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Benzannulated 6,5-Spiroketals from Donor−Acceptor Cyclopropanes

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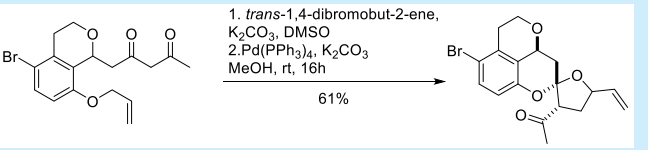
Supporting Information

ABSTRACT: A rapid and facile synthesis of benzannulated 6,5-spiroketals from vinyl 1,1-diacylcyclopropanes is reported. The method utilizes mild reaction conditions with good to excellent yields and high diastereoselectivity. This methodology was then used to construct the core of berkelic acid.



Numerous biologically active natural products, which have been isolated from both terrestrial and marine organisms, have been found to contain the spiroketal motif.[1] It is within this class of molecules that the relatively rare benzannulated spiroketals,[2] such as the chaetoquadrins (**1**),[3] berkelic acid (**2**),[4] and pinnatifinosides (**3**),[5] are found (Figure 1). Beyond the standard acid catalyzed cyclization of a dihydroxy ketone (or equivalent), current methods used to synthesize this moiety include transition-metal-catalyzed spiroketalizations,[6] cycloaddition strategies,[7] and oxidative radical cyclizations.[8]

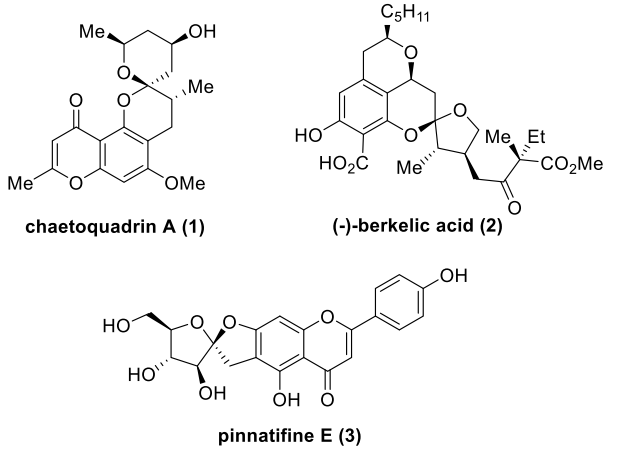
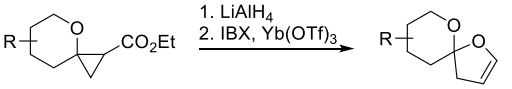


Figure 1. Representative benzannulated spiroketal containing natural products.

Donor−acceptor cyclopropanes have been utilized extensively in the literature to gain access to biologically active scaffolds, including numerous natural products.[9] Their unique reactivity allows for a rapid increase in structural complexity through various reaction processes including ring opening,[10] cycloadditions,[11] and rearrangements/ring expansions.[6c,12] However, only two reports using a ring expansion of donor−acceptor cyclopropanes to access spiroketals have appeared in the literature.[13] The first used a donor−acceptor cyclopropane to eventually make a dihydroxyketone which subsequently underwent a standard acid catalyzed spiroketalization to afford a 5,5-spiroketal.[13a] The most recent involved reduction of cyclopropyl esters to their corresponding primary alcohols followed by oxidation with hypervalent iodine complexes (Scheme 1).[13b] The presumed cyclopropyl aldehyde intermediate could then be treated *in situ* with a soft Lewis acid to facilitate ring expansion to the spirocyclic enol ether **5**. This study included the synthesis of one unsubstituted benzannulated spiroketal which was obtained in a 35% yield from the corresponding cyclopropyl ester. While elegant, the reaction conditions limit substrate scope and the oxidation state manipulations, requiring stoichiometric amounts of both reductant and oxidant, are viewed as less than ideal.

Scheme 1. Werz et al. Described the Reduction of Cyclopropyl Esters and Subsequent Oxidation with Hypervalent Iodine to Provide Spiroketals



We speculated that the treatment of vinylcyclopropane **6** with palladium(0) would not only isomerize the allyl ether to the labile vinyl ether, leading to the phenolate anion, but also facilitate cyclopropane ring opening via oxidative addition to produce the intermediate zwitterion **7** (Scheme 2).[14] The oxygen anion of intermediate lactol **7** could then attack the π-allyl complex, eventually leading to benzannulated 5,6-spiroketals of the general structure **8**.

To examine this concept, the β-keto ester **10a** was prepared from 2-hydroxyacetophenone **9** in four steps using adapted literature procedures (Scheme 3).[15] Treatment of the β-keto ester **10a** with 1,4-dibromo-*trans*-2-butene and potassium carbonate provided the vinylcyclopropyl adduct **6a** as a 2:2:1:1 mixture of diastereomers. The vinyl cyclopropane was found to be unstable to purification by silica gel column

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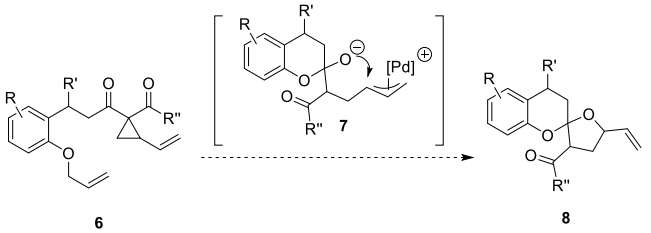
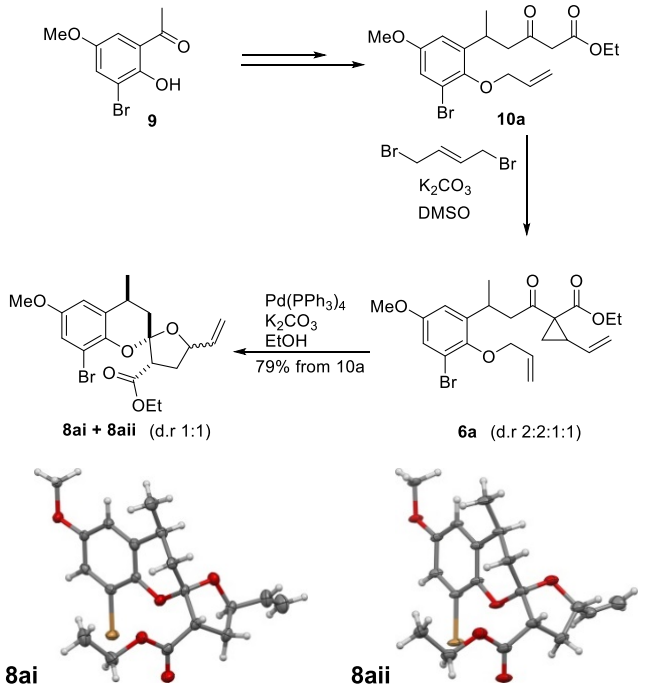
Scheme 2. Synthetic Strategy for the Formation of Benzannulated Spiroketals



Scheme 3. Synthesis of Benzannulated 6,5-Spiroketals 8a and Crystal Structure of Diastereomers 8ai (Left) and 8aii (Right)

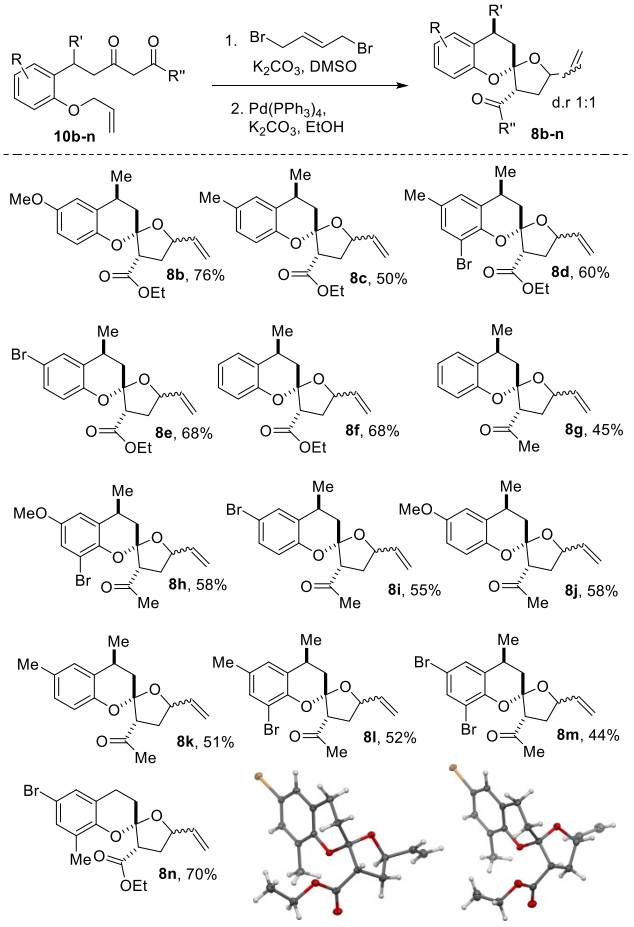


chromatography. However, treatment of the crude residue containing predominately **6a** with $Pd(PPh_3)_4$ (5 mol %) and K_2CO_3 in ethanol for 16 h at room temperature smoothly provided the benzannulated 6,5-spiroketal **8a** as a 1:1 mixture of diastereomers, as indicated by analysis of the ^1H NMR spectrum of the reaction mixture;[16] the diastereomers were readily separated by chromatography. Both isomers are a result of the anomeric effect with the relative stereochemistry set except at the vinyl group. This assignment was confirmed by single crystal X-ray structures of both isomers (Scheme 3).

Increasing the catalyst loading to 10 mol % had no significant impact on isolated yield; however, decreasing the catalyst loading to 2.5 mol % resulted in a lower isolated yield and required longer reaction times to reach completion.[16] An alternative source of Pd(0), tris(dibenzylideneacetone)-dipalladium, was also trialed; however, lower yields were observed. Ethanol was found to be the solvent which provided the highest yield, although other solvents such as THF could be used. Notably, when methanol was used transesterification was observed to provide the corresponding methyl ester.

With a procedure developed for the synthesis of benzannulated 6,5-spiroketals, we next examined the substrate scope (Scheme 4). Variation in the substitution of the aromatic

Scheme 4. Synthesis of Benzannulated 6,5-Spiroketals; ORTEP Diagrams of Both Isomers of 8n



portion of the substrate was examined first. Electron-rich substituents were well tolerated (**8b** and **8c**), as well as relatively neutral **8f** and **8g** and relatively electron-poor systems **8e**. Notably, under the spiroketalization reaction conditions no dehalogenation was observed, thereby preserving the additional functional group handle. Changing the substrate to a 1,3-diketone resulted, in general, in a slight decrease in yield. As for the β-keto ester substrate, both the tri- and tetrasubstituted aromatic systems with varying electronics were also well tolerated with negligible differences in isolated yield with the exception of the dibromo analog **8m**, which proceeded in a slightly lower yield (44%, over two steps). Removal of the methyl group in the benzylic position had no observable effect on diastereoselectivity (**8n**). Regardless of the substitution pattern and functional groups present, an excellent level of diastereoselectivity was observed in all cases, with complete control of the relative stereochemistry at all stereocenters except at the vinylic position, where no control at all was achieved.

In order to provide insight into the mechanism and features controlling the stereochemical outcome, a diastereomerically pure sample of **8ni** was subjected to the established reaction conditions (Scheme 5). After stirring at room temperature for 16 h a 1:1 mixture of the diastereomers (**8ni**/**ii**) was obtained, thereby indicating the reaction is under thermodynamic control.

Further examination of the reaction by shortening the reaction time from 16 h to 30 min led to the isolation of the

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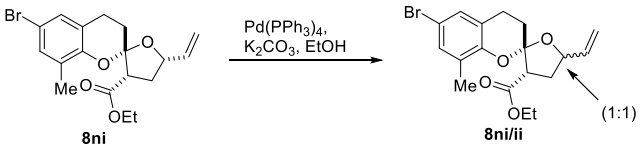
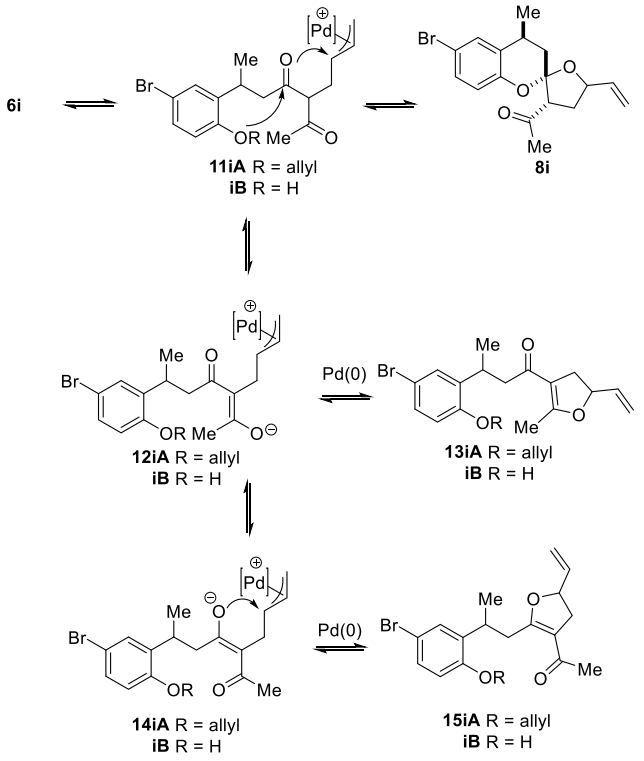
Scheme 5. Treatment of Benzannulated Spiroketal 8ni to the Established Spiroketalization Reaction Conditions Provided a 1:1 Mixture of Diastereomers (8ni/ii)



dihydrofuran **13iB** and traces of **15iB** (Scheme 6). These compounds are thought to arise from ring closure of the

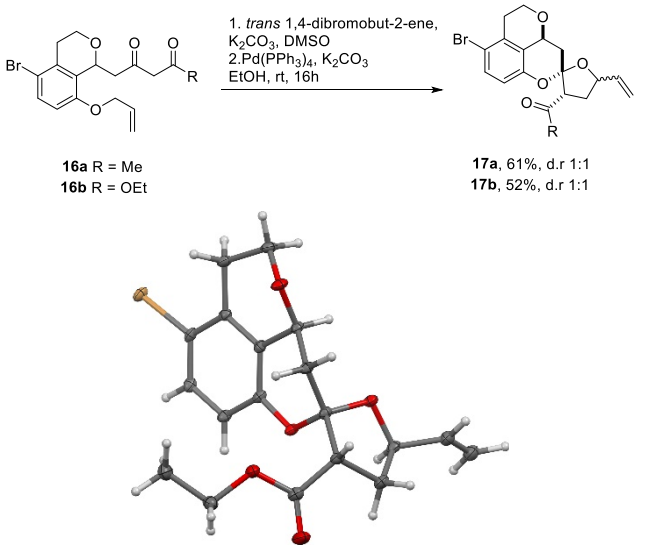
Scheme 6. Proposed Mechanism



enolates **12i** and **14i**, respectively. Treatment of the mixture of dihydrofurans under the standard reaction conditions provided the expected benzannulated spiroketals **8i**. Notably, analysis of the ^{1}H NMR spectra of aliquots of the reaction mixture at 3 and 8 h time points showed no evidence of any other intermediate, simply a varying ratio of **13iB**/**15iB** to **8i**. It remains unclear if the oxidative addition to the vinyl cyclopropane occurs prior to, or after, deallylation. Regardless, the conversion of dihydrofurans **13iB** and **15iB** to the spiroketals **8i** provides support for the proposed mechanism outlined above.

With a clearer picture of substrate scope and mechanism established, attention was turned to applying the newly developed methodology to the construction of the tetracyclic core of berkelic acid. Treatment of the benzopyran **16a**,[16] with 1,4-dibromobut-2-ene in the presence of potassium carbonate, provided the corresponding vinyl cyclopropane as an inconsequential 1:1:1:1 mixture of diastereomers (Scheme 7). The crude residue was subjected to the standard reaction conditions to afford the entire scaffold of berkelic acid **17a** as a 1:1 mixture of diastereoisomers in excellent yield.

Scheme 7. Synthesis of the Berkelic Acid Core and ORTEP Diagram of 17bi



In conclusion, we have disclosed a novel and highly efficient method to access benzannulated 6,5-spiroketals. The reaction proceeds at ambient temperatures to provide a diverse array of functionalized systems including the entire scaffold of berkelic acid. Current efforts are focused toward applying this methodology to the synthesis of benzannulated spiroketal containing natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00878.

Experimental procedures; characterization data and NMR spectra; crystallographic data for X-ray crystal structures of **8ai–ii**, **8ni–ii**, and **17bi–ii** (PDF)

Accession Codes

CCDC 1901377–1901382 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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