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A New Strategy for Efficient Synthesis of Medium and Large Ring Lactones without High Dilution or Slow Addition

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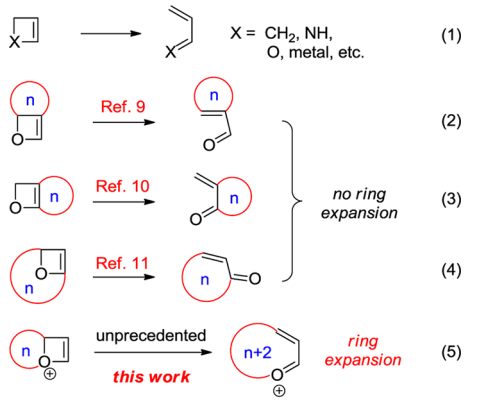
Supporting Information

ABSTRACT: We have developed an efficient method for medium and large ring lactone synthesis by a conceptually different ring-expansion strategy. The design of an unprecedented ring conjunction mode of oxetene, combined with the appropriate choice of a Lewis acid promoter and an additive, constitutes the key components of the new process. Enabled by this new approach, the reaction does not require high dilution or slow addition.

Medium and large ring lactones are widespread subunits in biologically active natural products and therapeutic agents.[1] The development of efficient strategies for their assembly has been a longstanding topic in organic synthesis. Although significant progress has been achieved in the past few decades, there remains a great need for new strategies. In particular, the efficient synthesis of medium ring lactones remains challenging due to unfavorable entropic and/or enthalpic factors in the ring-closing approaches, such as lactonization and ring-closing metathesis.[1−5] Current strategies to tune these largely inherent unfavorable kinetic and thermodynamic parameters are limited. For example, high dilution and/or slow addition have been constantly employed to minimize the competitive undesired dimerization process, but the effects are somewhat limited and unpredictable in terms of substrate generality and yield enhancement, let alone the consequent limitations in large-scale synthesis. Moreover, the majority of these processes are intramolecular, because an intermolecular approach would invoke additional complications to this already challenging task.

Recently, we have reported an 8-membered lactone synthesis enabled by the design of a class of new (1,6)-amphoteric molecules.[6] However, the process suffers from moderate efficiency and a limited scope. The use of an alkyl linker in place of the aryl linker between the oxetane and aldehyde moieties in the amphoteric molecules results in no desired lactone formation. The requirement of an aryl linker can be explained by the relief of the decreased product transannular interaction and the unfavorable entropy change as a result of the restricted substrate flexibility. In continuation of our efforts, here we describe a new intermolecular process for medium and large ring lactone synthesis with significantly improved efficiency and expanded scope by a conceptually different ring expansion strategy that obviates high dilution or slow addition.

Cyclobutenes and heterocyclobutenes are versatile species in organic synthesis. Their aptitude to undergo electrocyclic ring-opening to form (hetero)butadienes has led to the development of numerous useful processes (eq 1).[7] Among them, oxetenes



have received significant attention presumably because of their easy conversion to synthetically versatile α,β-unsaturated carbonyl compounds (e.g., alkyne-carbonyl metathesis).[8−11] Fusion of an oxetene unit with another ring provides access to various cyclic unsaturated carbonyl compounds. However, to the best of our knowledge, currently known oxetene-containing ring fusion topologies are limited to three types, i.e., fusion at the neighboring or diagonal carbon atoms, none of which lead to ring expansion (eqs 2−4).[9−11] We envisioned that the fusion of a ring unit only at the C(sp^3) and oxygen atoms could result in simultaneous ring expansion while oxetene ring-opening (eq 5). However, the design and realization of such ring expansion reactions are unprecedented.

We anticipated that the high reactivity of the oxetenium species in eq 5 would overcome the conventional unfavorable kinetic and/or thermodynamic factors typically impeding medium and large ring formation by ring-closing approach. However, the extremely unstable nature of this species also invokes a significant challenge for its formation. As shown in Scheme 1, inspired by a disconnection (path a) orthogonal to the oxetene ring-opening (path b), we hypothesized that the oxetenium species **C** can be formed via [2+2] cycloaddition

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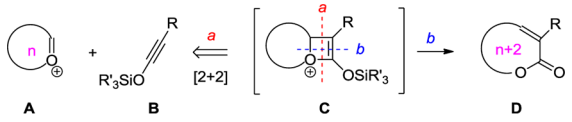
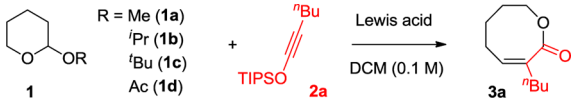
Scheme 1. Design of the Ring-Expansion Strategy



from a cyclic oxocarbenium (e.g., **A**) and an alkyne (e.g., **B**). We reasoned that the use of electron-rich siloxy alkynes[12] can facilitate the formation of the highly reactive intermediate **C**. Subsequent ring-opening and desilylation are expected to form **D**, thereby representing a new lactone formation process.

Initially, we targeted the most challenging 8-membered lactone formation, so we chose acetal **1a** as the 6-membered ring oxocarbenium precursor (Table 1). In the presence of a

Table 1. Condition Optimization



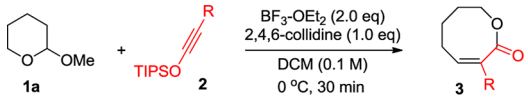
entry	1	reaction conditions	additive	yield[a]
1	**1a**	$TiCl_4$ (1.0 eq), -78 °C, 10 min	–	<5%[c]
2	**1a**	TMSOTf (1.0 eq), -78 °C, 30 min	–	<5%[c]
3	**1a**	$SnCl_4$ (1.0 eq), -78 °C, 10 min	–	<5%[c]
4	**1a**	$Sc(OTf)_3$ (5 mol%), rt, 12 h	–	<5%[c]
5	**1a**	$AgNTf_2$ (5 mol%), rt, 12 h	–	<5%[c]
6	**1a**	$Au(PPh_3)NTf_2$ (5 mol%), rt, 12 h	–	<5%[c]
7	**1a**	Et_2AlCl (1.0 eq), -78 ~ 0 °C, 7.5 h	–	16%[c]
8	**1a**	BF_3-OEt_2 (1.0 eq), 0 °C, 30 min	–	42%[b]
9	**1b**	BF_3-OEt_2 (1.0 eq), 0 °C, 35 min	–	7%[c]
10	**1c**	BF_3-OEt_2 (1.0 eq), 0 °C, 3.5 h	–	10%[c]
11	**1d**	BF_3-OEt_2 (1.0 eq), 0 °C, 45 min	–	64%[b]
12	**1a**	BF_3-OEt_2 (1.0 eq), 0 °C, 30 min	**4a** (0.5 eq)[e]	70%[b]
13	**1a**	BF_3-OEt_2 (1.0 eq), 0 °C, 30 min	**4a** (1.0 eq)[e]	<5%[d]
14	**1a**	BF_3-OEt_2 (2.0 eq), 0 °C, 30 min	**4a** (1.0 eq)[e]	91%[b]
15	**1c**	BF_3-OEt_2 (2.0 eq), 0 °C, 30 min	**4a** (1.0 eq)[e]	86%[b]
16	**1a**	BF_3-OEt_2 (2.0 eq), 0 °C or rt, 12 h	**4b** (1.0 eq)[e]	<5%[d]
17	**1a**	BF_3-OEt_2 (2.0 eq), 0 °C, 30 min	**4c** (1.0 eq)[e]	48%
18	**1a**	$HNTf_2$ (20 mol%), rt, 12 h	–	<5%[c]

[a]NMR yield with CH_2Br_2 as an internal standard. [b]Isolated yield. [c]The mass balance is a complex mixture. [d]The alkyne was recovered. [e]2,4,6-Collidine (**4a**), pyridine (**4b**), 2,6-di-*tert*-butylpyridine (**4c**).

range of typical Lewis acids (entries 1−6), such as $Sc(OTf)_3$, $TiCl_4$, $AgNTf_2$, and $Au(PPh_3)NTf_2$, the reaction of **1a** and siloxy alkyne **2a** in DCM (0.1 M) gave a mixture of unidentifiable products with essentially no desired lactone formation. Further survey revealed that Et_2AlCl and BF_3−OEt_2 could promote the desired process, albeit in low yields (16% and 42%). We next evaluated the effect of the acetal leaving group (entries 9−11). Bulky alkoxyl groups, such as O^{i}Pr and O^{t}Bu, significantly reduced the reaction efficiency, but the acetate group could slightly improve the yield (64%, entry 11). After considerable efforts, we found that the addition of a substoichiometric amount of 2,4,6-collidine (**4a**) improved the yield (entry 12). However, the use of equimolar **4a** completely shut down the reaction (entry 13). Further tuning indicate that the use of 2 equiv of BF_3−OEt_3 and 1 equiv of 2,4,6-collidine led to the highest efficiency (91% yield, entry 14). Acetal **1d** was equally efficient (entry 15). Other additives, such as pyridine (**4b**) and 2,6-di-*tert*-butylpyridine (**4c**), gave inferior results, indicating that the steric bulk of the additive is crucial (vide infra). Notably, the Brønsted acid $HNTf_2$ could not promote the present ring expansion reaction (entry 18).[6]

With the established standard conditions, we examined the reaction scope. A range of siloxy alkynes with different substituents reacted smoothly with acetal **1a** to afford the corresponding 8-membered lactones with high efficiency and stereoselectivity (only *Z* isomer, Table 2). Bulky substituents on

Table 2. Alkyne Scope



entry	R	product	yield[a]
1	*n*-Bu (**2a**)	**3a**	91%
2	*n*-Oct (**2b**)	**3b**	85%
3	$Ph(CH_2)_3$ (**2c**)	**3c**	77%
4	 (**2d**)	**3d**	89%
5	*t*-Bu (**2e**)	**3e**	84%
6	Ph (**2f**)	**3f**	64%
7	*n*-Oct  (**2g**)	**3g**	58%
8	$TIPSO(CH_2)_3$ (**2h**)	**3h**	62%

[a]Isolated yield, Z/E > 20:1.

the alkynes did not affect the reaction efficiency (entries 4 and 5). Arene- or alkene-conjugated alkynes were also suitable reaction partners (entries 6 and 7). While it is highly desirable to form lactone **3** without the α-substituent (R = H), the corresponding terminal siloxy alkyne was not successfully prepared in pure form.

The reaction also exhibits an excellent acetal scope (Table 3). Under our standard conditions, a range of 8-membered lactones could be obtained efficiently from the corresponding acetals with various substituents at different positions of the ring skeleton (entries 1−10). Fusion with an arene did not result in lower efficiency (entries 8 and 9). It is noteworthy that ketal **1n**, which bears a hindered reactive center, could smoothly afford the tetrasubstituted alkene **3r** as a single *Z* isomer (entry 10). The mild conditions are compatible with a diverse set of functional groups, such as silyl-protected alcohols, esters, azides, alkenes, and alkynes. In addition, our protocol can also be applied to the synthesis of lactones with other ring sizes (entries 11−17). For example, starting from the 5-, 7-, 8-, and 16-memberd ring acetals, the expected 7-, 9-, 10-, and 18-membered lactones were all formed in good to excellent yields. The existing stereocenters in acetal **1r** were not affected (entry 14). While the 7- to 9-membered unsaturated lactones were uniformly obtained as a single *Z*-alkene, the 10-membered lactone **3x** was obtained as a 1:1 mixture of Z/E isomers. However, only *E* isomer was observed for the large ring lactone **3y**. We believe that the configuration is determined by torquoselectivity during the oxetenium ring-opening, which can be affected by product ring size.[13] Unfortunately, highly oxygenated sugar-derived acetal **1w** is not reactive under our standard conditions (entry 18).

To further demonstrate the utility of our lactone formation reaction, we carried out iterative ring expansions (Scheme 2). Under the standard conditions, acetal **1v** was successfully expanded to form 7-membered lactone **3s** in 93% yield. After hydrogenation and reductive acylation, lactone **3s** was easily converted to acetal **5**, which was subjected to a second ring expansion with alkyne **2h** to form 9-membered lactone **6**. Thus, our protocol is in principle capable of assembling medium and large lactones of all sizes starting from a small ring acetal.

To probe the mechanism of the efficient ring expansion process, we carried out several control experiments. We reasoned

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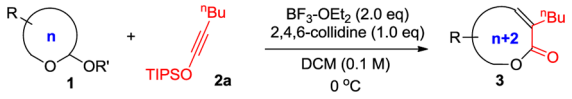
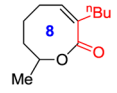
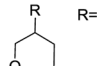
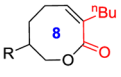
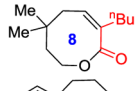
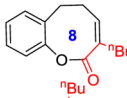
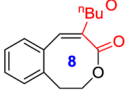
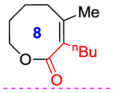
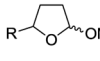
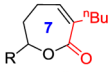
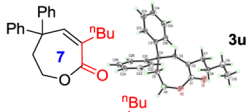
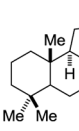
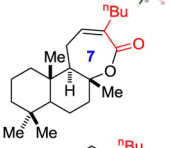
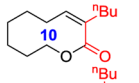
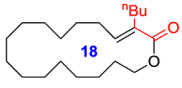
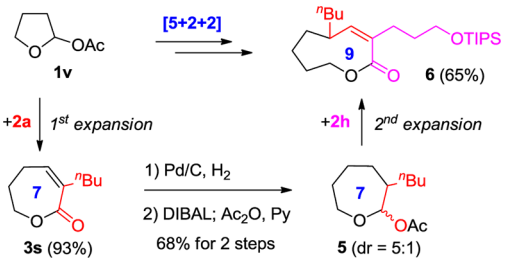
Table 3. Synthesis of Medium and Large Ring Lactones



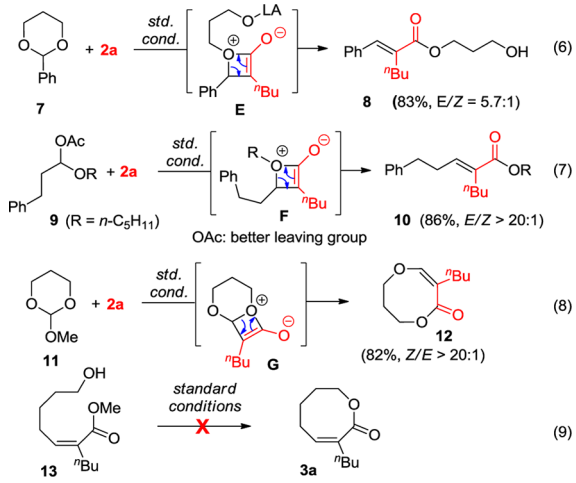
entry	acetal	1	product	3	yield[a]
1		1e		3i	83%
2[b]		R= OTBS (1f)		3j	75%
3[b]		OBz (1g)		3k	56%
4[b]		N_3 (1h)		3l	52%
5[b]		$OCH_2CH{=}CH_2$ (1i)		3m	65%
6[b]		$OCH_2C{\equiv}CH$ (1j)		3n	63%
7		1k		3o	92%
8[b]		1l		3p	72%
9		1m		3q	91%
10		1n		3r	77%
11		R= H (1o)		3s	93%
12		R= Ph (1p)		3t	70%
13[b]		1q		3u	75%
14		1r		3v	70%
15		1s (m =1)		3w	86%
16[c]	1t (m = 2)			3x	88%
17[d]	1u (m = 10)			3y	87%
18[e]		1w	–	–[e]	

[a]Isolated yield, Z/E > 20:1. [b]Run at room temperature. [c]Z/E = 1:1. [d]E/Z > 20:1. [e]No desired lactone formation; **1w** was recovered.

Scheme 2. Iterative Ring Expansions



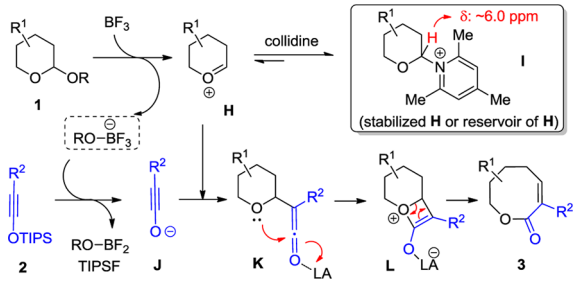
that cyclic acetal **7** and acyclic mixed acetal **9** would give linear ester products if the reactions proceed via the hypothesized oxetenium intermediates **E** and **F**, respectively (eqs 6 and 7). Indeed, the expected acyclic esters **8** and **10** were obtained in



good yield under our standard conditions. In contrast, from cyclic orthoester **11**, we anticipated the formation of a lactone product if the OMe could serve as the leaving group and thus the ring-fused oxetenium **G** could be formed (eq 8). As expected, the desired lactone **12** was obtained in 82% yield. Finally, subjecting linear unsaturated ester **13** to our standard conditions did not lead to the formation of lactone **3a** (eq 9), which ruled out the possible mechanism involving an initial acetal olefination followed by lactonization.

On the basis of the above observations, we have proposed a plausible mechanism (Scheme 3). The reaction begins with the

Scheme 3. Proposed Mechanism



BF_3-promoted formation of oxocarbenium **H** from acetal **1**. The resulting trifluoro(methoxy)borate next activates the siloxy alkyne to form ynolate **J**. The formation of TIPSF can be observed. Subsequent [2+2] cycloaddition between the two highly active species (**H** and **J**) forms oxetenium intermediate **L**, presumably by a stepwise mechanism via ketene **K**. Finally, electrocyclic ring-opening of **L** delivers the observed ring-expansion product **3**. While the exact role played by 2,4,6-collidine is still not clear, we propose that it can reversibly form the pyridinium **I** with the highly unstable oxocarbenium **H**. Thus, adduct **I** can be considered a reservoir of **H** to prevent its decomposition before reacting with ynolate **J**. We were able to observe a peak at δ ~6.0 ppm by in situ ^{1}HNMR, which is characteristic for this type of pyridinium species.[14] On the basis of the report by Fujioka and Kita, pyridine can also form a similar adduct, but this adduct is much less reactive than that from 2,4,6-collidine.[14] This result is consistent with our observation that the use of pyridine as additive resulted in no desired lactone formation (Table 1, entry 16). We believe that the superiority of 2,4,6-collidine is attributed to the excellent stabilization of the

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oxocarbenium intermediate while still maintaining sufficient reactivity for the subsequent lactone formation process.

In summary, by a conceptually different strategy, we have developed a highly efficient and general method for medium and large ring lactone synthesis. The design of an unprecedented ring conjunction mode of oxetene, combined with the appropriate choice of a Lewis acid promoter and an additive, constitutes the key components of the new process. Owing to this unusual ring expansion strategy, our lactone formation reaction, overcoming the unfavorable entropic and/or enthalpic factors typically encountered by ring-closing approaches, does not require high dilution or slow addition for high efficiency. The method also represents one of the few intermolecular reactions for medium and large lactone synthesis, thereby contributing to convergent synthesis. Moreover, the mild reaction conditions are compatible with a wide range of functional groups. An example of iterative ring expansions was also provided to demonstrate the great utility of our process. This efficient process, employing readily available substrates and reagents, is anticipated to find applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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