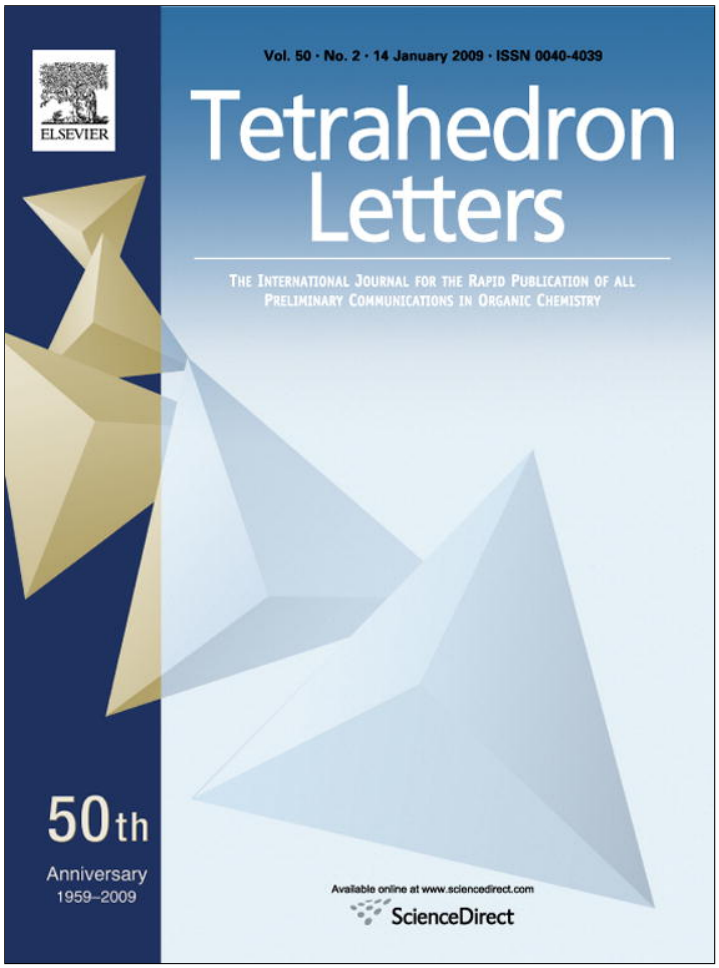

Tetrahedron Letters 50 (2009) 155–157

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An expeditious and high-yield formal synthesis of hirsutene using Rh(I)-catalyzed [(5+2)+1] cycloaddition

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ARTICLE INFO

Article history:
Received 18 July 2008
Revised 25 September 2008
Accepted 7 October 2008
Available online 11 October 2008

ABSTRACT

An expeditious and high-yield formal synthesis of hirsutene has been achieved. This synthesis features Rh(I)-catalyzed [(5+2)+1] cycloaddition to construct a bicyclic cyclooctenone, which can be efficiently transformed to bicyclic diketone, an advanced intermediate for racemic and asymmetric syntheses of hirsutene.

Due to their promising biological and medicinal activities together with their unique three-consecutive fused cyclopentane architecture, linear triquinane natural products (Fig. 1), isolated from plants, microbes, and marine organisms, have been attracting the attention of synthetic chemists as targets for total syntheses. Many elegant syntheses of linear triquinane natural products have been disclosed since the first report of this family of natural products.[1–6]

Recently, a very efficient tandem Rh(I)-catalyzed [(5+2)+1]/aldol cycloaddition process was developed by us to construct the triquinane skeleton and its analogs.[7] We successfully applied this tandem strategy in the total syntheses of (±)-hirsutene and (±)1-desoxyhypnophilin with high step economy. We were very interested in developing an asymmetric version of this tandem reaction to achieve asymmetric total syntheses of linear triquinane natural products. One obvious strategy to accomplish this is to develop an asymmetric Rh(I)-catalyzed [(5+2)+1] reaction that can control the stereochemistry of the bridgehead carbons of the bicyclic cyclooctenone (Strategy A, Scheme 1). Once these two chiral centers are established, the subsequent aldol condensation will give the correct stereochemistry of the other two bridgehead carbon centers in the triquinane architecture. Strategy A, if it can be realized, could provide a general approach for asymmetric synthesis of triquinane skeleton with various substitutents.

Strategy A uses the in situ [(5+2)+1]-generated enol ether in the subsequent aldol condensation to give a triquinane structure in one-pot. This tandem process can be changed to a stepwise one, strategy B (Scheme 1). Strategy B starts from a [(5+2)+1] reaction to give a bicyclic cyclooctenone, which, via traditional organic transformations, could be converted to a diketone. An aldol reaction can be applied to convert the diketone to the triquinane backbone. This stepwise strategy is expected to be efficient for the symmetric diketone (R^1 = H) since the unsymmetric case will have some regiochemistry problems with the aldol reaction. However, the most appealing point in strategy B is that, when a chiral catalyst is used, the symmetric diketone could be desymmetrized[8] to achieve asymmetric aldol condensation[9], leading to asymmetric synthesis of triquinane (Scheme 1).

Very recently, List and Chandler disclosed a catalytic, asymmetric transannular aldolization of cyclic diketone to synthesize bi- and tri-cyclic products.[10] They also applied this methodology to fulfill the total synthesis of (+)-hirsutene in 12 steps with an overall yield of 6% (Scheme 2). The key step in List's approach is an asymmetric aldol condensation to desymmetrize diketone **7**,

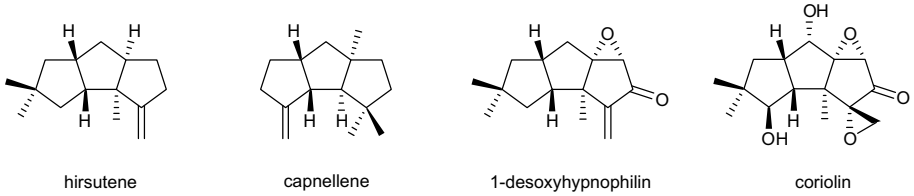

Figure 1. Selected triquinane natural products.

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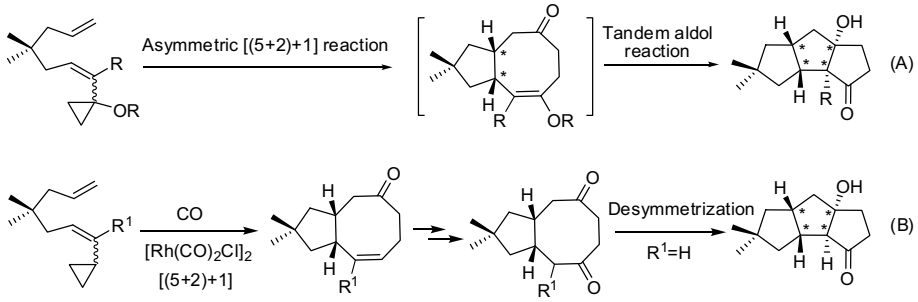
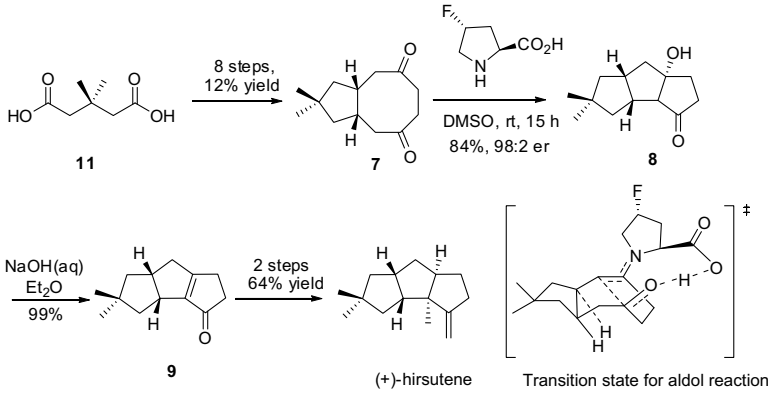
doi:10.1016/j.tetlet.2008.10.023



Scheme 1. Strategies applying [(5+2)+1] chemistry for synthesis of asymmetric linear triquinane skeleton.



Scheme 2. List's asymmetric synthesis of (+)-hirsutene.

where an organocatalyst, *trans*-4-fluoro proline was used. List's route represents the shortest asymmetric total synthesis of (+)-hirsutene to date. Here, we wish to report our formal synthesis of hirsutene (Scheme 3) using strategy B. This synthesis features our Rh-catalyzed [(5+2)+1] cycloaddition to efficiently reach the diketone intermediate **7**, an advanced intermediate for both racemic and asymmetric formal syntheses of hirsutene.

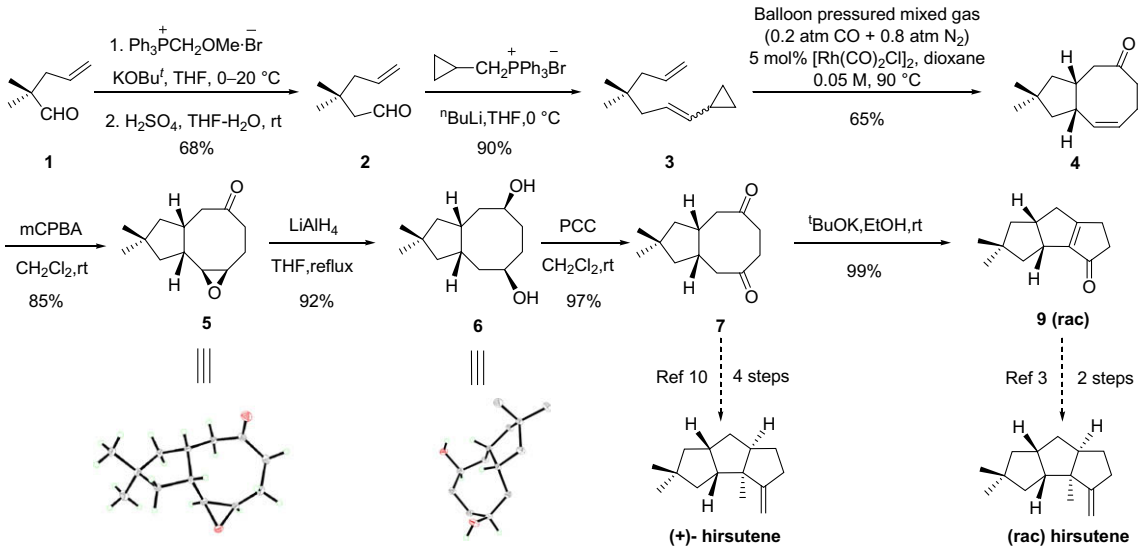
Our formal synthesis started from the preparation of the ene-vinylcyclopropane (Ene-VCP) substrate **3** for the [(5+2)+1] cycloaddition. Commercially available aldehyde **1** was converted to its homolog aldehyde **2** by Wittig reaction and hydration in one-pot with a reaction yield of 68%. Aldehyde **2** was then subjected to Wittig reaction to give the Ene-VCP **3** in 90% yield (the cis/trans ratio is 2:1). Applying the optimal Rh(I)-catalyzed [(5+2)+1] cycloaddition[7b] (0.2 atm CO+0.8 atm N_2, 5 mol% $[Rh(CO)_2Cl]_2$ as catalyst, dioxane as solvent, 90 °C), the bicyclic cyclooctenone **4** could be obtained from **3** and CO as a single cis-diastereomer with a reaction yield of 65%. The high stereoselectivity in the [(5+2)+1] cycloaddition is consistent with our previous observations.[7]

Epoxidation with mCPBA in dichloromethane converted **4** to its corresponding epoxide **5** in 85% yield. Epoxide **5** is a white solid at room temperature. Reducing the epoxide and the ketone functional groups in **5** by $LiAlH_4$ in refluxing THF gave diol **6** in high yield also as a white solid at room temperature. No regioisomer of the reduction of the epoxide was found. The stereochemistry of **5** and **6** was determined by X-ray diffraction (Scheme 3). PCC oxidation transformed **6** to diketone **7** with a reaction yield of 97%. The reduction and PCC oxidation steps could also be conducted consecutively without separation of the intermediate to give the target diketone **7** in 90% yield.

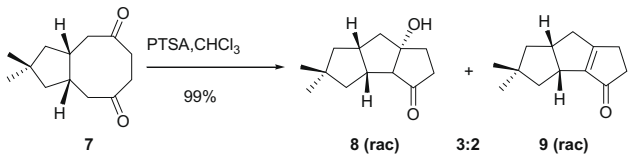
Diketone **7** was then subjected to $KOBu^t$ base-catalyzed aldol condensation. This operation gave tricyclic enone **9** quantitatively, which was assumed to be formed through consecutive aldol condensation (to give **8**) and dehydration (**8** to **9**). Under acidic reaction conditions, both **8** and **9** could be obtained (Scheme 4). Enone **9** can then be converted to hirsutene using Iyoda's route in 2 steps.[3] Therefore, our synthesis of **9** from commercially available aldehyde **1** represents a facile and formal synthesis of hirsutene in a racemic fashion. Syntheses from **1** to **9** require 7 steps with an overall yield of 30%, demonstrating the efficiency of the present strategy.[11] If we consider that both processes of **1** to **2** and of **5** to **9** can be conducted consecutively in one-pot without separation of the intermediates, the present strategy becomes more concise, further manifesting its high efficiency and step economy.[12]

In List's asymmetric version of hirsutene synthesis, the key step was the aldol condensation catalyzed by *trans*-4-fluoro proline to give asymmetric tricyclic intermediate **8** in 84% yield with an enantiomer ratio of 98:2 (Scheme 2).[10] Dehydration of asymmetric **8** by aqueous NaOH in ether quantitatively led to the formation of optically active **9**, which was then converted to the (+)-hirsutene using Iyoda strategy.[3] Due to the efficiency and step economy of the synthesis of diketone **7**, our formal synthesis can be easily transformed to an asymmetric formal synthesis if the aldol condensation uses List's organocatalysis strategy.

In summary, we have achieved an expeditious and high-yielding formal synthesis of hirsutene, featuring the application of our Rh(I)-catalyzed [(5+2)+1] chemistry as an efficient and powerful method to synthesize bicyclic diketones. This route can be transformed to a formal asymmetric synthesis if List's fluoro-substituted proline-catalyzed aldol condensation of the diketone is used. Using Rh(I)-catalyzed [(5+2)+1] chemistry to prepare other more complicated natural products is underway in our group.



Scheme 3. Formal synthesis of Hirsutene.



Scheme 4. Acid-catalyzed intramolecular aldol condensation.

Acknowledgments

We thank Peking University, the National Natural Science Foundation of China (20825205-National Science Fund for Distinguished Young Scholars, 20521202, and 20672005), and the Ministry of Education of China for financial support. We thank Dr. Andrew A. Leach of AstraZeneca for help in English.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.023.

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