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Synthesis of (−)-Berkelic Acid**

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Keywords

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Stierle and coworkers recently isolated berkelic acid (**1**) from an acid mine waste fungal extremophile (see Scheme 1).[1] The structure was determined to be a novel spiroketal based on the analysis of the NMR and mass spectral data. The relative stereochemistry of the side chain stereocenter (C-22) 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] (see Scheme 2). Addition of the enolate of *t*-butyl acetate to butyrolactone (**5**) afforded hemiketal ester **6** [6] which was converted to ketal ester **7** in 56% overall yield by treatment with Dowex 50WX8-400-H^+ in MeOH for 12 h at 25 °C. Reduction with DIBAL-H in ether at −78 °C afforded unstable ketal aldehyde **8**, which was treated with (±)-**3** and Dowex 50WX8-400-H^+ in MeOH for 12 h at 25 °C to provide a mixture of the tetracyclic acids that was treated with diazomethane to give a 4:1:4:1 mixture of tetracycles **9–12**, respectively. MMX calculations with conformational searching provided relative strain energies for **9–12** of 28.1, 28.6, 30.5, and 30.8 kcal/mol, respectively,[7] indicating that the desired product **9** is more stable than the other major product **11** by 2.4 kcal/mol. Therefore, we explored the further equilibration of this mixture by treatment with 0.2% TFA in $CDCl_3$ for 12 h 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 acid (±)-**3**.[8]

We report here 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 C-18 and C-19, the assignment of the relative stereochemistry at C-22 and the assignment of the absolute stereochemistry. As this work was being completed, Fürstner reported a synthesis of the enantiomer of the methyl ester of berkelic acid and reassigned the stereochemistry at C-18 and C-19.[9] We had difficulty in scaling up Gerlach's

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synthesis[3] of (*R*)-(−)-3 and modified it as shown in Scheme 3. BBr_3 deprotection[10] of **13** afforded the resorcinol in 97% yield, which was protected to give bis TBS ether **14**[11] in 94% yield. Halogen-metal exchange with *t*BuLi at −78 °C and addition of (*R*)-(+)-2-pentyloxirane [12] followed by deprotection[13] of the TBS ethers with KOH in EtOH at 55 °C for 8 h provided **15**. Carboxylation as previously described[2,3] gave (*R*)-(−)-3.

Ketal aldehyde **21** was prepared efficiently using Hanessian's procedure 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 >95% selectivity. Ozonolysis followed by reduction with $NaBH_4$ and protection provided **18** in 52% yield. Lactone **18** was converted to ketal aldehyde **21** using the procedure developed for the conversion of **5** to **8**. Addition of the lithium enolate of *t*-butyl acetate and ketal formation afforded **19** in 78% yield. DIBAL-H reduction gave aldehyde **21** (43%) and alcohol **20** (39%), which was subjected to Swern oxidation to give additional aldehyde **21** (52%).

Condensation of **21** with (*R*)-(−)-3 using Dowex 50WX8-400-H^+ in MeOH for 12 h followed by diazomethane esterification gave a 57% yield of an approximately 4:1:3:0 mixture of **22–25**, respectively, whose stereochemistry was assigned by analogy to **9–12** (see Scheme 5).[4] Surprisingly, attempted equilibration with 0.2% TFA in $CDCl_3$ had little effect, giving an approximately 2:trace:1:0 mixture of **22–25**. This was of considerable concern, because we had hypothesized that the stereochemistry at both C-15 and C-17 in the natural product was thermodynamically controlled. However, the MMX relative strain energies for **22–25** of 30.5, 31.0, 31.3, and 33.6 kcal/mol, respectively,[7,15] indicated that **22** is only 0.8 kcal/mol more stable than **24**, whereas model tetracycle **9** was more stable than **11** by 2.4 kcal/mol. Therefore the presence of considerable quantities of both **22** and **24** at equilibrium is not surprising.

Of greater concern, the ^1H 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 berkelic acid methyl ester (see supporting information) even taking into account the differences in the side chain. This 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.[9] The stereochemistry of berkelic acid was assigned based on an NOE from the methyl group (C-25) to H-16β and one H-20. However, MMX calculations indicated that the shortest distance from a methyl hydrogen in **1** is 2.61 Å to H-16β and 2.46 Å to H-16α. Therefore, if **1** were the structure of berkelic acid, there should be an NOE from the methyl group to both H-16β and H-16α. MMX calculations indicated that the observed NOE in berkelic acid to only H-16β fits compound **26**, with opposite stereochemistry at both C-18 and C-19. In this isomer, the shortest distance from a methyl hydrogen is 2.49 Å to H-16β and 3.51 Å to H-16α (see Figure 1). Furthermore, the relative strain energy of the four diastereomers of **22–25** with the stereochemistry inverted at both C-18 and C-19 are 28.9, 31.3, 32.8, and 33.3 kcal/mol respectively.[7,15] The desired isomer **27a** is calculated to be 3.9 kcal/mol more stable than the diastereomer of **24** with stereochemistry inverted at C-18 and C-19. This analysis suggested that the structure of berkelic acid is **26** rather than **1**.

Fortunately this was easy to establish. *ent*-**16** was converted to *ent*-**21** and condensed with (*R*)-(−)-3 with Dowex 50WX8-400-H^+ in MeOH (see Scheme 6). This reaction appears to be slower than that with **21**, requiring 60 h 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 on 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 berkelic acid methyl ester (see supporting information) suggesting that **26** is the structure of berkelic acid and that the stereochemistry at both C-15 and C-17 in the natural product is thermodynamically controlled.

The methyl ester is not a suitable protecting group for the benzoic acid because it can't 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 h and treated the crude tetracyclic salicylic acid with the partially deprotected side chain with allyl bromide and K_2CO_3 in DMF to give **28** (32%) and **29** (20%) without allylation of the primary alcohol of **29** (see Scheme 7).[16] Desilylation of **28** with TBAF/HOAc 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] and LiCl and *N*-methylimidazole[18] afforded an inseparable mixture of all four possible isomers. Fortunately, reaction of **30** and **31** as described by Kiyooka[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 isolated in 40% yield. A similar reaction using *N*-Ts(*R*)-valine resulted in 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 reduction instead of aldol reaction.[20]

Dess-Martin oxidation (85%) of the less polar isomer **33** and deprotection (78%) 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 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 H-20 and the methyl and ethyl groups on C-22.

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 alcohol center (C-21), which is lost in the Dess-Martin oxidation, rather than at C-22. 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** with those between the model compounds as is fully described in the supporting information leads to the tentative C-22 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 Fürstner's reassignment of the stereochemistry at C-18 and C-19, establishing the absolute stereochemistry, and tentatively assigning the stereochemistry at C-22. The synthesis proceeds with a longest linear sequence of only 13 steps in 2% overall yield using the novel condensation of (*R*)-(−)-3 and *ent*-**21** to efficiently and stereospecifically construct the tetracyclic core.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Stierle AA, Stierle DB, Kelly K. J Org Chem 2006;71:5357–5360. [PubMed: 16808526]
2. Bullimore BK, McOmie JFW, Turner AB, Galbraith MN, Whalley WB. J Chem Soc C 1967:1289–1293.
3. Rödel T, Gerlach H. Liebigs Ann Chem 1997:213–216.

4. Zhou J, Snider BB. Org Lett 2007;9:2071–2074. [PubMed: 17465557]
5. The mechanism of the reaction of 3 with 8 is fully discussed in our model study.[4] For a review of the oxa-Pictet-Spengler reaction, see: Larghi EL, Kaufman TS. Synthesis 2006:187–220.
6. Kim P, Olmstead MM, Nantz MH, Kurth MJ. Tetrahedron Lett 2000;41:4029–4032.
7. PCMODEL version 8.0 from Serena Software was used with MMX. Calculations were carried out on analogues with the pentyl side chain replaced by a methyl group to minimize irrelevant conformational complexity. We suspect that the relative energies of 10 and 12 are too low because the calculations do not fully reflect the additional stability of 9 and 11 due to the anomeric effect.
8. For another model study, see: a) Marsini MA, Huang Y, Lindsey CC, Wu KL, Pettus TRR. Org Lett 2008;10:1477–1480. [PubMed: 18336038] b) Huang Y, Pettus TRR. Synlett 2008:1353–1356. [PubMed: 19183702]
9. Buchgraber P, Snaddon TN, Wirtz C, Mynott R, Goddard R, Fürstner A. Angew Chem 2008;120:8578–8582.Angew Chem Int Ed 2008;47:8450–8454.
10. a) Dol GC, Kamer PCJ, van Leeuwen PWNM. Eur J Org Chem 1998:359–364. b) Sienkowska MJ, Farrar JM, Zhang F, Kusuma S, Heiney PA, Kaszynski P. J Mater Chem 2007;17:1399–1411.
11. Bharathi P, Zhao H, Thayumanavan S. Org Lett 2001;3:1961–1964. [PubMed: 11405755]
12. Prepared by hydrolytic kinetic resolution: Schaus SE, Brandes BD, Larrow JF, Tokunaga M, Hansen KB, Gould AE, Furrow ME, Jacobsen EN. J Am Chem Soc 2002;124:1307–1315. [PubMed: 11841300]
13. Jiang ZY, Wang YG. Chem Lett 2003;32:568–569.
14. Hanessian S, Gomtsyan A, Malek N. J Org Chem 2000;65:5623–5631. [PubMed: 10970301]
15. Calculations were carried out on analogues with both the pentyl and TBDPSOCH_2CH_2 side chains replaced by methyl groups to minimize irrelevant conformational complexity.
16. For the protection of a salicylic acid with two allyl groups, see: Migita A, Shichijo Y, Oguri H, Watanabe M, Tokiwano T, Oikawa H. Tetrahedron Lett 2008;49:1021–1025.
17. Iida A, Nakazawa S, Okabayashi T, Horii A, Misaki T, Tanabe Y. Org Lett 2006;8:5215–5218. [PubMed: 17078681]
18. Hagiwara H, Inoguchi H, Fukushima M, Hoshi T, Suzuki T. Tetrahedron Lett 2006;47:5371–5373.
19. a) Kiyooka, S-i; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. J Org Chem 1991;56:2276–2278. b) Kiyooka, S-i; Shahid, KA. Tetrahedron: Asymmetry 2000;11:1537–1542. c) Kiyooka, S-i; Shahid, KA.; Goto, F.; Okazaki, M.; Shuto, Y. J Org Chem 2003;68:7967–7978. [PubMed: 14535772] d) Kiyooka, S-i; Hena, MA. J Org Chem 1999;64:5511–5523. [PubMed: 11674615] e) Fujiyama R, Goh K, Kiyooka S-i. Tetrahedron Lett 2005;46:1211–1215.
20. For another example of very different yields with matched and mismatched aldehydes, see: Kiyooka, S-i; Maeda, H.; Hena, MA.; Uchida, M.; Kim, C-S.; Horiike, M. Tetrahedron Lett 1998;39:8287–8290.
21. In his synthesis of berkelic acid methyl ester, Fürstner states that the spectral data of the stereoisomer corresponding to 36, not 35, match well with those of the natural berkelic acid methyl ester. However, he later states that confident assignment of the configuration of the stereochemistry at C-22 mandates direct comparison with an authentic sample. The spectral data for our sample of 35 correspond 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.

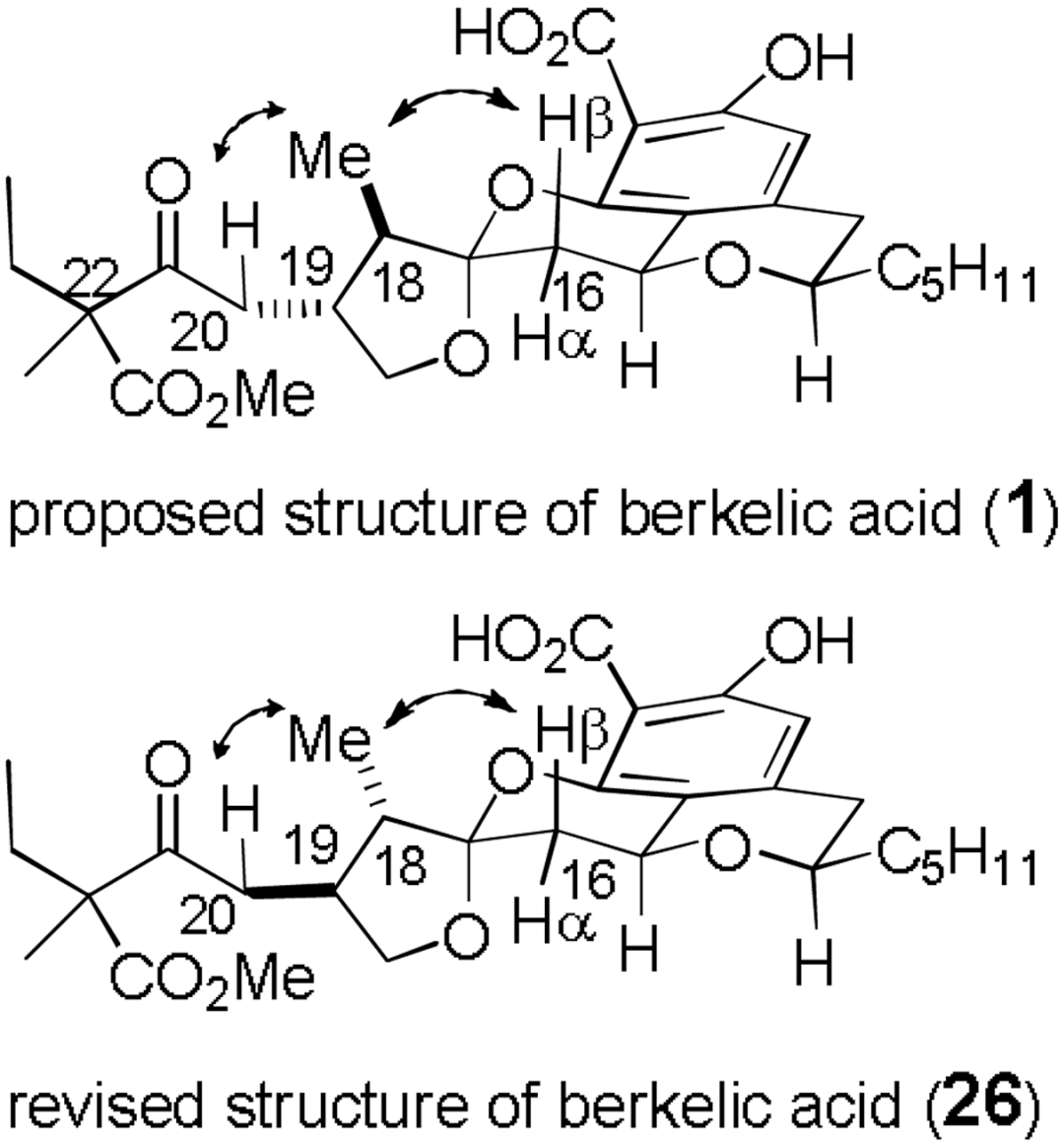
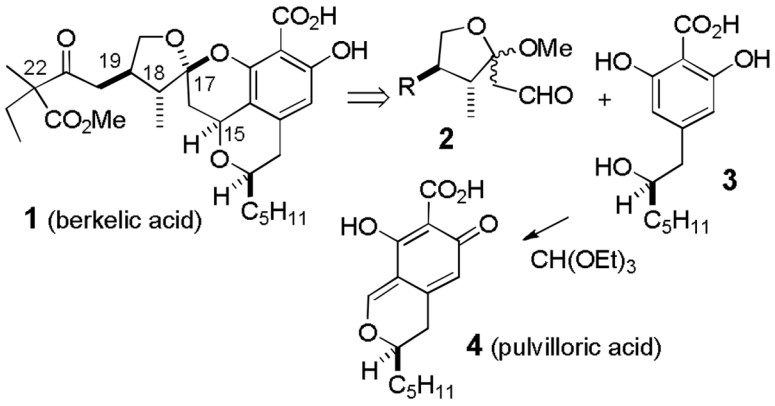
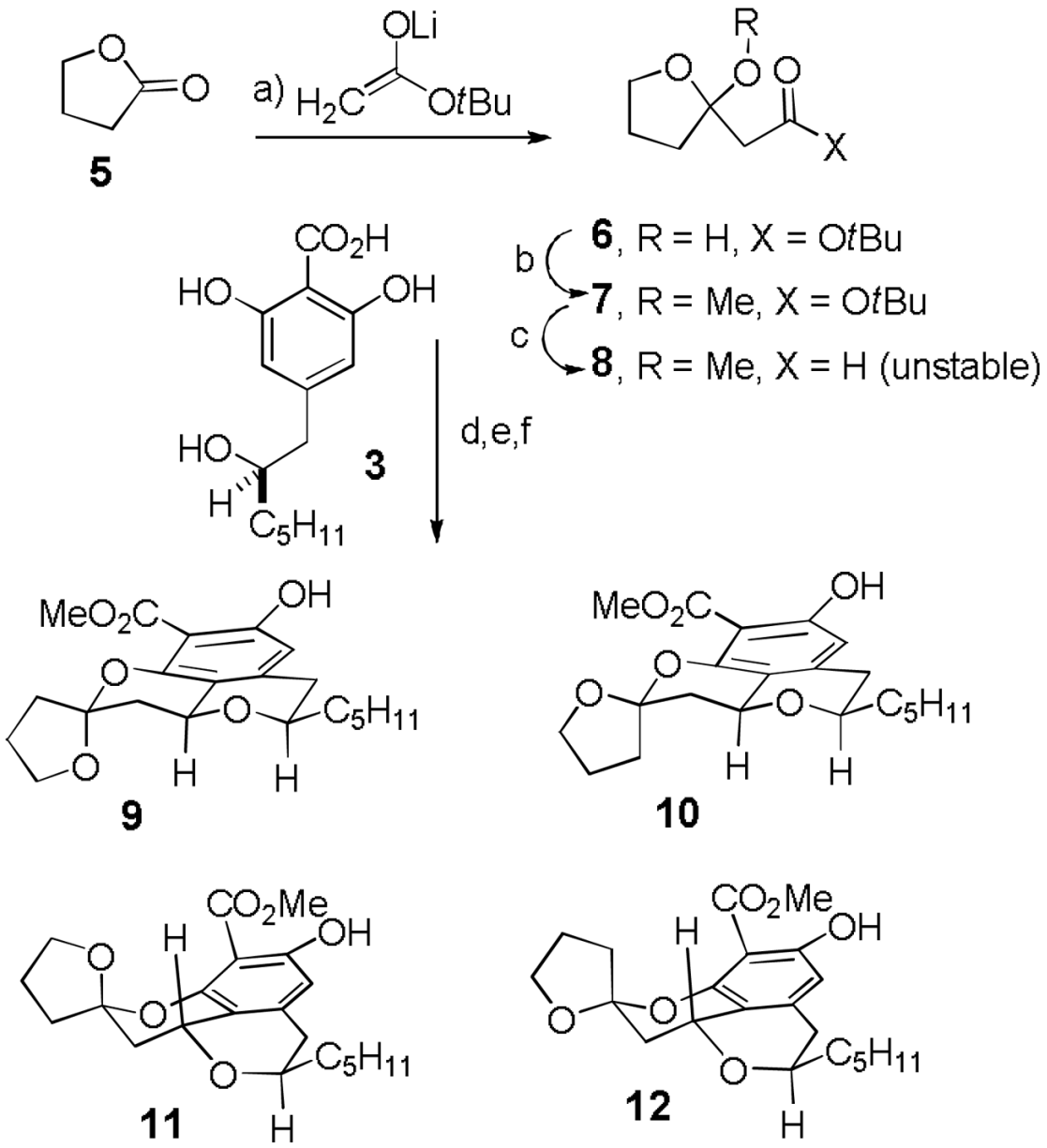


Figure 1.
Proposed and revised structures of berkelic acid showing NOEs to the methyl group.

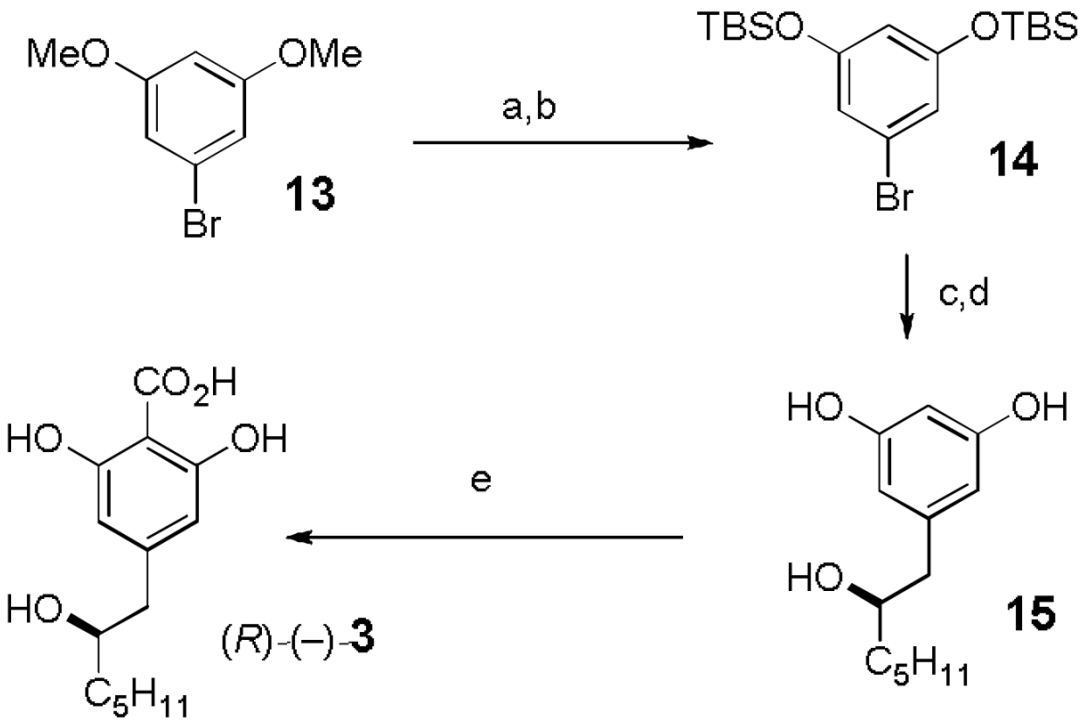


Scheme 1.
Retrosynthesis of berkelic acid (**1**).



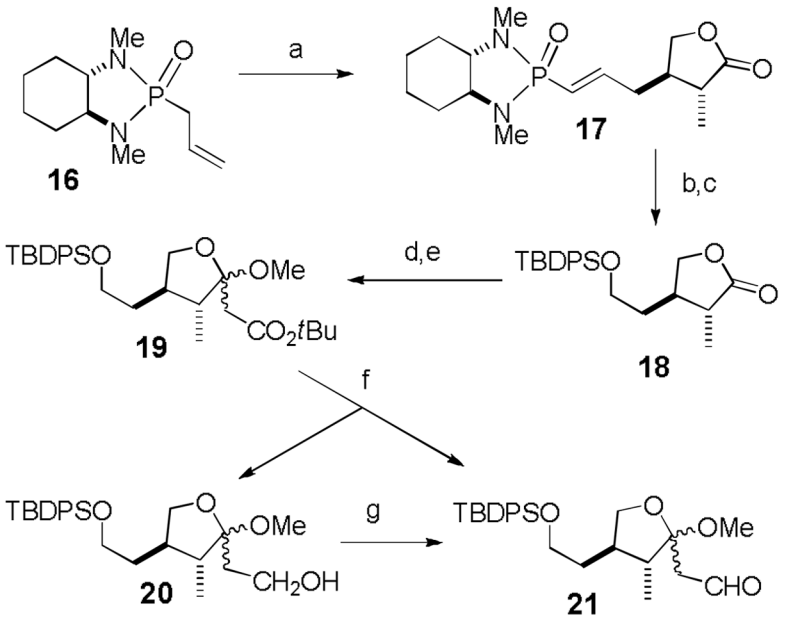
Scheme 2.

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, ether; f) 0.2% TFA in $CDCl_3$, 25 °C, 12 h (50% of **9** from **3**).



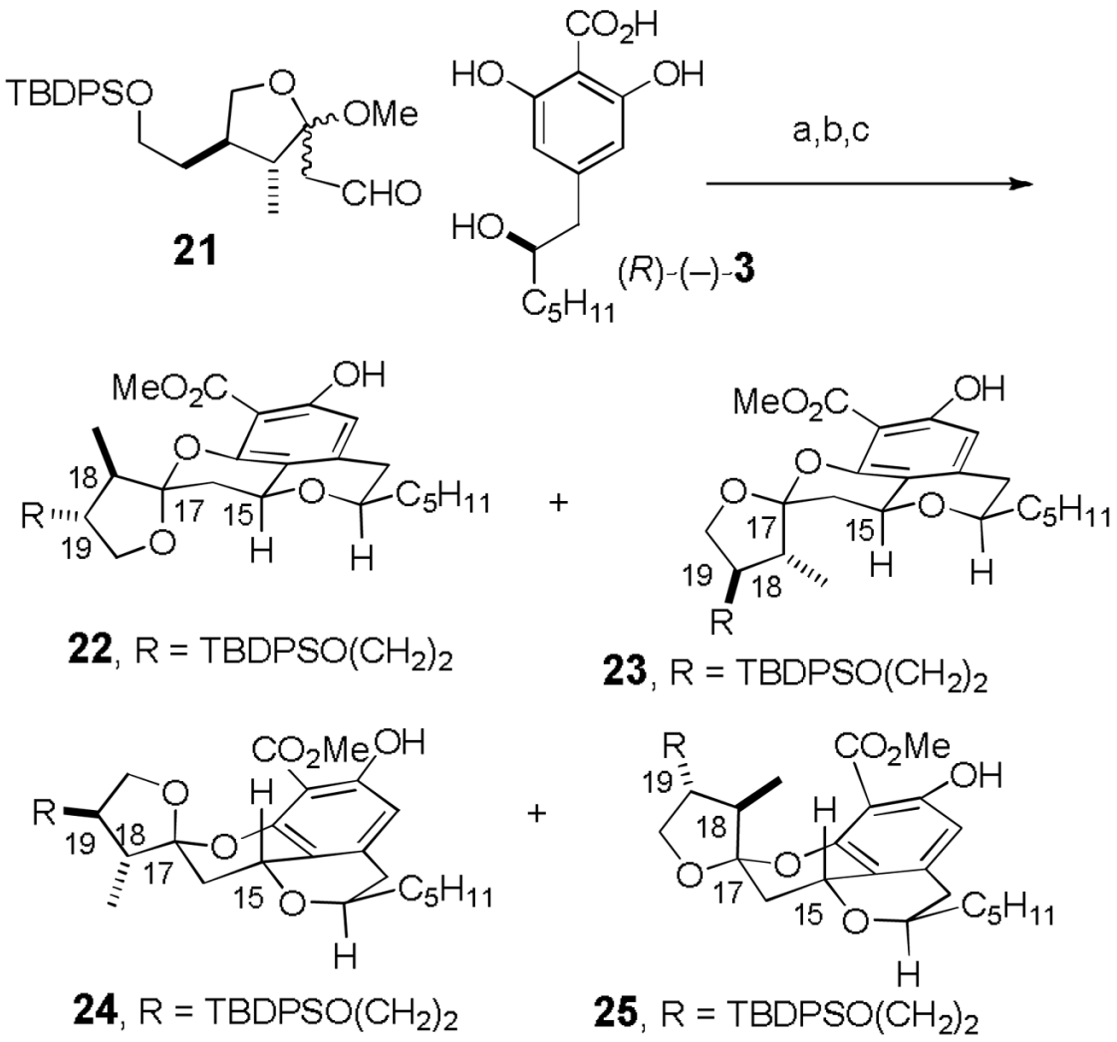
Scheme 3.

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%).

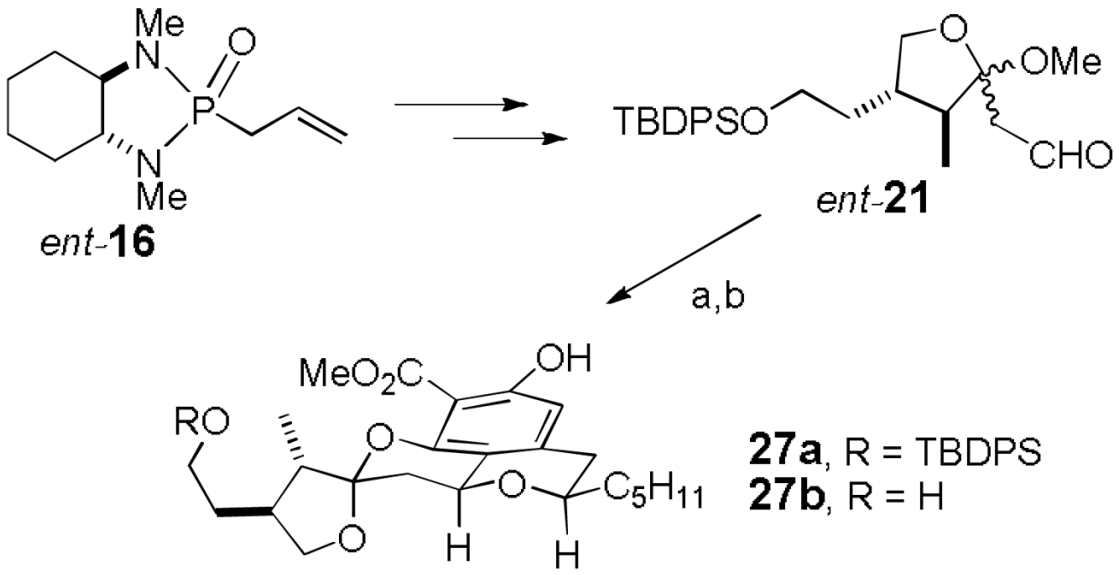


Scheme 4.

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, 1:1 MeOH/CH_2Cl_2, −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), 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%).

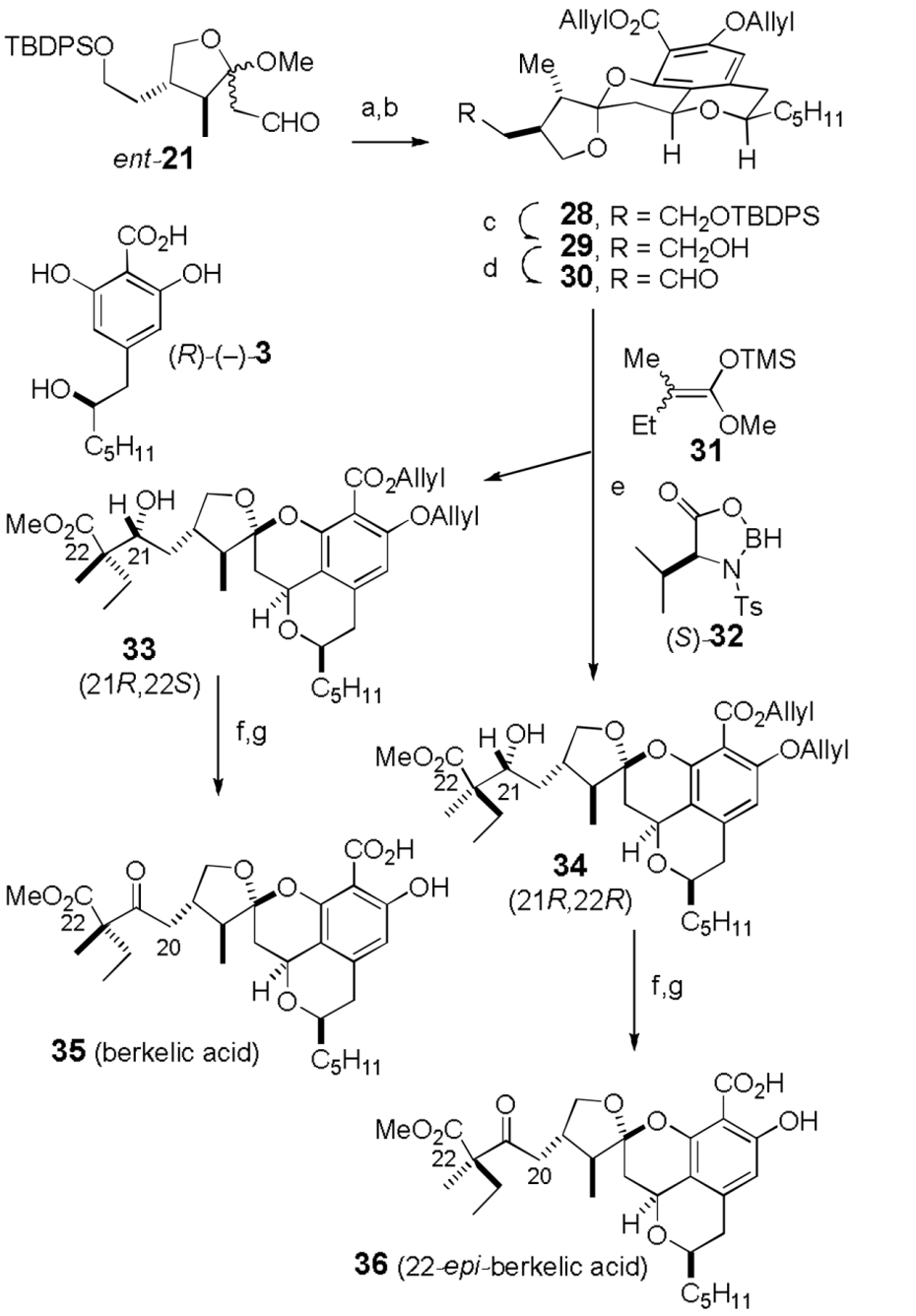


Scheme 5.
Reactions and conditions: a) Dowex 50WX8-400-H^+, MeOH, 25 °C, 12 h; b) CH_2N_2, ether; c) 0.2% TFA in $CDCl_3$, 25 °C, 12 h.



Scheme 6.

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



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 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) $Pd(Ph_3P)_4$ (0.2 equiv), HCO_2H (40 equiv), Et_3N (40 equiv), THF, 25 °C, 15 h (78% of **35**, 72% of **36**).