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Enantioselective Biomimetic Total Syntheses of Katsumadain and Katsumadain C

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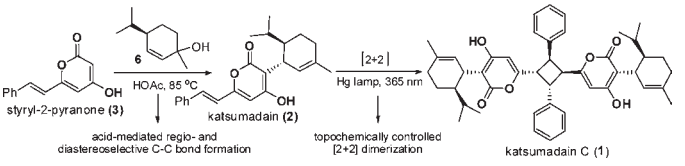
ABSTRACT



Enantioselective total syntheses of katsumadain and katsumadain C were achieved concisely through a biomimetic approach. Assembly of styryl-2-pyranone (3) and monoterpene 6 via acid-promoted regio- and stereoselective C−C bond formation afforded katsumadain (2), which underwent the photoinduced [2 + 2] dimerization in a head-to-tail mode to furnish katsumadain C (1).

Naturally occurring 2-pyranone derivatives constitute a large family of natural products that display diverse molecular architectures and a wide range of biological profiles, such as antitumor, antimicrobial, and anti-HIV activities.[1] Recently, katsumadain C (**1**, Figure 1) was isolated from the plants of *Alpinia katsumadai* by Kong and co-workers.[2] Preliminary biological evaluations showed that katsumadain C displayed significant growth inhibitory effects against SMMC-772 cells with IC_{50} at 4.8 μM and exhibited moderate antitumor activity against several other human tumor cell lines.

From the structural point of view, katsumadain C represents the first monoterpene substituted kavalactone dimer conjugated in the head-to-tail mode. The proposed biosynthetic pathway[2] suggests katsumadain C is derived from katsumadain (**2**) through a [2 + 2] cycloaddition (Figure 1). Indeed, **2** was also isolated from the same natural resource by Wang and co-workers in 2010.[3] The structure and relative configurations of **1** were determined by spectroscopic evidence, while its absolute configuration remains uncertain.

As part of our continuous interests in the total synthesis of natural products with a unique molecular architecture, important biological activity, and intriguing biosynthetic pathway,[4] we initiated a program to develop a synthetic strategy that will allow accessing structural analogues in addition to a large quantity of natural products for further biological studies. Herein we report our progress that leads to the first enantioselective biomimetic total syntheses of katsumadain and katsumadain C in a highly efficient, regio- and diastereocontrolled manner.

The synthetic strategy coupled with a plausible biosynthetic pathway for katsumadain C (**1**) is depicted in Figure 1. According to Kong's hypothesis,[2] katsumadain

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(1) (a) McGlacken, G. P.; Fairlamb, I. J. S. *Nat. Prod. Rep.* **2005**, *22*, 369–385. (b) Atul, G.; Vishnu, J. R. *Tetrahedron* **2009**, *65*, 7865–7913.

(2) Yang, C. S.; Wang, X. B.; Wang, J. S; Luo, J. G.; Luo, L.; Kong, L. Y. *Org. Lett.* **2011**, *13*, 3380–3383.

(3) Li, Y. Y.; Chou, G.; X.; Wang, Z. T. *Helv. Chim. Acta* **2010**, *93*, 382–388.

(4) Zhang, Z. Y.; Chen, J. H.; Yang, Z.; Tang, Y. F. *Org. Lett.* **2010**, *12*, 5554–5557.

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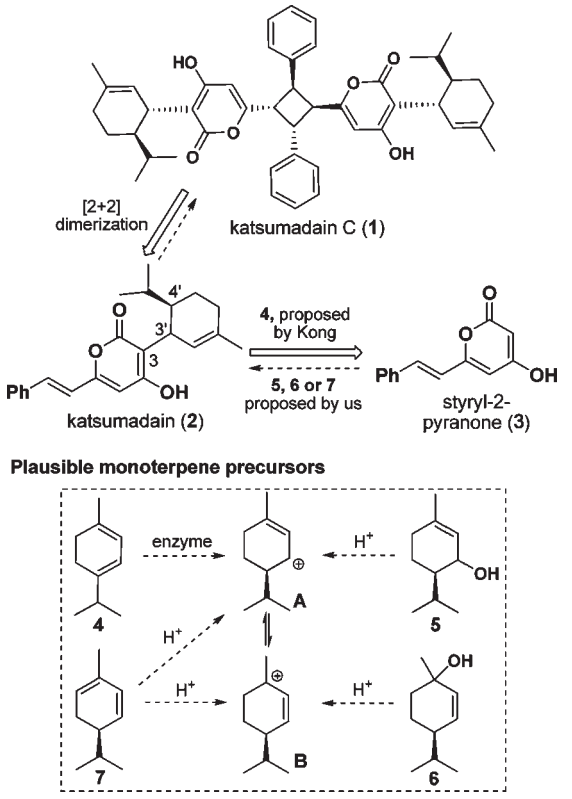


Figure 1. Proposed biosynthetic pathway for katsumadain C and bioinspired synthetic strategy.

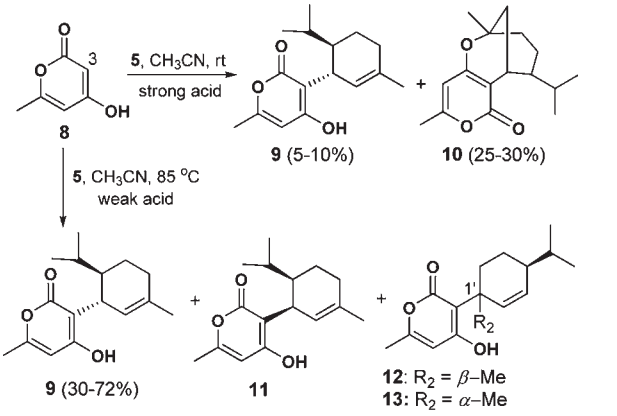
C is derived from katsumadain via a [2 + 2] dimerization. In turn, katsumadain could be generated from styryl-2-pyranone (**3**) and α-terpinene (**4**) via a C−C bond formation between C-3 and C-3′. In view of the fact that both **3** and **4** are achiral substrates, while katsumadain and kasumadain C were isolated as enatiopure compounds, the C−C bond formation should be an enzyme-catalyzed enantioselective process, which, though feasible in natural medium, would be rather challenging for synthetic chemists. Alternatively, we envision that some other easily accessible chiral monoterpenes, such as piperitol (**5**),[5] 2-menthen-1-ol (**6**),[6] or α-phellandrene (**7**), could also serve as the precursors for the biosynthesis of katsumadain. Within this context, the C−C bond formation between **3** and **5**, **6**, or **7** could proceed through S_N1 substitution via carbocation intermediate **A** under acidic conditions, with the stereochemical outcome controlled by the stereogenic centers at C-4′.

To validate our biosynthetic hypothesis and explore a feasible method for assembling the 2-pyranone and monoterpene fragments, a simple model study was conducted with commercially available triacetic acid lactone **8** and racemic allylic alcohol **5**[5b] as substrates. Notably, although

(5) For a leading review on synthesis of chiral monoterpenes, see: (a) Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Chem. Rev.* **2011**, *111*, 4036–4072. (b) Serra, S.; Brenna, E.; Fuganti, C.; Maggioni, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3313–3319.

(6) Kenji, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2133–2142.

Scheme 1. Acid-Promoted Assembly of Fragment **8** and **5**



the C-3 functionalization of **8** with an allylic alcohol acetate via Pd-catalyzed allylic substitution has been well documented,[7] the more direct acid-promoted S_N1 substitution with the allylic alcohol has rarely been investigated,[8] presumably due to the expected complicated regio- and diastereoselectivity issues. Thus, we performed a systematic condition screening on this transformation (for details, see Table-S1 of the Supporting Information). It was observed that when a strong Brønsted acid (2 N HCl or 2 N H_2SO_4) or Lewis acid ($TiCl_4$, BF_3•Et_2O, or TMSOTf) was employed with CH_3CN as solvent, only a trace amount of the desired product **9** (5−10% yield) was obtained (Scheme 1). Instead, compound **10**, possibly generated from **9** via an intramolecular etherification reaction, was isolated as the major product in 25−30% yield. We envisioned that the formation of **10** might be attributed to the relatively harsh acidic conditions, and therefore, some weak acids such as AcOH, HCOOH, PhCOOH, and CH_3CH_3COOH were examined in this transformation. Gratifyingly, it was found that in these cases **9** was isolated as the major product (30−55% yield) without formation of **10**. However, other byproducts **11**, **12**, and **13**, which are either the regio- or diastereoisomers of **9**, were isolated in substantial amounts (18−40% in combined yield). To further minimize the formation of byproducts, the solvent effect was then evaluated. Eventually, a satisfying result was obtained

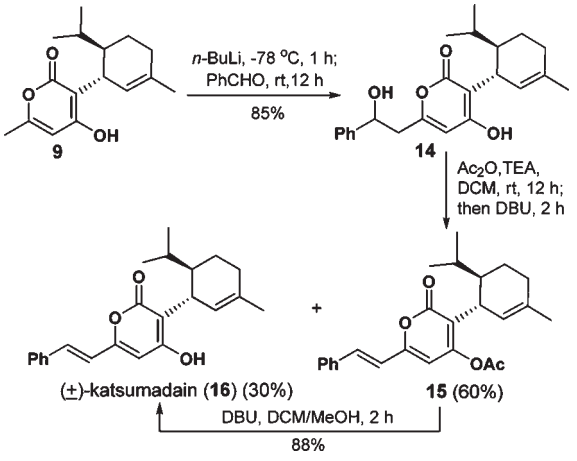
(7) (a) Moreno-Mañas, M.; Prat, M.; Ribas, J.; Virgili, A. *Tetrahedron Lett.* **1988**, *29*, 581–584. (b) Moreno-Mañas, M.; Ribas, J.; Virgili, A. *J. Org. Chem.* **1988**, *53*, 5323–5335. (c) Moreno-Mañas, M; Ribas, J. *Tetrahedron Lett.* **1989**, *30*, 3109–3112. (d) Prat, M.; Ribas, J.; Moreno-Mañas, M. *Tetrahedron* **1992**, *48*, 1695–1706.

(8) To the best of our knowledge, there is no study on C-3 functionalization of **8** with the allylic alcohol reported. The transformations using benzylic alcohol, propargylic alcohol, aldehyde, or styrene as resources for electrophiles are well documented; for selected examples, see: (a) Reddy, C. R; Srikanth, B.; Narsimha, R. N.; Shin, D. S. *Tetrahedron* **2008**, *64*, 11666–11672. (b) Huang, W.; Wang, J. L.; Shen, Q. S.; Zhou, X. G. *Tetrahedron* **2007**, *63*, 11636–11643. (c) Rueping, M.; Bootwicha, T.; Sugiono, E. *Adv. Synth. Catal.* **2010**, *352*, 2961–2965. (d) Hagiwara, H.; Kobayashi, K.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron* **2001**, *57*, 5039–5043. (e) Moreno-Mañas, M.; Papell, E.; Pleixats, R.; Ribas, J.; Virgili, A. *J. Heterocycl. Chem.* **1986**, *23*, 413–416.

by using AcOH as the promoter and a mixture of CH_3CN/H_2O (3:1) as the solvent, which provided **9** in 72% isolated yield, with only a trace amount of other byproducts observed.

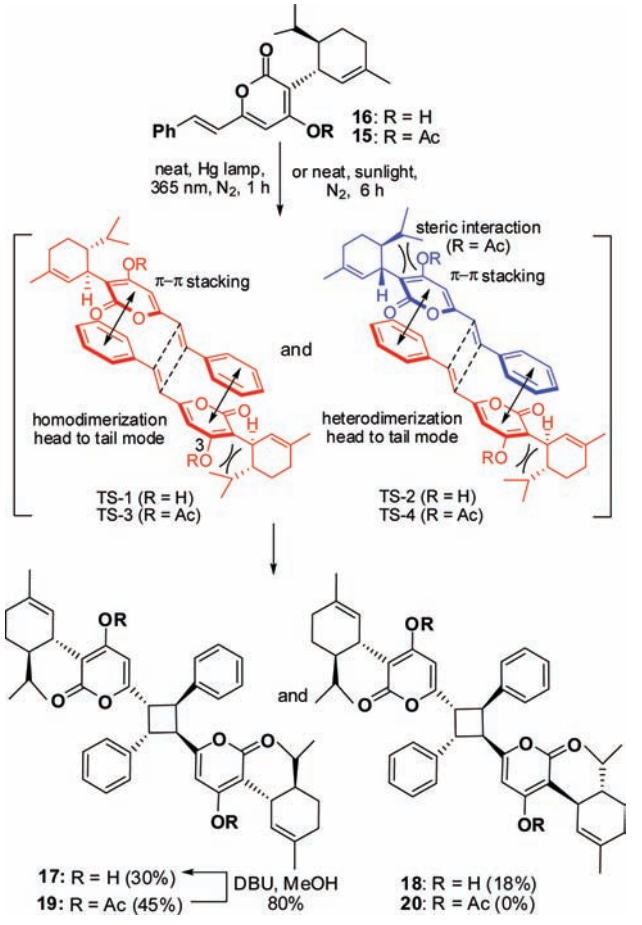
With the method for assembly of 2-pyranone and monoterpene fragments established, we next turned our attention to the synthesis of katsumadain. Thus, **9** was first treated with *n*-BuLi (2.5 equiv) at −78 °C to form the corresponding dianion intermediate which underwent nucleophilic addition to benzaldehyde to furnish **14** in 90% yield.[9] Upon treatment of **14** with Ac_2O/TEA followed by the addition of an excess amount of DBU,[10] **15** was generated in 60% yield, accompanied by the formation of a substantial amount of (±)-katsumadain (**16**) (30%). Removal of the acetyl group of **15** using DBU/CH_3OH led to (±)-katsumadain in 88% yield (Scheme 2). Notably, the transformations from **14** to **16** could be also operated in a one-pot manner, which resulted in a comparable overall yield (77%).

Scheme 2. Synthesis of (±)-Katsumadain



With (±)-katsumadain (**16**) in hand, various photochemical conditions involving different photoresources, solvents, and temperature were investigated to effect its [2 + 2] dimerization into (±)-katsumadain C. After extensive attempts, it was found that when **16** was irradiated with a mercury lamp (365 nm) in its solid state[11] in thin-film form under N_2 protection, the desired [2 + 2] dimerization proceeded smoothly to provide (±)-katsumadain C (**17**) in 30% yield. Interestingly, in addition to the recovery of 40% of starting material **16**, another product was isolated in 18% yield, whose structure was assigned as **18**. Apparently, (±)-katsumadain C (**17**) was generated from the homodimerization of one single enantiomer of **16** via transition state TS-1, while **18** was derived from the heterodimerization of two different enantiomers via transition state TS-2. In both cases the [2 + 2] dimerization proceeded dominantly in the head-to-tail mode, which could be attributed to the favorable electronic effect ($\pi-\pi$ stacking interaction between the phenyl ring of one molecule and the 2-pyranone ring of the other, as shown in Scheme 3) and steric effect (severe steric interactions could be imagined between the two monoterpene moieties in the head-to-head mode, which are not shown herein). The observation that the homodimerization was more favorable than the heterodimerization in the transformation might be ascribed to the trivial difference between the steric interactions associated with TS-1 and TS-2 (Scheme 3).

Scheme 3. Total Synthesis of (±)-Katsumadain C



Notably, when **15** was submitted to the same [2 + 2] reaction conditions, only the homodimerization product **19** was isolated in 45% yield, without formation of the heterodimerization product **20** being observed (with 45% of starting material **15** recovered). The structure of **19** was confirmed by its conversion to (±)-katsumadain C (**17**) after removal of the acetyl groups. This result indicated

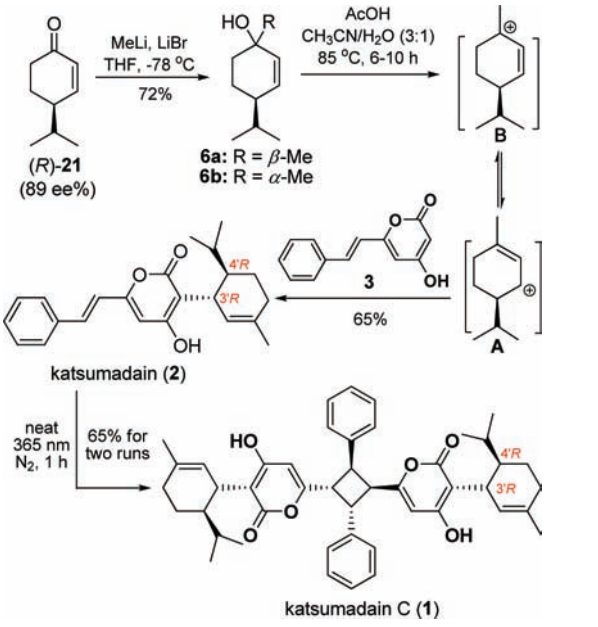
(9) Zhang, X. J.; McLaughlin, M.; Lizeth, R.; Munoz, P.; Hsung, R. P.; Wang, J.; Swidorski, J. *Synthesis* **2007**, *5*, 749–753.

(10) Oikawa, H.; Kobayashi, T.; Katayama, K.; Oikawa, H.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748–8756.

(11) For examples of photoinduced [2 + 2] dimerization in the solid state, see: (a) Ortmann, I.; Werner, S.; Kriiger, C.; Mohr, S.; Schaffner, K. *J. Am. Chem. Soc.* **1992**, *114*, 5048–5054. (b) Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2004**, *126*, 16553–16558. (c) Liu, J.; Wendt, N. L.; Boarman, K. J. *Org. Lett.* **2005**, *7*, 1007–1010. (d) Liu, D.; Ren, Z. G.; Li, H. X.; Lang, J. P.; Li, N. Y.; Abrahams, B. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 4767–4770. (e) Tan, H. B.; Zheng, C.; Liu, Z.; Wang, Z. G. *Org. Lett.* **2011**, *13*, 2192–2195.

that **15** displayed interesting self-recognition behavior (i.e., (+)-**15** + (+)-**15** or (−)-**15** + (−)-**15** via TS-3) in the [2 + 2] cycloaddition. So far it still remains unclear about the exact factors responsible for such phenomena;[12] however, simple analysis of the molecular model of **15** suggested that introduction of the acetyl group on the 3-OH will increase the steric hindrance around the 2-pyranone-monoterpene moiety (Scheme 3), which might render the transition state TS-4 much more sterically unfavorable than TS-3. It is worth noting that the [2 + 2] dimerization of **16** or **15** could also proceed upon direct exposure to sunlight, and comparable results were obtained. However, an attempt to improve the conversion of the transformation by elongating the reaction time proved fruitless, only leading to substantial decomposition of the starting material and product.

Scheme 4. Enantioselective Total Synthesis of Katsumadain C



With the racemic synthesis of (±)-katsumadain C (**17**) accomplished, the stage was then set for its asymmetric version. To this end, the chiral monoterpene (*R*)-cryptone (**21**) was prepared according to a known method in enantioenriched form (89% ee).[13] Treatment of **21** with MeLi/LiBr at −78 °C afforded a mixture of (1*S*,4*R*)-**6a** and its stereoisomer (1*R*,4*R*)-**6b** in a 3:1 ratio,[6] which could be used directly in the next step without separation. We envisioned that monoterpene **6** could be used as the surrogate of **5** in the following transformation due to the anticipated equilibrium between the carbocation **A** and **B**. Indeed, the assembly of styryl-2-pyranone (**3**)[14] with **6** worked well as expected under the optimized conditions (HOAc, CH_3CN/H_2O = 3:1, 85 °C, 6−10 h) to afford katsumadain (**2**) in 65% yield (Scheme 4).

Finally, the photoinduced [2 + 2] dimerization of katsumadain (**2**) (neat, Hg lamp, 365 nm, 1 h) proceeded smoothly to provide katsumadain C (**1**) in 45% yield, along with the recovery of 45% of starting material. The recovered **2** could be reused in the [2 + 2] cycloaddition with the same efficiency, and thus the overall yield of the reaction could be increased to 65% after two runs. Notably, the spectroscopic data of synthetic katsumadain and katsumadain C (^1H and ^{13}C NMR, IR, HRMS) were fully identical with those reported for natural products. Moreover, their measured optical rotations were also in agreement with those of natural substances (for katsumadain: $[\alpha]_D^{22}$ = +172.4, *c* 0.20, CH_3OH, lit.$[\alpha]_D^{22}$ = +170.0, *c* 0.40, CH_3OH; for katsumadain C: $[\alpha]_D^{22}$ = +140.4, *c* 0.10, $CH_3OH/CHCl_3$ (1:1), lit.$[\alpha]_D^{22}$ = +173.2, *c* 0.05, $CH_3OH/CHCl_3$ (1:1)), indicating that the absolute stereochemistries of C-3′ and C-4′ stereogenic centers of katsumadain and katsumadain C are *R* and *R* configurations respectively (Scheme 4).

In summary, the first enantioselective total syntheses of katsumadain and katsumadain C were achieved through an efficient and biomimetic strategy, which features an acid-mediated regio- and stereoselective C−C bond formation between styryl-2-pyranone (**3**) and monoterpene **6** to afford katsumadain (**2**), and a photoinduced topochemically controlled [2 + 2] dimerization of **2** to give katsumadain C (**1**). Our study provides strong evidence for the proposed biosynthtetic pathways of these two natural products. Moreover, it also paves the way to access large quantities of natural products as well as their analogs for further biological studies, which is underway in our laboratory and will be communicated in due course.

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

(12) Efforts to obtain the crystal structure of **15** to understand its unusual behavior in the [2 + 2] dimerization failed after extensive tries.

(13) Same procedure was employed as Baran's method, except for that (*R*)-catalyst was used; see: Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738–4744.

(14) Styryl-2-pyranone (**3**) was prepared according to the following references: (a) Katritzky, A. R.; Wang, Z. Q.; Wang, M. Y.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854–4856. (b) Bach, T.; Kirsch, S. *Synlett* **2001**, 1974–1976.