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Biomimetic Synthesis of the Tetracyclic Core of Berkelic Acid

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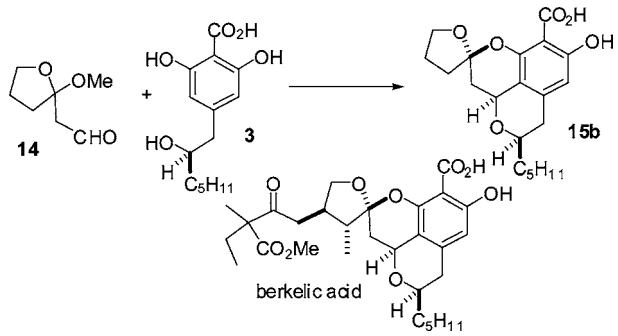
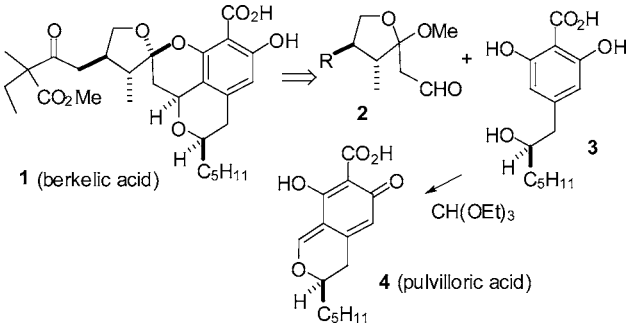
ABSTRACT



Acid-catalyzed condensation of 2,6-dihydroxybenzoic acid 3 with ketal aldehyde 14 in methanol at 25 °C, followed by CH_2N_2 esterification, gave a 4:1:4:1 mixture of diastereomers 15b–18b in 60% yield. Equilibration of this mixture with TFA in $CDCl_3$ provided tetracycle 15b (83% yield) with the complete skeleton of berkelic acid. A similar condensation at 0 °C afforded 15b–18b and a reduction product 19b, which was probably formed by a 1,5-hydride shift.

Stierle and co-workers recently isolated berkelic acid (**1**), a novel spiroketal with selective anticancer activity, from an acid mine waste fungal extremophile (see Scheme 1).[1] The structure was assigned on the basis of analysis of the NMR and mass spectral data. The absolute stereochemistry and the relative stereochemistry of the side chain stereocenter 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. 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 presumably biosynthetic, precursor to pulvilloric acid (**4**), has been prepared in both racemic[2] and optically pure forms.[3]

Scheme 1. Retro- and Biosynthesis of Berkelic Acid (**1**)



An oxa-Pictet−Spengler cyclization[4] of **2** and **3** should give isochroman **8** (see Scheme 2). These cyclizations are usually suggested to proceed by formation of oxocarbenium ion **6**, followed by a Friedel−Crafts cyclization to give **8**. It is also possible that the first step is an intermolecular

(1) Stierle, A. A.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357−5360.
(2) Bullimore, B. K.; McOmie, J. F. W.; Turner, A. B.; Galbraith, M. N.; Whalley, W. B. *J. Chem. Soc. C* **1967**, 1289−1293.
(3) Rödel, T.; Gerlach, H. *Liebigs Ann. Chem.* **1997**, 213−216.

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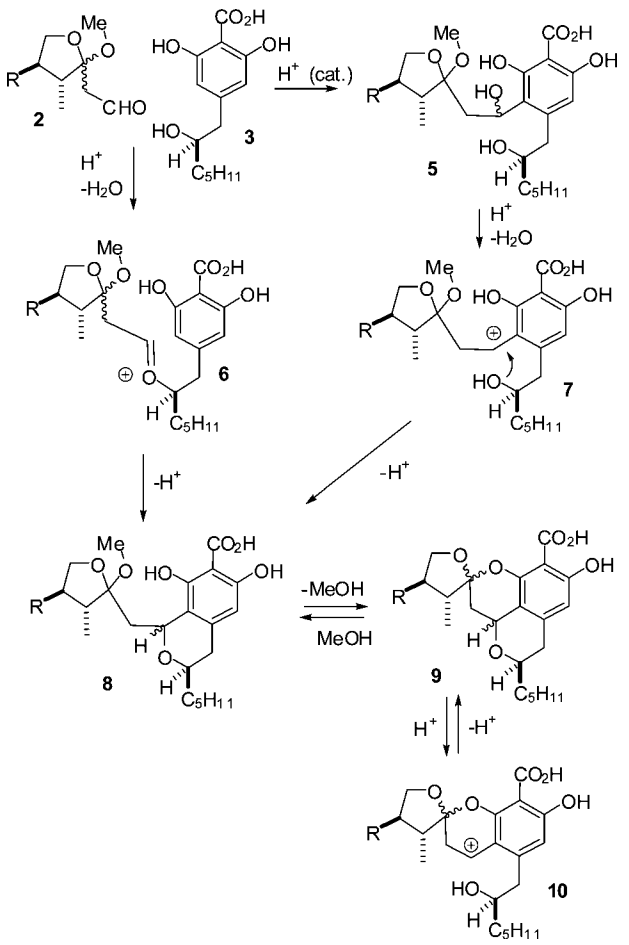
Scheme 2. Proposed Oxa-Pictet−Spengler Cyclization to Give **9**

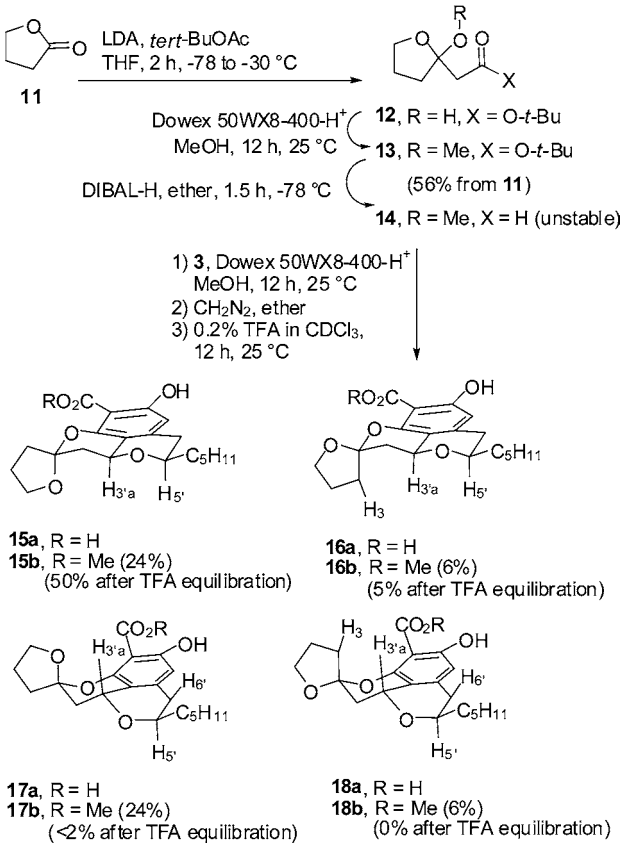


Friedel−Crafts reaction to give benzylic alcohol **5**. Protonation of the alcohol and loss of water will give the stabilized benzylic cation **7**[5] that will cyclize to give **8**. Ketal exchange with loss of methanol will give **9** with the complete tetracyclic core of berkelic acid.

This sequence generates two new stereocenters so that four isomers can be produced. The anomeric center of berkelic acid (**1**), with the oxygen of the tetrahydrofuran ring axial on the pyran ring, is probably in the more stable configuration. Therefore this center should be readily set by equilibration. Oxa-Pictet−Spengler cyclizations that give 1,3-disubstituted isochromans often give mainly the cis disubstituted products such as **8** under kinetically controlled conditions.[6] In some cases, equilibration via the benzylic cations analogous to **7** and **10** afforded mainly the more stable trans product.[7] Therefore it might be possible to use either kinetically or thermodynamically controlled conditions to obtain the desired diastereomer.

Model ketal aldehyde **14** was prepared to investigate this sequence (see Scheme 3). Addition of the lithium enolate of *tert*-butyl acetate to γ-butyrolactone (**11**) afforded ester **12** as a mixture of hydroxy ketone and hemiketal tautomers.[8] Reaction in acidic methanol converted this mixture to ketal ester **13** in 56% overall yield. Reduction of **13** with DIBAL-H at −78 °C provided crude ketal aldehyde **14**, which decomposed on chromatography and was used without purification.

Scheme 3. Preparation of Model **15b**



Reaction of acid **3**[9] with 2−3 equiv of crude ketal aldehyde **14** in MeOH containing Dowex 50WX8-400-H^+ for 12 h at 25 °C afforded a mixture of the desired tetracyclic acids **15a**−**18a** that was treated with diazomethane in ether to give a 4:1:4:1 mixture of methyl esters **15b**−**18b**, respectively, in 60% yield. The four isomers were separated and characterized spectroscopically. Molecular mechanics with conformational searching calculated relative strain energies for

(4) For a review see: Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, 187−220.

(5) Protonated *o*- and *p*-quinone methides are important resonance contributors stabilizing cation **7**.

(6) (a) DeNinno, M. P.; Schoenleber, R.; Perner, R. J.; Lijewski, L.; Asin, K. E.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1991**, *34*, 2561−2569. (b) Wünsch, B.; Zott, M. *Liebigs Ann. Chem.* **1992**, 39−45. (c) Anderson, B. A.; Hansen, M. M.; Harkness, A. R.; Henry, C. L.; Vincenzi, J. T.; Zmijewski, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 12358−12359. (d) Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3949−3956. (e) Bianchi, D. A.; Rúa, F.; Kaufman, T. S. *Tetrahedron Lett.* **2004**, *45*, 411−415.

(7) See ref 6d and footnote 15 in ref 6a.

(8) Kim, P.; Olmstead, M. M.; Nantz, M. H.; Kurth, M. J. *Tetrahedron Lett.* **2000**, *41*, 4029−4032.

(9) Prepared as described by Whalley in ref 2, except that 3,5-dimethoxyphenylacetyl chloride was treated with *n*-$C_5H_{11}MgCl$ and CuI rather than an organocadmium reagent.

15b−**18b** of 28.14, 28.56, 30.51, and 30.84 kcal/mol, respectively.[10] This suggests that isomers **15b** and **16b** with $H_{3'a}$ and $H_{5'}$ cis are significantly more stable than isomers **17b** and **18b** with these hydrogens trans. Isomers **15b** and **17b** with the tetrahydrofuran oxygen axial on the pyran ring are slightly more stable than **16b** and **18b**, respectively, as expected from the anomeric effect. The formation of **17b** as one of the two major products indicates that incomplete equilibration occurs under these reaction conditions.

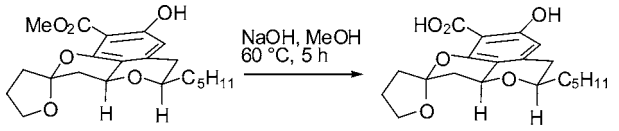
The coupling constants to $H_{3'a}$ are 10−12 and 5−6 Hz, indicating that this hydrogen is axial in all four conformers. The coupling constants between the benzylic methylene group and the axial hydrogen $H_{5'}$ in **15b** (J = 10.7, 4.2 Hz) and **16b** (11.7 and 3.9 Hz) are close to the values calculated for both **15b** and **16b** of 11.2 and 4.6 Hz. The coupling constants between the benzylic methylene group and $H_{5'}$ in **17b** (8.8 and 4.9 Hz) and **18b** (8.8 and 3.9 Hz) are close to the calculated values of 7.0 and 4.7 Hz for **17b** and 7.2 and 4.5 Hz for **18b**, suggesting that these molecules are mixtures of the conformer drawn with a boat ring and the pentyl substituent in a pseudoequatorial conformation and the chair conformer with an axial pentyl substituent.

The spiroketal stereochemistry can be assigned from the chemical shift of the axial proton $H_{3'a}$, which is in a 1,3-relationship to the anomeric center. The difference between the two diastereomers is especially pronounced in C_6D_6.[11] In this solvent, $H_{3'a}$ of **15b** and **17b** with an axial oxygen absorbs at δ 5.00 and 5.12, respectively, whereas $H_{3'a}$ of **16b** and **18b** with an equatorial oxygen absorbs at δ 4.41 and 4.63, respectively. Finally, NOEs between $H_{3'a}$ and $H_{5'}$ in **15b**, between $H_{3'a}$ and both H_3 and $H_{5'}$ in **16b**, between $H_{3'a}$ and both $H_{6'}$ and the side chain CH_2 group in **17b**, and between $H_{3'a}$ and H_3, $H_{6'}$, and the side chain CH_2 group in **18b** confirmed the stereochemical assignments.

The molecular mechanics calculations suggest that the desired isomer **15b** is most stable. Our structures **15b**−**18b** differ from simple isochromans in which the trans isomer may be more stable[7] because of the additional fused ring in **15b**−**18b**. Therefore equilibration of the mixture of four isomers should significantly increase the percentage of **15b** in the mixture. We were delighted to find that equilibration of the above 4:1:4:1 mixture of **15b**−**18b** with 0.2% TFA in $CDCl_3$ for 12 h provided a 20:2:1:0 mixture of **15b**−**18b**, respectively, from which **15b** could be isolated in 50% overall yield from acid **3**. The stereochemistry of **15b** was confirmed by X-ray crystal structure determination. Basic hydrolysis of pure **15b** completed the synthesis of berkelic acid model **15a**, which was contaminated with 5% of **16a** resulting from spiroketal equilibration during hydrolysis, in 83% yield (see Scheme 4).

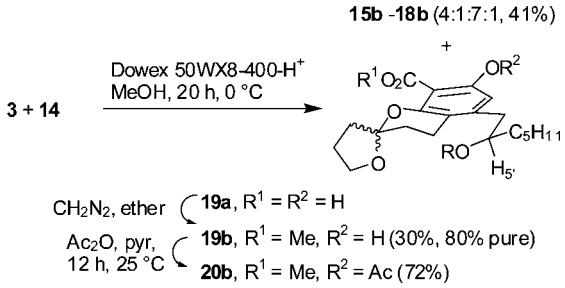
Our initial reactions of **3** and **14**, which were carried out at 0 °C rather than 25 °C, afforded a 4:1:7:1 mixture of **15b**−**18b**, respectively, in only 41% yield. Additionally, we isolated 30% of 80% pure reduced product **19b** as a mixture of diastereomers. Acetylation of impure **19b** afforded **20b**, which could be isolated in pure form in 72% yield (see Scheme 5).

Scheme 4. Synthesis of Tetracyclic Model **15a**



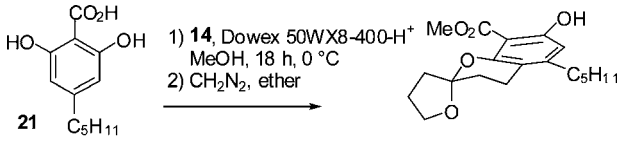
15b **15a** (83% containing 5% of **16a**)

Scheme 5



The formation of **19b** was unexpected and the presence of the two diastereomers complicated the structure proof. We therefore prepared acid **21**[12] by carboxylation of olivetol and treated it with **14** to generate the reduced product **22** in 27% yield (see Scheme 6).[13]

Scheme 6



21 **22** (27%, 90% pure)

Reduced products **19b** and **22** are probably formed by a second equivalent of aldehyde acting as a hydride donor. 1,3-Dioxane **23** could be formed from a benzylic alcohol analogous to **5** and a second equivalent of aldehyde (see Scheme 7). Protonation of **23** would give benzylic cation **24**, which could undergo a 1,5-hydride shift to give **25**. Hydrolysis of the aryl ester of **25** and spiroketalization would form **19a**. Alternatively, a benzylic alcohol analogous to **5**

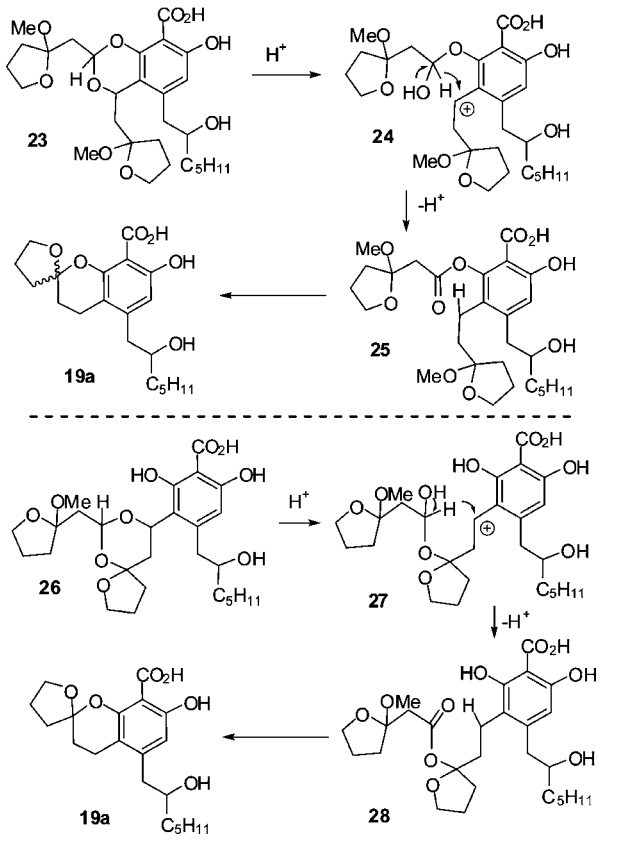
(10) PCMODEL version 8.0 from Serena Software was used with MMX. Calculations were carried out on analogues with the pentyl side chain replaced by a methyl group to minimize irrelevant conformational complexity.

(11) (a) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604−620. (b) Doubský, J.; Šaman, D.; Zedník, J.; Vašíčková, S.; Koutek, B. *Tetrahedron Lett.* **2005**, *46*, 7923−7926.

(12) (a) Asahina, Y.; Asano, J. *Ber. Dtsch. Chem. Ges.* **1932**, *65B*, 475−482. (b) Liu, G.; Szczepankiewicz, B. G.; Pei, Z.; Xin, Z.; Janowick, D. A. U. S. Patent Appl. 2002-072,516, 2002; *Chem. Abstr.* **2002**, *137*, 33535.

(13) The free phenol **22** could not be fully purified by chromatography. Pure **22** was obtained by conversion to the acetate ester, careful chromatography, and hydrolysis of the acetate with K_2CO_3 in MeOH.

Scheme 7



could react with a second equivalent of aldehyde to give 1,3-dioxane **26**. Protonation of **26** would give benzylic cation **27** that could undergo a 1,5-hydride shift to give ester **28**. Hydrolysis of the ester of **28** and spiroketalization would form **19a**. Only traces of these reduced products are formed when the reaction is carried out at 25 °C. This is consistent with the proposed mechanism because the highly ordered transition state for a 1,5-hydride shift should have a large negative entropy of activation and therefore be relatively favored at lower temperatures. 1,5-Hydride shifts of this type are uncommon, but some related examples have recently been reported.[14]

The formation of reduced product **19a** is inconsistent with the usually proposed mechanism for the oxa-Pictet−Spengler cyclization. If the isochroman ring is formed by an intramolecular Friedel−Crafts reaction of an oxocarbenium ion analogous to **6**, reduction by a 1,5-hydride shift is unlikely. Such a pathway is impossible for the conversion of **21** to **22** since there is no alcohol in the side chain. This suggests that the oxa-Pictet-Spengler cyclization of **3** to give **15**−**18** proceeds at least partially by a Friedel−Crafts reaction to give a benzylic alcohol analogous to **5** followed by cyclization to form the isochroman ring.[15]

In conclusion, acid-catalyzed condensation of acid **3** with ketal aldehyde **14** in methanol at 25 °C, followed by CH_2N_2 esterification, and equilibration with TFA in $CDCl_3$ affords tetracycle **15b** (50% overall yield) with the complete skeleton of berkelic acid. Application of this route to the total synthesis of berkelic acid (**1**) using a more highly functionalized ketal aldehyde **2**, in which R is a precursor to the side chain, is currently in progress.

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Supporting Information Available: Complete experimental procedures, copies of ^1H and ^{13}C NMR spectral data, and X-ray crystallographic data in CIF format for **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Yoshimatsu, M.; Hatae, N.; Shimizu, H.; Kataoka, T. *Chem. Lett.* **1993**, 1491−1494. (b) Krohn, K.; Flörke, U.; Höfker, U.; Träubel, M. *Eur. J. Org. Chem.* **1999**, 3495−3499. (c) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429−5431. (d) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683−1684.

(15) For another oxa-Pictet−Spengler cyclization that may proceed by both mechanisms, see: Zhang, X.; Li, X.; Lanter, J. C.; Sui, Z. *Org. Lett.* **2005**, *7*, 2043−2046.