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Observations in the synthesis of the core of the antitumor illudins via an enyne ring closing metathesis cascade

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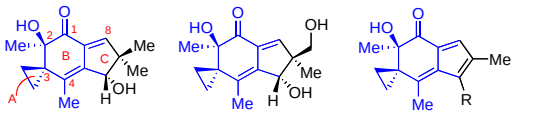
ABSTRACT

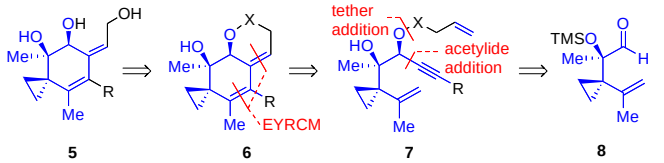
Observations concerning the synthesis of the core spirocyclic AB-ring system of illudins using an enyne ring closing metathesis (EYRCM) cascade are discussed. Substituent effects, in addition to optimization of the reaction conditions and the olefin tether for the key EYRCM reaction, are examined.

The illudins are a family of naturally occurring sesquiterpenes isolated from the poisonous mushroom, *Omphalotus illudens*.[1] Illudins M and S (**1** and **2**, respectively) are among the most cytotoxic members of this family of natural products. They inhibit DNA synthesis through a two-step sequence involving enzyme-assisted hydride/nucleophilic addition to the C8 enone followed by DNA alkylation through cyclopropyl-ring opening and B-ring aromatization.[2] Significantly, two semi-synthetic derivatives of illudin S (**2**), namely, acylfulvene (**3**) and irofulven (**4**), have shown very promising antitumor activity.[3] In particular, the hydroxymethyl derivative irofulven (**4**) has demonstrated efficacy in clinical trials for treatment of various cancers both as a monotherapy and in combination with other known chemotherapeutic agents.[4] In light of this promising therapeutic potential, these targets have received considerable interest from scientists, leading to several inventive syntheses.[5] We reported enantioselective syntheses of (−)-acylfulvene (**3**) and (−)-irofulven (**4**) employing a key enyne ring closing metathesis (EYRCM) cascade reaction.[6] Herein, we describe our observations in the context of related studies directed toward a general strategy for the synthesis of the functional spirocyclic pharmacophore common to all of these cytotoxic agents.



Our approach to the functional spirocyclic illudin core **5** relies on a tethered enyne ring closing metathesis cascade[7] to rapidly generate the cyclohexenyl B-ring (Scheme 1). An array of substrates **7**, poised for the key EYRCM, can be convergently assembled by the addition of a variety of acetylides to the key aldehyde **8**, followed by chemoselective addition of a suitable tethered olefin. Through this strategy, aldehyde **8** provides a platform for the rapid and convergent synthesis of a broad range of derivatives of the functional illudin core structure (Scheme 1).

In the context of these studies, we evaluated several olefin tethers for the key EYRCM using model substrates **9** in order to identify optimal tethers that were both stable to the EYRCM reaction conditions and were readily removable (Table 1). Both Grubbs' first- and second-generation metathesis catalysts (**G1**[8a] and **G2**[8b], respectively) were evaluated, with **G2** generally providing the desired product **10** with greater efficiency compared to **G1**. Under optimal EYRCM reaction conditions, neither the carbonate nor the carbamate tethers (Table 1, entries 1 and 2) provided the desired EYRCM product **10**. Instead, the carbonate tether fragmented to afford the corresponding propargylic alcohol,[9] and the Lewis basic carbamate likely reduced the activity of the **G2** metathesis catalyst through an unproductive coordination event. Interestingly, when the cyclohexyl (Cy) carbamate (Table 1, entry 3) was submitted to the EYRCM conditions, the product **10** was generated in 47% yield. We attribute this enhanced reactivity to the expected substrate preference to adopt the carbamate rotamer that positions the allyl substituent trans to the carbonyl. In this conformation



Scheme 1. Strategy to the functional illudin core **5**.

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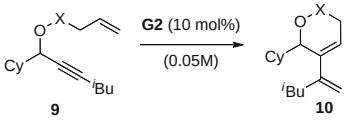
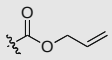
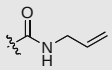
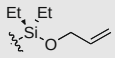
Table 1
Evaluation of olefin tethers for the EYRCM



Entry	Tether	Solvent	Temp (°C)	Time	Yield[a] (%)
1		PhH	65	1.5 h	0
2		PhMe	110	1.5 h	0
3		PhMe	110	1.5 h	47
4		PhH	80	6 h	15[b]
5		PhH	65	30 min	91
6		PhH	65	3 h	92

[a] Isolated yields.
[b] Isolated yield of free amide after TBS deprotection with TBAF.

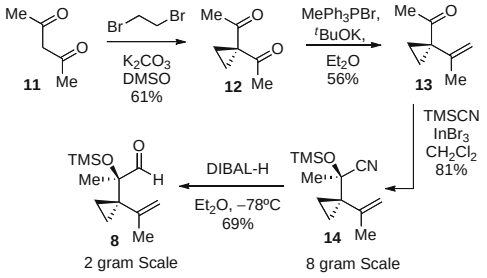
the olefin is oriented in close proximity to the alkyne and is poised for the ensuing EYRCM with minimal interference by the Lewis basic carbonyl. In light of this, we also prepared the *t*-butyldimethylsilyl allylamide (Table 1, entry 4), which would enable access to a more hydrolytically labile cyclic carbonate by treatment with tetra-*n*-butylammonium fluoride (TBAF). However, the tandem EYRCM–TBAF treatment provided the desired product in only 15% yield, due to the lability of the silylcarbamate under the EYRCM conditions.

None of the carbonate- or carbamate-based tethers proved superior to silicon-based olefin tethers[6] examined for this transformation. When the allylsilane tether, first reported by Grubbs and Yao,[10] was subjected to the EYRCM conditions, the desired product **10** was afforded in 91% yield (Table 1, entry 5) within 30 min. Furthermore, the allyloxysilane tether (Table 1, entry 6)[11] also provided the desired enyne metathesis product in 92% yield, albeit requiring a longer reaction time. Interestingly, in related systems we observed that the diethylallyoxysilane tether (Table 1, entry 6) was optimal as compared to the corresponding dimethyl and diisopropyl variants. The diethylallyloxysilane tether provided the best balance between stability and reactivity. The dimethylallyloxysilane tether was too labile under the EYRCM reaction conditions leading to premature desilylation, while the diisopropylallyloxysilane was both more difficult to prepare due to lower rate of etherification and gave the desired metathesis products in low yields.

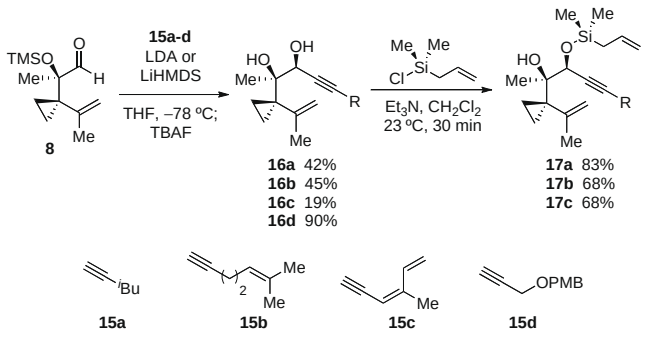
The two optimal silicon-based tethers for the key enyne metathesis (Table 1, entries 5 and 6) were utilized in the synthesis of the bicyclic core structure of the illudins. In addition to our previously described enantioselective synthesis of (+)-aldehyde **8**,[6] we also developed a simple, large-scale four-step synthesis of racemic aldehyde **8** from pentane-2,4-dione (**11**, Scheme 2) given the activity of both enantiomers of irofulven.[5g] Sequential double alkylation,[12] mono olefination, and $InBr_3$-catalyzed trimethylsilylcyanation[13] provided the versatile silyl cyanohydrin **14** in multi-gram quantities (Scheme 2). Reduction of the nitrile **14** with diisobutylaluminum hydride (DIBAL-H) readily provided the desired racemic aldehyde **8** in 69% yield on 2-gram scale. This facile synthesis allowed rapid access to multi-gram quantities of aldehyde **8** as the key precursor for the AB-ring system shared in illudins.[6]

Five readily available acetylides[14] **15a–d** were added to aldehyde **8** as the corresponding lithium acetylides to provide diols **16a–d** (Scheme 3).[6] The diastereoselectivity (ca. 6:1)[15] of these reactions was consistent with a Felkin-Ahn mode of addition. The allylsilane tether was introduced on substrates **16a–c** through selective silylation of the secondary hydroxyl group to afford the dienynes **17a–c** in 68–83% yields.

With the allylsilane substrates **17a–c** in hand, we examined their respective EYRCM reactions for accessing the functional bicyclic core common to the illudins (Table 2). These optimization studies were monitored directly by ^{1}H NMR analysis. Gratifyingly, when **17a** was submitted to the conditions established by the model substrate **9** (**G2**, 10 mol %, C_6D_6, 0.02 M, 65 °C, 1 h, entry 5, Table 1), the desired product **18a** was efficiently generated as the major product (Table 2, entry 1).[16] A plausible mechanism for the desired EYRCM pathway is shown in Scheme 4 (Path A). A minor amount (6%) of the uncyclized triene product **19a** was also observed as a result of an intermolecular cross-metathesis out competing the desired intramolecular ring closing metathesis at the C4–C5 olefin (Scheme 4, Path B). The formation of the intermolecular cross-metathesis product **19a** was greatly favored by increasing both the concentration from 0.02 M to 0.06 M and temperature from 65 °C to 80 °C in addition to reducing the catalyst loading to 5 mol % (Table 2, entry 2). Interestingly, 8% of the minor cyclopentenyl product **20a** was also observed under these conditions. It is plausible that the formation of this product corresponds to the

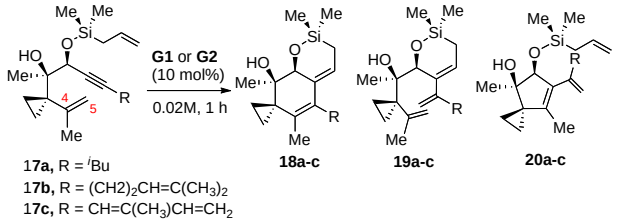


Scheme 2. Synthesis of the aldehyde **8**.



Scheme 3. Use of aldehyde **8** for synthesis of various dienynes.

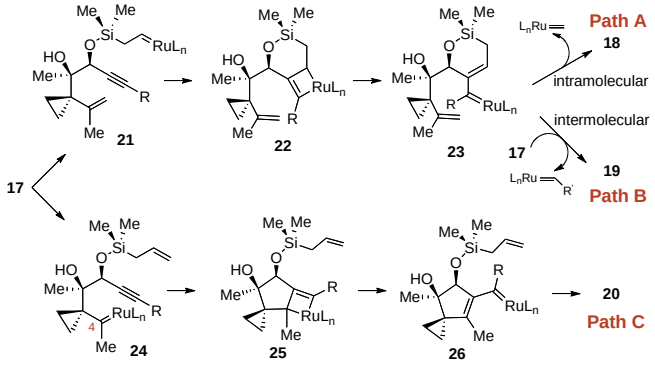
Table 2
The EYRCM with the allylsilane tether[a]



17a, R = ^{i}Bu
17b, R = $(CH2)_2CH=C(CH_3)_2$
17c, R = $CH=C(CH_3)CH=CH_2$

Entry	Substrate	Cat	Conditions	Results (%)				
				17	**16**	**18**	**19**	**20**
1	**17a**	**G2**	C_6D_6, 65 °C	—	—	94	6	—
2[b]	**17a**	**G2**	C_6D_6, 80 °C	—	—	—	92	8
3	**17b**	**G1**	C_6D_6, 65 °C	75	—	—	—	25
4	**17b**	**G1**	CD_2Cl_2, 40 °C	10	—	40	—	50
5	**17b**	**G2**	CD_2Cl_2, 40 °C	55	—	40	—	5
6	**17b**	**G2**	C_6D_6, 65 °C	10	—	90	—	—
7[c]	**17c**	**G2**	C_6D_6, 80 °C	46	54	—	—	—

[a] All experiments were conducted in NMR tubes under an atmosphere of argon, and product distribution was measured by direct integration of characteristic resonances for products. All experiments were stopped after 1 h unless otherwise noted.
[b] **G2** (5 mol %), 0.06 M concentration.
[c] Reaction time 32 h.



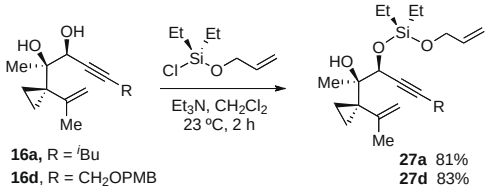
Scheme 4. Plausible mechanisms for the EYRCM reaction.

metathesis occurring first at the sterically congested C4–C5 gem-disubstituted olefin followed by enyne metathesis (Scheme 4, Path C).[17] The structure of cyclopentenyl product **20** was secured through X-ray analysis of a related derivative (vide infra).

We also explored the EYRCM reaction with substrate **17b** containing the trisubstituted olefin. Unexpectedly, when **17b** was submitted to **G1** in C_6D_6 at 65 °C (Table 2, entry 3), the five-membered ring substrate **20b** was the only observable product. By changing the solvent to CD_2Cl_2 and lowering the temperature to 40 °C, both the desired product **18b** and the undesired cyclopentene product **20b** were afforded in a 4:5 ratio (Table 2, entry 4). Significantly, the EYRCM conditions employing **G2** in C_6D_6 at 65 °C for 1 h generated the desired product **18b** exclusively (Table 2, entry 6). Interestingly, when the tetraenyne **17c** was exposed to the EYRCM reaction conditions (**G2**, 10 mol %, C_6D_6, 0.02 M, 80 °C, 32 h), none of the desired product **18c** was generated (Table 2, entry 7). Instead, over prolonged reaction times, desilylation occurred to generate **16c**, indicating that conjugation of the alkyne may significantly deactivate the substrate toward EYRCM.

Given the complications with oxidative desilylation of allylic silanes **18**,[6] we also explored the corresponding dialkylallyloxysilanes. Gratifyingly, the diethylallyloxysilane tethered substrates **27a** and **27d** were efficiently prepared through selective silylation of the secondary alcohol (Scheme 5).[18] ^{1}H NMR studies on the diethylallyloxysilyl substrate **27a** indicated that the EYRCM reaction to form the 7,6-bicycle **28a** (Table 3, entry 1) required higher reaction temperatures than those observed with the allylsilane tether (vide supra, entry 1, Table 2). The desired product **28a** was cleanly generated when subjected to the EYRCM reaction in toluene-d_8 at 110 °C (Table 3, entry 2). The heptacyclic silyloxy ring system **28** was very sensitive to isolation, hence we sought a tandem EYRCM-desilylation sequence. Using this method, we were able to directly isolate the corresponding triols **5a** and **5d** in 48% and 64% yields, respectively (Table 3, entries 3 and 4). Notably, the versatile product **5d** contains a *p*-methoxybenzyl (PMB) group poised for further elaboration toward the synthesis of various functional bicyclic illudin derivatives. Interestingly, when **27d** was subjected to this optimal EYRCM-TBAF condition we also isolated the diol **29d** in 17% yield (Table 3, entry 4). The formation of this product is consistent with the EYRCM pathway involving initial enyne metathesis at the C4–C5 olefin (vide supra, Scheme 4, Path C). The structure of **29d** was secured through X-ray crystallographic analysis of the corresponding bis-*p*-nitrobenzoate derivative.[19]

In summary, the subtle factors influencing the competing pathways in a critical EYRCM reaction were discussed. Our convergent approach to the bicyclic warhead of illudins involves the union of a readily accessible key aldehyde **8** with various lithium acetylides and optimal silicon-based olefin tethers to enable access to an array of dienynes **7**. A versatile EYRCM cascade reaction rapidly constructs the cyclohexenyl B-ring common to the illudins. Subtle changes in the EYRCM conditions greatly affect the outcome of the metathesis reaction, which can proceed through three different pathways to generate products **18**, **19**, and **20** (Scheme 4, Paths A–

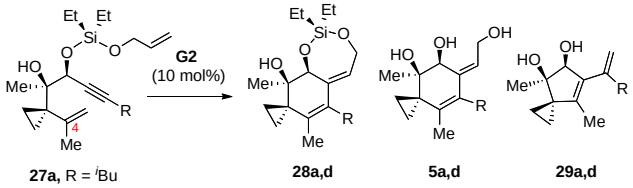


16a, R = ^{i}Bu
16d, R = CH_2OPMB

27a 81%
27d 83%

Scheme 5. Synthesis of the allyloxysilane tether substrates.

Table 3
The EYRCM with the allyloxysilane tether



27a, R = ^{i}Bu
27d, R = CH_2OPMB

Entry	Substrate	Conditions	Results (%)			
			27	28	5	29
1	**27a**	C_6D_6, 65 °C	33[a]	66[a]	—	—
2	**27a**	PhMe-d_8, 110 °C	—	99[a]	—	—
3	**27a**	PhMe, 110 °C, TBAF	—	—	48[b]	—
4	**27d**	PhMe, 110 °C, TBAF	—	—	64[b]	17[b]

[a] Experiments were conducted in NMR tubes under an atmosphere of argon and product distribution was measured by direct integration of characteristic resonances for products.
[b] Isolated yields.

C). This strategy provides ready access to the synthesis of various functionalized precursors to the core warheads of the illudin antitumor natural products. The evaluation of these fused bicycles in the synthesis of illudin derivatives and their respective biological evaluation will be reported in due course.

Acknowledgments

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15. For clarity only the major diastereomer is shown.
16. On larger scale, **18a** could be isolated in 76% yield using optimized EYRCM conditions.
17. It may also be plausible that the formation of product **20** occurs through initial complexation of the metathesis catalyst with the alkyne followed by EYRCM.
18. Diethylallyloxysilylchloride was prepared according to: Krolevets, A. A.; Antipova, V. V.; Popov, A. G.; Adamov, A. V. *Zh. Obsch. Khim.* **1988**, *58*, 2274.
19. The crystal structure of the corresponding bis-*p*-nitrobenzoate derivative of **29d** has been deposited at the Cambridge Crystallographic Data Center, please see: CCDC# 735275.