Natural Products

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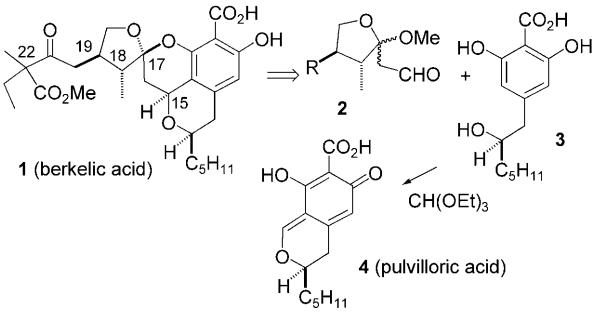
Synthesis of (−)-Berkelic Acid**

*Xiaoxing Wu, Jingye Zhou, and Barry B. Snider**

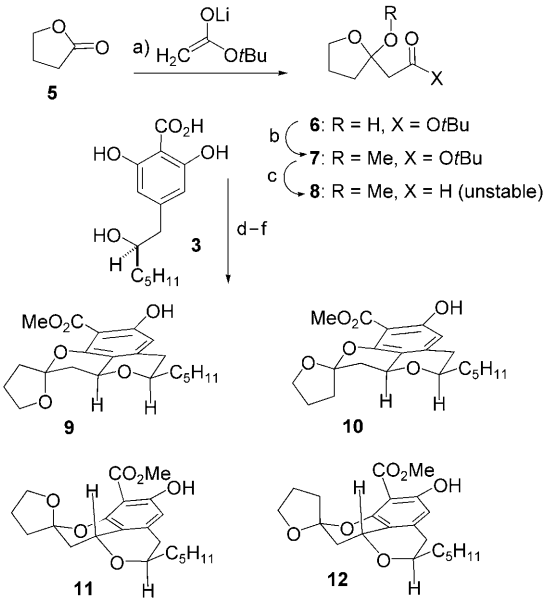
Stierle and co-workers recently isolated berkelic acid (**1**) from an acid mine waste fungal extremophile (Scheme 1).[1] The structure was determined to be a novel spiroketal from the analysis of the NMR and mass spectral data. The relative



Scheme 1. Retrosynthesis of berkelic acid (**1**).

stereochemistry of the side-chain stereocenter (C22) and the absolute stereochemistry were not assigned. Berkelic acid inhibits MMP-3 and caspase-1 and shows selective activity toward ovarian cancer OVCAR-3 with a GI_{50} of 91 nM. This potent and selective activity and its limited accessibility from natural sources make it a significant synthetic target. We thought that **1** should be accessible by a highly convergent route starting from ketal aldehyde **2** and 2,6-dihydroxybenzoic acid **3**. Acid **3**, a synthetic, and possibly biosynthetic, precursor of pulvilloric acid (**4**), has been prepared in both racemic[2] and optically pure form.[3]

In 2007,[4] we reported an efficient route to the tetracyclic core of berkelic acid by condensing racemic **3**[2] with model ketal aldehyde **8** in an oxa-Pictet–Spengler reaction[5] (Scheme 2). Addition of the enolate of *tert*-butyl acetate to butyrolactone (**5**) afforded hemiketal ester **6**[6] which was converted into ketal ester **7** in 56% overall yield by treatment with Dowex 50WX8-400-H^+ in MeOH for 12 hours at 25 °C. Reduction using DIBAL-H in diethyl ether at −78 °C afforded the unstable ketal aldehyde **8**, which was treated with (±)-**3** and Dowex 50WX8-400-H^+ in MeOH for 12 hours



Scheme 2. Reagents and conditions: a) LDA, *t*BuOAc, THF, −78 to −30 °C, 2 h; b) Dowex 50WX8-400-H^+, MeOH, 25 °C, 12 h (56% from **5**); c) DIBAL-H, ether, −78 °C, 1.5 h; d) (±)-**3**, Dowex 50WX8-400-H^+, MeOH, 25 °C, 12 h; e) CH_2N_2, diethyl ether; f) 0.2% TFA in $CDCl_3$, 25 °C, 12 h (50% of **9** from **3**). LDA = lithium diisopropylamide, DIBAL-H = diisobutylaluminum hydride.

at 25 °C to provide a mixture of the tetracyclic acids that was then treated with diazomethane to give a 4:1:4:1 mixture of tetracycles **9**–**12**, respectively. MMX calculations using conformational searching provided the relative strain energies for **9**–**12** of 28.1, 28.6, 30.5, and 30.8 kcal mol^{-1}, respectively,[7] indicating that the desired product **9** is more stable than the other major product **11** by 2.4 kcal mol^{-1}. Therefore, we explored the equilibration of this mixture by treatment with 0.2% TFA in $CDCl_3$ for 12 hours at 25 °C, which provided a 20:2:1:0 mixture of **9**–**12**, respectively, from which **9** could be isolated in 50% overall yield from (±)-**3**.[8]

We report herein the preparation of fully functionalized ketal aldehydes **21** and *ent*-**21** and their condensation with (*R*)-(−)-**3** leading to the first synthesis of (−)-berkelic acid, the reassignment of the stereochemistry at C18 and C19, the assignment of the relative stereochemistry at C22, and the assignment of the absolute stereochemistry. As this work was being completed, Fürstner and co-workers reported a synthesis of the enantiomer of the methyl ester of berkelic acid and reassigned the stereochemistry at C18 and C19.[9] We had difficulty in scaling up the synthesis[3] of (*R*)-(−)-**3** reported by Rödel and Gerlach, and therefore modified it as shown in Scheme 3. Deprotection of **13** using BBr_3[10] afforded the resorcinol in 97% yield, which was then protected to give compound **14**[11] in 94% yield. Halogen–metal exchange of **14**

[*] X. Wu, Dr. J. Zhou, Prof. B. B. Snider
Department of Chemistry, MS 015, Brandeis University
Waltham, MA 02454-9110 (USA)
Fax: (+1) 781-736-2516
E-mail: snider@brandeis.edu

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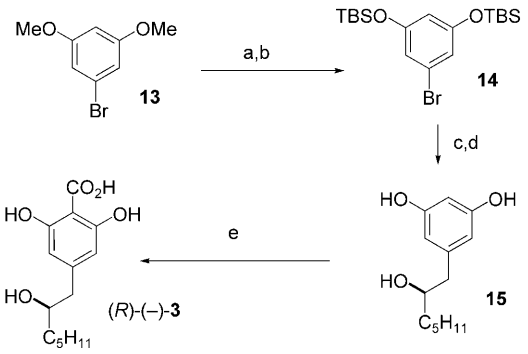
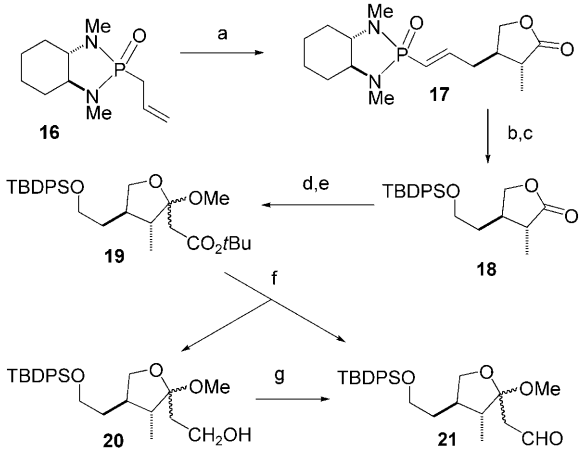


Scheme 3. Reagents and conditions: a) BBr_3, CH_2Cl_2, −78 to 25 °C, 12 h (97%); b) TBSCl, imidazole, DMF, 25 °C, 12 h (94%); c) *t*BuLi (2.2 equiv), THF, −78 °C, 30 min, then (*R*)-(+)-1,2-epoxyheptane (1.2 equiv), −25 °C, 16 h (74%); d) KOH, EtOH, 55 °C, 8 h (80%); e) CO_2, $KHCO_3$, glycerol, 150 °C, 5 h (59%). TBSCl = *tert*-butyldimethylchlorosilane, DMF = *N*,*N*-dimethylformamide.

with *t*BuLi at −78 °C and addition of (*R*)-(+)-2-pentyloxirane,[12] followed by removal[13] of the TBS groups with KOH in EtOH at 55 °C for eight hours provided **15**. Carboxylation as previously described[2,3] gave (*R*)-(−)-**3**.

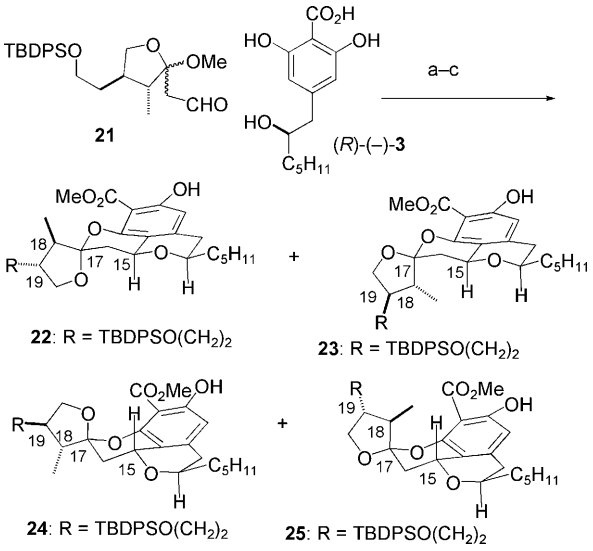
Ketal aldehyde **21** was prepared efficiently using the procedure reported by Hanessian et al., as shown in Scheme 4.[14] Metalation of **16** with *n*BuLi at −100 °C, addition of 2-butenolide at −100 °C, and trapping with excess MeI at −78 °C afforded **17** in 73% yield with greater than 95% selectivity. Ozonolysis and subsequent reduction with $NaBH_4$, and then protection with a TBDPS group provided **18** in 52% yield. Lactone **18** was converted into



Scheme 4. Reagents and conditions: a) *n*BuLi (1.2 equiv), −100 °C, 15 min, −78 °C, 10 min, recool to −100 °C, then 2-butenolide (1.2 equiv), −100 °C, 10 min, −78 °C, 30 min, then MeI (5 equiv), −78 to 25 °C, 4 h (73%); b) O_3, $MeOH/CH_2Cl_2$ (1:1), −78 °C, 20 min, then $NaBH_4$, −78 to 25 °C, 3 h; c) TBDPSCl, imidazole, DMF, 25 °C, 12 h (52% from **17**); d) *t*BuOAc (6 equiv), LHMDS (6 equiv), −78 °C, 1 h, −78 to 25 °C, 3 h; e) Dowex 50WX8-400-H^+, MeOH, 25 °C, 12 h (78% from **18**); f) DIBAL-H (4.1 equiv), diethyl ether, −78 °C, 1.5 h (39% of **20** and 43% of **21**); g) oxalyl chloride (3 equiv), DMSO (5 equiv), Et_3N (1 equiv), CH_2Cl_2, −78 °C, 2 h, −78 to −30 °C, 1 h (52%). TBDPS = *tert*-butyldiphenylchlorosilane, LHMDS = lithiumhexamethyldisilazide, DMSO = dimethylsulfoxide.

ketal aldehyde **21** using the procedure developed for the conversion of **5** into **8**. Addition of the lithium enolate of *tert*-butyl acetate and ketal formation afforded **19** in 78% yield. DIBAL-H reduction then gave aldehyde **21** (43% yield) and alcohol **20** (39% yield), which was then subjected to Swern oxidation to give additional aldehyde **21** (52% yield).

Condensation of **21** with (*R*)-(−)-**3** using Dowex 50WX8-400-H^+ in MeOH for 12 hours and subsequent diazomethane esterification gave a 57% yield of an approximately 4:1:3:0 mixture of **22**–**25**, respectively, for which the stereochemistry was assigned by analogy to **9**–**12** (Scheme 5).[4] Surprisingly, attempted equilibration using 0.2% TFA in $CDCl_3$ had little



Scheme 5. Reactions and conditions: a) Dowex 50WX8-400-H^+, MeOH, 25 °C, 12 h; b) CH_2N_2, ether; c) 0.2% TFA in $CDCl_3$, 25 °C, 12 h. TFA = trifluoroacetic acid.

effect, giving an approximately 2:trace:1:0 mixture of **22**–**25**, respectively. The presence of this mixture after equilibration was of considerable concern, because we had hypothesized that the stereochemistry at both C15 and C17 in the natural product was thermodynamically controlled. However, the MMX calculated relative strain energies for **22**–**25** of 30.5, 31.0, 31.3, and 33.6 kcal mol^{-1}, respectively,[7,15] indicated that **22** was only 0.8 kcal mol^{-1} more stable than **24**, whereas model tetracycle **9** was more stable than **11** by 2.4 kcal mol^{-1}. Therefore the presence of considerable quantities of both **22** and **24** at equilibrium was not surprising.

Of greater concern, the ^{1}H NMR spectrum of the desired product **22**, which could be isolated in low yield from the mixture, did not fit well with the data for the berkelic acid methyl ester (see the Supporting Information), even taking into account the differences in the side chains. This data suggested that the stereochemistry of the natural product is not the same as that of **22**, which has since been established by the synthesis of berkelic acid methyl ester by Fürstner and coworkers.[9] The stereochemistry of berkelic acid was assigned on the basis of an NOE between the methyl group (C25) and the β-hydrogen atom on C16 as well as an H atom on C20. However, MMX calculations indicated that the shortest

distances from a methyl hydrogen atom in **1** to the C16 Hβ atom is 2.61 Å, and to the C16 Hα atom is 2.46 Å. Therefore, if **1** were the structure of berkelic acid, there should be an NOE from the methyl group to both the C16 Hβ atom and C16 Hα atom. MMX calculations indicated that the observed NOE in berkelic acid to only the C16 Hβ atom fits compound **26**, which has the opposite stereochemistry at both C18 and C19. In this isomer, the shortest distance from a methyl hydrogen atom to the C16 Hβ atom is 2.49 Å and to the C16 Hα atom is 3.51 Å (Figure 1). Furthermore, the relative strain

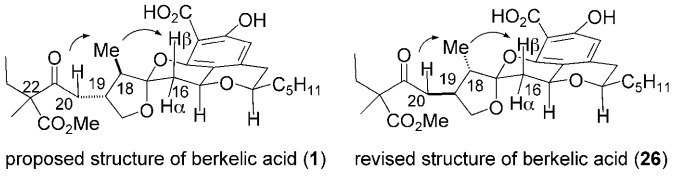
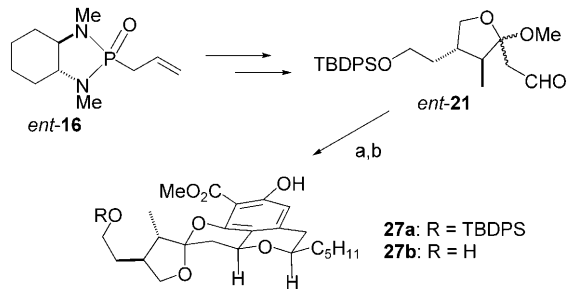


Figure 1. Proposed and revised structures of berkelic acid showing NOE correlations to the methyl group.

energy of the four diastereomers of **22**–**25** having the stereochemistry inverted at both C18 and C19 are 28.9, 31.3, 32.8, and 33.3 kcal mol^{-1}, respectively.[7,15] The desired isomer **27a** is calculated to be 3.9 kcal mol^{-1} more stable than the diastereomer of **24** having stereochemistry inverted at both C18 and C19. This analysis suggested that the structure of berkelic acid is **26** rather than **1**.

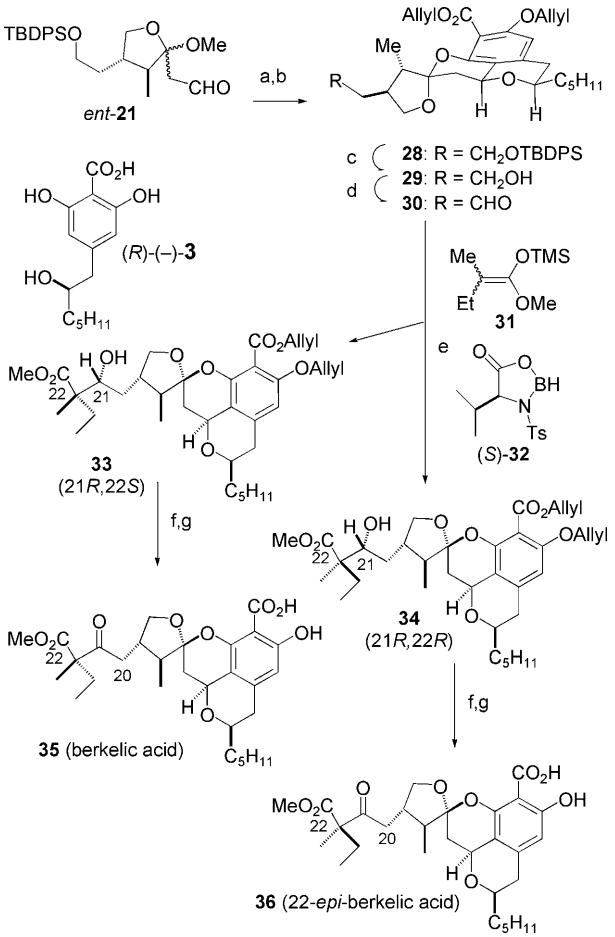
Fortunately this was easy to establish. Compound *ent*-**16** was converted into *ent*-**21** and condensed with (*R*)-(−)-**3** using Dowex 50WX8-400-H$^+$ in MeOH (Scheme 6). This reaction



Scheme 6. Reagents and conditions: a) (*R*)-(−)-**3**, Dowex 50WX8-400-H$^+$, MeOH, 25 °C, 60 h; b) CH_2N_2, diethyl ether (30% of **27a**, 22% of **27b**).

appears to be slower than that with **21**, requiring 60 hours for complete reaction, which led to partial cleavage of the TBDPS group. Esterification with diazomethane afforded 30% of **27a** and 22% of **27b** as the only products. No change occurred upon TFA equilibration, confirming that **27a** is much more stable than the other three diastereomers as calculated. As we had hoped the spectral data of **27a** fit well with those of the berkelic acid methyl ester (see the Supporting Information) suggesting that **26** is the structure of berkelic acid and that the stereochemistry at both C15 and C17 in the natural product is thermodynamically controlled.

The methyl ester is not a suitable protecting group for the benzoic acid because it cannot be cleaved in the presence of the side chain methyl ester.[9] Therefore we condensed *ent*-**21** and (*R*)-(−)-**3** with Dowex 50WX8-400-H$^+$ in MeOH for 60 hours and then treated the crude tetracyclic salicylic acid, having the partially deprotected side chain, with allyl bromide and K_2CO_3 in DMF to give **28** (32% yield) and **29** (20% yield) without allylation of the primary alcohol of **29** (Scheme 7).[16] Desilylation of **28** with TBAF/AcOH (1:1) afforded alcohol **29** in 86% yield so that the overall yield of **29** from *ent*-**21** is 48%. Dess–Martin oxidation of **29** afforded aldehyde **30** in 88% yield. Aldol reactions under strongly basic conditions did not work well. Reaction of **30** with trimethylsilyl ketene acetal **31**,[17] LiCl, and *N*-methylimidazole[18] afforded an inseparable mixture of all four possible isomers. Fortunately, reaction of **30** and **31** as described by Kiyooka et al.[19] using (*S*)-**32**, which is prepared in situ from *N*-Ts-(*S*)-valine and BH_3·THF, was selective for the *Si* face affording only two of the four aldol adducts from which pure **33** and **34** were each



Scheme 7. Reagents and conditions: a) Dowex 50WX8-400-H$^+$, MeOH, 25 °C, 60 h; b) allyl bromide, K_2CO_3, DMF (32% of **28** and 20% of **29** from *ent*-**21**); c) TBAF/AcOH (1:1) in THF, 12 h (86%); d) Dess–Martin (88%); e) *N*-Ts-(*S*)-valine, BH_3·THF, CH_2Cl_2, 0 °C, 30 min, 25 °C, 30 min, cool to −78 °C, add **30**, add **31**, −78 °C, 4 h (40% of **33** and 40% of **34**); f) Dess–Martin (85% from **33**, 77% from **34**); g) [Pd(Ph$_3$P)$_4$] (0.2 equiv), HCO_2H (40 equiv), Et_3N (40 equiv), THF, 25 °C, 15 h (78% of **35**, 72% of **36**). TBAF = *n*-tetrabutylammonium fluoride.

isolated in 40% yield. A similar reaction using *N*-Ts-(*R*)-valine resulted in a reduction to give primary alcohol **29**. Apparently, the stereochemical preferences of **30** and (*S*)-**32** are matched, while those of **30** and (*R*)-**32** are mismatched resulting in a reduction instead of an aldol reaction.[20]

Dess–Martin oxidation (85% yield) of the less polar isomer **33** and subsequent removal (78% yield) of both allyl groups with $[Pd(Ph_3P)_4]$, Et_3N, and HCO_2H afforded berkelic acid (**35**). The ^1H and ^{13}C NMR spectral data of **35** in both $CDCl_3$ and CD_3OD are identical to those of the natural berkelic acid. A similar sequence from the more polar isomer **34** afforded **36**. The spectral data of **36** are similar to those of berkelic acid, but there are significant differences, most notably in the ^1H NMR spectra for the hydrogen atom on C20 and the methyl and ethyl groups on C22.

The Kiyooka aldol reaction leads to two, rather than four, aldol products making it possible to isolate pure **33** and **34**. Unfortunately, this reaction controls the stereochemistry at the C21, which is lost in the Dess–Martin oxidation, rather than at C22. We prepared a series of analogous compounds from a model aldehyde and established their stereochemistry unambiguously. Comparison of the differences between the spectra of **33** and **34** to those between the model compounds, as is fully described in the Supporting Information, leads to the tentative C22 stereochemistry assignment shown.[21]

The optical rotation of synthetic berkelic acid (**35**), $[\alpha]_D^{22} = -115.5°$ ($c = 0.55$, MeOH), has the same sign as that of the natural product, $[\alpha]_D^{22} = -83.5°$ ($c = 0.0113$, MeOH), indicating that the absolute stereochemistry is as shown. The differing numerical values may result from the low sample concentration used for the natural product.

In conclusion, we have completed the first synthesis of (−)-berkelic acid (**35**), confirming the reassignment of the stereochemistry at both C18 and C19 by Fürstner and coworkers, establishing the absolute stereochemistry, and tentatively assigning the stereochemistry at C22. The synthesis proceeds with a longest linear sequence of only 13 steps in 2% overall yield by using the novel condensation of (*R*)-(−)-**3** and *ent*-**21** to efficiently and stereospecifically construct the tetracyclic core.

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[21] In the synthesis of berkelic acid methyl ester, Fürstner and coworkers state that the spectral data of the stereoisomer corresponding to **36**, not **35**, match well with those of the natural berkelic acid methyl ester. However, the report later states that confident assignment of the configuration of the stereochemistry at C22 mandates direct comparison with an authentic sample. The spectral data for our sample of **35** corresponds well to those of natural berkelic acid, while those of **36** do not, but the stereochemical assignment of **35** is based on comparison to analogues as described in the Supporting Information and thus is not fully secure.

