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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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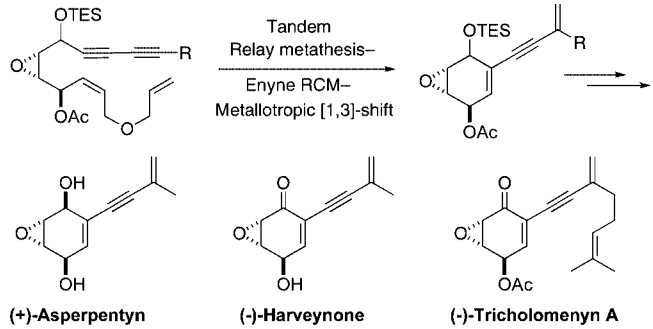
ABSTRACT



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 homologue (−)-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 iodocyclohexenone derivatives (bromoxone or its iodo analogue)[11] and appropriate 1,3-enyne counterparts for their total syntheses.

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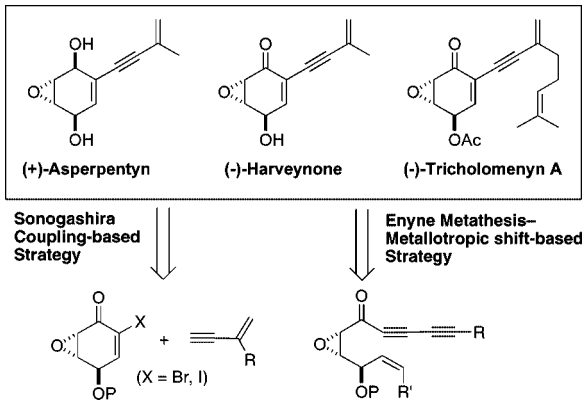
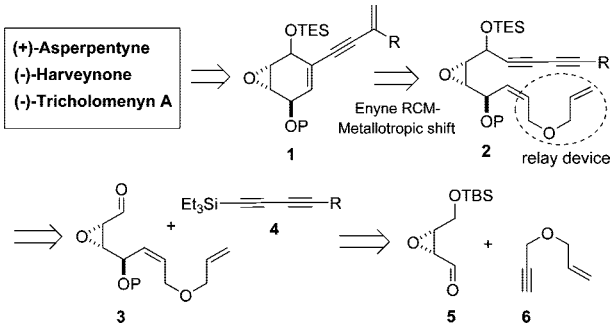
Scheme 1. Two Different Synthetic Strategies for (+)-Asperpentyn, (−)-Harveynone, and (−)-Tricholomenyn



We envisioned a conceptually new strategy relying on enyne metathesis[12]-based construction of the cyclohexene core with concomitant 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.

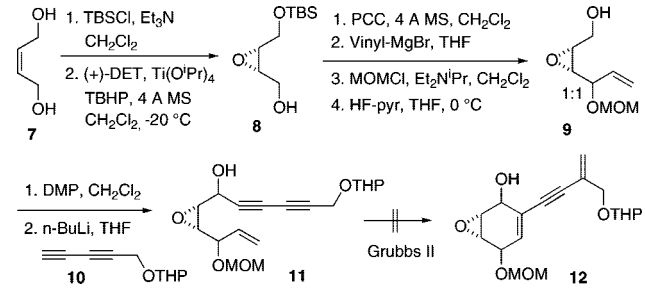
Retrosynthetically, we envisaged that cyclohexene derivative **1** with an appropriate R substituent would serve as a common advanced intermediate for all three natural product targets: (+)-asperpentyn, (−)-harveynone, and (−)-tricholomenyn A (Scheme 2). A direct precursor of **1** would be

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



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-butene-1,4-diol **7** in eight steps (Scheme 3). Following the known procedure involving the

Scheme 3. Model Study To Test the Enyne RCM



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 Grubbs 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

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(11) Synthesis of other epoxyquinoid natural products using bromoxone and its iodo analogues, see: (a) Moses, J. E.; Commeiras, L.; Baldwin, J. K.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987. (b) Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716. (c) Li, C.; Pace, E. A.; Liang, M. C.; Lobkovsky, E.; Gilmore, T. D.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 11308. (d) Shotwell, J. B.; Hu, S.; Medina, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett.* **2000**, *41*, 9639. (e) Porco, J. A., Jr.; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5790. (f) Lei, X.; Johnson, R. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 3913. (g) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3191.

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(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

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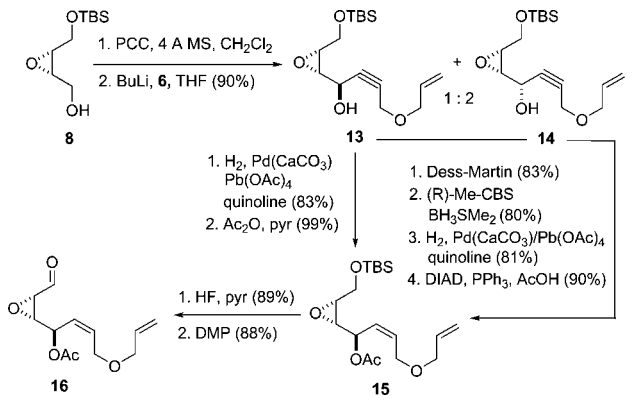
molecules, which is aldehyde **16** (Scheme 4). The synthesis

Scheme 4

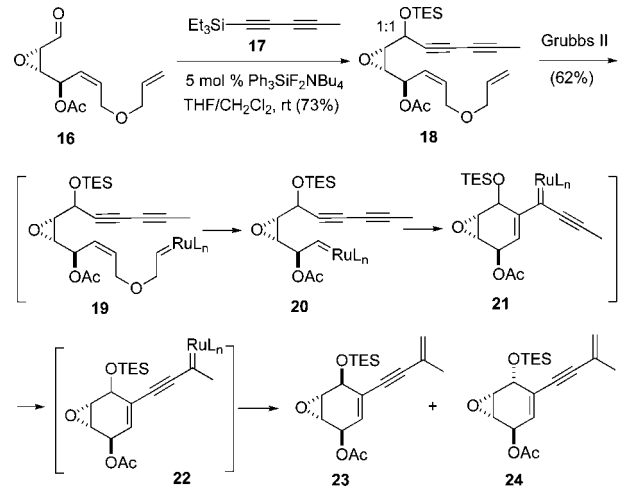


of **16** was commenced with the addition of acetylide derived from allyl propargyl ether **6** to an aldehyde derived from alcohol **8**, providing separable diastereomeric alcohols **13** and **14** in a 1:2 ratio. The desired β-epimer **13** was easily elaborated to acetate **15** via controlled partial 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

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



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

(19) A significant amount of overreduced product from hydrogenation of the terminal alkene was obtained when commercially available Lindlar catalyst without further poisoning was used.

(20) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214. Several attempts had been carried out to optimize the asymmetric reduction. By using 2 equiv of (*S*)-Me-CBS reagent, the ratio of α/β was increased slightly from 1:2 to 1:3, whereas higher stereoselectivity was observed when 2 equiv of (*R*)-Me-CBS was used, the α-isomer having the opposite stereochemistry at C4 was the major product and the ratio of α/β was up to 10:1.

(21) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.

(22) The preparation of TES-protected diyne **17** and **31** is described in the Supporting Information. For the compound **17**, see: Shakhovskoi, B. G.; Petrov, A. A. *Zh. Obsh. Khim.* **1967**, *37*, 1371.

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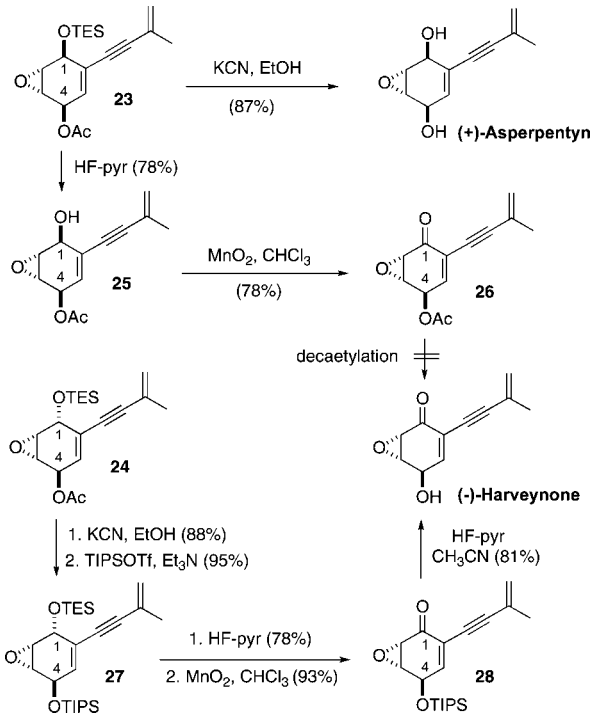
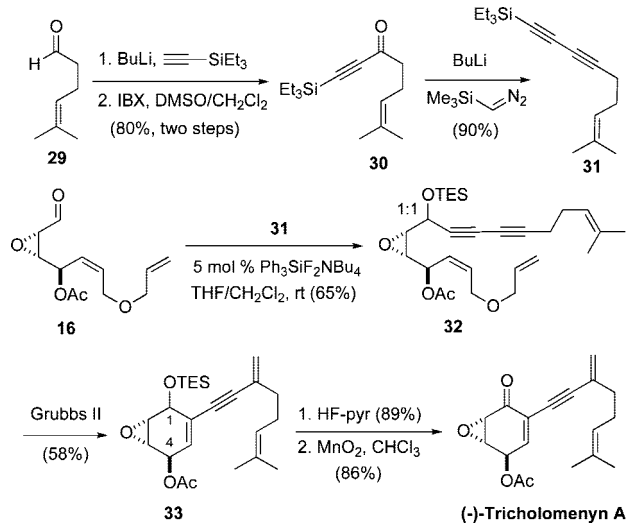
(24) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

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



Scheme 7. Completion of (−)-Tricholomenyn A



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.

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

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(25) (a) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151. (b) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107. (c) Colvin, E. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869.

(26) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115.