Tetrahedron Letters 55 (2014) 1826–1828

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Formal synthesis of soybean phytoalexin glyceollin I

Yuta Kohno, Masatsugu Koso, Masaki Kuse, Hirosato Takikawa *

Department of Agrobioscience, Graduate School of Agricultural Science, Kobe University, Rokkodai, Nada-ku, Kobe 657-8501, Japan

ARTICLE INFO

Article history:
Received 3 December 2013
Revised 23 January 2014
Accepted 28 January 2014
Available online 6 February 2014

Keywords:
Glyceollins
Phytoalexins
Claisen rearrangement
Suzuki–Miyaura cross coupling

ABSTRACT

Glyceollins are well-known phytoalexins isolated from soybean (*Glycine max*). An efficient three-step synthesis was developed for the preparation of the key intermediate in Khupse's glyceollin I synthesis. Claisen rearrangement-cyclization cascade reaction and Suzuki–Miyaura cross coupling were key steps in this method.

Since the 1960s, it has been commonly known that seedlings of soybean (*Glycine max*) respond to fungal infection or chemical injury with the rapid production of antifungal compounds.[1] In the 1970s, glyceollins I–IV (**1**–**4**) were isolated as phytoalexins from soybean.[2] As shown in Figure 1, these compounds are isoflavonoids with prenylated pterocarpan skeleton, and exhibit antifungal properties. Recently, in addition to their intrinsic antifungal activity, they have become recognized as exhibiting not only antiestrogenic but also anticancer activities.[3] Despite their interesting biological activities and a general awareness of their existence, only two syntheses of glyceollin I (**1**) have been disclosed so far;[4,5] the first was reported by Khupse and Erhardt in 2008,[4a] and the second was also reported by the same authors in 2011.[4b] Key intermediates of both syntheses were isoflav-3-enes **5a**[4a] and **5b**.[4] Thus, we initiated studies focusing on the novel synthesis of **1**, considering **5a** and **5b** as virtual target compounds. Here, we report our original and straightforward synthesis of **5a**, namely, a novel formal synthesis of glyceollin I (**1**).

Scheme 1 shows our synthetic plan. Our virtual target compounds **5a**/**b** are prepared by Suzuki–Miyaura cross coupling[6] between **A** and **B**. Synthesis of the chlorochromene **A** is made possible by the Claisen rearrangement-cyclization cascade reaction, which can convert **C** into **A** via the unstable Claisen adduct.[7] The allylic ether **C** is prepared from a commercially available starting material **D**. Boronic acids **B** were easily obtainable from 3-bromoresorcinol **E** using conventional methods.

Scheme 2 illustrates our synthetic route to the key intermediate **8**. The starting resorcinol derivative **6** was converted to the

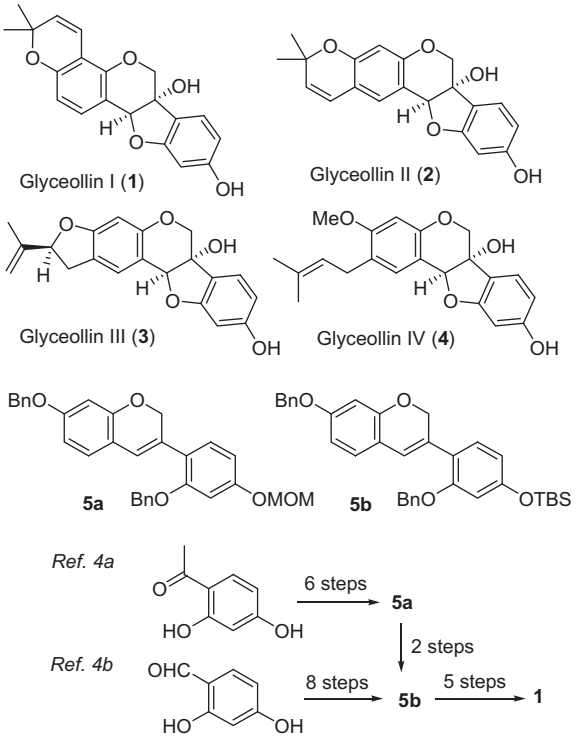
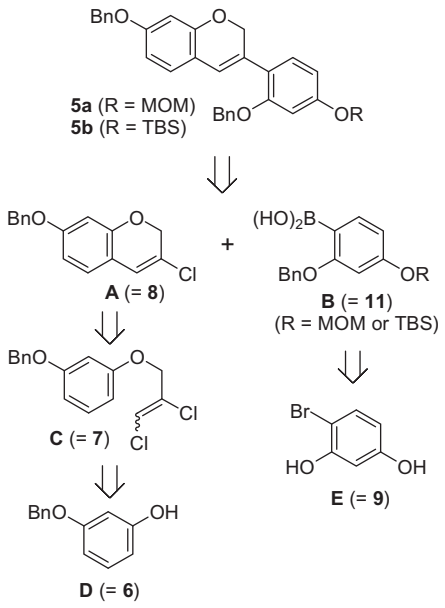


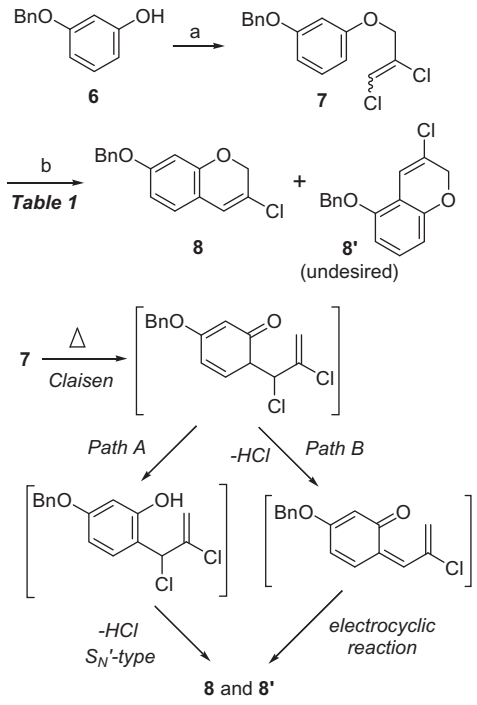
Figure 1. Glyceollins and their related compounds.

* Corresponding author. Tel./fax: +81 78 803 5958.
E-mail address: takikawa@kobe-u.ac.jp (H. Takikawa).

http://dx.doi.org/10.1016/j.tetlet.2014.01.142
0040-4039/



Scheme 1. Synthetic plan for **5a** and **5b**.



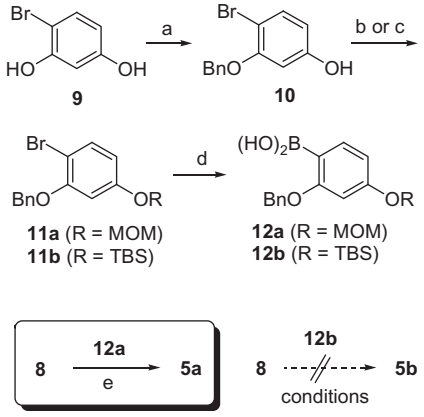
Scheme 2. Synthesis of **8**. Reagents and conditions: (a) $ClCH_2CCl{=}CHCl$, NaH, DMF (91%); (b) PEG-400, 270 °C, 15 min (49% after recrystallization).

corresponding allylic ether **7** in 91%. This was an *E*/*Z*-mixture (*E*/*Z* = ca. 2:1), because the commercially available 1,2,3-trichroro-1-propene was also an *E*/*Z*-mixture. This mixture was subjected to the next step, that is, Claisen rearrangement-cyclization cascade reaction, without further purification. This reaction was examined and summarized in Table 1. Thermal conditions in toluene resulted in no reaction (entry 1), whereas that in *o*-xylene resulted in decomposition (entry 2). We then used PEG-400 as a solvent. Reaction temperature was gradually increased to 220 °C, because the desired reaction did not appear to have begun at 120 °C, and the heating was maintained until **7** had almost disappeared (entry

Table 1
Studies on Claisen rearrangement-cyclization cascade

Entry	Solvent	Additive	Temp[a] (°C)	Time (h)	Yield[b]
1	Toluene	—	120	7	N.R.
2	*o*-Xylene	—	160	5	Decomp.
3	PEG-400	—	120–220	7	2%[c]
4	*o*-Xylene	$PhNEt_2$	170	15	N.R.
5	Decalin®	$PhNEt_2$	210	7	3%[c]
6	PEG-400	$PhNEt_2$	230	1	30%[c]
7	PEG-400	—	270	0.25	69%[c]

[a] Bath temperature.
[b] Isolated yield as a mixture of **8** and **8′**.
[c] The ratio of **8**:**8′** was around 5:2 in all cases.



Scheme 3. Synthesis of **5a**. Reagents and conditions: (a) BnBr, NaH, DMF (55%); (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2 (93%); (c) TBSCl, NaH, THF (91%); (d) *n*-BuLi, $B(OMe)_3$, THF (71% for **12a**; 69% for **12b**); (e) $Pd(PPh_3)_4$ (5 mol %), K_2CO_3, aq DMF, 80 °C (89%).

3). Thus, the desired chromene **8** was obtained as a mixture with the regioisomer **8′**. However, the isolated yield of a mixture of **8** and **8′** was only 2%. These results suggest the instability of **7** or **8**/**8′** under thermal conditions. One probable reason for degradation may be the resulting HCl; therefore, we attempted to prevent this degradation by adding $PhNEt_2$ (1.0 equiv) as an acid scavenger. Although $PhNEt_2$ is recognized as being effective against degradation (entry 4), the yield of **8**/**8′** was only 3%, even in refluxing decalin® (entry 5). We then used PEG-400 and observed a dramatic improvement in the yield (entry 6). However, we also found that the addition of $PhNEt_2$ made both the monitoring as well as the purification of **8**/**8′** significantly more difficult. Therefore, we tried high-temperature short-time conditions without $PhNEt_2$ (entry 7). By using a preheated bath at 270 °C, the reaction proceeded rapidly to give the desired **8**/**8′** with a 69% yield in 15 min. We noted that reactions using Lewis-acids,[8] and aqueous solvents[9] resulted in no reaction. We also noted that a mixture of **8** and **8′** was difficult to separate by chromatography, but was easily separated by recrystallization (from hexane), and the best yield of pure **8** was 49%.[10] It is expected that there are two possible pathways in this cascade, as described in Scheme 2. However, we are unable to discuss this matter here, because we have no experimental evidence.

With the key intermediate **8** in hand, our next challenge was Suzuki–Miyaura cross coupling. We prepared two boronic acids from 4-bromocresol (**9**). Mono-protection of **9** was attempted with moderate selectivity to give the corresponding mono-Bn ether **10** (55%; di-Bn ether 23%, regioisomer 4%).[11] This was protected in the usual manner to give **11a** and **11b** (93% and 91%, respectively), which were then converted into the corresponding boronic acids **12a** and **12b** (71% and 69%, respectively). Suzuki–Miyaura cross coupling between **8** and **12a** was then studied. Fortunately, the

reaction proceeded smoothly to give the desired adduct **5a** under the most commonly used conditions: $Pd(PPh_3)_4$, K_2CO_3, aq DMF. The best yield of 89% was observed when the freshly prepared $Pd(PPh_3)_4$ was used.[12] However, the cross coupling between **8** and **12b** was difficult to realize. The desired **5b** was not obtained at all under the above mentioned conditions, and a certain amount of ligand [P(*t*-Bu)$_3$, PCy_3, dppe, dppf, etc.], base (Cs_2CO_3, KF, etc.), and solvent (THF, dioxane, etc.) was tested according to the reported modified conditions.[13] However, in spite of our best efforts, **5b** was not obtained. In most cases, a certain amount of **8** was recovered, although **12b** disappeared. Notable by-products were deboronated products,[14] such as **6** and its TBS ether. Especially under aqueous conditions, **6** was obtained with a yield of up to 70% yield. According to Khupse et al., **5b** was a more advanced intermediate than **5a** but could be prepared from **5a**. Here, we were successful in the novel formal synthesis of glyceollin I (**1**). The overall yield of our virtual target compound **5a** was 40% in 3 steps based on **6** (Scheme 3).

In conclusion, we have realized the formal synthesis of glyceollin I. The novel and straightforward synthesis of the tentative target compound **5a** was achieved by starting from a commercially available **6**. We obtained an overall yield of 40% by taking three steps. Claisen rearrangement-cyclization cascade and Suzuki–Miyaura cross coupling were featured as the key steps. Our developed methodology enables us to synthesize not only glyceollins, but also a wide range of other isoflavones. The synthesis of glyceollins and other structurally related natural products is currently being carried out in our group.

Acknowledgments

We would like to thank Mr. S. Moriguchi (Kobe Univ.) for his support in this research.

References and notes

1. (a) Klarman, W. L.; Sandford, J. B. *Life Sci.* **1968**, *7*, 1095–1103; (b) Keen, N. T.; Sims, J. J.; Erwin, D. C.; Rice, E.; Partridge, J. E. *Phytopathology* **1971**, *61*, 1084–1089.
2. (a) Burden, R. S.; Bailey, J. A. *Phytochemistry* **1975**, *14*, 1389–1390; (b) Lyne, R. L.; Mulheirn, L. J.; Leworthy, D. P. *J. Chem. Soc., Chem. Commun.* **1976**, 497–498; (c) Lyne, R. L.; Mulheirn, L. J. *Tetrahedron Lett.* **1978**, *24*, 3127–3128.
3. (a) Tilghman, S. L.; Boué, S. M.; Burow, M. E. *Mol. Cell. Pharmacol.* **2010**, *2*, 155–160; (b) Salvo, V. A.; Boué, S. M.; Fonseca, J. P.; Elliott, S.; Corbitt, C.; Collins-Burrow, B. M.; Curiel, T. J.; Srivastav, S. K.; Shih, B. Y.; Carter-Wientjes, C.; Wood, C. E.; Erhardt, P. W.; Beckman, B. S.; McLachlan, J. A.; Cleveland, T. E.; Burow, M. E. *Clin. Cancer Res.* **2006**, *12*, 7159–7164; (c) Ng, T. B.; Ye, X. J.; Wong, J. H.; Fang, E. F.; Chan, Y. S.; Pan, W.; Ye, X. U.; Sze, S. C. W.; Zhang, K. Y.; Liu, F.; Wang, H. X. *Appl. Microbiol. Biotechnol.* **2011**, *90*, 59–68. and references cited therein.
4. (a) Khupse, R. S.; Erhardt, P. W. *Org. Lett.* **2008**, *10*, 5007–5010; (b) Khupse, R. S.; Sarver, J. G.; Trendel, J. A.; Bearss, N. R.; Reese, M. D.; Wiese, T. E.; Boue, S. M.; Burow, M. E.; Cleveland, T. E.; Bhatnagar, D.; Erhardt, P. W. *J. Med. Chem.* **2011**, *54*, 3506–3523.
5. Further improvements aiming at a multi-gram synthesis were also reported: Luniwal, A.; Khupse, R.; Reese, M.; Liu, J.; El-Dakdouki, M.; Malik, N.; Fang, L.; Erhardt, P. *Org. Process Res. Dev.* **2011**, *15*, 1149–1162.
6. Review: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
7. We later learned that a quite similar cascade reaction was reported: Gopal, D.; Rajagoparan, K. *Tetrahedron Lett.* **1986**, *27*, 5883–5884.
8. Cairns, N.; Hawood, L. M.; Astles, D. P.; Orr, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3095–3100.
9. Nicolaou, K. C.; Xu, H.; Wartmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 756–761.
10. *Properties of* ***8***: Mp 64–65 °C. ^{1}H NMR δ_H ($CDCl_3$, 300 MHz): 4.77 (d, *J* = 1.5 Hz, 2H), 5.02 (s, 2H), 6.46–6.54 (m, 3H), 6.84 (d, *J* = 8.1 Hz), 7.29–7.44 (m, 5H). ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 68.7, 70.1, 102.8, 108.3, 115.1, 121.5, 122.4, 126.8, 127.5, 128.1, 128.6, 136.7, 153.1, 159.8. HRESIMS *m*/*z* [M+H$^+$]: calcd for $C_{16}H_{14}ClO_2$: 273.0677; found, 273.0678.
11. This compound may be commercially available, but we prepared it by ourselves. For other preparation, see: Aikawa, K.; Miyazaki, Y.; Mikami, K. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 201–208.
12. *Preparation of* ***5a***: To a solution of **8** (0.31 g, 1.1 mmol) and **12a** (0.38 g, 1.3 mmol) in DMF (10 ml), $Pd(PPh_3)_4$ (64 mg, 55 μmol) and a solution of K_2CO_3 (0.31 g, 2.2 mmol) in H_2O (2 ml) were added under Ar. After stirring at 80 °C for 5 h, the reaction mixture was subjected to the usual extraction followed by chromatographic purification to give **5a** (0.49 g, 89%): mp 131–133 °C. ^{1}H NMR δ_H (acetone-d_6, 300 MHz): 3.44 (s, 3H), 4.94 (d, *J* = 1.2 Hz, 2H), 5.11 (s, 2H), 5.16 (s, 2H), 5.22 (s, 2H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.58 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.62 (s, 1H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H,), 7.28–7.54 (m, 11H). ^{13}C NMR δ_C (acetone-d_6, 75 MHz): 56.1, 69.0, 70.4, 71.1, 95.1, 102.5, 102.9, 108.9, 118.1, 121.9, 122.6, 128.3, 128.4, 128.6, 128.7, 128.8, 129.3, 129.4, 129.9, 130.0, 137.8, 138.3, 155.6, 158.2, 159.3, 160.5. HRESIMS *m*/*z* [M+H$^+$]: calcd for $C_{31}H_{29}O_5$: 481.2010; found, 481.2009.
13. Selected papers: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388; (b) Littke, A. F.; Chaoyang, D.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
14. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Vols. 1 and 2)*; Hall, D. G., Ed., 2nd ed.; Wiley-VCH KgaA: Weinheim, 2011.