Ring expansion via one-pot conversion of lactone acetals to cyclic enones. Synthesis of (±)-1-epi-xerantholide.

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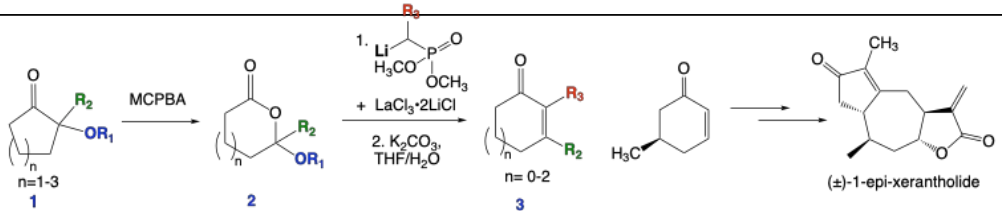
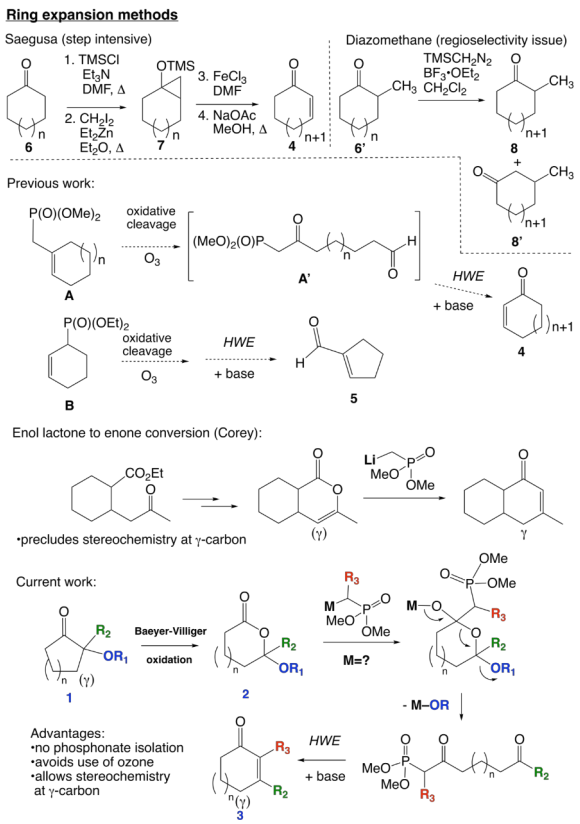
Supporting Information Placeholder



ABSTRACT: Baeyer-Villiger oxidation of α-alkoxy ketones **1** provides lactone acetals **2**, which react with the lithium salts of dimethyl(alkyl) phosphonates in the presence of $LaCl_3$•2LiCl to provide cyclic enones **3** in good to excellent yields after treatment with dilute aqueous potassium carbonate. Thus, five-, six-, and seven-membered lactones are converted to five-, six-, and seven membered cyclic enones. The utility of this two-step ring expansion method is demonstrated in the synthesis of (±)-1-epi-xerantholide from 5-methyl-2-cyclohexen-1-one.

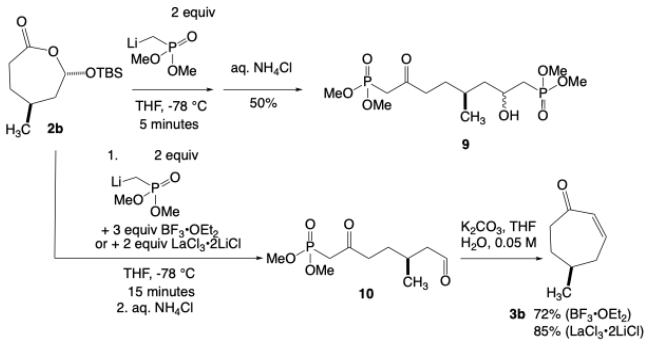
Medium-ring carbocycles form the core of numerous natural products and may be efficiently accessed by ring expansion reactions.[1] Two of the most popular methods for accomplishing this transformation include the Saegusa reaction,[2] involving the thermal or $FeCl_3$-mediated cleavage of silyloxy cyclopropanes, and the addition of diazomethane or its derivatives to cycloalkanones in the presence of Lewis acids (Scheme 1).[1b,3] Recently, we have shown that oxidative cleavage of allylic phosphonates produce carbonyl-tethered β-ketophos-phonates, which undergo intramolecular Horner-Wadsworth-Emmons (HWE) reactions[4] to produce cyclic enones and enals in good yields.[5] Depending on the structure of the allylic phophonate employed, the overall process results in either a ring expansion (**A→4**) or a ring contraction (**B→5**). Drawbacks of this method include the necessity of preparing and isolating the requisite allylic phosphonates, as well as the use of ozone for the oxidative cleavage step, which limits the substrate scope of the process. In an attempt to improve the utility of this reaction specifically for ring homologation, we envisioned that suitably modified lactones could serve as direct precursors of the carbonyl-tethered β-ketophosphonate intermediates.[6] Inspiration for this approach came from Corey's previously reported enol lactone to enone conversion.[7] To avoid the difficulties inherent in the regioselective preparation of enol lactones, as well as to expand the scope of enones prepared by this conversion (including those containing stereochemistry at the γ-carbon atom, Scheme 1), we decided to explore phosphonate anion addition to lactone acetals **2**, which could be readily prepared by regioselective Baeyer-Villiger oxidation[8] of cyclic α-alkoxyketones **1**.



Scheme 1. Ring expansion methods and previous/ current work on intramolecular HWE olefinations.

Herein we provide details of our investigations and an application of this new ring-expansion protocol to the synthesis of (±)-1-epi-xerantholide.

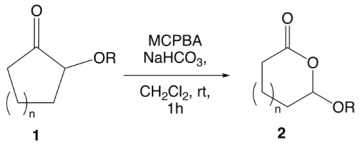
A series of α-alkoxy ketones (**1a**-**1h**), prepared by alkene or silyl enol ether dihydroxylation and protection reactions (see Supporting Information), were exposed to MCPBA at room temperature to afford the corresponding lactones (**2a**-**2f** and **2h**) regioselectively and in good to excellent yields (Table 1).[9] The reaction allows preparation of six-, seven-and eight-membered lactones from five-, six, and seven-membered cyclic ketones, and substrates bearing silyl ether or acetal oxygen protecting groups are well tolerated. One challenging substrate was the quaternary center-containing compound **1g** derived from 3-carene, which provided less than 10% yield of the corresponding lactone, likely due to steric hindrance at the ketone carbonyl carbon. It was subsequently found that similar lactones of the type **2j** (Table 2) could be prepared by acid-catalyzed cyclization of γ–keto-acids in alcohol solvents.[10]

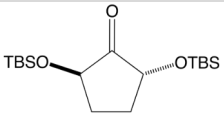
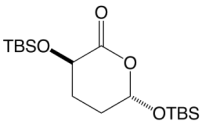
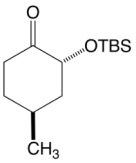
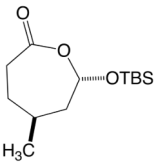
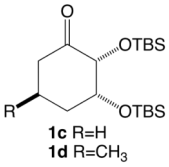
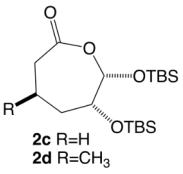
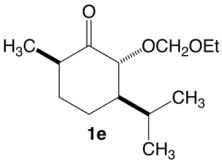
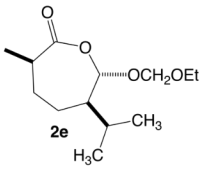
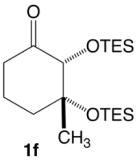
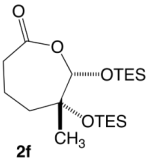
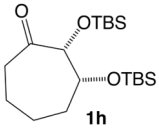
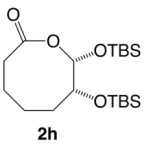


Scheme 2. The effect of BF_3•OEt_2 or $LaCl_3$•2LiCl on addition of phosphonate anions to lactones.

We next attempted the addition of the anion of dimethylmethyl phosphonate[5] to the representative lactone **2b** (Scheme 2). Treatment of 2 equiv dimethylmethyl phosphonate in THF at -78 °C with 2.2 equiv BuLi, followed by the addition of **2b** resulted in disappearance of starting material within 5 minutes at -78 °C; after quenching the mixture with saturated NH_4Cl solution, alcohol **9** was obtained in 50% yield as a mixture of diastereomers (Scheme 3). Reduction of the number of equivalents of phosphonate anion (1.1 equiv) yielded only **9** (35%) and recovered **2b**. Previous work by Lequeux[11] on the addition of α-difluorophosphonate anion to lactones indicated the beneficial effect of BF_3•etherate on reaction yields. Following this protocol, we treated dimethylmethyl phosphonate (2 equiv) with *n*-BuLi (2 equiv) at -78 °C in THF for 30 minutes, and then added BF_3•OEt_2 (3 equiv) before addition of **2b** (1 equiv). After stirring the reaction mixture for 15 minutes, complete consumption of the starting material was observed by TLC, whereupon saturated NH_4Cl solution was added. Dissolving the crude oil obtained after work up in 1:1 THF : H_2O (0.5 M) containing K_2CO_3 (4.5 equiv) provided cycloheptenone **3b** in 72% overall yield after 10 minutes stirring at room temperature. Utilizing $LaCl_3$•2LiCl (2 equiv) in place of BF_3•OEt_2 furnished **3b** in 85% isolated yeld.[12] Thus, the addition of Lewis acids appears to suppress premature opening of the lactol alkoxide intermediate at -78 °C.

Table 1. Regioselective Baeyer-Villiger oxidations[9] of ketones **1** with MCPBA.

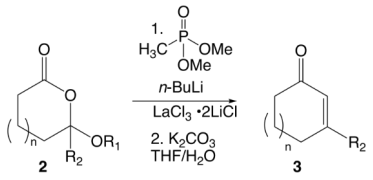


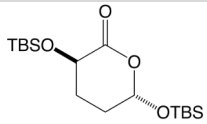
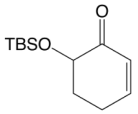
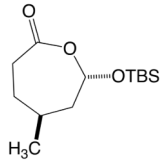
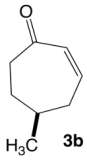
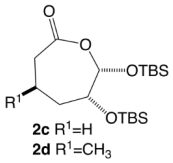
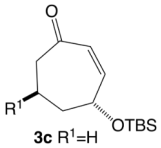
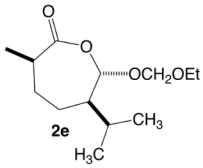
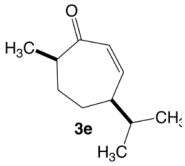
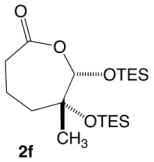
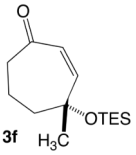
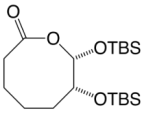
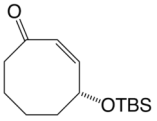
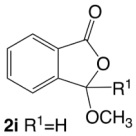
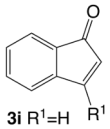
entry	1	2	yield **2**[a]
1			89[b]
2			73[c]
3			85[d] 76[e]
4			61[f]
5			82
6			<10[g]
7			92

[a] Isolated yields after column chromatography. [b] Obtained as a 1.6:1 mixture of *anti:syn* diastereomers.[22] [c] Obtained as a 1.4:1mixture of anti:syn diasteromers.[22] [d] Isolated yield of **2c**. [e]Isolated yield of **2d**. [f] Obtained as a 5:1 mixture of *anti:syn* diastereomers.[22] [g] For the synthesis of **1g**, see reference 23.

Due the lower equivalence of Lewis acid required and the slightly higher yields obtained, commercially available THF solutions of $LaCl_3$•2LiCl (0.6 M) were utilized in our subsequent studies.

Table 2. The lactone (**2**) to enone (**3**) conversion.

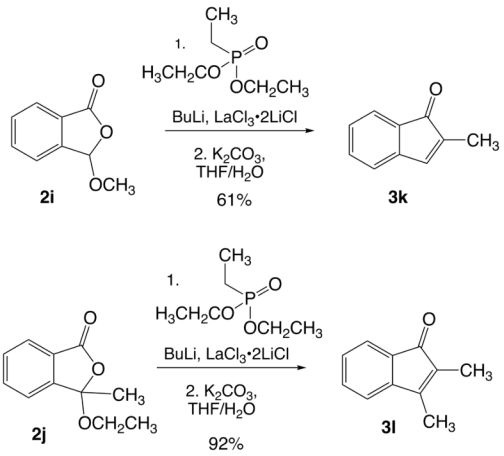


entry	2	3	yield 3[a]
1	 **2a**	 **3a**	58
2	 **2b**	 **3b**	85
3	 **2c** R^1=H **2d** R^1=CH_3	 **3c** R^1=H **3d** R^1=CH_3	68[b] 76[c]
4	 **2e**	 **3e**	58[d]
5	 **2f**	 **3f**	78
6	 **2h**	 **3h**	<10
7	 **2i** R^1=H **2j** R^1=CH_3	 **3i** R^1=H **3j** R^1=CH_3	64[e] 85[f]

[a] Isolated yields after column chromatography. [b] Isolated yield of **3b**. [c] Isolated yield of **3d**. [d] Obtained as a 10:1 mixture of *anti:syn* diastereomers. [e] Isolated yield of **3i**. [f] Isolated yield of **3j**.

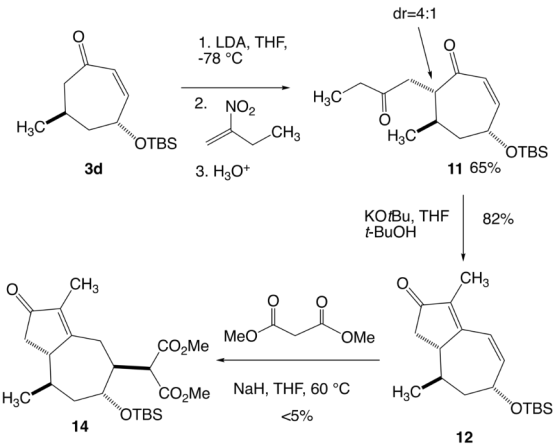
We next surveyed the scope of the two-step one-pot phosphonate addition/intramolecular HWE reaction on lactones **2a**-**2j**. Five-, six, and seven-membered lactones can be transformed cleanly into five-, six, and seven-membered cyclic enones in good to excellent yields, with the reaction tolerating the presence of TES (entry 5) and TBS ether (entries 1-3) protecting groups as well as ethoxymethyl acetals (entry 4)[21] and alkyl acetals (entry 7). Notably, the quaternary center-containing substrates **2f** and **2j** smoothly provided the corresponding enone products **3f** and **3j** in 78 and 85% yields, respectively. Only eight-membered lactone **2h** failed to produce the corresponding eight-membered enone **3h**, likely due to the well-known entropic penalty for cyclizations leading to eight-membered rings.

To explore the utility of this method for the preparation of α-substitued enones,[5] we next attempted the addition of the anion of diethyl ethyl phosphonate to lactones **2i** and **2j**. Gratifyingly, enone **3k** was obtained in 61% yield and enone **3l**, containing a tetrasubstitued olefin, was prepared in 92% yield.



Scheme 3. Formation of α-substitued enones with diethyl ethylphosphonate.

The sesquiterpene lactone xerantholide was isolated from the aerial parts of *Xeranthemum cylindraceum* by Hladon et al.[13] and was demonstrated to have significant cytostatic activity toward KB and HeLa-type tumor cells;[14] subsequently it was found to also possess anti-gonorrheal and anti-plasmodium activities.[15] To demonstrate the synthetic utility of the seven-membered cyclic enones available from the present ring-expansion protocol, we undertook a synthesis of (±)-xerantholide proceeding from enone **3b**. Exposure of the lithium enolate of **3b** to 2-methylenenitropropane according to the protocol of Alexakis[16] provided enone **11** as a 4:1 mixture of *anti*:*syn* diastereomers in 65% yield. Treatment of **11** with potassium *tert-butoxide* in THF and *t*-BuOH at 40 °C for one hour provided cyclopentenone **12** in 82% yield.[17] Attempted 1,6-addition[18] of the sodium salt of dimethyl malonate to **12** met with limited success, even under forcing conditions (sealed tube, 100 °C, 48 hours), with only starting material recovered from the reaction. Following the precedent of Ohmori,[19] it was subsequently found that 1,4-addition of dimethylmalonate to **11** under basic conditions proceeded smoothly to furnish **13**, which was immediately treated with a 1M solution of potassium *tert*-butoxide in THF at room temperature to provide **14** in 75% overall yield.[17] Compound **14** was treated with TBAF (2 equiv) in THF to remove the silyl ether, and hydrolysis of the methyl esters was accomplished with 2N NaOH in MeOH for 2 hours, to provide intermediate diacid **15**.

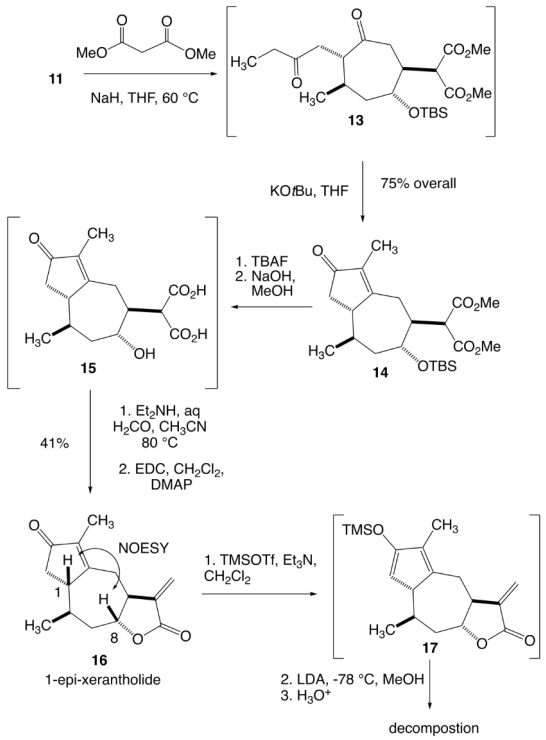


Scheme 4. Preparation of enone **14** from **3d**.

Exposure of the diacid to diethylamine in the presence of formaldehyde in CH_3CN at 80 °C for 2 hours accomplished decarboxylative methylenation;[20] treatment of the crude hydroxy acid with EDC and DMAP in CH_2Cl_2 overnight furnished **16**. Cross-peaks (C.1←→C.8) observed in the NOESY spectrum of **16** confirmed the relative stereochemistry of the compound, which possessed the epimeric configuration at C.1 relative to xerantholide.

Attempted isomerization at C.1 to xerantholide via low-temperature protonation of the cyclopentadienyl anion arising from LDA treatment of silyl enol ether **17** failed, providing instead extensive substrate decomposition. All other attempts to isomerize the C.1 position of compounds **11** and **12** under acidic or basic conditions proved fruitless.

In summary, we have demonstrated the utility of a one-pot lactone-acetal to enone conversion, leading to an efficient two-step ring homologation protocol that avoids the use of ozone and the isolation of phosphonate-containing intermediates. In addition, this process extends the utility of Corey's enol-lactone to enone conversion by allowing the preparation of products (for example, **3c**, **3d**, **3e**, and **3f**, Table 2) containing stereocenters at the enone γ-position.



Scheme 5. Synthesis of (±)-1-epi-xerantholide, **16**.

ASSOCIATED CONTENT

•Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

•Supporting Information

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds in Tables 1 and 2 and Schemes 3, 4, and 5 (PDF). The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors.

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21. The identity of the OR group of the lactone acetal does not appear to significantly affect the yield of the reaction. For example, ethoxymethyl acetal **2e** produced enone **3e** in 58% yield; replacing the ethoxymethyl group with a *tert*-butyldimethylsilyl group produced **3e** in 52% yield.
22. The diastereomeric mixtures obtained for Baeyer-Villiger products **2a**, **2b**, and **2e** arise from the corresponding diastereomeric impurities in the starting α-alkoxy ketones **1a**, **1b**, and **1e**, respectively.

23. Compound **1g** was prepared by PCC oxidation of the corresponding methoxy alcohol available from (+)-3-carene by epoxidation and acid-catalyzed methanolysis. See: Krishnaswamy, D.; Govande, V.; Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. Triphosgene: a versatile reagent for the synthesis of azetidine-2-ones. *Tetrahedron* **2002**, *58*, 2215-2225.