Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Kevin Ng, Vincent Tran, Thomas Minehan *

Department of Chemistry and Biochemistry, California State University, Northridge, 18111 Nordhoff Street, Northridge, CA 91330, USA

ARTICLE INFO

Article history:
Received 17 November 2015
Revised 1 December 2015
Accepted 8 December 2015
Available online xxxx

Keywords:
Ynol ethers
α-Alkylidene lactones
α-Benzylidene lactones
Tandem reactions
$BF_3{\cdot}OEt_2$ promotion

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*

* Corresponding author. Tel.: +1 818 677 3315; fax: +1 818 677 4068.
E-mail address: thomas.minehan@csun.edu (T. Minehan).

http://dx.doi.org/10.1016/j.tetlet.2015.12.041
0040-4039/

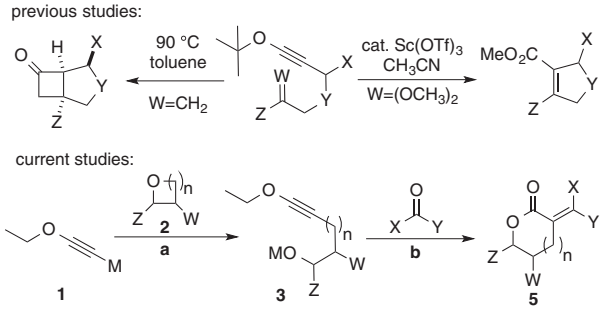
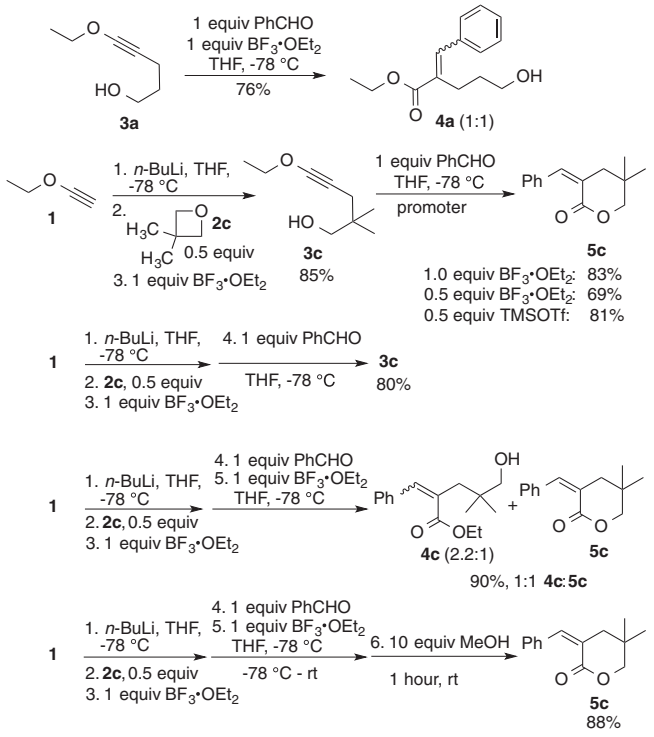


Figure 1. Previous and current studies.

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

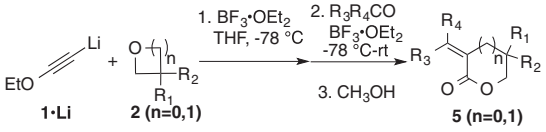


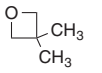
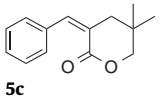
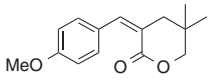
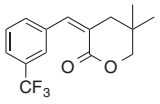
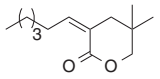
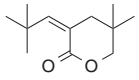
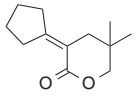
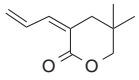
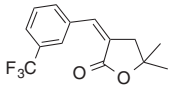
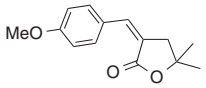
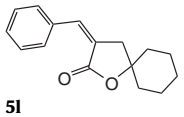
Scheme 1. Optimization of the **1**→**5** transformation.

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]



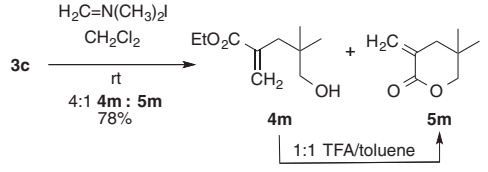
Entry	**2** (R_1 = R_2)	R_3R_4CO	Product	Yield[b]
1	 **2c**	PhCHO	 **5c**	88
2	**2c**	4-OMe—C_6H_4CHO	 **5d**	65
3	**2c**	3-CF_3—C_6H_4CHO	 **5e**	79
4	**2c**	$CH_3(CH_2)_4$—CHO	 **5f**	55
5	**2c**	$(CH_3)_3C$—CHO	 **5g**	87
6	**2c**	$(CH_2)_4CO$	 **5h**	67
7	**2c**	CH_2=CH—CHO	 **5i**	92
8	 **2j**	3-CF_3—C_6H_4CHO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

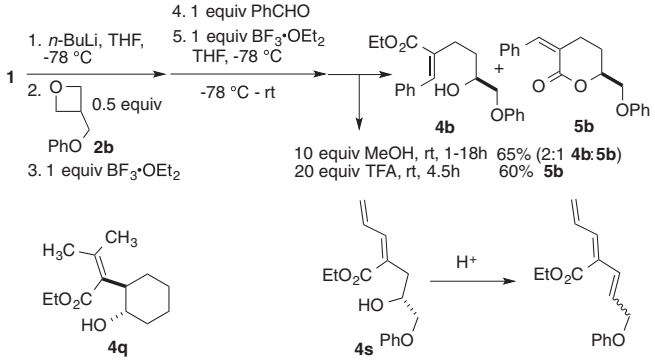
that an initially formed *E*-alkene[15,16] or *E*/*Z* mixture[17] obtained after the ynol ether–carbonyl metathesis reaction (cf. **4a** and **4c**) underwent acid-promoted *E*- to *Z*-isomerization, a process likely driven by relief of A[1,3] strain in the *E* isomer (Scheme 4).[10]

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).

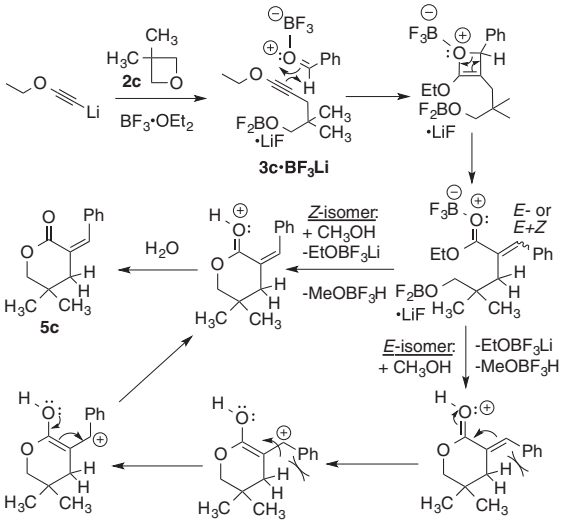
To extend this method to the synthesis of lactones without quaternary centers in the ring, we exposed (ethoxyethynyl)lithium to oxetane **2b** (0.5 equiv) and $BF_3{\cdot}OEt_2$ (1.0 equiv) in THF at −78 °C for two hours, followed by addition of benzaldehyde (1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv) and 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.

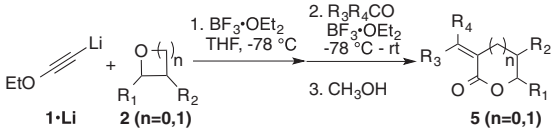
As can be seen in Table 2, this protocol allows a range of sterically and electronically diverse α-arylidene (entries 2, 3, and 7) and α-alkylidene (entries 4 and 5) γ-butyrolactones to be prepared in good to excellent yields. Interestingly, the intermediate unsaturated ester **4q** derived from the 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).

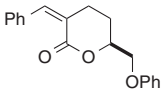
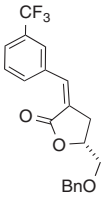
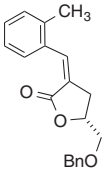
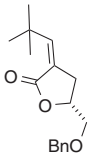
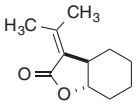
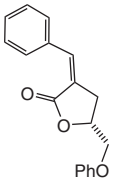
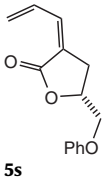
The *Z*-stereochemistry of the alkene products was verified by ^1H–^1H NOESY experiments, in which crosspeaks were observed between the vinyl proton and the allylic methylene protons of the lactone. In the case of lactone **5o**, an additional cross-peak between the methyl group of the 2-tolyl substituent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

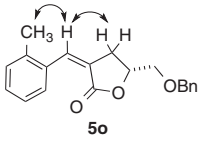


Figure 2. Cross-peaks observed in the ^1H–^1H NOESY spectrum of **5o**.

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

We acknowledge the National Institutes of Health (SC3 GM 096899-01) and the donors of the American Chemical Society Petroleum Research Fund (53693-URI) for their generous support of this research. We also acknowledge the UC Riverside Mass Spectrometry Facility for accurate mass determinations. This Letter is dedicated to Professor Peter Dervan on the occasion of his 70th birthday.

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

1. (a) Elford, T. G.; Hall, D. G. *Synthesis* **2010**, 893; (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426.
2. (a) Schall, A.; Reiser, O. *Eur. J. Org. Chem.* **2008**, 2353; (b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94; (c) Picman, A. K. *Biochem. Syst. Ecol.* **1986**, *14*, 255.
3. (a) Krabbe, S. W.; Johnson, J. S. *Org. Lett.* **2015**, *17*, 1188; (b) Brown, E.; Dhal, R.; Papin, N. *Tetrahedron* **1995**, *51*, 13061; (c) Papin, N.; Dhal, R.; Brown, E. *Nat. Prod. Lett.* **1994**, *4*, 303; (d) Takeda, R.; Hasegawa, J.; Shinozaki, M. *Tetrahedron Lett.* **1990**, *31*, 4159; (e) Takeda, R.; Hasegawa, J.; Shinozaki, M. *Proc. Phytochem. Soc. Eur.* **1990**, *29*, 201; (f) Murata, T.; Miyase, T.; Yoshizaki, F. *Chem. Pharm. Bull.* **2012**, *60*, 121.
4. Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 6361.
5. (a) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4621; (b) Lee, A. S.-Y.; Chang, Y.-T.; Wang, S.-H.; Chu, S.-F. *Tetrahedron Lett.* **2002**, *43*, 8489; (c) Sawant, M. S.; Katoch, R.; Trivedi, G. K.; Desai, U. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 843; (d) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584; (e) Yu, C.-M.; Hong, Y.-T. *J. Org. Chem.* **2004**, *69*, 8506; (f) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593; (g) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem.* **1999**, 1137; (h) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 733; (i) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120; (j) Moise, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 1695; (k) Moise, J.; Sonawane, R. P.; Corsi, C.; Wendeborn, S. V.; Arseniyadis, S.; Cossy, J. *Synlett* **2008**, 2617; (l) Charruault, L.; Michelet, V.; Genfit, J.-P. *Tetrahedron Lett.* **2002**, *43*, 4757.
6. (a) Miyake, T.; Uda, K.; Kinoshita, M.; Fujii, M.; Akita, H. *Chem. Pharm. Bull.* **2008**, *56*, 398; (b) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Scott, M. S.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1935; (c) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Perry, A.; Scott, M. S.; Whitwood, A. C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2008**, 4769.
7. For reviews of the chemistry of ynol ethers and the methods for the synthesis of ynol ethers, see: (a) Brandsma, L.; Bos, H. J.; Arens, J. F. In *The Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 751–860; (b)

Stang, P. J.; Zhdankin, V. V. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1969; p 994. Chapter 19; For reviews on the synthetic utility of ynolates and silyl ynol ethers, see: (c) Shindo, M.; Matsumoto, K. *Top. Curr. Chem.* **2012**, *327*, 1; (d) Shindo, M. *Tetrahedron* **2007**, *63*, 10; (e) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367; (f) Shindo, M. *Synthesis* **2003**, *15*, 2275; For reviews on the chemistry of ynamides, see: (g) Cook, A. M.; Wolf, C. *Tetrahedron Lett.* **2015**, *56*, 2377; (h) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560; (i) De Korver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem Rev.* **2010**, *110*, 5064; (j) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

8. (a) Zhao, W.; Li, Z.; Sun, J. *J. Am. Chem. Soc.* **2013**, 4680; (b) Zakarya, D.; Rayadh, A.; Samih, M.; Lakhlifi, T. *Tetrahedron Lett.* **1994**, *35*, 405; (c) Krashnaya, Z. A.; Levchenko, T. S.; Rudenko, B. A.; Kucherov, V. F. *Izv. Akad. Nauk SSR Ser. Khim.* **1965**, *2*, 313; (d) Tran, V.; Minehan, T. G. *Org. Lett.* **2011**, *13*, 6588; (e) Tran, V.; Minehan, T. G. *Org. Lett.* **2012**, *14*, 6100.
9. (a) Bachrach, S. M. *J. Org. Chem.* **2008**, *73*, 2466; (b) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080.
10. (a) Johnson, F. *Chem. Rev.* **1968**, *4*, 375; (b) Ramachandran, P. V.; Garner, G.; Pratihar, D. *Org. Lett.* **2007**, *9*, 4753. Treatment of **3a** and benzaldehyde with substoichiometric amounts of $BF_3{\cdot}OEt_2$ (0.5 equiv) in CH_2Cl_2 or THF at −78 °C also produced **4a** as a 1:1 mixture of *E*:*Z* alkene stereoisomers. No conditions were found that produced the *E*-isomer predominantly or exclusively..
11. For the preparation of epoxide **2l**, see: Djigoue, G. B.; Kenmogne, L. C.; Roy, J.; Poirer, D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6360.
12. Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.
13. For the preparation of oxetane **2b** see: Fitton, A. O.; Hill, J.; Jane, D. E.; Millar, R. *Synthesis* **1988**, *12*, 1140.
14. (a) Inanagana, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1989**, *1979*, 52; (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367; (c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7.
15. For theoretical work on the torquoselective **4e**-electrocyclic ring opening of cyclobutenes, see: (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989; (b) Kallel, E. A.; Wang, Y.; Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 6759; (c) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471; (d) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072.
16. For studies on *E*/*Z* selectivity of the reactions of ynolates with carbonyl compounds, see: (a) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840; (b) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912; (c) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945.
17. Whereas *E*-acrylic amides are selectively formed in $BF_3{\cdot}OEt_2$-mediated (0.5 equiv) reactions of ynamides and aldehydes at −78 °C, mixtures of *E*- and *Z*-alkene isomers are obtained when the analogous reaction is performed at 0 °C with unsymmetrical and sterically differentiated ketones: You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, 1656.

Please cite this article in press as: Ng, K.; et al. *Tetrahedron Lett.* (2015), http://dx.doi.org/10.1016/j.tetlet.2015.12.041