Natural Products

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Scalable Total Synthesis of (−)-Berkelic Acid by Using a Protecting-Group-Free Strategy**

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(−)-Berkelic acid (**1**; Figure 1) is a biologically active and architecturally unique secondary metabolite that was isolated in 2006 by Stierle and co-workers from a extremophilic

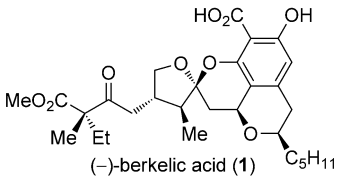
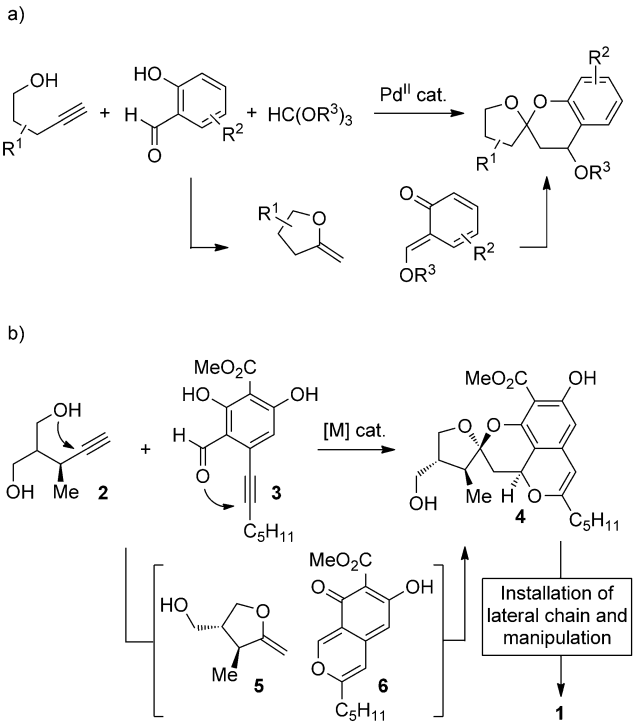


Figure 1. Structure of (−)-berkelic acid (**1**).

Penicillium species obtained from the surface waters of Berkeley Pit Lake in Butte, Montana (USA).[1] This lake was formed when an abandoned copper mine was flooded with infiltrating ground water, thus resulting in the formation of a highly acidic (pH 2.5) and metal contaminated ecosystem where only extremophiles could survive. The microorganisms that tolerate these extreme growth conditions are a precious, although very scarce, source of architecturally nonconventional and potentially bioactive natural products.[2] A good example of this is (−)-berkelic acid (**1**), which has a unique structure and a diverse biological profile. This compound was reported to inhibit the cysteine protease caspase-1 (98 μM) and matrix metalloproteinase MMP-3 (1.87 μM), as well as displayed selective activity against the human ovarian cancer line OVCAR-3 (GI50 = 91 nM).[1] To date, three research groups have accomplished the total synthesis of **1**.[3,4] It should be noted that the strategies used in all these total syntheses only delivered very low quantities of the natural product (3–11 mg). Nevertheless, they provided material enough for some new bioactivity studies which led to some contradictory results when compared to those reported by the isolation team.[5] So, the necessity for an in depth study on the biological activity of **1** as well as the more than likely future elimination of its natural source mandates a secured material supply.

Herein, we report a total synthesis of berkelic acid wherein all but the last step were executed on gram scale. This level of practicality was enabled by a highly stereoconvergent and modular synthetic strategy.

Recently, we developed a palladium(II)-catalyzed one-pot three-component coupling reaction for the diastereoselective construction of chroman spiroacetals (Scheme 1 a).[6]



Scheme 1. a) Synthesis of spiroacetals through a one-pot multicomponent cascade reaction (previous work; see Ref. [6]). b) Our strategy for the synthesis of **1** (this work).

The method relies on the in situ formation of an exocyclic enol ether and a *o*-quinonemethide, and the subsequent formal cycloaddition reaction between these two reagents. In principle, the reaction seems ideal for the construction of the berkelic acid skeleton; however, an easy way to introduce the additional pyran ring was initially far from evident. Upon

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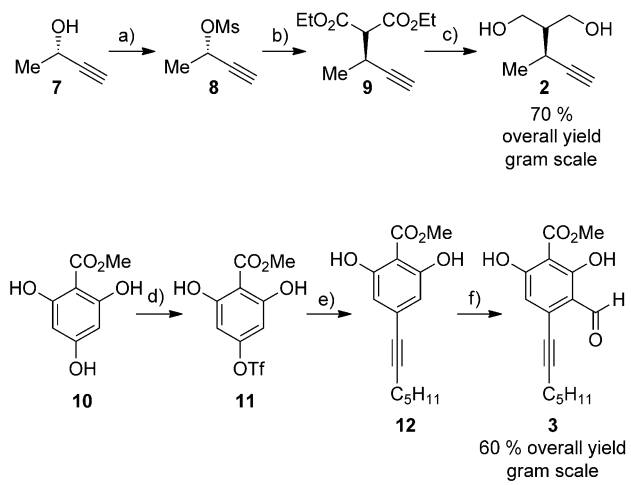
considering the ability of π-acid catalysts to activate alkynes, thus facilitating the intramolecular nucleophilic addition of alcohols and aldehydes,[7] we hypothesized that ideally a unique metal complex could promote the cycloisomerization of alkyndiol **2** to give the enol ether **5** and also the cycloisomerization of aldehyde **3** to give **6** (Scheme 1b). The formal cycloaddition reaction between the intermediates **5** and **6** would result in the formation of the core structure of berkelic acid **4** in an apparently very simple way.

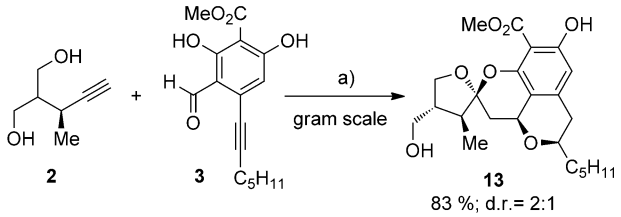
Although the proposed reaction was risky in terms of stereoselectivity, because just one chiral center (that of alkyndiol **2**) would induce the selective formation of the other three newly formed ones in **4** (including a desymmetrization in **2**), the process was very attractive from the synthetic point of view as it avoided the synthesis of starting materials having multiple stereocenters and tedious protection/deprotection steps. Once the compound **4** was obtained we were confident about the possibilities of completion the total synthesis of (−)-berkelic acid (**1**), because only the installation of the lateral chain and a few conventional functional group manipulations would remain.

Preparation of the key building blocks, **2** and **3**, was achieved in a concise and scalable way from commercially available starting materials. Specifically, chiral fragment **2** was synthesized from (*S*)-(−)-3-butyn-2-ol (**7**; 98% *ee*) in just three conventional chemical transformations (Scheme 2). Thus, initial mesylation of alcohol **7** led to the corresponding derivative **8**. Displacement of the mesylate by diethylmalonate in the presence of cesium fluoride through an S_N2 reaction furnished the diester **9**. Finally, reduction with lithium aluminium hydride provided the desired diol **2** in 70% overall yield and 96% *ee* (2.8 g scale).[8] Synthesis of building block **3** was also achieved in three steps (Scheme 2). Namely, triflic anhydride reacted selectively with the hydroxy group in *para*-position of commercially available ester methyl 2,4,6-trihydroxybenzoate (**10**) to provide compound **11**.[3b] Reaction of this intermediate through a Sonogashira-type cross-coupling reaction employing the potassium trifluoroborate salt derived from 1-heptyne was successful, thus allowing the synthesis of alkyne **12** in high yield.[9] Finally, introduction of the aldehyde functionality was achieved using a sequence involving an initial hydroxymethylation with formaldehyde in the presence of calcium chloride and subsequent oxidation with manganese dioxide. Every reaction was performed on a gram scale, thus providing the fragment **3** in 60% overall yield from **10** (4.8 g scale).



Scheme 2. Synthesis of building blocks **2** and **3**. Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C; b) diethyl malonate, CsF, THF, 45 °C; c) LAH, THF, 75 °C; d) Tf_2O, 2,6-lutidine, CH_2Cl_2, RT; e) potassium trifluoro(hept-1-yn-1-yl)borate, DIPEA, [$PdCl_2$(dppf)] (5 mol%), MeOH, 65 °C; f) formaldehyde, $CaCl_2 \cdot 2H_2O$, KOH, MeOH, RT and then MnO_2, CH_2Cl_2, RT. DIPEA = *N*-ethyl-*N*,*N*-diisopropylamine, dppf = 1,1′-bis(diphenylphosphino)ferrocene, LAH = lithium aluminium hydride, Ms = methanesulfonyl, Tf = trifluoromethylsulfonyl.

At this stage, with substantial quantities of fragments **2** and **3** in hand, we turned our attention to the key reaction of our synthesis, that is, the catalytic cycloisomerization of these compounds and subsequent formal cycloaddition reaction between the in situ formed intermediates **5** and **6** to give product **4** (Scheme 1). Our experience in cycloisomerization reactions indicated that our desired transformation could be catalyzed by a metallic complex derived from typical carbophilic Lewis acids.[10] In fact, we found that the reaction proceeded in the presence of 5 mol% of AgOTf. To avoid possible decomposition of compound **4** as a result of the presence of the new reactive pyran ring, we directly performed the hydrogenation of the carbon–carbon double bond of this pyran ring under conventional conditions (Scheme 3).



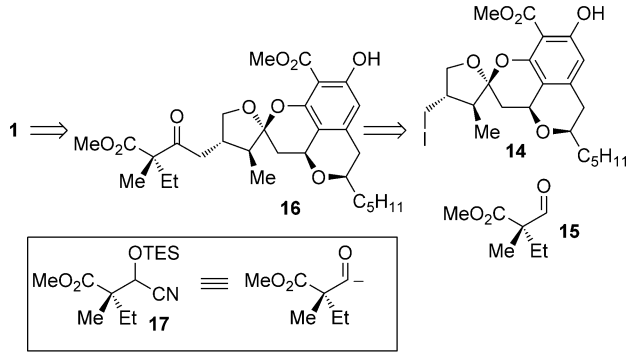
Scheme 3. Synthesis of the central core of **1**. Reagents and conditions: a) AgOTf (5 mol%), THF, 0 °C and then H_2, Pd/C (5 mol%), MeOH, −5 °C. THF = tetrahydrofuran.

It should be remarked that in this global transformation four new chiral centers are formed and, surprisingly, only two diastereoisomers were observed in the crude reaction mixture (d.r. = 2:1). Even more pleasant was the confirmation that the structure of the major diastereoisomer corresponded to that of the desired product **13** with all chiral centers and functionalities resembling those of the natural product. The minor isomer could be easily separated at an advanced stage, as it will be shown. Notably, this reaction could be performed on a gram scale with 83% yield (2.4 g of this material were synthesized). This new silver-catalyzed reaction allowed the assembly of the central core of the natural product, which contains four rings and five stereocenters, in just one step.

At this point we had achieved a formal synthesis of berkelic acid because intermediate **13** was an advanced intermediate in the total synthesis reported by Fürstner and co-workers.[3c] It should be also remarked that the introduction of the lateral chain at an advanced stage is beneficial and highly desirable because it makes the synthesis much more

modular and convergent. Thus, the required building blocks are simpler and the synthesis of analogues of the natural product in the quest for new and relevant bioactive compounds is much easier. In this context, the syntheses reported by the groups of Fürstner and Snider are remarkable.[3a,c] The coupling of the lateral chain in both routes relies on the use of an aldol reaction which requires a final oxidation step. This late-stage oxidation was problematic, as the electron-rich aromatic ring of the central core was highly susceptible to oxidation and protection of the free phenol as an allyl or TBS ether was required.

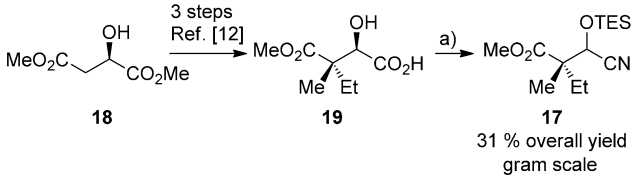
Having in mind these problems and considering that a scalable total synthesis should avoid tedious protection/deprotection steps, we devised a different strategy to introduce the lateral chain (Scheme 4). So, to avoid any redox



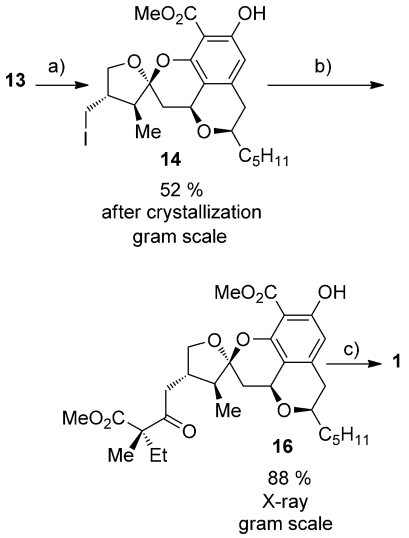
Scheme 4. Our devised strategy to introduce the lateral chain. TES = triethylsilyl.

process, we thought of using an umpolung alkylation reaction with iodide **14** and an appropriate acyl anion equivalent derived from aldehyde **15**. This reaction would deliver the berkelic acid methyl ester **16**, a direct precursor of the natural product **1**, in one step. Between the different acyl anion equivalents reported, we considered the use of the cyanohydrin **17** (Scheme 4).[11] We were able to synthesize this compound on a gram scale from commercially available dimethyl-D-malate (**18**) through the known hydroxyacid **19** (Scheme 5).[12] The cyanohydrin **17**,[13] obtained in 31% overall yield (1.0 g scale) as an inconsequential mixture of isomers at the cyanohydrin center, could be stored for long periods of time without problems.

With alcohol **13** and cyanohydrin **17** in hand we tackled the completion of the synthesis (Scheme 6). Thus, treatment



Scheme 5. Synthesis of cyanohydrin **17**.Reagents and conditions: a) 1. Bu_4NIO_4, $CHCl_3$, 65 °C; 2. TESCN, PNPCl, neat, RT. PNPCl = bis(triphenylphosphoranylidene)ammonium chloride.



Scheme 6. Final steps. Reagents and conditions: a) I_2, PPh_3, imidazole, Et_2O/CH_3CN (3:1), RT; b) 1. **17**, LDA, DMPU, THF, −78 °C and then **14**; 2. TBAF·3 H_2O, MeOH, RT; c) $(Bu_3Sn)_2O$, toluene, 115 °C. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one, LDA = lithium diisopropylamide, TBAF = tetrabutylammonium fluoride.

of alcohol **13** with PPh_3 and I_2 gave the iodide **14** as a crystalline solid. This was especially convenient as a single recrystallization from a mixture of dichloromethane and ethanol removed the undesired minor diastereoisomer produced in the previous step, thus allowing the isolation of **14** in 52% yield and enantiomerically pure form (1.6 g of **14** were obtained).[14] Additional treatment of this iodide **14** with the anion derived from cyanohydrin **17** finally furnished the diester **16** in 88% yield.[15] Again, this transformation could be performed on a gram scale (1.2 g of **16** was synthesized in one batch). X-ray crystallographic analysis of **16** confirmed it as the berkelic acid methyl ester.[16] It should be noted that diester **16** is a stable compound. In fact, we stored some of this product and we have not observed any decomposition. However as reported by other authors,[3c] **1** is not as stable as its ester **16**. So, to keep in our hands enough material for transformation into the natural product when required, the last step of our total synthesis was conducted on a small scale using $(Bu_3Sn)_2O$ for the selective cleavage the benzylic ester (Scheme 6). It should be noted that after a slight modification of the protocol described by De Brabander and co-workers to perform this last step,[3b] we were able to obtain 25 mg of compound **1** in one batch and we did not observe the formation of any other undesired product. The spectral data and optical rotation of synthetic **1** were in agreement with those for the natural sample and the synthetic (−)-berkelic acid reported in the literature.[1,3]

In summary, a practical and scalable route to (−)-berkelic acid (**1**) has been developed. The completed synthesis as it stands was accomplished with seven steps in the longest linear sequence and no more than 14 overall steps from three commercial materials (methyl 2,4,6-trihydroxybenzoate, (*S*)-(−)-3-butyn-2-ol, and dimethyl-D-malate). Notably, from (*S*)-(−)-3-butyn-2-ol, containing just one stereocenter, we

obtained the central core of the natural product, which contains five stereocenters, without the need of any other chiral reagent or catalyst. This transformation was achieved by a new silver-catalyzed reaction which allowed the construction of this central core in just one step. Also, a new strategy to introduce the lateral chain was applied. Moreover, all but the last step were conducted on a gram scale. As a result, we believe that the supply of **1** should no longer be an issue. It is also important to remark that the synthesis described herein does not require any protection/deprotection steps. Finally, the modular strategy should allow the easy production of several analogues of the natural product for our ongoing biological activity studies.

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