ORGANIC LETTERS

2011
Vol. 13, No. 19
5382–5385

An Enantioselective Formal Synthesis of Berkelic Acid

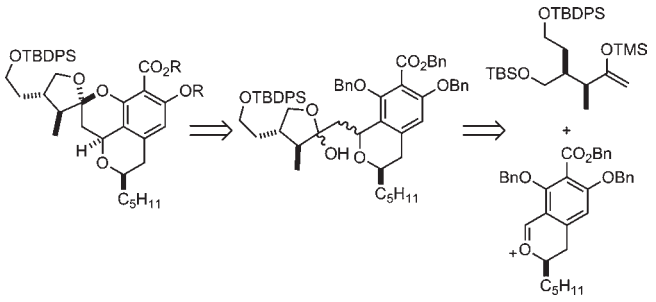
Michael C. McLeod, Zoe E. Wilson, and Margaret A. Brimble*

School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland, New Zealand

m.brimble@auckland.ac.nz

Received August 22, 2011

ABSTRACT



An enantioselective formal synthesis of berkelic acid is described. The key step involves a late-stage silyl enol ether addition to a benzannulated oxonium ion with subsequent spiroketalization leading to construction of the tetracyclic core. Thermodynamically controlled equilibration under acidic conditions affords the desired spiroketal configuration as a single diastereoisomer.

Berkelic acid (**1**) belongs to an increasing number of natural products isolated from organisms that inhabit extreme environments.[1] These so-called extremophiles live in habitats of high and low temperature, high pressure, high salt, and high and low pH. Berkelic acid was isolated as a secondary metabolite from a *Penicillium* species belonging to the latter category that survives in a flooded former copper mine with a pH of ~2.5.[2] The lake waters were also found to contain a number of heavy metals in high concentrations. Berkelic acid was found to inhibit caspase-1 (GI_{50} 98 μM) and matrix metalloprotease-3 (GI_{50} 1.87 μM) as well as exhibiting selective activity against the ovarian cancer cell line OVCAR-3 (GI_{50} 91 nM). The potent biological activity and remarkable structural architecture of this molecule have led to a number of efforts toward its total synthesis. After reassignment of the relative stereochemistry by synthesis of the methyl ester by Fürstner,[3] the first total synthesis of berkelic acid was reported by Snider.[4] Further total and formal syntheses have since been reported by the groups of De Brabander[5] and Pettus.[6]

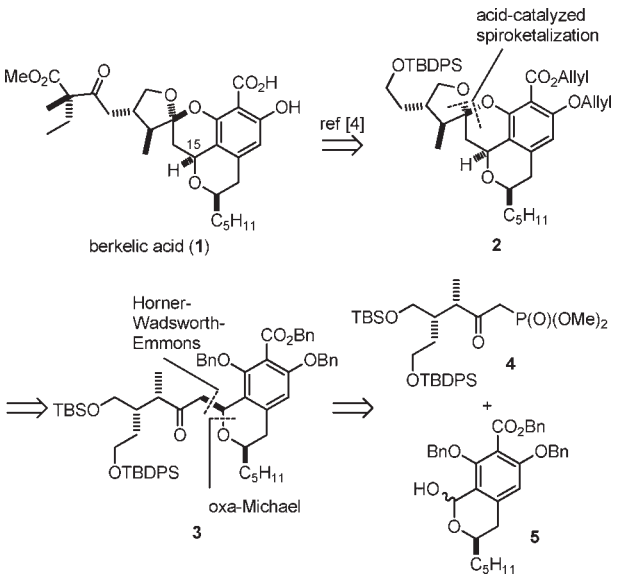
We wished to develop a synthesis of berkelic acid using a flexible and convergent approach that would allow future manipulation of its biological acitivity through analogue synthesis. Our retrosynthetic strategy of Snider's berkelic acid advanced intermediate **2** is outlined in Scheme 1. We envisaged that deprotection of the benzyl and TBS ethers of isochroman **3** under acidic conditions would result in spiroketalization to form **2**. In turn, **3** could be accessed by a Horner–Wadsworth–Emmons/oxa-Michael (HWE/oxa-M) cascade reaction of phosphonate **4** and lactol **5**. This route enables the late-stage formation of the spiroketal and C-15 stereocenters and could be readily adapted to the synthesis of analogues by coupling any 2-benzyloxy benzannulated lactol with a range of β-ketophosphonates.

Our retrosynthesis is supported by the previous synthesis of a berkelic acid model spiroketal reported by our group using an HWE/oxa-M strategy.[7] Deprotonation of phosphonate **6** with sodium hydride, followed by addition of

(1) Wilson, Z. E.; Brimble, M. A. *Nat. Prod. Rep.* **2009**, *26*, 44.
(2) Stierle, A. S.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357.
(3) (a) Buchgraber, P.; Snaddon, T. N.; Wirtz, C.; Mynott, R.; Goddard, R.; Furstner, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8450. (b) Snaddon, T. N.; Buchgraber, P.; Schulthoff, S.; Wirtz, C.; Mynott, R.; Furstner, A. *Chem.—Eur. J.* **2010**, *16*, 12133.
(4) (a) Wu, X.; Zhou, J.; Snider, B. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1283. (b) Wu, X.; Zhou, J.; Snider, B. B. *J. Org. Chem.* **2009**, *74*, 6245.
(5) Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350.
(6) Wenderski, T. A.; Marsini, M. A.; Pettus, T. R. R. *Org. Lett.* **2011**, *13*, 118.
(7) Wilson, Z. E.; Brimble, M. A. *Org. Biomol. Chem.* **2010**, *8*, 1284.

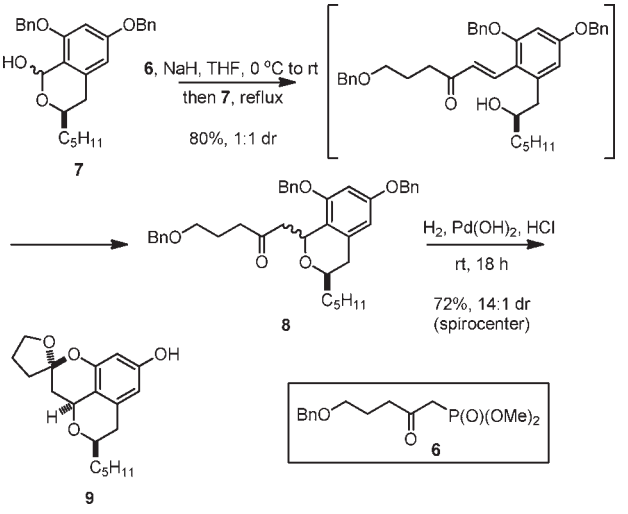
10.1021/ol202265g
Published on Web 09/14/2011

Scheme 1. Retrosynthetic Plan



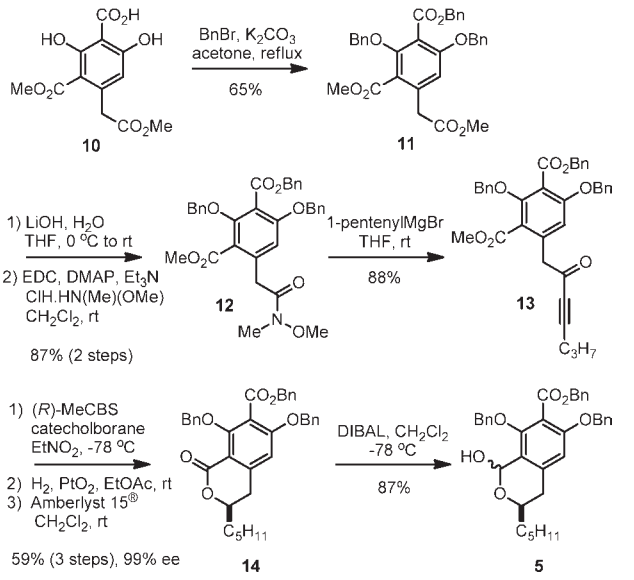
lactol **7**, provided isochroman **8** as a 1:1 mixture of diastereoisomers (Scheme 2). Hydrogenolysis of the benzyl ethers over $Pd(OH)_2$ resulted in formation of spiroketal **9**. As noted in a similar model system,[8] the acidic conditions used in the debenzylation step resulted in equilibration to form the desired thermodynamically favored *cis* isomer **9** exclusively, as a 14:1 mixture of anomers at the spirocenter.

Scheme 2. Model Studies



Synthesis of lactol **5** commenced from benzoic acid **10**[9] by benzyl protection of the carboxylic acid and two phenolic groups (Scheme 3). Selective hydrolysis of the aliphatic methyl ester **11** with LiOH followed by EDC coupling of the resultant acid with dimethylhydroxylamine hydrochloride afforded Weinreb amide **12**. Addition of 1-pentenylmagnesium bromide then afforded propargyl ketone **13**.

Scheme 3. Synthesis of Lactol **5**

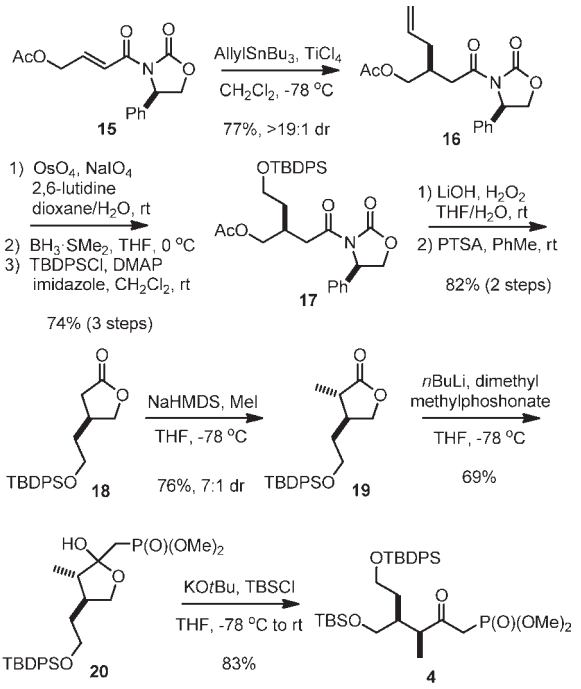


Attention next turned to the key chiral reduction step. After extensive screening of chiral reduction conditions, it was found that the use of an Me-CBS catalyst[10] with catecholborane imparted the highest levels of enantiocontrol for the reduction of **13**. Using THF as solvent resulted in moderate enantioselectivity (72% ee, HPLC). It has been recently reported that the enantioselectivity of CBS reductions of allenyl and propargyl ketones can be greatly enhanced by the use of nitroethane as the solvent.[11] Pleasingly, performing the reaction in nitroethane resulted in an increase in enantioselectivity to 99% ee. The selectivity displayed by the Me-CBS catalyst is the opposite to that predicted by the bulk of the chemical literature. This same observation has been reported for the CBS reduction of a similar ketone bearing a $-CH_2Ar$ group.[12] Selective reduction of the triple bond by hydrogenation over Adam's catalyst and cyclization with PTSA afforded lactone **14**. Finally, lactol **5** was prepared by DIBAL reduction of lactone **14** in CH_2Cl_2 at -78 °C with careful monitoring of the reaction by TLC to avoid over-reduction.

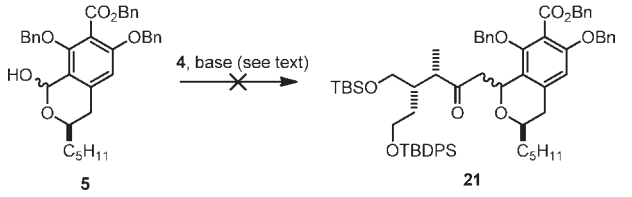
The preparation of phosphonate **4** required initial synthesis of lactone **19** (Scheme 4). A route to this lactone has recently been described by Snider et al. by conjugate addition of a chiral phosphonamide anion to 2-butenolide.[4] Our route commenced with $TiCl_4$-mediated conjugate addition of allyltributylstannane to α,β-unsaturated *N*-acyloxazolidinone **15**[13] affording allyl oxazolidinone **16** with excellent diastereoselectivity. The facial selectivity was determined by

(8) Zhou, J. Y.; Snider, B. B. *Org. Lett.* **2007**, *9*, 2071.
(9) Buechi, G.; Leung, J. C. *J. Org. Chem.* **1986**, *51*, 4813.
(10) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(11) Yu, C.-M.; Kim, C.; Kweon, J.-H. *Chem. Commun.* **2004**, 2494.
(12) Gooding, O. W.; Bansal, R. P. *Synth. Commun.* **1995**, *25*, 1155.
(13) See Supporting Information.

Scheme 4. Synthesis of Phosphonate **4**



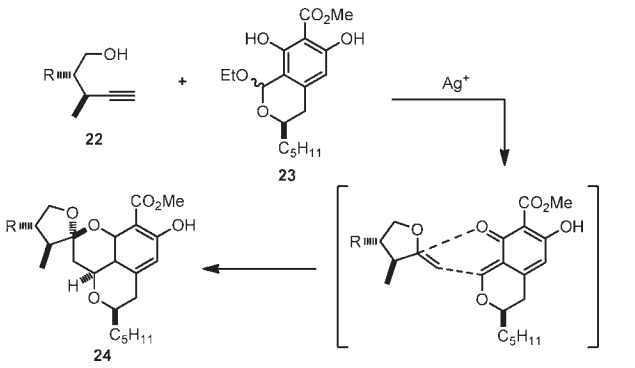
Scheme 5. Attempted HWE/oxa-M Cascade



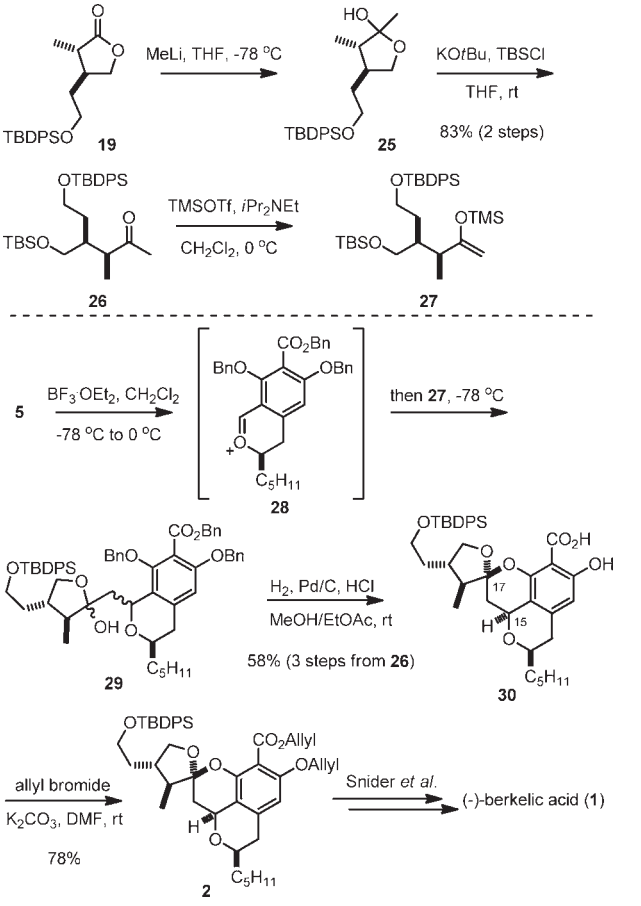
conversion to known lactone **19** (*vide infra*) and is in agreement with the reported Lewis acid promoted allylations of similar systems.[14] Oxidative cleavage of the olefin with $OsO_4/NaIO_4$ to the corresponding aldehyde followed by borane reduction and TBDPS protection provided **17**. It was necessary to perform the TBDPS protection step at relatively high concentrations (> 0.4 M) to avoid lactonization via displacement of the oxazolidinone by the free alcohol. The acetate and oxazolidinone were both cleaved by treatment with LiOH and H_2O_2 to afford a hydroxy acid that readily cyclized to lactone **18**. Methylation of lactone **18** proceeded in a 7:1 dr to afford **19**. The absolute stereochemistry of **19** was confirmed by comparison of the optical rotation to that reported by Snider.[4] Addition of lithiated dimethyl methylphosphonate to lactone **19** afforded phosphonyl substituted lactol **20** that underwent ring-opening and trapping as the TBS protected alcohol **4** using excess base and TBSCl.[15]

With phosphonate **4** and lactol **5** in hand, we next attempted the key HWE/oxa-M coupling. Phosphonate **4** was pretreated with base before addition of lactol **5** (Scheme 5). Disappointingly, none of the conditions screened (NaH, THF; K_2CO_3, Et_2O/H_2O; DBU, LiCl, MeCN or THF; KO*t*Bu, THF) resulted in any of the

Scheme 6. De Brabander's Cycloaddition Approach to Berkelic Acid[5]



Scheme 7. Formal Synthesis of (−)-Berkelic Acid (**1**)



(14) (a) Williams, D. R.; Mullins, R. J.; Miller, N. A. *Chem. Commun.* **2003**, 2220. (b) Wilding, E. E.; Gregg, J. J.; Mullins, R. J. *Synlett* **2010**, 793.

(15) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325.

desired product being isolated. This lack of reactivity is postulated to be due to the lactol-hydroxy aldehyde equilibrium favoring the unreactive ring-closed form in this case.

Faced with this reality, we proposed that the two fragments could be unified by addition of a silyl enol ether to an oxonium ion derived from lactol **5**. A similar approach was employed by De Brabander et al. in their synthesis of berkelic acid (**1**), using a silver-catalyzed dearomatization−cycloisomerization−cycloaddition cascade to couple fragments **22** and **23** and obtain advanced spiroketal intermediate **24** (Scheme 6).[5]

To this end, addition of methyllithium to lactone **19** and treatment of the resulting adduct **25** with KO*t*Bu and TBSCl afforded methyl ketone **26** (Scheme 7). Silyl enol ether formation with TMSOTf and Hünig's base proceeded smoothly to afford **27**. Lactol **5** was treated with $BF_3 \cdot OEt_2$, and the resulting oxonium ion was quenched by addition of silyl enol ether **27** at −78 °C. Pleasingly, after 30 min at −78 °C complete consumption of starting material was observed. Under these conditions the TBS ether was also cleaved, affording lactol **29** as a mixture of diastereoisomers. Previous synthetic studies directed toward berkelic acid have demonstrated that the two stereocenters at C-15 and C-17 can be equilibrated to the desired spiroketal configuration under acidic conditions.[3,4] The diastereomeric mixture of lactols **29** was therefore subjected to hydrogenation over 10% Pd/C in the presence of HCl. Under these conditions, debenzylation, spiroketalization, and thermodynamic equilibration occurred in one pot to afford spiroketal **30** as a single diastereoisomer in 58% yield from methyl ketone **26** after purification by chromatography. Finally, the formal synthesis of berkelic acid was completed by reaction of **30** with allyl bromide and K_2CO_3 to provide **2**, whose spectroscopic data and optical rotation agreed with the data reported.[4]

In conclusion, an enantioselective formal synthesis of the antitumor agent berkelic acid (**1**) has been completed by successful preparation of Snider's advanced intermediate **2**. The key steps in our synthesis include a silyl enol ether−oxonium coupling followed by debenzylation under acidic conditions to obtain the desired thermodynamically favored tetracyclic spiroketal. This synthetic approach can be readily employed for the synthesis of analogues of the natural product by simple reaction of any 2-benzyloxy benzannulated lactols with a range of silyl enol ethers.

Acknowledgment. This work was supported by the Royal Society of New Zealand Marsden Fund.

Supporting Information Available. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.