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Total Synthesis of Berkelic Acid

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Abstract: A productive total synthesis of both enantiomers of berkelic acid (**1**) is outlined that takes the structure revision of this bioactive fungal metabolite previously proposed by our group into account. The successful route relies on a fully optimized triple-deprotection/1,4-addition/spiroacetalization cascade reaction sequence, which delivers the tetracyclic core **32** of the target as a single isomer in excellent yield. The required cyclization precursor **31** is assembled from the polysubstituted benzaldehyde derivative **20** and methyl ketone **25** by an aldol condensation, in which the acetyl residue in **20** transforms from a passive protecting group into an active participant. Access to fragment **25** takes advantage of the Collum–Godenschwager variant of the ester enolate Claisen rearrangement, which clearly surpasses the classical Ireland–Claisen procedure in terms of diastereoselectivity. Although it is possible to elaborate **32** into the target without any additional manipulations of protecting groups, a short detour consisting in the conversion of the phenolic −OH into the corresponding TBS-ether is beneficial. It tempers the sensitivity of the compound toward oxidation and hence improves the efficiency and reliability of the final stages. Orthogonal ester groups for the benzoate and the aliphatic carboxylate terminus of the side chain secure an efficient liberation of free berkelic acid in the final step of the route.

Keywords: Anticancer agents · enzyme inhibitors · natural products · spiro compounds · total synthesis

Introduction

Natural products have a prestigious history in human medicine as drugs or drug precursors. As such, they continue to play an overly important role in particular for the treatment of chronic ailments, infectious diseases, and cancers, as well as for the modulation of the immune system. Changing paradigms in the pharmaceutical industry, however, have disfavored natural product chemistry during the last decades. The slow rate of discovery of relevant new hits from natural sources, difficulties in purification and structure assignment, undesirable levels of (stereochemical) complexity, as well as serious supply problems are often considered noncompetitive. Yet, the evolutionary wisdom encoded in the structure of a small molecule natural product lead may provide strategic advantages over compounds derived from more technology-based approaches to drug discovery,[1,2] in particular since nature's bounty remains relatively untapped.[3]

Berkelic acid (**1**) is a good example that illustrates both sides of the coin of contemporary natural product chemistry. This stereochemically dense secondary metabolite was isolated from an extremophilic *Penicillium* species harvested from the surface waters of Berkeley Pit Lake, a flooded former copper mine in Butte, Montana.[4,5] The environment of this lake is very hostile, with highly acidic waters (pH $\approx$2.5) rich in a plethora of heavy metal salts. Whereas the role of berkelic acid in the producing fungus is currently unknown, this compound was reported to display selective activity against the human ovarian cancer cell line OVCAR-3 (GI_{50} = 91 nM).[4] Moreover, it was reported to be a pronounced inhibitor of the cysteine protease caspase-1 (98 μM) as well as the matrix metalloproteinase MMP-3 (1.87 μM).[4] As emphasized by the isolation team, MMP-3 is upregulated in OVCAR-3 but not in other ovarian cancer cell lines,[4] even though it remains speculative at this point whether the reported inhibition of this particular enzyme and the cytotoxicity profile of berkelic acid are directly correlated or not.

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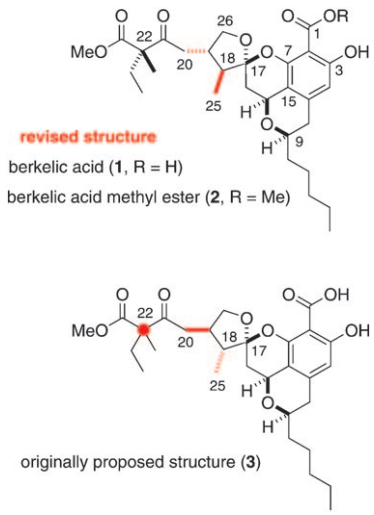
Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that play a key role in the degradation of the extracellular matrix.[6] Collectively, they are involved in various physiological and pathological processes responsible for, amongst others, osteoarthritis, rheumatoid arthritis, multiple sclerosis, cirrhosis and tumor metastasis.[7] The biological importance of this family of enzymes has led to significant interest in the development of small-molecule inhibitors of specific MMPs, which could lead to novel and effective therapeutic agents.[8] Most of the existing synthetic MMP inhibitors are peptide-derived and/or contain a functional group capable of bidentate chelation of the catalytic zinc ion within the MMP active site.[8,9] Since berkelic acid features neither of these structural elements, it may constitute an alternative starting point in the quest for pharmaceutically relevant MMP-3 inhibitors.

Attracted by the distinctive architecture of berkelic acid and intrigued by its promising biological properties, we initiated a program aiming at a secured access to this fungal metabolite and analogues thereof via total synthesis. In a preliminary Communication, we reported our route to berkelic acid methyl ester (**2**), which entailed a major reassignment of the stereostructure of the tetracyclic core of the target (Scheme 1).[10,11] Herein we present an account of further

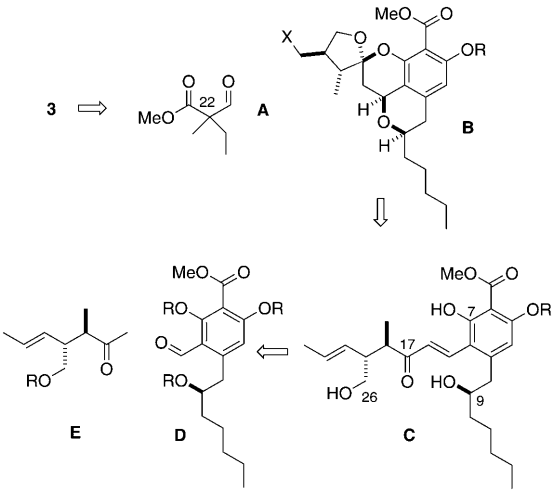


Scheme 1. Proposed and revised structures of berkelic acid. The all-carbon quarternary stereocenter at C22 remained unassigned in the original publication.[4]

synthetic efforts that address the deficiencies in our initial synthesis and allowed us to obtain both enantiomers of the free acid **1** itself. While this work was in progress, Snider and co-workers completed a synthesis of (−)-**1**, which confirmed our structural revision, established the absolute configuration and tentatively designated the stereochemistry of the C22-quaternary center.[12] Shortly thereafter, De Brabander and co-workers also reached (−)-**1** by emulating a conceivable biosynthesis route, and in so doing conclusively assigned the C22-(*S*) stereochemistry.[13]

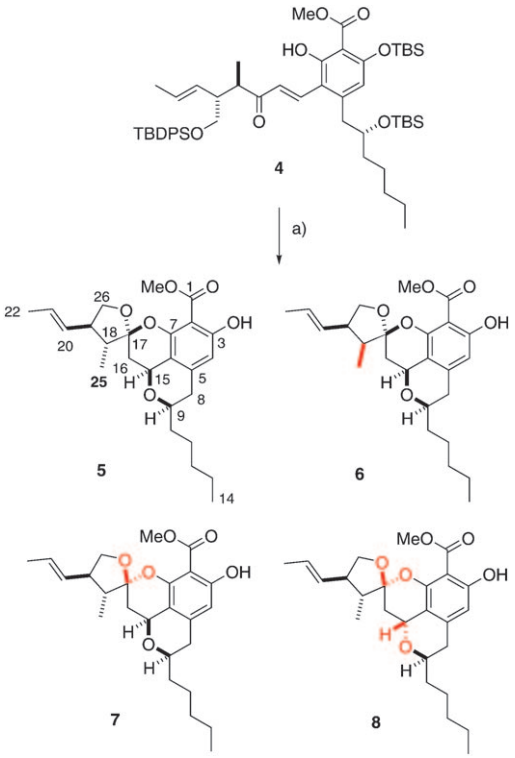
Results and Discussion

Structural issues and strategic considerations: Our original retrosynthesis was directed at structure **3** proposed by Stierle et al.[4] and had to take the then unknown stereochemistry of the all-carbon-quarternary center at C22 into account (Scheme 2). To this end, a convergent approach was pursued that would allow for the incorporation of either enantiomer of aldehyde **A** at a late stage. The suitably protected core structure **B** would be assembled by a Michael addition/spiroacetalization cascade from the linear precursor **C**, which would itself derive from aldehyde **D** and methyl ketone **E** by an aldol condensation.[10,14,15]



Scheme 2. Retrosynthetic analysis of the originally proposed but incorrect structure **3** of berkelic acid.

Much to our surprise, however, treatment of **4** as the synthetic equivalent of the envisaged cyclization precursor **C** with dilute HCl furnished an almost statistical mixture of the diastereomeric spiroacetal products **5–8** (Scheme 3).[10] In contrast to a previous model study by Snider,[11a] attempts to equilibrate the crude mixture by exposure to various acids were futile. Similarly, treatment of any of the pure isomers with PPTS rapidly regenerated the original product distribution. The structure of all four isomers could be established beyond doubt by extensive NMR studies and independently confirmed by a crystal structure analysis of **5**, the stereoisomer corresponding to the originally proposed core structure of berkelic acid.[10] However, the ^{13}C NMR of **5** revealed several significant deviations from the chemical shifts reported for the natural product that could not be attributed to the truncated side chain (Table 1). Most importantly, the shift of the C25 methyl group ($\delta = 14.38$ ppm) differed considerably from the corresponding signal in berkelic acid ($\delta = 11.9$ ppm). NOESY analyses and the solid-state structure of **5** revealed an unfavorable *syn*-periplanar arrangement of this C25 methyl branch and the C16 methylene group of the adjacent tetrahydropyran ring. Although isomers **6–8** avoid



Scheme 3. Key experiment suggesting that the originally proposed stereostructure of berkelic acid needed major revision: a) acetyl chloride, MeOH/CH_2Cl_2, 0 °C→RT, 91 % (**5**/**6**/**7**/**8** 0.9:1:0.8:1.3), cf. ref. [10].

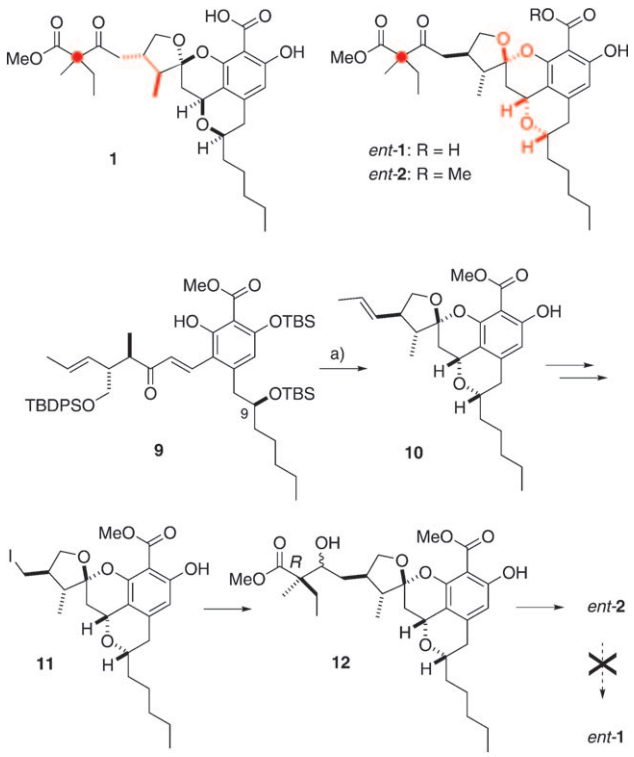
Table 1. Comparison of relevant ^{13}C NMR data of **5**–**8** and **10** with those of berkelic acid reported in the literature; numbering scheme as shown for **5** in Scheme 3. In this comparison, one must keep in mind that the synthetic samples are aromatic methyl esters, whereas the natural product has a free carboxylic acid at C1. Characteristic deviations within the chromane spiroacetal segment are highlighted in bold.

Position	Ref.[a]	**5**[b]	**6**[b]	**7**[b]	**8**[b]	**10**[b]
1	173.6	171.83	171.61	172.04	172.30	172.20
2	101.0	103.31	103.82	103.68	102.44	102.18
3	163.4	**161.20**	**160.67**	162.04	162.52	162.06
4	109.4	109.08	108.94	109.84	108.62	108.97
5	142.3	141.29	**140.86**	141.47	143.22	141.78
6	113.7	114.20	114.08	**117.02**	114.23	113.98
7	153.0	152.69	152.35	153.81	152.72	152.91
8	35.4	35.41	35.38	35.03	35.08	35.41
9	76.5	76.69	76.61	76.12	**73.56**	76.57
10	37.4	37.49	37.47	37.22	**36.41**	37.44
11	26.2	26.19	26.23	26.22	26.32	26.21
12	33.0	33.03	33.06	33.07	33.04	33.06
13	23.7	23.70	23.73	23.70	23.76	23.73
14	14.4	14.39	14.43	14.41	14.43	14.43
15	69.4	69.77	69.73	69.66	**63.29**	69.58
16	35.0	34.16	35.84	**39.41**	35.46	35.19
17	110.7	**112.38**	110.53	**111.69**	110.62	110.49
18	49.2	**50.98**	**47.15**	**51.99**	50.12	50.06
25	11.9	**14.38**	10.56	11.98	11.36	11.23
26	74.1	**72.42**	74.06	**72.94**	73.14	73.12

[a] Ref. [4]; in CD_3OD at 125 MHz. [b] In CD_3OD at 150.9 MHz. The solvent signal was used as reference and the chemical shifts are given relative to TMS ($\delta_C \equiv 49.0$ ppm). The samples were all measured under the same experimental conditions and the chemical shifts in the Table are given to two decimal places for the sake of better internal comparison.

such an eclipsing interaction, their spectral data did not match those of berkelic acid either (see Table 1).[10]

These results made clear that the original structure **3**[4] must be incorrect.[10,16,17] Based on the comprehensive data set and the inspection of molecular models we concluded that **1** or its antipode *ent*-**1** might describe this natural product correctly. In excellent agreement with this notion, treatment of compound **9** (which is nothing but the C9-epimer of **4**) with dilute HCl provided only one major product **10**, the NMR data and NOESY correlations of which nicely corresponded to those reported for the natural product (Scheme 4 and Table 1).[10] The stereostructure was confirmed by X-ray analysis of the derived iodide **11** (Figure 1).[18] This compound could then be converted into both C22 diastereoisomers of berkelic acid methyl ester, but the oxidation of the intermediate alcohol **12** containing an electron-rich phenol core was plagued by undesirable side reactions and was therefore rather low yielding.[10]



Scheme 4. Synthesis-driven structure revision for berkelic acid methyl ester exemplified for the 22*R* isomer. This synthesis had been performed before the absolute configuration of the natural product was known and led to what turned out to be the non-natural enantiomer: a) acetyl chloride, MeOH/CH_2Cl_2, 0 °C → RT, 94 % (d.r. ≥12.5:1), cf. ref. [10].

Even though the NMR spectra of the two C22 isomers of *ent*-**2** recorded at 600 MHz were subtly different, an unambiguous assignment of the rogue C22 quaternary center was not possible since no authentic sample of **2** could be made available for direct comparison. On the other hand, our attempt to form the free acid *ent*-**1** by selective cleavage of the methyl benzoate function in the presence of the aliphat-

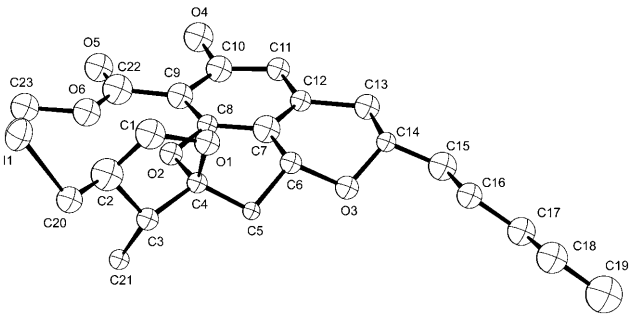


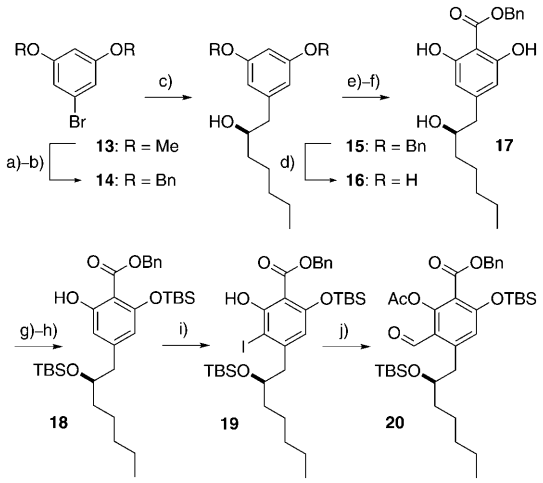
Figure 1. Structure of one of the two crystallographically independent molecules of **11** in the solid state. The anisotropic displacement parameter ellipsoids are drawn at the 50% probability level.[18]

ic methyl ester in the side chain remained unsuccessful (Scheme 4).[10] De Brabander and co-workers later found that $(Bu_3Sn)_2O$ in toluene accomplished this task, but in their case the reaction had to be stopped at partial conversion.[13]

The lessons learnt during our own synthesis-driven structure revision campaign, together with the additional information gathered by the Snider and De Brabander groups, defined the following objectives for the second phase of our project: First and foremost, the two esters must be distinguished by an orthogonal protecting group regimen to enable an effective release of free berkelic acid in the final step of the sequence. Moreover, the sensitivity of the electron-rich pentasubstituted aromatic ring in **1**, which plagued the efficiency of our initial effort, has to be tempered through adequate late-stage manipulations. If successful, these modifications should enable a convergent assembly of the target from relatively simple building blocks, while taking advantage of an efficient cascade reaction sequence for the formation of the complex polycyclic skeleton.[19] In combination with optimized fragment syntheses, this strategy should result in a productive, scalable and flexible second generation total synthesis of this promising target, which was realized as outlined below.

Preparation of the building blocks: The preparation of the key building blocks followed similar lines to our initial Communication[10] but was fully optimized for larger material throughput. Each route is concise and scalable and gives ready access to either enantiomer.

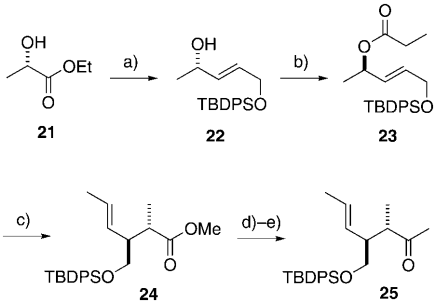
Specifically, the preparation of building block **D** began with Cu^I-catalyzed ring opening of (*R*)-pentyloxirane (> 99% *ee*)[20] by the Grignard reagent derived from 3,5-bis(-benzyloxy)-1-bromobenzene (**14**)[21] giving **15** (Scheme 5). Subsequent hydrogenolysis of the benzyl ethers and Kolbe–Schmitt carboxylation[22] of bis-phenol **16** afforded the corresponding carboxylic acid, which was converted into benzyl ester **17**. This group is orthogonal to the methyl ester in the side chain yet to be installed and can be cleaved under conditions that should not endanger the oxidation-sensitive phenol in the late stages of the synthesis. Global silylation of **17** followed by selective mono-desilylation and regioselective iodination gave **19**. Finally, lithium–iodine exchange,



Scheme 5. a) BBr_3, CH_2Cl_2, −78°C → RT, 95%; b) BnBr, K_2CO_3, DMF, 91%; c) [CuCl(cod)] (10 mol%), (*R*)-2-pentyloxirane, −50°C → RT, 74%; d) H_2, Pd/C (10% *w*/*w*), MeOH, quant.; e) CO_2 (1 atm), $KHCO_3$, glycerin, 150°C; f) NEt_3, BnBr, DMF, RT, 59% (over both steps); g) TBSCl, imidazole, CH_2Cl_2, 89%; h) K_2CO_3, MeOH, 45°C, 72%; i) *N*-iodosuccinimide, CH_2Cl_2, 85%; j) 1) MeLi, Et_2O, −105°C; 2) *t*BuLi, −100°C; 3) DMF, −105 → −35°C; 4) AcCl, −55 → −25°C, 75%. Bn = benzyl, cod = 1,5-cyclooctadiene, TBS = *tert*-butyldimethylsilyl.

reaction of the highly functionalized aryl–lithium intermediate thus formed with DMF, followed by quenching the reaction with acetyl chloride resulted in formylation of the arene[23] and acylation of the phenol to give product **20**. That attempts to acylate the phenol in a separate event met with failure suggests that the presence of two *ortho* carbonyl functions largely reduces its nucleophilicity. The presence of an acetyl group, however, was desirable as it would take an active role in the projected aldol condensation (see below).

A suitable synthesis of fragment **E** hinges on the efficient installation of the vicinal stereocenters (Scheme 6). Mindful of the prowess of the Claisen rearrangement[24] and recognizing that **E** should be accessible from a γ,δ-unsaturated carboxylic acid motif, ester **23** was prepared by Mitsunobu esterification[25] of known lactate-derived alcohol **22**[26] with propionic acid. Whilst this reaction proceeded well under a

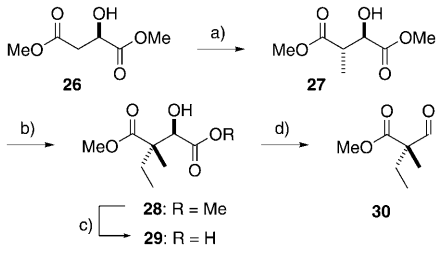


Scheme 6. a) Ref. [26] (96% *ee*); b) propionic acid, PPh_3, DIAD, toluene, 59% (93% *ee*); c) 1) LiHMDS, NEt_3, toluene, −78°C → RT; 2) $TMSCHN_2$, MeOH, 77–81% (over both steps *anti*/*syn* 96:4); d) Me(OMe)NH·HCl, *i*PrMgCl, THF, −25°C → RT, 95%; e) MeMgBr, −20 → 0°C, 92%. DIAD = diisopropyl azodicarboxylate, LiHMDS = lithium hexamethyldisilazide.

variety of conditions, a significant erosion of enantiopurity was observed when conducted in THF (96 → 83% *ee*). However, switching to the less polar toluene gave **23** in an acceptable 93% *ee*.

In our initial Communication, a standard Ireland–Claisen rearrangement of the silylketene acetal derived from *ent*-**23** (KHMDS, TMSCl, toluene)[27,28] provided, upon methylation, *anti*-**24** in good yield and acceptable diastereoselectivity (d.r. 10.2:1).[10] Whilst the minor diastereomer could be removed at a later stage, we were keen to find a more efficient method. Collum and Godenschwager have recently reported intriguing conditions for the enolization of acyclic ketones and esters.[29] As part of a sustained and comprehensive investigation of the nature and reactivity of lithium bases and enolates, these authors recognized that deprotonations of esters mediated by a combination of LiHMDS and NEt_3 in toluene are extremely fast and occur with unprecedented *E*/*Z* selectivity. Furthermore, the resultant lithium ester enolates themselves undergo Claisen rearrangement with outstanding levels of diastereoselection (*E*/*Z* >30:1) without needing to form the corresponding silylketene acetals in situ.[29] The fact that enolization occurs up to 20 times faster in the absence of THF and, in any event, the corresponding THF-ligated enolates fail to undergo efficient rearrangement renders this one of the most significant modern developments in Claisen chemistry. Indeed, rearrangement of **23** under the Collum–Godenschwager conditions afforded ester **24** in good yield and vastly improved diastereoselectivity (d.r. 96:4) on a gram scale after methylation of the crude acid. Subsequent transformation of **24** into the corresponding Weinreb amide[30] and addition of MeMgBr at low temperature readily gave the desired fragment **25**.

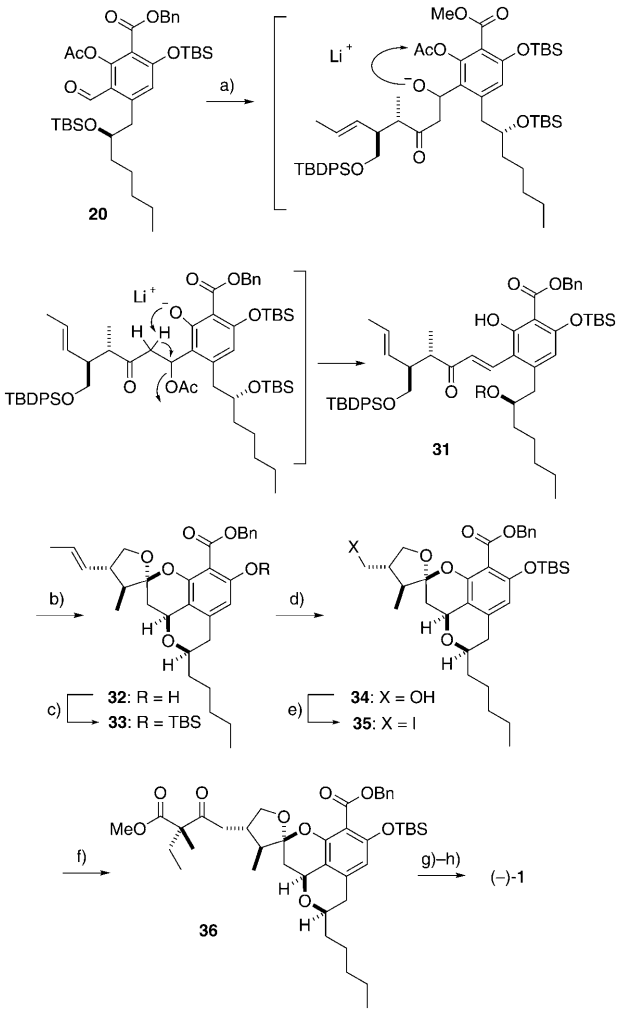
Fragment **A** containing the all-carbon quarternary center was prepared in either enantiomeric form by following a literature procedure (Scheme 7).[31] Thus, treatment of dimethyl-D-malate (**26**) with LDA (2.1 equiv) followed by C-alkylation of the resulting dianion with methyl iodide gave **27**. A second alkylation using ethyl iodide as the electrophilic partner furnished **28** (d.r. 95:5), which was selectively saponified to the corresponding α-hydroxy acid **29**. Electrochemical oxidative decarboxylation of **29** occurred in well reproducible 55–59% yield to give the required aldehyde **30**.[31]



Scheme 7. a) 1) LDA, THF, −78°C; 2. MeI, −70°C, 50%; b) 1. LDA, THF, −78°C; 2. EtI, −78 → 4°C, 60%; c) KOH, MeOH/H_2O (9:1), 94–99%; d) NEt_3, MeOH, Pt-electrodes, 24 V, 55–59%. LDA = lithium diisopropylamide.

All attempts to further improve this procedure or to effect the same transformation using chemical oxidants (i.e., NIS or NBS)[32] largely met with failure. While, in principle, *ent*-**30** could be accessed from the same starting material simply by reversing the order of the alkylation steps (i.e., ethylation prior to methylation), such a process resulted in significantly reduced enolate reactivity towards the second electrophilic partner and poorer levels of diastereoselection. Thus, we chose to prepare the antipode *ent*-**30** by the existing procedure beginning from dimethyl-L-malate (*ent*-**26**).

Fragment linkage and core assemblage: In analogy to our initial report, but now working in the correct stereochemical series,[10] fragments **D** and **E** were joined together by an aldol condensation. Specifically, the kinetic enolate of



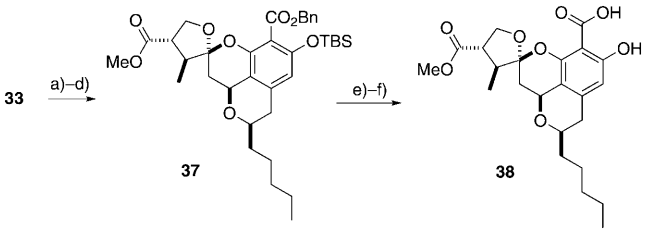
Scheme 8. a) **25**, LDA, THF, −78°C → RT, 65%; b) acetyl chloride, MeOH/CH_2Cl_2, 0°C → RT, 92%; c) TBSCl, imidazole, CH_2Cl_2, RT, 98%; d) 1. OsO_4 (2 mol%), N-methylmorpholine-N-oxide, acetone; 2. $Pb(OAc)_4$, CH_2Cl_2, RT; 3. $NaBH_4$, THF/H_2O, 0°C→RT, 80% (over three steps); e) I_2, PPh_3, imidazole, CH_2Cl_2, 94%; f) 1. *t*BuLi, Et_2O, −105°C, then **30**; 2. DMP, K_2CO_3, CH_2Cl_2, 0°C, 74% (over two steps); g) Bu_4NF, THF, 95%; h) H_2, $Pd(OH)_2$ (10% *w*/*w*), EtOAc, RT, 88%. LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, DMP = Dess–Martin periodinane.

methyl ketone **25** was reacted with aldehyde **20** to provide product **31** (Scheme 8). This transformation takes advantage of the acetyl group in the substrate, which migrates from the phenolic site in **20** to the more basic alkoxide generated in the initial step. The released phenoxide then promotes elimination of the resulting acetate ester to give the required enone **31**. Subsequent treatment with HCl/MeOH provided compound **32** as a single isomer in 92% yield through an obviously well-orchestrated triple-deprotection/1,4-addition/spirocyclization cascade; no sign of trans-esterification was observed.

At this juncture we considered a minor diversion from our initial synthesis, the latter stages of which had suffered from the fact that the free phenol in the assembled core was highly susceptible to oxidation.[33] As such, protection of the phenol as its TBS ether **33** resulted in a vast improvement, with the three-stage conversion to **34** proceeding in high yield. Despite the advantages offered by the new protecting group, its lability required some optimization of the reaction conditions. Specifically, during the oxidative cleavage of the intermediate diol formed by OsO_4-catalyzed dihydroxylation of **33**, the TBS group could be completely retained only if the stoichiometry of the oxidant was rigorously controlled. To this end, one equivalent of a stock solution of $Pb(OAc)_4$ in CH_2Cl_2 was added dropwise and the reaction monitored closely by TLC. Reduction of the resulting crude aldehyde with $NaBH_4$ in MeOH also led to partial deprotection; however, employing a milder mixed-phase THF/H_2O system left the TBS ether untouched. Conversion of alcohol **34** thus formed into iodide **35** again occurred with partial TBS deprotection, which was attributed to residual hydrogen iodide in the commercial iodine and/or to impurities in the imidazole. Gratifyingly, the use of freshly sublimed and recrystallized reagents allowed for full retention of the protective group.

For the final fragment coupling, the pre-nucleophile **35** was subjected to halogen–metal exchange at low temperature followed by the addition of aldehyde **30**. Oxidation of the resulting secondary alcohol with Dess–Martin periodinane[34] afforded fully protected berkelic acid **36**. Fluoride-induced desilylation followed by hydrogenolysis of the benzyl ester over Pearlman's catalyst[35] proceeded uneventfully to provide berkelic acid (−)-**1**. The recorded spectra for the synthetic samples were fully consistent with the published data, and the optical rotation of **1** was also in good agreement with those for natural and synthetic berkelic acid reported in the literature.[4,12,13] It should be noted, however, that we encountered problems in the purification, handling and storage of berkelic acid such that oxidative degradation was a common frustration. Only the use of carefully degassed solvents and storage in a matrix of frozen and degassed benzene resolved these issues. Suffice it to mention that the synthesis of non-natural berkelic acid (+)-**1** has also been accomplished by the same route (see the Experimental Section).

Finally, we prepared an analogue deprived of the side chain carrying the quaternary center (Scheme 9). This goal



Scheme 9. a) OsO_4 (5 mol%), NMO, acetone; b) $Pb(OAc)_4$, CH_2Cl_2; c) $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O 2:1, (2*E*)-butene; d) $TMSCHN_2$, MeOH, 0°C, 96% (over four steps); e) Bu_4NF, THF; f) H_2 (1 atm), $Pd(OH)_2$ cat., EtOAc, 85% (over both steps).

was easily attained by subjecting the crude aldehyde formed by the oxidative cleavage of the olefinic terminus in **33** to Pinnick oxidation[36] and esterification with trimethylsilyl diazomethane. Subsequent cleavage of the silyl group in **37** and hydrogenolysis of the remaining benzyl ester gave the truncated congener **38** for biological testing. With this material and our synthetic samples of analytically pure (−)-**1**, (+)-**1** and the 22*S*-diastereomer thereof in hand (cf. Experimental Section), we hope to resolve a puzzle resulting from contradictory reports from the groups of Stierle and Snider. Whereas the isolation team claimed highly selective cytotoxicity for berkelic acid against the OVCAR-3 tumor cells, as outlined in the Introduction,[4] the latter group found that their synthetic material did not show significant activity at 10^{-5} M concentration when profiled in the NCI 60 cancer cell-line assay.[12b] The results of our investigation will be reported in a separate publication in due time.

Conclusion

A concise and productive total synthesis of berkelic acid (**1**) has been accomplished that takes the structure revision previously proposed by our group into account and remedies the shortcomings of the original route.[10] Specifically, the tetracyclic core **32** of the target was assembled as a single diastereomer by a triple-deprotection/1,4-addition/spiroacetalization cascade, which proceeded with remarkable efficiency. The required cyclization precursor **31** was obtained from segments **20** and **25** by an aldol condensation, in which the phenolic acetate moiety adjacent to the aldehyde in **20** not only serves as a passive protecting group but also takes an active and productive role. The preparation of the methyl ketone **25** benefits from the Collum–Godenschwager modification of the ester enolate Claisen rearrangement, which proved superior to the classical Ireland–Claisen process in terms of diastereoselectivity. Although our previous work had shown that the elaboration of **32** into the target can be accomplished without any extra protecting group manipulation, the short detour of blocking the free phenolic site as a TBS-ether was found to be highly beneficial. Whilst this tactic added two extra steps to the longest linear sequence, it tempered the sensitivity of the pentasubstituted arene ring toward oxidation and hence greatly improved the

productivity and reproducibility of the route. The choice of orthogonal ester groups for the benzoate and the aliphatic carboxylate terminus of the side chain ensured an efficient release of free berkelic acid in the final step. Collectively, the modifications allowed us to obtain (−)-**1** in ≈5% yield over the 19 steps in the longest linear sequence. Moreover, the flexibility inherent to the successful blueprint qualifies it as a basis for a future synthesis-driven molecular editing of this interesting fungal metabolite.[37]

Experimental Section

The entire experimental section can be found in the Supporting Information, including compound characterization data and copies of NMR spectra.

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