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A single-flask synthesis of α-alkylidene and α-benzylidene lactones from ethoxyacetylene, epoxides/oxetanes, and carbonyl compounds

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ABSTRACT

Low temperature treatment of (ethoxyethynyl)lithium with epoxides or oxetanes in the presence of $BF_3{\cdot}OEt_2$, followed by addition of aldehydes or ketones and warming to room temperature, affords structurally diverse five- and six-membered α-alkylidene and α-benzylidene lactones (**5**) in good to excellent yields. This one-pot process, in which three new carbon–carbon bonds and a ring are formed, affords substituted α,β-unsaturated lactones of predominantly *Z*-configuration. The reaction likely occurs via alkyne–carbonyl metathesis of a hydroxy–ynol ether intermediate, acid-promoted alkene *E*- to *Z*-isomerization, and lactonization.

The α-alkylidene lactone moiety is found in numerous synthetically challenging and biologically important natural products, many of which possess anticancer, antimalarial, antibacterial, antifungal, antiviral, and/or anti-inflammatory activities.[1] Of particular significance are the numerous members of the α-methylene-γ-butyrolactone family of sesquiterpenes, to which belong the germacranolides, (pseudo)guaianolides, eudesmanolides, and the cembranolides.[2] Recently, synthetic attention has also been directed toward the α-benzylidene-γ-butyrolactones megacerotonic acid and shimobashiric acid, due to their heightened biological profile.[3]

The α-alkylidene lactone motif is typically constructed by the condensation of lactone enolates with aldehydes or iminium ions,[2b,4] by transition-metal mediated lactonizations,[5] or by Wittig or Horner–Wadsworth–Emmons-type reactions[6] between phosphorous ylides/phosphonate anions and carbonyl compounds.[1b] In the present Letter we describe a useful one-pot assembly α-alkylidene and α-benzylidene lactones from ethoxyacetylene, epoxides/oxetanes, and aldehydes or ketones.

Electron-rich alkynes, such as ynamines and ynol ethers, are functional groups that possess significant potential in organic chemistry for the formation of C–C bonds.[7] Due to their linear geometry, alkynyl ethers are relatively unhindered to approach by functional groups present in the same or different molecules; furthermore, alkynyl ethers can prospectively form up to three new bonds in a single reaction.[8] We have previously shown that *tert*-butyl ynol ethers bearing tethered alkenes form substituted cyclobutanones in high yields under mild thermal conditions (Fig. 1).[8d] Furthermore, ynol ethers bearing pendant acetal groups undergo Lewis-acid catalyzed intramolecular cyclocondensation reactions to produce alkoxycycloalkene carboxylates.[8e]

While ynol ether–carbonyl metathesis reactions are well known,[7,8] we wished to explore the possibility of employing this reaction in the context of a tandem bond-forming process that would allow the rapid build up of molecular complexity in a single step. Specifically, we sought to combine the *intermolecular* electrophilic reaction of an ynol ether and a carbonyl compound with an *intramolecular* nucleophilic trap of the intermediate unsaturated ester, accomplishing the formation of two new carbon–carbon bonds and a ring (Fig. 1, reaction b). In addition, the ynol ether substrate for this reaction (**3**, Fig. 1) can be prepared by ring opening of cyclic ether **2** with metalated ethoxyacetylene (M = Li or BF_3Li, Fig. 1, reaction a). Since Lewis acid is used to promote both of these reactions, the concept of combining these processes into a single transformation was appealing, and thus we sought conditions to accomplish the direct conversion of ynol ether **1** (M = H) to lactone **5**.

To explore the structural requirements for the tandem ynol ether–carbonyl condensation and lactonization transform (reaction b, Fig. 1), we combined equimolar amounts of ynol ether **3a**, benzaldehyde, and $BF_3{\cdot}OEt_2$ at −78 °C for 15 min (Scheme 1). Acyclic unsaturated ester **4a** was obtained in 76% yield as a ~1:1 *E:Z*

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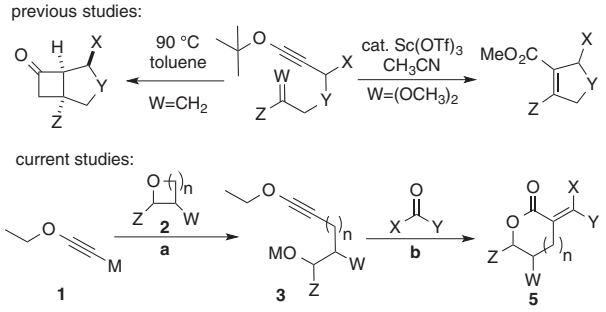
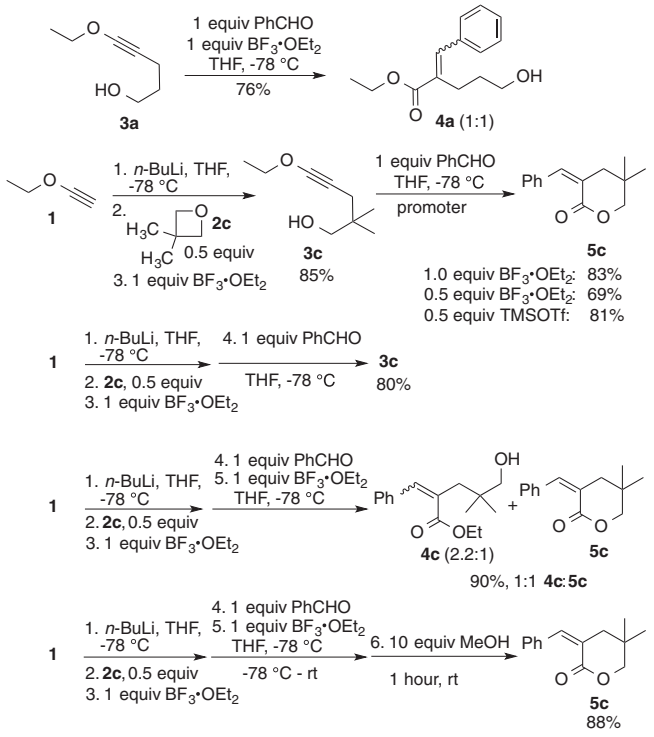


Figure 1. Previous and current studies.

stereoisomer mixture. Since no lactone was produced in this reaction, we reasoned that the gem-dimethyl (Thorpe–Ingold) effect[9] might facilitate the tandem processes of benzylidenation and lactonization. Thus, substrate **3c** was prepared (85% yield) by combining (ethoxyethynyl)lithium with 3,3-dimethyloxetane (0.5 equiv) and $BF_3{\cdot}OEt_2$ (1.0 equiv) in THF at −78 °C for 2 h. After isolation, **3c** was condensed with benzaldehyde in THF at −78 °C in the presence of $BF_3{\cdot}OEt_2$ (1.0 equiv) for 15 min, giving rise to lactone **5c** in 83% yield. Substoichiometric amounts of $BF_3{\cdot}OEt_2$ (0.5 equiv) or TMSOTf (0.5 equiv) in THF also promoted the efficient conversion of **3c** to **5c** (69% and 81%, respectively). Since $BF_3{\cdot}OEt_2$ was shown to be an efficient promoter for both reactions in THF at −78 °C, we proceeded to combine (ethoxyethynyl)lithium, 3,3-dimethyl-oxetane (0.5 equiv), and $BF_3{\cdot}OEt_2$ (1.0 equiv) in THF at −78 °C for two hours, followed by addition of benzaldehyde (1.0 equiv). After 15 min of reaction at −78 °C, only ynol ether **3c** was evident in the reaction mixture; extending the reaction time or warming to room temperature did not effect conversion of **3c** to **5c**. Instead, addition of one equivalent of $BF_3{\cdot}OEt_2$ at −78 °C after addition of the benzaldehyde resulted in a clean conversion to an inseparable 1:1 mixture of acyclic unsaturated ester **4c** (as a 2.2:1 mixture of

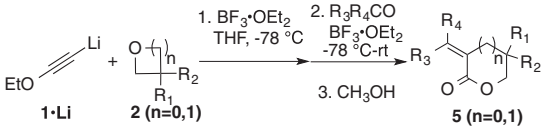


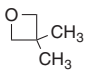
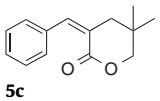
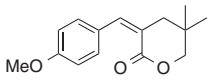
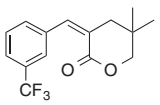
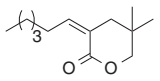
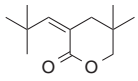
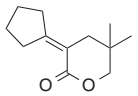
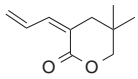
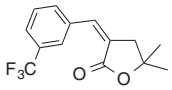
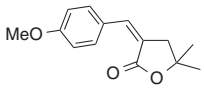
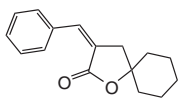
Scheme 1. Optimization of the **1**→**5** transformation.

stereoisomers) and lactone **5c**. We reasoned that lactonization of **4c** could be facilitated by the presence of a Brønsted acid in the reaction medium, and thus after warming the mixture to room temperature, methanol (10 equiv) was added (promoting the formation of HF and/or fluoroboric acids) and the reaction was allowed to stir for one hour. An 88% isolated yield of lactone **5c** was obtained after column chromatography.

Benzylidene lactone **5c** was obtained as a single isomeric alkene of *Z*-configuration (vide infra). Due to the excess amount of Lewis and Brønsted acids present in the reaction medium, it is possible

Table 1
Scope of the one-pot synthesis of lactones **5** from **1**[a]



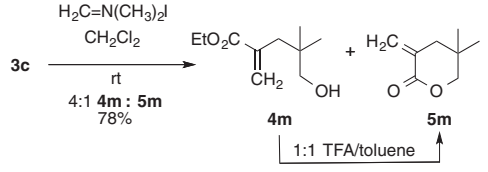
Entry	**2** (R_1 = R_2)	R_3R_4CO	Product	Yield[b]
1	 **2c**	PhCHO	 **5c**	88
2	**2c**	4-OMe—C_6H_4CHO	 **5d**	65
3	**2c**	3-CF_3—C_6H_4CHO	 **5e**	79
4	**2c**	$CH_3(CH_2)_4$—CHO	 **5f**	55
5	**2c**	$(CH_3)_3C$—CHO	 **5g**	87
6	**2c**	$(CH_2)_4CO$	 **5h**	67
7	**2c**	CH_2=CH—CHO	 **5i**	92
8	 **2j**	3-CF_3—C_6H_4CHO	 **5j**	71
9	**2k**	4-OMe—C_6H_4CHO	 **5k**	69
10	 **2l**[11]	PhCHO	 **5l**	54

[a] Reaction conditions: **1** (1 mmol) in THF (0.25 M) was treated with *n*-BuLi (1 mmol) and stirred for 15 min. Then **2** (0.5 mmol) and $BF_3{\cdot}OEt_2$ (1 mmol) were added and the mixture was stirred for 2 h. Then aldehyde or ketone (1 mmol) and $BF_3{\cdot}OEt_2$ (1 mmol) were added and the mixture was allowed to warm to rt. Then MeOH (10 mmol) was added and the mixture was stirred for one hour.
[b] Isolated yields after column chromatography.

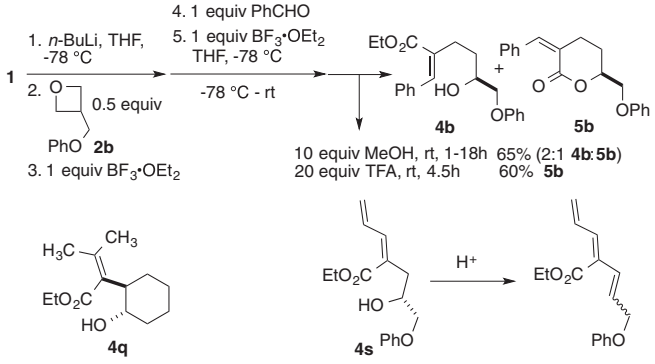
that an initially formed *E*-alkene[15,16] or *E*/*Z* mixture[17] obtained after the ynol ether–carbonyl metathesis reaction (cf. **4a** and **4c**) underwent acid-promoted *E*- to *Z*-isomerization, a process likely driven by relief of A[1,3] strain in the *E* isomer (Scheme 4).[10]

As shown in Table 1, both electron-rich and electron-deficient aromatic aldehydes (entries 1–3, 8–10) are suitable carbonyl components for the tandem process, furnishing α-arylidene δ-valerolactones and γ-butyrolactones in very good overall yields. In addition, hindered and unhindered aliphatic aldehydes (entries 4 and 5) and cyclopentanone (entry 6) smoothly combined with **1** and **2** to furnish the corresponding α-alkylidenes **5f**–**5h**. Employing the α,β-unsaturated aldehyde acrolein in the reaction gave rise to a 92% yield of diene **5i** (entry 7), a potentially useful substrate for Diels–Alder reactions. Only two carbonyl substrate types proved problematic for this process: the aromatic ketone benzophenone and formaldehyde gave complex mixtures and low yields (<10%) in tandem reactions involving **1** and **2c**. Intriguingly, reaction of **3c** with Eschenmoser's salt[12] in CH_2Cl_2 at room temperature gave rise to a 1:4 mixture of α-methylene δ-valerolactone (**5m**) and acyclic enoate (**4m**), which upon exposure to 1:1 TFA/toluene at room temperature for 30 min resulted in a quantitative conversion to **5m** (Scheme 2).

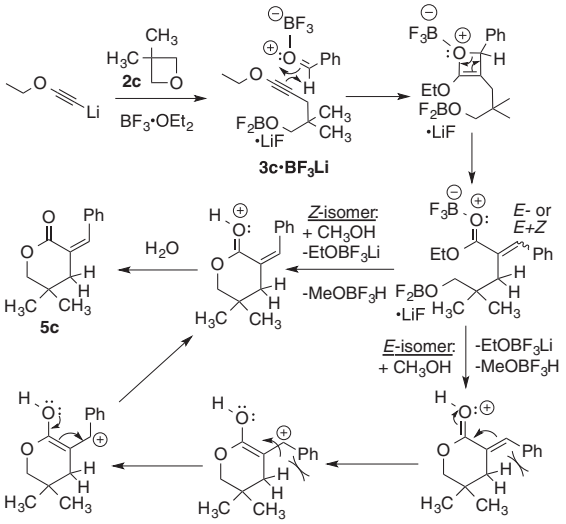
To extend this method to the synthesis of lactones without quaternary centers in the ring, we exposed (ethoxyethynyl)lithium to oxetane **2b** (0.5 equiv) and $BF_3{\cdot}OEt_2$ (1.0 equiv) in THF at −78 °C for two hours, followed by addition of benzaldehyde (1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv) and warming to room temperature. After stirring with methanol (10 equiv) for 1 h or overnight, an inseparable ~2:1 mixture of acyclic unsaturated ester **4b** and lactone **5b** was obtained in 65% yield. When the reaction mixture was treated instead with 20 equiv of TFA for 4.5 h, a 60% isolated yield of lactone **5b** was obtained after column chromatography (Scheme 3). It was subsequently found that TFA treatment was not necessary for the formation of γ-butyrolactones by this method; simply stirring the reaction mixture overnight at room temperature in the presence of 10 equiv of MeOH for the lactonization step gave the desired α-benzylidene and α-alkylidene products in good to excellent overall yields (Table 2).



Scheme 2. Formation of α-methylene lactone **5m**.



Scheme 3. Formation of lactones lacking quaternary centers.



Scheme 4. Proposed mechanism for formation of *Z*-alkylidene and benzylidene lactones.

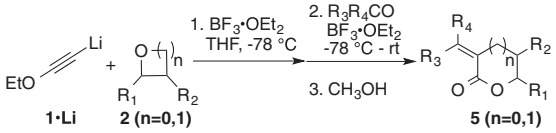
As can be seen in Table 2, this protocol allows a range of sterically and electronically diverse α-arylidene (entries 2, 3, and 7) and α-alkylidene (entries 4 and 5) γ-butyrolactones to be prepared in good to excellent yields. Interestingly, the intermediate unsaturated ester **4q** derived from the reaction of **1** with **2q** and acetone proved particularly sensitive to acid-promoted degradation during the prolonged stirring at room temperature required for the lactone-forming step. This difficulty could be circumvented by hydrolyzing crude **4q** (1:1 CH_3OH/1 N NaOH, 15 min, rt; H_3O^+) to the corresponding seco acid and then stirring overnight in the presence of 2,4,6-trichlorobenzoyl chloride (under Yamaguchi/Yonemitsu lactonization conditions)[14] to furnish butyrolactone **5q** in 62% overall yield. Diene **5s** was prepared in moderate overall yield (50%) from **1**, **2r**, and acrolein due to the formation of side products derived from acid-mediated elimination of the alcohol in intermediate **4s** (Scheme 3).

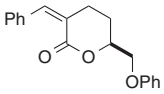
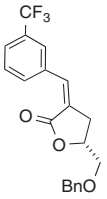
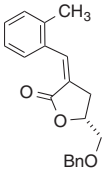
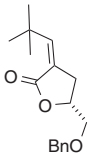
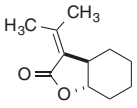
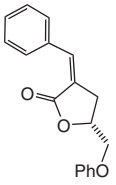
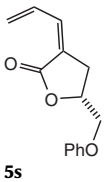
The *Z*-stereochemistry of the alkene products was verified by ^1H–^1H NOESY experiments, in which crosspeaks were observed between the vinyl proton and the allylic methylene protons of the lactone. In the case of lactone **5o**, an additional cross-peak between the methyl group of the 2-tolyl substituent and the vinyl proton can be detected (Fig. 2).

Based on the observations reported in Schemes 1–3, a possible mechanism for this transformation (Scheme 4) involves the initial formation of ynol ether **3**·BF_3Li from **1** and **2** in the presence of $BF_3{\cdot}OEt_3$, which then undergoes metathesis with an added carbonyl compound when it is activated by the second addition of $BF_3{\cdot}OEt_3$. The acyclic unsaturated ester intermediate, which may initially be produced as the *E* isomer due to torquoselective ring opening of the oxetene intermediate,[15–17] is then engaged in alkene *E*- to *Z*-isomerization[10,17] and lactonization processes that are facilitated both by $BF_3{\cdot}OEt_2$ and the Brønsted acid formed when methanol is introduced into the reaction medium. The olefin isomerization may take place either prior to[17] or after[10] lactonization; whereas **4c** is formed as a mixture of alkene isomers along with lactone **5c** (Scheme 1), intermediate **4b** (also isolated as an inseparable mixture with lactone **5b** after 18 h exposure to Brønsted acid after methanol addition) is of a single geometric configuration, suggesting that the *E*- to *Z*-interconversion process may take place before lactonization for some substrates.

In summary we have developed an efficient one-flask strategy for the synthesis of α-alkylidene and α-benzylidene lactones by

Table 2
Synthesis of lactones without ring quaternary centers[a]



Entry	2	R_3R_4CO	Product	Yield[b]
1	 **2b**[13]	PhCHO	 **5b**	60[c]
2	 **2n**	3-CF_3—C_6H_4CHO	 **5n**	81
3	**2n**	2-CH_3—C_6H_4CHO	 **5o**	80[d]
4	**2m**	$(CH_3)_3$C—CHO	 **5p**	75
5	 **2q**	$(CH_3)_2CO$	 **5q**	62[e]
6	 **2r**	PhCHO	 **5r**	85
7	**2r**	CH_2=CH—CHO	 **5s**	50

[a] Reaction conditions: **1** (1 mmol) in THF (0.25 M) was treated with *n*-BuLi (1 mmol) and stirred for 15 min. Then **2** (0.5 mmol) and $BF_3{\cdot}OEt_2$ (1 mmol) were added and the mixture was stirred for 2 h. Then aldehyde or ketone (1 mmol) and $BF_3{\cdot}OEt_2$ (1 mmol) were added and the mixture was allowed to warm to rt. Then MeOH (10 mmol) was added and the mixture was stirred overnight.
[b] Isolated yields after column chromatography.
[c] TFA (20 equiv, 4.5 h, rt) was used instead of methanol for the lactonization step.
[d] Product formed as a 5:1 *Z*:*E* alkene isomer mixture.
[e] The crude unsaturated ester was hydrolyzed (1 N NaOH/MeOH) and then subjected to Yamaguchi/Yonemitsu conditions for lactonization with 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP in benzene for 12 h (see Supporting materials).

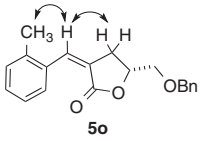


Figure 2. Cross-peaks observed in the ^1H–^1H NOESY spectrum of **5o**.

the combination of ethoxyacetylene, epoxides/oxetanes, and carbonyl compounds. This operation achieves the formation of three new carbon–carbon bonds and ring, thus affording a significant increase in molecular complexity. The reaction also provides *Z*-configured unsaturated lactones stereoselectively, and likely proceeds through the intermediacy of an acyclic unsaturated ester that undergoes acid-promoted alkene *E*- to *Z*-isomerization and lactonization. We are currently exploring the utility of this process in natural product synthesis, and our results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.041.

References and notes

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