Tetrahedron Letters 51 (2010) 5674–5676

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Formal total synthesis of (±)-hirsutic acid C using the tandem Rh(I)-catalyzed [(5+2)+1] cycloaddition/aldol reaction

Changxia Yuan, Lei Jiao, Zhi-Xiang Yu *

Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering, College of Chemistry, Peking University, Beijing 100871, China

ARTICLE INFO

Article history:
Received 15 June 2010
Revised 6 August 2010
Accepted 10 August 2010
Available online 14 August 2010

ABSTRACT

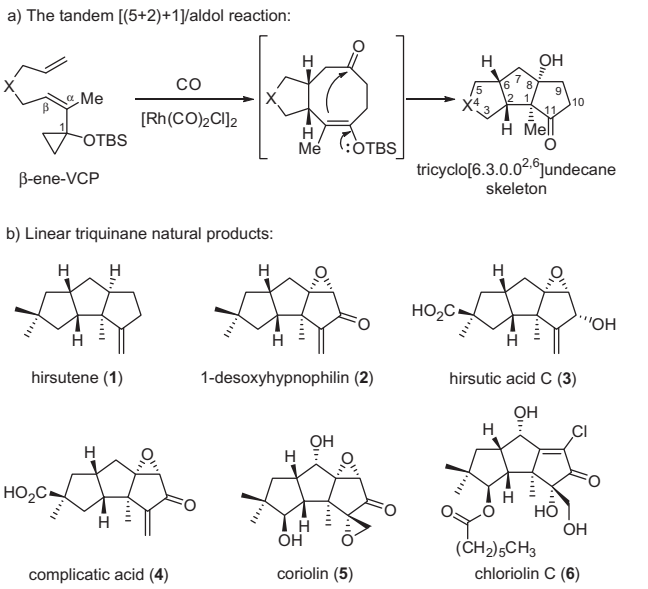
A concise formal total synthesis of the linear triquinane natural product (±)-hirsutic acid C has been achieved. This synthesis features a tandem Rh(I)-catalyzed [(5+2)+1] cycloaddition/aldol reaction as the key step to build the triquinane skeleton.

Utilization of transition-metal-catalyzed cycloaddition reactions in constructing polycyclic structures is strategically attractive due to their high efficiency and stereoselectivity.[1] To date, myriads of transition-metal-catalyzed cycloadditions shine their vantage points in complex molecule synthesis.[2] We are also very interested in developing new and efficient cycloaddition reactions for constructing polycyclic structures in high efficiency and step-economy.[3–5] One of these cycloadditions developed in our group is the Rh(I)-catalyzed [(5+2)+1] reaction that has great potential in the total synthesis of natural products containing eight-membered carbocycles or triquinane skeletons.[3,6,7] A tandem [(5+2)+1] cycloaddition/aldol reaction strategy has been found to be very efficient for the construction of tricyclo[6.3.0.0^{2,6}]undecane skeleton and this strategy has been successfully applied to the syntheses of two linear triquinane natural products, (±)-hirsutene and (±)-1-desoxyhypnophilin (Scheme 1).[6]

To further explore the synthetic utility of the tandem [(5+2)+1]/aldol reaction, another linear triquinane natural product, hirsutic acid C (**3**), was selected as our target molecule. This sesquiterpenoid natural product was isolated from *Stereum hirsutum* in 1947,[8] and a number of total syntheses have been reported since 1974.[9] In the previous total syntheses, the assembly of the multisubstituted linear triquinane core was achieved in several separate steps, thus leading to low efficiencies for the entire synthetic routes. We hope to construct this structure in a more efficient fashion by utilizing our tandem [(5+2)+1]/aldol reaction, and expect that such strategy will render a concise total synthesis of hirsutic acid C.

Compared with other members of the linear triquinane family, hirsutic acid C possesses a carboxylic acid-substituted quaternary stereocenter at the C4 position, rather than a *gem*-dimethyl-substituted carbon. Thus, we had to rely on a diastereoselective tandem [(5+2)+1]/aldol reaction to synthesize the tricyclic core structure using the cycloaddition precursor with a preexisted chiral center. In this reaction, we also wanted to explore the diastereoselectivity of the stereochemical induction process, which was not investigated in our previous studies. This test, if it was successful, would be worthy to guide further application of this strategy in total synthesis.

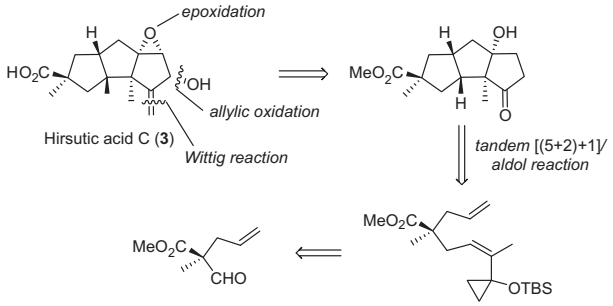
Our retrosynthetic analysis for hirsutic acid C is depicted in Scheme 2. It was envisioned that hirsutic acid C could be synthesized from the key tricyclic hydroxyketone in several conventional steps (Wittig reaction, allylic oxidation, dehydration, epoxidation,



Scheme 1. Tandem [(5+2)+1]/aldol reaction and some linear triquinane natural products.

* Corresponding author. Tel.: +86 10 6276 7735; fax: +86 6275 1708.
E-mail address: yuzx@pku.edu.cn (Z.-X. Yu).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.08.028

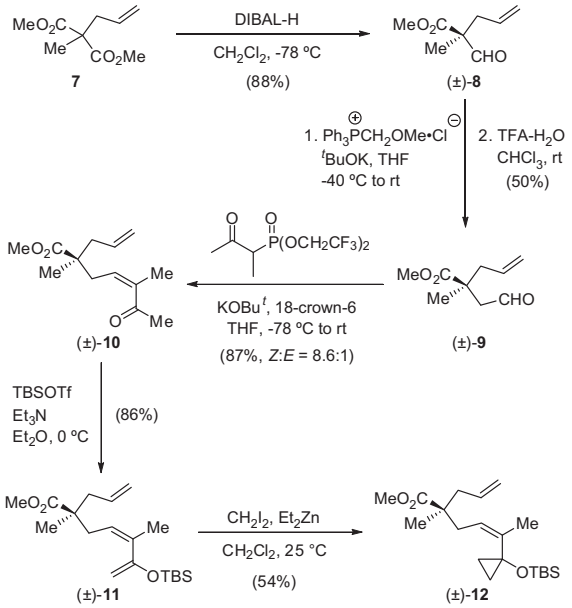


Scheme 2. Retrosynthesis plot of complicatic acid and hirsutic acid C.

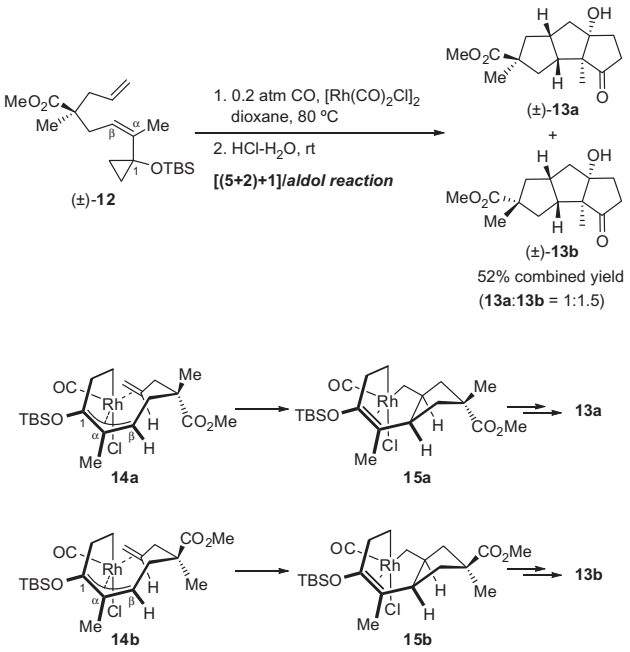
and reduction). The core architecture of tricyclic hydroxyketone could be addressed by Rh(I)-catalyzed [(5+2)+1]/aldol reaction of (*Z*)-1-siloxy-β-ene-vinylcyclopropane substrate previously developed in our laboratory.[3,6] The major challenge here is whether or not high diastereoselectivity could be achieved in this process.

We started the synthesis by preparing the β-ene-vinylcyclopropane substrate for the tandem [(5+2)+1]/aldol reaction (Scheme 3). The starting material, diester **7**, was converted into aldehyde **8** by DIBAL-H reduction under low temperature**.** Treatment of aldehyde **8** with methoxymethylenetriphenylphosphorane in THF and subsequent hydration of the formed enol ether under TFA–H_2O–$CHCl_3$ condition produced the homologated aldehyde **9** in 50% yield. The HWE reaction of aldehyde **9** under Still-Jin-modified conditions[10] afforded (*Z*)-α,β-unsaturated ketone **10** as the major isomer in excellent yield. Treatment of (*Z*)-enone **10** with TBSOTf and Et_3N in dry ether produced silylenol ether **11** in a good yield. Through Simmons-Smith cyclopropanation, silylenol ether **11** was converted into β-ene-VCP **12** in a moderate yield, but unfortunately, a minor amount of inseparable biscyclopropane byproduct was also generated.

With β-ene-VCP substrate **12** in hand, we began to explore the key tandem [(5+2)+1]/aldol reaction (Scheme 4). Exposure of β-ene-VCP **12** to the standard [(5+2)+1] cycloaddition conditions led to a smooth reaction, however, we found that two inseparable cycloadducts, **13a** and **13b**, were generated in a ratio of 1:1.5 in 52% combined yield (Scheme 4). This indicated that the cycloaddition reaction proceeded in a poor diastereoselectivity, and the desired product **13a** was the minor diastereomer.



Scheme 3. Synthesis of β-ene-VCP substrate **12**.

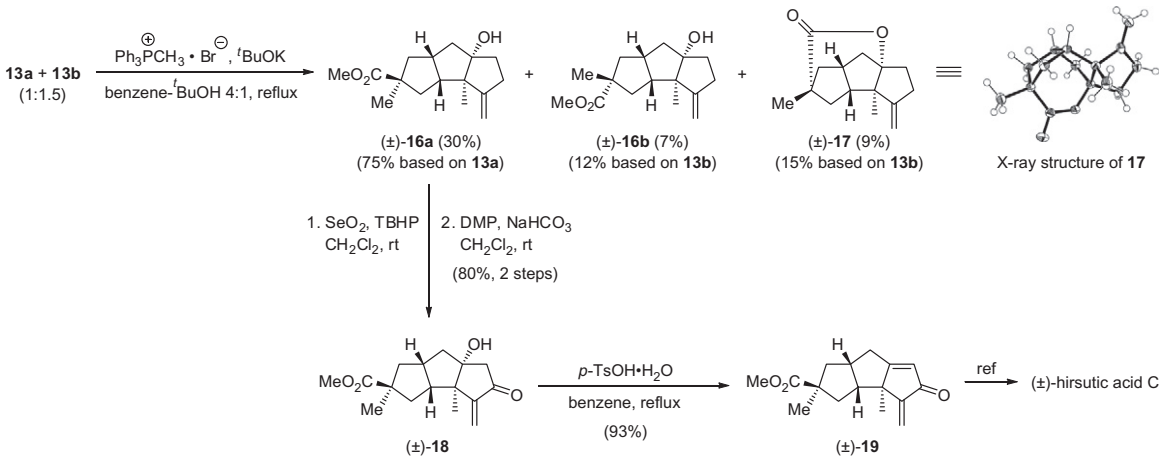


Scheme 4. The key tandem Rh(I)-catalyzed [(5+2)+1]/aldol reaction.

Considering the stereochemical process of the tandem reaction, we can understand the origin of the observed low diastereoselectivity (Scheme 4). The stereochemistry-determining step of the tandem reaction is the insertion of the alkene functionality to Cβ-Rh bond (**14a** to **15a** and **14b** to **15b**, respectively). In this step, if the methyl group occupies the pseudoequatorial position and the ester group occupies the pseudoaxial position, the desired diastereomer **13a** would be generated. However, the ester group and the methyl group have similar steric bulkiness, suggesting that the two diastereomeric alkene insertion transition states require similar activation energies and the two diastereomers **13a** and **13b** were generated in similar amounts. The diastereoselectivity could not be improved even though a bulky ester group on the tether was used (see the note in Ref. 11 for details). This indicated that, in the Rh(I)-catalyzed [(5+2)+1] cycloaddition, a quaternary stereocenter on the tether was not able to render a good stereocontrol. Although the diastereoselectivity was not satisfactory, this tandem reaction provides a rapid access to the core structure of the natural product. Thus, we decided to finish the synthesis of hirsutic acid C using the tricyclic cycloadduct **13a**.

The mixture of **13a** and **13b** was subjected to Wittig reaction conditions to achieve ketone olefination (Scheme 5). Interestingly, three products were obtained in this reaction, including the desired tricyclic enol **16a** (30%), the undesired **16b** (7%), and a cage-shaped tetracyclic lactone **17** (9%, confirmed by X-ray single-crystal diffraction analysis). This indicates that, the Wittig reaction of tricyclic ketone **13a** proceeded normally to afford the desired tricyclic enol **16a**. The Wittig reaction of tricyclic ketone **13b** produced the undesired tricyclic enol **16b**, which was further transformed into tetracyclic lactone **17** by intramolecular nucleophilic attack of the hydroxyl group to the ester group under basic conditions. Thus, the yield of the desired tricyclic enol **16a** was 75% based on the tricyclic ketone **13a**.

To complete the synthesis of hirsutic acid C, tricyclic enol **16a** was treated with SeO_2–TBHP and then Dess–Martin periodinane to produce the allylic oxidation product, hydroxy enone **18**, in a good yield. Then, hydroxy enone **18** was smoothly transformed into dienone **19** by acid-catalyzed dehydration in refluxing benzene (Scheme 5). Tricyclic dienone **19** gave identical ^1H and ^{13}C



Scheme 5. Completion of the synthesis. TBHP = *tert*-butyl hydroperoxide, DMP = Dess–Martin periodinane.

NMR spectra to those reported in the literature.[9k] Since this compound was an advanced intermediate in the synthesis of hirsutic acid C by Schuda,[9f] Ikegami,[9g] and Banwell,[9k] our present work here represents a formal total synthesis of (±)-hirsutic acid C.

In summary, a formal total synthesis of the linear triquinane natural product hirsutic acid C has been completed by a concise approach, where the known diester **7** was converted into the advanced tricyclic dienone intermediate **19** in 10 steps. To our knowledge, our work represents the shortest route toward this advanced intermediate in the total synthesis of hirsutic acid C.[9] Although the diastereoselectivity and efficiency of the crucial tandem [(5+2)+1]/aldol reaction is not satisfactory, the present work provides further information on the stereochemical control of the [(5+2)+1] reaction and highlights the compelling power of the Rh(I)-catalyzed [(5+2)+1] reaction in natural product synthesis.

Acknowledgments

We thank the Natural Science Foundation of China (20825205-National Science Fund for Distinguished Young Scholars, and 20672005), and the National Basic Research Program of China-973 Program (2010CB833203) for the financial support. We are also grateful to Mr. Feng Li and Mr. Yanlong Jiang who repeated the synthesis shown in Ref. 11.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.028.

References and notes

1. (a) Lauters, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49; (b) Yu, Z.-X.; Wang, Y.; Wang, Y. *Chem. Asian J.* **2010**, *5*, 1072.
2. Selected publications for transitional metal-catalyzed reactions to construct complex molecules: (a) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105; (b) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948; (c) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352; (d) Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781; (e) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2007**, *129*, 14456; (f) Woodin, K. S.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 7451; (g) Chrovian, C. C.; Knapp-Reed, K.; Montgomery, J. *Org. Lett.* **2008**, *10*, 811; (h) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424.
3. For Rh(I)-catalyzed [(5+2)+1] cycloaddition, see: (a) 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; (b) Huang, F.; Yao, Z.-K.; Wang, Y.; Wang, Y.; Zhang, J.; Yu, Z.-X. *Chem. Asian J.* **2010**, *5*, 1555; For the first report of the Rh(I)-catalyzed [5+2+1] reaction, see: (c) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876.
4. For Rh(I)-catalyzed [3+2] cycloadditions, see: (a) Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 7178; (b) Jiao, L.; Lin, M.; Yu, Z.-X. *Chem. Commun.* **2010**, *46*, 1059; (c) Li, Q.; Jiang, G.-J.; Jiao, L.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 1332.
5. For the Rh(I)-catalyzed [(3+2)+1] cycloaddition, see: (a) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528; For the first report of the Rh(I)-catalyzed [(3+2)+1] reaction, see: (b) Koga, Y.; Narasaka, K. *Chem. Lett.* **1999**, *7*, 705; For a recent report of [(3+2)+1] cycloaddition by Wang, see: (c) Li, C.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 3082.
6. Jiao, L.; Yuan, C.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 4421.
7. (a) Fan, X.; Tang, M.-X.; Zhuo, L.-G.; Tu, Y. Q.; Yu, Z.-X. *Tetrahedron Lett.* **2009**, *50*, 155; (b) Fan, X.; Zhuo, L.-G.; Tu, Y. Q.; Yu, Z.-X. *Tetrahedron* **2009**, *65*, 4709.
8. Heatley, N. G.; Jennings, M. A.; Florey, H. W. *Br. J. Exp. Pathol.* **1947**, *28*, 35.
9. Related total syntheses of complicatic acid and hirsutic acid C: (a) Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1974**, *15*, 3745; (b) Trost, B. M.; Shuey, C. D.; Dininno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284; (c) Shibasaki, M.; Yamazaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1982**, *23*, 5311; (d) Greene, A. E.; Luche, M. J.; Depres, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 2435; (e) Greene, A. E.; Luche, M. J.; Serra, A. A. *J. Org. Chem.* **1985**, *50*, 3957; (f) Schuda, P. F.; Phillips, J. L.; Morgan, T. M. *J. Org. Chem.* **1986**, *51*, 2742; (g) Nishida, M.; Iseki, K.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1990**, *38*, 3230; (h) Singh, V.; Tosh, D. K.; Mobin, S. M. *Tetrahedron Lett.* **2004**, *45*, 1729; (i) Austin, K. A. B.; Banwell, M. G.; Harfoot, G. J.; Willis, A. C. *Tetrahedron Lett.* **2006**, *47*, 7381; (j) Singh, V.; Pal, S.; Tosh, D. K.; Mobin, S. M. *Tetrahedron* **2007**, *63*, 2446; (k) Banwell, M. G.; Austin, K. A. B.; Willis, A. C. *Tetrahedron* **2007**, *63*, 6388.
10. Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* **1999**, *40*, 6725.
11. We have prepared a β-ene-VCP substrate **12′** with a bulky isopropyl ester group, hoping to achieve better stereocontrol. However, unfortunately, the diastereoselectivity of its tandem [(5+2)+1]/aldol reaction was not improved (see Supplementary data for details).