

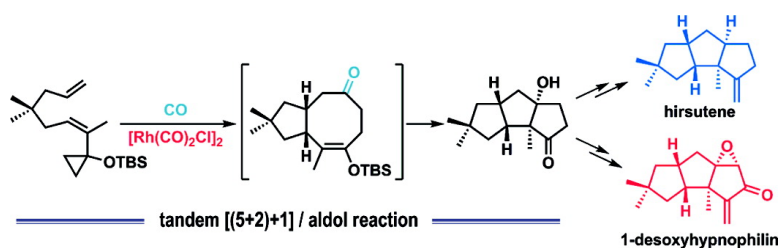
Article

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# Tandem Rh(I)-Catalyzed [(5+2)+1] Cycloaddition/Aldol Reaction for the Construction of Linear Triquinane Skeleton: Total Syntheses of (±)-Hirsutene and (±)-1-Desoxyhypnophilin

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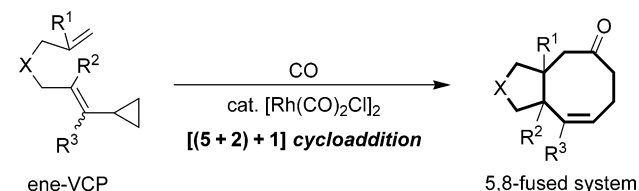
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**Abstract:** A tandem reaction involving a Rh(I)-catalyzed two-component [(5+2)+1] cycloaddition and an aldol condensation has been developed to construct the tricyclo[6.3.0.0<sup>2,6</sup>]undecane skeleton and its heteroatom-imbedded analogues. Meanwhile, this method has been successfully applied to natural product synthesis for the first time. The present strategy enables a straightforward approach to the natural linear triquinane skeleton, as demonstrated by concise and step economical syntheses of hirsutene and 1-desoxyhypnophilin, whereby the linear triquinane core is diastereoselectively established in one manipulation with correct placement of all stereocenters, including two quaternary centers. This first application of the Rh(I)-catalyzed [(5+2)+1] cycloaddition in natural product synthesis highlights the efficiency of this methodology for constructing complex fused ring systems.

## Introduction

Transition-metal-catalyzed cycloaddition reactions are actively pursued to tackle synthetic challenges and to achieve step economical synthesis of complex cyclic compounds.<sup>1,2</sup> Among them, designing transition-metal-catalyzed high-order cycloadditions to construct medium-sized rings is especially attractive since the traditional cyclization strategies to these ring systems are often difficult or inhibited due to unfavorable entropic factors and transannular interactions.<sup>2b</sup> To date, despite numerous transition-metal catalyzed high-order cycloadditions to access complex structures have been developed, only a few have been utilized in natural product synthesis.<sup>3</sup> We recently reported a Rh(I)-catalyzed two-component [(5+2)+1] cycloaddition of ene-vinylcyclopropanes (ene-VCPs) with CO for efficient construction of bicyclic cyclooctenones (Scheme 1).<sup>4</sup> This method has potential application in the construction of complex fused ring systems with eight-membered carbocycle imbedded as a key skeleton, which are widely found in many natural products of biological and therapeutical significances (e.g., taxol

**Scheme 1.** Rh(I)-Catalyzed Two-Component [(5+2)+1] Cycloaddition Developed in the Yu Group

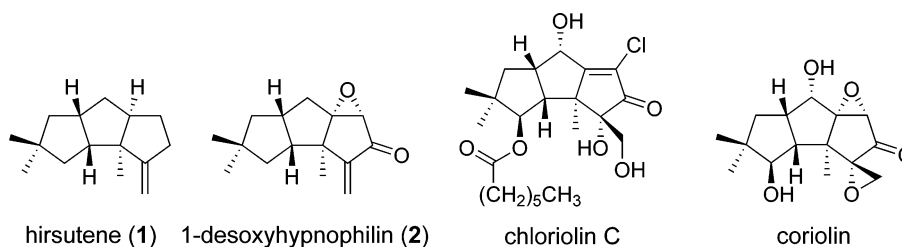


and pleuromutilin). In addition to fused eight-membered carbocycles, we wish to report that this [(5+2)+1] cycloaddition methodology could also access naturally existing tricyclo[6.3.0.0<sup>2,6</sup>]undecane skeleton, the linear triquinanes.

Linear triquinane natural products are a subset of polyquinanes, which constitute an important class of sesquiterpenoids (Figure 1).<sup>5</sup> Linear triquinane natural products are isolated from plants, microbes, and marine organisms, and they have been attracting continuous attention from synthetic chemists due to their promising biological activity and novel architecture.<sup>5</sup> Because of this, numerous strategies have been developed to construct the linear triquinane skeleton<sup>5a</sup> since its discovery in 1966.<sup>6</sup> However, most of the previous achievements require relatively long routes to sequentially establish three five-membered rings

- (1) (a) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25. (b) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind. (London)* **1997**, 765. (c) Wender, P. A.; Miller, B. L. *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, 1993; Vol. 2, pp 27–66.
- (2) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (c) Murakami, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 718.
- (3) Total synthesis utilizing transition-metal catalyzed high-order cycloadditions: (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1988**, *110*, 5904. (b) Wender, P. A.; Fujii, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137. (c) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323. (d) Ashfeld, B. L.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4535. (e) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505. (f) Trost, B. M.; Hu, Y.; Home, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781.

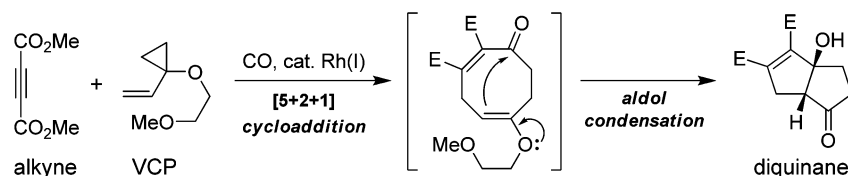
- (4) Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10060. We suggest here a new nomenclature for Rh(I)-catalyzed cycloaddition reactions: for three-component cycloaddition of vinylcyclopropane, alkyne, and CO, this is referred to as [5+2+1] cycloaddition; for two-component cycloaddition of ene-VCP and CO, this is referred to as [(5+2)+1] cycloaddition, where (5+2) part comes from one molecule, ene-VCP.
- (5) Reviews: (a) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647. (b) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671.
- (6) Comer, F. W.; Trotter, J. *J. Chem. Soc. Phys. Org.* **1966**, *1*, 11.



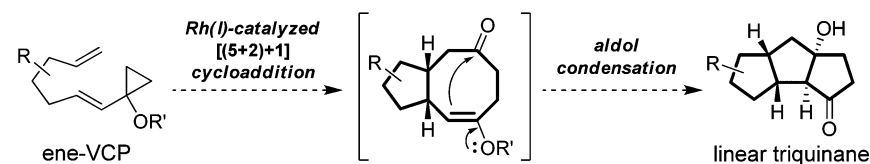
**Figure 1.** Linear triquinane natural products.

**Scheme 2.** Tandem Rh(I)-Catalyzed [5+2+1] Cycloaddition/Aldol Reactions

a. Three-component [5+2+1] / aldol reaction developed in Wender laboratory:



b. Designed two-component [(5+2)+1] / aldol reaction to produce linear triquinane:



of the triquinane system. In 2000, Wender and co-workers reported an elegant three-component [5+2+1] cycloaddition of VCP, alkyne, and CO (Scheme 2a).<sup>7</sup> In most cases, the final products obtained are diquinanes, which are formed via an aldol condensation of the first-step-generated [5+2+1] cycloadducts. Inspired by this discovery, we envisioned that an aldol reaction, in tandem with a Rh(I)-catalyzed two-component [(5+2)+1] cycloaddition,<sup>4</sup> could establish the linear triquinane architecture in a novel way (Scheme 2b). If this strategy can be realized, then we can achieve a more concise and efficient approach to this type of natural products. Therefore, two representative linear triquinanes, hirsutene (1) and 1-desoxyhyphnophilin (2), were selected as our synthetic targets. Herein, we present our endeavors toward the development of a tandem Rh(I)-catalyzed two-component [(5+2)+1] cycloaddition/aldol reaction as a general method to construct triquinane skeleton and its analogous, together with its application to the total syntheses of hirsutene and 1-desoxyhyphnophilin.

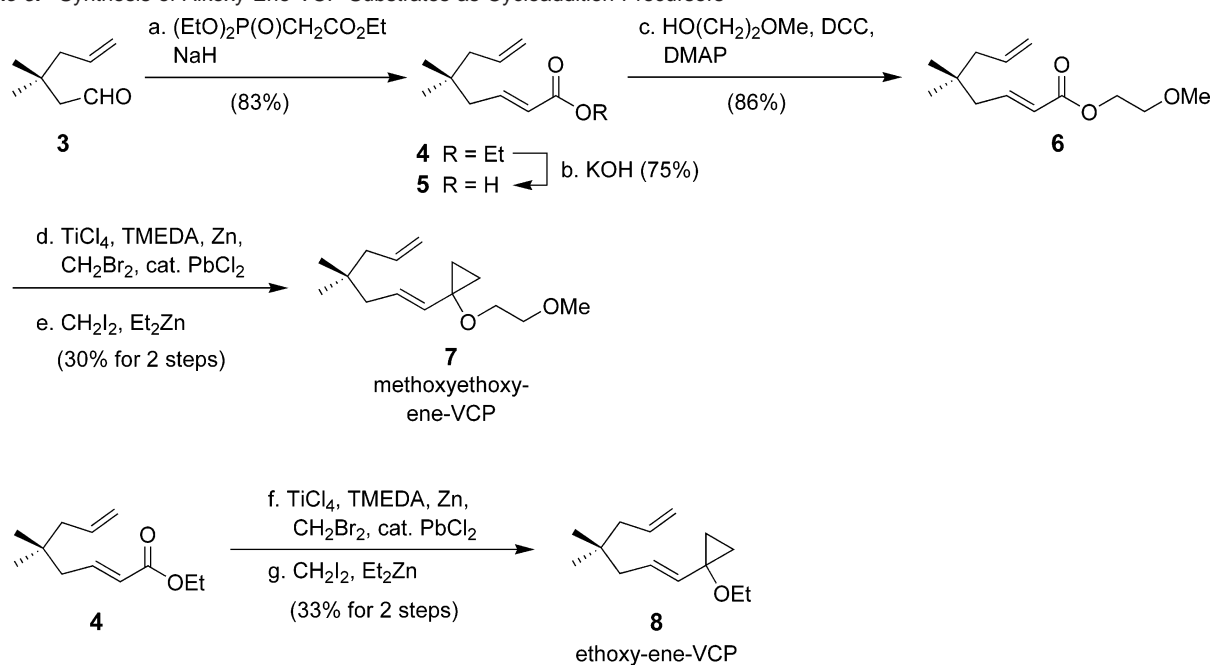
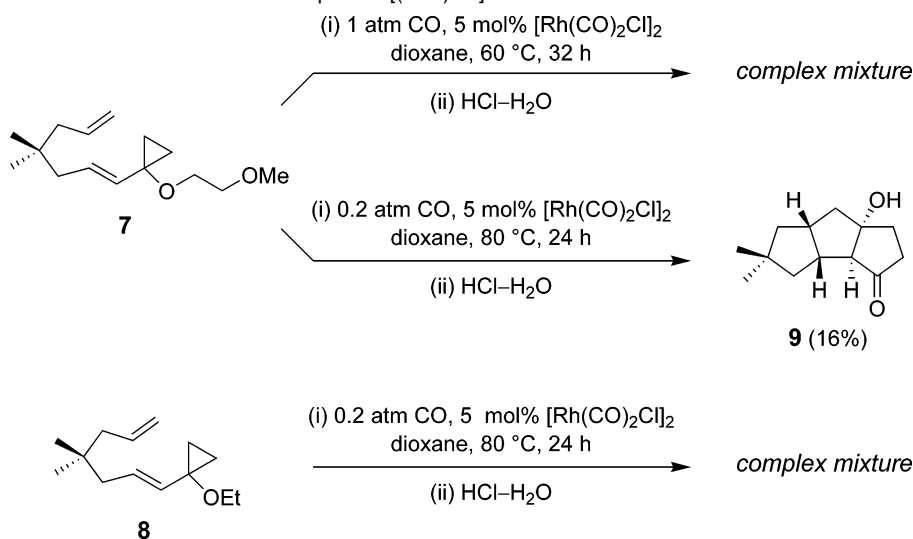
## Results and Discussion

**Initial Attempts in Developing the Tandem Two-Component [(5+2)+1]/Aldol Reaction.** Our strategy to construct the linear triquinane architecture relies on the development of a two-component version of the tandem [5+2+1]/aldol reaction. However, this design will encounter additional challenges compared to the original three-component tandem [5+2+1]/aldol reaction. In Wender's system, the substrates are vinylcyclopropanes, activated alkynes, and CO; whereas in our designed system, the substrates are ene-VCPs and CO (Scheme 2). Since the more reactive electron-deficient alkyne component in three-component [5+2+1]/aldol reaction is replaced by an intramo-

lecular alkene functionality, the most important issue with which we were concerned is whether the Rh(I)-catalyzed [(5+2)+1] cycloaddition could proceed on this new alkoxy-ene-VCP system. Especially important is that introducing an additional five-membered ring may disfavor the desired aldol condensation due to possible ring strain in the transition state, making the designed tandem reaction failed. Moreover, because two additional chiral centers are generated in our designed tandem process, it is also a critical challenge whether the correct relative stereochemistry of linear triquinane (cis-anti-cis) could be established via this approach.

With the above questions in mind, we started our initial attempt on the designed tandem two-component [(5+2)+1]/aldol reaction. Methoxyethoxy-ene-VCP 7, which has the same alkoxy group as the substrates in Wender's three-component [5+2+1]/aldol reaction,<sup>7</sup> was synthesized and selected as the first model substrate (Scheme 3). To our disappointment, when ene-VCP 7 was exposed to the reaction conditions of Wender's three-component [5+2+1]/aldol reaction (1 atm CO, 60 °C, dioxane as solvent), a complex mixture was obtained and no desired cycloadduct could be detected (Scheme 4). Then the previously optimized conditions for the two-component [(5+2)+1] reaction (0.2 atm CO, 80 °C, dioxane as solvent)<sup>4</sup> were used. To our delight, the desired tricyclic cycloadduct 9 was isolated in 16% yield as a single diastereomer (Scheme 4), though most of the starting material became a mixture of unidentified products. The relative configuration of cycloadduct 9 was determined by analogy to compound 15d, which has been confirmed to adopt the natural linear triquinane cis-anti-cis configuration by NOE experiment (see further for details). Although the yield is not satisfactory, this preliminary result confirmed that the designed tandem two-component [(5+2)+1]/aldol reaction is feasible for triquinane skeleton construction.

(7) For a tandem three-component [5+2+1]/aldol reaction to produce diquinanes, see: Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876.

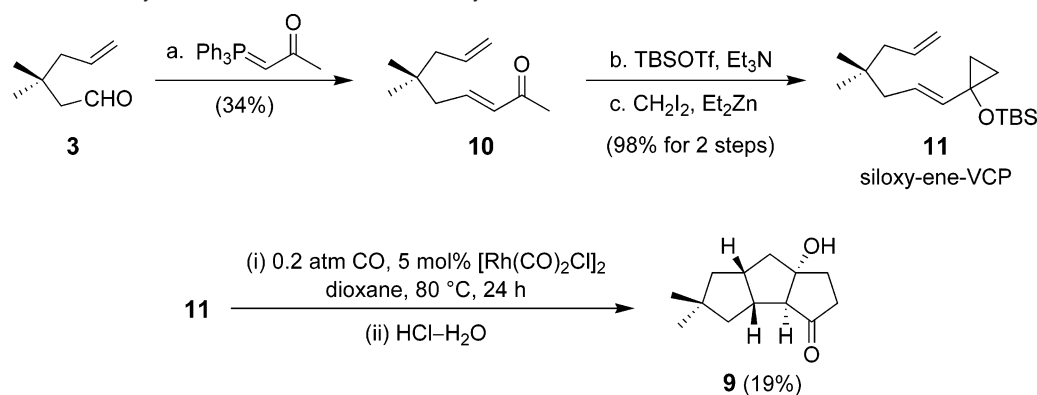
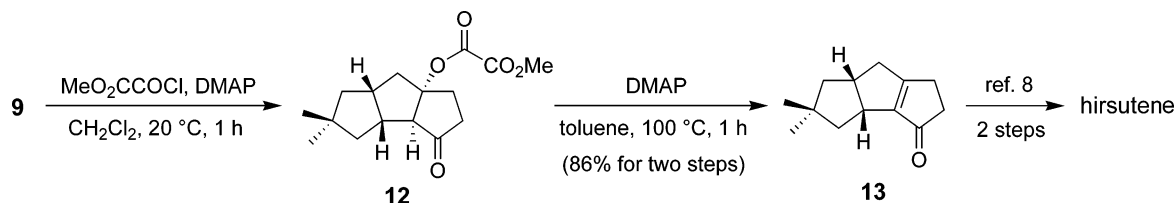
**Scheme 3.** Synthesis of Alkoxy-Ene-VCP Substrates as Cycloaddition Precursors**Scheme 4.** Initial Exploration of the Tandem Two-Component [(5+2)+1]/Aldol Reaction

Given that the *O*-substituent in the VCP moiety may play an important role in the tandem reaction, we conducted optimization on ene-VCP substrates. Ethoxy-ene-VCP **8** was synthesized (Scheme 3) and tested under the cycloaddition conditions, however, this substrate afforded none of the desired cycloadduct, but a complex mixture (Scheme 4). Then we turned our attention to siloxy-substituted ene-VCP substrate and synthesized *tert*-butyldimethylsiloxy-ene-VCP **11** (Scheme 5). It was found that, upon exposure to the cycloaddition reaction conditions, ene-VCP **11** underwent the desired tandem [(5+2)+1]/aldol reaction to furnish tricyclic cycloadduct **9** in 19% yield (Scheme 5). Although alkoxy-ene-VCP **7** and siloxy-ene-VCP **11** gave similar results, we preferred siloxy-ene-VCPs for further investigation due to their easier preparation.

Before we further describe our development of the tandem reaction, we want to point out that cycloadduct **9** can be converted to hirsutene after several manipulations (Scheme 6). Acylation of compound **9** with methyl oxalyl chloride afforded

oxalate **12**, which then underwent an elimination reaction in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) in hot toluene to give tricyclic enone **13**, a key intermediate in total synthesis of hirsutene by Iyoda and co-workers.<sup>8</sup> Therefore, the elaboration of **9** to **13** represents a formal synthesis of hirsutene. However, the low efficiency of the crucial tandem [(5+2)+1]/aldol reaction led to a low total yield of this route, and optimization studies to improve the yield of triquinane cycloadduct were required. Unfortunately, efforts in this line did not result in satisfactory improvement on the yield of cycloadduct **9**. Therefore, we decided to investigate this tandem reaction in detail by conducting more model reactions to identify factors affecting the reaction yield. This investigation is also worthwhile for studying the relative stereochemistry of the [(5+2)+1]/aldol cycloaddition products.

(8) Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1049.

**Scheme 5.** Synthesis of Siloxy-Ene-VCP Substrate **11** and Its Cycloaddition Reaction**Scheme 6.** Conversion of Tricyclic Ketone **9** to Hirsutene

**Model Reaction Study on the Tandem Two-Component [(5+2)+1]/Aldol Reactions.** Several new siloxy-ene-VCP substrates were designed to examine the possible factors affecting the efficiency of the reaction. First, to test the influence of the tether group between the alkene functionality and the VCP moiety, siloxy-ene-VCP substrates **14a** and **14b** with tosylamide and geminal diester as tether groups were synthesized as model substrates.<sup>9</sup> To our disappointment, when siloxy-ene-VCPs **14a** and **14b** were employed in the tandem reaction, there was no significant improvement on the reaction yields (Table 1, entries 1 and 2): both tosylamide and geminal-diester-tethered siloxy-ene-VCPs gave low yields of cycloaddition products, and most of the starting material was transformed to unidentified byproducts. This indicates that different tether groups have minor effect on the reaction, and we should concentrate our efforts on other aspects to improve the reaction yield.

We turned our attention to the substitution pattern on the vinylcyclopropane moiety. In the linear triquinane natural product, there is a methyl group attached to the  $\alpha$ -position of the exo terminal alkene. We envisioned that if a methyl substituted siloxy-ene-VCP were employed, then it would give a tricyclic cycloadduct with correct placement of the methyl group to build a quaternary carbon center, and this would avoid further manipulation for methyl installation. However, introducing a methyl group in the VCP moiety of ene-VCP will give either a *cis* or a *trans*-fused bicyclic cycloadduct, depending on the geometry of the C=C bond in VCP moiety: in previous [(5+2)+1] methodology development, we found that (*E*)-methyl substituted ene-VCPs give *trans*-[(5+2)+1] cycloadducts, while their *Z* counterparts produce *cis*-[(5+2)+1] cycloadducts.<sup>4</sup> Therefore, in order to achieve the desired *cis*-[(5+2)+1] cycloaddition, we synthesized (*Z*)-siloxy-ene-VCPs **14c–e** as model substrates.<sup>9</sup> To our excitement, the reactions of ene-VCPs **14c–e** produced tricyclic cycloadducts **15c–e** in acceptable yields with only one diastereomer generated (Table 1, entries

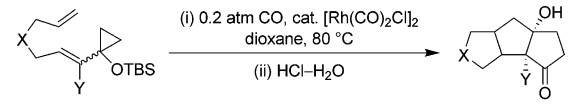
3–5). More excitingly, NOE experiment on product **15d** suggested that the stereochemistry of the cycloadduct was in agreement with the *cis*-*anti*-*cis* configuration of natural linear triquinanes. This assignment also confirms the configuration of other cycloadducts produced in the tandem [(5+2)+1]/aldol reaction. Interestingly, siloxy-ene-VCP **14f** with an elongated tether could also undergo the tandem [(5+2)+1]/aldol reaction to construct a 6,5,5-tricyclic skeleton diastereoselectively (Table 1, entry 6). It is notable that, when (*E*)-siloxy-ene-VCP **14g** was employed, the cycloaddition-step-generated *trans*-fused [(5+2)+1] cycloadduct<sup>4</sup> could not undergo the followed aldol condensation and the final product was bicyclic cyclooctadione **15g** (Table 1, entry 7). This suggests that the cycloaddition-step-generated fused 5–8 bicyclic compound have to adopt a *cis* configuration for the success of the tandem [(5+2)+1]/aldol reaction.

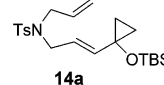
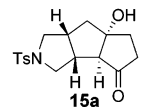
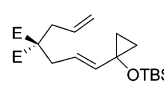
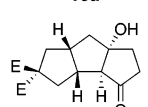
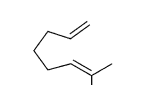
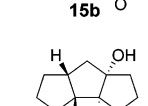
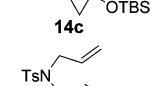
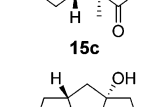
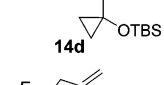
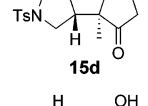
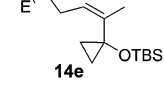
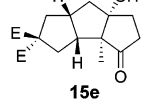
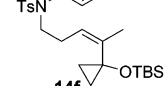
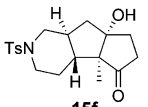
The above results show that the two factors, the geometry of VCP moiety (*cis* or *trans*) and the substitution pattern of VCP (methyl or H substitution), are very important in determining the stereochemistry of the [(5+2)+1] cycloaddition step, which in turn affects the possibility of the following aldol condensation. Here, we present our preliminary rationalization for the stereochemistry of the tandem [(5+2)+1]/aldol reaction (Scheme 7). The [(5+2)+1] cycloaddition is proposed to proceed through VCP cleavage, alkene insertion, CO insertion, and reductive elimination (Scheme 7a).<sup>4,10,11</sup> The 5–8 ring-fusion stereochemistry is determined by the irreversible alkene insertion step, giving either a *cis* or a *trans* 5–8 bicyclic product or both. For *Z*-ene-VCP substrate **A**, the *cis* alkene-insertion transition state **TS1-*cis*** is favored over the *trans* alkene-insertion transition state **TS1-*trans***, independent of the R substituent. Therefore, *cis*-

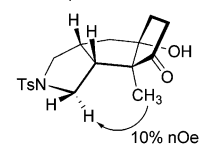
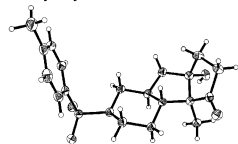
(10) Yu, Z.-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154.

(11) The configuration of the C=C bond in VCP determines the configuration of the  $\pi$ -allyl-rhodium species (Scheme 7). For *Z*-ene-VCP substrate **A**, where the C1 and C4 are in *cis* relationship,  $\pi$ -allyl-rhodium intermediates and transition states (**TS1-*cis*** and **TS1-*trans***) adopt configurations that C1 and C4 are in *cis* relationship. Alternatively, for *E*-ene-VCP substrate **B**, where the C1 and C4 are in *trans* relationship,  $\pi$ -allyl-rhodium intermediates and transition states (**TS2-*cis*** and **TS2-*trans***) adopt configurations that C1 and C4 are in *trans* relationship.

(9) Procedures for the synthesis of ene-VCPs **14a–g** are given in Supporting Information.

**Table 1.** Model Tandem Two-Component [(5+2)+1]/Aldol Reactions<sup>a</sup>


entry	substrate	mol % [Rh(CO) <sub>2</sub> Cl] <sub>2</sub>	time (h)	product	yield <sup>b</sup>
1		6	18		22%
2		5	20		28%
3		10	36		26% <sup>c</sup>
4		8	48		50% <sup>d</sup>
5		11	48		67%
6		9	36		52% <sup>e</sup>
7		6	24		50% <sup>f</sup>

nOe experiment for **15d**X-ray crystal structure of **15f**

<sup>a</sup> E = COOEt. <sup>b</sup> Isolated yield. <sup>c</sup> A trans-fused cyclooctanedione **15c'** was also isolated in 26% yield (see Supporting Information for details). <sup>d</sup> Based on recovered starting material. <sup>e</sup> A degradation product, enone **15f'**, was also isolated in 24% yield (see Supporting Information for details). Relative stereochemistry of **15f** was determined by X-ray crystallographic analysis. <sup>f</sup> Single diastereomer.

fused 5–8 bicyclic products will be formed. The preference of the cis alkene-insertion transition state over its trans counterpart can be well understood by considering the ring strains: the alkene-insertion transition states prefer to have the forming five-membered ring (C3–C4–C5–C6–C7) to be cis-fused with the Rh–C2–C3–C7–C8 ring to minimize the bicyclic ring strain. For *E*-ene-VCP substrate **B**, the alkene-insertion transition states still prefer to have the forming five-membered ring (C3–C4–C5–C6–C7) to be cis-fused with the Rh–C2–C3–C7–C8 ring to minimize the bicyclic ring strain. However, in this case, the cis alkene-insertion transition state suffers from an additional R–C4 steric repulsion, whereas this repulsion is absent in the

trans alkene-insertion transition state. When R = H, the R–C4 repulsion is minor so that **TS2-cis** is still favored over **TS2-trans**, leading to the cis 5–8 bicyclic products. However, when R = Me, the R4–C4 steric repulsion is severe, making **TS2-cis** disfavored compared with **TS2-trans**. Consequently, trans 5–8 bicyclic products are formed. The above analysis is supported by DFT calculations and detailed investigations are ongoing in our group. The stereochemistry of the aldol condensation following the [(5+2)+1] cycloaddition is less complicated (Scheme 7b). For cis cycloadduct, the cis-anti-cis condensation is favored over the cis-syn-cis condensation because of less steric repulsion encountered in the former transition state. However, for trans 5–8 cycloadduct, the following aldol condensation could not occur, possibly due to unfavorable ring strain.

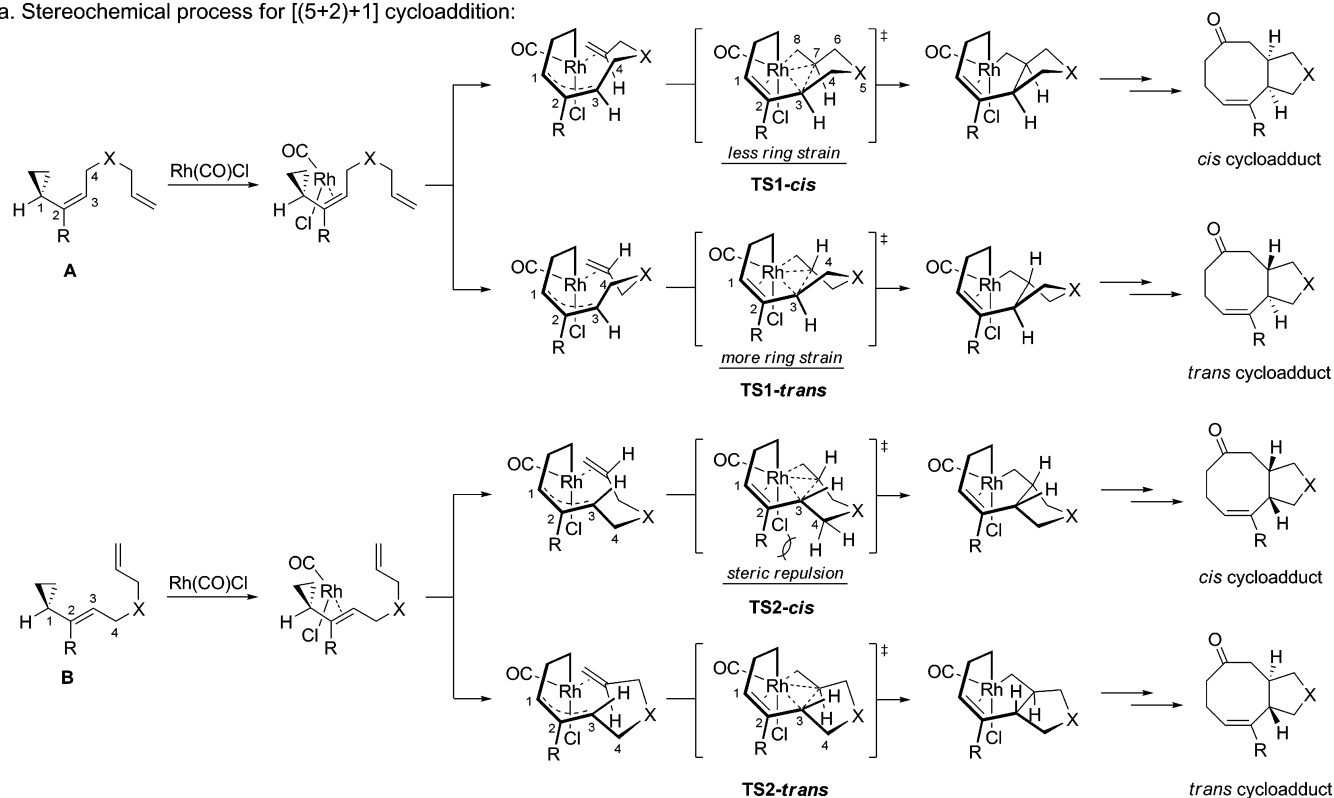
Through the model study, we obtained valuable information for the crucial reaction of the total synthesis work. First, the designed tandem two-component [(5+2)+1]/aldol reaction is feasible when siloxy-ene-VCPs are employed as substrates. Second, methyl substituted siloxy-ene-VCP substrate has been proved to be better than unsubstituted siloxy-ene-VCP substrate. Third, this tandem reaction could produce the desired diastereomer of the tricyclic cycloadduct, making it applicable to the synthesis of linear triquinane natural products. Encouraged by these positive conclusions, we started our work on the total syntheses of hirsutene and 1-desoxyhypnophilin.

**Retrosynthetic Analysis.** On the basis of the model study, we did the retrosynthetic analysis of the two natural products (Scheme 8). Hirsutene can be obtained from Wittig reaction of norketone **16** according to literature procedure.<sup>12a</sup> Norketone **16** is supposed to be derived from the key intermediate **18** through radical deoxygenation reaction. Alternatively, 1-desoxyhypnophilin is also envisioned to generate from the key intermediate **18** via Wittig reaction, allylic oxidation, dienone formation, and regioselective epoxidation.<sup>13</sup> On the basis of the previous model reaction study, cycloadduct **18** could be directly obtained from the tandem Rh(I)-catalyzed two-component [(5+2)+1] cycloaddition/aldol reaction of (*Z*)-siloxy-ene-VCP

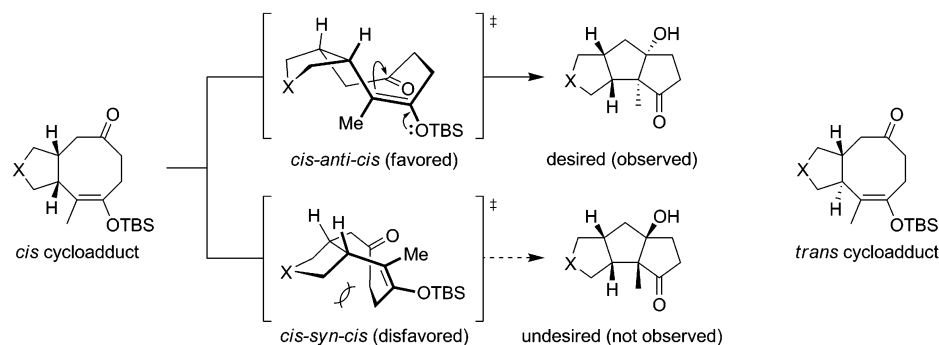
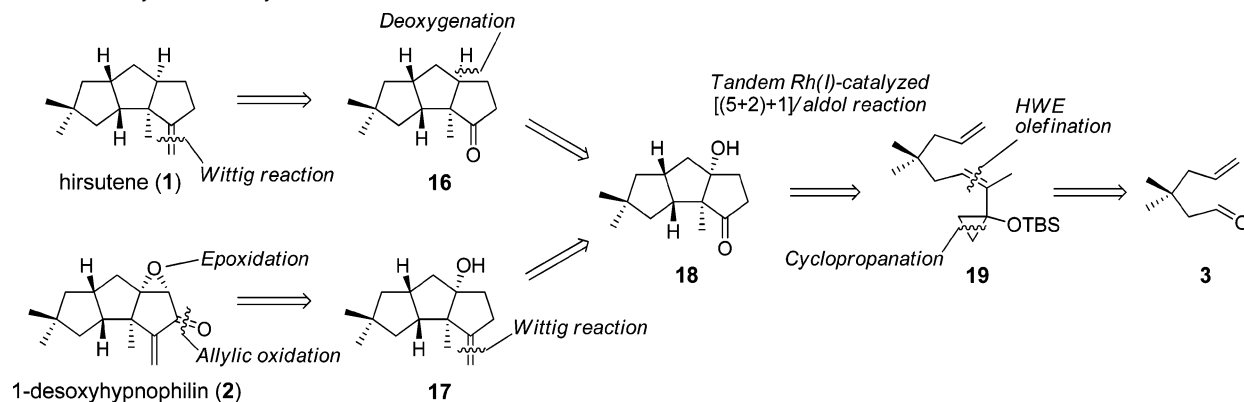
- (12) Hirsutene synthesis using the Wittig reaction of norketone **9**: (a) Sternbach, D. D.; Ensinger, C. L. *J. Org. Chem.* **1990**, *55*, 2725. Previous report of hirsutene synthesis: (b) Singh, V.; Vedantham, P.; Sahu, P. K. *Tetrahedron* **2004**, *60*, 8161. (c) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A. *Tetrahedron* **2004**, *60*, 535. (d) Wang, J.-C.; Krische, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5855. (e) Lee, H.-Y.; Kim, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10156. (f) Singh, V.; Vedantham, P.; Sahu, P. K. *Tetrahedron Lett.* **2002**, *43*, 519. (g) Anger, T.; Graalman, O.; Schröder, H.; Gerke, R.; Kaiser, U.; Fitjer, L.; Noltemeyer, M. *Tetrahedron* **1998**, *54*, 10713. (h) Oppolzer, W.; Robyr, C. *Tetrahedron* **1994**, *50*, 415. (i) Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K. *Tetrahedron* **1993**, *49*, 11189. (j) Ramig, K.; Kuzemko, M. A.; McNamara, K.; Cohen, T. D. *J. Org. Chem.* **1992**, *57*, 1968. (k) Hua, D. H.; Venkstaraman, S.; Ostrand, R. A.; Sinai, G.-Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.* **1988**, *53*, 507. (l) Disanyayaka, B. W.; Weedon, A. C. *J. Org. Chem.* **1987**, *52*, 2905. (m) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443. (n) Curran, D. P.; Rekiwicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (o) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (p) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (q) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621. (r) Funk, R. L.; Bolton, G. L. *J. Org. Chem.* **1984**, *49*, 5021. (s) Little, R. D.; Higby, R. G.; Moeller, K. D. *J. Org. Chem.* **1983**, *48*, 3139. (t) Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1982**, *23*, 3983. (u) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744. (v) Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* **1981**, 756. (w) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351. (x) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (y) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1979**, *101*, 6116.
- (13) 1-Desoxyhypnophilin synthesis: (a) Harrowen, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **2000**, *41*, 8985. (b) Harrowen, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 9157.

**Scheme 7.** Rationale for the Stereochemical Outcome of the Tandem [(5+2)+1]/Aldol Reaction

a. Stereochemical process for [(5+2)+1] cycloaddition:

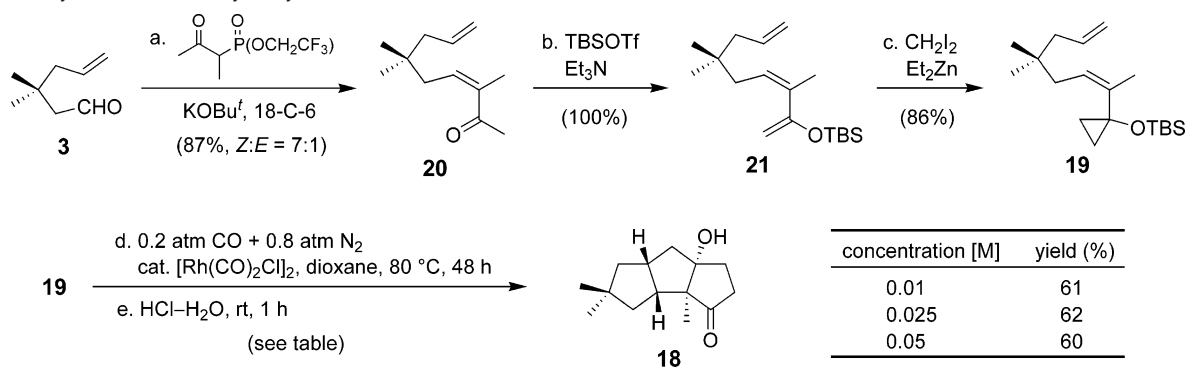
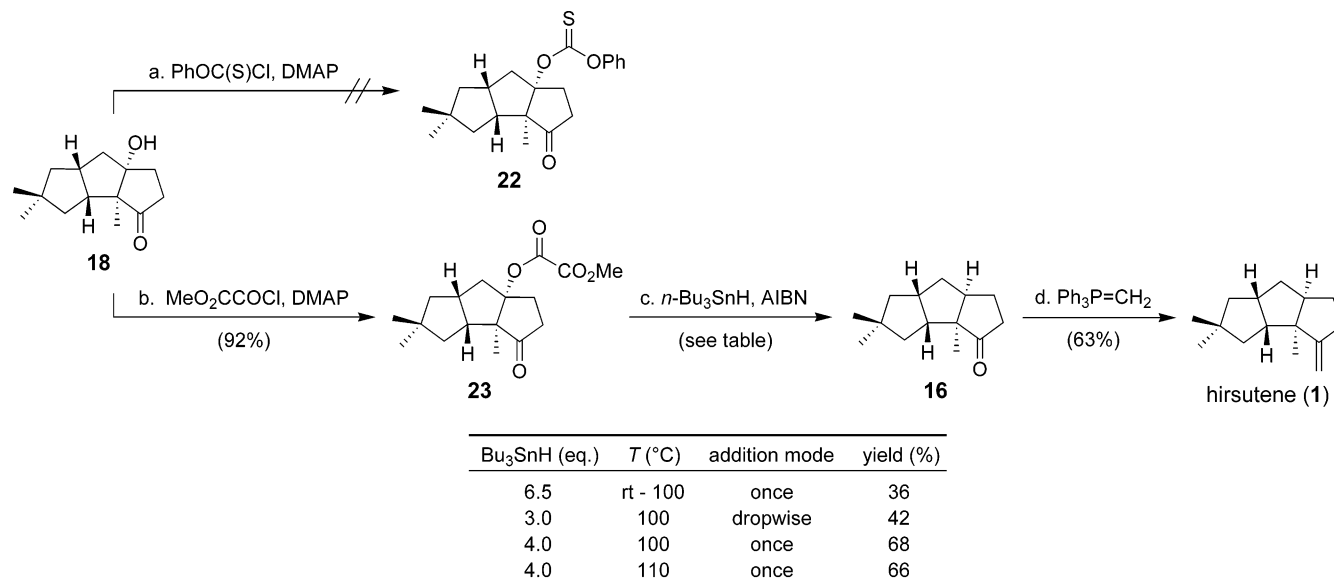


b. Stereochemical process for aldol condensation:

**Scheme 8.** Retrosynthetic Analysis

**19** with CO. In this complexity-increasing reaction, the linear triquinane skeleton can be established and appropriate functional groups can be in place for further modifications. The definitive substrate for the tandem reaction, (*Z*)-siloxy-ene-VCP **19**, could

be obtained from dimethylhexenal **3** through *Z*-selective Horner–Wadsworth–Emmons (HWE) olefination, silylenol etherification, and cyclopropanation reactions. The advantage of the present design is that most of the complexity increasing

**Scheme 9.** Synthesis of the Key Tricyclic Intermediate **18****Scheme 10.** Synthesis of ( $\pm$ )-Hirsutene

steps are condensed into a tandem process, while the remaining steps require only simple and ordinary conversions.

**Synthesis of Hirsutene.** The first step of the total synthesis was to prepare (*Z*)-siloxy-ene-VCP **19** that can be further elaborated to finish the total syntheses of two target molecules. The synthesis began with HWE reaction of dimethylhexenal **3** (Scheme 9), which occurred under Still–Jin-modified conditions<sup>14</sup> in 87% yield to afford (*Z*)- $\alpha,\beta$ -unsaturated ketone **20** as the major isomer. Treatment of (*Z*)-**20** with TBSOTf and Et<sub>3</sub>N in dry ether afforded silylenol ether (*Z*)-**21** quantitatively, which was then converted to pure (*Z*)-ene-VCP **19** in 86% yield through chemoselective cyclopropanation of the more electron rich olefin in compound **21**.

With (*Z*)-siloxy-ene-VCP **19** in hand, we began to explore the key reaction of the synthesis. Gratifyingly, exposure of ene-VCP **19** to [(5+2)+1] cycloaddition conditions<sup>4</sup> led to a smooth reaction, affording the desired tricyclic ketone **18** in 60–62% yield as a single diastereomer (Scheme 9), together with a small amount of bicyclic cyclooctadiene **15g** (10%). It was found that using low concentration of ene-VCP **19** did not improve the reaction yield (see the table in Scheme 9).

In order to finish the hirsutene synthesis, the hydroxyl group in the key intermediate **18** has to be replaced by hydrogen to furnish norketone **16**, and such transformation can be achieved

through a radical deoxygenation. Since a ketone functionality exists in the substrate, the preparation of the deoxygenation precursor has to avoid the use of strong basic conditions. Initially, *O*-phenyl carbonothioate **22** was selected as the precursor for radical deoxygenation.<sup>15</sup> However, the reaction of tricyclic ketone **18** with phenyl chlorothionoformate in the presence of DMAP failed to give thioester **22** (Scheme 10). Then methyl oxalate derivative, which was reported to be suitable for radical deoxygenation of a tertiary alcohol,<sup>16</sup> was taken into consideration. Gratifyingly, the reaction of methyl oxalyl chloride with intermediate **18** afforded the deoxygenation precursor **23** in 92% yield. We then conducted the tributylstannane-mediated deoxygenation of oxalate **23** at different temperatures and various stannane loadings (toluene as solvent), but the yields of norketone **16** always ranged from 30% to 40%. Fortunately, we finally found that adding the stannane reagent and AIBN to a refluxing toluene solution of substrate **23** in one portion (instead of gradually heating a solution of stannane, AIBN, and the substrate from room temperature to over 100 °C) can improve the isolated yields of norketone **16** to 66–68% (Scheme 10).

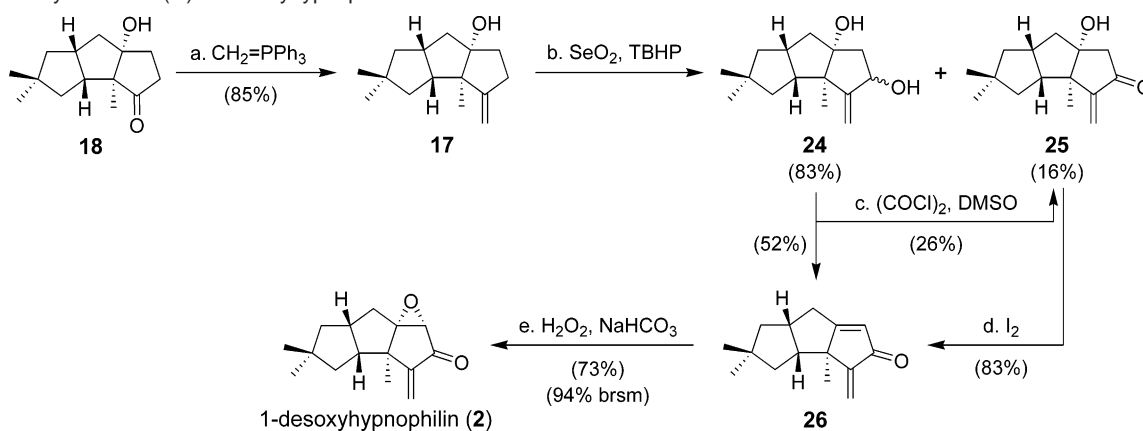
Finally, norketone **16** was transformed by Wittig reaction to hirsutene in 63% yield according to the reported procedure<sup>12a</sup>

(14) Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* **1999**, *40*, 6725.

(15) Pettus, T. R. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160.

(16) Dolan, S. C.; MacMillan, J. *Chem. Commun.* **1985**, 1588.



**Scheme 11.** Synthesis of (±)-1-Desoxyhypnophilin

(Scheme 10). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the synthetic hirsutene are in agreement with the reported data,<sup>12</sup> confirming that the tandem [(5+2)+1]/aldol reaction indeed produced the linear triquinane skeleton with correct relative configuration. The present synthesis of hirsutene is concise and efficient, requiring 8 steps with 11% overall yield from commercially available 2,2-dimethylpent-4-enal, while a recently reported synthesis from the same starting material requires 13 steps.<sup>12d</sup>

**Synthesis of 1-Desoxyhypnophilin.** Synthesis of 1-desoxyhypnophilin from the common key intermediate **18** requires more manipulations (Scheme 11). Wittig olefination of intermediate **18** occurred in 85% yield to furnish hydroxyl hirsutene **17**. Allylic oxidation of compound **17** by *t*-BuOOH (TBHP) in the presence of  $\text{SeO}_2$  provided a mixture of allylic alcohol **24** (83%) and hydroxyl enone **25** (16%). Since enone **25** is the desired precursor for dienone formation, oxidation of alcohol **24** was carried out to transform it to hydroxyl enone **25**. To our surprise, when submitted to Swern oxidation conditions, compound **24** gave only 26% of the normal oxidation product **25** and most of compound **24** was directly converted to dienone **26**. This unexpected oxidation-dehydration reaction might be caused by excess Swern oxidant present in the reaction system. The remaining hydroxyl enone **25** was dehydrated by refluxing in benzene with iodine to afford dienone **26** in 83% yield. Therefore, through oxidation and dehydration, compound **17** can be transformed to dienone **26** in 74% overall yield.

The final step for 1-desoxyhypnophilin synthesis was the epoxidation of the dienone intermediate. According to a recently reported procedure,<sup>13b</sup> we achieved regioselective epoxidation of dienone **26** in 73% yield (94% based on recovered starting material), giving rise to racemic 1-desoxyhypnophilin. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the synthetic 1-desoxyhypnophilin are identical to those reported.<sup>13</sup> This successful synthesis further demonstrated the efficiency of the crucial tandem [(5+2)+1]/aldol reactions, since the first synthesis of 1-desoxyhypnophilin completes in 15 steps,<sup>13</sup> whereas we finish its second total synthesis in 9 steps with 13% overall yield.

## Experimental Section

Selected experimental procedures for the preparation of **18**, **16**, **1** (hirsutene), **17**, **24**, **25**, **26**, and **2** (1-desoxyhypnophilin) appear below. Full experimental details for all compounds are given in the Supporting Information.

**cis-anti-cis-8-Hydroxy-1,4,4-trimethyltricyclo[6.3.0.0<sup>2,6</sup>]undecan-11-one (18).** A solution of ene-VCP **19** (62.7 mg, 0.203 mmol) in

anhydrous dioxane (8 mL) was degassed by bubbling  $\text{CO}/\text{N}_2$  (1:4 V/V) for 5 min. The catalyst  $[\text{Rh}(\text{CO})_2\text{Cl}]_2$  (6.0 mg, 15  $\mu\text{mol}$ ) was added in one portion and a light yellow solution formed, which was further bubbled by the above gas for 5 min. The solution was heated to 80 °C in an oil bath with stirring under a positive pressure of the mixture gas. After 48 h, TLC indicated the disappearance of the starting material. The resulting brown reaction mixture was cooled to room temperature and hydrolyzed by adding 1% HCl in EtOH (0.3 mL) and water (0.1 mL) and stirred at rt for 20 min. Solvent was evaporated and the residue was purified by flash column chromatography on silica gel (5 g, eluted with petroleum ether/ethyl acetate 5:1 to 3:1) to afford tricyclic compound **18** (28.2 mg, 62%) as a pale yellow oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.90 (s, 3H), 0.96 (s, 3H), 1.07 (s, 3H), 1.22 (dd,  $J = 9.6$  and 11.7 Hz, 1H), 1.37–1.56 (m, 2H), 1.60–1.74 (m, 3H), 1.85–1.97 (m, 2H), 2.07–2.16 (m, 1H), 2.25–2.37 (m, 1H), 2.47–2.58 (m, 2H), 2.77 (dd,  $J = 9.9$  and 19.2 Hz, 1H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.6, 26.5, 29.0, 32.1, 35.2, 40.3, 41.6, 42.1, 44.6, 48.6, 49.2, 60.0, 89.5, 221.8. MS (EI, 70 eV):  $m/z$  222 ( $\text{M}^+$ , 26), 207 (5.0), 189 (7.0), 165 (42), 149 (14), 113 (100), 95 (20). IR (neat):  $\nu$  2950, 2863, 1728, 1463, 1365, 1261, 1216  $\text{cm}^{-1}$ . HRMS Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_2$ : 222.1620. Found: 222.1621.

**cis-anti-cis-1,4,4-Trimethyltricyclo[6.3.0.0<sup>2,6</sup>]undecan-11-one (16).** To a stirred solution of tricyclic ketone **18** (55.0 mg, 0.247 mmol) and DMAP (46.5 mg, 0.381 mmol) in 4 mL of dry  $\text{CH}_2\text{Cl}_2$  was added methyl chlorooxalate (63.8 mg, 0.521 mmol) dropwise. After stirred at room temperature for 1 h, the resulting solution was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, eluted with petroleum/acetate 6:1) to give oxalate **23** (70.3 mg, 92%) as a colorless oil. A solution of oxalate **23** (20.9 mg, 0.0678 mmol) in 1.4 mL of degassed toluene was heated to reflux in an oil bath under argon. A solution of *n*- $\text{Bu}_3\text{SnH}$  (84 mg, 0.289 mmol) and AIBN (4.6 mg) in degassed toluene (1.0 mL) was added in one portion. The reaction mixture was stirred for another 45 min under reflux. The resulting mixture was cooled to room temperature and evaporated. The crude product was purified by flash column chromatography on silica gel (2 g, eluted with petroleum ether/ethyl acetate 20:1) to afford hirsutene norketone **16** (9.2 mg, 66%) as a colorless oil, which solidifies on standing.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.90 (s, 3H), 0.94 (s, 3H), 0.98–1.02 (m, 1H), 1.04 (s, 3H), 1.18 (dd,  $J = 11.6$  Hz, 1H), 1.32–1.48 (m, 2H), 1.56–1.76 (m, 3H), 2.00 (dddd,  $J = 6.2, 8.4, 9.8$ , and 13.1 Hz, 1H), 2.19–2.45 (m, 3H), 2.52 (dq,  $J = 3.4$  and 9.0 Hz, 1H), 2.80 (dt,  $J = 10.6$  and 8.7 Hz, 1H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  17.2, 22.3, 26.5, 29.2, 29.7, 34.2, 37.5, 41.1, 41.8, 43.3, 46.6, 48.8, 59.3, 224.8. The spectroscopic data was identical to that reported.<sup>12c</sup>

**(±)-Hirsutene (1).**<sup>12a</sup> To a solution of  $\text{KO}^t\text{Bu}$  (37.9 mg, 0.338 mmol) in  $^t\text{BuOH}$  (0.5 mL) and benzene (2.2 mL) was added at room temperature under argon methyltriphenyl-phosphonium bromide (134

mg, 0.375 mmol) in one portion and the resulting yellow solution was stirred at room temperature for 30 min. A solution of hirsutene norketone **16** (13.4 mg, 0.065 mmol) in dry benzene (1 mL) was added, and the reaction mixture was brought to reflux for 1 h in a 100 °C oil bath. The resulting mixture was cooled, poured into water, and extracted with petroleum ether. The combined extract was dried over MgSO<sub>4</sub> and evaporated. Flash column chromatography on neutral alumina provided crude hirsutene as a colorless oil (containing unidentified nonpolar impurities). Another column chromatography on AgNO<sub>3</sub> impregnated silica gel (eluting with petroleum ether and then petroleum ether/acetone 50:1 to 25:1) afforded pure (±)-hirsutene (8.3 mg, 63%) as a colorless oil. Spectroscopic data for hirsutene: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.92 (s, 3H), 0.95 (s, 3H), 0.99–1.04 (m, 1H), 1.05 (s, 3H), 1.21 (t, *J* = 11.7 Hz, 1H), 1.40–1.48 (m, 4H), 1.64 (ddd, *J* = 2.0, 8.4, and 10.6 Hz, 1H), 1.69–1.78 (m, 1H), 2.11–2.19 (m, 1H), 2.43–2.49 (m, 2H), 2.50–2.65 (m, 2H), 4.77 (s, 1H), 4.82 (s, 1H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 23.2, 26.8, 27.2, 29.7, 30.9, 38.6, 40.9, 41.9, 44.3, 49.0, 49.9, 53.4, 56.0, 103.5, 162.9. The spectroscopic data was identical to that reported.<sup>12a</sup>

**cis-anti-cis-8-Hydroxy-11-methylene-1,4,4-trimethyltricyclo-[6.3.0.0<sup>2,6</sup>]undecane (17).** To a solution of KOBu<sup>t</sup> (92.8 mg, 0.828 mmol) in <sup>t</sup>BuOH (1 mL) and benzene (4.5 mL) was added at room temperature under argon methyltriphenyl-phosphonium bromide (247 mg, 0.692 mmol) in one portion and the resulting yellow solution was stirred at room temperature for 30 min. A solution of hydroxy ketone **18** (28.0 mg, 0.126 mmol) in dry benzene (0.5 mL) was added and the reaction mixture was brought to reflux for 2 h in a 100 °C oil bath. The resulting mixture was cooled, poured into water, and extracted with petroleum ether. The combined extract was dried over MgSO<sub>4</sub> and evaporated. Flash column chromatography on silica gel (6 g, eluent with petroleum ether/ethyl acetate 10:1) provided hydroxy alkene **17** (23.4 mg, 85%) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.91 (s, 3H), 0.96 (s, 3H), 1.07 (s, 3H), 1.22 (dd, *J* = 8.4 and 12.3 Hz, 1H), 1.25 (s, 1H), 1.39 (ddd, *J* = 2.0, 7.8, and 12.0 Hz, 1H), 1.50 (dd, *J* = 5.3 and 8.4 Hz, 1H), 1.54–1.61 (m, 1H), 1.63–1.71 (m, 2H), 1.89 (ddd, *J* = 5.2, 8.8, and 12.8 Hz, 1H), 1.99 (dd, *J* = 9.2 and 13.7 Hz, 1H), 2.30–2.65 (m, 4H), 4.81 (m, 2H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 18.0, 27.2, 29.0, 29.5, 35.9, 40.0, 41.4, 42.7, 45.0, 49.1, 53.4, 55.5, 92.3, 105.2, 161.1. MS (EI, 70 eV): *m/z* 220 (M<sup>+</sup>, 18), 205 (11), 187 (6.0), 177 (12), 151 (12), 124 (10), 111 (100). IR (neat): *ν* 2950, 2864, 1650, 1463, 1365, 1069 cm<sup>-1</sup>. HRMS Calcd. for C<sub>15</sub>H<sub>24</sub>O: 220.1827. Found: 220.1827.

**cis-anti-cis-8,10-Dihydroxy-11-methylene-1,4,4-trimethyltricyclo-[6.3.0.0<sup>2,6</sup>]undecane (24).** To a stirred solution of hydroxy alkene **17** (38.3 mg, 0.174 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was sequentially added SeO<sub>2</sub> (13.0 mg, 0.117 mmol) and <sup>t</sup>BuOOH (65% aqueous solution, 70 mg, 0.50 mmol). The resulting solution was stirred at room temperature for 2 h and TLC indicated the reaction was complete. The reaction mixture was poured into water, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub>, and concentrated. Flash column chromatography on silica gel (5 g, eluted with petroleum ether/ethyl acetate 6:1 to 3:1) afforded diol **24** (34.2 mg, 83%) as a colorless oil and hydroxy enone **25** (6.3 mg, 16%) as a white solid. Spectroscopic data for **24**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.88 (s, 3H), 1.07 (s, 3H), 1.09 (s, 3H), 1.11–1.16 (m, 1H), 1.26 (s, 2H), 1.36–1.51 (m, 3H), 1.62–1.70 (m, 1H), 1.86 (dd, *J* = 2.5 and 14.0 Hz, 1H), 2.02–2.09 (m, 1H), 2.11 (dd, *J* = 5.4 and 14.0 Hz, 1H), 2.32–2.44 (m, 2H), 4.55 (br s, 1H), 4.98 (d, *J* = 1.0 Hz, 1H), 5.18 (d, *J* = 1.0 Hz, 1H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 19.3, 27.5, 29.6, 29.7, 39.2, 41.7, 41.9, 43.6, 45.0, 48.5, 54.7, 75.7, 92.2, 108.9, 165.8. MS (EI, 70 eV): *m/z* 236 (M<sup>+</sup>, 4.0), 218 (10), 203 (11), 179 (22), 166 (28), 126 (74), 122 (53), 109 (66), 95 (42). IR (neat): *ν* 3383, 2950, 2935, 2864, 1465, 1284, 1115, 1070 cm<sup>-1</sup>. HRMS Calcd. for C<sub>15</sub>H<sub>24</sub>O<sub>2</sub>: 236.1776. Found: 236.1784. Spectroscopic data for **25**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 0.92 (s, 3H), 1.09 (s, 3H), 1.14 (s, 3H), 1.23–1.29 (m, 3H), 1.45–1.52 (m, 1H), 1.58–1.77 (m, 3H), 1.98 (dd, *J* = 8.9 and 14.0 Hz, 1H), 2.46 (d, *J* = 18.1 Hz, 1H), 2.52–

2.65 (m, 1H), 2.61 (d, *J* = 18.1 Hz, 1H), 5.22 (s, 1H), 6.03 (s, 1H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 17.6, 26.5, 29.1, 39.9, 41.9, 42.8, 44.9, 49.1, 49.3, 52.8, 54.6, 87.0, 116.9, 155.4, 204.5. MS (EI, 70 eV): *m/z* 234 (M<sup>+</sup>, 14), 216 (6.0), 201 (6.0), 192 (7.0), 177 (6.0), 149 (5.0), 124 (100). IR (neat): *ν* 2952, 2935, 2866, 1726, 1635, 1465, 1384, 1267, 1116 cm<sup>-1</sup>. HRMS calcd. for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>: 234.1620. Found: 234.1620.

**11-Methylene-1,4,4-trimethyltricyclo[6.3.0.0<sup>2,6</sup>]undec-8-en-10-one (26).** To a stirred solution of oxalyl chloride (132 mg, 1.04 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at –78 °C was added a solution of DMSO (152 mg, 1.95 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) dropwise. The solution was stirred at –78 °C for 30 min and a solution of diol **24** (21.2 mg, 90 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added. After stirred at –78 °C for 30 min, the reaction mixture was allowed to warm to –30 °C and further stirred for 1.5 h. The reaction was recooled to –78 °C and neat Et<sub>3</sub>N (253 mg, 2.50 mmol) was added. The solution was stirred for 2 h and allowed to warm to room temperature. The reaction mixture was washed with aqueous HCl (2 M) and saturated NaHCO<sub>3</sub> and dried over MgSO<sub>4</sub>. Evaporation of the solvent gave the crude product as a brown oil. Flash column chromatography on silica gel (5 g, eluted with petroleum ether/ethyl acetate 20:1 to 3:1) afforded dienone **26** (10.1 mg, 52%) as a pale-yellow oil, and hydroxy enone **25** (5.4 mg, 26%) as a white solid. Spectroscopic data for **26**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.95 (s, 3H), 1.13 (s, 3H), 1.16 (s, 3H), 1.22–1.29 (m, 1H), 1.57 (d, *J* = 9.0 Hz, 2H), 1.81 (dd, *J* = 6.5 and 12.3 Hz, 1H), 2.24–2.34 (m, 1H), 2.36–2.46 (m, 1H), 2.71–2.84 (m, 2H), 5.15 (s, 1H), 5.88 (s, 1H), 5.89 (d, *J* = 1.4 Hz, 1H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 23.5, 27.4, 29.0, 32.6, 40.2, 44.1, 44.9, 48.1, 49.6, 51.7, 112.9, 123.1, 154.2, 189.9, 197.8. The spectroscopic data is identical to that reported.<sup>13b</sup>

**Dehydration of β-Hydroxyl ketone 25 to Form Dienone 26.** To a solution of hydroxy enone **25** (4.3 mg, 0.018 mmol) in benzene (2 mL) was added a small piece of iodine (2.9 mg, 0.012 mmol). The resulting solution was heated to reflux under stirring for 4 h and allowed to cool to room temperature. The reaction mixture was washed with aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution to remove iodine. The organic phase was dried over MgSO<sub>4</sub> and evaporated to give the crude product as a brown oil. Flash column chromatography on silica gel (2 g, eluted with petroleum ether/ethyl acetate 20:1 to 10:1) afforded dienone **26** (3.3 mg, 83%) as a colorless oil.

**(±)-1-Desoxyhypnophilin (2).**<sup>13b</sup> To a stirred solution of dienone **26** (10.5 mg, 0.0486 mmol) in THF (1.4 mL) and water (1.4 mL) at 0 °C was sequentially added NaHCO<sub>3</sub> (69 mg, 0.82 mmol) and H<sub>2</sub>O<sub>2</sub> (30% aqueous solution, 0.14 mL, 1.2 mmol) and the reaction mixture was stirred at 0 °C for 5 h. The reaction mixture was extracted with ether and the combined extract was dried over MgSO<sub>4</sub>. Evaporation of the solvent gave the crude product as a colorless oil. Flash column chromatography on silica gel (5 g, eluted with petroleum ether/ethyl acetate 20:1 to 10:1) afforded (±)-1-desoxyhypnophilin (8.2 mg, 73%) as a colorless oil, together with the recovered dienone **26** (2.4 mg, 23%). Spectroscopic data for 1-desoxyhypnophilin: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.92 (s, 3H), 1.12 (s, 3H), 1.16 (s, 3H), 1.17–1.26 (m, 1H), 1.48–1.56 (m, 2H), 1.80 (ddd, *J* = 1.4, 7.6, and 12.3 Hz, 1H), 1.99 (d, *J* = 8.7 Hz, 2H), 2.39 (dt, *J* = 11.5 and 9.2 Hz, 1H), 2.73 (tq, *J* = 8.6 and 11.1 Hz, 1H), 3.44 (s, 1H), 5.27 (s, 1H), 6.05 (s, 1H). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 17.5, 27.2, 28.9, 30.0, 39.1, 40.0, 42.5, 46.5, 49.5, 49.8, 61.0, 120.0, 153.2, 198.1. The spectroscopic data is identical to that reported.<sup>13b</sup>

## Conclusion

In summary, a tandem reaction involving a Rh(I)-catalyzed two-component [(5+2)+1] cycloaddition and an aldol condensation has been realized and successfully applied to the syntheses of (±)-hirsutene and (±)-1-desoxyhypnophilin. The present strategy enables a concise and step economical route to natural linear triquinanes, whereby their core structure is diastereo-

selectively established in a single step with correct placement of all stereocenters, including two quaternary centers. This first application of the Rh(I)-catalyzed [(5+2)+1] cycloaddition in natural product synthesis highlights the efficiency of this methodology for constructing complex fused ring systems. Further applications of the two-component [(5+2)+1] cycloaddition and the present tandem reaction are actively pursued in our group.

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**Supporting Information Available:** Experimental procedures, spectroscopic data, and NMR spectra for synthetic intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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