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ARTICLE *in* ORGANIC & BIOMOLECULAR CHEMISTRY · MARCH 2010

Impact Factor: 3.56 · DOI: 10.1039/b927219b · Source: PubMed

A flexible asymmetric synthesis of the tetracyclic core of berkelic acid using a Horner–Wadsworth–Emmons/oxa-Michael cascade†

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Received 23rd December 2009, Accepted 18th January 2010
First published as an Advance Article on the web 26th January 2010
DOI: 10.1039/b927219b

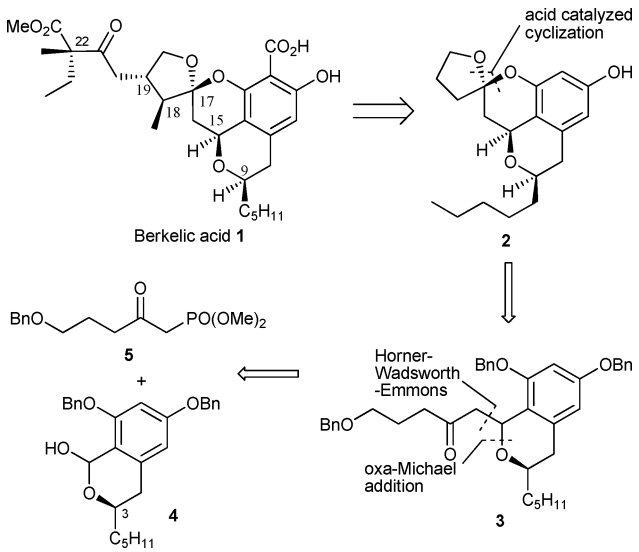
The one-pot Horner–Wadsworth–Emmons/oxa-Michael cascade followed by spiroketalisation affords the tetracyclic benzannulated spiroketal core of berkelic acid, an extremophile natural product with selective activity against ovarian cancer.

Since its isolation in 2006,[1] berkelic acid **1** has attracted significant interest due to its unusual source, medicinal potential and unprecedented tetracyclic structure.[2] Berkelic acid was isolated by Stierle *et al.* from a *Penicillium* fungus collected from Berkeley Pit Lake in Butte, Montana.[1] Berkeley Pit Lake formed when an abandoned copper mine filled with infiltrating ground water to give an extremely acidic (pH 2.5) and metal contaminated lake.[1] Berkelic acid is one of an increasing number of novel secondary metabolites isolated from extreme dwelling microorganisms[3] and inhibits caspase-1 (GI_{50} 0.098 mM) and matrix metalloprotease-3 (GI_{50} 1.87 μM), as well as exhibiting selective activity (GI_{50} 91 nM) against the OVCAR-3 (ovarian cancer) cell line.[1] The stereochemistry at C22 was initially not determined, but subsequent total syntheses established this stereocentre as (*S*) and reassigned the absolute stereochemistry at C18 and C19.[4–6]

The ambiguity in the chemical structure, together with future manipulation of biological activity through analogue synthesis prompts development of a flexible convergent approach to this important bioactive natural product. Furthermore, the planned bioremediation of Berkeley Pit Lake may eliminate the natural source of this compound. To this end, we herein report an enantioselective synthesis of the tetracyclic benzannulated spiroketal core **2** of berkelic acid **1** (Scheme 1).

Our retrosynthetic approach to the tetracyclic core of berkelic acid **2** is outlined in Scheme 1. It was envisaged that isochroman **3** would spontaneously undergo acid catalyzed spiroketalisation to give **2** upon debenzylation. In turn, isochroman **3** is accessed *via* union of chiral lactol **4** and phosphonate **5** using a novel Horner–Wadsworth–Emmons/oxa-Michael (HWE/oxa-M) cascade. The chiral centre at C3 in lactol **4** thus provides an anchor on which the absolute stereochemistry of the entire core structure is established.

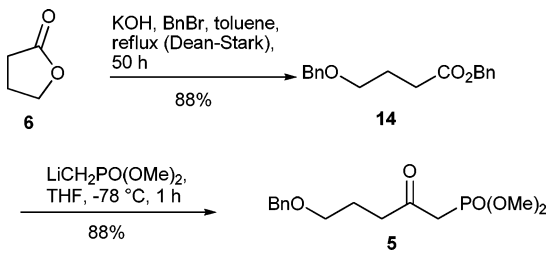
To our knowledge, the reaction of a chiral benzannulated lactol in a HWE/oxa-M cascade has not been used in natural product synthesis. However, achiral HWE/oxa-M cascades have been reported leading to an undesired by-product[7] and for the synthesis of simple 5-HT_{1D} antagonists and 5-HT reuptake inhibitors.[8]



Scheme 1 Berkelic acid **1**, the target tetracyclic core **2** and the synthetic strategy employed.

Compared to the previous biomimetic approaches to berkelic acid[4–6] the present strategy provides increased flexibility with the stereochemistry installed at a late stage and the HWE/oxa-M cascade allowing access to a range of berkelic acid analogues by reacting any 2-benzyloxy benzannulated lactol with a library of phosphonates derived from 5-membered lactones in two simple operations.

The required phosphonate coupling partner **5** was conveniently synthesised by ring opening of γ-butyrolactone with benzyl bromide followed by displacement with lithium dimethyl methylphosphonate (Scheme 2).



Scheme 2 Synthesis of phosphonate **5**.

The synthesis of the precursor for key lactol **4**, namely lactone **7**, began with dibenzylation of methyl orsellinate **8**[9] followed by conversion to amide **9**. The key steps involved addition of Weinreb amide **10**[10] to the toluate anion of **9** followed by enantioselective reduction of the resultant ketone **11** before cyclisation to lactone **7**.

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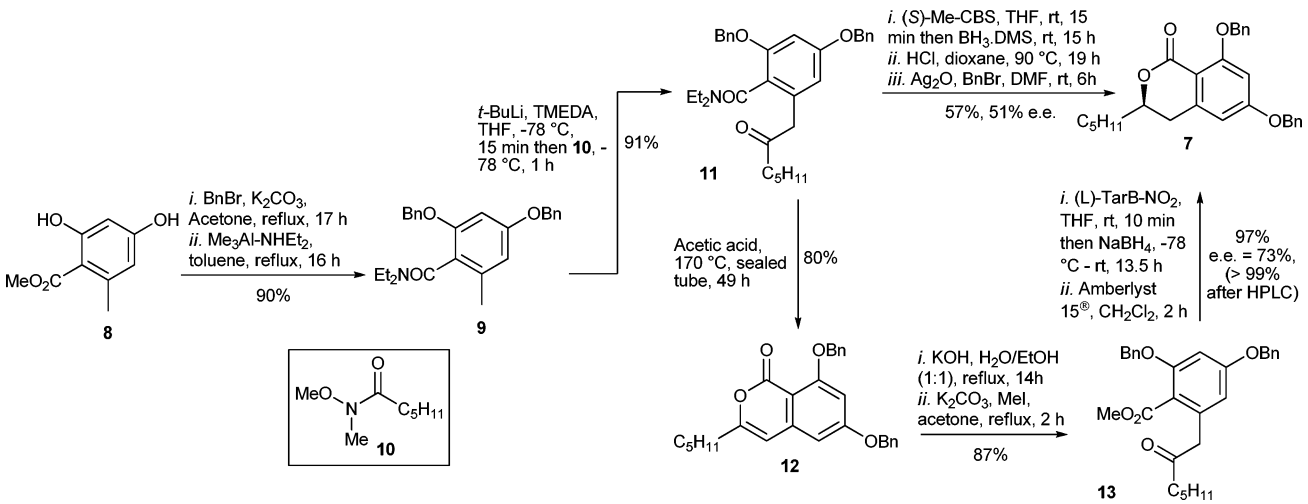
† Electronic supplementary information (ESI) available: Experimental procedures, full characterisation for all novel compounds, chiral HPLC traces for all chiral molecules and structural confirmation. See DOI: 10.1039/b927219b

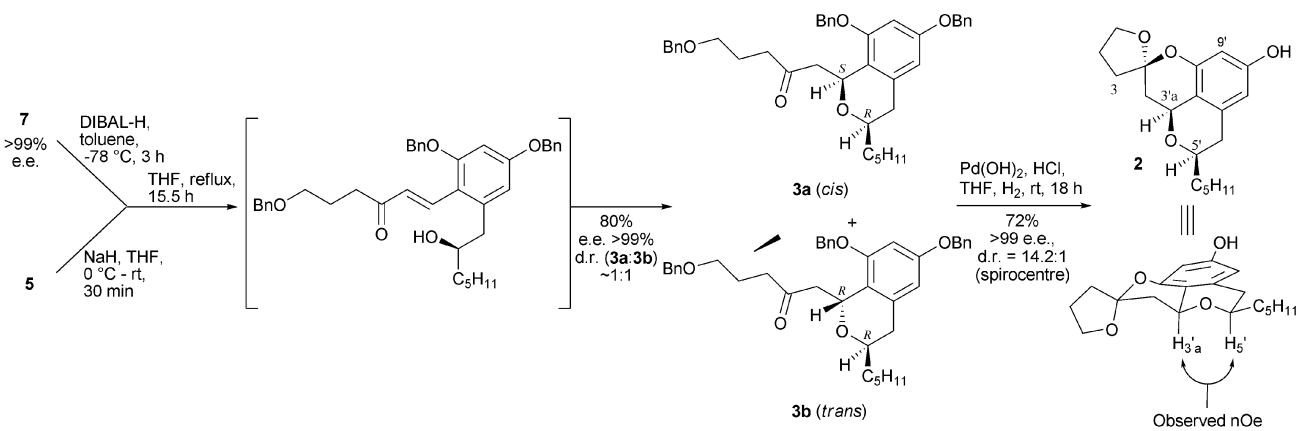
The toluate anion addition proceeded in high yield. An extensive range of chiral reductions were investigated using ketone **11** with the rotameric alcohols subjected to immediate cyclisation to lactone **7**, thus facilitating determination of the enantiomeric excess by chiral HPLC. Harsh conditions, resulting in partial deprotection of the phenol, were required to afford lactone **7** from the hydroxy amide in acceptable yield. Disappointingly, the best conditions, namely (*S*)-methyl-CBS[11] catalysed reduction, only resulted in a moderate yield (57%) and enantiomeric excess (e.e., 51%). In an attempt to improve the e.e. and yield for the chiral reduction/lactonisation step diethyl amide **11** was converted to a methyl ester **13**, thereby avoiding the formation of rotamers and facilitating the lactonisation step.

Earlier attempts to synthesise **13** by addition of the toluate anion of benzylated methyl orsellinate to Weinreb amide **10** were unsuccessful. Methyl ketone **13** was eventually formed by effecting cyclisation of ketone **11** to isocoumarin **12**, followed by ring-opening to the keto-acid and esterification. Methyl ester **13** rapidly reconverted to isocoumarin **12** in the presence of acid or base but with careful handling it could be subjected to further manipulation. Partial cyclisation of the alcohol obtained after the chiral reduction step was observed hence the mixture was routinely treated with Amberlyst 15® (H^+ resin) in dichloromethane to effect complete conversion to lactone **7**. Pleasingly, (L)-TarB-NO_2[12] reduction of **13** gave **7** in much improved yield of 97% and an e.e. of 73% (Scheme 3). Lactone **7** was easily purified by preparatory scale chiral HPLC affording essentially enantiopure **7** (>99% e.e.). Correspondingly, (D)-TarB-NO_2[12] afforded (*S*)-lactone (*ent*-**7**) with similar levels of enantiocontrol providing an enantiodivergent synthesis of **7** for future analogue synthesis.

Lactone **7** (>99% e.e.) was reduced with DIBAL-H and the crude lactol **4** added directly to the anion of **5** triggering a HWE/oxa-M cascade to afford isochroman **3** as an approximately 1 : 1 mixture of *cis* : *trans* isomers **3a** and **3b**. Using HCl in THF this ~1 : 1 mixture steadily equilibrated providing *trans* **3b** predominantly (see Supporting Information). Pleasingly, when this diastereomeric mixture of **3a** : **3b** (~1 : 1) was subjected to the deprotection/cyclization step, the desired *cis* configured tetracyclic core **2**, was obtained in 72% yield as a 14 : 1 ratio with its non-anomerically stabilised diastereomer (Scheme 4). This observation is in agreement with an earlier published synthesis of this tetracyclic core,[13] in which a mixture of the 4 possible spiroketals underwent equilibration to the desired product upon treatment with acid. The ^{1}H NMR of **2** was in agreement with this previously published model compound, differing only in the presence of a methyl ester at C9′.[13] A strong nOe was observed



Scheme 3 Synthesis of lactone **7**.



Scheme 4 HWE/oxa-M cascade and cyclisation to give tetracyclic core **2**.

between H3a′ and H5′, further confirming the *cis* relationship. The lack of nOe correlations between H3a′ and H3 also supported the fact that the major product was the anomerically stabilised spiroketal (see Supporting Information).

In summary, an efficient enantioselective synthesis of **2**, the tetracyclic core of berkelic acid has been achieved. Studies towards the total synthesis of berkelic acid using this methodology are ongoing and will be reported in due course.

We thank the Royal Society of New Zealand Marsden Fund for financial support, the University of Auckland for a University of Auckland Doctoral Scholarship (Z.E.W.) and Dr Jonathan Sperry (University of Auckland) for helpful discussions.

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