main-group hydrides, including L-Selectride, Stryker's reagent, and others, were unsuccessful in providing the desired ketone in appreciable amounts. However, we found that SmI_2 in the presence of TfOH was able to effect the 1,4-reduction selectively at low temperatures; by using TESOTf and water as a convenient source of TfOH we were able to obtain the desired ketone in 82% yield after aqueous workup. Although speculative at this juncture, the observed rate acceleration of enone reduction in the presence of TfOH may be due to a repartitioning of the mechanism to one that involves proton-coupled electron transfer.[24] Notably, the use of SmI_2 alone or with a number of standard additives (HMPA, H_2O, MeOH, *t*-BuOH, etc.) was less efficient.

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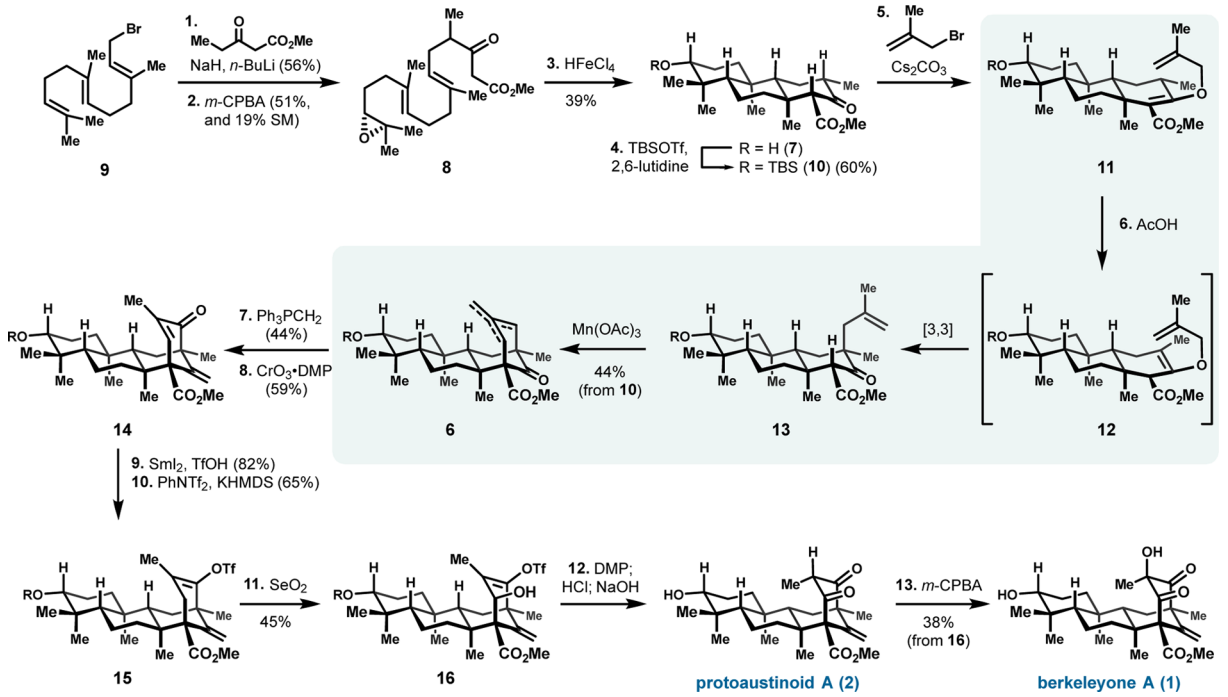
Scheme 1. Total Synthesis of Protoaustinoid A (2) and Berkeleyone A (1)[a]



[a]Reagents and conditions: (1) methyl 3-oxopentanoate (1.1 equiv), NaH (1.5 equiv), *n*-BuLi (1.1 equiv), THF (0.5 M), −45 → 0 °C, 1.75 h, 56%; (2) *m*-CPBA (1.0 equiv), CH_2Cl_2 (0.1 M), 0 °C, 50 m, 51% (9:1 dr) and 19% SM; (3) HCl (1.0 equiv), $FeCl_3$ (1.6 equiv), CH_2Cl_2−Et_2O (0.01 M), −78 → 23 °C, 12 h, 39%; (4) TBSOTf (1.4 equiv), 2,6-lutidine (1.6 equiv), CH_2Cl_2 (0.2 M), 0 → 23 °C, 1 h, 60%; (5) 3-bromo-2-methylpropene (2.2 equiv), Cs_2CO_3 (2.8 equiv), DMA (0.3 M), 40 °C, 12 h; (6) AcOH (0.2 M), 120 °C, 2 h; then $Mn(OAc)_3 \cdot 2H_2O$ (3.0 equiv), 60 °C, 2 h, 44% (2 steps); (7) Ph_3PCH_2 (20 equiv), PhMe (0.02 M), 90 °C, 24 h, 44%; (8) CrO_3 (103 equiv), 3,5-dimethylpyrazole (134 equiv), CH_2Cl_2, −20 → 23 °C, 12 h, 59%; (9) SmI_2 (14 equiv), TESOTf (6.2 equiv), H_2O (4.7 equiv), THF (0.01 M), −78 °C, 15 m, 82%; (10) $PhNTf_2$ (1.2 equiv), KHMDS (1.4 equiv), THF−PhMe (4:1, 0.08 M), 0 °C, 10 m, 65%; (11) SeO_2 (5.0 equiv), NaH_2PO_4 (15 equiv), 1,4-dioxane (0.1 M), 110 °C, 12 h, 45%; (12) Dess−Martin periodinane (1.7 equiv), CH_2Cl_2 (0.1 M), 0 → 23 °C, 35 m; aq. HCl; aq. NaOH; (13) *m*-CPBA (5.0 equiv), CH_2Cl_2 (0.1 M), 0 °C, 1.5 h, 38% (2 steps).

Enoxysilanes could be formed directly from the ketone obtained after enone reduction. However, these materials did not undergo the desired allylic oxidation in acceptable yields, even after a comprehensive examination of reaction conditions: Corey−Yu oxidation with several Pd-sources, bases, and oxidants,[22,23] as well as a wider examination of methodologies, including allylic bromination, SeO_2-mediated allylic oxidations,[25] Cr-based allylic oxidations,[26] the Kharasch reaction,[27] I(III)-based approaches,[28] among other methodologies did not lead to adequate allylic oxidation.[29] Several oxidation products were obtained that resulted from direct alkene oxidation, rather than through pathways that lead to allylic oxidation. Reasoning that the undesired nucleophilicity of the enoxysilane could be attenuated through the use of a more electron-deficient alkene, the vinyl triflate **15** was prepared using KHMDS and $PhNTf_2$ in 65% yield.

Although we are unaware of any reports of vinyl triflate allylic hydroxylation,[30] we found that treatment of the vinyl triflate **15** with SeO_2 in the presence of NaH_2PO_4 resulted in the formation of allylic alcohol **16**. Interestingly, if the mechanism of this transformation is in line with other alkene allylic oxidations with SeO_2, then this transformation must proceed via an unusual triflate of a hemiselenylacetal.[31] We anticipate that this oxidation approach will be a useful compliment to the Corey−Yu oxidation for scenarios wherein alkene oxidation via Rubottom-type pathways is competitive.[22] Alcohol **16** was oxidized to the corresponding ketone by treatment with Dess−Martin periodinane (DMP), which, after deprotection upon aqueous workup with HCl and NaOH, led to protoaustinoid A (**2**). In line with the isolation report, we found that protoaustinoid A (**2**) underwent aerobic oxidation to berkeleyone A (**1**),[2b] but could be prepared more efficiently using standard conditions for 1,3-diketone hydroxylation: treatment of protoaustinoid A (**2**) with *m*-CPBA in CH_2Cl_2 resulted in formation of berkeleyone A (**1**).[10]

Beginning with commercially available farnesyl bromide (**9**), we have synthesized berkeleyone A (**1**) in 13 steps. Several synthetic technologies developed through these studies may find utility in other contexts, including cyclization with an epoxide initiating group and a β-ketoester terminating group (**8** to **7**), isomerization−Claisen cyclization preceding radical cyclization (**10** to **6**), SmI_2 reduction of **14** promoted by the crucial addition of TfOH, and allylic hydroxylation of a vinyl triflate (**15** to **16**) to access a 1,3-diketone from a ketone. With a completed route to berkeleyone A (**1**) and access to a number of analogs with differing D-ring substitution patterns, materials are available to interrogate the structure−function relationships involved in berkeleyone A (**1**) derivatives binding to both caspase-1 and biosynthetic enzymes.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, ^{1}H- and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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