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.2i Significantly, two semi-synthetic derivatives of illudin S (2), namely acylfulvene (3) and irofulven (4), have shown very promising antitumor activity.3i 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.4i In light of this promising therapeutic potential, these targets have received considerable interest from scientists, leading to several inventive syntheses.5i We reported enantioselective syntheses of (−)-acylfulvene (3) and (−)-irofulven (4) employing a key enyne ring closing metathesis (EYRCM) cascade reaction.5i 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 vii 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 readily removable (Table 1). Both Grubbs’ first- and second-generation metathesis catalysts (G1viiiia and G2xb, 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 (entries 1 and 2, Table 1) provided the desired EYRCM product 10. Instead, the carbonate tether fragmented to afford the corresponding propargylic alcohol,ix 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 (entry 3, Table 1) 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 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-butylmethylsilyl allylamide (entry 4, Table 1), 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 tethersvi examined for this transformation. When the allylsilane tether, first reported by Grubbs and Yao,v was subjected to the EYRCM conditions, the desired product 10 was afforded in 91% yield (entry 5, Table 1) within 30 min. Furthermore, the allyloxysilane tether (entry 6, Table 1)vii also provided the desired enyne metathesis product in 92% yield, albeit requiring a longer reaction time. Interestingly, in related systems we observed that the diethylallyloxysilane tether (entry 6, Table 1) was optimal as compared to the corresponding dimethyl and disopropyl variants. The diethyallyloxysilane tether provided the best balance between stability and reactivity. The dimethylallyloxysilane tether was too labile under the EYRCM reactions conditions leading to premature desilylation, while the disopropallyloxysilane was both more difficult to prepare due to lower rate of etherification and also gave the desired metathesis products in low yields.

The two optimal silicon based tethers for the key enyne metathesis (entries 5 and 6, Table 1) were utilized in the synthesis of the bicyclic core structure of the illudins. In addition to our previously described enantioselective synthesis of (+)-aldehyde 8,vi 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.viii Sequential double alkylation,x mono olefination, and InBr3 catalyzed trimethylsilylcyanationxii 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 multigram quantities of aldehyde 8 as the key precursor for the AB-ring system shared in illudins.vi

Five readily available acetylidesxiv 15a–d were added to aldehyde 8 as the corresponding lithium acetylides to provide diols 16a–d (Scheme 3).vi The diastereoselectivity (ca. 6:1)xv 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 1H NMR analysis. Gratifyingly, when 17a was submitted to the conditions established by the model substrate 9 (G2, 10 mol%, C6D6, 0.02M, 65 °C, 1 h, entry 5, Table 1), the desired product 18a was efficiently generated as the major product (entry 1, Table 2).xvi 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 outcompeting 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 0.02M to 0.06M and temperature from 65 °C to 80 °C in addition to reducing the catalyst loading to 5 mol% (entry 2, Table 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 metathesis occurring first at the sterically congested C4–C5 gem-disubstituted olefin followed by enyne metathesis (Scheme 4, Path C).xvii The structure of cyclopentenyl product 20 was secured through X-ray analysis of the corresponding bis-enyne metathesis at the C4–C5 olefin (vide supra, Scheme 4, Path C).xvii

We also explored the EYRCM reaction with substrate 17b containing the trisubstituted olefin. Unexpectedly, when 17b was submitted to G1 in C6D6 at 65 °C (entry 3, Table 2), the five membered ring substrate 20b was the only observable product. By changing the solvent to CD2Cl2 and lowering the temperature to 40 °C, both the desired product 18b and the undesired cyclopentenyl product 20b were afforded in a 4:5 ratio (entry 4, Table 2). Significantly, the EYRCM conditions employing G2 in C6D6 at 65 °C for 1 h generated the desired product 18b exclusively (entry 6, Table 2). Interestingly, when the tetraenyne 17c was exposed to the EYRCM reaction conditions (G2 10 mol%, C6D6, 0.02M, 80 °C, 32 h), none of the desired product 18c was generated (entry 7, Table 2). Instead, over prolonged reaction times, desilylation occurred to generate 16c, indicating that conjugation of the alkyne may significantly deactivate the substrate towards EYRCM.

Given the complications with oxidative desilylation of allylic silanes 18,vi we also explored the corresponding dialkylallyloxysilanes as well. Gratifyingly, the diethylallyloxysilane tethered substrates 27a and 27d were efficiently prepared through selective silylation of the secondary alcohol (Scheme 5).xviii 1H NMR studies on the diethylallyloxysilyl substrate 27a indicated that the EYRCM reaction to form the 7,6-bicycle 28a (entry 1, Table 3) 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-d8 at 110 °C (entry 2, Table 3). 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 (entries 3 and 4, Table 3). 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 (entry 4, Table 3). 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. xix

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–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 illudin derivatives and their respective biological evaluation will be reported in due course.

Acknowledgments

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References


xv. For clarity only the major diastereomer is shown.

xvi. On larger scale, 18a could be isolated in 76% yield using optimized EYRCM conditions.

xvii. 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.


xix. 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.
Scheme 1.
Strategy to the functional illudin core 5.
Scheme 2.
Synthesis of the aldehyde 8.
Scheme 3.
Use of aldehyde 8 for synthesis of various dienynes.
Scheme 4.
Plausible mechanisms for the EYRCM reaction.
Scheme 5.
Synthesis of the allyloxysilane tether substrates.
Table 1

Evaluation of olefin tethers for the EYRCM.

![Chemical structure](image_url)

<table>
<thead>
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<td>PhMe</td>
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**Equation:**

$\text{Cy} \text{O} \text{X} \text{C} \equiv \text{C} \equiv \text{Bu} \rightarrow \text{Cy} \text{O} \text{X} \text{C} \equiv \text{C} \equiv \text{Bu}$

$G2 (10 \text{ mol\%}) \quad (0.05 \text{M})$

**Entry**

- **Entry 3:**
  - **Tether:** ![Tether Diagram](image)
  - **Solvent:** PhMe
  - **Temp (°C):** 110
  - **Time:** 1.5 h
  - **Yield (%):** 47%
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$^a$Isolated yields.

$^b$Isolated yield of free amide after TBS deprotection with TBAF.
The EYRCM with the allylsilane tether.$^a$

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$^a$ 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 hour unless otherwise noted.

$^b$ G2 (5 mol%), 0.06M concentration.

$^c$ Reaction time 32 h.
The EYRCM with the allyloxsilane tether.

Table 3

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<tr>
<td>4</td>
<td>27d</td>
<td>PhMe, 110 °C; TBAF</td>
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⁺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.