

Synthesis of the DFGH ring system of Type B Physalins: Highly Oxygenated, Cage-Shaped Molecules**

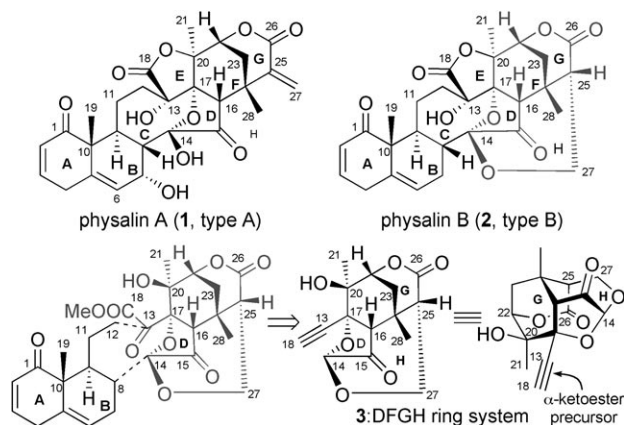
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Physalins, which are steroidal constituents isolated from *Physalis* plants, contain a unique 13,14-*seco*-16,24-cycloergostane skeleton. The structures of physalins A^[1] (**1**) and B^[2] (**2**; Scheme 1) were first determined in 1969, and so far phys-

knowledge, no studies on the synthesis of physalins (except for derivatization of the natural products) have been reported. Therefore, the structural requirements for their biological activity are not well understood. It seems that the role of the right part of type B physalins (DFGH ring system) would be worth investigating as opposed to the steroidal AB ring system. To elucidate the biological function of the interesting and unusual DFGH ring system, we focused on the development of suitable synthetic methodology for its preparation. Herein, we report the first synthesis of the compact, cage-shaped DFGH ring system of type B physalins.

We designed compound **3** as our synthetic target, as it should be useful both as a biological probe and as an intermediate for the total synthesis of various physalins. A convergent synthesis would be possible by assembly of the left (AB ring system) and right (DFGH ring system) parts between the C12–C13 and C8–C14 bonds after conversion of the terminal alkyne in **3** into an α -ketoester^[9] (Scheme 1). To establish an efficient synthetic methodology for the assembly of **3**, introduction of oxygen functionality and construction of the complex fused-ring system should be the key transformations. Our retrosynthetic analysis is outlined in Scheme 2. The H ring of **3** would be prepared by formation of a seven-membered acetal at C14 from primary alcohol **4** (path a) or by conjugate addition of the hemiacetal oxygen center of **5** to an α,β -unsaturated lactone (path b). Both **4** and **5** would be obtainable from **6** by formation of the lactone of ring G through opening of the epoxide ring at C22. To synthesize the highly functionalized tricycle **6**, which contains seven oxygen atoms in a framework of 11 carbon atoms, efficient introduction of oxygen centers and adjustment of the oxidation state without using extra protecting groups were important issues to be considered. After considering several possibilities, we concluded that the following retrosynthesis would be appropriate. The carboxylic acid **6** would be prepared by hydrolysis of seven-membered lactone **7**, which is expected to be synthesized by regioselective Baeyer–Villiger oxidation of ketone **8**. Regioselective intramolecular opening of the C14–C26 epoxide ring by the tertiary alcohol at C17 of **9** would give the key intermediate **8**. The two epoxide groups and the alkynyl group in **9** could be introduced into the *cis*-fused bicyclic intermediate **10** in a stereocontrolled manner. The *cis*-decalin core of enone **10**, which has a quaternary carbon center at C24, would be synthesized by Diels–Alder reaction of **11** and **12**, followed by the introduction of a one-carbon unit at the C25- and C20-positions.

Diels–Alder reaction of **11**^[10] with **12**^[11] occurred at 100 °C in toluene (Scheme 3), and the desired regioisomer **13** was obtained preferentially (**13/14** = 63:19). Reduction of the two carbonyl groups at C15 and C25 with DIBAL-H and



Scheme 1. Structures of physalin A (**1**) and B (**2**) and design for the DFGH ring system **3**.

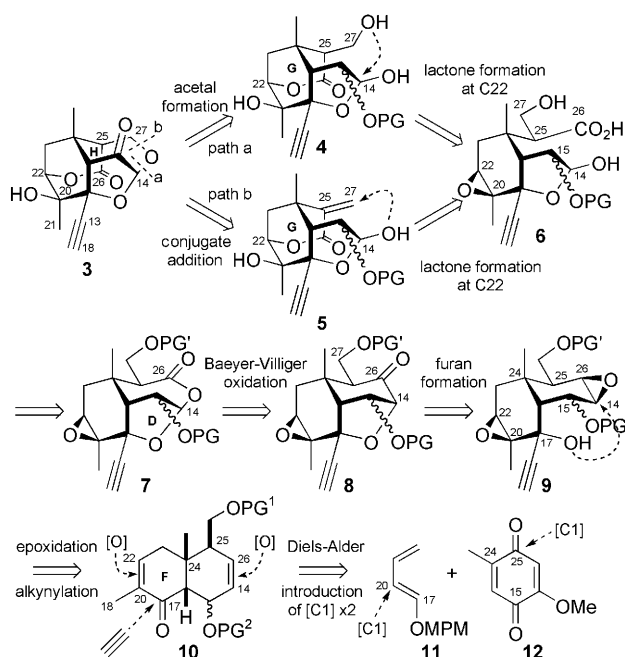
alins A–Z, I, and II have been identified.^[3] Physalins are characterized by a highly oxygenated, complex, fused-ring system. Type B physalins, such as physalin B (**2**), are composed of eight rings including an internal acetal ring (H ring, C(14)–O–C(27)–C(25)). Physalins show antitumor activity *in vitro* and *in vivo*.^[4] Furthermore, other unique activity of **2** has recently been reported. These include inhibition of hedgehog/GLI-mediated transcription,^[5] inhibition of PMA-induced (PMA = phorbol 12-myristate 13-acetate) NF- κ B activation,^[6] antiinflammatory and immunomodulatory activity,^[7] and inhibition of the ubiquitin-proteasome pathway.^[8]

Synthetic study is required to elucidate the molecular targets of physalins and to examine further the structure-activity relationship. Furthermore, these unique structures are intrinsically attractive to synthetic chemists. However, to our

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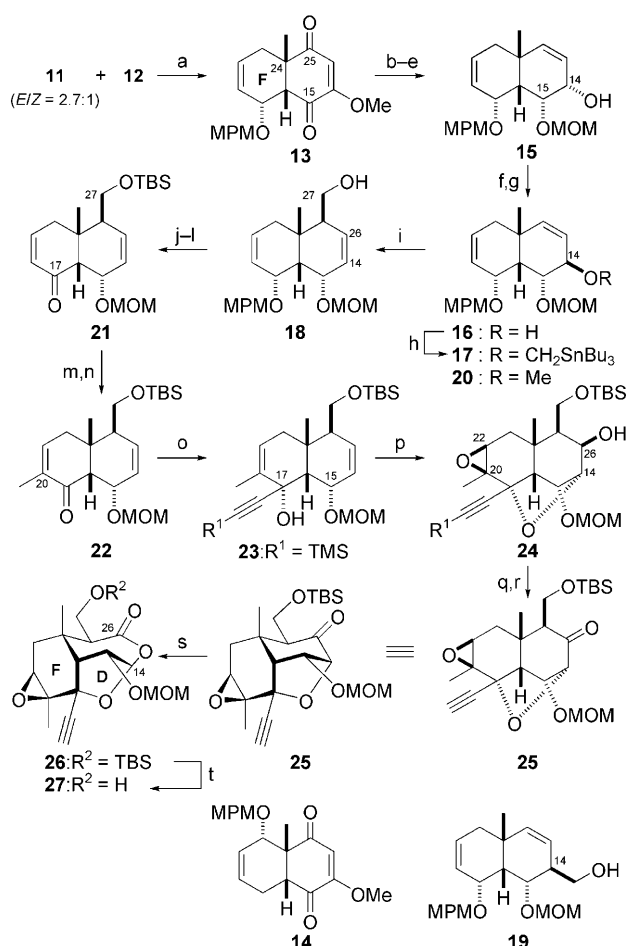
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.200900634>.



Scheme 2. Retrosynthetic analysis for the DFGH ring system **3** of type B physalins. PG = protecting group. MPM = *para*-methoxyphenylmethyl.

subsequent treatment with aqueous H_2SO_4 solution afforded the enone. The resulting secondary alcohol at C15 was protected with the MOM group and 1,2-reduction of the enone under Luche conditions^[12] gave α -allylic alcohol **15** in good yield. To obtain **18** from **15**, introduction of a hydroxymethyl group at C25 and migration of the double bond to C14–C26 were required. For this transformation a 2,3-Wittig rearrangement reaction^[13] of **17** was employed. Based on consideration for the stereospecificity of the 2,3-Wittig rearrangement, inversion of the configuration of the secondary alcohol at C14 of **15** was first conducted to introduce a β -hydroxymethyl group at C25. A Mitsunobu reaction^[14] using *p*-nitrobenzoic acid^[15] and subsequent methanolysis gave the secondary alcohol **16** in 86% yield. Treatment of **16** with $\text{ICH}_2\text{SnBu}_3$ ^[16] provided the rearrangement precursor **17**. Although 2,3-Wittig rearrangement toward the hindered C25 position, which is adjacent to the quaternary carbon center at C24, seemed to be challenging,^[17] fortunately the rearrangement of **17** using methyllithium in THF at 0°C gave the desired 2,3-Wittig adduct **18** in good yield (72%), together with the 1,2-Wittig adduct **19** (9%), the product of α elimination^[18] **16** (10%), and the protonation product **20** (5%).^[19,20]

With the *cis*-decalin intermediate **18** in hand, we next envisioned the attachment of pendant groups on the F ring (Scheme 3). Although **18** was obtained as an inseparable mixture with **19** and **16**, these undesired products could be separated after protection of the primary alcohol as the TBS ether and subsequent removal of the MPM group by DDQ oxidation. Oxidation of the allylic alcohol at C17 with MnO_2 provided **21** in 93% yield. Methylation of **21** at the α position of the enone was successfully performed by α iodination using the TMSN_3 /iodine reaction conditions developed by Sha and



Scheme 3. Synthesis of seven-membered lactones **26** and **27**. Reagents and conditions: a) toluene, 100°C, 3 days, (**13**, 63%; **14**, 19%); b) DIBAL-H, CH_2Cl_2 , 0°C; c) 10% aq H_2SO_4 , CH_2Cl_2 , RT (74%, over 2 steps); d) MOMCl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , reflux (98%); e) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH, RT (98%); f) DIAD, PPh_3 , $p\text{NO}_2\text{PhCOOH}$, THF, RT; g) K_2CO_3 , MeOH/ Et_2O (3:1), RT (86%, over 2 steps); h) $\text{Bu}_3\text{SnCH}_2\text{I}$, NaH, DMF/THF (1:1), RT (76%); i) MeLi in Et_2O , THF, 0°C (**18**, 72%; **19**, 9%; **16**, 10%; yields were determined by ^1H NMR spectroscopy; **20**, 5%); j) TBSCl, Et_3N , DMAP, CH_2Cl_2 , RT; k) DDQ, CH_2Cl_2 , pH 7 buffer, RT (68%, over 3 steps from **17**); l) MnO_2 , CH_2Cl_2 , RT (93%); m) TMSN_3 ; then I_2 , pyridine, CH_2Cl_2 , 0°C to RT; n) MeMgBr , $\text{Fe}(\text{acac})_3$, NMP, THF, 0°C (73%, over 2 steps); o) TMS-acetylene, $n\text{BuLi}$, CeCl_3 , THF, -78°C (96%); p) *m*CPBA (10 equiv), CH_2Cl_2 , 0°C to RT (73%); q) K_2CO_3 , MeOH; r) Dess–Martin periodinane, CH_2Cl_2 , RT (92%, over 2 steps); s) *m*CPBA, NaHCO_3 , CH_2Cl_2 , RT (92%); t) HF-pyridine, CH_2Cl_2 /pyridine (1:1), 0°C (93%). acac = acetylacetonate, Bu = butyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIAD = diisopropylazodicarboxylate, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformamide, *m*CPBA = *meta*-chloroperoxybenzoic acid, MOM = methoxymethyl, NMP = *N*-methylpyrrolidone, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

Huang,^[21] and a subsequent cross-coupling reaction using methylmagnesium bromide in the presence of $\text{Fe}(\text{III})$ catalyst and NMP.^[22] Addition of trimethylsilylacetylene to enone **22** in the presence of anhydrous CeCl_3 also proceeded with excellent regio- and stereoselectivity and gave **23**; no β elimination of the oxygen functionality at C15 was observed.

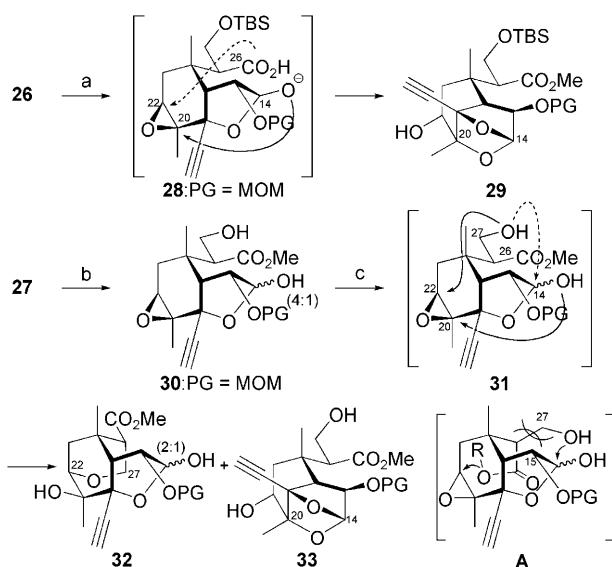
Next, epoxidation of the two olefin units (C14–C26 and C20–C22) of **23** and formation of the furan (D ring) were examined. As expected, epoxidation of both olefin units occurred in a completely stereoselective manner upon treatment of **23** with an excess amount of *m*CPBA, and subsequent opening of the epoxide ring by the tertiary alcohol at C17 proceeded regioselectively in one pot. Thus, furan **24** with a β -epoxide at C20–C22 was successfully obtained. The secondary alcohol at the C26 position of **24** was converted into ketone **25** after removal of the TMS group at the terminal alkyne position. Baeyer–Villiger oxidation of **25** proceeded with *m*CPBA and gave **26** with complete regioselectivity.^[23] The TBS protecting group was removed with HF·pyridine and afforded **27**.

Construction of the six-membered lactone (G ring) and seven-membered acetal (H ring) should be the final steps involved for the synthesis of the cage-shaped DFGH ring **3**. First, we tried hydrolysis of the seven-membered lactone **26** by treatment with LiOH in THF/water, expecting formation of the six-membered lactone (G ring) through the back-side attack of the β epoxide at C22 in a possible carboxylic acid intermediate **28** (see dashed arrow in Scheme 4). However, no formation of the lactone of ring G was observed; instead, attack of the hemiacetal oxygen atom on the epoxide ring occurred under hydrolytic conditions. The tricyclic acetal **29** was isolated after treatment with TMS diazomethane. Next, we tried to synthesize the seven-membered acetal (H ring) before formation of the lactone (G ring) by acid treatment of **30** to prevent the unwanted reaction of the hemiacetal and epoxide groups. Methyl ester **30** was prepared by methanolysis of the seven-membered lactone **27** with LiOH in MeOH; however, the subsequent treatment of **30** (crude product) with CSA resulted in the formation of a similar side product **33** and the tetrahydropyran **32**, which was formed by opening of the epoxide ring by the primary alcohol at C27. We assumed that

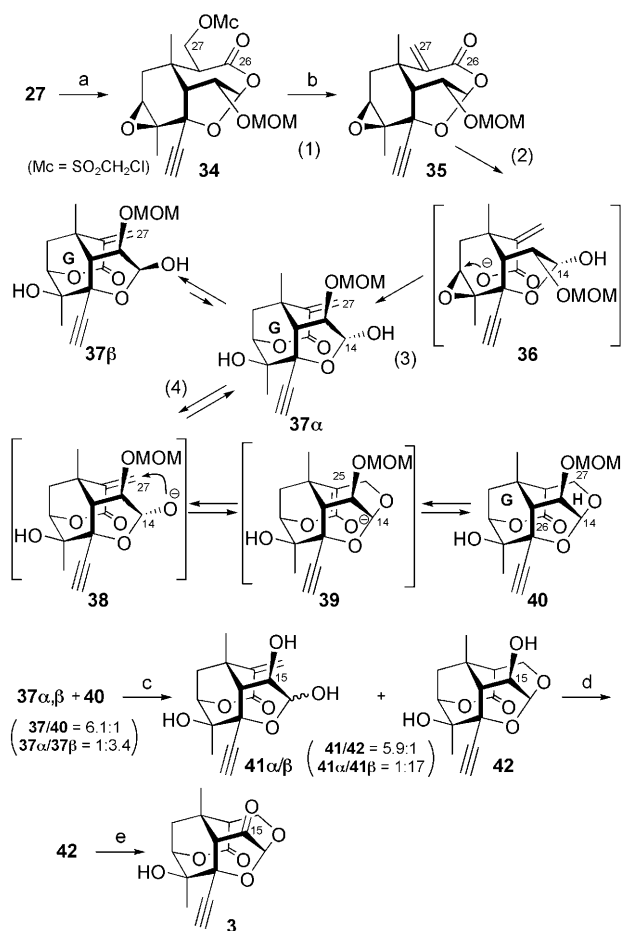
conformation **A** (Scheme 4), which would be preferable for construction of the GH ring, was disfavored owing to steric repulsion between the hydrogen atom on C15 and the substituents on C27. This steric interaction would explain why the formation of the desired lactone (G ring) and acetal (H ring) did not occur. Moreover, almost no reaction was observed when a solution of the seven-membered lactone **27** in AcOH was heated at 90 °C in the presence of potassium acetate.^[23] These results indicated that the oxonium ion was not easily generated from the acetal of ring D under these reaction conditions, and that ring closure of the seven-membered acetal by way of path a (Scheme 2) would be difficult.

To solve these problems, we next envisioned that α,β -unsaturated seven-membered lactone **35** might be employed as a precursor of the DFGH ring **3** (path b in Scheme 2). The conversion of the sp^3 carbon atom at C27 into an sp^2 carbon atom would decrease the steric repulsion with the hydrogen atom on C15, and thus formation of the lactone of ring G is expected to proceed smoothly. Primary alcohol **27** was first transformed into monochloromesylate **34**, and then β elimination was conducted under various reaction conditions (Scheme 5). Surprisingly, we found that treatment of **34** with LiOH in THF/H₂O gave the desired DFGH ring **40** (13%) directly, together with the unsaturated seven-membered lactone **35** (12%) and the expected lactones **37 α/β** (75%; $\alpha/\beta = 1:2.6$). Although the yield of **40** was not satisfactory, it was very impressive that a four-step domino sequence, 1) β elimination of **34** to **35**, 2) hydrolysis of seven-membered lactone of **35** to generate carboxylate **36**, 3) formation of the lactone of ring G through opening of the epoxide ring to give **37 α** , and 4) oxy-Michael addition promoted by a Brønsted base to give **40** through enolate **39**, proceed in one pot. We had not expected that the oxy-Michael reaction would proceed under basic conditions,^[24] as formation of the bridgehead enolate **39** is not favored because of ring strain. However, the crystal structure of physalins shows that C25 is highly distorted, probably because of the constrained ring structure, and thus exhibits partial planarity even though C25 is an sp^3 carbon atom.^[25] We tried various reaction conditions to increase the yield of **40**, but all attempts gave similar results; the ratio of **37/40** was 4 $\approx$ 6:1 and that of **37 α/β** was 1:2 $\approx$ 3. The mixture was successfully separated by HPLC methods, and treatment of the isolated **37 α** or **40** with LiOH also afforded a mixture of **37 α/β** and **40**.^[20] These outcomes suggest the existence of an equilibrium between the hemiacetals **37 α/β** and the acetal **40** under the aqueous basic conditions. In this equilibrium the undesired **37 β** , which cannot cyclize, is the major diastereomer and it was therefore difficult to improve the chemical yield of the desired DFGH ring **40**. However, it is important to note that the configuration of the hemiacetal was fixed as the α isomer, as in the natural product.

Treatment of the mixture **37 α/β** and **40** (**37/40** = 6.1:1, **37 α/β** = 1:3.4) with TMSBr afforded a mixture of **41 α/β** and **42** in good yield and without decomposition of the H ring, although the ratio of the α/β isomers remained changed (Scheme 5). After separation of **41 α/β** and **42** by HPLC methods, we finally succeeded in the synthesis of the target DFGH ring **3** by oxidation of **42**.



Scheme 4. Attempts at the formation of the G ring or H ring. Reagents and conditions: a) LiOH·H₂O, THF/H₂O (1:1), RT; then TMSCHN₂, Et₂O/MeOH (86%); b) LiOH·H₂O, MeOH, 0 °C; c) CSA, CH₂Cl₂, RT (**32**, 56%; **33**, 10% over 2 steps). CSA = (±)-camphorsulfonic acid.



Scheme 5. Synthesis of the DFGH ring system of type B physalins. Reagents and conditions: a) $\text{ClCH}_2\text{SO}_2\text{Cl}$, pyridine, 0°C (quant.); b) $\text{LiOH}\cdot\text{H}_2\text{O}$, $\text{THF}/\text{H}_2\text{O}$ (1:1), RT, 1.5 h (**40**, 13%; **37**, 75% ($\alpha/\beta = 1:2.6$); **35**, 12%); c) TMSBr , CH_2Cl_2 , 0°C (77%); d) HPLC separation on SenshuPak PEGSIL silica 120-5; eluent: $\text{AcOEt}/\text{hexane} = 2:1$ (**42**, quant.); e) Dess–Martin Periodinane, CH_2Cl_2 , reflux (70%).

In conclusion, we have achieved the first synthesis of the type B physalin DFGH ring system, which is a highly oxygenated, complex, fused-ring system. During the course of the synthesis, efficient methods for the preparation of intermediates **18** and **26** were developed by utilizing 2,3-Wittig rearrangement and Baeyer–Villiger oxidation. Moreover, we succeeded in the construction of the DFGH ring system through a four-step domino reaction, which included an unusual oxy-Michael addition, and that was carried out in one pot under simple basic conditions. Examination of formation of the H ring through two different approaches revealed that the oxy-Michael strategy (path b) was superior to the strategy that involved formation of the acetal (path a). These findings should be relevant to the biosynthesis of physalins. Evaluation of the biological activity of **3** and a total synthesis of physalin B (**2**) are currently underway.

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- [1] T. Matsuura, M. Kawai, R. Nakashima, Y. Butsugan, *Tetrahedron Lett.* **1969**, 10, 1083–1086.
- [2] T. Matsuura, M. Kawai, *Tetrahedron Lett.* **1969**, 10, 1765–1766.
- [3] For selected references, see: a) M. Kawai, T. Matsuura, *Tetrahedron* **1970**, 26, 1743–1745; b) S. S. Subramanian, P. D. Sethi, *Curr. Sci.* **1971**, 40, 85–86; c) L. R. Row, N. S. Sarma, K. S. Reddy, T. Matsuura, R. Nakashima, *Phytochemistry* **1978**, 17, 1647–1650; d) L. R. Row, K. S. Reddy, N. S. Sarma, T. Matsuura, R. Nakashima, *Phytochemistry* **1980**, 19, 1175–1181; e) M. Kawai, T. Matsuura, S. Kyuno, H. Matsuki, M. Takenaka, T. Katsuoka, Y. Butsugan, K. Saito, *Phytochemistry* **1987**, 26, 3313–3317; f) M. Kawai, T. Ogura, M. Nakanishi, T. Matsuura, Y. Butsugan, Y. Mori, K. Harada, M. Suzuki, *Bull. Chem. Soc. Jpn.* **1988**, 61, 2696–2698; g) M. Kawai, T. Ogura, B. Makino, A. Matsumoto, H. Yamamura, Y. Butsugan, M. Hayashi, *Phytochemistry* **1992**, 31, 4299–4302; h) M. Kawai, A. Matsumoto, B. Makino, H. Mori, T. Ogura, Y. Butsugan, K. Ogawa, M. Hayashi, *Bull. Chem. Soc. Jpn.* **1993**, 66, 1299–1300; i) B. Makino, M. Kawai, Y. Iwata, H. Yamamura, Y. Butsugan, K. Ogawa, M. Hayashi, *Bull. Chem. Soc. Jpn.* **1995**, 68, 219–226; j) B. Makino, M. Kawai, T. Ogura, M. Nakanishi, H. Yamamura, Y. Butsugan, *J. Nat. Prod.* **1995**, 58, 1668–1674; k) B. Makino, M. Kawai, K. Kito, H. Yamamura, Y. Butsugan, *Tetrahedron* **1995**, 51, 12529–12538; l) M. Kawai, T. Yamamoto, B. Makino, H. Yamamura, S. Araki, Y. Butsugan, K. Saito, *J. Asian Nat. Prod. Res.* **2001**, 3, 199–205; m) P.-C. Kuo, T.-H. Kuo, A. G. Damu, C.-R. Su, E.-J. Lee, T.-S. Wu, R. Shu, C.-M. Chen, K. F. Bastow, T.-H. Chen, K.-H. Lee, *Org. Lett.* **2006**, 8, 2953–2956; n) R. Chen, J.-Y. Liang, R. Liu, *Helv. Chim. Acta* **2007**, 90, 963–966; o) L. Qiu, F. Zhao, Z.-H. Jiang, L.-X. Chen, Q. Zhao, H.-X. Liu, X.-S. Yao, F. Qiu, *J. Nat. Prod.* **2008**, 71, 642–646.
- [4] For selected references, see: a) M. D. Antoun, D. Abramson, R. L. Tyson, C.-J. Chang, J. L. McLaughlin, G. Peck, J. M. Cassady, *J. Nat. Prod.* **1981**, 44, 579–585; b) H.-C. Chiang, S.-M. Jaw, P.-M. Chen, *Anticancer Res.* **1992**, 12, 1155–1162; c) M. Kawai, B. Makino, H. Yamamura, S. Araki, Y. Butsugan, J. Ohya, *Pharmazie* **2002**, 57, 348–350; d) H. I. F. Magalhães, M. L. Veras, M. R. Torres, A. P. N. N. Alves, O. D. L. Pessoa, E. R. Silveira, L. V. Costa-Lotufo, M. O. de Moraes, C. Pessoa, *J. Pharm. Pharmacol.* **2006**, 58, 235–241; e) A. G. Damu, P.-C. Kuo, C.-R. Su, T.-H. Kuo, T.-H. Chen, K. F. Bastow, K.-H. Lee, T.-S. Wu, *J. Nat. Prod.* **2007**, 70, 1146–1152.
- [5] T. Hosoya, M. A. Arai, T. Koyano, T. Kowithayakorn, M. Ishibashi, *ChemBioChem* **2008**, 9, 1082–1092.
- [6] N. J. Jacobo-Herrera, P. Bremner, N. Márquez, M. P. Gupta, S. Gibbons, E. Muñoz, M. Heinrich, *J. Nat. Prod.* **2006**, 69, 328–331.
- [7] a) A. T. Vieira, V. Pinho, L. B. Lepsch, C. Scavone, I. M. Ribeiro, T. Tomassini, R. Ribeiro-dos-Santos, M. B. P. Soares, M. M. Teixeira, D. G. Souza, *Br. J. Pharmacol.* **2005**, 146, 244–251; b) M. B. P. Soares, D. Brustolim, L. A. Santos, M. C. Bellintani, F. P. Paiva, Y. M. Ribeiro, T. C. B. Tomassini, R. Ribeiro-dos-Santos, *Int. Immunopharmacol.* **2006**, 6, 408–414.
- [8] I. Vandenberghe, L. Créancier, S. Vispé, J.-P. Annereau, J.-M. Barret, I. Pouny, A. Samson, Y. Aussagues, G. Massiot, F. Ausseil, C. Bailly, A. Kruczyński, *Biochem. Pharmacol.* **2008**, 76, 453–462.
- [9] Numbering of the carbon atoms corresponds to that of natural type B physalins.
- [10] S. D. Burke, J. E. Cobb, K. Takeuchi, *J. Org. Chem.* **1990**, 55, 2138–2151.
- [11] P. A. Wender, D. B. Rawlins, *Tetrahedron* **1992**, 48, 7033–7048.

- [12] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
- [13] a) W. C. Still, A. Mitra, *J. Am. Chem. Soc.* **1978**, *100*, 1927–1928; b) T. Nakai, K. Mikami, *Org. React.* **1994**, *46*, 105–209.
- [14] O. Mitsunobu, *Synthesis* **1981**, 1–28.
- [15] J. A. Dodge, J. I. Trujillo, M. Presnell, *J. Org. Chem.* **1994**, *59*, 234–236.
- [16] J. Åhman, P. Somfai, *Synth. Commun.* **1994**, *24*, 1117–1120.
- [17] a) T. Sugimura, L. A. Paquette, *J. Am. Chem. Soc.* **1987**, *109*, 3017–3024; b) K. Mori, M. Amaike, M. Itou, *Tetrahedron* **1993**, *49*, 1871–1878; c) Y. Hanzawa, M. Suzuki, Y. Kobayashi, *Tetrahedron Lett.* **1989**, *30*, 571–574.
- [18] Z. You, M. Koreeda, *Tetrahedron Lett.* **1993**, *34*, 2597–2600.
- [19] Yields of the products were calculated based on the integration ratios of **16**, **18**, and **19** determined from ¹H NMR spectroscopy.
- [20] See the Supporting Information.
- [21] C.-K. Sha, S.-J. Huang, *Tetrahedron Lett.* **1995**, *36*, 6927–6928.
- [22] G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199–1205.
- [23] Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, *94*, 9217–9219.
- [24] Kawai et al. reported the acid-induced transformation of type A physalins to type B physalins. Treatment of physalin A (**1**) with Brønsted acid gave the seven-membered acetal adduct and the benzylic-type rearrangement adduct, in which dehydration of the hydroxyl group at C7 occurred simultaneously, see: M. Kawai, T. Ogura, Y. Butsugan, T. Taga, M. Hayashi, *Tetrahedron* **1991**, *47*, 2103–2110.
- [25] M. Kawai, B. Makino, T. Taga, Y. Miwa, T. Yamamoto, T. Furuta, H. Yamamura, Y. Butsugan, K. Ogawa, M. Hayashi, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 222–226.