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Tandem Enyne Metathesis–Metallotropic [1,3]-Shift for a Concise Total Syntheses of (+)-Asperpentyn, (-)-Harveynone, and (-)-Tricholomenyn A

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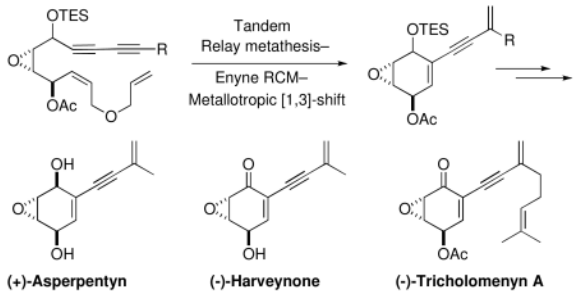
Abstract



A tandem reaction sequence involving relay metathesis-induced enyne RCM and metallotropic [1,3]-shift is an effective tool to construct cyclic alkenes with embedded 1,5-dien-3-yne moieties from acyclic precursors containing a 1,3-diyne. Total syntheses of (+)-asperpentyn, (-)-harveynone and (-)-tricholomenyn A have been accomplished by implementing this metathesis-based tandem reaction sequence as the key step.

Epoxyquinoids, a subclass of naturally occurring cyclohexane epoxides, display a broad range of structural variation and impressive biological activities, and thus have elicited significant synthetic and biological studies.[1] Among many naturally occurring epoxyquinoids, (+)-asperpentyn,[2] (-)-harveynone[3] and its prenylated homolog (-)-tricholomenyn A[4] have an embedded 1,5-dien-3-yne moiety (Scheme 1). Due to this structural characteristic, Ogasawara,[5] Johnson,[6] Taylor,[7] Maycock,[8] Negishi,[9] and Kitahara[10] utilized Pd-catalyzed Sonagashira or Stille coupling between the preformed 2-bromo- or iodocyclo-hexenone derivatives (bromoxone or its iodo analogue)[11] and appropriate 1,3-enyne counterparts for their total syntheses.

We envisioned a conceptually new strategy relying on enyne metathesis[12]-based construction of the cyclohexene core with concommitant installation of the 1,3-enyne moieties starting from the corresponding acyclic precursors. This new approach will harness a streamlined sequence of enyne ring-closing metathesis followed by metallotropic [1,3]-shift,[13] whereby the 1,5-dien-3-yne moiety will be directly installed on the incipient epoxycyclohexene ring. Herein we describe a successful application of this powerful tandem reaction to the concise syntheses of (+)-asperpentyn, (-)-harveynone and (-)-tricholomenyn A.

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Retrosynthetically, we envisaged that cyclohexene derivative **1** with an appropriate R substituent would serve as a common advanced intermediate for all three natural product targets: (+)-asperpentyn, (-)-harveynone and (-)-tricholomenyn A (Scheme 2). A direct precursor of **1** would be an acyclic 1,3-diyne-contaning compound **2** or its simpler variant lacking the relay device. The pivotal metathesis substrate **2** would be prepared through flouoride-catalyzed addition of silylated 1,3-diyne **4** to epoxy aldehyde **3**, which in turn would be derived from aldehyde **5**[14] and allyl propargyl ether **6**. To test the feasibility of the key step, alkene-tethered 1,3-diyne **11** was prepared from commercially available *cis*-2-buten-1,4-diol **7** in 8 steps (Scheme 3). Following the known procedure involving the Sharpless asymmetric epoxidation[15], the diol **7** was elaborated to epoxide **8**. Oxidation of the primary alcohol with PCC to generate aldehyde **5** was followed by addition of vinyl magnesium bromide, MOM-protection of the resultant secondary alcohol (1:1 mixture) and removal of the TBS group afforded primary alcohol **9**. After Dess-Martin oxidation[16] of the primary alcohol, a lithiated diyne derived from **10** was added to provide RCM substrate **11**. Disappointingly, however, treatment of **11** with Grubb's second-generation catalyst did not effect the ring closure to generate **12**. We assumed that the initiation was hindered by the steric congestion around the vinyl group.[17]

To overcome this hindered initiation, a relay metathesis strategy was adopted, which entails the preparation of more elaborated RCM substrate **2** containing the relay device.[18] Along this modified plan, the first goal is to synthesize a common intermediate that can branch off to different target molecules, which is aldehyde **16** (Scheme 4). The synthesis of **16** was commenced with the addition of acetylide derived form allyl propargyl ether **6** to an aldehyde derived from alcohol **8**, providing separable diastereomeric alcohols **13** and **14** in a 1:2 ratio. The desired β-epimer **13** was easily elaborated to acetate **15** via controlled partial hydrogenation[19] (H_2, $Pd/CaCO_3$, $Pb(OAc)_4$, quinoline, Hexane/EtOAc 1:1) and acetylation (Ac_2O, pyr, DMSO, DCM). For a more practical material throughput, without separation the mixture of two epimers, **13** and **14** were subjected to a four-step sequence to convert to **15**, which involves Dess-Martin oxidation of the secondary alcohols, (*R*)-Me-CBS mediated reduction,[20] partial hydrogenation of the triple bond, and Mitsunobu reaction with acetic acid.[21] Removal of the TBS group from **15**, followed by oxidation of the corresponding primary alcohol gave the aldehyde **16**.

For the synthesis of asperpetyne and harveynone, aldehyde **16** was reacted with triethylsilyl-1,3-pentadiyne **17**[22] and a catalytic amount of the anhydrous fluoride source tetrabutylammonium difluorotriphenylsilicate (TBAT),[23] providing enyne RCM substrate **18** after silyl concomitant protection of the secondary alcohol (Scheme 5). Treatmenent of **18** with Grubbs second-generation catalyst[24] in a dilute solution of CH_2Cl_2, a mixture of epimers **23** and **24** was isolated in 62% yield along with unidentified byproducts.

Based on the level of our understanding, we believe that the overall metathesis process started from the teminal alkene of the allyl ether relay device to form **19** initially, which then delivers the ruthenium moiety intramolecularly to the *cis*- alkene to generate a new propagating alkylidene **20**. Subsequent enyne RCM generating alkynyl Ru- alkylidene **21** would induce facile metallotropic [1,3]-shift to generate fully conjugated alkylidene **22**. The termination at the sterically less hindered carbon through **22** would ultimately deliver the final products **23** and **24**, thereby establishing 1,5-diene-3-yne substructure.[13]

After separation, the C1-*β*-epimer **23** was elaborated to (+)-asperpentyn through the removal of both the C1-TES group and C4-acetate in one step (KCN, EtOH 95%) (Scheme 6). Also, the TES-group on C1-*β*-epimer of **23** was selectively deprotected to generate alcohol **25** (HF·pyr, pyr, CH_2Cl_2, 0 °C), which was then oxidized to acetylated harveynone **26**. Unfortunately, under a variety of conditions, the C4-acetate of **26** could not be removed

probably due to the instability of the compound toward basic/nucleophilic conditions. To address this problematic deprotection under basic conditions, the C4-acetate of α-epimer **24** was first converted to a TIPS group generating **27**. The selective removal of the C1-TES group of **27** (HF·pyr, pyr, CH_2Cl_2), followed by oxidation (MnO_2, $CHCl_3$) afforded TIPS-protected form of harveynone **28**, which was successfully converted to (-)-harveynone after removal of the C4-TIPS group (HF·pyr, pyr, $CHCl_3$).

The total synthesis of (-)-tricholomenyn A was commenced with intermediate aldehyde **16** and triethylsilyl-1,3-diyne **31** (Scheme 7).[22] 1,3-Diyne **31** was prepared via Colvin's rearrangement[25] from ketone **30**, which in turn can be readily prepared from known aldehyde **29**.[26] The reaction between aldehyde **16** and silyl-1,3-diyne **31** in the presence of a catalytic amount (5 mol %) of tetrabutylammonium difluorotriphenylsilicate (TBAT)[23] provided silylated adduct **32** (1:1 epimeric mixture), which was subjected to RCM to generate **33** as a separable mixture of epimers. The removal of the TES-protecting group from **33** (HF·pyr) followed by oxidation (MnO_2, $CHCl_3$) delivered the target natural product (-)-tricholomenyn A in good yield.

In summary, we have developed a novel strategy to synthesize epoxyquinone natural products bearing a 1,5-diene-3-yne moiety via a tandem sequence of relay metathesis-induced ring-closing enyne metathesis and metallotropic [1,3]-shift. By using this strategy, we have accomplished the total syntheses of (+)-asperpentyn, (-)-harveynone and (-)-tricholomenyn A. The scope and utility of this metathesis-based tandem bond-forming reaction will be further explored using other natural product targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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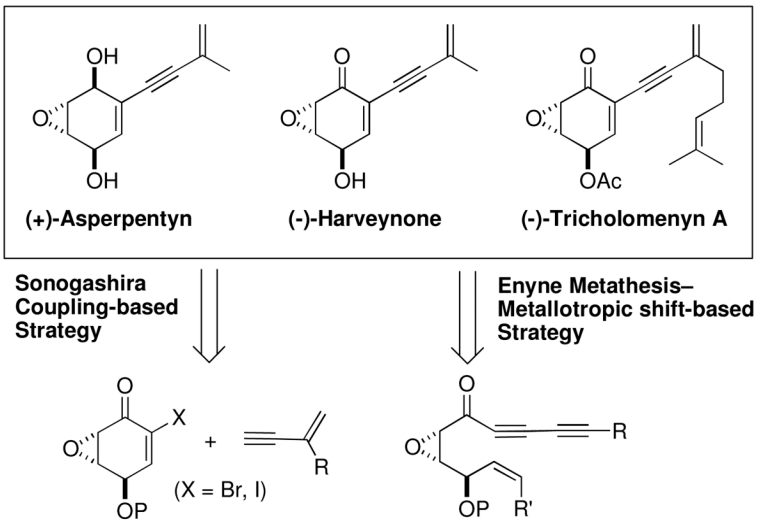
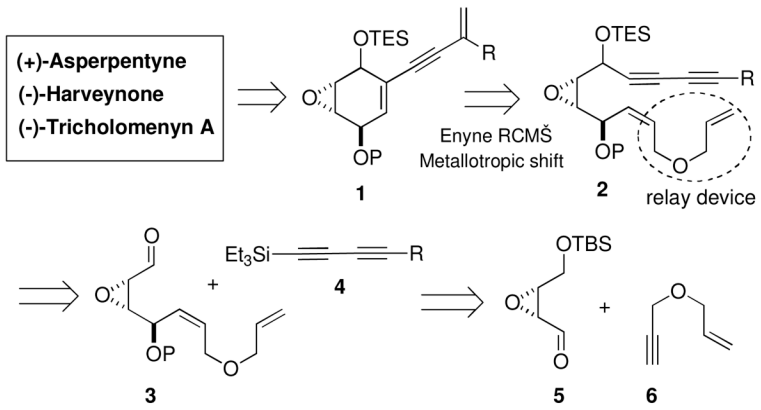
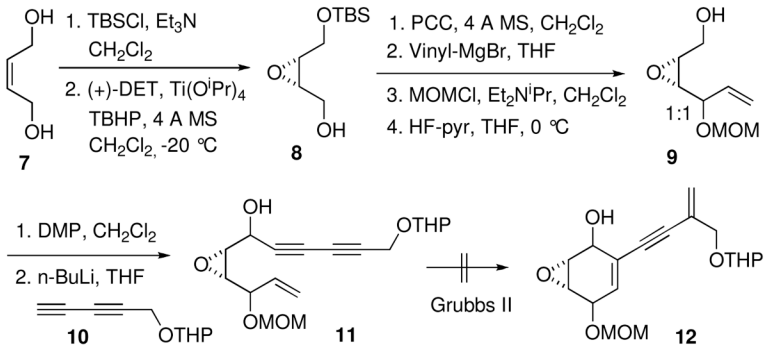


Scheme 1.

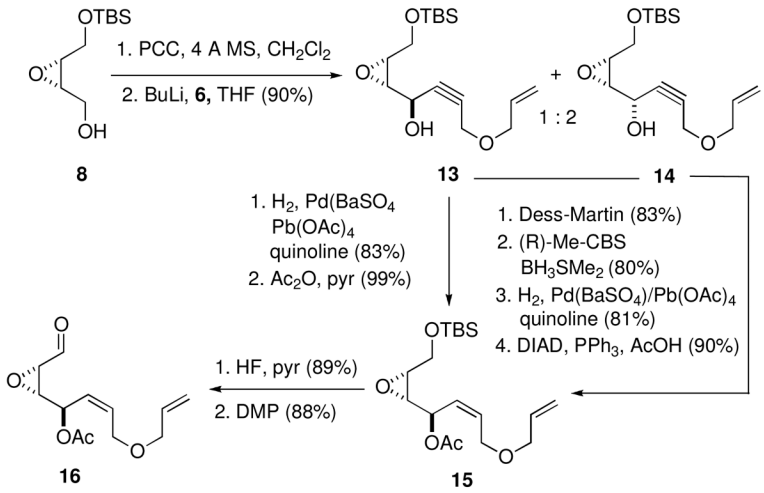
Two Different Synthetic Strategies for (+)-Asperpentyn, (-)-Harveynone, and (-)-Tricholomenyn.



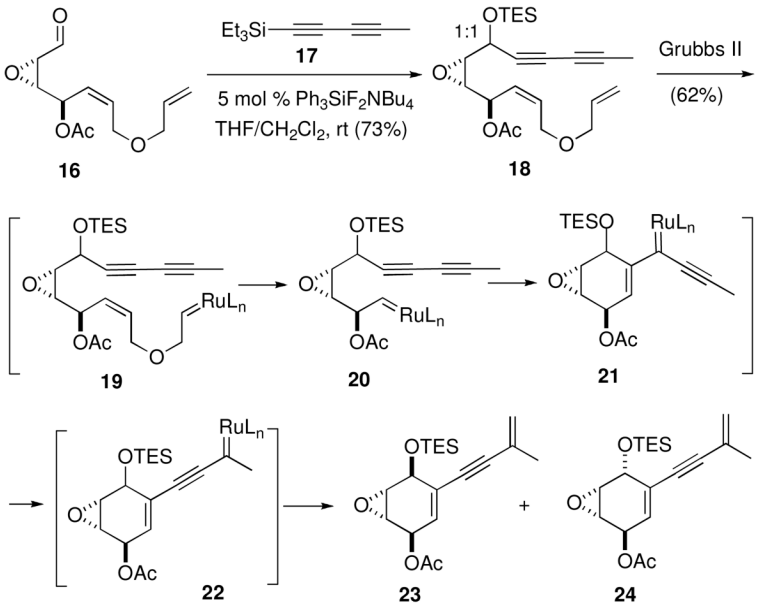
Scheme 2.
Retrosynthetic Analysis for the Total Syntheses of (+)-Asperpentyn, (-)-Harveynone, and (-)-Tricholomenyn.



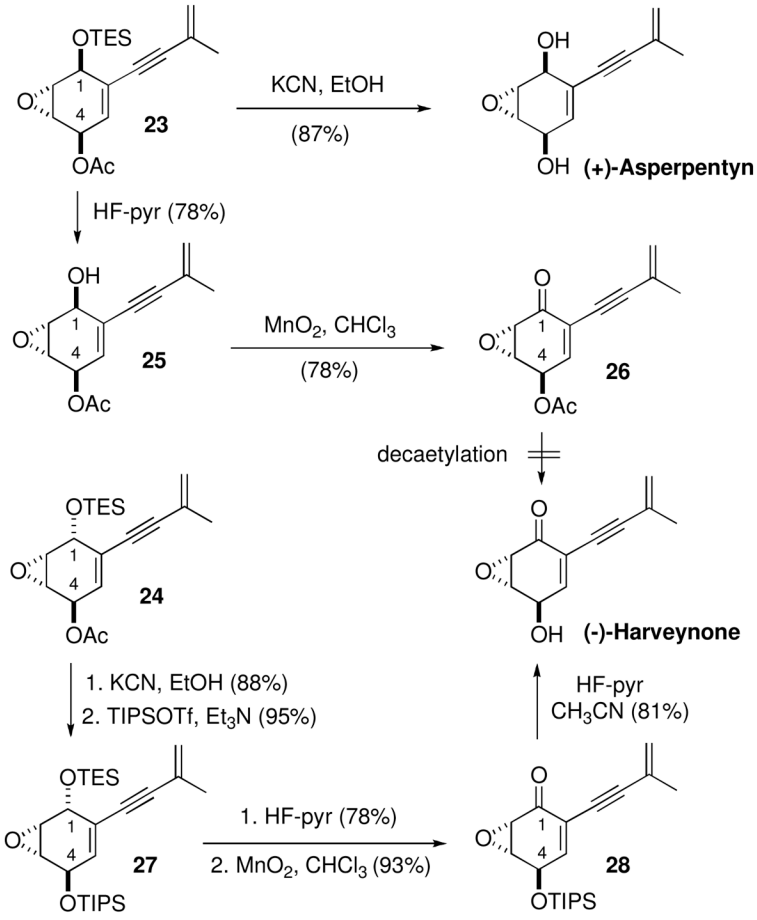
Scheme 3.
Model Study to Test the Enyne RCM



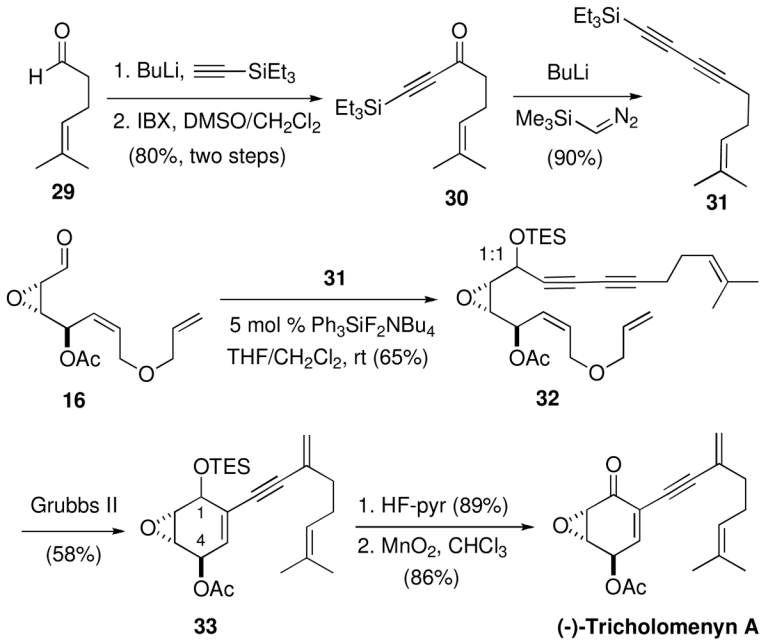
Scheme 4.



Scheme 5.
Enyne RCM and Metallotropic [1,3]-Shift.



Scheme 6.
Completion of (+)-Asperpentyn and (-)-Harveynone.



Scheme 7.
Completion of (-)-Tricholomenyn A.