Annulative Methods Enable a Total Synthesis of the Complex Meroterpene Berkeleyone A

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Supporting Information Placeholder

ABSTRACT: Synthetic pathways to complex meroterpenes derived from 3,5-dimethylorsellinic acid (DMOA) and farnesyl pyrophosphate have not been reported despite heavy biosynthetic and medicinal interest. Herein we report the first total synthesis of berkeleyone A, a potential gateway compound to a plethora of fungal-derived meroterpenes, in 13 steps. In addition, we have further developed a novel annulation reaction for the synthesis of hydroxylated 1,3-cyclohexadiones in a single step.

Meroterpene biosynthesis expands the diversity available to isoprenoid pathways alone and allows for the assembly of natural products with highly unique structural attributes.[1] Organisms belonging to the fungal kingdom in particular have become proficient at exploiting this broad chemical synthesis platform for complex metabolite production.[2] Specifically, approximately one hundred highly intricate and structurally variable natural products are assembled via the union of the polyketide fragment 3,5-dimethylorsellinic acid (DMOA, **1**) with the C-15 isoprenoid farnesyl pyrophosphate (Figure 1).[3] DMOA-derived meroterpene biosynthesis is believed to commence with a dearomative alkylation of **1** affording **12** after methylation and oxidation (Figure 2).[2-4] For the vast majority of members, a cyclase-mediated polyene cyclization ensues, affording postulated cationic intermediate **13** wherein the hindered C_{11}–C_{12} bond (berkeleyone numbering system) has been forged. This maneuver establishes two adjacent all-carbon quaternary stereocenters;[5] such motifs pose high synthetic challenge in comparison to the carbon-oxygen linkages present in numerous meroterpenes including DMOA-derived simplicissin (**7**) and tropolactone B (**8**) (Figure 1). Carbocation **13** can partition to either the basic bicyclo [3.3.1]nonane-containing scaffold (see berkeleyone A (**2**)) via proton loss and oxidation, or rearrange to the 5,6-fused ring system found in andrastin D (**10**) (and further oxidized terretonin compounds, see **9**) by migration of the C7–C8 bond followed by proton loss.[3-4] The former pathway, proceeding through **2**, offers potential

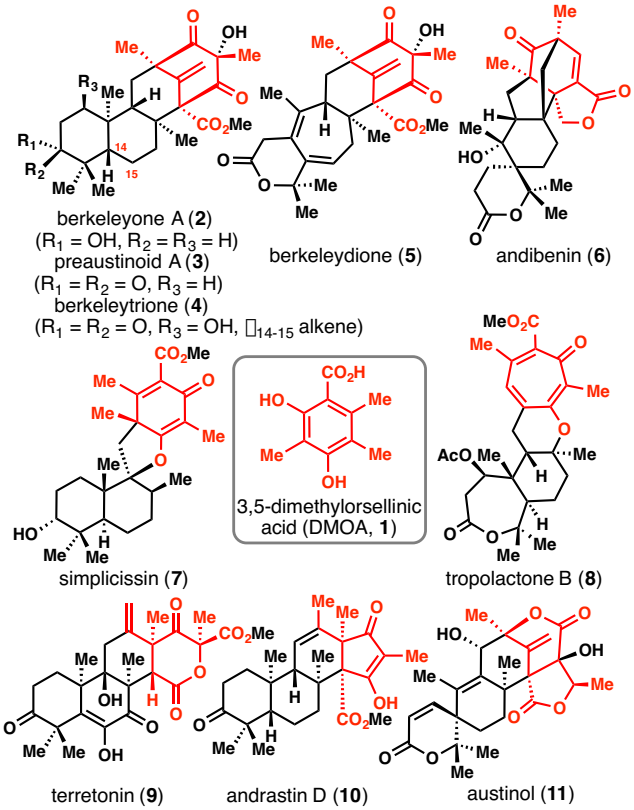


Figure 1. Complex fungal-derived meroterpenes stemming from 3,5-dimethylorsellinic acid (DMOA).

entry into nearly fifty natural products including preaustinoid A (**3**), berkeleytrione (**4**), berkeleydione (**5**), and austinol (**11**) by way of various oxidative transformations.[3,4,6] The latter pathway is believed to be responsible for the creation of approximately 35 distinct structures including **9**, **10**, and the various families listed (Figure 2).[3,4,7] Significant resources have been devoted to identifying the genes responsible for DMOA-derived meroterpene biosynthesis.[3,4,6-8] Herein we describe the first successful chemical synthesis of a complex DMOA-derived meroterpene. Utilizing an oxidative bond reorganization strategy and diketene annulation transform, we are able to gain entry into this complex meroterpene family in only thirteen steps from commercially available materials.

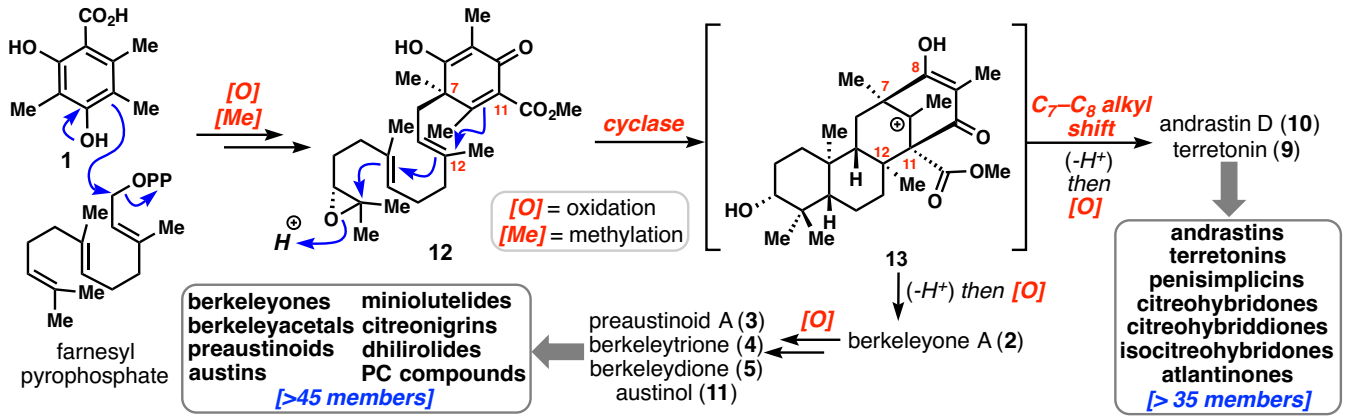
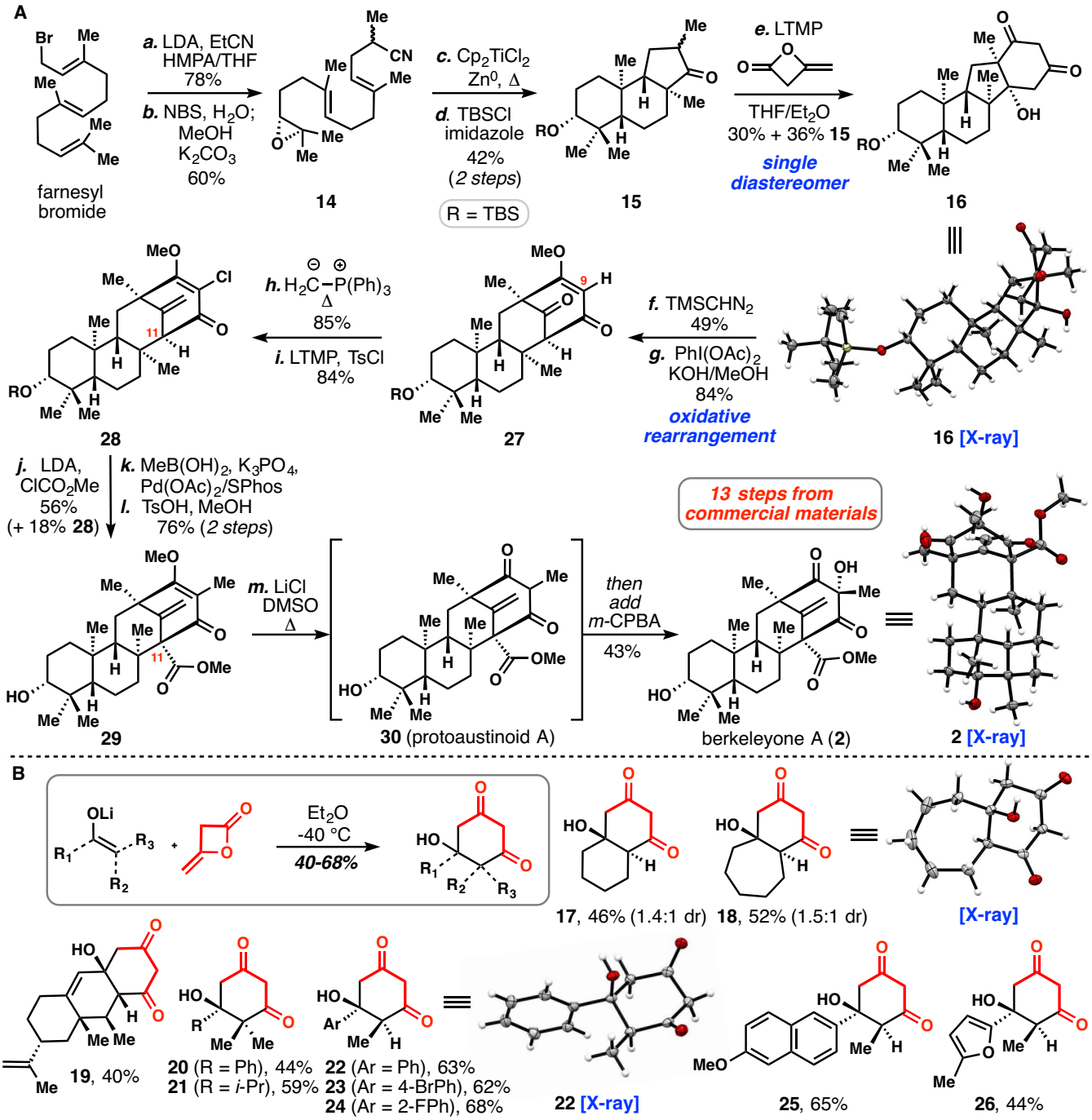


Figure 2. Simplified biosynthetic pathway leading to the majority of meroterpenes derived from DMOA (**1**) and farnesyl pyrophosphate.

We chose berkeleyone A (**2**) as our initial synthetic target as it potentially serves as a gateway compound to the largest assortment of DMOA-derived structures and is also an inhibitor of caspase-1 and interleukin-1β (IL-1β) production,[9] of interest to researchers studying inflammation and innate immunity.[10] In particular, after inflammasome generation in the monocytic leukemia cell line THP-1, **2** alleviated the production of IL-1β at concentrations similar to the standard caspase-1 inhibitor Ac-YVAD-CHO (Ac-Tyr-Val-Ala-Asp-CHO); moreover, **2** was the most potent of the berkeleyone natural products tested in this assay.[9] Berkeleyones were isolated from the fungal strain *Penicillium rubrum* growing in the Berkeley Pit, a former copper mine turned waste lake with various metal concentrations exceeding 500 ppm and a pH of approximately 2.5.[9,11-13] Despite effort by various laboratories, no fully synthetic routes exist to either a berkeleyone natural product *or any* of the DMOA-derived families represented by members **2**-**11** (Figure 1).[14] This is not surprising given their complexity–**2** in particular harbors eight stereogenic centers (four of which are all-carbon quaternary stereocenters) embedded within a dense tetracyclic framework.

Our synthesis began with commercially available farnesyl bromide, which was converted into **14** via alkylation of the nitrile anion derived from propionitrile, and epoxidation of the terminal alkene via the intermediacy of a bromohydrin (Scheme 1A). We envisioned that a reductive, titanocene-mediated epoxide opening cascade could construct the key 6/6-fused ring system present in this class of natural products.[15] Under conditions reported by Fernández-Mateos and co-workers (Cp_2TiCl_2, Zn^0, THF, 25 °C)[16] we obtained small quantities of desired ketone **15**, however performing this cyclization at elevated temperatures (60 °C) smoothly forged the 6/6/5-fused ring system in 42% isolated yield after silylation of the secondary alcohol. With efficient access to **15** we were well positioned to investigate the key diketene annulation which has remained untested outside of the polycyclic polyprenylated acylphloroglucinol (PPAP) synthetic problem.[17-19] Under optimized parameters, the sterically encumbered lithium enolate derived from **20** was found to engage diketene in the desired ring-opening/annulation process affording **16** as a single diastereomer in 30% isolated yield (36% of recovered **15** was also isolated). The structure of **16** was confirmed by single crystal X-ray diffraction. This bond-forming step constructs a hindered tetracyclic compound possessing four methyl groups in nearly axial orientations and attests to the highly reactive nature of this strained reagent.[20] Moreover, we have found that a number of lithium enolates will engage diketene in this formal [4+2] annulation process and the strength of this transformation lies in its ability to form sterically congested carbocyclic 1,3-diketones (Scheme 1B). The starting lithium enolates are prepared by either LTMP-mediated ketone deprotonation or trimethylsilyl enol ether cleavage with methyllithium. Cyclohexanone and cycloheptanone served as competent coupling partners although in these cases the *trans* diastereomer slightly predominates (see **17** and **18**, *trans*:*cis* ~ 1.5:1). Complex dienolates underwent efficient annulation (see **19**), as did enolates derived from highly sterically hindered ketones such as diisopropyl ketone and isobutyrophenone (see **20** and **21**). Finally, a variety of substituted propiophenones and related arylketones could be annulated in processes that form an additional stereogenic center with complete diastereoselectivity (see **22**-**26**). We are unaware of any existing synthetic methods to construct these motifs, which are envisioned to have a high potential for aromatization; **16**-**26** all represent novel chemical entities.



Scheme 1. (**A**) Short total synthesis of the gateway DMOA member berkeleyone A (**2**). (**B**) An annulation reaction of lithium enolates with diketene allows for one-step access to previously inaccessible cyclic 1,3-diketones. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, NBS = *N*-bromosuccinimide, Cp = cyclopentadienyl, TBS = *tert*-butyldimethylsilyl, LTMP = lithium tetramethylpiperidide, TMS = trimethylsilyl, Ts = *para*-toluenesulfonyl, SPhos = 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, DMSO = dimethylsulfoxide, *m*-CPBA = *meta*-chloroperbenzoic acid.

With five-step access to tetracycle **16**, we proceeded to evaluate the second pivotal transformation in the synthetic pathway–conversion of the 5,6-fused ring system into the hallmark bicyclo[3.3.1]nonane skeleton. Following *O*-methylation of the 1,3-diketone with trimethylsilyldiazomethane,[21] we found that our previously developed conditions for I(III)-mediated oxidative ring expansion ($PhI(OAc)_2$, KOH/MeOH) performed admirably in this polycyclic setting, affording **27** in 84% isolated yield.[17,18] A high-yielding Wittig olefination of the hindered ketone and chlorination of the C-9 position led to polycycle **28** in excellent yield. We envisioned that deprotonation of the highlighted bridgehead position (C-11) of **28** and acylation with methylchloroformate could

forge the final, challenging all-carbon quaternary of the target.[22] In contrast to the bicyclo[3.3.1]nonane trione system found in the PPAPs however, the C-11 proton in **28** is presumably far less acidic owing to the presence of only one neighboring carbonyl group. Nevertheless, deprotonation of **28** with LDA, followed by quenching the resulting bridgehead anion with methylchloroformate led to efficient acylation (56% isolated yield). It is of note that the aforementioned Wittig olefination proved problematic with the bridgehead ester already installed, presumably due to steric effects. Much to our delight, and in contrast to previous studies,[17,18] a direct vinyl chloride Suzuki coupling ($MeB(OH)_2$, $Pd(OAc)_2$/SPhos) was capable of installing the final requisite alkyl group at C-9 in excellent yield. Acidic cleavage of the *tert*-butyldimethylsilyl ether (TsOH/MeOH, 60 °C) afforded **29** in 76% yield over two steps. Krapcho-type demethylation (LiCl, DMSO, 120 °C) of **29** proceeded smoothly to generate the previously isolated DMOA metabolite protoaustinoid A (**30**), a biosynthetic precursor to berkeleyone A.[6e] While this transformation appeared efficient, the isolation of pure **30** proved somewhat problematic owing to limited compound stability. Ultimately, a superior process was developed wherein the demethylation reaction was telescoped with a *meta*-chloroperbenzoic acid (*m*-CPBA) oxidation at 0 °C. Under these conditions berkeleyone A (**2**), whose structure was confirmed by X-ray crystallographic analysis, could be isolated in 43% yield. Overall, only thirteen steps were needed to access this complex secondary metabolite from commercially available farnesyl bromide. Moreover, tetracycle **27**, accessible in only 7 operations, is envisioned to serve as a suitable point of divergence for chemical derivatization around the bicyclo[3.3.1]nonane nucleus, an area which is potentially involved in target binding.[9]

In summary, annulative methodology based on the chemistry of diketene, coupled with a strategic skeletal reorganization strategy, has opened the door to the chemical synthesis of the previously inaccessible DMOA-derived family of meroterpenes, a collection of nearly 100 secondary metabolites with fascinating structural features and exciting biological activity.[2,3,23] With efficient access to the prototypical bicyclo[3.3.1]nonane-containing member berkeleyone A (**2**), the stage is now set to explore the downstream oxidative chemistry both within and between these various meroterpene structural classes; such exercises will not only shine light on chemical aspects of complex meroterpene biosynthesis, but will also likely serve as a platform for the discovery of novel synthetic methodology.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data for all compounds and X-ray crystallographic data for **2**, **16**, **18**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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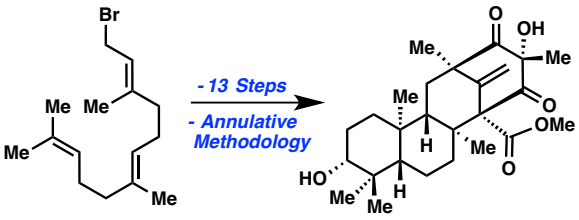

farnesyl bromide berkeleyone A