ORGANIC LETTERS

2012
Vol. 14, No. 13
3434–3437

Kinetically Controlled One-Pot Formation of DEFGH-Rings of Type B Physalins through Domino-Type Transformations

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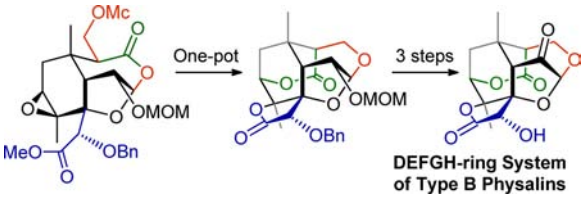
Received May 20, 2012

ABSTRACT



The characteristic DEFGH-ring system of type B physalins has been synthesized by means of a one-pot procedure incorporating domino-type ring transformations. Unexpectedly, we found that introduction of an α-hydroxyester functionality at C17 in ring E allowed the key 7-*endo* oxy-Michael reaction to proceed. Originally this was thought to be an unfavored process. This afforded the desired caged ring system to be formed in a kinetically controlled manner. Consecutive treatment with AcOH at 100 °C furnished the DEFGH-ring system in one pot.

Physalis plants contain a variety of steroidal constituents with highly oxygen-functionalized cyclic structures. These include physalin B[1] (**1**, a kind of type B physalin; Figure 1A) and withanolides.[2] Physalins are of interest not only because of their unique structures but also because they exhibit a wide range of biological activities, including antitumor, antimicrobial, antiparasitic, and immunosuppressive activities.[3] However, no structure–activity relationship studies of physalins have been reported, except for some work on derivatization of the natural products. Therefore, we became interested in total synthesis and structure–activity relationship studies of type B physalins, focusing especially on the complex and unique DEFGH-ring system **2** (Figure 1A).

We have previously reported a method for construction of the DFGH-ring system **3**, in which domino-type transformations[4] of key intermediate **4** give the cage-shaped molecule **7**; these were achieved by means of a simple treatment with LiOH in THF–H_2O (Figure 1B).[5] The domino sequence consisted of the following four transformations: β-elimination, hydrolysis of the seven-membered ring lactone (**4** → **5**), epoxide-opening G-ring lactone formation (**5** → **6**), and an unusual 7-*endo* oxy-Michael reaction to construct the H-ring (**6** → **7**). This fortunately provided an easy access to the complex physalin ring system. However, several attempts to improve the yield of **7** were unsuccessful, because **7** is in equilibrium

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(1) Matsuura, T.; Kawai, M. *Tetrahedron Lett.* **1969**, *22*, 1765.
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(4) Representative review: Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341.
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(6) Treatment of **6** (P = H) with acids such as PPTS, TMSBr, or $Yb(OTf)_3$ did not provide cage-shaped **7** (P = H).

10.1021/ol301394b
Published on Web 06/15/2012

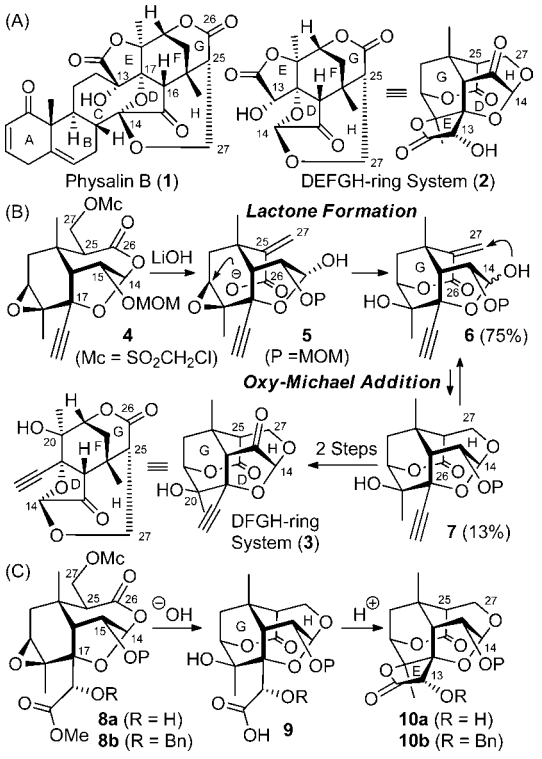


Figure 1. (A) Structures of physalin B (**1**) and DEFGH-ring system of type B physalins (**2**); (B) synthesis of DFGH-ring system (**3**) via domino-type transformation of **4** to **7**; (C) one-pot strategy for DEFGH-ring system.

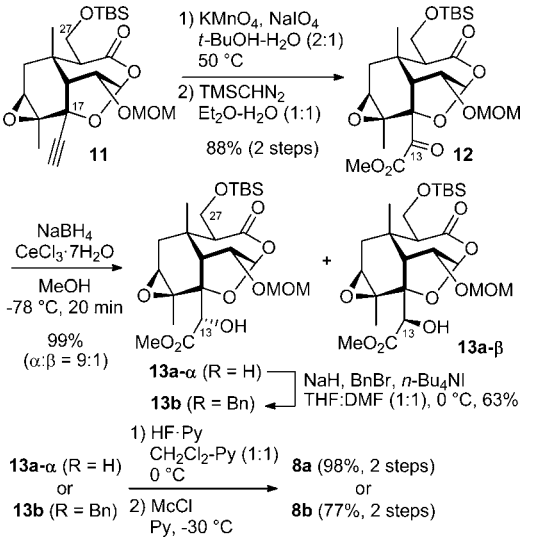
with hemiacetal **6** under basic conditions and **7** is thermodynamically unfavored (**6**:**7** = ca. 6:1).[6]

We hypothesized that an E-ring-installed substrate having a structure similar to that of the natural product might favor the cage-shaped molecule rather than the hemiacetal.[7] To obtain the E-ring, we envisioned an extension of the domino strategy, namely, simultaneous construction of the E-, G-, and H-rings in one pot. Herein we report a kinetically controlled synthesis of the DEFGH-ring system **2** by means of domino-type transformations that include an unprecedented stereoselective 7-*endo* oxy-Michael reaction.

Our approach to the DEFGH-ring system is illustrated in Figure 1C. We planned a domino-reaction sequence from a precursor such as **8a** with an α-hydroxyester at C17. Treatment of **8a** with hydroxide would generate the GH-ring similarly to the case of **4** and simultaneously hydrolyze the methyl ester to generate carboxylic acid **9**. Subsequently, acidification in one pot would promote γ-lactone (E-ring) formation to afford the DEFGH-ring system **10a**. We expected that the cage-shaped **10a** would be stabilized by the functionality at C17 and therefore its formation would be favored compared with the case of **7** under basic or acid conditions.

(7) Reflux of a suspension of physalin B (**1**) in 50% aqueous methanol was reported to give a 1.6:1 mixture of **1** and physalin C, which is the corresponding hemiacetal product. See: Makino, B.; Kawai, M.; Yamamura, H.; Araki, S.; Butsugan, Y. *Pharmazie* **2002**, *57*, 215.

Scheme 1. Synthesis of the Precursors **8a** and **8b** (P = MOM)



The precursors **8a** and **8b** were prepared as shown in Scheme 1. Oxidation of alkyne **11**[5] with $KMnO_4$ and $NaIO_4$[8] followed by treatment with $TMSCHN_2$ gave α-ketoester **12**. Chemo- and stereoselective reduction of the ketone was achieved under Luche conditions to afford the α-hydroxyester **13a-α** in good yield (α:β = 9:1).[9,10] Removal of the TBS group at C27 of **13a-α** and selective introduction of an Mc (monochloromethanesulfonyl) group at the primary alcohol provided the precursor **8a**. Bn-protected **8b** was also prepared by means of conventional procedures.

With the precursors in hand, ring transformations under various conditions were investigated (Table 1). When **8a** was treated with LiOH for 1.5 h, almost complete conversion to polar intermediates (likely carboxylic acid derivatives such as **9**) was observed according to TLC analysis. Subsequent acidification of the mixture with 1 N HCl afforded a less polar mixture of the desired DEFGH-ring **10a** and hemiacetal **15a** in 25% and 15% yields, respectively (entry 1). This result clearly indicated that the functionality at C17 greatly promoted formation of the cage-shaped molecule over the hemiacetal, in contrast to the reaction from **4**. Determination of the relative structure was accomplished by X-ray crystallographic analysis (Table 1). To enhance the chemical yields of products, we first focused on the effect of acidic conditions, because the initially employed method seemed inadequate for complete conversion of carboxylic acid **9** to the E-ring lactone. Several attempts revealed that treatment of the polar intermediates with AcOH−H_2O (20:1)[11] accelerated the process. Moreover, increasing the temperature improved the yields of

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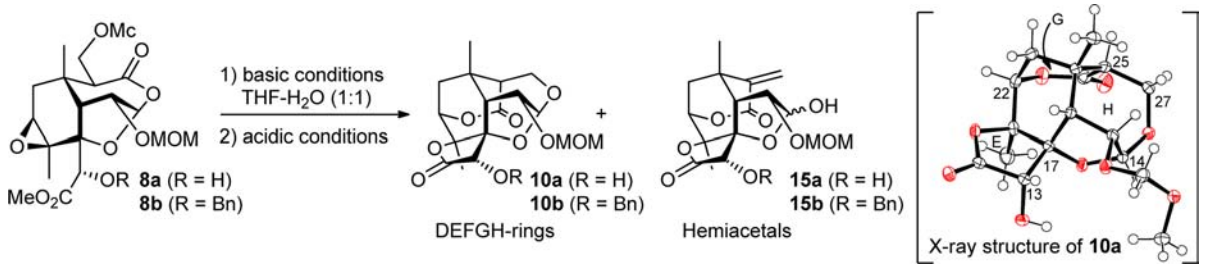
Table 1. Construction of the DEFGH-Ring System under Various Conditions



entry	precursors	basic conditions	acidic conditions	yield [%] of DEFGH-rings	yield [%] of Hemiacetals (α:β)
1	**8a**		1 N HCl aq, rt, 4 h	**10a**: 25	**15a**: 15 (β Only)
2	**8a**	LiOH·H_2O (4 equiv)	AcOH-H_2O (20:1), rt, 1 h	**10a**: 13	**15a**: 16 (1:4.9)
3	**8a**	rt, 1.5 h	AcOH-H_2O (20:1), 80 °C, 1 h	**10a**: 23	**15a**: 20 (1:5.4)
4	**8a**		AcOH-H_2O (20:1), 100 °C, 1 h	**10a**: 33	**15a**: 37 (1:6.1)
5	**8a**	LiOH·H_2O (4 equiv), rt, 10 min	**AcOH-H_2O (20:1) 100 °C, 1 h**	**10a**: 28	**15a**: 8 (β only)
6	**8a**	LiOH·H_2O (4 equiv), rt, 6 h		**10a**: 11	**15a**: 22 (1:5.5)
7	**8a**	LiOH·H_2O (4 equiv), 60 °C, 1.5 h		**10a**: 0	**15a**: 32 (1:6.3)
8	**8a**	LiOH·H_2O (10 equiv), rt, 1.5 h		**10a**: 13	**15a**: 23 (1:4.2)
9	**8b**	**LiOH·H_2O (4 equiv), rt, 1.5 h**		**10b**: 50	**15b**: 44 (1:2.1)
10	**10a**			**10a**: 4	**15a**: 83 (1:4.0)
11	**10b**	LiOH·H_2O (4 equiv)	AcOH-H_2O (20:1)	**10b**: 16	**15b**: 57 (1:2.6)
12	**15a** (α:β = 1:33)	rt, 1.5 h	100 °C, 1 h	**10a**: 1	**15a**: 70 (1:5.9)
13	**15b** (α:β = 1:2.0)			**10b**: 11	**15b**: 89 (1:2.5)

both products without causing a significant change in the ratio of **10a** and **15a** (Table 1, entries 2−4).

Next, optimization of the basic conditions was investigated, but other hydroxides such as NaOH, KOH, and Triton B did not give a satisfactory outcome. On the other hand, examination of the effects of reaction time and temperature in the LiOH-mediated reaction gave unexpected results. Namely, the formation of cage-shaped **10a** was predominant when the basic treatment was stopped after 10 min, although the total yield was low (entry 5). A longer reaction time or reaction at a higher temperature decreased the yield of **10a** and increased the yield of **15a** (entries 6 and 7). Treatment with an excess amount of LiOH gave a similar result (entry 8). These observations suggest that the H-ring structure is also less stable than hemiacetal under these basic conditions, similar to the case of **7**. Taking into account the yield of **10a**, we decided that the conditions of entry 4 were optimum. The treatment of Bn-protected **8b** under the optimum conditions provided the cage-shaped **10b** in better yield (50%, entry 9), along with the hemiacetal **15b** (44%).

We wondered why **10** was mainly produced even though it was likely to be thermodynamically unfavored in the equilibrium under basic conditions. First, we retreated both products under either acidic or basic−acidic one-pot conditions to confirm the thermodynamically preferred products. Heating **10** or **15** in AcOH−H_2O gave no other products, and **10** or **15** was recovered almost quantitatively (**10a**: 96%, **15a**: 100%). In contrast, treatment of **10** or **15** with LiOH generated the polar intermediate again, and subsequent acid treatment provided the hemiacetal **15** predominantly with a small amount of **10** (Table1, entries 10−13).[12] These results clearly indicated that the desired **10** is not mainly produced from **15** in a thermodynamically controlled pathway, but rather in a kinetically controlled manner. We propose a plausible pathway for the one-pot reaction from **8** as shown in Scheme 2A.

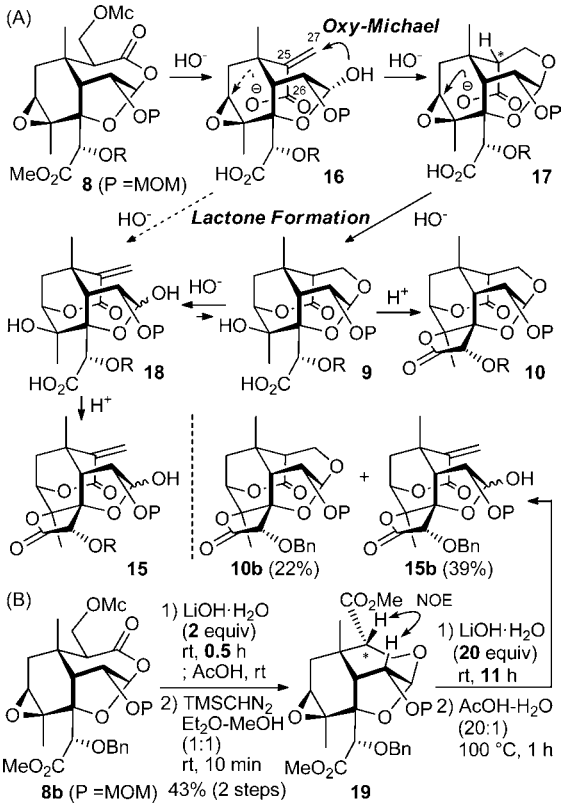
After β-elimination and hydrolysis of the seven-membered lactone, the unusual intramolecular 7-*endo* oxy-Michael reaction[13] of the flexible α,β-unsaturated carboxylic acid **16** to give **17** would occur before G-ring lactone formation. Then, cage-shaped **9** would be formed by epoxide-opening under kinetic control, and a further retro-oxy-Michael reaction would provide the undesired hemiacetal **18**. If this was the case, the unusual 7-*endo* oxy-Michael reaction giving **17** should proceed in a diastereoselective manner. Indeed, we succeeded in isolating the corresponding diester derivative **19** from **8b** as a single isomer, along with **10b** and **15b**,[12] when the reaction was conducted for 30 min with 2 equiv of LiOH (Scheme 2B). Furthermore, retreatment of the diester **19** with excess LiOH and AcOH provided **10b** and **15b**,[12,14] indicating that dicarboxylic acid **17** is an intermediate in this one-pot reaction. Thus, the functionality at C17 significantly changes the reaction

(12) See Supporting Information.

(13) As far as we know, there is no previous report of a simple intramolecular 7-*endo* oxy-Michael reaction. Simultaneous 5-*exo* ring formation occurs in most cases. For a representative report, see: Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.

(14) Since hydrolysis of diester **19** was so sluggish, the use of excess LiOH was required.

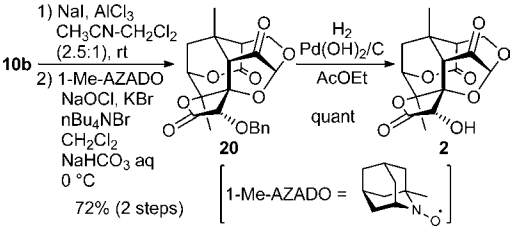
Scheme 2. (A) Plausible Mechanism for Formation of **10** and **15**; (B) Identification and Retreatment of Intermediate



pathway and allows successful construction of the cage-shaped molecule.

Removal of the MOM group in **10b** by treatment with NaI and $AlCl_3$[15] gave the corresponding alcohol without opening of the seven-membered H-ring (Scheme 3). The distorted alcohol could be oxidized with 1-Me-AZADO[16] to provide **20**. Finally, hydrogenolysis of Bn ether completed the synthesis of DEFGH-ring system **2**.

Scheme 3. Synthesis of **2**



In conclusion, we have achieved the first synthesis of the DEFGH-ring system **2** of type B physalins. The energetically disfavored DEFGH-ring system **10** was generated under kinetic control via stereoselective 7-*endo* oxy-Michael reaction. Evaluation of the biological activity of our compounds and further work directed at the total synthesis of type B physalins are underway.

Acknowledgment. We would like to thank Prof. Yoshiharu Iwabuchi (Tohoku University, Japan) for providing 1-Me-AZADO and also Prof. Masao Kawai (Nagoya Institute of Technology, Japan) for the valuable discussions. This work was partially supported by RIKEN project funding and a Grant-in Aid for Scientific Research (C) from JSPS. M.M. is a Research Fellow of JSPS.

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

The authors declare no competing financial interest.

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