Published in final edited form as:

Tetrahedron Lett. 2015 June 24; 56(26): 4039–4042. doi:10.1016/j.tetlet.2015.05.014.

Synthesis of the C₁–C₁₇ fragment of the archazolids by complex *cis*-homodimer cross metathesis

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Abstract

A synthesis of the C₁–C₁₇ fragment of the archazolids is described featuring a complex cross-metathesis coupling reaction between a *cis*-homodimer (prepared by silyl-tethered ring-closing metathesis) and the *Z,Z*-terminal triene containing “eastern domain” of the archazolid natural products. This cross-metathesis was only successful when using the *cis*- as opposed to the monomer or *trans*-homodimer, with the *cis*-dimer added batchwise to minimize *cis/trans*-isomerization. The product was obtained in an optimized 78% yield using the Hoveyda-Grubbs catalyst at 50 °C in toluene.

Graphical Abstract

Keywords

cross metathesis; VATPase inhibitor; homodimerization; silyl-tethered ring closing metathesis; *cis*-homodimer

The archazolids are now an established and promising class of natural products displaying subnanogram activity against a number of human and mammalian cancer cell lines (Figure 1).¹ Biological investigations have shown the archazolids capable of preventing both tumor metastasis² and trastuzumab resistance in breast cancer cells.³ More recently, studies by Hamm et al. suggest that the archazolids might represent a new strategy for treating glioblastoma multiforme (GBM), the most common and aggressive lethal brain tumor.⁴

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Supplementary Material

Analytical data and experimental procedures for new compounds **5**, **7**, **9–11**.

The activity of the archazolids has been linked to selective inhibition of the vacuolar-type ATPase (VATPase).⁵ Through a combination of sophisticated biochemical experiments⁶ and theoretical investigations,⁷ much is known about the interaction of the archazolids with the V-ATPase responsible for their activity. For instance it has been shown that the archazolids bind to the VATPase *c* subunits of the membrane-embedded *V_O*-rotor, and the C7- and C15-OH groups form important interactions with the I134 and Y142 residues respectively within this region of the protein.⁷

Herein we report a synthesis of the pharmacophorically important C1–C17 region of the archazolids. The synthesis features the use of a silyl-tethered ring-closing metathesis (RCM) reaction to produce a *cis*-homodimer that was critical to the success of a subsequent complex cross-metathesis fragment coupling. To our knowledge, the use a complex *cis*-homodimer to enable a high-yielding CM coupling has not previously been demonstrated. Moreover this approach avoids previously described challenges associated with generating the archazolid macrocycle by RCM,⁸ and sets the stage for a novel completion of the synthesis.⁹

Previously we have described syntheses of both the “eastern” (**1**)¹⁰ and “western” (**2**)¹¹ domains of the archazolids, and more recently results from the union of these fragments and attempted macrocyclization by RCM (Figure 2).⁸ Unfortunately we discovered that compound **2** was susceptible to a back biting process, thwarting our initial attempts at preparing the archazolid macrocycle by this method.

As part of ongoing investigations into alternative synthetic strategies, we began exploring potential cross-metathesis (CM) reactions of compound **3** (Scheme 1). This was deemed attractive as the proposed CM reactions were expected to be highly *trans*-selective, potentially more *trans*-selective than our originally designed RCM,¹² and made use of large amounts of the already prepared advanced intermediate **3**.⁸ Additionally we had previously demonstrated a successful CM of this substituted *Z,Z*-terminal triene with *cis*-1,4-diacetoxy-2-butene.¹⁰ Our studies began by examining the CM reaction of **3** with crotonaldehyde, as it was envisioned that the resulting aldehyde **4** could be further advanced using aldol- or similar chemistry. Ultimately it was found that with catalyst **Ru-II**¹³ and an excess of crotonaldehyde (6 equiv) in toluene (PhMe) at 60 °C, compound **4** could be obtained, however as a mixture of *cis/trans* isomers. Additionally, it was not the CM reaction per se that was the source of this contamination, as both isomers exhibited *trans*-coupling constants for the newly generated alkene. Rather isomerization of one of the internal alkenes had occurred during the course of the reaction.¹⁴ Thinking that the Lewis-basic tricyclohexylphosphine ligand of **Ru-II** might be responsible for this isomerization, we also attempted the reaction with the phosphine free catalyst **Ru-HG**¹⁵ to no avail. Again **4** was obtained with significant contamination by the same *trans*-isomer. Attempts to purify **4** by flash chromatography on silica also revealed that this trienal was quite sensitive in general to decomposition.

We therefore set out to perform a CM reaction that would avoid formation of a similarly sensitive compound, and that might also result in a more convergent synthesis by coupling a more complex substrate. To that end, the preparation of **5** by CM of **3** with ester **6**¹⁶ was

investigated under various conditions using Grubbs' first generation catalyst (**Ru-I**), **Ru-II**, and **Ru-HG** (Table 1). Because **6** was deemed the less precious of the two compounds, it was initially used in excess. While those reactions with **Ru-I** gave little to no conversion, both **Ru-II** and **Ru-HG** in PhMe at 50 °C gave primarily unreacted **3** and *trans*-dimer **7** with no evidence of the desired product (entries 1–5). Even when ester **6** was used as the limiting reactant (0.5 equiv., entry 5), only **7**, **3**, and small amounts of the isomerization product **8**¹⁷ were obtained from these reactions.¹⁸ Attempts to suppress homodimerization and favor the CM reaction by protection of the alcohol as its TBS-ether (**TBS-6**) gave no reaction at 50 °C (entry 6).¹⁹ Increasing the temperature to 80 or 100 °C for these reactions resulted in decomposition of **3** (entries 7, 8). This terminal triene has in fact proven to be somewhat sensitive to decomposition, even upon storage at temperatures above –20 °C. We also attempted the CM reaction of **3** with preformed dimer **7** following the strategy first outlined by O'Leary and co-workers for avoiding undesired self-metathesis (entries 9, 10).²⁰ It is worth noting that the purposeful synthesis of **7** by CM dimerization of **6** was accompanied by significant formation of ketone **8** (~1:1 mixture, see Supplementary Material for details) that we were unable to suppress to any great extent through the use of additives like benzoquinone²¹ or phenol.²² Nonetheless sufficient quantities of **7** were obtained that could be used in attempted CM with **3**. However, under the conditions tried, only starting materials were obtained from these reactions.

Homodimerization remains a significant problem for many CM reactions.²³ Various strategies have emerged to adjust the reactivity profile of one or both alkenes in these reactions that might then allow for high yields to be achieved.²⁴ For instance, manipulations of allylic alcohol functionality, like that in **6**, have often been successfully used to fine-tune the reactivity of a neighboring alkene for subsequent CM reactions.²⁵ While we have not yet exhaustively examined this strategy (i.e. we only investigated the corresponding TBS ether **TBS-6**), there are some limitations and other considerations that might make this approach non-ideal. Namely, whichever group is appended to the alcohol must be compatible with the remaining steps of our total synthesis (hence our choice of a TBS group). Otherwise this group would then need to be removed post-CM and swapped with another which adds steps to the sequence.

As an alternative strategy for achieving a CM-based conversion of **3** to **5**, we were intrigued to investigate *cis*-homodimer **9** as a potential coupling partner (Scheme 3). It was thought that **9**, with its *cis*-configured double bond, would be more readily engaged by the metathesis catalyst leading to more type I (consumable homodimer) behavior compared to the observed presumably type II (sparingly consumable) reactivity of *trans*-**7**.²² The synthesis of **9** was achieved by first tethering two equivalents of **6** with dichlorodiphenylsilane giving compound **10** that could be isolated in 83% yield. Silyl-tethered RCM of **10** led to the selective formation of a *cis*-siloxane **11**.²⁶ Desilylation with TBAF then gave **9** in 74% yield for the two steps. Not only did this sequence allow for the production of a more metathesis reactive *cis*-homodimer **9**, it also avoided the isomerization issues and formation of ketone **8** that plagued our synthesis of *trans*-dimer **7** by direct CM of **6**.

For the first time, through the use of compound **9** we were able to obtain the desired CM adduct **5** (Table 2). The yield increased slightly with increasing equivalents of **9** (10% for 1 equiv. vs. 18% for 3 equiv., entries 1, 2) and similar yields were obtained in either dichloromethane (DCM) or PhMe (data not shown). We generally opted for PhMe to eliminate evaporation problems during long reaction times. Catalyst **Ru-HG** outperformed catalyst **Ru-II** in these reactions, and yields were essentially the same after 24 h using either 5 mol% or 10 mol% catalyst (compare entries 2 and 4). In all cases for those reactions contained in Table 2, compound **9** was completely consumed, converted to either CM product **5** or *trans*-dimer **7**. We also observed small amounts (~10% relative to **5**) of what has been tentatively assigned as a stereoisomer of compound **5**. Similar to the CM reactions with crotonaldehyde, this isomer was not the result of an unselective CM reaction, as evidenced by an analysis of coupling constants in their ¹H NMR spectrum. Based on certain chemical shift trends we observed for previously prepared *E*-alkene containing trienes,¹⁰ we have tentatively assigned the structure as ^{6,7}-*trans*-**5**. In an attempt to suppress what could have been an acid-promoted isomerization of the ^{6,7}-alkene, we investigated the use of catalyst **Ru-Py**²⁷ containing basic bromopyridine ligands (entry 5). However, this catalyst gave primarily starting materials and some *trans*-**7** under the conditions tried. We also attempted the reaction using catalyst **Ru-tol**²⁸ featuring a *bis-N*-toluene substituted NHC ligand and designed for reactions of more sterically demanding substrates. At room temperature (21 °C), none of the CM product **5** was obtained and compound **3** could be recovered (entry 6). Upon increasing the temperature to 45 °C (DCM) or 50 °C (PhMe), a complex mixture was obtained (entry 7). It is thought that this mixture arises from reactions occurring at one or more of the internal alkenes present in **3**, able to be engaged by this less sterically encumbered catalyst. The best results for this series of experiments came from using 3 equivalents of **9**, in PhMe at 50 °C, and 15 mol% catalyst **Ru-HG** (added in 3 batches over 72 h, 5 mol% every 24 h). This gave a 26% isolated yield of **5** along with 63% recovered **3**, or 89% yield based on recovered starting material (brsm) (entry 8).

While this yield is on par with other reported complex CM couplings,²⁹ we had some concerns about material throughput. Particularly since compound **9** is completely consumed by these reactions, converted to *trans*-dimer **7**, and our highest yields were obtained using a fairly large amount (3 equiv.) of this compound. Under these conditions, this non-productive *cis-trans* isomerization accounts for a significant proportion of metathesis events that are occurring, and with each turnover there is the possibility of catalyst decomposition.³⁰ We therefore examined the reaction with **9** added in small batches to minimize its effective concentration and thereby limit this background reaction (Scheme 3). Starting with only 0.2 equivalents of **9** along with compound **3** and catalyst **Ru-HG** (2.5 mol%) in C₆D₆ (used to allow direct analysis by NMR) at 50 °C, the reaction was allowed to proceed until all of **9** had been consumed (typically 6 h). At this point additional **9** (0.2 equiv) and catalyst (2.5 mol%) were added and the reaction progress monitored as before. Once this second lot of **9** was consumed the process was repeated once more (total = 0.6 equiv. **9** and 7.5 mol% catalyst). Using these conditions, CM product **5** could be isolated in 78% yield (based on moles of **9**) or 47% from compound **3**. In addition to the enhanced yield, this reaction also consumed significantly less amounts of **9**, such that we have been able to produce sufficient quantities of **5** with which to continue our synthetic studies on the archazolid.

While there are certainly some unique features of the system we were investigating that conspired to influence our opting to explore a *cis*-homodimer for our CM, this strategy may find utility for other target compounds. To recap, when attempting a complex CM coupling, we encountered a common problem of homodimerization. Within the constraints of our reaction conditions, the *trans*-homodimer obtained was unreactive toward further metathesis. By using the corresponding *cis*-homodimer either in excess (3 equiv.) or as the limiting reagent (3×0.2 equiv.), high yields were achieved (89% brsm and 78% respectively). It is planned to investigate the generality of this approach for overcoming problems associated with homodimerization in other complex CM couplings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support from the National Institutes of Health (R15GM101580) is gratefully acknowledged.

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Figure 1.
Structure of the archazolid natural products.

Figure 2.
Previously reported esterification of **2** with **1** and attempted macrocyclization by RCM.

Scheme 1.CM reaction of **3** with crotonaldehyde giving an unstable mixture of *E*:*Z* isomers.

Scheme 2.
Synthesis of *cis*-homodimer **9**.

Scheme 3. Optimized synthesis of **5** by batchwise addition of **9** and catalyst.

Table 1Results from attempted CM of **3** with **6**.

Entry	Catalyst (5 mol%)	Temp. ^a	CM substrate (equiv.)	Result
1.	Ru-I	50 °C	6 (3.0)	no reaction (3 + 6) ^b
2.	Ru-II	50 °C	6 (3.0)	3 + 7
3.	Ru-HG	50 °C	6 (3.0)	3 + 7
4.	Ru-HG	50 °C	6 (1.0)	3 + 7
5.	Ru-HG	50 °C	6 (0.5)	3 + 7
6.	Ru-HG	50 °C	TBS- 6 (3.0)	no reaction (3 + 6)
7.	Ru-HG	80 °C	6 or TBS- 6 (3.0)	complex mixture ^c
8.	Ru-HG	100 °C	6 or TBS- 6 (3.0)	complex mixture ^c
9.	Ru-HG	50 °C	7 (3.0)	3 + 7
10.	Ru-HG	80 °C	7 (3.0)	complex mixture

^a All reactions were performed in degassed PhMe for 15 h unless otherwise indicated.^b No reaction was also observed for longer reaction times of 24 and 48 h.^c Compound **3** had completely decomposed after 3 h with no evidence for formation of **5**.

Table 2Results for CM of **3** + **9**.

Entry	Catalyst (mol %)	9 (equiv.)	Result (% yield) ^a
1.	Ru-HG (5)	1.0	5 (10) + 3 (82) + 7
2.	Ru-HG (5)	3.0	5 (18) + 3 (64) + 7
3.	Ru-II (5)	3.0	5 (trace) + 3 (85) + 7
4.	Ru-HG (10)	3.0	5 (19) + 3 (62) + 7
5.	Ru-Py (5)	3.0	3 + 9 + 7
6.	Ru-tol (5)	3.0	3 + 9 + 7 ^b
7.	Ru-tol (5)	3.0	complex mixture ^c
8.	Ru-HG (15) ^d	3.0	5 (26) + 3 (63) + 7

^a Isolated yields.^b Reaction performed at room temperature (21 °C).^c Reaction performed at 50 °C.^d Added in 3 batches over 72 h; 5 mol% per 24 h.