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β-Iodoallenolates as Springboards for Annulation Reactions

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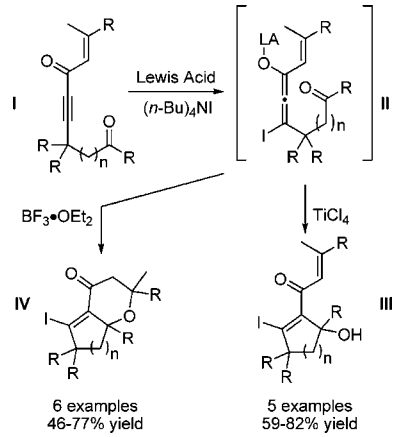
ABSTRACT



β-Iodoallenolates II, generated from alkynones I with tetra-*n*-butylammonium iodide and a Lewis acid, underwent selective single or double annulation, depending on the Lewis acid promoter. Treatment with $TiCl_4$ gave cyclohexenyl alcohols III, whereas $BF_3{\cdot}OEt_2$ gave oxadecalins IV. The scope and limitations of the two annulation reactions are described.

Platelet activating factor (1-*O*-alkyl-2(*R*)-(acetylglyceryl)-3-phosphorylcholine) is a small molecule messenger implicated in a number of inflammatory, respiratory, and cardiovascular diseases.[1] Phomactin A and phomactin D are potent antagonists of PAF: phomactin A inhibits platelet aggregation induced by PAF (IC_{50} 1.0×10^{-5} M) and binding of PAF to its receptors (IC_{50} 2.3×10^{-6} M), and phomactin D was found to be roughly twice as potent in these two assays.[2] These findings inspired us to pursue a synthetic strategy targeting the carbon skeleton of both phomactin A and D via common β-iodoallenoate intermediate A (Scheme 1).

β-Iodoallenolate intermediates generated from alkynyl esters and ketones participate in intermolecular addition reactions with aldehydes,[3] imines,[4] and epoxides[5] with high selectivity for the (*Z*)-iodoalkenone. Asymmetric addition of β-iodoallenolates to aldehydes has been reported using CBS catalysts.[6] Furthermore, tandem iodide-promoted conjugate addition/aldol cyclization has recently been used to generate highly functionalized cyclic systems.[7] Two different cycliza-

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(4) Timmons, C.; Kattuboina, A.; Banerjee, S.; Li, G. G. *Tetrahedron* **2006**, *62*, 7151–7154.

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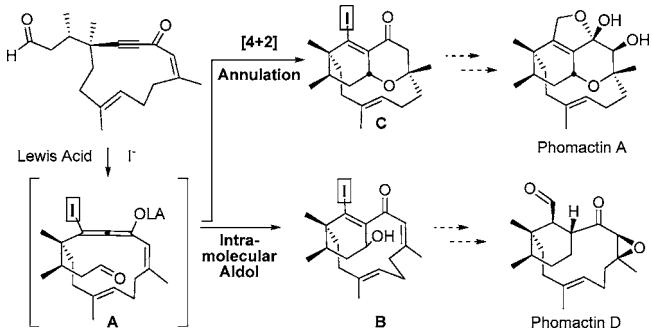
Scheme 1. β-Iodoallenolate-Mediated Cyclizations: Application to the Synthesis of Phomactins A and D

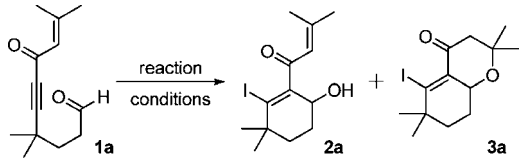


tion processes are reported here: the first is the intramolecular aldol reaction of β-iodoallenolate intermediates to generate cyclic β-iodoalkenones of type **B**, and the second is the intramolecular aldol reaction followed by conjugate addition of the hydroxyl group in a formal [4 + 2] annulation to give oxadecalins of type **C** (Scheme 1). To our knowledge, these are the first examples of cyclizations involving β-iodoallenolate intermediates.[8]

Alkynone **1a** was subjected to Lewis acidic conditions in the presence of iodide sources (Table 1). The optimal conditions for obtaining cyclohexenyl alcohol **2a** was found to be the combination of $TiCl_4$ and $(n\text{-Bu})_4NI$ (TBAI; entry 4), while$BF_3{\cdot}OEt_2$ and TBAI was found to be optimal for the formation of oxadecalin **3a** (entry 6). Experiments with $CeCl_3$ as Lewis acid[9] or sodium iodide as the iodide source were also performed, but only partial consumption of alkynone **1a** was observed (entries 1, 2, and 5). A stoichiometric amount of $BF_3{\cdot}OEt_2$ was required for the complete conversion of alkynone **1a** to oxadecalin **3a**: catalytic amounts of $BF_3{\cdot}OEt_2$ resulted in only partial consumption of alkynone **1a** (entry 7). The cyclization was successful with both TBAI and $(n\text{-Bu})_4NBr$ (TBAB), which gave the bromooxadecalin (entry 8).[10] The optimal reaction temperature for the conversion of alkynone **1a** to cyclohexenyl alcohol **2a** and oxadecalin **3a** was found to be −78 to 0 °C and −40 to 0 °C, respectively.

To explore the scope and limitations of the reaction, experiments aimed at selective mono- and bicyclization of a series of alkynones were performed (Tables 2 and 3). As shown in Table 2, the *gem*-dimethyl functionality (entry 2) was not required for monocyclization, but it did accelerate the cyclization. In addition, other ring sizes, such as 5- and 7-membered rings (entries 3 and 4), could be formed in moderate yield, and finally, tertiary alcohols (entry 6) could be formed in good yield, although a stronger Lewis acid was required.

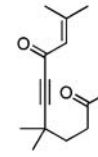
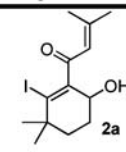
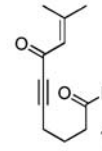
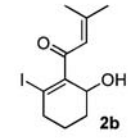
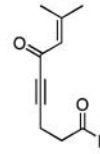
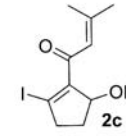
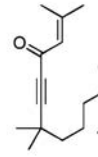
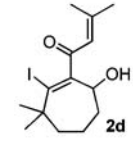
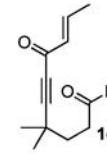
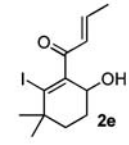
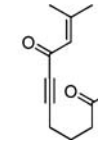
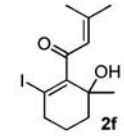
Table 1. Lewis Acid/Iodide Source Screen for Iodocyclization[a]



entry	conditions	T (°C)	ratio (**2a**:**3a**)	% conversion[e]
1	$BF_3{\cdot}OEt_2$/NaI	−40 to 0	1:1.7	~50
2	$TiCl_4$/NaI[b]	−78 to 0	6:1	~50
3	$TiCl_4$/TBAI[b]	−78 to 0	5:1	100
4	$TiCl_4$/TBAI	−78 to 0	>20:1	100
5	$CeCl_3$/NaI[c]	rt	>20:1	~50
6	$BF_3{\cdot}OEt_2$/TBAI	−40 to 0	<1:20	100
7	$BF_3{\cdot}OEt_2$/TBAI[d]	−40 to 0	2:1	~40
8	$BF_3{\cdot}OEt_2$/TBAB	−40 to rt	<1:20	100

[a] Reaction conditions: alkynone (1.0 equiv), Lewis acid (1.3 equiv), halide source (1.3 equiv), CH_2Cl_2 at the temperature indicated. [b] Run with 1.2 equiv of $TiCl_4$ and 1.1 equiv of iodide source. [c] Run with 1.2 equiv of $CeCl_3$ and 1.1 equiv of NaI in acetonitrile. [d] Run with 0.5 equiv of $BF_3{\cdot}OEt_2$. [e] Determined by ^1H NMR analysis of the crude reaction mixure.

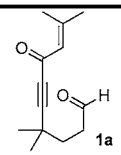
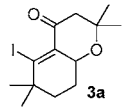
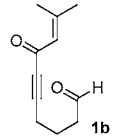
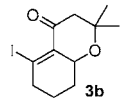
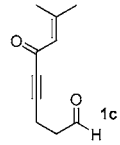
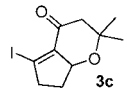
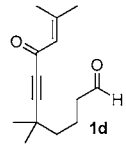
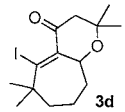
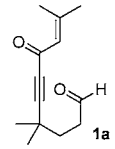
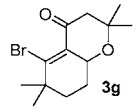
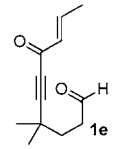
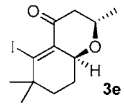
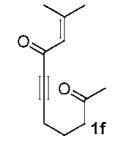
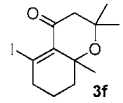
Table 2. Intramolecular β-Iodoallenolate Aldol Cyclization[a]

entry	substrate	conditions	product	% yield
1	 **1a**	$TiCl_4$, −78 °C to 0 °C, 2 h	 **2a**	82
2	 **1b**	$TiCl_4$, −78 °C to rt, 2 h	 **2b**	66
3	 **1c**	$TiCl_4$, −78 °C, 6.5 h	 **2c**	65
4	 **1d**	$TiCl_4$, −78 °C to rt, 5 h	 **2d**	59
5	 **1e**	$TiCl_4$, −78 °C to 0 °C, 2 h[b]	 **2e**	68
6	 **1f**	$AlCl_3$, −78 °C, 9 h[c]	 **2f**	75

[a] Reaction conditions: alkynone (1.0 equiv), $TiCl_4$ (1.3 equiv), TBAI (1.3 equiv), CH_2Cl_2, at the time and temperature indicated. [b] Run with 1.0 equiv of TBAI. [c] Run with 6.5 equiv of $AlCl_3$.

The results of the bicyclization experiments are summarized in Table 3. As observed with the monocyclization, the *gem*-dimethyl functionality was not required (entry 2).

Table 3. Bicyclization via Stepwise [4 + 2] Annulation[a]

entry	substrate	conditions	product	% yield
1	 1a	−40 °C to 0 °C, 3 h	 3a	77
2	 1b	−40 °C to rt, 3 h	 3b	75
3	 1c	−40 °C to rt, 4.5 h	 3c	58
4	 1d	–[b]	 3d	–[c]
5	 1a	−40 °C to rt, 7 h[d]	 3g	46
6	 1e	−40 °C to rt, 39 h	 3e	60
7	 1f	–[b]	 3f	–[c]

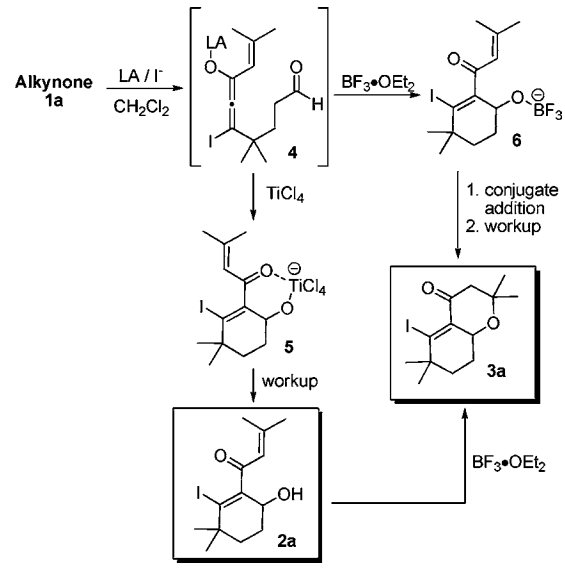
[a] Reaction conditions: alkynone (1.0 equiv), BF_3•OEt_2 (1.3 equiv), TBAI (1.3 equiv), CH_2Cl_2, at the time and temperature indicated. [b] See text. [c] Monocyclization products only. [d] TBAB was used instead of TBAI.

Cyclization to give the [5,6] bicycle was successful (entry 3); but formation of the [7,6] system did not occur (entry 4), even with excess Lewis acid, stronger Lewis acids, longer reaction times, and higher temperatures. The use of TBAB resulted in the formation of bromooxadecalin **3g** (entry 5) but required both a higher temperature and a longer reaction time than the TBAI cyclization (entry 1).

The use of a disubstituted olefin demonstrated that the cyclization was diastereoselective (entry 6). The relative stereochemistry of oxadecalin **3e** was confirmed by NOE experiments.[11] Ketone **1f**, however, did not cyclize to give the corresponding oxadecalin (entry 7). The intramolecular aldol reaction gave **2f**, but the second cyclization did not occur, presumably because the tertiary hydroxyl group is too sterically hindered to undergo cyclization. Extended reaction times and higher temperatures resulted in elimination of the tertiary alcohol. When intermediate alcohol **2f** was subjected to basic conditions, formation of the original ketone **1f** was observed.

The proposed mechanistic pathway for the two cyclization processes is shown in Scheme 2. Activation of the alkynone carbonyl group by the Lewis acid followed by addition of the iodide to the alkyne in a conjugate fashion gives β-iodoallenolate **4**. This intermediate then undergoes an intramolecular aldol reaction to give cyclohexenyl alcohol **5**, stabilized as its titanium chelate. Protonation of cyclohexenyl alcohol **5** upon workup would then generate cyclohexenyl alcohol **2a**.

Scheme 2. Proposed Mechanistic Pathway



Subjection of cyclohexenyl alcohol **2a** to BF_3•OEt_2 produced oxadecalin **3a**, indication of a stepwise [4 + 2] cyclization process. In contrast to the first step of the

(7) (a) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111–3114. (b) Douelle, F.; Capes, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 1931–1934. (c) Koseki, Y.; Fujino, K.; Takeshita, A.; Sato, H.; Nagasaka, T. *Tetrahedron: Asymmetry* **2007**, *18*, 1533–1539.

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(9) For the use of $CeCl_3$ as a Lewis acid to generate β-iodoallenolate intermediates, see: (a) Yadav, J. S.; Reddy, B. V. S.; Gupta, M. K.; Eeshwaraiah, B. *Synthesis* **2005**, 57–60. (b) Fujisawa, T.; Tanaka, A.; Ukaji, Y. *Chem. Lett.* **1989**, *7*, 1255–1256.

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cyclization sequence (β-iodoallenolate aldol reaction), which required stoichiometric amounts of Lewis acid (Table 1, entries 4 and 6), the second step of the bicyclization (conjugate addition) was effective using as little as 30 mol % $BF_3{\cdot}OEt_2$.

The different reactivity and selectivity observed with the two Lewis acids studied can be attributed to differences in their coordination properties. The selectivity is likely due to the fact that $TiCl_4$, unlike $BF_3{\cdot}Et_2O$, can engage in bidentate chelation.[12] Thus, the $TiCl_4$-promoted intramolecular aldol reaction is expected to proceed through intermediate **5**, and the rigid geometry of the Ti(IV) chelate is likely to disfavor formation of oxadecalin **3a** (Scheme 2). In contrast, $BF_3{\cdot}Et_2O$-induced cyclization would involve intermediate **6**, which is appropriately poised to undergo conjugate addition and generate oxadecalin **3a**.

In summary, we have demonstrated that β-iodoallenolate intermediates can participate in intramolecular aldol reactions, enabling conversion of alkynones into either monocyclic or bicyclic (oxadecalin) products containing β-iodoalkenone functionality. In most cases, selective formation of either product was possible, depending on the choice of Lewis acid. Application of this method to the synthesis of natural product targets is underway in the laboratory and will be reported in due course.

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Note Added after ASAP Publication. The structure of compound **2c** in Table 2, entry 3 was incorrect in the version published ASAP September 8, 2009; the correct version was published on the web September 24, 2009.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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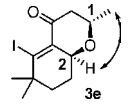
(11) The NOE spectrum (500 MHz, $CDCl_3$) showed a correlation between the methyl at C-1 and the proton at C-2, as shown. A correlation between the protons at C-1 and C-2 was not observed.



3e

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