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Synthesis of the Tetracyclic Core of Berkelic Acid Using Gold(I)-Catalyzed Hydroarylation and Oxidative Radical Cyclizations

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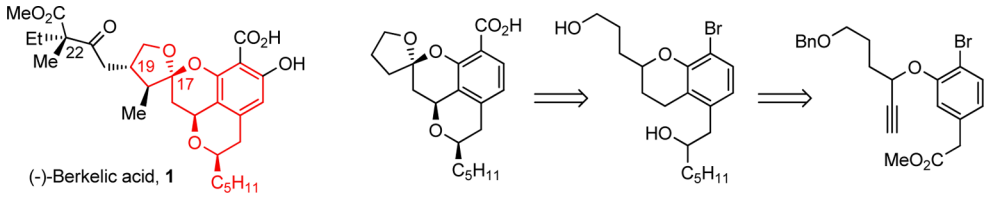
ABSTRACT



A synthetic approach to the tetracyclic core of berkelic acid is reported using gold(I)-catalyzed intramolecular hydroarylation and oxidative radical cyclizations to effect the key ring-forming steps. The carboxylic acid was introduced via a late-stage palladium-catalyzed carbonylation to afford the core tetracycle with the correct relative stereochemistry for the natural product.

Extremophiles are microorganisms which grow under harsh conditions such as at high temperature, high pressure, high salt concentrations, and low pH.[1] An example of a low pH environment is the Berkeley Pit lake in Butte, MT, that formed upon infiltration of groundwater into an abandoned copper mine. The acidic water (pH ~2.5) is contaminated with high concentrations of metal sulfates, and only certain microorganisms can survive in these extreme conditions. A *Penicillium* species isolated from the lake by Stierle et al.[2] produces berkelic acid (**1**), a novel metabolite with a highly substituted tetracyclic spiroacetal core. Enzyme assays established that berkelic acid inhibits the endopeptidase MMP-3 (GI_{50} = 1.87 μM) as well as the cysteine protease caspase-1 (GI_{50} = 0.098 nM). Screening at the National Cancer Institute revealed that berkelic acid exhibits selective activity against the ovarian cancer cell line OVCAR-3 in the nanomolar range (GI_{50} = 91 nM).

Prompted by a recent synthesis-driven structure revision by Fürstner et al.[3] the stereochemistry of berkelic acid at C-18 and C-19 was reassigned. Shortly after, Snider et al.[4]

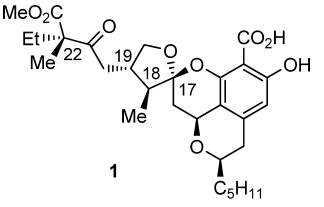


Figure 1. (−)-Berkelic acid, **1**. Stereochemistry as assigned by Snider.[4]

published the first total synthesis of (−)-berkelic acid (**1**), confirming the reassigned stereochemistry and establishing the absolute configuration (Figure 1). De Brabander et al.[5] synthesized berkelic acid by combining the two natural product inspired fragments spicifernin and pulvilloric acid using a [4 + 2] cycloaddition. Pettus et al.[6] have also

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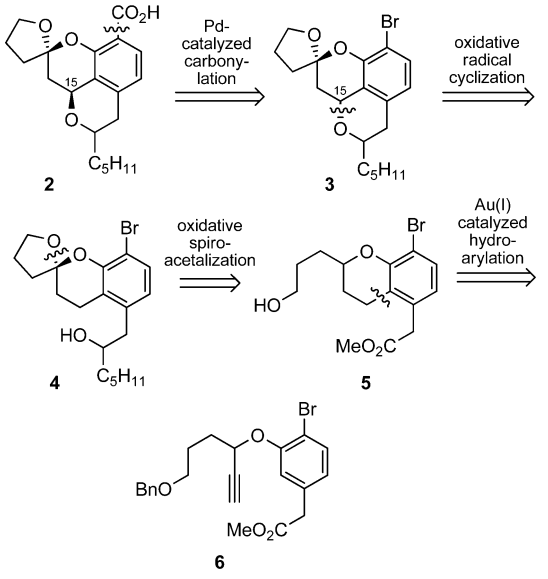
executed a racemic diastereoselective formal synthesis using a [4 + 2]-cycloaddition and earlier this year a highly efficient approach based on silver-catalyzed cycloaddition of an enol ether and an *o*-quinonemethide to form the tetracyclic core was described by Fañanás and Rodríguez.[7] Recently, our laboratory reported an enantioselective formal synthesis of berkelic acid via addition of a silyl enol ether to an aryl oxonium ion.[8] We now herein report a unique approach to the tetracyclic spiroacetal core of berkelic acid using a gold(I)-catalyzed hydroarylation and oxidative radical cyclizations to construct the tetracyclic spiroacetal core (Scheme 1).

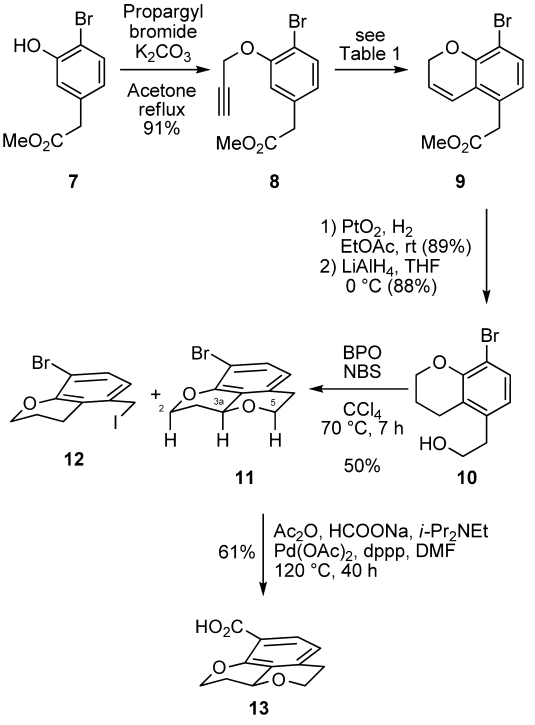
Scheme 1. Synthetic Strategy for the Tetracyclic Core of Berkelic Acid



Our initial attention focused on the tetracyclic chromane spiroacetal core structure **2** present in berkelic acid. As outlined in our retrosynthesis, it was envisaged that an oxidative radical cyclization could be used to form the C−O bond at the benzylic C-15 position (Scheme 1). The tetracyclic chromane structure **3** could be constructed by oxidative radical cyclization of alcohol **4** onto the benzylic carbon. In turn, precursor **4** could be synthesized by gold-(I)-catalyzed hydroarylation of alkyne **6** followed by oxidative radical spiroacetalization. Finally, a late-stage palladium-catalyzed carbonylation of bromide **3** allows introduction of the carboxylic acid **2** present in berkelic acid, utilizing the orthogonality of palladium and gold catalysis.[9]

The synthesis of the tricyclic scaffold **11** from chromane **10** (Scheme 2) was our initial goal. Esterification of

Scheme 2. Synthesis of Tricycle **13**



commercially available 3-hydroxyphenylacetic acid followed by selective bromination[10] at C-4 generated phenol **7**. Subsequent propargylation provided alkyne **8** which was then subjected to intramolecular C−C bond formation. Use of thermal conditions to effect Claisen rearrangement did not afford chromene **9,** presumably due to the absence of *gem*-dimethyl groups.[11] Transition metals, such as Pd,[12] Pt,[13] Ru,[14] Hg,[15] and Au,[16] have been demonstrated to activate aryl C−H bonds toward hydroarylation for cyclization.[17] Sames et al.[13] reported that $PtCl_4$ was the only suitable catalyst that delivered satisfactory yields to effect cyclization on similar substrates. However, use of $PtCl_4$ on parent substrate **8** gave only poor yields

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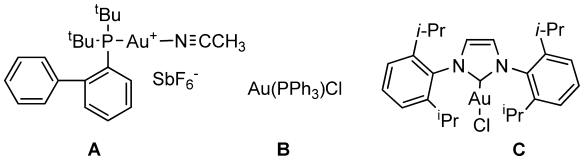
(Table 1, entry 1). Cationic gold(I) catalysts have been shown to be excellent catalysts for chromene formation.[18] The Echavarren group has reported the stable gold(I) catalyst **A**[19,20] (Table 1), which does not need a cocatalyst due to weak coordination of an acetonitrile ligand, whereas catalysts **B** and **C** need to be activated by a cocatalyst (typically a silver salt) to generate the active catalytic species. In the present work, conversion of **8** to **9** proceeded in good yield using all three gold catalysts **A**–**C** (Table 1, entries 2–4). Olefin **9** was then hydrogenated over Adam's catalyst (PtO_2), and subsequent reduction of the methyl ester with $LiAlH_4$ afforded alcohol **10**.

Table 1. Metal-Catalyzed Intramolecular Hydroarylation[a]



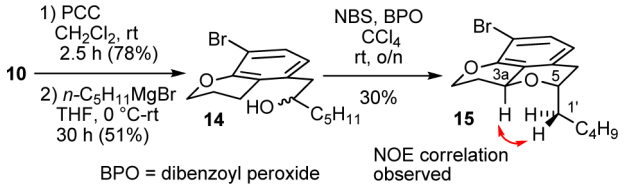
A B C

entry	cat.	conditions	**9**, yield (%)
1	$PtCl_4$[b]	DCE, 80 °C, MW, 1 h	23
2	**A**[c]	CH_2Cl_2, rt, 1.5 h	76
3	**B**/$AgSbF_6$[c]	CH_2Cl_2, rt, 1.5 h	72
4	**C**/$AgSbF_6$[c]	CH_2Cl_2, rt, 1.5 h	69

[a] All gold-catalyzed reactions were carried out in the dark. [b] 5 mol %. [c] 1 mol % catalyst and cocatalyst if required.

Attention next focused on the key oxidative radical cyclization using an oxa variant of the Hofmann–Löffler–Freytag reaction.[21] Applying the hypoiodite-induced free-radical conditions successfully employed for the formation of spiroacetals,[22] alcohol **10** was irradiated (60 W) in the presence of iodobenzene diacetate and iodine at room temperature. In this case, alcohol **10** was found to predominantly undergo a Norrish type I fragmentation to form iodide **12** (Scheme 2).[23] Treatment of alcohol **10** with DDQ, as reported by Pettus,[6] did not result in the formation of chromane **11**. After a survey of reagents and conditions, it was eventually found that treatment of **10** with NBS and dibenzoyl peroxide (BPO) successfully resulted in the direct formation of the tricyclic chromane **11** in 50% yield without any Norrish type I fragmentation product **12** observed.

Scheme 3. Radical Cyclization of Alcohol **14**



With tricyclic bromide **11** in hand, the late-stage carbonylation was next attempted. Neither lithium–halogen exchange nor Grignard-based halogen–metal exchange followed by introduction of carbon dioxide or Mander's reagent ($NCCO_2Me$) led to formation of the desired product.[24–26] Palladium catalyzed carbonylation of bromide **11** in a 2:1 mixture of DMF/MeOH in the presence of $Pd(OAc)_2$/dppp and Hünig's base under carbon monoxide at high temperature or pressure did not afford the desired carboxylic acid.[27] Pleasingly however, generation of carbon monoxide in situ using the modified conditions reported by Caille and co-workers[28] afforded the desired carboxylic acid **13** in 61% yield.

We next sought to introduce further substituents onto tricycle **11** and needed to establish whether a secondary alcohol was compatible with the subsequent cyclization. Toward this end, alcohol **10** was oxidized to the aldehyde and treated with *n*-pentylmagnesium bromide to afford secondary alcohol **14** (Scheme 3). Employing NBS with BPO successfully afforded the desired tricycle **15**, showing that a secondary alcohol precursor bearing the requisite side chain of berkelic acid could participate in the key oxidative cyclization. The *trans*-stereochemistry between H-3a and H-5 was assigned based on the observation of an NOE between H-3a and H-1′.

It was next decided to introduce the 6,5-spiroacetal unit present in berkelic acid by incorporation of an additional oxidative radical cyclization. In this case, a more substituted alkyne was required in the initial hydroarylation step in order to introduce the 5-membered spiroacetal ring. Alkylation of bromide **16** (Scheme 4) with phenol **7** afforded alkyne **6**. Intramolecular hydroarylation with Echavarren's catalyst **A** and subsequent hydrogenation with concomitant debenzylation over Adam's catalyst furnished chromane **5**. Radical spirocyclization using

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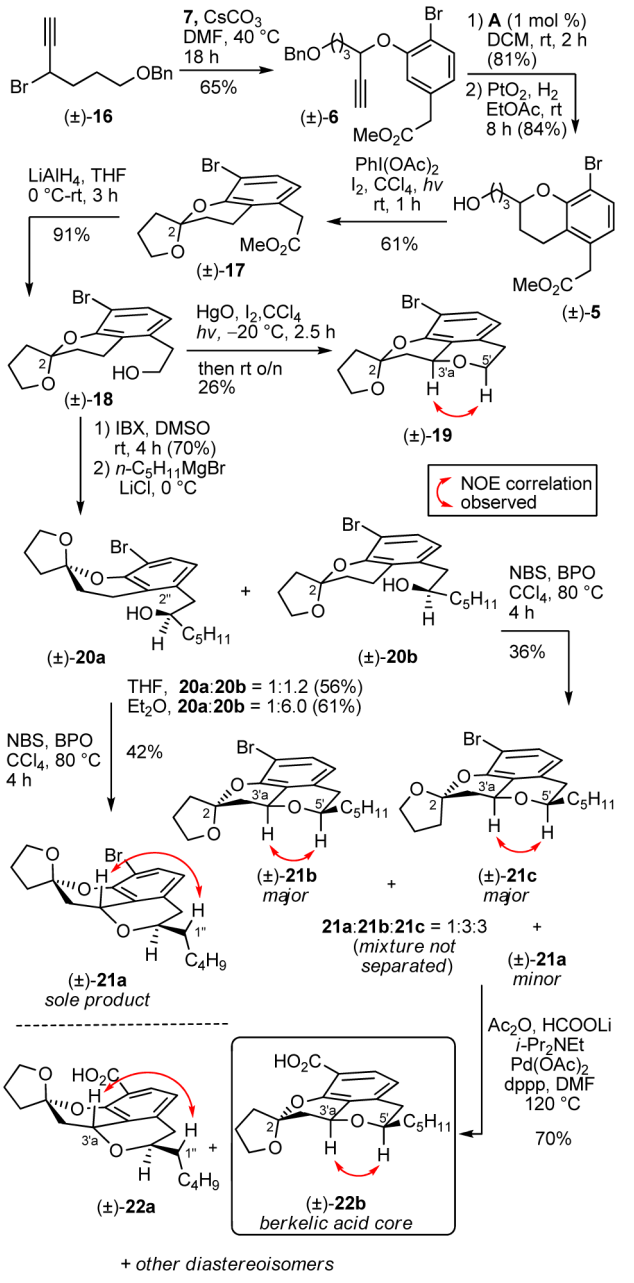
Scheme 4. Synthesis of the Tetracyclic Core of Berkelic Acid



$PhI(OAc)_2/I_2$ and subsequent reduction afforded spiroacetal **18** which was then subjected to radical cyclization using HgO and iodine to provide tetracycle **19** for which the stereochemistry was assigned based on the observation of an NOE correlation between H-3′a and H-5′ consistent with a *syn* 1,3-diaxial relationship together with the characteristic downfield chemical shift for H-3′a at δ 4.9 ppm (C_6D_6) due to the deshielding effect of the axial C2–O1 bond.[27] Finally, synthesis of the tetracyclic core of berkelic acid was initiated. Alcohol **18** was oxidized to the aldehyde with IBX followed by treatment with *n*-pentylmagnesium bromide to give a separable mixture of racemic secondary alcohol diastereomers **20a** and **20b**. Changing the reaction solvent from THF to diethyl ether increased the ratio of diastereomers from 1:1.2 to 1:6 favoring **20b**.

Each of the racemic diastereomers **20a** and **20b** was individually subjected to treatment with NBS and BPO. Diastereomer **20a** selectively afforded tetracycle **21a** as as the sole product. Compound **21a** exhibited a *trans* relationship between H-3′a and H-5′ as confirmed by an NOE correlation between H-3′a and H-1″. In contrast, cyclization of alcohol **20b** afforded an inseparable mixture of tetracycles **21b** and **21c** and a small amount of **21a** (ca. 3:3:1). Tetracycle **21b**, for which an NOE correlation was observed between H-3′a and H-5′, represents the stereochemistry of berkelic acid. The stereochemistry for **21c** was assigned based on a similar H-3′a to H-5′ NOE correlation, and the distinctive upfield shift of H-3′a due to the absence of a 1,3-diaxial oxygen.[29,30] Gratifyingly, palladium-catalyzed carbonylation of the mixture of **21a–c** with a 20-fold excess of acetic anhydride, lithium formate and DIPEA to generate CO in situ afforded the corresponding carboxylic acids in high yield. Chromatographic separation afforded **22b** and its (2,3′a)-epimer **22a**.[31] **22b** possesses the same relative stereochemistry as the tetracyclic core of berkelic acid.

In summary, we report a novel series of disconnections to access the tetracyclic core of berkelic acid using a combination of gold(I) catalyzed intramolecular hydroarylation and oxidative radical cyclizations. Notably, the stereochemistry obtained in the final free radical bromination and cyclization was dependent on the relative configuration of the C-2″ alcohol and C-2 spiroketal. A late-stage palladium-catalyzed carbonylation of an aryl bromide was used to introduce the carboxylic acid group onto the berkelic acid scaffold, affording the tetracyclic spiroketal **22b** possessing the correct relative stereochemistry for the natural product.

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Supporting Information Available. Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Predominant formation of **22a** and **22b** indicates some epimerization at C-2 during the carbonylation step.

The authors declare no competing financial interest.